The Basement Interviews Biological Open Source

Richard Jefferson, founder and CEO of CAMBIA, and leading light of the Biological Open Source Movement, talks to Richard Poynder

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Richard Jefferson was born in California in 1956, the son of music promoter and producer Carl Jefferson.² His mother, Hermeline, was a stage actress turned librarian.

Jefferson's parents divorced before he was born, so he and his two siblings lived with their mother in a single-parent household. As they were "financially challenged", says Jefferson, all the children had to pull their weight, and there were few treats. "I worked as a 4 am to 8 am paperboy most of my childhood. We never even had a family holiday — not one — and almost all my clothes were from 'goodwill' or Salvation Army."

After a brief period in what he refers to as "a pretty feeble Catholic elementary school", Jefferson entered the public school system, where he was put into a programme for "mentally gifted minors"

Although good at biology at school, Jefferson was more excited by physics and physical chemistry. Physics, he explains, offered "an underlying method in which you can distil the fundamental principles of life." By contrast, biology was just "a lot of cool observational stuff."

The best undergraduate

Jefferson's attitude to biology changed in 1974, however, when he went to the University of California in Santa Barbara (UCSB),³ and was exposed to what he calls "hardcore molecular biology." Specifically, one of the first lectures he attended was given by molecular biologist John Carbon,⁴ who talked about the research he had been doing on recombinant DNA⁵ during a recent sabbatical at Stanford University.

4 http://www.lifesci.ucsb.edu/mcdb/emeriti/carbon/index.html.

¹ This interview is based on two telephone conversations that took place on the 14th and 22nd of November 2005 and e-mail exchanges in September 2006.

² Carl Jefferson was initially a local automobile dealer and jazz fan. In 1972 he sold his Ford agency to found Concord Records, now a well-known US jazz record label, based in Beverly Hills, California. Originally known as Concord Jazz, it was an off-shoot of the Concord Jazz Festival in Concord, California established by Jefferson. http://en.wikipedia.org/wiki/Concord_Records.

³ http://www.ucsb.edu.

⁵ Recombinant DNA (rDNA) is an artificial DNA sequence resulting from the combining of two other DNA sequences in a plasmid. It is used for genetic transformation to produce genetically modified organisms. Some examples of recombinant DNA products are peptide hormone medications including insulin, growth hormone, and <u>oxytocin</u>. Vaccines can also be produced using recombinant processes. This was a key step in the development of transgenesis since it allowed scientists to produce GM

As he listened, Jefferson realised that Carbon was describing the same kind of "core unifying logic" that had thrilled him in his school physics, but had until now been absent from biology. Increasingly excited at what he was hearing, Jefferson began firing questions at Carbon, and the lecture turned into a two-way conversation, with the other students gazing on with glazed eyes.

The incident was sufficiently singular that Carbon recalls it vividly. As he explained to me by email: "I remember I talked about recent developments in recombinant DNA research (this was when that field was in its infancy). Rick Jefferson — as he was then known — asked several questions during the lecture, and then afterwards came up to talk with me, and to ask more questions. He was very excited about the research I described."

Jefferson was so enthralled, in fact that he immediately embarked on a campaign to persuade Carbon to let him work in his lab — an unheard of privilege for an undergraduate.

Eventually, says Carbon, "I invited him to help out, even though I had never taken a first year student into the lab previously. At first he helped out post-doctorals and grad students, but eventually he became more independent; more like a grad student when he was a senior. And he worked there until he graduated."

This was at the dawn of molecular biology, and Carbon's lab was one of only three or four labs in the world then working in the field.

Determined to learn as much as possible about molecular biology, Jefferson then began pestering the University of Edinburgh, in Scotland, to let him spend a year of his undergraduate studies in the lab of Ken Murray. "I managed — by perseverance — to push my way into a lab in a culture where undergrads just don't do that," says Jefferson. "And I spent a wonderful and instructive undergraduate year there when research on recombinant DNA was just beginning in Europe."

After returning to Santa Barbara and completing his degree, Jefferson moved to Boulder, Colorado, to do a PhD in the lab of David Hirsh.⁶

It wasn't long before Jefferson made an important contribution to molecular biology himself, developing a gene reporter system called GUS.⁷ This was revolutionary because it allowed molecular biologists for the first time to monitor exactly what was going on when they were trying to implant foreign

<u>organisms</u>. Paul Berg and Herb Boyer produced the first rDNA molecules in 1972. http://en.wikipedia.org/wiki/Recombinant.

⁶ Hirsh is a molecular biologist who became executive vice president and director of research at Synergen, Inc., a biotechnology company. In 1990 he became chairman of the department of biochemistry and molecular biophysics in the College of Physicians and Surgeons of Columbia University, and is now executive vice president for research at Columbia. http://cpmcnet.columbia.edu/dept/gsas/biochem/faculty/hirsh.html

⁷ GUS is based on a bacterial enzyme called β-glucuronidase.

genes into an organism. As Jefferson explains, before he developed GUS "people were just chucking stuff into blenders without any idea of what was happening!" As we shall, see GUS was later to become a key tool in the armoury of molecular biology.

At Boulder, Jefferson acquired a reputation for being a talented but somewhat maverick scientist. As the then head of department Bill Wood⁸ told me by email, "Richard was a flamboyant and impressive grad student here, who also drove us crazy at times."

Jefferson's view is that his colleagues simply didn't understand his obsession with methodology, and so didn't respect or appreciate what he was doing. "Everything in science is determined by the tools that fall into scientists' hands," he says. "And GUS is an example of really good methodology; it's a great tool."

In other words, scientists can be as brilliant as they like, but without the right tools they are limited in what they can achieve. Yet most researchers remain focused exclusively on the sexy business of pushing back the frontiers of knowledge, not on the quotidian task of creating the tools to enable cutting edge discoveries to be made. "Methodology has always been really dissed in science, and yet it is so important," complains Jefferson.

By the time he finished at Colorado, Jefferson had decided to shift the focus of his research: GUS had grown out of his work on worm embryonic development, but Jefferson had concluded that the genetic activity of plants is far more interesting. He began, therefore, to apply for funding to adapt GUS for plants.

To his anger and dismay, however, it took two years to get the necessary funding — a career hiccup, he later discovered, caused by the lukewarm references that David Hirsh had been writing for him.

Incidents like this were eventually to convince Jefferson that academia is not the meritocracy it claims to be, but an old boy's club. Too often, he complains, scientists' career prospects hang on decisions made in a non-transparent way, and on a "You scratch my back" basis.

However, in 1985 Jefferson eventually got funding from the National Institutes of Health⁹ to go to the Plant Breeding Institute in Cambridge, England.

Bench jockeys

For personal reasons, Jefferson's time at PBI was emotionally difficult. It was, however, a very productive period of his professional life. Discovering that adapting GUS was fairly straightforward, he turned his attention to other matters. And practically everything he touched, he says, "turned to gold".

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⁸ http://mcdb.colorado.edu/~wood

⁹ http://www.nih.gov.

Most notably, on June 1st 1987 Jefferson became the first person in the world to successfully plant a transgenic food crop. 10 In doing so, he beat biotech giant Monsanto to the punch by one day!

At PBI Jefferson also found himself working alongside a great many scientists from developing countries — an experience that was to convince him that researchers from the West routinely exploit their colleagues from less wealthy nations, using them as "bench jockeys" for their own ends.

The greatest victims of the academic Old Boys' Club, he concluded, are scientists from poorer nations, since those in the West are all too happy to stand on their backs to further their own careers.

This means, says Jefferson, that even those able to get to the West to do some research can generally only aspire to "do some science, publish a paper, and then disappear back into Africa or China, or wherever." Once back home they lack the necessary tools, the funds, and the opportunity to carry on with their research.

In the context of biotech, Jefferson concluded, this meant that those countries that had most to gain from molecular biology were the least likely to benefit from it.

Worse, this inequity was being exacerbated by an undesirable new development in science, as its traditional openness was giving way to a culture of secrecy and greed.

When he started in Carbon's lab, explains Jefferson, everybody shared data and not a single patent had been filed in the field. As the potential of biotechnology became apparent, however, a patenting frenzy had gripped the scientific community, with individual scientists and biotech companies falling over each other to secure intellectual property rights — not only in the basic tools of molecular biology, but in the raw material too.

There is no better example of the way in which core technologies were being appropriated than the fate of the two principle means for transferring genes into plants. The gene gun¹¹ developed at Cornell University had been patented, and the rights then sold on to DuPont — a transaction that earned for Cornell more money than the University had ever earned in royalties before. 12

Meanwhile, a technique utilising Agrobacterium tumefaciens 13 was itself rapidly being encircled by a sea of patents — patents that were later to

http://www.nysaes.cornell.edu/pubs/press/1999/genegun.html. http://www2.dupont.com/DuPont_Home/en_US/index.html.

¹⁰ That is, transgenic potatoes containing the <u>neomycin phosphotransferase II</u> and GUS marker genes.

¹³ Agrobacterium tumefaciens is a species of bacteria that causes tumours (commonly known as 'galls' or 'crown galls') in dicots. This Gram-negative bacterium causes crown gall by inserting a small

become the subject of intense litigation — as Syngenta,¹⁴ Monsanto¹⁵ and Dow¹⁶ all fought over the rights.¹⁷

While the increasing enclosure of the biotech commons was a growing source of frustration for scientists in the West, Jefferson saw that the consequences for developing countries were potentially devastating — since the hefty licensing fees required simply to engage in transgenesis threatened to lock them out of the considerable benefits that biotechnology promised, not least the ability to develop new plant varieties able to provide food security for their people.

More controversially, as initiatives like the Human Genome Project¹⁹ gathered pace, it was becoming evident that Western scientists and biotech companies were now intent on appropriating the very building blocks of life itself — by, for instance, patenting gene sequences.

Shared with the world

By now Jefferson had become convinced of the importance of making the basic tools of biotechnology freely available to all. Increasingly appalled at the way biotech was developing, he concluded that, whatever other people might do, he at least could act differently. In short, he decided to share GUS with the world.

So in 1987 he prepared 10,000 tubes of DNA sequences for use with GUS, wrote a comprehensive manual explaining how to use it with plants, and distributed lab packs to 500 research institutions around the world.

The result was instructive: Within a short space of time GUS was the most widely used reporter gene in the field. "Because Richard shared GUS freely, and because it worked effectively, everybody started using it," explains Gary Toenneissen, odirector of food security at the Rockefeller Foundation. "This meant that even though other reporter genes had become available, GUS was the tool of choice for most scientists."

segment of DNA (known as the T-DNA, for 'transfer DNA') into the plant cell, which is incorporated at a semi-random location into the plant genome. http://en.wikipedia.org/wiki/Agrobacterium.

The ownership issue seems to have been resolved by means of a cross-licensing agreement: http://www.isb.vt.edu/articles/feb0504.htm.

¹⁴ http://www.syngenta.com/en/index.aspx.

¹⁵ http://www.monsanto.com/monsanto/layout.

http://www.dow.com.

Transgenesis is the process of transferring genes of interest from the chromosomes of one individual into the chromosomes of another individual. The transferred genes are known as transgenes. http://www.sardi.sa.gov.au/pages/livestock/mw/gr/transgenesis.htm:sectID=521&tempID=120

¹⁹ The aim of The Human Genome Project (<u>HGP</u>) was to map the human genome down to the nucleotide (or base pair) level and to identify all the genes present in it. http://en.wikipedia.org/wiki/Human Genome Project

²⁰ http://www.goldenrice.org/Content1-Who/who Gary.html.

²¹ http://www.rockfound.org.

In short, although at the time not conscious of the parallel, Jefferson had independently come up with the same strategy as the Free Software Foundation (FSF),²² which was later to blossom into the Open Source Software Movement.²³ GUS became first choice for molecular biologists for the same reason as the Open Source server Apache²⁴ has become the most widely used web server software on the Internet: it was freely available, and it worked!

Jefferson also began to receive "bug reports" about GUS, enabling him to improve it. In doing so he demonstrated that Linus' Law — "given enough eyeballs, all bugs are shallow" — is as applicable in biological innovation it is in software development. All in all, says Toenniessen, GUS was "a good example of how the Open Source software model can work in biotechnology." ²⁷

As a consequence, GUS was to prove instrumental in helping scientists around the world create more efficient varieties of maize, wheat, rice, soybean and cotton — not least Western-based biotech companies like Monsanto, which used GUS to develop the now hugely successful and ubiquitous Roundup Ready soybean.²⁸

Excited by this turn of events Jefferson began to a hatch plan for a much grander project. Wouldn't it be great, he thought, if he could generalise what he had achieved with GUS throughout biotechnology?

By now Jefferson had also had first-hand experience of what he characterises as the "vicious, sophisticated but untidy, manipulative, staggeringly money-

The Open Source Movement is an offshoot of the Free Software Movement that advocates open source software as an alternative label for free software, primarily on pragmatic rather than

²² http://en.wikipedia.org/wiki/Free Software Foundation.

philosophical grounds. The movement was founded in 1998 by John "maddog" Hall, Larry Augustin, Eric S Raymond, Bruce Perens, and others. http://en.wikipedia.org/wiki/Open_source_movement.

24 The Apache HTTP Server is an open source web server for Unix-like systems, Microsoft Windows, Novell NetWare, and other platforms. Apache is notable for playing a key role in the initial growth of the World Wide Web, and continues to be the most popular web server in use, serving as the *de facto* reference platform against which other web servers are designed and judged.

http://en.wikipedia.org/wiki/Apache_server.

A bug is an error or defect in software or hardware that causes a program to malfunction. Often a bug is caused by conflicts in software when applications try to run in tandem. According to folklore, the first computer bug was an actual bug. Discovered in 1945 at Harvard, a moth trapped between two electrical relays of the Mark II Aiken Relay Calculator caused the whole machine to shut down. The word bug is now widely used in areas outside computing.

 http://www.webopedia.com/TERM/b/bug.html.
 Formulated by Eric S Raymond in his essay "The Cathedral and the Bazaar, more formally Linus's Law says, "Given a large enough beta-tester and co-developer base, almost every problem will be characterised quickly and the fix obvious to someone."

²⁷ Open Source software refers to computer software available with its source code, and under an Open Source licence. Such a licence permits anyone to study, change, and improve the software, and to distribute the unmodified or modified software. http://en.wikipedia.org/wiki/Open_source_software. Roundup Ready soybeans contain a gene that prevents damage from Roundup Ultra, the most popular non-selective, glyphosate-based herbicide. Roundup kills conventional soybeans, but with Roundup Ready soybeans farmers simply spray Roundup Ultra over beans and weeds alike to kill everything but the soybeans. http://ard.unl.edu/rn/0900/bean.html.

driven" process of biotech patenting. For when the University of Colorado had declined to patent GUS Jefferson had done so himself.

Explaining his decision to do so today, Jefferson says that at the time he was somewhat naïve about intellectual property (IP). At the back of his mind, he explains, was a vague thought that by patenting GUS he could use the royalties to fund the creation of new inventions.

Whatever the reason, the experience was to prove an important milestone in his IP education, since it led him to enter into what he now refers to as a "horrible Faustian Pact" with a highly-regarded US patent attorney called Leslie Misrock — a pact that was to lead to a great deal of pain, and eventually legal action.

But this was all the more reason to try and do something about things. And the best way of doing so, Jefferson concluded, would be to create an organisation focused on encouraging and supporting greater sharing of core technology. But how and where?

By the late 1980s Jefferson had become sufficiently disillusioned with the Old Boy's Club that he saw no opportunity of creating such an organisation within academia. What was needed, he concluded, was a more conducive environment. Consequently, he says, "I decided to leave the star maker machine: professorships and stuff. I had come to hate it with a passion."

After hitting an emotional low point in 1988, Jefferson was rescued by his friend Stephen Hughes,²⁹ whom he had first met in Edinburgh, in Ken Murray's lab. Hughes, he says, "dragged me off to Southern Italy with my tail between my legs."

At that time director of biotech research for an Italian food conglomerate, Hughes organised a six-month visiting professorship for Jefferson, and helped him sketch out his plans for the future.

"It was a very important time for me because Steve is a very creative man and gave me a lot of help," says Jefferson. "Many of the good ideas I came up with came out of discussions with Steve in those early days, in Mozzarella land."

Feeling that the kind of organisation he had in mind would be most effective if it were able to operate under the aegis of an international development body like the United Nations, in 1989 Jefferson accepted a post as the first molecular biologist with the UN's Food and Agricultural Organisation (FAO³⁰).

²⁹ Hughes is now a professor of genomics in society at Exeter University. He is also on CAMBIA's Board of Directors. http://www.centres.ex.ac.uk/egenis/staff/hughes.

³⁰ The Food and Agriculture Organisation is a specialised agency of the United Nations. Its role is to lead international efforts to defeat hunger. Serving both developed and developing countries, FAO acts as a neutral forum where all nations meet as equals to negotiate agreements and debate policy. It helps developing countries and countries in transition modernise and improve agriculture, forestry and fisheries practices and ensure good nutrition for all. Since its founding in 1945, it has focused special

Sadly, the FAO proved a false start. Within a short space of time it became apparent to Jefferson that the UN was just one more old boys' club — with member nations more focused on pursuing their own narrow interests than in helping the world's less wealthy nations feed themselves.

Disappointed by his inability to make headway, and disillusioned by the incestuous politics of the UN, in 1991 Jefferson left the UN, having determined that he would need to create a private initiative. Out of this disappointment and disillusionment would be born CAMBIA and the BiOS initiative.

CAMBIA is born

Fortunately, by now GUS had earned for Jefferson widespread respect and attention — not least from Rockefeller's Toenniessen.

Toenniessen is the man who initiated the quest for a biotechnology solution to the Vitamin A deficiency that was causing around 500,000 cases of blindness each year in the developing world, and contributing to around two million deaths — a guest that would eventually lead to the successful development of Golden Rice. 31

Keen to exploit Jefferson's considerable talent and abilities, in 1992 Toenniessen made funds available to send him out to Australia. There he was seconded to the Plant Industry division 32 of the Commonwealth Scientific and Industrial Research Organisation (CSIRO³³) in Canberra. His task was to troubleshoot the Rockefeller Foundation's rice biotechnology programs in Asia.

On his arrival in Australia, however, it was soon apparent that Jefferson also had his own agenda. No sooner was he settled in Canberra than he set about persuading the chief of the Plant Division, Jim Peacock, to find him lab and office space for the organisation he was determined to create.

Says Toenniessen with a laugh, "Jim told me, 'He finally bugged me so much about it that I gave him an old shack out at the back that we used to stick guys in who had retired, but who still wanted an office in order to get away from their wives!"

attention on developing rural areas, home to 70 percent of the world's poor and hungry people. http://www.fao.org.

http://www.pi.csiro.au.

³¹ Golden rice is a variety of rice produced through genetic engineering to biosynthesise the precursors of beta-carotene (pro-vitamin A) in the edible parts of rice. It was designed to produce Vitamin A precursor beta-carotene in the part of rice that people eat, the endosperm. The rice plant can naturally produce beta-carotene, which is a carotenoid pigment that occurs in the leaves and is involved in photosynthesis. However, the plant does not normally produce the pigment in the endosperm since the endosperm is not a tissue in which photosynthesis takes place.

http://en.wikipedia.org/wiki/Golden rice.

The Commonwealth Scientific and Industrial Research Organisation, http://www.csiro.au

Jefferson describes Peacock's "old shack" in less effusive terms. It was, he says, "an abandoned linoleum-clad prefab structure from the 1940s that had no heating, and was situated right next to a urinal. There was no furniture, no desk, no chair, and no phone."

Ever resourceful, however, Jefferson waited until Peacock went on a field trip and then launched a charm offensive on CSIRO's maintenance men. Inviting them to the local bar, he plied them with glasses of lager, and convinced them that his old shack needed urgent renovation. He also persuaded CSIRO's secretaries to volunteer their services to help with the administrative work needed to get CAMBIA up and running, and he cajoled and begged equipment manufacturers to donate the tools and apparatus needed in the CAMBIA lab: BioArrays³⁴ spectrometers,³⁵ HPLCs,³⁶ and so on.

"When Peacock returned he drove through the back lot and was startled to see the old shack had been turned into a swanky building," says Toenniessen. "There was a big sign on the front of the building saying CAMBIA, and young women were coming and going with various papers."

Laughing again, he adds, "It turned out that by using his personality, and his ability to connive, convince, and charm people, Richard had been able to jump the queue. So instead of having to wait two years for the work to be done, he got things fixed up before other people."

The incident, however, was to spark a long-running feud between Jefferson and Peacock, ending only when Jefferson relocated to CSIRO's Entomology Division.

But it was in that old shack next to a urinal that CAMBIA was finally born. After years of frustration and false starts, Jefferson had finally created the vehicle for fulfilling his ambition of making the world a better place.

For Toenniessen, sending Jefferson to Australia was to prove the start of a fruitful and symbiotic relationship. "Richard has had funding from us continuously for one thing or another since he went off to Australia, and in return we have used Richard," he explains. "For instance, we gave him the job of going around Asia teaching Asians in their own laboratories how to use new biotechnology techniques."

What Toenniessen is signalling is that, while the Rockefeller money had not been earmarked for CAMBIA,³⁷ he had not been fazed when Jefferson used some of it for that purpose, confident that the Rockefeller Foundation always receives good value for money from Jefferson.

³⁶ http://www.pharm.uky.edu/ASRG/HPLC/hplcmytry.html.

³⁴ http://www.postgenomeconsortium.com/bioarray.

³⁵ http://en.wikipedia.org/wiki/Spectrometer.

As we see in the interview, Jefferson apparently did!

BiOS

So what exactly is CAMBIA? Essentially, it's an umbrella organisation for the BiOS initiative. And the BiOS initiative consists of three separate projects: a licensing infrastructure to enable the sharing of biotech tools in a non-proprietary manner; a web-based collaboration platform; and a patent database.

The BiOS licences, then, are designed to actively encourage collaboration and technology sharing, and to discourage exclusiveness and hoarding.

The aim, explains Yochai Benkler in his book *The Wealth of Networks*, is to provide a "free model, with grant-back provisions that perform an openness-binding function similar to copyleft.³⁹ In coarse terms, this means that anyone who builds upon the contributions of others must contribute improvements back to the other participants."⁴⁰

Similar to the way that Open Source licences work in the software arena, therefore, BiOS licences facilitate the collaborative development of biotechnology solutions. While developers retain ownership of their own technology (and indeed are free to patent it), they commit not to withhold any improvements they make to the technology that they have licensed from other members of the BiOS community

CAMBIA also operates what Jefferson calls "a technological affirmative action program." So while licensees pay no royalties to use BiOS technology, those with the means to do so are asked to pay a support charge to enable CAMBIA to maintain the necessary infrastructure to ensure that licensees receive all the improvements, as well as the necessary biosafety data to meet regulatory requirements.

The aim is for wealthy members of the community to subsidise the less wealthy, and in practice this means that companies from OECD countries⁴¹ pay support charges, while those from developing countries do not.

³⁸ Biological Innovation for Open Society

³⁹ Copyleft is a play on the word copyright and is the practice of using copyright law to remove restrictions on the distribution of copies and modified versions of a work for others and require the same freedoms be preserved in modified versions. Most commonly, copyleft is implemented by a license defining specific copyright terms applied to works such as software, documents, music, and art. http://en.wikipedia.org/wiki/Copyleft.

⁴⁰ The Wealth of Networks, How Social Production Transforms Markets and Freedom, Yochai Benkler, Yale University Press, 2006, p. 242.

http://www.benkler.org/wealth of networks/index.php/Download PDFs of the book. A leading Open Source theorist, and Yale Law professor, Yochai Benkler coined the term commons-based peer production to describe a new model of economic production in which the creative energy of large numbers of people is co-ordinated (usually with the aid of the Internet) into large, meaningful projects, mostly without traditional hierarchical organisation or financial compensation. He compares this to firm production (where a centralised decision process decides what has to be done and by whom) and market-based production (when tagging different prices to different jobs serves as an attractor to anyone interested in doing the job).

⁴¹ Originating in 1948, The Organisation for Economic Co-operation and Development (OECD) is an international organisation of those developed countries that accept the principles of representative

This tiered model grew out of Jefferson's experience in patenting GUS. For while he had made GUS freely available, he subsequently realised that by asserting ownership of his invention he had given himself the option of defining licensing terms that promoted the sharing of technology, rather than the hoarding of it.

To obtain further funding for CAMBIA Jefferson decided to also license GUS to the large biotech companies under traditional licensing arrangements. This, however, took longer to achieve than he had anticipated, since in return for his services Misrock had insisted on becoming a 50/50 owner of the GUS patents, and now refused to co-operate. Jefferson was left with no alternative but to embark on an expensive legal battle to wrest back ownership of his own invention before he could license it.42

In the light of this unexpected delay, says Jefferson, it was often touch and go. "Sometimes we closed a deal within a week of a desperate payroll need at CAMBIA. They were very tense but heady times."

BioForge & Patent Lens

The second component of BiOS is an online platform called BioForge. 43 Like the Open Source Movement's SourceForge, 44 BioForge is a communal space where developers can announce details of new projects, jointly collaborate in the development of new technologies, and share experiences and findings with one another.

As Benkler puts it in his book, the goal is to "release the products of innovation into a self binding commons — one that is institutionally designed to defend itself against appropriation. It promises an iterative collaboration platform that would be able to collect environmental and local feedback in the way that a free software development project collects bug reports — through a continuous process of networked conversation among the user-innovators themselves." 45

To kickstart BioForge, Jefferson has seeded it with a number of CAMBIA's patented technologies, including GUSPlus⁴⁶ (an enhanced version of GUS)

⁴⁵ *Ibid.* p. 344.

democracy and a free market economy. There are currently thirty full members; of these, 24 are described as high-income countries by the World Bank in 2003. http://en.wikipedia.org/wiki/OECD.

Jefferson told me by email that this only became possible after his father's death, "when my inheritance (\$80,000) went 100% into hiring a lawyer to get my patents back from Misrock."

⁴³ http://bioforge.net/forge/index.jspa.

⁴⁴ SourceForge.net is a centralised location for software developers to control and manage open source software development, and acts as a source code repository. SourceForge.net is hosted by VA Software and runs a version of the SourceForge software. A large number of open source projects are hosted on the site (it had reached 113,690 projects and 1.25 million registered users as of February 2006), although it does contain a lot of dormant or single-user projects, http://sourceforge.net.

⁴⁶ GUSPlus is a new reporter gene for use in molecular biology. There are GUS*Plus* vectors for checking transformations and screening transformants, and special vectors for use with TransBacter strains. http://www.bioforge.net/forge/entry.jspa?externalID=41&categoryID=3

plus a number of technologies still in early-stage development: technologies like DaRT, 47 TransBacter, 48 and apomixis. 49

While Jefferson has been disappointed at the level of interest in BioForge, he views it as a very important part of the BiOS initiative forward.

Once again one is struck at the parallels between the development of CAMBIA and the development of the Free and Open Source software movements — not least their "independent" discovery of the benefits of openness and the sharing of technology.

Like Jefferson, Richard Stallman had also seen the need early on for an organisation and infrastructure focused on encouraging and promoting the development and sharing of core tools — a conclusion that in 1985 saw Stallman found the Free Software Foundation.

It is also worth noting that the year that Stallman founded the FSF (1985) was the year that Jefferson arrived at PBI, a move that was to trigger his decision (in 1987) to start sharing GUS with the world.

Similarly, the year that Jefferson left the FAO in order to create CAMBIA (1991) was the same year that Linus Torvalds⁵⁰ released the first version of the Linux kernel, ⁵¹ the heart of the GNU/Linux operating system ⁵².

We should also add that while Stallman had been working on the GNU Project⁵³ for two years prior to Jefferson sharing GUS, Torvalds would not

⁴⁷ DArT, or diversity arrays technology, enables researchers to analyse plant and animal genomes with no prior DNA sequence knowledge of the organism(s) being investigated.

http://www.bioforge.net/forge/entry.jspa?externalID=51&categoryID=4

http://www.bioforge.net/forge/entry.jspa?entryID=1. More on TransBacter a little later on.

Clonal reproduction of plants via seed, known as apomixis, has the potential to change plant breeding technology. Apomixis would allow farmers to perpetuate, cheaply and undiminished, the high yield gains from hybrids. http://www.bioforge.net/forge/kbcategory.jspa?categoryID=9.

Linus Torvalds is a Finnish software engineer best known for initiating the development of the Open Source operating system Linux. http://en.wikipedia.org/wiki/Linus Torvalds.

Linux (also known as GNU/Linux) is a Unix-like computer operating system. It is one of the most prominent examples of open source development and free software; unlike proprietary operating systems such as Windows or Mac OS, all of its underlying source code is available to the public for anyone to freely use, modify, and redistribute. Linux was the last and, arguably, most important component of the GNU/Linux system that Stallman had envisaged when he founded the FSF, and was to prove the spark to ignite the Open Source Movement. http://en.wikipedia.org/wiki/Linux.

The relationship between the Free and Open Source software movements is a troubled one. The

Open Source Movement is based on the work done by Richard Stallman on the GNU project. Essentially, the Free Software Foundation built the core components of the GNU/Linux operating system, but the kernel was later created by Linus Torvalds, and subsequently the entire system became known as the Linux operating system. In addition, the term Free Software was jettisoned by many in favour of Open Source Software. As Wikipedia puts it, "A group of people interested in free software and GNU/Linux decided to introduce a new marketing term for free software, seeking to position it as business-friendly and less ideologically loaded; this led to creating the term "Open Source" and a schism with Richard Stallman and his Free Software Foundation." http://en.wikipedia.org/wiki/Open Source Initiative.

⁵³ GNU is a <u>free</u> operating system consisting of a kernel, libraries, system utilities, compilers, and enduser applications. Its name is a recursive acronym for "GNU's Not Unix", which was chosen because

release the Linux kernel on to the Web for another four years, and it would be another twelve years before the Open Source Movement was founded.

In other words, at the time that Jefferson was with Hughes in Italy hammering out his ideas for CAMBIA, there was no Open Source Movement. Moreover, Jefferson was unaware of both Stallman and of the FSF. So while today Jefferson makes frequent reference to the Free and Open Source Software (FOSS)⁵⁴ movements, and highlights the parallels with what he is doing in order to better explain his objectives, he was not influenced by them in the early days.

There is, however, one important difference between developing software and developing biotech solutions. For where software developers have traditionally relied on the copyright system to assert ownership of their code, biotechnology developers have utilised the patent system. This is a logical development since software is more akin to a "physical" product — like a book or a film — than it is to the more intangible "products" of biotechnology, which are invariably new methods, inventions, and techniques. ⁵⁵

One consequence of this is that developing open models in the field of biotechnology has proved more challenging than it has been with software. Moreover, when developing new techniques and solutions in molecular biology, scientists are usually developing not a complete solution, but a component of a much larger and invariably highly complex solution. And in today's IP obsessed world, most, if not all, the other components will be subject to third-party patents.

Jefferson compares a typical biotech solution to a wheel in which each spoke belongs to a different owner. In order to make the wheel work, therefore, it is necessary first to establish the owners of all the constituent parts of the wheel, and then seek to obtain permission from each of them to use their respective component in the new wheel you hope to produce. "You cannot use the complete solution without all the parts, but each part may be separately patented," he says. "For this reason navigating rights in the biotechnology space is very, very difficult."

It also means that biotech developers are highly vulnerable to inadvertently infringing third party patents. "Patent transparency," says Jefferson, "is the lifeblood of the new Open Source model."

Enabling greater patent transparency, therefore, is the aim of the third component of the BiOS initiative, a patent database called Patent Lens.⁵⁶ As well as providing a powerful search engine, Patent Lens will later offer a range

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its design is Unix-like, but it contains no actual UNIX code. The plan for the GNU operating system was announced in September 1983 by Richard Stallman and software development work began in January 1984. http://en.wikipedia.org/wiki/GNU.

⁵⁴ http://en.wikipedia.org/wiki/FOSS.

The distinction is not as clear cut as that of course, and increasingly (and controversially) more and more software is being patented as well.

⁵⁶ http://www.patentlens.net/daisy/patentlens/patentlens.html.

of sophisticated landscaping capabilities to help the BiOS community circumnavigate the hugely complex relationships between patents.

In addition, there are plans to allow third parties to contribute to the database — providing information about patents, for instance, and commenting on their likely validity, and current licensing arrangements.

In this way, says Benkler, Patent Lens will provide a dataset of "who owns what tools, what the contours of ownership are, and by implication, who needs to be negotiated with and where research paths might emerge that are not yet appropriated and therefore may be open to unrestricted innovation." ⁵⁷

The biology stack

As we have seen while — in terms of intellectual property — the worlds of software and biotechnology are not mirror images, there are striking similarities in the way that both have generated open movements. This inclines one to ask: what is it that biological systems and computer systems share in common that has led to this?⁵⁸

Clearly there are similarities. First, a computer system is based on software code, which is composed of bits.⁵⁹ This code instructs the machine what tasks to perform, and when and how to do so. In an analogous way, biological systems are based on DNA code,⁶⁰ which instructs an organism what, how and when to perform certain essential functions.

Second, as computers systems have become increasingly complex, so software writers have tended to adopt a layered approach when writing the code that drives them — a model sometimes referred to as the "software stack".

So, for instance, a PC will have an operating system (e.g. Windows, UNIX, Linux etc.) to manage the hardware and software resources of a computer, and on top of this will run applications software (e.g. word processors, spreadsheets etc.). The applications software manages the capabilities of the computer to carry out the direct tasks that users ask it to perform. ⁶¹ In fact,

⁵⁷ Benkler, *supra*, p. 342.

We should perhaps add that the seeds of Open Access Movement can be located not so much later in time: Paul Ginsparg's preprint server arXiv was created in 1991, and Stevan Harnad's Subversive
 Proposal was posted online in 1994.
 A bit refers to a digit in the binary numeral system (base 2). For example, the number 1001011 is 7

bits long. Binary digits are almost always used as the basic unit of information storage and communication in digital computing and digital information theory. http://en.wikipedia.org/wiki/Bits.
60 Deoxyribonucleic acid (DNA) is a nucleic acid — usually in the form of a double helix — that contains the genetic instructions monitoring the biological development of all cellular forms of life, and many viruses. DNA is a long polymer of nucleotides (a polynucleotide) and encodes the sequence of the amino acid residues in proteins using the genetic code, a triplet code of nucleotides.

http://en.wikipedia.org/wiki/Dna.

61 Of course computer systems are based on binary two-state logic and biological systems on four-state logical coding possibilities of the genetic biochemical building blocks (DNA includes different amounts of the four bases adenine, thymine, guanine and cytosine, usually abbreviated A, T, G and C). We should also bear in mind that computers are digital, biological systems are analogue.

the operating system itself now usually consists of a number of different layers too. The lowest level, for instance, is the kernel, which is the first layer of software loaded into memory when a system starts up. ⁶²

And as molecular biologists have come to better understand the complex structure of biological systems, so they have increasingly turned to computer science to characterise their discoveries, including the concept of the software stack.

This is understandable: While DNA carries the genetic information for encoding proteins to allow cells to reproduce and perform their functions, for instance, it is actually messenger RNA that encodes and carries that information from the DNA to the sites of protein synthesis where the necessary translation required to produce a gene product actually takes place. In other words, like computer operating systems organisms are highly complex, and structured in multifaceted and layered way.

For this reason molecular biologists have come to describe DNA as operating in the lowest stack of an organism's system, while the more visible management tasks and general functionality take place in the higher levels of what is frequently called "the biology stack".

It was not until scientists began to understand the structure of DNA and the way it works, however, that this complex layered structure became evident.

As Jefferson points out, while scientists were aware of the outcomes of activity taking place in the lower layers of the biology stack prior to the development of molecular biology, they were ignorant about the invisible molecular processes that caused these observable outcomes. As he puts it, scientists were "wandering about at the high end of the stack, not realising that everything they did was being driven by the underlying operating systems that they didn't understand, and using a programming language that they didn't speak."

Monopolised

These similarities are interesting in their own right. But why are they important in the context of Biological Open Source? Because by comparing biological systems with computer systems we are able to see that biotechnology faces many of the same threats as software. It also points us to ways in which these threats can be averted, or at least minimised. More relevantly, it helps us to understand what Jefferson is trying to achieve with CAMBIA.

For as scientists have come to understand the underlying operating systems of organisms, and as they have begun to tinker with and adapt them (modifying them at the genetic level for instance), it has become increasingly apparent that — as with computer systems — there is a danger that the core

⁶² It should, however, be pointed out that the earliest computers did not have operating systems. As computers became more sophisticated and complex, however, it proved essential to build in operating systems.

technologies, methods, and discoveries of molecular biology could be monopolised in a way that would not only impede the progress of science, but discriminate against less wealthy nations. ⁶³

By patenting gene sequences, and the tools and processes for manipulating genes, for instance, a small group of multinational corporations could end up controlling the future direction and development of biotechnology, and in doing so act as a brake on innovation. In just such a way Microsoft, through its proprietary ownership of the Windows operating system, has been able to monopolise the personal computer. Amongst other things this has allowed it to exclude smaller companies like Netscape from the market, thereby stifling innovation and holding back the development of the PC.

Indeed, Microsoft has acquired such a powerful hold over the PC that it is taking the combined energies of the US and Europe anti-trust authorities — plus the Open Source Movement — to loosen its monopolistic grip. ⁶⁴

Today the same threat hangs over the future of biotechnology. What Jefferson saw before anyone else, points out Benkler in his book, is that "much of contemporary agricultural research depends on access to tools and enabling technologies — such as mechanisms to identify genes or for transferring them into target plants. When these tools are appropriated by a small number of firms and available only as part of capital-intensive production techniques, they cannot serve as the basis for innovation at the local level or for research organised on non-proprietary models." 65

In other words, the implications are most grave for developing nations, since they are least likely to be able to pay royalties to the large multinational biotech companies who will be able to control biotech through the large patent portfolios they are assembling.

As Benkler points out, the nature of this threat became all too evident when researchers began developing Golden Rice. [W]hen it came to translating the research into deliverable plants, he explains, researchers encountered more than seventy patents in a number of countries and six materials transfer agreements that restricted the work and delayed it substantially. 167

⁶⁷ Benkler, *supra*, p. 339.

⁶³ The premise is that since people are "discovering" gene sequences and "inventing" new methods for genetic manipulation they are then able to acquire patents on those gene sequences or new methods, and so acquire a 20-year monopoly on them.

⁶⁴ The antitrust issue is complicated by the fact that it is open to debate where you draw the line between an operating system and the applications software that runs on it. This was the main issue of contention in the United States v. Microsoft antitrust trial, which revolved around the question of whether Microsoft could legitimately claim that its web browser was part of the Windows operating system, or a separable piece of application software.

⁶⁵ Benkler, *supra*, p. 342.

⁶⁶ The research was conducted by Ingo Potrykus of the Institute of Plant Sciences at the Swiss Federal Institute of Technology, and Peter Beyer of the University of Freiburg.

Money to be made

But how did we get here? After all, historically the task of producing new plant varieties was viewed as primarily the responsibility of publicly-funded organisations like universities, 68 and commercial organisations took little interest in the task.

As a consequence, explains Toenniessen, everybody shared, and disputes over proprietary rights were rarely an issue. "Nobody took out a patent, and the closest thing you had to proprietary rights was plant breeders' rights, 69 which were only generally applied in developed countries on horticultural crops. Moreover with plant breeders' rights anybody could still use your variety to produce a new variety⁷⁰ — so in effect they were similar to the Open Source licences being developed by CAMBIA."

To understand what has changed, he continues, you just have to follow the money "Rice wheat, cassava, potatoes, you name it, historically there was no incentive for commercial companies to produce improved varieties, because the farmers could simply save the seeds. So there was little money to be made."

The one exception, he adds, was the development of hybrid varieties like hybrid maize.⁷¹ What is different about hybrid maize, of course, is that its seeds don't self-replicate in the way that natural varieties do.72 That means that it is more difficult for farmers to hold back seeds from one year's harvest to grow the following year's. Anyone developing hybrid maize, therefore, was assured of a steady income stream as farmers returned each year to buy seeds. 73

⁶⁸ As Toenneissen explains, universities in the US have a responsibility to produce varieties for the farmers within their States. "So Cornell is supposed to produce apple varieties for apple farmers in New York, and UC Davis is supposed to produce strawberry varieties for farmers in California. They are given money from the state, and from the federal government to do precisely that."

⁶⁹ Plant breeders' rights, also known as plant variety rights (PVR), are intellectual property rights granted to the breeder of a new variety of plant. These laws typically grant the plant breeder control of the seed of a new variety and the right to collect royalties for a number of years. This guarantees income for the breeder to cover the costs of research and development. Farmers may store the production in their own bins for their own use as seed, but further sales for propagation purposes are not allowed without the written approval of the breeder. Plant breeders' rights contain a wider array of exceptions than the general regime of patent law. Commonly, there is a defence for farm-saved seed for instance. There is also scope for compulsory licensing to allow public access to new varieties. http://en.wikipedia.org/wiki/Plant_breeders%27_rights.

To But you could not sell a plant that was exactly the same as the protected variety.

⁷¹ Hybrid maize was one of the first examples of genetic theory successfully applied to food production. When first introduced, it seemed almost miraculous; study hybrids convinced sceptical farmers that 'the professors' and their arcane science could do them some good. Strangely, the genetic basis of heterosis (hybrid vigour) was and still is unknown. Nearly all the field corn now grown in the United States and most other developed nations is hybrid corn Donald F. Jones at the Connecticut Agricultural Experiment Station, New Haven invented the first practical method of producing a highyielding hybrid maize in 1914-1917. http://www.genetics.org/cgi/content/full/148/3/923.

72 Strictly speaking, hybrids are not sterile, but their seeds tend to be low grade. So by buying new

seeds each year farmers can be sure of producing the better crops they are designed to produce. ⁷³ Interestingly, *The New York Times* reported in September 2006 that in recent years wheat is being replaced by maize by US farmers. Driving this change, explained the NYT, have been "advances in

With the development of biotechnology, however, the private sector quickly realised that there was now potentially a lot of money to be made from developing new plant varieties — since molecular biology promised not only allowed a massive step-change in the potential for developing new plant varieties, but across a much wider range of crops. It has also made it possible to do so in a much more rapid, effective — and so profitable — way.⁷⁴

In many ways, says Benkler, biotechnology was an inevitable end point of the escalating mechanisation of agriculture during the 20th Century, during which, he says, the agricultural sector was "incorporated into the capitalist form of production."75

One side effect of this mechanisation, adds Benkler, was the increased use of chemicals, not least because planting larger and larger fields of the same crop made plants more susceptible to pests and disease.

Again, molecular biology has enabled biotech companies to take this to the next level, by developing new plant varieties resistant to the chemicals now routinely applied — new plants like Roundup Ready for instance, which allows farmers to spray their crops with the herbicide Roundup Ultra⁷⁶ in order to kill weeds, without in the process harming the crop itself.

The attraction of Roundup Ready for Monsanto, of course, is that it commits farmers each year to buying both the seeds and the associated herbicide. Once again, this offers a step change in the potential profits that can be

The next logical step is to start using what is colloquially known as terminator technology. 77 For while they might not self-replicate in the same way as natural plant varieties, hybrid crops are not actually sterile and so can in

hybrid and genetically modified seeds for other crops. Major companies like Monsanto have been spending millions of dollars developing improved forms of corn, soybeans and cotton — not wheat and those investments are paying off handsomely. Seeds engineered to resist drought and insects have yielded huge gains and have helped produce record corn harvests the last three years." http://www.nytimes.com/2006/09/16/business/16wheat.html?_r=1&th&emc=th&oref=slogin.

As Jefferson puts it, with biotechnology hybrids began to be created "by inserting DNA rather than the more familiar method of introducing genetic material by pollen and egg infusion in a genetic cross." The Future of Food, Biotechnology Markets and Policies in an International Setting, Edited by Philip G Pardey, IFPRI, 2002, p. 75-92. http://www.ifpri.org/pubs/jhu/futurefood.htm. ⁷⁵ Benkler, *supra*, 333.

⁷⁶ Glyphosate, frequently sold under the brand name Roundup, was introduced in the late 1980s for non-selective weed control. It is now a major herbicide in selective weed control in growing crop plants due to the development of crop plants that are resistant to it. http://en.wikipedia.org/wiki/Herbicide.

⁷⁷ Terminator technology is the colloquial name given to proposed methods for restricting the use of genetically modified plants by causing second generation seeds to be sterile, thereby forcing farmers to buy new seeds from large agrobiotech companies each year, rather than saving seed from the previous year's crop. The technology was developed by the US Department of Agriculture and Delta and Pine Land Company in the 1990s. Since it is hugely controversial there has been a reluctance to commercialise the technology. However, on 16th August 2006, Monsanto announced that it had acquired Delta & Pine Land, along with its Terminator Seed Technology, sparking further controversy and protest, although Monsanto has previously given a commitment not to commercialise terminator technology.

theory be used for re-planting. The attraction of terminator technology is that allows biotech companies to develop non-reproducing proprietary seed.

Another factor that has driven the growing enclosure of the biological commons has been the gradual withdrawal of the state from many areas in which they had previously assumed responsibility.

During the 1980s, for instance, privatisation became an obsession in the UK, with Margaret Thatcher selling off over 40 state-owned businesses — dramatically affecting the lives of more than 600,000 workers in former nationalised industries. And one of those enterprises to be sold off by Thatcher was PBI⁷⁸ — which in 1987 was bought by Unilever for £66m, and subsequently sold on to Monsanto for £320m.⁷⁹

In parallel, governments in the West have been increasingly encouraging universities to assert ownership of any intellectual property generated by their faculty and then to "leverage it"— a process formally sanctioned in the US with the Bayh-Dole Act in 1980.⁸⁰

In many cases, this led to universities selling off their right in the IP to private industry. Those biotech companies that bought IP in this way, or developed their own IP, understandably argue that since they made a substantial investment in doing, they need to recoup that investment by aggressively asserting proprietary rights in it.

Jefferson does not disagree with this in principle, and he insists that he is not opposed to intellectual property *per se.* Nor, clearly, is he against the mechanisation of agriculture. The issue, he says, is one of degree, and right now the IP system is out of control. As a consequence, he says, it is hindering innovation rather than stimulating it. "I think it has reached a level of outrageous venality, short-sightedness and excess," he says with some passion, "It no longer seems to stimulate creativity, but fosters gaming and rent-extraction."

However, for Jefferson the danger lies not in biotech companies being given proprietary rights in plant varieties, but the way in which the current obsession with intellectual property allows and encourages them to acquire proprietary rights in core technologies.

This, he says, has put science in the absurd position of having provided mankind with the knowledge and expertise to feed the world, and significantly

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⁷⁸ The British Government sold PBI

⁷⁹ There is here also an interesting analogy with the way in which learned societies have since the war been elbowed aside by commercial publishers like Elsevier Science and Springer — a process that began when in 1951 Robert Maxwell <u>formed Pergamon Press</u>. This commercialisation of scientific publishing has been instrumental in the development of the Open Access movement.

⁸⁰ The Bayh-Dole Act or Patent and Trademark Law Amendments Act is a piece of United States legislation from 1980. Among other things, it gave US universities, small businesses and non-profits intellectual property control of their inventions that resulted from federal government-funded research. The act, sponsored by two senators, Birch Bayh of Indiana and Robert Dole of Kansas, was enacted by the US Congress on December 12, 1980. http://en.wikipedia.org/wiki/Bayh-Dole.

improve health and life expectancy, only to discover that that knowledge and expertise is unavailable to the people who need it most.

For regardless of whether the IP system now encourages or hinders innovation, it is clear that if the basic tools and building blocks of biotechnology are appropriated by the wealthy West, then scientists in developing countries will be powerless to tackle the huge problems of food security and human health that bedevil their people, and so these countries will have to continue going cap in hand to the West simply to feed their own people.

Once again, therefore, while this is bad news for farmers in the West, it is potentially disastrous for developing nations. What it means, says Benkler, is that "the industrial producers of seed are seen to be multinational corporations, and the industrialisation of agriculture is seen as creating dependencies in the periphery on the industrial-scientific core of the global economy."⁸¹

Biological Open Source

And the way to avoid this, says Jefferson, is Biological Open Source. That is, to re-craft the innovation infrastructure in a way that allows developers of biotech "applications" to assert proprietary rights over their "products", and to profit from that if they wish, while leaving the core tools and "operating systems" of molecular biology freely available to anyone who wants to use them. Only by moving to that position, he says, will we be able to introduce fair and open competition in biotechnology.

In short, biotechnologists need to adopt the same model as Open Source software developers, where the lower levels of the stack (the operating systems) are — like GNU/Linux — freely available to everyone, while the higher level applications built on top of these operating systems are able to be exploited in a proprietary way. ⁸² Thus people can freely download GNU/Linux from the Web, ⁸³ and then build proprietary applications — like Star Office ⁸⁴ — to run on top of it.

This model, argues Jefferson, encourages innovation while avoiding harmful monopolisation. And it is precisely what he did with GUS: as one of the essential tools for implanting genes when creating new plant varieties, GUS was made available to anyone who wanted to use it. So while large biotech companies like Monsanto were able to develop new proprietary plant varieties like Roundup Ready, and scientists in developing countries were equally free

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⁸¹ Benkler, *supra*, 334.

⁸² In reality the analogy is not as precise as that. Some in the Open Source Movement believe that all software should be open, or "free", and there is no shortage today of Open Source applications like word processors and web browsers like Firefox.

⁸³ http://www.linux.org/dist/download info.html.

StarOffice is <u>Sun Microsystems</u>' office suite software package, which is a commercialised version (containing some additional features) of the <u>open-source</u> codebase developed by <u>OpenOffice.org</u>. It includes a word processor, spreadsheet, presentation software, drawing tool and database. http://en.wikipedia.org/wiki/StarOffice.

to use it to create their own new varieties — varieties, for instance, more appropriate for their local climate, or geography.

In taking the Open Source software model to a totally new field, says Benkler, BiOS "offers the crispest example of the extent to which the peer-production model in particular, and commons-based production more generally, can be transposed into other areas of innovation at the very heart of what makes for human development — the ability to feed oneself adequately. 85

We should stress, however, that Jefferson did not create the Biological Open Source Movement single-handedly. While he may have been the first to develop some of the key concepts, others have independently arrived at the same, or similar, conclusions.

Moreover, unlike most free and open movements, there is today still no clearly defined and mutually agreed description of Biological Open Source. Indeed there isn't even yet a universally accepted umbrella term. Jefferson prefers Biological Open Source. Others, however, use terms like Open Source Biology, Open Biology, or even Open Biotech.

This is partly because many advocates are still unaware of what others are doing. In 2003, for instance, technology correspondent for *The Economist*, Neil Cukier, wrote an article about the origins of what he called Open Biotech without mentioning Jefferson. Open Biotech, he said, had its roots in the Human Genome Project (HGP).⁸⁷

In 1999, recounted Cukier, the head of the human genome analysis group at Britain's Sanger Institute, Tim Hubbard,⁸⁸ proposed using an Open Source licensing model for the genome sequence data that the HGP planned to make available on the Web.

Hubbard was concerned that if the HGP data were simply released into the public domain then private interests would appropriate them. As Hubbard explained to Cukier by email in 2003, he had the idea of using a copyleft licence while surfing the Web one day. Coming across a description of the Open Content Licence, ⁸⁹ it occurred to him that there might be a way to adapt the license "to something appropriate to the genome that had legal weight." The primary objective, he added, was to protect the sequence "from someone taking it, refining it and then licensing it in a way that locked everyone in."

⁸⁵ Benkler, supra, 343.

⁸⁶ Jefferson's preference for Biological Open Source is unsurprising. After all, while BIOS originally stood for "Biological Innovation for Open Society", the acronym works just as well with Biological Open Source, as BiOS!

⁸⁷ Open Source Biotech, Can a non-proprietary approach to intellectual property work in the life sciences? Kenneth Neil Cukier, *The Acumen Journal of Life Sciences*, Vol. I, Issue 3. September/October 2003. http://www.cukier.com/writings/opensourcebiotech.html.

http://www.sanger.ac.uk/Users/th.

⁸⁹ Written in 1998 by David Wiley, the Open Content Licence was heavily influenced by Richard Stallman's General Public Licence. http://opencontent.org/opl.shtml.

Several of Hubbard's colleagues liked the idea too, and after consultation with — amongst others — Richard Stallman, a "click-wrap contract" was drafted. This specified that if anyone were to refine a sequence by mixing the HGP's public draft version with extra sequence data, they would be obliged to release the end product into the public domain.

In the event, however, the draft licence was not used. As director of the Sanger Centre Sir John Sulston later explained, "[T]he idea met with a chorus of disapproval from those at the public databases. They argued that it went entirely against the principle, hard won over the previous decades, that data deposited in the databases were completely free⁹⁰ for anyone to use without restrictions."⁹¹

Unlike Jefferson, Hubbard was directly influenced by the Open Source Movement. So were Rob Carlson and Robert Brent, two molecular biologists at the Molecular Sciences Institute, in Berkeley. ⁹² In 2002 they appear to have been the first to use the term Open Source Biology.

They coined the term when writing a paper⁹³ requesting funds from DARPA⁹⁴ to "develop and maintain a body of publicly available technology, to foster a community of researches who contribute to this open-source technology repository, and to publicise the concept and the actual workings of open-source biology through meetings and the Web.

"Like the software movement from which it takes its name," they continued, "the Open Source Biology community will rely on individuals and small groups of people to take charge of (and receive credit for) maintaining and improving the common technology, open to all, usable by all, modifiable by all."

The near term goal, they added, was "to generate a set of interoperable components sufficient to comprise a basic 'kernel' or basic 'OS' for phage, 95 bacterial, viral, plant and animal systems."

The long-term objective, they concluded, was to work towards the day "when well-characterised molecular components, and the know-how to use them to design and implement new biological systems, will be available to anyone who wishes."

Sceptics

But while others have played their respective roles in the growing calls for greater openness in biotechnology, Jefferson must surely be seen as the

⁹⁰ A key principle of open licences is that by asserting ownership of their IP rights creators are able to specify how the licences material is used. Putting the material into the public domain, by contrast, allows anyone to do what they want with it.

⁹¹ The Common Thread: A Story of Science, Politics, Ethics and the Human Genome. Sir John Sulston, with Georgina Ferry. Corgi Books, 2002, p. 239.

⁹² http://www.molsci.org/Dispatch?action-WebdocWidget:4866-detail=1.

http://www.molsci.org/DARPA OSB Letter.pdf.

The US Defense Advanced Research Projects Agency, http://www.darpa.mil.

⁹⁵ A virus for which the natural host is a bacterial cell.

leading light. Not only was he the first person to think through the issues in an organised way, but it is he who has put flesh on the bones of what for others has essentially been a theoretical idea. The question then is: can CAMBIA succeed in its objectives?

After all, while GUS has been hugely successful, it clearly cannot on its own revolutionise biotechnology. Apart from anything else, there are patents on other essential tools for transgenesis — *Agrobacterium* for instance. Consequently anyone looking to develop a new plant variety still faces the need to pay expensive licensing fees for the privilege. And the point of CAMBIA, of course, was to generalise what was achieved with GUS.

The good news is that in February 2005, Jefferson and his colleagues at CAMBIA scored what appears to have been a spectacular goal, when they announced in *Nature*⁹⁶ that they had successfully circumvented the patent thickets surrounding *Agrobacterium*, developing a new technique for implanting genes called TransBacter.

Specifically, they have developed a way to modify several species of bacteria outside the *Agrobacterium* genus to enable the mediation of gene transfer in a number of different plants; a method that they plan to make available under a BiOS licence.

If it proves as successful as Jefferson hopes, TransBacter⁹⁷ will provide molecular biologists with an alternative to another of the key tools for practising transgenesis. A tool, moreover, for which they will not be hefty royalty fees, and which, like Linux, anyone will be able to adapt and develop — so long as they commit to share any improvements they make to it.

Without doubt TransBacter is potentially a big win for Biological Open Source. As Toenniessen reminds us, until now there have been only two ways of transferring genes (*Agrobacterium* and the Cornell gene gun), "and they are all patented up."

Nevertheless, there are sceptics. In June 2005, for instance, an editorial in *Nature Biotechnology*⁹⁸ argued that the problem with CAMBIA's open source approach is that finding a work-around for a biotech solution is — to borrow Jefferson's own metaphor — not unlike finding a wheel spoke and thinking that that is enough to move a cart.

Citing the problems encountered by the developers of Golden Rice, *Nature Biotechnology* pointed out that in order to produce new plant varieties,

⁹⁷ TransBacter is a collective name given to three species of bacteria, *Sinorhizobium meliloti*, *Mesorhizobium loti*, and *Rhizobium* that have been shown to be able to transfer genes to plants under certain circumstances. It is a new method of gene transfer for plants — or indeed any <u>eukaryotic</u> organism — using bacterial species outside the genus *Agrobacterium*. http://www.bioforge.net/forge/entry.jspa?entryID=1.

⁹⁶ *Nature*, 433, 629-633, 10th February 2005. http://www.nature.com/nature/journal/v433/n7026/abs/nature03309.html.

⁹⁸ *Open Sesame*, Nature Biotechnology, Volume 23, June 7th, 2005. http://www.bios.net/daisy/bios/810.

scientists need to use a wide range of other patented techniques and technologies, including selective markers, 99 promoters 100 and gene silencing technologies. 101

Since advocates of Biological Open Source are unlikely to be able to circumvent all of these patents, 102 let alone muster the necessary manpower to make the attempt, it concluded, "a completely patent-free way of creating a transgenic plant product seems a remote prospect." 103

The author of the editorial may have misunderstood the nature of the BiOS model — which does not assume a patent-free world, but one in which patented technologies are shared in a co-operative manner. Nevertheless, it serves as a timely reminder of the scope and breadth of the challenge BiOS

There is, says Andrés Guadamuz, co-director of the AHRC Research Centre for Studies in Intellectual Property and Technology Law, 104 an additional problem. As he told me by e-mail, "Obtaining a patent is a very expensive endeavour, and it is unlikely that an institution that has gone through this expense will offer its patent with an open licence. I have spoken with enough people from the commercial biotechnology field to corroborate the unlikeliness of their using this."

Indeed, while biotech companies have shown themselves to be willing to license CAMBIA's technology 105 it remains to be proven that they will be prepared to share their own patented technology (as opposed to improvements they have made to technology licensed from CAMBIA). 106 If Guadamuz is right, CAMBIA could turn out to be the only entity donating core technology to the BiOS community.

⁹⁹ A genetic marker is a known DNA sequence (e. g. a gene or part of gene) that can be identified by a simple <u>assay</u>, associated with a certain <u>phenotype</u>. Genetic markers can be used to study the relationship between an inherited disease and its genetic cause (for example, a particular mutation of a gene that results in a defective protein). It is known that pieces of DNA which lie near each other on a chromosome tend to be inherited together. This property enables the use of a marker, which can then be used to determine the precise inheritance pattern of the gene that has not yet been exactly localised. ¹⁰⁰ In genetics, a promoter is a DNA sequence that enables a gene to be <u>transcribed</u>.

http://en.wikipedia.org/wiki/Promoter.

The term gene silencing is generally used to describe the "switching off" of a gene by a mechanism other than genetic mutation. That is, a gene which would be expressed (turned on) under normal circumstances is switched off by machinery in the cell. http://en.wikipedia.org/wiki/Gene_silencing.

102 In the *Nature Biotechnology* profile of Jefferson Richard Jorgenson, professor of plant sciences at the University of Arizona, said "I'd say that selective markers may be the biggest challenge because a number of them — major herbicides, for example — are all patented." Nature Biotechnology, Volume 23, 6th June 2004, p 643. http://www.bios.net/daisy/bios/810. http://www.bios.net/daisy/bios/810.

http://www.law.ed.ac.uk/ahrb/people/view.asp?ref=50.

¹⁰⁵ In the interview Jefferson indicates that BASF has licensed technology from CAMBIA.

¹⁰⁶ In the *Nature Biotechnology* profile of Jefferson IBM's Carol Kovacs said, "In the pharmaceutical and biotech fields, if you don't provide intellectual property it is a severe disincentive to the private sector to innovate, and that's a bit different than in IT, where most larger competitors are broadly cross licensed already. This doesn't happen in [the drug industry]. It's a mistake to [apply] what worked in IT to ...pharmaceutical and biotech." Nature Biotechnology, Volume 23, 6th June 2004, p 643. http://www.cambia.org/daisy/bios/801/version/live/part/4/data.

When I put this point to Jefferson he did not reply directly, but confirmed that CAMBIA plans to "raise substantial resources to develop larger portfolios of patents related to core enabling technologies, with a view to making them available universally, and allowing them to be used to leverage much larger contributions to public good."

Some predict that it won't only be companies that prove reluctant to share their technology through BiOS. In a 2003 article in *The Acumen Journal of Life Sciences*, for instance, Cukier argued that in an environment where universities are increasingly expected to "leverage" their IP, most will be reluctant to adopt an open approach.

Pointing out that the US Bayh-Dole Act specifically encourages universities to profit from IP generated as a result of federally-funded research he concluded that stipulating open-source licences "may run foul of that." Already, he added, a professor at the University of California-Berkeley, Steven Brenner, 107 has had to make special arrangements with his school before being able to participate in an open-source bioinformatics project. 108

Guadamuz believes that a more fundamental problem is that BiOS licences are of necessity too complex — a consequence of having to adapte "a licensing model that has been designed to work with copyright into a system that would have to work with patents." ¹⁰⁹

As he told me by e-mail, "In my opinion, the success of open source and Creative Commons¹¹⁰ rests on relatively easy to understand licences. Each draft of the BiOS licences seems to get more complex, and the language more laboured. Were I a lawyer advising potential licensors, I would just tell them to stay away."

Moreover, adds, BiOS licences are inevitably viral in nature — i.e. they require that the same licence is used throughout the distribution chain. ¹¹¹ — This virality, ¹¹² he says, could prove a further disincentive to those considering licensing technology from BiOS.

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¹⁰⁷ http://compbio.berkeley.edu/people/brenner.

Open Source Biotech, Can a non-proprietary approach to intellectual property work in the life sciences? Kenneth Neil Cukier, *The Acumen Journal of Life Sciences*, Vol. I, Issue 3. September/October 2003. http://www.cukier.com/writings/opensourcebiotech.html.

109 http://www.bilete.com/bilete.com/writings/opensourcebiotech.html.

http://www.bileta.ac.uk/Document%20Library/1/Open%20Science%20-

^{%20}Open%20Source%20Software%20Licenses%20and%20Scientific%20Research.pdf.

¹¹⁰ Creative Commons (CC) is a non-profit organisation devoted to expanding the range of creative work available for others legally to build upon and share. Building on the concept of copyleft, it allows copyright owners to grant some of their rights to the public while retaining others through a variety of licensing and contract schemes including dedication to the public domain or open content licensing terms. The intention is to avoid the problems current copyright laws create for the sharing of information.

The viral clause, says Guadamuz, is in both 2.1 and 3.1 (and subsections). "The normal copyleft element in open source," he argues, "applies to 'improvements', or derivatives'."

¹¹² Copyleft licenses are sometimes referred to as viral copyright licences; because any works derived from a copylefted work must themselves be copylefted. Richard Stallman objects to this description, arguing that the GPL acts more like a spider plant as the spider plant is very easy to propagate.

Jefferson dismisses these suggestions. "[M]ost of the critics that I've read are academics with little or no practical experience in patent craft, biotechnology or in the realities of business and licensing," he says, adding that they "may not appreciate the nuanced differences between 'enabling technologies' and 'products' more than anything else; nor perhaps appreciate the norms we wish to foster."

Unilateral promise

Nevertheless, Guadamuz argues that a better way of achieving greater openness in biotechnology would be for the large biotech companies to emulate the Open Source strategy pioneered by IBM in 2005, when it made a unilateral promise not to assert a list of 500 patents against bono fide Open Source software developers. 113

"One of the main advantages of the use of a unilateral promise is that it helps to focus the access to scientific research to those who the patent owner would not consider to be a commercial threat or potential competition, which would erase some of the concerns about the possible incompatibility of open source models with the expenses and commercial value of research," Guadamuz told delegates at the BILETA Conference. 114

And since this solution does not require a licensing scheme, he added, "it eliminates some of the more complex contractual chains of distribution that can be found in viral contracts. Researchers could also gain in the knowledge that there will be a certain amount of knowledge that can be used without fear of infringement."

A 2005 editorial in *Red Herring* reached a similar conclusion. What is needed, it argued, is for a Monsanto or a pharmaceutical company like Merk to "take a giant leap, as IBM did when it embraced Open Source software, deciding to make money on higher-level applications rather than from basic tools."

The problem, *Red Herring* added, is that "it is not clear that drug companies and agricultural product makers are ready to play." ¹¹⁵ Indeed, it is highly unlikely that any large biotech company would make such a commitment today.

Clearly time will tell how successful Biological Open Source will prove, and what role CAMBIA will play in any such success. What is surely certain is that there will be increasing public pressure to rein in the number of biotechnology patents being issued. More and more people are becoming convinced that the current system is unsustainable, and increasingly they are saying so.

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¹¹³ http://www.theregister.com/2005/01/11/ibm patent donation.

The British & Irish Law, Education and Technology Association. http://www.bileta.ac.uk/default.aspx.

¹¹⁵ Open-Source Biotech, Red Herring, April 17th 2006. http://www.redherring.com/Article.aspx?a=16473.

In July 2006, for instance, a consumer group, a patent foundation and a stem cell scientist, challenged patents on human embryonic stem cells held by the Wisconsin Alumni Research Foundation. 116

In response, we can expect to see increasingly aggressive lobbying by biotech companies keen to protect their financial interests, much in the way that commercial publishers are actively lobbying against the Open Access Movement. 117

Such lobbying is already evident, and it is having some success: on July 14th 2006, for instance. ContraCostaTimes.com reported that a panel reviewing what benefits California taxpayers can expect to receive from their \$3 billion investment in stem cell research agreed to remove a discovery-sharing requirement that the biotech industry had vigorously opposed. 118

For the time being, therefore, secrecy and non-disclosure look set to remain the norm in biotechnology. A study published in 2002 in the Journal of the American Medical Association, for instance, found that as a result of the today's patenting frenzying, 47% of geneticists who requested information of findings from other researchers were rejected at least once. Ten percent of all requests for information in genetics were denied, leaving a quarter of researchers unable to replicate published results and forced to delay their own publications. 119

If nothing else, then, in addition to developing alternatives to patented technology, organisations like CAMBIA are going to have to devote a lot of effort to lobbying. They need to alert the public and policymakers to the significant problems that today's obsession with intellectual property is creating for the development of biotechnology, not just in medicine but in agbiotech.

The good news is that some biotech companies are beginning to question today's over-proprietary approach. In an article in Reason Online 120 in 2003, for instance, Ronald Bailey reported that gene-chip maker Affymetrix¹²¹ had proposed a controversial shift away from the current system, 122 where

¹¹⁶ http://www.mercurynews.com/mld/mercurynews/living/health/15075976.htm.

See for instance http://www.publishersweekly.com/article/CA448518.html.

¹¹⁸ Biotech leaders had argued that being forced to freely share their patented inventions with California research institutions could stymie stem cell research by removing financial incentives for companies to get involved. "We do not want to hurt this industry," agreed Jeff Sheehy, a member of the intellectual property task force of the state's stem cell agency. "We have a policy that industry has told us will not work for them." Biotech industry no longer has to share stem-cell research, ContraCostaTimes.com, July 14th 2006.

http://www.contracostatimes.com/mld/cctimes/news/nation/15043121.htm.

Eric G. Campbell, Brian R. Clarridge, Manjusha Gokhale, Lauren Birenbaum, Stephen Hilgartner, Neil A. Holtzman, and David Blumenthal. 2002. Data Withholding in Academic Genetics: Evidence from a National Survey. Journal of the American Medical Association 287 (4):473 - 479. Abstract online at: http://jama.ama-assn.org/cgi/content/abstract/287/4/473.

Policy Day, BIO2003: Reporter's Notebook, *Reason Online*, June 25th 2003. http://www.reason.com/rb/rb062503.shtml.

http://www.affymetrix.com.

http://www.affymetrix.com/corporate/outreach/ethics_policy/whoownsthegenome_review.pdf.

"entities like individual genes and proteins can be patented, to one in which things like genes, proteins, haplotypes, single nucleotide polymorphisms (SNPs), 123 and exons 124 are treated as 'catalogue items' — no more patentable than elements like iron, carbon, and oxygen."

Explaining the company's proposal to delegates at BIO 2003, 125 Affymetrix general counsel Barbara Caulfield argued that patents should only be awarded for functional inventions, such as new diagnostic tests or new drugs. Shifting away from genes to tangible inventions, she argued, would benefit industry in the long run by providing "more predictability, more rationality, and more stability," which would in turn "improve the biotech investment climate."

While this may not be quite the model envisaged by Jefferson, it suggests that more and more people are beginning to see the benefit of adopting a more open approach in biotech.

And if the broad principle could be accepted, then the next challenge will be to agree on the boundaries of what is and is not patentable. One current obstacle to consensus on this, perhaps, is that separate open initiatives are developing in different areas of biotechnology — biomedicine, genomics, bioinformatics, proteomics etc. Those working in these various areas often have diverse interests, and different priorities.

Open this, open that

As we have seen, although Jefferson developed BiOS independently of the free and open software movements, in retrospect he believes that they share a great deal in common with BiOS, and he makes frequent reference to them.

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¹²³ A haplotype, a contraction of the phrase "haploid genotype", is the genetic constitution of an individual chromosome. In the case of <u>diploid</u> organisms such as humans, the haplotype will contain one member of the pair of <u>alleles</u> for each site. A haplotype can refer to only one locus or to an entire genome. A genome-wide haplotype would comprise half of a diploid genome, including one allele from each allelic gene pair. In a second meaning, it refers to a set of <u>single nucleotide polymorphisms</u> (SNPs) found to be statistically associated on a single chromatid. With this knowledge, it is thought that the identification of a few alleles of a haplotype block can unambiguously identify all other polymorphic sites in this region. Such information is very valuable for investigating the genetics behind common diseases and is collected by the <u>International HapMap Project</u>.

http://en.wikipedia.org/wiki/Haplotype.

124 Exons are the regions of DNA within a gene that are not spliced out from the transcribed RNA and are retained in the final messenger RNA (mRNA) molecule. Exons of many eukaryotic genes is interrupted by segments of non-coding DNA (introns). The term "exon" was coined by Walter Gilbert in 1978. http://en.wikipedia.org/wiki/Exons.

http://www.bio.org/events/2003/speaker/session2.asp?tid=22.

Genomics is the study of an organism's genome and the use of the genes. It deals with the systematic use of genome information, associated with other data, to provide answers in biology, medicine, and industry. http://en.wikipedia.org/wiki/Genomics.

 ¹²⁷ Bioinformatics and computational biology involve the use of techniques from applied mathematics, informatics, statistics, and computer science, and chemistry, especially biochemistry to solve biological problems usually on the molecular level. http://en.wikipedia.org/wiki/Bioinformatics.
 ¹²⁸ Proteomics is the large-scale study of protein, particularly their structures and functions. This term

¹²⁸ Proteomics is the large-scale study of protein, particularly their structures and functions. This term was coined to make an analogy with genomics, and while it is often viewed as the "next step", proteomics is much more complicated than genomics. http://en.wikipedia.org/wiki/Proteomics.

Latterly, of course, he has also been deeply influenced by them — in developing the BiOS licences for instance.

But does Biological Open Source have anything in common with other open movements — movements like Creative Commons, Open Source Journalism, 129 Open Data, 130 Open Access, 131 and so on?

It does, says Jefferson, pointing out that as information becomes more pervasive, "we are seeing more abuses of it, and attempts to monopolise it. Moreover, these monopoly threats are more and more pernicious, and their results so evident, that people are putting a lot of effort into trying to fight them."

Nevertheless, he is keen to stress that Biological Open Source and Open Access (OA) have very different objectives, since "access to knowledge" (a2k)¹³² and a "capability to use knowledge", or c2uk, are not the same thing.

His point is that by simply calling for unfettered access to scientific knowledge, OA is an inadequate response to the problems that concern him, since knowledge alone is not very useful without the necessary tools, and the capability, to make use of that knowledge.

The Open Access Movement, therefore, is only half way there, he explains. "If you want to talk about Open Access, and to share all the data, that is fine," he says. "Indeed, I'm all for Open Access. But it is the capability to use knowledge that's key. There is a huge misunderstanding amongst pundits about this, and also among some practitioners too."

Jefferson also believes that while FOSS has proved a very useful model for what he has been trying to achieve, BiOS in its turn has something very valuable to offer the FOSS movements, particularly as more and more software is patented. "Now that thousands of patents are being issued covering algorithms, software and standards, the problems that CAMBIA BiOS has evolved to confront and overcome are now shared with that industry," he explains.

and reusing digital data upon which scientific advances are built, today much of it is being lost or underutilised because of legal, technological and other barriers. http://www.arl.org/sparc/opendata.

131 Open Access (OA) is the free online availability of digital content. It is best-known and most feasible for peer-reviewed scientific and scholarly journal articles, which scholars publish without expectation of payment. There are two roads to OA, with many variations. In open access publishing, also known as the "golden" road to OA, journals make their articles openly accessible immediately on publication. In open access self-archiving, also called the "green" road to OA, authors make copies of

http://en.wikipedia.org/wiki/Open_access.

their own published articles openly accessible, generally in a subject or institutional repository.

Open Source Journalism, a close cousin to <u>citizen journalism</u> or <u>participatory journalism</u>, is a term coined in the title of a 1999 article by <u>Andrew Leonard</u> of <u>Salon.com</u>.

Advocates of Open Data believe that, although there are substantial potential benefits from sharing

The Access to Knowledge movement (also known as "A2K") is a loose collection of civil society groups, governments, and individuals who seek to link access to knowledge to fundamental principles of justice, freedom, and economic development. http://en.wikipedia.org/wiki/A2K.

There is undeniably a growing threat. When earlier in this series, I interviewed Richard Stallman, for instance, he pointed out that one study had estimated that the GNU/Linux operating system theoretically infringes thousands of patents. 133 Since the owners of these patents have not generally asserted them against Open Source developers this has not been problematic. As the patenting frenzy spreads to software, however, the situation could change, and not only will FOSS developers find themselves susceptible to infringement claims, but as software becomes increasingly complex they confront the same spokes and wheel problem that threatens biotechnology today.

In other words, in its attempts to free biotechnology from the patent threat, BiOS has also undertaken some extremely useful work for software developers — or indeed any other field that may find itself threatened by a patent gold rush.

In this light, rather than failing in its efforts to port the copyleft model to biotechnology, therefore, BiOS has done important pioneering work that will assist the FOSS movements take their struggle to the next level. This potential synergy, says Jefferson, "has prompted much of our work on the Patent Lens."

In short, Jefferson expects Patent Lens to prove a vital tool not just for the biotech community, but for FOSS developers too, enabling them to monitor the patent landscape, identify threats, and ascertain areas where work arounds might be possible. And by providing greater transparency, it will reveal how the patent system is currently being used, and demonstrate the extent to which the public good is being harmed as a consequence.

With this wider brief in mind Patent Lens — which was originally limited to life sciences — has been extended to cover patents in all sectors. Currently it contains 2.5 million patents from the USPTO, ¹³⁴ EPO¹³⁵ and PCT. ¹³⁶

And while Jefferson's background is in plant molecular biology, he hopes that the BiOS initiative will have a much wider influence. As Red Herring reported in 2006, 137 Jefferson and his colleagues are already discussing collaboration

¹³³ As Stallman put it in his interview with me, "A lawyer in the US has reported finding 283 different US software patents, each forbidding something he found going on inside the many lines of Linux. And remember he was talking just about the kernel. The whole GNU/Linux system is 400 times bigger according to an estimate I read. So we could estimate 100,000 different patents each prohibiting something done in the whole system."

134 The United States Patent and Trademark Office. http://www.uspto.gov.

¹³⁵ The European Patent Office. http://www.european-patent-office.org/index.en.php.

¹³⁶ The Patent Cooperation Treaty (PCT) provides a unified procedure for filing patent applications to protect inventions internationally. A single filing results in a single search accompanied with a written opinion (and optionally a preliminary examination), after which the examination (if provided by national law) and grant procedures are handled by the relevant national or regional authorities. The PCT does not lead to the grant of an "international patent", which does not exist. http://en.wikipedia.org/wiki/Patent Cooperation Treaty.

¹³⁷ Open-Source Biotech, Red Herring, April 17th 2006.

http://www.redherring.com/Article.aspx?a=16473.

on a Biological Open Source approach to cancer diagnosis and therapeutics, with CAMBIA seeding the work by licensing its patents on telomerase, "an enzyme that restores DNA at the ends of chromosomes called telomeres," 138

Genius scientist

But what sort of man is Richard Jefferson? And why would a scientist devote his life to a cause that attracts huge resistance from those who benefit from the status quo, and criticism and obstruction from his academic colleagues?

Certainly he is no ordinary scientist: When talking about his influences, for instance, Jefferson cites not fellow scientists, but creative performers, including musicians and jugglers. He is also a talented musician himself, composing and performing on guitar and mandolin, and he has studied juggling and modern dance. 139

Talk to anyone who knows Jefferson, and sooner or later the word "naïve" crops up. Even his fans draw attention to this trait. "Rick was clearly the best undergrad I ever had go through my lab," says Carbon. "He was immensely enthusiastic about research — more so than any undergrad or grad student I have ever encountered. He was also very naïve, and came up with many ideas, most of which were not well thought out."

Toenniessen agrees that Jefferson is naïve. Nevertheless, he adds, he is also hugely talented, and extraordinarily single-minded. "Richard is a typical genius scientist. I have run into a few of them and they all tend to be very individualistic, and they don't usually have a lot of time for folks who aren't real sharp and catch on quickly, or who muddy the waters. They also don't usually get along with anyone who has a competing idea!"

Certainly, Jefferson has proved a challenging colleague. The dispute he had with CSIRO's Jim Peacock when he arrived in Australia, for instance, appears to have been a typical Jeffersonian moment. Interested to hear Peacock's view of things, therefore, I made a phone call to Australia.

While the voice that came down the line had a predictable Australian twang, the delivery was strangely staccato, as if Peacock were an army officer reporting an act of insubordination to a military tribunal. "What Richard did when he arrived here was what you might expect Richard to do," he said. "I gave him space and a lot of freedom, but before long he began to abuse that freedom by trying to bypass the system, and he convinced some of our workmen that they ought to give his needs higher priority than the needs of other scientists. As a result people got a little upset with him, and eventually he had to move to the Entomology Division."

¹³⁸ http://bioforge.net/forge/kbcategory.jspa?categoryID=12. As *Red Herring* explained, "Without telomeres, cells cannot divide, and they die. Unlike regular cells, cancer cells keep making telomerase so that they are kept intact. The hypothesis is that blocking telomeres with drugs should destroy cancer cells."

http://www.cambia.org/daisy/bios/478.html.

While conceding that the "WWII radio hut" he had allocated Jefferson was somewhat dilapidated, he insists that it was nevertheless "a wonderful building."

Suddenly appearing to relax, Peacock breaks into a deep chuckle. "You know, I never really fell out with Richard, and I still have great respect for him. But he has a half-life of people being able to tolerate him, and eventually he gets them offside."

When I ask Peacock if he concurs with Toenniessen's characterisation of Jefferson as a genius scientist he replies, slowly and carefully: "No. I wouldn't say Richard is a genius scientist. He's clearly a very bright guy — in fact he can think on his feet more quickly than anyone I know. He is obviously also excited by modern biotech science, and committed to trying to ensure the positive aspects of those new technologies are available to the developing world. But that is not so much because he wants to push a particular front of knowledge in a biological area, but because he is a technology freak; he's a very, very clever technologist in science."

Unsurprisingly, Jefferson sees his feud with Peacock in a quite different light. The problem, he says, was simply that Peacock couldn't handle having a younger, more famous alpha male in the band. As a result of GUS and his successful GM field trial, Jefferson explains, when he arrived in Australia he was a "thirty-six year old extremely famous plant molecular biologist, and Jim was a chief of one of the CSIRO divisions. So, it was a classic silver back gorilla thing!" 140

More importantly, he adds, Peacock is a traditional scientist, so they had very different world views. "I turned up on this fatal shore as a Young Turk molecular biologist with a weird world view about sharing and stuff. That was very, very contentious."

Whatever the cause and nature of their dispute, Peacock's characterisation of him appears to support Jefferson's claim that scientists generally only respect colleagues who do cutting edge research, and scorn those who prefer to devote their time and energy to creating new scientific tools. It was for this same reason, believes Jefferson, that Hirsh took a dislike to him.

Be that as it may, like Peacock, Hirsh portrays the matter as an issue of character, not Jefferson's professional interests. And his views appear not to have changed or mellowed over the years. Jefferson, he told *Newsweek* in 2004, was "the most difficult student I ever had". 141

¹⁴¹ Juggling Two Worlds; Richard Jefferson is bringing together scientists from rich and poor countries to fuel the interplay of ideas, Karen Lowry Miller, Newsweek, November 29th 2004, http://www.msnbc.msn.com/id/6539285/site/newsweek.

¹⁴⁰ Silverbacks are the strong, dominant troop leaders. If challenged by a younger or even by an outsider male, a silverback will scream, beat his chest, break branches, bare his teeth, then charge forward. Sometimes a younger male in the group can take over leadership from an old male. http://en.wikipedia.org/wiki/Gorilla.

Puzzled by this brief comment, I emailed Hirsh and asked him to clarify what he had meant. Hirsh, however, replied simply, "I think I am finished with Jeffersonian utterances, and I know I am so busy next week that I am not able to provide comments."

Compassion to all humans

When I shared the responses I received from Peacock and Hirsh with Jefferson he expressed little surprise, saying simply: "I guess my BiOS and CAMBIA influences are rarely scientists per se, and so having commentary from them is such a red herring." He added that I would be better talking to some of his friends.

So I contacted US-based juggler Jon Held, 142 who has known Jefferson since they were postgraduates together. What sort of person is Jefferson I asked? "Richard has an exceedingly generous heart," replied Held. "However, this may not be evident to the casual observer, or indeed even to the intimate one. Richard is not adept at the expression of compassion toward individuals, and this wreaks havoc on his interpersonal relationships. It narrows his ability to relate."

Why then, I wondered, does he feel so strongly about helping less advantaged people? "Though, at times, Richard can be rather grizzly," explained Held, "he does have compassion and hope and love for people. He has chosen to utilise his brilliance in a way that expresses compassion to all humans. He hopes to make a very real difference in how we, all of us, control our future, and he most likely will do so."

Ask Jefferson directly what motivates him and he replies that it's a question of fairness and decency. "Once you accept that fairness and decency are a very good set of rules to live by, then it isn't very difficult to hold up a litmus test and say: 'Is this promoting fairness and decency, or is it not?' And if it is not, then you do something about it."

What also motivates him, he adds, is passion. "My mother was an actress, and my dad was a music producer and promoter. For us there has to be passion. Not just passion for ourselves, but a passion to see that what we have done has made other people happy too."

I could see how this might explain Jefferson's frequent references to creative performance, but I was still left wondering what the connection was between creative performance and science. For an answer I turned to another of Jefferson's friends, San Francisco-based mandolin-player Mike Marshall. 143 who seemed about as perplexed as me. However, he forwarded me an e-mail he had received from Jefferson on the topic.

http://www.airjazz.com/jonheld.html
 http://en.wikipedia.org/wiki/Mike Marshall %28bluegrass musician%29.

"For me," Jefferson had written to Marshall, "the special craft and nuance of being able to perform night after night, and each time — with someone else — explore something difficult is inspirational to what I'm trying to do. Science without heart is pop music. Science desperately needs heart, discipline and it needs generosity of spirit."

Fundamentally, Held later told me, Jefferson sees the doing of science as a creative act. "Richard has a great love for pioneers of excellence, whether it be in music or juggling or in genetics. Creativity and the cultivation of creativity is his quest."

In addition, added Held, Jefferson believes science is an inherently democratic activity. "The BiOS directive is to remove power from the lofty few and distribute it to the many."

Much larger global starvation issues

Frankly I was still a little confused, uncertain whether I was party to an overelaborate mystification of science, or simply being dense. In quizzing Marshall, however, enlightenment of another kind came.

Marshall is as an organic food fanatic. For this reason, he says, he is deeply uncomfortable with GM food, and has "some pretty strong feelings" about the science that Jefferson engages in. 144

"Of course I know that I am living in the Bay Area¹⁴⁵ and have the income to afford these things .. [whereas] .. Richard is trying to solve some much larger global starvation issues that take him to some other places that are not effecting my life directly (yet)."

Marshall's comment focused my attention on the fundamental difference between Jefferson's objectives and worldview, and those of supporters of the other free and open movements.

For like Marshall, advocates of the other movements tend to be deeply embedded in Western-centric values and concerns. As such, they tend to support the cause because they believe in greater individual liberty, improved "quality of life", or simply because they believe these movements promise a more efficient way of doing things — not because they want to change the world in any dramatic way. And while most believe that they are supporting an inherently democratic cause, they do not see it as a life and death issue. As

¹⁴⁵ The San Francisco Bay Area, also known as the Bay Area, is a geographically diverse metropolitan area that surrounds the San Francisco Bay in Northern California.

¹⁴⁴ A genetically modified food is a food product derived in whole or part from a genetically modified organism (GMO) such as a crop plant, animal or microbe, such as yeast. Genetically modified foods produced by genetic engineering have been available since the 1990s. The principal ingredients of these GM foods are derived from soybean, maize, canola and cottonseed oil. http://en.wikipedia.org/wiki/GM food.

such, their philosophy is neatly captured in the title of Benkler's essay on peer production — "Sharing Nicely." 146

By contrast, Jefferson is very much concerned with life and death issues, since for him GM food is a way of preventing starvation, and improving the health of millions of people, not a threat to natural plant varieties due to genetic pollution, or a way of loading our tables with tasteless vegetables.

In this light, to view GM food exclusively as a quality of life issue is to take far too parochial a view. By its very nature, biotechnology raises questions about life and death, and about global equality. As Jefferson puts it, "What is distinctive about the life sciences is that they concern themselves with the most crucial aspects of human survival. After all, you need food and health to survive, and managing natural resources is really all about biological innovation."

It is not hard, therefore, to see why Jefferson is keen to stress the difference between Biological Open Source and Open Access. After all, the most frequent argument used by OA advocates for making scientific research freely available on the Web is because it will enable researchers to "maximise the impact of their research." 147

In other words, OA advocates appeal to researchers' self-interest by arguing that putting their papers on the Internet will make them more visible, and so enhance their career prospects. They do not argue that doing so will make it available to others on a more equitable basis. Besides, as Jefferson points out, making information available on the Web is not much good to scientists in the developing world unless they also have the tools and the capability to make use of that information.

So the aim is not simply to "open up" biological innovation, but to democratise it, and on a global basis. As the CAMBIA brochure puts it, the objective is to help "the disenfranchised of the world". 148 This is undoubtedly a far more radical objective than most (if not all) the other free and open movements.

Unlike most scientists, says Toenniessen, Jefferson "wants to see his science have real impact; an impact, moreover, that will benefit many, many people, particularly poorer people."

In this light one can see why Jefferson found academia to be too cramping, and why academia found Jefferson to be too threatening. As he says, CAMBIA has always been too much about "rocking the boat and disturbing the status quo."

http://openaccess.eprints.org/index.php?/archives/28-guid.html.

148 See the CAMBIA BIOS Initiative, at http://www.bios.net/daisy/bios/10/version/live/part/4/data.

¹⁴⁶ First published in *The Yale Law Journal*, Vol. 114, pp. 273-358, Yochai Benkler's paper Sharing Nicely" offers a framework to explain large scale effective practices of sharing private, excludable goods." http://www.benkler.org/SharingNicely.html.

147 See for example Stevan Harnad's *Maximising the Return on the UK's Public Investment in Research*.

Since he lives on the other side of the world, I had expected that scheduling time to speak with Jefferson would prove difficult. In the event, it was far easier to connect with him than with the others I have interviewed in this series. Indeed, not only did he prove more approachable, but he was by far and away the most obliging and courteous interviewee.

My challenge, however, lay in negotiating a straight line through Jefferson's Shandyesque replies. For not only did I struggle to understand some of the more abstruse terms and concepts of molecular biology implicit in any discussion of BiOS, but I discovered that Jefferson prefers to take the scenic route when talking.

I had at least been forewarned of this by Peacock, who had said — with one of his deeper antipodean chuckles — "Whenever I meet Richard I have to start smiling, because he will get excited about anything. And when he starts talking, he will add a clever aside to qualify what he has just said; this will be followed by a further aside to qualify the first aside, which in turn will engender another aside to qualify the second aside. By then what he is saying has become so complex that nobody has any bloody idea what he is talking about any more."

Fortunately, many of the side roads Jefferson took me down were highly entertaining, and peppered with humorous anecdotes and well-observed mimicry.

Jefferson was also more obliging than the other interviewees when I sent him the draft text. Not only did he read it (unlike most of the others), but he returned it with multiple editorial changes. He also added many references to friends and colleagues. "My journey has been with lots of fellow travellers (not in that sense) and many influences," he said in explanation. "I tried to put a few in there, and I hope you leave their names, as they paid the price of hanging with a irritating, obsessive guy, and should at least get some credit for it!"

What then do we conclude about Richard Jefferson? Without doubt he is an unusual and complex person. He is also undeniably a gifted scientist; sadly, however, a scientist frequently undervalued and misunderstood by his colleagues.

But is he as difficult a person as some portray him to be? I don't know. What I can say is that he was a perfect gentleman in his dealings with me. Indeed, were I asked to choose which of the people I have interviewed in this series I would most like to spend an evening in the bar with, Jefferson would undoubtedly be at the top of the list.

His greatest quality, however, is that he is a man determined to make a difference. And he is willing to live by the sword in order to do so. This, says Toenniessen, is an important point, since without someone with Jefferson's

skills and qualities it would not be possible to test whether Open Source models work in biological science.

"Not only does he know enough about IP to be able to create an Open Source platform," he explains, "but he is also enough of a scientist to be able to generate the kind of technologies that people really want to licence in order to prime the pump. That is why Richard is such a unique aspect of the Biological Open Source Movement."

But whether history will judge Richard Jefferson to have been a naïve idealist tilting at windmills, or a man able to see things more clearly than the rest of us, we cannot yet say.

The omens at least are good, for Jefferson is beginning to be recognised for his work. The Schwab Foundation for Social Entrepreneurship, for instance, has named him to their roster of Outstanding Social Entrepreneurs, and he regularly appears as a panellist and participant at the World Economic Forum's Davos meeting.

In 2003, *Scientific American* also chose him as one of their World's 50 Most Influential Technologists, naming him the World Research Leader for Economic Development. And even the digerati are beginning to hail him: in 2005 *Wired* named Jefferson a finalist for the Wired Rave Awards 'Scientist of the Year.' 152

But what is surely most gratifying for him is that other scientists are finally taking note. In 2005, for instance, the American Society of Plant Biology awarded him its Leadership in Science Public Service Award, for outstanding contributions to science and society. ¹⁵³

¹⁴⁹ Apart from Toenniessen, Jefferson has another influential backer in Carol Kovacs, head of IBM's Life Sciences division in Somers, New York.

http://www.schwabfound.org/schwabentrepreneurs.htm?schwabid=705.

http://www.weforum.org/site/knowledgenavigator.nsf/Content/Jefferson%20Richard%20A.

http://www.wired.com/wired/archive/13.03/rave_pr.html.

¹⁵³ http://www.aspb.org



The interview begins ...

RP: When and were you born?

RJ: I was born in 1956, in Santa Cruz, California.

RP: Can you say something about your family?

RJ: My parents are both dead now: My mom, Hermeline, died a little over a year ago; my dad ten years ago.

RP: They divorced when you were a child didn't they?

RJ: Even earlier! My parents split up before I was born. My mom drove me home from the hospital on the afternoon I was born, with me in a basket on the backseat of the car! So I was raised in a single parent household with my mother, and my older brother and sister.

RP: What did your parents do?

RJ: Both my parents were in performance art, and I think that is one of the features that has continuously coloured my life: the whole ethos of performance art.

RP: What were their respective professions?

RJ: My mother Hermeline was a stage actress; although when she found herself a single mother of three kids she decided it wasn't a very reliable income, and became a librarian. Later on she became a sculptress.

RP: And your father?

RJ: My father was a jazz music promoter and producer. There is in California a festival called the Concord Festival: My dad started that up. ¹⁵⁴ He also started a

¹⁵⁴ http://www.concordjazzfestival.com

record company called Concord Jazz¹⁵⁵ — which specialised in jazz and latin and went on to win Grammies and stuff. So he was into music and the recording and promoting business.

RP: Can you say something about your childhood and schooling?

RJ: If it's my background you are interested in I can give you some facts: I was conceived in the Claremont Hotel in Berkeley, born in Santa Cruz, and first lived in Brookdale, California 156 — population 200. We then moved to Santa Cruz, 157 where I started kindergarten.

To get a reliable job and a good schooling for us, my mother subsequently moved us to San Jose, in Silicon Valley. That was back when Silicon Valley was full of orchards — so there were few entrepreneurs, and very little hype. And for me it was really exciting to be near NASA Ames Research Labs 158 as a kid; later on I ended up working as a volunteer there.

As for my schooling: I think you could say that I didn't let it get in the way of my education [laughs].

RP: How do you mean?

RJ: Well, for the first three years I went to a pretty feeble Catholic elementary school. Fortunately, my mother eventually recognised that it was useless and put me into the public school system — which I loved.

Later I went to a Jesuit-run high school dominated by funky lay teachers who taught courses in existentialism and [laughs] Russian philosophy.

RP: This was when you were how old?

RJ: Oh, just normal high-school age; I wasn't like Mr. Precocious or anything.

¹⁵⁵ Concord Records is a well-known US jazz record label, based in Beverly Hills, California. Originally known as Concord Jazz, it was established in 1972 as an off-shoot of the Concord Jazz Festival in Concord, California by festival founder Carl Jefferson, a local automobile dealer and jazz fan who sold his Ford agency to found "the jazz label I can never find in record stores." Since then, the label has achieved international recognition, as well as 88 Grammy Award nominations and 14 Grammy Awards. In 1999, entertainment veterans Norman Lear and Hal Gaba purchased the label, helping the company to attract such artists as Barry Manilow, Peter Cincotti, Ozomatli, Ray Charles, and Maurice White. Today it has a family of labels that includes several key partnership and imprints, and Concord has amassed a catalogue of over 1,000 albums and 10,000 recordings of individual songs from vocal and instrumental artists. The company is now known as Concord Music Group. http://www.concordmusicgroup.com/labels/?label=concord%20picante.

http://en.wikipedia.org/wiki/Concord Records.

¹⁵⁶ http://www.brookdalecalifornia.com.

http://en.wikipedia.org/wiki/Santa_Cruz, California.

NASA Ames Research Center (ARC) is a NASA facility located at Moffett Federal Airfield, which spans the borders of the cities of Mountain View and Sunnyvale in California. It was founded it December 1939 as the second laboratory of the National Advisory Committee for Aeronautics (NACA), and moved to NASA in 1958. http://www.nasa.gov.

Mentally gifted minors

RP: You weren't considered to be in any way special at school?

RJ: Sure I was [laughs]: I always thought so! Actually, in public school I was in a program called mentally gifted minors. (I always imagined it consisting of guys with acetylene torches wandering around looking for precious veins of gold).

RP: So you were considered to be a brighter than average kid?

RJ: Yes, OK. [laughs]. It's true.

RP: Was that a big deal for you?

RJ: No, it wasn't a big deal. My mom never put any pressure on me. Or perhaps I should say that she put the maximum pressure on me. She used to say two things. First: "Just do your best"; second: "Let your conscience be your guide." So maybe she gave me the ultimate guilt trip.

RP: She was catholic right?

RJ: Nominally, but she had such *joie de vivre* and a great sense of humour that eventually she got tired of it, and realised what a furphy¹⁵⁹ it is. When she pulled me out of private school I think it was a secret relief for her. She didn't have to continue being so Catholic, and so life could be more fun!

RP: You said she became a librarian?

RJ: Yes, and that was real cool for me. She would bring home five or six books every night, and I would just devour them. I would read two or three a day, and many times I didn't even know what I was reading: I sometimes didn't bother looking at the author's name, or the title — I would just open it up and start reading.

RP: What were your early interests?

RJ: When I was young what I loved most was doing music and reading; and humour. I generally find, by the way, that although not all smart people are funny, pretty much all funny people are smart [laughs].

RP: When did you become interested in science?

RJ: Actually, I wouldn't say that science was ever an explicit interest. To me it's like oxygen, and the scientific method is like breathing. I don't have to think about it. But to most onlookers, I'd always been interested in it, as I did it so much.

¹⁵⁹ This is possibly from Joseph Furphy, widely regarded as the "Father of the Australian novel". Furphy mostly wrote under the pseudonym Tom Collins, and was extremely popular in Australia during the late 19th century. Furphy's popularity is thought to have influenced the usage of the Australian slang word furphy, meaning a "tall story." http://en.wikipedia.org/wiki/Joseph_Furphy

RP: Did you enjoy biology at school?

RJ: Well, I was really good at biology in high school. But at that time it didn't have a core unifying logic: It was just a lot of cool observational stuff, and I am not really a great trained observer who can sit and look at things, and then see the patterns of life. I would love to be that way, but I am not.

RP: Where do your science skills lie?

RJ: Basically there are two different kinds of scientist. There is the scientist who is driven to discover how things work, and most of good science is driven by people like that. Then there is the group that really digs figuring out how to figure it out. That's me.

RP: How do you mean: figuring out how to figure it out?

RJ: I mean inventing methods to solve problems that people couldn't solve before, using science as your canvass. For me the cool thing is that I have been able to combine my facility in science with my creativity in figuring out where — in terms of the big picture — thing are going. In a sense, you could hardly even call me a scientist.

So it's like software development: There is the low end of the stack and the high end of the stack, and they really require substantially different treatments. They also have different cultures associated with them. So it's really about what part of the innovation stack you live in.

RP: Is that what you meant when you said that you were not Mr. Precocious at school: Your skills are in methodology rather than discovery?

RJ: Yes. Instead of sitting around hammering out pieces of tungsten wire like Thomas Alva Edison¹⁶¹ I just *used* science — even from an early age. For that reason, my school science was all pretty mundane stuff: I wasn't cultivated to study Maxwell's equations¹⁶² when I was seven years old or anything.

¹⁶⁰ The term "stack" seems to be used in a number of different ways by software developers. http://en.wikipedia.org/wiki/Stack_(software). As discussed in the introduction, here, and later in the interview, Jefferson appears to be analogising the science innovation stack with the way in which computer systems utilise a number of layers. At its most simple, this will include an operating system (i.e. Windows, UNIX, Linux etc) on top of which will be built applications (e.g. word processors, spreadsheets etc.). As computing has become increasingly distributed, software developers now also talk about middleware. The ObjectWeb Consortium explain middleware this way, "In a distributed computing system, middleware is defined as the software layer that lies between the operating system and the applications on each side of the system." With the development of molecular biology, Jefferson argues, biotechnology can also be viewed as having a stack structure. One consequence of this, he implies, is that those sitting at the bottom of the stack provide the necessary tools and methodologies to allow those higher up the stack to make new discoveries.

¹⁶¹ Thomas Edison, the US inventor and businessman is considered to be the most prolific inventor, and he developed many important devices. During his life he obtained 1,093 patents in his name and was one of the first inventors to apply the principles of mass production to the process of invention. http://en.wikipedia.org/wiki/Thomas Edison

¹⁶² Maxwell's equations represent one of the most elegant and concise ways to state the fundamentals of electricity and magnetism. From them one can develop most of the working relationships in the field.

What really attracted my attention in science at high school, therefore, was physics, and physical chemistry. While I joke about Maxwell's equations, the fact is that when you have an underlying method in which you can distil the fundamental principles of life — be it by means of Newtonian mechanics or physics — you have access to a nugget that exposes you to totally new thinking. I found that really attractive. So while I enjoyed biology at school, it didn't give me the creative rush that physics did.

Hardcore molecular biology

RP: Nevertheless, you later became a molecular biologist?

RJ: Right, because during the first few weeks of university I was exposed to real hardcore molecular biology.

RP: This would be at the University of California in 1974?

RJ: Yes. The way it worked at UCSB¹⁶³ was that freshmen¹⁶⁴ were expected to attend lectures by professors in different fields. You could gain a credit by just sitting in a lecture hall with thirty other first-year students listening to professors talk about their work for an hour. The aim was to give students a sense of what professionals are like in science. And one of the first lectures I attended was given by John Carbon.¹⁶⁵

John had just returned from a sabbatical he had taken at Stanford where — with a guy named Paul Berg ¹⁶⁶ — he had basically invented recombinant DNA ¹⁶⁷ [laughs]. By that I mean that he had done probably the first experiments with recombinant DNA, and he was gearing up his whole lab to continue that work. At that time there were only three or four labs in the world that were doing anything similar.

Because of their concise statement, they embody a high level of mathematical sophistication and are therefore not generally introduced in an introductory treatment of the subject. http://hyperphysics.phy-astr.gsu.edu/hbase/electric/maxeq.html

¹⁶⁴ In the US a freshman is a first-year student at high school, college or university.

http://www.accessexcellence.org/RC/AB/BC/Paul_Berg.html

http://www.ucsb.edu

¹⁶⁵ UCSB's profile of Carbon indicates that Between 1963-1973 he and co-workers at Chicago-based pharmaceuticals and health care company Abbott Laboratories studied the biochemistry and genetics of transfer RNA, and were successful in elucidating the molecular mechanism of the genetic suppression of missense and frameshift mutations in bacterial systems. He arrived at Santa Barbara in 1968 as Associate Professor of Biochemistry, subsequently being appointed to the rank of Professor in 1970. http://www.lifesci.ucsb.edu/mcdb/emeriti/carbon
¹⁶⁶ Paul Berg became a professor of biochemistry at Stanford University School of Medicine in 1959,

¹⁶⁶ Paul Berg became a professor of biochemistry at Stanford University School of Medicine in 1959, when he was 33. He witnessed firsthand the history of recombinant DNA research and regulation, having been in the forefront of both movements.

¹⁶⁷ Recombinant DNA (rDNA) is an artificial DNA sequence resulting from the combining of two other DNA sequences in a plasmid. It is used for genetic transformation to produce genetically modified organisms. Some examples of recombinant DNA products are peptide hormone medications including insulin, growth hormone, and oxytocin. Vaccines can also be produced using recombinant processes. This was a key step in the development of transgenesis since it allowed scientists to produce GM organisms. Paul Berg and Herb Boyer produced the first rDNA molecules in 1972. http://en.wikipedia.org/wiki/Recombinant.

Anyway, as I sat in that lecture listening I felt like I was experiencing one of those cheesy television metaphors — you know, where everything else in the room goes out of focus, and there is this tunnel between you and the person you are looking at. During the lecture a succession of bored undergraduates wandered in in a desultory fashion — clearly thinking only about when they could get out and get laid — but he and I were making eye contact; and I just sat there breathing heavily, hardly able to believe what I was hearing. I realised that he was talking about the fundamental level of resolution of what made everything pull together.

RP: In other words, the fundamental principles of life that you were exposed to in school physics, but this time in biology?

RJ: Exactly. And remember this was way before DNA sequencing¹⁶⁸ or anything like that. So the work at Stanford that Carbon was describing had all been done with incredibly clever and circuitous technology, which I found fascinating.

RP: An important moment in your professional life then?

RJ: Absolutely. And so I went up to Carbon afterwards and said: "I've got to work in your lab". He said: "Whoa, hold your horses. First-month undergraduates don't work in labs."

RP: He wouldn't let you join the lab?

RJ: Well, first he tried to fob me off. When I insisted he said: "If you are really serious, come and see me tomorrow morning in my office."

I reckon the last thing he expected was that I would actually turn up, but at 7:30 the next morning I was sitting outside his office as eager as a puppy — not realising that molecular biologists are generally still sacked out at that time in the morning!

When he turned up he just said: "Oh God," and rolled his eyes. This time he tried to dissuade me by pulling down a copy of *Molecular Biology of the Gene* by Jim Watson. He gave it to me and said, "Listen, this is kind of dense and it's tough going but here is the story: If you are really interested I will loan you my copy of this book. Browse through it, read some, and come back and ask if you have some questions." He clearly thought that that would finally get rid of me.

But 24 hours later I had read the whole book, and I hadn't slept in order to do so. I rushed back to Carbon's office red-eyed and said: "God this is great. Do you have more? I want to do this. How can I do this?"

¹⁶⁸ Gene sequencing is the process of recording the exact sequence of nucleotides in the section of an organism's DNA corresponding to a specific gene. The complete genetic sequences of humans and many other organisms have now been determined. http://en.wikipedia.org/wiki/Genome_sequencing.
¹⁶⁹ James Dewey Watson KBE is one of the discoverers of the structure of the DNA molecule. In 1962 Watson, Francis Crick and Maurice Wilkins, were awarded a Nobel Prize for Physiology of Medicine, for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material. Molecular Biology of the Gene was Watson's first textbook. It set a new standard for textbooks, particularly through the use of concept heads — brief declarative subheadings. Its style has been emulated by almost all succeeding textbooks.

At that point he hired me on the spot to work part-time in his lab, and he ended up being the only scientist I would ever call a mentor.

He also suggested I do my degree in this very funky little invitation-only college of the University of California called the College of Creative Studies, which is based in Santa Barbara. ¹⁷⁰ So I did.

RP: The College of Creative Studies is a special college then?

RJ: It provides a very high-end university experience where you're more or less one-on-one with professors and build your own curriculum. It is autonomous and unique in the UC system, and grand fun. I think my final year there were four of us biology graduates in total.

Hog heaven

RP: And, as you say, you worked in Carbon's lab. That was an unusual privilege for a freshman I guess?

RJ: Indeed. But that was where Carbon had a stroke of genius. He said "You are only 18, so I can't yet hire you to do your own research. However, you can work 50% of your time learning lab craft — making solutions, preparing Petri plates¹⁷¹ and helping other people and so on. Then during the other half of your time you can start doing some research yourself."

From that point on I was in hog heaven. After all, this was the lab in which the first genome libraries 172 were created; where the first expression of a gene from a higher organism in bacteria was done; where the first centromere 173 was isolated; and where the first genome walking 174 was done. It was just phenomenal. The lab consisted of eight or nine postdoctoral fellows, a super-technician, one PhD student, and me — an 18-year old.

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¹⁷⁰ http://www.ccs.ucsb.edu

¹⁷¹ A Petri dish is a shallow glass or plastic cylindrical dish that biologists use to culture microbes. It was named after the German bacteriologist Julius Richard Petri who invented it in 1877 when working as an assistant to Robert Koch. http://en.wikipedia.org/wiki/Petri_plate
¹⁷² A complete collection of molecules in a stable form representing some aspect of an organism is

A complete collection of molecules in a stable form representing some aspect of an organism is called a library in molecular biology. A genomic library contains an example of each DNA sequence found in a particular genome (or the hereditary information of an organism), broken into manageable fragments. http://www.iscid.org/encyclopedia/Genomic Library

The centromere is a region on <u>chromosomes</u> with a special sequence and structure. The centromere plays a role in cellular division and the control of gene expression. http://en.wikipedia.org/wiki/Centromere.

The Genome walking is a PCR-based method for analysing unknown genomic DNA segments adjacent to a known sequence by use of adapter ligation in combination with the suppression PCR effect. Genome walking is performed on uncloned DNA and allows researchers to obtain genomic DNA fragments of up to 4 kb from a single 'walk' using long-distance PCR. Further walks can extend this information indefinitely by use of new gene-specific primers based on the sequence obtained in the previous step. http://www.evrogen.com/t9.shtml

And every day Carbon and the postdocs would be on the phone to the other three or four labs that were inventing what would become the recombinant DNA toolkit of molecular biology. Essentially, I was working with what were to become the icons of the field. God damn it, it was just fantastic.

RP: All these labs were sharing information with each other?

RJ: They were. When I started in molecular biology everybody shared information. That was the standard we all adopted. So even though we were competing with Ron Davis, ¹⁷⁵ for instance, we would talk to him almost every day. For me that was a really exciting kind of competition; and although I didn't know it at time the total number of patents in the field then was zero.

RP: By now you were clearly hooked on molecular biology I guess?

RJ: Absolutely. But the real epiphany came when I read a paper written by Ethan Signer¹⁷⁶ and Jon Beckwith.¹⁷⁷

RP: Tell me about it?

RJ: It was a twelve-hour experience that started around midday one day, and finished at about 1 am the next morning — with lights, and cherubim and seraphim coming down out of the sky. ¹⁷⁸ The epiphany came when I finally understood the paper.

RP: What was the paper about?

RJ: At that time people were worried about genetic circuitry, and these guys invented the concept of tricking an organism in order to teach you things you couldn't learn otherwise. Moreover, the technology they used was incredibly primitive, which meant that their method had to be extraordinarily sophisticated: they had to be so smart to squeeze the last ounce of wisdom out of a living system.

Anyway, Signer and Beckwith had written the most incredibly hard and elegant paper. While reading it I had to keep bothering postdocs to explain things. When I finally got it I just walked around the lab in a daze, bumping into equipment. It was just such a huge big rush.

Signer and Beckwith, by the way, had done their postdocs in France with Jacques Monod 179 during the dawn of beta-galactosidase, and the development of the operon

¹⁷⁵ Ron Davis is the Director of the Stanford Genome Technology Center. He was a Professor of Biochemistry and Genetics at the Stanford University School of Medicine and co-founder of <u>ParAllele</u>. He pioneered many of the early techniques developed using recombinant DNA and helped conceive of novel methods for genetic linkage analysis. http://biox.stanford.edu/clark/davis.html

¹⁷⁶ http://web.mit.edu/bin/cgicso?query=ethan+signer.

http://beck2.med.harvard.edu.

http://en.wikipedia.org/wiki/Hierarchy of angels.

¹⁷⁹ Jacque Monod was a French biologist and a Nobel Prize Winner in Physiology or Medicine in 1965. Born in Paris, he was awarded also with several other honours and distinctions, among them the medal of the *Legion d'honneur*. Monod (along with François Jacob) is famous for his work on the *lac* operon. Study of the control of expression of genes in the *lac* operon provided the first example of a

theory. 180 Later on during my postdoc, I got to be pretty good friends with Ethan — who proved as marvellous in practice as he was in theory!

We had countless great walks around the streets of Cambridge Massachusetts at night in the rain, talking about science and society and forming the thought germ of what would become CAMBIA.

RP: You worked in Carbon's lab for all four years of your undergraduate period did you?

RJ: Actually, I spent a year in Edinburgh, Scotland, in the Department of Molecular Biology.

RP: Wasn't it a bit early in your career for a sabbatical?

RJ: Yes, but I was so full of energy, and after two years at UCSB, and working 12 hour days in the lab, I was feeling in need of exploring the world a bit, to see what these other top class molecular biology labs were like. And I wasn't just a lab rat — the idea of living and exploring overseas was really exciting. So I applied for a Year Abroad program at UCSB to go to Britain, and was promptly rejected.

RP: You are going to tell me that once again you prevailed?

RJ: I am. You see, there was this utterly top-class lab in Edinburgh Scotland, run by Ken and Noreen Murray¹⁸¹ (this would have been 1975). They were running an incredibly vigorous program at the cutting edge of European molecular genetics, and I was really fascinated by their work, and that of the others in Edinburgh, including Ed Southern¹⁸² at the MRC Mammalian Genome Unit¹⁸³ (jokingly known as the Mammalian Gnome Unit).

So instead of just hanging my head when the University of California Education Abroad Program said no, I took a different path.

RP: Why did they say no?

transcriptional regulation system. He also suggested the existence of mRNA molecules that link the information encoded in DNA and proteins. http://en.wikipedia.org/wiki/Jacques_Monod.

83 http://www.hgu.mrc.ac.uk.

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¹⁸⁰ An operon is a group of key nucleotide sequences including an operator, a common promoter, and one or more structural genes that are controlled as a unit to produce messenger RNA (\underline{mRNA}). Operons occur primarily in prokaryotes and nematodes. They were first described by François Jacob and Jacques Monod in 1961. The *lac* operon consists of three structural genes, a promoter, a terminator, and an operator. The three structural genes are: *lacZ*, *lacY*, and *lacA*. *lacZ* encodes β-galactosidase (LacZ), an intracellular enzyme that cleaves the disaccharide lactose into glucose and galactose. *lacY* encodes β-galactoside permease (LacY), a membrane bound transport protein that pumps lactose into the cell. *lacA* encodes β-galactoside transacetylase (LacA), an enzyme that transfers an acetyl group from acetyl-CoA to β-galactosides. Only *lacZ* and *lacY* appear to be necessary for lactose catabolism. http://en.wikipedia.org/wiki/Lac_operon.

http://www.dundee.ac.uk/pressoffice/grad2000/postgrad/murray.htm.

¹⁸² Sir Edwin Mellor Southern is a 2005 <u>Lasker Award</u>-winning molecular biologist. http://en.wikipedia.org/wiki/Edwin_Southern.

RJ: I had pretty average grades the first two years of University. I spent outrageous hours in the lab actually 'doing' science, and playing music, and chasing girls; so there wasn't much time left for doing assigned homework. I did well on all the exams, but I just didn't have the time or patience for assignments. Thank god for the Music Department, in which I always got A's to counterbalance the somewhat ordinary marks from other subjects I cared little about.

RP: So how did you prevail?

RJ: I decided to write directly to Ken Murray and others at University of Edinburgh, and I asked John Carbon to write as well. That was very effective. I discovered that my application had never even made it to Edinburgh, it had been trapped in a bureaucratic "no"-machine at UC.

So when they were queried directly from Edinburgh about this ambitious (read; annoyingly persistent) student from UCSB, they ultimately yielded, and I made the cut.

RP: You went to Edinburgh for a year?

RJ: Yes. It was incredible. The morning I arrived at Waverly Station in Edinburgh, exhausted from the overnight train ride from London, I took a cab to the Department of Molecular Biology, and turned up at Ken Murray's office at 08:00 am.

But I didn't realise that the UK was more formal in its education system — I was used to hanging out with full professors, who would be called by their first names and so

Anyway, I showed up at "The Professor" office as an un-announced visitor, and just breathlessly said, "I'm here and ready to work in your lab". Ken was rather gobsmacked, ¹⁸⁴ but he had such grace (or was so disconcerted) that he passed me over to his top lab guys and basically said "they'll figure out something for you"

And did they ever! My lab mentor, who went on to become a close friend and is now CAMBIA Board Director, was Steve Hughes. At the time Steve was Ken's senior lab technician — an honourable profession in the UK — and had already achieved a great deal in identifying and characterising restriction enzymes. 185

RP: So you learnt a lot there then?

¹⁸⁴ utterly astounded

¹⁸⁵ A restriction enzyme (or restriction <u>endonuclease</u>) is an <u>enzyme</u> that cuts double-stranded <u>DNA</u>. The enzyme makes two incisions, one through each of the phosphate backbones of the double helix without damaging the bases. The chemical bonds that the enzymes cleave can be reformed by other enzymes known as ligases, so that restriction fragments carved from different chromosomes or genes can be spliced together, provided their ends are complementary (more below). Many of the procedures of molecular biology and genetic engineering rely on restriction enzymes. The term restriction comes from the fact that these enzymes were discovered in E. coli strains that appeared to be restricting the infection by certain bacteriophages. Restriction enzymes therefore are believed to be a mechanism evolved by bacteria to resist viral attack and to help in the removal of viral sequences. http://en.wikipedia.org/wiki/Restriction enzyme.

RJ: Absolutely. Steve taught me so much there. He first got me purifying Bam HI, ¹⁸⁶ a restriction enzyme that wasn't commercially available. Actually almost none of them were commercially available then, and they were the basic tools of the new molecular biology.

So I spent hundreds of hours in a cold room purifying these enzymes, and later T4 DNA 187 and RNA ligases, the critical enzyme used to join recombinant DNAs. DNA ligase was available commercially from one company, but it cost an arm and a leg. I ended up purifying about a million dollars worth at current commercial rates. I horsetraded those tubes of ligase and BamHI for many other rare enzymes — I wandered across the road to the Mammalian Gnome Unit and traded these for some that I and a several others at the lab had not yet tried.

And on one of those enzyme trading trips, I met Ed Southern, who had just returned from Zurich, where he'd invented a very critical technology (he went on to invent many more). 188

RP: And your exploration of the European scene was all as exciting as you had

RJ: Yes. The time in Edinburgh was incredibly productive for me, and a blast. I rode my bike thousands of kilometres around Europe, played trumpet in as many as five orchestras around town, and generally had the pedal to the metal.

And when I brought a thermos of new enzymes back to Santa Barbara the next year I was *really* welcomed, and John Carbon and Ed Orias 189 let me set up my own little research program on Tetrahymena rDNA, 190 which I more or less ran myself.

Anyway, Steve Hughes went on to staple his many papers together, get a PhD, and many years later we ended up in the same field of plant molecular biology, and he ultimately became director of plant biotechnology for Unilever.

Then with some degree of closure, later on he hired me for six months as a visiting professor in southern Italy right after my Plant Breeding Institute postdocs, when I had burnt out on the star-machine and had these nascent, fermenting CAMBIA ideas and new science paradigms to design. I sat and talked with Steve on a southern Italian farm — with plenty of "design fluid" (what our friend Chris Fields 191 used to call Laphroaig ¹⁹²) ... But I'm getting way ahead of myself.

¹⁸⁸ Southern invented the <u>Southern blot</u>, now a common laboratory procedure used for <u>DNA</u> analysis. The <u>northern blot</u> is a similar procedure for <u>RNA</u>, playing off the Southern name. The <u>western blot</u> is a further pun on the Southern blot, but is an important research tool in protein detection. http://en.wikipedia.org/wiki/Edwin_Southern.

¹⁸⁶ BamHI is a restriction enzyme. http://www.thelabrat.com/restriction/BamHI.shtml.

¹⁸⁷ T4 is a bacteriophage of E. coli.

Orias is a Research Professor of Genomics in the Molecular, Cellular and Developmental Biology department at the University of California, Santa Barbara. http://www.lifesci.ucsb.edu/mcdb/emeriti/orias/index.html.

See http://en.wikipedia.org/wiki/Telomerase.

http://crl.nmsu.edu/Staff.pages/Technical/chris.htm.

¹⁹² Laphroaig is a single malt Scotch whisky distillery situated on the island of Islay off the West coast of Scotland. http://en.wikipedia.org/wiki/Laphroaig.

RP: Ok, let's step back for a minute. When you finished at UCSB you did a PhD at the University of Colorado at Boulder. Why Colorado?

RJ: Well, I applied to all the usual places: Harvard, MIT, Berkeley, places like that. But John Carbon said to me: "You can go to these places, but they can't teach you much that you don't already know. The real challenge of molecular biology isn't going to be the "doing of the stuff"; it will be "the stuff that you do". What you need, therefore, is a place where they talk about the questions to ask, and which systems to use and such. And right now the best place in the world to find people who are actually thinking about the biology, and talking to each other about how it should be developed, is Boulder, Colorado.

I said "Colorado, Jesus Christ, you don't think Stanford?" And he replied "No."

So I applied to the University of Colorado, and I also applied to MIT, Berkeley and Harvard, and I was offered places with full scholarships at all of them.

RP: How does one go about being offered full scholarships at a range of different universities?

RJ: There's the strange phenomenon in the States with the first rung graduate schools — kind of like professional sports teams. What happens is that the same top dozen or so students get into the top six or seven graduate schools, and then those universities actually fly the students out to visit, with the aim of convincing them to join up. It's like being in a first round draft pick. ¹⁹³

So I went to look at them. My expectation was that I would love Berkeley, admire MIT, find Harvard arrogant and ignore Colorado. As it happened, Berkeley didn't work for me, and I really didn't click with MIT. They were so arrogant; their attitude was: "We don't care who you are because we are going to turn you into an MIT grad." Then I went to Harvard, which I didn't think I was going to enjoy, but I did, as it was dominated by some Berkeley profs who'd just moved out there, and a bunch of great grad students.

RP: So why did you opt for Colorado?

RJ: I was just blown away by Boulder. When I visited they put me up with a couple of grad students, one of whom had just taken second-place in the Winfield Banjo Competition (a big thing ¹⁹⁴). The other one was a Danish bicycle racer. I thought that was great, as I was completely into playing music and biking. That banjo player on my first night there introduced me to Sam Bush & New Grass Revival, ¹⁹⁵ Doc Watson ¹⁹⁶ and John Hartford. ¹⁹⁷ And that was just the first night.

See http://www.wvfest.com/media/showrelease.html?id=80.

¹⁹³ See http://en.wikipedia.org/wiki/NFL Draft.

¹⁹⁵ New Grass Revival was a <u>progressive bluegrass</u> band from 1971 to 1989. http://en.wikipedia.org/wiki/New Grass Revival.

¹⁹⁶ Arthel Lane "Doc" Watson is a guitar player, songwriter and singer of bluegrass, folk, country, blues and gospel music. http://en.wikipedia.org/wiki/Doc_Watson.

Then the next morning I sat in on a first-year graduate student lecture given by Bill Wood. 198 Bill Wood had just been brought in as head of department at Colorado and he was the youngest guy in the National Academy. 199

Anyway, as I looked around I could see the entire faculty was there, listening to this grad student lecture. It was so cool; it was so collegial. And that really coloured everything that subsequently went on in my life — it was the realisation that when you combine the technology with the methodology, and you add collegiality, you have really got the subject nailed.

RP: Did Colorado live up to your expectations?

RJ: It exceeded them. Colorado was very, very important to me. It shaped me as a student; not because of the coursework — there was a year of hard coursework but that was irrelevant — but because I was given carte blanche to go into depth with the technology in incredibly good labs, and surrounded by very bright people who were grand fun.

My first lab "rotation" was in a remarkable lab run by Tom Cech, 200 who later won a Nobel Prize for the key discoveries that he and his group made around that time. (I wish I could bask in that glory, but I was only there for three months). Then I worked in Mike Yarus' lab, ²⁰¹ one of the great thinkers in RNA and, again, a marvellous team-builder. And this was before I even started on what would become my thesis.

And it helped shape me as a person. I played guitar in all these cafes and bars in town to supplement my graduate stipend. I became friends with the great professional jugglers of Boulder, including Airjazz²⁰² the national champions, and all these other incredible performers who became my mentors about discipline and teamwork, and taught me juggling, dance and circus arts, and made me laugh harder than I'd thought possible.

¹⁹⁷ John Cowan Hartford (December 30, 1937– June 4, 2001) was an American country and bluegrass composer and musician known for his mastery of the fiddle and banjo, as well as for his witty lyrics, unique vocal style, and extensive knowledge of Mississippi River lore. http://en.wikipedia.org/wiki/John Hartford.

⁸ http://mcdb.colorado.edu/~wood.

http://www.nationalacademies.org.

Thomas Robert Cech is a Nobel Laureate in chemistry. His main research area is that of the process of transcription in the nucleus of cells. He studies how the genetic code of DNA is transcribed into RNA. http://cechlab.colorado.edu/projects.html. http://bayes.colorado.edu:9080/yarus_lab.

Airjazz was a group of jugglers whose use of choreography, movement and style had a global influence on juggling. http://www.airjazz.com. In 1982 Airjazz won the 1982 National Team Juggling Championship. In 1984 they appeared on the *Tonight Show with Johnny Carson*). Airjazz, Jefferson told me by e-mail, were "my best friends and inspirations during grad school" and were " then the national and international juggling association champions, and great artists, choreographers etc. Jefferson himself is a juggler, mandolin and guitar player. As his bio for a 2005 conference put it, "When Richard's not developing new technologies and new methods of collaboration in the life sciences, he devotes time to his family and musical and circus-arts interests, performing on guitar and mandolin in new acoustic styles, and juggling."

In fact they even helped me in the lab after we were done practising in the field house each night. I remember a great night, after a marathon five-hour juggling practice in which all four of us went back to the lab, where I had a major cloning experiment to plate; and we all sat at the bench — Peter, 203 Jon and Kezia 204 (Airjazz) plating bacteria on Petri dishes. The lab director came in and was utterly over the moon, as Airjazz were major "performance stars" at the time, on Johnny Carson and so on. ²⁰⁵

RP: Your supervisor at Colorado was David Hirsh wasn't it?

RP: Right. David was a very accomplished professional scientist and ran a remarkable lab. However, I had to fight to do what I did. Hirsh really didn't like me much, nor my focus on tool-building.

In fact, he apparently still doesn't! Not long ago he went on record with Newsweek [laughs] saying that I was his most difficult student ever. 206 But you know what: he was the most difficult PhD supervisor I had ever! So that part of it wasn't so easy.

GUS

RP: It was while you were at Colorado that you developed the β -glucuronidase system, 207 more commonly known as GUS?

RJ: [Laughs]. Yea, GUS sounds like a garage mechanic from Alabama or something doesn't it! But what I wanted to invent with GUS was a system that would make it possible to know the exact moment when a cell knows that it isn't what it used to be.

RP: Can you explain what you mean?

RJ: Well, we already had a system for observing how cells divide in the nematode. ²⁰⁸ The beauty of that system was that a nematode is only a millimetre long, and when you look at it in a microscope you can watch every single division from the time it is

²⁰³ <u>http://poetofmotion.com</u>.

²⁰⁴ Kezia Tenenbaum.

²⁰⁵ John William "Johnny" Carson was an American actor, comedian and writer best known for his iconic status as the host of *The Tonight Show Starring Johnny Carson*.

²⁰⁶ Juggling Two Worlds; Richard Jefferson is bringing together scientists from rich and poor countries to fuel the interplay of ideas, Karen Lowry Miller, Newsweek, November 29th 2004. http://www.msnbc.msn.com/id/6539285/site/newsweek.

GUS (β -glucuronidase) is a reporter gene system. As such it is a tool for the assessment of gene activity in transgenic plants. β-glucuronidase is an enzyme from the bacterium *Escherichia coli* that converts a colourless dye to a blue dye. So a simple colour test is all that is needed to check whether the GUS protein is being produced in the plant. In the words of a *Red Herring* article, GUS is an "indicator that tells where a gene is, how much it expresses, and when it acts." Open-Source Biotech, April 17th, 2006. http://www.redherring.com/Article.aspx?a=16473&hed=Open-Source+Biotech. The Wikipedia entry is at: http://en.wikipedia.org/wiki/GUS reporter system.

²⁰⁸ A nematode is a parasitic worm of the class Nematoda. http://en.wikipedia.org/wiki/Nematode.

just a memory of mum and dad as a single cell zygote²⁰⁹ right up until the time it hatches — which takes about six to eight hours.

During that time you can look at all the divisions, and trace the lineage. It was a neat system, and it was being used by a number of labs including ours. (Parenthetically, a major collaborator with our lab was the group in Cambridge UK headed up by John Sulston.²¹⁰ Who'd have thought our paths would cross so many years later as advocates for open science?)

However, I was interested in a specific aspect of cell division. That is, the point at which when a cell divides it knows it is going to be a muscle cell, even though it looks just the same as it used to; while another cell will know it is going to be a nerve cell, yet it too looks just the same as it used to. So the question that interested me was how a cell knows it is going to be, say, a nerve cell, ²¹¹ and at what point it knows it.

In short, I wanted to create a system where we could look at a totally unperturbed biological system and say: "At what point does a cell know that it is different from its progentiros, and what is responsible for this differentiation?"

RP: How did you go about the task?

RJ: Essentially, I wanted to invent a non-destructive system for analysing gene action, and I wanted to invent it from scratch — because all the other systems didn't meet my needs. In that sense it was very much like .. [pause] .. developing software from scratch: you set the specifications and standards for what you want to do, and then you go about doing it.

Anyway, all told it took me six or seven years to create GUS, including a number of false-starts. And I had to teach myself all the DNA work, the protein and enzymology, the organic synthesis of substrates and the monoclonal antibody²¹² technology in the process. And I had to do it very much in the face of resistance from Hirsh, and a general disinterest and scepticism from others.

²⁰⁹ A zygote is a cell that is the result of fertilisation. That is, two haploid cells — usually (but not always) an ovum from a female and a sperm cell from a male — merge into a single diploid cell called the zygote (or zygocyte). http://en.wikipedia.org/wiki/Zygote.

²¹⁰ Sir John Edward Sulston. Sulston played a central role in both the <u>Caenorhabditis elegans</u> (worm) and <u>human genome</u> sequencing projects. He had argued successfully for the sequencing of *C. elegans* to show that large-scale genome sequencing projects were feasible. As sequencing of the worm genome proceeded, the project to sequence the human genome began. At this point John was made director of the newly established Sanger Centre (now the <u>Wellcome Trust Sanger Institute</u>), located in Cambridgeshire, UK. See the introduction for his role in Biological Open Source. http://en.wikipedia.org/wiki/John E. Sulston.

http://en.wikipedia.org/wiki/John E. Sulston.

211 The point is that during cell division each daughter cell receives a complete set of the genetic information contained in the parent cell — that is, each cell contains a complete set of genes. Since any cell could be used in one of many different ways e.g. to create an eye, a liver, or, say skin, it has to know to use proteins in a different way. In other words, each cell inherits the complete genetic instructions but it will use only a part of that genetic information for a specialised purpose. http://en.wikipedia.org/wiki/Cell division.

Monoclonal antibodies (mAb) are <u>antibodies</u> that are identical because they were produced by one type of <u>immune cell</u>, all <u>clones</u> of a single parent cell. Given (almost) any substance, it is possible to create monoclonal antibodies that specifically bind to that substance; they can then serve to detect or purify that substance. This has become an important tool in biochemistry, molecular biology and medicine, http://en.wikipedia.org/wiki/Monoclonal antibody.

RP: Why?

RJ: Because methodology has always been really dissed and taken for granted²¹³ in science. And yet it is so important. Most people want to work at the top level of the stack.

RP: And in spite of the frictions, you persisted with this?

RJ: Yep. Persistence seems to be one of my main personality traits. But to his great credit, even though he didn't care for me or the project, David Hirsh did give me almost total freedom to invent within a fine, well resourced lab, and my co-supervisor Bill Wood played the carrot to David's stick to keep me from "spitting the dummy".

RP: OK, so you wanted to create a system for analysing gene action. As I understand it, GUS is what is known as a "reporter gene system". How does it work?

RJ: A reporter gene is a gene you put under the control of — typically next to — another gene that you are interested in. If and when the gene you are interested in reacts in a certain way the reporter gene will make a protein to signal what has happened.

RP: By changing colour?

RJ: It can do a variety of different things. If you add a certain chemical, for instance, the reporter gene will turn blue, or some other colour, or become fluorescent — thereby reporting on the gene you are interested in.

In many ways, genes are like code.²¹⁵ But the problem is that you can't know where a gene acts, when it acts, and how much difference it makes unless you can interpret that code. So GUS is a generic tool that you can put next to any gene you are interested in and ask those sorts of questions. GUS allows you to see when and where, and to what degree, a gene has worked.²¹⁶

RP: So if you were trying to transfer a gene into a plant in order to genetically modify it you could attach GUS to the gene you are transferring. Then you can establish whether you have successfully inserted the gene, and whether it is doing what you wanted it to do, by simply adding a chemical and watching to see if it changes colour?

²¹³ To diss is to treat, mention, or speak to rudely. http://wordnet.princeton.edu/perl/webwn?s=diss.

²¹⁴ In molecular biology, a reporter gene (often simply reporter) is a gene that researchers attach to another they wish to study in cell culture, animals or plants. Researchers use a reporter to easily identify those that have taken up the gene, or which have incorporated it in the desired way into their chromosomes. A common reporter is the gene that encodes jellyfish green fluorescent protein, which causes cells that express it to glow green under UV light. Another important reporter codes for an enzyme luciferase, which catalyses a reaction with a luciferin to produce light.

http://en.wikipedia.org/wiki/Reporter_gene.

²¹⁵ In dead in green the convergent that a proper that the convergent that the converg

out the functions of a machine, genes provide the information for cells to divide, develop and function properly. One major difference, of course, is that where computers are digital nature is analogue.

216 More detail at: http://en.wikipedia.org/wiki/GUS reporter system.

RJ: Right. Whether the gene had succeeded, and also where it had gone, and how much difference it had made. In a sense it is a meter, a genetic meter that allows you to measure what is happening where you wouldn't otherwise be able to.

I told you about the epiphany I had with Signer and Beckwith's work. Well, basically they are the guys who invented the concept of tricking an organism in order to teach you things you couldn't learn otherwise

RP: How would you get a foreign gene into a plant?

RJ: The best way to get a gene into a plant is to use what biology has already invented. There is, for instance, a little bacterium that lives in the soil called Agrobacterium. Over millions of years this has evolved to the point where it can inject its DNA into a plant: It puts its genes into a plant, and then makes little tumours in which it grows, and which feed it compounds.

RP: So by using the natural technique that Agrobacterium has developed, molecular biologists can transfer genes from one plant into another?

RJ: Right. About 25 years ago it was discovered that you could actually whip out the genes that the bacteria wanted to thrust into the plant and replace them with genes that you want to put into the plant. In a sense you are filling it with little Brad Pitts, in little Trojan horses!²¹⁷

RP: And by attaching GUS to that gene you can establish whether you have been successful?

RJ: Exactly. Until GUS you couldn't know whether you had succeeded, because everything happens at such a small scale: you can't just look at it and see how things are going.

So GUS became the first molecular heuristic²¹⁸ for plants; the first way of turning the unseen processes of transgenesis into the seen. Before I developed GUS for plants people were just chucking stuff into blenders without any idea of what was happening!

Worms to plants

RP: When you created GUS in Hirsh's lab you were working with worm embryonic development. It was only later that you adapted it for plants. Why?

²¹⁷ In the 2004 film Brad Pitt played Achilles, who is shown coming out of the Trojan Horse. http://www.imdb.com/title/tt0332452 In fact, ancient historians argue that Achilles was dead by the time the Trojan Horse was built.

http://ancienthistory.about.com/cs/grecoromanmyth1/f/achilleshorse.htm

218 A heuristic is a particular technique of directing one's attention in learning, discovery, or problemsolving. http://en.wikipedia.org/wiki/Heuristic.

RJ: For a combination of reasons. First, animal embryo development — the nematode that I told you I worked with — is really rigid. It's like clockwork, a wind-up toy: always the same tick, tick, tick, tick. Essentially the developmental pathway is like a program, and I found that really not very interesting, scientifically or personally.

RP: Plants are different?

RJ: Yes, and I was fascinated by what happened with plants in agriculture. Since plants can't run away from the environment they have to adapt and do fascinating things. This in turn means that their genes change on a minute-to-minute basis.

If you are sitting in a room next to a house plant, for instance, there is probably more gene activity going on in that house plant than there is in you, because it has to change all the time. If you add CO₂ to it for fuel, for instance, it can't just go [funny voice of pompous old man] "This isn't as good as home cooking", and run off.

So I was excited by what happens in an environment where a zillion things are changing as part of a complex eco system. And I was especially interested in the turning point of those changes: how do we know when they change? What is the metric?

So I wrote a proposal to develop GUS for plants on the basis that it would allow us to ask questions about how genes worked in the real world.

RP: Was it easy to adapt GUS for plants?

RJ: Well, it certainly wasn't easy to get funding! I was rejected for two years in a row — even though mine was probably the most successful postdoc you will ever see in the field.

RP: But you got funding eventually?

RJ: Yes. What must have been around my tenth and last pending application was to the US National Institutes of Health. ²¹⁹ By then I expected just another "piss off" letter in response. So I couldn't believe they had given it to me.

Moreover, they had done something that none of the others had done, which was to include the reviews of my proposal. Their letter said — in total transparency — exactly who was on the panel, and what they had said.

RP: Presumably the reviews were good.

RJ: I think that I got three points away from a perfect score. The comments effectively said: "This is high risk, but if it works out it stands to revolutionise plant science, blah, blah, blah." Then I noticed another had commented, "This guy has a

²¹⁹ The National Institutes of Health (NIH) is an agency of the United States Department of Health and Human Services and is the primary agency of the United States government responsible for medical research. The Institutes are responsible for 28% - about \$28 billion - of the total biomedical research funding spent annually in the U.S, with most of the rest coming from industry. http://www.nih.gov.

great record of doing technology development, so in spite of the recommendation from his supervisor we think that you should give him this."

RP: Ok, I see: David Hirsh had been sabotaging your applications?

RJ: Well, that's a bit of a stretch, but it turned out that one reason I had such a hard time was that he had written letters of recommendation saying things like: "Jefferson thinks incredibly quickly, and speaks even faster." [Sighs].

One of the things I have learned over the years is that creating methods doesn't get you grants: it just gets you tired. [Jefferson sounds tired as he speaks].

Plant Breeding Institute

RP: But the upshot was that you got an NIH postdoctoral fellowship to go to the Plant Breeding Institute in Cambridge?²²⁰

RJ: Right, but it ended up, Richard, that I was just so burnt out [sounds weary]. I had spent seven years building this system — which actually hadn't worked for the first six years, and no-one believed I'd succeed — and then had to face two years of getting knocked back from postdocs that would allow me to adapt it for plants. There was a pretty good dose of personal misery, undermined self-confidence, and then the hell I went through putting everything together.

It was at that point I realised that the world I had found myself in was so much of an old boys' club. Moreover, club decisions are mostly made in a totally non-transparent way, and those making them are interested primarily in promoting their own prestige and power.

I attracted the ire of my postdoc supervisor, for instance, because he had wanted to further his career around GUS and all the other work we did, but I sent out details of GUS to everybody before I had even published a paper. Anyway, this realisation really coloured the development of CAMBIA and the BiOS initiative.

RP: Let's come to the way you "shared" GUS in a minute. Perhaps you could tell me why you chose to go to the Plant Breeding Institute first?

²²⁰ The Plant Breeding Institute (PBI) was established in 1912 (at the instigation of the then Board of Agriculture) within the Cambridge University School of Agriculture. The early work of the PBI was entirely devoted to the breeding of improved varieties of wheat, particularly with regard to better grain quality. Later it also worked on barley and peas. In 1985 the Agricultural and Food Research Council's Forward Policy proposed that its research institutes should be re-organised into eight 'super' institutes. This was closely followed (1987) by the sale of the PBI breeding programmes and farm site to a private company (Unilever) under the government's privatisation policy. The non-privatised part of the PBI (the Cambridge Laboratory) was integrated into the Institute of Plant Science Research, which included the John Innes Institute (Norwich) and the Nitrogen Fixation Laboratory (Sussex). In 1990 the majority of the PBI's scientific staff were relocated to newly built facilities at the John Innes Institute where they formed the 'Cambridge Laboratory'. Over its 75 year history the PBI produced over 130 new varieties of wheat, barley, oats, triticale, potatoes, field beans, maize, oilseed rape, clover, sugarbeet and grasses.

RJ: Because by then I knew I needed to work on plants and agriculture, and at that time the Plant Breeding Institute was one of the only places contemplating plant genetics at that level. The others included the Max Planck Institute²²¹ in Koln, Germany, and the CSIRO²²² in Canberra, Australia.

I also wanted to work with somebody who was not in The Old Boys' Club, and I had met this guy at PBI called Mike Bevan.²²³ He seemed a very pleasant fellow, was quite anti-establishment back then, and he was about my age.

RP: I guess we are now around 1985?

RJ: That's right, and the three years I was at PBI were extraordinarily fascinating and productive, in terms both of my intellectual and personal development. However, they were pretty tough emotionally — although that may have been why my personal development occurred of course.

RP: In what way was your time at PBI fascinating and productive?

RJ: Things were changing extremely quickly, and I discovered that there were a comparatively small number of people in molecular biology who could really see the possibilities. So it was soon clear to me that you could have quite an impact if you had that kind of mind. And everything I touched at that time turned to gold — or at least scientifically.

RP: Indeed, amongst other things you planted the world's first GM^{224} crop.

RJ: [laughs] That's right, on June 1^{st} 1987. Monsanto planted their first food crop on June 2^{nd} — so I beat them by a day! It was so cool, and a total accident. The previous year they'd put some tobacco in the ground, but this was the first food crop in the field.

In fact, I only discovered I had beaten them later, when I gave a talk at some conference. I came on right after some flashy Monsanto presentation, where the guy announced grandly [Jefferson adopts self-important corporate voice]. "June 2nd 1987: the day of the world's first transgenic food".

Shortly after I stepped up — a lanky, moustachioed postdoc with a set of those ancient blue diazo slides with hairs on them — and said: [changes to a relaxed, hippylike voice]" Sorry guys, we planted 2,000 transgenic potatoes on June 1st 1987; you can come and help pick them." Oh man, it was so much fun!

²²¹ http://www.mpi-sb.mpg.de

The Commonwealth Scientific and Industrial Research Organisation, http://www.csiro.au

http://www.jic.bbsrc.ac.uk/staff/michael-bevan/index.htm

²²⁴ By far the most common genetically modified (GM) organisms are crop plants. A genetically modified plant is derived in whole or part from a genetically modified organism (GMO) such as a crop plant, animal or microbe such as yeast. Genetically modified foods have been available since the 1990s. The principal ingredients of GM foods currently available are derived from genetically modified soybean, maize and canola. http://en.wikipedia.org/wiki/Genetically_modified_food.

At PBI I was also lucky to meet a remarkable friend named Sara Melville, ²²⁵ a mature PhD student at Cambridge, who later went on to do some important work on tropical parasitology, and was influential in sequencing the trypanosome genome. ²²⁶ I probably learned as much or more that later shaped me and CAMBIA from her as I did from anyone else, and most of it was about the human side of empowerment; to be honest it was crucial knowledge to guide me and CAMBIA when I left PBI in 1989.

It was also at the PBI that I recognised the enormous seductive power of methodology in the broadest sense, its social sense. And I began to learn about the dangerous nature of helping.

RP: How do you mean?

RJ: Well, I had grad students and postdocs working with me — or for me — who were from places like China, Africa, India, Mexico, and Poland; in other words, all places that are economically disadvantaged.

It was immediately clear to me that these people were as smart as anybody else, and much more committed. Yet they knew that the very best they could hope for was to do some science, publish a paper, and then disappear back into Africa or China, or wherever.

RP: So PBI gave you an insight into how The Old Boys' Club works on the international stage?

RJ: Exactly. Essentially these people were being used as bench jockeys to further the careers of scientists in the developed world. I thought to myself "What a goddamn waste of resource."

The problem was that there was no infrastructure to enable them to go home and apply their skills locally, and no commitment to make it happen. I was just livid about that wasted opportunity. I thought, "These guys are committed, they know what they are doing, they are as smart as anybody else, but they are not rich."

Bangladesh to Berkeley

RP: Presumably it was this realisation that led to your decision to make GUS freely available. By allowing anyone to use it you were hoping to demonstrate the "power of methodology in it broadest sense" Specifically, to make sure that a core biotechnology tool was accessible to everyone?

RJ: Yes. I was sick of the star-maker machinery, The Old Boys' Club; and I had just about spit the dummy on that.

²²⁵ http://www.path.cam.ac.uk/pages/melville.

African trypanosomes are single-celled eukaryotic parasites that replicate in the blood of mammals. They are transmitted by tsetse flies, found only in sub-Saharan Africa. *Trypanosoma brucei* subspecies cause sleeping sickness in humans, with 3-500,000 cases and over 2 million disability-adjusted life years (DALYs) lost annually. http://www.who.int/tdr/diseases/tryp.

By now I had adapted GUS for plants — which wasn't particularly difficult to do by the way — and the classic way things move in science is that at that point powerful professors at places like UCLA²²⁷ or Harvard would say: [paternalistic drawl] "Hey, Richard, I understand you've got this cool system. Can I take a look?"

So you would get it to them before anybody else; and they would enhance their power and prestige by using these cool new tools before anybody else.

The point is that science is directed by the tools you have in your hand: If you have a hammer you hit a nail. And the way it works it that the guy putting hammers in people's hands discovers that the hands that are out there are also the hands that will scratch his back, and so on.

And I hated that. I had seen it work with my postdoc, and it meant that the joy of molecular biology was being destroyed for me by this ugly bitter taste of power playing.

RP: How then did you go about making GUS available to everyone?

RJ: With a bunch of friends I prepared around 10,000 tubes of plasmid DNA clones²²⁸ and sequences that could be used with GUS, and I made a pretty big manual explaining everything I knew about how to use it with plants. Then I sent it out to maybe 500 labs around the world — in other words, to absolutely everybody in the field. Essentially, I flooded the world with every bit of know-how about GUS I had.

And when requests started coming in from other labs I treated them equally. If somebody, say, in Bangladesh wanted it, and their request came in ahead of a request from Berkeley, Bangladesh got it before Berkeley. Moreover, I didn't wait for publication before doing all this.

RP: The point here is that scientists normally put their research into the public domain by publishing details of it in a scholarly journal. That way they can ensure that they get the credit for their work, not someone else?

RJ: Right. So instead of treating it that way, I sent GUS to everybody before I published a peer reviewed paper. ²²⁹ In addition, during the course of that year and the next I gave maybe 200 talks on GUS, and on our field trial, in about twenty countries. That way I obviously got plenty of credit for it. And I took along the "kits" of GUS and the clones to give out — like Johnny Appleseed. ²³⁰ I remember one meeting

A plasmid is a <u>DNA</u> molecule separate from the <u>chromosomal DNA</u> and capable of autonomous replication. http://en.wikipedia.org/wiki/Plasmid.

²²⁷ The University of California, Los Angeles. http://www.ucla.edu.

The paper was published in <u>The EMBO Journal</u> in December 1987. http://www.pubmedcentral.gov/articlerender.fcgi?artid=553867.

²³⁰ Johnny Appleseed, born John Chapman (1774 –1845), was an American pioneer nurseryman, and missionary for the Church of the New Jerusalem, founded by Emanuel Swedenborg. He introduced the apple to large parts of Ohio, Indiana, and Illinois by planting small nurseries. He became an American legend while still alive, portrayed in works of art and literature, largely because of his kind and generous ways, and his leadership in conservation. http://en.wikipedia.org/wiki/Johnny Appleseed.

where I literally had a bucket of eppendorf tubes²³¹ with GUS plasmids to distribute — I think it was in Jerusalem.

In fact, I decided that the full methodology and all the hints should be published in a special way that everyone could access at no cost — EMBO Journal was expensive and pretty limited in its availability. So I used a little "newsletter" magazine called Plant Molecular Biology Reporter. 232 A small A5-format cost-free mailout to the several thousand members of the International Society of Plant Molecular Biology; 233 not really peer-reviewed I think, but totally free and easy to open up and use on a lab bench.

So I re-wrote the manual for GUS and published it in that little magazine, which was dutifully sent out and has now had thousands of citations. At that time, there was no Public Library of Science, ²³⁴ nor any other free journals, but I guess the need was there, and to some extent the mechanism, so I used it.

RP: And after disseminating GUS so widely you saw it really took off?

RJ: Yes. It was really a blast. Within a year everything had changed: I could see that it was allowing people to ask questions they couldn't ask before, and they were transforming plants — important crop plants. ²³⁵ In fact, Monsanto's Roundup Ready soybeans that now seem to cover the world, were all derived from a single transgenic line made by Agracetus in Wisconsin, ²³⁶ using GUS as their main tool.

I could also see that people were doing experiments that were previously out of the loop. That really influenced how I later went about making CAMBIA and BiOS work.

RP: What you learned I guess is that — as with Open Source software — if you provide biotech tools to as many people as possible you allow them to build on it very quickly; and presumably they also help to improve it, since there are more people to spot problems and, as software developers put it, "fix the bugs".

RJ: Right. Any technique, whether it be software or molecular biology, never starts out really good. It has to be tuned before you can optimise it. ²³⁷

²³¹ Microcentrifuge tubes or microfuge tubes are small, cylindrical plastic containers with conical bottoms and an integral snap cap. They are used in biochemistry to store and centrifuge small amounts of liquid.

232 http://pubs.nrc-cnrc.gc.ca/ispmb/reporter.html.

http://www.uga.edu/ispmb.

Public Library of Science (PLoS) is a nonprofit open access scientific publishing project aimed at creating a library of scientific journals and other scientific literature under an Creative Commons license, and has been publishing since 2003. http://www.plos.org.

As *Red Herring* commented, "GUS is widely credited for enabling many breakthroughs in plant

biotech, including the development of one of Monsanto's first and most profitable agricultural products, Roundup Ready soybeans. Mr Jefferson first provided GUS and all the know-how to use it for free to hundreds of labs around the world." Open-Source Biotech, April 17th, 2006. http://www.redherring.com/Article.aspx?a=16473&hed=Open-Source+Biotech. http://en.wikipedia.org/wiki/Agracetus.

As Gary Toenniessen pointed out to me, GUS was not the only gene reporter system developed, "but since Richard shared GUS with everybody started using it. Sharing it also meant that everybody helped to improve, so the development of GUS is a great exemplar of the Open Source model in action."

RP: Your experience with GUS seems very similar to the experience of Richard Stallman²³⁸ when he was at MIT in the 1970s. His response was to write the "free" operating system GNU, which he then shared with the world.

RJ: I guess. Although I didn't realise it until five or ten years ago, I was doing this stuff in molecular biology in parallel with what Stallman was hammering away with in the software arena. So you're right: my experience seems to have been very similar to that of Free and Open Source programmers.

RP: I am also struck at the way you talk about biotechnology having an "innovation stack". I wonder if we could push the analogy a little further, and suggest that engaging in molecular biology is a little like hacking the operating system of life?

RJ: Sure. As I said earlier, genes are like code, and in biological innovation there is a low and middle level to the stack. But almost everybody else has been wandering about at the high end of the stack, not realising that everything they did was being driven by the underlying operating systems that they didn't understand, and using a programming language that they didn't speak.²³⁹ The fact is that focusing on the lower levels can be staggeringly productive and exciting.

My obsession with methodology from Carbon's lab in the 70s and the early 1980s onwards was based on the belief that it would enable the field to advance at a great pace. As I said, everything in science is determined by the tools that fall into scientists' hands. And GUS is an example of really good methodology; it's a very useful tool

RP: You say you shared GUS before publishing details of it. Another way in which people ensure they get credit for their work, of course, is to use the intellectual property system. ²⁴⁰ IP also allows them to assert ownership of what they have

An acclaimed hacker, his major accomplishments include Emacs (and the later GNU Emacs), the GNU C Compiler, and the GNU Debugger. He is also the author of the GNU General Public License (GNU GPL or GPL), the most widely-used free software license, which pioneered the concept of the copyleft. In June 1971, as a first year student at Harvard University, Stallman became a programmer at the MIT AI Laboratory, where he became a regular in the hacker community. It was as a result of a dispute at MIT that Stallman decided to launch the Free Software Movement. An interview with Richard Stallman is available here: http://poynder.blogspot.com/2006/03/interview-with-richard-stallman.html.

This goes to Jefferson's earlier point about how at university molecular biology seemed to him to provide a "fundamental level of resolution of what made everything pull together." Indeed, it is a point that came out in a companion interview I did with Harold Varmus, and a comment he made to NPR's Susan Stamberg in 1999 about how the future of medical research now lies in "the development of a notion of the gene as a physical entity that we can understand, manipulate, dissect and use to advance the great themes in medicine." What clearly also links Open Source and Biological Open Source is that like today's complex software projects, gene-level medical research requires an increasing degree of openness to be effective. http://poynder.blogspot.com/2006/06/interview-with-harold-varmus.html.

In law, intellectual property (IP) is an umbrella term for various legal entitlements which attach to certain types of information, ideas, or other intangibles in their expressed form. The holder of this legal entitlement is generally entitled to exercise various exclusive rights in relation to the subject matter of the IP. IP includes copyright, patents, trademarks, trade secrets and design rights. http://en.wikipedia.org/wiki/Intellectual property.

created. I'm told that when you originally developed GUS at the University of Colorado you suggested to the technology transfer office that the University patent it, but they said it wasn't worth it?

RP: Well, it's not so much that I suggested it. It was held to be procedural to consider it. I was required to make a disclosure to the university office, which I did; but I heard nothing back for six months or a year. When I asked them what was happening they said [mimics a self-important bureaucratic voice] "Er... Well, actually, we're not interested: We're not going to pursue it, you can do what you want."

RP: Why did they decline to patent it?

RJ: First, patenting at Universities was just taking off back then. The Bayh-Dole Act, which started the Klondike patent filing frenzy, ²⁴¹ had only been made law about four vears earlier. Second, as I said earlier, there was a general disinterest in methodology at most universities: They just weren't into inventing technology or tools, which is what I meant when I talked about methods developers being dissed.

RP: You eventually patented GUS yourself didn't you?

RJ: Yes. Although I hadn't published details of GUS I had made it available to people informally. In around 1985, however, ICI²⁴² approached me and said they wanted to file their own patent. They said "Listen, we've got to file a patent, and we want to cite a GUS patent when we do. How about we give you \$3,000 towards hiring your own lawyer, and you can file all your own patents".

RP: Had not disclosing details of GUS in the way you had disqualified you from patenting it?

RJ: No. Because of the US grace period²⁴³ I still had time.

RP: Given your views on making enabling technology freely available some might nevertheless be puzzled as to why you patented GUS?

RJ: They might. But this was the mid-1980s, and at that point I was pretty naïve about intellectual property. To be honest, I didn't really understand patents, or their implications [laughs]. I knew that they were associated with inventions, but I wasn't all together sure why. However, I thought it might at least give me an opportunity to raise some money to make new inventions available.

It was later that I began to realise the potential GUS offered to do really important things. By then I had become convinced — really, really passionately convinced that core technology has to be available to everybody.

²⁴¹ The Klondike Gold Rush was a frenzy of gold rush immigration to and gold prospecting along the Klondike River near Dawson City in the Yukon Territory, Canada, after gold was discovered in the late 19th century. http://en.wikipedia.org/wiki/Klondike Gold Rush.

²⁴² Imperial Chemical Industries. http://www.ici.com/ICIPLC/home/index.jsp.

²⁴³ A unique aspect of US patent law is that an inventor has a one-year grace period after publication or sale to file a patent application, whereas in most other countries patent rights are lost if an application is not on file when a public disclosure, publication or sale takes place.

But the journey to learn that was really hard. After filing patent applications for my ideas, I really had no way to carry them further.

RP: Tell me about the hard journey?

RJ: Sure. When I went to a plant molecular biology meeting in 1985 or 86 in Tamarron Colorado, I met a very good young plant molecular biologist named Gloria Coruzzi, 244 who told me over a beer that her sister Laura Coruzzi 245 was a top patent attorney in New York, and her boss Leslie Misrock²⁴⁶ the Senior Partner at Pennie & Edmonds²⁴⁷ was keenly interested in my technology and would like to talk to me.

Well I was flattered, but I was also something of a rube.²⁴⁸ I went to New York and met with Laura and Leslie. Leslie was often called the father of patent biotechnology law in the US, and had pioneered many important (and in retrospect I think regrettable) precedents in US patent practice.

RP: What precedents are you referring to?

RJ: He won the *ex parte* Hibberd case which opened up plants as subject of US utility patents.²⁴⁹ He pioneered getting patent law involved in research partnerships — he guided the formation of the big Agrigenetics Research Consortium which began the process of Universities signing away their patent rights for cash, and so forth. He was a legend in the field.

RP: So he helped you patent GUS?

RJ: Yes. He told me in this gruff, avuncular way, "Stick with me kid, you'll be wearing shoes" ... and "don't worry about the expense, we'll take care of that later" and "I've never lost a patent case in my life ... I'll do this for you" and finally "we don't need paperwork, kid, I'll do all this for a 50:50 partnership".

Well, I was out of my league then — way out. I felt like Han Solo²⁵⁰ negotiating with Jabba the Hutt. 251 There was only one way that was going to go. He ended up

http://www.nyu.edu/fas/biology/faculty/coruzzi/index.html.
 http://www1.jonesday.com/lacoruzzi.

Leslie Misrock was a trial and appellate lawyer who was the first in the profession to develop a biotechnology practice group — long before the possibilities of biotechnology were clear to most. Earlier in his career, Leslie was for years an active participant in the long-lasting litigations on the Ziegler and Natta patents relating to the manufacture of plastics. He died of prostate cancer in 2001. http://globalrph.healthology.com/globalrph/1677.htm.

Founded in 1883, Pennie & Edmonds closed in December 2003. http://www.bizjournals.com/washington/stories/2003/12/22/story6.html.

an awkward, unsophisticated person from a rural area; rustic.

²⁴⁹ In 1985 the ex parte Hibberd case allowed patent rights to be issued for plant varieties regardless of whether the plant is obtained through asexual or sexual reproduction. Following that decision, the US PTO began accepting patent applications for such plants, despite the fact that Congress had never given the PTO authority to grant utility patents for sexually reproducing plants. In re Hibberd, 227 USPQ. 443, 1985 WL71986 (1985).

²⁵⁰ Han Solo is a character in the fictional <u>Star Wars</u> universe. He was played by <u>Harrison Ford</u> in three of the six Star Wars films. http://en.wikipedia.org/wiki/Han Solo.

prosecuting the GUS patent estate and getting them to patent grant, ²⁵² and in the process I got a unique learning exercise in patent prosecution, patent practice and business as it's conducted — a completely different phenomenon than that understood and portrayed by academics. It was vicious, sophisticated but untidy, manipulative, staggeringly money-driven, and ultimately I felt very sullied and unhappy being associated with the process.

And I remember at first being so honoured when he'd call a partners strategy meeting in New York; we'd have maybe five partners and associates from P&E over bagels and coffee for three hours, while Leslie and the Associate handling the prosecution would talk to me about the patents. They all grunted, nodded and sagely murmured at Leslie's comments. I was pretty impressed by the legal talent in the room, until later it dawned on me that they'd said nothing, but had each billed for the three hour meeting, making that meeting another whopping number on the deficit side of my billing sheet.

RP: You weren't aware at the time of the financial implications of hiring Misrock?

RJ: No. He "deferred" the billing until later, saying "trust me kid"; and that when they issued, we'd be in clover and my dream of CAMBIA would be funded. Whoooeee was I taken.

This was a long, drawn out process that continued until the early mid-90s, when the first of my GUS patents was issued — ironically on Pearl Harbor Day, 1993.

Completely censored

RP: You had by now come to believe that in order for biotechnology to be truly beneficial its core enabling technologies need to be available to everybody; and your experience at PBI had convinced you that if this were to happen it would offer particular benefits to the developing world. Your idea, therefore, was to create an organisation that would promote these aims, and you planned to use money from the GUS patents to fund it. But let's come back to the patent story later, because in 1989 you joined the UN's Food and Agriculture Organisation (FAO). You saw the UN as a platform for the creation of CAMBIA right?

RJ: Actually, I had been working as a consultant for the FAO for a while, in Kenya and Zimbabwe, just before becoming a staff member, and after a stint on a farm in Italy. But yes, in 1989 I was hired as the UN's first senior staff molecular biologist.

RP: Tell me about it?

RJ: This was just after I left PBI, having abandoned any hope of CAMBIA happening within academia. Steve Hughes had driven up from Italy and loaded me and my

252 In patent terminology prosecuting means getting a patent through the patent office to patent grant.

²⁵¹ Jabba the Hutt is a fictional character in <u>Star Wars</u>. He first appeared on film in <u>Star Wars Episode</u> <u>VI: Return of the Jedi</u> (1983) as an obese, slug-like alien. The character's role is primarily antagonistic. http://en.wikipedia.org/wiki/Jabba_the_Hutt.

belongings into an old Fiat station wagon, and driven me to Caserta, ²⁵³ where he found me a temporary position at a company he worked at as Biotech Director in the South of Italy, in Mozzarella land!

I used the grace period this provided to heal from the hard times at PBI, and to start to envision the CAMBIA concept in more complexity, both scientifically and socially. I had come to see that the best way to be concerned about the developing world is to treat its people with respect as human beings, and recognise that they too have capabilities — in biological innovation as in any other area. But they need to have access to tools to do so.

And if you think about it, while the social aspects of human rights — governance, freedom of speech and all that — are widely discussed, the most fundamental human right is the freedom, or the capability, to make and use tools to solve problems. Yet the technological implications of this have not been subject to any policy or social governance oversight. It has been free marketed to the point of becoming deeply saddening.

What is distinctive about the life sciences is that it is the single most crucial activity for human survival: after all, you need food and health to survive, and managing natural resources is really all about biological innovation.

But I still didn't know enough about the real world, and so thought working with the UN would help. Ironically, I found myself in a joint division with the International Atomic Energy Agency, based in Vienna ²⁵⁴ It was pretty cool to have a blue UN Passport called a "Laissez Passer" that said "Molecular Biologist" right next to the hologram of the UN Logo.

But yes, you're right: I thought joining FAO would enable me to oversee the creation of a United Nations-sponsored initiative that would provide unfettered access to the tools of biotechnology at the low end of the stack. An initiative, in other words, like CAMBIA. Oh boy was I wrong.

RP: In what way?

RJ: It turned out that there were some fascinating politics, going on at FAO. Specifically, at that time an initiative called the International Centre for Genetic Engineering and Biotechnology [ICGEB²⁵⁵] was being set up by the United Nations Industrial Development Organisation [UNIDO²⁵⁶]. ICGEB was to be a Vienna-based international agency sponsored by the government of Italy, and the Italian government was pushing to have it located in Italy.

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²⁵³ http://en.wikipedia.org/wiki/Caserta.

The International Atomic Energy Agency is the world's centre of co-operation in the nuclear field. It was set up as the world's "Atoms for Peace" organisation in 1957 within the United Nations family. http://www.iaea.org

http://www.icgeb.org http://www.unido.org

But it was clear to me that they were building a white elephant. It looked like they wanted to develop the Trieste area research park with the foreign affairs money of the government of Italy.

RP: So in trying to establish CAMBIA at the UN you found yourself competing with a government-sponsored initiative?

RJ: Right.

RP: What happened?

RJ: As I pieced it together from some friends who knew the inner workings of the Italian Government, and of the UN system, a very senior official of the International Atomic Energy Agency at the United Nations was told by his superiors in Italy to stop me from developing CAMBIA, on the grounds that it could interfere with or compete with the ICGEB. After all, ICGEB was a big Italian government-driven initiative. I was just a one-guy-in-an-office initiative.

The upshot was that I was completely censored: I was told that I couldn't use the fax, e-mail, or phone, to do anything connected with CAMBIA.

Since the ICGEB proved to be something of a boondoggle²⁵⁷ this was a tragic turn of events.

RP: But you didn't give up on CAMBIA?

RJ: Well, by now I had spent hundreds and hundreds of hours developing ideas and proposals, and writing hundreds of letters — so I decided to develop it all out of my home. I would wait until my official work day was over, and then go home and do it all from there. And that was the catalyst for me leaving the FAO

RP: At this point you decided that CAMBIA had to be a private initiative?

RJ: Exactly.

RP: So what did you learn from your time at the UN?

RJ: My time at the FAO taught me that inter-governmental bureaucracy is designed to completely stifle initiative. CAMBIA was so much about rocking the boat and disturbing the status quo that there was no way any international institution at that time was going to support it.

²⁵⁷ According to Wikipedia Boondoggle was originally a North American term that has come to refer to the performance of useless or trivial tasks whilst appearing to be doing something important. In the United States, the key feature of this "art" is the waste of time and/or money involved. In Canada [and perhaps Australia] the term has come to mean, more specifically, a government scandal involving the wasting or misallocation of public funds causing a project to be well over-budget, frequently more than double or triple the original cost. http://en.wikipedia.org/wiki/Boondoggle

Still, there are some great souls in the system and somehow they keep chipping away to make a difference their way. The UN really has to learn how to avoid abuse and maintain some accountability for its inputs, if not its actions.

Smoke and mirrors

RP: You left the FAO in 1991. Talk me through the process of setting up CAMBIA as a private initiative?

RJ: To talk about my "setting up" CAMBIA is to give me more credit than I deserve! It was more like continually eking out survival while marketing the concept of CAMBIA

RP: How then did you eke out survival?

RJ: It was the usual smoke and mirrors: I had a letterhead and a concept, and hundreds of documents about it; but I didn't have any money to hire anybody except, that is, a really good scientist and friend named Kate Wilson. 258

Kate is a really top class scientist by the way. She was a Cambridge Tripos, ²⁵⁹ and she got a Harvard PhD. She has also worked on the editorial staff of *Nature*. ²⁶⁰

RP: Again, however, you did eventually get funding?

RJ: Yes, the first funding breakthrough came when I convinced Gary Toenniessen at the Rockefeller Foundation to provide a small short-term grant. Until then the only funding I had was what I saved up as an FAO employee.

RP: Why did you move to Australia to set up CAMBIA?

RJ: Because the Rockefeller money was the only funding we got for a long time, and Gary Toenniessen explicitly hired me to troubleshoot their whole rice program. At that point Rockefeller was putting around \$8 million a year into largely Asian, but also Latin American, laboratories.

RP: When I spoke to Gary Toenniessen he said his understanding was that Rockefeller had funded you to go to Australia to do rice-related molecular biology research based at CSIRO's Plant Industry Group, not to set up CAMBIA.

²⁵⁸ Kate Wilson is now science co-ordinator at CSIRO's Wealth for Oceans Flagship. http://www.csiro.au/news/newsletters/0509_oceans/meet.htm.

http://www.csiro.au/news/newsletters/0509_oceans/meet.htm.

http://www.csiro.au/news/newsletters/0509_oceans/meet.htm.

^{260 &}lt;u>Nature</u> is one of the oldest and most reputable scientific journals, first published on 4 November 1869. Having an article published in *Nature* is very prestigious, and the articles are often highly cited, leading to promotions, grant funding, and attention from the mainstream media. Because of these positive feedback effects, competition among scientists to publish in high-level journals like Nature and its closest competitor, Science, can be very fierce.

RJ: Yeah, and also to develop the training and technology packages to support all the Rockefeller rice scientists all over Asia. I guess I ended up travelling to every lab that did biotech in the developing world. As a result, by the late 1990s I was by far the most experienced person in the world in terms of knowing what was really going on on the ground in agricultural biotech in that part of the world.

RP: Gary Toenniessen also shared with me an anecdote about how you established CAMBIA at CSIRO. As he tells it, when the chief of the Plant Industry Group Jim Peacock went off on a month's trip you took the division's maintenance men out to a bar and persuaded them to refurbish your lab. When Peacock came back he found you sitting in a fancy office, with a big sign on the front of the building saying CAMBIA in large bright letters. [Jefferson laughs]. Is that right?

RJ: That sounds like a lovely story — I wish it was true — but the reality is that there was nothing to set up; it's not like CAMBIA is this giant institution. ²⁶¹

RP: Nevertheless, it was in Australia that you finally got CAMBIA up and running?

RJ: Sure. What actually happened, by the way, was that I came out on a one-year agreement for Jim Peacock to host me, but I soon discovered that he had a completely different world view to me.

Moreover, Jim Peacock's idea of hosting me was to give me one room in an abandoned linoleum-clad prefab from the 1940s that had no heating, and was situated right next to a urinal. There was no furniture, no desk, no chair, and no phone — so I had to buy all these things out of my \$100,000 Rockefeller grant, \$60,000 of which was supposed to be travel money. We had to buy second-hand furniture and spent a lot of time sanding it and fixing it up. I also had to pay Kate, myself and a technician out of that grant, and to finance the setting up CAMBIA. ²⁶²

RP: You nevertheless stayed on in Australia, and CAMBIA is still headquartered there?

RJ: Right, I came for a year and discovered that in spite of Jim Peacock [laughs] the quality of the science is very good here. The quality of life is also very high, and unless there is a big change in plate tectonics we are irretrievably in the same time zone as most of the world's population.

So we are uniquely positioned to talk as human beings to most of the world, and still enjoy clean air and open space, which I need.

RP: Eventually, however, you transferred to the Entomology Division at CSIRO?

²⁶¹ CAMBIA has around 25 employees today. http://www.cambia.org/daisy/cambia/599.html.

²⁶² Clearly there was some ambiguity as to how the Rockefeller money was to be spent! But it seems that further funds have become available for CAMBIA: In 2004 it was widely reported that Rockefeller had awarded CAMBIA a grant of \$1 million (http://onthecommons.org/node/470). And in December 2005 CAMBIA announced that in a joint venture with the International Rice Research Institute (IRRI), a new strategy intended to "galvanise agricultural research focused on poverty alleviation and hunger reduction" CAMBIA had received a \$2.55M grant from The Ministry of Foreign Affairs of Norway. http://www.bios.net/daisy/bios/1374/version/live/part/4/data.

RJ: Well, after a year and a half at Plant Industry the friction with Jim Peacock was really irritating me. Fortunately, Max Whitten — who was the chief of the Entomology Division — was very supportive. Max is a wonderful guy, and I was able to base our little operation in his division while we negotiated with CSIRO to take over — lease — the building we are in now, which at the time was in mothballs.

RP: And how did you get more funding? The Rockefeller starter grant couldn't have gone very far. Were you now receiving royalties form the GUS patents?

RJ: Indeed, it was hand to mouth for a long time. Rockefeller kept increasing our funding, but never to develop the institute, just to do all the rice biotech and support work in Asia. So we never had any funding to bootstrap the independence of CAMBIA.

As you say, my original business plan for CAMBIA had assumed that by this time I'd be running on royalties for GUS, but the first patents hadn't issued until 1993. And worse, even though everyone in the industry respected me, and used GUS, we were unable to close a licence deal until quite a bit later — I think 1995 or 6 — when I was able to get my patents free of Misrock. It became very clear over the years that Leslie had very different priorities than I did, and perhaps an agenda I didn't understand with regard to my patents.

RP: OK, because as part of your agreement with him, Misrock had become a co-owner of the patents.

RJ: Yes. And remember he was deeply associated with many of the major players in the agbiotech industry. I had assumed this meant we'd close good amicable licensing deal for GUS (which everyone was using and liked), and I'd get some cash flow into CAMBIA. Boy was I gullible.

The day my patent issued I heard from several companies saying they'd like to license. One note from Harry Klee, 265 then at Monsanto said, "Hey Richard, congratulations on the patent. Good stuff. We'd like to license. Be greedy, but not too greedy". Seriously that's a pretty good paraphrase. You'd think with that on the table I'd be able to close a deal. Dream on.

RP: Are you saying that Misrock refused to sanction licensing deals for GUS?

RJ: I'm saying that Leslie wasn't replying to faxes, letters, emails, or anything. And he wasn't responding to approaches from some of the companies like DuPont who had been very keen for a licence. It sure looked like another agenda to me. So

²⁶³ Maxwell ("Max") John Whitten was chairman of CAMBIA.

²⁶⁴ It took seven and a half years to get the GUS patents through the patent office. Jefferson filed for his first one in 1986. By e-mail Jefferson explained that there are a number of GUS patents. "I have three US patents, and one UK patent covering GUS and Glucuronide Permease, and further ones covering Glucuronide repressor." For further information see, http://www.hos.ufl.edu/kleeweb.

CAMBIA — the dream — was auguring in²⁶⁶ because I couldn't raise any money even to buy a centrifuge, hire a technician, pay rent, or any of the many other things we needed.

RP: How and when did you resolve the situation?

RJ: Strangely enough, it happened because my father died. During his last week, I got a chance to get to know my step-brother Don, whom I'd never really spent time with. He's high-end business man with about as little in common with me as possible. He lives across the street from Bill Gates and does real-estate development and hunting.

But he has huge integrity and passion for family, and when he heard how I was being treated, he really got mad, and put me in touch with a friend of his who was senior partner at a firm specialising partnership disputes. After much legal sabre rattling, and with legal billings curiously pretty much matching my inheritance from Dad, I was able to get my patents back from Misrock.

RP: So finally you had the funding you needed to keep CAMBIA going?

RJ: Well it took another stroke of luck first. Having patents, even with people wanting to license the invention, still needs extraordinary talent at negotiating and closing deals. This was yet another skill that I utterly lacked at the time.

Again, however, serendipity stepped in. My old friend Bob Rabson, who had been a strong supporter of my ideas since the mid-80s, and who ran the US DOE's Energy Biosciences Division, ²⁶⁷ had long urged me to meet his son, a patent attorney. I resisted for years, disliking nepotistic introductions, but ultimately I agreed, and it was a breakthrough.

Mike Rabson²⁶⁸ was working at the time as senior rain-maker in biotech licensing at Wilson Sonsini in Palo Alto.²⁶⁹ He has all the top qualifications: PhD, JD²⁷⁰ Yale, and ex-USPTO examiner — in short, a serious top dog. But unlike most folks with those qualifications he has integrity and a huge heart — which he hates to admit.

Anyway, he took over licensing CAMBIA's technology — both GUS and later ones — almost as a favour (i.e. billings seemed never to reflect the hours we spent. I was his smallest client by a factor of nearly 100!).

Learning at the master's feet, by the way, was fantastic. He closed deals with all the majors, and as we went we learnt just how useful — even essential — the technology was for them. Sometimes we closed a deal within a week of a desperate payroll need at CAMBIA. They were very tense but heady times. But I also learned of the

²⁶⁶ collapsing

http://www.er.doe.gov/bes/eb/ebhome.html.

http://www.cambia.org/daisy/cambia/1497.html.

http://www.wsgr.com/WSGR/Index.aspx.

http://en.wikipedia.org/wiki/Juris Doctor.

The first major biotech company to license GUS was DuPont.

capriciousness of licensing and the extraordinary transaction costs that were necessary to get closure. Even with a hot technology.

Mike has continued to help us, and is now on our Board, while also being General Counsel of Maxygen. ²⁷²

RP: And in this way you finally had enough cash to get CAMBIA up and running?

RJ: Yes, but always just in time, and the first five years we'd sink it into payroll while developing the ideas for CAMBIA on the fly. I guess over the years we pumped about four or five million dollars of GUS licensing revenue into CAMBIA. Not what most business people would describe as a wise investment!

RP: Why did you choose the name CAMBIA?

RJ: CAMBIA originally stood for the Center for Application of Molecular Biology to International Agriculture. Legally, however, we are just "CAMBIA", and we only use the acronym in our logo. CAMBIA means "change" in Italian and Spanish. That is what we are about: system change.

RP: How?

RJ: The purpose of CAMBIA is to level the playing field in an upward direction. So rather than saying that in order to help disadvantaged people we have to bring other people down to some particular level, we argue that it is the other way around: we need to bring the capabilities of disadvantaged people up to the point where they can solve their own problems, and under their own priority set.²⁷³

RP: In the context of CAMBIA this clearly means changing the environment for biological innovation by removing access barriers to the enabling technology. The point about making GUS freely available in the way that you did, for instance, was that while it enabled large multinational biotech companies like Monsanto to develop new plant varieties, it also allowed scientists in developing countries to exploit the technology — to create new plant varieties more suited to their climate for example.

RJ: Exactly. And yet today almost no development paradigm explicitly or adequately respects the right for everyone to make and use tools — which is so fundamental to humans. As a consequence, the less wealthy are completely disempowered, from both the social and technical tools to help themselves. That's what we want to change.

RP: In other words, to change things so that less wealthy nations are empowered to be more self-sufficient in biotech, particularly in ways that can improve food security?²⁷⁴

²⁷² http://www.maxygen.com.

CAMBIA's constitution is available here: http://www.cambia.org/daisy/cambia/1809.html.

The FAO states that food security exists "when all people, at all times, have access to sufficient, safe and nutritious food to meet their dietary needs and food preferences for an active and healthy life." For a map see: http://www.fao.org/es/ess/faostat/foodsecurity/FSMap/map14.htm.

RJ: Yes, although not just "biotech", but any science-empowered biological innovation. The problem today is that we have siloed the capability of engaging in biological innovation to a small number of entities, sometimes people, sometimes companies, sometimes countries.²⁷⁵

RP: I guess what happened with Agrobacterium exemplifies the point you are making. As I understand it, Agrobacterium is the most widely used method for genetically modifying plants. The problem, however, is that Monsanto owns key patents on the technology. So while anyone wanting to develop new plant varieties can freely use GUS to monitor what they are doing when implanting genes into a plant, they have to pay licensing fees to a large Western company in order to actually get the genes in. And while there are alternatives to Agrobacterium — the gene gun developed at Cornell University for instance the second content of the point you are making.

RJ: There are hundreds of patents on *Agrobacterium*, and the rights to these are owned by a number of different entities. Certainly Monsanto has some of the dominant ones, as does Syngenta²⁷⁸ and Bayer.²⁷⁹ So, yes, this poses serious problems.

The big breakthrough we made recently was to develop a new technology for doing the same thing as *Agrobacterium*. We have called it called TransBacter. ²⁸⁰

Licensing infrastructure

RP: I'd like to come to TransBacter a little later. Can we talk about BiOS first? BiOS is CAMBIA's primary initiative right?

http://www.nysaes.cornell.edu/pubs/press/1999/genegun.html.

Most obviously this capability has been siloed through the use of patents. A recent commentary in *Nature Biotechnology* reported that as much as 20% of the human genome is now claimed by patents, of which two thirds are owned by private firms. It added "By one measure, over two-thirds of the DNA related patents make claims that are legally problematic because they are overbroad or improperly disclosed or because they overlap other patent claims. "Navigating the future(s) of biotech intellectual property, Kenneth Neil Cukier, *Nature Biotechnology*, Volume 24, Number 3, March, 2006. http://www.nature.com/nbt/journal/v24/n3/full/nbt0306-249.html.

276 Agrobacterium-mediated transformation of plants is one of the most widely used means of making

transformed plants. Although much of the basic research that led to *Agrobacterium*-mediated transformation was done in public institutions, the private sector now holds many of the key patent positions. Patent rights were obtained by the private sector either from internal research and development, or from public institutions in the form of licenses, often exclusive licenses, by acquisition of spin-off companies formed to commercialise public research, or occasionally by assignment. For CAMBIA's analysis see: http://www.bios.net/daisy/patentlens/tech_landscapes/78.html.

Technology rights to the gene gun were sold to DuPont in 1990, resulting at that time in the largest

Technology rights to the gene gun were sold to <u>DuPont</u> in 1990, resulting at that time in the largest payment ever made to Cornell for royalties under a patent.

http://www.syngenta.com/en/index.aspx.

http://www.bayer.com.

²⁸⁰ TransBacter is a new method of gene transfer for plants — or indeed any <u>eukaryotic organism</u> — using bacterial species outside the genus *Agrobacterium*. TransBacter is designed to be a work-around to the many patents covering *Agrobacterium* transformation and thus aims to overcome the current IP restrictions to the commercialisation of products created using bacteria-mediated gene transformation in plants. http://bioforge.net/forge/entry.jspa?entryID=1.

RJ: Yes. BIOS — Biological Innovation for Open Society — which is often called Biological Open Source (hence the lower case 'i' is sometimes used) is an umbrella initiative designed to explore and create new R&D paradigms, practices and policies in order to address the neglected priorities of disadvantaged communities by tapping the potential of their own creativity.

The aim is to achieve lasting solutions, not just around food security, but also agricultural productivity, human and animal health, and natural resource management.

RP: Essentially we are talking about Open Biology²⁸¹ aren't we?

RJ: Yes, but I don't really like that term much. We see "biology" as simply a field of study, a topic really; whereas biological innovation, or more narrowly biotechnology, reflects the use of that knowledge to actually "do" stuff. And that's a big distinction.

Some academics who use the term "open biology" are really talking about ensuring that the academic research enterprise is made easier. Our view is that that is good but insufficient. I don't really care much about academic research if it can't ultimately impact on the lives of disadvantaged people. And to achieve that we need new innovation systems, significant changes in business practice, and structural reform at the level of patent offices.

But the aim of BiOS is not just to advocate for change but to help enable it, by developing an appropriate licensing infrastructure, providing tools for open technology development, sharing and use, and facilitating patent transparency with informatics

RP: OK, let's start with the licensing aspect: As I understand it, you have developed a number of biotech licences that work in a similar way to Open Source licences?

RJ: Yes. The BiOS licenses are the main tools we use for sharing technology. We don't, by the way, anticipate being a one-stop shop for all the Biological Open Source licences. What we want to do is to promote the concepts, and to explore the potential limitations and challenges, and to foster creative solutions to these challenges.

To that end we have spent quite a long time working on licensing, and through the BiOS foundation we are establishing a certification program like the OSI²⁸²— but for biotech licences.

RP: CAMBIA has already drafted a number of BiOS licences hasn't it?

RJ: Yes. Our first licence was developed for plant molecular enabling technologies, ²⁸³ and it has already been adopted by a number of companies and non-

²⁸¹ As noted in the introduction to this interview there appears today to be no widely agreed definition of Open Source Biology. As we see, Jefferson was leery about the term Open Biology, and the CAMBIA web site describes the BiOS licences as "Biological Open Source Licences".

The Open Source Initiative (OSI) is a non-profit corporation dedicated to managing and promoting the Open Source Definition for the good of the Open Source community, specifically through the OSI Certified Open Source Software certification mark and program. http://www.opensource.org/index.php.

283 http://www.cambia.org/daisy/PELicense/751.

profits in both the developing and the developed world. A similar licence for healthrelated technologies is currently being drafted. There is also considerable interest in the use of BiOS licences for the sharing of genetic resources, and so a license for genetic resource indexing technologies is now also available. 285

RP: You said earlier that you patented GUS while you didn't fully understand the patent system. As it happens, your decision was fortuitous: you later discovered that asserting ownership not only allows you to use the royalties for a worthy cause, but it gives you greater control over how the patented technology is used? What we've learned in recent years, for instance, is that simply placing biotech tools, or data, into the public domain allows others to appropriate them?

RJ: That's right. Its pretty easy to come up with strategies — especially with DNA sequence — to co-opt what seems to be public domain, and build restrictions around it that basically privatise public goods.

Of course useful information placed into the public domain can be used and developed into patentable products by large companies, which is compatible with the intent of patents. However when patents place restrictions on use of that material or information unjustly, and preclude competitive activity, they create very real impediments to fair and socially valuable innovation. And I would assert that these are also causing great inefficiencies in our innovation system, by extracting rents from the process of competitive innovation.

The rice or Arabidposis genome project, for example, placed masses of information into what they thought was the public domain. 286 Private companies in the developed world with modern labs and computer equipment were then able to take this information and quickly move it into patent applications for genetic markers, ²⁸⁷ targets for herbicides, specific genotypes ²⁸⁸ related to nutrition, fibre quality, and so on. As a consequence, the rights to much of the potential resulting technology, and even to "composition of matter" over the genes themselves have now largely been acquired by a few multinational corporations.

Similarly and more perniciously, with the Arabidopsis sequencing, smallish companies got in and bulk sequenced most of the genome, and claimed it in US patent applications. Then before these are published, using "continuation" practice in US patent law, ²⁸⁹ they were able to cherry-pick those DNA sequences that the public

http://www.cambia.org/daisy/GRITLicense/750.

²⁸⁴ http://www.cambia.org/daisy/cambia/1188.

http://mips.gsf.de/projects/plants/gen/publications.html.

A genetic marker is a known DNA sequence (e. g. a gene or part of gene) that can be identified by a simple <u>assay</u>, associated with a certain <u>phenotype</u>. A genetic marker may be a short DNA sequence, such as a sequence surrounding a single base-pair change (single nucleotide polymorphism), or long one, like microsatellites. http://en.wikipedia.org/wiki/Genetic marker.

The genotype is the specific genetic makeup (the specific genome) of a plant or organism, in the form of DNA. http://en.wikipedia.org/wiki/Genotype.

²⁸⁹ A "continuation application" is a patent application filed by an applicant who wants to pursue additional claims to an invention disclosed in an earlier application of the applicant (the "parent" application) that has not yet been issued or abandoned. The continuation uses the same specification as the pending parent application, claims filing date priority of the parent, and must name at least one of the same inventors as in the parent. http://en.wikipedia.org/wiki/Continuing patent application.

sector scientists subsequently showed were interesting and important, using the original priority date of their filing to obtain patents at a later date — essentially patents that "own" genes, the function of which the public paid for elucidating.

And of course these "smallish" companies were already controlled by "largish" companies, notably Monsanto. And their entire work product, and that of the entire public sector that proves value of a gene, is now also Monsanto's. And the founders — typically respected academics — became very rich by selling out. It's the public that is poorer however.

Within a year or so, the public had also sequenced these. So the idea that an "incentive" was needed to sequence them was clearly silly. It was asset stripping plain and simple.

RP: So instead of releasing a new technology or information into the public domain, there is a real advantage in asserting ownership of it — because doing so allows you to specify how it is used. What BiOS and Open Source licences have in common, for instance, is that they both use the structure of the IP system to subvert it. Where the IP system was designed to maximise proprietary rights, for instance, BiOS and Open Source licences use it to foster greater sharing?

RJ: Indeed. Usually the licences used with patented technology impose strict conditions on the user, commonly involving fees or royalties for use of the materials or methods, or both. Instead of royalties, BiOS licensees must agree to new norms reflected by legally binding conditions in order to obtain a license; conditions that require them to share the specific technology that they're licensing, to preserve the right for others to use it, and to agree to work towards improving it.

RP: And this is what copyleft does: Open Source licences exploit copyright law to achieve the opposite effect of copyright — insisting on sharing rather than taking a proprietary approach. In a sense, they turn copyright on its head. ²⁹⁰

RJ: Yes, to a point. And in most ways, that's what we do with our BiOS licences; however, we have to use patents, and patents are expensive; so we have to use them judiciously.

RP: So there are no royalty or licensing fees associated with BiOS licences?

RJ: No. BiOS licenses are available at no cost. There is, however, an optional support agreement.²⁹¹ Effectively this is an improvement-sharing service, and it is based on an organisation's ability to pay.

http://www.bios.net/daisy/PELicense/252. The fee arrangements are here: http://www.bios.net/daisy/PELicense/252/1179.html.

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Whereas copyright law, by default, automatically restricts the right to make and redistribute copies of an author's work, a copyleft licence uses copyright law in order to ensure that every person who receives a copy of a work has the same rights to study, use, modify, and also redistribute both the work, and derived versions of the work as long as the same license terms apply to all redistributed versions of the work. Thus, in a non-legal sense, copyleft is the opposite of copyright. http://en.wikipedia.org/wiki/Copyleft.

The Technology Support Services Subscription Agreement can be viewed at

Only companies based in OECD countries are asked to pay, for instance, and big companies pay more than smaller companies. In that sense we operate a technological affirmative action program, and we expect the private sector, especially large corporations, to subsidise our ability to share improvements with third parties, especially those in disadvantaged situations. So it's a sort of technological affirmative action to bootstrap SMEs and industry in less developed countries, and to help SMEs even in industrialised countries.

RP: It's a tiered subscription service in effect?

RJ: Yes. It is not dissimilar to what Red Hat does.²⁹² There are no licensing fees, but people pay to ensure we have the ability to keep our website live, to continue to collate, quality control and test improvements, and to send out the materials.

RP: Open Source licenses allow licensees to develop commercial products from licensed software. Is this the case with BiOS licences too?

RJ: It is, One particularly powerful implementation of the Open Source concept is that what is made widely available is not necessarily the product solution, but the enabling technology that allows a product to be developed, and that can be further modified to develop other products to suit people's needs. That is what we aim to achieve with the BiOS licences.

RP: Would I be right in thinking that the analogy here is that where an Open Source operating system like Linux is made freely available to everyone, software developers are permitted to build and sell commercial applications and services on top of that operating system?

RJ: That's right. But they cannot appropriate the fundamental "kernel" of the technology, or keep any improvements exclusively to themselves.²⁹⁴

RP: As you say, however, unlike Open Source licences — which are based around the copyright system — BiOS licences leverage the patent system?

RJ: They do. And as a consequence what we are doing is so much harder than Open Source copyright licensed software.

RP: Why is that?

RJ: Well, for a start software enjoys the physical protection of its compiled code.

²⁹² Red Hat, Inc. is one of the largest and most recognised companies dedicated to Open Source software. http://www.redhat.com.

²⁹³ In computer science, the kernel is the central part in most <u>operating systems</u>. It is a piece of software responsible for the communication between hardware and software components. While early kernels might have had 100,000 lines of code, kernels of modern Unix successors like Linux can have upwards of 4.5 million lines. http://en.wikipedia.org/wiki/Kernel_%28computer_science%29.

294 As *Science* put it in an article in June 2006, the aim is "to disaggregate the tools of innovation from

the products of innovation, so that companies would compete at the level of products and services, not on their ability to get to the starting gate." Out to break biotech's IP stranglehold, Cormac Sheridan, Science, 7th June, 2006. http://www.bios.net/daisy/bios/1860/version/live/part/4/data.

RP: You mean that unless the source code is made available it is very hard for anyone to copy software. ²⁹⁵ By the same token, however, making the code available — but releasing it under an Open Source licence — allow software developers to ensure that it is shared?

RJ: Right. That was the issue for the Open Source people, and by building a community that did do that, using the very, very simple tool of copyright, they were able to achieve their purpose. The copyleft licence is a very clever device, but essentially a very simple one. It is not dependent on other things in the outside world.

RP: The key point perhaps is that where copyright protects a tangible object — which in the case of software is computer code — a patent protects new ways of doing things: new methods, techniques, and technologies.

RJ: Yes. And while it is obvious if you are using someone else's code — if they make their code known, and you look at that code and see a piece of it, it is apparent — with patents the entire concept can be patented, and so you could be doing something with absolutely no knowledge that you are infringing a patent.

RP: This means that the ability for patents to fence off the "science commons" is much greater than the ability for copyright to appropriate the "software commons"?

RJ: Right. Even though you may never have heard of the patent owner, have not been inspired by them, and haven't pinched their code — and even though you have done nothing except what to you is painfully obvious — you nevertheless discover that what you have developed is protected by a patent. That makes biological innovation very difficult. Interestingly, in those jurisdictions where software and algorithms can now be patented, this same problem has become of great importance in software and IT too.

RP: And when you have the hugely complex solutions that are typical in biotechnology a single patent on just one part of a large solution can hold the entire solution to ransom?

RJ: Indeed. A useful analogy is to think of a cart with a wheel that has six spokes in it. Now imagine that, due to the nature of that wheel, if one of those spokes was removed the wheel would no longer turn. So you can't move the cart with that wheel unless all the spokes are intact. That's how it is with biotechnology, because each part of the technology (each spoke of the wheel) is wrapped up in complex relationships and interdigitations. You cannot use the complete solution without all the parts, but each part may be separately patented.

For this reason navigating rights in the biotechnology space is very, very difficult, and valuation is both troublesome and antithetical to common cause for improvements of the whole "wheel".

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²⁹⁵ The human-readable source code is necessary in order to modify software programs since the computer-executable code generated from "compiling" the source code is inexplicable to humans. Decompilation is very difficult. Moreover, a great deal of the original programmer's instructions, including commentary, notations, and specifications, are not included in the translation from source to object code during compilation.

RP: The differences you point to mean that BiOS licences²⁹⁶ are more complex than Open Source and Creative Commons licences. Critics argue that this is likely to act as a disincentive for anyone thinking of embracing Open Source Biology. ²⁹⁷ Would you agree? ²⁹⁸

RJ: Well, most of the critics that I've read are academics with little or no practical experience in patent craft, biotechnology or in the realities of business and licensing. Those who do have such experience will confirm that the Devil, or in our case the Divine, is in the details. Definitions matter a great deal when there is a good chance that entities not party to the agreement may have rights which could impinge on the freedoms we wish to see flourish.

And when innovation timelines are long, as they are in life sciences-enabled industries like food, agriculture, natural resource management, public health and medicine, there are extraordinary economic outlays and legal exposures to be accommodated.

The real disincentive is amateurism, dilettantism and improper attention to the real world challenges we have to overcome to see products and services developed that improve people's lives, and to change innovation opportunities for disadvantaged but creative people.

In a sense, Richard, this is why I really don't like the term "Open Biology" In my view it connotes a "movement" amongst scientists, by scientists, and for scientists. I assert that the real need is for scientists and science to become integrated into society, and when it is well done, small-to-medium business is a very effective tool to help this happen. It's really not just about sharing amongst scientists; it's sharing the capability to use science within and amongst societies.

RP: Another important difference between what you are doing and what the Open Source Movement is doing is that copyright arises automatically when a creative work is born. That means that there is no need to register it, and so Open Source developers can simply attach an Open Source licence to their code and post the software on the Web. Patents, however, have to be applied for, which means that biotech developers first have to obtain a patent, and then they have to ensure that anyone using the technology signs a BiOS licence indicating their agreement to the terms?

²⁹⁷ Andrés Guadamuz comments on the BiOS licence: "This is a worthwhile effort to create a viable 'Open Source' licence of patented materials. However, even in its draft stages it is easy to see that the language seems stretched and unclear in many instances — something that could turn away some potential licensors who could find the complex explanation of the terms and conditions difficult to navigate." *Open Science: Open Source Software Licenses and Scientific Research*, Andrés Guadamuz, 20th BILETA Conference, April 2005.

http://www.bileta.ac.uk/Document%20Library/1/Open%20Science%20-

%20Open%20Source%20Software%20Licenses%20and%20Scientific%20Research.pdf.

²⁹⁶ http://www.bios.net/daisy/bios/BiOS licenses.html.

Guadamuz concludes, "there appears to be an inherent problem in porting a licensing model that has been designed to work with copyright into a system that would have to work with patents."

http://www.bileta.ac.uk/Document%20Library/1/Open%20Science%20%20Open%20Source%20Software%20Licenses%20and%20Scientific%20Research.pdf.

RJ: Yes. However, as I say, the problems of patents covering software have now made this issue a compelling area of converging concern between the software world and that of the more traditional patent-dominated fields such as biotechnology. Now that thousands of patents are being issued covering algorithms, software and standards, the problems that CAMBIA BiOS has evolved to confront and overcome are now shared with that industry. And that has prompted much of our work on the Patent Lens.

RP: Yes, I want to come to Patent Lens in a moment. Critics point out, however, that it costs on average \$7,500 in the US alone to file for a patent, and so anyone who has had to make that level of investment will be reluctant to share the technology without charge. Is that a big problem for Biological Open Source?

RJ: It's an issue. But again, critics should do their homework. The great majority of patents are never licensed at all at any price, and cost much more in their obtention than \$7,500. We fall so easily into calling it "their" or "our" technology. I think this colours our discussion somewhat, and implies that we are talking about real property, with real and immediate value.

It is not the intellectual property that has intrinsic and enduring value *per se*, but its manifestation in tangible processes, products and services that creates value and wealth in society. Thus, while a holder of property rights may wish a monetised return for that particular right, when properly incentivised and motivated we feel that many if not most such property rights holders would be delighted to see their own capability to use technology to create value increased through the grant-backs of improvements, through the investment-insurance devices of the non-assert covenants³⁰⁰ and the decrease in costs associated with the shared biosafety data provisions.

La, la land

RP: You said that like Open Source licences, BiOS licences permit commercial products to be developed. Unlike the General Public Licence³⁰¹ — the most widely used Open Source licence — however, the BiOS licence does not prohibit licensed technology from being used to develop downstream proprietary products?³⁰² In that

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²⁹⁹ The act of obtaining.

i.e. agreements not to assert rights against certain third parties.

³⁰¹ The GNU General Public License (GNU GPL or simply GPL) is a widely-used free software license, originally written by Richard Stallman for the GNU project. The primary difference between the GPL and more "permissive" free software licenses such as the BSD License is that the GPL requires that derivative works of GPL-licensed programs are also licensed under the GPL. In contrast, BSD-style licenses allow for derivative works to be redistributed as proprietary software. http://en.wikipedia.org/wiki/GNU General Public License.

³⁰² As the CAMBIA web site puts it, "There must be an essential distinction between the tools of innovation, and the products of innovation ... The implications for the impacts of exclusionary IP regimes in tools and their use (analogous to operating systems, programming languages and standards of interoperability) or in their applications (analogous to product lines or service relationships in software companies) are very different." *The CAMBIA BIOS Initiative* http://www.bios.net/daisy/bios/10/version/live/part/4/data.

sense it doesn't have the same viral quality as the GPL, but is more like the BSD³⁰³ licence?³⁰⁴

RJ: It is much more like the BSD, and it has to be because of the nature of biological technology. The idea that everything has to be shared perfectly, and that if you use something, to develop a new product, then that new product has to be shared with the world, is to live in la, la, land.

In biotechnology the virality — or what in our Patent Lens we call it the extensibility of a licence — is potentially very undesirable; it is a reach through that basically ensures that any benefit is captured by the first provider, or in fact by no one.

It is better to acknowledge that people have their own priorities, their own business models and their own needs. So long as we can stave off any hint of monopolisation it is perfectly possible to respect those needs.

So BiOS licenses ensure that the base technology remains the property of whatever entity developed it, but all licensees obtain access to improvements, and other information. In other words, ownership of the technology stays with the owner, who grants all licensees a world-wide, non-exclusive, royalty-free right to make and use the licensed technology and improvements.

RP: The aim then is not so much to share the technology with the whole world, but with a community of like-minded people who have agreed to work together to develop biotech tools? What Benkler in his book The Wealth of Networks calls a "self-binding commons?"305

RJ: Well, not exactly. I'm not interest in fostering a closed system of biotechnology developers and scientists, interested in sharing within a club. I'm keen to keep our eye on the main game: we have to see that the capability to use and to influence the development of such technology to improve human well being (and not just science career advancement alone) is shared broadly and fairly. All BiOS licences are nonexclusive, and licensees covenant to share improvements, making them available for use, even though they may be patented, to all other licensees.

Additionally, owners of technology or an improvement made available under a BiOS licence many not assert IP rights over that technology, or any improvements to it,

http://www.benkler.org/wealth of networks/index.php/Download PDFs of the book.

³⁰³ Berkeley Software Distribution (BSD) is the <u>Unix</u> derivative distributed by the <u>University of</u> California, Berkeley, starting in the 1970s. The name is also used collectively for the modern descendants of these distributions. The permissive nature of the BSD license allows companies to distribute derived products as proprietary software without exposing source code and sometimes intellectual property to competitors. This permissiveness also makes BSD code suitable for use in Open Source products, and the license is compatible with many other Open Source licenses. What is distinctive about the BSD licence in this context is that it does not include a clause requiring a specific licensing model for derivative works, which means that products created using BSD-licensed code can be used in proprietary software. http://www.bios.net/daisy/bios/BiOS_licenses.html.

³⁰⁴ Critics of the GPL often describe the licence as being "viral", in so far as its terms require that all derived works must in turn be licensed under the GPL.

³⁰⁵ Benkler, *supra*, p. 342. p. 344.

against other BiOS licensees. Participants also share biosafety data and other information needed to meet regulatory requirements for use in commercial products.

So they cannot assert rights to exclude others from using any improvements, even patented improvements, against the licensor and other licensees that are contributors within a "protected commons". 306

RP: You say that virality is potentially dangerous in biotech. Some have pointed out that BiOS licences nevertheless do include a viral element. If they didn't, in fact, you wouldn't be able to ensure that sub-licensees shared improvements with the community would you? 307

RJ: I suspect that this demonstrates that critics may not appreciate the nuanced differences between "enabling technologies" and "products" more than anything else, nor perhaps appreciate the norms we wish to foster.

I find it counterproductive to use one word such as "virality" as a wholesale description for what is a complex concept that will have to be sculpted into definitions and intentions of licenses. What most people mean about "virality" is described in the statement from the GPL that anything created with and encompassing GPL'd code must be licensed under GPL.

This is not even vaguely consonant with our license intent, much as I'd personally like it if the world worked that way. If someone uses TransBacter and GUSPlus (licensed under CAMBIA's PMET BiOS Licence³⁰⁸) to create a strain of rice that is resistant to drought, that rice line can be dealt with any way the inventor wishes: with Plant Breeders rights, with patents or indeed as public domain. They must just agree not to stop others using *that particular toolkit* from doing so to make a competing product, or indeed anything else.

RP: How are the BiOS licences being received?

RJ: Very well; that's the cool thing. We haven't make a big deal about it, but BASF, which is a huge German multinational, has executed a BiOS licence, and even paid up. ³⁰⁹

resource. http://en.wikipedia.org/wiki/Tragedy of the anticommons.

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³⁰⁶ The various open movements have made great play of the concept of "the commons". In particular, they emphasise a phenomenon referred to "The Tragedy of the Anticommons", which occurs when rational individuals (acting separately) collectively waste a given resource by under-utilising it. This is the canonical justification for the *takings clause* in the US Constitution and eminent domain generally. This happens when too many individuals have rights of exclusion (such as property rights) in a scarce resource. This situation (the "anticommons") is contrasted with a *commons*, where too many individuals have privileges of use (or the right not to be excluded) in a scarce resource. The <u>tragedy of the commons</u> is that rational individuals, acting separately, may collectively *over-utilize* a scarce

³⁰⁷ Guadamuz points out that there are nevertheless viral clauses in the <u>BiOS Licence</u>. As he wrote to me by email: "The viral clause is in both 2.1 and 3.1 (and subsections. The normal copyleft element in Open Source applies to 'improvements', or derivates. See also his article at http://www.ncjolt.org/Vol7_I2/HTML/Gonzalez.htm.

Plant Molecular Enabling Licence. http://www.cambia.org/daisy/PELicense/751.

³⁰⁹ An article in *Science* says Jefferson identified <u>BASF Plant Science</u> among its first 50 licensees. The article adds, "As a latecomer to plant biotechnology, he says it has a more limited portfolio of technologies than its rivals and therefore has less room for manoeuvre in cross-licensing agreements.

RP: I'm curious about your attitude to intellectual property. You are not anti-intellectual property. You simply object to it being abused?

RJ: Correct. Although I have great and increasing sympathy for those who, seeing the system so abused, wish it to disappear. I find the way it's used, and its current excesses, pretty and unpalatable these days. But indeed, when thoughtfully guided, over sighted and used judiciously and transparently, I'm optimistic we can use IP for social benefit.

RP: What, then, is the appropriate role for intellectual property today?

RJ: Boy that is a tough question to answer in a couple of pithy phrases. I think it has reached a level of outrageous venality, short-sightedness and excess. It no longer seems to stimulate creativity, but fosters gaming and rent-extraction. And I don't see intellectual property as currently practised helping much with "the advance of science and the useful arts" as the US Constitution cites as a prime motivation for the patent system.

You know when Thomas Jefferson was Secretary of State he was also the first US patent commissioner (he was the third president of the US after that 310). At that time he personally reviewed every patent application. And his motivation for granting a patent was to encourage disclosure of ideas and inventions that would not have been made public without such an incentive. And then, that "teaching" would stimulate others to learn from it and build upon it.

Now that particular Jefferson was a real smart guy and these patents had to be non-obvious to him to be granted. What was sensible about that was that if someone as bright as TJ has to conclude "Yea, that's a good idea that would take people a long time to figure out without this patent" before it is patented, then you are putting the bar really high. And if you put the bar high then you reward and encourage really creative people to disclose these ideas that are critical to social advancement.

But these days, the extremely rapid progress of science and technology, with weekby-week publication in journals and routine Internet sharing of protocols, data and ideas, the granting of patents in exchange for such sharing of information — the fundamental justification for patents — seems absurd, unnecessary and anachronistic.

RP: So the fundamental problem is that the standard for deciding whether a patent application describes a justifiably innovative advance to warrant a patent has fallen?

'They represent a very extreme example of why this is needed'."Out to break biotech's IP stranglehold, Cormac Sheridan, *Science*, 7th June, 2006. http://www.bios.net/daisy/bios/1860/version/live/part/4/data. Thomas Jefferson was the third President of the United States (1801–1809), author of the United

States Declaration of Independence (1776), and one of the most influential Founders of the United States. He also served as the second Governor of Virginia, first United States Secretary of State, and second Vice President. As Secretary of State, Jefferson was responsible for the Patent Office. http://en.wikipedia.org/wiki/Thomas_Jefferson. As Richard Jefferson later says, his father t old him that he was related to Thomas Jefferson.

RJ: Two things have happened: First, the bar has dropped so incredibly low that any slug that gets there first can crawl over and get a patent. Eben Moglen³¹¹ colourfully calls the patent system a "gumball machine". You just pay up and get the patent.

Second, this is happening with such volume and with such low standards that we now have a system that is conferring rights that are meaningless but sadly not valueless, as they are presumed valid and are a powerful tool for rent-extraction in a form of legalised extortion. Lately this has been called patent trolling. ³¹²

RP: Intellectual property has got a little big for its boots then?

RJ: [laughs] Oh, you are really kind. More accurately, it has become a clergy-ridden, highly Byzantine liturgy. The structure of patents, the volume of them, the formality of them, the complexity of their interplay, all this can only be interpreted by the highly privileged, bloated clergy of patent law. And this clergy positions itself as essential. Even to read a single patent in a way that a human can understand is a terribly difficult thing for a non-patent professional.

The whole system has been hijacked by a clergy and has reached a point where highly-intelligent business people can look at a patent and have no idea how to navigate the sense of its claims, or worse, to see the complex patterns of the numerous interlocking patents and claims that may occlude progress.

Licensing infrastructure

RP: An important component of the Biological Open Source ethos — as with the Open Source Movement, is collaborative development. The second component to BiOS, therefore, is BioForge. This is Biological Open Source's equivalent to SourceForge is it?

Yes. BioForge is meant to be a collaboration infrastructure. It provides document-sharing and discussion tools for the creation and improvement of technologies within a protected commons. What we did was to tap into people like Brian Behlendorf,³¹³ who helped us with the first version of it. You know Brian and his company CollabNet?³¹⁴

RP: Sure, the guy who helped develop the Open Source web server Apache, and cofounded the Apache Software Foundation. 315

³¹¹ Eben Moglen is General Counsel of the Free Software Foundation and Professor of Law and Columbia University. http://emoglen.law.columbia.edu.

Patent troll is a derogatory term used to describe a patent owner, frequently a small company, which enforces patent rights against accused infringers, but does not manufacture products or supply services based on the patents in question. Patent trolls focus their business on the enforcement of intellectual property rights. http://en.wikipedia.org/wiki/Patent_troll.

http://www.collab.net/about/estaff/brian.html

http://www.collab.net.

http://www.apache.org.

RJ: Right. Brian is a great guy and very kindly allowed us to use his CollabNet product for the first year.

RP: When you talk about a "protected commons" you are talking about private discussion groups are you?

RJ: That's only a component of the concept. It's actually the suite of capabilities — technologies — that are protected by legal and normative instruments that makes it protected. In principal, any group of BiOS-licensed technologies is intrinsically a part of a protected commons, irrespective of the BioForge.

The terms of use of these technologies ensures — or strives to ensure — that the common capability to use the technologies will be protected from misappropriation, and the users will be protected in their rights to use the technology.

To extend that protection, for instance with patenting, we may need a place to improve the technology secure in the knowledge that only those who agree to the mode of sharing are party to it. BioForge is a portal for protocol development and sharing, for commenting on patents and potential restrictions, and for accessing tools in both a public and a secure environment.

The point is that owners of improvements may wish to patent them, so we think it may be necessary to provide a space for confidential, non-public disclosure of improvements to all licensees.

As a tool for extension of a protected commons, therefore, BioForge provides a secure platform where discussion concerning an invention, or improvement, can take place without the invalidation of future patent applications, or the misappropriation of information by third parties.

RP: How successful is BioForge proving?

RJ: The first year was a sobering learning experience for us. I would even go so far as to say it was very disappointing: we had to learn that the culture of innovation completely, *completely*, dictates the effectiveness of the tool; and the culture of software innovation evident in the Open Source Movement could not be more different than the culture of biological innovation.

So it is in a very primitive and early stage, and it hasn't taken off to our satisfaction yet. But it will; it will just need a lot more social science savvy and creative use of new incentives.

RP: I believe CAMBIA has been buying patents, and now has patents on around twelve different technologies. Am I right in thinking that you are doing this because — as Guadamuz predicted — biotechnologists are indeed proving reluctant to share technology that has cost them thousands of dollars in patent fees to develop? If so, can we expect to see CAMBIA take a greater role in acquiring and owning patents, which it will then make available under BiOS licences?

³¹⁶ http://www.cambia.org/daisy/cambia/intellectual property.html.

RJ: So far, CAMBIA only owns patents covering inventions by myself or other CAMBIA staff and our colleagues. The only "buying" of patents was the acquisition of right and title to patents that had been developed and owned by me before CAMBIA was formed and, in one case, restoring CAMBIA's title to a patent covering work done at CAMBIA, but which had been paid for by another entity. So we haven't started buying IP yet, *per se*, and we will only do so when we develop sufficient resources to do so strategically.

We do, however, plan to raise substantial resources to develop larger portfolios of patents related to core enabling technologies, with a view to making them available universally, and allowing them to be used to leverage much larger contributions to public good.

RP: Certainly you have kick-started BiOS with a number of technologies. This includes GUSPlus³¹⁷— which I guess is an enhanced version of GUS— the Diversity Arrays Technology, ³¹⁸ and apomixis. ³¹⁹ The idea is that you place them on BioForge and invite people to collaborate in their development? ³²⁰

RJ: Well those are some examples; they are some of the best we have been able to come up with so far. But our vision of enabling people to make tools in a concerted fashion, and to make them freely available is much greater than that.

After all, while Linux is vastly more significant than what we have produced so far, I'm sure that the Open Source people would say that their vision is much more encompassing than the individual products that they have hacked to date.

Patent transparency

RP: Let's move on to Patent Lens then. As you said, one of the greatest problems facing biotechnology today is that the technology is very granular. Consequently any one solution can fall foul of a host of dominant patents, unforeseen rights, and patent thickets. ³²¹ Patent Lens, then, is the third plank in CAMBIA's strategy. As I understand

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³¹⁷ GUS*Plus* is a new reporter gene for use in molecular biology. There are GUS*Plus* vectors for checking transformations and screening transformants, and special vectors for use with TransBacter strains. http://www.bioforge.net/forge/entry.jspa?externalID=41&categoryID=3
³¹⁸ DArT, or diversity arrays technology, enables researchers to analyse plant and animal genomes with

no prior DNA sequence knowledge of the organism(s) being investigated.

http://www.bioforge.net/forge/entry.jspa?externalID=51&categoryID=4

319 Clonal reproduction of plants via seed, known as apomixis, has the potential to change plant

breeding technology. Apomixis would allow farmers to perpetuate, cheaply and undiminished, the high yield gains from hybrids. http://www.bioforge.net/forge/kbcategory.jspa?categoryID=9.

There are currently eleven active projects on BioForge.

http://www.bioforge.net/forge/kbcategory.jspa?categoryID=1.

³²¹ In several key industries, including semiconductors, biotechnology, computer software, and the Internet, the current patent system is creating a patent thicket: an overlapping set of patent rights requiring that those seeking to commercialise new technology obtain licenses from multiple patentees. The patent thicket is especially thorny when combined with the risk of hold-up, namely the danger that new products will inadvertently infringe on patents issued after these products were designed. http://ideas.repec.org/p/wpa/wuwple/0303005.html.

it, Patent Lens is a large patent database that you have developed in order to help people navigate the patent landscape.

RJ: Exactly right. And I would stress that a database is a necessary evil here; it is something you have to develop. Ultimately, however, it is the informatics of how that data is turned into knowledge, used, shared and sculpted that makes it valuable.

RP: Right, so Patent Lens simply provides the raw material. The intelligence lies in analytical tools that can mine that raw material. And the raw material in this case is patent documents: that is, the documents describing the technology, or method, for which a patent application is being made, and which are filed with patent offices when an application is made?³²²

RJ: Yes, and Patent Lens covers patents from most of the major jurisdictions. 323 It also covers all of life sciences, not just agriculture. Moreover, it is our intention eventually to include pretty much every patent in the world. In a couple of years, therefore, I expect it to be a very serious, comprehensive integrated public resource for patents.³²⁴

RP: What you are describing sounds very like the kind of database that companies like Thomson Corporation provides. ³²⁵ How does Patent Lens differ from Thomson's databases?³²⁶

RJ: We will never charge for it; that is our firm policy.

RP: Certainly Thomson charges a lot of money to search on its patent data. Indeed, some might find this ironic, since the first principle of the patent system is that patent applicants are awarded a time-limited monopoly on condition that they place details of their invention in the public domain?

Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearchbool.html&r=4&f=G&l=50&co1=AND&d=PTXT&s1=cambia.ASNM.&OS=AN/cambia&RS=AN/ca

³²² For a sample patent document see US patent number 5,599,670, one of Jefferson's GUS patents at: http://patft.uspto.gov/netacgi/nph-

mbia.

323 The major jurisdictions today are the US Patent & Trademark Office, the European Patent Office,

The major jurisdictions today are the US Patent & Trademark Office, the European Patent Office, and the second of the and the Japan Patent Office. Often referred to as the Trilateral Offices, these three offices process more than 85% of all patent applications filed world-wide, including PCT applications. http://www.trilateral.net.

324 There are growing calls (from both specialists and non-specialists) for a global patent database,

particularly now that all the major patent offices have started providing access to patent information on the Web. Recently, for instance, there was a call on the Patent Information Users Group mailing list, for a "WIPO sponsored global database where everyone in the world could go to search the world's publicly available patent information." The proposal was also that data from the US National Library of Medicine's medical citation database MEDLINE be merged with the patent data. http://piug.derwent.co.uk/archive/piug/1302.html. Some moves in this direction appear to be under way with Open Patent Services, but the scope and remit of OPS appears to be a little unclear. http://ops.espacenet.com.

http://www.thomson.com.

The Thomson Corporation describes itself as a "global provider of integrated information solutions" to business and professional customers." Amongst other things, its Thomson Scientific division sells a wide range of patent information and services, including the Derwent World Patents Index database, and the MicroPatent, Aureka and Delphion patent information services, http://scientific.thomson.com

RJ: Ha, ha, ha. Yea, Thomson and firms like them are a real treat. It's a classic example of how free marketeering has run amuck — a system that closes off information that really should be public, and then puts a toll gate in front of it. That is exactly what we don't want to see.

RP: So companies like Thomson are bad guys?

RJ: No. It's not like Thomson is doing a bad thing: They are just meeting a perceived need, and aggregating data that while public, is piecemeal. If anything it's the public sector that has dropped the ball here.

Anyway, we feel pretty passionately that this information — of all the information out there — is an absolute public good, and that it is a fundamental human right for people to be able to freely inspect it, and to challenge, query and learn from it, not just the privileged few who can afford to pay the Thomsons of the world to access it.

RP: How else will the Patent Lens differ from commercial information providers?

RJ: A second difference is that we will be turning it into a community annotated resource, where every patent application and patent can be "peer-reviewed". So we will be adding what amounts to a specialised and sophisticated Wiki to it, making it a commentable resource.

This will allow the public, including highly informed scientists and business people, to contribute comments on everything related to a patent, ranging from prior art that should be considered in its grant or revocation; sharing rumours about how a patent is being licensed, and even sending requests for license information that are publicly scrutinised.

A third difference is that we also plan to integrate business information into it, allowing people to see the power chains developing as a result of the acquisition of intellectual property.

A fourth difference is that we will publish APIs to encourage all users who wish to access the knowledge, and query it, to be able to do so.

A fifth difference is that when the data is in a well integrated and parsed form, we'll make it available for local implementations in the less developed world — for instance by patent offices or science agencies and universities — at cost or below.

Finally, and most importantly, the meta-data we are creating will allow users to obtain a "big picture" understanding of the patent landscapes. That above all will make Patent Lens stand out from the crowd.

RP: You often talk of the need for "patent transparency". That's really what you are trying to achieve with Patent Lens is it?

RJ: Yes. Right now the giant elephant in the room that no one wants to talk about is the way in which power is being consolidated by means of the intellectual property system.

RP: So the explosion in patenting that we are witnessing in biotech is not only allowing the private appropriation of more and more of the science commons, but it is doing this in a non-transparent way?

RJ: Exactly. And this is partly because business and patent databases are not harmonised. So while some in the business community with extravagant resources to pour into lawyers' BMWs are able to exploit both types of database, the citizenry normal people, sound small and medium enterprises, policy makers and scientists themselves — aren't.

Indeed, scientists — who are routinely used by the system — are complicit in the process, by neglect most often, not malice. They are so comfortable with the world of self-promotion and internally consistent incentives that they really don't want to know how their science is being co-opted to constrain options for development.

This is somewhat different to the Open Source software world. The culture there is very different in many ways, although what looks like greater altruism in the software world may just be a tighter congruence of interests: software developers actually use their software. It would be a rare thing for a medical biotechnologist, by contrast, to medically benefit in a reasonable time frame from the lab work she does.

So the Patent Lens database is a good step in the right direction, but it is just a first step. 327

The next step is to develop very sophisticated claims analysis parsing informatics, and to build up graphical tools that can create technology landscapes of patents and their status for many jurisdictions.

RP: So the data is just the starting point: the value lies in mining it and presenting it in a transparent way so that non-specialists can see what is happening?

RJ: Indeed. One of our goals is to shatter the fear, uncertainty and doubt, or FUD, ³²⁸ that surrounds patents — by providing a mechanism that can map out the patent

³²⁸ Fear, uncertainty, and doubt (FUD) is a sales or marketing strategy of disseminating negative (and vague) information on a competitor's product. The term originated to describe misinformation tactics in

³²⁷ A *Nature Biotechnology* editorial in May 2006 comments, "With the proliferation of gene patents and the increasing profusion of biotech patents and licenses with overlapping and competing rights, the ability to interpret and filter intellectual property (IP) has never been more important. Last month's announcement by Australian start up CAMBIA, and its initiative BIOS (Biological Innovation for Open Society), of the creation of an open-access patent database collating IP data from several national patent offices promises to radically improve that process." It adds, "CAMBIA's 'Patent Lens' is a freely accessible IP database that contains 2.5 million patents from the USPTO, EPO and PCT, together with a powerful search engine (http://www.bios.net/daisy/bios/patentlens.html). The interface makes possible searches of the full text of patents from all these patent databases. The database can only become more useful as its coverage is extended elsewhere (for instance, to Japan), but its intrinsic value is already clear. It is estimated that under exploitation of technical information (an estimated 80% of which is published in patent documentation and nowhere else) costs European industry alone \$20 billion each year — simply because the inability to access relevant patent information results in duplication of effort or the creation of products that overlap with prior art." Patently Transparent, Nature Biotechnology, Vol. 24, Number 5, May 2006.

http://www.bios.net/daisy/bios/daisy/bios/1824/version/live/part/4/data.

landscape and indicate whether a certain area is a minefield, or a green field opportunity.

RP: One of the first things you mapped was Agrobacterium wasn't it?

RJ: We have done several big analyses of *Agrobacterium* using the technology landscapes component of Patent Lens³²⁹; and we will be adding a great many more similar landscapes in the next year or two.

The good news is we while the patent nightmare is horrible, we are discovering that it is not *as* horrible as you might think — because most patents refer to old technologies.

RP: Presumably doing patent landscapes around Agrobacterium helped you develop TransBacter: you looked at the patent thickets surrounding Agrobacterium, and found a way of working around them?

RJ: Well, we don't like to use the term "work around", because it implies that we are inventing the same thing, but without the restrictions. The term we choose to use — and I think it is a good one to use Richard — is "work beyond".

In other words, we don't want to simply work around a cumbersome set of restrictions: we want to treat those restrictions as both a challenge and as an inspiration, and go way beyond them. We want to ensure that the next technology to emerge not only has the freedom to operate that our licence provides, but is actually better than the one it is replacing. So we want it to be a very positive move.

But to answer your question: yes, after spending years analysing *Agrobacterium* we used the results to work beyond it, and developed TransBacter as a result.

We hope that TransBacter will prove a seminal invention, by the way — not necessarily because it is so important in itself, but because it is such a good example of how things can be done differently.

RP: In talking about Biological Open Source you make frequent comparisons with the Open Source Software Movement. There are a growing number of other "free" and "open" movements today, including Open Access, Creative Commons, Open Data, Open Spectrum, Open Journalism, Open Politics, and so on. Why do you think all these open movements are springing up? What's the big picture here?

the computer hardware industry and has since been used more broadly. FUD is a manifestation of the appeal to fear. Although initially attributed to IBM, in the 1990s and later the term has been more usually associated with industry giant Microsoft. The Halloween documents (leaked internal Microsoft documents whose authenticity was verified by the company) use the term FUD to describe a potential tactic, as in "OSS is long-term credible ... [therefore] FUD tactics can not be used to combat it." More recently, Microsoft has issued statements about the "viral nature" of the GNU General Public License (GPL), which Open Source proponents purport to be FUD. Microsoft's statements are often directed at the GNU/Linux community in particular, to discourage widespread Linux adoption, which could hurt Microsoft's market share. http://en.wikipedia.org/wiki/FUD.

http://www.cambia.org/daisy/AgroTran/767.html.

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RJ: Several things are driving this. As information becomes more pervasive, for instance, we are seeing more abuses of it, and attempts to monopolise it. Moreover, these monopoly threats are more and more pernicious, and their results so evident, that people are putting a lot of effort into trying to fight them.

In addition, people perceive IP expertise to be a lucrative new business opportunity, so a cottage industry of IP specialists is developing, and this is encouraging further abuses, and new threats of monopolisation.

While the various free and open movements have a lot in common, however, we also need to stress their differences. Open Access, for instance, is not the same as Open Source, or indeed Biological Open Source.

RP: What differences are you thinking about?

RJ: Open Source is about the capability to use something, and so the focus is not just on getting it out there but getting it out there complete with every bit of enablement necessary for anyone to use it, including the legal permissions.

RP: You mean that Open Source implies making available not just the end product (the software), but also the ability to adapt that end product (i.e. the code)? The focus of Open Access, by contrast, is exclusively on making scientific research freely available, not on providing the tools or expertise to exploit that research.

RJ: Precisely. Again, it is the capability to use this stuff, Richard, that is the critical feature

So it is not just about getting it out there. After all, that has always been the ethos of scientific publication, and that is *all* that science publication does. Publication doesn't get the whole know-how package out there; it doesn't get the permissions package out there; ³³⁰ and it is not designed to address the infrastructure — the physical constraints — issues. ³³¹ To be truly Open Source you need these other things too.

RP: And presumably you would see Biological Open Source having more in common with Open Source than Open Access? When you distributed GUS, for instance, you didn't just release the basic information, but you also made available a detailed handbook explaining how to use it, plus thousands of tubes of DNA sequences?

RJ: That's right. It might help to see the difference if you think about the term A2K, or Access to Knowledge. We are not about A2K, but C2UK, or Capability to Use Knowledge. That is also what BiOS is about, and it is what Open Source is about.

RP: Knowledge is not enough in itself.

³³⁰ Indeed, there is some disagreement between the different factions of the Open Access Movements as to whether Open Access implies also using Creative Commons licences.

https://arl.org/Lists/SPARC-IR/Message/340.html.

331 Again, very few Open Access advocates appear to see it in the context of the digital divide. An exception is Professor Subbiah Arunachalam. http://poynder.blogspot.com/2006/05/why-india-needs-open-access.html.

RJ: Precisely. There is a huge misunderstanding amongst pundits about this, and also among some of the practitioners too. If you want to talk about Open Access, in which you share all the data, that is fine. Indeed, I'm all for Open Access.

But it is the capability to use knowledge that's key. And that capability must encompass the ability to deliver innovation, complete with freedom to operate and other permissions, along with the investments necessary to make a change in something other than a career. So the Open Access Movement is only half way there.

Utterly love people

RP: I want to finish by returning to Richard Jefferson the man. Earlier on you referred to Thomas Jefferson as being a great-great grand uncle of yours. Is that for real?

RJ: Actually, I have no evidence of a link, but my dad, who liked that sort of thing, assured me he had traced the family tree back to Thomas' brother or perhaps another more distant connection. But my dad died before we reached any conclusions, and frankly I have little interest in it. Mostly I think of Thomas Jefferson as an eponymous inspiration.

RP: The name Jefferson suggests Anglo Saxon origins I guess.

RJ: Sure, we are substantially Anglo Saxon. However, one of my great grandparents was Portuguese; and my mother was an Irish and French hybrid. So we have all the usual European genes there!

RP: Nevertheless, the main branches of your family have been in America for a good few generations?

RJ: Oh, yea. In fact, my dad was a sixth generation Californian. So we were not like fresh off the boat.

RP: You mentioned that your parents divorced before you were born. How often did you see your father as you grew up?

RJ: As I said, we were raised by my mother. So I saw my father about once a year, at an uncomfortable lunch at which my brother, sister and myself had to be on good behaviour at some restaurant that dad viewed as a treat, but we thought of as torment (we were from the other side of the tracks from dad).

Later, however, we ended up becoming extremely good friends, and it turned out that he and I had an awful lot of similarities. So it was kind of fun to become pals with him later in life. I guess genetics really does work!

RP: What age were you when you became friends?

RJ: I started to get to know him pretty well in my 20s, while I was at university and in grad school. Later, when I was an adult, we got together whenever we could internationally. When I was working for the FAO, for instance, I did a lot of work in Asia. At one point my father was on tour in Japan with the Concord Jazz All Stars, and Joe Pass, ³³² so I zipped over to Japan and hung with those guys for a while. That kind of thing was not uncommon later in life.

RP: You mentioned you had two siblings. Are they scientists too?

RJ: One is. My brother Mike is a very fine senior physicist with IBM. Like me, he is a tool builder, and he is an inventor of some very interesting technologies in optical data storage at IBM Almaden Research labs.³³³ He won the Kingslake medal a few years ago,³³⁴ and he does single-handed transpacific sailboat racing and other pretty extreme stuff.

My sister is a very good musician, a gardener, a French language teacher, a passionate supporter of what we are doing here, and she works in a violin shop in Berkeley.

RP: And you now have your own family?

RJ: Yes, although that is quite recent: I was an inveterate bachelor until about five years ago, when I married an old friend of mine. Osmat is a plant virologist, ³³⁵ and a Druze from the Lebanon. ³³⁶

RP: How did you meet her?

RJ: I first met her in Colombia about twelve years ago, and we dated off and on for seven years. Then one day at the urging of a good friend, Susan McCouch³³⁷ — who was on sabbatical at CAMBIA — I just called her up and asked if she was interested in taking a holiday with me.

We had an incredibly nice time, and after she went back to Madison — where she was living at the time — we found ourselves talking a lot on the phone. Eventually we just decided we should live together.

RP: You are both in the same line of business then?

³³² Joe Pass was a virtuoso jazz guitarist. With guitarist <u>Herb Ellis</u> Pass recorded the very first album on the new <u>Concord Jazz</u> label, entitled simply "JAZZ/CONCORD" (#CJS-1), along with bassist <u>Ray Brown</u> and drummer <u>Jake Hanna</u>. http://en.wikipedia.org/wiki/Joe_Pass.

333 Located in Silicon Valley, Almaden Research Center is one of eight IBM Research Division

facilities worldwide and a premier industrial research laboratory. At Almaden, some of the finest minds in the industry focus on basic and applied research in computer science, magnetic and optical storage technology, physical and materials science and technology, and scientific and technical application software. http://www.almaden.ibm.com

http://www.spie.org/AboutSPIE/index.cfm?fuseaction=Awards_Kingslake.

³³⁵ Osmat Azzam Jefferson is now a BioForge Senior Scientist. http://www.cambia.org/daisy/bios/about_BiOS/team.html.

The Druze are a small, distinct religious community based mostly in the Middle East, whose religion resembles Islam, but is influenced by Greek philosophy and other religions. The Druze reside primarily in Lebanon, Israel, Syria, Turkey and Jordan. http://en.wikipedia.org/wiki/Druze 337 http://en.wikipedia.org/wiki/Druze

RJ: More or less. Osmat was in charge of virology at the International Rice Research Institute, ³³⁸ and when we finally got together she was a project manager in the optical mapping of the rice genome.

RP: And you have a young child now?

RJ: Yes, a totally fantastic four and a half year-old daughter called Tanja.

RP: You drew a parallel between yourself and Richard Stallman earlier. He, like you, is from a single parent family. When I spoke to him he talked a lot about his constant search for a community, and I asked him if he thought there was a connection between that and the fact that his family had split up when he was a child. He agreed that there could indeed be a connection. You too seem very keen on the idea of building communities ...?

RJ: Oh very much.

RP: Do you think there is any connection between your urge to create communities and the fact that your family broke up when you were a child?

RJ: I am so embedded in my own self-image that you are probably in a better position to answer that than I am.

However, I would hesitate to draw too strong a parallel between Richard Stallman and me in that regard. The impetus for me is that I utterly love people. I don't know Richard personally, but we have friends in common, and they indicate that he's not a great fan of people. I love people; and I totally enjoy their company. I love listening to their stories, making them laugh and sharing the wine and the music and so on.

There was an editorial in *Nature Biotechnology*, ³³⁹ by the way, that compared me to Linus Torvalds. That parallel may not be too straightforward either, as I'm told that Linus is notoriously introverted, whereas I am notoriously extrovert.

RP: I'm curious as to why you have put so much effort into the cause of Biological Open Source. Gary Toenniessen told me that you could have got your own lab at any number of different universities and you could have been a highly successful academic. But you gave up on academia, preferring instead to devote all your energies to developing CAMBIA. Why?

RJ: What Gary perhaps meant is that I could have had my own lab and tenure at a major university if I was willing to play that game. Actually I did try to establish CAMBIA while associated with a university — in fact I tried every University in Oregon! — through applying for professorships. But none that I applied to wanted an initiative in house that would invent (rather than discover) and then give away the

The International Rice Research Institute (IRRI) is an autonomous, non-profit agricultural research and training organization with offices in more than ten nations. The Institute's main goal is to find sustainable ways to improve the well-being of present and future generations of poor rice farmers and consumers while at the same time protecting the environment. http://www.irri.org 339 *Open Sesame*, Nature Biotechnology, Volume 23, June 7th, 2005, http://www.bios.net/daisy/bios/810

inventions to people who are not powerful. They wanted fairly conventional grantsmanship and career track; no shaking the tree.

So I realised early on that I can't respect a system which, while it is clearly a very productive system by its own metrics, makes you a creature of itself. It becomes clear from day one that in order to advance yourself you have to get this type of grant, be on this committee, be part of that academy, publish these types of papers and so on.

RP: Some might say: what's wrong with that?

RJ: I won't say what is wrong with it. Let's just say that it wasn't right for me. The outcomes of University work are about self-promotion, and the last step of deliver to society is "publication", not engagement, tuning and delivery. And the idea that society should help focus the questions that they ask is not very attractive to academics. Certainly it was clear to me that the system isn't helpful to others in the way that I would want it to be.

I also realised that I needed to learn so much that I couldn't have learned in that system. And it would also have been so self-gratifying to take part in that world — and I recognised an element in myself that was attracted to the system. An element I had to fight.

RP: Why?

RJ: Because I know I am really, really bright, and I am really, really articulate. And if you have those qualities and find yourself in a system that values them, then you can so easily end up spending all your time stroking your soul, instead of stoking your soul.

RP: You seem to have an unusual attitude to life. Most people tend to say to themselves: "This is the world I am part of; this is what has to be done in order to succeed; this then is what I will do." But you don't? Why?

RJ: In some ways perhaps because I came from a performing arts family: as I said, my mother was an actress, and my dad was a music producer and promoter. For us there has to be passion. Not just passion for ourselves, but a passion to see that what we have done has made other people happy too.

So if I am going to be really creative, and make a real difference, it has got to be by looking into other people's eyes and seeing their happiness, their spark, their laughter. What's certain is that you can't do that in academia. The problem with the narcissism of academia is that the only *real* arbiter for success is whether it has made *you* happy.

Not a raving socialist

RP: In what situations do you find yourself looking into people's eyes and see that you have made them happy?

RJ: Well, it gets harder and harder. I got out of the "development set" when I began to realise the seduction of trying to help people is in many ways as bad as academia, since it is just as narcissistic. It's like I have had to flee from one support network to another [laughs], and then I abandoned that one too!

To put it bluntly, I don't know the answer to your question. I wish I did. But certainly the most personally satisfying times for me are when I am asked to give talks — especially in inter-disciplinary settings — and I give a really good presentation, when I nail it.

RP: What is a really good presentation?

RP: For me a really good presentation is where I feel I am on a roll in explaining my ideas, and I see people in the audience having an "ah ha" moment.

Or it could be when a postdoc or, god forbid, somebody more senior than a postdoc, comes up to me afterwards and says "Man, I see what you mean." That is when it is really good.

You know, maybe the single hardest feature of trying to create systemic change, through strategic structural intervention — and that's really what CAMBIA BiOS is about — it that the immediacy of impact is just not there. You have to have the absurd discipline and confidence that something with a ten or twenty year horizon will and must happen. But that also means that there really isn't much positive reinforcement along the way. In fact, it's probably the hardest feature of holding it all together — not being seduced by short term metrics, or the blandishments of having people being dependent on us.

RP: Given your passion for helping the developing world I assumed that you must have some political affiliation, or at least a powerful political conviction. However, when I asked Gary Toenniessen about your politics he assured me, "Richard is a typical liberal academic, not a raving socialist." Biological Open Source doesn't have to be about helping the less advantaged: it could just be viewed as a way of making biotechnology more efficient. Why do you also want to help the developing world?

RJ: Just decency, and a belief in fairness. My whole life has been draped around this fairness thing. Once you accept that fairness and decency are a very good set of rules to live by, then it isn't very difficult to hold up a litmus test and say: "Is this promoting fairness and decency, or is it not?" And if it is not, then you do something about it. It is such a simple idea, but the fact is that if things aren't fair then you either do something about it, or you become part of the problem.

RP: Let me turn my question around: if it is fairness and decency that motivate you, why choose Biological Open Source as the vehicle for promoting that, and not some other worthy cause?

RJ: One reason is the chops I guess. No great artist can perform unless they have got the chops, or what you might call the technological skills. That is utterly critical Richard: to be able to contribute to any thing, whether it is in art or music, you have got to have your chops.

And the chops for me was science: I was really very good at it. It was the canvas on which I could go beyond my Jackson Pollock.³⁴⁰ I could actually do really creative and fantastic things: It was the area where my creativity could find so much technical capability that I didn't have to think about it any more. And that is the point at which you become creative.

And of course the more fundamental and non-negotiable reason is that biological innovation — whether in public health, natural resource management or agriculture — is at the root of economic and social development, and so the bedrock from which human societies can build

After all, it's food, health, environment and economy that are the core requirements for people to achieve anything for themselves. That means they must be biological innovators. Yet we've been removing this capability from the equation in ways that are unjust and ultimately counterproductive for everyone.

RP: Gary Toenniessen suggested that I ask you what you view as success.

RJ: Oh, man. Well it certainly isn't being on any boards or committees, or in academies. That would be embarrassing actually. I have never gotten any prizes, and I am not on any committees or boards — I am just not that kind of person, and everyone seems to know it ... [pause] ... actually I did get one prize: just last year the American Society of Plant Biology³⁴¹ gave me a little crystal clock. I found it particularly ironic, by the way, that since I got it in Seattle it was set for Pacific Daylight Time, and I couldn't figure out how to change the time to Australian time. So I left it with a friend in the USA who really deserved it more than me.

That was the first time scientists ever gave me any award, or any recognition, and I have got to say it gave me a really mixed feeling.

RP: Why?

RJ: Well, it was so cool to have my peers say that what I am doing is worthwhile. But then I realised that the thing that was making me feel good was not their recognition of what I was doing, but the fact that their recognition demonstrated that this community could be reached. I had almost written off the academic world as being unreachable. It was weird.

But to go back to Gary's question. For me, success — at least in my drive for CAMBIA BiOS — will happen when our approach has so much traction that this way of democratising innovation becomes the norm, and I no longer feel that my inputs are necessary or unique. Then I can take a break and explore other avenues of creativity and life.

³⁴⁰ Paul Jackson Pollock was an influential American painter and a major force in the abstract expressionist movement. His work was a great influence in 20th century art. http://en.wikipedia.org/wiki/Jackson Pollock.

http://www.aspb.org Jefferson received the 2005 American Society of Plant Biology "Leadership in Science Public Service Award" for outstanding contributions to science and society.

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