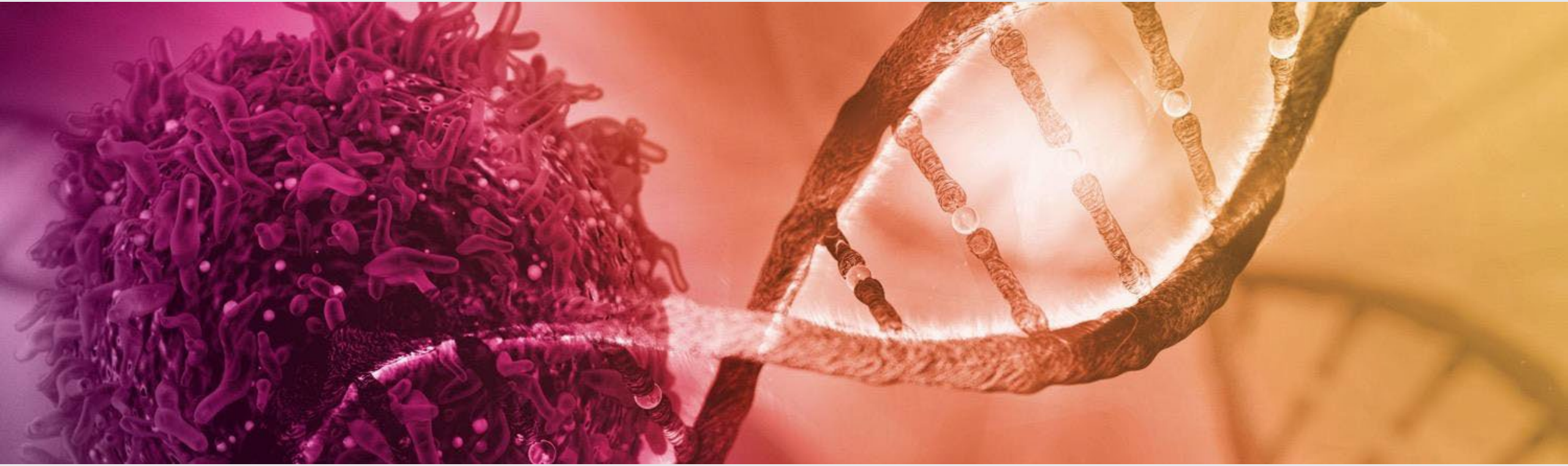
ACHILLES THERAPEUTICS
transformative T cell therapy



Multicentre, prospective research protocol for development of a clonal neoantigen-reactive T cell therapy pipeline across multiple tumour types

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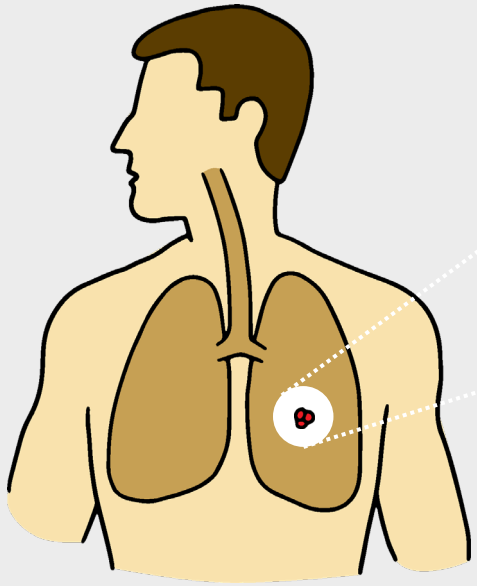
Background

- Cancer cells **accumulate mutations in their DNA** over time. Many of the mutations lead to **changes in the proteins encoded** by the mutated genes, which can then be recognised by the immune system as '**foreign**'
- These **cancer-specific 'neo-antigens'** can potentially be exploited by immunotherapies such as Adoptive Cell Therapy (ACT) and Checkpoint Inhibitors (CPIs)
- The **mutations occurring before the initial cancer** transformation event are carried by all of the cells of the growing cancer and are known as **'clonal' mutations**
- Mutations that **subsequently occur are known as 'subclonal' mutations** and are not present in all of the cancer cells, hence these are less likely to produce complete response, i.e. the elimination of the whole cancer cell population

Achilles has developed proprietary technology to **target all tumor cells**



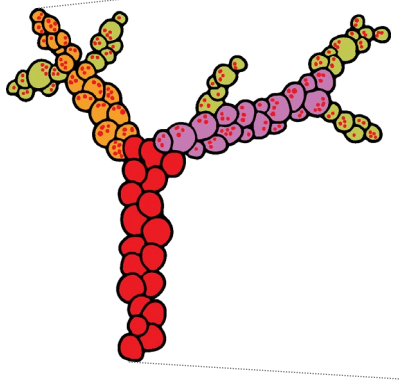
Tumors are **clonal in origin** and originate from a group of cells that are exactly the same

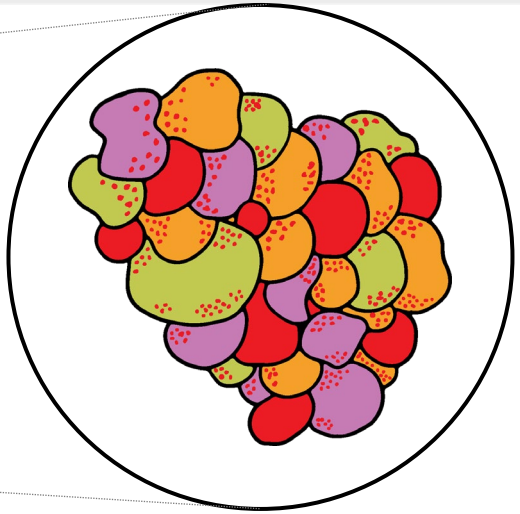
Tumors evolve, developing many new mutations resulting in **heterogeneity** that enables them to evade targeting[1]

To kill all of the tumor cells we believe you need to target the **clonal neoantigens formed early in tumor evolution**

Achilles has developed proprietary technology (using TRACERx) to identity the original tumor mutations **present on all cancer cells**, **clonal neoantigens**

We are able to identify and **target multiple clonal neoantigens** with our Clonal Neoantigen Targeting T cell therapy, or cNeT





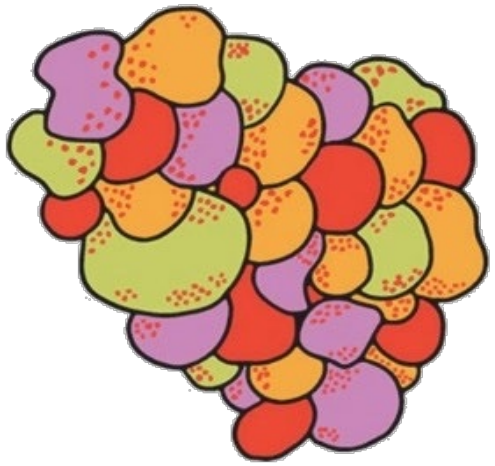
Clonal neoantigens are present on **primary tumors and all metastases**

1. Gerlinger et al., NEJM, 2012

Background

Tumour Infiltrating Lymphocyte (TIL)

- TIL has delivered **long-term durable disease control** in multiple solid tumor settings[1-4]
- T cell expansion is **non-specific** with no control over which antigens are targeted and the approach results in subclonal targeting, reducing chances of complete disease control
- Requires **very high (non-physiological) levels of IL-2** that result in T cell exhaustion and reduced anti-tumor activity[5]



Red: clonal neoantigens

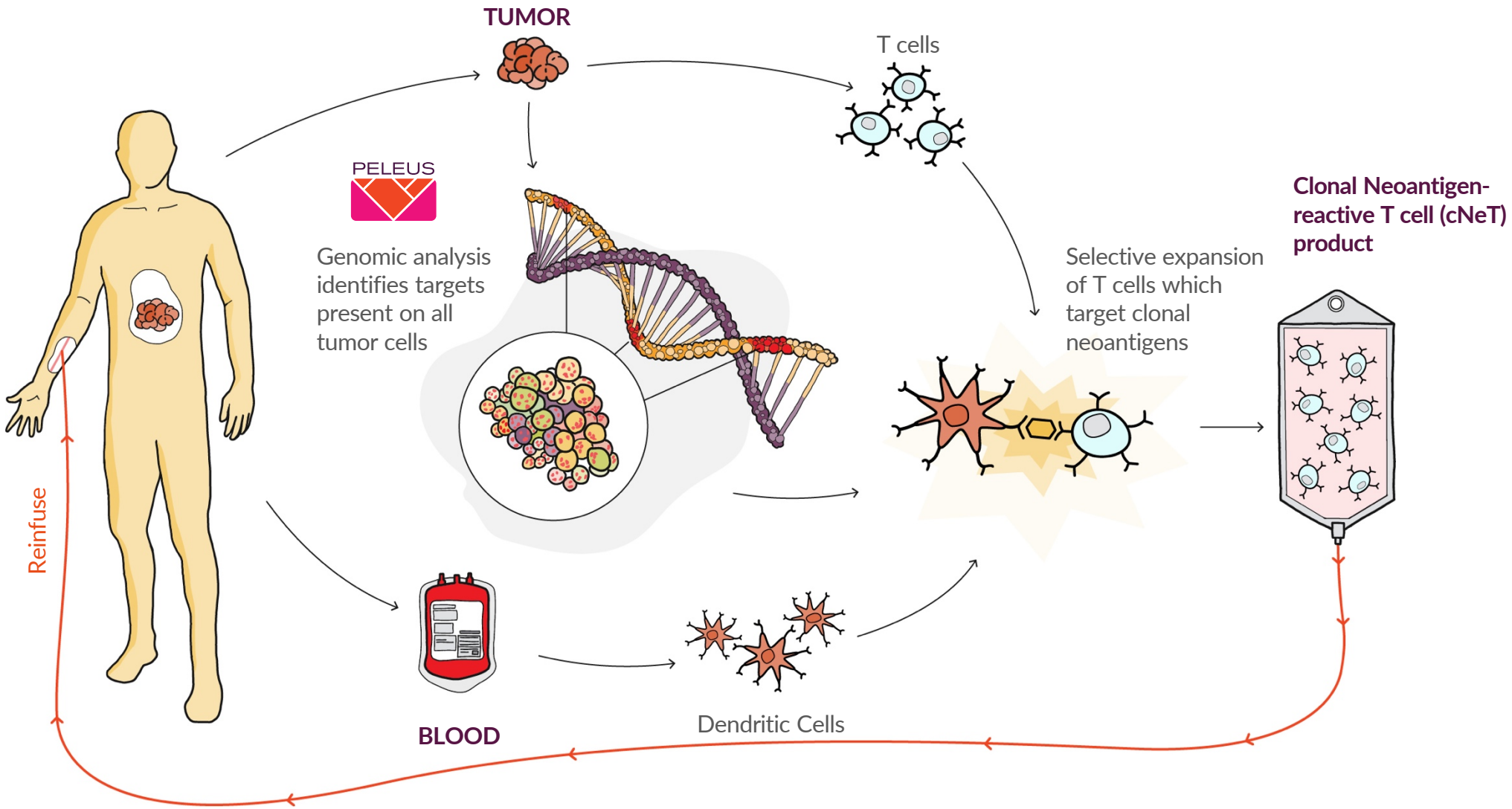
Purple, green and orange: subclonal neoantigens

Clonal Neo-antigen Reactive T Cell (cNeT)

- Ability to **measure** antigen-specific potency and **monitor** antigen-specific T cell engraftment and expansion
- Provides **precision targeting of clonal neoantigens** shown to correlate with the anti-tumor activity of TIL[6] and checkpoint inhibitors[7]
- Clonal neoantigen targeting provides a means to target **all the tumor cells**
- Using **dendritic cells** to drive T cell expansion reduces the need for IL-2 expansion, **producing a fitter T cell**

1. Besser et al., Clin. Can. Res., 2010
2. Forget et al., Clin. Can. Res. 2018
3. Rosenberg et al., Clin. Can. Res. 2015
4. Moffitt Investigator Sponsored Study update at AACR April 2020
5. Gattinoni et al. J Clin Invest, 2005
6. Lauss et al., Nature Comm, 2017
7. Snyder et al., NEJM, 2014

Background

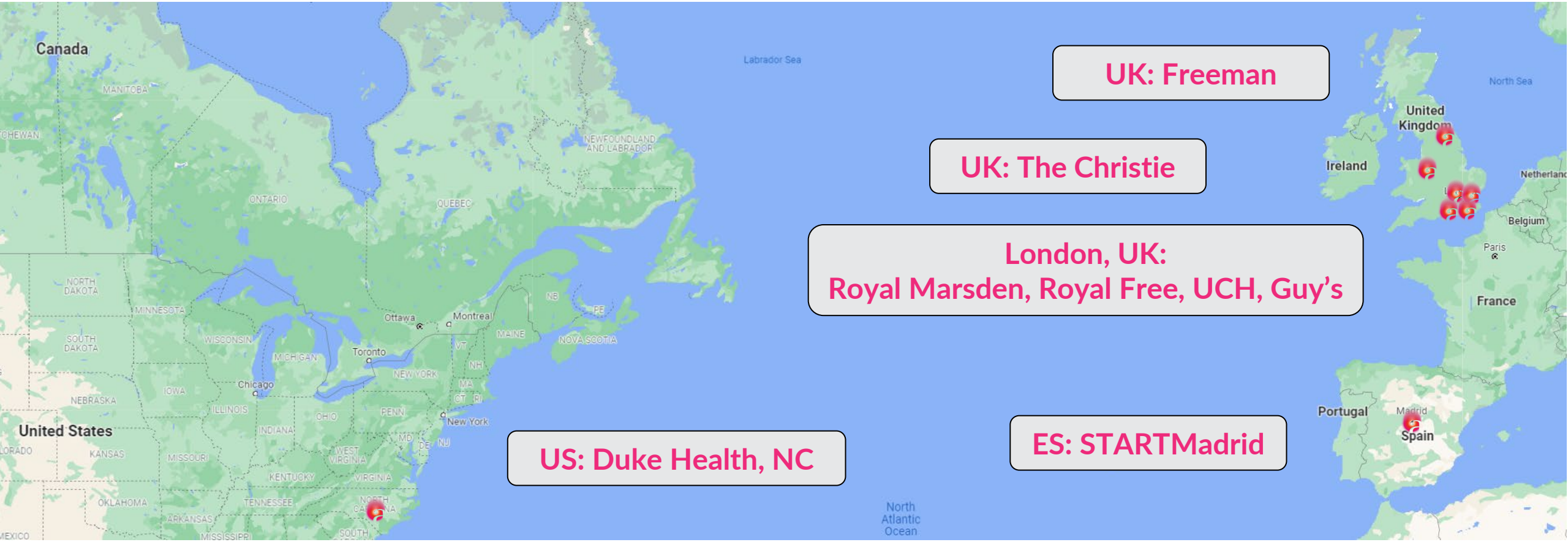


Methods

- The **Material Acquisition Platform (MAP)** study (NCT03517917) is a prospective research protocol collecting tumour tissue and blood in a range of cancers **(Lung, Melanoma, Head and Neck, Renal, Bladder and Breast)**
- This study was developed to explore the ability to produce cNeT – using **PELEUS and VELOS** platforms – **across indications** and to evaluate factors that may affect the baseline tumour, TIL intermediates and final cNeT products
- In addition, we are exploring **leukapheresis** as a means to use **blood as a source material** to produce a cNeT product

Methods

- The study commenced in **February 2018** initially in **Lung and Melanoma** with the aim of recruiting **300 participants**
- MAP has since expanded into **8 active sites in the UK, EU and US**, with 17 tumour procurement channels in **6 tumour indications** and have established operation pipelines to **support subsequent, international, first-in-human studies**



Methods

Key inclusion/exclusion criteria

- **Inclusion**
  - Patient scheduled for surgical excision and/or collection of multiple tissue samples via image or device guided biopsy or has a superficial skin/subcutaneous metastasis or lymph node metastasis that can be safely accessed for the purposes of the study
  - Hb ≥ 10g/dL(without transfusion support for at least 3 weeks)
- **Exclusion**
  - Pregnant or breastfeeding
  - Known/laboratory confirmed diagnosis of an infectious disease preventing inclusion of tissue into cell manufacturing suite
  - Patients who are currently participating in a clinical trial involving an unlicensed medical product
  - Patients receiving immunosuppressive treatments or who require regular treatment with steroids at a dose higher than prednisolone 10 mg/day (or equivalent)

Methods

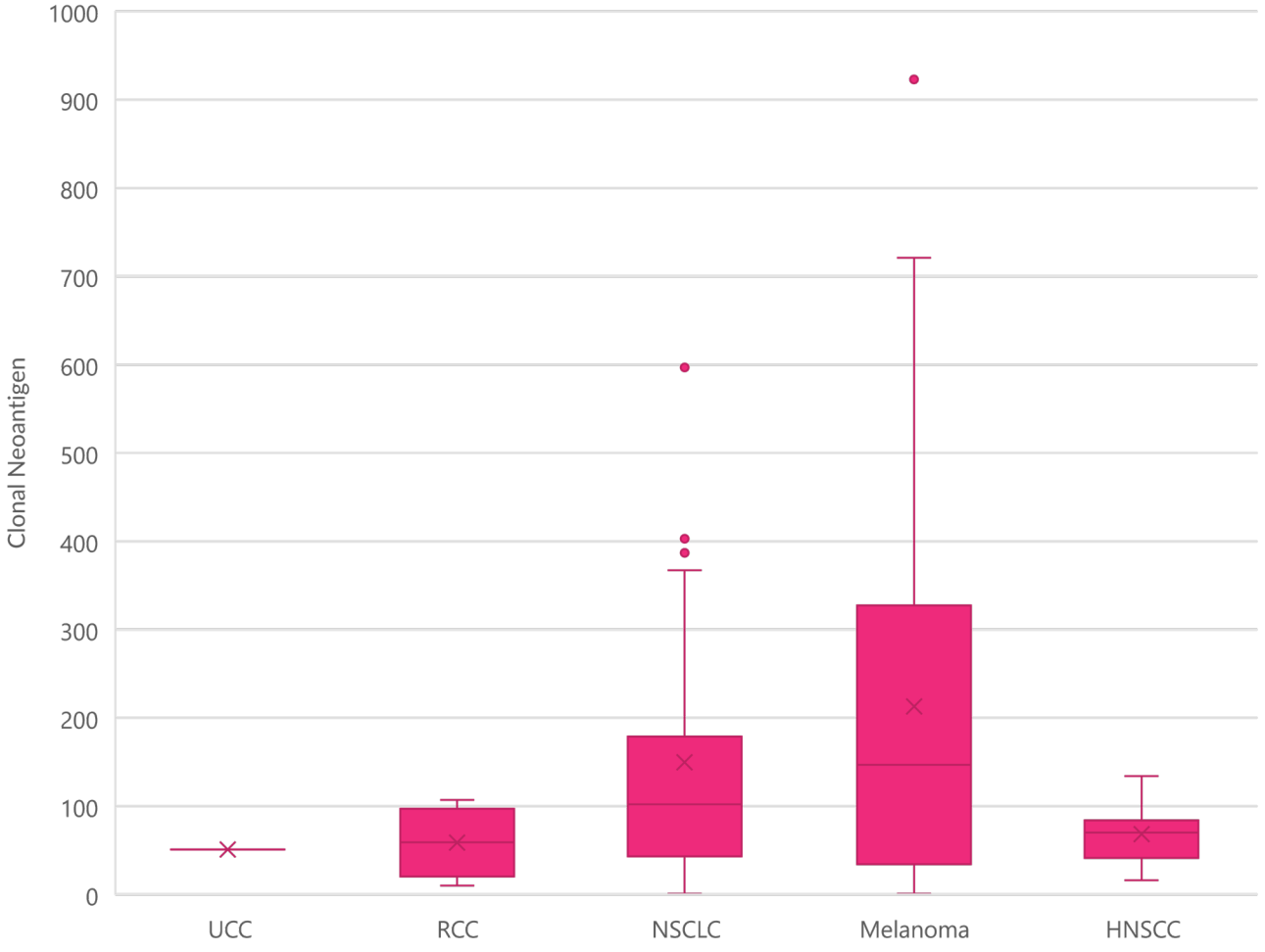
- Patients are identified prior to standard of care debulking/resection
- If eligible, patients are required to attend 3 visits (1 being carried out on the day of their surgery)
  - **Visit 1: Screening**
    - Baseline history, medications and assessments (including blood sampling and pregnancy testing) in the weeks prior to surgery
  - **Visit 2: Day of surgery/procedure**
    - Blood samples – source of genetic material for PELEUS and analyses required for exploratory end points
    - Whole blood collection – source of monocyte for VELOS
    - Resection of tumour material - source of TILs for VELOS
  - **Visit 3: Safety Follow-up**
    - To include procurement related adverse events

Results

Patient summary

- Ninety patients **(n=90) enrolled** at time of submission
- Median age of **67 years**
- 54 **(60.0%) are male**
- **59 (65.6%) had tissue procurement at first diagnosis**, 31 at relapse
- 19 (21.1%) had **received prior systemic anti-cancer therapy**
- From samples processed (n=74), the **median number of native TIL** was $45.9x10^6$ (range: $0.14x10^6$-$161x10^7$)
- There was **no significant difference in native TIL** numbers between newly diagnosed and recurrent (p=0.307), or treatment-naïve and pre-treated (p=0.149) patients

Results



- At time of data cut-off for submission, **n=90 samples** had undergone analysis with **PELEUS™**
- A median of **71 clonals** were identified in Head and Neck samples (n=16)
- This is consistent with what we observe in large **public data sets (TCGA) where the median is 68**
- This is a lower median than **NSCLC (107) and Melanoma (156)**
- Data for **renal (n=4) and bladder (n=1) still immature** at time of data cut-off

Results

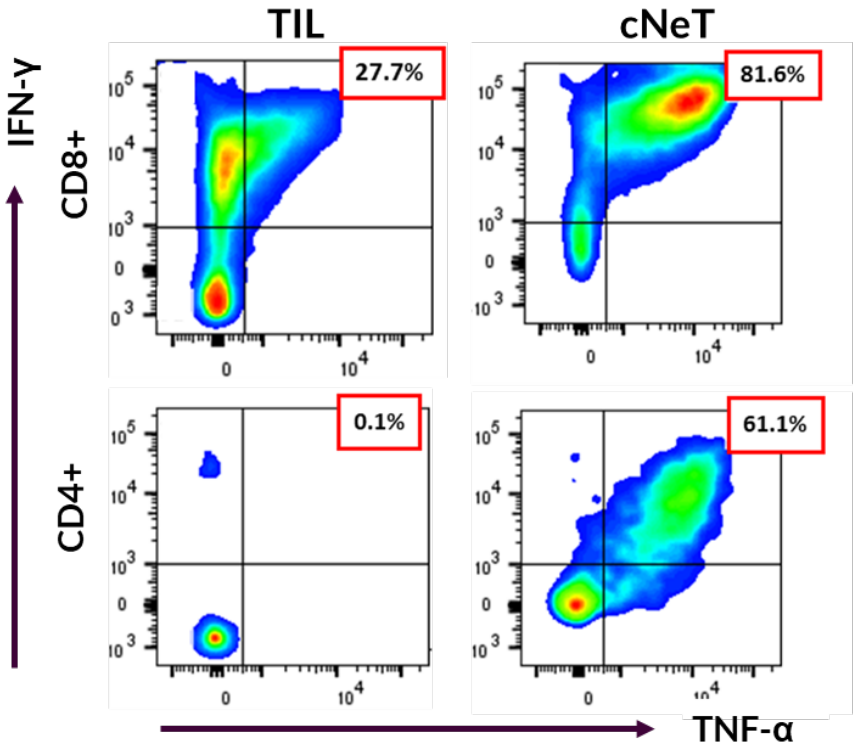
- **VELOS™ manufacturing process** expands **TILs** from tumour fragments whilst **monocyte-derived dendritic** cells are generated from whole blood

- These are then co-cultured after dendritic cells are **pulsed with neoantigen peptides** (determined by PELEUS™) to drive the expansion

- The process delivers both **CD4+ and CD8+ T cells**. There is a strong body of pre-clinical data which shows **CD4+ and CD8+** T cells can work in concert to deliver **robust and durable responses**[1-3]

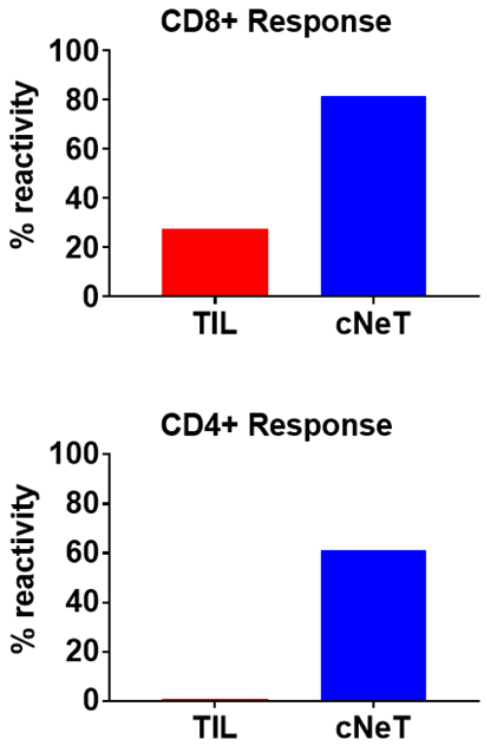
T cell specificity and potency[4]

Cytokine secretion measured through flow cytometric analysis, *n=1*



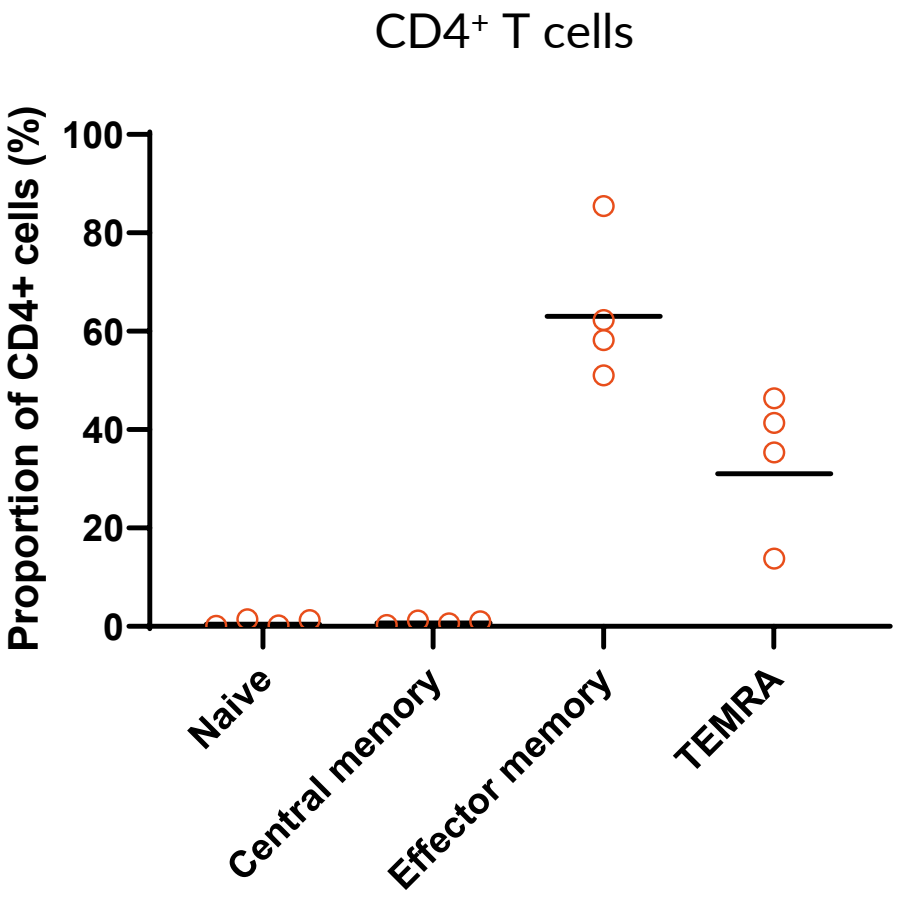
T cell specificity and potency[4]

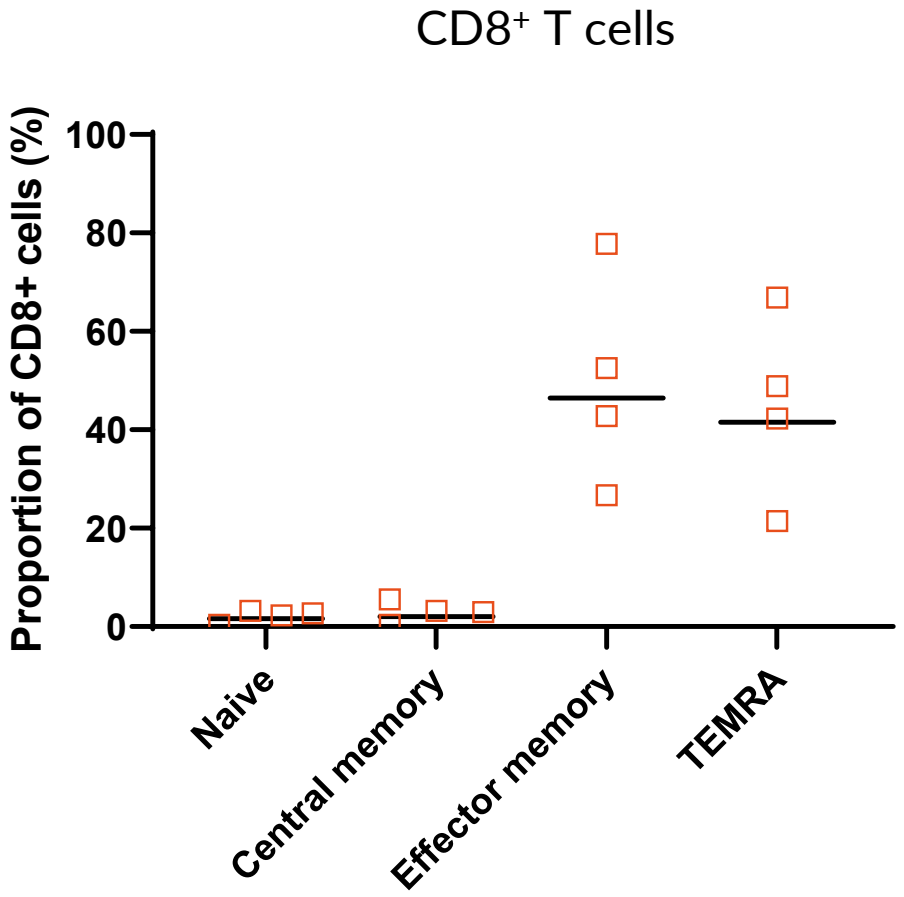
% reactivity, *n=1*



1. Hunder et al., NEJM, 2008;
2. Church et. al., Eur J Immunol, 2014;
3. Antony et al. J Immunol, 2005;
4. Achilles' data measuring the production of inflammatory cytokines in response to clonal neoantigens

Results



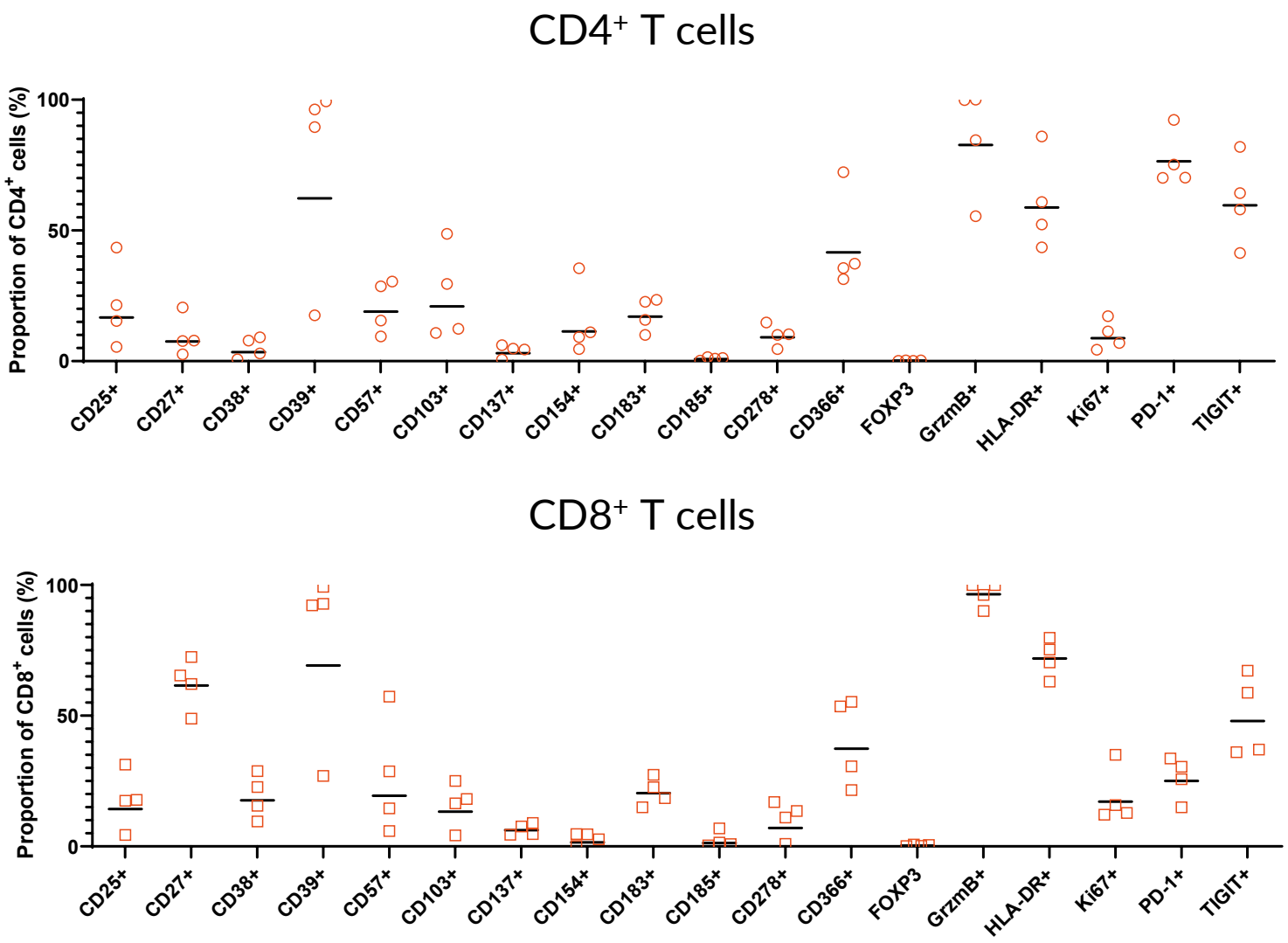


Memory phenotype is dominated by effector memory cells in the process

Full phenotyping of all CD4+ and CD8+ cells

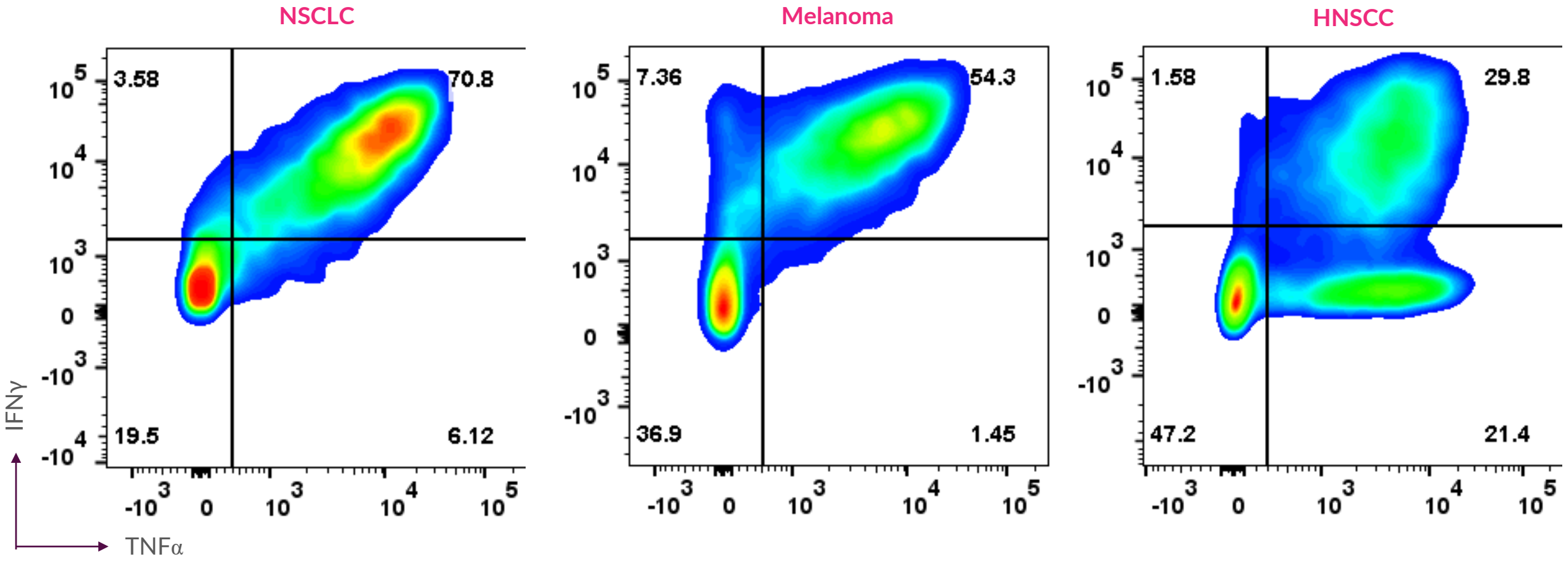
Favourable pattern of phenotypes within both cell types:

- **Conservation of CD25** expression
- **High levels of CD27** expression in CD8+ cells
- **Low expression of CD57**



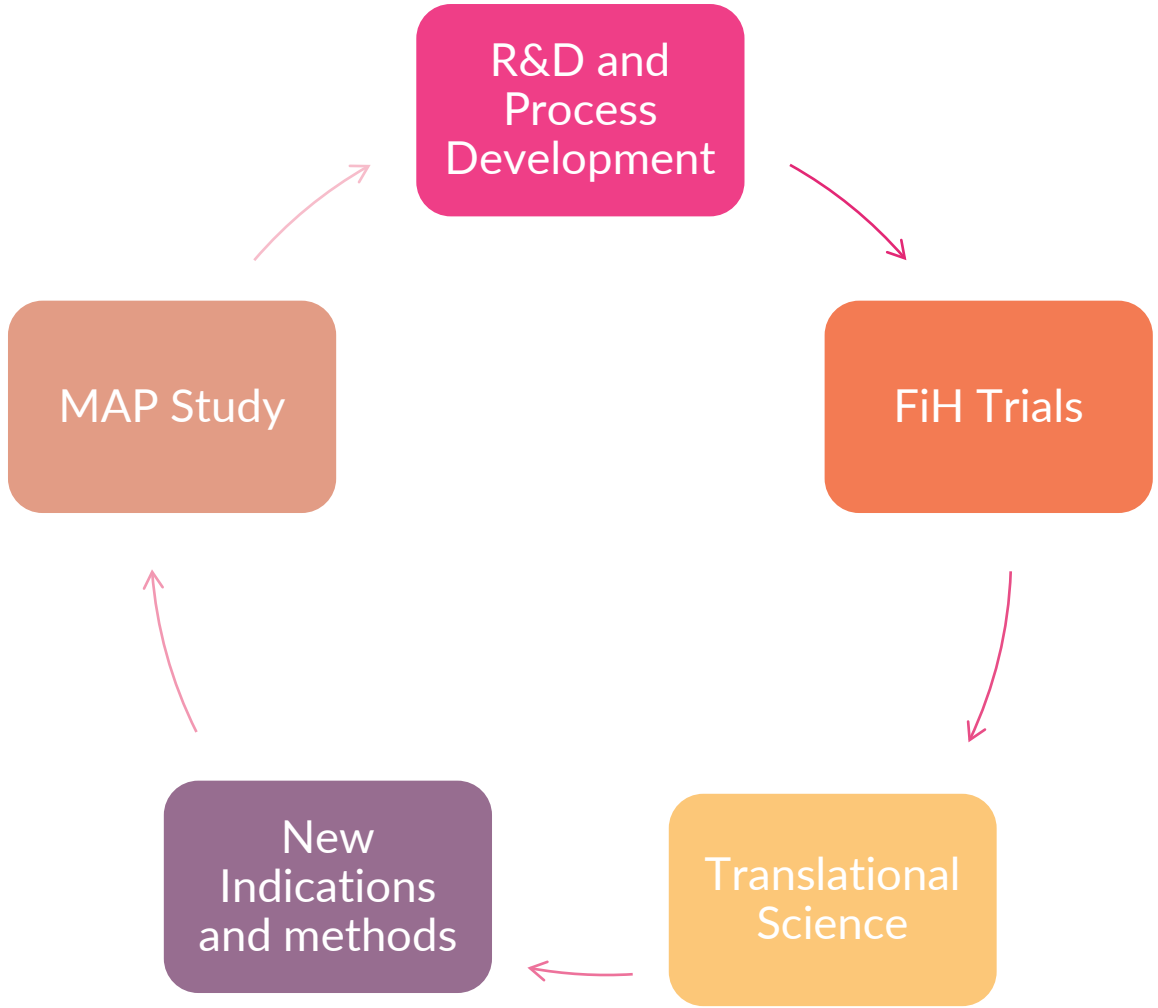
VELOS™ generates with highly potent cNeT cells

Gated CD3⁺-Overnight stimulation with neoantigen peptide pools



Conclusions

- The **Material Acquisition Platform (MAP)** study has been extremely successful in the accumulation of a broad set of tumour-related materials
- MAP continues to expand into new countries and indications
- Initial data suggests **TIL extraction and cNeT production is possible across a range of solid malignancies** and patient characteristics
- Elucidating this information will help to enable the **expansion of Achilles' interventional trials of cNeT** products in new indications
- Future participants will help establish the possibility **of blood-derived cNeT products**, without need for surgical procurement of tissue



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Achilles' Teams

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- Supply Chain
- Clinical Operations
- Clinical Development

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