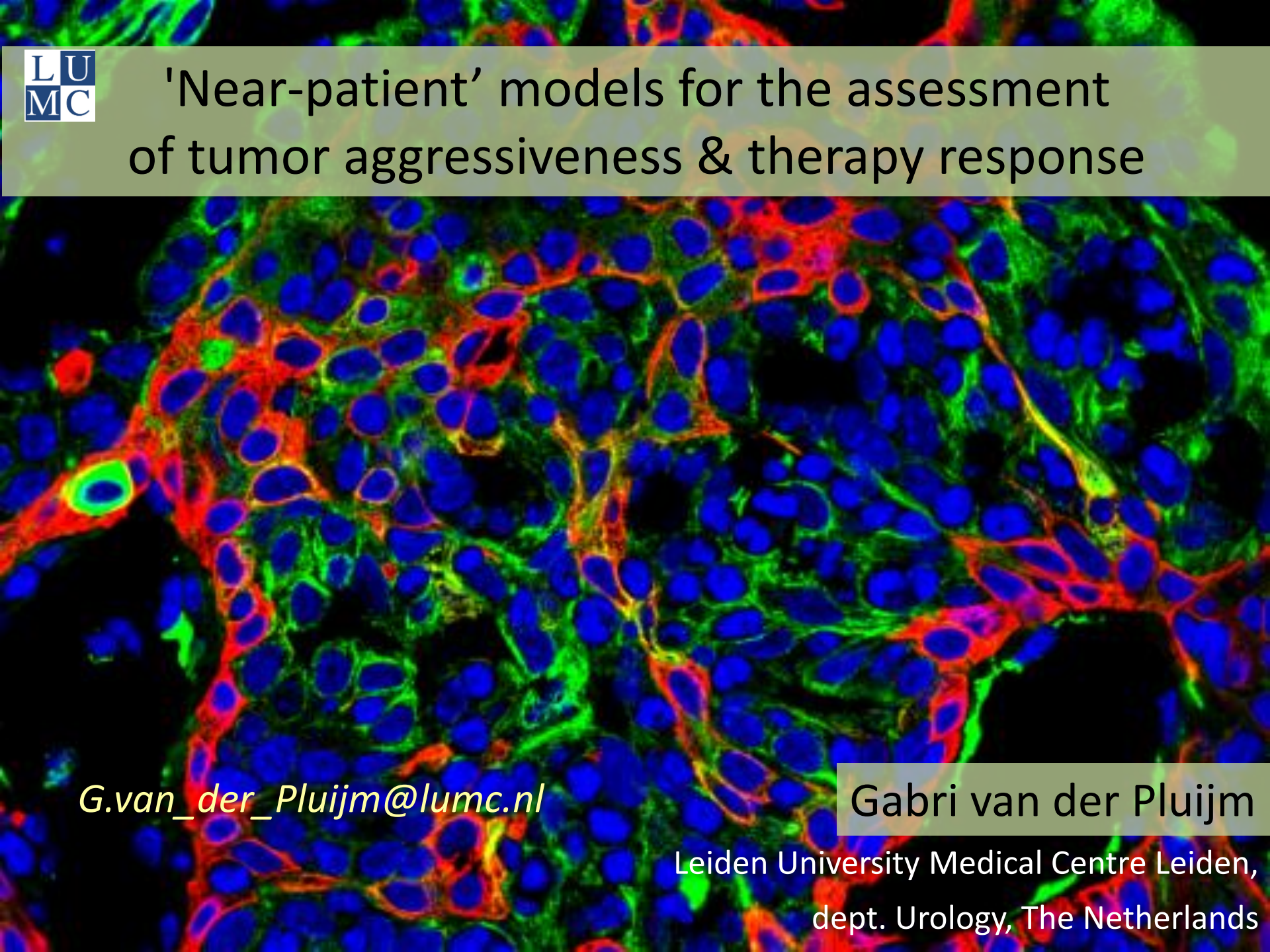
'Near-patient' models for the assessment of tumor aggressiveness & therapy response



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Gabri van der Pluijm

Leiden University Medical Centre Leiden,

dept. Urology, The Netherlands

Outline

- Clinical problem of urological cancers

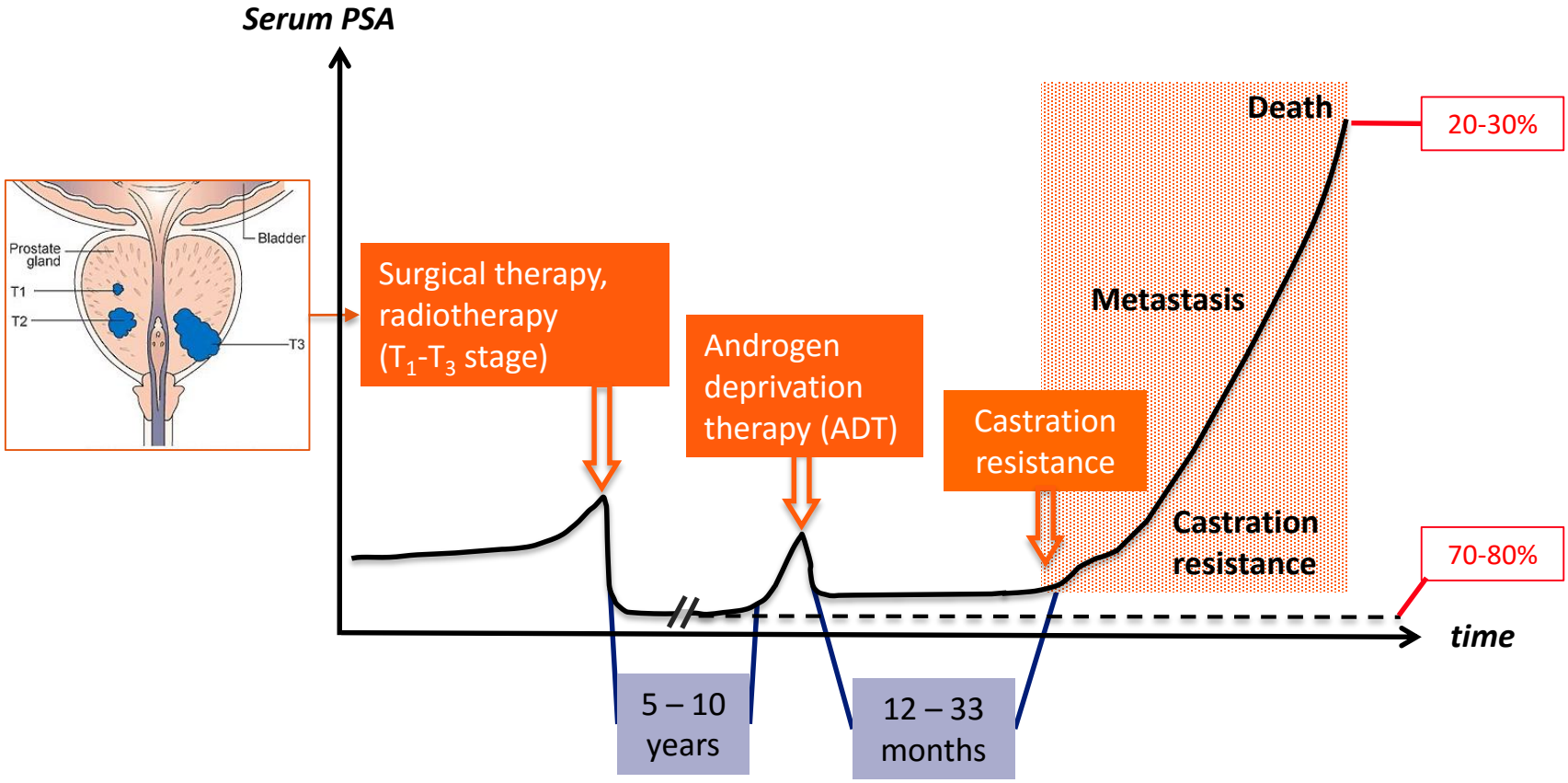
- ‘Near-patient” disease models

  Tumor progression (functional studies)

  Development of novel therapy

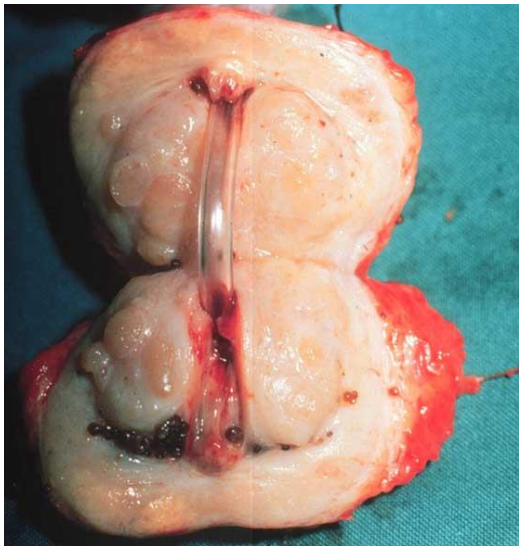
Clinical Problem of Prostate Cancer

- most frequent cancer in men
- second leading cause of cancer death in males
- after prostatectomy or radiotherapy of the primary tumor, a subset of T1-T3 “organ confined” cancers progress towards incurable metastasis



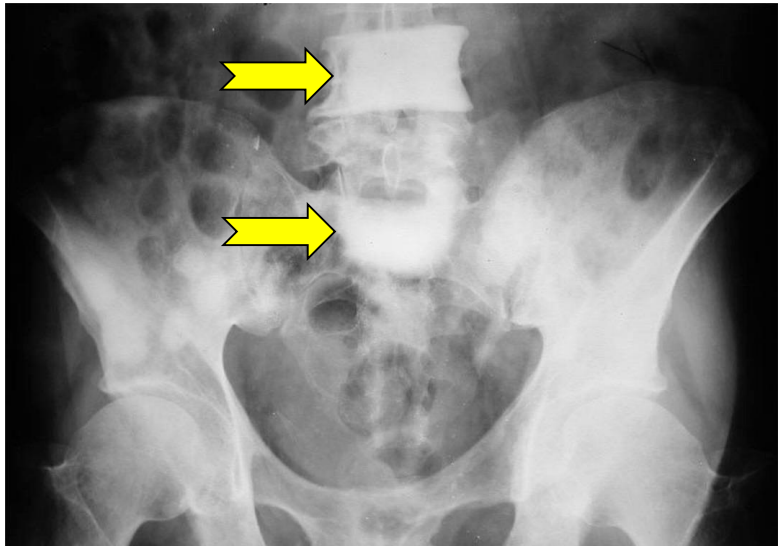
The problem!

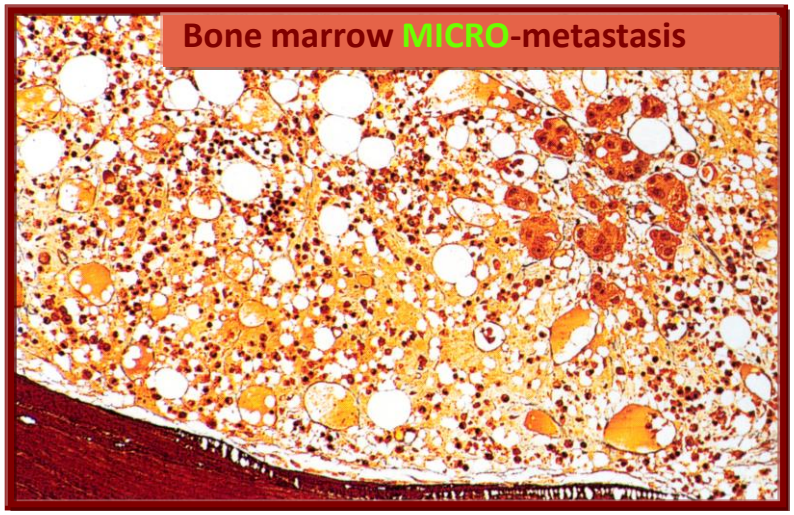
Stage: T1-3

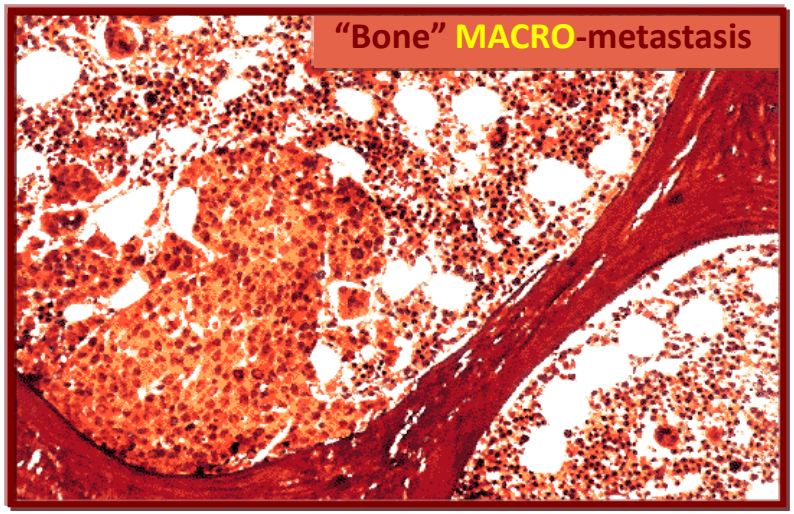


20-30%

Bone metastases

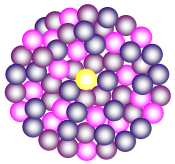




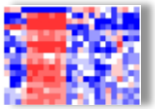


Mechanism(s) ? Novel Therapy?

Cancer Cells



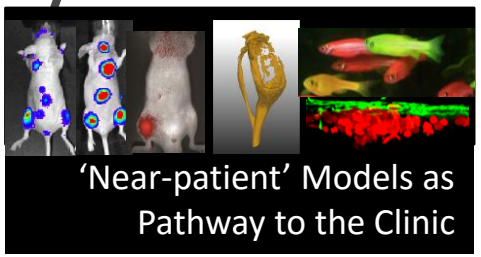
Molecular Profiling

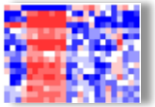


BioMedical Imaging
-Novel Imaging Agents
-Improved Detection of MRD
-Companion diagnostics

Clinical Problem
Lethal Metastasis (MRD)
Therapy Resistance
Intra-Tumor Heterogeneity

Functional Studies



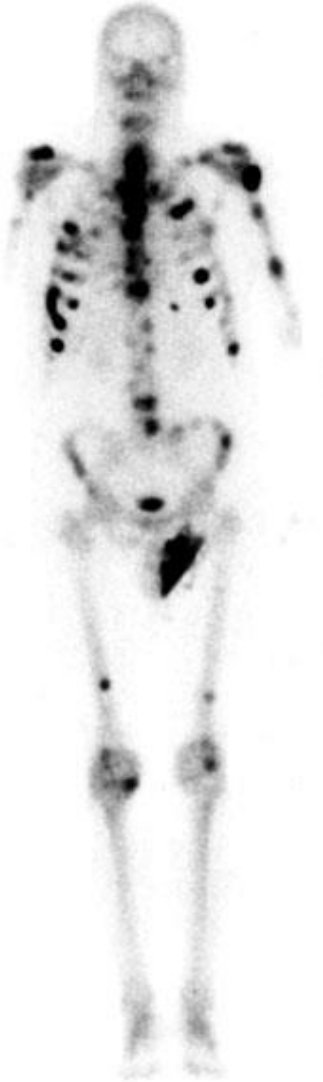


Supportive Stroma
- Primary tumor
- Metastasis

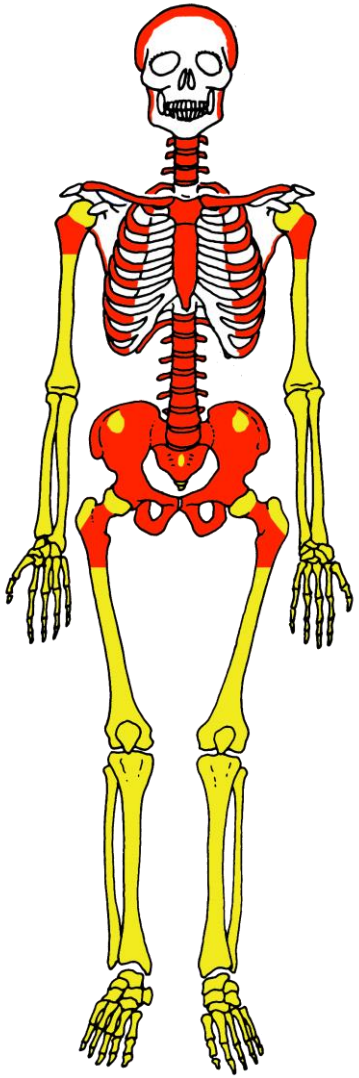
Molecular Profiling

→ Novel Therapy
→ Drug Respositioning
Nanodrug Delivery

'Anatomical' osteotropisms



Bone Metastases



Red marrow distribution

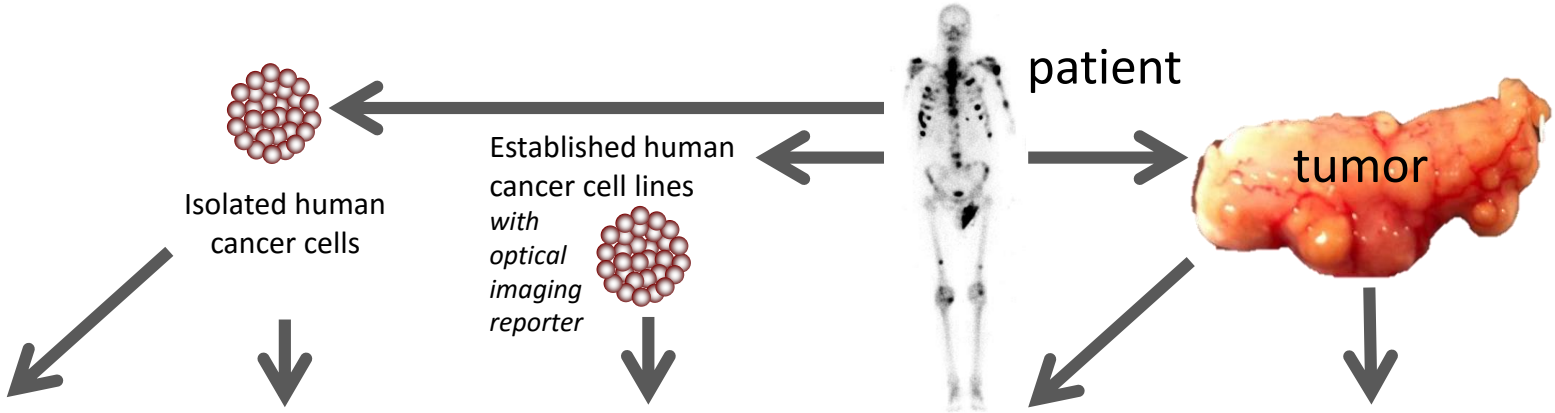
Major Aim

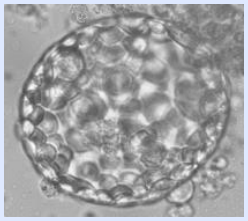
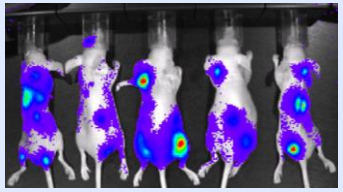
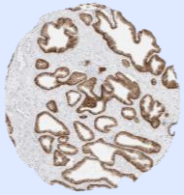
1) better identify newly diagnosed cancer patients with ostensible localized disease that are at risk of disease progression.

2) select novel, effective inhibitors of perturbed, key pathways and predict an individualised therapy response in patients (personalised medicine).

'Near-patient' prostate cancer models for the assessment of disease prognosis and therapy response. (Period 2015-2021)

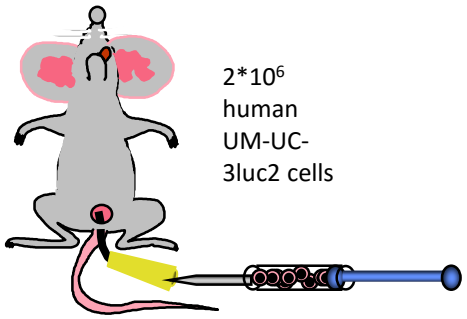
‘Near-patient’ models



IN VIVO	***IN VITRO***	***IN VIVO***	***IN VIVO***	***EX VIVO***
				
Zebrafish	**2D Cultures Spheroid/Organoid**	**Xenografting in immunodeficient mice**	**Patient-derived Xenografting (PDX)**	**Tumor Slice cultures**

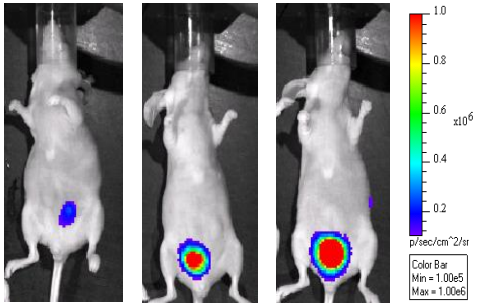
Bladder cancer orthotopic *in vivo* xenograft model

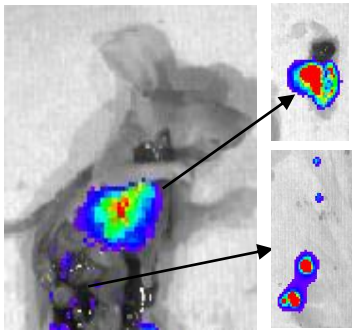
Preclinical model using bioluminescent imaging of orthotopically inoculated UM-UC-3luc2 cells

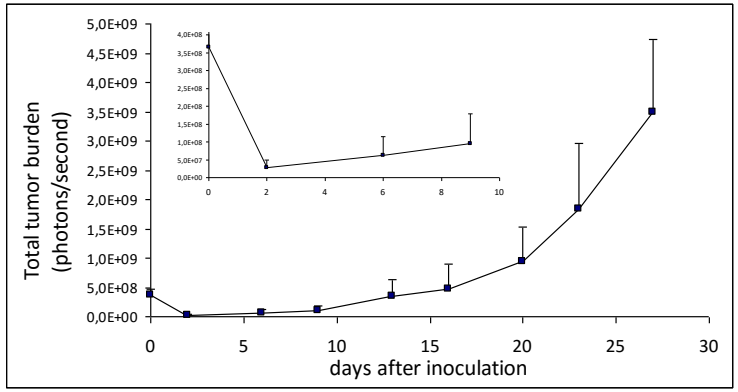


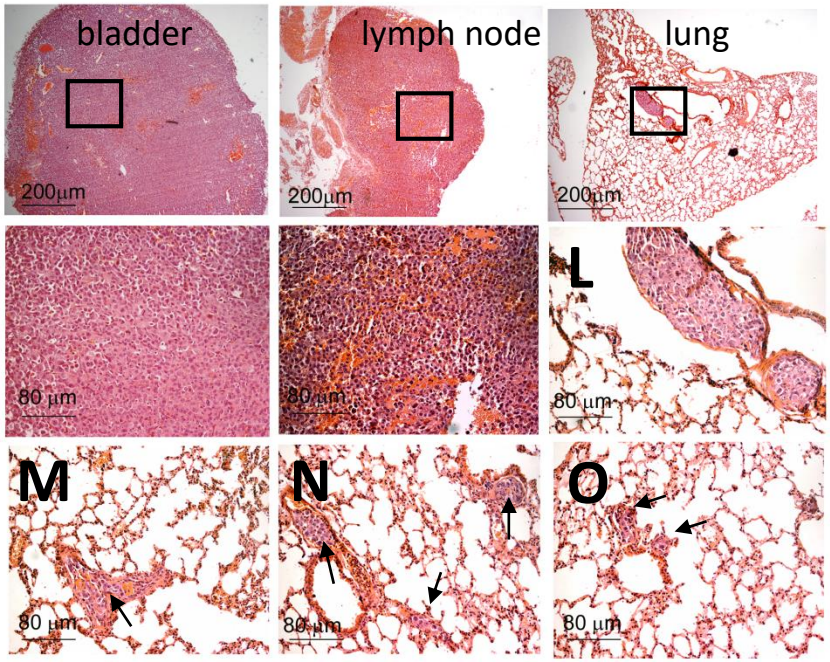
$2*10^6$ human UM-UC-3luc2 cells

Nude BalbC mouse

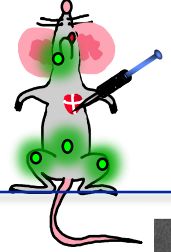




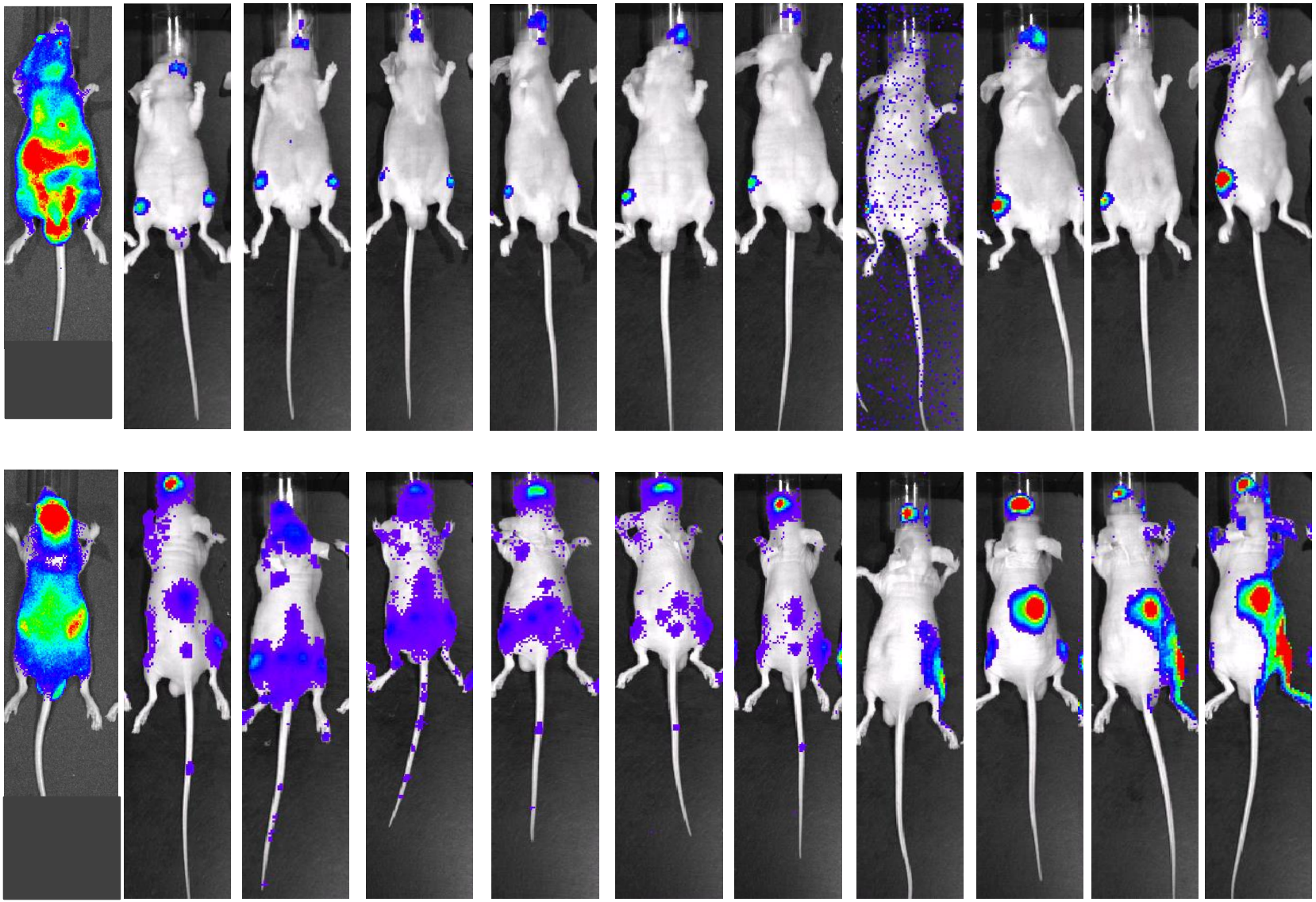




Van der Horst et al European Urology 2011

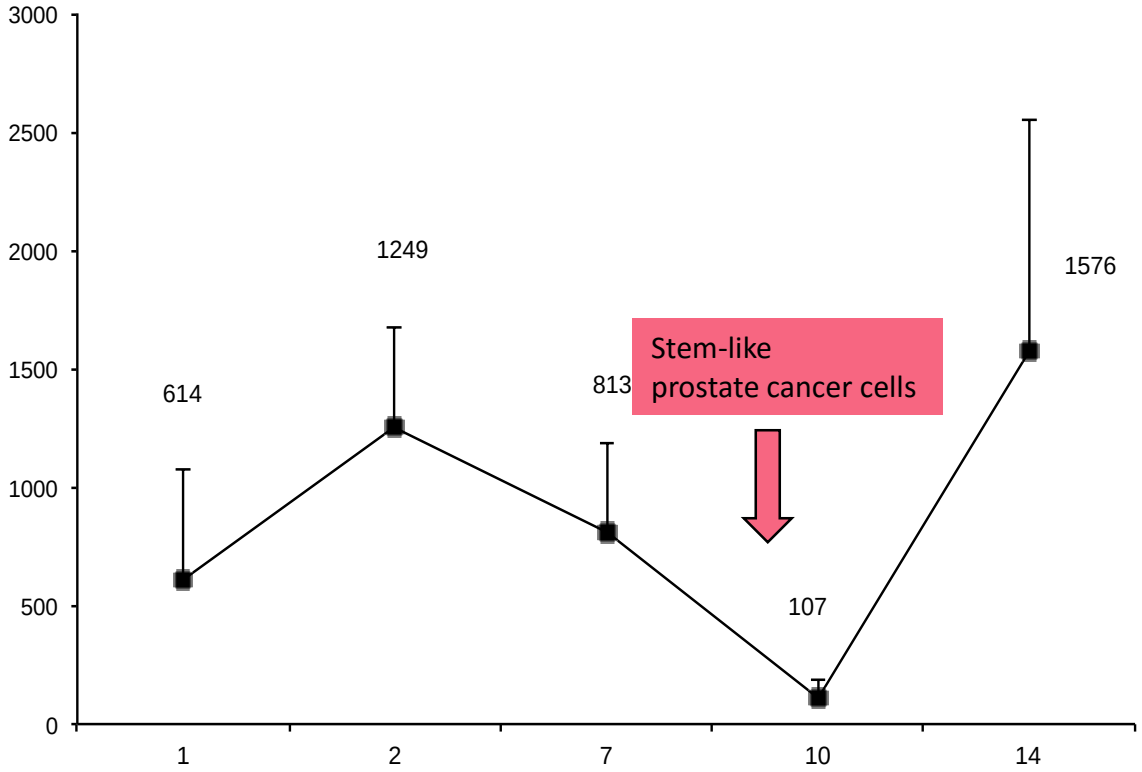


Kinetics of Bone Metastasis (PC-3M-Pro4luc2)

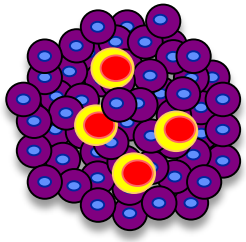


Seed & Soil in real time

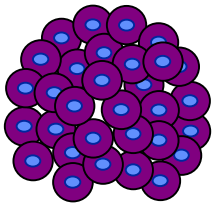
Cell Number in Tibial Bone Metastasis



ALDH^{high} subpopulation & cancer stem/progenitors

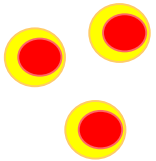


ALDEFLUOR® Assay



ALDH^{low}

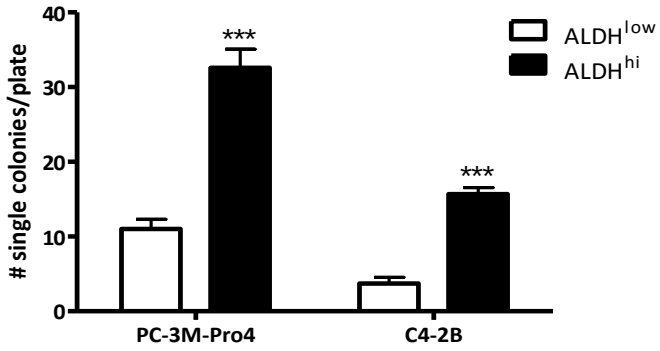
Differentiated
Epithelial Phenotype



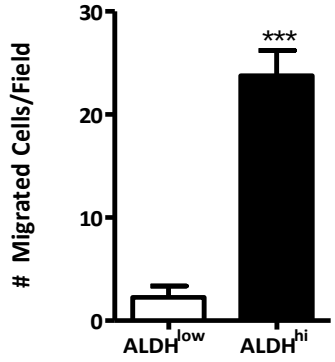
ALDH^{high}

Mesenchymal Phenotype
Stem/progenitor cells
($\alpha 2^{hi}$, CD44^{hi},αv^{hi},CK5^{+})

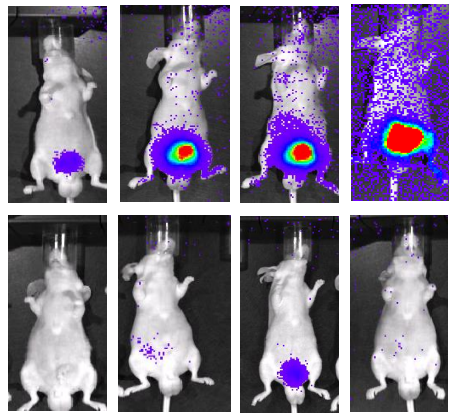
Clonogenicity



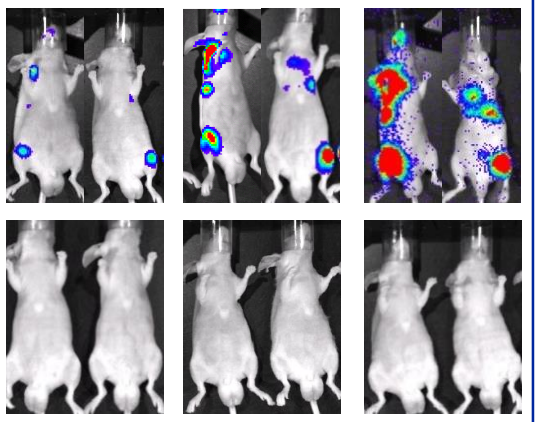
Migration



Tumorigenicity

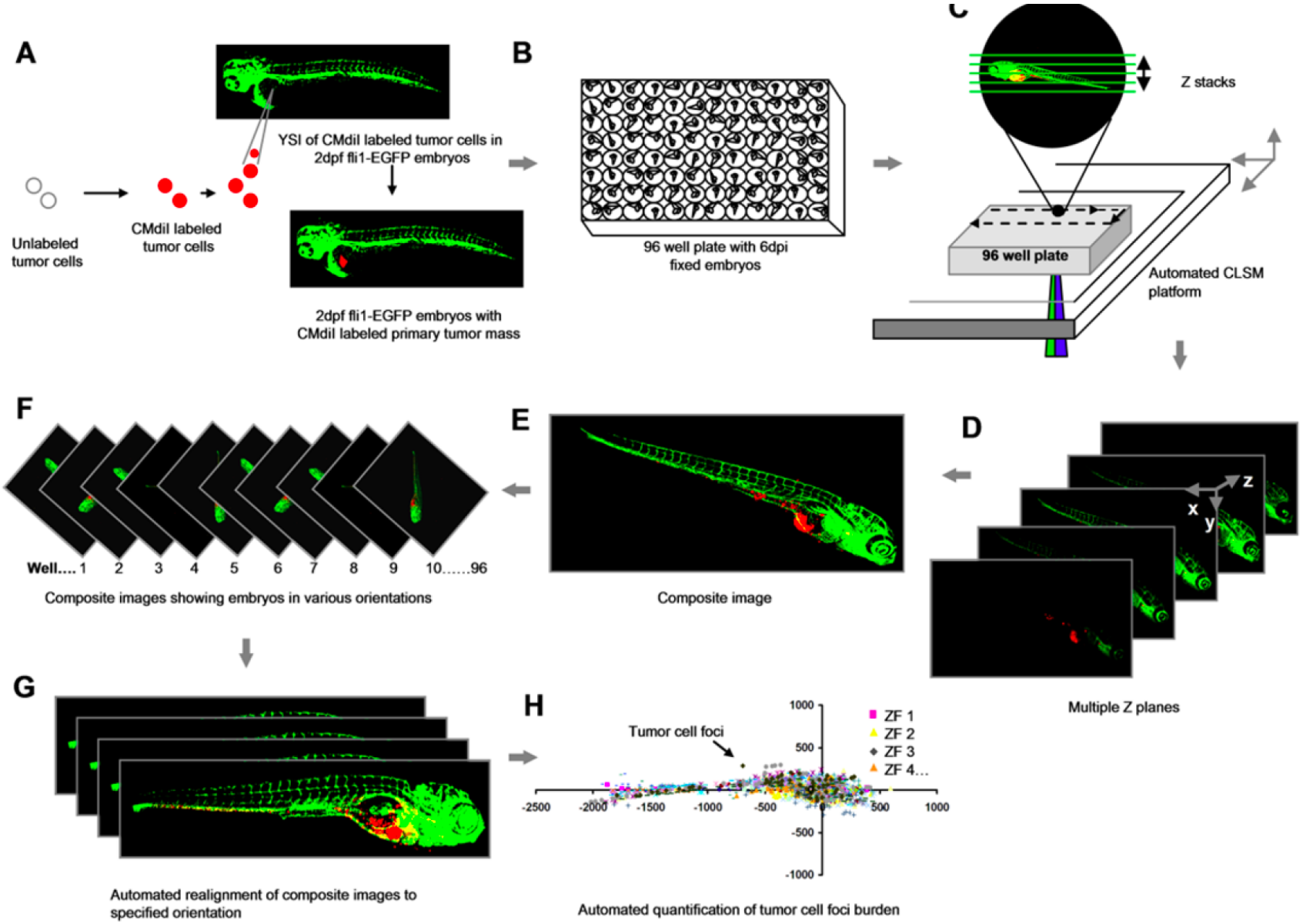


Bone Metastasis

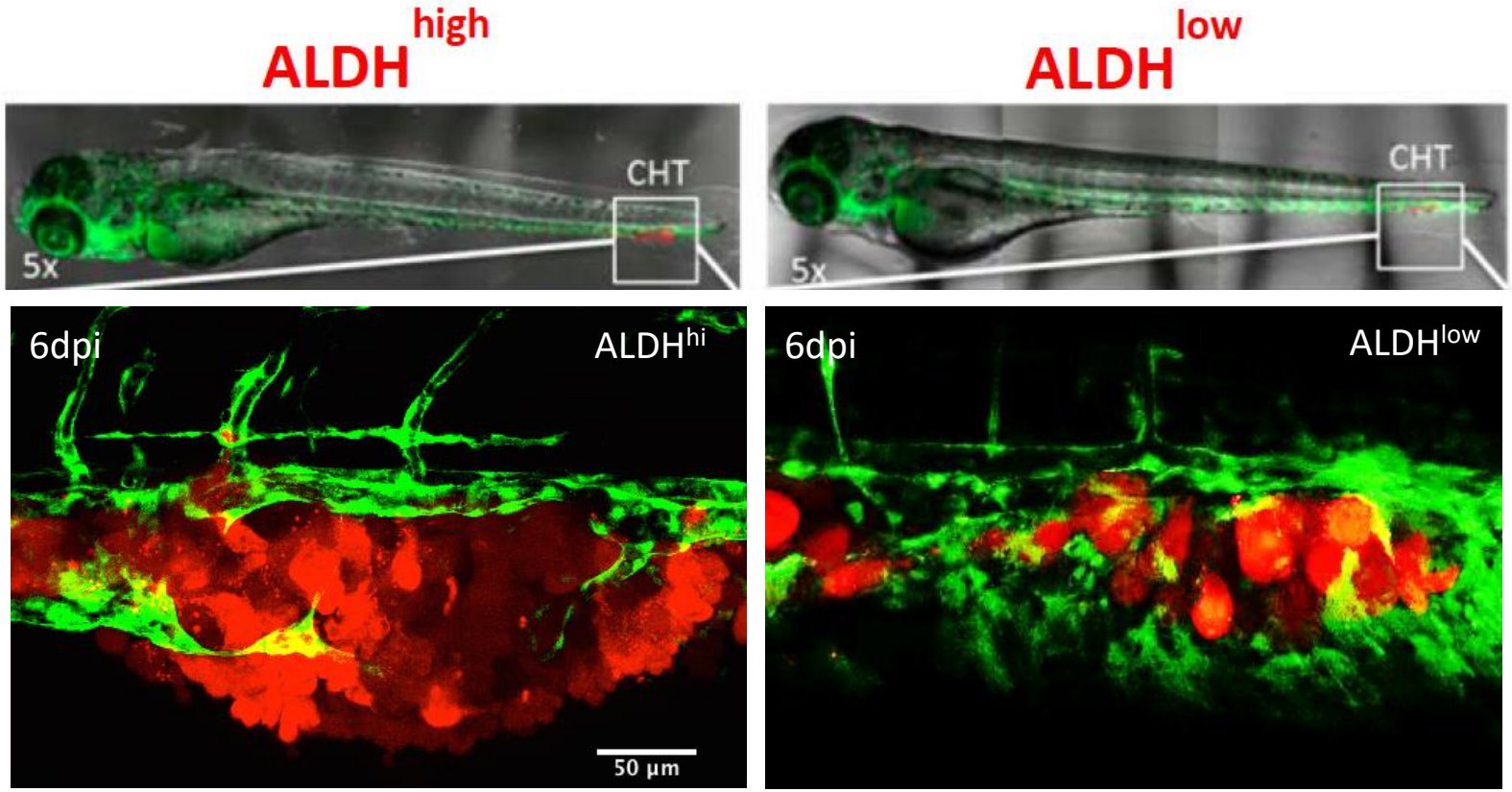


van den Hoogen et al.Cancer Res; (2010) , Clin Exp Metastasis 2011

Strategy for quantification of tumor dissemination in zebrafish

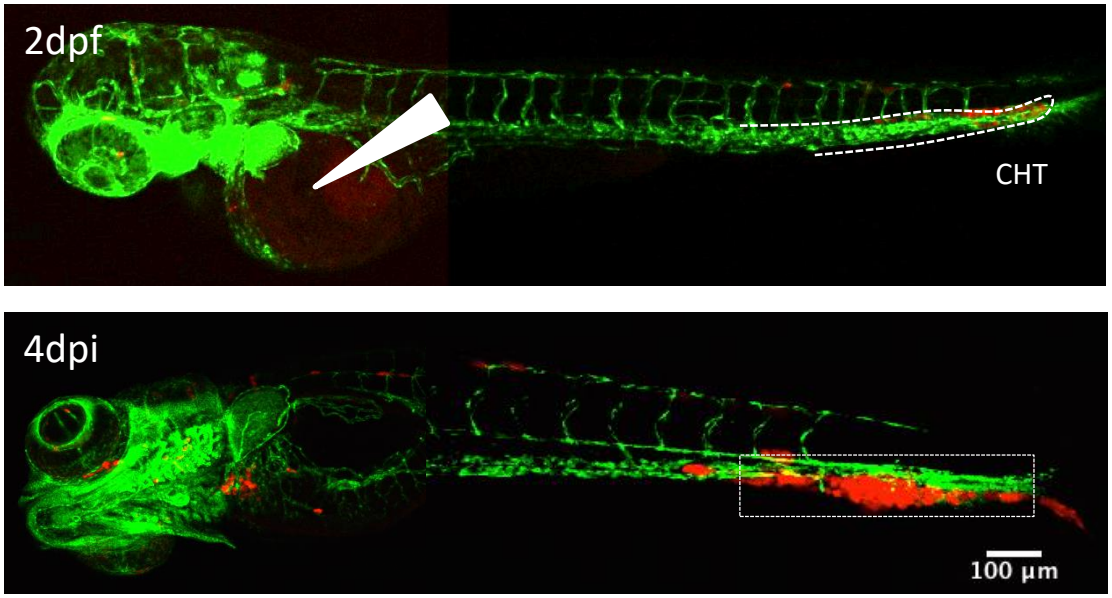


Prostate Cancer Stem-like Cells are identified as Metastasis-initiating Cells in the Zebrafish Model

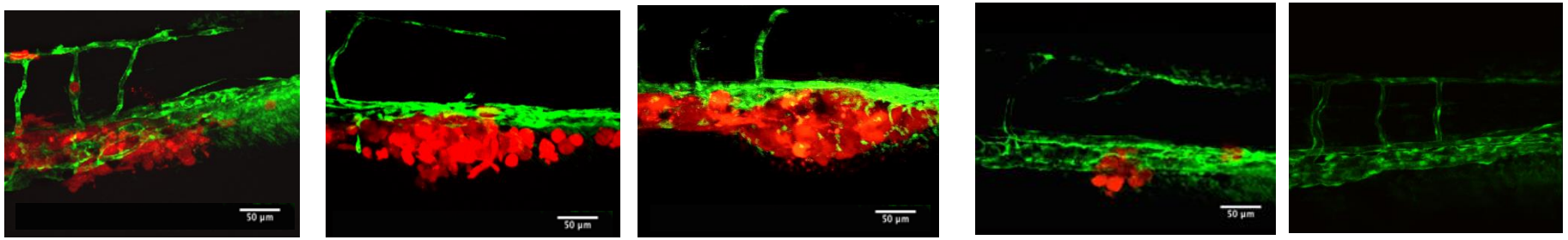


Zoni et al. Cancer Res. (2015)

human cancer xenograft model for studying metastatic onset



MDA-MB-231/B1 | UMUC-3 | PC-3M-Pro4 | Prostate cancer | Bladder cancer



invasive cancers — *less aggressive cancers*

Zoni E. et al. Cancer Res. 2015 Jun 1;75(11):2326-36.
Drabsch Y, et al. Breast Cancer Res. 2013 Nov 7;15(6):R106.
Mercatali L et al. Int J Mol Sci. 2016 Aug 22;17(8).

Development of Novel Therapy for Urological Malignancies

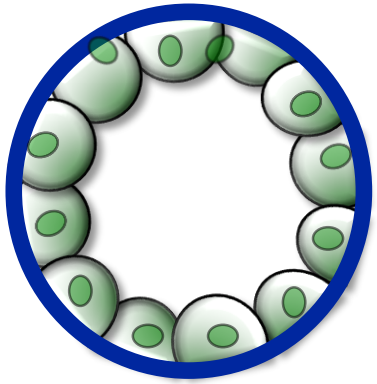
- Drug discovery & development
- Drug repositioning/repurposing
- Nanodrug delivery
- Targeting chemotherapy resistance
- Companion diagnostics

Oncological Epithelial Plasticity

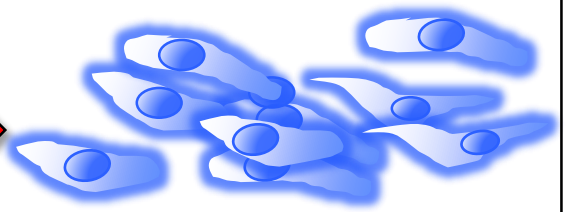
Sessile, Epithelial phenotype

Pharmacological compounds

Invasive, Mesenchymal Phenotype



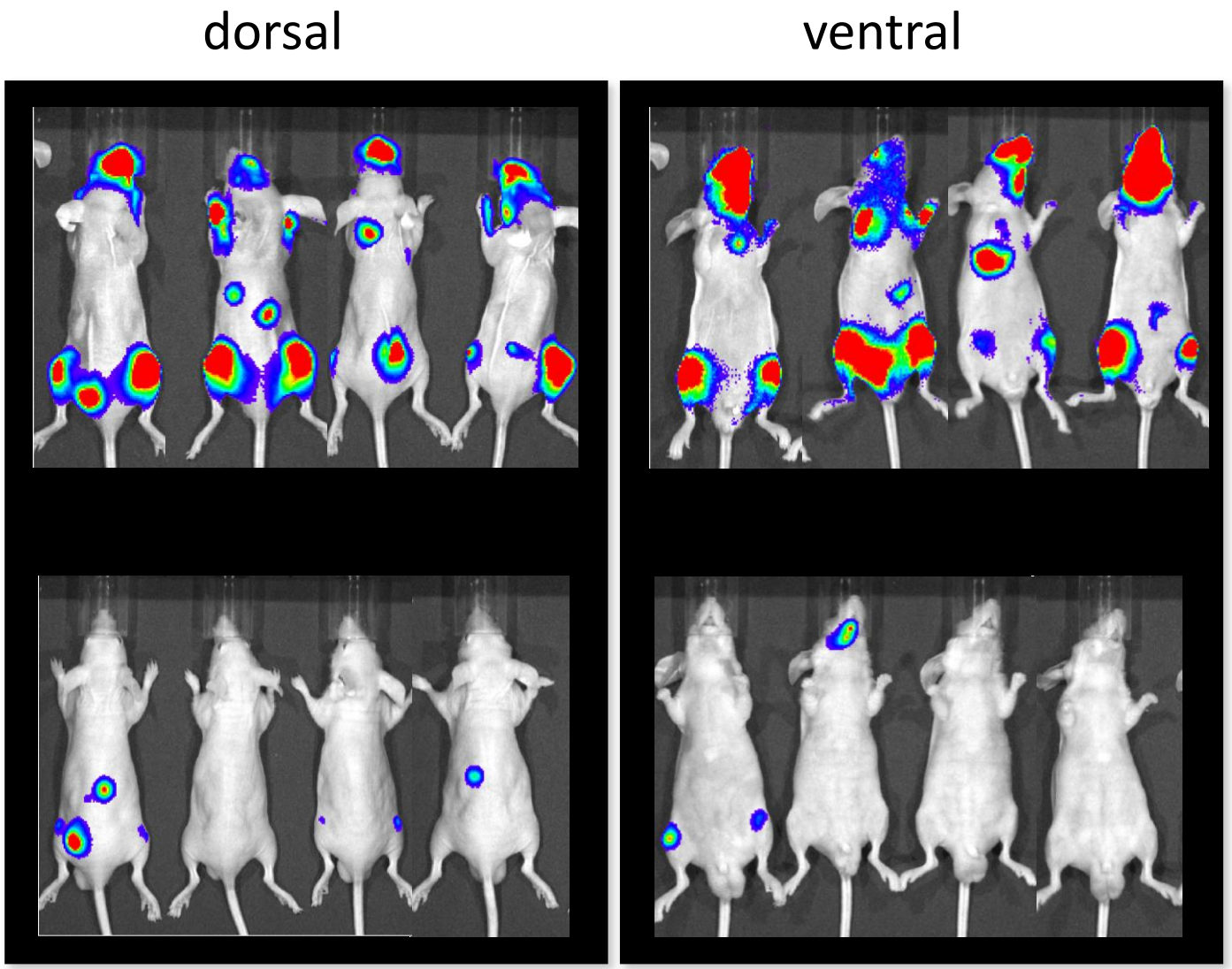
EMT



Therapy resistance
Stem/progenitor properties
Angiogenesis
Survival

OCD155 inhibits Bone Metastasis in Prostate Cancer

(PC-3M-Pro4 luciferase expressing, day 35)



Drug Repurposing/Repositioning

Safety profile and clinical properties are well studied and understood,

Considerably reduction of failure in later stages of clinical development

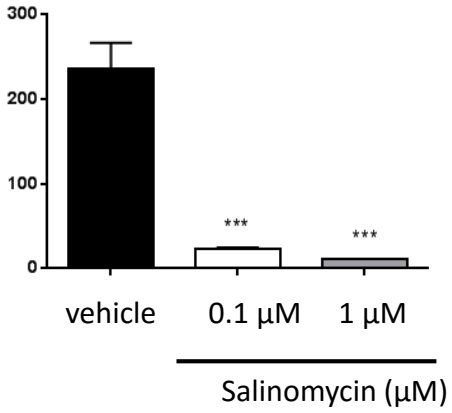
Antibiotic (Salinomycin)

Anti-depressant (Penfluoridol)

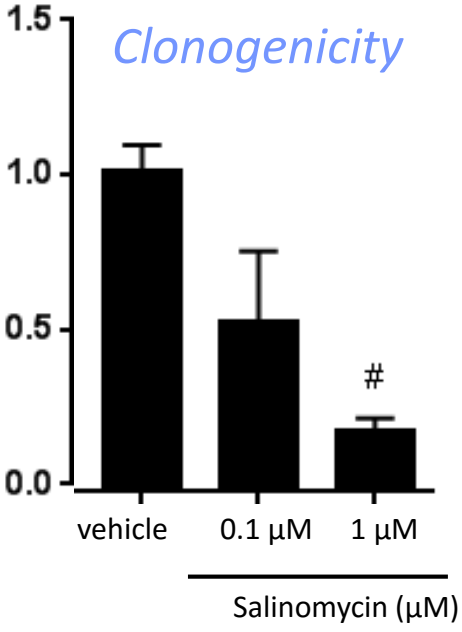
Anti-tumorigenic & anti-metastatic properties of salinomycin

In vitro

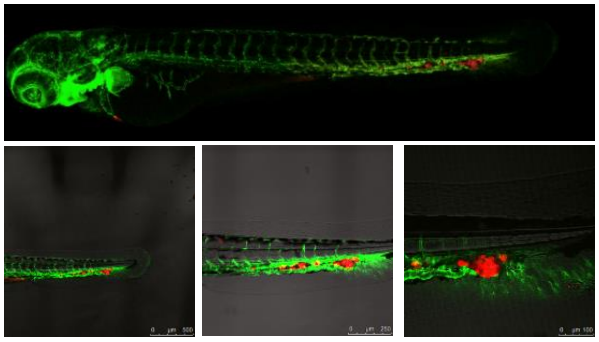
Migration

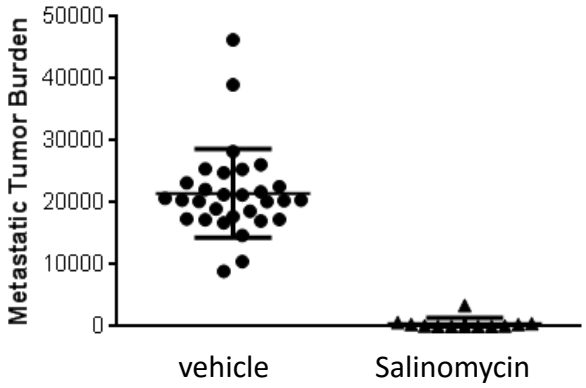


Clonogenicity

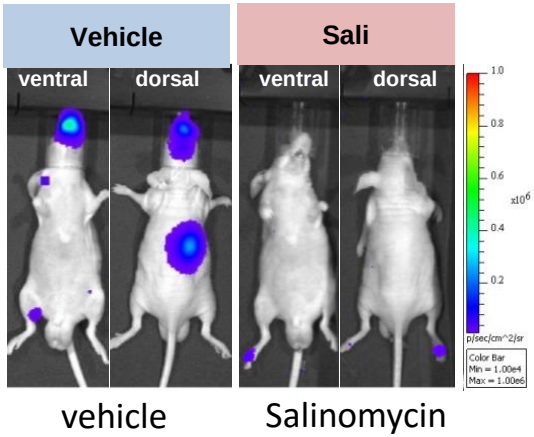


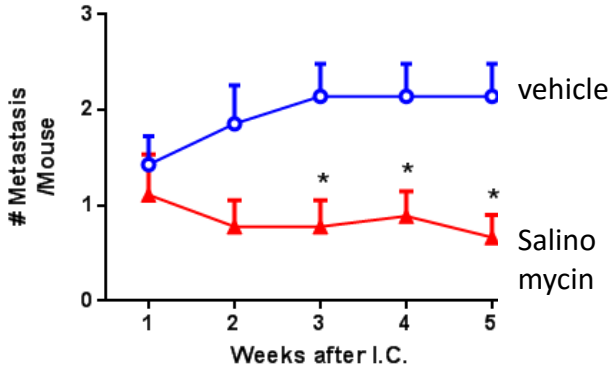
Zebrafish model





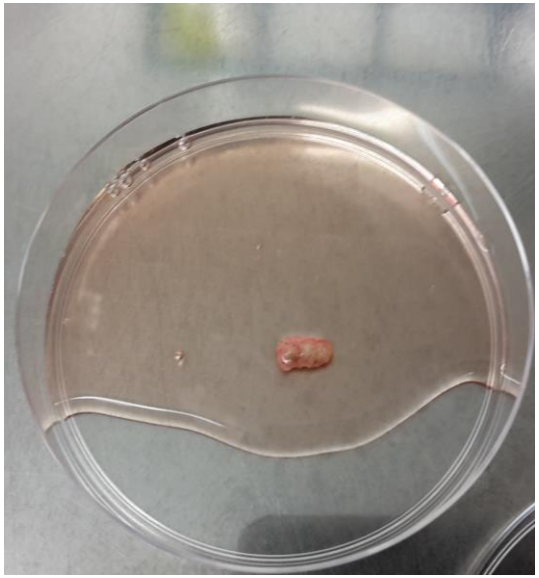
Preclinical mouse model

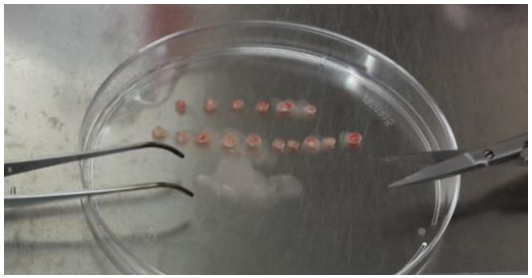


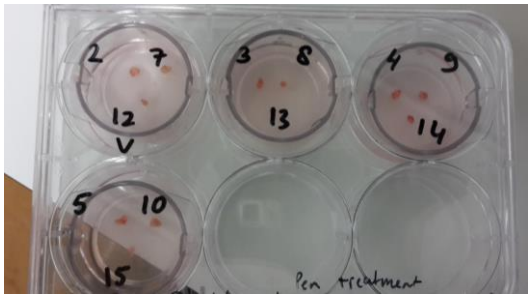


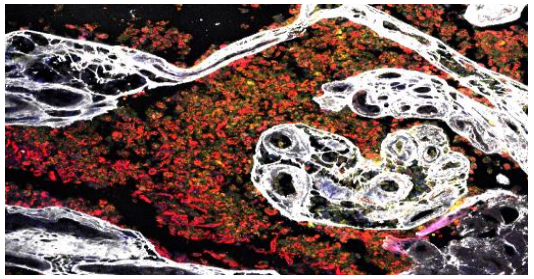
patient-tumor slices cultured *ex vivo*

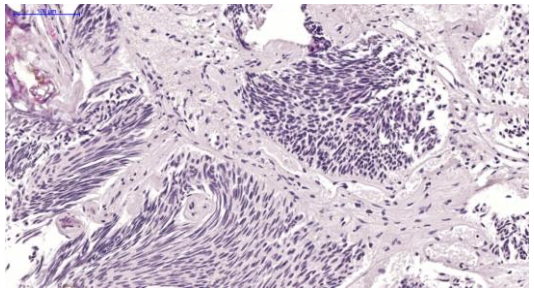
Patient-derived Tumor material → Treat tumor pieces with compound → Fix, embed, cut, stain & analyze,



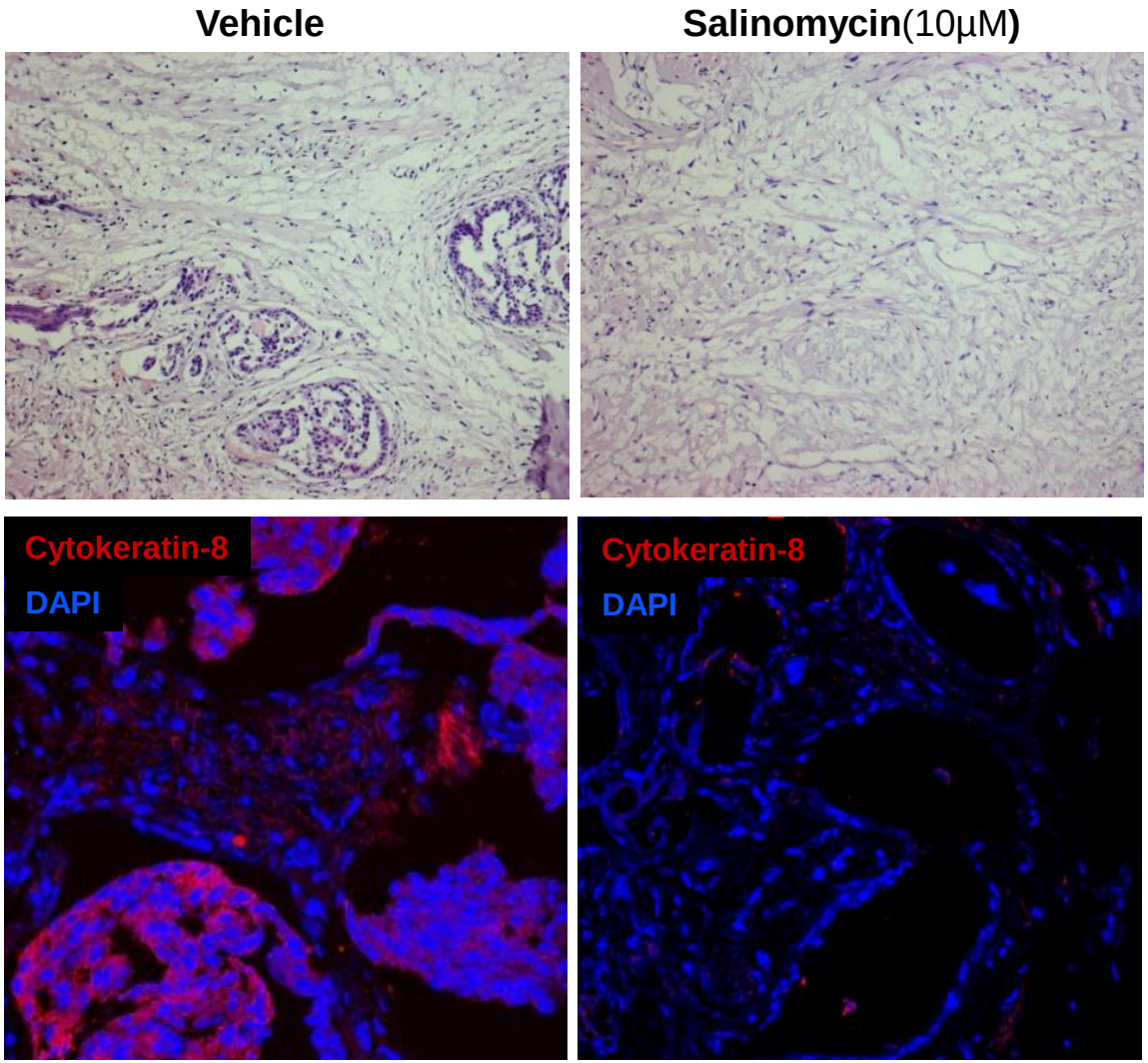




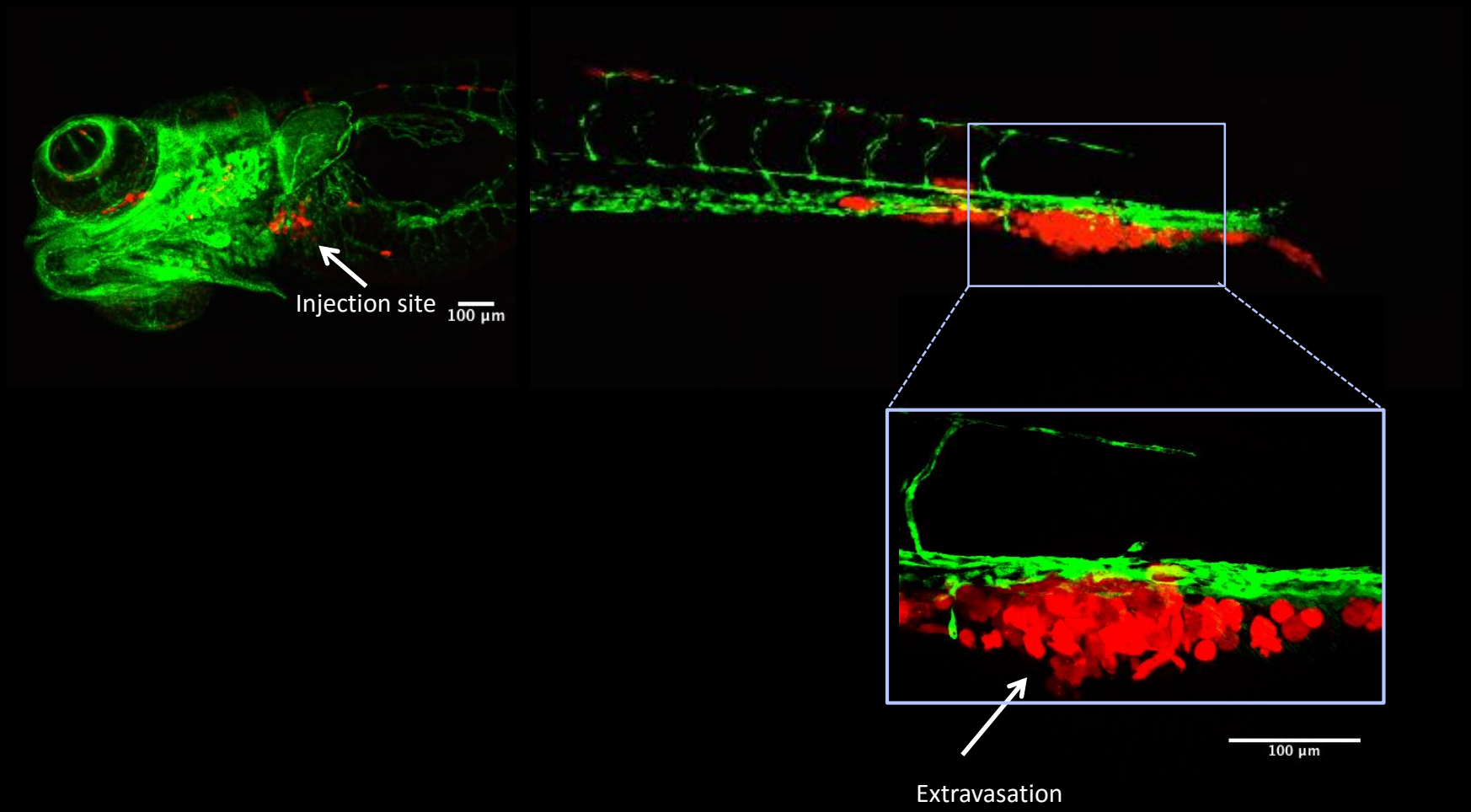




Patient-derived prostate cancer slices cultured ex vivo



Dissemination and metastasis of bladder cancer cells

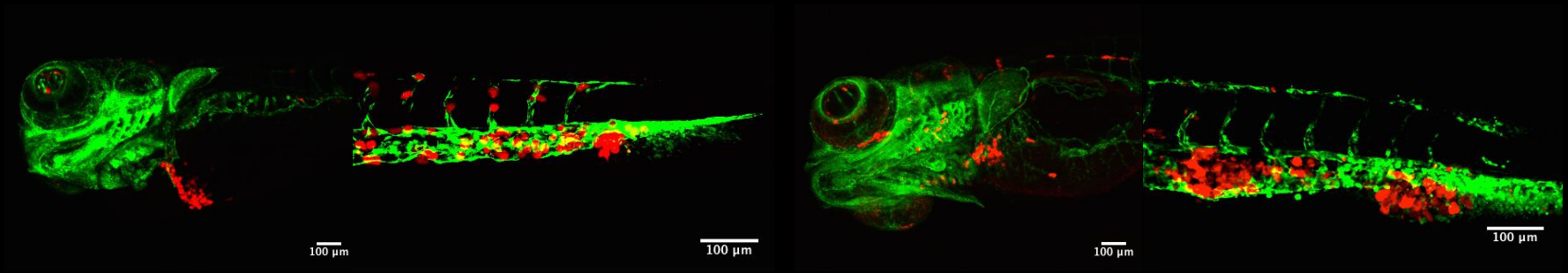


Treatment with **salinomycin** of bladder cancer cells

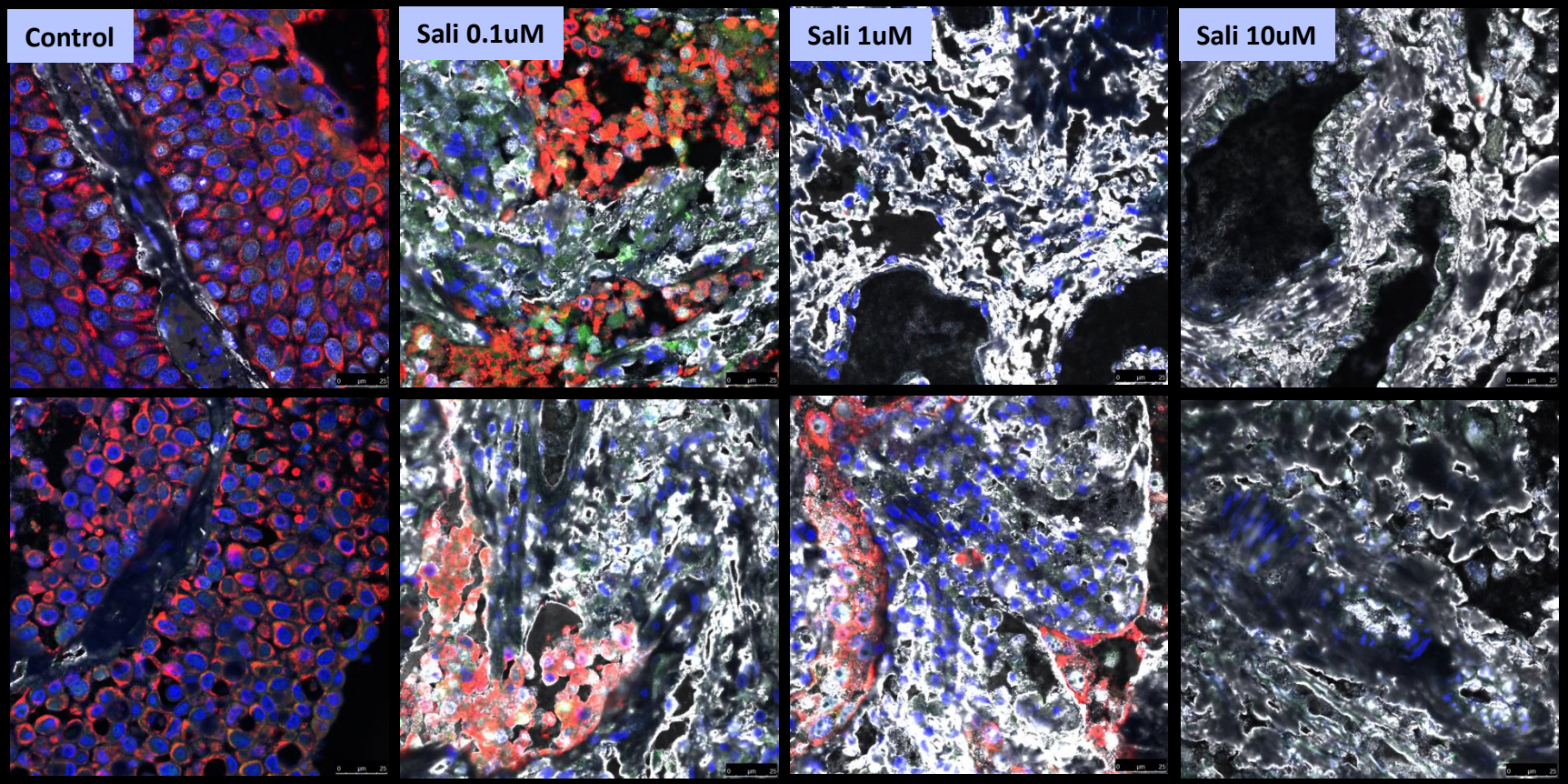
2 dpi

4 dpi

Vehicle



Salinomycin in *ex vivo* cultured tumor slices from urothelial carcinoma



Pancytokeratin
DAPI
PCNA
Collagen

Cationic Amphipilic Drugs

Review

Cancer incidence in patients with schizophrenia and their first-degree relatives – a meta-analysis

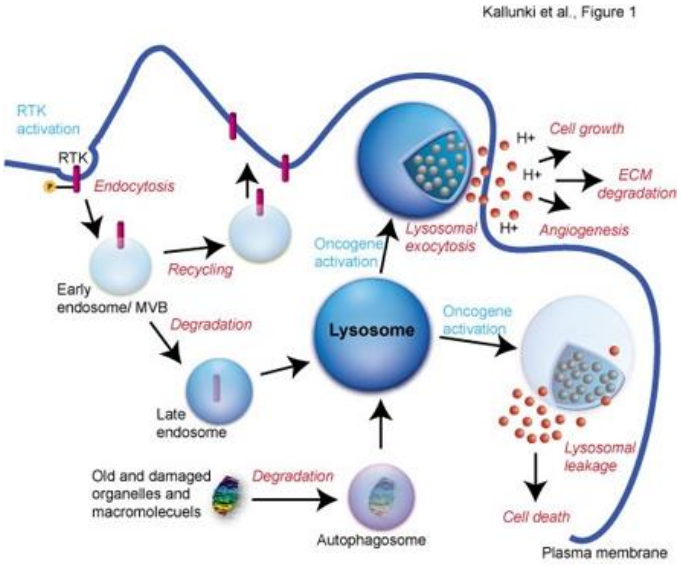
Catts VS, Catts SV, O'Toole BI, Frost ADJ. Cancer incidence in patients with schizophrenia and their first-degree relatives – a meta-analysis.

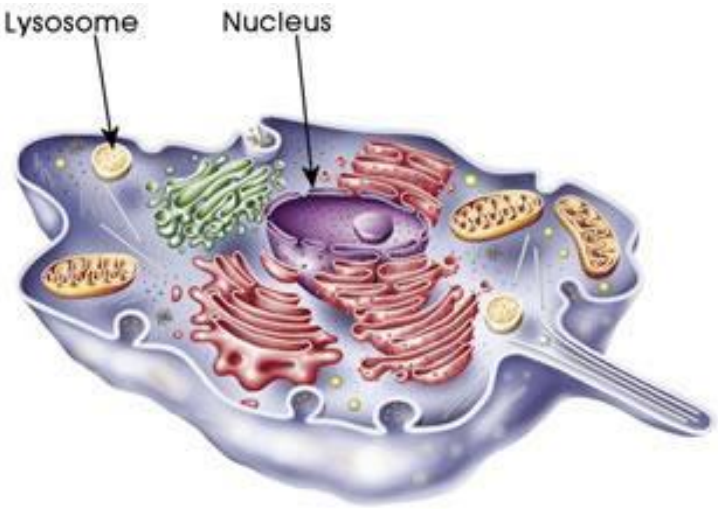
V. S. Catts[1], S. V. Catts[1,2], B. I. O'Toole[3], A. D. J. Frost[2]
[1]School of Medicine, The University of Queensland, St

Acta Psychiatr Scand. 2008 May;117(5):323-36.

- Lower incidence of cancer in schizophrenia patients
- Cationic Amphiphilic Drugs (CADs) often used as anti-depressants/psychotics

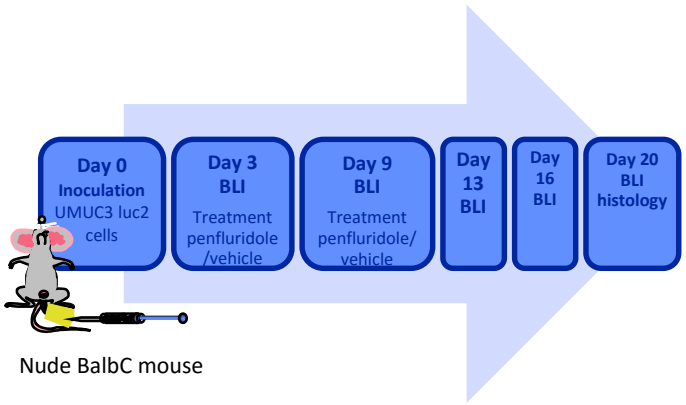
  Known to induce lysosomal cell-death



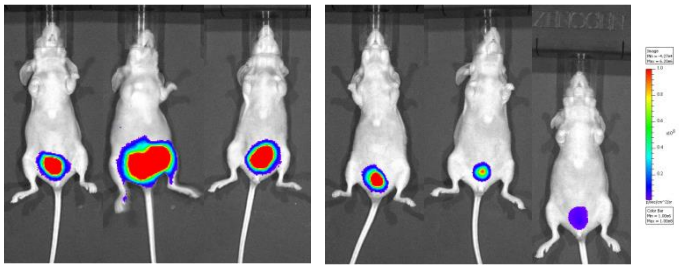


Catts VS et al 2008, Mortensen PB 1989, Dalton et al 2006, Petersen et al. 2013

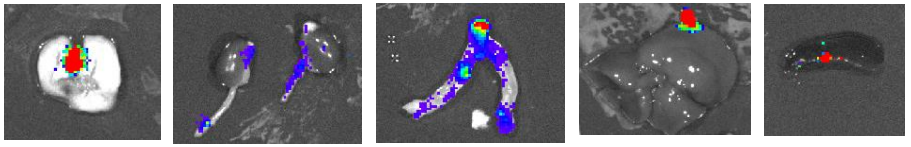
Bladder cancer orthotopic *in vivo* xenograft model



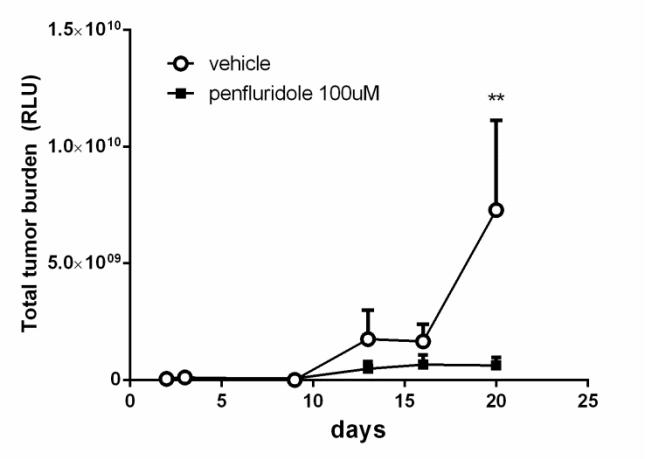
Nude BalbC mouse

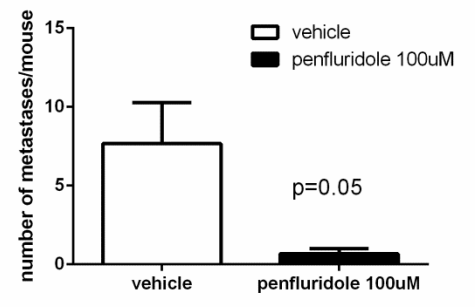


vehicle penfluridole 100µM



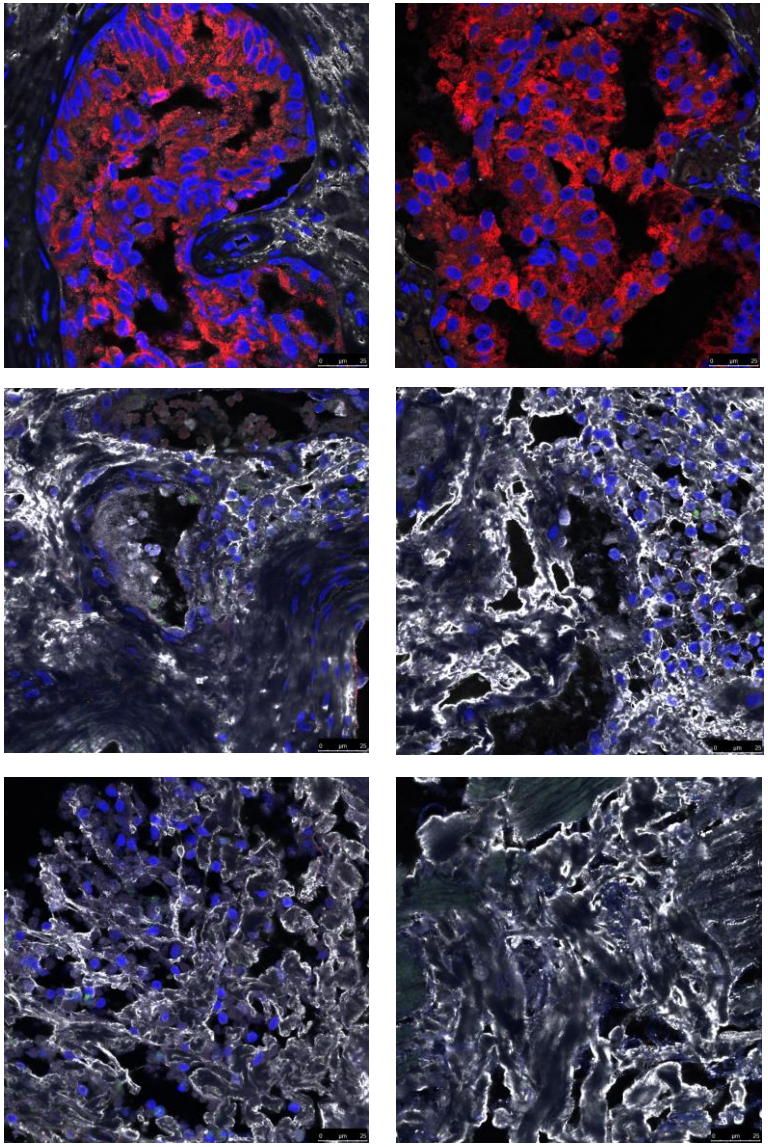
Lungs Kidney and ureter Uterus and ovaries Liver Spleen





High grade papillary urothelial cell carcinoma with invasion in stroma. (Non muscle invasive)

Day 3 Day 7



vehicle

10uM penfluridol

50uM penfluridol

Pancytokeratin
DAPI
Collagen

Sunmary & Conclusions

- Each disease model has specific intrinsic limitations

  lack of functioning immune system (PDX, xenografting)
  lack of cellular and extracellular stroma (cell cultures, organoids)
  species differences (mice, zebrafish..)
  etc.

- ‘weaknesses’ can be exploited for the study of mechanisms of tumor progression & the identification of novel therapeutic targets !

- Clinical validation of preclinical findings in human tissues facilitates clinical translation

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dept. Urology

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