UCSF Medical Center

Tumor Cell Drug Penetration for Individualized Cancer Treatment

Introduction

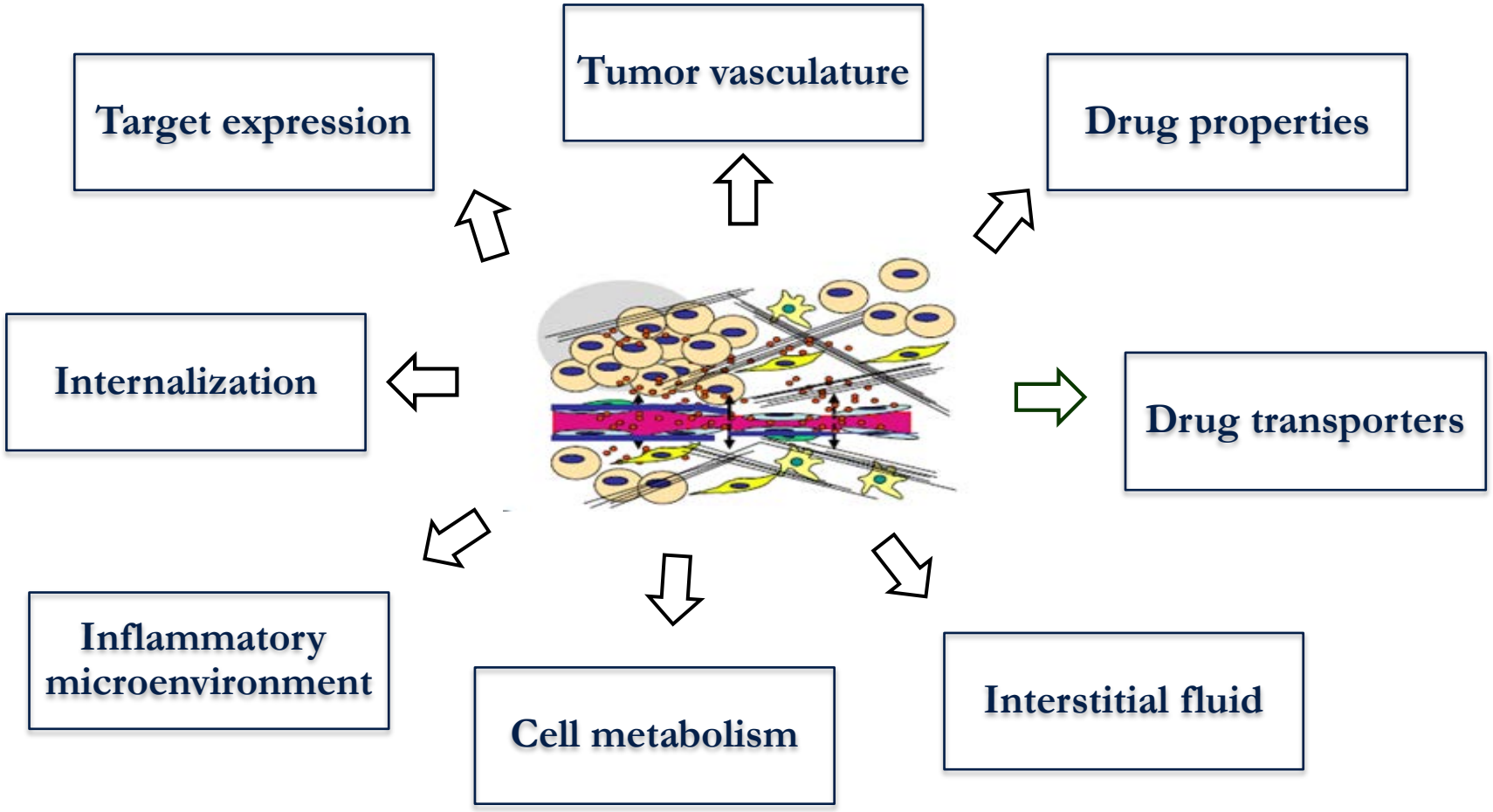
Imke H. Bartelink, PharmD PhD
Clinical Pharmacology Fellow
Department of Medicine/Munster lab
UCSF

Transitioning to
Senior pharmacometrician
Medimmune

i.h.bartelink@gmail.com

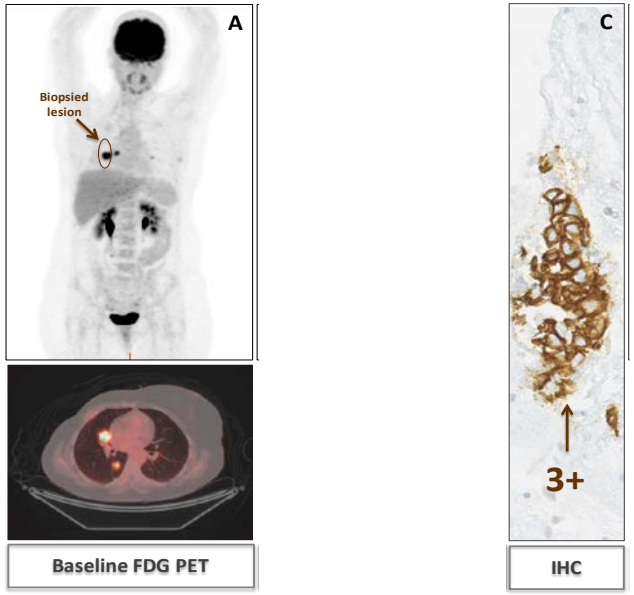
AstraZeneca MedImmune

Why is drug distribution in tumor tissue heterogeneous?

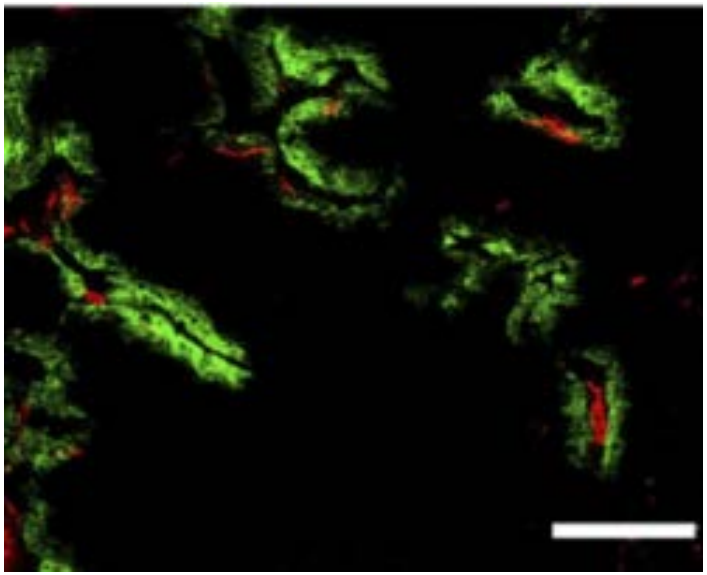


Study heterogeneity in drug distribution on multiple levels

Example of ado-trastuzumab emtansine (T-DM1), antibody drug conjugate in HER2 positive breast cancer



Macroscopic level



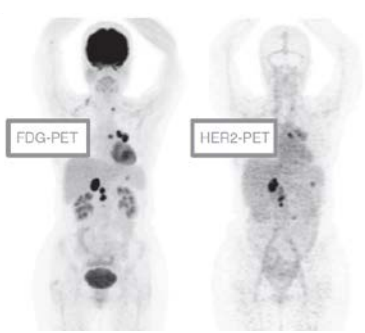
Microscopic level
(xenograft model)

*Cilliers et al. AAPS Journal 2016, V 18; 5; 1117–1130

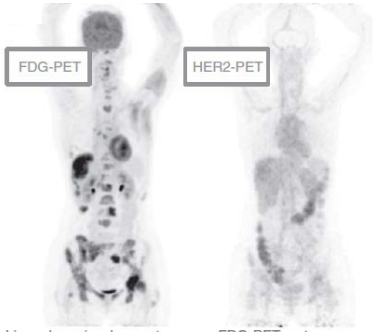
Tumor drug penetration correlates with treatment outcome

ZEPHIR study: ^{89}Zr-Trastuzumab HER2+ imaging in 56 HER2+ mBC patients prior to T-DM1 predicts response

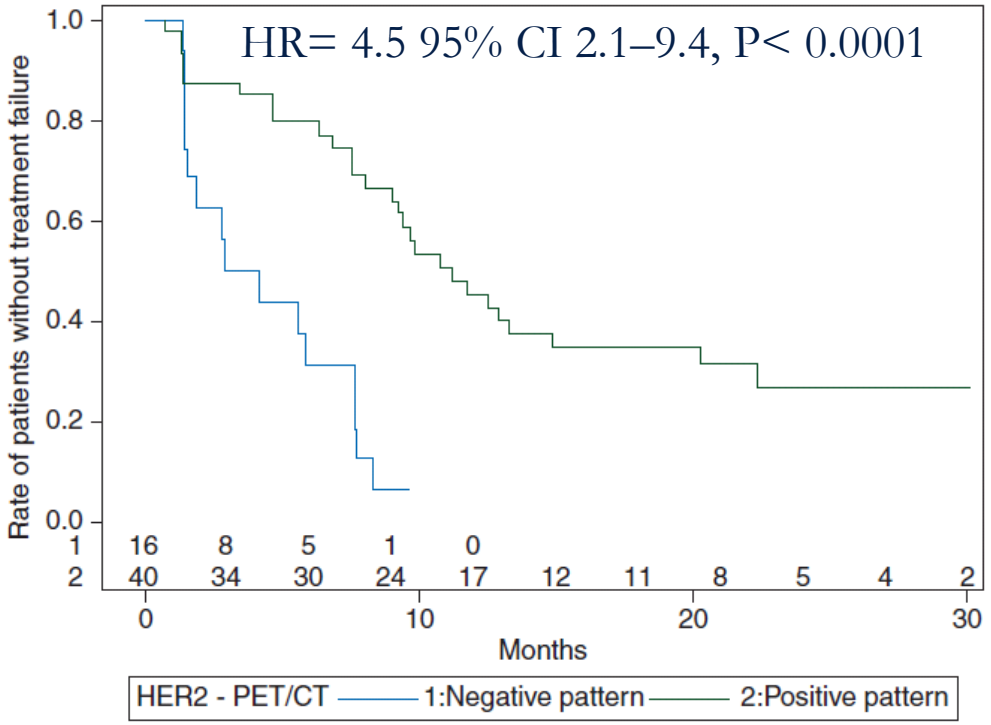
Example patients baseline



HER2+ pattern



HER2- pattern



Gebhart G. et al Annals of Oncology 27: 619–624, 2016

UCSF Medical Center

Learning/ discussion points

Techniques to determine drug penetration

- PET/CT, MALDI-MSI, fluorescence labeling
- Different techniques provide information on multiple scales
- Limitations and opportunities

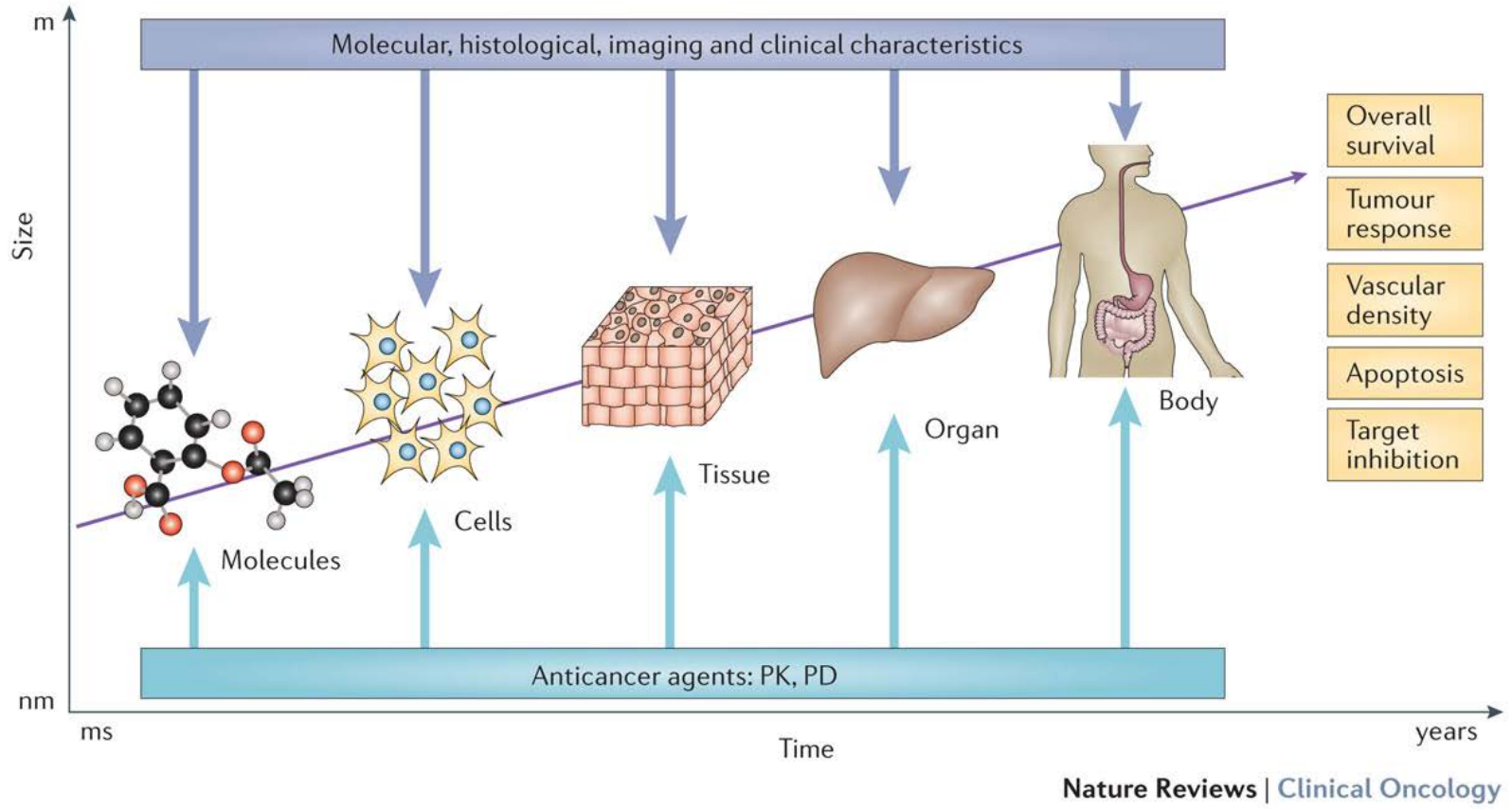
Studies to improve drug penetration in tumor (cells)

Key challenges to implement tumor cell drug penetration to individualize therapy

- Integration of data of multiple sources → PKPD using spatial data[1]
- Prospective studies needed

1. Cilliers et al. AAPS Journal 2016, V 18; 5; 1117–1130

Applying imaging for optimal development and precision dosing, multiscale approach needed



Barbolosi, D. *et al.Nat. Rev. Clin. Oncol.* 2015.204

Extra slides

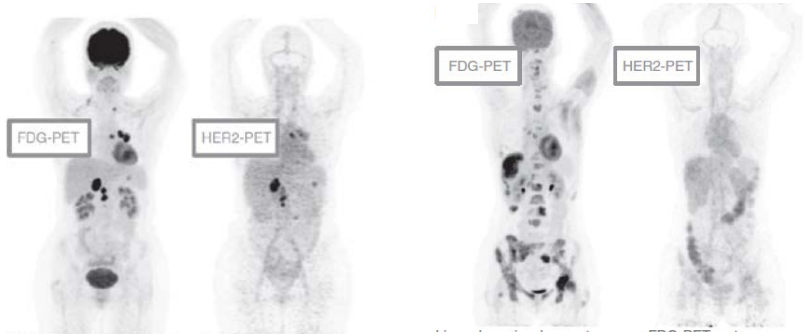
Can we individualize therapy to improve outcomes?

- **Using imaging to determine tumor-absorbed doses**
  - Somatostatin receptor-based molecular imaging
  - mIBG imaging

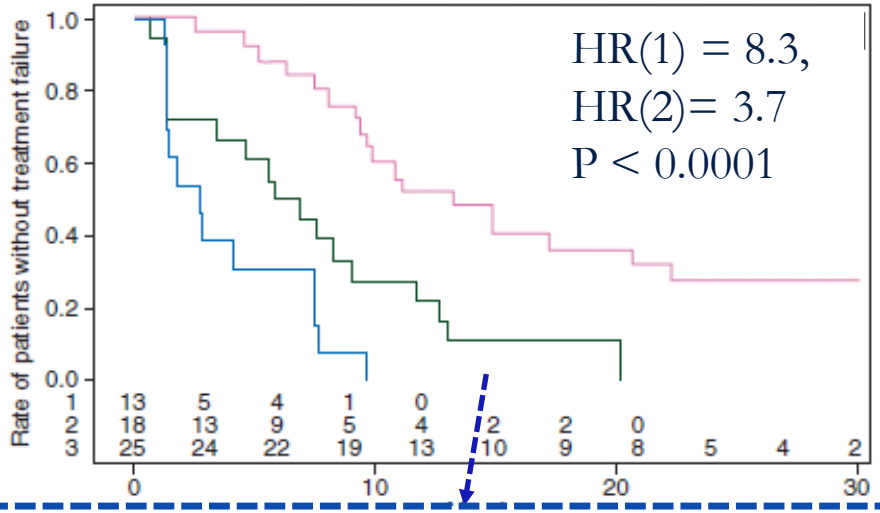
Information of drug penetration may guide patient selection

HER2 pattern + early metabolic response by FDG-PET
PPV and NPV 100%

Example patients



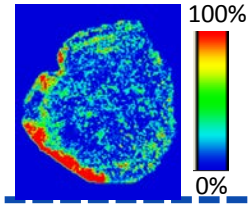
HER2+ pattern **HER2- pattern**



Metabolic response: Δ FDG–PET/CT 2 wee

Hypothesis: variability in response due to heterogeneity in microscopic distribution payload?

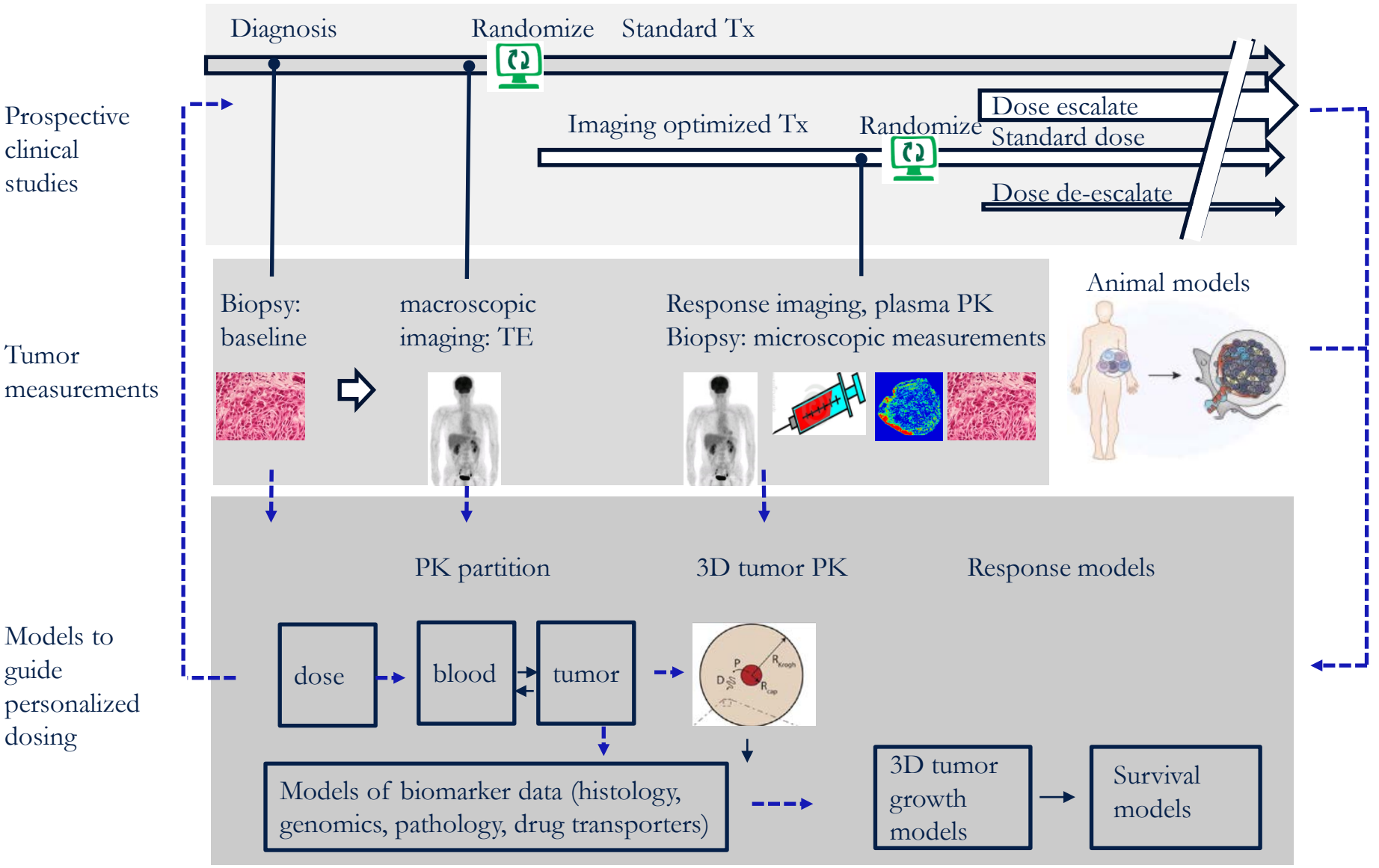
MALDI-MSI



Gebhart G. et al Annals of Oncology 27: 619–624, 2016

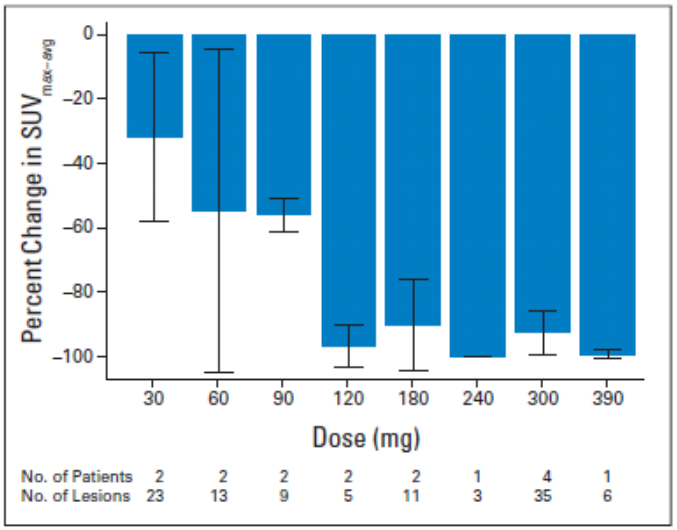
UCSF Medical Center

Vision of precision dosing



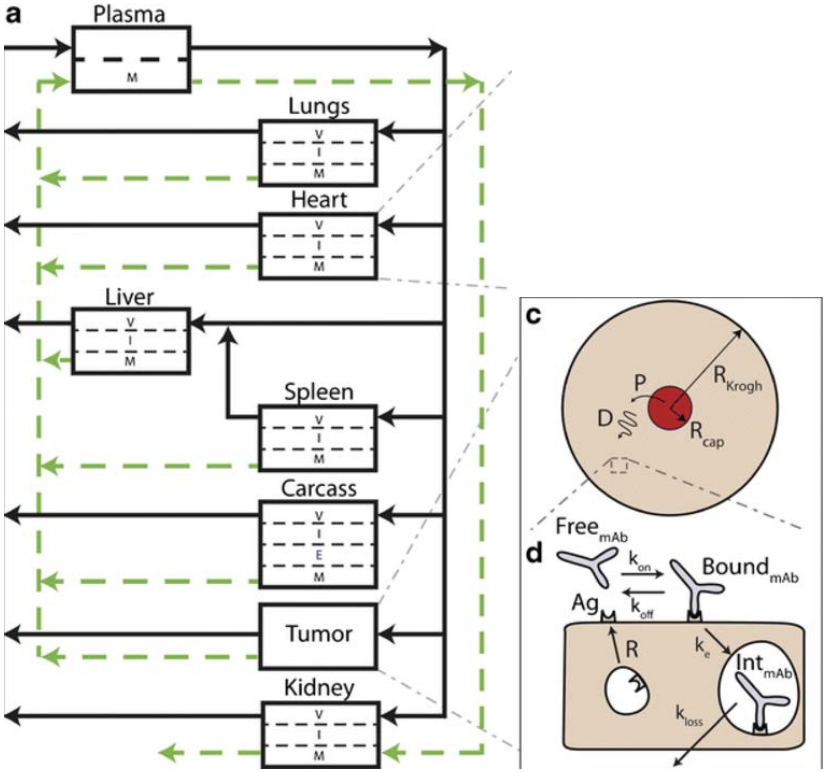
Example of imaging to optimize drug development

- Example of target engagement visualization to guide optimal biological dose (OBD)
  - 16-[18F]fluoro-dihydrotestosterone imaging in phase 1 of ARN-509, a Novel Antiandrogen
  - The approved dose was much lower than the traditional maximum



Rathkopf J et al. Clin Oncol 31:3525-3530.

Pharmacokinetic models are needed to integrate information of drug penetration into clinical decision making



Example model to predict tumor penetrance of payload T-DM1

*Cilliers et al. AAPS Journal 2016, V 18; 5; 1117–1130