Advances in Cancer Immunotherapy
Moffitt Cancer Center
December 7, 2013

VGTI FLORIDA

Cancer Vaccines And Immunotherapy for Breast Cancer

Keith L. Knutson, Ph.D.

Disclosures

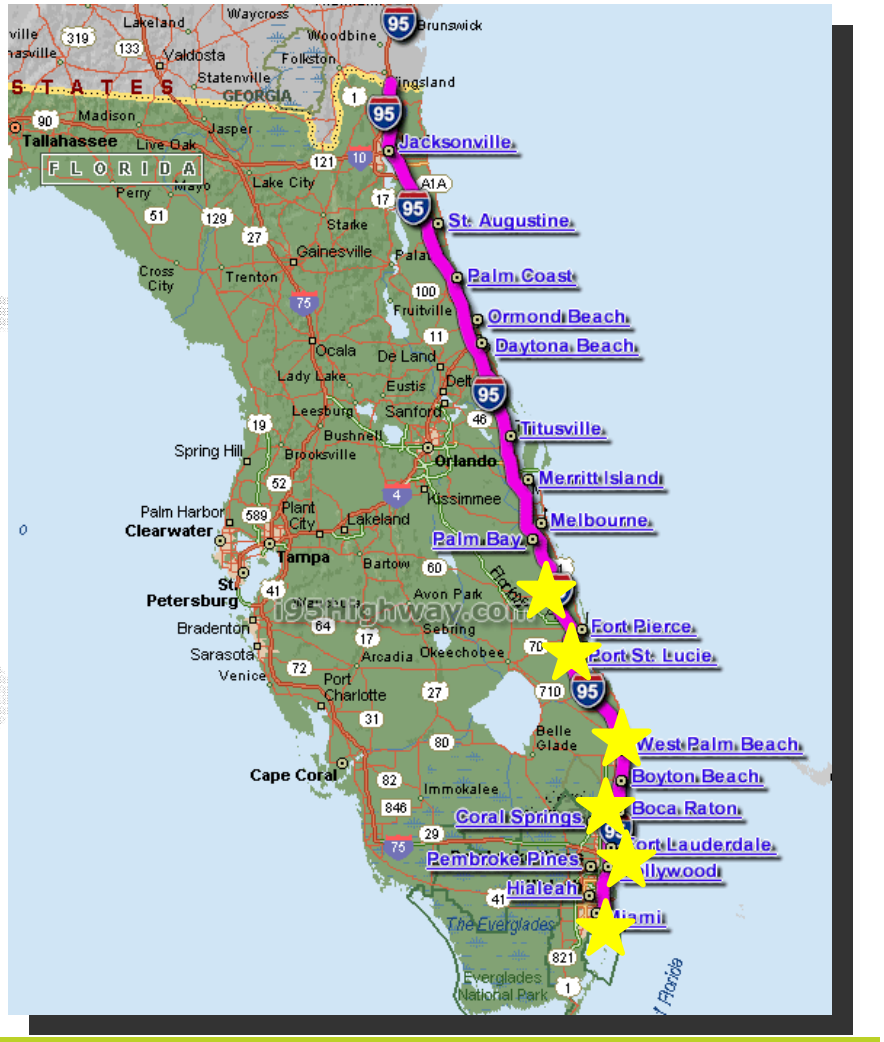
- Scientific Advisory Boards
  - ***TapImmune, Inc.,*** **Seattle, WA**
  - ***Antigen Express, Inc.,*** **Boston, MA**
  - ***Galena Biopharmaceuticals (in process),*** **Lake Oswego, OR**
  - ***Intelligent Immunity,*** **Fort Lauderdale, FL**

State-of-the-Art Laboratories

- 100,000 sq./ft. facility with 9 large research labs
- Currently have 8 research groups
- Expansion to nearly 20 research groups in future

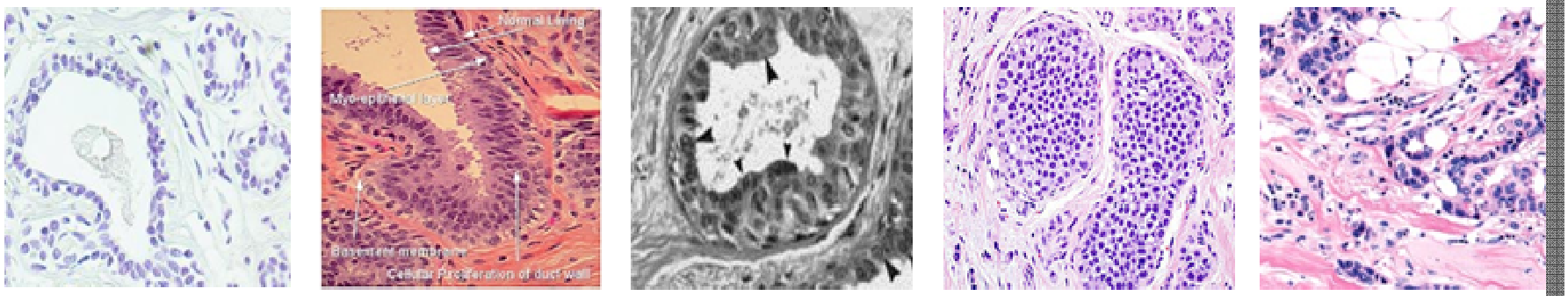
Working with the Community
The Research Coast

Jupiter Medical Center
Martin Health Systems
Memorial Cancer Institute
Broward Health
University of Miami



Progression of Breast Cancer

Normal duct | Intraductal hyperplasia | Intraductal hyperplasia with atypia | Intraductal carcinoma in situ | Invasive ductal carcinoma



Disease progression paradigm →

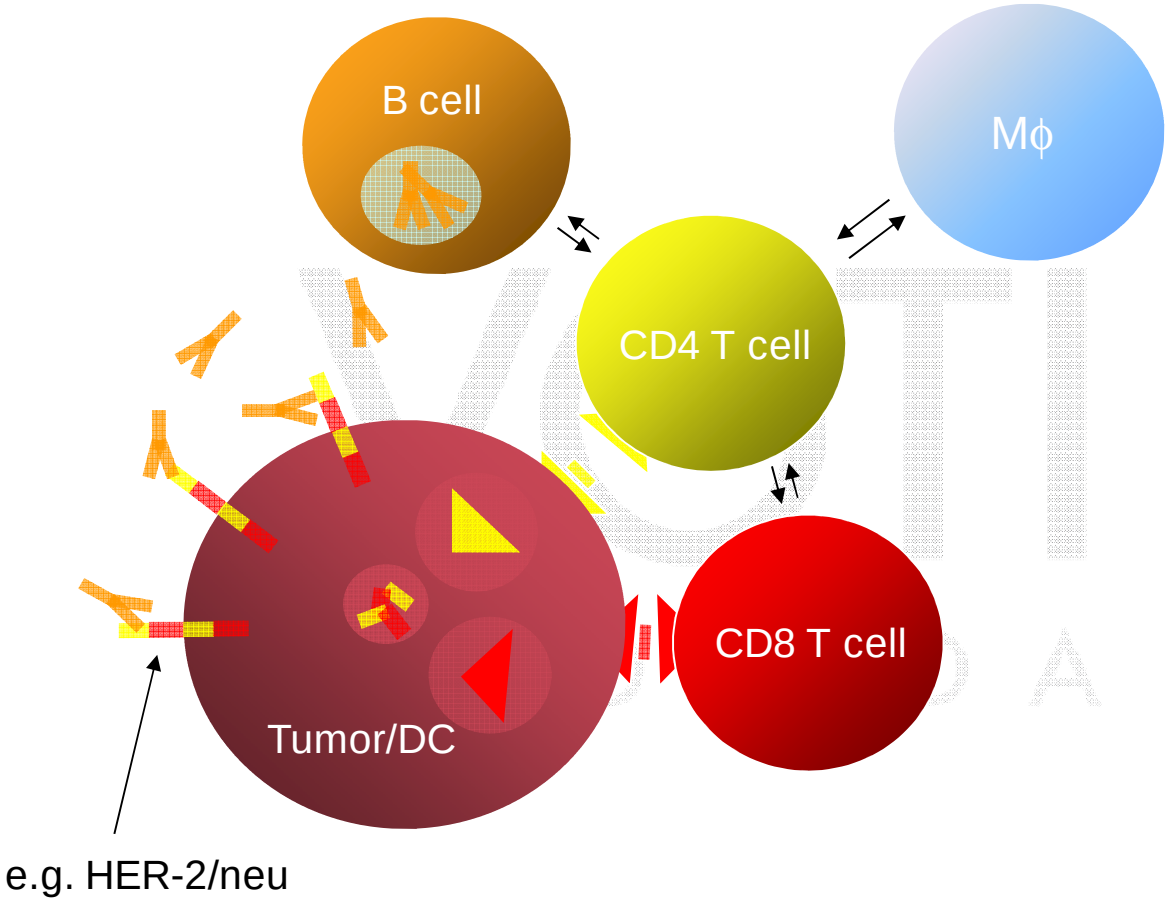
Breast Cancer are Burdens

Breast cancer in the USA 2012: 227K new cases, 40K deaths

Florida Prevalence: 273,000 Women
Breast Cancer Costs in US: $66,000,000,000
0.56% of the 2010 Gross Domestic Product

National Cancer Institute
Scitovsky, 1978

The adaptive immune response



CD4 "helper" T cells

- *Inflammation*
- *Antibodies*
- *Macrophages*
- *Neutrophils*

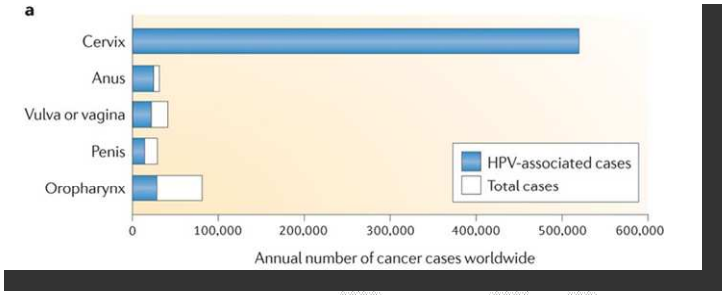
CD8 "cytolytic" T cells

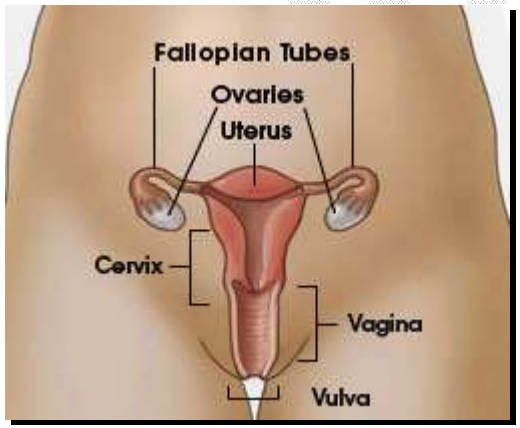
- *Tumor lysis*

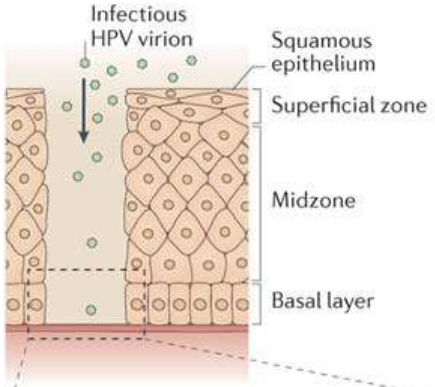
B cells

- *Antibodies*
- *Signaling*
- *ADCC*
- *Complement*

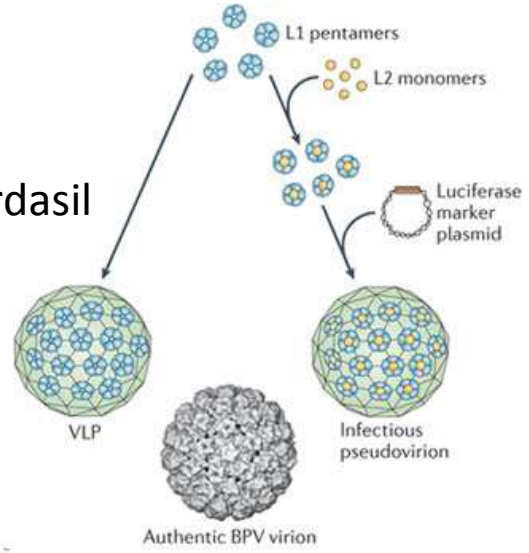
The Mechanism Challenge

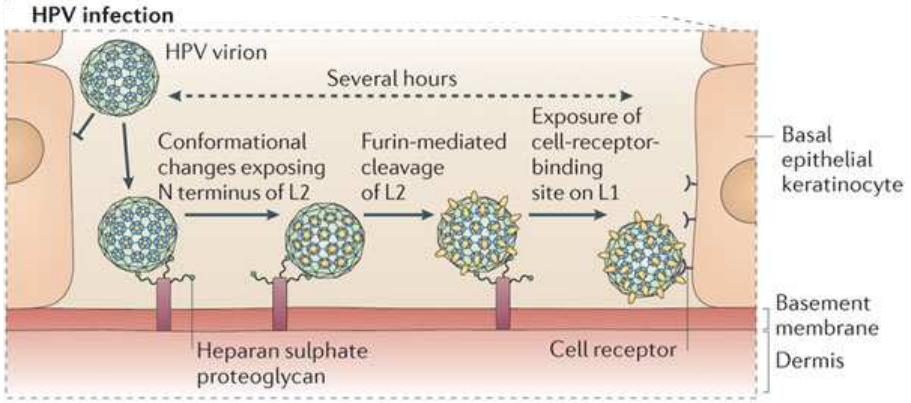




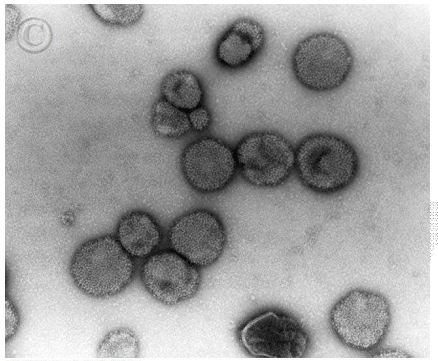


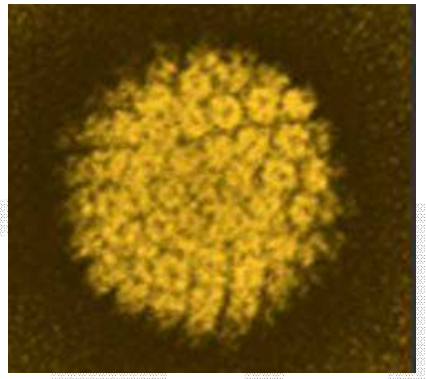
Gardasil

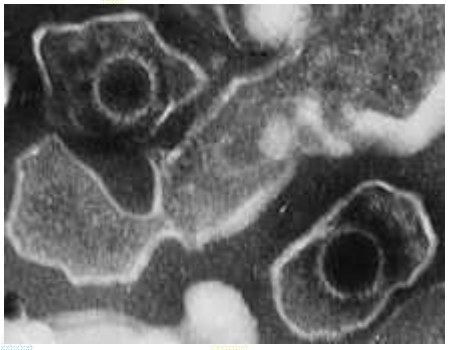




Does a virus cause breast cancer?







Archives of Virology

© Springer-Verlag 2001
Printed in Austria

Arch Virol (2001) 146: 171–180

MMTV-like *env* gene sequences in human breast cancer

Brief Report

Y. Wang[1], I. Pelisson[2,*], S. M. Melana[2], V. Go[1], J. F. Holland[2], and B. G.-T. Pogo[2,3]

[1]Mechanism of Disease Therapy, Department of Pathology, Mount Sinai School of Medicine, New York, New York, U.S.A.
[2]Department of Medicine, Division of Medical Oncology, Mount Sinai School of Medicine, New York, New York, U.S.A.
[3]Department of Microbiology, Mount Sinai School of Medicine, New York, New York, U.S.A.

Accepted July 3, 2000

Short Communication

Identification of human papillomavirus DNA gene sequences in human breast cancer

C-Y Kan[1], BJ Iacopetta[2], JS Lawson[*,1] and NJ Whitaker[1]

[1]School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW 2052, Aust... Western Australia, Nedlands, Australia

Human papilloma viruses (HPVs) are accepted as being carcinogenic in human ce... HPVs may also have a role in human breast cancer is based on the identificatio... immortalisation of normal human breast cells by HPV types 16 and 18. For this investig... and fresh frozen at −70°C from 50 unselected invasive ductal breast cancer specimens... (PCR) for HPV type 16, 18 and 33 gene sequences. We show that HPV 18 gene seq... breast tumours in Australian women. Overall, 24 (48%) of the 50 samples were HPV po... grade, patient survival, steroid receptor status, ERB-2, p53 expression and mutation were... have a role in human breast cancer. We speculate that HPVs may be transmitted by hand... ... may ... to the breast.

British Journal of Cancer (2005) **93,** 946–948. doi:10.1038/sj.bjc.6602778 www.bjcancer...

Keywords: human papilloma virus; human breast cancer; grade of tumour; patient mortality; hormone receptor status; abnormal p53 protein expression; p53 mutations and ERB-2 expression

[CANCER RESEARCH 55, 39–45, January 1, 1995]

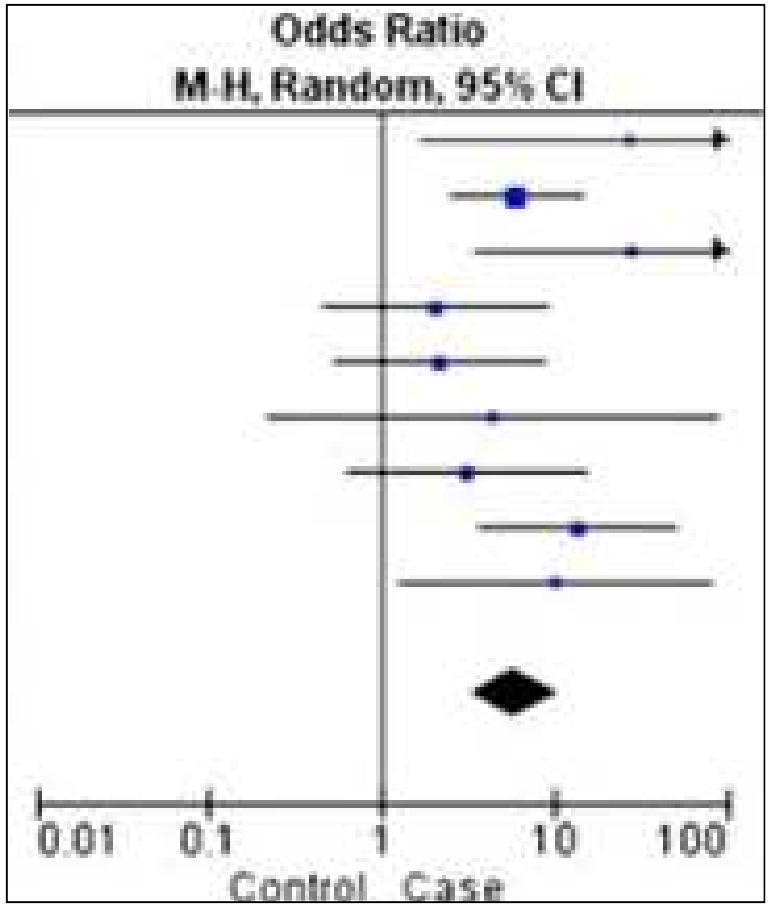
Advances in Brief

Epstein-Barr Virus in Epithelial Cell Tumors: A Breast Cancer Study[1]

Louise G. Labrecque, Diana M. Barnes, Ian S. Fentiman, and Beverly E. Griffin[2]

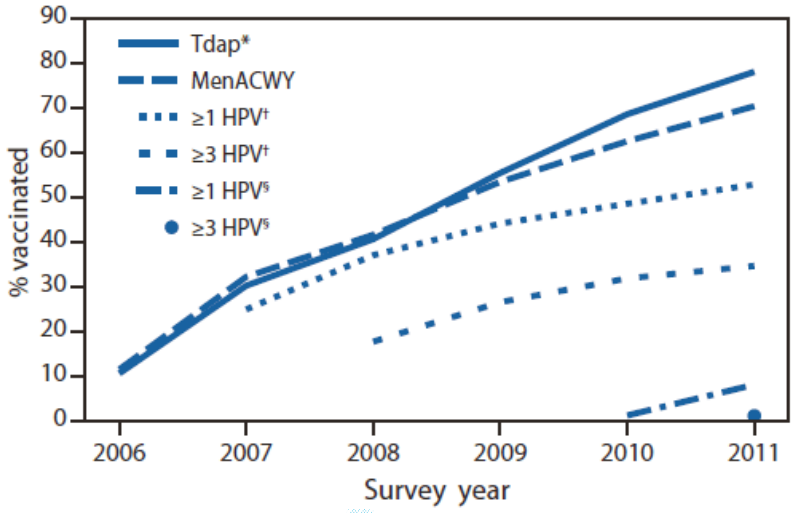
Department of Virology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London, United Kingdom, W12 0NN [L. G. L., B. E. G.], and Imperial Cancer Research Fund Clinical Oncology Unit, Guy's Hospital, London, United Kingdom SE1 9RT [D. M. B., I. S. F.]

HPV is associated with an increased risk developing breast cancer



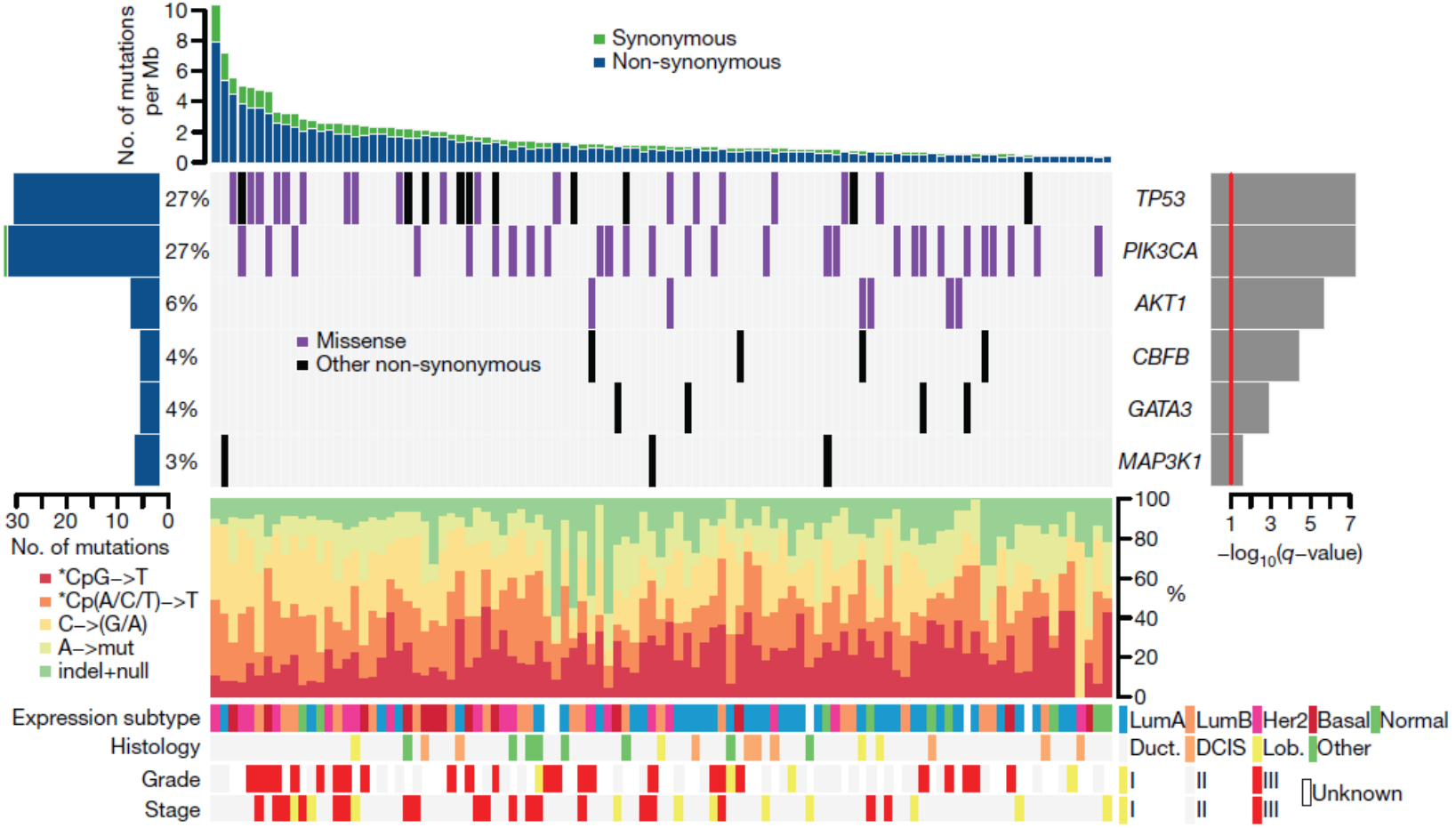
International Journal of Gynecological Cancer. 22(3):343-347, March 2012.

- 25% of B Ca
- HMEV transformation
- Portends 6-fold increased risk

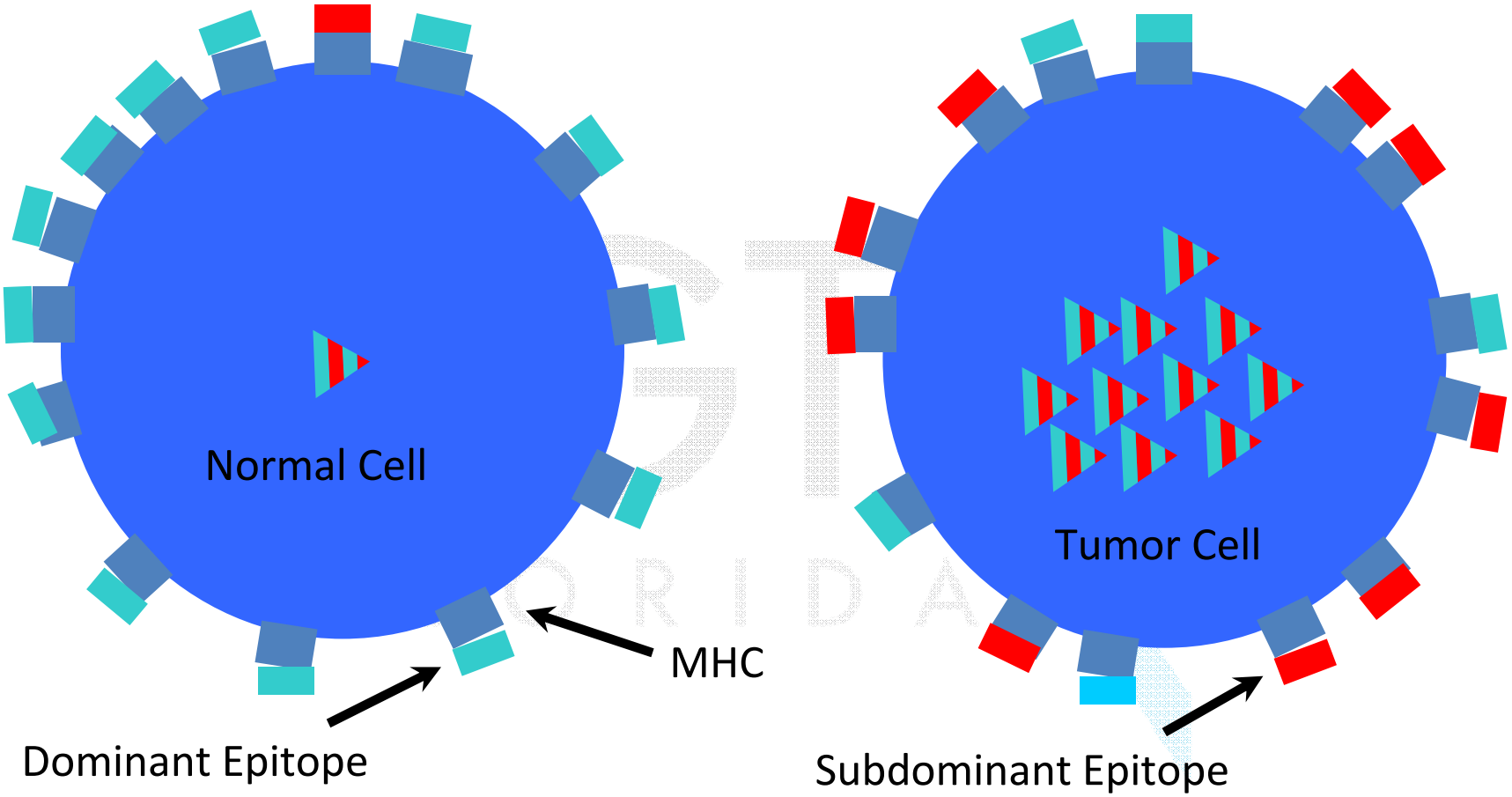


Sequence analysis of mutations and translocations across breast cancer subtypes

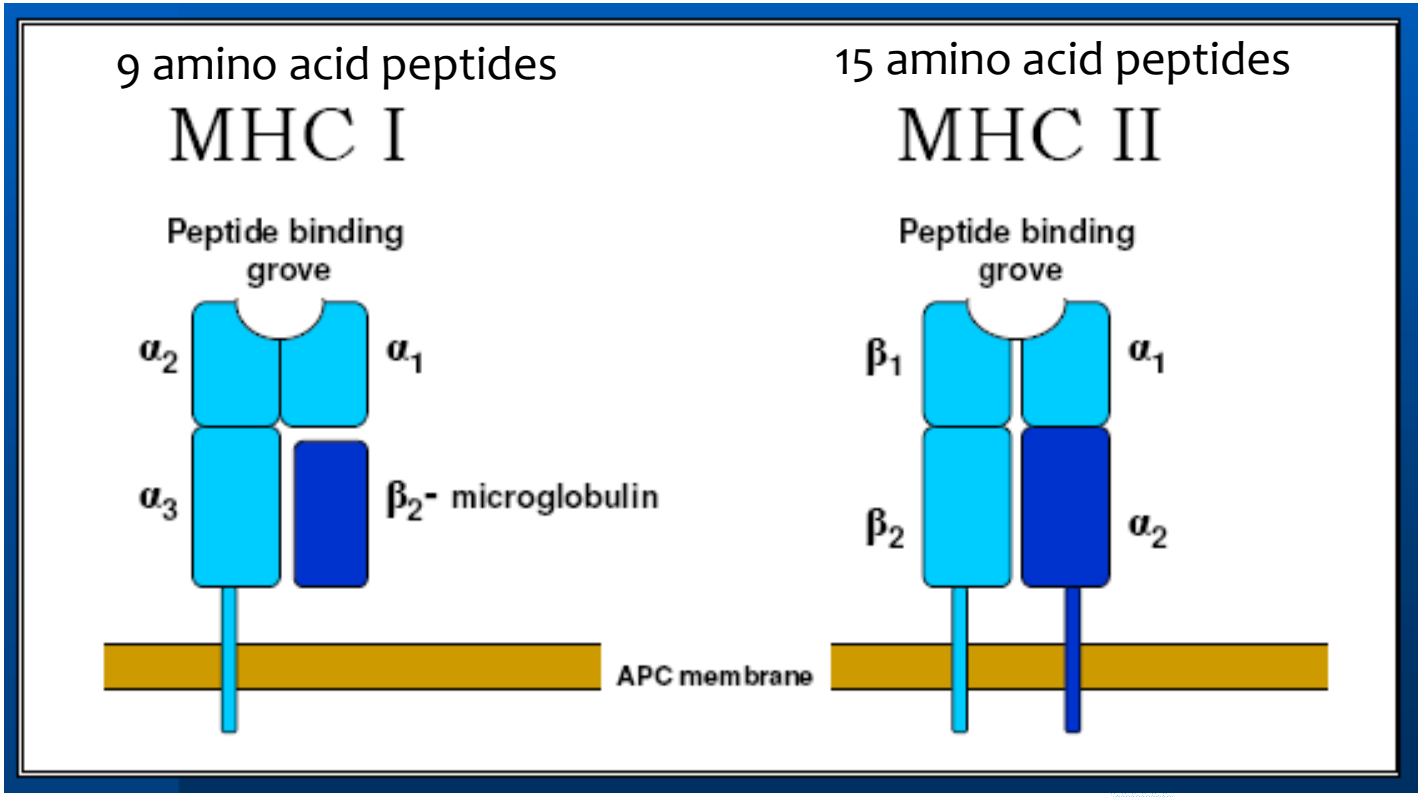
21 JUNE 2012 | VOL 486 | NATURE | 405



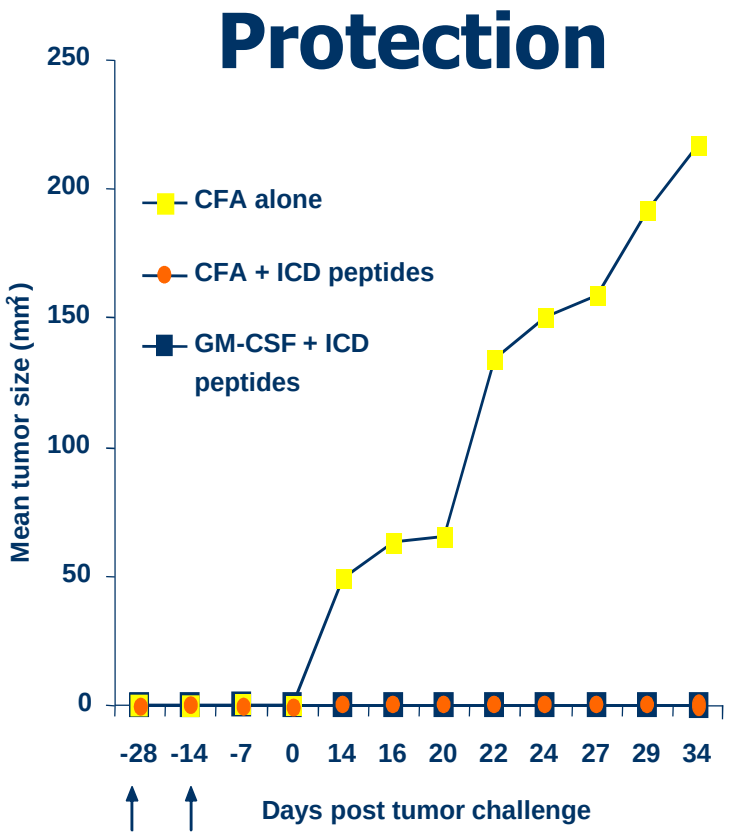
Overexpressed Self Proteins can be Tumor Antigens

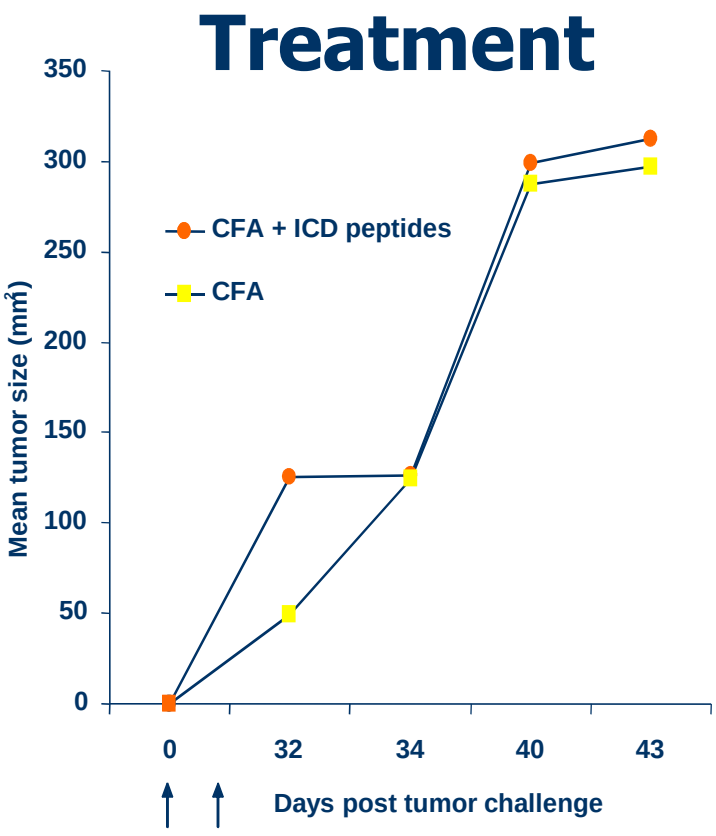


Structures of MHC Class I and II



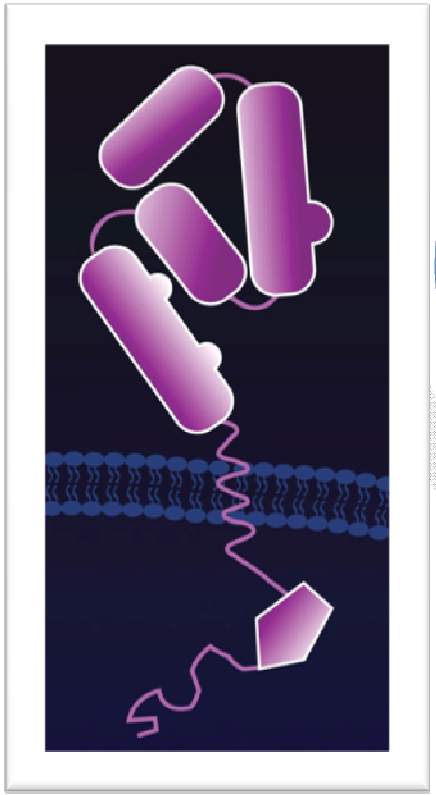
The Role of Cancer Vaccines





Knutson et al., *Clin Breast Cancer,* 2001

Self Antigen Vaccines

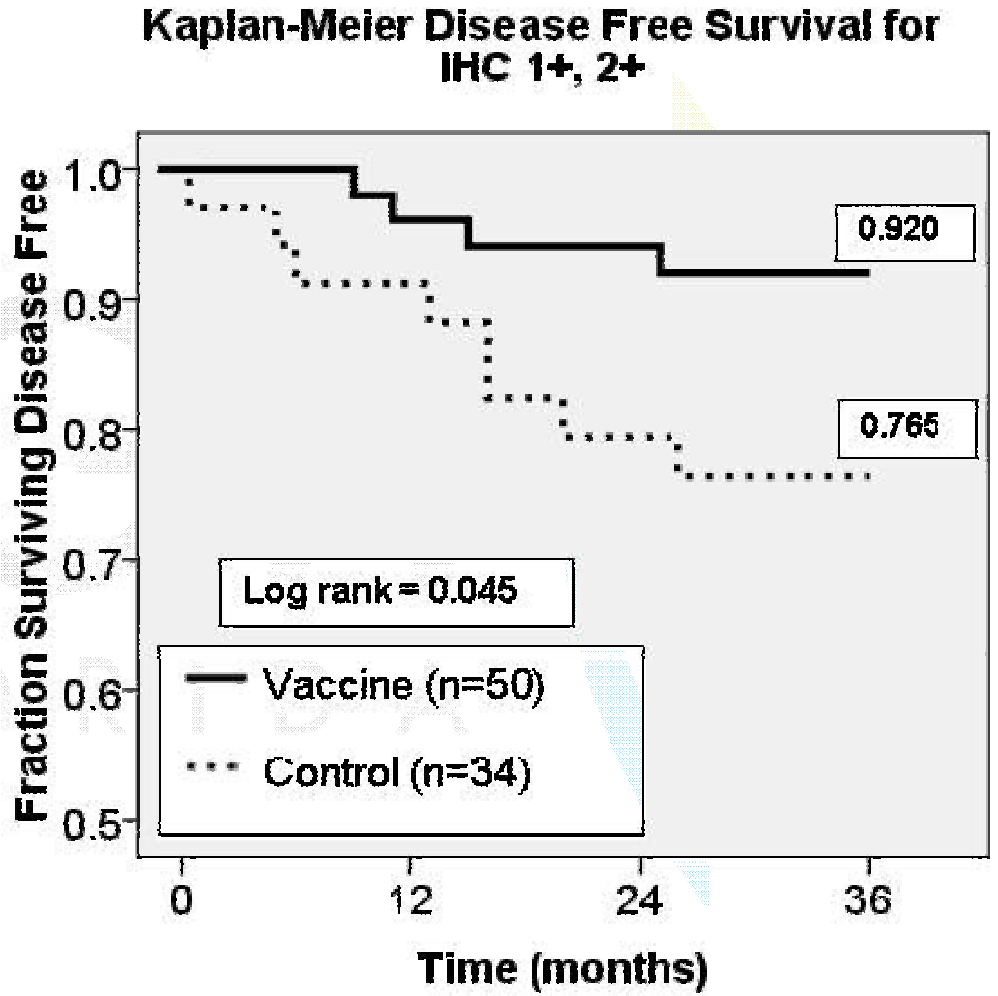


Vaccines for Prevention of Recurrence Ag-Specific
HER-2/FRα/CEA/IGFBP2

JCI 2001
JCO, 2002
Clin Cancer Res, 2002
Clin Cancer Res, 2010
CII, 2010
JCO, 2007
J Clin Immunol, 2004
JCO, 2004
Blood, 2004

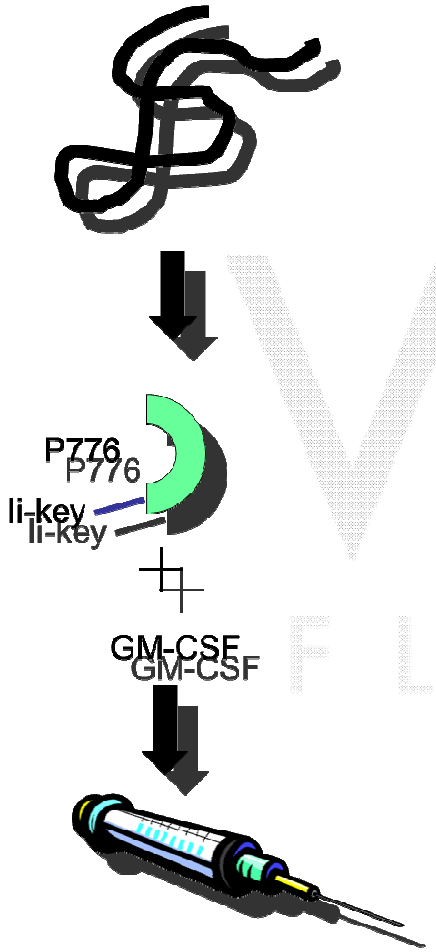
- Ag Express – Phase III HER2 CD4 MD Anderson
- TapImmune – Phase I HER2 CD4 VGTI Mayo
- Galena – Phase III E75 MD Anderson
- VaxOnco – Phase I FRα VGTI Mayo
- UPenn – Phase III ICD Czernieki
- TapImmune – Phase I HER2 CD4/8 VGTI Jupiter/Martin
- iImmune – Phase I HER2 - Trastuzumab VGTI

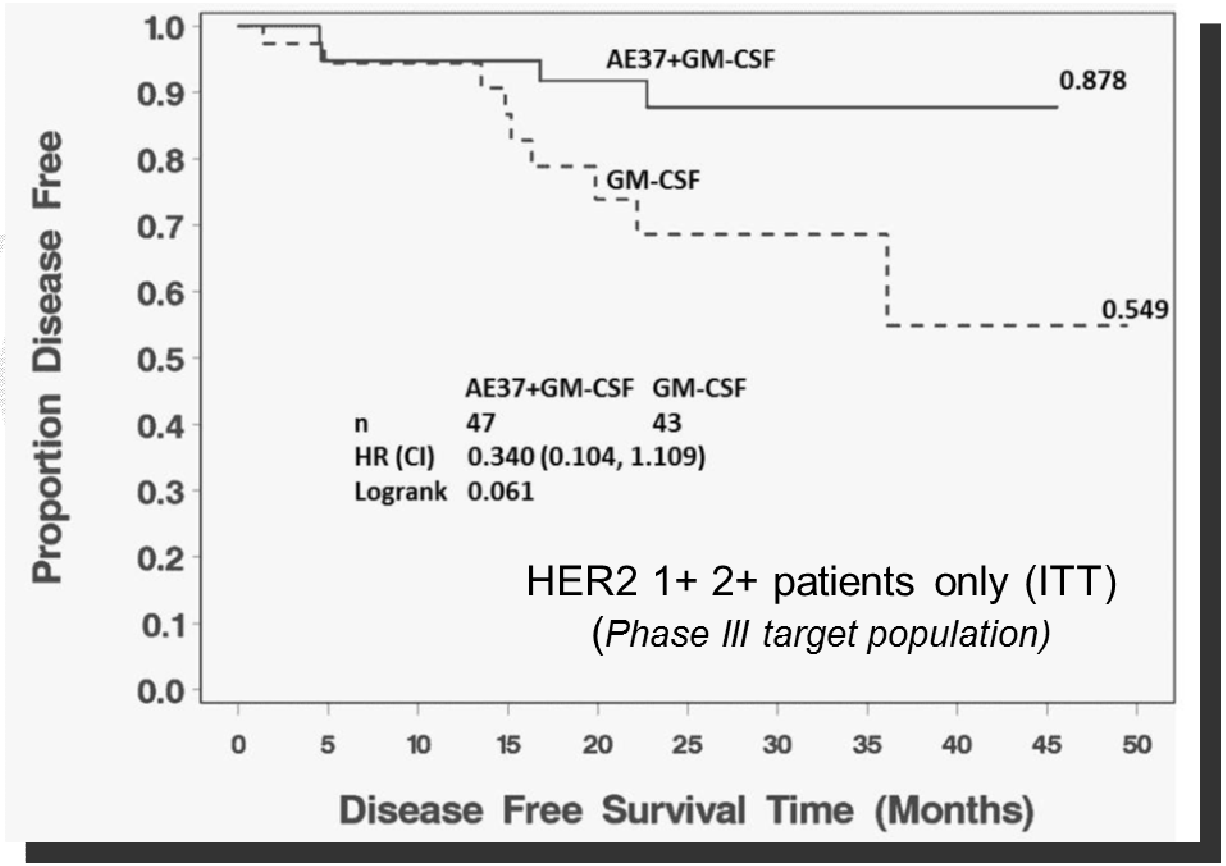
HER-2 vaccines prevent recurrence



Peoples-Galena

HER-2 vaccines prevent recurrence

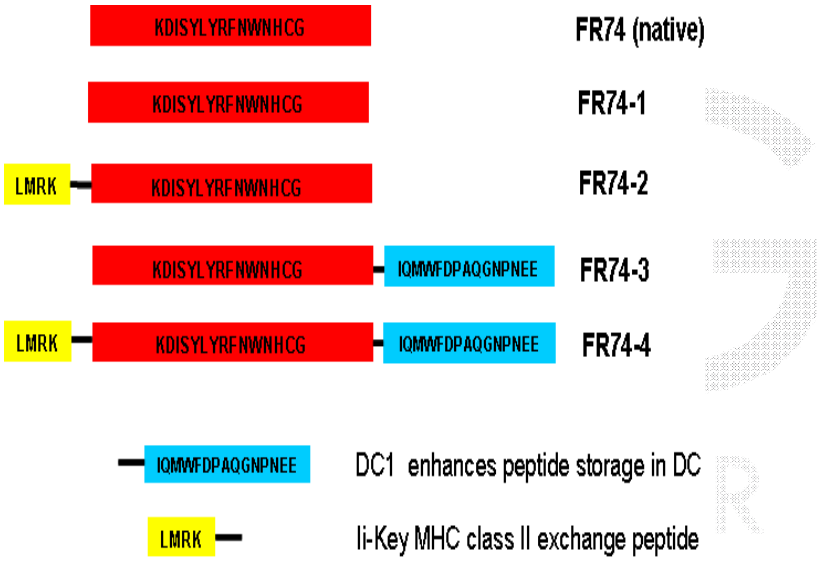


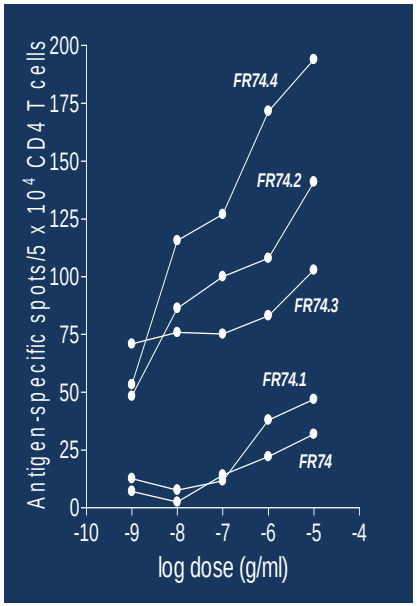


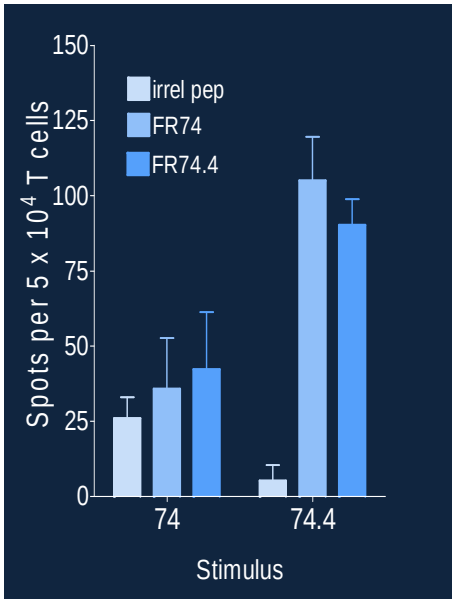
Von Hofe-Antigen Express

Enhancing class II peptide responses with peptide modifications

Peptide modifications elicit better immunity by improving the presentation of the antigen from dendritic cells

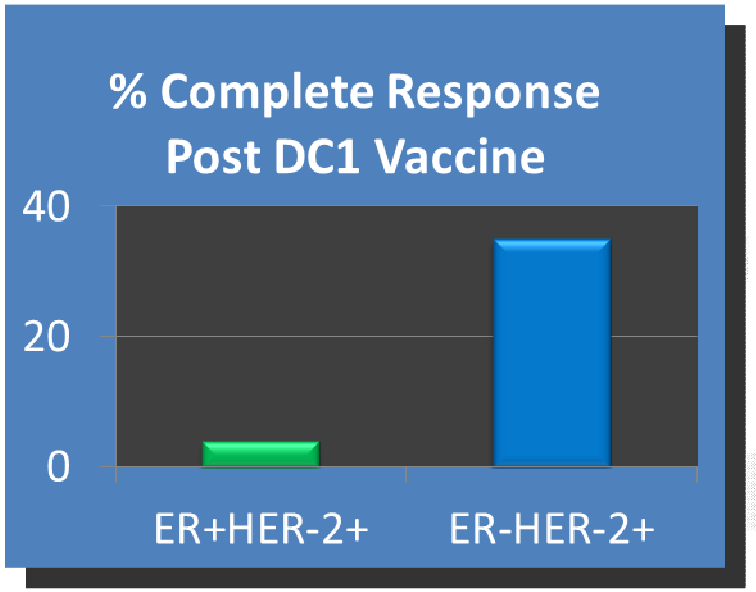




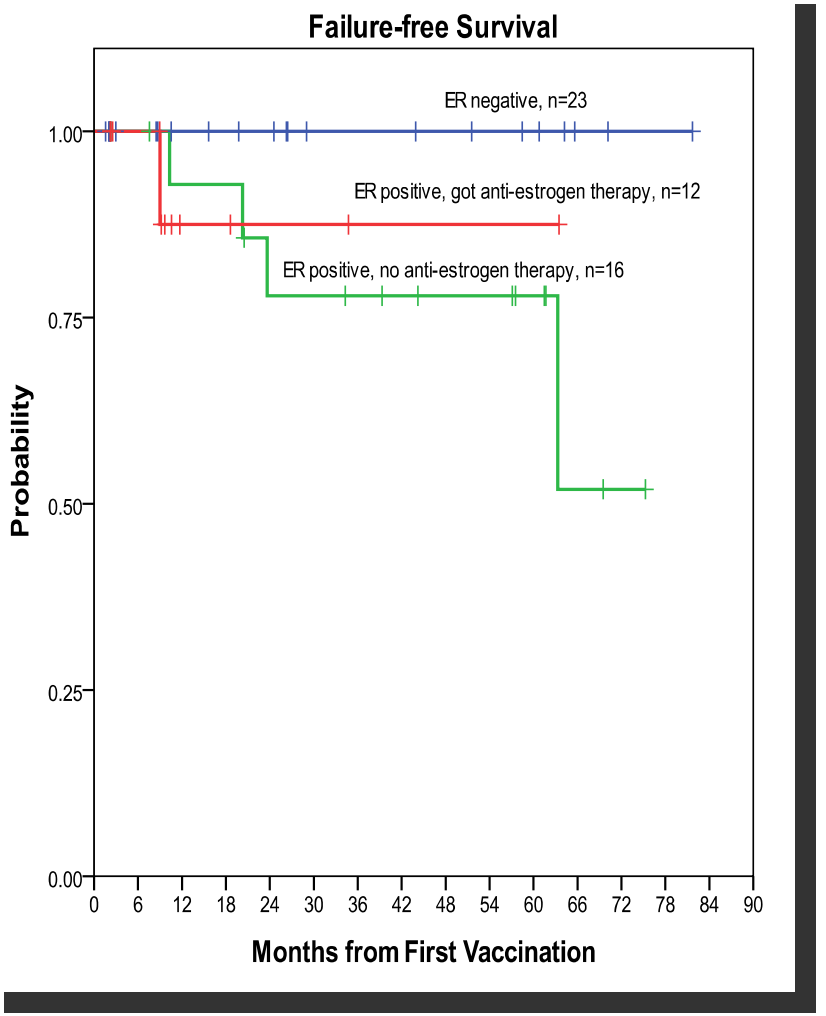


Erskine, 2011 JI

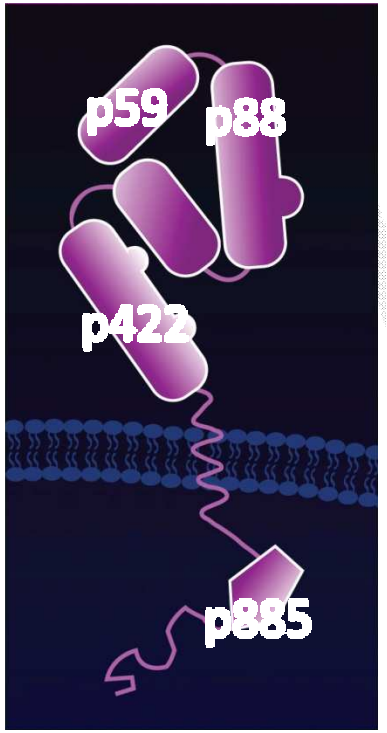
HER-2 vaccines induce regression in DCIS patients



Czerniecki-UPenn



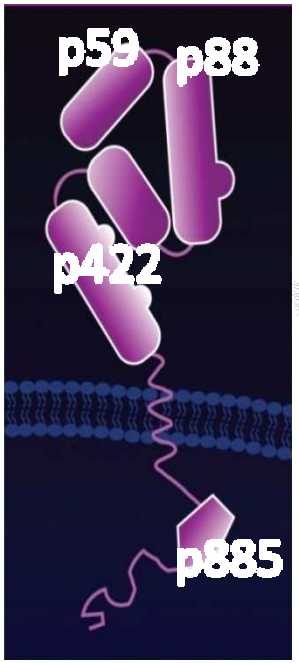
New Generation HER-2/neu Vaccines



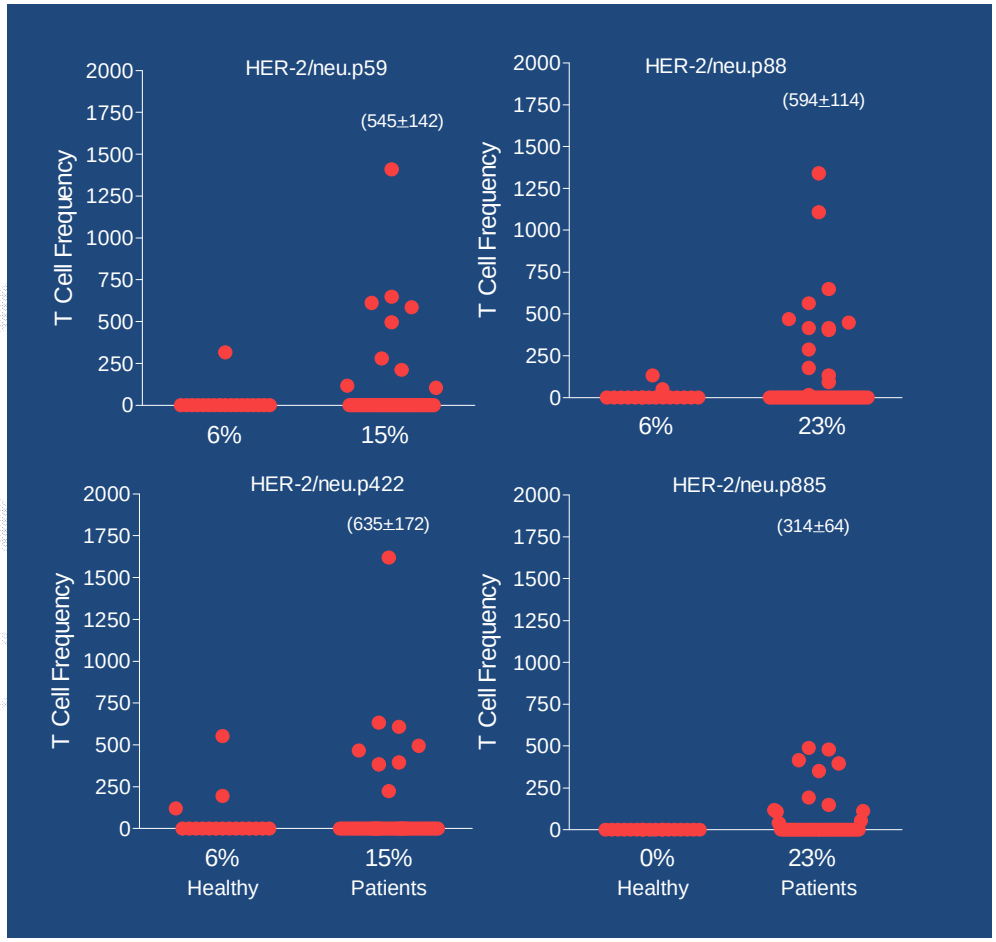
- **Phase I Clinical Trial**
  - Four helper T cell epitopes w/GM-CSF
  - One arm:
    - 2+(FISH+) and 3+
  - Three mos. following last dose of trastuzumab
    - Disease-free.
  - Objectives
    - Immunogenicity (i.e. proof of principle)
    - Safety
    - Feasibility

- Advantages of this HER-2 vaccine
- Targets helper T cell lymphocytes which help to coordinate the immune response and to generate long-term immunity
- Can be given to women regardless of HLA status, ie available to all eligible women

Epitopes selected on the basis of natural immunity

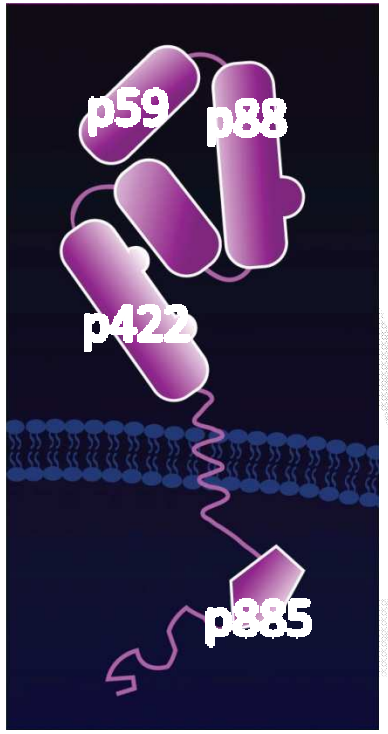


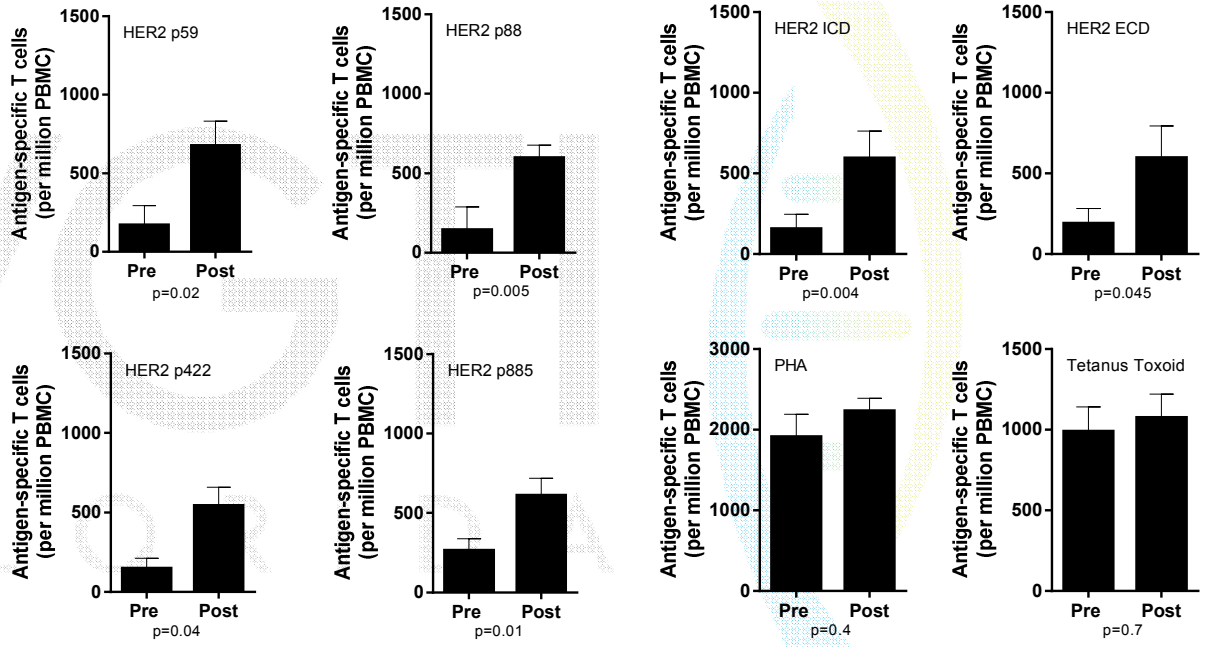
DRB1*0101, DRB1*0301
DRB1*0401, DRB1*0404
DRB1*0405, DRB1*0701
DRB1*0802, DRB1*0901
DRB1*1101, DRB1*1201
DRB1*1302, DRB1*1501
DRB3*0101, DRB4*0101
DRB5*0101



Karyampudi et. al., Clin Cancer Res. 2010 Feb 1;16(3):825-34. Epub 2010 Jan 26.

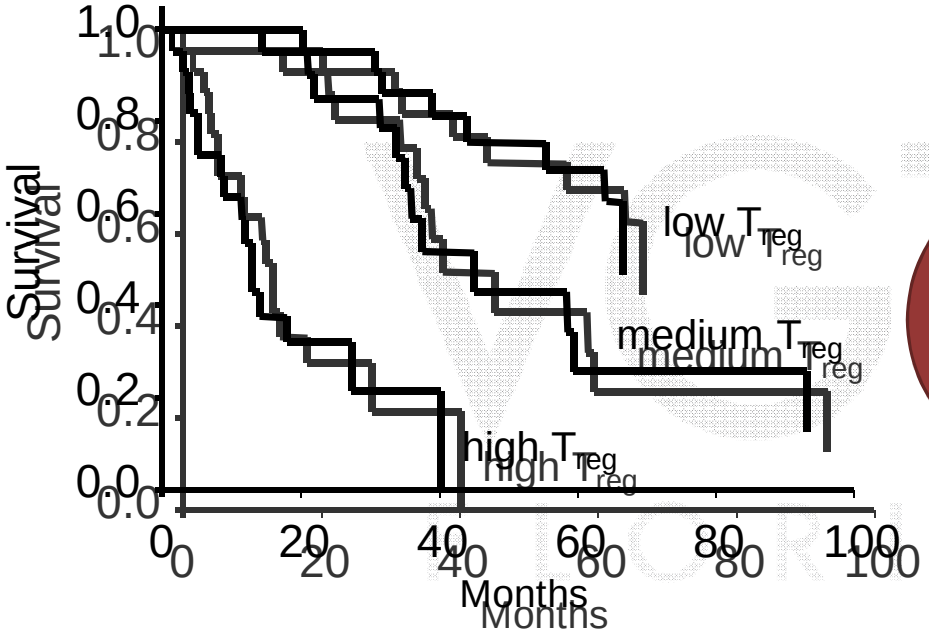
New Generation HER-2/neu Vaccines





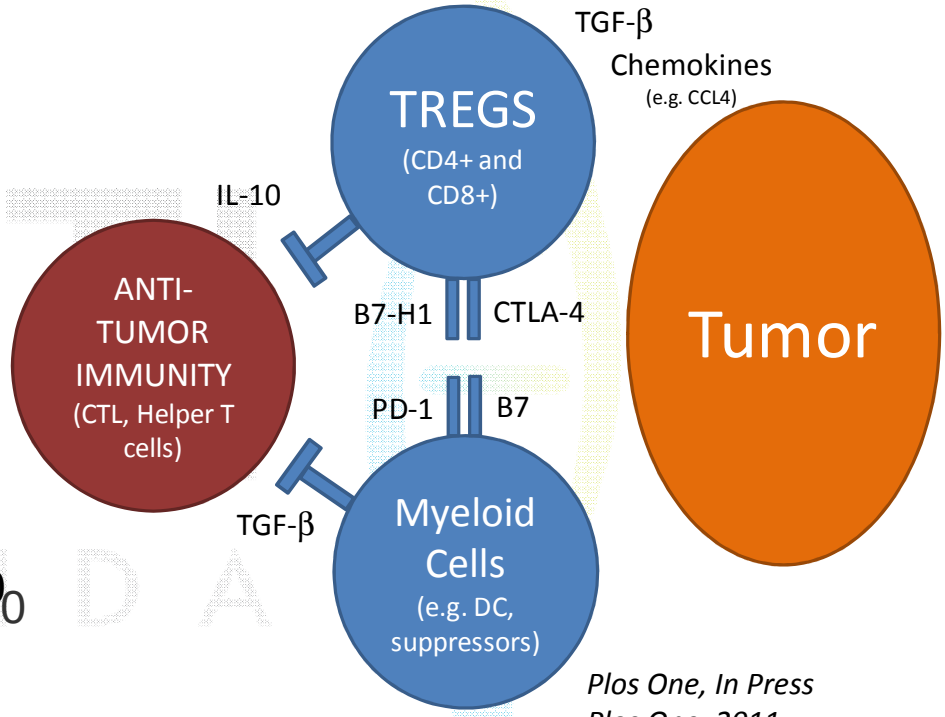
~90% of patients independent of HLA-DR genotype

Suppression/Tolerance



Low T_{reg} 66.4 mos. Vs. High T_{reg} 12.8 mos P<0.0001

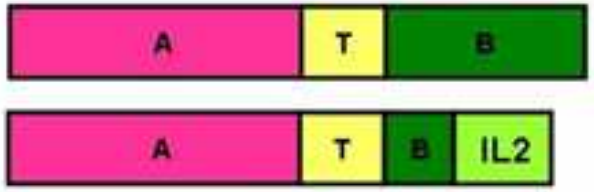
Low T_{reg} 66.4 mos. Vs. High T_{reg} 12.8 mos P<0.0001



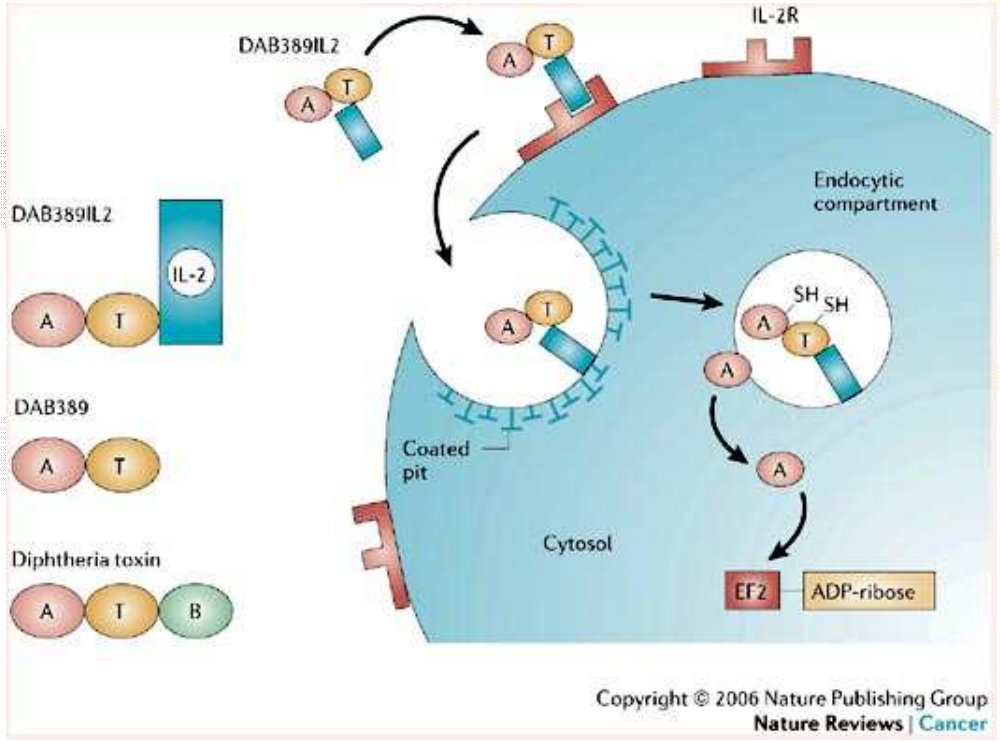
Plos One, In Press
Plos One, 2011
Nature Med 2003
J Immunol 2013
J Immunol 2006
Nature Med 2004

Depletion of Tregs with IL-2-immunotoxin blocks tumor growth

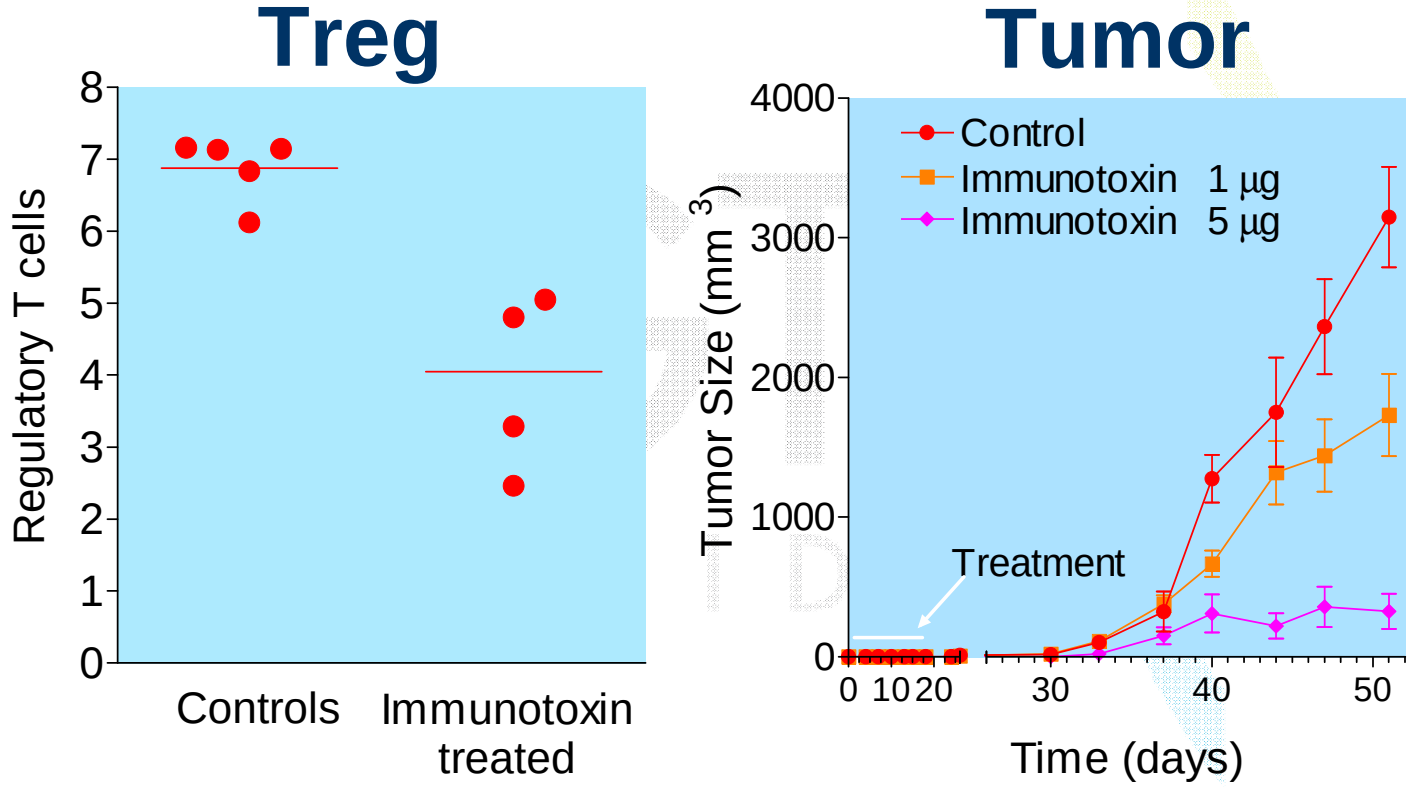
Diphtheria Toxin (DT)



DT388-IL2

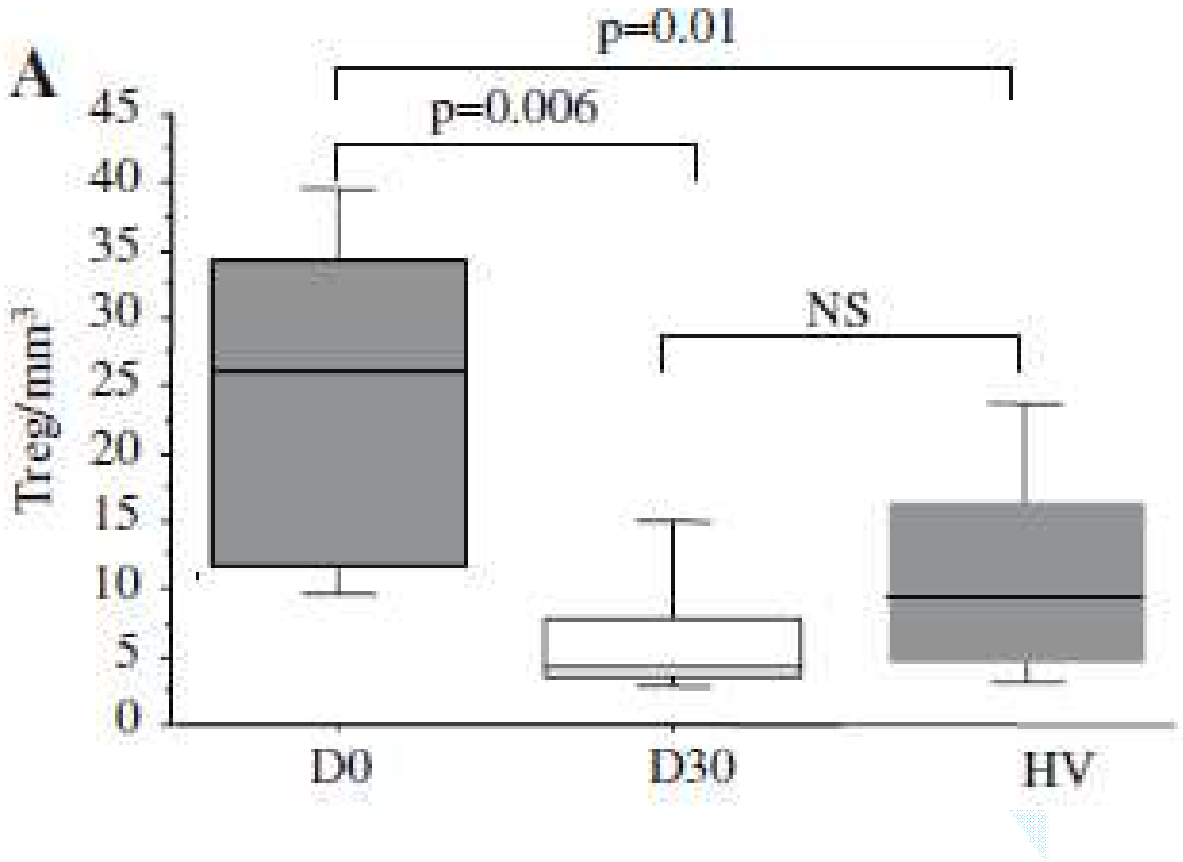


Treg depletion leads to sustained tumor protection



Knutson et al, 2006, JI 177:84

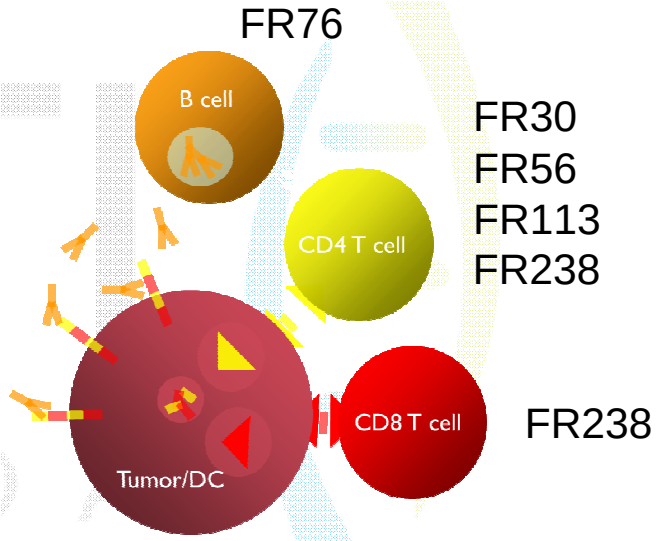
Metronomic cyclophosphamide depletes Tregs in cancer patients



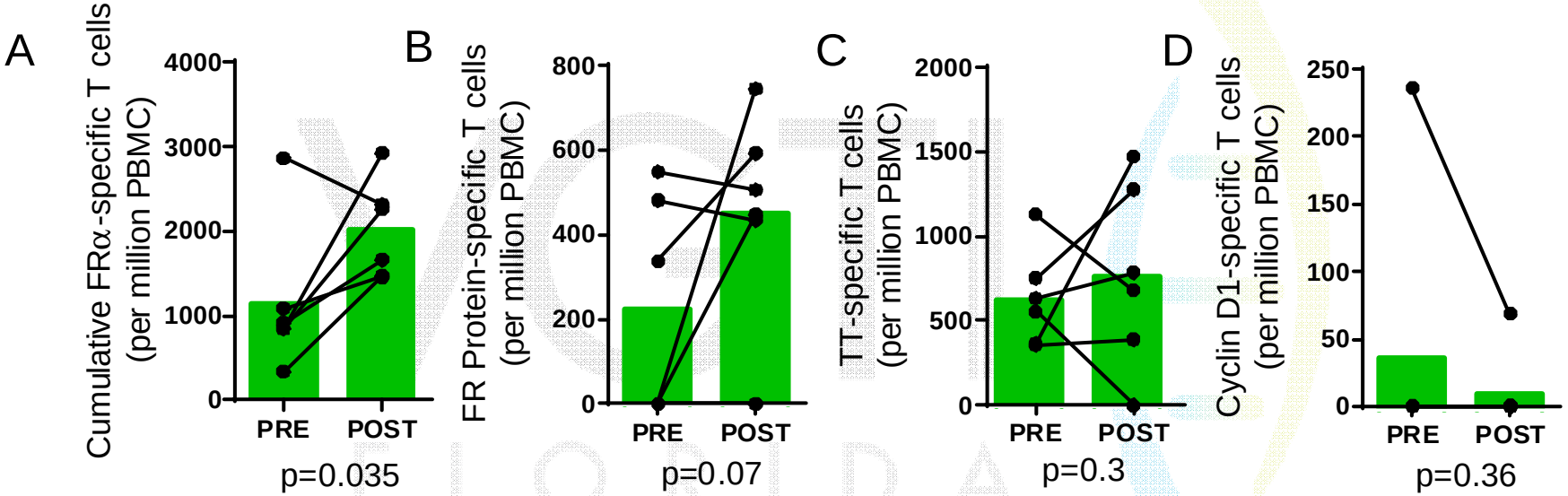
Cancer Immunol Immunother (2007) 56:641–648
DOI 10.1007/s00262-006-0225-8

Phase I Clinical Trial-Combination Approach

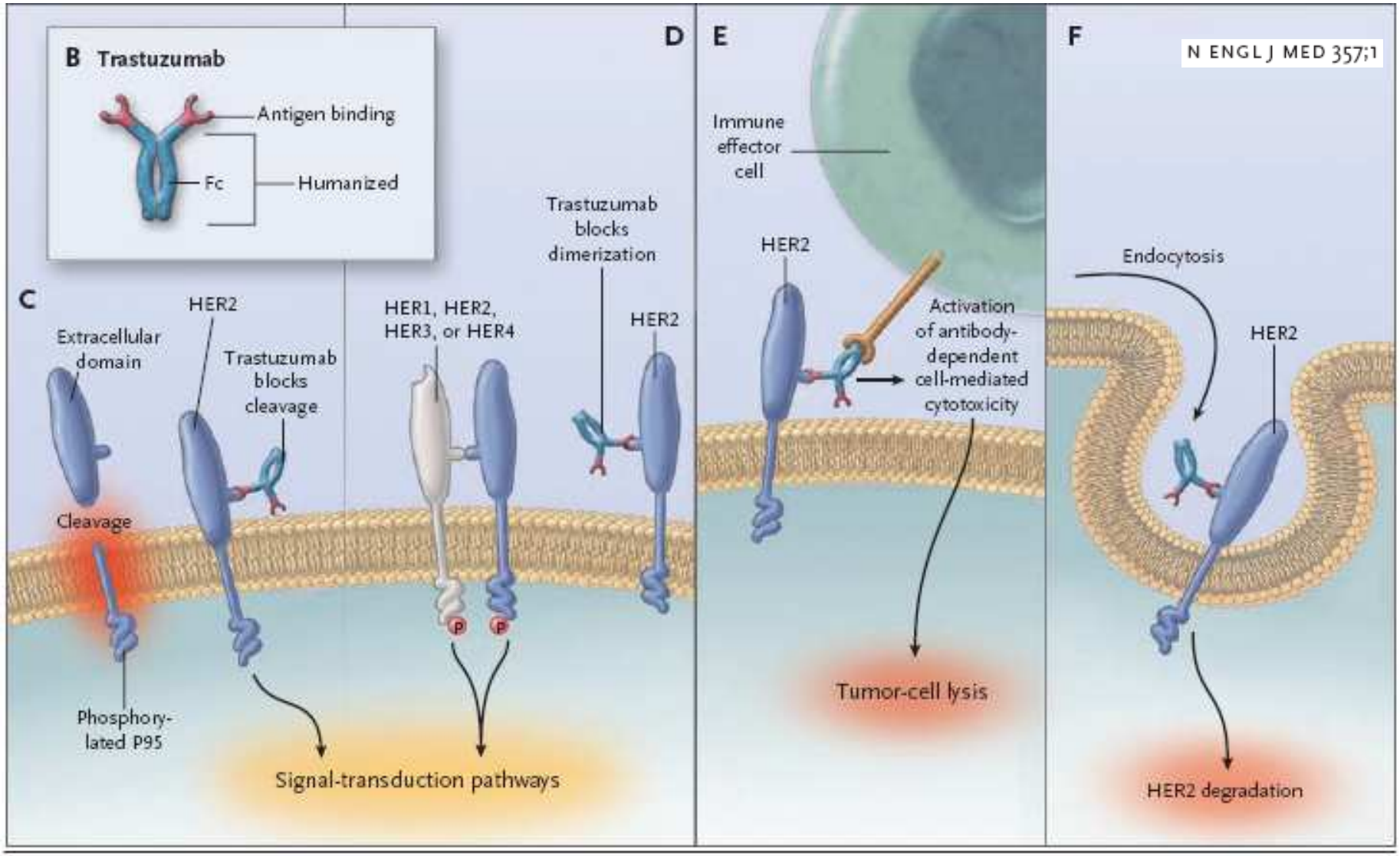
- Target-Folate Receptor Alpha
- Four T cell epitopes and one antibody epitope w/GM-CSF
- Two arm:
  - Cyclophosphamide or Ontak followed by vaccine
- Setting: Breast Cancer.
  - Disease-free.
- Objectives
  - Immunogenicity (i.e. proof of principle)
  - Safety
  - Feasibility



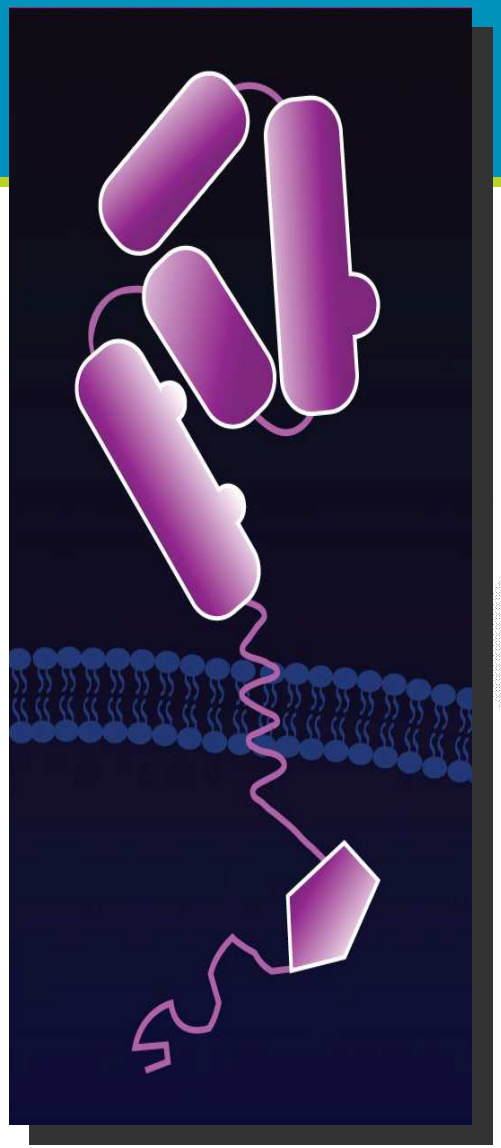
Generation of folate receptor alpha immunity



Proposed mechanisms of action of trastuzumab

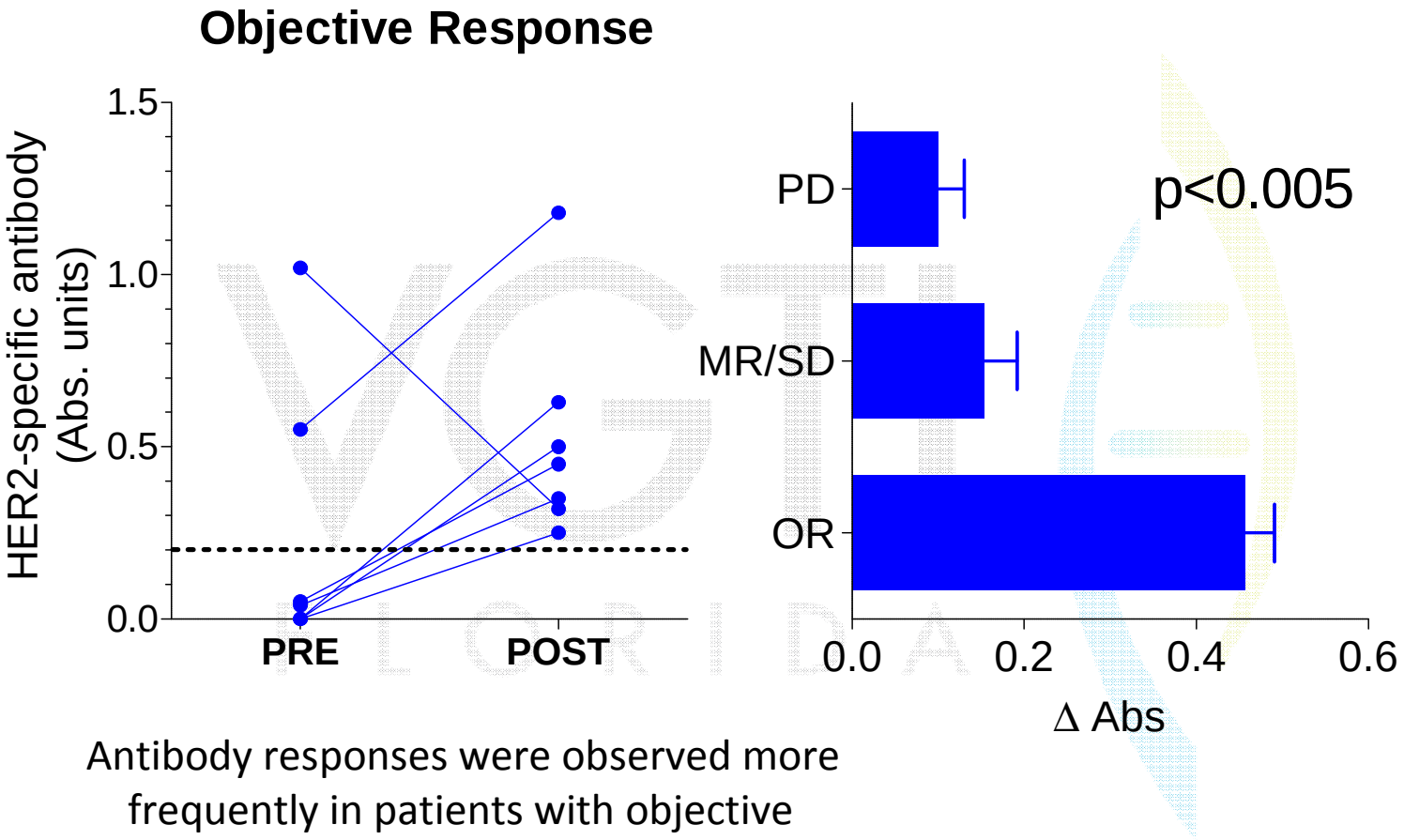


HER2+ MBC Management 1st-line with trastuzumab



- Activity of trastuzumab as single 1st-line agent for HER2+ MBC
  - Response 25-30%
  - TTP ~ 3-6 mo
- Mostly use combined chemotherapy + trastuzumab
  - Response 50-80%
  - TTP ~ 11-14 mo

Induction of anti-HER2 IgGλ antibodies in responding metastatic breast cancer

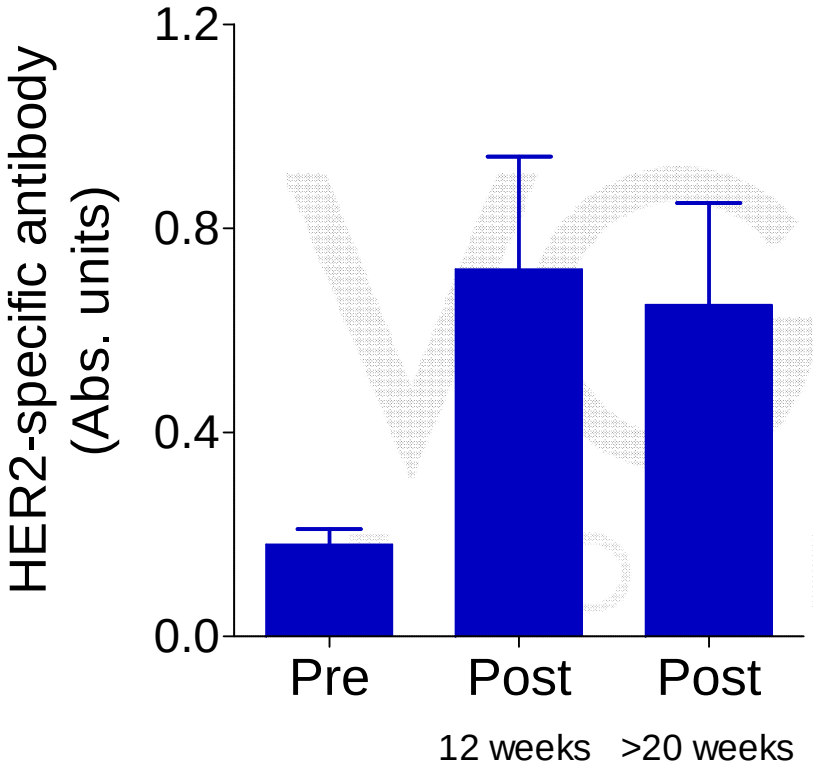


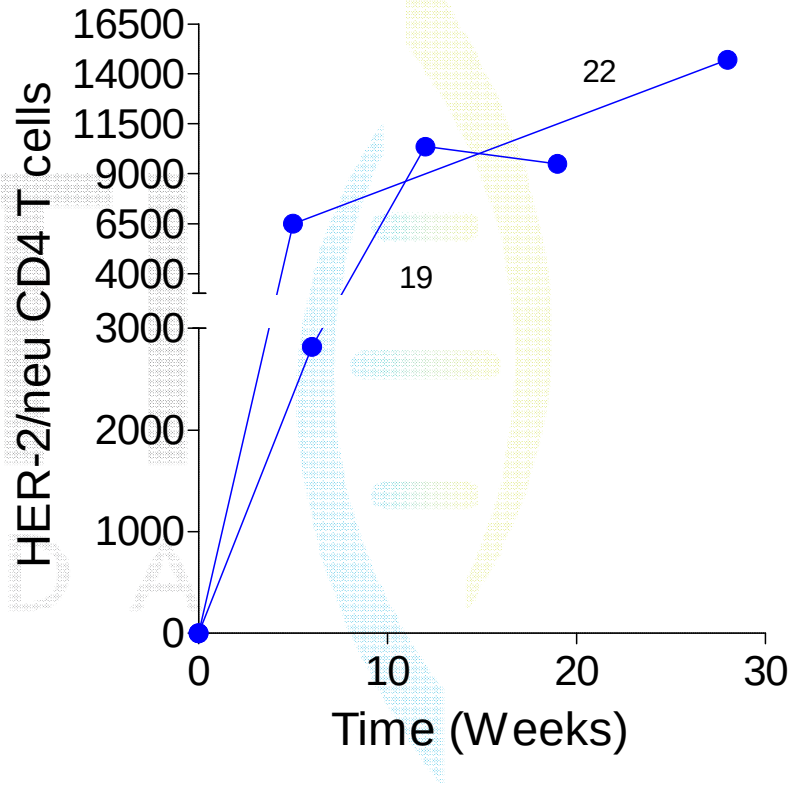
Antibody responses were observed more frequently in patients with objective responses

Taylor, C. et al. *Clin Cancer Res* 2007;13:5133-5143

Combination trastuzumab and chemotherapy may act like a vaccine

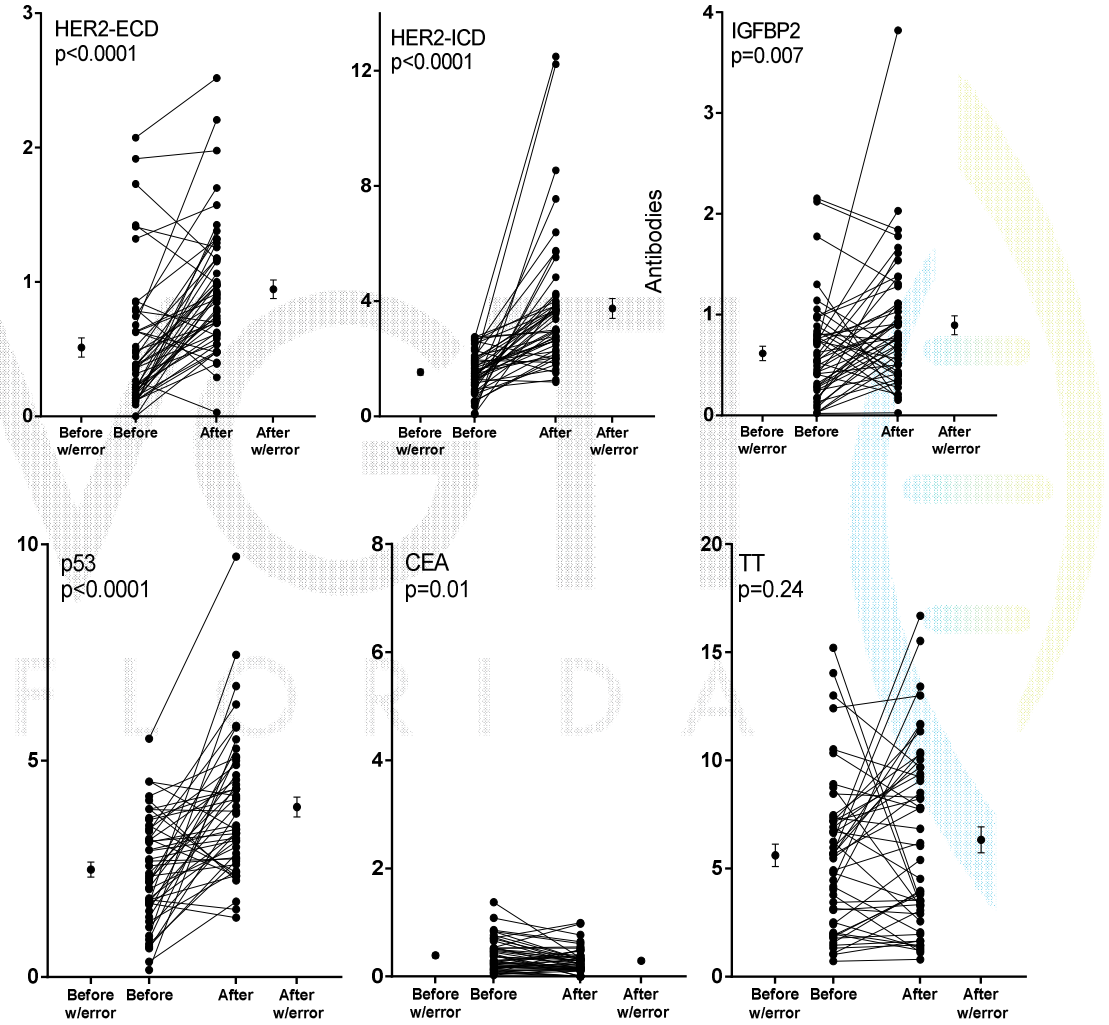
Persistent Responses: Immune Memory?





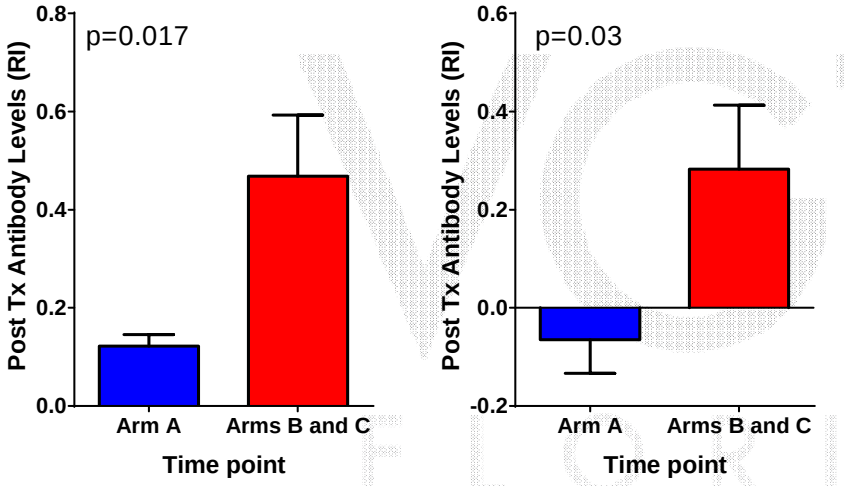
Taylor, C. et al. *Clin Cancer Res* 2007;13:5133-5143

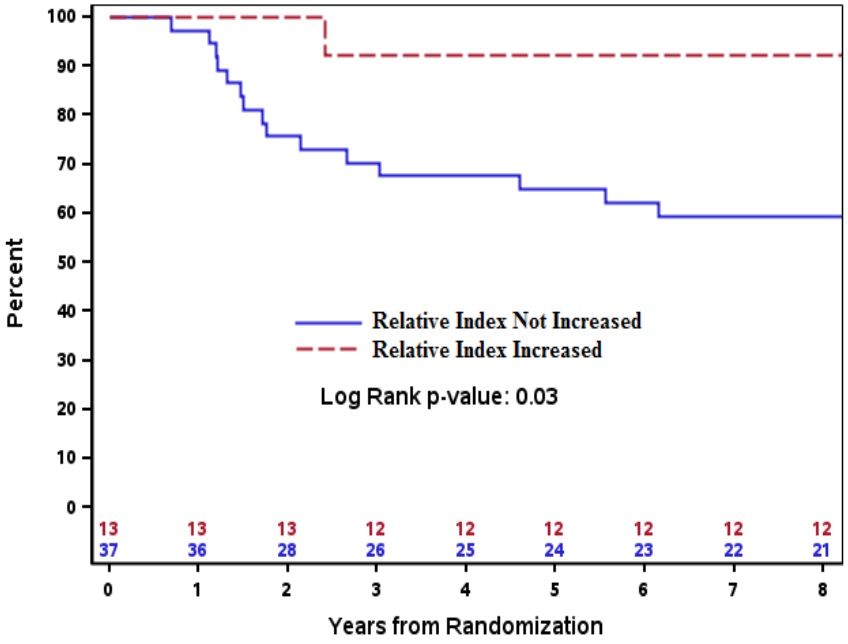
Combination trastuzumab and chemotherapy induces epitope spreading to multiple tumor antigens in patients with HER-2 breast cancer



Knutson, ASCO, 2013

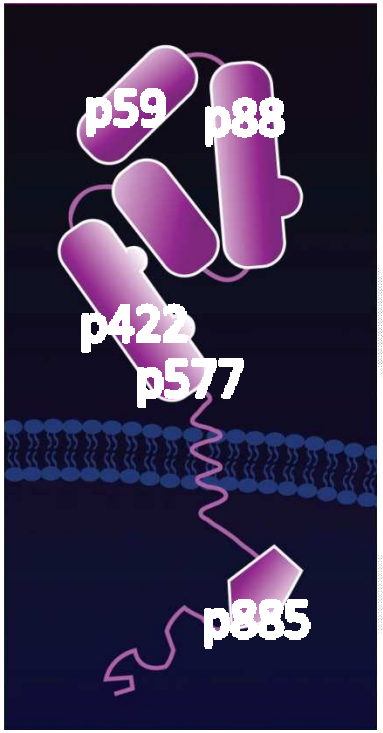
The generation of antibody responses to HER2 is associated are associated with improved disease-free survival





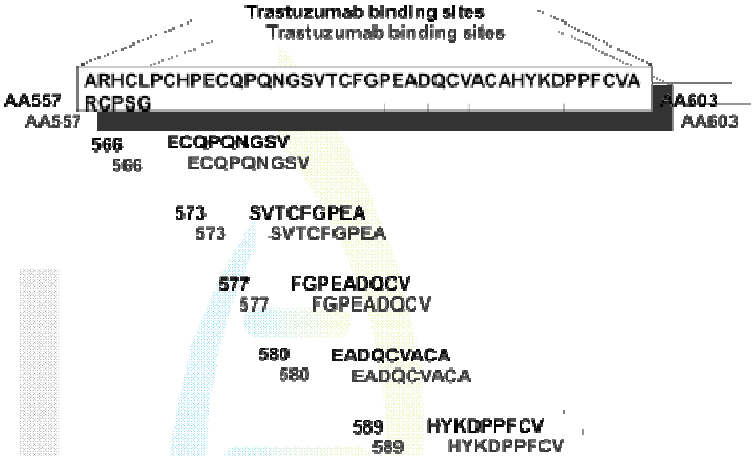
Knutson, ASCO, 2013

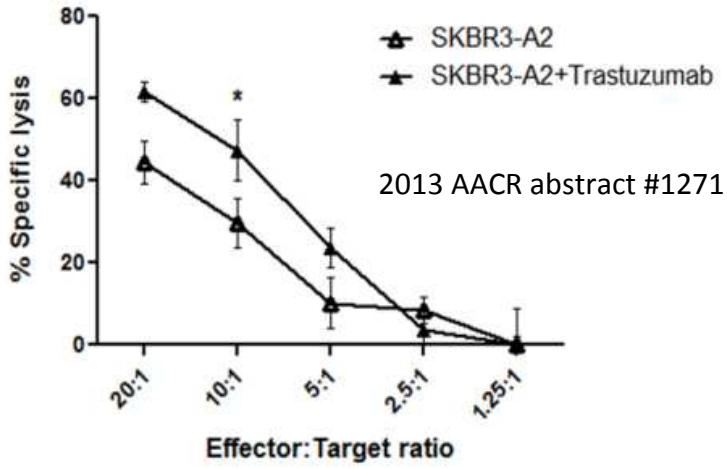
HER-2/neu vaccine in combination with trastuzumab



Phase I Clinical Trial

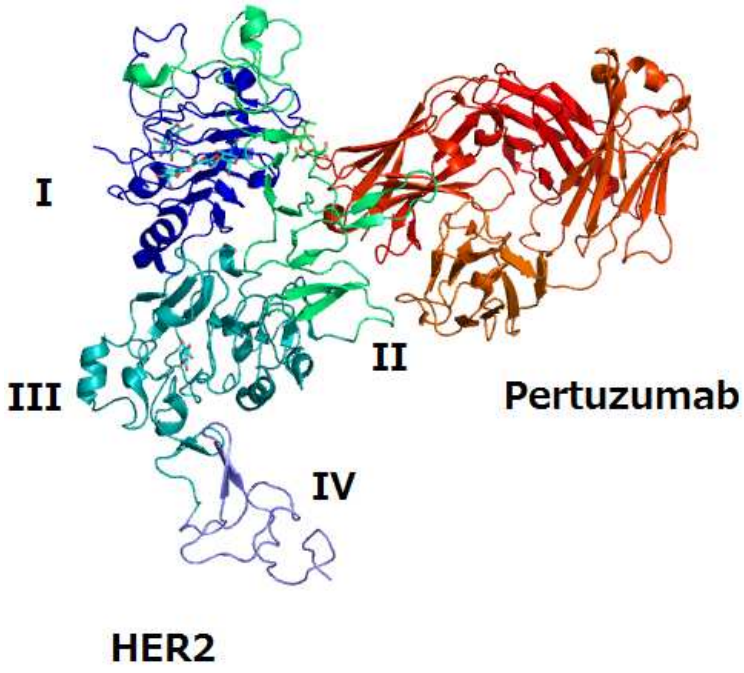
- Helper T cell and HLA-A2 epitope, p577 w/GM-CSF
- One arm:
  - Vaccine + Trastuzumab
- Stage IV
- Objectives
  - Immunogenicity (i.e. proof of principle)
  - Safety
  - Feasibility

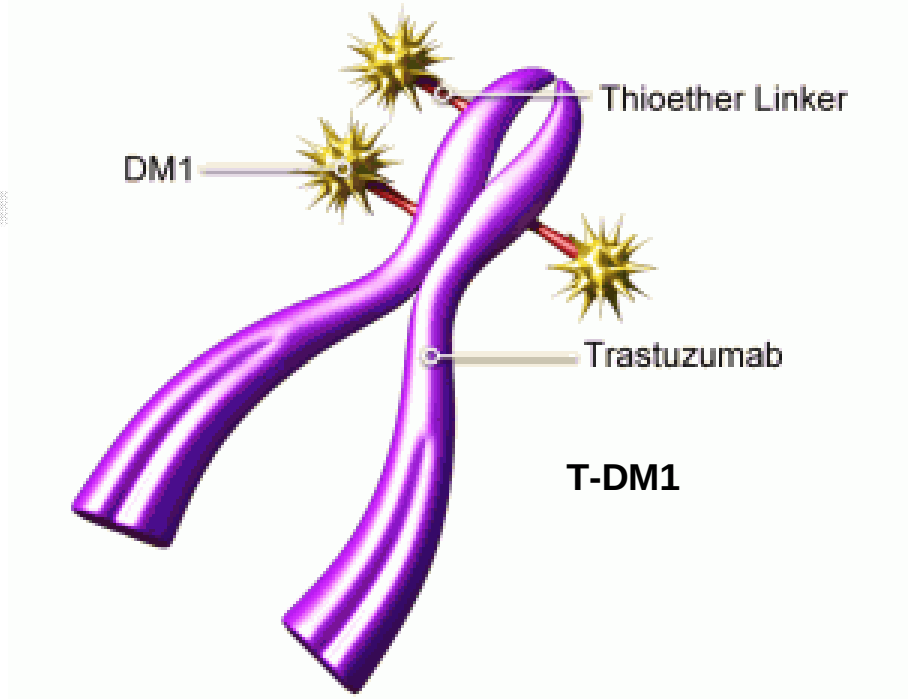




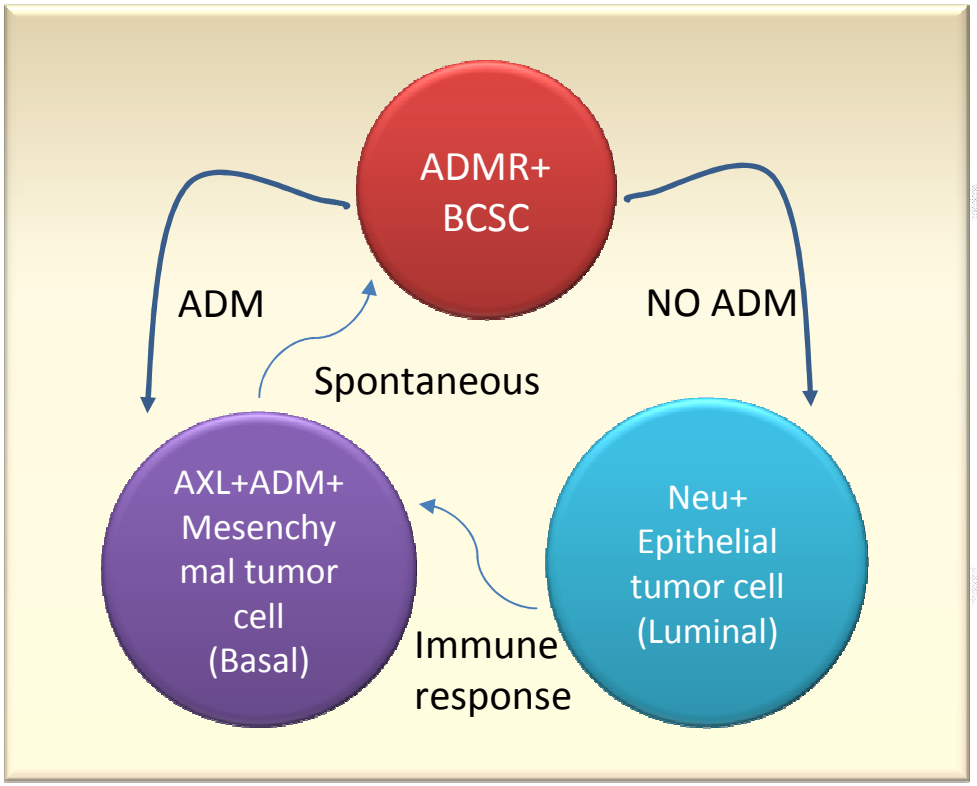
2013 AACR abstract #1271

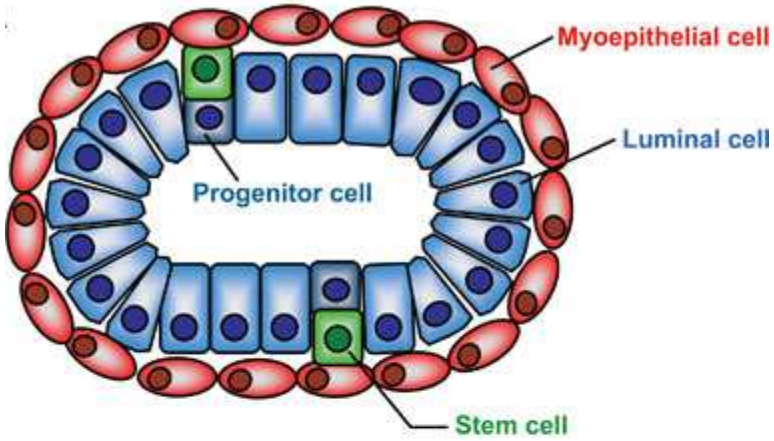
Newer monoclonal antibodies for HER2+ breast cancer





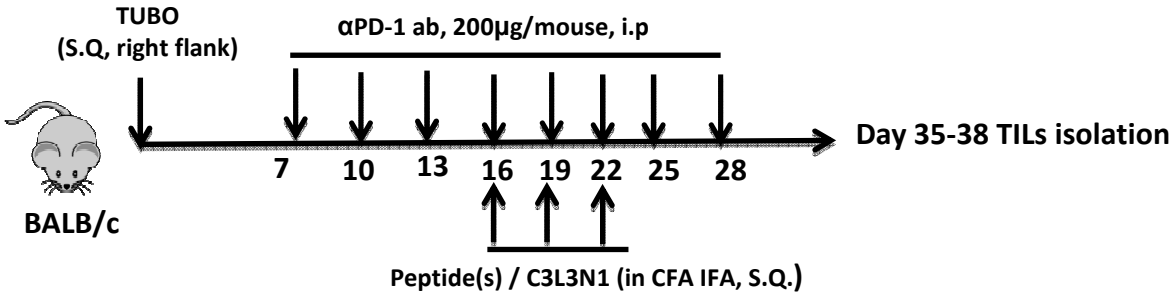
Breast Cancer Stem Cell Vaccines

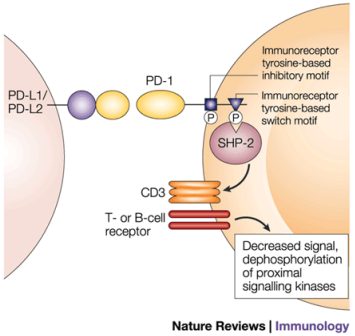


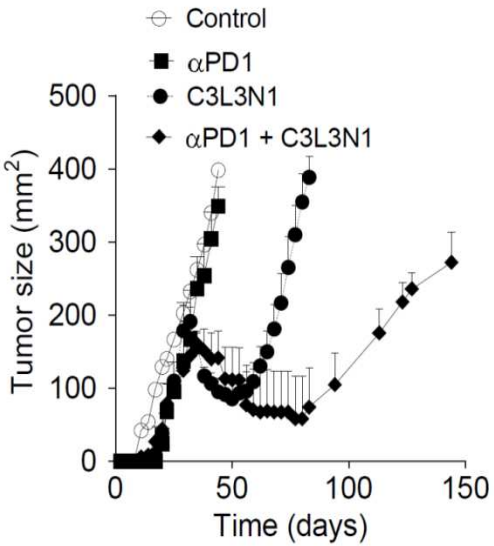


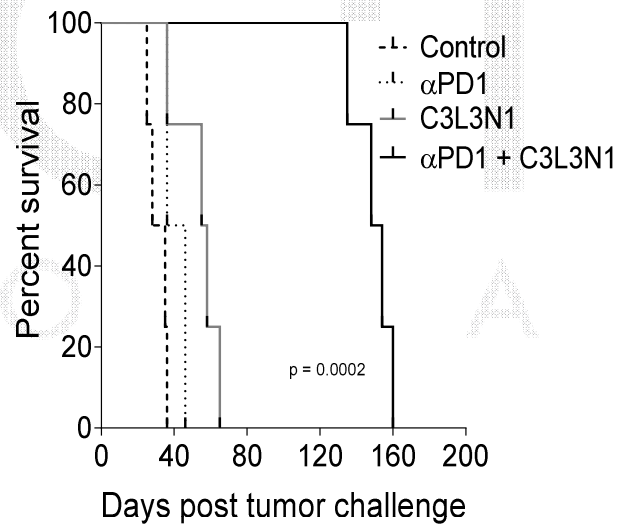
Cancer Res., 2011
Oncogene, 2013
Cancer Res, 2010
Cancer Res, 2009
Cancer Res, 2012
Sem Cancer Biol, 2007
J Immunol, 2006
Cancer Res, under review

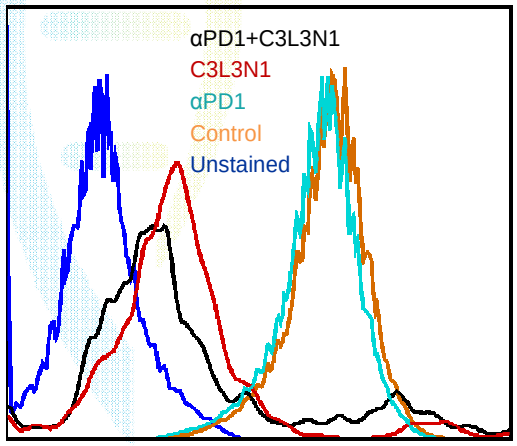
Combination therapy results in complete regression and sustained progression free survival











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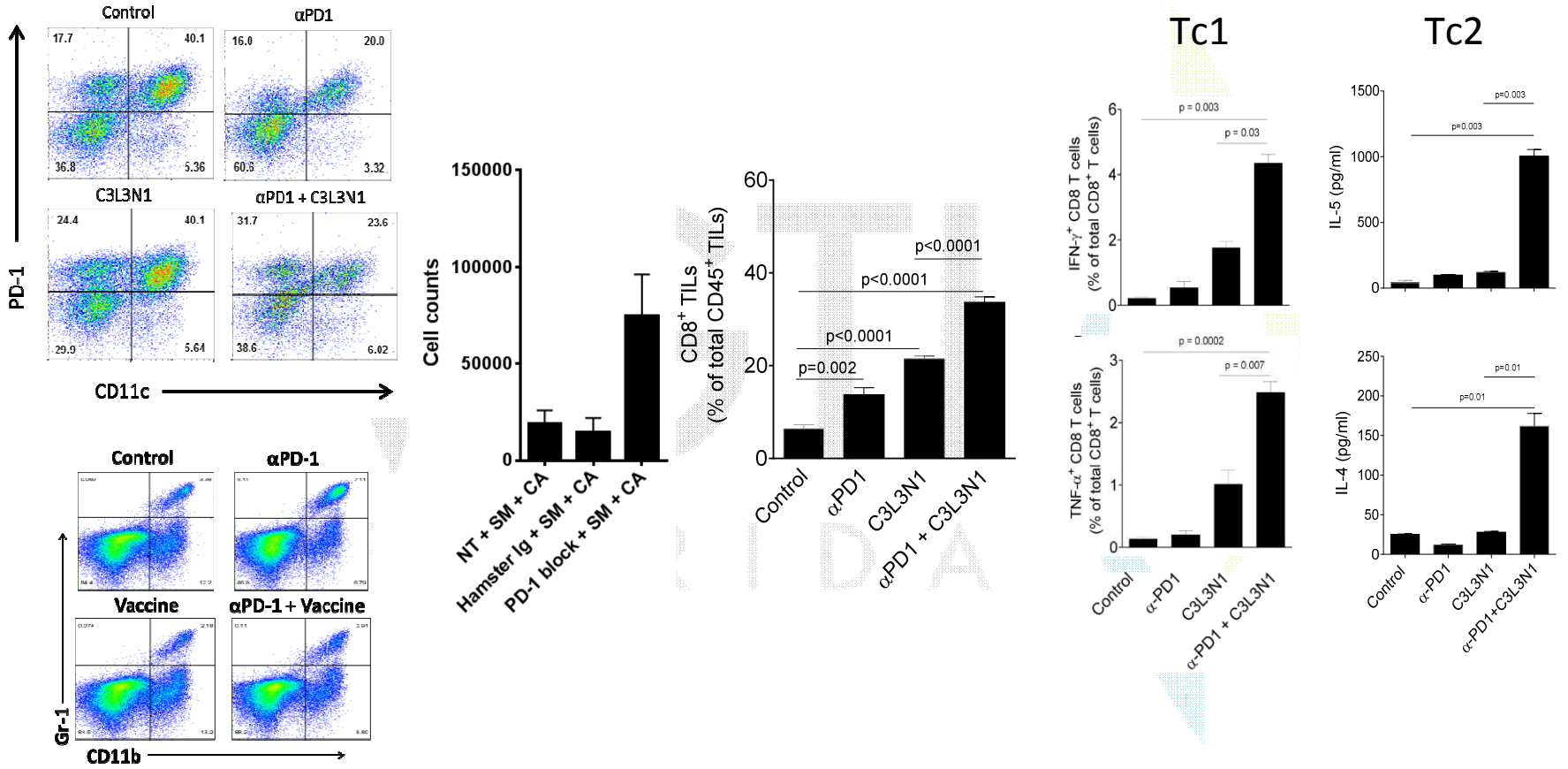
Combination therapy results depletes regulatory myeloid cells in tumors



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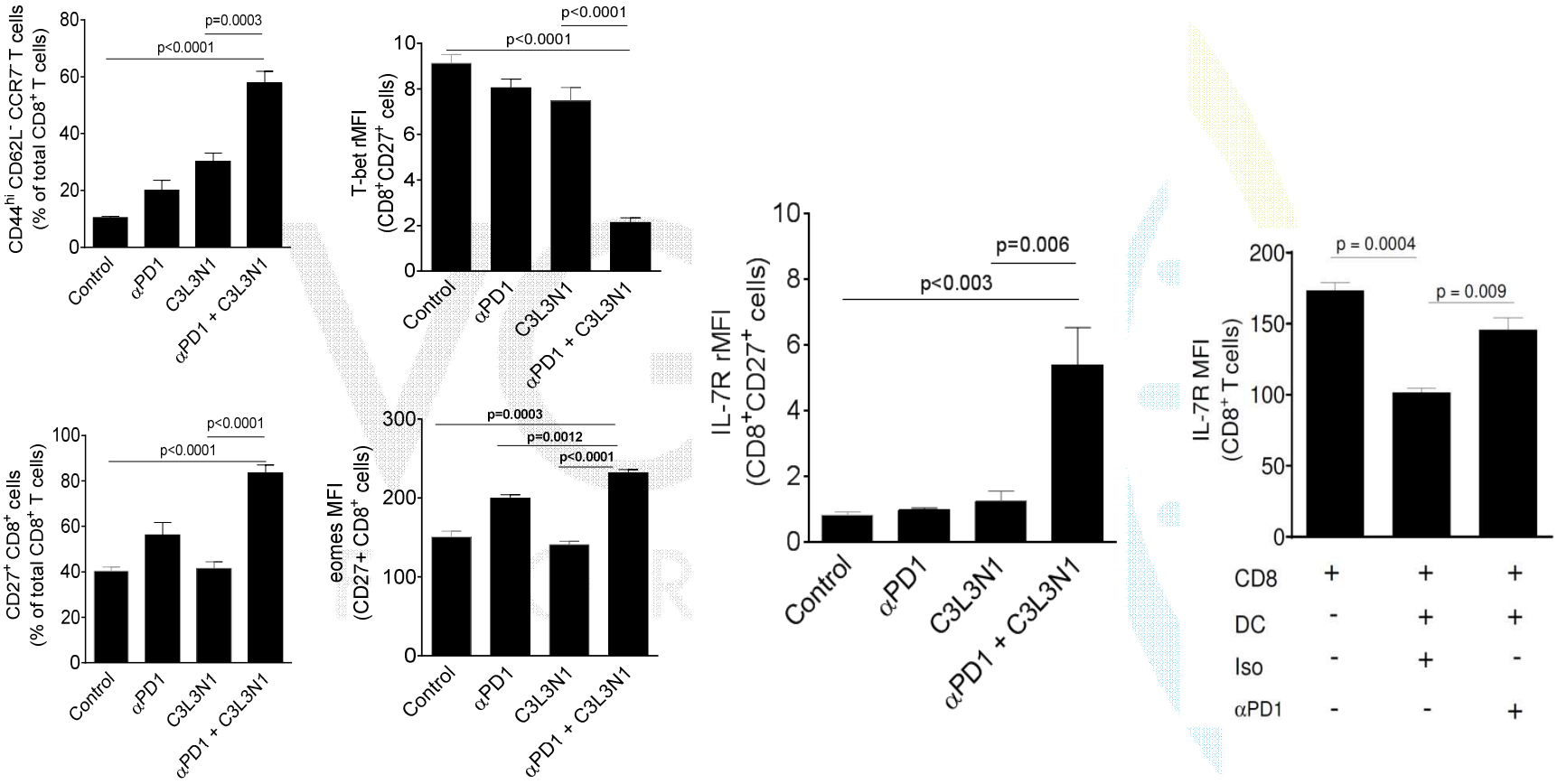
Combination therapy results higher infiltration of memory precursor effector T cells



Karyampudi, 2013

Conclusions

- **Vaccination for the prevention of breast cancer, secondary and primary is a reality.**
- **There are three possible choices of antigens that could be targeted.**
  - *Microbial antigens*
  - *Mutated self antigens*
  - *Normal self antigens*
- **Vaccination against self antigens is <u>already underway</u> and showing great promise in preventing recurrence among patients with no evidence of disease.**
- **In advanced disease such as stage IV breast cancer in which there is residual disease, combination approaches are likely to be more effective.**

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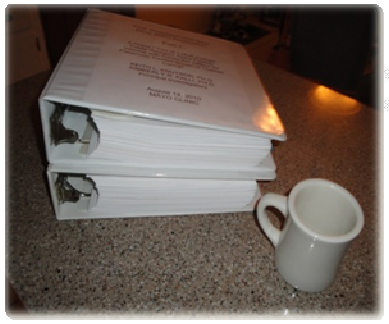

Outside

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