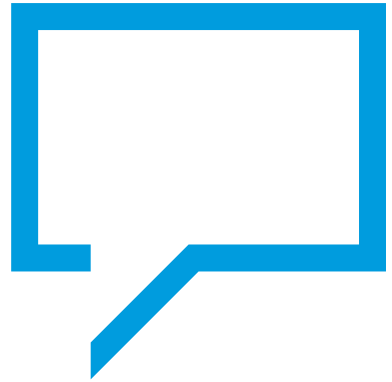
MAYO CLINIC | School of Medicine and Science



BREAST CANCER VACCINES

Are They For Real?

Keith L. Knutson, Ph.D.

20th Annual Breast Cancer Education Conference
January 22, 2022 - Virtual

DISCLOSURES

- Marker Therapeutics, Inc.
  - Cancer Vaccines and T Cell Therapy – Houston Tx
  - Scientific Advisory Board (unpaid)
  - Several Patent Licensing Agreements (Mayo)
- Kiromic, Inc.
  - Cancer Vaccines/CAR T cell therapy – Lubbock, TX
  - Scientific Advisory Board
  - Stock owner
- Antigen Express, Inc.
  - Cancer Vaccines – Cambridge, MA
  - Scientific Advisory Board (Paid)
- AffyImmune
  - CAR T cell therapy – Cambridge, MA
  - Scientific Advisory Board (Paid)
  - Ownership
- Macrogenics, Inc.
  - Biologics – Bethesda, MD
  - Grant funding
- Leidos
  - Biologics – Reston, VA
  - Collaborations
- Bolt Therapeutics
  - Biologics – Redwood, CA
  - Grant Funding

LEARNING OBJECTIVES

1. Basics of the immune system
2. How vaccines are used in breast cancer
3. What is targeted with vaccines
4. Understand pathways to regulatory approval

THE ADAPTIVE IMMUNE SYSTEM IS THE TARGET OF VACCINES

CD4 T cells

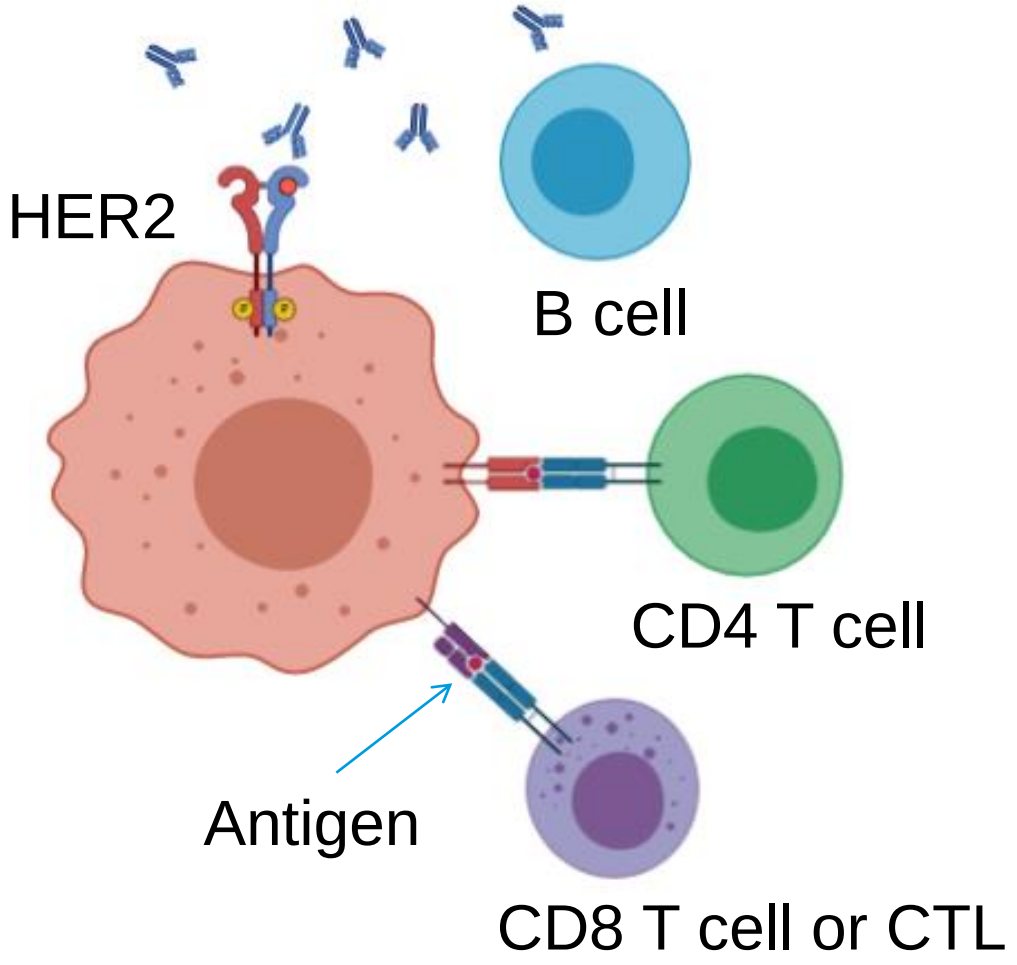
- Inflammation (macrophages and neutrophils)
- Induction of antibody-producing cells
- Activate/maintain cytotoxic T cells
- Immune-surveillance
- Epitope-spreading
- Direct cytotoxicity

CD8 T cells

- Tumor lysis

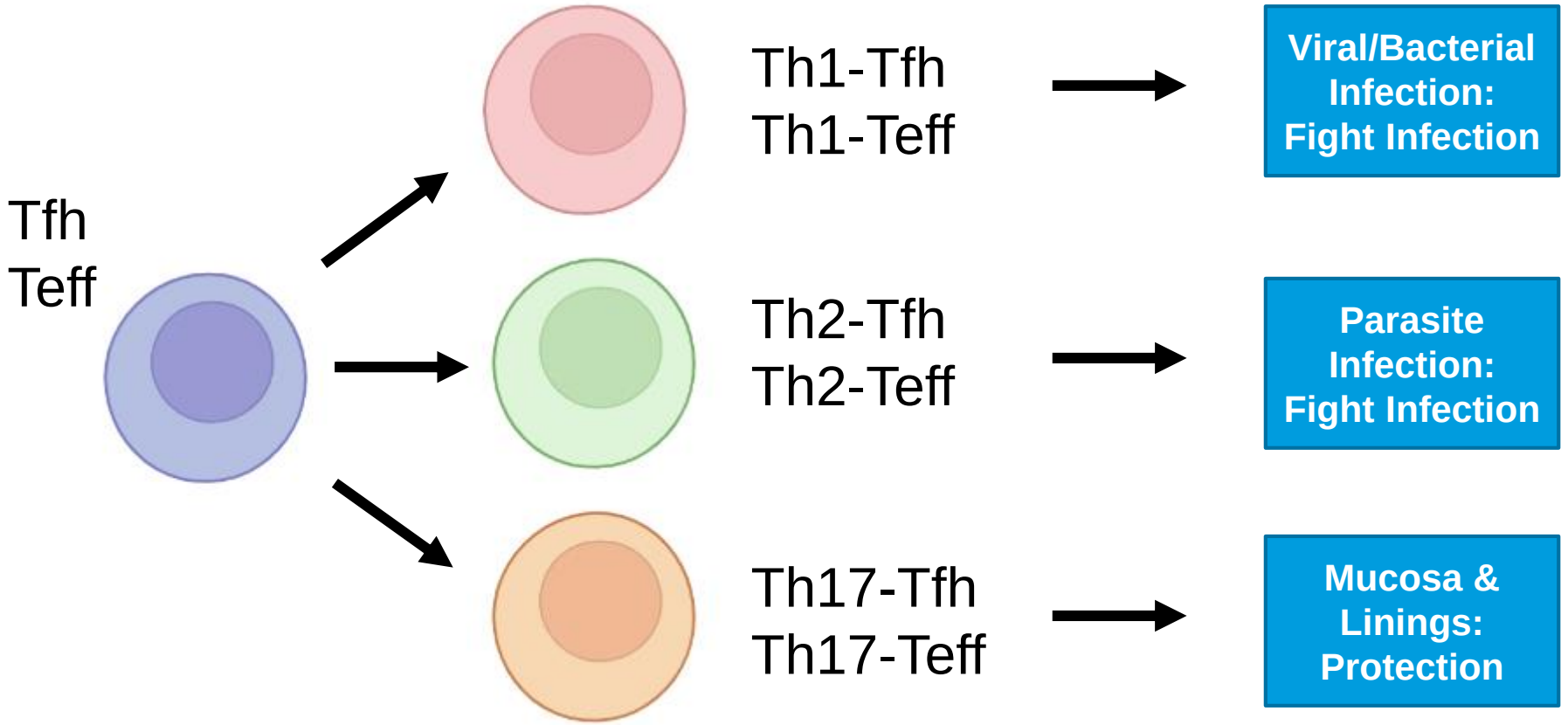
B cells

- Antibodies
- Signaling
- ADCC
- Complement



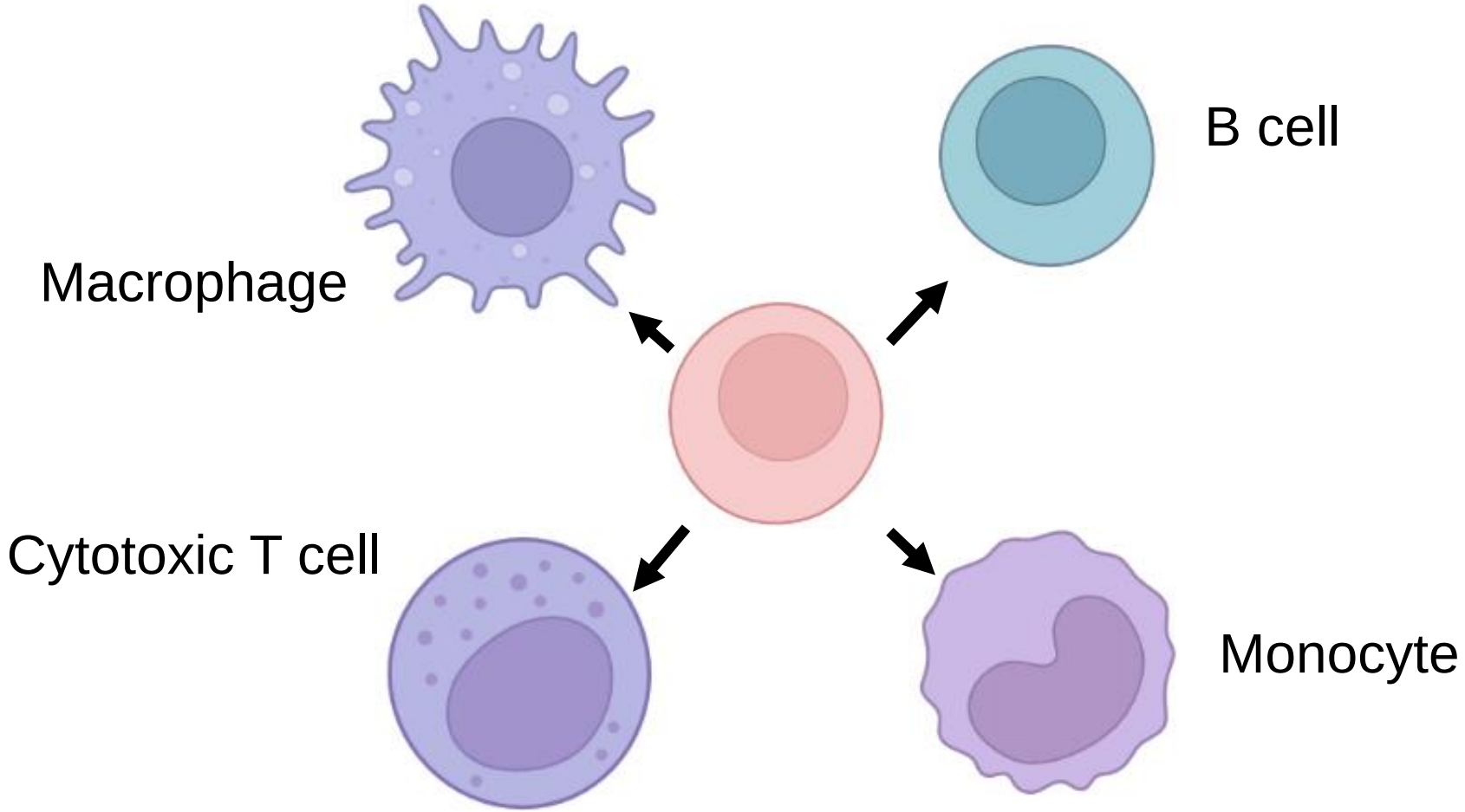
Biorender

THERE ARE DIFFERENT TYPES OF IMMUNE RESPONSES



Biorender
Annual Rev Immunol, 2020

TH1 IMMUNITY, GENERALLY, IS THE TARGET FOR CANCER VACCINES



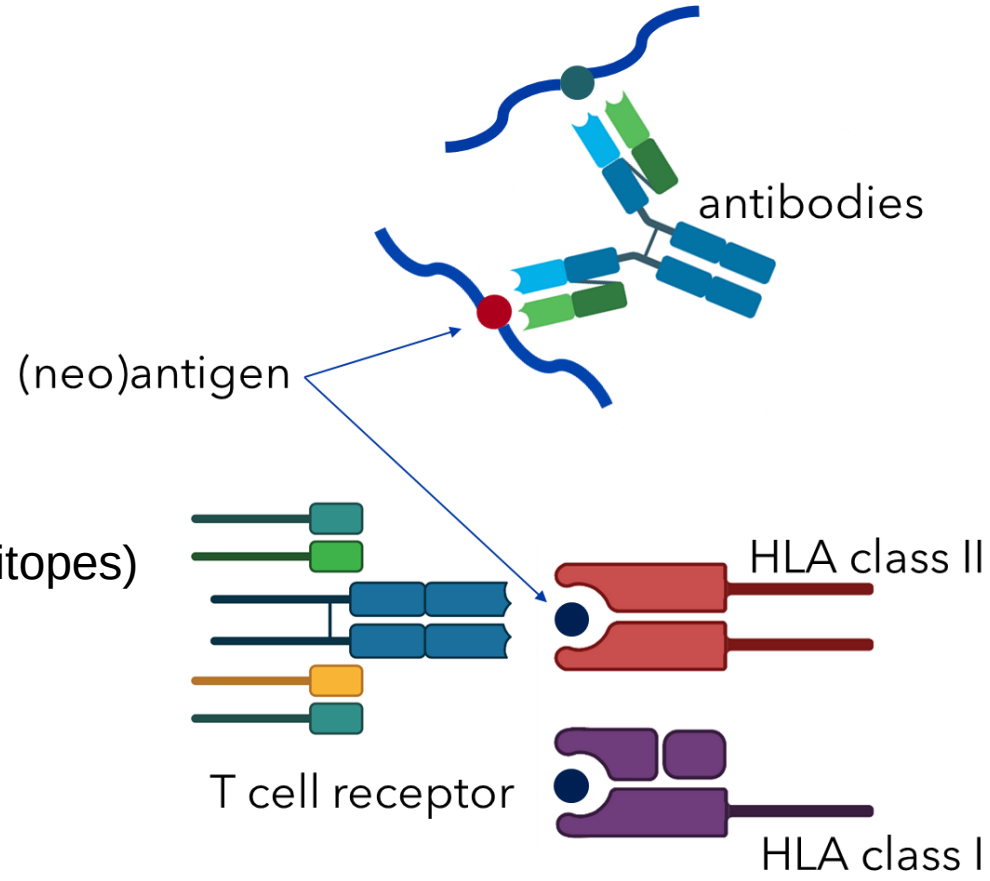
Biorender

VACCINATION MAY BE USEFUL FOR CANCER IN MANY WAYS

Therapeutic	Maintenance	Prevention
↓	↓	↓
Tumor shrinkage	**Prevention of relapse**	**Prevent incidence**
Provenge		Hepatitis B Virus Human Papilloma Virus

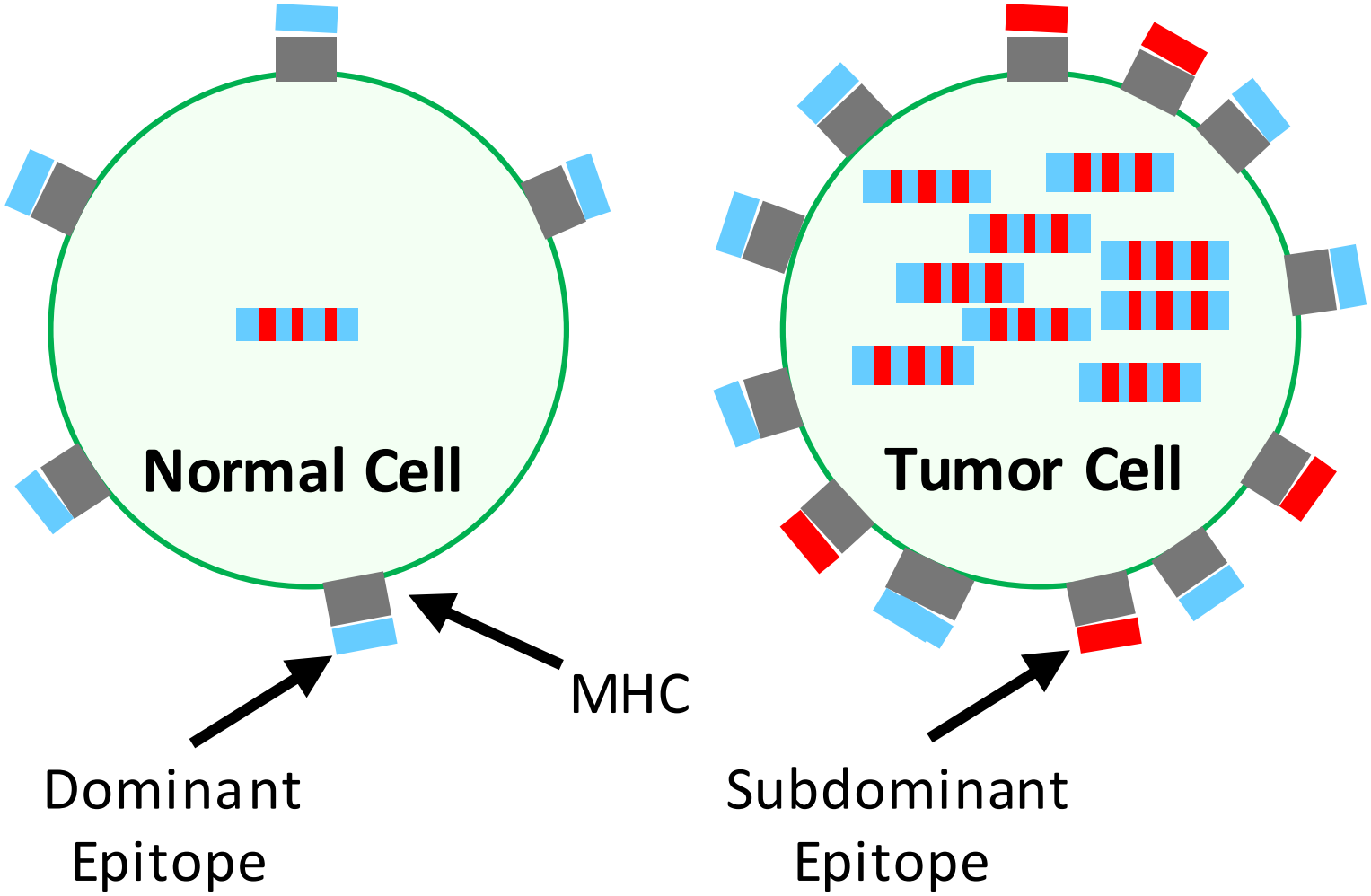
IDENTIFYING VACCINE TARGETS FOR CANCER

- Goal: Target tumor-specific antigens
- Types of cancer neoantigens
  - Protein
  - Carbohydrates
  - Nucleic acid
  - Lipid
- Protein antigens targeted in cancer
  - Microbial
  - Self protein derived neoantigens (subdominant epitopes)
  - Mutated protein derived neoantigens
- Platforms
  - Peptide, Nucleic acid, protein
  - Cell-based
  - Virus or bacteria



MAYO CLINIC

OVEREXPRESSED SELF PROTEINS ARE CANCER ANTIGENS



Cibotti, R., *Proc Natl Acad Sci U S A*, 1992. **89**(1): p. 416-20

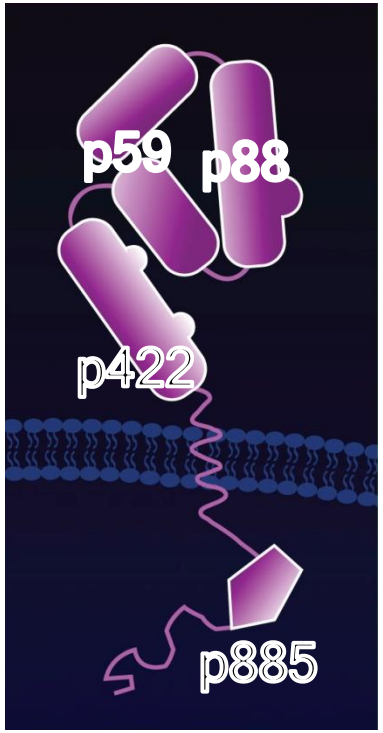
IN SOME CASES, IT IS NECESSARY TO IDENTIFY PARTS OF PROTEINS TO MAKE VACCINES

			IC_{50} nM to purified HLA													
Sequence	Peptide Name	Position[¶]	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

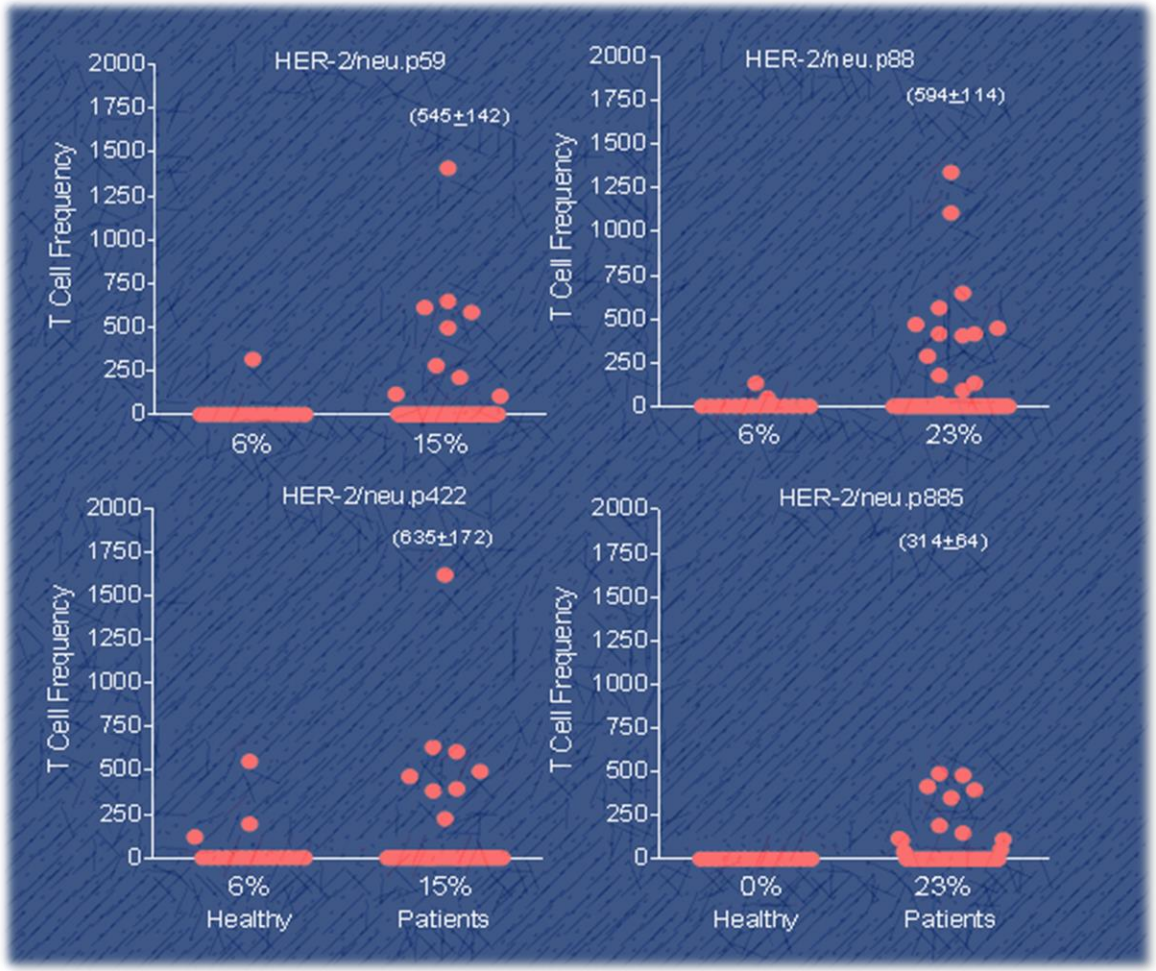
[¶]Position of N-terminal amino acid; ND=not determined; Peptides that constitute degenerate pool are in bold

Karyampudi, *Cancer Res*, 2010

NATURAL IMMUNITY IN PATIENTS CAN HELP IDENTIFY RELEVANT PARTS OF PROTEINS FOR VACCINATION

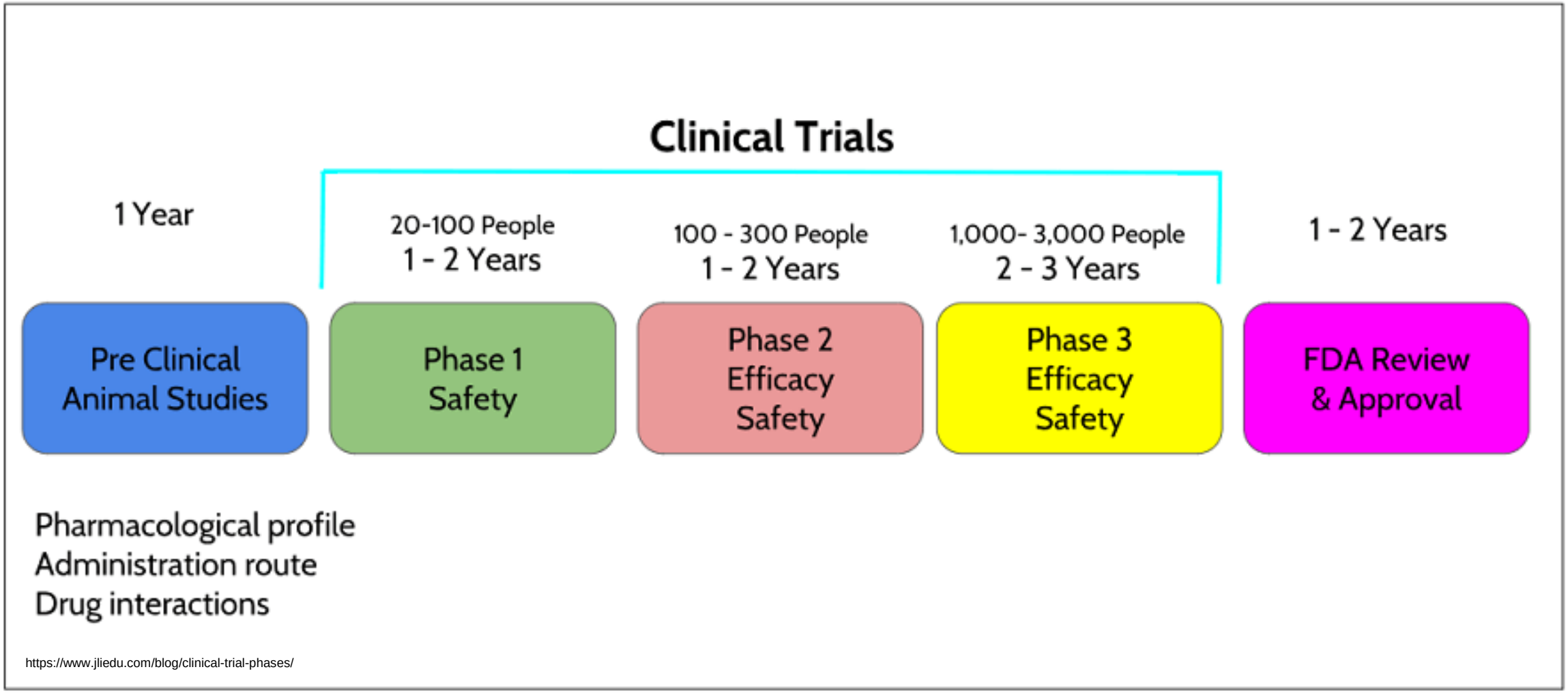


DRB1*0101, DRB1*0301
DRB1*0401, DRB1*0404
DRB1*0405, DRB1*0701
DRB1*0802, DRB1*0901
DRB1*1101, DRB1*1201
DRB1*1302, DRB1*1501
DRB3*0101, DRB4*0101
DRB5*0101



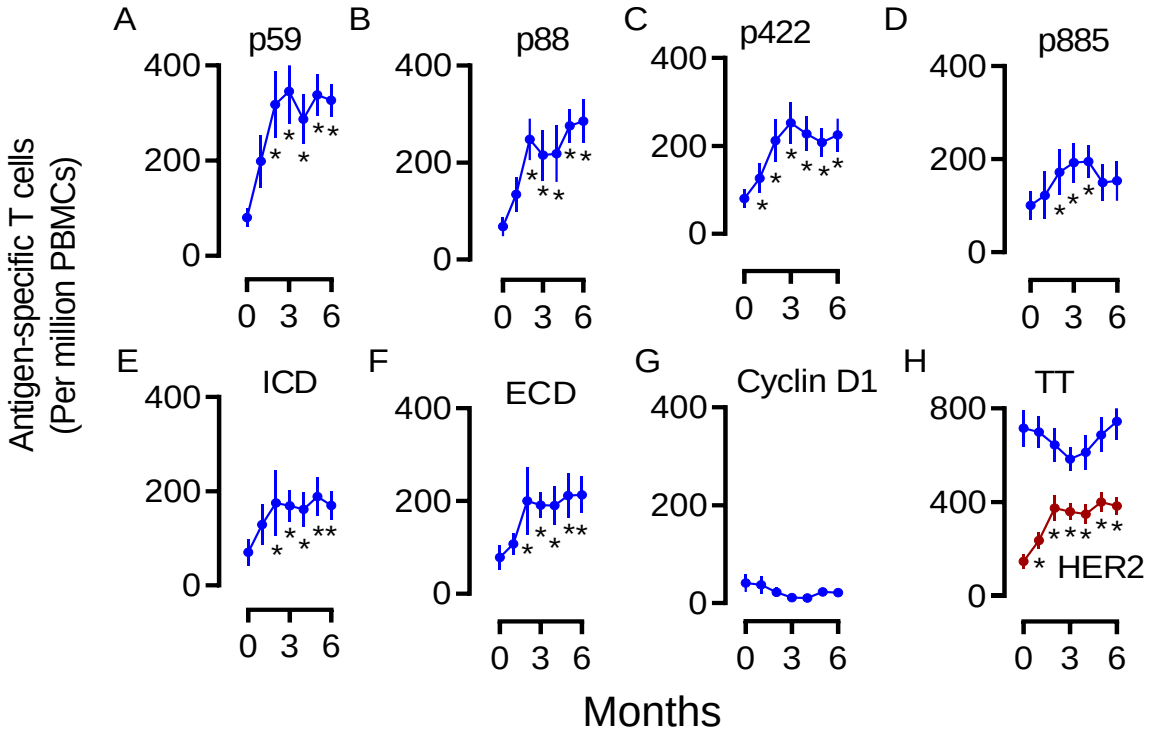
Karyampudi et. al., Clin Cancer Res. 2010
Knutson KL and Ishioka G, 2007, HLA DR binding peptides and their uses. Patented 12/740,562.

DEVELOPMENT OF VACCINES IS A LONG PROCESS

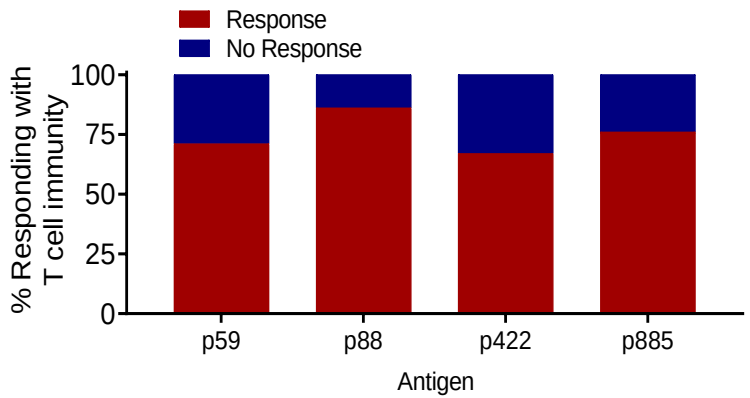


https://www.jliedu.com/blog/clinical-trial-phases/

PATIENTS WITH CANCER CAN BE IMMUNIZED



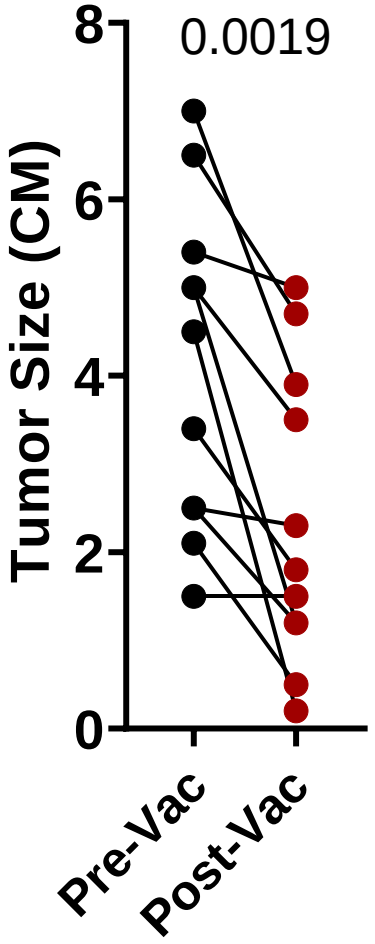
100% of patients demonstrated immunity following vaccination



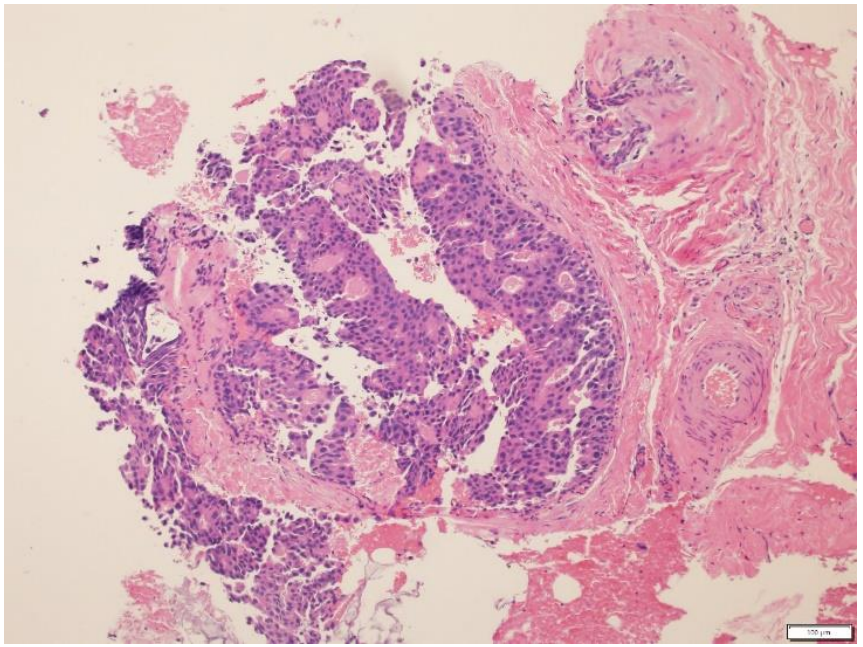
Stages II-III, 22 patients, NED

Knutson et. al., 2020 Clinical Cancer Research

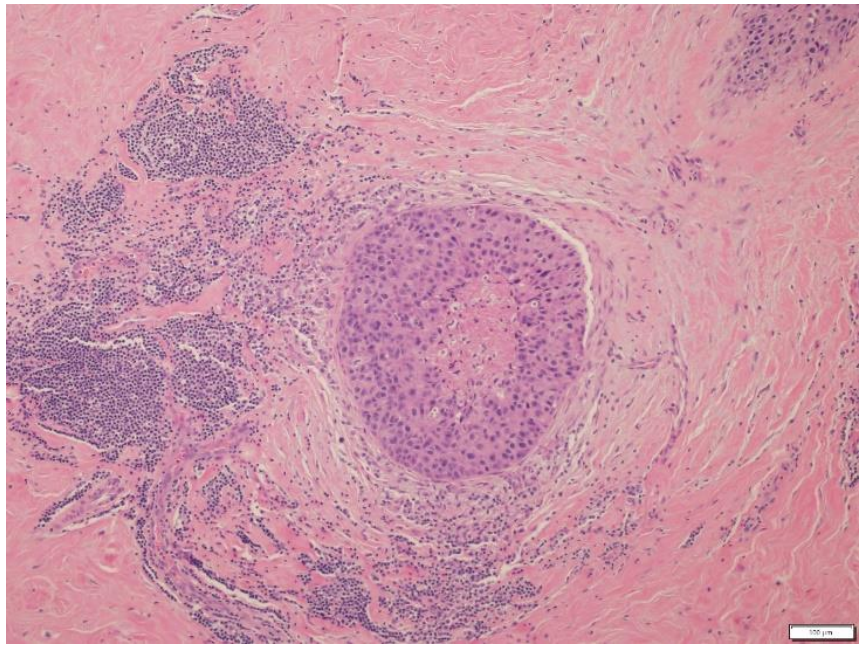
VACCINES CAN INDUCE INFILTRATION IN TUMORS AND CAUSE REGRESSION



Pre-vaccination

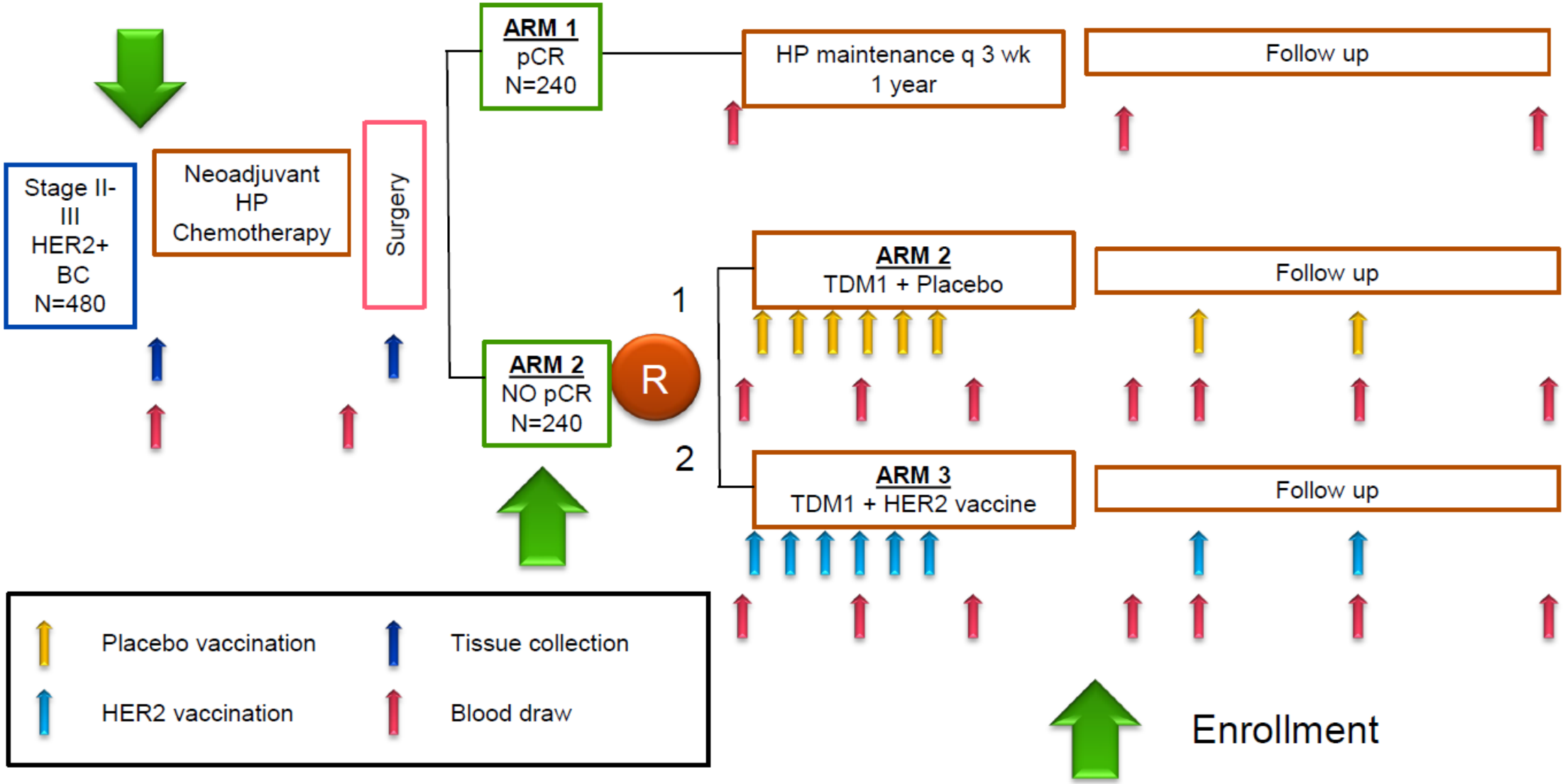


Post-vaccination

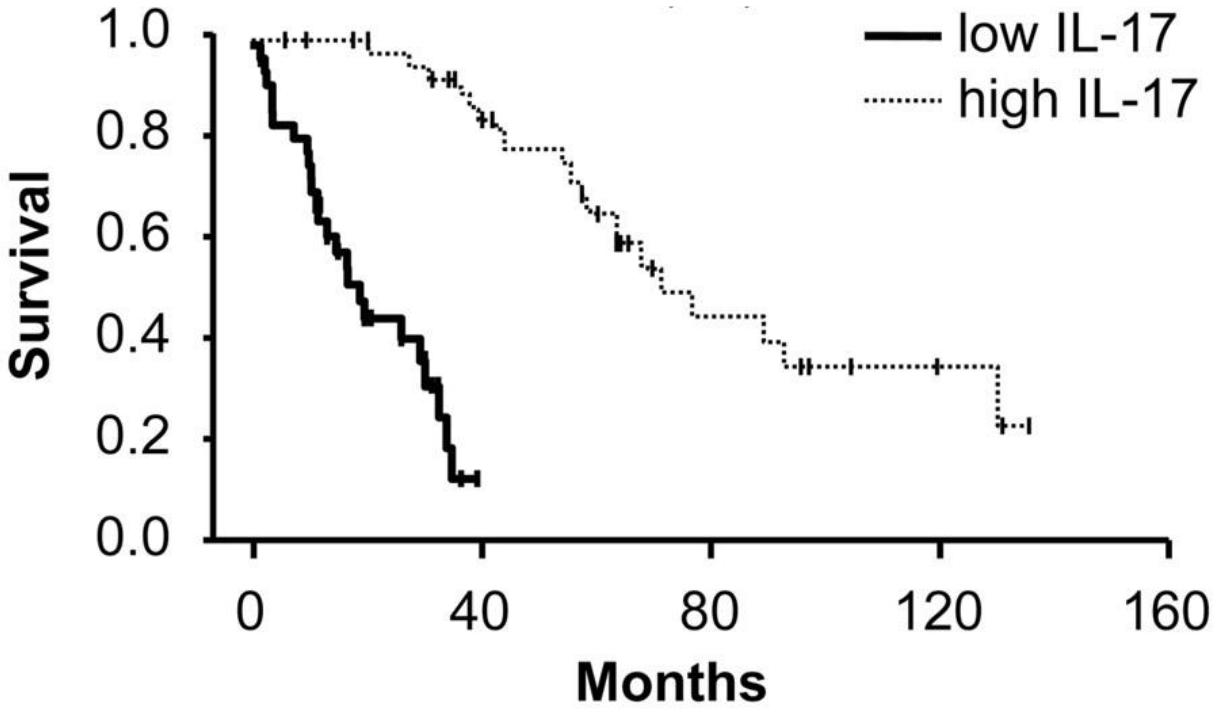


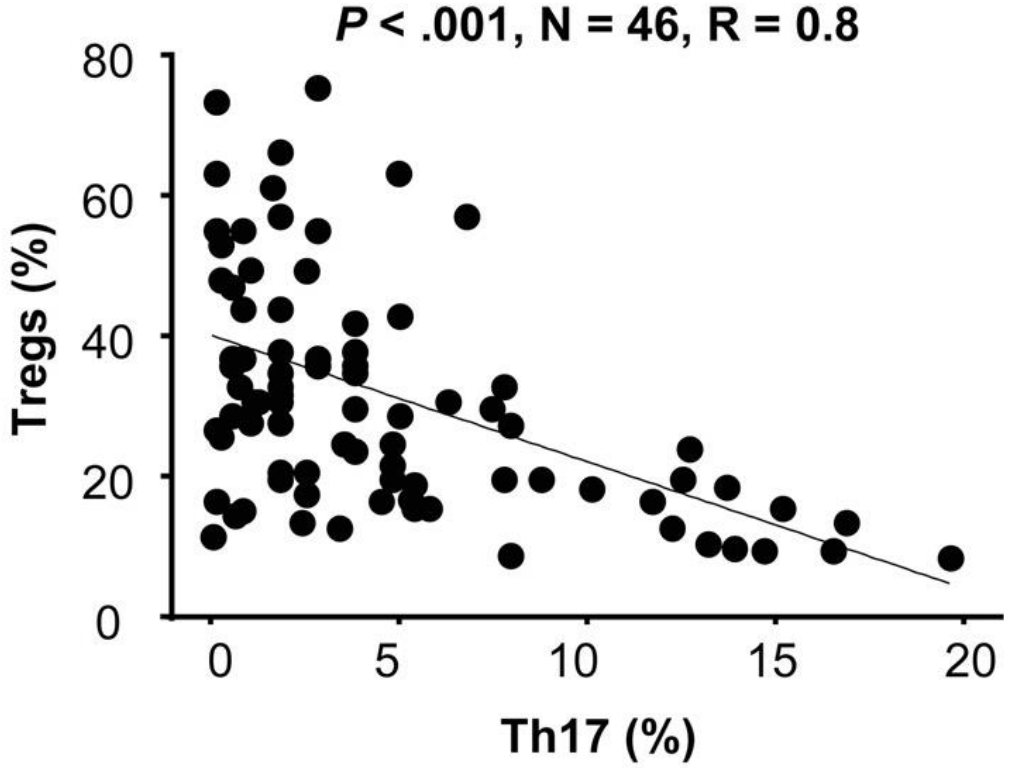
Knutson, unpublished observations

PHASE II CLINICAL TRIALS TO PREVENT RECURRENCE IN COMBINATION WITH ADJUVANT THERAPY REQUIRE CONTROL ARMS



NATURAL IMMUNITY INFORMS ON THE TYPE OF IMMUNE RESPONSE REQUIRED FOR EFFECTIVE VACCINES

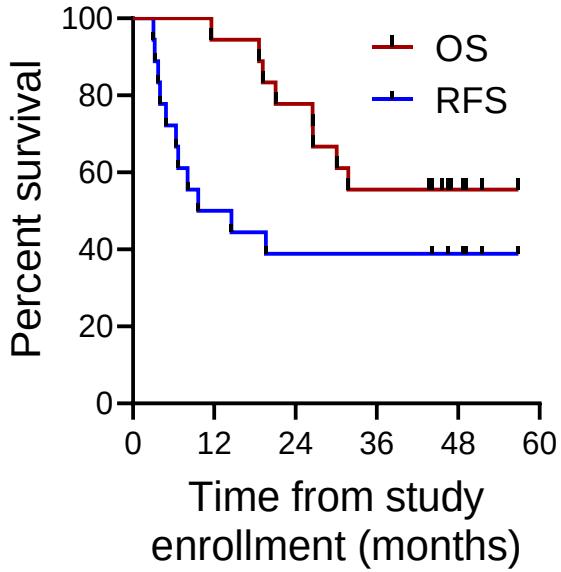


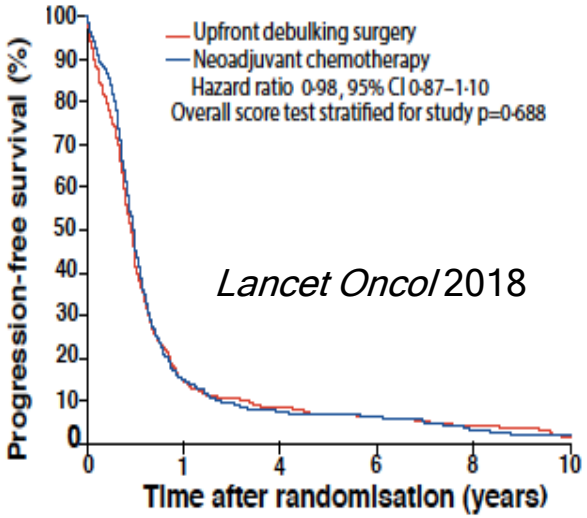


Confirmatory studies:
Lan C, *et al*: Cell Tissue Res, 2013
Zeng Y, *et al*: Int J Clin Exp Med, 2015

Kryczek I, *et al*: Blood, 2009

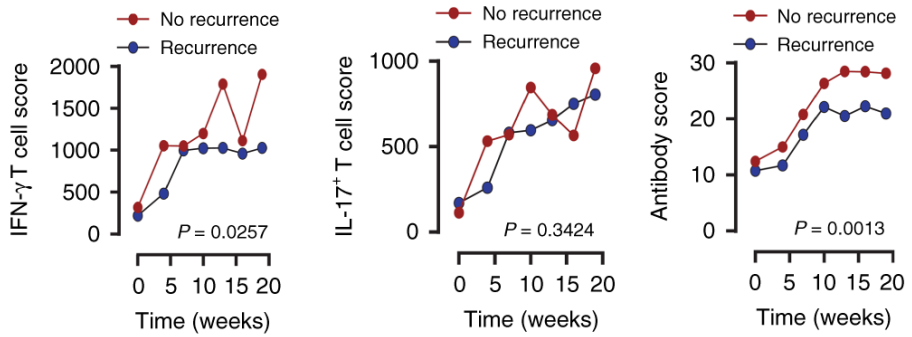
PATIENTS WITH OVARIAN CANCER CAN BE PROTECTED FROM DISEASE RECURRENCE WITH VACCINE ALONE



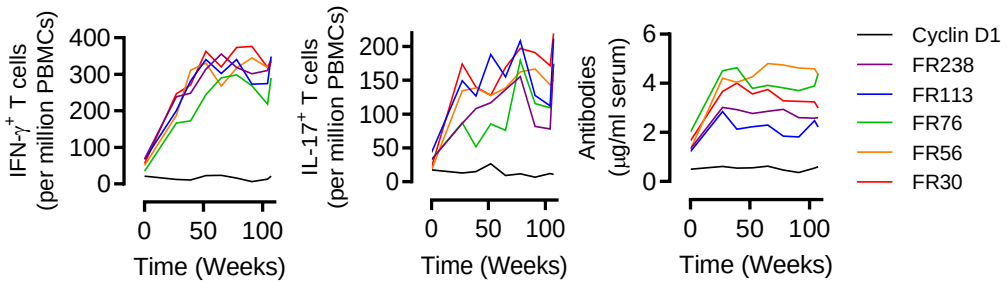


Lancet Oncol 2018

Immunity correlates with outcome

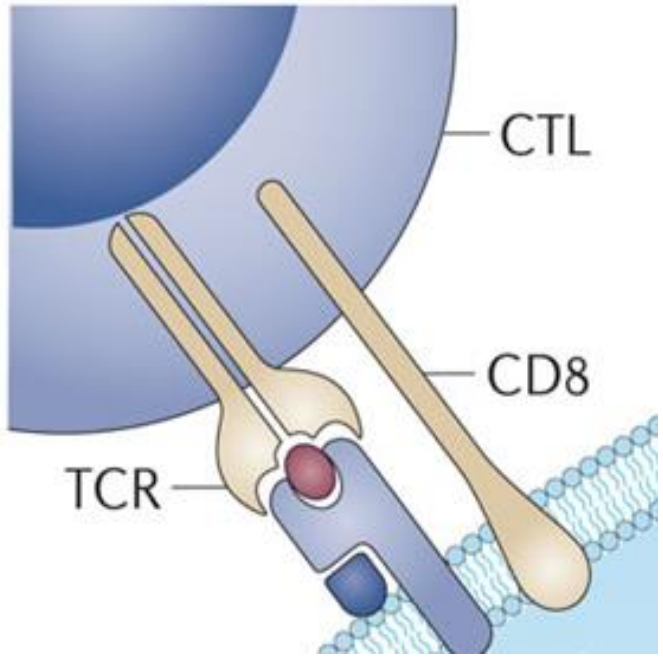


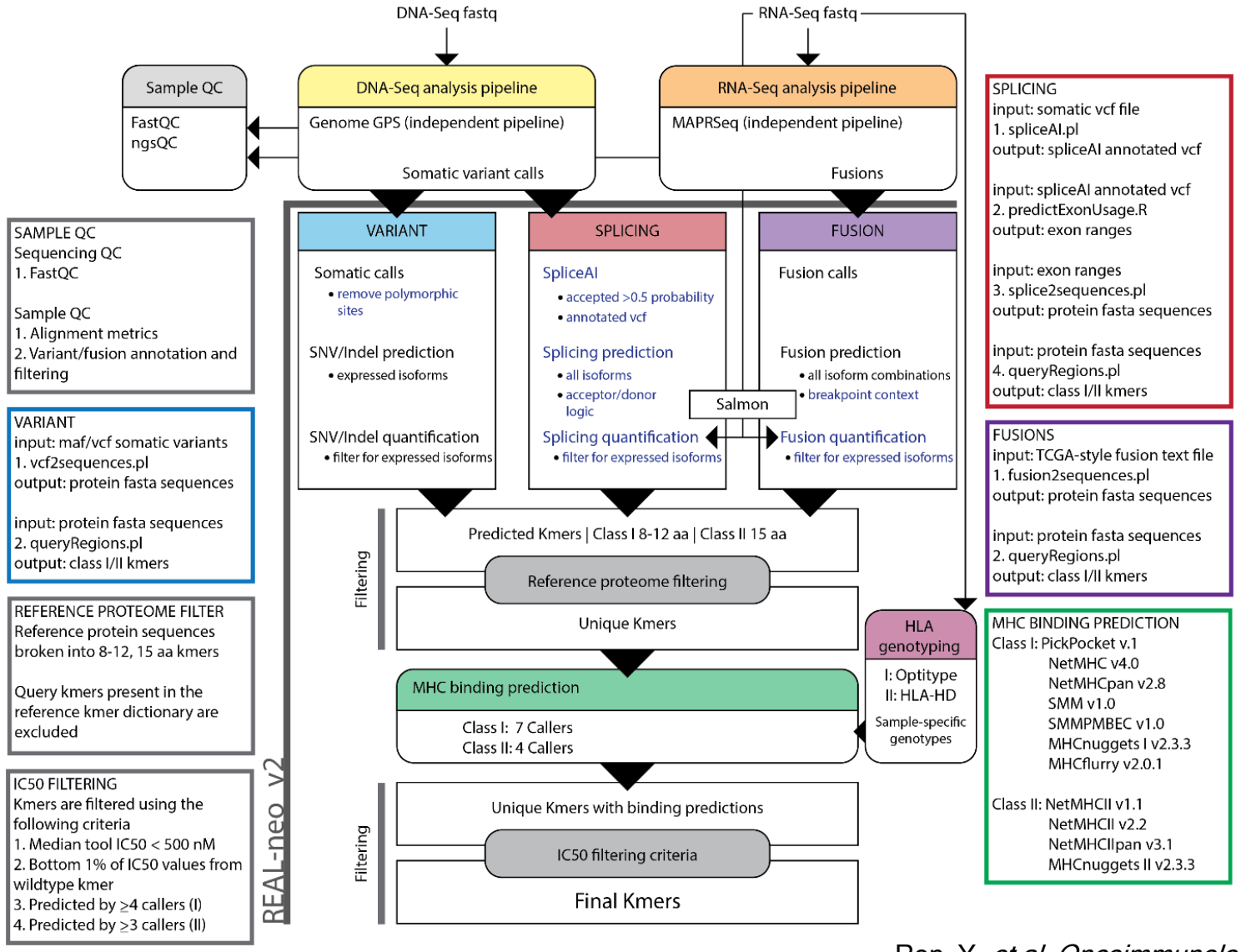
Immunity is persistent (no recurrence patients)



Block, *Nat Commun*, 2020

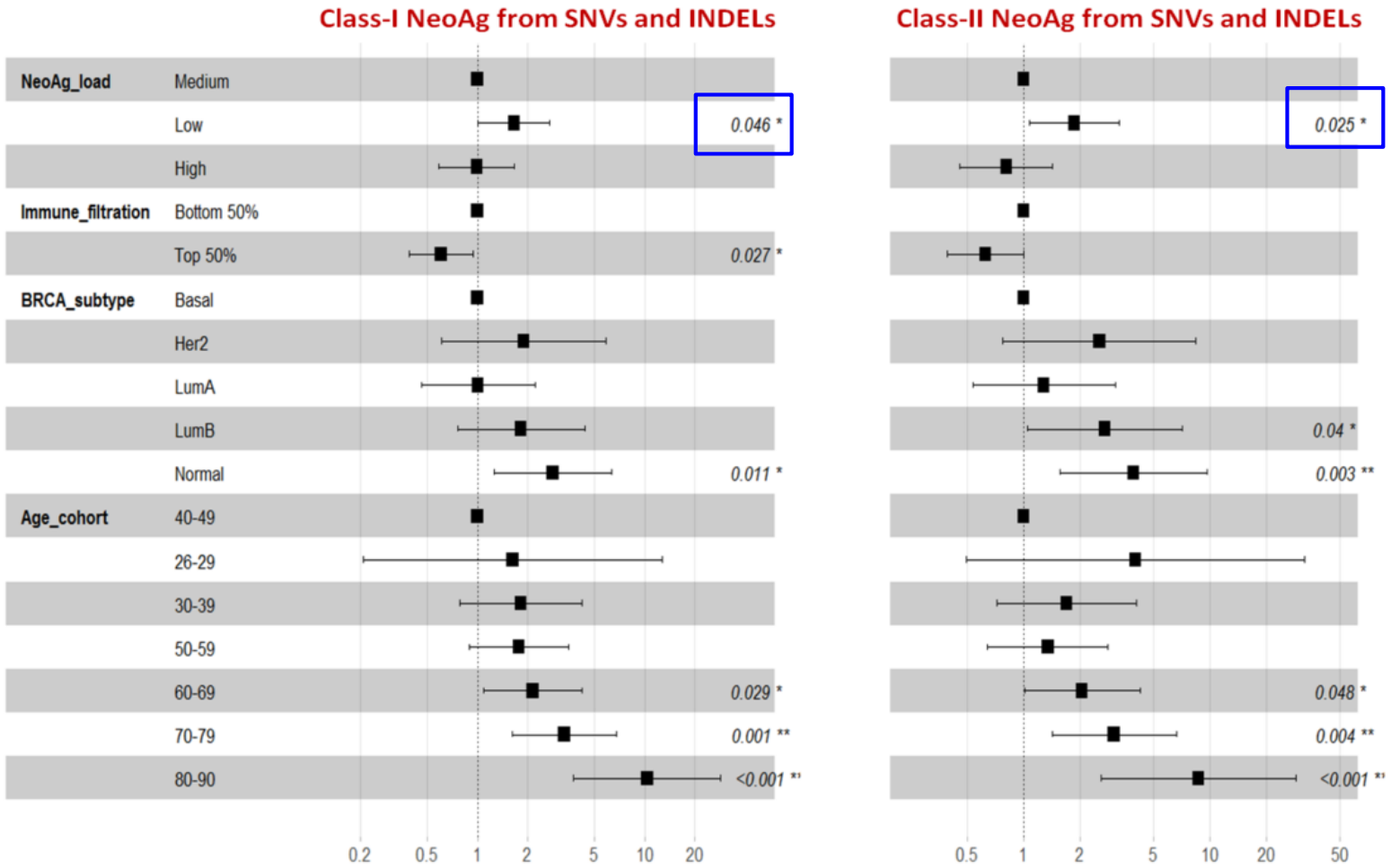
MUTATED PROTEINS ARE VACCINE TARGETS





Ren, Y. *et al. Oncoimmunology*, 2020

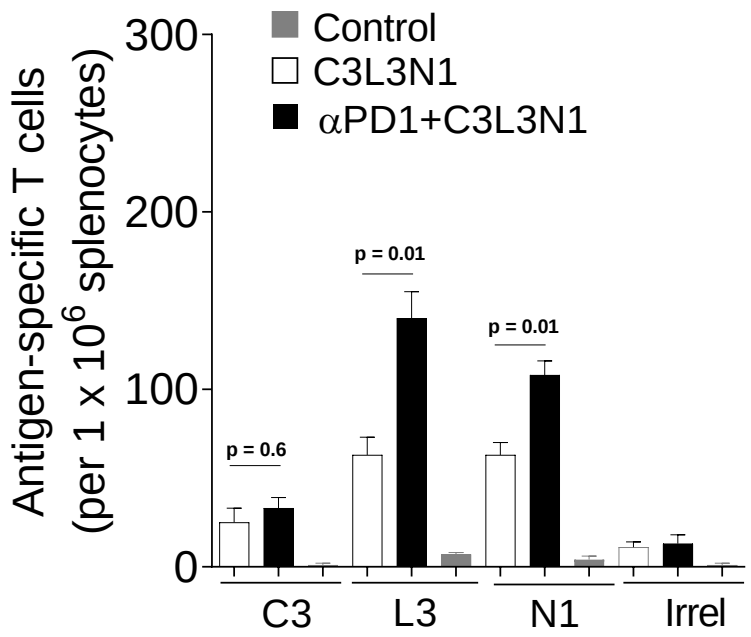
THE LEVELS OF MUTATED PROTEINS IN BREAST CANCER IS ASSOCIATED WITH BETTER SURVIVAL

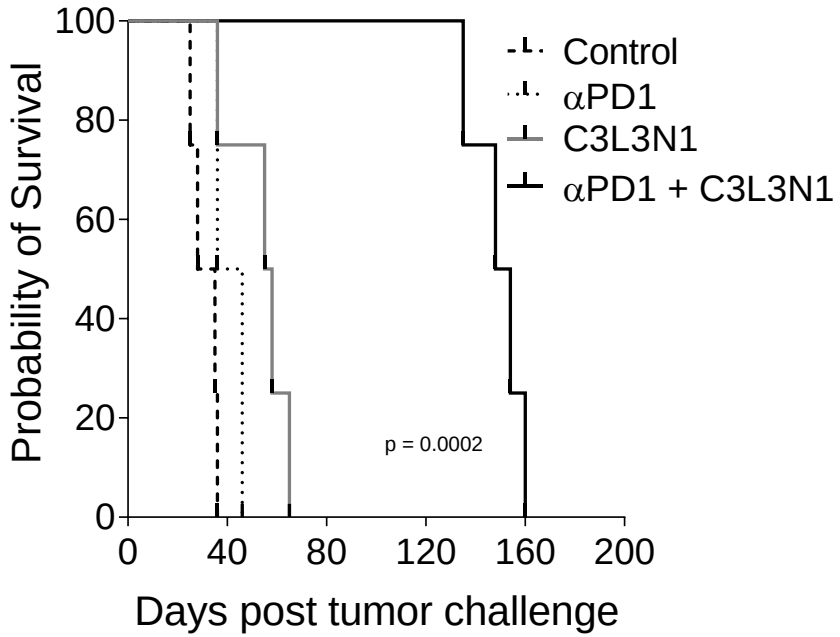


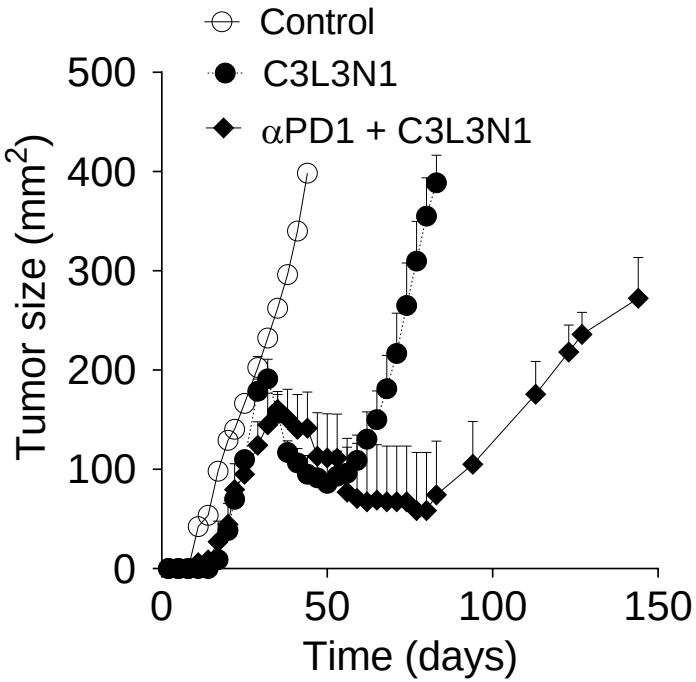
Cox Proportional Hazard model: adjusted for TIL, Breast Cancer Subtypes, Age, and Mutation Burden

Ren, Y. *et al. Oncoimmunology*, 2020

VACCINATION IMPROVES IMMUNE CHECKPOINT BLOCKADE EFFECTIVENESS

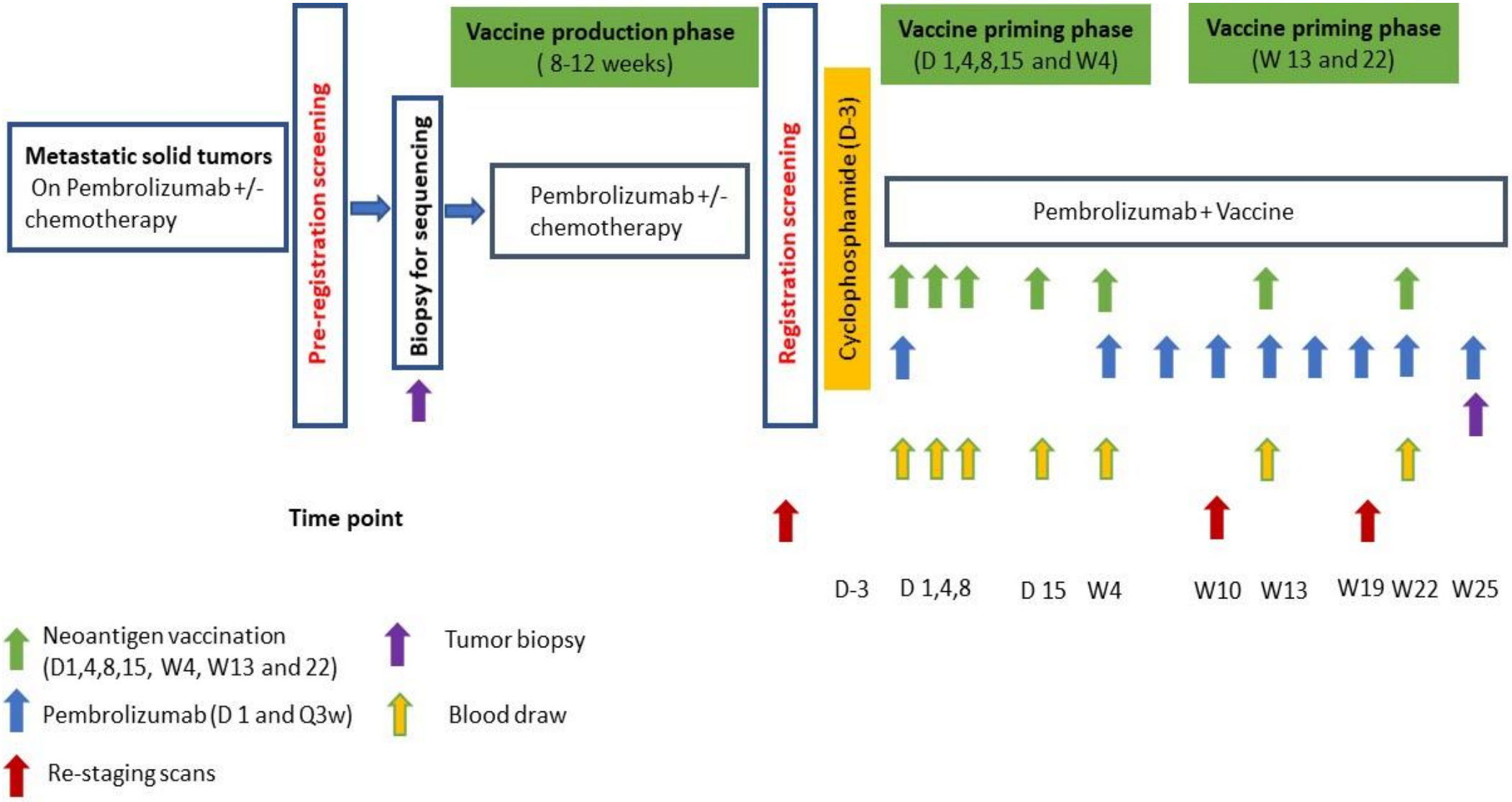






Karyampudi, L.. *et al. Cancer Res.*, 2014

NEW TRIAL TESTING KEYTRUDA IN COMBINATION WITH VACCINE IS STARTING AT MAYO CLINIC



A PREVENTION VACCINE IS BEING DEVELOPED BY THE NBCC, THE MAYO CLINIC, AND THE NATIONAL CANCER INSTITUTE

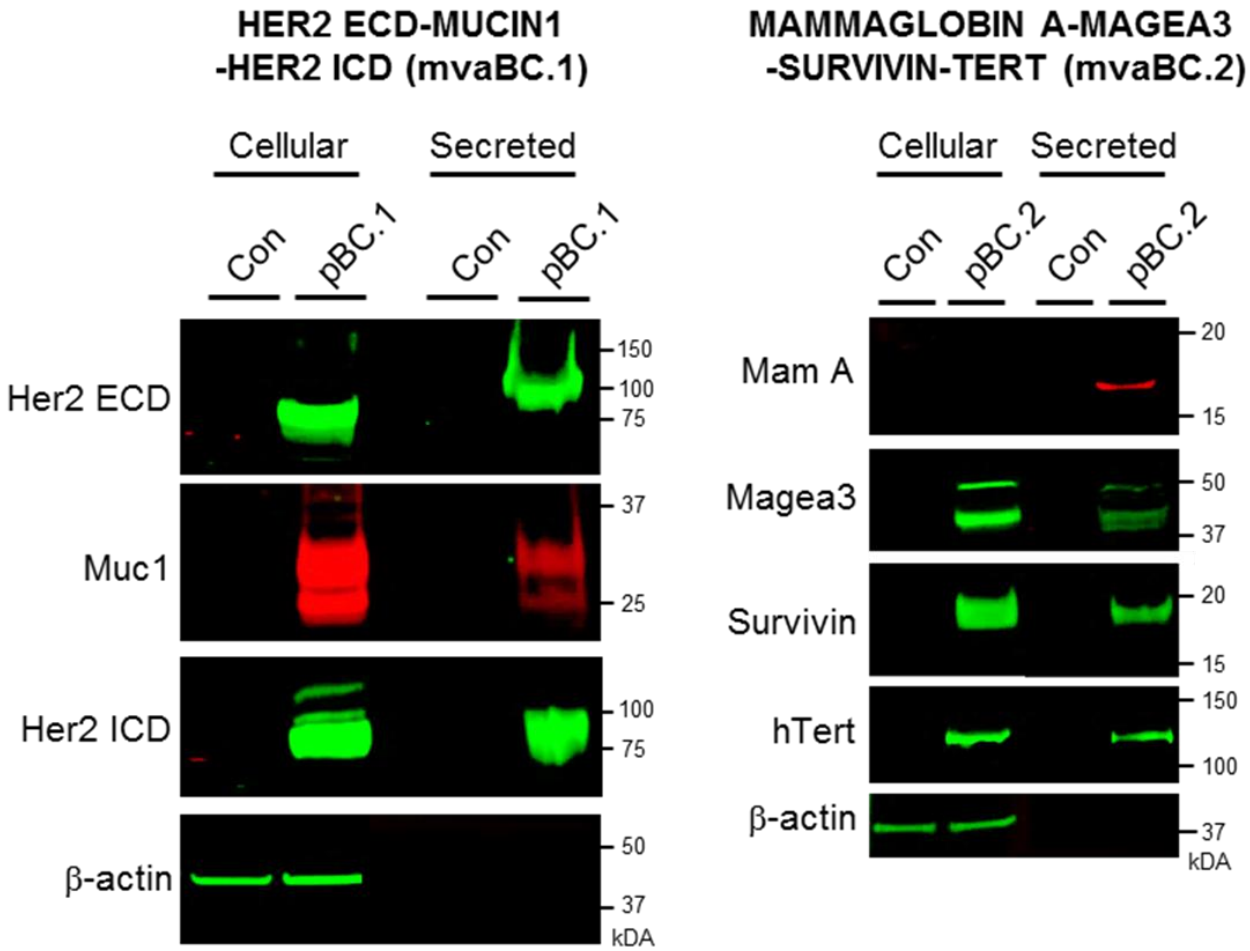
- To develop a vaccine that targets all three major subsets of breast cancer
- To develop a vaccine that reduces the incidence of breast cancer

NBCC
National Breast Cancer Coalition

NIH NATIONAL CANCER INSTITUTE
Division of Cancer Prevention

A PREVENTION VACCINE NEEDS TO TARGET MANY PROTEINS

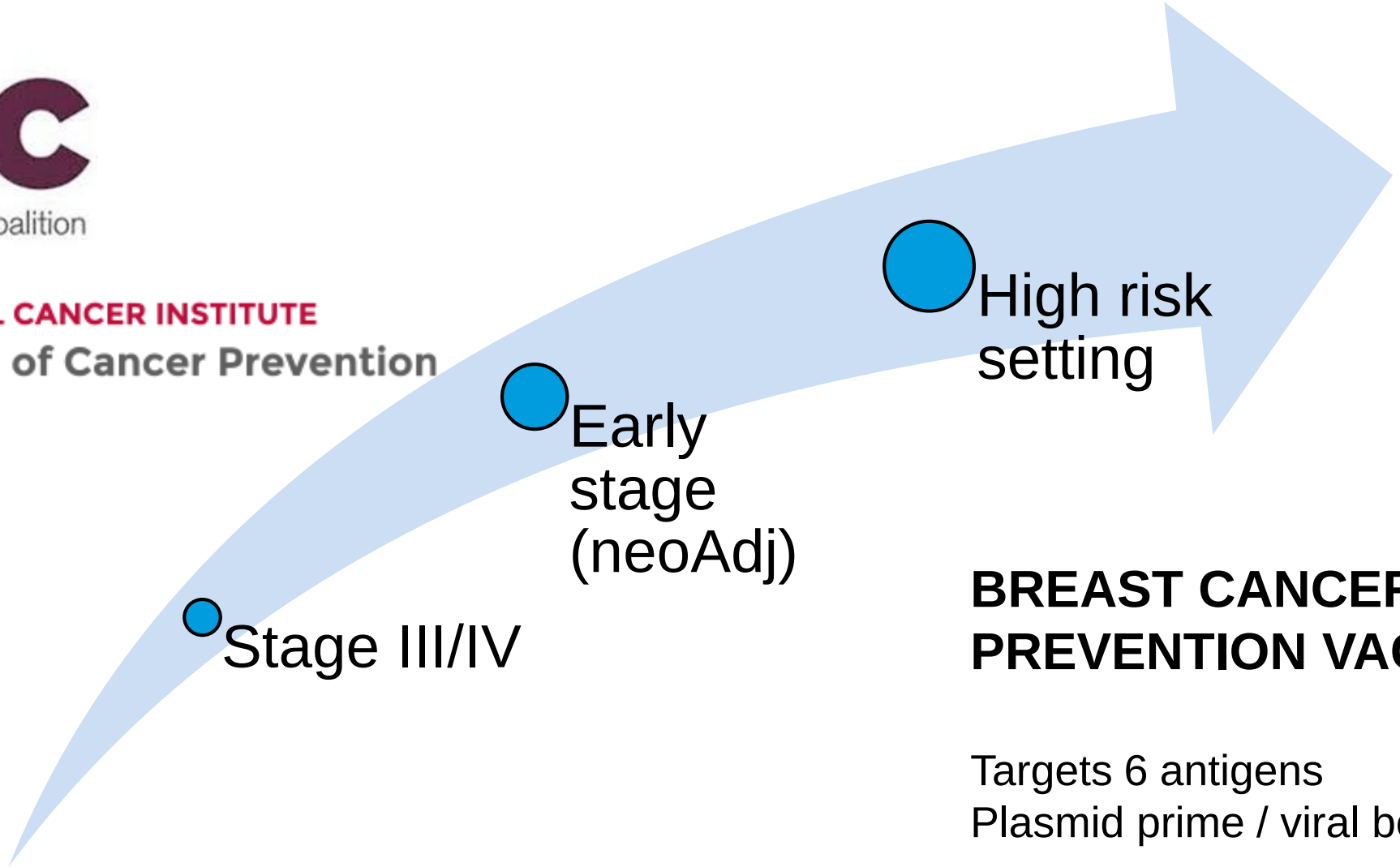
- HER2/neu
  - Expressed in majority of breast cancers and amplified in 20%.
- MAGE3
  - Expressed in ~50% of breast cancers.
- MUC1
  - Overexpressed in 90% of breast cancer.
- Survivin
  - Overexpressed in more than 90% of breast cancer.
- Mammaglobin A
  - Expressed 10 fold-higher in 40-80% of breast cancers.
- hTERT
  - Overexpressed in more than 90% of breast cancer.



DEFINING THE CRITICAL PATHWAY FOR A PREVENTION VACCINE

National Breast Cancer Coalition

NIH NATIONAL CANCER INSTITUTE
Division of Cancer Prevention



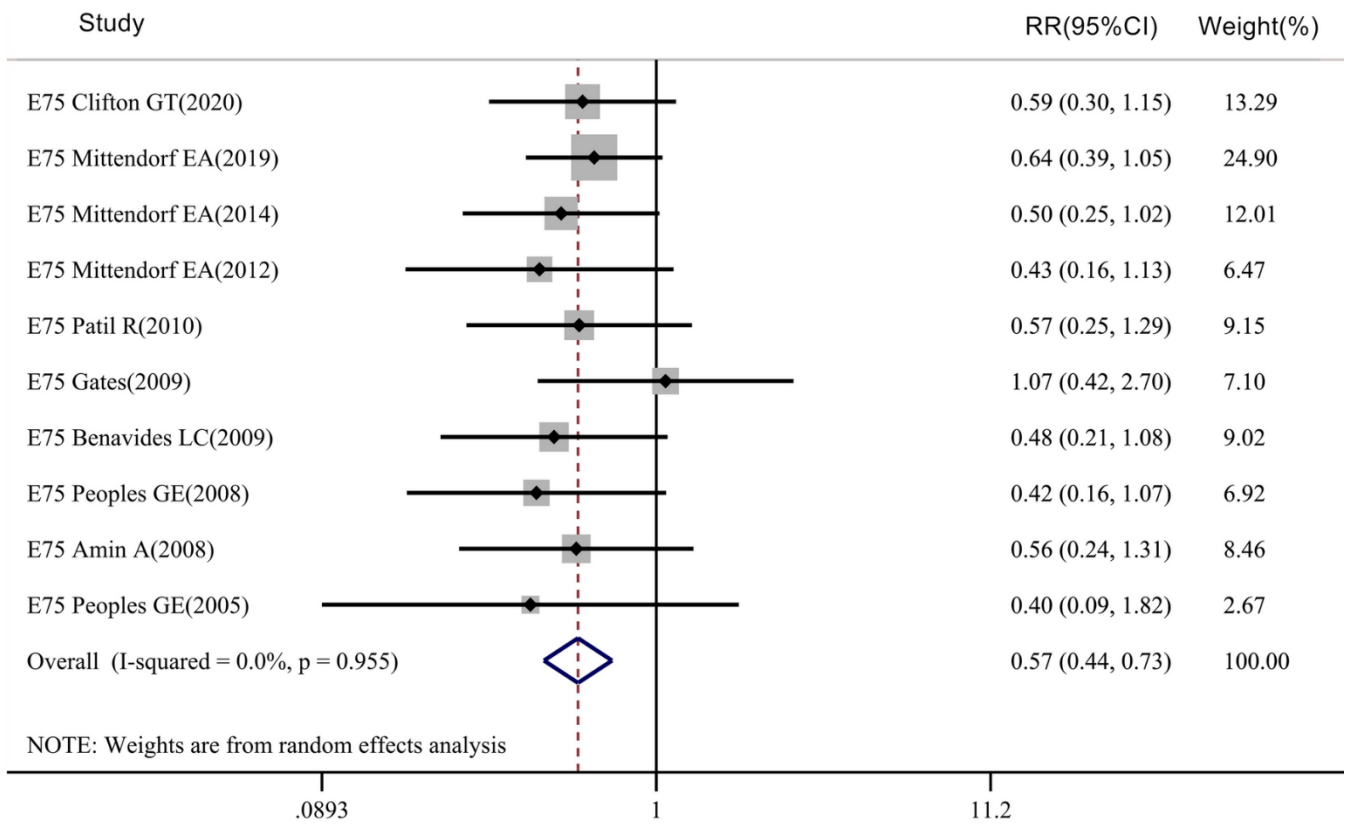
BREAST CANCER PREVENTION VACCINE

Targets 6 antigens
Plasmid prime / viral boost

CONCLUSIONS

- Vaccines for cancer are used in both the therapeutic and prevention settings
- Vaccines target overexpressed proteins or mutated proteins
- Vaccines are potentially useful alone or combination with immune checkpoint blockade
- Vaccines can provide benefit to patients with breast cancer

META-ANALYSIS OF NELIPEPIMUT-S VACCINE SHOWS BENEFIT



You, et. al., *Cancer Cell Intl*, 2021

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NBCC

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Fran Visco, J.D.
Artemis Vaccine Team

Other

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Martin Cannon, Ph.D. University of Arkansas
Nora Disis, M.D. UW
Mac Cheever, M.D. UW
Doug McNeel, M.D. Ph.D. U Wisconsin
Glynn Wilson, Ph.D. Tapimmune
Eric von Hofe, Ph.D. Antigen Express
Robert Hagopian, Polypeptide Group
Anna Degen, Pepscan

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R01 113861
R01 152045
Mayo Ovarian Cancer SPORE
Mayo Breast Cancer SPORE
Mayo Comp Cancer Center
Komen Foundation
Mayo CTSA
MOCA
VaxOnco
TapImmune
Andersen Foundation
Cancurables
National Breast Cancer Coalition
Department of Defense BCRP
Department of Defense OCRP
Jill and Rafic Dahan

Jacoby Center for Breast Health
Center of Individualized Medicine

THANK YOU

QUESTIONS & DISCUSSION