Australian Government
Department of Health
Therapeutic Goods Administration

Regulation, ethics and reimbursement of novel biological therapies in Australia – an update

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TGA Health Safety Regulation

Australian Government
Department of Health
Therapeutic Goods Administration

Objectives

- Introducing ‘novel biologics/gene therapy products’
- Regulatory pathways and guidelines

Therapeutic Goods Administration (TGA)

- A group within the Australian Government Department of Health
- Regulates the safety, quality and efficacy of therapeutic goods in Australia
- Regulates medicines, devices, biologicals and blood
- Operates under cost recovery arrangements

Novel Biologics

- Could include:
  - **Gene therapy** - seeks to modify or introduce genes into a patient's body with the goal of durably treating, preventing or potentially even curing disease.
  - **Genome editing** - is a technique by which DNA is inserted, replaced, removed, or modified at particular locations in the human genome for therapeutic benefit in order to treat disease. Usually relies on use of "molecular scissors" (nuclease) to make precise cuts in the patient's DNA at a specific location in the genome.
  - **Cell therapy** - is the administration of viable cells into a patient's body to grow, replace, or repair damaged tissue for the treatment of a disease.
  - **Tissue engineering** - seeks to restore, maintain, improve, or replace damaged tissues and organs through the combination of scaffolds, cells, and/or biologically active molecules.

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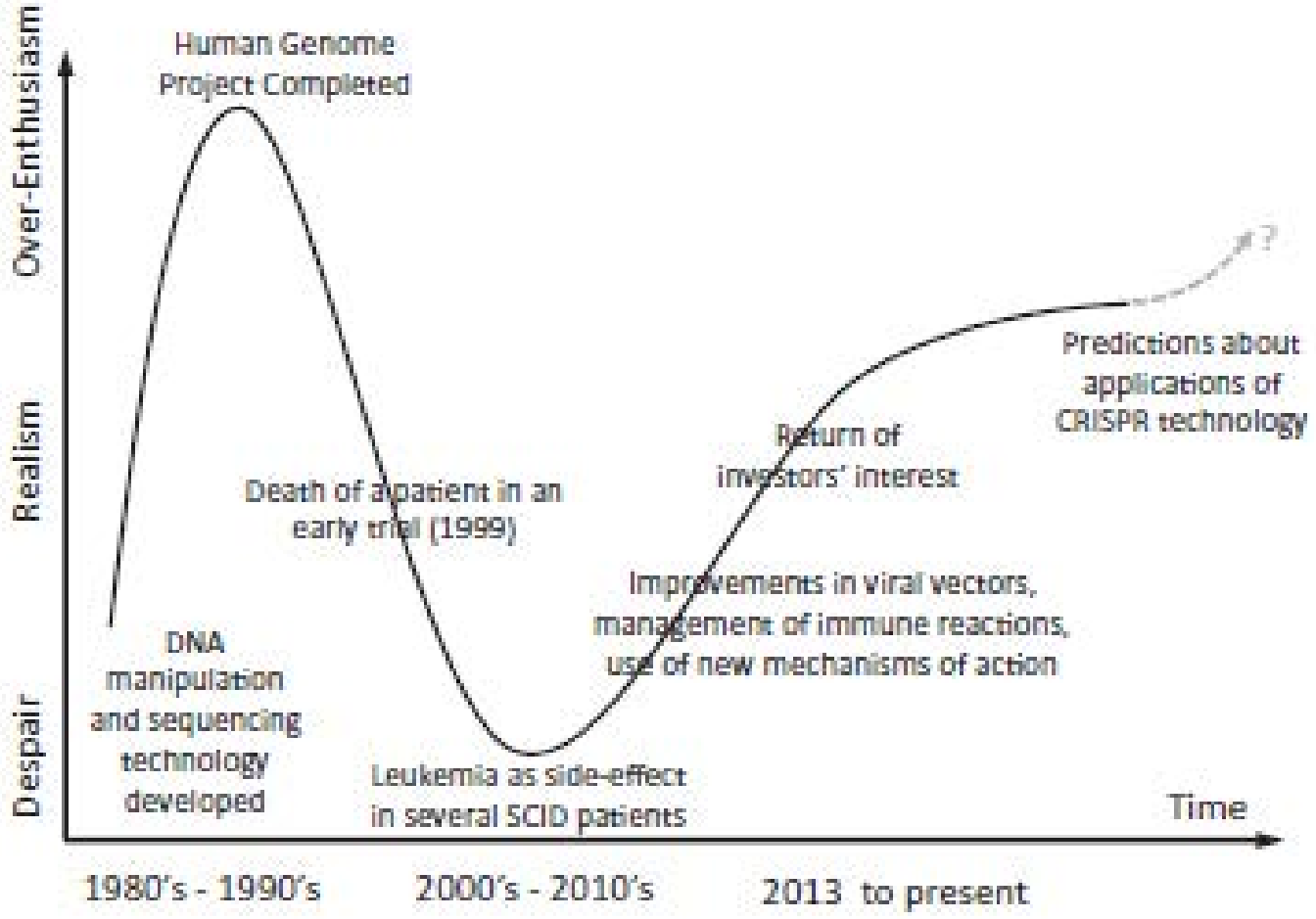
Definition of Gene Therapy Products

- **FDA** defines human gene therapy products as all products that mediate their effects by transcription or translation of transferred genetic material and/or by integrating into the host genome, and that are administered as nucleic acids, plasmids, viruses, such as adenoviral vectors, or genetically engineered micro-organisms, such as bacteria.

- **The European Union (EU)** uses the term Advanced Therapy Medicinal Products (ATMPs) to describe gene therapy vectors, tissue engineered products and somatic cell therapies. Gene therapy medicinal products (GTMPs) generally consist of a vector or delivery formulation/system containing a genetic construct engineered to express a specific transgene ('therapeutic sequence') for the regulation, repair, replacement, addition or deletion of a genetic sequence. The active substance is the nucleic acid sequence(s), or genetically modified microorganism(s), virus(es) or gene modified cells.

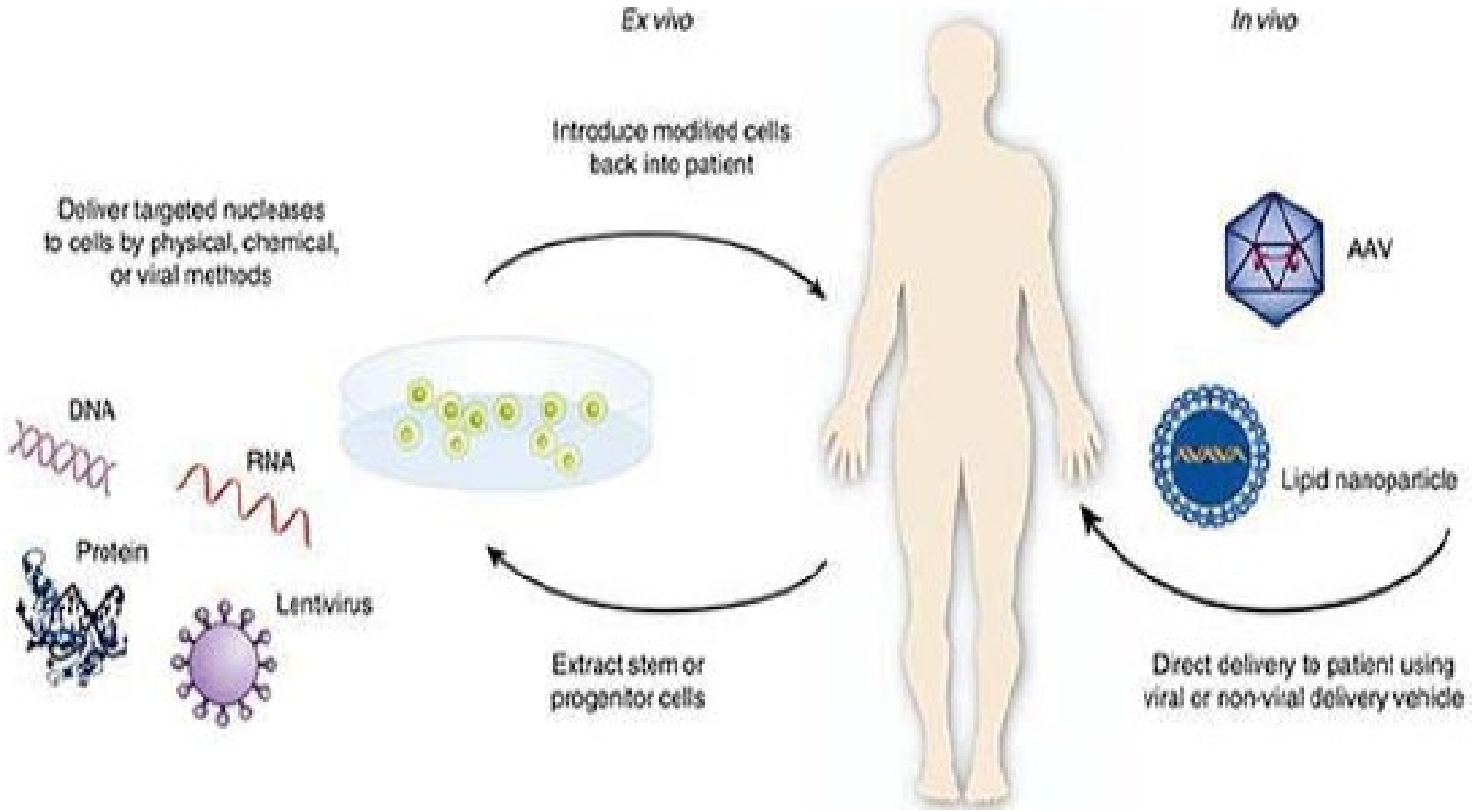
- **TGA** has not yet adopted a definition of gene therapy

Ups and Downs of Gene Therapy



From Kaemmerer, Bioengineering and Translational Medicine, 2018, 3:166-177

Administration of the Gene Therapy Product



Risks Associated with Gene Therapy Products

- Genetic modifications, whether *ex vivo* or *in vivo*, introduces the risk for delayed adverse effects, due to:
  - the permanent nature of change;
  - the potential for off-target genome modifications that can lead to aberrant gene expression, chromosomal translocation, induce malignancies, etc.;
  - the risk for insertional mutagenesis when integrating vectors are used, and the associated risk of tumorigenicity; and/or
  - the possibility of an immune response to the genome-editing components or the expressed transgene.

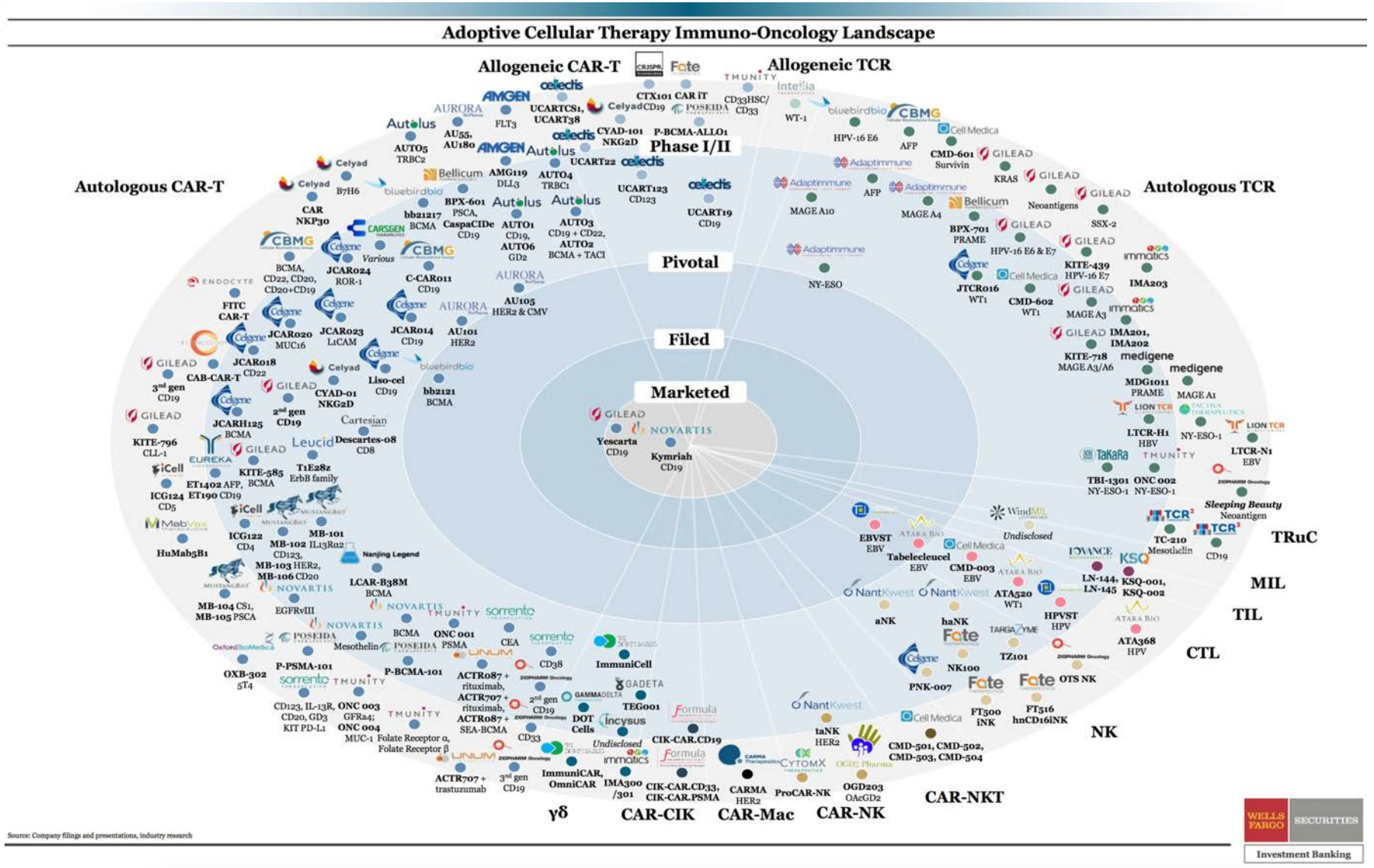
Commonly Used Gene Therapy Products/Vectors

Product/Vector Type	Propensity to Modify Genome	Long Term Follow-up Observations
Plasmid	No	No
RNA	No	No
Poxvirus	No	No
Adenovirus	No	No
Adeno- associated virus	No	Product specific (2-5 years)
Herpesvirus	No, but may undergo latency/reactivation	Yes
Gammaretrovirus	Yes	Yes
Lentivirus	Yes	Yes
Transposon elements	Yes	Product specific
Microbial vectors for gene therapy (MVGT)	No, but may persist and undergo reactivation	Product specific
Genome editing products (e.g. TALEN, CRISPR, meganucleases)	Yes; permanent changes to the host genome	Yes

- 70% of vectors in clinical trials are of viral origin, however the original viral element may be small.
- The most advanced vectors are already 90% synthetic.

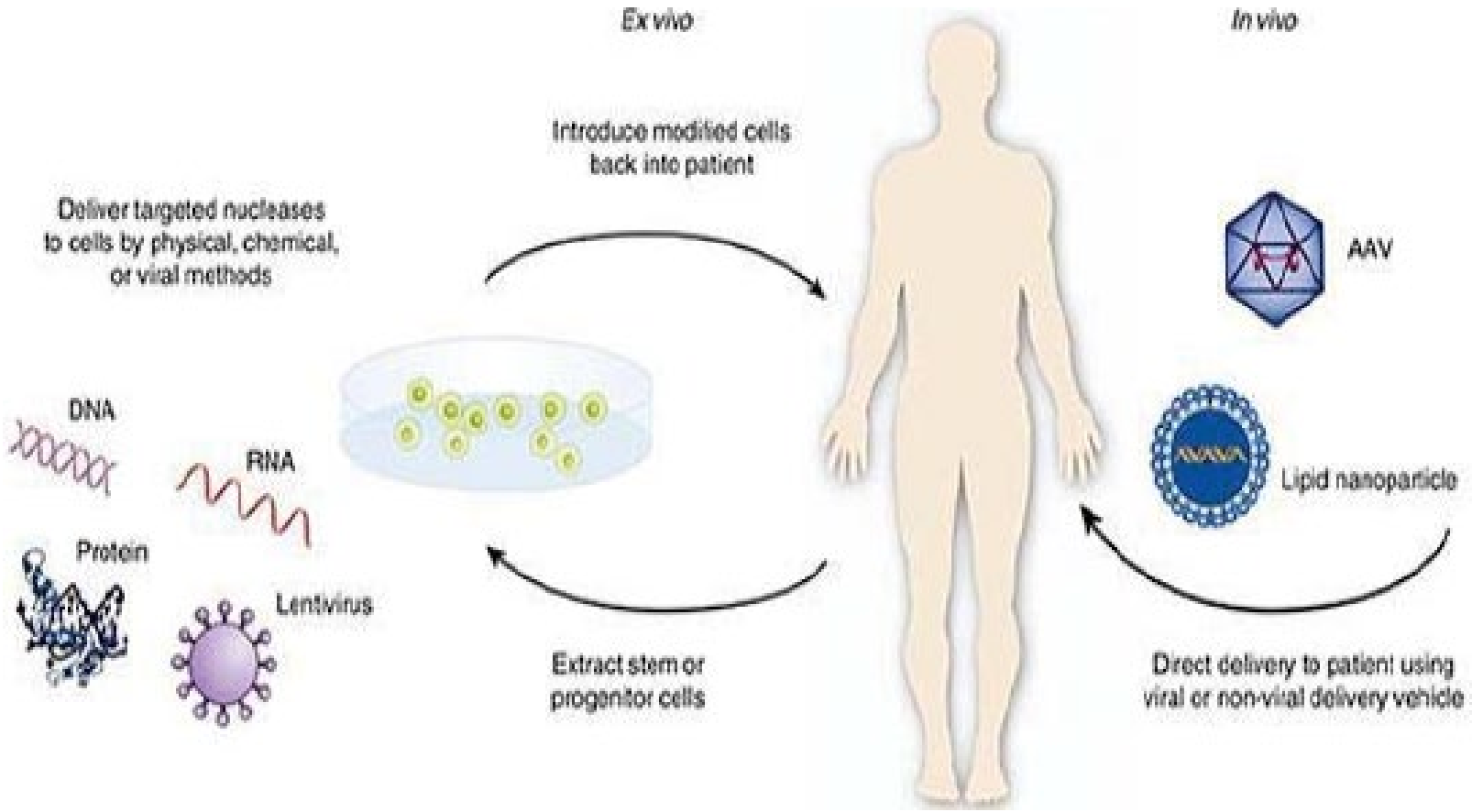
Some Marketed Gene Therapy/Immunotherapy Products

Kymriah® (tisagenlecleucel):	• Novartis Pharmaceuticals Corporation; a cancer immunotherapy that directs genetically modified autologous (using a lentivirus) T-cells to target leukemia cells that have a specific antigen (CD19) on the surface (FDA in Aug 2017, EC in August 2018 , TGA in Dec 2018)
Yescarta® (axicabtagene ciloleucel):	• Gilead Sciences Inc./Kite Pharma, Inc.; a cancer immunotherapy that directs genetically modified autologous (using a lentivirus) T-cells to target large B-cell lymphoma cells (FDA in Oct 2017, EC in August 2018)
Strimvelis® **(**autologous CD34+ enriched cell fraction…)	• Orchard Therapeutics Ltd; contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence): gene therapy for children with adenosine deaminase severe combined immunodeficiency (ADASCID) (approved by the EMA in May 2016)
Luxturna® (voretigene neparvovec):	• Spark Therapeutics, Inc.; the first gene therapy for a rare genetic disease, biallelic RPE65 mutation-associated retinal dystrophy; Luxturna uses a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as a vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision (FDA in Dec 2017)
Zolgensma® (onasemnogene abeparvovec-xioi):	• AveXis, Inc; the gene therapy (the adeno-associated virus (AAV) 9) treats children under 2 years of age with spinal muscular atrophy, an inherited neuromuscular disease that causes progressive loss of muscle function. (FDA in May 2019)



291 CAR-T products in development, 161 in trials

Administration of the Gene Therapy Product

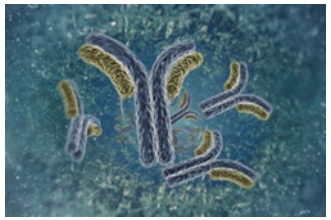


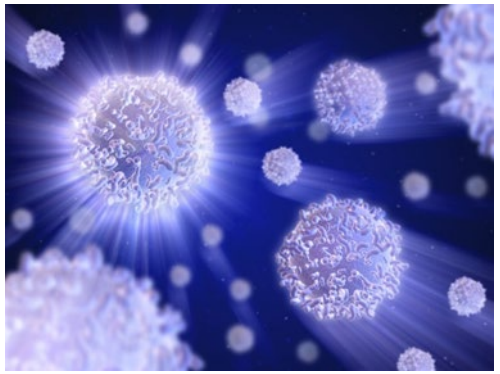
Regulatory Pathways

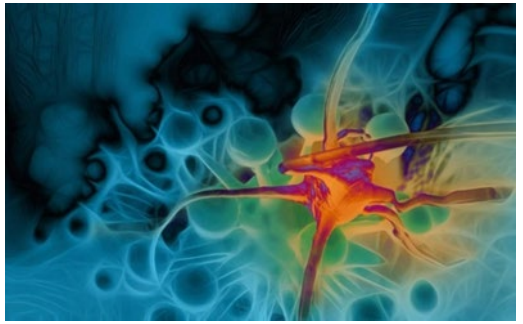
Type of gene therapy	Regulatory pathway	Example	For further information
Ex vivo (gene is delivered to cells outside of the body, which are then transferred back into the body)	Class 4 biological	CAR-T cells (human cells)	see Australian regulatory guidelines for biologicals (ARGB)
In vivo (gene is transferred to cells inside the patient's body)	Prescription medicine	Adeno-associated virus	Australian Regulatory Guidelines for Prescription Medicines (ARGPM)

Clinical trials

- Two schemes:
  - The **CTN** Scheme is a **notification** process
  - The **CTX** Scheme is an **approval** process
- Genetically modified human cells (Class 4 biologicals) are not able to be supplied under the CTN Scheme and must be submitted under the CTX scheme (unless a trial with the same product for the same indication has been approved in a comparable jurisdiction)







Guidelines for registration/approval for supply

Good source of guidelines which have or are expected to be adopted by TGA:

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-gene-therapy

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