MAYO CLINIC
Cancer Center

Vaccines for Breast Cancer

BCEA Annual Education Conference
Oct. 05,2019

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Department of Immunology

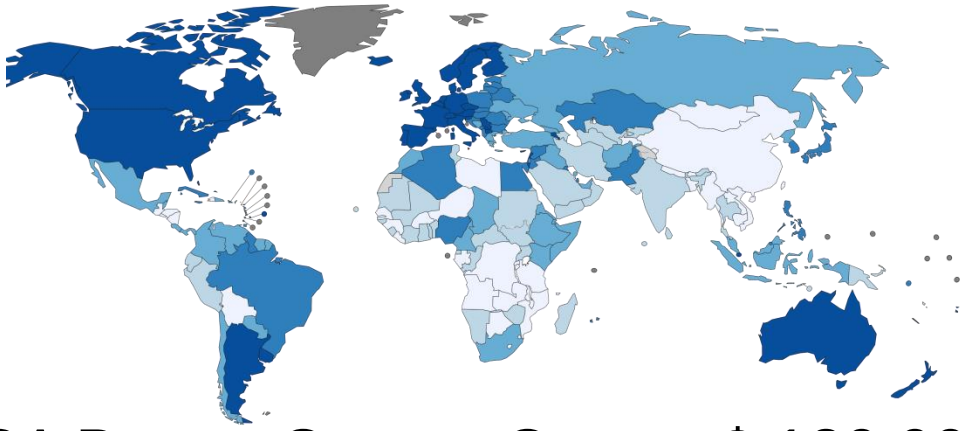
Conflict of Interest

- **Marker Therapeutics, Inc.**
  - **Cancer Vaccines and T Cell Therapy – Houston Tx**
  - **Scientific Advisory Board (unpaid)**
  - **Several Patent Licensing Agreements (Mayo)**
- **Kiromic, Inc.**
  - **Cancer Vaccines – Lubbock, TX**
  - **Scientific Advisory Board (Stock)**
- **Antigen Express, Inc.**
  - **Cancer Vaccines – Cambridge, MA**
  - **Scientific Advisory Board (Paid)**
- **Macrogenics, Inc.**
  - **Biologics – Bethesda, MD**
  - **Grant funding**

Breast Cancer

Worldwide: 1950K cases/year, 650K deaths/year

USA BREAST: 240K cases/year, 40K deaths/year
USA OVARIAN: 22K cases/year, 14K deaths/year



Estimated USA Breast Cancer Costs: $ 180,000,000,000

1% of the GDP

The adaptive immune system in the body's drug making machinery

CD4 "helper" T cells

- Inflammation (macrophages and neutrophils)
- Antibodies
- Induce/Enhance cytotoxic T cells
- Immune-surveillance
- Epitope-spreading

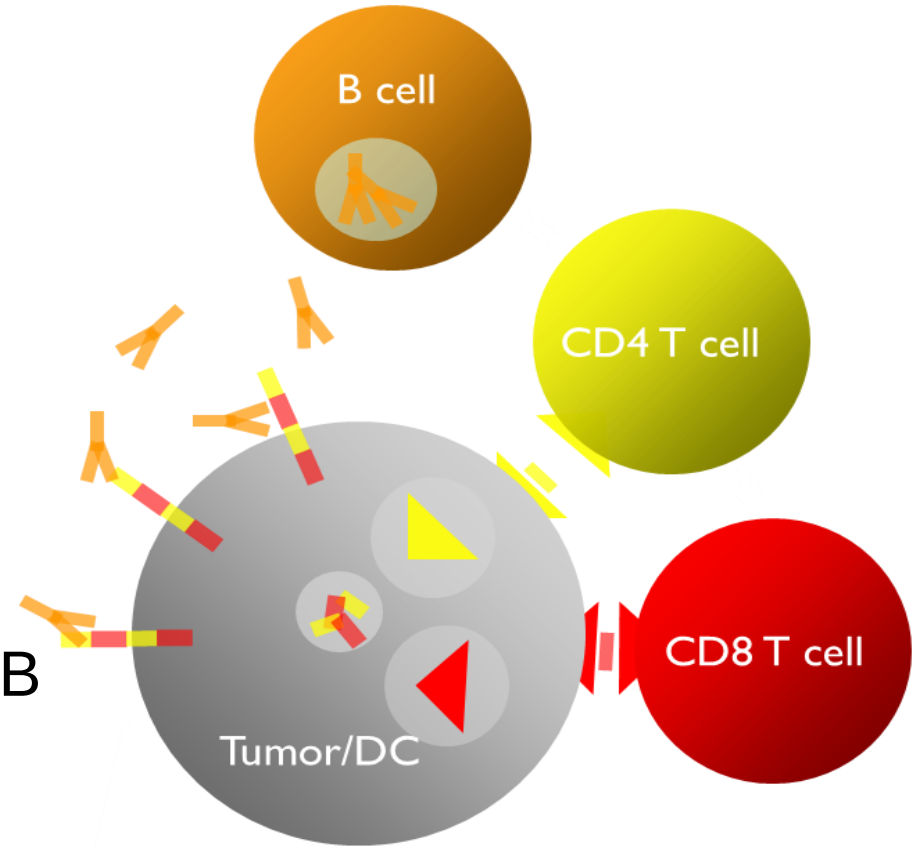
CD8 "cytolytic" T cells

- Tumor lysis

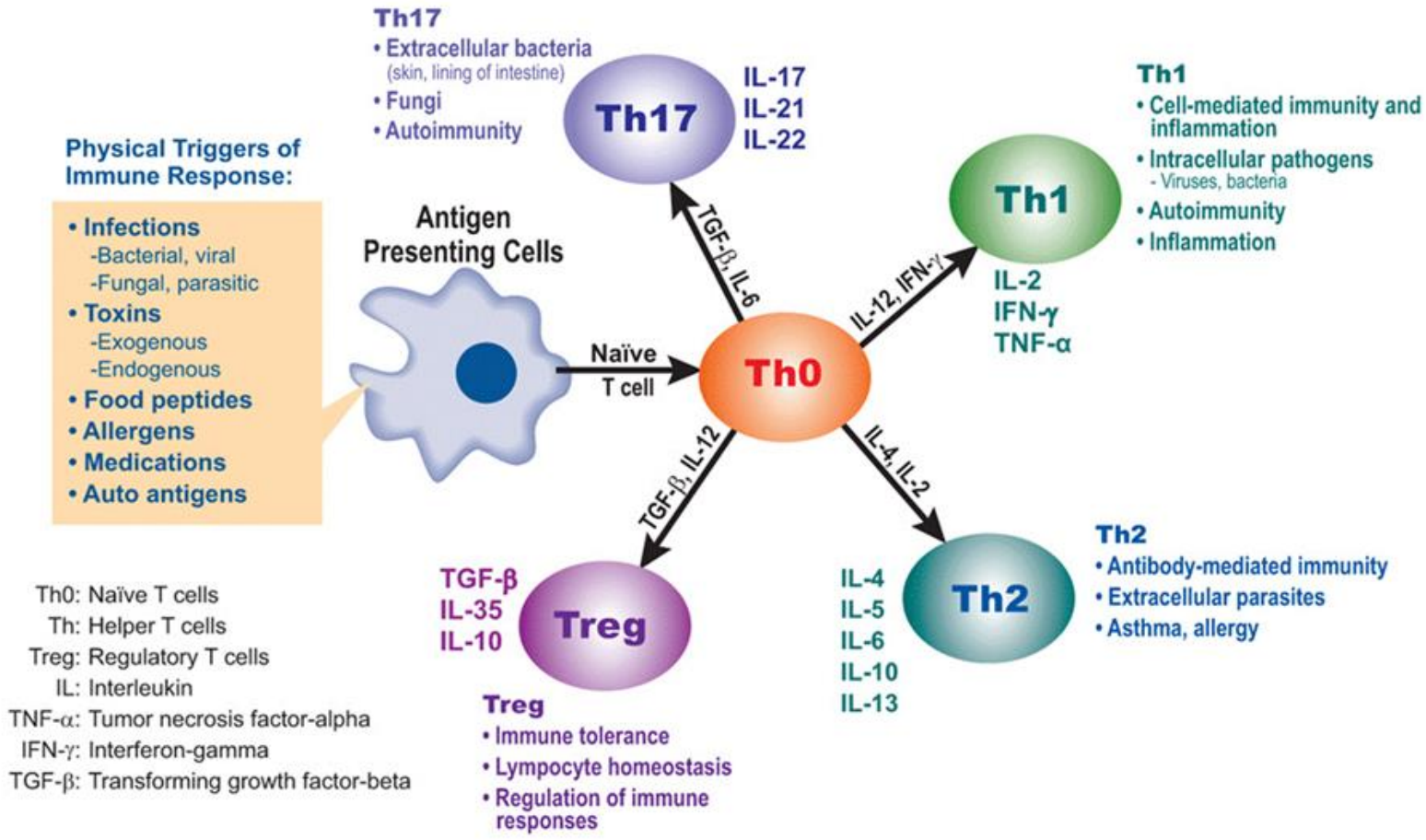
B cells

- Antibodies
- Signaling
- ADCC
- Complement

12 million unique T and B cells per teaspoon of blood



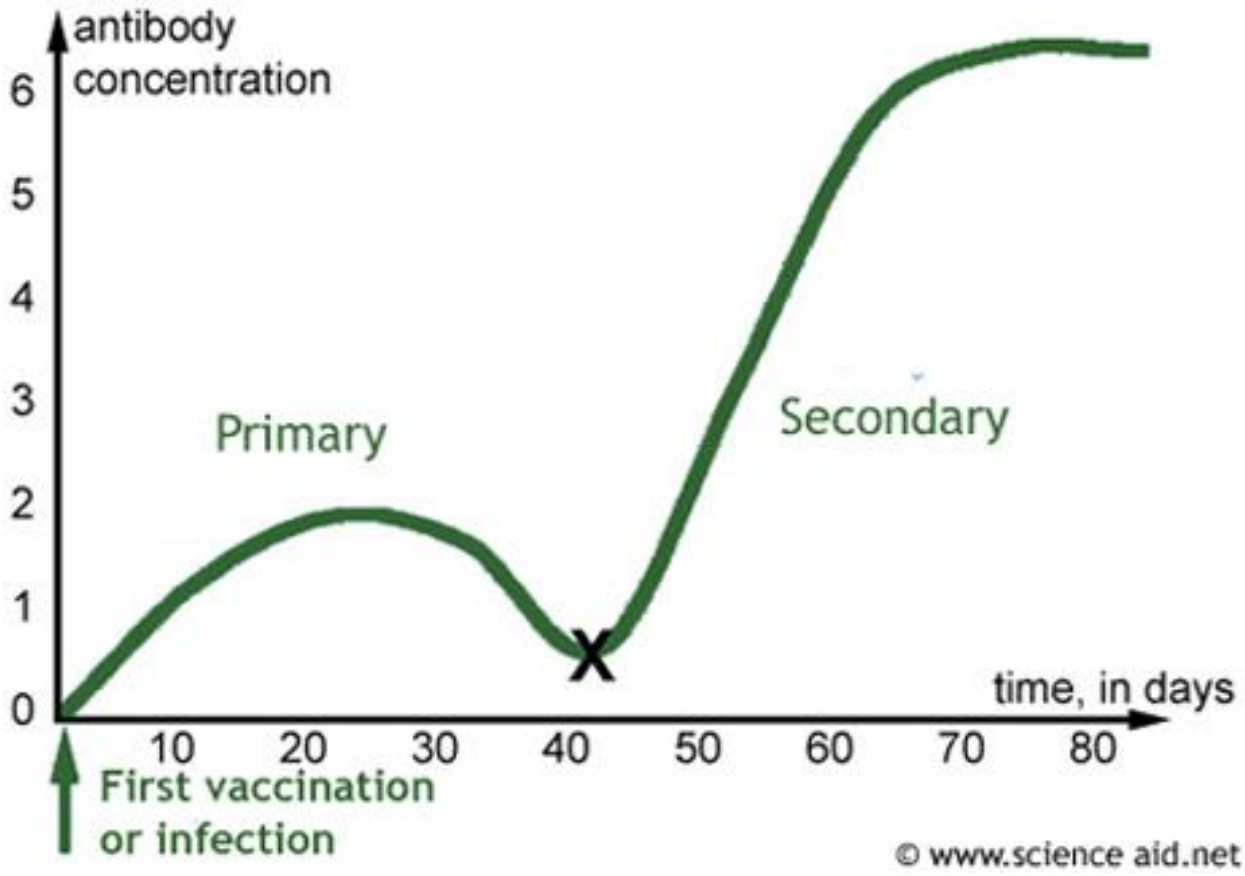
Differentiation of the adaptive immune response



Immune-based approaches for cancer

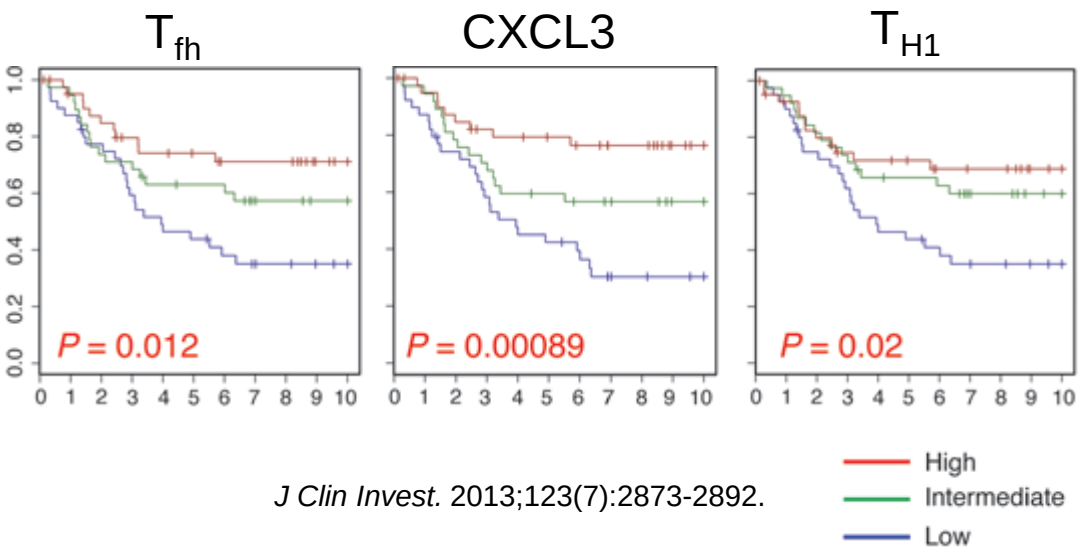
- Cancer vaccines
- Monoclonal and other antibodies
- Adoptive T cell therapies
- Immune checkpoint blockade and reversal of immune suppression

Vaccination is used to heighten the sensitivity of the immune system to tumor antigens



The Immune System Naturally Responds to Breast Cancer – The T Cell Response is Associated with Improved Survival

HER-2 Breast Cancer – 10 Year Survival Analysis



J Clin Invest. 2013;123(7):2873-2892.

Patients with Breast Cancer Demonstrate Elevated T cell and Antibody Immunity to Several Tumor Antigens

Disis et al., 2000, *Breast Cancer Research and Treatment*

Kalli et al., 2008, *Cancer Research*

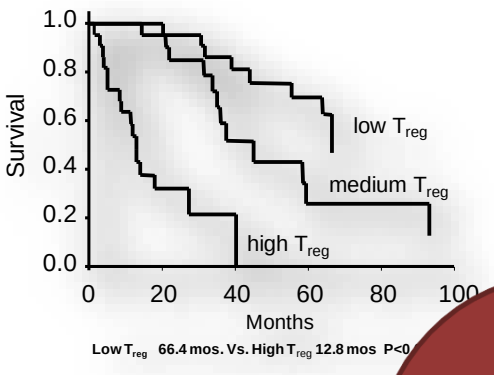
Karyampudi et al., 2013, *Plos One*

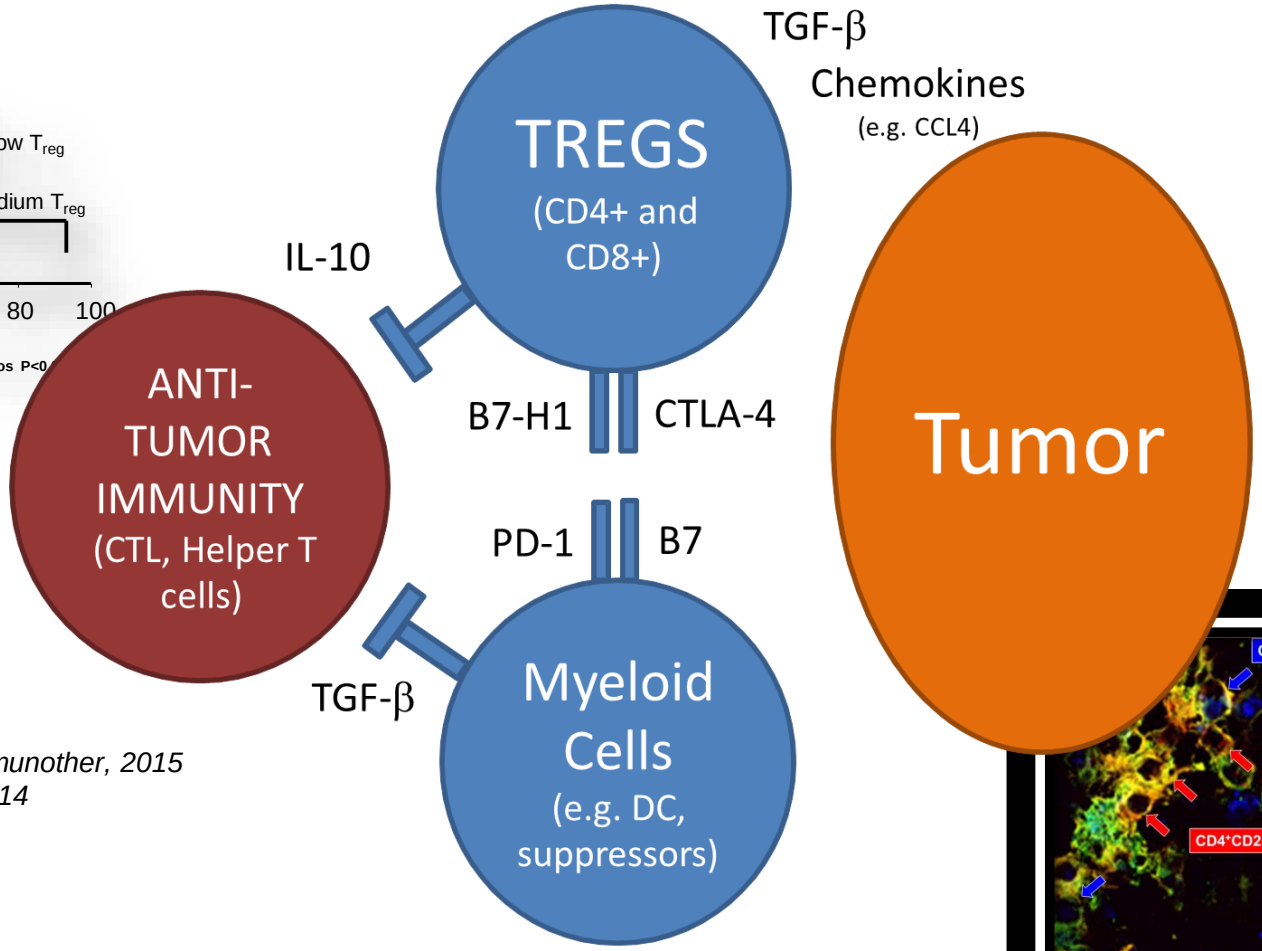
Krempski, et al. 2011, *Journal of Immunology*

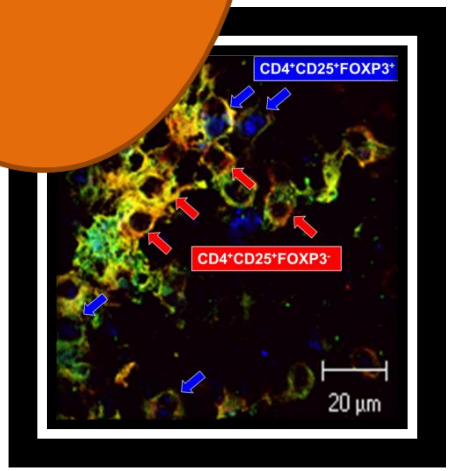
Karyampudi, et al., 2014, *Cancer Research*

Knutson, et al., *2006, Journal of Clinical Oncology*

Immune suppression in the cancer microenvironment blocks anti-tumor immunity







Cancer Res, 2016
Cancer Immunol and Immunother, 2015
Cancer Immunol Res, 2014
Plos One, 2013
Plos One, 2011
J Immunol 2013
J Immunol 2009
J Immunol 2006
Nature Med 2004
Nature Med 2003

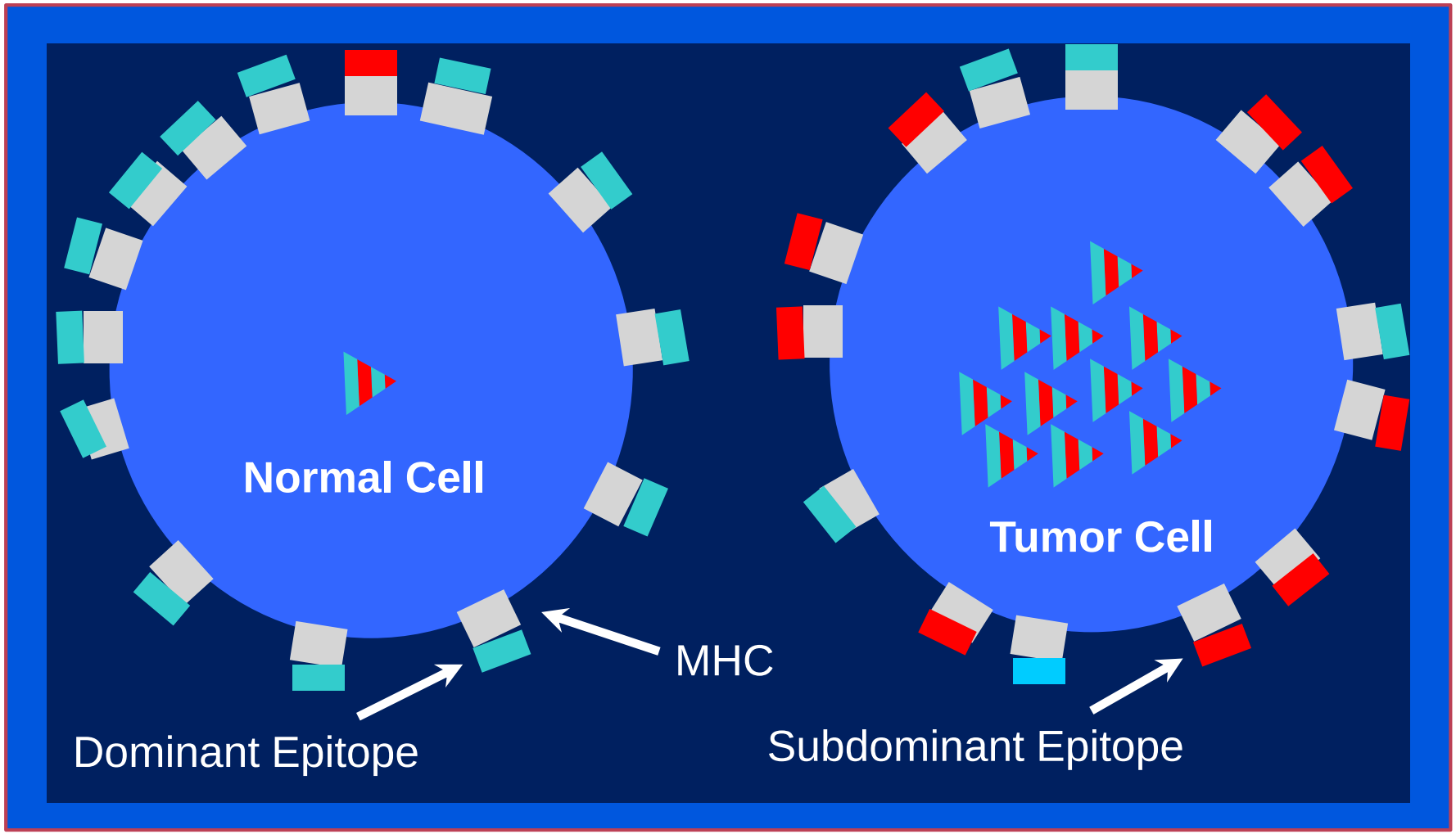
Target neoantigen choices for a cancer vaccine

- **Microbial neoantigens**
- **Amino acid mutation neoantigens.**
- **Frameshift / fusion neoantigens**
- **Splicing variant neoantigens**
- **Indel neoantigens**

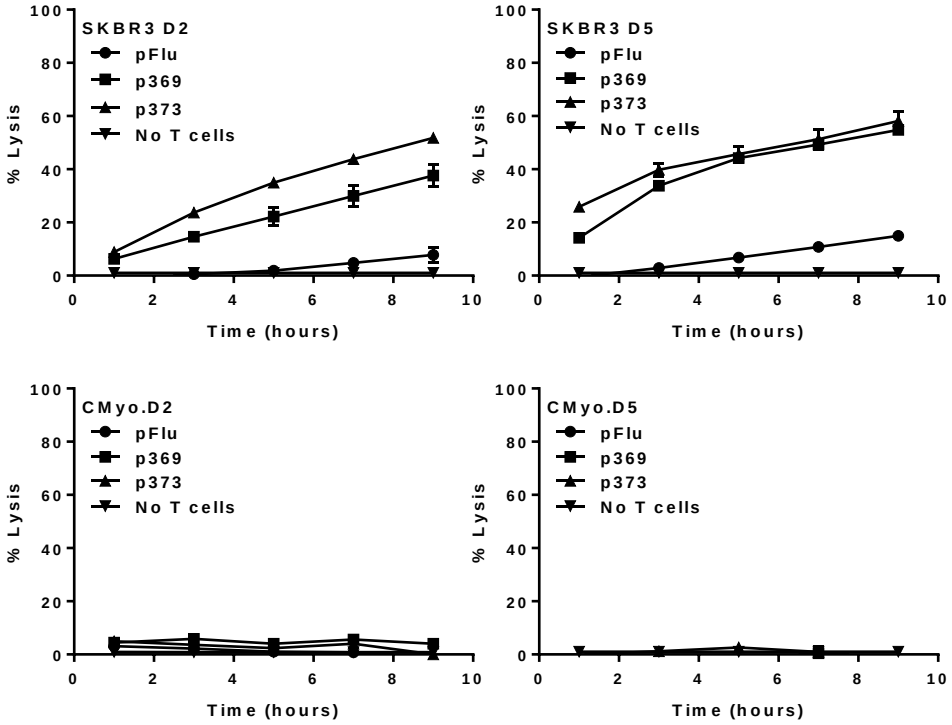
Mutation derived

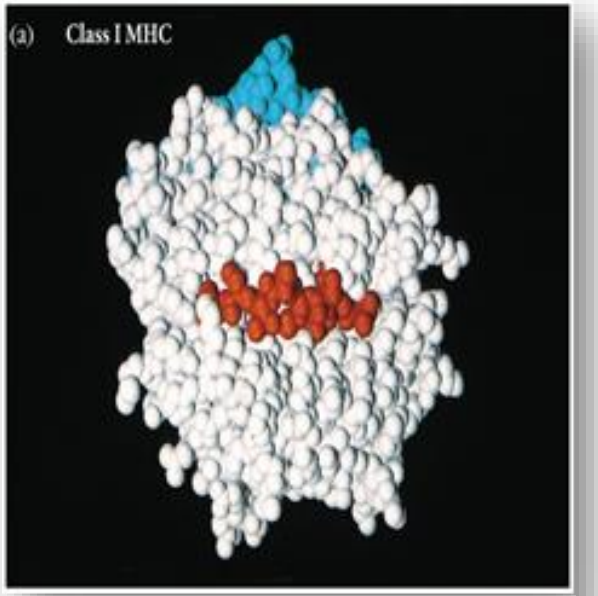
- **Nonmutated ‘self’ antigens (subdominant neoantigens)**

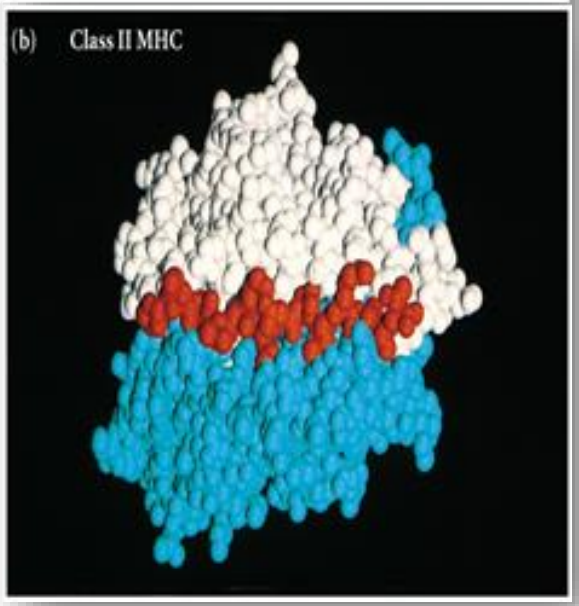
Overexpressed self proteins as a source of tumor neoantigens



Normal healthy HER2+ cardiomyocytes are not recognized by HER2 neoepitope specific T cells



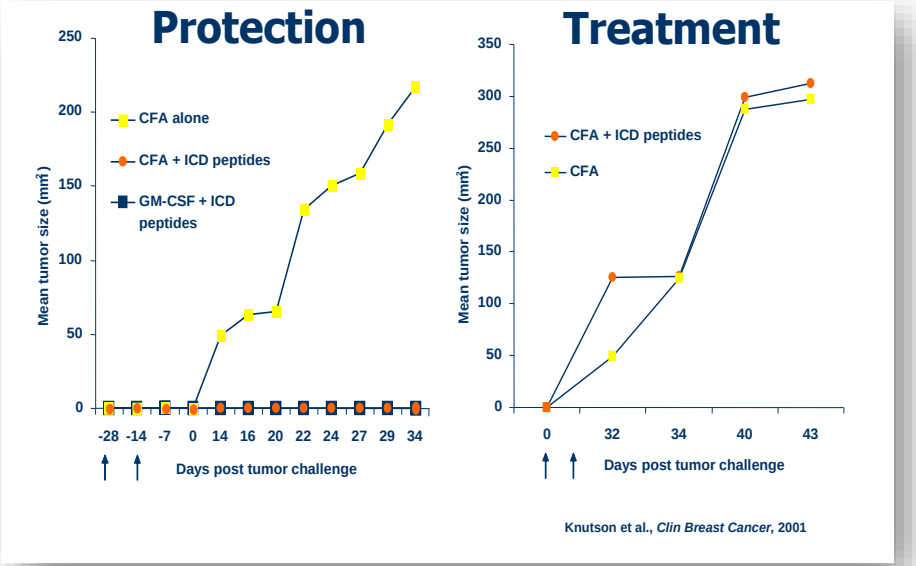




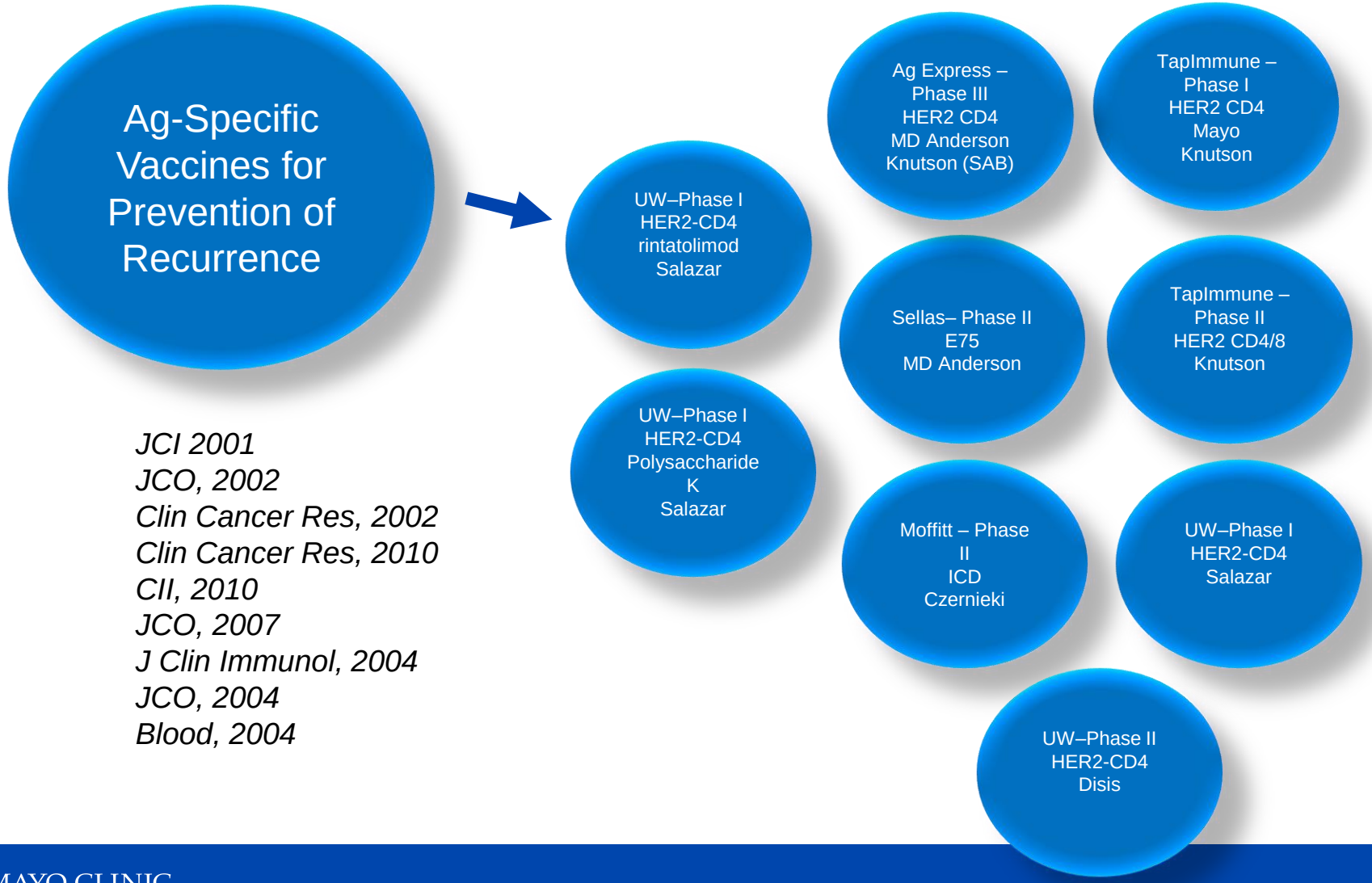
Early generation HER2 vaccines

- ECD Vaccine
- ICD Vaccine (Phase I/II)
- HLA-A2 Vaccine (Phase II)
- E75 Vaccine

Knutson KL, et al., JCI 2001
Disis ML, et al., JCO, 2002
Knutson KL, et al., Clin Cancer Res, 2002



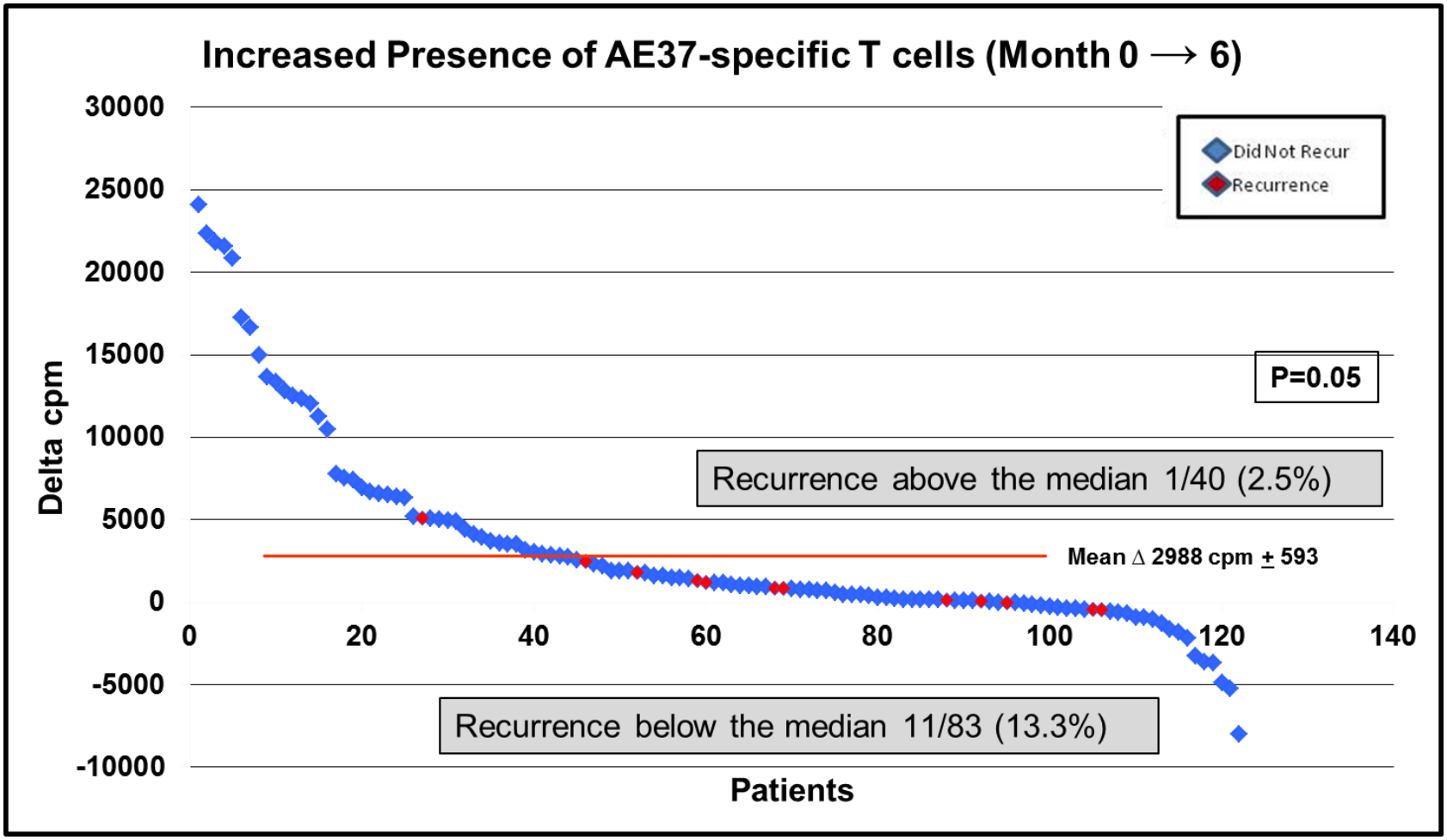
HER2 vaccines to protect against disease recurrence in breast cancer



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

Development of immunity to vaccine is associated with reduced relapse

increased response – reduced relapse



Courtesy of Eric von Hofe

Vaccine Prolongs Remission in Triple-Negative Breast Cancer

SAN FRANCISCO -- Treatment with a novel peptide vaccine appeared to delay disease recurrence in triple-negative breast cancer (TNBC) patients with low HER2 expression, a subgroup analysis of a phase II trial found.

At a median follow-up of 26.1 months, disease recurrence occurred in 7.5% of TNBC patients who received nelipepimut-S (NeuVax) compared with 26.7% in the control arm (HR 0.26, 95% CI 0.08-0.81, *P*=0.01), reported Guy T. Clifton, MD, of San Antonio Military Medical Center in Texas.

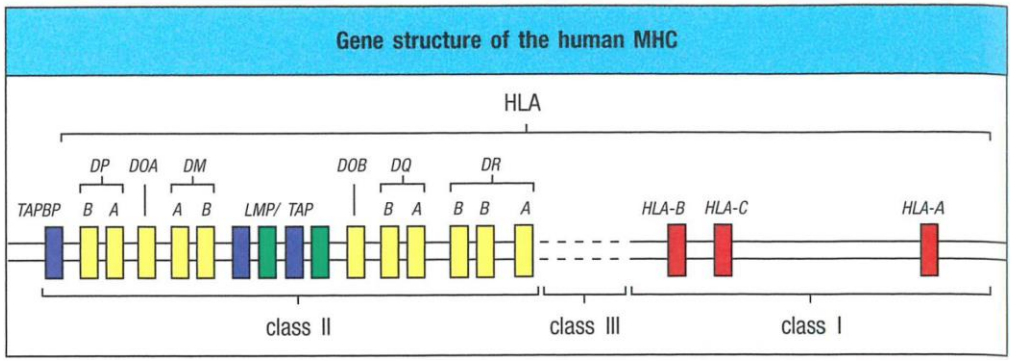
"We think the results are intriguing in light of what we now understand as far as triple-negative breast cancer being a more immunogenic subtype of breast cancer that's more responsive to immunotherapy," he said during his presentation here at the ASCO-SITC Clinical Immuno-Oncology Symposium.

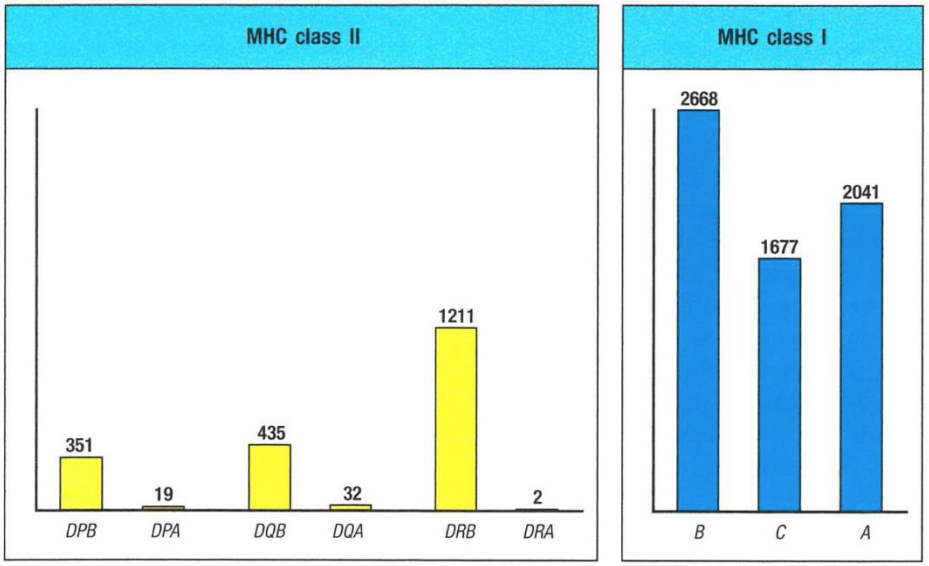
In the NeuVax and control arms, respectively, rates of disease-free survival (DFS) among the 97 TNBC patients were:

- 92.6% versus 70.2% at 24 months
- 82.3% versus 70.2% at 36 months

Human MHC Locus

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





Janeway, 9th Ed

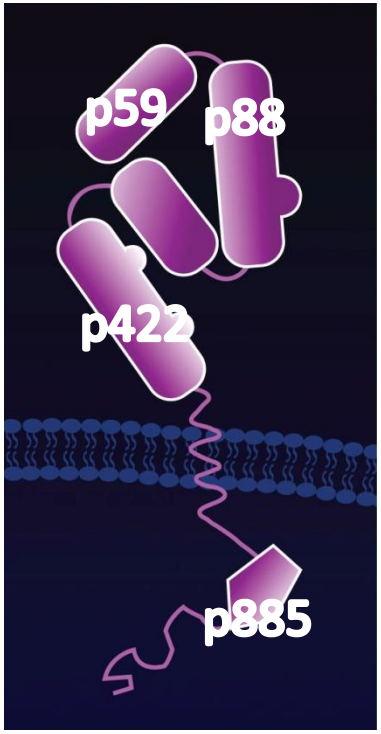
Binding of predicted HER2 neoantigens to purified HLA-DR

Sequence	Peptide Name	Position[¶]	IC_{50} nM to purified HLA													
			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
NLELTYLPTNASLSF	**HER-2/neu.59**	**59**	**4.9**	**7356**	**6.2**	**2.7**	**38**	**7.2**	**94**	**3055**	**30**	**141**	**105**	**23**	**ND**	**29**	**189**
LTYLPTNASLSFLQD	HER-2/neu.62	62	9.7	3364	19	16	80	15	426	4081	213	150	47	132	141	1633	173
IQEVQGYVLIAHNQV	HER-2/neu.77	77	57	7763	111	178	102	35	213	302	165	3438	103	75	13,508	546	1361
YVLIAHNQVRQVPLQ	HER-2/neu.83	83	28	454	53	104	1185	92	300	358	208	302	1.9	679	649	124	18
HNQVRQVPLQRLRIV	**HER-2/neu.88**	**88**	**950**	**971**	**840**	**78**	**1303**	**80**	**85**	**6644**	**21**	**42**	**270**	**340**	**ND**	**18**	**173**
MEHLREVRAVTSANI	HER-2/neu.347	347	9.6	2970	533	12	200	9.7	95	4345	262	221	23	86	ND	81	216
LREVRAVTSANIQEF	HER-2/neu.350	350	17	3913	43	8.2	50	12	456	5187	661	161	1.5	27	ND	163	94
LSVFQNLQVIRGRIL	**HER-2/neu.422**	**422**	**1.3**	**345**	**6.3**	**33**	**26**	**7.1**	**148**	**859**	**9.6**	**486**	**80**	**33**	**ND**	**67**	**17**
RGRILHNGAYSLTLQ	HER-2/neu.432	432	2.4	710	480	129	2845	5.6	5077	430	773	40	1.3	5.4	358	562	82
LRSLRELGSGLALIH	HER-2/neu.455	455	7.1	ND	896	14	603	142	1075	594	309	498	16	24	16,142	549	726
VLGVVFGILIKRRQQ	HER-2/neu.666	666	67	2449	177	335	101	17	35	ND	12	268	17	185	ND	958	38
SRLLGICLTSTVQLV	HER-2/neu.783	783	80	2923	85	13	90	9.0	634	137	80	446	4.7	39	3567	481	392
PIKWMALESILRRRF	**HER-2/neu.885**	**885**	**12**	**30**	**14**	**250**	**161**	**664**	**312**	**3620**	**133**	**66**	**349**	**3.3**	**ND**	**62**	**3.4**
IKWMALESILRRRFT	HER-2/neu.886	886	16	10	37	1075	435	1795	515	9282	136	241	1118	11	ND	340	3.3
FSRMARDPQRFVVIQ	HER-2/neu.976	976	29	35	512	2224	855	1423	798	1481	49	6867	240	1408	901	227	45

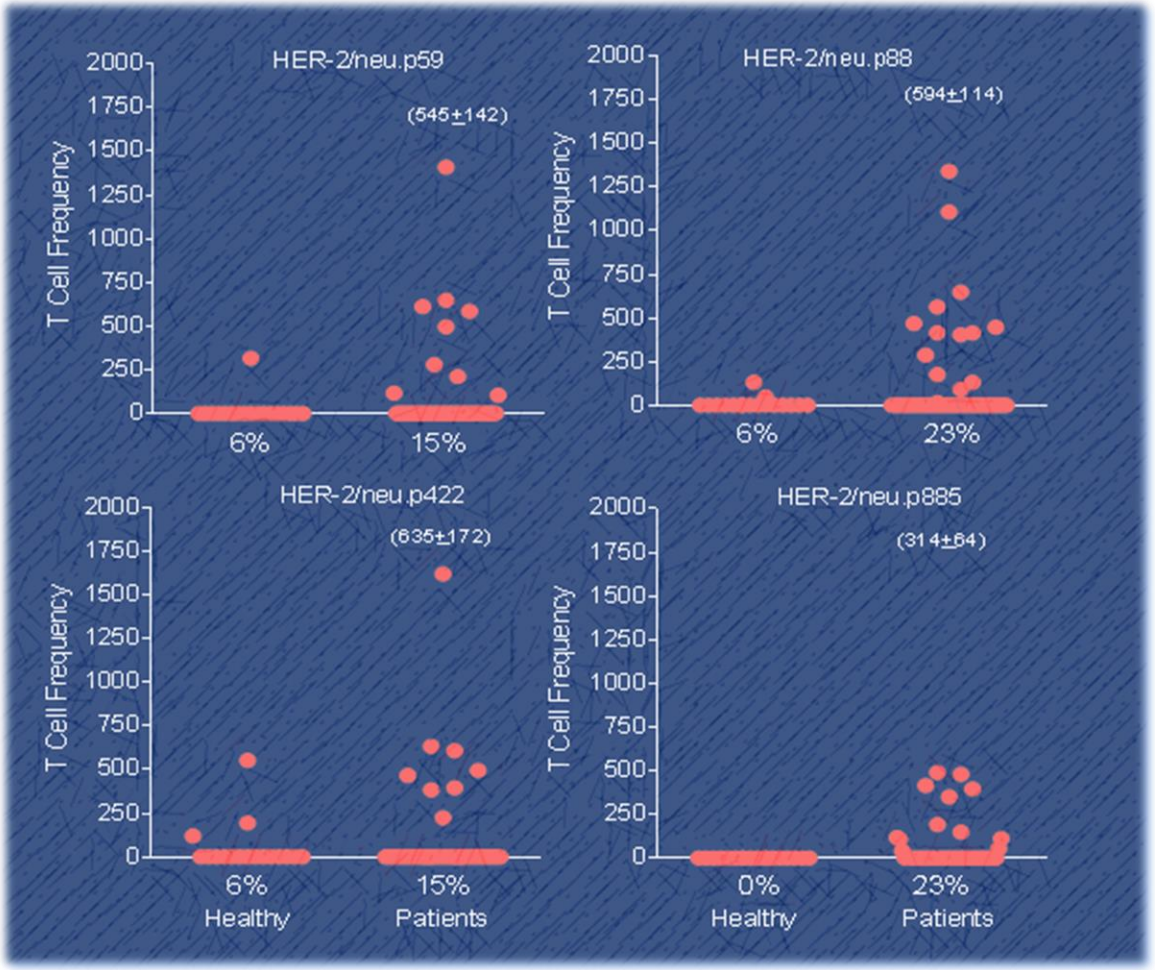
[¶]Position of N-terminal amino acid; ND=not determined; Peptides that constitute degenerate pool are in bold

Karyampudi, *Cancer Res*, 2010

Detection of pre-existent immunity

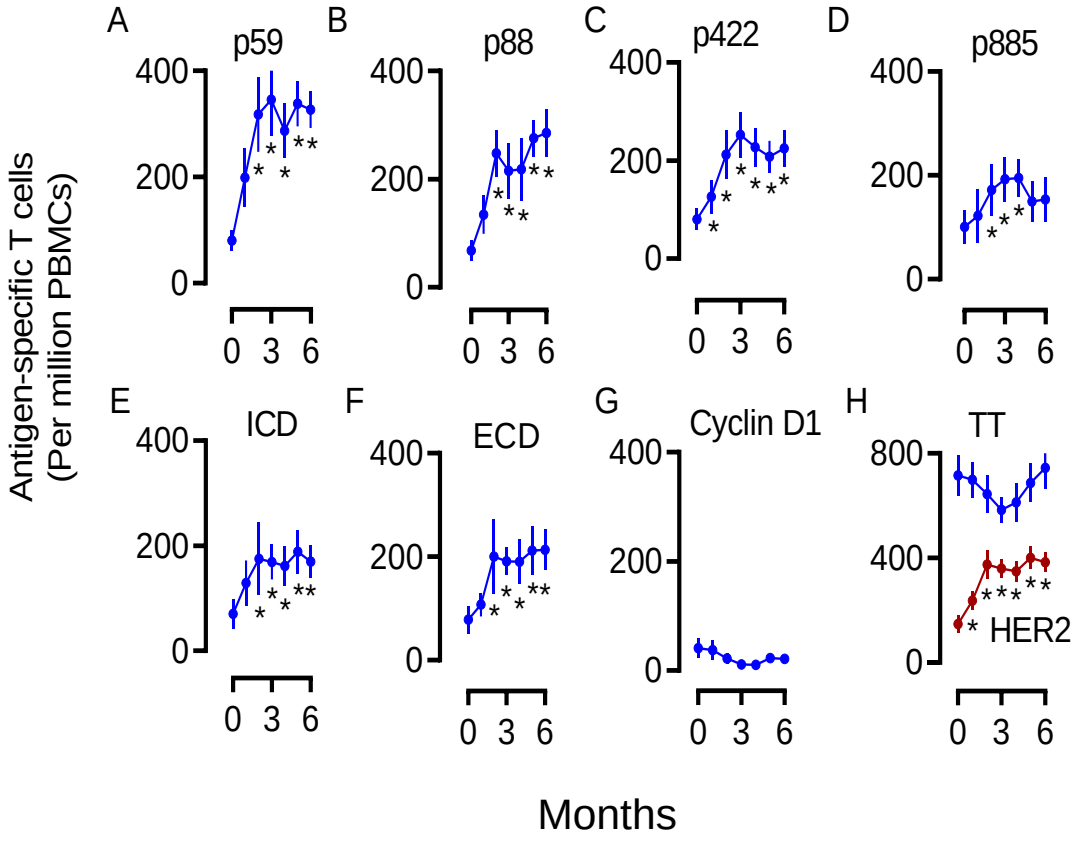


DRB1*0101, DRB1*0301
DRB1*0401, DRB1*0404
DRB1*0405, DRB1*0701
DRB1*0802, DRB1*0901
DRB1*1101, DRB1*1201
DRB1*1302, DRB1*1501
DRB3*0101, DRB4*0101
DRB5*0101



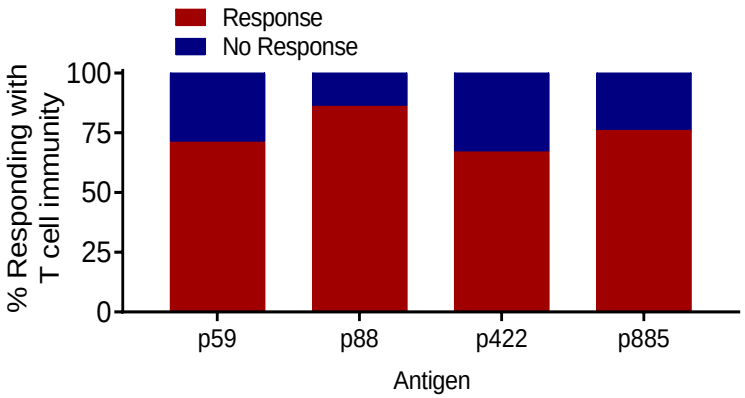
Karyampudi et. al., Clin Cancer Res. 2010
Knutson KL and Ishioka G, 2007, HLA DR binding peptides and their uses. Patented 12/740,562.

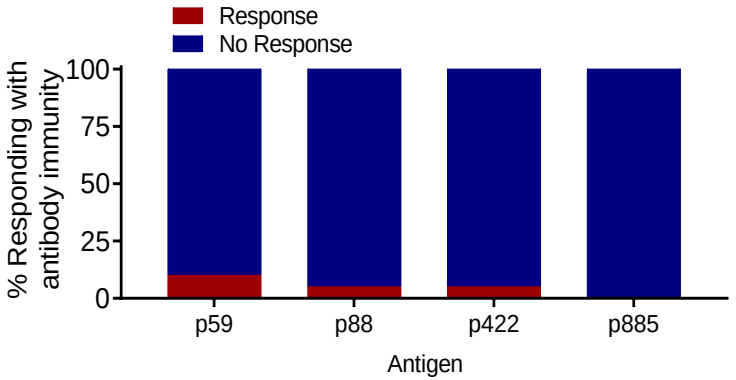
Vaccine induces immunity to naturally processed antigens

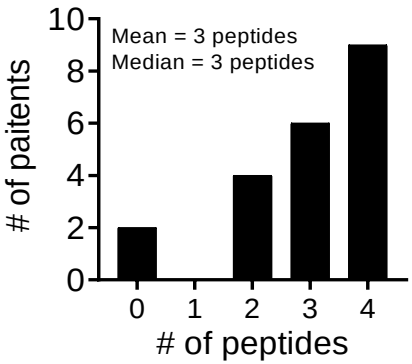


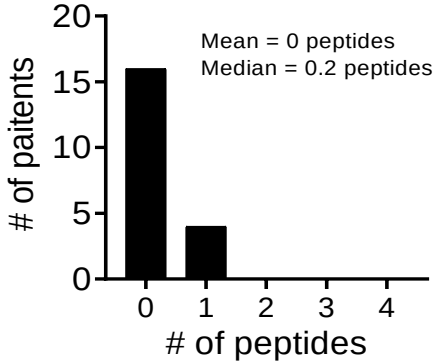
Knutson et. al., 2019 under review

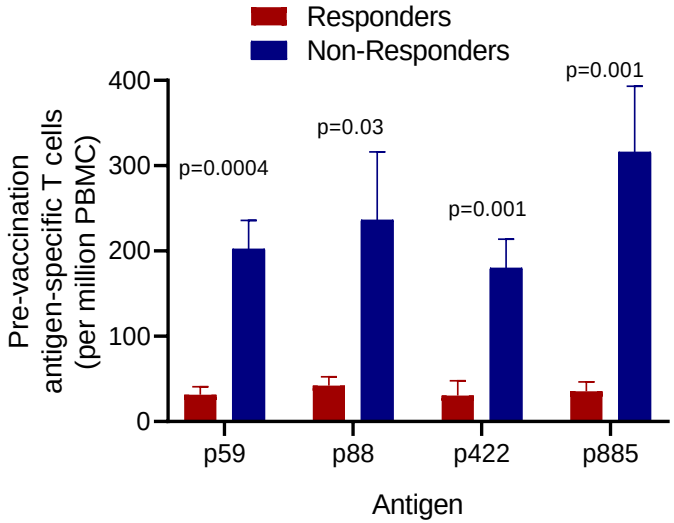
Majority of patients can be vaccinated



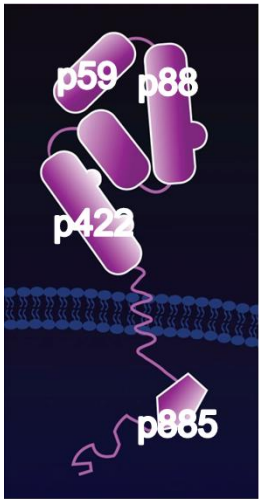








Generation of durable HER2-specific T cells in majority of patients with resected HER2 breast cancer



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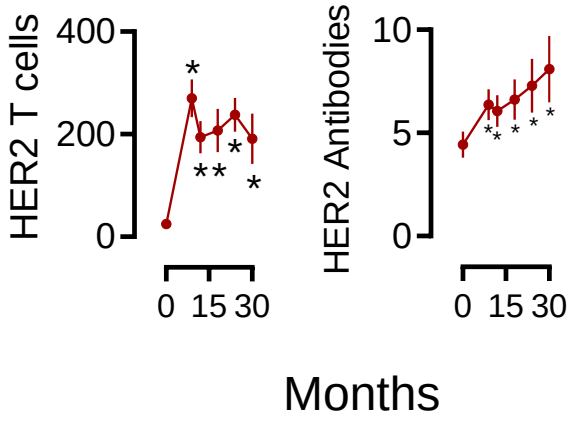
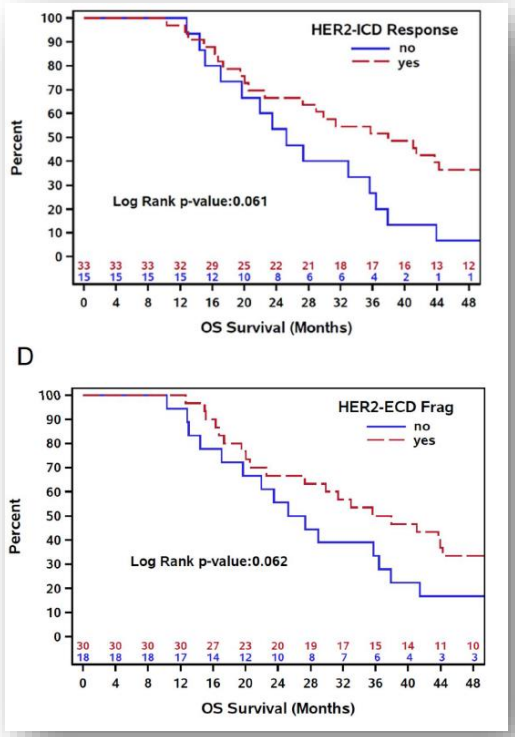
DRB1*1302, DRB1*1501
DRB3*0101, DRB4*0101
DRB5*0101

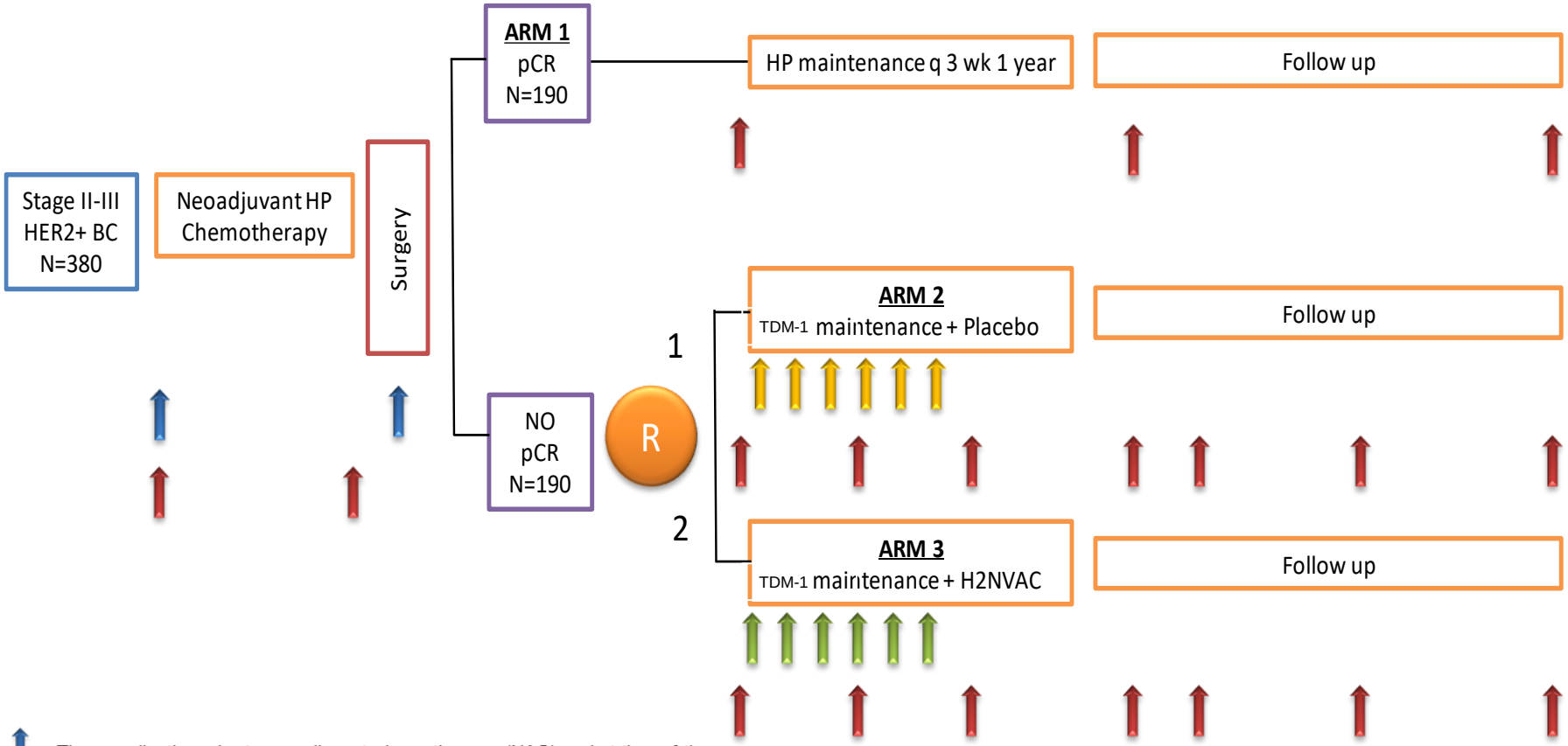


Knutson et. al., 2019 under review



Norton, *Breast Cancer Res Treat,* 2018
Knutson, *Cancer Res* 2016
Taylor, *Clin Cancer Res*, 2007

BC170530: Phase II resected advanced HER2+ breast cancer



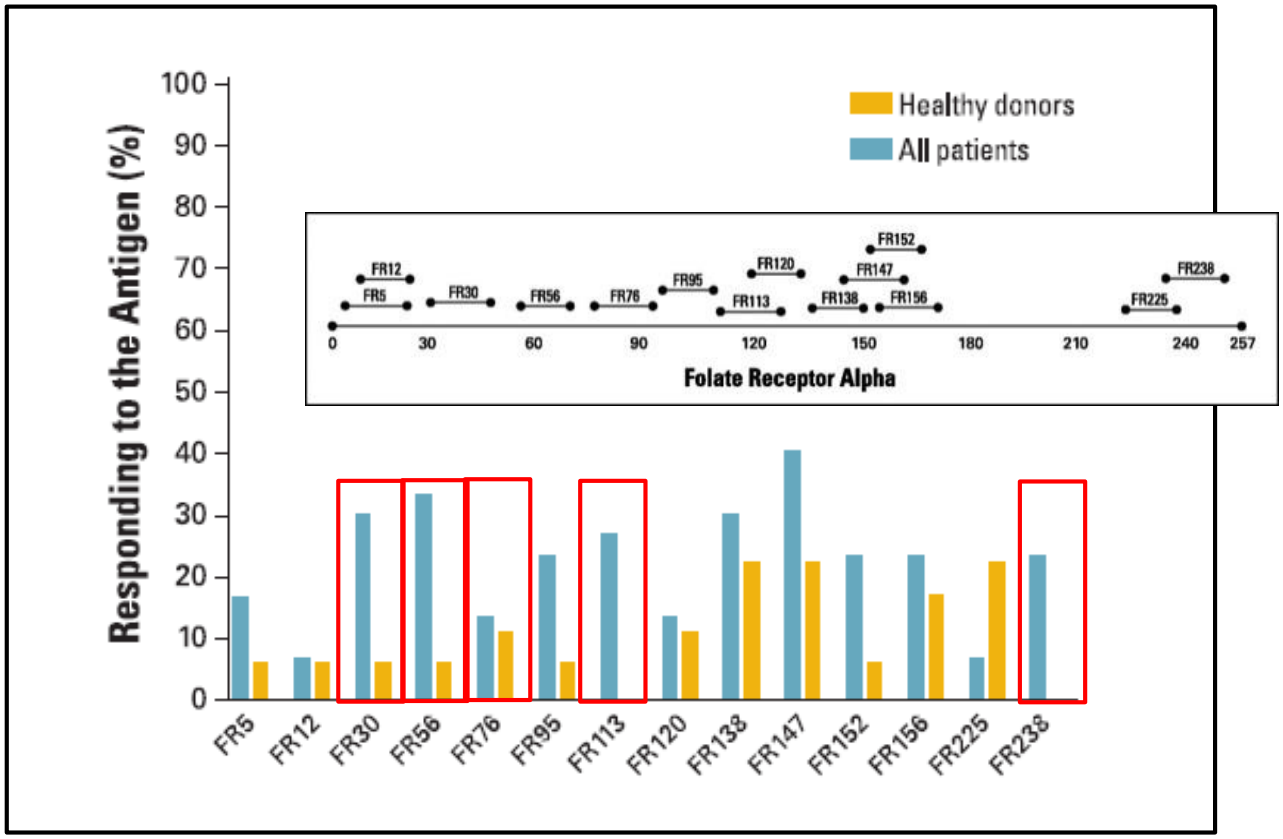
Tissue collection prior to neoadjuvant chemotherapy (NAC) and at time of the surgery.

Research blood draw prior to NAC and at the time of surgery. For patients with pCR, research blood draw will be collected on cycle 1 of maintenance with trastuzumab and pertuzumab (HP), 30 days and 24 months after completion of HP. For patients without pCR, who will be randomized, research blood draw will be collected on cycle 1, 4, 7 of maintenance HP as well as 30 days, 3, 12, and 24 months after completion of HP.

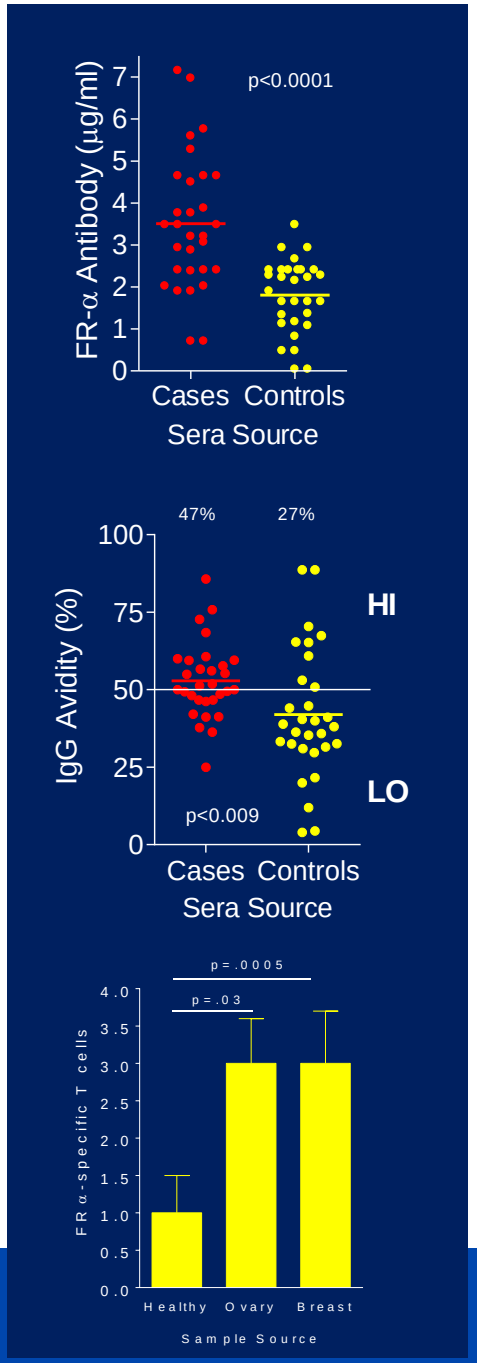
Placebo vaccination every 4 weeks for 6 cycles.

HER2 vaccination every 4 weeks for 6 cycles.

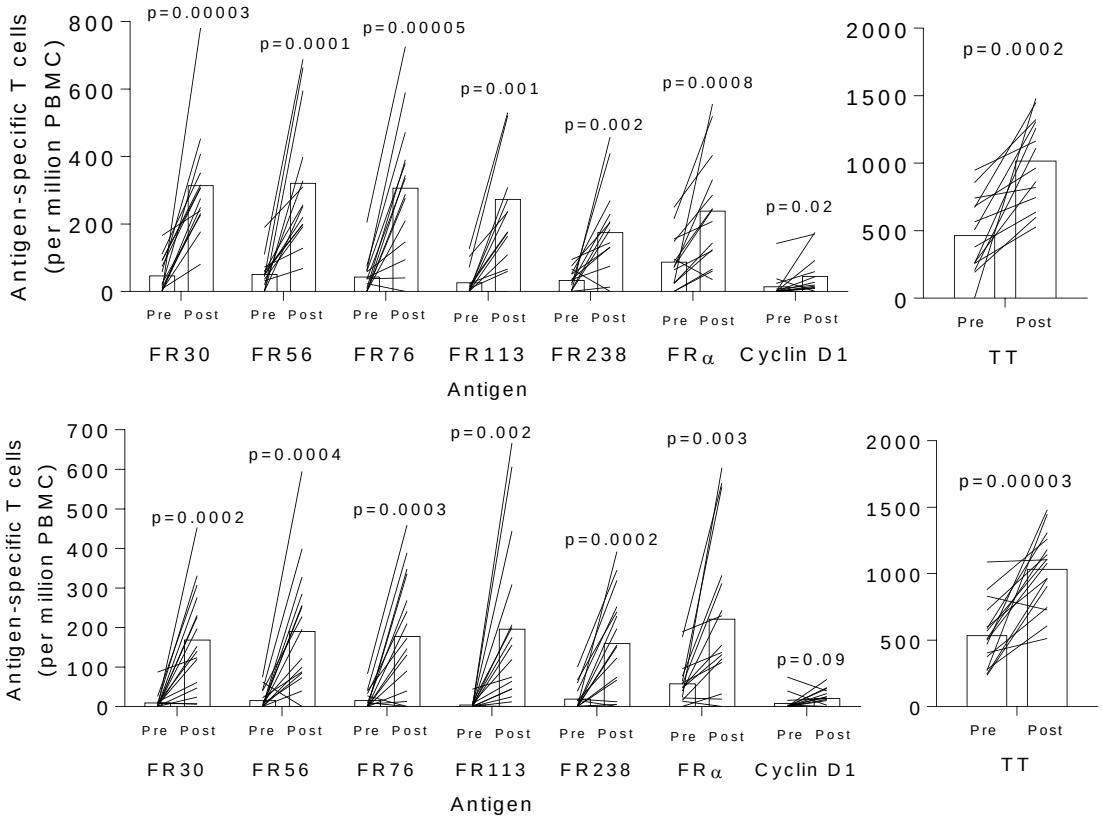
Spontaneous immunity to the folate receptor alpha in cancer patients



Knutson, K. L. et al. **JCO;** 24:4254-4261 2006



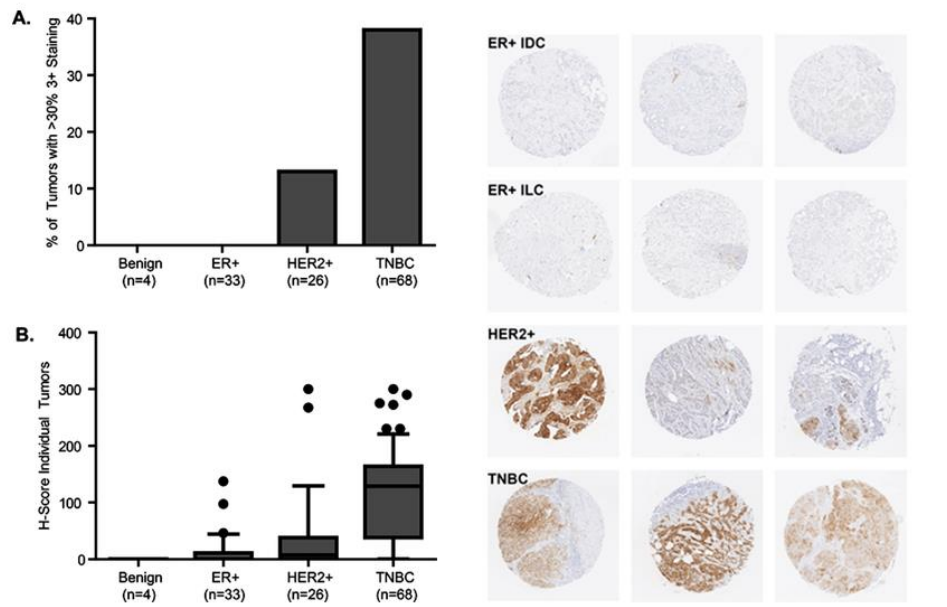
Folate receptor alpha peptide vaccine generates immunity in breast and ovarian cancer patients



Kalli, Block *Clin Cancer Res*, 2018

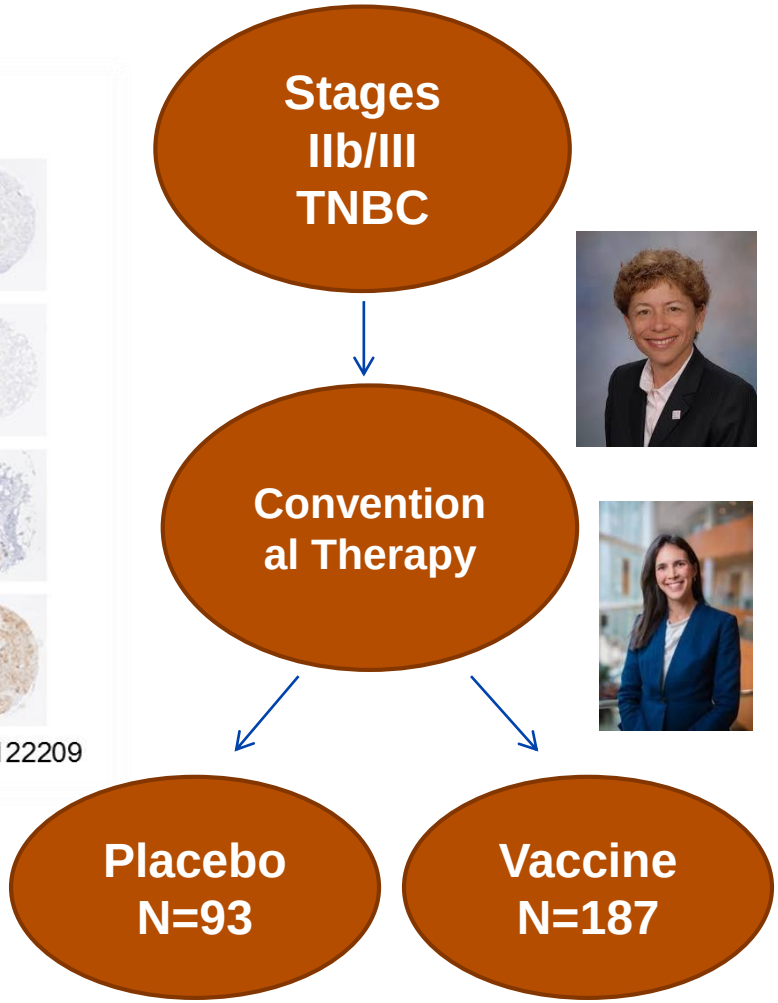
BC141410: FRa Vaccination to Prevent Progression of Triple Negative Breast Cancer

FRa is preferentially overexpressed in TNBC

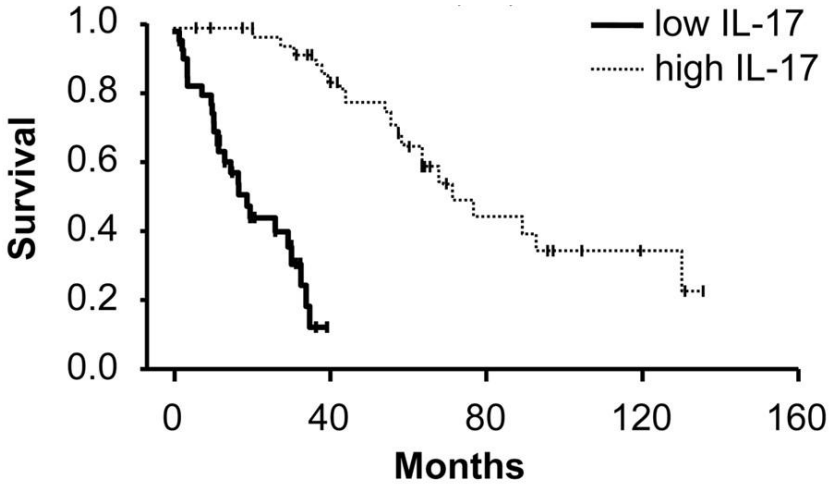


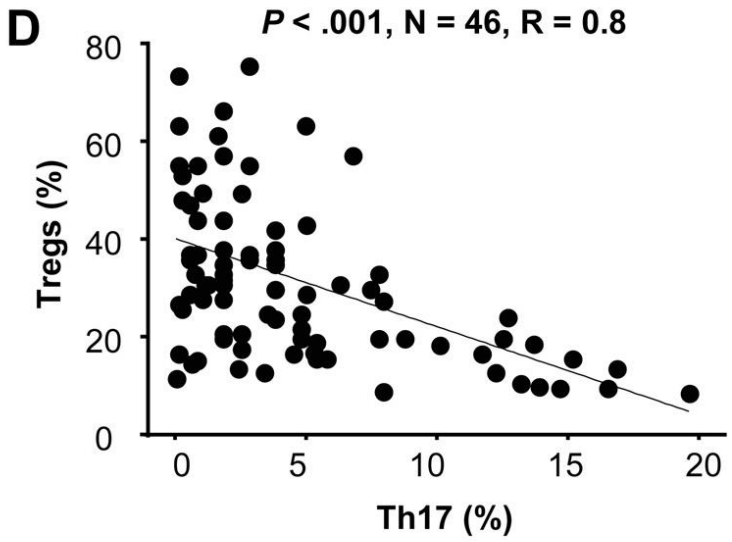
Necela BM, PLoS ONE 10(3): e0122209. doi:10.1371/journal.pone.0122209

- **Multicenter Phase II Trial to Test Whether Vaccine Prevents Recurrence in Patients Diagnosed and Treated for TNBC**



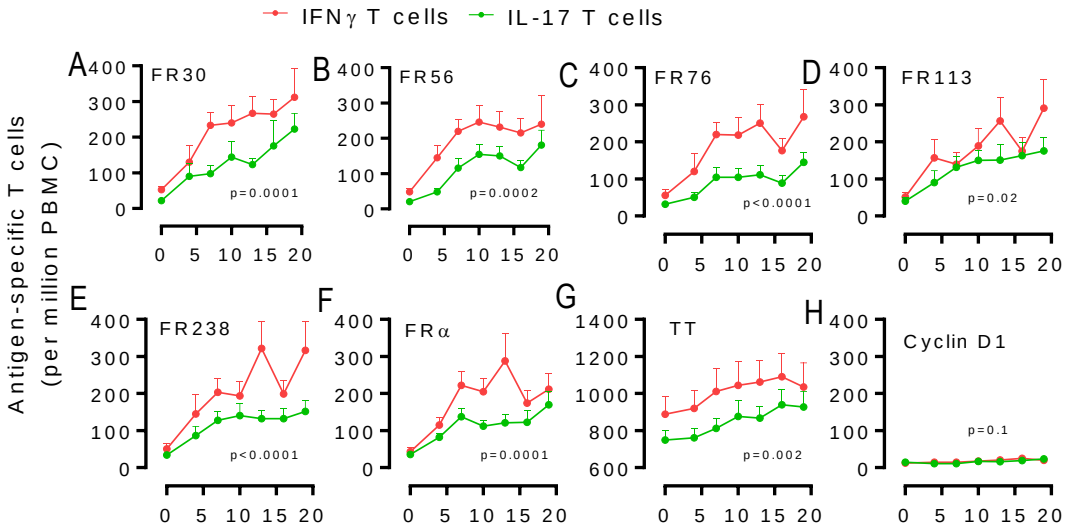
IL-17 association with improved survival in ovarian cancer

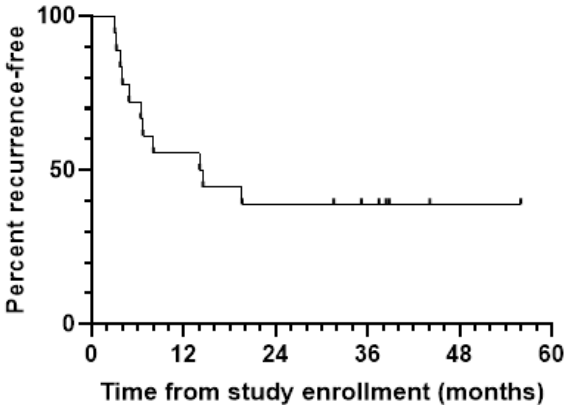




Kryczek *et al.,* JI 2011

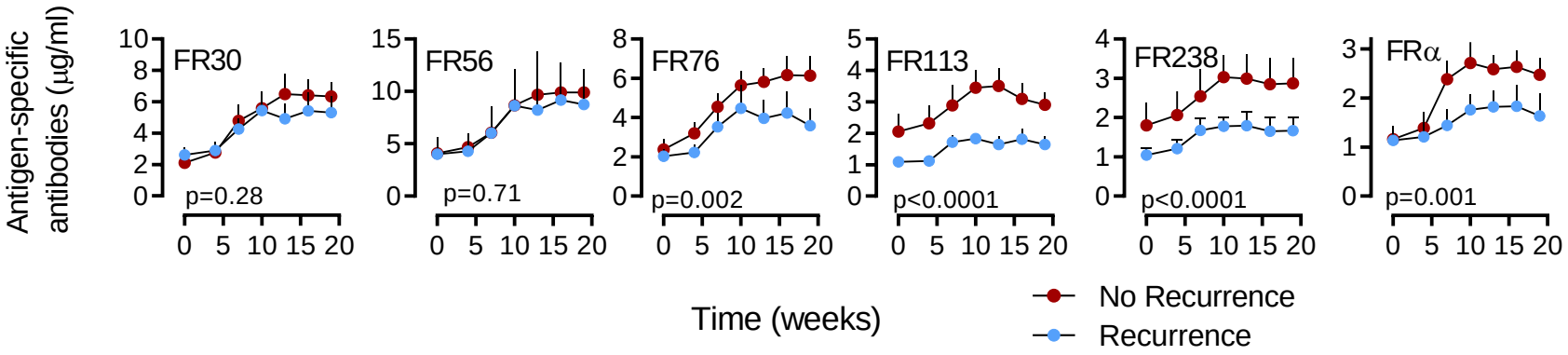
Th17-inducing vaccines generate Th1 and Th17 immunity





Block, 2017, Unpublished Observations, SPORE P8

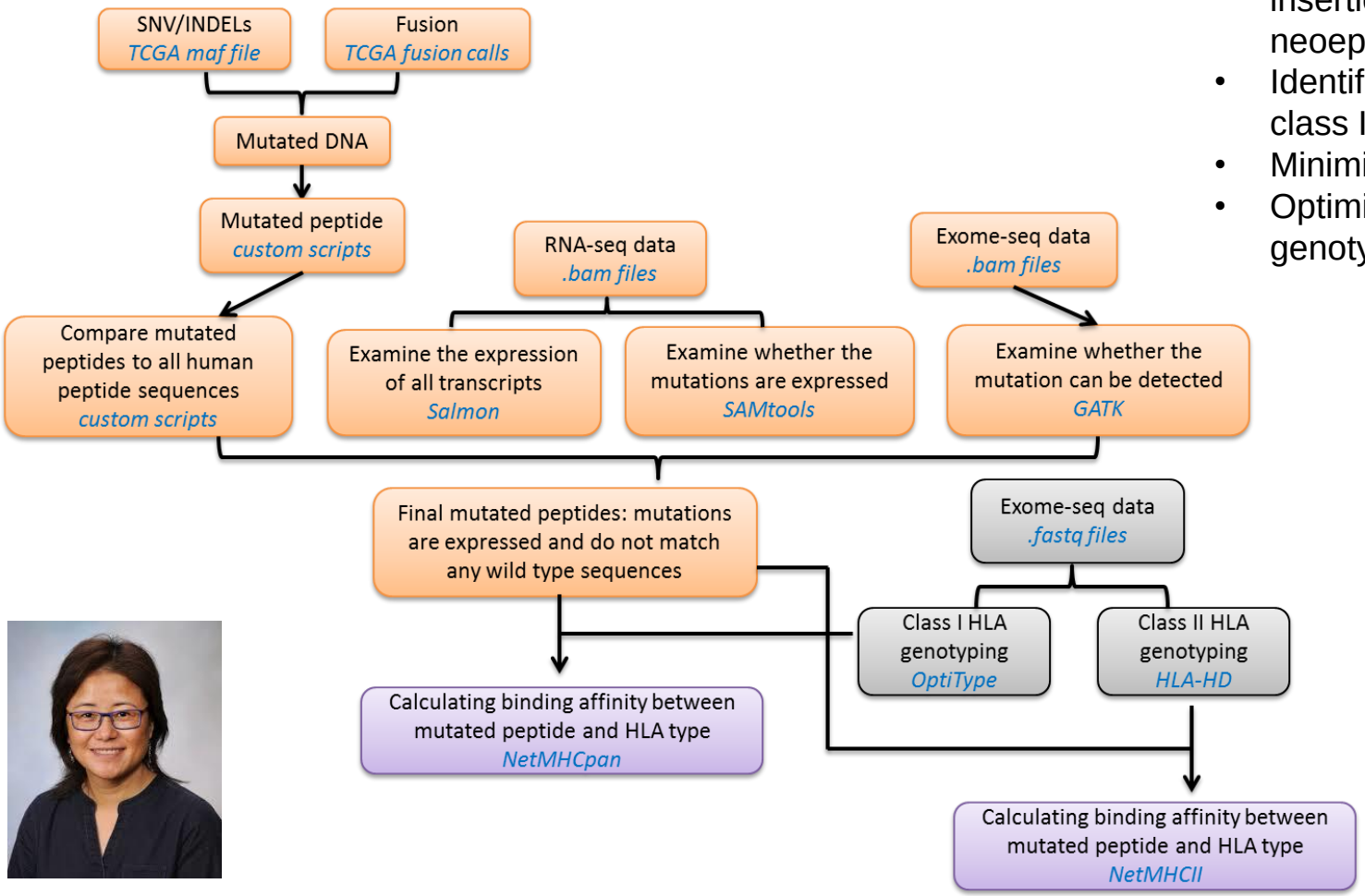
The generation of antibody immunity is associated with improved survival



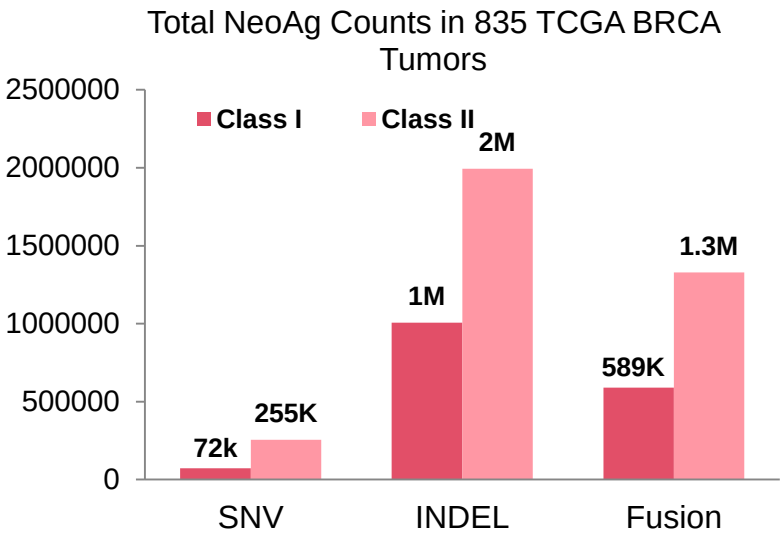
Block, 2017, Unpublished Observations, SPORE P8

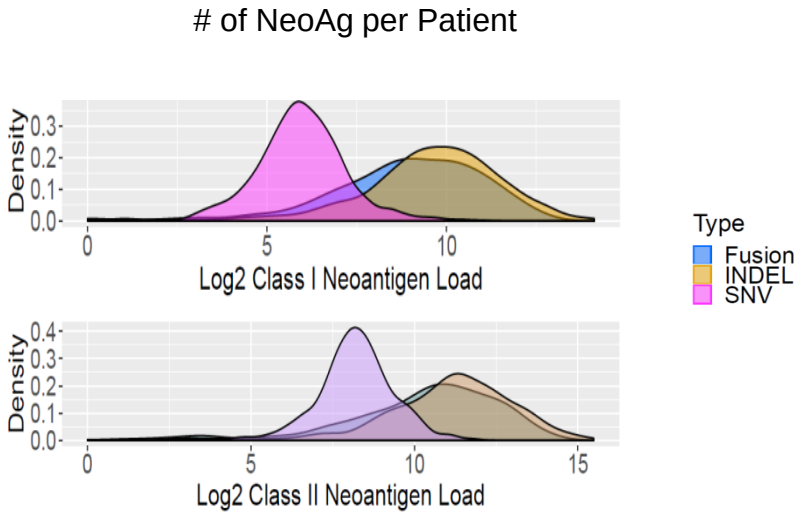
Neoantigen discovery bioinformatics pipelines

- Maximized discovery of insertional and deletional neoepitopes
- Identification of MHC class I and class II
- Minimized cross-reactivity
- Optimized HLA genotyping

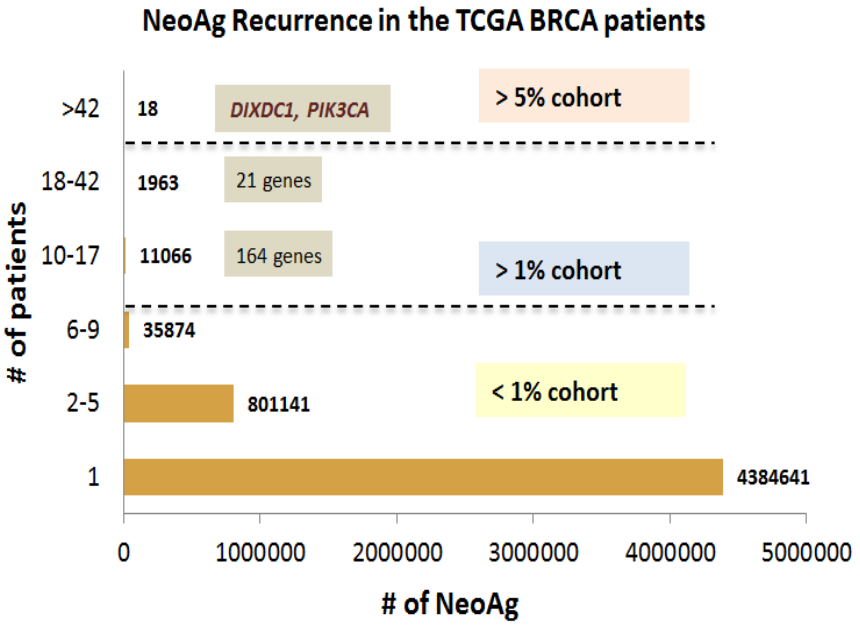


Breast cancer appears to be enriched in the type of neoantigens that are highly immunogenic





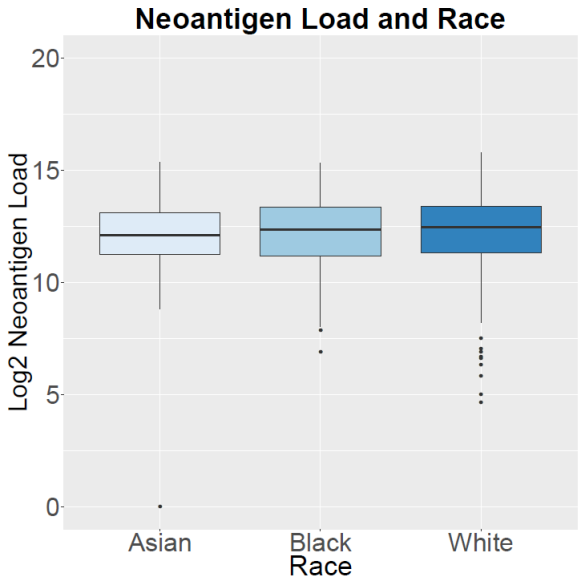
Neoantigens are largely private making every product different

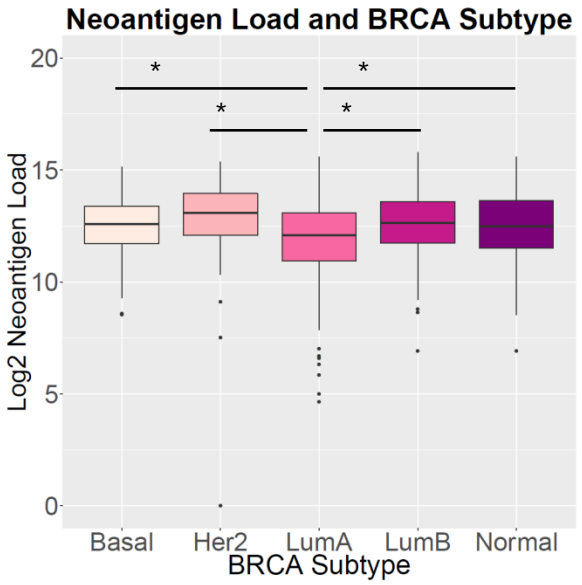


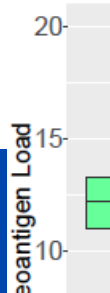
Peptide	# Patients	Gene	Mutation type	Mutation
EALEYFMKQMNDARH	71	PIK3CA	SNV	p.M1004I, p.H1047R
ALEYFMKQMNDARHG	70	PIK3CA	SNV	p.M1004I, p.H1047R
LEYFMKQMNDARHGG	70	PIK3CA	SNV	p.M1004I, p.H1047R
QEALEYFMKQMNDAR	68	PIK3CA	SNV	p.M1004I, p.H1047R
EYFMKQMNDARHGGW	66	PIK3CA	SNV	p.M1004I, p.H1047R
YFMKQMNDARHGGWT	57	PIK3CA	SNV	p.M1004I, p.H1047R
FMKQMNDARHGGWTT	47	PIK3CA	SNV	p.M1004I, p.H1047R
GRTAVGTTRIFRKRN	48	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
MGRTAVGTTRIFRKR	48	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
VTYALHGQY	48	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
KQWFSPSNGRKRSYF	47	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
LSKQWFSPSNGRKRS	47	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
RTAVGTTRIFRKRNG	47	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
SKQWFSPSNGRKRSY	47	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
QWFSPSNGRKRSYFS	46	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
RIFRKRNGGSKENDI	45	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
TRIFRKRNGGSKEND	45	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs
LMGRTAVGTTRIFRK	44	DIXDC1	FS INDEL	p.S60fs, p.P61fs, p.S271fs, p.P272fs

7

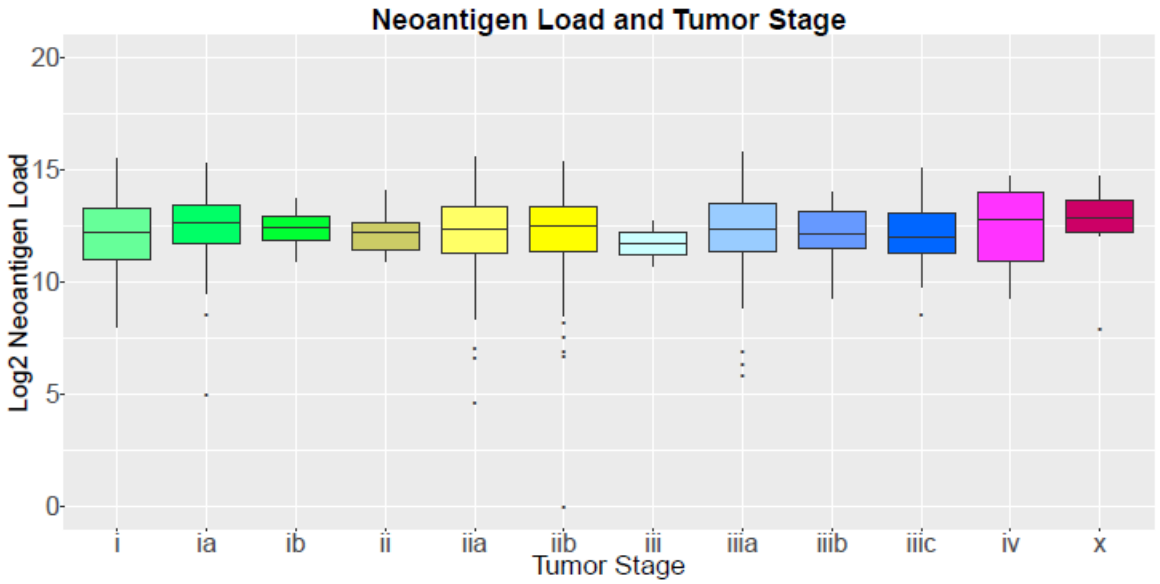
Mutation rates in different types of breast cancer



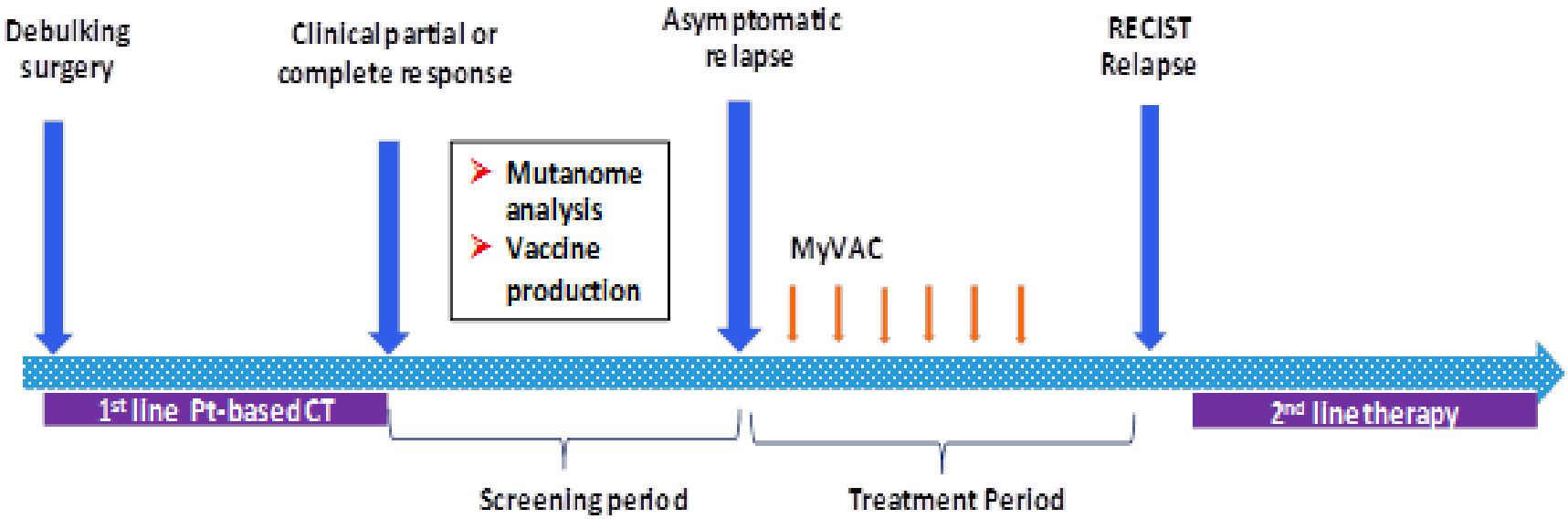




Mutation rates in different types of breast cancer

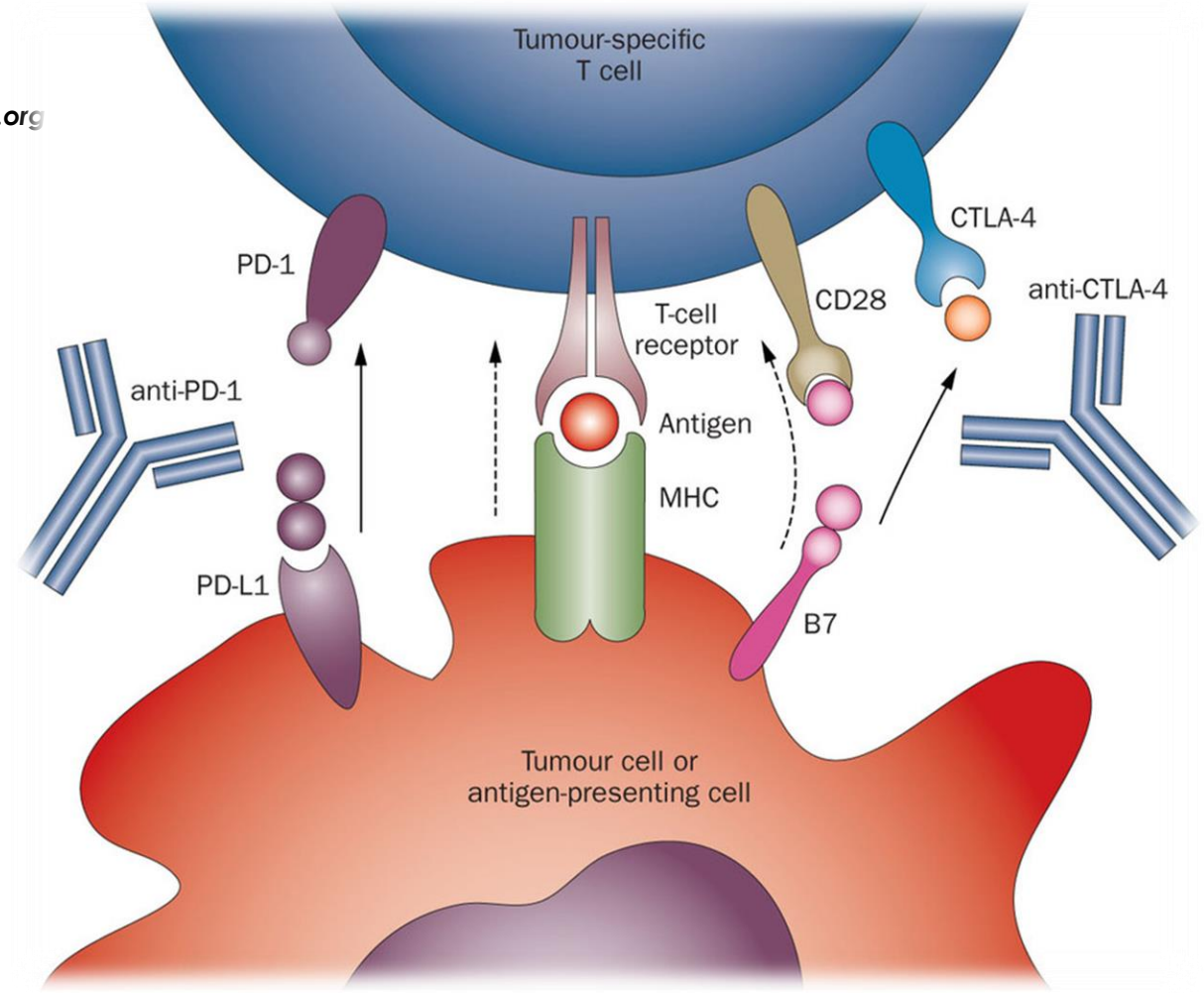


Neoantigen-based trial

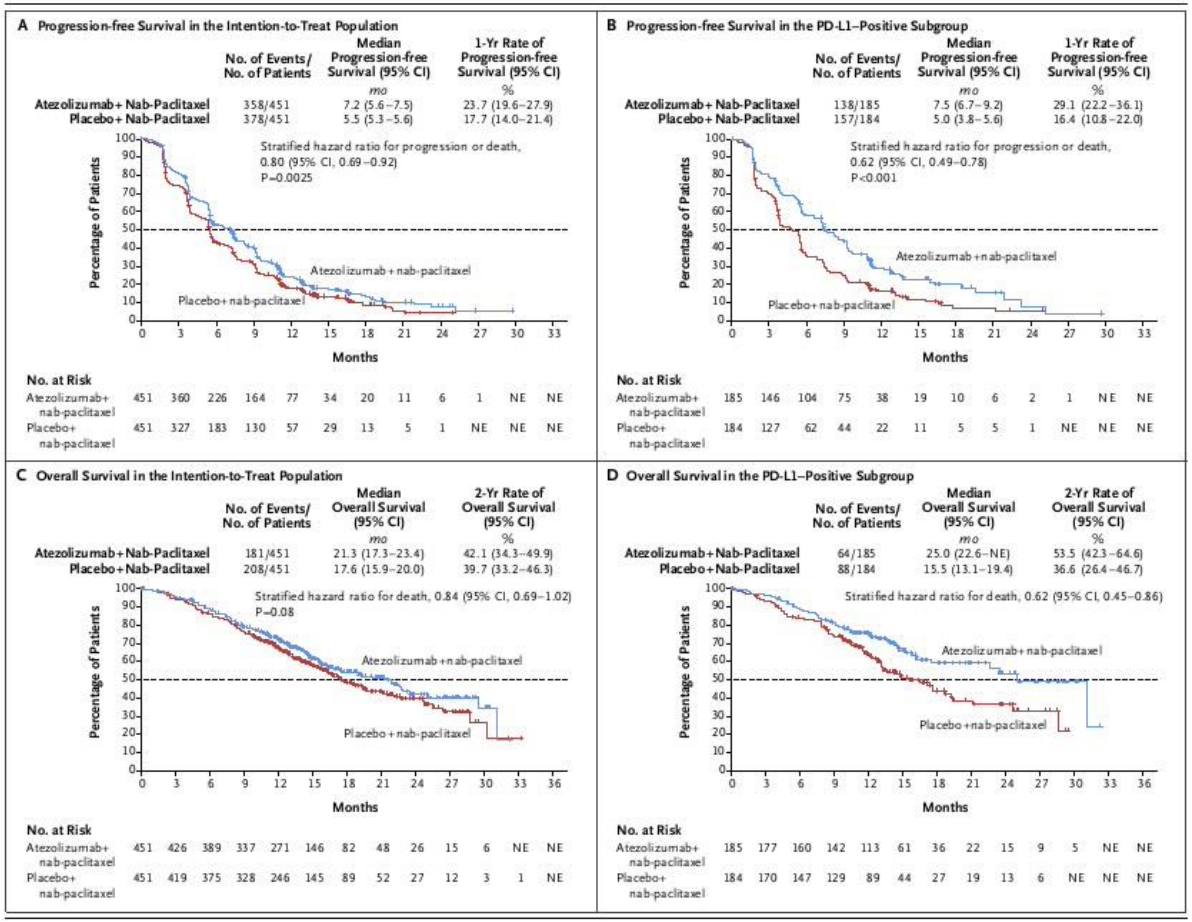


The Checkpoint Blockade Revolution

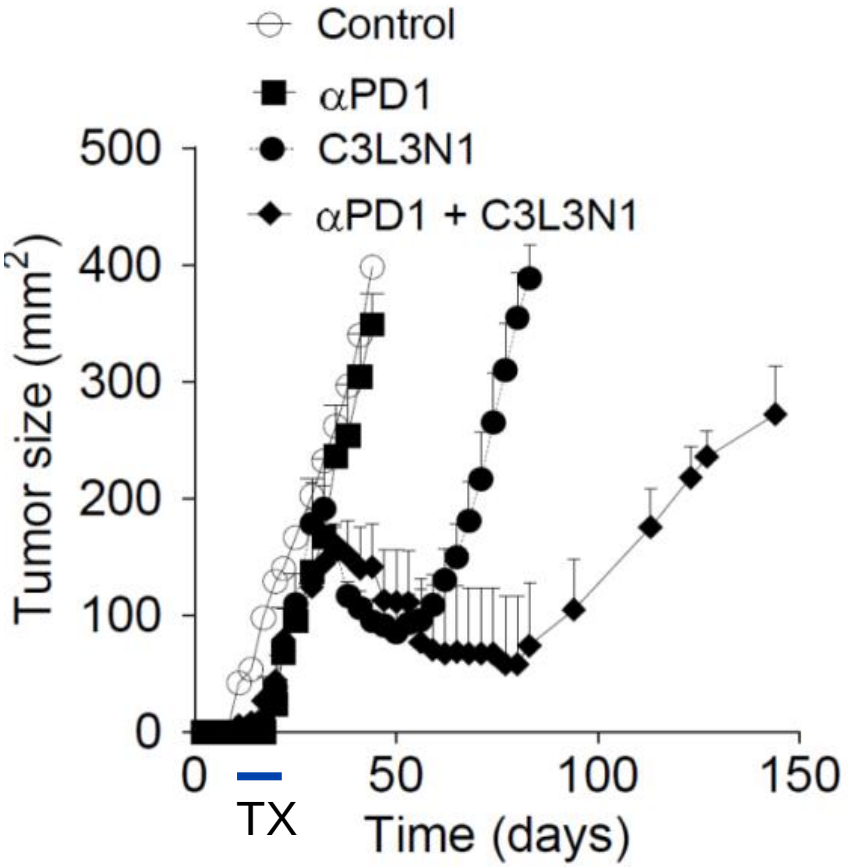
Lymphomation.org

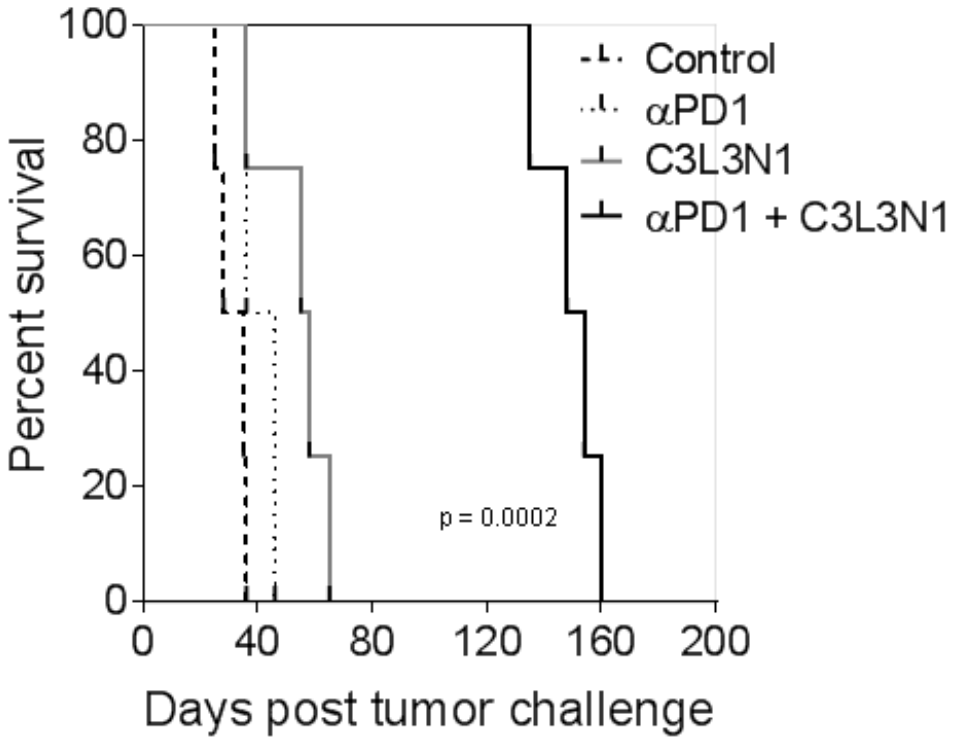


Immune checkpoint blockade for TNBC



Combination therapy results in complete regression and sustained progression free survival

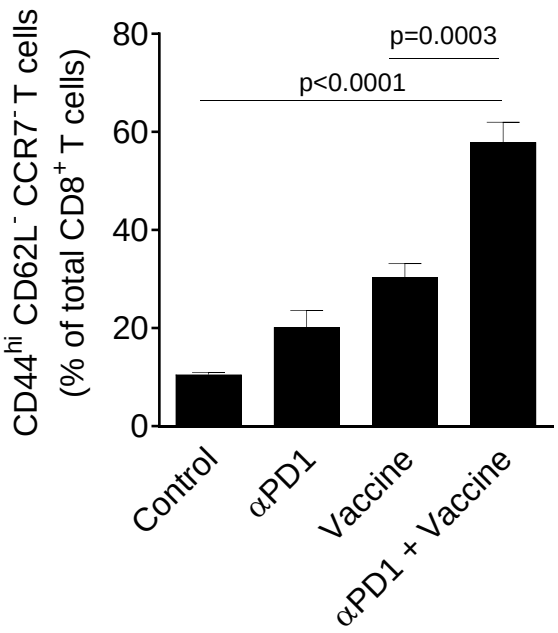


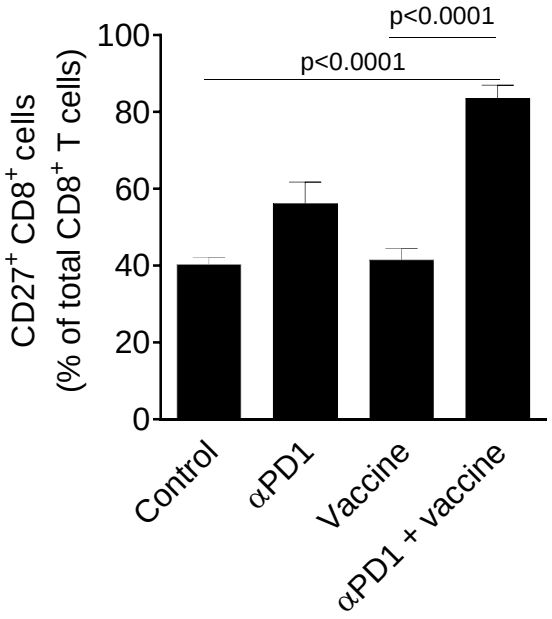


~75% Complete Regression Rate

Karyampudi, et al. *Cancer Res*. 2014

Combination therapy results higher infiltration of memory effector T cells





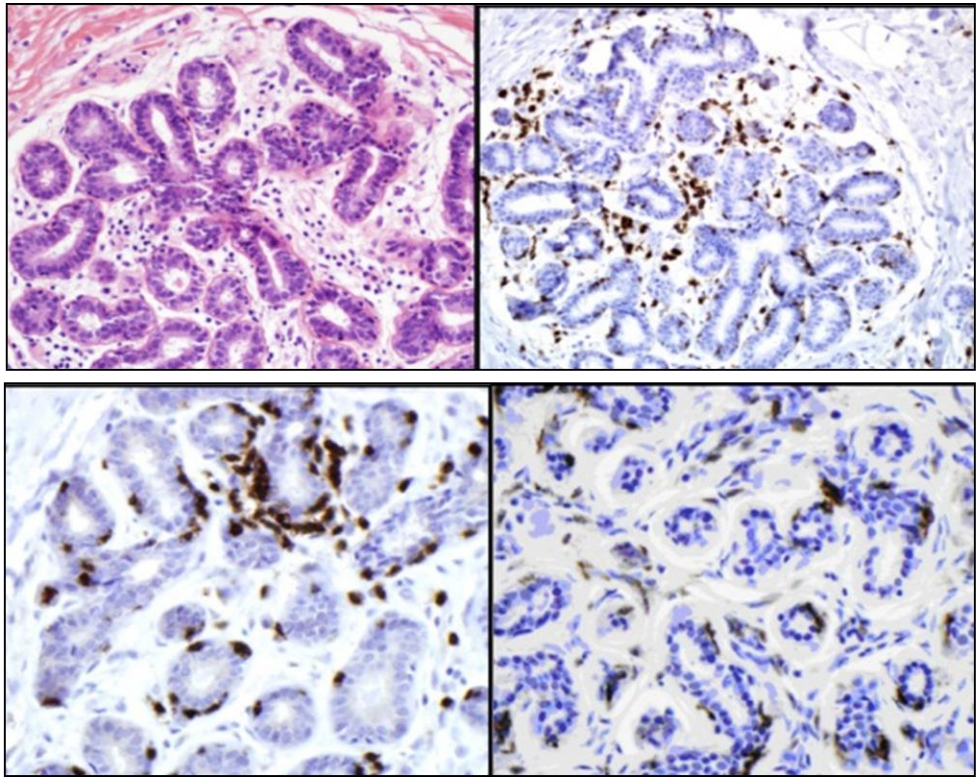
Karyampudi, et al. *Cancer Res.* 2014

Goals

- To develop a vaccine that targets all three major subsets of breast cancer
- To develop a vaccine that reduces the incidence of breast cancer
- To develop a vaccine that prevents death from breast cancer
- To develop a safe and cost-effective vaccine

NBCC
National Breast Cancer Coalition

The mammary gland has a mucosal immune system



NBCC
National Breast Cancer Coalition

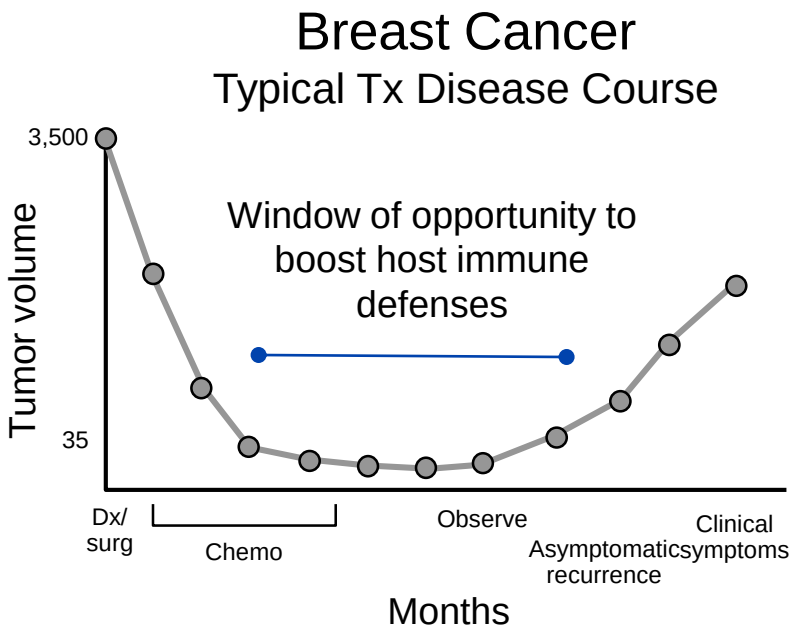
- **HER2/neu (185 kDa) (OC 30%)**
  - Cell surface growth factor receptor.
  - Angiogenesis, proliferation, embryonic development.
  - Expressed in majority of breast cancers and amplified in 20%.
  - Associated with aggressive behavior.
- **MAGE3 (34 kDa) (OC 100%)**
  - Limited to placental trophoblast cells and germ cells of the testes
  - Function is not known.
  - Expressed in ~50% of breast cancers.
- **MUC1 (225-500 kDa) (OC 95%)**
  - Large membrane glycosylated protein – lubrication/hydration.
  - Overexpressed and aberrantly glycosylated in 90% of breast cancer.
- **Survivin (16 kDa) (OC 85%)**
  - Anti-apoptosis protein.
  - Extensive expression in fetal and embryonic development. Not expressed in normal differentiated cells.
  - Expressed in more than 90% of breast cancer.
- **Mammaglobin A (10 kDa) (OC ?)**
  - Secretory protein of unknown function.
  - Very limited expression in normal healthy tissue and expressed 10 fold-higher in 40-80% of breast cancers.
- **hTERT (126 kDa) (OC 100%)**
  - Main protein component of the telomerase enzyme, an enzyme that maintains the length of chromosomes.
  - Not expressed in dividing cells but overexpressed in more than 90% of breast cancer.

NBCC
National Breast Cancer Coalition

1) To develop a vaccine that targets all three major subsets of breast cancer
2) To develop a vaccine that reduces the incidence of breast cancer
3) To develop a vaccine that prevents death from breast cancer
4) To develop a safe and cost-effective vaccine

Product	Indication	Preclinical	Phase 1	Phase 2
FR with anti-PD-L1	Ovarian Cancer			
FR DC Vaccine	DC			
FR	Triple-Negative Breast Cancer			
FR	Platinum-Sensitive Ovarian Cancer (Fast Track)			
HER2/neu	Surgically Resected Breast Cancer			
HER2/neu	DCIS			
HER2/neu, MUC1, hTERT, MammA, Survivin, MAGEA3	Prophylactic			

Conclusions



- More needs to be done in the disease free period to boost host immunity against cancers at high risk for relapse
- Vaccines can be developed that target aberrantly expressed proteins. Useful for preventing disease recurrence?
- Repolarizing immune response may improve outcomes.
- Checkpoint activity appears to be limited for TNBC but may be improved by inclusion of vaccines.

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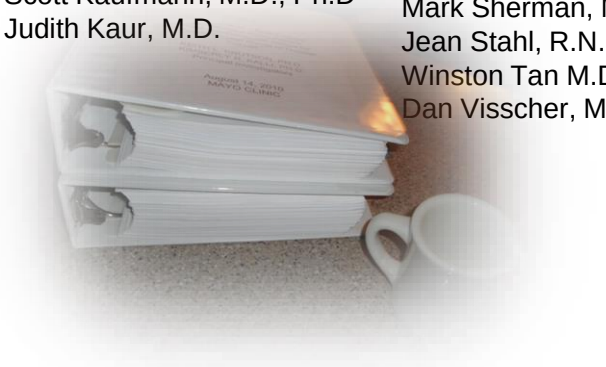

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