Biomarkers - Oncology and Inflammation

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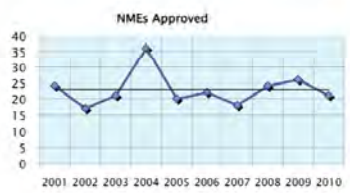
Swiss Federal Institute of Technology Zurich

Issues with drug discovery

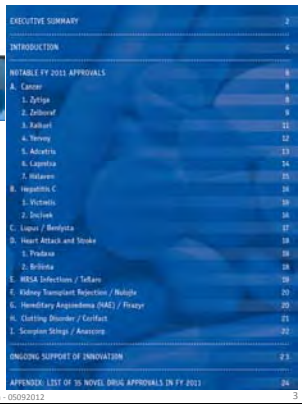
Ten Year Average
NME* Approvals Per Year



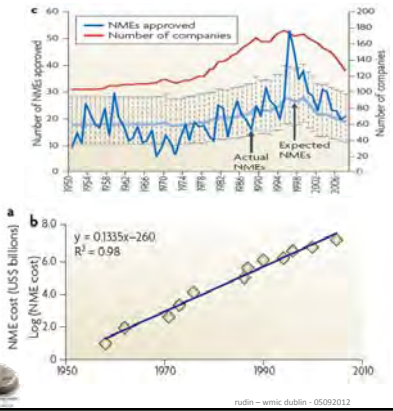
Calendar Year	NMEs Approved
2001	24
2002	17
2003	21
2004	36
2005	20
2006	22
2007	18
2008	24
2009	26
2010	21

*www.**fda**.gov*

biomarkers - imaging



Issues with drug discovery



Constant output in NMEs

Exponential growth of R&D expenditures

Munos et al. Nat Rev Drug Disc (2009)

Issues with drug discovery

According to the latest annual review of pharma R&D value by Deloitte and Thomson Reuters, *Measuring the Return from Innovation*, the average cost of bringing a new product successfully to market among the top 12 research-based pharmaceutical companies worldwide increased by 26.3% from US$830 million in 2010 to US$1,048 million in 2011.

Over the same period, the number of late-stage compounds in development dropped from 23 on average per company to 18 per company. Moreover, the average R&D Internal Rate of Return (IRR) among the companies analysed was down from 11.8% in 2010 to 8.4% this year

Issues with drug discovery

The Critical Path Initiative

to '***ensure that basic scientific discoveries translate more rapidly into new and better medical treatment by creating new tools to find answers of how the safety and efficacy of new medical products can be demonstrated in faster time frames, with more certainty, at lower cost and with better information***'

[http://www.fda.gov].

CPI - biomarkers

critical Path Initiative (FDA) / Innovative Medicine Initiative (EMEA)

clinical endpoint	how a patient feels, functions or survives
biomarker	objective measurement associated with pathological process /therapeutic intervention with prognostic quality
surrogate	validated biomarker that substitutes for a clinical endpoint

biomarkers - imaging

biomarkers should be

- **non-invasive**
- **should allow for follow-up studies**
- **focal**
- **simple**
- **low-cost**

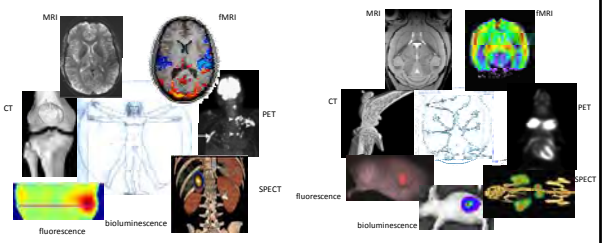
non-invasive imaging providing

- **morphological**
- **physiological**
- **metabolic**
- **cellular**
- **molecular**

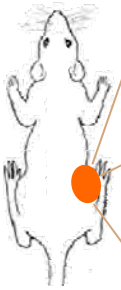
readouts in temporo-spatially resolved manner

→ **potential biomarkers for patient staging / stratification, proof of mechanism and therapeutic efficacy**

multimodal imaging inherently translational



optimal method depends on question to be answered

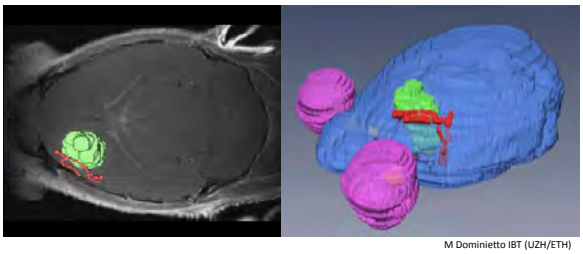


molecular constituents: e.g. receptor expression
→sensitivity (low concentrations)
→specificity (minimal cross-contamination of signals)
→spatial resolution
→temporal resolution

physiology: e.g tumor perfusion
→temporal resolution (analysis of bolus passage)
→spatial resolution
→sensitivity

morphology: e.g. volume, shape, heterogeneity
→spatial resolution
→high soft-tissue contrast
→sensitivity
→temporal resolution

tumor: structural imaging



M Dominietto IBT (UZH/ETH)

detection of space occupying lesions (native contrast or contrast enhancement)

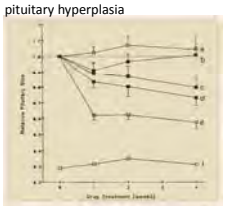
staging – texture / heterogeneity, infiltration of adjacent tissue, tumor volume

therapy assessment – RECIST (response criteria of solid tumors)

therapy effect on tumor volume

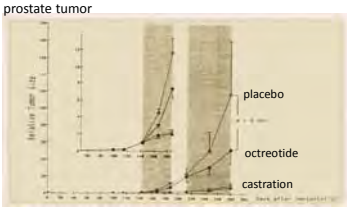
effect of octreotide treatment on hormone dependent tumors expressing SST receptors

estradiol induced pituitary hyperplasia



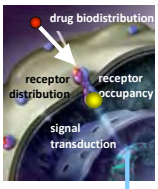
Rudin et al. MRM (1986)

Dunning R3227-H prostate tumor



Siegel et al. Cancer Res (1986)

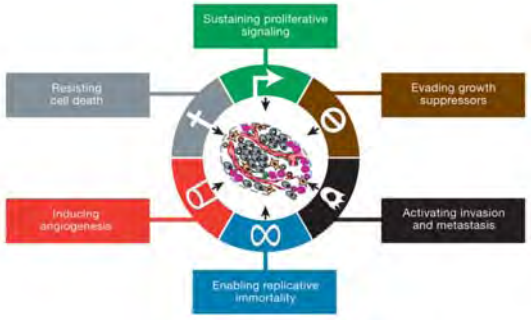
information from imaging data



system response

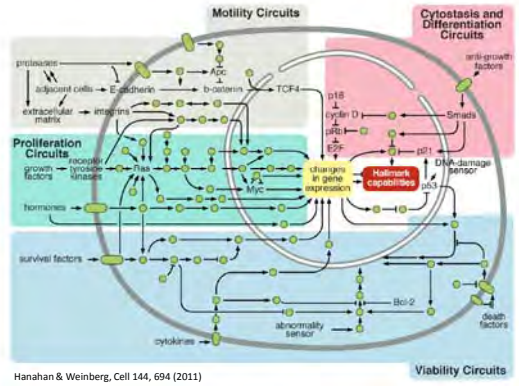
molecular imaging	- drug biodistribution - target expression - receptor occupancy - signaling pathways
hires structural imaging	- in vivo morphometry - in vivo morphology - disease phenotyping/dx
functional imaging	- physiological measurements - functional MRI - functional receptor imaging
cellular imaging	- cell migration & fate - cell therapies

the hallmarks of cancer (1st generation)



Hanahan & Weinberg, Cell 144, 694 (2011)

intracellular signaling networks in cancer



Hanahan & Weinberg, Cell 144, 694 (2011)

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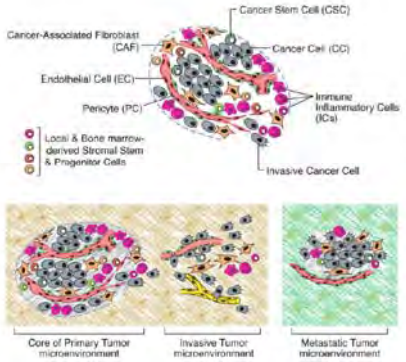
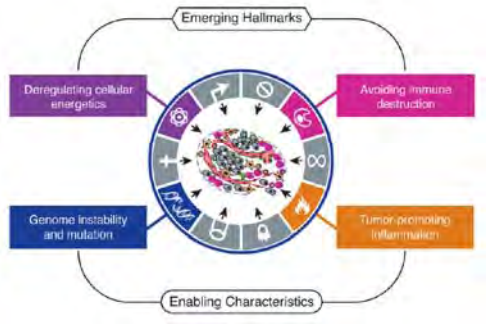


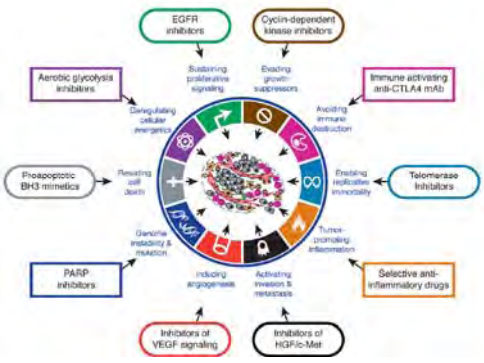
Hanahan & Weinberg, Cell 144, 694 (2011)

the hallmarks of cancer (2nd generation)



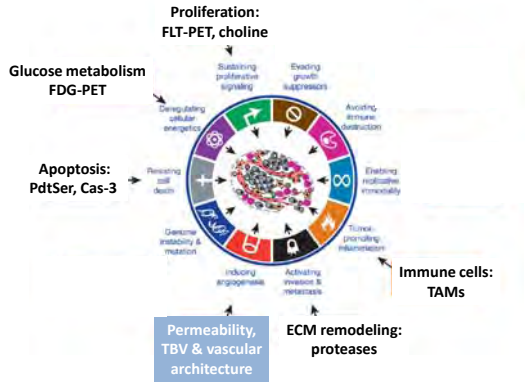
Hanahan & Weinberg, Cell 144, 694 (2011)

the hallmarks of cancer (2nd generation)



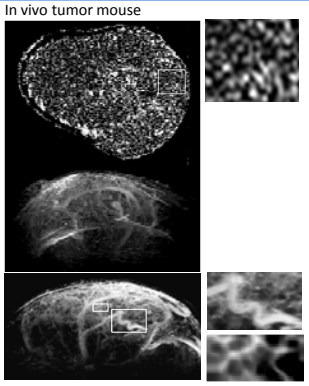
Hanahan & Weinberg, Cell 144, 694 (2011)

Imaging cancer hallmarks



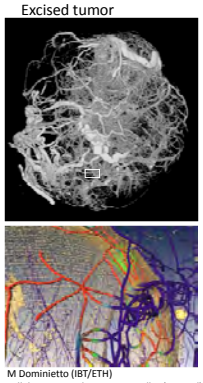
assessment of tumor vascular architecture

In vivo tumor mouse



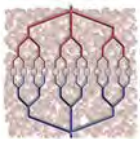
D Vats, D Ratering (IBT/ETH)

Excised tumor



M Dominietto (IBT/ETH)
collaboration with S Lang, B Müller (U Basel)

how to characterize tumor vascular architecture?



normal tissue

hierarchical architecture
efficient perfusion

tumor

chaotic
inefficient perfusion

structure

volume
surface
diameter distribution
fractal dimension
lacunarity

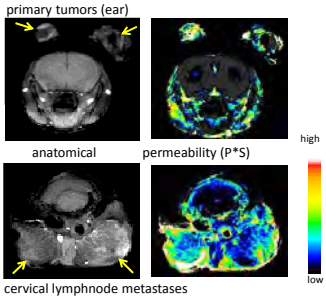
function

perfusion
permeability

bulk measures of (tumor) vascularity

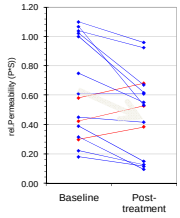
vascular permeability and tumor blood volume maps in murine B16 melanoma model

primary tumors (ear)



cervical lymphnode metastases

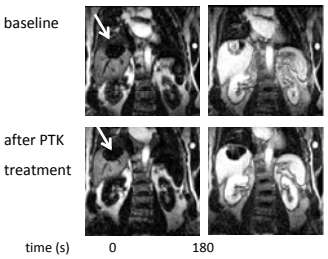
effect of VEGF-R inhibitor vatalanib on vascular permeability of cervical lymphnode metastases

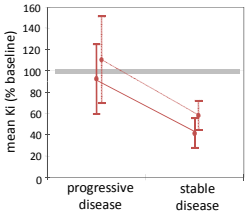


Rudin et al. (2005) NMR Biomed 18: 308-321

vascular permeability with DCE-MRI: translation

enhancement of a liver metastasis at baseline and 30 hours after treatment with PTK 787





Morgan et al. (2003) J Clin Oncol 21:3955–3964

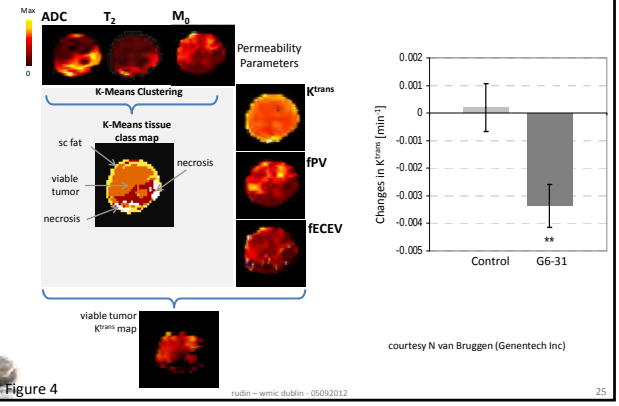
vascular permeability biomarker - issues

approved CA (GdDTPA's) small hydrodynamic radius → highly leaky
→ reduced dynamic range
- novel CAs: larger hydrodynamic radius

tumor heterogeneity not accounted for by conventional analysis
- tissue classification (e.g. based on multiparametric MRI readouts
- pattern analysis techniques

multiparametric analysis of vascular permeability with DCE-MRI

tissue classification



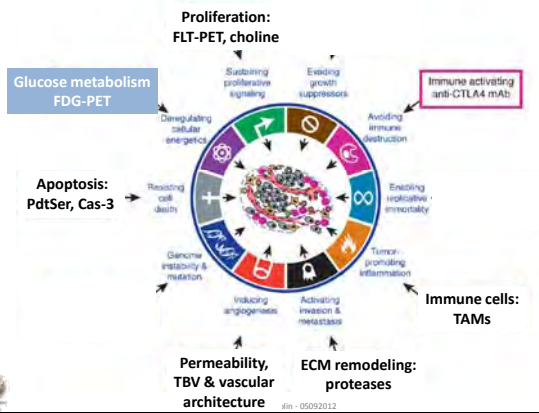
courtesy N van Bruggen (Genentech Inc)

Figure 4

multimodal imaging of angiogenesis: parameters/modeling

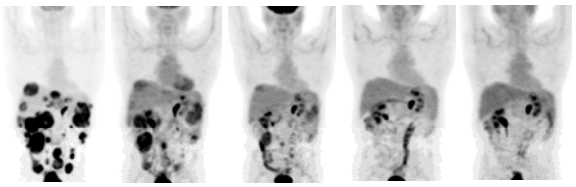
parameter	biological information	mod	process
vascular permeability	sites of angiogenesis	MRI	angiogenic ‚endpoint': vessel morphology and physiology
vumor blood volume	total vascularization	MRI	
TBV and vessel size	vascular architecture	MRI	
hypoxia	tumor oxygenation	PET	angiogenic signaling
HIF1a and HIF activity	hypoxia signaling	OPT	
VEGF	proangiogenic signaling	OPT	
adhesion molecules	activated endothelium	OPT	tumor-host tissue interaction
proteases	ECM degradation	OPT	
inflammatory cells	Immune response / ECM degradation	MRI	

Imaging cancer hallmarks



therapy effects on tumor glucose metabolic activity

A Van den Abbeele (DFCI)

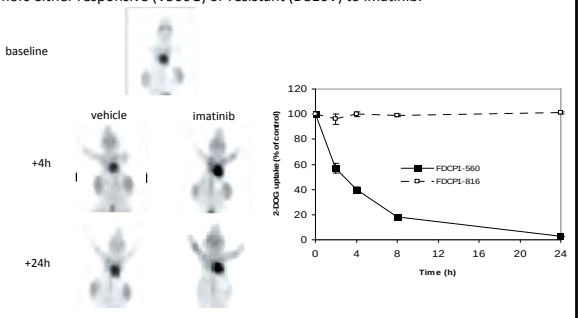


^{18}F-FDG PET provides evidence of biological response to imatinib, within hours/days and earlier than classical CT measurements

early post-treatment SUV values predict long term response both in mouse model and human patient

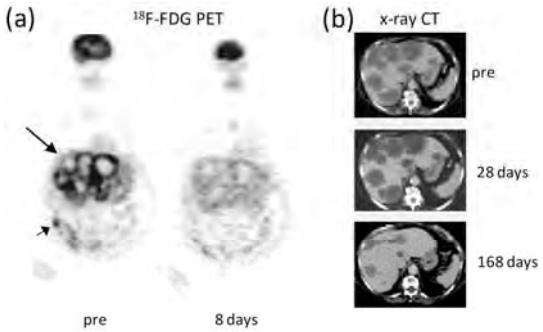
therapy effects on FDG activity: translation to mouse

murine tumors of FDC-P1 cell lines expressing c-KIT mutations that render the tumors either responsive (V560G) or resistant (D816V) to imatinib.



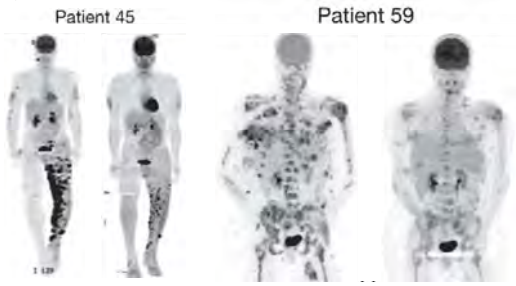
Cullinane et al. (2005) Cancer Res 65: 9633

therapy effects on tumor glucose metabolic activity



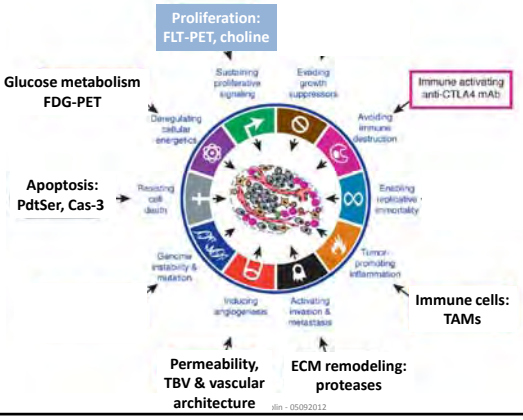
therapy effects on tumor glucose metabolic activity

clinical efficacy of PLX4032 (RG7204), a potent inhibitor of oncogenic B-RAF kinase activity, in patients with *BRAF*-mutant melanoma



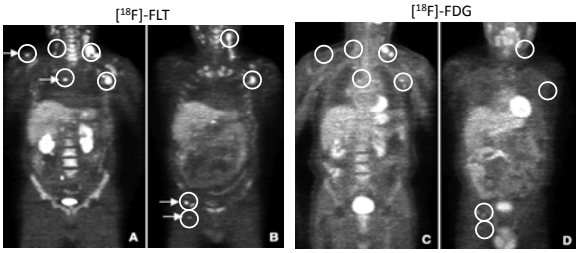
G Bollag, et al. (2010) Nature 467: 596–599

Imaging cancer hallmarks



comparison FDG- versus FLT-PET for tumor detection

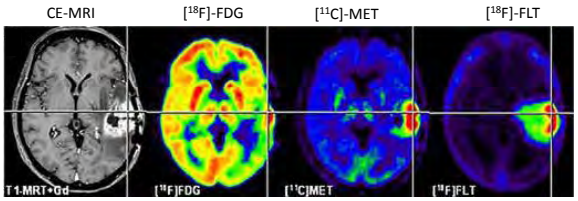
lymphoma



Buck AK et al, Cancer Res 2006;66:11055-11061

comparison FDG- versus FLT-PET for tumor detection

Glioblastoma multiformae



MPI Cologne, Germany

potential tumor therapy MRI biomarker

- DCE-MRI: alterations in vascular permeability → angiogenesis

- **ADC mapping: changes in water diffusivity – celluarity / apoptosis**

Moffat BA et al. (2005) PNAS 102: 5524-9
Functional diffusion map: A noninvasive MRI biomarker for early stratification of clinical brain tumor response

Khayal IS et al (2010) NeuroOncology 12: 908-16
Evaluation of diffusion parameters as early biomarkers of disease progression in glioblastoma multiforme

- **MRS: effects on tumor glucose or lipid metabolism**

Gallagher FA et al. (2009) PNAS 106: 19801-4
Production of hyperpolarized [1,4-$^{13}C_2$]malate from [1,4-$^{13}C_2$]fumarate is a marker of cell necrosis and treatment response in tumors

deriving quantitative data from imaging data sets

how to translate imaging information into meaningful biological information?

→ morphometric analysis

→ densitometric analysis

1) translate intensity into concentration
   PET: activity
   MRI: relaxivity change
   FMT: intensity
   } ∝ amount of tracer in voxel: weighted sum of all compartments

2) correct for confounding contributions (scattering, absorption, transport/diffusion, chemical exchange/metabolism, bleaching,….)

3) dynamic modeling of concentrations in individual compartments

4) relate model parameters to biological process

Robustness / reproducibility of measurement

Estimates of various error sources

a) Experimental

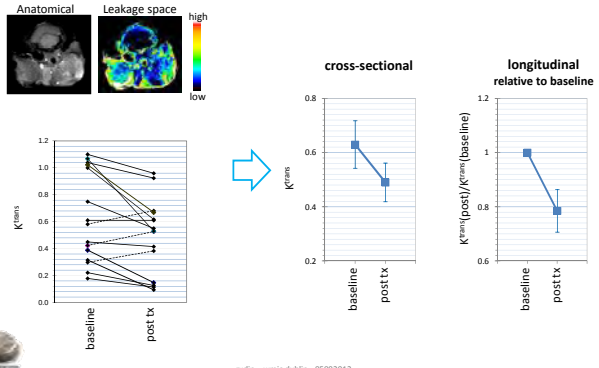
Instrumental	**phantom studies**
Biological	**intraindividual** **Interindividual**
Procedural	**reproducibility of procedures** **automated procedures**

b) Data Analysis

automated using validated procedures
semiautomated
operator-interactive

Robustness / reproducibility of measurement

B16 melanomas: cervical lymphnode metasases



deriving concentrations from signal intensities: PET

Local activity proportional to local concentration of radioisotope

$$Q(\vec{r}) = -\frac{dN(\vec{r})}{dt} = \lambda \cdot N(\vec{r})$$

Injected dose per gram of tissue: %ID/g

$$\%ID/g = \frac{c_t \cdot v_t}{D_{inj}} \cdot \frac{1}{m_t} \cdot 100\%$$

Standardized uptake value: SUV

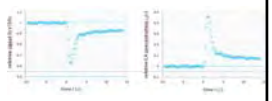
$$SUV = [\%ID/g] \cdot M/100 = \frac{c_t \cdot v_t}{D_{inj}} \cdot \frac{1}{m_t} \cdot M$$

$$SUV' = [\%ID/g] \cdot S/100 = \frac{c_t \cdot v_t}{D_{inj}} \cdot \frac{1}{m_t} \cdot S$$

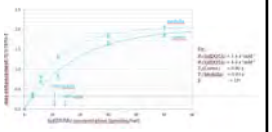
deriving concentrations from signal intensities: MRI

Assumption: relaxivity depends linearly on amount of tracer in voxel

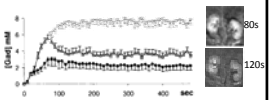
$$R_i = R_{i0} + r_i \cdot c_{t,p} \cdot v$$



Issues:
deviations from linearity



mixed contrast e.g. R_1 & R_2 (ambiguities)



Receptor affinity from concentrations

Receptor Binding

Receptor Binding: $L + R \leftrightarrow RL$

Equilibrium constant:

$$K_d = \frac{k_{off}}{k_{on}} = \frac{[L] \cdot [R]}{[RL]}$$

(principle of microreversibility):

$$k_{off} \cdot [RL] = k_{on} \cdot [R] \cdot [L]$$

Mass conservation for receptor:

$$[R_T] = [R] + [RL]$$

yields

$$K_d = \frac{[L]}{[RL]} \cdot ([R_T] - [RL])$$

or

$$\frac{[RL]}{[R_t]} = \frac{[L]}{K_d + [L]}$$

or the Scatchard equation:

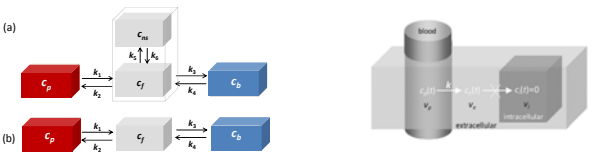
$$\frac{[RL]}{[L]} = -\frac{1}{K_d} \cdot [RL] + \frac{[R_T]}{K_d}$$

Imaging yields concentration in a voxel

Voxel comprises multiple compartments, therefore $c_t(t)$ corresponds to volume averaged concentration of CA across these compartments, i.e.

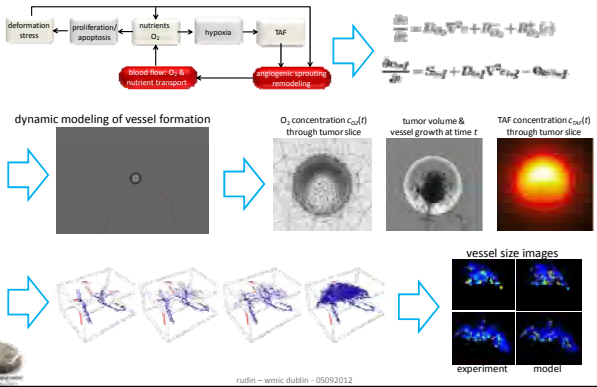
$$c_t(t) = \frac{1}{V} \Sigma_i \; v_{ti} \cdot c_{ti}(t)$$

Multicompartment models to deconvolve individual contributions



→ Determination of $c_{ti}(t)$ for compartment of interest

phyiological modeling



biomarkers: facilitating transition from discovery to clinics?

today there are only few examples of using imaging information to facilitate the translation from mouse to man

- too early to tell
- technical issues: tools used for mouse imaging not appropriate for clinical setting
  - not approved
  - not standardized (i.e. not suited for multi-center trials)
  - not properly validated
  - not quantitative
  - …
- preceived issues: e.g. acceptance/expectations by drug developer
- a mouse is a model for man – not man!

translational biomarkers – a multimodality approach