Antigenic heterogeneity in high grade glioma: *combinational targeting offsets antigen escape*

Meenakshi Hegde, MD
Center for Cell and Gene Therapy
Texas Children's Cancer Center
Baylor College of Medicine
Houston, Texas

Disclosure

- Nothing to disclose

Overview

- High Grade Glioma (HGG)
- Immunotherapy for HGG
- Adoptive T cell Therapy
- Antigenic heterogeneity and escape
- Combinational targeting
- Conclusion
- Future directions

High Grade Glioma (HGG)

- **Origin:** glia
- **Pathology:** WHO III & IV (AA & GBM)
- **Frequency:** 10-15% of CNS Tumors
- **Therapy:** Surgery → XRT+/- chemotherapy
- **Outcomes:** 5yr PFS AA ~23%; GBM ~16%

Cohen KS *Neuro Oncol* 2011 (ACNS0126); Finlay JL *JCO* 1995 (CCG-945)

High Grade Glioma (HGG)

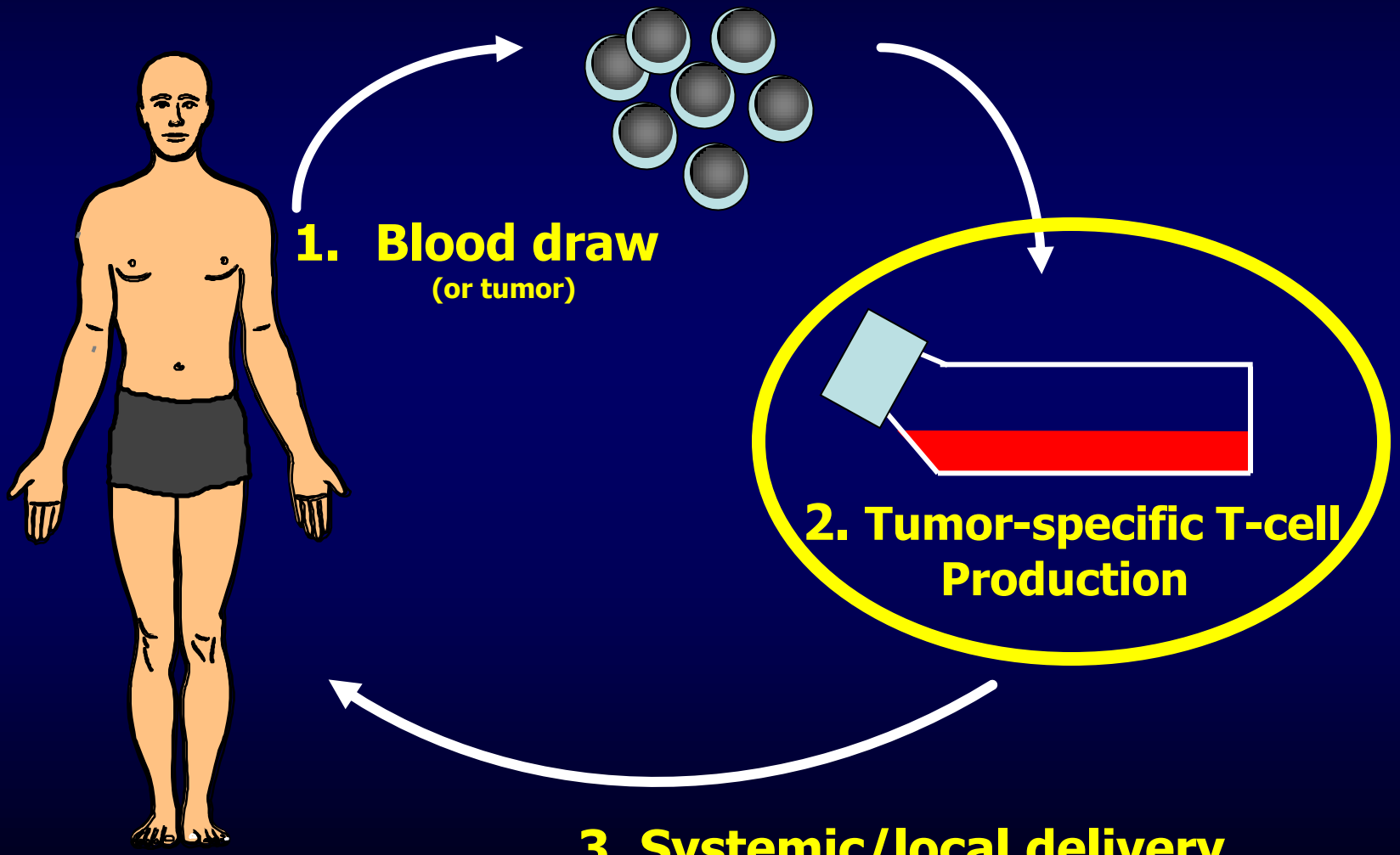
- **Limitations of standard therapy**
  - GTR difficult; location & invasive nature
  - Resistance to chemotherapeutic agents
  - Treatment related neurotoxicity
- **Immunotherapy has the potential to improve outcome**

MacDonald TJ *Neuro Oncol* 2011; Feun LG *Neuro Oncol* 1994

Immunotherapy for HGG

- **Tumor vaccines**
  - DC vaccines
  - Whole tumor cell vaccines
  - Peptide vaccines
- **Monoclonal antibodies (MAb)**
  - Bevacizumab
- **Adoptive T cell therapy**
  - Tumor infiltrating lymphocytes (TILs)
  - Cytotoxic T lymphocytes (CTLs)
  - Genetically engineered T cells

Adoptive T cell Therapy: *the concept*



Adoptive T cell Therapy: *for cancer*

- **Tumor-antigen specific**
- **Good bio-distribution; self-amplify**
- **Adapt to the changes in tumor microenvironment**
- **Recognize internal antigens** (if processed)
- **Have and recruit multiple effector mechanisms**

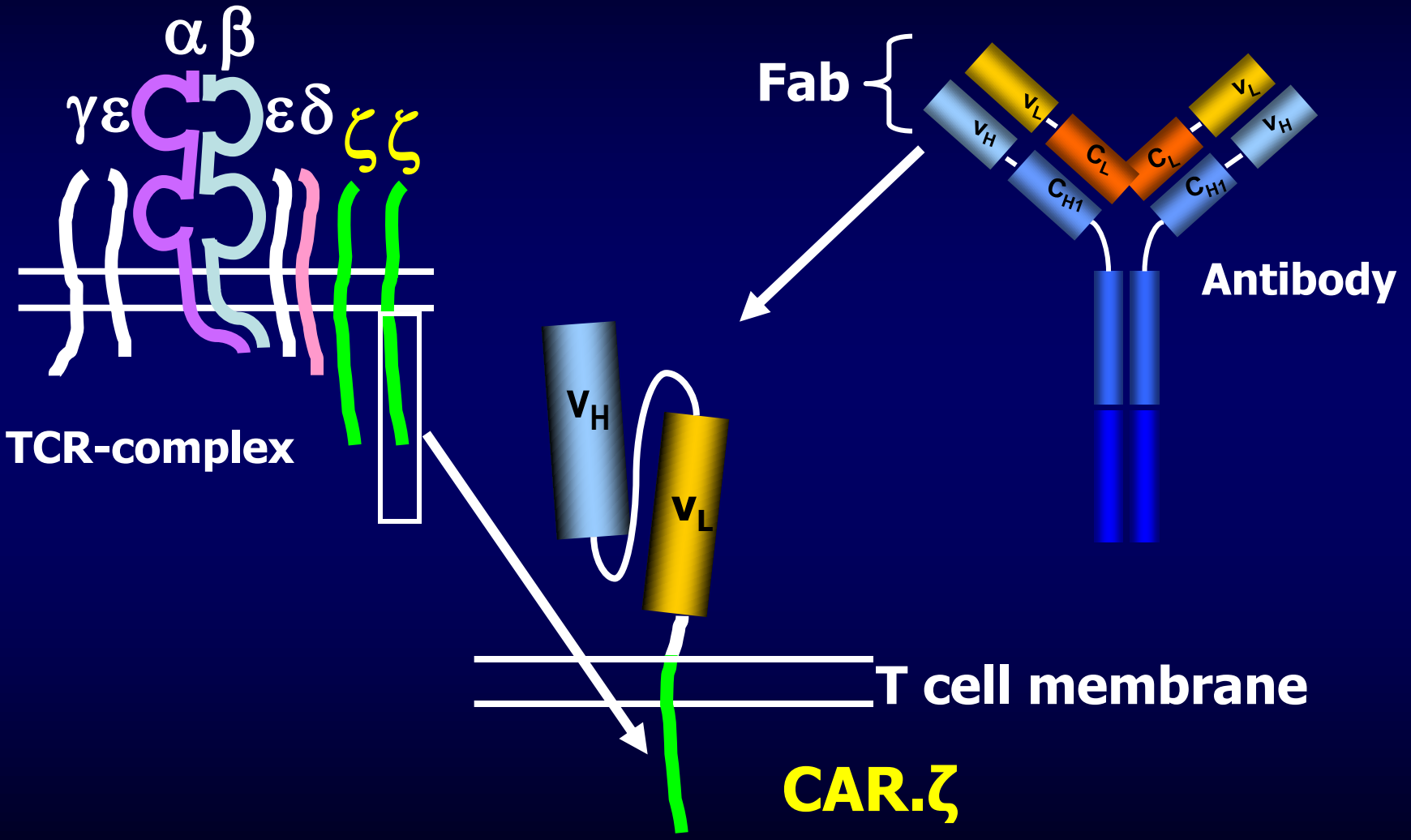
Ahmed el al. *PCNA* 2010; Heslop and Brenner. *Curr Opin Imm* 2010

Adoptive T cell Therapy: *limitations*

- **Reliability of generating T cells**
- **MHC-dependence**
  - MHC down-regulation
  - Defects in antigen-processing
- **Inhibitory T cells:** T_{H2}; T_{reg}
- **Limited *in vivo* expansion**

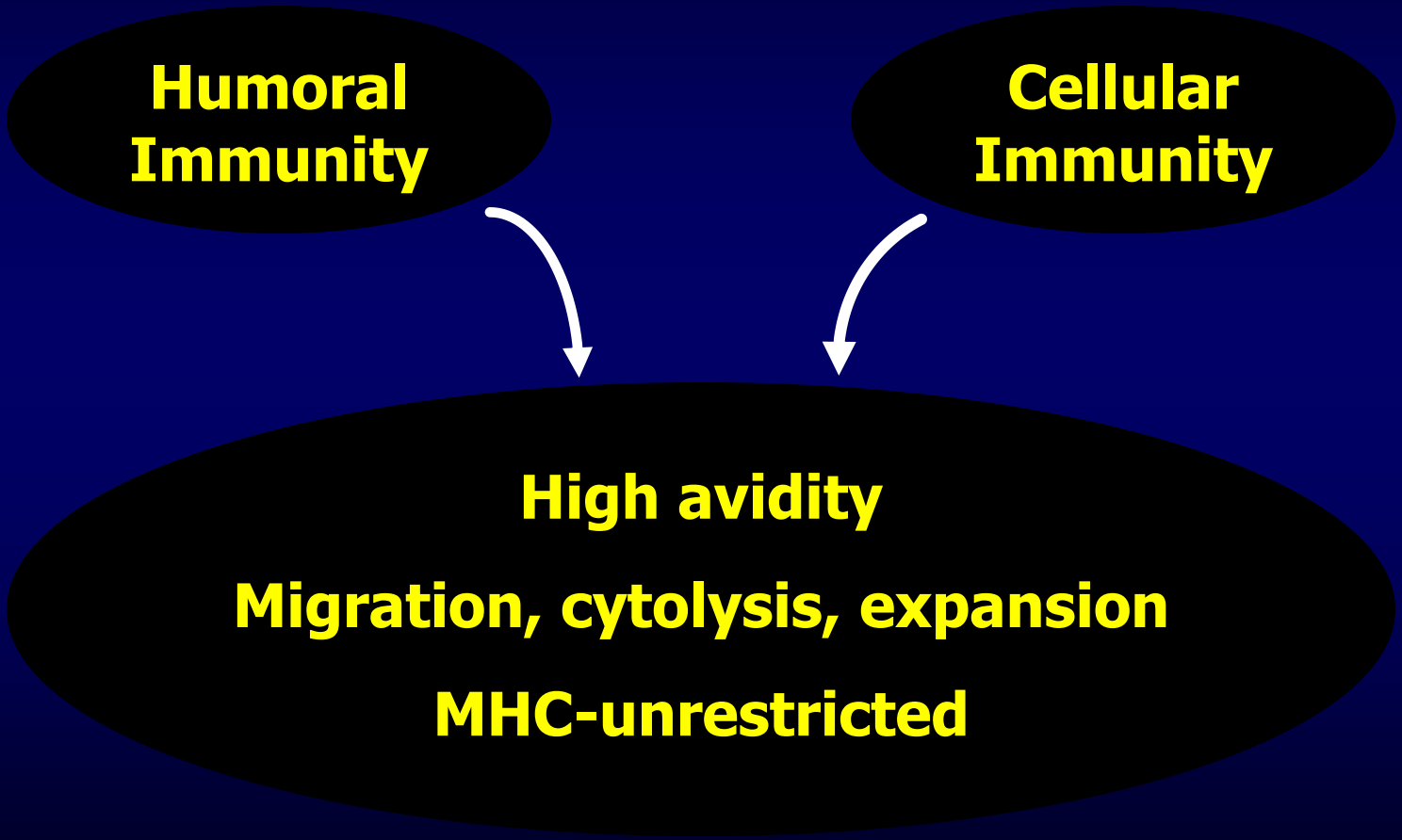
Ahmed el al. *PCNA* 2010; Heslop and Brenner. *Curr Opin Imm* 2010

Chimeric Antigen Receptor (CAR)



Eshhar et al. *PNAS* 1993

CAR T cells: *advantages*



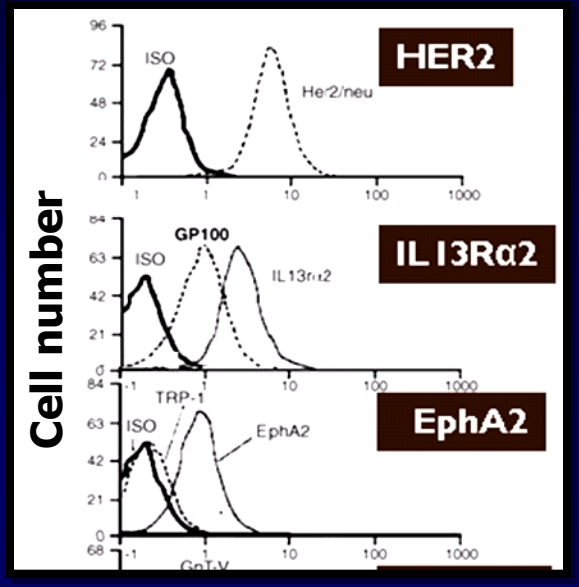
CAR T cells: *application*

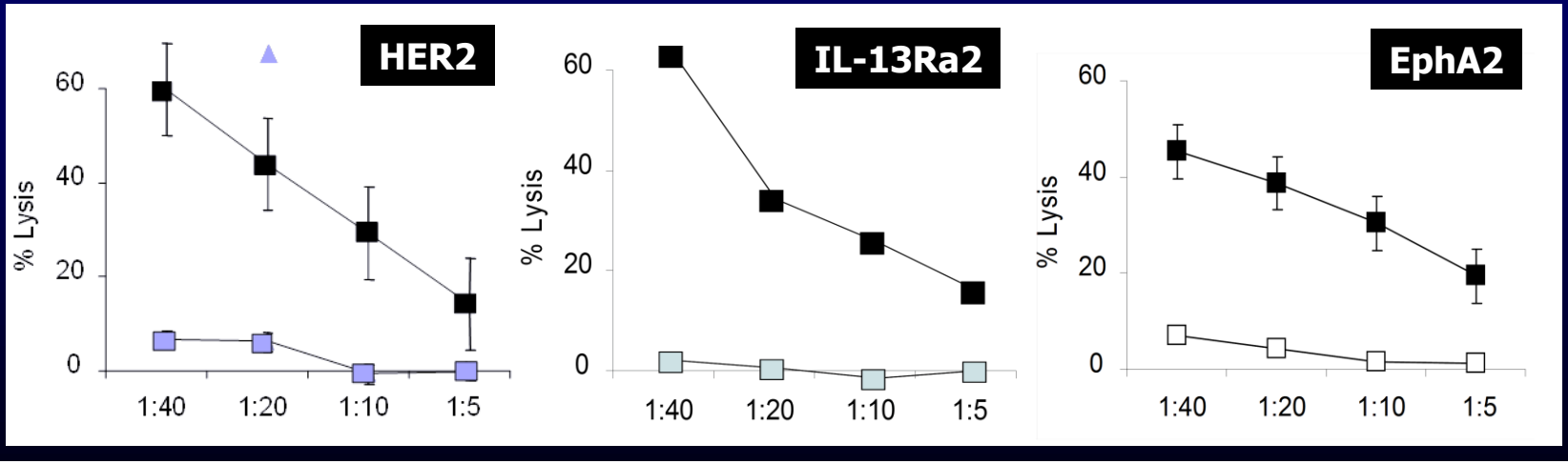
- **Target antigen:**
  - Present on tumor cells
  - Surface expressed
  - Very low or no expression on normal cells
- **Early clinical trials:**
  - Hematological malignancies and solid tumors

Pule MA *Nat Med* 2008; Porter DL *NEJM* 2011; Grupp SA *NEJM* 2013

CAR T cells: *targeting HGG antigens*

- **IL13Rα2**
- **HER2**
- **EphA2**
- **EGFR*v3***

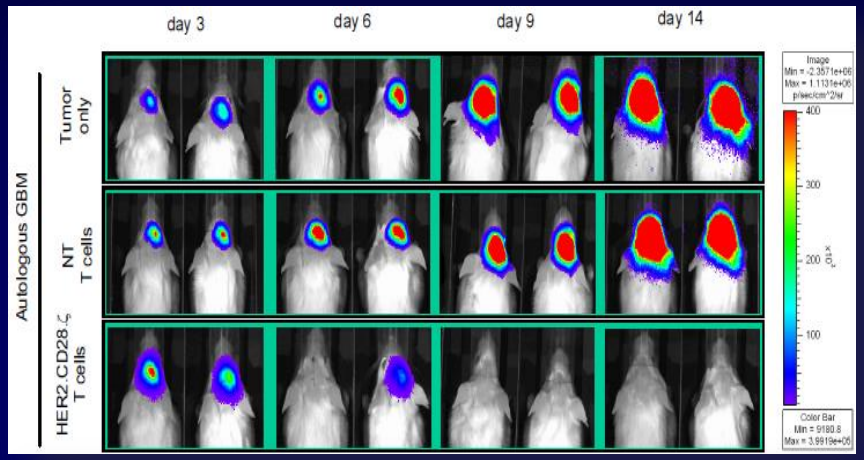


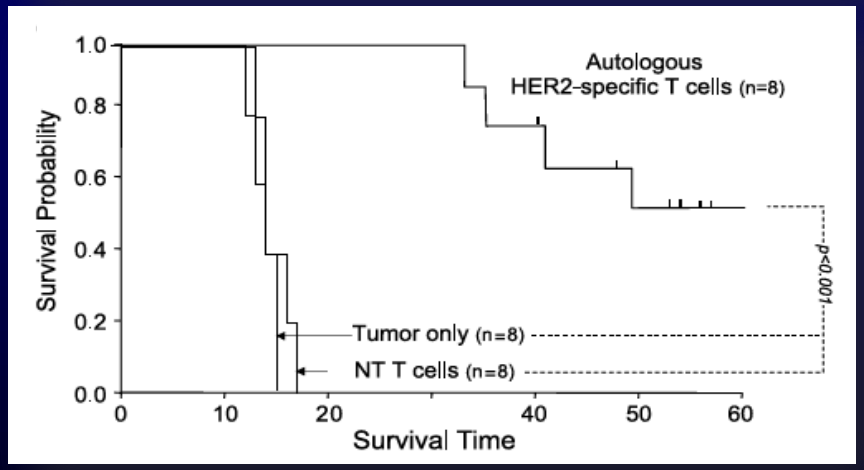


Glas *Ann Neurol* 2010; Ahmed *Clin Can Res* 2010; Chow *Mol Ther* 2013

CAR T cells: *targeting HER2 in HGG*

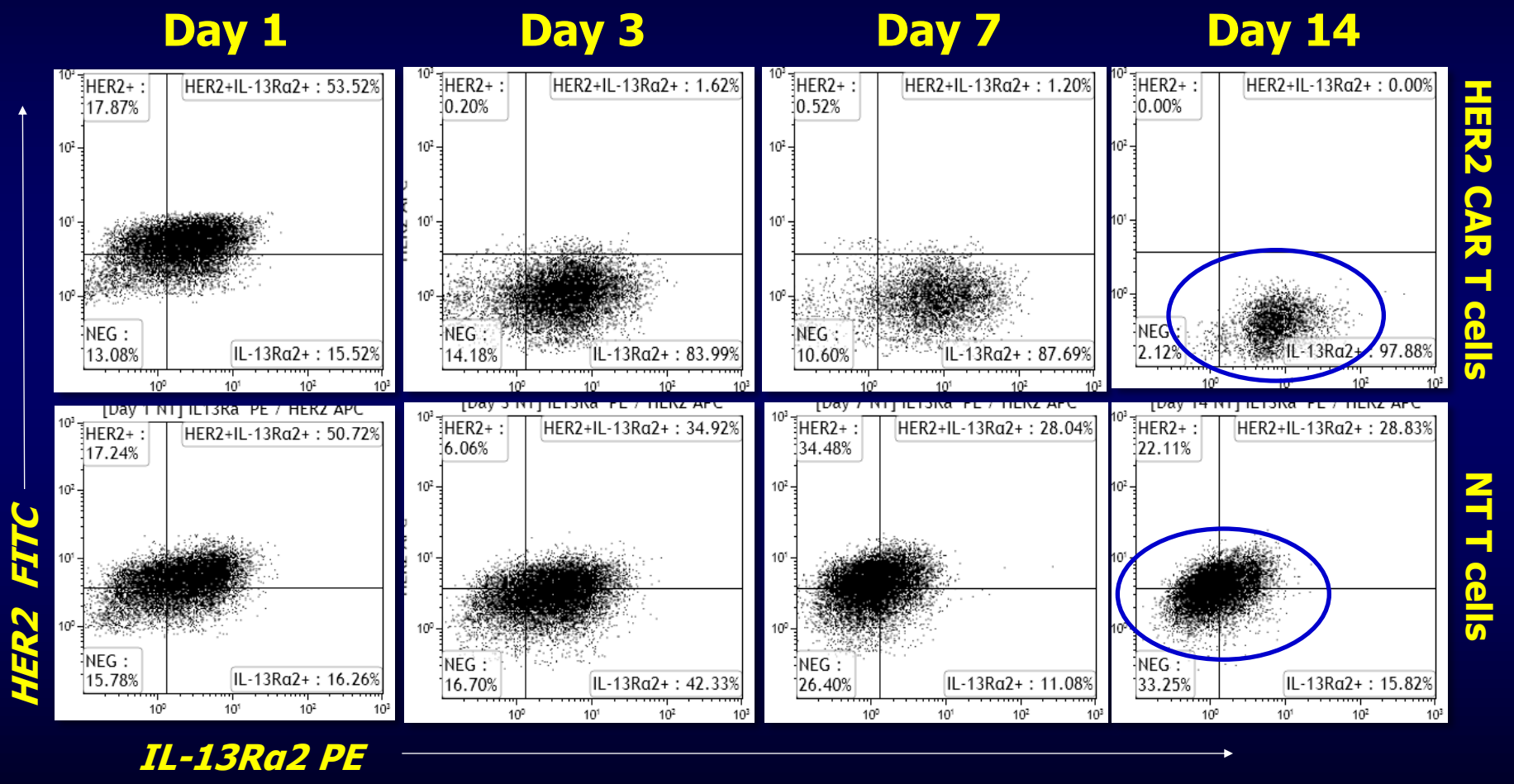
- **Preclinical:** improved OS & PFS
- **Clinical:** ongoing phase I/II studies
- **Treatment failures in animal model**
  - Limited T-cell activation
  - Antigen escape





Ahmed N et al., *Clin Cancer Res* 2010, HERT-GBM NCT01109095

Antigen escape

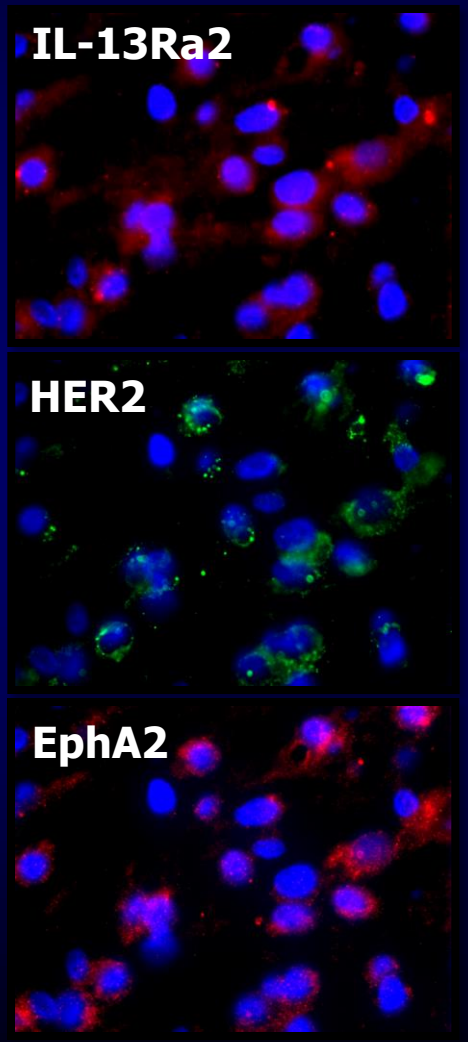


Hegde et al., *Mol Ther in press*

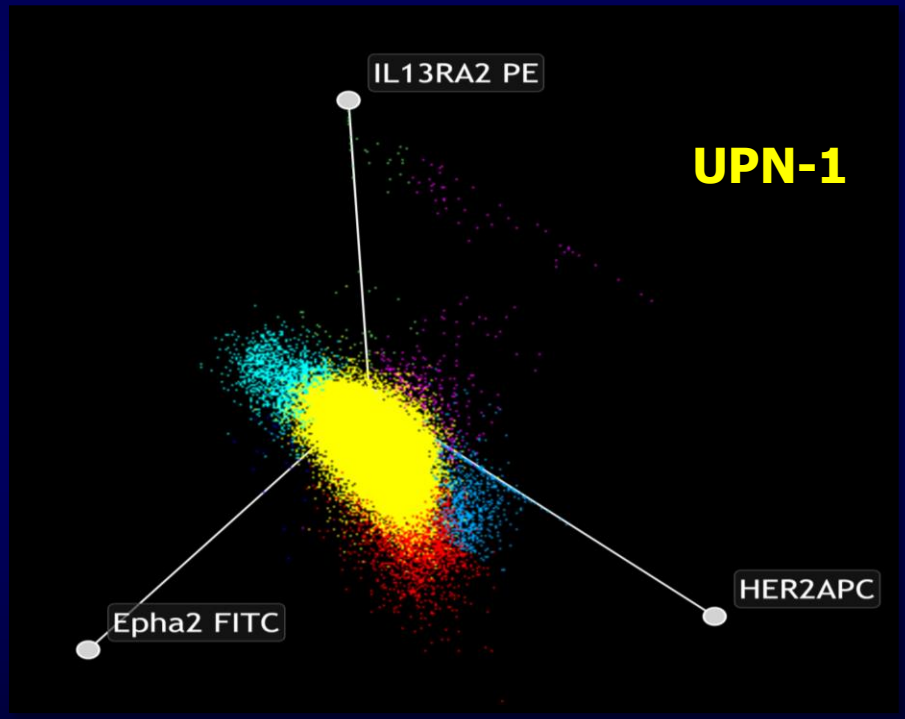
Primary HGG: *antigenic heterogeneity*

Immunofluorescent stain

UPN-4

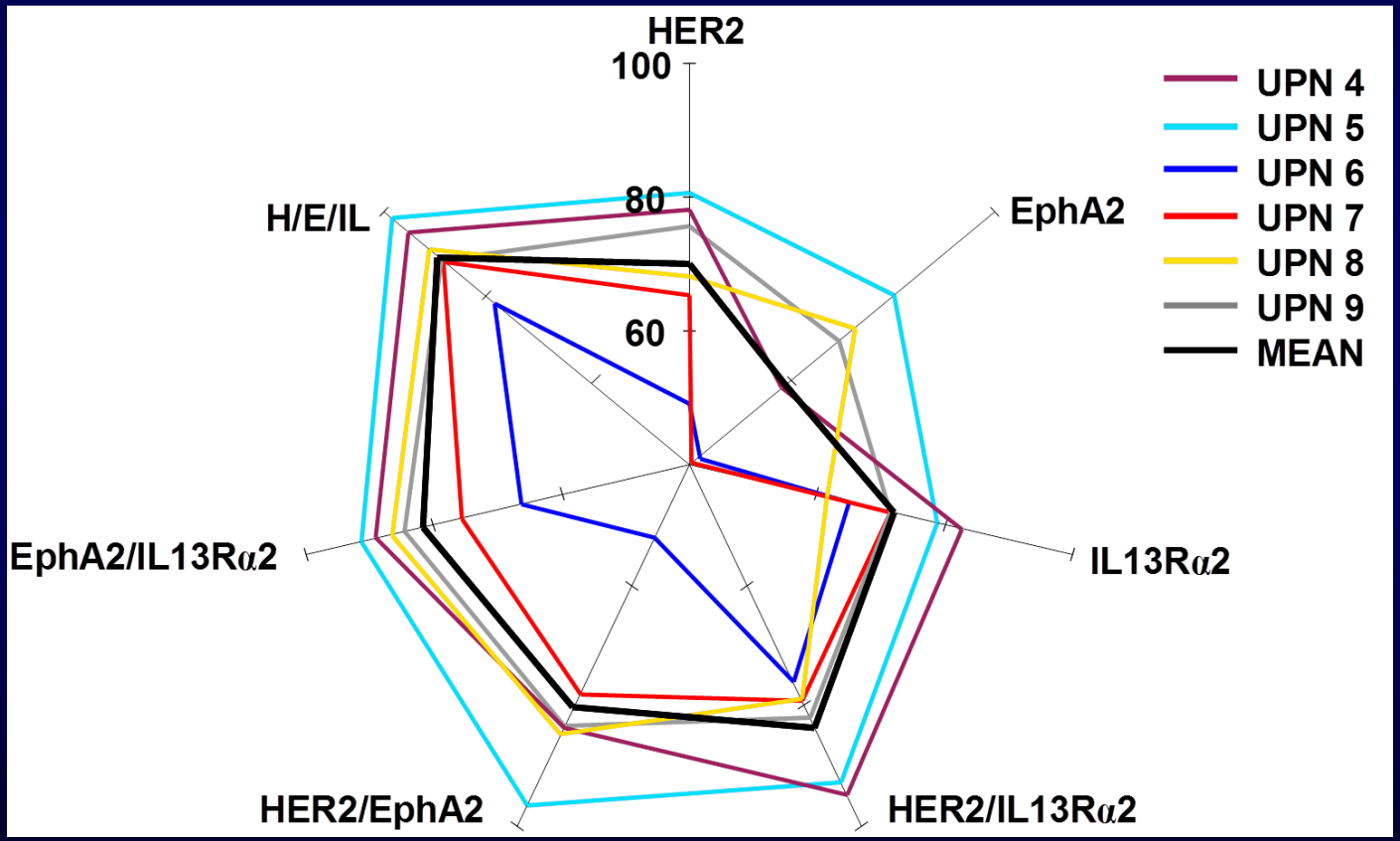


Flow cytometry



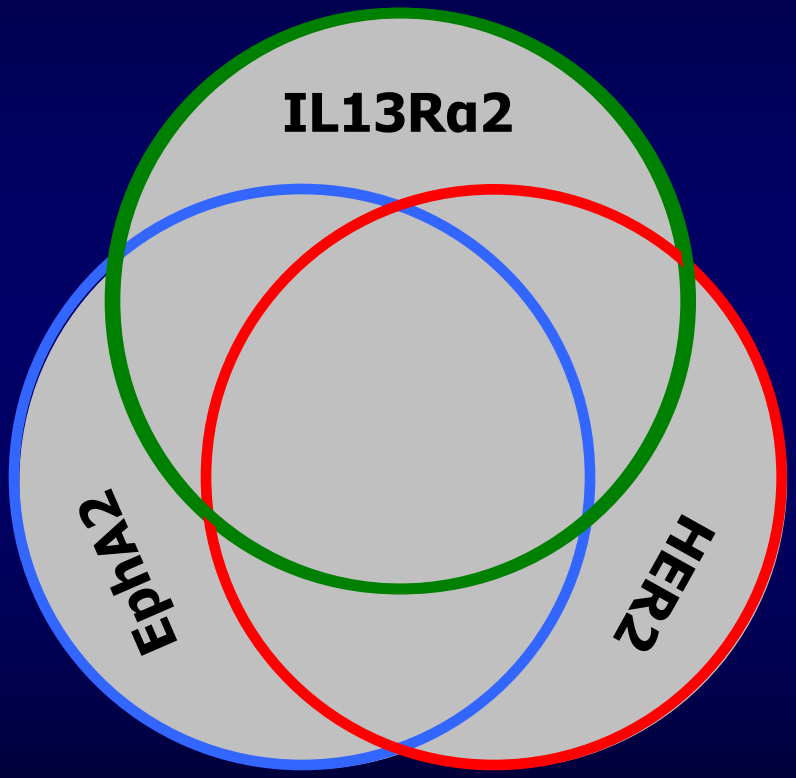
Hegde et al., *Mol Ther in press*

Primary HGG: *hierarchy of antigen expression*



Hegde et al., *Mol Ther in press*

Primary HGG: *prevalence of antigens*



~ 75%

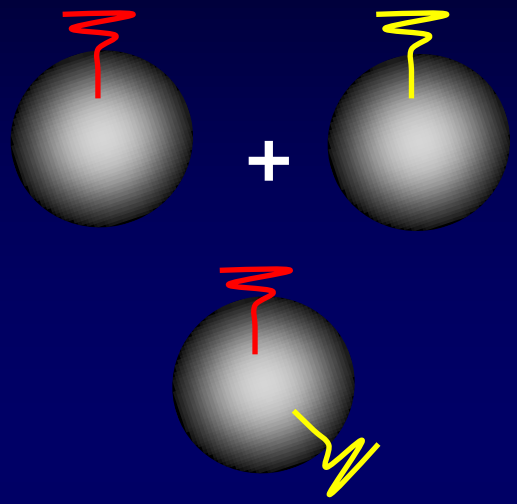
~ 95%

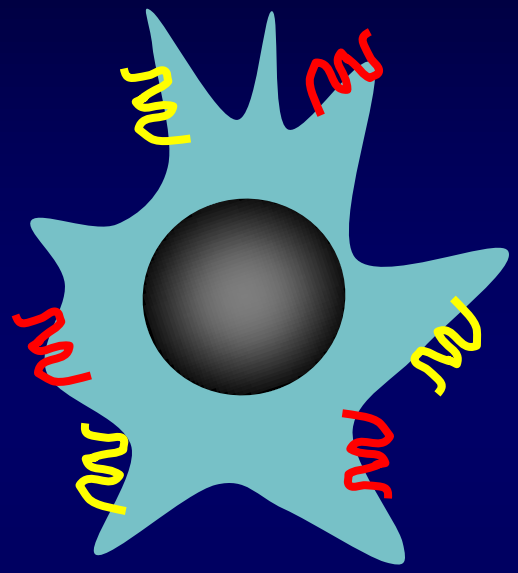
~ 98%

IL-13Rα2 or HER2 vs. H or I or E $p < 0.05$

Hegde et al., *Mol Ther in press*

Targeting Multiple Antigens





Possible advantages

- **Circumvent tumor escape**
  - Heterogeneous expression of target
  - Down regulation of target
  - Antigen loss variants
- **Improve T cell activation**

Weitjens et al. *Genes Ther* 2000

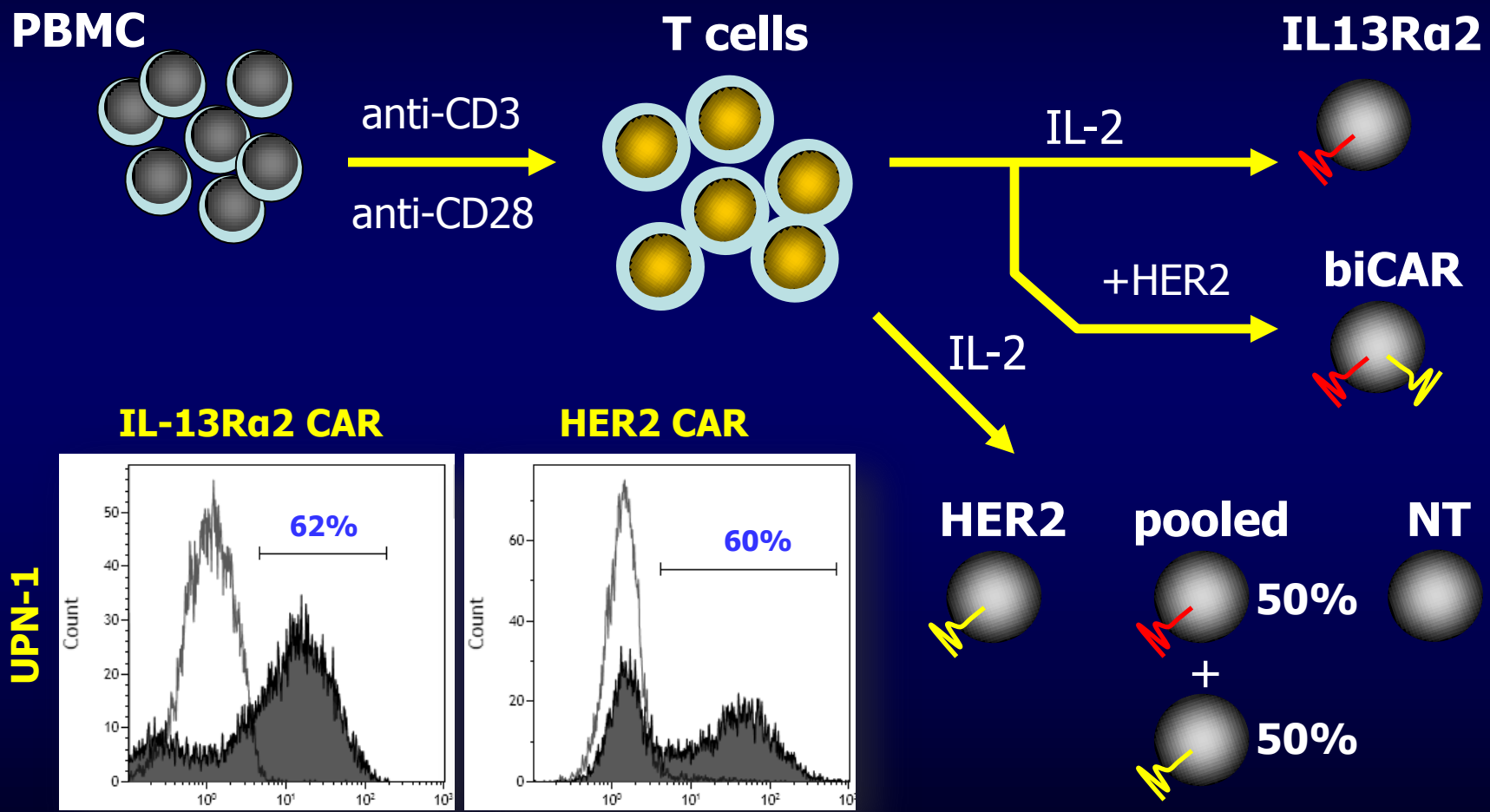
Target antigens: *HER2 and IL13Rα2*

- **HER2** (ErbB-2)
  - Expressed in 80% of HGG
  - Cell growth and differentiation
  - Poor prognosis
- **IL13Rα2**
  - Expressed in >80% of HGG
  - Adhesion and invasion properties

HER2 or IL13Rα2 ~ 95%

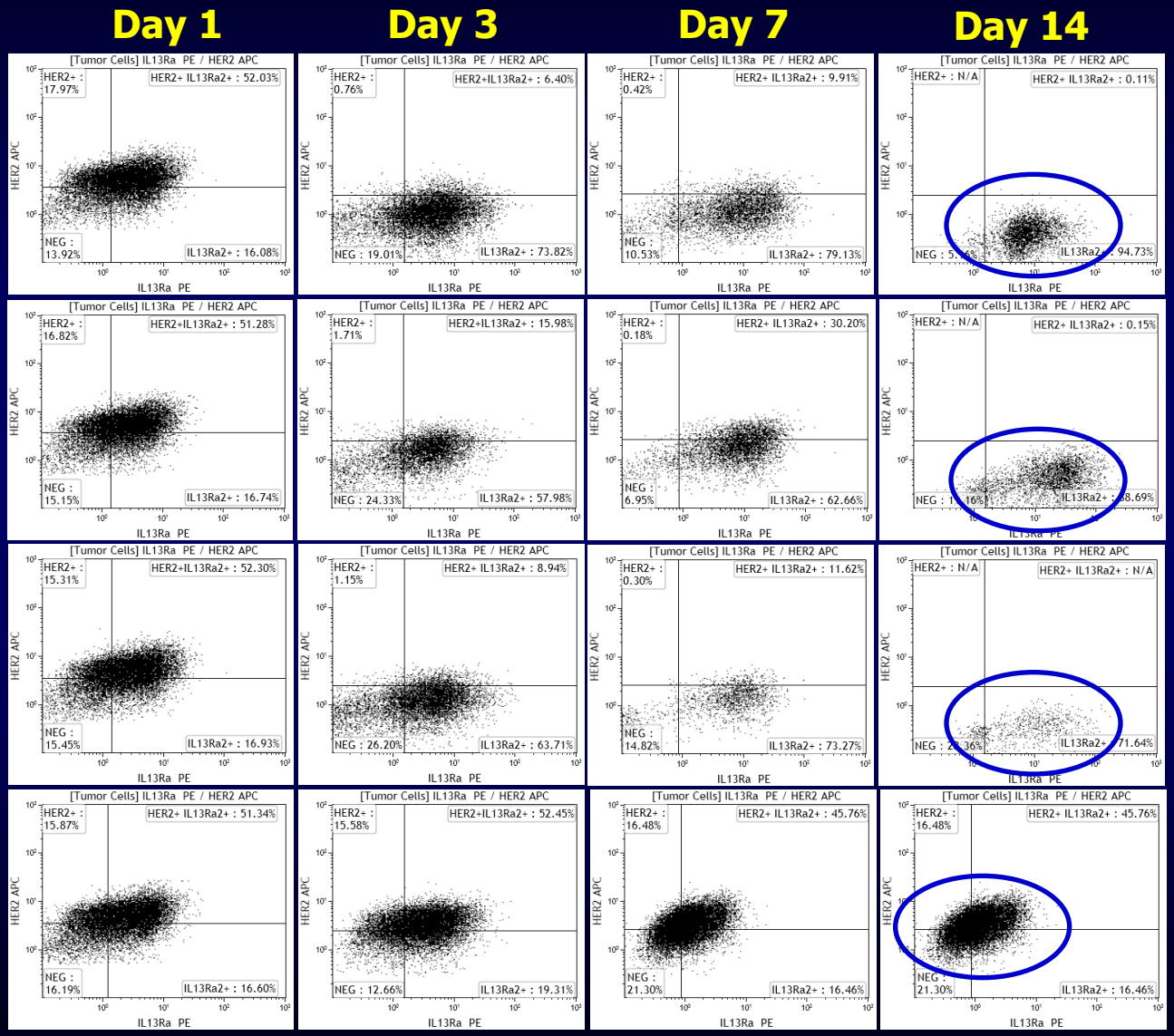
Zhang JG et al. *Clin Cancer Res* 2007; Jarboe JS et al., *Cancer Res* 2007

Bispecific CAR T cells (biCAR T cells)



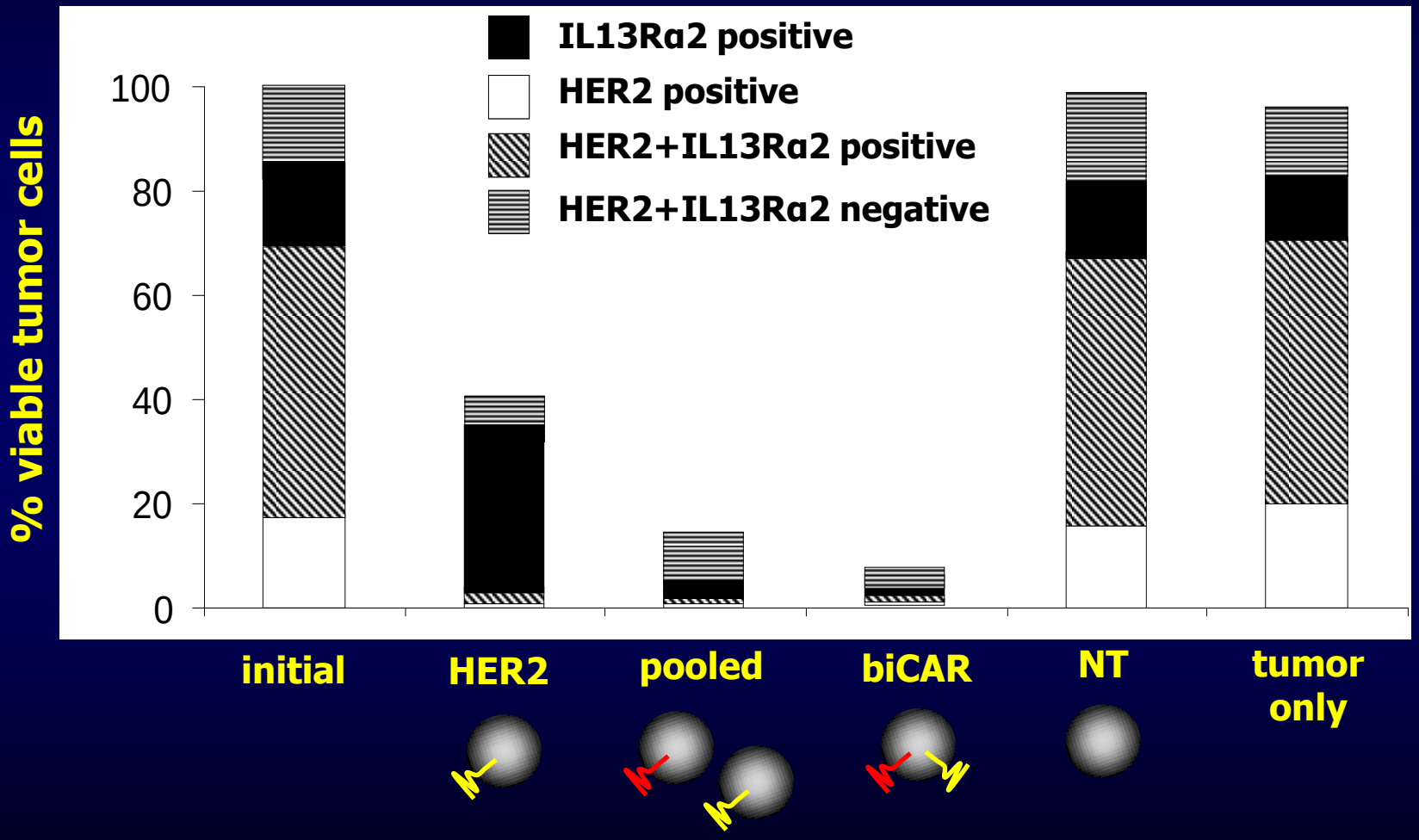
Hegde et al., *Mol Ther in press*

biCAR T cells: *improved tumor killing*



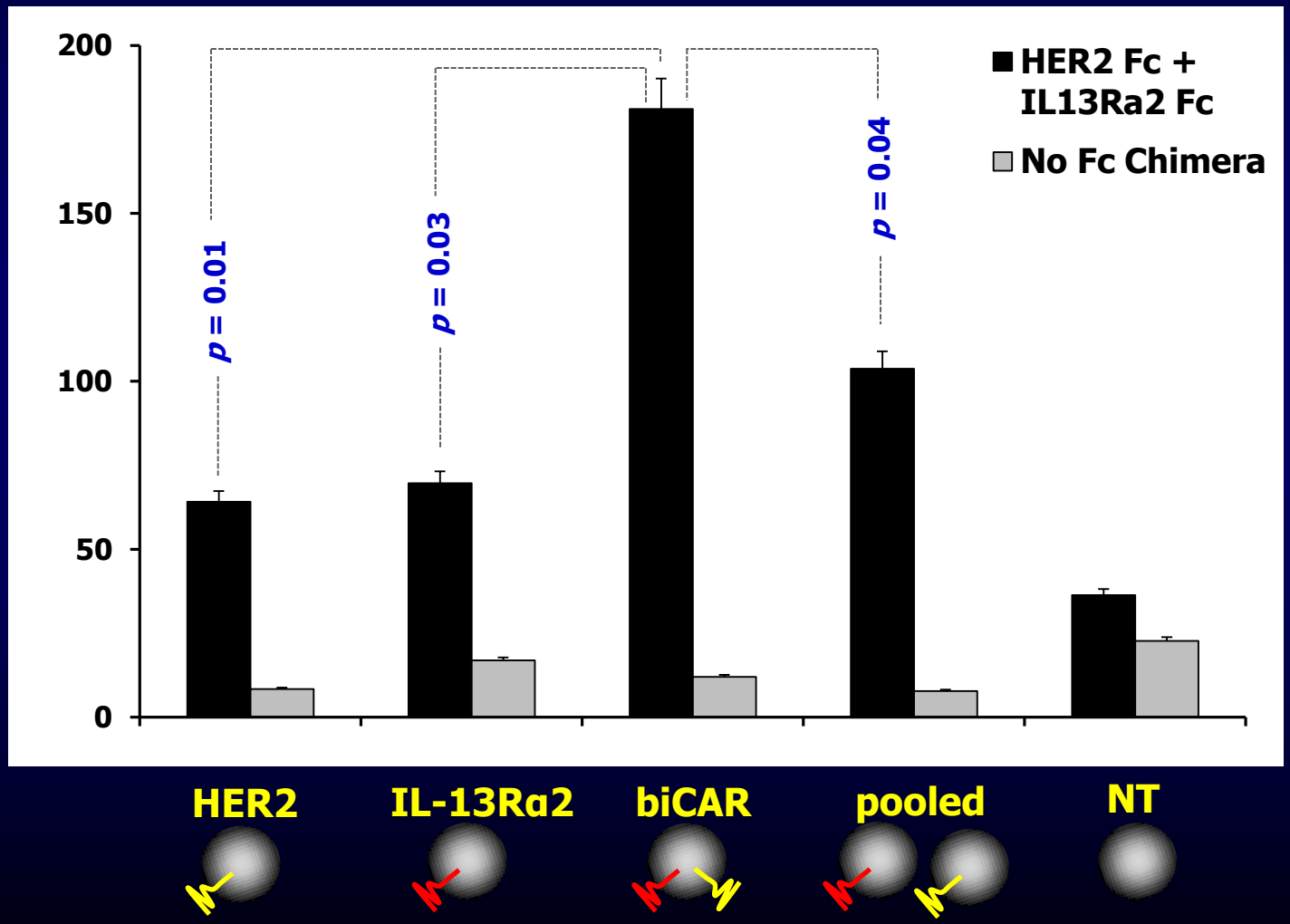
Hegde et al., *Mol Ther in press*

biCAR T cells: *offset antigen escape*



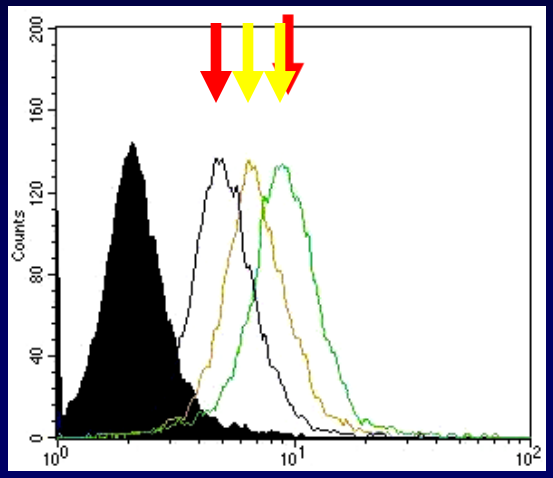
Hegde et al., *Mol Ther in press*

biCAR T cells: *increased T cell proliferation*

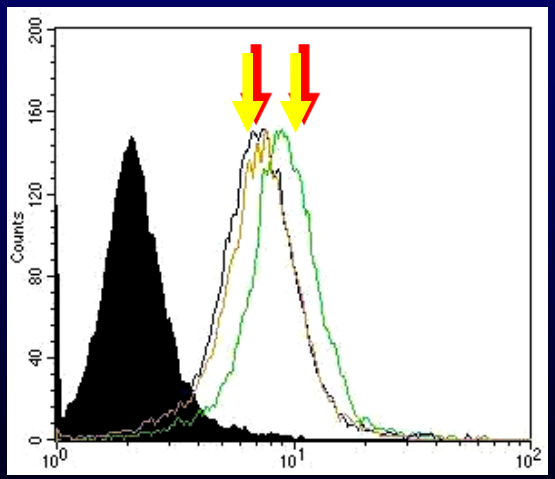


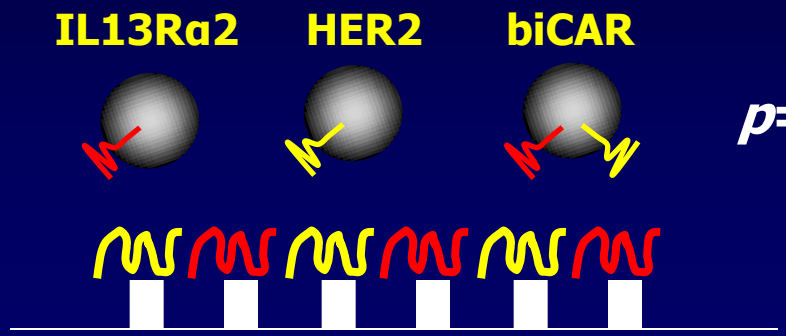
Hegde et al., *Mol Ther in press*

biCAR T cells: *enhanced signaling*

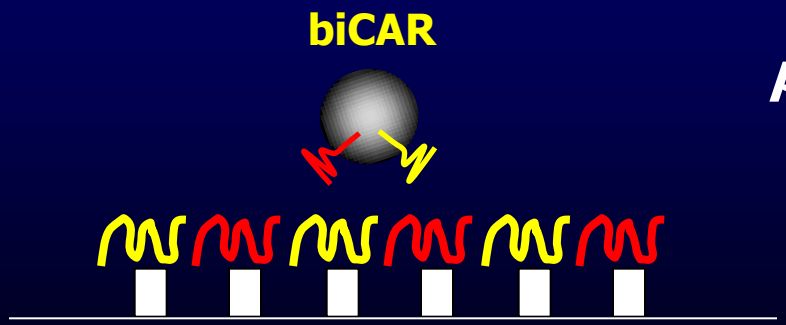


pZap70 →





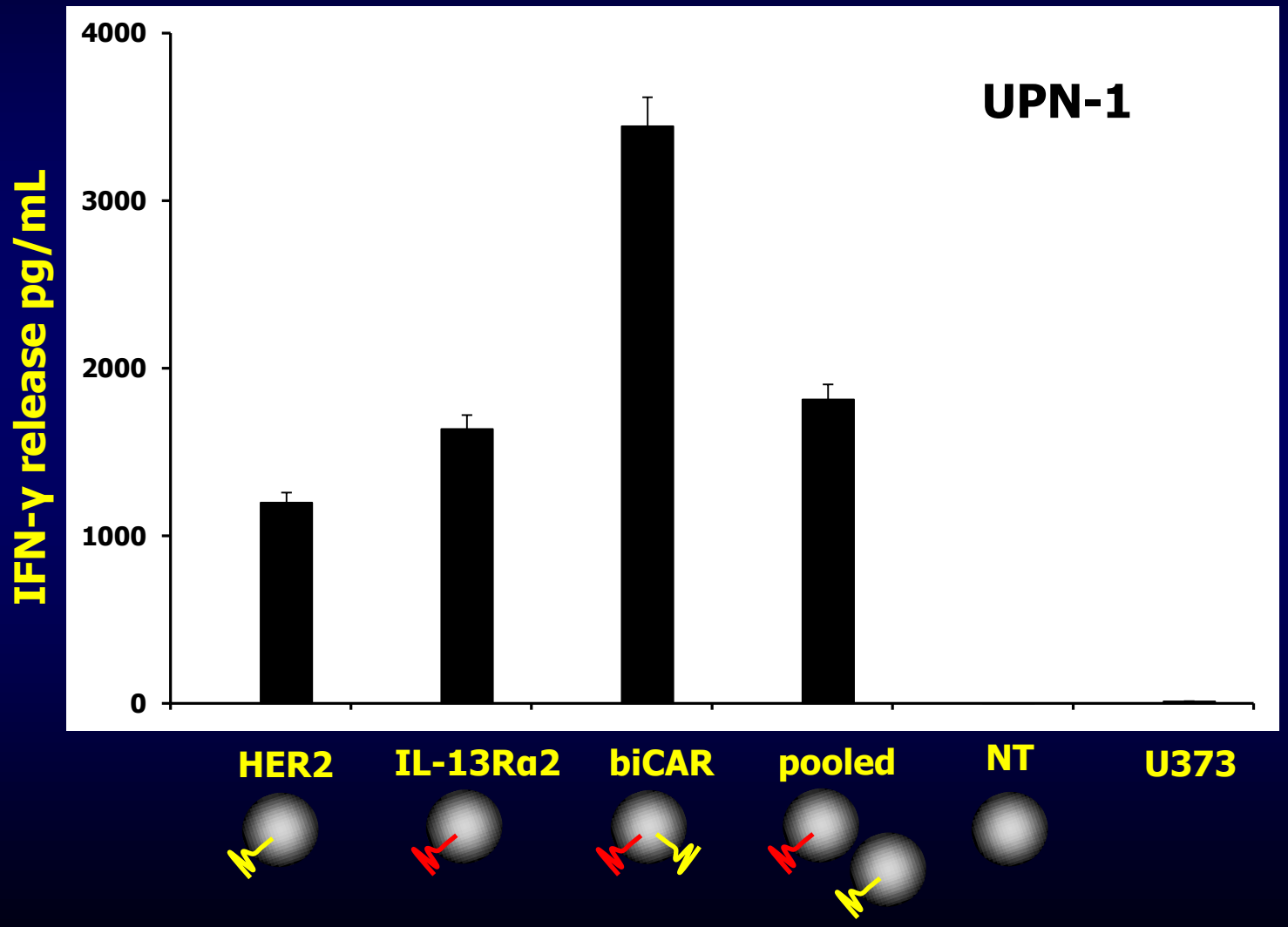
p=0.01



p=0.1

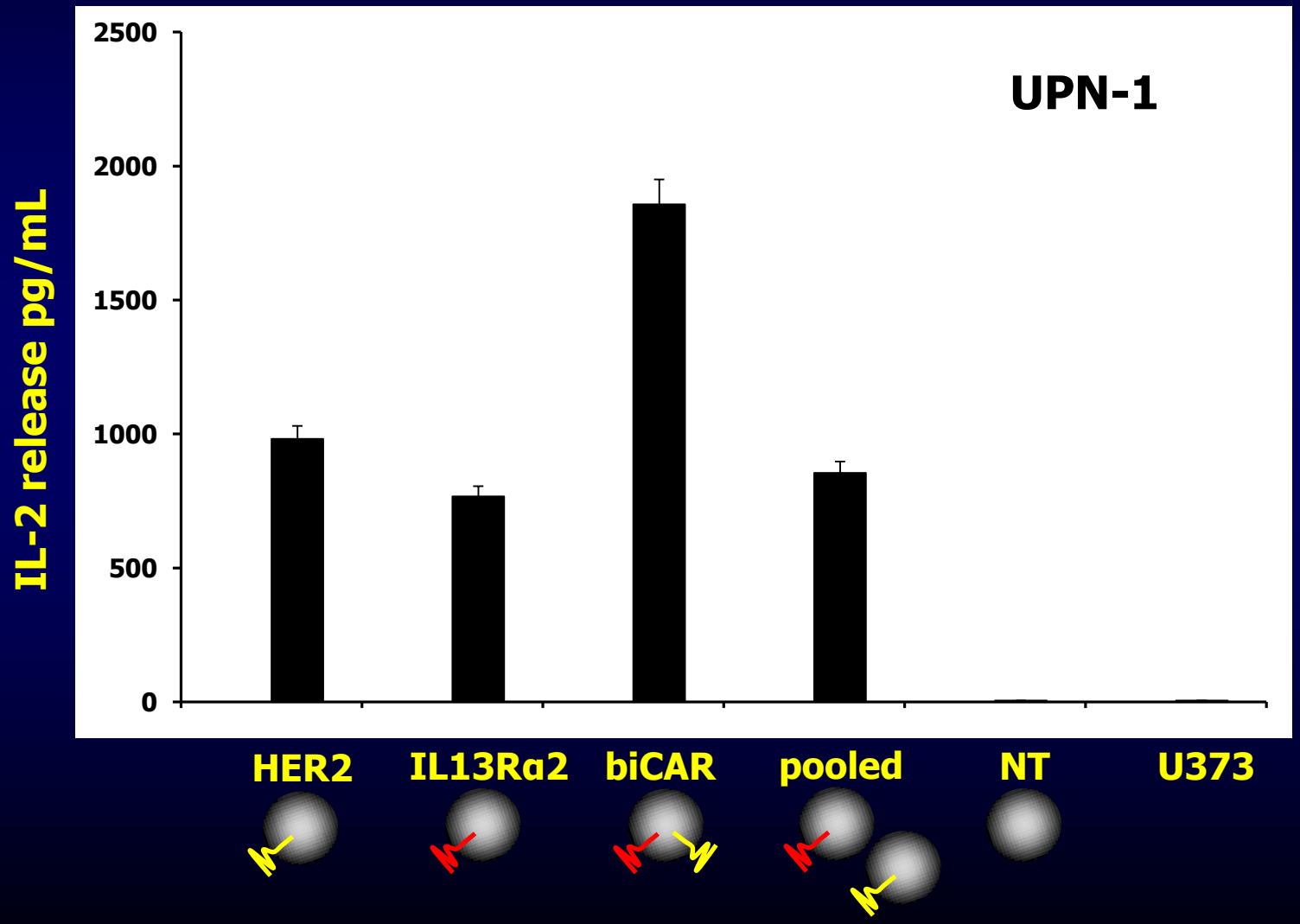
Hegde et al., *Mol Ther in press*

biCAR T cells: *IFN-γ*



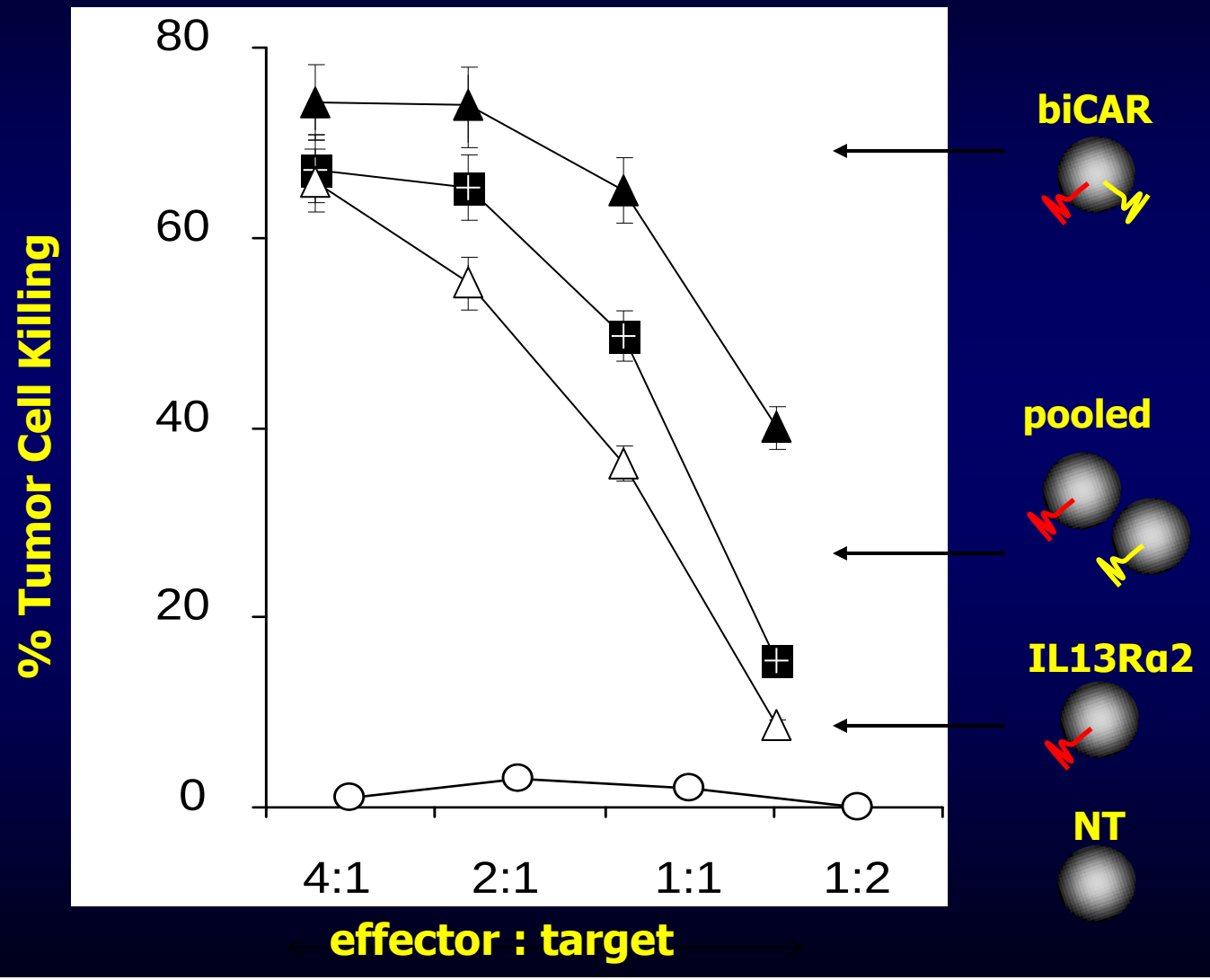
Hegde et al., *Mol Ther in press*

biCAR T cells: *IL-2*



Hegde et al., *Mol Ther in press*

biCAR T cells: *cytolytic activity*



Hegde et al., *Mol Ther in press*

Orthotopic xenograft model *of HGG*

Day 6

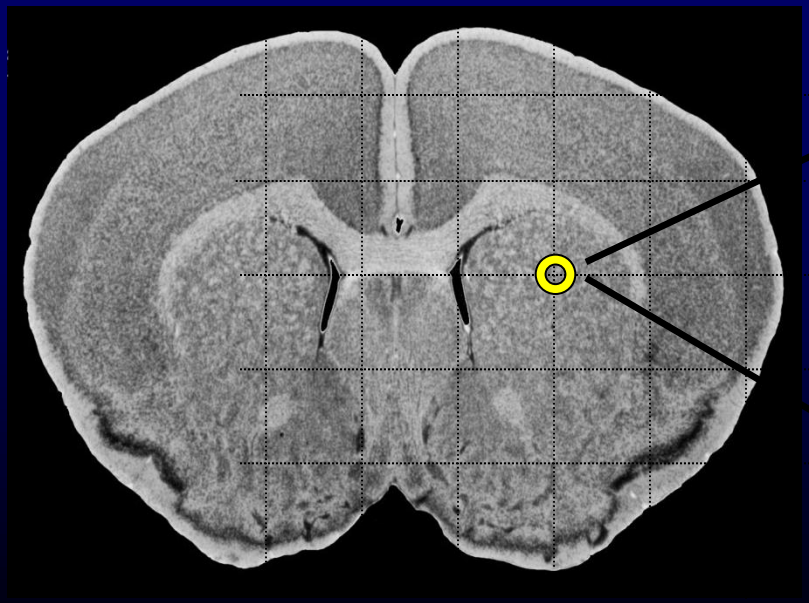
Day 150

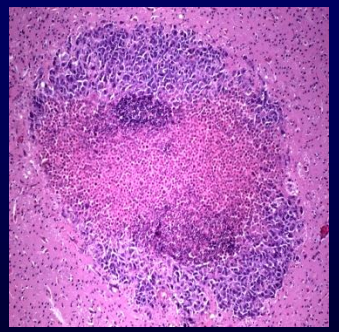
Serial Bioluminescence

eGFP.FFLuc U373
$2.5x10^5$ cells

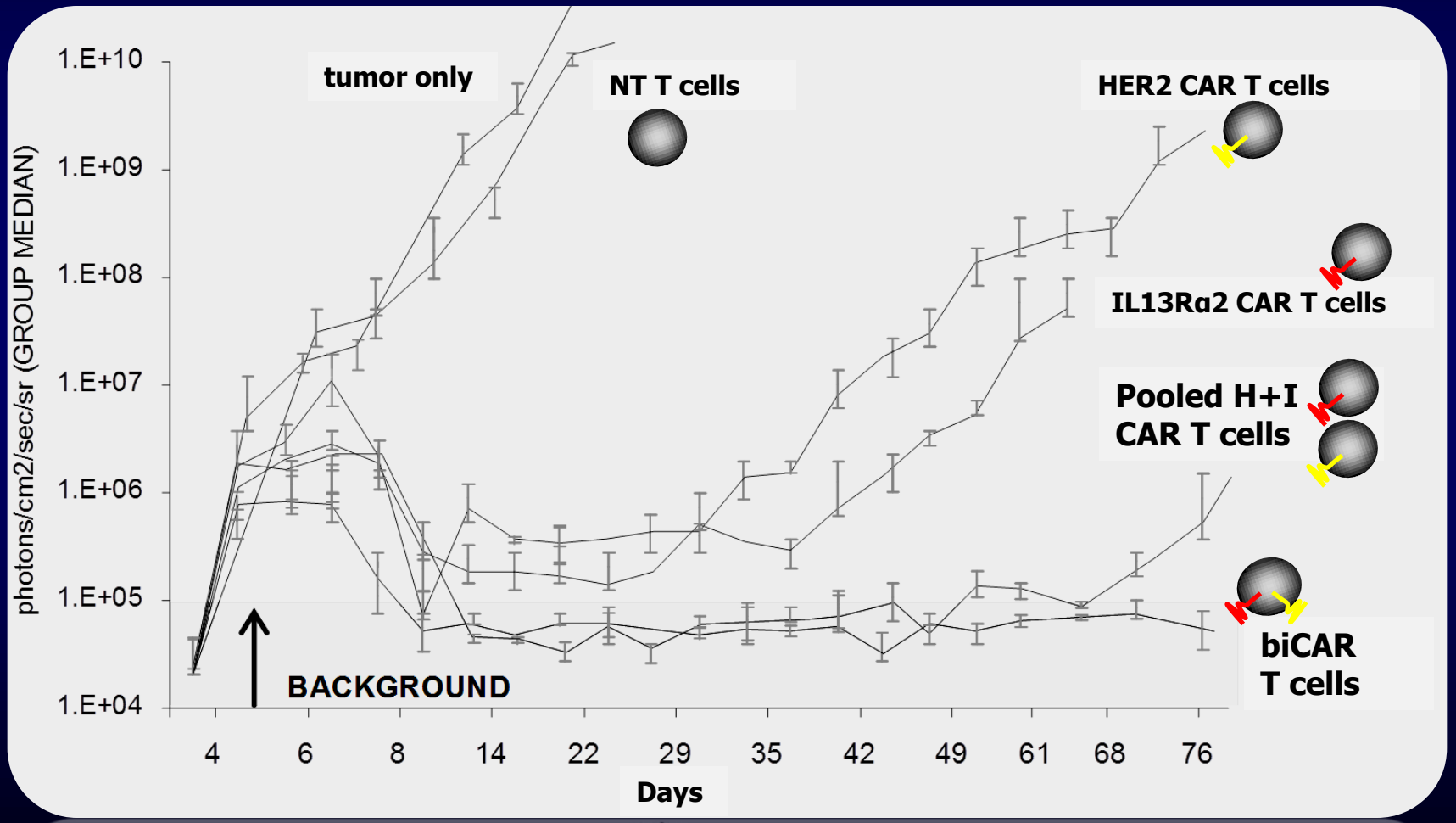
T cells
$2x10^6$ cells

Survival Analysis



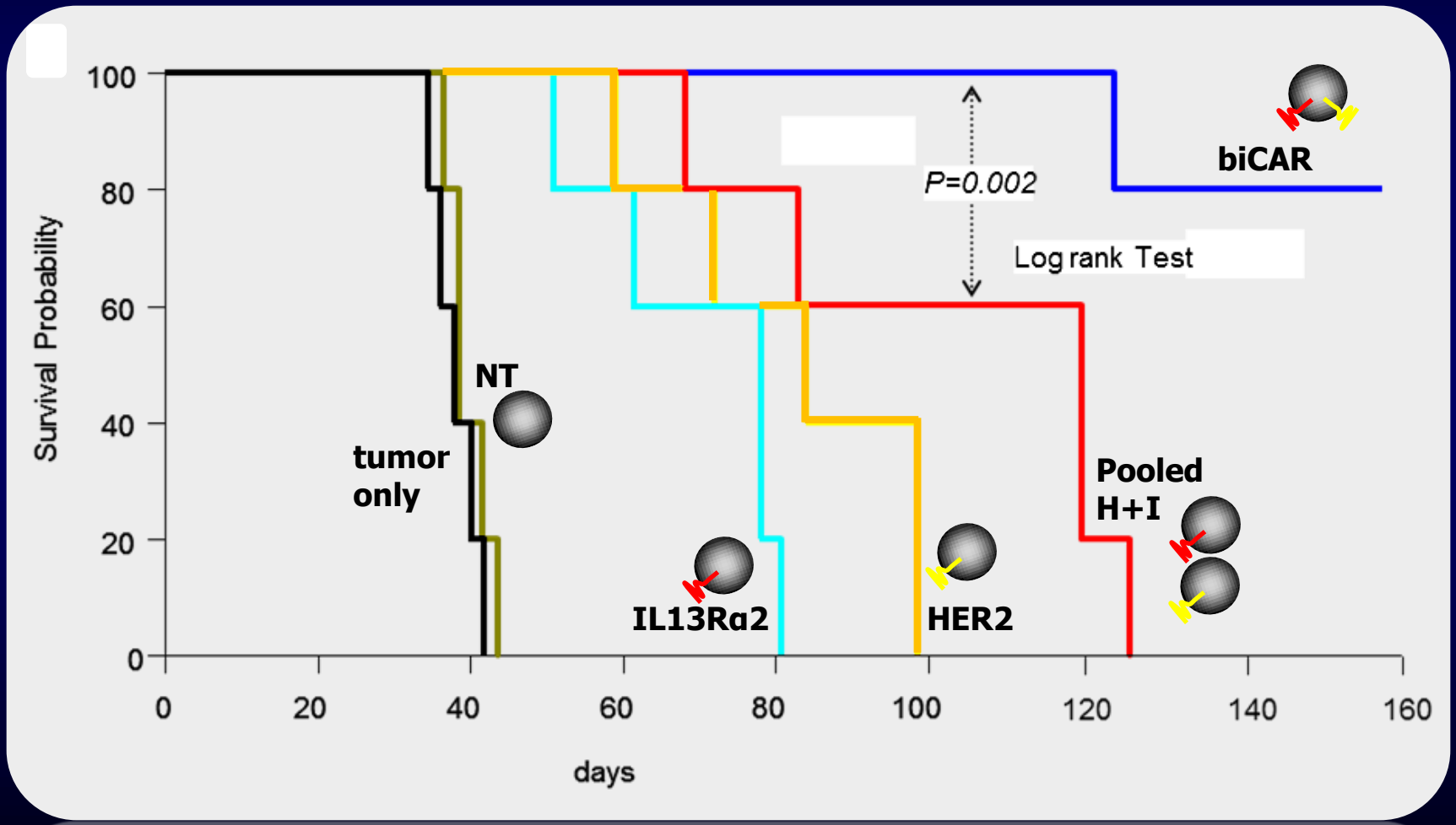


biCAR T cells: *sustained tumor regression in vivo*



Hegde et al., *Mol Ther in press*

biCAR T cells: *improved survival probability*



Hegde et al., *Mol Ther in press*

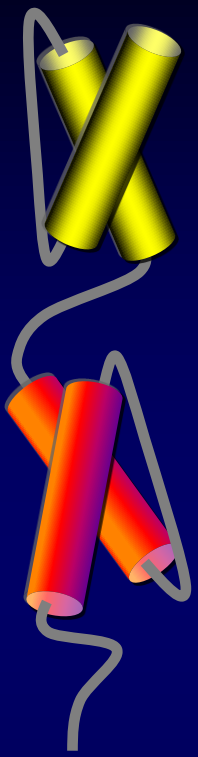
Conclusion

- The pattern of heterogeneity in HGG justifies co-targeting multiple antigens
- Combinational targeting offsets antigen escape and improves tumor control
- biCAR T cells

  Advantages
  - Single product
  - Allows for using smaller dose of T cells

  Limitations
  - Increased cost
  - Labor intensive

Future Directions



- **HER2/ IL-13Rα2 specific TanCAR**
  - Surface expressed
  - Recognizes two different tumor antigens distinctly
  - Enhanced T cell activation on engaging two targets simultaneously

Advantage

  - Single construct can render T cells bispecific

Grada and Hegde et al., *Nucleic acids* 2013

Future Directions

- **Universal CAR T cell product for HGG**
  - Target multiplex of antigens
  - Personalize therapy
- **Tumor and tumor microenvironment**
  - Glioma-restricted antigen HER2
  - Tumor endothelial marker 8 (Tem8)

Acknowledgements

Nabil Ahmed
Helen Heslop
David Poplack
Malcom Brenner

Susan Blaney
Murali Chintagumpala


Amanda Corder


Tiara Byrd


Vita S Brawley

Eric Yvon
Stephen Gottschalk
Yvonne Kew

Texas Children's Cancer Center
Center for Cell and Gene Therapy
Methodist Hospital
Baylor College of Medicine

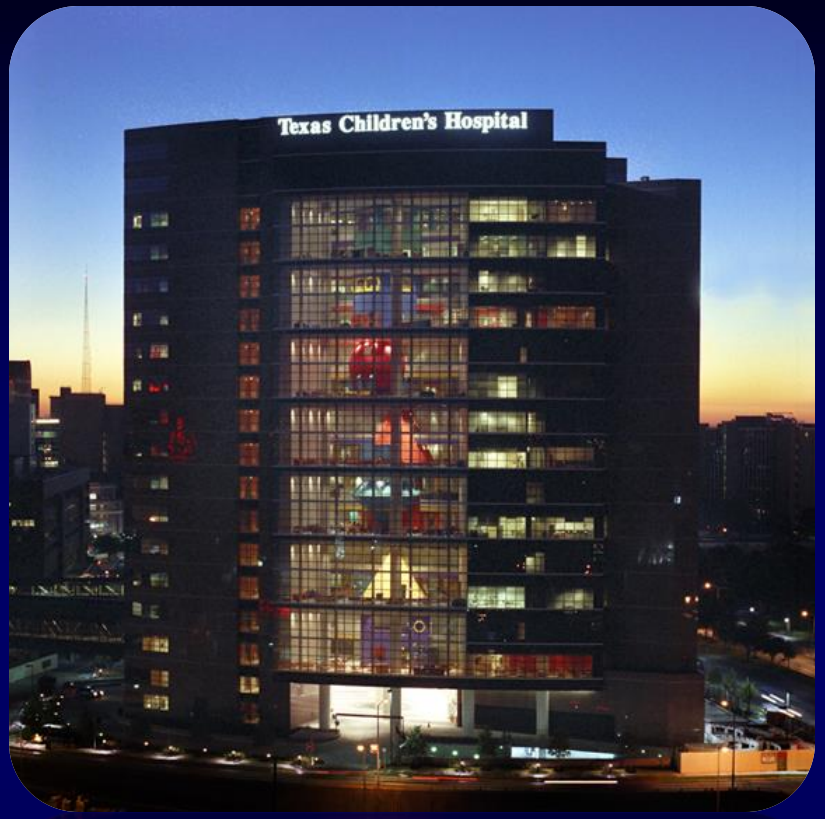
Alex's Lemonade Stand
FOUNDATION FOR CHILDHOOD CANCER™

STAND UP TO CANCER™

CureSearch for Children's Cancer

Hyundai Hope On Wheels®
Helping Kids Fight Cancer

Texas Children's Cancer Center



Center for CAGT Cell and Gene Therapy

BCM Baylor College of Medicine | Methodist The Methodist Hospital | Texas Children's Hospital

BCM Baylor College of Medicine