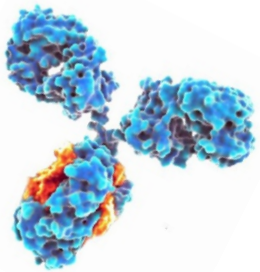
Immunotherapy
A Practical Perspective
A view from the dark side

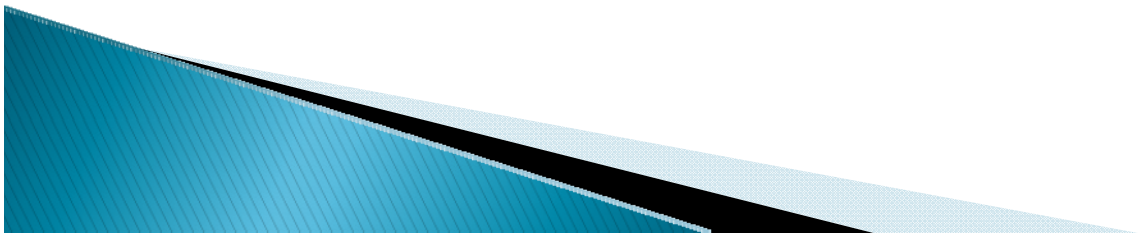
SITC symposium, April 4-5 2013



Thomas Davis, MD
Celldex Therapeutics, Inc.

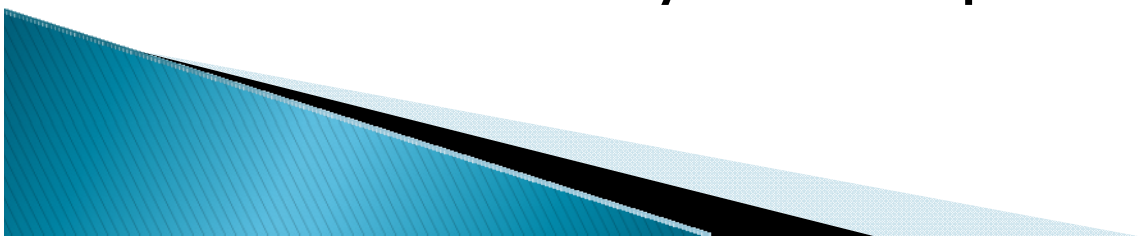
Why is practicality important?

- Robust science is always the highest goal
- Our intent is to help people
- Within our system, effective agents require commercial marketing to make them available to patients
- The path through the regulatory and commercial gauntlet is therefore unavoidable
- Commercialization ultimately defines success, encouraging further development



The Corporate Mindset

- Broad view and final endpoint is critical
  - Keep next steps and final ambition in mind
- Build value with minimal risk
  - Biphasic interest curve
    - Exciting early data or proven technology more viable
- Single agent or simple development preferable
- Fail early and learn
- IP and competition are critical
- Limited ability to talk publicly

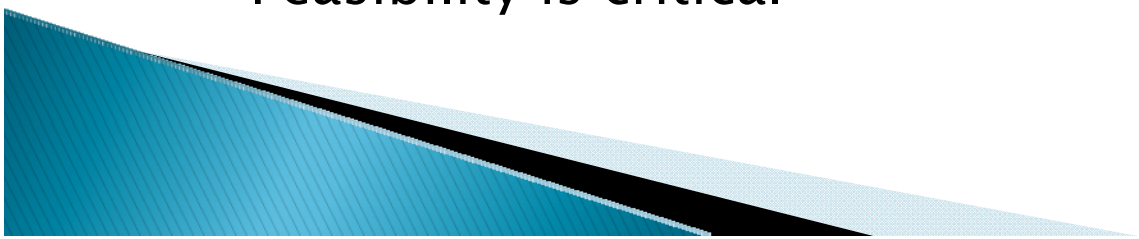


Platform validation

- Antibodies are no longer “immunotherapy”
- “Checkpoint inhibitors” have validated generic immune activation approaches
  - Had a tenuous start
- Vaccines are still not accepted readily
  - RR versus OS
  - Manufacturing and Marketing complexity of DC vaccine has compromised the field
- Individual vaccine platforms are even harder to validate
  - Proof of principle important

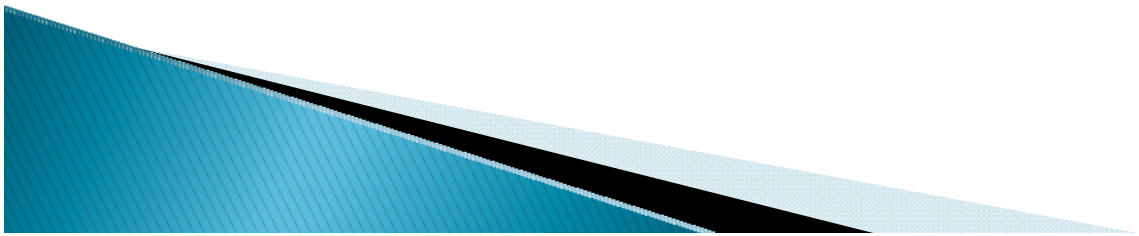
Current Biotech Expectations

- Smaller companies more prepared to accept risks
  - Partnering or Commercialization important
  - While small companies are loath to halt development, the standards are still similar to larger companies
- More potent effects are important
  - Fail early is still important
  - Modest OS benefits are very difficult to prove efficiently
  - Immune response alone may be inadequate
  - It is hard to justify expensive advanced development based upon the subtler aspects of the Immune Response Criteria
- Reasonable path to approval
  - Feasibility is critical

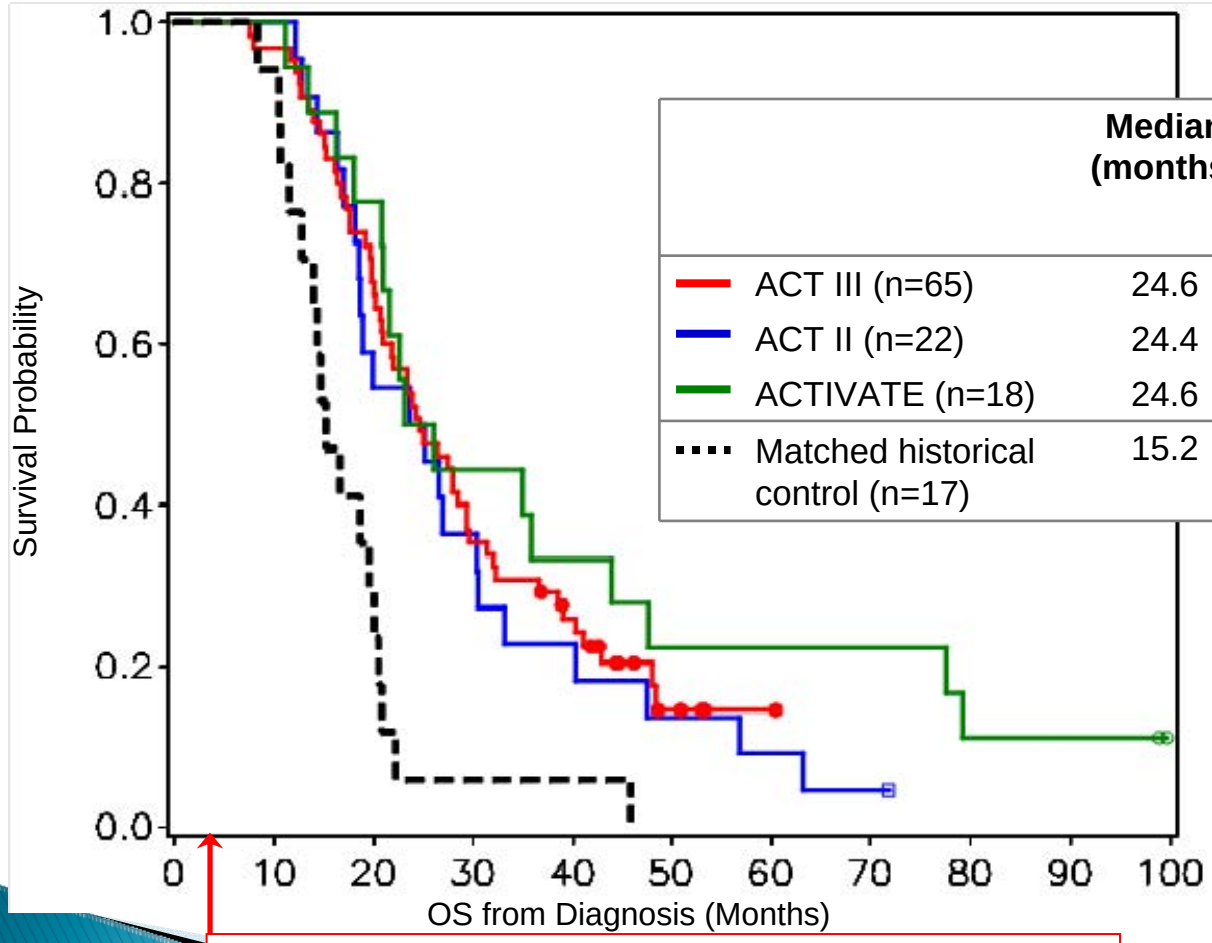


Celldex – Internal Combination in Pipeline

CANDIDATE	INDICATION	PHASE 1	PHASE 2	PHASE 3
Rindopepimut	Front-line Glioblastoma	ACT IV Registration Trial		
CDX-011	Breast Cancer	EMERGE Trial		
Rindopepimut	Recurrent GBM	ReACT Trial		
CDX-1135	Dense Deposit Disease	Pilot		
CDX-1127	Lymphoma, Cancer			
CDX-301	HSC Transplantation			
CDX-1401	Multiple Solid Tumors			



Rindopepimut: both PFS and OS improvement against non-study comparators



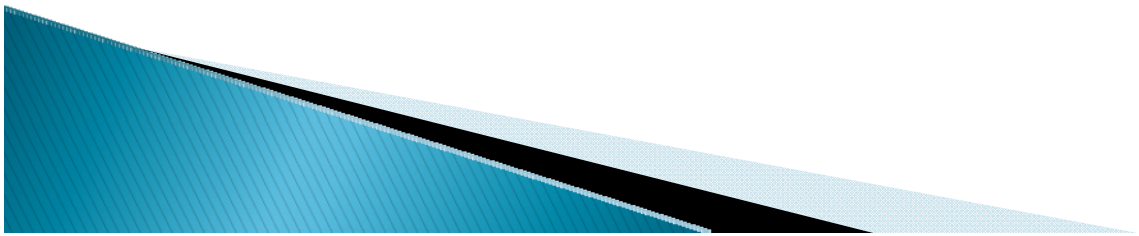
	Median (months)	OS at 24 Months	OS at 36 Months	Comparison to Historical Control
ACT III (n=65)	24.6	52%	31%	p = <0.0001
ACT II (n=22)	24.4	50%	23%	p = 0.0034
ACTIVATE (n=18)	24.6	50%	33%	p = 0.0003
Matched historical control (n=17)	15.2	6%	6%	

Vaccinations begin approximately 3 months after diagnosis

Median duration of follow-up:
ACT III: 48.7 months
ACT II: 71.8 months
ACTIVATE: 99.3 months

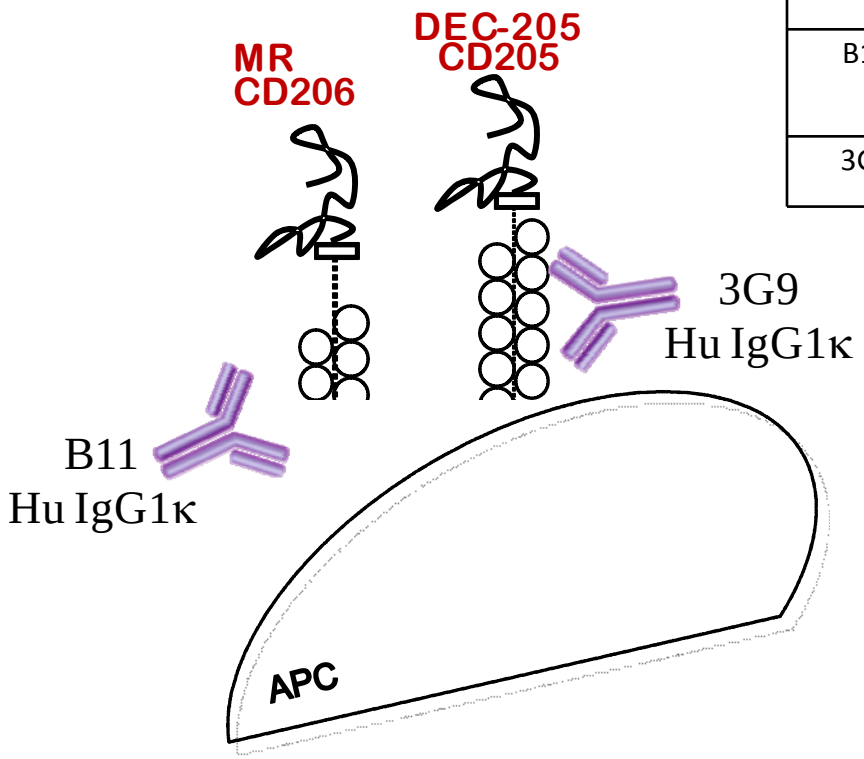
Approaches to improving anti-tumor immunity

- Enhanced immunity to protein vaccines by antigen delivery to DCs in situ
  - Targeting antigens with mAbs to MR and DEC-205
- Enhancing T cell responses with co-stimulation
  - Development of an anti-human CD27 agonist mAb
- Expansion of DC subsets
  - Flt3L-back in the clinic

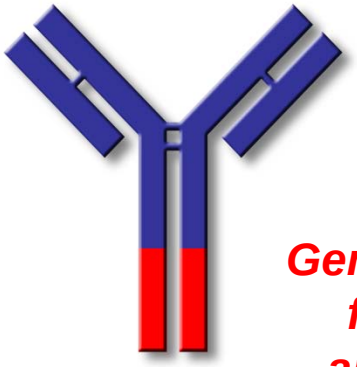


Antigen delivery to C-type lectin receptors

Antibody	Specificity	APC Binding in human tissues	Affinity KD (M)
B11	Mannose receptor	Dermal DCs, Interstitial DCs, macrophages in most tissues	~7 x 10^{-10}
3G9	DEC-205	DCs in lymph nodes, tissue DCs	~2 x 10^{-10}



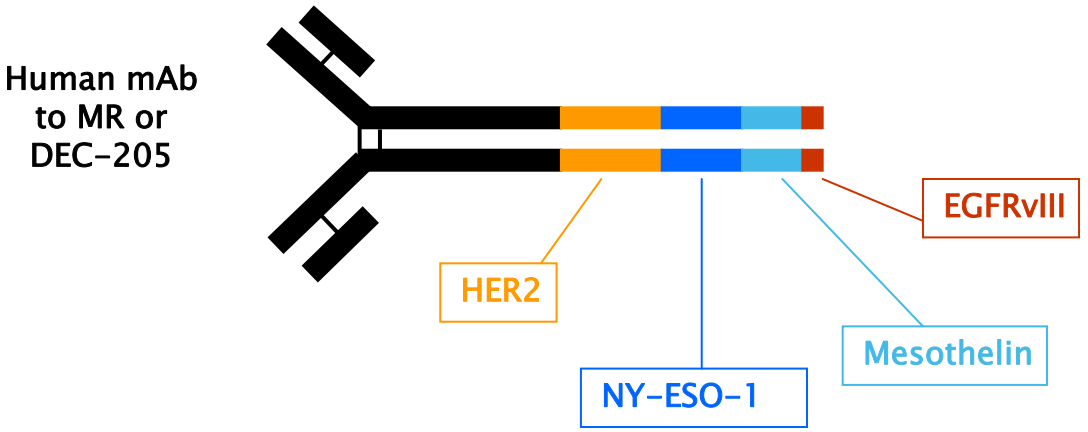
Recombinant antibody product



Genetically fused antigen

Dendritic Cell Targeting vaccines Opportunities

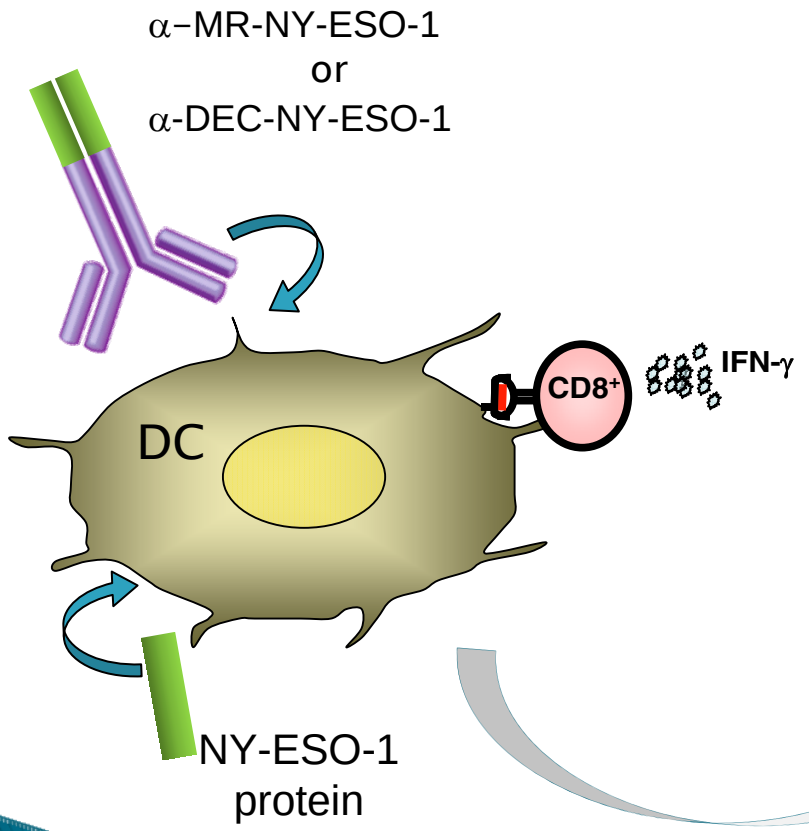
- Multiple antigen constructs



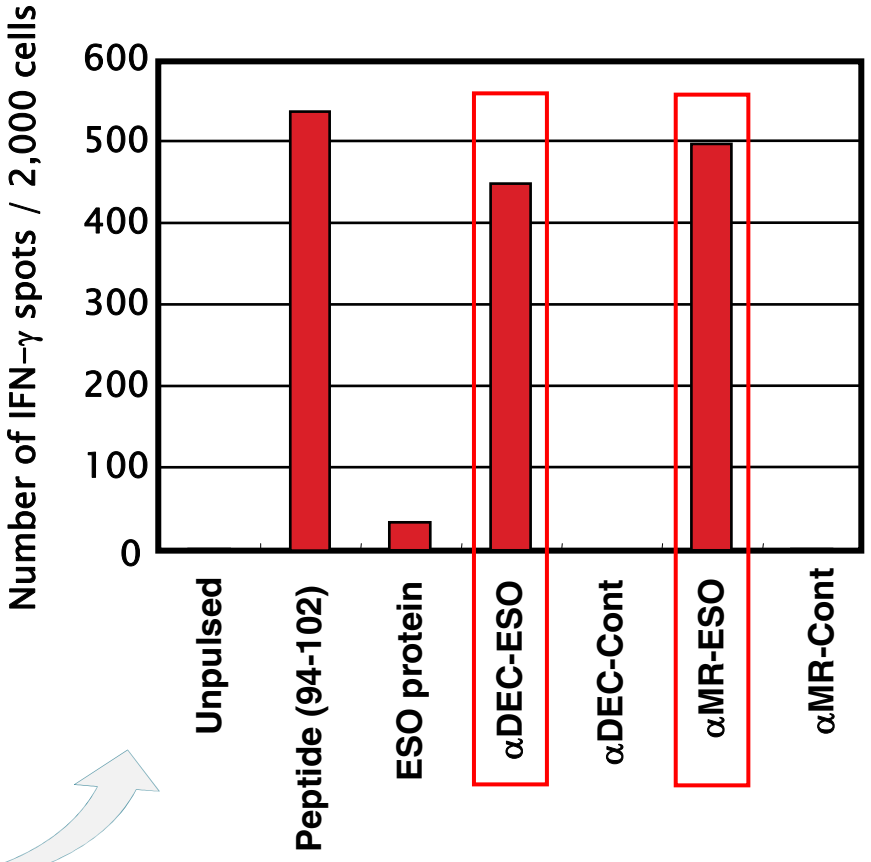
- Prime boost with viral vectors

- Combination studies with immune modulators
  - Anti-CTLA-4, FLt3 ligand, anti-CD27…

Targeting improves cross-presentation of NY-ESO-1

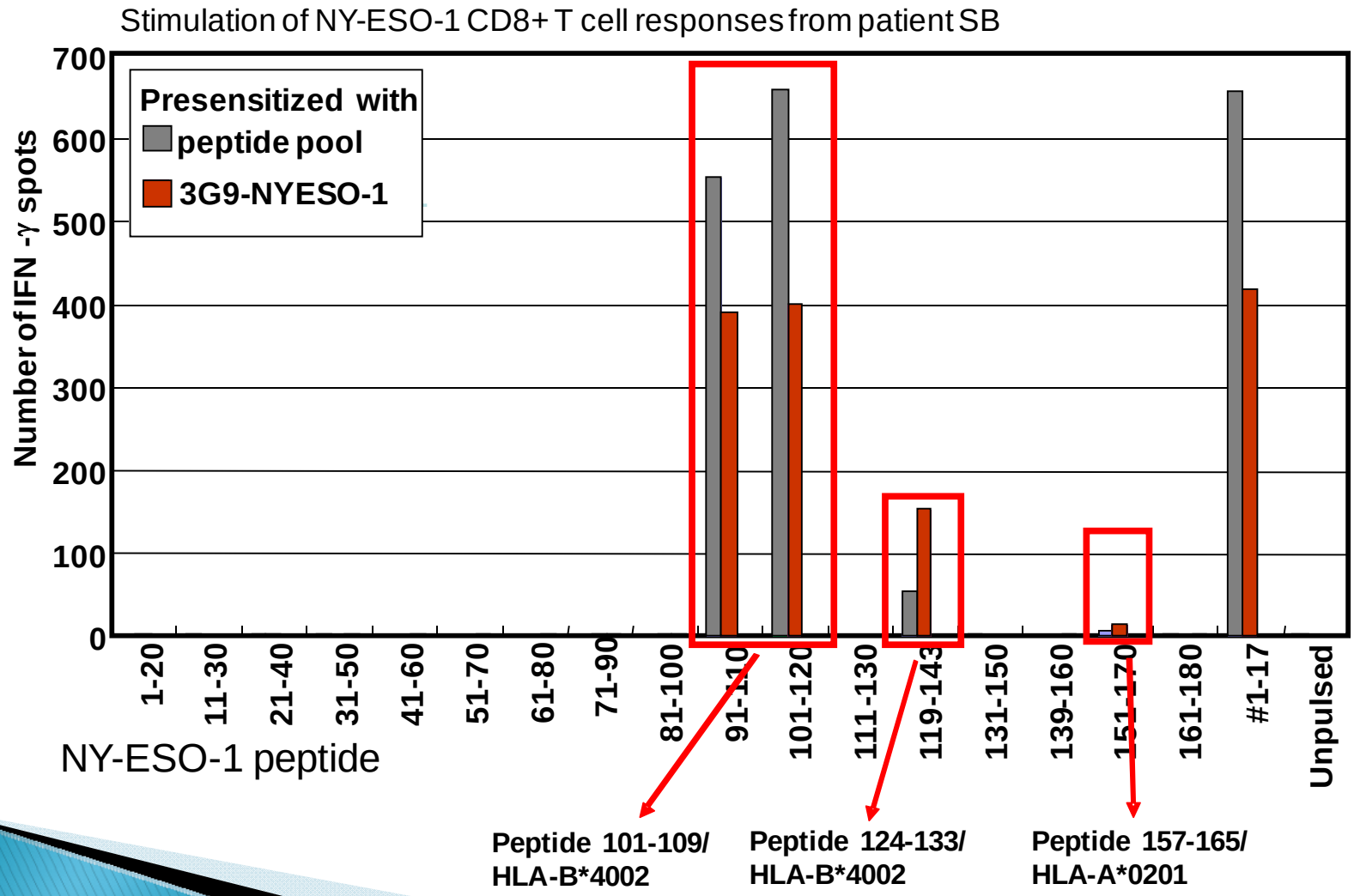


Recognition by NY-ESO-1-specific CD8⁺ T cell clone



Takemasa Tsuji et al J Immunol. 2011, 186: 1218

Presentation of multiple NY-ESO-1 MHC I epitopes



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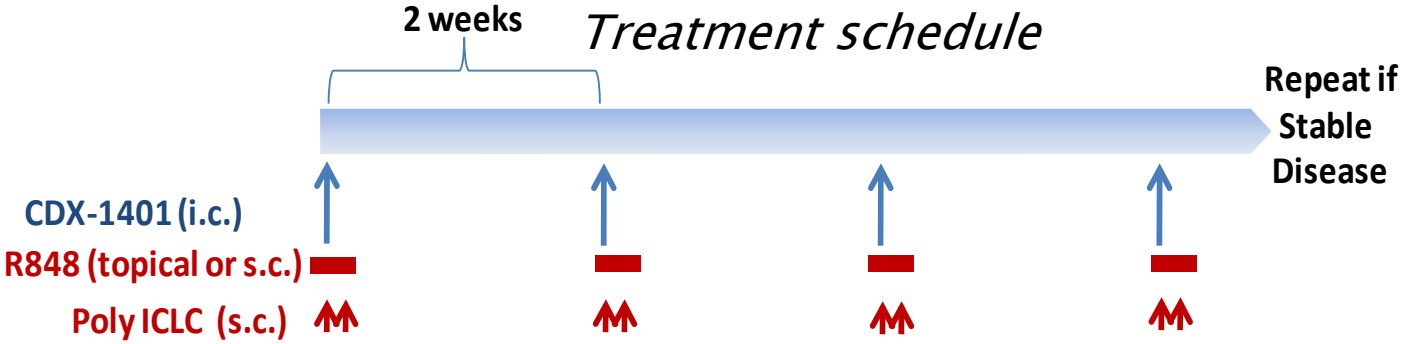
Phase 1 CDX-1401 (3G9-ESO) trial



Cohort 1
0.1 mg CDX-1401 i.c.
500 μg topical resi
N = 9 / NY-ESO-1+ = 3

Cohort 2
1 mg CDX-1401 i.c.
500 μg topical resi
N = 8 / NY-ESO-1+ = 3

Cohort 3
3 mg CDX-1401 i.c.
500 μg topical resi
N = 6 / NY-ESO-1+ = 3

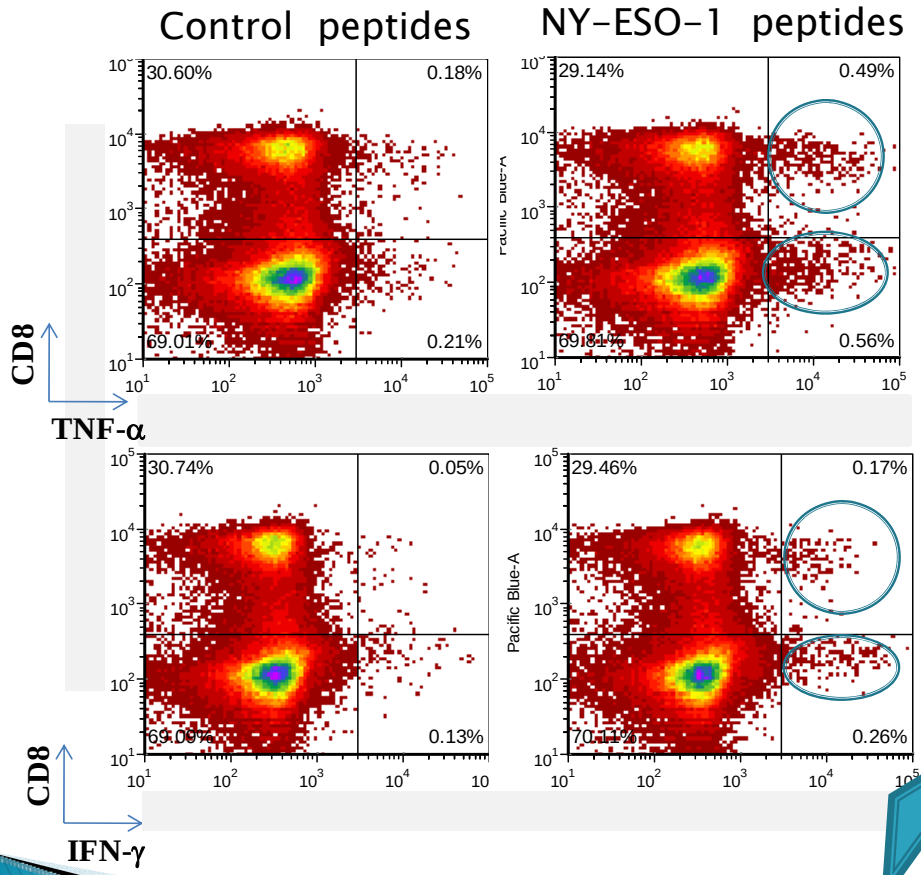
Cohort 4
1 mg CDX-1401 i.c.
2 mg Poly ICLC s.c.
N = 5 / NY-ESO-1+ = 3

Cohort 5
1 mg CDX-1401 i.c.
20-500 μg s.c. resi
N = 7 / NY-ESO-1+ = 7

Cohort 6
1 mg CDX-1401 i.c.
500 μg s.c. resi
2 mg Poly ICLC s.c.
N = 6 / NY-ESO-1+ = 6

- **Advanced melanoma and other cancers**
- **45 patients enrolled, no SAEs**
- **Of 38 pts analyzed, 12 pts with SD (up 13 Mo)**
- **3 with documented tumor shrinkage**

CDX-1401: T cell responses



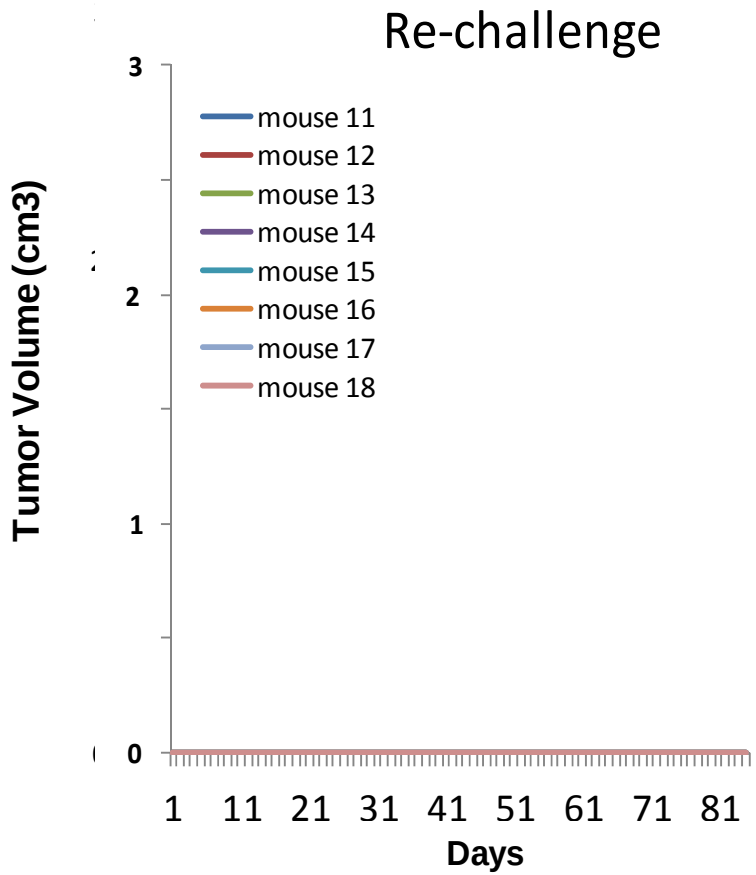
#	CDX-1401	Adjuvant	Pre	Post
1	0.1 mg	Topical Resi		
2				
3				
4				
5				
6				
7				
8				
1	1.0 mg	Topical Resi		
2				
3				
4				
5				
6				
7				
1	3.0 mg	Topical Resi		
2				
3				
4				
1	1.0 mg	Poly ICLC		
2				
3				
4				
5				
1	1.0 mg	S.C. Resi		
2				
3				
4				
5				
1	1.0 mg	S.C. Resi + Poly ICLC		
2				
3				
4				
5				
6				

On-going

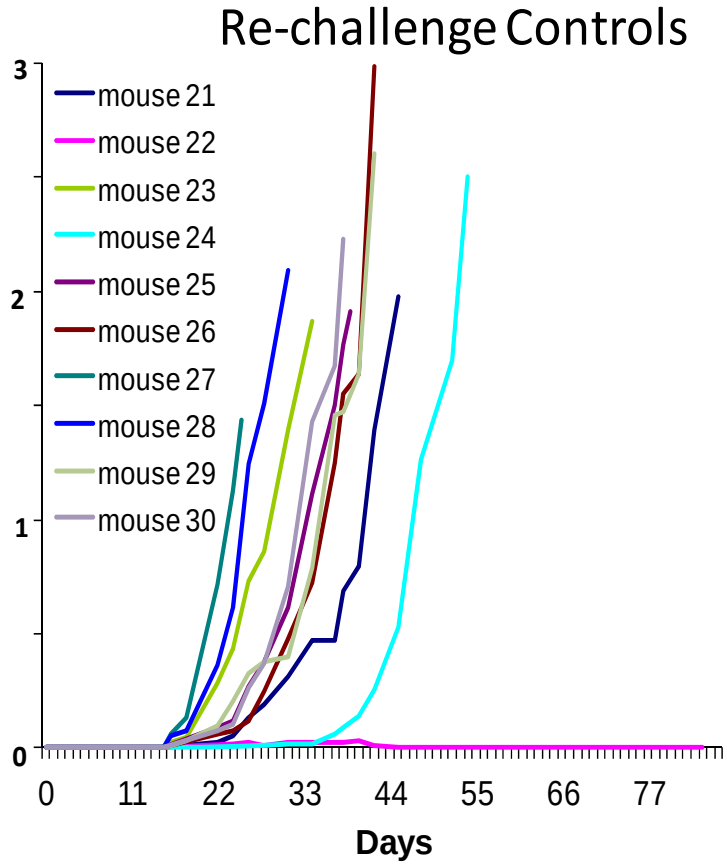
CD27: a critical regulator of T cells

- **Member of the TNF-receptor superfamily** (CD40, 4-1BB,OX-40)
  - Single ligand is CD70 (tightly regulated)
  - Constitutively expressed on most T cells and a subset of B and NK cells
- **Co-stimulatory molecule**
  - Role in generation and long-term maintenance of T cell immunity
  - Role in NK cell differentiation/activation
- **CD27 activation:**
  - Signaling through Traf2, Traf5
  - Activation of the NF-κB pathway
  - Cell survival, activation, proliferation

Efficacy of CDX-1127 in colon carcinoma model (CT26) in huCD27 Tg mice



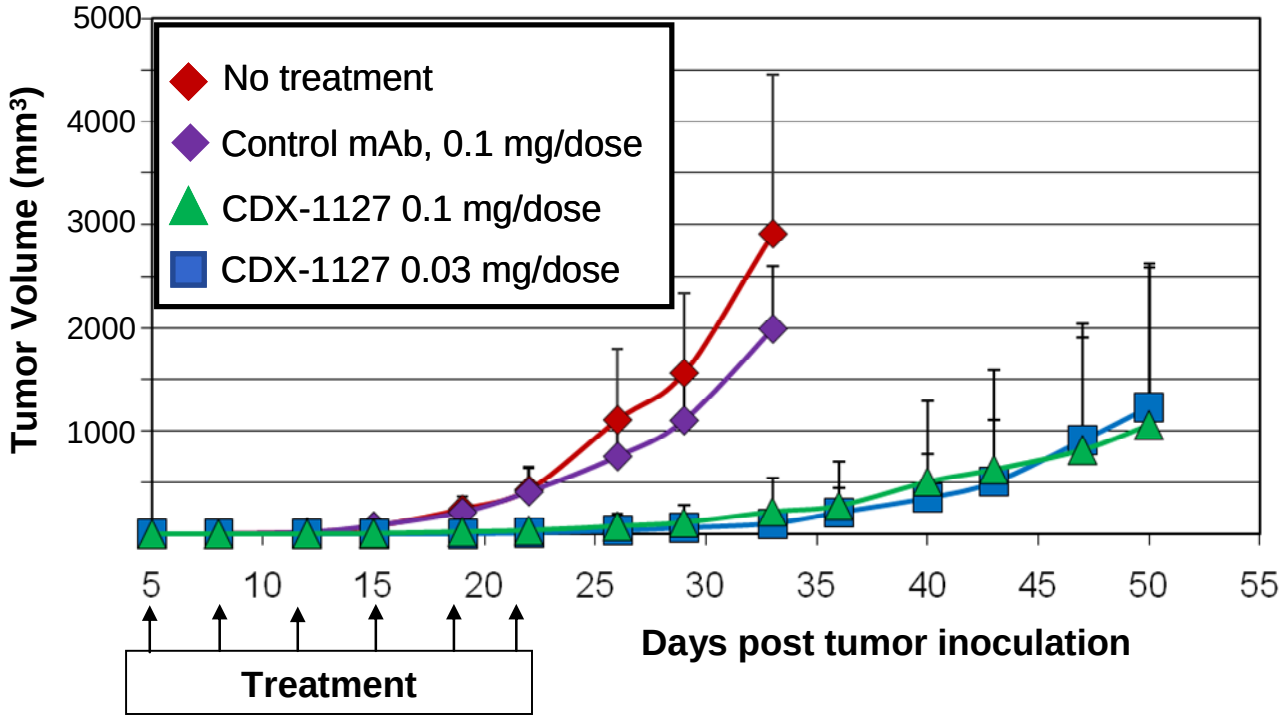
10^4 CT26 cells s.c. on day 0
(day 99 relative to 1st inoculation)



10^4 CT26 cells s.c. on day 0

Treatment of Human Lymphoma with CDX-1127

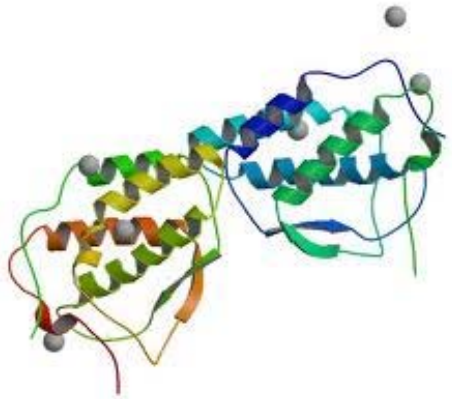
Xenograft model of human B lymphoblastic tumor cell line (Raji) in SCID mice



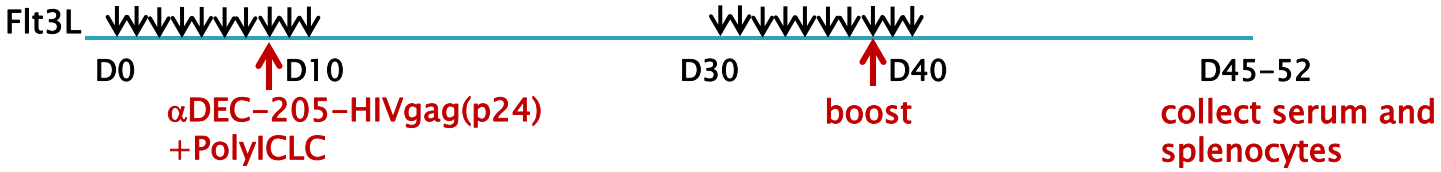
Similar efficacy with other human B and T cell tumor lines- Daudi, Namalwa, CCRF-CEM

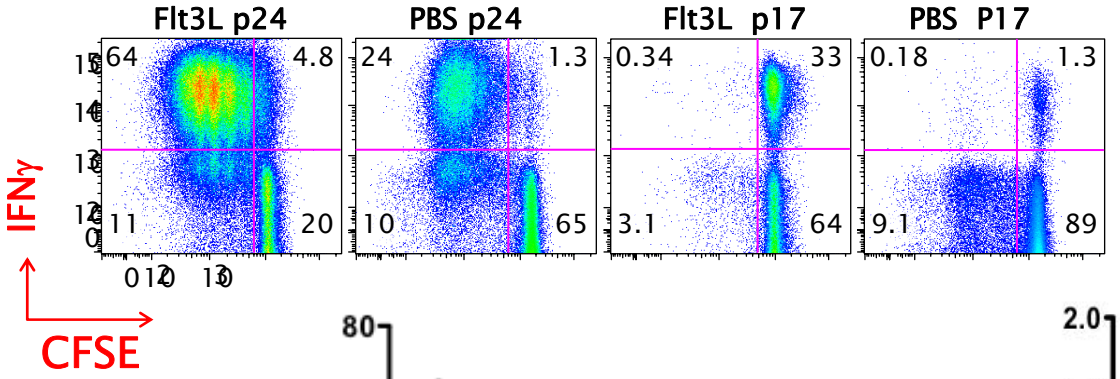
CDX-301: FMS-like tyrosine kinase 3 Ligand (Flt3L)

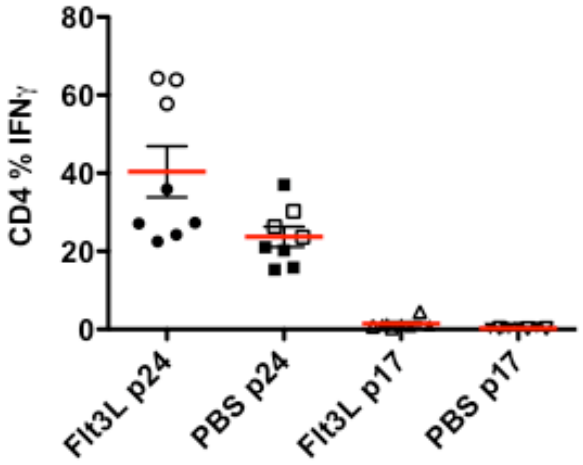
- Flt3L: potent stem cell mobilizer and dendritic cell growth factor
- Previous clinical studies (Immunex/Amgen) demonstrated safety and biological activity (>500 subjects dosed)
- Program acquired from Amgen in 2009
- Multiple clinical opportunities

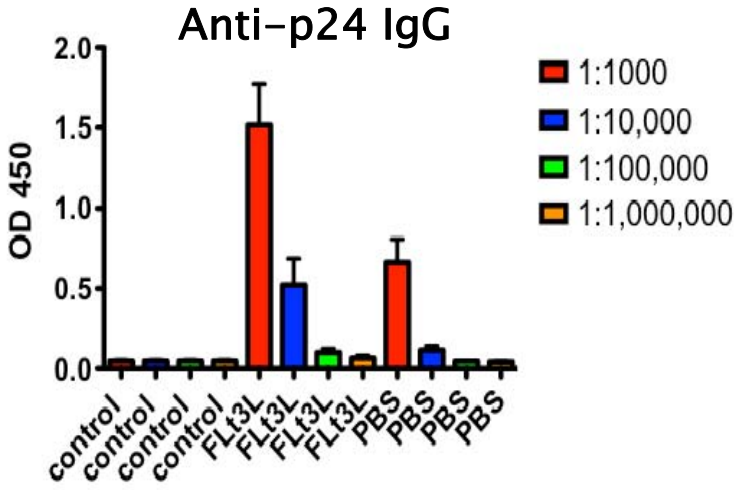


FLt3L improves T cell expansion and IgG response to DEC-205 targeted vaccine









Niro Anandasabapathy and Ralph Steinman