Advance Therapy Medicinal Products (ATMPs) Pharmacy Teaching Session

Autumn 2018

Nisa Khan

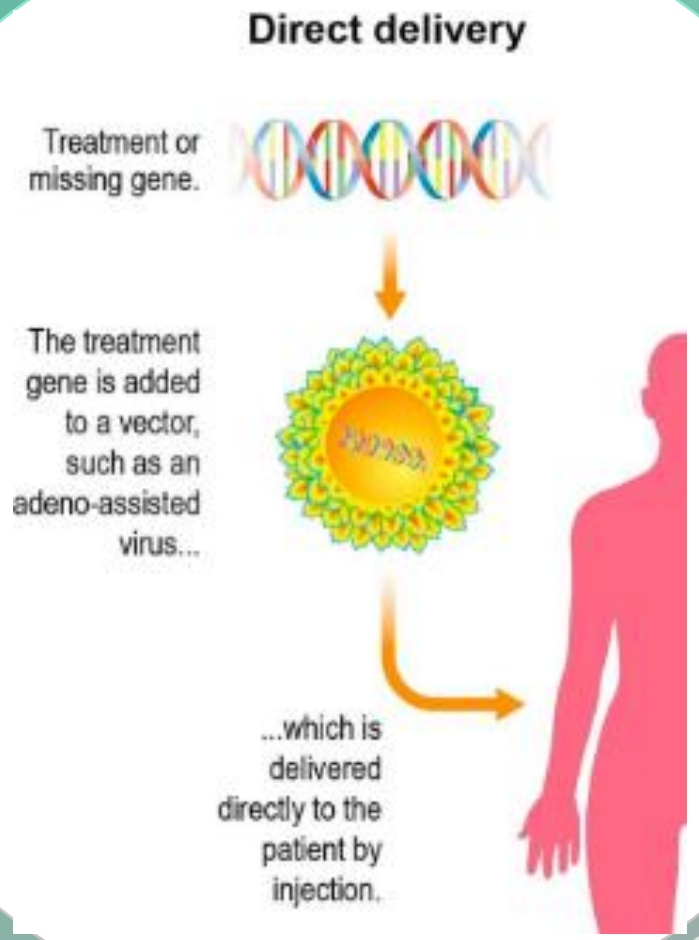
Overview

- Definitions
- Why now?
- Pipeline
- iMATCH

- Impact of ATMPs for Pharmacy
  - Governance
  - Management of toxicity
- Clinical Trials
- Licensed Products
- Summary

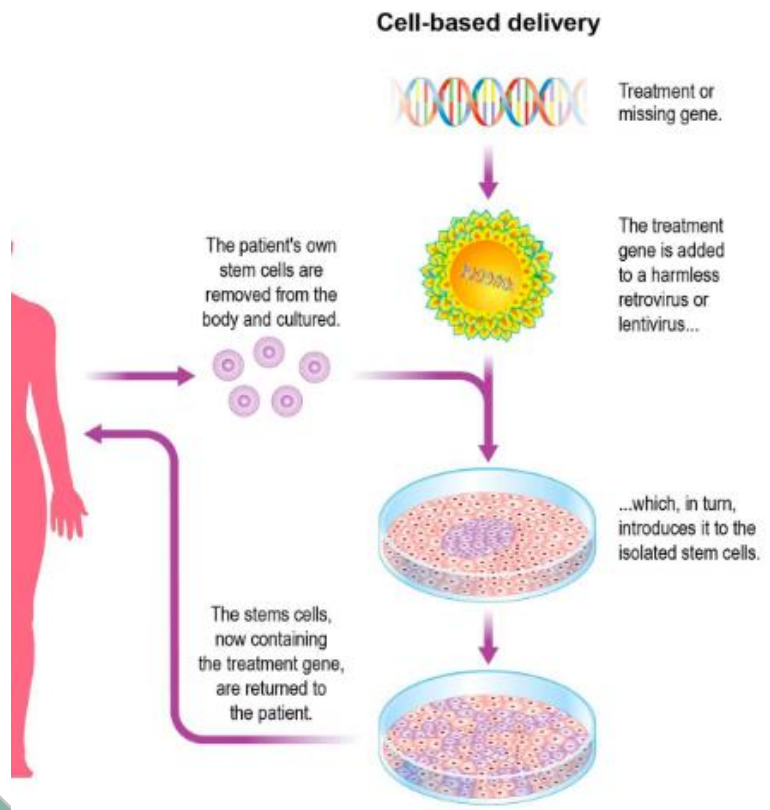
Advanced Therapy Medicinal Products (ATMPs) are one of three types of medicine

- Gene Therapy Medicines
- Somatic Cell Therapy Medicines
- Tissue Engineered Medicines



Gene Therapy Medicines:

- Contain genes that lead to a therapeutic, prophylactic or diagnostic effect.
- Work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases.
- A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.
- The vector used to carry the gene can be a virus which is made safe to use.



Tissue-engineered medicines:

Contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

Somatic-cell medicines:

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.

CAR T Cell Video Link

Why Now?

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FDA Approves Second CAR T-Cell Therapy for Lymphoma

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May 22, 2018, by NCI Staff

On May 1, the Food and Drug Administration (FDA) approved the CAR T-cell therapy tisagenlecleucel (Kymriah) for adults with certain types of non-Hodgkin lymphoma, making it the second CAR T-cell therapy approved for lymphoma and the second FDA approval for this drug.

Last year, FDA approved another CAR T-cell therapy, axicabtagene ciloleucel (Yescarta), for the treatment of diffuse large B-cell lymphoma (DLBCL). CAR T-cell therapy is a type of immunotherapy that involves a one-time infusion of a patient's own immune cells that have been

NHS England 70 YEARS OF THE NHS 1948 - 2018

News

NHS England announces groundbreaking new personalised therapy for children with cancer

5 September 2018

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First two CAR-T cell medicines recommended for approval in the European Union

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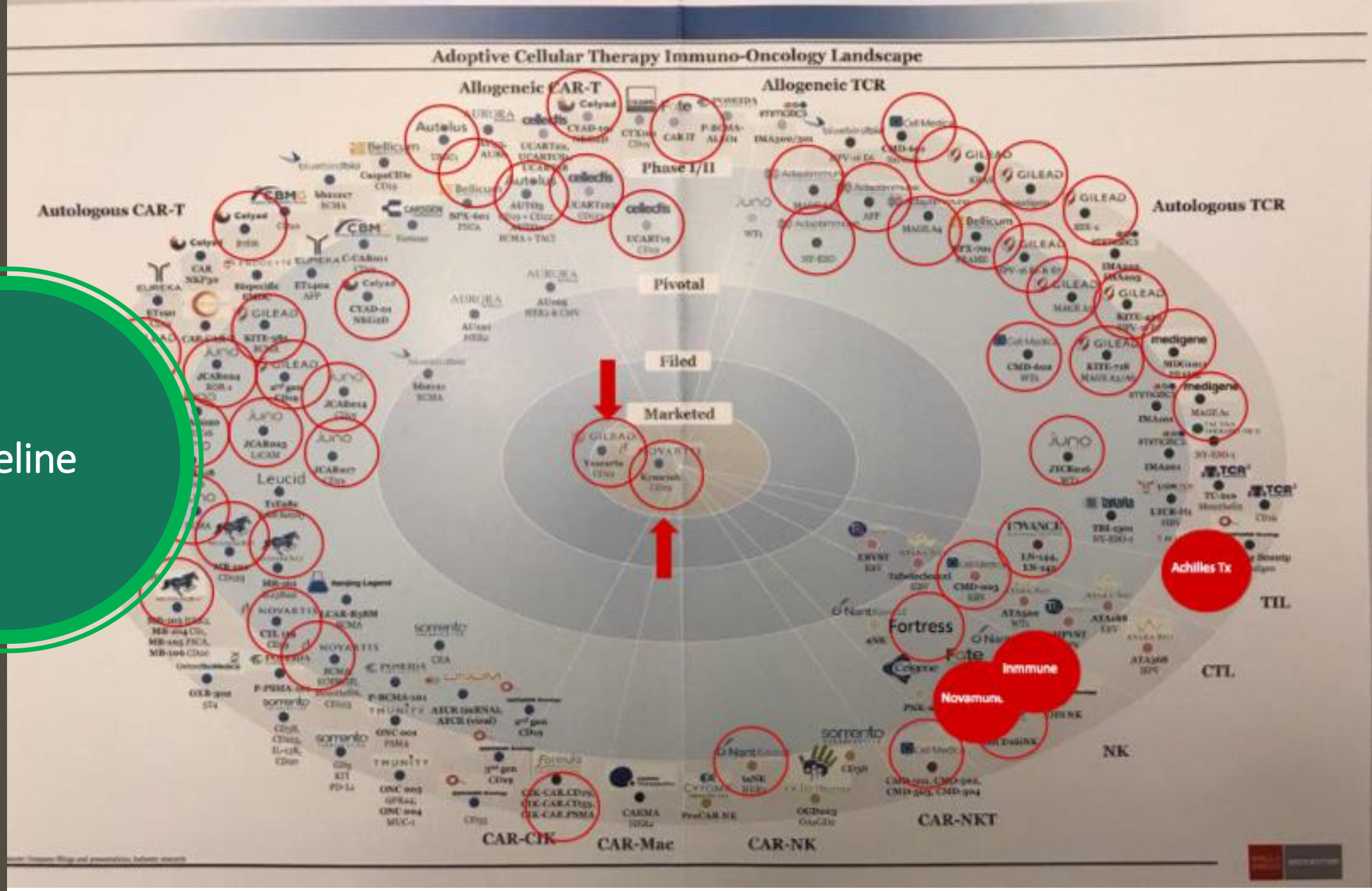
Press release 29/06/2018

Development of Kymriah and Yescarta supported through PRIME

The European Medicines Agency (EMA) has recommended the first two marketing authorisations for chimeric antigen receptors (CAR) T-cells medicines in the European Union (EU). Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) are advanced therapies for blood cancer. They belong to a new generation of personalised cancer immunotherapies that are based on collecting and modifying patients' own immune cells to treat their cancer

Pipeline


Adoptive Cellular Therapy Immuno-Oncology Landscape
Allogeneic CAR-T
Allogeneic TCR
Autologous CAR-T
Autologous TCR
Phase I/II
Pivotal
Filed
Marketed
Achilles Tx
Immune
Novamun.
Fortress
TIL
CTL
NK
CAR-NKT
CAR-CIK
CAR-Mac
CAR-NK

Indications of advanced therapy trials

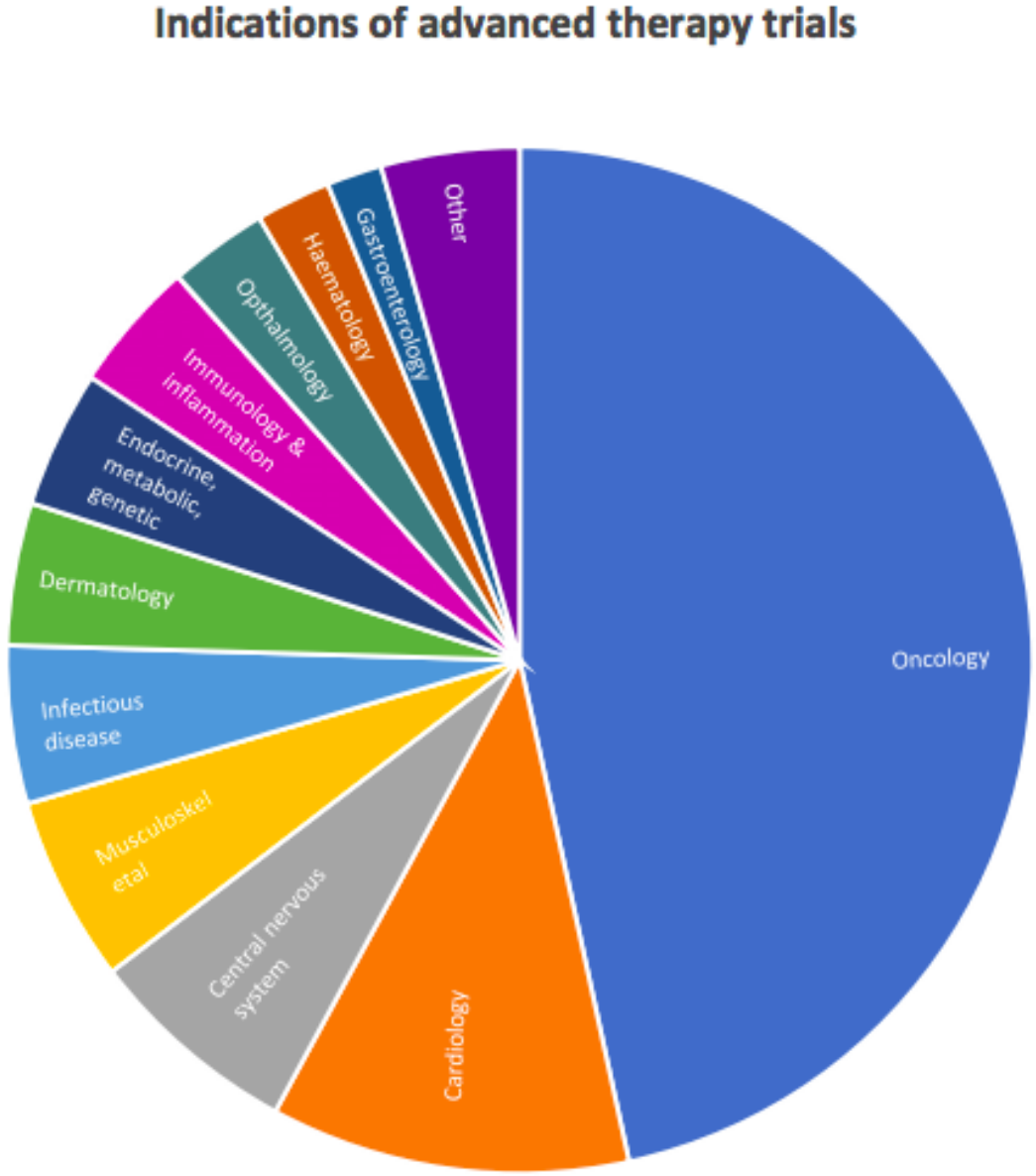


Figure 1: Disease indications of past and current clinical trials as of 31st December2016. Oncology CAR-T products dominate the field, with regenerative somatic cell therapies comprising a major fraction of trials. Source: Alliance for Regenerative Medicine Data Report 2016.

Pipeline continued

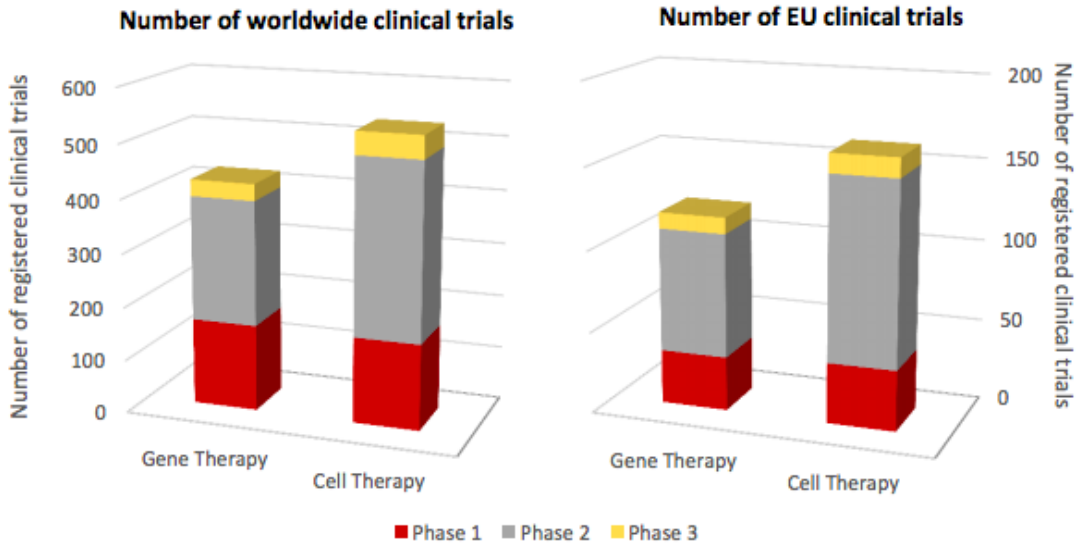
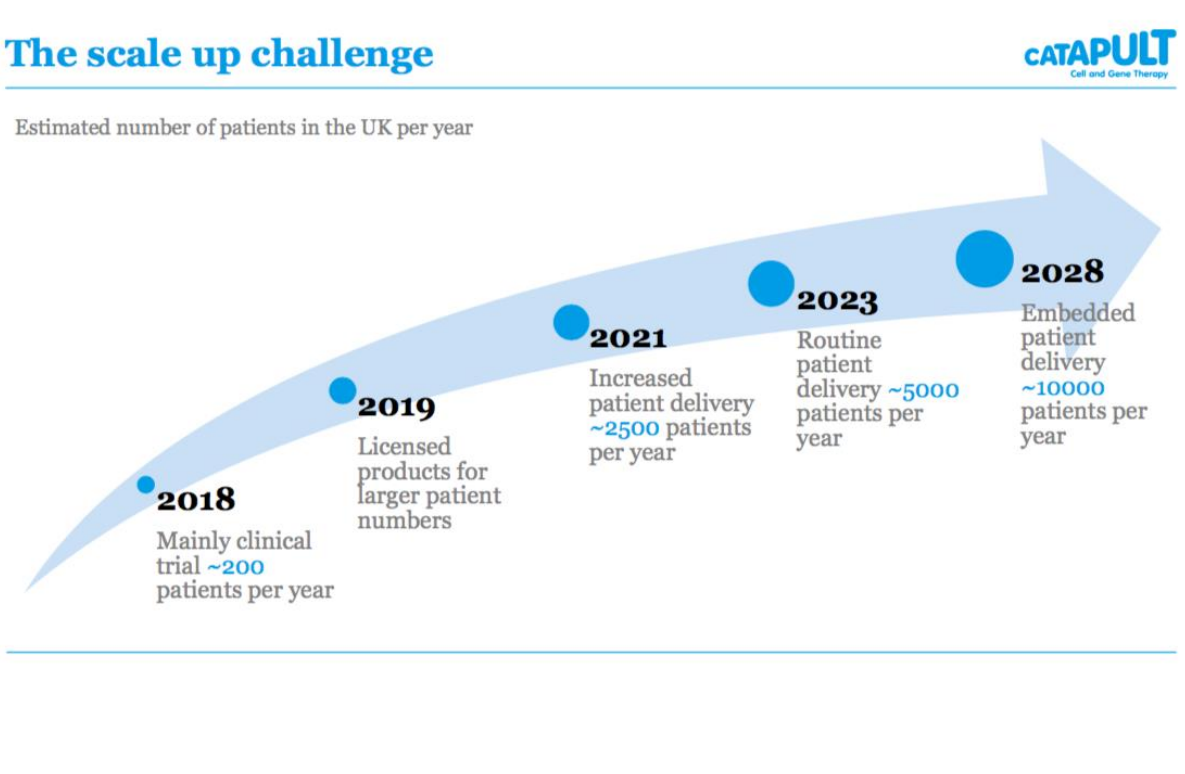


Figure 3: Number of advanced therapy clinical trials worldwide and within EU, stratified by phase. Ethical restrictions prevent advanced therapies from undergoing phase I testing in healthy volunteers. Because early-phase trial subjects are patients, most pilot trials include efficacy endpoints, and are thus categorised as phase I/II trials. The classification of pilot trials as phase II explains the relatively high number of phase II trials compared to phase I. Few advanced therapies have yet reached phase III. Source: Alliance for Regenerative Medicine Data Report 2016.



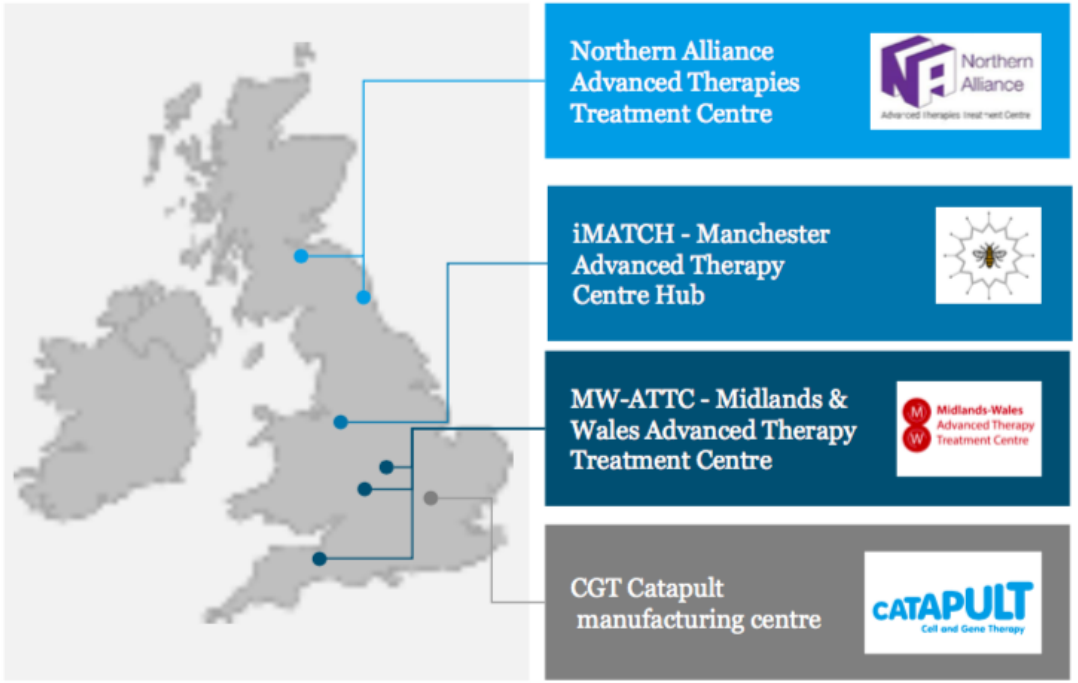
iMATCH

Innovative Manchester Advanced Therapies Centre Hub

September 2017
Innovate UK and Catapult launch a call for 3 advanced therapy treatment centres (ATTC)

Advanced Therapy Treatment Centres

CATAPULT Cell and Gene Therapy



The network of Advanced Therapy Treatment Centres will develop and deliver systems for the delivery of cutting edge cell and gene therapies.

- The network will increase the ability of the NHS to deliver disruptive medicines
- The centres will develop systems and processes within the trusts and hospitals capable of delivering advanced therapies at scale to patients across the NHS
- The learnings and systems from the initial centres will be rolled out to other centres in the UK

iMATCH - Pharmacy Deliverables

1

Governance Framework

2

Recruitment & Training

3

Electronic Prescribing of ATMPs

Pharmacy Governance

Human Tissue Authority

Pharmacy

CATAPULT Cell and Gene Therapy

Cells taken from patient	Manufacture	Supply chain	Arrival at hospital	Delivery to patient	Payment

NHS England

Clinical Sites
Integrated T&C procurement
Patient management
Trial management
Trained Clinical team
Pharmacy
Distributed manufacturing

Data Service
Scheduling
Tracking & Tracing
Data and information collection
Database & Registry development

Analytical Service
Lab and assay developments
Companion Diagnostics

Supply Chain
SC mapping and development
Interface with data service
Patient sample repositories

Practicalities

- Cell products are frozen to -160 degrees C
- Stored in Liquid Nitrogen tanks – in nitrogen vapour
- Temperature monitoring required throughout the whole process
- Managed by the Stem Cell Lab team – expertise in handling cells and ensuring correct supply to the ward for the correct patient.

Pharmacy Governance - Locally

Pharmacy delegate handling of CAR T Cells to the Stem Cell Lab

(SOP of delegated duty)

Pharmacy conducted initial lab visit and lab competed a self assessment

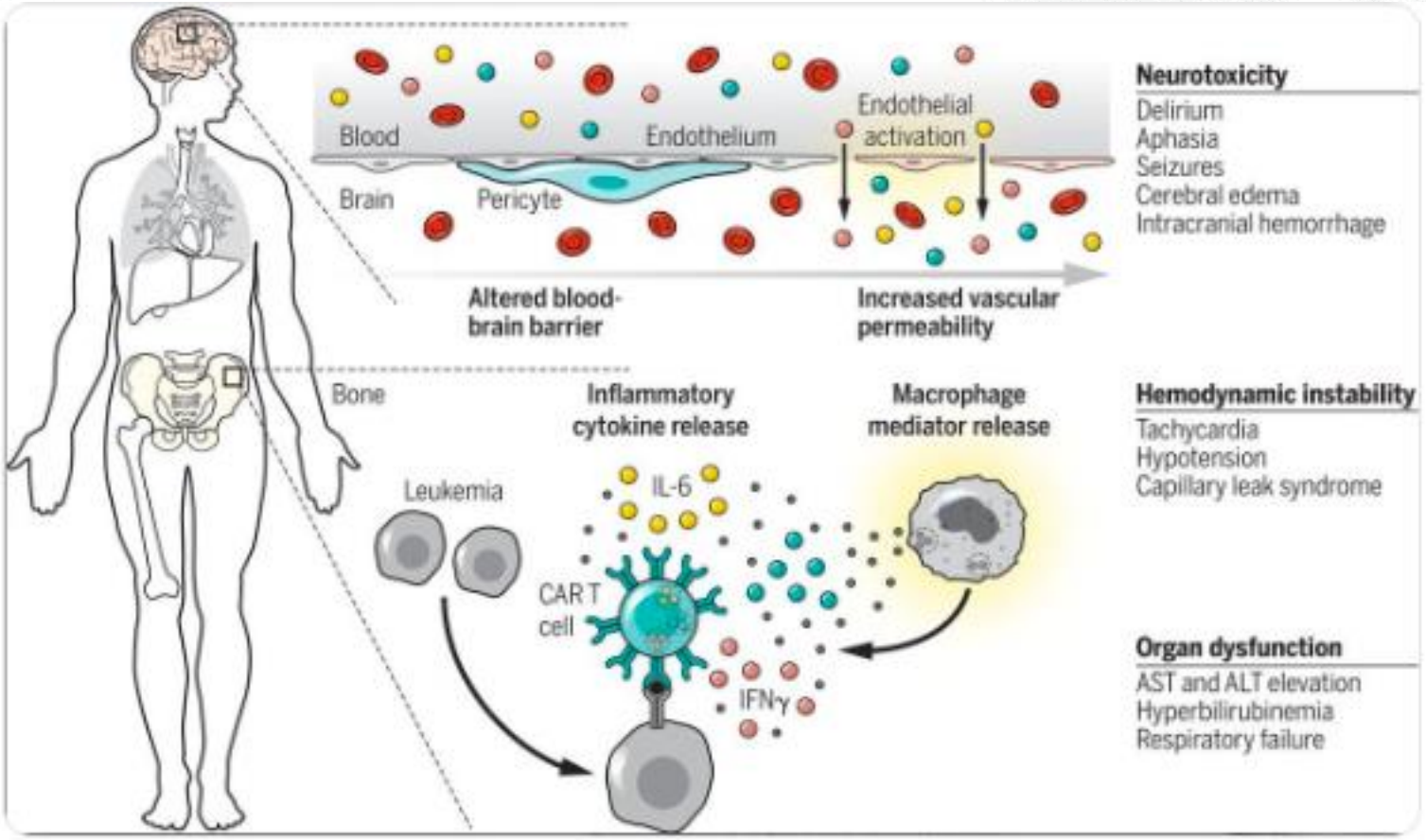
Pharmacy Stem Cell Lab Audit Plan in place

- Quarterly visits to monitor all CAR T Cell activity (trials and commissioned)
- Attendance of month combined transplant meeting for non-conformance/deviations to be discussed.
- Annual re-audit and spot check audit on 1 study

Practical Implications for Pharmacy

- Pre-conditioning Chemo
  - Cyclophosphamide and Fludarabine
  - Day -7 and -6
- Prescribing CAR T Cells
  - Range of cells can be prescribed
  - Units such as PFU or VP
  - On iQemo:
    - pharmacist screens,
    - Stem Cell Lab HTA DI releases
- Cytokine Release Syndrome and other toxicities

Toxicities from CAR T Cell Therapy



Tocilizumab – first line treatment for CRS

Tocilizumab

- Dose of 8mg/kg MAX 800mg in a single dose
- Up to 3 doses in one day, 8 hour intervals
- Maximum 4 doses allowed in total
- Given as a 1 hour infusion in 100 ml 0.9% sodium chloride
- Will be made at ward level, using aseptic technique
- Vials and accompanying worksheets to be stored in the emergency cupboard (fridge)

Doses used in clinical trials can from 4-8mg/kg, depending on the clinical trial – trial-specific worksheets will also be available.

Ward training required to ensure understanding of different doses within a clinical trial setting

Open CAR-T Clinical Trials – CALM Study

Phase I, open label, dose-escalation study to evaluate the safety, expansion and persistence of a single dose of UCART19 (allogeneic engineered T-cells expressing anti-CD19 chimeric antigen receptor), administered intravenously in patients with relapsed or refractory CD19 positive B-cell acute lymphoblastic leukaemia (B-ALL) CALM study (UCART19 in Advanced Lymphoid Malignancies)

Treatment:

Fludarabine 30mg/m^2 IV infusion for 3 days over 15/30 minutes from D-7 to D-5.
Cyclophosphamide 500mg/m^2 IV infusion over 1 hour for 3 days from D-4 to D-2
Alemtuzumab IV 8mg /day for 5 days from D-7 to D-3.

UCART19 cells Day 0

UCART19 dose level	UCART19 dose expressed in number of cells (number of vials)	
	Patient weight < 66 kg	Patient weight ≥ 66 kg
DL-1	$6x10^5$ cells (1)*	
DL1	$6x10^6$ cells (1)*	
DL2	$6x10^7$ cells (3)	$8x10^7$ cells (4)
DL3	$1.8x10^8$ cells (9)	$2.4x10^8$ cells (12)

Open CAR-T Clinical Trials – AUTO-2 Study

A single arm, open label, multicentre, phase I/II study evaluating the safety and clinical activity of AUTO2, a CAR T cell treatment targeting BCMA and TACI in patients with relapsed or refractory multiple myeloma

Treatment:
Fludarabine 30mg/m2 IV infusion in 100ml 0.9% sodium chloride over 30 minutes
Cyclophosphamide 300mg/m2 IV infusion in 100ml 0.9% sodium chloride over 30 minutes
On days -6, -5, -4

AUTO-1 cells Day 0

Cohort number	Cell dose
1 (Dose level 1)	15×10^6 RQR8/APRIL CAR positive T cells
2 (Dose level 2)	75×10^6 RQR8/APRIL CAR positive T cells
3 (Dose level 3)	225×10^6 RQR8/APRIL CAR positive T cells
4 (Dose level 4)	600×10^6 RQR8/APRIL CAR positive T cells
5 (Dose level 5)	$900\text{-}1200 \times 10^6$ RQR8/APRIL CAR positive T cells

Approved Products - Kymriah

NOVARTIS:

Kymriah® (tisagenlecleucel)

Approved indications are for the treatment of:

- paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse;
- adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Licensed Products – Yescarta

Kite (Gilead):

Yescarta™ (Axicabtagene Ciloleucel)

Approved indications are for the treatment of:

- adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified,
- primary mediastinal large B-cell lymphoma (PMBCL),
- high-grade B-cell lymphoma,
- DLBCL arising from follicular lymphoma (transformed follicular lymphoma, or TFL).

Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

When do we start?

- Accreditation by JACIE
- Selection by NHS England as a commissioned centre.
  - Payment process still TBC
- Approval from Novartis and Gilead as a site.
  - Site evaluation and training
- Local readiness of all affected departments (including private patients).

Summary

- ATMPs are medicinal products
- Cell therapy products are personalized, high-risk medicines which Pharmacy must have oversight and the overall responsibility rests with the Chief pharmacist.
- Toxicity from cell therapy products is likely – need to understand how to treat and support.
- Each treatment is different.