

ANTIGENS AND TOXICITY WITH DESIGNER T CELLS

Why the Different Experiences with CEA?

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No commercial relationships to disclose.

CEA Study Types

ANTIGEN	RECOGNITION TYPE	Ab/TCR Domain	GEN	MODE	STRATEGY	IL2	TOXICITY
CEA IgTCR	Surface	A3B3	1	INFUSE 10^{11}	1	-IL2/ +IL2	NO
CEA Ig28TCR	Surface	A3B3	2	INFUSE 10^{10}	3	-IL2	NO
CEA TCR	MHC-I	A3B3 peptide	1	ENGRAFT 2×10^8	2	+IL2	GI
CEA IgTCR	Surface	N-A1	1	ENGRAFT $>10^{10}$	2	+IL2	LUNG

Toxicity

- o Lack of toxicity with lack of benefit
- o Toxicity with lack of benefit
- o Lack of toxicity with benefit
- o Toxicity with benefit

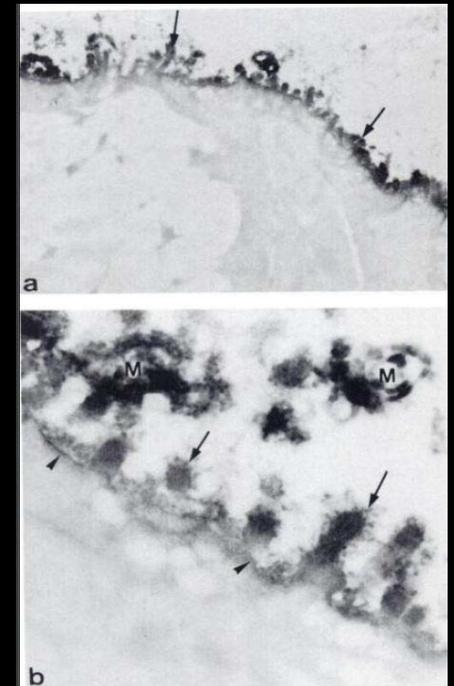
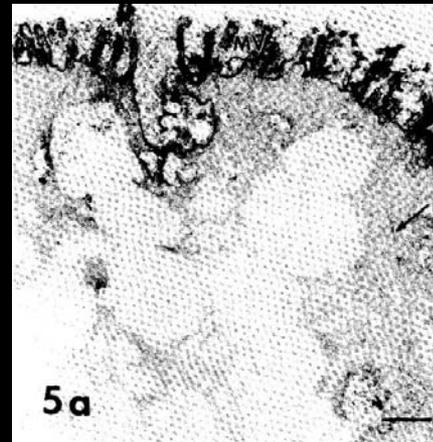
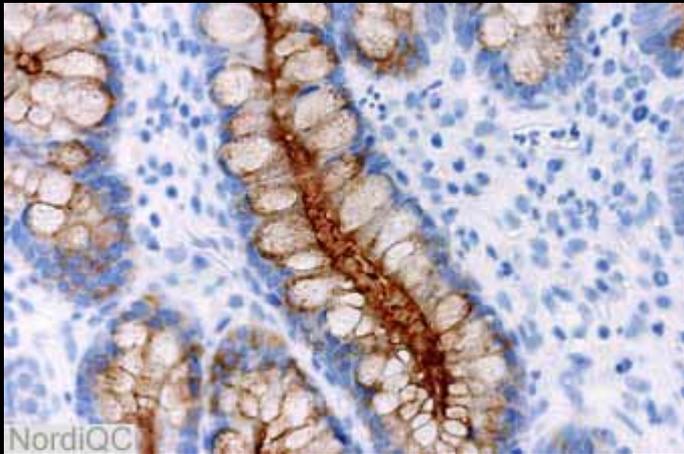
Why the different toxicities for CEA targeting by TCR versus IgTCR?

Parkhurst et al, ASGCT 2010

- o Cloned murine TCR for HLA-A2 presented CEA peptide
- o TCR gene transfer (not CAR ~ 1st gen), 3 subjects
 - Lymphodepletion
 - 2-4 x 10⁸ cells
 - 1-20% engraftment
- o Toxicity against bowel, all had grade 2/3 diarrhea
 - T cell infiltration
 - epithelial destruction
- o Some tumor partial response noted
- o However, concluded not safe to target CEA

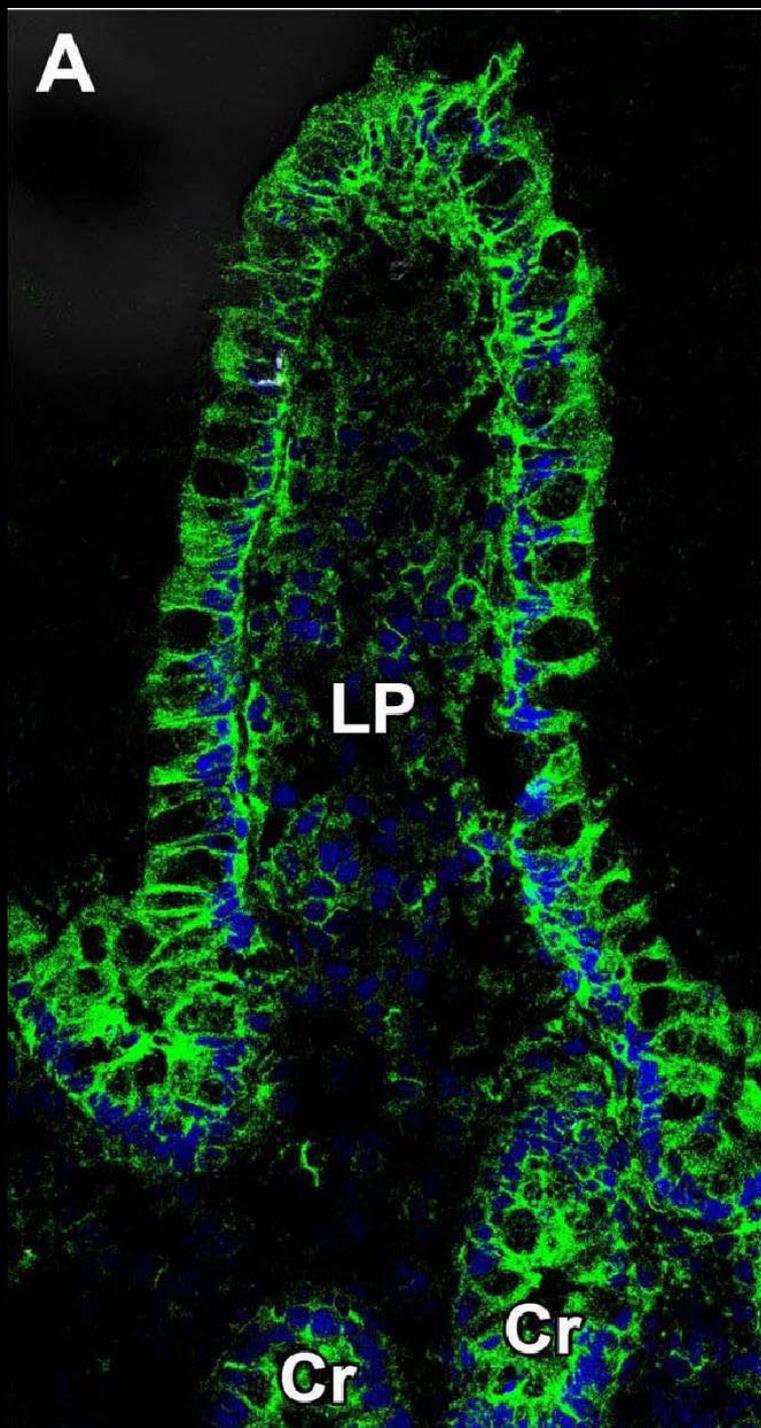
What is the difference???

CEA on enterocytes

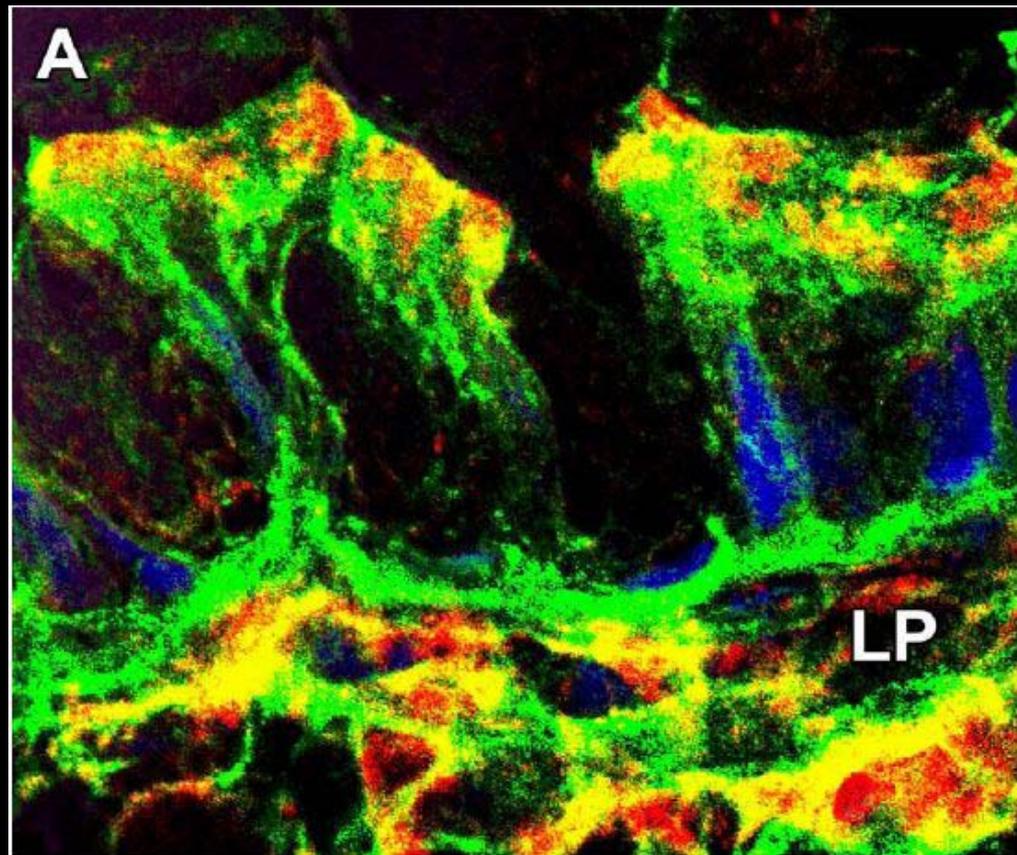


Antigen sequestration:
CEA confined to microvilli

A



MHC class I on enterocytes



Topology MHC I:
Primarily basal expression

Topology

(on epithelial cells)

- o Toxicity correlates with accessibility of Ag
- o Apically polarized expression may **sequester** Ag from T cell attack (IgTCR)
- o MHC-peptide expression is polarized to favor T cell detection and attack (TCR transfer)
- o *BUT* ... not clear that all polarized expressions are protective: GI (yes), ducts (bile, pancreas, etc?), airway (alveoli, bronchioles?)

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CEA IgTCR	Surface	NA1	1	ENGRAFT $>10^{10}$	2	+IL2	LUNG

Why the different toxicities for CEA targeting by different Abs in the IgTCR?

Hawkins, 2010

- o Ab used for detecting tumor antigen
- o 3 subjects, no toxicity
 - Mild lymphodepletion (F x5d)
 - Up to 5×10^{10} cells
 - In effective engraftment
- o 4 subjects, lung toxicity? 4/4 SOB, ICU transfer
 - Full lymphodepletion (C x2d, F x5d)
 - Up to 5×10^{10} cells
 - More effective engraftment
- o Some tumor partial response noted
- o Suspended by IRB

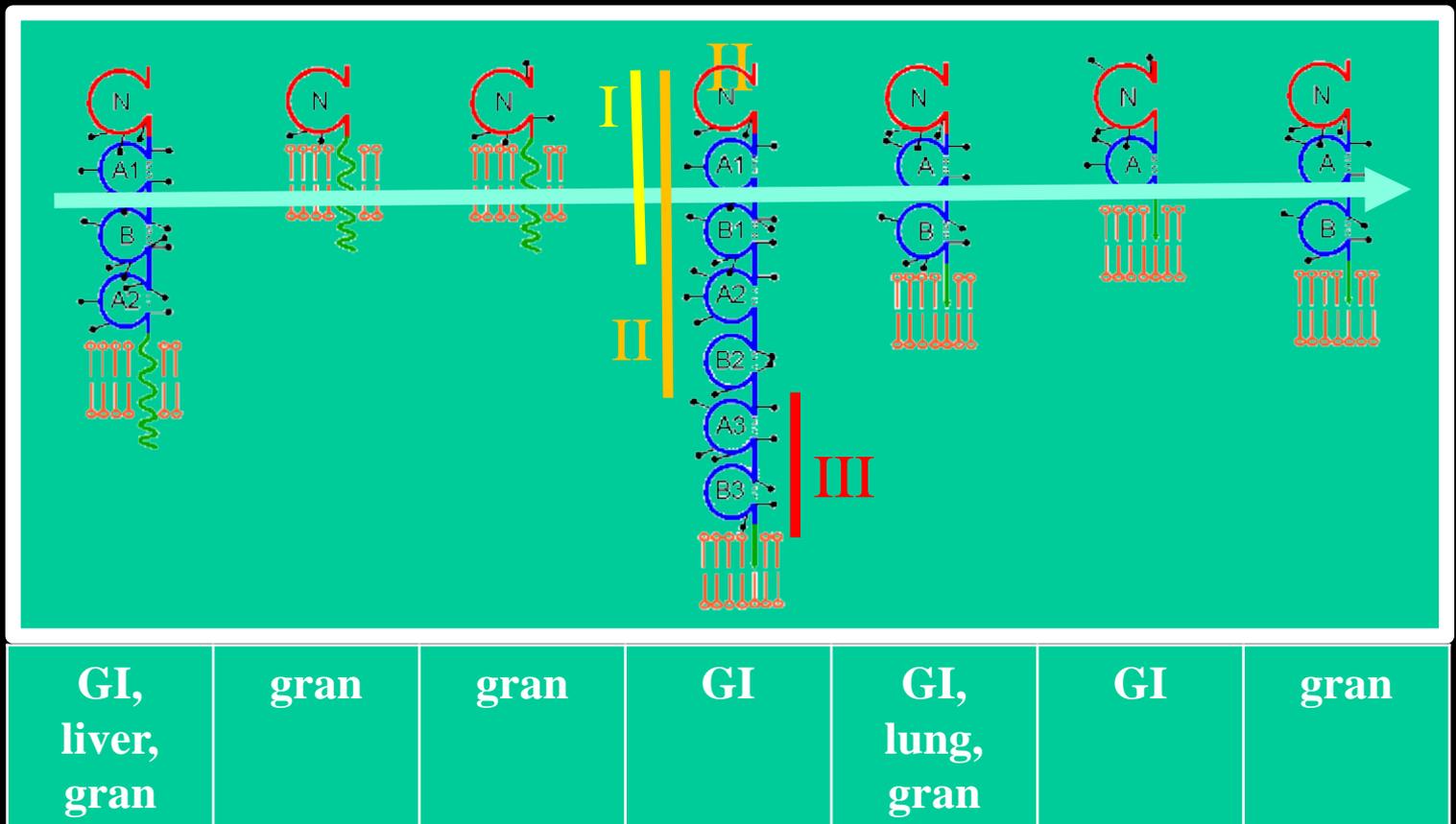
What is the difference???

CEA targeting features

Ab/TCR Domain	ANTIGEN	TISSUE	LOCATION	TOXICITY
A3B3	CEA	GI	APICAL	NO
A3B3	MHC-peptide CEA	GI	BASAL	GI
N-A1	CEA CEACAM6	LUNG GI GRAN	? APICAL N/A	LUNG

CEA-related molecules

protein	CEACAM1	CEACAM3	CEACAM4	CEACAM5 CEA	CEACAM6	CEACAM7	CEACAM8
old name	BGPa	CGM1a	CGM7	CEA	NCA-90	CGM2	NCA-95
CD	CD66a	CD66d		CD66e	CD66c		CD66b



Antigen epitope targeting

- o Epitopes can matter
- o Normal tissue expression can depend on whether epitopes shared with other genes
- o Unintended target Ags = Off-target toxicity

Caveats

- o Con: Fewer cells in the safe examples:
 - with toxicity = engraftment, many cells, longer
 - without toxicity = infusion
 - 1st gen 10^{11} cells, but transient with infusion
 - 2nd gen no toxicity but only minimal response
 - Only mid-dose level achieved
- o Pro:
 - But 1st gen infused
 - could show benefit (CEA)
 - reveal toxicity with low numbers infused (G250)

Lessons on target Ag selection

- o What normal tissues are expressing?
 - Essential/Non-essential
 - Specific Abs may differ
 - Epitopes matter
- o What is topology of expression?
 - Epithelial cancers
 - Antigen Expression
 - CEA Luminal
 - Lewis Y Luminal
 - Class I Basal
 - Her2 Basal
 - CA IX Basal