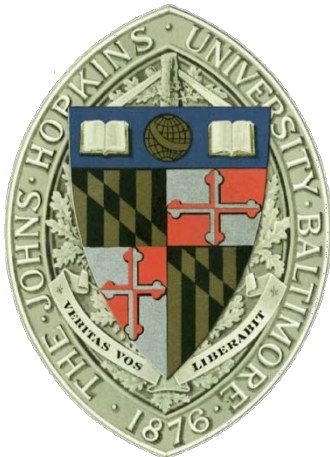


Computational Modeling and Bioinformatics of Cancer Angiogenesis at the Molecular, Cellular, Tissue, and Whole-Body Scales

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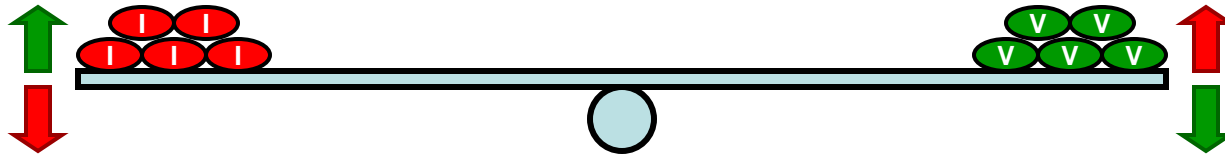
Breast cancer heterogeneity

- Cancer is a complex and heterogeneous disease, manifested at every scale (genetic and epigenetic; protein; cellular; tumor microenvironment (eg, cancer cells, vascular, lymphatic, immune); whole body.
- Breast cancer is the most commonly diagnosed female malignancy in the United States. Approximately 210,000 new cases of invasive breast cancer have been diagnosed in 2010 and 40,000 patients have died from it.
- Triple-negative breast cancers (TNBC) are more aggressive than other breast cancers (ER+; PR+, HER2+) and more likely to metastasize and recur; the survival rates are significantly lower.
- There are multiple types of TNBC with distinct genetic signatures and drug response, e.g. basal like (BL-1 and BL-2), androgen receptor signaling (LAR), and mesenchymal-like (M and MSL) subtypes.
- We show that response to anti-angiogenic therapy is sensitive to the tumor microenvironment; personalized medicine.

Angiogenesis (neovascularization) - growth of new blood vessels from pre-existing microvasculature

- Physiological (development, exercise, wound healing)**
- Pathological (cancer, age-related macular degeneration)**
- Over 70 diseases and engineered tissues are angiogenesis dependent**

Balance between endogenous pro- and anti-angiogenic factors



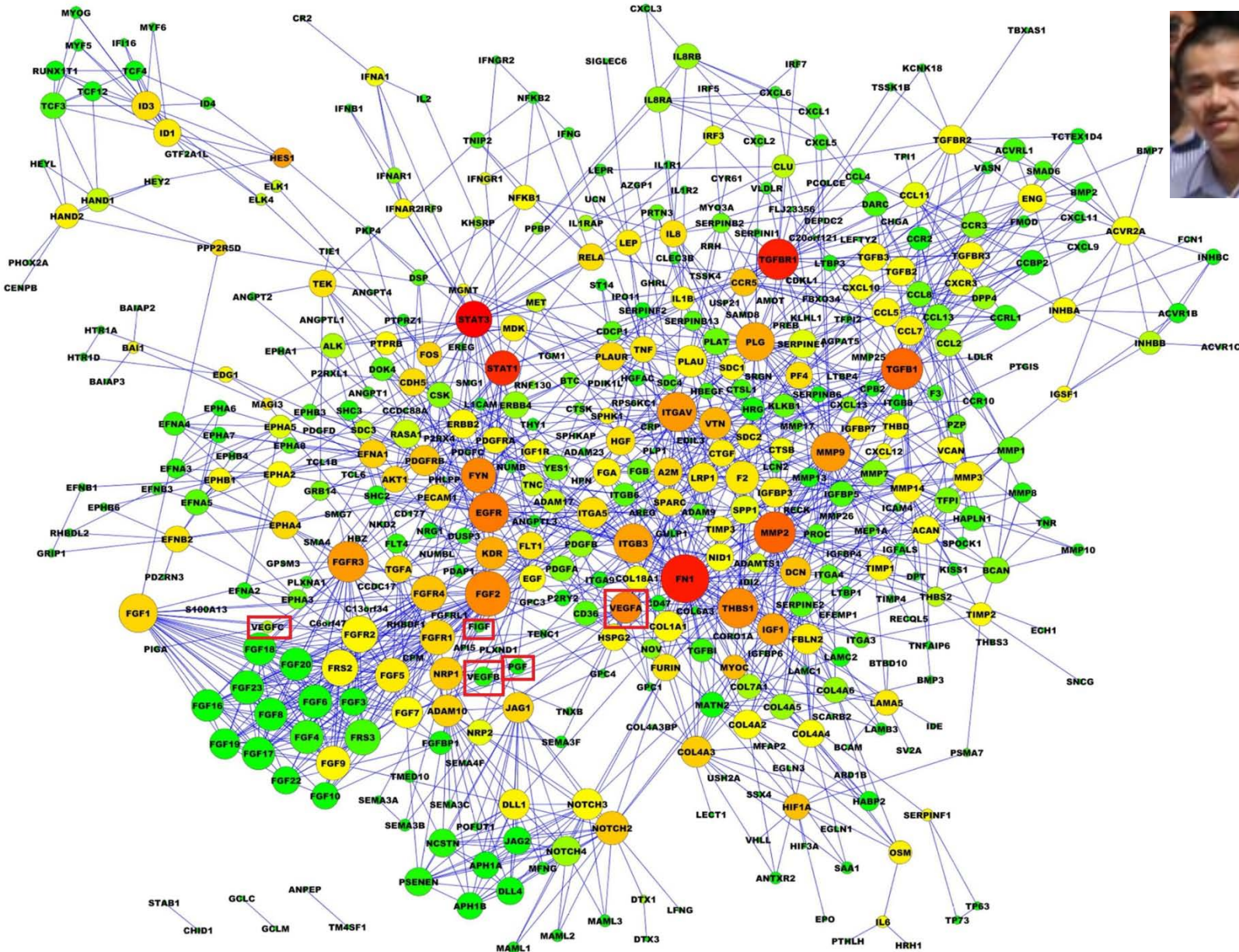
Molecular Inhibitors

Thrombospondin-1
Collagen IV and XVIII fragments
CXC chemokine Platelet Factor-4
Tissue Inhibitors of Metalloproteinases
Pigment Epithelium Derived Factor (PEDF)
...

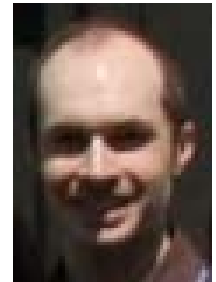
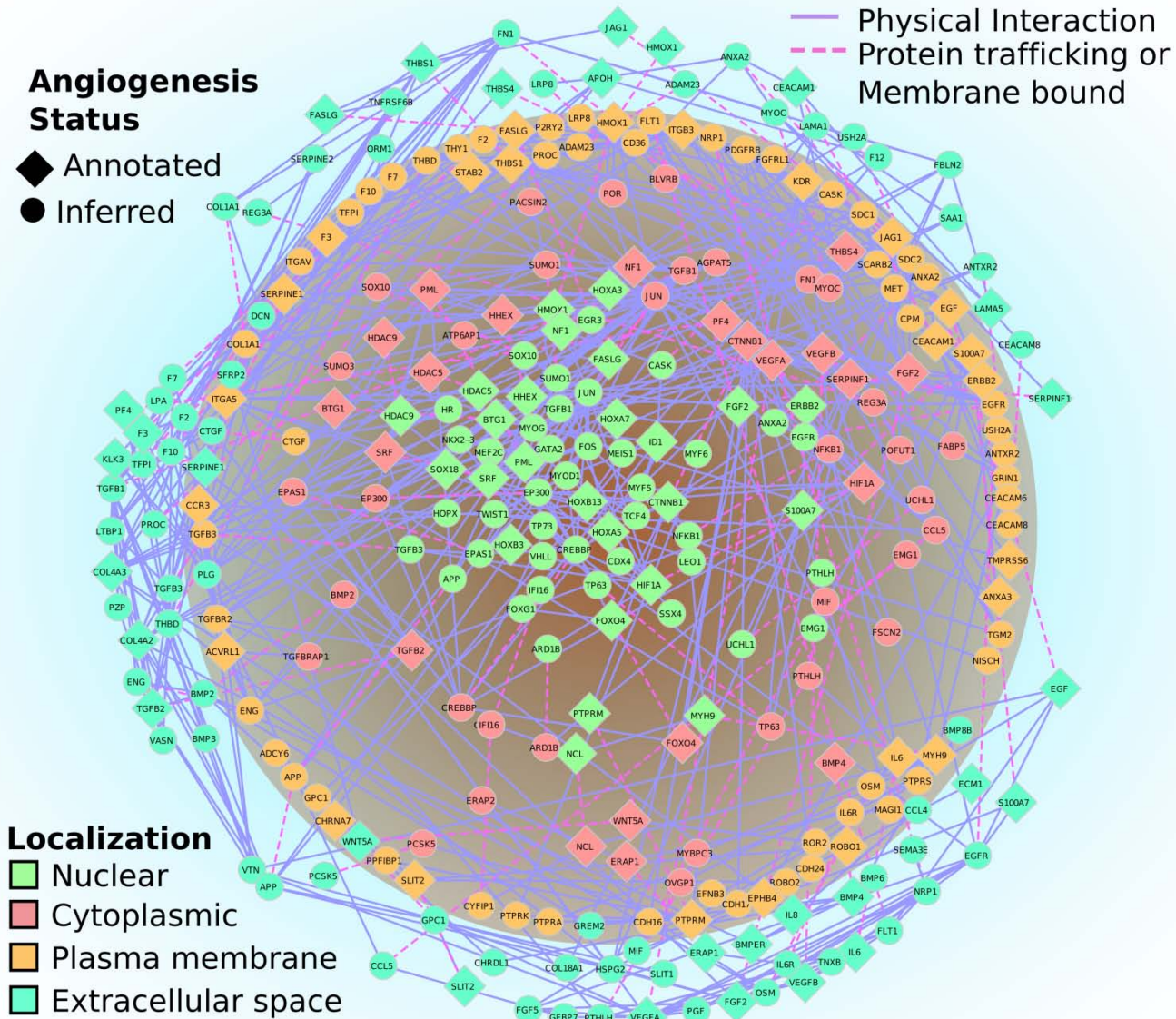
Molecular Activators

Vascular Endothelial Growth Factor
Fibroblast Growth Factor (FGF)
Platelet-Derived Growth Factor (PDGF)
Matrix Metalloproteinases (MMPs)
Transforming Growth Factor- β (TGF)
...

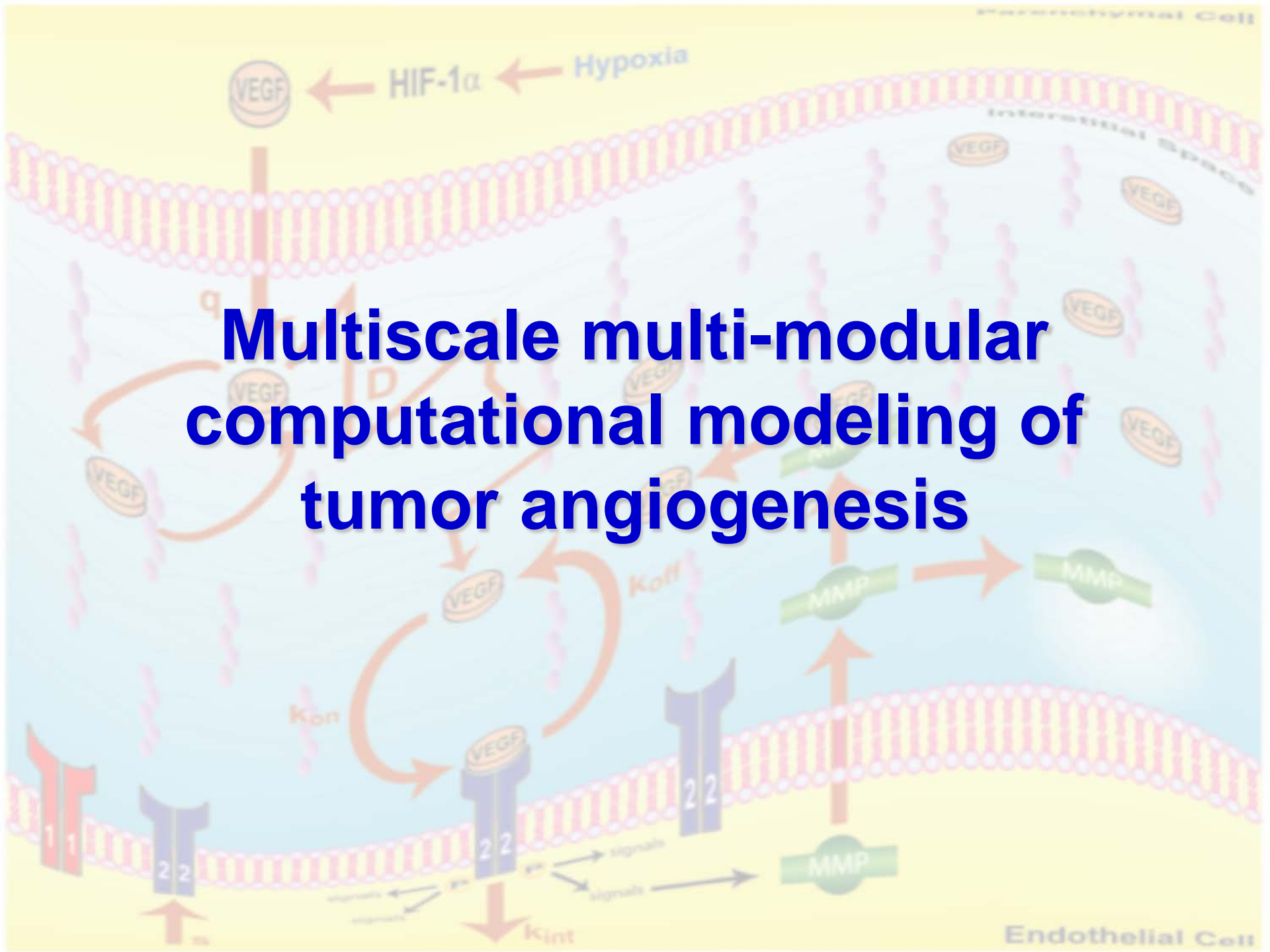
The Angiome: Protein-protein interaction (PPI) angiogenic network



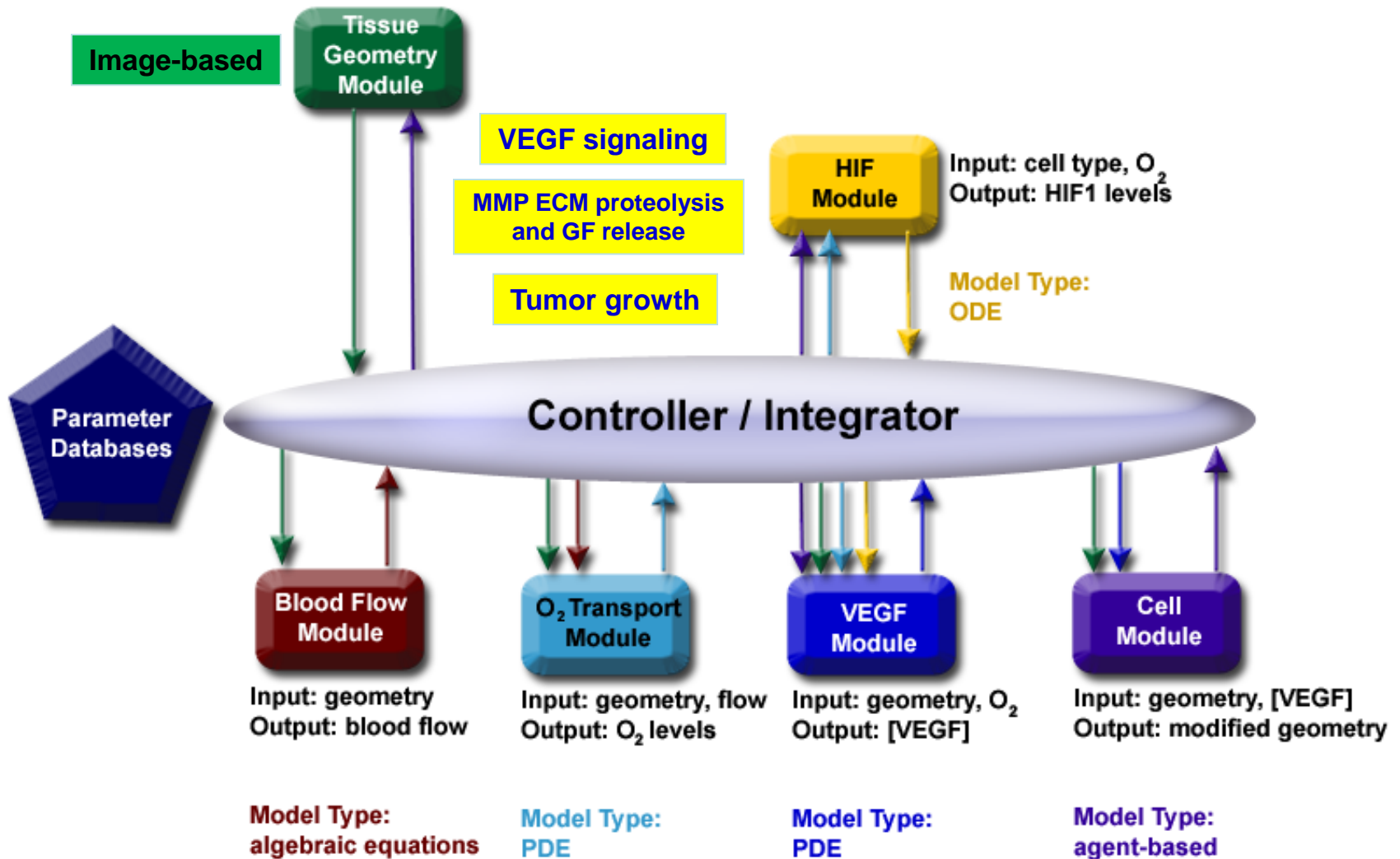
Angiome PPI with cellular localization



Multiscale multi-modular computational modeling of tumor angiogenesis



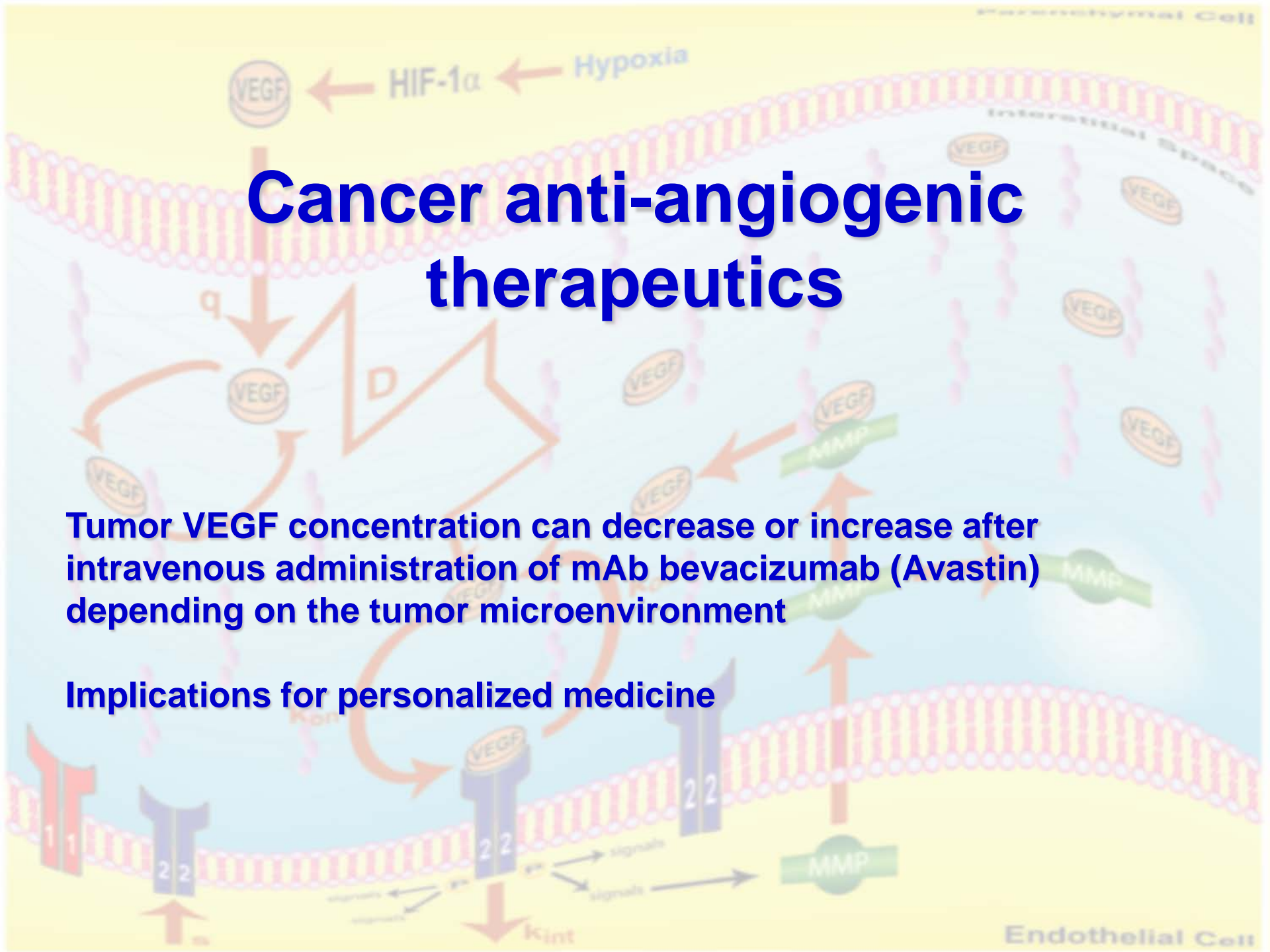
Multiscale multi-module computational framework



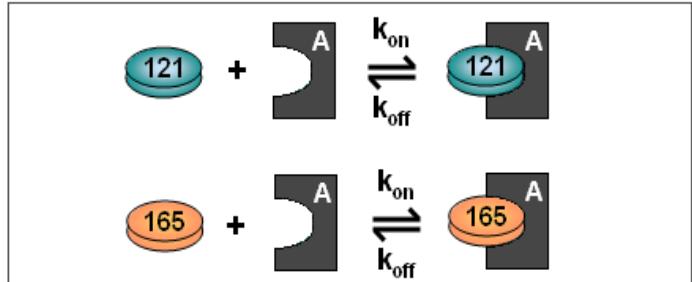
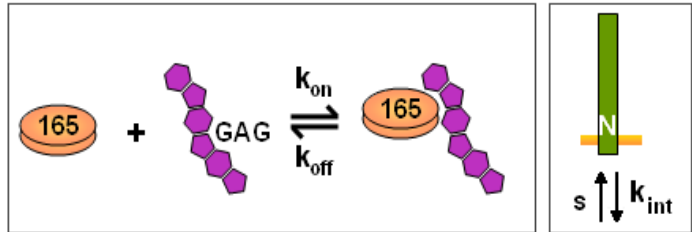
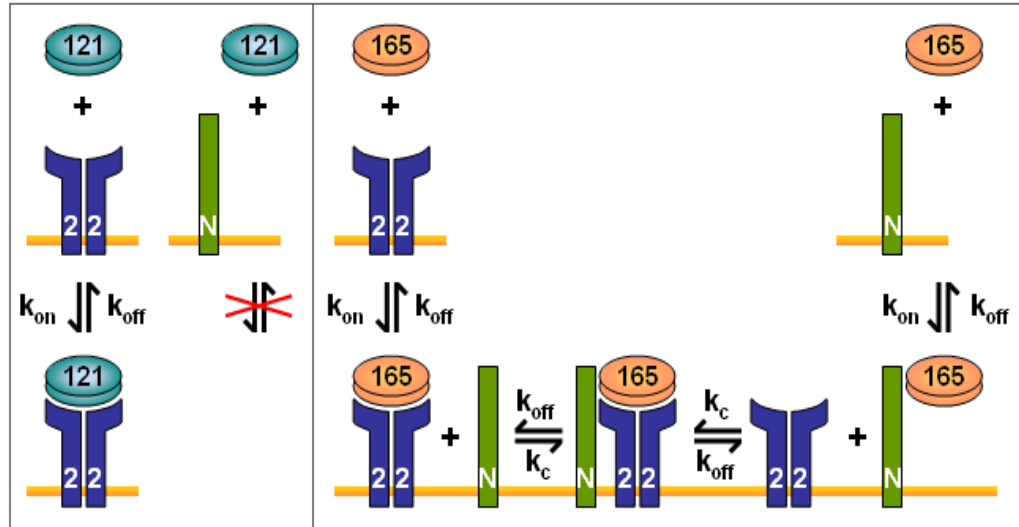
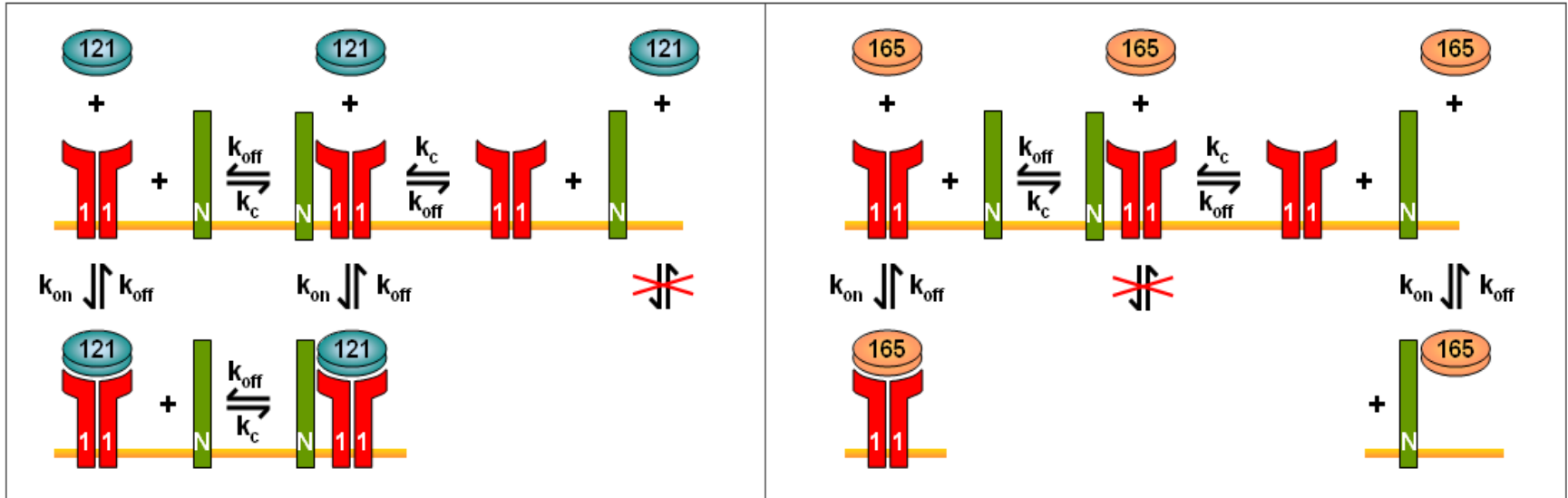
Cancer anti-angiogenic therapeutics

Tumor VEGF concentration can decrease or increase after intravenous administration of mAb bevacizumab (Avastin) depending on the tumor microenvironment

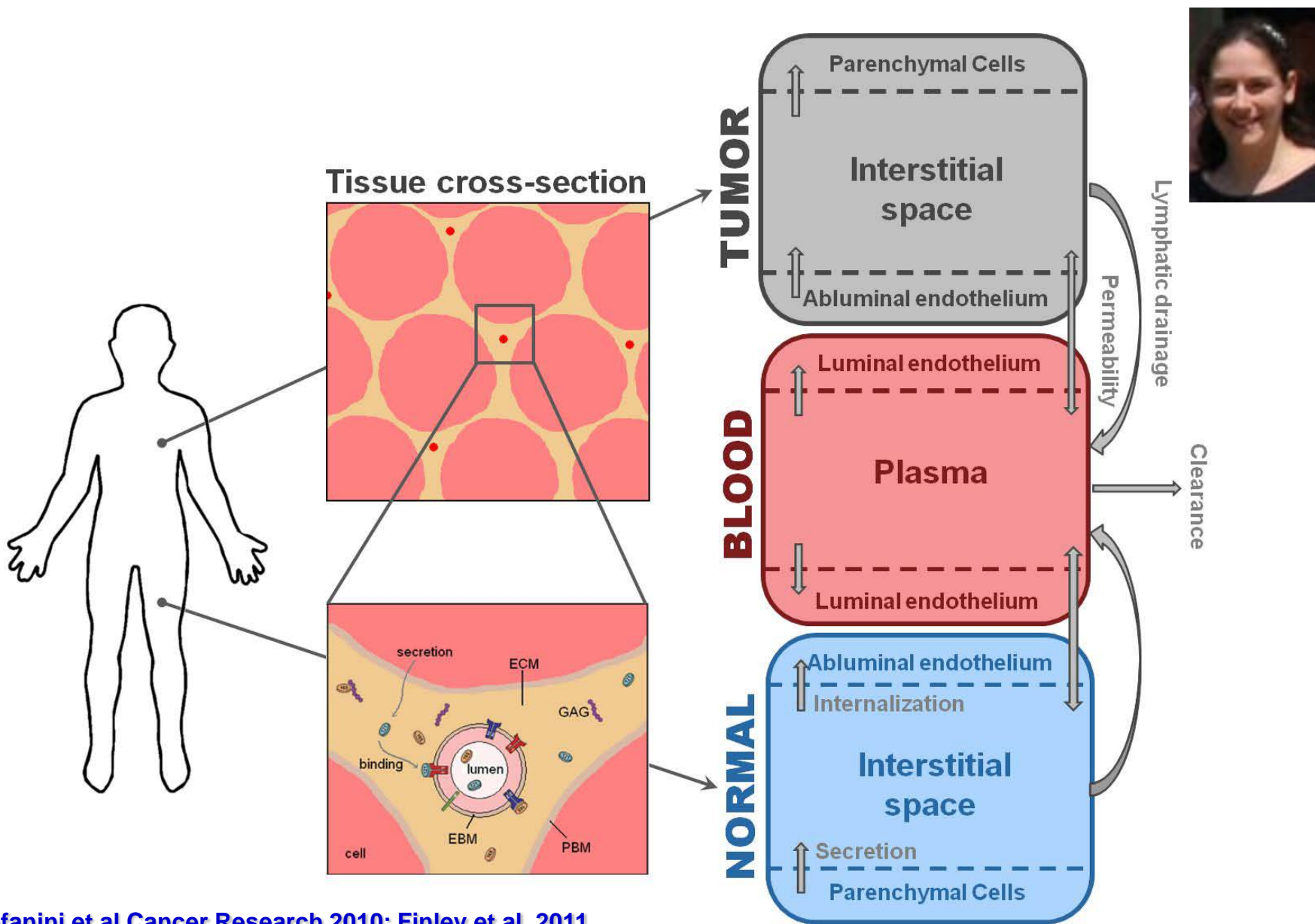
Implications for personalized medicine



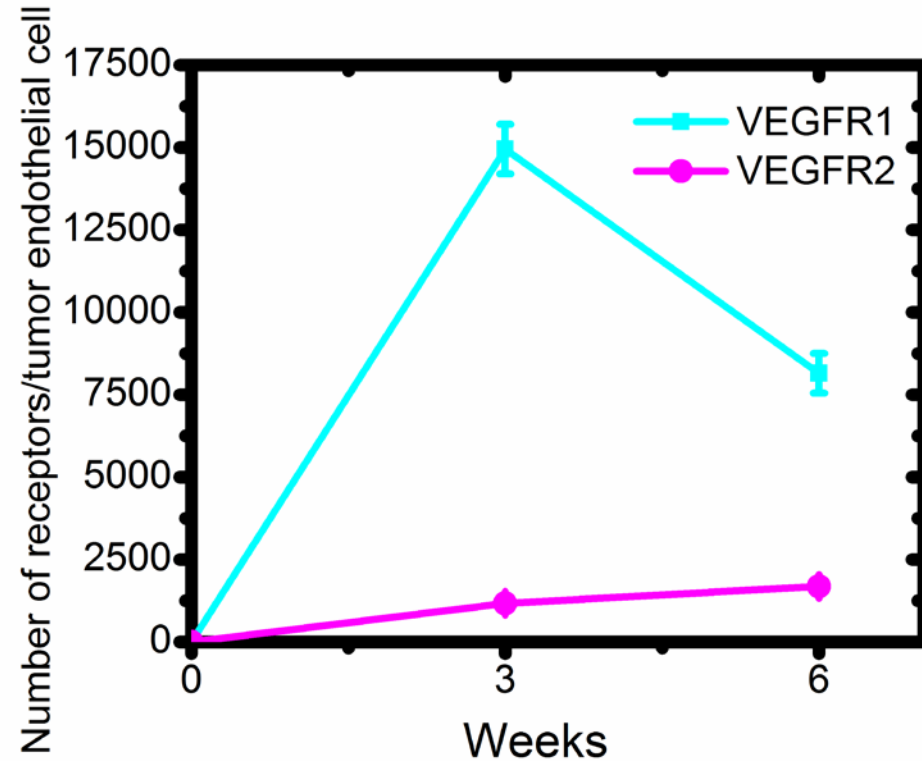
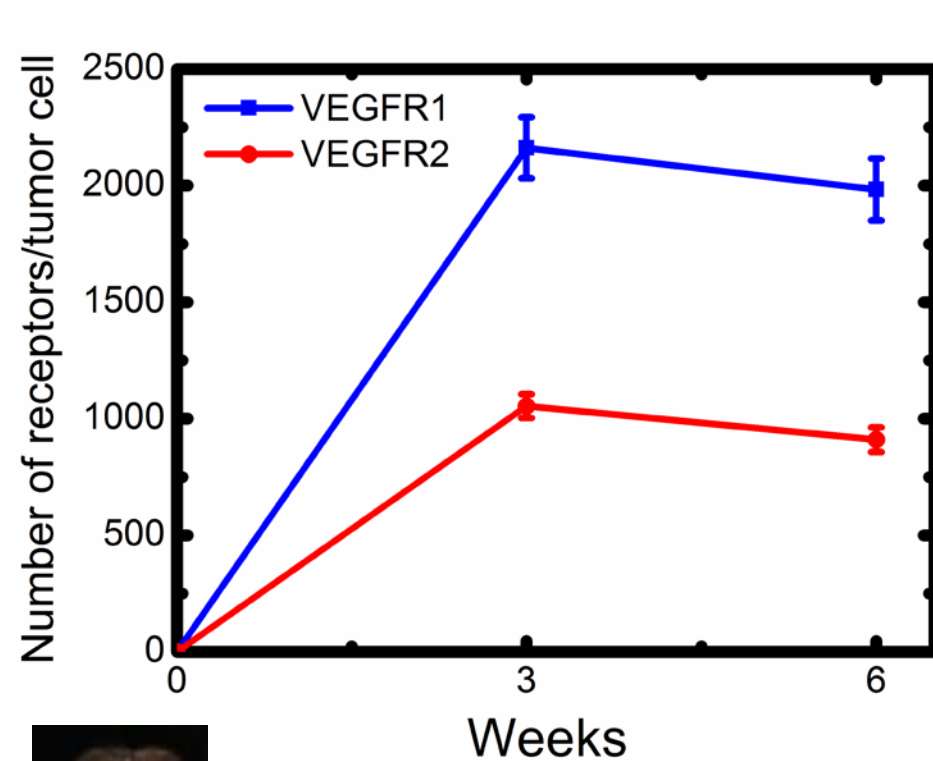
VEGF-VEGFR interactions



Whole-body multiscale model of VEGF distribution

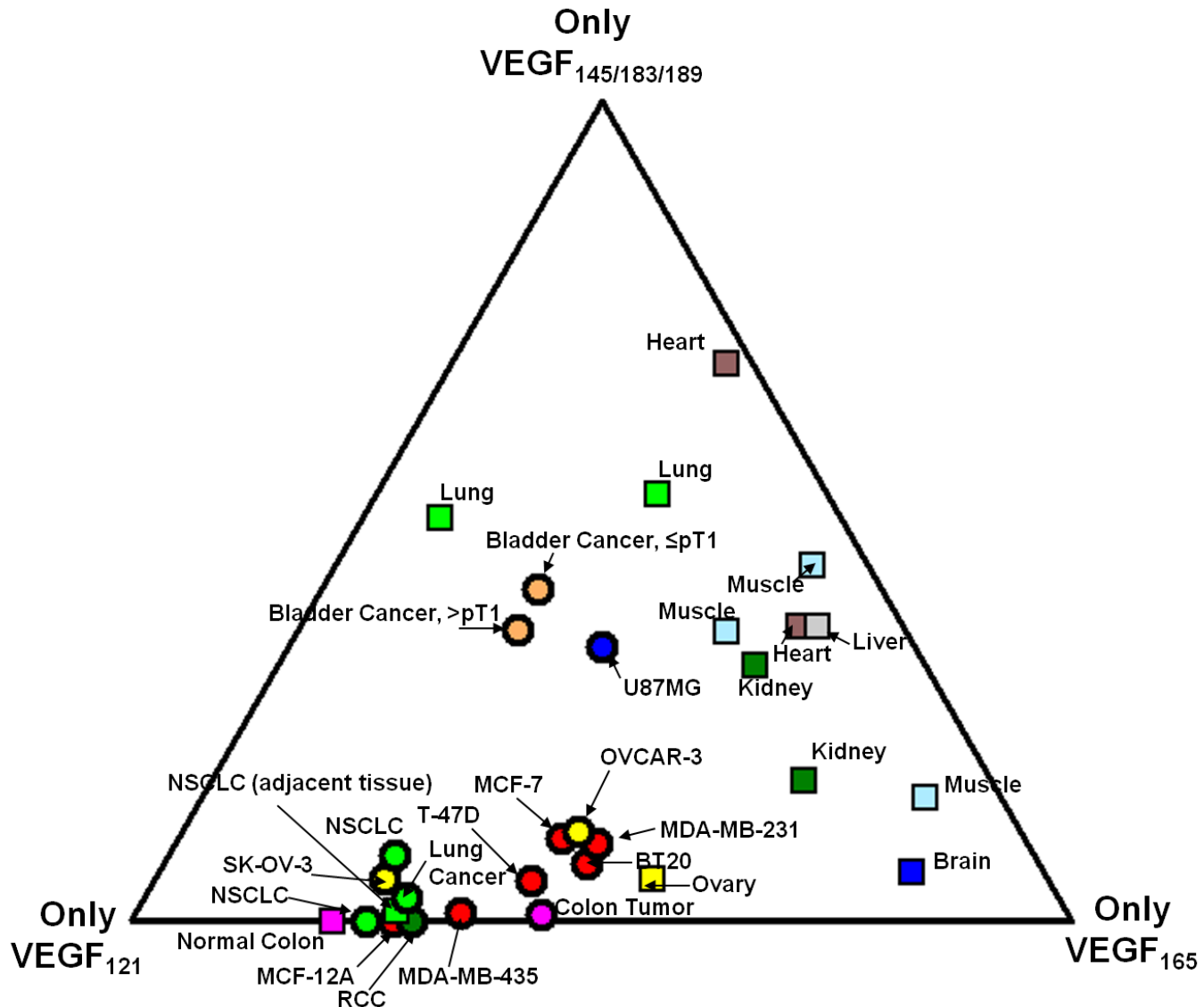


Quantitative flow cytometry measurements of receptor density on endothelial and tumor (MDA-MB-231) cells

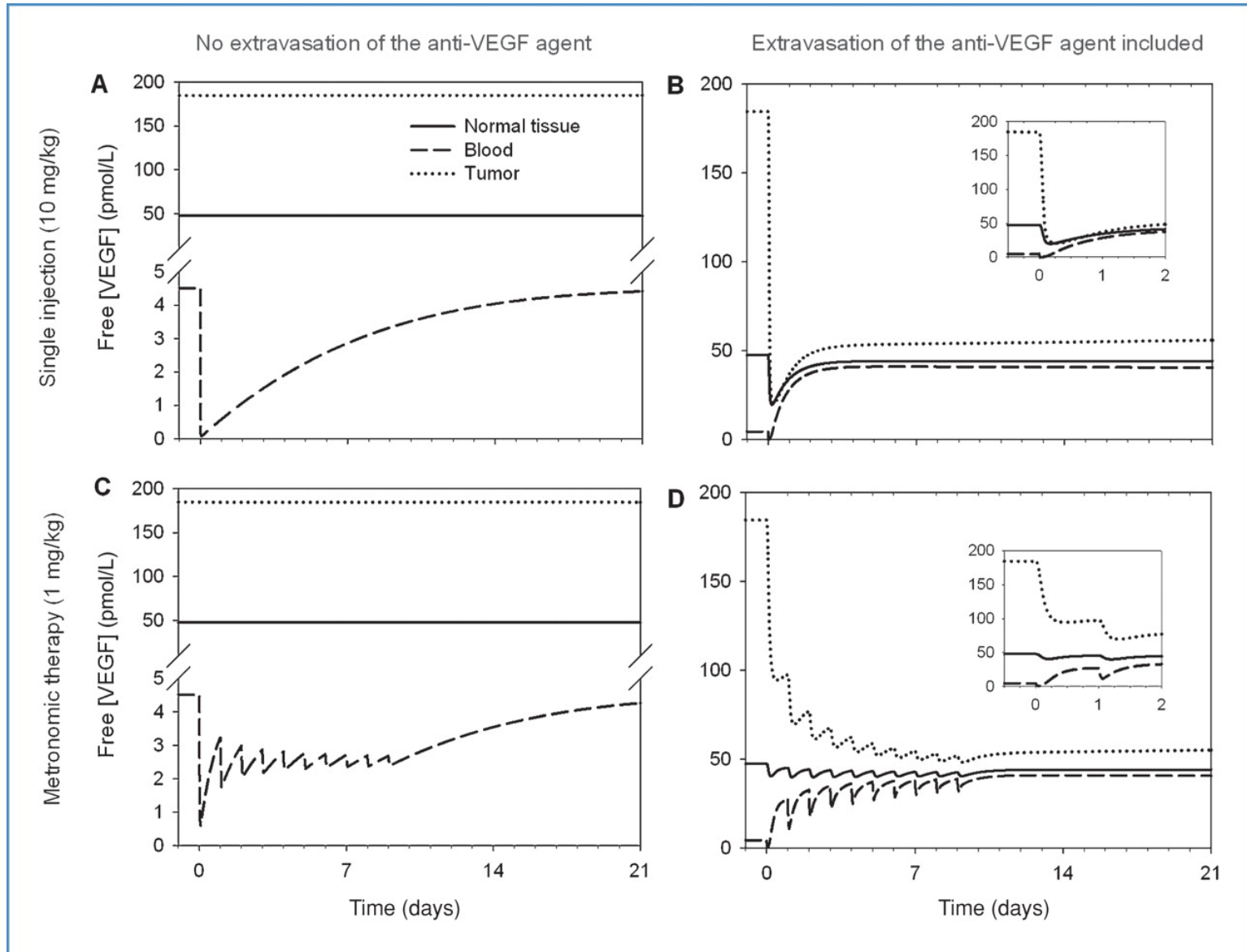


	3 weeks	6 weeks
Tumor size	$0.62 \pm 0.17 \text{ cm}^3$	$1.5 \pm 0.12 \text{ cm}^3$

Experimental expression of VEGF_{121/165/xxx} isoforms



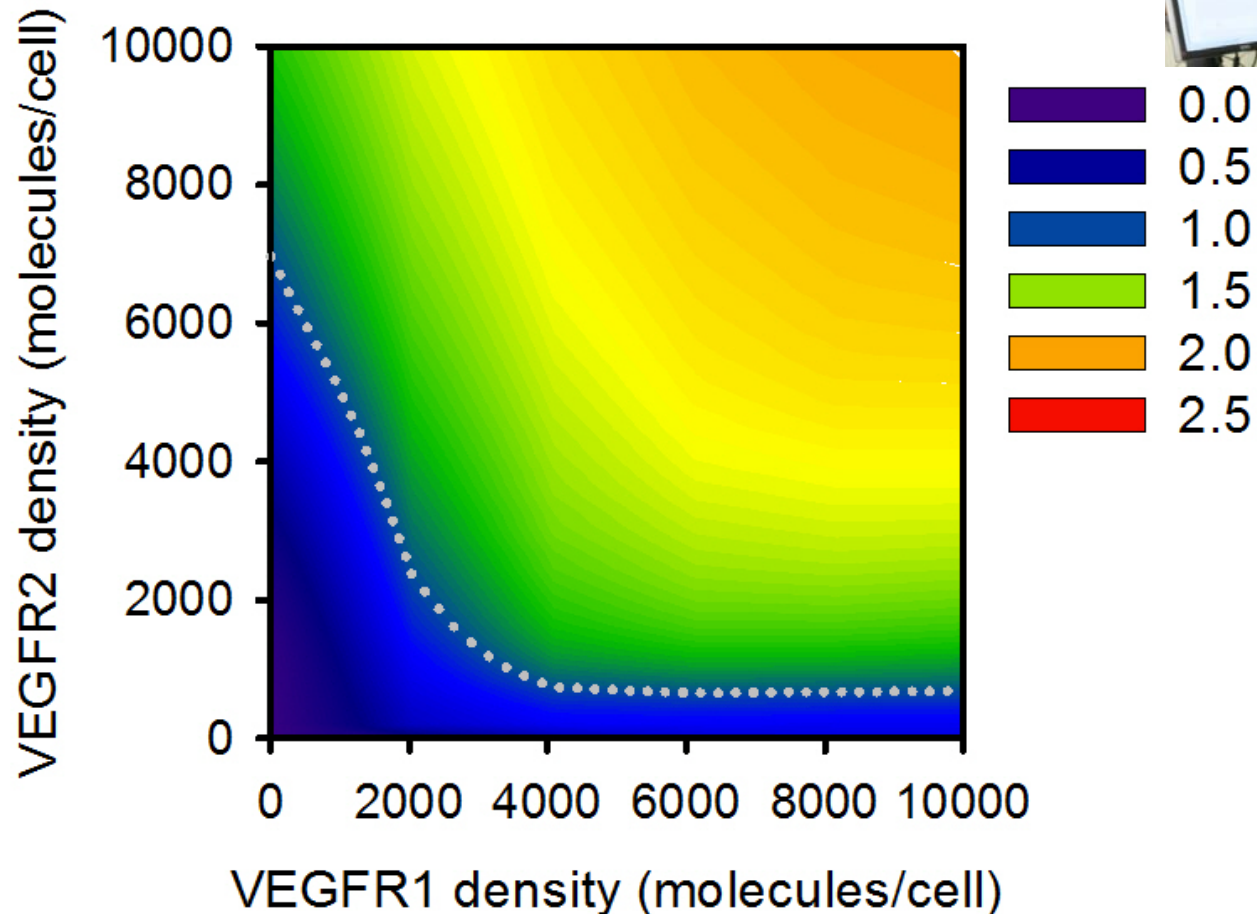
mAb extravasation causes plasma VEGF increase



Predicted response of tumor interstitial VEGF to bevacizumab

Effect of tumor microenvironment - Personalized Medicine

$\text{NRP1} = \text{NRP2} = 10,000$ molecules/cell



Acknowledgments

Collaborators:

Johns Hopkins University

Zaver Bhujwala (ICMIC - In Vivo Cellular and Molecular Imaging
Center/Radiology/Oncology)

Venu Raman (ICMIC, Radiology/Oncology)

Kristine Glunde (ICMIC, Radiology/Oncology)

Dmitri Artemov (ICMIC, Radiology/Oncology)

Arvind Pathak (ICMIC, Radiology/Oncology)

Marie-France Penet (ICMIC, Radiology/Oncology)

Antonio Wolff (Oncology)

Joel Bader (Biomedical Engineering)

Supported by NIH grants R01 CA138264, R21 CA138264, R21 CA152473,
The Safeway Foundation for Breast Cancer