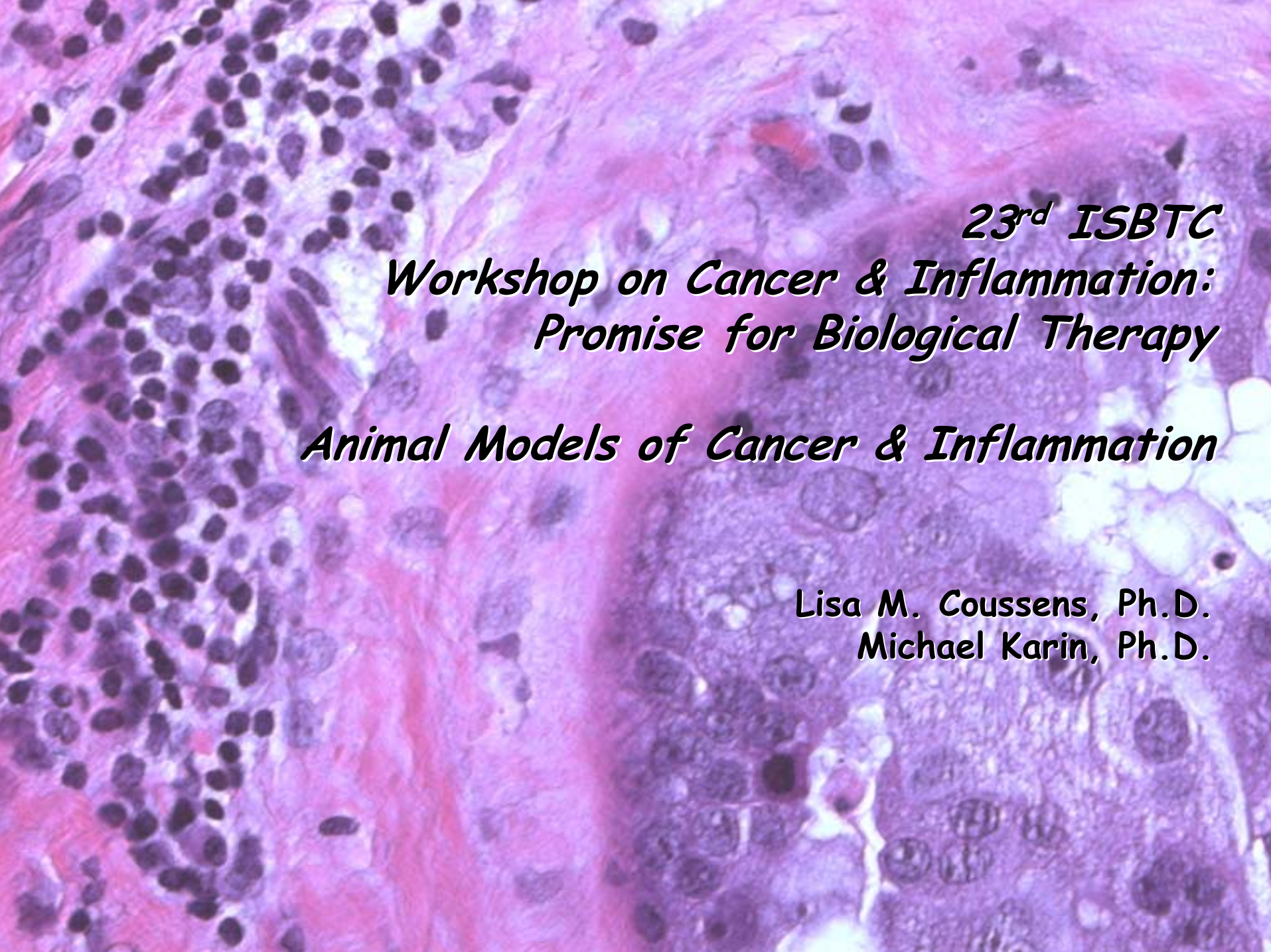
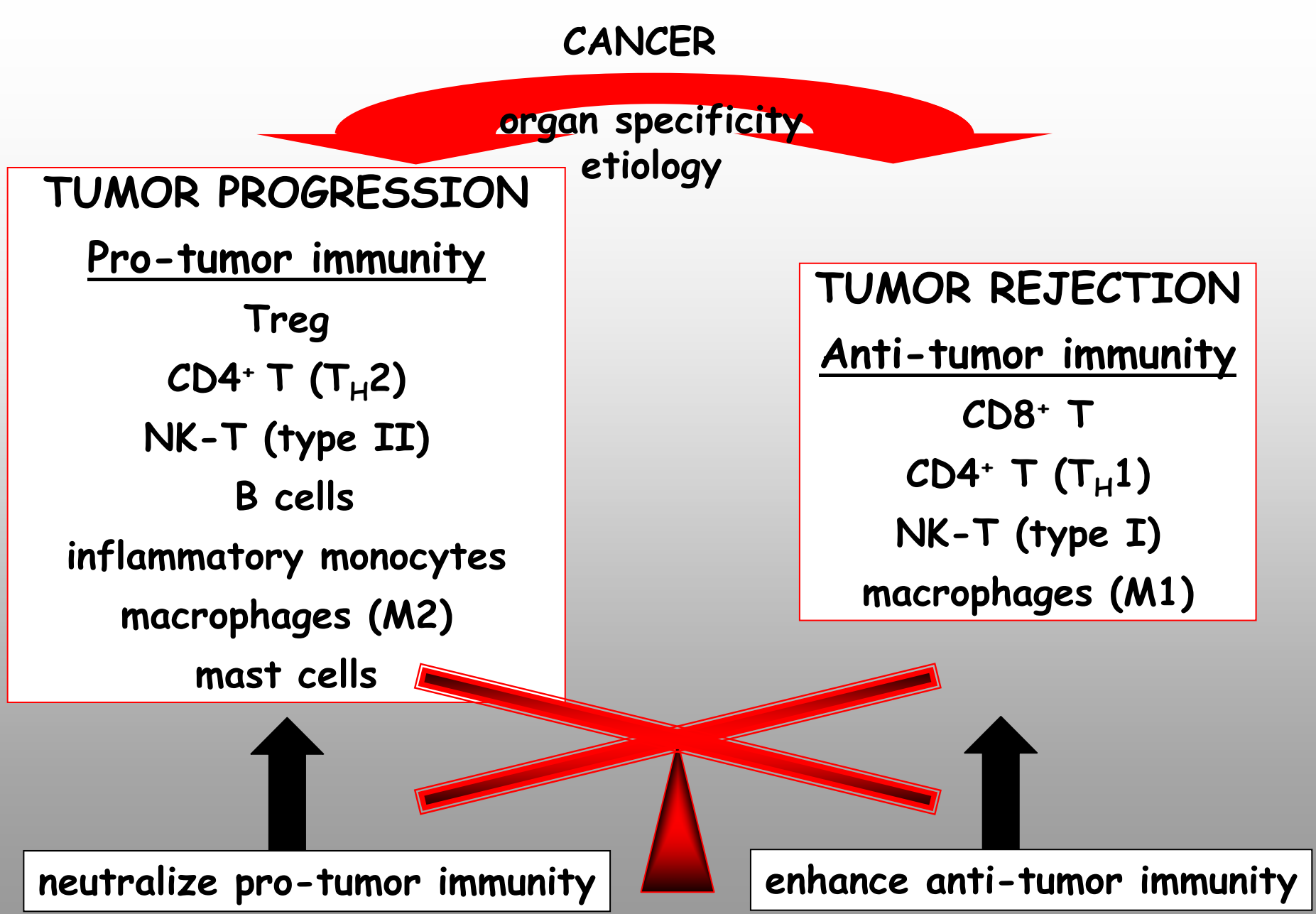


23rd ISBTC
Workshop on Cancer & Inflammation: Promise for Biological Therapy

Animal Models of Cancer & Inflammation

Lisa M. Coussens, Ph.D.
Michael Karin, Ph.D.



Modified from Suzanne Ostrand-Rosenberg

"The biology is elegant but it is going to be difficult to translate this into a drug"

"The complexity of the innate immune system is far greater then that of the tumor cell"

In vivo Approaches: Animal Models of Human Cancer Development

Xenografts

1- , 2-stage *chemical* carcinogenesis

Genetically engineered (GE) transgenic (oncogenes)

GE transgenic (tumor suppressor)

GE with rare spontaneous activation of dormant oncogenes

Tissue-specific chronic inflammation

Organ-Specific Mouse Models of Human Cancer Development

Brain
Mammary
Prostate
Colon
Pancreas
Lung
Liver
Kidney
Mesothelium
Non-melanoma skin
Ovarian
Skin
Cervical
Bone
Hematologic

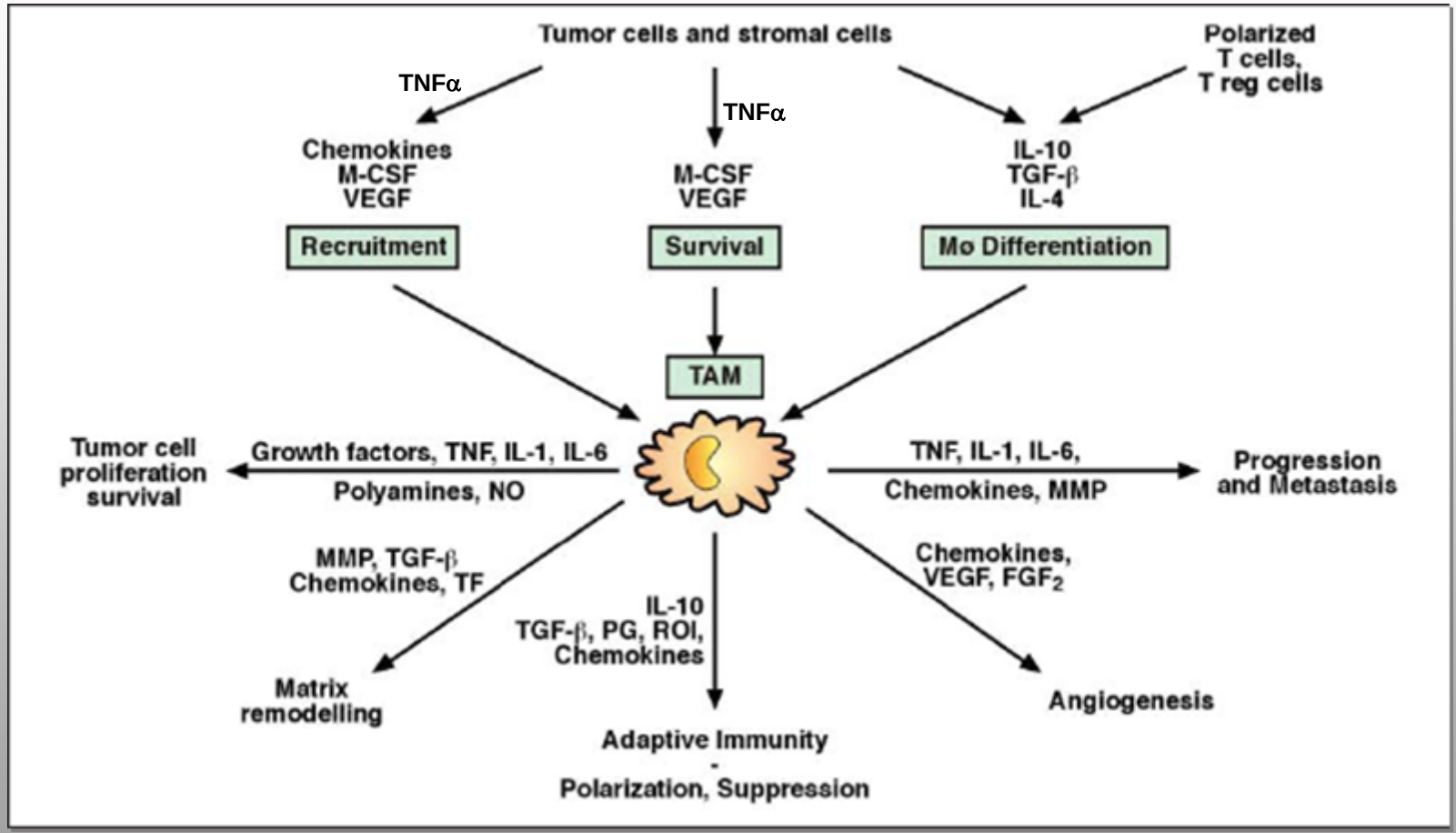
Important questions

1. Can we identify cellular and molecular components that are common to all cancer-promoting inflammatory responses?
2. Innate immune cells directly and indirectly potentiate cancer risk through the diversity of bioactive mediators they deliver to neoplastic tissues. While the evidence for some mediators is strong (MMPs, some cytokines, angiogenesis), for others there is less evidence (reactive oxygen species, reactive nitrogen species)
3. What are the physiological roles of the polarized chronic pro-tumorigenic immune response and what will be the side effects of inhibiting it?
4. How does long-term usage of non-steroidal anti-inflammatory drugs reduce cancer recurrence?
5. The adaptive immune system: Whereas some studies have provided convincing data supporting the concept that the immune system exerts a protective role against certain tumor types, other studies show enhanced tumor progression in some settings; thus malignant outcome is etiology-, context- and organ-dependent.

Studying specific cell populations

1. Mouse genotypes harboring homozygous null deletions in genes encoding regulators of adaptive immunity (RAG1, RAG2, CD4, CD8 etc.)
2. Mouse genotypes harboring genetic modifications in genes encoding regulators of innate immunity (cKIT, CSF, myd88 etc.)

What do Leukocytes Deliver?



From Balkwill & Mantovani, Cancer Cell 2005

Usefull hints

1. Look for models with predictable disease progression.
2. Faster models are good for the postdoc
3. Defined events in progression – premalignant, invasive, metastatic.
4. Similar to human disease
5. Aim to identify patient subpopulations that will respond to a specific therapy.
6. Use immune competent mice.
7. Strain differences change the tumor phenotype and the immunophenotype. B6 is biased towards a Th1 resonse while FVB is biased towards a Th2 response.
8. two main approaches – a cell based approach – targeting different immune cells, and a signaling based approach, targeting specific signaling pathways either in epithelial cells or in immune subopulations

We chose to concentrate on the inflammation and not on tumor immunology, yet it is clear that even with this respect the inflammatory microenvironment can suppress an anti tumor immune response

Participants

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