A Bispecific Chimeric Antigen Receptor Molecule Enhances T cell Activation Through Dual Immunologycal Synapse Formation and Offsets Antigen Escape in Glioblastoma

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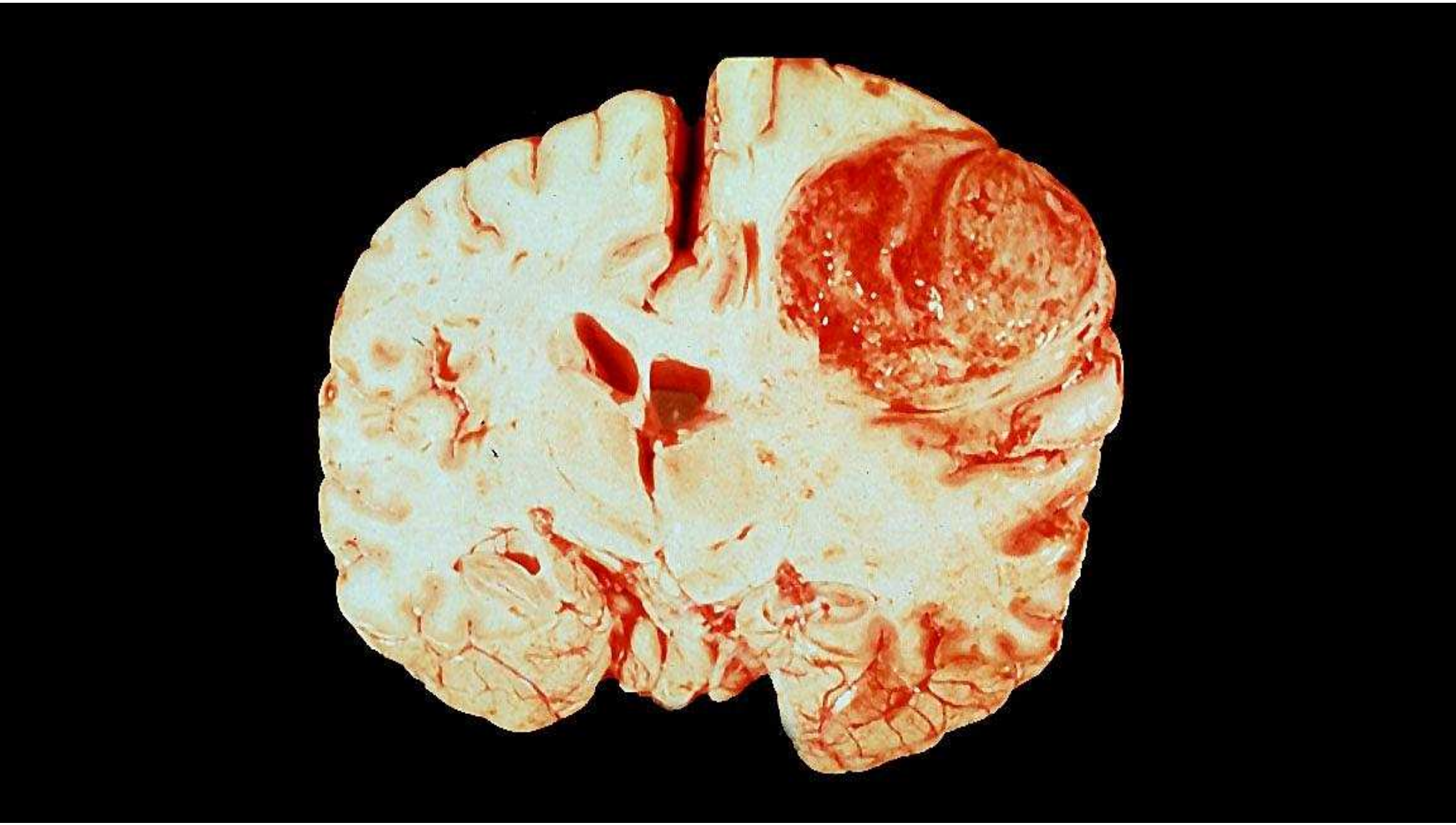
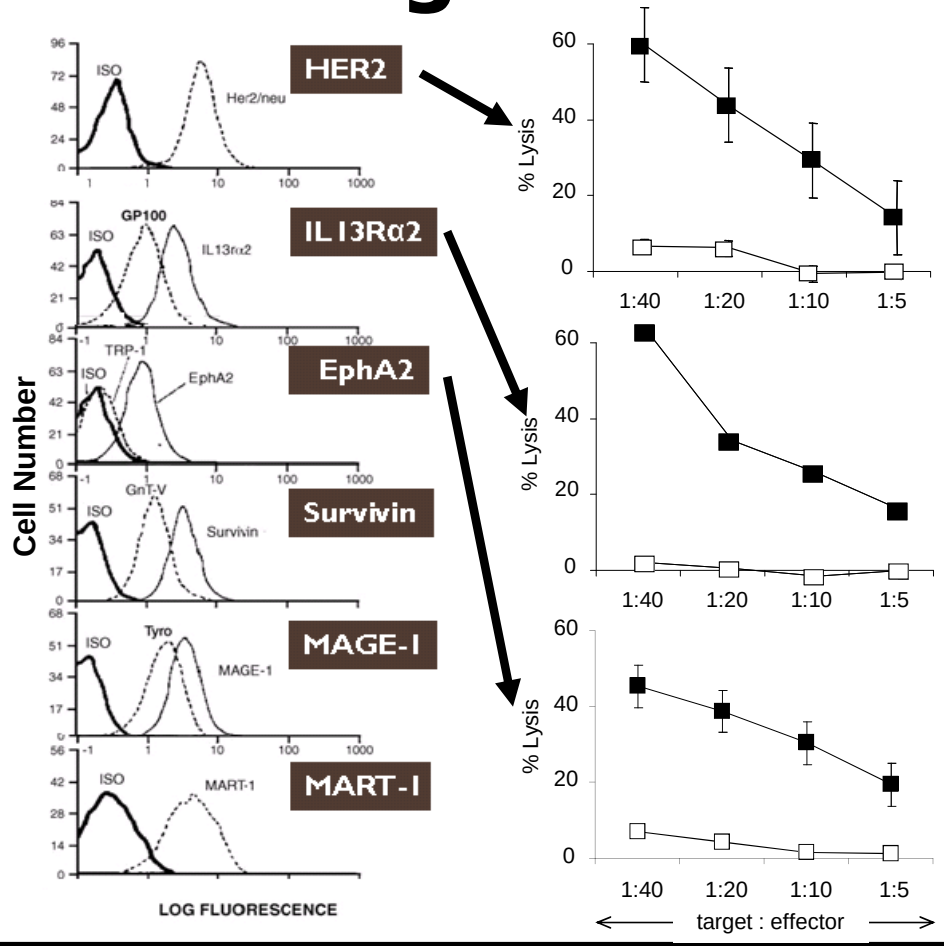


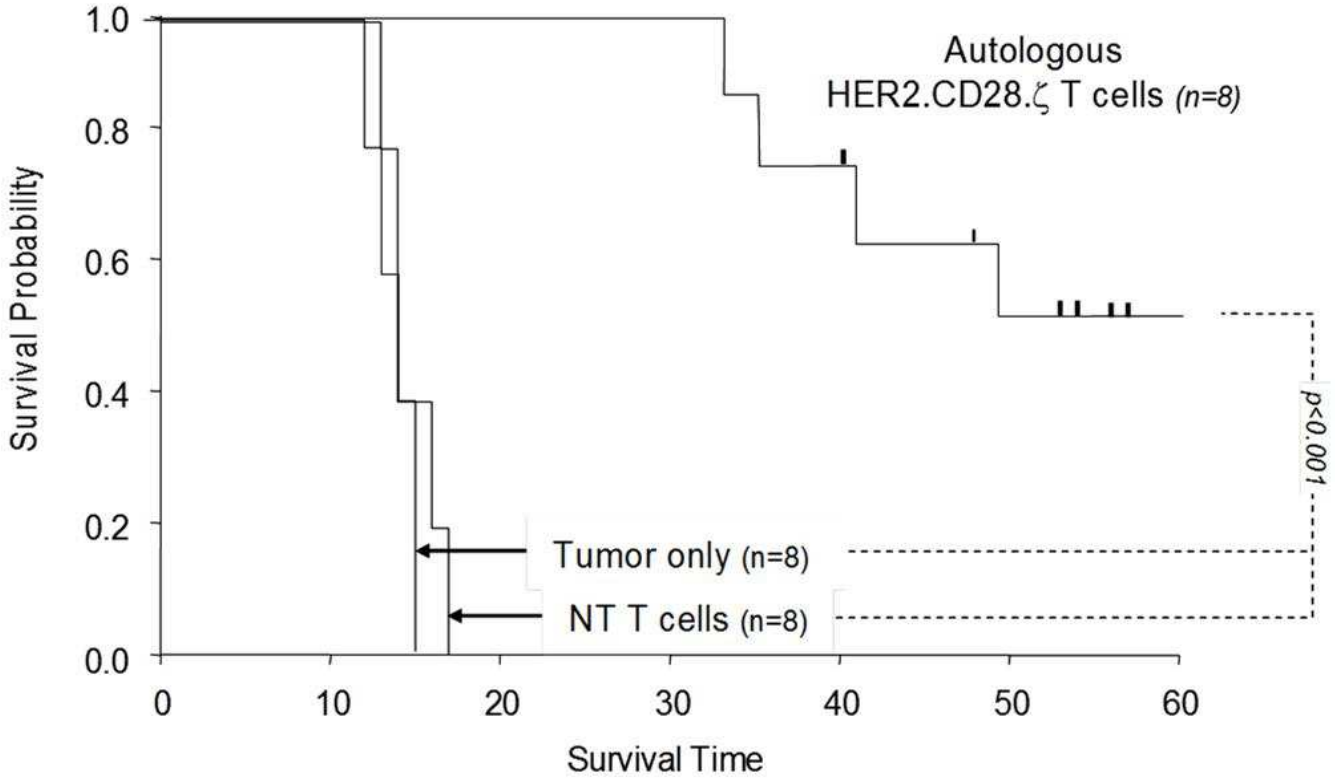
Glioma Antigens

- HER2
- IL13Rα2
- EphA2
- EGFR*v3*
- Survivin
- MAGE-I
- MART-I



Ahmed et al. *Clin Can Res* 2010; Krebs et al. Mol Ther 2013; Chow KH et al. *Mol Ther* 2013

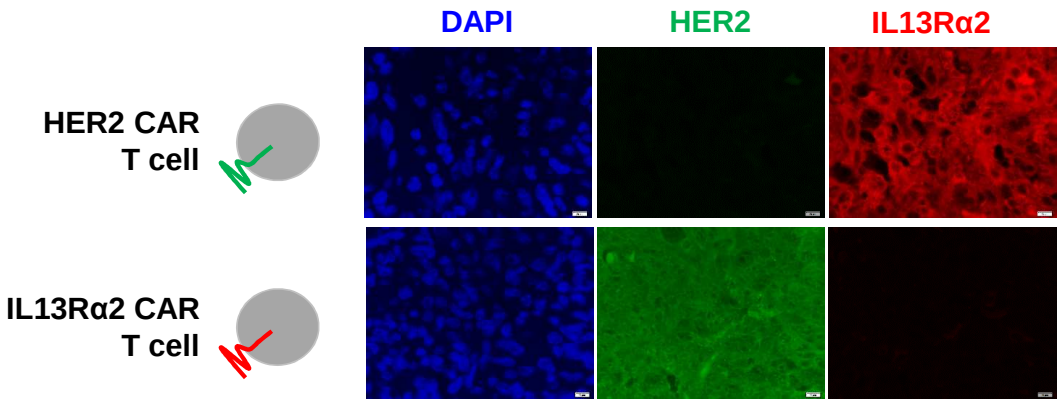
CART cells vs. GBM

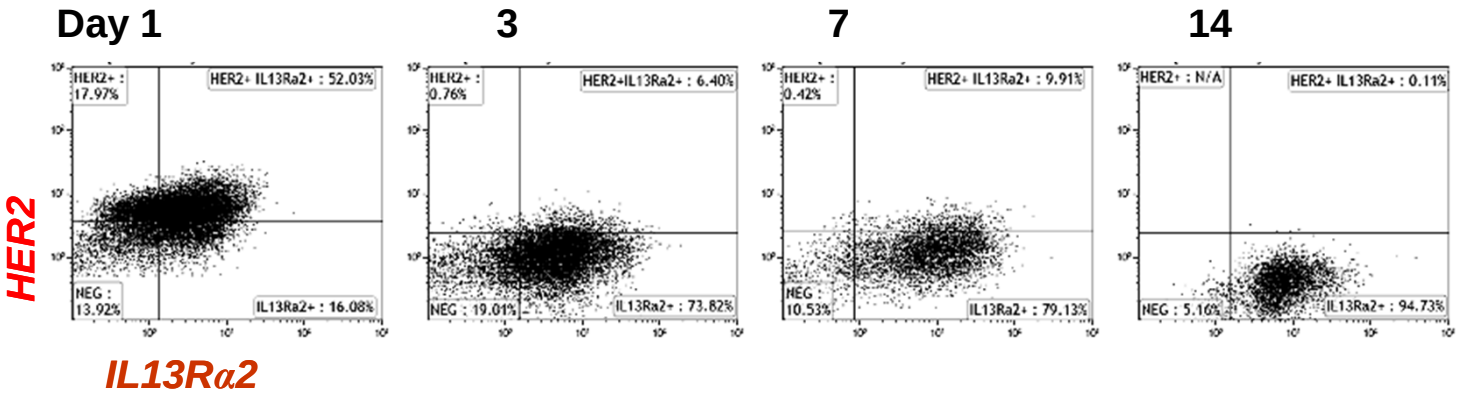


Ahmed and Salsman et al. *Clin Can Res* 2009

Antigen Escape

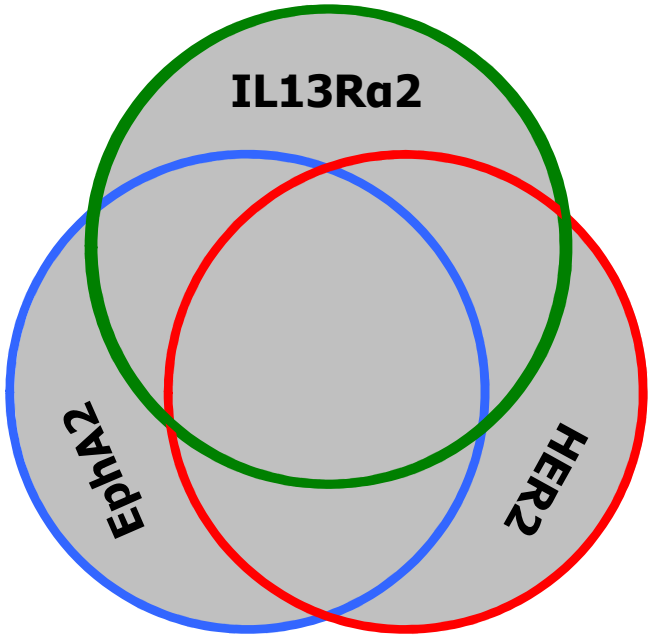
Meena Hegde





Hegde et al. *Mol Ther* 2013; Bielamowicz et al. *Frontiers in Oncology* 2014

GBM: *intratumoral heterogeneity*



~ 70%

p<0.0001

~ 93%

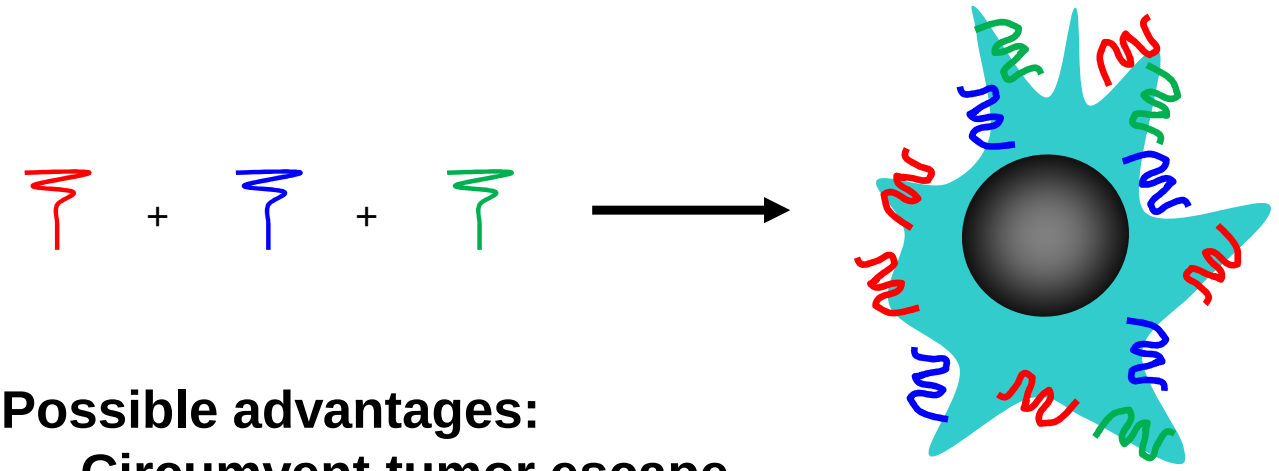
P>0.05

~ 98%

20 GBM (surgical excision)
- **Flowcytometry on ≥100,000 cells**
- **IFC on 5+ cuts; 6+ hpf; 200+ cells/ hpf**

Hegde et al. *Mol Ther* 2013

Hypothesis



Possible advantages:

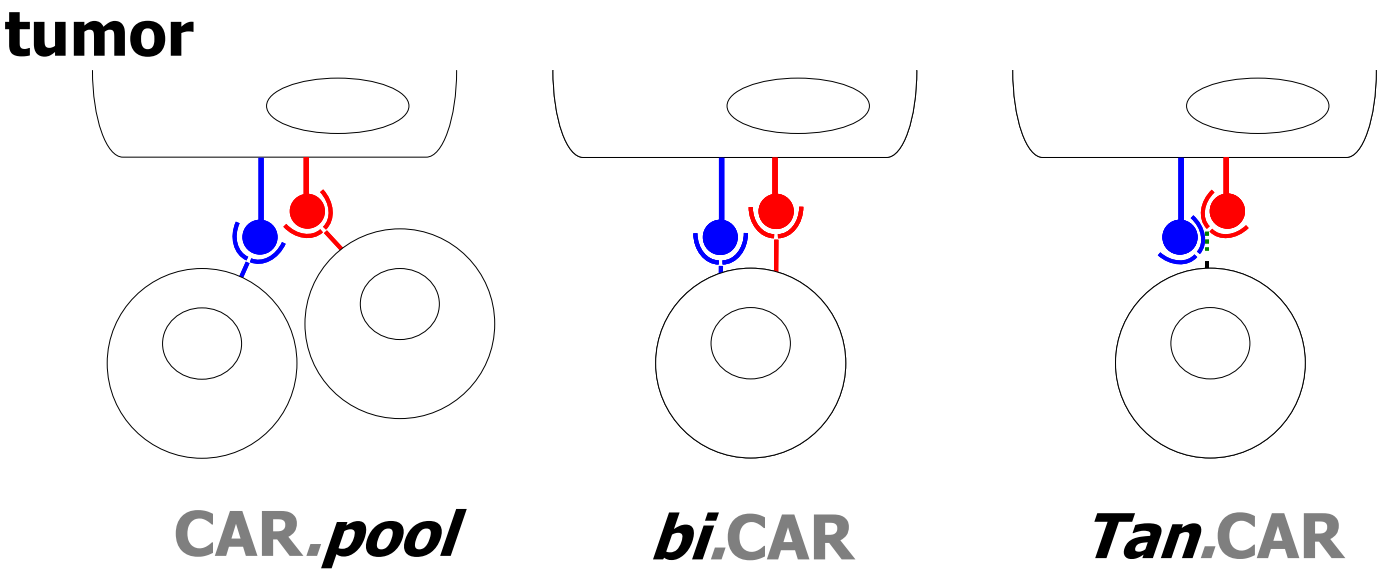
Circumvent tumor escape

- Heterogenous expression of target
- Down regulation of target
- Antigen loss variants

Improve T cell activation

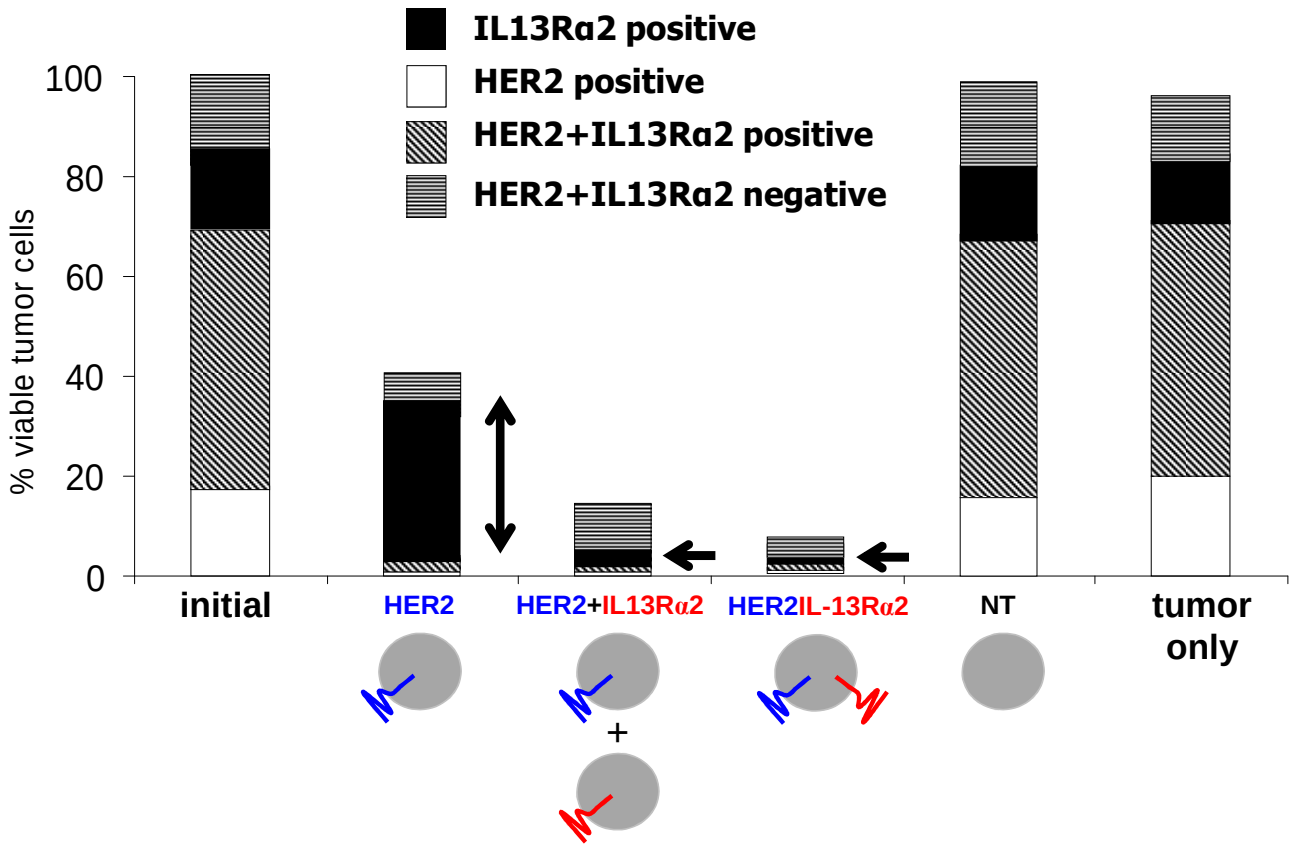
Hegde et al. *Mol Ther 2013*

Multiplex T cell Products

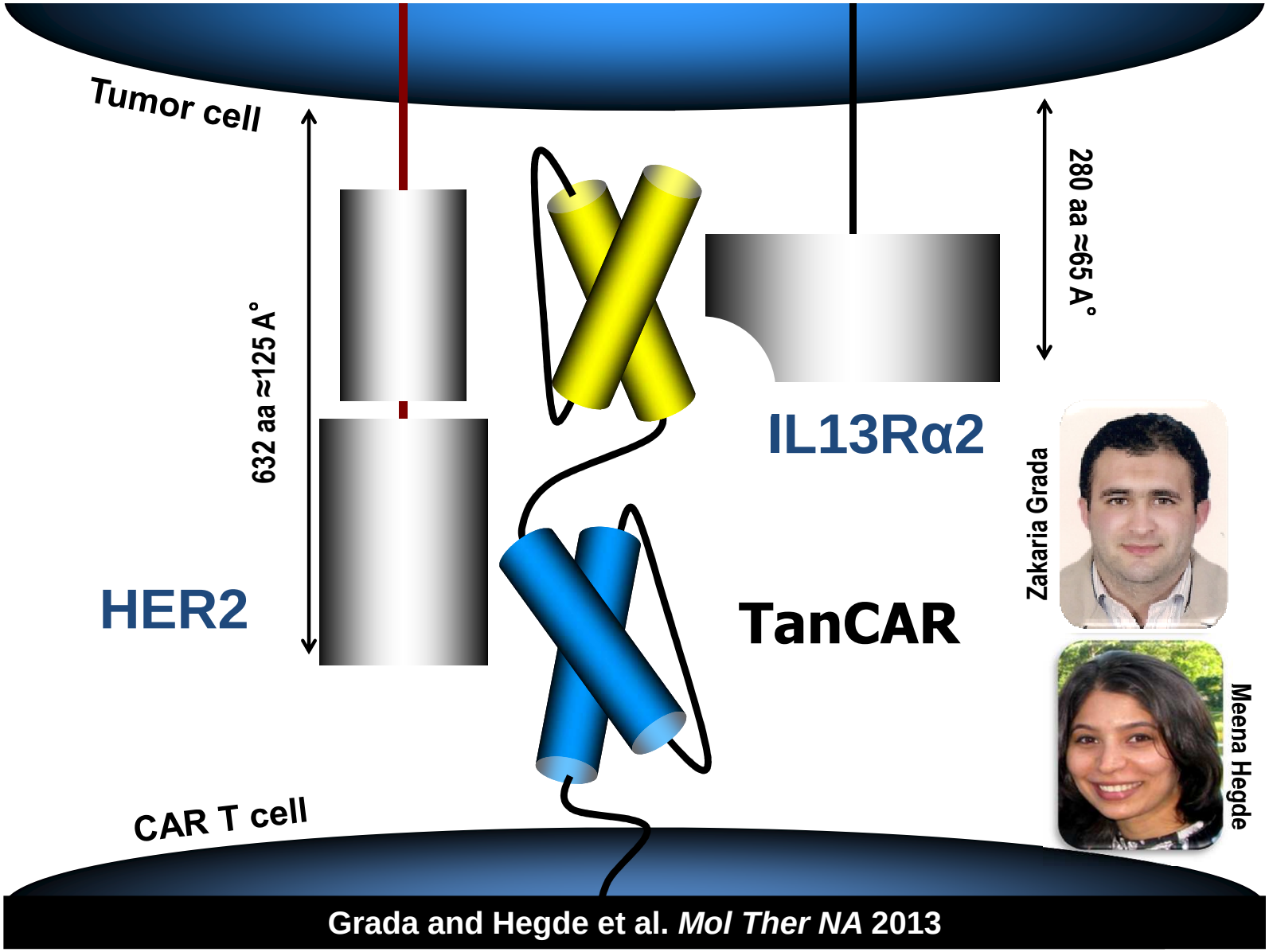


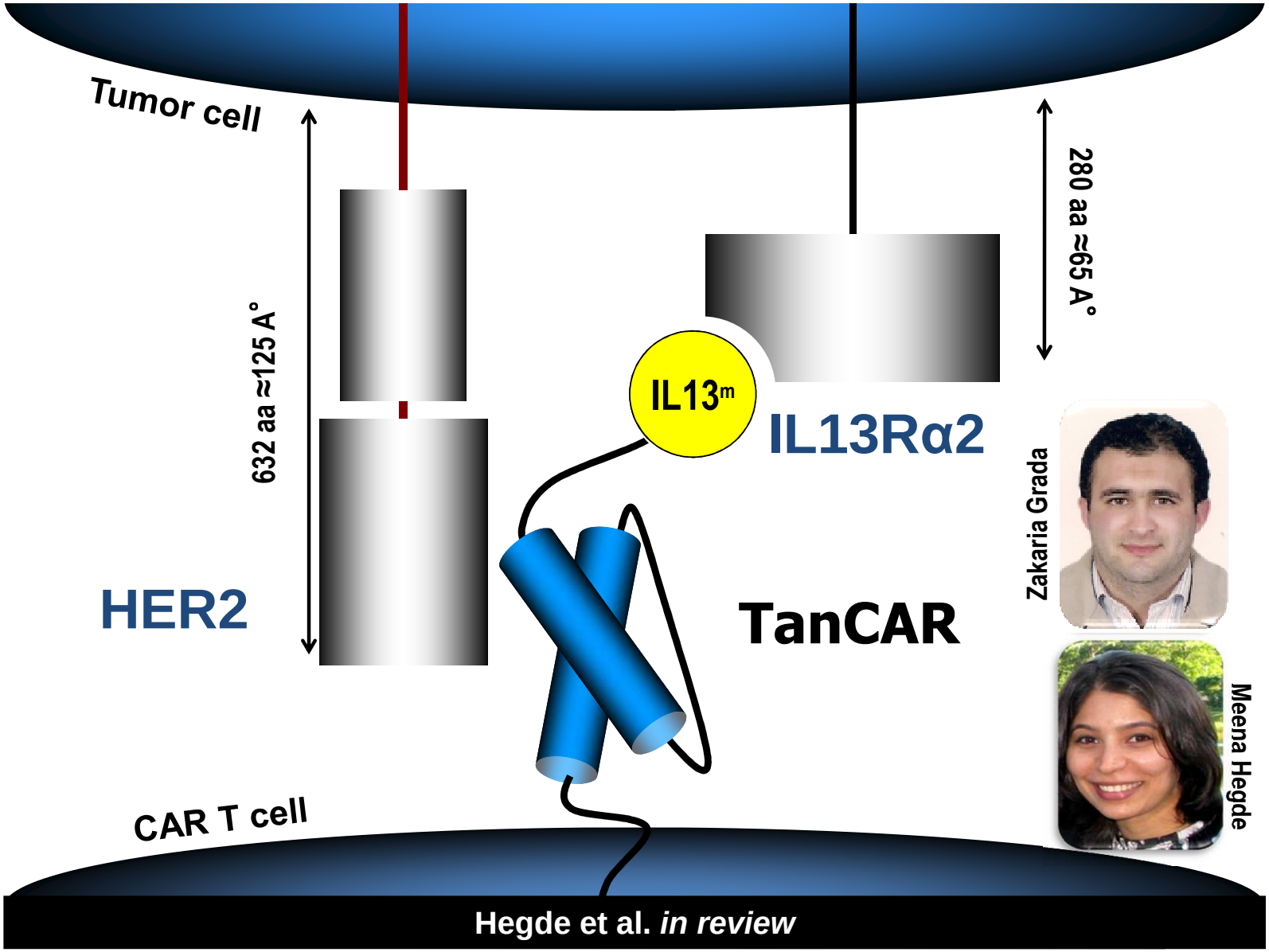
Hegde et al. *Mol Ther* 2013; Grada and Hegde et al. *Mol Ther NA* 2013

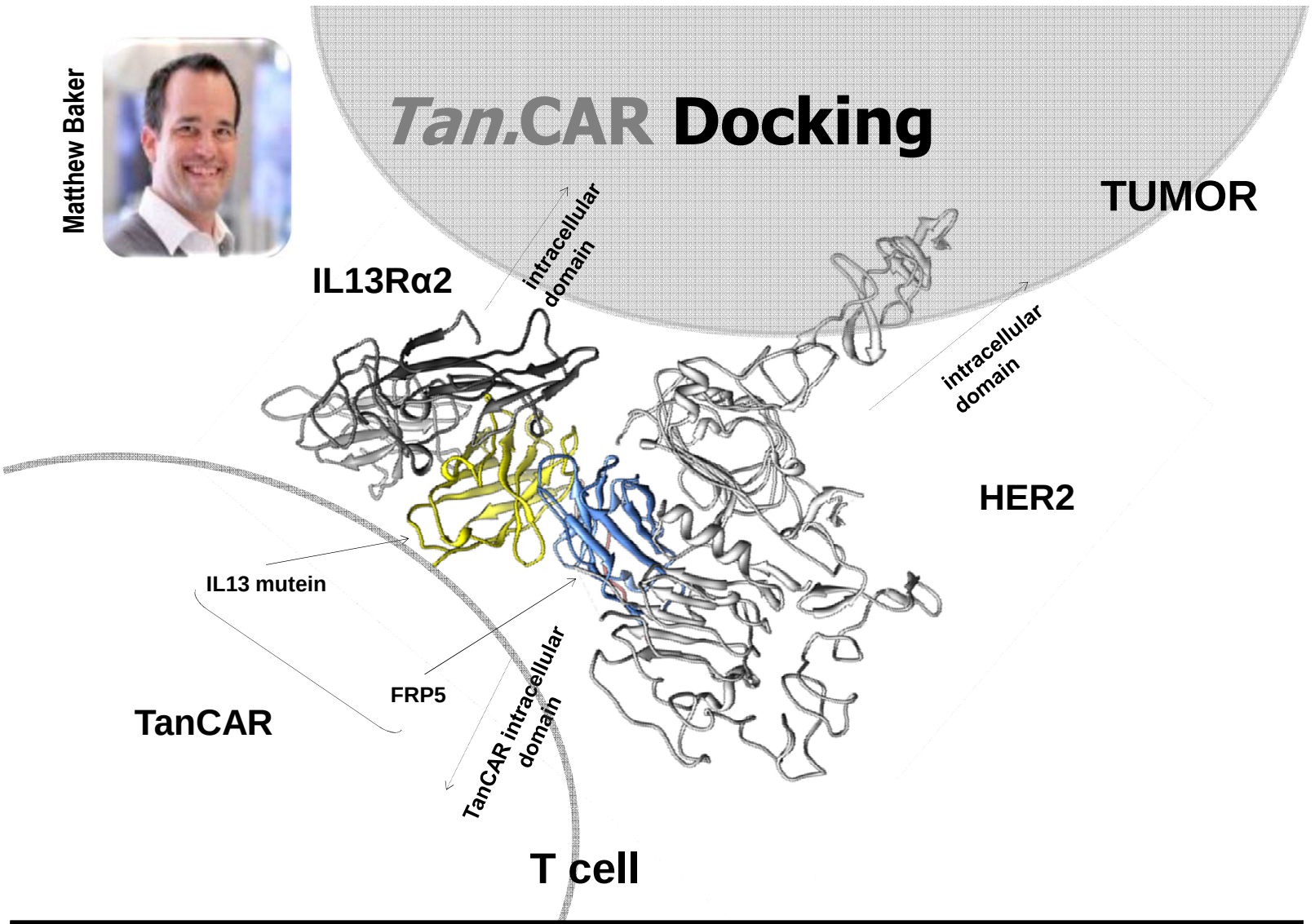
Offsetting Antigen Escape



Hegde et al. *Mol Ther* 2013

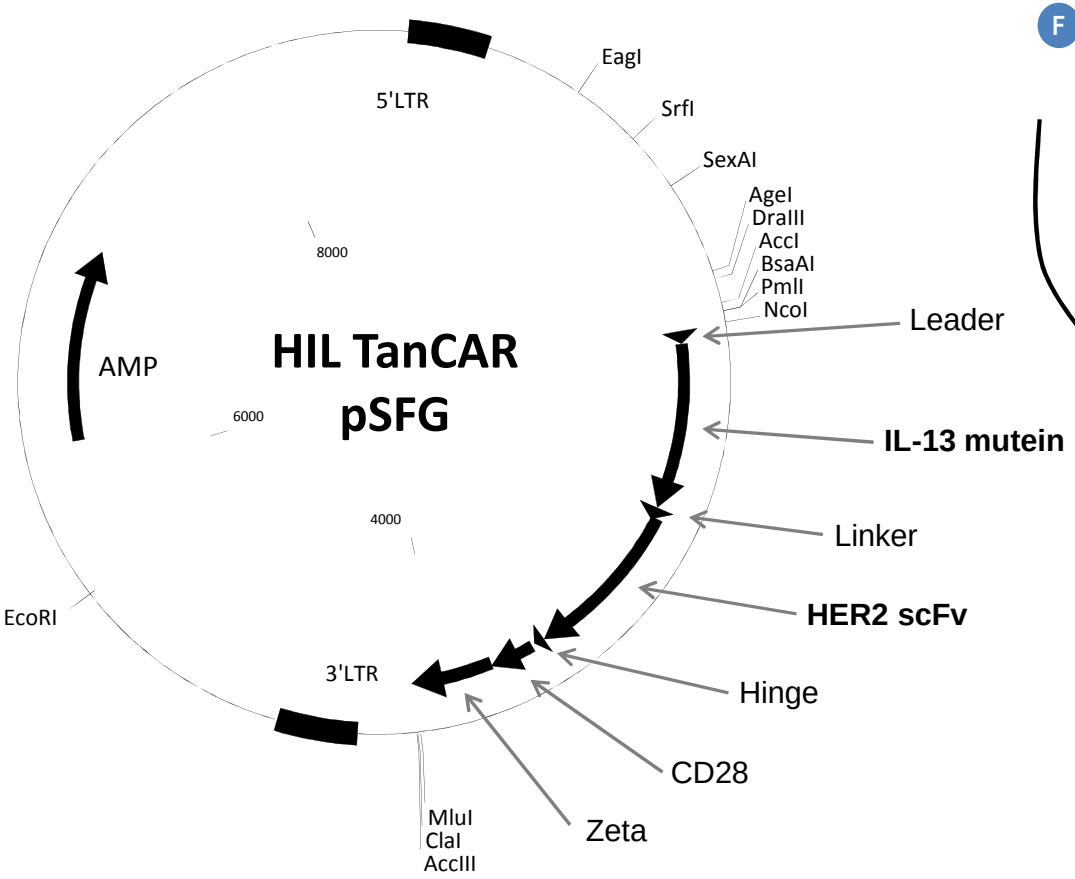

Tumor cell
632 aa ≈125 A°
280 aa ≈65 A°
IL13Rα2
HER2
TanCAR
Zakaria Grada
Meena Hegde
CAR T cell
Grada and Hegde et al. *Mol Ther NA* 2013

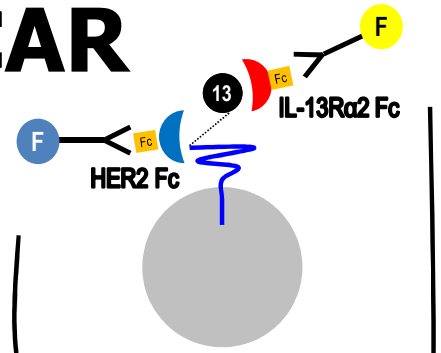

Tumor cell
632 aa ≈125 A°
280 aa ≈65 A°
IL13m
IL13Rα2
HER2
TanCAR
Zakaria Grada
Meena Hegde
CAR T cell
Hegde et al. *in review*

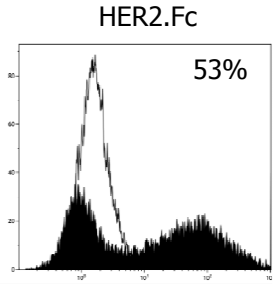


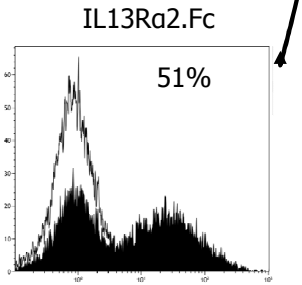
Hegde et al. *in review*

HER2 IL13Rα2 TanCAR









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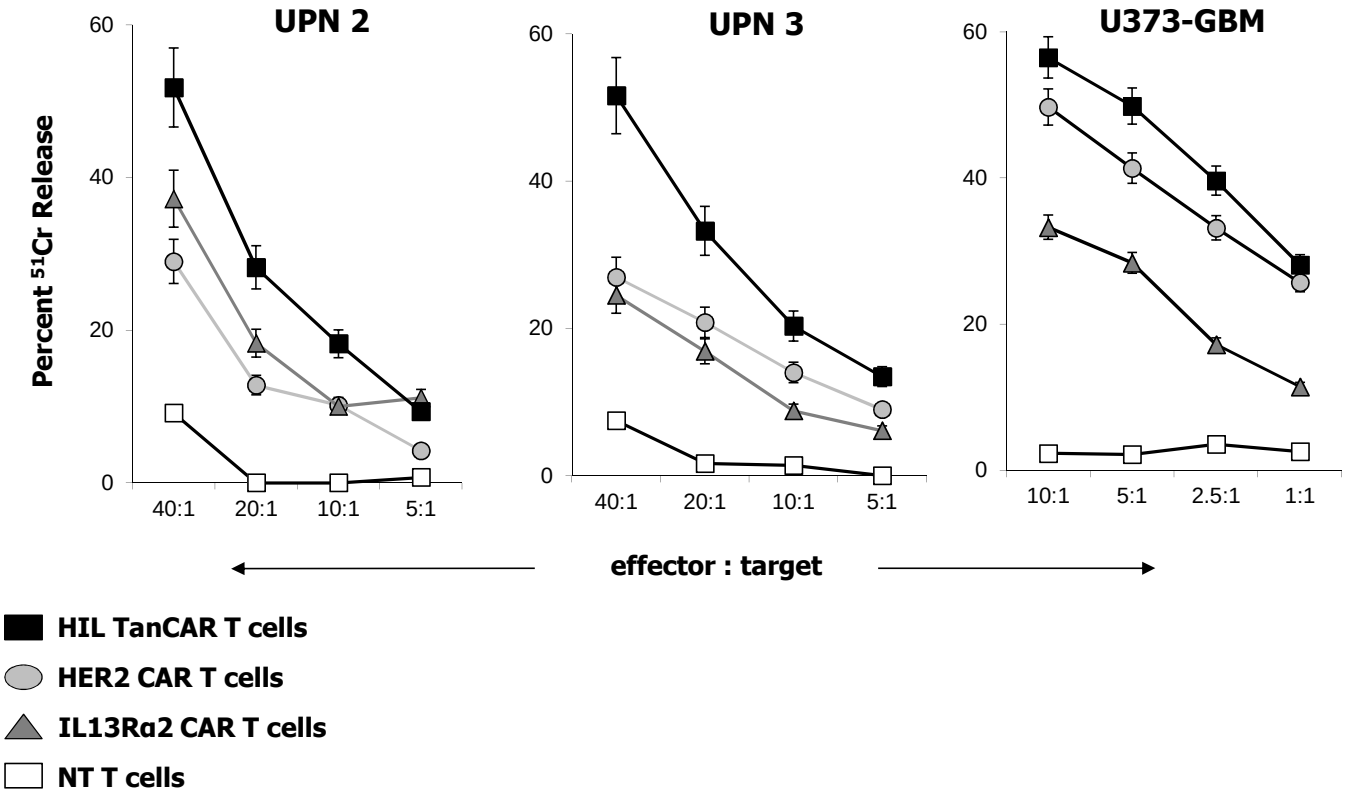
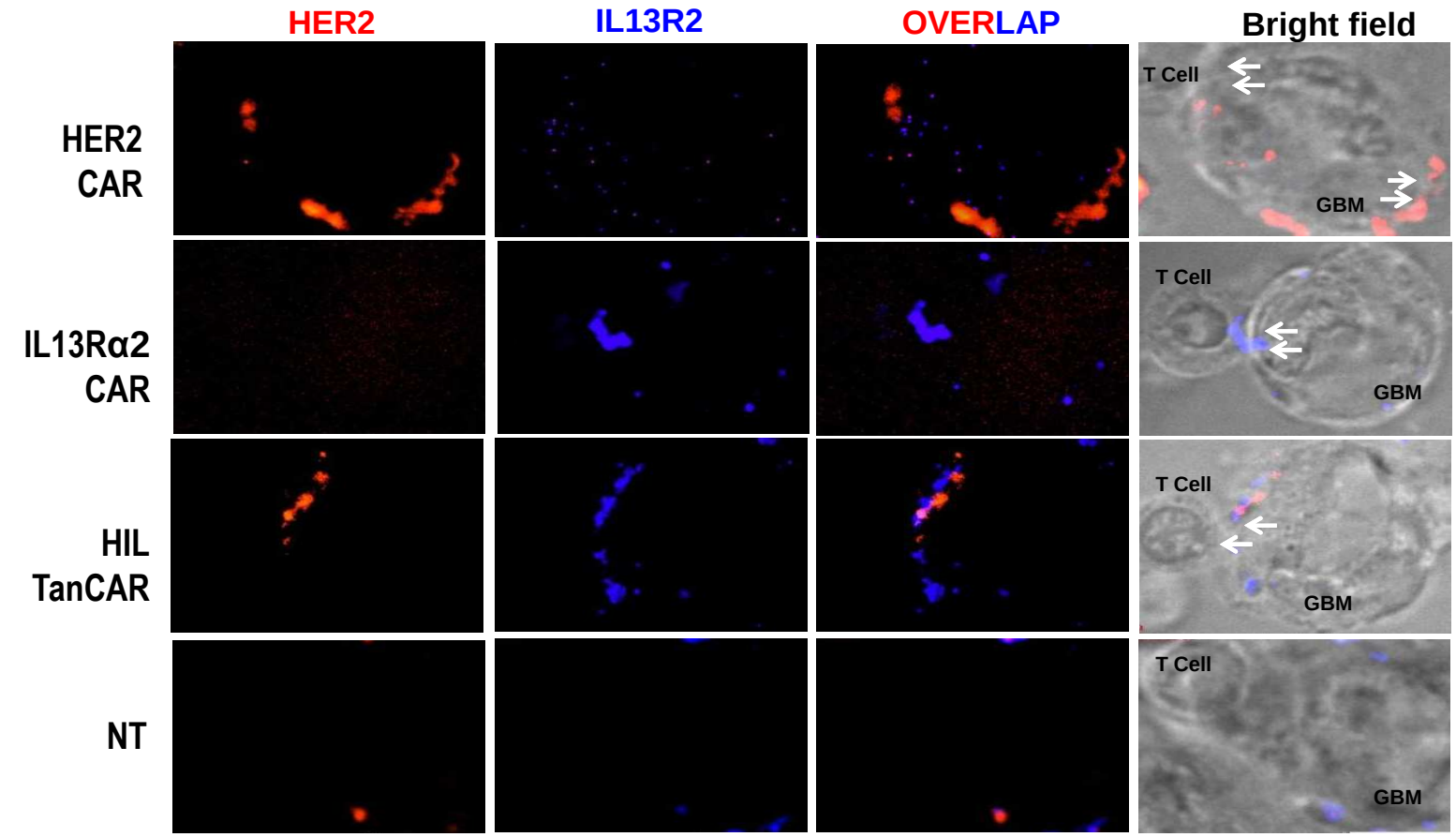
Enhanced Cytolysis



Hegde et al. *in review*

HIL TanCAR Synapse



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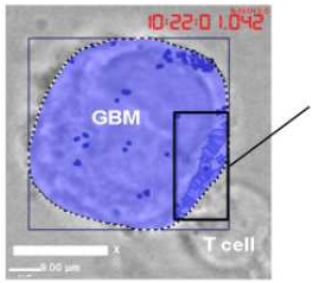
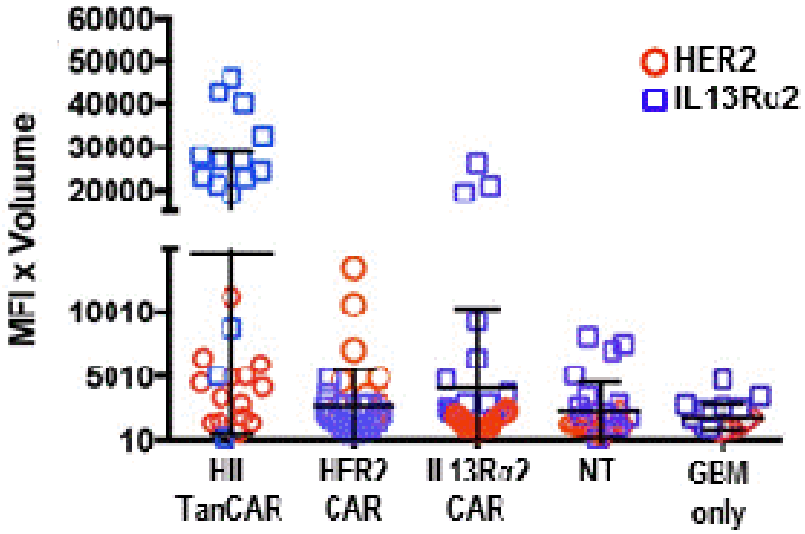
Larger HIL TanCAR Synapse



Immunological Synapse (IS)



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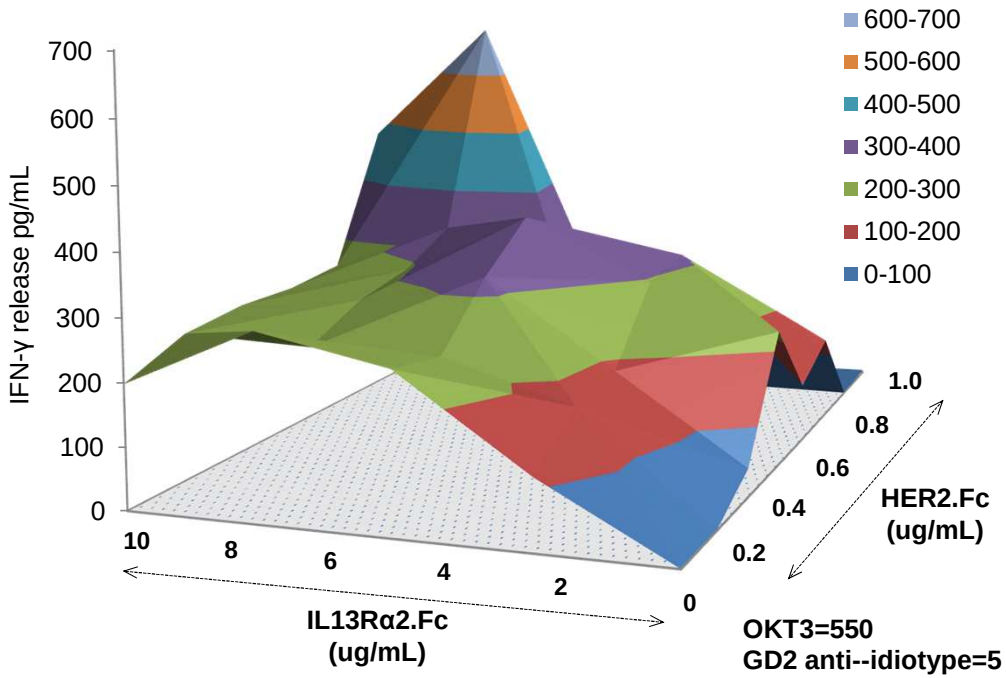
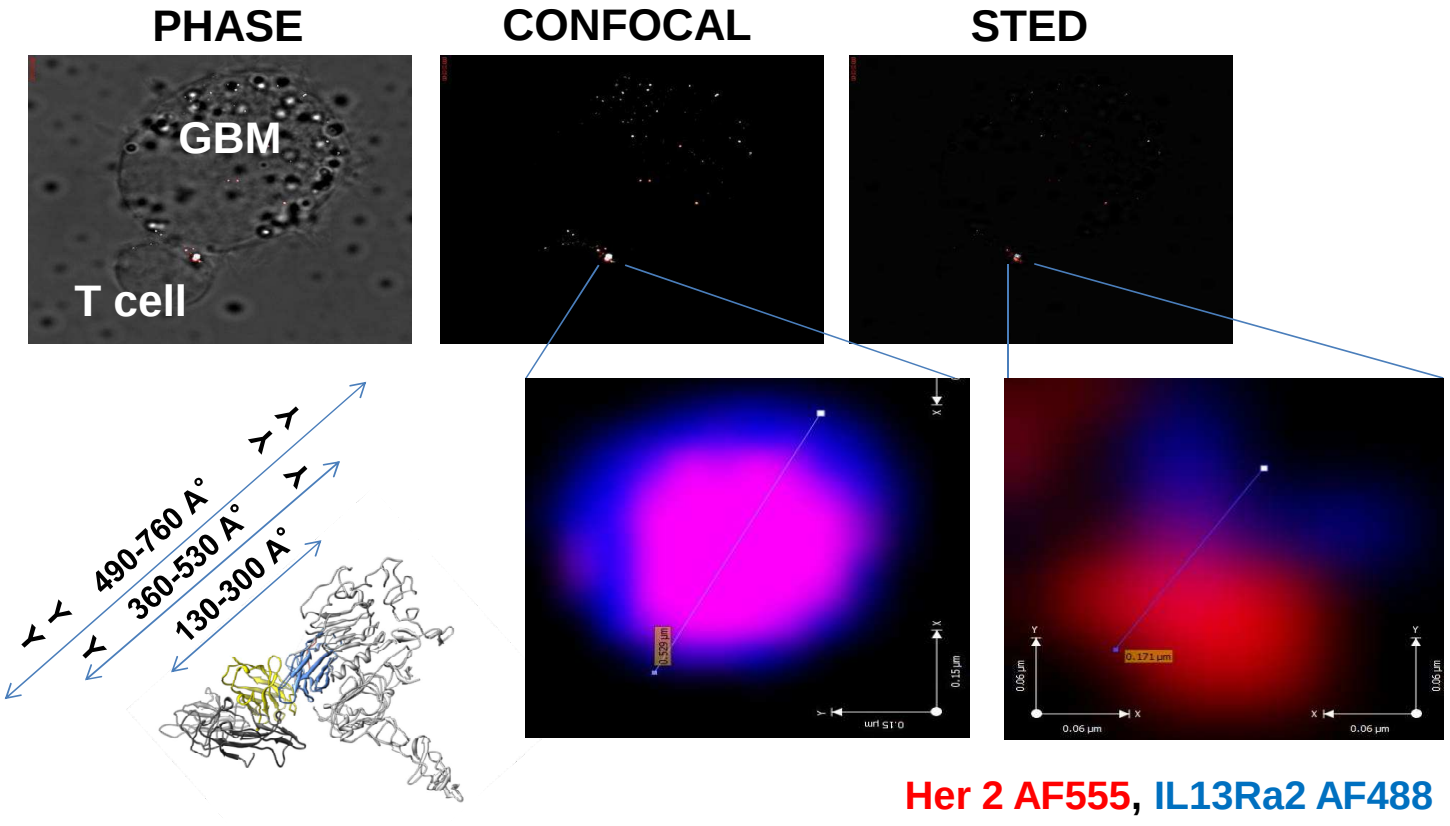
Dynamics of Activation: IFNγ



Hegde et al. *in review*

Can TanCAR Co-engage Targets?



Her 2 AF555, IL13Ra2 AF488

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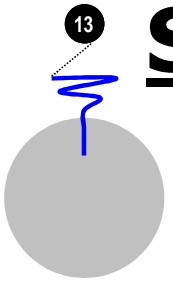
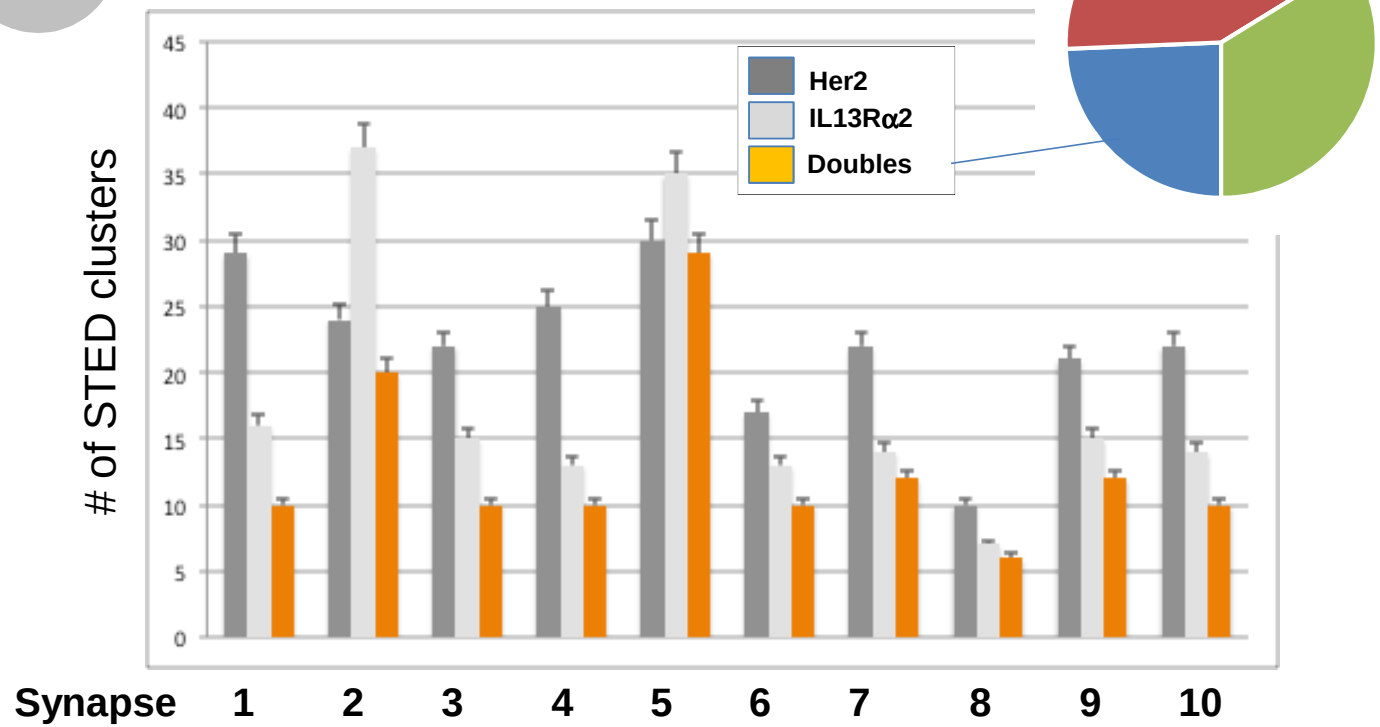
Simultaneous Engagement?



Tan.CAR T cells



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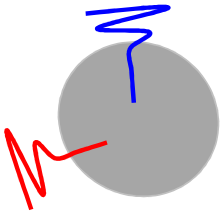
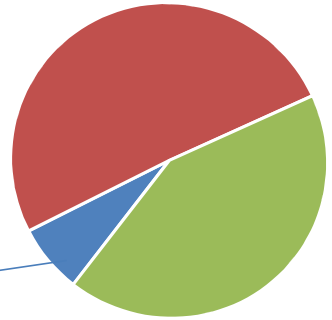
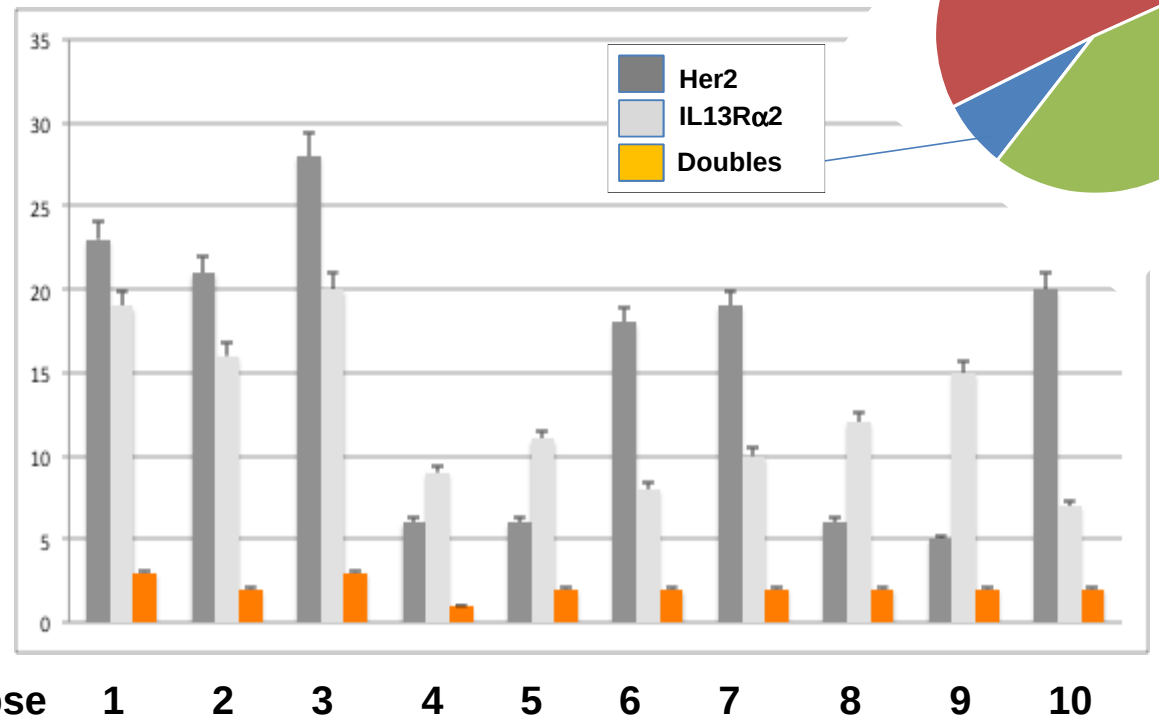
Unimodal Synapse



bi.CAR T cells





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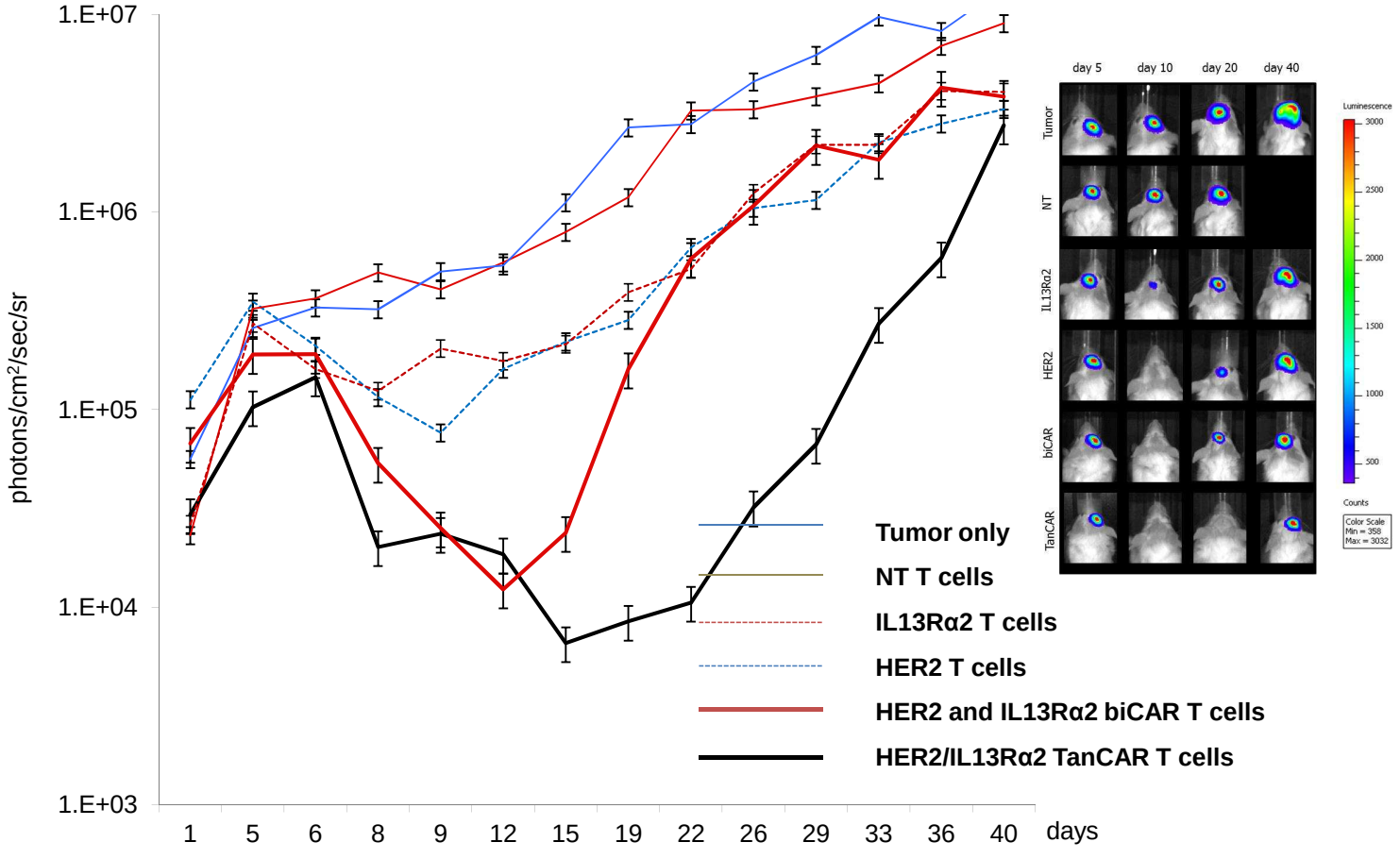
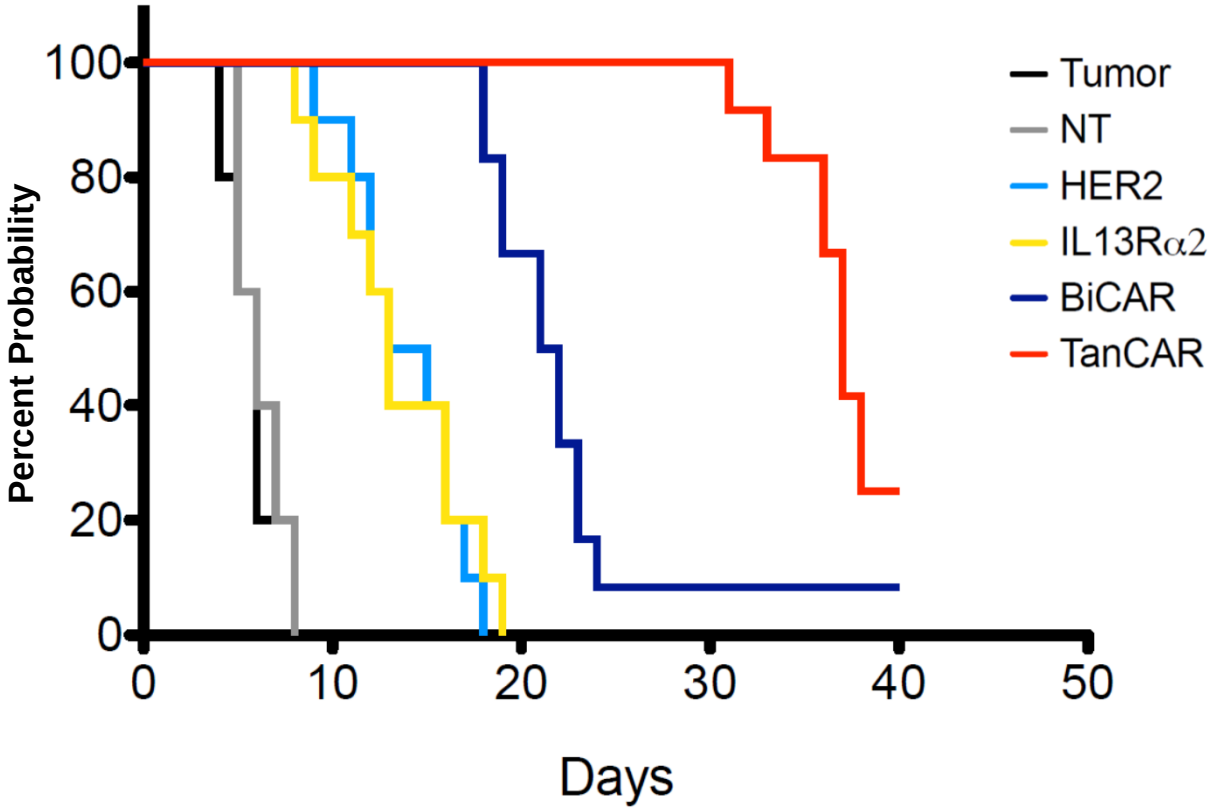
Anti-glioma *in vivo* Activity



Hegde et al. *in review*

Improved TTP



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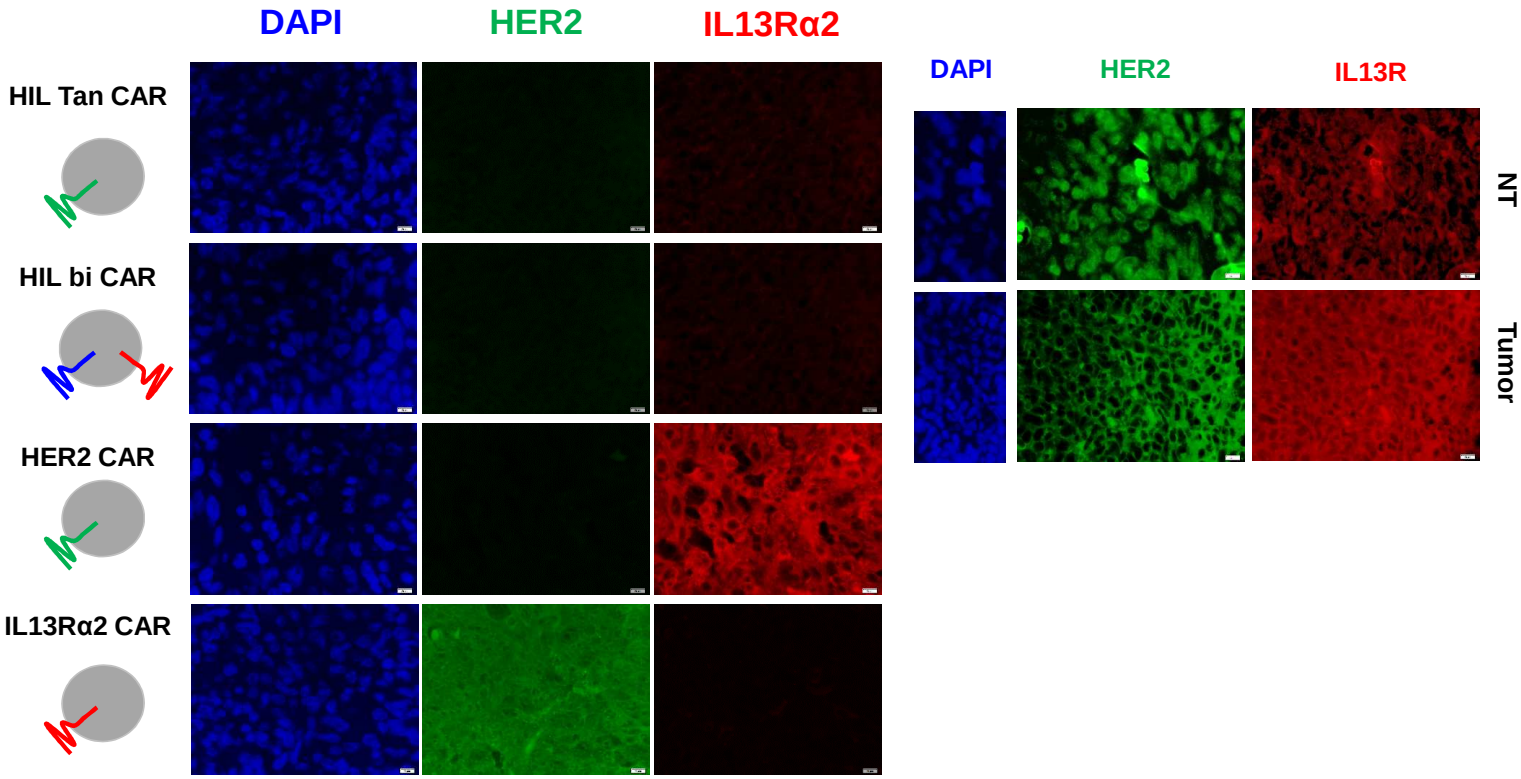
Mitigating Antigen Escape



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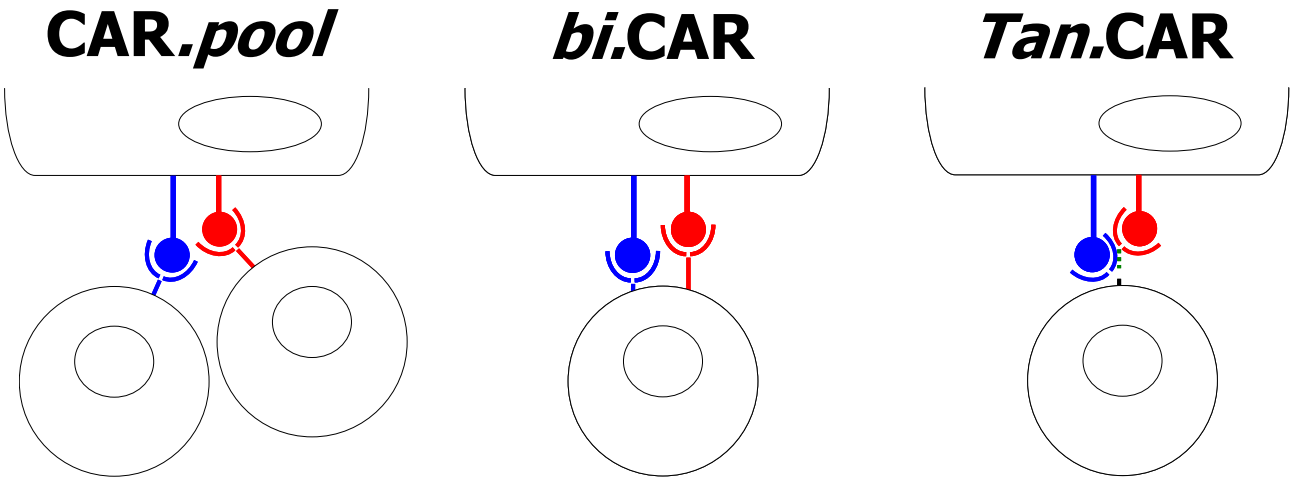
Conclusion: *TanCAR T cells*



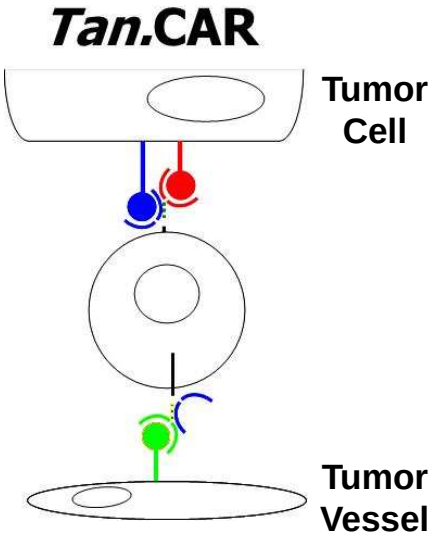
offset antigen escape

offset antigen escape **+ enhance T cell activation**

offset antigen escape **+ enhance T cell activation + selective synergy**

Hegde et al. *Mol Ther* 2013; Grada and Hegde et al. *Mol Ther NA* 2013; Byrd and Hegde

Future



TanCAR Molecules

CIS: HER2/GD2

TRANS: TAA/TEM8

Target the tumor PROFILE

Custom-made vs. Universal CART
Develop an RNA platform

HIL TanCAR in a Phase I trial …..

Hegde et al. *Mol Ther* 2013; Grada and Hegde et al. *Mol Ther NA* 2013; Byrd and Hegde

NOSTROPOLIS 2015

present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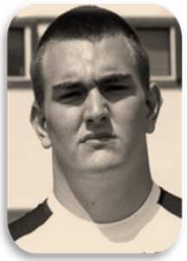
Daniel Landi


Kristen Fousek

past


Alexia Ghazi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CPRIT CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

STAND UP TO CANCER