

Immunocore Ltd  
iSBTc Washington 30<sup>th</sup> October 2009

Bent Jakobsen  
*Chief Scientific Officer*

*Immunocore*

## Breaking immune tolerance to cancer

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- The immune system has more cytotoxic potential and versatility than can be achieved with a single-target drug
- Breaking immune tolerance to cancer would be most potently achieved with T cells and requires 2 components:
  - More sensitive detection of antigens
  - More potent T cell activation

## Engineering of T cell receptors for breaking tolerance to cancer

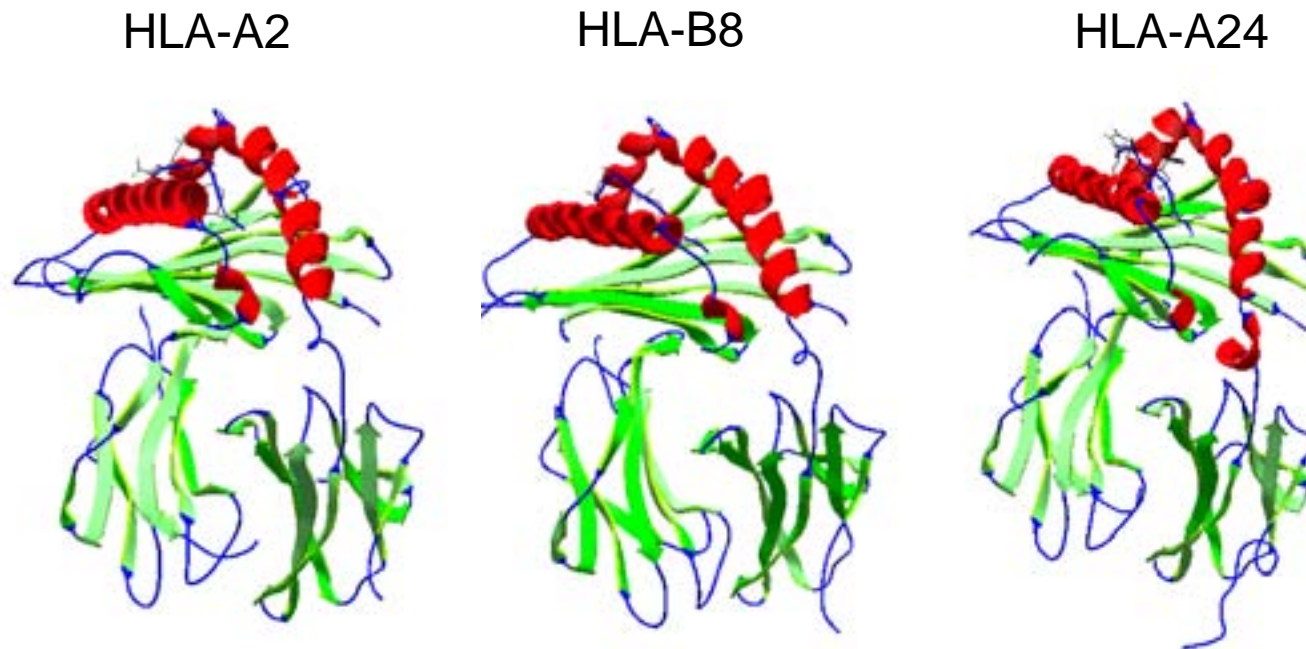
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- Concept: breaking tolerance to cancer by introducing one supra-physiological T cell response (which could not have come through thymic selection)
- Aim: engineering high affinity TCRs to detect low levels of tumor associated peptide antigens and
  - Express TCR on T cells – adoptive therapy approach
  - Fuse TCR to anti-CD3 Ab – T cell re-direction approach

## All class I HLA/peptide antigens can be made as recombinant proteins

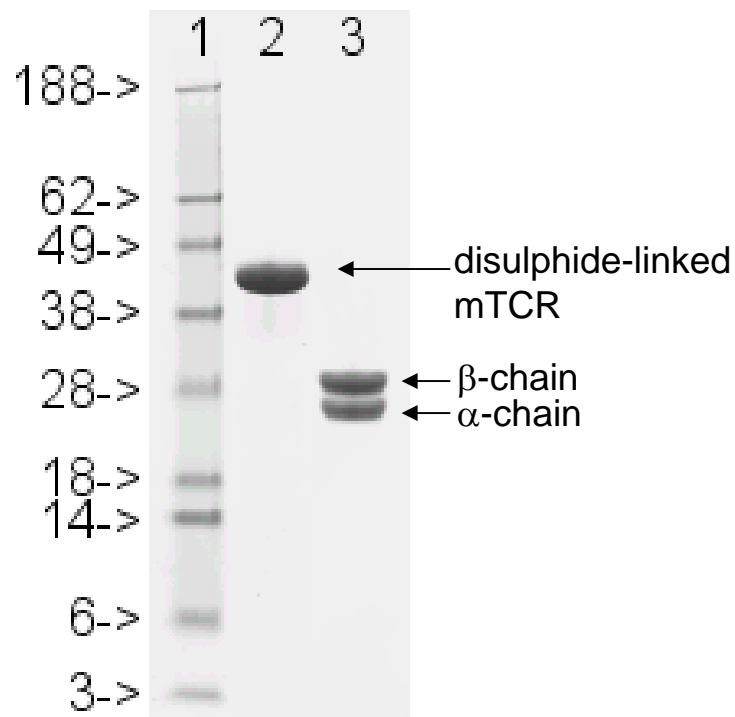
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- All HLA types available in-house
- New peptides synthesized and HLA complex folded by routine procedure



# Engineering soluble monoclonal TCRs

Purified, soluble mTCR

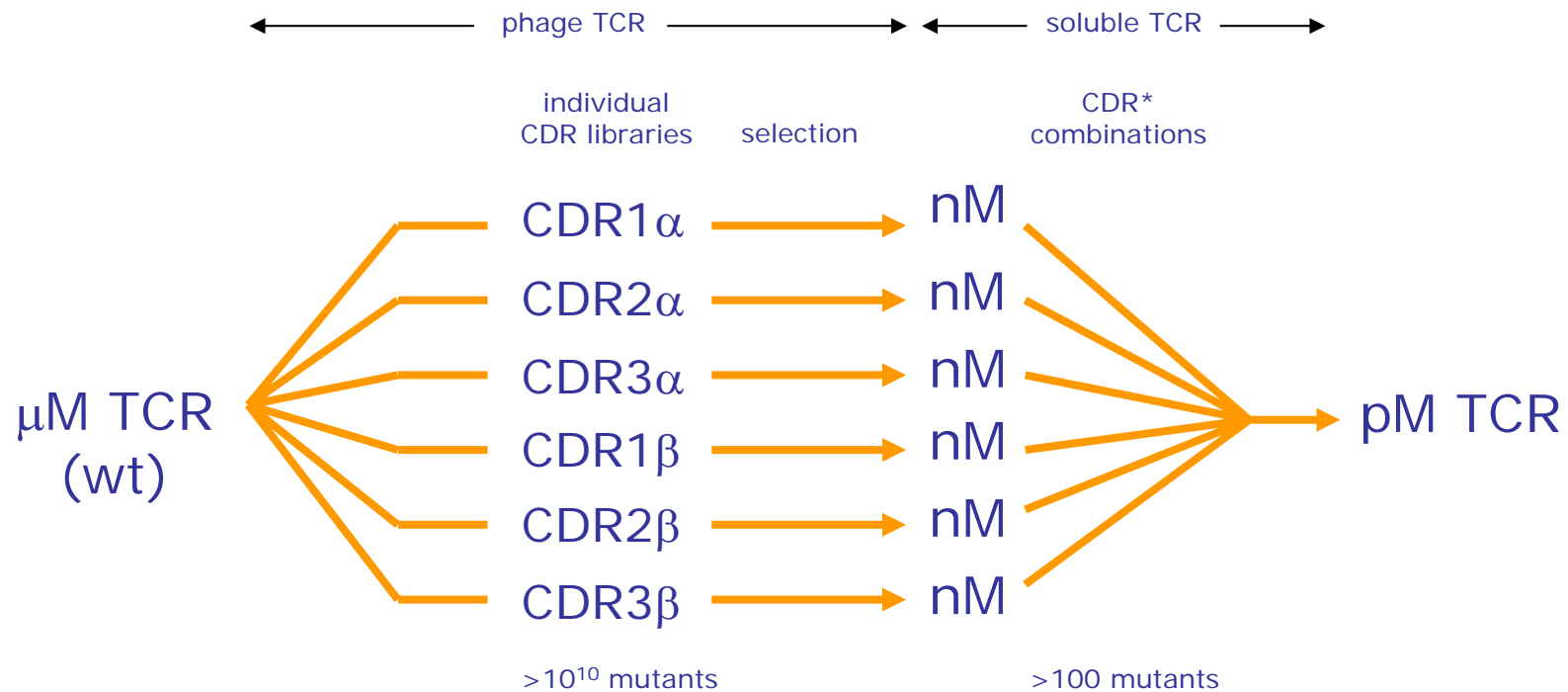


- The two mTCR chains,  $\alpha$  and  $\beta$ , are produced in *E.coli*
- The  $\alpha$  and  $\beta$  chains are refolded (chemically controlled reaction)
- mTCRs are purified by ion exchange and size filtration
- mTCRs are stable at room temperature for months
- mTCRs retain authentic structure:



# Engineering high affinity mTCRs by molecular evolution

## 2 step affinity generation: phage display selection and CDR\* combination



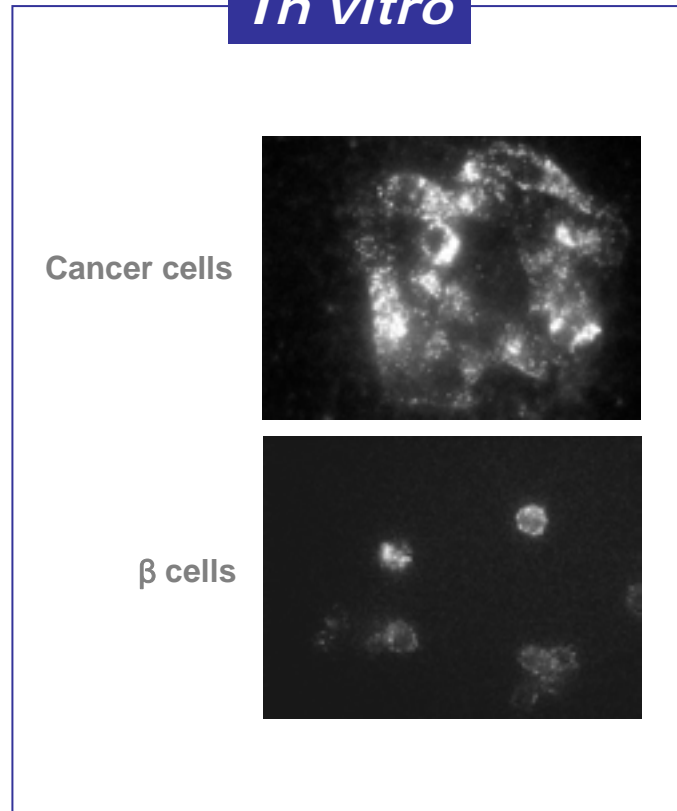
## Engineered high affinity mTCRs – examples

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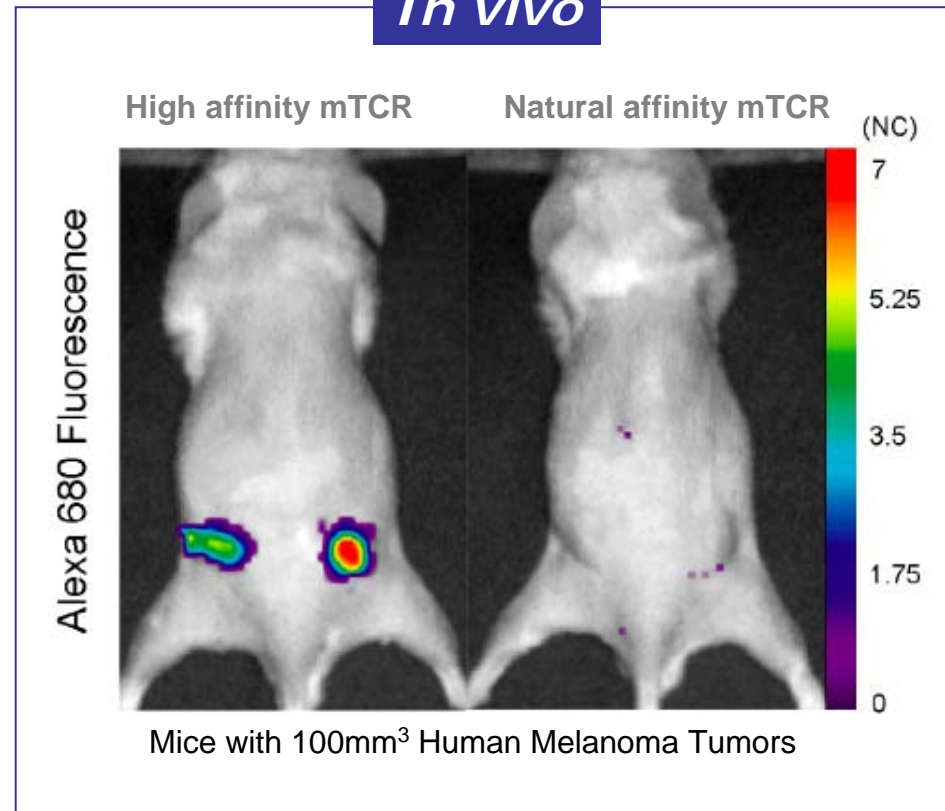
Antigen	Affinity- $K_D$	Binding half-life
NY-ESO 1 ----->	32 $\mu$ M 26 pM	7 s 19 h
MAGE-A3 ----->	281 $\mu$ M 58 pM	nd 9 h
Telomerase ----->	38 $\mu$ M 65 pM	3 s 39 h
gp100 ----->	85 $\mu$ M 11 pM	nd 33 h
WT1 ----->	96 $\mu$ M 16 pM	nd 15 h

# Specific Cell Targeting with Fluorescently Labeled mTCRs

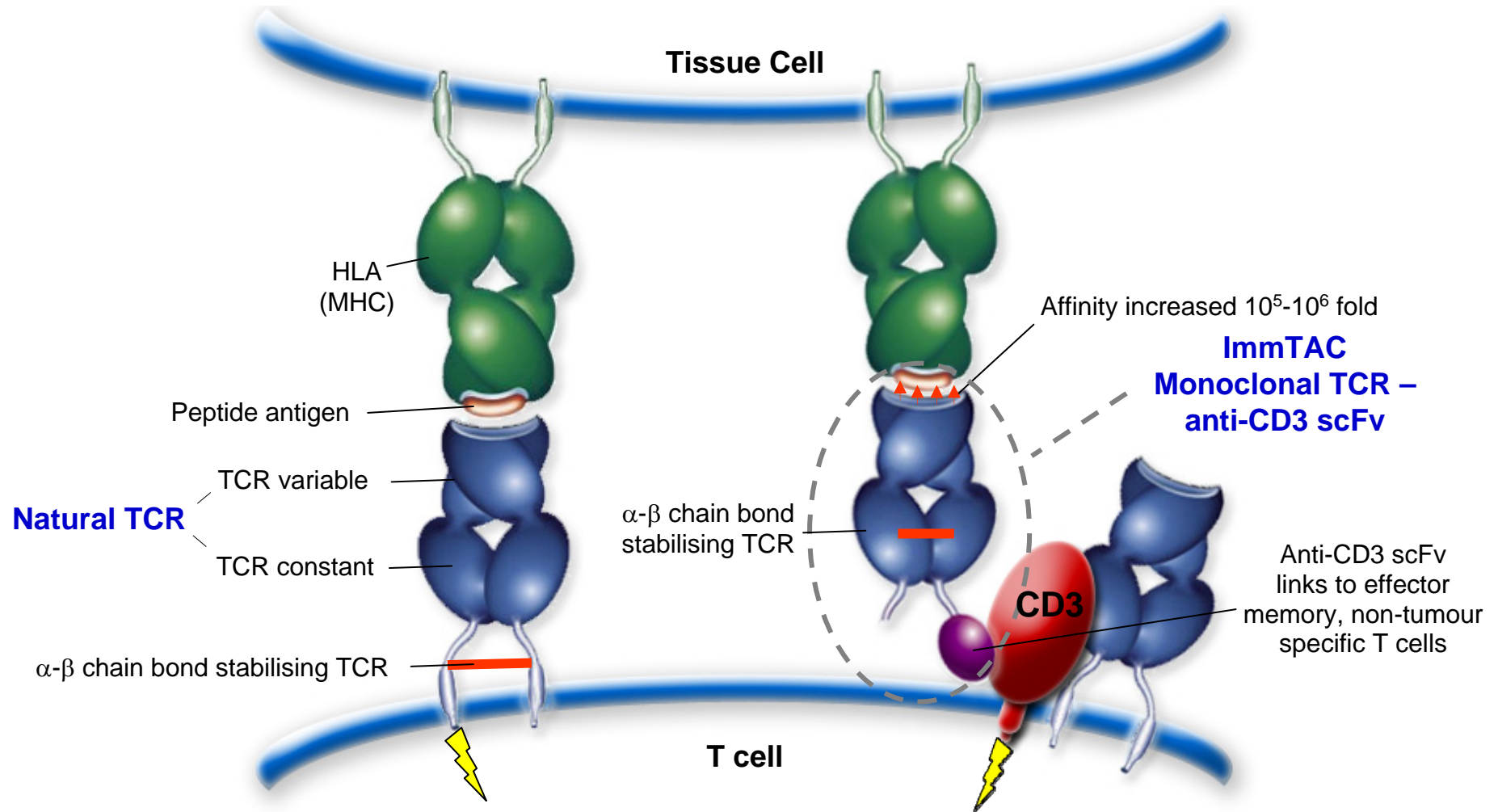
***In vitro***



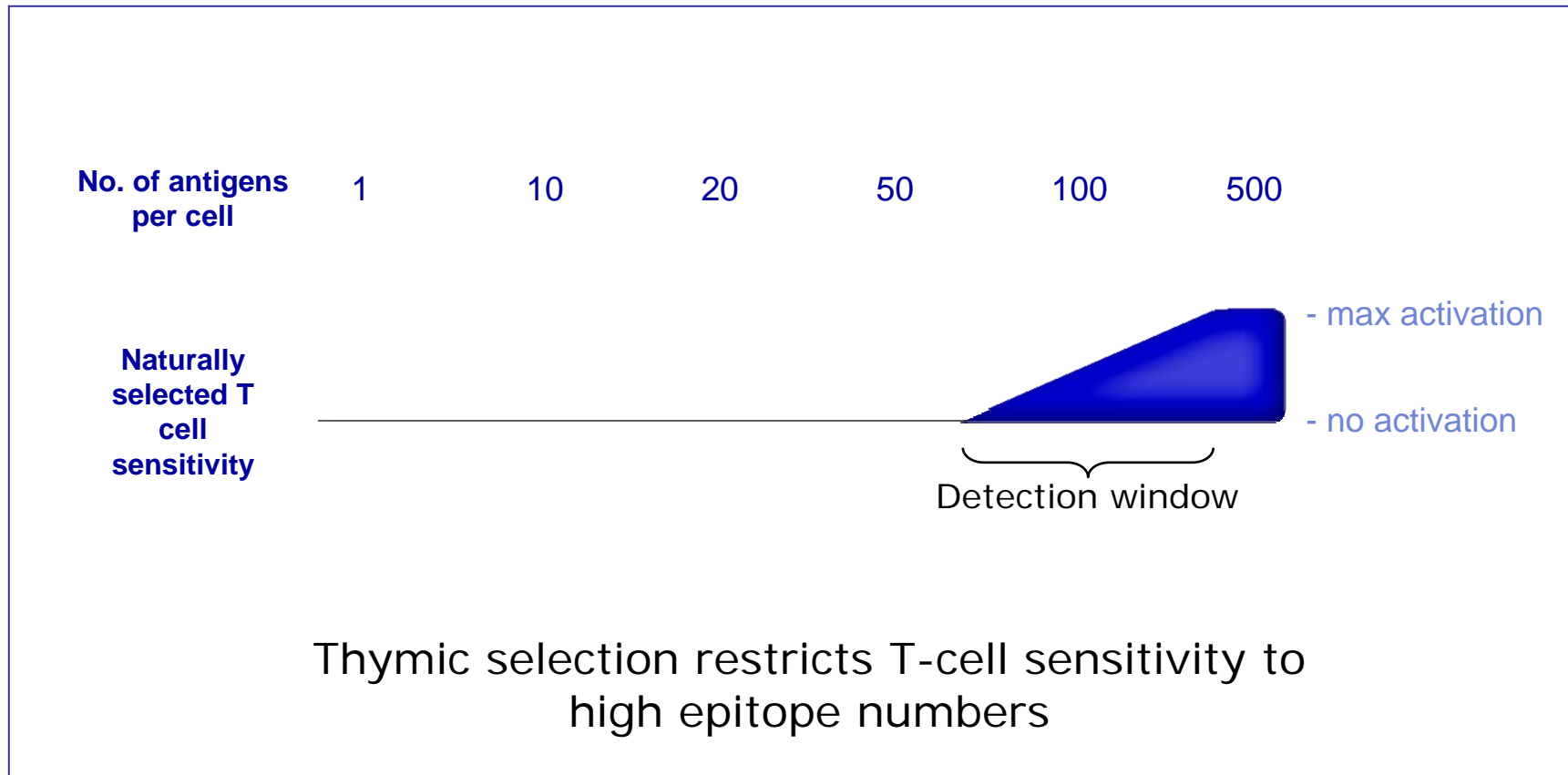
***In vivo***



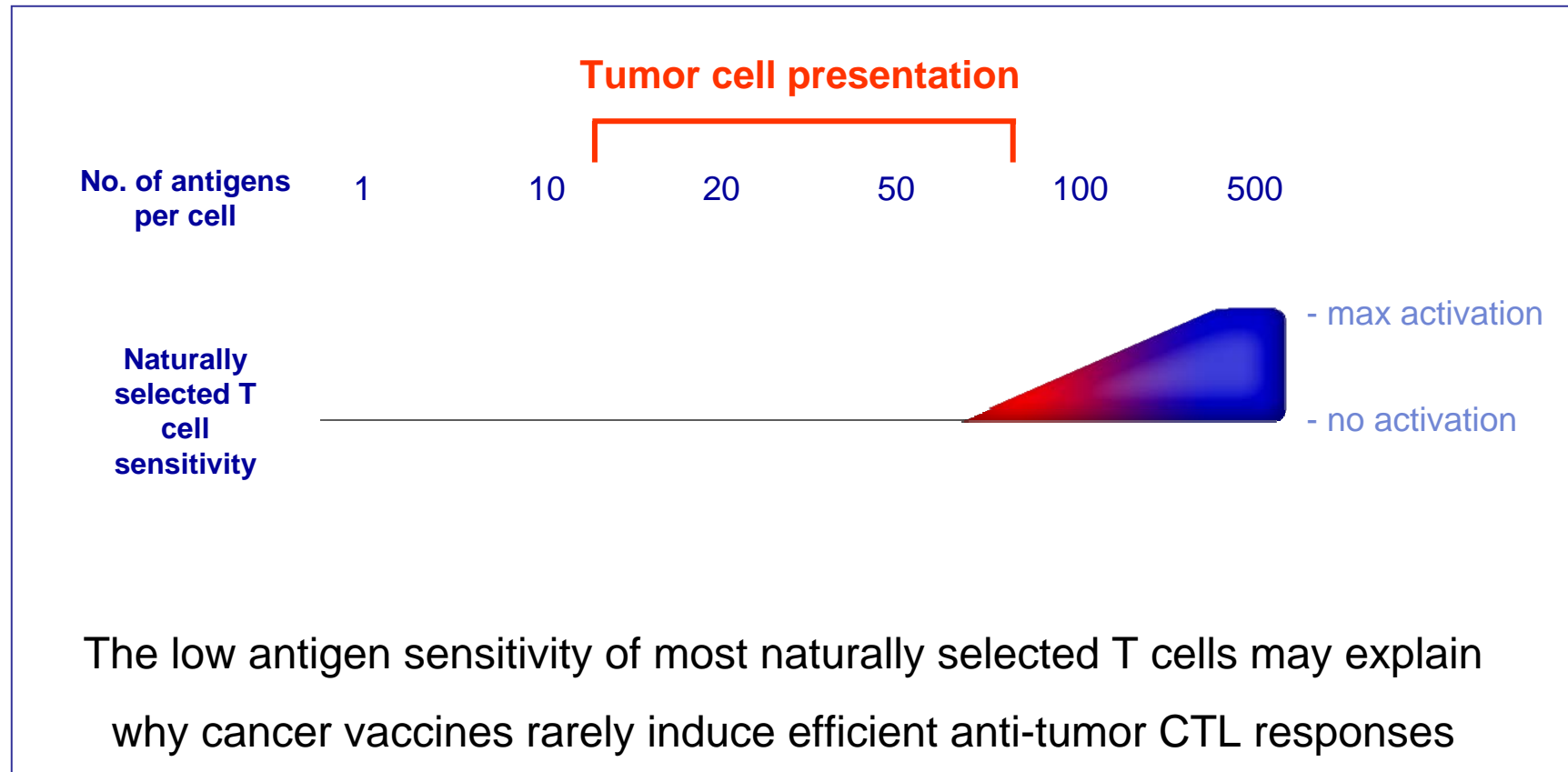
# Re-directed Effector Memory T cell ( $T_{em}$ ) killing by ImmTAC



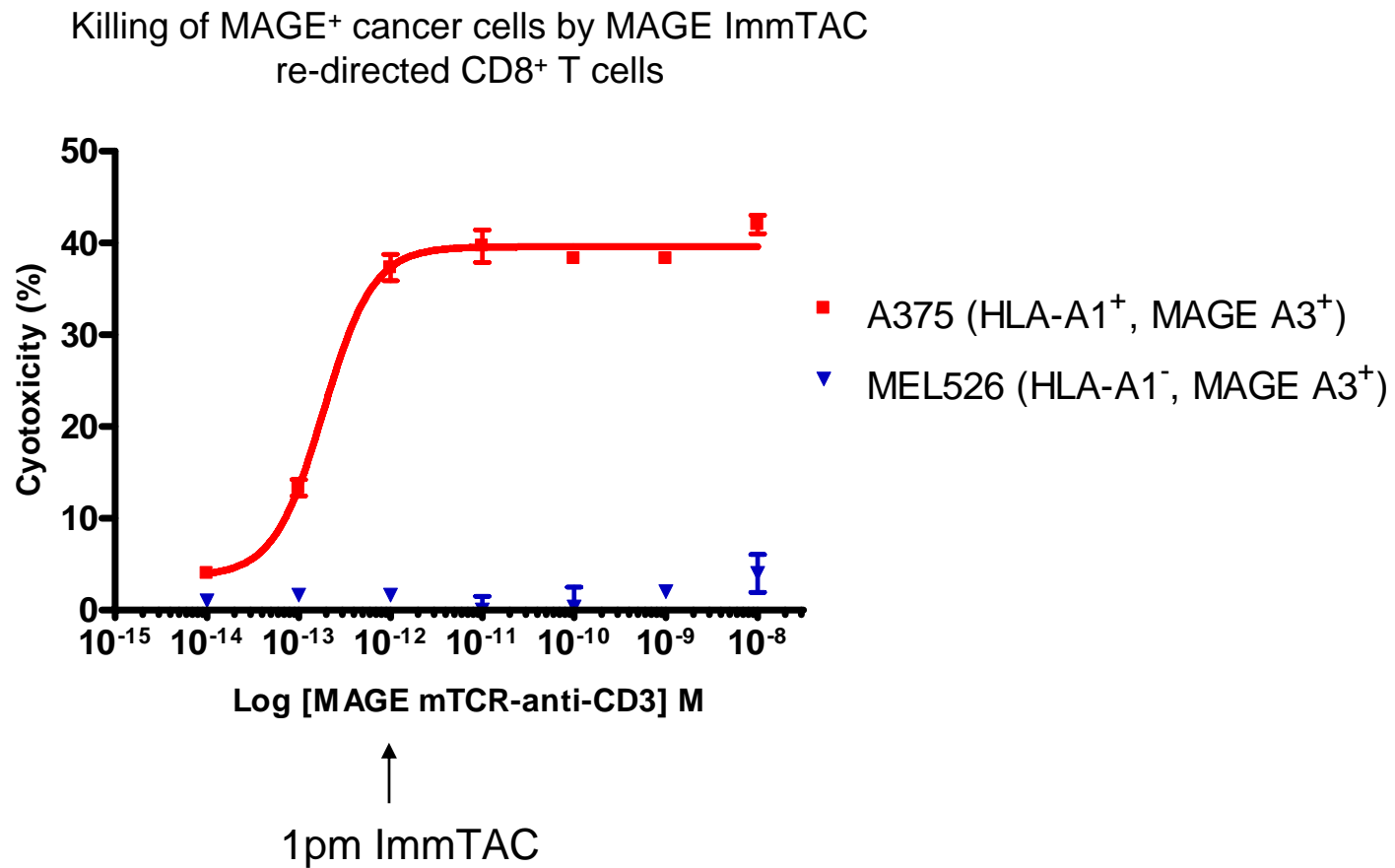
## Early-life selection of T cells restrains anti-cancer potency



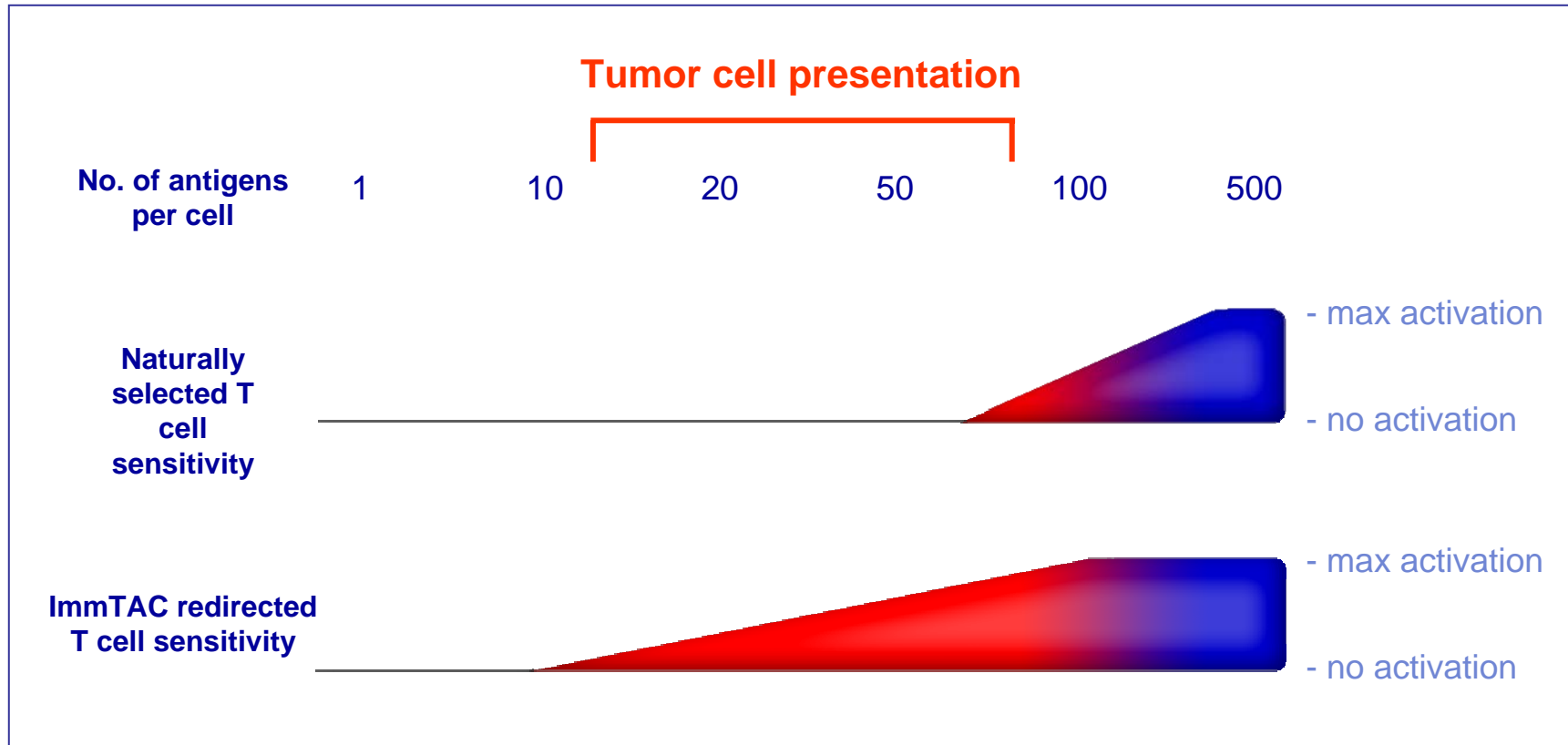
## Tumor down-regulation of TAAPs results in very low target numbers



## Killing Assay with MAGE A3 ImmTAC and EBV-specific T cells



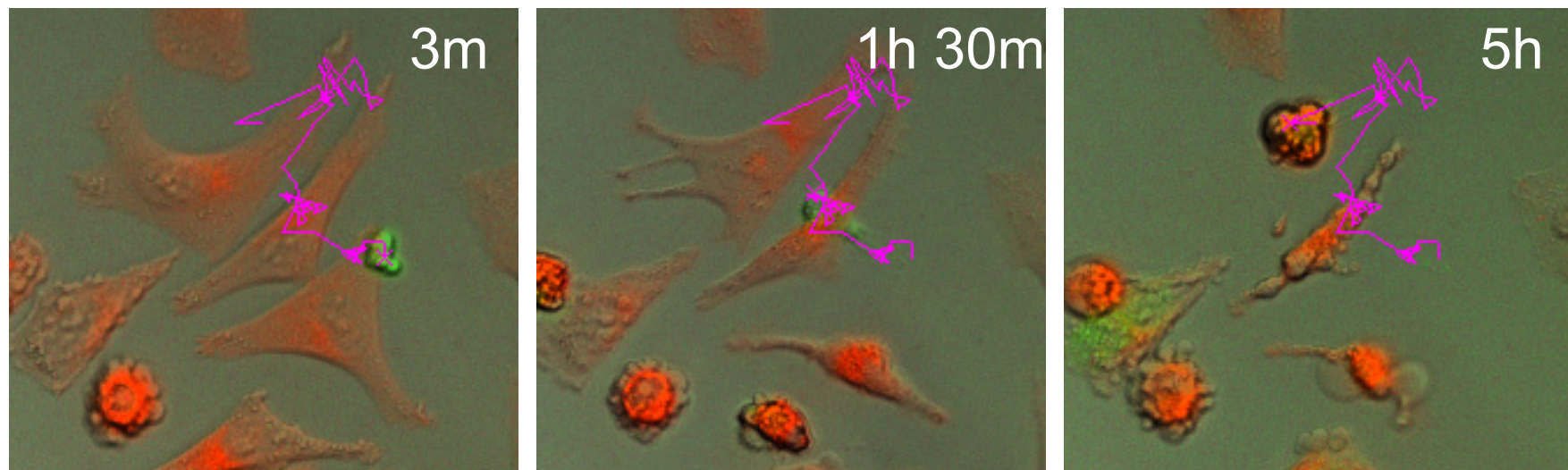
# ImmTACs overcome tumour escape



## ImmTAC directed serial killing

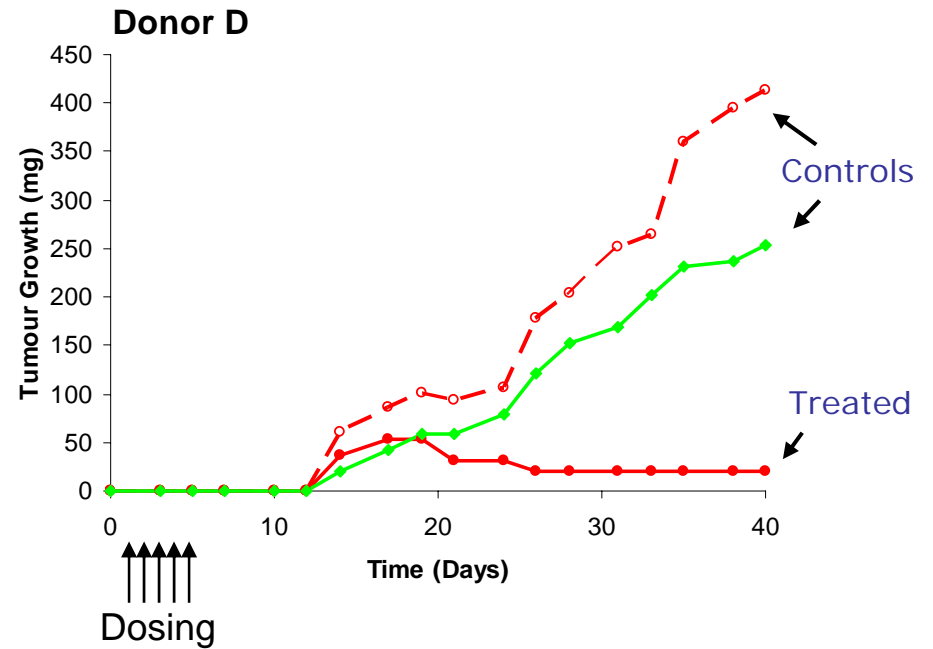
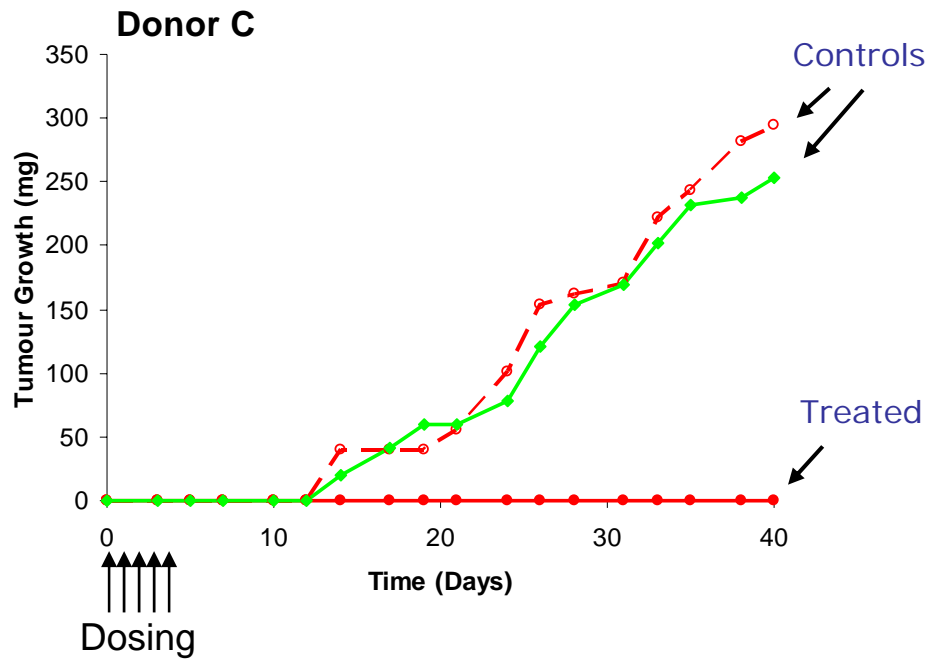
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The **pink trace** shows the movement of an EBV-specific T cell (**green**) as it sequentially kills 3 tumour cells 'decorated' with gp100 ImmTAC

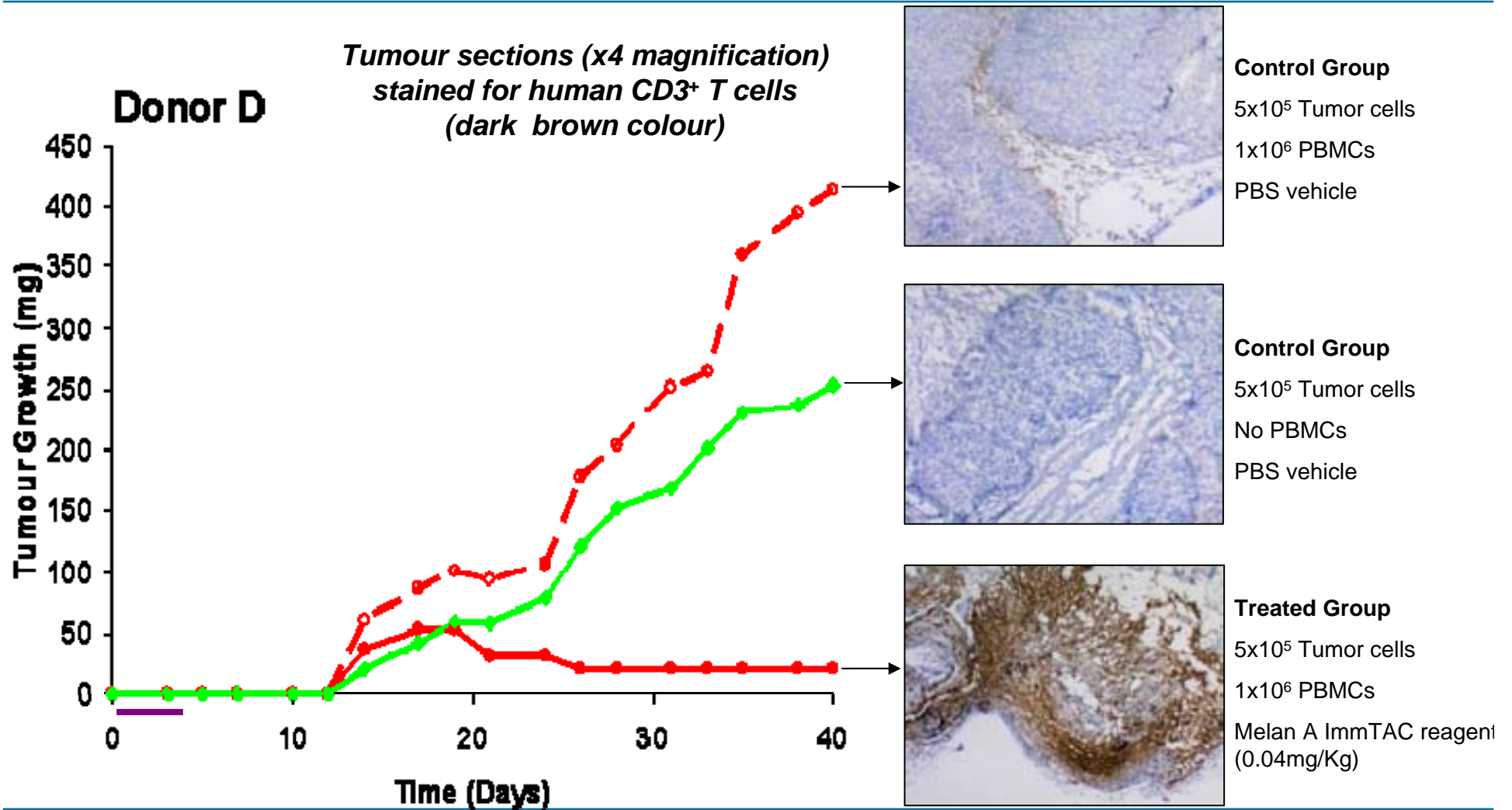


# Control of human tumor cell line by ImmTAC in mice

- ◆— Human tumour cells (MeI526)
- Human tumour cells (MeI526) + Human blod cells (PBMCs)
- Human tumour cells (MeI526) + Human blood cells (PBMCs) + ImmTAC (0.04mg/Kg)



# Melan-A ImmTAC stimulates PBMC tumor infiltration *in vivo*



## Current targets and TCR Pipeline

Antigen target	HLA type	Cancer Indications
Gp100	HLA-A2	Melanoma
NY-ESO 1	HLA-A2	Multiple myeloma
Telomerase	HLA-A2	Head and neck, pulmonary, renal
WT-1	HLA-A2	Leukaemia, ovarian, colorectal, renal
MAGE A3	HLA-A1	NSCLC, RCC, HCC
PSCA	HLA-A2	Prostate, bladder, pancreatic
Survivin	HLA-A2	SCLC, breast, HCC
Her-2neu	HLA-A2	Breast
WT-1	HLA-A24	Leukaemia, ovarian, colorectal, renal
MAGE A3	HLA-A2	NSCLC, RCC, HCC

Antigen target	HLA type	Infectious Disease Indication
HIV gag	HLA-A2	HIV AIDS
HCV	HLA-A2	Hepatitis C

# Summary

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- Human T Cell Receptors can be engineered as monoclonal TCRs:
  - soluble, stable proteins
  - pico-molar binding affinities for HLA-peptide
  - fusions to anti-CD3 scFv -> **ImmTACs**
- **ImmTACs**
  - Re-direct non-tumour specific Effector Memory (EM) T cells
  - Activation and killing against tumour cells presenting <10 antigens
- Pipeline of ImmTACs targeting multiple cancers
- First clinical trial scheduled 2010:
  - gp100 in melanoma

# Thank you

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Katy Adams, Rebecca Ashfield, Emma Baston, Edward Beaumont, Alan Bennett, Frayne Bianchi, Giovanna Bossi, Jo Brewer, Brian Cameron, Rebecca Dennis, Martin Ebner, Jessie Gavarret, Andrew Gerry, Jane Harper, Namir Hassan, Andy Johnson, Yi Li, Nat Liddy, Nikolai Lissin, Tara Mahon, Yvonne McGrath, Peter Molloy, Sam Paston, Nick Pumphrey, Malkit Sami, Deborah Sutton, Penio Todorov, Annelise Vuidepot, Dan Williams, Fang Yuan

## Collaborations:

Carl June  
Michael Kalos  
Jim Riley  
Meir Glick  
Jonathan Boulter  
Andy Sewell  
David Price  
George Fu Gao  
Per Thor Straten  
Enzo Cerundolo  
Erik Hooijberg  
Pierre Coulie  
Cassian Yee

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