WHAT ARE ATMPs AND WHY DO THEY MATTER?

Dr Dave Seaward
Founder and Engineering Director
E: enquiries@3pinnovation.com

3P innovation LTD
Tournament Fields,
Bosworth Avenue,
Warwick, UK
CV34 6NH

This second blog in the series will look at advanced therapy medicinal products (ATMPs), as they are known in Europe, or cellular and gene therapy (C&GT) products in the US

The first blog in the series made the case that price and cost of goods for life saving ATMPs are currently too high. It also explained that a lack of skills is constraining the sector; this is driven by the way that processes have evolved from academic lab procedures.

The author, Dr David Seaward, 3P Founder and Projects Director, suggested that ATMPs can be likened to Rolls-Royces — hand crafted by highly skilled artisans at the turn of the 20th century. Cars revolutionised transport and Ford revolutionised their manufacture. ATMPs are about to revolutionise the treatment of many life limiting diseases.

How will their essentially lab-based manufacture be revolutionised to turn them into mass market “Fords”? This second blog digs into the background of ATMPs and provides a primer for those not familiar with the field.

INCEPTION

Biotech isn't new. Indeed, the ancient Egyptians and Sumerians were known to use fermentation to make bread and cheese. They had also discovered how to make beer. These were almost certainly accidental discoveries with no underpinning knowledge, unlike how we can now manipulate the underlying principles of biology.

It was Hungarian Károly Ereky who is seen to be the father of biotechnology and it is he who first coined the term in 1919 in a book called Biotechnology of Meat, Fat and Milk Production in an Agricultural Large-Scale Farm.

He described a technology based on converting raw materials into a more useful product and believed that biotechnology could provide solutions to societal crises, such as food and energy shortages. What we recognise as modern biotech kickstarted when Watson and Crick elucidated the structure of DNA in 1953.

It then took a couple of decades before humankind figured out how to transfer DNA between organisms using a technology termed recombinant (or chimeric) DNA, which uses enzymes to cut and paste DNA sequences of interest together. Recombined DNA sequences can be placed into vehicles called vectors that ferry the DNA into a suitable host cell where it can be copied or expressed. These vectors are usually viruses.

It was the discovery of rDNA that led to the formation of Genentech in 1976 (now part of Roche). Herbert Boyer (University of California, San Francisco) and Stanley Cohen (Stamford University) had worked out how to cut and paste DNA together and introduce DNA into bacteria.

DNA model built by Crick and Watson in 1953, on display in the Science Museum, London (Public Domain)

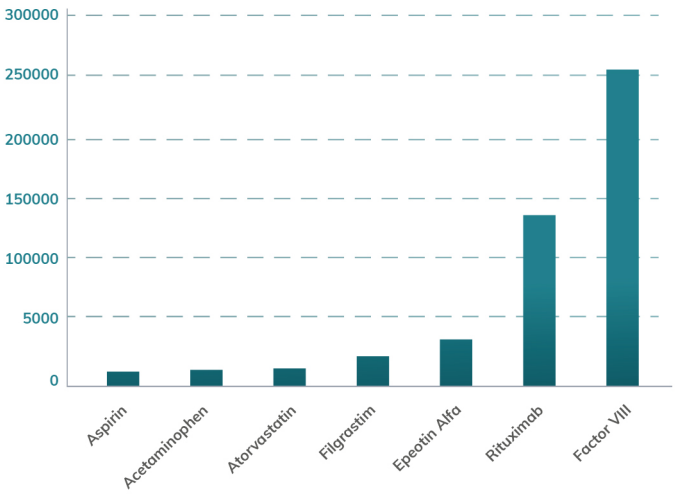
Together, they came up with the idea of splicing human DNA into bacterial DNA and insert it into a host bacterium, which would then produce human proteins. This is the concept that founded the modern biotech industry. By 1977, they had produced the first human protein somatostatin (a growth hormone inhibitor) in bacteria and, shortly afterwards, human insulin, which revolutionised diabetes treatment when licensed to Eli Lilly in 1982. Many believe that what semiconductors and computers were to the latter half of the 20th century, biotechnology will be to the 21st century. If the size of corporate deals and funding rounds is anything to go by, then investors certainly think so.

COMPLEXITY: SIZE MATTERS

To follow on from the semiconductor analogy, it's worth considering that the transistor was invented in 1947. The complexity of electronic chips has roughly followed Moore's law, which states that the number of transistors doubles every 2 years ... to the point when chips have upwards of 50 billion transistors.

A similar trend is self-evident for the complexity of pharmaceuticals. Conventional drugs are often referred to as "small molecules," whereas biopharmaceuticals are called "large molecules." This can be demonstrated by listing a variety of well know pharmaceuticals against their size (as measured by mass using Daltons). See sidebar. The number of transistors is a good analogue for the complexity of the chip. Similarly, the size of a molecule is a good analogue for the complexity of a pharmaceutical. ATMPs require very complex processes to ensure robust manufacture and, as discussed previously, this drives up the cost of goods.

The size in Daltons of various Pharmaceuticals



APPROVALS AND CLINICAL TRIALS

ATMPs are used to treat a variety of complex diseases and have the potential to revolutionise the lives of patients. Many of these products can be administered as a one-off treatment, offering life-long benefits or curing a disease.

They typically target a disease's root cause by augmenting, repairing, replacing or regenerating organs, tissues, cells, genes and metabolic processes within the patient. The primary focus is on cancer treatment but, as the following table of some EU/FDA approvals demonstrates, ATMPs are being applied to a wide range of conditions. Although research is currently dominated by CAR-T therapies (more of which later) and approvals for stem cell (HPC) treatments, it should be noted that the industry only left the lab just over a decade ago.

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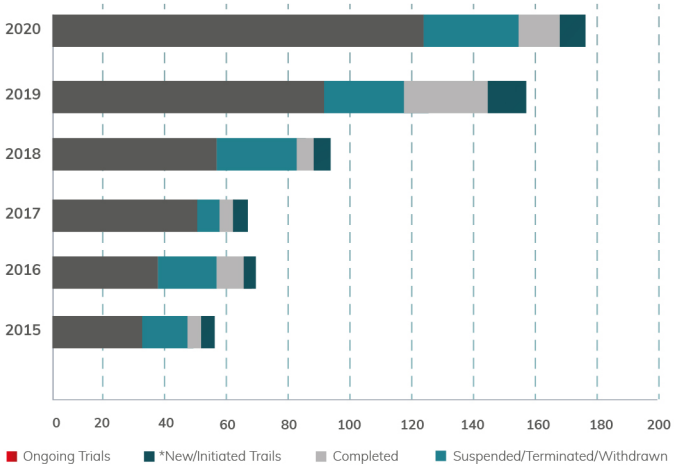
TRADE NAME	DEVELOPER	CONDITION	APPROVAL DATE
Chondrocelect™	TiGenix	Cell Therapy to repair knee cartilage	Oct 2009 withdrawn 2017
Provenge™	Dendreon Corp	An autologous cellular immunotherapy for the treatment of prostate cancer	April 2010
Laviv (Azficel-T)	Fibrocell Technologies	An autologous cell therapy for the treatment of nasolabial fold wrinkles in adults (it is a dermal filler using the patient's own cells).	June 2011
Laviv (Azficel-T)	Fibrocell Technologies	Nasolabial fold wrinkles in adults	June 2011
Hemacord™	New York Blood Center	The first approved haematopoietic progenitor cell (HPC cord) blood for disorders affecting the haematopoietic (blood forming) system.	Nov 2011
Gintuit™	Organogenesis Incorporated	An allogeneic cell therapy for topical application to a surgically created vascular wound bed in the treatment of mucogingival conditions	March 2012
HPC Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank	HPC cord blood for disorders affecting the haematopoietic (blood forming) system	May 2012
Ducord™	Duke University School of Medicine	HPC cord blood for disorders affecting the haematopoietic (blood forming) system	Oct 2012
Glybera™	uniQure	Gene therapy for lipoprotein lipase deficiency (LPLD)	Oct 2012 withdrawn 2017
Allocord™	SSM Cardinal Glennon Children's Med. Center	HPC cord blood for disorders affecting the haematopoietic (blood forming) system	May 2013
HPC Cord Blood	LifeSouth Community Blood Centers, Inc.	HPC cord blood for disorders affecting the haematopoietic (blood forming) system	June 2013
MACI™	Vericel	Tissue based therapy to repair knee cartilage	June 2013 withdrawn 2014
Provenge™	Dendreon	Advanced prostate cancer	Sept 2013 withdrawn 2015
Holoclar™	Holostem	Tissue based therapy for limbal stem-cell deficiency caused by burns	Feb 2015
Imlygic™	Amgem (BioVex)	Gene Therapy for Metastatic Melanoma	Dec 2015
HPC Cord Blood	Bloodworks	HPC cord blood for disorders affecting the haematopoietic (blood forming) system	Jan 2016
Strimvelis™	GSK	Gene therapy for adenosine deaminase (ADA) and severe combined immune-deficiency (SCID)	May 2016
Zalmoxis™	MolMed	Cell therapy for patients with high risk of haematological malignancies	Aug 2016
Clevecord™	Cleveland Cord Blood Center	HPC cord blood for disorders affecting the haematopoietic (blood forming) system	Sept 2016
Spherox™	CO.DON	Tissue based therapy to repair knee cartilage	Jul 2017
Luxturna™	Spark Therapeutics	Gene therapy for loss of vision owing to inherited retinal dystrophy	Dec 2017
Alofisel™	TiGenix	Cell therapy for Crohn's disease related to anal fistulas	Mar 2018
HPC Cord Blood	MD Anderson Cord Blood Bank	HPC cord blood for disorders affecting the haematopoietic (blood forming) system	June 2018
Kymriah™	Novartis	CAR-T therapy for acute lymphoblastic leukaemia	Aug 2018
Yescarta™	Gilead	CAR-T therapy for non-Hodgkin lymphoma	Aug 2018
Luxturna™	Novartis	Gene therapy for inherited retinal disease (mutations in both RPE65 genes)	Nov 2018
Zynteglo™	BlueBird Bio	Gene therapy for blood disorder beta thalassemia	Jun 2019
Zolgensma™	Novartis	Gene therapy for spinal muscular atrophy type I	Mar 2020

Libmeldy™	Orchard Therapeutics	Gene therapy for metachromatic leukodystrophy	Dec 2020
Tecartus™	Kite Pharma	CAR-T therapy for mantle cell lymphoma and acute lymphoblastic leukaemia	Dec 2020
Breyanzi™	Juno Therapeutics	CAR-T therapy for B-cell lymphoma	Feb 2021
Abecma™	Celgene/Bluebird Bio/BMS	Gene therapy for multiple myeloma	
Stratagraft™	Statatech Corp	An allogeneic cell therapy for topical application to burns	June 2021
Skysona™	Bluebird Bio	Gene therapy for cerebral adrenoleukodystrophy	July 2021
Rethymic™	Enzyvant Therapeutics GmbH	An allogeneic cell therapy using thymus tissue to treat congenital athymia, a rare immune disorder	Oct 2021

Given the above (relatively short) list of approved ATMPs, it is interesting to note that, in 2021, www.cancerresearch.org found that

- "The global cellular therapy pipeline added 2073 active agents, 572 more when compared with the 2020 update, representing a 38% increase in the past year compared with a 48% increase from 2019 to 2020.
- "There are 1358 active cell therapy trials, an increase of 78% compared with the 762 active cell therapy trials reported in 2019, with a sustained increase of 43% and 24% between 2020 to 2021 and 2019 to 2020, respectively.
- "CAR-T cell therapies continue to dominate the landscape, comprising 49% (668) of all cell therapy trials active in 2021."

Similarly, the UK's cell and Gene Catapult analysed UK-only trials and observed the same trends in growth.



UK based ATMP trials (https://ct.catapult.org.uk/clinical-trials-database)

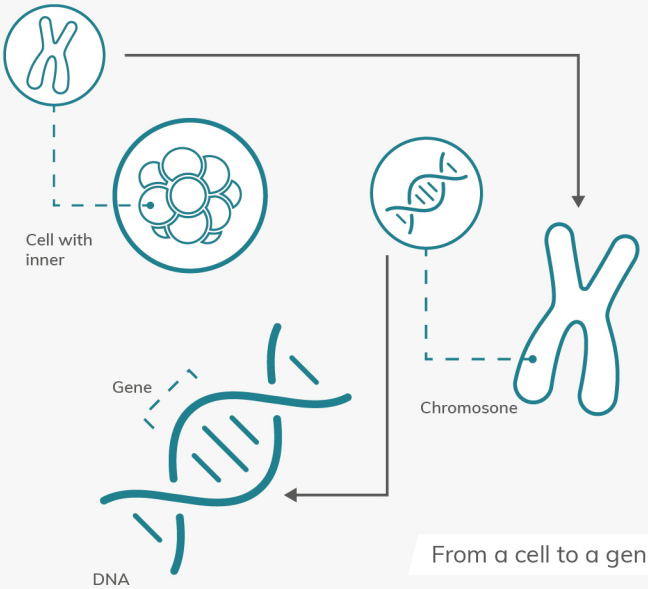
As an "outsider looking in," it really feels as if humankind is on the cusp of great medical leaps forward during the next 10–20 years, as more of these treatments leave the lab, have successful clinical trials and enter commercial manufacture.

SO WHAT ARE ATMPS?

As mentioned previously, ATMPs involve the manipulation of cells and genes. Cells are the basic building blocks of all living things; they contain chromosomes that, in turn, contain DNA.

Genes are small sections of DNA that carry genetic information and the instructions to make proteins. These proteins are essential to healthy living as they build and maintain the body.

Many genetic disorders are characterised by the lack of or incorrect production of an essential protein.



From a cell to a gene

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FROM A CELL TO A GENE

Cell and gene therapy are overlapping fields of biomedical research and treatment. Both therapies aim to treat, prevent or cure disease, and attempt to create a change within the patient at the cellular level. However, cell and gene therapies work quite differently. Gene therapy involves the transfer of genetic material, usually in a carrier known as a vector. The gene alters the targeted cells of the body. These adjusted cells create a therapeutic effect. Cell therapy involves the modification of cells outside the body followed by the transfer of those modified cells with the relevant function into the patient.

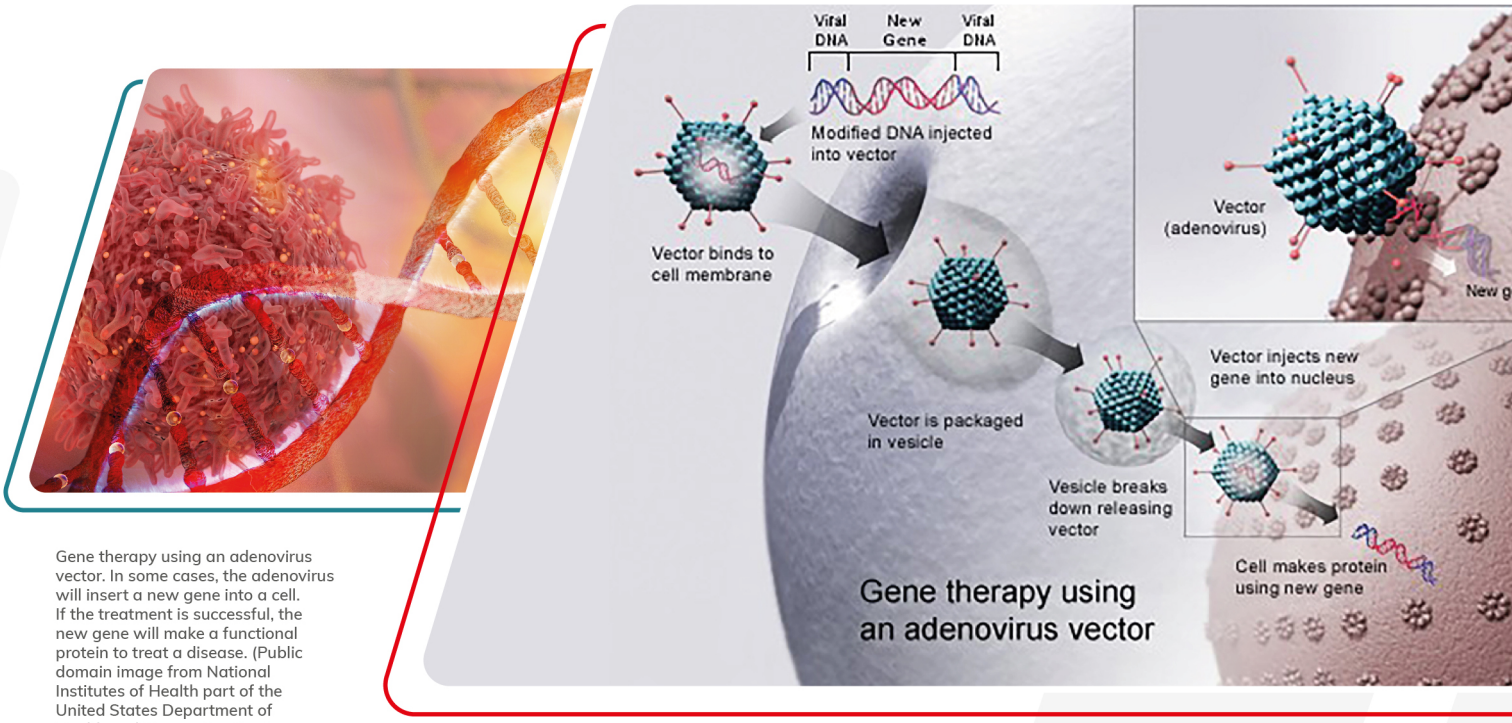
When it comes to gene therapy, the most common method of delivery is via a modified virus (the "vector"). The virus is typically modified to be harmless (to humans) and to deliver the gene therapy. A variety of viruses are used, including the adeno-associated virus (AAV), lentivirus, Herpes Simplex Virus (HSV) and retrovirus as they are considered to be safe and effective.

By way of example, the Oxford/AstraZeneca COVID-19 vaccine, ChAdOx1, and the Johnson and Johnson vaccines both used an adenovirus vaccine vector. To replicate, viruses introduce their genetic material into their host's cells and trick them into using it as blueprints for viral proteins.

Gene therapies exploit this mechanism by substituting a virus's genetic material with therapeutic DNA. Infected cells replicate to produce the therapeutic protein (often damaged or missing in the ill patient) and can become a permanent part of the patient's DNA in those "infected" cells.

Cell therapy tends to be classified as either autologous or allogeneic. Auto means self; so, as the name implies, cells are harvested from a patient and modified outside the patient before being returned to the same donor. Allo means other, such that allogeneic therapies typically have a cell bank derived from just one patient. These cells are altered before being placed into many different patients.

The main difference between autologous and allogeneic therapies is the source of the cells. Allogeneic therapies can be manufactured in large batches from unrelated healthy donor tissues, such as bone marrow and lymphocytes like natural killer (NK) cells or T cells. Autologous therapies have, by contrast, to be manufactured as a single batch from, and for, the patient being treated. Currently, autologous treatments are often a last resort, typically for a terminal cancer patient. This means that manufacture is very much "time critical" and any production errors risk the life of the patient.



Gene therapy using an adenovirus vector. In some cases, the adenovirus will insert a new gene into a cell. If the treatment is successful, the new gene will make a functional protein to treat a disease. (Public domain image from National Institutes of Health part of the United States Department of Health and Human Services)

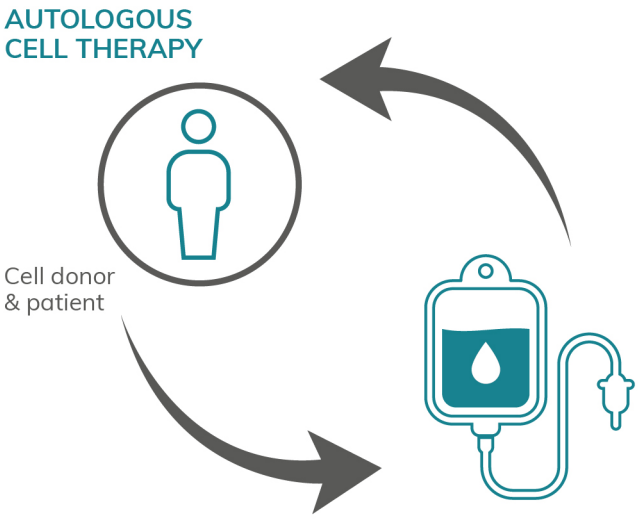
AUTOLOGOUS VERSUS ALLOGENEIC CELL THERAPIES

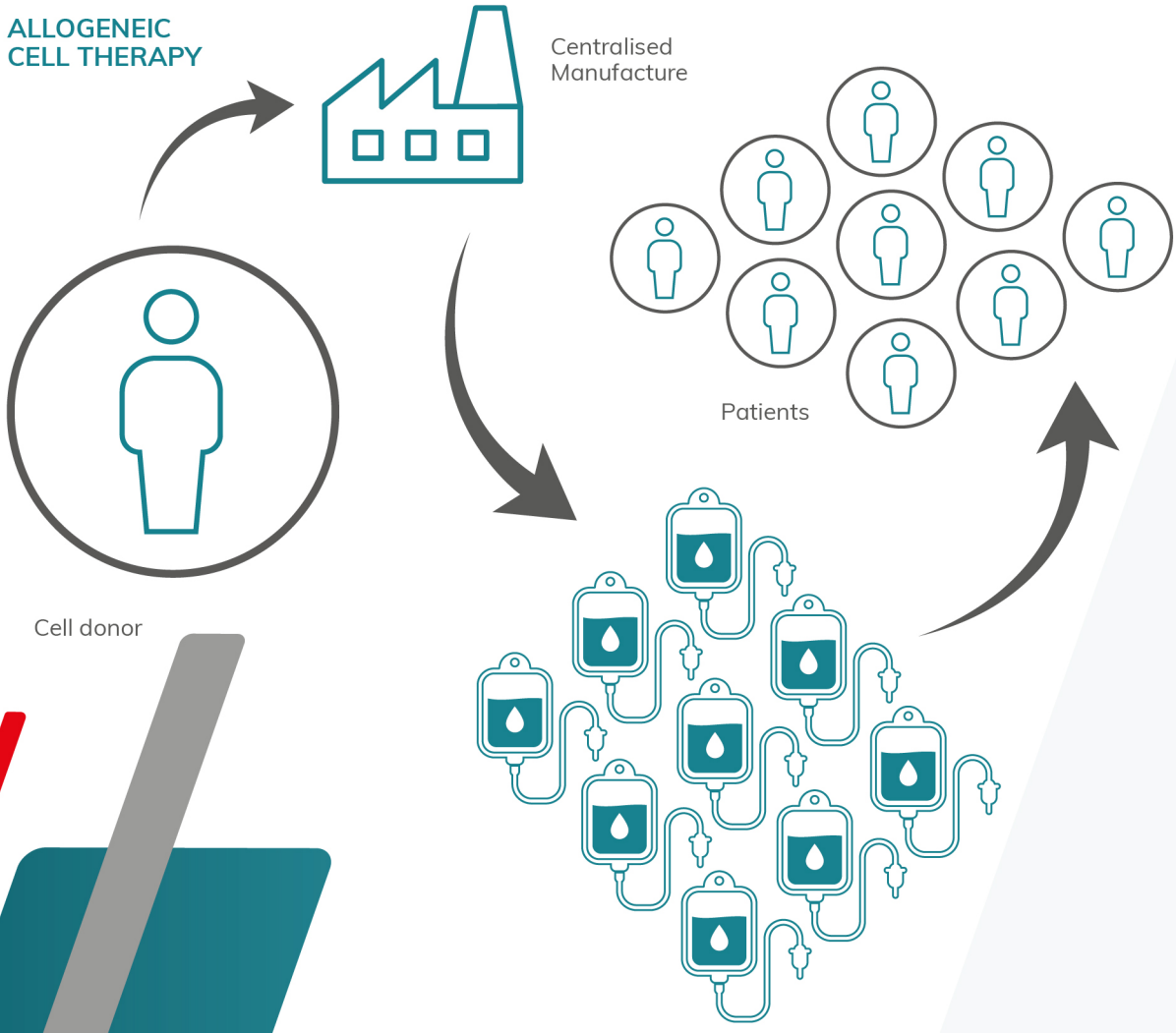
One ATMP therapy that's currently gaining significant attention is CAR-T or chimeric antigen receptor T-cells. These are genetically engineered to produce an artificial T-cell receptor for use in immunotherapy. The receptors are chimeric because they combine both antigen-binding and T-cell activating functions into a single receptor.

The associated receptor proteins are genetically engineered to give T-cells the ability to target a specific protein. They train a patient's immune system to identify and destroy cancer cells. T-cells are harvested from the cancer patient (autologous) or derived from a healthy donor (allogeneic).

They are genetically modified and then infused into the patient to attack their cancer. After CAR-T cells are infused into a patient, they teach the immune system to continually act against any cancer cells they encounter.

When they come in contact with their targeted antigen on a cancer cell, CAR-T cells bind to it and become activated. They then proceed to proliferate and kill the cancer cell. Kymriah, the first FDA-approved CAR-T cell therapy was approved in 2017. Since then, four more have been approved and many more are in late-stage development.





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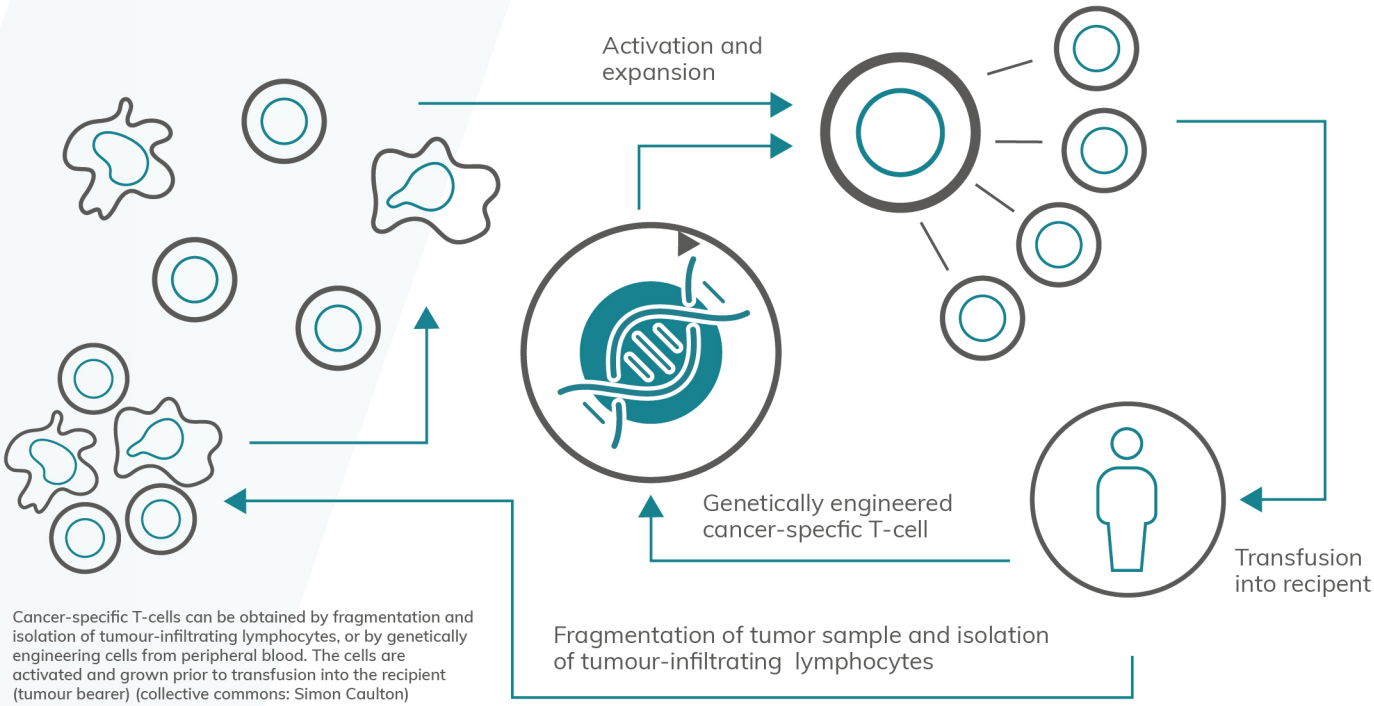
ADOPTIVE T-CELL THERAPY



Cancer-specific T-cells can be obtained by fragmentation and isolation of tumour-infiltrating lymphocytes, or by genetically engineering cells from peripheral blood. The cells are activated and grown prior to transfusion into the recipient (tumour bearer) (collective commons: Simon Caulton)

This blog has provided a primer into some of the historical context and the various technologies behind ATMPs. Hopefully, the reader appreciates the underlying science and the diseases that can be controlled or cured. Given the proven success of many of these technologies, it's likely that the next technical revolution for humankind will be biotechnology.

In the next blog, the author takes a look at some of the megadeals within the ATMP sector and where this is happening within the world (spoiler alert: Cellicon Valley and the Golden Triangle). In the fourth blog, the author sets the scene for automation with a reprint of a tweaked 2013 paper discussing the costs and scale-up risks for medical devices.

It is pertinent to this series of blogs and was originally written before much of the current ATMP sector existed. The fifth blog describes how ATMPs are currently manufactured and what they future may hold for their automation.

SIDEBAR

Aspirin:

discovered in 1897 (179 Daltons)

Acetaminophen:

discovered in 1878 (more commonly known as paracetamol and launched in 1956 as Panadol, 151 Daltons)

Atorvastatin:

discovered in 1985 (better known as Lipitor for cholesterol control, 558 Daltons)

Filgrastim:

approved in 1991 (recombinant DNA used to increase the white blood cell count and successfully treats HIV/AIDS, 18880 Daltons)

Epoetin alfa:

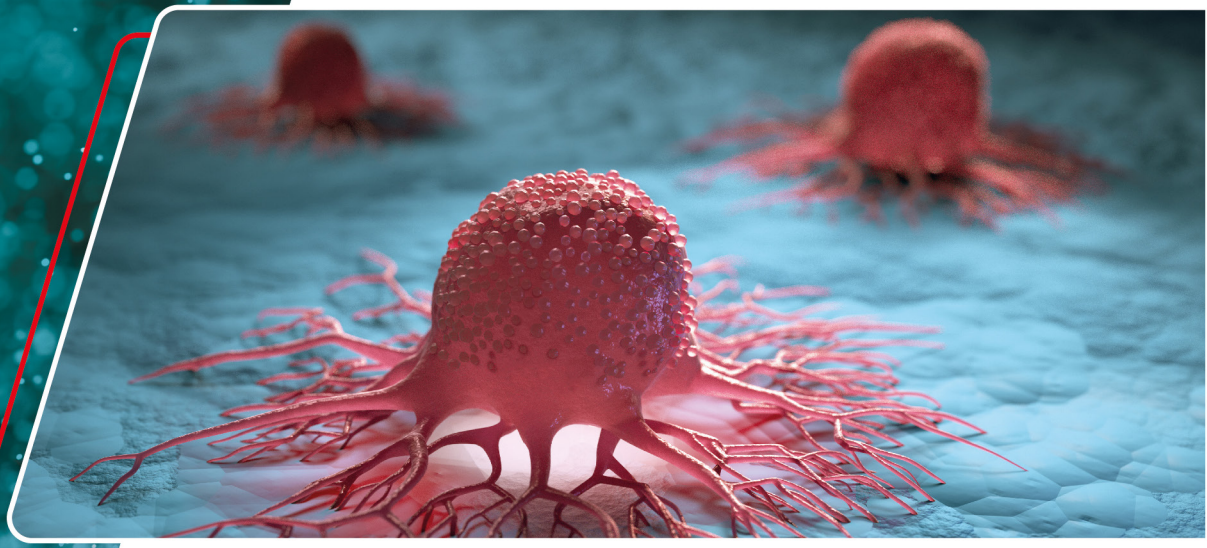
approved in 2007 (used to treat anaemia, commonly associated with chronic kidney failure and cancer chemotherapy, 30,400 Daltons)

Rituximab:

approved in 1997 (a monoclonal antibody used to treat certain autoimmune diseases and types of cancer, 145,000 Daltons)

Factor VIII:

approved in 1992 (an essential blood-clotting protein, also known as anti-haemophilic factor, 264,400 Daltons)



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