

Resuscitating Immune Surveillance Against Cancer

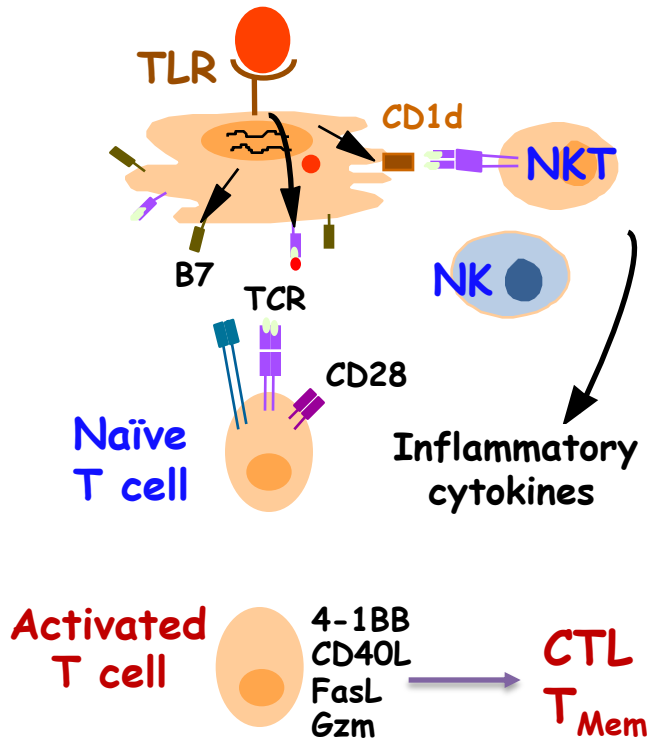
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Biochemistry and Cancer Biology
Meharry Medical College School of Medicine**

**Vanderbilt-Ingram Cancer Center
Vanderbilt University**



Pathogen



Innate

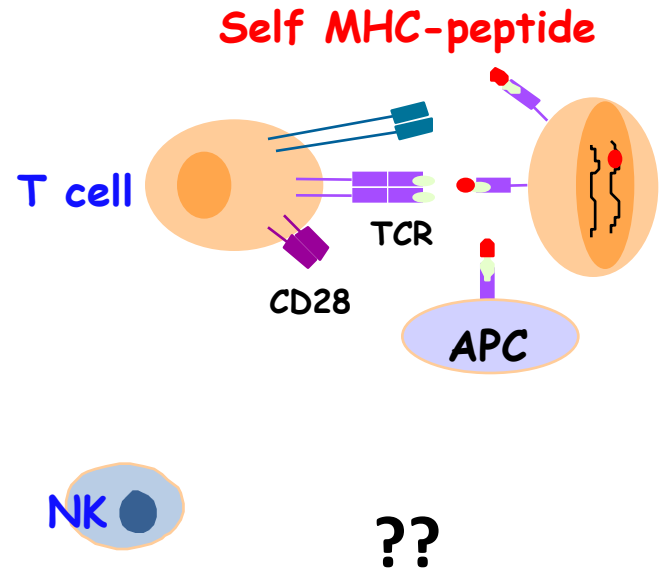
Stress-induced
Rae-1/HL60/MULT



Adaptive

Tumor

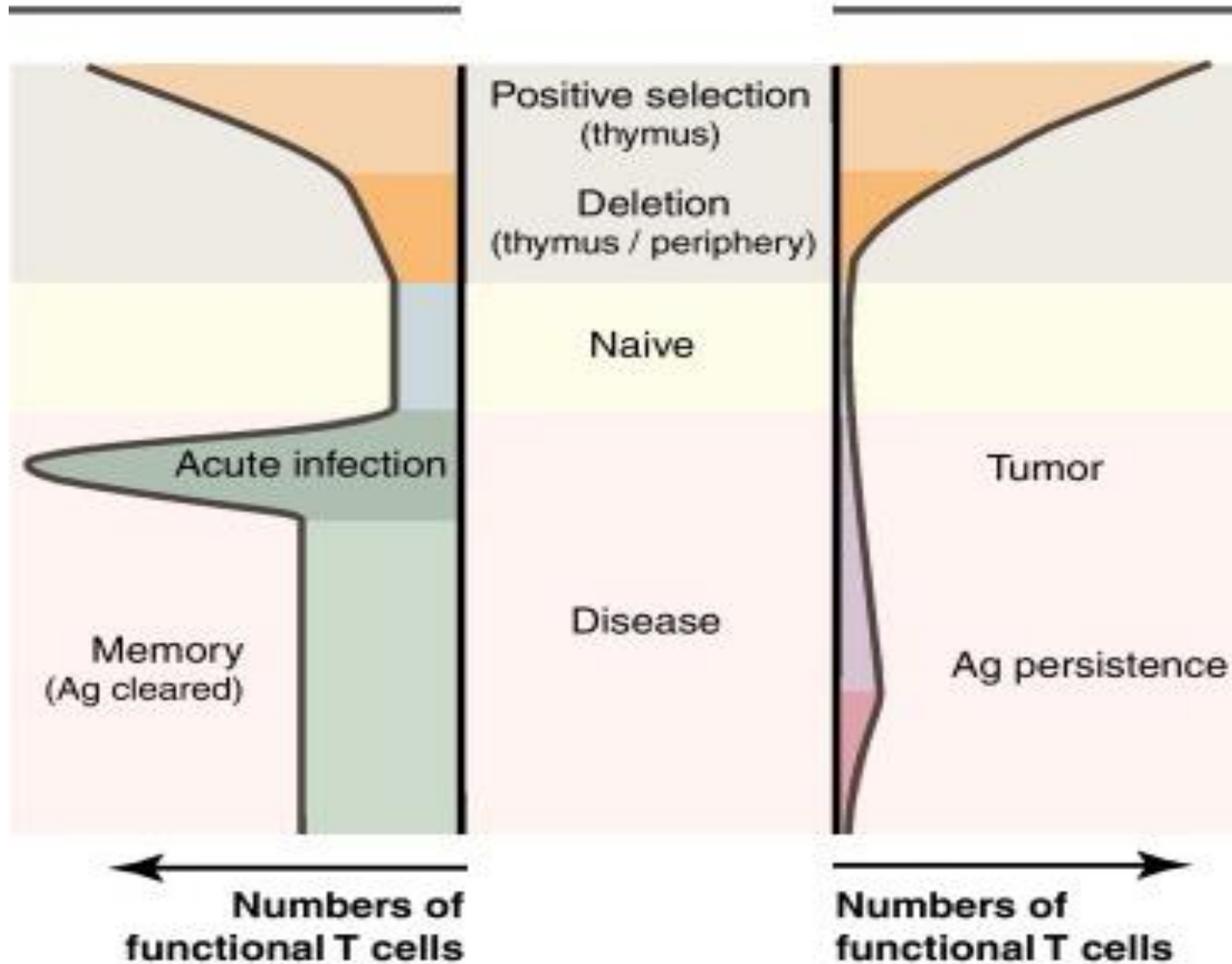
Transformed normal cells



??

**Non-self
Anti-pathogen**

**Self
Anti-tumor**



Does our immune system react to tumors?

Virchow R. Berlin, Germany

Handbuch der speciellen Pathologie und Therapie,
ed. Bd. 1, Erlangen, 1854

- Noted enlarged supra-clavicular nodes due to 'leucoreticular infiltrates' as one of the earliest sign of gastrointestinal malignancy (Virchow's node).
- Suggested a relationship between immune inflammation and tumorigenesis.

Identification of Cancer Antigens

Presence on a human melanoma of multiple antigens recognized by autologous CTL.

Van den Eynde B, Hainaut P, Hérin M, Knuth A, Lemoine C, Weynants P, van der Bruggen P, Fauchet R, Boon T.

Int J Cancer. 1989; 44:634-40

A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma

Van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, Boon T.

Science. 1991; 254:1643-7

Cancer-germline self antigens

Humans: **MAGE**, BAGE, GAGE, RAGE, **NY-ESO**, **MUCINS**

Mouse: **P1A**

Do T cells develop against self antigen P1A?

**TCRP1A
transgenic mice**



DBA/2, B10.D2



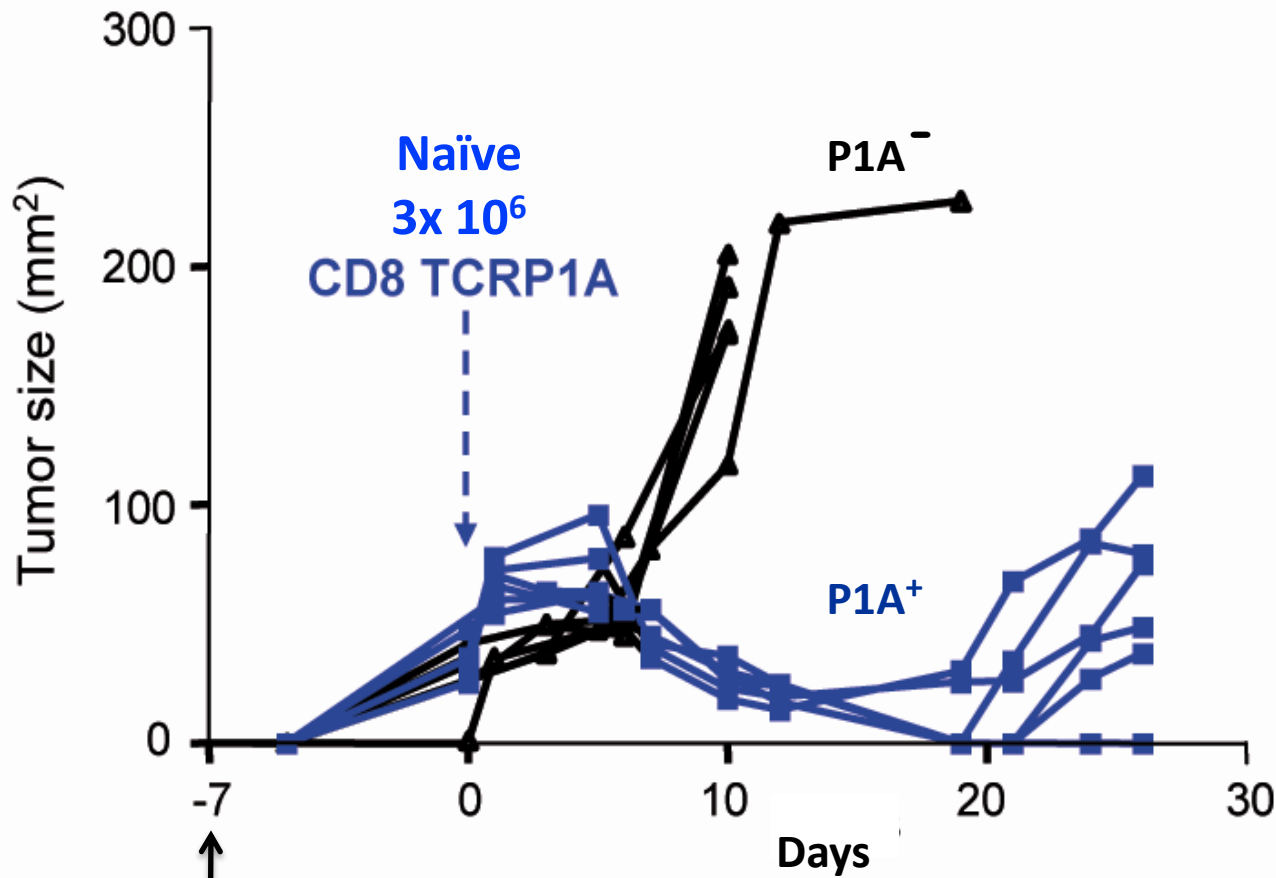
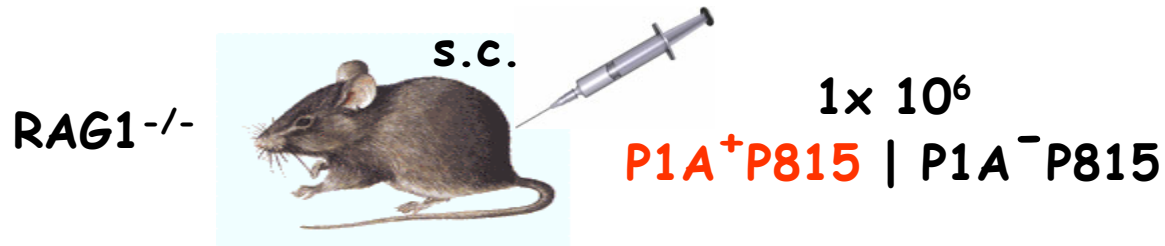
TCR anti-L^d:P1A (LPYLGWLVF)

Thymocyte-Intrinsic Genetic Factors Influence CD8 T Cell Lineage Commitment and Affect Selection of a Tumor-Reactive TCR

Shanker A, Auphan-Anezin N, Chomez P, Giraud L, Van den Eynde B, Schmitt-Verhulst A-M.

J Immunol. 2004, 172: 5069-5077

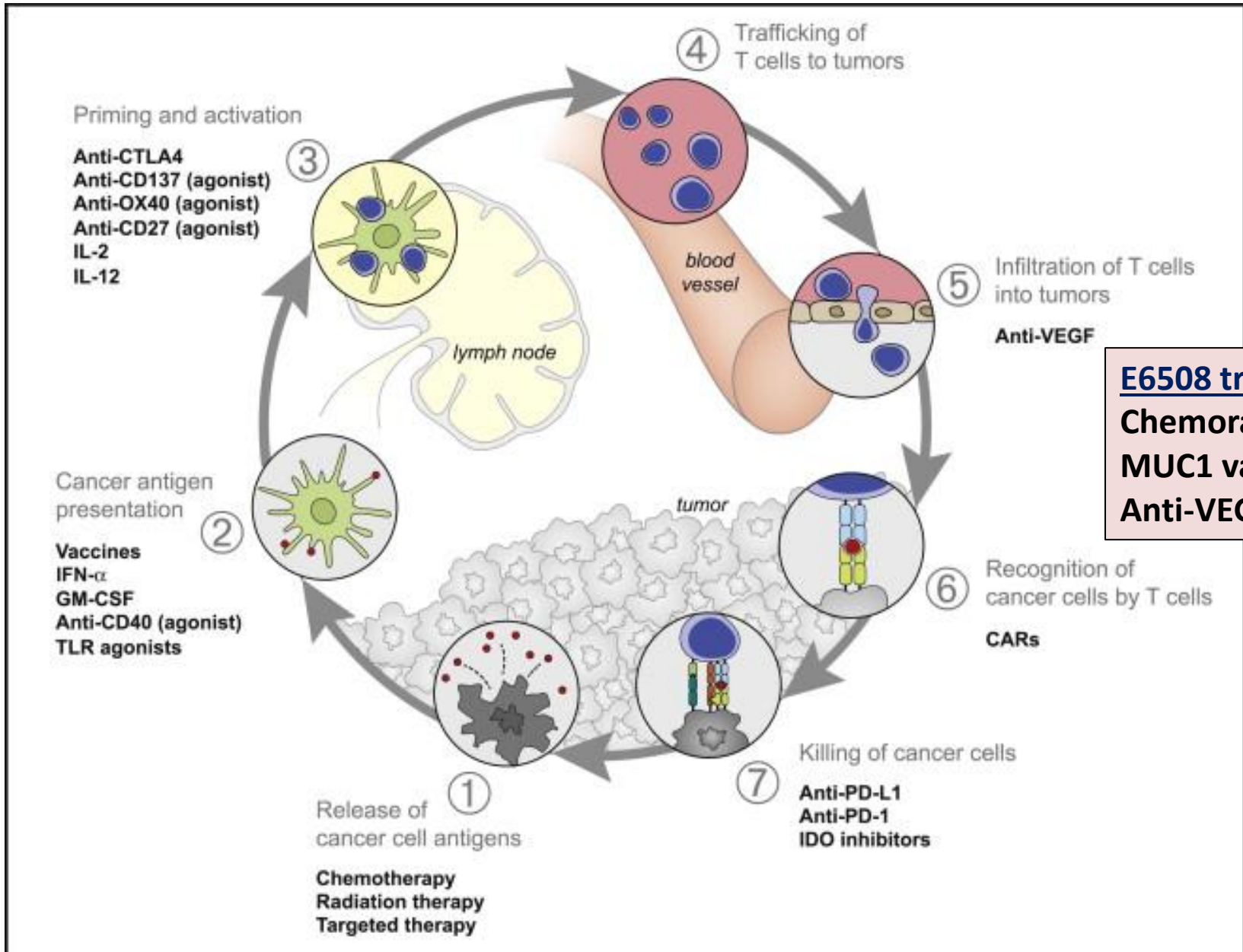
P1A-specific T cell function



Tumor escape variants lose P1A but retain MHC and co-stimulatory molecules

Tumor

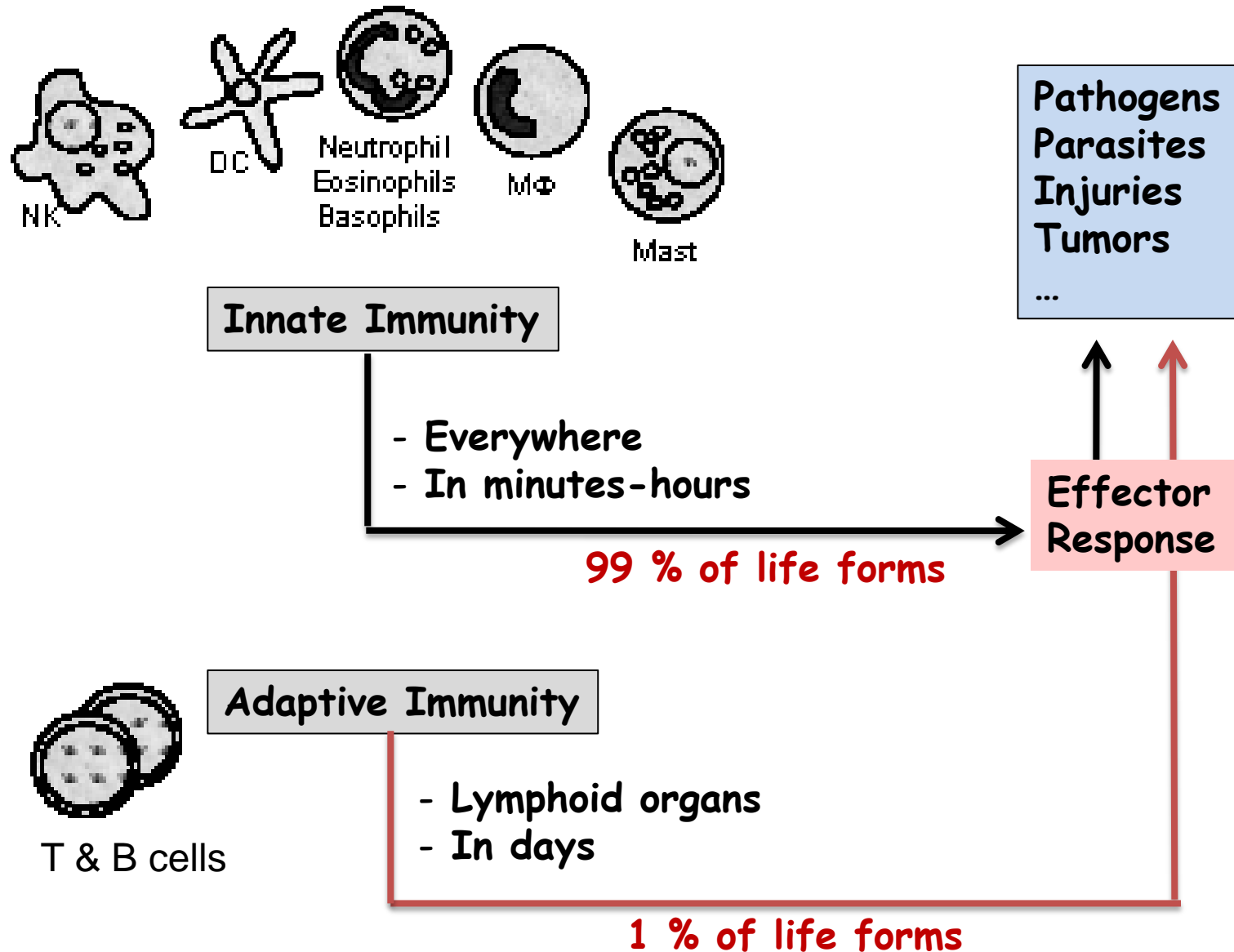
The Cancer-T Cell Immunity Cycle



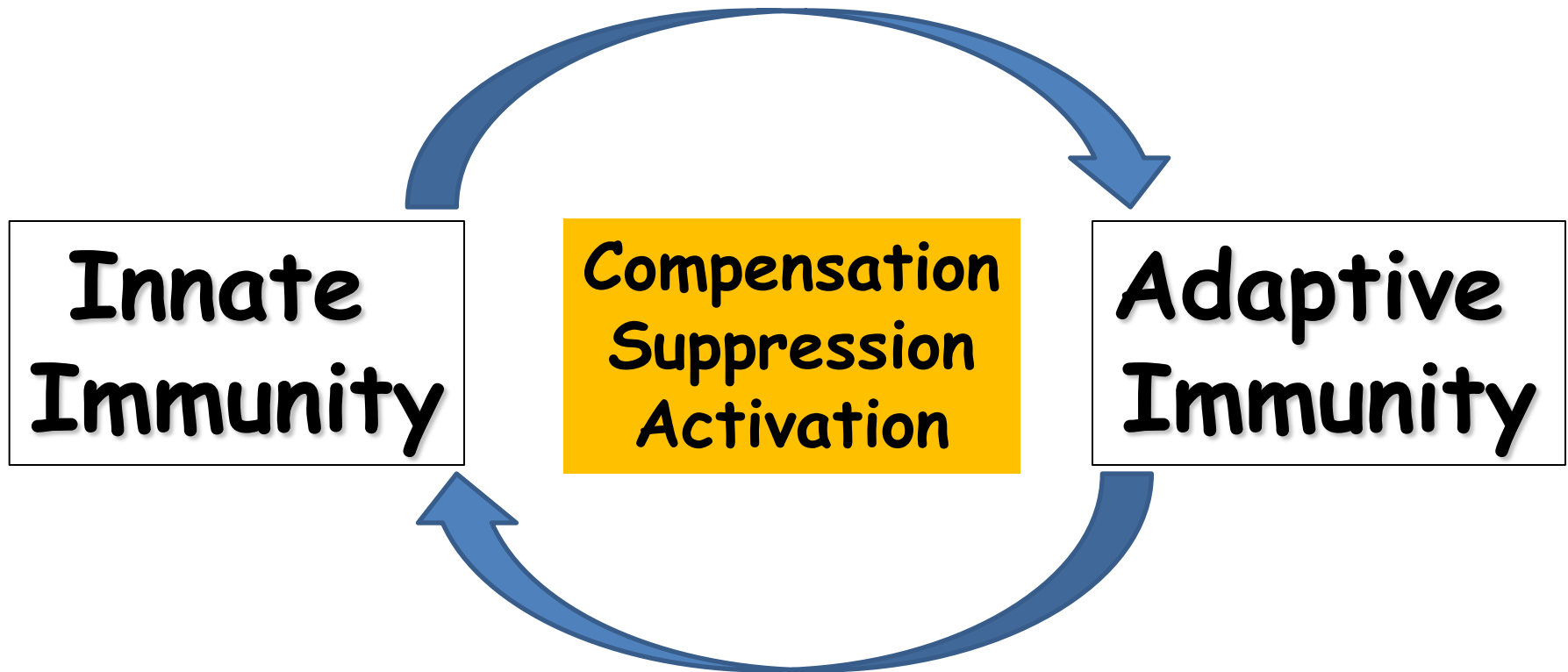
E6508 trial:
Chemoradiation+
MUC1 vaccine+
Anti-VEGF

**Therapeutic success in most cancers
has not improved beyond 17%.**

Conceptual dichotomy of immune system



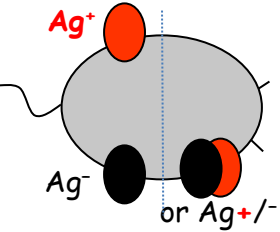
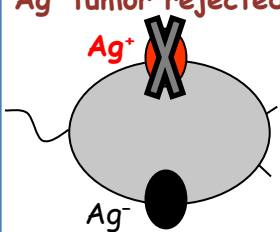
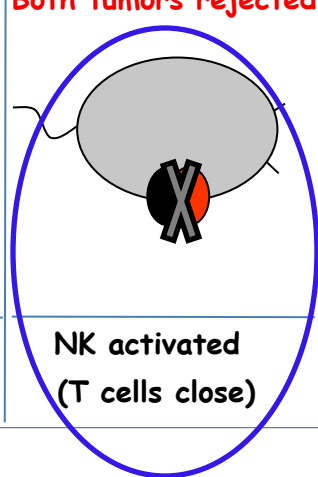
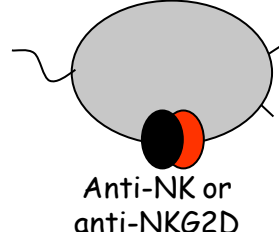
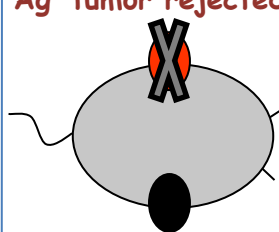
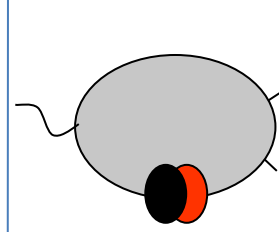
Integrated Network



**Bidirectional cooperativity
in immune functions**

Shanker and Marincola 2011 *Cancer Immunol Immunother*
Malhotra and Shanker 2011 *Immunotherapy*
Shanker 2010 *Immunol Letters*

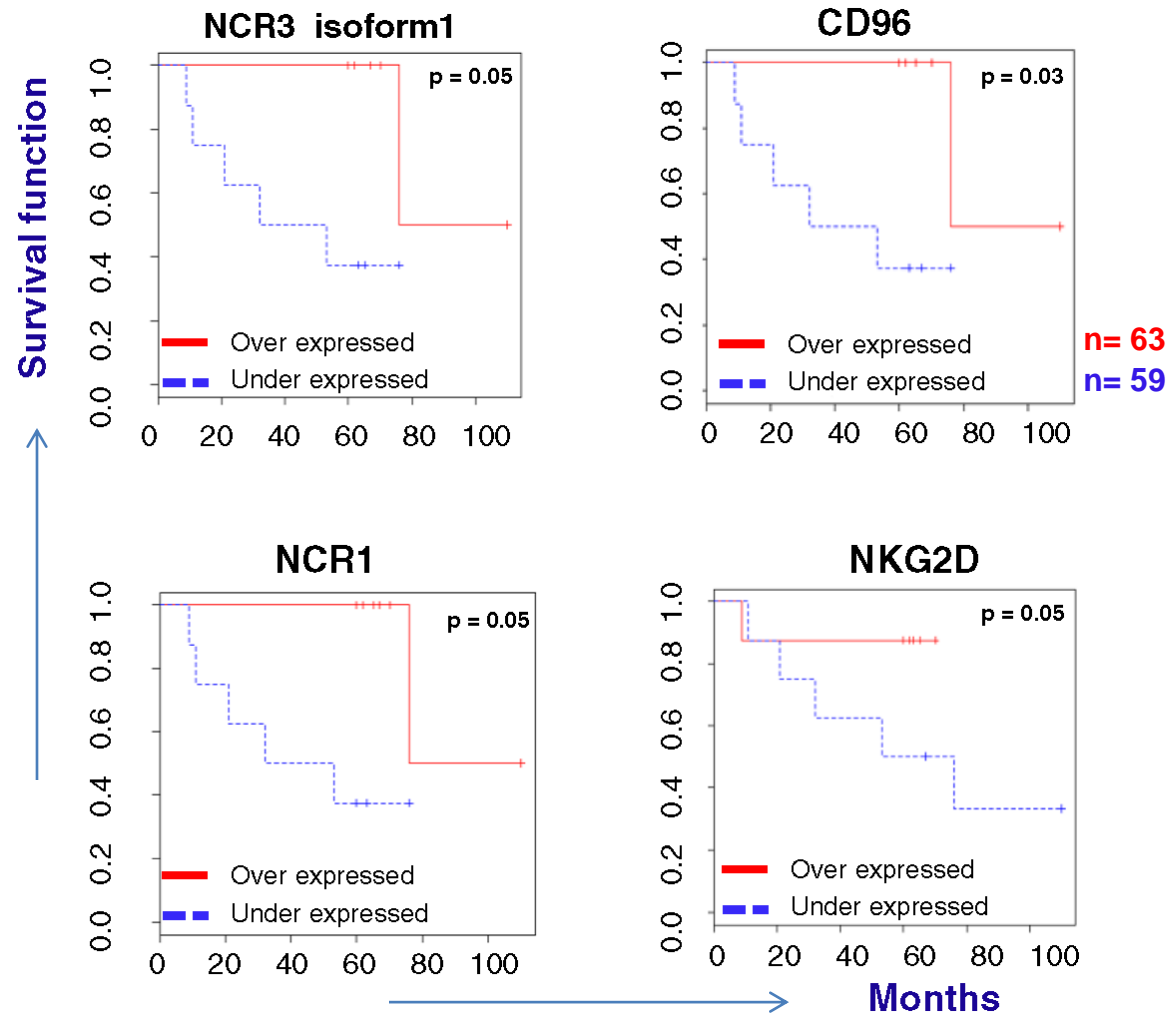
CD8 T Cell Help for Innate Activity

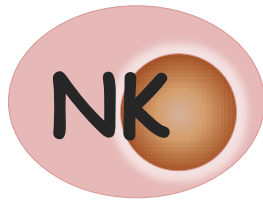
RAG ^{-/-} (NK alone)	Infused with P1A Ag-specific CD8 T cells				
	RAG ^{-/-} (both NK + T)		RAG ^{-/-} γ c ^{-/-} (T alone)		
 <p>Ag⁺ Ag⁻ or Ag^{+/-}</p> <p>Tumors grow</p>	 <p>Ag⁺ tumor rejected</p> <p>Ag⁻ tumor grows</p>	 <p>Both tumors rejected</p> <p>NK activated (T cells close)</p>	 <p>Anti-NK or anti-NKG2D</p> <p>Tumors grow</p>	 <p>Ag⁺ tumor rejected</p> <p>Ag⁻ tumor grows</p>	 <p>Tumors grow</p>
No NK activity (T cells absent)	No NK activity (T cells distant)			T cells activated (NK cells absent)	

NK cells become activated at the site of ongoing T cell response.

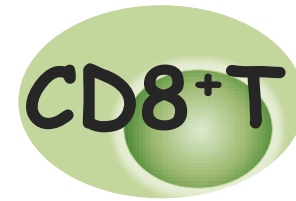
Shanker et al, *J Immunol*, 2007; Shanker et al, *Immunology*, 2010

Relapse free survival of breast cancer patients associated with NK cell activation





→
**Functional
Cooperativity**
←



?+

?+

Bortezomib

**Notch1 -signaling
(DLL1)**

J Immunol 2007
Immunol 2010
CII 2011
J Transl Med 2013

JNCI 2008
J Immunol 2008
Cancer Res 2009
Mol Cancer Res 2010

Cancer Res 2011
J Blood Lymph 2013

Project I

**Dissect the
mechanisms of
T cell-NK cell
functional
cross-talk**

NCI U54 CA163069

Project II

**Define the
effects of
bortezomib
on immune
functions**

NIMHD U54 MD007593
NCI 1SC1 CA182843

Project III

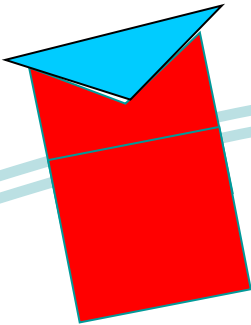
**Investigate
Notch
regulation of
anti-cancer
immunity**

NCI P50 CA090949
NCI 1R01 CA175370

Projects II + III

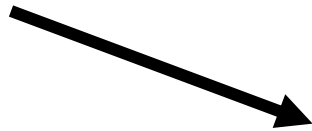
**Therapeutic modulation of lymphocyte
antitumor function**

Death
Receptors



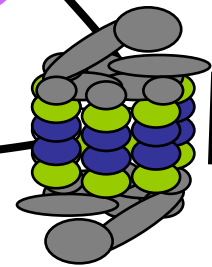
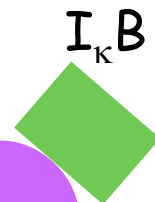
Caspase Activation

APOPTOSIS



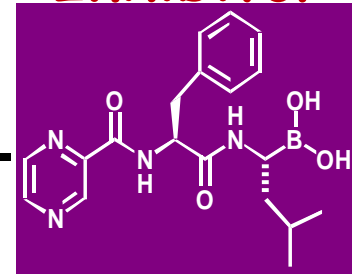
NF_κB

I_κB



Proteasome

Proteasome
Inhibitor

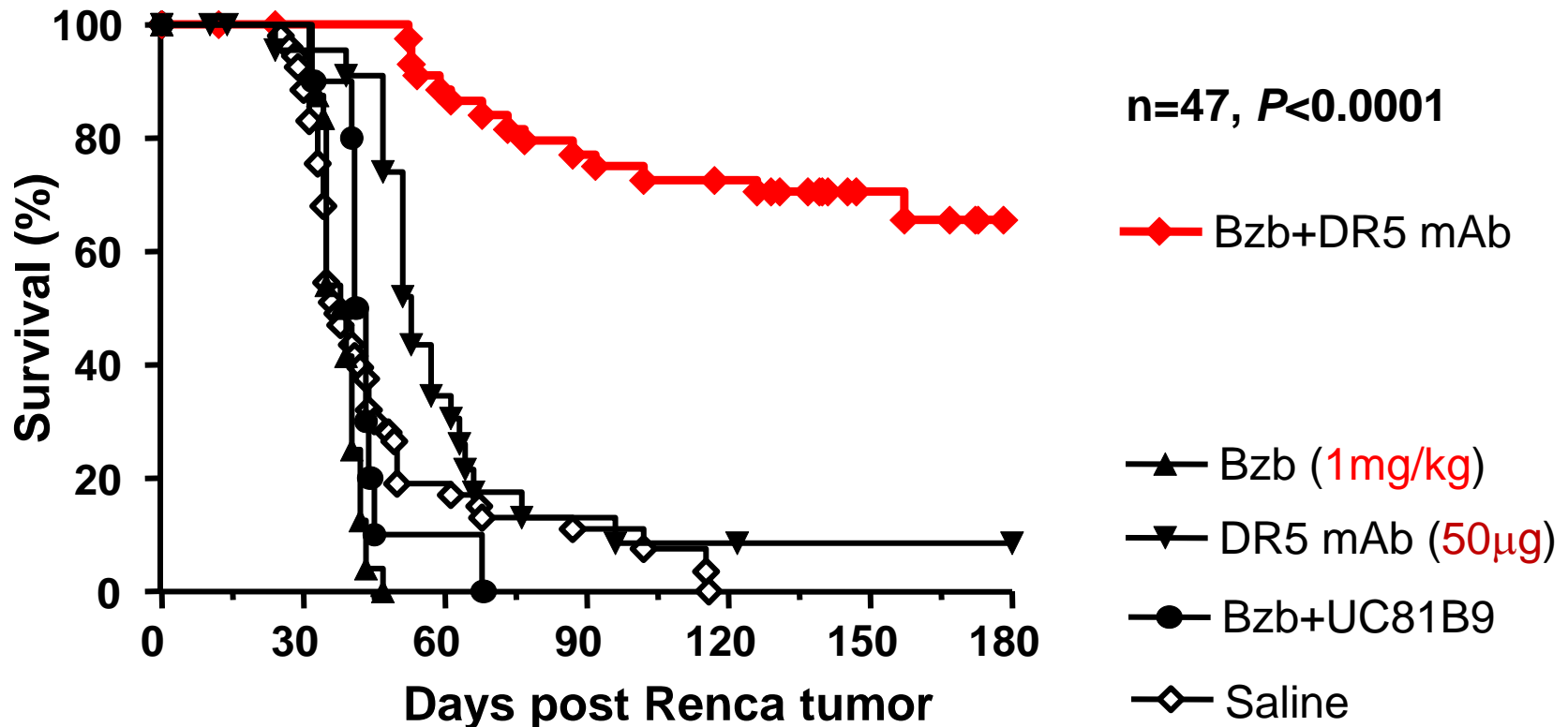


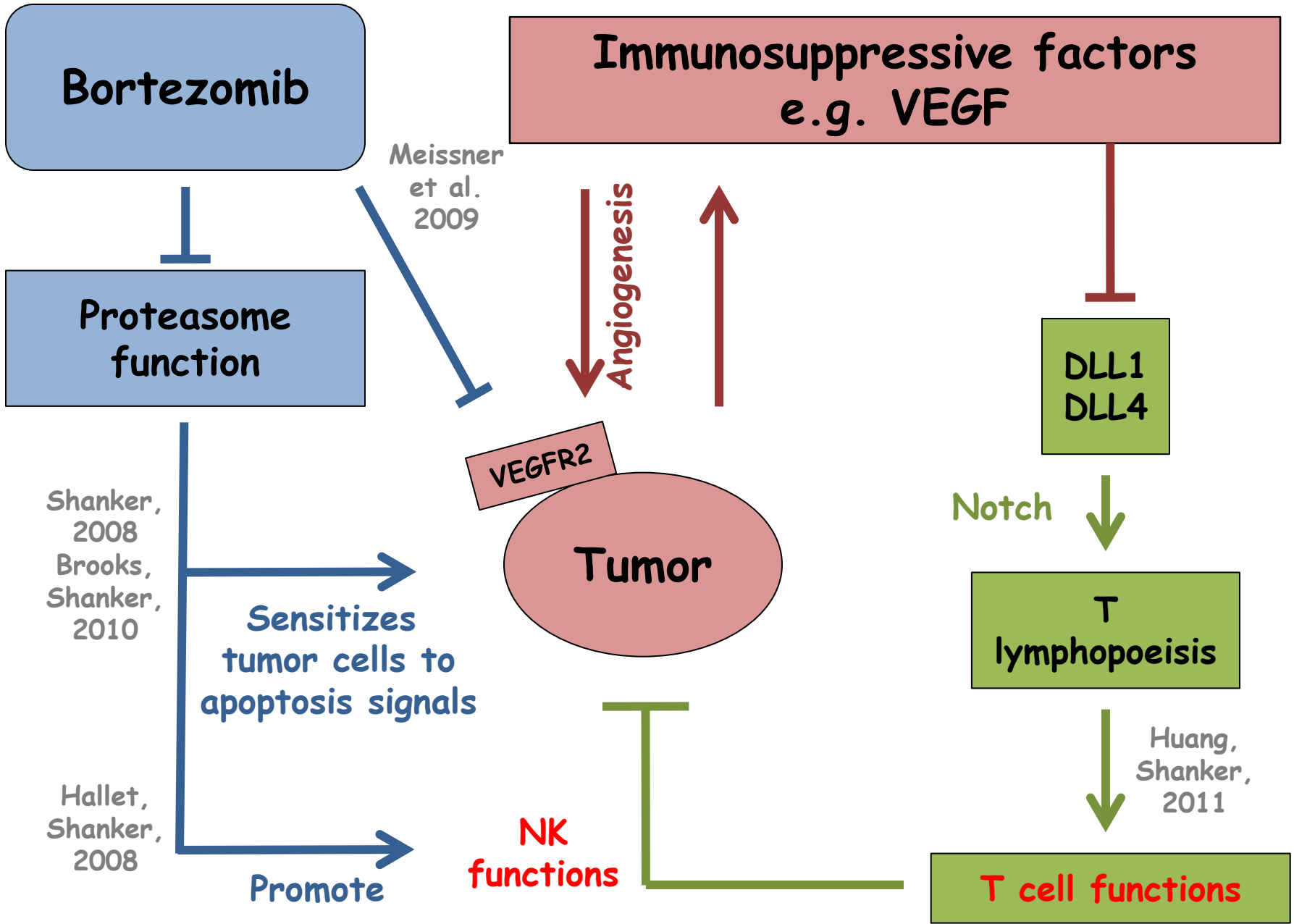
Bortezomib



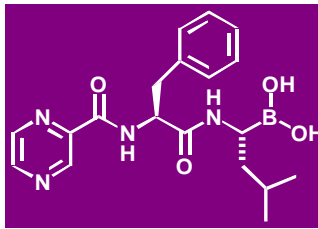
Bortezomib helps reject resistant solid tumors

Shanker A, Brooks AD, Tristan CA, Wine JW, Elliott PJ, Yagita H, Takeda K, Smyth MJ, Murphy WJ, Sayers TJ. **JNCI 2008,100:649-662**





Dipeptidyl boronate



MW = 384

Half life= 9-15 h

IC₅₀= 7 nM

Bortezomib

Proteasome function

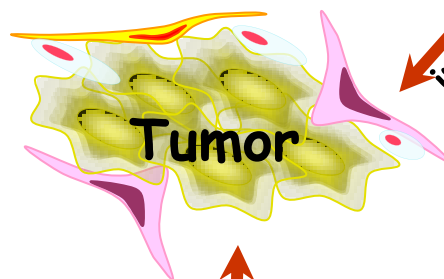
Notch Signaling

DLL1

Molecular targeting

Overcome immunosuppression

Improve lymphocyte differentiation & function



Reduction of tumor burden

T cell + NK cell transfers