IP considerations in COVID-19 vaccine development: tensions and tools

"Intellectual property" (IP) is the name given to ideas, creations and inventions which have value, but do not exist tangibly. Research and development creates IP that can be recorded in the form of a patent, a trademark, a design, copyright or kept as a trade secret. As opposed to a trade secret, which, by definition must be kept secret, the recorded IP can be used by the owner not only for their own purposes but also in collaboration with others. The owner may sell or license the rights to the IP for a fee. Licenses may be limited to a specific territory or to a specific field of use. The owner may also choose to give a license to IP for free, or commit to non-enforcement of its IP rights.

Novel and inventive COVID-19 vaccines represent valuable IP that could be protected by patents. However, given that a patent application is not published until about 18 months from its initial filing date, we cannot yet see how bio-pharma companies developing COVID-19 vaccines are managing the IP coming out of current research, who is filing patents, and where patents are being filed. Given the nature of a pandemic affecting most of the world's population, its rapid spread, and the critical need for speed in innovation, some may question whether any IP developed in this area should be subject to protection by private parties to begin with.

However, based on prior experience, we can predict that many a patent application is currently being filed that covers vaccine technology against COVID-19. Our prediction is based on, for example, the number of patent filings for Ebola vaccines. During the largest outbreak of Ebola since the virus was first discovered in 1976, the patent filings for vaccines between the 2013–2016 epidemic soared (see Figure 1). Looking at applications published between 2011 and 2020, companies from the US and China were the top filers for the Ebola vaccine technology.

In parallel, the US and the Chinese governments formed an alliance to share information to tackle the outbreak together. US and Chinese companies then followed. In 2017, in the spirit of further fostering private-public partnerships in tackling epidemics, the governments of Norway and India, the U.K. Wellcome Trust, the Bill & Melinda Gates Foundation, and the World Economic Forum launched CEPI, following a series of expert consultations convened by WHO. For Ebola, the vaccine that came to the forefront was rVSV-ZEBOV. It was developed by Canada's National Microbiology Laboratory who took the vaccine as far as Phase I clinical trials. Large injections of money from the US and Canadian government and other public bodies and finally a licence to Merck finally pushed the vaccine into production in 2019. This was the first FDA approval for a vaccine for Ebola.

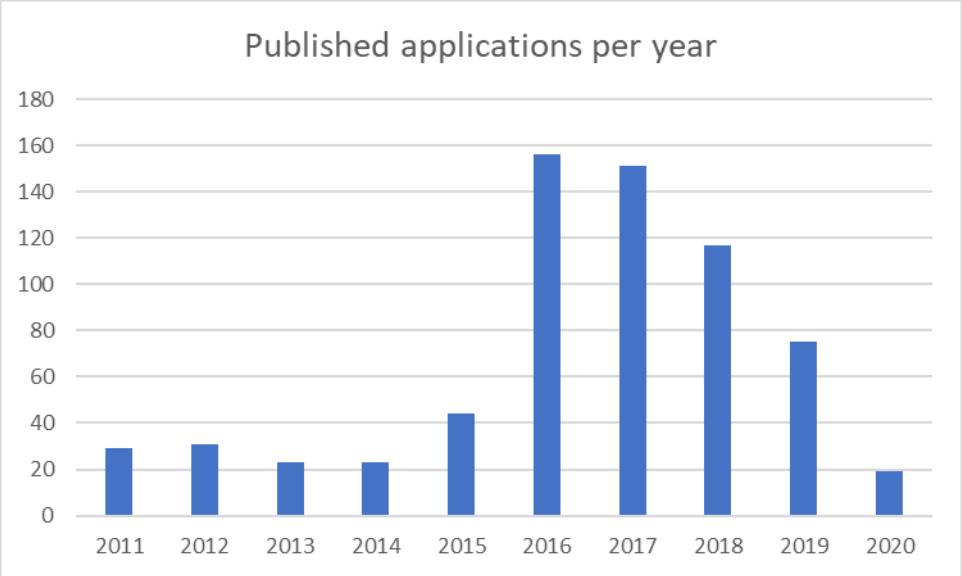

Figure 1: As illustrated by the graph, the number of applications being published concerning Ebola went up dramatically from 2015 onwards and has now returned to before-outbreak level. As publication normally occurs 18 months after filing, this means inventors were very quick off the mark filing applications in 2013/2014, not long after the outbreak began.

Here we discuss the challenges in managing IP in view of concern about public relations during a time of crisis, and possible accessible solutions that could aid in handling IP in a research emergency, such as finding an effective vaccine for prevention of COVID-19. We believe that, as evidenced by the Ebola vaccine campaign, patent protection, rapid information sharing, and collaboration are not necessarily mutually exclusive endeavours.

Tension

Bio-pharma companies typically rely on the time limited exclusivity provided by intellectual property rights in order to drive the generation of new drugs and treatments. Innovating in the bio-pharma industry is time consuming and carries with it a large risk of failure, which results in high costs. IP rights, typically patents, provide bio-pharma companies with a 20 year exclusive term to prevent others from copying the patented invention, giving them space to innovate and to develop a treatment based on the patented invention. Many attempts will fail, but for the small minority that succeed, the exclusivity provided by a patent may allow the company some time to exclusively profit from the sales which in turn finances the bio-pharma R&D for new medicines. This makes the risk of failing in roughly about 90% cases worth the reward that the 10% of successes provide.

The idea behind patent rights is to encourage companies to share their research, instead of hiding it, in order to benefit society and inspire further innovation. The limited time of exclusivity is only given to an applicant who discloses their invention in the patent application in such a complete way that others can make and use the invention after it expires. In fact, the entire generics industry relies on this information to make generic medicines after the expiration of the innovator industry patent.

However, in an emergency such as a pandemic, speed and flexibility are essential. One can argue that the patent system is not built for speed; patent applications are published on a searchable database only 18 months after filing, and granted patents expire after 20 years. This could be seen as creating a significant speed bump in the road of research particularly when time is of the essence.

So, why not just publish all the research that comes out of the development of COVID-19 vaccine, and collaborate without the speed bumps that IP protection is perceived to create?

Whilst this may seem like a solution to the problem when there is a need for speed, it may be short-sighted. This is at least partly because it is possible that many inventions that come out from development of a vaccine could be applied in development of other vaccines or in some other field of technology altogether, and this may be the case whether they fail or succeed against for COVID-19. Thus filing patent applications can be prudent to ensure investment in future vaccine development - if no protection exists, it is unlikely that development of such approaches would be financed further, and important innovative treatment approaches could die altogether for lack of investment.

Moreover, many technologies used in vaccine development require the use of research that is already are covered by existing patents. The technology platforms used for making vaccines, such as lentivirus and adenovirus-based vectors, mRNA technology, protein conformation stabilizers, and specific adjuvants are all examples of technologies that are covered by vast numbers of patents. Identifying all these patents in the first place can be like trying to find all the differently sized and shaped LEGO® pieces that one finds necessary to make a new structure, and looking for them after they have been spread all over the yard. Once all the pieces are found, collaboration will still require navigation of these patents via licences or other agreements, effectively slowing the process down once again.

How the bio-pharma industry has managed COVID-19 IP and patents in particular, will be interesting to see once patent applications begin to publish. The difference between COVID-19 and Ebola is that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread to a pandemic, and that the affected nations include not only poor and developing countries with very limited resources, but also rich and highly developed countries.

As is well known in academia and in the industry, and also evidenced by the story of the Ebola vaccine development; collaboration is key to speeding up research, especially research towards major therapies or treatments for diseases such as COVID-19. We believe there are three major roadblocks for speedy establishment of collaborative research: (1) how to rapidly find out which patents cover any given platform technology, (2) who owns or has a license to them, and (3) if necessary, how to get access to those patents in a timely manner.

Tools to help in finding patents for a platform technology and determining ownership

There are already a variety to tools available to firstly find, and secondly gain access to, patent protected IP.

Patents and patent applications, after 18 months, are published in freely accessible databases. One can also choose to publish any new invention after application filing but before the 18 months is up, which can speed up the flow of information. However, while the applicant is published on the cover of a patent, it does not reveal any possible licensees and more importantly, it does not tell what, if any, product is being developed or sold that uses the invention. Furthermore, an interested party still has to find the relevant patent documents associated with the platform technology of interest.

In the U.S., patents that cover small molecule drugs, must be listed in a database called the ‘Orange Book’ maintained by the U.S. Food and Drug Agency (FDA). This is to assist generics manufacturers to assess when the patents expire so that they can plan to enter the market. A similar, albeit more limited, list is also available from WIPO who maintain a relatively recently established, voluntary database called ‘Pat-INFORMED’, developed by the World Intellectual Property Office (WIPO) and the International Federation of Pharmaceutical Industrial Associations (IFPMA), in collaboration with 20 international pharmaceutical companies, and which provides information on patent documents and authorized medicines in the market, addressing jurisdictions around the world. However, no

databases currently exist that list patents covering either biologics or platform technologies, such as viral vectors which are being utilized, e.g., in vaccine development. Thus, the current way to find out who owns what in the life sciences field, and what technology is covered by which patents, is performed on a one by one searching and analysis basis, thus making it fairly inefficient, time consuming, and relatively expensive.

It would be helpful if the information relating to biologics, vaccines and technologies, such as viral vectors, was more readily available and the owners and licensees could be easily identified. The Pat-INFORMED database provides a potential model. As a matter of fact, suggestion to this effect seems to have already been set forth in an article by Corey Salsberg, VP, Global Head of IP Affairs at Novartis in his 2017 article discussing the Pat-Informed initiative, where he noted "[i]n a second phase, Pat-INFORMED will expand to all therapeutic areas and explore the inclusion of complex therapeutics.

While we recognize creating such a database would require significant up-front classification effort, particularly in the area of platform technologies, and constant maintenance and participation of most if not all players involved in the bio-pharma industry, such database could provide a significantly improved way for to identify technologies and collaboration partners in a time of crisis.

Tools to speed up getting access to patents

Once relevant patents have been identified and their owners tracked down, accessing the IP typically involves getting a license to use it. Absent legally binding pledges to provide free licenses or not to enforce IP relating to, for example COVID-19 vaccine development, licensing negotiations are often very time consuming.

During the coronavirus pandemic, time-limited pledges to offer a license "for free" or to refrain from enforcement of patents have been introduced. For example, several private companies set up a time-limited free licensing scheme called the 'Open Covid Pledge'. It provides template license agreements for companies to license part or all of their technology for field (COVID-19) and time restricted uses (e.g., until WTO declares the pandemic over). However, it is unclear what happens after the time limit expires. Notably the bio-pharma industry is absent from the participant list. This is not surprising for many reasons. For example, time restriction will not be helpful for pharmaceutical product development that typically requires many years. Perhaps the only workable "blanket pledge" could be a field-specific free license to a COVID-19 vaccine without time limitations. We see this option highly unlikely to be adopted by the bio-pharma industry.

In general, if parties are willing and the technology involves a limited number of patent holders, individual licensing agreements can be negotiated relatively quickly between the parties in order to allow access to an invention. Licensing can be tailored in a myriad of ways and can be, for example, exclusive, non-exclusive, or restricted to a particular field or geographical area. Many such licences will have been concluded and used during the coronavirus pandemic. However, barring some "emergency" license template, negotiating licenses can be a very time consuming endeavour.

However, if parties are not willing, many countries provide emergency provisions for a company to seek for access and/or the government to declare that access to a patent protected invention must be allowed. These provisions are known as compulsory licenses. Such licences, and their use in the coronavirus pandemic by various countries, and also by individual life sciences companies, is discussed in detail in an earlier HGF publication. This type of licence is quite rare as it requires certain legal hurdles are overcome, and it requires an interested party to apply for the licence to the patent office, or for government intervention to grant the licence. All of which is likely to be slow and relatively adversarial between the parties which does not lend itself to inspiring collaboration.

Even if the parties are willing, if the innovation necessitates use of multiple complementary inventions owned by different parties it will be even more difficult, time consuming, and very expensive to negotiate with possibly tens of patent owners for separate licenses. The concept of patent pools has been developed to address this challenge and successfully used to speed up development of, e.g., electronics and telecom industry. A patent pool essentially allows a "one-stop-shop" for accessing multiple the inventions with a relatively "prescribed" license where the value of the patent to the overall technology has been typically pre-evaluated by an independent party. Care must be taken to design the pools to avoid anti-trust issues, but in principle, pooling of patents that are either complementary or standard-essential for innovative products have been successfully established and used. These pools can be tied with simplified terms that are considered "fair, reasonable and non-discriminatory (F/RAND)". However, pools are only useful if the value of each patent can be fairly assessed and attributed to the overall technology. Pools are exceedingly rare in the bio-pharma industry.

We are aware of only two disease-directed patent pools: the Pool for Open Innovation against Neglected Tropical Diseases initiated by GlaxoSmithKline (GSK), which is referred to as the BIO Ventures for Global Health (BVGH) pool, and the Medicines Patent Pool (MPP) initiated by UNITAID. According to MPP, they negotiate with patent holders for licences on life-saving medicines and the licences permit multiple manufacturers to produce and distribute generic versions of patented medicines in developing countries. The MPP licences also provide the freedom to develop new treatments such as fixed-dose combinations – single pills composed of several medicines – and special formulations for children.

In mid-May 2020, the World Health Organization embraced a proposal to create a voluntary pool to collect patent rights, regulatory test data, and other information that could be shared for developing drugs, vaccines, and diagnostics for COVID-19. However, recent comments from at least some pharma industry players suggest resistance to the idea of a COVID-19 patent pool.

COVID-19 vaccine development

There are currently 102 candidate COVID-19 vaccines that researchers are working on in the UK, USA, Germany, China, and Australia, nine of which are in clinical trials. Examples of these vaccines are highlighted along with their respective owners and platform technologies here.

It is clear that nearly all of the vaccine front-runners under development have been built on a technology that was previously developed, and is likely to involve multiple parties (lentivirus vectors, adeno-virus vectors, mRNA to name a few). In some cases, like the inactivated vaccines, this knowledge and technology has been developed and applied in various vaccines over many decades, and while many patents have already expired, many patents are still likely in force that cover the most recent improvements. In other cases, like Inovio or Novavax, the vaccines relate to specific proprietary technology that has been developed relatively recently by these companies.

As the general idea of a COVID-19 patent pool has not yet been embraced by the pharma industry, additional proposals for streamlining licensing arrangements for vaccine development will need refining to ease future collaborative efforts. While pledges to provide vaccines at cost or for free to developing countries, or to give free licenses to generics to produce a COVID-19 vaccine once developed are helpful, these approaches are not meant for speeding up development or fostering collaborations. They are meant for ensuring access to already developed vaccines. Perhaps the idea of technology-specific platforms could be developed further. For example, if a certain virus vector were to become a standard for a certain class of vaccines, would the industry be willing to collaborate

by pooling the "standard essential" parts of the vector technology to a pool and provide a generic simplified license to the tools in that pool.

Although simplified licensing efforts would need much further planning, sharing information could be an easier area to negotiate. The already existing pharma company compliance with the Orange Book and the broad participation in the Pat-Informed database suggest that the industry could be willing to subscribe to the idea of sharing information about therapeutics other than small molecule drugs. While a database listing patents relating to vaccine development platforms and companies owning the technology is unlikely to spring up in the next couple of months to provide assistance for the rush to develop COVID-19 vaccines, it would be a worthwhile and useful endeavour to undertake now, so that the speed of vaccine development is faster in the future and we are better prepared for epidemic and pandemic situations.

We remain curious to follow up what kinds of patent applications have been filed for the COVID-19 vaccines when the 18 month publication time approaches, and it will be interesting to see how the industry will handle the IP in distributing access to any successful vaccines.

Vaccine Platform Technologies and Their Applications in Treating Covid-19

Viral vector vaccines – there are currently three high profile viral vector vaccines in development by the University of Oxford with AstraZeneca based in the UK, Cansino Biologics based in China, and Shenzhen Geno-Immune Medical Institute also based in China. The vaccine under development by Cansino is undergoing Phase 2 clinical trials in over 100 patients, and is therefore the most advanced Covid-19 vaccine in terms of pipeline. This vaccine uses a non-replicating adenovirus vector Ad5 originally developed for an Ebola vaccine which carries genes encoding the coronavirus spike protein. The adenovirus enters directly into human cells and causes the cell to produce the spike protein which is then detected by the immune system and causes the body to produce antibodies directed towards the coronavirus spike protein. The phase 2 trial is taking place in Tongji Hospital in Wuhan; the suspected epicentre of the pandemic. So far, results have shown that the vaccine produces virus-specific antibodies and T cells within 14 days of administration (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31208-3/fulltext).

mRNA vaccines – there are currently two notable mRNA vaccines under development by Biontech based in Germany, and Moderna based in the US. The Moderna mRNA-1273 vaccine was the first to enter in-human phase 1 clinical trials after receiving FDA Fast Track designation, and is being tested on volunteers at the Kaiser Permanente Washington Health Research Institute. The vaccine uses Moderna's proprietary mRNA platform technology. It comprises the mRNA encoding the coronavirus spike protein ready for translation into the spike protein within immune cells of a patient. The vaccine took only 42 days to develop from obtaining the genetic sequence of the novel coronavirus to testing in humans. Positive test results have recently been announced as of May 18th (https://www.modernatx.com/modernas-work-potential-vaccine-against-covid-19).

DNA vaccines – there are fewer examples of DNA vaccines. The most notable is that developed by Inovio in the USA collaborating with the Wistar Institute, the University of Pennsylvania, Université Laval and the University of Texas. It is the only company working on a covid-19 vaccine that already has a successful MERS vaccine. The INO-4800 vaccine is based, similar to Moderna, on Inovio's platform technology; a DNA delivery smart device that they have already developed. Interestingly, plasmid vectors carrying DNA encoding the spike protein are delivered to the patient intradermally or intramuscularly via electroporation using the Inovio CELLECTRA® device. One inside cells of the body, the cells can produce the coronavirus spike protein antigen from the gene encoded on the plasmid

(https://www.inovio.com/our-focus-serving-patients/covid-19/).

Protein vaccines – vaccines using this type of technology are further behind the others, having only reached animal trial stage. However, two companies working with this type of vaccine have taken more unique approaches to vaccine design. Novavax from the USA have developed a nanoparticle which holds spike protein antigens on its surface to mimic the coronavirus structure and activity within the body. The vaccine contains both Novavax proprietary nanoparticle technology and its saponin based Matrix-M® adjuvant technology to enhance the immune response (https://ir.novavax.com/news-releases/news-release-details/novavax-initiates-phase-12-clinical-trial-covid-19-vaccine). Whereas, the University of Queensland are using recently developed 'molecular clamp' technology to stabilise a synthetic version of the coronavirus spike protein.

Inactivated vaccines – this platform is probably considered as the most traditional form of vaccine in which a deactivated version of the virus is delivered to patients. Two entities working in this space are the Wuhan Institute of Virology collaborating with Wuhan Institute of Biological Products, and Sinovac both based in China. The Wuhan Institute has already gained notoriety in the pandemic for filing defensive patent applications covering the use of Gilead's antiviral drug Remdesivir for treatment of Covid-19(https://www.trialsitenews.com/wuhan-institute-of-virology-china-sought-to-patent-gileads-remdesivir/). This is the second vaccine in China to enter phase 2 trials in humans.

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With contribution from Dr Lauris Kemp on the Ebola patent trends.