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The Development and GMP manufacture of adoptive T cell therapies

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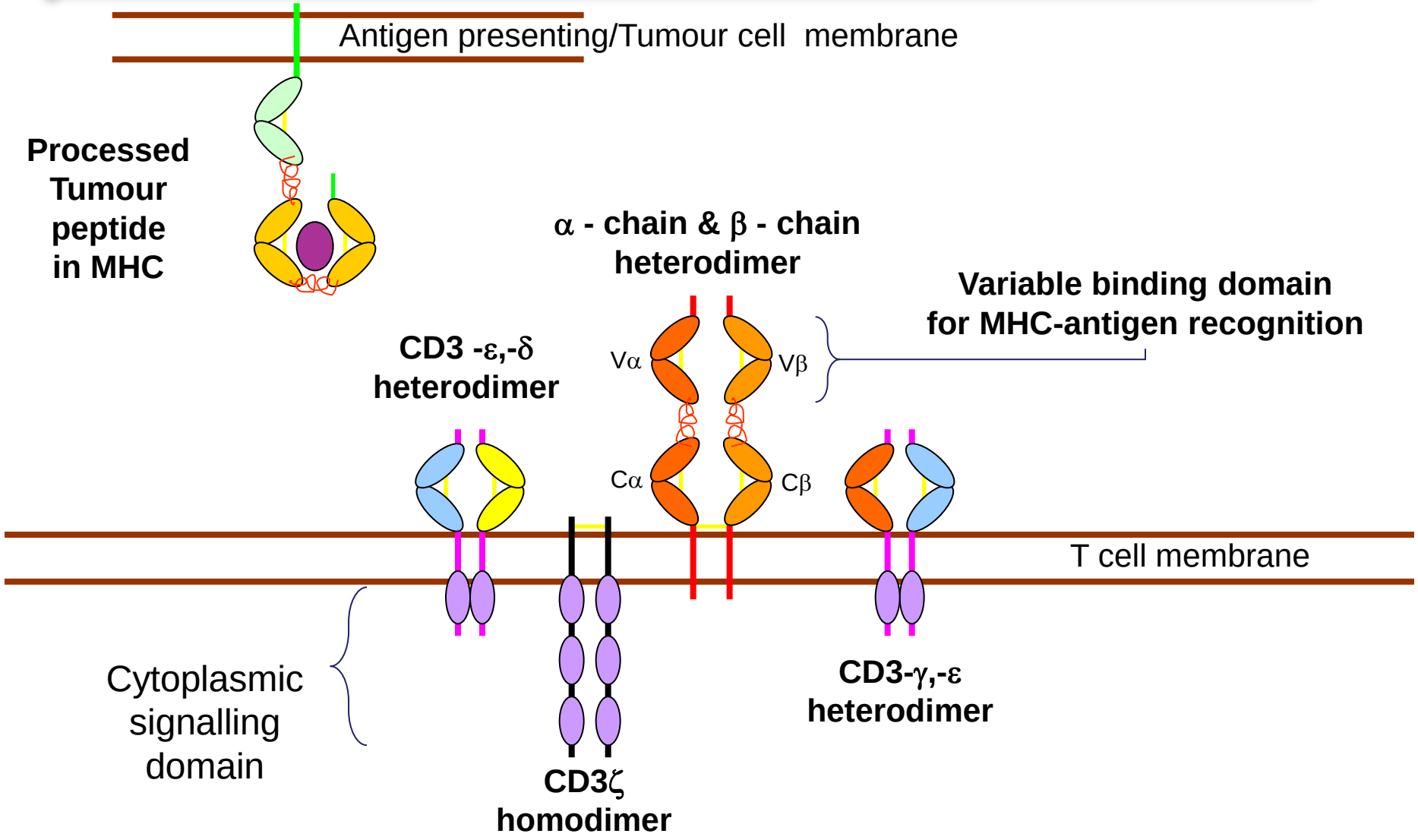
Making nature and technology work for you ©

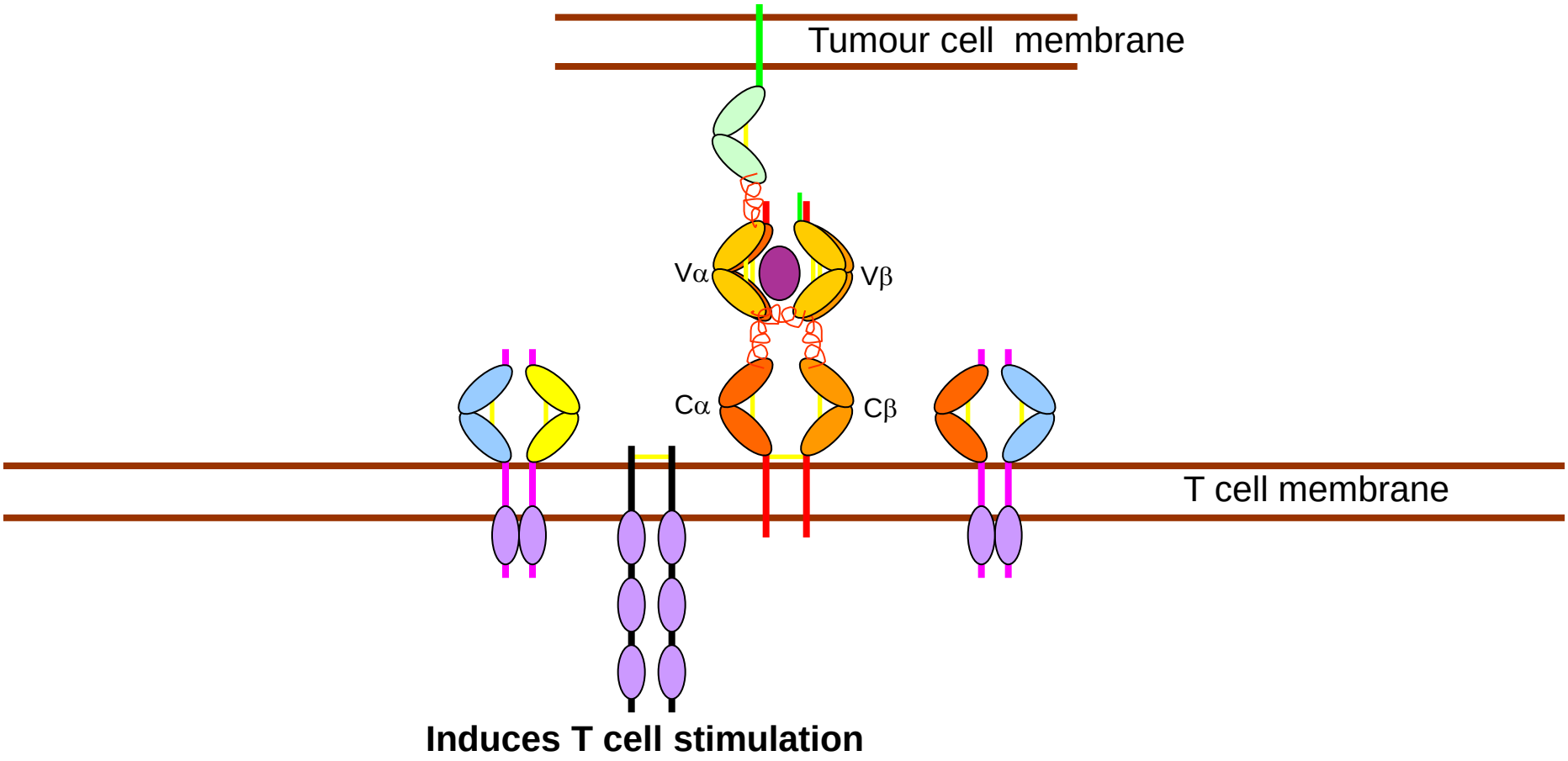
Overview

- T cell immunotherapy overview
- Origin of the University of Manchester CTU
- ATMP products & current clinical trials and treatments
- Associated toxicity & Challenges for the industry

T-cell receptor or CD3 complex



T-cell receptor & MHC complex



Adoptive T cell Therapy for Cancer

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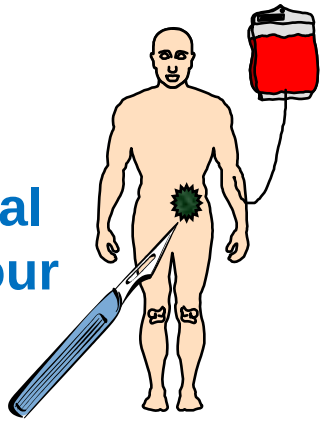
Expansion of tumour specific T cells

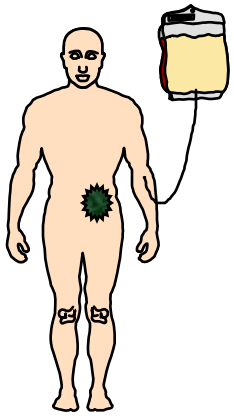
Collect T-cells from Patient

T-cells returned to Patient

(1) Natural anti-tumour T cells

(2) Engineered anti-tumour T cells





1 - Natural anti-tumour T cells for Therapy

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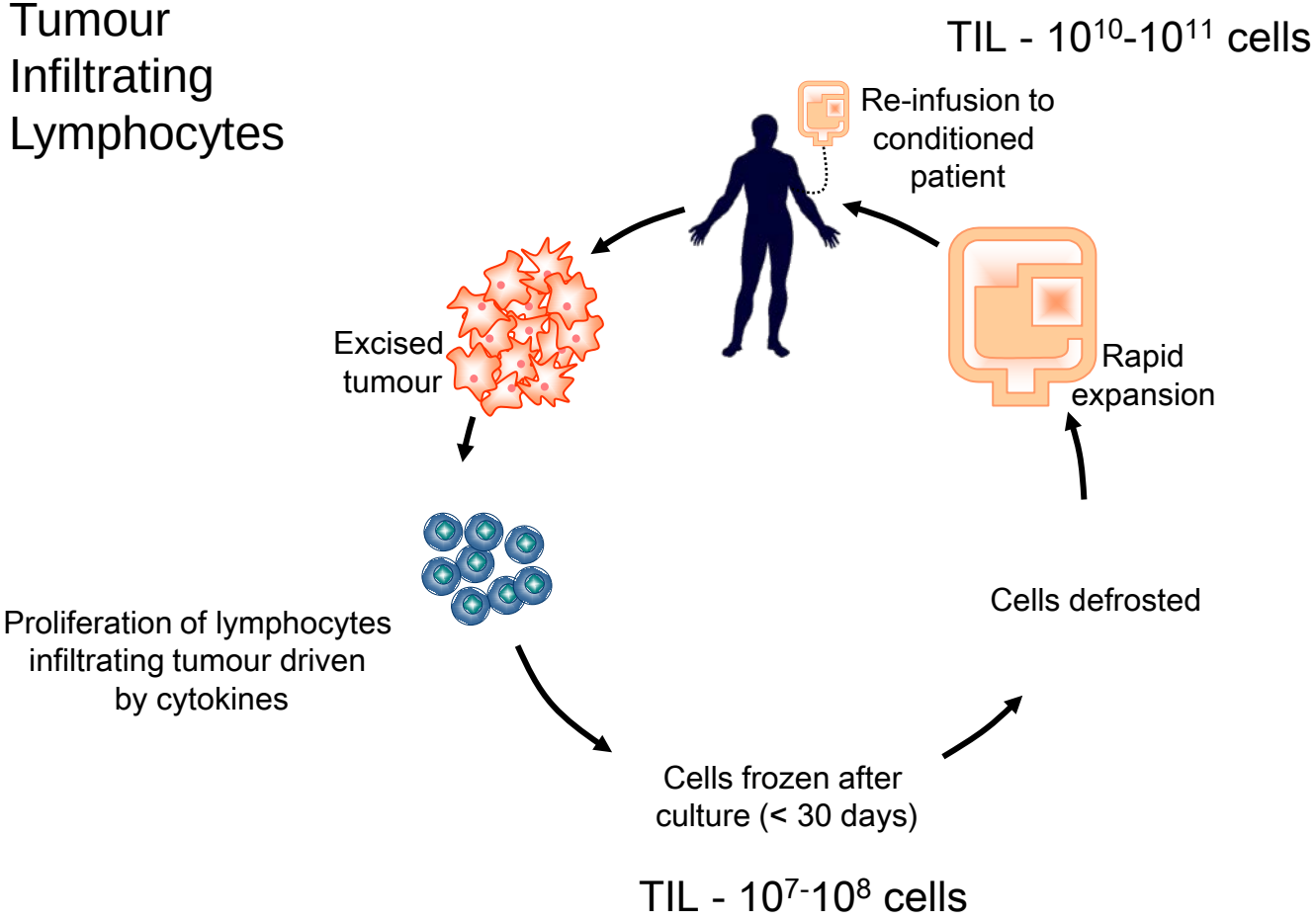
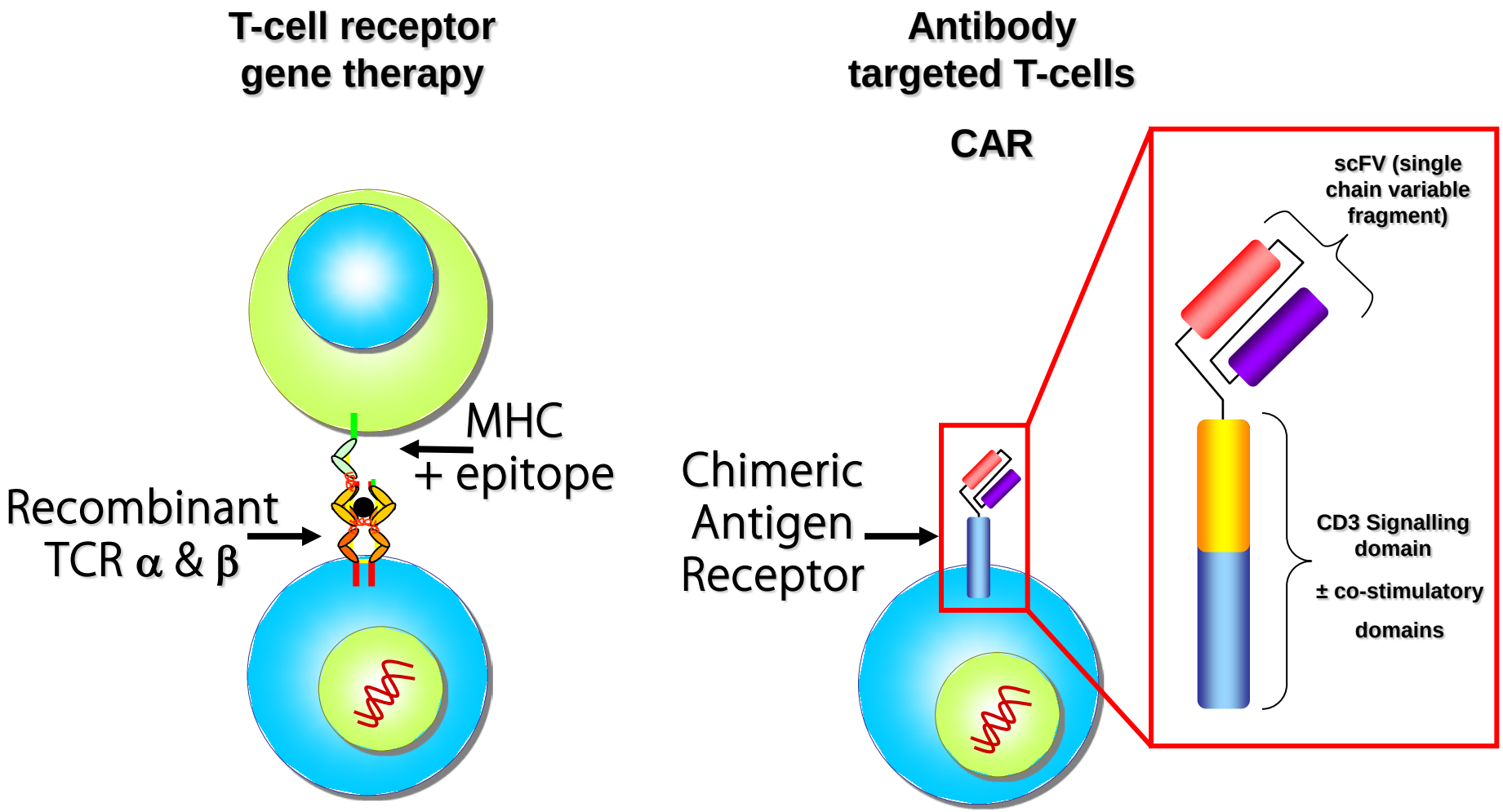
Tumour Infiltrating Lymphocytes



2 - Gene engineered - T cells for Therapy



Gene engineered T cells for Therapy

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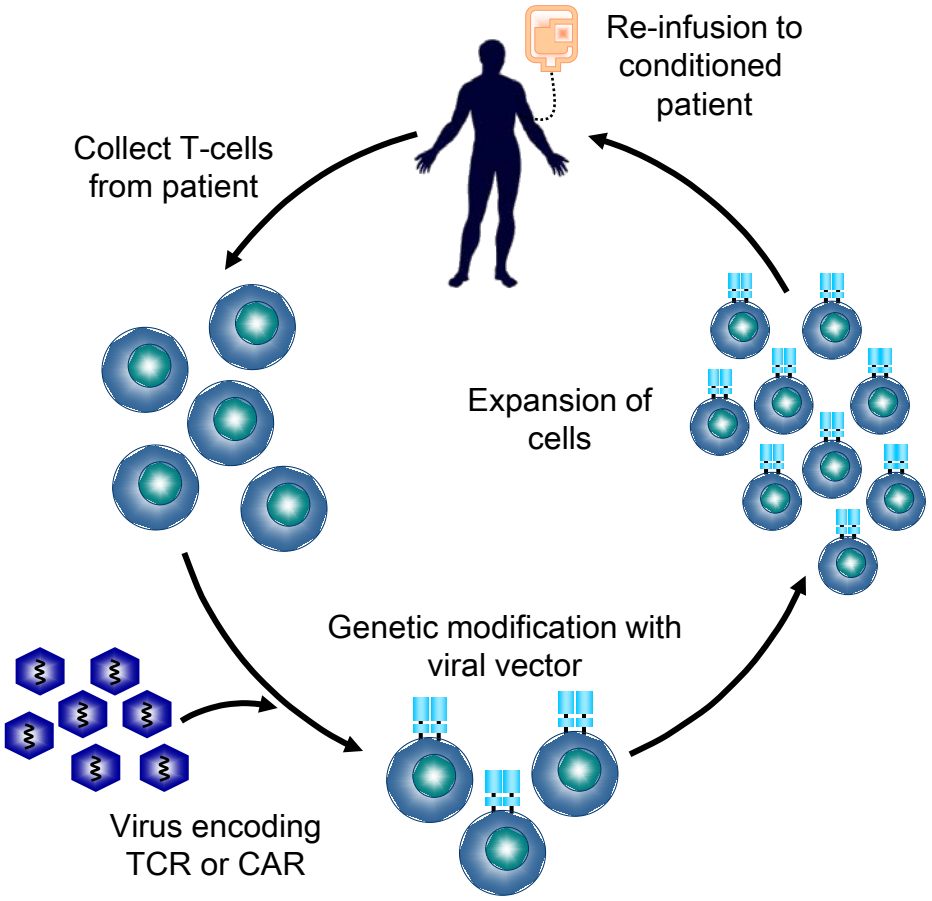
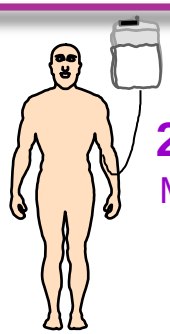


A brief history of the UoM CTU….

1990 to 2003

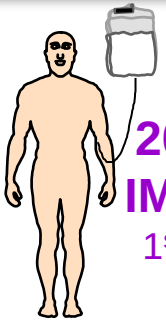
UoM – Prof Robert Hawkins

Basic science immunotherapy of cancer



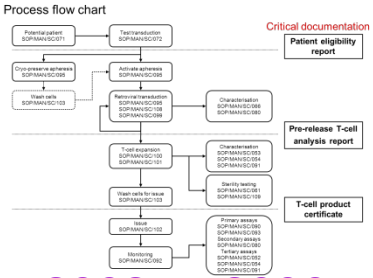
2007 to 2010

MFEz & aCD19z Trials



2011 CTU MHRA IMP & MS licence

1st patient treated Oct 2011 under MS special



2003 to 2006

MFEz & aCD19z PD & PQ

Dec 2008 to Feb 2010

CTU inception to opening

Cellular Therapeutic Unit - Objectives

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- Continue existing Gene therapy T Cell trials
- Develop novel cell therapy treatments for cancer and other diseases
- Must be effective, flexible and safe systems of cell engineering
  5 products simultaneously
- Develop and train staff
- Simple and effective Quality management system
- Modular processing methods that can be used across products
- MHRA IMP & MS specials licences

Cellular Therapeutics Unit (CTU)

- Move away from classical clean rooms
- Isolator technology controlled aseptic environment
- Protects patients cells from infection or contamination
- Allows rapid decontamination with vaporised hydrogen peroxide without chemical residues
- Allows multi product processing

Cellular Therapeutics Unit - Trials

The University of Manchester

- CAR - A Phase I Study of CD19 Specific T cells in CD19 Positive Malignancy
  - Up to 20 patients – open to recruitment 6/20 treated response in 3/6

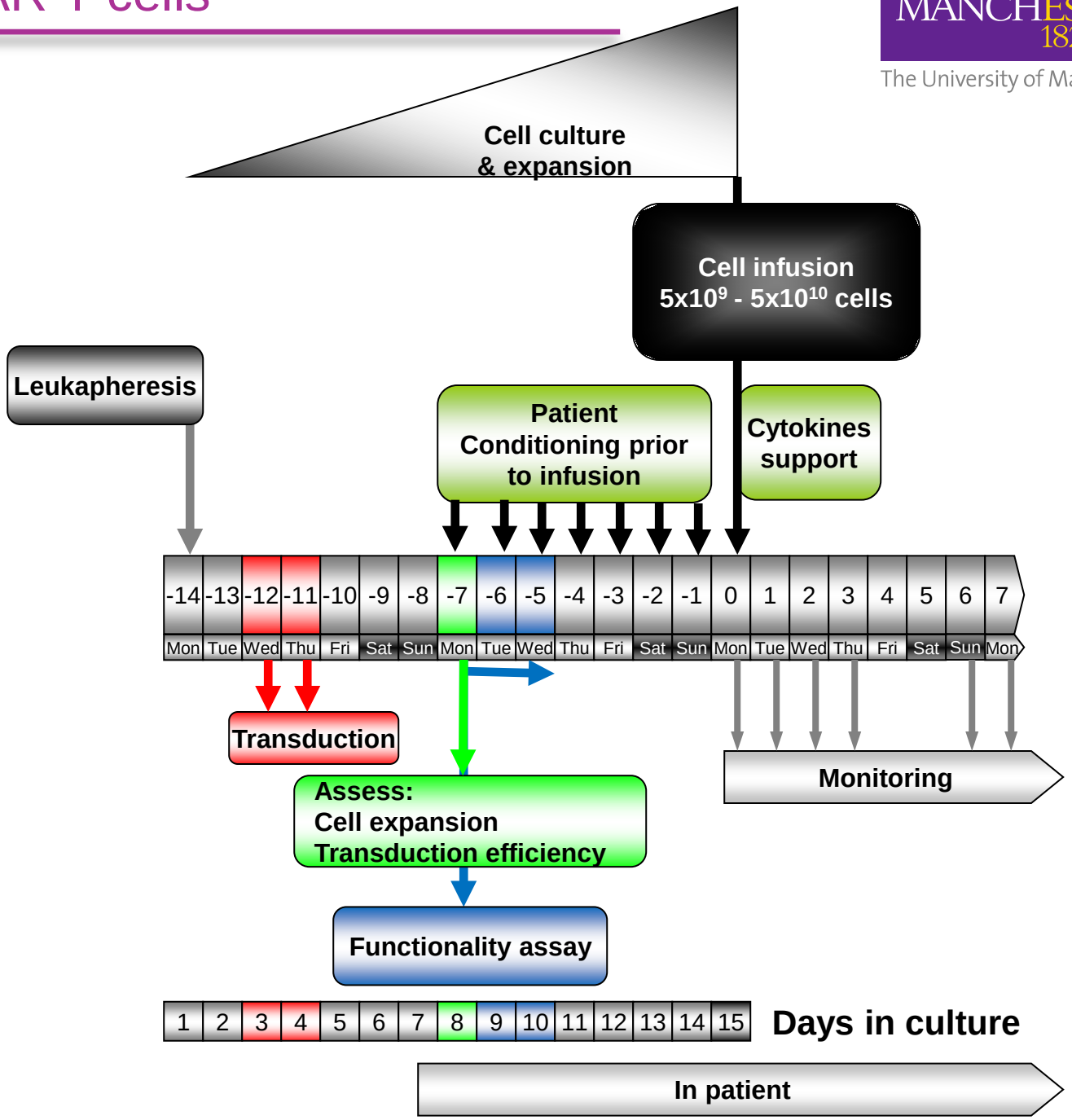
- TIL - METILDA - Randomised Phase II Study in Metastatic Melanoma to Evaluate the Efficacy of Adoptive Cellular Therapy with Tumour Infiltrating Lymphocytes (TIL) and Interleukin-2 Dose Assessment
  - Up to 90 patients – Opened March 2014

cellulartherapeutics® **with the EU FP7 ATTACK - consortium**

- TCR - NY-ESO-1/LAGE-1 peptide expressed in a subset of tumours:
  [1] ATTACK Trial 1 - Oesophagogastric cancer – single arm
  - Up to 28 patients across – Opened Sep 2014

  [2] ATTACK Trial 2 - Metastatic melanoma Standard vs Optimised manufacturing
  - Up to 42 patients – Planned to open Q3 2015

Anti-CD19z CAR T cells



Adoptive T cell Therapy for Cancer: CAR immunotherapy – anti-CD19 T cells

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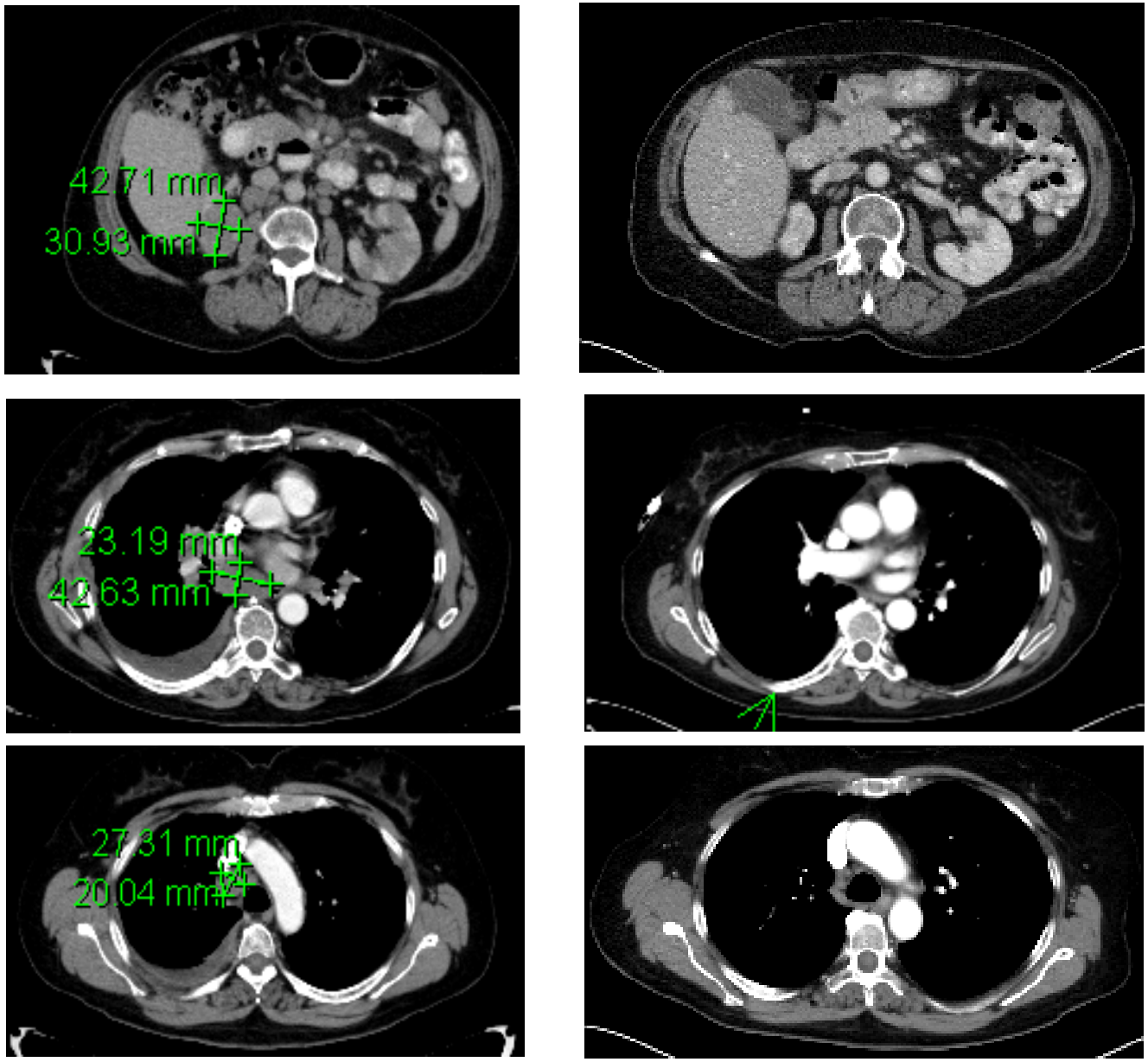
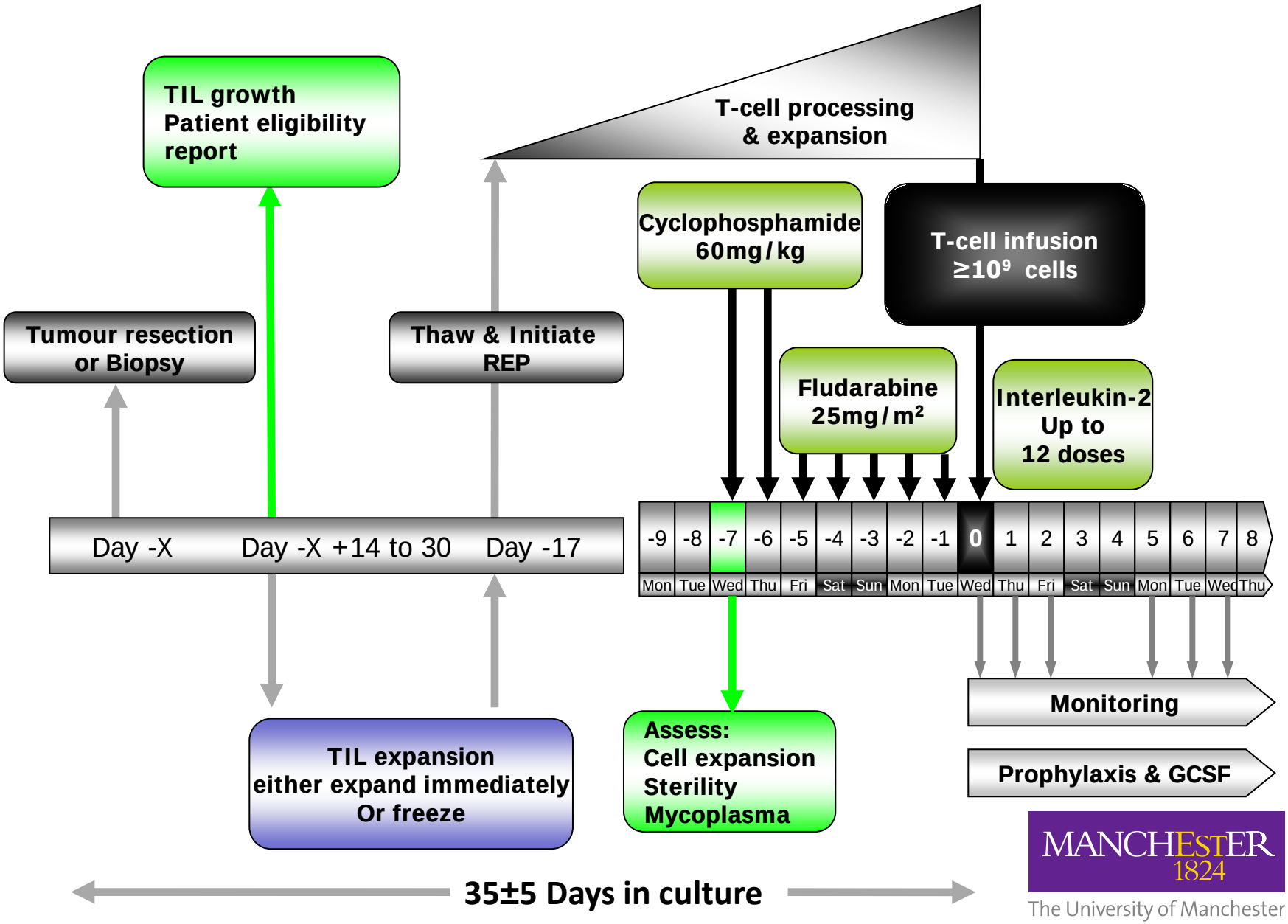
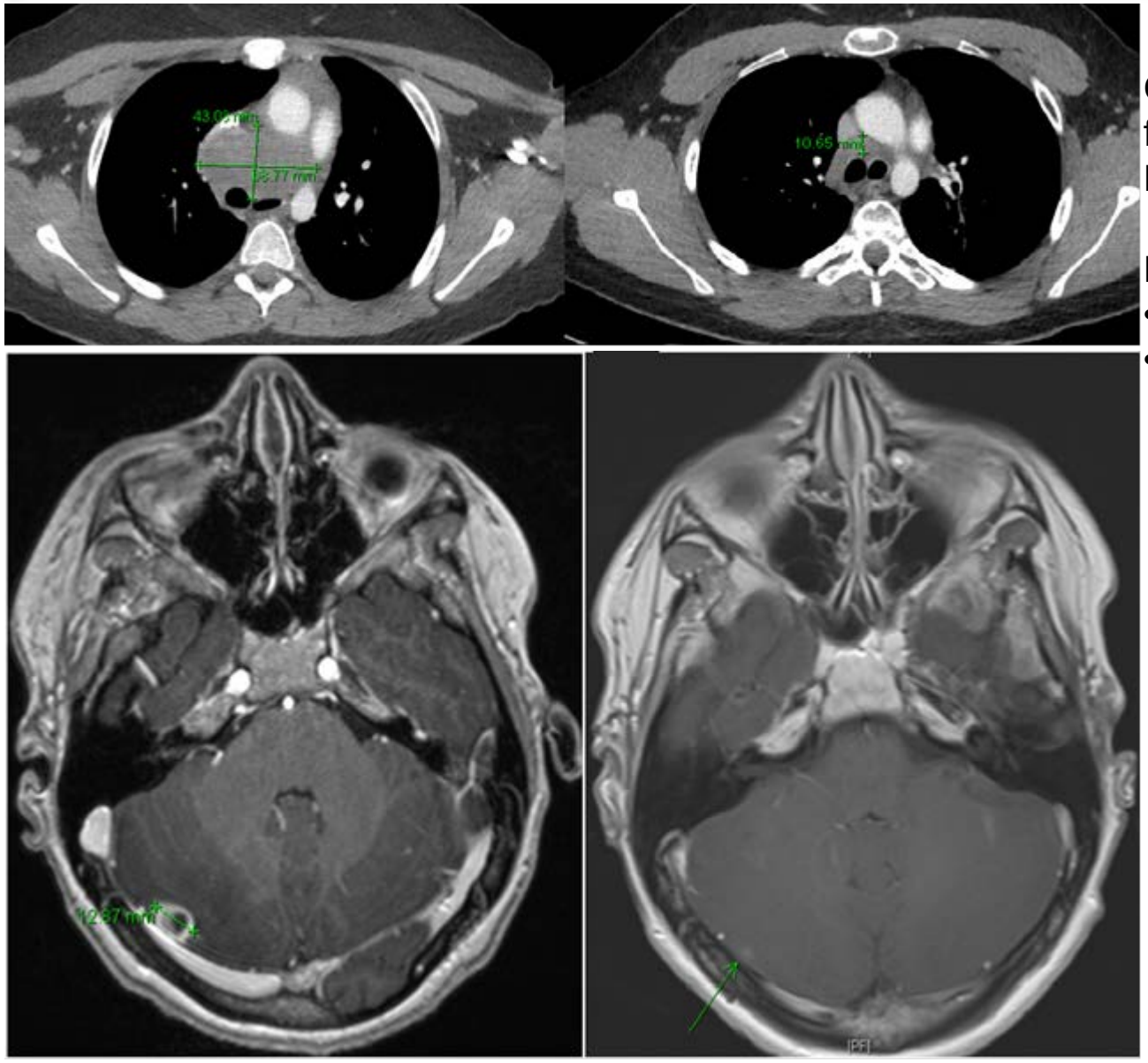


Natural T cell therapy - TIL



Adoptive T cell Therapy for Cancer: TIL Immunotherapy



CTU manufactured cell therapy for Metastatic Melanoma in MS special Aug 2012

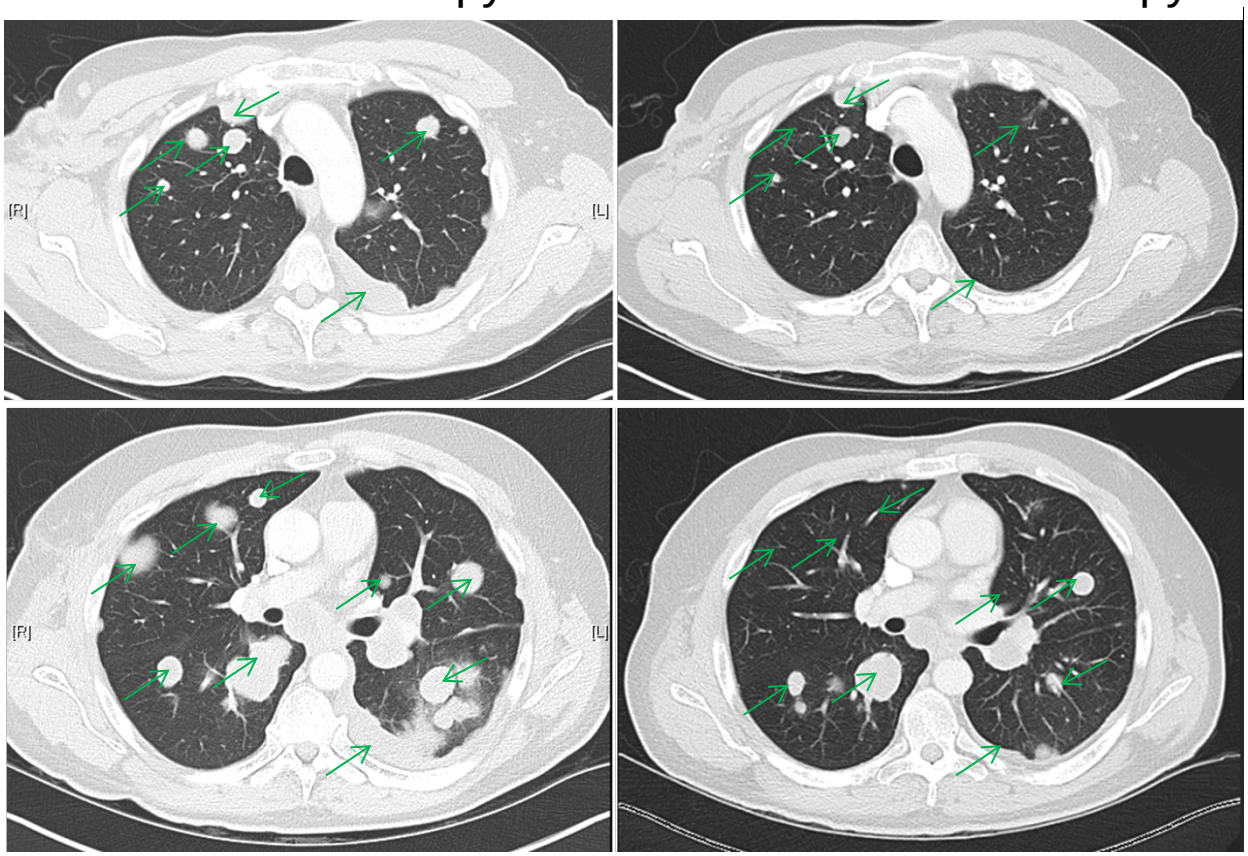
Patient response 24 months

- large mediastinal lymph node
- Cerebellar metastasis

Adoptive T cell Therapy for Cancer: TIL immunotherapy

Before cell therapy

6 weeks after cell therapy



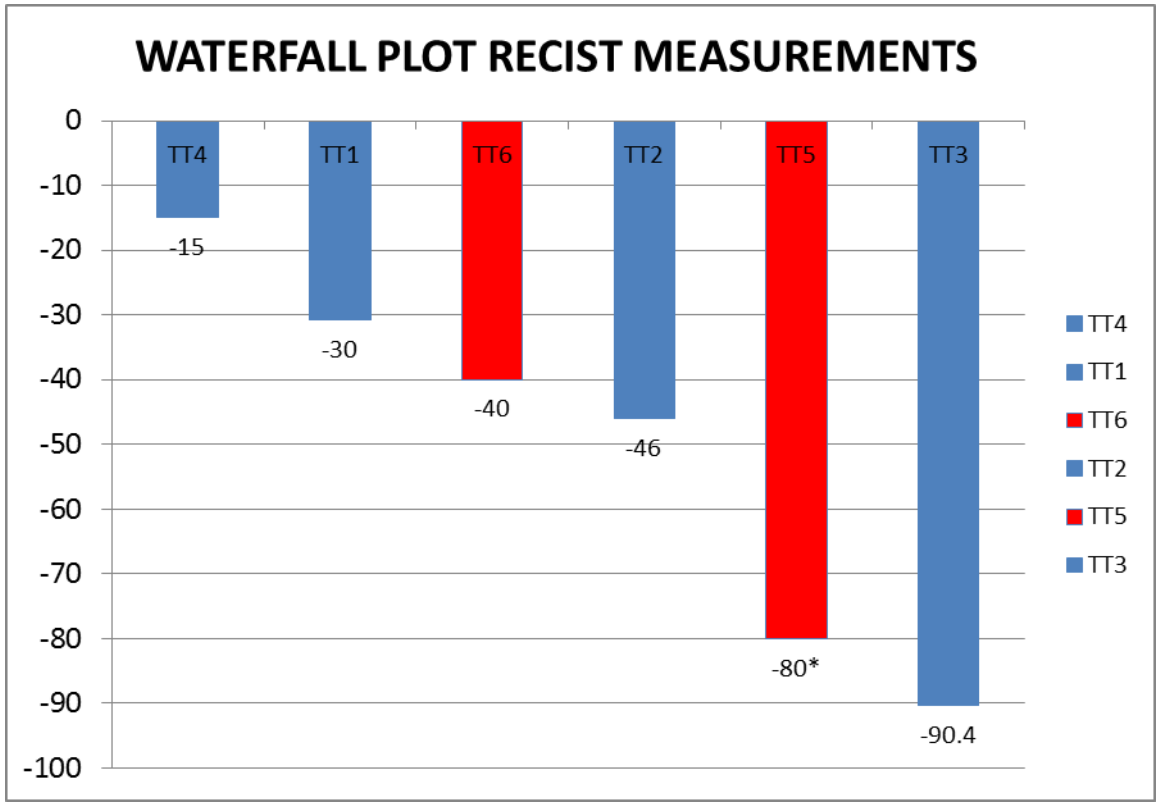
CTU manufactured cell therapy for Metastatic Melanoma in MS special Jul 2013

Patient response 6+ weeks

- Sub cutaneous
- Lung
- Axillary disease

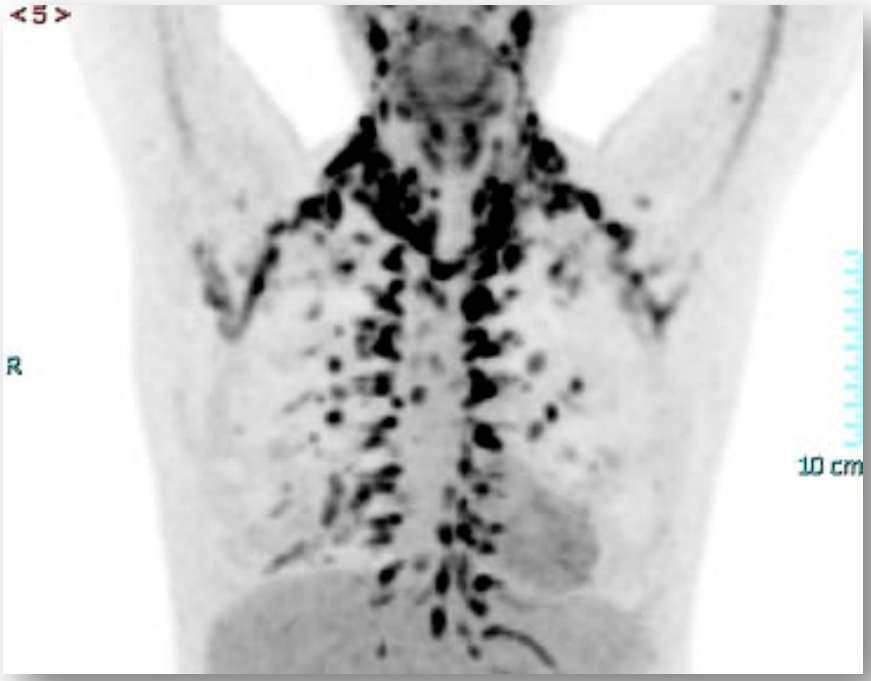
Adoptive T cell Therapy for Cancer:
TIL immunotherapy: 6 MS specials patients

Encouragingly all patients have had some tumour reduction so far…

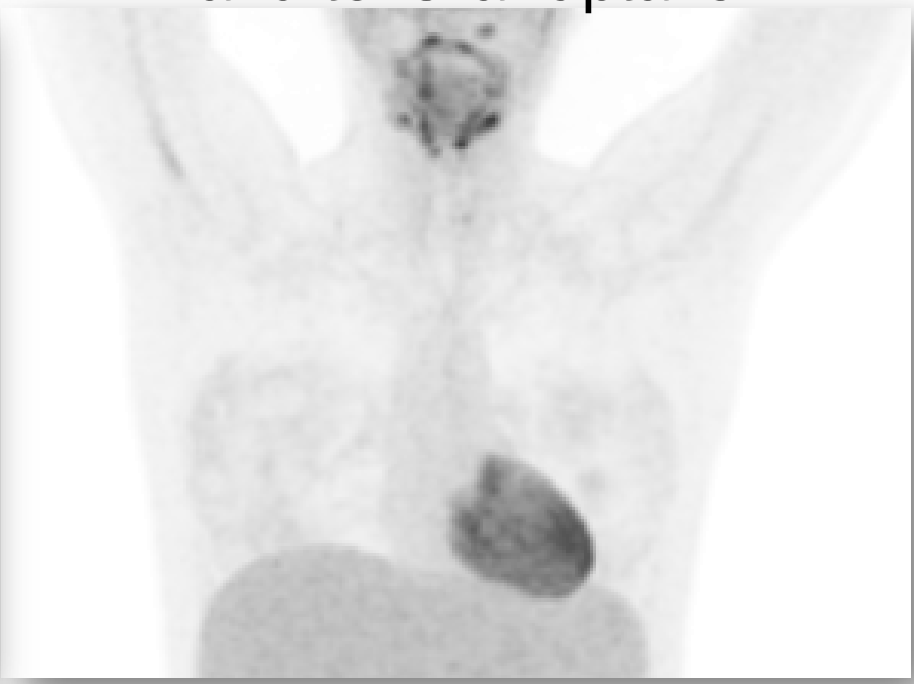


Synovial sarcoma Adoptive Therapy with: TCR Immunotherapy therapy - NY-ESO-1 Engineered T Cells.

Baseline PET scan
January 2, 2013



Day 101
April 19, 2013. Normal heart and tonsilar uptake

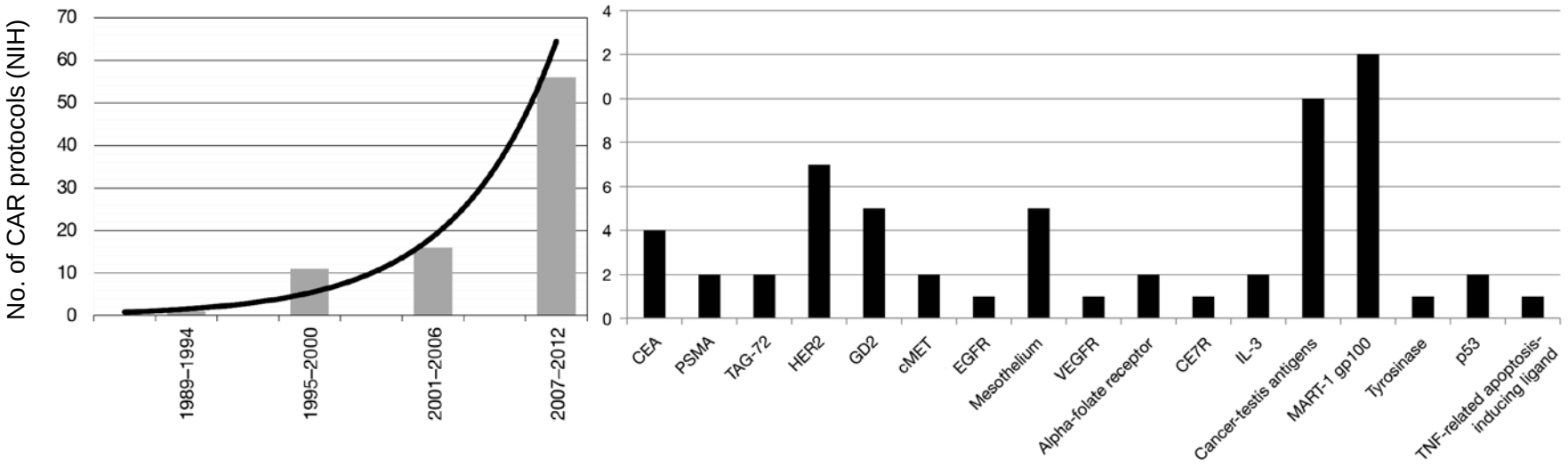


Courtesy of
Dr Crystal L. Mackall

NATIONAL CANCER INSTITUTE

ADAPTIMMUNE
transforming T cell therapy

CAR service history

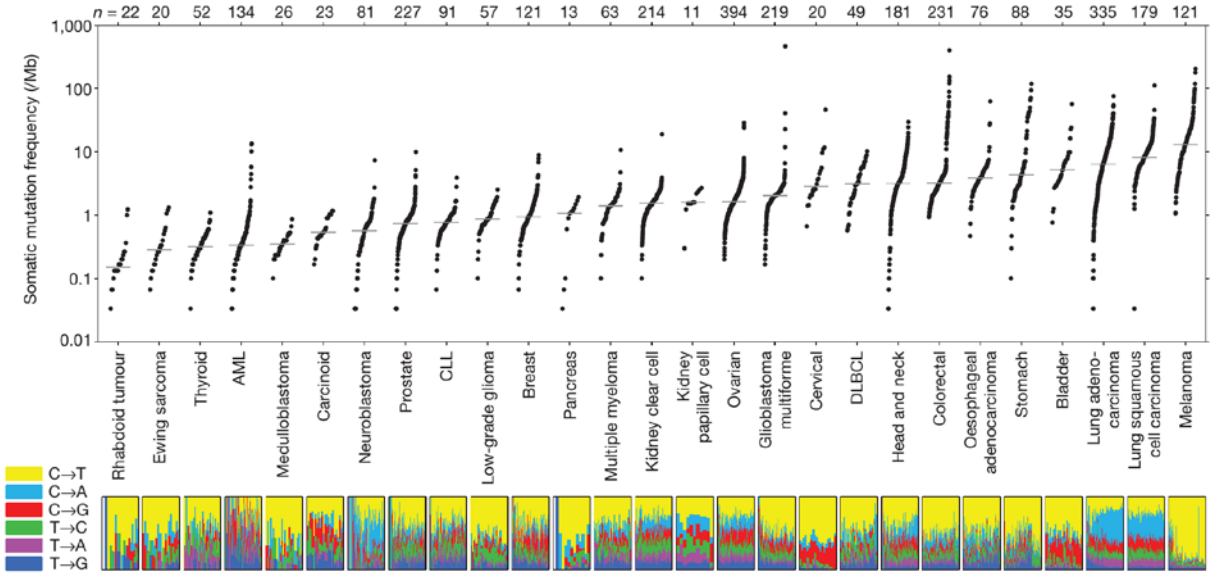


- September 2013 there were 111 protocols registered NIH
  - 104 of which targeted cancer, with more than 500 subjects dosed
  - 40 protocols address haematological malignancies & 34 targeting CD19
- Key factors:
  - The target antigen is expressed on the cell surface
  - Good clinical evidence in CD19+ tumors at multiple centres

Jacqueline Corrigan-Curay et al., *Molecular Therapy*, **22**, 1564-1574

TIL immunotherapy

- TIL
  - Isolation of TIL from tumour is complex and unpredictable
  - Unknown target difficult to prove specific functionality
    - trials using functional TIL did not correlate with efficacy
  - TIL therapy
    - Response in 40 to 50% of patients of which 20 to 35% CR
  - Current theory
    - highly mutated cancer > frequency of tumour specific T cells



Michael Lawrence et al., *Nature*, 2013, **499**, 214–218

TCR immunotherapy

- TCR
  - HLA dependant
    - Patient must screen positive for HLA and antigen
    - High rate of screen fails

    i.e. HLA-A2 approx. 40%

    NY-ESO-1/LAGE-1 approx. 30-40% in Oesophago-Gastric cancer

    - 1 to 2 in every 10 screened

  - Evidence of activity in:
    - Melanoma – Response 9/18 (CR 4/18)
    - Synovial sarcoma – Response 10/16 (CR 0/16)
    - Multiple myeloma – Response 13/20 (CR N/A)

Toxicity associated with current T cell immunotherapy

- Systemic conditioning chemotherapy
  - Systemic conditioning chemotherapy - lympho/neutropenia & sepsis
  - IL-2 – Pulmonary oedema/fevers/riggers

- Off target activity effects of cancer immunotherapy:
  - TCR associated toxicity seen with high-avidity TCRs targeting off tumour epitope
    - MART-1, GP-100, CEA & MAGE-A3
  - CAR associated off target toxicity
    - Carbonic anhydrase (CA) IX - Bile duct
    - CEA
  - TIL
    - vitiligo & uveitis

- Active therapy in bulky tumours
  - Cytokine release syndrome
  - Tumour lysis syndrome

Challenges for the industry

- Scale up to treat large numbers of patients
  - Just in time manufacturing
  - Shortage in manufacturing capability
  - Labour intensive facilities and processes
  - Secure supply of critical reagent & CoGs
- GMP vector for CAR & TCR therapy
  - Shortage in manufacturing capability
  - Cost barrier to do early phase trials
- Shortage of treatment centres
  - Intensive chemotherapy
  - High dose IL-2 management

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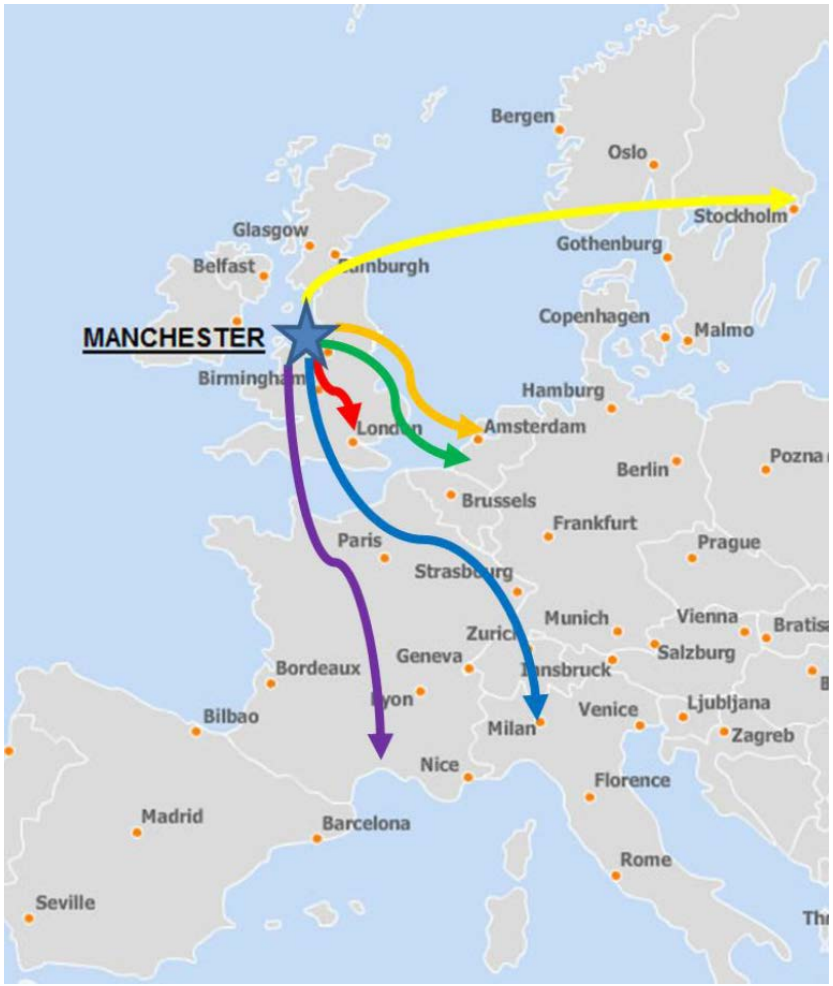
ATTACK

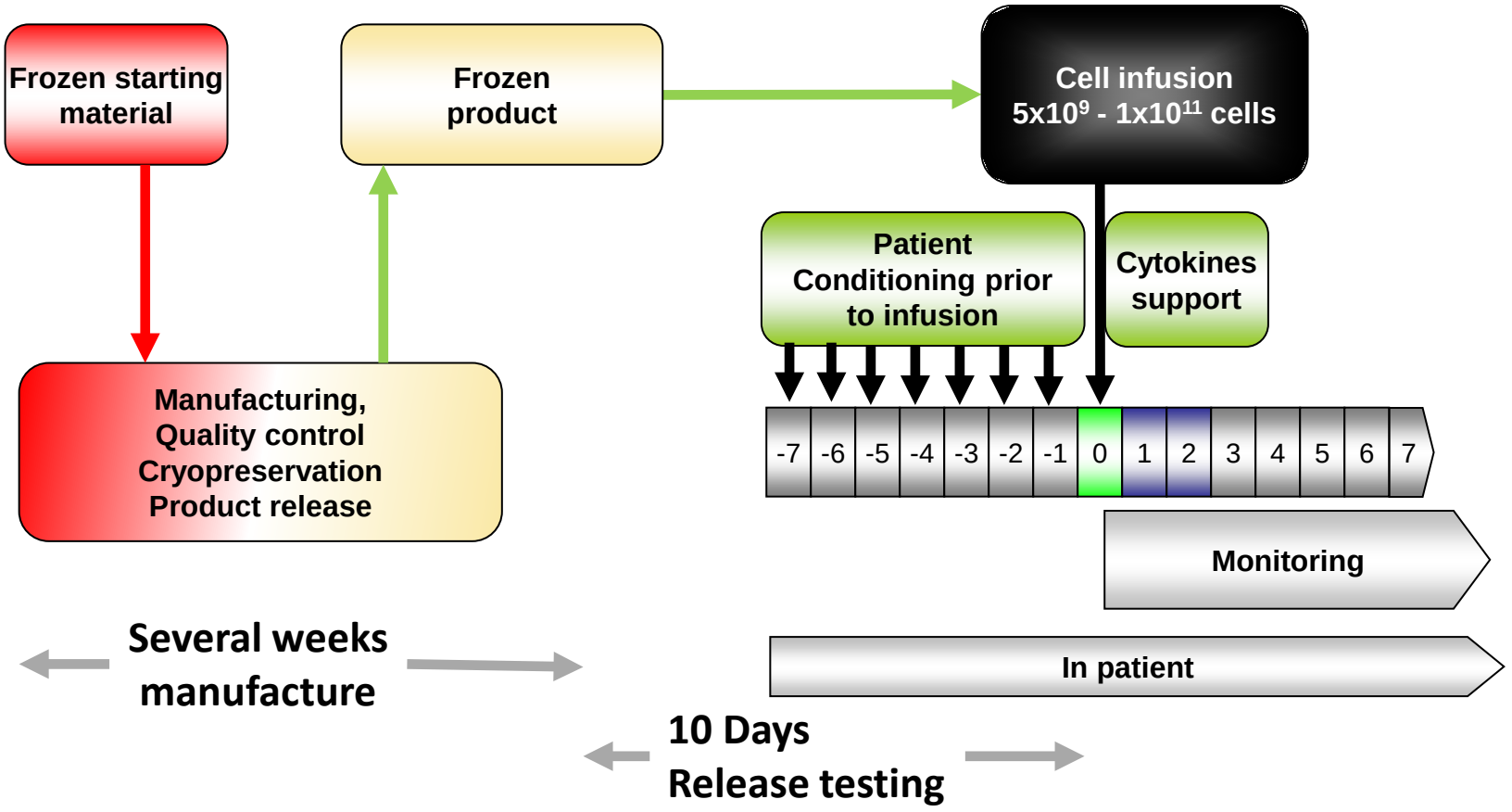
ATTACK
ADOPTIVE ENGINEERED T CELL TRIALS TO ACHIEVE CANCER KILLING

- Multicentre Phase II
  - 2 trials with up to 70 patients
  - Trial 1 – Single arm Oesophago/gastric cancer with n=28 patients
  - Trial 2 - Melanoma 2^{arm} n=42 patients
  - Centralised Production
    - Manchester & Amsterdam
  - Start Q3 2014



Scale up requires scheduled manufacturing & treatment

NY-ESO-1 TCR T cells Phase II clinical trials – Oseophago/Gastic cancer & Melanoma



Future of manufacturing?.....in the CAR industry

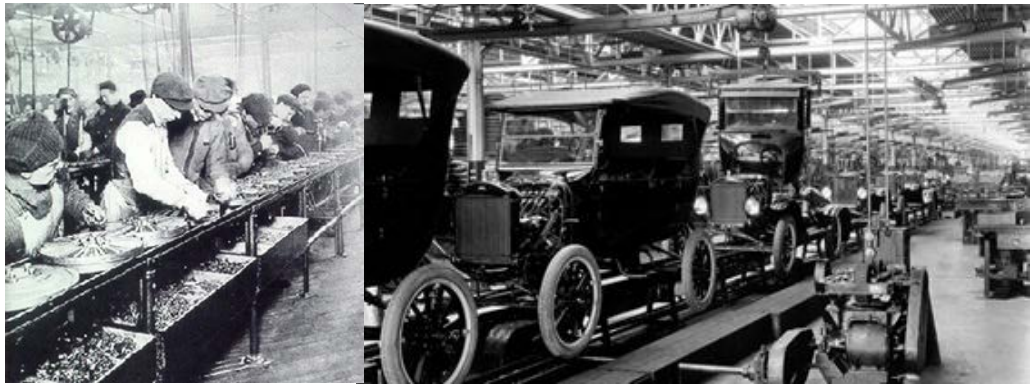
- To date less than 1,000 patients treated globally
- High value products & clinical results have lead to a movement from chemical drugs to biotherapeutics to ATMPs
- Huge increase in pharmaceutical interest
- Regulations have adapted to industry requirements (e.g.):

  - ATMP regulations

  - Multi product manufacturing

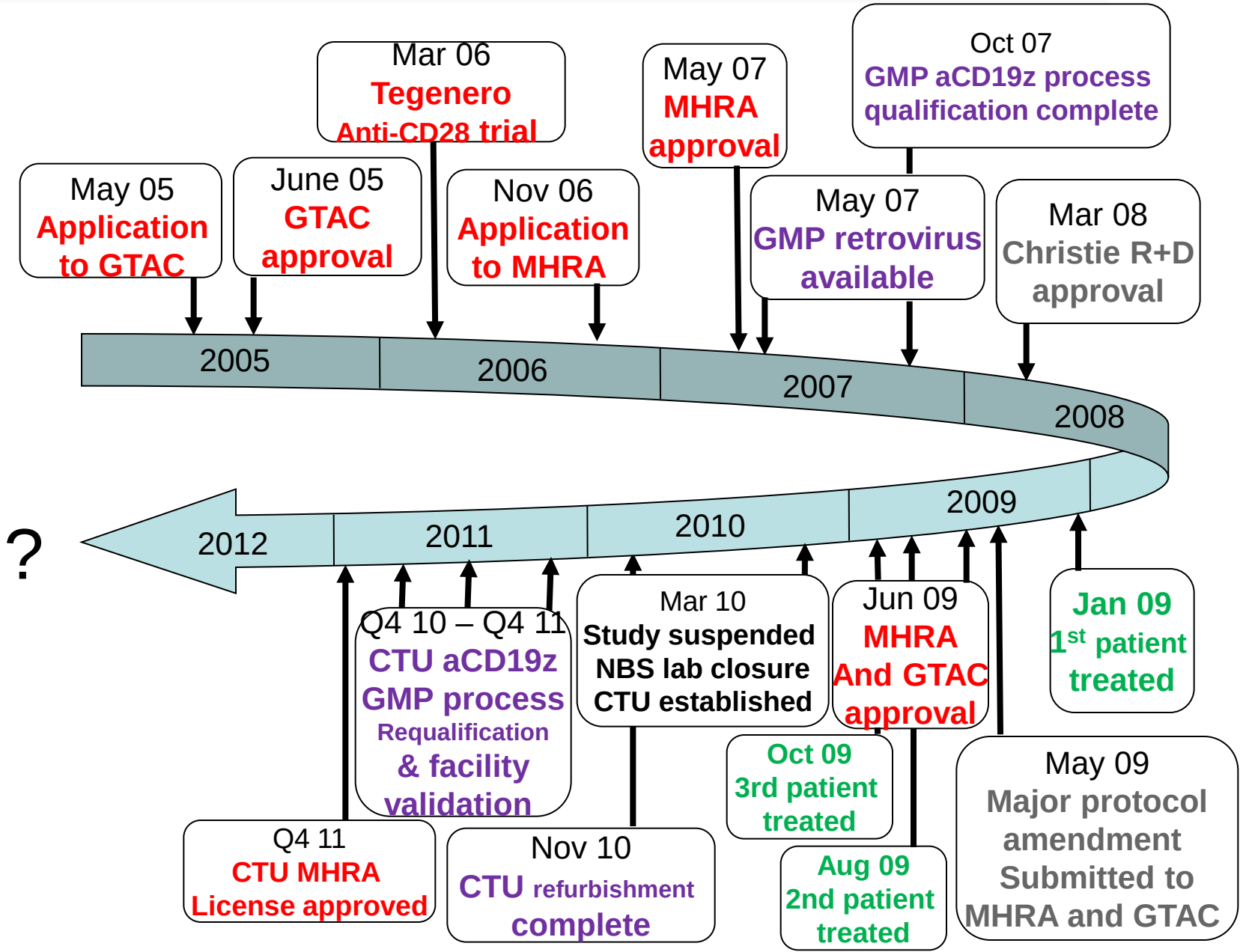
  - Risk management principles (ICH Q9)

1914

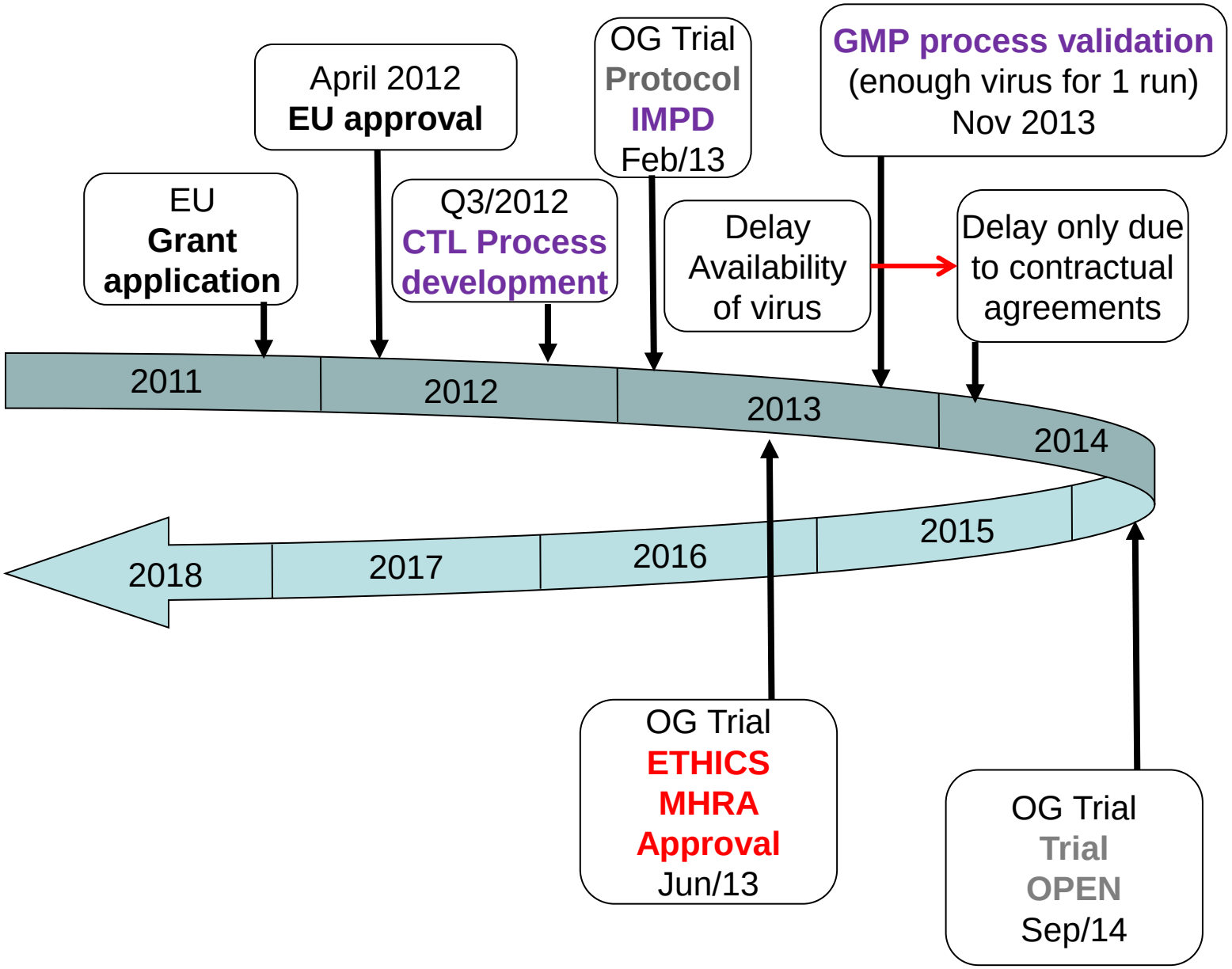


2014

CD19 trial timeline – lack of experience as an industry



NYESO-1 T cells – better understanding



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Vijay Ramani

ADOPTIVE ENGINEERED T-CELL TARGETING TO ACTIVATE CANCER KILLING