ACTIVATING ANTI-PANCREATIC CANCER IMMUNITY

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Professor & Director
Center for Immunology

Together, Taking on Cancer’s Toughest Challenges
DISCLOSURES

• Cofounder and Vice President of Protein Foundry, a biotech startup that manufactures recombinant chemokines for biomedical research.

• CXCL12 locked dimer technology and the use of CXCL12 as an anticancer agent have been patented and licensed to Watosa Bio, LLC.

• Member, Scientific Advisory Board, Watosa Bio LLC
PANCREATIC CANCER – A FATAL DISEASE WITH INCREASING INCIDENCE

Projected Cancer Deaths

Pancreas Cancer
• Late diagnosis
• Highly metastatic
• Numerous genetic / epigenetic changes
• Chemotherapy & Radiotherapy resistant
• Unique tumor microenvironment
  • Pronounced immune suppression & evasion

Pancreatic Cancer Action Network
GOAL: REIGNITE PANCREATIC TUMOR IMMUNE MICROENVIRONMENT

Can STING agonist stimulate anti-pancreatic cancer immunity?
STIMULATES INTERFERON GENES (STING)

cyclic dinucleotides (CDS)

2’3’-cGAMP

IKK → NF-KB

TBK-1 → IRF-3, STAT6

Cytokines Produced through Multiple Pathways

T Cell Priming

T Cell Activation & Proliferation

Activated T cells induce tumor cell death

Tumor Cell Destruction
**APPROACH**

- **KRas\textsuperscript{LSL-G12D/+}\textsuperscript{LSL-R147A};pdxCre (KPC)**
  - Conditionally express overactive KRas and inactive p53 mutations
  - Isolated PDA cancer cells

- **Syngeneic graft pancreatic carcinoma cells to C57BL/6 mice**
  - KPC1242 carcinoma cells
  - \(1 \times 10^6\) cells engrafted to dorsal subQ or orthotopically to pancreas
  - Inject murine STING agonist (DMXAA)
STING TREATMENT INCREASES SURVIVAL AND DECREASES PDA TUMOR SIZE

Jing et al., Journal for ImmunoTherapy of Cancer, 2019
STING AGONIST INCREASES LEVELS OF PANCREATIC CANCER KILLING T CELLS

Jing et al., Journal for ImmunoTherapy of Cancer, 2019
STING AGONIST INCRESSES INFLAMMATORY ANTI-CANCER TUMOR ASSOCIATED MACROPHAGES

Jing et al., Journal for ImmunoTherapy of Cancer, 2019
INCREASED INFLAMMATION IN STING AGONIST TREATED PANCREATIC TUMORS

Jing et al., Journal for ImmunoTherapy of Cancer, 2019
CHEMOKINE PRODUCTION IN STING AGONIST TREATED KPC TUMORS IN VIVO

** Macrophages

<table>
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<th>CCL2</th>
<th>CCL3</th>
<th>CCL4</th>
<th>CCL5</th>
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- PBS: [Data]
- DMXAA: [Data]

** Macrophages

- PMNs

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<th>CXCL-1</th>
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- PBS: [Data]
- DMXAA: [Data]

** T cells

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Jing et al., Journal for Immunotherapy of Cancer, 2019

DMXAA

Vehicle
STING AGONIST TREATMENT:

• Increases survival

• Abrogates tumor growth and progression in an immune competent mouse model

• Increases CTL infiltration and activation

• Inflames pancreatic tumors

• Reprograms suppressive M2-TAMs into inflammatory M1-TAMs

• Increases cross-presenting dendritic cells

• Activates proinflammatory signaling in pancreatic cancer
STING AGONIST PROMOTES ANTI-TUMOR IMMUNITY IN PANCREATIC CANCER
If you want to go fast, go alone.

If you want to go far, go together.

– African Proverb

• Dwinell Laboratory
  • Donna McAllister
  • Nick Barnekow
  • Laura McOlash
  • Natasha Moussouras
  • Emily Vonderhaar
  • Mahmoud Abu Eid
  • Kathy Boyle, PhD

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