Richard Jefferson

Science as Social Enterprise

The CAMBIA BiOS Initiative

Nearly four billion people live on daily incomes lower than the price of a latté at Starbucks. Most of them make dramatically less than that—and from that income, they must acquire their food, their medicine, their shelter and clothing, their education, and their recreation, and they must build their future and their dreams. Their lives, and the quality of their lives, hinge on biological innovation.

Biological innovation is the ability to harness living systems for our social, environmental and economic well-being. It is the oldest and most fundamental form of human innovation, involving as it does the getting of food, the striving for health, the making of homes, and the building of communities. The wealth created over the millennia through the domestication and husbandry of plants and animals has powered human society.

Of all areas of biological innovation, agriculture is the most important, affecting our environment, our health, our economies, and the fabric of our societies. The world's poorest nations depend largely on agriculture for their economic survival as well as their food, fuel and fiber. The challenges of innovation to create and sustain productive and environmentally sound agriculture are even more pronounced in these societies. Any failure to do so has enormous implications for the global community, over and above the social, economic, and environmental impacts.

For thousands of years biological innovation has been informed and guided by keen observation and the accumulation and sharing of generations of empirical knowledge. Farmers selected better crop varieties and livestock breeds, and devel-

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oped management strategies to maximize their performance. Seeds were shared as a practical matter of survival and each improvement formed the basis for further innovation. Because seeds of most crop plants breed true, the ease of sharing, and the barriers to doing so were minimal. As with digital information, it is hard *not* to share, and hard to impose limits on sharing, so norms evolve to maximize value from this inevitability.

> Extraordinary efficiencies occur when the tools of innovation are shared, are dynamically enhanced, have increased levels of confidence (legal and otherwise) associated with their use, and are low or no-cost.

But the post-Enlightenment explosion of possibility that began when the unprecedented power of science became focused on food, agriculture, health, medicine and environment seemed to dwarf all previous attainments. And indeed in the past hundred years, with the advent of genetics, the pace has been gathering; the last thirty years has seen an unprecedented dynamism in life sciences that is being hailed as a "biotechnology revolution." But in this revolution, biotechnology is rarely being applied to the critical issues of alleviating poverty, eliminating hunger, stewarding natural resources, and preventing or curing the diseases of the disadvantaged. The margins are small, the markets are modest, and the challenges are great. Are the paradigms and practices that have emerged to harness science for society sufficient to engage, and even solve, these seemingly intractable problems?

Today control over agricultural biotechnology is effectively limited to a few multinational corporations who integrate seeds, agrichemicals, and biotechnology. This disturbing consolidation of power is matched with a trend toward "me-too," big-ticket "innovations" of remarkable dullness. How many herbicide-tolerant big acreage crops are enough? Similar trends are surfacing among the large pharmaceutical companies, collectively known as "big-pharma": how many blockbuster lifestyle drugs does society need?

Within the value system they respect, and according to their own success metrics of profitability, big agriculture and big pharma are not abject failures, but they surely are not enough.

To address the myriad challenges of agriculture, environment and health that are local in nature and modest in market or profit margins will require vigorous, competitive, local-scale small to medium enterprises creating a business and innovation ecology. It will also require a biological innovation culture where the costs of innovation are low, and the power and relevance of technology are high. It will require leveraging the contributions of diverse people and institutions to create tools that better engage science into an integrated and economically sustainable social agenda.

The mission of CAMBIA, of which I am the founder, is to advance this set of required capabilities so that biological innovation can address the human challenges of the 21st century; the BiOS (Biological Open Source) Initiative is CAMBIA's mechanism for achieving its mission.

The term "open source" describes a paradigm for software development associated with a set of innovation practices. The concept evolved out of the "free software" movement, and is often merged into the expression "free and open source software." (See text box.) Several features together qualify a project as "open source."[1] These include full disclosure of enabling information including documented source code and the use of legal instruments such as copyright licenses to confer both permissive rights and responsibilities; they bind contributions into a commons that is accessible to all who agree to share alike. Typically, certain practices and cultural norms are associated with distributive innovation, although this is by no means required; some very successful free and open source software projects have only a few serious contributors, while others have thousands.

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How Do you Make Money in Open Source?

Free and open source software has rapidly engendered highly productive and profitable business models that create value from the non-rivalrous[2] use of software components. Examples of such software include the famous Linux operating system, the Apache web server, databases such as MySQL, myriad programming languages such as Perl and Python, and the Firefox web browser. These types of open source projects, co-developed by thousands of programmers, and shared through creative licensing which demands covenants of behavior rather than financial consideration from the licit community of users, have transformed the information and communications technology (ICT) sector.

Most of the high-profile free and open source software projects that have affected both the sector and the public's imagination have been "tools" and platforms, rather than end-user applications. These allow users to build fully commercial web applications, with high functionality, on robust, dynamic platforms, with no reach-through financial obligations. The economic success stories of free and open source software thus are not Linux and Apache, but eBay and Google. The business models that are shaking the ICT world are not the modest ones selling support for open source products, such as Red Hat Linux. The signal successes are commercial enterprises that create wealth by providing new social value. Many ask, "How do you make money in open source?" The answer: you make money not by selling open source, but by *using* open source.

associated with their use, and are low or no-cost. Rent extraction from the process of innovation is reduced, transactions costs are minimized and developers focus their resources on creating revenue by providing products and services and enlarging markets.

This concept is fully generalizable—although clearly the specifics are not—and a large part of CAMBIA's BiOS initiative explores and extends the software metaphor. BiOS strives to create new norms and practices for dynamically designing and creating the tools of biological innovation, with binding covenants to protect and preserve their usefulness, while allowing diverse business models for wealth creation, using these tools.

In the first part of this paper I discuss the simultaneous burst of knowledge in molecular biology and the precipitous decline of a commons of tools, using examples from plant biotechnology. I develop a practical model of innovation, highlighting how biological innovation is stymied or deflected to high margin applications if tools are not freely available, continuously improving and embodying the permission to deliver work product into markets. I explore parallels, divergences and resonance with open source paradigms in software engineering. The rest of the paper focuses on CAMBIA BiOS Initiative activities: the BiOS Framework, the PatentLens, and the BioForge, and the creation of a "commons of capability" through which new actors, including farmers and small-to-medium enterprise, can use science to create viable innovations relevant to their needs.

POWER, TOOLS, AND THE COMMONS OF CAPABILITY

Twenty-eight years ago, I began a project to develop a set of tools—of techniques—in molecular biology that could help researchers in that field visualize how genes and cells functioned. Like virtually all scientific work, and most technology development, it was inspired and informed by what came before. And like all tools and methods, it depends on the use of other tools and methods.

Some years earlier, Ethan Signer, Jonathan Beckwith, and others had made a remarkable contribution to our toolkit for understanding how genes worked in bacteria. They conceived of a single tool that would allow scientists to learn how genes turn on and off in a bacterium. The tool "hooked up" the beta-galactosidase gene (called lac) for which they had simple measurement tools and assays, to another gene (called trp) for which measurement was difficult, but whose behavior they were keen to understand. In so doing, they measured the trp gene by actually measuring lac. This *tour de force* of microbial genetics used publicly available technologies and methods—in fact it was then unthinkable that there would be any other kind. This occurred well before the advent of recombinant DNA, which now allows apparently sophisticated genetic experiments to be done very simply. And it occurred well before anyone had even contemplated patents on life sciences.

Years later, I thought, why not use the same concept to understand how cells in animals and plants work? Why not have the organisms talk to us about their environment, through their genes? I set out to develop a parallel system, using a different enzyme and gene that could function in these new organisms. The one I chose was prosaically called GUS.

As I worked, I became increasingly aware that the availability of tools, and their capabilities, completely dictated the science that was done, and who was doing it. As an undergraduate at the University of California and the University of Edinburgh, I worked in some of the key laboratories responsible for inventing recombinant DNA methodology. I watched, time and again, how an entire field of scientific endeavor would almost instantly change course when a new technique—tool—was provided.

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When I first developed the GUS technology, the scientific community I was originally working within—which studied animal embryo development—was not very interested; the tool just wasn't needed much. My first paper on this topic was received with an ill-stifled yawn. But I moved my interests to plants and agriculture, during the heady dawn of plant molecular genetics.

Efforts to transfer beneficial genes into key crops such as cotton, soybean, maize, and rice were running into a brick wall. There was no way to visualize success, nor to measure and improve on first steps. The GUS reporter system made visualizing genes and their action in plants very easy and efficient—it was proving to be a very powerful tool at the right time.

In 1985 I arrived for my postdoctoral research at the Plant Breeding Institute (PBI) in Cambridge, England, a vigorous international group of colleagues who were at the cutting edge of technology development and exploration in molecular plant sciences. The Plant Breeding Institute was also one of the few sites in the world that combined the patient and disciplined craft of successful agricultural innovation, such as plant breeding and agronomy, with the impatient and fermenting world of molecular biology. As well, the Plant Breeding Institute was still at that time an entity focused on the public good, a non-profit institute that earned substantial income for the U.K. government through royalties on its own crop varieties.

At Plant Breeding Institute, my colleagues[3] and I designed and conducted the first field test of a transgenic food crop. It was also the first BioSentinel experiment: a gene we wished to study was fused to the GUS gene, to conduct a field trial asking a fundamental question about how genes act under field conditions. We used public money, in the public sector, to ask a fundamental question for the public. The field was planted on June 1, 1987—completely by chance one day before Monsanto's first field trial. The lessons of the field trial were fascinating. We found that gene activity in a field is extraordinarily variable, and our preconceived laboratory-based notions of how genes worked would turn out to be very inadequate when dealing with field populations. Our technology, though cutting-edge, was not up to the questions that real-world agriculture presents.

The Plant Breeding Institute was an international institute, with students and scientists from all over the world. The institute had a reputation for brilliant wheat breeding and genetics, so most of the countries whose agriculture depended on cereal production would send their scientists to us for training. Many of the students and postdoctoral fellows in the Molecular Genetics department came from India, Pakistan, Turkey, the Middle East, China, Africa, Latin America, and Eastern Europe. Most of them indicated that this period in Cambridge was their one shot at career establishment. If they published a paper or two in a good journal, they had a reasonable chance of employment back home. And some of them confessed that they likely would not be able to use the new biotechnologies to effect any change in their home agriculture or economy. Not only did they lack the finances and infrastructure to make use of these high-tech tools, but the tools were better for science than for problem solving.

These people were exemplary of perhaps the most crucial but neglected resource for social advancement through science: dedicated and capable people. I observed, however, that instead of using their own experience to inform the science that was being done and the technologies being developed, their own world-views and self-images were rapidly aligning to the incentive and reward system of the prevailing and fashionable science trends. And their energy to change the options in their home countries was dissipating.

By early 1987, after intensive experimentation in-house, we had assembled hundreds of copies of a GUS kit of dozens of DNA molecules and a comprehensive "how-to" manual. I rewrote the big "GUS Manual" and sent it to a mass-mailed newsletter called *Plant Molecular Biology Reporter*, which was distributed free to thousands of scientists rather than initially publishing a peer-reviewed scientific paper, which I eventually did.[4] The grapevine is also a powerful communications tool in science; soon many people were hearing about this new technology that would let them see the cells and tissues where their gene was functioning. It would also allow let them optimize gene delivery experiments; this was an urgent priority for both industry and academia. At that time no important commercial crop had been genetically engineered, so requests started flooding in for the GUS system. And I started sending out hundreds, even thousands of samples, and the User's Manual, all with no licenses, to scientists in dozens of countries, in both the private and public sectors. I only included a letter saying that while I had filed for a patent on the system, I wanted everyone to use it, and royalties—if any resulted—would go back to creating the next generation of technology.

I sent the kit to scientists at Agracetus in Wisconsin who were working, with little success, on transferring genes to soybeans. They had no idea if the genes they were introducing with their new process were actually making it into the right cells. One of those scientists, Paul Christou, told me of their thrill when they were able to immediately visualize gene transfer with the blue color of the GUS test, and soon succeeded at introducing genes into soybeans for the first time. And they could only do it with GUS, which also had no apparent restrictions. They were delighted, of course, as was Monsanto, for whom they worked.[5]

That work with GUS turned out to be the single biggest money maker in plant biotechnology, possibly ever in agriculture. Monsanto developed its RoundUp Ready™ soybean line, which it ultimately used to breed most of the transgenic soybean plants now covering the world, using GUS to select plants.

Within a year after we began widely distributing the GUS technology, hundreds of new avenues of plant science were emerging. Within two years, breakthroughs in maize, soybean, cotton, and many other crops occurred. New technologies were invented that used the tool in its very creation and optimization, such as particle bombardment (the tool that Agracetus had been exploring) and critical improvements were made to core technologies such as gene transfer by *Agrobacterium*. GUS demonstrated that one powerful new tool, widely distributed, could rapidly change an entire field.

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The idea of *intentionally* changing the directions of inquiry and the demographics and economics of problem-solving by designing and providing new tools would shape the next thirty years of my professional life. With increasing exposure to the realities of practical agriculture, intellectual property, policy and business, my definition of "tool" matured. It came to include not just the technologies needed for scientific investigation, but also the critical normative, economic, policy, legal and business instruments to convert investigation into socially and economically sound innovations. A business model really can be a tool.

Enclosing the Toolkit: The Case of *Agrobacterium*

But while this period hinted at the vast potential for new tools emerging from molecular biology to lead to rapid innovation, it also saw the rush to privatize the kinds of tools that had always been seen as a commons, as exemplified by the adventures of *Agrobacterium*. When I started to work at Plant Breeding Institute, plant molecular genetics was in its infancy, and only three or four major institutions had serious capability in this nascent field. All of them were using

Agrobacterium-mediated transformation as their fundamental tool for transferring genes to plants.

Several years earlier, several public research teams had discovered an astonishing biological phenomenon.[6] A soil bacterium long known to be the agent of a familiar plant disease called crown gall was found to cause these tumors on plants by a hitherto unforeseen mechanism. The bacterium—*Agrobacterium*—actually inserted into the plant, by "natural" genetic engineering, a component of its own genome, and in so doing reprogrammed the plant to produce a "gall" and new food for the bacterium. This phenomenon, a sort of biological Trojan horse, was thought to be unique in the biological realm. And everyone in plant biology saw that it was to be a critical tool in the development of new options of biotechnology.

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The groups that first made the discoveries were all in the public sector, funded largely by public monies; they could all see that *Agrobacterium* would be a fundamental tool of the field. In spite, or perhaps because of all this, the gold rush for patenting started. And not only did the pioneer groups in the field file patents; over the next twenty years over a thousand patents were filed—and granted in many nations—that covered various aspects of *Agrobacterium*-mediated gene transfer. Some were so minor and trite as to be laughable were they not presumed valid by law, but they still produced a thicket of rights, nearly impenetrable even to the specialist.

And of course the pioneering patents were fought over viciously. To monetize the patents, the rights were sold to the highest bidder. But the rights were not clear; bitter wrangling over primacy with the fundamental patents continued for almost twenty years before any legal clarity emerged. Of course the winning bidders ended up being large multinational companies, notably Monsanto (either directly or by acquisition); and in most cases the payments to universities and institutes were negligible or even negative. But the effect of increasingly consolidating these patents in a few hands was anything but negligible.

Soon, public and private sector scientists were patenting their developments as a matter of course. Some of these findings became powerful patent estates that potentially blocked most of the world's agricultural enterprises from using these tools without permission, often at any price. For example, Japan Tobacco discovered and patented a method to use *Agrobacterium* to transfer genes into rice and other cereal crops.

The case of *Agrobacterium* was repeated with many subsequent technologies, ranging from genetic selections, to the wholesale patenting of promoters and genes,[7] to gene inactivation technologies (such as RNAi and co-supression). Again, the contents of many patents were breathtakingly obvious to all practitioners in the field, but for small- to medium-sized enterprises these patents still served as a real disincentive to innovate. They also extracted huge rents from industry, and raised transaction costs to an unbearable level, mostly because the patent landscapes were so opaque and complex. This trend has accelerated markedly and now applies to medical as well as agricultural technologies. The consequences are clearly that only the biggest-ticket targets are getting attention. But blockbusters alone don't make for good agriculture, good environmental management or good public health.

In 1985 the sector was viewed as exhilarating, entrepreneurial and vibrant, with almost unlimited possibility for doing good in world agriculture; within a decade or so it had all but stalled into a corporate oligopoly, with vertical integration, ossified and oppressive business models, and massive patent portfolios tying up almost every key technology and platform used in the field. And though nearly all the pioneering discoveries were made in the public sector, they were not reserved for public use or for the small-to-medium enterprise sector that the public trusts. It is no surprise then that the public now views the entire agricultural biotechnology sector—as manifest in the outcry against GMOs—as being a tawdry exercise in failed promises, industry consolidation, public sector abandonment and simplistic agendas. Perhaps the greatest crisis that has emerged from this corporate control of problem-solving in agriculture is that the public now seems to have very little confidence in the use of *any* science in agriculture! This has indeed been a case of throwing the baby out with the bathwater.[8]

Biotech Bazaar: Tools for Sale

At the Plant Breeding Institute, I was working with colleagues from scientific cultures that had historically used the discoveries and technologies that came before to grapple with the next generation of scientific challenges, with the tacit understanding that this process would naturally yield real-world solutions, such as plant varieties and agronomic processes. After all, the Plant Breeding Institute paid its way in the world by doing just this.

But that world was collapsing. The distinction between discovery and invention was being blurred as patents were filed on each component; that process entirely altered the dynamic of translation into true innovation: delivering the products of science and technology to the marketplace. It was now possible to control the tools and platform discoveries themselves, not just the products that they created.

In the early 1980s with the passing of the Bayh-Dole Act, universities in the United States were actively encouraged to patent their work products. The Act's fundamental policy goal was to see publicly- funded science and technology better used by society, by encouraging industry to adopt it. The trend of public agencies using the patent system exploded internationally into a filing frenzy. No one foresaw then that the fragmentation of the platforms and tools would make it so complex, so expensive and so intractable to assemble the "freedom to operate and freedom to innovate." Nor did we see that the resulting innovations themselves would be so few, so stodgy, and so slow to reach the marketplace.

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At almost the same time, the advent of recombinant DNA and the ability to determine DNA and protein sequences massively increased scientists' ability to explore, understand, and manipulate living systems, or at least living organisms. So every new life sciences discovery could be, and often was, dressed up as an invention and subject to patent; as the patent claims were granted, they cast a huge net over the possible options. Public sector coalitions would frequently compete with private big-science, and who usually won the plum of patent monopoly? The privatized efforts. Was this right, or necessary?

I began my own foray into patents and their importance when I arrived in Cambridge in 1986. I discovered close relationships between some large companies and the public-sector institute where I was based, shaped by personal histories and friendships. I didn't view this as a bad thing. I shared all my ideas and technologies with them from the outset. In fact, I shared with pretty much anyone who was interested, thinking that—in economic terms—my ideas were non-rival; sharing didn't cost me the ability to use them myself. How wrong I would later prove to be.[9] And how times were changing.

One company, ICI,[10] was keen to use GUS in its commercial development programs; like many companies it was mostly interested in having clear rights to do so. ICI suggested that I patent my technology so it could be sure it would have access to GUS in the future. I didn't understand the logic at the time, but I took the first steps and filed a patent in the United Kingdom and the United States, with a filing date in 1986. The University of Colorado, where the first stages of the work had been done, had waived its interest in patenting it.

Thus began a long and painful learning process of partnerships with powerful attorneys in which I watched patent-craft by The Masters. It took almost seven years for my first patent to issue in the USA, and nine years for the one with most of the valuable claims. Even when it was issued, complex agendas and issues[11] kept me from licensing the patents or even having a clear title for quite some time. This delay wrought havoc with my ambitions to use patents to create and fund CAMBIA, and when revenue did come in, it was in sporadic bursts, and barely in time to make payroll.

As a technology, GUS has had a surprisingly long shelf-life, and is unusual in being a largely stand-alone technology. If one has the "right" to put a gene into a plant, GUS remained a useful and legally usable tool to monitor that gene and its activity. But it turned out that even that right, the legal permission to transfer a gene to a plant, proved to be a critical and contentious issue because patents are opaque and licensing rights even more so, and because advances in the life sciences are so interdependent.

Wheels and Spokes: The Interdependency of Technologies

The patent system is so complex it is almost awe-inspiring. Single patent documents can run to hundreds of pages, with arcane language that few understand, and rights that courts interpret and re-interpret on the fly. Thousands of these can exist in a single field of innovation, with many thousands more latent in the system. One or two—or none—may be, or may unexpectedly become, dominant. Fundamental biological processes, such as the ubiquitous gene-regulation mechanism, RNAi, have been patented. Most of the important genes of many important organisms—humans, rice, maize, mice- have been subject to patent applications and sometimes grants, many of them contestable by many separate claimants. The platforms on which we must build are privatized and enclosed, but the owners and their ambitions are completely unclear; the platform for future innovation is built on shifting sand.

But worse, while the ownership of the "patent" itself is usually a matter of public record, the ownership of the *rights*—the most important feature of a patent — is completely obscured. Nowhere, in most jurisdictions, is there recorded or available the patterns of power: who owns what rights. A university may own hundreds of patents, and may have sold off the rights to any of the useful ones, but who bought them? The answer is rarely clear.

When a small company licenses a patent, or develops its own patent portfolio, to whom has it licensed and on what terms? The patterns of power and ownership are as important—and in the aggregate perhaps more important—than any other feature of a patent grant. And yet we have no public information whatsoever, except in piecemeal and scattered disclosures. Some jurisdictions, including Brazil and France, do impose a responsibility on licensees to disclose—at least to the patent office. But most do not. And none make it easy to find this information. This makes it difficult, if not impossible, for a researcher in a small- or medium-scale enterprise to assemble all the licenses or capabilities needed to refine and adapt a tool and ultimately to create an innovation that will help meet basic needs.

And researchers need this information because few discoveries stand on their own, and even fewer inventions. Not only do they each depend on the pre-existing knowledge base; they almost always incorporate components of many other technologies in their execution. This is particularly true of "meta-technologies," tools and technologies with broad effects used by communities of innovators quite distant from the tool's original inventor.

Consider the wheel, perhaps a six-spoked wheel. In some ways, it is the most fundamental and important tool in society. It has countless uses unanticipated by its inventors; most were made by people who are not wheel-builders. The wheel is only useful when it is used for something, such as moving a cart; its economic value to society lies not in the price of the wheel, but in the wealth created through the use of the wheel.

If it takes all six spokes for this wheel to turn, and each of these spokes is potentially different in some way, we have a good metaphor for a modern biological technology. Increasingly, biological technologies are not self-contained; rather they are rather interdependent technologies that require multiple key methods and components to function. If one spoke is withheld, no wheel is built. If one spoke is broken the wheel will jam. And then the cart cannot move forward. By analogy, the most powerful technologies can be considered as "wheels," requiring a number of "spokes" to function. For instance, the ability to transfer a gene to a crop plant may require dozens of individually protected, discrete technologies. Denial of access to any one of these "spokes" obstructs not only the use of the technology, but its improvement. Only when the core technology is in place, with full functionality, can it be subject to iterative and cooperative shaping to meet diverse users' needs.

Unfortunately, even placing one or more key methods or components into the public domain allows no leverage to bring other components into a collective whole with broad access. Virtually all the practices of academic scientists promote the belief that "good science" can, almost by magic, transform itself into public or private goods. It can't. In fact, by failing to deliver such goods with broad and preserved access, the public sector science community is complicit by neglect, because the true stranglehold rests where much less public sector effort is expended: in the process of converting invention and discovery into innovation, by building and using wheels.

Virtually all the practices of academic scientists promote the belief that "good science" can, almost by magic, transform itself into public or private goods. It can't.

But we can change this landscape, if we provide one or more of the spokes to all the wheel-builders and users with covenants of behavior, rather than financial consideration (outlined later as BiOS licenses). If a user can access a spoke only by promising to share spokes, or improvements, then the whole logic can change.

This is where we find the leverage: change the logic of copyright licenses in software to allow free and open source software to exist, and do the same for patent licenses or Materials Transfer Agreements (MTAs) in BiOS. Then we can regain a full complement of spokes, and see the "wheels" of real innovation turn rapidly and deploy on many roads, creating wealth through their use.

How Fear, Uncertainty, and Doubt Can Deter Innovation

Uncertainties over intellectual property rights undermine the long-term and sustainable pursuit of innovation by making projects look more risky to potential partners and investors. This risk combines with others characteristic of early stage technology development: lack of a fully-specified business model, concerns over potential technology effectiveness, and the absence of a well-established delivery channel. Together they generate the fear, uncertainty and doubt (FUD, in the awkward but widely used acronym) that is the core impediment to technology development. Currently, every worldwide industry that depends intensively on science and technology experiences FUD. Sometimes a competitor is the focus; sometimes the bleak patent situation alone can lead an investor, client, customer and/or the public to lose confidence in the prospects of creating a viable technology-driven enterprise.

In the face of the uncertainties associated with the complex and opaque patent situation, multinational private-sector firms have responded by acquiring large IP portfolios and negotiating cross-licensing arrangements to obtain platforms of enabling technologies. Even so, these companies still often find themselves with constrained freedom to operate. Faced with the uncertainty of patent rights, they seem to be involved in a sort of mutually assured destruction.

In contrast, the public-good sector, and small-to-medium enterprises have only fragmentary portfolios, often made up of publicly-developed technology and modest non-fixed capital pools that they believe can be expanded by their eagerness to license them out, but they are at a grave disadvantage; they face a monopsony.

Unfortunately, this approach not only destroys public value and confidence; it is also ineffective in ensuring a sustainable private competitive advantage. As the expense of sequestering intellectual property outside the public domain in iterative patents has increased, some leading technology firms have decided that an open source model may yield higher private, as well as public, returns. A notable example is IBM Corporation; in a bold recent move it is stimulating a universally accessible "protected commons" of patents in a pool available for any open source development. As the world's largest patent holder, IBM could be viewed as a "rights maximalist;" over 500 of its key software patents have been made available to all—including competitors—who choose to use them under open source rules. Within days, Sun Microsystems followed suit with another 1600 patents, and a myriad of other companies are doing the same. The snowball effect continues, as companies realize that their sector makes progress when the standards and the toolkits are clear, open, of high quality and consistently available.

Clearly, true wealth creation will come not through extracting rent from a tool, but through *using* a continuously improving toolkit, with continuously decreasing costs of innovation and a continuously expanding group of tool users. Diverse and prosperous agriculture, robust public health and sustainable natural resource management are the publicly valuable goals we must keep in clear sight. The tools associated with their improvements must be plentiful, powerful and affordable.

As the ICT sector realized, we also need an open source movement in biological innovation that can empower public and private sector innovators with the tools, platforms and paradigms to allow rapid and efficient life-sciences innovations for neglected priorities and new opportunities.

CREATING CAMBIA, MAKING CHANGE

In the mid-1980s, when I first formulated the ideas that became CAMBIA, I did not intend to build an institution; I spent much time between 1987 and 1990 trying unsuccessfully to convince universities or later the United Nations or the CGIAR[12] system to take on and host CAMBIA's mission. But the complexity and edgy nature of the mission, the need to integrate diverse skills and strategies, and the entrepreneurial spirit, ultimately required an independent base.

In early 1992 I moved to Canberra, Australia, to begin a project on behalf of the Rockefeller Foundation, troubleshooting its rice biotechnology network in Asia. At this point CAMBIA was not a legally incorporated body, but had reams of letterhead and surprising credibility. Our job was to travel to virtually every laboratory in the developing world that had Rockefeller Foundation support—and over the next eight years this must have been hundreds—to help develop, improve, and apply their biotechnology capabilities, especially as they pertained to rice molecular biology. We developed and provided to many hundreds of labs—perhaps over a thousand—the most effective and widely used "vectors" in plant molecular biology, the pCAMBIA series, and provided courses and workshops in the science and increasingly over time, in intellectual property management. In hundreds of working visits to China, Indonesia, India, the Philippines, Thailand, Vietnam and many other countries of Asia, Africa and Latin America, we forged a sense of the possibilities if we had new types of technologies, and new communities to improve and share them.

During these years, as we became more sophisticated about licensing and understanding the patent systems, we also became more aware of the yawning gulf between biotechnology rhetoric and innovation realities in most of the world. On the one hand we saw a large, untapped population of dedicated and knowledgeable problem solvers, committed to solve problems of real substance to their countries and peers—but they lacked the usable technologies that would improve their situation. We also saw that the science itself was not up to the job: the research being conducted in the early days of plant molecular biology (and sadly still now) is intensely reductionist, whereas the problems of agriculture and society are integrated into complex systems. On the other hand, if we could design and provide tools that fit the problem and the hand of the tool-user, we could rapidly and effectively change the entire platform of problem solving, as long as the tools were dynamic and could embody the permissions to integrate into real-world innovation. CAMBIA was conceived to integrate and to address these issues.

Outlined in the earliest CAMBIA prospectus was the premise of using patent revenues to create a sustainable funding base. We surmised that we would ask a fair, tiered licensing fee of each company that was using the technology, proportionate to their ability to pay. A big company pays a lot, mom-and-pop companies pay peanuts, developing countries pay nothing. Then we would use the resulting revenue stream to invent and distribute the next generation of technology. At the time it looked like a logical and efficient way to move the sector forward with fair and open competition, not for the capability to innovate, but for the innovations themselves.

This worked to some extent, in that CAMBIA exists and might not have done so without patent revenues. Companies that licensed the technology range from giants like Monsanto, Dupont, Pioneer, Bayer, BASF, and Syngenta down to entities as small as the Hawaiian Papaya Growers Cooperative. But we also realized we could not generalize or scale it as a business model in the current climate of fragmented rights and capabilities. The transaction costs of negotiating licenses, as more and more "spokes" were required to move forward, would simply be impossible to bear for any but the highest-margin applications.

CAMBIA addresses these challenges through three interdependent activities:

1. *The BiOS Framework* creates, validates and promulgates licensing tools, along with the norms and new business models to make use of strategies for "open source" creation, improvement, and sharing of enabling technology.
2. *The Patent Lens* is a platform to focus, understand, and investigate the patent rights and to inform practitioners and policy-makers.
3. *CAMBIA's own research* into creating and distributing key "pump-priming" enabling technologies is made available through our online interface, the BioForge.

The BiOS Framework

Biological Open Source is a nascent movement, evocative of the transformative changes in information and communications technologies (ICTs) wrought by free and open source software (FOSS). The two movements share some goals: seeing transformational effects on a sector, and increasing the democratic involvement in problem solving; we are learning many lessons from the software world, and will continue to. But it would be a mistake to push the comparison too far. BiOS concepts have emerged from twenty years within the life sciences and human development culture, to address the needs and challenges of biological innovation.

The idea of using patent licenses not to extract a financial return from a user of a technology, but rather to impose a covenant of behavior, is the single feature

Patent Lens: A Platform for Understanding IP Landscapes

CAMBIA's Patent Lens includes one of the world's most comprehensive full-text searchable databases of patents; cost-free and available to anyone, it has a seven-year history of continued growth in features and power. It incorporates the full text of applications and granted patents from the U.S. Patent and Trademark Office, Patent Cooperation Treaty (PCV) database, European and Australian jurisdictions, and their status and family relationships in many dozens of countries. Its fast and user-friendly search engine has a nuanced interface and presents common and harmonized data structures so that these jurisdictions can be searched simultaneously.

The Patent Lens is becoming an increasingly important resource as the fee-requiring "value-added" patent data providers continue to consolidate. Because no national patent office has taken on the task of harmonizing collections over many jurisdictions, the role of the "patent clergy' remains central, and the gate-keeper functions of the information providers remain onerous. National and regional patent offices provide quite variable free patent searching; some are appallingly primitive while others, like the European Patent Office, are quite sophisticated. Patent offices, however, have complex relationships with commercial providers such as Thomson, which actually provide the patent offices with integrated searching functions for their own in-house use. To further complicate the situation, commercial providers have been calling for a reduction in the role of national patent offices as "value added" providers. The need for a public good provider has never been greater.

Patent Lens focuses on user-adaptability, integration, annotation capability and availability to the world community for free; these key features render it particularly helpful in efforts to restore public good and transparency as the *raison d'etre* of intellectual property systems.

Technology Intellectual Property (IP) Landscapes

IP Landscapes are analyses of key platform technologies, and the IP positions associated with their development and use. They build on and use the patent database, but include much more than a collection of relevant patents. Each landscape is a searching and analysis effort involving many person-months, by CAMBIA staff and soon others, who have particular knowledge of the science and technology and of patent claims. Typically, patent "professionals" within law firms accumulate billable hours by providing the same information over

of BiOS that is most resonant with Free and Open Source Software. We[13] worked with small companies, university offices of technology transfer, attorneys and large multinational corporations to understand their concerns and experiences, and then create a platform to share productive and sustainable technology.

and over for different customers, and charging full fees again to update them periodically. Increasingly we wish to do something no fee-requiring patent data provider will ever do: turn the landscapes into living repositories of constantly updated information, so no more updates will ever be required.

The goal is to use the harmonized datasets to create a facility where distributed and diverse users can generate, link, and dynamically annotate patent landscape analyses through web interfaces. The landscapes will ultimately become maps and decision support tools so users can distinguish greenfields from minefields in the long path from discovery to practical delivery of an innovation.

We have created a substantial number of such landscapes, in an early, hypertext-linked but basically flat structure. But we aim to enable the preparation of many more, by many people, by leveraging informatics to create ready frameworks and linkages between world patent literature and such resources as PubMed Central, and Google Scholar whose relevance engines can enrich the process. Ultimately we see the navigation of technology landscapes as being a critical feature in research and development decision making, but people will only use them when their costs, in both time and money, are negligible and the relevance and utility of the guided decisions are clear.

Patents, Policies & Practices

This component includes tutorials that guide users in reading and interpreting patents; the aim is to make novices more sophisticated about the nuanced realities of intellectual property, particularly patents. It also includes Policy & Practices papers that describe and advocate for informed and productive changes in international, regional and national forums and laws.

The goal is to forge a learning resource that participants in innovation systems at all levels—scientists and engineers, business and legal professionals, citizens and policy-makers—can use to learn of critical and timely issues relevant to improving the public good and social and economic value by engaging with the patent system.

The standards of modern patents are widely viewed as execrable; though many patents are presumed valid by law, they are at best frivolous and often egregious. We aspire to provide the public with tools to recognize and overturn such patents where they undermine progress or are being used without a long-term and well-articulated stake in industry or society.

The basic premise underlying that license is that we would not charge any fee for use of the "basket" of technologies with the patent estate being offered. By making the license cost-free, we hoped to induce the most valuable contribution to the license community: "freedom to innovate." In exchange for full, unfettered commercial rights to our technologies, licensees are required to comply with three conditions:

- They will share with all BiOS licensees any improvements to the core technologies as defined, for which they seek any IP protection.
- They agree not to assert over other BiOS licensees their own or third-party rights that might dominate the defined technologies.
- They agree to share with the public any and all information about the biosafety of the defined technologies.

Several further features of BiOS Certified licenses are very important:

- The definitions are critical. The core capabilities (enabling technologies, platforms) and their scope must be carefully defined to allow confidence in the development of viable business models that use these BiOS licensed technologies.
- The BiOS License structure must be scalable, and it should be generalizable, capable of development within these guidelines, and overseen by diverse institutions. We recognized that different technology sets have very different implications in the innovation chain, and that the agreement must accommodate different sectors (e.g., agricultural and medical) and different economic circumstances (industrialized and less-developed countries). Therefore we developed a suite of licenses around several different enabling technologies CAMBIA developed. We created them around our own technologies to have first-hand learning platforms from which we could generalize and help others create their own BiOS-Certified programs.

As we have gained experience with our first-generation licenses through the concerns and suggestions of many licensees and potential licensees, we have aimed to create a "brand" of Biological Open Source (BiOS) that is independent of institution. The BiOS certification program will help ensure that core BiOS characteristics are sculpted into forms that allow institutions to preserve their own cultures and priorities. They may do this through the medium of patent licensing or through materials transfer agreements (MTAs), a common form of bailment used to provide materials for life sciences research, such as bacterial strains, plant lines, cell cultures or DNA.

The certification approach has been particularly valuable in software development, through the activities of the Open Source Initiative (opensource.org) which overseas the branding of such licenses associated with copyright of free and open source software. However, life sciences are extremely sector-specific and technology-specific, and it is impossible to forecast or fully anticipate the emerging patent rights; these facts complicate BiOS certification and licensing. Of course these same challenges also render patent-based BiOS licensing and MTAs even more necessary.

Patent Lens: A Platform for Understanding IP Landscapes

With funding from the Rockefeller Foundation, in 1999 CAMBIA began to develop an integrated, full-text database of patents in the agricultural sciences. Under the initial guidance of Dr. Carol Nottenburg, then CAMBIA's Director of Intellectual Property, the CAMBIA IP Resource became a prominent web-based data tool to investigate patents in this field. Over the years, both the ambitions and the capabilities of the CAMBIA Patent Lens team grew,[14] and PatentLens has now become one of the world's foremost cost-free resources for full-text searching and understanding patents in many jurisdictions and in all classifications. Patent Lens (www.patentlens.net) harmonizes, parses and presents worldwide patent and technology data in a full-text searchable and highly integrated manner.

However, it is much more than a patent database. PatentLens is an integrated response to the massive complexity and opacity of the world of patents. It is intended as a public platform to enable many actors to investigate and share analysis of relevant IP issues, and to foster community involvement in overseeing and guiding the patent system.

The patent system has grown so rapidly and become so complex and opaque that even the most privileged and skilled clergy of patent law can only parse a tiny area of specialized knowledge, and that tiny area changes daily. This fragmentation has made it almost impossible to thoughtfully and factually assess the consequences of action and inaction: How can the consequences of policy be modeled or validated when patents are treated as fungibles? How can efficient progress in sectors critical to social progress, such as health, environment, and agriculture, be secured when the rights are tangled in a skein of patents?

The goal of the Patent Lens is to use the power of informatics and community to harmonize and make transparent the world of patents, so that thoughtful individuals, institutions and agencies can guide thoughtful and humane reform of the innovation system and to spur efficient and socially relevant innovation. This is an essential platform if we are to make use of the patent system itself to expand and protect a technology commons, and to collectively target breakthrough inventions, work-arounds and "work-beyonds"[15] and to make thoughtful and informed partnerships.

BioForge: Field of Dreams?

BioForge was initially launched as a web-based collaboration platform to take CAMBIA's pump-priming technologies—including Transbacter (described later), a new generation GUS called GUSPlus, and a novel genetic fingerprint technology called DArT—and throw open the gates to enlightened self-interest. We wanted scientists to try Transbacter in diverse bacteria and crops to create an open source and effective toolkit. The first version of the web facility was based on a very credible collaborative software development platform created by Brian Behlendorf[16] and his colleagues at Collabnet. We had hoped—in retrospect, perhaps naively—to see a surge of interest: scientists from around the world, initially from the public sector, would register, log on, and offer to collaborate to improve these tools, and to share their thoughts and actions.

BioForge: The Challenge of Aligning Incentives and Rewards

In initially designing BioForge, we had hoped that scientists in public sector institutions would come to see the value of working together to build powerful common toolkits to solve problems. Clearly most public entities endorse and even encourage *the notion* of pulling together to solve intractable social and economic problems: market failures. Indeed, this is the best justification for the very existence of a public sector. But if the toolkit does not encourage scientists to solve problems for their self interest, it will be irrelevant. And if such participation carries a cost—in real time and resources—that is yet another disincentive.

Furthermore, while discovery and occasionally invention are activities within the public purview in universities and government agencies, innovation—the delivery of new and tangible improvements to society—is not. Hence it is not part of academic science culture to be aware of the challenges to innovation. Nor does academia do much to reward sharing. The metrics for success are almost always being "first" in a field of endeavor that is widely hailed as being important and timely. The grind of innovation, with its need for long timelines and the building of confidence at many stages of product or process delivery, has little appeal and less relevance to academic advancement. In fact, the market increasingly rewards those who monetize or sequester the necessary components of innovation—a perverse set of incentives if there ever was one.

The initial response was mildly enthusiastic, but within a few months we realized that the actual engagement and contribution of scientific or personal resources was miniscule. While the BioForge has almost a thousand registered users, very few of them have substantially assisted the listed projects, technically or scientifically. However, many of the registered users are from India, China, and other countries widely viewed as out of the mainstream of cutting-edge biological research. This may reveal a latent need or desire for a better-crafted collaboration culture. We also believe it reflects CAMBIA's reputation as a provider of enabling technology. Thousands of our pCAMBIA DNA vectors toolkits are in use in almost every country, so this "market" knowledge and confidence could also be skewing the numbers. Still, at this stage BioForge has yet to create a vibrant web-connected community that actually does anything. We use it constantly, as a transparent and inclusive "lab notebook" for our own work at CAMBIA.

To address the issue of enhancing contributors' reputations (see BioForge text box), CAMBIA has started a software development project called Karmeleon to create open source, modular, software-mediated reputation metric tools. We hope that people in many collaborative and distributive projects can use these tools, and tune them to their diverse needs, ranging from online review of scientific publications through to research collaboration and product development. Our premise is

Discoveries are routinely patented; while they are only part of the complex web of capabilities that must be aggregated to create wealth, owners can game them for short-term financial gain at the expense of sectoral progress.

Success with a BioForge project—or any cooperative project with long timelines and complex feedback loops—requires aligning incentives and rewards. The most prominent metric for academic advance is reputation, but the tools for recognizing and enhancing reputation are still very primitive, including publication in high-impact peer-reviewed journals and serving on committees and review panels to cement relationships.

BioForge lacks any mechanism to demonstrate its contributors' influence and success to the community at large, or to those entities and individuals that have power over professional advancement. It takes an exceptional scientist to work toward improving a technology if she or he has no personal stake in its success.

The long timelines of agricultural and medical research and product development all but forbid direct feedback when an innovation enters the marketplace. This is a key justification for vertically integrated companies: to ensure that managerial oversight creates these links. If we wish to see alternative, distributive innovation in sectors with such challenges, we must create intermediate, interconnected and valuable feedback that enhances contributors' reputations, as well as new incentive pulls to participate.

that individuals should be rated on their contributions by accredited (rated) peers in a transparent manner, but using sophisticated, multivariate metrics to reflect the complex and diverse nature of the value of their contributions. Beyond their professional value, these contributions can and often do have important community and utility implications.

If we make valid, less "game-able" metrics available, users can develop confidence in the value of one another's contributions, and provide rewards as their community norms dictate: career advancement, peer reputation, funding and so on. But the reputation metrics must be adaptable to the culture where the contributor is working and being evaluated. Our initial drafts of Karmeleon use three metrics: Community value, Utility value, and Professional value. Scores in each category in turn impact the "gravitas" of a user; we hope this will encourage more sensible ratings to emerge.

The first generation of BioForge taught us something fairly obvious: that the cultures of software engineering and the life sciences overlap very little. Software developers live online. Their tool—the computer - is their window to the Internet. Their product, software code, can be tested almost instantly and can be evaluated, rejected or accepted almost as quickly. The engineer can build on tested code, and be fairly confident of a secure base. In the life sciences, experiments can take

An "Apollo Project" for Biological Innovation?

Several months after we published our TransBacter paper in *Nature*, *Nature Biotechnology*—the most prominent scientific journal in the commercial biotechnology sector—published an editorial expressing skepticism that a true open source movement could happen in biotechnology, given the extent of entrenched norms and interests.[19] The title of the editorial, "Open Sesame," implied that a vision as clearly utopian and impractical as that of open source for biotechnology would need a magic incantation in order to become reality.[20] The article did conclude, however, that an open source movement in biotechnology might just take root if, in an "Apollo Project" of some type could be used to forge a common ground to develop new collaboration norms, tools, business models and science around some mutually agreeable and highly desirable goal.[21]

While we at CAMBIA do not agree with the editors of *Nature Biotechnology* that the only way forward for open source in biotechnology is a grand-scale "Apollo project" of the type they suggested, we do agree that it may be an attractive option

What would a 21st century Apollo project to spur biological innovation look like? If the BiOS Initiative and the movement need such a platform from which to explore, create and coordinate new modes of problem solving using life sciences, what will that platform be? First, the project would require a socially and economically highly desired goal for which a technological intervention of great promise can be articulated. The project would need to focus on catalyzing new opportunities for problem solving, not just on creating an

months or years; validation, scaling and quality assurance take even longer. And the process can be so expensive or so specific to circumstances that it may never be replicated by another entity.

We are cautiously optimistic that as we introduce new, recognized and respected "reputational" tools, if we nurture high profile and energetic champions for particular projects, and if we create new incentive and reward systems, we will be able to move the BioForge from a field of dreams into a productive and focused mechanism for distributive innovation.

Beyond the Thicket: Transbacter

By about 2000, my colleagues at CAMBIA and I had seen so much "me-too" science going on around the world and the vast increases in patenting and vertical industry integration. We also saw public support eroding for genetic modification and then for all scientific interventions in agriculture. So we decided it was time to act more aggressively.

imposed "solution." It would not have a linear impact, nor would it merely improve the cost effectiveness of conventional paradigms.

To engage both the scientific and the business community, such a coordinated effort would offer an intellectually exciting proving ground for new collaborative approaches and new science and must require interdisciplinary skills. The imagination and creative energy of science would be harnessed, but much of science is intensely self-absorbed. An interesting problem will attract much more attention than a mundane one.

The platform activities would afford opportunities for "spin off" value for other initiatives and activities, and would have impacts beyond its target goals. A broad constituency must see some merit in various components of the project—so that diverse, even divergent interests would build coalitions.

The project would also have a credible promise, or proof of principle.[22] It would not be too risky—or too safe. While it may be somewhat encumbered by intellectual property, it would not yet be completely constrained. If the target has a suite of challenging IP thickets, that would be a platform for new strategies—of decision support, collaboration and invention—to emerge, allowing us to hone these capabilities. It would be in a field with few entrenched interests, or those interests must be diffuse or distracted. If major economic interests push back too early, they could slow or stall the effort.

Finally—and critically—it would also be in an arena where civil society, industry and academia can engage constructively towards a détente, and where they can explore and validate new models of social enterprise and business, as well as new economic and innovation strategies.

We decided to attack the first and most prominent thicket of patent rights—that around *Agrobacterium*— which represented the beginning of the patent rush in agricultural biotechnology. We chose this technology not because we believe that it presents a unique or critical bottleneck to many new entrants into the sector, or because anyone has called for these patents to be revoked or broadly licensed. In fact, these tools have little market pull now. The "scorched earth" policy in the agricultural biotechnology sector has left virtually no inventive entities queuing up to develop products, and no public desire for such products.

Rather, we wanted to show the potential for a new combination: what if we combined patent informatics and transparency with creative, targeted scientific research, and new normative and licensing tools? What if we used it to build a true public commons of technology—or rather "rebuild" a public commons of capability. We sought not a silver bullet, but rather a platform to test and explore our hypothesis that in alternate universes of innovation, tools and foundational discoveries could be constantly improving common goods, and that prosperous industries and business could be built on them.

Assessing the Patent Landscape

In about 2000, we began a comprehensive analysis of the patent situation surrounding *Agrobacterium*-mediated gene-transfer (AMGT), the process I discussed earlier. We intended to publish a simple white paper describing this key thicket of rights. But the task proved much more complex. Ultimately we published the first analysis online; almost 400 pages, and covering the top few hundred patents,[17] it has since seen two major updates. Over 1000 users downloaded it. But as we began to realize the extent of the problem, we also realized that it could not be attacked piece by piece. As we analyzed the "patent landscape," we noted that all of the patents used a common language and set of definitions that dated to the original filings: that the inter-kingdom gene transfer was achieved as a unique event mediated by a particular bacterial species, *Agrobacterium tumefaciens*.

Definitions are the key to a patent; they are critical in a patent prosecution to establish the metes and bounds of the claimed invention, and to guide courts in the event of a dispute. And the pioneering inventions typically establish precedent that persists. In the case of *Agrobacterium*-mediated gene transfer, it was widely believed and promoted that *Agrobacterium* was a one-off; a unique situation in biology. To this day most scientific papers baldly state that it is the only such situation.

The Strategy

My logic, and that of most biologists trained in evolution, is that if something happens once in life, it probably happens many times—maybe ubiquitously. We think of a "one-off" because we can rarely see other instances. So I began looking for hints in the literature that other bacterial species could transfer genes to plants, either natively or with a bit of convincing. And I found hints aplenty. So we set out—again with support from the Rockefeller Foundation—to find or generate the capacity for benign plant-associated bacteria to conduct gene transfer, and thus to develop a system that would be competent to transfer genes to plants, which was not infringing any *Agrobacterium* patents. If we could do this, the toolkit would clearly fall outside all the patents over AMGT, rendering hundreds, even thousands of patents irrelevant as blocking tools, but useful as "background science and technology."

We further speculated that we would be able to develop a system that was not only free and clear of the onerous *Agrobacterium* thicket, but would ultimately be superior to *Agrobacterium* as a technology. *Agrobacterium* is a plant pathogen, which normally causes disease in susceptible plants. Plants—even non-susceptible ones—seem to know this, and become stressed. We reasoned that by using totally benign symbionts, we'd eliminate the stress on the plant, and open new opportunities for genetic enhancement. If we could make the technology more efficient and wide-acting than *Agrobacterium*, a wholesale migration to the use would occur, even by academics. This would infiltrate the new open source norms into that most conservative of communities.

The R&D

The process turned out to be more straightforward than most anyone expected, and we published our results, which described a new system called "Transbacter," in *Nature*[18] on February 10, 2005. After nearly two years of hard work by a skilled laboratory staff, we described in that paper how we had induced three different genera of benign plant bacteria to transfer genes to three different genera of plants. These plants included the world's most important crop, rice, over which Japan Tobacco held dominant rights, and broadleaf plants, over which Monsanto held dominant rights.

The capability of *Agrobacterium* to transfer genes to plants is virtually identical at a molecular level to the ubiquitous system by which virtually all bacteria exchange genetic material, and even by which proteins and other molecules are secreted. This similarity allowed us to excise and move this capability on a fairly well-defined DNA construct into the benign symbionts. We were able to test the system with the most sensitive tools in the sector: the open-sourced GUSPlus reporter system.

The paper received exceptional coverage in the press, ranging from the *New York Times* and *Science* to *Nature Biotechnology* and the *Economist*, but not just for its scientific contributions.

The BiOS Licensing Framework

To share this technology, perhaps counter-intuitively, we filed patents on it. At first glance, this is anathema to open sharing. But we were learning the lessons of positive selection and the ugliness of patent gaming and trolling (for an example, see appendix). As we developed the new technology we also developed, in parallel, draft licensing templates for a prototype "BiOS" license, as I described earlier. Two years later, we have over fifty licensees, including large multinational corporations, small companies, and diverse public sector institutions. We have recently streamlined this technology to be more universal and easily disseminated, and have distributed over 300 kits of the new materials. Traction is building as the technology is improving.

But this is not really transformative, merely illustrative and instructive. Real transformation occurs when completely new actors are brought into innovation systems, and when radically new options for problem solving emerge.

This is our next ambition.

BIOSENTINELS: A 3D VISION FOR EQUITABLE INNOVATION

The most powerful impact of the scientific method has been to help us understand what had been incomprehensible; it has also helped us visualize and measure the parameters of the natural world. The importance of measurement cannot be overstated. Without the ability to measure—to see the consequences of an experiment or intervention—we cannot understand it, or improve or build upon it. The future

The Role of Measurement in the Next Green Revolution

It is often said—and it is true—that the Green Revolution, which so transformed the agricultural and economic fabric of Asia and much of the rest of the world, passed Africa by. The Green Revolution is not largely about plant breeding, although the short-stature varieties garner great attention. Rather the great advances were in the availability and management of inputs in agriculture. Water, nitrogen, phosphorus, potassium, acidity and countless micro-nutrient and abiotic stresses can each separately and together constitute major production constraints, as well as input costs, to an agricultural system. Combine this complexity with the countless impacts of biotic challenges such as pests and diseases, especially cryptic or latent soil-borne diseases, and creating any kind of profitable and ecologically sustainable farming becomes horrifically complex in the best of circumstances. Little wonder that industrial agriculture's greatest successes—with their concomitant problems—come from homogenizing these environments with massive inputs and then breeding and managing these artificial and unstable conditions to get maximum yields.

These options are not available for transforming low-input, low-output agriculture into a prosperous enterprise. When capital, infrastructure and communications are precarious, it becomes even more crucial to accurately and judiciously source and apply suitable nutrition, and to guide management decisions well.

The management of natural resources, whether endogenous or enhanced by inputs, is the most critical and challenging bottleneck in agriculture. It will be the lynchpin of the next Green Revolution. It is also the component most amenable to measurement. But here is the conundrum: to have a sustainable and scalable impact, such management decisions must be made by local problem solvers, and many such people are extraordinarily poor. They cannot afford to measure, and they cannot afford not to.

of biological innovation will similarly hinge on turning the unseen into the seen, and to sensibly report on the world around us so we can better respond.

Most critically, we must *democratize* these abilities, both to measure and to respond, in order to *diversify* agro-ecosystems and environments and *decentralize* the problem-solving capability. We will achieve this by fostering scientific method and harnessing local knowledge and commitment in communities that have previously been ignored or treated as passive recipients of help. This is our 3D vision, and the BioSentinel project will be the platform for exploring and realizing this vision.

In many vineyards around the world, rosebushes are attractively located at the end of each row. This curious planting regime does not reflect some shared aesthetic among winemakers or grape-growers. Rosebushes are sensitive to certain fungal diseases that affect grapevines more than the grapes themselves. If they plant and observe roses, growers can easily see the early stages of fungal infection on the roses, and can take measures to prevent disease in the grapes. The rose is a natural BioSentinel.

For the last 15 years CAMBIA has been working on the components necessary to generalize this phenomenon.[23] Now, with the advent of new scientific understanding, new proofs of principle, and the BiOS Framework, this work can now be brought to scale. With initial support from the Lemelson Foundation, we are beginning to create an open source platform to use plants as versatile living BioSentinels to measure and report on the status of their environment.

> [W]e are beginning to create an open source platform to use plants as versatile living BioSentinels to measure and report on the status of their environment.

Imagine a plant—not necessarily a food plant—that has been engineered as an instrument to produce a colour, a smell, or a shape that indicates the level of nitrogen or another essential nutrient in the soil. This plant will be developed in a collaborative, open sourced environment with components that are BiOS licensed and held in public trust. It will be a cost-free instrument that allows any farmer to better judge the condition of her cropping system, and to create wealth by making careful decisions, informed by measurements of the unseen parameters that influence her crop and its environment.

But the BioSentinel project involves much more than engineering one plant to make one color in a glasshouse. It is no mere academic curiosity. We intend to develop the platform to create a modular toolkit for the public and private sectors alike. We envision mixing and matching components to sense virtually any parameter (nutrient, water, pathogen), transmission of this signal via open standards, and reporting on this parameter with any of several different detection systems (color, fluorescence, smell, form). We also intend to consider all the quality assurance, regulatory and other parameters necessary for diverse collaborators to create practical and deliverable innovations. The BioSentinels will cost nothing to manufacture, once developed. They will cost nothing to use. But they will add value through the information they make available.

This platform will be built using technologies developed under BiOS license, guided by sophisticated patent informatics to ensure permissive use, and will pioneer new collaborative research methods that enshrine and perpetuate permissive use by all parties. The platform need not create GMO foods, but will create new communities of informed decision makers who are empowered to evaluate and improve their own ecologies and economies.

CONCLUSION

At the start of the twenty-first century, science is at a critical juncture. Four centuries of inquiry, discovery, and invention have created a base of knowledge that has the potential to provide people everywhere, in all circumstances, with nourishment, improved health, and longer life. But the institutional mechanisms that ostensibly exist to encourage the application of science to practical problems are today hindering that very process. The norms that have evolved around gate-keeping have created new clergy, new impediments and new inefficiencies. Without a systemic change, science's promise will not be available for those who most need it, and the promise of a truly diverse, robust and fair innovation culture may elude us.

Patents are at the heart of the system of institutions that convert basic scientific knowledge into practical applications. The modern patent system was intended to advance the public good by balancing the disclosure of ideas and the transparent definition of limited property rights. Today, it has degenerated into an instrument that is often misused to obstruct the public good through enclosure of ideas and obscure assertion of property rights that have no concomitant social benefit. To the shared dismay of both scientists and thoughtful citizens, patent systems and the myriad gaming practices they have spawned today are impeding innovation as a social enterprise, and continuing to deprive most of the world's population of such fundamentals as adequate nutrition, access to health care services, and clean water. This does not have to be. It is up to us to reclaim the beauty of science as a democratized tool for social advancement and wealth creation. It is up to us to write the terms of the compact. It is up to us to move beyond rhetoric and into constructive engagement in reforming our innovation systems for economic robustness and social justice.

We invite reader comments. Email <editors@innovationsjournal.net>.

APPENDIX. CO-OPTING THE COMMONS: A NEGATIVE EXPERIENCE OF POSITIVE SELECTION

For nearly seven years, with expenditures of over $100,000, CAMBIA has battled Syngenta, the large Swiss agribusiness, in European Patent Office opposition proceedings and appeals over the validity and scope of Syngenta's patents on "Positive Selection." These broad patents (e.g. EP 601092, but with counterparts in the USA) were granted with sweeping claims that conferred on Syngenta an absolute monopoly on "positive selection" in plants.

Positive selection is the provision of a benign compound—such as a sugar—that an organism cannot use without the action of a new gene; thus it "selects" for those organisms that have acquired that gene. Positive Selection is one of the most basic tools in genetics, used since the beginning of microbial genetics; all the bacterial genetics in the 1950's and 60's was based on one bacterial strain gaining the ability to grow on new sources of carbon and energy. When I started working with plants, it was thus immediately obvious to me (and presumably to anyone not employed at the patent office) that we could easily adapt this concept to plant genetics, to determine when a new gene had been added to a crop plant, and that a good first use would be my GUS gene.

So I began adapting GUS for this purpose, around the time I started sending out GUS kits and information, and giving hundreds of lectures on its use. While this mode of distribution was to dramatically change the field, it also allowed some aspects of the system to be co-opted. Our ideas and hard work were basically turned from "non-rival" goods that were available for all as we intended, into a private monopoly that could, and did, suppress innovation by competitors.

Scientists at a Danish sugar company, DANISCO, filed a patent well after I had given them the GUS gene, and after I had given public lectures on the use of GUS for such purposes. In this patent, they were granted broad claims to all uses of positive selection, with any compound and any gene in any plant. This breathtaking scope of claims was based solely on experiments described in the applications that used the GUS gene to activate a biological compound that would allow plant cultures that had GUS to stay green and be "selected." This was fundamentally what I had already reported at international meetings, with data showing that it worked. Like many scientists, when I reported it at international congresses, I intended to see it shared with everyone. DANISCO's intention clearly was not.

The potential value of this patent estate caught the eye of Heinz Imhof, then chairman of Novartis, who intervened personally to buy the patent applications from DANISCO outright. These patents then served as powerful ammunition in the patent war chest of Novartis, which went on to merge with other companies in the vertical integration frenzy of agricultural biotech, to become Syngenta. The evolving strategy of Mutually Assured Destruction by Patent Estate between the large multinationals required just such weapons.

The breadth of the claims as granted in Europe—together with their counterparts in the USA—ensures that any entity using the approach of conferring a growth advantage on a cell or plant to obtain transgenic plants would be infringing. This left only the use of antibiotic resistance and herbicide resistance as the means of selecting transformed plants. The adverse public response to such antibiotic gene use is well documented.

Thus the environmentally attractive and benign technology of cleaving a sugar and growing preferentially, with no antibiotics, was denied to the world's agriculture community by one group of patents, whose entire rationale was derived from work that I had intended to make public. But with the patent, it was "enclosed."

I had several meetings with Imhof and others at Syngenta; I attempted to make the case that using GUS to garner such a powerful and oppressive patent position was unjust and inappropriate and would ultimately be a pyrrhic victory for the sector. The discussions went nowhere.

So we made use of one of the few remedies afforded in the patent system to small players: the opposition process. Once patents are granted in Europe, they can immediately be challenged if one submits to the European Patent Office (EPO) prior art that had not been considered. Our contention in the EPO was that much public work, as well as my own work, including my public disclosure of the basic idea, pre-dated the filings and would thus invalidate the novelty requirement for the patent. We also argued that the patent was obvious in light of the pervasive use of positive selection in every other biological system for many years. We also asserted that the patent did not sufficiently enable one to practice the invention, and in particular, did not merit the breadth of claims granted.

The opposition process is widely touted as much more affordable than litigation. No doubt this is true. Instead of paying several million dollars to lawyers so we could be screwed by a multinational corporation in front of a judge, we only had to pay a hundred thousand or so for the same privilege, but in front of a panel of patent professionals. Of course reconsiderations of patent validity are conducted by the very same entity—the administrative machine of the patent office - that made the initial patent grant. So even in the face of what we felt to be compelling prior art, and convincing case law, the deck was stacked in favor of the status quo.

Watching the process, and the craft and gaming skills involved, was an eye-opener for me. Until one has actually endured the multi-year posturing, arguing, heartache and expense, there can be no clear way to convey the dysfunction of the system, or its debilitating effect on inventors. We achieved only modest inroads in restricting the breadth of their claims. But we did consume years of time and huge amounts of money, in a failed bid to restore for public use a key application of a technology that I had developed and had inadvertently let a multinational pull into its private fiefdom. The opposition process is not available in the United States, so the opportunity to lose extravagant sums of money there was denied to us.

What did Syngenta do with this technology? With the example they claimed using GUS, nothing. They never made a single product using that tool, nor did they develop it further. But they used the broad claims, granted by both the European and U.S. patent offices, to ensure that no other player—large or small—attempted positive selection without becoming beholden to them. Later, from DANISCO, they acquired other examples of positive selection protocols which worked pretty well and were protected under the umbrella of the broad claims, they made them "available" under a research license to unsuspecting scientists in the public sector. This "research license" strategy is one of the most pernicious co-opting approaches used by large private-sector companies. Once a tool is used under such a license, the only way to then release a product is through after-the-fact negotiations for a "commercial license." Several friends have gone through this process and reported a bare-knuckled strategy that gives the licensee almost no share in the benefit of the product they developed. Few takers, of course.

What are the lessons. Don't share? This is not a lesson I cleave to, nor a recipe for social progress. Could it have happened otherwise? Absolutely. This example was a case study of how "open source" licenses could be crafted and protect the public commons, yet allow the private sector to build prosperous businesses using that commons of technology. Perhaps I should have only sent the GUS gene and disclosed the information to those who agreed to terms by which they would share improvements that specifically used GUS; then the entire broad positive selection concept would likely have stayed available to all entities—public and private, large and small—that wished to explore its use. As would the many modifications on which others had filed patents. Just imagine: what would happen if the public sector technology transfer professionals had access to such a leverage tool to further the power of the commons toolkit and advance their mission?

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1. For example <www.opensource.org>.
2. In economics, a good is considered either rivalrous (rival) or nonrival. Rival goods are goods whose consumption by one consumer prevents simultaneous consumption by other consumers. In contrast, nonrival goods may be consumed by one consumer without preventing simultaneous consumption by others. Most examples of nonrival goods are intangible goods. (from Wikipedia, 2007).
3. Mike Bevan, my principal collaborator, went on to play a key role in coordinating the public sector sequencing of the Arabidopsis genome . Arabidopsis is the workhorse model plant of biotechnology, and was the first plant to have its entire DNA sequence described in the literature. The public efforts to create a public good, like some of mine, were likely co-opted by the secretive wholesale filing of patents on the Arabidopsis genome by Mendel Biotechnology, an affiliate of Monsanto. These patents have only recently surfaced (<www.patentlens.net>) but pre-dated the public effort by as much as two years, thus potentially capturing or hijacking much publicly-funded work, through a legal, though unpalatable practice called 'after-claiming'.
4. R.A. Jefferson, T. A. Kavanagh, and M. W. Bevan (1987), "GUS fusions: beta-glucuronidase as a sensitive and versatile gene fusion marker in higher plants." *European Molecular Biology Organization Journal,* December 20; 6(13): 3901–3907. Apparently it has been read often, as it has been cited in the scientific literature thousands of times. To our delight, however, the user's manual in Plant Molecular Biology Reporter has been similarly cited, and likely more influential, in the precursor to the Open Access publishing movement.
5. Monsanto later engaged Agracetus in a heated patent battle for the right to do genetic manipulations in soybeans, and ultimately purchased Agracetus and its patents. At this point the patents owned by Agracetus ceased being seen as reprehensible and unfair, and were defended as pillars of rectitude.
6. These scientists included groups led by Mary Dell Chilton, Marc van Montagu, Eugene Nester, Jeff Schell, Pat Zambryski and others, at the University of Washington, the University of Ghent, the Max Planck Institute, and elsewhere.

7 See forthcoming "Patent Landscape on Plant Genomes."

8. Jefferson, R.A. (2001). "Transcending Transgenics: Is there a baby in that bathwater, or is it a dorsal fin?," in *The Future of Food*," edited by Phil Pardey (International Food Policy Research Institute with Johns Hopkins Press), pp75-91.
9. See Appendix on positive selection.
10. Imperial Chemical Industries; its plant work was later absorbed into Zeneca and then into Syngenta.
11. More details on the complexities of this period can be found in Richard Poynder's online interview of me: The Basement Interview: Biological Open Source, <http://poynder.blogspot.com/2006/09/interview-with-richard-jefferson.html>
12. The Consultative Group on International Agricultural Research, <www.cigar.org>, a consortium of 15 agricultural research institutes and many governments, is the principal non-profit entity engaged in agricultural development through science for poverty reduction.

13. Dr Marie Connett, CAMBIA's Deputy CEO, a scientist, patent agent, and IP Manager, jumped into the deep end when she joined in 2005, and found herself working round the clock on creating the license, consulting with dozens of technology transfer professionals, lawyers, industry colleagues and scientists.
14. The Patent Lens was featured in an editorial in *Nature Biotechnology* (2006, 24:474), called “Patently Transparent” which was disarmingly positive about our PatentLens activity providing a critical breath of transparent fresh air to the patent frenzy that is creating a crisis in biotechnology. The PatentLens team, led for the last two years by Dr. Marie Connett, still has its original three software informatics specialists, Greg Quinn, Doug Ashton and Nick Dos Remedios, and has been strengthened by additional talent, including Paul Freeland, Neil Bacon and Josh Cole.
15. A work-beyond refers to a created technology which both bypasses and transcends the proprietary technology it seeks to replace. Transbacter, described later, is an example of a 'work around', which will become a work-beyond when its efficacy and uptake increases.
16. Brian Behlendorf is the Chairman of the Apache Software Foundation, and a driving force in the creation of the Apache Web server, one of the most widely used open source software tools in the world, with nearly 70% of the world wide web making use of it.
17. See <www.patentlens.net>. The first version was mostly a tour de force by Carolina Roa Rodiguez with guidance from Carol Nottenburg. -
18. *Nature,* 2005, 433:629-633. “Gene Transfer to Plants by Diverse Species of Bacteria.”

19 An outstanding article by Kenneth Cukier appeared about a year later: “Navigating the Future(s) of Biotech Intellectual Property,” *Nature Biotechnology* (2006) 24:249-251. It articulately described the increasing impasse in biotechnology caused by misuse of the IP system, and featured CAMBIA's BiOS Initiative very prominently and favorably. The metaphor Kenn used in this paper-that of maritime navigation and commerce - is extremely apt and informative. His paper is strongly recommended.

20. “Open Sesame,” *Nature Biotechnology* (2005), 23:633. Clearly the authors did not have a young child to remind them that “Open Sesame” was the incantation that would open the cave in which thieves had already sequestered stolen riches, a suitable parable for the misuse of the patent system.
21. The Apollo project was the concerted effort by the United States government to reach the moon before the Soviet Union did. The long-term focus may have been to reach the moon, but the project's real purpose was to coordinate massive scientific, engineering and technological progress with industrial development, while building and preserving a societal and political confidence associated with success. It wasn't really about reaching the moon, it was about being able to reach the moon.

22 In the absence of jet aircraft, rocket propulsion and supersonic flight, the idea of space flight would have seemed ludicrous to many.

23. This work has benefited particularly from early contributions of Kate Wilson and Steve Hughes, both Members of CAMBIA, now with CSIRO and Exeter University, respectively. Summarized in, e.g. R. A. Jefferson (1993), “Beyond Model Systems: New Strategies, Methods, and Mechanisms for Agricultural Research,” *Biotechnology R & D Trends*, Volume 700 of the Annals of the New York Academy of Sciences, December 21, 1993. pp 53-73; Wilson, K. J, A. Sessitsch, J. C. Corbo, K. E. Giller, A. D. L. Akkermans, and R. A. Jefferson (1995), “β-Glucuronidase (GUS) transposons for ecological and genetic studies of rhizobia and other Gram-negative bacteria.” *Microbiology* 141: 1691-1705.