Institutional readiness: governance and operational considerations for delivering ATMPs in hospitals

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Who are LAT and the ATTCs?

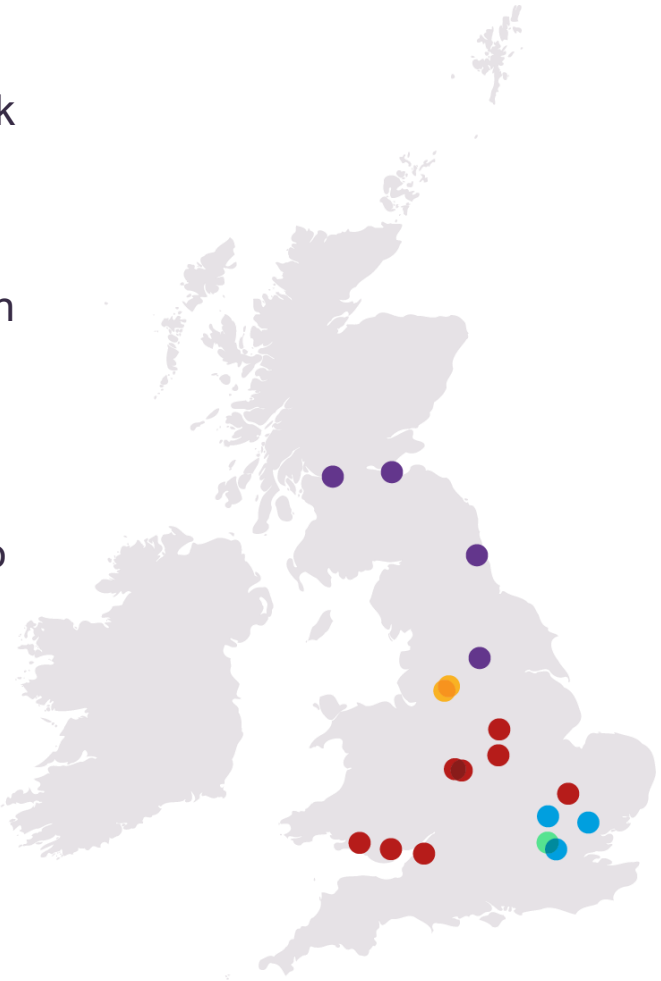
The ATTC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund

London Advanced Therapies (LAT) is funded by Research England

The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.

This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic

Find out more at https://www.theattcnetwork.co.uk/



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Dosing considerations for Advanced Therapy Medicinal Products (ATMPs)

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Recap: What are ATMPs?

- An ATMP is a biological medicinal product that can be classified into 3 main types:
  - **Gene Therapy Medicinal Products (GTMP)**: contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases.
  - **Somatic-cell Therapy Medicinal Products (sCTMP)**: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;
  - **Tissue-Engineered Medicines (TEM)**: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue

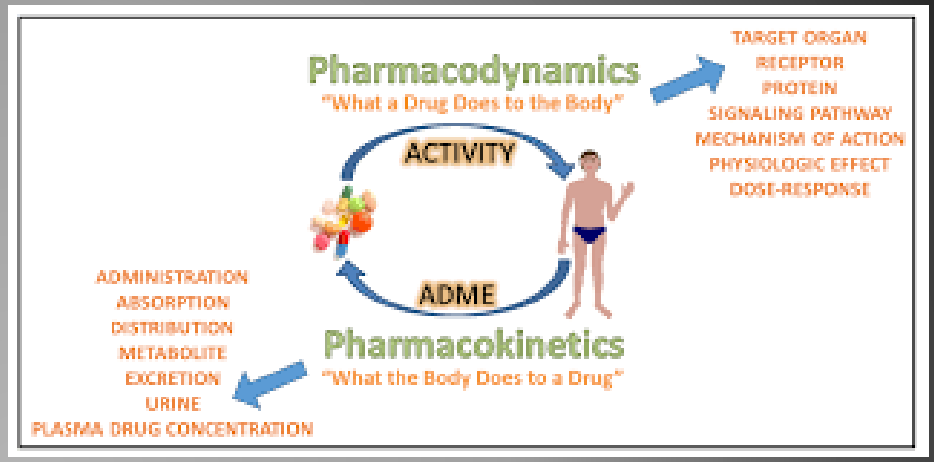
https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

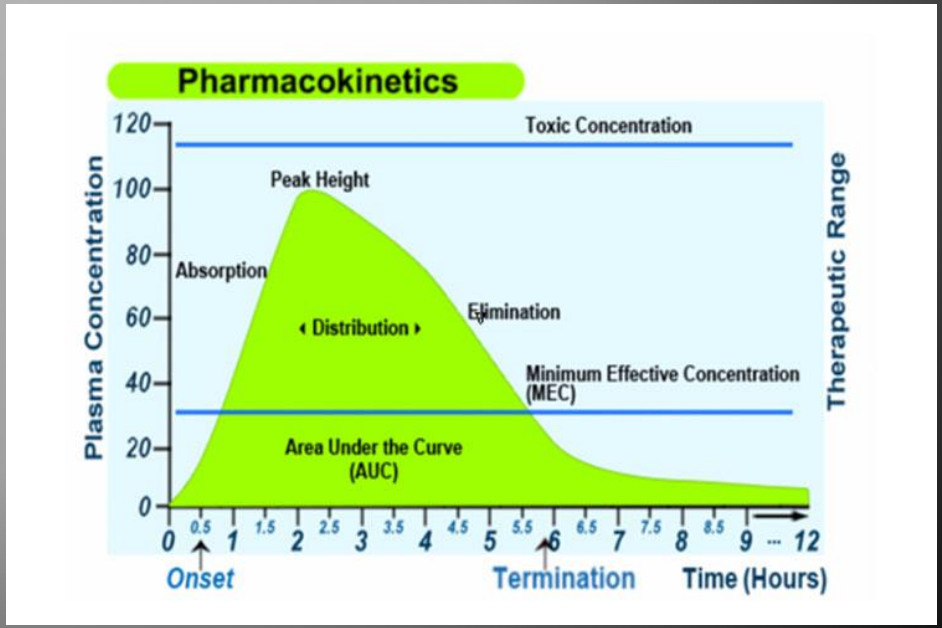
Outline of presentation

- Basic concepts:
  - How dosing of ATMPs differ from traditional pharmaceuticals
- Will briefly discuss what may affect dosing:
  - In vivo Gene Therapy
  - Cell based Ex vivo Gene Therapy
  - Somatic Cell Therapy
  - Will not cover tissue-engineered therapy

Traditional Pharmaceuticals

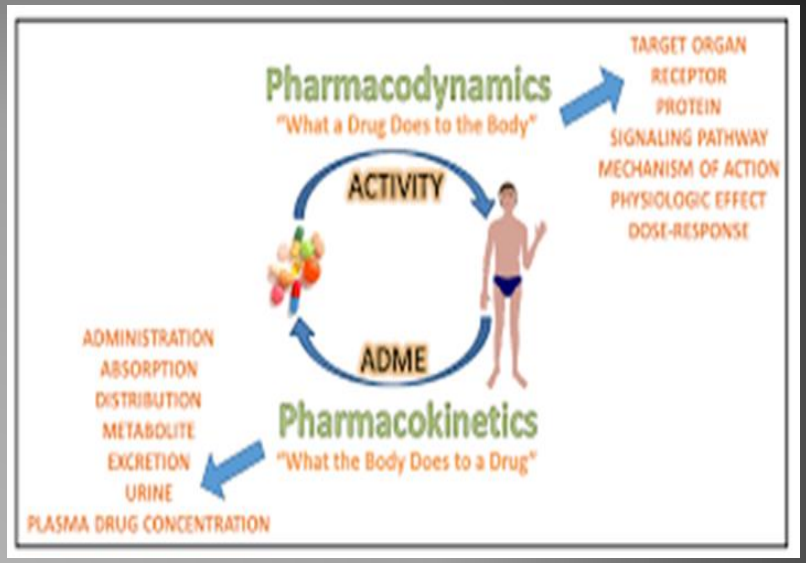
- Typically used to manage diseases/ reduce symptoms
- Dose selection based on:
  - Pharmacokinetics (PK) and
  - Pharmacodynamics (PD)

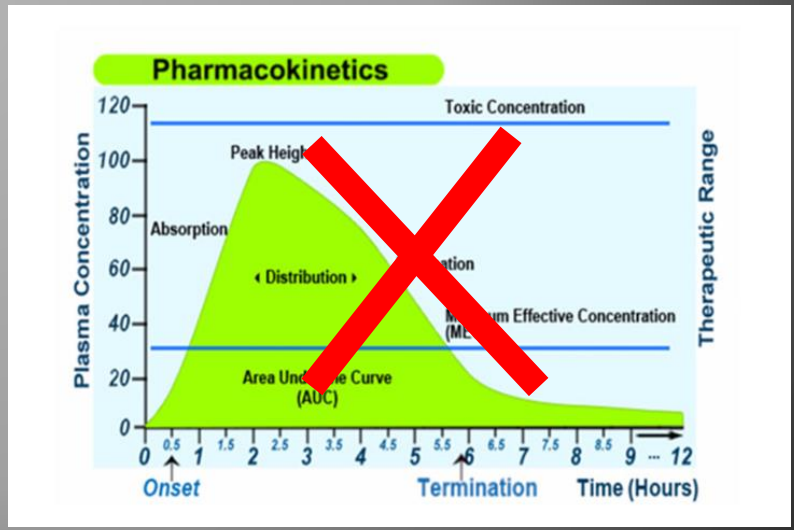




ATMPs

- Cell and gene therapy to target cause of disease; potentially to cure
- Classical pharmacokinetic profile typically does not apply
  - 'Acting dose' can be very different to administered dose
  - Designed to expand, proliferate, differentiate following administration
  - Effects may persist for long periods/life-long
- Pharmacodynamic properties may be a better predictor





Traditional pharmaceuticals vs. ATMPs (1)

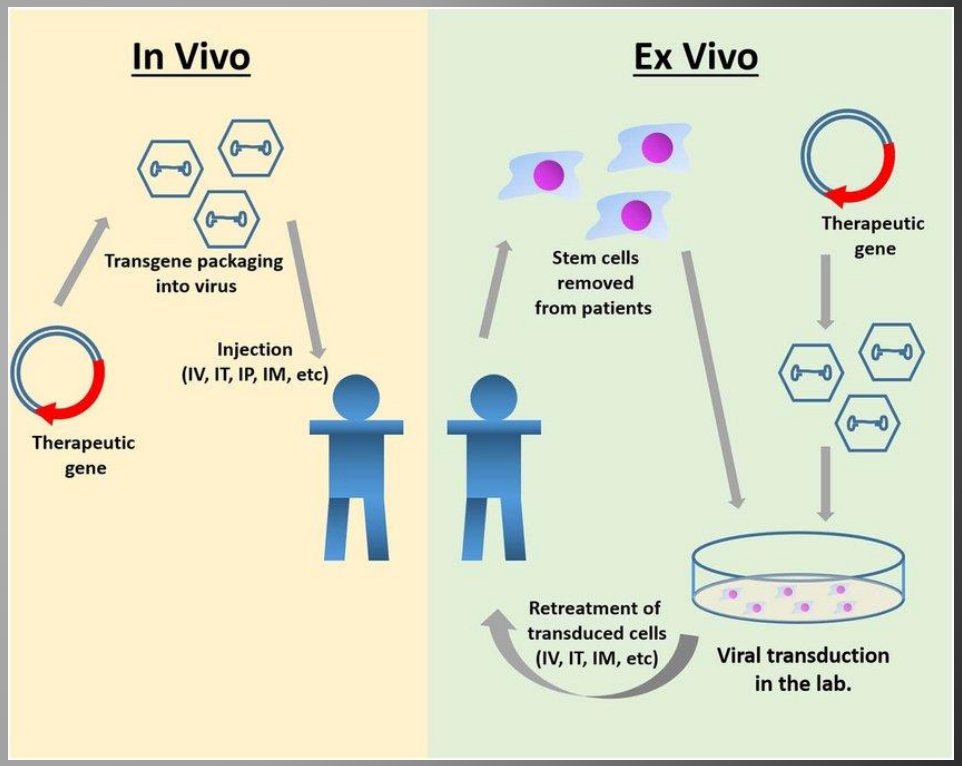
	Traditional Pharmaceuticals	ATMPs
Starting Materials	Homogeneity of starting materials Chemical nature, predictable activity	Biologic products: Cellular material, viral vectors, nucleic acid Fragile Characteristics variable
Manufacturing process:	Reproducible and reliable on a large scale Automated	Complex process; Small scale; specialist manufacturing facilities; individualised treatments Manual processes
	Sterility of final product can be assured and tested	Due to nature of products final product sterility may not be possible
Final Product	Homogeneity of final product between batches	Likely heterogeneity between batches

Traditional pharmaceuticals vs. ATMPs (2)

	Traditional Pharmaceuticals	ATMPs
Stability	Final product usually	Living medicines, fragile products; patient specific
Storage	Room Temp/ambient 2°C to 8°C -15°C to -25°C (very few)	Specialist storage: -80°C or below -150°C under LN2 Vapour
Handling	Robust	Fragile products Careful handling during thaw process Potency of final product very dependant appropriate handling

Gene Therapy Medicinal Product (GTMP)

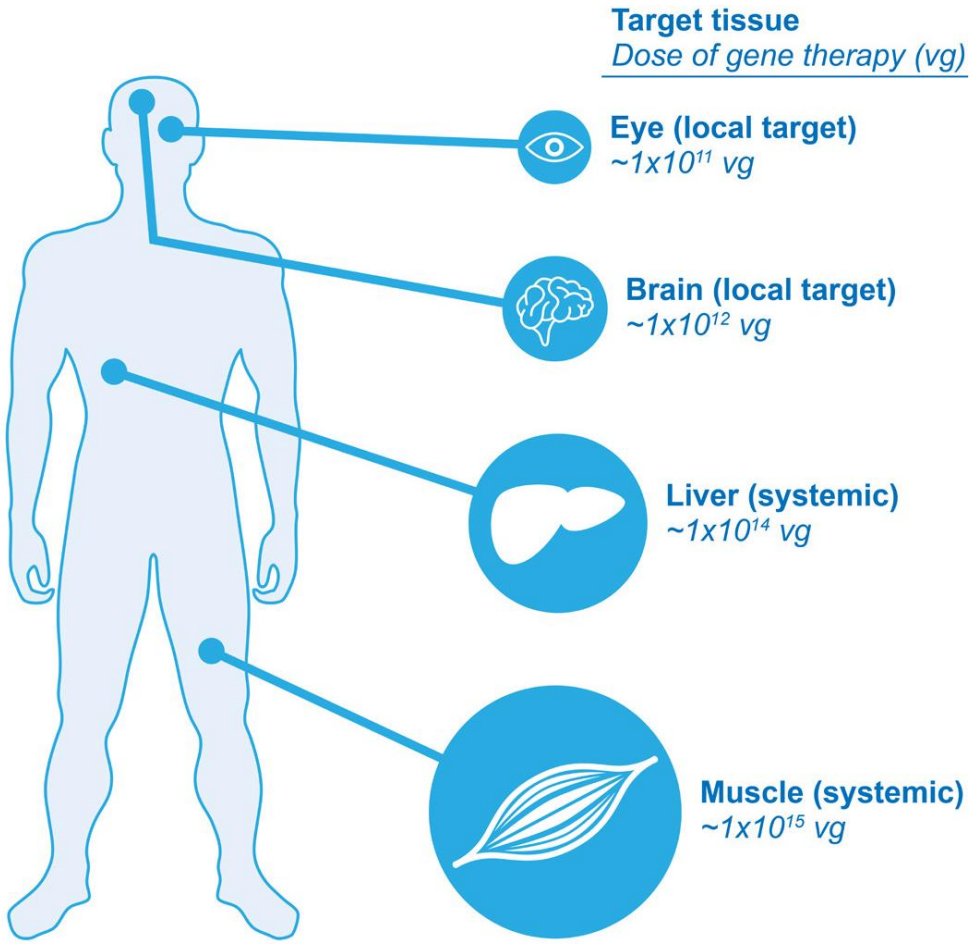
- Used to introduce genetic material into cells
  - To compensate for abnormal genes
  - To make a beneficial protein
  - Introduce a normal copy of gene to restore function of a protein



In vivo GTMP

- Need to express gene in the right tissue, at the right level, for the right amount of time
- Viruses often used as a vector
- Licenced products available
  - e.g. IMLYGIC® (talimogene laherparepvec)
    - Oncolytic Viral therapy for Melanoma
    - Uses HSV-1
    - Local administration
    - -80^{o}C Storage
- Majority still in clinical trials

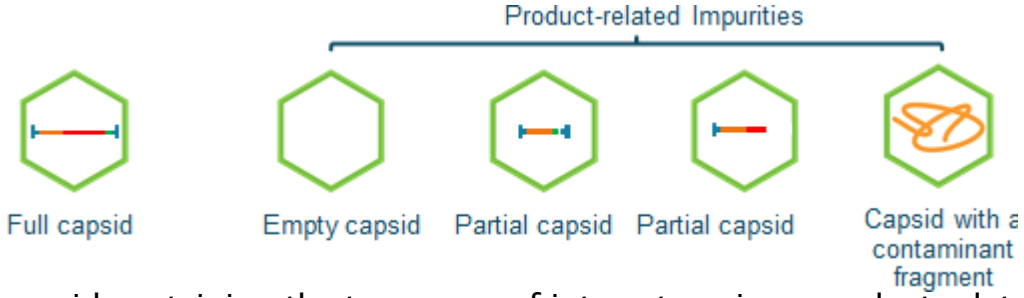
What dose and where?



Ref: for diagram

Adeno Associated Virus

- AAV-based vector systems most actively used vectors for in vivo GT
  - Versatility in targeted applications and safety profiles compared to other viruses
- Challenges with dosing:
  - Manufacture



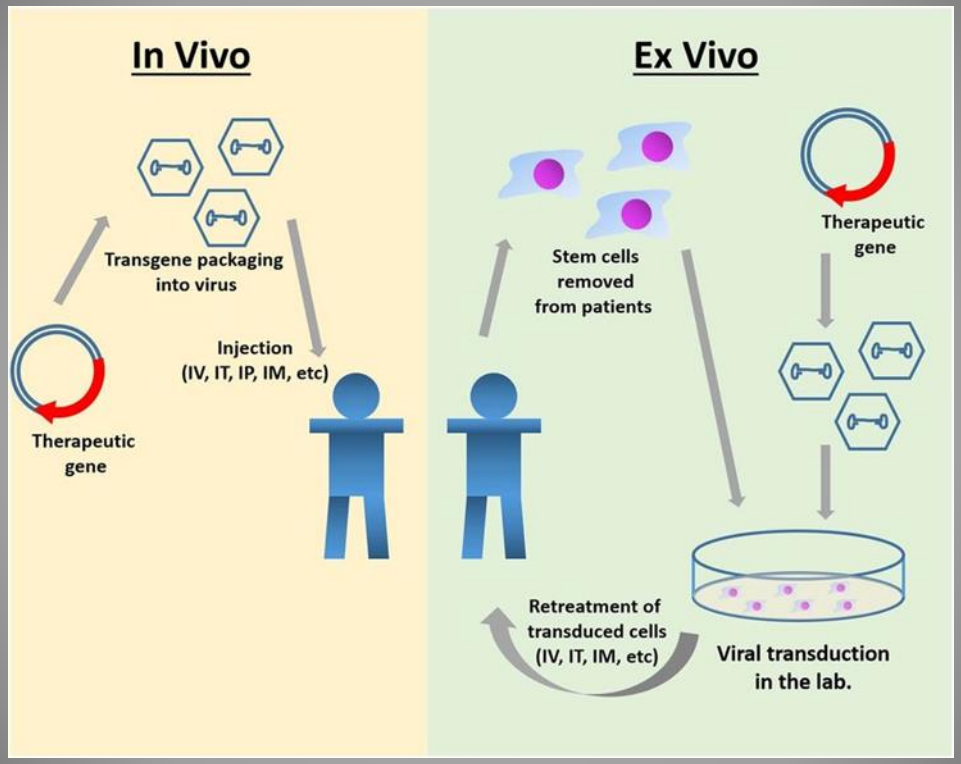
- Figure 1. Along with the full capsid containing the transgene of interest, various product related impurities can be present such as empty capsid with the transgene missing, partial or truncated fragments of the gene or capsid with contaminant gene from the host cell.

Tingting Li, Tie Gao, Hongxu Chen, Zuzana Demianova, Fang Wang, Mukesh Malik, Jane Luo, Handy Yowanto, Sahana Mollah SCIEX, Brea, CA. Determination of Full, Partial and Empty Capsid Ratios for Adeno-Associated Virus (AAV) Analysis

Challenges with In vivo GTMP

- Multiple other factors
  - Transduction in vivo; rates can be variable
  - Effective transcription and protein expression
    - Enough protein to have desired effect in the correct place at the correct time
  - Immune response to viral vector
    - Effect of impurities
  - Losses due to handling:
    - Strict storage requirements
    - Strict thawing process
    - In-use time post thaw to maximise potency

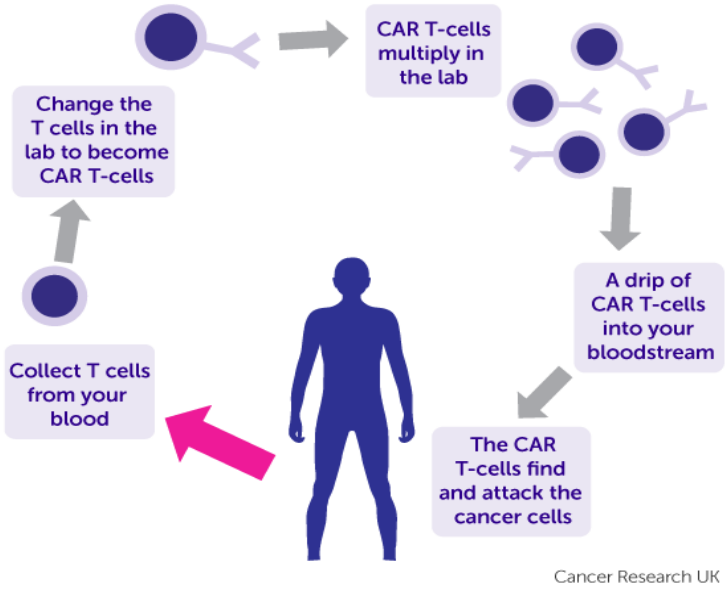
Ex-vivo (cell based) Gene Therapy



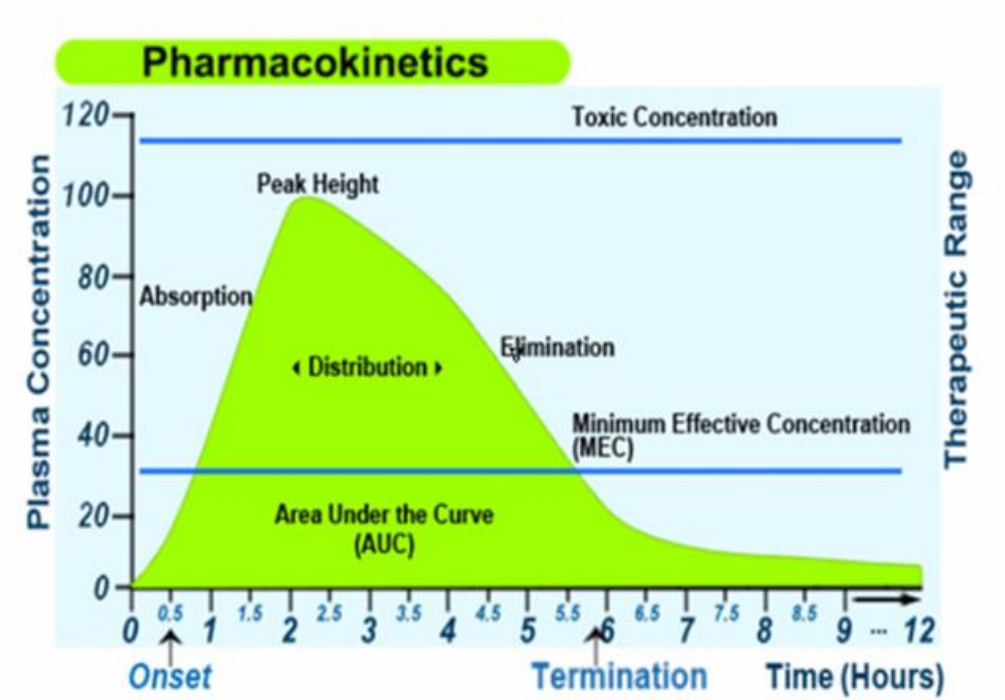
Cell based Ex vivo Gene Therapy

CAR-T cell therapy

- Autologous genetically modified T-cells to express CAR
- Dosing expressed as number of CAR-positive viable T cells
  - Lymphodepleting chemotherapy to allow expansion
  - Activated, proliferate and become cytotoxic



Pharmacokinetics of traditional pharmaceutical



Pharmacokinetics of CAR-T

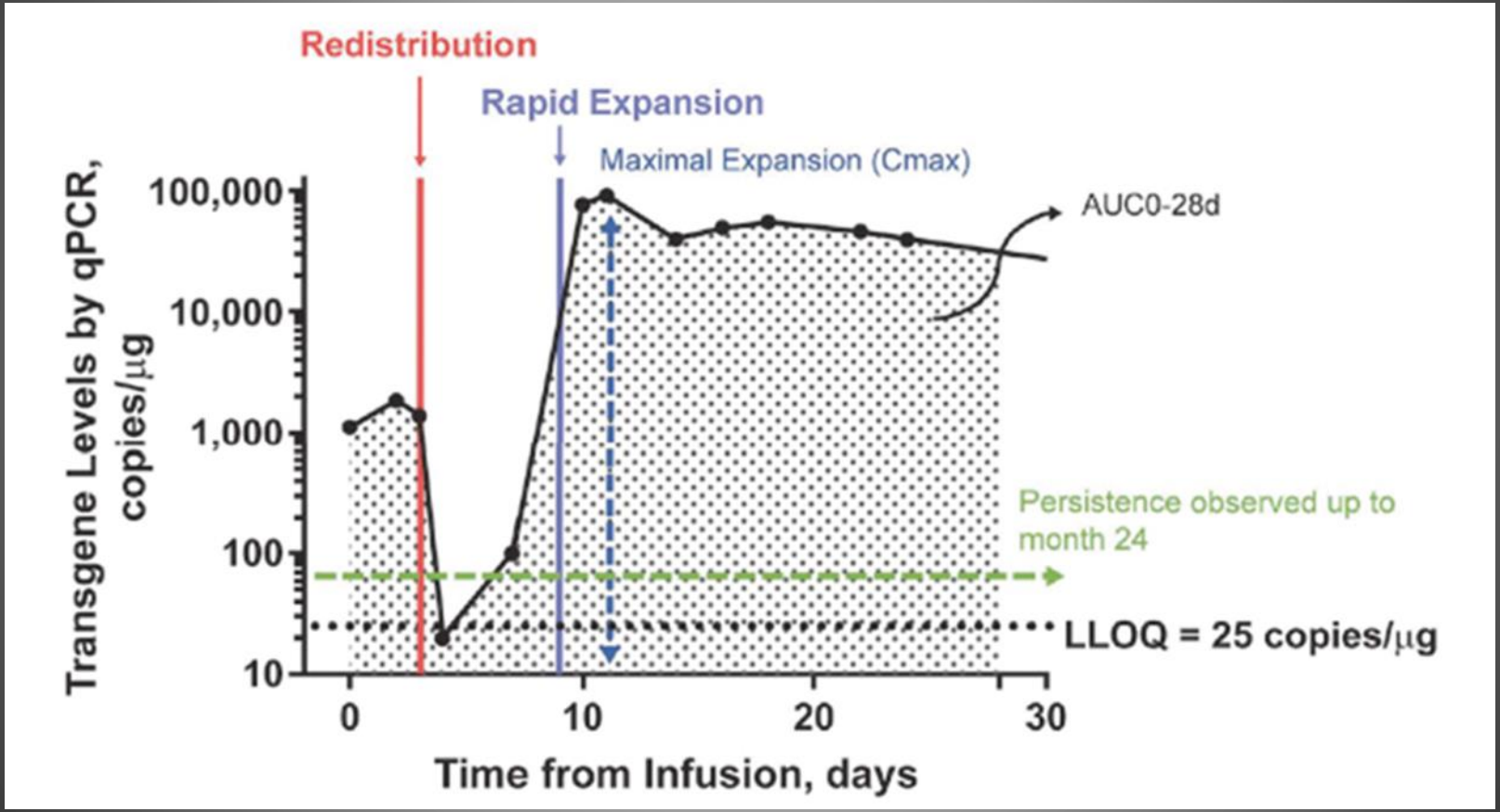


Figure 1: Pharmacokinetic profile of a CD-19 targeted CAR-T // Mueller KT et al., Blood Journal 2017

CAR-T dosing challenges

- Adverse effects:
  - Cytokine Release Syndrome (CRS) – well known toxicity related to CAR-T mechanism of action
    - Release of inflammatory cytokines: IL-6, IFN-g, TNF
    - Tocilizumab and steroids effective
    - May reduce overall effect of CAR-T therapy
  - Neurotoxicity – can be pronounced
    - Do not fully understand mechanism

- Need to reduce adverse effects and increase therapeutic effect of CAR-T cell therapy

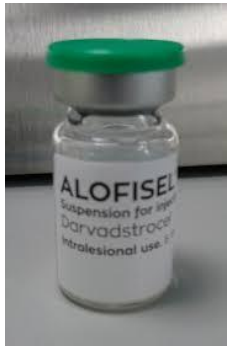
Potential strategies to reduce adverse effects:

- Adaptive split dosing of CAR-T
  - Dosing based on toxicity response therefore limit overall toxicity
  - Potentially can give higher total doses
- Suicide genes:
  - CAR-T cells genetically engineered to include suicide gene that can induce apoptosis be activated by an extra-cellular molecule
- ON-switch:
  - CAR-T cells engineered to only function in the presence of both tumor antigen and a benign exogenous molecule

Other challenges

- Manufacture process complex
  - Only one product for one patient at a time
  - Autologous starting materials
  - Ex vivo transduction however
    - Heterogeneous mixture of T-cells
    - Quality of T-cells dependant on donor
- Losses due to handling:
  - Strict storage requirements
  - Thawing process
  - In-use time post thaw to maximise potency

Somatic cell Therapy

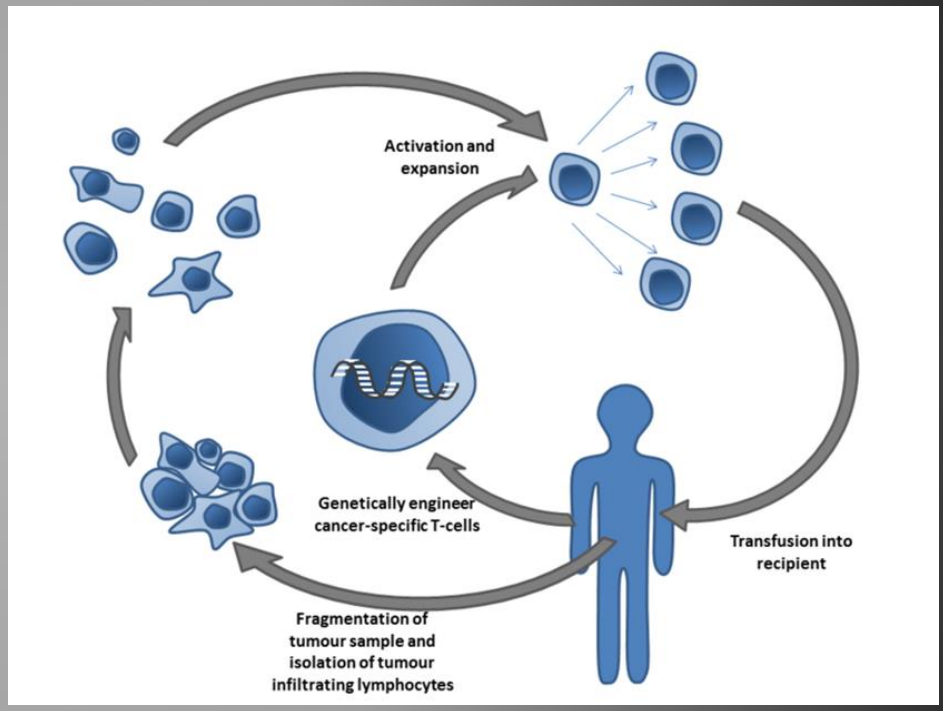


- Darvadstrocel (Alofisel)
  - Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue
    - Licenced treatment for complex perianal fistulas
    - Cells can help to reduce inflammation and support growth of new tissue – encourages the fistula to heal and close
    - Given as fixed dose via local administration: injection into the walls of the fistula
    - Single manufacture site, small scale
    - Poor stability – 72 hours shelf life = on demand, made to order treatment

Tumor-infiltrating lymphocytes (TIL) therapy

Adoptive cell therapy (ACT) using TIL is a personalized cancer treatment

- Currently being studied in a wide range of tumors
- Treatment may include high-dose lymphodepleting chemotherapy, infusion of the expanded and activated T cells and interleukin-2 (IL-2) injections



Summary

- Many challenges to optimising dosing of ATMPs
  - Do not follow typical PK profile of traditional medicines
  - Nature of ATMP – starting materials and final product:
    - Heterogeneous characteristics
    - Fragility
  - Mode of action
  - Complex manufacturing process
  - Stability
  - Storage and handling

Additional information:

- Pan-ATTC Pharmacy Working Group
  - Expertise across the NHS
  - Promote good practice, identify and resolve pharmacy issues
- Develop resources to enable delivery of ATMPs in the NHS
  - Available on ATTC website

Q&A

Please add any question you have into the Q&A box

Please fill in feedback survey, your input is really valuable to us

Next webinar,

Introduction to ATMP manufacturing

10th December, 4pm, Prof Ivan Wall, Aston University