The Rhineland Biopatent Gazette

brought to you by Michalski Huettermann & Partner Patent Attorneys - Issue 5/2015

Duesseldorf/Munich, **04 December 2015** The times they are a'changing – particularly in the Biopatent discipline. Biopatent professionals live in a quickly developing world, which is sometimes hard to keep pace with. Michalski • Huettermann & Partner Patent Attorneys have decided to produce relief to this situation, and are proud to present a new information service related to Patent issues in Biotechnology. This newsletter issues on an irregular basis in order to provide information with respect to actual events, as well as in-depth-analyses of long-term developments. Patent Attorneys from our firm explain the meaning of recent developments and decisions affecting the Biopatent community, and provide expert insight into what's going on behind the scenes. In this issue, we report about the CAFC's denial to rehear *en banc* the Sequenom case, plus a new Humira patent that claims an unusal indication.

CAFC will not rehear Sequenom

Still, EP counterpart of invalidated US patent used in UK litigation

In issue 2/2015 of the Rhineland Biopatent Gazette, we have reported about the decision *Ariosa Diagnostics v. Sequenom*, in which the CAFC applied the logic of the Supreme Court decisions *Mayo v. Prometheus* and *Ass' for Molecular Pathology v. Myriad* for the first time.

The CAFC confirmed the 1st instance invalidation of US Patent No 6258540 (the "'540 patent"), which relates to noninvasive prenatal testing (NIPT) of fetal characteristics, including aneuploidea, by analysis of blood samples taken from pregnant women. The patent claims were found to not be directed to patent eligible subject matter, and thus invalid under 35 USC § 101.Claim 1 of the patent was as follows:

1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.

As expected, Sequenom, which is based in San Diego, filed a petition for rehearing *en banc*, which the full CAFC denied last Wednesday, maintaining that the patent was invalid. Hence, Sequenom's infringement allegation against Ariosa continues to remain moot.

In their petition, Sequenom argued that that the court's decision was inconsistent with Supreme Court precedent in *Diamond v. Diehr*, *Mayo v. Prometheus* and *Ass' for Molecular Pathology v. Myriad*. Further, Sequenom argued that the decision was a threat to patent protection in multiple fields of invention.

Sequenom was backed by numerous third parties. By August 27, 2015 twelve Amicus Curiae Briefs had been filed in support of Sequenom's petition for rehearing *en banc*.

One of the Amicus Curiae Briefs was filed by the IPO (Intellectual Property Owner's Association). Therein, it is discussed, *inter alia*, that „Sequenom presented substantial evidence that its claims do not unduly preempt the use of cell-free fetal DNA found in pregnant women's

New Humira patent claims depression as 2nd indication

But depression is a also a side effect

Abbvie, maker of the world's best selling drug, the anti-TNFα antibody Humira®, has received acceptance for European patent EP1924287B1 on Jan 14, 2015.

The patent claims anti-TNFα antibodies, including Humira, for use in the treatment of depression, by subcutaneous administration, but not perispinal administration.

Secondary literature (Losleben and Himmerich, 2008) speculates about an activating effect of TNFα on the Hypothalamic–Pituitary–Adrenal axis (HPA), which might be causative for depression.

The patent itself discusses that hypersecretion of pro-inflammatory cytokines such as TNFα has been reported in depressed patients, suggesting that cytokine-mediated pathways could be involved in the etiopathogenesis of depression (Levine et al., 1999; Sluzewska et al., 1996; Tuglu et al. 2003).

Further, it is discussed that clinical studies (Penninx et al., 2003, Trzonkowski et al., 2004) also reported an association between high levels of inflammatory markers (TNFα) and depressed mood in aged patients, suggesting that depressed mood causes and/or is caused by systemic inflammation.

Patentee also discusses that increased serum TNFα concentrations have been associated with both major depression disorder and multiple sclerosis (Mikova et al., 2001), and that increased levels of cytokines in depressed patients can be normalized after chronic

+ from our firm +

Article on Immune Checkpoint Inhibitors published by mAbs

As already announced, MH partner Dr. Ulrich Storz has authored an article on IP issues of Immune Checkpoint Inhibitors**.**

Immune checkpoint inhibitors („ICI") are drugs that interfere with tumor escape responses. Some members of this class are already approved, and treated as future blockbusters already now.

Many companies have developed patent activities in this field. The article focuses on the patent landscape related to ICI, to make it a little bit less confusing. Please inquire here for a reprint of said article.

MH Partner speaks at World ADC Congress

MH Partner Ulrich Storz will give a lecture at the World ADC Congress Berlin, 8-10 February 2016. Ulrich will speak on day 2 of the congress about the Intellectual Property Perspective on the Requirements for Successful ADC Drug Development.

blood.“. The Brief went on in that „the claims at issue require separating, or fractionating, components of blood, (...) amplifying the cffDNA it contains, then identifying paternally inherited genes therein.“ The Brief also stated that „to demonstrate that its claims do not unduly preempt use of cffDNA and therefore recite patent-eligible subject matter, Sequenom showed that other groups have analyzed cffDNA without fractionating the pregnant women’s blood containing it.“

Not surprisingly, Ariosa, Sequenom's adversary, filed a response on said petition on October 19, 2015, in which they asserted, *inter alia*, that “there is no reason for this appeal to be reheard en banc and, moreover, no basis on which this Court should disturb the panel's conclusion”. Ariosa went on that the CAFC "faithfully applied Supreme Court precedent“, and concluded that Sequenom's petition should be denied.

So far, so good. What is surprising is that said IPO Brief was signed, *inter alia*, by Roche. Interestingly, Roche has acquired Ariosa on December 2, 2014 for more than 600 mn USD, to get access to their non-invasive prenatal tests (NIPT) technology, called „Harmony™“, which uses cffDNA from pregnant women. It thus appears that Ariosa, in their response on the petition, argued completely contrary to what their parent company, Roche, subscribed to in the IPO Amicus Curiae Brief.

Apparently, and the authors of the Rhineland Biopatent Gazette share this attitude, does Roche consider the threat arising from the Myriad decision to be so existential that they took the risk into account that their Brief might cause the CAFC to change its mind, affirming the validity of Sequenom’s and, eventually, confirming Sequenom’s infringement claim against Ariosa - which would have significantly devalued Roche’s investment. This, however, has not happened, obviously.

Earlier, Sequenom stated that the invalidity decision would have little impact on their business. On Dec. 3, 2014, Sequenom had signed an agreement with High Throughput Sequencing Pioneer Illumina, also of San Diego, according to which the two firms pooled their NIPT IP and license the technology out. Illumina has so far not commented on the potential impact of the decision on the patent pool agreement with Sequenom.

The CAFC decision does not directly affect the validity of corresponding patents in jurisdictions outside the United States. On March 16, 2015, Illumina and their subsidiary, Verinata Health, sued UK-based Premaitha Health, who offer an NIPT test in Europe, for infringement of two patents Sequenom has contributed to the pool, EP(UK)0994963B2 and EP(UK)1981995B1. The former is the European counterpart of the '540 patent that was revoked by the CAFC.

The European patent was maintained in amended form on May 10, 2012 after an opposition by Maryland-based NIPT company Ravgen Inc. Claim 1 of the amended version is similar to its US counterpart:

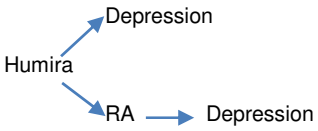
1. A detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample, wherein said nucleic acid is a paternally inherited sequence which is not possessed by said pregnant female.

The decision was not appealed, and can thus not be regarded as established granting practice. It however appears that the validity of the European counterpart of the '540 patent is quite strong after having survived the opposition. Still, UK courts have a reputation of not being particularly patentee-friendly, and have in the past antidepressant treatment with serotonin re-uptake inhibitors (SSRIs) (Tuglu et al., 2003).

As the patent admits, “classical” Humira indications like RA and Psoriasis may also cause depression.

In this case, Humira would only indirectly treat depression, which would be a mere secondary symptom of the disease that is the actual Humira target. This pathogenesis has for example been suggested by the DORADO study (Elgendi et al., 2015).

Is “treatment of depression” thus a true 2nd medical indication ? Or is it merely a symptom that coincides with true indications that can be causatively treated with Humira ?



In other words: Does this alleged new indication deserve patent protection under Art 54 (5) EPC ?

Interestingly, the Humira label says that up to 10% of the patients may experience depression as a side effect.

It is difficult to imagine a 2nd medical indication claim on the treatment of a symptom, which at the same time is a side effect caused by the same drug, at least as long as the patent claim is not restricted to a specific patent cohort which does not experience depressions as a side effect.

And, in case depression is just a secondary symptom of diseases like RA and Psoriasis, it appears that the claims would have to be restricted to a patient cohort where depression is caused by said primary diseases.

In October 2015, the patent has been opposed by two anonymous parties represented by strawmen.

So far, none of the two parties has argued on the inconsistency of claiming the treatment of depression with Humira® when depression is also a side effect of the treatment therewith.

Despite novelty attacks, the opponents also emphasize that the data provided in the patent which render a direct causative relationship between TNFα and depression are insufficient.

Find the congress website here.

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Archive

To obtain a neat overview of the quickly changing world of Biopatents, find prior issues of the Rhineland Biopatent Gazette here.

invalidated quite a few Biotech patents that had been granted by the European Patent Office (see issue 1/2014 of the Rhineland Biopatent Gazette).

On the other hand, according to a survey carried out by the present author, higher generation NIPT patents exist, both assigned to Sequenom/Illumina/ Verinata as well as to others like Ravgen or Ariosa, where the claims comprise more restrictions, thus making their validity appear even more robust.

In their 2014 fourth quarter and full-year performance report, Sequenom's CEO said that the decision would not significantly affect their business, while licensing fees and royalties from said pool for 2015 would provide between 6 and 14 mn USD of revenue, while the pool had 21 licensees, including Quest Diagnostics, the Mayo Clinic, as well as two Japanese companies, SRL and GeneTech.
I
t remains to be seen how strong the patent pool will be perceived by competitors, and if they will go on asking for licenses instead ignoring the patents therein, or challenging their validity.

Back to the Sequenom case, the CAFC decision comprised a concurring opinion by Judge Robert Linn, who wrote that he joined the court in invalidating the '540 patent only because he was bound by the „sweeping language" in the Supreme Court decision *Mayo v. Prometheus*. The consequence of that broad language, so Judge Linn, resulted in "excluding a meritorious invention from the patent protection it deserves and should have been entitled to retain".

Sequenom can, and probably will, appeal this decision to the Supreme Court. While the latter denies most petitions due to the sheer volume of cases, Judge Linn's concurring opinion may make it difficult for the Supreme Court to not institute such appeal. This will again open a new round for Amicus Curiae Briefs. Our firm will establish a respective initiative for European biotech companies to sign, backed by BIO's chief legal counsel, Hans Sauer.

So far, Humira has not yet been approved for the treatment of depression. If Abbvie goes for that, they would probably write the new indication into the label. Biosimilar manufacturers would have to carve out this indication from their labels, as provided under Art 11 of EU Directive 2001/83/EC.

But would health insurance funds cover the costs of depression therapy with Humira ?

And, can the patent be enforced, considering the recent case law in the UK (Warner Lambert v Actavis [2015] EWHC 72 (Pat)) and Germany (I-2 U 54/11 "Cistus Incanus", OLG Duesseldorf).

The above considering, the commercial value of the new patent remains slightly enigmatic.

Michalski · Huettermann & Partner are getting personal... Today: Harald Bienert

Dipl.-Ing. Harald Bienert was born 1972 in Moers/Germany and studied Electrical Engineering at Ruhr-Universität Bochum, where he obtained his diploma in 1999. In parallel he was working as student co-worker implementing control algorithms and performed qualification tests for mobile devices in an international testlab.

After graduating, he worked five years as development engineer for test solutions in the area of mobile communication technologies and participated in the development of test specifications. Subsequently he was working as SW-Architect in the development department of a big German manufacturer for mobile devices, where he focused on implementing different protocols for data transmission.

In 2007 Harald Bienert started his qualification in intellectual property rights. He is chartered German patent attorney since 2010. Also in 2010 he joined Michalski Hüttermann & Partner Patent Attorneys. Harald Bienert is registered in the list of representatives before the European Patent Office and admitted as European Trademark and Design Attorney.

Harald Bienert is native German speaker, and fluent in English and Spanish.

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