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Metabolic Reprogramming to Improve Immunotherapy

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Metabolic Reprogramming to Improve Immunotherapy

The overall goals of this concept are to:

- **generate a mechanistic understanding of the metabolic processes that support robust anti-tumor immune responses *in vivo***
- **determine how the metabolic landscape of the tumor microenvironment affects immune effector functions**
- **use this information to manipulate (or reprogram) the metabolic pathways used by the tumor, the effectors of the immune response, or both to improve cancer immunotherapy**

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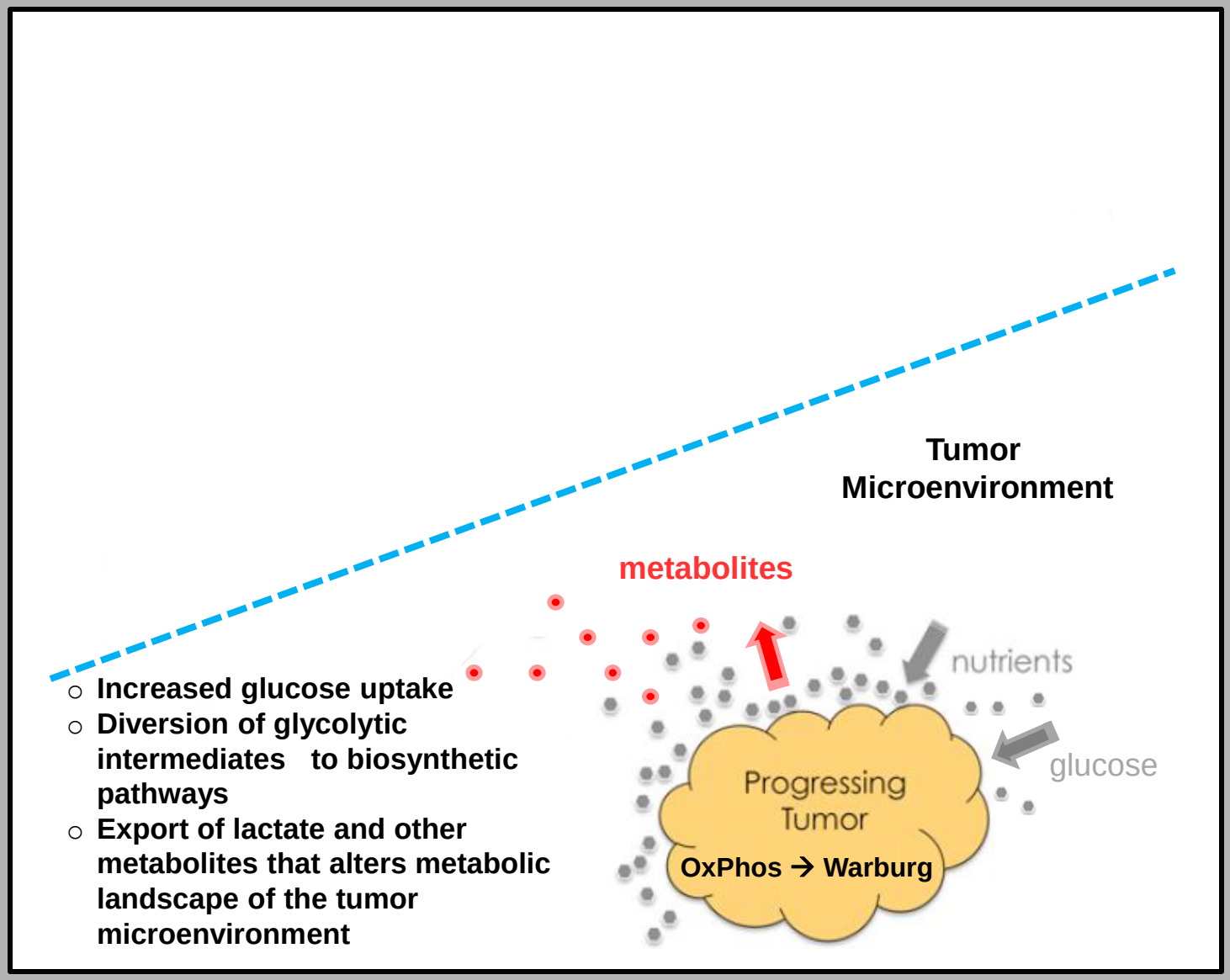
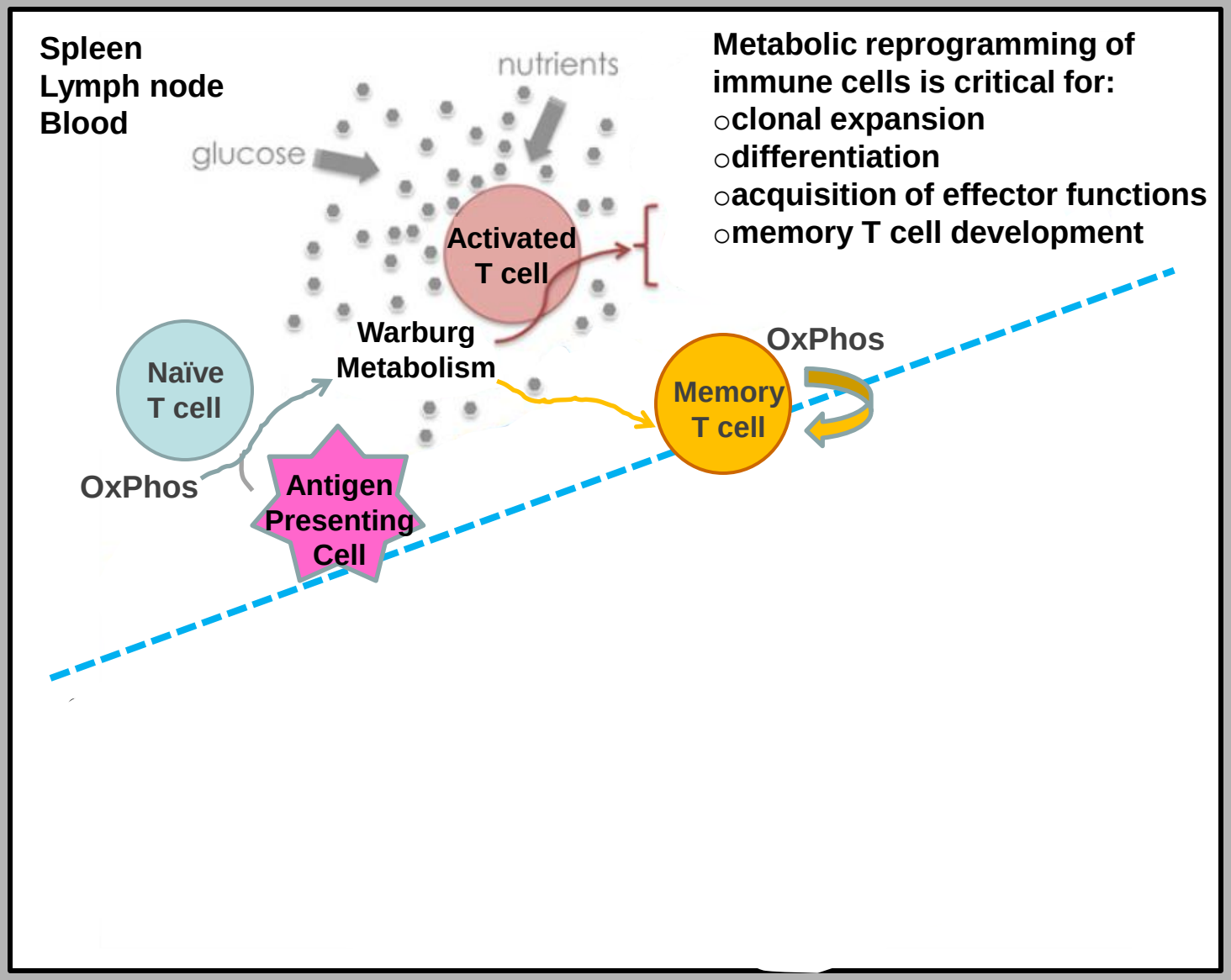
Cancer Cells Reprogram Metabolism to Support Growth and Survival



Adapted from Pearce, EL. 2013. Immunity 378: 633-643,

Activated Immune Cells Undergo Metabolic Reprogramming



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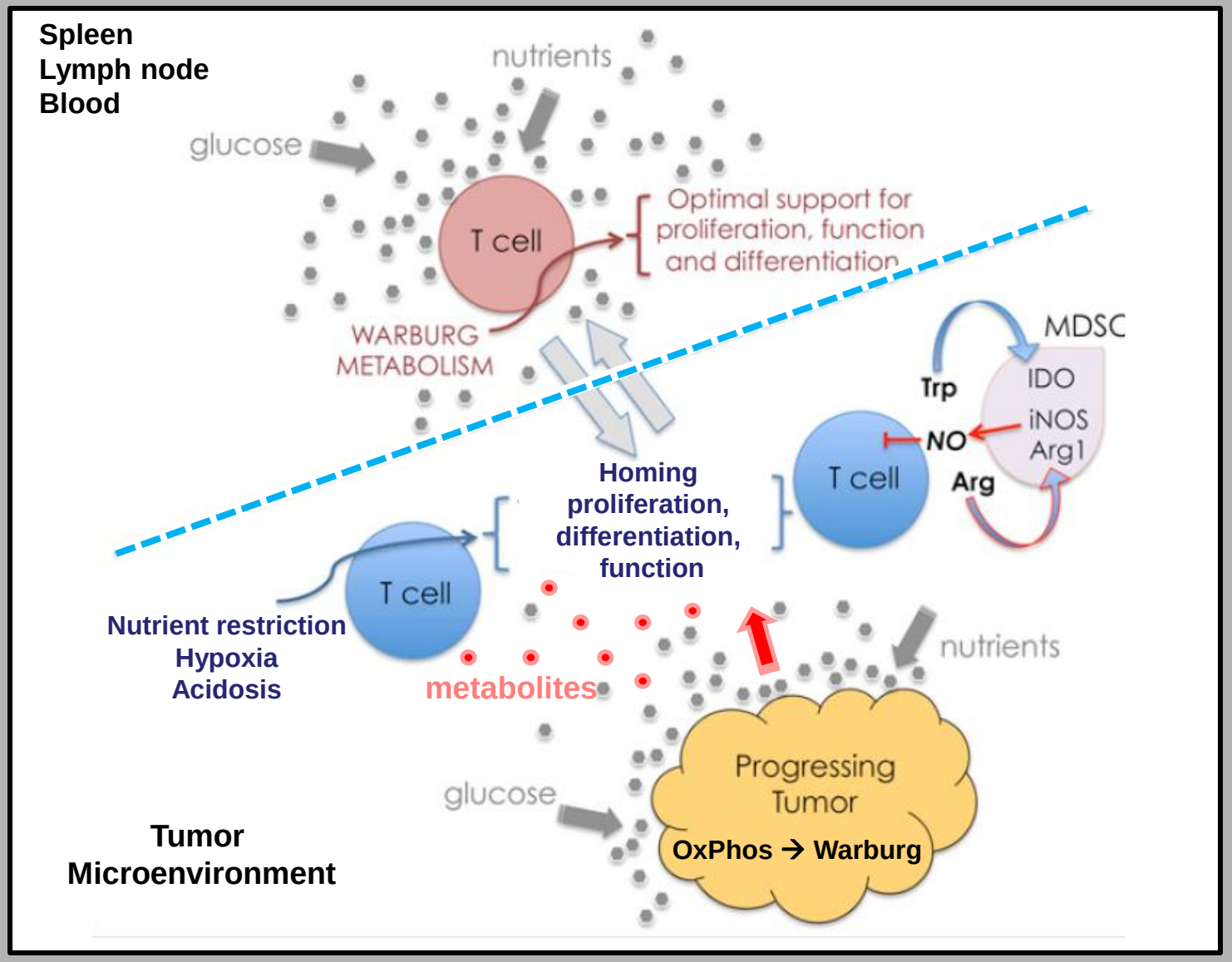
Tumor Metabolic Landscapes can Regulate Anti-Tumor Immune Function



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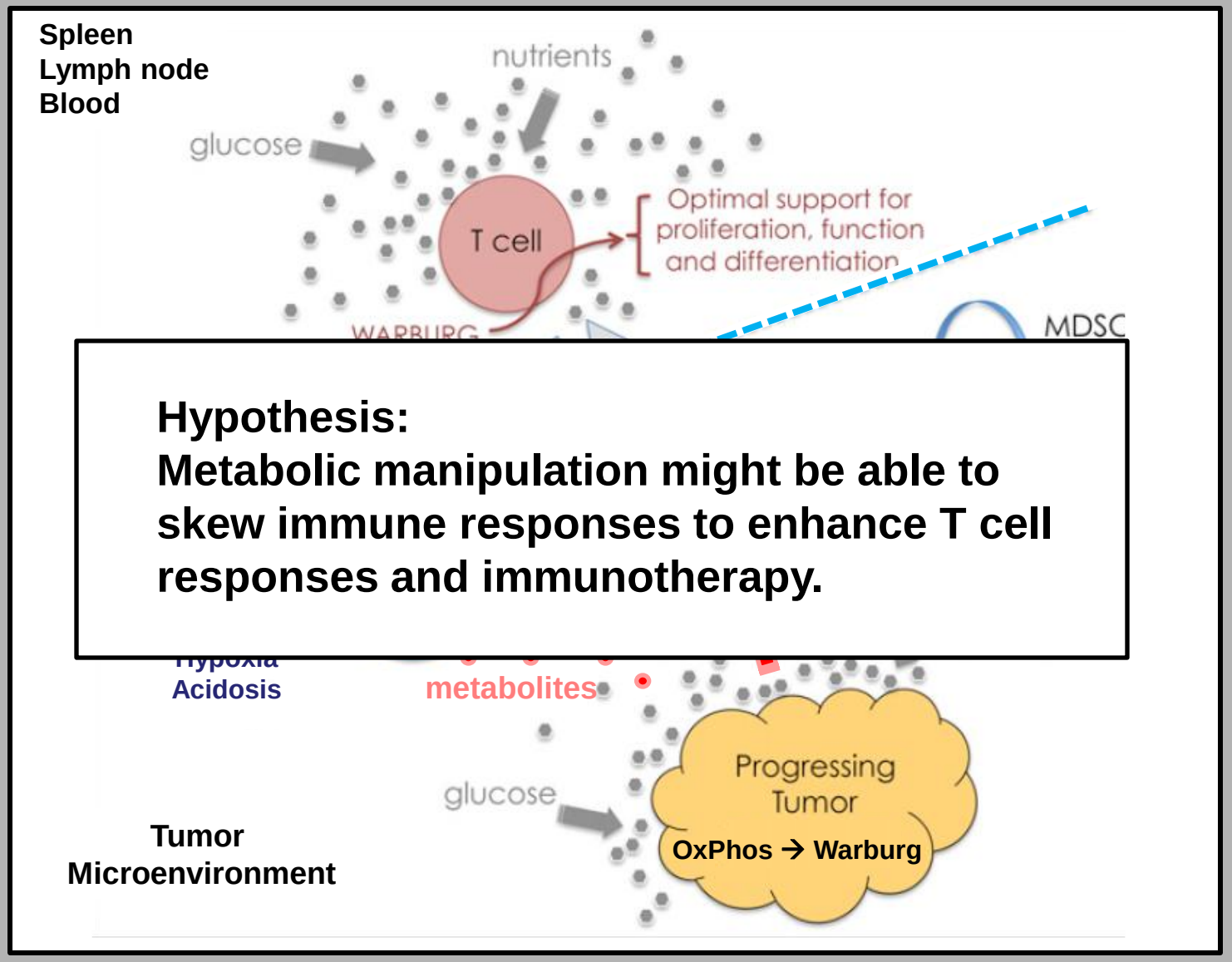

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Address Knowledge Gap and Path Forward

Overarching Directions for Future Studies:

a) **Approaches to reprogram the metabolism of anti-tumor immune cells (either *ex vivo* or *in vivo*) to improve immunotherapy (homing, effector function, and/or persistence)**

b) Approaches to target cancer cell metabolism to impair cancer cell survival without compromising anti-tumor immunity.

Path Forward:

- **Catalyze collaborations between tumor immunologists, cancer biologists, computational modelers and tool/technology specialists aimed at developing innovative approaches to utilize metabolic reprogramming to improve cancer immunotherapy.**

Specific Challenges

Examples :

- **How do the metabolic environments in normal tissues, immune tissues, and tumors affect immune cell development and/or effector function?**
- **How do specific metabolites affect various immune states such as activation, anergy, development of long-lived memory cells versus short-lived effector cells, and homing to their proper niche?**
- **Do metabolites act as signaling molecules in transcription that effect cellular differentiation?**

Implementation Plan

Goal: Encourage new collaborations focused on tumor immunometabolism

Mechanism:

- **Supplement existing NCI funded grants to support collaborative research projects through revision applications (formerly called competing supplements).**

Funding Opportunity:

- **PAR with no budget set-aside.**
- **Standard Receipt Dates; beginning March, 2014.**
- **Active in FY15 - FY18.**

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Examples of Collaborations

- A cancer biologist with an existing NCI RO1 focused on cancer cell metabolism could form a collaboration with a tumor immunologist and a systems biologist to develop computational models of metabolic interactions
- A tumor immunologist with an existing NCI RO1 focused on metabolic events associated with activated T cells could form a collaboration with a cancer biologist studying metabolism and with an in vivo imager to study homing.

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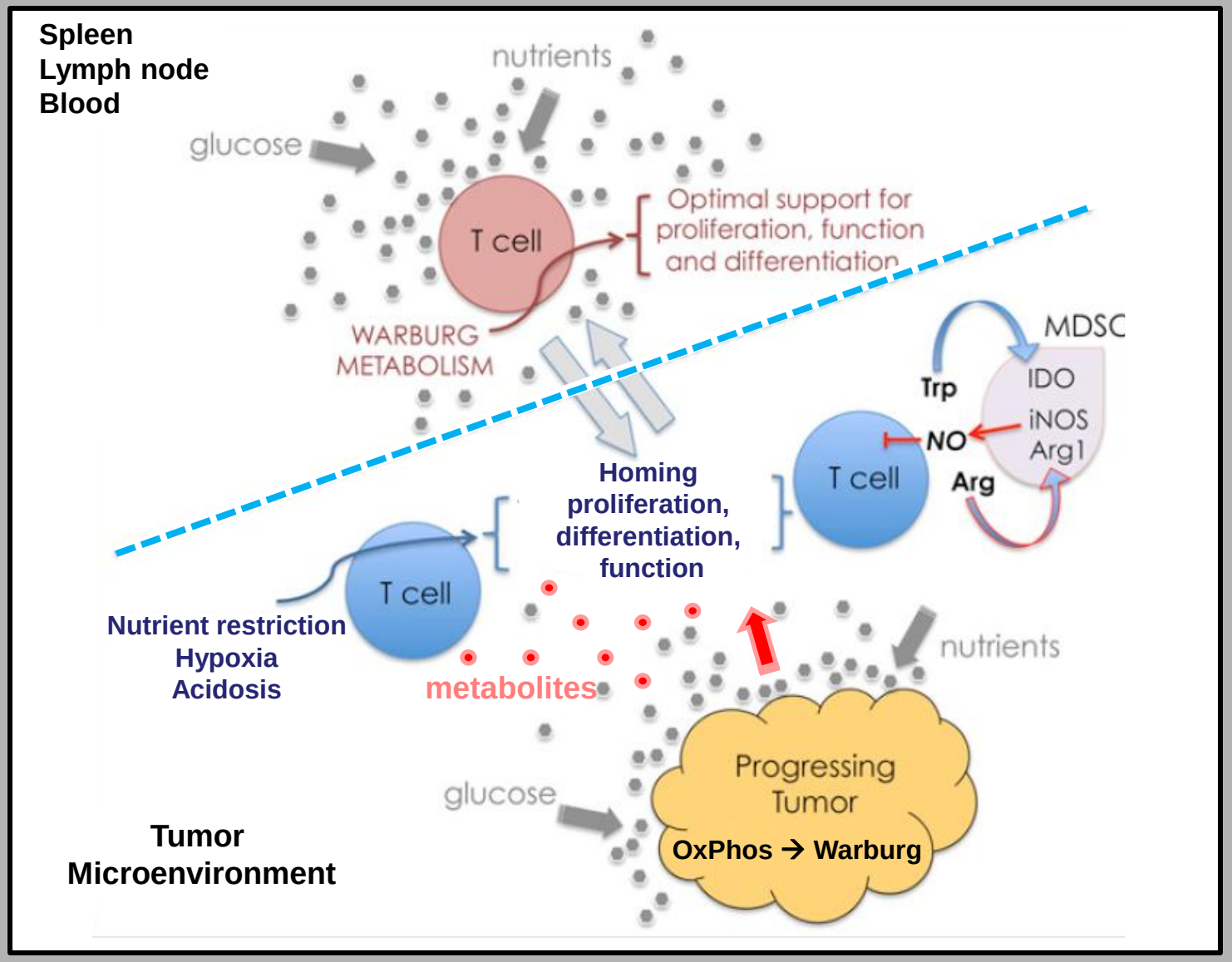
Collaboration Criteria

- Must propose cross-disciplinary research involving cancer biologists and immunologists aimed at complementary areas of metabolic research and, if justified, a metabolomics, computational tools, or imaging component.
- May support up to three collaborating groups, including the PI of the parent grant
- Must be complementary to the parent grant
- Must have a minimum of two years remaining on the parent grant at the time of award

Tumor Metabolic Landscapes can Regulate Anti-Tumor Immune Function



Questions?

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Portfolio Analysis

Searching the NIH Reporter for applications that cross reference the terms immunotherapy, metabolism, and cancer netted only five applications that would minimally meet the outlines of this FOA - only one R21 specifically included metabolic reprogramming of immune cell populations to improve immunotherapy.

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NCI/DCB Activities to Promote Research Collaborations (APRC) 1998-2010

- **The APRC program supported new interdisciplinary collaborations to bridge disparate fields and expand the pool of scientists working in cancer research.**
- **The APRC provided administrative supplements to support 2-3 collaborating units (from complementary fields) focused on achieving specific research objectives by pooling their respective expertise and efforts.**
- **Funding decisions were made rapidly, allowing collaborations to initiate quickly.**
- **The annual allocation to DCB for the program was $1-1.5M. Over the years, it funded 437 collaborations, with a peak in 2004 of 85 consortia.**
- **An independent evaluation after the conclusion of the APRC assessed its success. Among the conclusions: " Most impressive, the majority of the investigators thought that they could not have accomplished their work without APRC funding."**