Pharmacy Teaching Session Slides (All ATMPs)

Organisation: iMATCH, Manchester University NHS Foundation Trust

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Advanced Therapy Medicinal Products (ATMPs)

Pharmacy Teaching Session
January 2019

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Manchester University
NHS Foundation Trust

Overview

- Definitions
- Examples
- iMATCH A coordinated strategy to scale-up advanced therapies for patients in Manchester
- Impact of ATMPs for Pharmacy
- Clinical Trials
- Licensed Products
- Summary

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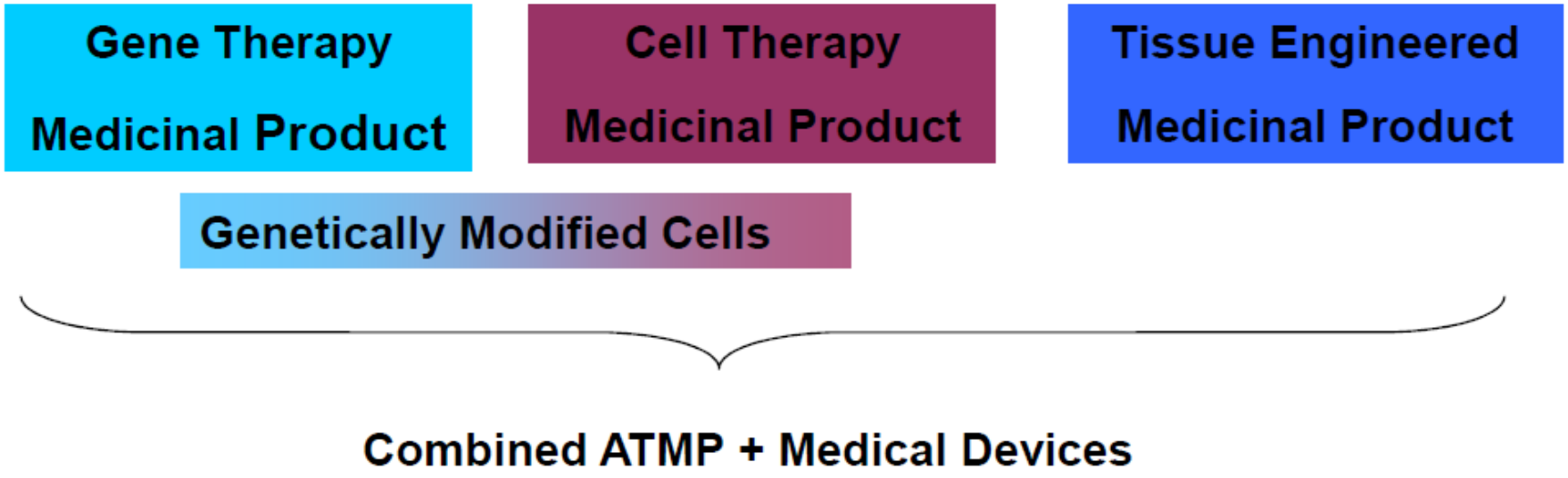
What are ATMPs?



Gene Therapy

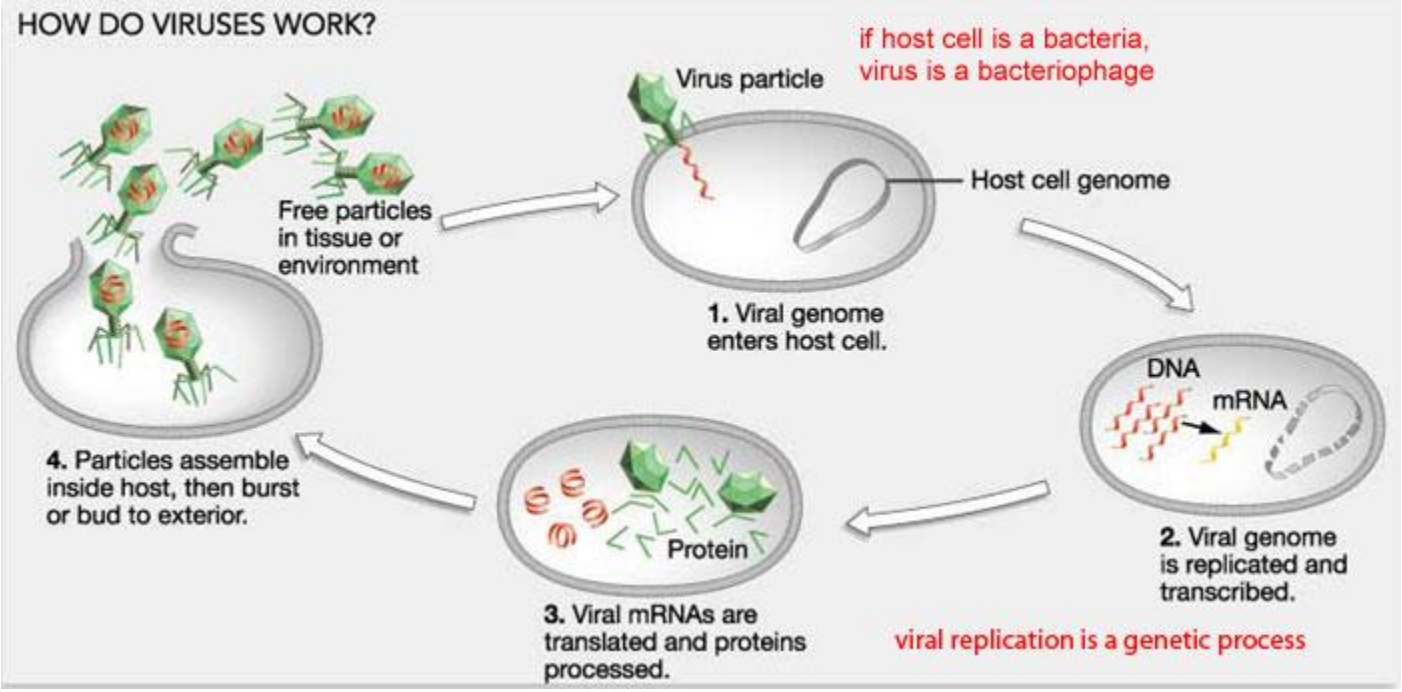
GTMP means a biological medicinal product which has the following characteristics:

- It contains an active substance which contains or consists of a recombinant nucleic acid used in, or administered to human beings, with a view to **regulating, repairing, replacing, adding or deleting a genetic sequence**;

- Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Examples - Genetically Modified Viruses

Viral Replication



Examples – Viral Vectors

		Adenovirus	Adeno-associated virus	Alphavirus	Herpesvirus	Retrovirus / Lentivirus	Vaccinia virus
Particle characteristics	Genome	dsDNA	ssDNA	ssRNA (+)	dsDNA	ssRNA (+)	dsDNA
	Capsid	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Complex
	Coat	Naked	Naked	Enveloped	Enveloped	Enveloped	Enveloped
	Virion polymerase	Negative	Negative	Negative	Negative	Positive	Positive
	Virion diameter	70 - 90 nm	18 - 26 nm	60 - 70 nm	150 - 200nm	80 - 130 nm	170 - 200 X 300 - 450nm
	Genome size	39 - 38 kb	5 kb	12 kb	120 - 200 kb	3 - 9 kb	130 - 280 kb
							
	Family	*Adenoviridae*	*Parvoviridae*	*Togaviridae*	*Herpesviridae*	*Retroviridae*	*Poxviridae*
Gene Therapy Properties	Infection / tropism	Dividing and non-diving cells	Dividing and non-diving cells	Dividing and non-diving cells	Dividing and non-diving cells	Dividing cells*	Dividing and non-diving cells
	Host genome interaction	Non-integrating	Non-integrating*	Non-integrating	Non-integrating	Integrating	Non-integrating
	Transgene expression	Transient	Potential long lasting	Transient	Potential long lasting	Long lasting	Transient
	Packaging capacity	7.5 kb	4.5 kb	7.5 kb	> 30 kb	8 kb	25 kb

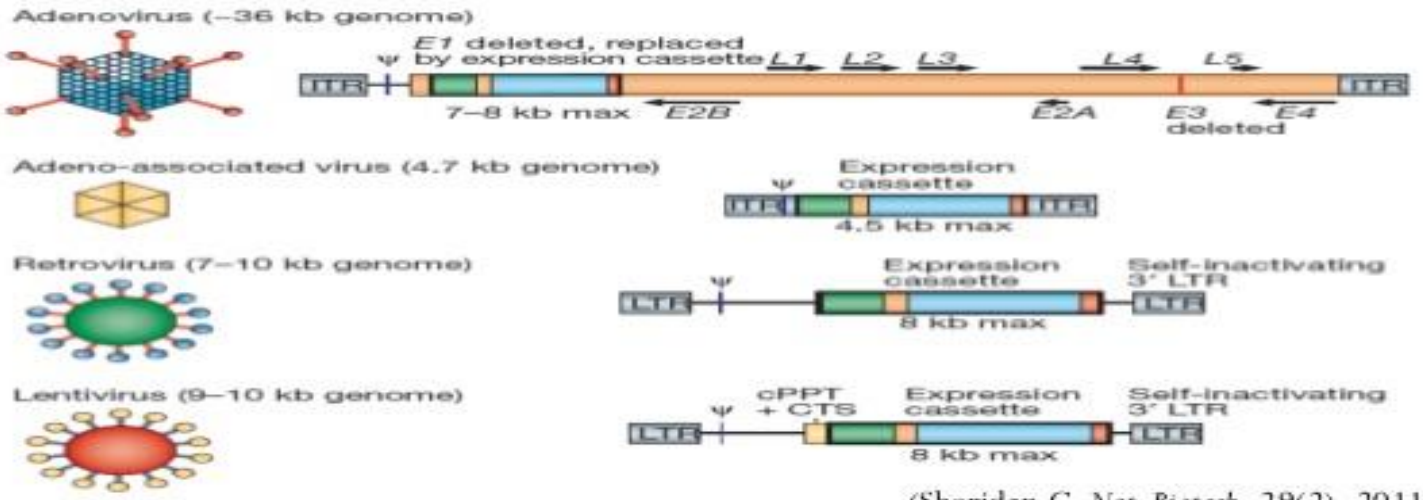
Examples – Viral Vectors

Vector for gene delivery

- **Viral delivery system:**

  retrovirus, adenovirus, adeno-associated virus,

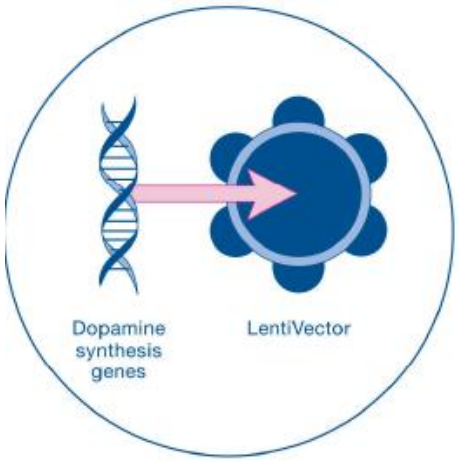
  vaccinia virus, Herpes simplex virus



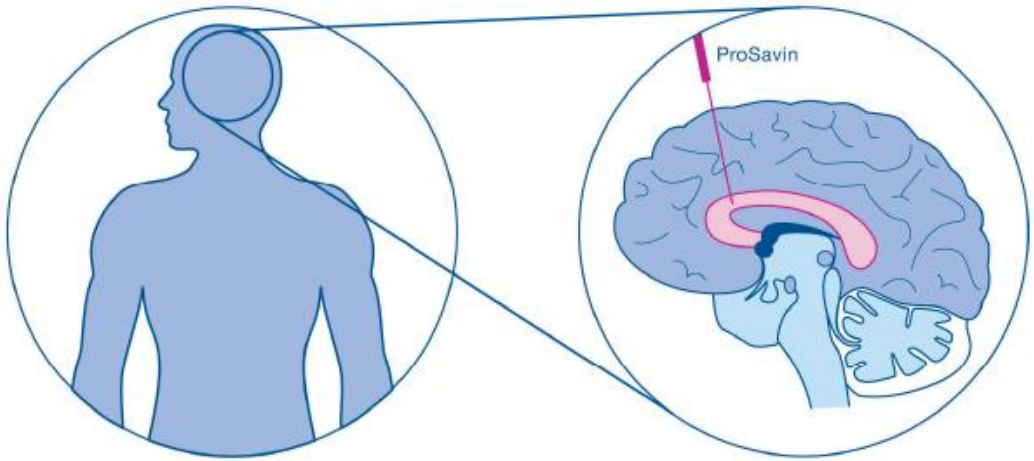
(Sheridan C. *Nat. Biotech.* 29(2), 2011)

Examples

- **Genetically modified viruses** e.g. adenovirus, herpes simplex, lentivirus



ProSavin



ProSavin administered to striatum

https://www.youtube.com/watch?v=8QuwC16G3m0

Examples - Oncolytic Viruses

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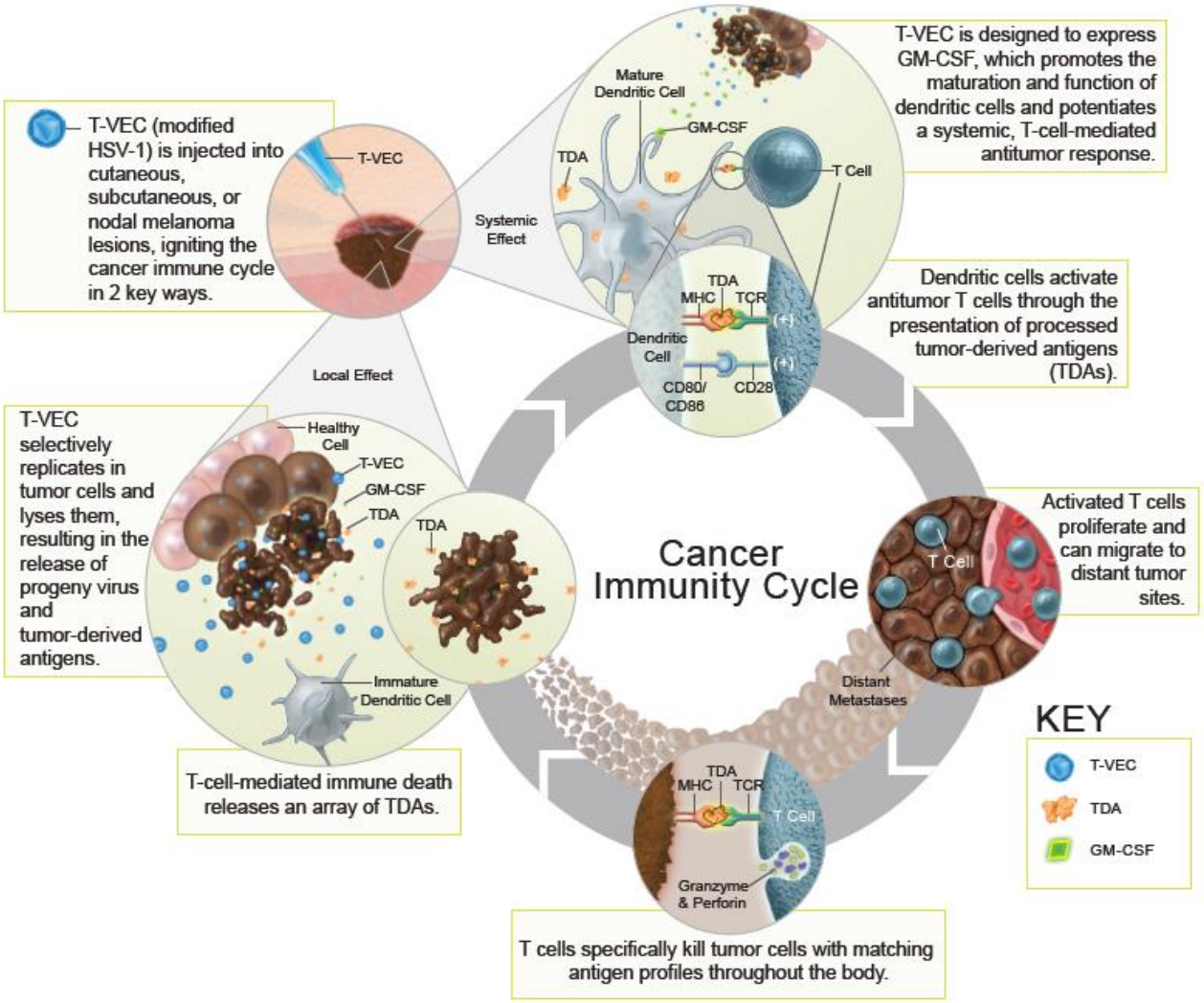

HSV: herpes simplex virus type-1

Examples - Genetically modified cells

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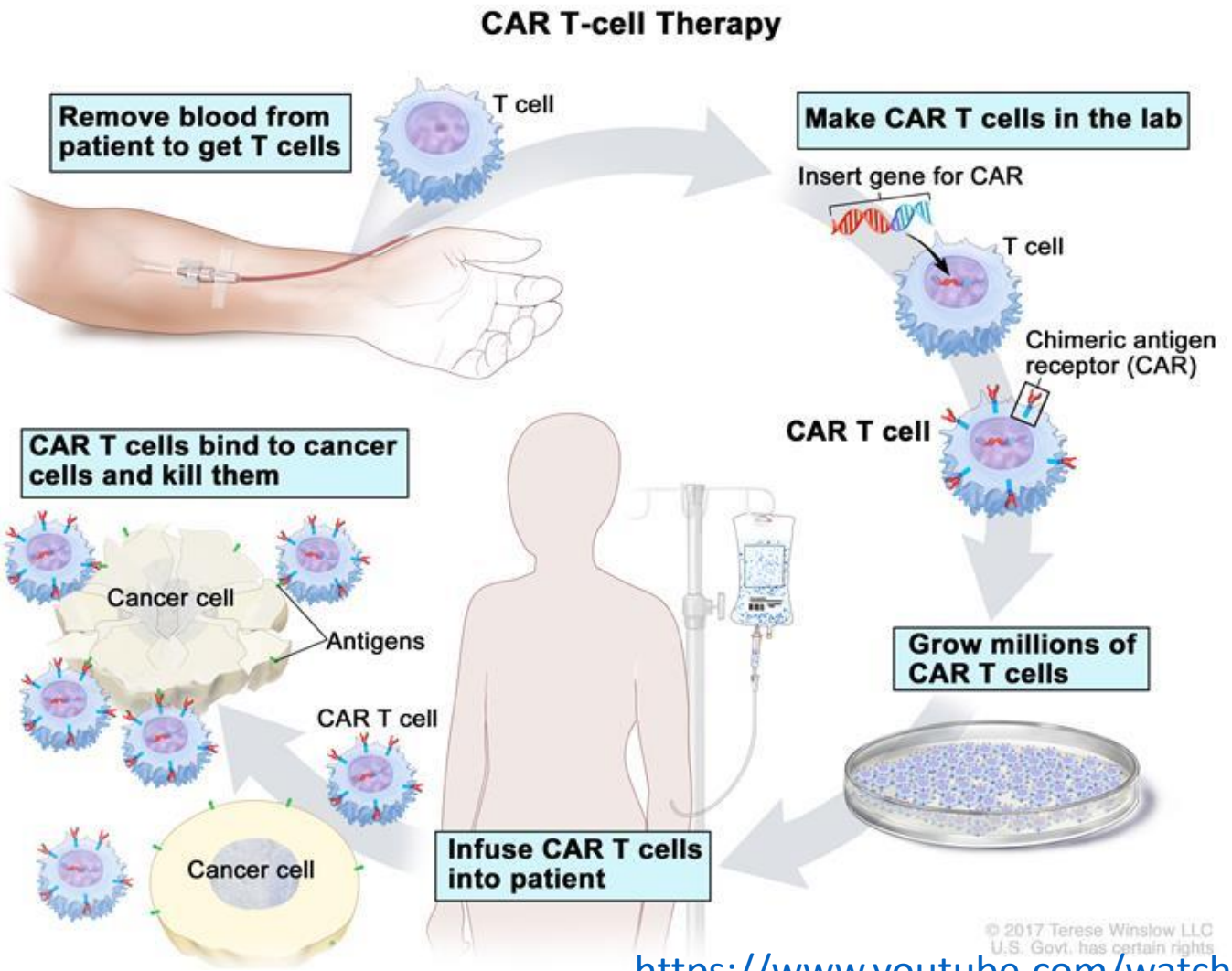


https://www.youtube.com/watch?v=mXADrg_ckhI

Somatic Cell Therapy

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

• contains or consists of cells or tissues that have been subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are **not intended to be used for the same essential function(s)** in the recipient and the donor;

• is presented as having properties for, or is used in or administered to human beings, with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

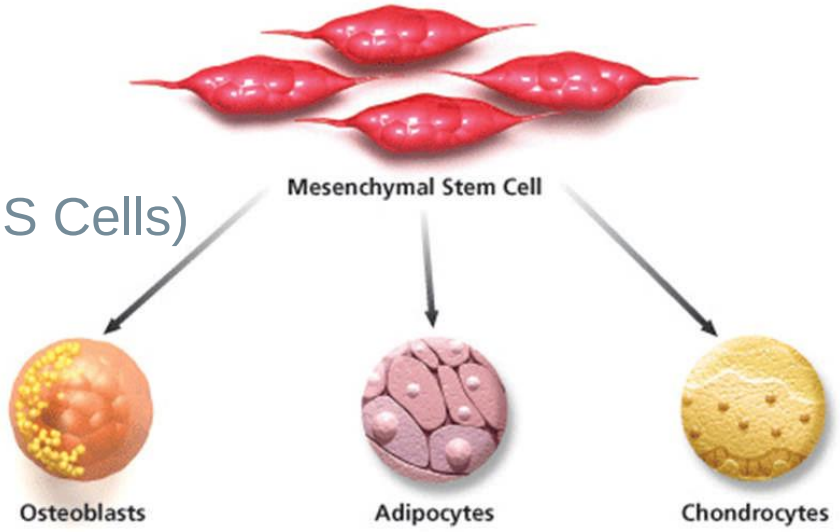
Examples

- Adult Cells **autologous or allogenic** cells
  - **– adult stem cells** (multipotent)
    (ChondroCelect, cartilage repair)
  - **– differentiated cells**
    (dendritic cells, cancer immunotherapy)

- **Embryonic stem cells** (pluripotent)
  (blindness, spinal injury)

- **Induced pluripotent stem cells** (iPS Cells)

- **Xenogenic Cells**



https://www.bbc.co.uk/news/av/health-36450628/stem-cells-used-in-stroke-treatment

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Tissue Engineered Products

• Tissue engineered product means a product that:
– contains or consists of **engineered cells or tissues**, and
– is presented as having properties for, or is used in or administered to human beings with a view to **regenerating, repairing or replacing** a human tissue.

A TEP may contain:
– cells or tissues of **human or animal** origin, or both
– the cells or tissues may be **viable or non-viable**
– additional substances i.e. **scaffolds or matrices**

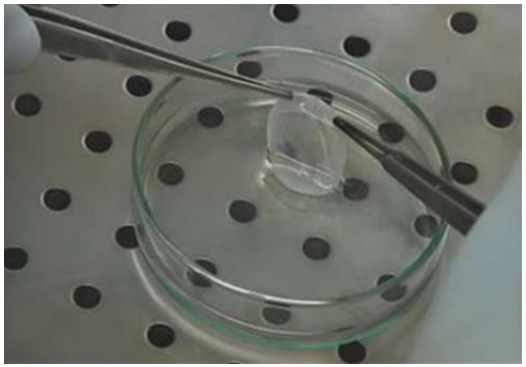
Examples

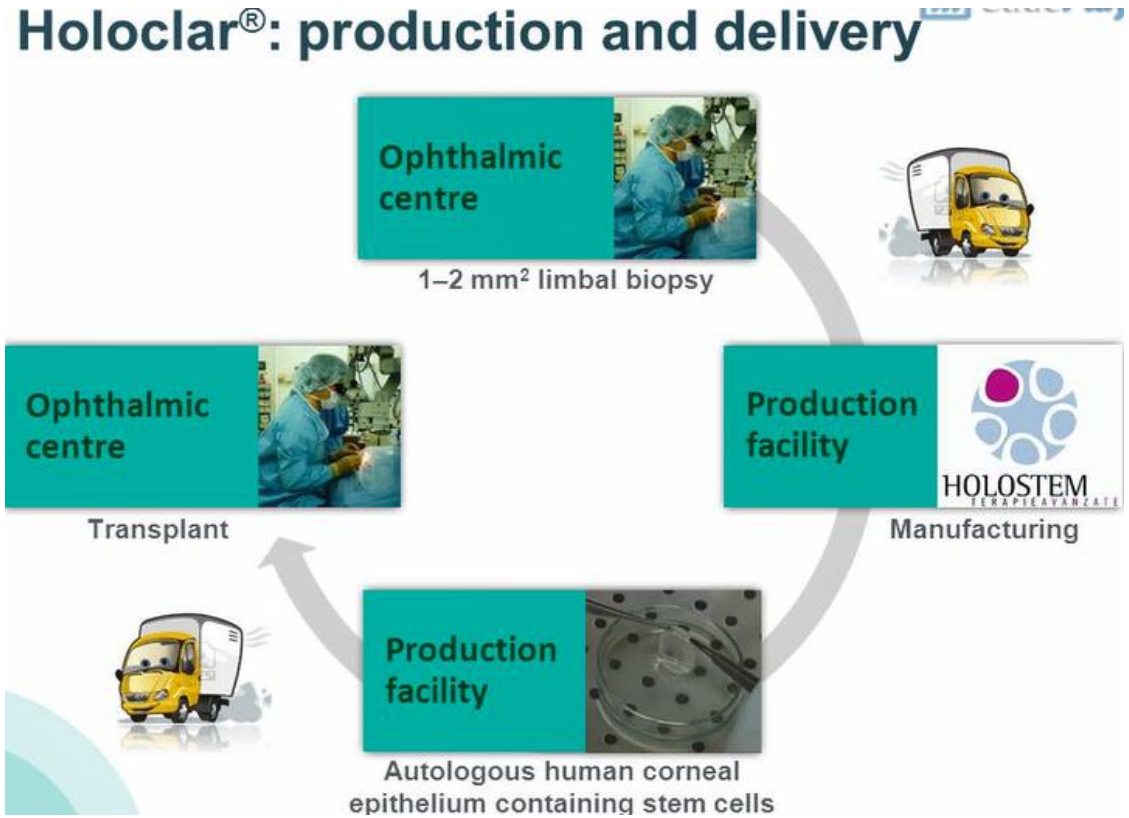
- **In vitro Cultured Skin** repair for burns or chronic wounds
- **Neo-organs** (corneal, blood vessel, liver, cartilage or bone tissue)
- **Tissue Engineered Trachea**

Examples

Holoclar first EMA-approved therapy for limbal stem cell deficiency due to ocular burns
Uses autologous stem cells
4 UK centres

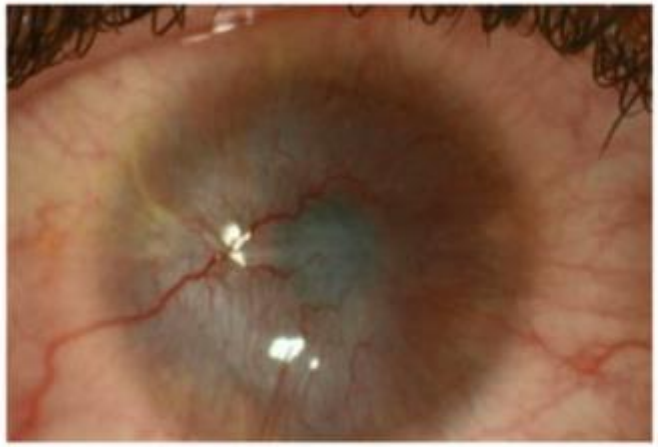
HOLOCLAR





Examples

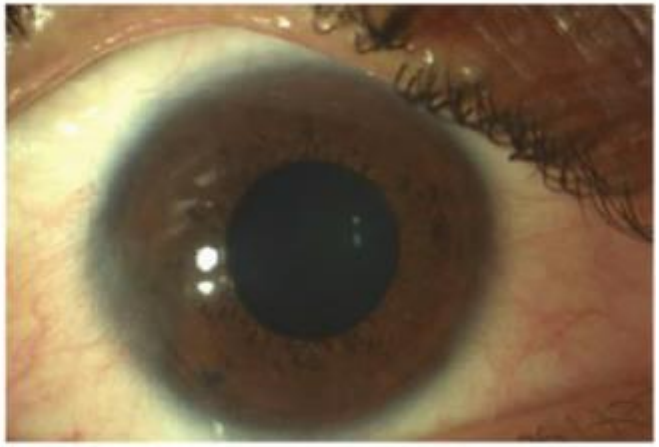
Before Holoclar®



Pre-surgery:

- Chemical burn, 3years from the accident
- No previous surgery
- Neovascularization in 4 quadrants with central corneal involvement

After Holoclar®



1 year post Holoclar implant:

- Avascular corneal surface with regular and stable epithelium
- Best Corrected Visual Acuity: 0.9

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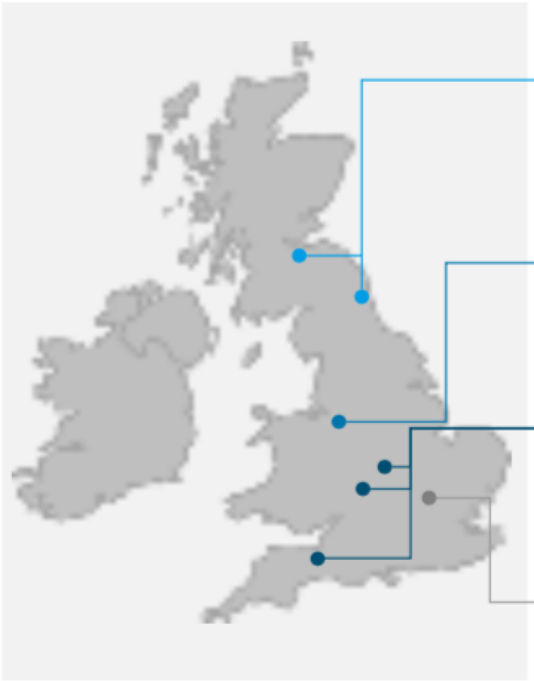
Innovate Manchester Advanced Therapy Centre Hub

Advanced Therapy Treatment Centres

CATAPULT Cell and Gene Therapy



Northern Alliance Advanced Therapies Treatment Centre

iMATCH - Manchester Advanced Therapy Centre Hub

MW-ATTC - Midlands & Wales Advanced Therapy Treatment Centre

CGT Catapult manufacturing centre

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

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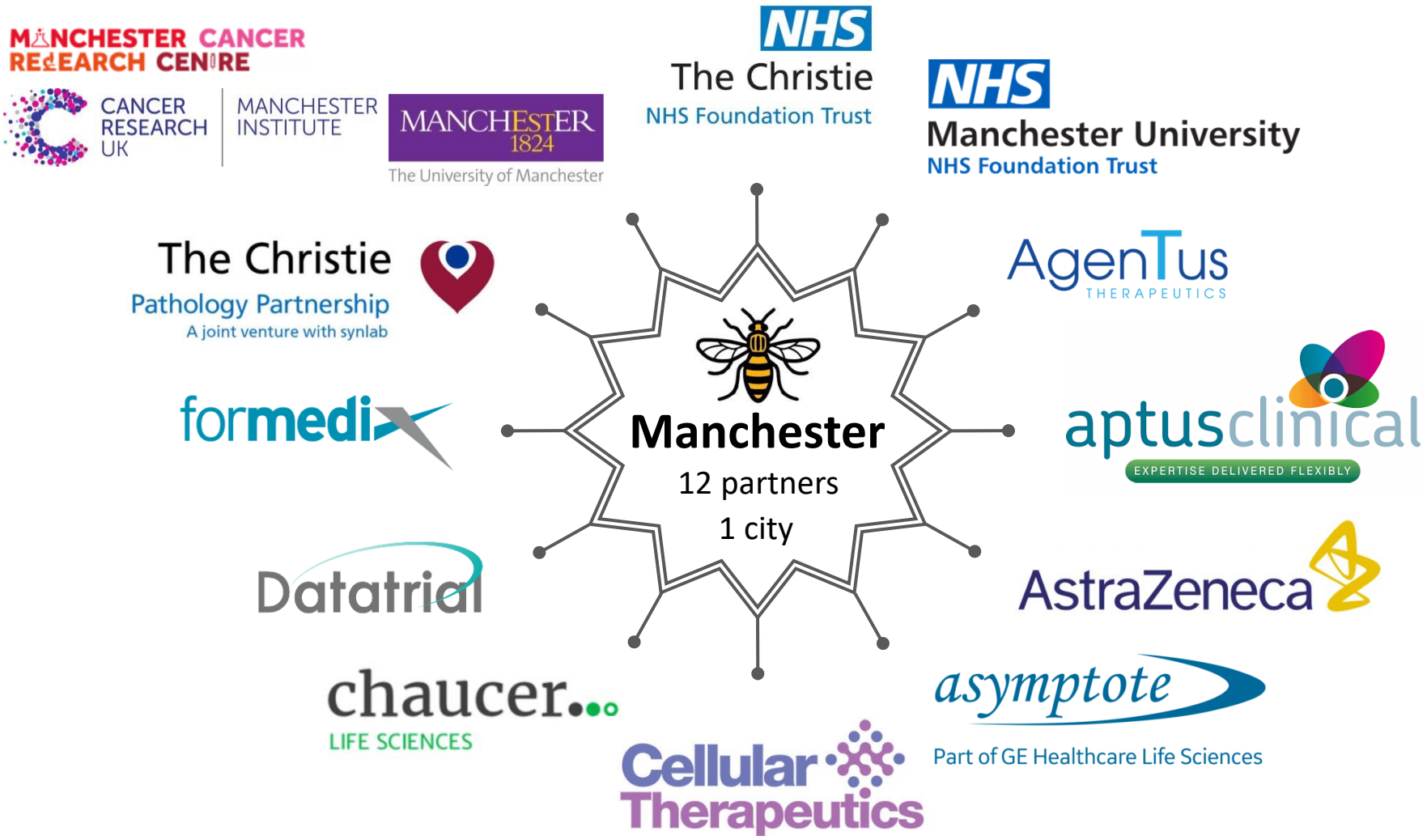
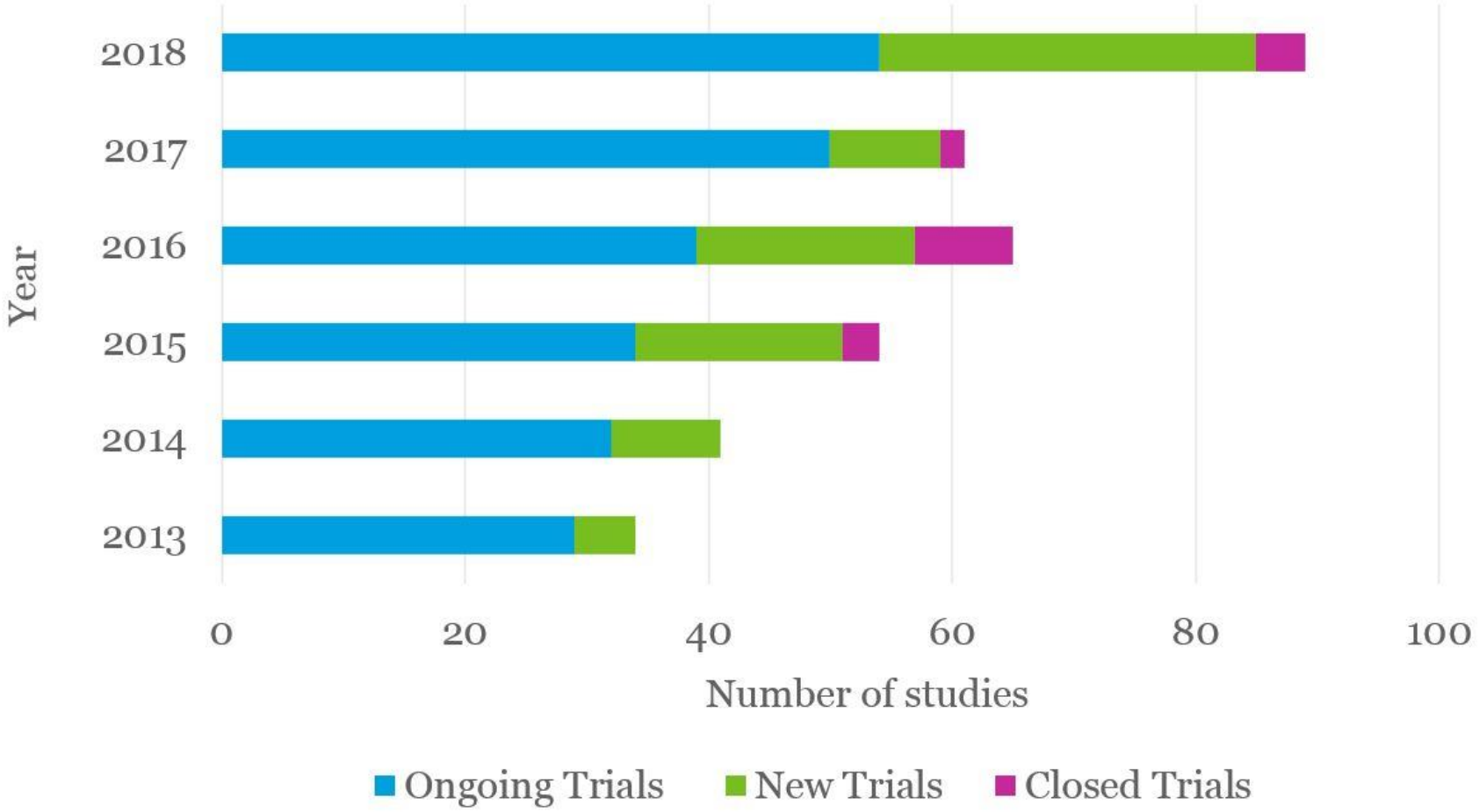
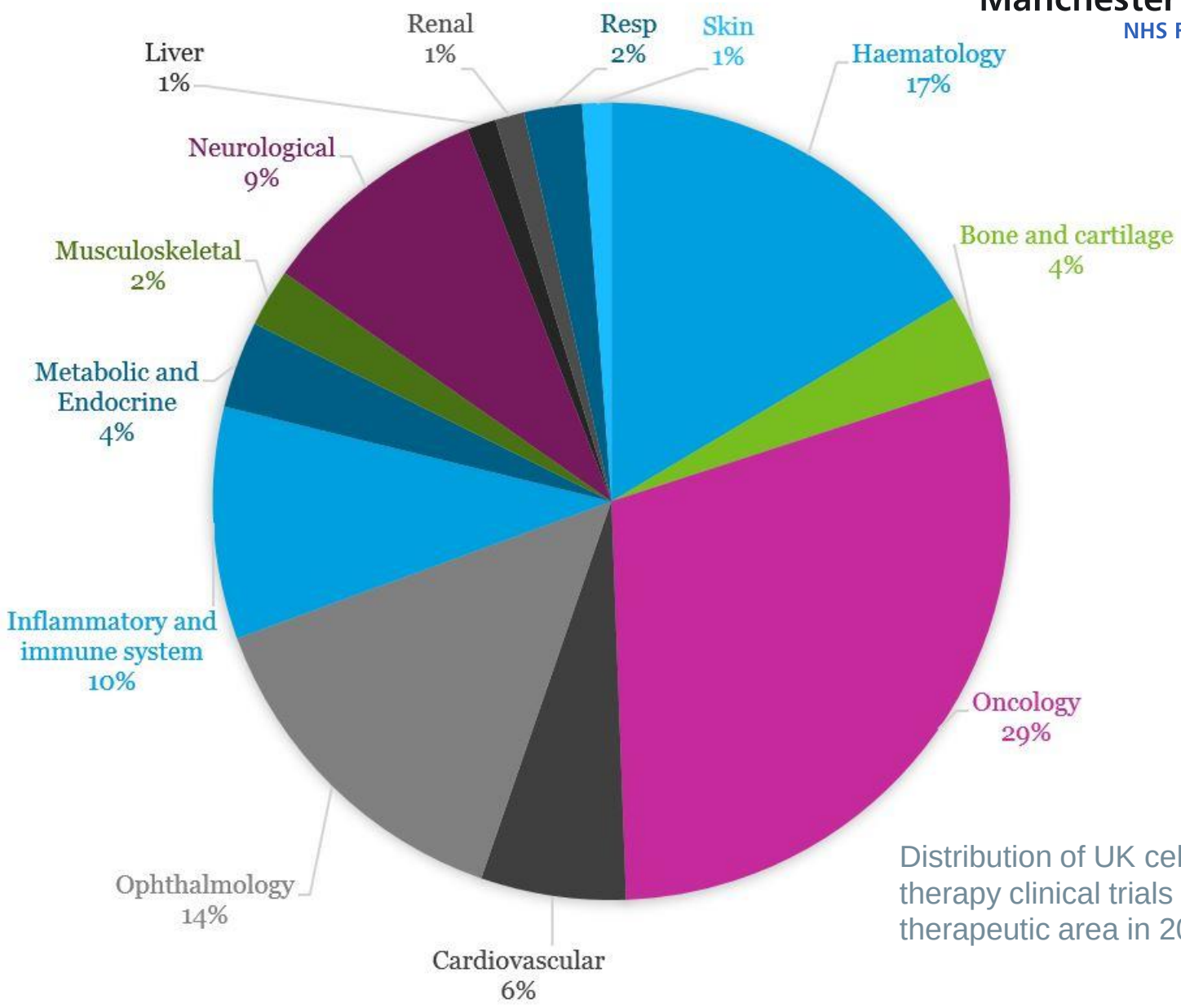
Innovate Manchester Advanced Therapy Centre Hub -

Original partners 2018



The 2018 clinical trials database shows that there are 85 cell and gene therapy clinical trials ongoing in the UK.





Distribution of UK cell and gene therapy clinical trials according to therapeutic area in 2018.

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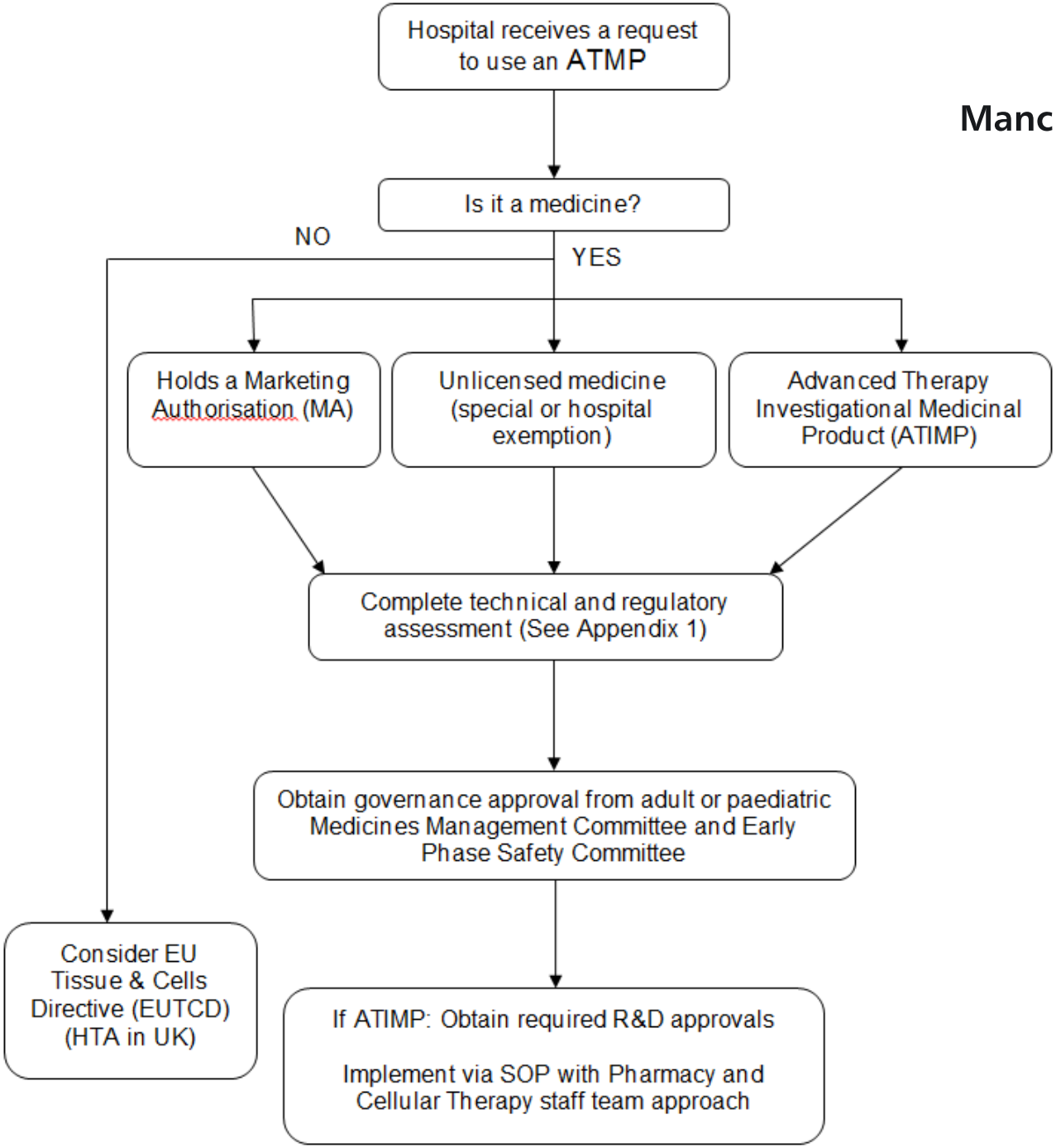
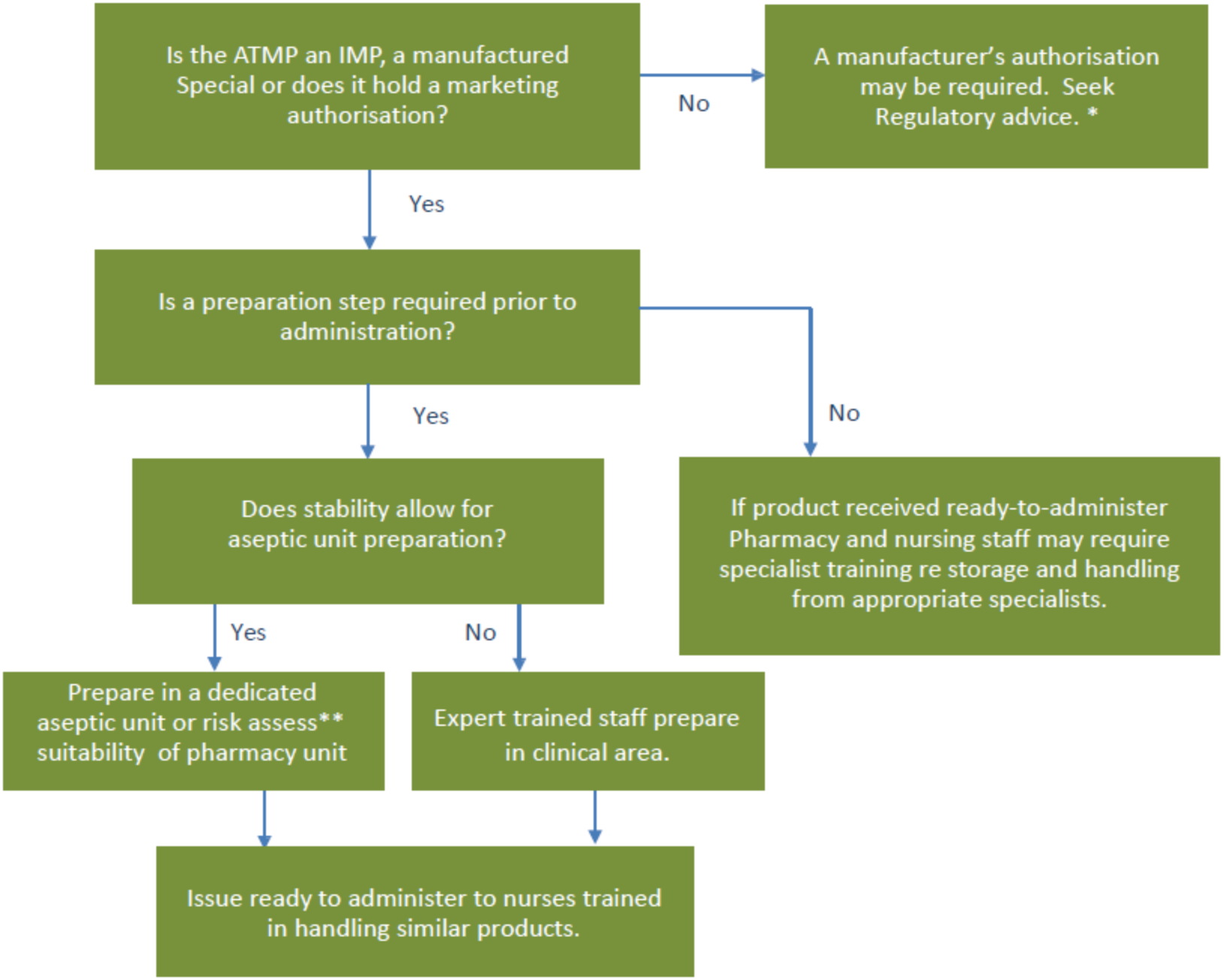
Impact on Pharmacy

Governance

- Prescribed
- Prepared
- Administered
- Monitored
- ATMP Policy
- ATMP Assurance Group (MO)
- SOPs
- Audit
- Inspection
- Accreditation- JACIE
- GCP compliance
- Staff training
- Expert panel (Biological Safety Officer) approval


Hospital receives a request to use an ATMP
Is it a medicine?
NO
YES
Holds a Marketing Authorisation (MA)
Unlicensed medicine (special or hospital exemption)
Advanced Therapy Investigational Medicinal Product (ATIMP)
Complete technical and regulatory assessment (See Appendix 1)
Obtain governance approval from adult or paediatric Medicines Management Committee and Early Phase Safety Committee
Consider EU Tissue & Cells Directive (EUTCD) (HTA in UK)
If ATIMP: Obtain required R&D approvals
Implement via SOP with Pharmacy and Cellular Therapy staff team approach


Is the ATMP an IMP, a manufactured Special or does it hold a marketing authorisation?
No
A manufacturer's authorisation may be required. Seek Regulatory advice. *
Yes
Is a preparation step required prior to administration?
No
Yes
If product received ready-to-administer Pharmacy and nursing staff may require specialist training re storage and handling from appropriate specialists.
Does stability allow for aseptic unit preparation?
Yes
No
Prepare in a dedicated aseptic unit or risk assess** suitability of pharmacy unit
Expert trained staff prepare in clinical area.
Issue ready to administer to nurses trained in handling similar products.

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Impact on Pharmacy - Regulation

Directive 2001/20/EC **"Clinical Trials Directive"** on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use	**SI 2004 No.1031** **The Medicines for Human Use (Clinical Trials) Regulations 2004**
Directive 2005/28/EC **"GCP Directive"** laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products	**SI 2006 No.1928** **The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006**
ATMP Regulation 1394/2007 On Advanced Therapy Medicinal Products and amending Directive 2001/83/EC and Regulation 726/2004	**SI 2010 No.1882** **The Medicines for Human Use (ATMP and Miscellaneous Amendments) Regulations 2010**
EU Tissues and Cell Directives: **Directive 2004/23/EC** Framework for a harmonised approach to the regulation of tissues and cells Standards for activities involving tissues & cells for human application **Directives 2006/86/EC & 2006/17/EC** Technical Directives with detailed requirements for safety reporting / traceability / coding / processing / preservation / storage / distribution	**SI 2007 No.1523** **The Human Tissue (Quality and Safety for Human Application) Regulations 2007**
Directive 2009/41/EC on the contained use of genetically modified micro-organisms (Recast) Directive 90/219/EC (as amended by Directive 98/81/EC) now consolidated	**SI 2000 No.2831** **GMO (Contained Use) Regulation 2000** as amended
Directive 2007/47/EC amending Council Directive 90/385/EEC relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market	**SI 2012 No.1426** **The medical Devices (Amendment) Regulation 2012**

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Impact on Pharmacy

Regulation

- MHRA, HTA, HRA, GTAC, HSE, DEFRA, HFEA
- Clear traceability from manufacture to recipient, anonymised
- Contracts with clear responsibilities between manufacturer/tissue establishment/institution
- Records to be kept for 30 years
- Informed consent, PIS
- Patient alert card
- HSE Notification

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Impact on Pharmacy

Handling requirements

- Cryo-preserved
- Shelf-life
- Biosafety class/containment level, HSE/SACGM requirements
- Spillages
- Decontamination/inactivation
- Waste management – Appendix 6 Trust Policy
- PPE
- Transportation
- Shedding
- Temperature monitoring

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Impact on Pharmacy

Toxicity/Pharmacovigilance

- Cytokine Release Syndrome
- Safety reporting
- Long term follow up / unknown risks

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Licensed Products – CAR T

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.

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Licensed Products – CAR T

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.

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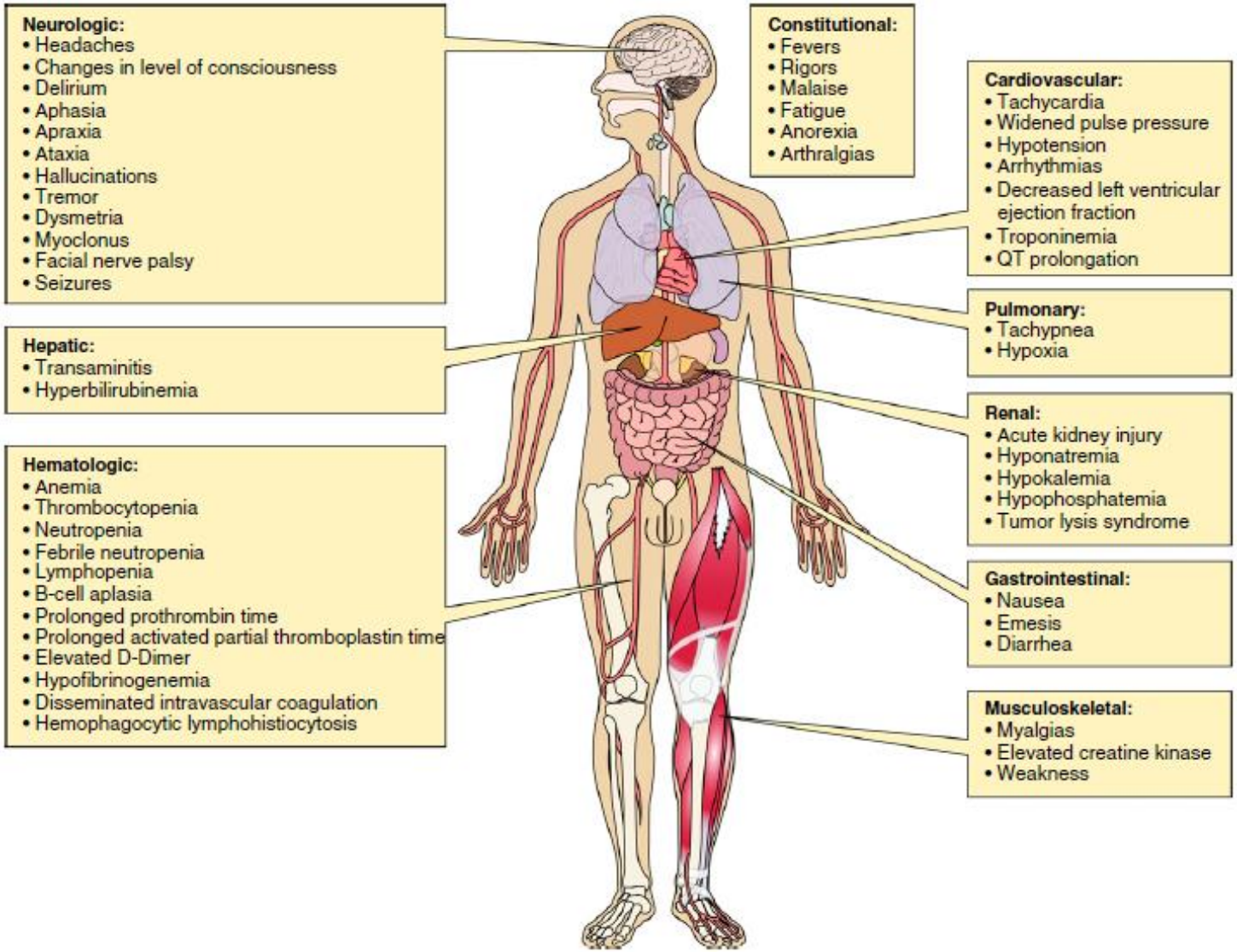
Toxicities from CAR-T Cell Therapy



Tocilizumab

- Monoclonal antibody against IL6 receptor.
- 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

Summary

- ATMPs are innovative and potentially life-changing treatments

- ATMPs **are** medicines
  - Subject to the same requirements as for other medicinal products
  -Chief Pharmacist responsible for governance and management
    Even if not actually handled in Pharmacy

- Toxicity from cell therapy products is likely – need to understand how to treat and support.

References

Advanced Therapy Medicinal Products – UCL 2011
Prosavin. OxfordBioMedica
Holoclar Chiesi’s commitment to limbal stem cell deficiency (LSCD) and future directions - Chiesi
The Cell and Gene Therapy Catapult UK clinical trials database. Catapult 2018
CRS Talk – Tholouli.E 2018