Innovation: Clonal neoantigen specific tumour-infiltrating lymphocytes for cancer treatment

The issue

In 2017, Achilles Therapeutics approached the MHRA to discuss quality, non-clinical, clinical and regulatory aspects of ATL001, an advanced therapy medicinal product consisting of autologous clonal neoantigen reactive T cells derived from patients' tumour-infiltrating lymphocytes. The proposed initial indication was for the treatment of non-small cell lung cancer.

By sequencing a patient's own tumour, comparing it to the germline DNA of the patient and applying bioinformatics algorithms, it is possible to identify tumour-specific mutations. Additionally, independently, human leukocyte antigen-typing of the germline blood sample is performed. All of this information is then integrated to predict which of the mutations will be the most likely candidates.

The corresponding neoantigen peptides are manufactured and cultured with antigen presenting cells, which can process them for presentation to T cells. Using these clonal neoantigen peptides (to specifically expand clones of tumour-infiltrating lymphocytes) enhances the number of tumour-infiltrating lymphocytes able to recognise such neoantigens and to target the cells that express them. This is effectively an anti-cancer treatment that is specific to the individual patient and should specifically target all cancer cells as the clonal neoantigens are contained within each and every cancer cell.

How the MHRA helped

Advanced therapies, such as ATL001, are complex products and their development has for many years been hampered by myriad scientific, technical and manufacturing challenges. The MHRA's scientific assessors advised that this type of therapy, i.e. not only personalised but also autologous and does not involve any gene modification, needed new thinking, especially regarding the non-clinical support.

The MHRA also gave advice on the manufacturing of the product and clinical advice on the protocol design. Advice on the protocol allowed for endorsement of aspects such as eligibility criteria, safety monitoring and engagement of a Data Safety Monitoring Committee. This also assisted the MHRA to conduct a timely review at the time of submission of the application.

'The MHRA demonstrated an excellent understanding of the challenges that would be faced when bringing a novel therapeutic combining attributes of autologous cell therapy with highly personalised and exquisite antigen targeting to patients' said Sean Russell, Director of Regulatory Affairs at

Achilles Therapeutics. ‘Early engagement with MHRA through scientific advice enabled us to prospectively agree the frameworks of not only the non-clinical package, but also areas of manufacturing and the clinical trial design that would ultimately be part of a clinical trial application. We were able to align with the assessors on the areas that were going to be most critical when it came to the review of the application and hence focus our efforts accordingly.’

Outcomes

Through close collaboration with the MHRA, Achilles Therapeutics has managed to take its investigational clonal neoantigen-based therapy from a concept into the clinic in less than three years obtaining MHRA approval in January 2019 to begin first-in-human trials in both lung cancer and melanoma.

The MHRA’s Licensing Director, Dr Siu Ping Lam, said:

‘The MHRA’s Clinical Trials Unit has a strong reputation for providing high calibre scientific advice, particularly to support First Time in Human clinical trials. This example is a demonstration of our pragmatic, scientific approach and flexible regulatory application, in support of innovation via early engagement and early clinical trial approval. It is further evidence of the MHRA’s standing as a world-leading innovative regulator.’

How we can help you

Contact the Innovation Office to find out more about accessing expert knowledge, guidance and experience that could help you develop ideas and save time and money. Use the hashtag #HealthInnovation to find out more.

Information on Citizens’ Rights

To receive the Ambassador’s newsletter with updates and details of future meetings, email us at uknationals.initaly@fco.gov.uk.

Information on your rights under the Withdrawal Agreement can be found in the attached handout on citizens’ rights (PDF, 244KB, 2 pages).

More information on our upcoming British citizens outreach meetings can be found here.

Intellectual property and the transition period

The UK and EU have ratified the Withdrawal Agreement. This allows the UK to depart the EU on 31 January 2020 and for the transition period (1 February 2020 to 31 December 2020) to begin.

During this time, EU law will continue to operate as it does now in the UK. The Intellectual Property (IP) system will continue as it is until 31 December 2020.

There will be no disruption to IPO services or changes to the UK IP system during this transition period. The IPO will convert almost 1.4 million EU trade marks and 700,000 EU designs to comparable UK rights at the end of the transition period. These will come into effect on 1 January 2021.

The arrangements in the IP section of the Withdrawal Agreement take effect at the end of the transition period. These arrangements provide legal certainty and protect the interests of rightsholders and users of the IP framework.

The Withdrawal Agreement ensures continued protection of existing EU-level IP rights in the UK after the end of the transition period.

This will ensure existing UK IP rights can be managed appropriately in line with existing domestic arrangements.

EU trade marks

The UK will remain part of the EU trade mark system throughout the transition period that ends on 31 December 2020. EU Trade Marks (EUTM) will continue to extend to the UK during this time.

We will not create comparable UK trade mark rights on 31 January 2020. These rights will be created at the end of the transition period under the terms of the Withdrawal Agreement.

Businesses, organisations or individuals that have applications for an EUTM which are ongoing at the end of the transition period will have a period of nine months from the end of the transition period to apply in the UK for the same protections.

EU trademark protection and comparable UK trademarks

The UK will remain part of the EU registered community design system throughout the transition period. Registered community designs (RCD) will continue to extend to the UK during this time. We will not create comparable UK designs on 31 January 2020. These rights will be created at the end of the transition period under the terms of the Withdrawal Agreement.

Businesses, organisations or individuals that have applications for an RCD

which are ongoing at the end of the transition period will have a period of nine months from the end of the transition period to apply in the UK for the same protections.

Changes to EU and international designs and trade mark protection after the transition period

Unregistered designs

The UK will remain part of the EU unregistered community design system throughout the transition period. This means that two- and three-dimensional designs (including, for example, clothing designs and patterns) disclosed in the UK or an EU Member State can be automatically protected in both territories as unregistered Community designs. This right provides three years of protection from copying.

In accordance with the Withdrawal Agreement, unregistered community designs arising before the end of the transition period will continue to be protected in the UK for the remainder of their three-year term.

Designs disclosed in the UK after the end of the transition period may be protected in the UK through the supplementary unregistered design, which will protect two- and three-dimensional designs for three years.

Changes to unregistered designs after the transition period

International registrations designating the European Union

During the transition period, international registrations for trade marks and designs protected via the Madrid and Hague systems which designate the European Union will continue to extend to the UK.

In accordance with the terms of the Withdrawal Agreement, international registrations for trade marks and designs that have been protected before the end of the transition period will continue to be protected in the UK after 31 December 2020. We are continuing to work with the World Intellectual Property Organization (WIPO) on the mechanism to ensure continued protection.

Changes to international trade mark registration after the transition period

Rights of representation

During the transition period, UK legal representatives will continue to have the right to represent clients before the EU Intellectual Property Office (EUIPO).

The Withdrawal Agreement (WA) ensures that UK legal representatives can continue to represent their clients before the EUIPO in cases that are ongoing at the end of the transition period.

The WA also states that the UK will not amend address for service rules for the comparable UK rights for a period of three years after the end of the transition period.

Patents

You can apply for a European patent through us or direct to the European Patent Office (EPO) to protect your patent in more than 30 countries in Europe, using the (non-EU) European Patent Convention (EPC).

As the EPO is not an EU agency, leaving the EU does not affect the current European patent system. Existing European patents covering the UK are also unaffected.

European patent attorneys based in the UK continue to be able to represent applicants before the EPO; see the news story on the EPO website.

Supplementary Protection Certificates

During the transition period, businesses can continue to apply for and be granted SPCs for patented pharmaceutical and plant protection products using the current system.

The current SPC legal framework in the UK is maintained during the transition period, and existing UK SPCs granted under that system continue to be valid.

SPCs are not granted as EU-wide rights, but rather as national rights. It was therefore not necessary for the UK and the EU to agree the creation of a comparable right to ensure continued protection of existing SPCs in the UK at the end of the transition period.

Instead, the Withdrawal Agreement ensures that SPC applications which are pending at the end of the transition period will be examined under the current framework. Any SPC which is granted based on those applications will provide the same protection as existing SPCs.

Changes to SPC and patent law after the transition period

Exhaustion of rights

Currently, exhaustion of IP rights occurs in the UK when an IP-protected good is placed on the market anywhere in the EEA, by or with the right holder’s permission.

This means that rights holders (such as the owner of a brand) may not prevent the movement of those goods within the EEA. These goods are known as parallel goods, which are genuine goods (that is, they are not counterfeit).

In the Withdrawal Agreement, the EU and UK have agreed that IP rights exhausted in the EU and the UK before the end of the transition period shall remain exhausted in both areas.

The agreement ensures legal certainty and continuity during the transition period and provides continuity in the immediate term for businesses and consumers.

Exhaustion of IP rights and parallel trade after the transition period

Copyright

Continued reciprocal protection for copyright works between the UK and the EU is assured by the international treaties on copyright. This is independent of our relationship with the EU so is not addressed in the Withdrawal Agreement.

Current cross-border copyright arrangements which are unique to EU member states (such as cross-border portability of online content services and reciprocal protection for databases) will continue to apply to the UK until the end of the transition period.

The status of these cross-border arrangements after the end of the transition period will depend on the future relationship between the UK and EU.

The Withdrawal Agreement ensures any database rights that exist in the EU and UK at the end of the transition period will continue to be recognised in both territories for the remainder of their term.

Changes to copyright law after the transition period

Businessman fined for operating illegal waste site

A businessman with about 25 years' experience in the waste industry has been fined £4,500 for operating a waste recycling site in Telford without an environmental permit.

On Monday, Telford Magistrates Court also ordered Brian Anthony Woods, 64, of St George's, Telford, who operated the site at The Old Granville, Granville Road, Donnington Wood, Telford, to pay £7,101.65 prosecution costs and £120 surcharge.

A Regulation 44 Order was made under the Environmental Permitting (England and Wales) Regulations 2016 to clear the waste on the site before 26 July 2020 and not to bring any additional waste on site. It was estimated that since the last hearing in August 2019, when sentence was deferred for Woods to clear the waste on site, around 500 cubic meters of waste had been removed and around 6000 cubic meters of waste was still on site.

Woods, who had pleaded guilty at an earlier hearing to 2 charges relating to operating a regulated facility, involving the storage of waste not authorised by an environmental permit, had stored around 6,500 cubic metres of waste. The court heard that he had previous convictions in 2011 for environmental offences committed during 2009 and 2010, but had continued to flout the law.

Woods was a director of Granex Recycling Ltd, which was dissolved in April

2017 but prior to that recovered waste plastics, processed these and produced plastic pellets for re-use in the plastics industry.

Environment Agency Officers inspected the site in December 2016 following information that unauthorised waste activity was taking place. During their inspection officers found a building containing plant equipment and plastics in various stages of processing, as well as scrap plastic items stored in large haphazard stockpiles of up to 3 to 4 metres in height. They also found a large compound, filled with used plastic window frame pieces, which limited access onto the site.

Exemptions from the requirement to hold a permit for the waste handling activities taking place at the site had been registered but the inspection revealed the activities were not being carried out to the environmental standards required.

In January 2017, the Environment Agency told Woods to stop waste management activities. Later that month he put forward a remediation plan. However, a follow up inspection showed there was still a significant amount of waste, with little reduction in the amount of waste or improvement in how it was stored. A notice was served under Section 59(1) of the Environmental Protection Act 1990, requiring the company to remove specified waste by June 2017. When officers visited again in June, they found no change in waste quantity or how it was stored.

In August 2017, Environment Agency officers returned to the site but found it locked. Large amounts of plastic waste and wooden pallets could still be seen. A visit in March 2019 revealed 80% of the waste seen in 2016 remained on site.

After the hearing, Environment Agency officer Steve Cawthorne said:

> The illegal and uncontrolled storage of waste, which could have led to a fire, gave considerable cause for concern. In addition, the lack of sealed drainage on site meant fire water runoff could have entered the watercourse and harmed human health had there been a fire. So we are pleased with the penalties imposed by court.
>
> Waste crime is a serious offence with tough penalties as it can damage the environment and undermine those who operate legally. Storing such large amounts of waste also poses a serious risk to the environment and human health. This case sends out a clear message that we will not hesitate to take action to ensure the protection of the environment and avoid harm to health.

Government decision on Northern Rail

Transport Secretary Grant Shapps has announced that, from 1 March 2020, the government will take over running services on the Northern network.

The government recognises that the rail network in the north has fallen far short of delivering the service passengers need and deserve.

This comes after the Transport Secretary announced on January 9 that the Northern franchise was no longer financially sustainable and would only be able to continue for a small number of months.

Transport Secretary Grant Shapps said:

> This is a new beginning for Northern, but it is only a beginning.
>
> Northern's network is huge and complex and some of the things which are wrong are not going to be quick or easy to put right. But I am determined that Northern passengers see real and tangible improvements across the network as soon as possible.
>
> The railways were invented in the north. Last year the Prime Minister promised that we would give the railway back to the places it was born, giving more power over services, fares, and stations to local leaders.
>
> Today (29 January 2020) marks the first small step towards the north taking back control of its railways and its people taking back control of their travelling lives.
>
> There will be no more leaving behind. This government is committed to levelling-up.

The government is committed to delivering real and tangible improvements across the network as quickly as possible, and will introduce a series of measures including;

- introduce a number of electric trains from elsewhere on the network, boosting capacity for commuters into Manchester and Leeds
- lengthening platforms at 30 stations by the spring, in addition to the 30 already completed, to allow longer trains to run
- all existing trains will be deep-cleaned and the approach to cleaning reviewed to ensure passengers experience the service they deserve from the first train to the last
- we will build on the recent agreement with ASLEF and improve the reliability of Sunday services

The government also recognises the scale of the challenge ahead. The Northern network is huge and complex – serving over 108 million passenger journeys a

year on 2800 daily services, calling at 528 stations.

To ensure a new vision for the railway is put in place the Transport Secretary has asked Robin Gisby and Richard George, who lead the public-sector operator, to prepare a plan in their first 100 days.

This will be a top to bottom review of everything from operational management, to rostering patterns and, most critically, customer experience, to make sure we leave no stone unturned in improving this franchise for passengers.

It will also include setting up a cross-industry task force to deliver recommendations for improving capacity and performance.

Many of Northern's problems are infrastructure-related. The Transport Secretary has instructed the leadership of the public-sector operator to sit down with Network Rail and build a comprehensive new masterplan to review congestion around Manchester.

Continuing to assess the Castlefield Corridor, as well as key junctions and interactions across the wider network to develop a series of interventions which will actually deliver the improvements required. Further interventions around Leeds will also be considered.

The government is also reiterating that today's decision in no way reflects on the staff of Northern. They are dedicated, hard-working and committed to their customers. The government wants to provide reassurance that this decision will not affect jobs or introduce changes to fares or tickets for passengers.

The Prime Minister has been clear that this government is committed to providing the north with a greater say in the running of its railway, with local leaders having more power over local services, timetables, fares and stations.

Today's decision represents a step towards that and delivering a railway focused on the needs of its passengers.

Northern Trains Limited