

The main entrance at the administrative headquarters of the Max Planck Society in Munich

RNAi patents under siege

Precarious Tangle

The Max Planck Society has joined forces with a biotech company and is suing three prominent US institutions. Billion dollar patents are at stake; just what lawyers have been waiting for.

Today's research and development projects often require co-operation between scientists and researchers from different organisations. Such joint ventures are intended to provide a synergy that will benefit the common project. At an early stage, the knowledge developed is usually transferred to an industrial partner for commercialisation. Commercialisation is, however, costly. Thus, the industrial partner is likely to insist that inventions made in the course of the co-operation are patented, and that the right to exploit patented technology lies exclusively with them.

Arrangements like this often point to trouble. Take, for example, the current conflict around RNAi patents.

RNAi patents under close scrutiny

RNA interference (RNAi), the promising new way to manipulate living cells by gene silencing (see box on page 52), can be used in scientific research as well as in disease therapy. The anticipated pharmaceutical and medical applications of this new technology are enormous. Thus, it is hardly astonishing that biotech companies are racing to create RNAi-based commercial drugs in order to claim a share in this potential billion dollar market. A strong patent position is, therefore, essential for the companies to recover investments for the development of RNAi therapeutics. There are a few early key patents on RNAi therapeutics. Nobel laureates Andrew Fire and Craig Mello hold patents on the use of long double-stranded RNAs for inducing RNAi-mediated gene knockdown in worms and other organisms.

Then there are the so-called Tuschl I and II patents (named after co-inventor Thomas Tuschl) directed to small 21-23 nucleotide RNAs as mediators of RNAi (Tuschl I) and the use of synthetic siRNA duplexes with 3'-overhangs for RNAi (Tuschl II) in mammalian cells. Since it is difficult to introduce long dsRNA into mammalian cells, the Tuschl inventions, and particularly the Tuschl II invention, are expected to become the next platform for developing RNAi therapeutics.

The rights in the above Tuschl I invention and corresponding patent applications have been assigned to the Max-Planck-Gesellschaft e.V. (Max Planck Society), a leading non-profit academic research institution in Germany, along with three US institutes, the Whitehead Institute for Biomedical Research (Whitehead), the Massachusetts Institute of Technology (MIT), and the University of Massachusetts Medical Center (U. Mass.).

By contrast, the Tuschl II invention and corresponding patent applications have been assigned exclusively to the Max Planck Society. The Max Planck Society has exclusively licensed their rights over the Tuschl II invention to Alnylam Pharmaceuticals, Inc. (Alnylam) for the development of RNAi therapeutics.

Mighty opponents

This is the background for an extraordinary lawsuit filed on July 1, 2009 with the Boston Massachusetts District Court (Case No.: 1:2009cv11116) by plaintiffs Max-Planck Society, Max-Planck-Innovation GmbH, their technology transfer agency ▶▶

►► (in the following known collectively as the Max Planck Society), and Alnylam against Whitehead, MIT and U. Mass as defendants.

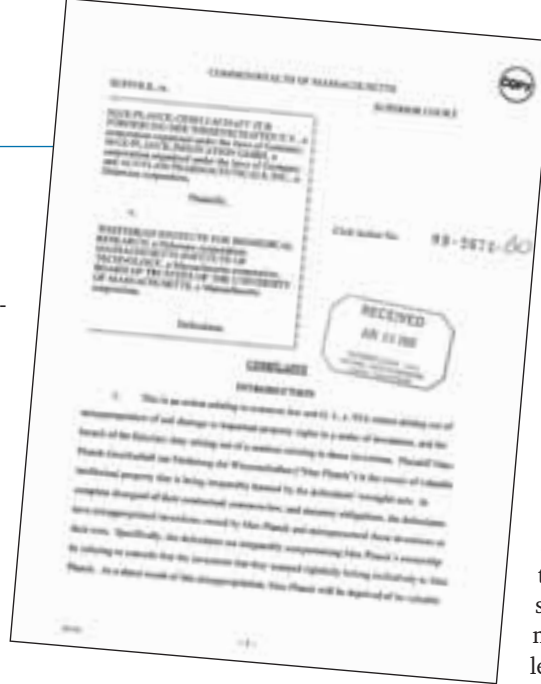
Though the lawsuit is still only at an early stage, the publicly available files already comprise several hundreds of pages and attorneys say that they read like a TV crime thriller. For the parties, not only a lot of money is at stake, but also their good reputation.

A lawsuit like a TV crime thriller

The Max Planck Society asserts that the defendants are attempting to misappropriate the rights of the Max Planck Society and their licensee Alnylam with regards to the Tuschl II invention, since they have, without authorisation, included part of the Tuschl II invention in Tuschl I US patent applications. On the other side, Whitehead and the other co-assignees say that the incorporation did not imperil Max Planck's Tuschl II invention.

Also, that, under the Joint Invention and Joint Marketing Agreement that both parties had signed, Whitehead had assumed primary responsibility for securing patent protection for the Tuschl I invention. Since the incorporation of Tuschl II information was necessary to support the patentability of Tuschl I applications, this approach was covered by the agreement. In fact, Tuschl II patents have been granted in 33 countries worldwide, including in the US, Europe and Japan, whereas patents for the Tuschl I invention have so far only been granted in Australia and New Zealand, with a European patent close to being granted.

What is the story behind this? In an affidavit presented to the district court, co-inventor Thomas Tuschl declared that the Tuschl I invention was made during his time as a post-doctoral fellow in a laboratory at Whitehead in collaboration with the other Tuschl I



The first page of the Max Planck Society's complaint to the Boston Massachusetts District Court from Juli 26th 2009.

co-inventors. For the Tuschl I invention, a provisional US patent application (USSN 60/193,594) was filed. In the US, a provisional application need not contain all the details necessary to demonstrate patentability and does not mature into an issued patent unless, within 12 months, a non-provisional or utility application, is

filed that includes those details.

Tuschl says that the later Tuschl II invention was made after he had started his own laboratory at the Max Planck Society, solely by himself and the other Tuschl II co-inventors, and that the results were also published in scientific journals such as *Nature*, with the Tuschl II inventors always as the only authors. According to Tuschl, the Tuschl II invention demonstrates for the first time that synthetically produced, 19-23 nucleotide siRNAs with 3'-overhangs can cause RNAi in mammalian cells. Tuschl says that this was a groundbreaking research, since prior to the Tuschl II invention researchers, also seeking the publication of the Tuschl I invention in a scientific journal, had believed that small dsRNAs, including siRNAs, would not silence genes in mammalian cells. For the Tuschl II invention, the first European patent, application 00 126 325.0, was filed by Max Planck Society.

The Tuschl II invention is considered to be the most promising and lucrative technology platform for developing RNAi therapeutics. It should be noted here that Thomas Tuschl is not only one of

RNA interference

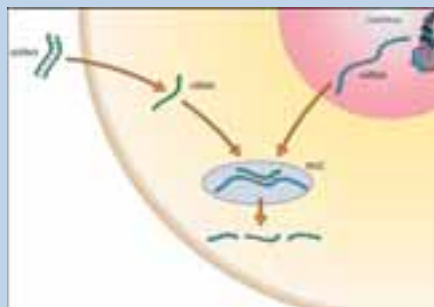
A Discovery that Electrifies the Drug Making Industry

RNAi technology is currently making so many waves, but how does it work?

RNAi is a system within living cells that helps to control which genes are active and how active they are. It is based on two types of small RNA molecules: microRNA (miRNA) and small interfering RNA (siRNA). RNAi is initiated by the enzyme DICER, which cleaves long double-stranded RNA (dsRNA) molecules into short fragments of about 20 nucleotides.

One of the two strands of each fragment, the so-called guide strand, is then incorporated into the RNA-induced silencing complex (RISC). The guide strand base pairs with a complementary sequence of a target messenger RNA (mRNA), and

induces its cleavage by a so-called argonaute endonuclease which is a catalytic component of the RISC complex. As a



Small RNA molecules activate a cellular response, able to destroy a specific mRNA – and thus to knock down a specific gene.

result, the concentration of the target mRNA is reduced; as is, consequently, its translation into the encoded protein. RNAi can be used for both the downregulation and upregulation of genes, by simply synthesising double-stranded RNA with a sequence complementary to a gene of interest and introducing it into a cell or organism where it activates the RNAi system and can cause a drastic decrease in the expression (knockdown) of the targeted gene.

In 2006, Andrew Fire and Craig Mello shared the Nobel Prize in Medicine for their pioneering work on RNAi.

-MS-

the inventors, but also a co-founder of Alnylam, the Max Planck Society's exclusive licensee, and a co-plaintiff.

Then, after the Tuschl I provisional US patent application had been converted into a utility application, the Max Planck Society became aware that it not only contained information about the Tuschl I and one Tuschl I provisional application, but also information about the Tuschl II invention.

Pressing questions

How could this have happened? According to Tuschl's affidavit, he had continued to communicate with two of his Tuschl I co-inventors during work leading to the Tuschl II invention. He says that prior to submitting the *Nature* paper about the Tuschl II invention he had given a copy of the manuscript to one of the Whitehead Tuschl I co-inventors for comments. Tuschl says that he had been asked by this Tuschl I co-inventor for permission to include the *Nature* data in Tuschl I applications, which he had refused, since he did not have the authority to do so. In his affidavit, Tuschl explains in detail the source from which the Tuschl II information was copied into the Tuschl I utility application, i.e. from the paper in *Nature*, from a publication in *Genes & Development*, and from the first EP patent application.

There is also an affidavit by the Max Planck Society's European patent attorney declaring that he had been asked by Whitehead's US patent attorney for permission to include Tuschl II information in Tuschl I applications. He says that he had rejected this since the two inventions were obviously distinct and independent.

The Max Planck Society claims it had no knowledge that Tuschl II information was included in Tuschl I applications, and that when it became aware of this after some discussions, it had agreed that Tuschl II data could remain in Tuschl I applications, provided that this did not jeopardise the Max Planck Society's property interests.

Double patenting concerns

However, the matter became critical when U. Mass. licensed its interests in the Tuschl I applications separately from the other three co-owners, and when the United States Patent and Trademark Office (USPTO) notified the parties that it would reject Tuschl II applications on obvious-type double-patenting grounds, if the Tuschl II information remained in Tuschl I ap-



How relevant was the research work that RNAi pioneer Tom Tuschl (small picture) did at the Max Planck Institute for Biophysical Chemistry in Goettingen, Germany, between 1999 and 2003?

plications. Double patenting is not allowed in the US (and elsewhere), and means that once an invention is disclosed in one patent, the USPTO will not allow the same invention (or obvious variants of it) to be doubly protected by a second patent.

In the meantime, US patents 7,056,704 and 7,078,196 have been granted for the Tuschl II invention, and in Europe patent EP 1 407 044. But according to the Max Planck Society, the USPTO will very shortly issue a Notice of Allowance for a Tuschl I US patent application including Tuschl II information, i.e. a notice that the USPTO intends to issue a patent. The Max Planck Society says that, if that happens, it would effectively lose all its property rights to the Tuschl II invention. European patent EP 1 407 044 is currently under opposition. One of the opponents is Sirna Therapeutics, Inc. (a subsidiary of Merck & Co., Inc.), a direct competitor of the Max Planck Society's exclusive licensee Alnylam and holder of a Tuschl I license from U. Mass.

The Max Planck Society and its licensee Alnylam have, therefore, requested that the district court issues a preliminary injunction ordering that no issuance fee shall be paid on any Tuschl I application, unless all co-assignees of the application agree that the fee shall be paid, in order to prevent Tuschl I patents from entering into force and to so preserve the status quo while the lawsuit is pending.

Tuschl II an independent invention?

It appears to be likely that the district court will grant a preliminary injunction to protect the Max Planck Society from any potential damage, since there is strong evidence that Tuschl II ►►

►► is, in fact, an independent invention. The Max Planck Society says that the defendants have also admitted that they have no ownership rights, but it remains to be seen whether this is the last word.

The fact that a preliminary injunction has been issued would not constitute any prejudice that, at the end of a closer scrutiny, the court might delete all Tuschl II information from Tuschl I applications. This is not a case of classic invention theft, since the Max Planck Society holds patents on the Tuschl II invention, and, additionally, is also a co-applicant of the Tuschl I invention. Thus, the bottom line is that the Max Planck Society is not deprived of its right to exploit the Tuschl I and II inventions.

The important questions that the court will have to answer will be on what the parties have, in fact, contractually agreed for the Tuschl I invention, particularly regarding future developments and improvements, and whether Whitehead had breached its contractual and fiduciary duties when including the Tuschl II information in Tuschl I applications. The Max Planck Society argues that, under the Joint Invention and Joint Marketing Agreement, Whitehead has primary, but not exclusive, responsibility for the prosecution of the Tuschl I applications, with the proviso that the remaining joint owners are reasonably informed and given the opportunity to comment and advise.

The fight has just started

The Max Planck Society's motivation for this lawsuit is that they might lose their monopoly on the Tuschl II invention. Alnylam's motivation, however, is that it will lose its competitive advantage if their exclusive license from the Max Planck Society is undermined by licenses granted by the co-owners of Tuschl I applications. In fact, as described above, competitor Sirna Ther-

apeutics holds a Tuschl I license from U. Mass and is one of the opponents of the Max Planck Society's Tuschl II European patent EP 1 407 044.

The fight for exclusive rights and a share of this billion-dollar market has started.

MICHAEL SCHNEIDER

Michael Schneider holds a diploma and a doctoral degree in biochemistry and is a patent attorney and partner in the Munich office of the international law firm Hammonds.



Photo: BostonSpring/Wikipedia

The Whitehead Institute for Biomedical Research (Cambridge, Massachusetts) is keen after the Tuschl II patents. The multi-billion-dollar question is: Has Whitehead, without authorisation, included part of the Tuschl II invention in Tuschl I US patent applications? Whitehead says, "No", the incorporation "did not imperil Max Planck's Tuschl II invention".

Millipore's strategic move

Reaching Out for Europe

Life science technologies provider Millipore (Billerica, Massachusetts) has acquired a small Oxford University spin-off. While some might be surprised by the takeover of Bioanalab Ltd., given the two organisations' (seemingly) differing business interests, it's actually a logical move. Millipore is a huge company of 5,900 employees that offers not only laboratory water purification and filtration products (as most people think) but also a broad range of services around bioprocessing as well as drug discovery and development.

By snapping up the small Oxford University spin-off Bioanalab (see photo), Millipore acquires a British contract research organisation (CRO) that specialises in the analysis of biological therapeutics for the

pharmaceutical industry, thus broadening Millipore's service portfolio for drug development companies.



Of course, it's not just Bioanalab that Millipore is interested in. The company's location is equally important. The transaction enables the US giant Millipore to expand its biopharmaceutical services business into Europe, as Millipore's Jonathan DiVincenzo openly admits, "[This] acquisition will allow us [to establish] a presence in the fast-growing European biotech market." The groundwork is done. -wk-

Qiagen, the busy builder

Headquarters 2.0

Qiagen is going to invest €30 million for an enlargement of the company's current headquarters in Hilden, Germany. The three new premises for research, production and administration will have a total area of 16,500 m². According to Qiagen, they will fit the "highest ecological standards", consuming 30% less energy than comparable facilities. Up until completion in December 2010, the provider of sample and assay technologies for molecular diagnostics and research intends to engage an additional 500 people, to fill the new rooms.

Qiagen's building activities, however, are not only proceeding in Germany. In China, the firm will soon move into a new regional headquarters; in Switzerland, the present research and production site will be extended to 4,000 m²; and the US headquarters will soon grow by 5,100 m². -wk-