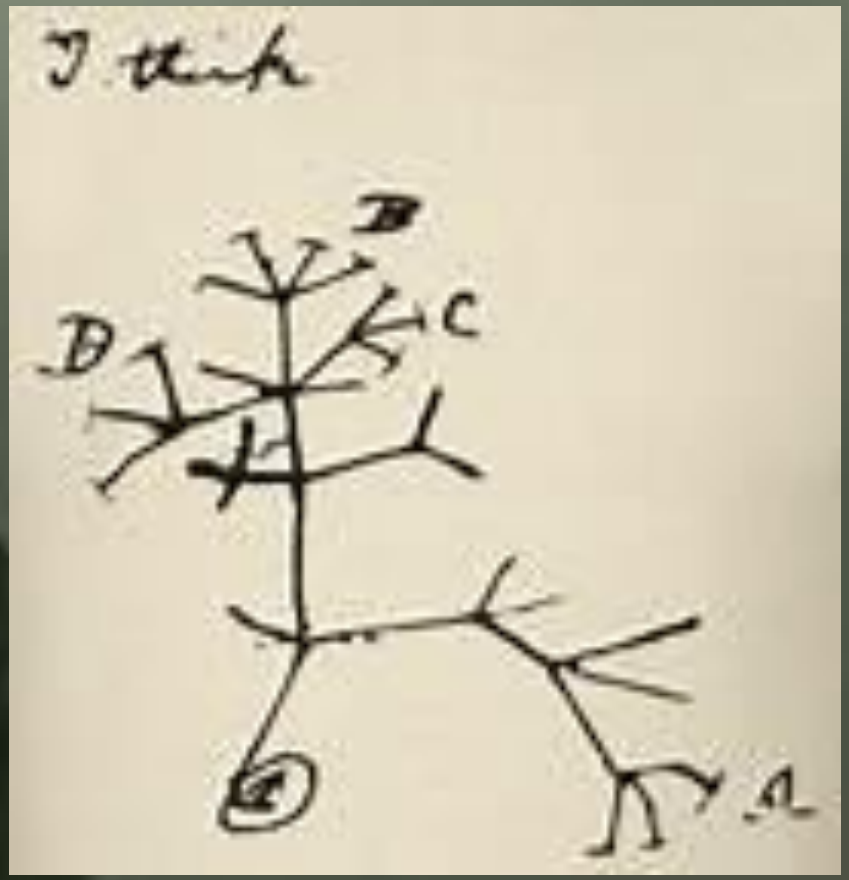
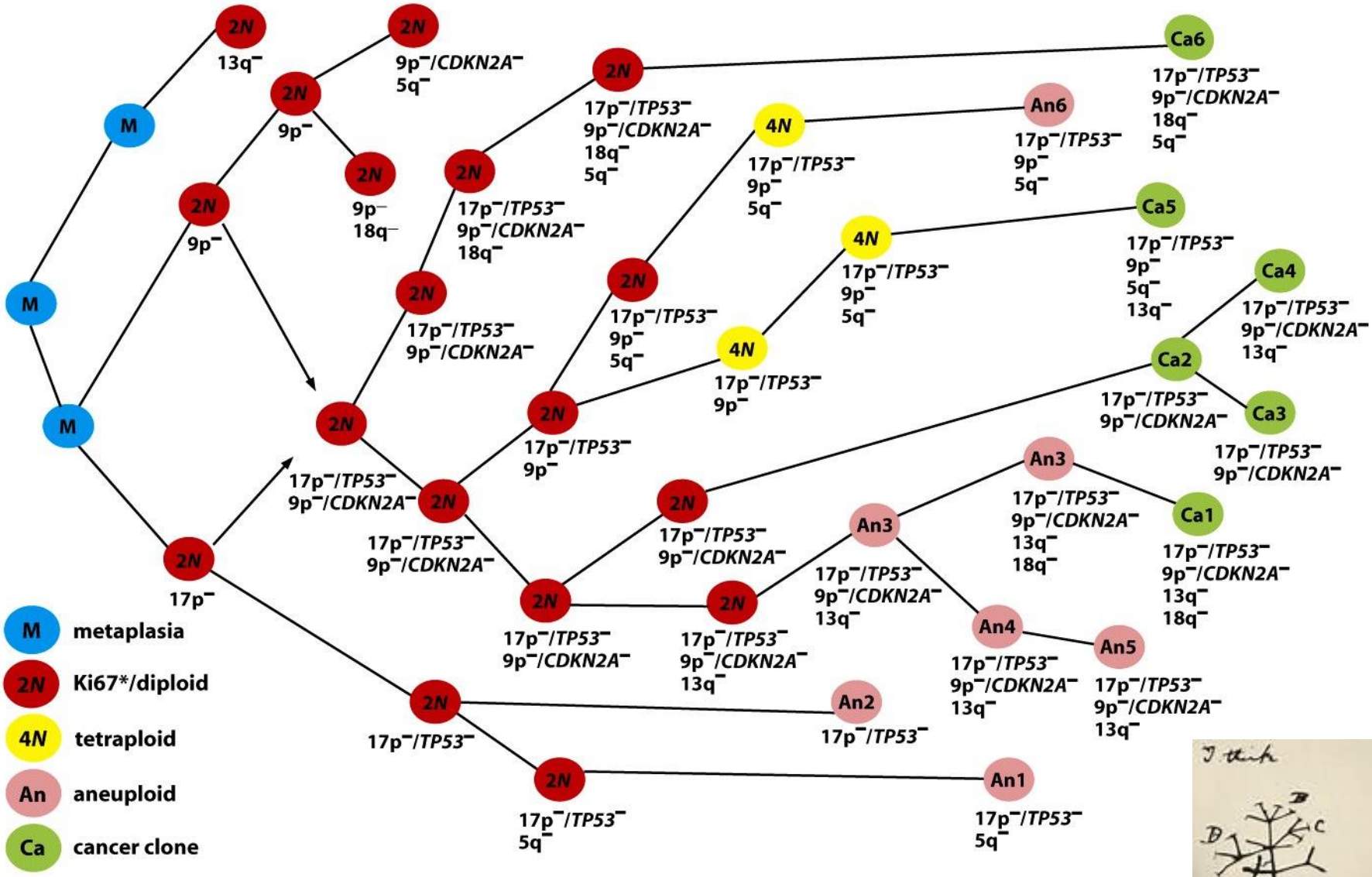
Molecular Imaging in The Precision Medicine Era: Challenges and Perspectives



ONE CELL OF ORIGIN, MULTIPLE GENOTYPES WITHIN THE VERY SAME CANCER

(...and, *I think*, different molecular diseases just affecting the same organ)



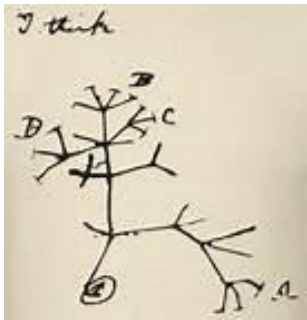
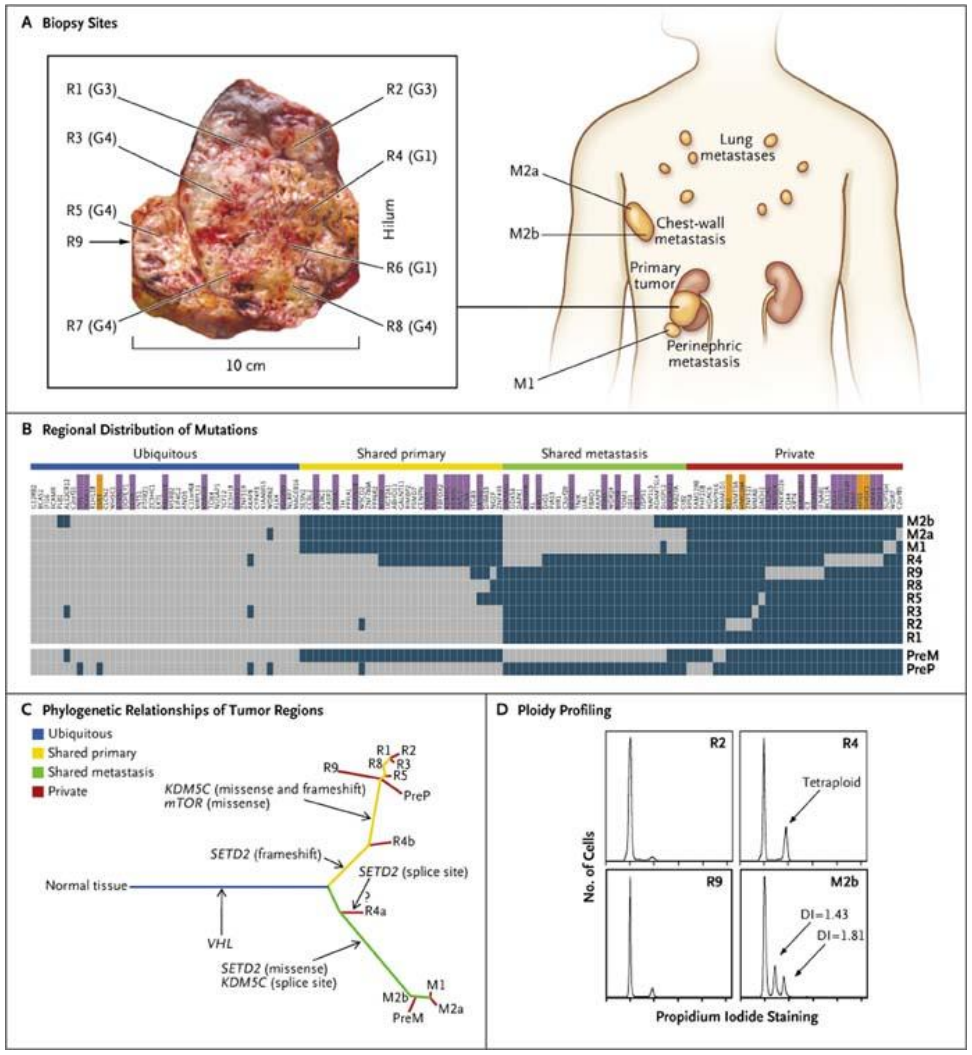


Figure 11.11b *The Biology of Cancer* (© Garland Science 2007)

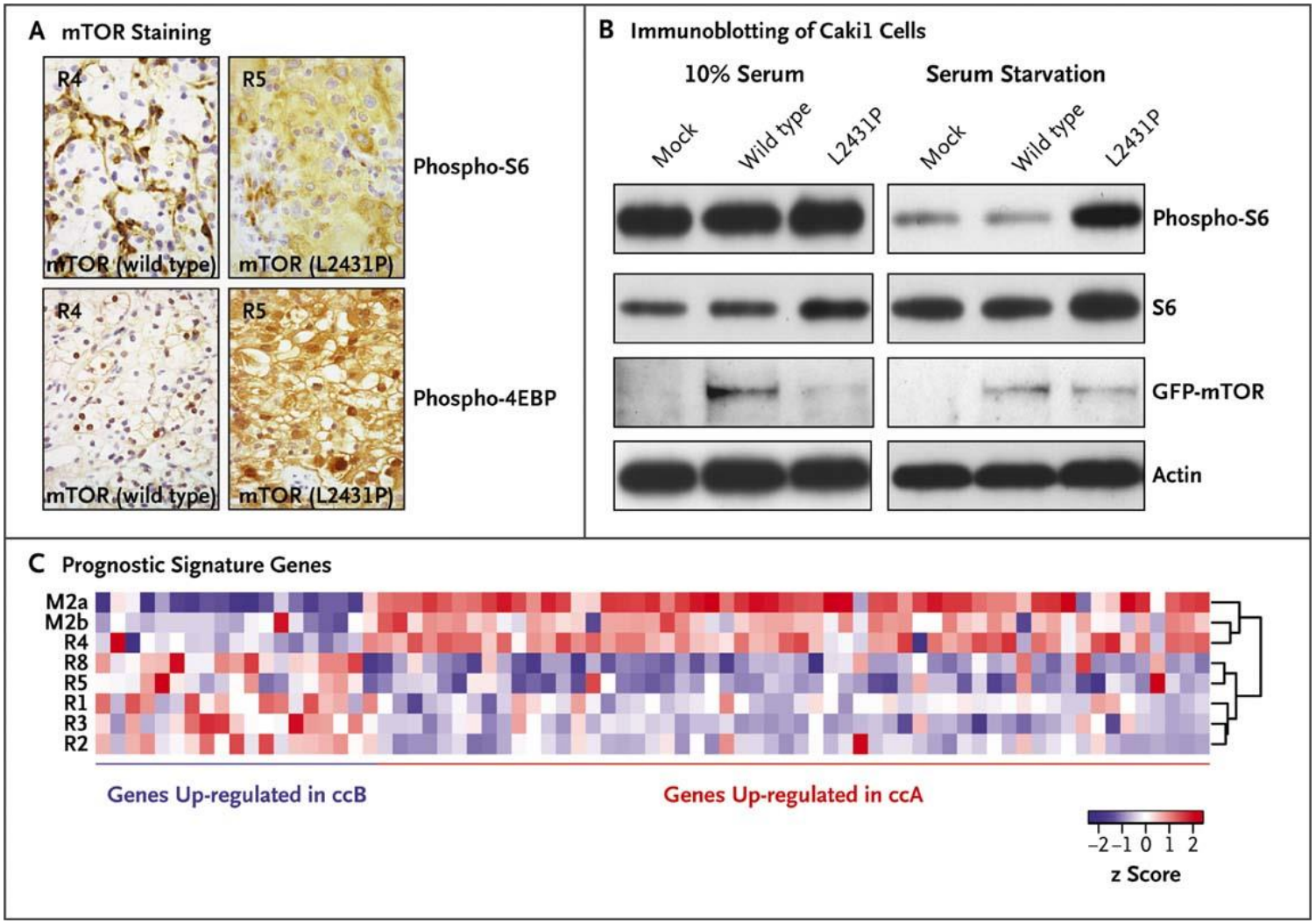
GENETIC INTRATUMOR HETEROGENEITY AND PHYLOGENY IN PATIENT



Gerlinger M et al. N Engl J Med 2012;366:883-892

The NEW ENGLAND JOURNAL of MEDICINE

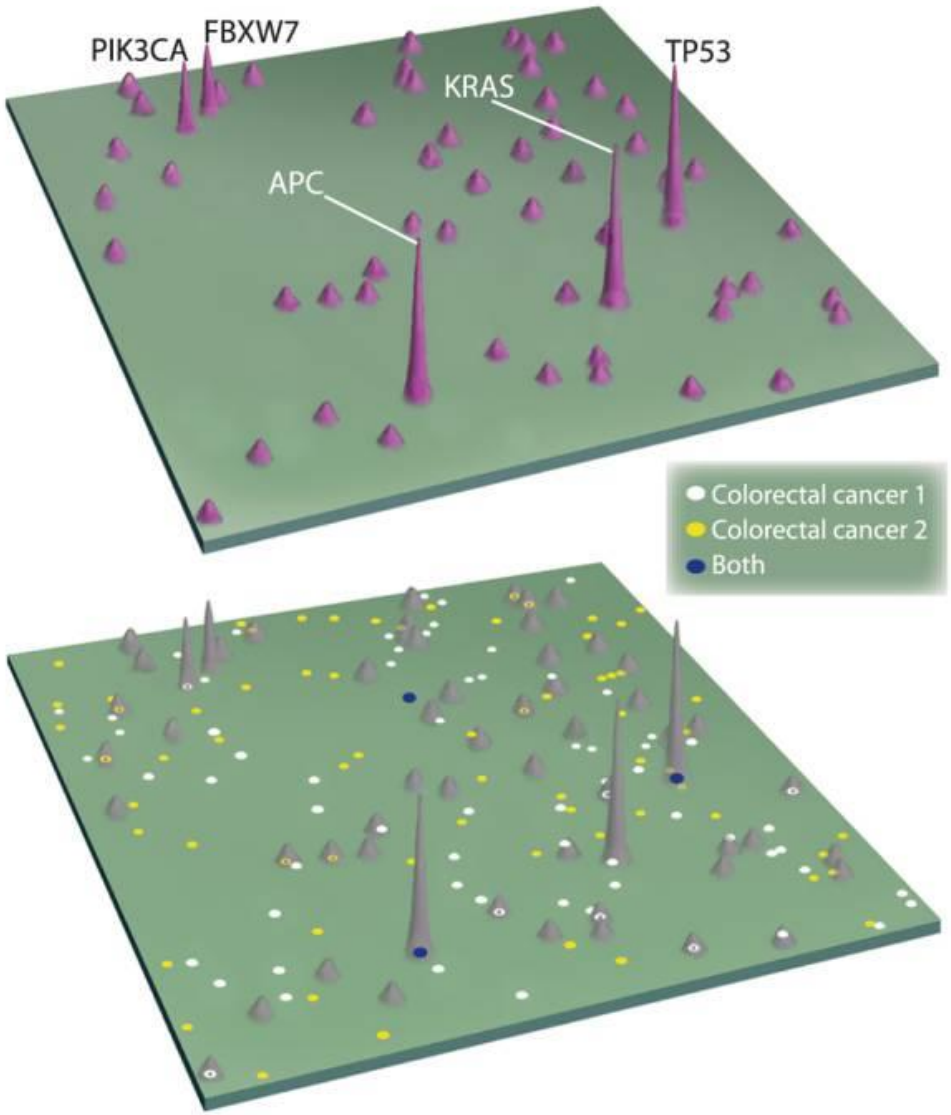
CORRELATIONS BETWEEN GENOTYPE AND PHENOTYPE IN PATIENT 1



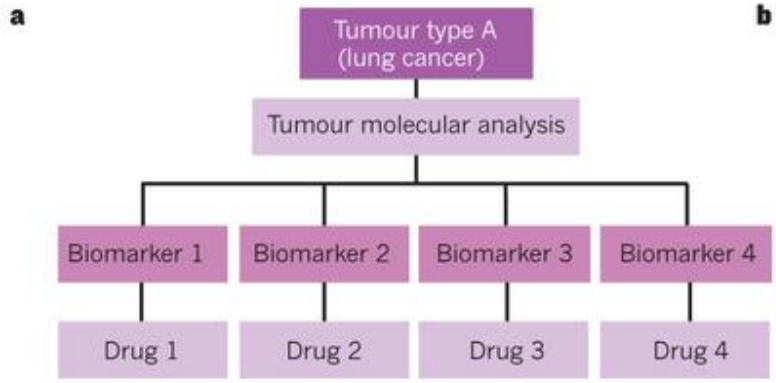
Gerlinger M et al. N Engl J Med 2012;366:883-892

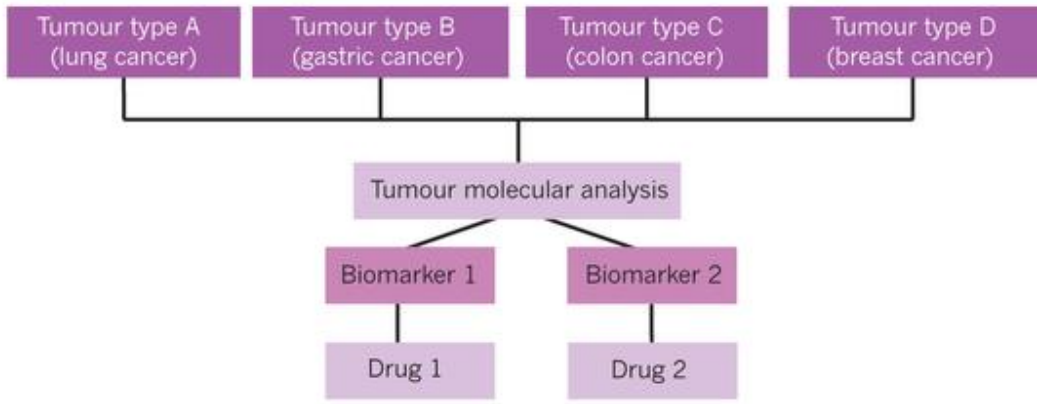
The NEW ENGLAND JOURNAL of MEDICINE

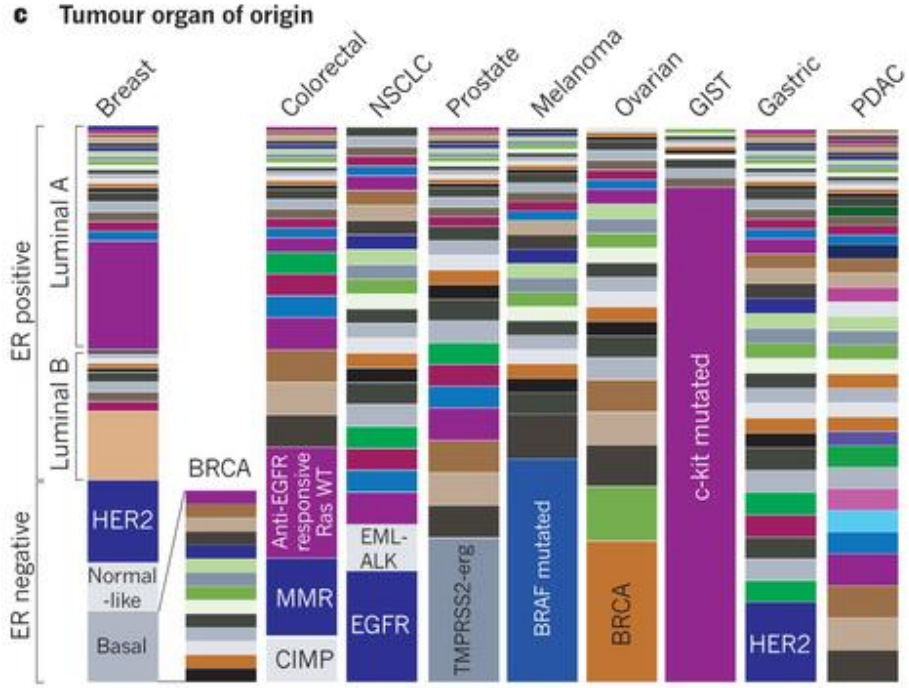
Mutation landscapes of individual tumors and the prediction of driver mutations in cancers

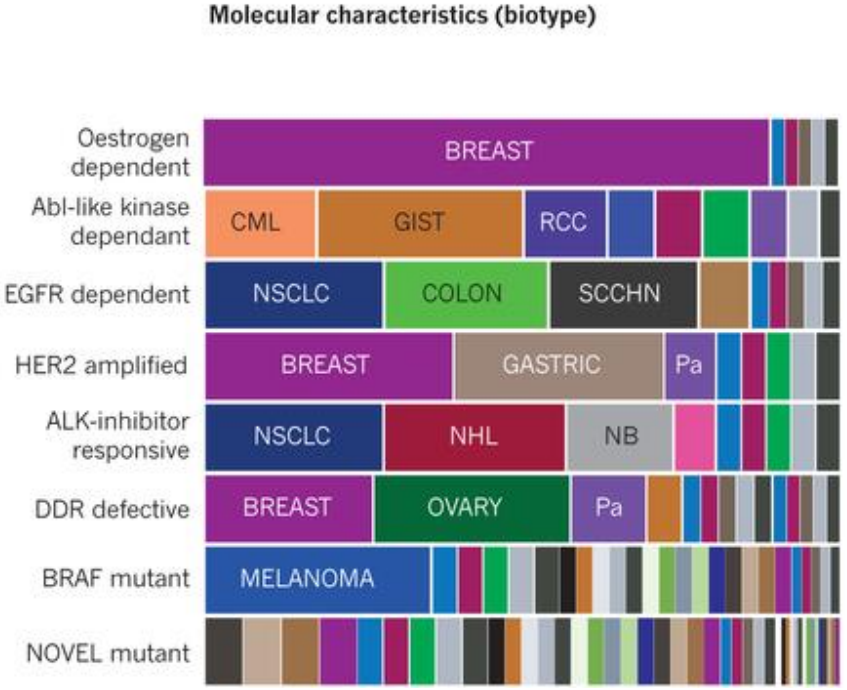


Umbrella and Basket trials: treating mutations, nor tumors (…nor patients)



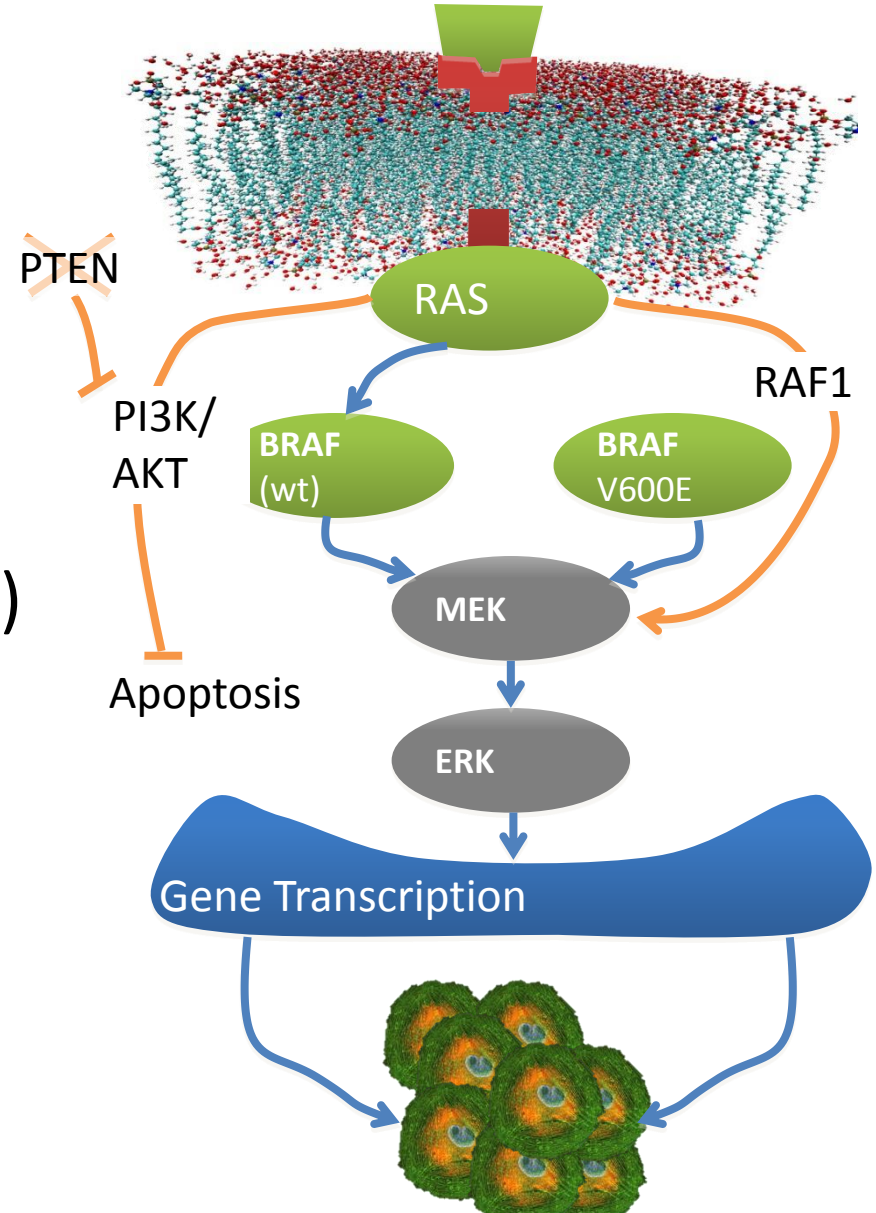






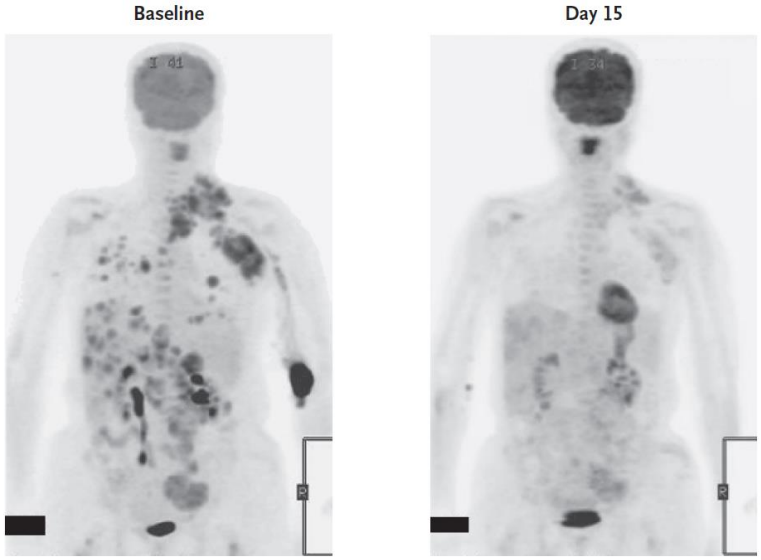
Vemurafenib

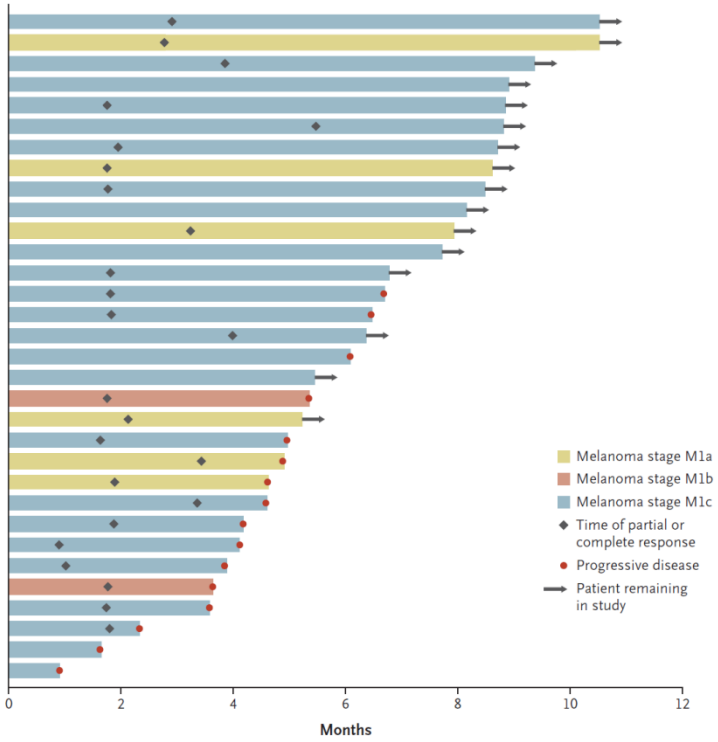
- Inhibits BRAF Activity
- BRAF-V600E Mutants are specially sensitive to blocking of BRAF activity
- Moderate Toxicity (Targeted)

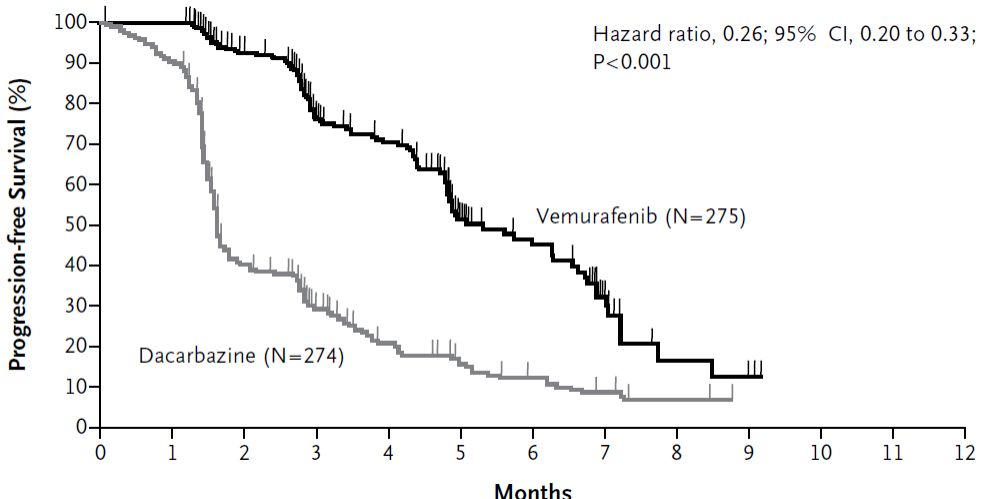


Clinical Trial

- Phase II trial
- Patients received Vemurafenib twice daily until disease progression
- 49 Melanoma patients



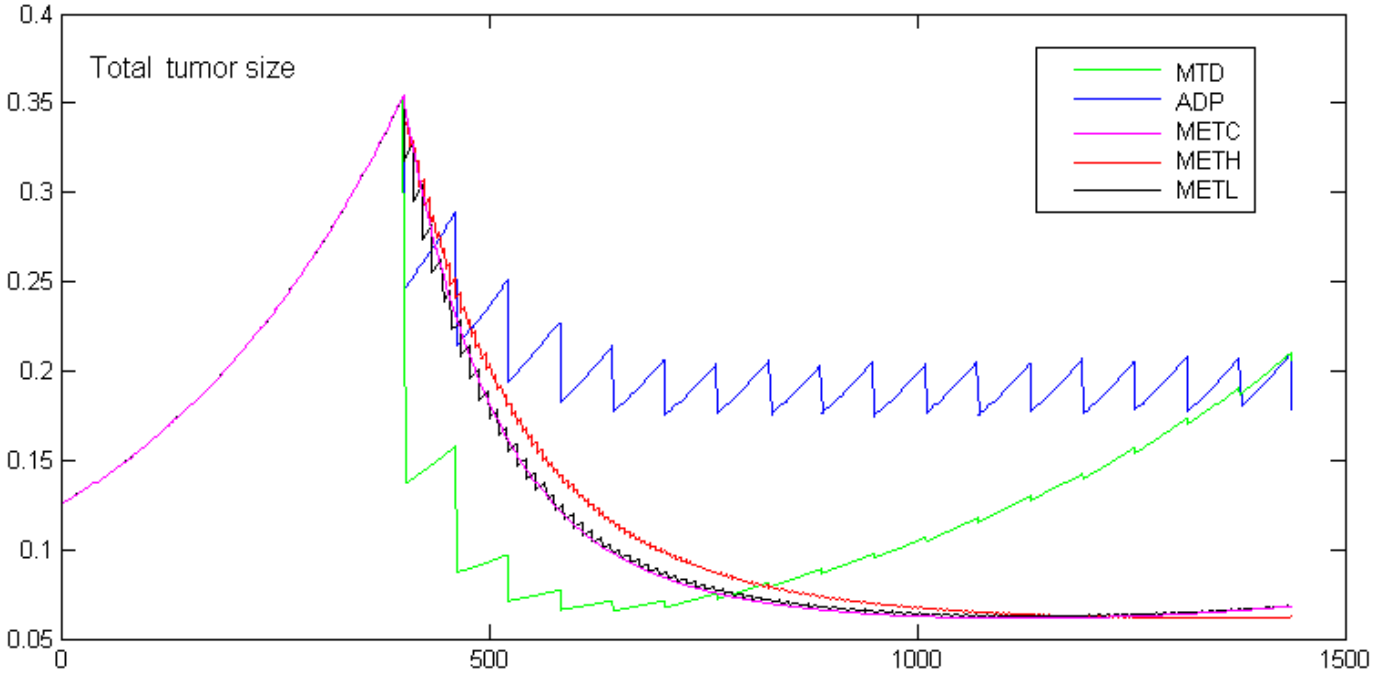




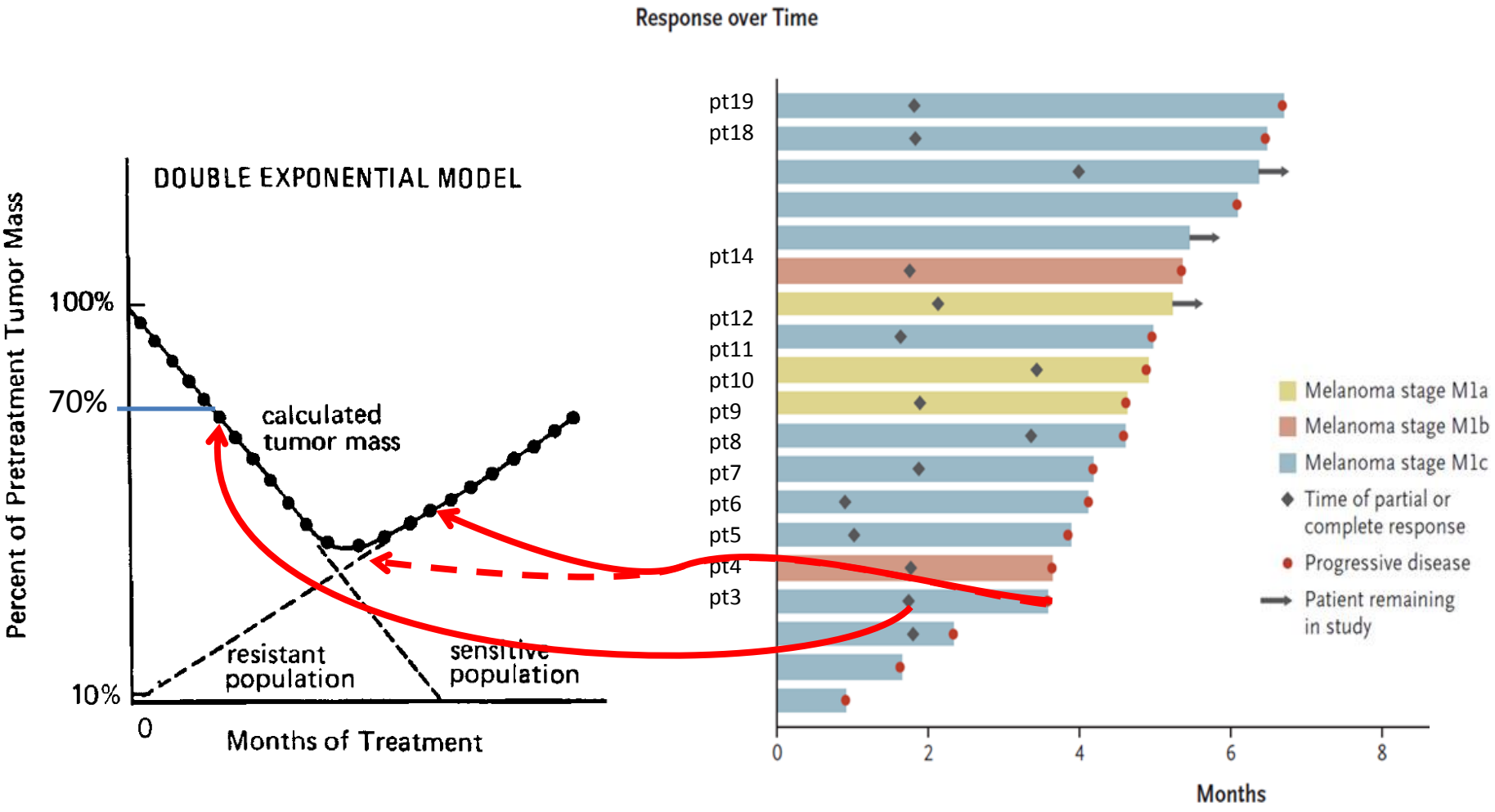
Flaherty et al. 2010. N Eng J Med 363;9

How much can we improve on these results — especially in terms of extending the duration of disease control — through combination therapy or even by manipulating the dose and schedule of single-agent therapy?[13] When should this therapy

Smalley et al. N Engl J Med 2010, 363;9

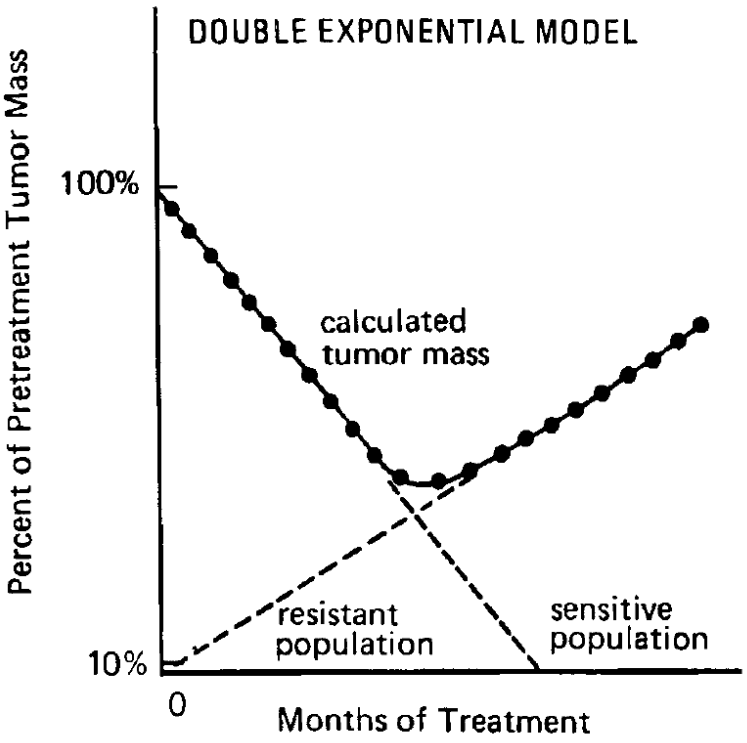


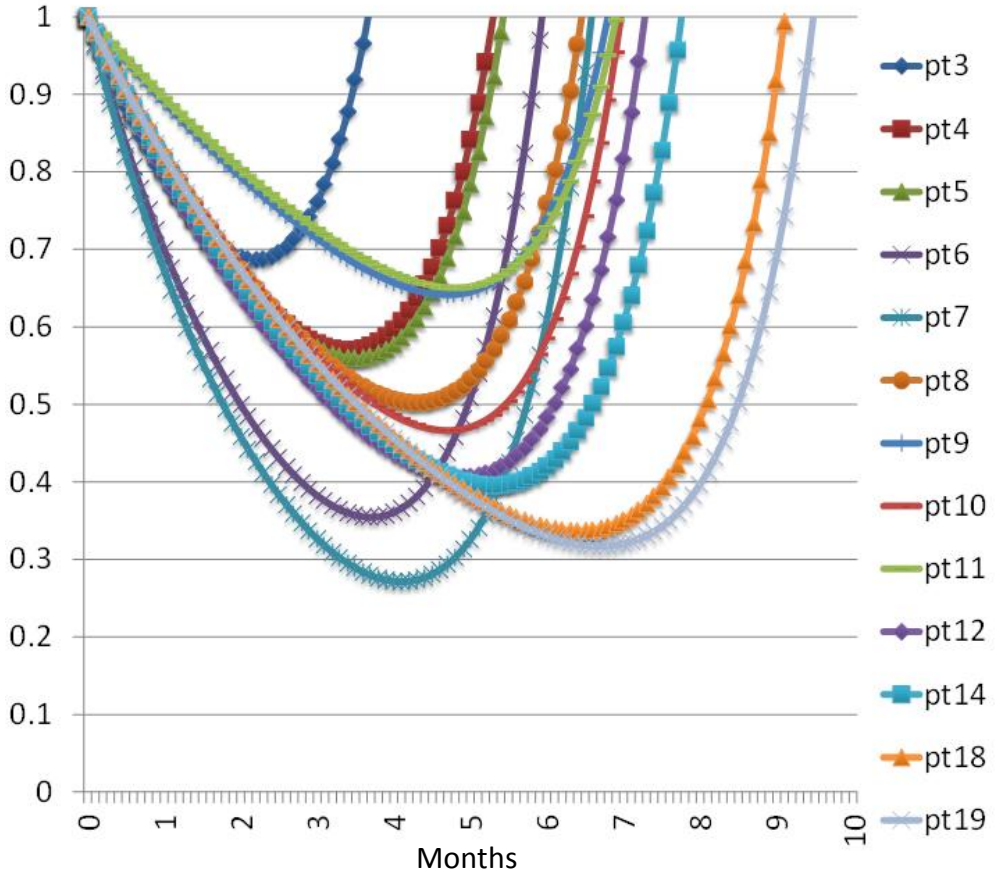
Gatenby, Silva 2009, Cancer Res 2009; 69 4894-4903



Hokanson Et al., 1977. Cancer 39:1077-1084

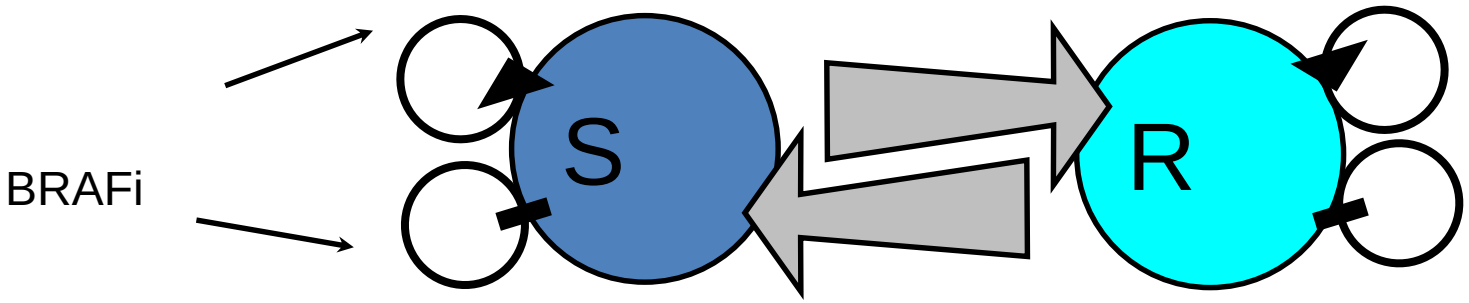
Patient Treatment Response Regression





DOSE SCHEDULING?

PLASTICITY TO SENSITIVITY?

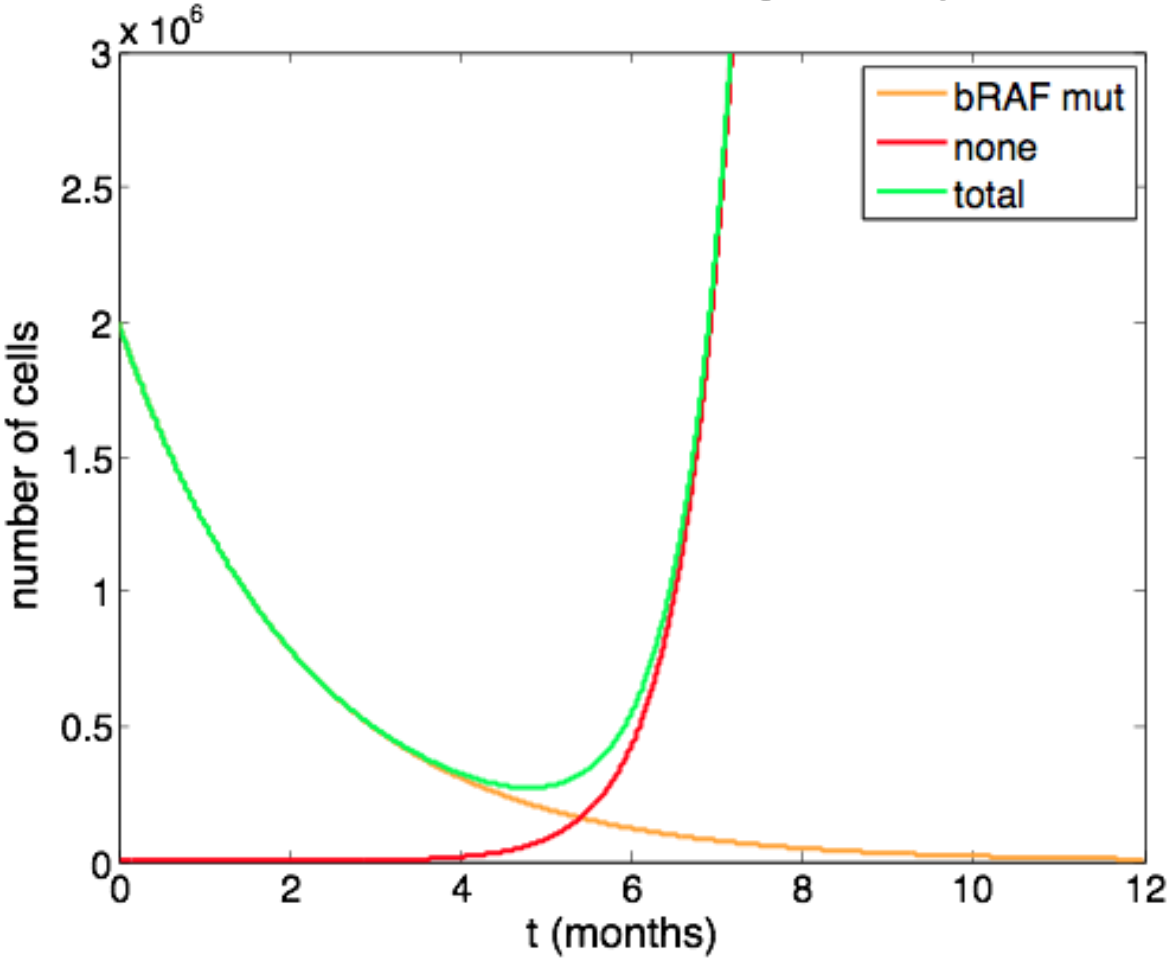


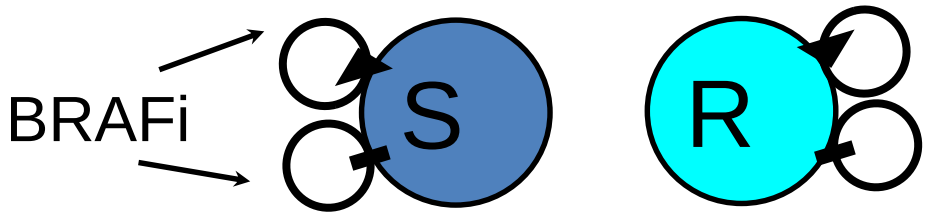
BRAFi sensitive

BRAFi resistant

$$\begin{cases} \dfrac{dS}{dt} = p_S S - d_S S + \alpha_S R - \gamma_S S \\ \dfrac{dR}{dt} = p_R R - d_R R - \alpha_S R + \gamma_S S \end{cases}$$

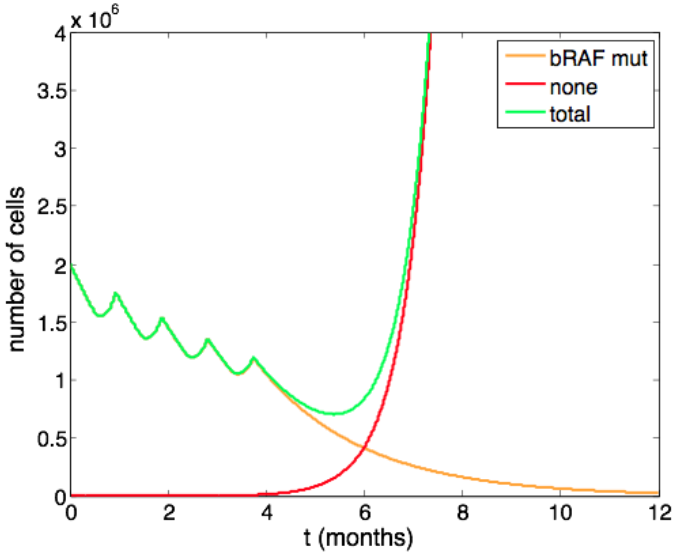
continuous drug exposure



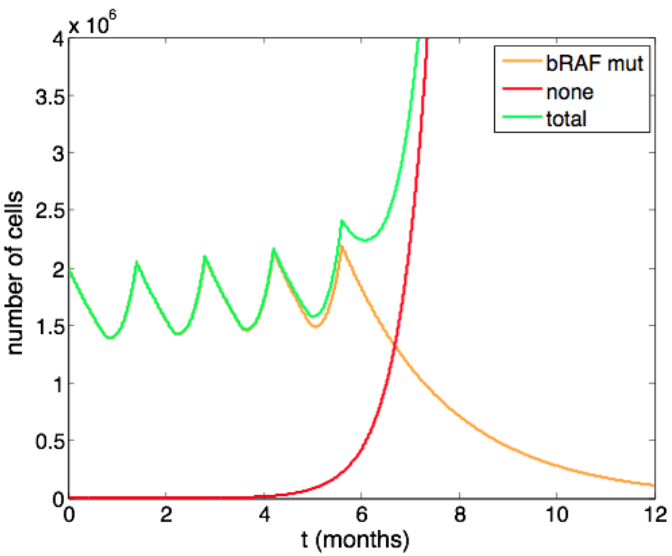


Scheduling affects tumor volume until resistant cells take over

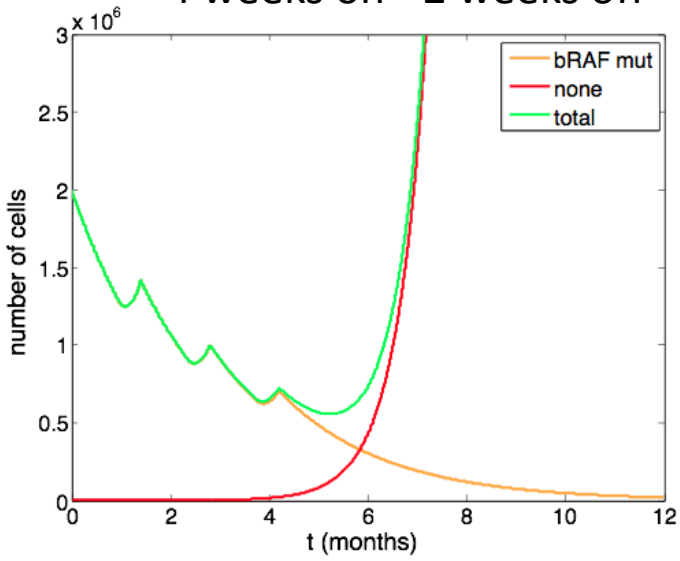
2 weeks on - 2 weeks off



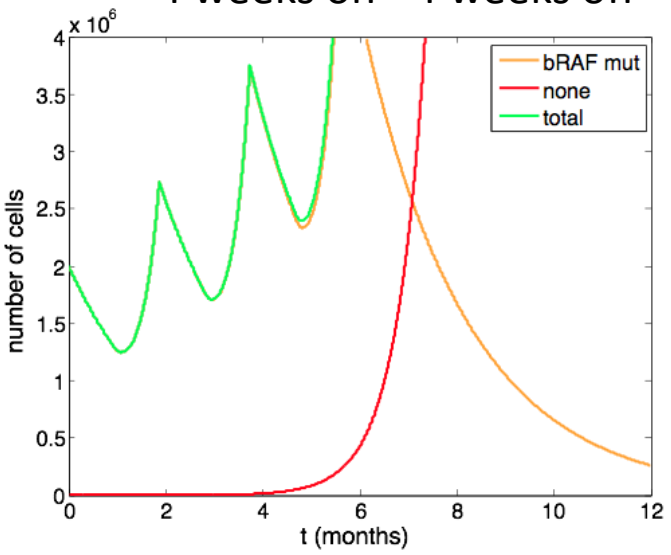
3 weeks on - 3 weeks off



4 weeks on - 2 weeks off

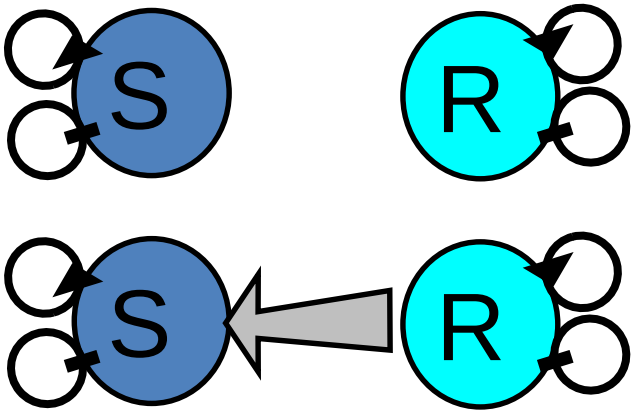


4 weeks on - 4 weeks off

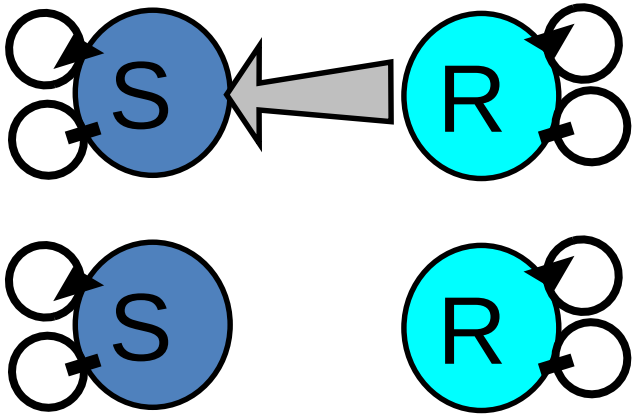


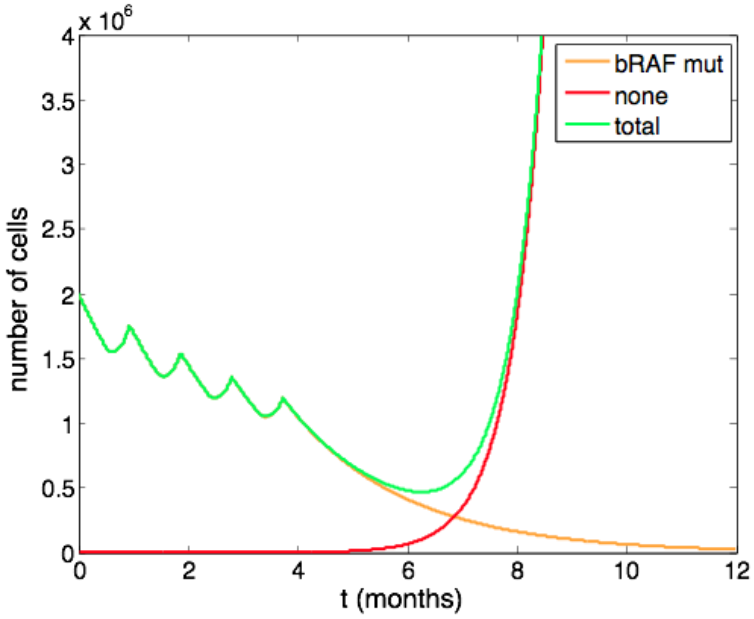
Drug + sensitizer works better simultaneously

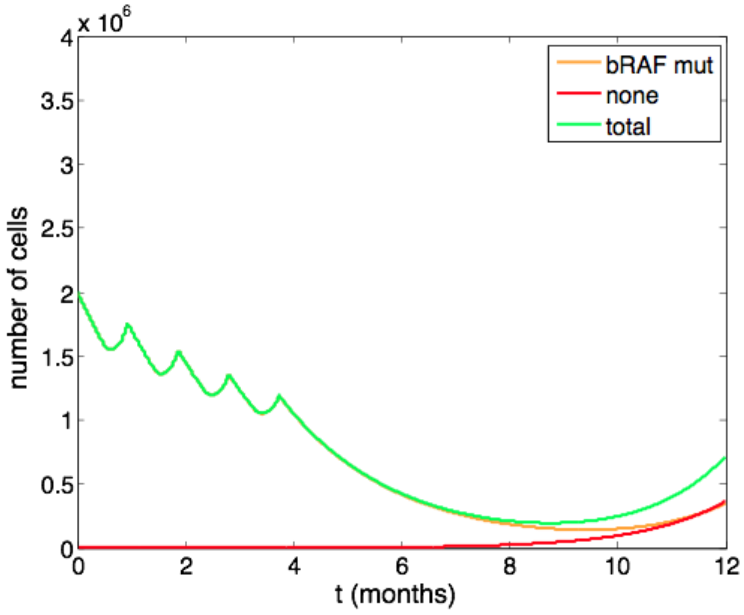
BRAFi



BRAFi







Summary I

- Cancers are moving targets, due to their genomic instability.
- Next generation sequencing allows to determine key driver mutations in cancers…
- …which are potentially heterogeneous in the very same patient (design of umbrella trials- II).
- Targeted therapies are designed to target mutated genotypes, that may be shared by different cancer types (design of basket trials).
- There is a need to develop real time diagnosis of the population dynamics within any given cancer patient, in a minimally invasive manner, to orient treatment regimens and possible drug combinations: development of liquid biopsies

IMAG(IN)ING THE TUMOR MICROENVIRONMENT IN EXPERIMENTAL MELANOMA MODELS

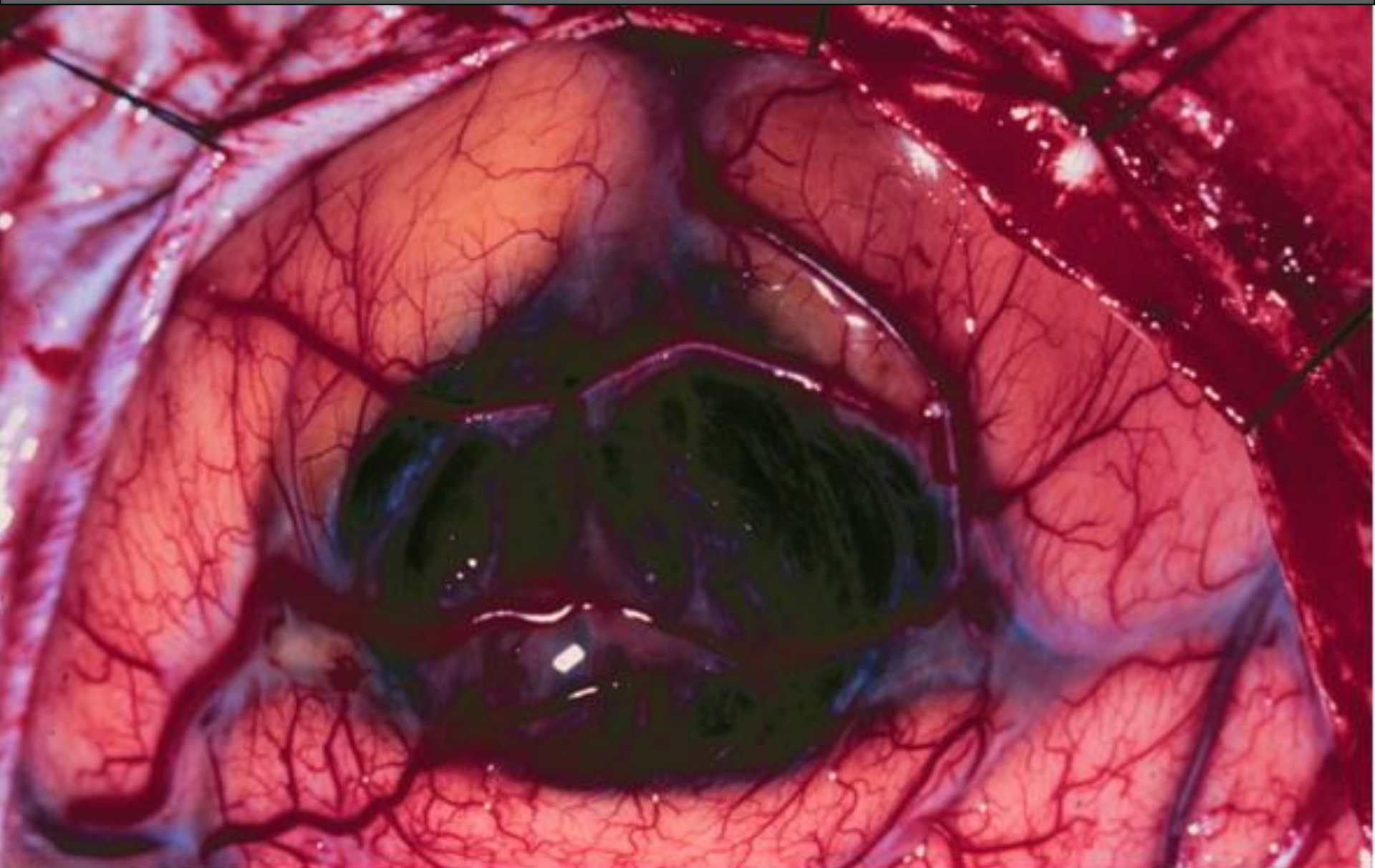
ANGIOGENESIS AND VASCULAR FUNCTION CONTROL IN EXPERIMENTAL TUMORS

Vasoactive peptides and their angiogenic/vascular permeability functions

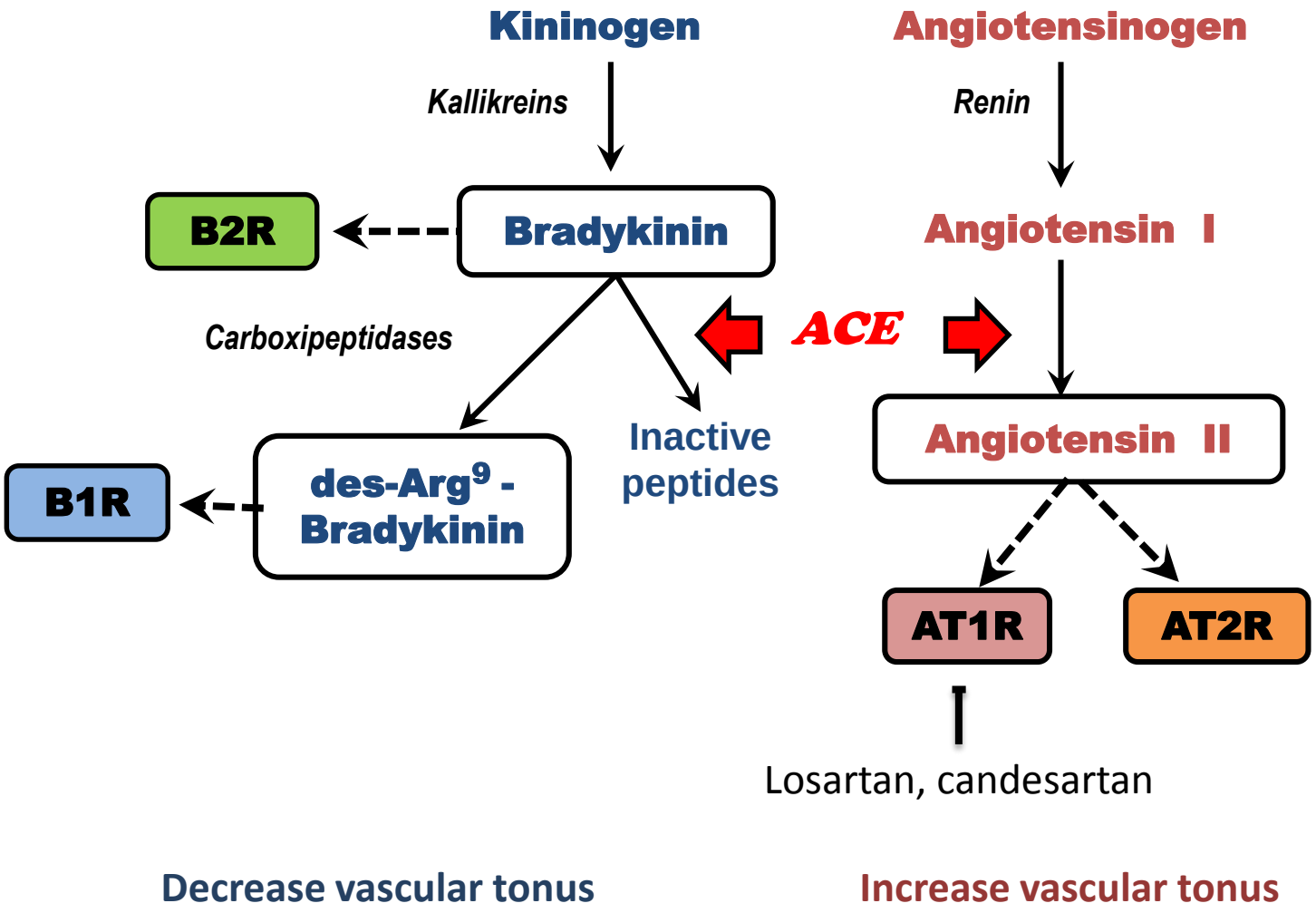
- ✓ Angiotensin II antagonists and bradykinin antagonism
- ✓ Imag(in)ing tumor vasculature function and interfering with tumor perfusion

TUMOR VASCULARIZATION AND ANGIOGENESIS

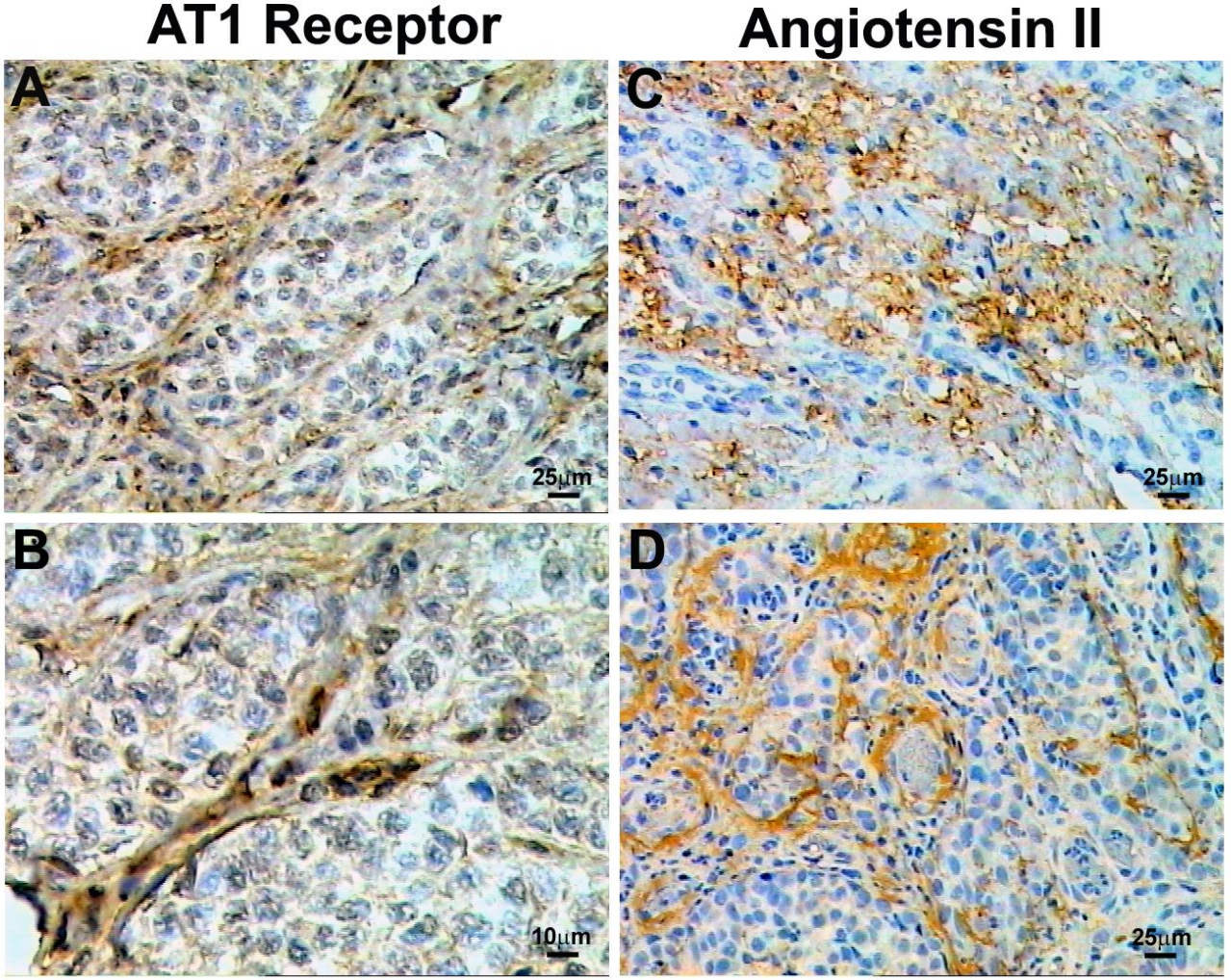
Tumors are highly vascularized, but tumor vessels are non-functional and aberrant



ANGIOTENSIN II, BRADYKININ AND DES-ARG-BRADYKININ CONTROL THE VASCULAR TONUS AND OTHER ENDOTHELIAL CELL FUNCTIONS ANGIOTENSIN CONVERTING ENZYME (*ACE*) CONNECTS BOTH SYSTEMS

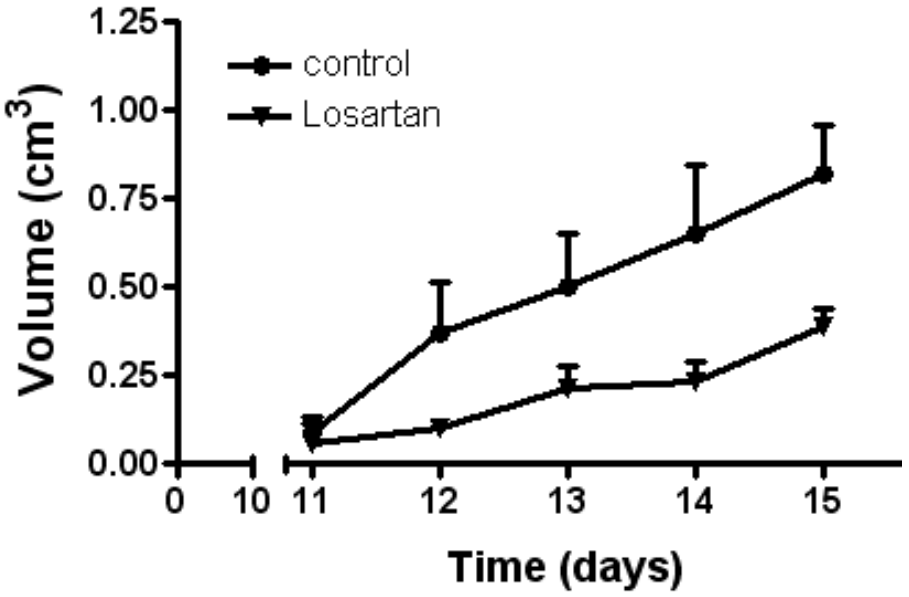


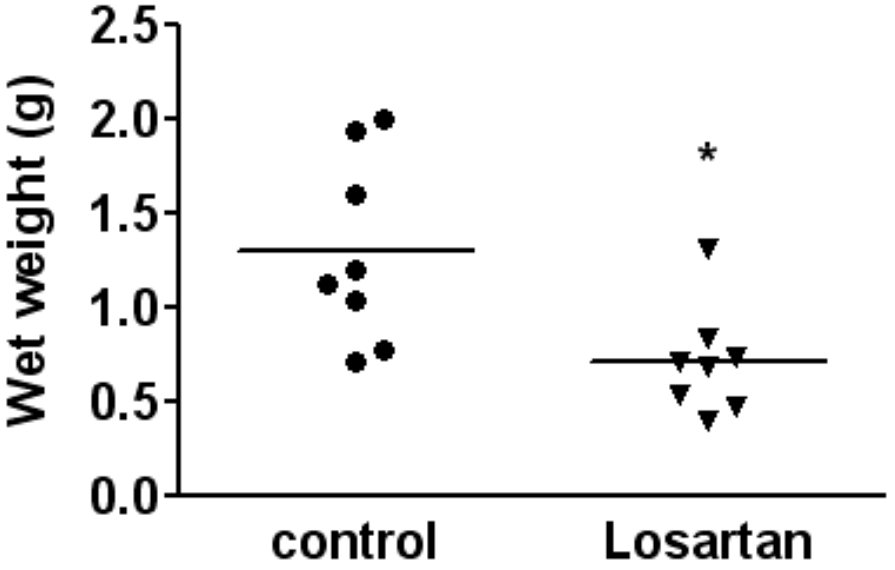
PRESENCE OF AT1 RECEPTORS AND ANGIOTENSIN II IN HUMAN MELANOMA TISSUES



Otake et al.(2010) *Cancer Chemother Pharmacol* 66:79-87

ANGIOTENSIN II ANTAGONISTS LIMITED MURINE MELANOMA GROWTH

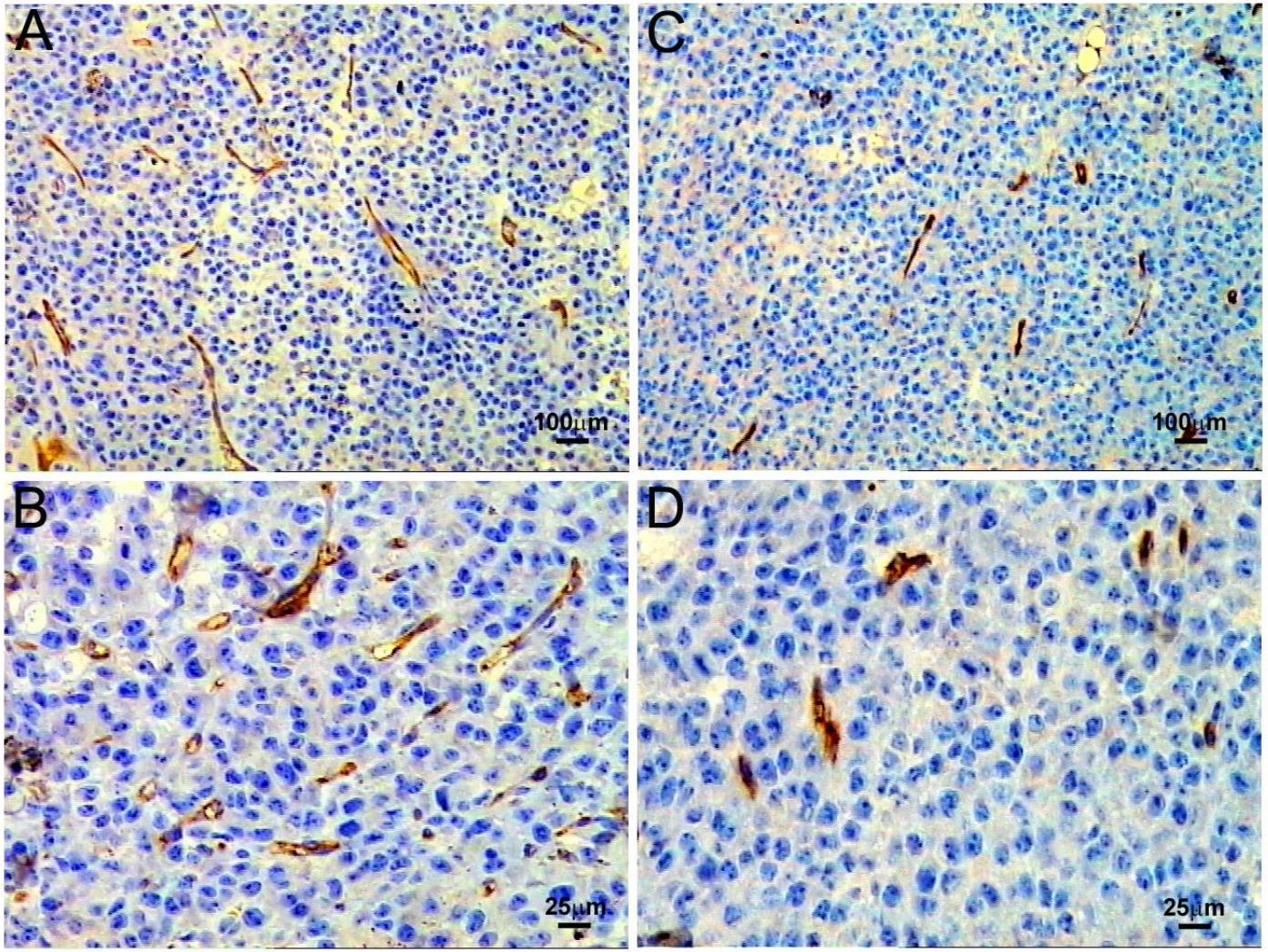




Maximal tolerated dose of Losartan

Otake et al.(2010) *Cancer Chemother Pharmacol* 66:79-87

MICROVASCULAR DENSITY (MVD) WAS DECREASED UPON LOS TREATMENT



Otake et al.(2010) *Cancer Chemother Pharmacol* 66:79-87

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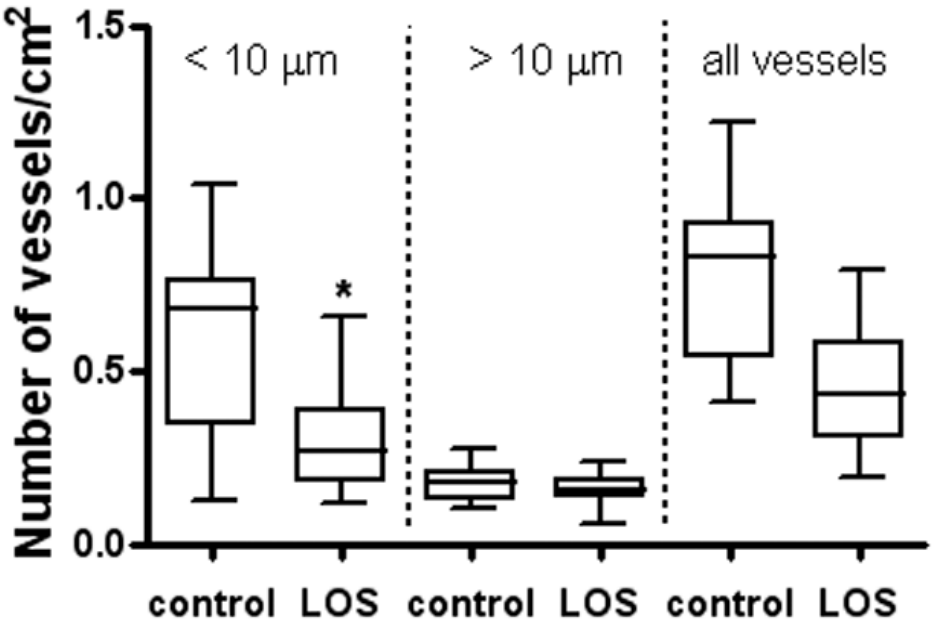
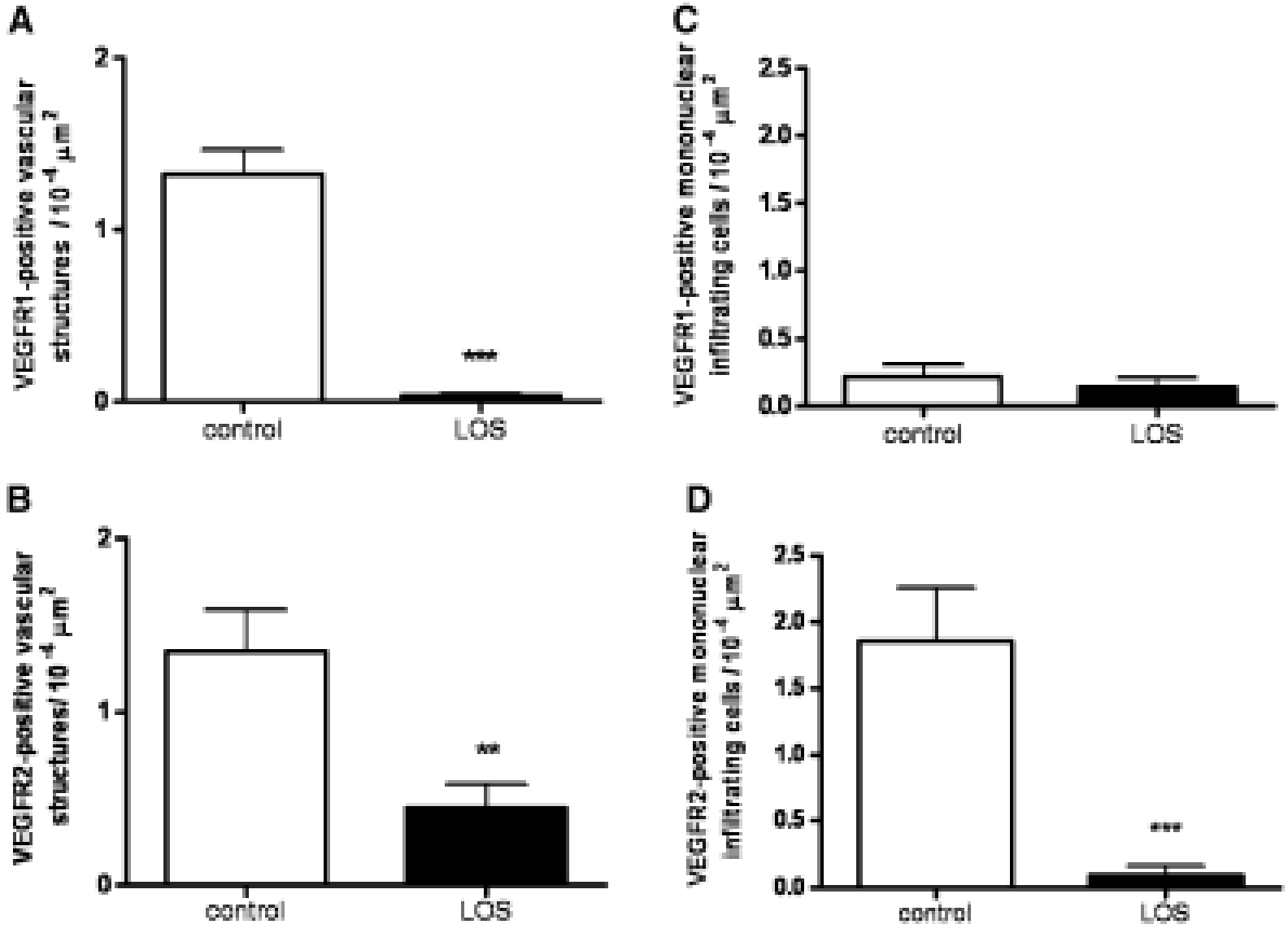


Otake et al.(2010) *Cancer Chemother Pharmacol* 66:79-87

LOSARTAN INTERFERED WITH THE RECRUITMENT OF VEGFR2 POSITIVE CELLS TO TUMORS



Otake et al.(2010) *Cancer Chemother Pharmacol* 66:79-87

VOLUME 29 · NUMBER 22 · AUGUST 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Angiotensin Receptor Blockade and Risk of Cancer in Type 2 Diabetes Mellitus: A Nationwide Case-Control Study

Chia-Hsuin Chang, Jou-Wei Lin, Li-Chiu Wu, and Mei-Shu Lai

PNAS

Losartan inhibits collagen I synthesis and improves the distribution and efficacy of nanotherapeutics in tumors

Benjamin Diop-Frimpong[a,b,c], Vikash P. Chauhan[a,c], Stephen Krane[d], Yves Boucher[a,1,2], and Rakesh K. Jain[a,1,2]

[a]Department of Radiation Oncology, Edwin L. Steele Laboratory, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114; [b]Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology, Cambridge, MA 02139; [c]School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138; and [d]Department of Medicine, Rheumatology, Bulfinch-165, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114

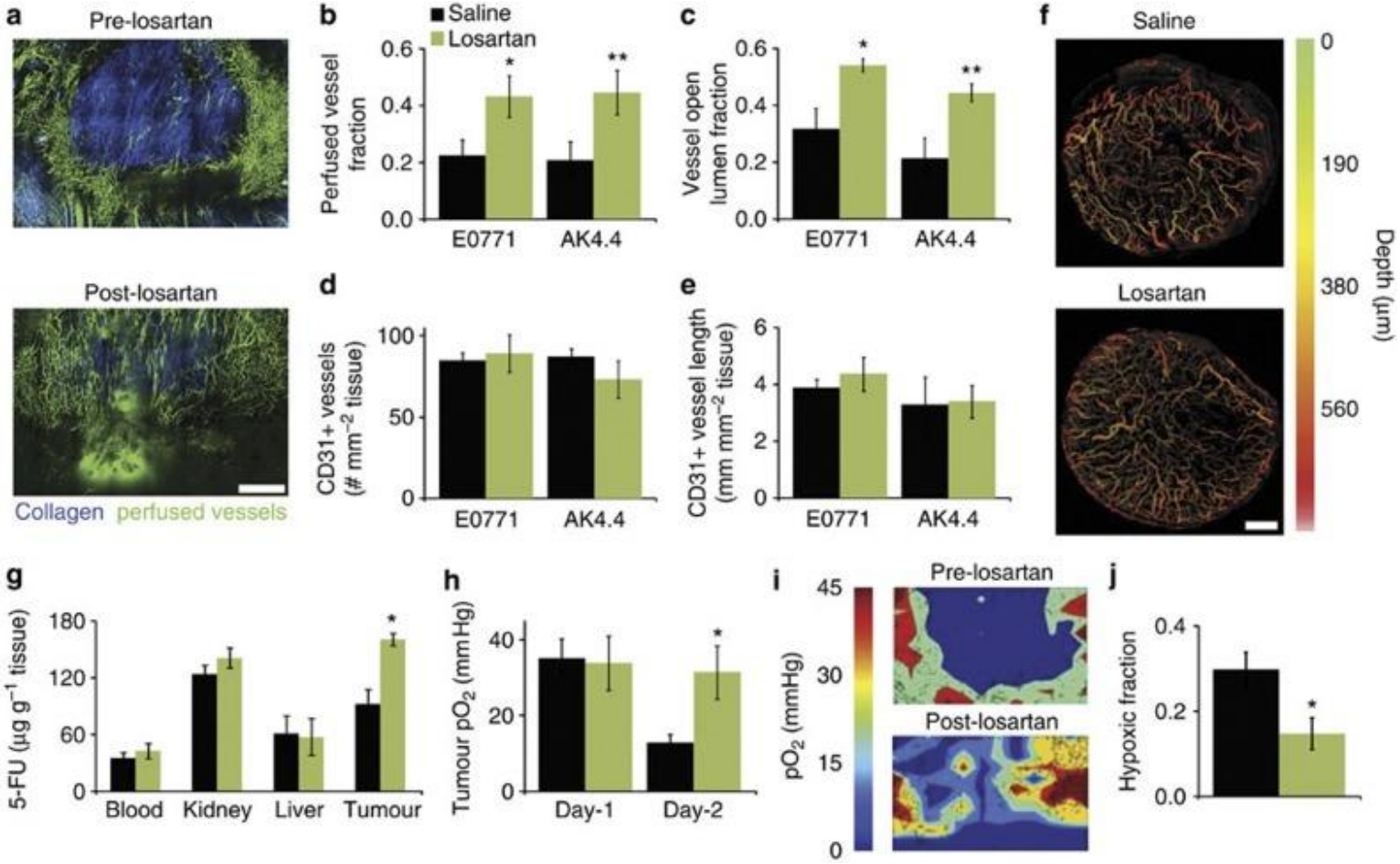
Contributed by Rakesh K. Jain, December 21, 2010 (sent for review October 20, 2010)

Low dose of losartan

NAT COMMUN. 2013;4:2516. DOI: 10.1038/NCOMMS3516.

ANGIOTENSIN INHIBITION ENHANCES DRUG DELIVERY AND POTENTIATES CHEMOTHERAPY BY DECOMPRESSING TUMOUR BLOOD VESSELS

CHAUHAN VP[1], MARTIN JD, LIU H, LACORRE DA, JAIN SR, KOZIN SV, STYLIANOPOULOS T, MOUSA AS, HAN X, ADSTAMONGKONKUL P, POPOVIĆ Z, HUANG P, BAWENDI MG, BOUCHER Y, JAIN RK.



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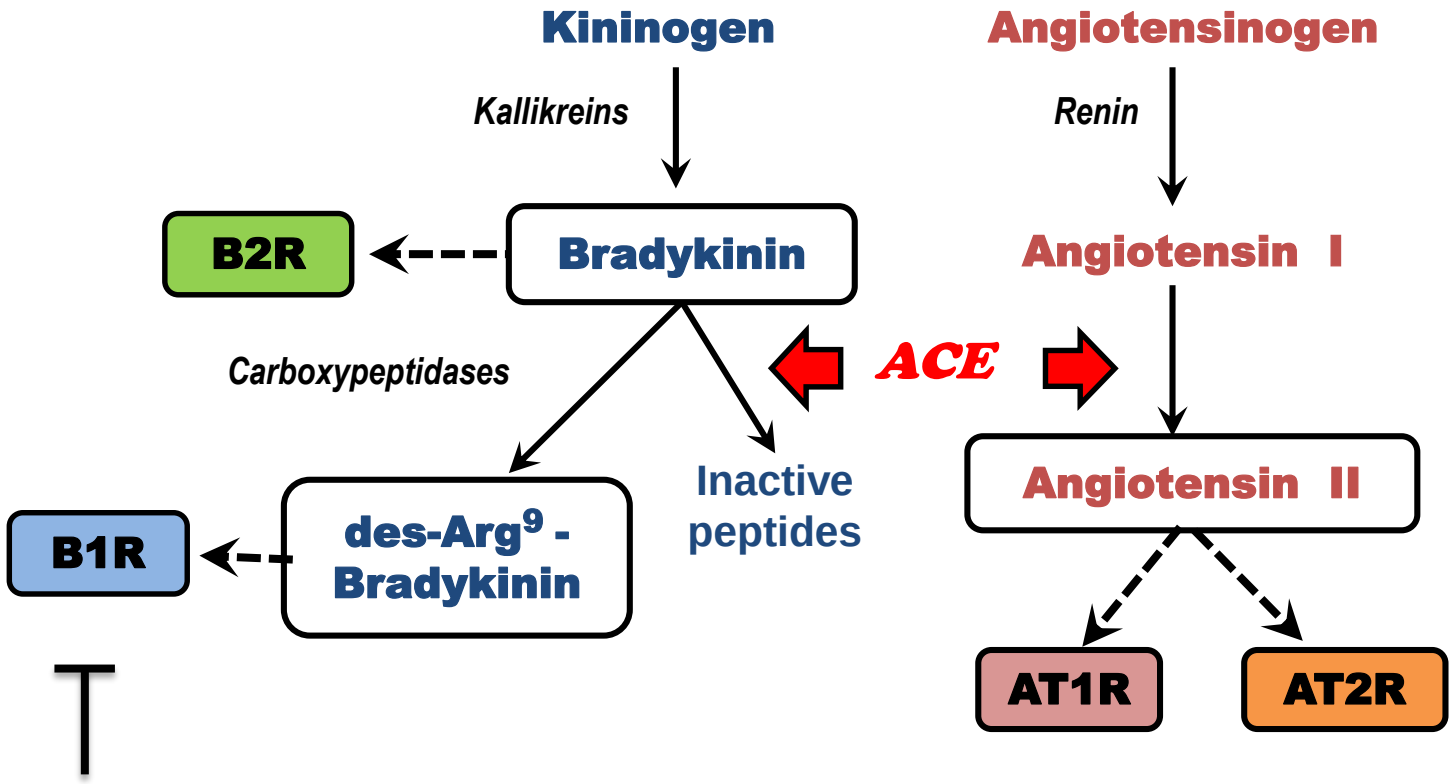


R-715, R-954

Decrease vascular tonus

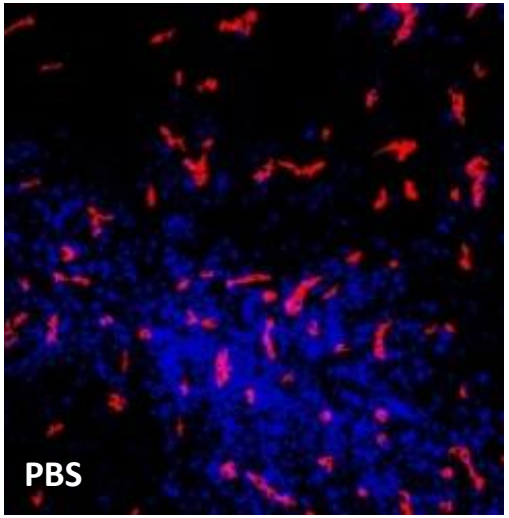
Increase vascular permeability

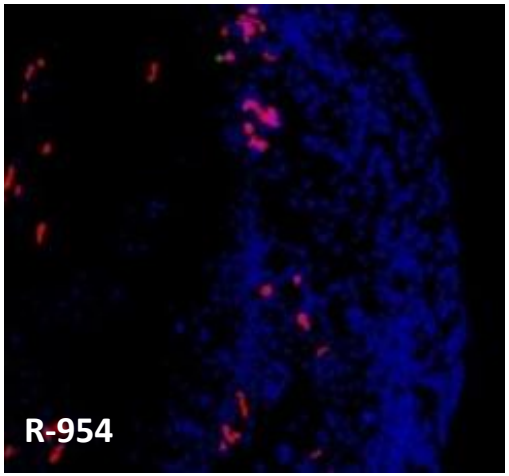
Increases vascular tonus

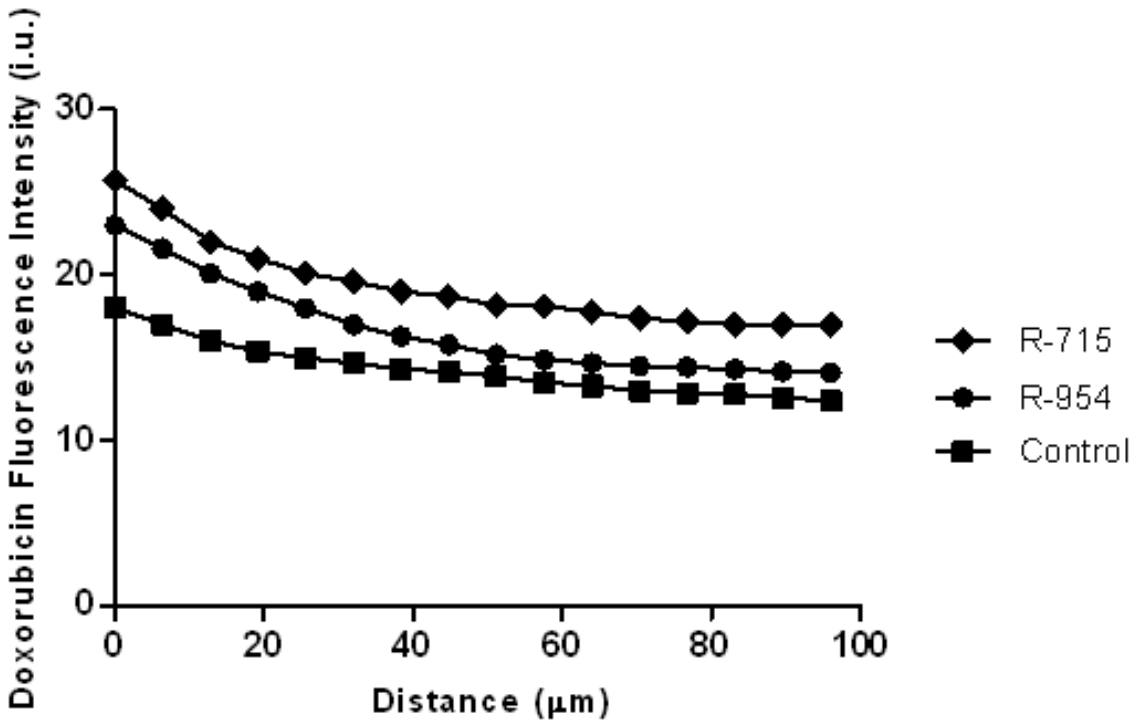
Induces angiogenesis

THE BKR1 ANTAGONISTS R715 AND R954 INCREASED DOXORUBICIN UPTAKE WITHIN TUMORS

CD31/Doxorubicin





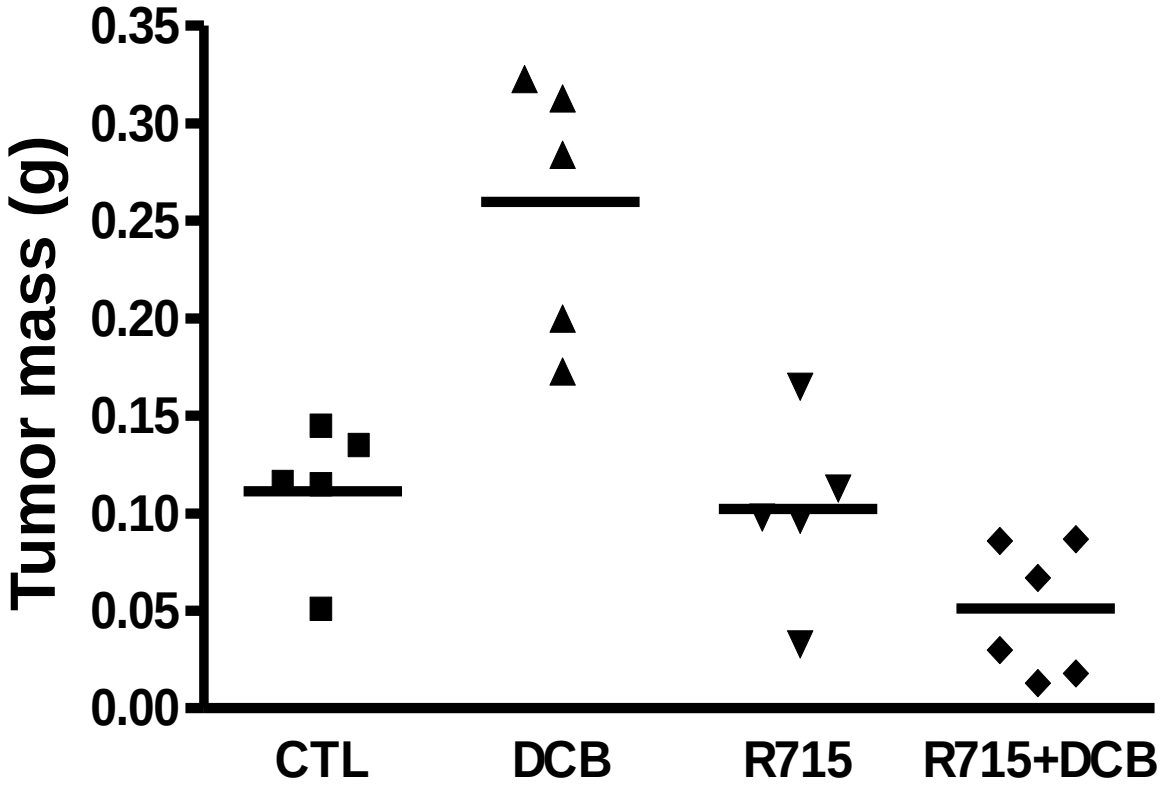


...adverse effects of R954/R715 include a transient increase in blood pressure

US2007015715-A1 Nantel *et al.* Derwent Innovations Index 2007-239159.

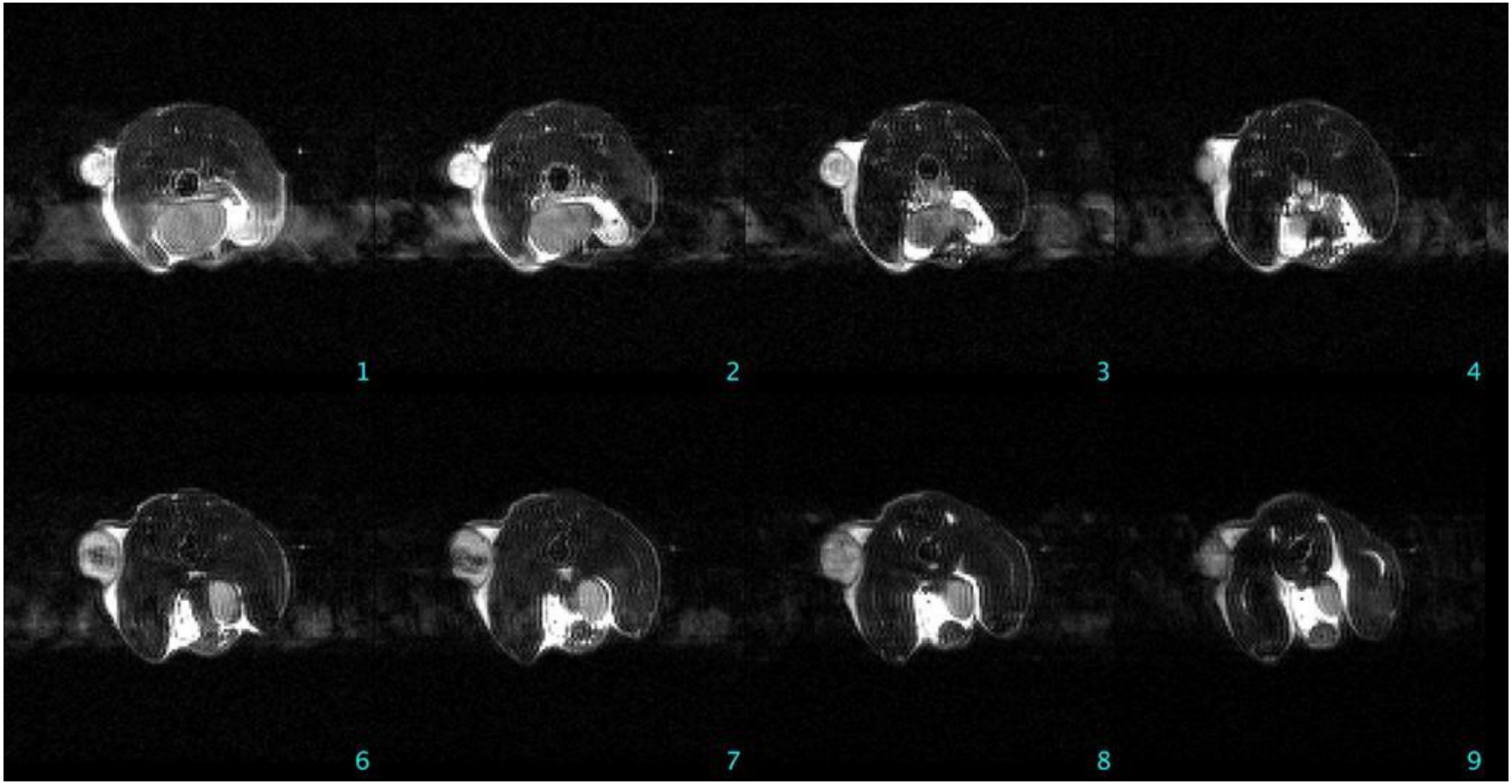
Costa el al. (2014). Cancer Lett. 345: 27-38

THE BKR1 ANTAGONIST R715 IMPROVED THE EFFICACY OF DACARBAZINE (DCB) IN MURINE MELANOMAS



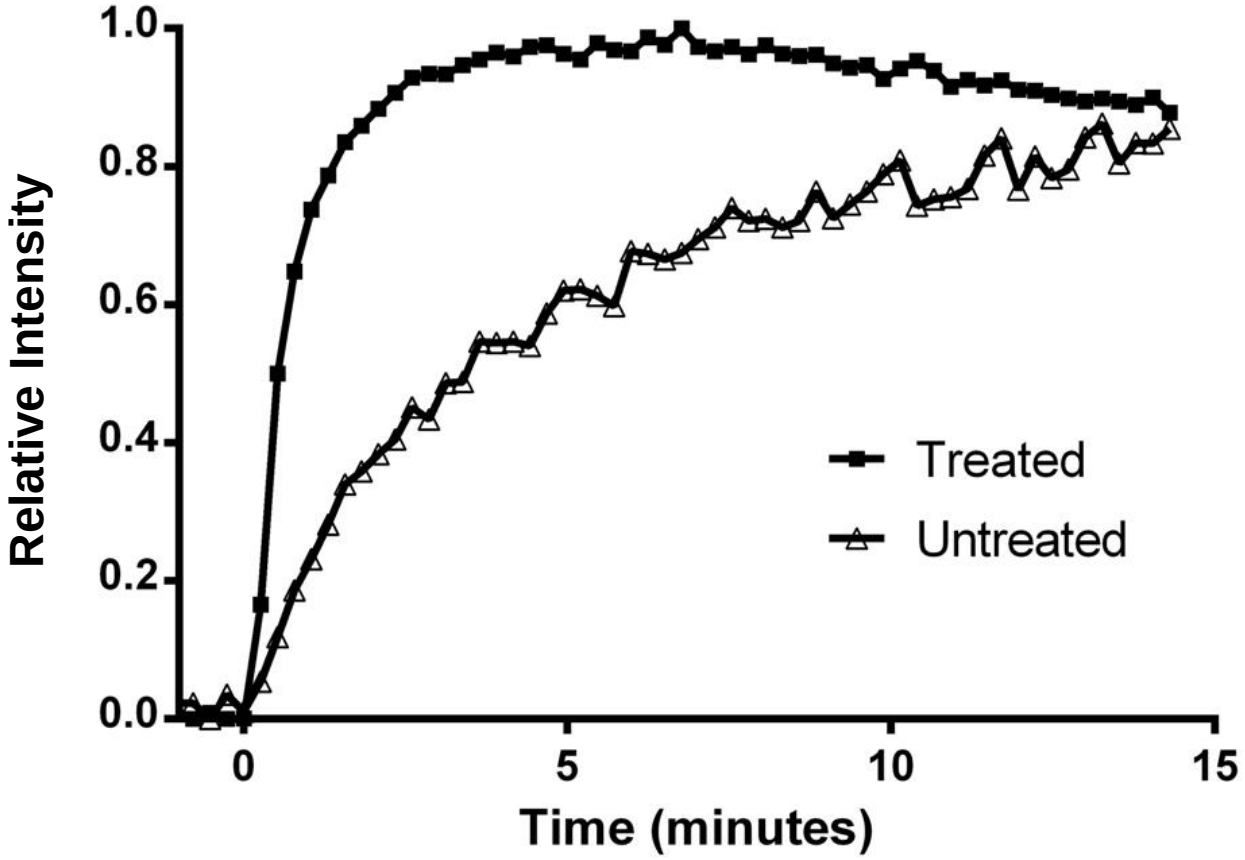
LNS Andrade

MRI STUDIES OPEN THE PERSPECTIVE OF EVALUATING DIFFERENT VARIABLES OF TUMOR PHYSIOLOGY

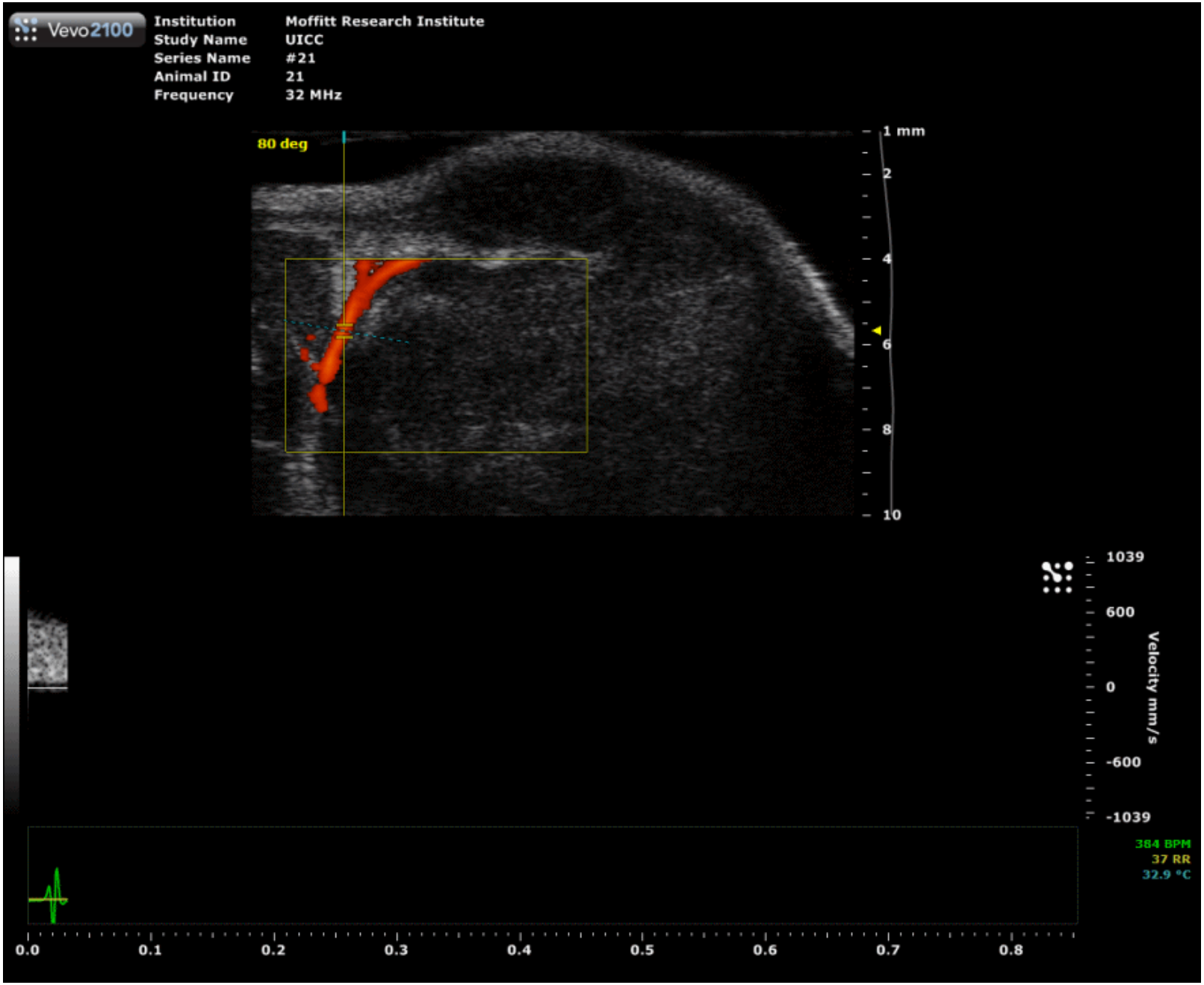


Chammas et al., in preparation

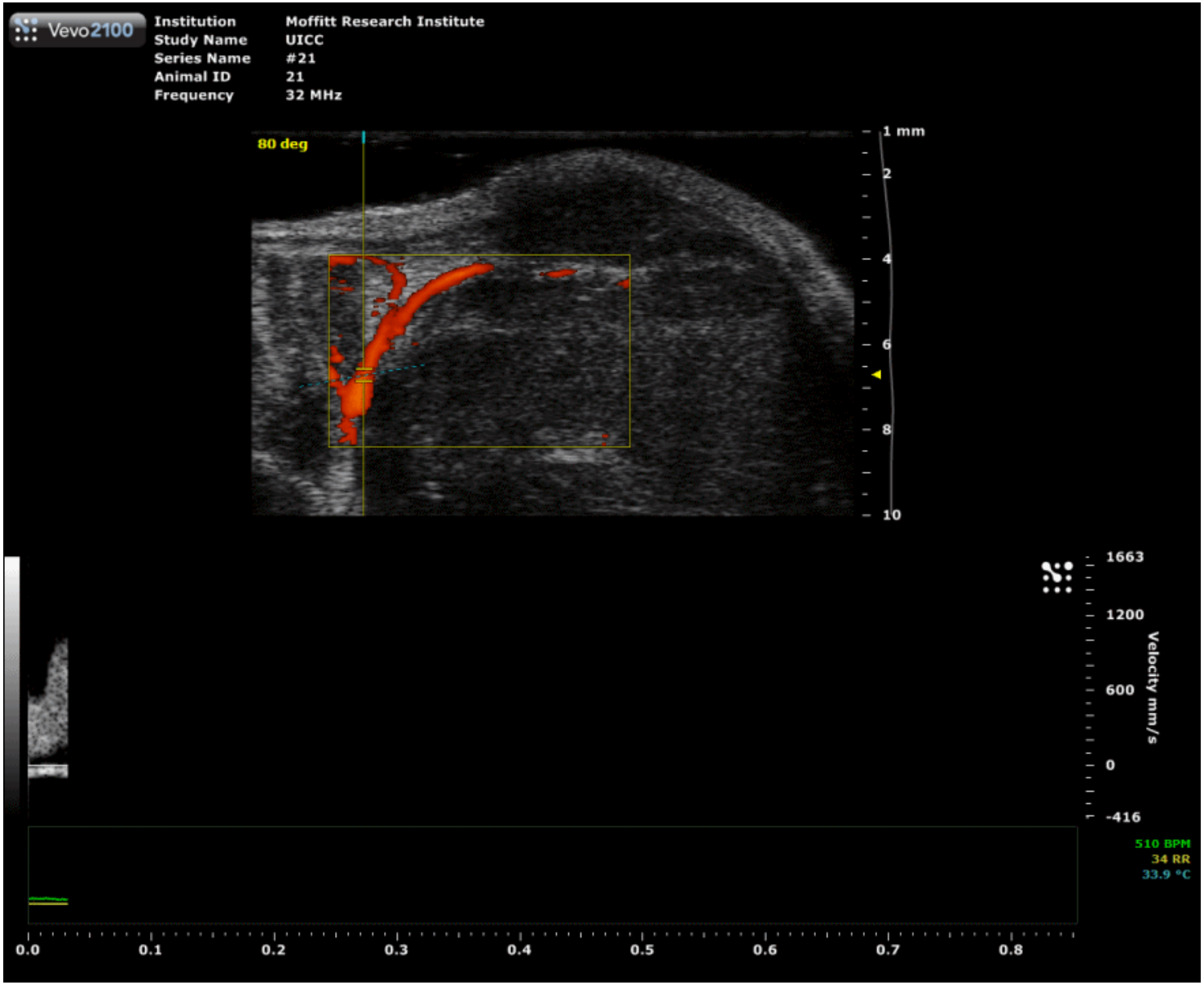
SUCH AS DIFFUSION OF CONTRASTING AGENTS WITHIN THE TUMOR, AS A PROXY OF TUMOR PERFUSION



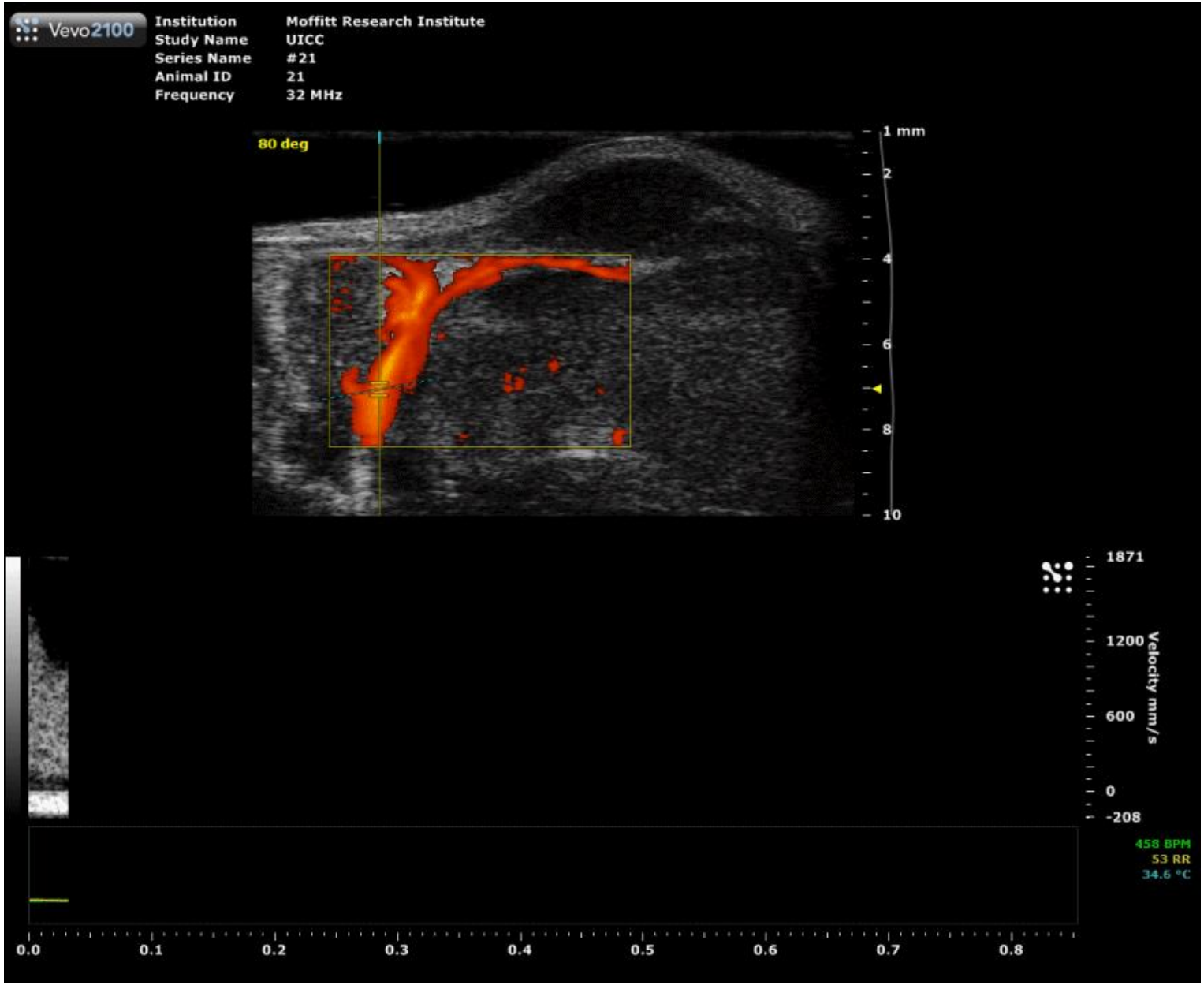
Chammas et al., in preparation



Chammas et al., in preparation



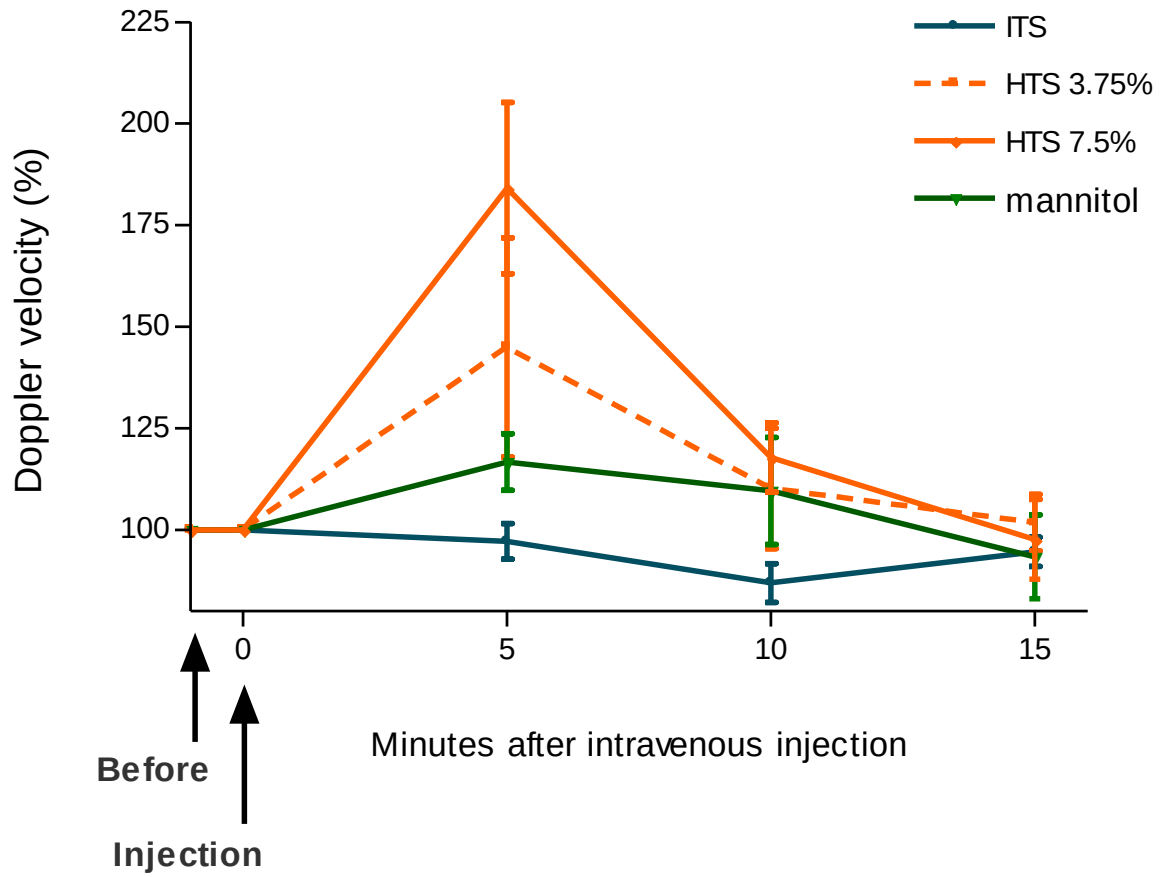
Chammas et al., in preparation



Chammas et al., in preparation

DOPPLER STUDIES

B16-F10 melanoma



Chammas et al., in preparation

SUMMARY

Both angiotensin II and its receptor (AT1) are present within the tumor microenvironment of human melanomas and murine melanomas.

The antihypertensive agent Losartan has a dual function, controlling not only the vascular tonus, but also controlling angiogenesis.

Off label indications of old drugs (Losartan, e.g.) may help managing cancer patients.

Opportunity for an academic clinical trial

Bradykinin receptor 1 antagonists may lead to secondary local and transient hypertension, favouring drug delivery to experimental tumors. Transient increase in tumor perfusion can also be induced through usage of hypertonic saline solutions.

Multimodality imaging allowed for devising a strategy of combination therapy to improve drug delivery .