SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

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Society for Immunotherapy of Cancer

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Developing New Immunotherapies in Preclinical Models and Humans

Elizabeth M. Jaffee, M.D.

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#SITC2016

Presenter Disclosure Information

Elizabeth M. Jaffee, M.D.

I have the following financial relationships to disclose

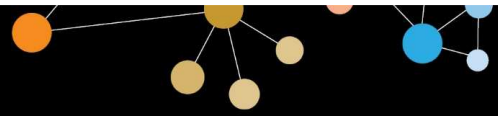
I will be discussing the investigational use of:

- GVAX
- Listeria Monocytogenes – mesothelin

Both licensed to Aduro Biotech with potential to receive royalties

Consultation activity: BMS, Adaptive Biotech, MedImmune, Incyte, Merck

Grants: Aduro, BMS, Roche



How can we accelerate immunotherapy to successfully treat currently resistant cancers?

GI Cancers as Example: Emerging Successes

- PD-1 blockade shows responses in microsatelite instability (MSI) high tumors
  - MSI high tumors have a large mutational burden
  - Mutational burden recruits T cells and so these tumors look like melanomas
  - PD-1 blockade activates the infiltrating T cells
  - 2% of pancreatic cancer patients benefit
  - 10% of colorectal cancer patients benefit

- Vaccines alone show some evidence of clinical regressions in pancreatic cancer patients but hard to beat chemotherapy in metastatic disease

- Unfortunately most GI cancers do not respond to single agent immunotherapy

Challenges for cancers that do not naturally respond to current checkpoint therapy

- Need methods to induce functional effector T cells – most patients don't have them

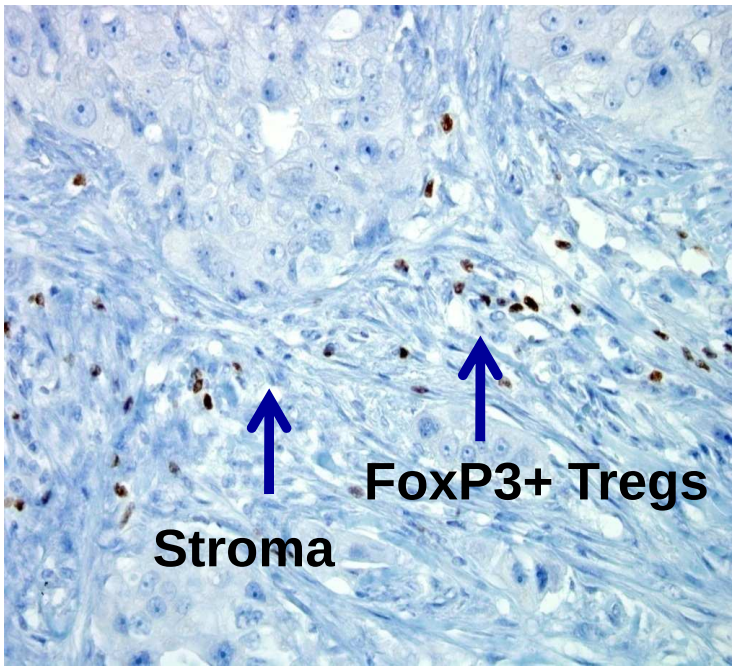
- Each cancer type and subtype have a unique TME
  - Need to elucidate the specific suppressive mechanisms to have a clinical effect
  - We need to design "science in patient" studies that acquire pre- and post treatment tissue to uncover the signals that need to be modified

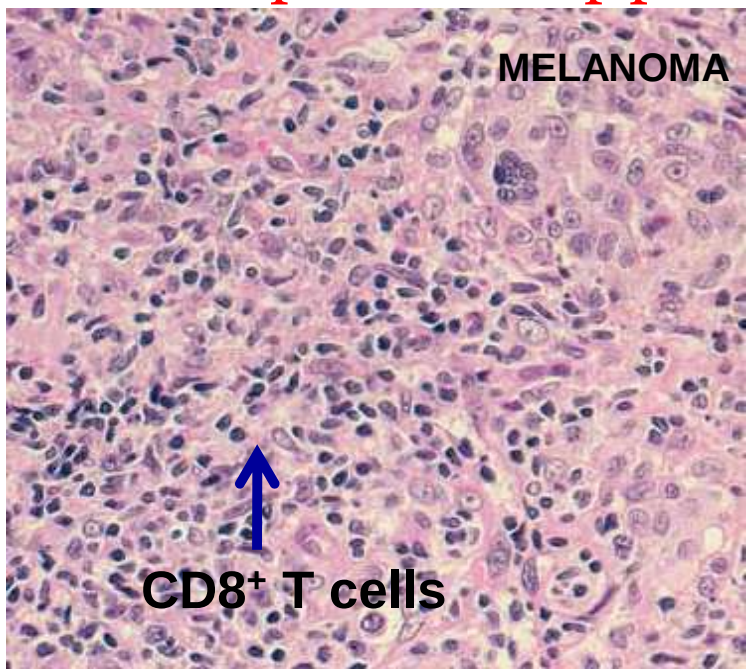
- Developing combinations efficiently requires new trial designs and FDA clinical development pathways

Lack of effective T cells is one difference between single agent immune checkpoint responders and non-responders

The checkpoints expressed in each cancer's tumor microenvironment is likely unique to the genetic, epigenetic and inflammatory changes that drive the cancer and its progression

Invasive pancreatic tumors lack infiltration of effector T cells: Vaccines are first step of multistep process!

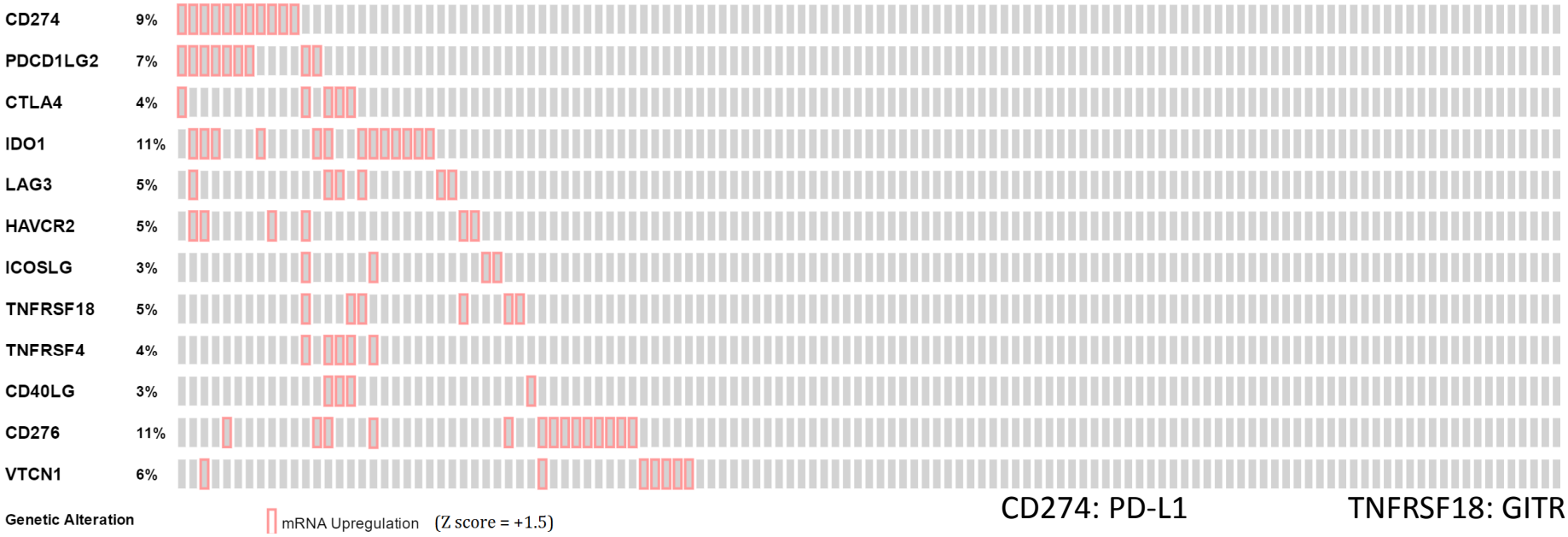




Pancreatic cancers are infiltrated with immune suppressive regulatory T cells (Tregs) and MDSCS (not shown)

50% of Melanomas have spontaneous infiltration of effector T cells

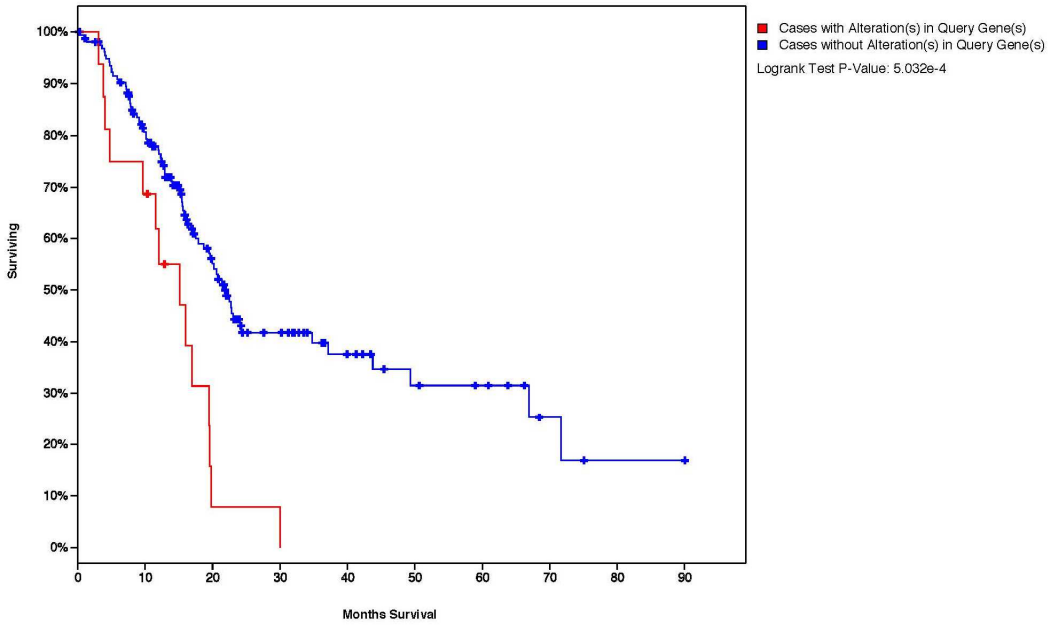
TCGA Data: Upregulation of Multiple Immune Targets in Pancreatic Cancer Which Differ by Patient Tumor



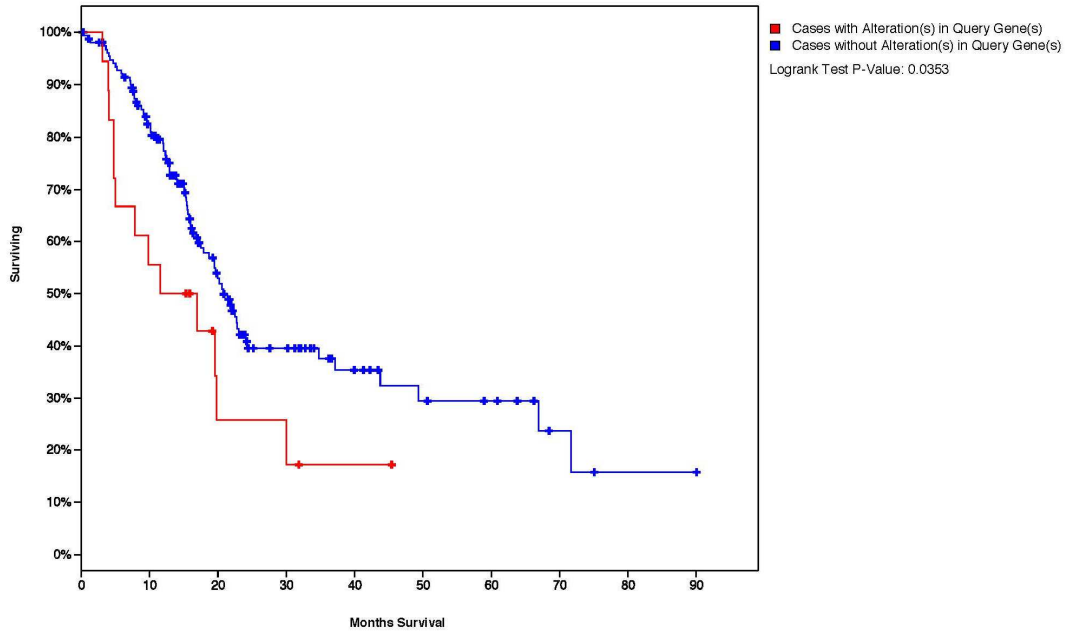
Altered in 47 (38%) of 123 cases/patients using z-score threshold +1.5

CD274: PD-L1
PDCD1LG2: PD-L2
PDCD1: PD-1
HAVCR2: TIM-3
ICOSLG: ICOS-L
TNFRSF18: GITR
TNFRSF4: OX40
CD276: B7-H3
VTCN1: B7-H4

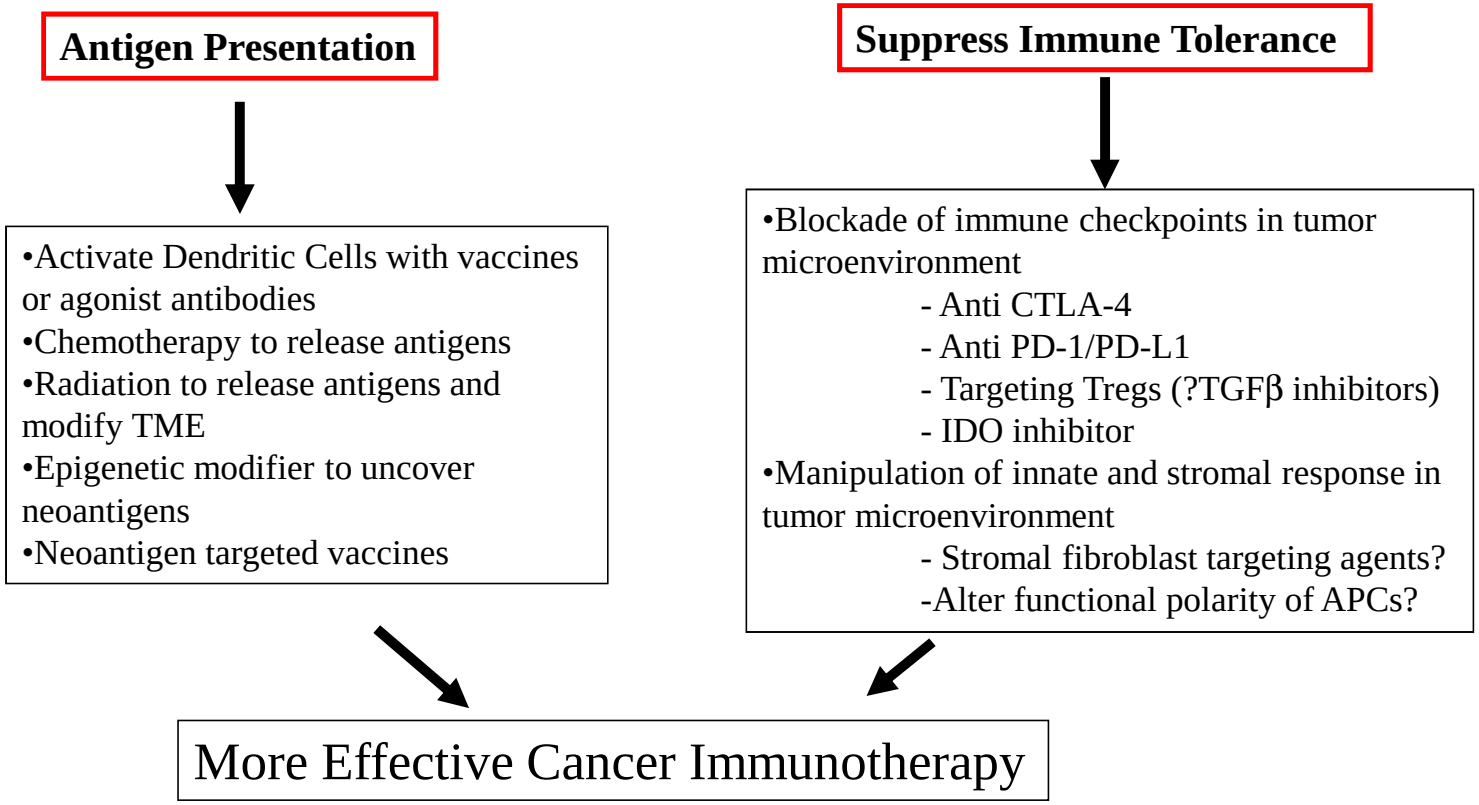
TCGA Data suggests PDL1 Upregulation correlates with shorter term survival



TCGA Data suggests IDO1 upregulation correlates with shorter term survival



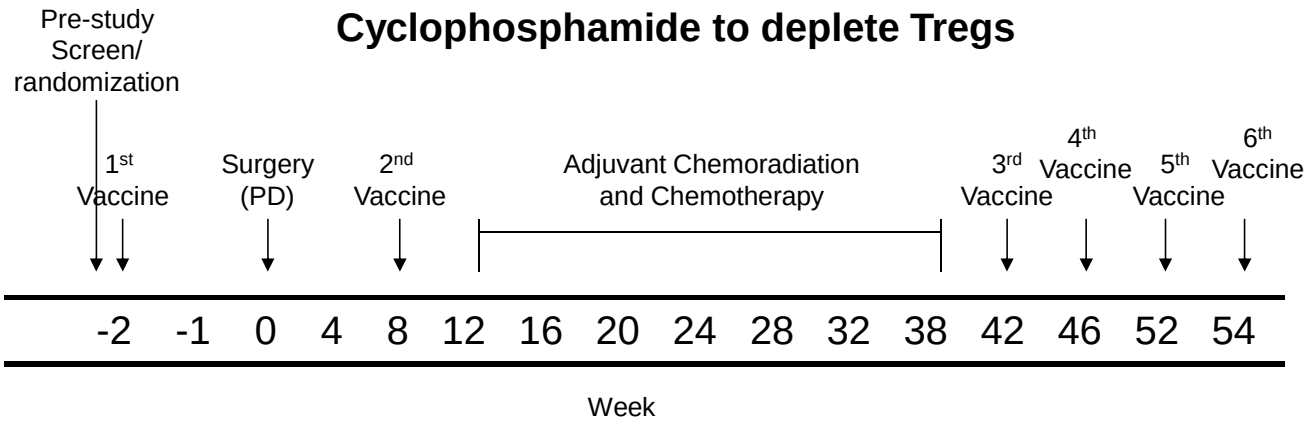
Naturally Non-Immunogenic Cancers Require a 2-Step Process to Reprogram the TME and Optimize Immunotherapy



Modified from *Soares, Zheng, Edil, and Jaffee Cancer J. 2012*

(Neo)adjuvant Pancreatic Cancer Vaccine Study Provides New Evidence for ANTITUMOR Immunity

Cancer Immunology Research, 2014



Arm A: Vaccine alone Arm B: Vaccine + low dose IV Cy Arm C: Vaccine + metronomic Cy

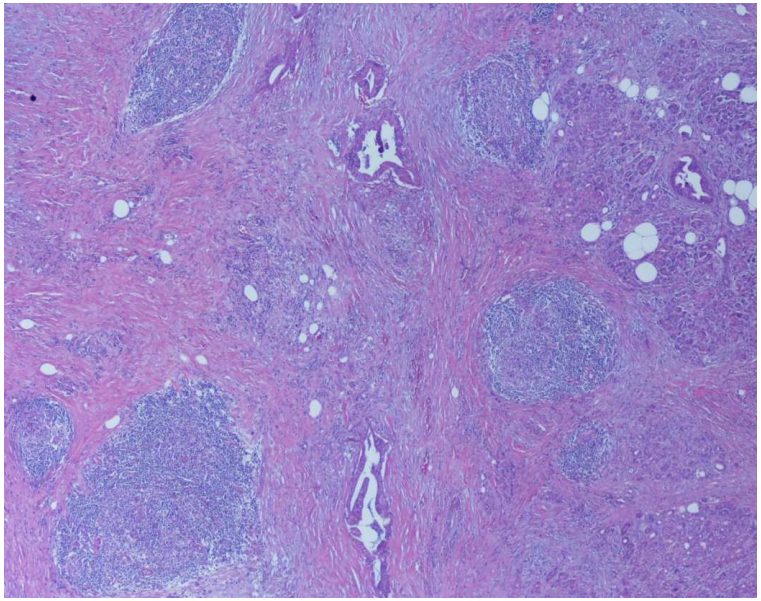
Lei Zheng, M.D./Ph.D.

Chris Wolfgang M.D./Ph.D.

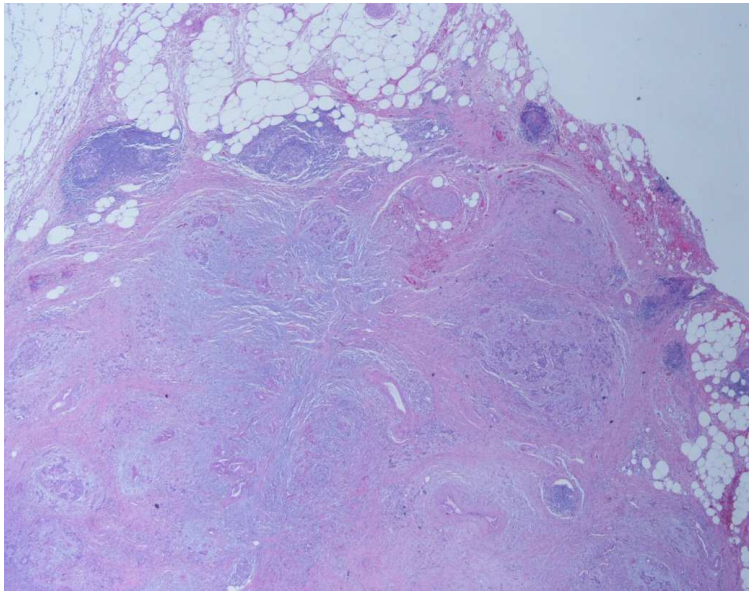
Dan Laheru, M.D.

Eric Lutz, Ph.D.

Lymphoid Aggregates found in 2 location patterns in vaccinated patients 2 weeks after a single vaccine

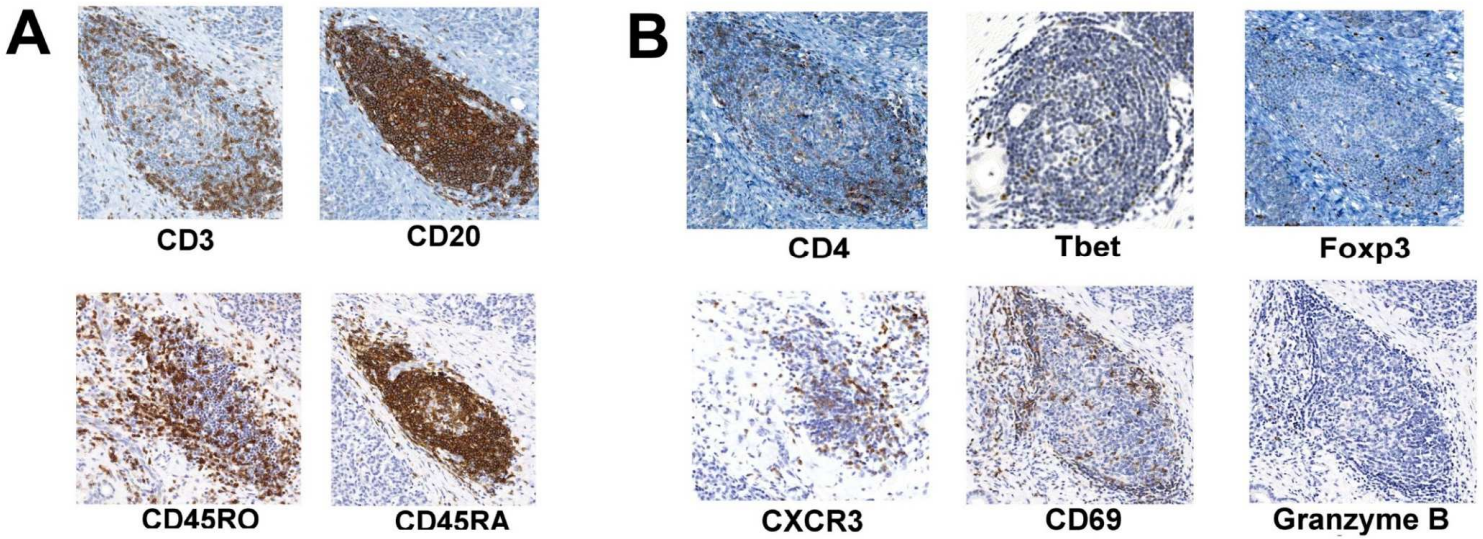


Intratumoral

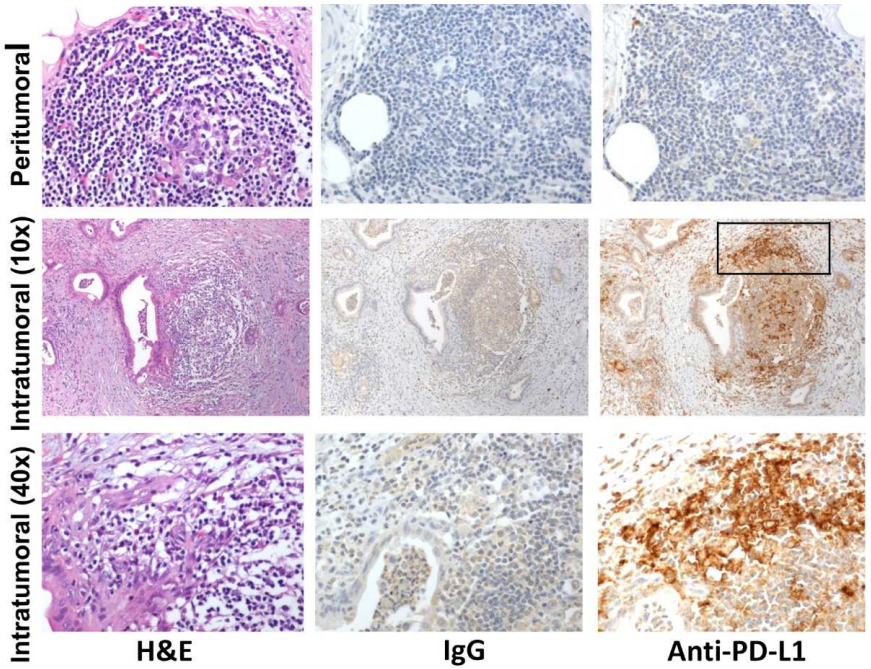


Peri-tumoral

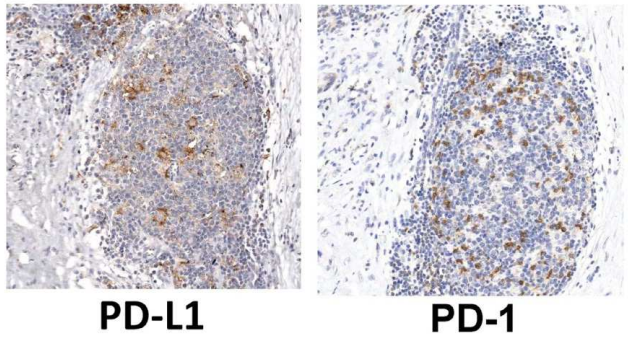
Lymphoid Aggregates Are Sites of Immune Activation and Regulation – Not Cytoloysis



PD-1/PD-L1 pathway is upregulated in vaccine induced lymphoid aggregates

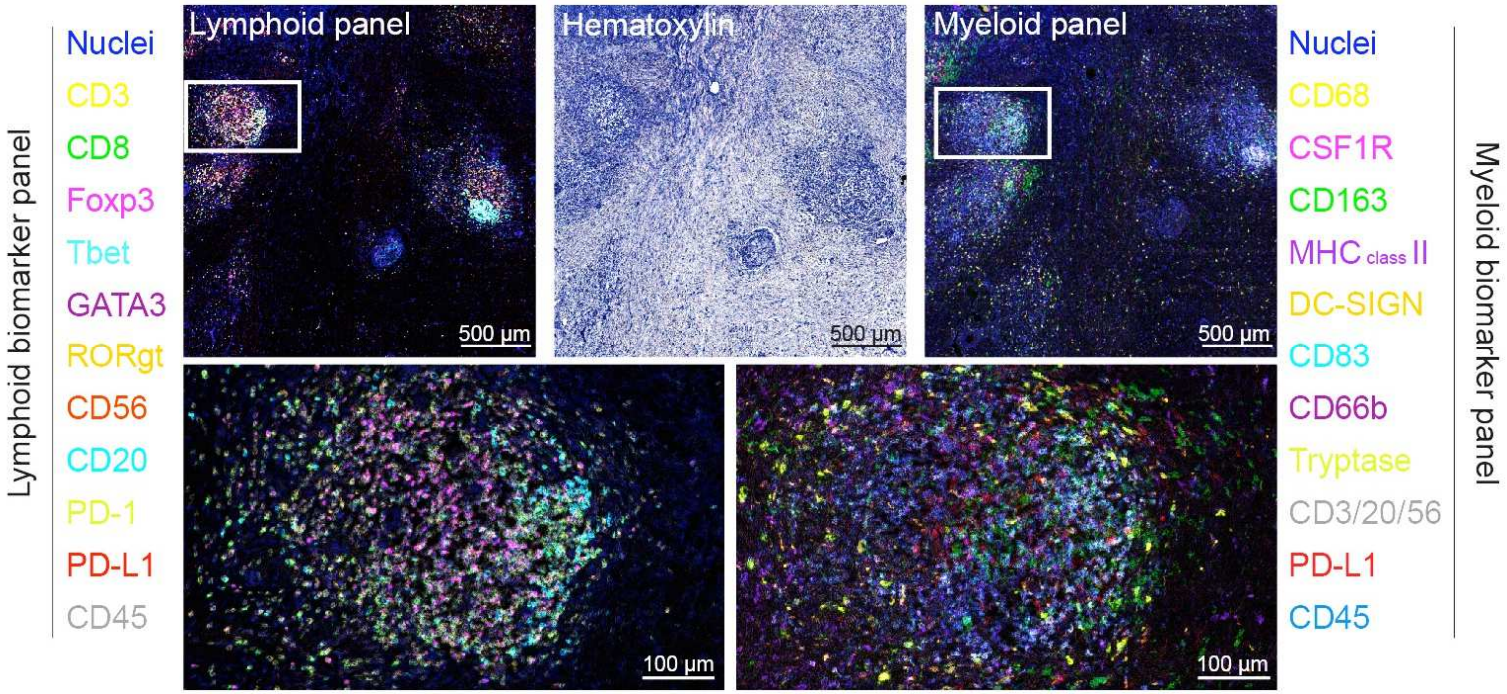


Co-localization



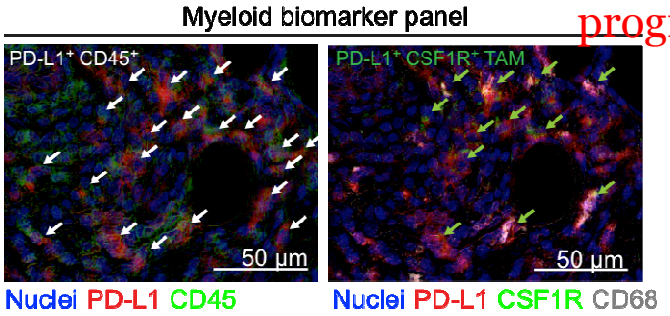
Two panels of 12-color multiplex IHC depicted tumor immune infiltrates in pancreatic cancer tissues

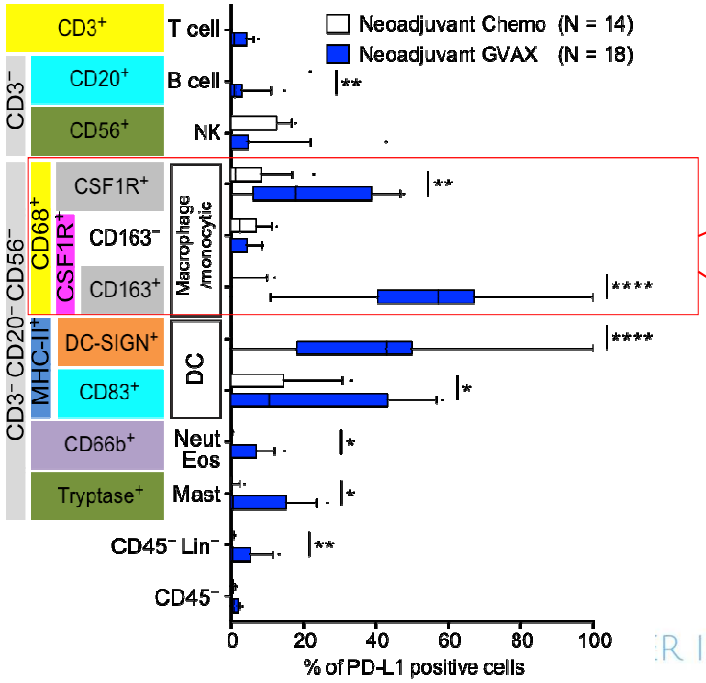
Human PC tissue, neoadjuvant GVAX

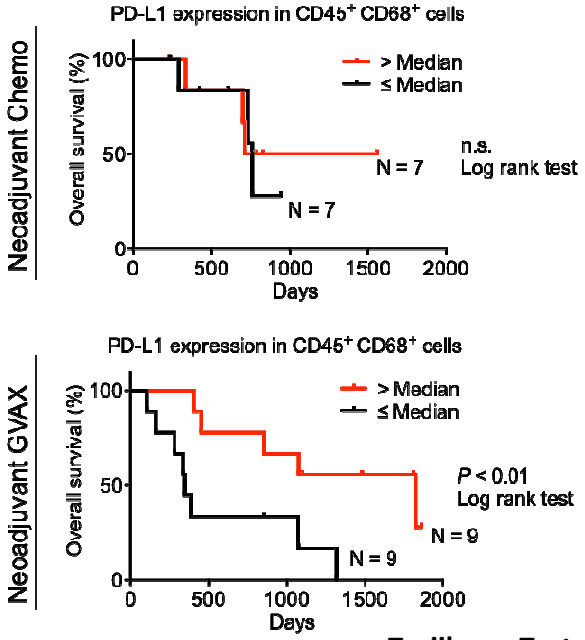


Tsujikawa T, Jaffee, Coussens et al. Unpublished data

Neoadjuvant GVAX therapy associated with PD-L1 upregulation in myeloid cell lineages correlates with prognosis – marker of T cell infiltration?

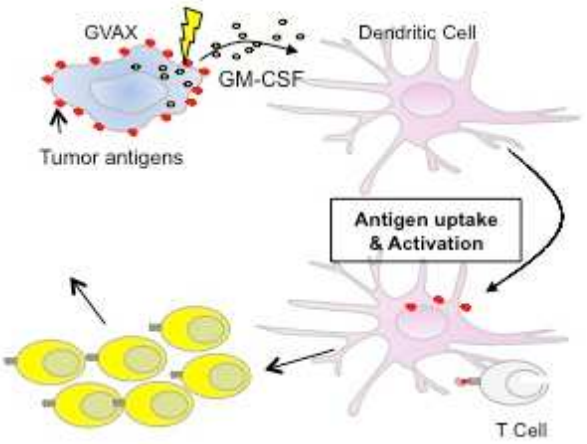






Tsujikawa T, et al. Unpublished data

Neo-Adjuvant Study of Vaccine +/- PD-1 Blockade



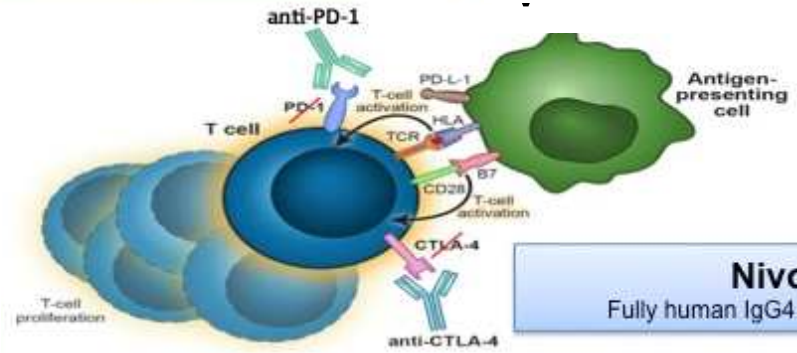
GVAX Pancreas
Whole-cell tumor vaccine

Evaluate changes in T cell Activation and infiltration

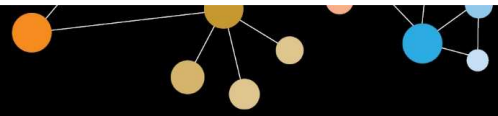
Evaluate changes in PD-L1 expression on tumors and monocytes

Evaluate immune signatures of response

+/-

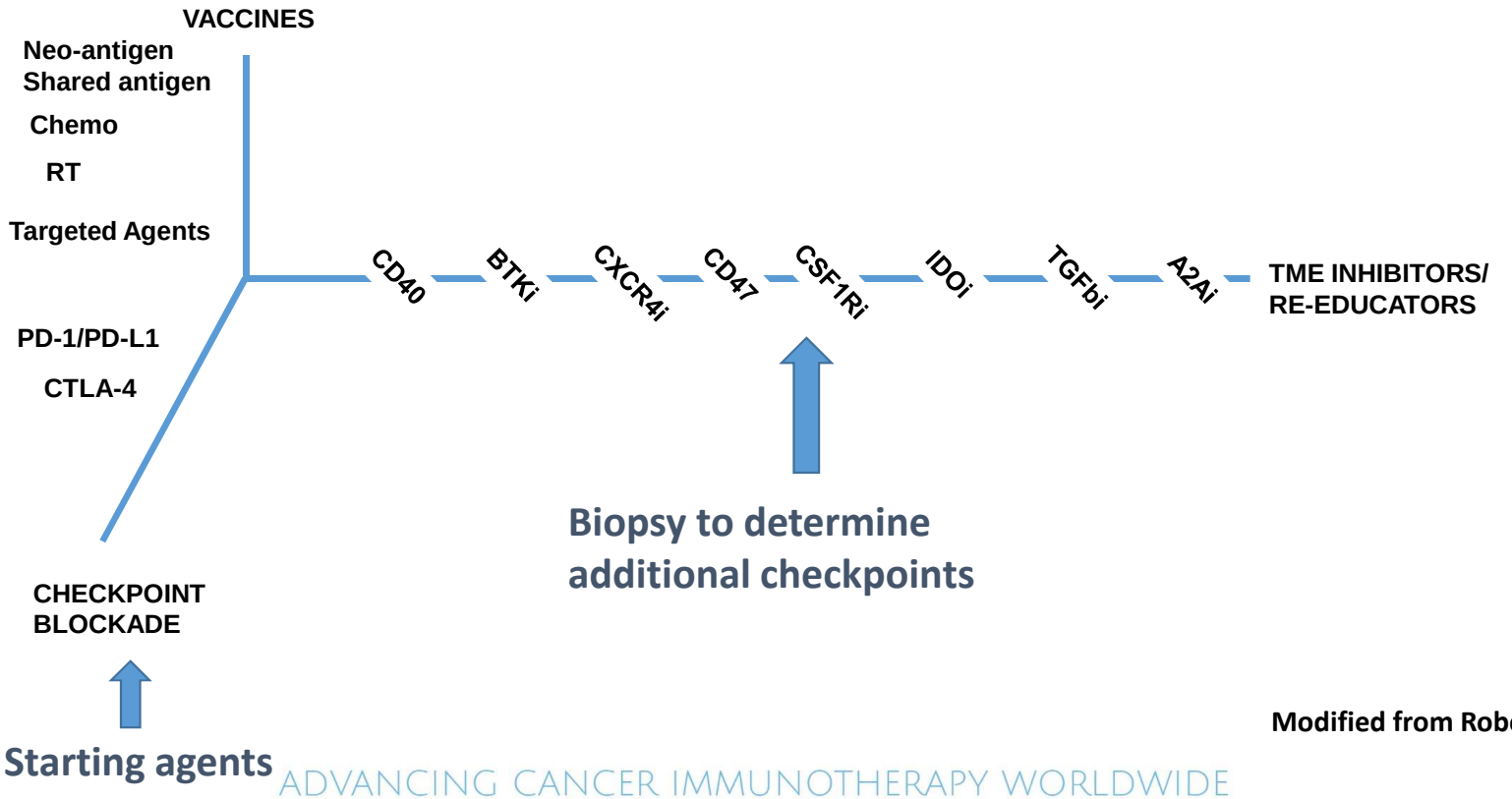


Nivolumab
Fully human IgG4 antibody against PD-1



How do we move from signal to outright effective activity in GI cancers?

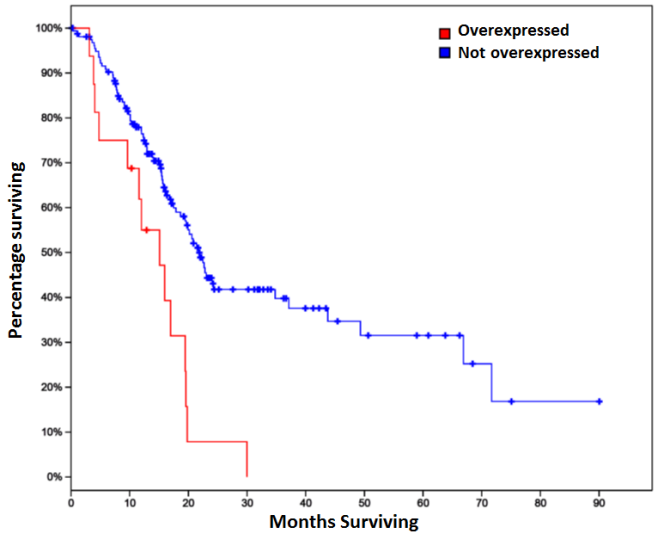
Combination Therapy Strategy For Less Immunogenic Tumors



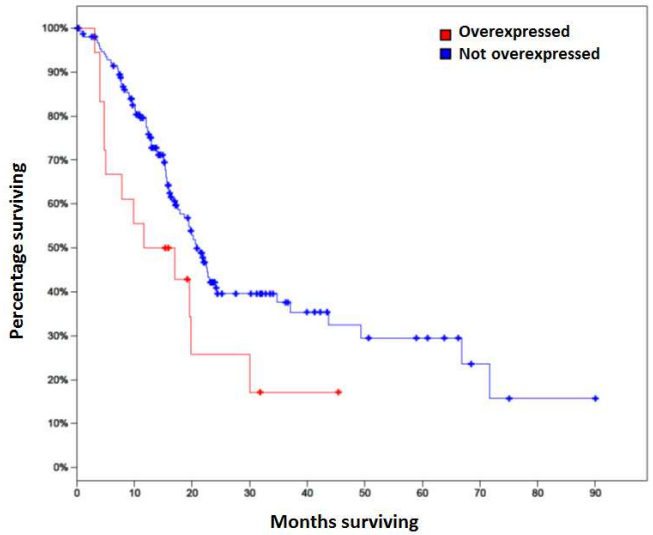
Modified from Robert Vonderheide

Personalized selection of immune checkpoint inhibitors

A subset of untreated pancreatic cancers upregulate immune checkpoints and have worse survival



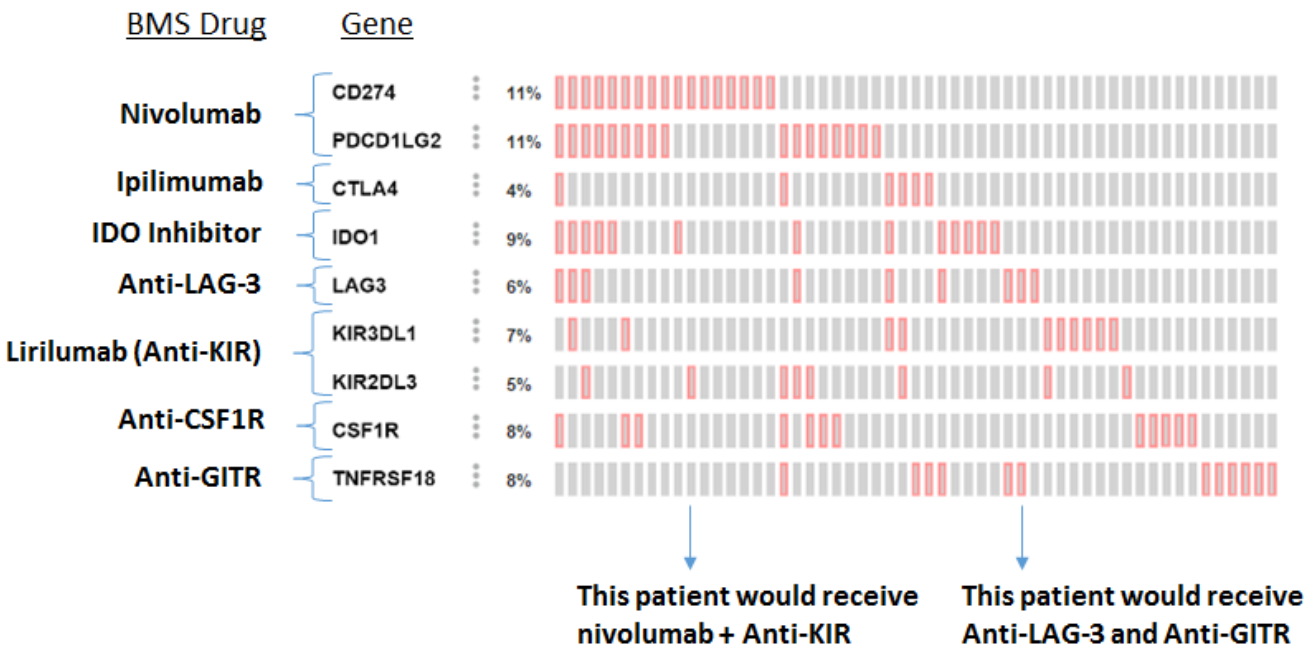
PD-L1 (p=5.0 x 10-4*)*



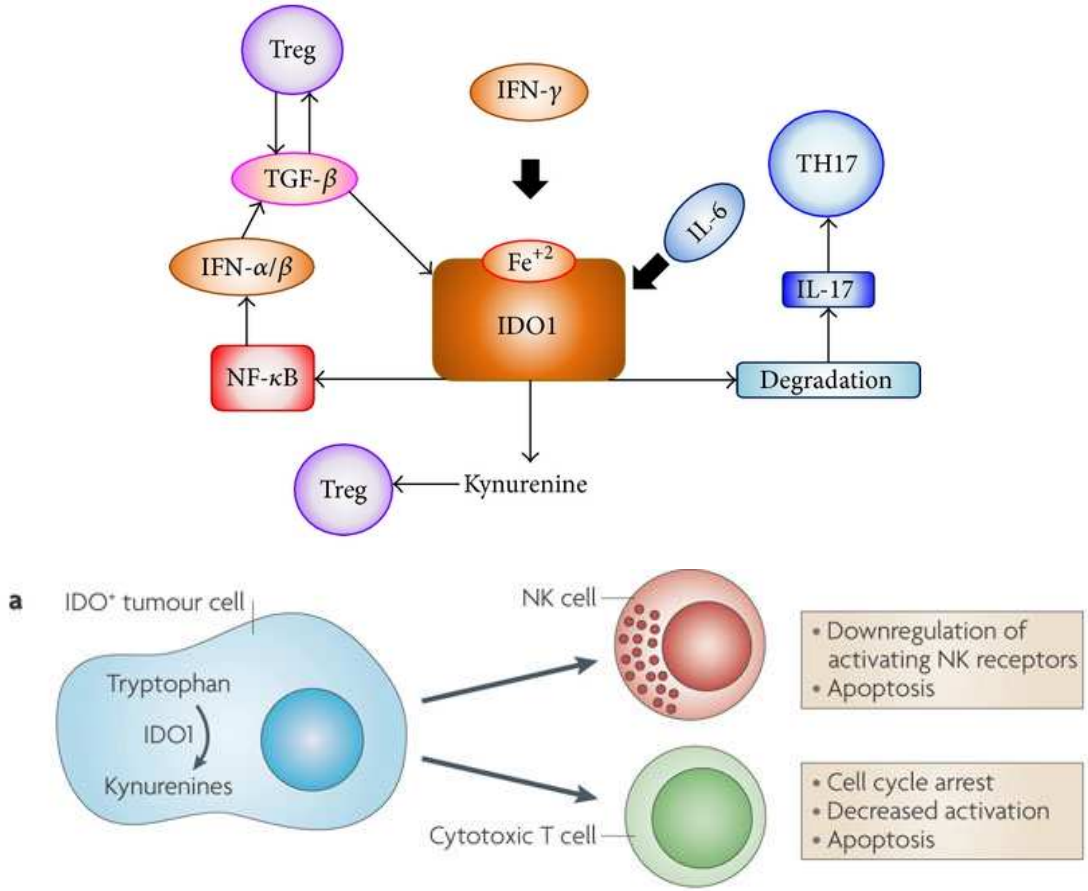
IDO (p=0.035)

Personalized selection of immune checkpoint inhibitors

Selection of immune checkpoints based on upregulation of immune escape pathways in each patient

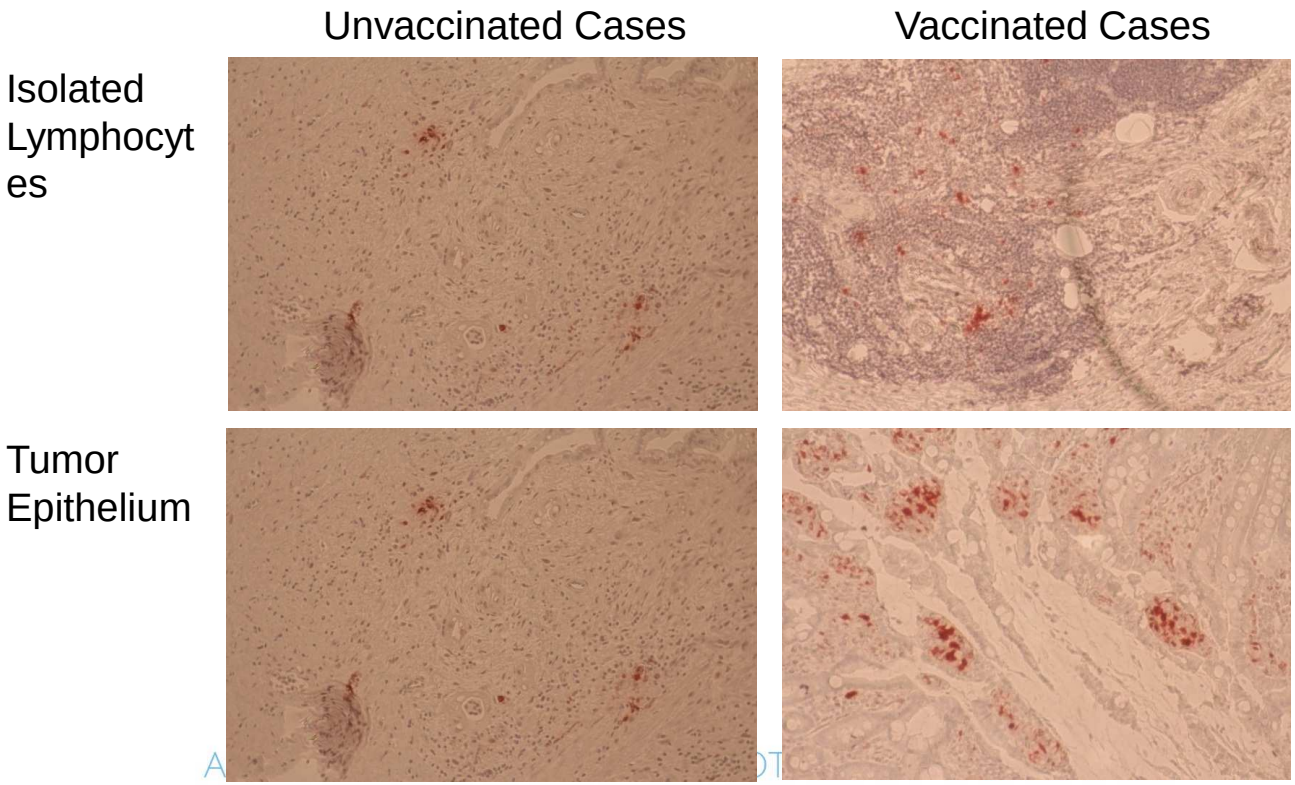


IDO causes increase in Tregs and depletes cytotoxic T cells

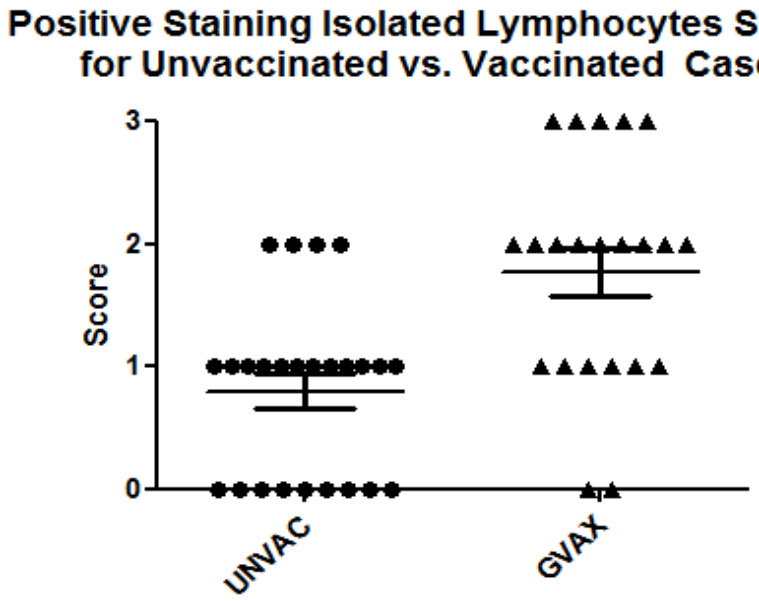


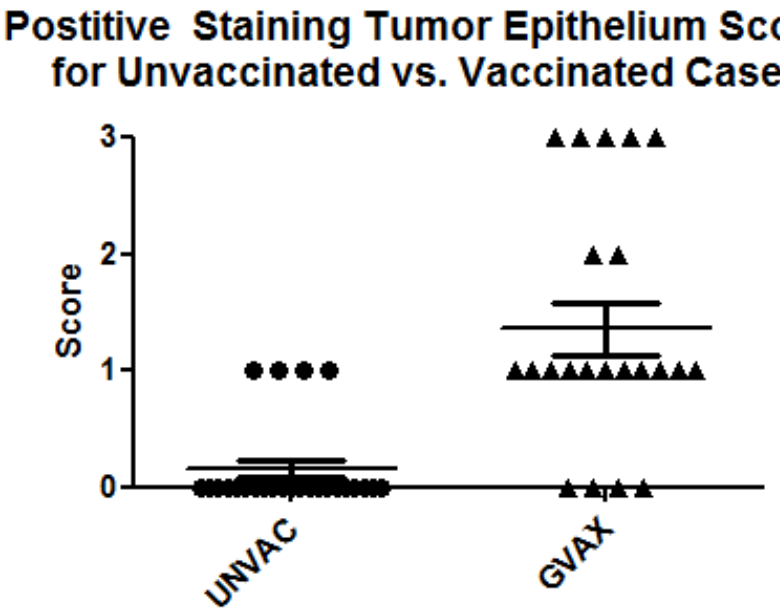
Lob et al. Nature Reviews Cancer. 2009

GVAX Vaccination increases IDO (Indolamine 2,3-Dioxygenase) expression in the tumor epithelium and lymphocytes in human PDAs

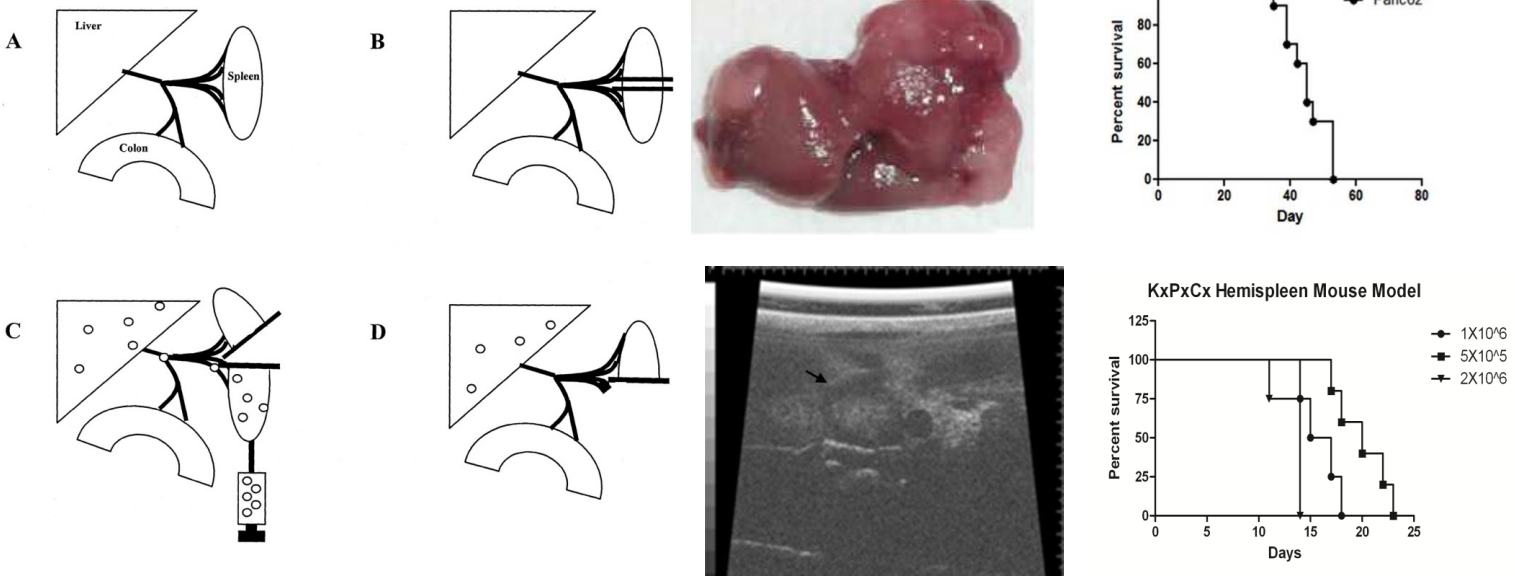


GVAX Vaccination increases IDO expression in the lymphocytes and tumor cells in human PDAs





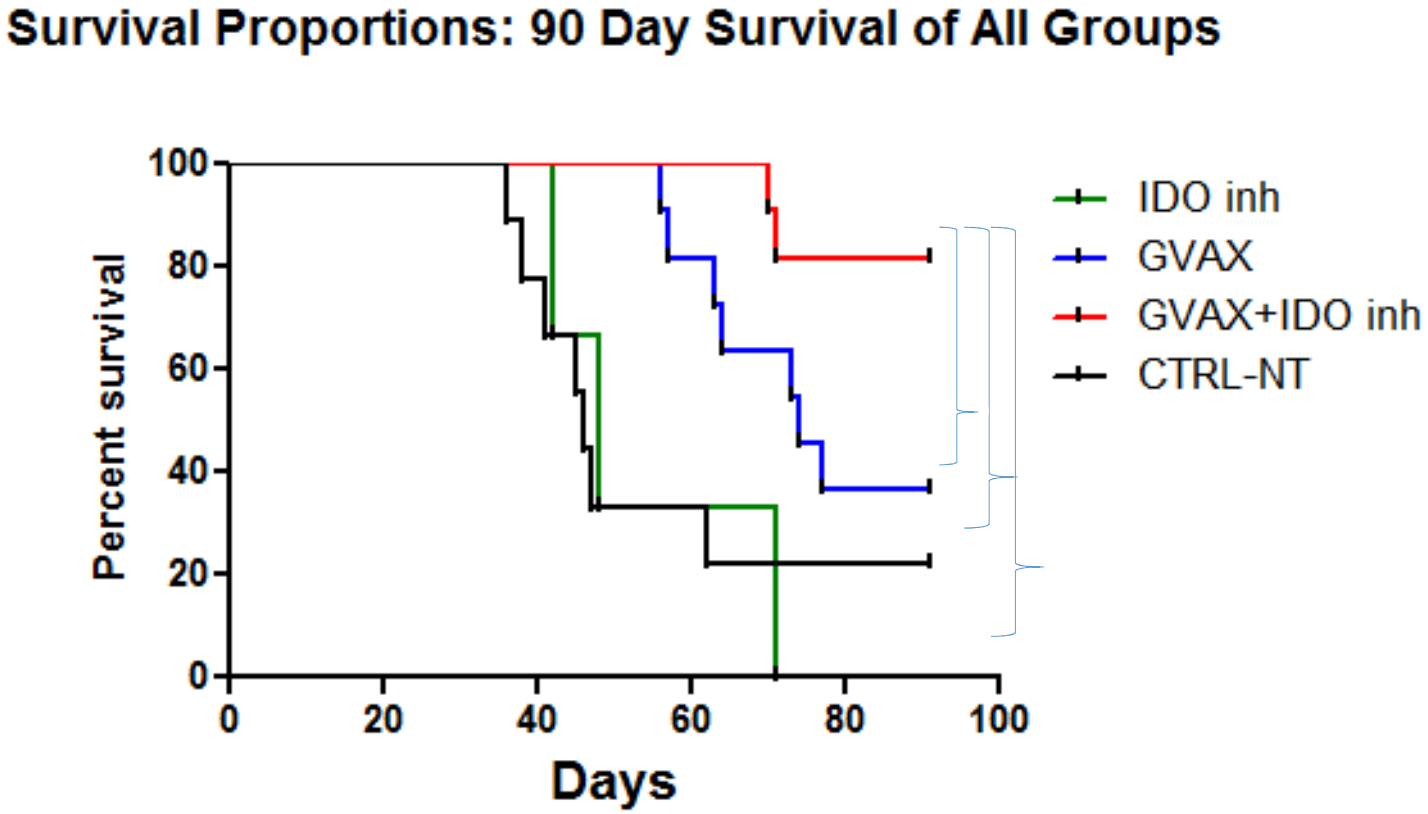
Syngeneic Mouse Hepatic Metastasis Model by Hemispleen Injection



Jain et al. Annals Surg. Onc. 2003

Soares et al. JoVE. 2014

Inhibition of IDO combined with GVAX increases survival in liver metastasis mouse model



Study planned to combine anti-PD-1 + vaccine and anti-IDO

SUMMARY

- Non-immunogeneic cancers lack adequate numbers of effector T cells
- These cancers require a 2-STEP approach to reprogram the TME and induce the most effective anticancer immunity
- The first is induction of the best effector T cells
- The second is modulation of multiple checkpoints within the tumor microenvironment
- The best approach is to personalize combination checkpoints to an individual's tumor which is based on:
  - A tumor's genetic evolution
  - Prior therapies (chemotherapy/radiation/immunotherapy)

Scientific Partners

Dan Laheru
Dung Le
Eric Lutz
Lei Zheng
Todd Armstrong
Bob Anders
Sara Solt
Guanlan Mo

Chris Wolfgang
Ralph Hruban
Joe Herman
John Cameron
Carol Judkins
Rich Schulick
Barish Edil
Raka Bhattacharya
Tianna Dauses

Lisa Coussens
Takahiro Tsujikawa

NCI GI Spore NCI RO1 Skip Viragh Pancreatic Cancer Center

Aduro Biotech PANCAN AACR BMS and Merck Bloomberg-Kimmel Institute

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