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)
GENETIC INTRATUMOR HETEROGENEITY AND PHYLOGENY IN PATIENT

CORRELATIONS BETWEEN GENOTYPE AND PHENOTYPE IN PATIENT 1

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

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? When should this therapy be started?
Patient Treatment Response Regression

**Double Exponential Model**

- Percent of Pretreatment Tumor Mass
- Months of Treatment

Graph showing the response of different patient populations (pt3 to pt19) over months of treatment.
DOSE SCHEDULING?

PLASTICITY TO SENSITIVITY?

\[
\begin{align*}
\frac{dS}{dt} &= p_S S - d_S S + \alpha_S R - \gamma_S S \\
\frac{dR}{dt} &= p_R R - d_R R - \alpha_S R + \gamma_S S
\end{align*}
\]
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 + sensitizers works better simultaneously.
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
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.

- Bradykinin activates B2R, with carboxypeptidases converting it to des-Arg⁹-Bradykinin, which activates B1R.
- ACE deactivates Bradykinin.
- Angiotensin I, generated by Renin, is converted to Angiotensin II by ACE, activating AT1R and AT2R.
- Losartan and candesartan decrease vascular tonus.

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**Key Points:**
- Angiotensin II and Bradykinin interact via ACE.
- Bradykinin and des-Arg⁹-Bradykinin control vascular tonus.
- ACE connects both systems.
- Losartan and candesartan affect vascular tonus.

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**Diagram Notes:**
- Kininogen is cleaved by Kallikreins to produce Bradykinin.
- Bradykinin activates B2R, converting to des-Arg⁹-Bradykinin which activates B1R.
- Angiotensinogen is cleaved by Renin to produce Angiotensin I, which is converted to Angiotensin II by ACE.
- Angiotensin II activates AT1R and AT2R.
- Losartan and candesartan can affect vascular tonus through AT1R.
PRESENCE OF AT1 RECEPTORS AND ANGIOTENSIN II IN HUMAN MELANOMA TISSUES

ANGIOTENSIN II ANTAGONISTS LIMITED MURINE MELANOMA GROWTH

Maximal tolerated dose of Losartan

MICROVASCULAR DENSITY (MVD) WAS DECREASED UPON LOS TREATMENT

MICROVASCULAR DENSITY (MVD) WAS DECREASED UPON LOS TREATMENT
LOSARTAN INTERFERED WITH THE RECRUITMENT OF VEGFR2 POSITIVE CELLS TO TUMORS
Angiotensin Receptor Blockade and Risk of Cancer in Type 2 Diabetes Mellitus: A Nationwide Case-Control Study

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

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

Benjamin Diop-Frimpong, Vikash P. Chauhan, Stephen Krane, Yves Boucher, and Rakesh K. Jain

Contributed by Rakesh K. Jain, December 21, 2010 (sent for review October 20, 2010)
ANGIOTENSIN INHIBITION ENHANCES DRUG DELIVERY AND POTENTIATES CHEMOTHERAPY BY DECOMPRESSING TUMOUR BLOOD VESSELS

CHAUHAN VP, MARTIN JD, LIU H, LACORRE DA, JAIN SR, KOZIN SV, STYLIANOPoulos T, MOUSEA AS, HAN X, ADSTAMONGKONKUL P, POPOVIC Z, HUANG P, BAWENDI MG, BOUCHER Y, JAIN RK.
Angiotensin II, Bradykinin and des-Arg-Bradykinin control the vascular tonus and other endothelial cell functions. Angiotensin converting enzyme (ACE) connects both systems.

- Bradykinin is produced from kininogen by kallikreins and carboxypeptidases. It binds to B2R and B1R.
- Angiotensinogen is converted to Angiotensin I by renin.
- ACE metabolizes Angiotensin I to Angiotensin II.
- Angiotensin II binds to AT1R, increasing vascular tonus, and to AT2R, decreasing vascular tonus.
- Bradykinin and des-Arg⁹-Bradykinin bind to B1R, increasing vascular permeability.

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

The BKR1 antagonist R715 improved the efficacy of dacarbazine (DCB) in murine melanomas.

Tumor mass (g)

- CTL
- DCB
- R715
- R715+DCB

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
DOPPLER STUDIES

B16-F10 melanoma

Doppler velocity (%)

Minutes after intravenous injection

Injection

Before

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.