

Modelling Holobiont Evolution
for a Better Understanding of
Symbiosis, Dysbiosis, and
Human Health

"Where There's Muck,
There's Brass" - Money
in the Microbiome

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Choose 16S rRNA Gene
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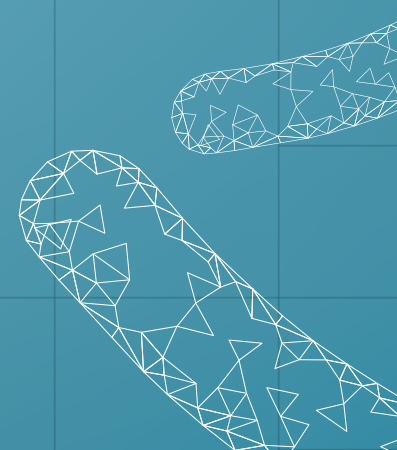
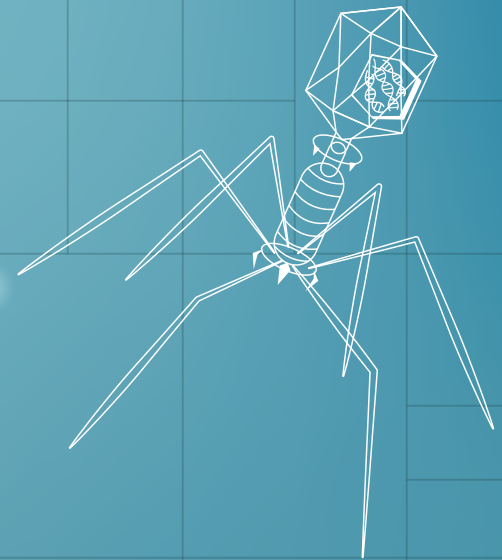
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THE VEDANTA OPPOSITION: A HEALTHY SIGN OF A MATURING INDUSTRY

ANALYSIS BY CRAIG THOMSON | PATENT PARTNER, HGF LIMITED &
RACHEL FETCHES | INTELLECTUAL PROPERTY LITIGATION PARTNER, HGF LIMITED
NEITHER CRAIG NOR RACHEL HAVE EVER PROVIDED LEGAL ADVICE TO VEDANTA BIOSCIENCES

As we move towards marketing approval for microbiome therapeutics, the “value” of the microbiome industry is increasing exponentially. This will inevitably result in disputes between the leading competitors seeking to protect their key intellectual property (IP) rights, including patent monopoly rights. Whilst some may regret the ramping up of competitive behaviours, this should be seen as part of the healthy development of an increasingly commercially relevant industry.

Despite the increasing commercial value of patents in this area, Patent offices are relatively inexperienced at examining patent applications relating to therapeutic microbiome compositions. A granted patent provides a 20-year monopoly and to be valid, the invention must be new, inventive and sufficiently disclosed. Some early patents granted in this field may prove to have broader claims than is justified by their technical contribution or disclosure. Legal challenges are likely to narrow or knock-out such patents but at present, it is difficult for third-parties to be certain about their freedom to operate position.

A subtler benefit of such challenges is the effect they have on the way patents are examined. For example, when one strain of bacteria is demonstrated to treat IBD, examiners may have to consider if it is acceptable to claim the use of any member of the genus of that strain for treating any form of autoimmune disease? Decisions issued by the courts and patent offices in response to challenges from third parties will guide such considerations of examiners, leading to more consistent examination. Indeed, it is vital for the industry’s progress that we see consistently good decisions being made so that the microbiome patent landscape develops in a fair and commercially relevant manner.

The most significant challenge to patent rights in the therapeutic microbiome field to-date is the recently issued decision in the “Vedanta Opposition”. The patent (European Patent No. 2575835) was granted to the University of Tokyo (UoT) in October 2016. It relates to work derived from the Honda lab and was exclusively licensed to Vedanta Biosciences, Inc. The CEO of Vedanta was quoted in October 2016 as saying

“This European patent is an important addition to our global intellectual property portfolio”, “The claims issued put Vedanta in a very favorable position to commercialize drugs based on bacterial consortia in the second largest market in the world.”

The principle claim was granted for:

“A composition for use in a method of treating or preventing a disease selected from infectious disease, autoimmune disease or allergic disease in an individual, the composition comprising, as an active ingredient, bacteria comprising spore-forming bacteria belonging to *Clostridium* clusters IV and XIVa in combination, which combination induces proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells in said individual.”

Within the 9-months after grant, the European Patent Office (EPO) received six Oppositions from Seres Therapeutics, Nestec and four anonymous parties. The Opposition hearing lasted three days and almost 130 documents were considered. Ultimately, the patent was maintained by the EPO’s Opposition Division (OD) but in an amended form, with a narrower claim scope; this decision has been appealed and it will likely be at least 2 years until the Appeal is heard.

The principal amended claim accepted by the OD is as follows (amendments shown as tracked changes).

“A composition for use in a method of treating or preventing a disease

selected from infectious disease autoimmune-disease or allergic disease in an individual by inducing proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells, the composition comprising, as an active ingredient, bacteria belonging to the genus *Clostridium* comprising spore-forming bacteria belonging to the genus *Clostridium* clusters IV and XIVa in combination, which combination induces proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells in said individual."



One of the most commercially interesting aspect of the proceedings was UoT's strategic decision to voluntarily remove "autoimmune disease" from the claims, leaving infectious disease and allergic disease. This means that UoT forfeited its granted protection for the treatment of autoimmune disease in Europe but also avoided public analysis of the patentability of that aspect of the claimed invention. One possible motivation could be the publication of a Poster Presentation that disclosed the colitis model data present in the patent. This may affect the novelty and inventiveness of claims for the treatment of autoimmune disease using the claimed bacteria. UoT have since filed two divisional patent applications, which are not published as yet. We expect, however, that one of these new filings claims the treatment of autoimmune disease, kicking the analysis of patentability of that aspect of the claimed invention into the long grass.

The definition of the bacteria in the claims was fiercely argued during the OP. UoT argued that the application from which the patent was derived merely refers to the genus *Clostridium* as an umbrella term that could mean any bacterium in the entire phylogenetically and taxonomically diverse group of bacterial strains within in the recited "clusters". The OD

was not convinced. Whilst they accepted that the term "genus" was ambiguous, they concluded that the application as filed must have been restricted to only bacteria belonging to the genus *Clostridium*. This forced UoT to amend the claims such that any non-*Clostridium* bacteria that are members of the recited clusters are unlikely to fall within the claims.

The OD then considered if there was sufficient evidence that the bacteria of the claims were capable of inducing the claimed T-cell response and thereby treating infectious and allergic diseases. The OD held that there was sufficient evidence. The data in the patent demonstrated that 46 strains of bacteria of the genus *Clostridium* were able to induce a strong Foxp3+-T-cell response in the colonic lamina of mice. Forty-one of the 46 strains were found to belong to one of the recited clusters and based on this, the OD concluded there was no reason to doubt that the bacteria of the claimed clusters were responsible for the observed T-cell response.

The patent contained data of both systemic and local effects in an allergic model following treatment with the claimed compositions. Consequently, the OD acknowledged that there was sufficient evidence to support the claim for the treatment of allergic disease. No evidence demonstrating effects on an infectious disease model were provided. It may be counter-intuitive that induction of a T-cell response would be useful for treating infectious disease. However, reference was made to a review suggesting that Treg induction can play a role in minimising deleterious effects of an immune response to infection. Consequently, induction of Tregs

can perform a role in broadly treating the effects of infectious disease. UoT were able to establish the T-cell response created by the claimed bacteria and on that basis the OD held that there were sufficient data to underpin a claim to the treatment of infectious disease.

The last element of the claim raises one of the wider difficulties for prospective patentees in the microbiome field. This is the fact that existing Fecal microbiota transplant (FMT) therapies inherently disclose the claimed bacteria of the recited clusters and so could have provided the claimed therapeutic effect, even if this had not been appreciated at the time. Valid inventions in the microbiome arena will be based on the recognition that the use of bacteria of the claimed clusters has a new therapeutic effect. The claims are therefore purpose-limited – that newly appreciated purpose must be part of the claims. In this case, the microbial composition is used to treat infectious and allergic diseases **“by inducing proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells in said individual”**.

Why this limitation matters is because of the potential difficulties of enforcing second use claims of this type in the national courts. While granted centrally, a European patent is effectively a bundle of national rights. Third parties who want to “clear the way” can both centrally oppose as well as bring validity challenges in the national courts. Patentees, however, must enforce their patent against potential infringers (direct or indirect) in the relevant national court(s). For second use claims, there is a tension between the principle that people must be free to use known or “old” methods or products against the desire to incentivise patentees to invent new uses for known compositions in return for a monopoly right. Certainty as to liability for infringement for third parties is also important. However, for direct infringement, the legal test of what the relevant intention is to infringe a second use claim is not well defined. Where such claims have been considered, the national courts have differed in their approach. What is the position of a provider of FMT if their patient has an allergic disorder, would they infringe the claims as amended by the OD? Even if they were not found to directly infringe, might they be infringing indirectly by providing “the means essential”, i.e., the transplanted matter. As the value of the microbiome field increases, all of this will need to be litigated in the national Courts.

Where does the OD’s decision leave Vedanta commercially? UoT have appealed the decision, which has a suspensive effect. Three of the opponents have also appealed the decision. The patent family’s commercial value pivots on the relative importance of autoimmune treatments (not now covered in the patent) to infectious or allergic treatment (currently covered in the patent). It will be interesting to see how UoT proceed with seeking protection for compositions for treating autoimmune diseases in the newly filed divisional applications. The claims of the granted patent may be upheld as granted, as amended or restricted further during the Appeal proceedings. The Boards of Appeal are more rigorous than the OD, so UoT can expect a rough ride. Although the parties’ grounds for appeal have not been filed yet, it is clear that the patent may be vulnerable. The evidence of therapeutic benefit in relation to infectious disease seems to be the most difficult for UoT to substantiate. Does the patent disclose sufficient data to select those infectious diseases that

would have a net benefit from Treg induction via administration of the recited bacteria? A restriction of this disease to treating excessive inflammation caused by the immune responses to infection may be more acceptable. The amended claims are focused on the invention having clinical effect specifically via the induction of Foxp3-positive regulatory T cells, and through the use of bacteria of the genus *Clostridium* in the recited clusters. If the Opponents can show evidence that the therapeutic benefit demonstrated in the patent is not from selecting those specific bacteria, and/or that it is not the recited T-cell induction that provides the benefit, the patent would be vulnerable.

Monitoring further developments as this case moves through the EPO’s Appeal procedures and any national court litigation, is likely to reveal more insight into what the future holds for patent protection in the therapeutic Microbiome field.