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.