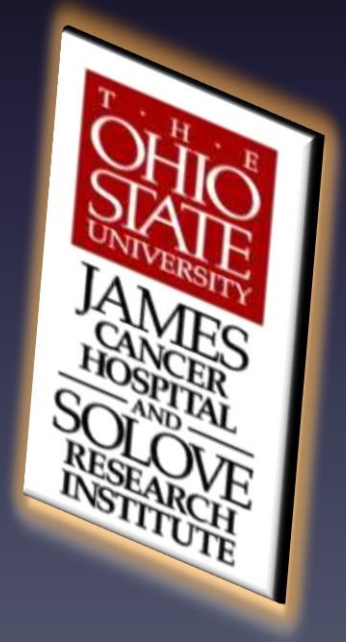
A paradigm shift: Cancer therapy with peptide B-cell epitopes and peptide immuno-therapeutics targeting multiple solid tumor

HER-2 B-CELL EPITOPE-BASED CANCER VACCINES AND COMBINATION IMMUNOTHERAPIES WITH EGFR (HER-1), HER-3, VEGF, IGF-1R , PD-1 , PD-L1 & LAG3

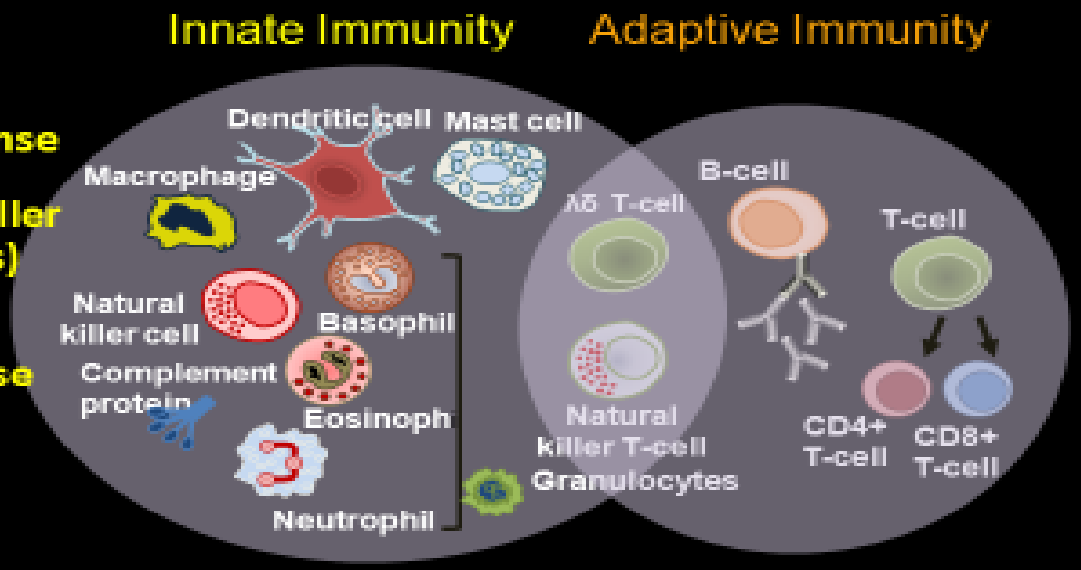
World Vaccine & Immunotherapy Congress
San Francisco Airport Marriott Waterfront,
San Francisco, CA
2-5 December 2019



Immune System Function and Immune Response

Identify and destroy foreign or abnormal cells in the body

- **Nonspecific**
- **First line of defense**
- **WBCs (natural killer cells, neutrophils)**
- **Activation of adaptive response**



- Specific
- Adapts specifically to diverse stimuli
- B-cell antibody production
- T-cell stimulation
- Memory functions

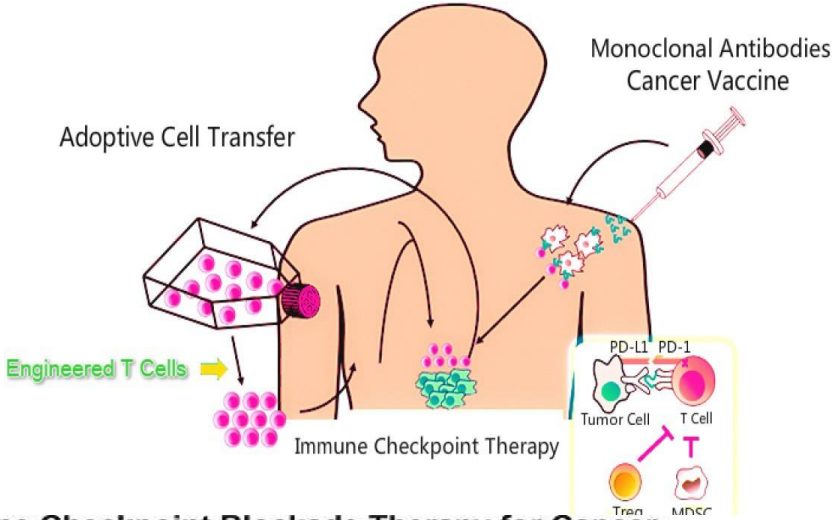
Immune surveillance:

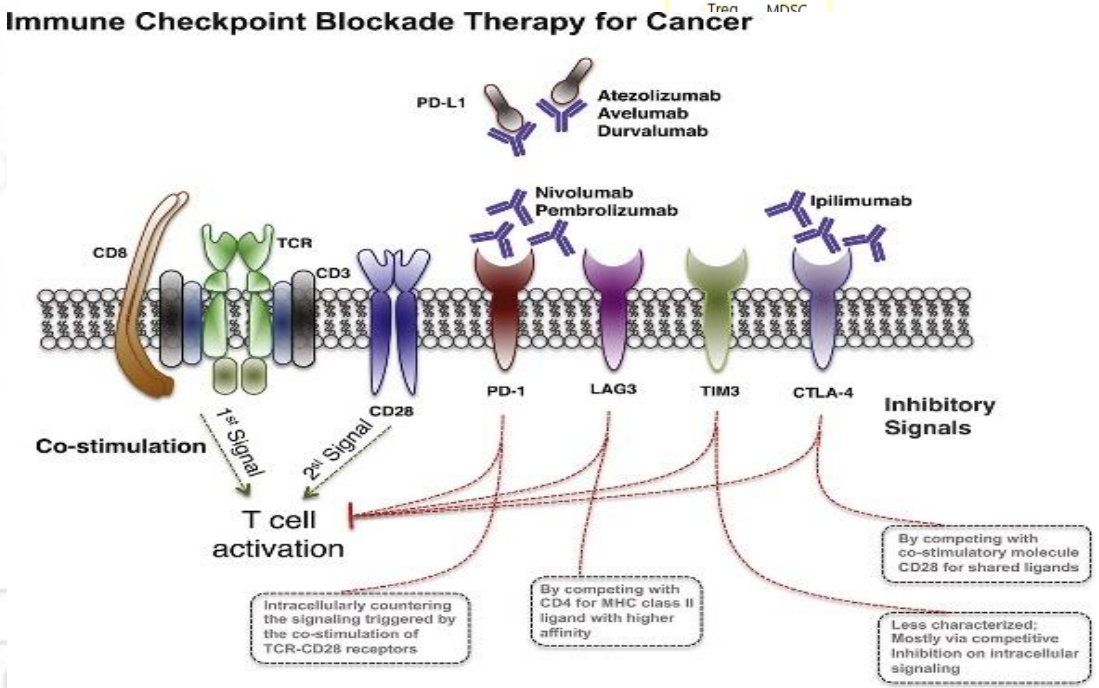
- **Involves both innate and adaptive immune mechanisms**
- **Goal of immunotherapy for cancer: to "educate and liberate" underlying anticancer immune responses**

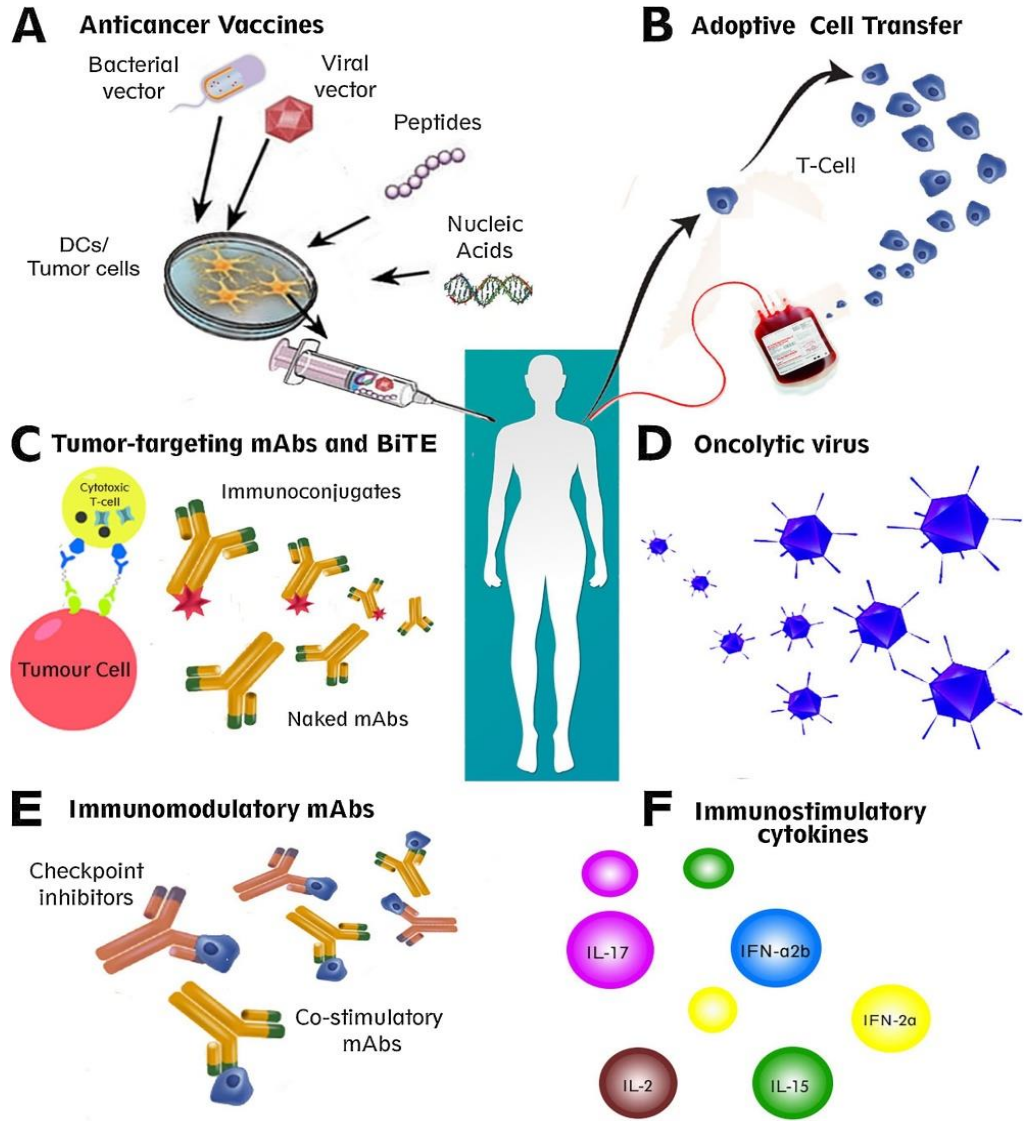
Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

Slide credit: clinicaloptions.com

Different strategies the immune system can be harnessed to target cancer



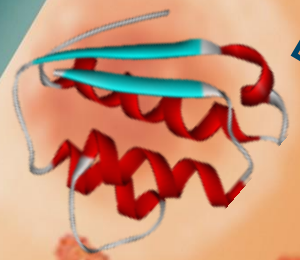




Critical Reviews in Oncology/Hematology/2018, 128,3042

HARNESSING B-CELLS FOR CANCER VACCINES and IMMUNO-ONCOLOGY

ENGINEERING CHIMERIC B-cell & "Promiscuous" T cell epitope vaccine



IS THERE A BETTER WAY TO MAKE ANTIBODIES TO TREAT CANCER?

Teaching B-cells to make antibodies using **peptide antigens**

Monoclonal antibodies are manufactured in a facility

HER-2: ROCHE (Trastuzumab) Herceptin®
(Pertuzumab) Perjeta®

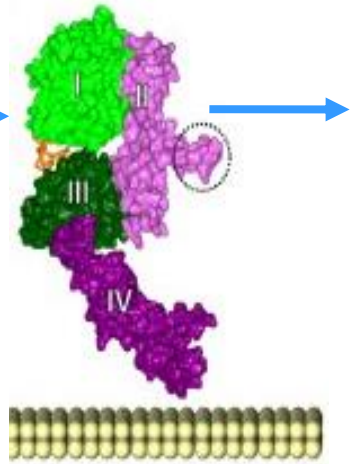
PD-1: MERCK'S (Pembrolizumab) Keytruda®
BMS (Nivolumab) Opdivo®

PD-L1: Atezolizumab)Tecentric®

B-cells are cells in the human body that naturally produce millions of antibodies

OVERALL STRATEGY

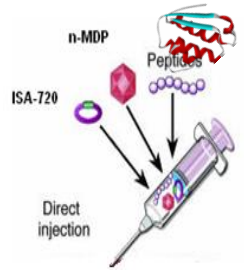
ANTIGENICITY & IMMUNOGENICITY
Prediction B-cell epitopes from Primary Sequence
Identify 5-10
B- CELL EPITOPES

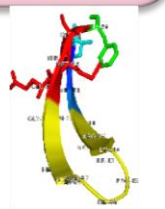
EPITOPE REFINEMENT STRATEGY

1. 3D STRUCTURES/ MODELING
2. AG/AB COMPLEXES
3. MUTAGENESIS STUDIES
4. FINALIZE 5 B-CELL EPITOPE SELECTION

LEAD DESIGN
CONFORMATIONAL B-CELL EPITOPE & CHIMERIC VACCINE WITH (MVF) T-CELL "*PROMISCUOUS*" EPITOPE



HER-1, HER-2, HER-3, VEGF, IGF-1R & PD-1



SYNTHESIS & CHARACTERIZATION OF 5 PEPTIDE MIMICS

GENERATE ANTIPEPTIDE ANTIBODIES IN RABBITS TO 5 CHIMERIC VACCINES

***in vitro* TESTING: PROLIFERATION, PHOSPHORYLATION; IMMUNOGENICITY, ADCC, APOPTOSIS & INVASION**

LEAD CANDIDATE OPTIMIZATION:

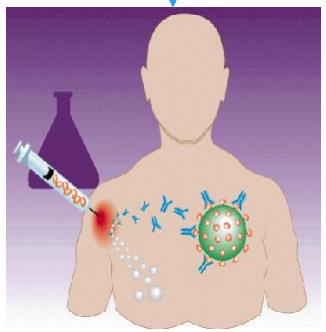
- CORRELATES OF EFFICACY BASED ON COMBINED *in vitro* ASSAYS.
- SELECTION OF BEST PEPTIDE MIMICS AND PEPTIDE VACCINES

: *in vivo* TESTING in TRANSGENIC, SYNGENEIC & TRANSPLANTABLE MOUSE MODELS

IDENTIFICATION: FINAL VACCINE & PEPTIDE MIMIC CANDIDATES

TEST: EFFICACY OF COMBINATION IMMUNOTHERAPY IN MICE

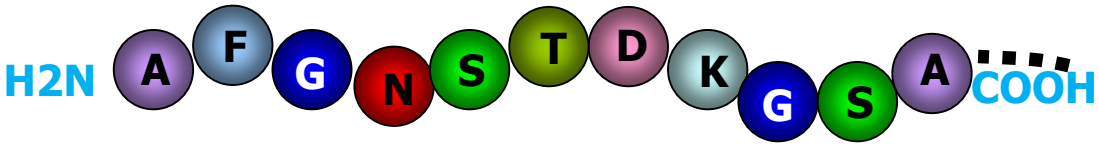
COMBINATIONS IDENTIFIED



Human Clinical
Safety & Toxicity

New Paradigm: WHY B-CELL PEPTIDE VACCINES/THERAPEUTICS

PEPTIDES



As VACCINES

- Majority of vaccine studies designed to elicit CTL's no approved
  - T- cell vaccine by FDA- likely due to lack of checkpoint
- B & T Cell epitopes easily identified to stimulate antitumor immune responses
- Active immunization with antigenic B-cell peptides – can stimulate patient's own immune system to develop specific high affinity
- *natural* polyclonal antibodies- superior to treatment with mAbs
- Must contain both a conformational B-cell epitope, a "Promiscuous" T-cell epitope and requires an adjuvant/vehicle

As THERAPEUTICS

- Inhibitors of signaling pathways and Receptor:ligand interactions
- Less immunogenic than recombinant proteins or mAbs
- Generally small quantities are necessary to activate target receptors
- Degradation to amino acids may be advantageous
- Stabilized for enhanced stability

ADVANTAGES OF B-CELL PEPTIDE APPROACH

PEPTIDE VACCINES

- Safe, nontoxic, highly stable, cost effective and easily manufactured
- No oncogenic material included
- Elicits B and T cell memory responses
- Stimulates patient's own immune system to produce polyclonal antibodies
- Multi-epitope approach leads to broad antigen recognition and universal coverage ("promiscuous" T cell epitope)
- Elicit potent anti-tumor responses
- Break tumor tolerance

As PEPTIDE THERAPEUTICS

- safe and viable therapeutic goal
- effective blocking signaling pathways
- high affinity, selectivity and potency

DISADVANTAGES OF PRESENT THERAPIES

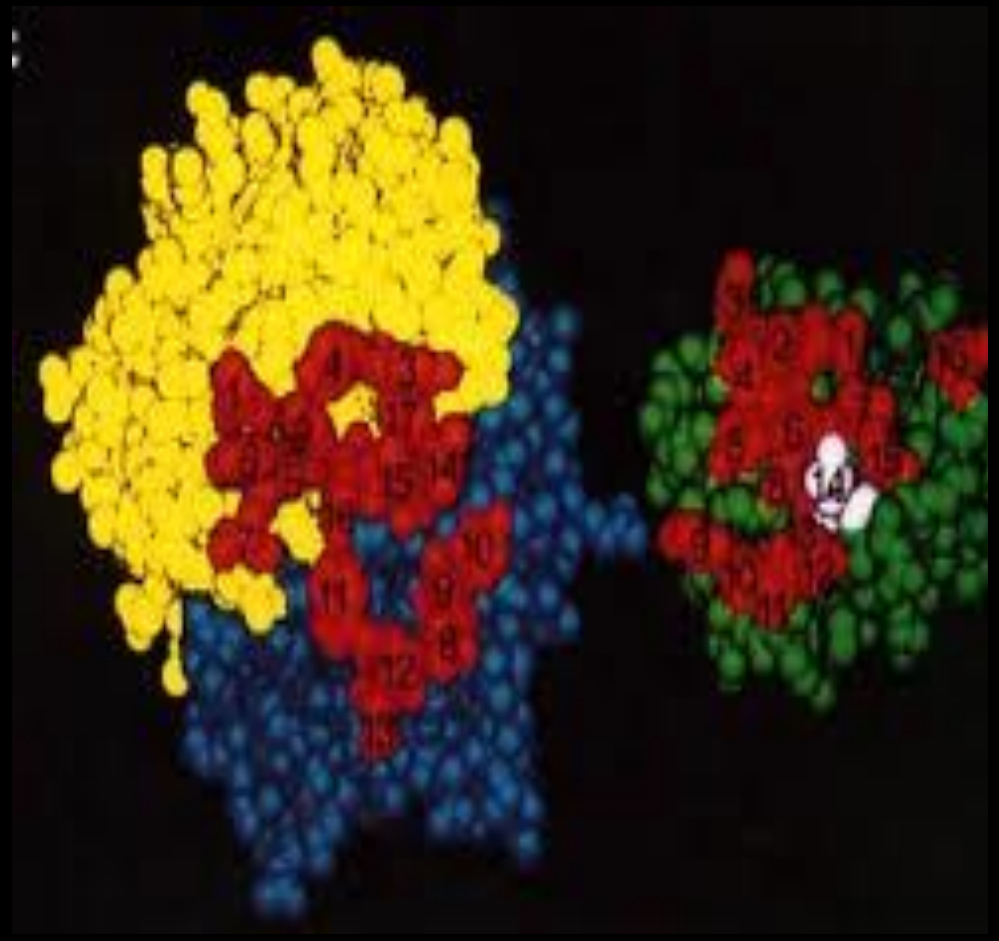
HUMANIZED MAB'S

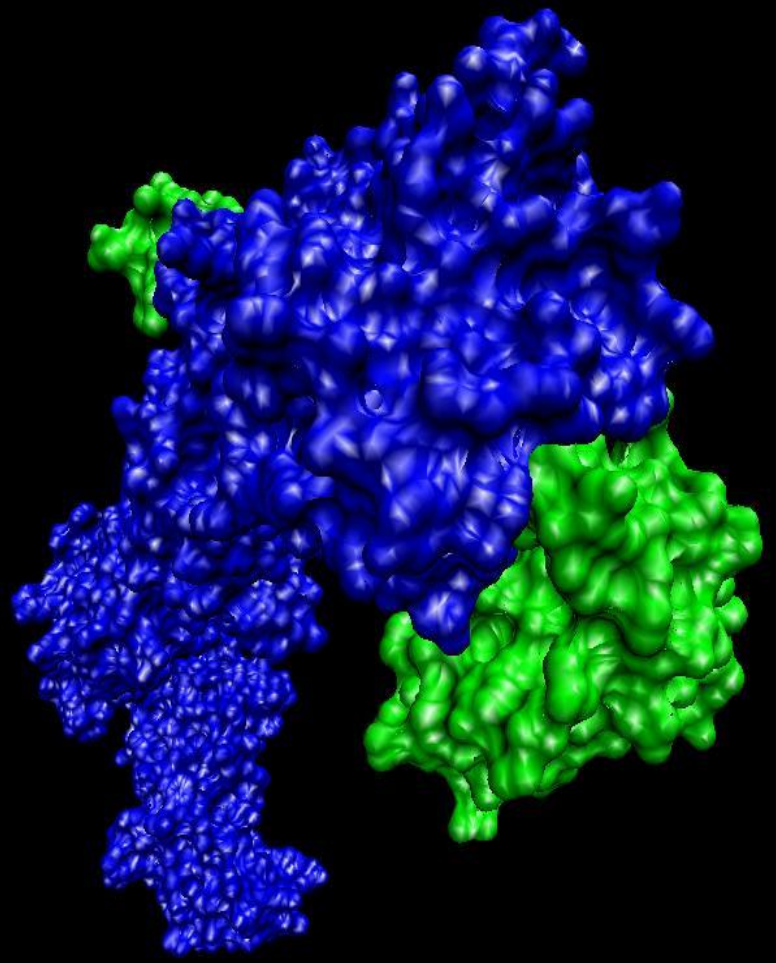
- Poor penetration across tissues
- Ineffective tumor targeting
- Half life 12 days- requires infusion of weakly large quantities of humanized antibodies-resulting in toxicity
- Treatment is very expensive
- Cross-linking leads potential Immunogenicity
- Cardiotoxicity, GI perforation
- NO IMMUNOLOGICAL MEMORY
- TREATMENT NOT A CURE
- RESISTANCE to Targeted Therapies

SMALL MOLECULE RTK'S

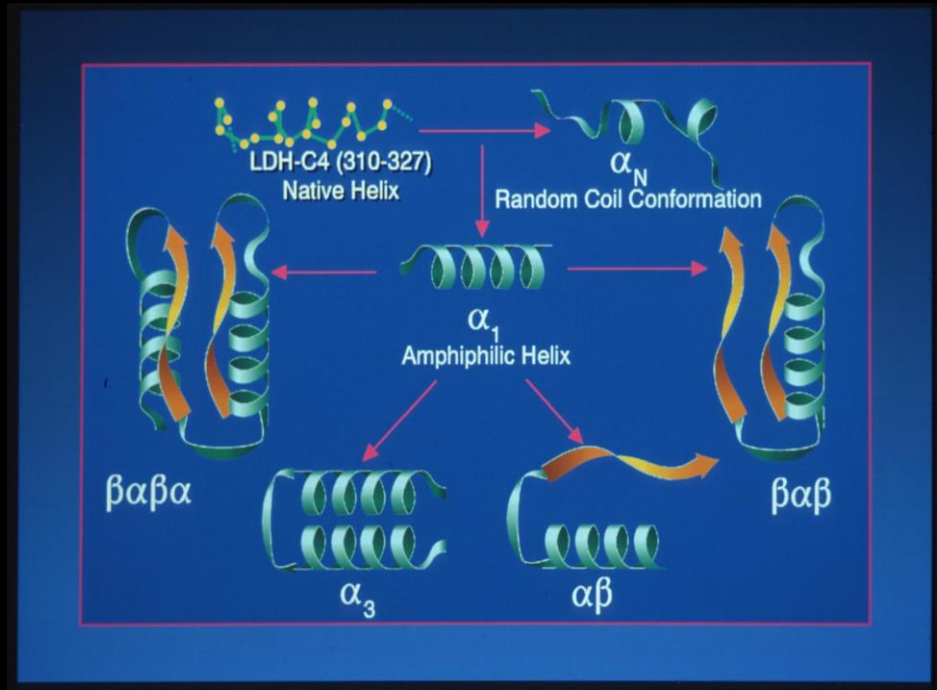
- Highly toxic, non-specific activity,
- serious side effects

Antibody B-Cell epitopes are conformational





Designing Conformational B-Cell Peptide Epitope is a requisite to elicit high affinity Ab responses

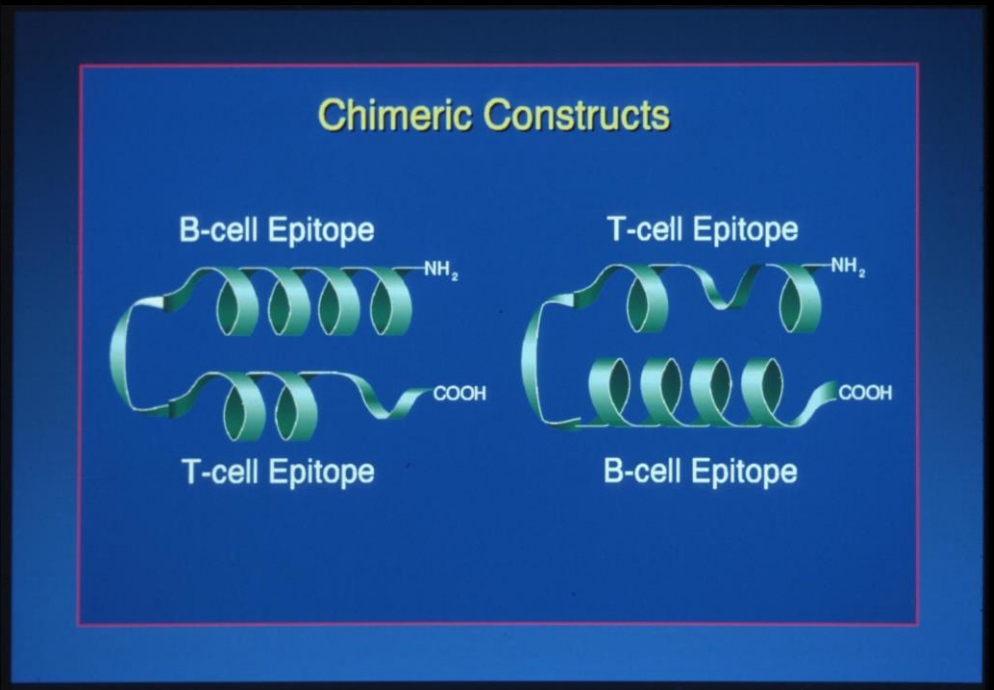


Kaumaya, P.T.P., Berndt, K., Trewhella, J., Kezdy, F.J. and Goldberg, E. (**1990)** *Synthesis and Biophysical Characterization of Topographic Immunogenic Determinants with αα Topologies*. **Biochemistry,** 29,13-23

Kaumaya, P.T.P., VanBuskirk, A., Goldberg, E. and Pierce, S.K. (1992) *Design and Properties of Topographic Immunogenic Determinants of a Protein Antigen (LDH-C_4) as Vaccines*. **J. Biol. Chem.**, 267, 6338-6346

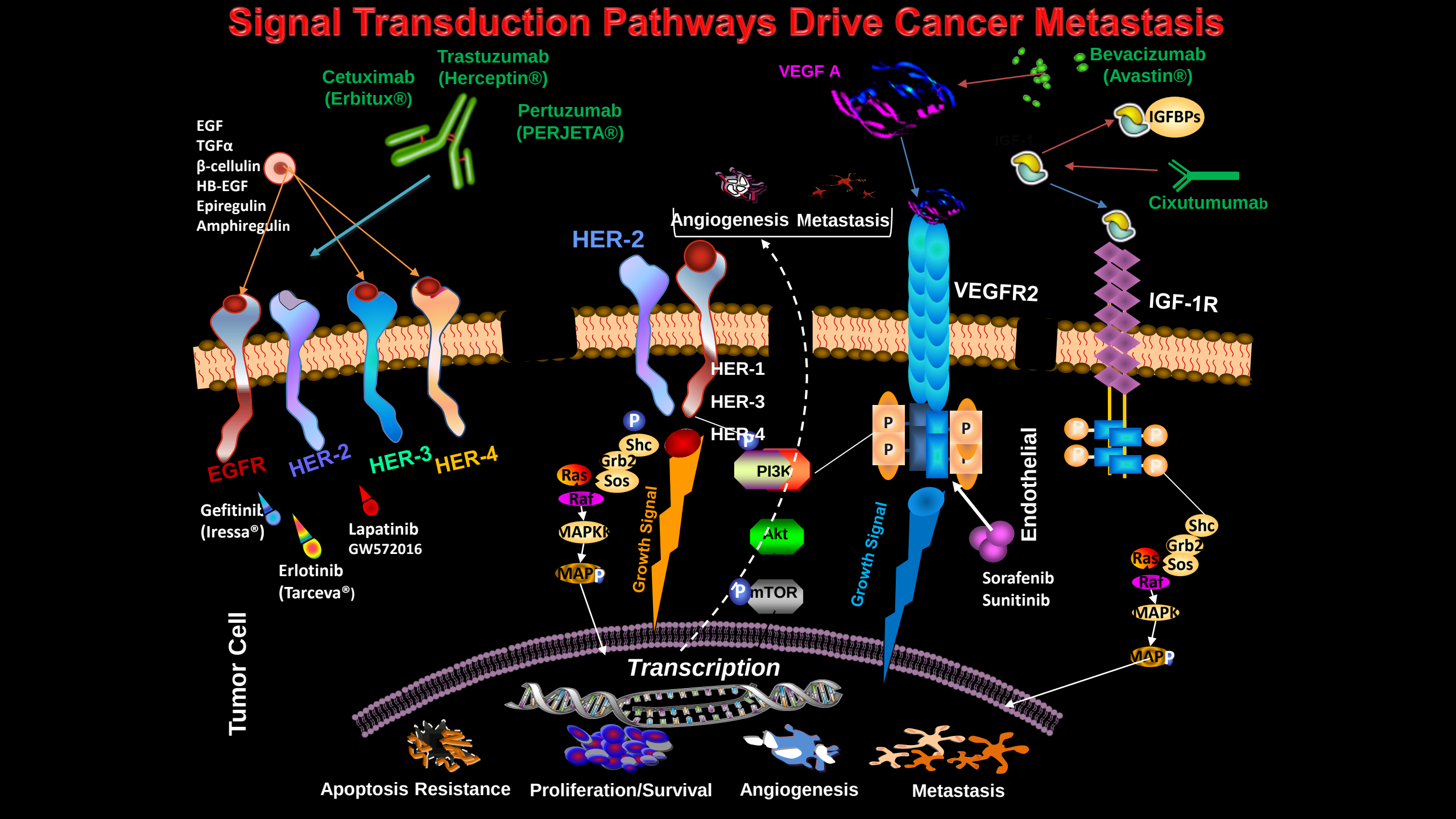
Kobs-Conrad, S., Lee, H., DiGeorge, A.M. and Kaumaya, P.T.P. (1993) *Engineered Topographic Determinants with αα, ββ, and βαβα Topologies show High Affinity Binding to Antigen LDH-C_4*. **J. Biol. Chem.,** 268, 25285-25295

Inclusion of Promiscuous T cell Epitopes required to broaden Immune Response- Universal Vaccine

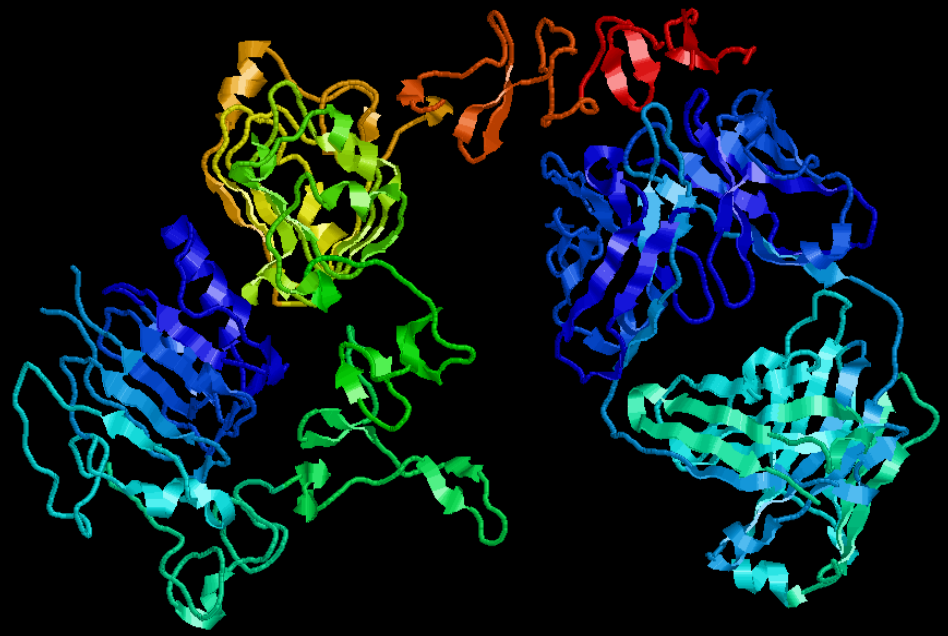


Kaumaya, P. T. P., Feng, N., Kobs-Conrad, S., Seo, Y.H., VanBuskirk, A. M., and Sheridan, J. F. (**1992**). *Immunogenicity and Antigenicity of a Promiscuous T cell Epitope and a Topographic B cell Determinant of the Protein Antigen LDH-C_4.* **PEPTIDES: Chemistry and Biology**, (Eds Smith, J. A. & Rivier, J), Escom, Leiden, pp. 883-885.

Kaumaya, P.T.P., Seo, Y.H., Kobs, S., Ngua, l., Sheridan, J. and Stevens, V. **(1993)** *Peptide vaccines incorporating a "promiscuous" T cell epitope bypass certain haplotype restricted immune responses and provide broad spectrum immunogenicity*. **J. Molec. Recog**. 6, 81-94.


Signal Transduction Pathways Drive Cancer Metastasis
Cetuximab (Erbitux®)
Trastuzumab (Herceptin®)
Pertuzumab (PERJETA®)
EGF
TGFα
β-cellulin
HB-EGF
Epiregulin
Amphiregulin
EGFR
HER-2
HER-3
HER-4
Gefitinib (Iressa®)
Erlotinib (Tarceva®)
Lapatinib GW572016
VEGF A
Bevacizumab (Avastin®)
IGFBPs
IGF-1
Cixutumumab
Angiogenesis
Metastasis
HER-2
HER-1
HER-3
HER-4
VEGFR2
IGF-1R
Endothelial
Shc
Grb2
Sos
Ras
Raf
MAPKK
MAPK
PI3K
Akt
mTOR
Growth Signal
Growth Signal
Sorafenib
Sunitinib
Tumor Cell
Transcription
Apoptosis Resistance
Proliferation/Survival
Angiogenesis
Metastasis

HER-2 & Trastuzumab COMPLEX

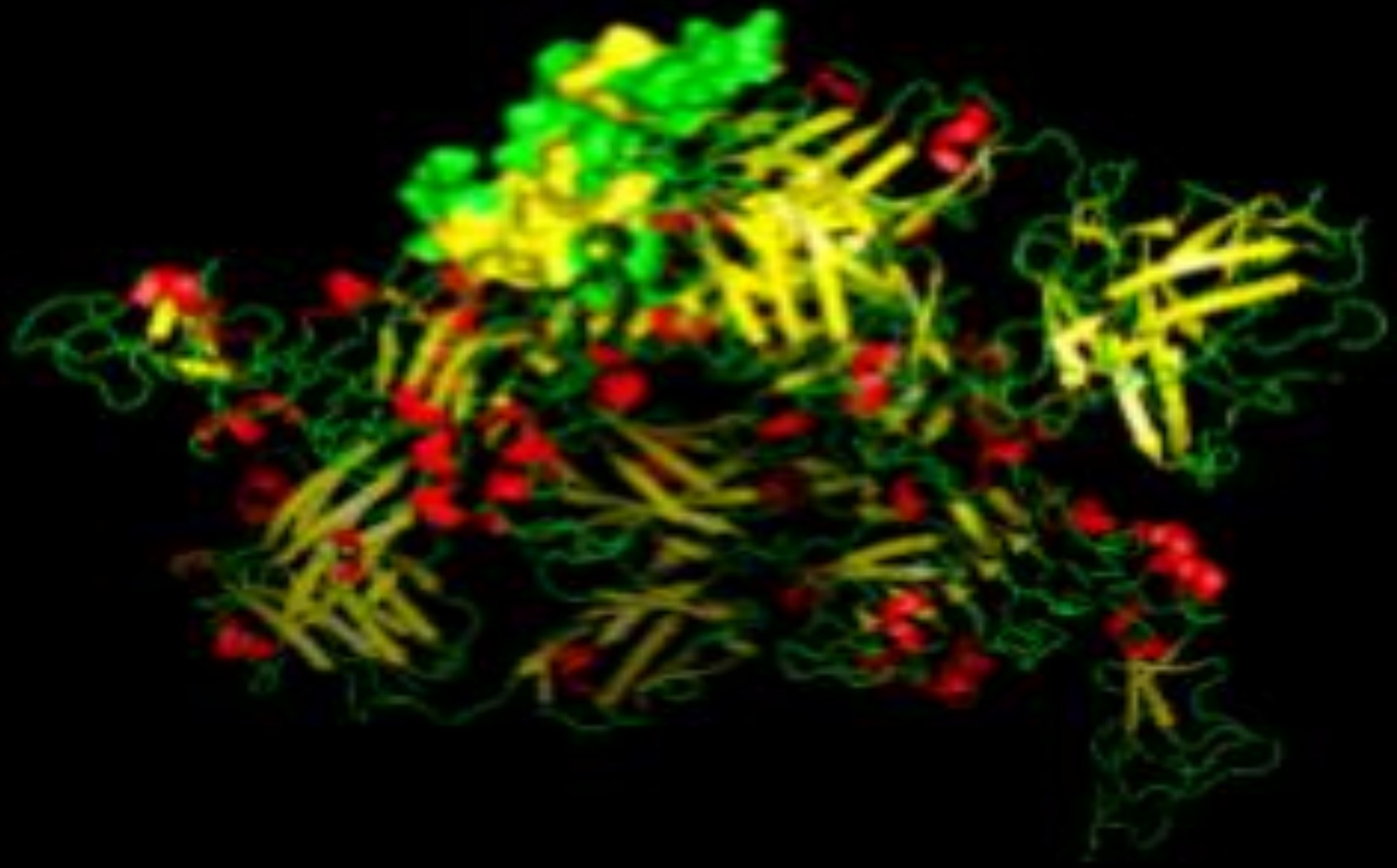


2nd GENERATION ENGINEERED HER-2 VACCINE

Designation	Peptide	Sequence	M.Wt. (da)
MVF 563 CYC	**563-598** peptide with 3 disulfide bonds	H_2N-*KLLSLIKGVIVHRLEGVE*-**GPSL**- CHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVA-COOH	6181
MVF 585 CYC	585-598 peptide with one disulfide bond	H_2N-*KLLSLIKGVIVHRLEGVE*-GPSL- VACAHYKDPPFCVA-COOH	3856
MVF 597 CYC	**597-626 peptide with one disulfide bond**	**H_2N-*KLLSLIKGVIVHRLEGVE*-GPSL- VARCPSGVKPDLSYMPIWKFPDEEGACQPL**	**5672**
MVF 613	**613-626** peptide	H_2N-*KLLSLIKGVIVHRLEGVE*-GPSL- IWKFPDEEGACQPL-COOH	3977

Garrett et al., & Kaumaya (2007) *Novel Engineered Trastuzumab Conformational Epitopes Demonstrate In Vitro and In Vivo Antitumor Properties against HER-2neu.* J. Immunol. 178 (11),7120-7130

HER-2 AND PERTUZUMAB COMPLEX

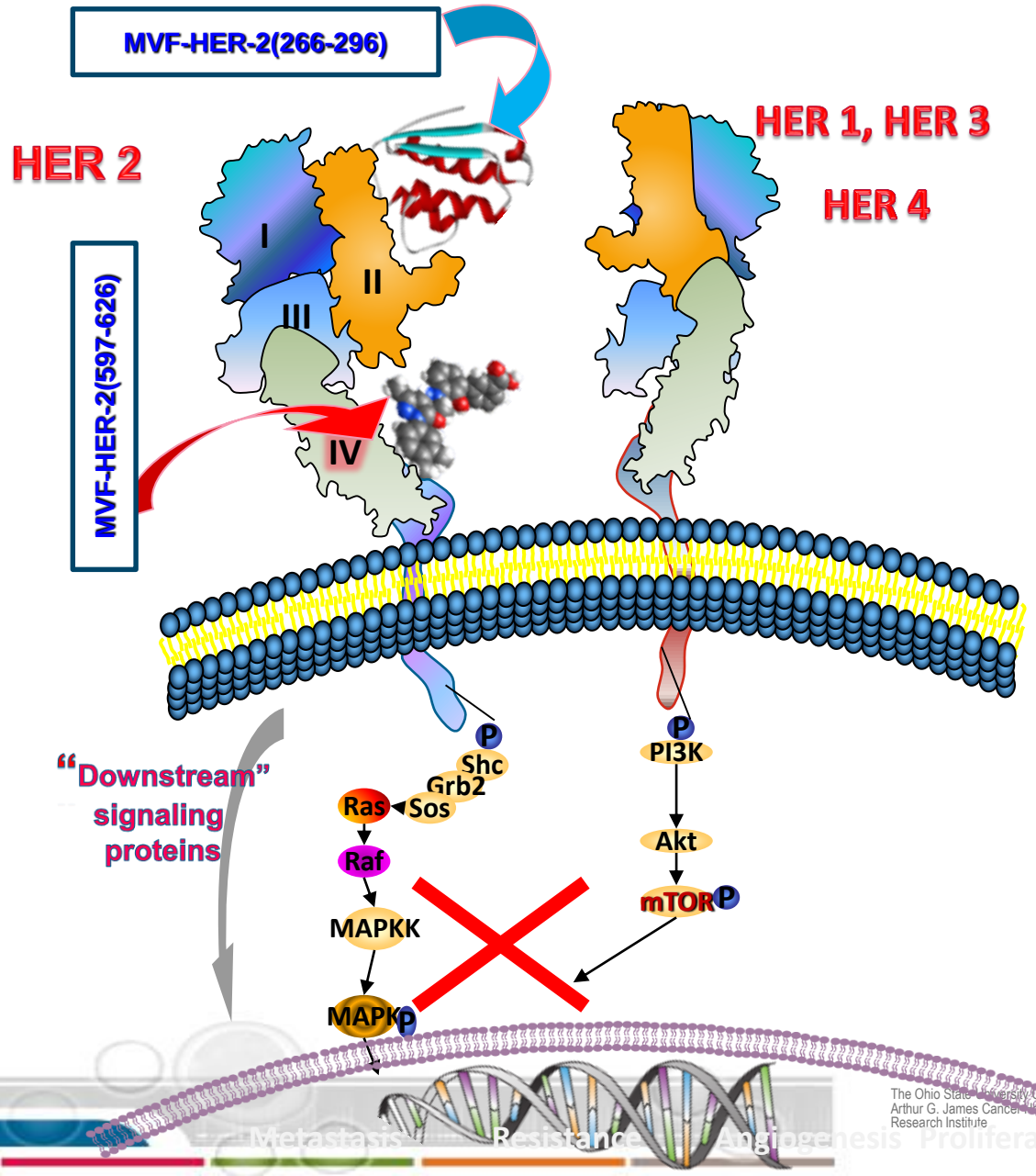


PEPTIDE VACCINES HER-2/PERTUZUMAB STRUCTURE

Designation	Peptide	Sequence	M.Wt. (da)
MVF 266 CYC	266-296 peptide with one disulfide bond	H_2N-*KLLSLIKGVIVHRLEGVE*-GPSL-LHCPA LVTYNTDTFESMPNPEGRYTFGASCV-COOH	5423
MVF 298 CYC	298-333 peptide with two disulfide bonds	H_2N-*KLLSLIKGVIVHRLEGVE*-GPSL-ACPYNYLSTD**V**G**S**CTLVCP**LH**NQEVTAEDGTQRCE**K-COOH**	6297
MVF 315 CYC	315-333 peptide with one disulfide bond	H_2N-*KLLSLIKGVIVHRLEGVE*-GPSL-CP**LH**NQEVTAEDGTQRCE**K-COOH**	4493

Allen et al., & Kaumaya, (2007) *Peptide Vaccines of the HER-2/neu Dimerization Loop are Effective in Inhibiting Mammary Tumor Growth in vivo*. **J. Immunol. 179, 472-482**

PHASE I/IIB CLINICAL TRIAL- COMBINATION OF MVF-HER-2 PEPTIDES 266-296 (pertuzumab-like) & 597-626 (trastuzumab-like)



- NCI Funds- CA 135608: $750,000
- FORE CANCER RESEARCH-$150,000
- OSU CCC Pelotonia-$100,000

◆ GMP Vaccine Manufacturing

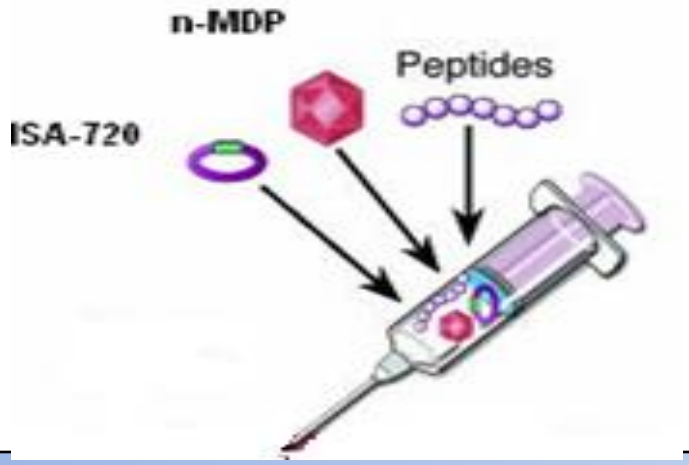
- FDA IND FEB 2012
- BBIND # 14633
- IRB- OSU 09138-MAY 2012-2010C0075

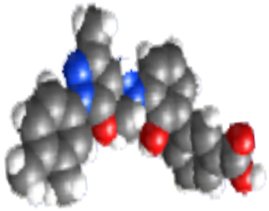
✓NCI Trial Identifier: 2011-00920
✓ClinicalTrials.gov Identifier: NCT-01376505

- Trial Accrual-2012@ OSU James Cancer Hospital
- Primary Aims: Determine OBD, safety, toxicity and correlate immune effects

Phase II Efficacy Trial Start Dec 2018

Dose Levels:





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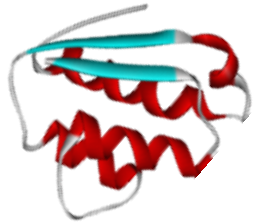
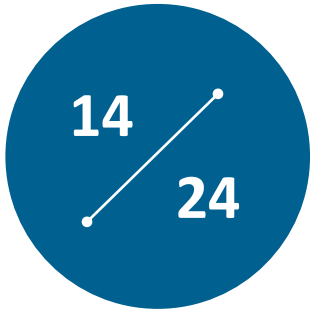


MVF-HER-2-597-626 MVF-HER-2-266-296

Total Phase 1: 51 Patients			
Dose level (patients)	MVF-HER-2(597-626) + MVF-HER-2(266-296) mg	Nor-MDP(mg)	Vehicle: Seppic ISA 720 volume (ml)
1 (6)	1.0 + 1.0 = 2.0 mg	0.025	1.0
2 (6)	1.5 + 1.5 = 3.0 mg	0.025	1.0
3 (6)	2.0 + 2.0 = 4.0 mg	0.025	1.0
4 (6)	2.5 + 2.5 = 5.0 mg	0.025	1.0

HER-2 VACCINE (B-VAXX) PI & IND Holder: Pravin Kaumaya ; Licensed to IMUGENE

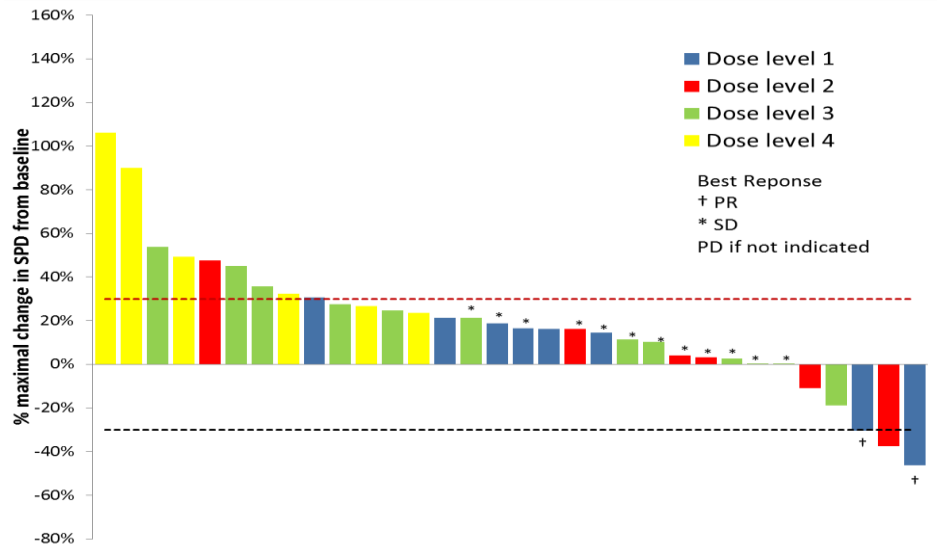
ENCOURAGING PHASE 1 TRIAL RESULTS

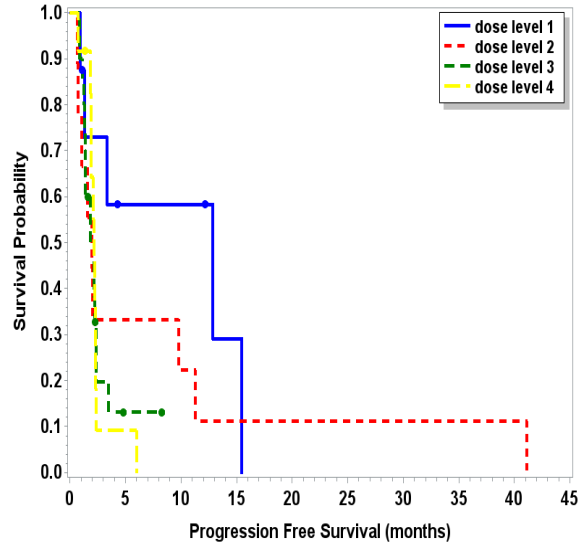


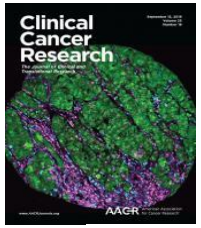
Patients had stable disease

- *2 out of 24 patients had partial response.*
- *1 patient had PFS at 40+ months*
- *6 patients received 6 months boost*

NO TOXICITY OBSERVED







Phase I Immunotherapy Trial with Two Chimeric HER-2 B-cell Peptide Vaccines Emulsified in Montanide ISA 720VG and Nor-MDP Adjuvant in Patients with Advanced Solid Tumors. Tanios Bekaii-Saab, Robert Wesolowski, Daniel H. Ahn, Christina Wu, Amir Mortazavi, Maryam Lustberg, Bhuvaneswari Ramaswamy, Jeffrey Fowler, Lai Wei, Jay Overholser, **and Pravin T.P. Kaumaya**.

Online First on February 25, 2019; DOI: 10.1158/1078-0432. *Clinical Cancer Research* (CCR-18-3997)

***Highlighted in the Immunotherapy section*: Clin Cancer Res. June 15, 2019, 25 (12), 3495-3507;**

AACR American Association for Cancer Research FINDING CURES TOGETHER

Abstract CT 017: AACR PRESENTATION APRIL 01, 2019

Phase Ib Immunotherapy Trial with a Combination of Two Chimeric (Trastuzumab-like and Pertuzumab-like) HER-2 B Cell Peptide Vaccine emulsified in ISA 720 and nor-MDP Adjuvant in Patients with Advanced Solid Tumors, Immunological Response and Clinical Outcome. Bekaii-Saab T, Wesolowski R, Ahn DH, Wu C, Mortazvi A, Lustberg M, Fowler J, Wei L, Overholser J, **Kaumaya PTP**

PHASE II TRIAL ongoing at the James Cancer Hospital:

PI:P Kaumaya

Funding NIH R01 CA CA84356 & NIH R21 CA13508 to PTPK

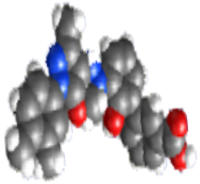
The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

The James Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

17

THE VACCINE WORKS IN INNOVATIVE WAYS



MVF-HER-2-597-626
Trastuzumab-like

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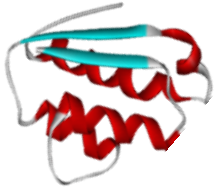
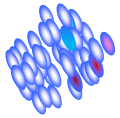
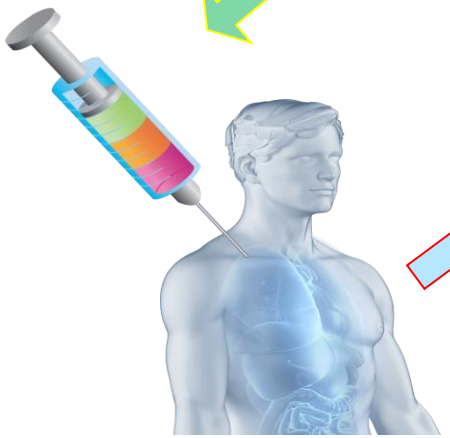


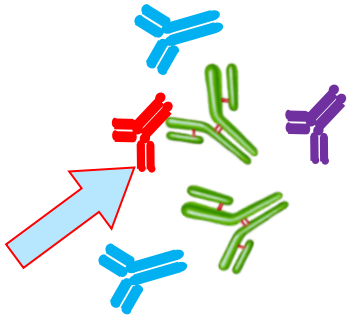
MVF-HER-2-266-296
Pertuzumab-like

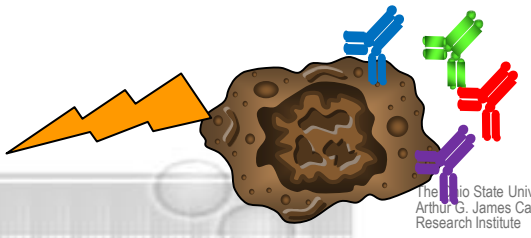
ISA-720 montanide

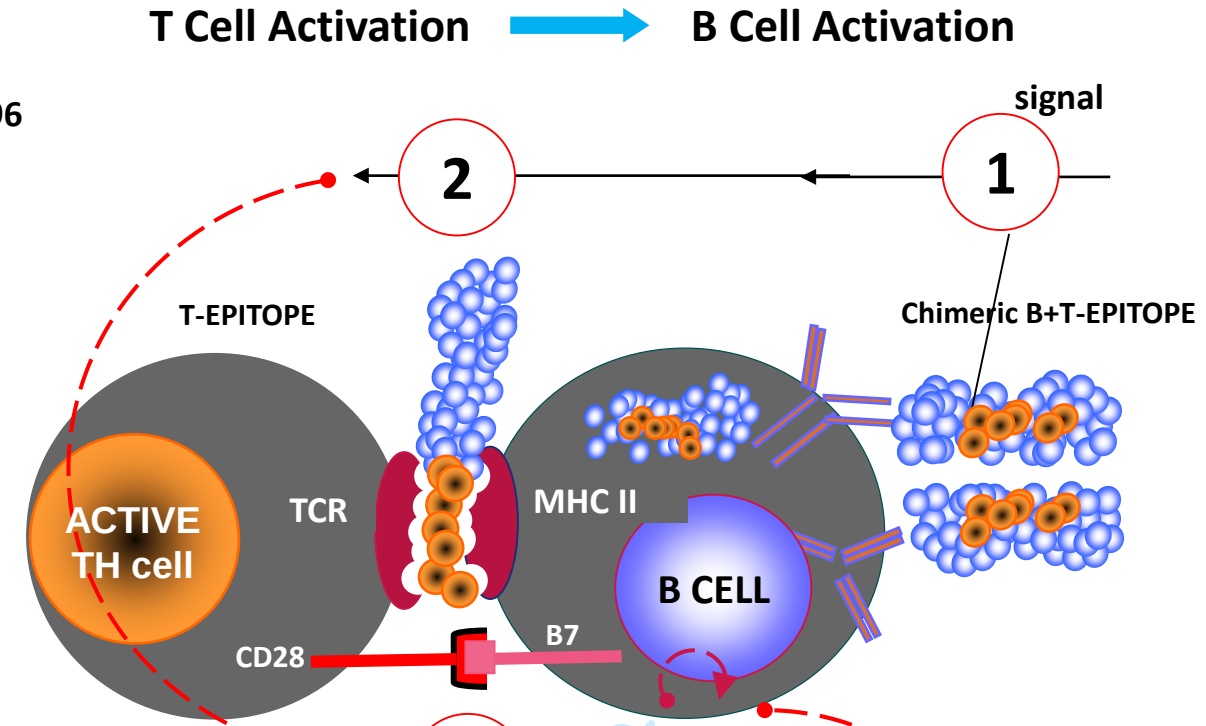


Nor-MDP Adjuvant









OSU Immunotherapy & Vaccine Program LICENSED TO IMUGENE

Developmental Phase: Pre clinical

OSU- INNOVATIVE TECHNOLOGY

	Discovery & Design	Synthesis, Immunogenicity & *in vitro* assays	*In vivo* Transgenic mice, Syngeneic & Tumor Challenge
1st GEN. HER-2 Vaccine (316-339 + 628-647)			US 7,060,284; US 7,666,430; *Cancer. Res.* (2000) 60,3782-3789 *J. Immunol.* (2003),170,4242-4253. *J.Clin.Oncol* (2009) 27(31),5270-5277.
2nd GEN. HER-2 Vaccine (597-626 + 266-296)			US 7,691,396 B2; US/697,578; PCT06/23672; AU2006261342; JP2008-517193; EP6785065 ; CA2,612,394; US 9,452,204 B2 Sep 26, 2016 ; NZ564,951. J.Immunol (2007)178,7120-7130; *J.Immunol* (2007)179, 472-482
VEGF mimics P3 & P4			US 11,052,721; *J.Biol.Chem* (2011) 286(15),13612-13624
Combination Therapy HER-2 mimic (266-296) + VEGF mimic (P3 & P4)			US 2010/0234283 A1; *J.Biol.Chem* (2011) *286(15),16326-13637*
Immunotherapy HER-2 Vaccine + VEGF mimic			US 2010/0234283A1; *Future Oncology* (2011) 7,807; OncoImmunology (2012) 1:7,1048-1060
Combination HER-2 vaccine + VEGF + Taxol			US 2010/0234283 A1; OncoImmunology (2012) 1:7, 1004-1016
HER-1 (EGFR)			US2016/0002313A1; J. Immunol (2013); 191:217-227
HER-3 Vaccine/Therapy			US2016/0002313A1; Jan7, 2016; OncoImmunology 3:10, e956005,2014
IGF-1R Vaccine/Therapy			US2016/0002313A1; Jan7, 2016; OncoImmunology 3,10, e956012 2014
COMBINATIONS: HER-1; HER-2; HER-3, IGF-1R			US2016/0002313A1; Jan7, 2016 Human Vaccines & Immunotherapeutics 11:6, 1368--1386; 2015
VEGF Vaccine			US 11/052,721; US2005/0233964A1 ; Gynecol Oncol (2010) 119 (3) 562
Autoimmune Disease *Retro-inverso D- Peptide*			US 7,220,822 B2; J. Immunol (2001), 167(1):578; J. Immunol (2002) 169 (4), 2180

Clinical Phase Phase I

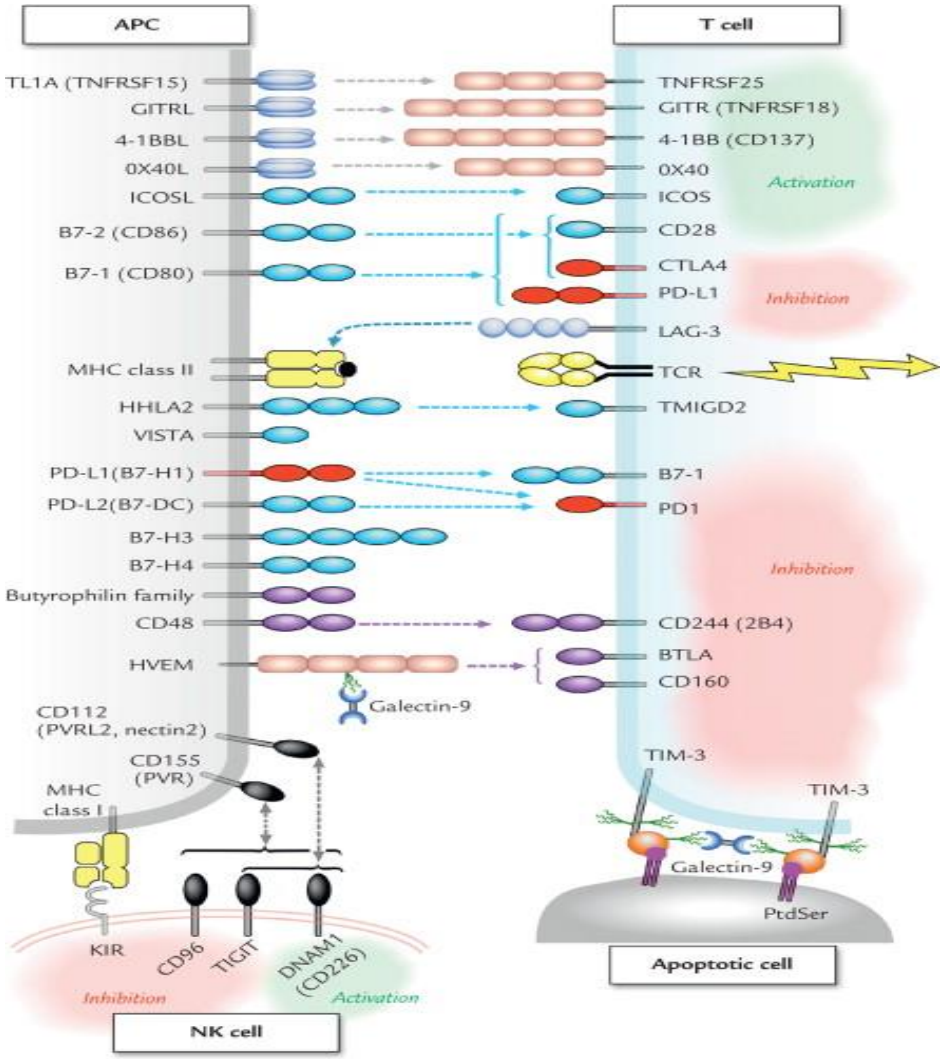
NCI-CA84356
BB-IND- 9803
IRB CO108
COMPLETED

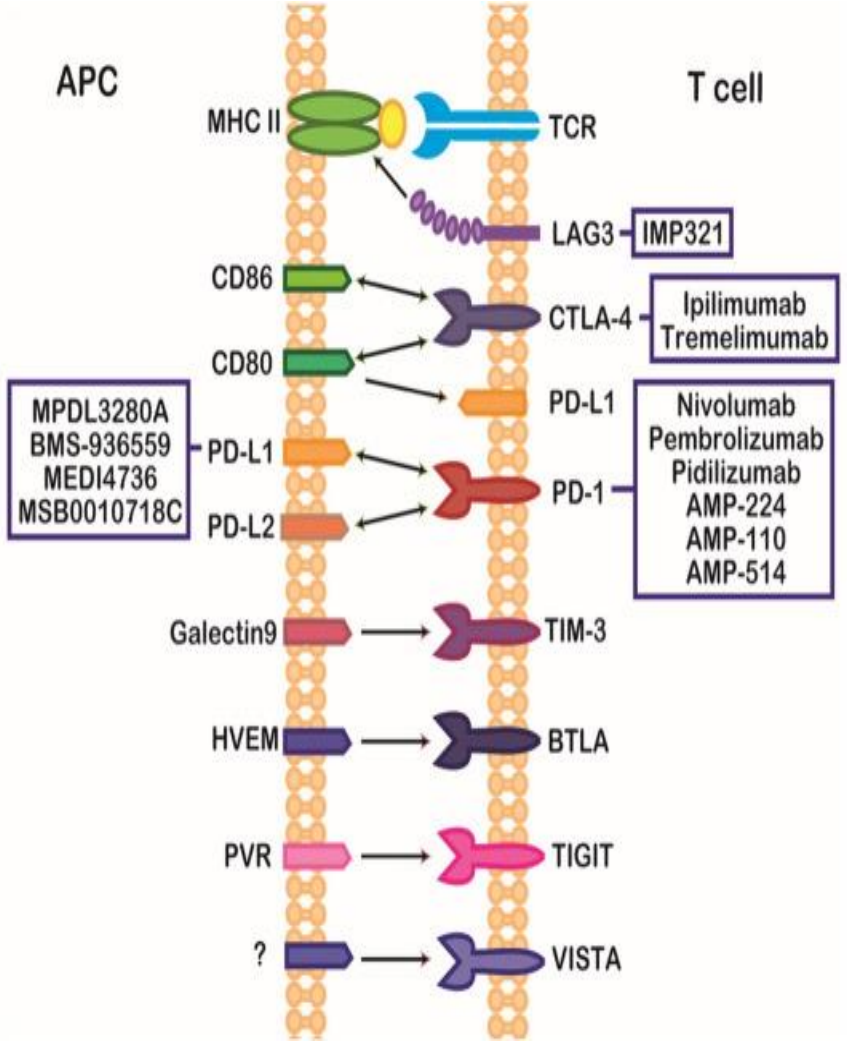
NCI FUNDING – CA135608
FDA/IND #14633
IRB 2010 C0075
NCT01376505
TRIAL JAMES
Cancer Hospital
Phase I completed

Product Development Phase II & III

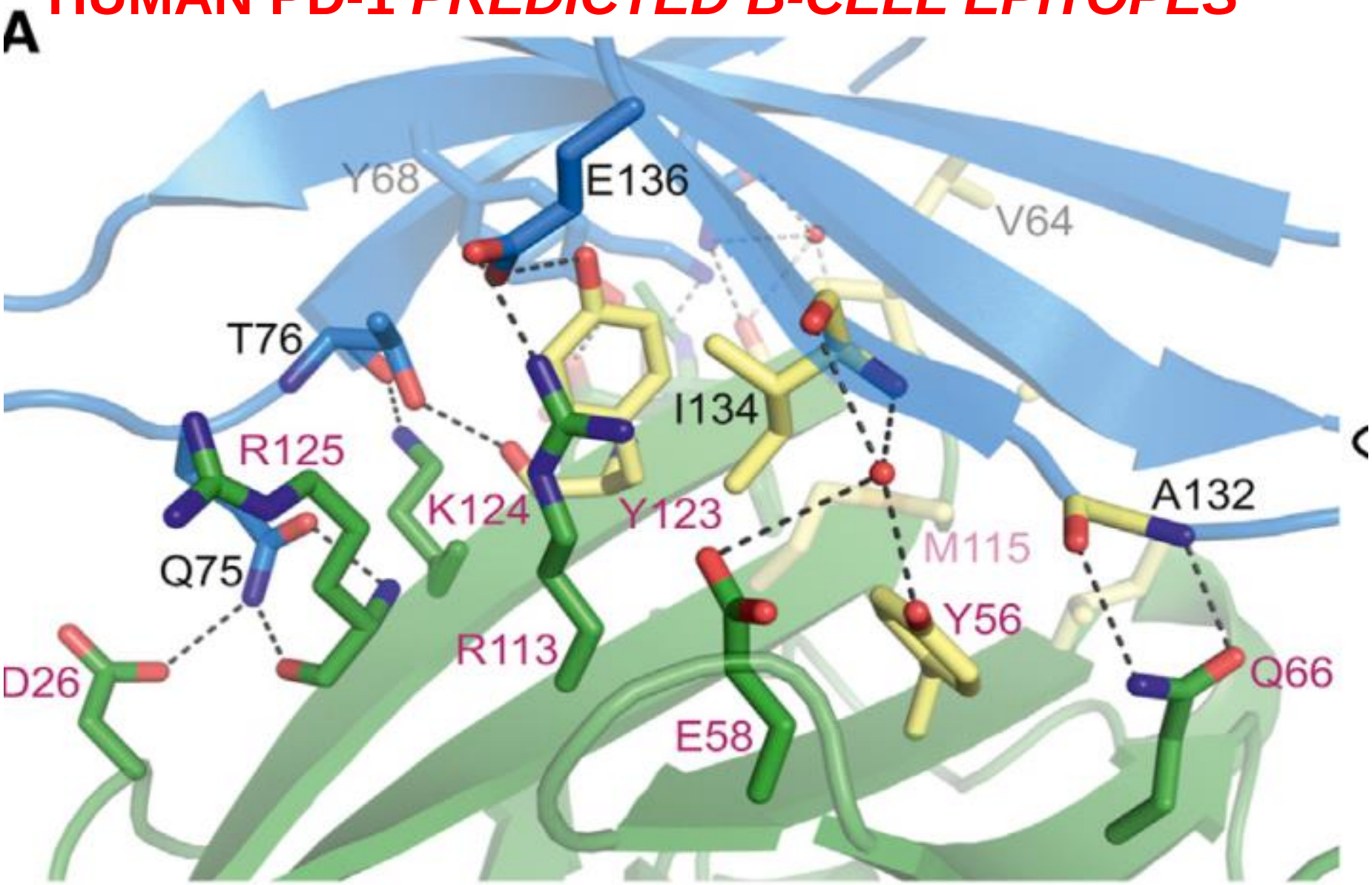
PHASE II opened DEC 2018
NCT01376505
NCI FUNDED

IMMUNE CHECKPOINT INHIBITORS MAY LEAD TO THE NEXT-GENERATION CANCER IMMUNOTHERAPY

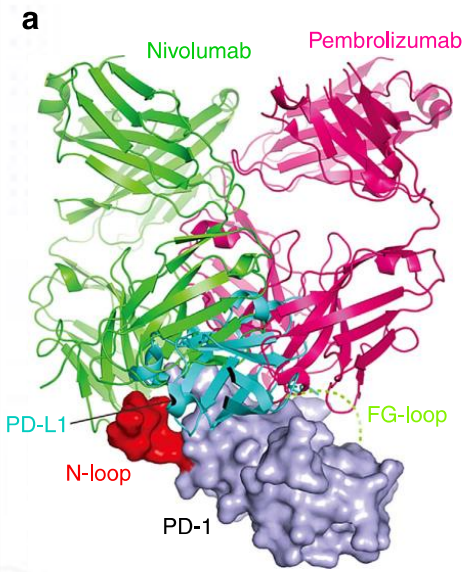




HUMAN PD-1 *PREDICTED B-CELL EPITOPES**



PD-1 B CELL VACCINES IDENTIFIED



PEPTIDES	AMINO ACID SEQUENCES OF SYNTHESIZED PD-1 PEPTIDES
PD-1 (32-50)	H_2N-^{32} V-L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F^{50}-$CONH_2$
AC-PD-1 (32-50)	CH_3CONH-^{32} V-L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F^{50}-$CONH_2$
MVF-PD-1 (32-50)	KLLSLIKGVIVHRLEGVE-GPSL- V-L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F-CONH2
PD-1 (45-64)	H_2N- ^{45}K-L-A-A-F-P-E-D-R-S-Q-P-G-Q-D-C-R-F-R^{64} $CONH_2$
Ac-PD-1 (45-64)	CH_3CONH^{45}K-L-A-A-F-P-E-D-R-S-Q-P-G-Q-D-C-R-F-R^{64} $CONH_2$
MVF-PD-1 (45-64)	KLLSLIKGVIVHRLEGVE-GPSL^{45}K-L-A-A-F-P-E-D-R-S-Q-P-G-Q-D-C-R-F-R^{64} $CONH_2$
PD-1 (73-90)	H_2N-^{73}D-F-H-M-S-V-V-R-A-R-R-N-D-S-G-T-Y-L^{90} -$CONH_2$
AC-PD-1 (73-90)	CH_3CONH-^{73}D-F-H-M-S-V-V-R-A-R-R-N-D-S-G-T-Y-L^{90} -$CONH_2$
MVF-PD-1 (73-90)	KLLSLIKGVIVHRLEGVE-GPSL- ^{73}D-F-H-M-S-V-V-R-A-R-R-N-D-S-G-T-Y-L^{90} -CONH2
PD-1 (92-110)	H_2N-^{92}G-A-I-S-L-A-P-K-A-Q-I-K-E-S-L-R-A-E-L^{110} -$CONH_2$
AC-PD-1 (92-110)	CH_3CONH-^{92}G-A-I-S-L-A-P-K-A-Q-I-K-E-S-L-R-A-E-L^{110} -$CONH_2$
MVF-PD-1 (92-110)	KLLSLIKGVIVHRLEGVE-GPSL-^{92}G-A-I-S-L-A-P-K-A-Q-I-K-E-S-L-R-A-E-L^{110} -CONH2

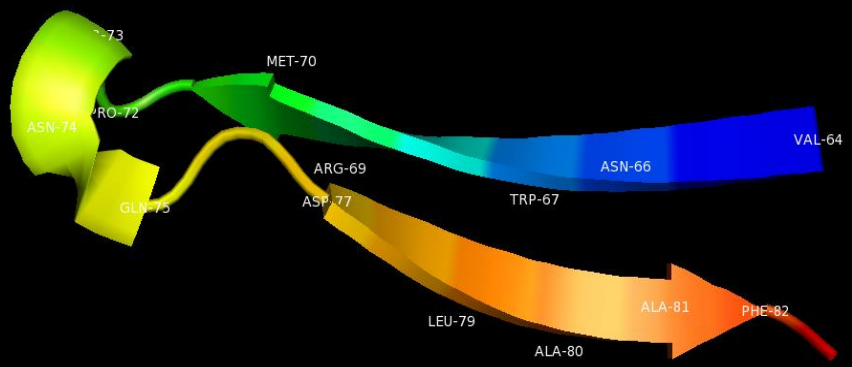
PD1-Vaxx PD-1 epitope

PD1-Vaxx peptide vaccine

Engineered HUMAN PD-1 *B-CELL EPITOPES*

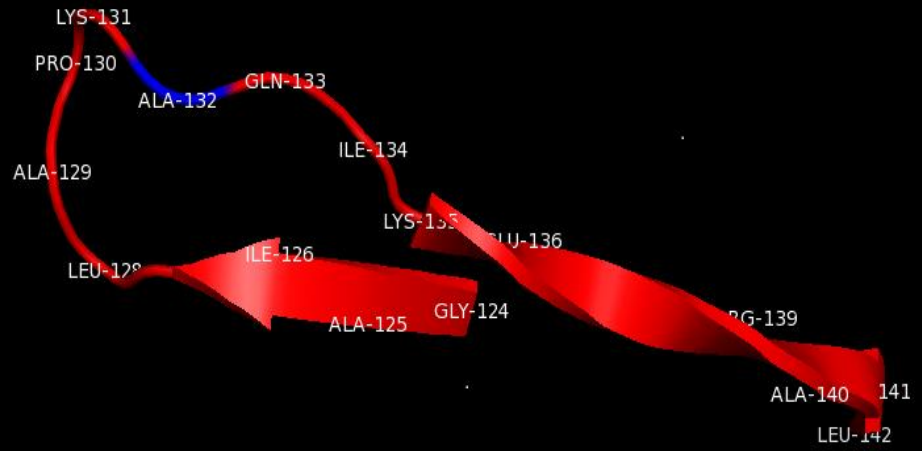
PD-1: 32-50:

^{32}V-L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F^{50}



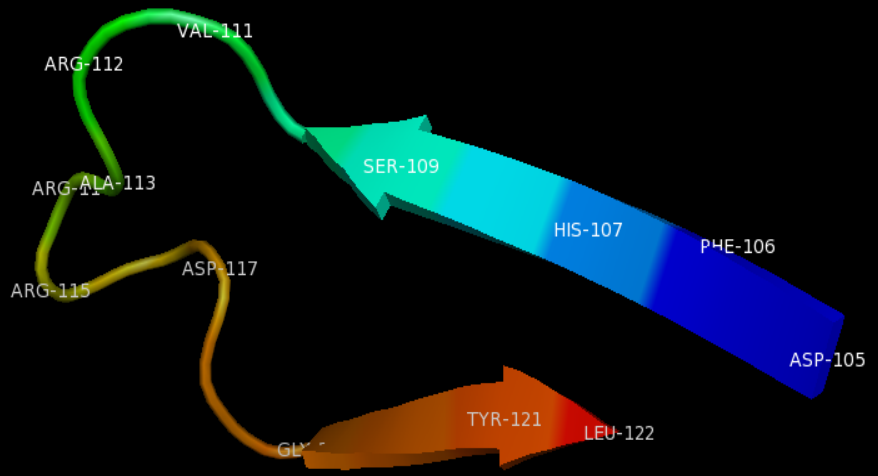
PD-1: 92-110:

^{92}G-A-I-S-L-A-P-K-A-Q-I-K-E-S-L-R-A-E-L^{110}



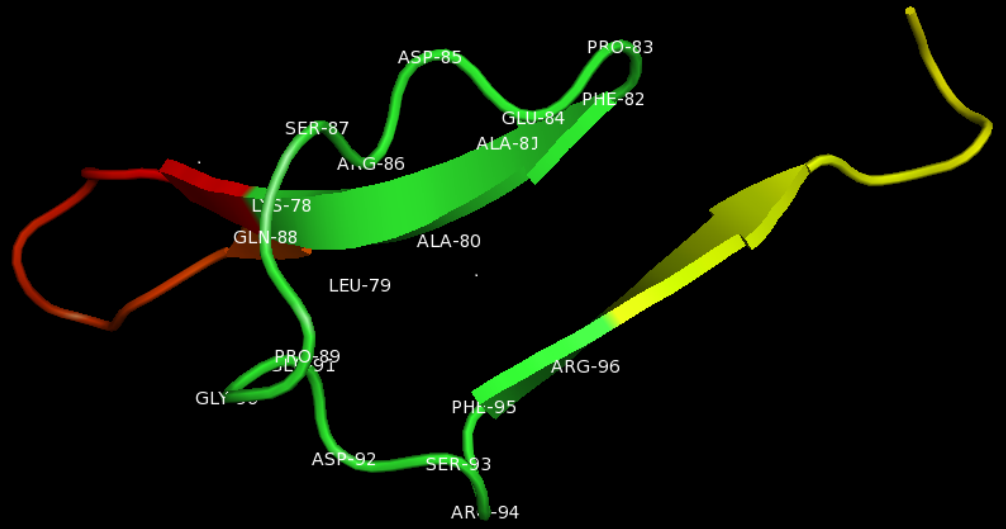
PD-1: 73-90:

^{73}D-F-H-M-S-V-V-R-A-R-R-N-D-S-G-T-Y-L^{90}

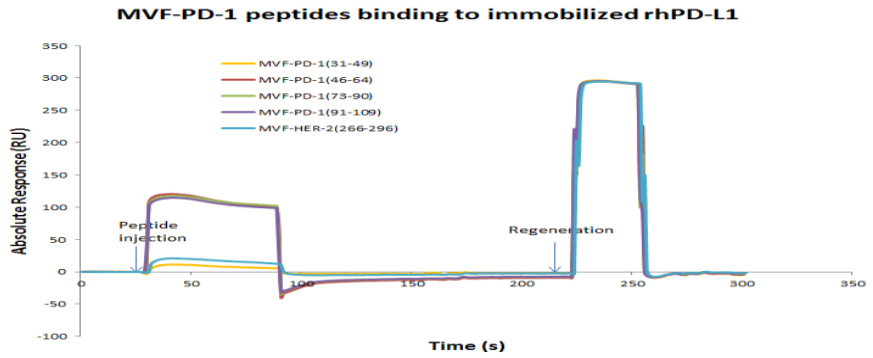


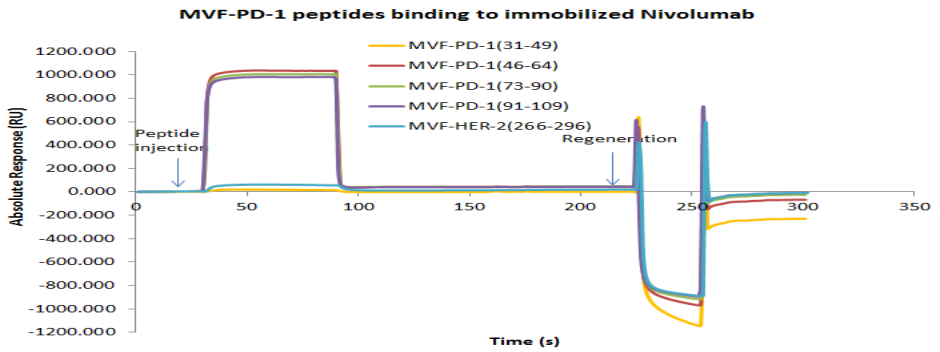
PD-1 45-64:

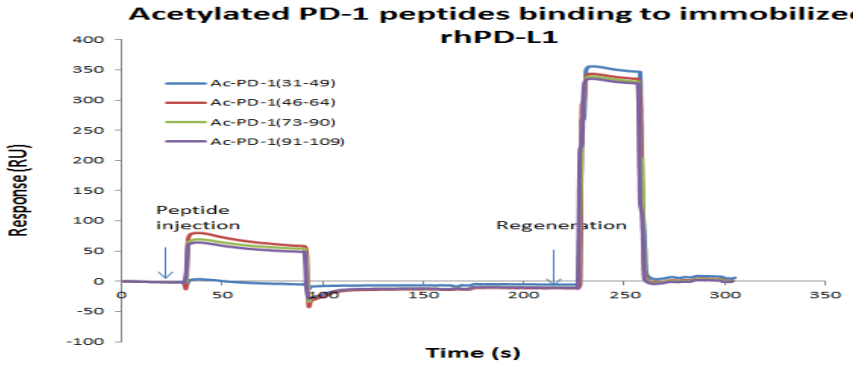
^{45}K-L-A-A-F-P-E-D-R-S-Q-P-G-Q-D-C-R-F-R^{64}

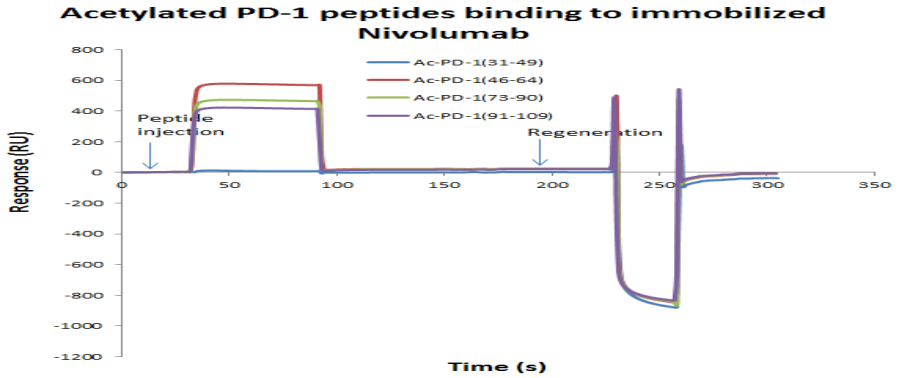


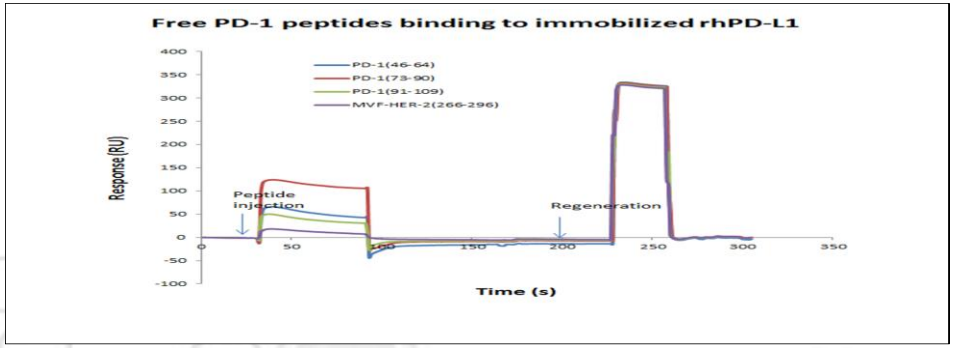
BINDING of HuPD-1 B-CELL EPITOPES to rPD-L1 & NIVOLUMAB

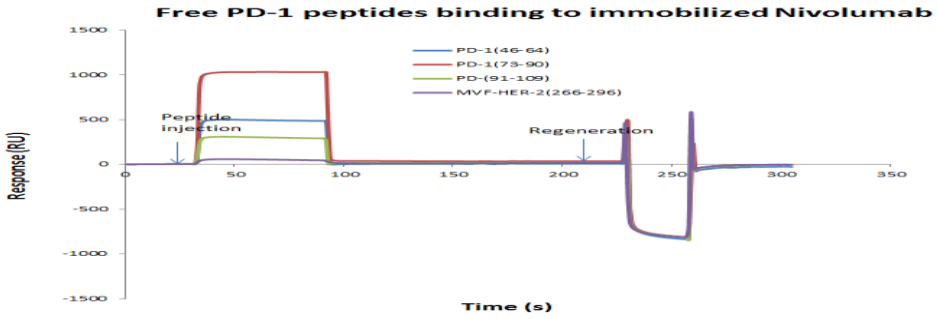






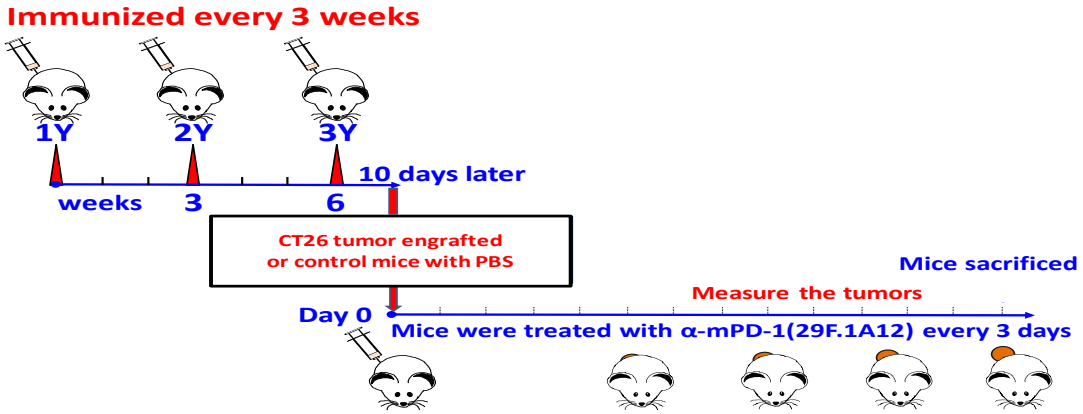




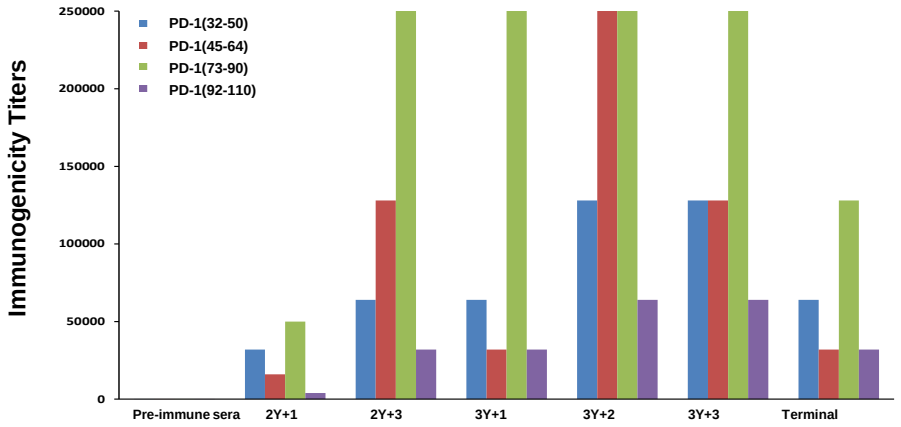


EPITOPE SCREENING OF HUMAN PD-1 B-CELL EPITOPES IN SYNGENEIC Balb/c CT26 COLON CANCER MODEL

A



B



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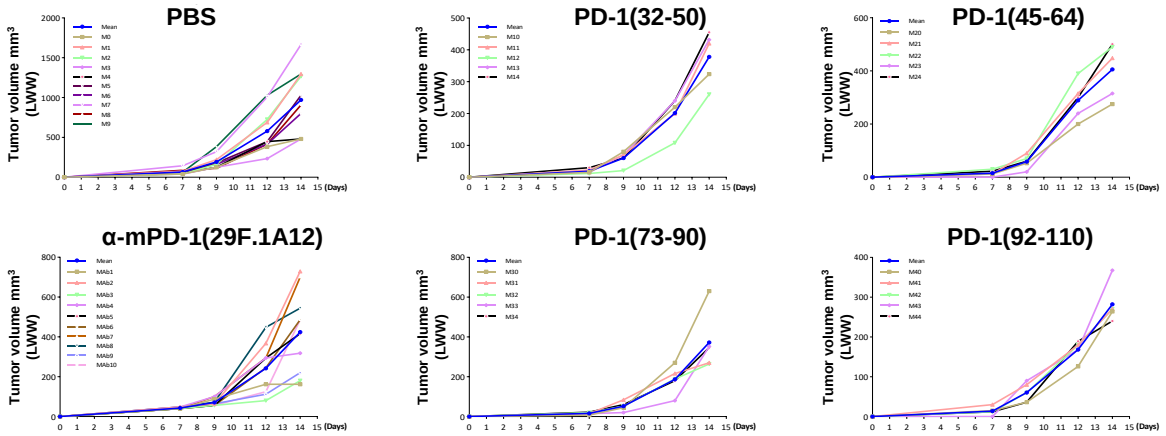
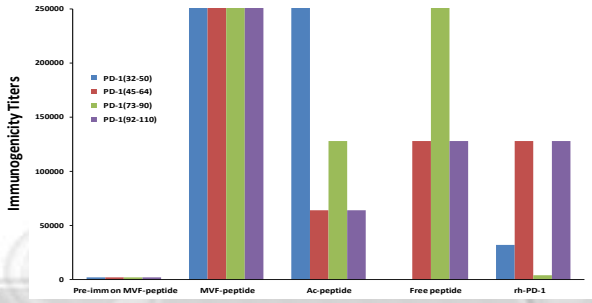
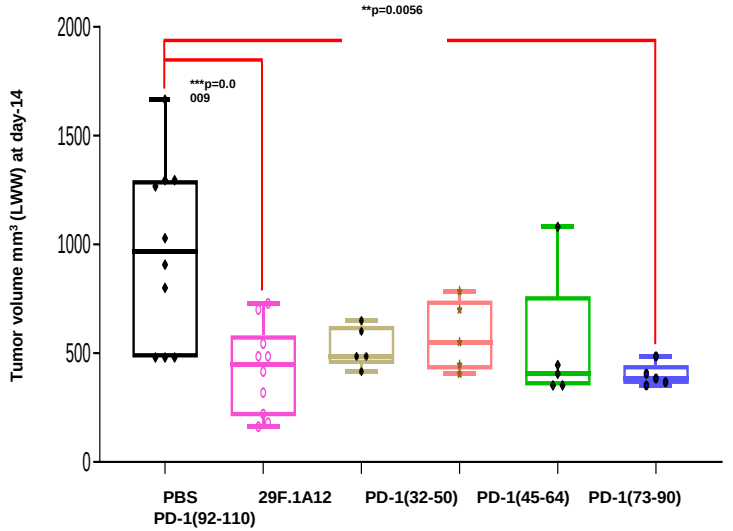


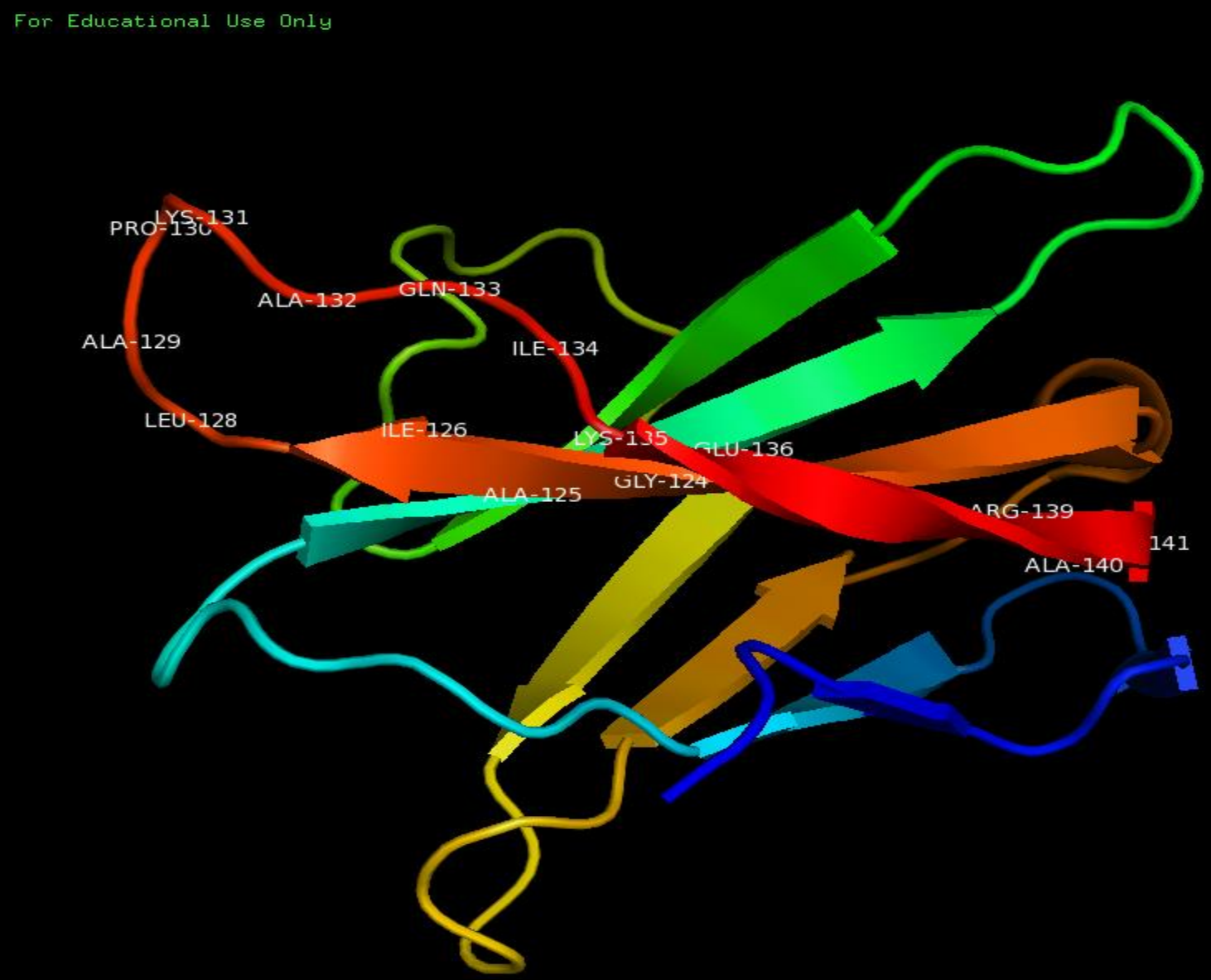
D



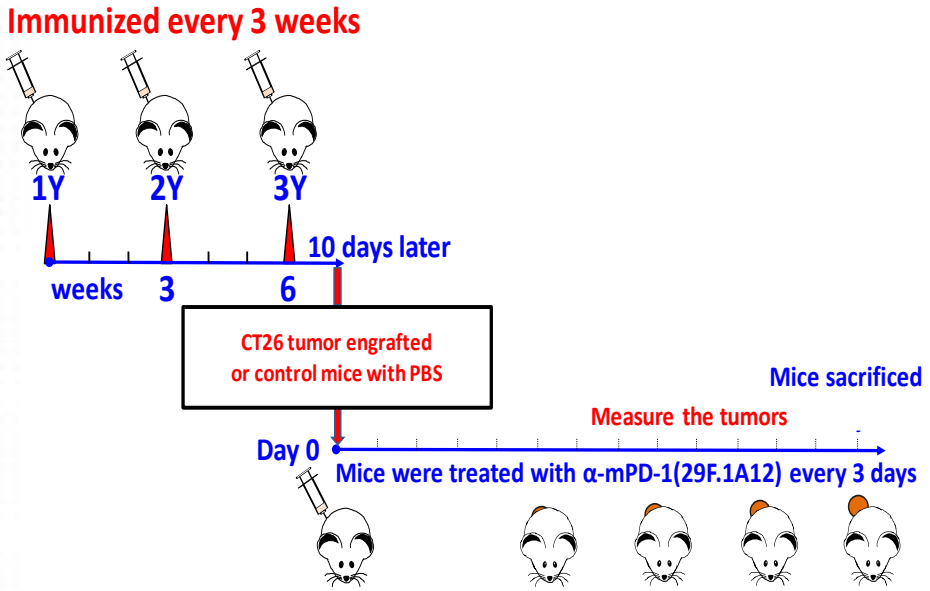
E

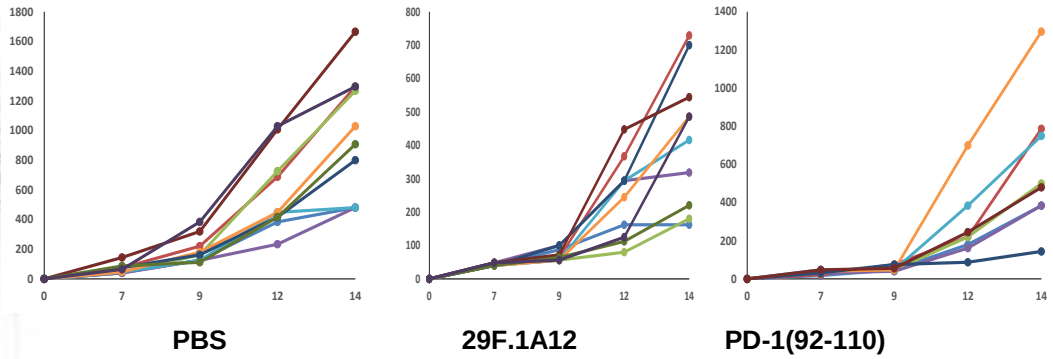


HUMAN PD1-Vaxx (92-110)

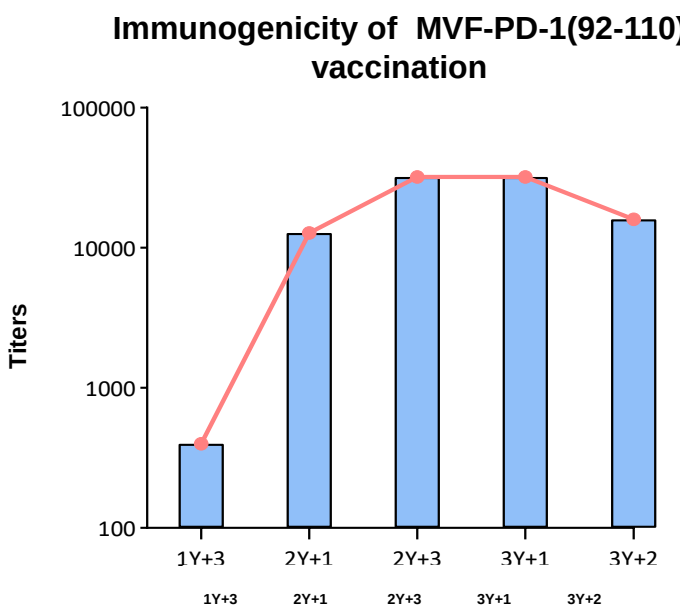


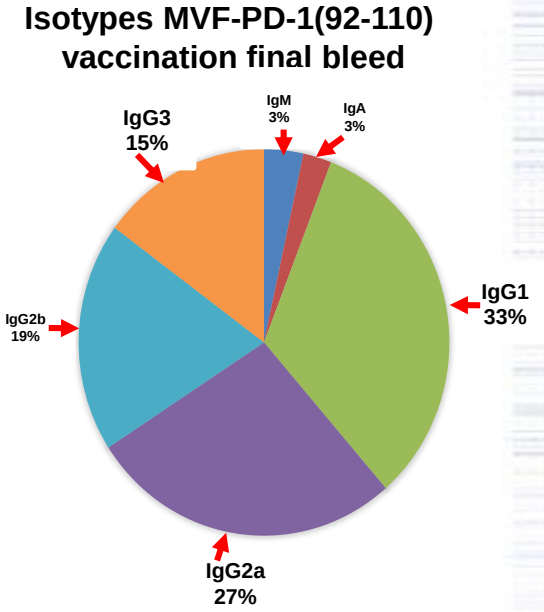
HUMAN PD-1 B-CELL EPITOPE (92-110) INHIBIT TUMOR GROWTH IN SYNGENEIC Balb/c CT26 COLON CANCER MODEL

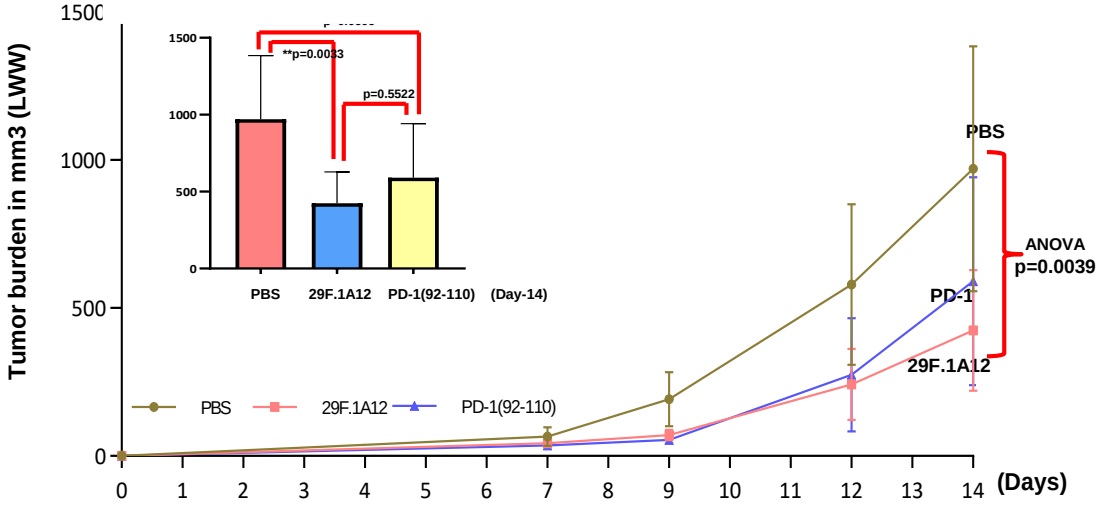




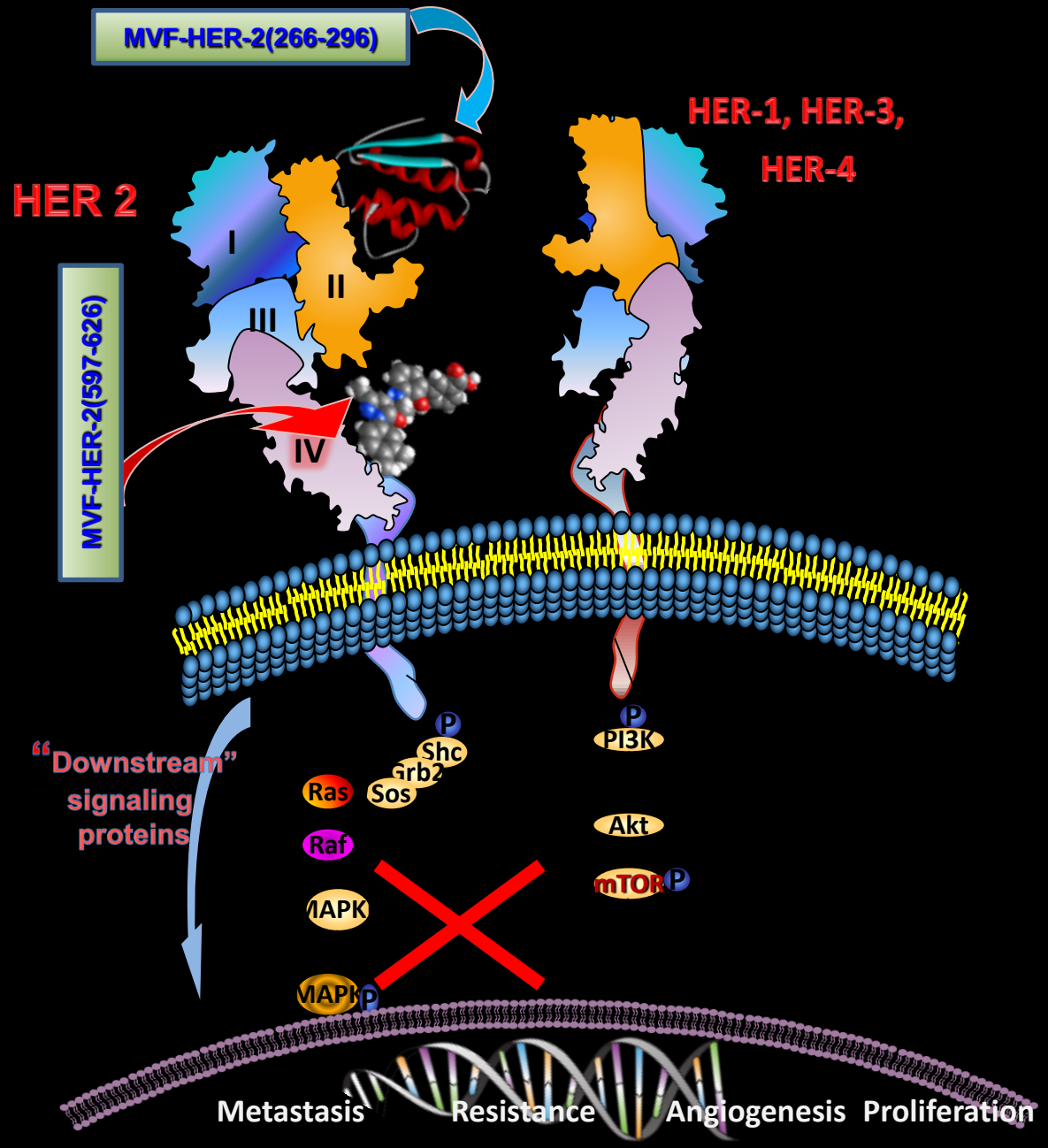
Individual tumor growth in each group in mm³ (LWW) by days



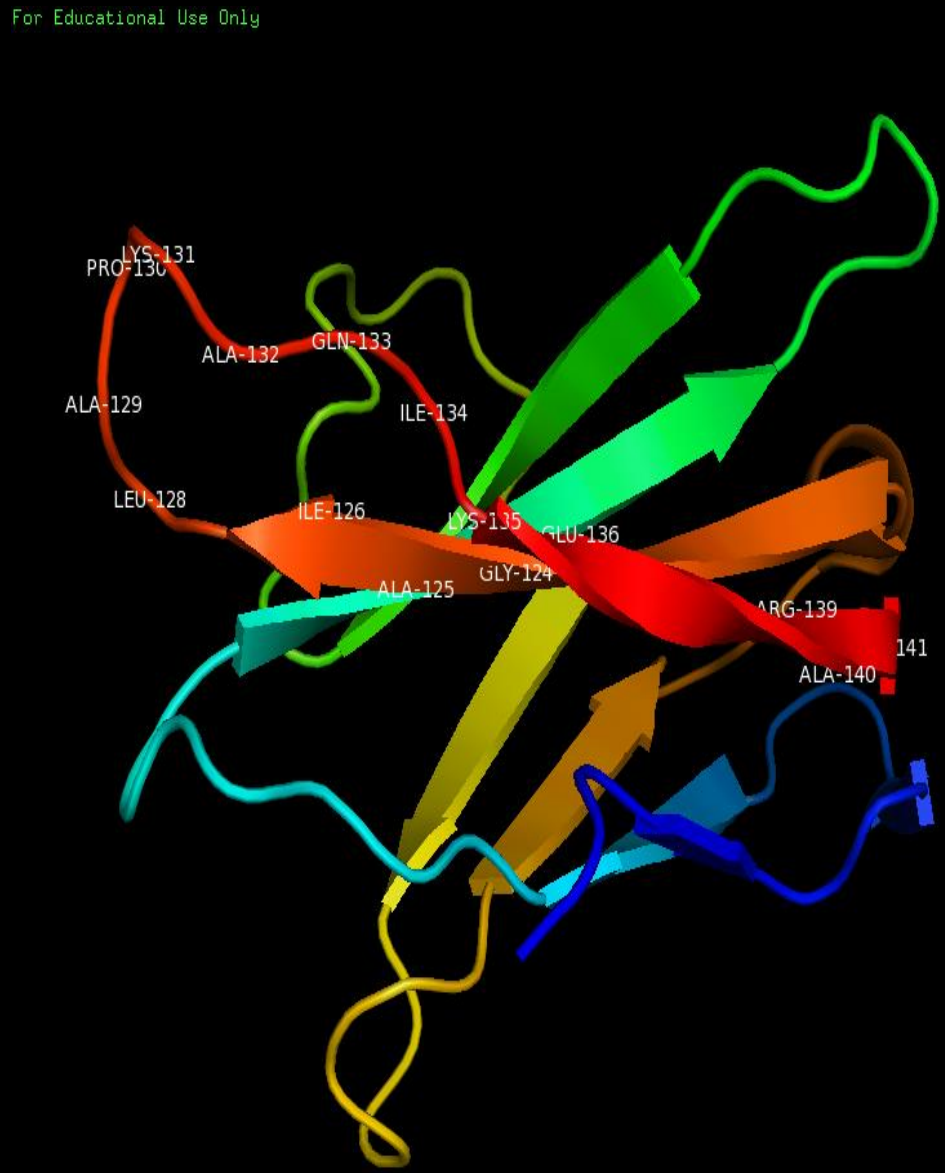




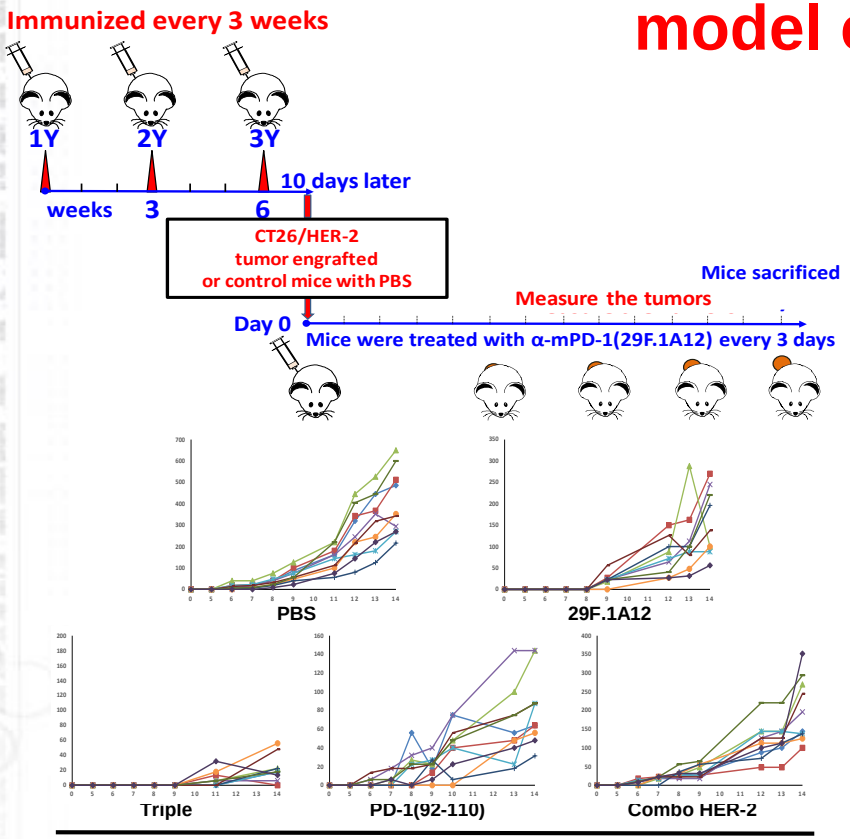
COMBINATION OF MVF-HER-2 PEPTIDES



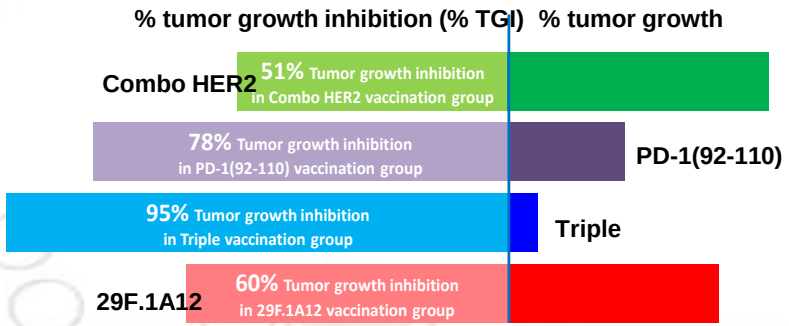
HUMAN PD1-Vaxx (92-110)

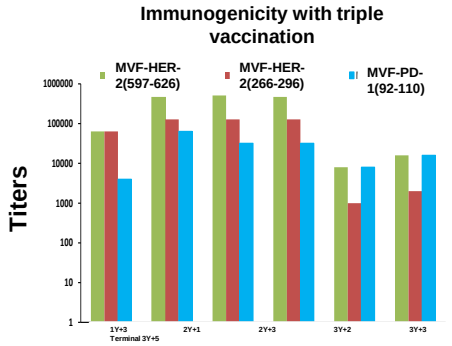


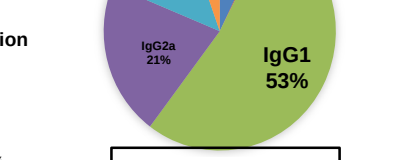
Combination B-Vaxx & PD1-Vaxx synergistically inhibit tumor growth in Balb/c model challenged with CT26/HER

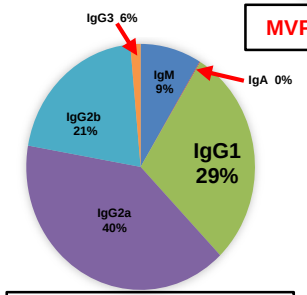


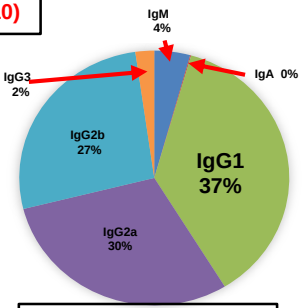
Individual tumor growth in each group tumor burden in mm^3 (LWW) by days

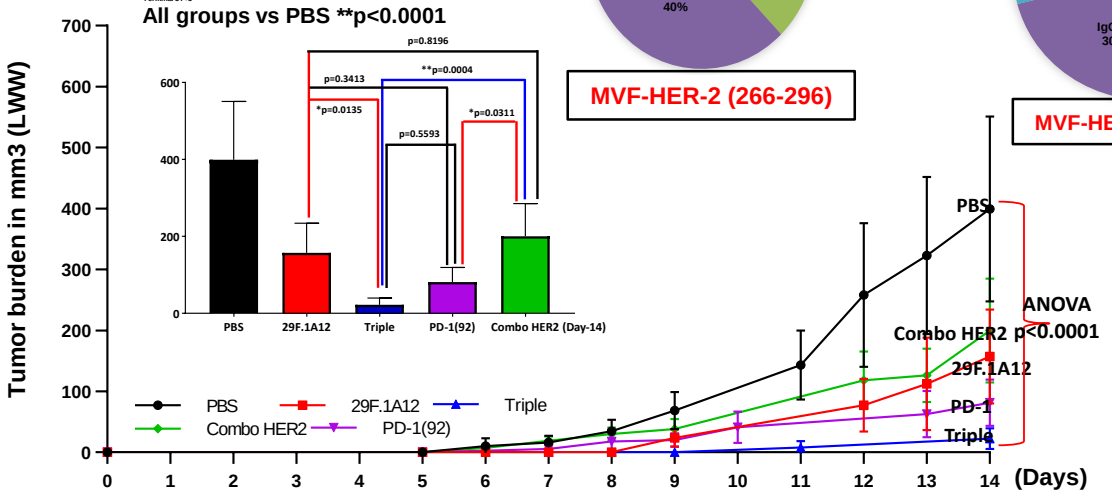




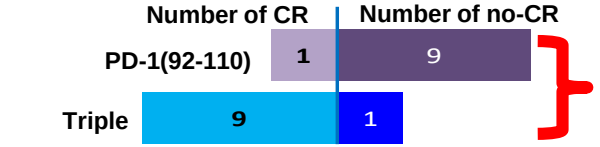


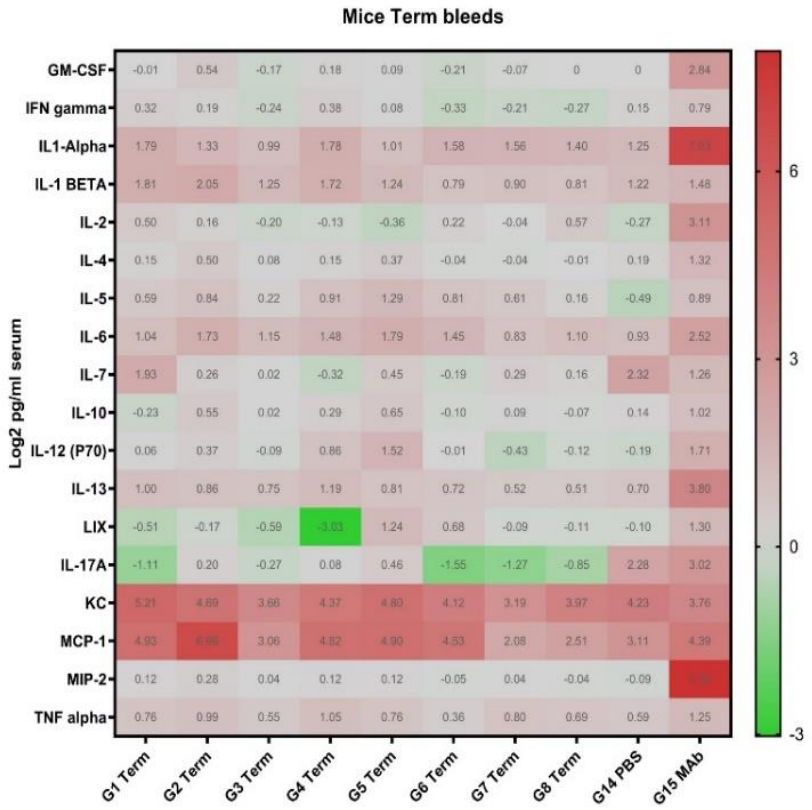


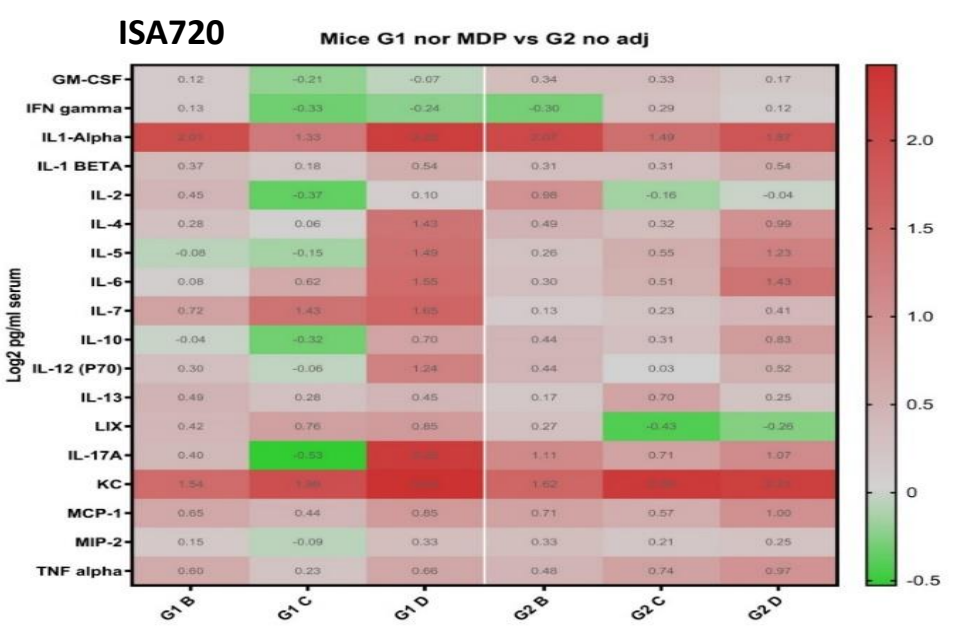


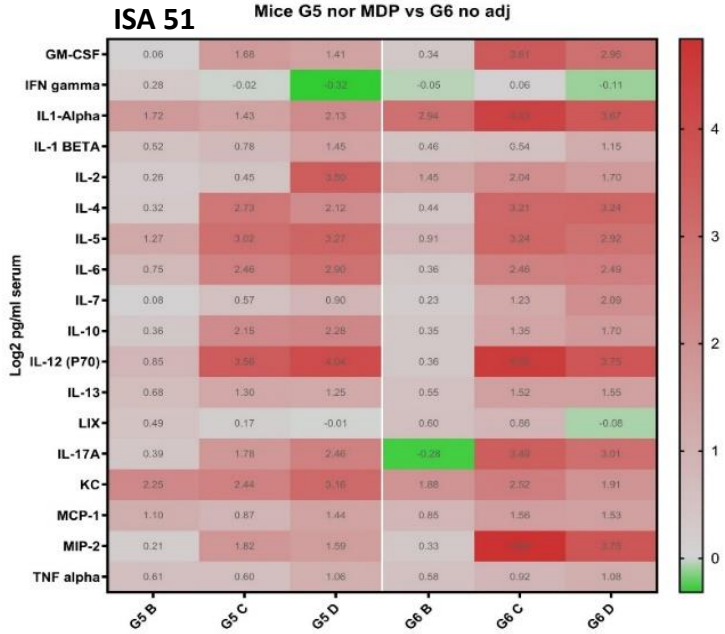


No. of Mice	PBS	29F.1A12	Triple	PD-1(92)	Combo HER-2
CR	0	0	**9**	**1**	0
no-CR	10	9	**1**	**9**	10







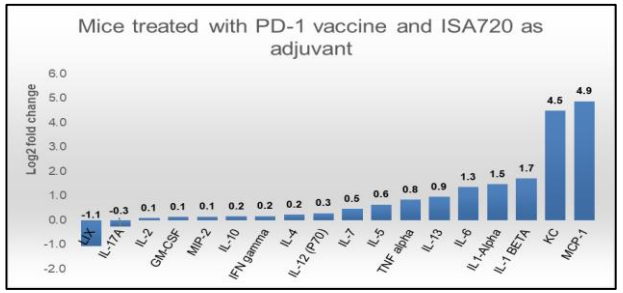


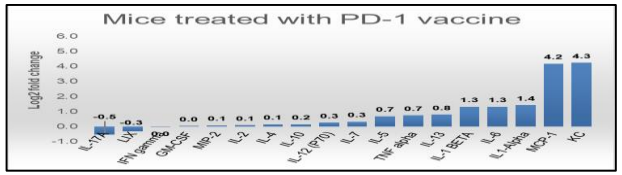
Group 1	MVF-PD-1(92-110)	nor MDP	ISA 720	3 week interval
Group 2	MVF-PD-1(92-110)	no adjuvant	ISA 720	3 week interval
Group 5	MVF-PD-1(92-110)	nor MDP	ISA 51	3 week interval
Group 6	MVF-PD-1(92-110)	no adjuvant	ISA 51	3 week interval

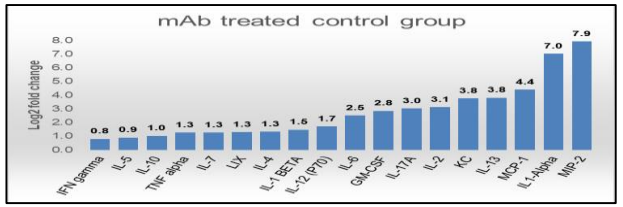
Group 3	MVF-PD-1(92-110)	nor MDP	ISA 720	2 week interval
Group 4	MVF-PD-1(92-110)	no adjuvant	ISA 720	2 week interval
Group 7	MVF-PD-1(92-110)	nor MDP	ISA 51	2 week interval
Group 8	MVF-PD-1(92-110)	no adjuvant	ISA 51	2 week interval

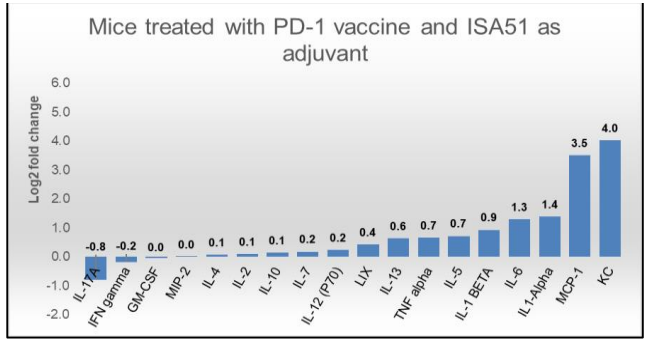
Group 14 PBS control group

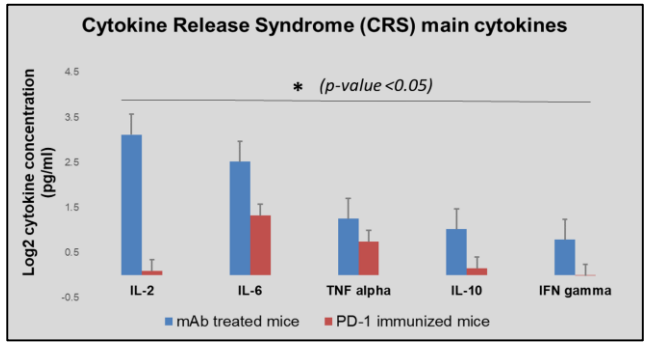
Group 15 29F.1A12 mAb positive control











PD-1 VACCINE DO NOT EXHIBIT TOXICITY OR AUTOIMMUNITY

- All mice vaccinated over a period of 9 weeks showed no signs of scruffiness, lesions, and lethargy
- Organs (spleen, liver, heart, lung, kidney, and tumor) from the Balb/c mice vaccinated with combination peptides (HER-2 and PD-1) were collected from mice and submitted for analysis at the Comparative Pathology & Mouse Phenotyping Core facility of the Comprehensive Cancer Center department of Veterinary Biosciences (Pathologist: Krista M. D. La Perle, DVM, PhD, Dipl. ACVP)
- No significant lesions were noted in any of the organs submitted for histologic evaluation.
- There were also no overt biochemical abnormalities noted.
- **Results indicate the HER-2 vaccines are synergistic with PD-1 vaccine by inhibiting tumor growth in animal models**

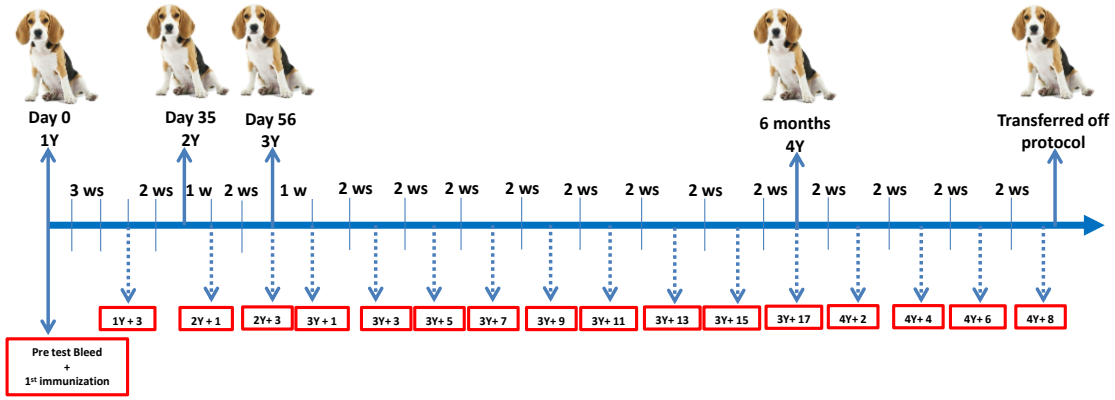
Figure 6

Immunogenicity, Safety and Toxicity Profile in Beagle Dogs

A

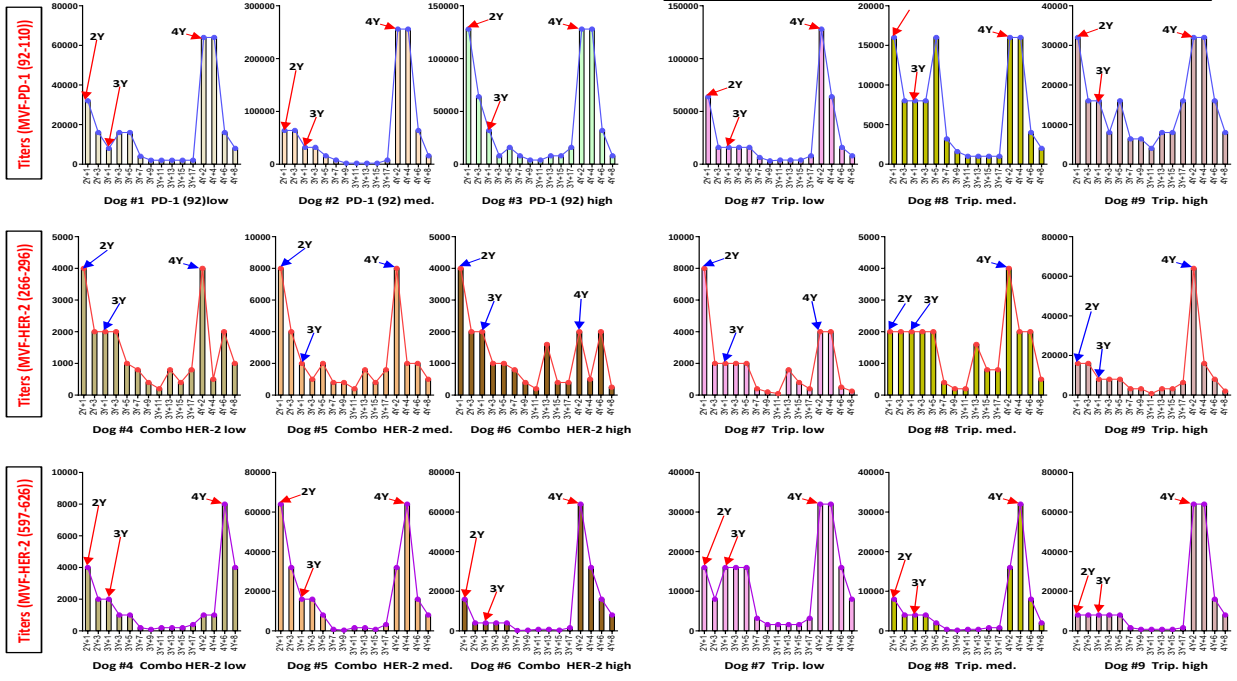
Treatment	Dog ID	concentration	dose each peptide
MVF-PD-1 (92-110) nor-MDP, ISA720	#1-CGA	low dose	1.0mg
	#2-CGB	medium dose	1.5mg
	#3-CJV	high dose	3.0mg
MVF-HER-2 (266-296) & MVF-HER-2 (597-626) nor-MDP, ISA720	#4-CKN	low dose	0.5mg/0.5mg
	#5-CLS	medium dose	1.0mg/1.0mg
	#6-CME	high dose	1.5mg/1.5mg
MVF-PD-1 (92-110)& MVF-HER-2 (266-296) & MVF-HER-2 (597-626) nor-MDP, ISA720	#7-CMT	low dose	1.0mg/0.5mg/0.5mg
	#8-CMW	medium dose	1.5mg/1.0mg/1.0mg
	#9-CNE	high dose	3.0mg/1.5mg/1.5mg
MVF, nor-MDP, ISA720	#10-CNF	Negative control	1.5mg

B



C

Immunized with triple peptide MVF-PD-1 (92-110): MVF-HER-2(266-296) and MVF HER-2 (597-626)



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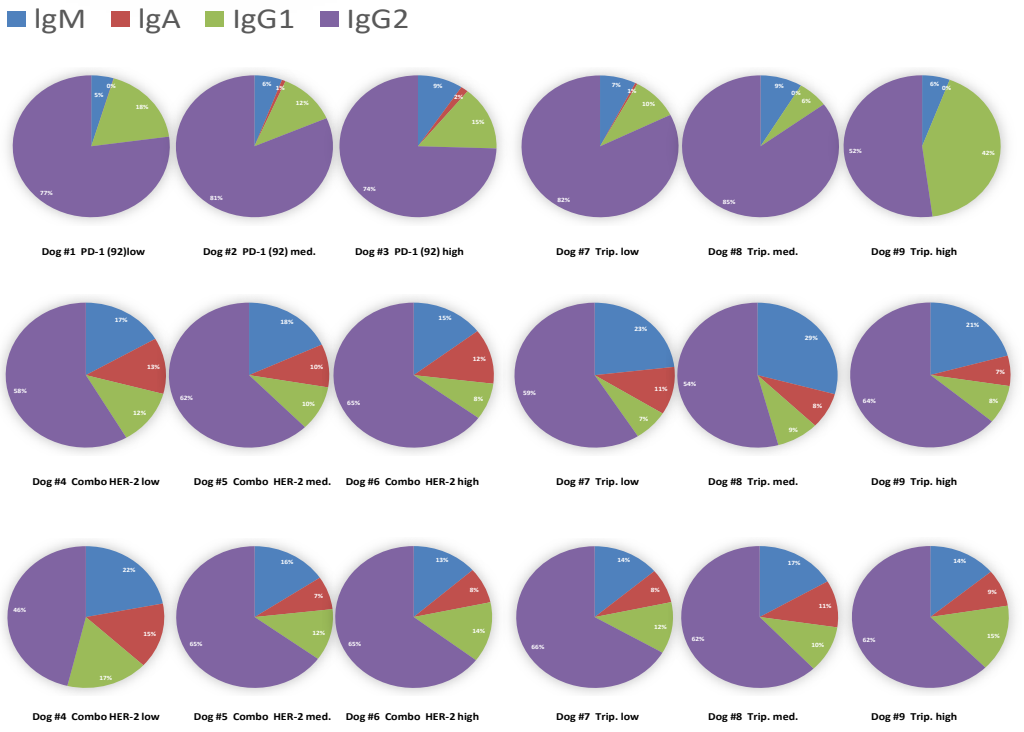
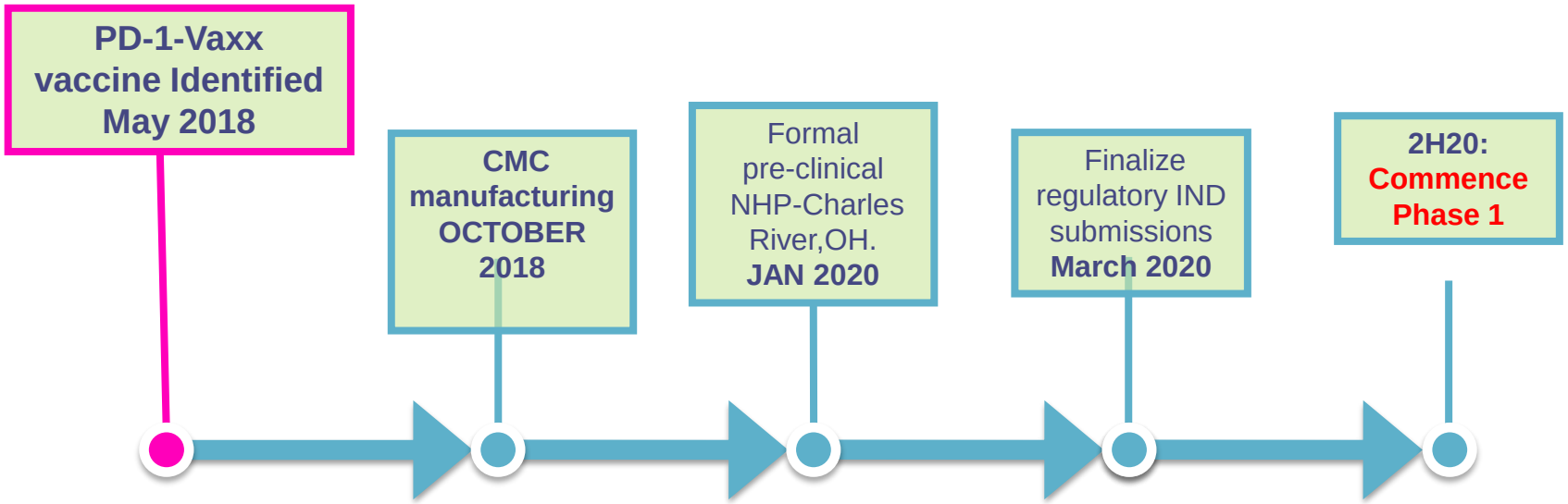
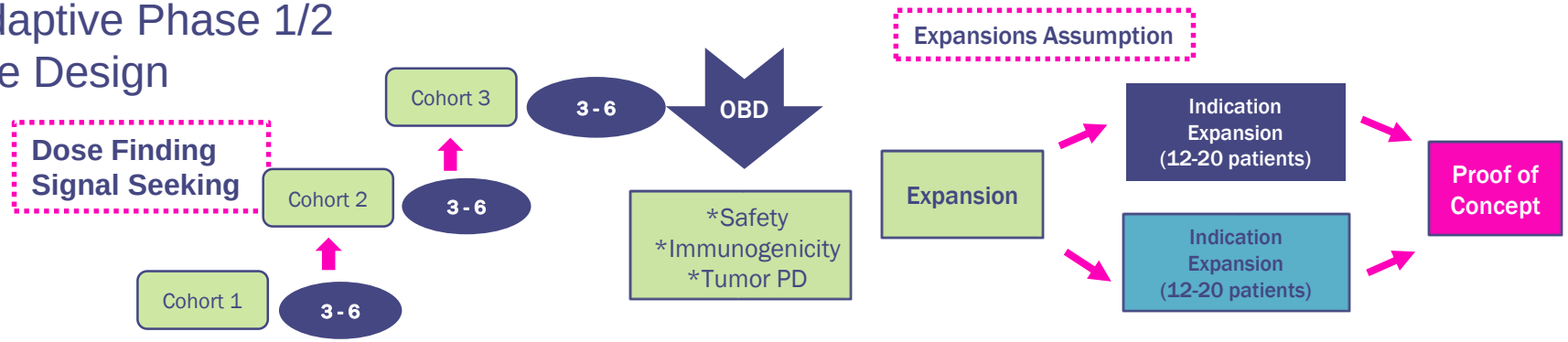


PD-1 VACCINE PHASE 1 DEVELOPMENT PATH 2018-2020:
IMUGENE LTD



Proposed Adaptive Phase 1/2
PD-1 Vaccine Design



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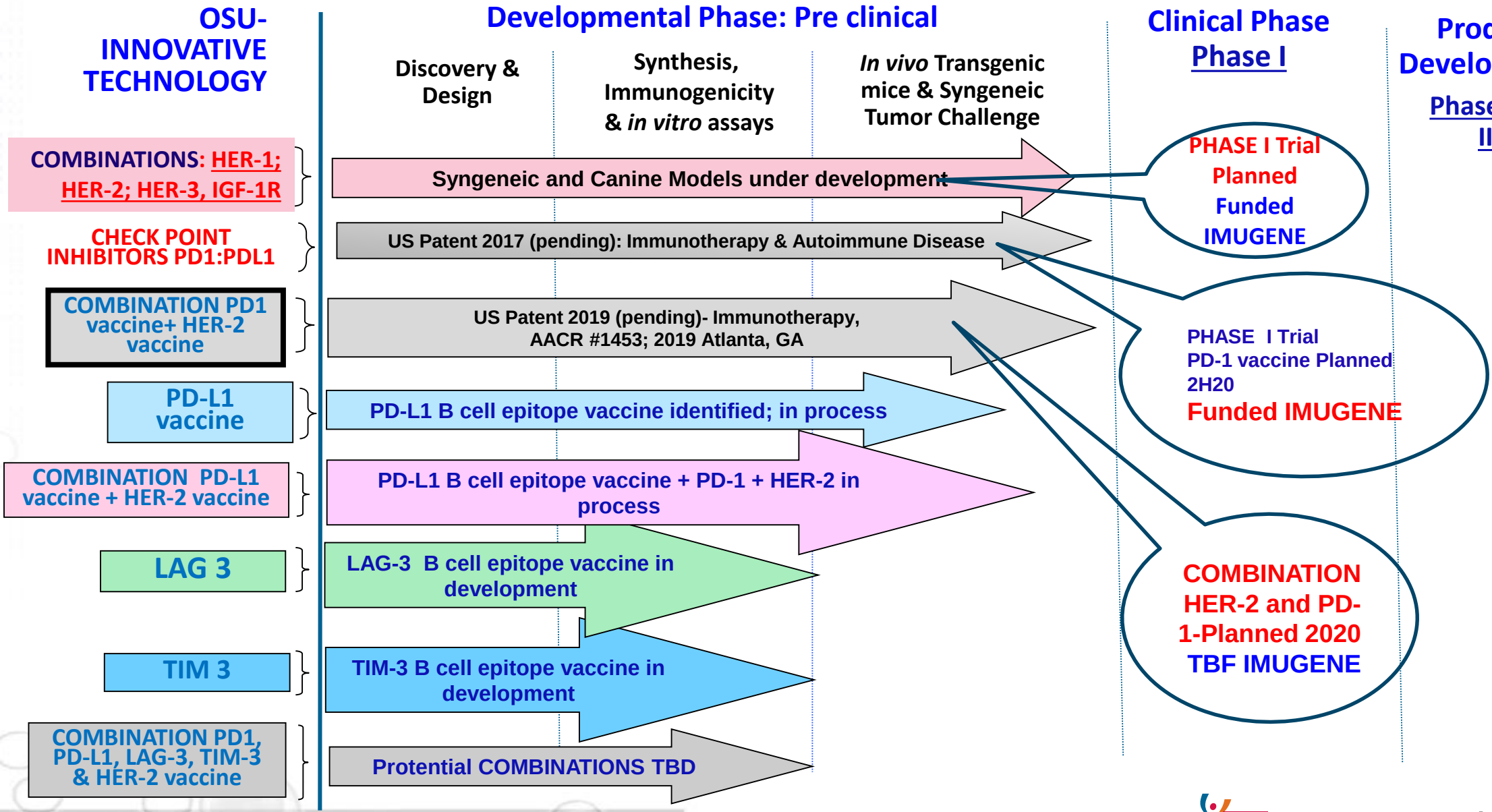

Novel Peptide-Based Immunotherapeutic Vaccines

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THANK YOU FOR YOUR ATTENTION