ARDAT

Working towards safe and effective Advanced Therapy Medicinal Products

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Accelerating Research & Development for Advanced Therapies

What is gene therapy and what is its potential?

Advanced Therapy Medicinal Products (ATMPs) are medicines that are based on genes, tissues or cells. One class of ATMPs are gene therapies, which work by introducing a "recombinant" gene or other nucleic acid (e.g., DNA or RNA) sequence into the body in order to treat, diagnose or prevent a disease.

Gene therapy has the potential to treat a wide range of diseases by restoring the normal function of affected tissues and cells, for example, by correcting or replacing a faulty disease-causing gene.

Rare diseases, of which there are at least 6,000 described, are usually serious, chronic and, in many cases, lifethreatening conditions, which can affect people of all ages. In the European Union, it is estimated that there are approximately 30 million people affected by a rare disease.

Approximately 80% of rare diseases are caused by a change in the DNA of single gene (mutation), which results in the loss or impairment of the function of the protein encoded by that gene. Gene therapy, by delivering an appropriate therapeutic gene / nucleic acid sequence to correct or replace the faulty diseasecausing gene, can treat such diseases by restoring normal function in affected tissues or cells. By targeting the cause of the disease, gene therapy may potentially enable disease management without the need for additional treatments.

To deliver the therapeutic gene/nucleic acid sequence into the cells where it is needed, a delivery system ("vector") is required. As viruses have evolved over millions of years to deliver genetic material into cells, many delivery systems are based on modified versions of these viruses. For gene therapy, vectors based on adenoassociated viruses (AAVs) are often used. These "recombinant" AAV vectors (rAAVs) do not contain any infectious viral genes and consist of a protein shell ("capsid") which contains the therapeutic gene/nucleic acid sequence. Of a total of 13 ATMPs that have received authorisation for use in the European Union, there are already two AAV-based gene therapies approved as treatments for inherited rare diseases.

Who are we?

The ARDAT consortium – "Accelerating Research and Development for Advanced Therapies" is a collaboration between academic institutions (Universities and Research Centres), small and medium-sized businesses, and European Federation of Pharmaceutical Industries and Association (EFPIA) members, which is due to run until November 2025 and is funded by the Innovative Medicines Initiative (IMI).

Why is ARDAT necessary?

The field of gene therapy is in an unprecedented moment of expansion and technological innovation, which is reflected by the number of ongoing and completed clinical trials in Europe and beyond. For AAV-based therapies alone, there are at least 30 ongoing clinical trials in the Europe and over 260 ongoing and completed trials worldwide. Despite this, a number of challenges

need to be overcome before we can ensure that as many patients as possible have the opportunity to receive safe, effective and high-quality treatments through clinical trials and authorisation of new medicines, as soon as possible.

What are the challenges we face?

At the moment, some patients are excluded from treatment if they have been previously exposed to the viral vector (e.g., preexisting immunity due to a previous exposure to the vector) as they may produce antibodies that result in the destruction ("neutralisation") of the therapy before it can reach its target cells. This also means that patients can potentially only receive one dose of the therapy.

Sometimes, after treatment with a gene therapy, the patient can initiate an immune response to either the viral vector itself or the product of the recombinant gene (i.e., a therapeutic protein). In some cases, this can cause undesirable adverse effects and/or result in loss of the therapeutic effect. At the moment, it is not easy to predict when such effects will happen.

There is currently some uncertainty about how long the effect of the treatment will last or "persist" due to immune responses in the patients, and possibly other factors.

Gene therapies, and other ATMPs, are highly complex to develop and manufacture. This can result in high treatment costs which, in some cases, can limit the access of patients to treatment.

To meet the challenges described above, the ARDAT consortium intends to:

Develop models and standardised methods to allow better prediction and understanding of whether a particular therapy is likely to produce immune responses in patients, which may cause adverse effects, stop the treatment from working, or cause a loss of longterm treatment effectiveness – this will allow a more informed decision to be made on whether the benefits of a therapy outweigh the associated risks, for each individual patient.

Investigate approaches to permit patients with preexisting immunity to a particular therapy to receive treatment, such as the design of novel [AAVbased?] vectors which are less likely to produce immune responses and are more selective for target cells and/or pretreatments to safely and temporarily remove or block the formation of antibodies that can inactivate the therapy.

Try to understand better what happens to gene (or cell) therapies once they have been given to a patient (i.e., how they are metabolised in cells and tissues) so that improvements can be made to the design of viral vectors [gene, cell and tissuebased therapies] to ensure that they work for longer in the patient.

Interact with the Regulatory Authorities responsible for the evaluation, approval [and reimbursement] of gene and cell/ tissuebased therapies to explore the ways in which the findings of the ARDAT consortium can streamline the process of developing these therapies to ensure that they reach patients as soon as possible.

Project methodology

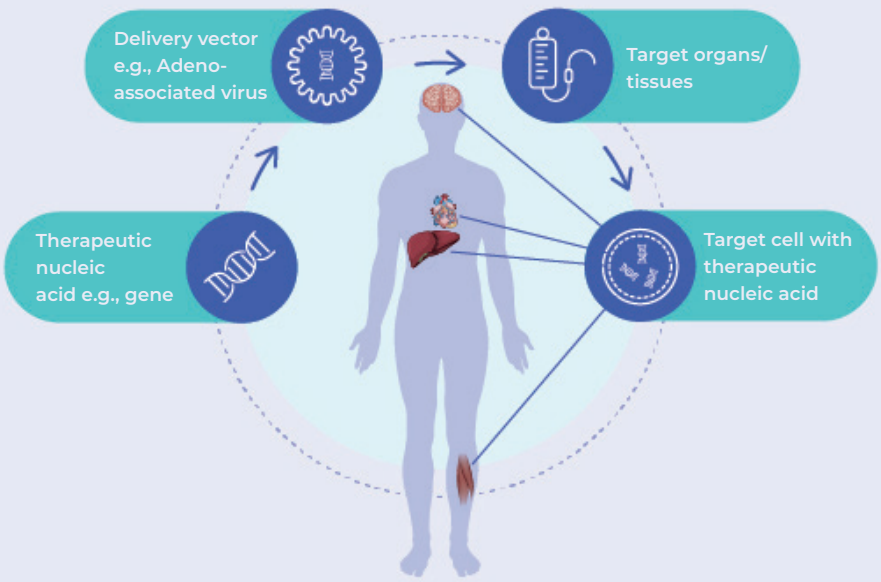
ARDAT Biobank

To help us understand why a particular therapy will produce an undesirable immune response in an individual patient, ARDAT is establishing a “biobank” of biological samples (such as cells, blood and cerebrospinal fluid) obtained (with their informed consent and appropriate measures to assure anonymity and data confidentiality) from participants who have received ATMPs in clinical trials conducted by ARDAT consortium partners. These samples will be catalogued and analysed systematically to identify characteristics (“biomarkers”) that may be associated with an increased likelihood of serious adverse events (such as transaminitis) and to help in the development of tests to predict whether these events are likely to occur in future patients.

Many patients receiving ATMPs, also receive immunosuppressive treatment at the same time to minimise the possibility of adverse events associated with immune responses to the therapy and maximise the possibility that the treatment will work. The samples donated to the biobank will also be analysed to determine how well these treatments work and perhaps to compare different treatments to ensure that the most appropriate immunosuppressive treatment is chosen for each patient.

ARDAT Databases

During the project, the ARDAT consortium will establish databases to provide a repository for both publicly available information and data generated by the project regarding immune responses to ATMPs, approaches to minimise immune reactions caused by ATMPs (e.g., immunosuppression protocols) and nonclinical and clinical studies describing how these therapies distribute and/or are shed (excreted) from the body.
It is hoped that these resources, which pool the efforts of academic research groups and industry, will help to accelerate the development of future ATMPs and will bring more treatment to patients with unmet needs.



Approach to gene therapy for rare and non rare diseases
(Different tissues / cells can be targeted depending on the exact type of vector and disease to be treated.)

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