IMUGENE
Developing Cancer Immunotherapies

ASX: IMU

Science Series
CHECKvacc

23rd February 2022

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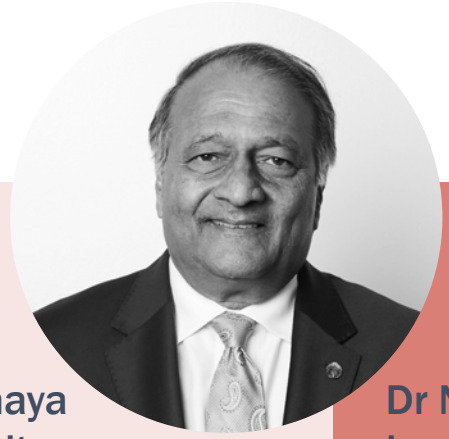
Speakers

Leslie Chong
Imugene CEO & MD

Mrs Chong has over 20 years of oncology experience in Phase I – III of clinical program development, including leadership role involvement in two marketed oncology products. She was previously Senior Clinical Program Lead at Genentech, Inc., in San Francisco. Genentech is widely regarded as one of the world's most successful biotech companies with a strong oncology franchise including the best-selling breast cancer drug Herceptin.



Prof Yuman Kaumaya
Ohio State University

Prof Kaumaya is Professor of Medicine in Department of Ob/Gyn at the OSU Wexner Medical Center and the James Comprehensive Cancer Center. Prof Kaumaya is internationally recognized as an expert in the fields of vaccine research with emphasis on peptide vaccines for cancer, viral diseases as well as peptide therapy for autoimmune diseases. He conducts research in the areas of tumor immunology, mechanisms of tumor cell-immune cell interactions, and immune mechanisms. He is an inventor on several issued and pending patents for Peptide Vaccines and Therapeutic Technologies. He has lectured worldwide and has published over 130 peer-reviewed articles in major scientific journals.

Dr Nimali Whithana
Imugene Snr Director of Clinical Science

Dr Withana has over 18 years of drug development experience spanning both academia and industry. Most recently she was the Lead Country Medical Manager for the Breast Cancer and Cancer Immunotherapy portfolios including bevacizumab, trastuzumab emtansine, ipatasertib and atezolizumab at Hoffman-La Roche New Zealand. Prior to that, she was the Clinical Scientist Lead across Phase I – III global oncology trials at Genentech.
Dr Withana received her academic training at Stanford University and The Peter MacCallum Cancer Centre majoring in Immunology and Molecular Medicine. She has an in-depth understanding and grasp of the development process with experience in R&D, Clinical Trials and Patient Advocacy.

Three Novel Technology Platforms

IMUGENE
Developing Cancer Immunotherapies

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Developing Cancer Immunotherapies

PLATFORM	onCARIytics	CF33 Oncolytic Virus		B Cell Immunotherapy	
	CF33-CD19 CAR T Combination Therapy	**CHECKvacc "Armed" PD-L1 Virus**	**VAXINIA Parental Virus**	**HER-Vaxx**	**PD1-Vaxx**
CLINICAL TRIALS	**TBC** Phase 1 Solid Tumours N = TBD USA & TBD celularity EUREKA THERAPEUTICS	**COH TNBC IST** Phase 1 Tripe Negative Breast Cancer N = 30-36 USA (COH only) IND Enabled	**MAST** Phase 1 Metastatic Solid Tumours N = 52-100 USA & AUS IND Enabled	**HERIZON** Phase 1b/2 Gastric Cancer N = 36 Asia & Eastern Europe	**IMPRINTER** Phase 1 Non-Small Cell Lung Cancer N = 24-52 USA & AUS IND Enabled Roche
		DOMINICA Phase 1 Solid Tumours N = TBD USA & TBD		**nextHERIZON** Phase 2 Metastatic Gastric Cancer N = 30 USA, AUS, South Korea IND Enabled	
				neoHERIZON Phase 2 Neoadjuvant Gastric Cancer N = 72 Germany & South Korea MERCK Pfizer	

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

COMBINATION IMMUNOTHERAPIES

PD-1 , PD-L1, CTLA-4, TIGIT, TIM3 & LAG3

IMUGENE Science Series

23rd Feb 2022

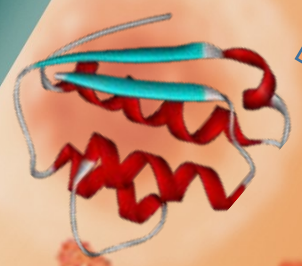
THE OHIO STATE UNIVERSITY JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

College of Medicine & Public Health · The Ohio State University

OHIO STATE Wexner Medical Center

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

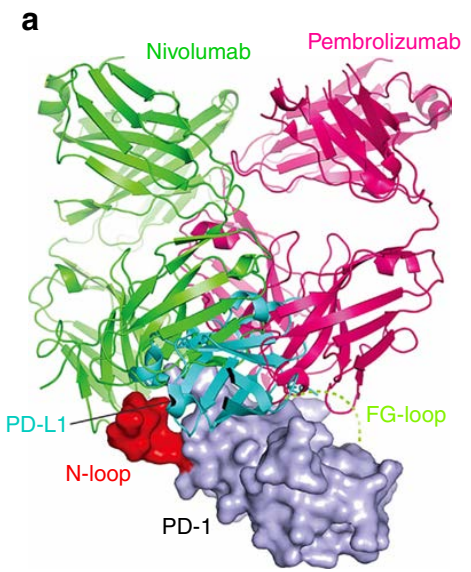
HER-2: ROCHE (Trastuzumab) Herceptin®
(Pertuzumab) Perjeta®

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

POTENTIAL PD-1 B CELL EPITOPE VACCINES IDENTIFIED



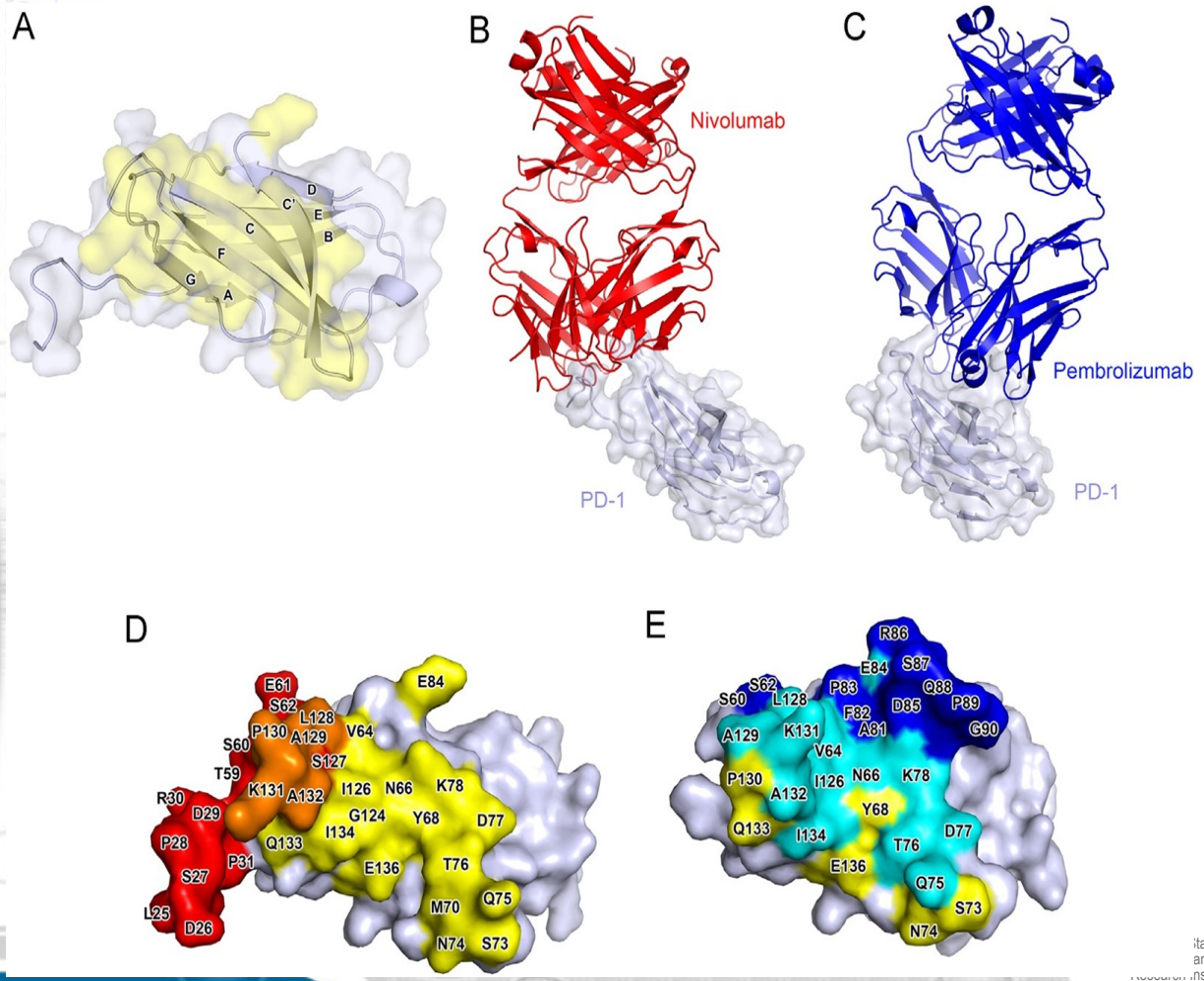
PEPTIDES	AMINO ACID SEQUENCES OF SYNTHESIZED PD-1 PEPTIDES
PD-1 (32-50)	H_2N-^{32} V-L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F^{50}-$CONH_2$
AC-PD-1 (32-50)	CH_3CONH-^{32} V-L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F^{50}-$CONH_2$
MVF-PD-1 (32-50)	KLLSLIKGVIVHRLEGVE-GPSL- V-L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F-CONH2
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

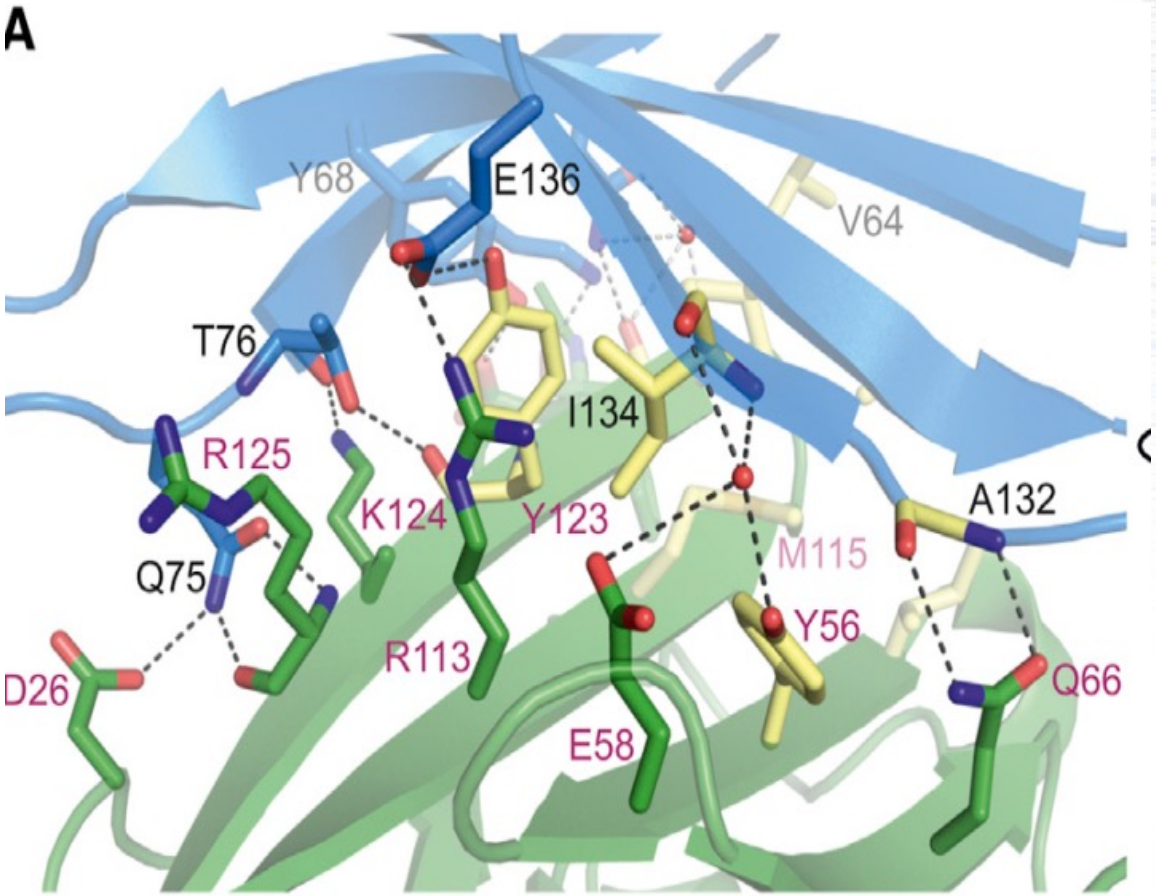
PD1-Vaxx PD-1 epitope

PD1-Vaxx peptide vaccine

ENGINEERING HUMAN PD-1 B-CELL EPITOPES

Pravin T. P. Kaumaya , Linlin Guo , Jay Overholser , Manuel L. Penichet& Tanios Bekaii-Saab (2020) ***Immunogenicity and antitumor efficacy of a novel human PD-1 B-cell vaccine (PD1-Vaxx) and combination immunotherapy with dual trastuzumab/pertuzumab-like HER-2 B-cell epitope vaccines (B-Vaxx) in a syngeneic mouse model,***
OncoImmunology, 9:1, 1818437, DOI: 10.1080/2162402X.2020.1818437





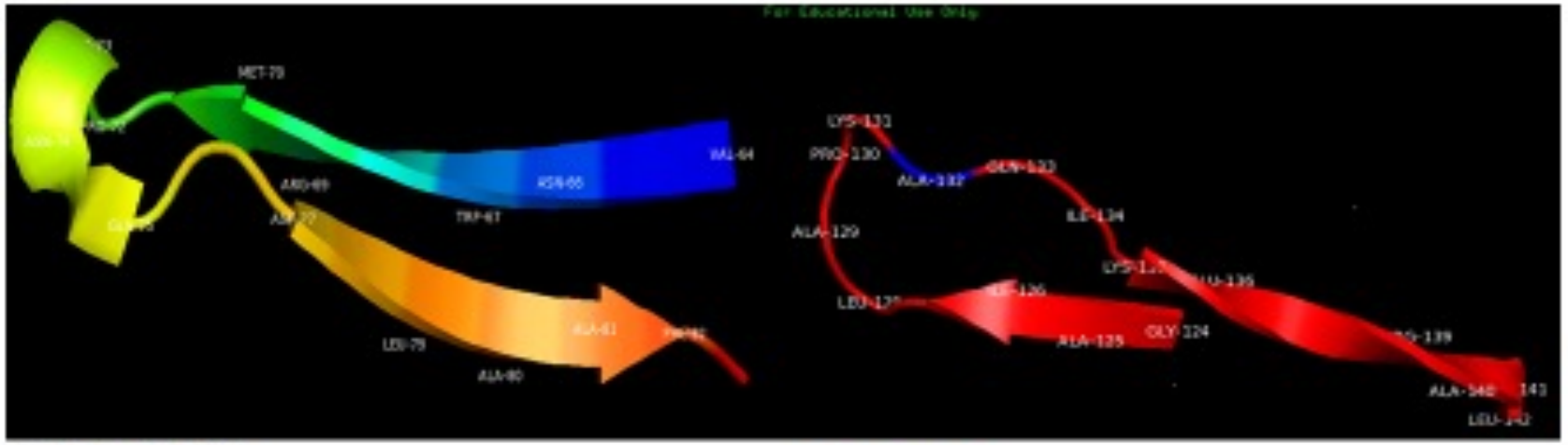
HUMAN PD-1 PREDICTED B-CELL EPITOPES*

PD-1: 32-50:

L-N-W-Y-R-M-S-P-S-N-Q-T-D-K-L-A-A-F

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}

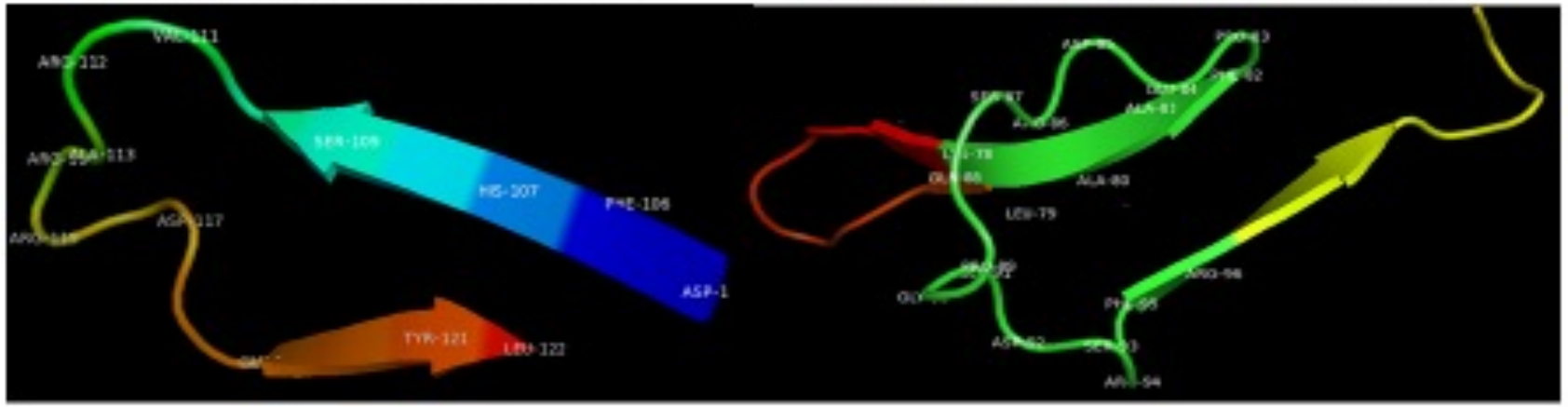


PD-1: 73-90:

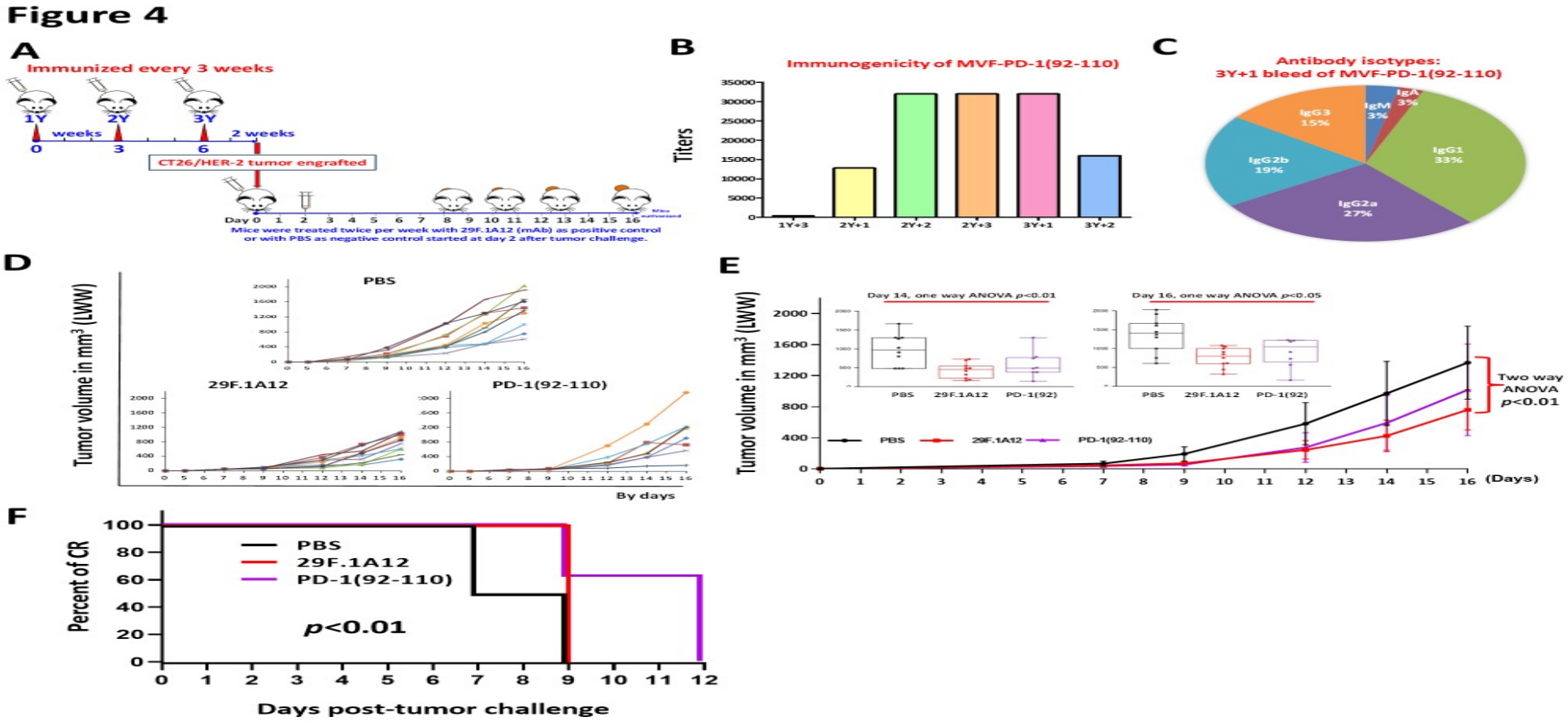
^{73}D-F-H-M-S-V-V-R-A-R-R-N-D-S-G-T-Y-L^{90}

PD-1 45-64:

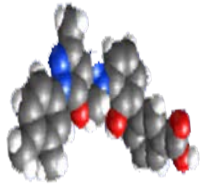
^{45}K-L-A-A-F-P-E-D-R-S-Q-P-G-Q-D-C-R-F-R^{64}



HUMAN PD-1 B-CELL EPITOPE (92-110) PD1-Vaxx INHIBIT TUMOR GROWTH IN SYNGENEIC BALB/c CT26 COLON CANCER MODEL

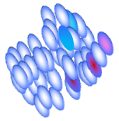


THE VACCINE WORKS IN INNOVATIVE WAYS

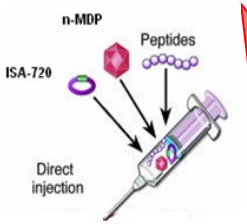


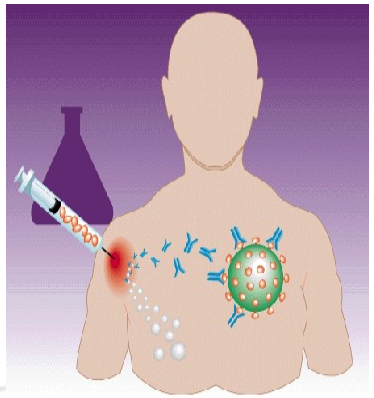
MVF-PD-1-Vaxx

ISA-720 montanide



Nor-MDP Adjuvant





T Cell Activation → B Cell Activation

signal 2

signal 1

T-EPITOPE

B+T-EPITOPE

ACTIVE TH cell

TCR

MHC II

B CELL

CD40L

CD40

CYTOKINES

3

signal

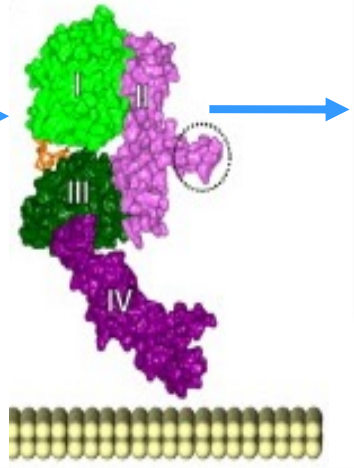
HER - 2 Polyclonal Antibody Secretion

Tumor cell

4

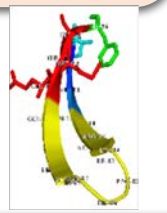
OVERALL STRATEGY

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

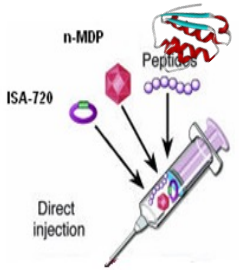


EPITOPE REFINEMENT STRATEGY

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, PD-L1
CTLA-4, TIGIT, TIM3, LAG3

SYNTHESIS & CHARACTERIZATION OF 5 PEPTIDE MIMICS

GENERATE ANTIPEPTIDE ANTIBODIES IN RABBITS TO 5 CHIMERIC VACCINES

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

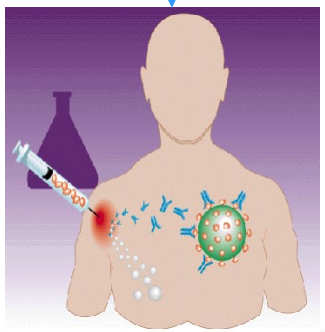
LEAD CANDIDATE OPTIMIZATION:
- CORRELATES OF EFFICACY BASED ON COMBINED *in vitro* ASSAYS.
- SELECTION OF BEST PEPTIDE MIMICS AND PEPTIDE VACCINES

: *in vivo* TESTING in TRANSGENIC, SYNGENEIC & TRANSPLANTABLE MOUSE MODELS and Challenge with cancer cell lines

IDENTIFICATION: FINAL VACCINE & PEPTIDE MIMIC CANDIDATES

TEST: EFFICACY OF COMBINATION IMMUNOTHERAPY IN MICE

COMBINATIONS IDENTIFIED



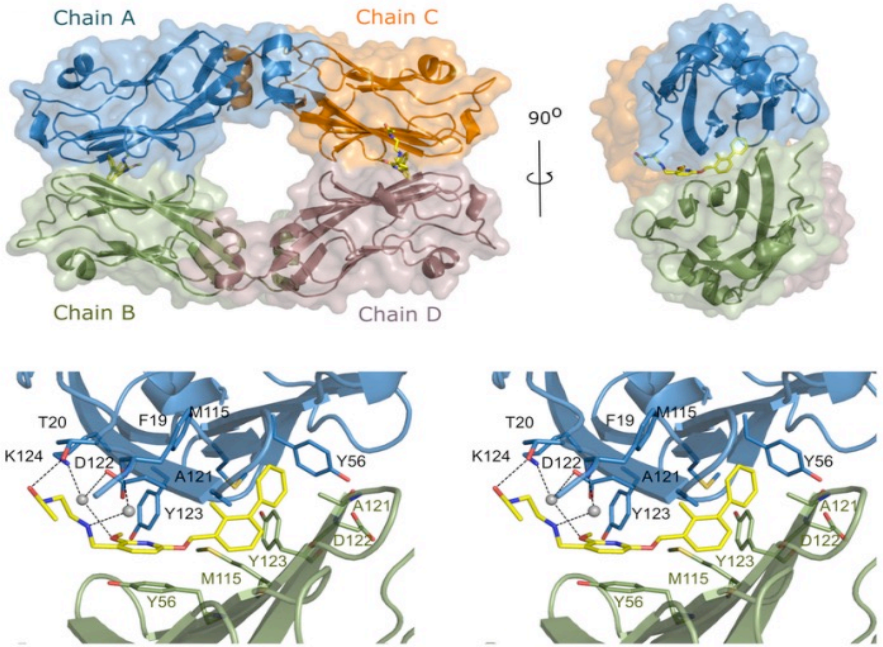
Human Clinical
Safety & Toxicity

PDL1-B-Cell Epitope Vaccines Prediction, Design and Immunogenicity

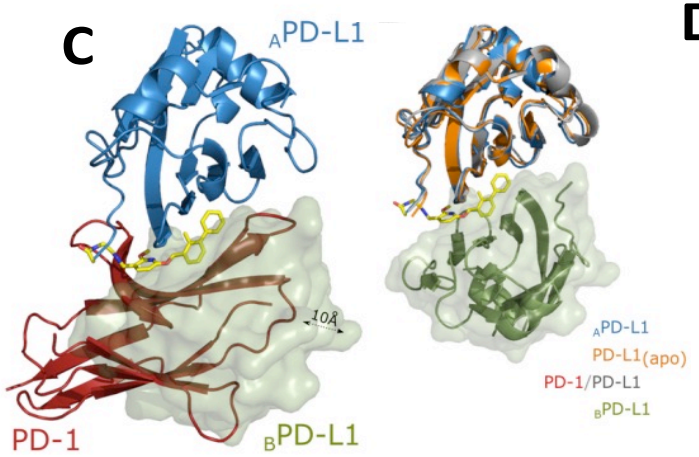
A

PEPTIDES	AMINO ACID SEQUENCES OF SYNTHESIZED PEPTIDES
PD-L1 (36)	H_2N-^{36}L-I-V-Y-W-E-M-E-D-K-N-I-I-Q-F-V-H-G^{53}-$CONH_2$
MVF-PD-L1 (36)	H_2N-KLLSLIKGVIVHRLEGVE-GPSL-^{36}L-I-V-Y-W-E-M-E-D-K-N-I-I-Q-F-V-H-G^{53}-$CONH_2$
PD-L1 (50)	H_2N-^{50}F-V-H-G-E-E-D-L-K-V-Q-H-S-S-Y-R-Q-R^{67}-$CONH_2$
MVF-PD-L1 (50)	H_2N-KLLSLIKGVIVHRLEGVE-GPSL-^{50}F-V-H-G-E-E-D-L-K-V-Q-H-S-S-Y-R-Q-R^{67}-$CONH_2$
PD-L1 (95)	H_2N-^{95}Y-R-C-M-I-S-Y-G-G-A-D-Y-K-R-I-T-V-K^{112}-$CONH_2$
MVF-PD-L1 (95)	H_2N-KLLSLIKGVIVHRLEGVE-GPSL-^{95}Y-R-C-M-I-S-Y-G-G-A-D-Y-K-R-I-T-V-K^{112}-$CONH_2$
PD-L1 (130)	H_2N-^{130}V-T-S-E-H-E-L-T-C-Q-A-E-G-Y-P-K-A-E^{147}-$CONH_2$
MVF-PD-L1 (130)	H_2N-KLLSLIKGVIVHRLEGVE-GPSL-^{130}V-T-S-E-H-E-L-T-C-Q-A-E-G-Y-P-K-A-E^{147}-$CONH_2$
TT3-PD-L1 (130)	H_2N-FNNFTVSFWLRVPKVSASHL-GPSL-^{130}V-T-S-E-H-E-L-T-C-Q-A-E-G-Y-P-K-A-E^{147}-$CONH_2$

B



C



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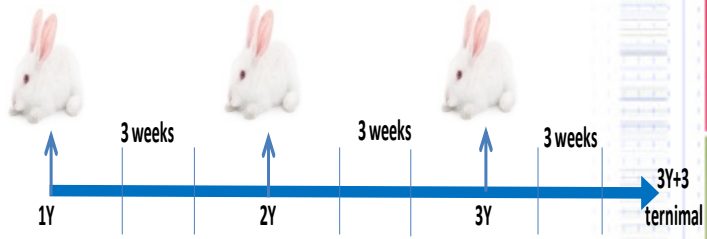

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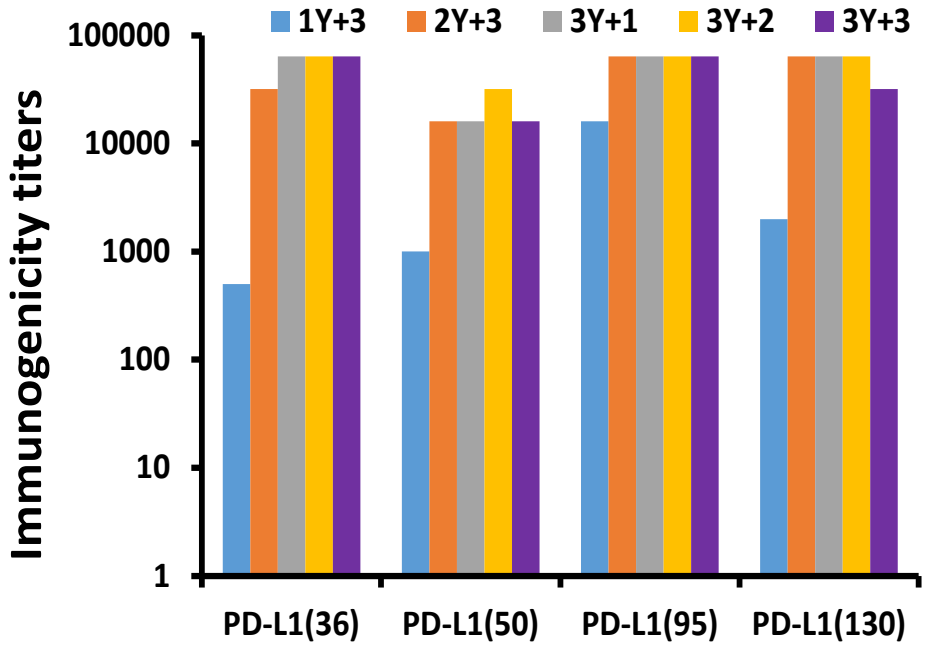
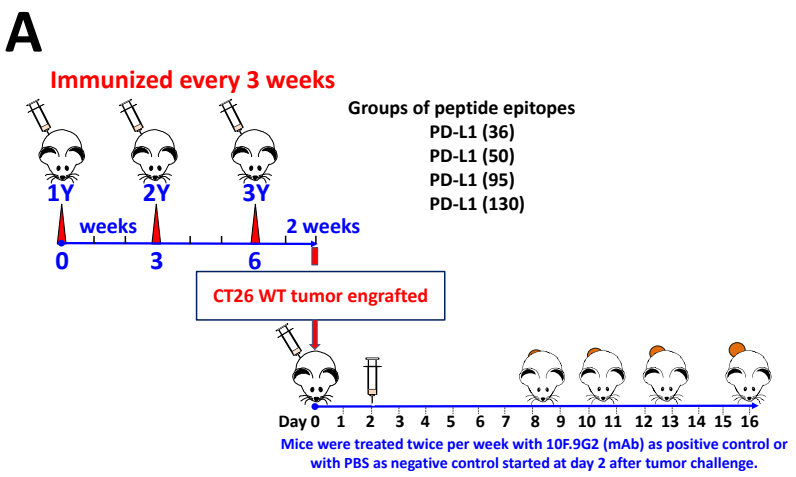
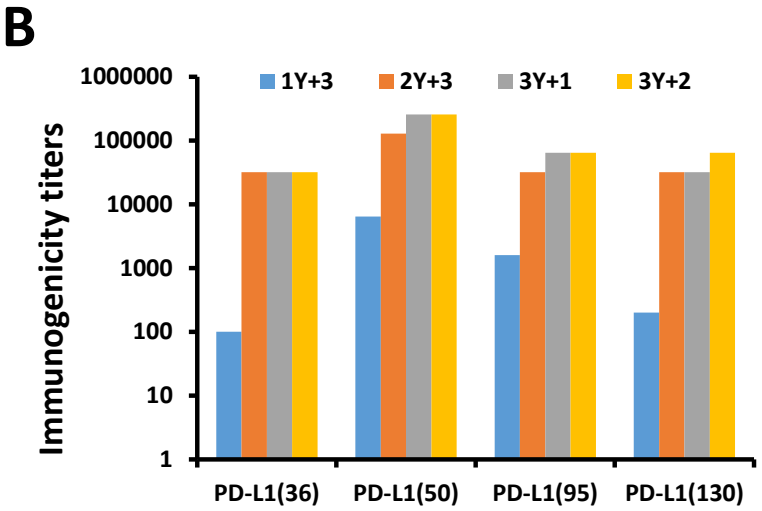
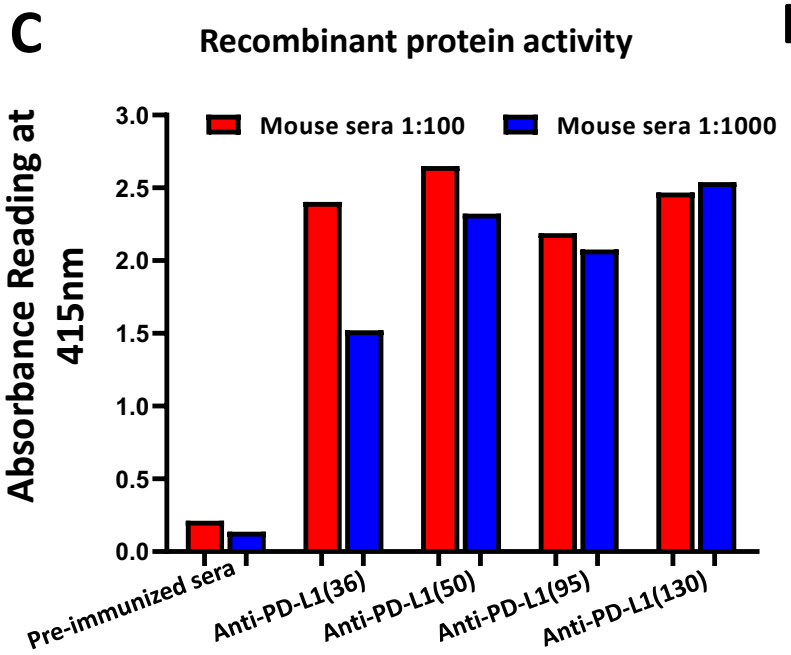
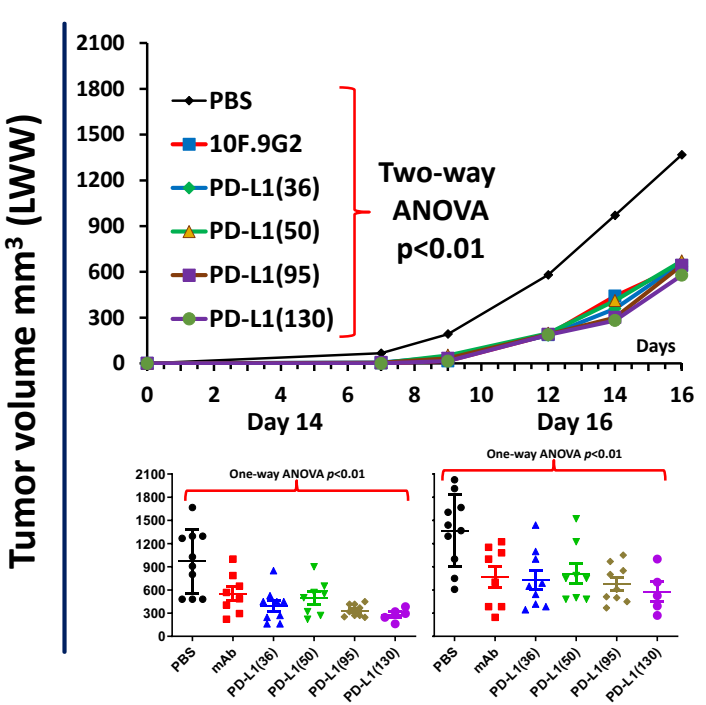


PREDICTED PDL1-B-Cell Epitopes: Initial Screening as MVF Chimeric Peptides in Syngeneic BALB/c-CT26 Tumor Model

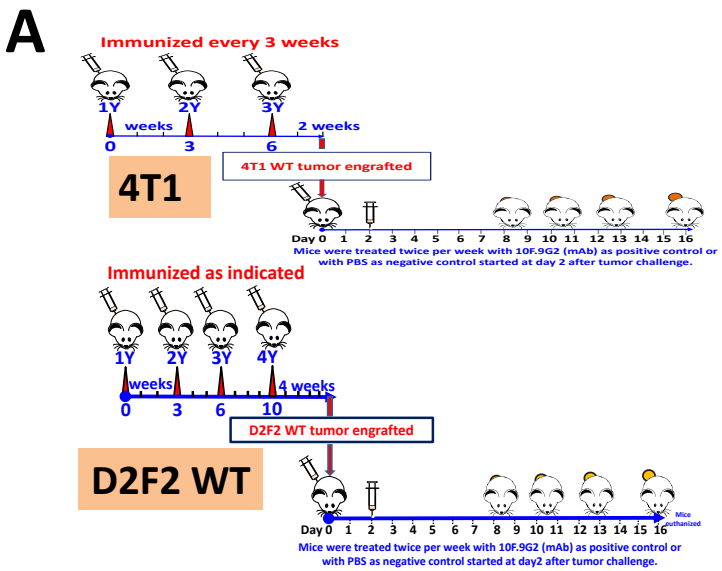


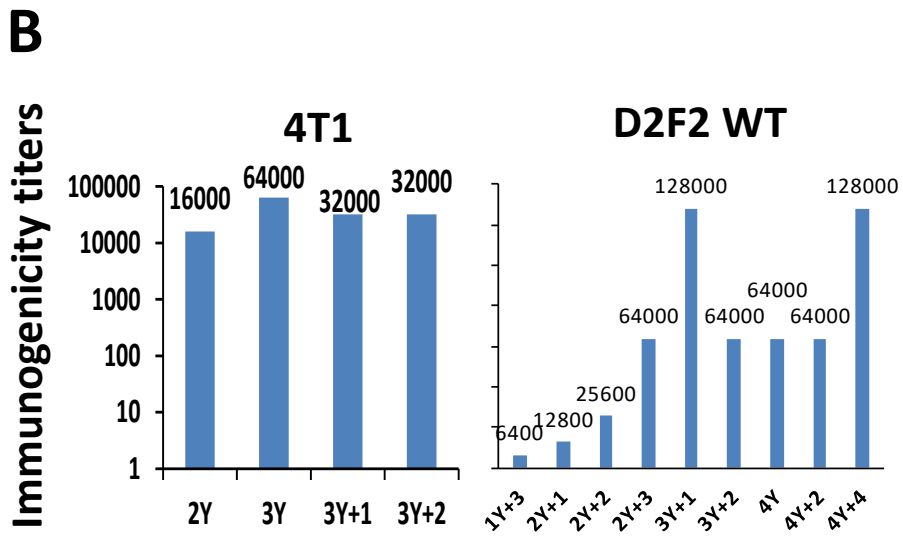


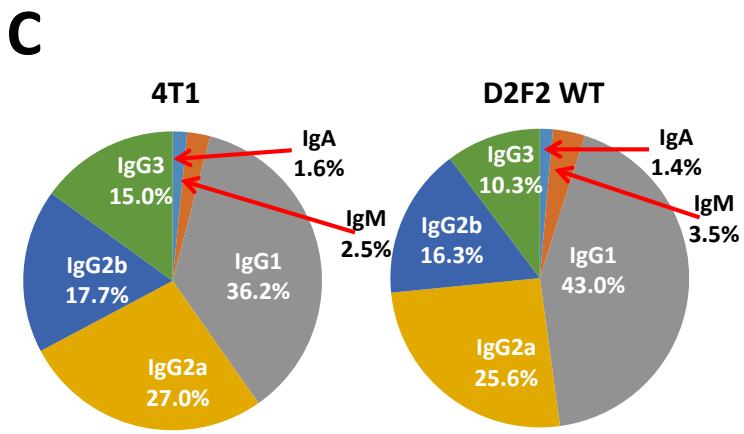


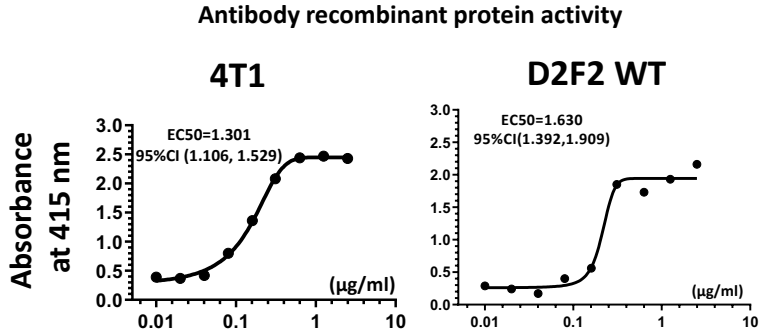


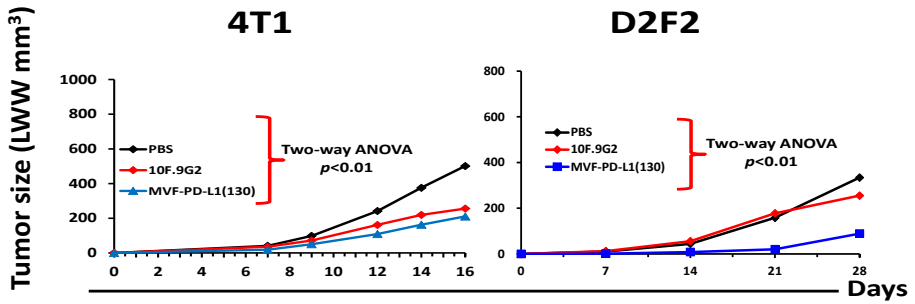
Syngeneic BALB/c Immunized with MVF-PDL1(130-147) Challenged with D2F2 WT and 4T1 carcinoma cells

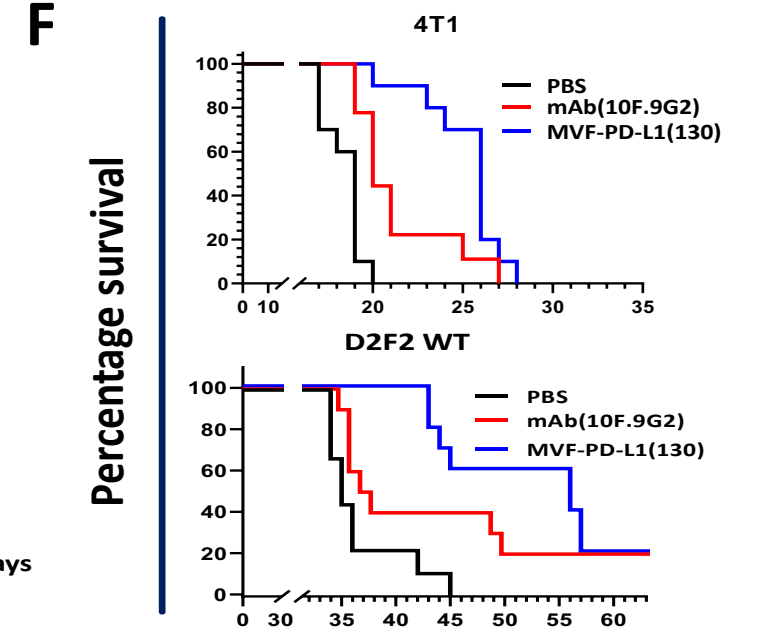




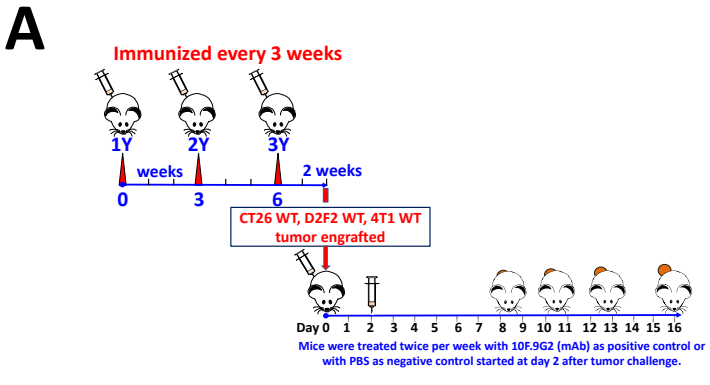


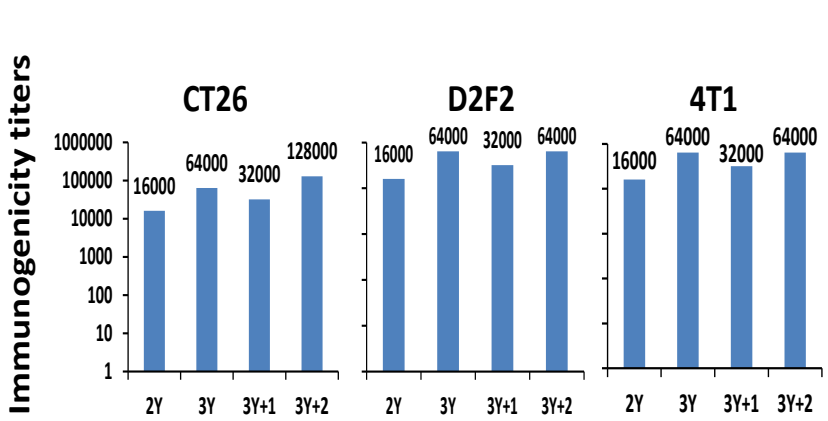


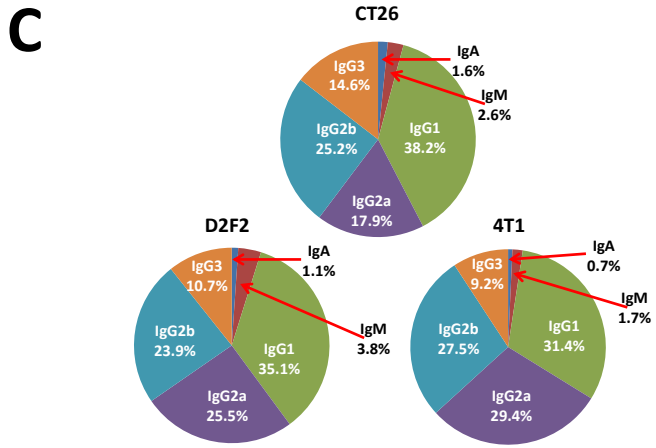


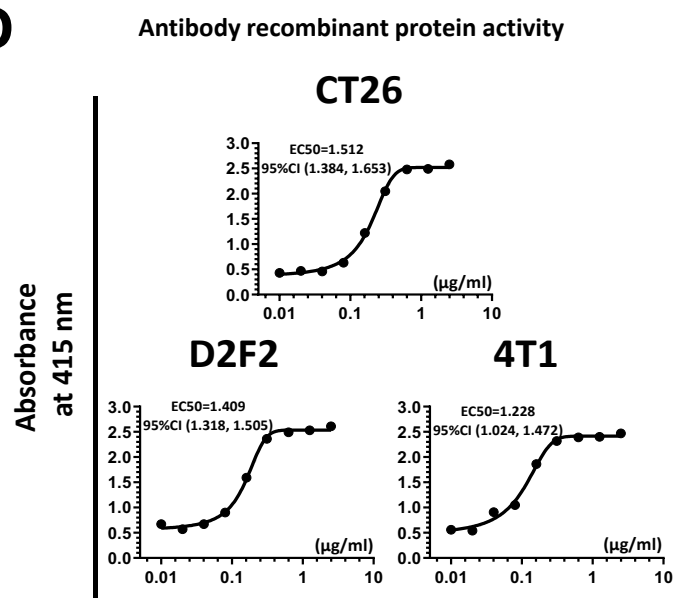


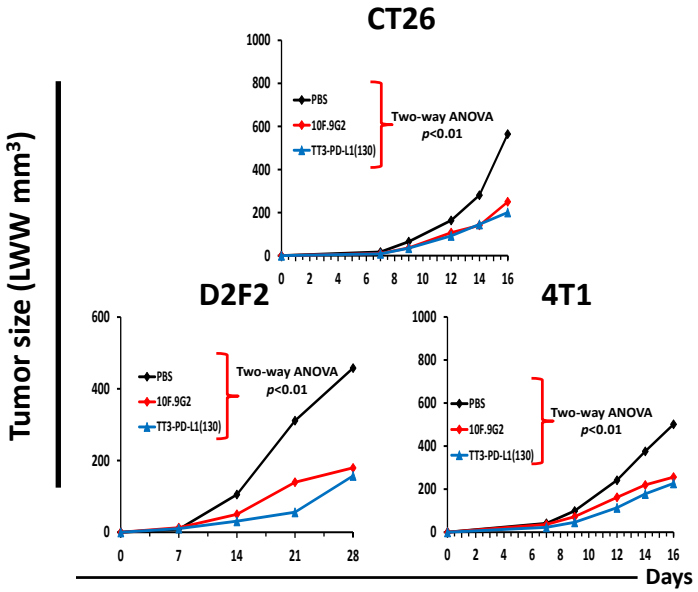
Syngeneic BALB/c Immunized with TT3-PD-L1 (130-147) Challenged with CT26, D2F2, and 4T1 Carcinoma cells

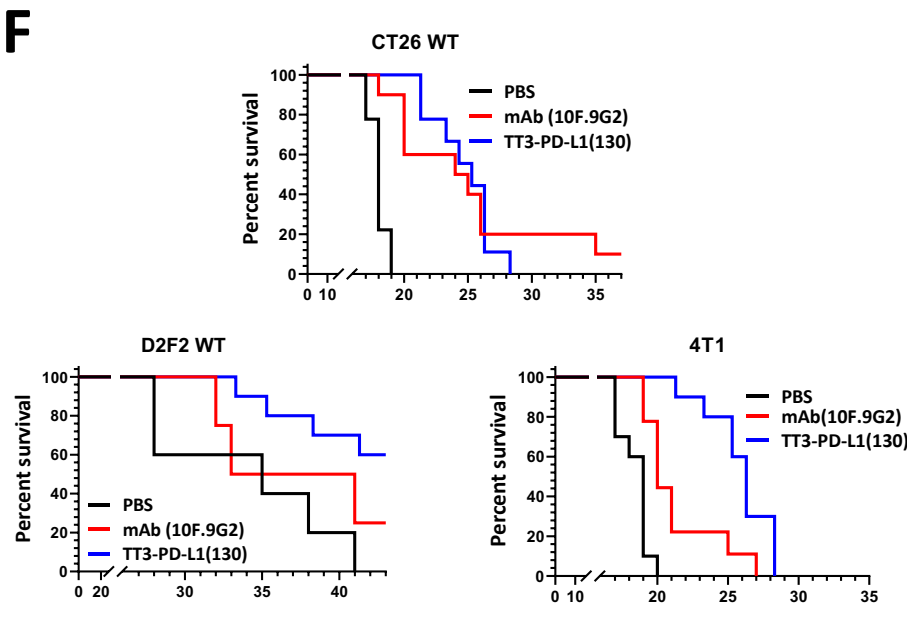




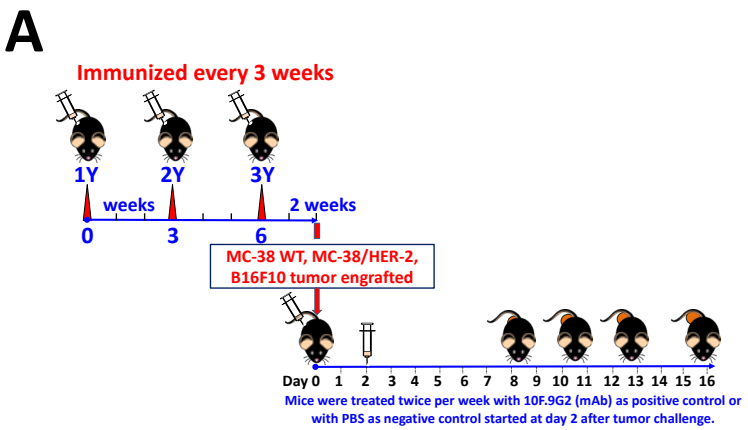


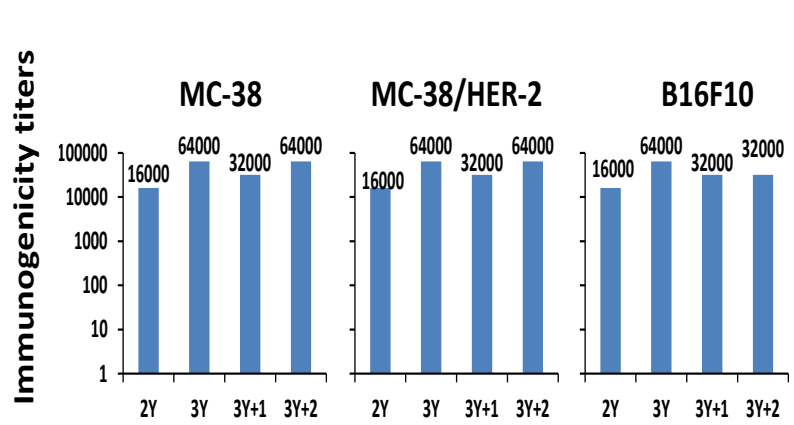


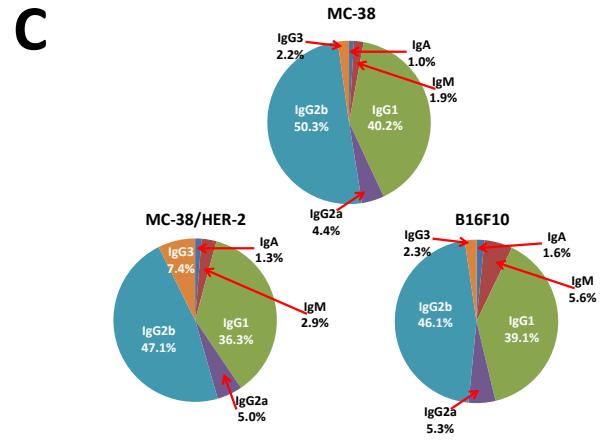


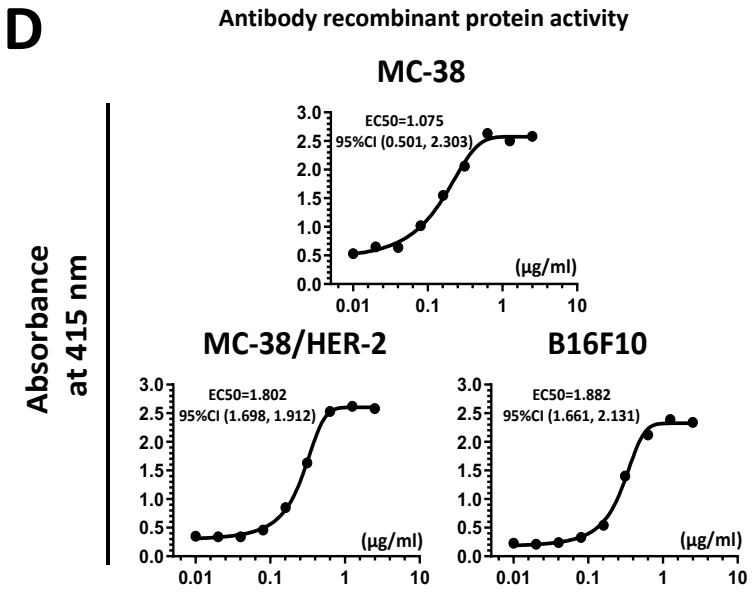


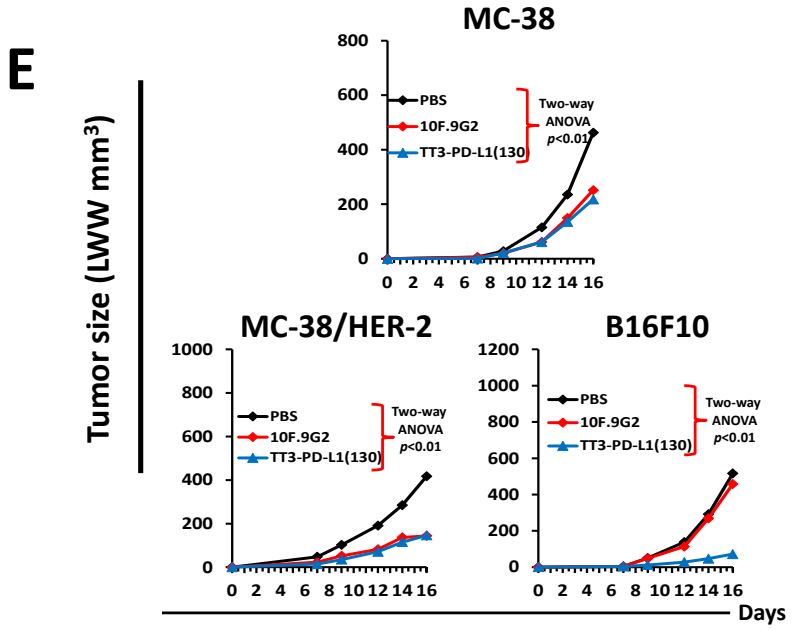
Syngeneic C57BL6/J immunized with TT3-PDL1(130-147) challenged with MC38, MC-38/HER-2,B16-F10 carcinoma cells

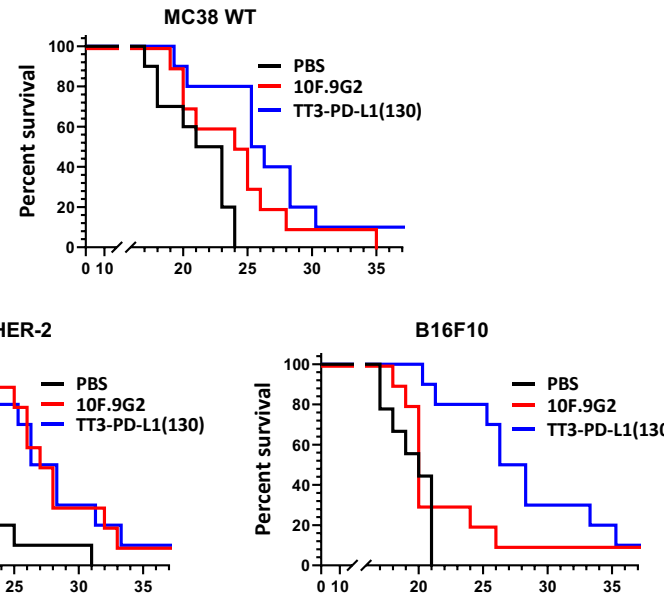




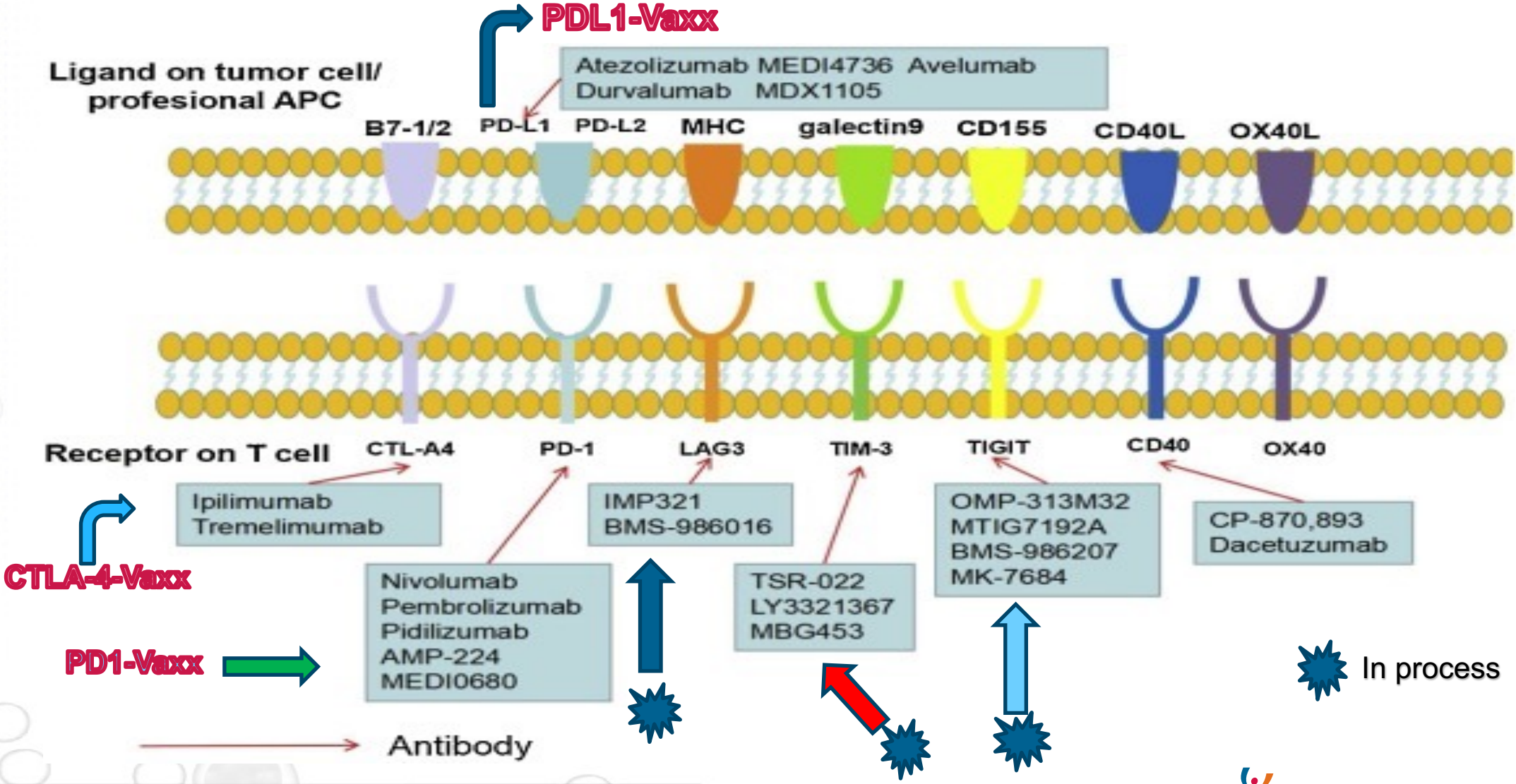






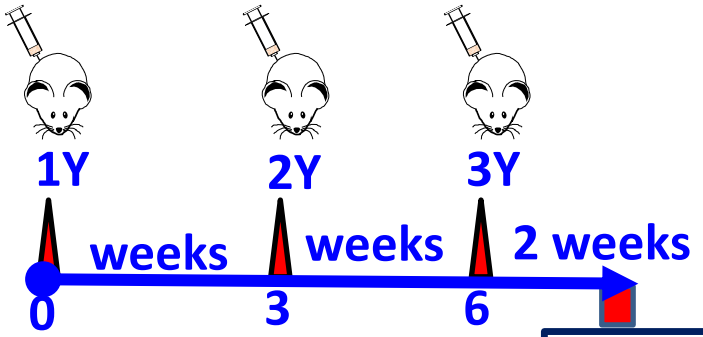


NOVEL TARGETS, AGENTS and Rational COMBINATIONS in IMMUNO-ONCOLOGY



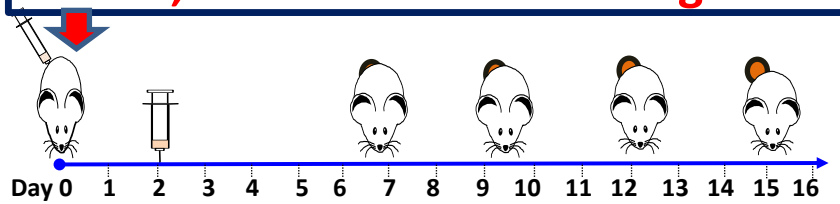
CTLA-4 peptide epitope vaccines identified

BALB/c
Immunized
every 3 weeks

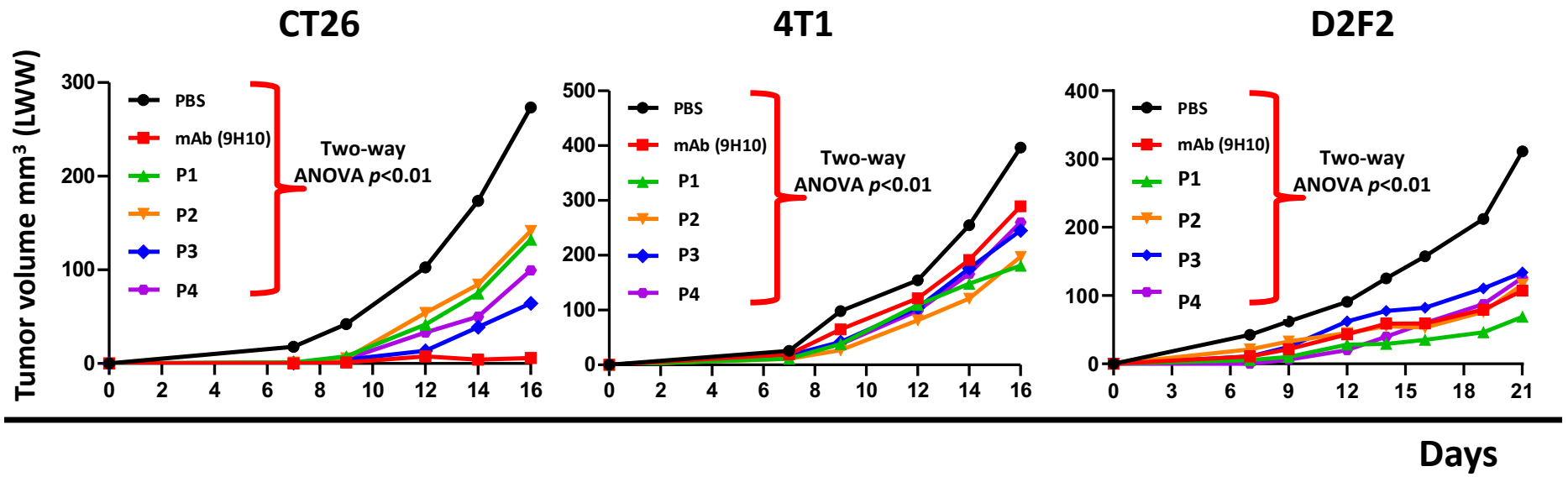


Mice were immunized with:
P1, P2, P3 or P4 CTLA-4 peptide epitope vaccine

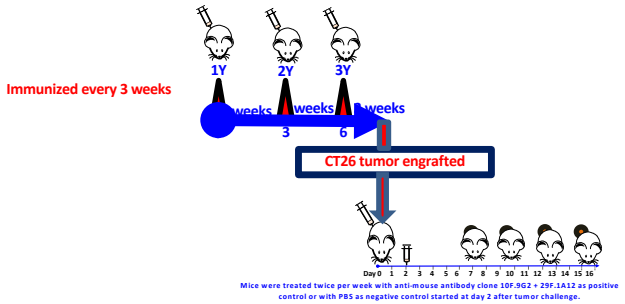
CT26, 4T1 or D2F2 tumor engrafted



Mice were treated twice per week with anti-mouse antibody clone 9H10 as positive control or with PBS as negative control started at day 2 after tumor challenge.



NOVEL CHECKPOINT INHIBITOR VACCINES
Rationale Combinations in ONCOIMMUNOLOGY
PD-1, PD-L1 and CTLA-4 VACCINES



V29: PD1-Vaxx + PD-L1 (36) or PD-L1(130)

BALB/c mice challenge with CT26

Negative control: PBS
POSITIVE CONTROL: mAb (10F.9G2 + 29F.1A12);
Combo1: **(MVF-PD-1(92)**+**MVF-PD-L1(36)**
Combo2: (**MVF-PD-1(92)**+**MVF-PD-L1(130)**

V30: CTLA-4 + PD-L1

BALB/c mice challenge with CT26

Groups:
PBS;
mAb: **mAbs (10F.9G2 + 9H10);**
V30 G5: Combo1: (**MVF-CTLA-4 (PK1)**+ **MVF-PD-L1(36)**;
V30 G6: Combo2: (**MVF-CTLA-4 (PK1)**+ **MVF-PD-L1(130)**
V30 G7: Combo3: **(MVF-CTLA-4 (PK2)+ MVF-PD-L1(36)**
V30 G8: Combo4: **(MVF-CTLA-4 (PK2)+ MVF-PD-L1(130)**

V31: PD1-Vaxx; PD-L1 (36); PD-L1(130)

BALB/c mice challenge with CT26
Groups:
V31 G0: PBS
V31 G1: mAb: **mAb (10F.9G2);**
V31 G5: **MVF-PD-1(92)**
V31 G6: **MVF-PD-L1(36)**
V31 G7: **MVF-PD-L1(130)**

V32: CTLA-4 Peptide Mimics

BALB/c mice challenge with CT26 tumor cells then treat as follows;
Treatment time: Day1, Day2, Day5, Day7, Day9, Day12, Day14, Day16;
(Dose of 0.2mg/mouse before day14, dose of 0.5mg/mouse at day14 and day16)

Groups:
V32 G0: PBS:
V32 G1: mAb: mAb (9H10)
V32 G5: **CTLA-4 (PK2)**
V32 G6: no immunization before challenge, post challenge treat with **Ac-CTLA-4**
V32 G7: no immunization before challenge, post challenge treat with **D-CTLA-4**
V32 G8: no immunization before challenge, post challenge treat with **RID-CTLA-4**
V32 G9: no immunization before challenge, post challenge treat with **RIL-CTLA-4**

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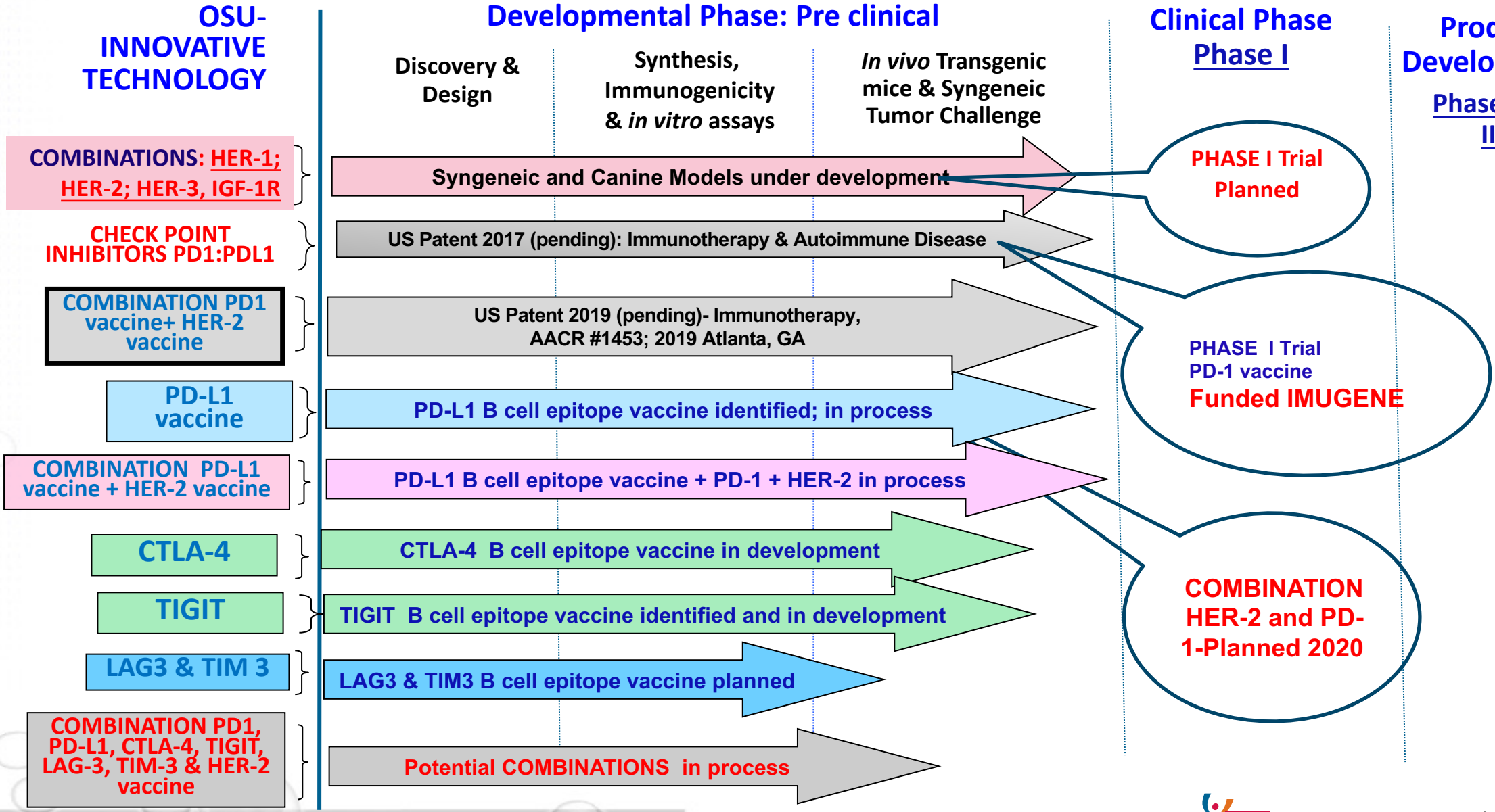
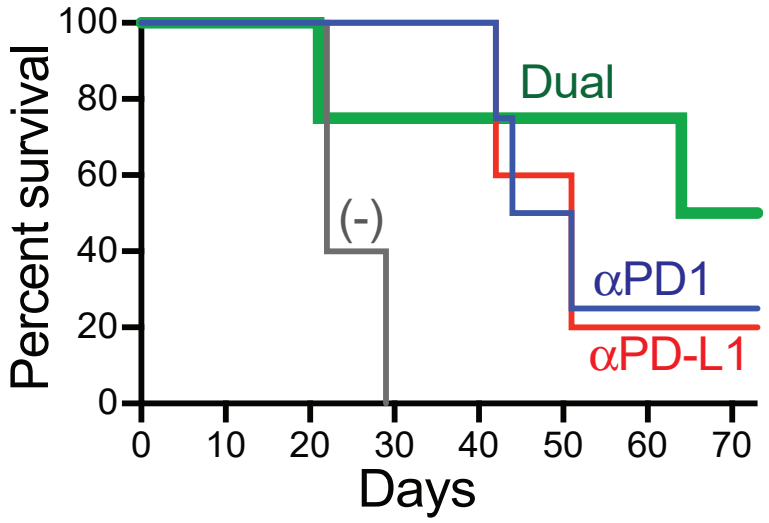
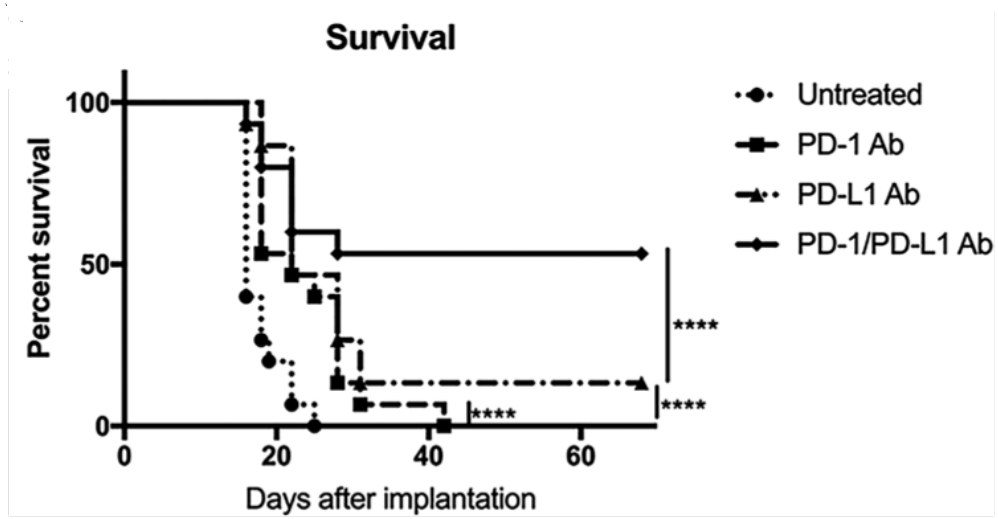


Why PD-1/PD-L1 Combination?



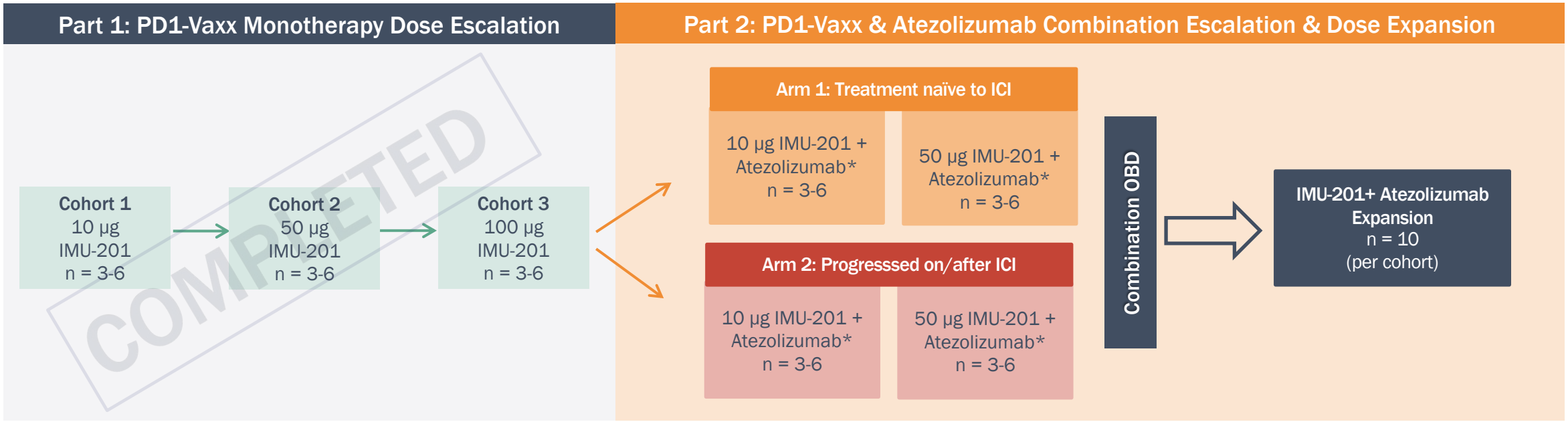
Burrack etal. Combination PD-1 and PD-L1 Blockade Promotes Durable Neoantigen-Specific T Cell Mediated Immunity in Pancreatic Ductal Adenocarcinoma, Cell Reports *28*, 2140–2155

https://clinicaltrials.gov/ct2/show/NCT03936959?term=NCT03936959&draw=2&rank=1, bispecific PD1/PDL1 antibody Phase 1, Eli Lilly LY3434172, and Beigene, BGB-A333 Alone and in Combination With Tislelizumab https://clinicaltrials.gov/ct2/show/NCT03379259



Hartley etal. Programmed Cell Death Ligand 1 (PD-L1) Signaling Regulates Macrophage Proliferation and Activation Cancer Immunol Res; 6(10) October 2018 Combined therapy with PD-1/PD-L1 antibodies induced early tumour regression and tumour-free survival in melanoma

IMPRINTER:
PD1-Vaxx Phase 1 Study Design



Phase	Part 1: Monotherapy Dose Escalation	Part 2: Combination Escalation & Expansion
Indication	Advanced/metastatic non-small cell lung cancer expressing PD-L1 (TPS>50) and progressed on/after ICI	Advanced/metastatic non-small cell lung cancer expressing PD-L1 (TPS>50) Arm 1: treatment naïve for ICI Arm 2: progressed on/after ICI (fresh biopsy)
Objectives	Primary: Safety, OBD Monotherapy & Combination, Secondary: ORR, PFS, OS, Exploratory: Biomarker	
No. of Patients	**Approx. 9-18**	**Approx. 32-44**
Site Location	Australia & USA	

*840mg Atezolizumab every 2 weeks = Q2W

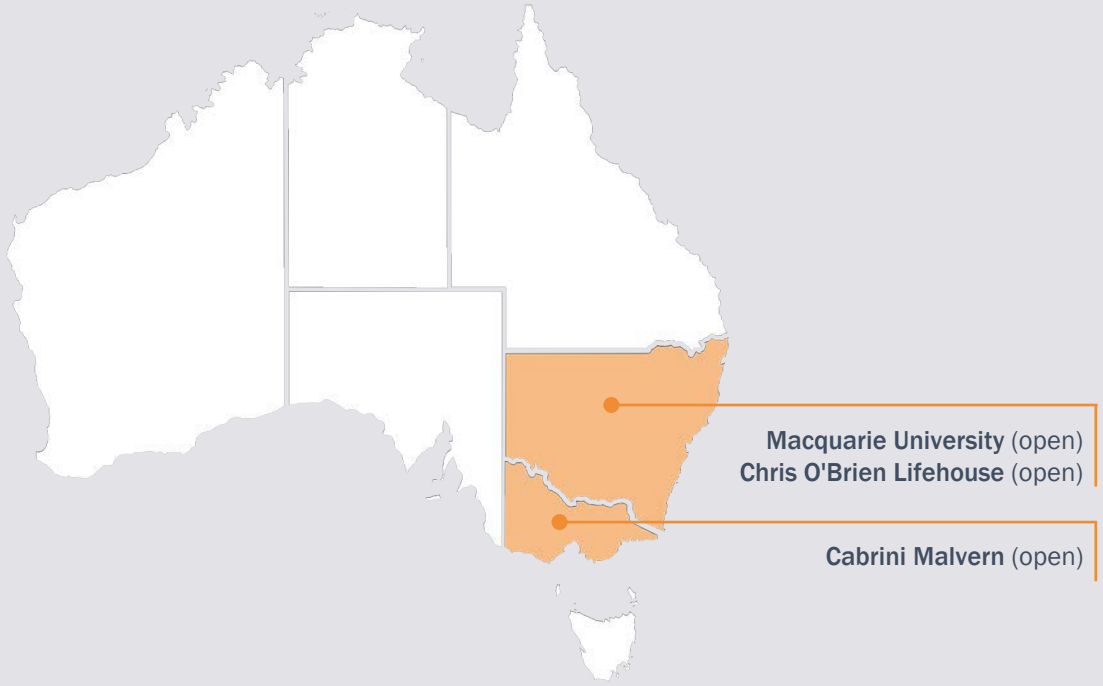
IMPRINTER:
PD1-Vaxx Phase 1 Monotherapy Dose Escalation Complete

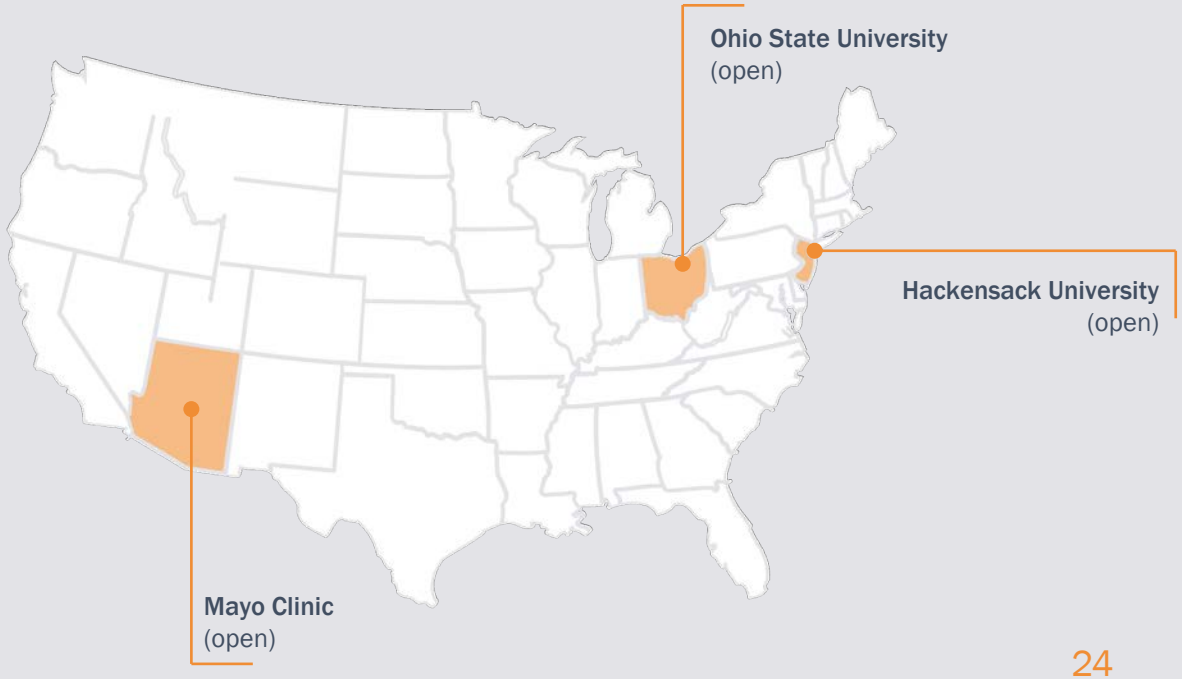
IMUGENE
Developing Cancer Immunotherapies

Current Status

MILESTONES

1st Patient Dosed Cohort 1	Cohort 1 Cleared	1st Patient Dosed Cohort 2	Cohort 2 Cleared	1st Patient Dosed Cohort 3	Cohort 3 Cleared
30 Nov 2020	Jan 2021	Feb 2021	April 2021	August 2021	January 2022





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