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Intellectual Property Management Strategies to Accelerate the Development and Access of Vaccines and Diagnostics: Case Studies on Pandemic Influenza, Malaria and SARS

Anatole Krattiger
Arizona State University

Stanley P. Kowalski
Franklin Pierce Law Center, stanley.kowalski@law.unh.edu

Robert Eiss
Oxford Centre for Innovation

Anthony Taubman
World Intellectual Property Organization

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Inside This Issue:

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20050054846	6531313	WO2004022760
5674502	6635246	WO2005018539
5766601	6669943	WO2005020889
5882650	6740325	WO2005027825
5897873	6743900	WO2005090584
5916879	6866853	WO2005107797
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Intellectual Property Management Strategies to Accelerate the Development and Access of Vaccines and Diagnostics:
Case Studies on Pandemic Influenza, Malaria and SARS

Meeting hosted by WIPO, the World Intellectual Property Organization, Geneva, Switzerland, April 2006

Anatole Krattiger
Research Professor
Biodesign Institute
Arizona State University
Tempe, AZ 86336, USA
anatole@asu.edu

Stanley Kowalski
MIHR and Franklin Pierce Law Center
203 Loudon Road
Unit No. 618
Concord, NH 03301, USA
skowalski@piercelaw.edu

Robert Eiss
CEO, MIHR
Oxford Centre for Innovation
Mill Street
Oxford OX2 0JX, UK
robert.eiss@mihr.org

Anthony Taubman
Head, Life Sciences Program
WIPO
34 chemin des colombettes
1211 Geneva 20, Switzerland
Anthony.taubman@wipo.int

Executive Summary

Achieving global access to vaccines, diagnostics, and pharmaceuticals remains a challenge. Throughout the developing world, intellectual property (IP) constraints complicate access to critically essential medical technologies and products. Vaccines for malaria and pandemic strains of influenza, as well as diagnostic and vaccine technologies for SARS, are not only relevant to global public health but are particularly critical to the needs of developing countries. A global access solution is urgently needed. This article offers a timely case-by-case analysis of preliminary patent landscape surveys and formulates options via patent pools and other forms of creative IP management to accelerate development and access. The analysis of the feasibility of patent pools reveals several impediments to patent pools: these include anti-trust considerations, bargaining difficulties caused by asymmetric interests and asymmetric rights among IP holders (*e.g.* improvement *vs.* foundational patents), and the difficulties of securing financial support given the significant transaction costs associated with pools.

Because of the above conceptual and operational hurdles, patent pools do not appear to be a feasible way to accelerate development. Other mechanisms, however, can ameliorate IP constraints. For example, a key IP constraint related to pandemic influenza vaccines R&D appears to have been resolved when MedImmune secured the assembly of all relevant reverse genetics IP and pledged broad access. Clearly, the landscape is complex and multi-dimensional. Licensing systems are not the only is-

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The views expressed in this document are those of the authors and do not necessarily reflect those of all the participants at the meeting, their respective institutions, or the publishers or donors. The present document does not represent a consensus but is intended to reflect the varied discussions that took place at the Geneva meeting, which itself was built on a research project and the results of interviews with many stakeholders from around the world.

Krattiger A, S Kowalski, R Eiss and A Taubman. 2006. Intellectual Property Management Strategies to Accelerate the Development and Access of Vaccines and Diagnostics: Case Studies on Pandemic Influenza, Malaria and SARS. *Innovation Strategy Today* 2(2):67-122.
www.biodevelopments.org/innovation/index.htm

sue. Measures must also be taken to limit regulatory hurdles and enable the swift, legal production of pandemic influenza vaccines to meet the needs of developing countries. This is why a comprehensive analysis is so necessary.

From a strictly legal perspective, IP systems work through the power to exclude. However, as this study's exploration and formulation of creative licensing strategies reveals, it is also true that IP can be structured and managed to work through the "power to include."

Principal results

Several important results emerged from this study of patent pools. First, one key constraint is related to a platform technology—**reverse genetics**—that is essential for rapidly developing influenza vaccines effective against H5N1. One company was able to resolve this constraint by assembling all the relevant IP and becoming a single licensing authority. Creating such a one-stop licensing authority would accelerate development, but it is not clear that a commercial entity would be willing to license a bundle of IP rights for developing country use.

Second, while the need for **patent pools** has been generally assumed (along with the determination of the possible kinds of such pools), there may be no immediate need for them. More importantly, implementing a patent pool in any of these three areas (pandemic influenza, malaria, and SARS) does not appear feasible for the following reasons:

1. **Anti-trust** considerations are real and may not be easily overcome in the quickly developing field of biotechnology.
2. Because they do not have **aligned interests,** it is doubtful that key players will agree to a patent pool. Without an industrially standardized suite of platform technologies, a situation that is unlikely to change in the near future, businesses compete at every level and have no reason to share their discoveries with their competitors. The best-known use of patent pools is in the electronics industry, which extracts value from IP through the finished product (*e.g.*, DVD players sold to consumers). In biotechnology, however, value can be preserved and extracted at numerous levels of development. Moreover, the industry is made up of not only very large corporations but also very small start-ups. Their interests are usually opposed, which makes this field generally inimical to pool formation.
3. It would be a formidable obstacle to identify a donor willing to fund the **significant cost** of establishing a patent pool, especially in an area of limited commercial interest.

In the particular case of **pandemic influenza**, the apparent resolution of IP issues related to reverse genetics technology suggests that other constraints besides IP are now more significant (*e.g.*, finding effective adjuvant technologies to extend antigen efficacy). More broadly, the speed of R&D is a major constraint. Further down the road, manufacturing capacity to produce a pandemic influenza vaccine rapidly and in sufficient quantities will be a crucial factor. International coordination and leadership from an appropriate type of organization are urgently needed to anticipate and overcome these obstacles. Although IP issues permeate these areas, patent pooling *per se* is not expected to accelerate R&D or to leverage the additional investments required for manufacturing.

Building appropriate partnerships might be the best way to accelerate global access for pandemic influenza vaccines. This would close gaps and might also cover R&D, manufacturing, *etc.*, but not necessarily all the areas needed. Sound technology transfer agreements must be achieved, and it will be critically important to attend to such matters preemptively, since in a pandemic there will be no time for the global community to be "tied up in legal formality."

Malaria is an extremely difficult disease that has eluded modern science for a long time, but recent advances are promising. In contrast to pandemic influenza research, which has been led by private sector efforts funded significantly by the public sector, malaria vaccine R&D is being pursued through product development public-private partnerships (PDPs). Recent investments by the Bill and Melinda Gates Foundation have provided an enormous push to accelerate malaria vaccine development. The PDP that deals with malaria, the Malaria Vaccine Initiative (MVI) under PATH, was also consulted and is closely engaged in the present project.

Vaccines are the world's best hope for combating pandemic influenza and malaria, but for **SARS** the strategies are uncertain. SARS patent applications can be organized into vaccines, diagnostics, and therapeutic agents. For vaccines, the fundamental underlying technology is the DNA sequence of the SARS ge-

nome, which was sequenced by four different institutions, almost simultaneously. In this area, the NIH in the U.S. led the way to a consortium for developing a common licensing approach, with the ultimate objective of forming a patent pool for the SARS genome. Discussions are still underway.

In the area of diagnostics, there are two leaders (Sanofi Pasteur and the University of Hong Kong). It is most unlikely that their interests could be aligned, not least because they are not operating in competing environments. Another obstacle to pooling is that diagnostic research is still immature (the same applies even more strongly to therapeutic agents). It is impossible to pool "tentative" IP or patent applications before they are issued because no one knows how essential the IP is, how valuable it is, or whether it confers market power (critical for assessing antitrust considerations). Further discussions about patent pooling for SARS are not likely to lead to viable options, with the possible exception of the work on the SARS genome already underway.

For H5N1, malaria, and SARS, patent pooling does not seem to be the best approach for spurring innovation and achieving global access to vaccines and medical technologies. So within the context of these case studies, let us consider a few other options that are not exhaustive but can help us delimit the possibilities:

1. Compulsory licensing

Given the number of licenses and the significant time that is frequently required to issue a compulsory license, this option might not allow a developing country to quickly develop a vaccine. Moreover, even raising the possibility of compulsory licensing might significantly deter future private-sector investments in vaccine R&D. A false alarm, in which an outbreak used to justify compulsory licensing was misjudged, would be especially harmful for just this reason.

If and when an H5N1 vaccine reaches the market, the international pressure to produce it in large quantities and distribute it to every corner of the world will be so huge that no major delays from IP can be expected (or tolerated). It would be incredibly damaging for any company to hold a country ransom. For pandemic influenza, compulsory licensing will likely be unnecessary, although the option should always remain on the table.

No product has yet been developed for malaria, so it is premature to analyze this area in more detail. This applies even more to SARS. In all three areas, therefore, R&D should proceed without considering compulsory licensing at this time.

2. Patent pools

In all three case studies, a patent pool seems premature at best and irrelevant at worst. It is simply not a feasible strategy option right now. The key reasons for this conclusion are:

- The interests of the players are not aligned,
- The cost of establishing a pool (many millions of US dollars)—much less the funds required to maintain the pool—could not easily be funded,
- Antitrust considerations are real and might require significant legal expenses to be overcome,
- No product exists that needs its IP to be pooled; rather, the priority should be on licensing production and ensuring product availability.

In future, patent pools are likely to be useful in the areas related to malaria platform technologies.

3. Portfolio completion (or other "non-pooling" IP management approaches)

This option has potential for all of the three case studies, but especially for malaria. Capacity building and networking elements should be emphasized. The latter is a critical precursor to licensing, since institutional and personal relationships are key drivers. These are further described below.

4. IP logistics

IP logistics is the basis for any in- and out-licensing strategy. The strategy is to utilize the institutional capacity of PDPs, key developing country institutions that are at the forefront of innovation, and prospective vaccine manufacturers.

5. Pre-negotiated royalty rate model

Although this approach might be worth considering further, it would likely require substantial academic inputs. It would also not be immediately relevant to pandemic influenza, SARS, or malaria. Its further study, however, is worthwhile.

6. Encourage developing countries to accelerate R&D and vaccine production through appropriate IP management initiatives

This should be considered from the perspective of international development policy, incentives, and

specific initiatives. In other words, discussions must really be framed in the context of not only encouraging developing countries in this area, but also providing lead institutions with the specific tools needed to implement it.

7. Take no action

This approach is not worth any serious consideration. These three case studies, most notably of pandemic influenza and to a lesser degree malaria, provide us with important knowledge that gives us the chance to significantly change how we view and use IP in developing countries. If we fail to pursue new IP management initiatives that creatively strengthen partnerships and build institutions, we lose not only the chance to help millions of people who will suffer and die from these three diseases, but also the positive repercussions of these changes for many other R&D efforts and initiatives related to diseases of the poor.

8. Special focus on pandemic influenza

Many experts believe that a pandemic outbreak, probably in Asia, is virtually certain to occur in the near future. Because most people will have little or no immunity to it, its effects will be catastrophic, particularly on the economies and people of poorer countries in Southeast Asia.

Given the high stakes, it is very much an understatement to announce that more coordination and capacity building in public sector IP management is urgently needed in relation to avian influenza. Such efforts could focus on PDPs and developing country institutions that will be or are already interacting with companies. The program could work to assist licensing between the private sector and institutions in developing countries. A company in a developed country, for example, could license the rights to manufacture avian influenza drugs and/or vaccines to a country in Southeast Asia, such as Vietnam. Such an endeavor would require a program coordinator to provide basic information about licensing, technical assistance with manufacturing/production, guidelines for seeking regulatory approval, and assistance with planning distribution and access schemes nationally and within the Southeast Asian region. Specifically, the program could be built upon a review of the IP management strategies of relevant institutions in such areas as:

- Patenting policies,
- Common approaches to licensing,
- Conducting freedom to operate analyses (FTOs), which establish in a detailed, product-by-product basis where licenses are needed and how to in-license relevant IP,
- Technology assistance related to IP (*e.g.*, license models, commercial arrangements, milestones, *etc.*),
- Linking IP management with clinical research, trials, and regulatory data (data protection, confidentiality, *etc.*),
- The future need perhaps for patent pools of platform technologies, and
- How open source licensing might be applied to vaccines.

1. IP management to accelerate "global access"

1.1 Background

The increasing threat of an influenza pandemic has focused attention on developing safe and effective vaccines. While pandemic influenza has received much international attention as an "acute emergency," particularly from high-income countries, malaria already *is* a "chronic emergency" for millions of people. We can use the urgency associated with the potential of a pandemic influenza to hasten in general the development of medicines for developing countries. Because we live in a post-TRIPS world, this task can only be achieved by effectively and creatively addressing IP issues.

To accelerate vaccine development and early access by developing countries, we need a comprehensive strategy that anticipates as much as possible the IP issues that may arise at every step of vaccine production. IP must be considered in a broader context of *innovation* management. This includes:

- research and development capacity (including clinical trials),
- regulatory policies and frameworks,
- manufacturing capabilities,
- market access and distribution,
- trade issues, and
- IP management.

These six components are dynamically linked: a change in one produces change(s) in the others. Failing to address these components as a system will therefore thwart success. This is why effective IP management requires the early identification and effective resolution of issues that will arise from product development to introduction. It is also why IP management is so important for Global Access. Like all of the other innovation components, IP issues are dynamically inter-linked with the other components in every stage of the innovation process.

1.2 Defining Global Access

Four ***criteria*** should guide global access strategies (Krattiger *et al.* 2006):

- availability: to the global market place, development agencies, health services, and ultimately to those who are the poorest and most in need;
- affordability: low prices for end-users and those institutions that finance its procurement and distribution;
- acceptability: technological, economic, and social acceptability to all stakeholders (government policy makers, development agencies, health services, and end-users); and
- adoptability: by government policy makers, development agencies, health services, and end-users, which requires that the vaccine can be introduced within existing or achievable capabilities and systems.

1.3 Innovation Management to Achieve Global Access

Achieving Global Access requires an understanding of health innovation systems, particularly in developing countries (Morel et al 2005). We can better understand how innovation occurs in biomedicine through an analysis that relies on a framework of the six Components of Innovation:

- R&D (*i.e.*, laboratory and clinical studies),
- Appropriate regulation to ensure safety and efficacy,
- Manufacturing that meets international quality standards,
- Appropriate IP management,
- Delivery of immunization services in the public and private sectors, and
- Procurement and distribution internationally.

As stated above, the six Components of Innovation cover all aspects of the vaccine innovation process. There are no others. This is an important aspect of the theory, because it implies that thorough attention to all six creates success. The public sector, however, usually carefully plans each R&D step while disregarding the other components. This non-integrative approach should be changed to improve the chances of success. For example, the preparation of regulatory dossiers and related Investigational New Drug (IND) filings (a task of another component) will be important throughout the innovation process.

In terms of IP management, the overall goal is to use IP tools and management practices to accelerate access by the poor in developing countries to a high-quality vaccine in the necessary quantities at the lowest sustainable price. Operationally, this means 1) establishing IP management capabilities according to best practices for "humanitarian use", 2) in-licensing necessary IP, materials, and background IP to obtain FTO, 3) implementing a patenting, confidentiality, know how, and material transfer strategy in support of humanitarian use, and 4) publishing results as appropriate to facilitate use by others. We stress global access and IP in this study because quite often those who handle IP create larger barriers for themselves and their projects by not taking into account the interrelations of the six Innovation Components. In other words, while each IP constraint may have multiple solutions, the best solution will be found by taking a broad, dialectical approach to the Innovation Components.

2. A review of IP management options and "pooling" mechanisms

2.1 Background

Patents and other forms of statutory protection are rights granted at the national level. The TRIPS accord under the WTO, however, encourages the global harmonization of patent systems, and patent filings in developing countries are increasing steadily. Unfortunately, this will not solve the problem of Global Access to new drugs and vaccines. This is often because

obtaining the license for a patent does not mean that it can be applied to new inventions and/or improvements, especially in advanced technological fields (*e.g.*, biotechnology, where the importance of patents is equal to know-how (or "intellectual capital"), access to markets, and trademarks).

Intellectual capital, or intangible assets, consists not only of IP (patents, copyright, trademarks, trade secrets, etc.), but also goodwill, any knowledge that can be converted into value (*e.g.*, product/market knowledge for differentiation as a key competitive advantage), human capital (tacit knowledge, know-how, relationships), and other forms of intellectual assets (codified, know-how, customer lists, and relationships). What more proof do we need of a "knowledge economy"? Actually, the knowledge economy is essentially over. Increasingly, what counts today is "social capital." Human networks make things happen, not the inert, underlying data and information. Indeed, the value of IP depends on its use. And for IP to be used as widely as possible, it must be sold or licensed. This requires networking and transactions between people who know and trust each other.

2.2 *From IP to forms of IP assembly and licensing*

Inventions are often assembled using patents and other forms of IP from third parties: marketable technologies and technology platforms are essentially bundles of IP. By itself, however, mere assembly will not make an invention commercially useful. Other steps of technology transfer are required: product development, regulatory aspects, and alliances with third parties. These forms of technology transfer can be grouped into six different types:

1. Licensing—principally IP bundles of an entire range of inventions required to practice FTO,
2. Turn-key investments—typically through foreign direct investments (FDI),
3. Mergers and acquisitions (M&As),
4. Strategic alliances (collaborations, joint ventures, corporate partnerships),
5. Donations, and
6. Capacity building.

Though not exhaustive, Table 1 lists the main types of mechanisms that specifically deal with licensing and, by extension, royalty collections. The main types of approaches are listed by with examples.

A recent example of IP assembly relevant to pandemic influenza vaccine development is the case of MedImmune and reverse genetics technology. Prior to late 2005, at least four institutions had to be considered to obtain FTO. MedImmune reduced this to one, and immediately publicly announced that it would permit any public-sector institution to use reverse genetics without enforcing its IP. This extremely rapid development was very welcome for those seeking to accelerate R&D into pandemic influenza vaccines, partly because it reduced risk, and partly because the licensing for reverse genetics suddenly became so much simpler.

But while the MedImmune/reverse genetics story is very encouraging, it represents only one possible avenue for IP assemblage. Another often discussed and frequently misunderstood model is patent pooling. The following section outlines different pooling arrangements and highlights the opportunities and limitations of pooling.

2.3 *The importance of IP assembly and the use of patent pools*

The essential purpose of IP management is to get freedom-to-operate (FTO) for a given product in a given market. Assembling IP is therefore an essential step in innovation management. But having FTO alone does not bring a product to market, much less provide it to the poor in developing countries. In this context, the value of so-called "patent pools" is often over-estimated. A pool simplifies the assembly of IP, but does not in itself do much or necessarily lead to technology transfer or market access and distribution.

A patent pool is a voluntary agreement between two or more patent owners to license one or more of their patents to one another or to third parties. In other words, they are "the aggregation of intellectual property rights which are the subject of cross-licensing, whether they are transferred directly by patentee to licensee or through some medium, such as a joint venture, set up specifically to administer the patent pool" (Klein 1997). Patent pools are especially useful for developing industry standards. One of the first patent pools was created for the manufacturing of sewing machines in the mid-19th century (Merges 1999). Other examples include aircraft manufacturing, glass manufacturing, and radio technology. In all of these cases, the pools contributed significantly to industry standards (*e.g.*, radio waves). More recently, patent pools were created to

Table 1: Types of IP assembly and licensing mechanisms

Type of Mechanism or Service	Characteristics	Examples
Royalty collection agencies: Collection of royalties for a small fee by one entity on behalf of its members.	Useful if licensing industries are already established; can be created by industry itself.	American Soc. of Composers, Authors and Publishers; British Soc. Plant Breeders
Information clearing houses: Broad term denoting a mechanism matching providers of goods, services, or info.	Useful for the exchange of specific information related to an activity or industry; does not facilitate tech transfer *per se*.	BioBin, BINAS; portals to country or industry biotech; training programs
Technology clearing houses 1. Web-based IP auctions and licensing, including business-to-business.	Appropriate for general purpose technologies, platform technologies, bundles; limited ability to spread tech transfer further.	Virtual trading floors, patent auctions
2. Public sector initiatives dealing with training, good practices, and the bundling of technologies	Appropriate for development; furthers tech transfer.	Public Intellectual Property Resource for Agriculture (PIPRA)
Open-source innovation clearing houses: Sites where anyone can post ideas or inventions and anyone is allowed to turn the ideas into products	Potentially appropriate for open-source licensing and the diffusion of tangible research materials.	Barry Nalebuff and Ian Ayres "Why Not?" or Half-Bakery
Brokers and other forms of facilitators: Typically focused on creating public-private partnerships and providing "managed" tech transfer.	Appropriate for charting new territory and bringing public and private actors closer.	African Agricultural Technology Foundation (AATF); Global Alliance for Vaccines and Immunization (GAVI)
IP management services: Comprises a wide range of entities, both public and private, assisting institutions in managing their IP assets.	Good for addressing systemic issues; establishes new modes of interaction.	Law firms, management consultants, global non-profit entities (e.g., MIHR), and academic training
IP commercialization agents 1. Commercial entities dedicated to commercialization of 3rd party IP.	Highly effective business model; useful to learn from their experiences and adapt to serve nascent private sectors.	BTG Ltd.; certain specialized law firms
2. Mixed commercial and public good objectives	Useful to learn from their experiences and adapt the model to other biotech sectors.	Concept Foundation
Integrated commercial services: A range of services for M&As, spin-offs, including IP audits, business valuation, due diligence, etc.	There could be a need for a non-profit merchant-bank-type institution to provide services to small/medium size enterprises.	Merchant Banks; venture capital investment services
Patent pools: A voluntary agreement between two or more patent owners to license one or more of their patents to one another or third parties	Pooling unlikely to change the underlying structural barriers to tech transfer; difficult to establish because industry players have divergent strategic interests; in partial/modified form, effective for tech transfer.	Internal, company specific pools; portfolio pooling; cooperative pooling; third party aggregations; forced pooling
Other public tech transfer and financing mechanisms	These range from education and training institutions to consortia in health and certain specialized UN programs (including south-south transfers).	
Company-to-company arrangements (including collaborations, joint ventures, strategic partnerships, and corporate partnering)	Some of the most ubiquitous and efficient systems of tech transfer, rarely requiring public sector assistance; different government policies either encourage or thwart them. This is certainly an area where many governments could do much to reform their policies and regulations, especially by reducing the red tape and administrative burdens on foreign private investments.	

Source: Krattiger 2004.

enable standard settings in Digital Versatile Discs (DVDs), video games, and Motion Picture Experts Group 2 (Standard-Compressed Video at 4-9 Mbps (MPEG2) compression technology). The latter was formed by private- and public-sector participants in 1997: Columbia University, Fujitsu, General Instrument, Lucent, Matshushita, Mitsubishi, Philips, and Sony. Among other considerations, a patent pool:

- must include patents that are valid and not expired,
- must not constitute an aggregation of competitive technologies by setting a single price for them,
- must have an independent expert to determine whether a patent is essential to complement technologies in the pool,
- must not disadvantage competitors in downstream product markets, and
- must not collude on prices outside the scope of the pool (*i.e.*, on downstream products).

In the development of drugs and vaccines, however, setting standards is not such a key issue, which may explain why patent pools have not been critical for commercializing these products. Nonetheless, the issue of "research tools" in the life sciences has led to a call for patent pooling in the U.S. Companies and institutions involved in biotechnology research are encountering widespread delays due to the near-universal patenting of research techniques that were traditionally available in the public domain. Uncertainty over the prospective costs of licenses, royalty "stacking" that creates uncompetitive costs, delays in obtaining licenses, and the differing definitions of "pure research versus product development" across different territories are all inhibiting biotechnology R&D in many areas.

Those who advocate patent pools as a solution to this problem should keep in mind that they are expensive to establish and maintain. Unless a given technology reaches a certain economic threshold, there is no financial incentive to establish a pool. Figure 1 illustrates that the economic feasibility of a pool is determined by:

- number of pool participants,
- number of patents held by each pool participant,
- likelihood of a patent being useful for a given platform,
- number of patents required to assemble a viable platform,
- market value of the assembled platform, and
- cost to assemble and maintain the pool.

Figure 1 assumes that some 25 IP rights holders would be required to establish a meaningful pool for vaccines. It would include DNA sequences, expression systems, process technologies, antigens, adjuvants, excipients, and delivery devices. The likelihood of patents being useful for this platform is estimated at 20%. The net present cost of such a pool, for a 5-year life span, would be approximately $30 million. Unless the pool value exceeds this figure by many multiples, it is quite clear that a patent pool in the area of vaccines could hardly be considered economically feasible. This is summarized in Table 2. Interestingly, a recent study by Patrick Gaulé (2006; see paper on page 123) reaches the same conclusion through a different approach.

Several years ago the concept of patent pooling was a very hot topic of discussion (*e.g.*, see Essential Inventions 2005, or www.cptech.org/cm/patentpool.html). They were often viewed as the solution to obtaining access to patents, but this pooling and cross-licensing, particularly when structured as a horizontal agreement leading to market domination, leads to another difficulty. Patent pools are open to potential abuses and immediately raise anticompetitive cartel and antitrust considerations in the US, Europe, and elsewhere. The European Commission is reviewing the Technology Transfer Block Exemption Regulation, which currently covers cross-licensing and patent pools but only to a very limited extent. The DVD patent pool referred to above was approved by the EC in 2000, as was a more recent patent pool covering MPEG technology, but no general guidelines have been issued for instances when there are more than two parties or where the parties may be in competition (Strickland 2003). More nuanced papers are now being published that consider precisely these antitrust issues (*e.g.*, van Zimmeren 2006).

2.4 Section conclusions

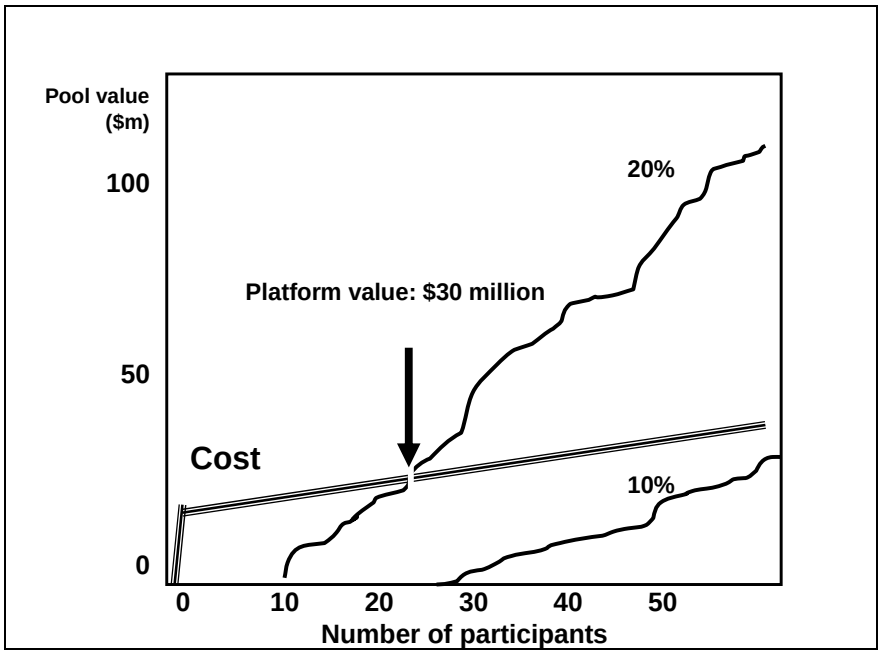
Patent pools are, at this stage, of limited value for the life sciences, particularly for vaccines. This is because:

1. Anti-trust considerations are real and cannot easily be overcome in the fast developing areas of molecular genetics.
2. Ensuring that key players will agree to form a pool is far form certain because the interests of the various players are not aligned.

3. Identifying a donor who would be willing to pay the significant costs of establishing a pool up front, especially in an area of limited commercial interest, is a formidable obstacle.

Other groups have recently reached similar conclusions, although they did not specifically consider these three diseases (see for example van Zimmeren et al. 2006, Gaulé 2006; see paper on page 123).

Figure 1: The economics of patent pools in health-related biotechnology applications



Source: Modified after figures provided by Boston Consulting Group.

Table 2: Summary and Pros/Cons of Patent Pools

Pros	Cons	Conclusions
Integrates complementary technologies Reduces transaction costs Clears blocking positions Avoids costly infringement litigation Promotes the dissemination of technology Levels the playing field	Difficult to agree on the value of individual patents contributed to a pool Complex to set up and avoid anti-trust problems (collusion and price fixing) May inflate licensing costs through non-blocking or unnecessary patents Complex when many patents are under litigation, as is the case with biotechnology May shield invalid patents and thus prevent much technology from entering the public domain	Pooling unlikely to change the underlying structural barriers to industrial biotechnology transfer to developing countries Difficult to get going because industry players have divergent strategic interests and use their IP portfolios heavily to strategically position themselves Appropriate for the biotechnology industry to create Unlikely to benefit from UN involvement In modified form, potentially effective for technology transfer

Source: Krattiger 2004.

3. The challenges of pandemic influenza

3.1 Overview: the biology of the influenza virus and traditional vaccine strategies

Flu virus is distinguished from most pathogenic viruses by its extreme variability. Over time the virus can change its surface antigens so completely that an immune response to one infection gives little or no protection against a subsequent infection. Two independent processes are at work: antigenic drift and antigenic shift. Antigenic drift results from random mutations in the RNA. Transcription of RNA is more error-prone than that of DNA, and the mutation rate of RNA viruses is therefore much higher than that of most organisms. Antigenic shift occurs when two different viral strains (*e.g.*, human and avian) infect the same host cell. This could occur in an intermediate host, such as swine. The two strain virions can then recombine RNA strands, generating a new pandemic strain with altered host ranges and/or pathogenicities.

Thus, a virus benign for one species can be lethal in another, and it is believed that influenza pandemics recorded in the 20th century arose when an avian strain recombined with a human strain, creating a pandemic virus against which humans had little or no pre-existing immunity and that was able to efficiently infect human mucosa and be transmitted through contact or air-borne droplets.

Traditional Influenza Vaccines: The temporal and geographic variability of flu strains has produced a unique global vaccination policy. Flu viruses arising in humans and birds are under world-wide surveillance that is coordinated by the WHO. Samples are sent to National Influenza Centers (110 centers in 80 countries) for identification. New strains are then forwarded to the WHO Collaborating Centers for Influenza Reference and Research in London, Atlanta, Melbourne, and Tokyo. Twice yearly the data are reviewed and WHO experts then meet to agree the optimal mix of flu virus strains to be incorporated in the following season's flu vaccine. Normal epidemic flu vaccine incorporates antigens from three strains: two Type A and one Type B. (Type B flu is typically less severe than Type A, and shows less variability). The three approved flu virus strains are supplied by the WHO Collaborating Centers, free of charge, to vaccine companies, which then have about six months to optimize the production process for the virus in eggs, carry out an accelerated small clinical trial to demonstrate safety and immunogenicity (Europe only), and begin production of bulk vaccine for distribution. There are two production cycles annually, one each for the Northern and Southern hemispheres.

Almost all flu vaccines currently approved for sale are grown in specially produced embryonated chicken eggs. Specially bred, germ-free flocks of chickens are reared in dedicated facilities in huge numbers. (In the 1990s, the Medeva flu vaccines plant at Speke, Liverpool, was the third-largest consumer of eggs in the UK.) The seed virus strains are injected into the eggs, which are then incubated. The resulting virus particles are harvested from the allantoic fluid, isolated by centrifugation and then processed into the vaccine preparation, which can be whole killed virions or virions treated to remove most of the RNA but with the protein antigens intact. About 250-300 million doses of trivalent flu vaccine are made each year, the upper figure representing approximately full capacity. Each dose has 15 g each of the three flu strains approved for that year. Most vaccine also includes the mercury-based preservative, thimerosal (thiomersal). Some vaccine is produced in one-shot disposable syringes, with most of the remainder distributed in ten-dose vials (where a preservative is essential). In rare cases, recipients of the vaccine have an allergic reaction to the traces of egg protein present. It has also been claimed, although most experts dismiss this, that some adverse reactions are due to thimerosal.

Extensive investments have been made in developing alternative manufacturing processes based on growing the virus in mammalian cells cultured in fermenters. Vaccines made by the two most advanced processes, from Solvay (Holland) and Baxter/Immuno (Austria, Czech Republic), are currently in late-stage clinical trials, but they are not expected to gain broad regulatory approval for a year or two. Chiron (U.S.) has recently announced that its cell-culture flu vaccine has completed Phase II clinical trials in Europe and that it intends to file an IND

application in the U.S. Aventis Pasteur (France) has recently concluded a deal with Crucell (Holland) to use the latter's PER.C6 mammalian cells to make epidemic and pandemic flu vaccines.

Production of seed strain from wild isolate: As described above, wild flu isolates generally grow poorly in eggs. The WHO Collaborating Centers therefore create reassortant strains to combine genes from the wild isolates with genes from a strain selected for efficient production in eggs. This is achieved by infecting eggs with both strains and selecting reassortants with the desired combination of genes. Occasionally, it is difficult to produce the required reassortant, or the best strain produced still has a poor yield in eggs. In some years, this has caused a shortfall of vaccine supply.

3.2 The science and technology related to the development of a pandemic influenza vaccine

In the event of an H5N1 global influenza pandemic, it is estimated that at least 4 billion eggs would be needed to produce adequate quantities of vaccine. This is also an old technology, in use for well over 50 years, that relies on a combination of hard work, scientific and technical expertise, and a certain modicum of educated guesswork; however, it is a well-established methodology and is not protected by IPR.

But H5N1 influenza virus poses a unique problem: due to its peculiar virulence, it rapidly kills embryonated chicken eggs. A more focused, non-egg technology is necessary, and the only available option is reverse genetics, a modern molecular technique for producing reference virions. A precise methodology, it can produce custom-made virions. Chicken eggs are not used; instead, cell cultures are co-transfected with a series of cDNA plasmids that encode the viral genes under the control of RNA polymerase. Of the eight viral gene segments, researchers can select and molecularly modify the exact ones that are desired for the final reference virus: there is no element of chance. Within the cultured cells, the viral genes are expressed, proteins synthesized, and the virions assembled and subsequently harvested and purified. This high-tech approach is protected by IP rights.

Three advantages of reverse genetics are directly relevant to pandemic influenza:

- A suitable vaccine production strain can be engineered in as little as two weeks;
- It avoids the problem of the original wild strain killing the egg because all the manipulations can be carried out in mammalian cell culture; and,
- It enables the efficient creation of non-pathogenic strains, reducing the risk of live virus escaping during the manufacturing process and allowing the use of less stringent (and costly) biological containment facilities.

Seed virus can be cultured in embryonated eggs, or alternatively, via cell-culture technology (*e.g.*, green monkey Vero cells) for vaccine production. A seed virus generated via reverse genetics could be grown in embryonated eggs if the deadly virulence is first eliminated via molecular techniques. However, in the event of a pandemic H5N1 influenza, egg-culture might be a poor and possibly unworkable option: it takes too long, too many eggs are needed, and chicken populations may already be decimated or diseased by the avian H5N1 influenza strain. Industrialized cell tissue culture would therefore be the preferred method for vaccine production. Still, this method presents a series of challenges: it requires substantial investment, optimization, scale-up, and, of course, there are IP rights issues. A virus therefore might need to be cultured via a combination of egg-based and cell-based techniques—*i.e.*, by whatever method possible.

DNA vaccines are another possible method for dealing with a global H5N1 pandemic. These vaccines are not related to the above technologies, which all rely on the traditional protein/peptide vaccination, possibly bolstered with adjuvant. In DNA (or genetic) vaccines, viral genes are cloned into a plasmid. The plasmid is then injected into the patient, where some of the plasmids migrate into cells and then to the nucleus; the viral genes are expressed, ultimately generating an immune response. This is a promising technology because it does not require eggs, cell cultures, or prolonged cold storage facilities. However, it is still unproven in humans and primates (the so-called "simian barrier"), and may therefore be remote in terms of deployment.

3.3 The evolving IP landscapes of vaccines for pandemic influenza

The IP landscape surrounding vaccine development is complex. In the case of pandemic influenza, the components include:

1. RNA molecular technology (including reverse genetics),
2. DNA recombinant technology (including attenuation mutants),
3. Cell culture production systems,
4. Adjuvants,
5. Excipients,
6. Vaccine production, and
7. Antigen delivery *(e.g.,* liposomal systems).

It is beyond the scope of this study to review the possible patents for all seven components. Rather, the objective is to map the field, identify key players based on their IP stakes, and devise overall strategies to address IP in a manner that will facilitate the deployment and use of vaccines. After conducting a detailed, thorough review of the scientific literature and patent landscape surrounding the development and production of vaccines for pandemic flu, a total of 128 potentially relevant issued patents or patent applications were identified. There are many assignees or applications (a detailed list of patents is given in Appendix A), but the major ones are given in Table 3.

If one considers IP as the main criterion, these are the key players in pandemic flu vaccine research: Aviron Inc., Baxter A.G., Chiron Inc., MedImmune Vaccines, Merck & Co., Inc., Michigan State Univ., Mt. Sinai School of Med., SmithKline Beecham, Inc., St. Jude's Children's R.H., and WARF (U of Wisconsin)

Less than a year ago, reverse genetics was the predominant issue, but since then MedImmune secured exclusive licensing rights to all key patents from the different inventors/institutions (Aviron Inc., Mt. Sinai School of Medicine, St. Jude's Children's Hospital, etc.). The company has assured researchers that research licenses can be obtained, and it has been forthcoming in extending licenses. To what extent this may impact the costs of a final

Table 3: Summary of patents related to pandemic influenza vaccines

Category/Step	Total No of Patents/Applications	Total No of Assignees	Principal Assignees
Reverse Genetics	29	6	Aviron Inc. MedImmune Vaccines (*8 Plasmid System*) Mt. Sinai School of Med. St. Jude's Children's R.H.
Mutants	9	4	Aviron Inc. MedImmune Vaccines Mt. Sinai School of Med. WARF (Wisconsin)
Cell Culture	21	9	Baxter A.G. Chiron Inc. Michigan State Univ. St. Jude's Children's R.H.
Adjuvant	11	11	Baxter A.G. MedImmune Vaccines
Excipient	5	4	Merck & Co., Inc. SmithKline Beecham, Inc.
Vaccines	36	24	Baxter A.G. Chiron Inc. MedImmune Vaccines Merck & Co., Inc. SmithKline Beecham, Inc.
Delivery	17	12	Baxter A.G. Chiron Inc. SmithKline Beecham, Inc.

product, if and when it becomes available, remains to be established. Importantly, MedImmune has a live attenuated vaccine on the market in other vaccine areas but does not have the technological capacity to bring a pandemic flu vaccine to market for use in humans. Licensing will therefore be a major strategy for MedImmune, although how this will work for products entering developed and developing country markets remains to be seen. Similarly, it is not clear at this stage whether MedImmune would be willing to share its know-how related to reverse genetics with a potential vaccine manufacturer in a developing country.

As noted before, the principal requirements for a pandemic flu vaccine will be the ability to make a huge number of doses as rapidly and cheaply as possible. Infrastructure to distribute and administer the vaccine throughout the world will also be required, but that is outside the scope of this paper. Advance warning of a potential pandemic is likely to be as little as 6-9 months**.** Two doses of vaccine will likely be required to stimulate immunity. As capacity stands today, the vaccine (or most of it) will have to be produced in eggs, and will probably contain alum adjuvant to enable the use of a reduced amount of antigen. Work at GlaxoSmithKline has shown that as little as 1.9 g of antigen, with alum adjuvant, can induce a strong immune response in clinical trials. The use of whole killed virion rather than purified antigen ("split virion") will maximize the number of doses available by avoiding processing losses. Regardless of the precise formulation of the vaccine, however, the use of reverse genetics will be essential.

3.4 Section conclusions

In late 2005, MedImmune completed the assembly of all relevant IP related to reverse genetics. Fortunately for the international community, MedImmune announced that it would grant wide access to the technology. This means that other constraints are more significant, such as the ownership of whichever adjuvant will eventually be used. There, the solution is a matter of price. More broadly, the speed of R&D is a major constraint, as is the manufacturing capacity to rapidly produce sufficient quantities of a pandemic influenza vaccine. To meet this challenge, international coordination and leadership from an appropriate type of organization is urgently required.

4. The complexities of malaria vaccines

4.1 The science

Malaria is caused by *Plasmodium falciparum* and *Plasmodium vivax*. The complex life cycle of these organisms includes stages in the human host and Anopheline mosquito vector. The *Plasmodium* parasite has four life stages:

1. A sexual stage (primarily intra-mosquito),
2. Sporozoite stage (intra-vascular),
3. Liver stage (intra-hepatocytic),
4. Merozoite stage (intra-erythrocytic).

The *Plasmodium* parasite has evolved a complex means of surviving and propagating. It evades detection by the human immune system by hiding inside liver and red blood cells, by presenting different antigens at the various life stages, and also by having a variable and complicated protein structure that can hide the immunoreactive portions of its proteins so as to further evade detection.

Vaccine development has focused primarily on about 40 *Plasmodium* antigens, of which 12 have been the focus of more intense research and development. In general, malaria vaccines can be broadly placed into categories that parallel the four life stages of the *Plasmodium* parasite:

1. Preerythrocyte vaccines targeting the initial infection (vascular) or liver stage (hepatocytic) of the disease,
2. Vaccines against the blood stage (erythrocytic) of the disease,
3. Vaccines blocking *Plasmodium* parasite transmission to mosquitoes (“altruistic vaccines”), and
4. Anti-disease agents.

Due to the sophisticated biology of the *Plasmodium* parasite, successful vaccine development will likely require the inclusion of several antigens, possibly from different stages of the *Plasmodium* life cycle. Several promising vaccines currently under development include:

- Vaccines developed using the MSP-1 malaria antigen, from the merozoite stage of the *Plasmodium* life cycle, have yielded promising results, with good immunogenicity and animal model data. However, IP issues encumber this antigen. Multiple patents with overlapping claims mean that it is not readily available. For access, licenses would be required from at least eight entities.
- The RTS,S vaccine consists of selected sequences from the circumsporozoite protein (sporozoite stage) fused to the hepatitis B virus surface antigen, co-expressed together with unfused hepatitis B antigen in recombinant yeast cells. This vaccine has been shown to be safe, immunogenic, and efficacious. It is currently undergoing pediatric evaluation trials and has been shown to protect children for up to 18 months.
- A novel approach is to use DNA constructs encoding multiple *Plasmodium* peptide epitopes and thrombospondin-related adhesion protein (called "DNA METRAP") to generate T-cell mediated immune responses against the liver-stage (hepatocytic) of malaria. Using a "prime-boost" technique, the immune response of the DNA vaccine can be significantly increased when it is followed by administration of a modified vaccina virus Ankara (MVA).
- The use of radiation-attenuated sporozoites of *Plasmodium falciparum* and *P. vivax* as antigens may prevent infection in 90% of those vaccinated for at least one year. However, this is a labor-intensive approach, requiring the actual dissection of the mosquito salivary glands and extraction of the sporozoites. Nevertheless, this technology may have possible application in developing countries.
- Malarial toxin glycosyl phosphatidyl inositol may offer another route for vaccine production. This approach does not prevent infection but instead reduces the mortality and severity of the disease. It has been shown to be a good candidate vaccine with promising protective effects observed in mammalian studies.

4.2 *The evolving IP landscapes of malaria vaccines*

The biological complexity of the *Plasmodium* parasite, coupled with the historically chronic nature of the malarial plague, has led to the development of numerous vaccination research programs and a concomitant array of interconnected IP rights known as "patent thickets." With up to 40 possible antigens of interest, and at least 10 of these under intensive development, the number of patents and assignees has grown so much that, without rational IP management systems, progress towards moving vaccines to developing countries could be seriously delayed or even blocked. A good example of an antigen tangled up in IP rights constraints is MSP-1. It exhibits good immunogenicity, but the presence of a number of patents, overlapping claims, and a gaggle of potential licensors presents a virtual tangle of barbed wire obstructing access to this otherwise attractive system.

In this context, Alta Biomedical Group LLC conducted a malaria antigen patent access project for the Malaria Vaccine Initiative (MVI) at PATH. The goal was to ensure market access to vaccines that are most likely to receive regulatory approval in the foreseeable future by identifying potential patent roadblocks and proposing a mechanism for access to key patents. Building on a patent landscape developed by Falco-Archer that covered the ten most advanced MSP-1 malaria antigens (many of which are in clinical trials), the Group's findings in March 2005 identified 167 patent families filed by 75 different entities. When prioritized, 23% of the 167 families were considered to be "moderate to high priority based on the claim language, length of estimated patent life, and overlap with the advanced vaccine projects" (Alta Biomedical). 21 organizations held them, the majority of which were held by companies, 20% by public sector institutions, and nearly 20% were already accessible to MVI through their partnerships.

Alta Biomedical further reviewed several models of IP management, including the creation of a formal patent pool. They concluded that malaria antigen patents "may not be good candidates for a formal pool," partly because of anti-trust considerations, and partly because for any given antigen only a few licenses would be required. There would also be little business interest because of the modest for-profit potential. They concluded that at this stage the most effective approach for MVI would be to continue to in-license the necessary IP.

A selective patent landscape analysis (Table 4) was performed in this study, focusing on four different vaccine systems (excluding MSP-1). Two of these vaccine systems are being researched and developed

Table 4: Summary of patents related to four malaria vaccine systems

Vaccine Category	Total Patents/Patent Applications	Total Assignees or Applicants	Principal Assignees or Applicants
DNA ME-TRAP Vaccine	16	2	Oxxon Pharmaccines ISIS Innovation
Recombinant Circumsporozoite Protein Vaccine (RTS,S)	44	4	SmithKline Beecham
Radiation Attenuated *P. falciparum* Sporozoite	6	3	Sanaria
Glycosyl-Phosphatidyl Inositol (GPI)	7	3	RMF Dictagene

by MVI partnering institutions (see also Tables in Appendix B for a detailed list of patents):

- DNA ME-TRAP Vaccine (Oxford University, assigned to Oxxon Pharmaccines, ISIS Innovation)
- Recombinant Circumsporozoite Protein Vaccine (RTS,S) (SmithKline Beecham).

As a practical application of MVI's mission to encourage partnering institutions to coordinate efforts and synergize their respective IP portfolio potentials, SmithKline and Oxford University are collaborating to test the Oxford MVA-based vaccine in combination with the SmithKline RTS,S/ASO2A vaccine. Such a coordination of scientific efforts, made possible by coordinating IP rights, is a prime example of the effective implementation of the MVI mission.

4.3 Section conclusions

Malaria is an extremely difficult disease that has eluded modern science for a long time. Recent advances, however, are promising. In contrast to pandemic influenza, where the private sector is taking the lead through significant investments by the public sector into private companies, R&D is characterized by product development public private partnerships (PDPs). Recent investments by the Bill and Melinda Gates Foundation have provided an enormous push to accelerate malaria vaccine development. The PDP that deals with malaria, the Malaria Vaccine Initiative (MVI) under PATH, was also consulted and is closely engaged in the present project.

At some stage, vaccine production will need to move to the private sector because the public sector generally lacks key capabilities (*e.g.*, manufacturing, reaching markets, and dealing with regulatory challenges). Thus, for each promising malaria vaccine, it will be necessary to form PDPs for manufacturing and even for distribution. For example, during the research and development phase, science and research capacity are critical, as are market prospects and IP/legal environments. Although production *per se* comes later, important decisions about the choice of technologies for scale-up, the location of production, investment requirements, and others, will have to be made. These are, in turn, strongly influenced by existing manufacturing capacities and IP systems. Likewise, during product development and production, the capacity to manufacture at cGMP standards becomes critical, as are other factors, such as the drug/vaccine regulatory framework. During the commercialization, distribution, and delivery phase, socio-economic acceptance and access to national and international markets are key drivers. Public and private sectors have much to offer each other in these phases, and because each phase affects the success of the others, partnerships should be sought very early on in the process.

5. The mysteries of SARS

5.1 Technology brief

Severe acute respiratory syndrome (SARS) dramatically appeared in Asia in February of 2003. Before the outbreak could be contained, SARS spread to over 24 countries, causing 8,098 cases of illness and claiming the lives of 774 victims. The causative agent

of SARS is the SARS-associated coronavirus (SARS-CoV). The genome of the SARS virus is a single strand of RNA, 30,000 nucleotides in length, folding into regular repeating patterns that form helical secondary structures.

The palm civet and the raccoon-dog may be the natural reservoirs for SARS-CoV, and live animal markets in Southern China might have been the source of the SARS jump from animals to humans. Symptoms include flu-like complaints, fever, headache, cough, and shortness of breath. Pneumonia is a common complication.

SARS spreads from human to human by proximal contact. The transmission mechanism is respiratory droplets spread by sneezing or coughing. These virus-laden mucoid projectiles are deposited into the mouth, eyes, or nose of those within one meter of the source.

Strategies for a SARS vaccine include a spike-1 protein based subunit vaccine, whole-killed or attenuated virions, or an engineered adenovirus expressing from one to several different protein components of the SARS virus. The later strategy has the added advantage of stimulating both humoral (B cells) and cellular (T cells) immune responses.

5.2 IP summary

The perceived threat of SARS prompted a rapid, intense scientific push to characterize the SARS virus. Naturally, there was a concomitant push to protect the fruits of these innovative initiatives via numerous patent filings, which included patent applications on the SARS genome and even the virus. Although part of the rationale for this patent push was defensive, the parallel increase in diagnostic and therapeutic patent applications suggests the possibility of PDPs for profitable reasons.

Pooling the patent covering the SARS virus genomic sequences was proposed and widely publicized as a possible way to consolidate the IP fragmentation that followed the flurry of research in the wake of the 2003 threat. Potential participants included the Bernhardt-Nocht Institute, the British Columbia Cancer Agency, the Centers for Disease Control, Erasmus Medical Center, and Hong Kong University (Versitech Ltd.). Without this consolidation of IP rights, licensing costs for the requisite IPR for vaccines, diagnostics, and therapeutics may be prohibitive. In this case, therefore, patent pooling could provide access to SARS IP rights and thereby serve the greater public good.

The suddenness of the SARS threat prompted an IP rights "gold rush." Unsurprisingly, there has been a plethora of SARS related patent applications but a paucity of actually issued patents. Finally, because SARS represents an acute, yet apparently ephemeral, crisis, the lack of a palpable public health threat means that it remains an open question as to how the value of the IP related to SARS will impact any subsequent IP management strategies.

5.3 Section conclusions

SARS appeared out of nowhere. Much of the concerns in 2003 were due to the risks of a previously unknown virus. This led to tremendous efforts to sequence the genome and to a myriad of patent applications (Table 5 lists a summary of the main assignees; see Appendix C for details). Much of the identified IP is in the form of patent applications, and it is quite likely that few of them will become patents. Unlike pandemic influenza, for which the best hope is a vaccine, the future strategies

Table 5: Principal patents related to SARS vaccines, diagnostics and therapeutics

Technology Category	Total Patents/Patent Applications	Total Assignees or Applicants	Principal Assignees or Applicants
Vaccine	45	26	U.S. Government Sanofi Pasteur Chiron Corporation University of Hong Kong
Diagnostics	28	17	Sanofi Pasteur University of Hong Kong
Therapeutics	15	5	The Brigham & Woman's Hospital, Inc. B.C. Cancer Agency, Canada

for SARS are uncertain. The patent applications have to be looked at in terms of vaccines, diagnostics, and therapeutic agents. For vaccines, the fundamental underlying technology is the DNA sequence of the-SARS genome, which has been sequenced by four institutions, almost simultaneously. In this area, the leadership of the NIH and others led to a consortium to develop a common licensing approach with the ultimate objective of forming a patent pool for the SARS genome. These discussions are still underway.

In the area of diagnostics, there are two players in the lead (Sanofi Pasteur and the University of Hong Kong) and other diverse minor players. It is most unlikely that their interests could be aligned. A further obstacle to pooling is the immature state of diagnostic research (the same applies even more strongly to therapeutic agents). It is quite impossible to pool patent applications before they are issued, and before it is known to what extent the IP is essential (one of the critical conditions for avoiding anti-trust issues).

6. Development and assessment of IP management options

6.1 Introduction

Through critical analyses, focused patent reviews, and reviewing key references, a number of creative IP options were framed and evaluated. As these options are reviewed, tested, and refined, some of them may provide a starting point from which to move ahead with feasibility studies aimed towards implementation. The following sub-sections detail these options and summarize the substantial analyses of each option in relation to pandemic influenza, malaria, and SARS. Furthermore, since pandemic influenza occupied a central stage in this project due to its urgency, a special sub-section (no 6.11) is devoted to it.

6.2 Formulation of IP management options

Malaria, pandemic influenza, and SARS differ significantly not only in terms of the pathogen and pathogenicity but also in:

- institutional frameworks,
- market dynamics,
- political attentions,
- global context, and
- IP landscape.

Vaccines for each disease, therefore, confront different IP management constraints and opportunities. The following section presents, analyzes, and discusses seven options to facilitate the IP management aspects of vaccine developments, although one option (No. 6) is substantially broader than any of the others. The different options presented here, therefore, are not necessarily exclusive. Each option begins with a simple and brief definition, continues with a broad analysis, and then presents a preliminary recommendation on whether and how the option might apply to the three cases under consideration.

Strategies related to making vaccines available to developing countries have significant IP implications. The institutional context of vaccine development will also significantly affect which option might be the most feasible. For malaria, the majority of the R&D programs are under the auspices of MVI through a product development public-private partnership (PATH), and so the situation is quite different from pandemic influenza, for which the private sector is taking the lead. Discussions about each option are structured to include the role played by institutional contexts in addition to the other issues raised above.

6.3 Compulsory licensing

Definition

According to TRIPS, countries can issue compulsory licenses to national producers in national emergencies, provided that a series of complex conditions are met. The country must have the manufacturing capacity to produce the patented invention and must also have attempted to negotiate a license in good faith (although the WTO Council recently instituted a waiver to the original TRIPS agreement that allows developing countries without manufacturing capabilities to import patented drugs from sources other than the originator company). Compulsory licensing has to be initiated by governments and may take one or more years to complete; it is a complex process and requires significant government resources and experience.

Analysis

Production under compulsory licenses presents several operational challenges. Patent holders are unlikely to license and transfer their know-how under compulsory licenses, so companies in developing countries will need to develop it internally. Exports, moreover, may only be made to certain countries under specific conditions, which limits economies of scale and potentially increases production costs significantly.

Compulsory licensing may be a beneficial tool—for example as a negotiation strategy—although international IP standards mandated by TRIPS already allow member nations considerable discretion to enact laws and provisions that not only meet treaty obligations but also support national innovation policies, development priorities, and cultural values. This includes voluntary pricing and licensing arrangements. Other options primarily relate to national policies and laws beyond the purview of this document (*e.g.*, permitting and regulating the government use of patented inventions, taking actions through patent courts to protect public interests, and the judicious framing of competition law and policy). Importantly, when compulsory licenses are issued, the licensor has no obligation to transfer not only know-how/trade secrets but also any safety, efficacy, or clinical data. In other words, the compulsory license may be limited to the information disclosed in a patent specification, which frequently represents only an early "best mode" of an invention. It will not include subsequently developed and/or ancillary technical know-how or related show-how.

Applicability and Feasibility

Given the range of necessary licenses and the time required to issue a compulsory license, this option might not permit a developing country to quickly develop a vaccine. Moreover, even raising the possibility of compulsory licensing would significantly deter future investments. A false alarm scenario, in which the outbreak used to justify compulsory licensing was misjudged, would be particularly harmful because it might become a future disincentive for developing pandemic flu-related vaccines and technologies. Granted, the threat of a compulsory license can prompt an early agreement, but it is always wisest to seek a commercial license early.

If and when a product reaches the market, the international pressure to produce the vaccine in large quantities and to distribute it to every corner of the world will be so huge that no major hold ups due to IP will be tolerated. It would be incredibly damaging for any company to hold any country ransom. For this reason, it is unlikely that compulsory licensing will be a useful strategy, at least not for pandemic influenza, although the option should always remain on the table.

With malaria, since no product is yet developed it would be premature to analyze it in more detail. The same applies even more to SARS.

In all three areas, R&D can proceed without the need for any compulsory licensing.

6.4 *Patent pools*

Definition

Although there are many forms of patent pools, such an arrangement fundamentally consists of the interchange (cross-licensing) of rights to essential patents by a number of companies, as well as an agreed framework for out-licensing the pooled IP to third parties, including an agreed pricing and royalty sharing scheme.

Analysis

As pro-competitive arrangements, patent pools are aimed at IP assembly. They seek to resolve patent conflicts (reducing litigation), settle disputes over blocking patents (accelerating product development and FTO), and facilitate arrangements for licensing patents in the pool to outside members (accelerating the setting of standards and reducing licensing transaction costs). They exploit economies of scale by integrating the technical complementarities of the pool members.

From a legal perspective, pools require careful anti-trust considerations to avoid potential, perceived, or real anti-competitive behavior by pool members or, more importantly, by the pool itself. From an operational perspective, only essential patents can be included in a pool. And finally, from a business perspective, the interests of the various IP holders need to be aligned in order to bring them to the table (pools are invariably voluntary arrangements).

At this stage, it is unclear which patents might be essential for vaccines for the three diseases discussed in this study, so it may be premature to discuss whether or not any assembly of potential patents

would be subject to the antitrust guidelines for IP licensing established by the U.S. Department of Justice (DOJ) and the U.S. Federal Trade Commission (FTC). Even a pool established outside the U.S. could trigger U.S. antitrust considerations, because many entities that would be members of pools are U.S.-based or have substantial U.S. operations.

Moreover, while a patent pool is very useful for platform technologies that need to establish industry-wide standards (*e.g.*, DVD, MP3), its value is much less when industry interests are not aligned. In the context of research on vaccines—an evolving field with no platform and with no technology clearly in the lead—industry interests can hardly be considered aligned. Indeed, the technology has not matured to the stage where industry standards can even be contemplated. At this stage in the R&D of innovative technologies, few companies will have an interest in giving their rivals preferential access to their technologies. Companies also typically become cautious about anti-trust issues when a patent pool is suggested, which might hinder participation.

Patent pools serve the assembly of IP, not the transfer of technologies *per se*. Although the DOJ and FTC observe that "by promoting the dissemination of technology, cross-licensing and pooling arrangement are often pro-competitive," in the context of technology transfer and collaboration with developing country partners, patent pools would mainly assist with licensing IP. But these countries would not necessarily benefit equally from sharing know-how, show-how and trade secrets.

A patent pool can have advantages: IP can be licensed through an efficient "one-stop" shop. Significant research and administrative costs would decrease dramatically. Speed and efficiency would be greatly increased. But a pool is not the only way to achieve these objectives.

Applicability and Feasibility

Patent pooling has been more focused in the realm of DVD technologies, where it makes sense to generate revenue through sales and not licensing. Such patent pools help to clear blocking positions. But in regards to patent pools for public health initiatives, it appears that there is little likelihood that companies will give up their exclusive IP rights, at least in the case of adjuvant technologies. Pools tend to arise organically because the owners of IP are mutually stymied; this has not yet happened for vaccines. The technology is not at the same level of maturity as in the DVD industry.

Still, it is worth noting that patent pools can be set up in many configurations, which will then drive the options that participants will consider as they assemble new patent pools. Under certain circumstances, the patent pool concept might provide greater impetus for exploration and discussion. However, as stated above, most other aspects of vaccine production are likely not sufficiently mature to fit into such an IP management strategy. As the technologies develop and the industry matures, this option might be more interesting.

Given the current state of research, a patent pool seems premature at best and irrelevant at worst for all three case studies. The key reasons are:

- The interests of the players are not aligned.
- The cost of establishing a pool (many millions of US dollars) could not easily be funded, much less the required funds to maintain the pool.
- Antitrust considerations are real and would require significant legal expenses to be overcome.
- Overall, there is no product for which IP needs to be pooled; rather, the priority should be on downstream licensing for production and the availability of the pandemic influenza vaccine. Platform technologies may be significant in the future for malaria.

6.5 Portfolio completion (and other co-ordinated IP management approaches)

Definition

In this IP management model, a non-profit entity in-licenses the different IP pieces that may be required to produce a vaccine in a developing country, including know-how/trade secrets. This entity is restricted to negotiating access to IP and know-how for use in developing country markets (as defined, for example, by the World Bank). Within developing countries, the entity would also oversee and facilitate clinical testing, the establishment of a manufacturing base, distribution, and other related regulatory issues.

Analysis

It should first be mentioned that this option could be considered the "industry standard." Any company that brings a product to the market will need to in-license a range of IP as well as know-how/trade secrets from a range of players in order to obtain FTO.

Depending on the industry, player, and market dynamics, the entity may also sub-license the bundled IP portfolio for manufacturing elsewhere by third parties. Although companies routinely do this, the non-profit sector has been slow to perceive this basic strategy. As a result, non-profits working to benefit developing countries sometimes approach third parties relatively late, which often leads to complications, and, in cases where royalties are involved, to higher prices. Once an institution has invested significant sums in product R&D, the bargaining power to obtain licenses is reduced.

However, industry does not perceive non-profit entities and other companies in the same way. The key issue is often not competition but product stewardship and guarantees that only a high-quality, safe, and effective product will reach the market. Approaching licensors later, therefore, may be in a non-profit's interest because it can demonstrate its success.

The first step for this option is an IP logistics evaluation. Given the available technologies and players, what would be the fastest and cheapest way to create a vaccine? This requires identifying the key technologies at every step of vaccine development, production, and deployment. The IP holders for each step must also be identified, after which it would be possible to map out various logistical combinations (perhaps 5-6) and evaluate specific paths with the highest likelihood of success.

Donor funding would be required to negotiate access to the technology, and a solid scientific/legal panel would also be needed to evaluate the IP logistics. The entity in charge of determining the options and negotiating for access would need to be trustworthy, credible, professional, and apolitical.

Applicability and Feasibility

This option has potential for all three case studies, particularly for malaria. Capacity building and networking elements appear to be key elements for success. Since institutional and personal relationships are key drivers, networking is a critical precursor to licensing.

6.6 IP logistics to facilitate global access

Definition

U.S. Congressman Sharrod Brown has introduced a bill (H.R. 4131) that would provide for compulsory licensing of patents in the event of a severe public emergency, such as the outbreak of an H5N1 influenza pandemic. But as reassuring as this might sound, it is like putting on a Kevlar® vest after having heard the gunshot. Such an approach is most likely too little, too late.

What is needed is an alignment of technologies, IP, and options. In other words, a preconceived, prearranged, logistical plan is essential well in advance of a pandemic outbreak or Phase III testing of a malaria vaccine. Logistics involves identifying, assembling, and organizing resources across the innovation matrix; hence, a logistical approach dictates that the resulting product, or vaccine, will need to be:

- produced rapidly, efficiently, safely, and reliably,
- using the lowest optimal dosage of antigen,
- with the highest immunological response,
- and delivered in the most efficient manner.

In the case of pandemic influenza, the components of the technological landscape to consider in expediting the production and use of a vaccine include:

1. RNA molecular technology (including reverse genetics),
2. DNA recombinant technology (including attenuation mutants),
3. Cell culture production systems,
4. Adjuvants,
5. Excipients,
6. Vaccine production,
7. Antigen delivery (for example, liposomal systems).

A comprehensive view of the IP landscape requires a careful technological analysis of alternative pathways to make the vaccine, from RNA molecular technology to vaccine delivery. This means lining up the technologies, then the IP holders, and then developing a logistical plan to deal with FTO issues.

Analysis

An IP logistics approach determines the optimal vaccine production/delivery steps, who owns the IP for each technological "step" in vaccine production, and which IP thickets might need to be resolved. This will require sophisticated input from leading researchers in the field of vaccine science. An alignment based on optimal technologies and corresponding optimal IP might involve several technology and IP holders. Again, with pandemic influenza as the example, this could include the best reverse

genetics technology, combined with an optimal adjuvant, cell culture system, and delivery mechanism. This would make it possible to make the best vaccine in the shortest period of time … when that time arises. After determining the best approach, it will be necessary to negotiate access with the IP holders. Fortunately, because this would be a vertical and not a horizontal arrangement of IP, the possibility of antitrust complications may be diminished.

IP logistics is a methodical, organized approach for delineating and assessing access to the best technology alignments for rapidly producing and deploying a vaccine. Its advantages suggest that there may be other models for which IP logistics would also provide a foundation.

Applicability and Feasibility

IP logistics is the basis for any in- and out-licensing strategy. The key strategy again relates to institutional capacity within PDPs, key developing country institutions that are at the forefront of innovation, and prospective future vaccine manufacturers.

6.7 Pre-negotiated "royalty rate" model

Definition

This presumably untried option has some similarities to a patent pool. It would bring parties together to pool their IP, but it differs from a traditional cross-licensing patent pool in that the parties agree in advance to share the profits from a successful vaccine. The "winner" (*i.e.*, the company that first reaches the market) would receive a higher portion of the royalties, but all parties would receive a pre-determined royalty rate. In this model there is a reasonable distribution of risk and an equitable sharing of reward.

For example, assume that six companies, A, B, C, D, E, and G join the "royalty rate model." Each would allow the others access to their own patents. Assume that Company A successfully develops a vaccine, then Company A would gain the largest share of the profit, but the other companies also profit at the pre-determined rate for accessing the technology. The proposal would provide guaranteed access to the "winning" technology at a pre-agreed price. This option provides companies with a kind of "insurance"—it is not a winner take all system—that provides the incentive for companies to enter the patent pool. For no up-front cost, a company gives up rights but is not precluded from accessing the IP of others. The entity that administers this would also be able to license to a 3rd party if all member companies agree.

Analysis

Many of the same concerns regarding patent pools are likely to apply. Because this option has presumably not been tested so far, it is not known whether industry and academia would agree to it: not everyone may want to participate, and so the possibility that critical IP owners will holdout could torpedo such a strategy from the start. Those with the most promising patent portfolios may not wish to enter since their investments in innovation are based on the proposition that they will be the winning team. This proposal presupposes a level-playing field in technology development, which is not really the case with technologies pertinent to pandemic influenza at this stage.

Nevertheless, having all of the other relevant patents assembled for one-stop access could dramatically reduce research and development costs for such a company. A risk/benefit analysis may suggest that participation is worthwhile, especially since even if they win, their "loss" is predetermined, (*i.e.*, their risk is paid for by their acceptance of a reduced share of the ultimate revenue flow). They don't get the whole cake, just a tasty slice.

Applicability and Feasibility

This concept may very well be worth considering further, but it would require substantial academic inputs. Indeed, relevant academic groups may be valuable partners in its future conceptualization. It would not seem to be immediately relevant to pandemic influenza, SARS, or malaria. Nevertheless, it is hoped that the concept will be further studied and elaborated upon so that it could potentially become a useful model.

6.8 Encourage developing countries to accelerate R&D and vaccine Production through stronger linkages related to IP management

Variant 1: Encourage low-income countries to develop and manufacture vaccines

Definition

A vaccine could be developed for developing countries by a developing country that is outside of the global IP regime. This would involve accessing

whatever patent and patent-related documentation is available and using this to develop and produce a vaccine.

Analysis

Research and development funds would be required from donors. Such efforts, however, would duplicate those already underway in both the public and private sectors, but with the added caveat that the critically important ancillary know-how would not be available, since the IP holders would not be partners in this sort of scheme. Indeed, it is unlikely to make vaccines available before private companies. Export issues are also a very big problem: the vaccine might be illegal to import into countries that recognize even one patent used to develop or produce the vaccine, or for the vaccine itself.

Besides the obvious R&D capacity considerations, once a product was exported to countries where one or several patents are issued, some level of IP management/licensing might still be required.

Variant 2: Facilitate international linkages with centers of excellence, both public and private, in innovative developing countries

Definition

The capability to undertake health innovation in many developing countries is rapidly growing. Such Innovative Developing Countries (IDCs) have the capacity to develop, manufacture, ensure the safety, and market new health products and to develop, test, and introduce new health policies or strategies. They are distinguished by their rapidly growing strength in health innovation, as illustrated by expanding patenting and publishing activities; increasing investments in technology by both the public and private sectors; rapidly growing numbers of health technology companies; and health systems able to analyze, evaluate, and adopt new practices and technologies.

This innovation capability provides an underleveraged opportunity to accelerate the development of new products, policies, and strategies for diseases of the poor. The primary mission of an *Initiative for Health Product Innovation in Developing Countries* would be to accelerate the translation of new knowledge into health innovations that are relevant to diseases of the poor and to economic growth, taking into account national priorities and sensitivities. The Initiative could promote innovation through programs to:

- support research on health innovation systems;
- promote collaboration and coordination among countries to develop, disseminate and implement good practices; and
- implement demonstration projects. (Morel et al 2005b)

Analysis

Although only proposed in 2004 at a Bellagio meeting organized by the Rockefeller Foundation, MIHR, and Arizona State University, and first published in 2005, the idea of IDCs has garnered significant attention. The concept has several appealing features with the potential for major impacts: the streamlining of resources, the conduct of R&D close to the location of the overwhelming health needs in developing countries, and proximity to neighboring countries with lower incomes and resources. Since IDCs are partly defined as countries with public and private R&D institutions that patent inventions to a certain degree, it follows that IP management is emerging as an important field. In order to strengthen this, the proposed strategy would target specific initiatives centered on pandemic flu, malaria, and/or SARS through a two-pronged approach:

- The formation of a consortium of R&D institutions to funnel potentially valuable health-related IP to IDCs, thus promoting access to improved health technologies for poorer populations in developing countries. A consortium would need to be assembled that would provide a defined mechanism for licensing and IP management. Technologies of possible interest to developing countries would be made available, and public-private partnerships for product development would be facilitated.
- The formation of a "Sister Institutions" program. R&D centers in a developing country would form an on-going, mutually beneficial relationship for capacity building and experience sharing in IP management and licensing. Based on the Technology Managers for Global Health (TMGH) experience (an AUTM initiative), it is clear that U.S. and Canadian universities are prepared to reach out to their developing country counterparts to provide training and capacity building experiences, including internships and visiting staff exchanges. This concept could be expanded to in-

clude private-private interfaces, as well as a combination of private-public programs. Whereas the "Sister Institutions" program seeks to strengthen IP management capabilities, this proposal would promote linkages for specific product development R&D (viz., pandemic influenza, malaria and/or SARS).

Applicability and Feasibility
This aspect fits broadly into the overall IP management strategic formulations for international development policies, incentives, and specific initiatives. The concept is designed not only to encourage developing countries but to assist leading institutions with the specific tools necessary for its implementation.

6.9 Take no action

Definition
Let market forces determine the development and distribution of a vaccine.

Analysis
While market forces are essential for developing a vaccine, it is unlikely that they would quickly move a vaccine to market, particularly the "invisible" market of the very poor in developing countries. It is generally accepted that for vaccines, there is no *a priori* market to drive development. This is the heart of the problem. With the "take no action" approach, countries will likely to plan to adopt compulsory licensing, which will decrease present and future investments and innovation in vaccine technologies, research, and development. In other words, what ensues is a downward spiral, a race to the bottom, with no winners … only losers.

Applicability and Feasibility
These three case studies, most notably of pandemic influenza and to a lesser degree malaria, provide us with important knowledge that gives us the chance to significantly change how we view and use IP in developing countries. If we fail to pursue new IP management initiatives that creatively strengthen partnerships and build institutions, we lose not only the chance to help millions of people who will suffer and die from these three diseases, but also the positive repercussions of these changes for many other R&D efforts and initiatives related to diseases of the poor.

The "do nothing approach" raises the critical question of whether or not to even seek IP rights protection, a question that is important to consider and work through because some have strongly advocated against the global harmonization of IP rights. While this approach may be an option in developing countries where IP rights to not protect key technologies, the crucial question is really what IP is required to further research, develop, and commercialize an urgently needed medical product. IP rights also play a critical, indispensable role in attracting investments.

6.10 Open source and capacity building

Over the past several years, pandemic influenza received a lot of attention. Within the context of this potential threat, IP *per se* is surely an important and constant consideration. But an "integration" of IP into a wider product development strategy is also crucial. It allows for a contextual model of analysis that addresses the interrelated facets of the influenza challenge. This information must be presented to the general population to galvanize public opinion and put pressure on leaders to act. This must be followed by "organization": maintaining momentum with public and political support for constructing an organization that will facilitate global access. A six step action agenda could:

1. Assess and then communicate the level of the threat.
2. What tools are available now? Soon? Later?
3. Determine the level of national infrastructure that supports vaccine development and distribution, *i.e.*,
   - Manufacture,
   - Distribution,
   - Storage, and
   - Administration.
4. Policy development will be key.
5. Finances are critical because gaps must be filled for short-, medium- and long-term special groups.
6. Legal and IP issues are interwoven throughout.

The fundamental premise is that without the presence of the first three, there may not be any need to address any potential IP constraints.

In terms of institutional structure, a Global Fund/PATH hybrid organization with a global mandate specifically for managing technologies and IP

related to avian and pandemic influenza should be created. This would be a one-stop shopping entity for access. This organization would have both global managerial authority and financial accountability (precedents include successful AIDS initiatives). Specifically serving the needs of developing countries, the organization would serve medium- and longer term-needs by managing finances, technology and IP.

Within the broad discussion of IP issues, the concept of open source inevitable arises. Often mentioned as a possible option, it likely raises more questions than it answers. For example, what would be the effects and consequences of going with open source in health innovation? A proposed model needs to be carefully and critically evaluated. OECD best practices for licensing genomic technology might be a place to start this sort of discussion.

However broad the discussion of IP issues might be, it is important to note that training in IP rights management is critical for both developed and developing countries. It is a universal condition for success. Building IP institutions will require long-term focused action in order to lead to sustainable results, and more *pro bono* services are needed for developing countries (*e.g.*, PIIPA and PIPRA), a contribution that has also been an important part of WIPO's mission and agenda.

6.11 Specific issues related to Pandemic influenza

The Threat

Unlike SARS, anthrax, and HIV/AIDS, "influenza" is not viewed as an exotic, unknown threat. Indeed, the public's perception in developed countries that "Nobody dies from infectious disease" may be what has restrained public alarm, especially for a menace as familiar as "influenza." The word "influenza" itself may hide the real threat level (imagine if the word "plague" were used instead). Such inappropriate perceptions about a pandemic influenza must be corrected. Influenza is generally not perceived to be a major public threat but rather like a bad cold. Mistakenly, people assume that they already know what "the flu" is, including the highly lethal avian influenza H5N1.

Tools, Vaccines, and Drugs

The H5N1 strain of influenza virus does not replicate well under laboratory conditions, which will dramatically reduce the capacity for vaccine production. To reduce the amount of virus antigen, trial vaccine must be adjuvanted. Safe and widely used in other vaccines, alum adjuvant is a very practical option that is not covered by a patent. However, this should not rule out work on other potentially superior adjuvants, since alum may still not prove suitably antigen sparing (*e.g.*, Chiron has developed a proprietary adjuvant).

In terms of vaccine production, scale-up issues are not necessarily specific to the antigen(s). At the moment, if vaccine could be mass-produced via tissue culture, it would still be very sophisticated but costly. Egg-based production is therefore the (current) feasible approach. Orienting the approach via the worst-case scenario, it is critically important to find ways to optimize the use of current technologies that can be quickly scaled-up.

Infrastructure Issues

Issues relating to infrastructure can be conceptualized under four broad headings:

1) Manufacture:
   a. Process Technology IP,
   b. Cell vs. egg,
   c. Available plants/facilities,
   d. New plants,
   e. Regional/country location,
   f. "Competition" with existing vaccine production, and
   g. Technology transfer issues.
2) Distribution (technology and politics). Would there be coverage if there were a vaccine? PDP vaccine achieves only 50% coverage in India….
3) Storage.
4) Administration.

A reverse genetics-engineered reassortment virus incorporating genes from the surface antigens of pandemic virus and the internal genes of another virus influenza virus can be prepared in about two weeks and distributed to all vaccine companies. The critical issue is to make sure that the HN51 strain replicates well in production facilities and is immunogenic. Only then should we deal with scale-up timing issues.

The next consideration revolves around vaccine distribution policy. This decision would be made by political and not economic or epidemiological factors. For example, even if Argentina had an advance purchasing agreement with Germany for vaccines

and Poland did not, it would be inconceivable that doses would not be sent to Poland before Argentina. This is why Vietnam is developing its own vaccine manufacturer—it realizes that it would not be able to rely on an outside supply.

Price spikes would potentially confuse distribution (both globally and within each country). A good supply response is the best way to dampen these (theory and evidence of asset and commodity price bubbles tells us this). The best response is to globally distribute a more than adequate supply—not a targeted distribution of a less than adequate supply.

Policy

Broadly speaking, policy issues can be conceptually reduced to five components:

1) Regulatory convergence (this will also help create more flexible international markets for influenza vaccines),
2) Global fund with a global mandate,
3) Removing barriers to IP and technology-transfer,
4) Education and capacity building, and
5) A distribution policy for limited production (both within country and trans-nationally).

The "Global Fund" concept is a possible institutional mechanism for overcoming obstacles and advancing feasible agendas. In terms of an institutional structure, a Global Fund/PATH hybrid organization with a global mandate specifically for managing technologies and IP related to avian and pandemic influenza should be created. This would be a one-stop shopping entity for global access. With the precedent of existing successful AIDS initiatives, the organization would have both global managerial authority and financial accountability.

- Unlike PATH, the Global Fund would not develop vaccines. The advantages of a "Global Fund" type set-up with a "global mandate" are:
  - It helps to "pull activities together". Indeed, the original Global Fund was created because other players were not/could not pull together;
  - It has political legitimacy/authority;
  - It is accountable;
  - It "gets others off the hook", a useful political advantage;
  - It is a managerial authority and can write contracts;
  - It would be taking on an already working model. It "has precedent".
- The emphasis here is on the word "manage" not so much on the word "coordinate". Management equals authority, that is, action.

With regard to pandemic influenza, there appears to be a general lack of leadership. The suggested organization would fill this void and begin to address those needs that established organizations and their leadership have not adequately addressed.

Legal issues

Focusing on issues related to IP, legal considerations might be premature if there are still outstanding and serious problems vis-à-vis the above issues. However, IP challenges are likely on the horizon with some of the newer technologies; given the multi-step process in vaccine research, development, production, and deployment, the question of whether IP issues are resolved remains open.

7. Conclusion and proposed follow-up

7.1 Intellectual asset management for the building of international partnerships and the creation of value

This comprehensive paper examines options and possible modalities of patent pool arrangements related to the development of a pandemic (avian) flu vaccine, SARS diagnostics and treatments, and malaria vaccines. It identified critical issues affecting the current and future provision of vaccines to developing countries and analyzed several possible solutions related to the three infectious diseases. The results of these case studies clearly indicate that creative/dynamic management of IP is integral to fostering global access for critically essential vaccines in the developing world.

The study incorporated:

1. Analysis of patent landscape and literature,
2. Consideration of potential IP constraints,
3. Development of various business models to overcome and manage IP constraints in a proactive manner, and
4. Evaluation of the comparative advantages of the

various business models, as well as the determination of which one(s) are most appropriate for the different health challenges.

This analysis carefully considered the feasibility of patent pools in relation to IP issues and the changing contexts of vaccine R&D, including product divergence across markets, the rapid emergence of suppliers in developing nations, potential arrangements to be forged between the R&D based industry and emerging suppliers, and the role of PDPs. In the case of SARS, a patent pool related to genomic data is already being pursued through the U.S. Public Health Service. They are completing a licensing strategy. Vaccine technologies were emphasized in the analysis because IP has an increasing potential to act as a disincentive and hamper or block vaccine R&D. This is especially true of critical technologies such as recombinant and sub-unit vaccines.

The research tool access problem is of course a general challenge for the scientific community. Creative resolutions in the health sciences, however, may find the most fertile ground in the context of global health products, since they represent non-commercial or low margin R&D and industry may be more amenable to shared schemes. Indeed, we are learning through the experience of PDPs that companies have several motivations to work collaboratively and share IP that is relevant to neglected diseases with the public sector. These motivations include corporate social responsibility and strategic considerations, such as positioning for emerging markets or the cross-applicability of neglected disease research and platform technologies for commercial projects.

7.2 MIHR and PIPRA

Depending on the particular needs of the scientific challenge, an emerging range of IP management tools can be applied (*e.g.*, patent pools, humanitarian licensing, clearing house reduction of transaction costs, open source schemes). However, it is important to note that existing *ad hoc* experiments in IP management are often inefficient or fragmented. MIHR and PIPRA have discussed the need for an organized effort to identify where and when current or emerging IP management strategies might best be applied so that their application can be facilitated. There are a number of platforms in need of analysis, platforms that should be given thoughtful attention by research agencies and foundations concerned with development. This includes qualitative research to identify public-sector best practices that encourage commercial development but obtain the broadest public benefit. Inventories of IP rights currently held by the public sector (and their licensing status) could assist inventors. Most importantly, scalable models of collaborative marketing and pooling that would enable greater research access could be explored and piloted.

On this latter point, PIPRA has noted that there are opportunities that have yet to be explored. In the health arena, MIHR and PIPRA have discussed the instructive precedent of the Single Nucleotide Polymorphism consortium, which is exemplary for a number of reasons, not least of which is their combined use of defensive publishing and patenting to achieve a well-defined goal. iEdison, the invention disclosure databank for NIH-sponsored research, also offers a particularly interesting prospect. A PIPRA-like organization in health, first tested as a pilot with a limited subset of NIH-funded technologies, is therefore a model worthy of serious consideration. Propitiously, the licensing information (to varying degrees of accuracy) has been collected already in iEdison. MIHR has not yet advanced such discussions within NIH. But it is one possible direction.

In sum, the challenge is to identify the specific enabling technology platforms around which the alignment of public-private interests are ripe. Even more importantly, the key players who should be brought together to discuss such a consortium-based approach need to be identified. If the formative days of PIPRA provide any roadmap, what is required is:

1. leadership from one or more of the core IP owners,
2. a supportive donor to provide management/analysis support, and
3. a trusted third party catalyst.

References

Clark J *et al.* Patent Pools: A Solution to the Problem of Access in Biotechnology Patents? *United States Patent and Trademark Office*, December 5, 2000

DiMasi, J.A., *Risks in new drug development: approval success rates for investigational drugs.* Clin Pharmacol Ther, 2001. **69**(5): p. 297-307.

Essential Inventions. 2005. Essential Patent Pool for AIDS (EPPA). Background Information. Essential Inventions: Washington DC. www.essentialinventions.org

Gaulé P. 2006. Towards Patent Pools in Biotechnology? Innovation Strategy Today Vol 2, No 2. pp 123-134. www.biodevelopments.org/innovation/index.htm

Klein JI. 1997. An address to the American Intellectual Property Law Association on the subject of cross-licensing and antitrust law. www.usdoj.gov/atr/public/speeches/1123.htm

Krattiger, AF. 2004. Financing the Bioindustry and Facilitating Biotechnology Transfer. *IP Strategy Today* No. 8-2004. www.bioDevelopments.org/ip

Krattiger A, RT Mahoney, JD Clemens and R Curtiss. 2006. The Introduction of New Vaccines into Developing Countries IV: Global Access Strategies. Submitted.

Lall, S., *Indicators of the Relative Importance of IPRs in Developing Countries*, in *Intellectual Property Rights and Sustainable Development*. 2003, International Centre for Trade and Sustainable Development: Geneva.

Lee, J., Zong-Tae Bae and Dong-Kyu Choi, *Technology Development Processes: A Model for a Developing Country with Global Perspective.* R&D Management, 1988. **18**: p. 235-250.

Mahoney, R., *Policy Analysis: An Essential Research Tool for the Introduction of Vaccines in Developing Countries.* Journal of Health, Population and Nutrition, 2004. **22**.

Mahoney, R., K Lee and MK Yun, *The evolution of biotechnology in Korea: a Framework for Analysis; a case study of the vaccine industry.* Innovation Strategy Today, 2005.

Merges RP. 1999. Institutions for Intellectual Property Transactions: The Case of Patent Pools. August, 1999 Revision. University of California at Berkeley (Boalt Hall) School of Law. http://www.law.berkeley.edu/institutes/bclt/pubs/merges/pools.pdf

Moran M, A.R., J Guzman, J Diaz, C Garrison, *The new landscape of neglected diseases*. 2005, Wellcome Trust: London.

Morel CM, T Acharya, D Broun, A Dangi, C Elias, NK Ganguly, CA Gardner, RK Gupta, J Haycock, AD Heher, PT Hotez, HE Kettler, GT Keusch, AF Krattiger, FT Kreutz, S Lall, K Lee, R Mahoney, A Martinez-Palomo, RA Mashelkar, SA Matlin, M Mzimba, J Oehler, FG Ridley, P Senanayake, P Singera and M Yun. 2005a. Health Innovation Networks to Help Developing Countries Address Neglected Diseases. *Science* VOL 309:401-404. 15 JULY 2005.

Morel C, D Broun, A Dangi, C Elias, C Gardner, RK Gupta, J Haycock, T Heher, P Hotez, H Kettler, G Keusch, A Krattiger, F Kreutz, K Lee, R Mahoney, RA Mashelkar, Hongki Min, S Matlin, M Mzimba, J Oehler, R Ridley, P Senanayake, H Thorsteinsdóttir, PA Singer and Mikyung Yun. 2005b. Health Innovation in Developing Countries to Address Diseases of the Poor. *Innovation Strategy Today* 1(1):1-15. www.biodevelopments.org/innovation/index.htm

PATH 2006. http://www.malariavaccineroadmap.net/index.html

Strickland P. Patent Pools and Cross Licences are Under Review. *News Exchange (Licensing Executive Society of Britain and Ireland)* **90** April-May 2003.

van Zimmeren E, V Verbeure, G Matthijs, and G Van Overwalle. 2006. A Royalty Collection Clearinghouse for Diagnostic Testing: the Solution to Ensure Access to *and* Use of Patented Genetic Technology? *WHO Bulletin*, in press.

Notes

1 See also Lall 2003; Mahoney 2004; Mahoney *et al* 2005.

2 The U.S. Patent Office issued a useful paper on this issue which concluded that patent pooling in the research tools area could be valuable and pro-competitive (see Clark 2000).

3 There were three flu pandemics in the 20th century. All of them spread worldwide within 1 year of being detected:

- 1918-19, "Spanish flu" (Type A H1N1) caused the highest number of known flu deaths: more than 500,000 people died in the U.S. Estimates for worldwide mortality range from 20 to 60 million. In India alone over 7 million are estimated to have died. Many died within the first few days; others died of complications soon after. Unlike typical epidemic flu, which kills predominantly the old, the infirm, and the very young, nearly half of those who died were young, healthy adults.
- 1957-58, "Asian flu" (Type A H2N2) caused about 80,000 deaths in the United States and 1 million worldwide. First identified in China in late February 1957, the Asian flu spread to the United States by June 1957.
- 1968-69, "Hong Kong flu" (Type A H3N2) caused approximately 34,000 deaths in the United States and an estimated 700,000 worldwide. This virus was first detected in Hong Kong in early 1968 and spread to the United States later that year. Type A H3N2 viruses still circulate today.

Both the 1957-58 and 1968-69 pandemic viruses were a result of the reassortment of a human virus with an avian influenza virus. The origin of the 1918 pandemic virus is unclear. Once a new pandemic influenza virus emerges and spreads, it typically becomes established among people and circulates for many years (Source CDC Website, Nguyen-Van-Tam, J, Hampson, A, The epidemiology and clinical impact of pandemic influenza *Vaccine* (2003))**21** 1762-1768 .

4 Gerdil, C. The annual production cycle for influenza vaccine. *Vaccine* (2003) **21** 1776-1779

[5] Solvay's cell culture flu vaccine has recently been approved for sale in the Netherlands.

[6] Adapted from "Intellectual Property Rights and Vaccines for Developing Countries," WHO Meeting Report, 19-20 April, 2004.

[7] Evidently, there are exceptions to this. For example, reverse genetics would be one such platform technology. But the IP situation surrounding reverse genetics is "simple" by any standard and hardly requires even talk of a patent pool.

[8] The term "health innovation" includes the development of new drugs, vaccines, and diagnostics, as well as new techniques in process engineering/manufacturing and new approaches/policies in health systems and services.

[9] www.tmgh.org

Appendices

The following tables are intended solely as illustrative examples of overall patent landscapes, and are not intended, either implicitly or explicitly, as comprehensive or complete listings.

A. Patents related to certain recombinant vaccine productions and pandemic influenza

Table A1. Reverse Genetics

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
5166057	Filed: May 22, 1990; ; Issued: November v24, 1992	Recombinant negative strand RNA virus expression-systems	Palese; Peter (Leonia, NJ); Parvin; Jeffrey D. (Belmont, MA); Krystal; Mark (Leonia, NJ)	The Mount Sinai School of Medicine of The City University of New York (New York, NY)
5578473	Filed: March 10, 1994; ; Issued: November 26, 1996	Recombinant negative strand RNA virus	Palese; Peter (Leonia, NJ); Parvin; Jeffrey D. (Belmont, MA); Krystal; Mark (Leonia, NJ)	Aviron, Inc. (Mountain View, CA)
5820871	Filed: June 6, 1995; ; Issued: October 13, 1998	Recombinant negative strand RNA virus expression systems and vaccines	Palese; Peter (Leonia, NJ); Garcia-Sastre; Adolfo (New York, NY)	The Mount Sinai School of Medicine of the City University of New York (New York, NY)
5854037	Filed: June 1, 1994; ; Issued: December 29, 1998	Recombinant negative strand RNA virus expression systems and vaccines	Palese; Peter (Leonia, NJ); Garcia-Sastre; Adolfo (New York, NY)	The Mount Sinai School of Medicine of the City University of New York (New York, NY)
6001634	Filed: June 29, 1998; ; Issued: December 14, 1999	Recombinant negative strand RNA viruses	Palese; Peter (414 Highwood Ave., Leonia, NJ 07605); Garcia-Sastre; Adolfo (1249 Park Ave., #8D, New York, NY 10029)	
6524588	Filed: March 24, 1997; ; Issued: February 25, 2003	Attenuated vaccination and gene-transfer virus, a method to make the virus and a pharmaceutical composition comprising the virus	Hobom; Gerd (Arndtstrasse 14, D 35392 Giessen, DE); Neumann; Gabriele (Maintal, DE); Menke; Annette (Marburg, DE)	Hobom; Gerd (Giessen, DE)
6544785	Filed: July 14, 2000; ; Issued: April 8, 2003	Helper-free rescue of recombinant negative strand RNA viruses	Palese; Peter (Leonia, NJ); Garcia-Sastre; Adolfo (New York, NY); Brownlee; George G. (Oxford, GB)	Mount Sinai School of Medicine of New York University (New York, NY)
6649372	Filed: November 28, 2000; ; Issued: November 18, 2003	Helper-free rescue of recombinant negative strand RNA virus	Palese; Peter (Leonia, NJ); Garcia-Sastre; Adolfo (New York, NY); Brownlee; George G. (Oxford, GB); Fodor; Ervin (Oxford, GB)	Mount Sinai School of Medicine of New York University (New York, NY)
6,887,699	Filed: September 14, 1999; Issued: May 3, 2005	Recombinant negative strand RNA virus expression systems and vaccines	Palese; Peter (Leonia, NJ); Garcia-Sastre; Adolfo (New York, NY)	MedImmune Vaccines, Inc. (Mountain View, CA)
6951754	Filed: April 27, 2001; ;	DNA transfection system for	Hoffmann; Erich (Memphis,	St. Jude Children's Research

	Issued: October 4, 2005;	the generation of infectious influenza virus	TN)	Hospital (Memphis, TN)
20020164770	Filed: April 27, 2001; Publication: November 7, 2002	DNA transfection system for the generation of infectious influenza virus	Hoffmann, Erich; (Memphis, TN)	St. Jude Children's Research Hospital
20030035814	Filed: October 4, 2001; Publication: February 20, 2003	Recombinant influenza viruses for vaccines and gene therapy	Kawaoka, Yoshihiro; (Middleton, WI) ; Neumann, Gabriele; (Nanuet, NY)	
20030129729	Filed: October 1, 2002; Publication: July 10, 2003	Novel methods for rescue of RNA viruses	Parks, Christopher L.; (Boonton, NJ) ; Sidhu, Mohinderjit S.; (Scotch Plains, NJ) ; Udem, Stephen A.; (New York, NY) ; Kovacs, Gerald R.; (Morristown, NJ)	
20040002061	Filed: February 12, 2003; Publication: January 1, 2004	Signal for packaging of influenza virus vectors	Kawaoka, Yoshihiro; (Middleton, WI)	
20040029251	Filed: April 25, 2003; ; Publication: February 12, 2004	Multi plasmid system for the production of influenza virus	Hoffman, E; (Sunnyvale, CA) ; Jin, Hong; (Cupertino, CA) ; Lu, Bin; (Los Altos, CA) ; Duke, Greg; (Redwood City, CA) ; Kemble, George; (Saratoga, CA)	MedImmune Vaccines, Inc.
20040142003	Filed: August 28, 2003; Publication: July 22, 2004	Helper-free rescue of recombinant negative strand RNA virus	Palese, Peter; (Leonia, NJ) ; Garcia-Sastre, Adolfo; (New York, NY) ; Brownlee, George G.; (Oxford, GB) ; Fodor, Ervin; (Oxford, GB)	
20040219170	Filed: April 20, 2004; Publication: November 4, 2004	Viruses encoding mutant membrane protein	Kawaoka, Yoshihiro; (Middleton, WI)	
20040241139	Filed: July 19, 2001; Publication: December 2, 2004	Recombinant influenza viruses with bicistronic vRNAs coding for two genes in tandem arrangement	Hobom, Gerd; (Giessen, DE) ; Menke, Annette; (Marburg, DE) ; Meyer-Rogge, Sabine; (Laubach-Munster, DE)	
20050003349	Filed: May 27, 2004; ; Publication: January 6, 2005	High titer recombinant influenza viruses for vaccines and gene therapy	Kawaoka, Yoshihiro; (Middleton, WI)	
20050032043	Filed: April 7, 2004; Publication: February 10, 2005	Recombinant negative strand RNA virus expression systems and vaccines	Palese, Peter; (Leonia, NJ) ; Garcia-Sastre, Adolfo; (New York, NY)	
20050037487	Filed: May 27, 2004; Publication: February 17, 2005	Recombinant influenza vectors with a PolII promoter and ribozymes for vaccines and gene therapy	Kawaoka, Yoshihiro; (Middleton, WI) ; Hamm, Stefan; (River Vale, NJ) ; Ebihara, Hideki; (Winnipeg, CA)	
20050158342	Filed: December 22, 2004; Publication: July 21, 2005	Multi plasmid system for the production of influenza virus	Kemble, G; (Saratoga, CA) ; Duke, G ; (Redwood City, CA)	
20050186563	Filed: March 29, 2005; ; Publication: August 25, 2005	DNA transfection system for the generation of infectious influenza virus	Hoffmann, Erich; (Memphis, TN)	
20050221489	Filed: May 17, 2005; Publication: October 6, 2005	Recombinant negative strand virus rna expression systems and vaccines	Garcia-Sastre, Adolfo; (New York, NY) ; Palese, Peter; (Leonia, NJ)	
20050266026	Filed: May 20, 2005; Publication: December 1, 2005	Multi plasmid system for the production of influenza virus	Hoffmann, Erich; (Memphis, TN) ; Jin, Hong; (Cupertino, CA) ; Lu, Bin; (Los Altos, CA) ; Duke, Gregory; (Redwood City, CA) ; Kemble, G; (Saratoga, CA) ; Chen, Z; (Cupertino, CA)	
CN1624116	Publication date: 2005-06-08;	Artificial recombined influenza virus and its application	CHEN HUALAN (CN); YU KANGZHEN (CN); TIAN GUOBIN (CN)	HARBIN VETERINARY INST CHINESE (CN)
WO2005062820	Published: 2005-07-14;	MULTI PLASMID SYSTEM FOR THE PRODUCTION OF	DUKE GREG (US); KEMBLE GEORGE (US)	MEDIMMUNE VACCINES INC (US); DUKE GREG (US);

		INFLUENZA VIRUS		KEMBLE GEORGE (US)
WO2005115448	Published: 2005-12-08;	MULTI PLASMID SYSTEM FOR THE PRODUCTION OF INFLUENZA VIRUS	HOFFMANN ERICH (US); JIN HONG (US); LU BIN (US); DUKE GREGORY (US); KEMBLE GEORGE (US); CHEN ZHONGYING (US)	MEDIMMUNE VACCINES INC (US); HOFFMANN ERICH (US); JIN HONG (US); LU BIN (US); DUKE GREGORY (US); KEMBLE GEORGE (US); CHEN ZHONGYING (US)

Table A2. Mutants

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
6090391	Filed: February 23, 1996;;Issued: July 18, 2000;;;	Recombinant tryptophan mutants of influenza	Parkin; Neil T. (Belmont, CA)	Aviron (Mountain View, CA)
6022726	Filed: December 20, 1994;;Issued: February 8, 2000;	Genetically engineered attenuated viruses	Palese; Peter (414 Highwood Ave., Leonia, NJ 07605); Muster; Thomas (Nussadorser Lande 11, A-1190 Vienna, AT); Masayoshi; Enami (Heiwashukusha C-54-33, Heiwamachi 3-20-10, Kanazawa, Ishikawa 921, JP); Bergmann; Michael (10 E. 95th St., #10, New York, NY 10128)	
6316243	Filed: June 6, 1995;;Issued: November 13, 2001;	Genetically engineered attenuated double-stranded RNA viruses	Palese; Peter (414 Highwood Ave., Leonia, NJ 07605)	
6322967	Filed: July 10, 2000;;Issued: November 27, 2001;;	Recombinant tryptophan mutants of influenza	Parkin; Neil T. (Belmont, CA)	Aviron (Mountain View, CA)
6528064	Filed: November 26, 2001;;Issued: March 4, 2003;;	Recombinant trytophan mutants of influenza	Parkin; Neil T. (Belmont, CA)	Med Immune Vaccines, Inc. (Gaithersburg, MD)
6843996	Filed: December 1, 1999;;Issued: January 18, 2005;;	Immunogenic composition comprising an influenza virus with a temperature sensitive PB2 mutation	Parkin; Neil T. (South San Francisco, CA); Coelingh; Kathleen L. (Mountain View, CA)	Medimmune Vaccines, Inc. (Mountain View, CA)
6,866,853	Filed: December 9, 2002;Issued: March 15, 2005;	Interferon inducing genetically engineered attenuated viruses	Egorov; Andrei (Vienna, AT); Muster; Thomas (Vienna, AT); Garcia-Sastre; Adolfo (New York, NY); Palese; Peter (Leonis, NJ); Brandt; Sabine (Vienna, AT)	Mount Sinai School of Medicine of New York University (New York, NY)
6872395	Filed: April 12, 2001;;Issued: March 29, 2005;;	Viruses comprising mutant ion channel protein	Kawaoka; Yoshihiro (Madison, WI)	Wisconsin Alumni Research Foundation (Madison, WI)
6974686	Filed: December 20, 2002;;Issued: December 13, 2005;	Recombinant tryptophan mutants of influenza	Parkin; Neil T. (Belmont, CA)	MedImmune Vaccines, Inc. (Mountain View, CA)

Table A3. Cell Culture

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
4,783,411	Filed: October 22, 1984; Issued: November 8, 1988	Influenza-A virus vaccine from fish cell cultures	Gabliks; Janis (103 Cabot St., Newton, MA 02158)	

RE33,164	Filed: February 18, 1987; Issued: February 13, 1990;	Influenza vaccine production in liquid cell culture	Brown; Karen K. (Kansas City, MO); Stewart; Richard C. (Merriam, KS)	Mobay Corporation (Pittsburgh, PA)
5550051	Filed: December 1, 1994; ; Issued: August 27, 1996;	Avian embryo cell aggregate biomass for producing virus/virus antigen and method for producing virus/virus antigen	Mundt; Wolfgang (Vienna, AU); Woehrer; Wilfried (Bad Voeslau, AU); Dorner; Friedrich (Vienna, AU); Eibl; Johann (Vienna, AU)	Immuno Aktiengesellschaft (Vienna, AU)
5,753,489	Filed: June 7, 1995; Issued: May 19, 1998	Method for producing viruses and vaccines in serum-free culture	Kistner; Otfried (Vienna, AT); Barrett; Noel (Klosterneuberg/Weidling, AT); Mundt; Wolfgang (Vienna, AT); Dorner; Friedrich (Vienna, AT)	IMMUNO AG (Vienna, AT)
5,824,536	Filed: June 17, 1996; Issued: October 20, 1998	Influenza virus replicated in mammalian cell culture and vaccine production	Webster; Robert G. (Memphis, TN); Kaverin; Nicolai V. (Moscow, RU)	St. Jude Children's Research Hospital (Memphis, TN)
5840565	Filed: August 21, 1996; ; Issued: November 24, 1998;	Methods for enhancing the production of viral vaccines in PKR-deficient cell culture	Lau; Allan S. (San Francisco, CA)	The Regents of the University of California (Oakland, CA)
5,989,805	Filed: November 10, 1997; ; Issued: November 23, 1999	Immortal avian cell line to grow avian and animal viruses to produce vaccines	Reilly; John David (Lansing, MI); Taylor; Daniel C. (East Lansing, MI); Maes; Roger (Okemos, MI); Coussens; Paul M. (Lansing, MI)	Board of Trustees operating Michigan State University (East Lansing, MI)
6,146,873	Filed: October 15, 1997; Issued: November 14, 2000;	Production of orthomyxoviruses in monkey kidney cells using protein-free media	Kistner; Otfried (Vienna, AT); Barrett; Noel (Klosterneuburg/Weidling, AT); Mundt; Wofgang (Vienna, AT); Dorner; Friedrich (Vienna, AT)	Baxter Aktiengesellschaft (Vienna, AT)
6344354	Filed: June 16, 1998; ; Issued: February 5, 2002;	Influenza virus replicated in mammalian cell culture and vaccine production	Webster; Robert G. (Memphis, TN); Kaverin; Nicolai V. (Moscow, RU)	St. Jude Children's Research Hospital (Memphis, TN)
6,455,298	Filed: September 29, 1998; ; Issued: September 24, 2002;	Animal cells and processes for the replication of influenza viruses	Groner; Albrecht (Fasanenweg, DE); Vorlop; Jurgen (Marburg, DE)	Chiron Behring GmbH & Co. (Marburg, DE)
20030073223	Filed: July 12, 2002; ; Published: April 17, 2003;	Animal cells and processes for the replication of influenza viruses	Groner, Albrecht; (Seeheim, DE) ; Vorlop, Jurgen; (Marburg, DE)	Chiron Corporation
20030119183	Filed: September 16, 2002; ; Published: June 26, 2003;	Processes for the replication of influenza viruses in cell culture, and the influenza viruses obtainable by the process	Groner, Albrecht; (Seeheim, DE)	Chiron Corporation
6,656,720	Filed: July 12, 2002; Issued: December 2, 2003;	Animal cells and processes for the replication of influenza viruses	Groner; Albrecht (Seeheim, DE); Vorlop; Jurgen (Marburg, DE)	Chiron Behring GmbH & Co. (Marburg, DE)
6,686,190	Filed: December 13, 2000; Issued: February 3, 2004;	Methods for enhancing the production of viral vaccines in cell culture	Lau; Allan S. (San Francisco, CA)	The Regents of the University of California (Oakland, CA)
20040142450	Filed: November 5, 2003; ; Published: July 22, 2004;	Lung epithelial cell line for propagating viruses	Seo, Sang Heui; (Taejon, KR) ; Webster, Robert C; (Memphis, TN)	
20050202553	Filed: February 15, 2005; ; Published: September 15, 2005	Animal cells and processes for the replication of influenza viruses	Groner, Albrecht; (Seeheim, DE) ; Vorlop, Jurgen; (Marburg, DE)	CHIRON BEHRING GMBH & CO

6,951,752	Filed: December 10, 2001; Issued: October 4, 2005;	Method for large scale production of virus antigen	Reiter; Manfred (Vienna, AT); Mundt; Wolfgang (Vienna, AT)	Bexter Healthcare S.A. (Kanton Zurich, CH)
WO9216619	Publication date: 1992-10-01;	Expression Of Influenza Nucleoprotein Antigens In Baculovirus	ROTA PAUL A (US); BLACK RENNE A (US)	US ARMY (US)
WO9924068	Publication date: 1999-05-20;	Immortal Avian Cell Line To Grow Avian And Animal Viruses To Produce Vaccines	REILLY JOHN DAVID; TAYLOR DANIEL C; MAES ROGER; COUSSENS PAUL M	UNIV MICHIGAN (US)
WO2005024039	Publication: 2005-03-17;	Improved Method For Generating Influenza Viruses And Vaccines	WEBSTER ROBERT GORDON (US); WEBBY RICHARD JOHN (US); OZAKI HIROICHI (US)	ST JUDE CHILDREN S RES HOSPTIA (US); WEBSTER ROBERT GORDON (US); WEBBY RICHARD JOHN (US); OZAKI HIROICHI (US
WO2005113758	Publication: 2005-12-01;	Process For The Production Of An Influenza Vaccine	TREPANIER PIERRE (CA); DUGRE ROBERT (CA); HASSELL TOM (CA)	ID BIOMEDICAL CORP (CA); ID BIOMEDICAL CORP OF WASHINGT (US); TREPANIER PIERRE (CA); DUGRE ROBERT (CA); HASSELL TOM (CA)

Table A4. Adjuvants

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
5,679,356	Filed: January 5, 1995; ; Issued: October 21, 1997	Use of GM-CSF as a vaccine adjuvant	Bonnem; Eric M. (Mr. Vernon, NH); Chaudry; Imtiaz A. (North Caldwell, NJ); Stupak; Elliot (West Caldwell, NJ)	Schering Corporation (Kenilworth, NJ)
6024963	Filed: November 17, 1998; ; Issued: February 15, 2000;	Potentiation of immunogenic response	Becker; Robert S. (Henryville, PA); Biscardi; Karen (South Sterling, PA); Ferguson; Laura (Bethlehem, PA); Erdile; Lorne (Stroudsberg, PA	Connaught Laboratories, Inc. (Swiftwater, PA)
6090406	Filed: February 26, 1990; ; Issued: July 18, 2000;	Potentiation of immune responses with liposomal adjuvants	Popescu; Mircea C. (Plainsboro, NJ); Weiner; Alan L. (Lawrenceville, NJ); Recine; Marie S. (Hamilton Township, NJ); Janoff; Andrew S. (Yardley, PA); Estis; Leonard (Upton, MA); Keyes; Lynn D. (Upton, MA); Alving; Carl R. (Bethesda, MD)	The Liposome Company, Inc. (Princeton, NJ)
6,372,223	Filed: June 12, 2001; Issued: April 16, 2002	Influenza virus vaccine composition	Kistner; Otfried (Vienna, AT); Barrett; Noel (Klosterneuburg/Weidling, AT); Mundt; Wolfgang (Vienna, AT); Dorner; Friedrich (Vienna, AT)	Baxter Aktiengesellschaft (Vienna, AT)
6485729	Filed: August 11, 1999; ; Issued: November 26, 2002;	Neuraminidase-supplemented compositions	Smith; Gail Eugene (Wallingford, CT); Matthews; James T. (Allamuchy, NJ); Kilbourne; Edwin D. (Madison, CT); Johansson; Bert E. (Armonk, NY); Wilkinson; BE. (Higganum, CT); Voznesensky; Andrei I. (West Hartford, CT); Hackett; Craig S. (Wallingford, CT); Volvovitz; Franklin (Woodbridge, CT)	Protein Sciences Corporation (Meridien, CT)
6534065	Filed: May 30, 2000; ; Issued: March 18, 2003; ;	Influenza vaccine composition with chitosan adju-	Makin; Jill Catherine (Liverpool, GB); Bacon; Andrew	West Pharmaceutical Services Drug Delivery & Clini-

		vant	David (London, GB)	cal Research Centre (Nottingham, GB)
6565849	Filed: March 2, 2001; ; Issued: May 20, 2003; ; ;	Methods of enhancing activity of vaccines and vaccine compositions	Koenig; Scott (Rockville, MD)	MedImmune, Inc. (Gaithersburg, MD)
6641816	Filed: March 9, 2001; ; Issued: November 4, 2003;	Use of poxviruses as enhancer of specific immunity	Chevalier; Michel (Beaurepaire, FR); Meignier; Bernard (Thurins, FR); Moste; Catherine (Charbonnieres-les-Bains, FR); Sambhara; Suryaprakash (Markham, CA)	Aventis Pasteur S.A. (Lyons Cedex, FR)
6649172	Filed: March 16, 2001; ; Issued: November 18, 2003	Amphipathic aldehydes and their uses as adjuvants and immunoeffectors	Johnson; David A. (Hamilton, MT)	Corixa Corporation (Seattle, WA)
6797276	Filed: February 25, 1999; ; Issued: September 28, 2004;	Use of penetration enhancers and barrier disruption agents to enhance the transcutaneous immune response	Glenn; Gregory M. (Cabin John, MD); Alving; Carl R. (Bethesda, MD)	The United States of America as represented by the Secretary of the Army (Washington, DC)
WO9952549	Published: 1999-10-21	ADJUVANT COMPOSITIONS	FRIEDE MARTIN (BE); HERMAND PHILIPPE (BE)	SMITHKLINE BEECHAM BIOLOG (BE); FRIEDE MARTIN (BE); HERMAND PHILIPPE (BE)

Table A5. Excipient

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
6231860	Filed: September 21, 1998Issued: May 15, 2001	Stabilizers for live vaccines	Fanget; Bernard (Saint-Germain-sur-l'Arbresle, FR); Francon; Alain (Bessenay, FR)	Pasteur Merieux Serums & Vaccins (Lyons, FR)
6391318	Filed: June 1, 1998Issued: May 21, 2002	Vaccine compositions including chitosan for intranasal administration and use thereof	Illum; Lisbeth (Nottingham, GB); Chatfield; Steven Neville (Berkshire, GB)	West Pharmaceutical Services Drug Delivery & Clinical Research Centre (Nottingham, GB)
20040049150	Filed: August 12, 2003Published: March 11, 2004	Vaccines	Dalton, Colin Cave; (Rixensart, BE) ; Easeman, Richard Lewis; (Brentford, GB) ; Garcon, Nathalie; (Rixensart, BE)	SMITHKLINE BEECHAM CORPORATION
20040138165	Filed: October 30, 2003Published: July 15, 2004	DNA vaccine formulations	Volkin, David B.; (Doylestown, PA) ; Evans, Robert K.; (Soudertown, PA) ; Bruner, Mark; (Norristown, PA)	Merck & Co., Inc.
EP0906110	Publication: 1999-04-07	DNA VACCINE FORMULATIONS	VOLKIN DAVID B (US); EVANS ROBERT K (US); BRUNER MARK (US)	MERCK & CO INC (US)

Table A6. Vaccine

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
5674502	Filed: June 5, 1995Issued: October 7, 1997	Cross-reactive influenza a immunization	Ennis; Francis A. (Shrewsbury, MA)	University of Massachusetts Medical Center (Worcester, MA)
5766601	Filed: April 7, 1995Issued: January 16, 1998	Cross-reactive influenza a immunization	Ennis; Francis A. (Shrewsbury, MA)	University of Massachusetts Medical Center (Worcester, MA)
5897873	Filed: February 23, 1995Issued: April 13, 1999	Affinity associated vaccine	Popescu; Mircea (Plainsboro, NJ)	The Liposome Company, Inc. (Princeton, NJ)
5,916,879	Filed: November 12, 1996Issued: June 29, 1999	DNA transcription unit vaccines that protect against avian influenza viruses and methods of use thereof	Webster; Robert (Memphis, TN)	St. Jude Children's Research Hospital (Memphis, TN)

5882650	Filed: August 13, 1997Issued: March 16, 1999	Cross-reactive influenza A immunization	Ennis; Francis A. (Shrewsbury, MA)	University of Massachusetts Medical Center (Worcester, MA)
6,008,036	Filed: May 22, 1998Issued: December 28, 1999	Method for purifying viruses by chromatography	Fanget; Bernard (Saint-Germain-sur-l'Arbresle, FR); Francon; Alain (Bessenay, FR)	Pasteur Merieux Serums et Vaccins (Lyons, FR)
6136606	Filed: April 29, 1998Issued: October 24, 2000	Influenza vaccine compositions	Chatfield; Steven Neville (London, GB)	Medeva Holdings BV (Amsterdam, NL)
6,146,873	Filed: October 15, 1997Issued: November 14, 2000	Production of orthomyxoviruses in monkey kidney cells using protein-free media	Kistner; Otfried (Vienna, AT); Barrett; Noel (Klosterneuburg/Weidling, AT); Mundt; Wofgang (Vienna, AT); Dorner; Friedrich (Vienna, AT)	Baxter Aktiengesellschaft (Vienna, AT)
6,221,365	Filed: March 20, 1998Issued: April 24, 2001	NucA protein of Haemophilus influenzae	Jones; Kevin F. (New York, NY)	American Cyanamid Company (Madison, NJ)
6,245,532	Filed: October 9, 1998Issued: June 12, 2001	Method for producing influenza hemagglutinin multivalent vaccines	Smith; Gale E. (Middlefield, CT); Volvovitz; Franklin (New Haven, CT); Wilkinson; Bethanie E. (Middletown, CT); Voznesensky; Andrei I. (West Hartford, CT); Hackett; Craig S. (Wallingford, CT)	Protein Sciences Corporation (Meriden, CT)
6337181	Filed: December 21, 1998Issued: January 8, 2002	Method of specifying vaccine components for viral quasispecies	Stewart; Jeffrey Joseph (1 Club Rd., Chatham, NJ 07928); Litwin; Samuel (8328 Roberts Rd., Elkins Pk., PA 19027); Watts; Perry (8328 Roberts Rd., Elkins Pk., PA 19027)	
6337070	Filed: January 8, 1998Issued: January 8, 2002	Polypeptides for use in generating anti-human influenza virus antibodies	Okuno; Yoshinobu (Toyonaka, JP); Isegawa; Yuji (Takatsuki, JP); Sasao; Fuyoko (Ibaraki, JP); Ueda; Shigeharu (Nishinomiya, JP)	Takara Shuzo Co., Ltd. (Kyoto-Fu, JP)
6531313	Filed: October 26, 2000Issued: March 11, 2003	Invasive bacterial vectors for expressing alphavirus replicons	Goudsmit; Jaap (Amsterdam, NL); Sadoff; Jerald C. (Bluebell, PA); Koff; Wayne (Stony Brook, NJ)	International Aids Vaccine Initiative (New York, NY)
20020156037	Filed: September 7, 2001Published: October 24, 2002	DNA vaccine formulations	Volkin, David B.; (Doylestown, PA) ; Evans, Robert K.; (Soudertown, PA) ; Bruner, Mark; (Norristown, PA)	Merck & Co., Inc.
6635246	Filed: December 5, 2001Issued: October 21, 2003	Inactivated influenza virus vaccine for nasal or oral application	Barrett; Noel (Klosterneuburg/Weidling, AT); Kistner; Otfried (Vienna, AT); Gerencer; Marijan (Vienna, AT); Dorner; Friedrich (Vienna, AT)	Baxter Healthcare S.A. (Zurich, CH)
6669943	Filed: June 11, 1999Issued: December 30, 2003	Attenuated negative strand viruses with altered interferon antagonist activity for use as vaccines and pharmaceuticals	Palese; Peter (Leonia, NJ); Garcia-Sastre; Adolfo (New York, NY); Muster; Thomas (Vienna, AT)	Mount Sinai School of Medicine of New York University (New York, NY)
6740325	Filed: July 30, 2001Issued: May 25, 2004	Peptide-based vaccine for influenza	Arnon; Ruth (Rehovot, IL); Ben-Yedidia; Tamar (Mazkeret Batya, IL); Levi; Raphael (Yahud, IL)	Yeda Research and Development Co. Ltd. (Rehovot, IL)
6743900	Filed: February 15, 2001Issued: January 1, 2004	Proteosome influenza vaccine	Burt; David S. (Ormeaux, CA); Jones; David Hugh (Baie D'Urfe, CA); Lowell;	ID Biomedical Corporation of Quebec (Ville St. Laurent, CA)Appl. No.: 788280

			George H. (Hampstead, CA); White; Gregory Lee (Montreal, CA); Torossian; Kirkor (Verdun, CA); Fries, III; Louis F. (Columbia, MD); Plante; Martin (Montreal, CA)	
6,866,853	Filed: December 9, 2002Issued: March 15, 2005	Interferon inducing genetically engineered attenuated viruses	Egorov; Andrei (Vienna, AT); Muster; Thomas (Vienna, AT); Garcia-Sastre; Adolfo (New York, NY); Palese; Peter (Leonis, NJ); Brandt; Sabine (Vienna, AT)	Mount Sinai School of Medicine of New York University (New York, NY)
6,884,613	Filed: August 24, 2001Issued: April 26, 2005	Selective precipitation of viruses	Le Doux; Joseph M. (Decatur, GA); Yarmush; Martin L. (Newton, MA); Morgan; Jeffrey R. (Sharon, MA)	The General Hospital Corporation (Boston, MA)
20040109877	Filed: November 14, 2003Publication: June 10, 2004	Attenuated negative strand viruses with altered interferon antagonist activity for use as vaccines and pharmaceuticals	Palese, Peter; (Leonia, NJ) ; Garcia-Sastre, Adolfo; (New York, NY) ; Muster, Thomas; (Vienna, AT)	Mount Sinai School of Medicine of New York University (New York, NY)
20050054846	Filed: September 4, 2003Publication: March 10, 2005	Method for generating influenza viruses and vaccines	Webster, Robert Gordon; (Memphis, TN) ; Webby, Richard John; (Memphis, TN) ; Ozaki, Hiroichi; (Memphis, TN)	
20040265987	Filed: February 25, 2004Published: December 30, 2004	Methods of producing influenza vaccine compositions	Trager, George Robert; (San Mateo, CA) ; Kemble, George; (Saratoga, CA) ; Schwartz, Richard M.; (San Mateo, CA) ; Mehta, Harshvardhan; (Fremont, CA) ; Truong-Le, Vu; (Campbell, CA) ; Chen, Zhongying; (Los Altos, CA) ; Pan, Alfred A.; (Walnut Creek, CA) ; Tsao, Eric; (Potomac, MD) ; Wang, Chiaoyin Kathy; (Sunnyvale, CA) ; Yee, Luisa; (Los Altos, CA) ; Balu, Palani; (Cupertino, CA)	Medlmmune Vaccines, Inc.
CN1618956	Publication date: 2005-05-25	Virus strain for preventing poultry influenza and its animal infection model	CHEN ZE (CN)	WUHAN INST OF VIROLOGY CAS (CN)
CN1632124	Publication date: 2005-06-29	Gene encoding hemagglutinin protein of H5 avian influenza virus and its application	CHEN HUALAN (CN); JIANG YONGPING (CN); BU ZHIGAO (CN)	HARBIN VETERINARY RES INST CAA (CN)

WO02064757	Publication date: 2002-08-22	INFLUENZA VIRUSES WITH ENHANCED TRANSCRIPTIONAL AND REPLICATIONAL CAPACITIES	HOBOM GERT; MENKE ANNETTE	ARTEMIS PHARMACEUTICALS GMBH (DE)
WO2004022760	Publication date: 2004-03-18	GENERATION OF RECOMBINANT INFLUENZA VIRUS USING BACULOVIRUS DELIVERY VECTOR	GRABHERR REINGARD (AT); EGOROV ANDREJ (AT); POOMPUTSA KANOKWAN (TH); ERNST WOLFGANG (AT); KITTEL CHRISTIAN (AT); KATINGER HERMANN (AT)	POLYMUN SCIENT IMMUNBIO FORSCH (AT); GRABHERR REINGARD (AT); EGOROV ANDREJ (AT); POOMPUTSA KANOKWAN (TH); ERNST WOLFGANG (AT); KITTEL CHRISTIAN (AT); KATINGER HERMANN (AT)
WO2005018539	Publication date: 2005-03-03	INFLUENZA HEMAGGLUTININ AND NEURAMINIDASE VARIANTS	YANG CHIN-FEN (US); KEMBLE GEORGE (US); LIU C G (US)	MEDIMMUNE VACCINES INC (US); YANG CHIN-FEN (US); KEMBLE GEORGE (US); LIU C G (US)
WO2005020889	Publication date: 2005-03-10	FUNCTIONAL INFLUENZA VIRUS-LIKE PARTICLES (VLPS)	ROBINSON ROBIN A (US); PUSHKO PETER M (US)	NOVAVAX INC (US); ROBINSON ROBIN A (US); PUSHKO PETER M (US)
WO2005027825	Publication date: 2005-03-31	RECOMBINANT PARAINFLUENZA VIRUS EXPRESSION SYSTEMS AND VACCINES COMPRISING HETEROLOGOUS ANTIGENS DERIVED FROM METAPNEUMOVIRUS	FOUCHIER RONALDUS ADRIANUS MAR (NL); VAN DEN HOOGEN BERNADETTA GERA (NL); OSTERHAUS ALBERTUS DOMINICUS M (NL); HALLER AURELIA (US); TANG RODERICK (US)	MEDIMMUNE VACCINES INC (US); VIRONOVATIVE BV (NL); FOUCHIER RONALDUS ADRIANUS MAR (NL); VAN DEN HOOGEN BERNADETTA GERA (NL); OSTERHAUS ALBERTUS DOMINICUS M (NL); HALLER AURELIA (US); TANG RODERICK (US)
WO2005090584	Publication date: 2005-09-29	INFLUENZA VACCINE BASED ON FOWL PLAGUE VIRUSES	WAGNER RALF (DE); KLENK HANS-DIETER (DE)	PHILIPPS UNI MARBURG (DE); WAGNER RALF (DE); KLENK HANS-DIETER (DE)
WO2005107797	Publication date: 2005-11-17	INFLUENZA VIRUS VACCINES	PODDA AUDINO (IT); POPOVA OLGA (IT); PICCENETTI FRANCESCA (IT)	CHIRON CORP (US); PODDA AUDINO (IT); POPOVA OLGA (IT); PICCENETTI FRANCESCA (IT)
WO2005113756	Publication date: 2005-12-01	METHOD	HANON EMMANUEL (BE); NEUMEIER ELISABETH (DE); NOZAY FLORENCE	GLAXOSMITHKLINE BIOLOG SA (BE); SAECHSISCHES

			(BE)	SERUMWERK (DE); HANON EMMANUEL (BE); NEUMEIER ELISABETH (DE); NOZAY FLORENCE (BE)
WO2005116258	Published: 2005-12-08	INFLUENZA HEMAGGLUTININ AND NEURAMINIDASE VARIANS	YANG CHIN-FEN (US); KEMBLE GEORGE (US)	MEDIMMUNE VACCINES INC (US); YANG CHIN-FEN (US); KEMBLE GEORGE (US)
WO2005116260	Publication date: 2005-12-08	INFLUENZA HEMAGGLUTININ AND NEURAMINIDASE VARIANTS	YANG CHIN-FEN (US); KEMBLE GEORGE (US); SUBBARAO KANTA (US); MURPHY BRIAN (US)	MEDIMMUNE VACCINES INC (US); US GOVERNMENT (US); YANG CHIN-FEN (US); KEMBLE GEORGE (US); SUBBARAO KANTA (US); MURPHY BRIAN (US)
EP0366238	Publication date: 1990-05-02	Influenza vaccinal polypeptides.	YOUNG JAMES FRANCIS; DILLON SUSAN B; ENNIS FRANCIS A; DEMUTH SANDRA G	SMITHKLINE BEECHAM CORP (US); ENNIS FRANCIS A (US)
EP0366239	Publication date: 1990-05-02	Purification process for recombinant influenza proteins.	YOUNG JAMES FRANCIS; JONES CHRISTOPHER S	SMITHKLINE BEECHAM CORP (US)
EP1216053	Publication date: 2002-06-26	INFLUENZA VACCINE	D HONDT ERIK (BE); HEHME NORBERT (DE)	SMITHKLINE BEECHAM BIOLOG (BE); SAECHSISCHES SERUMWERK (DE)

Table A7. Delivery

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
5643577	Filed: October 23, 1992Issued: July 1, 1997	Oral vaccine comprising antigen surface-associated with red blood cells	Pang; Gerald Toh (Newlambton, AU); Clancy; Robert Llewellyn (Newlambton, AU)	The University of Newcastle Research Associates Limited (AU)
5756104	Filed: June 5, 1995Issued: May 26, 1998	Liposome-containing intranasal vaccine formulation	de Haan; Aalzen (Weesp, NL); Geerligs; Harmen J. (Weesp, NL); Wilschut; Jan C. (Weesp, NL)	Duphar International Research B.V. (Weesp, NL)
5,853,763	Filed: June 6, 1995Issued: December 29, 1998	Method for delivering bioactive agents into and through the mucosally-associated lymphoid tissue and controlling their release	Tice; Thomas R. (Birmingham, AL); Gilley; Richard M. (Birmingham, AL); Eldridge; John H. (Birmingham, AL); Staas; Jay K. (Birmingham, AL)	Southern Research Institute (Birmingham, AL); The UAB Research Foundation (Birmingham, AL)
5882649	Filed: January 6, 1997Issued: March 16, 1999	Oral vaccine comprising antigen surface-associated with red blood cells	Pang; Gerald Toh (New South Wales, AU); Clancy; Robert Llewellyn (New South Wales, AU); Cripps; Allan William (Curtin, AU); Dunkley; Margaret Lorraine (New South Wales, AU)	Flustat Pty. Ltd. (AU)
5919480	Filed: June 23, 1997Issued: July 6, 1999	Liposomal influenza vaccine composition and method	Kedar; Eliezer (Jerusalem, IL); Babai; Ilan (Petach Tivka, IL); Barenholz; Yechezkel (Jerusalem, IL)	Yissum Research Development Company of the Hebrew University of Jerusalem (Jerusalem, IL)
5985318	Filed: March 16, 1995Issued: November 16, 1999	Fusogenic liposomes that are free of active neuraminidase	Ford; Martin James (Beckenham, GB)	Burroughs Wellcome Co. (Research Triangle Park, NC)
6048536	Filed: April 2, 1997Issued: April 11, 2000	Vaccine compositions	Chatfield; Steven Neville (London, GB)	Medeva Holdings BV (Amsterdam, NL)

6,096,291	Filed: December 27, 1996Issued: August 1, 2000	Mucosal administration of substances to mammals	Betbeder; Didier (Aucamville, FR); Etienne; Alain (Toulouse, FR); de Miguel; Ignacio (Toulouse, FR); Kravtzoff; Roger (Fourquevaux, FR); Major; Michel (Toulouse, FR)	Biovector Therapeutics, S.A. (Labege Cedex, FR)
20040082531	Filed: October 29, 2003Published: April 29, 2004	Dna expression vectors	Catchpole, Ian Richard; (Stevenage, GB) ; Ellis, Jonathan Henry; (Stevenage, GB) ; Ertl, Peter Franz; (Stevenage, GB) ; Rhodes, John Richard; (Stevenage, GB)	SMITHKLINE BEECHAM CORPORATION
20040087521	Filed: April 16, 2001Published: May 6, 2004	Nucleic acid pharmaceuticals-influenza matrix	Donnelly, John J.; (Havertown, PA) ; Dwarki, Varavani J.; (Alameda, CA) ; Liu, Margaret A.; (Rosemont, PA) ; Montgomery, Donna L.; (Chalfont, CA) ; Parker, Suezanne E.; (San Diego, CA) ; Shiver, John W.; (Doylestown, PA) ; Ulmer, Jeffrey B.; (Chalfont, PA)	Merck & Co., Inc.
6824793	Filed: November 28, 2000Issued: November 30, 2004	Use of hyaluronic acid polymers for mucosal delivery of vaccine antigens and adjuvants	O'Hagan; Derek (Berkeley, CA); Pavesio; Alessandra (Padua, IT)	Chiron Corporation (Emeryville, CA); Fidia Advanced Biopolymers Srl (Brindisi, IT)
20050009008	Filed: July 11, 2003Published: January 13, 2005	Functional influenza virus-like particles (VLPs)	Robinson, Robin A.; (Dickerson, MD) ; Pushko, Peter M.; (Frederick, MD)	
6,861,244	Filed: August 13, 2003Issued: March 1, 2005	Inactivated influenza virus vaccine for nasal or oral application	Barrett; Noel (Klosterneuburg/Weidling, AT); Kistner; Otfried (Vienna, AT); Gerencer; Marijan (Vienna, AT); Dorner; Friedrich (Vienna, AT)	Baxter Healthcare S.A. (Zurich, CH)
20050186225	Filed: March 3, 2005Published: August 25, 2005	Adenovirus formulations	Evans, Robert K.; (Souderton, PA) ; Volkin, David B.; (Doylestown, PA) ; Isopi, Lynne A.; (Sellersville, PA)	MERCK AND CO., INC
20050197308	Filed: December 20, 2004Published: September 8, 2005	Vaccines	Dalton, Colin Cave; (Rixensart, BE) ; Easeman, Richard Lewis; (Brentford, GB) ; Garcon, Nathalie; (Rixensart, BE)	SmithKline Beecham Biologicals s.a.
WO2005117958	Published: 2005-12-15	VACCINE COMPOSITIONS COMPRISING VIROSOMES AND A SAPONIN ADJUVANT	COLLER BETH-ANN (BE); HENDERICKX VERONIQUE (BE); GARCON NATHALIE MARIE-JOSEPHE (BE	GLAXOSMITHKLINE BIOLOG SA (BE); COLLER BETH-ANN (BE); HENDERICKX VERONIQUE (BE); GARCON NATHALIE MARIE-JOSEPHE (BE)
EP0620277	Issued: 1994-10-19	Nucleic acid pharmaceuticals	DONNELLY JOHN J (US); MONTGOMERY DONNA L (US); DWARKI VARAVANI J (US); PARKER SUEZANNE E (US); LIU MAGARET A (US); SHIVER JOHN W (US); ULMER JEFFREY B (US)	MERCK & CO INC (US); VICAL INC (US)

B. IP related to selected malaria vaccine approaches

Table B1. DNA ME-TRAP Vaccine and Related Patents (PATH Affiliation)

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
US20050025747	Published: February 3, 2005Filed: May 27, 2004	Vaccine	Laidlaw, Stephen; (Wantage, GB) ; Skinner, Mike; (Wantage, GB) ; Hill, Adrian V.S.; (Oxford, GB) ; Gilbert, Sarah C.; (Oxford, GB) ; Anderson, Richard; (Headington, GB)	Isis Innovation Ltd.
US20040213799	Published: October 28, 2004Filed: October 16, 2003	Methods and reagents for vaccination which generate a CD8 T cell immune response	McMichael, Andrew; (Beckley, GB) ; Hill, Adrian V.S.; (Old Headington, GB) ; Gilbert, Sarah C.; (Headington, GB) ; Schneider, Jorg; (Barton, GB) ; Plebanski, Magdalena; (Melbourne, AU) ; Hanke, Tomas; (Old Marston, GB) ; Smith, Geoffrey L.; (Oxford, GB) ; Blanchard, Tom; (Banjul, GM)	Oxxon Pharmaccines Limited
US20040131594	Published: July 8, 2004Filed: September 2, 2003	Methods and reagents for vaccination which generate a CD8 T cell immune response	McMichael, Andrew; (Beckley, GB) ; Hill, Adrian V.S.; (Old Headington, GB) ; Gilbert, Sarah C.; (Headington, GB) ; Schneider, Jorg; (Barton, GB) ; Plebanski, Magdalena; (Melbourne, AU) ; Hanke, Tomas; (Old Marston, GB) ; Smith, Geoffrey L.; (Oxford, GB) ; Blanchard, Tom; (Banjul, GM)	
US20040018177	Published: January 29, 2004Filed: July 15, 2003	Vacination method	Hill, Adrian V.S.; (Oxford, GB) ; McShane, Helen; (Oxford, GB) ; Gilbert, Sarah; (Oxford, GB) ; Schneider, Joerg; (Oxford, GB)	
US20030138454	Published: July 24, 2003Filed: February 19, 2002	Vaccination method	Hill, Adrian V. S.; (Oxford, GB) ; McShane, Helen; (Oxford, GB) ; Gilbert, Sarah C.; (Oxford, GB) ; Reece, William; (Newtown, AU) ; Schneider, Joerg; (Barton, GB)	Oxxon Pharmaccines, Ltd.
US 6,663,871	Issued: December 16, 2003Filed: December 9, 1999	Methods and reagents for vaccination which generate a CD8 T cell immune response	McMichael; Andrew (Beckley, GB); Hill; Adrian V. S. (Old Headington, GB); Gilbert; Sarah C. (Headington, GB); Schneider; Jorg (Barton, GB); Plebanski; Magdalena (Melbourne, AU); Hanke; Tomas (Old Marston, GB); Smith; Geoffrey L. (Oxford, GB); Blanchard; Tom (Banjul, ZA)	Oxxon Pharmaccines Ltd. (Oxford, GB)
US 5,972,351	Issued: October 26, 1999Filed: December 5, 1994	Plasmodium falciparum MHC class I-restricted CTL epitopes derived from pre-erythrocytic stage antigens	Hill; Adrian Vivian Sinton (Oxford, GB); Gotch; Frances Margaret (Oxford, GB); Elvin; John (Oxford, GB); McMichael; Andrew James (Horton-cum-Studley, GB); Whittle; Hilton Carter (The Gambia, GB	Isis Innovation Limited (Oxford, GB)
WO9856919	Published: 1998-12-17	METHODS AND	MCMICHAEL ANDREW	ISIS INNOVATION (GB);

		REAGENTS FOR VACCINATION WHICH GENERATE A CD8 T CELL IMMUNE RESPONSE	JAMES (GB); HILL ADRIAN VIVIAN SINTON (GB); GILBERT SARAH CATHERINE (GB); SCHNEIDER JOERG (GB); PLEBANSKI MAGDALENA (GB); HANKE TOMAS (GB); SMITH GEOFFREY LILLEY (GB); BLANCHARD TOM (GM)	MCMICHAEL ANDREW JAMES (GB); HILL ADRIAN VIVIAN SINTON (GB); GILBERT SARAH CATHERINE (GB); SCHNEIDER JOERG (GB); PLEBANSKI MAGDALENA (GB); HANKE TOMAS (GB); SMITH GEOFFREY LILLEY (GB); BLANCHARD TOM (GM)
EP1616954	Published: 2006-01-18	Methods and reagents for vaccination which generate a CD8 T cell immune response	MCMICHAEL ANDREW JAMES (GB); PLEBANSKI MAGDALENA (AU); BLANCHARD TOM (GB); HANKE TOMAS (GB); SCHNEIDER JOERG (GB); GILBERT SARAH CATHERINE (GB); HILL ADRIAN VIVIAN SINTON (GB); SMITH GEOFFREY LILLEY (GB)	OXXON THERAPEUTICS LTD (GB)
EP1612269	Published: 2006-01-04	Use of replication-deficient adenoviral vector to boost CD8+ T cell immune response to antigen	SCHNEIDER JOERG (GB); GILBERT SARAH CATHERINE (GB); HANNAN CAROLYN MARY (AU); HILL ADRIAN VIVIAN SINTON (GB)	ISIS INNOVATION (GB)
EP1589108	Published: 2005-10-26	Methods and reagents for vaccination which generate a CD8 T cell immune response	MCMICHAEL ANDREW JAMES (GB); PLEBANSKI MAGDALENA (AU); BLANCHARD TOM (GB); HANKE TOMAS (GB); SCHNEIDER JOERG (GB); GILBERT SARAH CATHERINE (GB); HILL ADRIAN VIVIAN SINTON (GB); SMITH GEOFFREY LILLEY (GB)	OXXON THERAPEUTICS LTD (GB)
EP1335023	Published: 2003-08-13	Methods and reagents for vaccination which generate a CD8 T cell immune response	MCMICHAEL ANDREW JAMES (GB); HILL ADRIAN VIVIAN SINTON (GB); GILBERT SARAH CATHERINE (GB); SCHNEIDER JOERG (GB); PLEBANSKI MAGDALENA (GB); HANKE TOMAS (GB); SMITH GEOFFREY LILLEY (GB); BLANCHARD TOM (GM)	OXXON PHARMACCINES LTD (GB)
EP1214416	Published: 2002-06-19	USE OF REPLICATION-DEFICIENT ADENOVIRAL VECTOR IN THE MANUFACTURE OF A MEDICAMENT TO BOOST CD8+ T CELL IMMUNE RESPONSE TO ANTIGEN	SCHNEIDER JOERG (GB); GILBERT SARAH CATHERINE (GB); HANNAN CAROLYN MARY (GB); HILL ADRIAN VIVIAN SINTON (GB)	ISIS INNOVATION (GB)
EP0979284	Published: 2000-02-16	METHODS AND REAGENTS FOR VACCINATION WHICH GENERATE A CD8 T CELL IMMUNE RESPONSE	MCMICHAEL ANDREW JAMES (GB); HILL ADRIAN VIVIAN SINTON (GB); GILBERT SARAH CATHERINE (GB); SCHNEIDER JOERG (GB);	OXXON PHARMACCINES LIMITED (GB)

			PLEBANSKI MAGDALENA (GB); HANKE TOMAS (GB); SMITH GEOFFREY LILLEY (GB); BLANCHARD TOM (GM)	
EP0753009	Published: 1997-01-15	MALARIA PEPTIDES	HILL ADRIAN VIVIAN SINTON (GB); AIDOO MICHAEL (GB); ALLSOPP CATHERINE ELIZABETH MA (GB); LALVANI AJIT (GB); PLEBANSKI MAGDALENA (GB); WHITTLE HILTON CARTER (GM)	ISIS INNOVATION (GB)
EP0633894	Published: 1995-01-18	PEPTIDES OF AN ANTIGEN, CAPABLE OF RECOGNITION BY OR INDUCTION OF CYTOTOXIC T LYMPHOCYTES, AND METHOD OF THEIR IDENTIFICATION.	HILL ADRIAN VIVIAN SINTON (GB); GOTCH FRANCES MARGARET (GB); ELVIN JOHN (GB); MCMICHAEL ANDREW JAMES (GB); WHITTLE HILTON CARTER MEDICAL (GM)	ISIS INNOVATION (GB)

Table B2. Recombinant Circumsporozoite Protein Vaccine (RTS,S) and Related Patents (PATH Affiliation)

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
US20050002958	Published: January 6, 2005Filed: February 27, 2004	Vaccines	Cohen, Joseph; (Rixensart, BE) ; Garcon, Nathalie; (Rixensart, BE) ; Voss, Gerald; (Rixensart, BE)	SmithKline Beecham Biologicals SA
US20050197308	Published: September 8, 2005Filed: December 20, 2004	Vaccines	Dalton, Colin Cave; (Rixensart, BE) ; Easeman, Richard Lewis; (Brentford, GB) ; Garcon, Nathalie; (Rixensart, BE)	SmithKline Beecham Biologicals s.a.
US 20050054726	Published: March 10, 2005Filed: October 11, 2004	Vaccine	Thomsen, Lindy Louise; (Stevenage, GB)	SMITHKLINE BEECHAM CORPORATION
US 20050143284	Published: June 30, 2005Filed: September 9, 2004	Vaccination	Thomsen, Lindy Louise; (Stevenage, GB) ; Tite, John Philip; (Stevenage, GB)	SMITHKLINE BEECHAM CORPORATION
US 20050208068	Published: September 22, 2005Filed: August 30, 2004	Malaria immunogen and vaccine	Milich, David R.; (Escondido, CA) ; Birkett, Ashley; (Escondido, CA)	
US 20050038239	Published: February 17, 2005Filed: June 14, 2004	Novel compositions	Catchpole, Ian; (Stevenage, Hertfordshire, GB)	SMITHKLINE BEECHAM CORPORATION
US 20040082531	Published: April 29, 2004Filed: October 29, 2003	Dna expression vectors	Catchpole, Ian Richard; (Stevenage, GB) ; Ellis, Jonathan Henry; (Stevenage, GB) ; Ertl, Peter Franz; (Stevenage, GB) ; Rhodes, John Richard; (Stevenage, GB)	SMITHKLINE BEECHAM CORPORATION
US 20040067236	Published: April 8, 2004Filed: October 24, 2003	Immunogenic compositions comprising liver stage malarial antigens	Cohen, Joe; (Rixensart, BE) ; Druilhe, Pierre; (Paris, FR)	SMITHKLINE BEECHAM CORPORATION
US 20040133160	Published: July 8, 2004Filed: October 8, 2003	Vaccine delivery device	Dalton, Colin Clive; (Rixensart, BE)	SMITHKLINE BEECHAM CORPORATION
US 20040047869	Published: March 11, 2004Filed: September 30, 2003	Adjuvant composition comprising an immunostimulatory oligonucleotide and a tocol	Garcon, Nathalie; (Rixensart, BE) ; Gerard, Catherine Marie Ghislaine; (Rixensart, BE) ; Stephenne, Jean; (Rix-	SMITHKLINE BEECHAM CORPORATION

			ensart, BE)	
US 20040076633	Published: April 22, 2004Filed: September 23, 2003	Use of immidazoquinolinamines as adjuvants in dna vaccination	Thomsen, Lindy Loise; (Hertfordshire, GB) ; Tite, John Philip; (Stevenage, GB) ; Topley, Peter; (Hertfordshire, GB)	SMITHKLINE BEECHAM CORPORATION
US 20040043038	Published: March 4, 2004Filed: September 3, 2003	Vaccines	Momin, Patricia Marie; (Brussels, BE) ; Garcon, Nathalie Marie-Josephe; (Wavre, BE)	SmithKline Beecham Biologicals S.A.
US 20040049150	Published: March 11, 2004Filed: August 12, 2003	Vaccines	Dalton, Colin Cave; (Rixensart, BE) ; Easeman, Richard Lewis; (Brentford, GB) ; Garcon, Nathalie; (Rixensart, BE)	SMITHKLINE BEECHAM CORPORATION
US 20040013695	Published: January 22, 2004Filed: August 4, 2003	Oral solid dose vaccine	Vande-Velde, Vincent; (Rixensart, BE)	SMITHKLINE BEECHAM CORPORATION
US 20040013688	Published: January 22, 2004Filed: July 3, 2003	Vaccines to induce mucosal immunity	Wise, Donald L.; (Belmont, MA) ; Trantolo, Debra J.; (Princeton, MA) ; Hile, David D.; (Medford, MA) ; Doherty, Stephen A.; (Newmarket, NH)	Cambridge Scientific, Inc.
US20030133944	Published: July 17, 2003Filed: November 18, 2002	Vaccine composition against malaria	Cohen, Joseph; (Ixelles, BE)	SmithKline Beecham Biologicals s.a.
US20020172692	Published: November 21, 2002Filed: December 18, 2001	Vaccine composition against malaria	Cohen, Joseph; (Ixelles, BE)	SmithKline Beecham Biologicals s.a.
US 20030054337	Published: March 20, 2003Filed: August 15, 2001	Malaria immunogen and vaccine	Birkett, Ashley J.; (Escondido, CA)	
US 20020058047	Published: May 16, 2002Filed: April 24, 2000	VACCINES	GARCON, NATHALIE; (WAVRE, BE) ; MOMIN, PATRICIA MARIE CHRISTINE ALINE FRANCOISE; (BRUSSELLS, BE)	SMITHKLINE BEECHAM CORPORATION
US 6,372,227	Issued: April 16, 2002Filed: April 24, 2000	Vaccines	Garcon; Nathalie (Wavre, BE); Momin; Patricia Marie Christine Aline Francoise (Brussells, BE)	SmithKline Beecham Biologicals, s.a. (Rixensart, BE)
US 6,623,739	Issued: September 23, 2003Filed: February 24, 2000	Vaccines	Momin; Patricia Marie (Brussels, BE); Garcon; Nathalie Marie-Josephe (Wavre, BE)	SmithKline Beecham Biologicals s.a. (Rixensart, BE)
US 6,558,670	Issued: May 6, 2003Filed: April 29, 1999	Vaccine adjuvants	Friede; Martin (Court St Etienne, BE); Hermand; Philippe (Court St Etienne, BE)	SmithKline Beechman Biologicals s.a. (Rixensart, BE)
US 6,169,171	Issued: January 2, 2001Filed: September 18, 1997	Hybrid protein between CS from plasmodium and HBSAG	De Wilde; Michel (Glabais, BE); Cohen; Joseph (Brussels, BE)	SmithKline Beecham Biologicals (s.a.) (Rixensart, BE)
US 5,928,902	Issued: July 27, 1999Filed: December 4, 1996	Hybrid protein between CS from plasmodium and HBsAg	De Wilde; Michel (Glabais, BE); Cohen; Joseph (Brussels, BE)	SmithKline Beecham Biologicals (s.a.) (Rixensart, BE)
US 6,146,632	Issued: November 14, 2000Filed: July 2, 1996	Vaccines	Momin; Patricia Marie (Brussels, BE); Garcon; Nathalie Marie-Josephe (Wavre, BE)	SmithKline Beecham Biologicals s.a. (Rixensart, BE)
US 5,750,110	Issued: May 12, 1998Filed: February 17, 1995	Vaccine composition containing adjuvants	Prieels; John Paul (Brussels, BE); Garcon-Johnson; Nathalie Marie-Josephe Claude	SmithKline Beecham Biologicals, s.a (GB2)

			(Wavre, BE); Slaoui; Moncef (Rixensart, BE); Pala; Pietro (Rixensart, BE)	
US 5,112,749	Issued: May 12, 1992Filed: October 2, 1987	Vaccines for the malaria circumsporozoite protein	Brey, III; Robert N. (Rochester, NY); Majarian; William R. (Pittsford, NY); Pillai; Subramonia (Rochester, NY); Hockmeyer; Wayne T. (Pittsford, NY)	Praxis Biologics, Inc. (Rochester, NY)
WO2005112991	Published: 2005-12-01	VACCINES	CHOMEZ PATRICK (BE); COLLIGNON CATHERINE PASCALINE (BE); VAN MECHELEN MARCELLE PAULETTE (BE)	GLAXOSMITHKLINE BIOLOG SA (BE); CHOMEZ PATRICK (BE); COLLIGNON CATHERINE PASCALINE (BE); VAN MECHELEN MARCELLE PAULETTE (BE)
WO2005049079	Published: 2005-06-02	VISCOUS, NON-POLYMORPHIC, NON-WATER SOLUBLE LIQUID ADJUVANTS	LONGACRE SHIRLEY (FR)	PASTEUR INSTITUT (FR); CENTRE NAT RECH SCIENT (FR); LONGACRE SHIRLEY (FR)
WO2005039634	Published: 2005-05-06	VACCINE COMPOSITIONS COMPRISING AN INTERLEUKIN 18 AND SAPONIN ADJUVANT SYSTEM	BRUCK CLAUDINE ELVIRE MARIE (US); GERARD CATHERINE MARIE GHISLAI (BE); JONAK ZDENKA LUDMILA (US)	GLAXOSMITHKLINE BIOLOG SA (BE); SMITHKLINE BEECHAM CORP (US); BRUCK CLAUDINE ELVIRE MARIE (US); GERARD CATHERINE MARIE GHISLAI (BE); JONAK ZDENKA LUDMILA (US)
WO2005025614	Published: 2005-03-24	IMPROVEMENTS IN VACCINATION	BEMBRIDGE GARY PETER (GB); CRAIGEN JENNIFER L (GB)	GLAXO GROUP LTD (GB); BEMBRIDGE GARY PETER (GB); CRAIGEN JENNIFER L (GB)
WO2004016241	Published: 2004-02-26	ANTIGENIC COMPOSITIONS	VANDERVELDE VINCENT (BE)	GLAXOSMITHKLINE BIOLOG SA (BE); VANDERVELDE VINCENT (BE)
WO9805355	Published: 2002-04-21	VACCINE COMPOSITION AGAINST MALARIA		SMITHKLINE BEECHAM BIOLOG (BE)
WO9952549	Published: 1999-10-21	ADJUVANT COMPOSITIONS	FRIEDE MARTIN (BE); HERMAND PHILIPPE (BE)	SMITHKLINE BEECHAM BIOLOG (BE); FRIEDE MARTIN (BE); HERMAND PHILIPPE (BE)
WO9911241	Published: 1999-03-11	OIL IN WATER EMULSIONS CONTAINING SAPONINS	GARCON NATHALIE (BE); MOMIN PATRICIA MARIE CHRISTINE (BE)	SMITHKLINE BEECHAM BIOLOG (BE); GARCON NATHALIE (BE); MOMIN PATRICIA MARIE CHRISTINE (BE)
WO9856414	Published: 1998-12-17	OIL IN WATER VACCINE COMPOSITIONS	GARCON NATHALIE (BE); MOMIN PATRICIA MARIE CHRISTINE (BE)	SMITHKLINE BEECHAM BIOLOG (BE); GARCON NATHALIE (BE); MOMIN PATRICIA MARIE CHRISTINE (BE)
WO9310152	Published: 1993-05-27	HYBRID PROTEIN BETWEEN CS FROM PLASMODIUM AND HBsAG	DE WILDE MICHEL (BE); COHEN JOSEPH (BE)	SMITHKLINE BEECHAM BIOLOG (BE)
EP1327451	Published: 2003-07-16	Adjuvants for vaccines	MOMIN PATRICIA MARIE (BE); GARCON NATHALIE MARIE-JOSEPHE (BE)	GLAXOSMITHKLINE BIOLOG SA (BE)
EP1201250	Published: 2002-05-02	Immunogenic compositions comprising liver stage malarial antigens	COHEN JOE (BE); DRUILHE PIERRE (FR)	SMITHKLINE BEECHAM BIOLOG (BE); PASTEUR INSTITUT (FR)

EP1198243	Published: 2002-04-24	USE OF CPG AS AN ADJUVANT FOR MALARIA VACCINE	COHEN JOSEPH (BE); GARCON NATHALIE (BE); VOSS GERALD (BE)	SMITHKLINE BEECHAM BIOLOG (BE)
EP0957933	Published: 1999-11-24	VACCINE COMPOSITION AGAINST MALARIA	COHEN JOSEPH (BE)	SMITHKLINE BEECHAM BIOLOG (BE)
EP0735898	Published: 1996-10-09	VACCINES	MOMIN P M (BE); GARCON N MARIE-J (BE)	SMITHKLINE BEECHAM BIOLOG (BE)
EP0614465	Published: 1994-09-14	HYBRID PROTEIN BETWEEN CS FROM PLASMODIUM AND HBsAG.	DE WILDE MICHEL (BE); COHEN JOSEPH SMITHKLINE BEECHA (BE)	SMITHKLINE BEECHAM BIOLOG (BE)
JP7501213T	Published: 1995-02-09	HYBRID PROTEIN BETWEEN CS FROM PLASMODIUM AND HBsAG		

Table B3. Radiation Attenuated P. falciparum Sporozoite Vaccine and Related Patents

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
US 20050220822	Published: October 6, 2005Filed: May 20, 2005	Methods for the prevention of malaria	Hoffman, Stephen L.; (Gaithersburg, MD) ; Luke, Thomas C.; (Brookville, MD)	
US 20050208078	Published: September 22, 2005Filed: April 22, 2005	Methods for the prevention of malaria	Hoffman, Stephen L.; (Gaithersburg, MD) ; Luke, Thomas C.; (Brookville, MD)	
WO2004045559	Published: 2004-06-03	METHOD FOR THE PREVENTION OF MALARIA	HOFFMAN STEPHEN L (US); LUKE THOMAS C (US)	HOFFMAN STEPHEN L (US); LUKE THOMAS C (US)
WO0025728	Published: 2000-05-11	CHROMOSOME 2 SEQUENCE OF THE HUMAN MALARIA PARASITE PLASMODIUM FALCIPARUM AND PROTEINS OF SAID CHROMOSOME USEFUL IN ANTI-MALARIAL VACCINES AND DIAGNOSTIC REAGENTS	HOFFMAN STEPHEN (US); CARUCCI DANIEL (US); GARDNER MALCOLM (US); VENTER J CRAIG (US)	HOFFMAN STEPHEN (US); CARUCCI DANIEL (US); GARDNER MALCOLM (US); VENTER J CRAIG (US)
EP1563301	Published: 2005-08-17	METHOD FOR THE PREVENTION OF MALARIA	HOFFMAN STEPHEN L (US); LUKE THOMAS C (US)	SANARIA INC (US)
EP0600884	Published: 1992-12-30	PROTECTIVE FOUR AMINO ACID EPITOPE AGAINST -i(PLASMODIUM VIVAX) MALARIA.	HOFFMAN STEPHEN L (US); CHAROENVIT YUPIN (US); JONES TREVOR R (US)	US NAVY (US)

Table B4. Glycosyl-Phosphatidyl Inositol (GPI) Based Vaccine and Related Patents

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
US 6,958,235	Issued: October 25, 2005Filed: February 14, 1997	Recombinant protein containing a C-terminal fragment of plasmodium MSP-1	Longacre-Andre; Shirley (Paris, FR); Roth; Charles (Rueil-Malmaison, FR); Nato; Faridabano (Antony, FR); Barnwell; John W. (New York, NY); Mendis; Kamini (Columbo, LK)	Institute Pasteur (Paris, FR); New York University (New York, NY)
US 6,113,917	Issued: September 5, 2000Filed: April 25, 1995	Modified polypeptides for enhanced immunogenicity	Fasel; Nicolas Joseph (Epalinges, CH); Reymond; Christophe Dominique (Prilly, CH)	RMF Dictagene S.A. (CH)

WO2004005532	Published: 2004-01-15	SOLID-PHASE AND SOLUTION-PHASE SYNTHESIS OF GLYCOSYLPHOSPHATIDYLINOSITOL GLYCANS	SEEBERGER PETER H (US); HEWITT MICHAEL C (US); SNYDER DANIEL (US)	MASSACHUSETTS INST TECHNOLOGY (US); SEEBERGER PETER H (US); HEWITT MICHAEL C (US); SNYDER DANIEL (US)
WO9634105	Published: 1996-10-31	MODIFIED POLYPEPTIDES FOR ENHANCED IMMUNOGENICITY	FASEL NICOLAS JOSEPH (CH); REYMOND CHRISTOPHE DOMINIQUE (CH)	RMF DICTAGENE SA (CH); FASEL NICOLAS JOSEPH (CH); REYMOND CHRISTOPHE DOMINIQUE (CH)
EP0826050	Published: 1998-03-04	MODIFIED POLYPEPTIDES FOR ENHANCED IMMUNOGENICITY	FASEL NICOLAS JOSEPH (CH); REYMOND CHRISTOPHE DOMINIQUE (CH)	RMF DICTAGENE SA (CH)
EP0540719	Published: 1993-05-12	DICTYOSTELID EXPRESSION VECTOR AND METHOD FOR EXPRESSING A DESIRED PROTEIN.	FASEL NICOLAS JOSEPH (CH); REYMOND CHRISTOPHE DOMINIQUE (CH)	RMF DICTAGENE SA (CH); RMF DICTAGENE SA (CH)
JP11504215T	Published: 1999-04-20	Modified polypeptides for enhanced immunogenicity		

C. SARS patents related to vaccines, diagnostics and therapeutic agents

Table C1. Vaccines

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
US20050208060	Published: September 22, 2005Filed: November 15, 2004	Vaccine composition	Haensler, Jean; (Valency, FR)	Aventis Pasteur S.A.
US20050069869	Published: March 31, 2005Filed: August 4, 2004	SARS nucleic acids, proteins, antibodies, and uses thereof	Ambrosino, Donna; (Avon, MA) ; Hernandez, Hector; (Canton, MA) ; Greenough, Thomas; (Shrewsbury, MA) ; Luzuriaga, Katherine; (Harvard, MA) ; Somasundaran, Mohan; (Shrewsbury, MA) ; Babcock, Gregory J.; (Marlborough, MA) ; Thomas, William D. JR.; (Somerville, MA) ; Sullivan, John; (West Boylston, MA)	
US20050032222	Published: February 10, 2005Filed: June 21, 2004	Modified viral particles with immunogenic properties and reduced lipid content useful for treating and preventing infectious diseases	Cham, Bill E.; (Queensland, AU) ; Maltais, Jo-Ann B.; (San Ramon, CA) ; Bellotti, Marc; (Pleasanton, CA)	
US20050025788	Published: February 3, 2005Filed: June 4, 2004	Systemic delivery of non-viral vector expressing SARS viral genomic vaccine	Chou, George Chin-Sheng; (Hsin-Shi, TW	
US20050002953	Published: January 6, 2005Filed: May 4, 2004	SARS-coronavirus virus-like particles and methods of use	Herold, Jens; (Puchheim, DE)	
US20050031630	Published: February 10, 2005Filed: April 2, 2004	Novel adjuvant capable of specifically activating the adaptive immune response	Pizzo, Salvatore V.; (Bahama, NC) ; Hart, Justin P.; (Durham, NC) ; McLachlan, James B.; (Raleigh, NC) ; Staats, Herman F.; (Hillsborough, NC) ; Abraham, Soman N.; (Chapel Hill, NC)	
US20040258688	Published: December 23, 2004Filed: March 12, 2004	Enhanced antigen delivery and modulation of the immune response therefrom	Hawiger, Daniel; (Branford, CT) ; Nussenzweig, Michel; (New York, NY) ; Steinman, Ralph M.; (Westport, CT) ; Bonifaz, Laura; (Del Alvaro Obregon, MX)	
US20050031592	Published: February 10, 2005Filed: November 13, 2003	Methods and compositions for inducing immune responses and protective immunity by priming with alpha virus replicon vaccines	Doolan, Denise L.; (Rockville, MD) ; Brice, Gary L.; (McKees Rock, PA) ; Dobano-Lazaro, Carlota; (Barcelom, ES) ; Chulay, Jeffrey D.; (Chapel Hill, NC) ; Kamrud, Kurt I.; (Apex, NC) ; Smith, Jonathan F.; (Cary, NC)	NAVAL MEDICAL RESEARCH CENTER
US20040170649	Published: September 2, 2004Filed: June 20, 2003	Method of treating and preventing infectious diseases via creation of a modified viral particle with	Cham, Bill E.; (Sheldon, AU) ; Maltais, Jo-Ann B.; (San Ramon, CA)	

		immunogenic properties		
US20040009943	Published: January 15, 2004Filed: May 12, 2003	Pathogen vaccines and methods for using the same	Semple, Sean C.; (Vancouver, CA) ; Tam, Ying Kee; (Vancouver, CA) ; Chikh, Ghania; (Vancouver, CA) ; Hope, Michael J.; (Vancouver, CA)	Inex Pharmaceuticals Corporation
US20040006001	Published: January 8, 2004Filed: May 12, 2003	Ferritin fusion proteins for use in vaccines and other applications	Carter, Daniel C.; (Huntsville, AL) ; Li, Chester Q.; (Madison, AL)	
US20040013641	Published: January 22, 2004Filed: April 18, 2003	Disease prevention by reactivation of the thymus	Boyd, Richard; (Victoria, AU)	Monash University
US20040071709	Published: April 15, 2004Filed: April 14, 2003	Corona-virus-like particles comprising functionally deleted genomes	Rottier, Petrus Josephus Marie; (Groenekan, NL) ; Bosch, Berend-Jan; (Utrecht, NL)	
WO2005120565	Publication: 2005-12-22	SARS VACCINES AND METHODS TO PRODUCE HIGHLY POTENT ANTIBODIES	JIANG SHIBO (US); HE YUXIAN (US); LIU SHUWEN (CN)	NEW YORK BLOOD CT (US); JIANG SHIBO (US); HE YUXIAN (US); LIU SHUWEN (CN)
WO2005117965	Publication: 2005-12-15	METHODS FOR PREPARING IMMUNOGENIC CONJUGATES	SCHNEERSON RACHEL (US); KUBLER-KIELB JOANNA (US); MAJADLY FATHY (US); LEPPLA STEPHEN H (US); ROBBINS JOHN B (US); LIU DARRELL T (US); SHILOACH JOSEPH (US)	US GOVERNMENT (US); SCHNEERSON RACHEL (US); KUBLER-KIELB JOANNA (US); MAJADLY FATHY (US); LEPPLA STEPHEN H (US); ROBBINS JOHN B (US); LIU DARRELL T (US); SHILOACH JOSEPH (US
WO2005117960	Publication: 2005-12-15	SARS DNA VACCINE AND ITS PREPARING METHOD, THE USE OF SPIKE GENE OF CORONAVIRUS FOR VACCINE	ZENG YIXIN (CN); HUANG WENLIN (CN); WANG JIAN (CN); TAN HAIDE (CN); LIU PENG (CN); PAN ZHIGANG (CN); FENG QISHENG (CN); LI JIANG (CN); HUANG LIXI (CN); ZHANG MIAOHUA (CN); CHEN LIZHEN (CN	CANCER CT SUN YAT SEN UNIVERSI (CN); ZENG YIXIN (CN); HUANG WENLIN (CN); WANG JIAN (CN); TAN HAIDE (CN); LIU PENG (CN); PAN ZHIGANG (CN); FENG QISHENG (CN); LI JIANG (CN); HUANG LIXI (CN); ZHANG MIAOHUA (CN); CHEN LIZHEN (CN)
WO2005118813	Publication: 2005-12-15	NUCLEIC ACIDS, POLYPEPTIDES, METHODS OF EXPRESSION, AND IMMUNOGENIC COMPOSITIONS ASSOCIATED WITH SARS CORONA VIRUS SPIKE PROTEIN	ALTMEYER RALF (CN); NAL-ROGIER BEATRICE (CN); CHAN CHEMAN (CN); KIEN FRANCOIS (CN); KAM YIU WING (CN); SIU YU LAM (CN); TSE KONG SAN (CN); STAROPOLI ISABELLE (FR); MANUGUERRA JEAN-CLAUDE (FR)	PASTEUR INSTITUT (FR); HONG KONG PASTEUR RES CT LTD (CN); ALTMEYER RALF (CN); NAL-ROGIER BEATRICE (CN); CHAN CHEMAN (CN); KIEN FRANCOIS (CN); KAM YIU WING (CN); SIU YU LAM (CN); TSE KONG SAN (CN); STAROPOLI ISABELLE (FR); MANUGUERRA JEAN-CLAUDE (FR)
WO2005081716	Publication: 2005-09-09	DNA VACCINES TARGETING ANTIGENS OF THE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS (SARS-CoV)	WU TZYY-CHOOU (US); HUNG CHIEN-FU (US); KIM TAE WOO (KR)	UNIV JOHNS HOPKINS (US); WU TZYY-CHOOU (US); HUNG CHIEN-FU (US); KIM TAE WOO (KR)
WO2005072087	Publication: 2005-08-11	SYSTEM AND METHODS FOR NUCLEIC ACID AND POLYPEPTIDE SELECTION	WILLIAMS RICHARD B (US)	PROTEONOVA INC (US); WILLIAMS RICHARD B (US)

WO2005071093	Publication: 2005-08-04	CHIMPANZEE ADENOVIRUS VACCINE CARRIERS	CIRILLO AGOSTINO (IT); COLLOCA STEFANO (IT); ERCOLE BRUNO BRUNI (IT); MEOLA ANNALISA (IT); NICOSIA ALFREDO (IT); SPORENO ELISABETTA (IT)	ANGELETTI P IST RICHERCHE BIO (IT); CIRILLO AGOSTINO (IT); COLLOCA STEFANO (IT); ERCOLE BRUNO BRUNI (IT); MEOLA ANNALISA (IT); NICOSIA ALFREDO (IT); SPORENO ELISABETTA (IT)
WO2005063801	Publication: 2005-07-14	CORONA-VIRUS-LIKE PARTICLES COMPRISING FUNCTIONALLY DELETED GENOMES	ROTTIER PETRUS JOSEPHUS MARIE (NL); BOSCH BEREND JAN (NL)	UNIVERSITEIT UTRECHT HOLDING B (NL); UNIV UTRECHT (NL); ROTTIER PETRUS JOSEPHUS MARIE (NL); BOSCH BEREND JAN (NL)
WO2005056584	Publication: 2005-06-23	NOVEL STRAIN OF SARS-ASSOCIATED CORONAVIRUS AND APPLICATIONS THEREOF	VAN DER WERF SYLVIE (FR); ESCRIOU NICOLAS (FR); CRESCENZO-CHAIGNE BERNADETTE (FR); MANUGUERRA JEAN-CLAUDE (FR); KUNST FRANCK (FR); CALLENDRET BENOIT (FR); BETTON JEAN-MICHEL (FR); LORIN VALERIE (FR); GERBAUD SYLVIE (FR); BURGUIERE ANA MARIA (FR); AZEBI SALIHA (FR); CHARNEAU PIERRE (FR); TANGY FREDERIC (FR); COMBREDET CHANTAL (FR); DELAGNEAU JEAN-FRANCOIS (FR); MARTIN MONIQUE (FR)	PASTEUR INSTITUT (FR); CENTRE NAT RECH SCIENT (FR); UNIV PARIS 7 (FR); VAN DER WERF SYLVIE (FR); ESCRIOU NICOLAS (FR); CRESCENZO-CHAIGNE BERNADETTE (FR); MANUGUERRA JEAN-CLAUDE (FR); KUNST FRANCK (FR); CALLENDRET BENOIT (FR); BETTON JEAN-MICHEL (FR); LORIN VALERIE (FR); GERBAUD SYLVIE (FR); BURGUIERE ANA MARIA (FR); AZEBI SALIHA (FR); CHARNEAU PIERRE (FR); TANGY FREDERIC (FR); COMBREDET CHANTAL (FR); DELAGNEAU JEAN-FRANCOIS (FR); MARTIN MONIQUE (FR)
WO2005054473	Publication: 2005-06-16	GENETICALLY MODIFIED PLANTS COMPRISING SARS-CoV VIRAL NUCLEOTIDE SEQUENCES AND METHODS OF USE THEREOF FOR IMMUNIZATION AGAINST SARS	CHYE MELEEN; LI HONGYE; SATHISHKUMAR RAMALINGAM; POON LITMAN LEO; PEIRIS SRIYAL MALIK JOSEPH	UNIV HONG KONG (CN)
WO2005049080	Publication: 2005-06-02	VACCINE COMPOSITION ADMIXED WITH AN ALKYLPHOSPHATIDYLCHOLINE	HAENSLER JEAN	SANOFI PASTEUR (FR)
WO2005035556	Publication: 2005-04-21	SARS-CORONAVIRUS VIRUS-LIKE PARTICLES AND METHODS OF USE	HEROLD JENS (DE)	IGUAZU BIOSCIENCES CORP (US); HEROLD JENS (DE)
WO2005030122	Publication: 2005-04-07	INACTIVATED HOST CELL DELIVERY OF POLYNUCLEOTIDES ENCODING IMMUNOGENS	XU FENG (US)	CHIRON CORP (US); XU FENG (US)
WO2005027963	Publication: 2005-03-31	METHODS AND COMPOSITIONS FOR THE GENERATION OF A PROTECTIVE IMMUNE RESPONSE AGAINTS SARS-CoV	NABEL GARY J (US); YANG ZHI-YONG (US); HUANG YUE (US); KONG WING-PUI (US)	US HEALTH (US); NABEL GARY J (US); YANG ZHI-YONG (US); HUANG YUE (US); KONG WING-PUI (US)

WO2005021713	Publication: 2005-03-10	VECTORS EXPRESSING SARS IMMUNOGENS, COMPOSITIONS CONTAINING SUCH VECTORS OR EXPRESSION PRODUCTS THEREOF, METHODS AND ESSAYS FOR MAKING AND USING	ANDERSON KARL D; HOLTZ-CORRIS KATHLEEN M; CHUBET RICK; ADAMS DANIEL; COX MANON	PROTEIN SCIENCES CORP (US)
WO2005021707	Publication: 2005-03-10	SEVERE ACUTE RESPIRATORY SYNDROME DNA VACCINE COMPOSITIONS AND METHODS OF USE	VILALTA ADRIAN (US); EVANS THOMAS G (US); QUONG MELANIE W (US); MANTHORPE MARSTON (US)	VICAL INC (US); VILALTA ADRIAN (US); EVANS THOMAS G (US); QUONG MELANIE W (US); MANTHORPE MARSTON (US)
WO2005016247	Publication: 2005-02-24	DNA SEQUENCES, PEPTIDES, ANTIBODIES AND VACCINES FOR PREVENTION AND TREATMENT OF SARS	HOFFMAN STEPHEN L (US); LIANG HONG (US); SIM KIM LEE (US)	PROTEIN POTENTIAL LLC (US); HOFFMAN STEPHEN L (US); LIANG HONG (US); SIM KIM LEE (US)
WO2005016246	Publication: 2005-02-24	MODIFIED VIRAL PARTICLES WITH IMMUNOGENIC PROPERTIES AND REDUCED LIPID CONTENT USEFUL FOR TREATING AND PREVENTING INFECTIOUS DISEASES	CHAM BILL E (AU); MALTAIS JO-ANN B (US); BELLOTTI MARC (US)	LIPID SCIENCES INC (US); CHAM BILL E (AU); MALTAIS JO-ANN B (US); BELLOTTI MARC (US)
WO2005013904	Publication: 2005-02-17	SARS NUCLEIC ACIDS, PROTEINS, VACCINES, AND USES THEREOF	LU SHAN (US); CHOU TE-HUI W (US); WANG SHIXIA (US)	UNIV MASSACHUSETTS (US); LU SHAN (US); CHOU TE-HUI W (US); WANG SHIXIA (US)
WO2005012538	Publication: 2005-02-10	ACCELERATED VACCINATION	NABEL GARY J (US); SULLIVAN NANCY J (US); GEISBERT THOMAS W (US); JAHRLING PETER B (US)	US GOVERNMENT (US); NABEL GARY J (US); SULLIVAN NANCY J (US); GEISBERT THOMAS W (US); JAHRLING PETER B (US)
WO2004108937	Publication: 2004-12-16	CELL SURFACE EXPRESSION VECTOR OF SARS VIRUS ANTIGEN AND MICROORGANISMS TRANSFORMED THEREBY	SUNG MOON HEE (KR); KIM CHUL JOONG (KR); JUNG CHANG MIN (KR); HONG SEUNG PYO (KR); LEE JONG SU (KR); CHOI JAE CHUL (KR); KIM KWANG (KR); SHUNICHI KURODA (JP); POO HA RYOUNG (KR)	BIOLEADERS CORP (KR); M D LAB (KR); BIOLEADERS JAPAN CORP (JP); KOREA RES INST OF BIOSCIENCE (KR); SUNG MOON HEE (KR); KIM CHUL JOONG (KR); JUNG CHANG MIN (KR); HONG SEUNG PYO (KR); LEE JONG SU (KR); CHOI JAE CHUL (KR); KIM KWANG (KR); SHUNICHI KURODA (JP); POO HA RYOUNG (KR)
WO2004092360	Publication: 2004-10-28	THE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS	RAPPUOLI RINO (IT); MASIGNANI VEGA (IT); STADLER KONRAD (DE); GREGERSEN JENS-PETER (DE); CHIEN DAVID (US); HAN JANG (US); POLO JOHN (US); WEINER AMY (US); HOUGHTON MICHAEL (US); SONG HYUN CHUL (US); SEO MI YOUNG (US); DONNELLY JOHN J (US);	CHIRON CORP (US); RAPPUOLI RINO (IT); MASIGNANI VEGA (IT); STADLER KONRAD (DE); GREGERSEN JENS-PETER (DE); CHIEN DAVID (US); HAN JANG (US); POLO JOHN (US); WEINER AMY (US); HOUGHTON MICHAEL (US); SONG HYUN CHUL (US); SEO MI YOUNG (US); DONNELLY JOHN J (US); KLENK HANS

			KLENK HANS DIETER (DE); VALIANTE NICHOLAS (US	DIETER (DE); VALIANTE NICHOLAS (US)
WO2004091524	Publication: 2004-10-28	RESPIRATORY VIRUS VACCINES	MONATH THOMAS P (US); KLEANTHOUS HAROLD (US)	ACAMBIS INC (US); MONATH THOMAS P (US); KLEANTHOUS HAROLD (US)
WO2004085633	Publication: 2004-10-07	A NOVEL HUMAN VIRUS CAUSING SEVERE ACUTE RESPIRATORY SYNDROME (SARS) AND USES THEREOF	CHAN KWOKHUNG; GUAN YI; NICHOLLS JOHN MALCOLM; PEIRIS JOSEPH SRIYAL MALIK; POON LITMAN; YUEN KWOKYUNG; LEUNG FREDERICK C	UNIV HONG KONG (CN)
WO2004064759	Publication: 2004-08-05	USE OF TRYPTANTHRIN COMPOUNDS FOR IMMUNE POTENTIATION	VALIANTE NICHOLAS (US)	CHIRON CORP (US); VALIANTE NICHOLAS (US)
WO2004060308	Publication: 2004-07-22	THIOSEMICARBAZONES AS ANTI-VIRALS AND IMMUNOPOTENTIATORS	BARSANTI PAUL (US); BRAMMEIER NATHAN (US); DIEBES ANTHONY (US); LAGNITON LIANA (US); NG SIMON (US); NI ZHI-JIE (US); PFISTER KEITH B (US); PHILBIN CASEY (US); VALIANTE NICHOLAS (US); WANG WEIBO (US); WEINER AMY (US)	CHIRON CORP (US); BARSANTI PAUL (US); BRAMMEIER NATHAN (US); DIEBES ANTHONY (US); LAGNITON LIANA (US); NG SIMON (US); NI ZHI-JIE (US); PFISTER KEITH B (US); PHILWAGMAN ALLAN (US); WANG WEIBO (US); WEINER AMY (US)
WO2004005493	Publication: 2004-01-15	ANIMAL PROTEIN FREE MEDIA FOR CULTIVATION OF CELLS	REITER MANFRED; MUNDT WOLFGANG; GRILLBERGER LEOPOLD; KRAUS BARBARA	BAXTER INT (US); BAXTER HEALTHCARE SA (CH)
EP1571204	Publication: 2005-09-07	Leukocyte stimulation matrix	SCHOLZ MARTIN DR (DE)	LEUKOCARE GMBH (DE)
EP1553169	Publication: 2005-07-13	Coronavirus, nucleic acid, protein, and methods for the generation of vaccine, medicaments and diagnostics	VAN DER HOEK CORNELIA (NL)	AMSTERDAM INST OF VIRAL GENOMI (NL)
EP1526175	Publication: 2005-04-27	Coronavirus, nucleic acid, protein and methods for the generation of vaccine, medicaments and diagnostics	VAN DER HOEK CORNELIA (NL)	AMSTERDAM INST OF VIRAL GENOMI (NL)
EP1508615	Publication: 2005-02-23	Coronavirus, nucleic acid, protein, and methods for the generation of vaccine, medicaments and diagnostics	VAN DER HOEK CORNELIA (NL)	AMSTERDAM INST OF VIRAL GENOMI (NL)
FR2862981	Publication: 2005-06-03	New isolated and purified strain of coronavirus associated with severe acute respiratory syndrome, useful for preparing diagnostic reagents and vaccines, also derived proteins, nucleic acids and antibodies	VAN DER WERF SYLVIE; ESCRIOU NICOLAS; CRESCENZO CHAIGNE BERNADETTE; MANUGUERRA JEAN CLAUDE; KUNST FRANCK; CALLENDRET BENOIT; BETTON JEAN MICHEL; LORIN VALERIE; GERBAUD SYLVIE; BURGUIERE ANA MARIA	PASTEUR INSTITUT (FR); CENTRE NAT RECH SCIENT (FR)

Table C2 : Diagnostics

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
US20050214748	Published: September 29, 2005Filed: November 8, 2004	Peptide-based diagnostic reagents for SARS	Wang, Chang Yi; (Cold Spring Harbor, NY) ; Fang, Xinde; (Fresh Meadows, NY) ; Chang, Tseng Yuan; (West Islip, NY) ; Liu, Scott; (Lake Grove, NY) ; Lynn, Shugene; (Taoyuan, TW) ; Sia, Charles; (North York, CA	
US20050112559	Published: May 26, 2005Filed: September 29, 2004	Compositions and methods for diagnosing and preventing severe acute respiratory syndrome (SARS)	Leung, Tze Ming Danny; (Ma On Shan, HK) ; Tam, Chi Hang Frankie; (Shatin, HK) ; Ma, Chun Hung; (Siu Sai Wan, HK) ; Lim, Pak Leong; (Ma On Shan, HK) ; Chan, Kay Sheung Paul; (North Point, HK)	THE CHINESE UNIVERSITY OF HONG KONG
US20050106563	Published: May 19, 2005 Filed: September 8, 2004	Epitope profiles of SARS coronavirus	Huang, Jen-Pin; (Sindian City, TW) ; Chen, Lee-Hsuan; (Taipei City, TW)	Genesis Biotech Inc.
US20060003340	Published: January 5, 2006Filed: August 13, 2004	Multi-allelic molecular detection of SARS-associated coronavirus	Kostrikis; Leondios G.; (Limassol, CY)	Birch Biomedical Research, LLC
US20050095618	Published: May 5, 2005Filed: July 28, 2004	Compositions and methods for diagnosing and treating severe acute respiratory syndrome (SARS)	Tsui, Kwok Wing; (Ma On Shan, HK) ; Fung, Kwok Pui; (Shatin, HK) ; Waye, Mary Miu Yee; (Shatin, HK) ; Lo, Yuk Ming Dennis; (Kowloon, HK) ; Chim, Siu Chung Stephen; (Wan Chai, HK) ; Chiu, Wai Kwun Rossa; (Tai Po, HK) ; Tam, Siu Lun John; (Shatin, HK) ; Chan, Kay Sheung Paul; (North Point, HK)	The Chinese University of Hong KongShatinHK
US20050112554	Published: May 26, 2005Filed: July 9, 2004	Characterization of the earliest stages of the severe acute respiratory syndrome (SARS) virus and uses thereof	Zhao, Guoping; (Shanghai, CN) ; Heng Xu, Rui; (Guangdong, CN) ; Wu, Xinwei; (Guangdong, CN) ; Tu, Changchun; (Jilin, CN) ; Song, Huai-Dong; (Shanghai, CN) ; Li, Yixue; (Shanghai, CN) ; Hou, Jinlin; (Guangdong, CN) ; Xu, Jun; (Guangdong, CN) ; Min, Jun; (Guangdong, CN)	
US20050039220	Published: February 17, 2005Filed: May 27, 2004	Imageable animal model of SARS infection	Yang, Meng; (San Diego, CA) ; Xu, Mingxu; (La Jolla, CA)	
US20050136395	Published: June 23, 2005Filed: May 10, 2004	Method for genetic analysis of SARS virus	Mittmann, Michael P.; (Palo Alto, CA) ; Schell, Eric B.; (Mountain View, CA)	Affymetrix, INC
US20050142536	Published: June 30, 2005Filed: April 30, 2004	Method and kit for the detection of a novel	Laue, Thomas; (Bremen, DE)	

		coronoavirus associated with the severe acute respiratory syndrome (SARS)		
US20050266397	Published: December 1, 2005Filed: April 22, 2004	Methods for identification of coronaviruses	Ecker, David J.; (Encinitas, CA) ; Hofstadler, Steven A.; (Oceanside, CA) ; Sampath, Rangarajan; (San Diego, CA) ; Blyn, Lawrence B.; (Mission Viejo, CA) ; Hall, Thomas A.; (Oceanside, CA) ; Massire, Christian; (Carlsbad, CA)	
US20050181357	Published: August 18, 2005Filed: March 24, 2004	High-throughput diagnostic assay for the human virus causing severe acute respiratory syndrome (SARS)	Peiris, Joseph S.M.; (Hong Kong, CN) ; Yuen, Kwok Yung; (Hong Kong, CN) ; Poon, Lit Man; (Hong Kong, CN) ; Guan, Yi; (Honk Kong, CN) ; Chan, Kwok Hung; (Hong Kong, CN) ; Nicholls, John M.; (Hong Kong, CN) ; Leung, Frederick C.; (Hong Kong, CN)	
US20050009009	Published: January 13, 2005Filed: March 24, 2004	Diagnostic assay for the human virus causing severe acute respiratory syndrome (SARS)	Peiris, Joseph S.M.; (Hong Kong, CN) ; Yuen, Kwok Yung; (Hong Kong, CN) ; Poon, Lit Man; (Hong Kong, CN) ; Guan, Yi; (Hong Kong, CN) ; Chan, Kwok Hung; (Hong Kong, CN) ; Nicholls, John M.; (Hong Kong, CN)	
US20040265796	Published: December 30, 2004Filed: January 23, 2004	Methods and kits for detecting SARS-associated coronavirus	Briese, Thomas; (White Plains, NY) ; Lipkin, W. Ian; (New York, NY) ; Palacios, Gustavo; (New York, NY) ; Jabado, Omar; (New York, NY)	
US20050100883	Published: May 12, 2005Filed: November 12, 2003	Peptide-based diagnostic reagents for SARS	Wang, Chang Yi; (Cold Spring Harbor, NY) ; Fang, Xinde; (Fresh Meadows, NY) ; Chang, Tseng Yuan; (West Islip, NY) ; Liu, Scott; (Lake Grove, NY) ; Lynn, Shugene; (Taoyuan, TW) ; Sia, Charles; (North York, CA)	
US20050095582	Published: May 5, 2005Filed: November 3, 2003	Compositions and methods for detecting severe acute respiratory syndrome coronavirus	Gillim-Ross, Laura; (Mechanicville, NY) ; Taylor, Jill; (Albany, NY) ; Scholl, David R.; (Athens, OH) ; Wentworth, David E.; (Guilderland, NY) ; Jollick, Joseph D.; (Athens, OH)	Diagnostic Hybrids, Inc. AndHealth Research Incorporated
WO2005103706	Publication: 2005-11-03	REAGENTS, DEVICES AND METHODS FOR PROTEOMIC ANALYSIS WITH APPLICATIONS INCLUDING	HOFFMANN GEOFFREY WILLIAM (CA)	HOFFMANN TECHNOLOGIES CORP (CA); HOFFMANN GEOFFREY WILLIAM (CA)

		DIAGNOSTICS AND VACCINES		
WO2005103259	Publication: 2005-11-03	SARS-COV NUCLEOCAPSID PROTEIN EPITOPES AND USES THEREOF	KELVIN DAVID (CA); PERSAD DESMOND (CA); CAMERON CHERYL (CA); BRAY KURTIS R (US); LOFARO LORI R (US); JOHNSON CAMILLE (US); SEKALY RAFICK-PIERRE (CA); YOUNES SOUHEIL-ANTOINE (CA); CHONG PELE (CA)	UNIV HEALTH NETWORK (CA); BECKMAN COULTER INC (US); UNIV MONTREAL (CA); NAT HEALTH RES INST (TW); KELVIN DAVID (CA); PERSAD DESMOND (CA); CAMERON CHERYL (CA); BRAY KURTIS R (US); LOFARO LORI R (US); JOHNSON CAMILLE (US); SEKALY RAFICK-PIERRE (CA); YOUNES SOUHEIL-ANTOINE (CA); CHONG PELE (CA)
WO2005056781	Publication: 2005-06-23	USE OF PROTEINS AND PEPTIDES CODED BY THE GENOME OF A NOVEL STRAIN OF SARS-ASSOCIATED CORONAVIRUS	VAN DER WERF SYLVIE (FR); ESCRIOU NICOLAS (FR); CRESCENZO-CHAIGNE BERNADETTE (FR); MANUGUERRA JEAN-CLAUDE (FR); KUNST FRANCK (FR); CALLENDRET BENOIT (FR); BETTON JEAN-MICHEL (FR); LORIN VALERIE (FR); GERBAUD SYLVIE (FR); BURGUIERE ANA MARIA (FR); AZEBI SALIHA (FR); CHARNEAU PIERRE (FR); TANGY FREDERIC (FR); COMBREDET CHAN	PASTEUR INSTITUT (FR); CENTRE NAT RECH SCIENT (FR); UNIV PARIS 7 (FR); VAN DER WERF SYLVIE (FR); ESCRIOU NICOLAS (FR); CRESCENZO-CHAIGNE BERNADETTE (FR); MANUGUERRA JEAN-CLAUDE (FR); KUNST FRANCK (FR); CALLENDRET BENOIT (FR); BETTON JEAN-MICHEL (FR); LORIN VALERIE (FR); GERBAUD SYLVIE (FR); BURGUIERE ANA MARIA (FR); AZEBI SALIHA (FR); CHARNEAU PIERRE (FR); TANGY FREDERIC (FR); COMBREDET CHANTAL (FR); DELAGNEAU JEAN-FRANCOIS (FR); MARTIN MONIQUE (FR)
WO2005054469	Publication: 2005-06-16	ANTI-SARS MONOCLONAL ANTIBODIES	BERRY JODY (CA); JONES STEVEN (CA); YUAN XIN YONG (CA); GUBBINS MIKE (CA); ANDONOV ANTON (CA); WEINGARTI HANA (CA); DREBOT MIKE (CA); PLUMMER FRANK (CA)	CANADA NATURAL RESOURCES (CA); BERRY JODY (CA); JONES STEVEN (CA); YUAN XIN YONG (CA); GUBBINS MIKE (CA); ANDONOV ANTON (CA); WEINGARTI HANA (CA); DREBOT MIKE (CA); PLUMMER FRANK (CA)
WO2005018538	Publication: 2005-03-03	SEVERE ACUTE RESPIRATORY SYNDROME (SARS) POLYPEPTIDES, ANTIBODIES TO SARS POLYPEPTIDES AND THE USE THEREOF IN DIAGNOSTIC, VACCINATION AND THERAPEUTIC APPLICATIONS	LI FRANK Q (US); LAI WAN-CHING (US); CHU YONG LIANG (US)	VAXIM INC (US); LI FRANK Q (US); LAI WAN-CHING (US); CHU YONG LIANG (US)
WO2005016132	Publication: 2005-02-24	DIAGNOSTICS FOR SARS VIRUS	KWANG JIMMY (SG); LING AI EE (SG); OOI ENG EONG (SG); CHNG HIOK HEE (SG)	TEMASEK LIFE SCIENCES LAB (SG); KWANG JIMMY (SG); LING AI EE (SG); OOI ENG EONG (SG); CHNG HIOK HEE (SG)
WO2005005658	Publication: 2005-01-20	METHODS AND	LI ZE (CN); TAO	CAPITAL BIOCHIP

		COMPOSITIONS FOR DETECTING SARS VIRUS AND OTHER INFECTIOUS AGENTS	SHENGCE (CN); CHENG JING (CN)	COMPANY LTD (CN); UNIV TSINGHUA (CN); LI ZE (CN); TAO SHENGCE (CN); CHENG JING (CN)
WO2005005596	Publication: 2005-01-20	CHARACTERIZATION OF THE EARLIEST STAGES OF THE SEVERE ACUTE RESPIRATORY SYNDROME (SARS) VIRUS AND USES THEREOF	ZHAO GUOPING (CN); XU RUI HENG (CN); WU XINYAN (CN); TU CHENG (CN); SONG HUAI-DONG (CN); LI YIHONG (CN); HOU JINLIN (CN); XU JUN (CN); MIN JUN (CN)	CHINESE NAT HUMAN GENOME CT AT (CN); GUANGDONG CT FOR DISEASE CONTR (CN); GUANGZHOU CT FOR DISEASE CONTR (CN); CHANGCHUN UNVERSITY OF AGRICUL (CN); RUIJIN HOSPITAL AFFILIATED TO (CN); SHANGHAI INST FOR BIOLOG SCIEN (CN); NANFANG HOSPITAL FIRST MEDICAL (CN); GUANGDONG J TECH SCIENCE DEV C (CN); SECOND AFFILIATED HOSPITAL OF (CN); ZHAO GUOPING (CN); XU RUI HENG (CN); WU XINYAN (CN); TU CHENG (CN); SONG HUAI-DONG (CN); LI YIHONG (CN); HOU JINLIN (CN); XU JUN (CN); MIN JUN (CN)
WO2004111274	Publication: 2004-12-23	NUCLEIC ACID SEQUENCES THAT CAN BE USED AS PRIMERS AND PROBES IN THE AMPLIFICATION AND DETECTION OF SARS CORONAVIRUS	SILLEKENS P T G (NL)	BIOMERIEUX B V (NL); SILLEKENS P T G (NL)
WO2004111187	Publication: 2004-12-23	METHODS FOR IDENTIFICATION OF CORONAVIRUSES	ECKER DAVID J (US); HOFSTADLER STEVEN A (US); SAMPATH RANGARAJAN (US); BLYN LAWRENCE B (US); HALL THOMAS A (US); MASSIRE CHRISTIAN (US)	ISIS PHARMACEUTICALS INC (US); ECKER DAVID J (US); HOFSTADLER STEVEN A (US); SAMPATH RANGARAJAN (US); BLYN LAWRENCE B (US); HALL THOMAS A (US); MASSIRE CHRISTIAN (US)
WO2004108756	Publication: 2004-12-16	SARS CORONAVIRUS PEPTIDES AND USES THEREOF	CAMPBELL WILLIAM (CA); JIA WILLIAM (CA); ZHOU QUN (CA)	PEGASUS PHARMACEUTICALS GROUP (CA); CAMPBELL WILLIAM (CA); JIA WILLIAM (CA); ZHOU QUN (CA)
EP1584628	Publication: 2005-10-12	Viral protein	LEE FANG-JEN (TW); YU CHIA-JUNG (TW); CHANG MING-FU (TW); HO HONG-NERNG (TW)	YUNG SHIN PHARM IND CO LTD (TW)
FR2862974	Publication: 2005-06-03	Use of proteins, peptides or antibodies for detecting and serotyping coronavirus associated with severe acute respiratory syndrome	VAN DER WERF SYLVIE; ESCRIOU NICOLAS; CRESCENZO CHAIGNE BERNADETTE; MANUGUERRA JEAN CLAUDE; KUNST FRANCK; CALLENDRET BENOIT; BETTON JEAN MICHEL; LORIN VALERIE; GERBAUD	PASTEUR INSTITUT (FR); CENTRE NAT RECH SCIENT (FR)

Table C3 : Therapeutics

Patent or Application Number	Dates	Title	Inventors	Assignee and/or Applicant
US20050276818	Published: December 15, 2005Filed: May 17, 2005	Uncharacterized ORF3 in SARS-coronavirus is a cyclic-AMP-dependent kinase and a target for SARS therapy	Godzik, Adam; (San Diego, CA) ; Sikora, Sergey; (San Diego, CA)	
US20050267071	Published: December 1, 2005Filed: November 1, 2004	Inhibitors of coronavirus protease and methods of use thereof	Freire, Ernesto; (Baltimore, MD) ; Ottenbrite, Raphael; (Midlothian, VA) ; Xiao, Yingxin; (Gaithersburg, MD) ; Velazquez-Campoy, Adrian; (Zaragoza, ES) ; Leavitt, Stephanie; (Belmont, CA) ; Bacha, Usman; (Baltimore, MD) ; Barrila, Jennifer; (Baltimore, MD)	Fulcrum Pharmaceuticals, Inc.
US20050282154	Published: December 22, 2005Filed: October 5, 2004	Angiotensin-converting enzyme-2 as a receptor for the SARS coronavirus	Farzan, Michael R.; (Cambridge, MA) ; Li, Wenhui; (Boston, MA) ; Moore, Michael J.; (Cambridge, MA)	The Brigham and Women's Hospital, Inc.
US20050113298	Published: May 26, 2005Filed: September 13, 2004	Receptor binding peptides derived from the SARS S protein	Farzan, Michael R.; (Cambridge, MA) ; Li, Wenhui; (Boston, MA)	The Brigham and Women's Hospital, Inc.
US20050069558	Published: March 31, 2005Filed: July 23, 2004	Crystals and structures of SARS-CoV main protease	Bonanno, Jeffrey B.; (San Diego, CA) ; Sauder, J. Michael; (Carlsbad, CA) ; Fowler, Richard; (San Diego, CA) ; Romero, Richard; (San Diego, CA)	Structural GenomiX, Inc.
US20050107324	Published: May 19, 2005Filed: July 12, 2004	Modulation of CEACAM1 expression	Bennett, C. Frank; (Carlsbad, CA) ; Dobie, Kenneth W.; (Del Mar, CA) ; Jain, Ravi; (Carlsbad, CA)	
US20050075307	Published: April 7, 2005Filed: July 12, 2004	Modulation of aminopeptidase N expression	Bennett, C. Frank; (Carlsbad, CA) ; Jain, Ravi; (Carlsbad, CA)	
US20050071892	Published: March 31, 2005 Filed: June 25, 2004	Techniques and applications of establishment of SARS-CoV primate model	Qin, Chuan; (Beijing City, CN) ; Wei, Qiang; (Beijing City, CN) ; Jiang, Hong; (Beijing City, CN) ; Zhu, Hua; (Beijing City, CN) ; Gao, Hong; (Beijing City, CN)	
US20050004063	Published: January 6, 2005Filed: May 19, 2004	Inhibition of SARS-associated coronavirus (SCoV) infection and replication by RNA interference	Kung, Hsiang-Fu; (Hong Kong, CN) ; He, Ming-Liang; (Hong Kong, CN) ; Zheng, Bo-Jiang; (Hong Kong, CN) ; Guan, Yi; (Hong Kong, CN) ; Lin, Marie Chia-Mi; (Hong Kong, CN) ; Peng, Ying; (Hong Kong, CN)	
US20040229219	Published: November 18, 2004Filed: April 29, 2004	Method of inhibiting human metapneumovirus and human coronavirus in the prevention and treatment of severe acute respiratory syndrome (SARS)	Gallaher, William R.; (Pearl River, LA) ; Garry, Robert F.; (New Orleans, LA)	
US20050100885	Published: May 12,	Compositions and meth-	Crooke, Stanley T.;	

	2005Filed: April 26, 2004	ods for the treatment of severe acute respiratory syndrome (SARS)	(Carlsbad, CA) ; Ecker, David J.; (Encinitas, CA) ; Sampath, Rangarajan; (San Diego, CA) ; Freier, Susan M.; (San Diego, CA) ; Massire, Christian; (Carlsbad, CA) ; Hofstadler, Steven A.; (Oceanside, CA) ; Lowery, Kristin Sannes; (Vista, CA) ; Swayze, Eric E.; (Carlsbad, CA) ; Baker, Brenda F.; (Carlsbad, CA) ; Bennett, C. Frank; (Carlsbad, CA)	
US20050186575	Published: August 25, 2005Filed: December 30, 2003	Corona-virus-like particles comprising functionally deleted genomes	Rottier, Petrus Josephus Marie; (Groenkan, NL) ; Bosch, Berend Jan; (Utrecht, NL)	
WO2005019410	Publication: 2005-03-03	RNAI AGENTS FOR ANTI-SARS CORONAVIRUS THERAPY	TANG QUINN T (US); LU PATRICK Y (US); XIE FRANK Y (US); LIU YIJIA (US); XU JUN (US); WOODLE MARTIN C (US)	INTRADIGM CORP (US); TANG QUINN T (US); LU PATRICK Y (US); XIE FRANK Y (US); LIU YIJIA (US); XU JUN (US); WOODLE MARTIN C (US)
WO2004096842	Publication: 2004-11-11	SARS VIRUS NUCLEOTIDE AND AMINO ACID SEQUENCES AND USES THEREOF	PLUMMER FRANK (CA); FELDMANN HEINZ (CA); JONES STEVEN (CA); LI YAN (CA); BASTIEN NATHALIE (CA); BRUNHAM ROBERT (CA); BROOKS-WILSON ANGELA (CA); HOLT ROBERT (CA); UPTON CHRISTOPHER (CA); ROPER RACHEL (US); ASTELL CAROLINE (CA	BC CANCER AGENCY (CA); PLUMMER FRANK (CA); FELDMANN HEINZ (CA); JONES STEVEN (CA); LI YAN (CA); BASTIEN NATHALIE (CA); BRUNHAM ROBERT (CA); BROOKS-WILSON ANGELA (CA); HOLT ROBERT (CA); UPTON CHRISTOPHER (CA); ROPER RACHEL (US); ASTELL CAROLINE (CA)
EP1533370	Publication: 2005-05-25	Novel atypical pneumonia-causing virus	DE JONG JAN CORNELIS (NL); BESTEBROER THEODORUS MARINUS (NL); SIMON JAMES HENRY MATTHEW (NL); FOUCHIER RONALDUS ADRIANUS MAR (NL); OSTERHAUS ALBERTUS DOMINICUS M (BE)	VIRONOVATIVE B V (NL)

Towards Patent Pools in Biotechnology?

Patrick Gaulé
Chair in Economics and Management of Innovation
College of Management of Technology
Ecole Polytechnique Fédérale de Lausanne
CDM Odyssea Station 5
1015 Lausanne, Switzerland
patrick.gaule@epfl.ch

Executive Summary

A growing number of voices are raising concerns about the impact on biomedical innovation of fragmented intellectual property rights. Although systematic analysis is lacking, there is anecdotal evidence of fragmented patent landscapes—including in such highly significant public health cases as malaria vaccine development. It has often been suggested that patent pools (agreements where patent holders agree to license their IP as a package) could help to solve this problem. The rationale for patent pools is simple: by reducing the number of necessary transactions and by simplifying patent landscapes, they can reduce transaction costs and facilitate technology transfers. Yet, despite this potential and the success of patent pools in other sectors (notably consumer electronics), they remain largely untested in biotechnology. In this paper, we seek to explain this fact and to evaluate the future prospects for the use of patent pools in biotechnology.

As patent pools are horizontal agreements between patent holders, they can be anticompetitive and are regulated by competition authorities. Despite a more favourable outlook from these authorities, the biotechnology industry still believes that patent pools are an antitrust litigation risk. In both the United States and Europe the key antitrust requirement is that all patents included in the pool should be essential. The consumers electronics pools fulfilled this requirement by showing that they included only patents necessary for compliance with the technical standard which underpinned the pool (such as MPEG and DVDs). The lack of standards and long product development cycles in biotechnology make it difficult to show that pooled patents are complementary. Hence, the current antitrust requirements are an important obstacle to the formation of patent pools in biotechnology.

A second suggested explanation emphasizes other ways of dealing with fragmented patent landscapes—cross-licensing and aggregations of rights by one party through exclusive licenses. In biotechnology exclusive use is often more profitable than licensing so that industry will tend to prefer these alternatives to patent pools. Note also that the important patent portfolios held by universities and specialized research firms imply that more patents are available for exclusive licenses, which facilitates aggregation of rights by one party.

The above considerations lead us to be relatively pessimistic about the prospects for biotechnology patent pools in the present regulatory and industrial context. The usefulness of institutions to facilitate transactions in the market for technology nevertheless suggests that patent pools may have a role to play in biotechnology in the future.

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www.biodevelopments.org/innovation/index.htm

What is a Patent Pool?

A growing number of voices are raising concerns about the impact on biomedical innovation of fragmented intellectual property rights. Although systematic analysis is lacking, there is anecdotal evidence of fragmented patent landscapes—including in such highly significant public health cases as malaria vaccine development. It has often been suggested (for example, UPSTO 2000, FTC 2002, OECD 2002, WHO 2005, WHO 2006[1]) that patent pools (agreements where patent holders agree to license their IP as a package) could help to solve this problem. The rationale for patent pools is simple: by reducing the number of necessary transactions and by simplifying patent landscapes, they can reduce transaction costs and facilitate technology transfers. Yet, despite this potential and the success of patent pools in other sectors (notably consumer electronics), they remain largely untested in biotechnology.

Definition

Throughout this paper we use the following definition from the European Commission's guidelines on technology transfer agreements (European Commission, 2004, hereafter "EC guidelines"):

> *"The notion of technology pools covers agreements whereby two or more parties agree to pool their respective technologies and license them as a package."*

It is useful to emphasize some differences between patent/technology pools as defined above and other ways of aggregating IP that have sometimes been associated with patent pools.

Focusing on reciprocal access to IP rights, *cross-licensing agreements* are very common. But while a patent pooling agreement may also include reciprocal access to IP, it differs from a cross-licensing agreement in that it explicitly allows for (package) licensing to third parties.

Non-voluntary patent pools are at odds with our definition of patent pools as agreements. One example is the proposal to form a non-voluntary patent pool for AIDS, in which holders of patents essential to the production of antiretrovirals would be invited to join the pool and accept capped royalties; should they decline, compulsory licenses would be sought (Essential Inventions, 2005).[2]

Patent clearing houses and *single licensing authorities* share many characteristics with patent pools, although they aim to be more comprehensive in scope, which is problematic from the viewpoint of competition law. Resnik (2003) proposes a single licensing authority (which he calls a patent pool) for biotechnology that would rely on voluntary participation and operate like collective rights management associations for copyrighted music. Van Zimmeren et al. (2006) discuss a royalty collection clearing house for diagnostic testing.

Recent practice

Despite the recent surge of interest in patent pools, they remain relatively rare. In the last decade, only four pools have solicited and obtained business reviews from the U.S. Department of Justice (others may be pending).[3] These four pools (the MPEG-2 pool, the 3G platform, and the two DVD pools) are the best known, summarized in Table 1, and are well documented elsewhere; nonetheless, a couple of observations on what they have in common are worthwhile:

- *Technologies covered.* All four abovementioned pools are in the electronics/video content industry, are intimately linked to a technical standard, and appeared during the formation of emerging technologies that are now dominant (with the exception of the most recent, 3G, that has not yet become mainstream).
- *Membership.* The pool members/licensors are usually large vertically integrated firms (e.g., Toshiba, Philips, Sony). Membership is open to anyone who wants to join, and an external review process is in place to determine whether patents considered for inclusion in the pool are valid and essential for the standard.
- *Licensing terms.* The licensing terms are typically standard, publicly disclosed, non-discriminatory, fairly linear (with small up-front fees), and open to anyone who wants to license. The licensing terms are designed for specific types of consumer goods, such as an MPEG-2 decoding product, a DVD player, a DVD recorder, a DVD disc, etc.

So far, the modern patent pool has been closely linked to a technical standard and is designed to facilitate large-scale technology licensing (with a total of 790 patents (134 families) owned by 24 different licensors and more than thousand licensees, the

MPEG-2 patent pool is an excellent example.)[4] Significantly, the few other pools that have been formed (IEEE 394, DVB-T, AVC/H.264, MPEG-4) share the same features as those outlined above.

Table 1: The four well-known pools in the modern era

Technology	Administrator	Formation Year	Members
MPEG-2 Digital Video Digital standard for video compression	MPEG LA	1997	Alcatel, Canon, CIF Licensing, Columbia University, France Télécom, Fujitsu, General Instrument, GE Technology Development, Hitachi, KDDI Corporation, LG Electronics, Matsushita, Mitsubishi, Nippon Telegraph and Telephone Corporation, Philips, Robert Bosch, Samsung, Sanyo Electric, Scientific Atlanta, Sharp, Sony, Thomson Licensing, Toshiba, and Victor Company of Japan.
DVD (3C)	Philips	1998	Philips, Sony, Pioneer
DVD (6C)	DVD 6C licensing agency	1999	Hitachi, Matsuhita, Mistubishi Electric, Time Warner, Toshiba, Victor Company of Japan
3G Platform Third generation mobile phones	3G Patents Limited	2001	Alcatel, Bosch, Cegetel, the Electronics and Telecommunications Research Institute, France Telecom, Fujitsu, KPN, Korea Telecom, LG Telecom, Matsushita Electric Industrial, Mitsubishi Electronic Corp., NEC, NTT DoCoMo, Samsung Electronics, Siemens, SK Telecom, Sonera, Sony, and Telecom Italia Mobile

Sources: www.mpegla.com; www.3gpatents.com ; www.dvd6cla.com/ ; www.licensing.philips.com/licensees/conditions/dvd/

Other interesting types of pools

Of course, new types of pools may emerge that do not conform to the above practices (although they may raise fresh antitrust issues). A potential SARS patent pool may be one example. Shortly after the severe acute respiratory syndrome (SARS) outbreak in February 2003, patent applications covering sequences of the genome of the SARS coronavirus were filed by several research teams around the globe (Simon et al., 2005).[5] Some have argued that this may result in a complex, uncertain IP situation that could delay the development of SARS vaccines and diagnostic tools (ibid.). As a result, the four parties known to own key patent applications[6] (CDC) have expressed their willingness to form a patent pool and enable wide access to the SARS genome (Simon et al. 2005).

But consider the differences between the SARS patent pool and the consumer electronics pools. The SARS patent pool will not be in an industry characterized by all-important network effects or be closely linked to a standard. For the moment, the licensors are not vertically integrated firms but universities and public institutions,[7] and so there will be far fewer licensees. Most importantly, however, the commercial products in which the licensed technology will be embedded do not yet exist and will be developed by the licensees after extensive R&D efforts. Therefore, the licensing policy of the SARS patent pool might be quite different from other modern patent pools.

Yet another type of patent pool could emerge in the context of research consortiums and other research collaborations. Participants could commit *ex ante* to contribute patents to the pool that result from their joint research efforts. The parties could then use the pool to jointly manage IP and to support the exchange of unpatented technical information and know-how between the parties.[8] The SNP consortium is especially interesting in this regard. A non-profit foundation that has discovered 1.5 million SNPs,[9] it has made all the related information available to the public without IP restrictions. Financed by the Wellcome Trust and large pharmaceutical firms—Pfizer, GlaxoSmithKline, Aventis, AstraZeneca, Novartis, Roche, Bayer, etc.—the initiative may owe much to these corporate sponsors' desire to undermine attempts by biotech tool companies to obtain proprietary positions on SNPs, as Agrawal & Garlappi (2002) and Cockburn (2004) suggest. A patent pool with low, non-

discriminatory licensing terms might have achieved the same objectives while at the same time providing some cost-recovery through royalties.

More generally, consortia or research collaborations may find pooling attractive for collectively managing IP rights and/or as an institutionalized mechanism for sharing non-patented information. This type of patent pool, however, falls outside the parameters of this Chapter because of its different rationale.

The Rationale for Patent Pools in Biotechnology

The anti-commons in biomedical research

The rationale for patent pools in biotechnology is intricately linked to a problem identified in a famous article by Heller and Eisenberg (1998): the anti-commons in biomedical research. Their argument echoes earlier concerns about university patenting and the patentability of genomic sequences. However, they stress that the costs of patents in the early stages of biomedical research stem not only from the standard restrictions that patents place on use but also from the specific problems of fragmented IP rights. They suggest that when the development of a commercial product requires access to multiple patents, negotiating access with different patent owners may be prohibitively difficult and costly. Too many property rights lead to the under-use of valuable resources, which Heller and Eisenberg consider "the tragedy of the anti-commons, " a mirror image of the tragedy of commons (ie. the irony about patenting being an attempt to solve the tragedy of the commons but leading to an apparent tragedy of the anti-commons).

The strength of the anti-commons thesis rests on two assumptions that are very difficult to test: (1) that developing commercial biomedical products requires access to many different IP rights and (2) that negotiating access with different patent owners is prohibitively difficult and costly. On the first point, the number of biotechnology patents has certainly increased dramatically over the last decade, although by itself that does not necessarily imply greater fragmentation. Walsh et al. (2003) report from interviews with biotechnology industry IP practitioners that preliminary freedom to operate searches can sometimes find hundreds of patents relevant to a candidate product but that on closer inspection "there may be, in a complicated case, about 6-12 that they have to seriously address, but that more typically the number was zero."

Enough anecdotal evidence exists, however, to suggest that the fragmentation of rights in biotechnology is sometimes a serious concern. One of the well-known cases is malaria vaccine development, where up to 39 families were found to be potentially relevant to the development of a vaccine from the protein antigen MSP-1 protein (IPR Commission, 2002:127).

Patent pools and transaction costs

In this subsection, we discuss how patent pools may reduce transaction costs when IP rights are fragmented between several entities. Forming a patent pool, for example, may lower costs associated with patent mapping. Firms or other entities that are considering whether to develop a product need to identify what patents they need to license to get freedom to operate. They will usually start by searching databases with keywords, which can yield hundreds of patents. For each of these, they then need to decide whether their products would be infringing and, if so, whether the patent is valid. This is difficult to do because of the inherent uncertainties over the breadth and validity of patents.[10] In other words, identifying important patents in a technological area can cost a lot.

The identification process described above is very similar to the independent review used by modern patent pools. In such reviews, an expert evaluates the essentiality and validity of patents that pool members want to include in the pool. This is done not only to show regulatory authorities that the pool is likely to integrate complementary patent rights but also for marketing reasons, because "a license with patents that have not been evaluated by an outside expert will lack credibility and be difficult to sell" (Horn, 2003). In short, potential licensees can more surely presume that patents are valid and important if they are included in the pool than otherwise, which lowers the cost of patent mapping. This may offset the cost of the review, especially if the number of potential licensees is large.

The patent pool also clarifies the patent landscape by sending a signal to potential licensees that the patents are available for licence, in principle at non-discriminatory rates.[11] That brings us to a second type

of transactions costs associated with bargaining over licences and licensing terms.

Patent pools also have the obvious but important advantage of considerably reducing the number of licences that need to be negotiated. For instance, suppose that there are m licensors and n potential licensees; if each licensee negotiates with each licensor, then $m \cdot n$ licences need to be negotiated. However, if each licensee negotiates with a pool that includes all licensors that number reduces to n licences.[12] Patent pools in electronics went even further by specifying standard and non-discriminatory terms and making them publicly known. These terms appear to be "take it or leave it" offers, so not only the number of licences goes down but the negotiations also become much simpler and may even disappear. Still, biotechnology patent pools will likely differ considerably from modern patent pools—and they might not go as far in specifying licence terms in advance.

Nevertheless, it is important to realize that if licensees have lower transaction costs with a patent pool, this is because much of the hard work has already taken place in negotiations between pool members. In particular, they will have agreed on a formula to split pool revenues, which is a central element of the pooling arrangement.[13] Because patent pools require some sort of agreement between the patent owners on the respective value of their inventions, they may encounter the same problems (asymmetries of information, cognitive bias, etc.) that prevent deals from being reached in other types of technology transactions.

In summary, transaction costs with a patent pool tend to be incurred upfront and by the licensors. Forming a pool can therefore be seen as a marketing effort by patent holders. In addition to this important distribution effect, patent pools can also reduce total transaction costs by simplifying patent landscapes and facilitating technology transactions.

The Regulatory Environment

As horizontal agreements between patent owners, patent pools have long aroused the suspicion of competition authorities. The early history of patent pools shows that such suspicion was sometimes warranted,[14] but regulators have come to recognize that patent pools can be pro-competitive. An important step in that direction was the issuance in 1995 of new IP licensing guidelines in the US. Nevertheless, the biotechnology industry still believes that patent pools are a substantial antitrust litigation risk (Seide et al. 2001), a concern strengthened by the few safe harbours contained in regulations for patent pools[15] (Beeney, 2002; Janis, 2005) and the lack of relevant case law. Understanding the extent to which competition law limits the prospects for biotechnology patent pools is important for evaluating their usefulness,[16] and so we outline some key aspects of the relevant regulations in the most important antitrust jurisdictions, the European Union and the U.S.

Regulatory Requirements in Europe

The main guidance source for applying competition law to patent pools in Europe is the 2004 guidelines on the application of article of the EC Treaty to technology transfer agreements ("EC guidelines"). The guidelines recognize that patent pools may restrict competition (EC guidelines §213) but they also acknowledge their pro-competitive effects, particularly by reducing transaction costs and by setting a limit on cumulative royalties to avoid double marginalization (§214). The key factor that distinguishes pro- and anti- competitive pools is the nature of the pooled technologies:

- As a general rule, the Commission considers the inclusion of substitute technologies in a pool a violation of article 81(1)[17] (§219).
- Conversely, when the pool is composed only of technologies that are essential (defined as having no substitute (§216)), the creation of the pool is considered pro-competitive (§220).
- If the pool includes complementary but non-essential technologies, the agreement is likely to be caught by Article 81(1) when the pool has a significant position on any relevant market (§221).

Although the Guidelines develop a number of factors for assessing technology pools of non-essential technologies, these apply only when technologies in the pool become non-essential after technological developments (§222)—not for the formation of new pools. Finally a number of guidelines on restraints commonly found in pools are specified. For example, when a pool has a dominant market position, royalties and other licensing terms should be fair and non-discriminatory and licenses should be non-exclusive (§226); licensors and licensees must be free to develop competing products and standards and to grant licenses outside the pool (§227); grant back

obligations should be non-exclusive and limited to developments important to the use of the pooled technology (§228).

Regulatory requirements in the U.S.

The 1995 Antitrust Guidelines for the Licensing of Intellectual Property ("U.S. Guidelines") are less detailed than their European counterparts, but a number of business review letters from the Department of Justice antitrust division offer additional guidance.[18] According to the U.S. Guidelines, cross-licensing and pooling arrangements "may provide procompetitive benefits by integrating complementary technologies, reducing transaction costs, clearing blocking positions, and avoiding costly infringement litigation." The following practices were deemed to be anticompetitive: collective price or output restraints and, in certain cases, grant-backs, settlements involving cross-licensing between horizontal competitors, and exclusion from a pooling arrangement.

In the Sony letter and subsequent letters, the Department of Justice adopted a two-step procedure for reviewing proposed patent pools. It sought to determine "(i) whether the proposed licensing program is likely to integrate complementary patent rights and (ii), if so, whether the resulting competitive benefits are likely to be outweighed by competitive harm posed by other aspects of the program" (Sony letter). In all four business review letters, the Department of Justice found that the pooled patents were essential (and therefore complementary) in the sense of having no substitutes.[19] It thus remains to be seen whether and under what conditions a pool with complementary but non-essential patents would be acceptable.

The first three review letters added other requirements that are summarized in these terms by the USPTO white paper (2000): "(1) the patents in the pool must be valid and not expired, (2) no aggregation of competitive technologies and setting a single price for them, (3) an independent expert should be used to determine whether a patent is essential to complement technologies in the pool, (4) the pool agreement must not disadvantage competitors in downstream products markets, and (5) the pool participants must not collude on prices outside the scope of the pool, e.g., on downstream products."

Implications for patent pools

As the preceding sub-sections make clear, the antitrust analysis of patent pools in both Europe and the United States focuses on the nature of the pooled patents. Patent pools including substitute technologies are deemed anti-competitive and are subject to challenges from competition authorities. On the other hand, patent pools with only essential patents are pro-competitive to the extent that they do not engage in anticompetitive practices with regard to the dissemination of the technology (.such as downstream price fixing) What is less clear is whether competition authorities would accept patent pools that include patents meeting a weaker definition of complementary or where essentiality is likely but difficult to prove.

There are two reasons why this matters for biotechnology patent pools. First, biotechnology lacks standards. As several commentators have pointed out, this poses a problem for patent pools because essential patents cannot be defined as those that are necessary to comply with the standard. In the context of diagnostic generics, Ebersole et al. (2005) have argued for creating standards to facilitate patent pooling. Elsewhere, Horn (2003) suggests that with a defined field of use the absence of standards need not be of consequence.

Second, in the SARS and avian flu[20] cases, and perhaps in many biomedical research areas for which patent pools would be of most interest, final products have yet to be developed. But when final products do not yet exist it seems to be *ipso facto* especially difficult to determine which patents are essential. Indeed, the point behind forming a pool may be to reduce uncertainty by ensuring that licensees can have access to all the IP they may need, even if it later turns out that they do not need a particular piece of IP.

Alternative to Pooling

A strong objection to biotechnology patent pools is that biotechnology patent owners will not want to form pools. Unfortunately, the traditional literature on patent pools is of little guidance here because it focuses on the conditions under which pools would be pro-competitive and thus agreeable to courts or competition authorities. The analyses begin with the assumption that a group of patent owners wants to

form a pool; this was not something that needed to be explained or discussed in detail. Indeed a weird result of economic models of patent pools (Shapiro 2001; Choi 2002; Lerner and Tirole 2004; Sung-Hwan 2004; Aoki and Nagaoka 2004; Lerner, Tirole and Strojwas 2005) is that patent owners almost invariably want to pool if they are allowed to, the exception being that sometimes an essential patent owner can obtain a stronger bargaining position by waiting to enter the pool.

To meaningfully discuss whether biotechnology patent owners will be interested in forming patent pools, we must consider not only pooling versus non-exclusive licensing but also other counterfactuals, particularly pooling versus cross-licensing and pooling versus the aggregation of the relevant rights by one entity through exclusive licenses.

Aggregation of rights by one entity through exclusive licenses as an alternative to pooling

Economic papers on patent pools have always assumed that aggregation of rights by one entity through exclusive licenses was impossible.[21] In fact, doing otherwise might have resulted in only trivial results, an entirely legitimate assumption in the context of consumer electronics pools because patent owners are typically large manufacturing firms. Exclusive licensing deals between horizontal competitors with significant market shares are unlikely to meet antitrust requirements. Even if they could, large manufacturing firms typically are unwilling to grant exclusive licenses. Granting exclusive licenses is tantamount to leaving the market in exchange for royalty payments, which is usually not the best strategy for firms with assets and investments that complement their patents.

In the biotechnology industry, however, many important patents are owned by universities or specialized research firms that lack full development capacity—much less production capabilities. Consequently, they are more than happy to grant exclusive licenses. Such exclusive licenses, moreover, are unlikely to be challenged by antitrust authorities because they do not suppress competition (as may be the case between two vertically integrated firms). Thus, in biotechnology the aggregation of rights by one entity through exclusive licenses can frequently be a simpler alternative to pooling. Box 1 illustrates this point with an example of a patent thicket re-

Box 1: Consolidation of patent rights in reverse genetics

The Technology: Reverse genetics is a new technique to develop influenza vaccines. One of its great advantages over the conventional method (via hen's eggs) is that vaccines can be developed more quickly, which would be essential in the event of a pandemic. Reverse genetics can also be used to develop interpandemic flu vaccines (which has to be done again every year for the new flu season), but its advantage fades because manufacturers have more time to develop the vaccine (Fedson, 2005).

Reverse genetics IP rights: Reverse genetics technology was developed and refined by Peter Palese of Mount Sinai School of Medicine ("Labs rush to cultivate bird flu vaccine. Reverse Genetics allows creation of weakened virus", 2004). Other refinements were developed by Yoshihiro Kawaoka of the University of Wisconsin and by Robert Webster of St. Jude Children's Hospital in Memphis (ibid.). The initial technology was licensed by Mount Sinai to Aviron; Medimmune acquired those rights when it purchased Aviron in 2002 (ibid.).

The IP rights for reverse genetics were thus divided between four portfolios (Fedson 2005, "MedImmune Expands Patent Estate for Reverse Genetics with New Rights from Mount Sinai School of Medicine" 2005):

- Medimmune Fundamental Reverse Genetics Portfolio (WO 91/03552) [i.e. the initial Mount Sinai technology]
- Mount Sinai School of Medicine Plasmid Rescue Portfolio (WO 01/04333)
- Wisconsin Alumni Research Foundation Plasmid Rescue Portfolio (WO 00/60050)
- St. Jude Children's Research Hospital Dual Promoter Plasmid Rescue Portfolio (WO 01/83794)

Medimmune has recently acquired exclusive licenses from the portfolios of Wisconsin, St. Jude, and Mount Sinai School of Medicine ("Technology for Faster, Safer Development of Pandemic Flu Vaccine Licensed by Mount School of Medicine" 2005; "MedImmune Expands Patent Estate for Reverse Genetics with New Rights from Mount Sinai School of Medicine" 2005).

Conclusions: The IP rights situation described above was arguably a classical case of a patent thicket with fragmented IP rights and uncertainty about technology ownership. The option of a patent pool for this technology was raised (Fedson 04), but instead the situation was resolved by one patent owner acquiring exclusive licenses from the other ones. Note that Medimmune is a vertically integrated biotechnology firm and that the other patent owners were academic institutions.

solved by the aggregation of rights by one patent owner.

Patent pooling versus cross-licensing

A key difference between a patent pool and a cross-licensing agreement is that in the former the patent owners agree to license to third parties that do not themselves contribute patents to the pool. The decision to license the aggregated technology to third parties is very similar to the decision to license a patent when patent rights are not fragmented. On the one hand, licensing to third parties will bring royalty revenues. On the other hand, it may increase competition for products embedding the IP of the licensors. There are clearly many technologies where the second effect (profit dissipation) outweighs the first (generation of royalty revenues).

Consider the example of two pharmaceutical firms possessing a patent on a novel drug but being unable to produce and commercialize it without infringing each other's patent.[22] The simplest solution to the blocking positions is a cross-licence that leads to a duopoly on the market. However, both firms can do better by buying or selling an exclusive license to the other firm; the resulting monopoly will be more profitable than the combined duopoly rent that divides a bargaining surplus between the two firms. On the other hand, a patent pool would be worse than a cross-licence because the entry of new firms would dissipate oligopoly rents faster than the royalty payments would rise. Therefore, the most profitable option is the aggregation of rights by one firm. If the aggregation of rights is not possible for antitrust or other reasons, then the cross-licence will be preferred to a pool.

We thus agree with Grassler and Capria (2003) who argue that for patents covering components of downstream pharmaceuticals products, pooling is not attractive for patent holders. It is clear, however, that many life science patents are not directed to the actual therapeutic products but instead cover research tools that can be used to develop and test pharmaceutical products. Using patent pools to aggregate such research tools may be helpful.

Conclusions

Our enquiry first attempted to clarify what a patent pool is in theory and in practice. Although patent pools have a common core (an agreement to license to third parties as a package), the term can cover different practices. We mentioned but did not explore the possibility that an agreement could be made *ex ante* (i.e., before inventions have been made) between members of a research collaboration or consortium. Instead, we analyzed the much better known example of the MPEG patent pool, which several others have imitated. The MPEG patent pool is an institution intimately linked to a technical standard and designed to facilitate large-scale technology licensing. Although inspired by the examples of MPEG and DVD, the SARS patent pool and other biotechnology patent pools will likely be a different type of practice, particularly with respect to the form of the licensing terms.

The main reason for the interest in biotechnology patent pools is that they could be an *ex post* practical solution to address the fragmentation of IP rights and its potential anti-commons effects. We suggested that patent pools might lower total transaction costs by clarifying patent landscapes and reducing the number of necessary transactions. Pooling also modifies the repartition of transaction costs to the benefit of licensees, which allows patent owners to make their technology more attractive.

We then briefly introduced the regulatory (i.e., antitrust) environment in which patent pools operate in Europe and the U.S. The key concern is the relationship between the pooled patents. Given the early development stages of some technologies and the lack of standards, the requirement that all essential patents should be included may be difficult for biotechnology patent pools. It may also undo part of their rationale. The future of biotechnology patent pools will largely depend on whether regulatory authorities will accept a weaker test than essentiality or will develop special guidelines for biotechnology patent pools. For example, it might be possible to design a safe harbour around a requirement that the patents in the pool can be licensed independently.

An important point that we developed in the last section of this paper is that patent pooling and independent licensing are not the only options available to owners of complementary patent rights. The alternatives—i.e., cross-licensing and the aggregation of

rights by one entity through exclusive licenses—are particularly relevant in the context of biotechnology. This is because exclusive use in biotechnology is often more profitable than licensing. The owners of patent rights will tend to prefer aggregation of rights by one entity through exclusive licenses and cross-licensing. In addition, universities and specialized research firms hold important patent portfolios, which facilitate the aggregation of rights since more patents are available for exclusive licenses. In other words, the particular structure of the biotechnology industry and the non-alignment of industry interests make aggregation of rights through exclusive licenses easier and patent pooling more difficult than in other industries.

Finally, we would like to place our discussion in the broader context of markets for technology. The downsides of patents and their exclusionary power can be largely mitigated by the existence of a well-functioning market for technology. In such a market, patent rights can be licensed to multiple entities and transferred to those best placed to use them. Unfortunately, it is not clear that markets for technology function well. Heller and Eisenberg (1998) have expressed a predominantly pessimistic view of markets for technology in biomedical research by emphasizing the costs of bundling rights, the heterogeneity of patent owners, and cognitive biases. Other authors are more optimistic about these markets (e.g., Arora et al., 2001), but it is to be expected that information asymmetries and uncertainty over the value, breadth, and validity of patents are impediments to transactions between multiple patent owners. Given these market imperfections, many mutually beneficial bilateral transactions that would otherwise be concluded do not happen, which ultimately thwarts innovation in biomedical research overall. Thus, there must be value in mechanisms and institutions that can facilitate transactions in the market for technology. Patent pools can provide this value, and so they may have a role to play in biotechnology despite the current obstacles to their use.

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References

Letter from Charles James to Ky Ewing, November 12, 2002. [3G Letter]

Letter from Joel Klein to Carey Ramos, 10 June 1999. [Toshiba Letter]

Letter from Joel Klein to Garrard Beeney, December 16, 1998. [Sony Letter]

Letter from Joel Klein to Gerrard Beeney, 26 June 1997. [MPEG Letter]

"Labs rush to cultivate bird flu vaccine. Reverse Genetics allows creation of weakened virus" (2004) San Francisco Chronicle

"Technology for Faster, Safer Development of Pandemic Flu Vaccine Licensed by Mount School of Medicine". (2005) Mount Sinai Press Office

"MedImmune Expands Patent Estate for Reverse Genetics with New Rights from Mount Sinai School of Medicine" (2005). PR Newswire.

AGRAWAL, A. & GARLAPPI, L. (2002) Public Sector Science and the 'Strategy of the Commons' (Abridged). *Best Paper Proceedings, Academy of Management*.

AOKI, R. & NAGAOKA, S. (2004) The Consortium Standard and Patent Pools. *The Economic Review,* 55**,** 346-56.

AOKI, R. & NAGAOKA, S. (2005) Coalition formation for a consortium standard through a standard body and a patent pool: theory and evidence from MPEG2, DVD and 3G. *Institute of Innovation Research Working Paper,* 05.

ARORA, A.; FOSFURI A. AND GAMBARDELLA, A. (2001) *Markets for technology; the economics of innovation and corporate strategy,* Cambridge, MA, The MIT Press.

BEENEY, G. (2002) Pro-Competitive Aspects of Intellectual Property Pools: A Proposal for Safe Harbor Provisions.

BIO (2002) Testimony of the Biotechnology Industry Organization on Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy before the Federal Trade Commission and the Department of Justice.

CARLSON, S. (1999) Patent pool and the antritrust dilemma. *Yale Journal of Regulation,* 16**,** 359-98.

CHOI, J. P. (2002) Patent Pools and Cross-Licensing in the Shadow of Patent Litigation. *CesInfo Working Paper*.

COCKBURN, I. (2003) O Brave New Industry, That Has Such Patent in It! Reflections On the Economics of Genome Patenting. IN KIEFF, F. (Ed.) *Perspectives on properties of the human genome project.* Academic Press.

COCKBURN, I. (2004) The Changing Structure of the Pharmaceutical Industry. *Health Affairs,* 23**,** 10-22.

EBERSOLE, T.; GUTHRIE, M. AND GOLSTEIN, J. (2005) Patent pools and standard setting in diagnostic genetics. Nature Biotechnology 23(8):937-938

EUROPEAN COMMISSION (2004) Guidelines on the application of article 81 of the EC Treaty to technology transfer agreements. *Official Journal,* C 101. [EC Guidelines]

FEDERAL TRADE COMMISSION (2003) To Promote Innovation: The Proper Balance Of Competition Law and Policy. A Report by the Federal Trade Commission.

UNITED STATES DEPARTMENT OF JUSTICE AND FEDERAL TRADE COMMISSION (1995) Antitrust Guidelines for the Licensing of Intellectual Property [US Guidelines]

FEDSON, D. (2004) Vaccine Production and Pandemics: Reverse Genetics IP and Pandemic Influenza Vaccination. Presentation at the meeting "High Tech IP Issues in a Global Marketplace" Stanford Law School, May 17-18.

FEDSON, D. (2005) Preparing for Pandemic Vaccination: An International Policy Agenda for Vaccine Development. *Journal of Public Health Policy,* 26**,** 4-29.

GILBERT, R. (2004) Antitrust for Patent Pools: A Century of Policy Evaluation. *Stanford Technology Law Review*.

GOLD, R. (2003) SARS Genome Patent: Symptom or Disease ? *The Lancet,* 361**,** 2002-3.

GRASSLER, F. & CAPRIA, M. A. (2003) Patent pooling: Uncorking a technology transfer bottleneck and creating value in the biomedical research field. *Journal of Commercial Biotechnology,* 9**,** 111-8.

HELLER, R. & EISENBERG, R. (1998) The Anticommons in Biomedical Research. *Science,* 280**,** 698-701.

HORN, L. (2003) Alternative approaches to IP management: One-stop technology platform licensing. *Journal of Commercial Biotechnology,* 9**,** 119-27.

ESSENTIAL INVENTIONS (2005) Essential Patent Pool for AIDS: Background Informaion.

JANIS, M. (2005) Aggregation and Dissemination Issues in Patent Pools. IN COLLISON, W. (Ed.) *Issues in Competition Law and Policy.* ABA.

KLEIN, J. (1997) An Address to the American Intellectual Property Law Association, on the Subject of Cross-Licensing and Antitrust Law.

LEMLEY, M. & SHAPIRO, C. (2005) Probabilistic Patents. *Journal of Economic Perspectives,* 19**,** 75-98.

LERNER, J. & TIROLE, J. (2004) Efficient Patent Pools. *American Economic Review,* 94**,** 691-711.

LERNER, J., TIROLE, J. & STROJWAS, M. (2005) The Design of Patent Pools: The Determinants of Licensing Rules. *NBER Working Paper*.

MERGES, R. (2001) Institutions for Intellectual Property Exchange: The Case of Patent Pools. IN DREYFUSS, R. (Ed.) *Intellectual Products: Novel Claims to Protection and Their Boundaries.* Oxford University Press.

OECD (2002) Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidences and Policies

RESNIK, D. (2003) A Biotechnology Patent Pool: An Idea Whose Time Has Come? *Journal of Philosophy, Science and Law,* 3.

SEIDE, R., LECOINTE, M. & GRANOVSKY, A. (2001) Patent Pooling in the Biotechnology Industry. *Licensing Journal,* 27**,** 28-9.

SHAPIRO, C. (2001) Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting. IN JAFFE, A., LERNER, J. & STERN, S. (Eds.) *Innovation Policy and the Economy.* Cambridge, MA, MIT Press.

SIMON, J., ET AL. (2005) Managing severe acute respiratory syndrome (SARS) intellectual property rights: the possible role of patent pooling. *Bulletin of the World Health Organization,* 83**,** 707-10.

SUNG-HWAN, K. (2004) Vertical Structure and Patent Pools. *Review of Industrial Organization* 25**,** 231-50.

USPTO (2000) Patent Pools: A Solution To The Problem of Access to Biotechnology Patents ? United States Patents and Trademark Office.

VAN ZIMMEREN ET AL. (2006) A royalty collection clearing house for diagnostic testing: the solution to ensure access and use of patented genetic technology? WHO Bulletin 84(5):352-59

WALSH, J.; ARORA, A.;COHEN, W. (2003) Research Tool Patenting and Licensing and Biomedical Innovation. IN COHEN, W. & MERILL., S. (Ed.) *Patents in the Knowledge-Based Economy.* Washington, DC, National Academies Press.

WHO (2005) Genetics, genomics and the patenting of DNA: Review of potential implications for health in developing countries, Geneva, World Health Organization, Human Genetics Program.

WHO (2006) Public health, Innovation and Intellectual Property Rights. Report of the Commission on Intellectual Property Rights, Innovation and Public Health. Geneva, World Health Organization.

Notes

[1] WHO (2006:68) concludes, "Patent pools of upstream technologies may be useful in some circumstances to promote innovation relevant to developing countries. WHO and WIPO should consider playing a bigger role in promoting such arrangements."

[2] Admittedly, this would bear some resemblance to the well-known patent pool formed in 1917 to enable the wartime manufacture of aircraft under the instigation of U.S. Secretary of Navy Franklin Roosevelt (both attempting to address an international crisis).

[3] Business review letters are statements by the Department of Justice on its current antitrust enforcement intentions with respect to a particular practice.

[4] According to the web site of the entity operating the MPEG patent pool, http://www.mpegla.com accessed 22/04/06.

[5] The Bernhardt-Nocht Institut, the British Columbia Cancer Agency, the Centers for Disease Control and Prevention, Erasmus Medical Center, and Hong Kong University

[6] The Centers for Disease Control and Prevention (CDC), Health Canada, Coronovative, and Versitech. CDC is a branch of the U.S. department of Health and Human Services. Health Canada is Canada's ministry of health, Coronovative is a spinoff from Erasmus Rotterdam University, and Versitech is the technology transfer office from Hong Kong University.

[7] Thus the pool members can hardly be described as profit maximizers. Another oddity of the SARS patent pool is that the underlying patents were only patent applications when the parties announced their intention to pool. It remains to be seen if a patent pool can be formed before these applications are granted.

[8] That is, sharing know-how and unpatented information would be less sensitive because of the resulting joint ownership of the patents. This point is made in UPSTO (2000).

[9] SNP stands for Single Nucleotide Polymorphisms, common human genetic variations which are of great value in biomedical research and drug discovery.

[10] In the words of Lemley and Shapiro (2005): "The actual scope of a patent right, and even whether the right will withstand litigation at all, are uncertain and contingent questions. This uncertainty is not an accident or mistake. Rather, it is an inherent part of our patent system, an accommodation to the hundreds of thousands of patent applications filed each year, the inability of third parties to participate effectively in determining whether a patent should issue, and the fact that for the vast majority of issued patents, scope and validity are of little or no commercial significance."

[11] This point is made in Simon (2005): "The formation of such a patent pool would send a powerful signal to putative licensees (e.g. vaccine manufacturers) that patent owners mean to make their IP rights available from standard rates."

[11] Clearly the number of potential licensees may change with a pool; some licensors may also be licensees, and the pool need not include all licensors, but the point is clear enough.

[13] Compare with Merges (2001) who identifies the two central principles of a pool as (1) consolidate property rights in a central entity (i.e., the contract); and (2) establish a valuation mechanism to divide up the royalty stream.

[14] Consider for instance the Harrow's pool that came up in a case before the U.S. Supreme Court (*E. Bement & Sons v. National Harrow*) in 1902. According to Gilbert (2004), "The pool grew to 22 firms accounting for over 90 percent of all manufacturing and sales of float spring tooth harrows in the United States. Each firm was required to adhere to uniform price schedules for the sale of all products manufactured under the National Harrow license. The pool set uniform license terms that fixed prices for licensed products, required that the licensee make or sell only the licensed products, and obligated licensees not to challenge the patents and to defend the patents if challenged by others."

[15] Safe harbors serve as shortcuts in antitrust analyses to determine whether a particular agreement is procompetitive.

[16] A more comprehensive review would also have to consider the patent misuse defense in the context of biotechnology patent pools (see Gosh and De Shield, 2005), but patent misuse and antitrust violations are very closely related.

[17] Article 81(1) of the EC treaty prohibits agreements that have as their object or effect the restriction of competition.

[18] We will refer to these as the MPEG Letter, the Sony Letter, the Toshiba Letter, and the 3G Letter; see the bibliography for details.

[19] Compare: "The Portfolio combines patents that an independent expert has determined to be essential to compliance with the MPEG-2 standard; there is no technical alternative to any of the Portfolio patents within the standard" (MPEG letter); "it appears reasonably likely that the pool will combine only complementary patents for which there are no substitutes for the purpose of compliance with the Standard Specifications" (Toshiba letter); "it appears that the Licensors intend to license through the pool only complementary patents for which there are no substitutes" (Sony letter); "the limitations of patents to those 'technically' essential to compliance […] provide

reasonable assurance that patents combined in a single PlatformCo for a 3G radio interface technology will not be substitutes for one another" (3G letter).

[20] See Box.

[21] Of course, aggregation of rights can also be made through non-exclusive licensing and in certain circumstances that may be the simplest solution. However, if the licensed patents are complementary, the price of the licenses will be higher and the revenues of the licensors will be lower under independent licensing than under a pool. Shapiro (2001) first established this.

[22] Our hypothetical might be the result of a patent race with two research groups submitting applications for different aspects of the same discovery.

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