



## Technology overview

Using adeno-associated viral (AAV) derived vectors as the vehicle of choice for delivery of therapeutic genes, AMT has been able to design and validate probably the world's first stable and scalable AAV manufacturing platform. This proprietary platform can be applied to a large number of rare (orphan) diseases caused by one faulty gene. Following clinical testing in more than 60 trials, AAV vectors are generally considered to be safe.

### **Technologies:**

AMT has developed a broad technology platform specifically designed to overcome major challenges associated with gene therapy. The following key technologies and capacities clearly differentiate our approach from other gene delivery systems:

- Platform vector technology
- Platform manufacturing technology
- Clinical development and regulatory expertise
- Modular platform focused approach

### **Platform vector technology**

One of the key challenges in gene therapy is to identify a delivery vehicle (vector) that can effectively and safely carry a gene into the target cells and its nucleus. AMT's AAV platform vectors offer the potential for safe and effective gene delivery. AAV vectors are generally considered safe and have been tested in over 60 clinical trials to date.

'Wild type', or naturally occurring AAVs, are non-pathogenic and do not in themselves cause disease in humans. Before use as vectors, these naturally occurring AAVs are 'stripped' so that they cannot replicate. The genes in wild type, and hence in our modified AAV vectors, are not able to integrate into the genome of the patient, unlike many other gene vectors. Instead a special version of a gene (extra-chromosomal) is created in each nucleus that guarantees long-term, persistent activity in the target cells. Non-integration is an important factor in determining the safety of our vector technology as it essentially eliminates the risk of inducing cancer, a risk seen with some other, non-AAV vectors.



Efficacy in patients requires lasting therapeutic gene expression in the target tissue. The extra-chromosomal version created after administration of the AAV-based gene therapy induces persistent therapeutic gene activity. Also, AAV can be used to target both dividing and non-dividing cells. Other gene therapy platforms cannot deliver genes into non-dividing cells. Targeting non-dividing cells has the added advantage of limiting the loss of activity of the gene therapy. Our experience with Glybera® for lipoprotein lipase deficiency (LPLD) has demonstrated that our technology is able to provide multi-year, tissue-targeted expression of the therapeutic protein following one-time administration.

#### **Platform manufacturing technology**

AMT has succeeded in developing a proprietary platform manufacturing technology that allows safe, effective, cGMP compliant, economically feasible and commercially scalable manufacturing of our products. In the past, the production of gene therapy products, especially AAV-based vectors, has been hampered by the challenges of scaling-up to commercial production (traditionally carried out in mammalian cells) in an economic way.

AMT's novel approach is based on the use of a combination of baculoviruses and insect cells. It is a highly flexible process that can be easily and quickly adapted to produce a wide variety of products based on our vector technology, thereby significantly reducing the time needed for development.

#### **Clinical development and regulatory expertise**

AMT believes it has all the necessary skills to advance a product through every stage of clinical development and regulatory filing. We have established close links to the regulatory bodies and seek early discussions to ensure that our trials are in conformity with legal requirements. In developing and submitting Glybera® for approval, we have managed the entire process.

#### **Modular platform focused approach**

Using unique manufacturing technology, AMT is able to package a wide range of therapeutic genes into the relevant vector in a modular way. Therefore, we expect to be able to address a large number of disease indications. Based on the modular concept of our technology – the same vector type may carry different genes for different diseases – there is the possibility of faster development times, lower cost of development and lower sales infrastructure.