New Technology for Drug Delivery

Histopathological biomarkers to predict the accumulation of cancer nanomedicine in murine and human tumors

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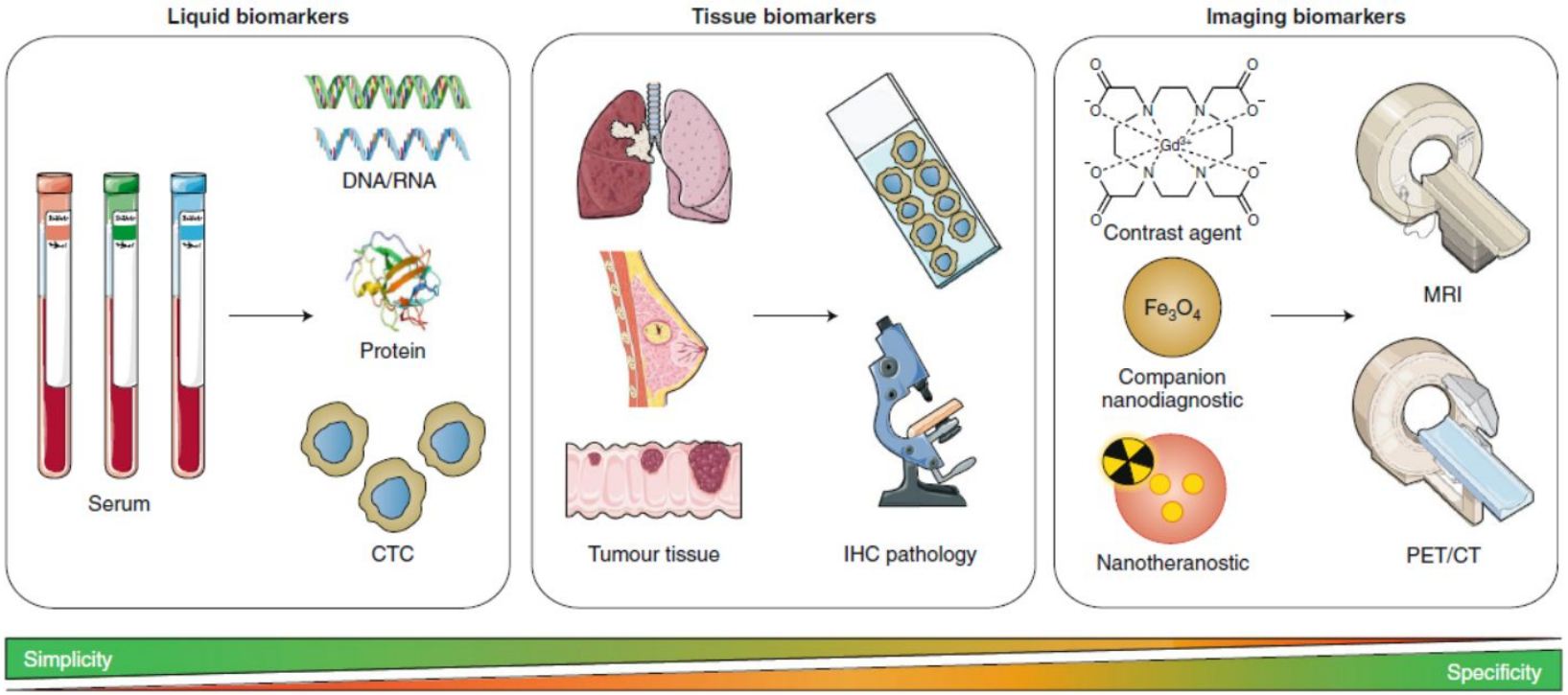
Advanced Delivery Science

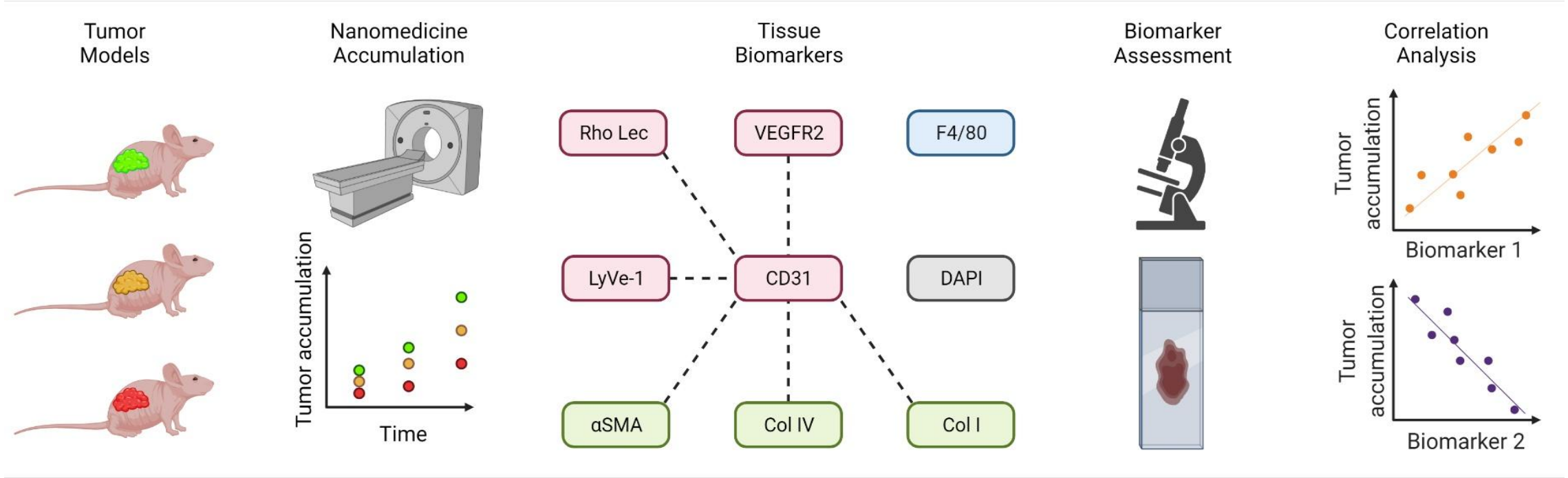
Patient stratification – why do we need it?

- **FDA granted Doxil accelerated approval** in 1999 for the treatment of metastatic ovarian cancer on the basis of three phase II studies that **showed tumor regression** in 20 of a total of 145 women **(13.8%)** (whose tumors did not respond to paclitaxel- or platin-based therapies)

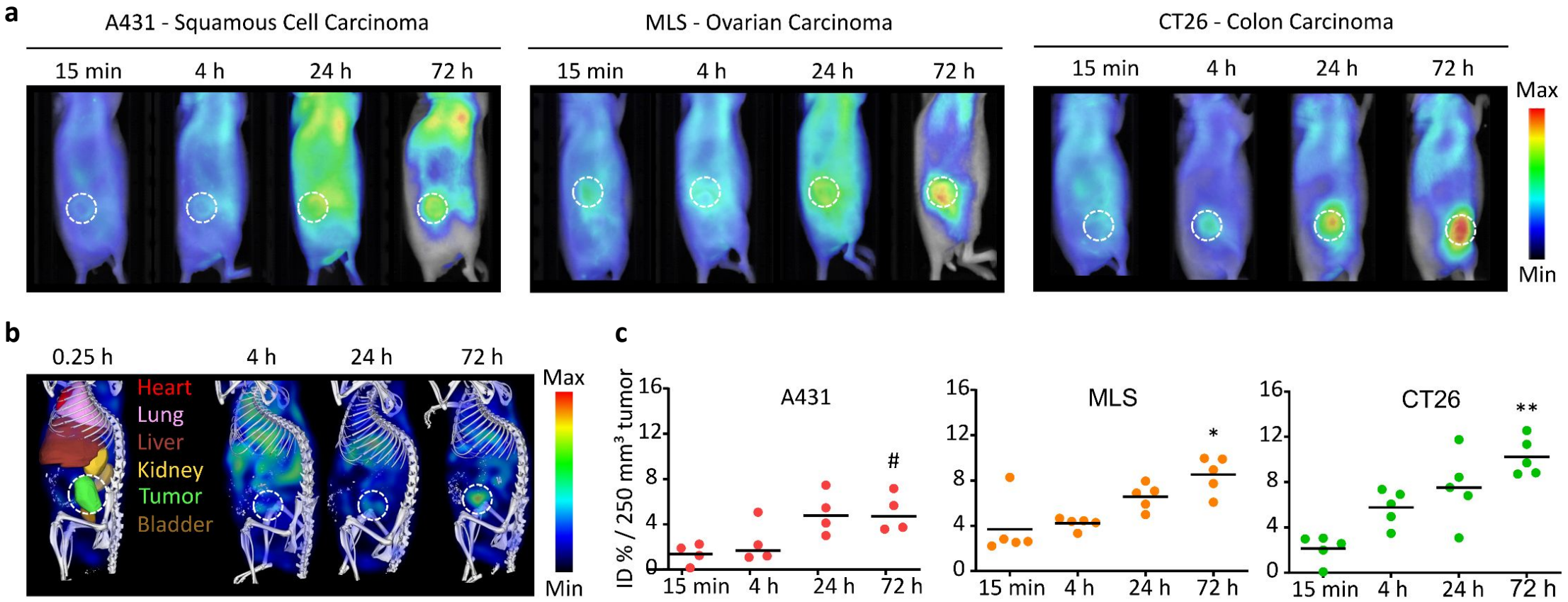


cancernetwork.com; van der Meel, Sulheim, Shi et al., 2019

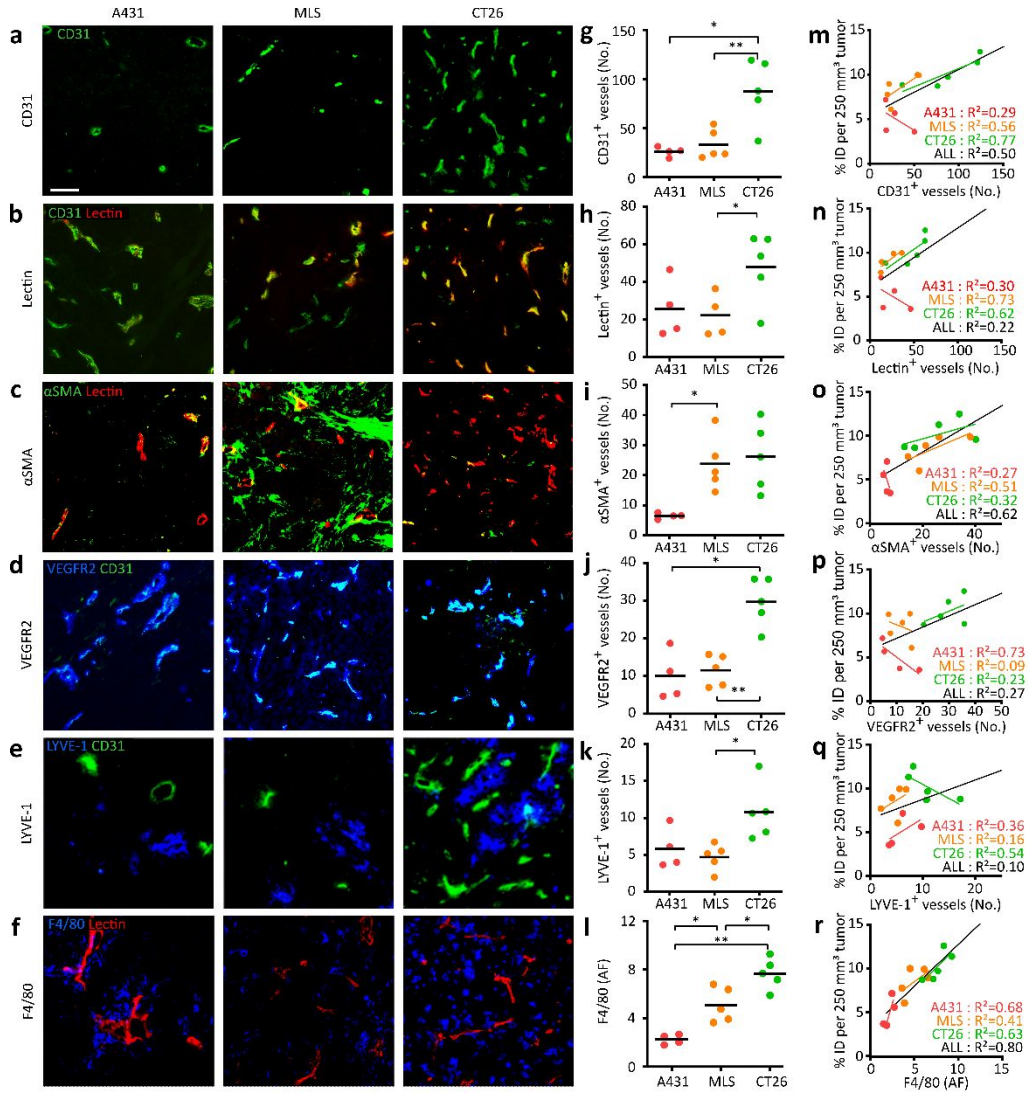
Connecting tumor accumulation to histological biomarkers

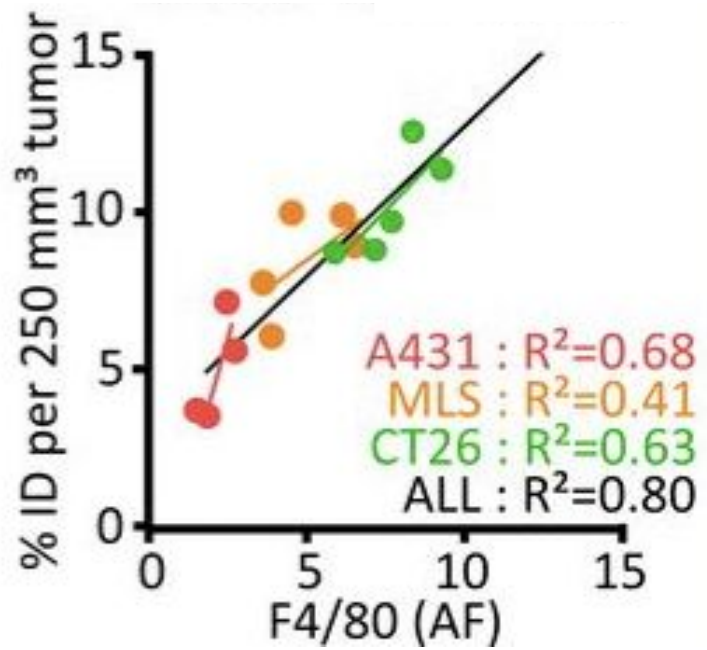


CT-FMT-based detection of accumulated polymers in 3 tumor models

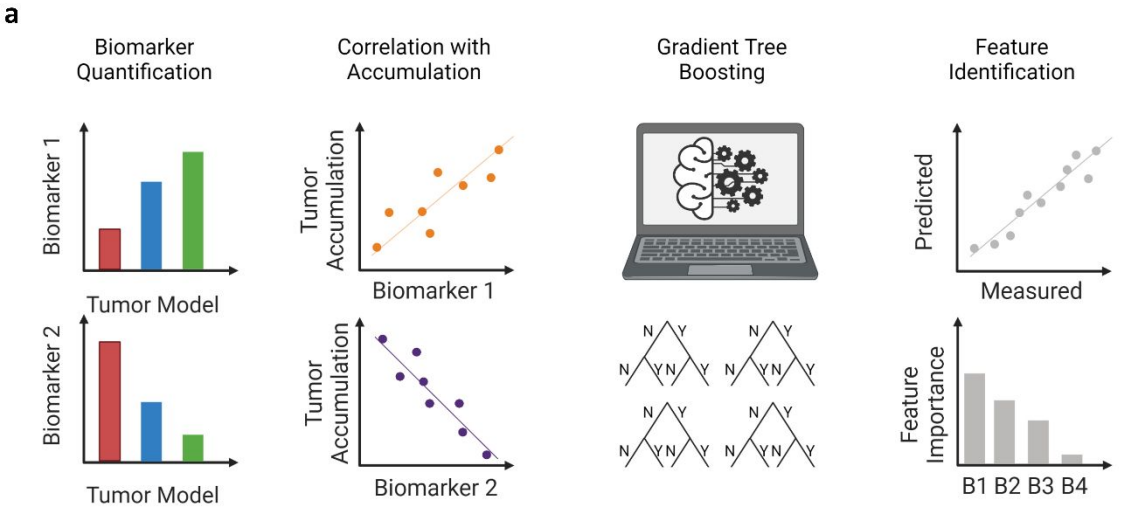


Characterizing the TME and linking it to accumulation

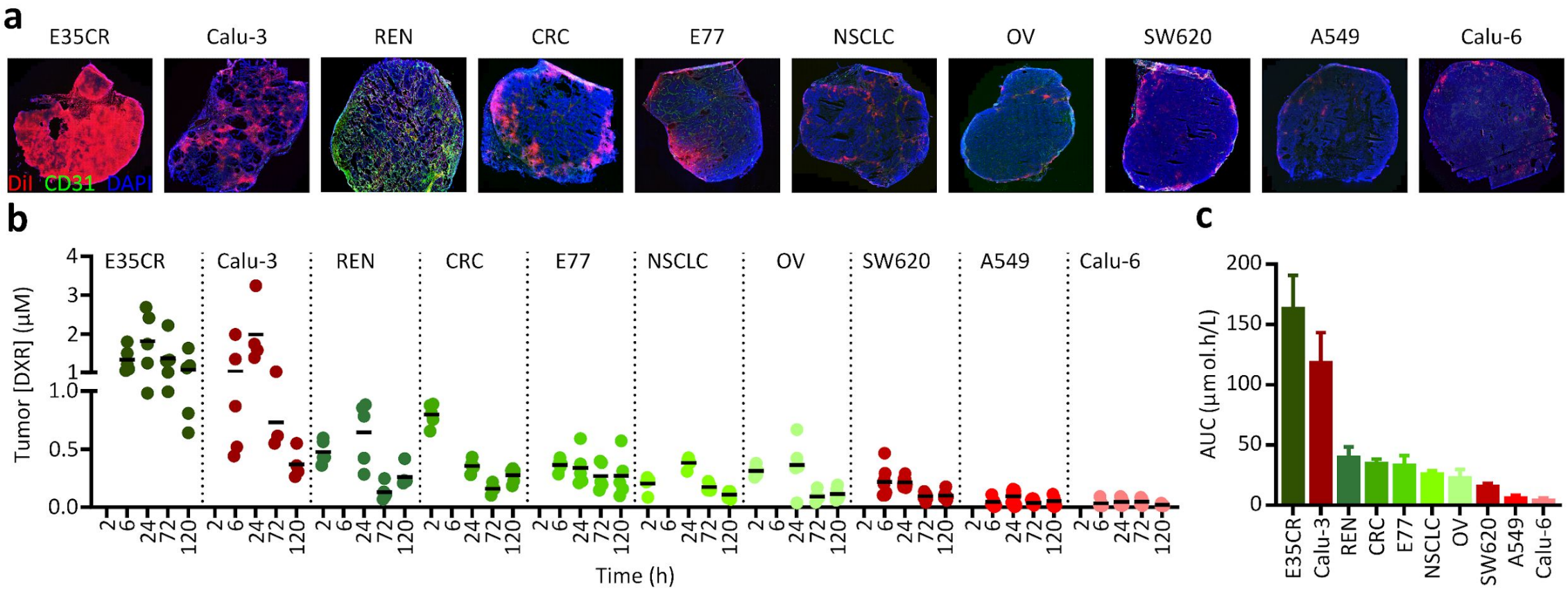




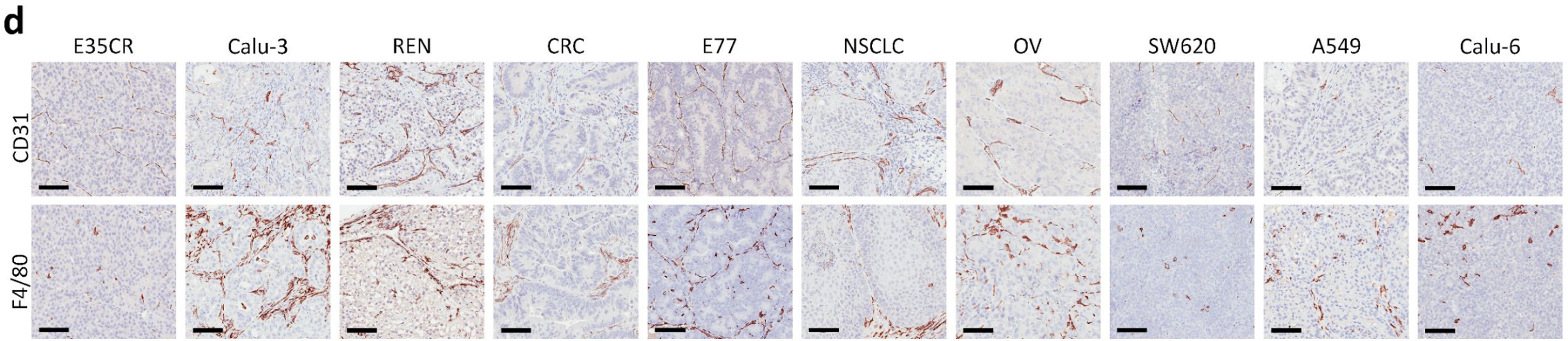
Gradient Tree Boosting identify important features



Extending the data set with 10 tumor models + Doxil

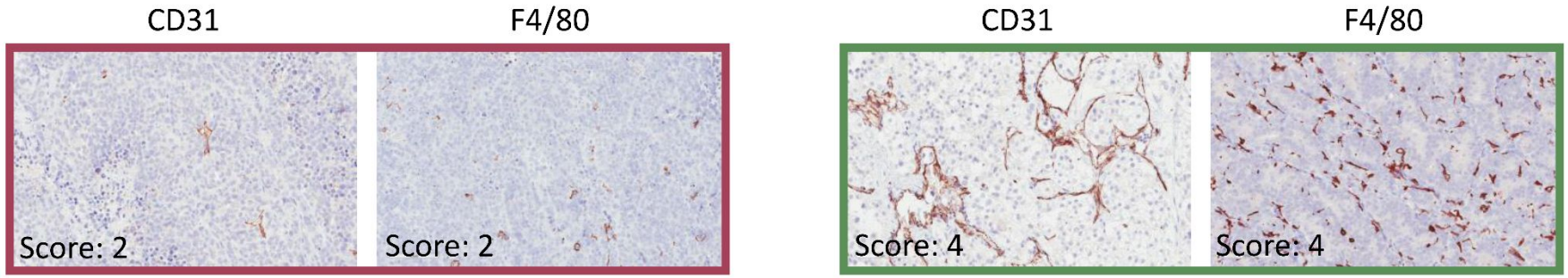


How can we simulate a clinical situation in our preclinical study?



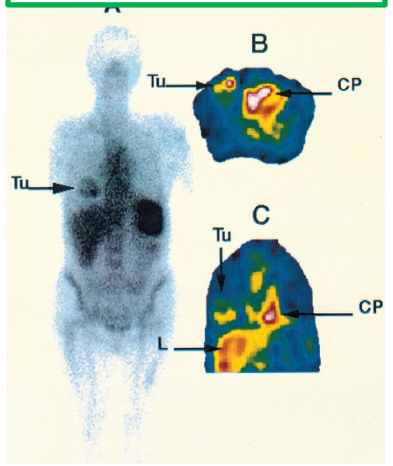
Scoring of murine tumors for the exclusion of likely low accumulaters

a



A historical control to proof the concept in a clinical setup

SCC bronchus



Breast

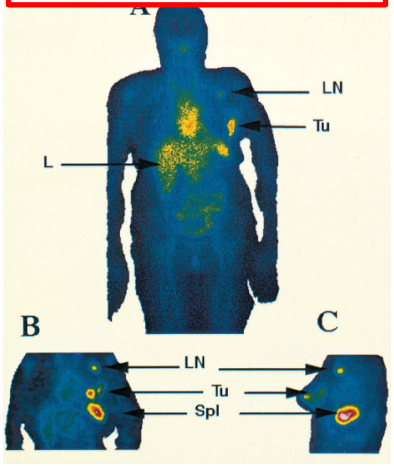


Table 3 Patient details: histology, stage, and results of gamma camera imaging and estimated tumor uptake from ROI analysis

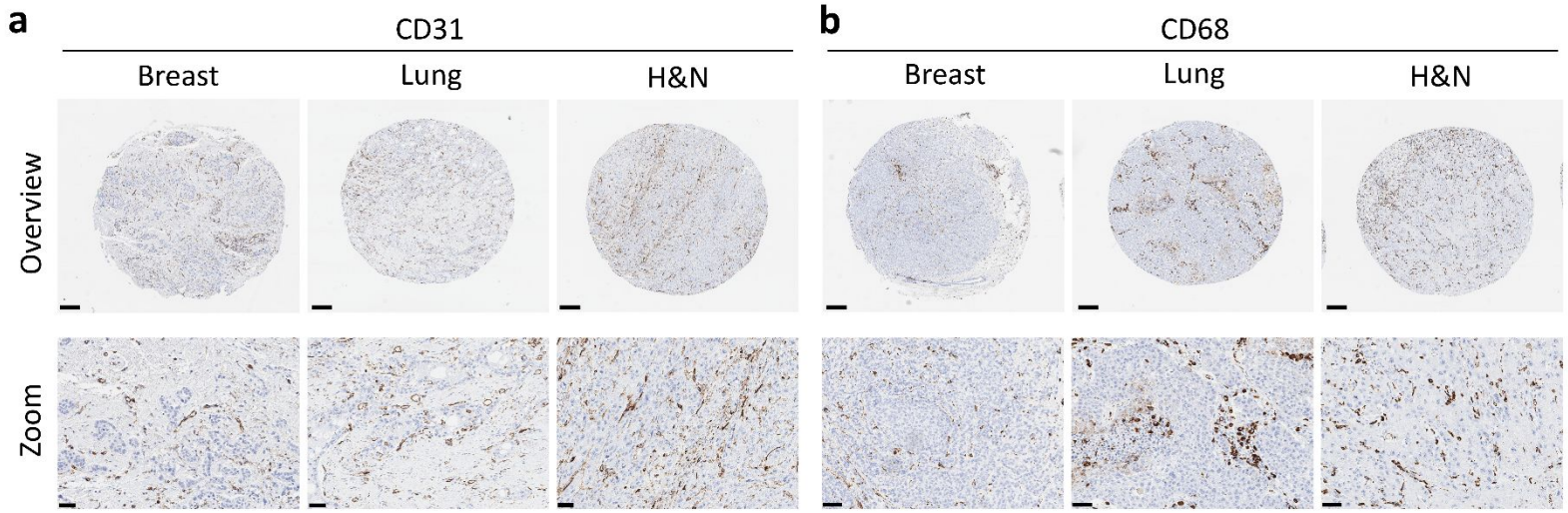
Patient	Tumor	Stage	Whole body scan	SPECT	Total % injected dose[a]	% ID/kg[b]
1	SCC[c] bronchus	T4N0M0	Positive	Positive	1.7	12.5
2	SCC bronchus	T4N0M0	Positive	Positive	1.6	25.4
3	Breast (ductal)	T4N2M1	Negative	Negative		
4	SCCHN	T3N2M0	Positive	Positive	3.5	46.8
5	Breast (ductal)	T4N1M0	Positive	Positive	0.3	2.7
6	Breast (ductal)	T4N2M1	Positive	Positive	1.5	3.9
7	Breast (ductal)	T3N2M0	Positive	Positive	1.7	9.5
8	SCCHN	T4N0M0	Positive	Positive	0.7	24.2
9	SCCHN	T3N1M0	Positive	Positive	1.0	32.0
10	SCC cervix	FIGO IIIB	Negative	Positive	NA	NA
11	Breast (ductal)	T4N2M0	Positive	Positive	1.4	5.2
12	SCC bronchus	T2N0M1	Negative	Negative		
13	SCCHN	T3N2M0	Positive	Positive	0.6	9.0
14	SCCHN	T3N0M0	Positive	Positive	1.6	53.0
15	SCC bronchus	T3N0M1	Positive	Positive	2.6	16.7
16	Glioma (AA)	Inoperable	Negative	Positive	NA	NA
17	Glioma (GBM)	Inoperable	Negative	Positive	NA	NA

[a] Tumor uptake determined from ROI on 72 h whole body scan.
[b] Percentage injected dose/kg calculated from estimated tumor volume.
[c] SCC, squamous cell cancer; AA, anaplastic astrocytoma (grade III); GBM, glioblastoma multiforme (grade IV); NA, not assessable (tumor uptake was only measurable from whole body scans).

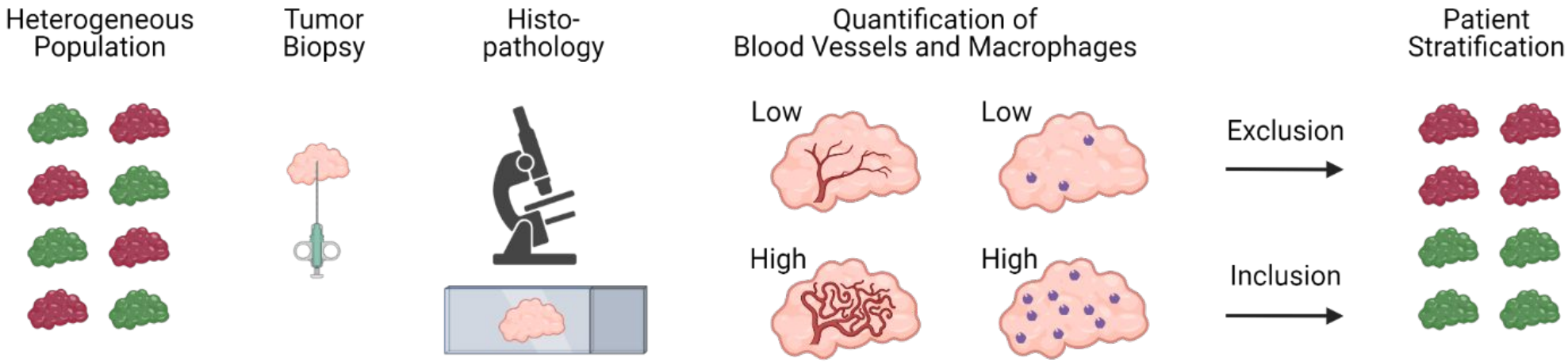
- The archive of UKA's pathology provided tissue microarrays of 10 patients per tumor type (SCC bronchus, SCC H&N and Breast) to perform CD31 and CD68 stainings

Harrington et al., 2001

CD31 and CD68 to identify low accumulating tumors



Summarizing Perspective



- Next steps:
  - Establish collaborations with companies to facilitate the translation of nanochemotherapies
  - Develop a protocol for the implementation in clinical trials

Acknowledgements

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Saskia von Stillfried
Peter Boor

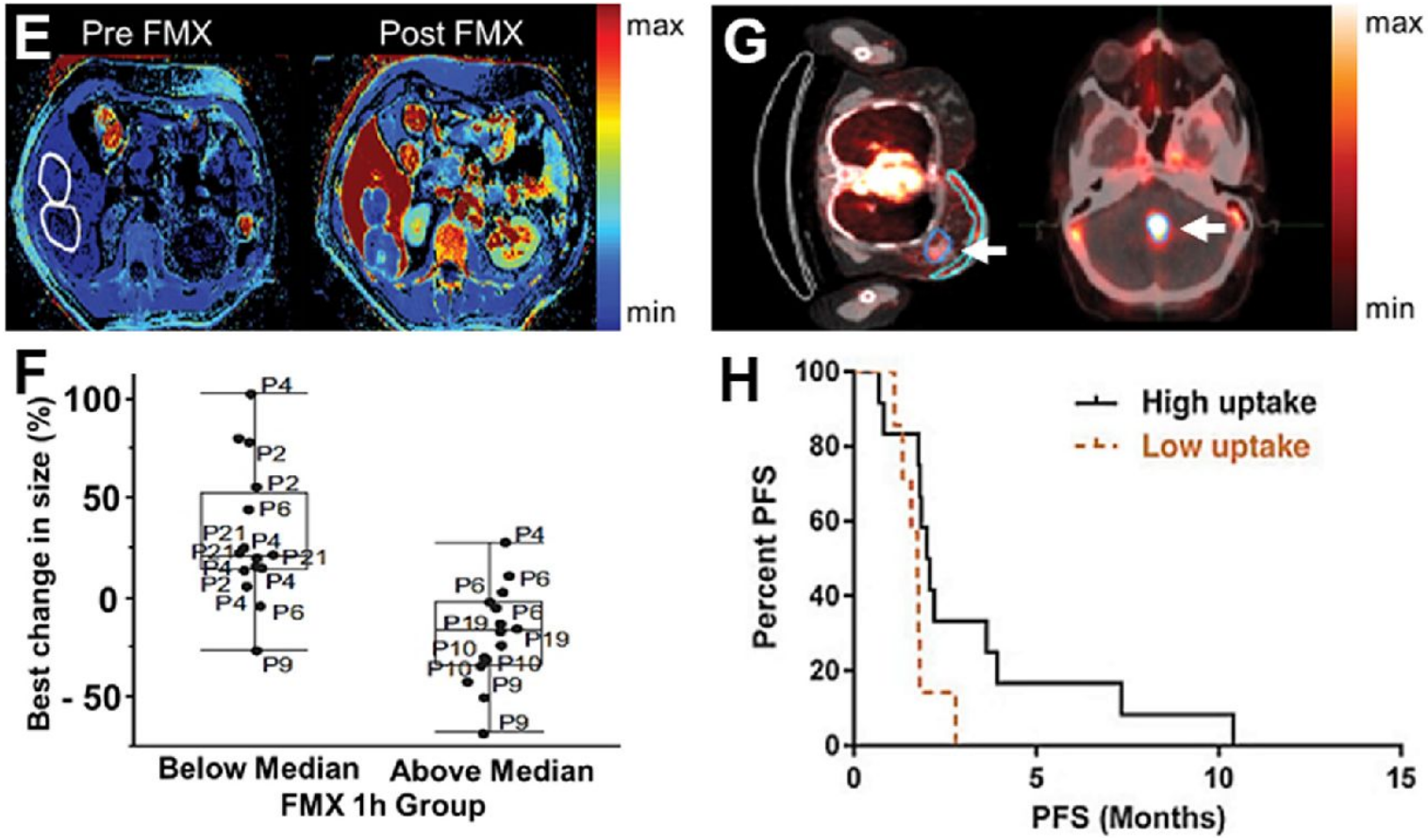
Meet me
at poster 271!

AstraZeneca

Jennifer I. Moss
Sanyogitta Puri
Simon T. Barry
Marianne B. Ashford

Imaging to preselect patients in nanomedicine

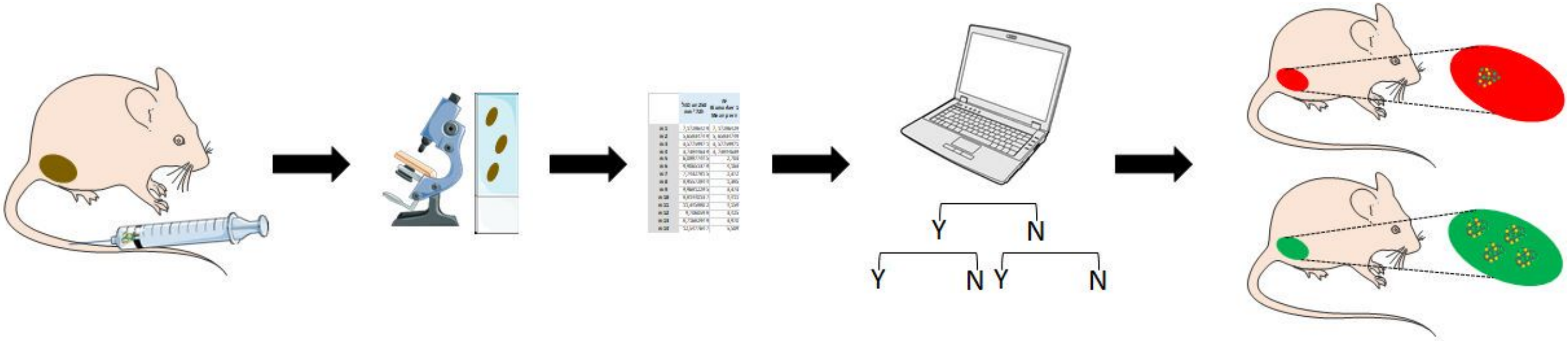
- Problem: highly heterogeneous outcomes for nanomedicine-based anticancer therapies
  - Imaging to enable patient preselection



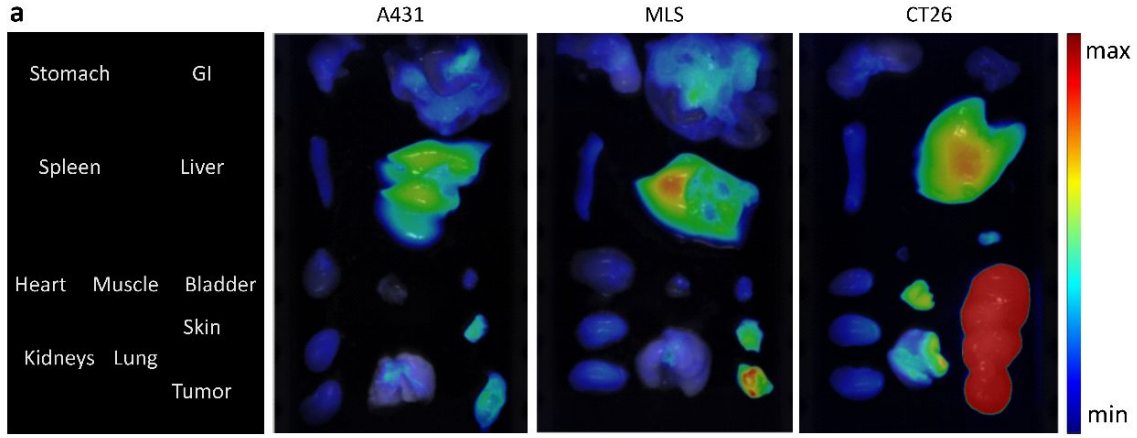
Ramanathan et al., Clin Cancer Res, 2017; Lee et al., Clin Cancer Res, 2017; Golombek et al., Adv Drug Deliv Rev, 2018

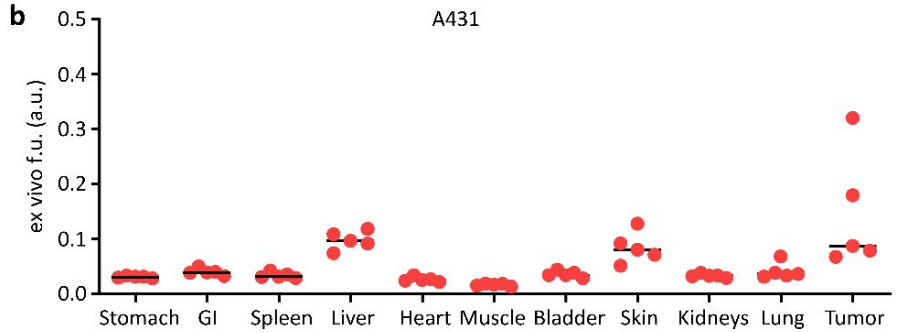
Study setup

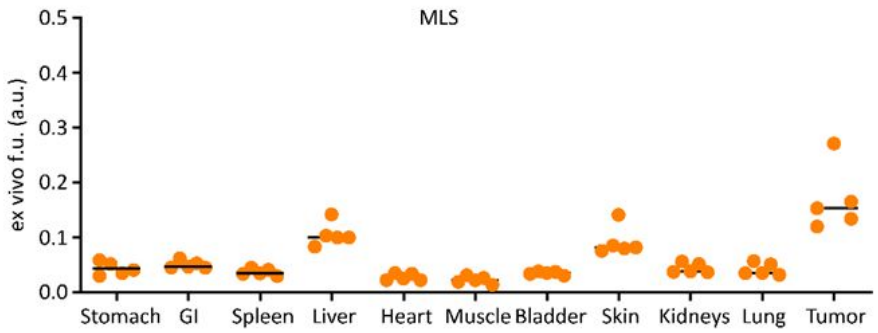
- Workflow:
  - tumor-bearing mice (A431, MLS or CT26)
  - i.v. injection of fluorophore-labelled pHPMA polymers (10-20 nm)
- CT-FMT, US and immunohistology

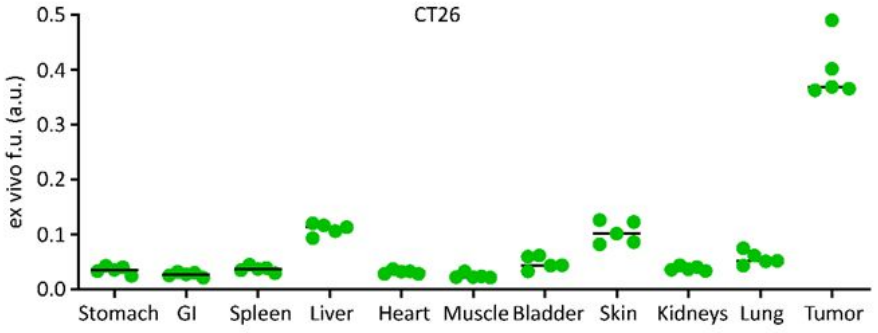


Organ distribution

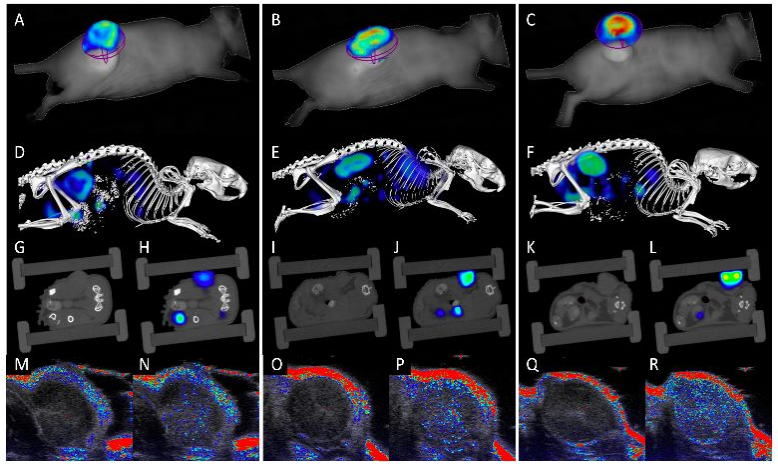


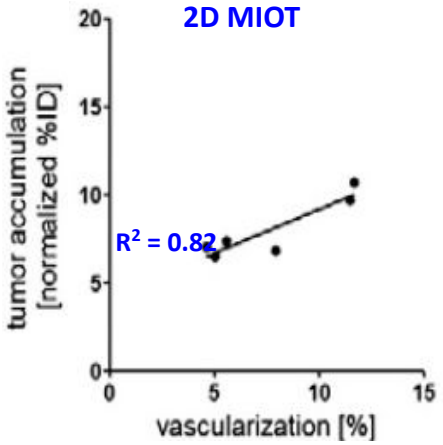


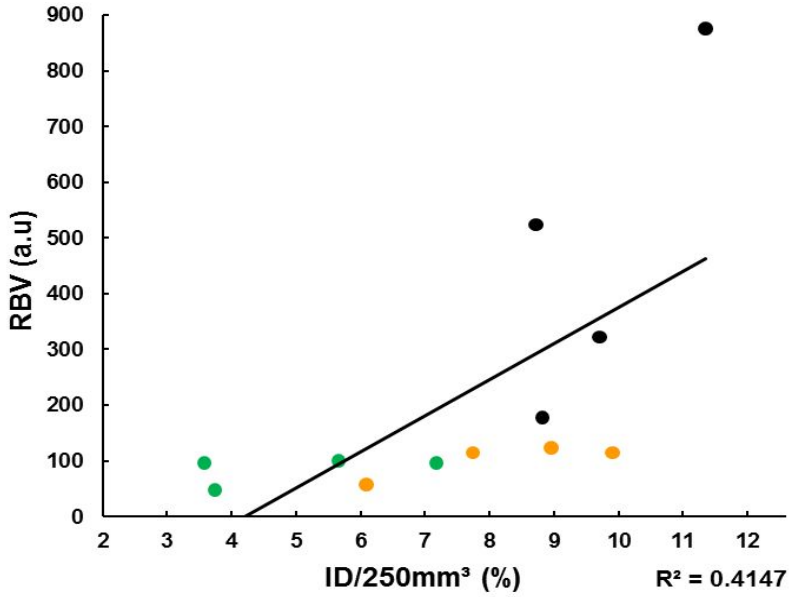


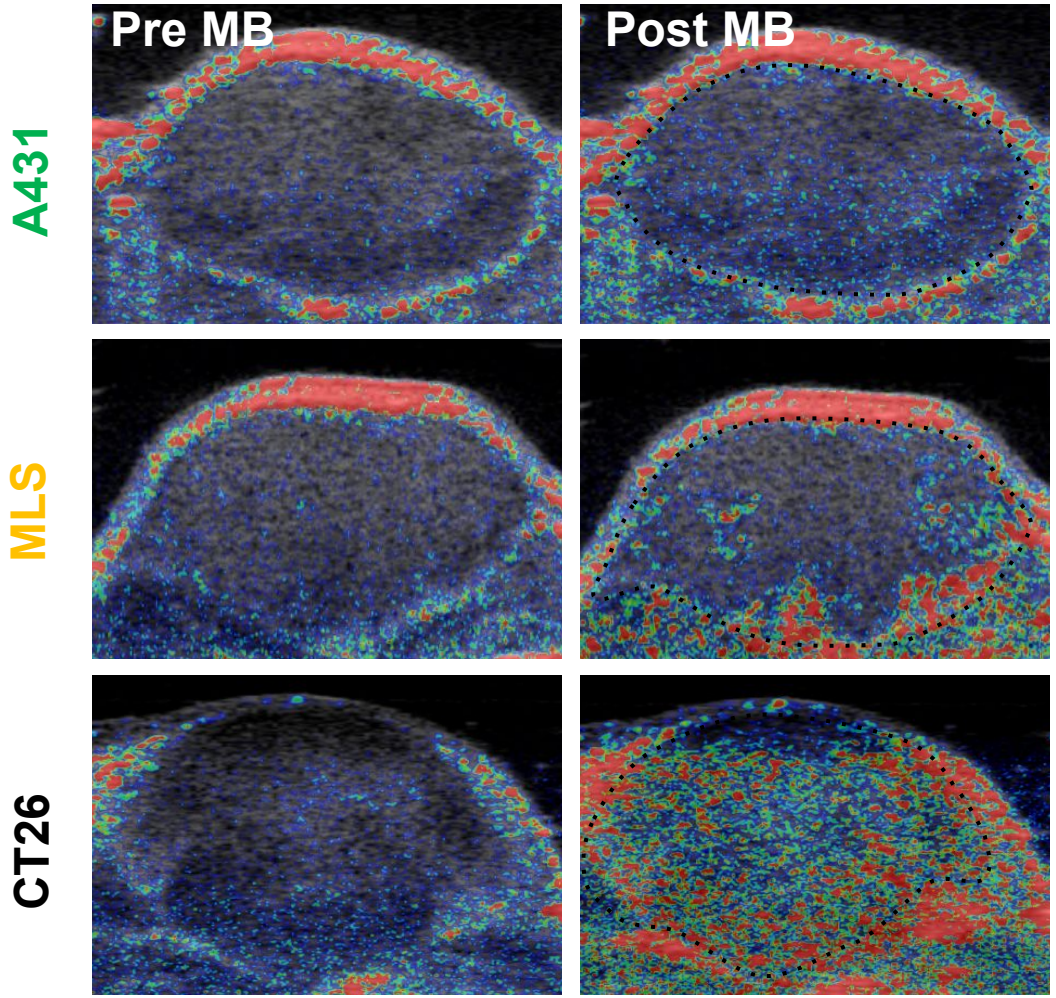


CeUS of tumor perfusion as an indirect imaging biomarker





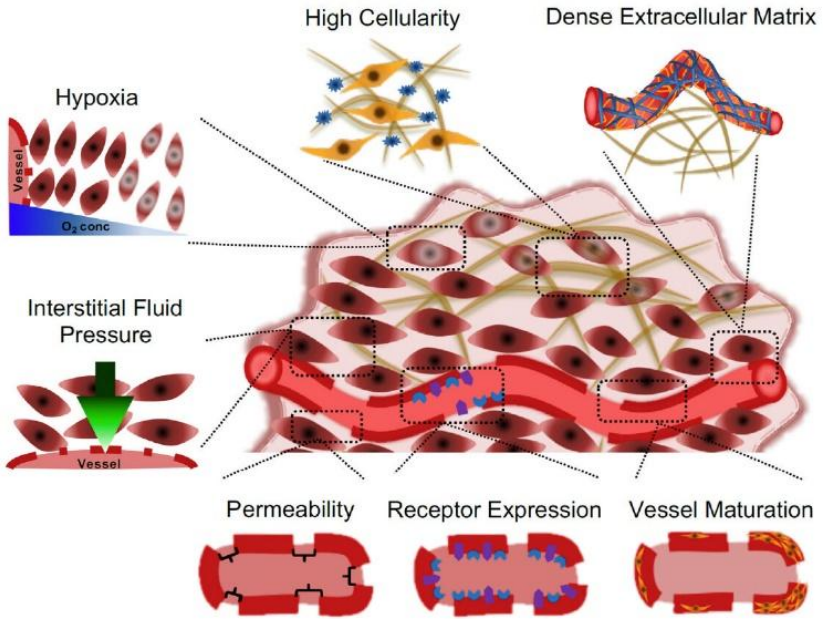


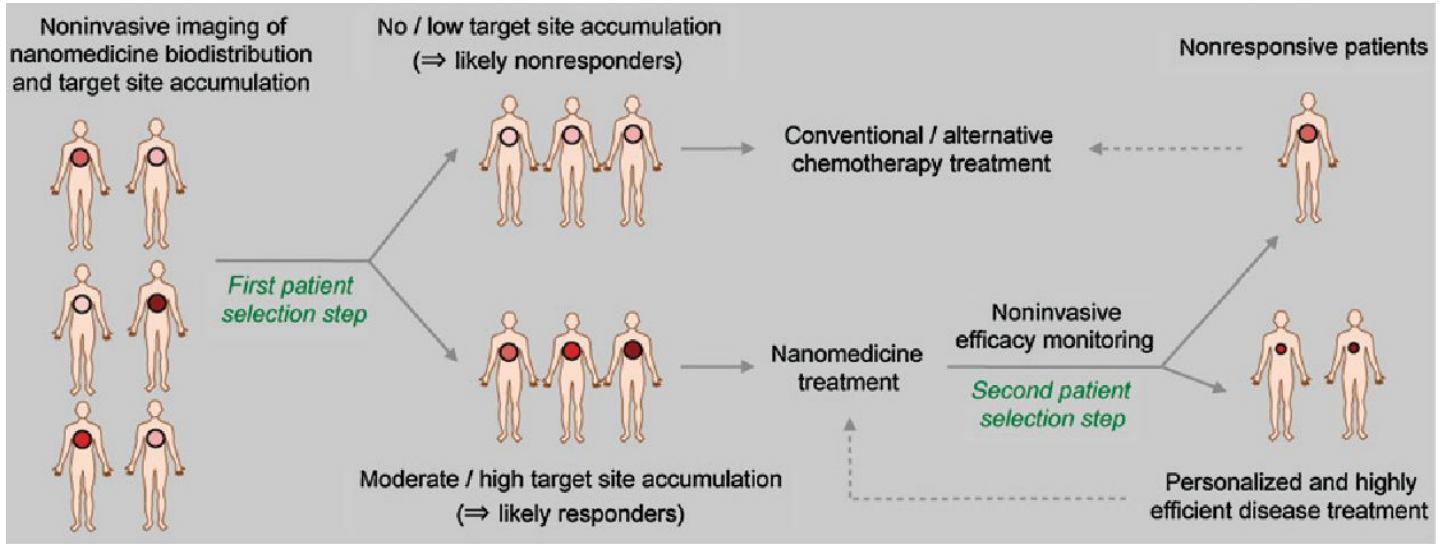


Theek et al., J Control Release, 2014

Background

- Idea: tumor biopsies to predict nanomedicine accumulation

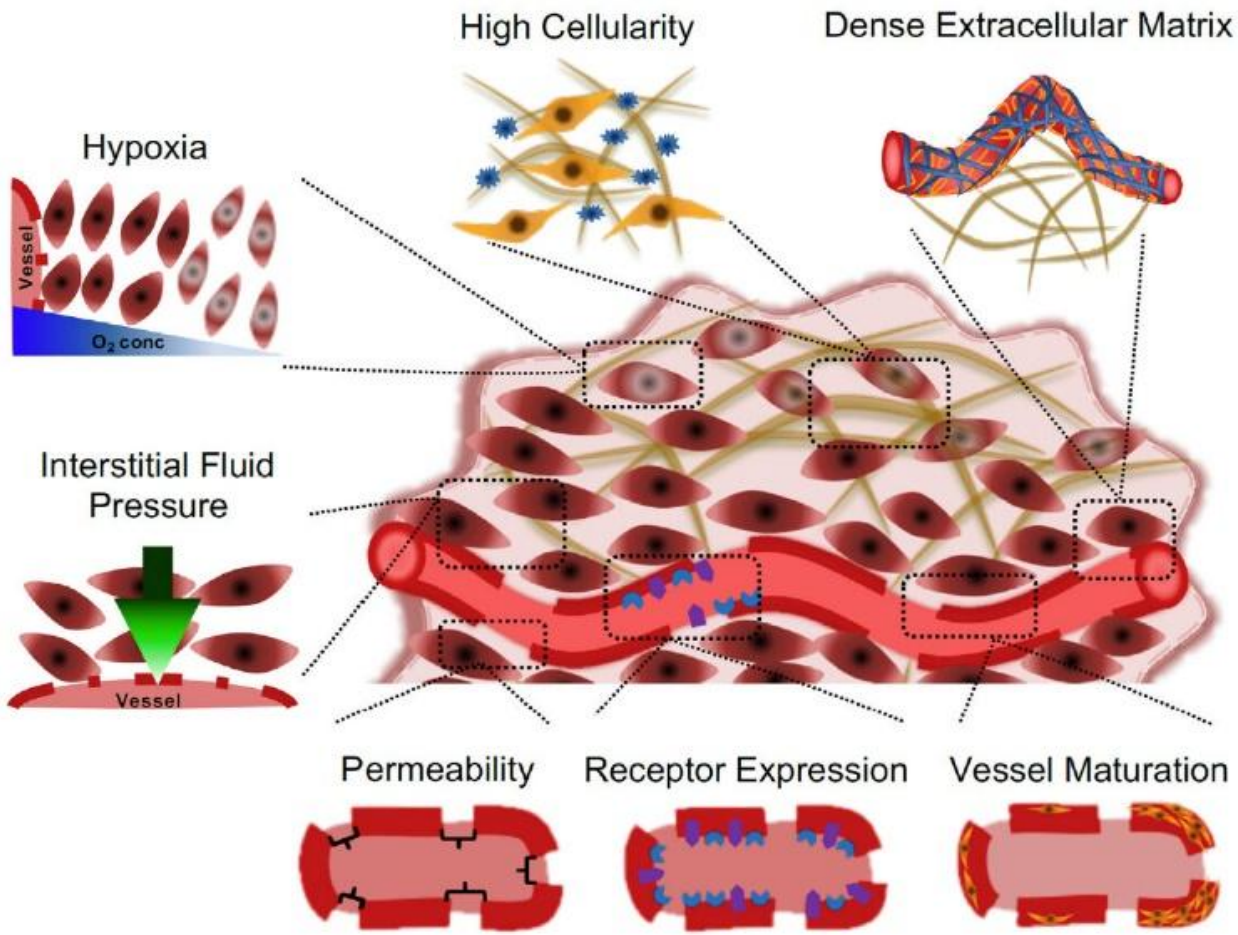




Golombek et al., Adv Drug Deliv Rev, 2018; Lammers et al.,Clin Cancer Res, 2012

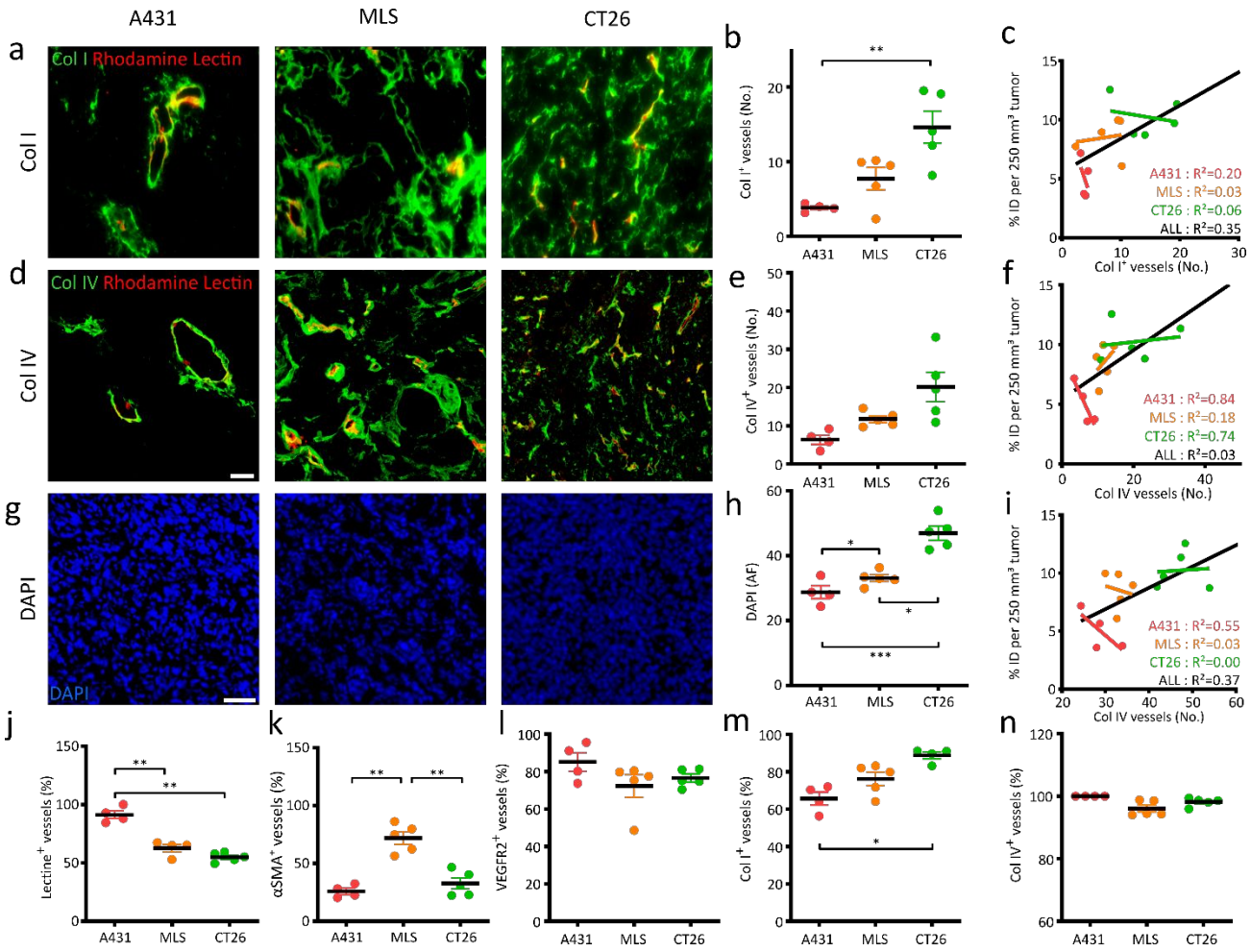
Evaluated biomarkers

- Vasculature: Rhodamine lectin, CD31, aSMA, VEGFR2, LyVe1
- Extracellular Matrix: Collagen I, Collagen IV, Hyaluronic acid
- Macrophages: F4/80, spatial distribution of macrophages

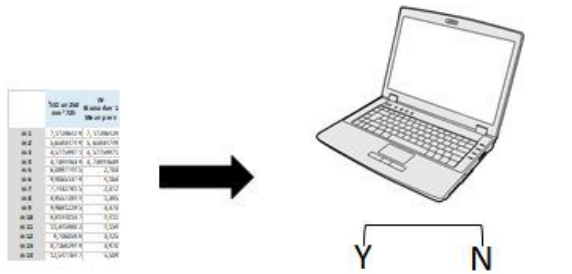


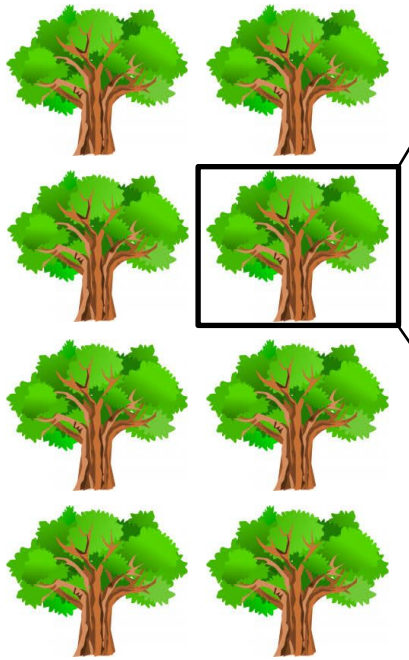
Golombek et al., Adv Drug Deliv Rev, 2018

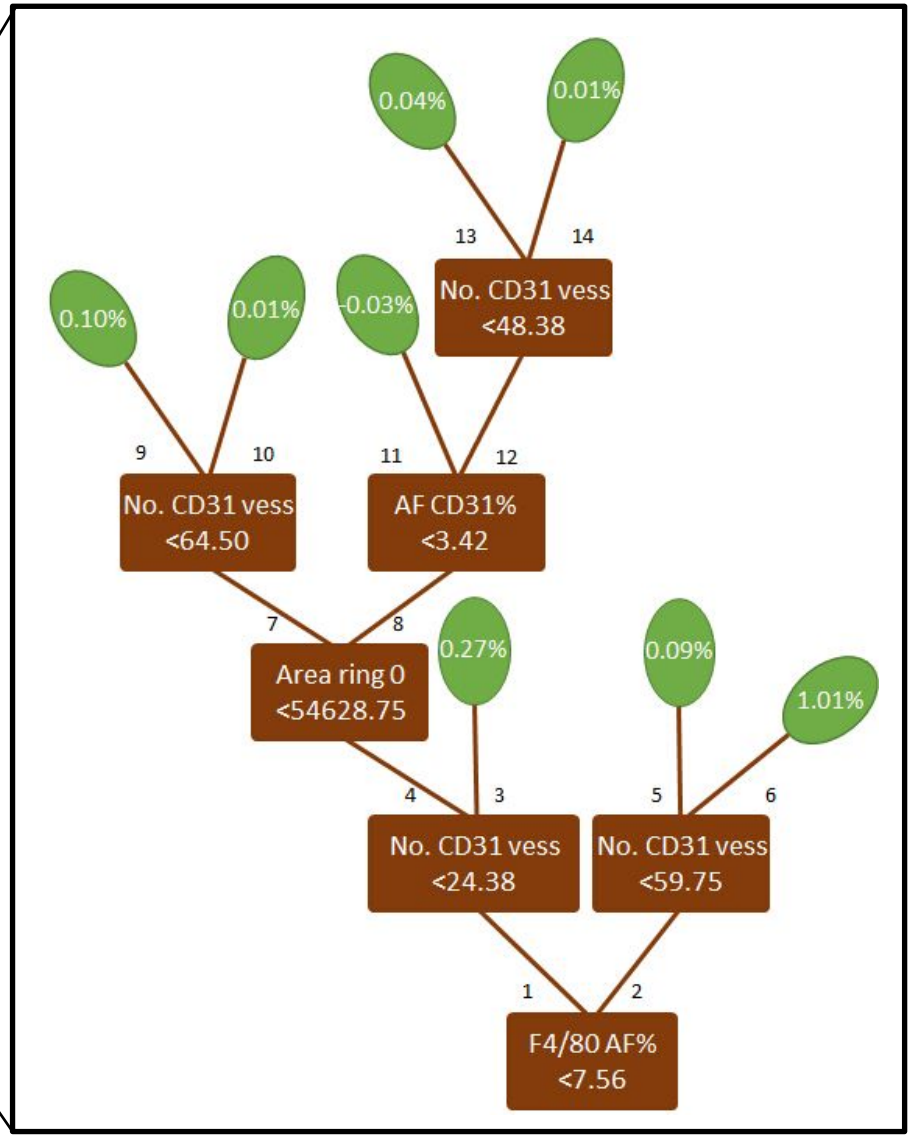
Extension on screened biomarkers



Workflow of gradient-tree boosting machine learning

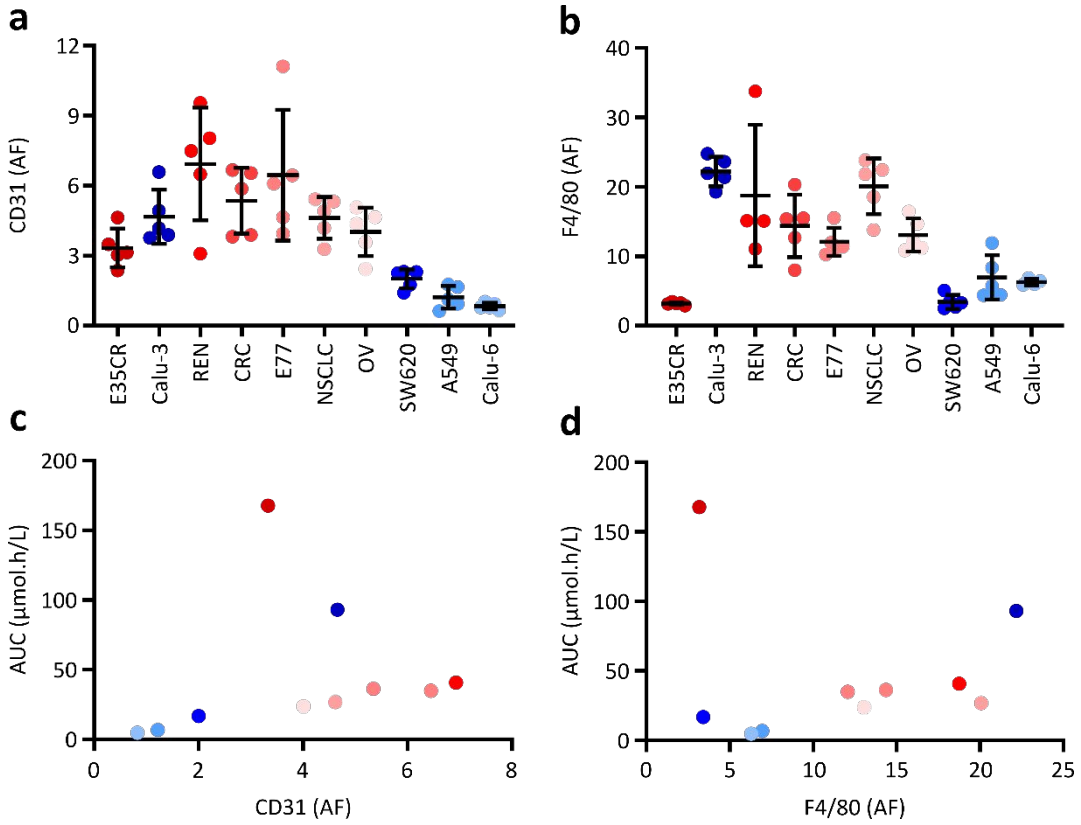






https://www.medwaytowns.org.uk/non-scouting-activities/2011-10/kent-free-trees-scheme

Area fraction values of CD31 and F4/80



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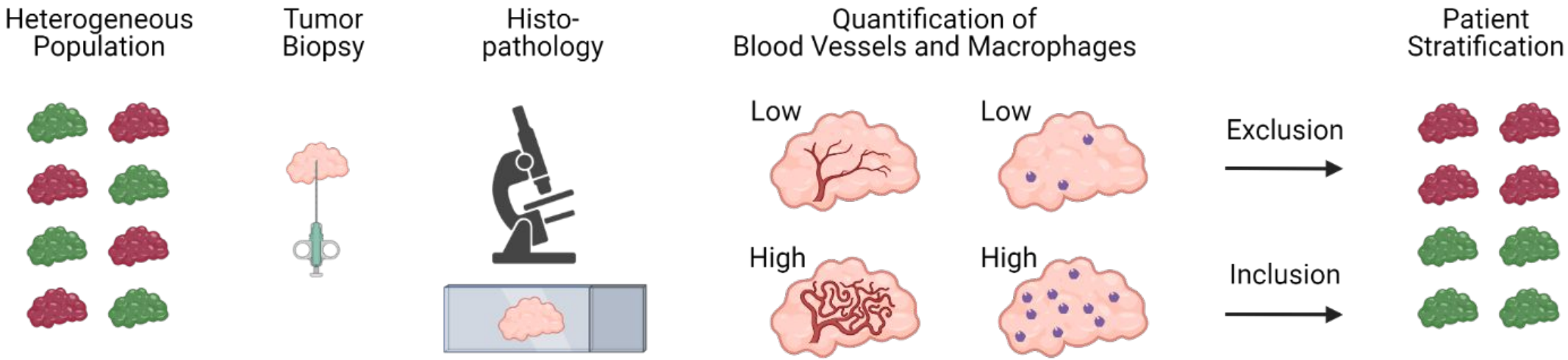
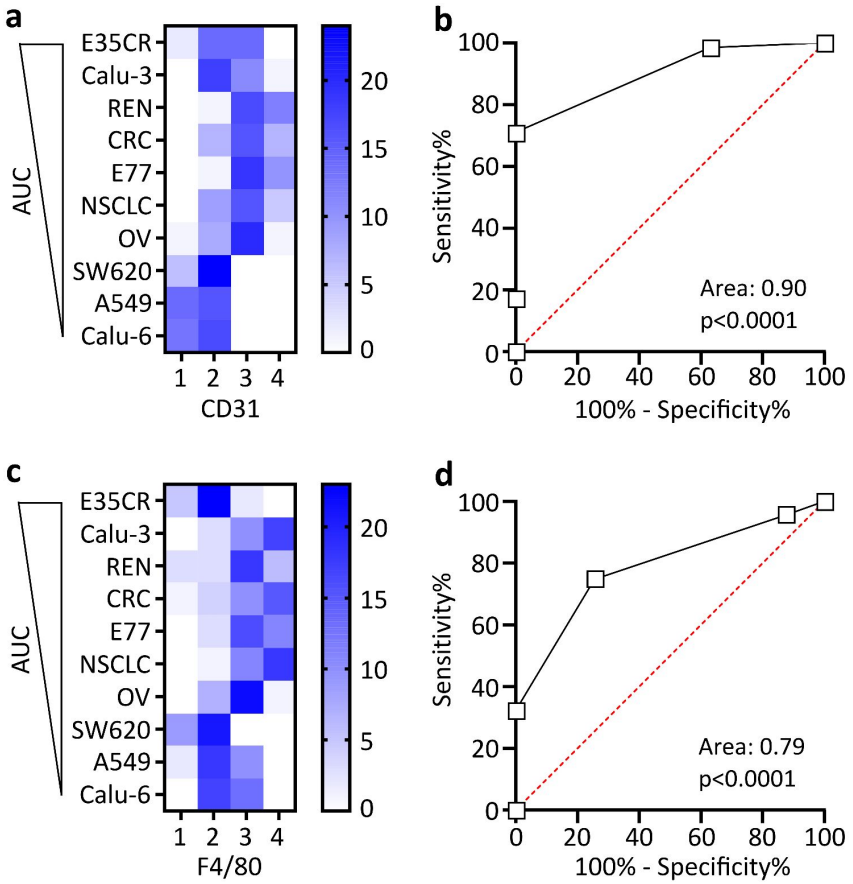
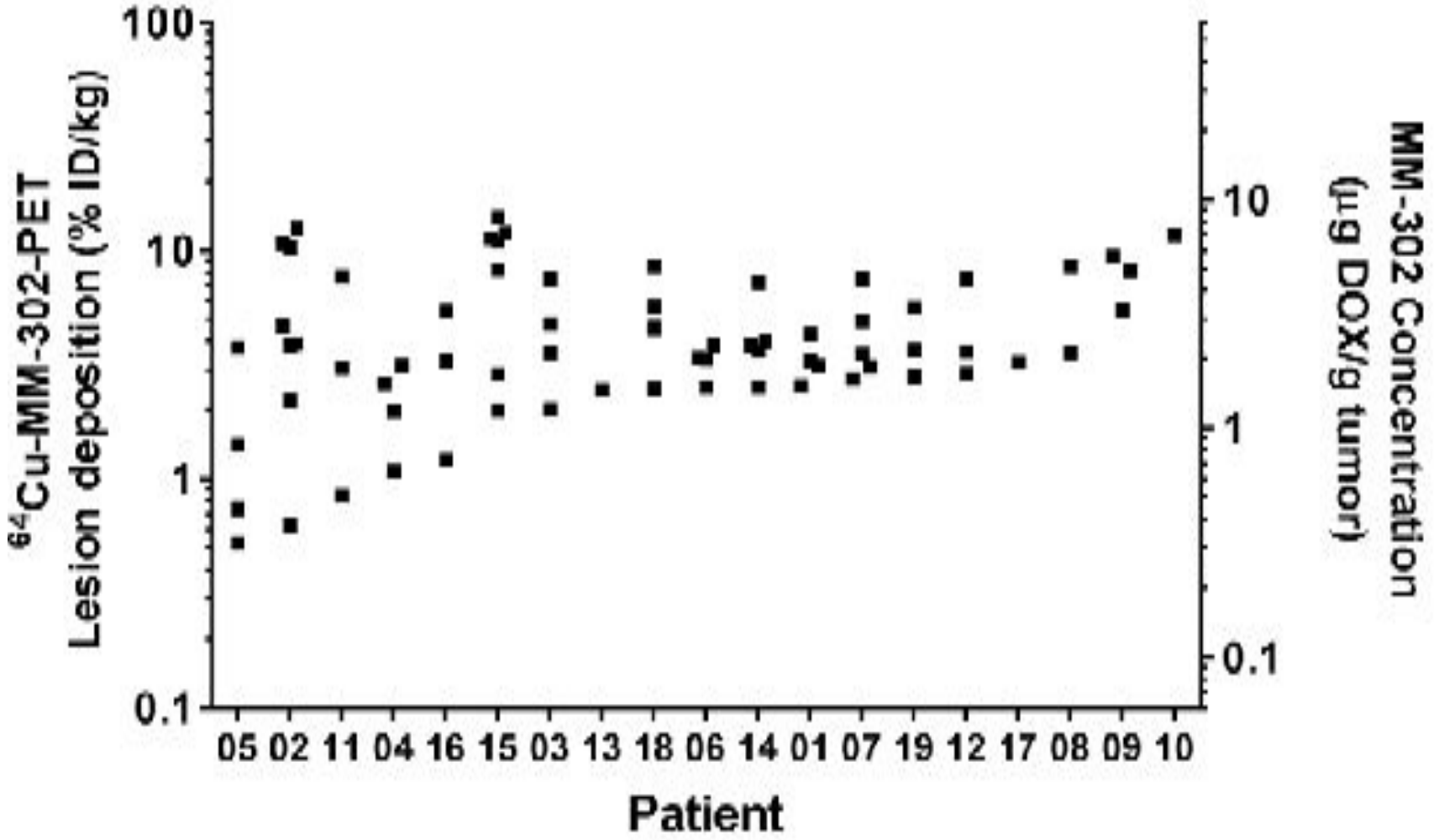


Performance of individual biomarkers in scoring

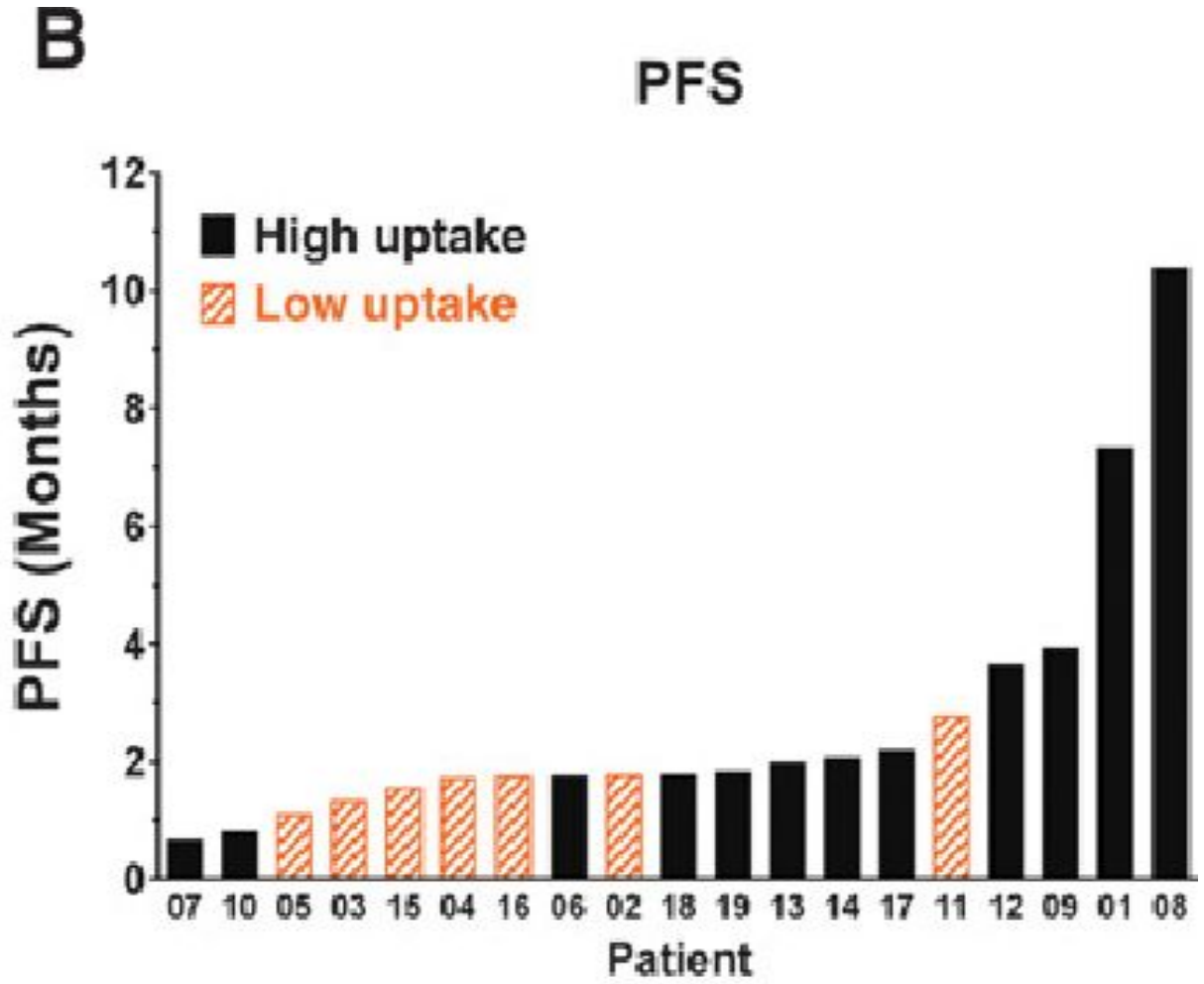


Companion diagnostics displays drug accumulation



Lee et al., Clin Cancer Res, 2017

Higher accumulation does not guarantee best response



Lee et al., Clin Cancer Res, 2017

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I or one of my co-authors have **the following financial interest** or **relationship(s)** to disclose with regard to the subject matter of this presentation:

Employment: Jennifer I. Moss, Sanyogitta Puri, Simon T. Barry, Marianne B. Ashford (AstraZeneca)