Patent Consolidation and Equitable Access: PATH's Malaria Vaccines

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ABSTRACT

This chapter shares the results of a project that analyzed the potential for consolidating patents in the malaria vaccine field. Goals include streamlining access to critical patents, advancing the development of products, and providing equitable access to the innovations. The study assessed the current status of the relevant patents and surveyed the holders of key patents to determine the availability for licensing. Other key activities included prioritizing patents with respect to a vaccine's potential for success, identifying potential patent roadblocks by discussing the issue with patent holders, and proposing a mechanism for accessing key patents in the field of malaria vaccines. The potential role for some form of patent consolidation or technology trust, including pooling patents and technology, was explored. This chapter does not recommend developing a broad-based technology trust for existing malaria-antigen patents. Instead, several other steps are recommended to consolidate available rights and improve access for future patent families.

1. INTRODUCTION

Malaria is one of the most widespread and deadly tropical diseases. There are more than 300 million cases and more than one million deaths each year. Ninety percent of the cases occur among children in Sub-Saharan Africa. Developed countries have largely eradicated the disease through hygiene, effective drugs, and the reduction of mosquito breeding grounds via wetlands clearing, chemical treatment to control mosquito populations (early on, with DDT), and water-system management. For many reasons, including costs as well as the challenge of managing potential environmental and health effects of chemical parasite removal, these approaches have not been as effective in developing countries. Alarmingly, various factors are now spreading malaria into areas previously free of infection. New approaches to prevention and treatment are sorely needed.

No safe, effective vaccine for malaria exists. Developing a vaccine is a priority because of one especially exacerbating problem: the malaria parasite and the insects that carry it are becoming resistant to existing drug treatments and therapeutic-control measures. A malaria vaccine could greatly reduce the effects of the disease in terms of suffering and lives lost. It also could prevent the spread of malaria more cost effectively than any existing treatment. Vaccine use would reduce the need for expensive, often unaffordable medicines and remediate the problem of drug-resistant parasites. Moreover, vaccine use would reduce the need for chemical treatment to control mosquito populations, thus minimizing negative environmental effects.

Developing a malaria vaccine, however, presents big challenges. Above all, there is an economic challenge. Developing a vaccine for which there is a great medical need but no profitable market requires a clear, sustained source of funding. Fortunately, a variety of public, private,

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and philanthropic efforts are targeting the problem. In particular, the Bill & Melinda Gates Foundation is providing philanthropic funding to product-development partnerships. The Malaria Vaccine Initiative (MVI) is the main recipient of funding and the catalyzing force for malaria vaccine development. MVI seeks to accelerate vaccine development through multiple approaches including partnering and the funding of promising projects. Addressing challenges simultaneously on multiple fronts, MVI has dozens of partners in ten ongoing vaccine projects worldwide.

2. THE CHALLENGE OF DEVELOPING A VACCINE

2.1 *Technical challenges*

Developing an effective malaria vaccine presents significant technical challenges:

- Malaria is caused by different parasite species in different countries and has variants within those species. The main species in terms of global health are *Plasmodium vivax*, found mainly in Asia and South America, and *P. falciparum*, found mainly in Sub-Saharan Africa.
- Malarial parasites have several different stages in their life cycle, some of which are short in duration or occur within the host's cells, making the parasites difficult to target with a vaccine.
- During each stage of the malaria parasite's life cycle, it produces a number of different antigens (substances that can evoke an immune response in humans), some of which may be useful in developing a vaccine. There may be several thousand potential target antigens, only a few dozen of which have been studied for use, either separately or in combination, as potential vaccines.

Because of these technical challenges, malaria-vaccine research has continued for decades. Only very recently has a vaccine been shown to be effective in Phase 2 clinical trials[1] in adults and then in children in Africa.[2]

2.2 *Commercialization challenges*

Given the encouraging results of the Phase 2 clinical studies, there is a strong possibility that a malaria vaccine may be ready for regulatory approval in five to ten years. The prospect of manufacturing, delivering, and paying for a vaccine, however, now raises commercial challenges:

- Different populations need very different vaccine products. For example, a vaccine for children in endemic areas is not likely to be suitable as a traveler's vaccine.
- Funding mechanisms are needed. Without clear definitions and estimates of the various markets, it is difficult for companies to justify the expense associated both with speculative vaccine development and with more straightforward manufacture and marketing costs. To help provide certainty for the various markets, MVI is working on a model that takes a variety of vaccine products and market needs into account. Current market projections make it clear that even after development costs have been handled and an approved vaccine is ready for manufacture and marketing, continued public and philanthropic funding will be required in many markets in developing countries.
- Delivery channels are needed to get vaccines to the areas where they are needed.

2.3 *IP challenges*

The possibility of commercializing an effective malaria vaccine raises significant IP challenges. Many patents, some with overlapping claims, cover malaria antigens that may be needed for vaccine development. Such a "patent thicket" is daunting because it is likely that more than one antigen will be needed for an effective vaccine. Unfortunately, accessing many patents one at a time via traditional licensing or partnering could tie up resources needed to develop and deliver the vaccines. Moreover, the negotiations required to access

key patents could delay the delivery of the vaccine. Indeed, access to key patents might not even be available, which would affect investment decisions upstream in the development pipeline about vaccine candidates. Because of this, it may not be possible to pursue the most powerful vaccine candidates if companies holding valuable malaria-vaccine IP are unwilling to license to others even if they are not developing a malaria vaccine themselves. Assessing the availability of access to key patents becomes a priority.

3. PATENT AVAILABILITY

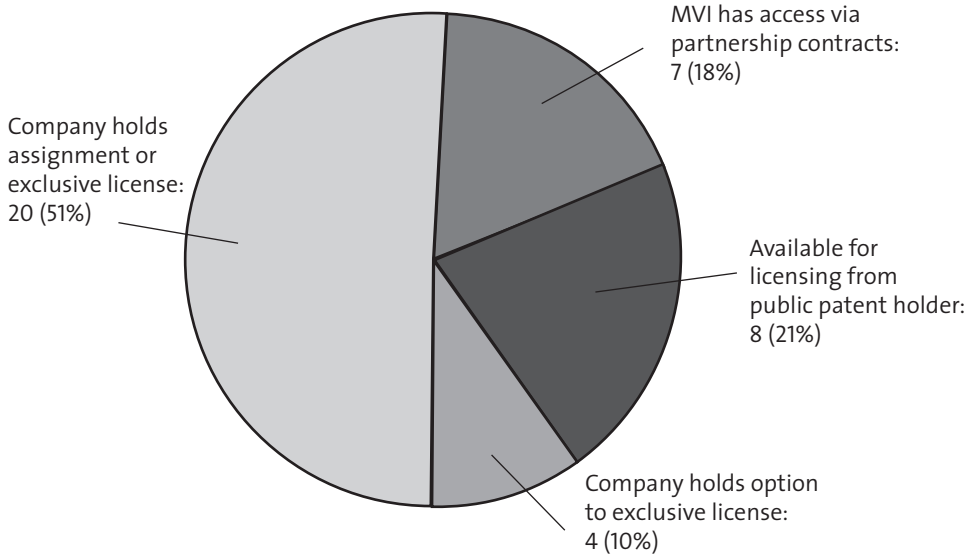
3.1 *The antigen patent landscape*

Ten malaria antigens were selected for review based on their use in the most-advanced vaccine development projects—clinical trials or late-stage preclinical studies. The antigens come from several key malaria parasites, most significantly *P. falciparum* and *P. vivax*, and from multiple phases of the parasite life cycle. Public patent databases were used to collect and organize patents and patent applications with claims covering these ten antigens. The patent landscape contained 167 patent families filed by 75 different organizations (sometimes in combination with other organizations).

Alta Biomedical worked with key MVI business and scientific staff and Falco Archer to review and prioritize the 167 patent families. A total of 39 out of 167 patent families (23%) were ranked as moderate to high priority based on the patent status (pending, issued, lapsed, or expired), length of estimated patent life, territory, and overlap between claims and vaccine-candidate attributes. The 39 patents were held by 21 organizations. Alta Biomedical met in person or by telephone with 16 of these organizations. Four of the remaining organizations were in direct contact with MVI; the fifth was not approached.

In early 2005, information from direct interviews and from MVI contacts led to grouping the 39 patent families into four categories (Figure 1). Some of the priority patents covered only one antigen; some covered multiple antigens. The distribution of patents over the ten antigens is shown in Figure 2.

Figure 1: Distribution of Priority Patents: Priority Patent Families by Licensing Category



3.2 *Ensuring equitable access*

Before this study, almost half of the priority patents were removed from access by public patent holders (not private companies). Significantly, 69% (27) of the moderate- to high-priority cases originally were filed by a public entity. Five of those were filed jointly with a company. By the time of the study, only 21% (8) remained available for licensing from the public entity. Thus, almost half of the priority cases were removed from access due to actions taken by the patent holder.

To ensure that in the future public entities provide ongoing access, MVI is working with multiple groups of stakeholders to develop recommended practices. This work has involved active participation in meetings with licensing practitioners through the Licensing Executives Society (LES)[3] and the Association of University Technology Managers (AUTM)[4], including the latter's special interest group Technology Managers for Global Health (TMGH).[5] In addition, MVI and Alta Biomedical have participated in smaller group discussions on equitable-access approaches, and in global health IP meetings such as those organized by the Centre for the Management of Intellectual Property in Health Research and Development (MIHR).[6]

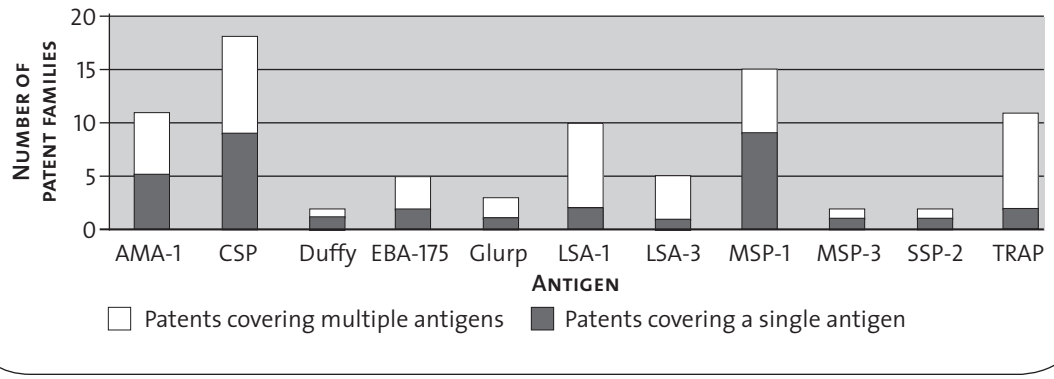
3.3 *Patent pooling*

To speed the delivery of vaccines to market, it would help to simplify licensing transactions for the malaria-antigen patents needed for potential vaccine products. One possible approach to simplifying licensing transactions would be to consolidate the necessary patents in a patent pool that could be accessed by any party with one license on reasonable terms. To understand this approach and assess its usefulness in the malaria-antigen area, one must consider information about past patent pools, about how patent pools are being used today, and about how patent pools are contemplated for use in health care.

In the past, patent pools sometimes have been used for anticompetitive purposes, such as collusion and price fixing. To prevent this, the U.S. Department of Justice (DOJ) and the Federal Trade Commission have set up guidelines to ensure that patent pools are "procompetitive." The guidelines include the following:[7]

- Patents in a pool should cover *complementary* technologies that can be used together as the basis for products.
- Patents should not cover *competing* technologies that could be used separately to address the same market need.
- Under the best of circumstances, an *independent standard-setting body* would establish criteria, or standards, in the field to set guidelines for what technology can be included in a patent pool.

Figure 2: Distribution of Priority Patents: Priority Patent Families by Antigen



- An *independent expert* should determine which patents fit the guidelines for inclusion in the pool.
- The pooled patents should be available on a *nonexclusive* basis.
- The pooled patents should be *available separately from the individual patent holders* on a nonexclusive basis so potential licensees are not forced to license the entire pool.
- The pooled patents should be available to all parties on *nondiscriminatory terms*.

It is unclear how these guidelines would apply to the malaria-antigen patents. While the last four points can be addressed, whether patents for multiple malaria antigens can meet the requirements of complementary versus competitiveness is uncertain, and what would be considered an independent standard-setting body is unclear.

As far as complementary versus competitive technologies, individual antigens may well be viewed as both. Arguably, they could be used together or separately to develop distinct vaccines. In particular, Richard Johnson of Arnold & Porter has raised a general concern that, based upon analysis of DOJ guidelines, universities may have difficulties creating a pool that includes "*a large fraction of the potential research and development in an innovation market*."[8] This may be viewed as an antitrust concern. Given the modest number of key patents for any single antigen, the large number of target antigens, and the inclusion of more than one antigen in many vaccine product candidates, efforts that consolidate patents for only one antigen do not seem of broad value to the field.

As far as standards in the field, it is possible that an organization such as the National Institutes of Health or the World Health Organization might develop a consensus or set standards that require a vaccine to include antigens from more than one stage of the parasite life cycle, although even then there are multiple candidate antigens from each stage that could be used separately.

Also, a licensee may not need access to, for example, all of the ten most-advanced antigen candidates to develop its planned vaccine. In that situation, it seems possible that the DOJ might view the separate antigens as requiring separate pools.

Two other areas have been proposed for formal patent pools in the health care field: the Severe Acute Respiratory Syndrome (SARS) genome (proposed by holders of SARS genome patents)[9] and the Acquired Immune Deficiency Syndrome (AIDS) essential patents (proposed by Essential Inventions, Inc.).[10] Both suffer from some of the same issues: many patent holders, the lack of an independent standard-setting body, and (perhaps most critically) the inclusion of potentially competing technologies within the same pool (Table

Table 1: Proposed Patent Pools in Health Care

Technology	Number of patent holders (approximate)	Complementary technology	Competing technology	Independent standard-setting body
SARS genome	5	Yes	Yes	Needs to be identified
Malaria antigens	21	Yes	Yes	Needs to be identified
AIDS essential technologies	23	Yes	Yes	Needs to be identified

1). The proposed SARS pool may have the advantage of being early in the product-development life cycle, with patent holders and others aware that resolving patent access may be essential to stimulating investment in product development.

3.4 *Business issues with patent pools*

Several business issues could make a formal malaria-antigen patent pool challenging. For companies currently developing vaccines covered by patents, the patents are likely part of a core business strategy for which a patent pool may be an anathema. Their participation in such a pool may be unlikely.

Moreover, setting up a patent pool can be expensive, with large up front costs for developing the pool's legal framework, taking the pool through regulatory review, and performing a legal review of the patents considered for inclusion in the pool. In the electronics industry, a large-company member of the pool typically contributes much of the up-front funding. That option, however, seems unlikely in the case of malaria antigens. While a small portion of the pool's licensing income typically covers the expense of a commercially successful pool, it seems unrealistic to seek significant licensing income from a malaria vaccine for some of the world's poorest nations. Furthermore, such a goal would run counter to the mission of developing a vaccine that is broadly affordable and available.

A final concern about a potential malaria-antigen patent pool is a simple business issue—very few entities would be interested in accessing any particular antigen patent. For example, if a company was developing a vaccine using two antigens, it would not need access to patents that cover others. An antigen used in one vaccine candidate may be included in a second vaccine candidate, but in combination with a different antigen or antigens. One can easily imagine a scenario where companies would not need access to a broad set of patents, but would prefer to pick and choose. This suggests that an individual access, or clearinghouse, approach might be preferable to a patent pool.

3.5 *Patent pool alternatives*

A pragmatic course would be to obtain access to the key patents that are available through license or assignment. Access by MVI or another organization on behalf of the field could ensure that these patents do not present a potential roadblock. In addition, MVI has developed constructive partnerships with key corporate holders of malaria patent rights and can continue to develop these partnerships as needed.

This strategy could lead to a clearinghouse approach, with IP rights accessible on a pick-and-choose basis by multiple potential partners or licensees, thus avoiding the DOJ approval issues. The approach also could simplify the licensing transaction by setting up, in advance, arrangements that provide assured access at a known cost (similar to setting up a patent pool in advance). But a clearinghouse does not resolve the concern that key patents could remain outside the clearinghouse. Ideally, a clearinghouse would include all the necessary patents for each antigen. Obtaining access to all the necessary patents would require working with companies to include their patents in the clearinghouse, which is not an impossible task but one that puts the transaction burden up front on the party trying to set up the clearinghouse. It seems more reasonable to work directly with companies when it becomes clear that access will be needed to a specific company technology. The relationship may involve not just straight licensing but, among other things, co-development, manufacturing contracts, partnering, and marketing. It might make sense to wait to develop such a relationship until the needs are clearer.

4. CONCLUSIONS

The results of the MVI study suggest that developing a broad-based technology trust for existing malaria antigen patents is not a good idea for several reasons. As the findings above should make clear, with few exceptions the patents held by public and academic institutions have been assigned or exclusively licensed to private companies. The patents are not currently available for licensing from the original public-institution patent holders. While it may be possible to sublicense the patents from the current private holders, doing so is likely to be difficult and costly; engaging patent holders in contributing to a patent pool or

clearinghouse also could be difficult. While the concept of a technology trust or patent pool may still be useful for patents to be filed in the future, even some of those would be under option for license by the private companies holding the existing patents. In addition, the number of high-priority cases for any malaria antigen is small, as is the number of entities likely to seek access to any given patent family. This makes the expense of a patent pool even less justifiable.

Other than a broad-based technology trust, there are several effective ways to consolidate available rights and improve access for future patent families in the malaria vaccine field, including:

- Taking assignment to or licensing the limited number of high- or moderate-priority patent families to ensure access. Holding these patents could be useful for developing products or for cross-licensing with private patent holders.
- Developing policy and public statements about why these priority patents are being held on behalf of the field, including a statement regarding the intention to allow access by others.
- Continuing to develop constructive partnerships with the corporate holders of the remaining key patents, as needed.
- Reviewing the geographic limitations of existing patents held by private companies, and considering approaches to vaccine development that do not infringe on these patents, for example, considering production by firms capable of high-quality, less-expensive production and manufacture in middle-income countries not covered by patents.
- Negotiating with patent holders for access to their know-how for development outside the patent coverage area.
- Educating public and academic patent holders about malaria-vaccine development issues in patenting and licensing as well as about balanced approaches that can meet institutional goals and accelerate the development of patents into useful vaccines. This would help to ensure that future actions by public research institutions do not create ongoing access problems.
- Working to develop consensus about when patenting makes sense, as well as the benefits of pooling for future inventions not yet patented or licensed.
- Gathering and developing model language to use in patent strategies and licenses covering malaria-vaccine technology that can ensure the development of appropriate, affordable products for markets in developing countries.
- Working with national and international leaders to encourage broad usage and a common approach for the field. Possible partners in this endeavor include MVI, The Rockefeller Foundation, MIHR, AUTM, LES, U.S. federal laboratories, and leading U.S. and international universities. ■

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1 Phase II trials are conducted on population groups of around 20–300 and are designed to determine dosing levels and assess clinical efficacy of a vaccine. Phase II builds on the initial safety studies of the vaccine (Phase I) and forms the basis for Phase III studies (typically randomized controlled trials on 300–3,000 or more people).

2 www.malariavaccine.org.

3 www.lesi.org.

4 www.autm.net.

5 www.tmgh.org.

6 www.mihr.org.

7 From presentations by Jorge Goldstein of Sterne Kessler Goldstein and Fox, PLLC; Richard Johnson of Arnold & Porter; Brian Stanton of the National Institutes of Health, Office of Technology Transfer; Lawrence Sung of the University of Maryland School of Law; numerous Department of Justice publications; and other Internet sources.

8 From a presentation by Richard Johnson of Arnold & Porter at the Association of University Technology Managers Annual Meeting on 4 February 2005 in Phoenix, Arizona.

9 www.who.int/bulletin/volumes/83/9/707.pdf.

10 www.essentialinventions.org.