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Version final

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

Inventor file Jason Chin

1. The invention

1.1 Historical background

Prof. Jason Chin´s nominated invention is in the field of synthetic biology. The aim of this field is the design and construction of new biological functions and systems not found in nature. Prof. Chin´s patented development of a new ribosome which works with a novel genetic code can be considered radical – changing the belief that some components in a cell, such as the ribosome, are un-evolveable because they are absolutely essential for the cell to work.

The ribosome´s task is to synthesize the proteins the cell needs from amino acid molecules, according to the information stored in the genetic code. Prof. Chin succeeded in creating a second, fully independent ribosome ('orthogonal ribosome') - in an insulated pathway within the cell. The new ribosome is able to read a new, more complex, artificial genetic code not found in nature, allowing the creation of completely new types of proteins. Together with Prof. Chin's earlier inventions, this lays the foundation for the design and production of new types of proteins and agents for therapeutic purposes.

Prof. Chin[1] began studying for his B.A. in chemistry at the University of Oxford, but soon found the chemistry curriculum to be *"incredibly traditional."* Following the advice of Professor John Sutherland, an organic chemistry professor - who told him to not limit himself to what is covered in class and instead seek out for the periphery where there is most scope for discovery - Prof. Chin became interested in how to apply the principles of chemistry to living systems. After finishing his B.A., Prof. Chin continued on a Masters degree project in Sutherland's laboratory, where he used genetic engineering to get bugs to synthesize an antibiotic called cephalosporin.

In 1996 Prof. Chin obtained a Fulbright scholarship to work on his PhD at Yale University focusing on developing chemical tools for studying and manipulating protein-DNA interactions within cells. Interestingly, although studying chemistry, he mostly took graduate biology classes and, by the end of the first year, was equally trained in both disciplines. Whilst working on his PhD, Prof. Chin succeeded in designing one of the first functional miniature proteins – a development which required combinatory biology techniques, which were not available at the time in the lab at Yale. Whilst studying for his PhD, Prof. Chin learned to be self-sufficient, to establish solid foundations for his work and to follow his curiosity whatever the cost. "Once you solve a problem", he says, "*You have two choices: either you can keep solving the same problems or find new problems that are exciting.* "

In 2001, following his PhD, he moved to the Scripps Research Institute in San Diego, joining the research group of Peter Schultz as a post doc. In the same year, Schultz succeeded in modifying the transfer RNA in the bacteria Escherichia Coli in such a way that he could add a new, not naturally occurring, aminoacid on proteins being made by the bacterium. Escherichia coli is an example of a prokaryote, a type of cell which does not have a true membrane-bound nucleus. Prof. Chin, however, was intrigued by the idea of getting more complex, eukaryotic cells to produce proteins containing unnatural amino acids. This required the creation of a new transfer RNA-enzyme pair which Prof. Chin eventually achieved, with his colleague Ashton Cropp (now assistant professor at the University of Maryland). This development – which revealed a major

[1] The following paragraphs are mainly based on Pain, E. (2010): Expanding the Genetic Code, Sep 17, 2010, in: Science Career, http://sciencecareers.sciencemag.org/career_magazine/previous_issues/articles/2010_09_17/caredit.a1000091

element of the 'cell factory' for the production of synthetic protein – was patented by Scripps.

In 2003, Prof. Chin returned to the UK with a tenure-track position at the Medical Research Council´s Laboratory of Molecular Biology (MRC-LMB) in Cambridge. While he had secured the position just a few months into his post doc at Scripps, there was still the need to define, before his return, what he was planning to work on next. The inspiration came from a lecture given by Venkatraman Ramakrishan (a later Nobel prize winner) who explained in molecular detail how ribosomes decode genetic information.

> *"It was amazing….in chemistry…we have good control over how to make small molecules, but we do not know how to assemble polymers of defined sequence. The ribosome is a paradigm of a molecular assembler….so I asked myself…what will it take to convert the ribosome from something that makes natural proteins into something able to assemble….new, different types of chemical entities…"* (Prof. Chin, cited in Pain 2010).

Upon arriving in Cambridge, Prof. Chin assembled a team and *"…they went to work on engineering new translational machinery that would allow living cells to produce proteins that contain none of the amino acids nature uses. Until then, just one type of amino acid could be added into proteins at a time. Chin started by making this process more efficient, complementing E. coli's natural translational machinery with an artificial ribosome. He then had to figure out how to insert more than one unnatural amino acid into the same protein. To do this, he had to overcome a limitation imposed by the natural genetic code: most of the available triplets were already taken, corresponding to a specific, natural amino acid. There was little room to add more. So Chin set out to write an entirely new genetic code based on quadruplets of genetic letters instead of triplets.* [2]

Using this approach, Prof Chin made living cells that produce proteins containing two distinct, novel amino acids – achieving a crucial second step towards producing entirely unnatural proteins.

Prof. Chin is continuing his work in this field. By 2010, his group had increased to 15 researchers and in March 2012, the MRC announced that it would fund and set up a 'Centre for Synthetic and Chemical Biology' within the LMB to be headed by Prof. Chin.[3] According to Dr Ranmali Nawaratne, Senior Business Manager at MRC Technology[4] (the technology transfer agents for the MRC), *"…the MRC recognises Jason Chin's unique expertise and contribution to the field and has therefore funded additional posts, equipment and space at this Centre".*

To date, Prof. Chin has received an array of prizes for his ground-breaking research, including the Royal Society's Francis Crick Prize Lecture in 2009 and the European Molecular Biology Organization (EMBO) Gold Medal in 2010.

1.2 Technological features and major benefits

To explain the nature of Prof. Chin's invention it is necessary to understand in basic terms how a ribosome builds a protein. Proteins are found in almost every cell. They facilitate and enable biological functions such as transporting metabolites, pumping ions, catalysing (i.e., speeding up) chemical reactions or recognising semiochemicals. The building blocks of these proteins are amino acids. There are 20 such 'standard' building blocks used by cells ('standard amino acids') that can be linked together in chains to form proteins. The sequence of the amino acids determines the form of the

[2] Pain (2010)

[3] http://www.mrc.ac.uk/Newspublications/News/MRC008531

[4] http://www.mrctechnology.org/

protein (e.g., where they fold) and ultimately the type and function of the resulting protein. There is a need for a plan, a blueprint, on how a cell is supposed to assemble these 20 aminoacids into the needed proteins. This blueprint is stored in the genetic code of the cell. For actually producing the protein, the cell copies the genetic code from the genes (i.e., the DNA sequence embodied in the genes) into a messenger RNA (mRNA). In a process called translation, ribosomes then read the information stored in the mRNA to produce the actual protein.

The information in the mRNA (i.e., the genetic code) is stored in a sequence of three so-called nucleotide molecules. These are labelled with three letters, whereby a certain three-letter combination denotes a certain amino acid. For, example the triplet 'TGC' denotes the aminoacid 'cysteine', and once the ribosome recognises the 'TGC' triplet, it knows that it has to insert now a 'cysteine' aminoacid into the growing chain that will ultimately become the protein. The actual translation process between the mRNA and the ribosome is somewhat more complicated and performed by so-called transfer RNA molecules (tRNA molecules). These tRNA molecules behave like mirror molecules of the mRNA molecules (much like a key and a lock), and they are also loaded with the respective aminoacid. Because of the key-lock shape, the tRNA molecule can dock to the respective mRNA molecule and deliver the ribosome also with right proteins:

> *"Think of the whole process of producing a necklace (the protein) that can be made up by different types of pearls. The ribosome takes the role of the machine that puts the pearls in the desired sequence on the necklace, based on the information stored in the mRNA. The tRNA is another component of the assembly line which delivers the actual pearls to the ribosome for placement on the necklace".* (Interview Prof. Jason Chin).

Prof. Chin and his team first succeeded in creating a new ribosome in a cell which is a copy of the naturally occurring one, but in an insulated pathway and fully independent of the first ribosome (hence the name 'orthogonal', an analogy from mathematics denoting two independent dimensions). They then modified the new ribosome to be able to read 4-letter nucleotide sequences/genetic codes ('quadruplets') instead of the naturally occurring three letter genetic codes ('triplets').

The advantage of a four-letter code is that it makes a much larger number of codes available to denote aminoacids. This gives rise to the opportunity to allow the reading and processing of aminoacids, which are not naturally occurring (e.g., produced synthetically). Prof. Chins´ invention also enables a protein building process to take place, whereby several 'artificial' amino acids with new properties can be added to the chains that make up the proteins. Before, it was only possible to add, inefficiently and with serious effort, only one artificial aminoacid.

In order to turn the cell into a veritable factory for new proteins, the tRNA molecules also need to be modified. This work – i.e., modifying the machine that delivers the pearls to the necklace building machine, to use the analogy quoted before - was the subject of the earlier research work of Prof. Chin performed at Scripps in the U.S.

The possibilities of the new 'protein factory' technology are manifold: In the short run, already existing therapeutic agents can be modified by adding/replacing aminoacids with new artificial ones. In the long run, completely new, designer-built molecules can be anticipated. One particular vision is to create huge libraries of cells/bacteria producing a sizable number of variants of an 'artificially created' protein/molecule, a vision which would be possible with the technology: *"You can then see how a certain pathogen (e.g., a virus) reacts to the presence of the various molecules. While it will not be affected by many or most variants, some variants will prove deadly to the pathogen, and that´s then the variant/molecule you would like to use for treatment."*

2. The market

Prof. Chin´s discoveries are in different stages of commercialisation, although none have been introduced into the markets as yet.

So far, his work at Scripps on the tRNA has progressed farthest in the commercialisation process, while commercial exploitation of the work on the new ribosome at MRC-LMB is in the initial phases:

- Commercialisation of the patented tRNA technology is taking place primarily through the biotech firm Ambrx (California) which has licensed the technology. Ambrx is using this technology under the ReCODE brand to develop a variety of drugs for the protein therapeutics market:[4] The product pipeline shows 10 drugs in various stages of development. The most advanced is an agent called "ARX201" which is in phase-II clinical trials (leaving only the hurdle of phase-III before actual market introduction). Other drugs are either at the beginning of phase-I clinical trials or at pre-clinical stages. The drugs under development are likely to have various applications in oncology and to be used in the treatment of multiple sclerosis, diabetes, obesity and heart failure.

  Ambrx has partnering agreements with a number of big pharmaceutical firms, such as Pfizer, Eli Lilly, EMD Serono (in particular for ARX201) and – most recently, as of September 2011 – with Bristol-Myers Squibb.[5] The latter will make an upfront payment of US$ 24 million to Ambrx as well as milestone payments and royalty payments on worldwide sales for diabetes and heart-failure related drugs under development. Overall, Ambrx has succeeded in attracting as many as nine venture capital firms to invest funds amounting almost to US$ 100 million. While there is not yet a viable product on the market, the picture clearly reflects high levels of confidence in the firm and in the underlying technology. Ambryx's IP position is very strong, given that the company – beyond the core patent for Prof. Chins technology– has possession of, or control over, 600 patents.

- *"MRC Technology is considering a number of options in relation to the commercialisation of Jason Chin's technology, as the technology lends itself to commercialisation via the spinout route, as well as via the provision of multiple non-exclusive licences"* explained Dr Ranmali Nawaratne. MRC Technology has had negotiations with both venture capitalists and commercial organisations to explore these options. MRC Technology also has access to the MRC's Development Gap Fund – which is used for proof of concept work, to add value to early-stage technology.

- The anticipated timeline, when the first therapeutic agents based on the ribosome patent will be available for pre-clinical trials, is estimated at around three years from now for alterations of existing agents. For the development of larger-scale libraries and completely new molecules the timeline is likely to extend to 15 to 20 years. However, there seems to be consensus in the field that the technology will have considerable impact both commercially and in the research area.

High investor confidence in the new technologies, at least when it comes to proteins, is underpinned by market forecasts for the global protein therapeutics market:[6]

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[4] Homepage of Ambrx, http://www.ambrx.com/wt/home/index, as of December 29, 2011.

[5] http://www.fiercebiotech.com/press-releases/bristol-myers-squibb-and-ambrx-announce-collaboration-novel-biologics-progr-0

[6] Maheshwari, S. (2011): 4. Global protein therapeutics market: beefing up towards futuristic growth, http://www.pharmaphorum.com/2011/10/11/global-protein-therapeutics-market-beefing-up-towards-futuristic-growth/

> "*The global pharmaceutical market is foreseeing an upcoming era of scientifically engineered proteins in the laboratory, known as 'Therapeutic Proteins' for usage in pharmaceutical purposes. These proteins are synthesized by large-scale cultivation of genetically engineered host cells, which translate artificially transected genes encoding for the proteins of interest... the therapeutic proteins market is estimated to increase by around 9.6% from 2010, to reach a value of around US$102.4 billion in 2011. This growth is supported by the high efficiency of therapeutic proteins due to their targeted approach devoid of side effects on the human body to a large extent, the increasing prevalence of chronic diseases, and significant on-going research for improving the drug delivery mechanisms of the therapy... It is likely that the protein therapeutics market will dominate the pharmaceuticals industry in future. Although the protein therapeutics market is significantly smaller than the pharmaceutical market, the comparative growth of the protein therapeutics market is considerably higher than the overall pharmaceutical market growth. The major factors expected to drive the industry in coming years include aging population and increasing prevalence of chronic diseases, increasing penetration of health insurance, growth of next-generation products with reduced immunogenicity, greater effectiveness, and improved safety of products.*"

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

3.1 The benefits of patenting and employing an IPR strategy

Within the biotechnology industry the long development cycles in bringing a product to market and the need to recuperate high R&D expenditures mean that patents play a key role in enabling companies to thrive.

With regard to patenting, Prof. Chin comments:

> *"The driver for my research is to do things that are new and innovative, and within the MRC this naturally leads to patents….my goal is not to generate patents, but to innovate….patents are a means of protecting R&D investments…we report early on possible patentability and why some research may be valuable and then it is up to the MRC to decide if they patent or not…the research itself is not affected by the patents"*

To handle the commercialisation process, the MRC uses a technology transfer company called MRC Technology, which exclusively manages the IP from the MRC, and from other research organisations. MRC Technology has an IP and licensing department with about 25 staff, including a number of business managers who all have a scientific background. Each business manager liaises with members of the group of researchers assigned to them in order to identify the elements in their discoveries which could, potentially, become (patented) inventions. Although MRC Technology's IP and licensing department includes a legal team their focus is on contractual issues and the company outsources its patent attorney work - allowing it to choose the best patent attorneys based on the specific technology expertise required.

Besides the IP and licensing department, MRC Technology has a business development team, which is responsible for technology scouting and a range of other functions. The company also has a separate Centre for Therapeutics Discovery, comprising around 80 scientists with a strong industry background, who help to develop and commercialise research discoveries. This Centre is not only open to MRC Research facilities but to other research facilities, in the UK and abroad, that are working in the relevant fields (antibodies, small molecules).

In terms of the IPR strategy pursued, one of the first steps in the commercialisation process is to look at whether an R&D result can be patented. If it can, it will be patented. For Prof. Chin´s invention a whole portfolio of patents was created to protect the various possible applications. The next step is to decide whether the invention should be commercialised via a start-up firm, or via a license to an existing firm. Platform technologies, from which several products can be derived, are most likely to be the subject of new start-ups, while R&D results which lead to single products are more likely to be out-licensed.

In commercialising Prof. Chin's invention, the MRC's Development Gap Fund was crucial, as Ranmali Nawaratne identifies:

An important step to convince potential investors is *"…to show added-value to early-stage inventions and to demonstrate that the invention is commercially viable. Usually, basic R&D alone will not suffice which is why the Development Gap Fund is so important. It adds value to the package and makes it more interesting for investors."*

3.2 Patent statistics and patenting trends

The MRC has a strong track record in commercialising the outputs from its research; the licensing income to the MRC reached £61.69m in 2010/11. This brings the total cash generated from MRC intellectual property since 1998 to more than £550m. In 2010/11 12 patent applications were made by MRC Technology and 32 patents were granted. In addition, three spin out companies have been created since 2008.

According to an analysis by TU Ilmenau, the nominated patent EP1907545 by the MRC was applied for in 2006 via the world–PCT route. It has been granted by the EPO in 2010 and is in force in the following countries: DK, GE, FR, IE, CH, SE, GB, BE, IT, NL, CA and the U.S. Jason Chin has been to date involved in some 26 patent applications, with patent protection being sought for in 13 countries plus EP (10 with 3 patents granted)/WO (16). These patents have been to date cited by other inventors 100 times.

The nominated patent family and the patents relating to it have been so far not cited by other patent applications. This is an indication that the patents describe a fundamental invention in a very specific field with not yet broad application. However, academic publications by Jason Chin referring to the inventions have been already cited by other patent applications.

TU Ilmenau was able to identify 190 patents, which at least in their description refer to orthogonal gene pairs, currently around 20 per year. The ranking is led by AMBRX (42 applications), followed by Scripps (38) and the MRC (15).

In the Web of Science, TU Ilmenau found 51 publications of Jason Chin at his time at Scripps and the MRC. These articles have been cited by some 1,112 other articles. 17 publications deal in particular with orthogonal gene pairs. These articles have been cited in 438 other publications.

4. Conclusions

All of the evidence collected points to a break-through invention in the field of synthetic biology which has great commercial promise.

Prof. Chin identified the following critical success factors for his work:

- The presence of a ground-breaking idea, one that is so different and innovative that it will change the scientific world and transform how people think about problems in science. In the absence of such an idea, the likely impact of research will be minimal and easily reproducible (because others would in any way also find the solutions).

- The presence of an environment that is supportive of people working on long-term challenging projects: *"The MRC Laboratory of Molecular Biology in Cambridge is such a place. It has been able to carry forward a tradition of asking big questions, as evidenced by the number of Nobel prize winners it has hosted, such a place also has competent people in charge who understand that there is good reason to believe that something will eventually work (as opposed to other institutions where you will hear many people argue why it will NOT work)"*
- The presence of colleagues *"…who are engaged and enthusiastic about what you are doing, a good team, where everybody is asking really important questions".*
- The presence of stable funding for vey basic research questions over a longer period of time (at least five years). Prof. Chin mentioned the importance of the MRC funds to this end, and also those of the European Research Council (ERC grants).
- The presence of a supportive community of scientists, such as the European Molecular Biology Organisation (EMBO): *"EMBO is a very supportive and forward looking organisation which has, for example, a very good young investigator programme".*

Prof. Chin also noted that the type of science he is conducting- Synthetic biology- is under-represented in the EU overall, when compared to the U.S.

According to Ranmali Nawaratne, the main success factors for effective technology transfer are to have a foundation of solid, cutting edge R & D; strong management to bring together scientific, legal and commercial expertise to develop a solid commercial plan; and the backing and financial resource to translate early-stage research into healthcare benefits.