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

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1. The invention

1.1 Historic account

There are as many 1.2 million cases of myocardial infarction (commonly known as heart attack) annually in the United States; the yearly incidence rate is in the order of 600 cases per 100,000 people. It was, however, not before the early 1990s that diagnostic tests became available, which could reliably detect myocardial infarcts, saving countless lives ever since. This achievement can be attributed to Prof. Hugo Katus. His long-year development of cardiac-specific troponin T immunoassays *"…meant that the textbooks on the diagnosis, risk stratification and treatment algorithms of acute coronary syndrome had to be rewritten."*[1]

Prof. Hugo Katus studied medicine between 1970 and 1976 at the University of Heidelberg, and hereinafter became assistant physician ('Assistenzarzt') at the University clinic. While practicing his profession, he was soon confronted with the unsatisfactory situation regarding the diagnosis of heart attacks:

> *"…at that time myocardial infarction was detected in clinical practice by analysing both time dependent changes on the ECG (electrocardiogram) and changes of blood levels of enzymes such as creatine kinase (CK), lactate dehydrogenase (LD) or their isoforms (CKMB). However, both the ECG recordings and blood enzyme measurements are of very poor diagnostic power for the detection of myocardial infarction…I was confronted with many chest pain patients who were not identified as having a heart attack and were not treated properly due to the poor discriminatory power of available diagnostic tools for myocardial infarction. Thus I was well aware of the urgent need for better tests."*
> (Prof. Katus)

There were two main problems with the then available test: First, the diagnostics were not able to recognise less extensive myocardial infarctions. This was a problem because the prognosis (1-year outcomes) for patients with small infarction was as poor as that for patients with larger infarctions. Secondly, the blood tests used back then recorded changes in enzyme levels in the blood that were not specifically attributable to a heart condition, but could originate also from other body parts (e.g., skeletal muscle damage due to physical activity).

Prof. Katus conducted experiments in between 1975 and 1978 in the area of muscle physiology. He found out that cardiac and skeletal muscles exhibited different contractile properties, which led him to believe that the structure of proteins involved in the contraction process must be different between heart and skeletal muscle. This was an indication that a protein exists, which is uniquely related to heart muscle activity and could be used, if detected in the blood, to make inferences on the current condition of the heart.

During that time there were considerable advances made to measure proteins in blood, and Nobel prices were awarded to the new developments in the field (Nobel price by Milstein and Köhler, Nobel price by berson and Yeallow). This set the background for Prof. Katus 2.5 year research fellowship at the lab of Prof. Edgar Haber at the Harvard Medical School in 1978. Prof. Haber´s research group worked primarily on the use of antibodies as diagnostic and therapeutic tools.

[1] Ozkan, J. (2010): Pioneer in Cardiology: Hugo A. Katus, MD, PhD, FESC, in: Circulation – European Perspectives in Cardiology, August 27, 2010.

Upon arriving, Prof. Katus had little knowledge in molecular biology or immunology – main disciplines at work in the lab -, but the learning curve was steep due to the inspiring environment, and Prof. Katus was able to obtain critical know-how for his further developments. The Harvard lab was at that time primarily experimenting with radioactively labelled antibodies: the antibodies were injected into the body, and were to accumulate at the sites the infarct would occur, allowing thus the imaging of the infarct. However, when it came to the actual application of this particular approach in a clinical set-up, Prof. Katus was quite sceptical:

> *"I realised that infarct imaging with labelled antibodies is too complex, time consuming, and expensive to be useful in clinical practice, and I decide to start on the development of highly specific immunoassays to measure…proteins…in blood as a diagnostic tool….this decision was derived from the hypothesis that the detection of cardiac-specific molecules in blood with highly specific immunoassays would markedly improve diagnostic precision compared with the standard enzyme assays."* (Prof. Katus, cited in Ozkan 2010).

While the idea was there and started to materialise, a considerable number of technical and non-technical barriers had to be overcome upon Prof. Katus return to Heidelberg in 1980.

On the technical side, the following steps had to be taken:

- First, there was the need to develop protocols for the extraction of myofibrillar[2] proteins from human hearts, and there was the need to obtain sufficiently high quantities of high quality purified troponin T.
- Second, there was the need to produce monoclonal[3] antibodies of high specificity and high sensitivity. For this it was necessary to create special cell lines from cells called hybridoma cells, which would secret these antibodies. Monoclonal antibodies constituted a critical component of the immunoassay envisaged.
- Third, the actual immunoassay had to be developed with the required performance characteristics in terms of sensitivity, specificity and precision. This was needed to test the validity of the hypothesis (and document the usefulness) of troponin T measurements for the detection of heart attacks.
- Forth, there was the big hurdle to take of the various stages of clinical trials.

The non-technological barriers were:

- The need to find a powerful industrial partner for robust assay development and clinical translation of the work: *"Only a strong industrial partner had the means in terms of logistics and market power for thorough test development, analytical characterisation, the execution of the demanding clinical trials or marketing…the leader of the R&D department at Böhringer Mannheim was acquainted with my then boss, we therefore met and presented our project, and the idea was eventually taken up….we had some funding for initial processes, access to*

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[2] *"A myofibril (also known as a muscle fibril) is a basic unit of a muscle. Muscles are composed of tubular cells called myocytes, also known as muscle fibers, and these cells in turn contain many chains of myofibrils. Myofibrils are composed of long proteins such as actin, myosin, and titin, and other proteins that hold them together"* (cited from WIKIPEDIA, http://en.wikipedia.org/wiki/Myofibril)

[3] "Monoclonal antibodies are antibodies, hence immunologically active proteins, which are produced as clones from a unique parent cell and which act bind to specific molecules. This binding can be measured with various techniques. For example, a specific monoclonal antibody for troponin T would bind to the troponin T, and by measuring this binding one would be able to determine the levels of troponin T present. Monoclonal antibodies are different from polyclonal antibodies that are produced by the human body in an immunological response against infiltrating antigens (e.g., organisms that enter the human body) and which can bind to many different molecules the antigen is composed of." (derived from Wikpedia, http://de.wikipedia.org/wiki/Monoklonaler_Antik%C3%B6rper).

competence of assay developers…we would not have succeeded alone in the lab." (Prof. Katus)

Roche Diagnostics, formerly Böhringer Mannheim, points to long-standing relationships with Prof. Katus. When Boehringer Mannheim was presented with the research, the firm – who was at that time also the leading supplier for a number of enzyme-based diagnostic assays in cardiology – determined that the new troponin T assay would not be a threat to existing product line-ups. Rather, it was an opportunity for a new innovation, which would be able to fill a gap in the available means to diagnose cardiac infarcts.

Klaus Hallermayer from Roche Diagnostics recounts:

> *„There was always a good, open and fair cooperation with Prof. Katus. Such good collaboration is a basic pre-condition for success. Furthermore, Prof. Katus did not only excel in terms of his outspoken scientific expertise. He was also keen and able to demonstrate that the scientific results were of particular relevance for practitioners, i.e. cardiologists, in the clinics. This is also a tremendously important factor for the take-up of the troponin T assay."*

- Once the difficult transition from a novel idea to clinical application was to a larger extent achieved, Prof. Katus attempted to publish the results, with (initially) no success: *"…the work was rejected due to concerns that it might confuse the community (then using still the enzymes as a diagnosis for myocardial infarction)"* (Prof. Katus, cited in Ozkan 2010). In our interview, Prof Katus further added that *"…the subject of better diagnostic tests was not a prime issue discussed at that time by cardiologists, and there was also little understanding of the new concept"*.
- Third, *"…the largest publication record on troponin T belonged to those who applied the test on large clinical samples, not those who invented the idea, developed the assay, and promoted the translation".* (Prof Katus, cited in Ozkan 2010). According to Prof. Katus, many publications did not mention him as author or cited him, but then again, *"…because I did not insist and fought to be cited or listed as co-author every time, this helped increase outreach and broader acceptance…*"
- Forth, *"…the general acceptance…was not only due to a better sensitivity or specificity for acute…diagnosis…but more by the demonstration that troponin-positive patients derive benefit from targeted and more aggressive treatment."* This means that the test results did not only tell the practitioners about the condition of a patient, it also provided guidance and indications on treatment options.

To give an idea about the timescale: It was not until 1983 that that cardiac troponin T could be distinguished from skeletal troponin T. The patent itself was filed in 1989, roughly a decade after the research started. It took another decade to change practice in medicine.

The journey might have been difficult, but it is not over, according to Prof. Katus. The sensitivity of the assays has been improved over time, and a high sensitivity troponin T assay was developed. It became apparent from the new assay that only slightly elevated troponin T levels could indicate micro damages resulting from non-infract conditions such as pulmonary embolisms, myocarditis, stress cardiomyopathy or chemotherapy. Even strain on the heart resulting from physical activity could be measured. Most importantly, it was found that increased troponin T levels in populations, which consisted of supposedly healthy individuals, were associated with a higher mortality rate. "With these new findings we are somewhat back in the position we have been with the original troponin T test….we can measure the troponin levels, can see the higher mortality rates, but we still have, for example, to assess the treatment options." (Prof. Katus). Prof. Katus is now medical director of the largest

cardiologic department in Europe at the University of Heidelberg. He has received various prizes, such as the Poster prize of the German Association of Cardiologists (1995), the innovation prize for German industry (1996) or the Franz Loogen prize from the Association of Cardiology, heart and circulatory research (1999). Prof. Katus is still pushing his research agenda, including improvements in the application and use of troponin T.

1.2 Technological features and major benefits

1.2.1 How it works

The technology in question is an immunoassay[4] for cardiac troponin-T. Troponin T is a muscular protein that is only found in the thin filaments of the hearts contractile apparatus. In the healthy heart, Troponin T regulates the contraction of the heart muscle (myocardium) by facilitating the interaction between the 'molecular motor' myosin and actin that carry energy into the muscle. In the event of a heart attack, areas of the heart are cut off from blood supply, and heart cells begin to die. In the process of cell death, called myocardial necrosis, troponin T dissociates from the contractile apparatus and is released into the blood stream. Circulating troponins are then measured by the immunoassay.

"Two types of tests for troponins…are available: a traditional quantitative test that provides an actual measurement of troponin, and a newer qualitative test that simply reports the result as positive or negative. The quantitative test takes 30-60 minutes, and helps distinguish between myocardial infarction and unstable angina. The qualitative test takes 15 minutes and is used in emergency rooms in which rapid patient care decisions can be made based on the presence or absence of troponins… troponin tests require less than 1 mL of blood. Collection of the sample takes only a few minutes…levels greater than 50 ng/l indicate a person has had a significant myocardial injury, such as an infarction, and is at an increased risk for future serious heart events. Levels between 50 ng/l and 14 ng/L indicate a grey zone in which troponins may also indicate other heart disorders, or chronic kidney failure."[5]

1.2.2 Benefits

While there may be as many 1.2 million heart attacks, for example, each year in the U.S., the diagnostic challenge is much bigger if one were to include also patients presenting with chest pain who do not rule in for a heart attack. In fact, only the amount of persons presenting with chest pain is 10 times the number of those presenting with an acute coronary syndrome. With the troponin T assay

- Troponin T assays could assess risk profiles for around 12 million subjects presenting with chest pain in the US per year.
- The detection rate of myocardial infarcts increased by 25% to 35%. This means that while older-enzyme based assays could detect 600,000 cases in the U.S. per year, the new test allow for the identification of 780,000 cases, an additional 180,000 cases in the U.S. alone.

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[4] An immunoassay is a specific type of biochemical test that measures the presence or concentration of a substance (referred to as the "analyte") in solutions that frequently contain a complex mixture of substances. Analytes in biological liquids such as serum…are frequently assayed (i.e., measured) using immunoassay methods. In essence, the method depends upon the fact that the analyte in question is known to undergo a unique immune reaction with a second substance, which is used to determine the presence and amount of the analyte. This type of reaction involves the binding of one type of molecule, the antigen, with a second type, the antibody. (taken from Wikipedia, 30 March 2012, http://en.wikipedia.org/wiki/Immunoassay)

[5] taken from http://medical-dictionary.thefreedictionary.com/troponins+test, and slightly modified by Prof. Katus

- If the newly identified cases are treated according to guidelines, mortality rates (30-day survival) decrease from 5.1% to 1.6%. These figures translate, conservatively, into 17,000 lives that can be saved per year in the U.S. alone.
- High-sensitivity troponin T levels allow for the identification of further cases. Even minute elevated levels of troponin T in blood of a patient with acute coronary syndrome indicate a high risk and mandate invasive procedure (by contrast, in coronary syndroms without elevated high sensitivity troponin no invasive procedure should be performed). Administrating proper treatment based on the analysis of high sensitivity troponin levels is estimated to be able to lead to around 34,800 lives saved in the US each year by proper care.

2. The market

The troponin (T/I) immunoassays have been declared the gold standard for the diagnosis of heart attacks (more specifically: myocardial infarcts) in treatment and diagnostic guidelines throughout the world, even if Troponin T levels should be always checked with other data. The work of Katus is generally considered key for the success and widespread use of troponin assays.

The troponin T immunoassay is part of the market of cardiac markers. This market was forecast to exceed US$ 1 billion globally by 2017, growing at a compound annual growth rate (CAGR) of 6% during 2010 and 2017, according to a report by GLOBAL DATA in 2010. Given its pioneering role it stands to reason to expect that Roche is the market leader with a 21% share in 2010. Other important players were Abbott Laboratories, Siemens, Alere and Beackman Coulter. These top players accounted for 66% of the market. The remaining market is quite fragmented, but there is an increased M&A activity visible, according to Global Data. Roche Diagnstics was and still is for some limited amount of time, due to its patent protection, the sole supplier of troponin T assays, while the other manufacturers produce troponin I assays.

An important segment of cardiac marking is point-of-care (POC) markets. The market for POC cardiac markers is the said to be the most dynamic POC segment, according to a white paper on in vitro diagnostics: *"In 2007, most cardiac-arker testing was done in acute-care settings on patients in the midst of a cardiac event. The POC market..was estimated at US$ 325 million in 2007 and will increase to US$ 650 million by 2012".* The paper which draws on 2008 data from Kalorma market research also states that as knowledge of cardiac diseases expands, new (types of) markers are going to be developed, hereby also expanding of what can be considered cardiac markers. However, as indicated above, troponin T/I assays are the gold standards and new refined versions of such assays – so-called high-sensitivity assays – *"...are even more analytically robust...they will reduce the limit of detection by another 10-to 100-fold".6*

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

3.1 Motives and benefits of patenting and employed IPR strategy

For Prof. Katus, the joint patent with Böhringer/Roche Diagnostics played a pivotal role for the success of the troponin T assay. Foremost, it enabled the collaboration between the Heidelberg University and Böhringer/Roche Diagnostics. Concerning the

[6] Paxton, A. (2010): Keeping in step with the perfecting of troponin, http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=cap_today%2F0110%2F0110b_perfecting_of_troponin.html&_state=maximized&_pageLabel=cntvwr

IPR strategy followed by Roche Diagnostics, the firm decides on a case-by-case level for each of its product which IP strategy to employ:

> „*With regard to troponin T, we opted for patent protection in order* to *have our R&D expenses covered and to achieve market leadership.* (Klaus Hallermayer, Roche Diagnostics)

Without the patent protection, it stands to reason to assume that Böhringer would not have invested its resources into the commercialisation of the assay. This assessment is in line with the generally high importance of patents one can observe in the bio-pharmaceutical industry. Patents in this industry are 'bargaining chips' and a clear measure for economic value.

In addition to the collaboration-enabling role, the patent also yielded licensing income from Roche to the Heidelberg University. But for Prof. Katus, there was also another even more important benefit:

> *"The patent is extremely important for me emotionally as an inventor, because a patent is the single proof that you have been the one who came up with the solution first, that you have been behind the idea. For me, this is more important than many of the prizes I received, or many of the publications"* (Prof. Katus)

The patent was hence a key instrument for the further acceptance of the troponin T by the cardiology community, in that its protective function and evidence of who invented the assay gave leeway to allow others to use the assay in their studies and assessments, even if they did not mention or collaborate with Prof. Katus on their studies.

However, in the mid-1990s, a glitch troubled the IPR and R&D strategy. Besides troponin T, there is also another form of cardiac-specific troponin, troponin I. And while the team around Prof. Katus was also working on this specific troponin, a UK researcher was faster and published his main results on the usage of troponin in an assay first. Because this researcher did not, however, patent his results a situation ensued where a number of manufacturers would produce tropononin I assays, while Roche Diagnostics would be the sole supplier of troponin T assays.

Roche Diagnostics assesses the impact of the troponin I publication as followws:

> *"The fact that the competing troponin I was later published by a UK researcher was of course not beneficial for achieving the maximum possible market share. But in any case the patent has secured and enabled our technology leadership, especially (but not only) in the beginning. While the troponin T and I assays are similar, the troponin T assay still enjoys benefits over the troponin I assays, in particular in patients with kidney-related conditions. The patent is also protecting the various improvements of the assay which have been implemented since then."* (Klaus Hallermayer, Roche Diagnostics)

While the patent reaches now the end of its lifetime, the expiry will not have too much of an economic impact for Roche. This is because the appearance of the troponin I assays has already pre-empted some of the economic developments which can be usually expected when patents expire.

3.2 Patent statistics and patenting trends

The nominated patent on the troponin T immunoassay was applied for in 1989 by Boehringer Mannheim (now Roche Diagnostics) in Germany. Further applications followed via the EPO (the EP patent was granted in 1995), the U.S. (granted in 201/2002), Japan (granted 1996/1998) and Hong Kong (granted 1998). The patent family was cited a total of 14 times (without self citations). The patent is now beyond the maximum running of a patent of 20 years and expired, except for the U.S. where an extension has applied for and where the patent is hence still in force. The nominated patent was the first to mention troponin T in the context of immune assays,

and made sure that only Roche Diagnostics delivered troponin T immunoassays to the market.

However, since Prof. Katus ground breaking invention there have been also other patents filed by different firms mentioning troponin T and immunoassays in either their titles, abstracts or claims. These patents relate, for example, to subcomponents of the test or to testing environments. For example, patent EP1481246 from the firm Abbot claims a *"…microfabricated sensor…wherein said biomolecule is an antibody capable of binding an analyte selected from the group consisting of human chorionic gonadotrophin, troponin I, troponin T, troponin C,…".* Since 1989, there have been a total of 214 such 'related' patents applied for. Roche Diagnostic leads the list of applicants in this field with 53 inventions, followed by Biosite Diagnostics (21) and Abott (20). Whereas Biosite has been actively patenting since the 1990s, Abbot has started filing patent applications only since 2003.

Searching for "troponin and Katus H*" in the WEB OF KNOWLEDGE /Thomson Reuters /Web of Science Citation Report reveals between 1987 and 2912 a total of 202 publications by the inventor with a significant number of 10,098 citations so far and an average citation rate of 439.04 per year. Interestingly, the original publication on the troponin T assay invention is being cited only 220 times although in the year 2011 for example 1,193 original publications are found under "cardiac troponin and diagnosis" in PubMed. The fact that troponin T immunoassays are still a hot topic is reflected by the finding that in 2011 there have been more than 1,200 publications on troponins for detection of heart diseases and the inventors group contributed 13 to this number. Even in 2012 the inventor has published 4 articles on troponins for diagnosis of heart diseases.

Overall, patent statistics and publication statistics underline the pivotal role of Prof. Katus´s inventions and offer clear indications that the inventions and the related research have had considerable impact.

4. Conclusions

The evidence collected points to a very valuable patent not only in commercial terms, but also in terms of societal benefits as well as its impact on the research field and on the field of medical practice. The invention is also a textbook example of effective science-industry collaboration, and an example where medical research measurably leads to the savings of lives. However, the process towards success was a tedious one.

The following factors were contributing to the success, according to Prof. Katus:

- The need to stick with an idea and get involved in detail with it over a long period of time: *"I would recommend to young researcher that they should not jump from one hot topic to the next, but rather stick to an idea they trust. You need to take the time, and success takes its time, it cannot be normally achieved within two to three years….even if there is a failure, the know-how gained will benefit career paths."*
- There is a need for a strategic partnership with industry.
- There is a need to have an academic community that is behind the idea. To achieve that, the publication path should be 'opened' in that the inventors should not try to force their names into each and every publication. Sharing of research results is thus a significant virtue.
- Having patent protection is essential to protect the basic know-how, but also to protect the inventor and his emotional state. This is something publications cannot achieve: *"It is decisive to have moved something and to have the patent documents that."*