A hybrid multiscale computational framework to personalize and optimize cancer therapy

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Context

Important progress has been made in cancer therapy over the past 10 years

- a wider range of therapeutic options
- more specific molecules that reduce side effects
- more individualized therapies

However, tumour development becomes more complex with therapies

- resistance to treatment
- selection of the most aggressive phenotypes

The new objectives

- rationalize the use of the therapies
- combine the therapies to enhance the effects
- adapt the therapies with the evolution of the tumour and patient states

Why the need for a virtual tumour ?

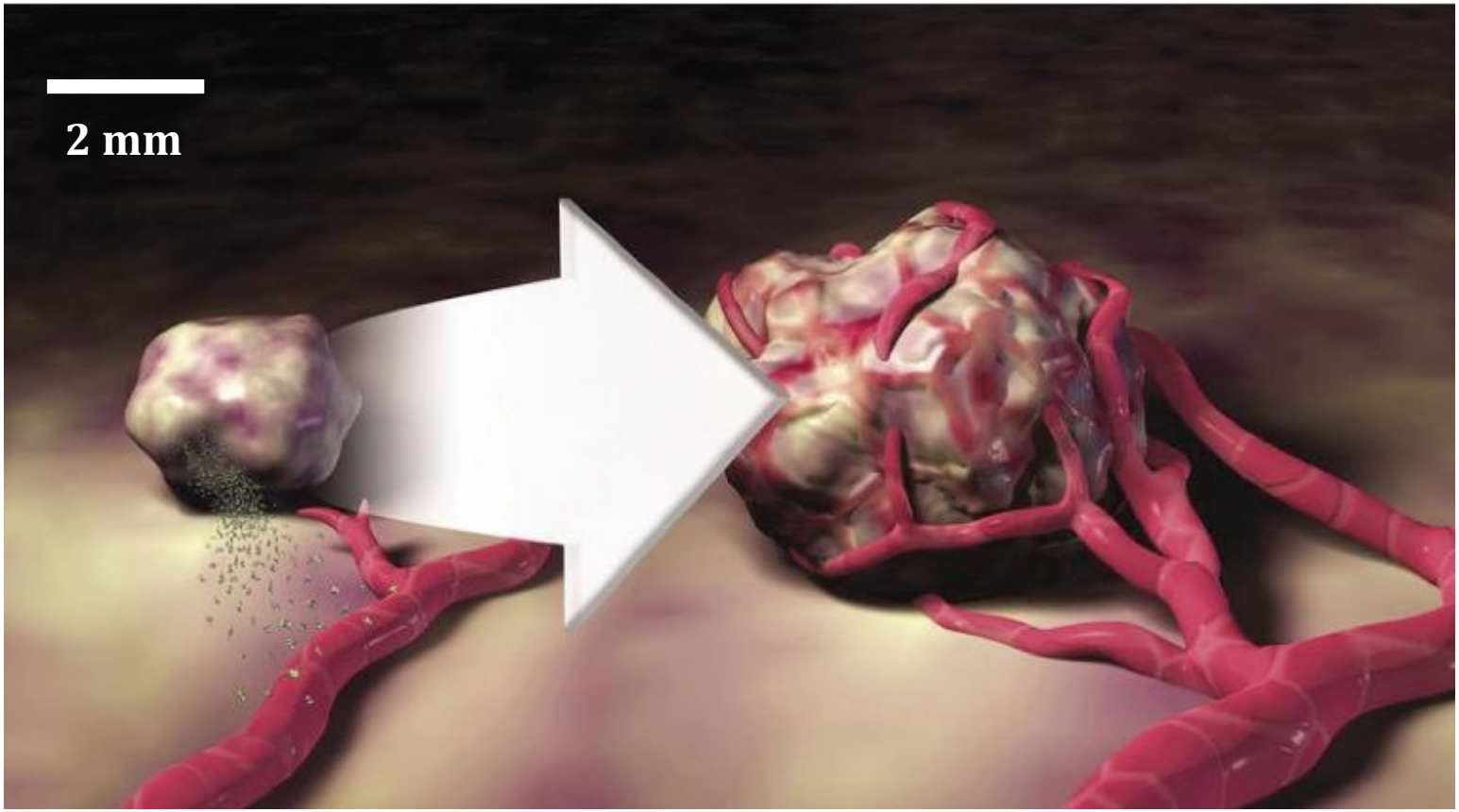
Provide an integrated vision of the phenomenon

Gives the ability to make virtual experiments

- to test hypotheses
- to better understand the system
- to predict the system's reaction
- to optimize the solutions

Development of a solid tumour

Avascular growth **Vascular growth**



hypoxia induces VEGF release

VEGF induces angiogenesis

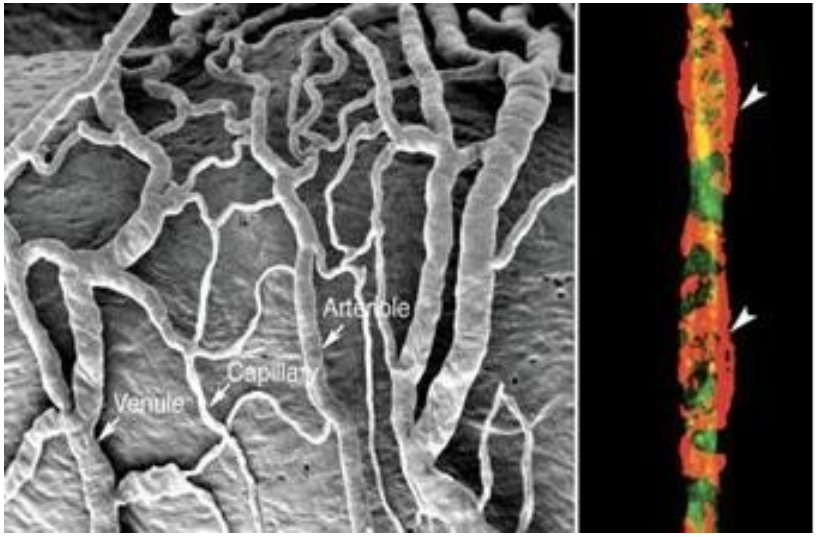
Development of a solid tumour

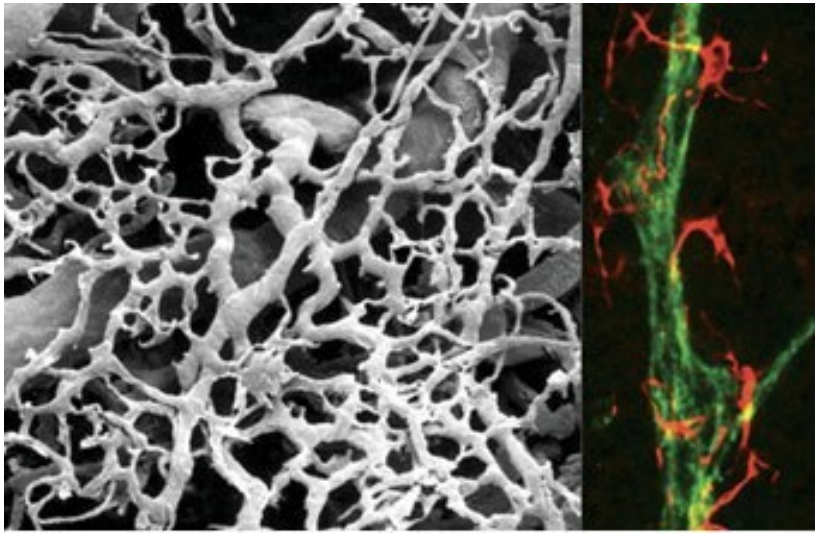
Avascular growth **Vascular growth**

hypoxia induces VEGF release

Cells escape from the tumour mass

Normal *vs* tumoral vascular network





Normal network

- organized network
- impermeable vessels
- pericytes coverage (red)

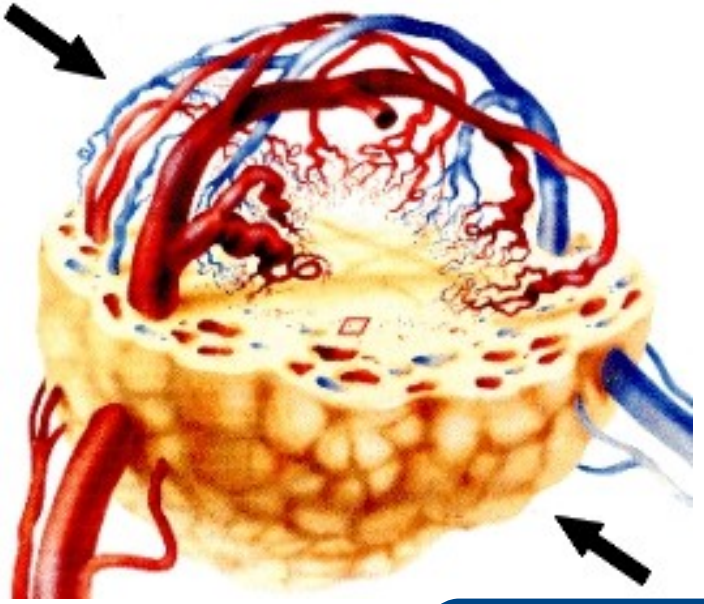
Tumour network

- disorganized (abnormal, dense and tortuous)
- permeable vessels
- no pericytes coverage (red)

Therapeutic modes under consideration

Antivascular agents

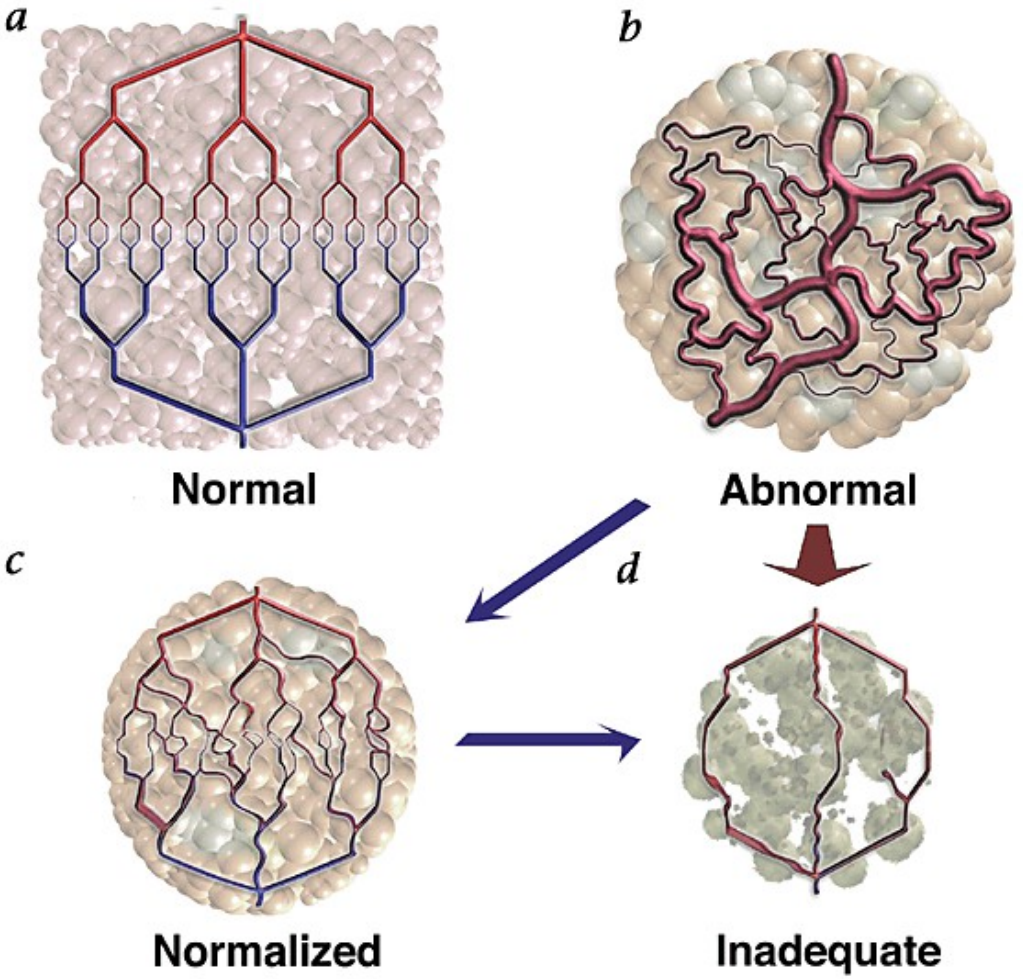
target = vessels



Cytotoxic molecules

target = tumour cells

Therapeutic coupling

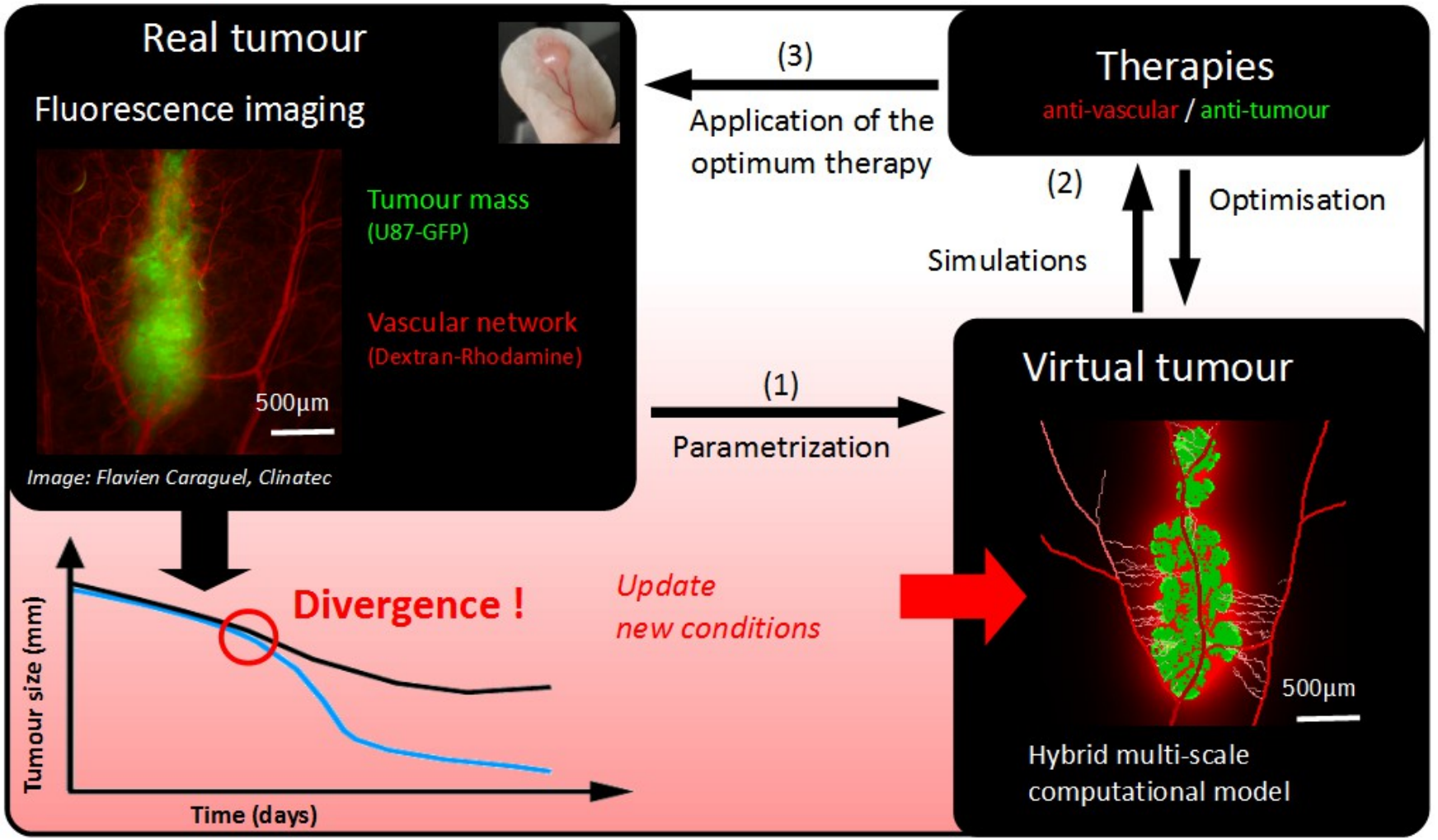


Antivascular agents can **temporarily normalize** the vascular network

The delivery of cytotoxic molecules to the tumour is **transiently improved**

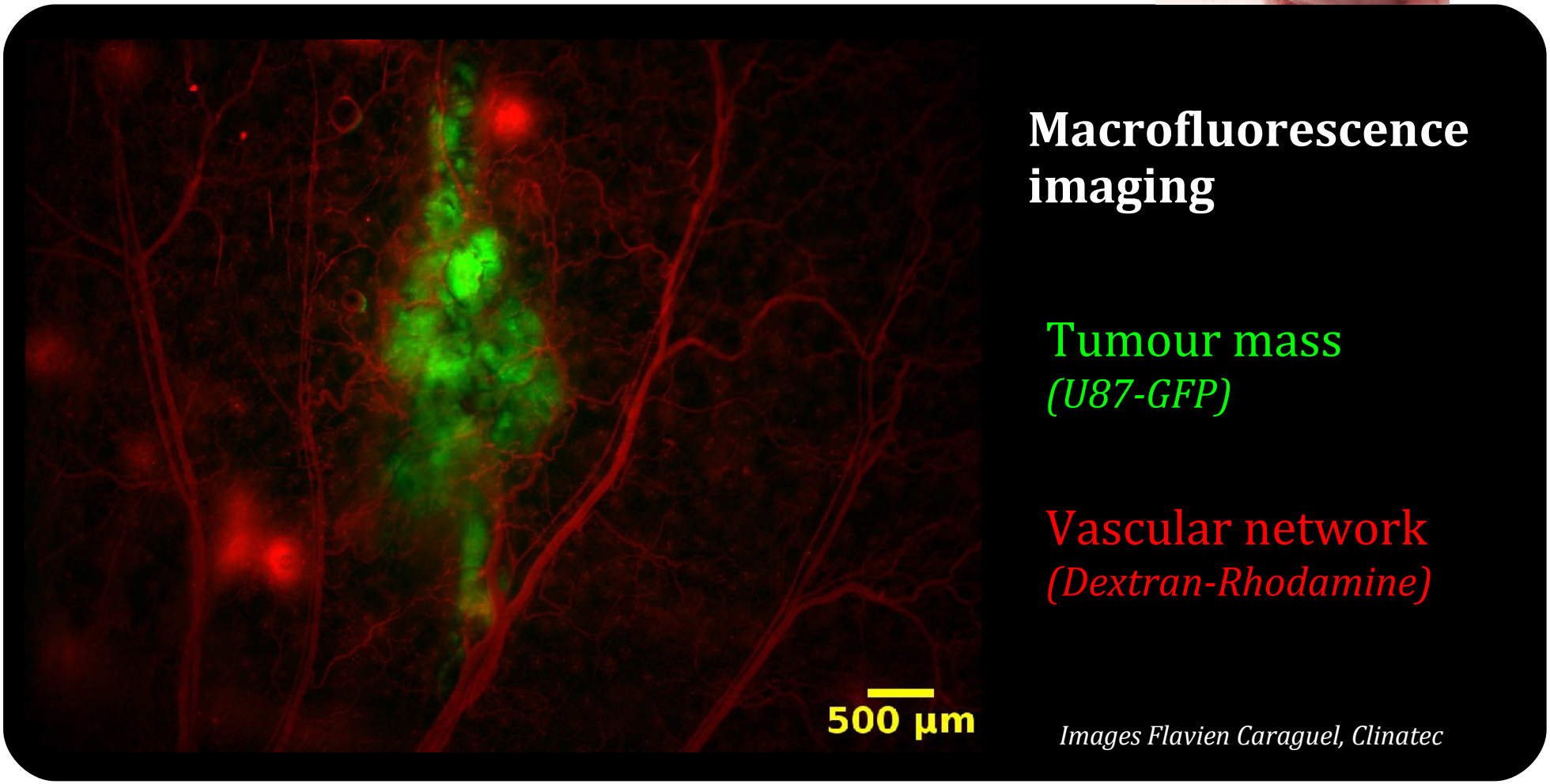
Therapeutic window

Computer-assisted therapeutic strategy



Experimental model

in vivo observation through the mouse pinna



Macrofluorescence imaging

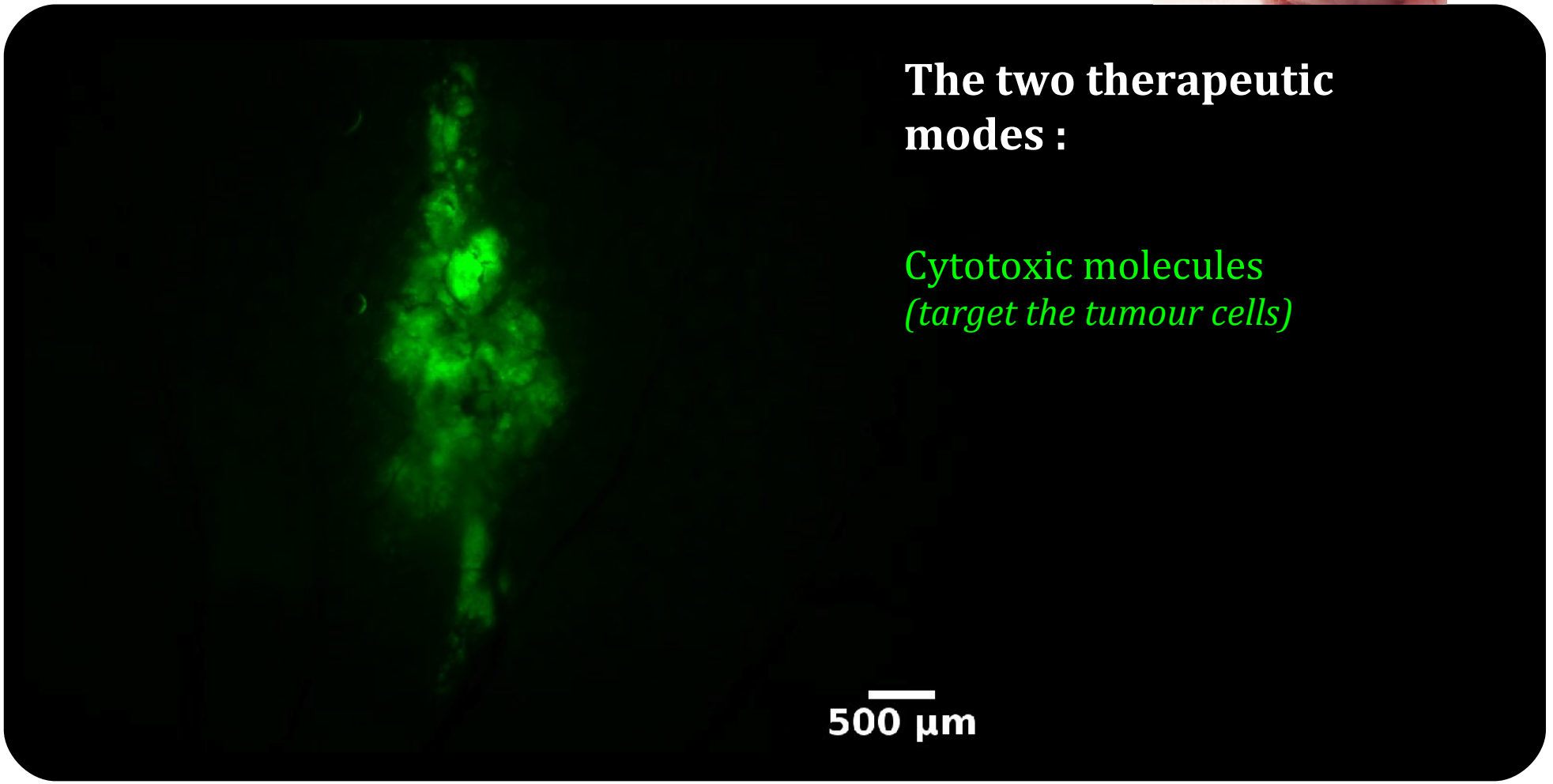
Tumour mass
(U87-GFP)

Vascular network
(Dextran-Rhodamine)

Images Flavien Caraguel, Clinatec

Experimental model

in vivo observation through the mouse pinna

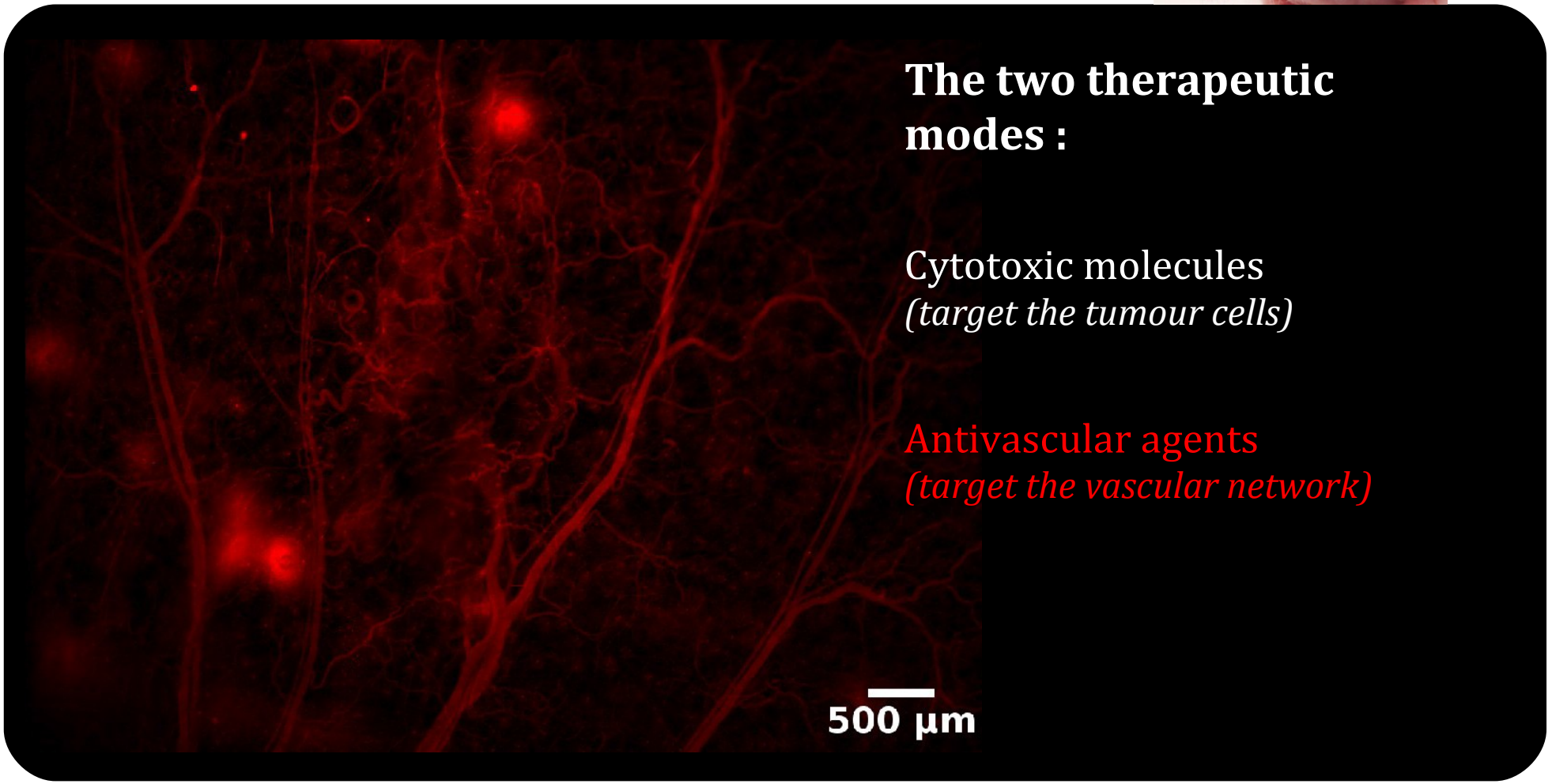


The two therapeutic modes :

Cytotoxic molecules
(target the tumour cells)

Experimental model

in vivo observation through the mouse pinna



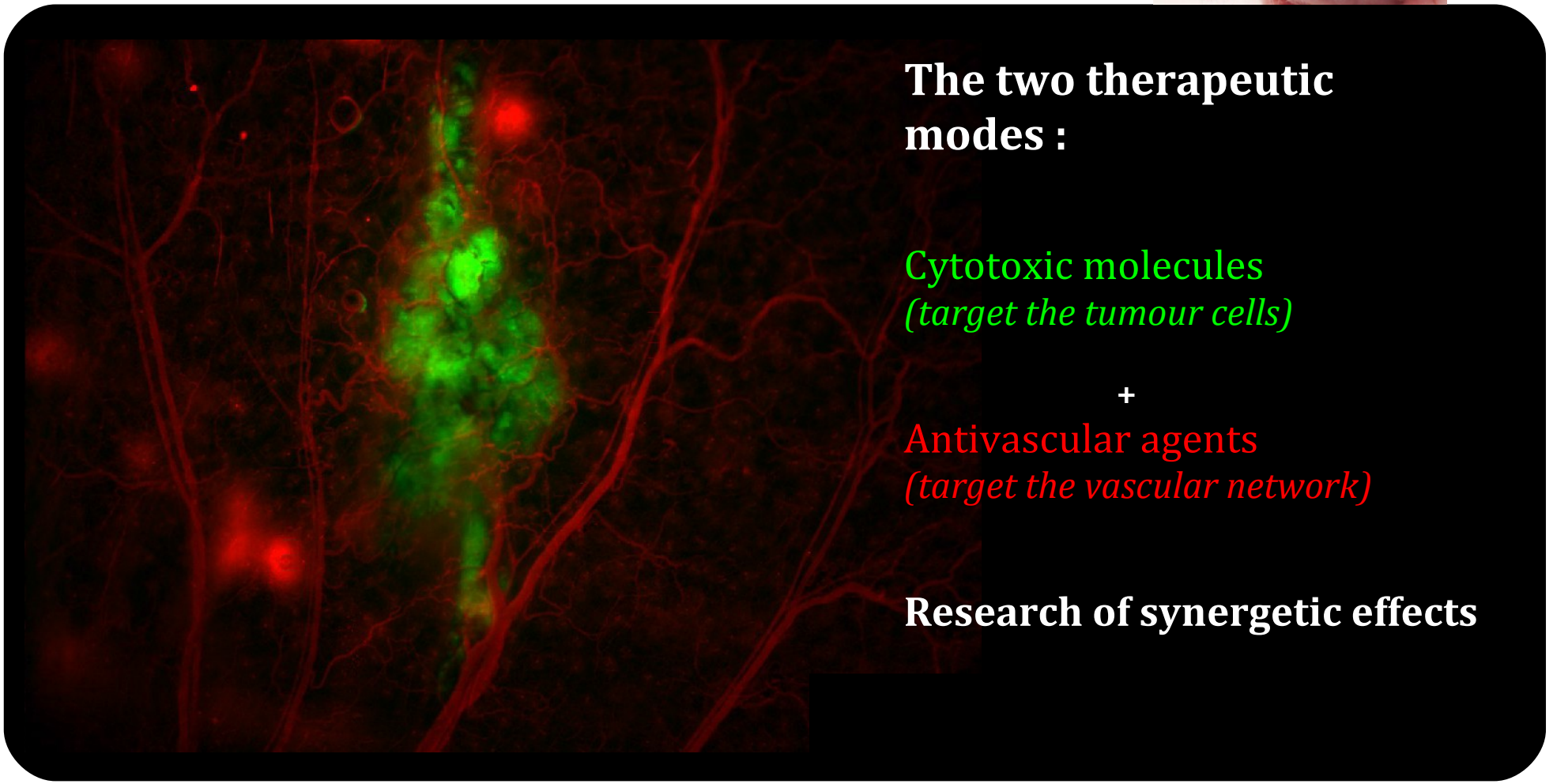
The two therapeutic modes :

Cytotoxic molecules
(target the tumour cells)

Antivascular agents
(target the vascular network)

Experimental model

in vivo observation through the mouse pinna



The two therapeutic modes :

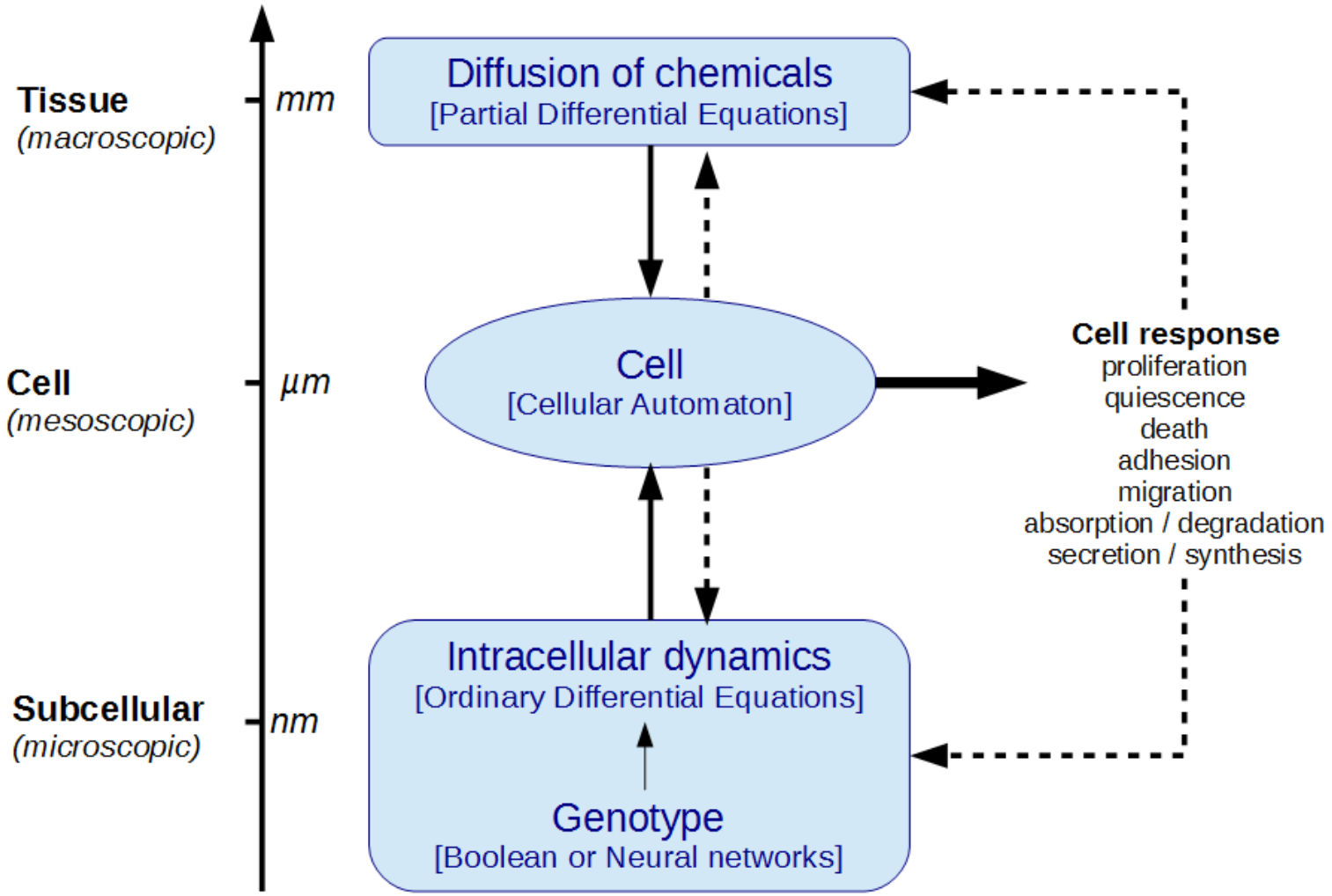
Cytotoxic molecules
(target the tumour cells)

+

Antivascular agents
(target the vascular network)

Research of synergetic effects

A cell-centred hybrid multiscale model

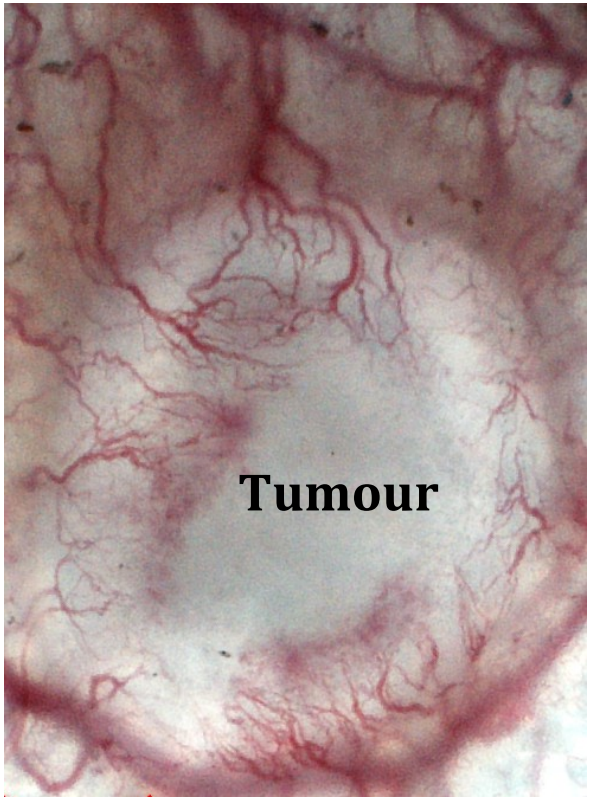


The computational model

Tumour growth, metastatic invasion
Cell cycle, metabolism and death

Angiogenesis, vascular adaptation
Vessels permeability, diffusion of therapeutic molecules and oxygen

Image Ecrins Therapeutics



The computational model

Tumour growth, metastatic invasion
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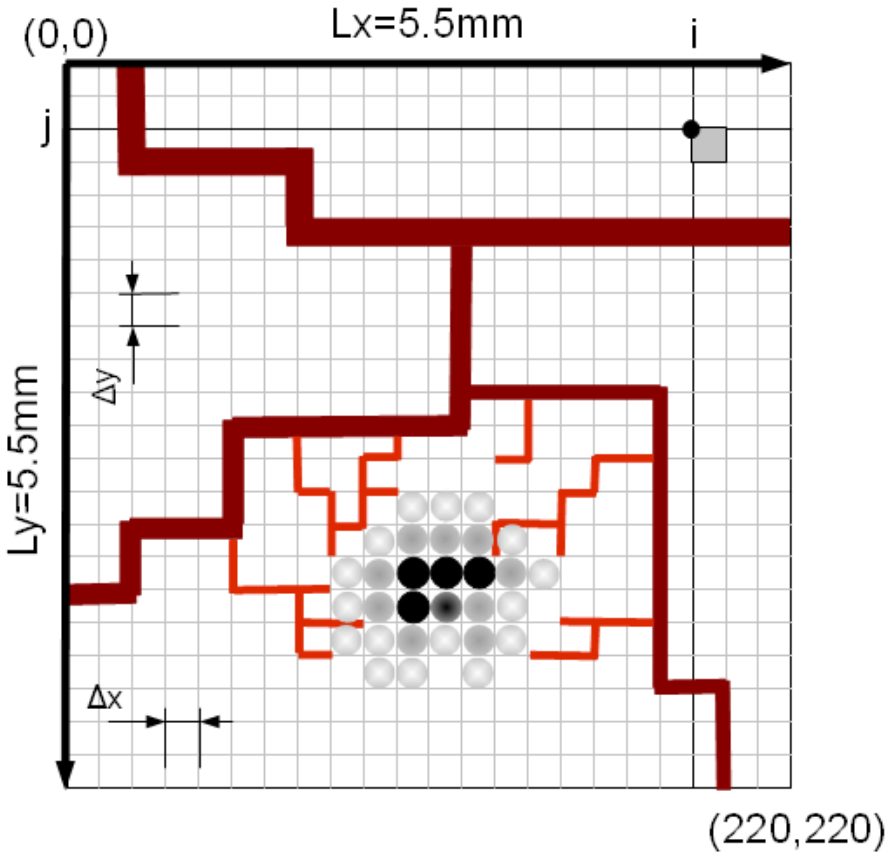


Diffusive species

Proteases

Matrix degrading enzyme *(m)*

$$\frac{\partial m}{\partial t} = D_m \nabla^2 m + \alpha_m n_{i,j} - \nu_m m$$

Endothelial cell

Vascular degrading enzyme *(p)*

$$\frac{\partial p}{\partial t} = D_p \nabla^2 p + \alpha_p P_{i,j} - \nu_p p$$

Proliferative cell

Growth factors *(V)*

$$\frac{\partial V}{\partial t} = D_V \nabla^2 V + \alpha_V Q_{i,j} - \nu_V V - \lambda_V W_{i,j} min(V, V_{max})$$

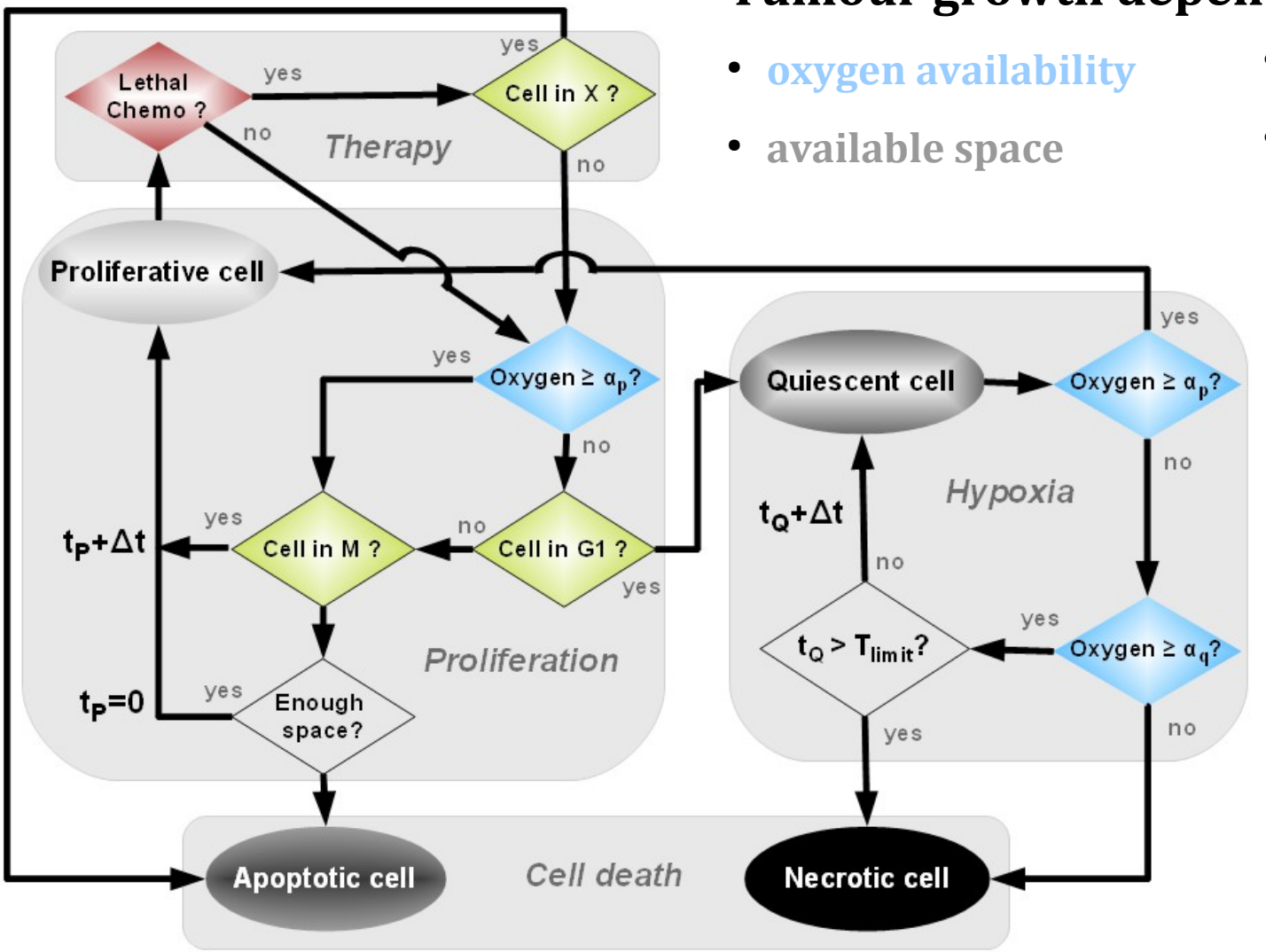
Quiescent cell *Vessels "weight"*

Oxygen *(O)*

$$\frac{\partial O}{\partial t} = D_O \nabla^2 O + \gamma_v W_{i,j} (O_v - O) - k_{i,j} O$$

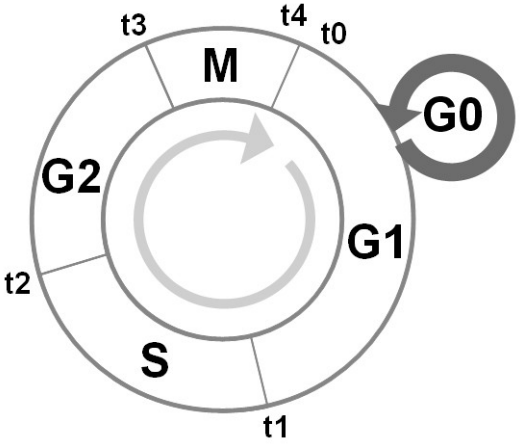
Vessels "weight" *kn, kp, kq*

Modelling tumour growth



Tumour growth depends on:

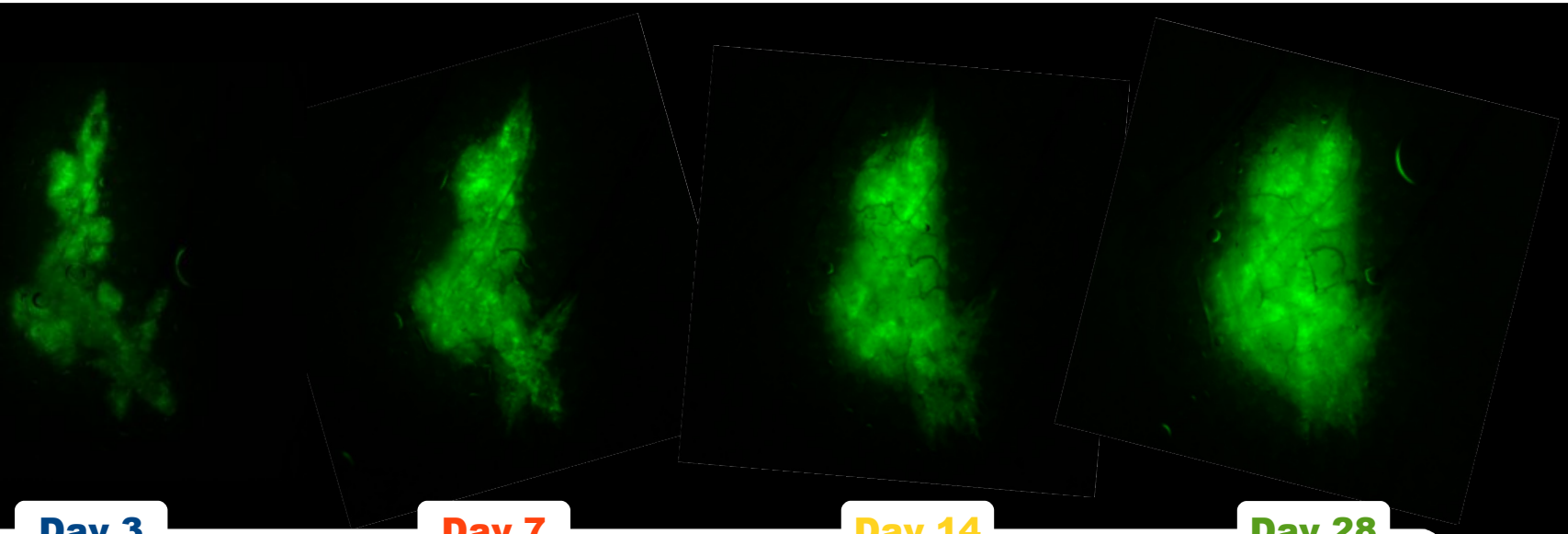
- oxygen availability
- available space
- cell cycle
- concentration of cytotoxic molecules

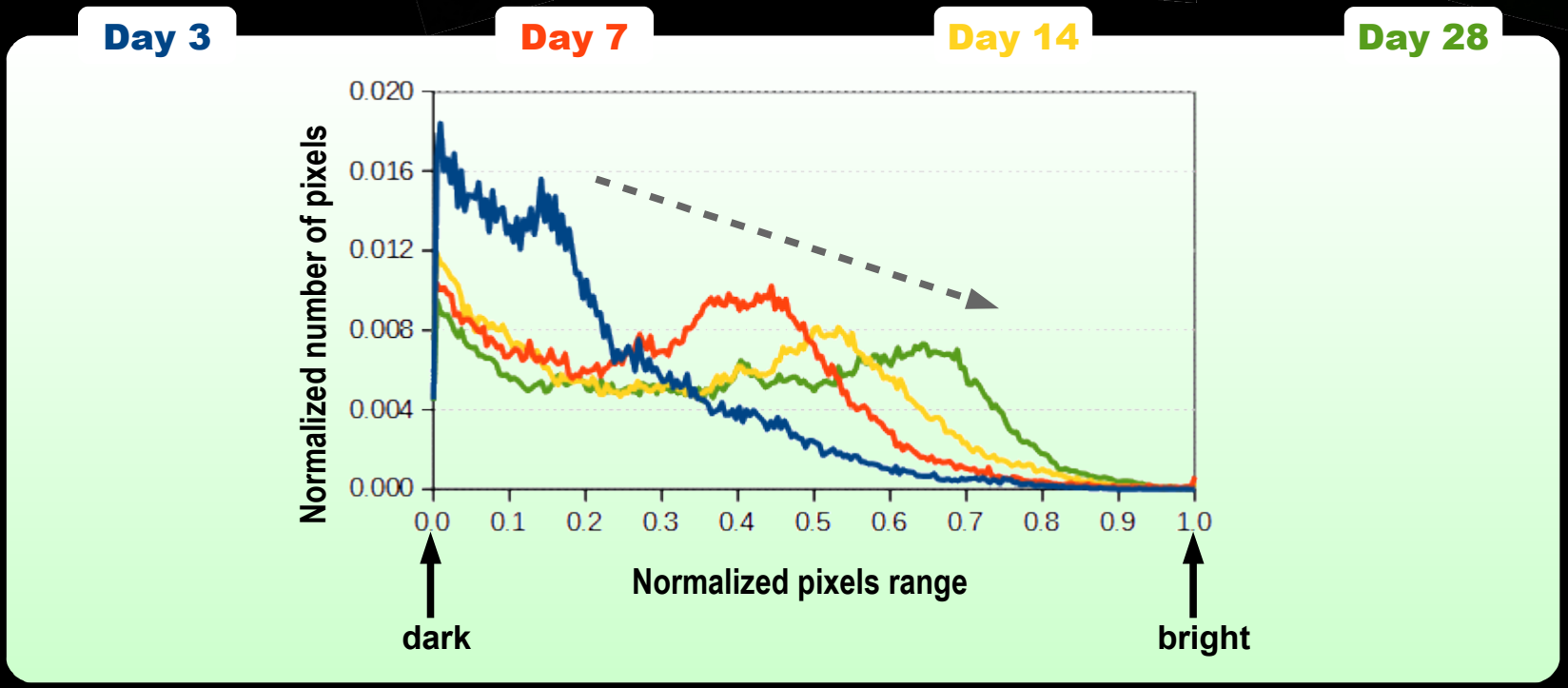


Tumour growth : texture and size

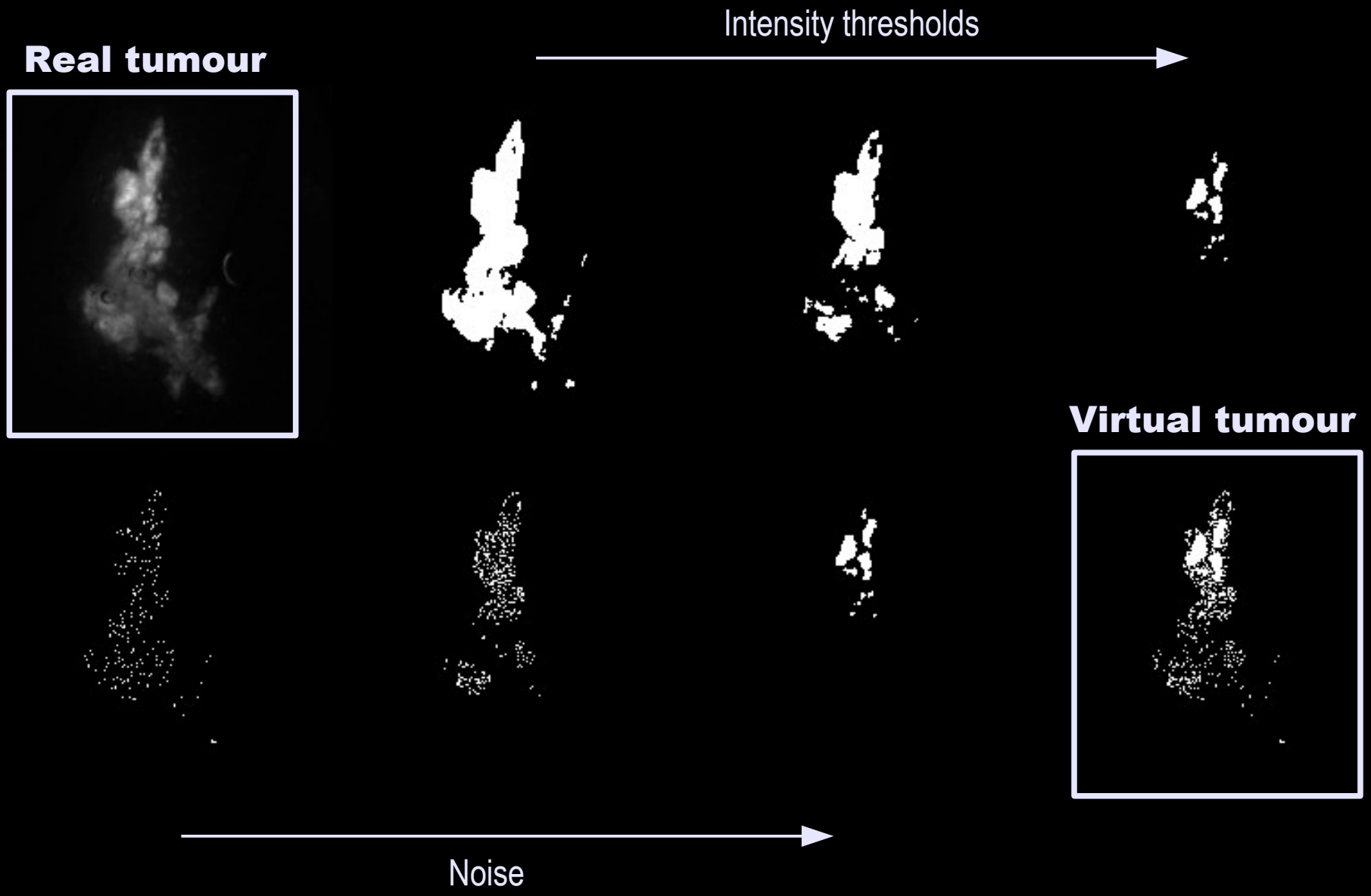
Real tumour

U87-GFP





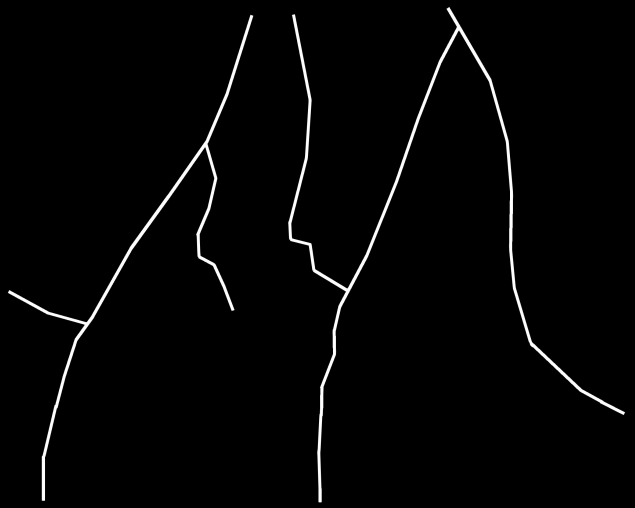
Initialization of the tumour



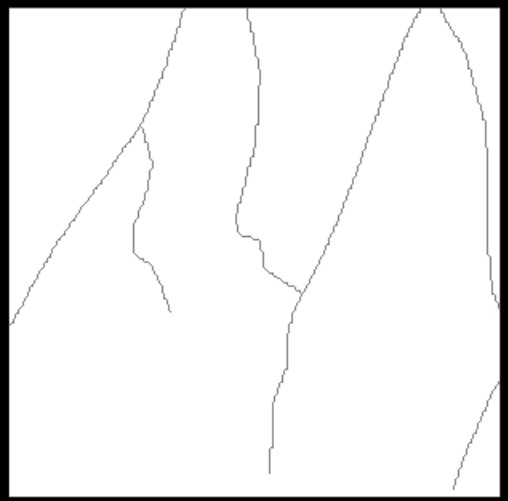
Initialization of the tumour

Bright field image

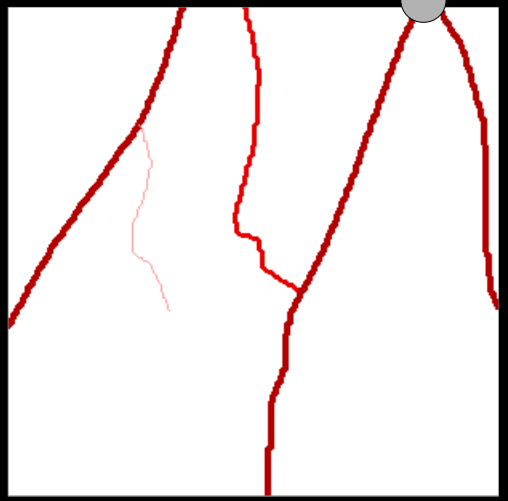
Vascular skeleton



Cropped image

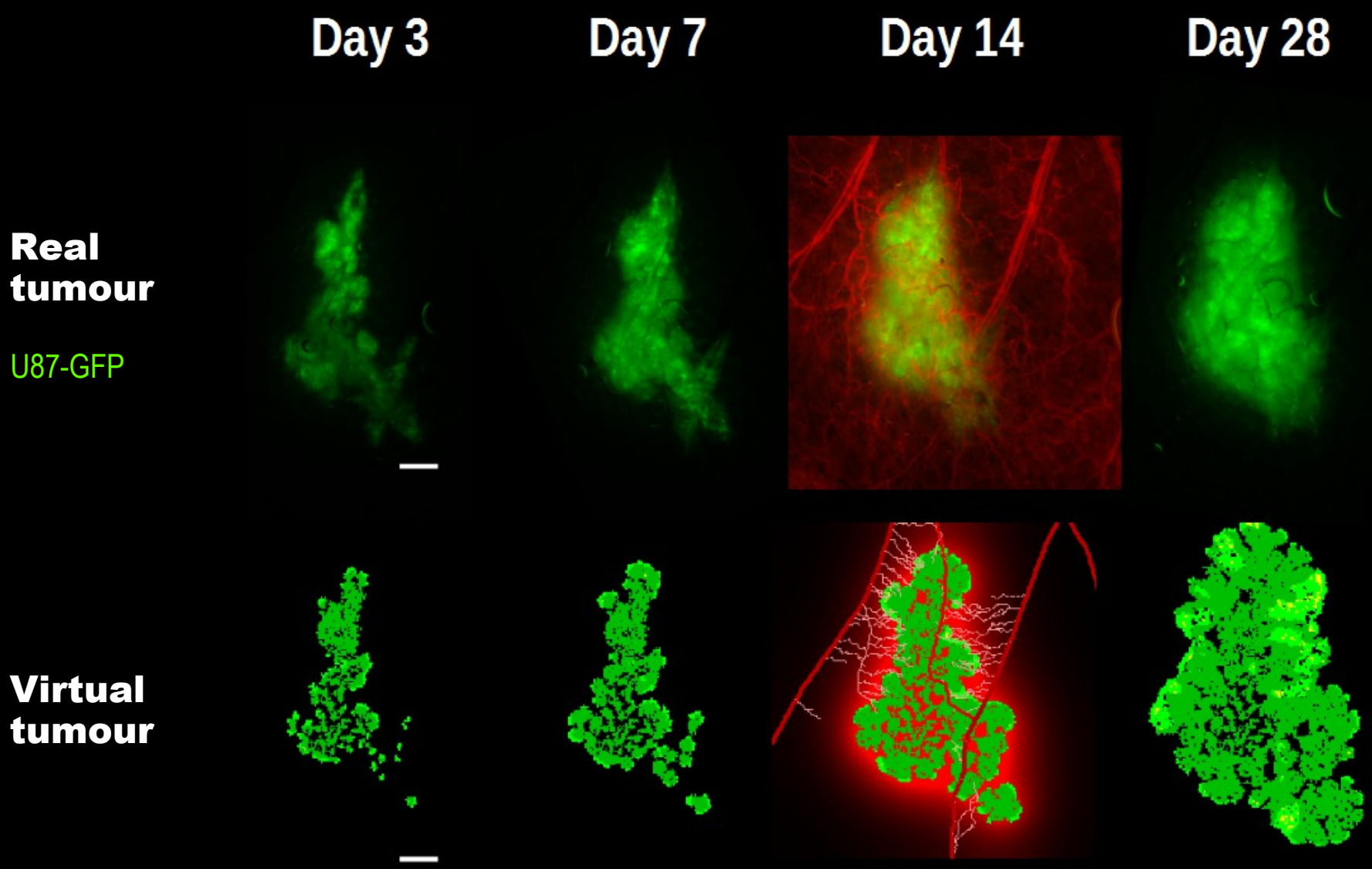


Perfusion

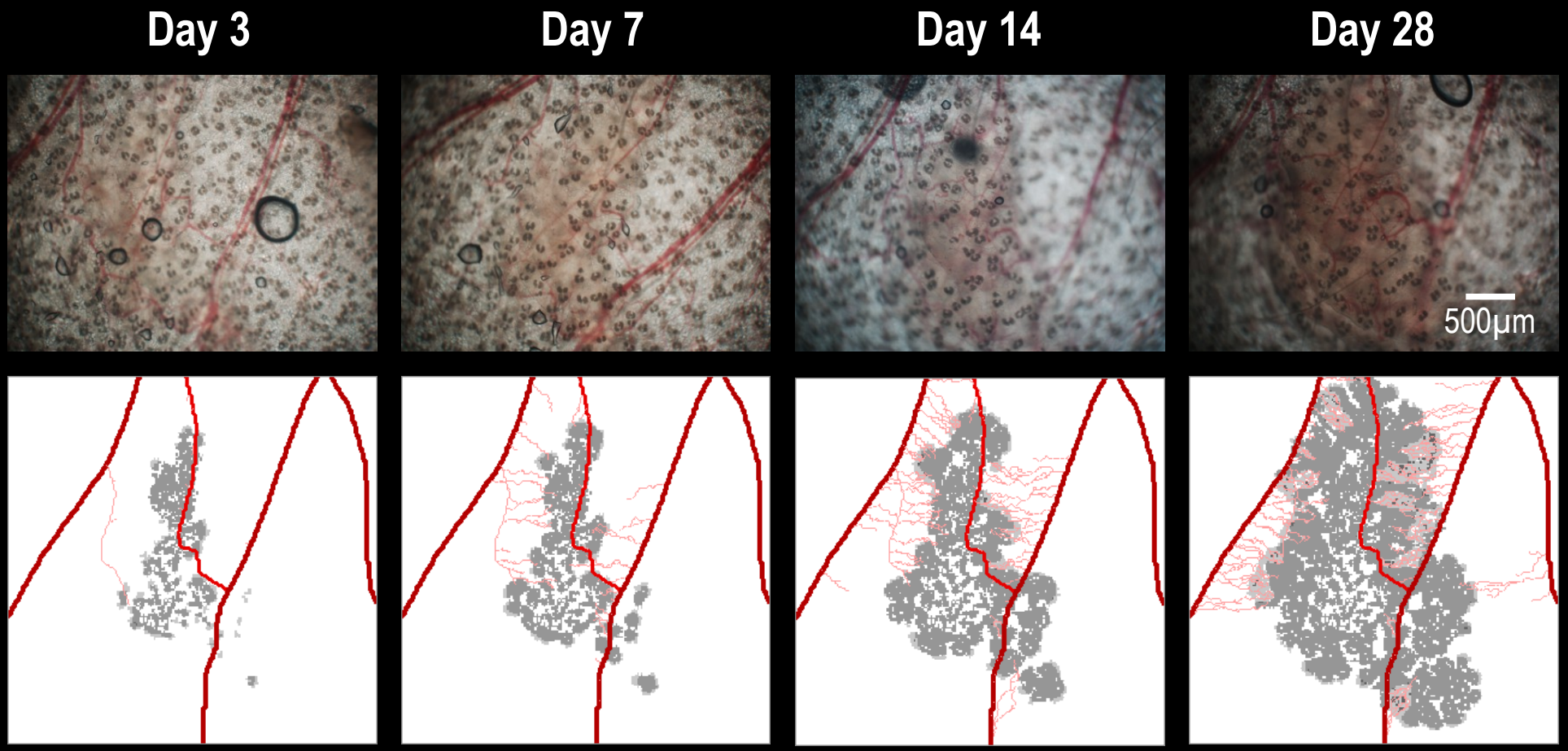


Initial vasculature + tumour

Real *vs* virtual tumour

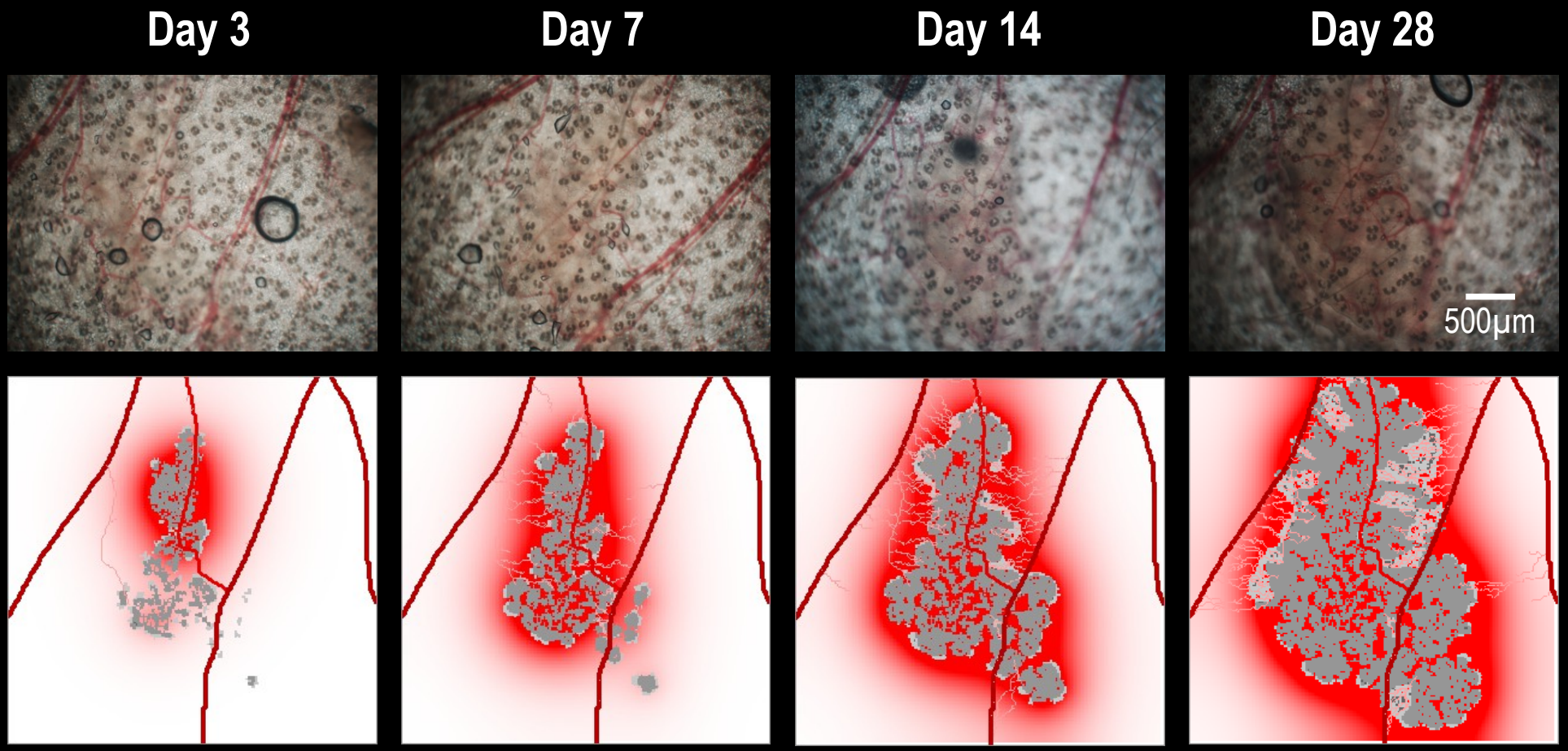


Real *vs* virtual tumour



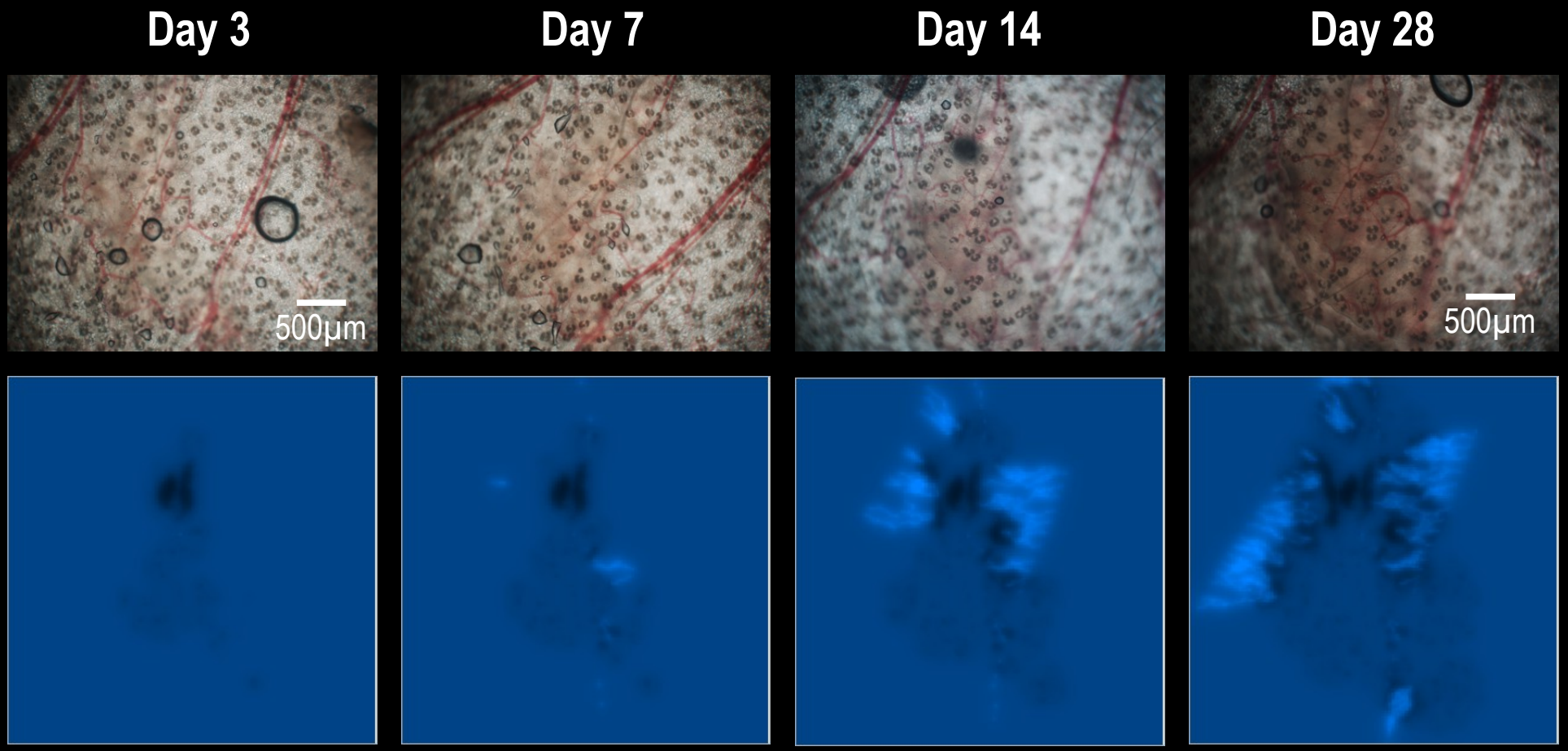
Angiogenesis

Real *vs* virtual tumour

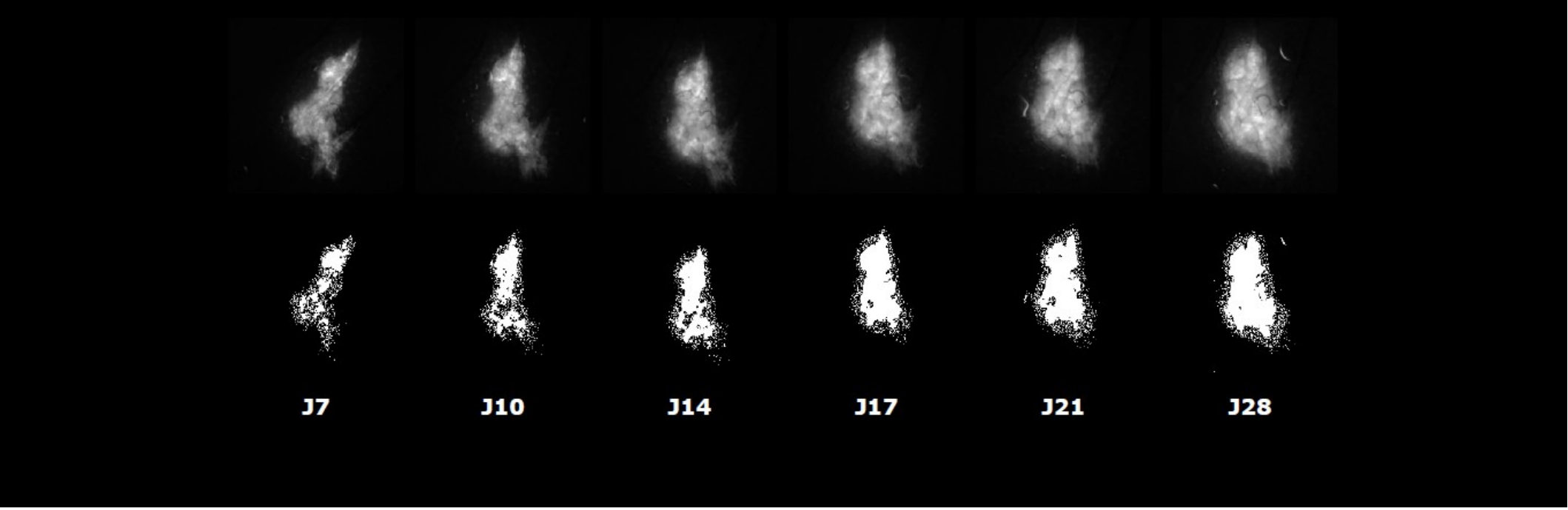


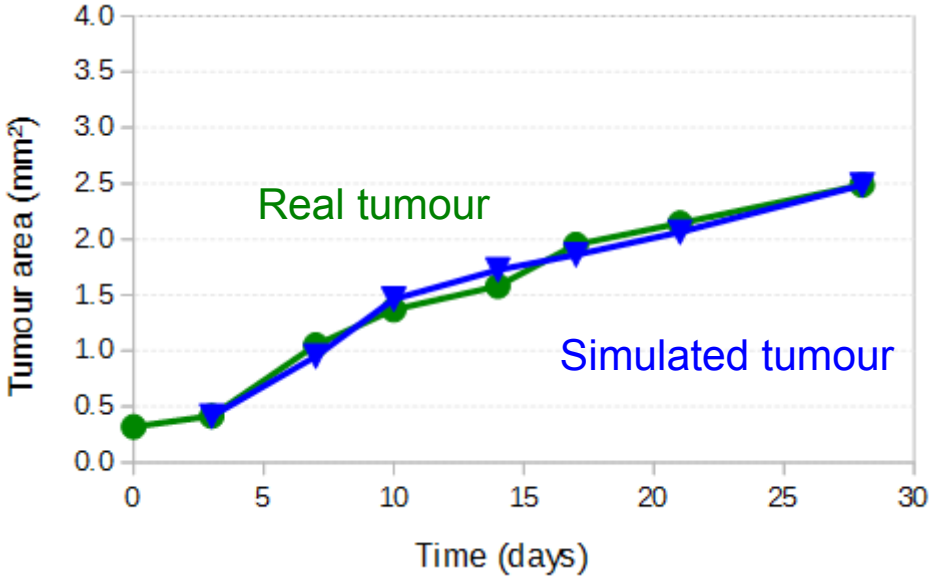
Angiogenesis + VEGF diffusion

Real *vs* virtual tumour



Growth without treatment





Model validation

✔ Comparison of simulated and observed kinetics of tumour development

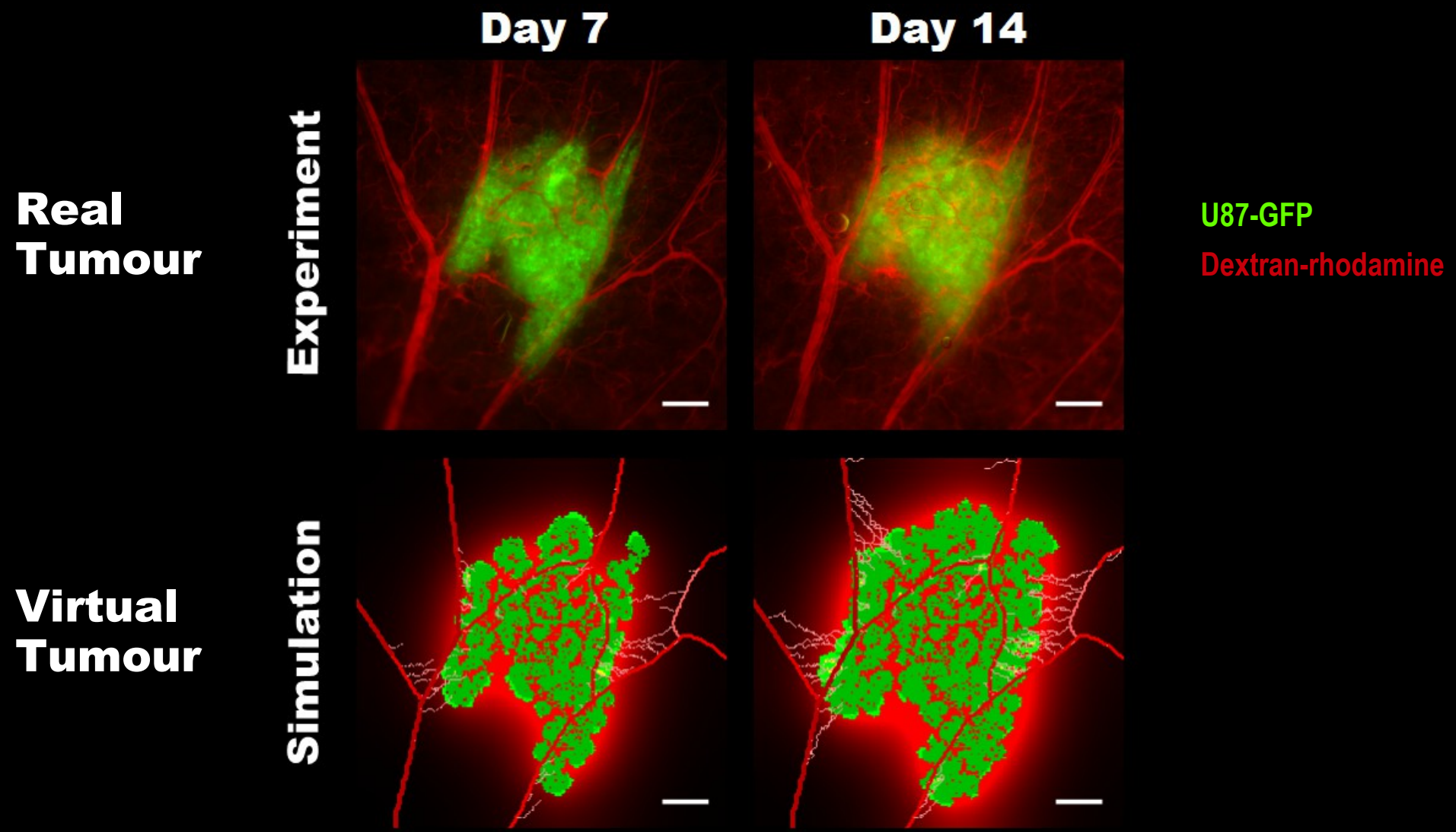
✔ Comparison of virtual and histological tumour slices

✔ **Adjustment of parameters and validation of hypotheses**

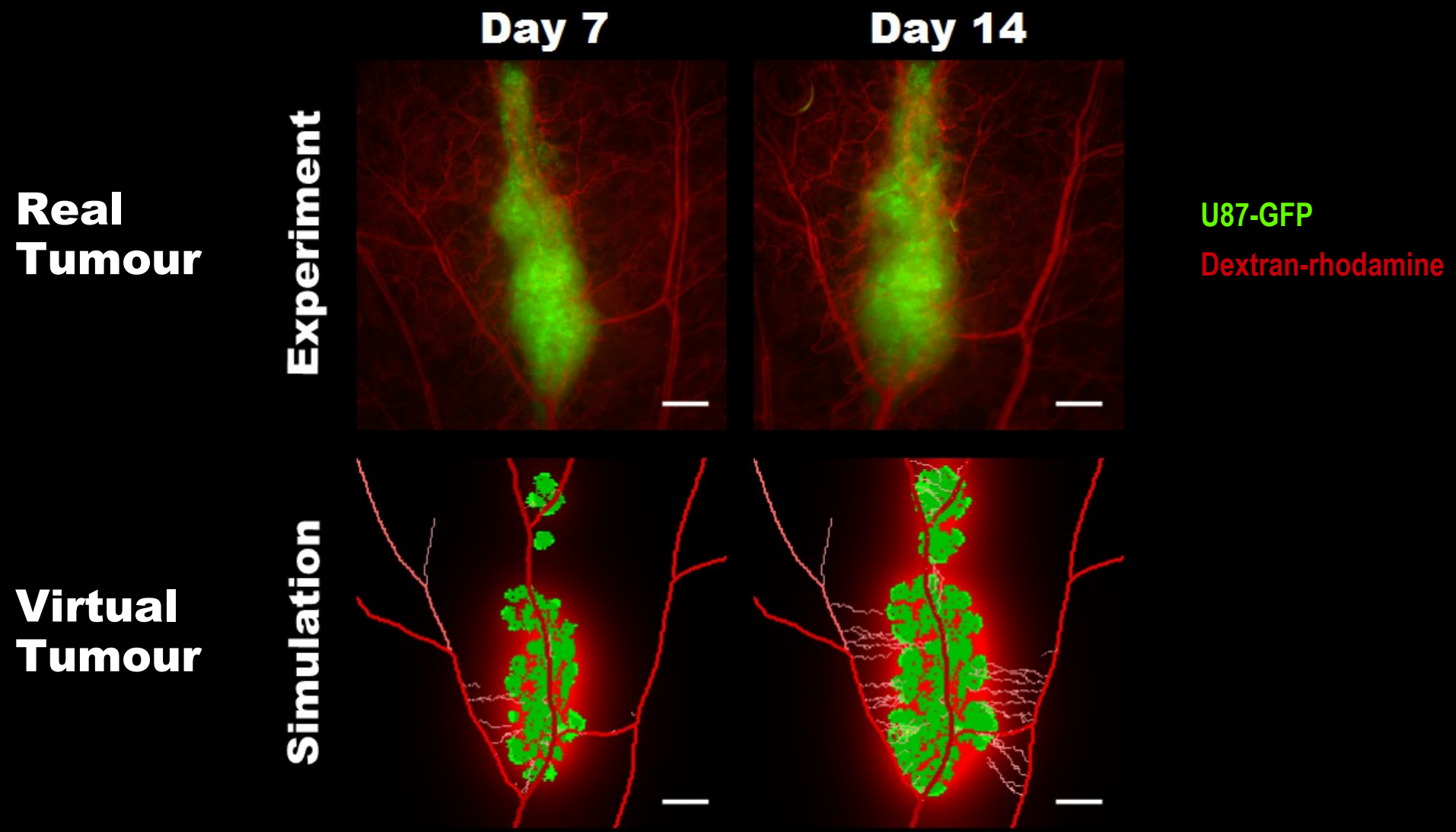
Parameters adjusted

- Durations of cell cycle phases and level of variability
- **Oxygen thresholds for transition to quiescence (hypoxia) and for cell death**
- Oxygen consumption rates for each cell type
- Vessels permeability to oxygen
- Diffusion, production/consumption rates of vascular proteases

Real *vs* virtual tumour



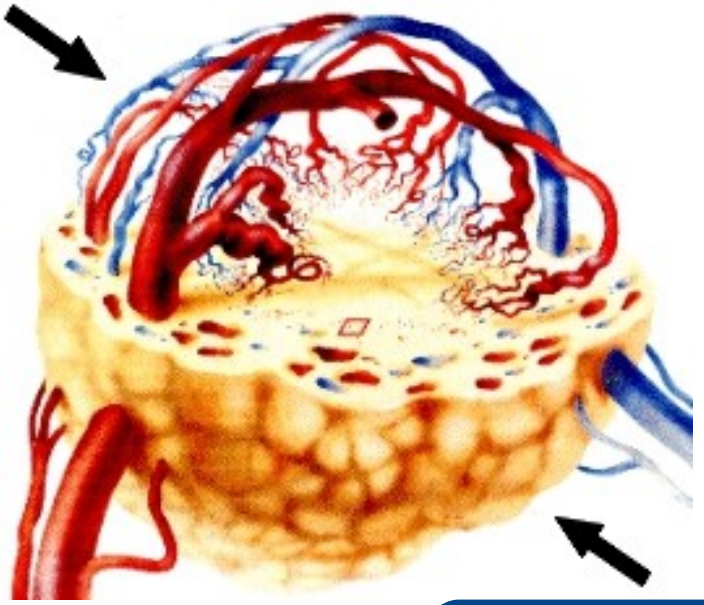
Real *vs* virtual tumour



Therapies

Antivascular agents

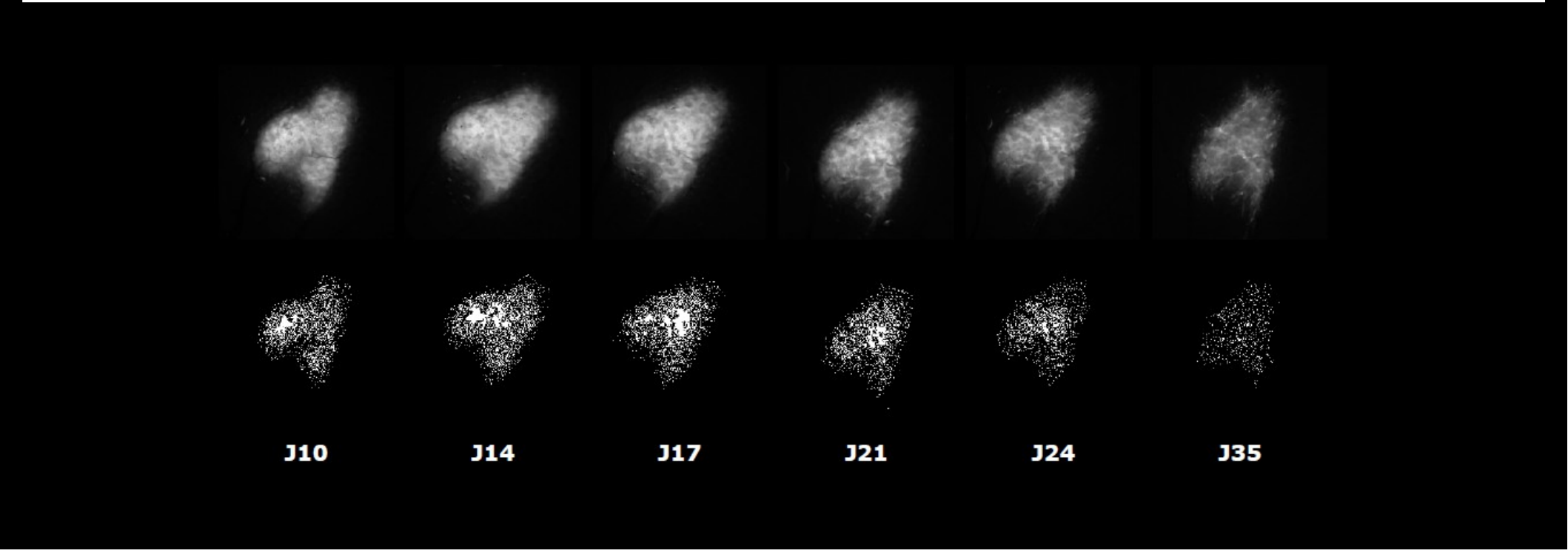
target = vessels



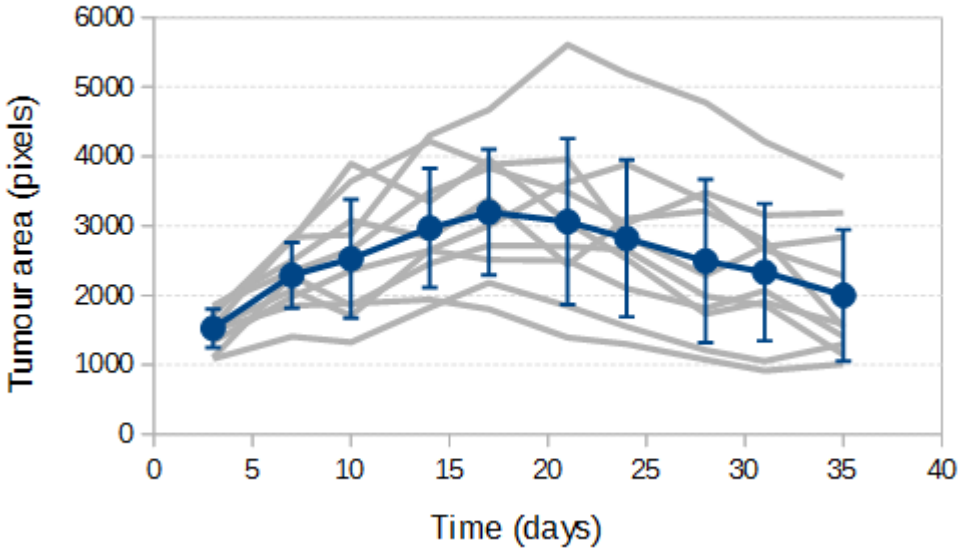
Cytotoxic molecules

target = tumour cells

Growth with cytotoxic treatment (temodal)



Average evolution from 12 tumours

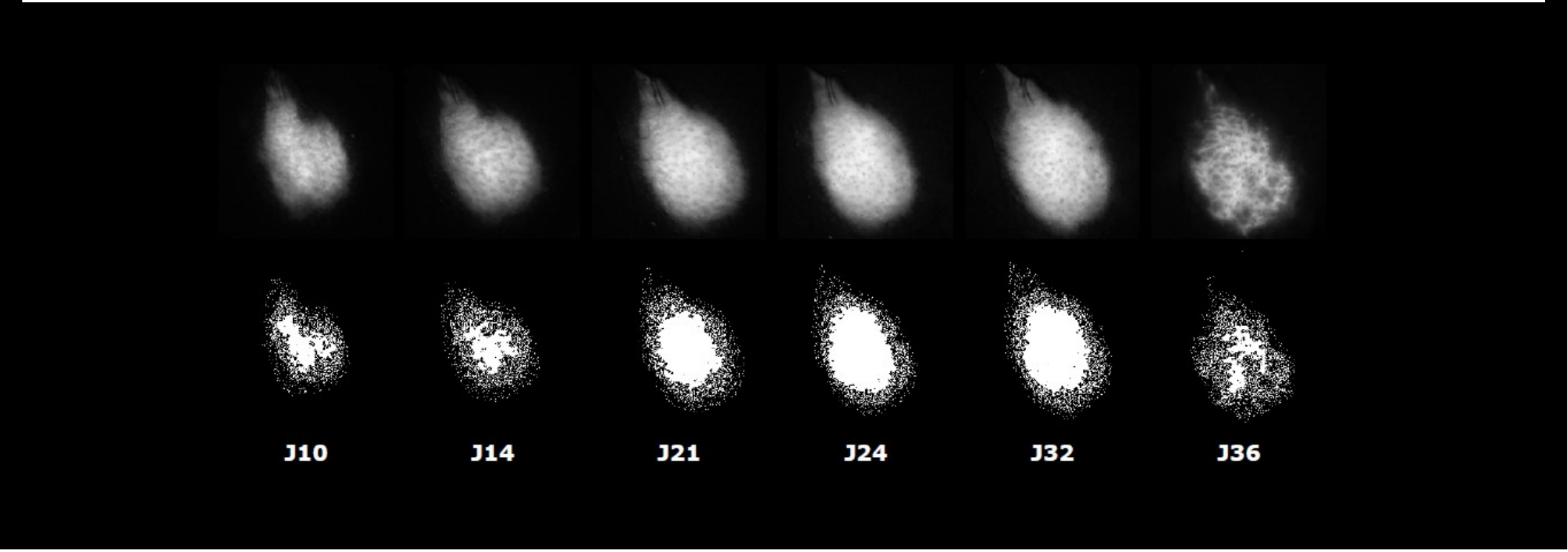


Dosage

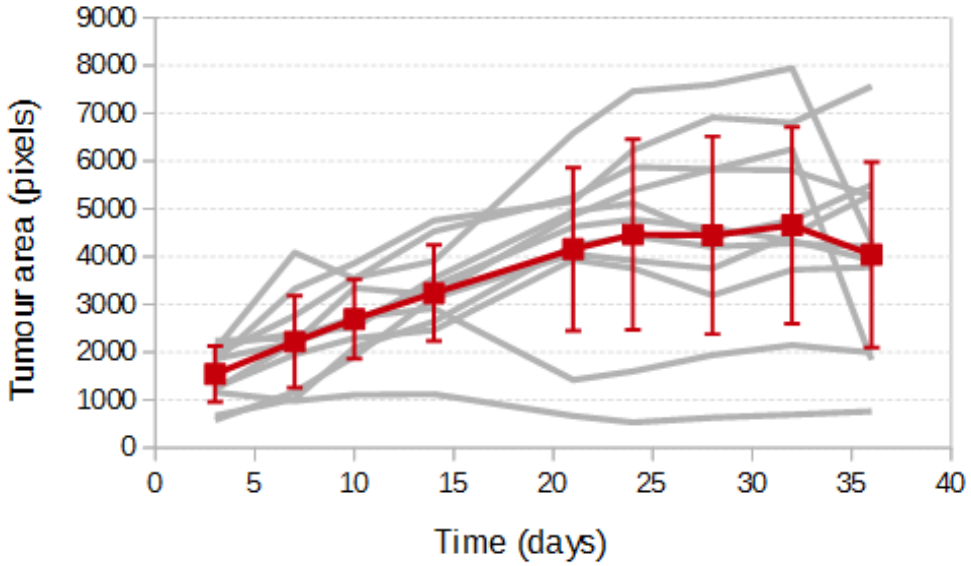
50mg/kg (in food)

5 consecutive days (days 14 to 18)

Growth with antivasclar treatment (avastin)



Average evolution from 12 tumours

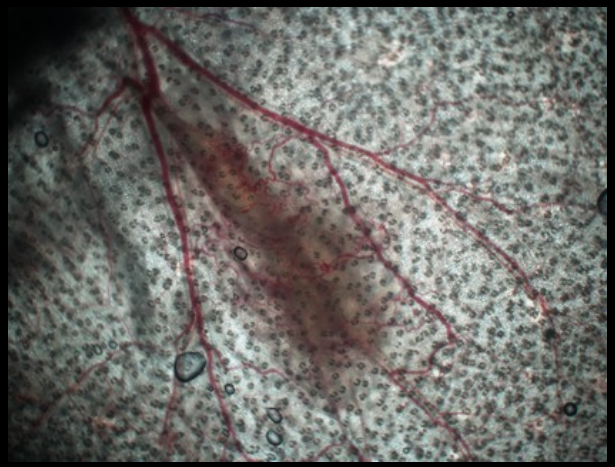


Dosage

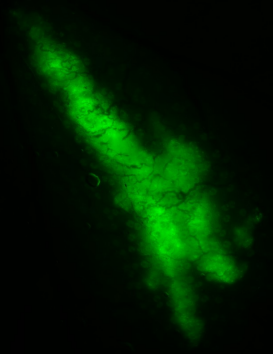
10mg/kg (IP injection)

Every 3 days in average (days 14, 17, 22, 25, 28)

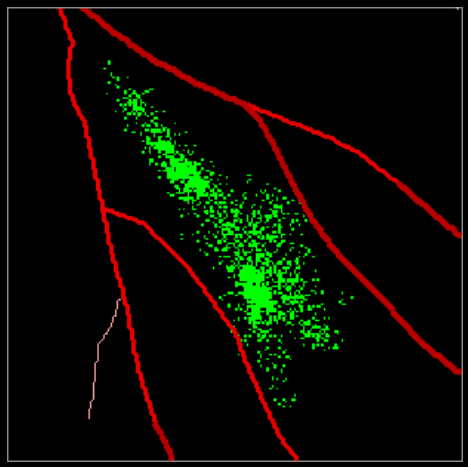
Tumour case 1 (higly vascularized)



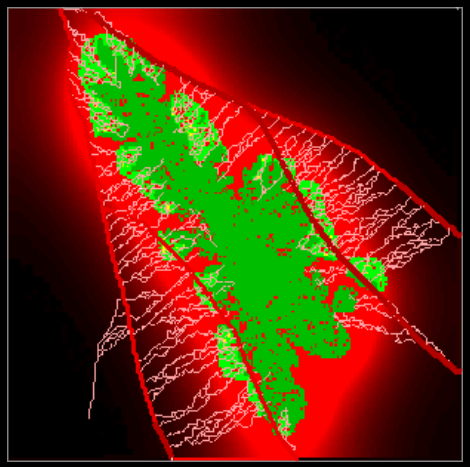
Vascular network (day 3)



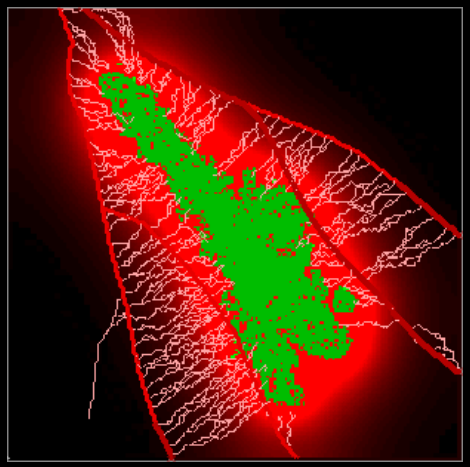
GFP-Image (day3)



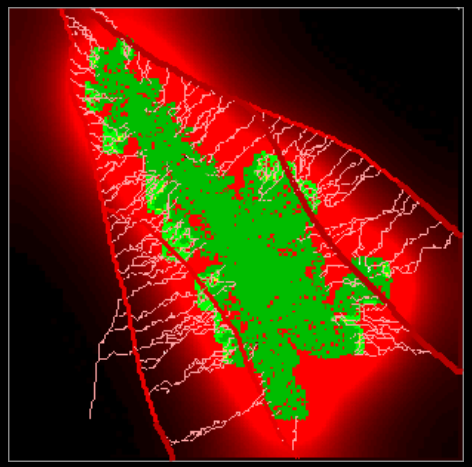
Simulation (day 3)



Simulation without treatment (day 34)

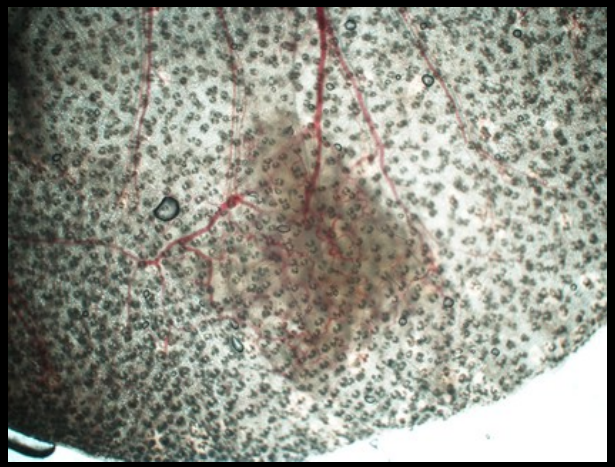


Simulation with temodal (day 34)

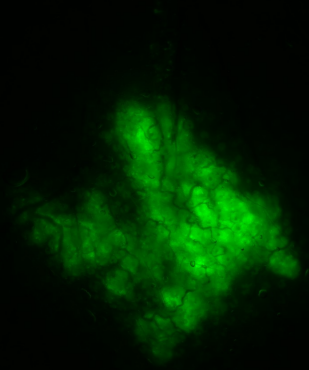


Simulation with avastin (day 34)

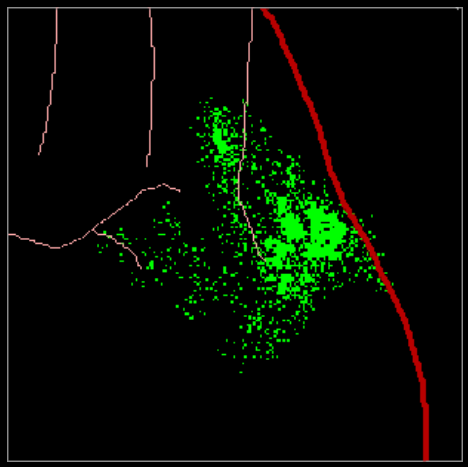
Tumour case 2 (weakly vascularized)



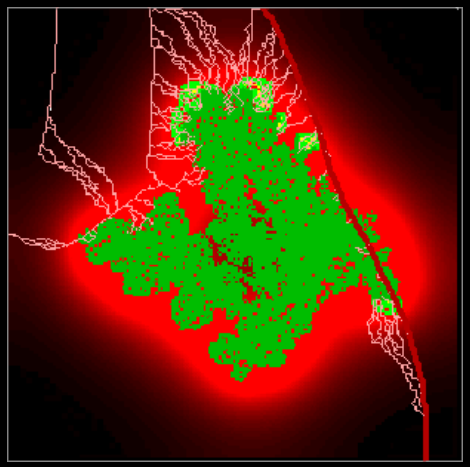
Vascular network (day 3)



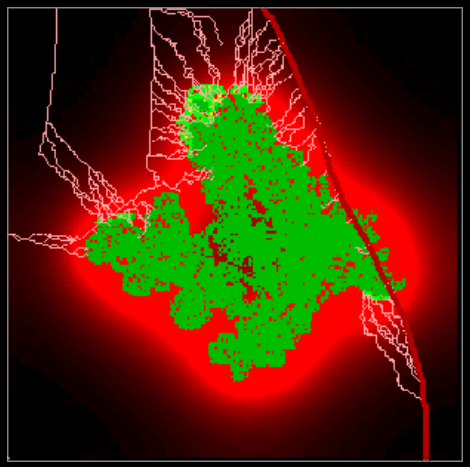
GFP-Image (day3)



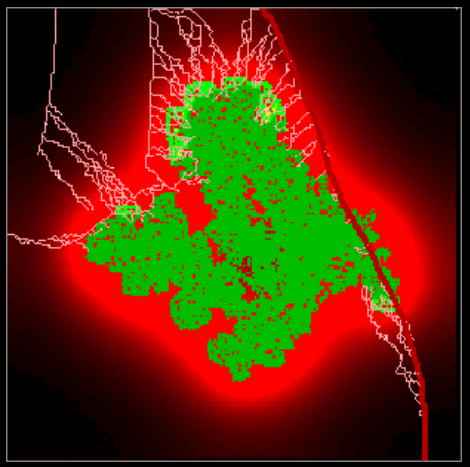
Simulation (day 3)



Simulation without treatment (day 34)



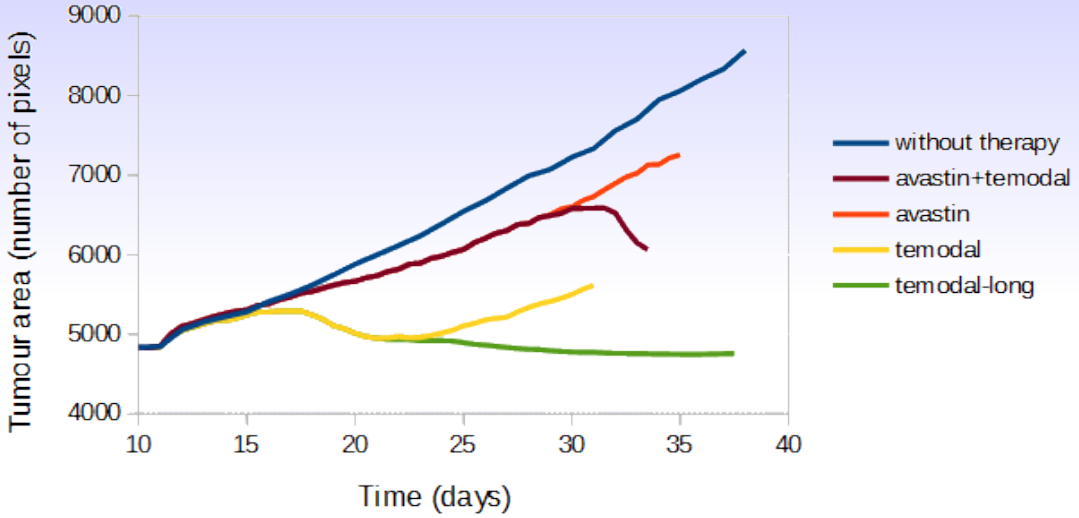
Simulation with temodal (day 34)

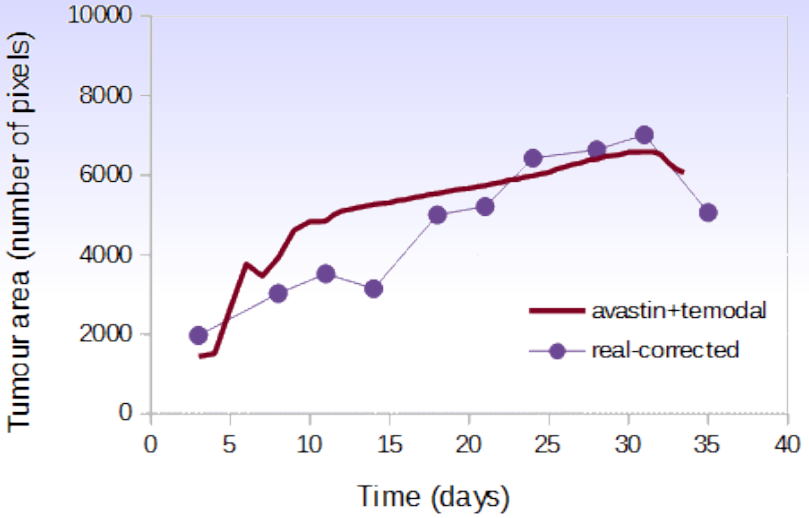


Simulation with avastin (day 34)

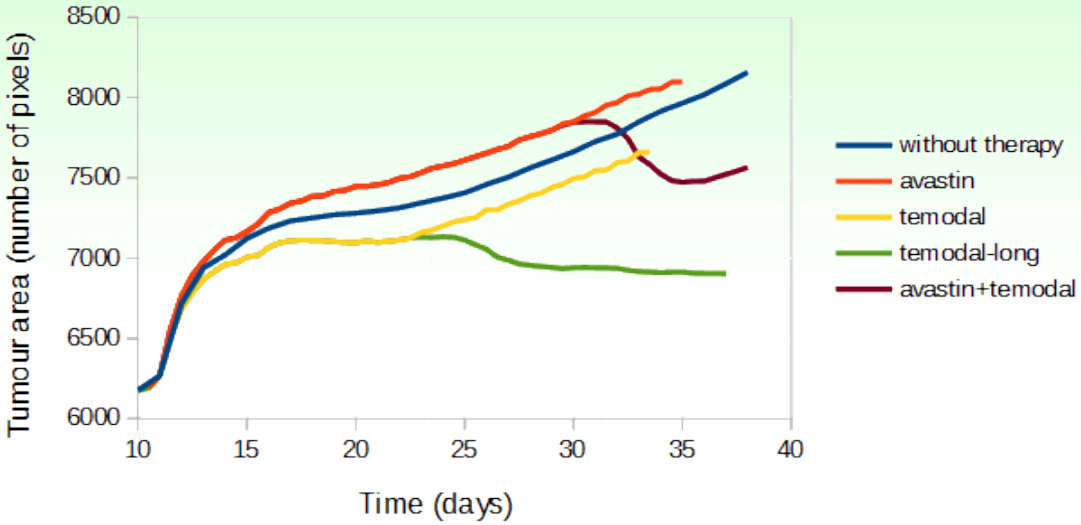
Predictions

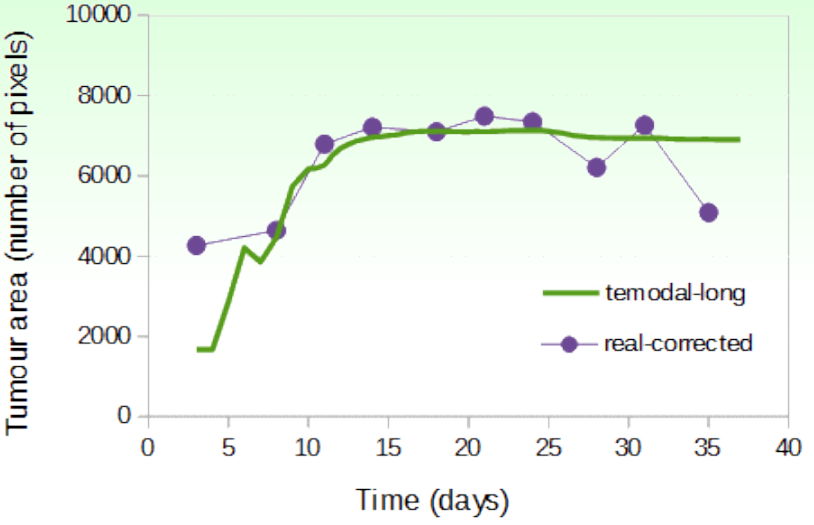
Tumour case 1 (highly vascularized)



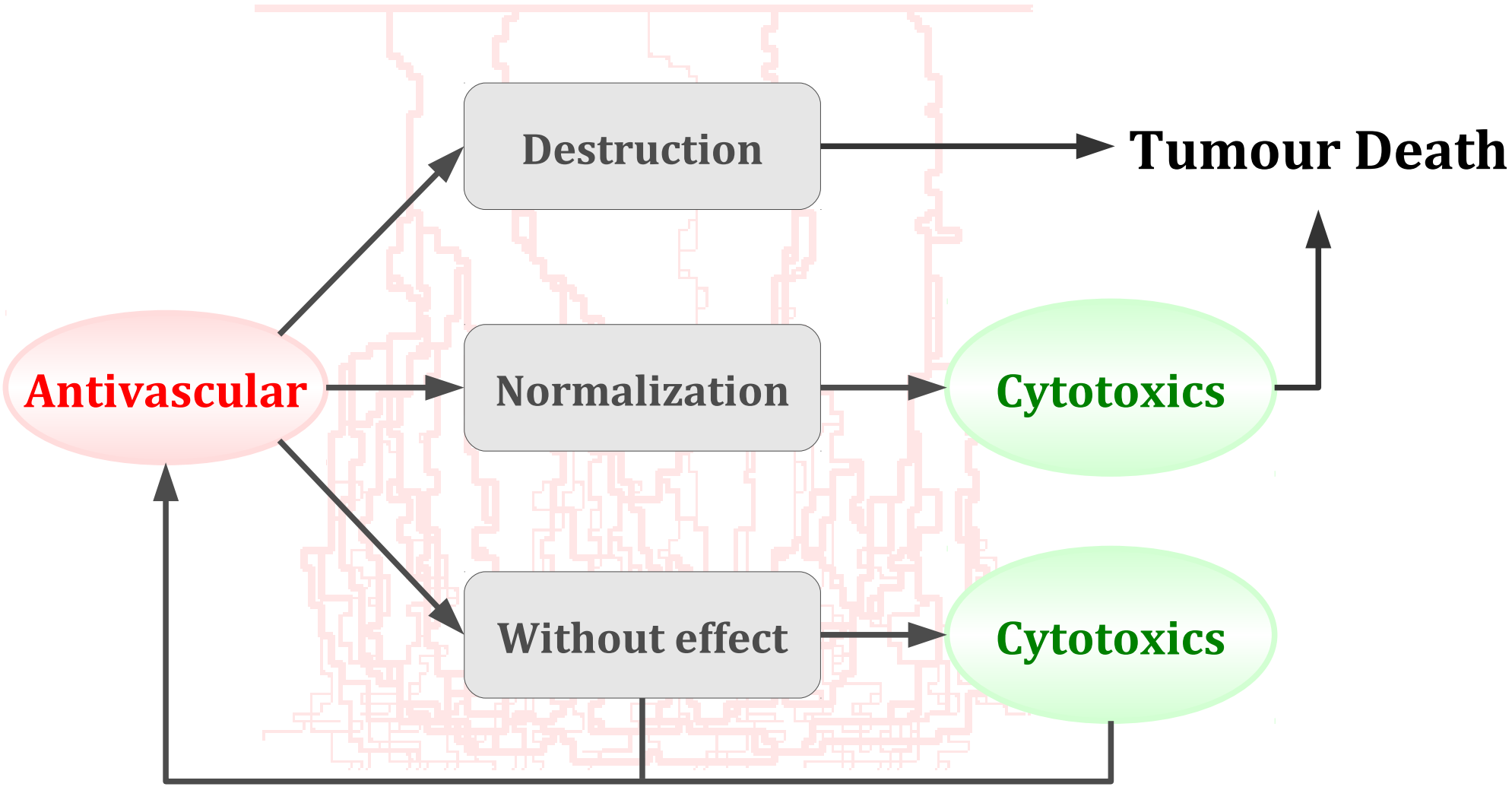


Tumour case 2 (weakly vascularized)





Therapeutics coupling



The next step ...

	Phase 1	Phase 2
Experimental model	Sub-cutaneous implantation of U87-GFP tumours cells in matrigel *Nude mice (immuno-deficient)*	Intra-cerebral implantation of C6 or 9L tumour cells *Wistar rat*
		
Virtual model	2D isotropic tissue	3D anisotropic brain tissue
Control	Intravital fluorescence microscopy, immuno-histology	MRI, immuno-histology
Action	Cytotoxics and antivascular	Cytotoxics, antivascular and radiotherapy

Partners

Techniques for biomedical engineering and complexity

Cell & tissue dynamics and functional microscopy

Nicolas Glade, Arnaud Chauvière, Anne-Cécile Lesart (computational modelling)
Marie-Paule Montmasson, Malika Hamel (experimental cell models, histology)
Arnold Fertin, Yves Usson (image analysis)

Clinatec *Biomedical research centre*

Flavien Caraguel , Boudewijn van der Sanden (*in vivo* models, intavital imaging)

Grenoble Institute of Neurosciences

Emmanuel Barbier, Benjamin Lemasson (brain tumour models, MRI)
François Estève (brain tumours, radiotherapy)

Grenoble Images, Speech Signal and Control

Mazen Alamir, Mirko Fiacchini (control theory and optimization)

Ecrins Therapeutics

Andrei Popov, Aurélie Juhem (development of antivascular molecules)

Abstract

The design of a patient-specific virtual tumour is an important step towards personalized medicine since the virtual tumour can be used to define the most adapted and efficient treatment protocol. However this requires to capture the description of many key events of tumour development, including angiogenesis, matrix remodelling, hypoxia, cell heterogeneity that will all influence the tumour growth kinetics and degree of tumour invasiveness. To that end, an integrated hybrid and multiscale approach has been developed based on data acquired on a preclinical mouse model as a proof of concept. Fluorescence imaging is exploited to build case-specific virtual tumours and to validate their spatiotemporal evolution. The validity of the model will be discussed as well as its potential to identify the best therapeutic strategy for each individual tumour case.