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Presenting the (economic) value of patents nominated for the European Inventor Award 2012

Inventor file Gilles Gosselin

1. The invention

1.1 Historic account

This invention is about a potent drug in the fight against hepatitis B. Invented by Dr. Gilles Gosselin in France, it set the fight against an illness that chronically affects 350 million people worldwide and leads to countless deaths every year. The drug has been successfully commercialised.

Dr. Gilles Gosselin started his research in 1972 when he prepared a first Thesis at the University of Montpellier II in organic chemistry at the lab of Prof. Jean Louis Imbach. After finishing his first Thesis in 1975, he went on to become assistant professor at the University of Oran in Algeria. In 1979, he returned to France to work with his doctoral supervisor at the University of Montpellier and started to prepare his PhD in the lab. He led a group of two to three people and studied nucleoside analogues.

Dr. Gosselin remembers:

“We were synthesising new compounds, but we were chemists not virologists....we needed to collaborate with researchers from the biological side to actually test our molecules against viruses, tumors and so on....we were friends with a number of labs in France, Belgium and in the U.S....many of those screened compounds against a variety of pathogens, but HBV¹ was usually not on the list.....however, one lab in the U.S. at the University of Alabama (Birmingham), led by Prof. Jean-Pierre Sommadossi, did also check against HBV...so what we did with all of the labs [...] we sent the compounds and they screened the compounds against pathogens...” (Dr. Gosselin)

Research on this topic continued for some time, and it was not until 1997 when the research team synthesised a specific class of nucleoside analogues that showed remarkable effects in the lab of Prof. Sommadossi:

“It turned out that several of these analogues were active against HBV...and while there were already nucleoside molecules on the market which would be active against HBV, they would also be active against HIV viruses....this meant that we had found a drug specific for HBV with potential advantages if the subjects taking are not co-infected with HIV...” (Dr. Gosselin)

The next steps came rather fast. In the summer of 1997, Prof. Sommadossi founded the firm Novirio that would later (in 2002) become (i.e., be renamed) Idenix Pharmaceuticals. The two French researchers teamed up with Prof. Sommadossi for the development of telbivudine. The company was established in three different locations, namely in Cambridge/Massachusetts (headquarters), Montpellier (France, where most of the chemistry-related work was done) and in Cagliari, Italy (today, the company has only two locations, in the U.S. and in France). In August 1998, the institutions involved in the development and discovery of the drug – Novirio/Idenix, CNRS (Centre National de la Recherche Scientifique) and the University of Montpellier II - also applied jointly for patent protection.

The next step was the creation of a ‘collaborative lab’ (laboratoire coopératif) in Montpellier in January 1999. Dr. Gosselin recounts:

“At the time, the collaborative lab was a novel idea....it was a cooperation between Novirio/Idenix, the University of Montpellier II

¹ hepatitis B virus

and the CNRS....in essence the university provided Idenix with the lab premises and equipment, Idenix had their researchers perform their research there and I, having been paid by the CNRS back then, was allowed by the CNRS to manage the lab.....in the beginning we were only two persons, but we quickly grew to a group of around 20...the lab was very useful in supporting the start-up phase and became a role model for similar approaches later in France.” (Dr. Gosselin)

The firm decided to push telbivudine for preclinical development for the treatment of chronic HBV infection.² Pre-clinical studies in animal models were very promising: In woodchucks infected with HBV, virus DNA levels (HBV viremia) decreased by up to 8 logs in the treated animals, while lamivudine, a competing drug developed earlier, led to a decrease of only 0.5 logs with the same dose. Furthermore, telbivudine was well tolerated and no drug-related toxicity was seen through 4 weeks of treatment and 4 weeks of follow up. Experiments with monkeys provided further re-assuring results.

The drug entered eventually the different stages of clinical trials, at the later stages of which Dr. Gosselin was not involved any more with further development, testing and commercialisation of the drug. Idenix teamed up with Novartis for the different costly clinical trial phases (phase III) in 2003. The cooperative lab was closed in 2006, after Idenix could afford its own lab premises (which are still in Montpellier); however, the collaborative ties with the University of Montpellier and CNRS have continued to date. Telbivudine passed Phase III clinical trials and received FDA approval in 2006 and approval in the EU in 2007.³ In order to concentrate on the development of other hepatitis C and HIV drugs, Idenix Pharmaceuticals, amended the collaboration agreement with Novartis in 2007, whereby Novartis will have full responsibility for ongoing and future clinical trials and exclusive commercialisation rights. In return, Idenix and CNRS receive a royalty on worldwide product sales.⁴

Interestingly, there were few pronounced barriers in the development process, as perceived by the involved actors, except for the typical ones experienced in the development of any drug such as initiation of costly phase-III clinical trials or the need to scale up drug production from the laboratory to clinical trial phase application. David Standing from Idenix recounts:

“One of the beauties is the simplicity of the molecule, a mere image of natural molecules...it is not chemically modified in any way....it has very low toxicity levels...therefore it was very clean...the whole development process stands out as smooth and uneventful.”

Dr. Gilles Gosselin is still actively researching new anti-viral drugs (specifically, against hepatitis C) and nucleoside analogues. He is still CNRS Research Director and also now Idenix Senior Scientist Fellow.

1.2 Technological features and major benefits

Telbivudine is an example of a nucleoside analogue, a specific type of antiviral drug. Until the end of 2011, the FDA approved around 50 antiviral drugs, and half of them have a nucleoside structure. Most drug developments either fight retroviruses (e.g., HIV) or different forms of herpes viruses. However, considerable efforts are being undertaken to develop nucleoside analogue treatments also for other types of viruses such as hepatitis B and hepatitis C viruses.

All the nucleoside analogues work the same way: *“...The...virus replicates by making copies of its viral DNA or RNA genome . The nucleoside/nucleotide analogues fool the*

² Gosselin, G. et al. in *Frontiers in Nucleosides and Nucleic Acids*, R.F. Schinazi & D.C. Liotta eds, IHL Press (Tucker, USA), pp. 309-318 (2004)

³ http://www.nature.com/nrd/journal/v6/n4/box/nrd2295_BX1.html

⁴ <http://www.marketwatch.com/story/idenix-pharmaceuticals-changes-pact-for-tyzeka-bivo>

hepatitis B virus into thinking they are normal building blocks for DNA. Essentially, the virus is unable to replicate. Nucleoside/nucleotide analogues do not prevent all viral replication, but they can substantially lower the amount of virus in the body.”⁵

All “...current treatments suppress but [do] not eradicate hepatitis B virus (HBV). Therefore, most patients will require long durations if not life-long treatment to maintain virus suppression and to derive continued clinical benefit.”⁶

A physician today has the choice of seven medications against HBV, among which is also telbivudine. The general treatment approach, which is widely accepted, is described below:

“There are 7 [FDA-] approved therapies for hepatitis B: 2 formulations of interferon (standard [Roferon A and Intron A]⁷ and pegylated [Pegasys and PegIntron]) and 5 oral nucleoside/nucleotide analogues: lamivudine [EpiVir-HBV], adefovir [Hepsera], entecavir [Baraclude], telbivudine [Tyzeka, Sebivo], and tenofovir [Viread].

The initial decision regarding which drug to use involves a choice between interferon vs. nucleoside/nucleotide. Interferon has the advantage that it is administered for a finite duration and is not associated with specific drug-resistant mutations, but it has to be administered parenterally [by injection], is associated with many side effects, and is contraindicated in patients with decompensated liver disease.

Nucleoside/nucleotide analogues have the advantage that they are administered orally and have very little side effects, but they have to be administered for many years which may lead to selection of drug-resistant mutations. Among the nucleoside/nucleotide analogues, entecavir, telbivudine, and tenofovir have more potent antiviral activity; and entecavir and tenofovir have higher genetic barrier to resistance.

Selection of the initial therapy is critical as resistance to the first drug may diminish the response to other drugs due to cross-resistance.”

As far as possible advantages and disadvantages of the individual drugs are concerned, Cox & Tillmann⁸ provided a comparison based on available studies. However, they note that the comparison can be in many parts be made only indirectly, as there has been no single study to check all drugs in parallel using the same test set-up. Drug resistance is a primary challenge. With regard to telbivudine, the report first notes that the drug is effective (more effective than the older lamivudine), is well tolerated and has lower resistance rates than lamivudine. Yet, and notwithstanding the fact that no head-to-head comparison was possible/done, treatment of choice rests with the very potent entecavir and tenofovir. However, these two drugs are, in most countries, rather expensive. Telbivudine as an effective drug could have an important role as a cheap first line of treatment, because it does not show cross-resistance with entecavir. This means that patients could start out on telbivudine and, once resistance occurs, switch to entecavir. The authors conclude that “...telbivudine could be attractive if priced reasonably as it will allow entecavir to be used as second-line drug without overlapping in vivo resistance profile.”

⁵ http://www.emedicinehealth.com/hepatitis_b_treatment/page5_em.htm

⁶ Lok, A. (2009), as cited in http://www.hivandhepatitis.com/hep_b/news/2009/032709_aa.html

⁷ Brackets cite the trademark protected brand names.

⁸ Cox, N. & Tillman, H. (2011): *Expert Opinion in Emerging Drugs*, Vol. 16(4), pp. 713-729.

2. The market

Some 2 billion people have been infected worldwide by hepatitis B, and around 350 million must be considered chronic carriers. At least 1 million of the chronically infected individuals die each year from e.g. cirrhosis or hepatocellular carcinoma following the HBV infection. Hepatitis B is a typically blood-borne disease: High viral loads (a large amount of virus in the blood), very low minimum amount of blood to transmit the HBV and a high risk of infection following needle stick injury with positive HBV blood characterise the disease. There are vaccines against HBV available which are highly effective, and state-sponsored vaccine programmes have, especially in the developed world, reduced the prevalence of chronic infections. However, several million people are still being newly infected each year.

While 80% of the chronically infected are in Asia (China has the largest incidence)⁹, it is generally believed that due to difficult access of the population in developing countries to medical facilities and treatment, the market size for drugs such as the patented invention is still mainly determined by Western countries. Nonetheless, the market for treatment of chronic hepatitis B is large, not the least because of serious risks of co-morbidity (cancer, liver failure, etc.) and the fact that many HBV infections go unnoticed because there are no symptoms.

A research report by Global data puts the global market for HBV therapeutics at US\$ 1.3 billion in 2009 and expects a compound annual growth rate (CAGR) of 1.3% up till 2017.¹⁰ Cox & Tillmann⁸ assess the market as follows:

"...the global market for hepatitis B drugs exceeded the sales figure of US\$ 950 million in 2009 and is expected to generate > US\$ 1 billion by 2014. There are currently seven major HBV drugs dominated by antiviral nucleoside therapy. Entecavir and tenofovir are reputed to be the market leaders and are the gold standard for the treatment of chronic HBV replacing lamivudine and adefovir due to increase resistance patterns of the latter. Projected sales in 5-8 years are expected to decline owing to patent expiration of entecavir and tenofovir...."

The report further assesses that there are considerable price differences across different countries for the various drugs. This impacts the respective market shares. With respect to telbivudine Cox & Tillmann say that

"...in areas where telbivudine is slightly more expensive or even cheaper than lamivudine, telbivudine is attractive because its resistance profile does not spoil entecavir. The cost of telbivudine is an excellent example where price can prevent an effective drug from getting its achievable market share. In Europe and the U.S., telbivudine has very little market share due to its exorbitant costs compared to more effective comparators. However, in Hong Kong where telbivudine is reasonably priced, it is used rather frequently."

Telbivudine is sold under the brand names of Sebivo (in Europe) and Tyzeka (in the U.S.) by Novartis.

As for future drugs, owing also to the envisaged patent expiration of the main effective drugs and the likely decrease in price due to the introduction of generics, both Dr. Gosselin and the review see little potential for upcoming new drugs for HBV treatment, "...unless they offer some true advantage."

⁹ http://www.nature.com/nrd/journal/v6/n4/box/nrd2295_BX1.html

¹⁰ <http://reports.innovaro.com/reports/hepatitis-b-pipeline-assessment-and-market-forecasts-to-2017>

3. The role of patents and Intellectual Property Rights (IPR)

3.1 Motives and benefits of patenting and employed IPR strategy

As with all cases in the pharmaceutical industry - which is characterised by long and costly development cycles, with little possibility to recollect R&D and development expenses unless there is patent protection – patents are also important for telbivudine.

Dr. Gosselin explains:

“The patents were important for the development, and apart from providing income streams (e.g., in the form of licensing revenue to CNRS), the patents provide rules for collaboration and for acting in the market. The patents have had an impact, as we had more money for the lab, more money to create new molecules, and more people were working on solving the various problems... for me patenting is important, but more so is success in the market the patents are the kind of publication that provide trust and more money.” (Dr. Gosselin)

This view is also re-iterated by David Standring from Idenix who believes that the initial patent has provided trust and reputation beyond the initial invention: *“The telbivudine patent was for us as firm important although we now focus on other things. It demonstrates to potential investors that we have the opportunities and can see the whole process towards market introduction through.”*

3.2 Patent statistics and patenting trends

The nominated patent is part of a large family of patents. Depending on the definition of patent family used, there are as many as 15 patent families (INPADOC definition) to 25 families (if one were to look only at priority filings in different countries, ‘simple families’) on the analysed invention. The family has one application at world level, three at European level and 10 U.S. patent publications. The earliest publication was in 1998, the latest in 2011. The European patent in question was granted in 2005.

Dr. Gilles Gosselin is co-author of a further 74 families (‘simple families’), Prof. Imbach of 84 and third co-inventor M. Bryant of 63. The work of these inventors together resulted in the creation of 139 patent families, half of which are concerned with HBV and its treatment.

Patent applications relating to hepatitis in their titles, abstracts or claims have been applied for since the 1950s. Since 2000, there have been more than 1,000 patent applications in this field every year. Overall, 21,602 patent families have been applied for to date. Most patents relate to HBV (5,097). Filing activity for HBV-related patents has increased continuously with time. This is also true for HCV, for which we have found a total of 4,128 patent applications. However, while in the 1980s and 1990s there were more patent applications for HBV, the situation has reversed after 2000. The leading applicants in the field of HBV are Merck (116), U.S. Health (114) and GlaxoSmithKline (95). CNRS is ranked 7th on this list.

Reverting to the inventors, Prof. Imbach (32 applications) and Dr. Gosselin (28 applications) are ranked third and fourth in terms of HBV-related patents (the first two ranks are by Chinese researchers from DALI University in China, which patented all their inventions in 2010). The patents of Prof. Imbach and Dr. Gosselin have been cited a total of 81 times by other patent applications, indicating considerable impact of the invention on overall inventive activity in the field.

4. Conclusions

The patents and the invention itself have proven their commercial and societal value as evidenced by the patients benefiting from the drug and sales/licensing revenues

achieved. Furthermore, it has helped create a start-up firm and sustained research in the field, with respective employment effects.

For Dr. Gosselin key success factors are a working collaboration in an interdisciplinary environment and between science and industry, the implementation of the said collaborative laboratory in the start-up phase and *"...perseverance, but also luck."*