

MARTA BARISA, SENIOR FELLOW

FISHER LAB

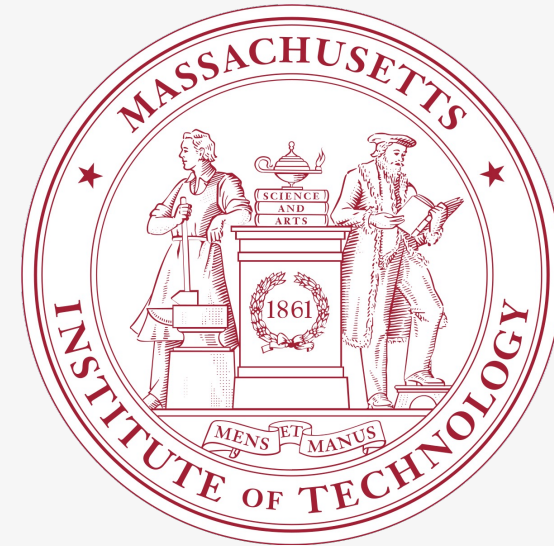
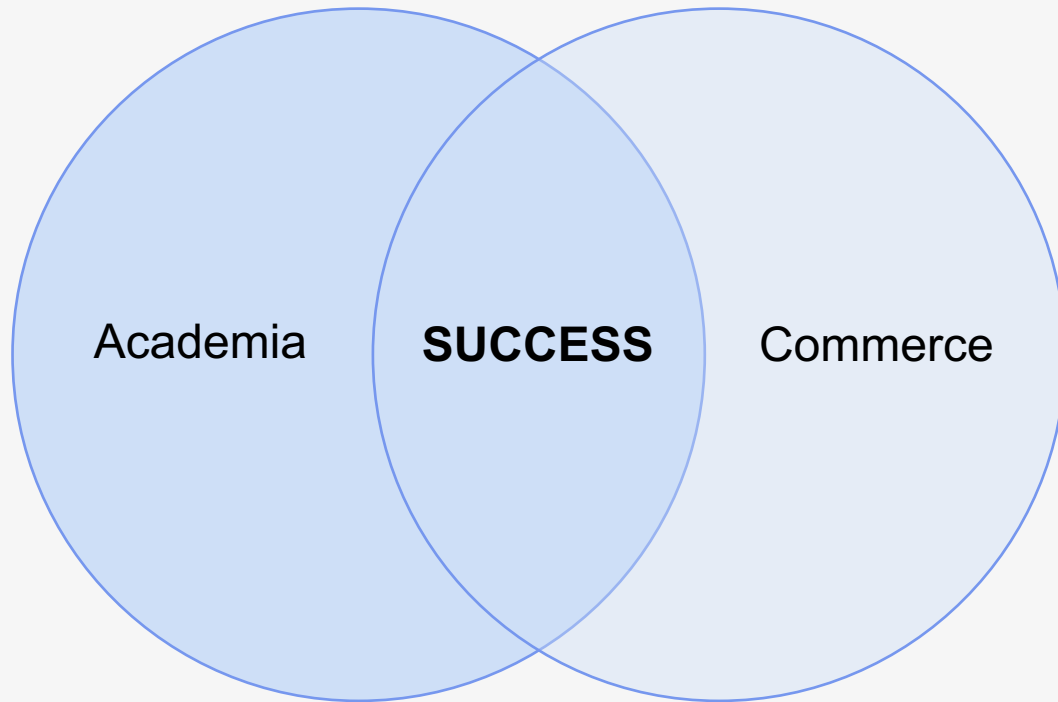
ZAYED CENTRE, UCL GOS ICH



UCL

Innate Lymphocyte Engineering: It Doesn't Have To Be Difficult





WHITEHEAD
INSTITUTE

Engineered $\gamma\delta$ T Product Manufacture



jonathan.fisher@ucl.ac.uk

www.fisher-labs.com

Paediatric oncologist
Clinician & group leader



25th July, 08:30-10:30: Workshop A

Weaponizing Gamma Deltas in the Tumour Microenvironment to Enhance Solid Tumour Therapy

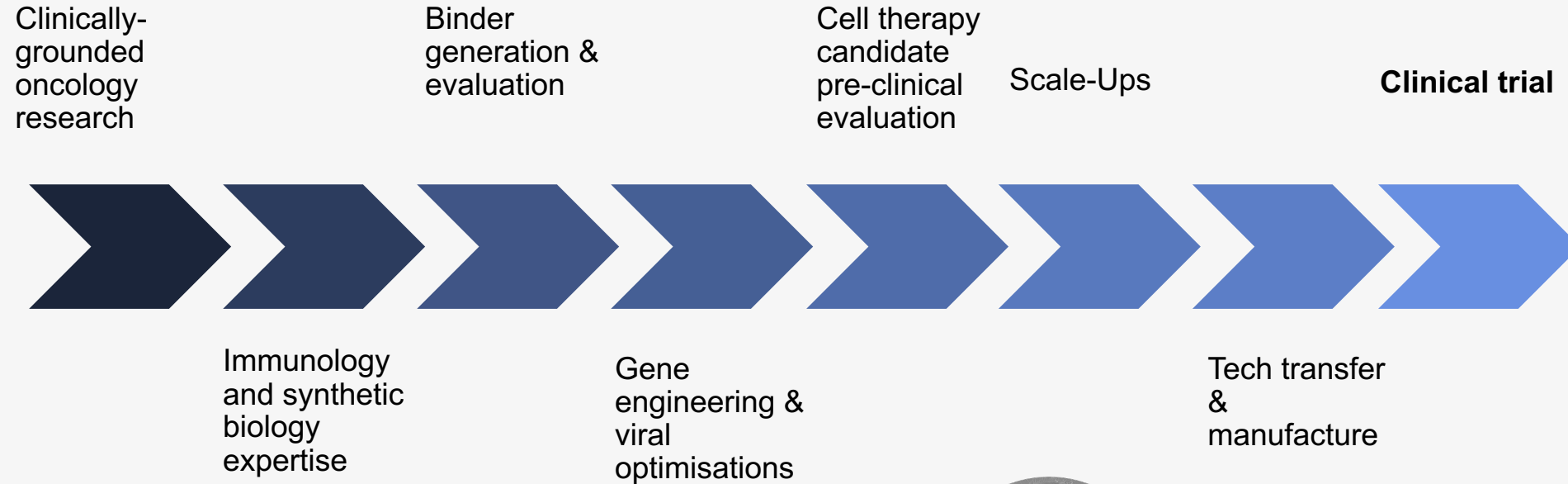
26th July, 14:00-14:30: Engineering GDT Cells to Optimize Therapy

Modelling Gamma Delta T cell homing and persistence to enhance therapeutic delivery

Clinically practicality

1. Human context wherever possible
2. Solid tumour focus
3. Binder generation and evaluation
4. $\gamma\delta$ T cell activation & expansion
5. Cytokine milieu
6. Scale
7. **Lentiviral transduction**

$\gamma\delta T$ @ UCL



All IP under one roof



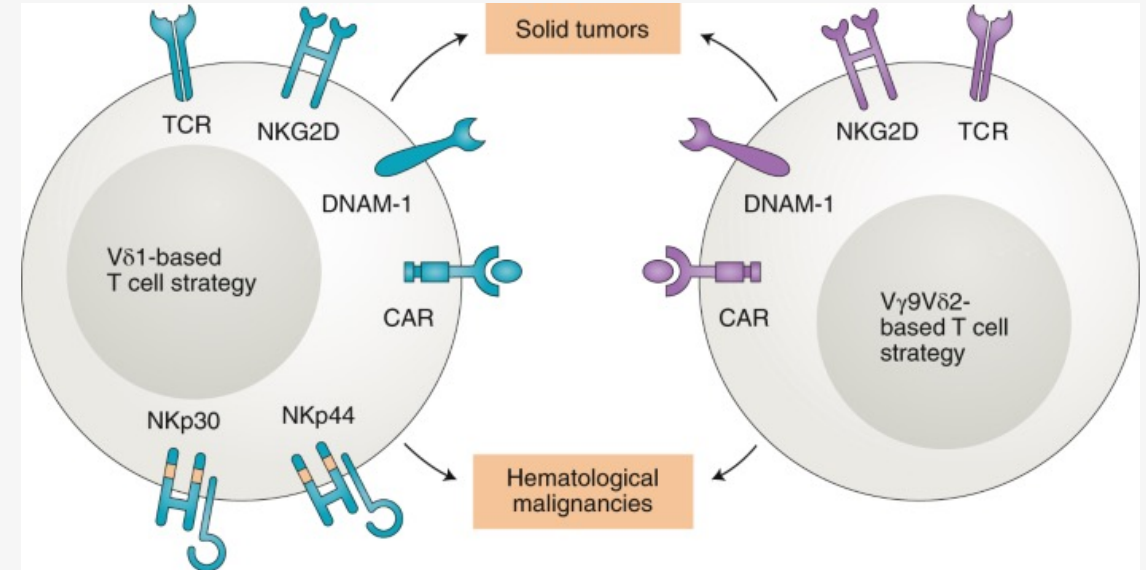
Prof. Farzin Farzaneh
As honorary UCL Prof



Innate $\gamma\delta$ T biology matters, *but*

...

it's a series of inputs that we can nudge in one direction or another with synthetic engineering



$\gamma\delta$ T cell activation & expansion

Frozen leukapheresate

Shorter expansion is better

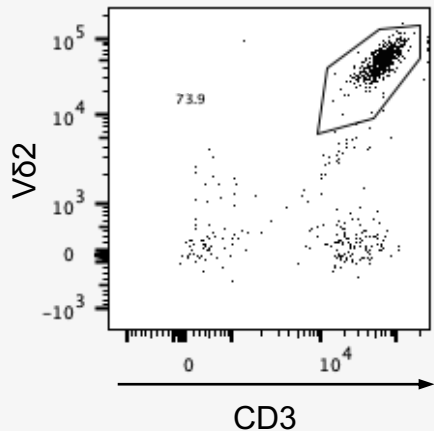
Quality > Quantity

Clinic will be ultimate readout

Scientifically-oriented trial design

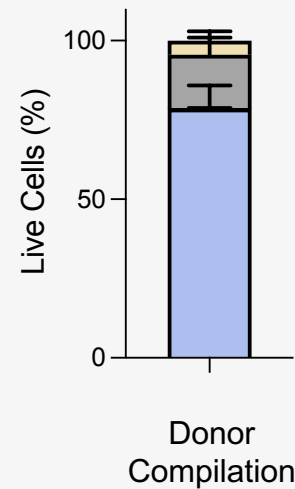
Aminobisphosphonates

V γ 9V δ 2

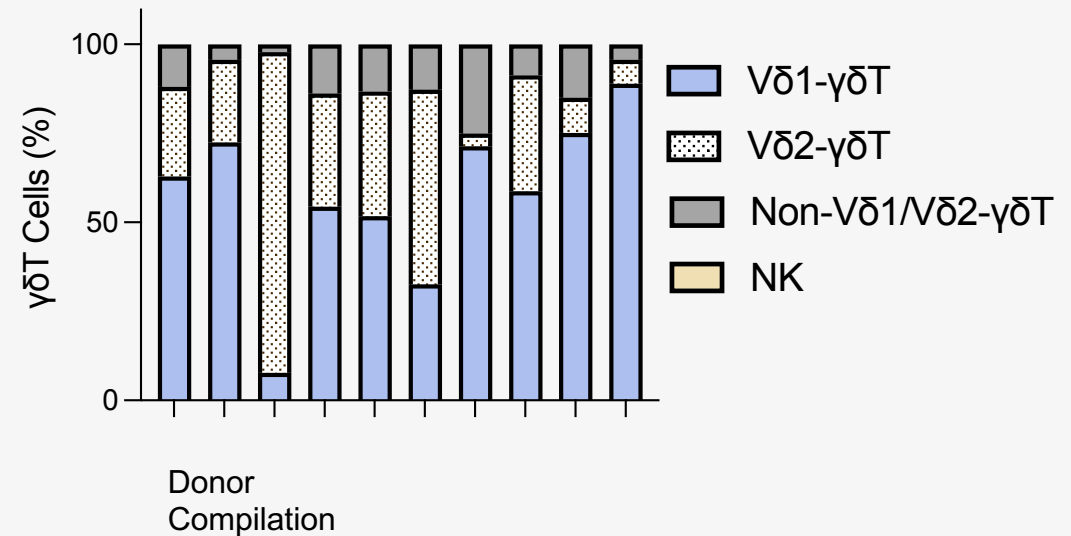


OKT-3 & mAb-based

V δ 1



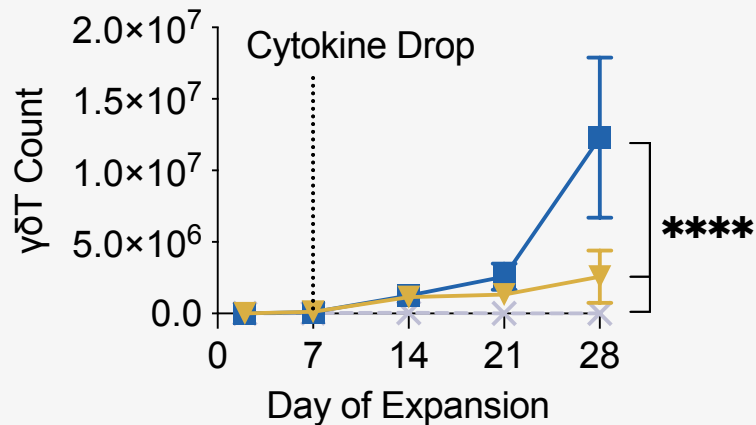
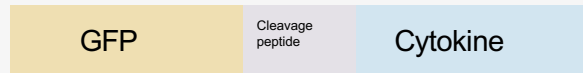
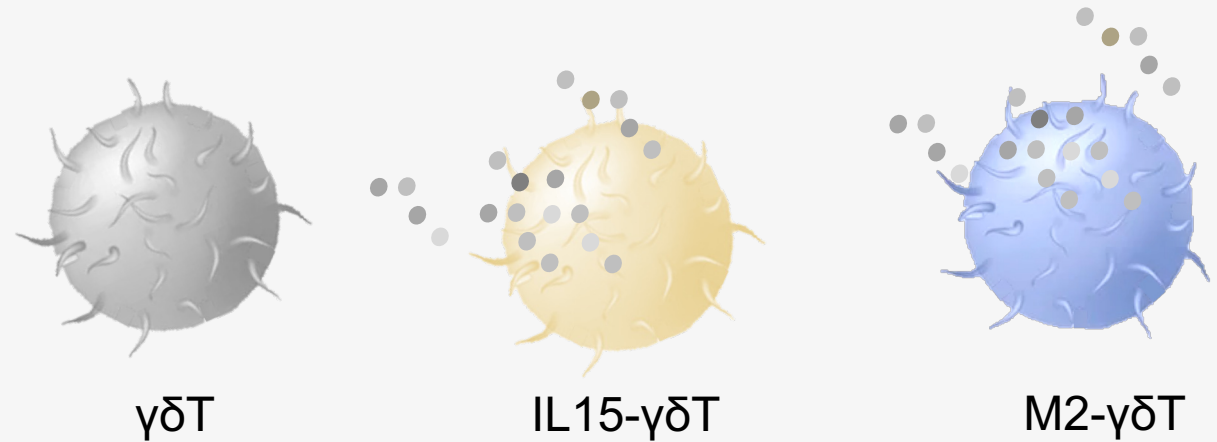
Pan- $\gamma\delta$



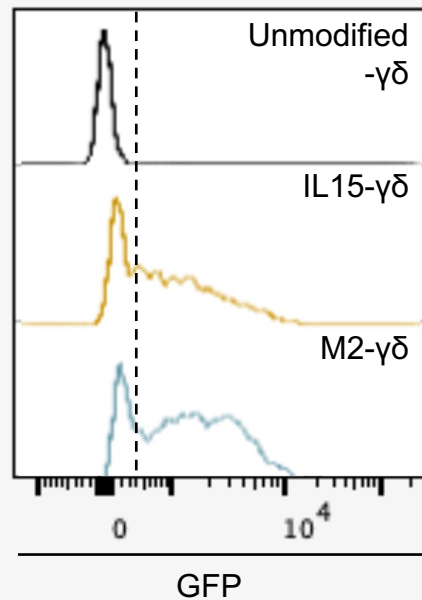
Cytokine Milieu

Common γ -chain cytokines

Cytokine addiction



× Unmodified- $\gamma\delta$ ▼ IL15- $\gamma\delta$
 ■ M2- $\gamma\delta$



Synthetic cytokines outperform natural cytokines

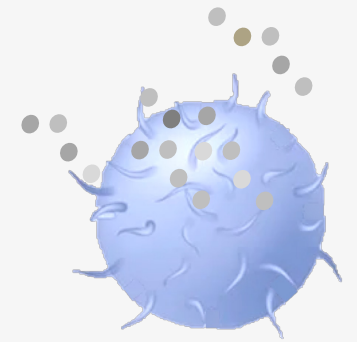
Important for flipping TME

Scale



Format: -OPS & -CAR

Specificity: GD2, pan-cancer Ag targeting library



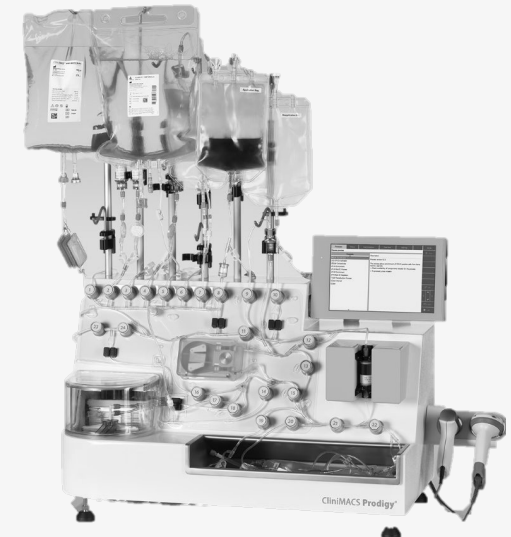
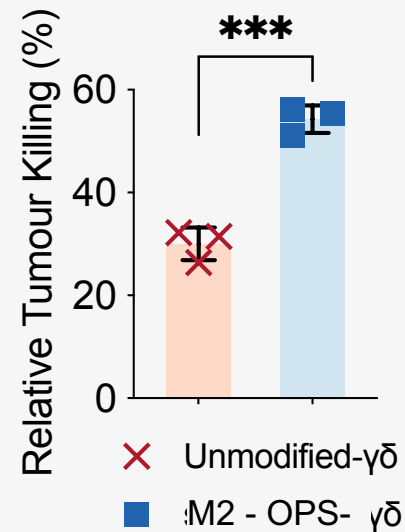
M2-effector- $\gamma\delta$ T



$>10 \times 10^6$ $\gamma\delta$ T cells/cm²



Retention of function

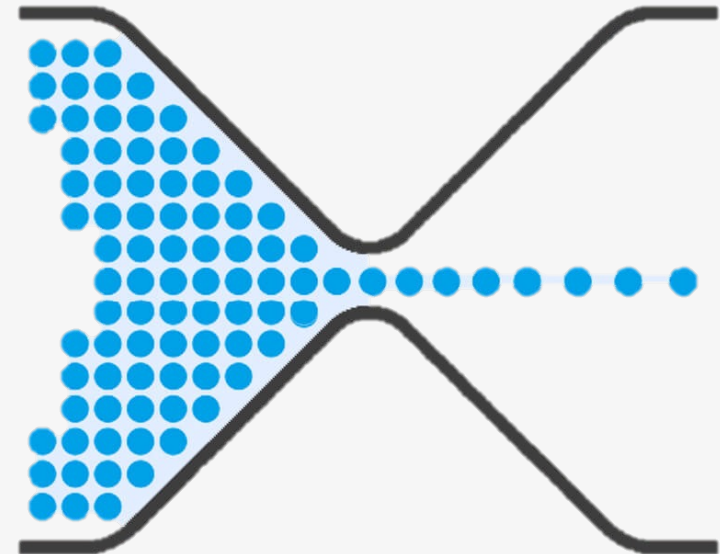


Lentiviral Transduction

Bottleneck for Allo Translation

$\gamma\delta$ T and NK cells

Toxicity, low efficacy, high MOI & cost



Why lentivirus?

Regulatory and clinical experience

non-viral systems

Product viability & health

non-viral systems

Larger construct size

retrovirus

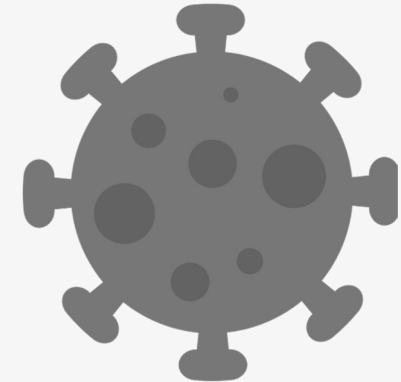
Enhanced safety profile (& regulatory burden)

retrovirus

Easier concentration & storage

retrovirus

VSVg lenti



UCL lenti



Priority filed Feb-22

UCL Lenti Development

Test on V γ 9V δ 2 at standard MOI 15:

- Mock TD
- × VSVg
- ◆ UCL Lenti

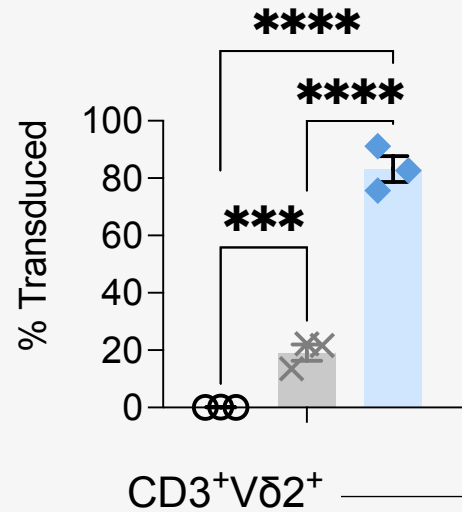
Bicistronic

No *spinoculation*

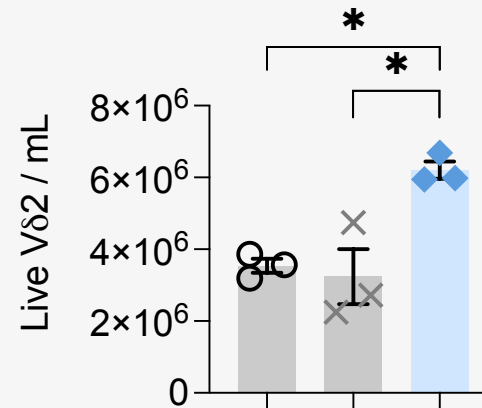
No *enhancers*

Enhancers decreased $\gamma\delta$ T viability

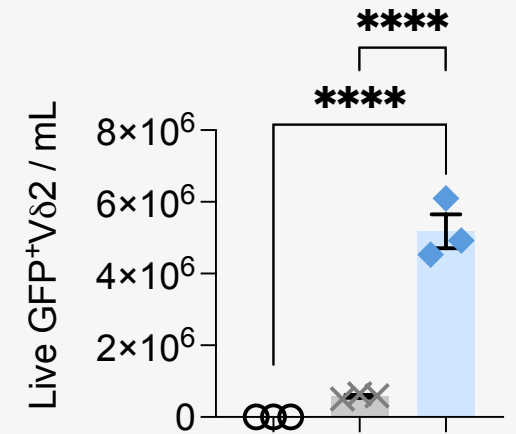
TD Efficiency



Viability



Transduced Product Yield

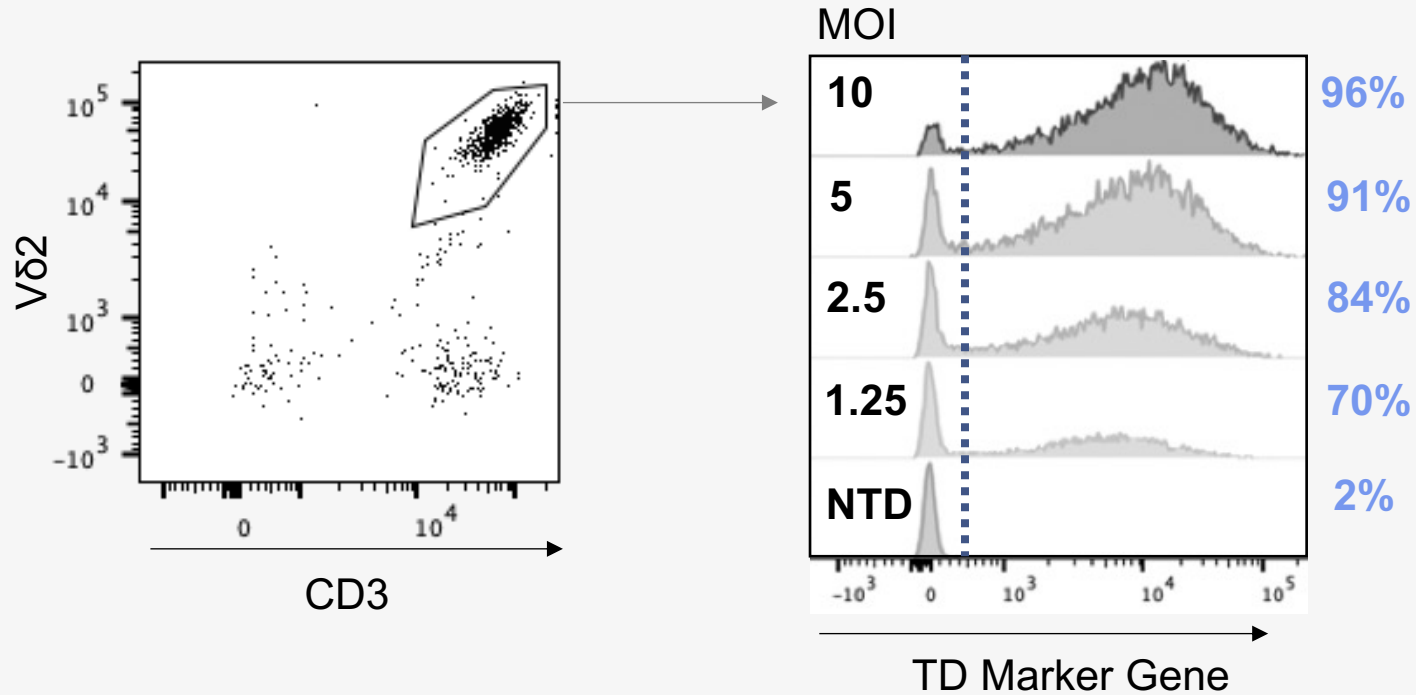


~10x greater TD product yield

UCL Lenti Development

MOI Titer

Bisphosphonate-stimulated V γ 9V δ 2 cells



No *spinoculation*

No *enhancers*

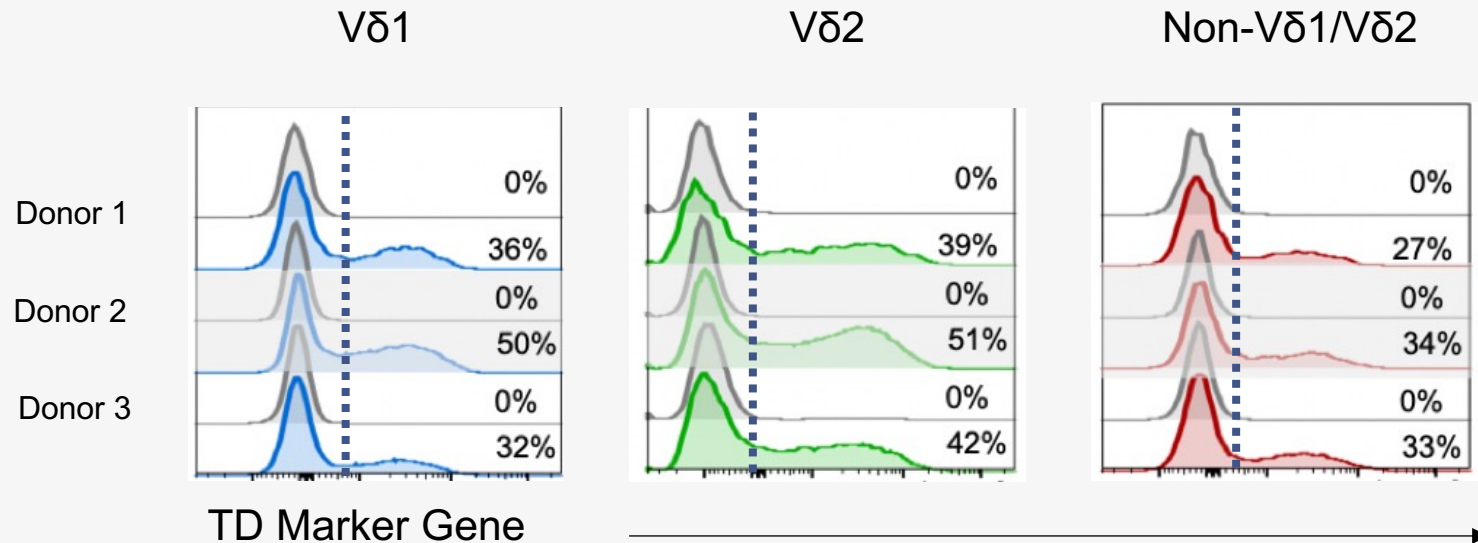
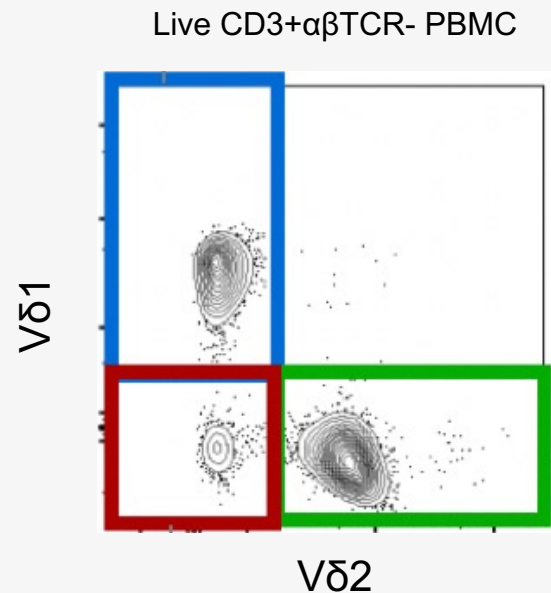
UCL Lenti: Effective for all $\gamma\delta$ T types

MOI 2, OKT-3-based activation

Translationally-relevant bicistronic construct

No spinoculation

No enhancers



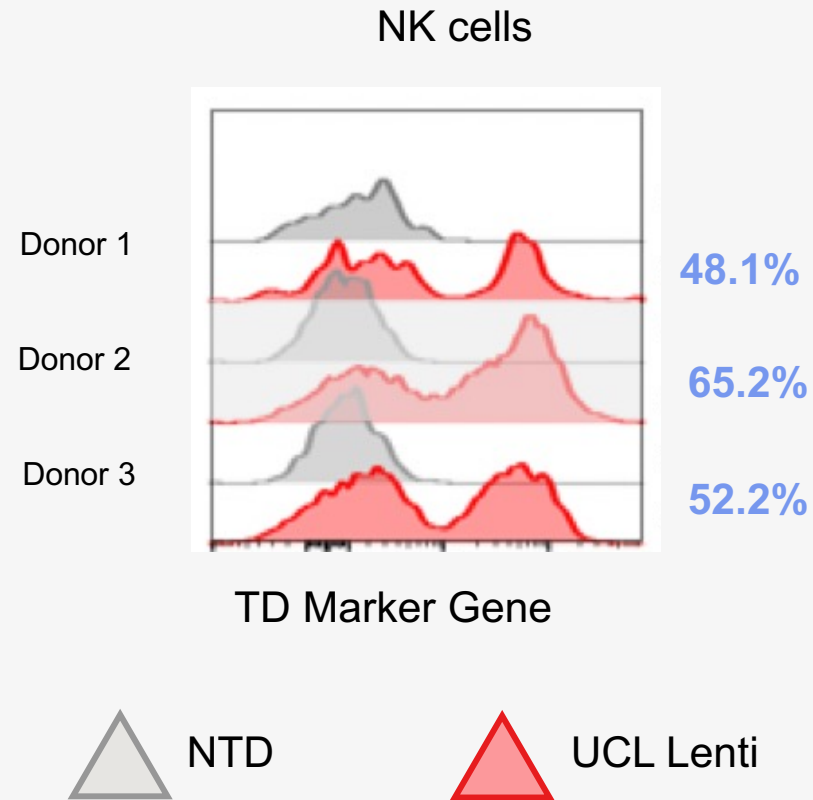
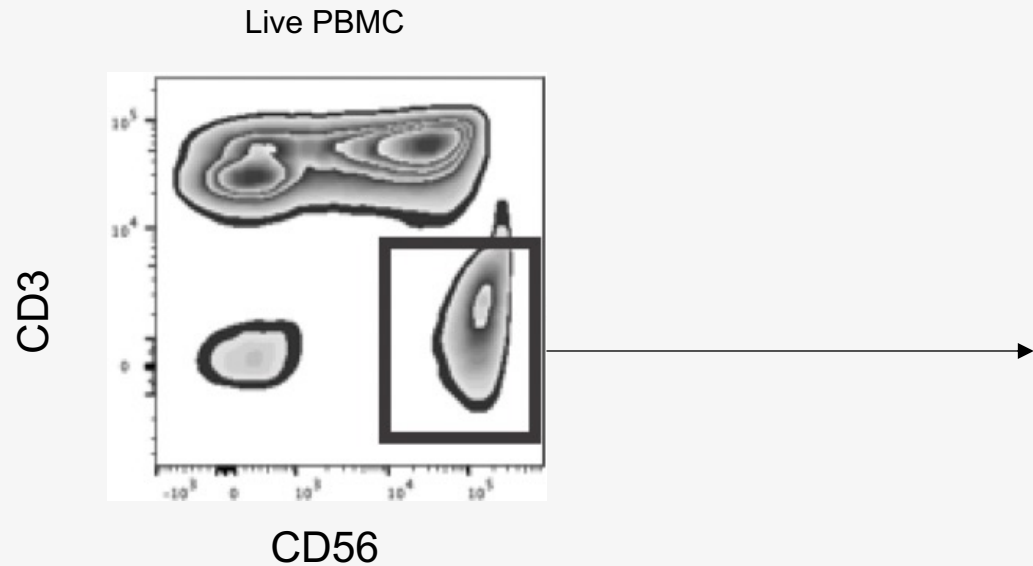
UCL Lenti: NK transduction

MOI 2

Translationally-relevant bicistronic construct

No spinoculation

No enhancers

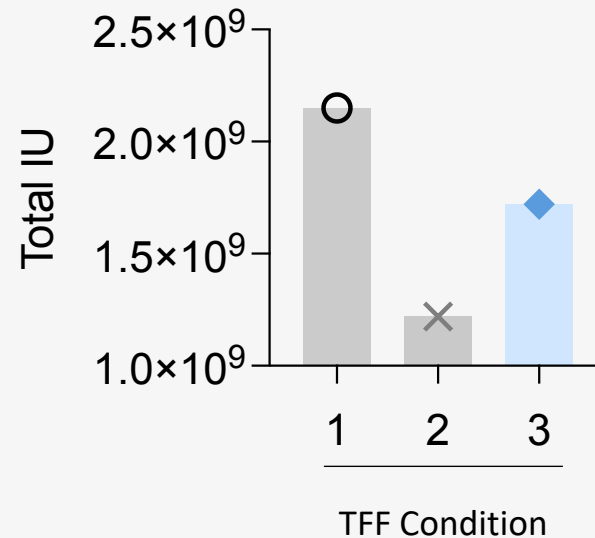
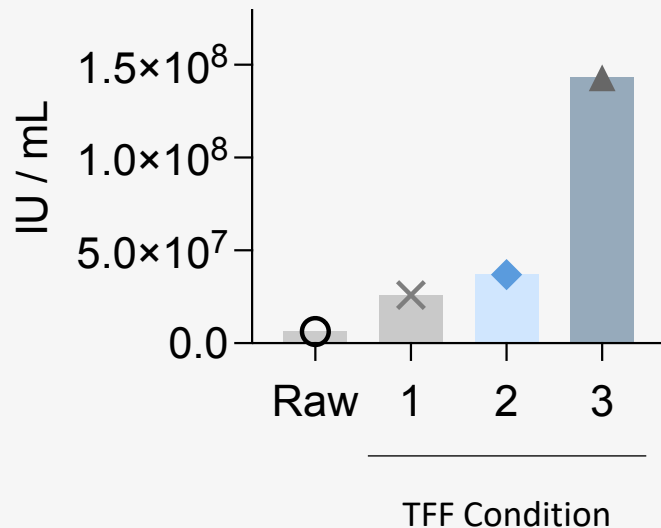


UCL Lenti: Where are we now?

Medium scale optimisations

Superc concentration & storage

Infectious unit yield optimisation: similar yield to VSVg



- Optimised transfection
- Optimised collection media
- Optimised concentration protocol

What next?

Transfer to suspension system

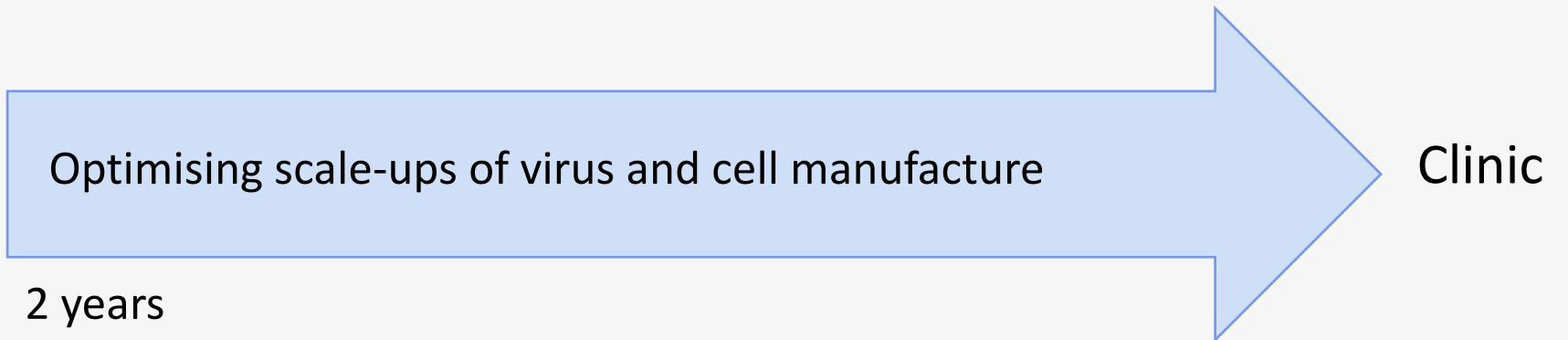
- Bioreactors
- Harvest and concentration optimisation
- Producer & packaging cell lines

In Summary

1. Developing pipelines across different $\gamma\delta T$ subsets
2. Armoured –OPS & armoured –CAR $\gamma\delta T$ engineering
3. At-scale engineered product manufacture
4. Synthetic cytokine evaluation
5. **UCL lenti process optimisation & translation**



UCL TECHNOLOGY
FUND
£££





m.barisa@ucl.ac.uk



Dr Daniel Fowler



Alba Southern



jonathan.fisher@ucl.ac.uk

www.fisher-labs.com

<https://www.ucl.ac.uk/child-health/research/developmental-biology-and-cancer/cancer/jon-fisher-research-page>

Dr Enrique Miranda-Rota
Eleni Vassalou
Beth Hawkins
Angeliki Kanouta
Callum Nattress
Prof. John Anderson
Prof. Kerry Chester
Dr John Counsell



Great Ormond Street
Hospital for Children
NHS Foundation Trust

