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Cancer: An angiogenic disease?

ESMO-EA CR Joint symposium:

Targeted therapies: Promises,
successes and failures

Disclosure slide

- No Conflicts of Interest to declare

Cancer: An angiogenic disease?

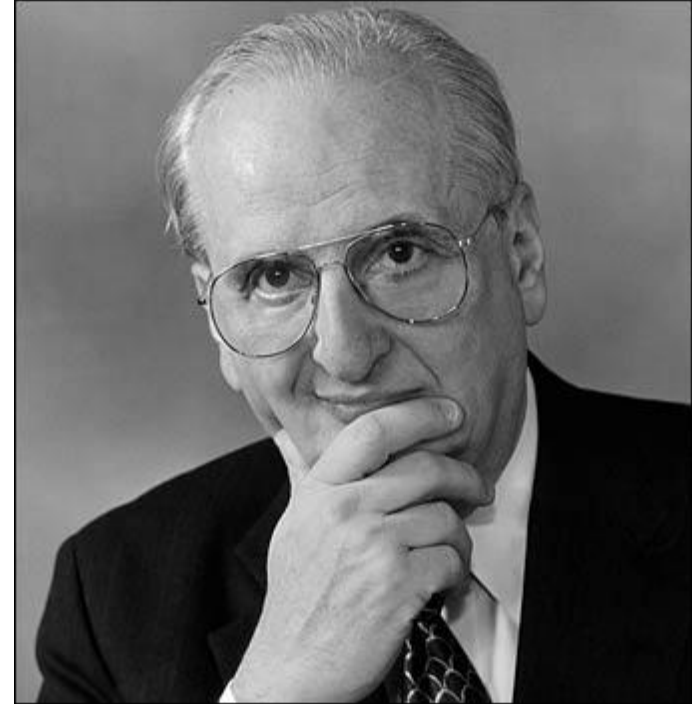
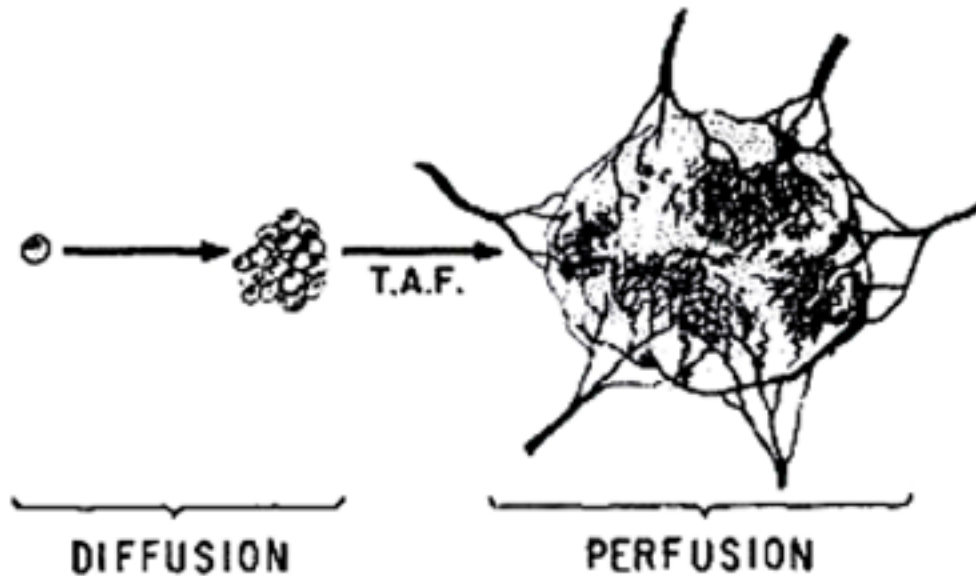
- Angiogenic switch- tumor exit from dormancy
- Angiogenesis and tumor progression
- Angiogenesis and metastasis
- Angiogenesis and response to therapy
- Tumor vascularization, beyond angiogenesis
- Angiogenesis and tumor detection



The angiogenic switch hypothesis

Judah Folkman 1933-2008

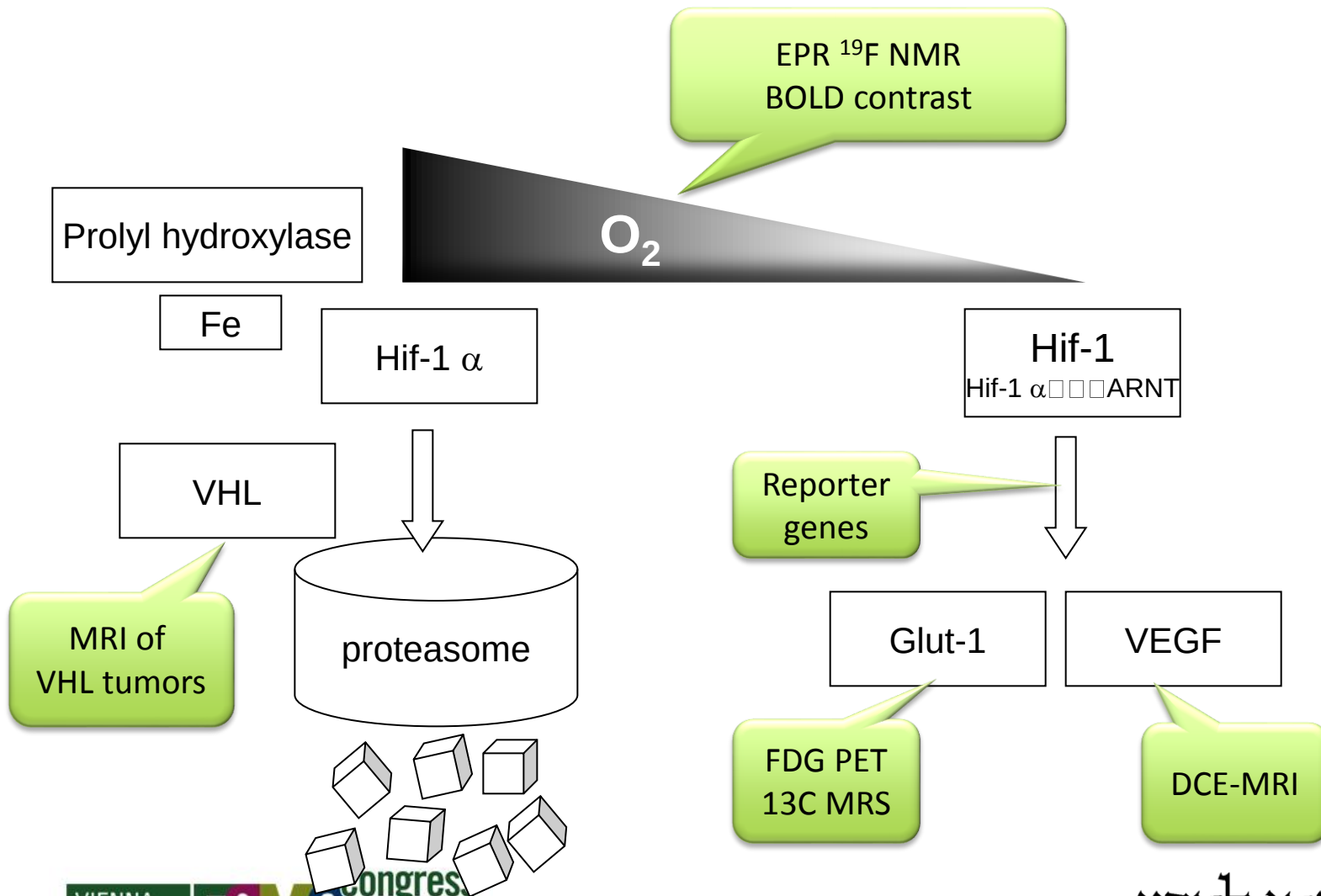
Tumor angiogenesis



Folkman J, Merler E, Abernathy C, Williams G. Isolation of a tumor factor responsible for angiogenesis. J Exp Med. 1971;133:275-288.



Inducing angiogenesis



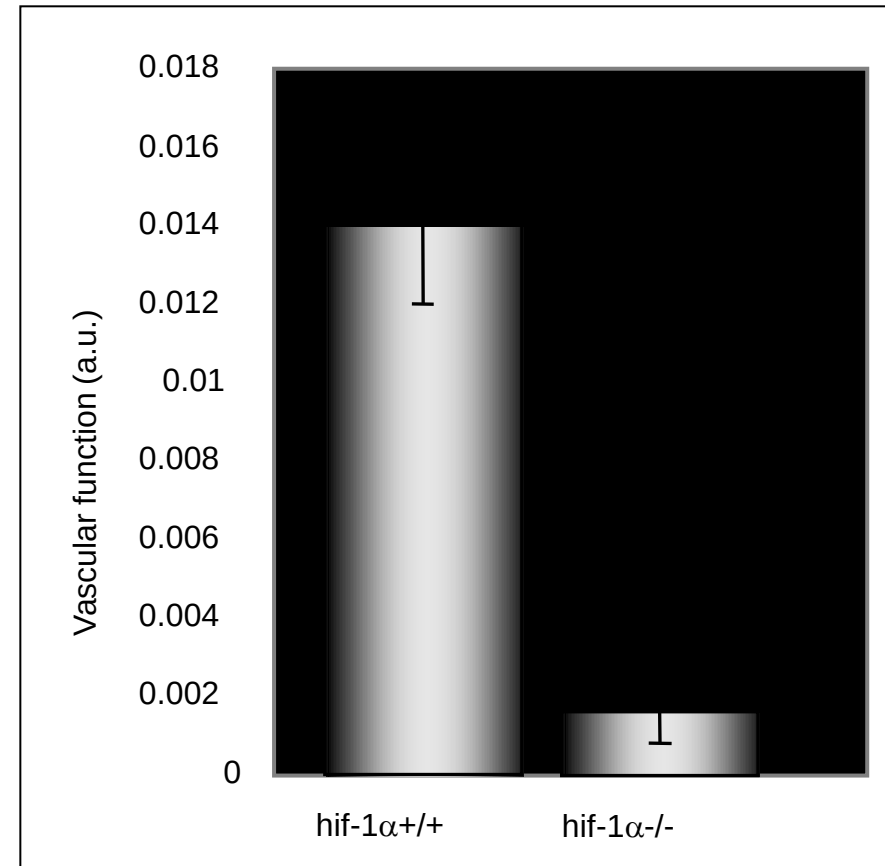
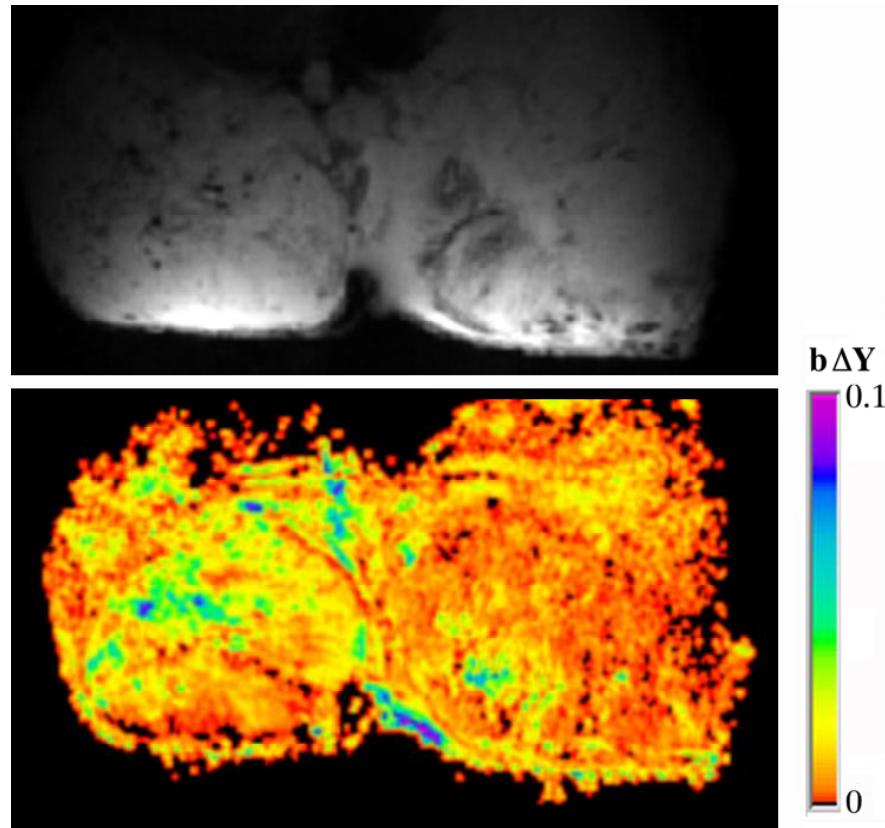
MRI of Hif-1 in tumor angiogenesis

hif-1 α ^{+/+}

hif-1 α ^{-/-}

BOLD contrast MRI

Functional vessels detected by signal change in response to hyperoxia.



Carmeliet et al Nature 1998



Angiogenic switch- tumor exit from dormancy

Imaging the angiogenic switch in ovarian cancer

Transformation

Proliferation

Hypoxia

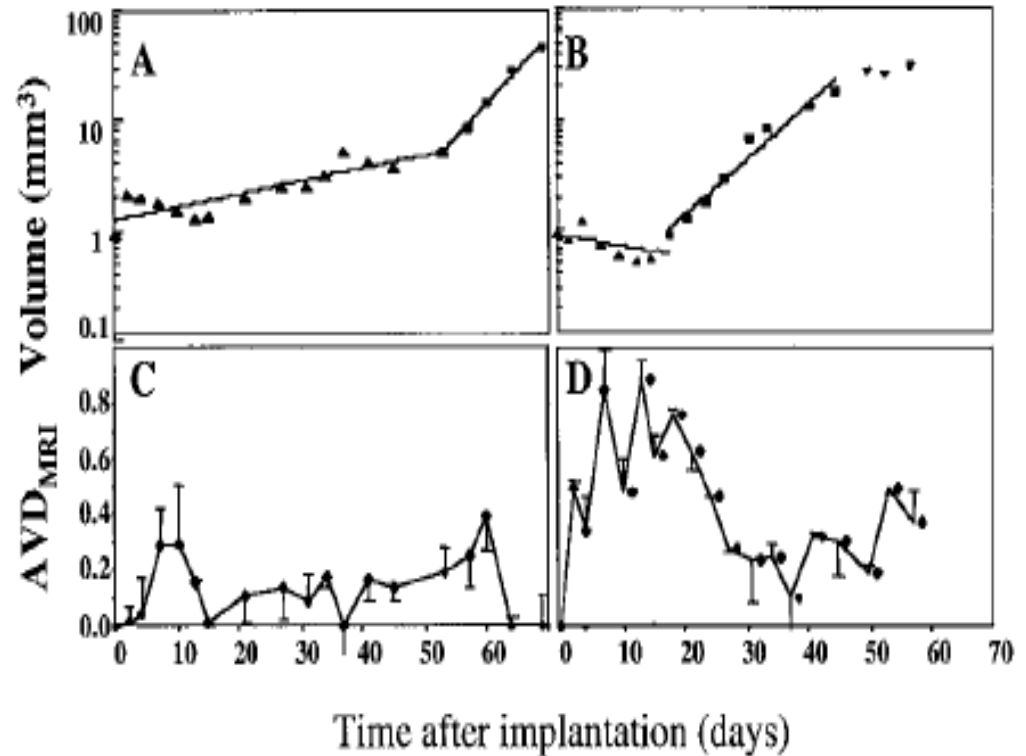
Dormancy

VEGF

Angiogenesis

Normoxia

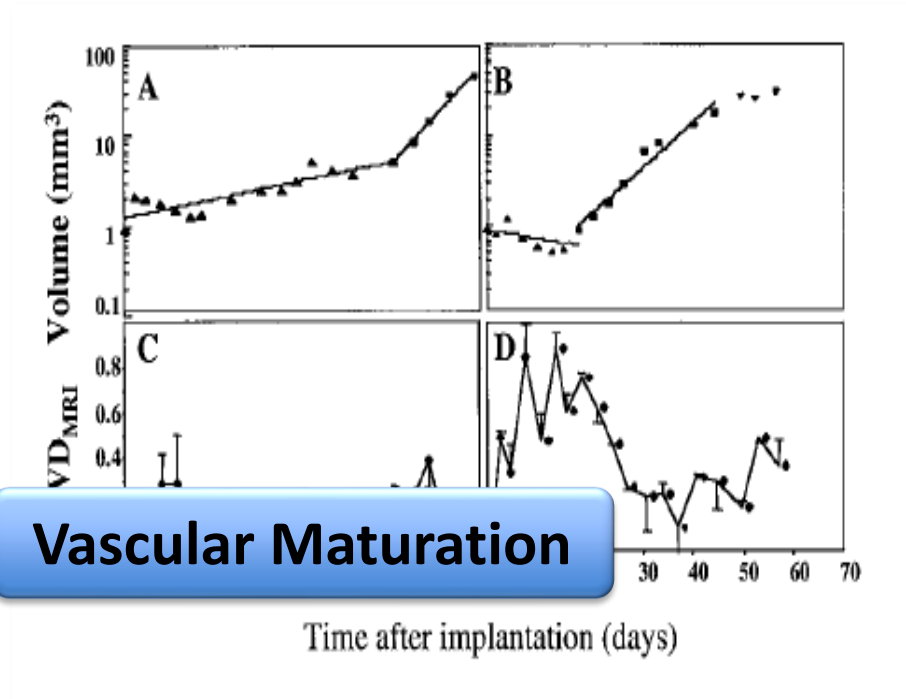
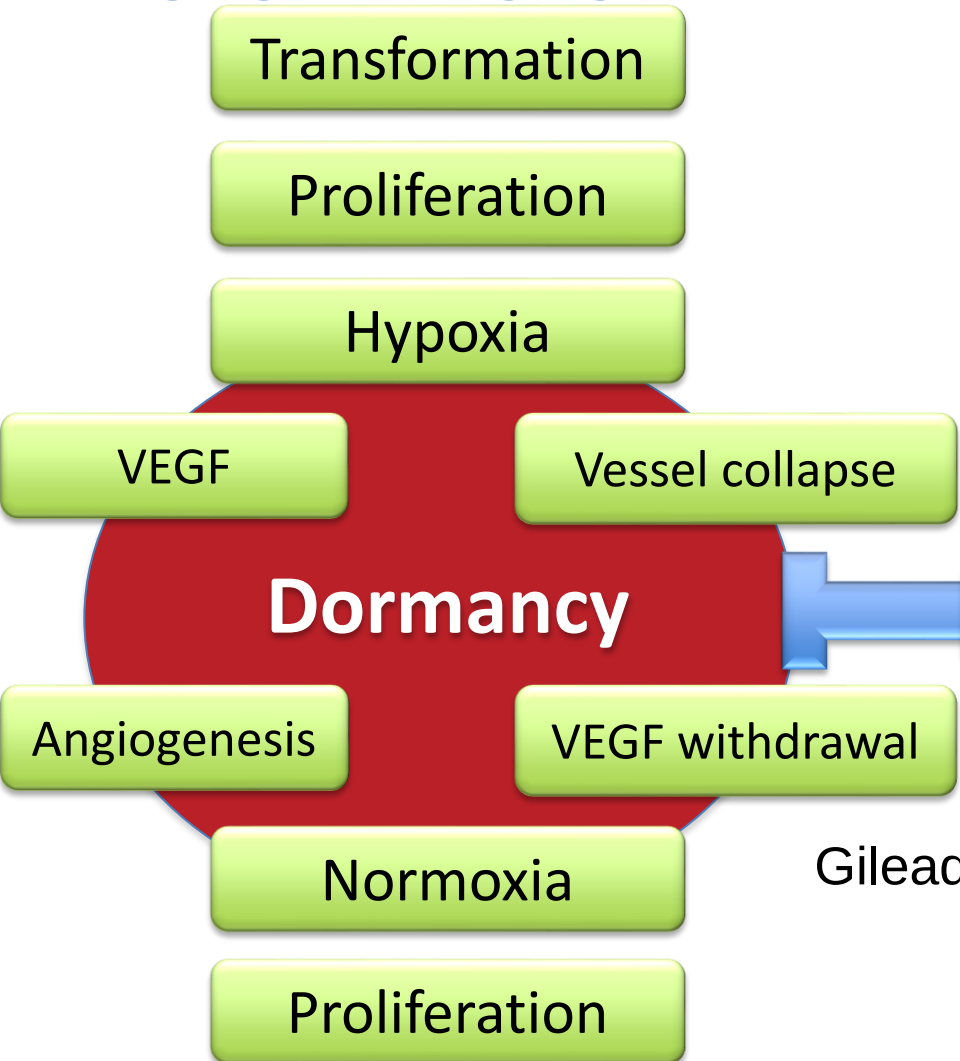
Proliferation



Gilead Neoplasia, IJC 2004; Gilad IJC 2005



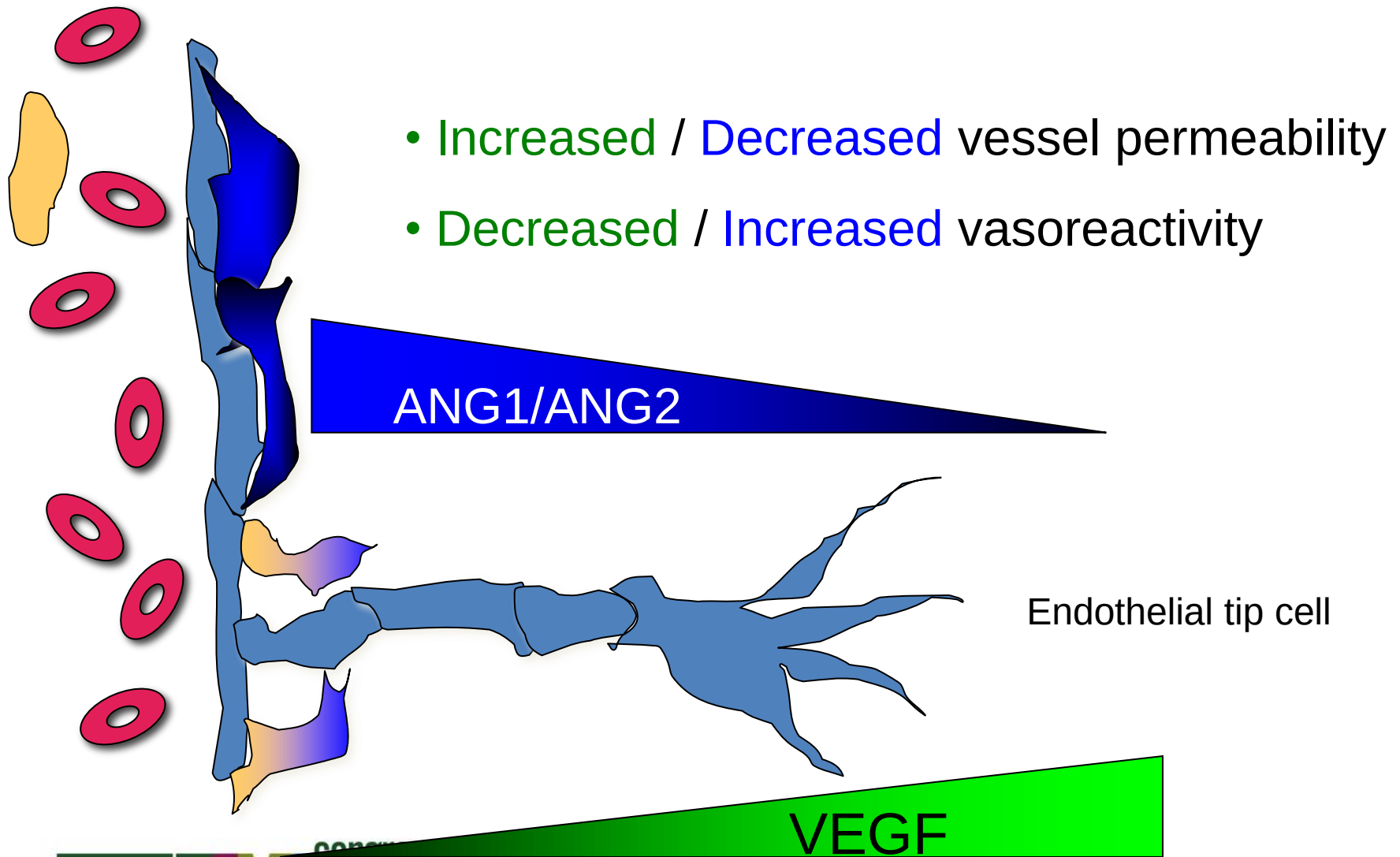
Imaging the angiogenic switch in ovarian cancer



Gilead Neoplasia, IJC 2004; Gilad IJC 2005



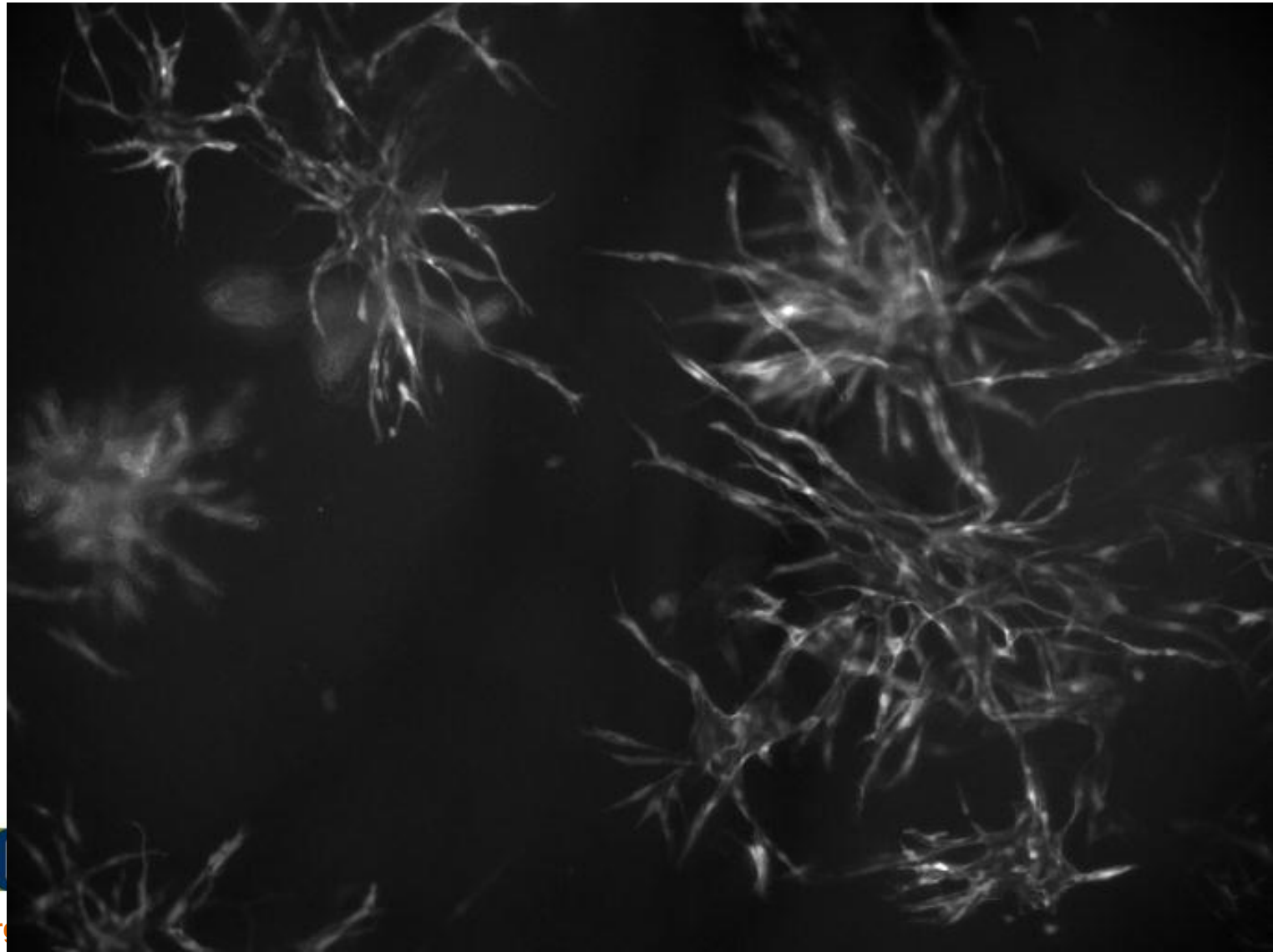
Sprouting Angiogenesis vs Vascular maturation



Sprouting angiogenesis



Michal Weiler-
Sagie



A professional headshot of a man with a shaved head and a friendly smile. He is wearing a white lab coat over a maroon shirt and a grey and white striped tie. On the left side of his lab coat, there is a circular emblem with a blue border and a yellow interior, featuring a stylized building. Below the emblem, the text "Assaf A. Glad MD" is printed in a blue, cursive-style font. The background is a soft, out-of-focus blue and grey.



ESMO Low CO

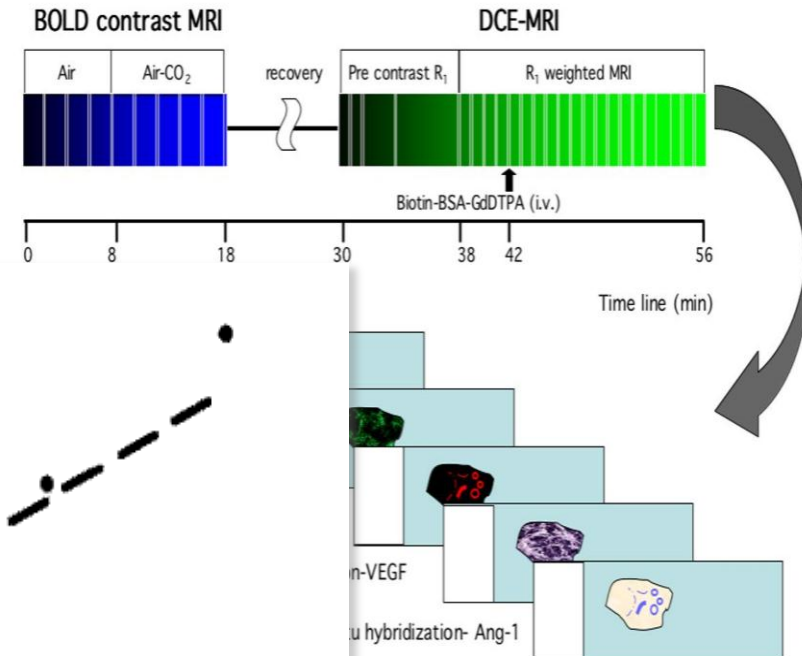
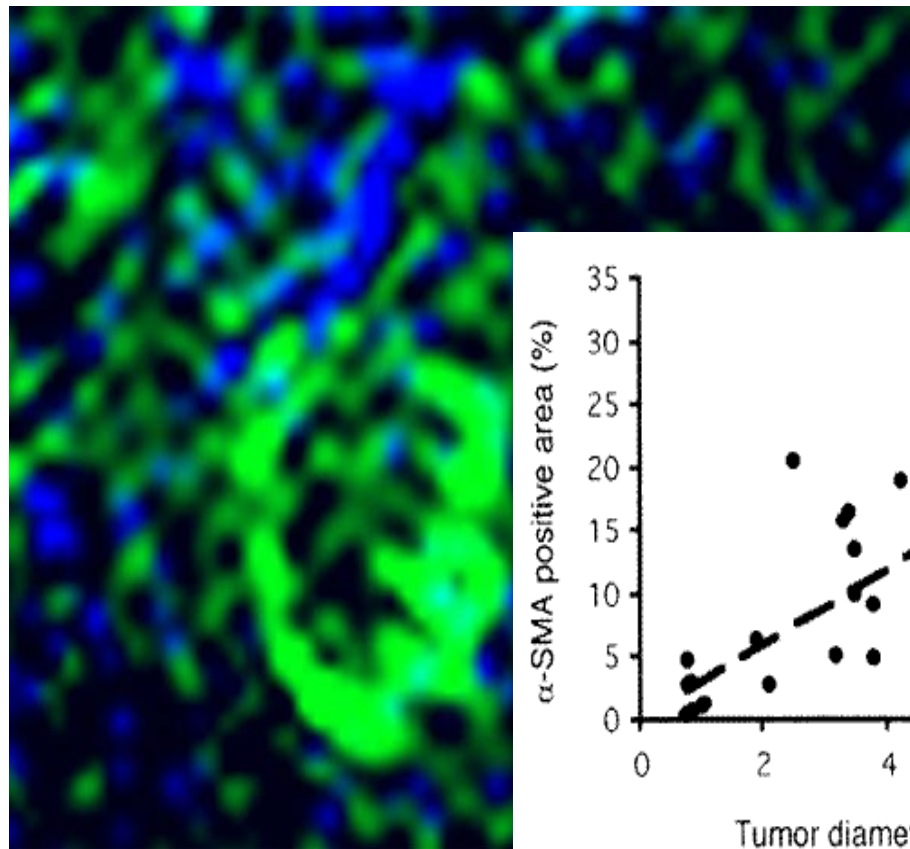
www.esmo2012.org

 מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE



Angiogenesis and tumor progression

Uncoupling between vascular maturation and permeability:
MLS human epithelial ovarian carcinoma in nude mice



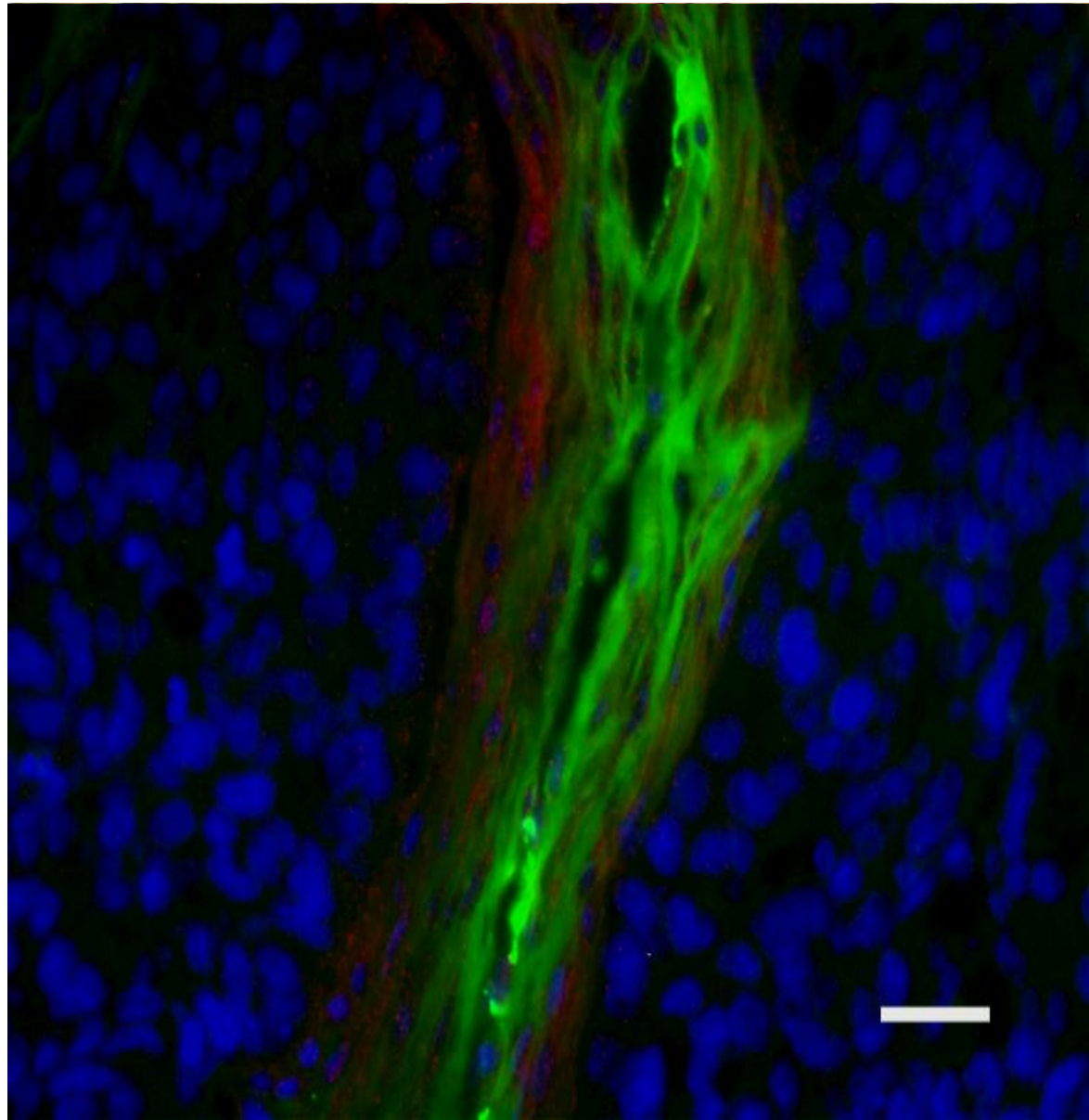
Assaf Gilad et al Int J Cancer 2005

Host-tumor interactions in angiogenesis and vascular maturation

Blue DAPI

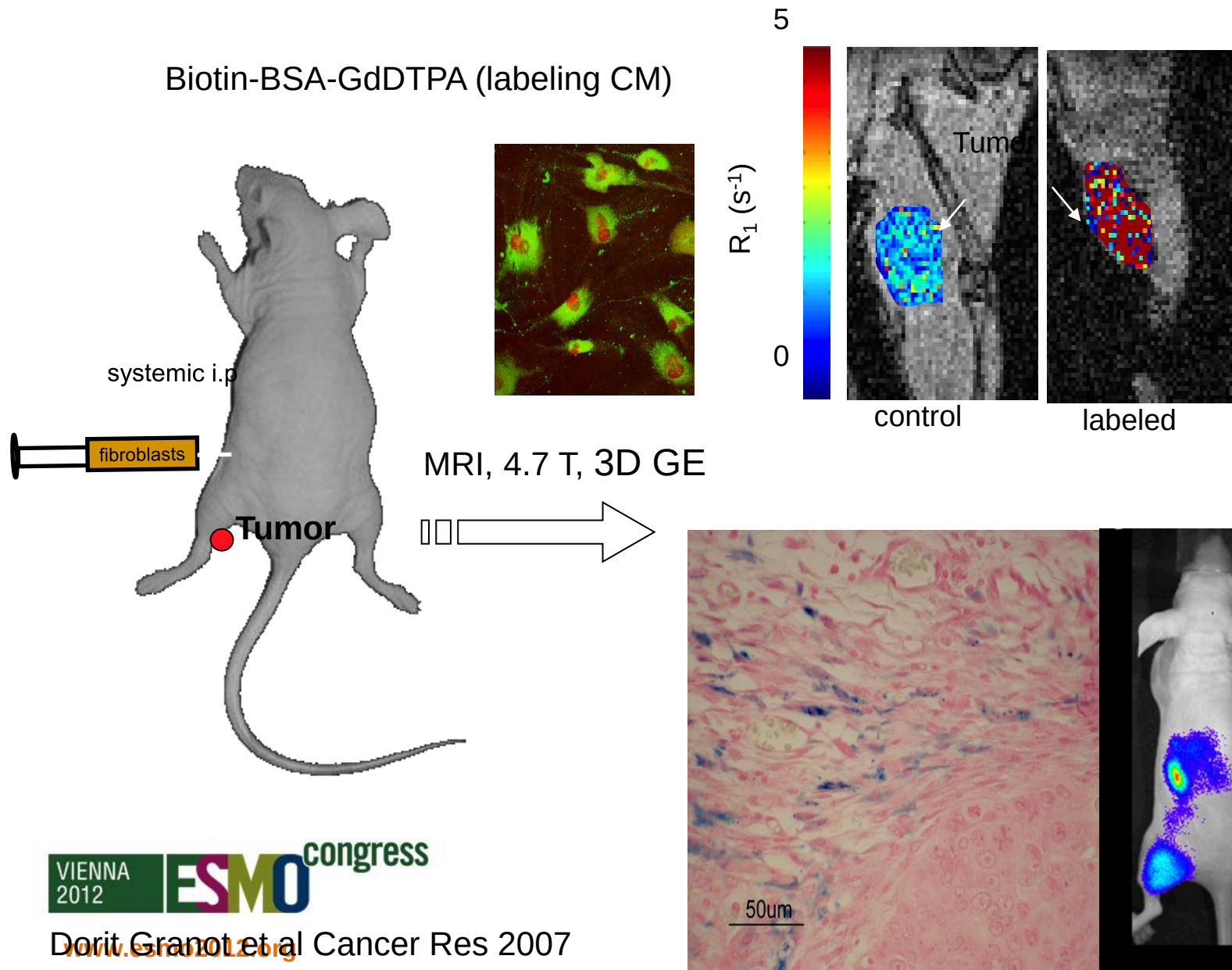
Red α SMA

Green biotin-BSA



Gilead et al Int J Cancer 2004

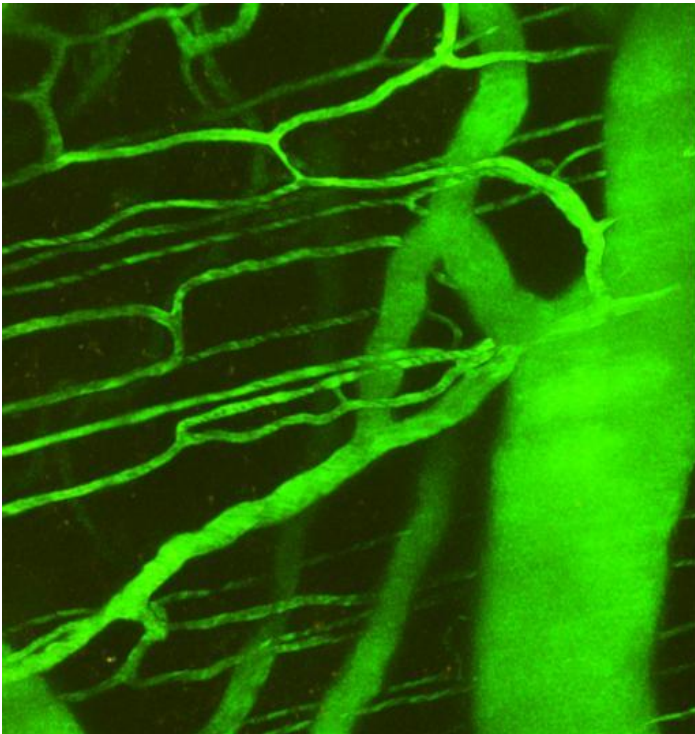
Fibroblasts recruitment into ovarian carcinoma tumors



Dorit Granot

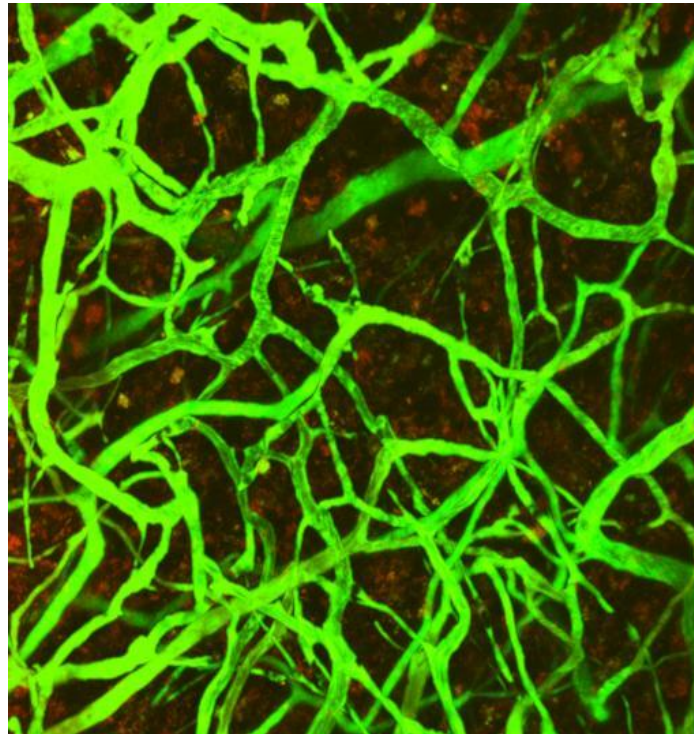
Two photon microscopy

Recruitment of fibroblasts into ovarian carcinoma tumors



Subcutaneous skin flap

No tumor



Subcutaneous skin flap

Ovarian carcinoma

Addadi et al intravital microscopy



Yoseph Addadi



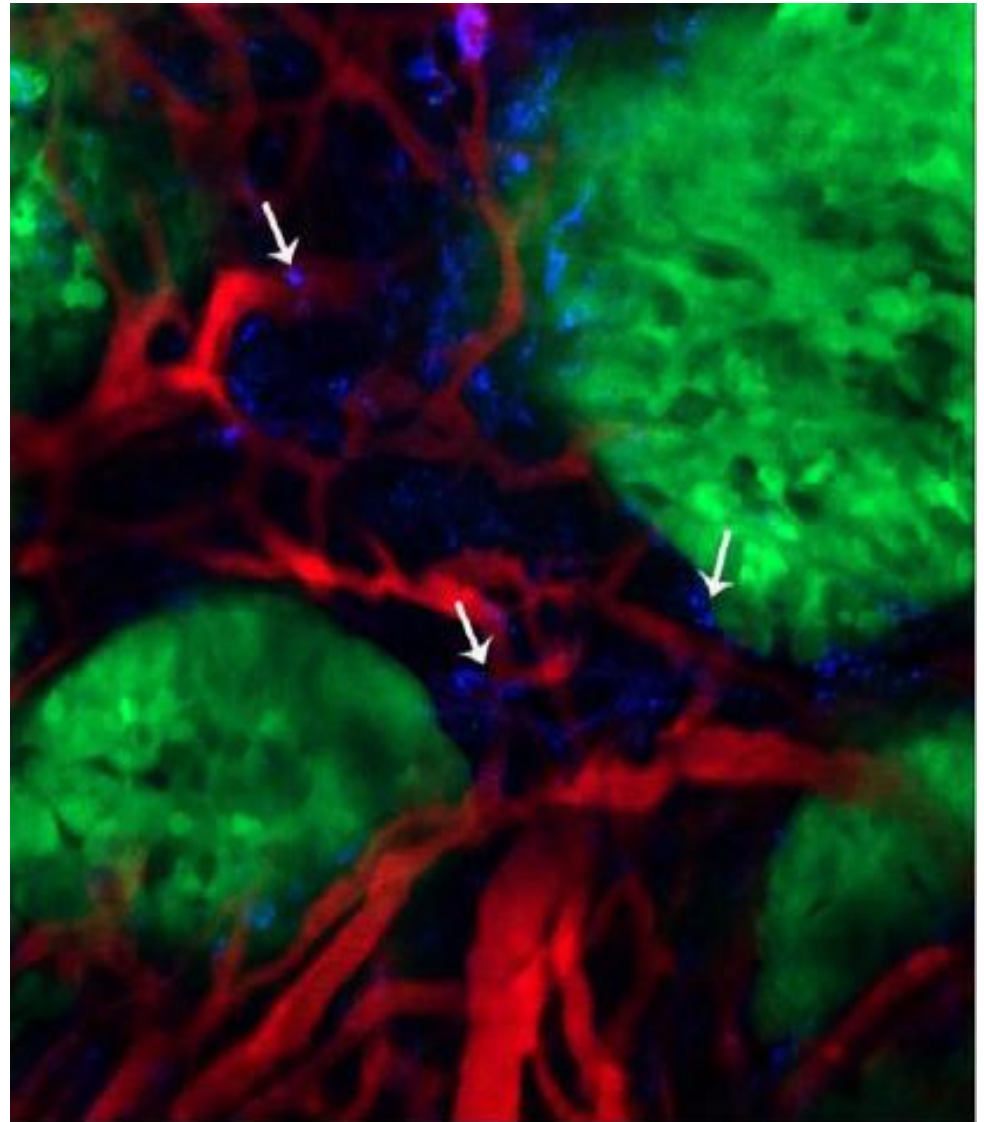
Fibroblast trans-differentiation to myofibroblasts

Green MLS EGFP
 ovarian tumor

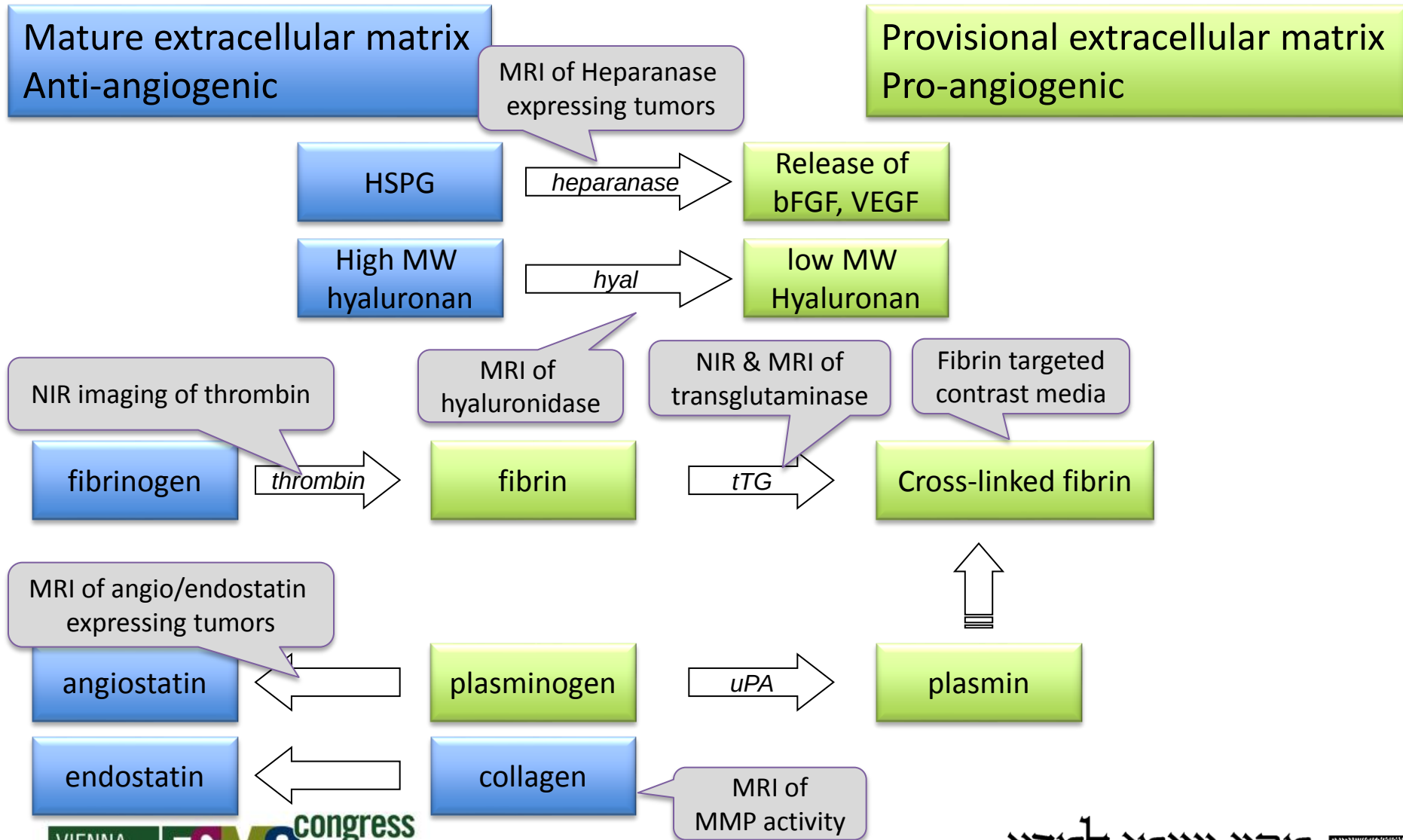
Blue alphaSMA-DsRed
 fibroblasts

Red Blood vessels: DiD
 iv

Addadi 2012, unpublished

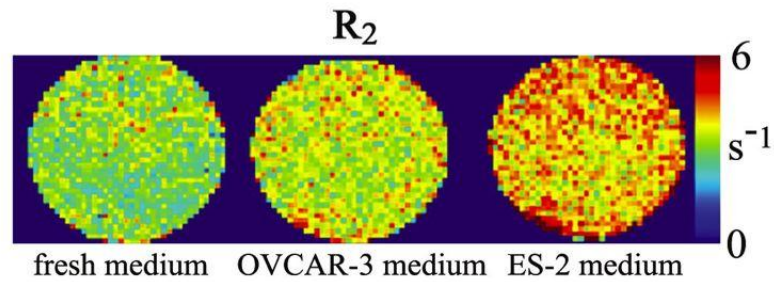


Overcoming antiangiogenic inhibition

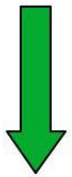


In vitro

Conditioned media from
ovarian carcinoma cells

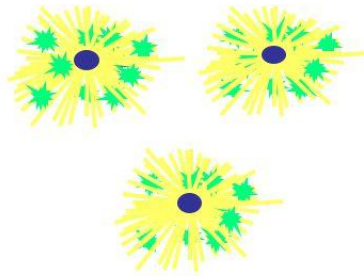


High MW hyaluronan
anti-angiogenic

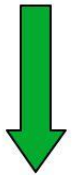


Hyal-2

Low relaxivity

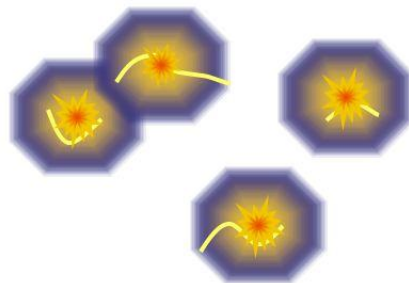


Low MW hyaluronan
pro-angiogenic



Hyal-1

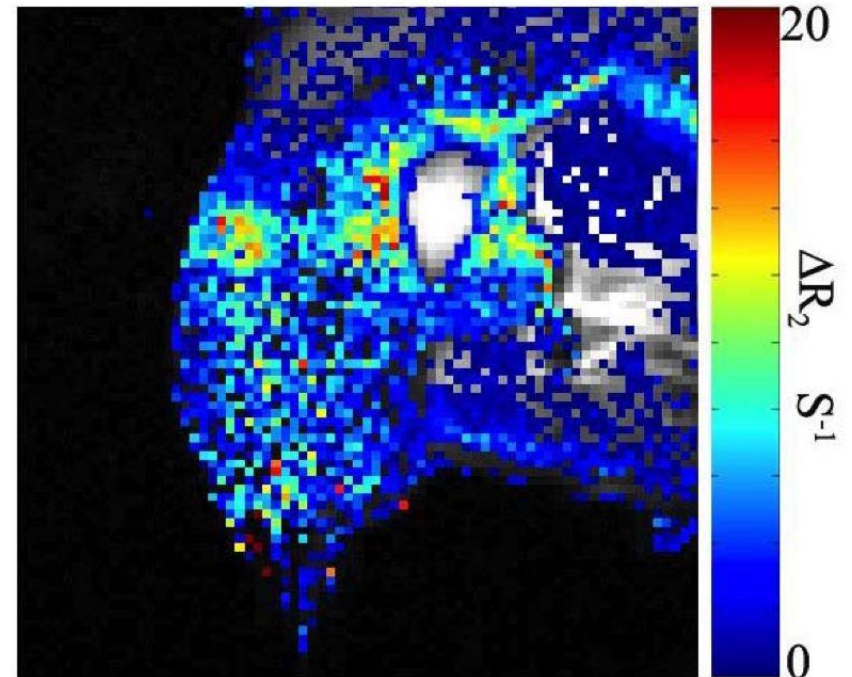
High relaxivity



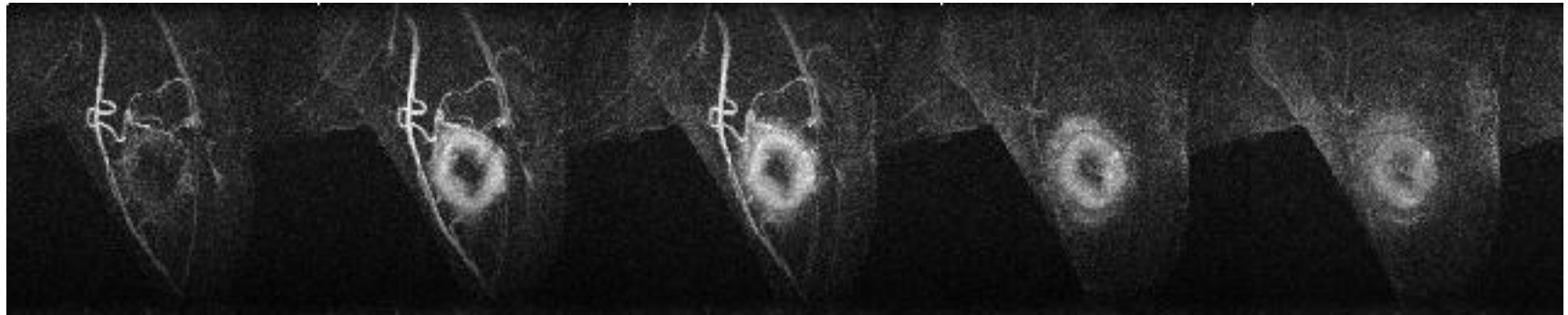
Complete degradation
di-tetra saccharides

In vivo

MLS human ovarian carcinoma tumor



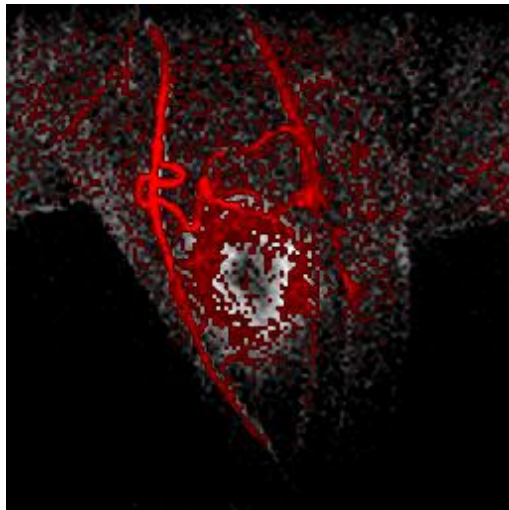
Separation of leak and drain: *in vivo* avidin chase



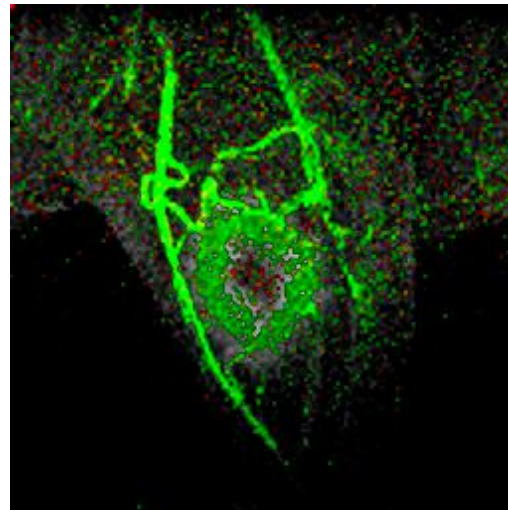
1
Contrast enhancement
(0-3 min postcontrast)

30 60
Avidin chase
(60-72 postcontrast)

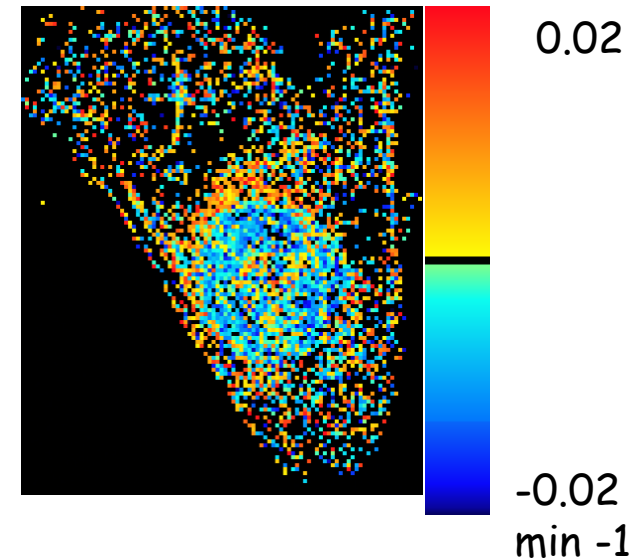
70 120 min
Avidin
Rate of drain



Red: signal increase



Green: signal decrease



0.02

-0.02
min -1



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Acknowledgements



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