

## **Technology Transfer Issues in Biotechnology**

**Ganguli, Prickril, Khanna Eds**

### **The future of global health networks**

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Global health emerged as a major worldwide concern in the years approaching the turn of the millennium, for it had become all too apparent that the 20<sup>th</sup> century, with all of its advances in life sciences and medicine and improvements in health, had only widened the disparities between the rich and poor countries and between the rich and poor within countries. The concern was heightened by two additional factors. First, the recognition that health is an important determinant of economic productivity and growth, social development, and ultimately political stability, and second because health, and access to health care were becoming more widely accepted as fundamental human rights, requiring nations to make a social commitment to provide health care services and improve the health status for all of their citizens. The Alma Ata Declaration of 1978 was the political expression of this dream, and provided a target, health for all by the year 2000, however much of a stretch that goal was. In fact, it did not succeed, and by a number of criteria, many fueled by the emergence of HIV and AIDS, health disparities grew instead of narrowed. Realizing this, and as the year 2000 approached, a set of Millenium Development Goals (Table 1) were developed to focus on poverty reduction. Although representing as much a stretch as the goals of Alma Ata, the MDG's are at the center of efforts to improve health status and reduce health disparities around the world, for at least 6 of the 8 MDG's are directly or indirectly related to improving health or dependent on improved health.

In the intervening years since Alma Ata, television has made it possible to show the world as it is, with all its blemishes, civil wars, genocides, violence, natural disasters, famines, disease, and disastrous political leaders and worse governments. The media have also put a human face on the deadly statistics of the ongoing global pandemic of HIV infection and AIDS, aided by the many rock stars, actors, and sports figures who either have been infected themselves or are otherwise moved to help to mobilize the needed resources for people in developing countries where access to life saving anti-retroviral drugs has been limited by affordability, availability and a lack of political will and commitment to equity in health. But HIV and the AIDS pandemic are only a part of the health gap, however important a part. There is far too little attention or resources given to other infectious diseases, with the possible exception of malaria and tuberculosis, one reason for there being a “Drugs for Neglected Diseases Initiative”, or to the pandemic of cardiovascular disease, stroke, diabetes, and obesity, or to unipolar depression and other mental health concerns, or to road traffic accidents and other causes of trauma including wars and land mines, civil disputes, and violence against women and children.

The primary issue in this discussion, however, is to explore how we can mobilize new research, appropriate use of intellectual property, and scientific advances to serve the benefit of all in need. After all, drugs, vaccines, and medical devices are not just commodities like an iPod or a designer dress.

### **Knowledge for all:**

The new millennium represents a unique opportunity to ponder the past and fix the future. It began with a sense of excitement and opportunity which, based on the technological advances

developed in the last decades of the 20<sup>th</sup> century, would make it possible for all in the new century to enjoy a better and more healthy life. The information technology revolution had not only increased the capacity of humans to communicate instantaneously around the world, but also to create and manage knowledge with the same speed. The race to sequence the human genome, and the ultimate triumph of the public sector genome project over the private-for-profit effort to compile and sell the information encoded in our DNA, insured that the complete genome data was deposited in the public domain, where it represents a veritable storehouse of knowledge for all to use. It succeeded because exceptional new technology for rapidly sequencing large chunks of DNA permitted the assembly of a virtual team around the world, managed by a core and visionary group supported by public funds, with the access to cutting edge informatics applications and the capacity for centralized data analysis and publication in real time. Fortunately, there was both determination and resources to insure that this information would remain a global public good. This should be a paradigm to emulate, but it doesn't actually happen very often.

### **Knowledge sequestration:**

New knowledge is the product of effort and innovation, but it is not necessarily available unless disseminated and it is not useful unless it is applied. New knowledge is also the currency of academia and the private sector, and therefore dissemination and application typically occur under a set of constraints. For example, academic career advancement depends on scientific productivity and the publication of new information and insights in journals of the highest quality possible. Information is, therefore, generally not released in real time, but rather is contained within the laboratory and the institution until sufficient to warrant publication or a public presentation. Information is released in packets over time, often without the details in methodology to allow

others to build on the report, and when of a particularly innovative or breakthrough nature, may be kept from public disclosure until a patent application has been filed, although the introduction in 1995 of provisional patent applications in the U.S. has generally eliminated the need for such delays since a provisional patent application can consist of just the manuscript, a cover sheet and a short statement of the scope of protection that will be claimed in the eventual utility application. The private sector pharmaceutical and biotechnology industries also control the release of the information they generate, and because career paths are not so dependent on publication as they are in academia, it is easier to restrict submission of papers. While delayed publication is not necessarily practiced, the time to dissemination may be quite long if it stands to financially benefit the company. This is what we mean by knowledge sequestration.

When there is patent protection for intellectual property, knowledge sequestration may be imposed in other ways. For example, the patent holder could give permission for the IP to be used in research, but as soon as there is the hint of product development the IP holder can control the application of the new findings to the development side of R&D. This hold can only be more complicated when there are a series of stacking patents involved, increasingly the case, since there must be an agreement drawn with all of the relevant stake holders. It is not impossible to get beyond these barriers, however, and there are examples of new Public-Private-Partnerships (or PPP's) for product development that have successfully managed these hurdles when they relate to priority issues of global health importance, and an organization with deep pockets, such as the Gates Foundation, is involved in funding the PPP.

### **New research models:**

Research for most of the 20<sup>th</sup> century centered around particularly gifted, or occasionally extremely lucky investigators, who organized a laboratory funded by public, institutional, or private money based on defined research projects. At the basic end of the spectrum, research was hypothesis driven, or at the least hypothesis testing, and designed to develop fundamental knowledge about how things worked, whether in the natural or the life sciences. In health and biomedical research, we became increasingly reductionist, honing down on cells, and then subcellular structure, then molecules, then genes and so on. The laboratories involved were run by a principal investigator who assumed the responsibility for directing the work that was by and large carried out by post-doctoral and pre-doctoral students, occasional undergraduates, and technicians and various assistants. Large labs could be very large indeed, including large amounts of money and increasingly expensive instrumentation. Success was going from grant to grant, with publications on the findings being the essential proof that progress was being made to the peer reviewers who made judgements on who was to be funded and how much they were to receive. Researchers moved up the academic ladder, based on grants received and papers published. It was no secret that the culture was dominated by a “publish or perish” mentality, and successful investigators got grants, published papers, got more grants, and were promoted. To make it all work funding agencies grew their bureaucracy to administer the process, and created a breed of very committed and very knowledgeable science administrators who ran the enterprise. But to make advances that actually improved the health of people (or animals, or plants) basic research findings had to be translated into clinical relevance for the biology of cells, organs, individuals and populations, and products that could be delivered and could make a difference had to be commercialized. To connect upstream research to downstream product development required a different set of perspectives and skill. Academic researchers were rarely interested in

determining how to produce a drug at scale and how to package and deliver it in way that was both safe and effective. This R&D part of the process, in essence converting a chemical that could just as easily kill as cure you into a useful drug, has become the preserve of industry. Universities might hold the patents for chemicals or drug targets but it takes industry to make the products that people can use.

How has the research model changed and can it facilitate the hand over from basic to applied research? For one, industry is doing more and more basic research in-house, and academic scientists are increasingly branching out to form small biotechnology companies. Second, sources of funding are increasingly coming to academic laboratories from industry, with a focus on areas already identified as of interest to the companies. Third, funders interested in research for product development for neglected diseases, such as the Gates Foundation, are using an industry paradigm for milestone research support. Nowhere is this better exemplified than in the Gates Foundation's Grand Challenges in Global Health Program. Finally, because research is becoming increasingly interdisciplinary, multi-investigator, more oriented towards translation of basic findings for clinical use and the integration of social and biomedical science there is a better opportunity for academic institutions to recognize accomplishments in applied research and create new pathways for academic advancement. No longer can the academic credo be summed up simply as "publish or perish". It is essential that academic institutions and their faculty understand that the role of such institutions – at least in the field of health - is the generation, dissemination, translation, application, implementation and evaluation of knowledge for the benefit of the global population. The vision must be one of education, research and service in a fiscally responsible manner, and not just a financial return on institutional investments in its research capacity.

## The Changing Role of Patents in Academic Research

Historically, there was a clear distinction between the roles of academic scientists and corporate scientists in the discovery of new therapies and prophylaxes – academic scientists elucidated the underlying mechanisms of disease, and corporate scientists applied this knowledge to create new interventions and preventatives. Academic scientists therefore rarely entered the world of patenting. When they did, they either did it on their own account, owning and paying for the patents themselves, or the patents were owned by the government agencies which funded their work. These governmental funding agencies had the responsibility for developing the patents but had cumbersome bureaucracies and frequently adopted well intentioned policies that had the unfortunate side effect of actively discouraged corporate investment in developing these patents.

In the late 1970's a new paradigm started to emerge.

First, the nature of science changed with the development of recombinant DNA techniques and the explosion of cellular and molecular biology. The creation of monoclonal antibodies is an example wherein the results of academic research could be more immediately translatable into therapeutic modalities.

Second, a realization dawned that the public good would be better served by policies that encouraged closer collaboration between academic scientists and their counterparts in industry. Institutional Patent Agreements were implemented first by the Department of Health, Education and Welfare and then by the National Science Foundation, which allowed a significant number of

academic institutions to own the patents that resulted from the work these two agencies had funded if the institutions created the infrastructure to commercialize the work in a “timely” fashion..

The benefits of this “test marketing” of institutional ownership and management of intellectual property were immediately apparent and were extended to all federal funding agencies and made a general right with the passage of the Bayh-Dole Act of 1980. The amendments to the Stevenson-Wydler Act in 1986 extended many of the same opportunities to US Federal Laboratories.

### **The Triple Helix and the Economic Impact of the New Paradigm**

Etzkowitz coined the term the “Triple Helix” to describe the complex interplay between government, academia and industry that has resulted from the combination of changes in science and changes in public policy in the US since 1980. There are two clear consequences of these new interactions:

- Diversified high technology clusters have grown up round all the major research universities and a number of federal laboratories in the US;
- \$40 billion of economic activity and 270,000 jobs are attributable to the results of academic technology transfer.

### **The Contributions of Public Sector Research to New Drug Discovery**

Nowhere have the benefits of the “Triple Helix” been more broadly seen than in the discovery of new drugs and vaccines, although the extent of this impact has not been systematically documented to date. The bright line hand-off of responsibilities in the historical paradigm of



academia elucidating disease mechanisms and industry discovering cures is no more. Just as industry in itself investing more in to basic research, increasingly academia is discovering the cures and handing them off to industry to develop them. A study currently under way reveals that since 1980 over 100 drugs, biologics and vaccines have been discovered by U.S. public sector researchers (working in national laboratories, universities, hospitals and not-for-profit research institutes) and have been successfully licensed to companies that have gone on to demonstrate safety and efficacy and have received FDA approval. Public sector researchers in other countries – especially the UK, Canada and Australia – have made similar contributions to public health.

Public sector research is not driven by the financial imperative to discover cures for large populations, and fully 25% of the new drugs discovered in public sector research over this period were to treat orphan disorders – defined in the U.S. as patient population of less than 200,000. This has important ramifications for the potential for academic research to discover cures for conditions that only afflict developing countries and that will not be large revenue generators.

### **The Spread of the New Paradigm Worldwide**

Some countries have always had rules that allowed for institutional ownership of inventions, as opposed to ownership by the inventing professor or the funder of the research, generally the government. Those that followed one of these two alternative models have started to adopt the US model. The UK was the first to follow suit, when the Thatcher government eliminated the National Research and Development Corporation as the patenting and licensing agent for British Universities. Over the second half of the 1990's and accelerating into the first decade of the twenty first century other countries have adopted the U.S. model. Outside of the U.S., academic

institutions do not generally have the substantial discretionary funds that U.S. institutions have access to from tuition, philanthropy and indirect costs, so funding the investments in staff and patenting needed to capitalize on their inventions often requires waiting for governmental initiatives.

## **The Role of Patents in the Academic Mission**

### Patents and Publishing

Historically patenting and publishing were thought to be in conflict – a scientist can only do one thing at a time, and if forced to prioritize most academic scientists would still choose to publish first and patent second. U.S. patent law allows an inventor a year after they publish their work to apply for a patent, so U.S. rights would still be available to scientists making this choice, but outside of the U.S., in general an “absolute novelty” rule applies, and no rights would be available outside the U.S. Where these represent “markets” for a product there may still be pressure to withhold publication until filing for patent protection has been accomplished.

The landscape changed with the GATT treaty, when the U.S. introduced provisional patent applications. These can range in sophistication from a cover sheet added to a manuscript or grant application all the way up to a traditional utility patent application. They give the applicant a year to file a full utility application, Provisional patent applications eliminated the conflict between publishing and patenting, although this is probably still somewhat mysterious to the majority of academic researchers..

## Patents and the Power to Dictate the Terms of Development

In some quarters, patents are regarded as antithetical to the open collaborative nature of science. This view is mistaken. Patents are themselves a form of publication – all patents now are published 18 months after their initial filing – and the very reason that patents were enshrined in the U.S. Constitution was to encourage inventors to disclose their inventions so that others could build on them and make further advances.

It is true that after a patent has issued on an invention even performing scientific research on the invention is an infringement of the patent. While many scientists think there is a “research exemption” the only research exemption under patent law is to the right to make and test a drug in order to be able to submit an Abbreviated New Drug Application to the FDA so as to be in a position to start sales of the drug the first day after the patent has expired.

However, there is a convention amongst academic institutions not to enforce patents against each other and to seek licenses from each other for scientific research. Academic institutions granting exclusive licenses to companies for commercial development always reserve the right for themselves, and hopefully for other academic institutions to perform further research without taking a license and paying fees.

Rather, patents pertain solely to the commercial development of a scientific discovery. They allow the holder of the patent to control the way in which it is developed – or indeed to ensure that it isn’t developed at all.

### Patents versus Licensing

That control is exercised through licensing. A patent holder can decide to issue an exclusive license to develop a new product to just one company. In this case the price for the product will probably be high. Alternatively, the patent holder can decide to allow multiple licenses to the drug, in which case prices will likely be lower. The risk in this approach is that no company will be prepared to make the substantial investment needed to prove that the drug is safe and effective for the first time.

For diseases that strike both the developed and the developing world, it is, of course, possible to do both, carving up the world into two (or more regions) and licensing exclusively in the developed world, where monopoly profits can repay the cost of development, and licensing non-exclusively in the developing world so that the product can be sold at generic prices or cost plus some level of profit.

Over the past five or six years, the pharmaceutical industry has been forced by the sheer weight of public opinion to accept just such a “two tier” pricing scheme for selected drugs, particularly anti-retrovirals, where it controlled worldwide patents. It is incumbent on the public sector when it invents, patents and licenses a drug or vaccine to ensure that its licensing practices are designed to generate two tier pricing from the outset. Industry has now embraced this approach.

For diseases that afflict only the developing world, it may be necessary to seek philanthropic funding for clinical development (perhaps through one of the public-private drug development partnerships) and to keep exclusive rights available to induce a developing country drug company to invest in developing a manufacturing process, retaining the right to seek a second source to “keep them honest” and ensure that prices stay low.

### **Managing Intellectual Property in Research Networks**

Global research and development networks are critical in developing drugs to treat the diseases of the developing world. Only a global network can bring together all the resources needed to attack a disease effectively:

- Sophisticated academic laboratories in the west, and increasingly in some middle income nations, to secure government and philanthropic funding and to lead the scientific effort;
- Sophisticated academic laboratories in the heavily affected countries to translate the first groups’ discoveries into therapeutic modalities that will be accepted by society and are practicable under local conditions;
- Clinical centers in the affected countries to provide access to patients for clinical development;
- Manufacturers in developing countries to manufacture and distribute products of high quality, up to international standards, and at affordable prices for the developing world.

Local manufacture can be particularly important, because many pharmaceutical companies only secure patents in the US, Europe and Japan, and while there may be freedom to sell in the developing world, there will likely not be freedom to manufacture in these countries to supply the developing world. Having a manufacturer outside these regions can obviate the need to obtain licenses in order to manufacture for export, and the costs of manufacture, including production facilities, can be substantially reduced as well.

It is likely that for some years to come such a research network will be based primarily on the sophistication and capability in academic institutions in the west, with increasing contributions over time from institutions in middle and lower income countries. It would be valuable at the outset of such a network to designate one of these institutions as the intellectual property manager for the consortium. Each member of the research consortium should, in turn, designate an intellectual property manager who will represent them on an IP committee for the group which will take decisions on IP matters

The lead institution should be charged with developing a consortium agreement, which all members of the consortium will sign, that spells out the expectations of all the parties with respect to:

- How the intellectual property will be managed;
- How it will be paid for;
- How it will be licensed;
- Whether it is intended that intellectual property generate income for the consortium;

- If so, how any income will be distributed.

Another topic that should be covered in the consortium agreement is whether any of the parties own background rights – patents that will need to be licensed to conduct the program and to make and sell any resultant products. They should be prepared to grant a research license to the consortium members to carry out the project, and should specify under what terms they will grant licenses for commercial production.

It is important that there be regular meetings of the IP committee by conference call, and if possible at least once a year in person. This could be organized at the same time as an annual scientific program review meeting, or it could be held at the annual meeting of the Association of University Technology Managers.

## **Summary**

Global public goods are an important consideration for academic institutions involved in structuring patenting and licensing agreements. This pertains most specifically to research funded by the public sector, but should also become a part of all patenting and licensing decisions, regardless of the source of funds. Changes in the nature of research funding, including multi-sectoral support from the public and private sectors, and in the nature of research teams and their increasingly interdisciplinary constitution, including both other academic institutions and industry, require new vision in the management of IP and in setting goals for institutional and professional attainment and career pathways. New operating procedures will need to be crafted for the new

networking and multi-institutional format of research and the management of intellectual property  
in behalf of the public.



### **Table 1. The Millenium Development Goals**

**Goal 1: Eradicate extreme poverty and hunger**

**Goal 2: Achieve universal primary education**

**Goal 3: Promote gender equality and empower women**

**Goal 4: Reduce child mortality**

**Goal 5: Improve maternal health**

**Goal 6: Combat HIV/AIDS, malaria and other diseases**

**Goal 7: Ensure environmental sustainability**

**Goal 8: Develop a Global Partnership for Development**