Anti-angiogenic Cancer Therapies Targeting the VEGF Pathway

Stacey D. Finley
Department of Biomedical Engineering
University of Southern California

MSM Consortium Meeting
4 September 2013

USC University of Southern California

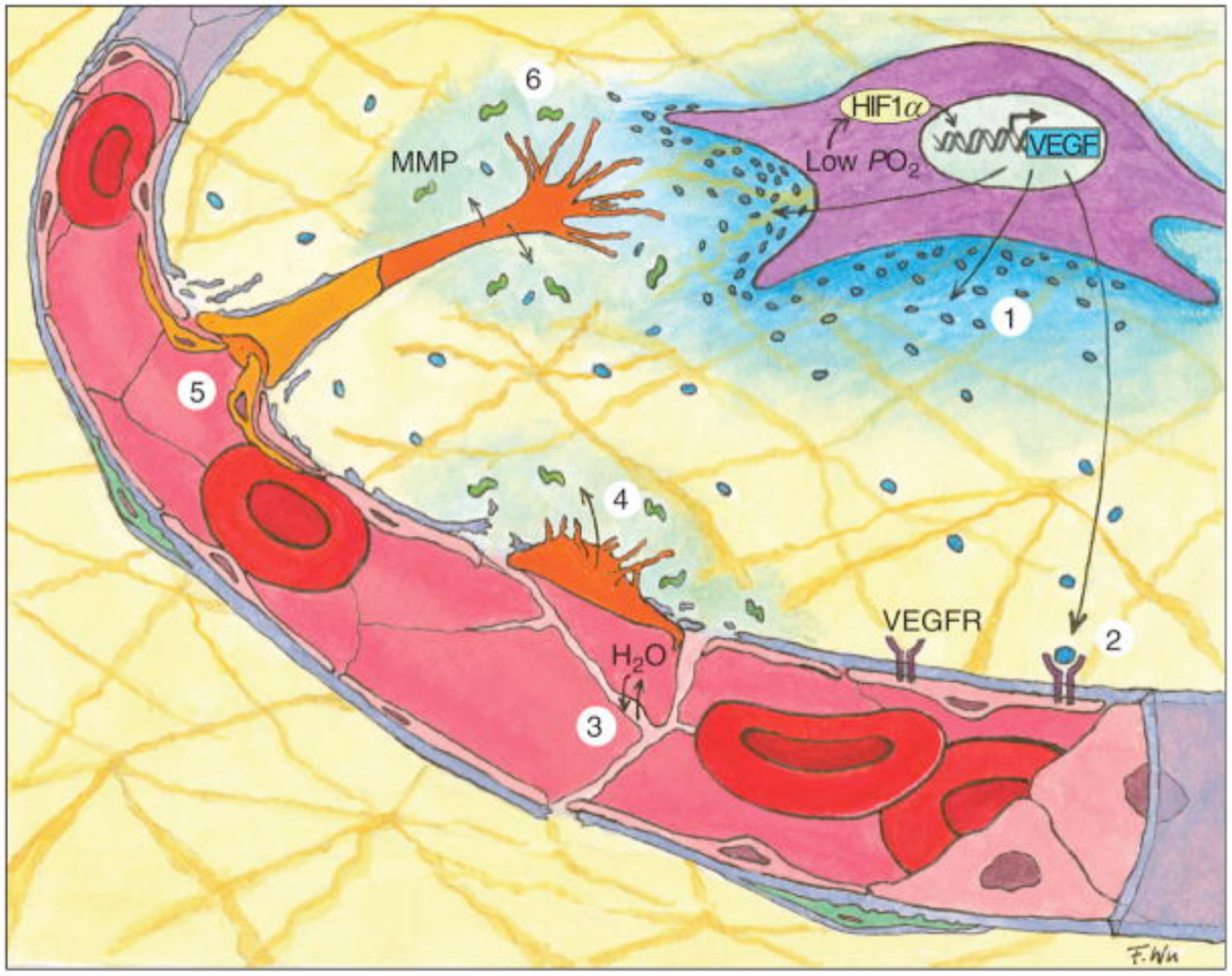
Angiogenesis

- Formation of new capillaries from pre-existing blood vessels
- Important in developing and adult animals
- Governed by a balance of promoters and inhibitors

Physiological	Pathological
Organ development	**Cancer**
Reproduction	Retinopathy
Wound healing	Arthritis
Exercise	Peripheral artery disease
	Stroke
	…

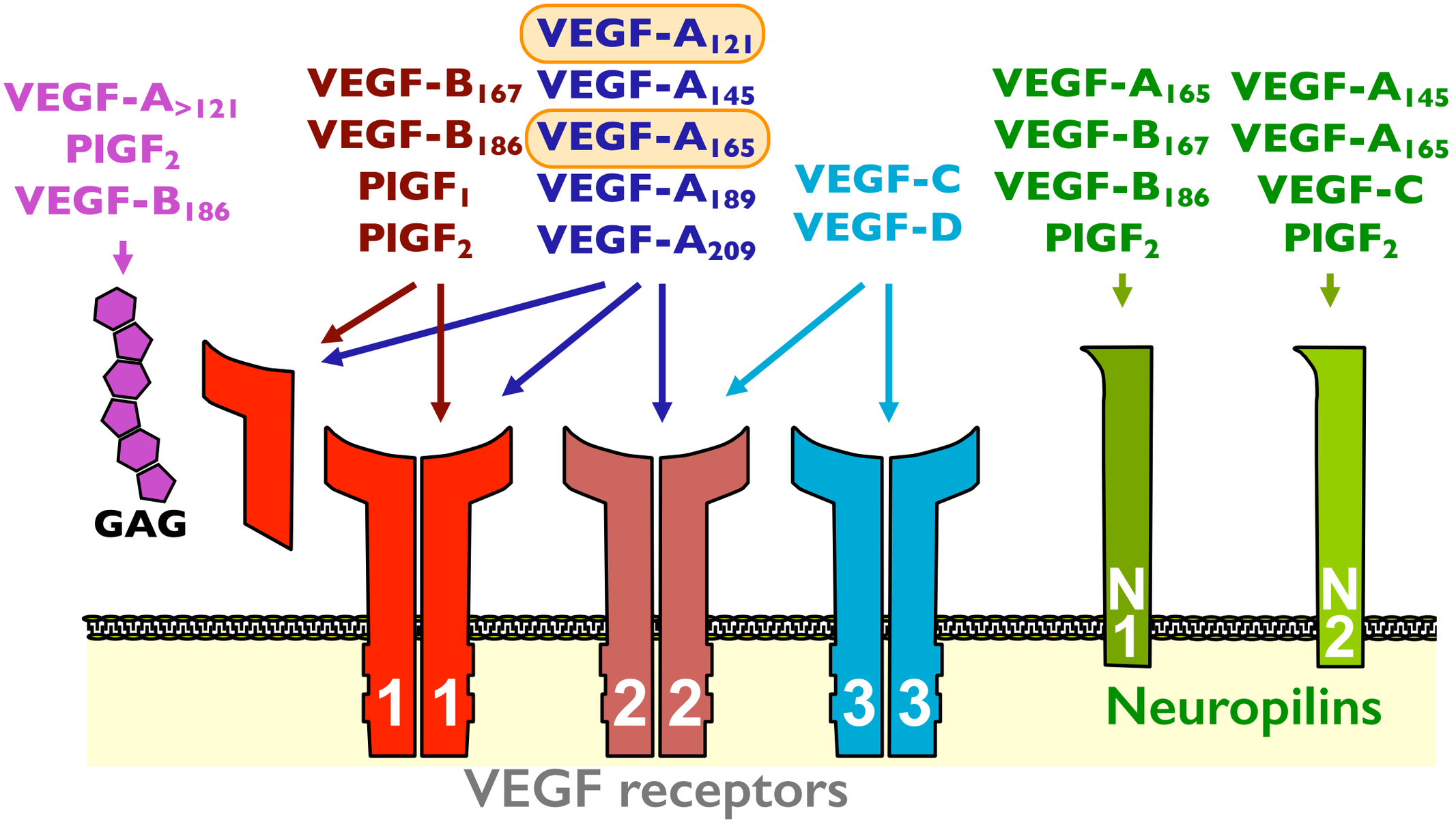
VEGF family: target for cancer therapy

- **V**ascular **E**ndothelial **G**rowth **F**actor (VEGF)
  - Potent regulator of angiogenesis
  - Acts in response to many stimuli, including hypoxia
  - Stimulates cell proliferation, migration, and survival
- **Targeted in cancer therapies**



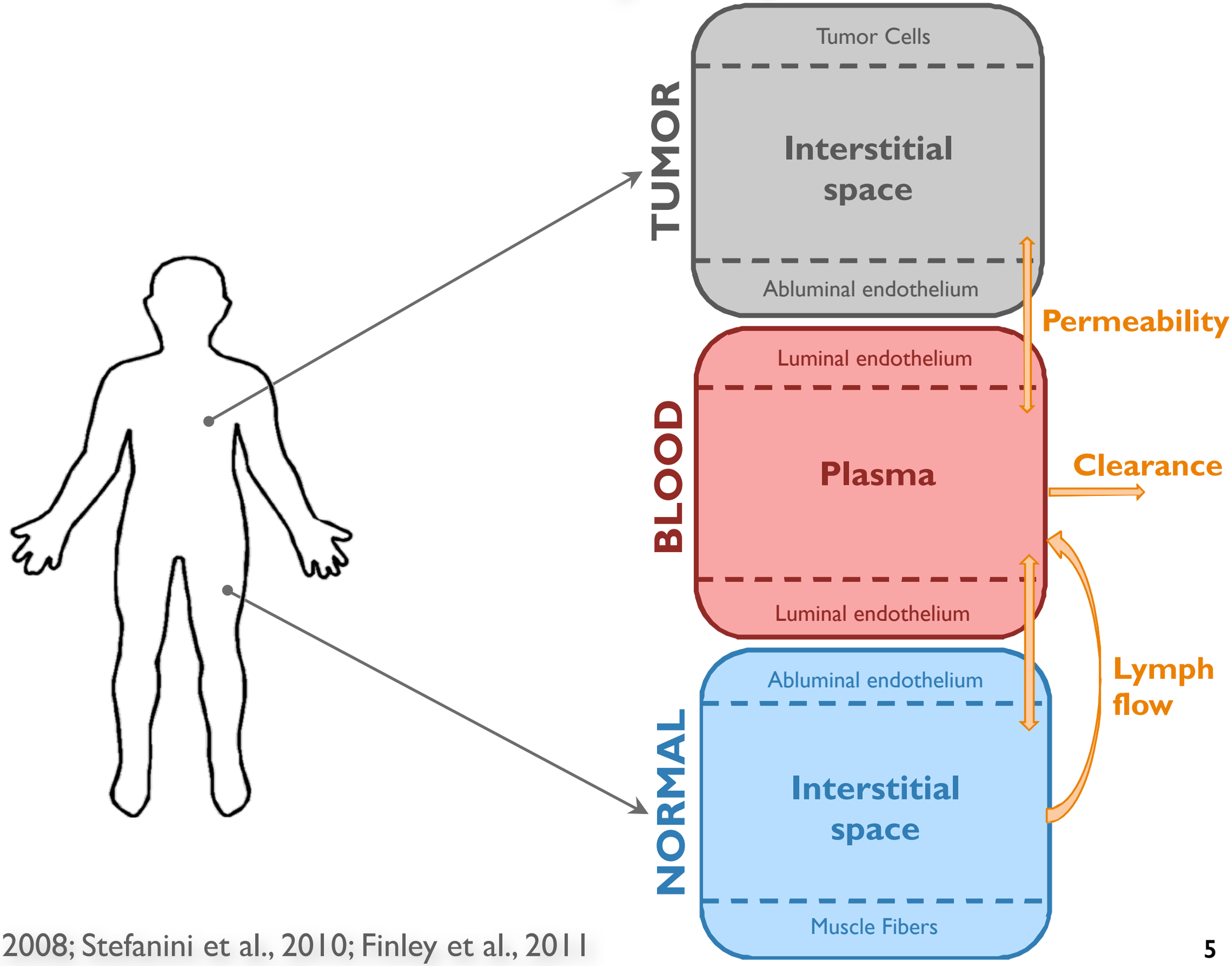
drawing by Florence Wu

VEGF family: prime for systems biology modeling

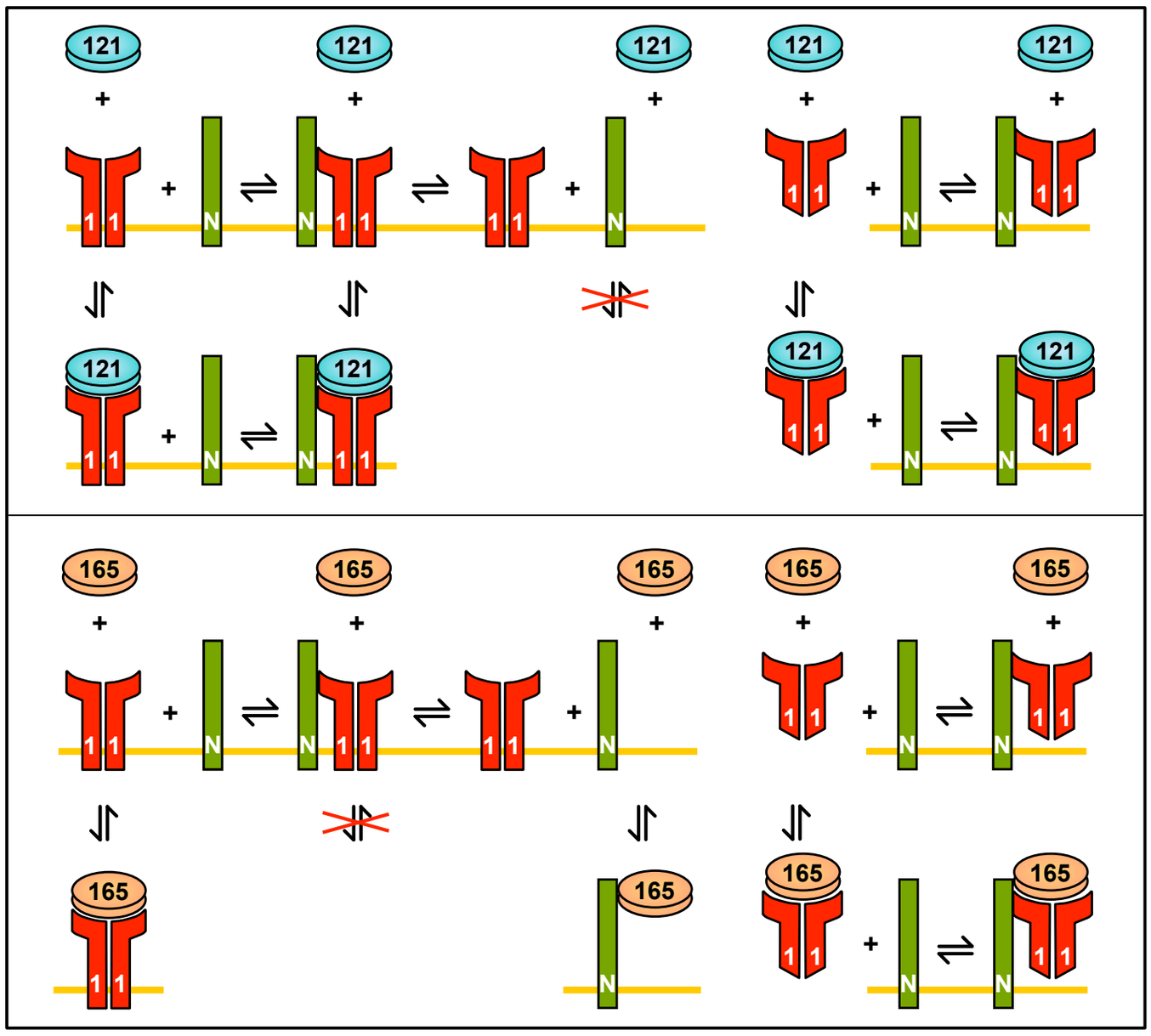


We have developed a molecular-detailed computational model of VEGF to predict the effect of therapeutics that target the VEGF pathway

Methods: Multi-scale whole-body compartment model

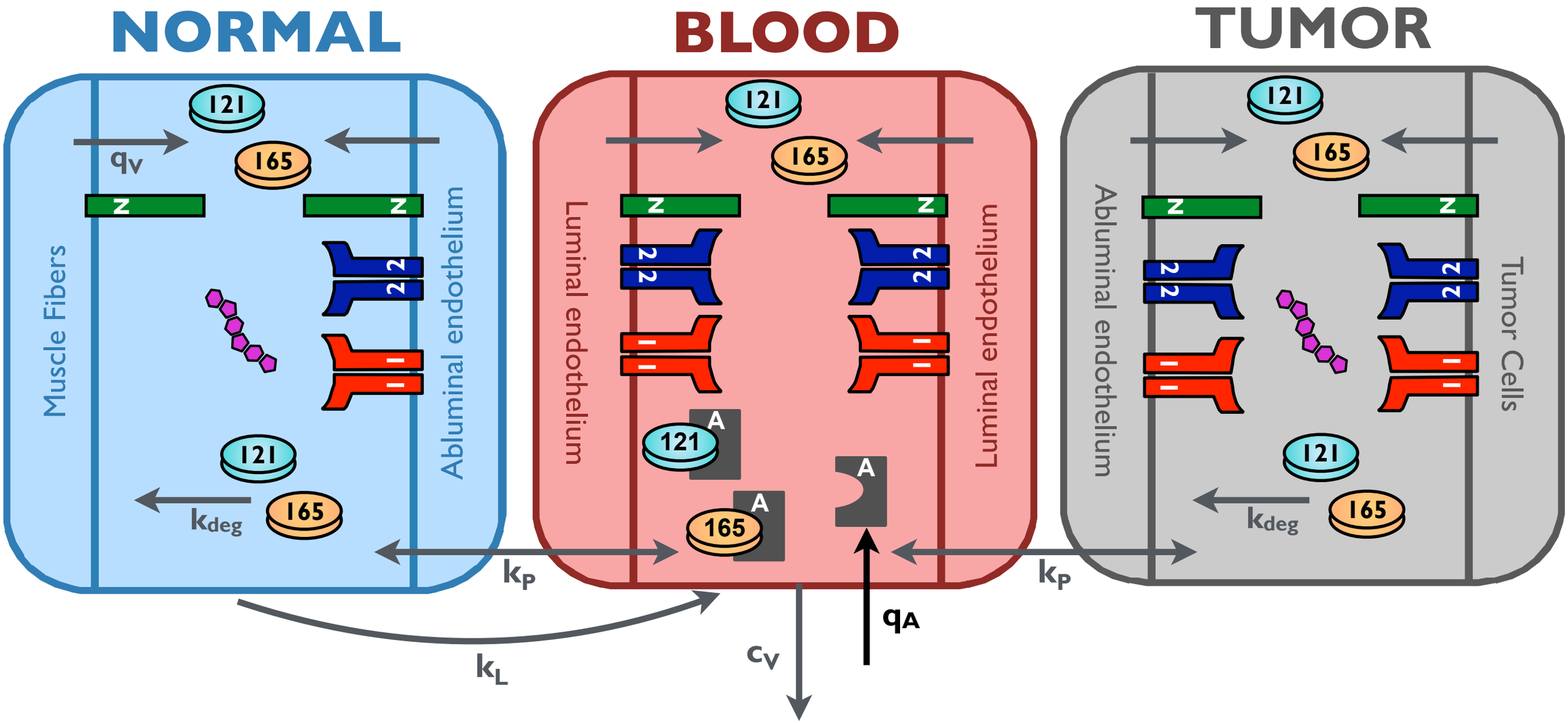


Stefanini et al., 2008; Stefanini et al., 2010; Finley et al., 2011

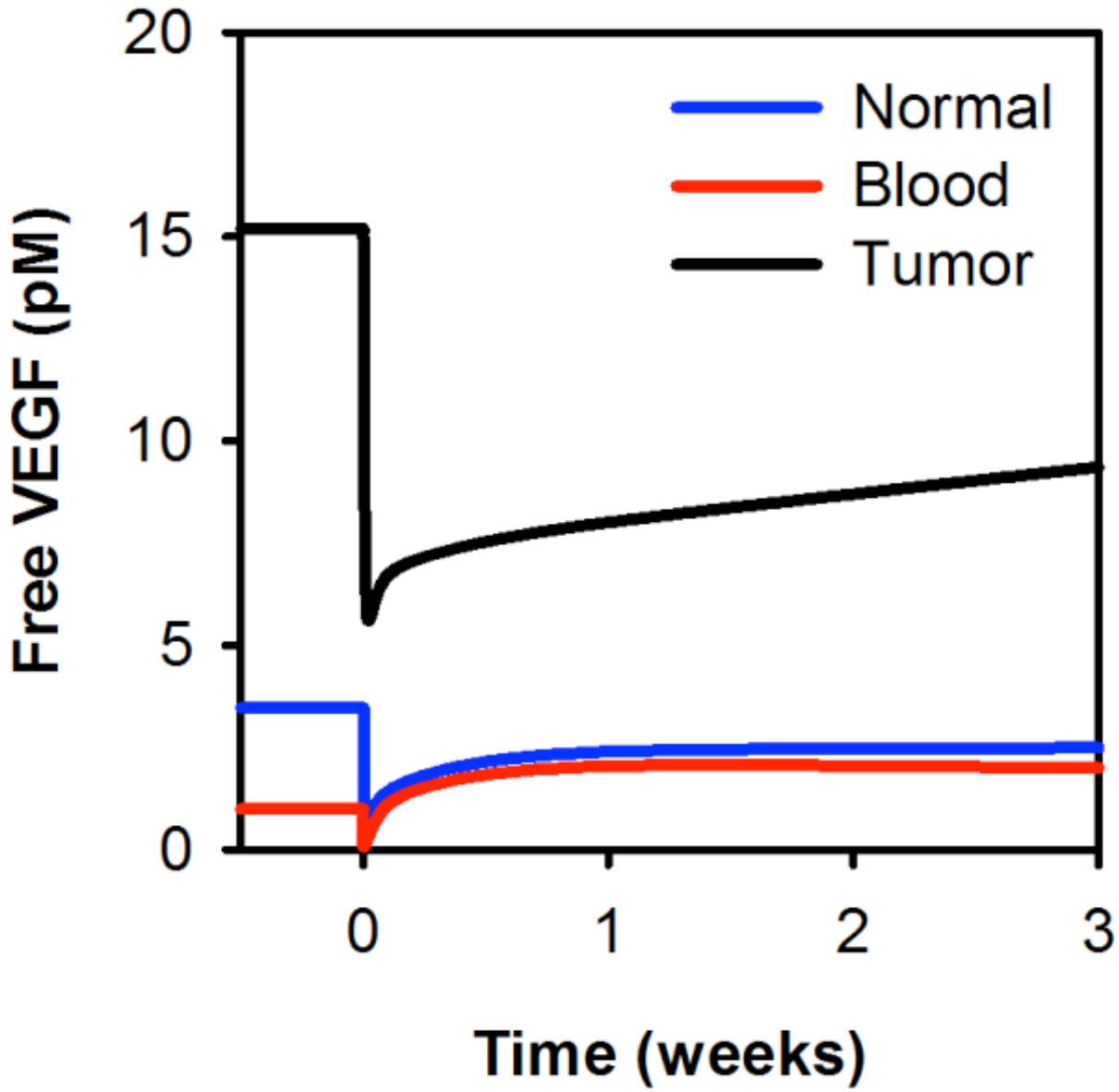


Model includes 154 ODEs to predict the concentrations of all molecular species in each compartment

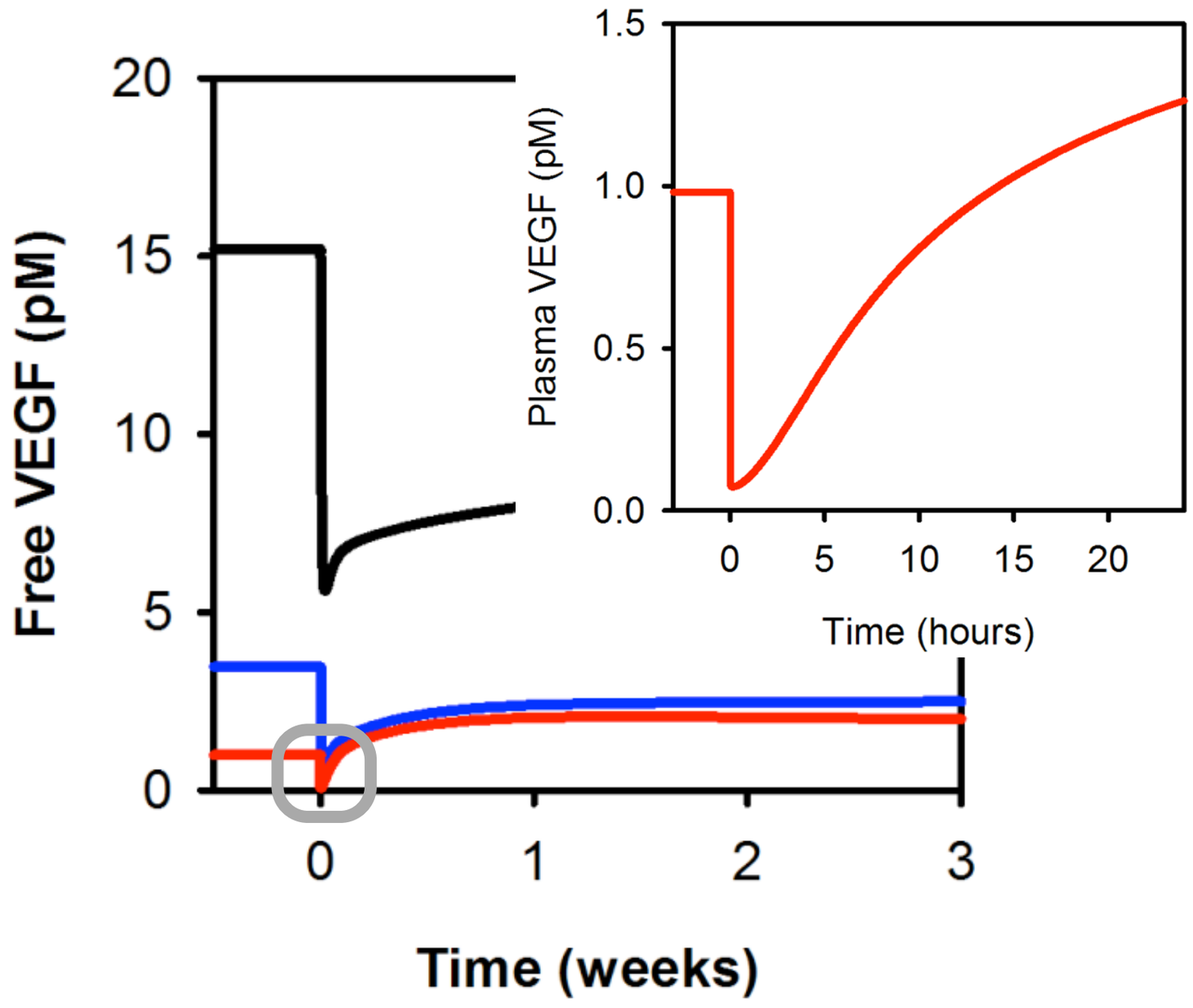
Simulating VEGF-targeted therapy



Model predicts response to anti-VEGF treatment

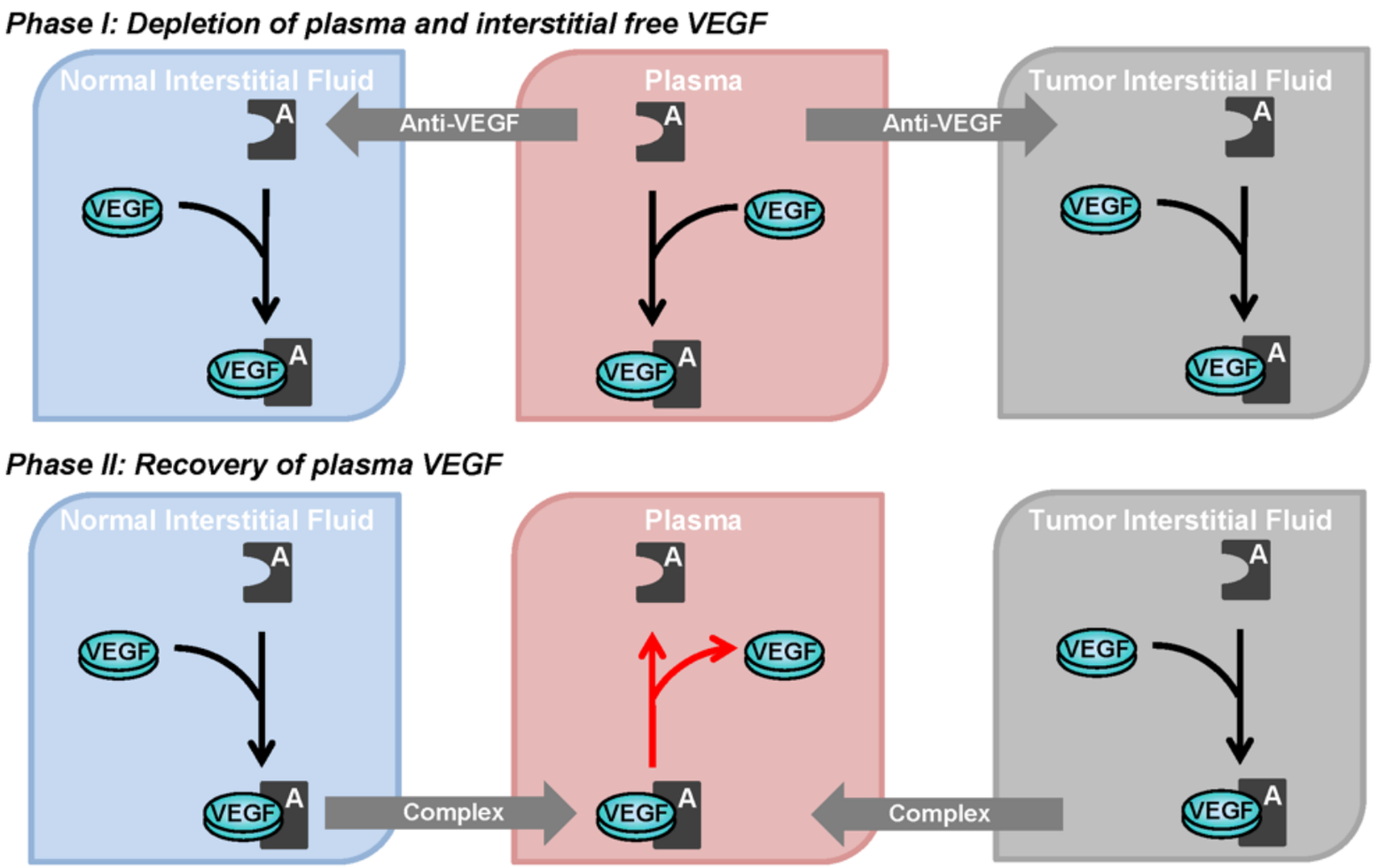


Model predicts response to anti-VEGF treatment



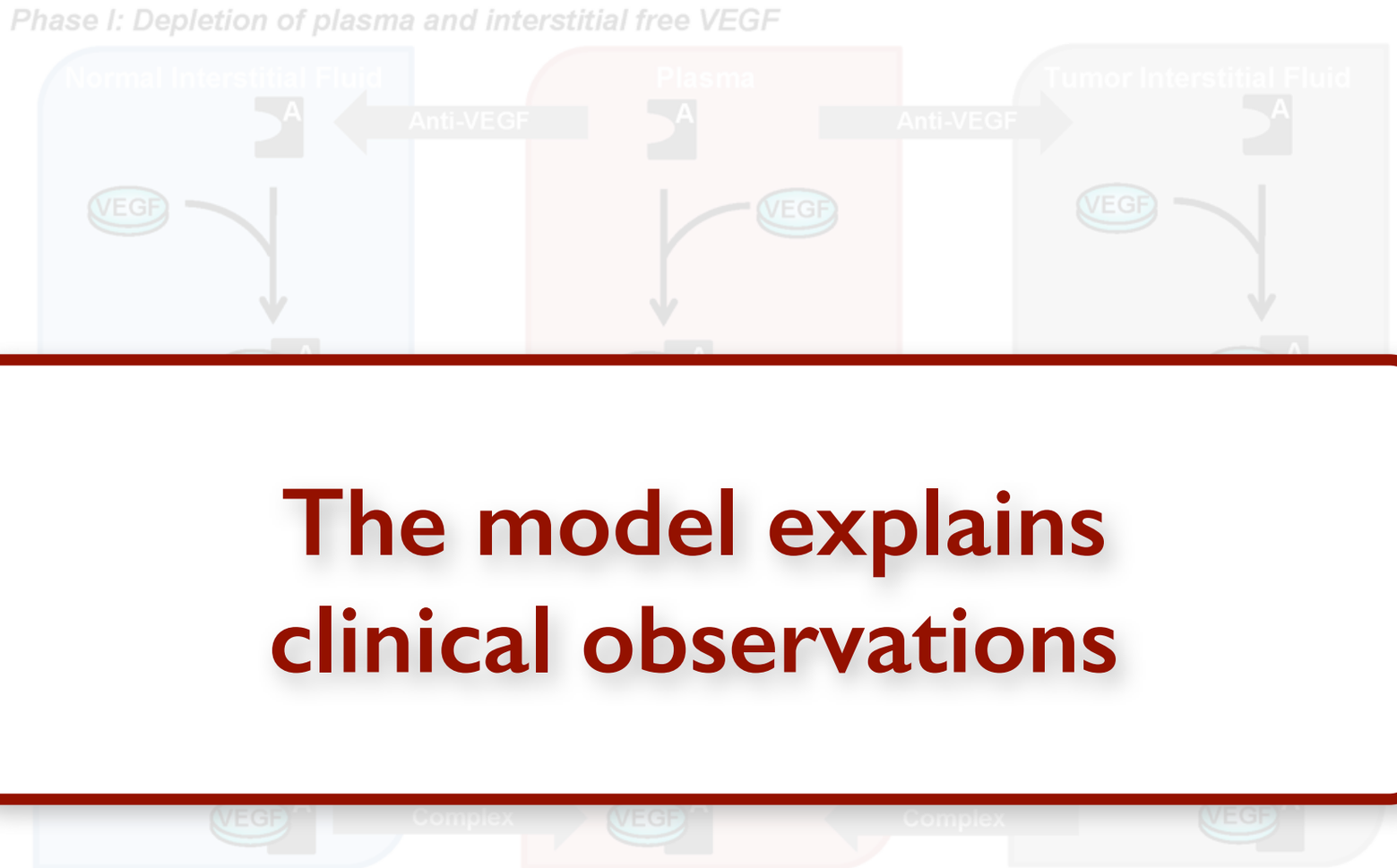
Plasma VEGF initially decreases, and then rebounds above the pretreatment level

Explanation of response to anti-VEGF therapy



Stefanini et al., Cancer Res, 2010
Finley and Popel, J Natl Cancer Inst, 2013

Explanation of response to anti-VEGF therapy



The model explains clinical observations

Stefanini et al., Cancer Res, 2010
Finley and Popel, J Natl Cancer Inst, 2013

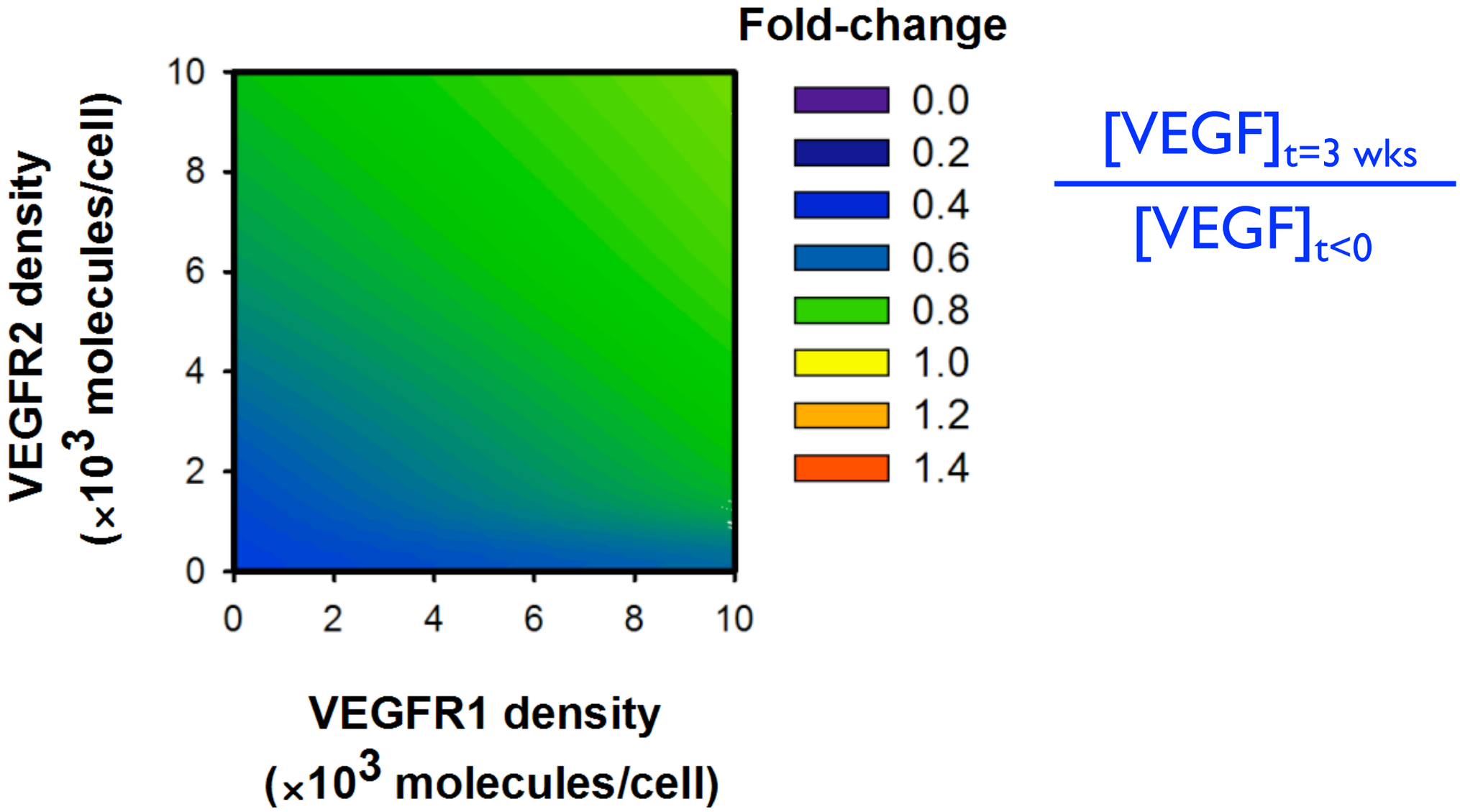
Quantifying the effect of treatment

- "Fold-change" of **free (unbound) VEGF in the tumor**
  - Compares free VEGF before treatment and VEGF at 3 weeks post-treatment
  - Fold-change = $\frac{[VEGF]_{t=3\ wks}}{[VEGF]_{t<0}}$

- Values of the fold-change:
  - = 1: No change
  - > 1: Free VEGF increased
  - < 1: Free VEGF decreased, **"therapeutic response"**

Finley et al. BMC Syst Biol, 2011

Effect of receptor expression on tumor cells

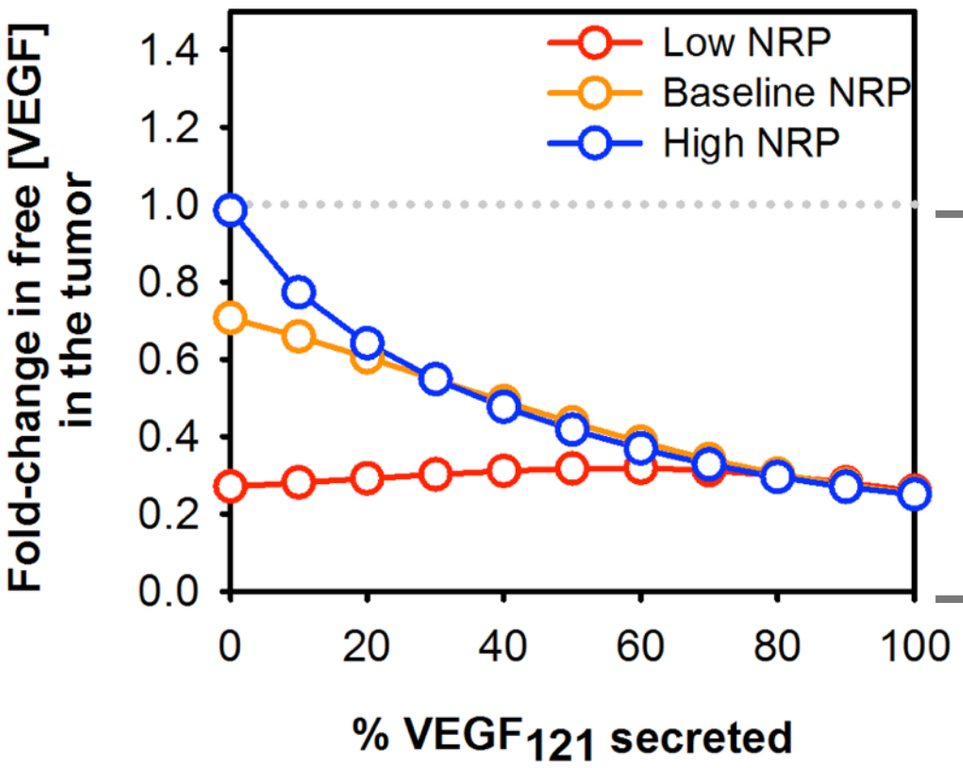


Tumor VEGF is depleted following anti-VEGF treatment

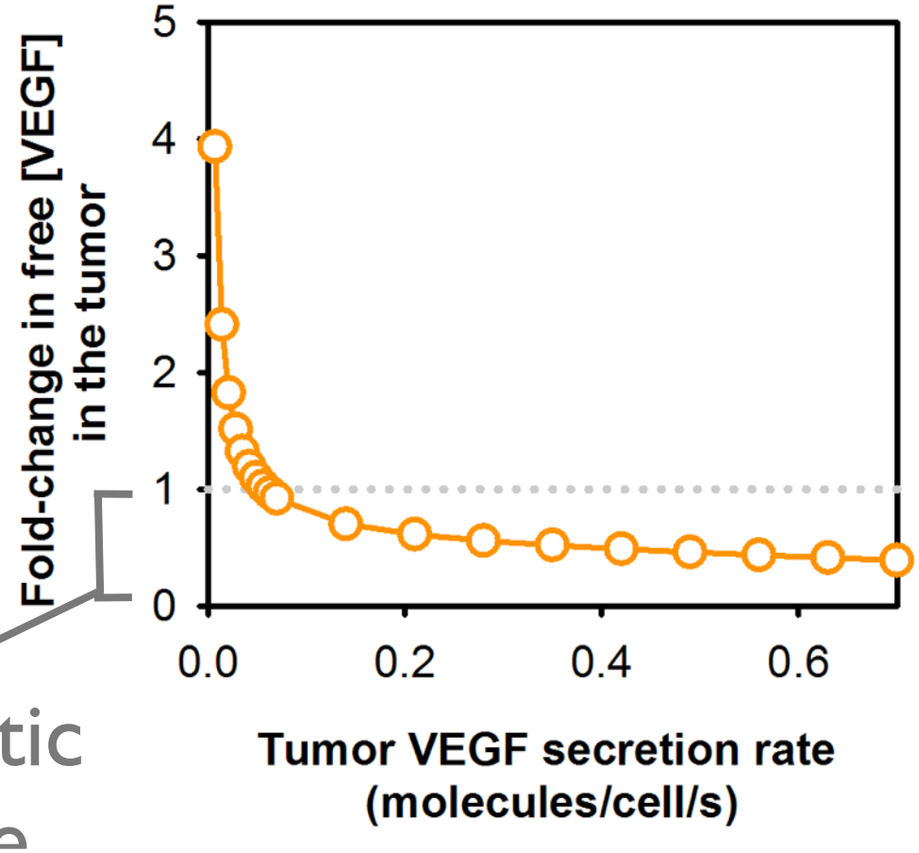
Finley and Popel, J Natl Cancer Inst, 2013

Effect of tumor secretion of VEGF

Relative secretion ratio



Absolute secretion rate

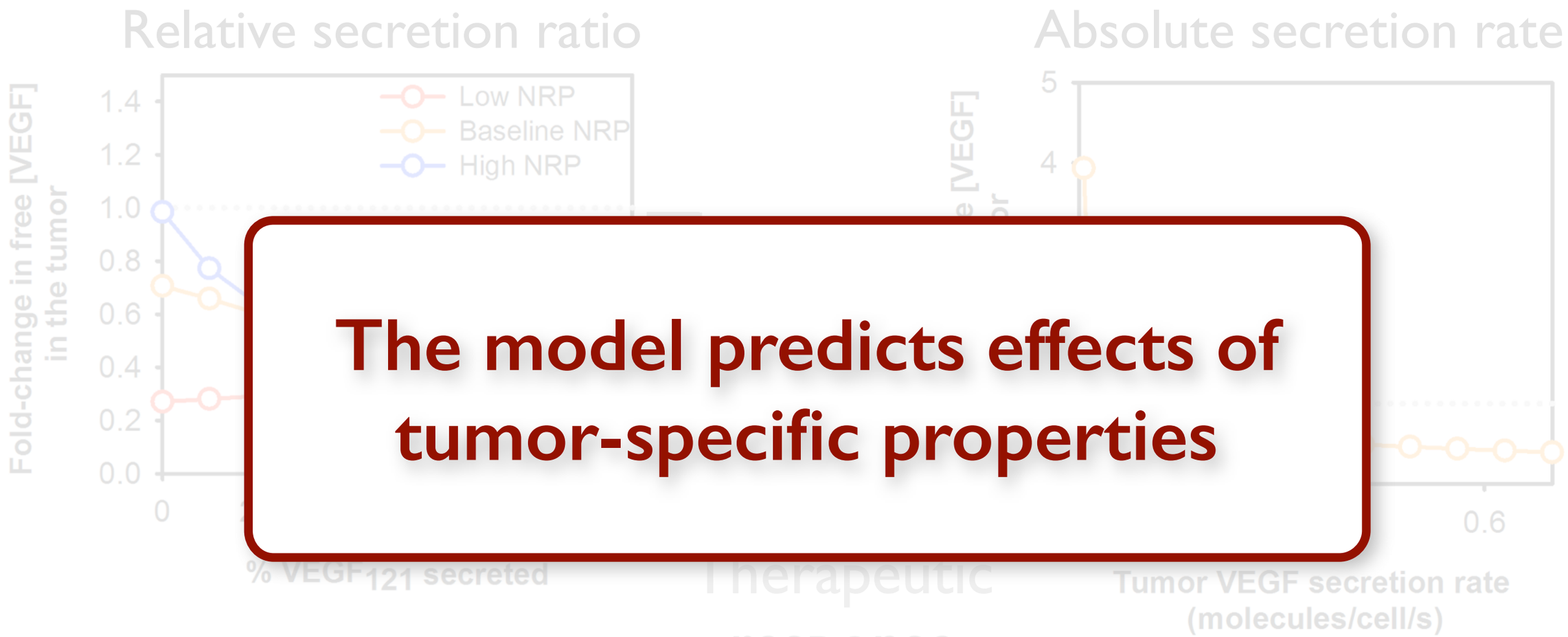


Therapeutic response

Response of tumor VEGF depends on tumor microenvironment

Finley and Popel, J Natl Cancer Inst, 2013

Effect of tumor secretion of VEGF

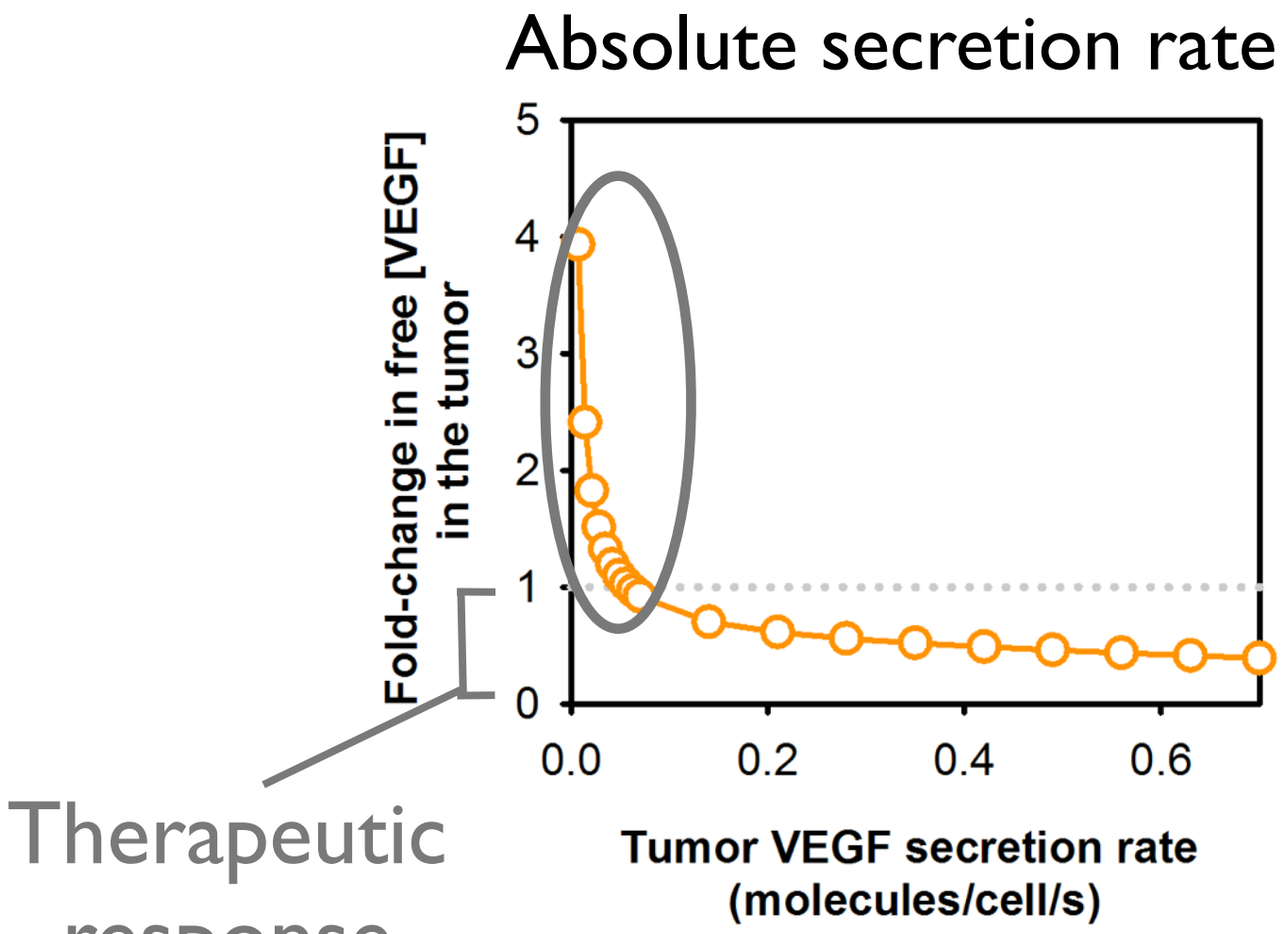


The model predicts effects of tumor-specific properties

Response of tumor VEGF depends on tumor microenvironment

Finley and Popel, J Natl Cancer Inst, 2013

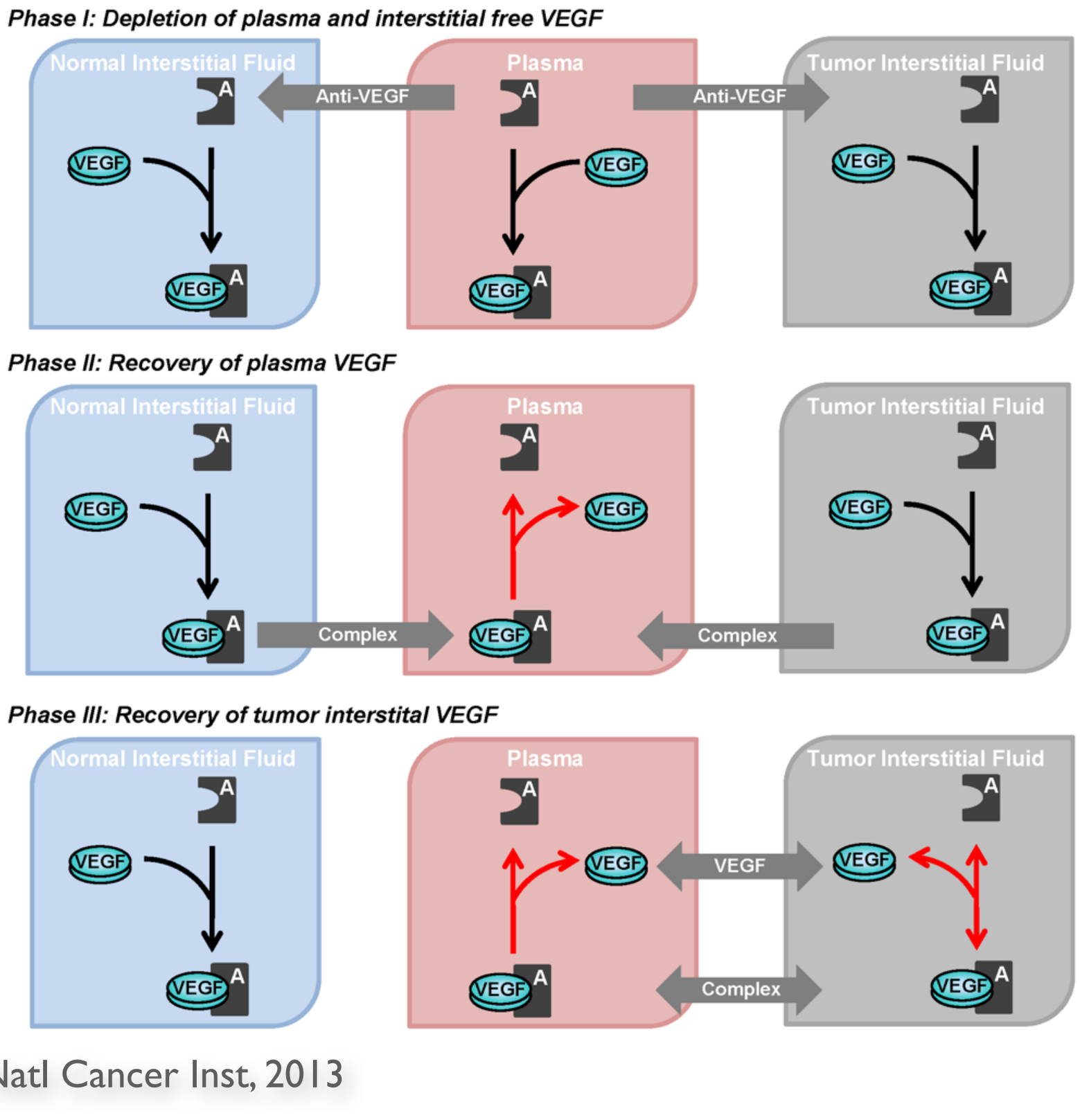
Effect of tumor secretion of VEGF



Response of tumor VEGF depends on tumor microenvironment

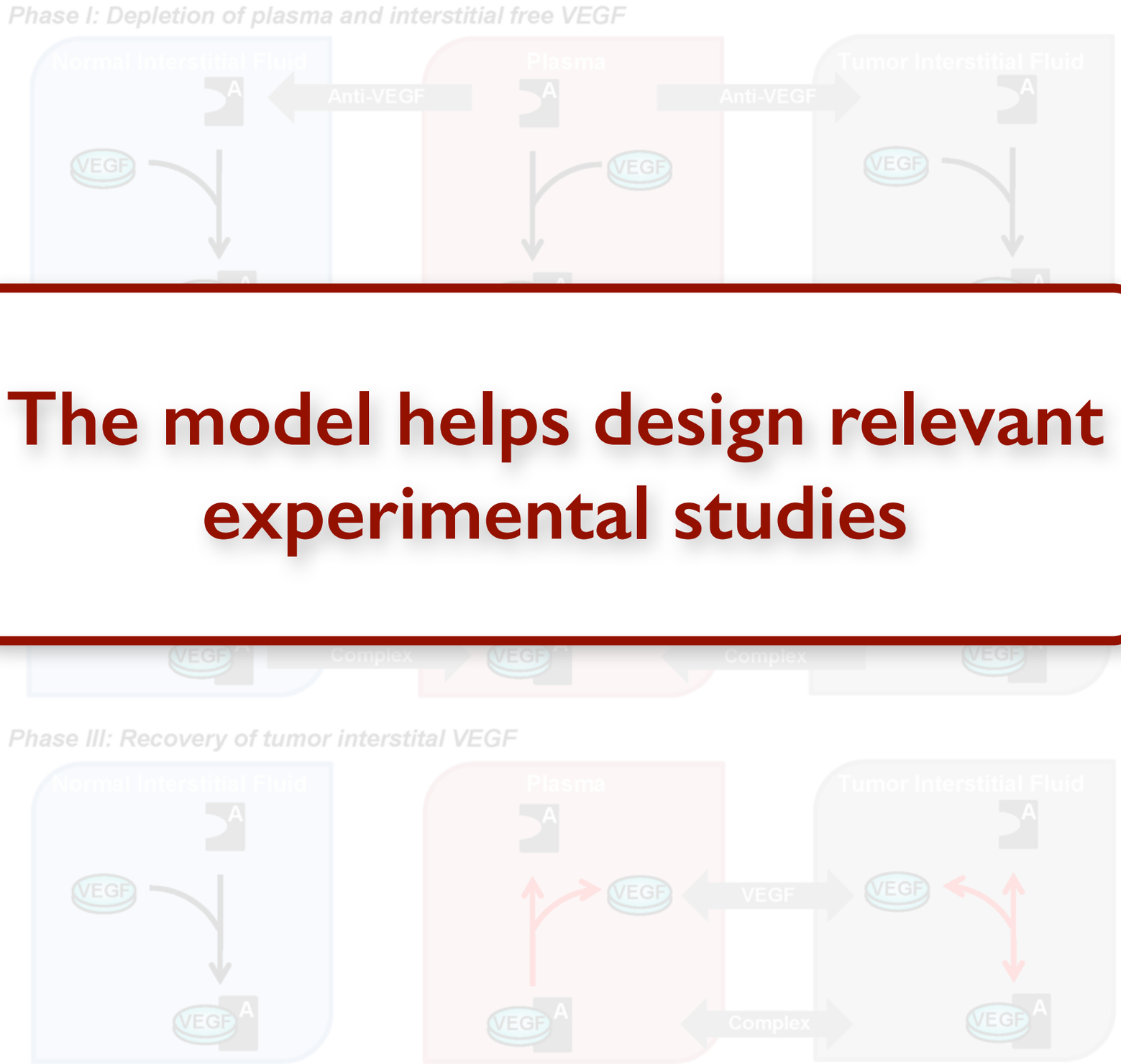
Finley and Popel, J Natl Cancer Inst, 2013

Explanation of response to anti-VEGF therapy



Finley and Popel, J Natl Cancer Inst, 2013

Explanation of response to anti-VEGF therapy



The model helps design relevant experimental studies

Finley and Popel, J Natl Cancer Inst, 2013

Conclusions

- The model predicts the level of tumor VEGF following anti-VEGF treatment
- Anti-VEGF treatment robustly decreases interstitial VEGF for most tumor parameters
- The model predicts that anti-VEGF therapy may have counter-therapeutic effect for some tumors
- Clinical applications:
  - Anti-VEGF mechanism of action
  - Personalized medicine

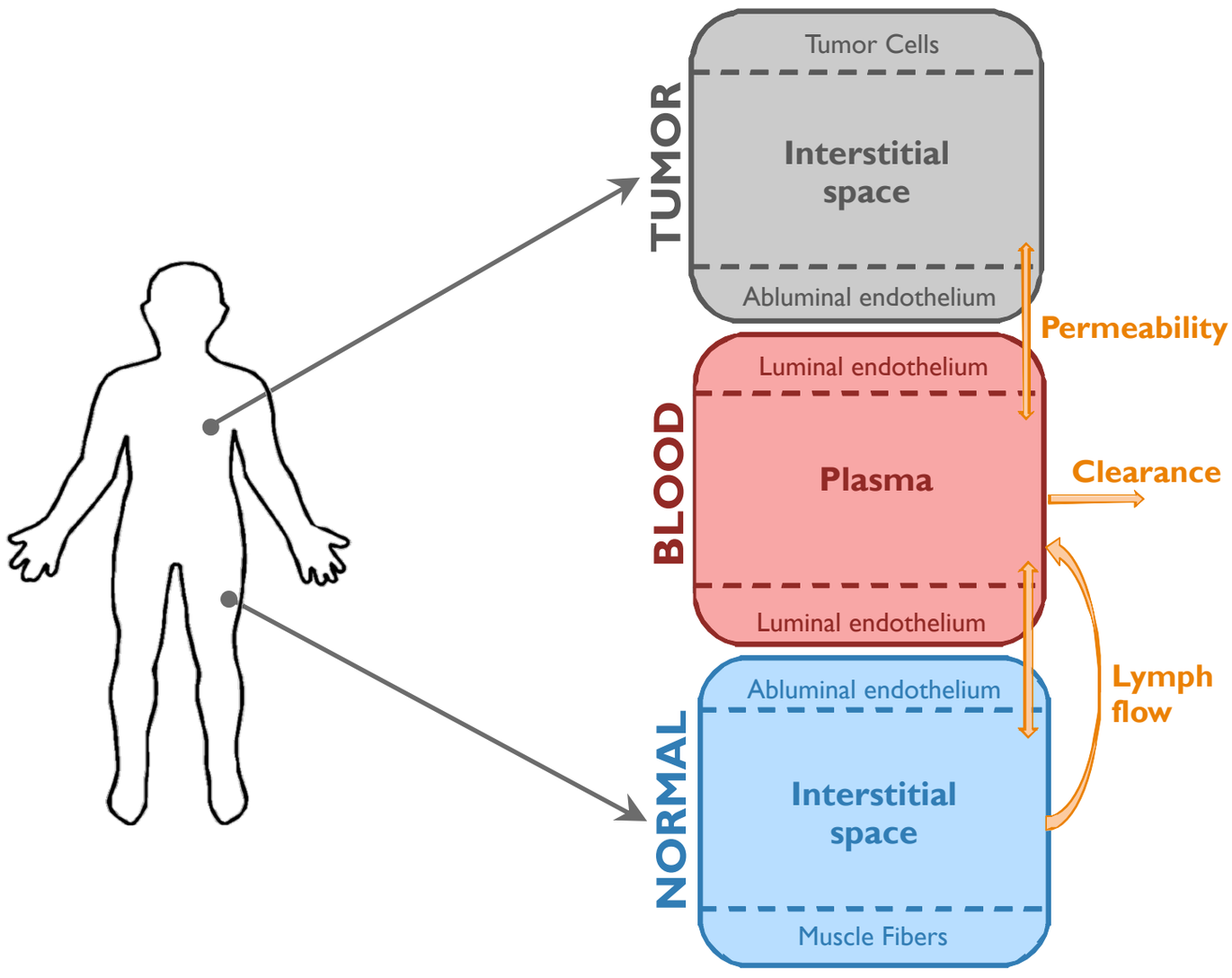
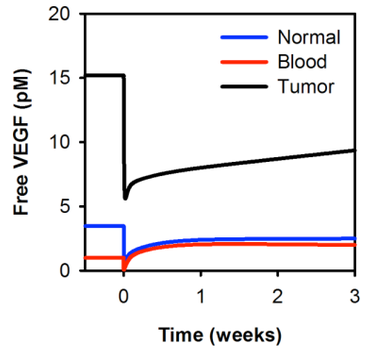
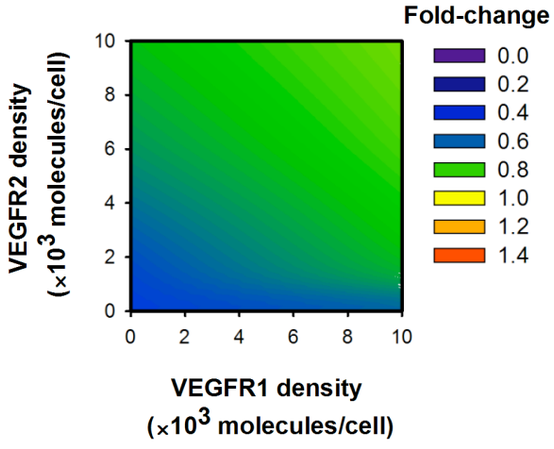
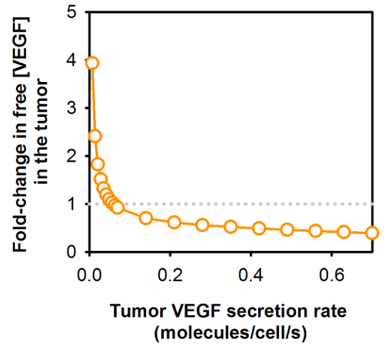
Acknowledgements

Prof. Aleksander Popel

Systems Biology Laboratory
Lawrence Chu
Esak Lee
Kerri-Ann Norton
Niranjan Pandey
Spyros Stamatelos

Lab Alumni
Manjima Dhar
Marianne Stefanini
Phillip Yen

JOHNS HOPKINS
MEDICINE
SCHOOL OF MEDICINE

This work was supported by:
NIH R01 CA138264, F32 CA154213,
and the UNCF/Merck Science Initiative

Anti-angiogenic Cancer Therapies Targeting the VEGF Pathway