Immune Checkpoint Inhibitor Associated Myocarditis: Pathophysiology

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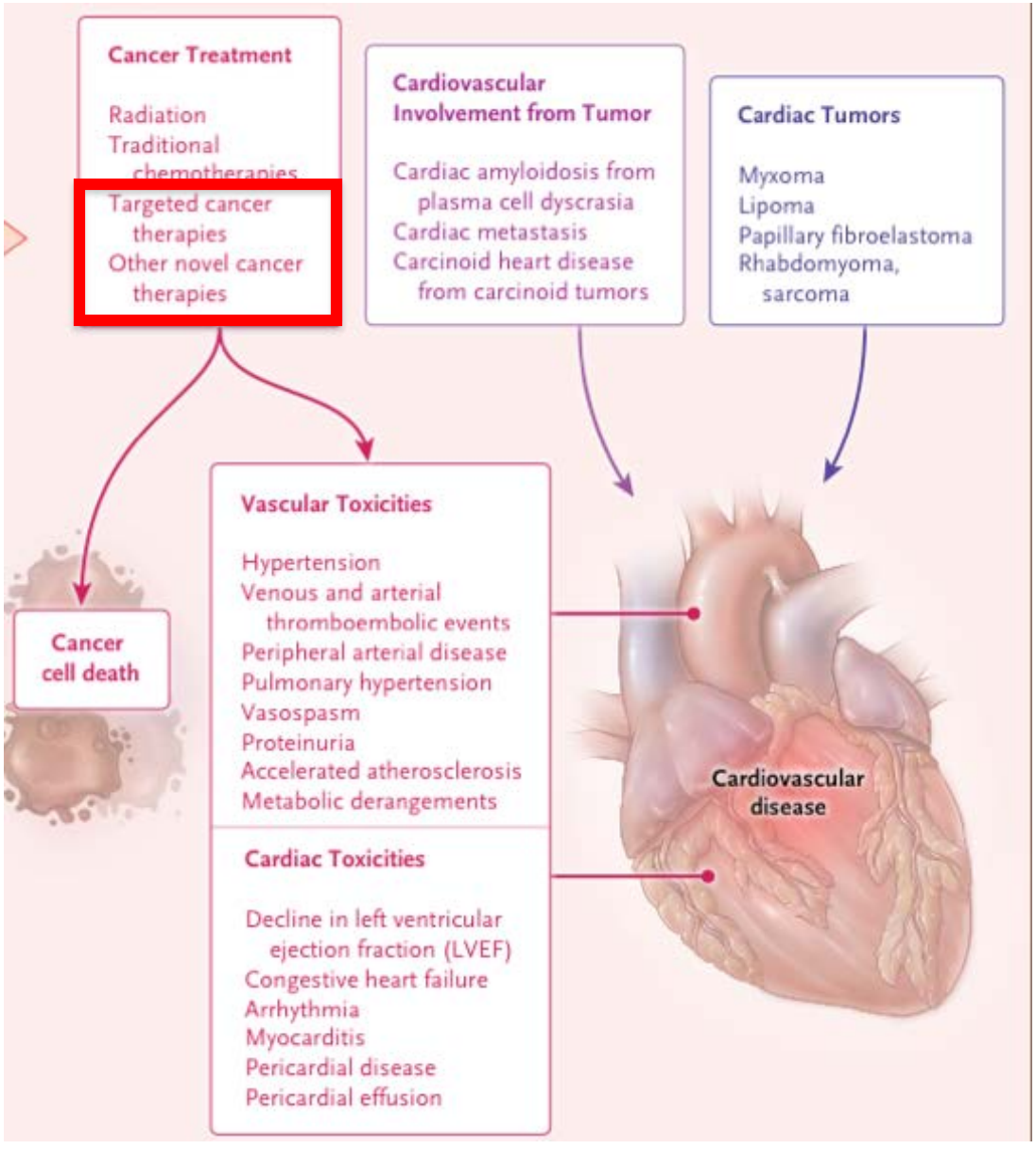
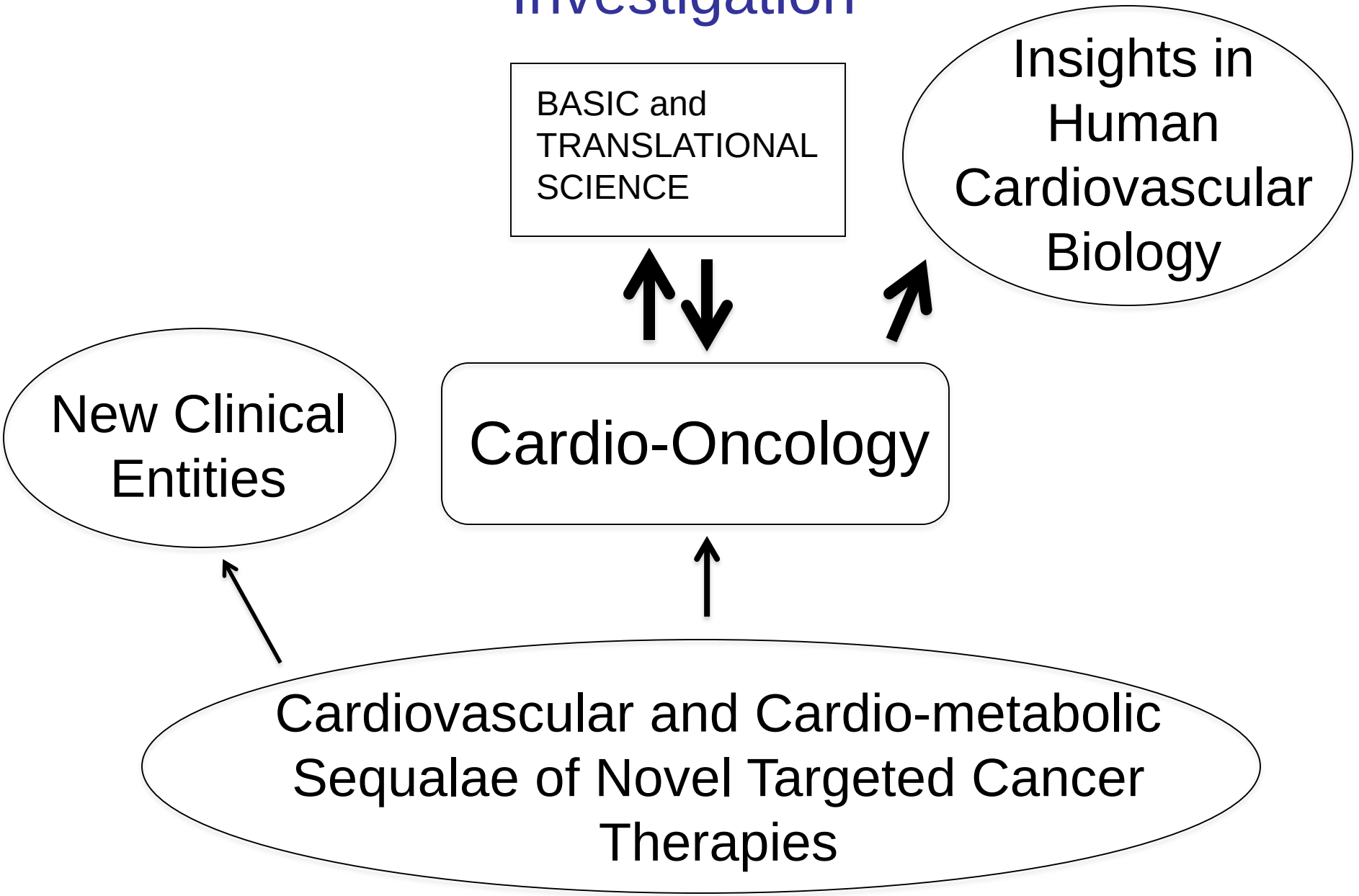
World of Cardio-Oncology



Moslehi. *NEJM*. 2016. 375(15):1457-1467

Cardio-Oncology: Novel Platform for Investigation



Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome

<u>Clinical Questions</u>
Incidence?
Clinical presentation?
Treatment?

↑

Immune Checkpoint Inhibitor-Associated Myocarditis

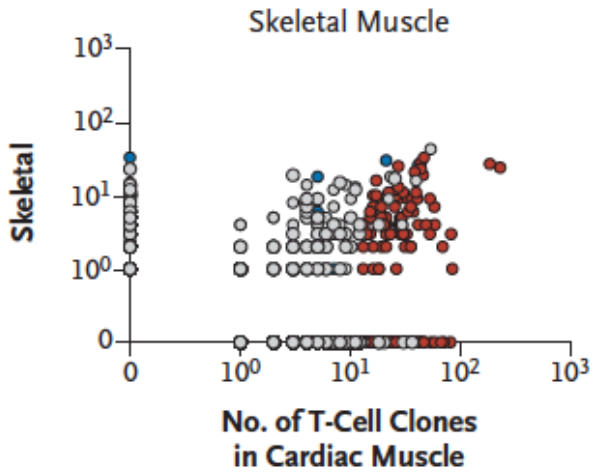
→

<u>Who is at risk?</u>
Precision or Personalized Medicine
- CV risk factors
- Autoimmune risk factors
- Tumor risk factors
- ?Genetic risk factors

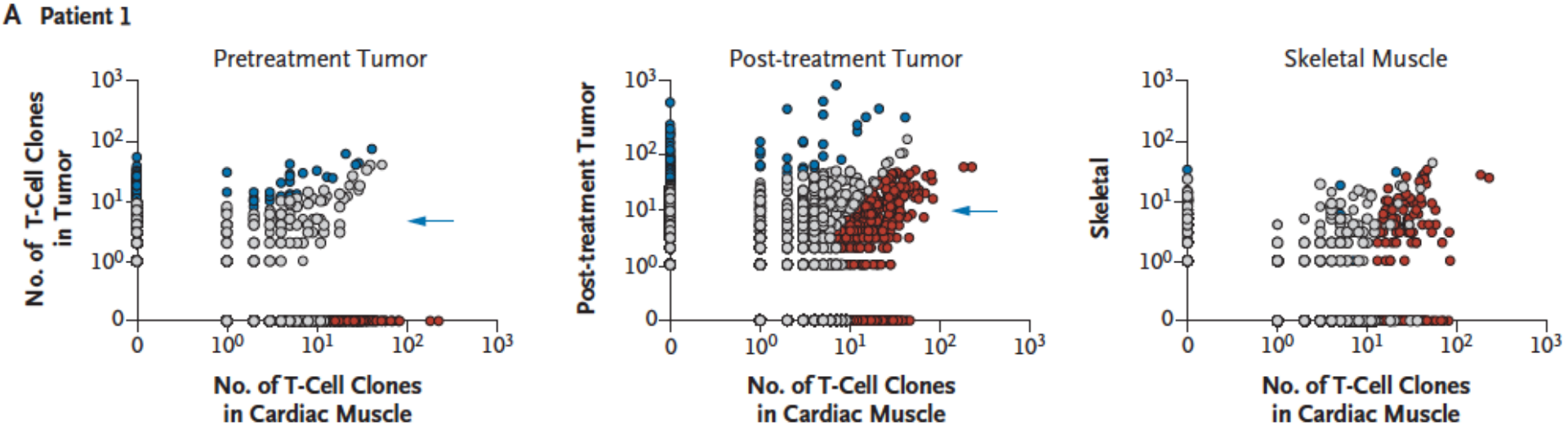
Can better understanding of the molecular pathophysiology help us identify patients at risk?

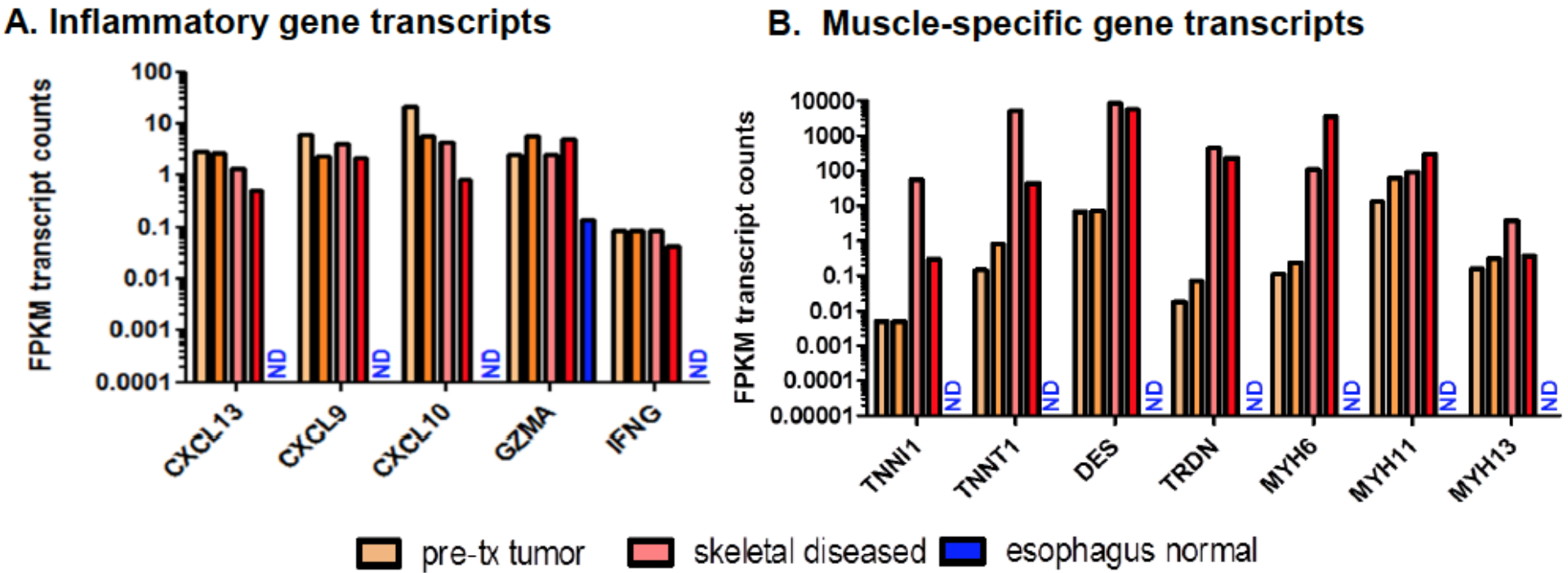
- What caused T cell infiltration into heart and muscle?
  - Why these organs only?
- Other triggers of myocarditis–
  - Viral?
  - Other insult?
- Genetic Differences?
  - MHC Haplotype?
  - Tumor genetics (whole exome sequencing)?
  - Germline?

Insights into Mechanisms of Toxicity

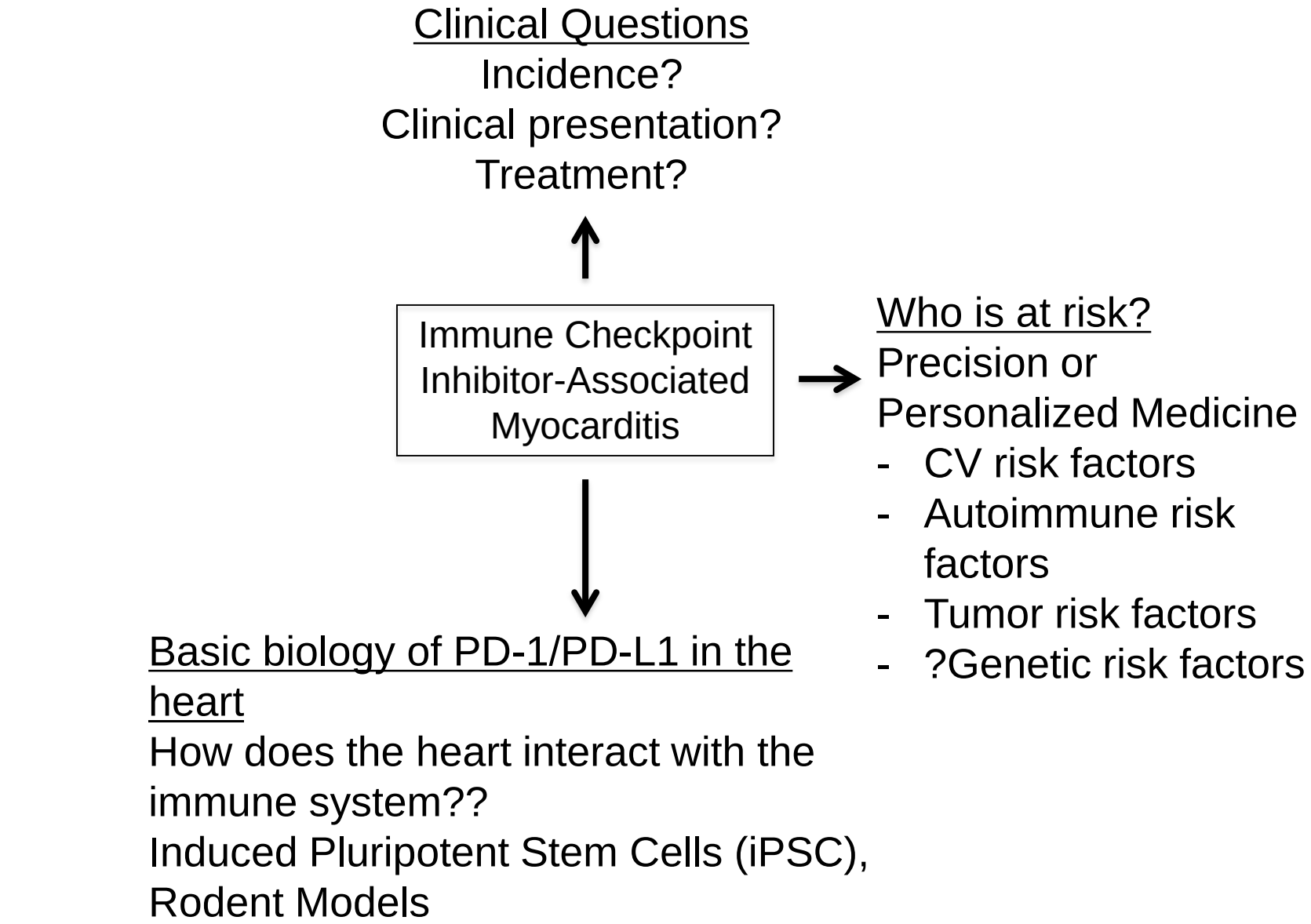


Insights into Mechanisms of Toxicity





Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome



Cardiomyopathy in PD-1 KO Mice

Autoimmune Dilated Cardiomyopathy in PD-1 Receptor–Deficient Mice

Hiroyuki Nishimura [1] Taku Okazaki [1] Yoshimasa Tanaka [2]
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Shigef

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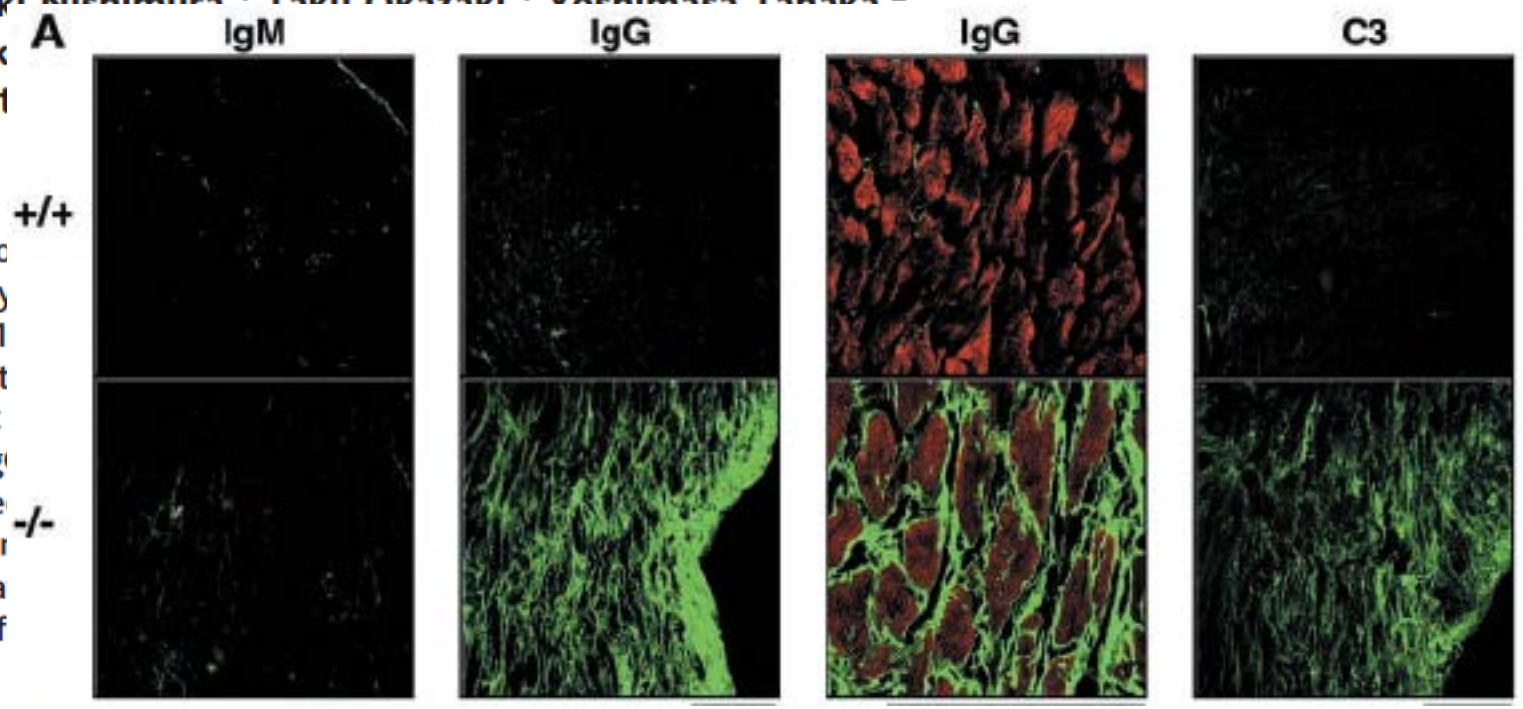


Nishimura. *Science*.2001.

T Cell-Mediated Myocarditis in PD-1/PD-L1 Deficient MRL Mice

PD-1 deficiency results in the development of fatal myocarditis in MRL mice

Jian Wang[1], Il-mi Okazaki[1,2], Taku Yoshida[1,4], Shunsuke Chikuma[1], Yu Kato[1,4], Fumio Nakaki[1], Hiroshi Hiai[3], Tasuku Honjo[1] and Taku Okazaki[1,2]

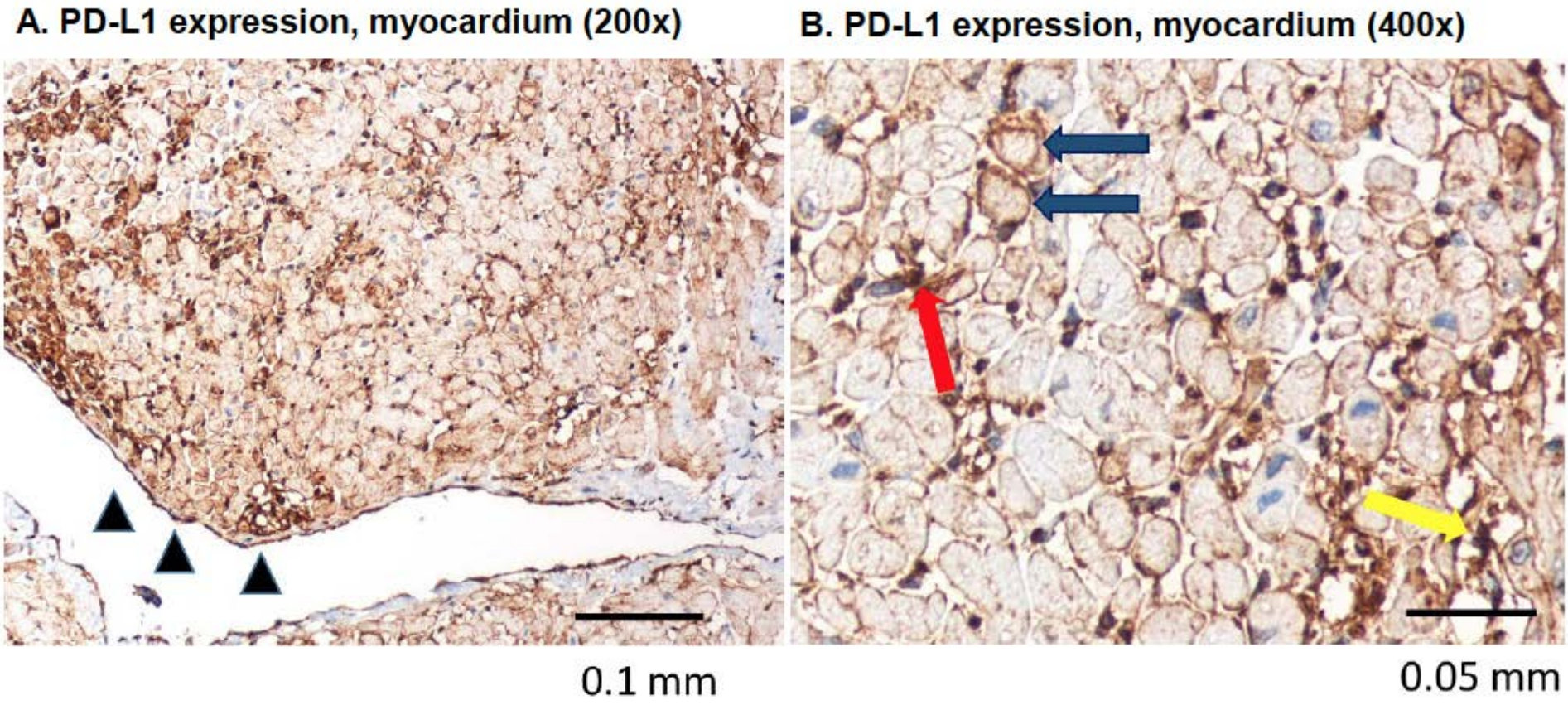
Programmed Death Ligand 1 Regulates a Critical Checkpoint for Autoimmune Myocarditis and Pneumonitis in MRL Mice[1]

Julie A. Lucas,* Julia Menke,* Whitney A. Rabacal,* Frederick J. Schoen,† Arlene H. Sharpe,† and Vicki R. Kelley[2]*

MRL/MpJ-*Fas*^{lpr} (MRL-*Fas*^{lpr}) mice develop a spontaneous T cell and macrophage-dependent autoimmune disease that shares features with human lupus. Interactions via the programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway down-regulate immune responses and provide a negative regulatory checkpoint in mediating tolerance and autoimmune disease. Therefore, we tested the hypothesis that the PD-1/PD-L1 pathway suppresses lupus nephritis and the systemic illness in MRL-*Fas*^{lpr} mice. For this purpose, we compared kidney and systemic illness (lymph nodes, spleen, skin, lung, glands) in PD-L1 null (−/−) and PD-L1 intact (wild type, WT) MRL-*Fas*^{lpr} mice. Unexpectedly, PD-L1$^{-/-}$;MRL-*Fas*^{lpr} mice died as a result of autoimmune myocarditis and pneumonitis before developing renal disease or the systemic illness. Dense infiltrates, consisting of macrophage and T cells (CD8$^+$ > CD4$^+$), were prominent throughout the heart (atria and ventricles) and localized specifically around vessels in the lung. In addition, once disease was evident, we detected heart specific autoantibodies in PD-L1$^{-/-}$;MRL-*Fas*^{lpr} mice. This

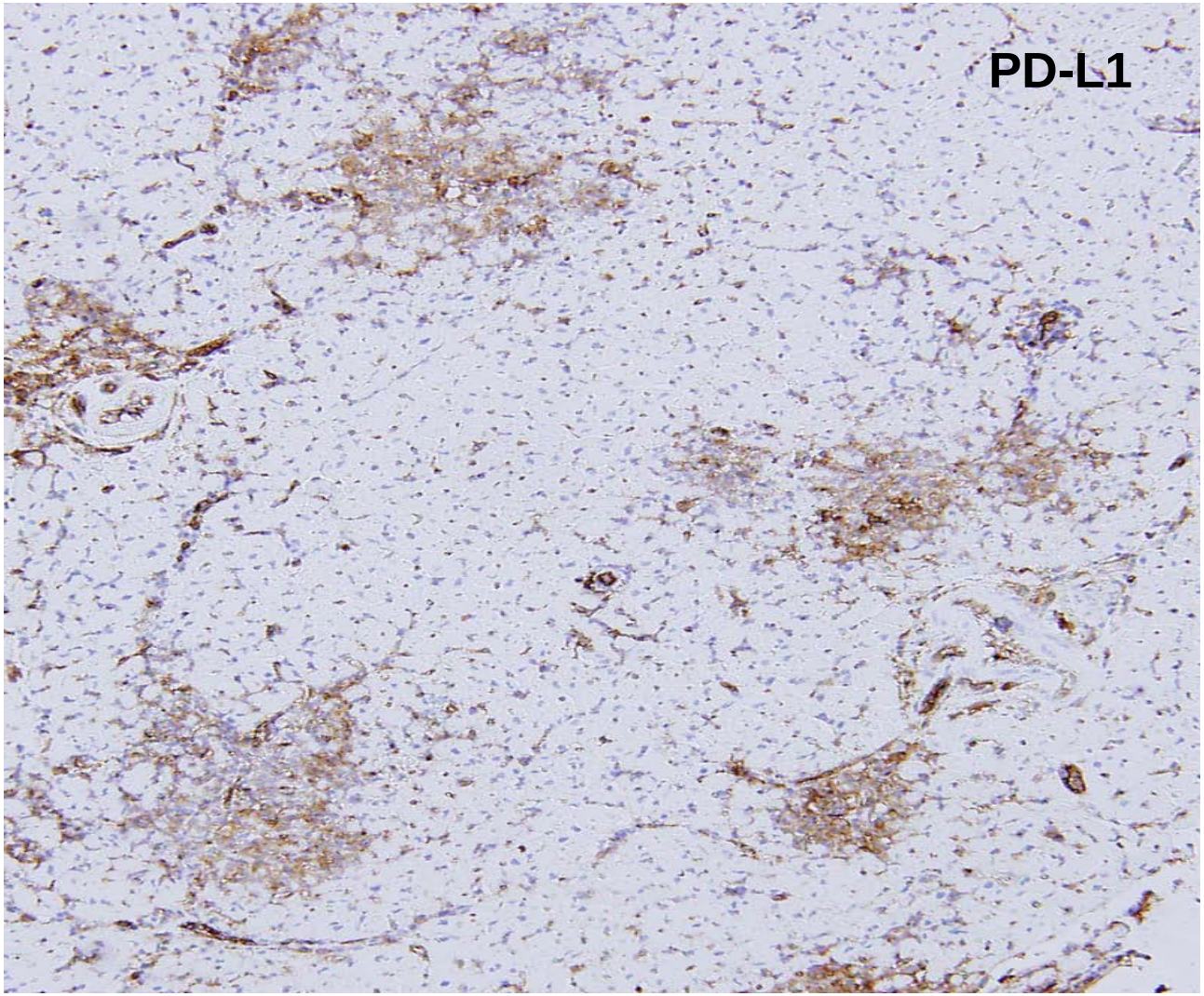
Wang et al. *Int. Immunol*. 2010. Lucas et al. *JI*. 2008.

PD-L1 Expression in the Injured Myocardium



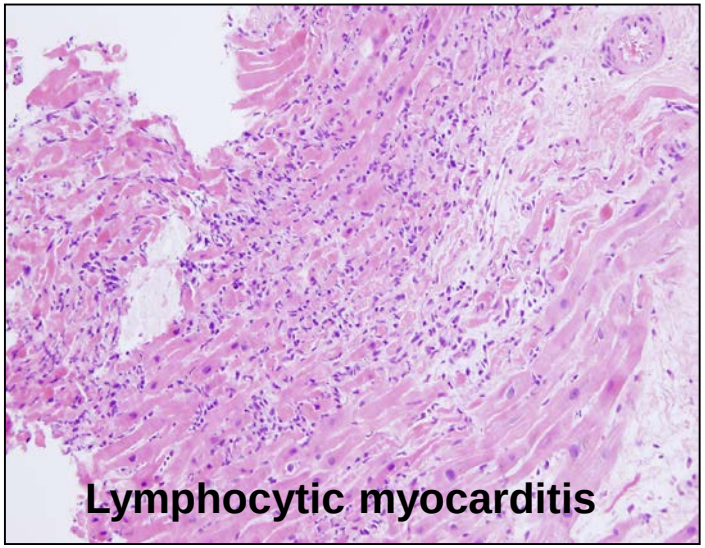
In collaboration with Janis Taube, Bob Anders, Luis Diaz, Johns Hopkins

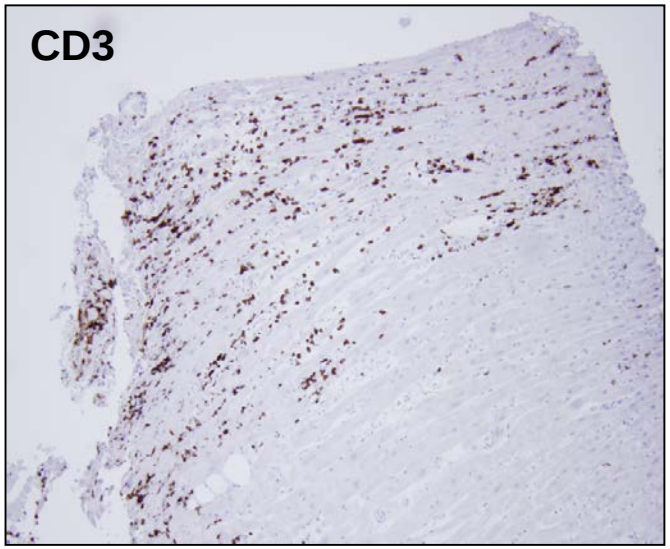
PD-L1 Upregulation in Myocarditis as a Complication of Anti-PD-1/Anti-CTLA-4 Therapy for Melanoma

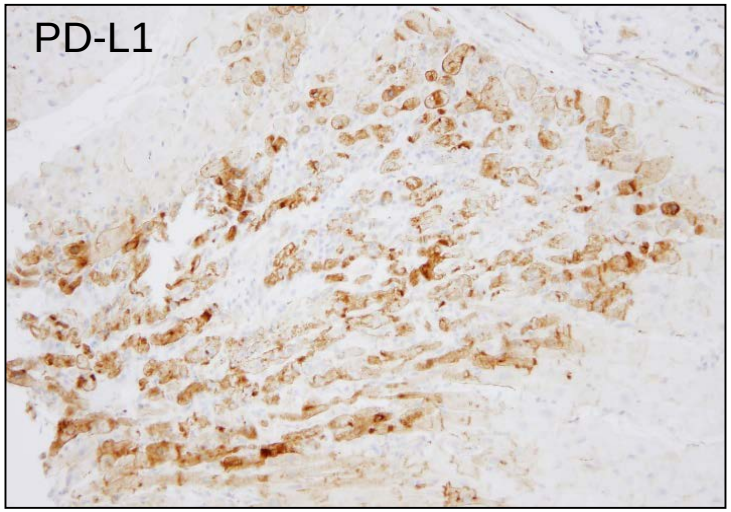


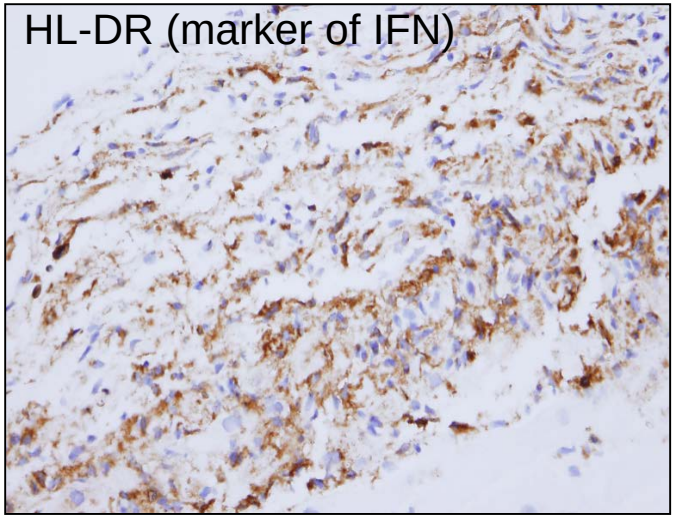
Andy Lichtman, Brigham and Women's Hospital

Myocarditis as a complication of anti-PD1/anti LAG3 Rx of Carcinoma



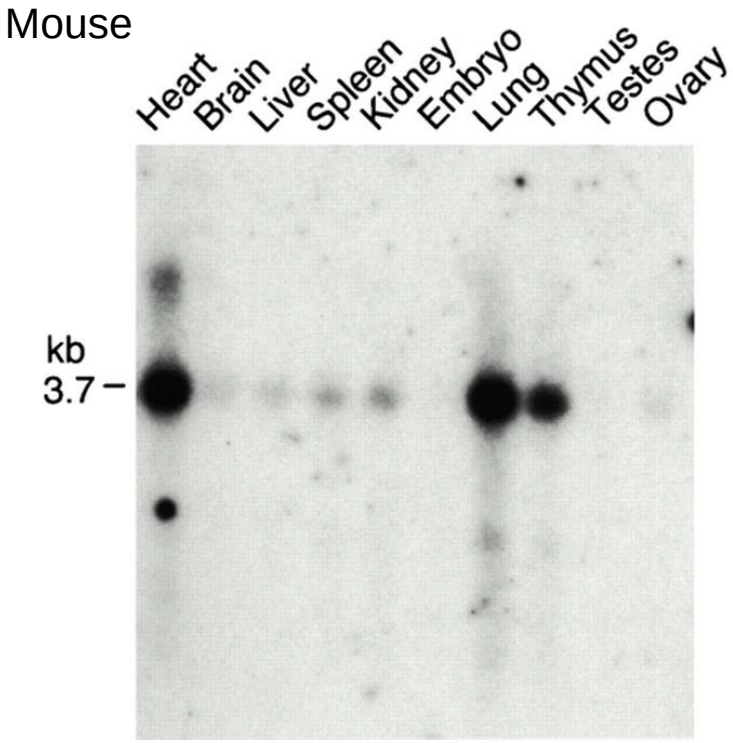






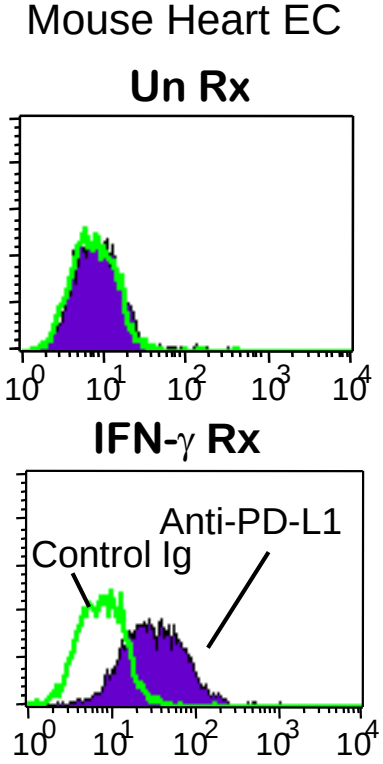
Expression of PD-L1 in mouse heart and mouse heart endothelial cells

PD-L1 mRNA in heart



Freeman G J et al. J Exp Med 2000

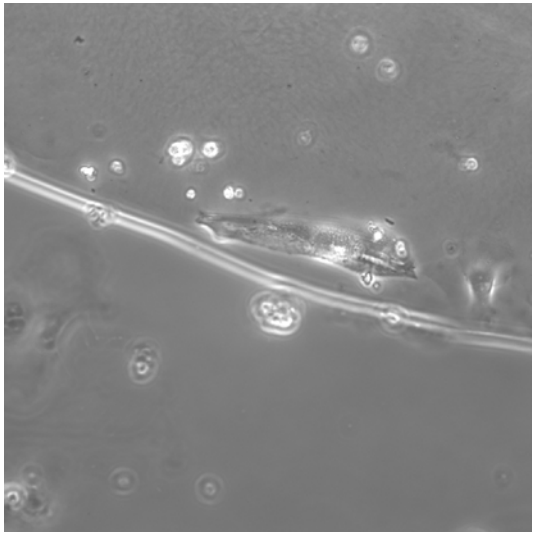
IFNγ induction of PD-L1

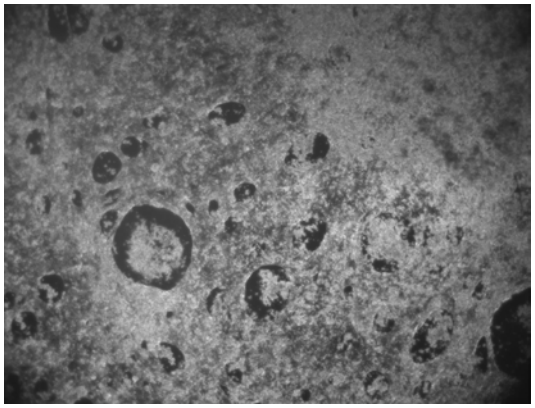


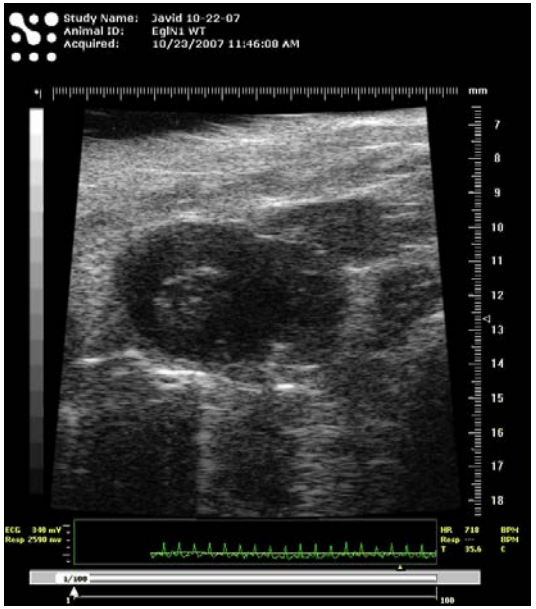
Rodig N, Lichtman AH, Freeman G. Eur. J. Immunol. 2003

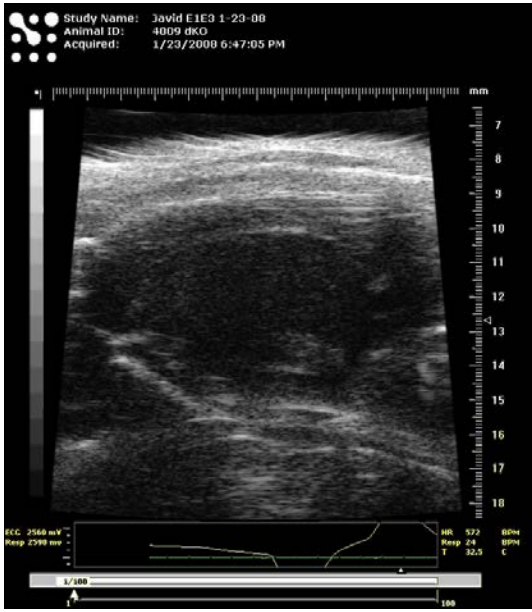
Pre-Clinical Platform for Assessing and Understanding Cardiotoxicity of Novel Compounds

- Cell based models –
  - Isolated mouse or rat myocytes or endothelial cells/smooth muscles cells
  - Induced pluripotent stem cells (iPS)
    - Genetic manipulation – CRISPR/Cas9
    - “Personalized” medicine
- Zebrafish
- Rodent models –
  - Mechanistic understanding of cardiotoxicities
    - Sunitinib, Sorafenib
  - Transgenic mice can allow for defining “on-target” vs. “off-target” effects









Conclusions

- Myocarditis is a new clinical phenomenon that ia a rare (but clinically significant) complication of cancer immunotherapy
  - Initial mechanistic studies show that robust T cell and macrophage infiltrates
- Biological plausibility for this new clinical phenomenon
  - Central role for PD-1/PD-L1 in the heart
- Need for multi-institutional to understand the pathophysiology of myocarditis and multi-pronged approach to understand who is at risk of developing myocarditis

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