FIRST THERAPY USING CRISPR/CAS9 'MOLECULAR SCISSOR' APPROVED: PATENT STORM IN SIGHT?

This past month, Vertex Pharmaceuticals received approval from the UK Medicines & Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA) to market the first therapy using CRISPR/Cas9 technology, the so-called 'molecular scissor', which can very selectively and effectively cut DNA in order to inhibit the expression of a gene (knock out), decrease its expression levels (knock down) or insert a gene so that it is then expressed (knock in).

As is well known, the discovery in 2012 of the CRISPR/Cas9 mechanism and its enormous potential in the field of biotechnology earned Jennifer Doudna and Emmanuelle Charpentier the Nobel Prize in Chemistry in 2020.

The therapy created by Vertex, branded Casgevy, makes it possible to effectively treat patients suffering from sickle cell anaemia, a serious genetic and hereditary (autosomal recessive) disorder that results in a painful deformation of red blood cells caused by a mutation in the gene controlling the production of haemoglobin. Specifically, in the gene coding for the haemoglobin β-chain, an adenine is replaced by a thymine (A→T transversion), which leads to the replacement of the amino acid glutamic acid (encoded by the GAG triplet) with the amino acid valine (encoded by the GTG triplet) at position 6 of the protein. Since glutamic acid and valine have different chemical-physical characteristics (the former is hydrophilic, while the latter is hydrophobic), the mutated haemoglobin is less soluble, so that it precipitates, forming fibrils in the red blood cells and causing the latter to take on the characteristic sickle shape (hence the name of the disease).

The particularity of the therapy developed by Vertex lies in the fact that it does not intervene in the gene coding for the mutated β-chain of haemoglobin, but very significantly reduces the expression of a gene (called *BCL11A*) that silences the production of foetal haemoglobin. The latter type of haemoglobin is only produced during intrauterine life and is able to protect children with the E6V mutation for a few months after birth, until it is replaced by the 'adult' version. As early as the middle of the last century, it was hypothesised that the reactivation of foetal haemoglobin production, even in adults, would prevent the formation of sickle red blood cells, and indeed, studies and research lasting more than 60 years have proved this hypothesis correct, the clinical application of which has now finally been achieved.

Until now, no truly effective treatment for sickle cell anaemia has been available, which is why Casgevy gives hope to the thousands of people suffering from this very painful disease that can lead to a significant reduction in life expectancy.

Curiously, although it was Vertex that developed the first treatment using the CRISPR/Cas9 technology, in the US the patents protecting it are owned by the Broad Institute at MIT and Harvard and licensed by them to Editas Medicine (a

pharmaceutical company that also has its own sickle-cell anaemia treatment in the pipeline).

The history of CRISPR/Cas9 patents is very complicated, having been to date the subject of countless disputes and litigations on both sides of the Atlantic Ocean.

To summarise, Feng Zhang, a researcher at the Broad Institute, claimed paternity of the CRISPR discovery and thus of having achieved this result before Jennifer Doudna (at the University of California, Berkeley) and Emmanuelle Charpentier (now at the Max Planck Institute, Germany). Although the Nobel Prize has been awarded to Doudna and Charpentier, the US courts have (at least so far) upheld Zhang's claim and have therefore (for the time being) essentially attributed ownership of the patents to the Broad Institute. This ruling is not yet completely final because some of the various appeals against it are still pending.

On the European side, the situation is less clear, and the various fronts involved, including the Broad Institute, on the one hand, and the University of California, Berkeley, on the other, are still fighting it out, so nothing is settled yet. And it is on the basis of the patent rights held by Emmanuelle Charpentier and the University of California, Berkeley in Europe that Vertex, through a partnership with CRISPR Therapeutics (of which Charpentier is a partner), has been able to develop Casgevy.

Whether Editas and the Broad Institute will take action to protect their exclusive patent rights following Vertex's start of commercialisation of Casgevy in the US is certainly possible, but difficult to predict at present. Through these actions, Editas and the Broad Institute would seek to monetise – finally, 11 years after its discovery – the first real practical and commercial application of the CRISPR/Cas9 technology. And this would make perfect sense, considering that, according to some initial estimates, this therapy could have – at least in theory – a market of around 60 billion dollars.

On the other hand, actions of this kind could have negative reputational repercussions for the Broad Institute (which is a non-profit organisation): it could be deemed insensitive to the needs of the many people with sickle cell anaemia and, therefore, be accused of behaving in such a way as to hinder the usability of the therapy developed by Vertex.

However, the parties involved could also reach an agreement whereby Vertex would pay a royalty to Editas for the marketing of the Casgevy therapy. Should they even agree on a rather small royalty (e.g. 5% of revenues), this could still amount to very substantial sums (e.g. USD 3 billion).

All that remains for us to do, therefore, is to wait for Editas' moves and Vertex's possible countermoves, as well as further developments in what has now become the CRISPR/Cas9 patent saga.

The approval of the first therapy using the CRISPR/Cas9 technology, and the events briefly summarised above, bring to the surface the thorny issue of the reasonableness and ethical acceptability of patent exclusivity in the pharmaceutical sector, especially for those patent exclusivities involving disruptive and particularly innovative technologies capable of having a very significant impact on the ability to cure serious and disabling diseases and, therefore, ultimately on people's health and lives.

In this regard, back in 2006, the Council of the Organisation for Economic Co-operation and Development (OECD) issued Recommendations calling for the adoption of a broad, non-discriminatory licensing system (similar to FRAND licences) for biotechnological inventions and key genetic technologies (to which CRISPR/Cas9 certainly belongs). This arrangement has so far not been implemented

by any government, but the sector is constantly evolving and, therefore, the situation could also change quickly.

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