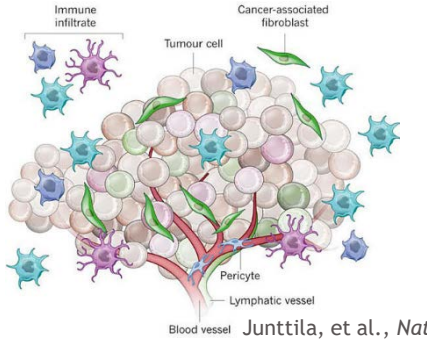


Junttila, et al., *Nature* 2013

II-ON Request for Proposal (RFP): Tumor Microenvironment Modulation Thematic Research Center Key Questions

- **KEY QUESTIONS FOR RFP CHALLENGE:**
  1. Stromal biology
     - Preclinical models containing stromal content
     - Comprehensive understanding of **CAF/ECM landscape** across patient indications and how this may be modulated by SOC therapies
  2. Myeloid Biology: animal models with better myeloid engraftment, and comprehensive understanding of myeloid landscape across patient indications and how modulated by SOC therapies
  3. Novel preclinical models: stratified models that are translatable for the particular tumor genetics/phenotype of interest
  4. Approaches to measure pH of the tumor microenvironment to design optimal pH-selective therapeutics

  Further details on 4 categories for consideration in slides that follow this announcement
- **RFP GUIDELINES:**
  - Total budgets (direct + indirect) **generally should not** exceed USD $250k-350k/ 12 month funding period
  - Please utilize II-ON Proposal Template for your submission
  - Collaborating with multiple institutions encouraged
- **TIMELINES FOR SUBMISSION:**
  - Letters of Intent due **April 9, 2021** to II-ON Core Team
  - Invitations to Submit Full Proposal sent April 16, 2021
  - **Full proposals due April 30, 2021**
  - Communication of decisions in May 2021

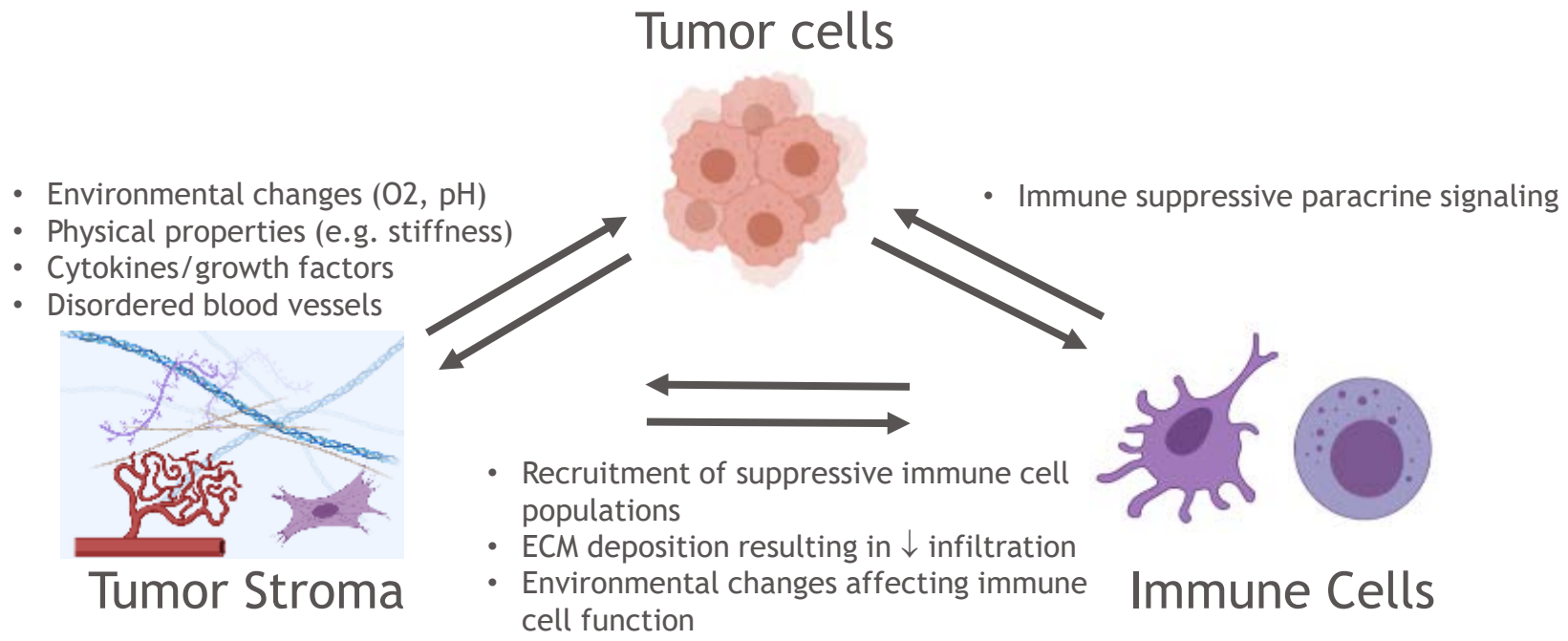
WE NEED YOUR HELP TO COMMUNICATE THIS GRANT OPPORTUNITY AT YOUR INSTITUTION!!

Please reach out to your II-ON Research Liaison or IIONCommunications@bms.com

1. Stromal Biology pipeline is a newer area of focus

Mission: discover and develop modality-agonistic therapeutics to modify the stroma to expand and initiate responses to IO & tumor-targeted therapies

Enhance pipeline of therapeutics that broaden or deepen responses to therapy
Extend to tumor settings with limited response to unlock and initiate responsiveness

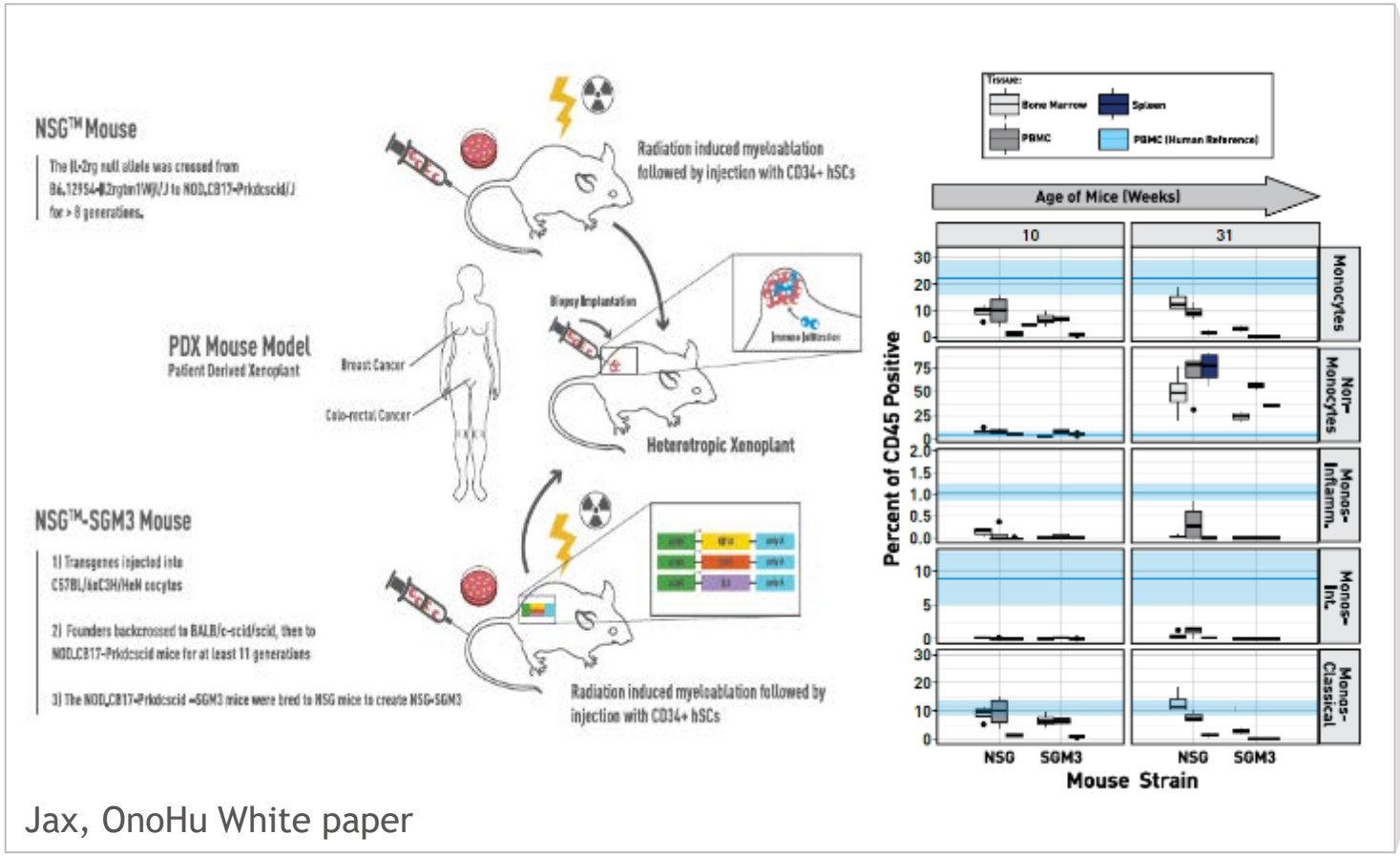


1. Stromal Biology pipeline is a newer area of focus and active area for collaborations

Key research areas to address in a proposal may include:

- **Syngeneic models** containing stromal content reflective of human disease
- **In vitro models** that recapitulate 3D tumor microenvironment to better predict MOA and efficacy of our stromal therapies
- Comprehensive understanding of **CAF/ECM landscape** across patient indications and how modulated by SOC therapies
- Datasets parsing CAF **heterogeneity** (e.g. iCAFs and myCAFs) and **functionality**

2. Myeloid Biology: translatable preclinical models and characterization of myeloid landscape across patient populations



Jax, OnoHu White paper

Key research areas to address in a proposal may include:

- Syngeneic models mapping to human disease states
- Humanized models with better myeloid engraftment
- Models to better predict MOA and efficacy of our myeloid therapies
- Comprehensive understanding of myeloid landscape across patient indications and how modulated by SOC therapies
- Datasets parsing myeloid heterogeneity and functionality

3. *Ex vivo* human tumor systems are needed to de-risk the differences between human and murine biology

Background:

- We work in genetically engineered immunocompetent murine models, but need to de-risk early that the biology and functional dependencies we uncover there are translatable to humans.

Key research areas to address in a proposal may include:

- Is there a path to procure “stratified” tumor explants for translational validation?
- Are there other models that would help us reduce this risk, including 3D organotypic models?
- Short of a selective pharmacological tool, are there other emerging technologies that will enable us to validate target dependencies and mechanistic biology in human clinical models?

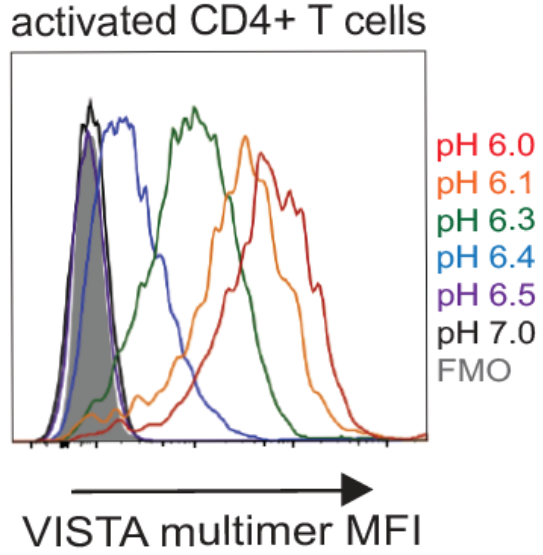
4. Approaches to measure pH of the tumor microenvironment to design optimal pH-selective therapeutics

Background:

Interest in pH was driven by novel biology discovered when investigating VISTA, a negative regulator that binds to an unknown ligand on T cells.

Vista has unusually high histidine content, suggesting that Vista activity may change with pH.

Indeed, binding of VISTA to T cells increases as the pH drops (Johnston, et al *Nature* 2019)



Johnston, et al *Nature* 2019

What problems can we solve by leveraging low pH in tumors?

Antibodies can be engineered to bind preferentially at low pH, resulting in a conditionally active biologic to:

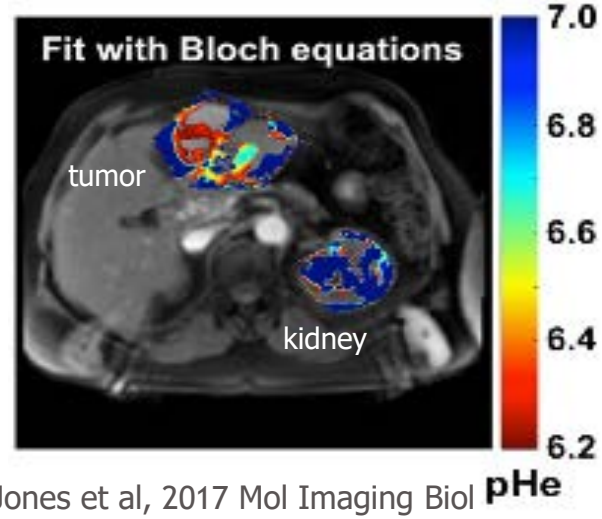
- Improve PK (VISTA): Modulate exposure and reduce TMDD peripheral sinks
- Improve therapeutic index (CTLA4): overcome dose-limiting toxicity, enhance therapeutic exposure, and reduce peripheral activation

4. Approaches to measure pH of the tumor microenvironment to design optimal pH-selective therapeutics: opportunities for collaborations

Key research areas to address in a proposal may include:

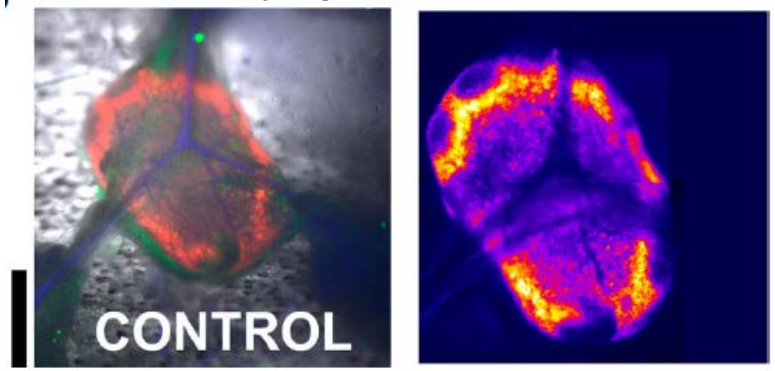
- How heterogeneous is the pH of the tumor microenvironment?
- Can we effectively measure tumor pH in patients?
- What other locations in the body have low pH?
  —Lymph nodes, other immune compartments
- How do immune cells function at low pH?

Ovarian cancer pH imaging



Jones et al, 2017 Mol Imaging Biol

Lymph nodes



Wu et al, 2020 Nature Communications