PREDICTING CANCER BEHAVIOR BASED ON *IN SILICO* MODELING AND *IN VIVO/ IN VITRO* MOLECULAR IMAGING APPROACHES

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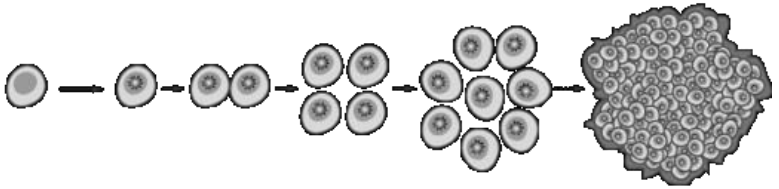
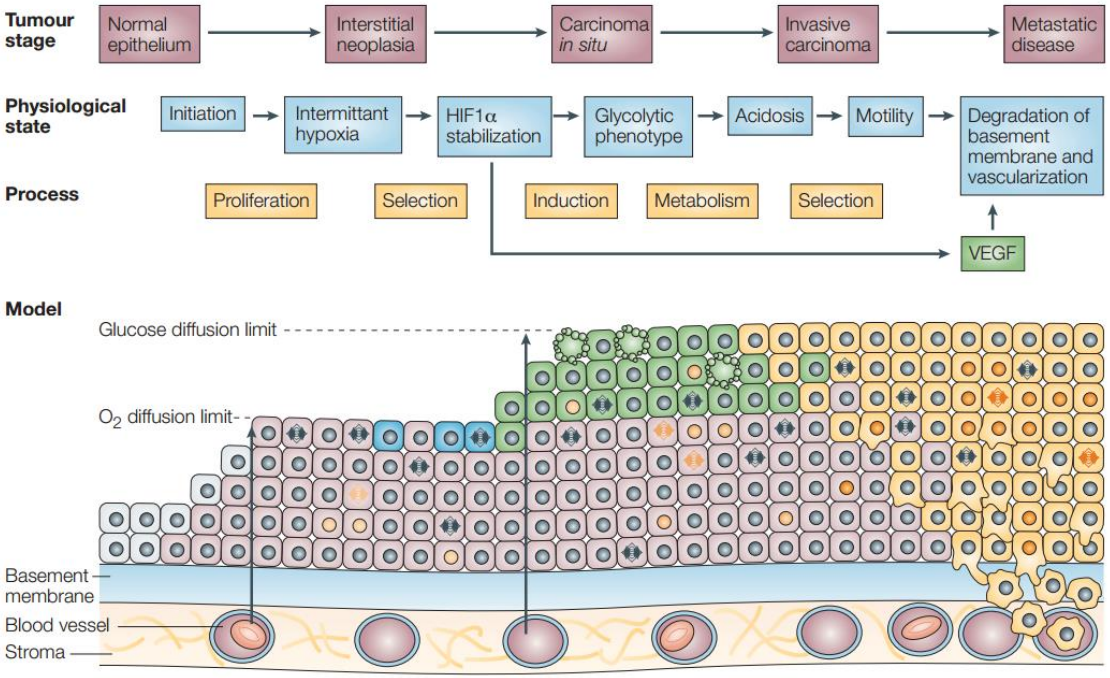
Heraklion, 13-14/10/2017

CANCER GROWTH





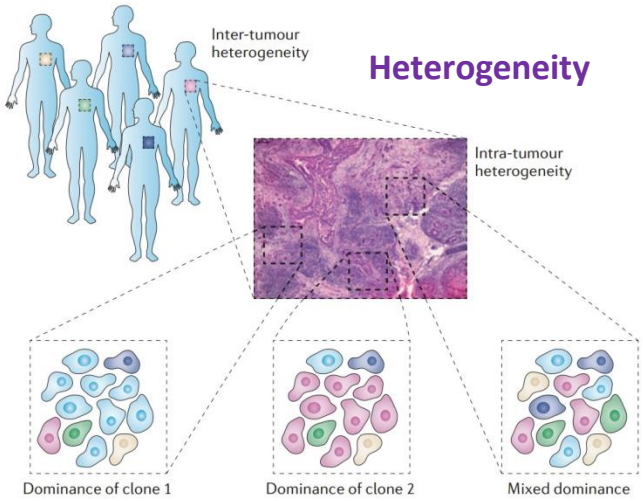
Model for cell–environment interactions in carcinogenesis. Early carcinogenesis proceeds **from normal tissues** through initiation to a hyperplastic state to interstitial neoplasia, progressing to carcinoma *in situ*. Until this stage, epithelial cancers are **avascular**, as shown by histopathology. Following **breakdown of the basement membrane**, cells gain access to existing and newly formed blood and lymphatic vascular routes for **metastasis**. The stages of tumor growth and their associated physiological states are diagrammed, showing that progression from one stage to the next is governed by state processes. Normal epithelial cells become hyperproliferative following induction. As they reach the oxygen diffusion limit, they become **hypoxic**, which can either lead to cell death (apoptotic cells shown with blebbing) or adaptation of a **glycolytic phenotype**, which allows cells to survive. As a consequence of glycolysis, lesions become acidotic, which selects for motile cells that eventually breach the basement membrane. As cancer progression proceeds, the **mutations** in cells increase (nuclei shown as light orange for one mutation and darker oranges for more mutations).
HIF1α, hypoxia-inducible factor-1α; **VEGF**, vascular endothelial growth factor.

R. A. Gatenby and R. J. Gillies, Nature Reviews Cancer: 4(11):891-9., Nov 2004

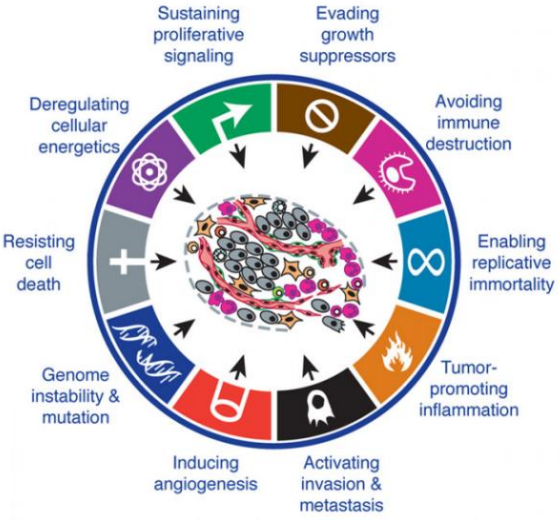
CANCER IS COMPLEX

Cancer is a complex biological system

- involving many interconnected biological phenomena
- spanning in different spatial and temporal scales
- showing high inter- and intra-tumoral heterogeneity
- characterized by adaptation in terms of plasticity, resistance and relapse



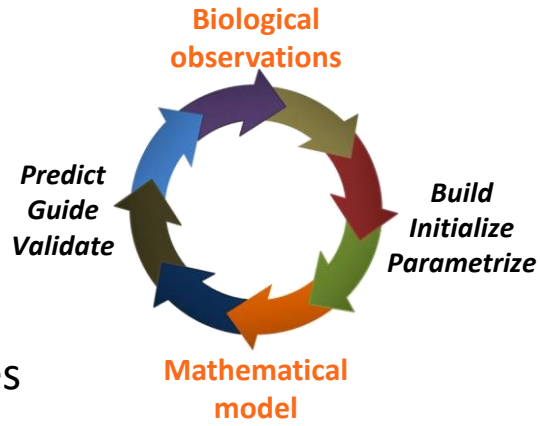
Heterogeneity



Hallmarks of Cancer

A. Marusyk, V. Almendro, and K. Polyak, Nature Reviews Cancer: 12, 323-334, 2012
D. Hanahan and R. A. Weinberg, Cell 144, March 4, 2011

HOW *IN SILICO* MODELS CAN HELP?



Mathematical and computational model

- allow many hypotheses to be explored
- incorporate multiple information from multiple sources
- handle multiple coupled variables and explore the role of the parameters involved
- track each individual component of the biological system as evolves in time and space, as well as the behavior of the whole multicellular system
- **predict** the systems behavior in a variety of conditions, which is often difficult to achieve experimentally
- **produce** new hypotheses
- **guide** experimental planning
- **validate the hypotheses with the biological observations in an iterative manner until a faithful and reliable model is found!**

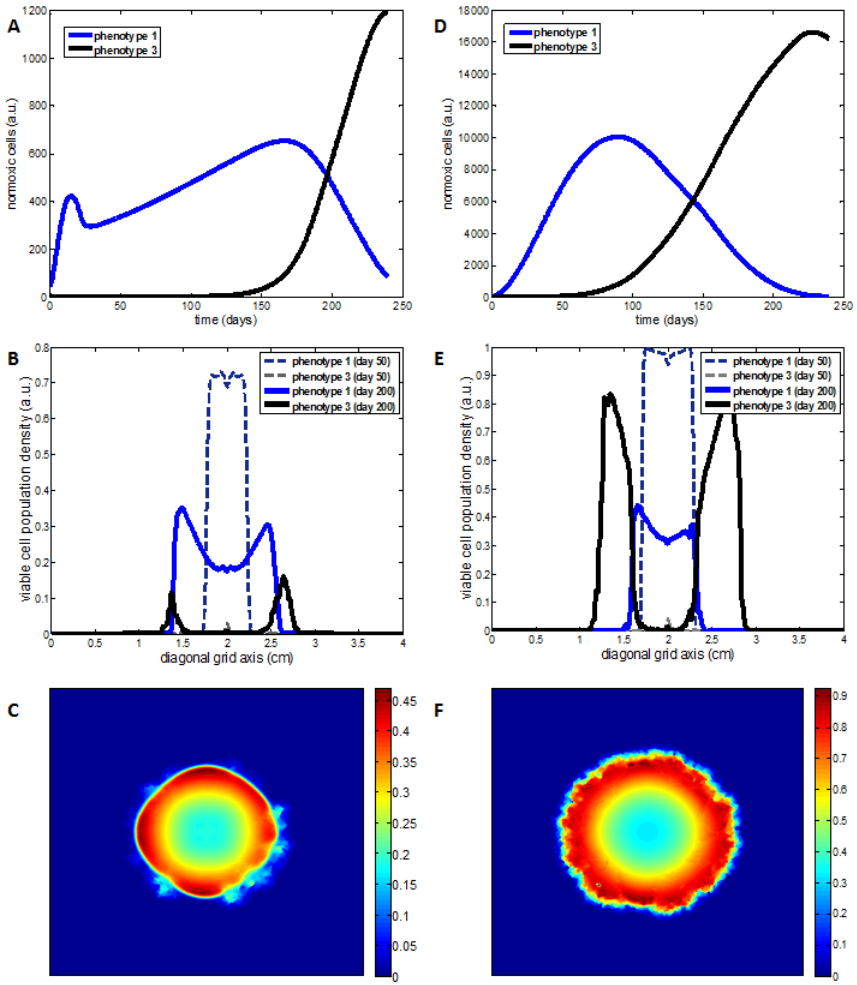
MODELING APPROACHES ADOPTED

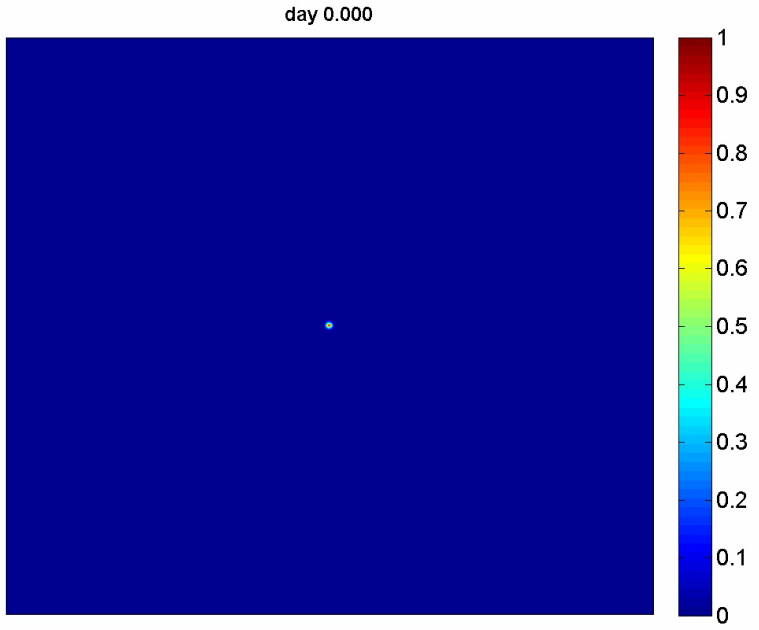
A. Macroscopic, tissue-level model

- **Deterministic, continuous approach: mean field average in space and time**
  - A system of coupled reaction-diffusion-chemo/hapto taxis equations
- **Describes the interactions between:**
  - Cancer cells (which are in different states i.e. normoxic, hypoxic, necrotic and can have different properties i.e. more/less proliferative and more/less invasive)
  - Tumor microenvironment (i.e. vasculature and ExtraCellular Matrix (ECM))
- **Applied in brain tumors (Hinow et al., Math Biosci Eng. 6(3), 2009, Swanson et al., Cancer Res, 71(24), 2011)**
- **Extended to account for polyclonal cell populations (Tzamali et al. PlosOne 2014)**
  - two cancer subpopulations (a more proliferative and a more invasive) form the initial tumor and have distinct phenotypic characteristics that do not change throughout tumor evolution
  - these cancer populations are in a constant competition for space and resources within the tumor microenvironment
- **Solved in 2D** using the Alternative Direction Implicit (ADI) method of finite differences on regular lattice
- **Limitations**
  - Biomechanical description of the tumor microenvironment is NOT considered in the current setup
  - **The whole is not always the sum of its parts! -Aristotle**

PROLIFERATIVE & INVASIVE PHENOTYPES

Poorly-vascularized **Well-vascularized**



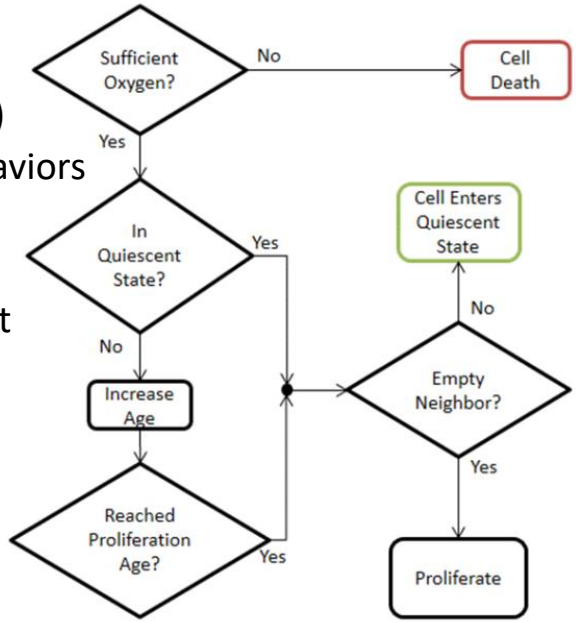


E. Tzamali , G. Grekas, K. Marias, V. Sakkalis, PlosOne, 2014

MODELING APPROACHES ADOPTED

B. Individual, cell-based model

- **Discrete or hybrid, discrete-continuous (HDC) approach**
- **Each cancer cell is described by a discrete cellular automaton (CA)**
  - CA are capable of producing a great variety of unexpected behaviors
  - Cells follow biologically-or experimentally inspired rules
  - Cells are allowed to divide, move or die
  - Cells interact locally with each other and the microenvironment
  - Movement can be stochastic and can adopt different motility mechanisms ranging from individual to collective strategies triggered by different cell-cell and cell-matrix adhesion forces
- **The chemicals of the tumor microenvironment are continuous variables described by partial differential equations**
- **Individual cell-based models** are more suitable to describe *in vitro* experiments and small-sized tumors
- **Solved in 2D regular lattice**
- **Limitations:** Computationally expensive



Anderson A. *et al.*, Cell 127, 905-915, 2006 | Tzedakis G., Tzamali E., Marias K., Sakkalis V., Cancer Informatics 14(Suppl 4):67-81, 2015 | Tzedakis G., Liapis E., Tzamali E., Zacharakis G., Sakkalis V., IEEE-EMBC, 2016 | Oraiopoulou M.E., Tzamali E., Tzedakis G., Vakis A., Papamatheakis J., Sakkalis V., Hindawi Biomed Research International, Basic and Translational Advances in Glioblastoma (Special Issue), 2017 (*accepted paper*)

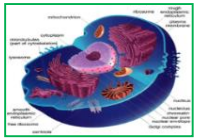
ADVANCED IN MULTI-LEVEL COMPUTATIONAL MODELS, BUT DATA POOR

- *In silico* models are detailed enough, but lack parameters that are roughly estimated or taken for granted as theoretical values based on bibliography.
- We are data poor in most clinical settings! Only some of these are physiological parameters available in routine examinations.

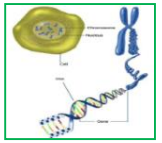
Spatial

1m…

1mm…



1μm…

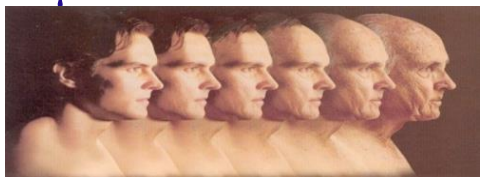


1nm…

Temporal

1ns…

…1s…



…70 years

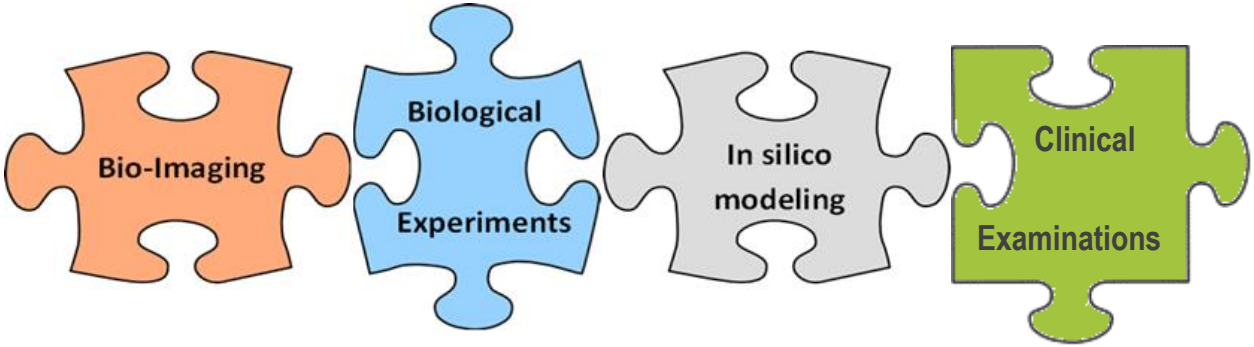
Organs & Systems

INCREASE PREDICTIVE POWER AND CLINICAL RELEVANCE

Collaboration between experimentalists, modelers and clinicians

- Develop mathematical models that faithfully represent the biological processes.
- Design and conduct biological experiments with the aim of parametrizing/constraining the mathematical models
- Both *in vitro* and *in vivo* studies are important steps of model parametrization and validation before translating to clinical cases

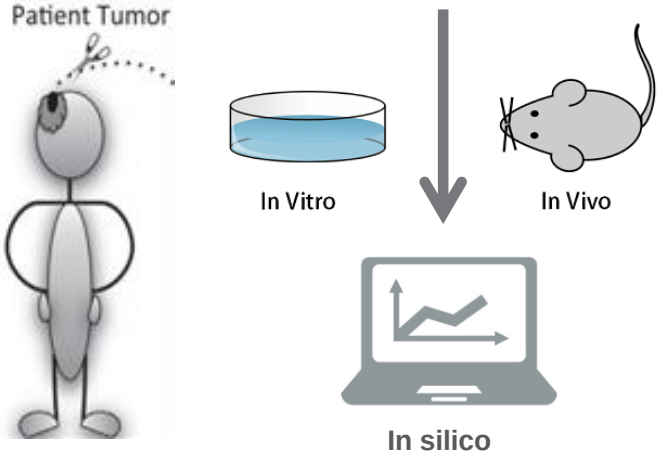
Incorporate information derived from advanced imaging techniques into *in silico* models



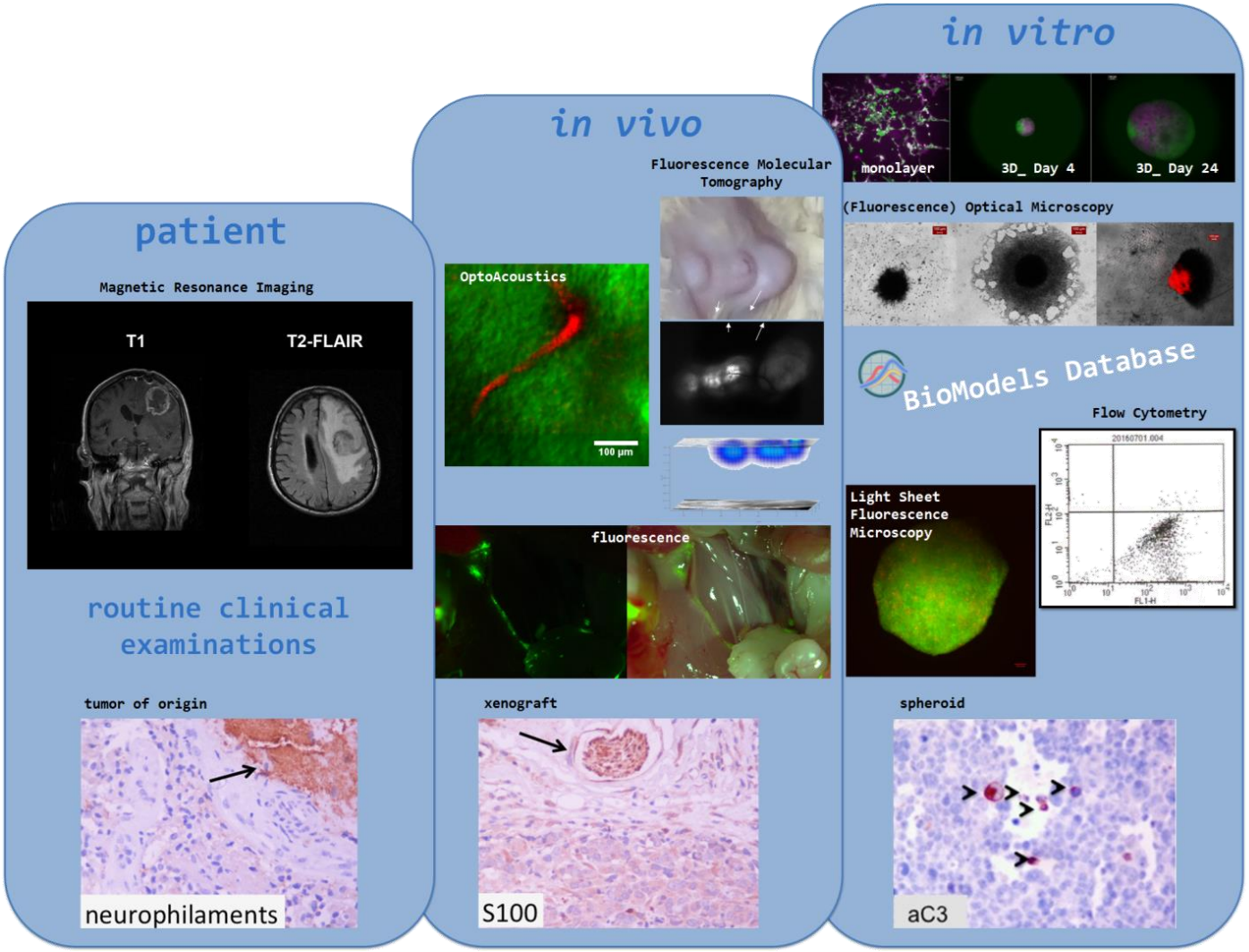
CURRENT RESEARCH INTEREST

- **Focus:** Glioblastoma (GB) , a malignant brain tumor with extremely poor prognosis for the patient. Therapy treatment in GB patients fails mainly due to its extensive inter- and intra-tumoral heterogeneity and its high recurrence potential.
- **Approach:** We combine *Basic and Translational Research* such that clinical, *in vitro* and *in vivo* **patient-specific** data are used to initialize, parametrize and validate GB predictive mathematical models.

  - Patient-derived GB cells are collected during the gross resection or biopsy of patients when still naive from treatment
  - Patient-derived xenografts
  - *In vitro* primary cultures

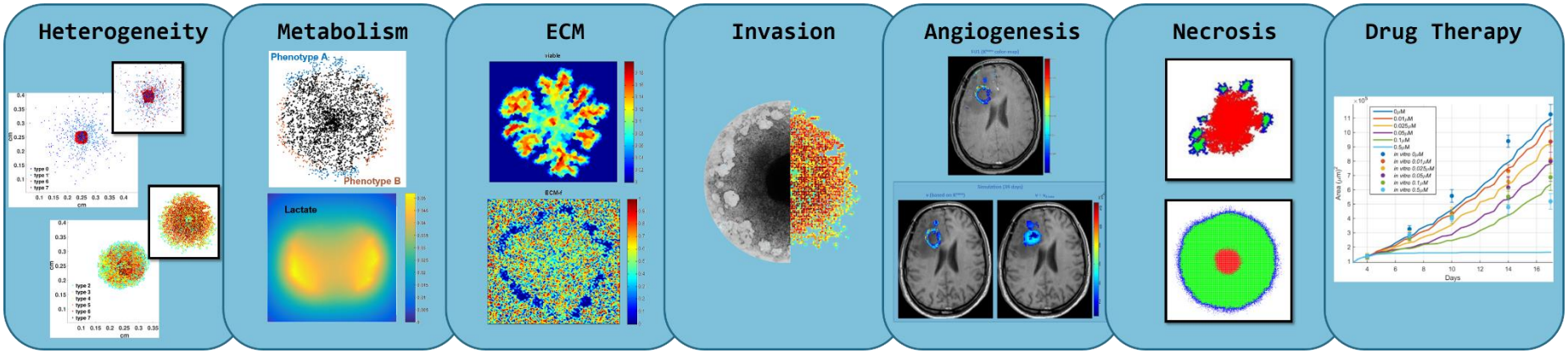


AVAILABLE DATA PER GB PATIENT



FUTURE WORK

The integration of **computational approaches** with **experimental and clinical data**, along with advanced **imaging techniques** is more than important in understanding **brain tumor pathophysiology/pathobiology** and tumor progression in a **patient-specific way**. Our main aim is to ***design a preclinical drug screening tool promoting effective personalized therapy***.

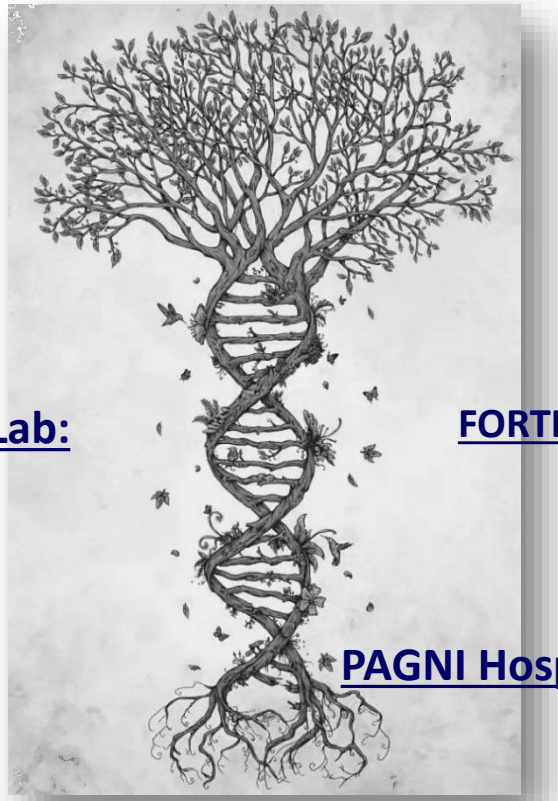


ACKNOWLEDGEMENTS

FORTH – ICS - CBML:
Vangelis Sakkalis
Eleftheria Tzamali
Georgios Tzedakis
Mariam-Eleni Oraiopoulou

FORTH - IMBB - Gene Expression Lab:

Joseph Papamatheakis



FORTH – IESL – *In vivo* Imaging Lab:
Giannis Zacharakis
Stylianos Psycharakis

PAGNI Hospital - Neurosurgery Clinic:
Antonios Vakis
Katerina Manolitsi

Other:

Evangelos Liapis
Elias Drakos
Despina Tsoukatou

Thank You