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In vivo models as a platform for the discovery of new therapies in exocrine pancreatic neoplasms

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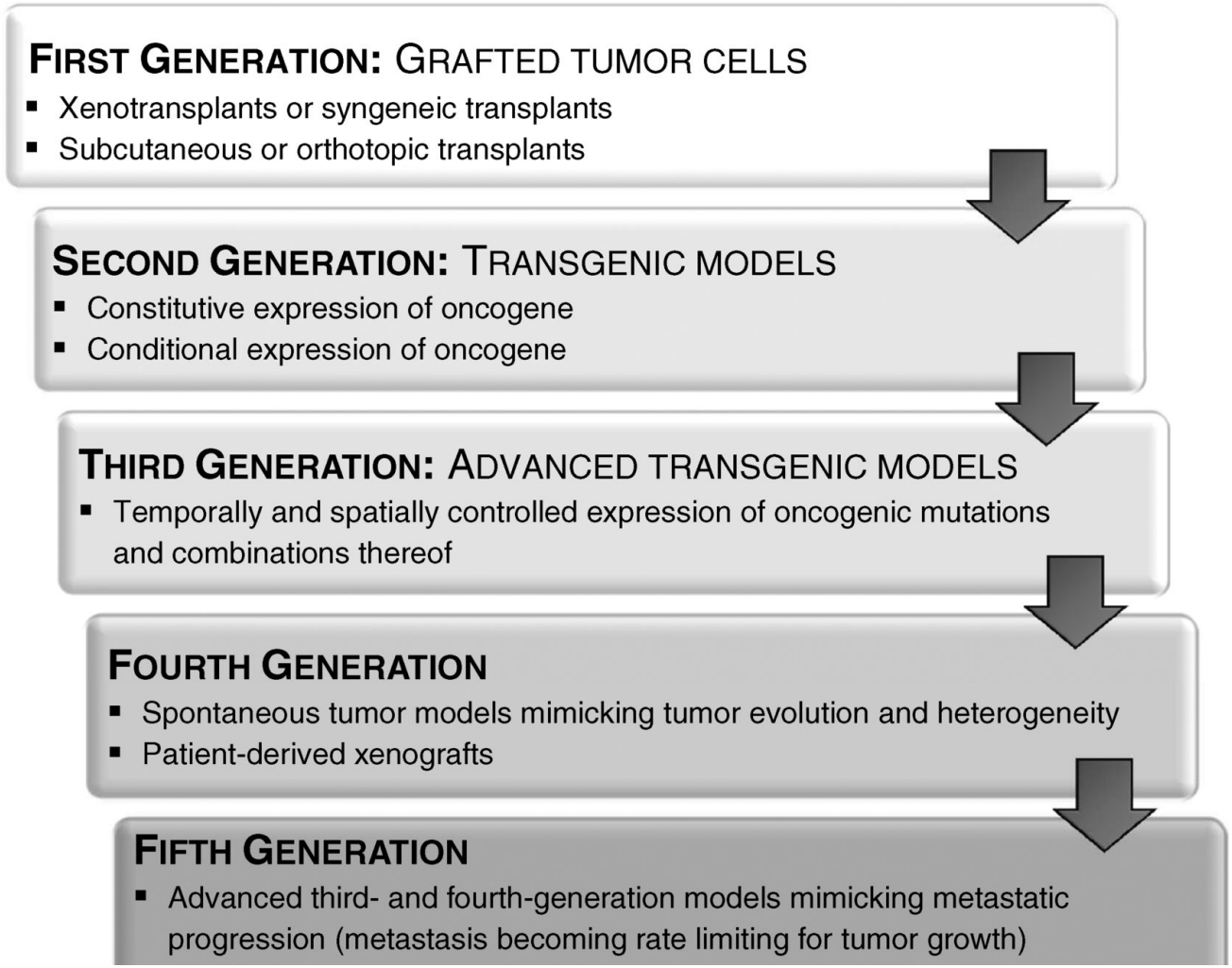
IN SUPREMÆ DIGNITATIS 1343

Why we use mice for our cancer models?

- Small size, easy to handle and take care of
- Easily available from commercials and far cheaper than other mammal animals (many mice can be treated at the same time)
- Genetically best characterized of all mammals
- Accommodation of nude mice to human tumor models
- Relatively rapid tumor growth in mice makes them useful in cancer research and drug screening

Evolution of mouse cancer models



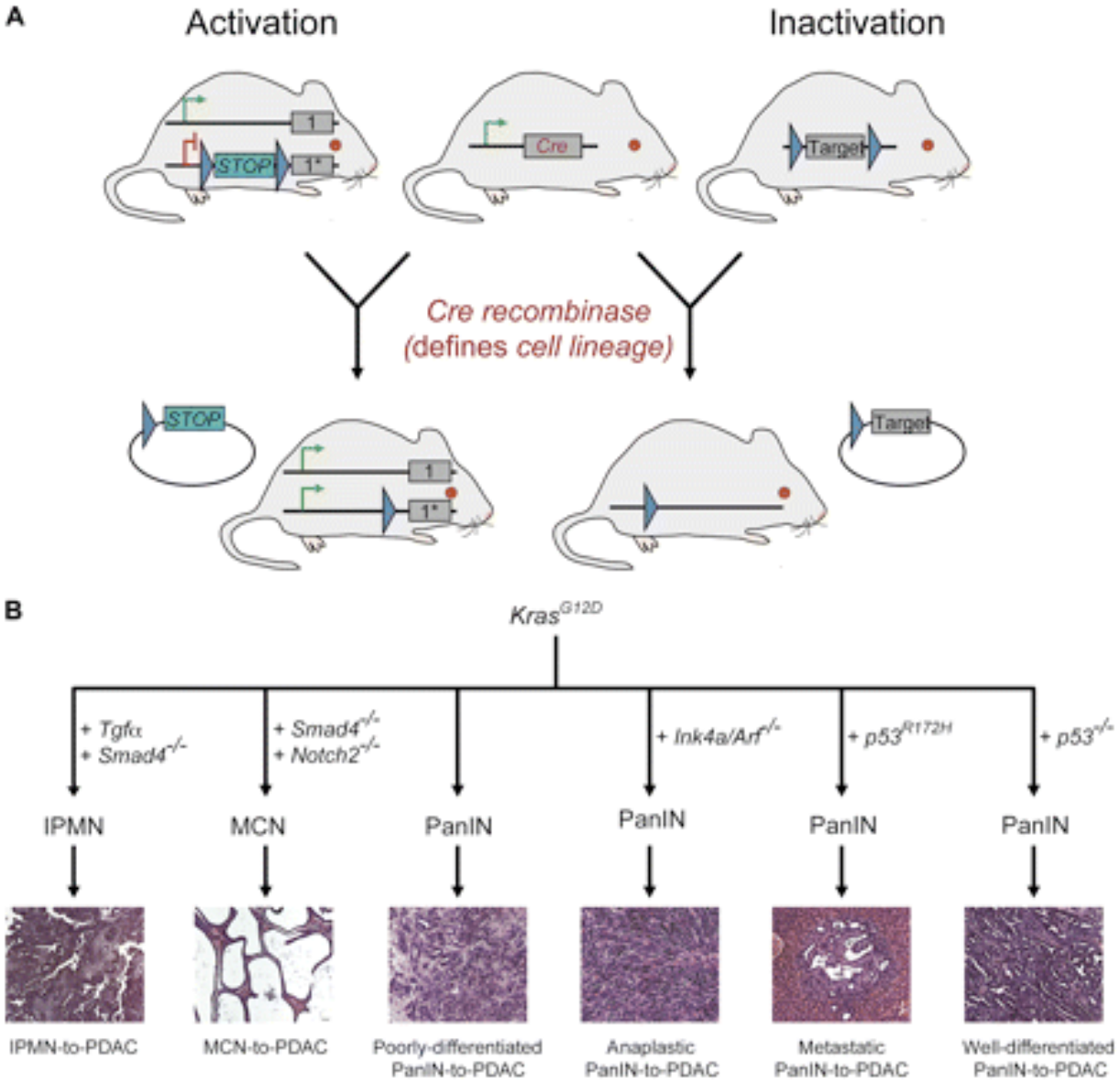
Böck B C et al. Cancer Res 2014;74:4671-4675

GEM Mice in pancreatic cancer

Mutant KRAS-driven models:

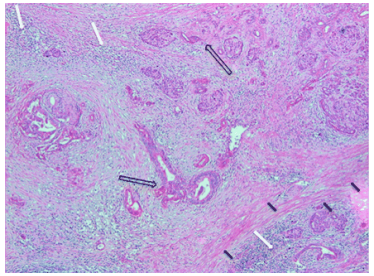
(A) Cre/loxP-mediated conditional activation or inactivation of genes can be used for targeting oncogenes and tumour suppressors in the pancreas

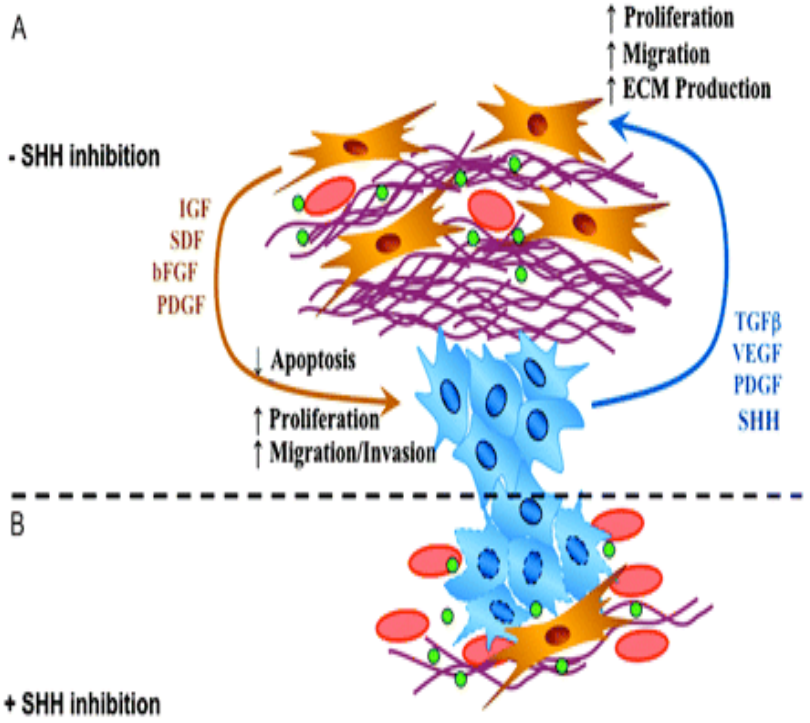
(B) GEMMs develop tumours that resemble different types of human preneoplastic lesions and PDAC with varying latency depending on the induced genetic alterations



The advantages of pancreatic GEMMs

- These models maintain an intact immune system and develop tumors histologically similar to human PDACs, including a dense desmoplastic stroma reaction





Olive et al. (Science 2009) showed that PDAC GEMMs

1) are poorly perfused and vascularised

2) significantly less sensitive to gemcitabine treatment compared to the transplanted tumors (but sensitive to Hh inhibitor)

… but these models failed to predict response to IPI-92 in clinical trials (Rhim et al. 2014)

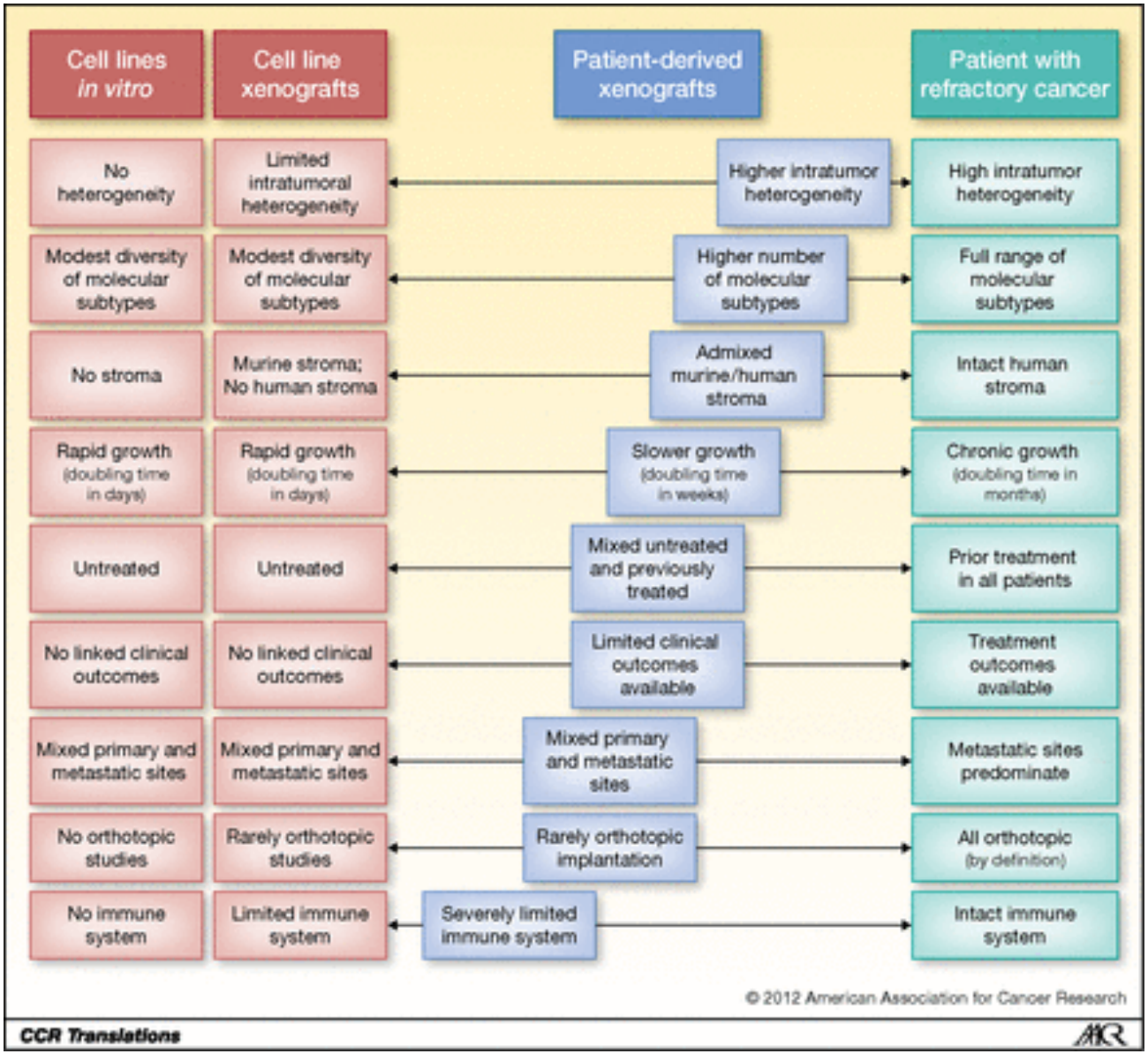
… and their drawbacks

- **Not all tissue specific promoters are specific** (i.e. since the commonly used transcription factor PDX1 is expressed in the developing foregut (stomach and duodenum) as well as in the epidermis, tumor development may occur in extrapancreatic organs, potentially affecting pancreatic carcinogenesis and responses to therapeutic approaches, as well as the life span of mice)

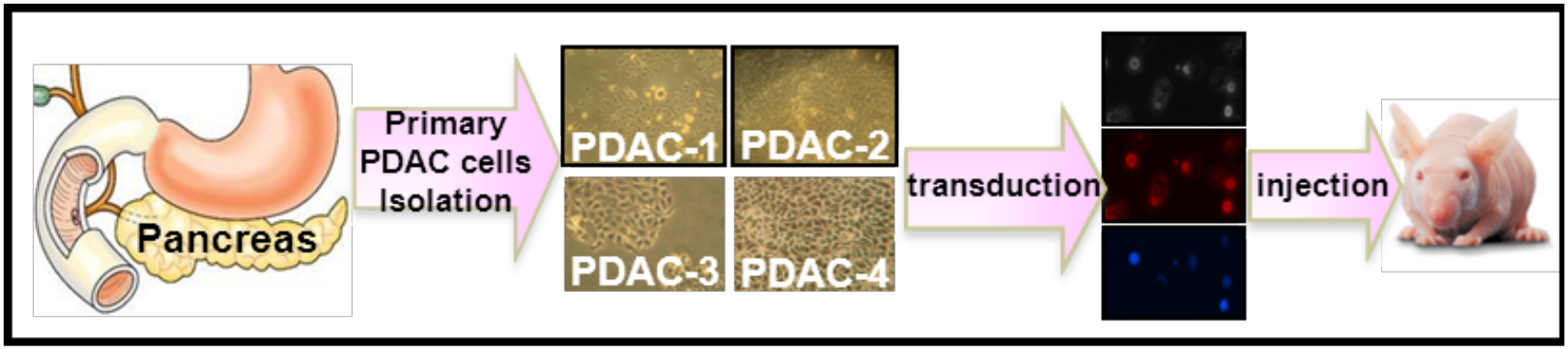
- Mutant KrasG12D is activated **during mice embryogenesis**, which probably does not reflect the acquisition of sporadic mutations in adult cells in humans

- Their dependence on a **few critical genetic lesions**, such as KRAS and P53, might not reflect the genetic diversity that exemplifies human PDAC

Avatar mice or PDX

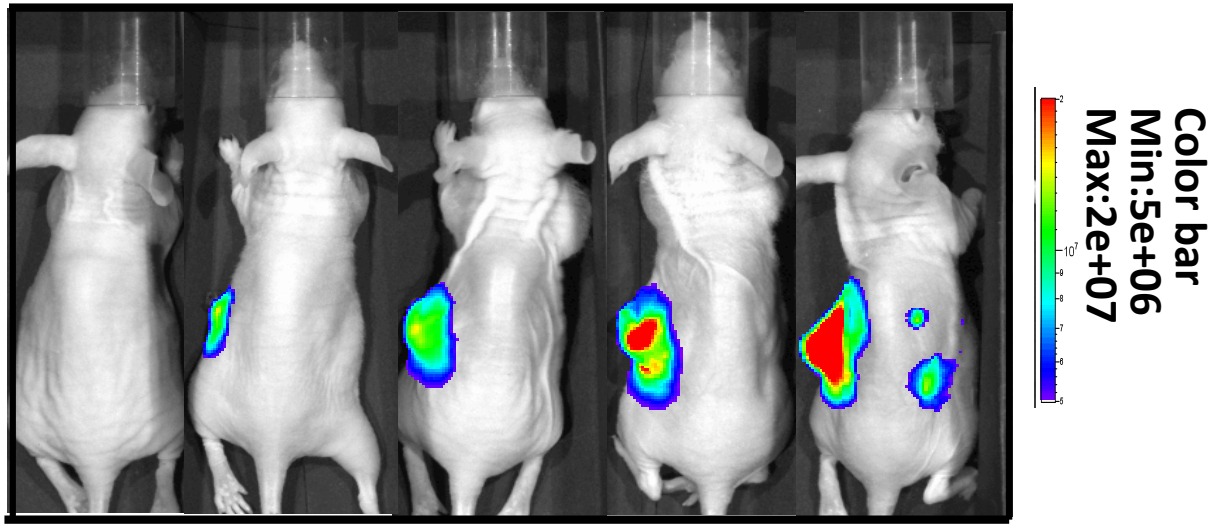


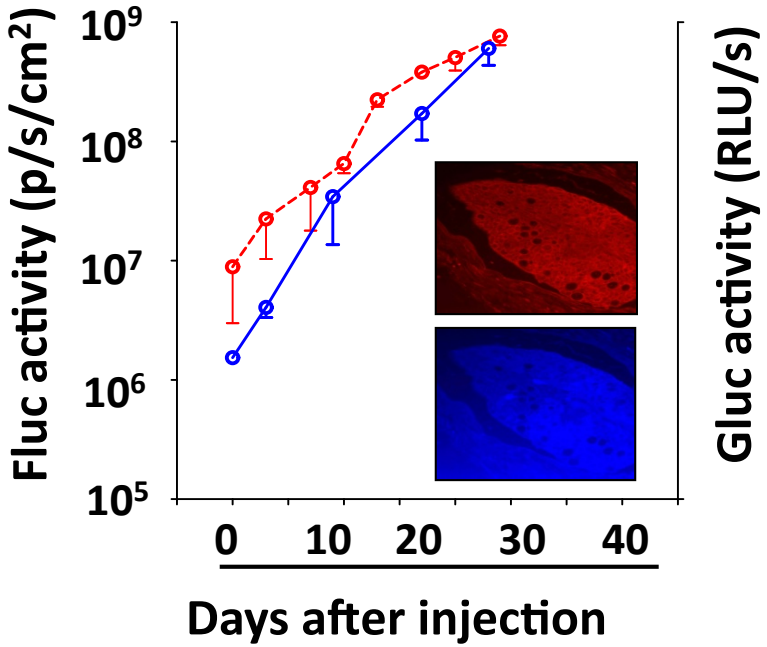
Our models:
new orthotopic bioluminescent models, with primary cell cultures



Avan et al, Cancer Res 2013

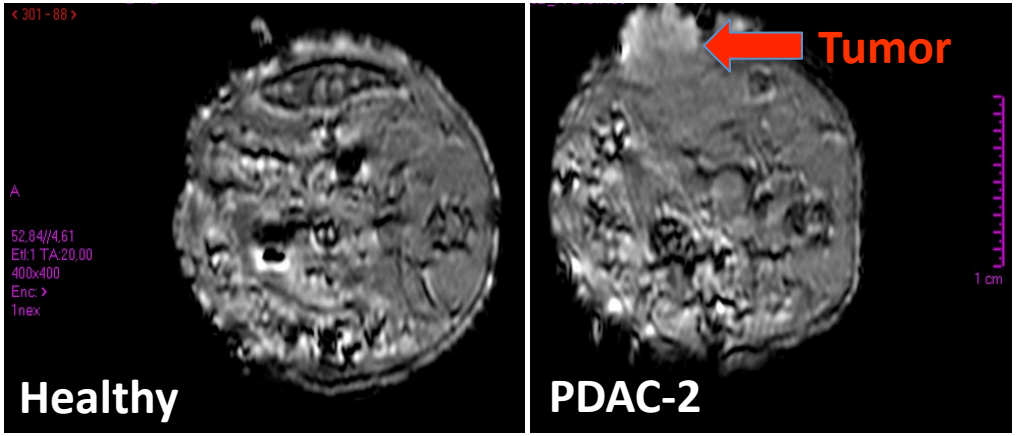
Bioluminescence



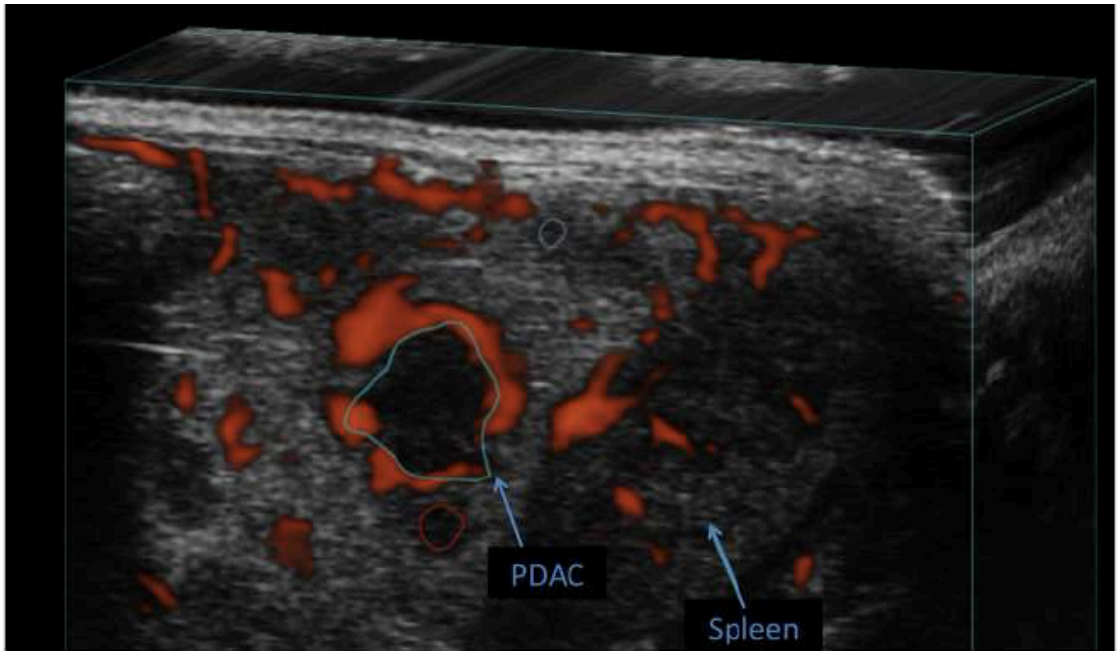


Other imaging

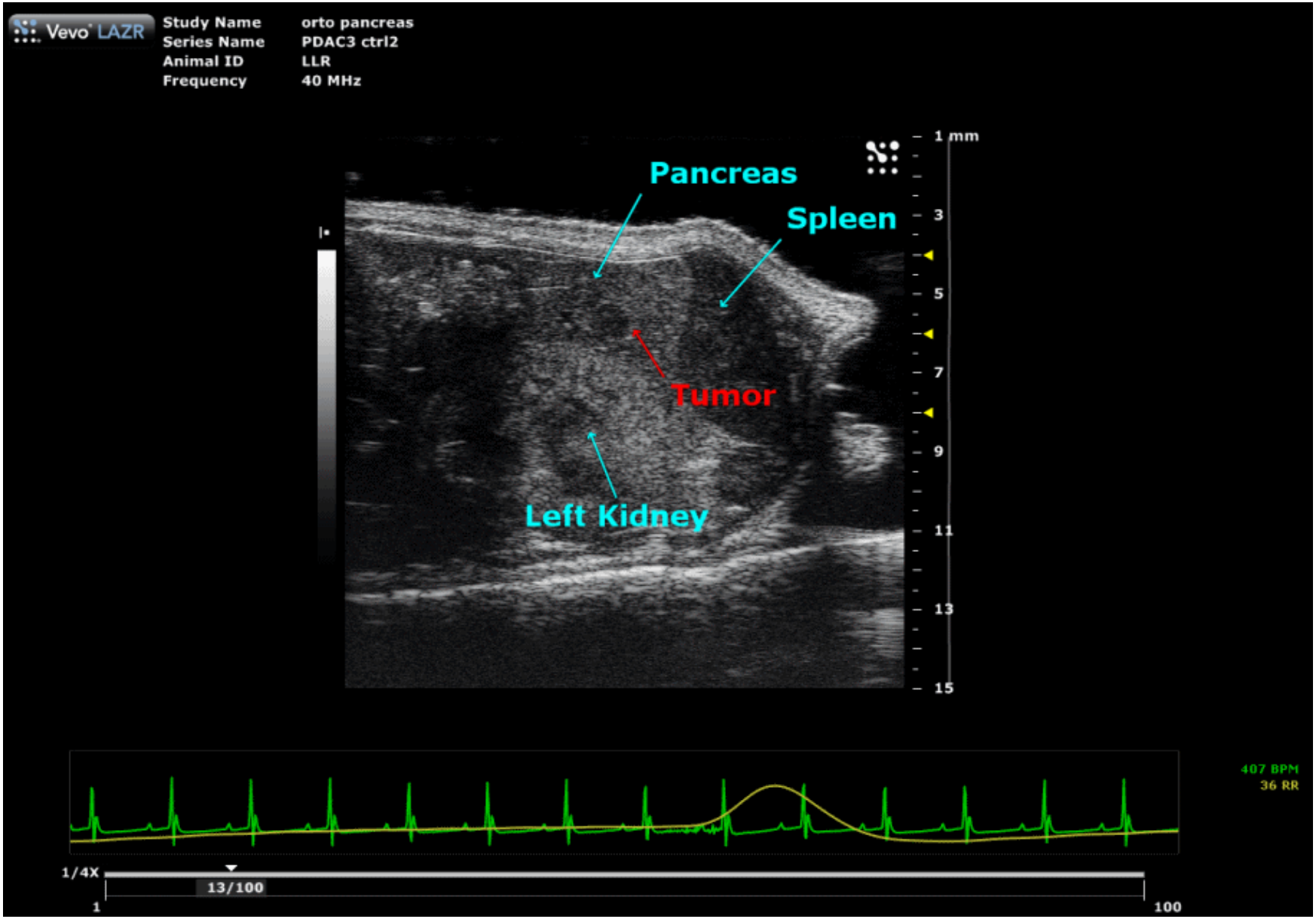
MRI



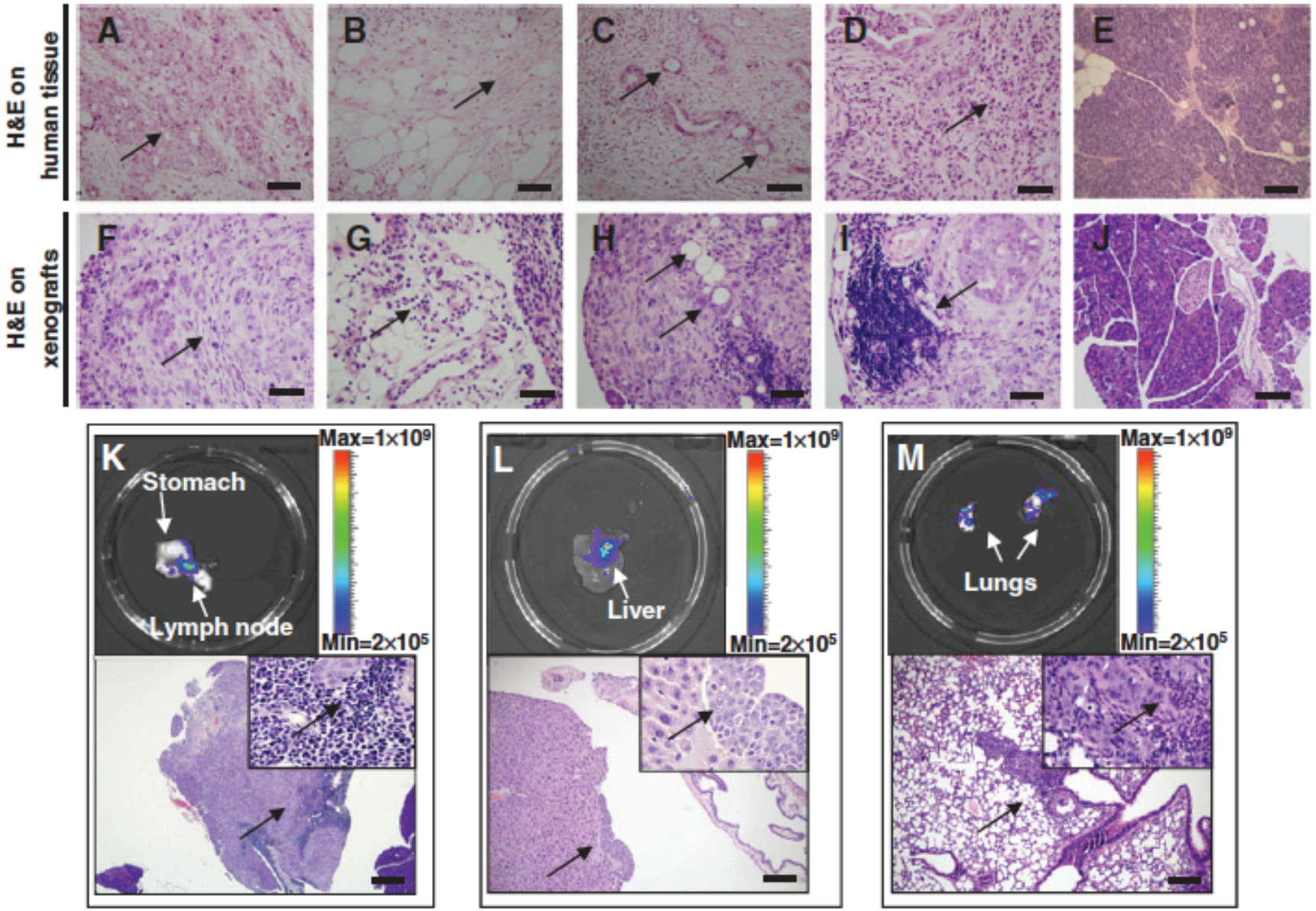
Echo-doppler



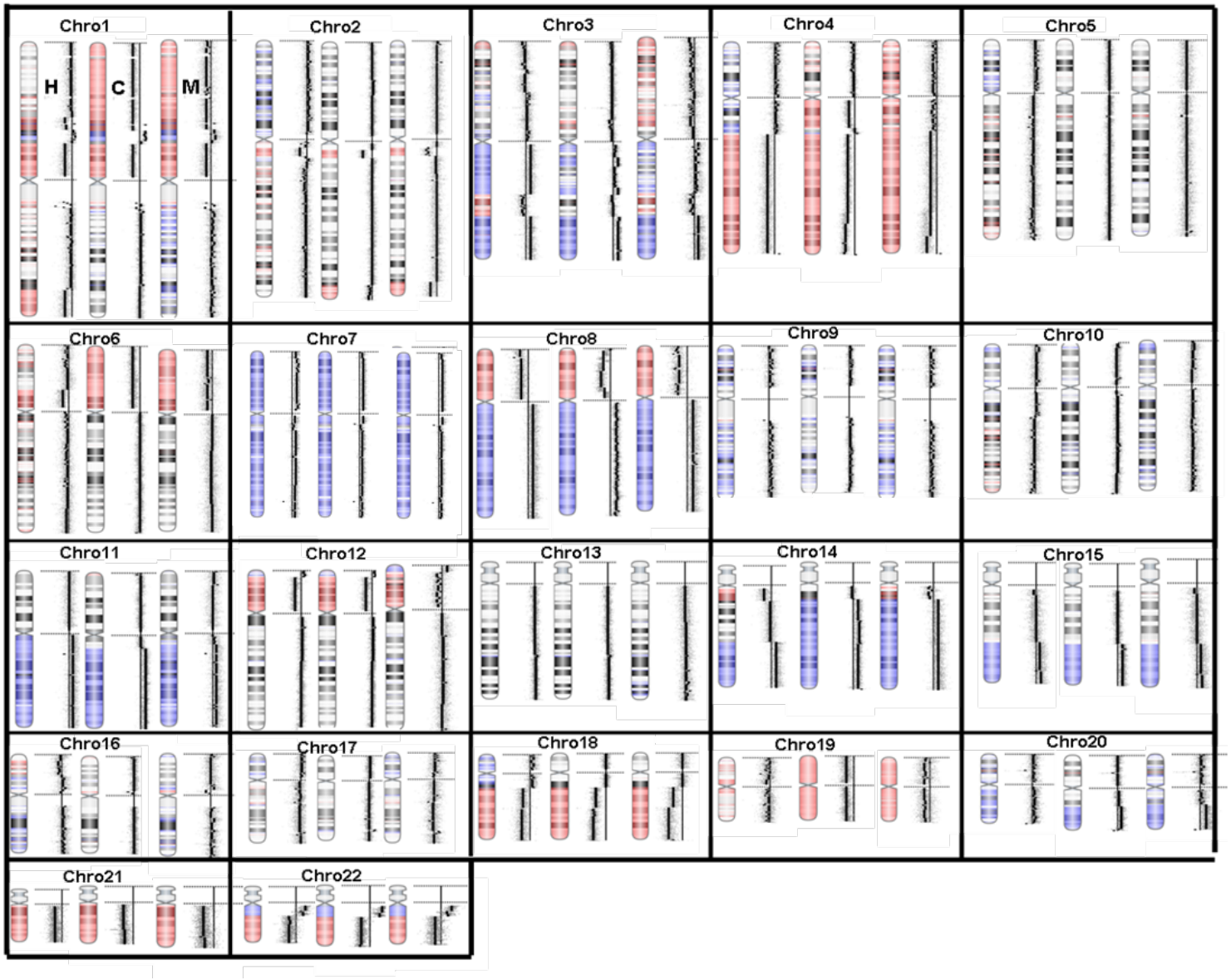
High-frequency ultrasound



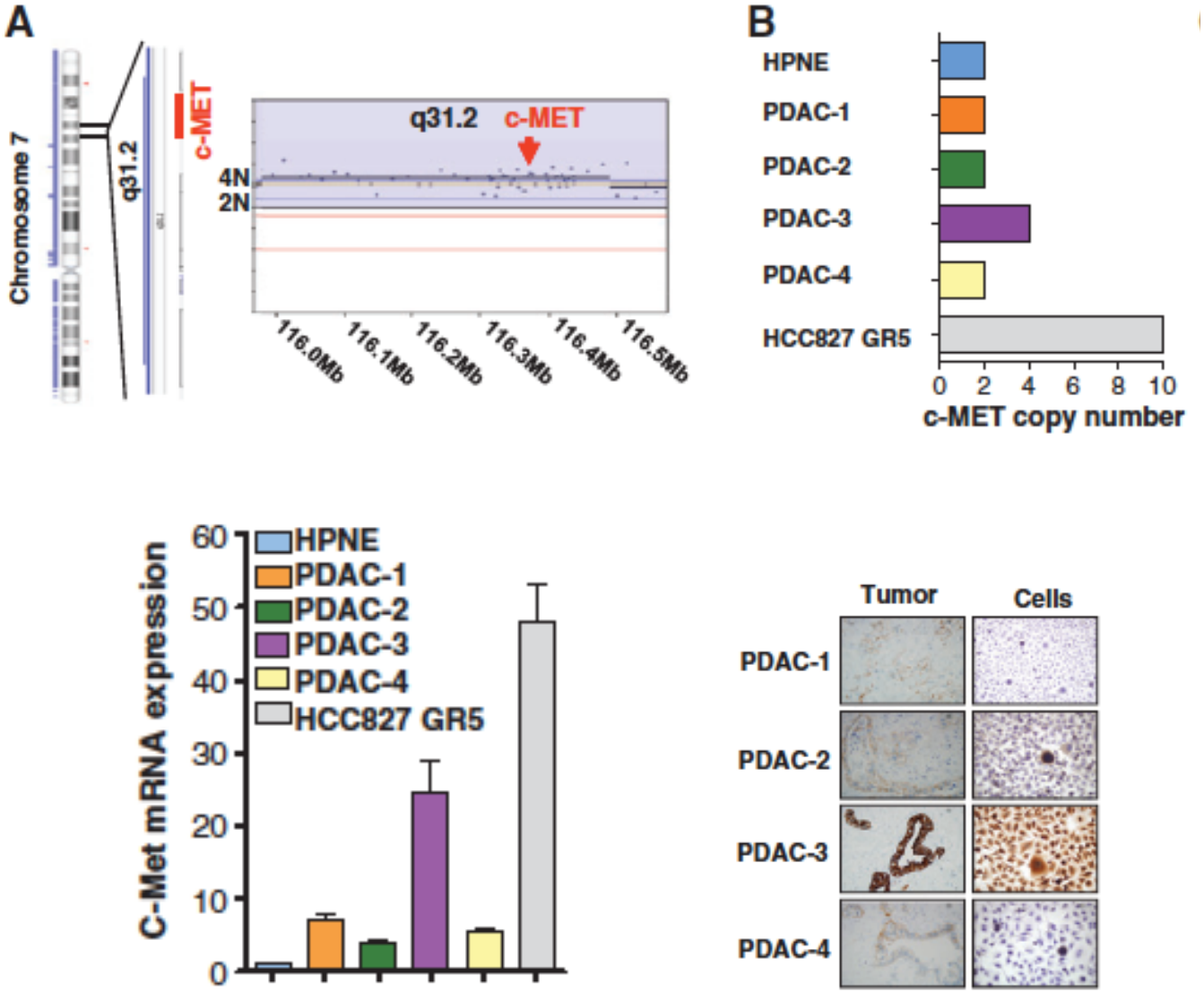
Histological features and metastasis



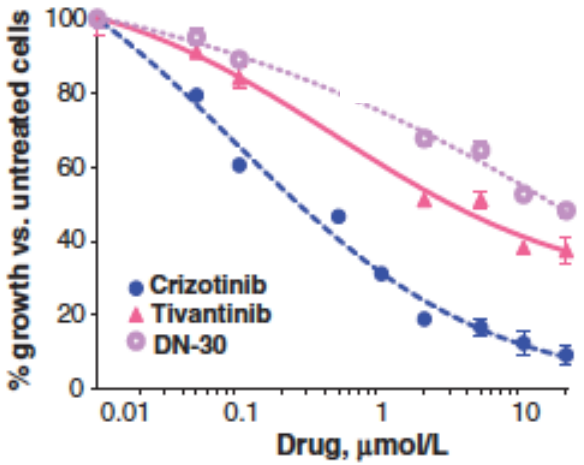
Genetics of the PDAC3 model

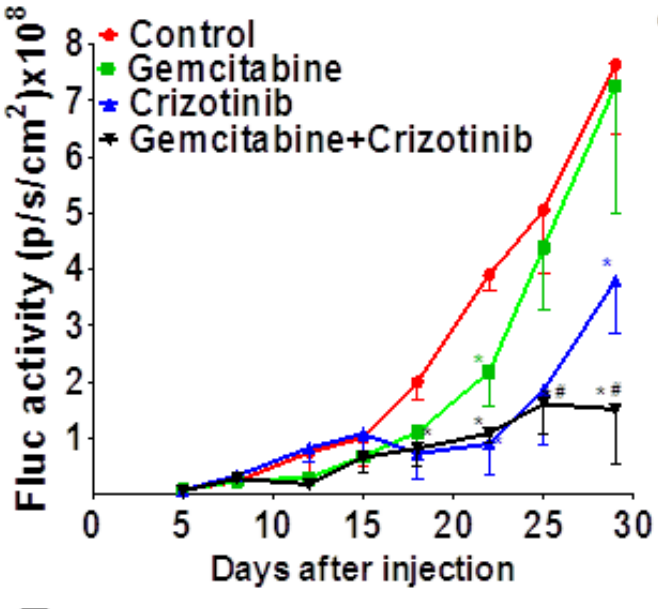


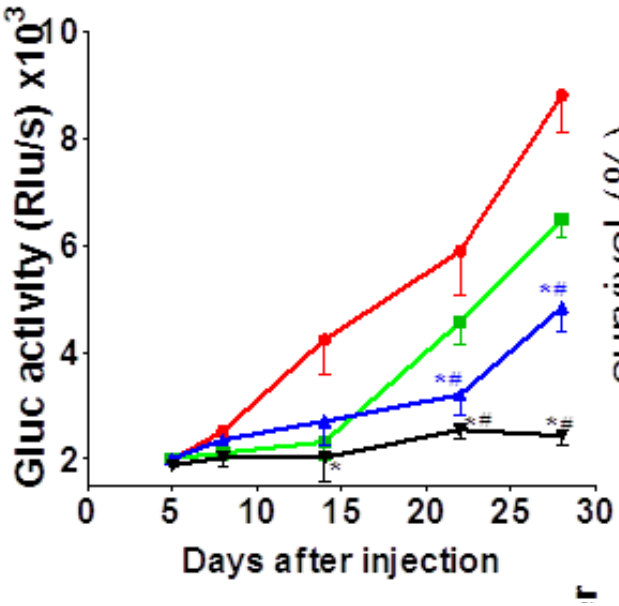
c-Met in the PDAC-3 model

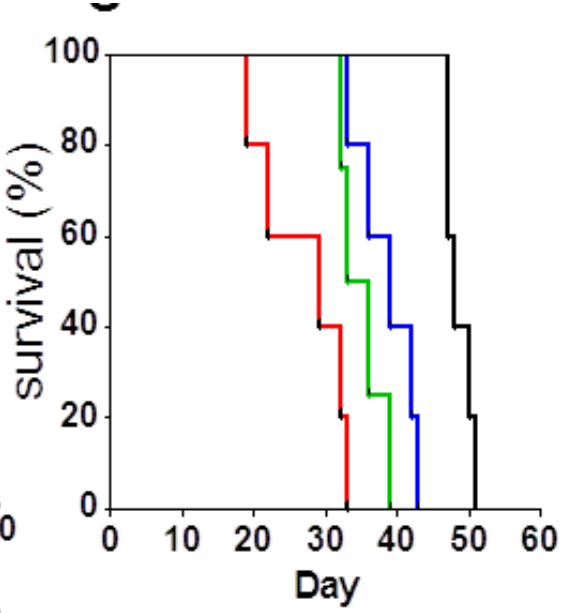


BLI measurement of tumor growth and survival

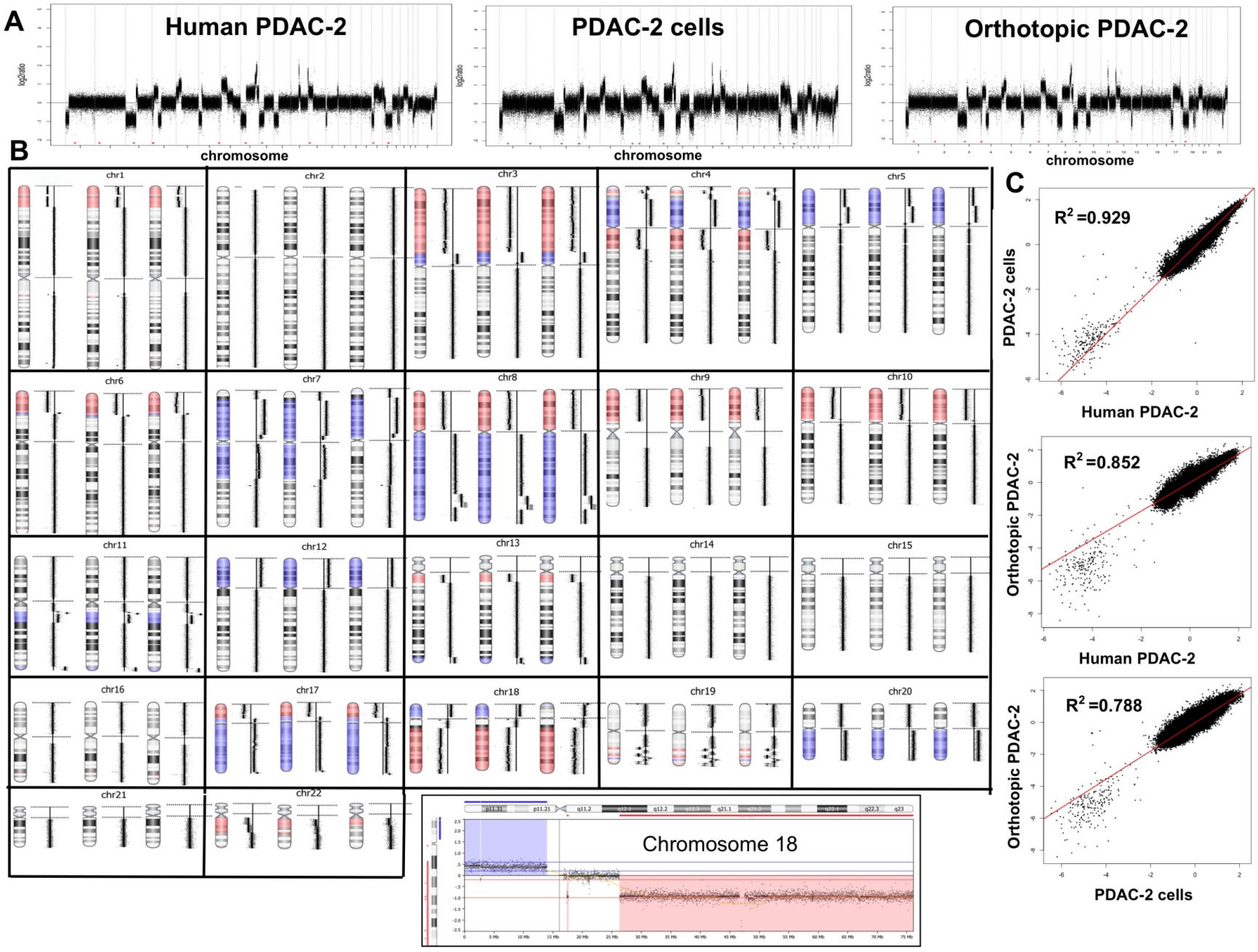






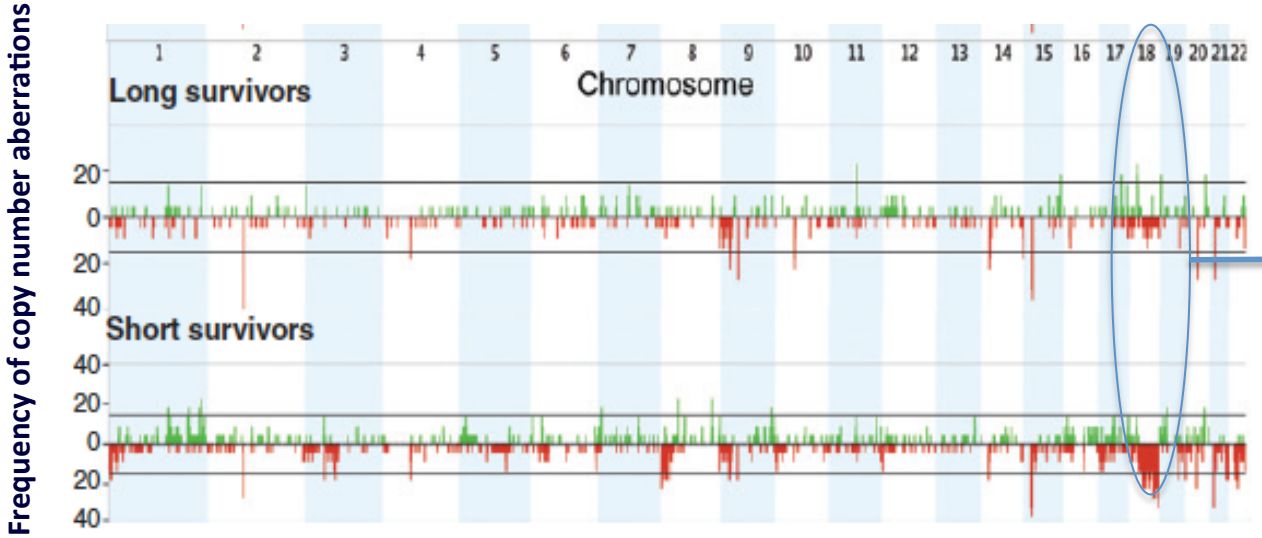


Another model (PDAC2)



Genomic study

array-CGH data in 44 radically resected pts



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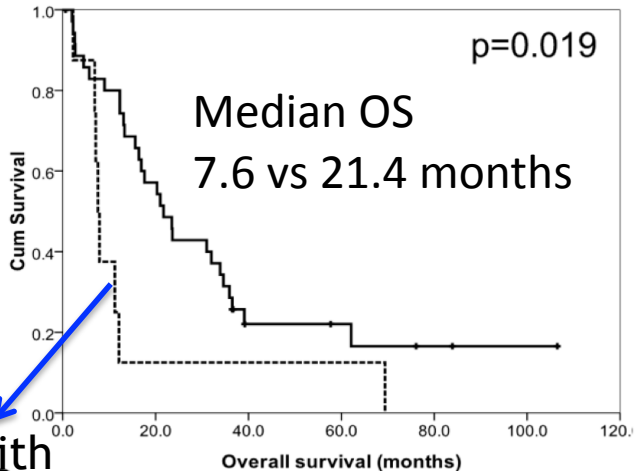
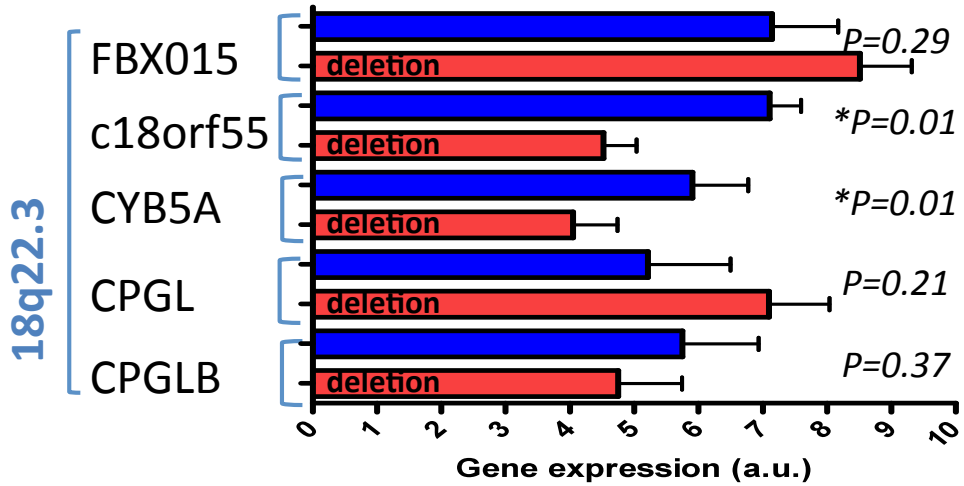


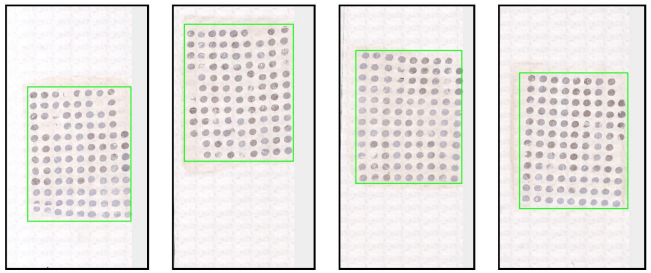
with loss

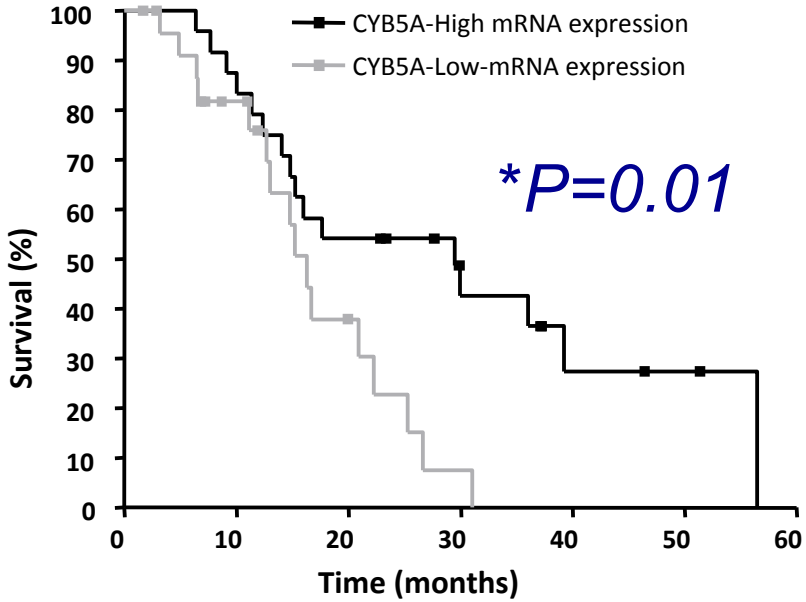
Lee, Giovannetti et al., Clin Cancer Res 2012

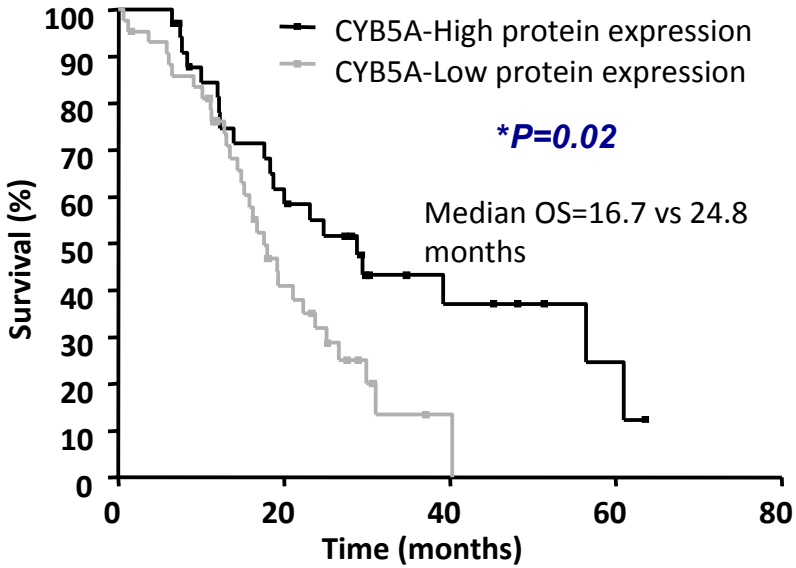
Genomic study, part II



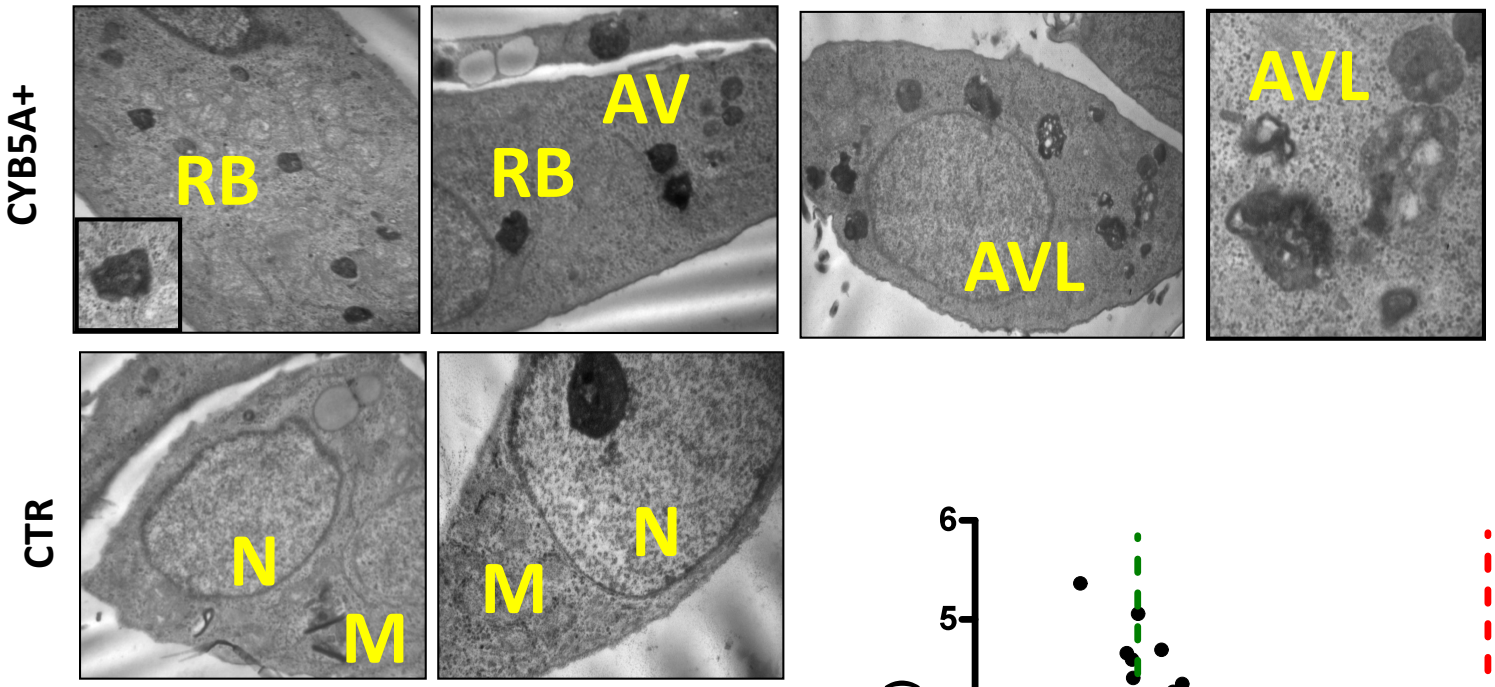
TMA
N=100

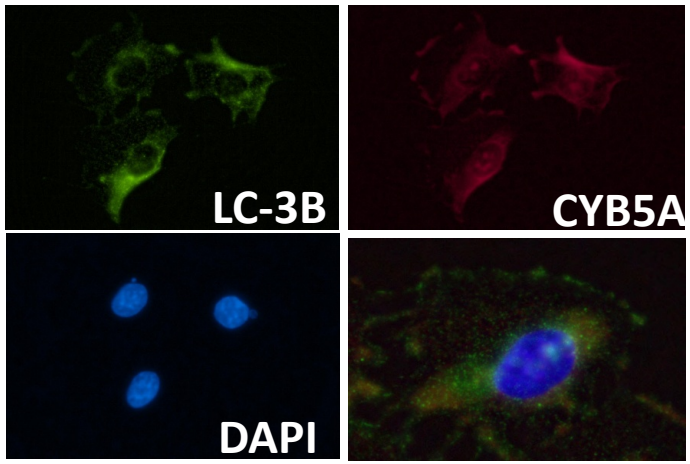


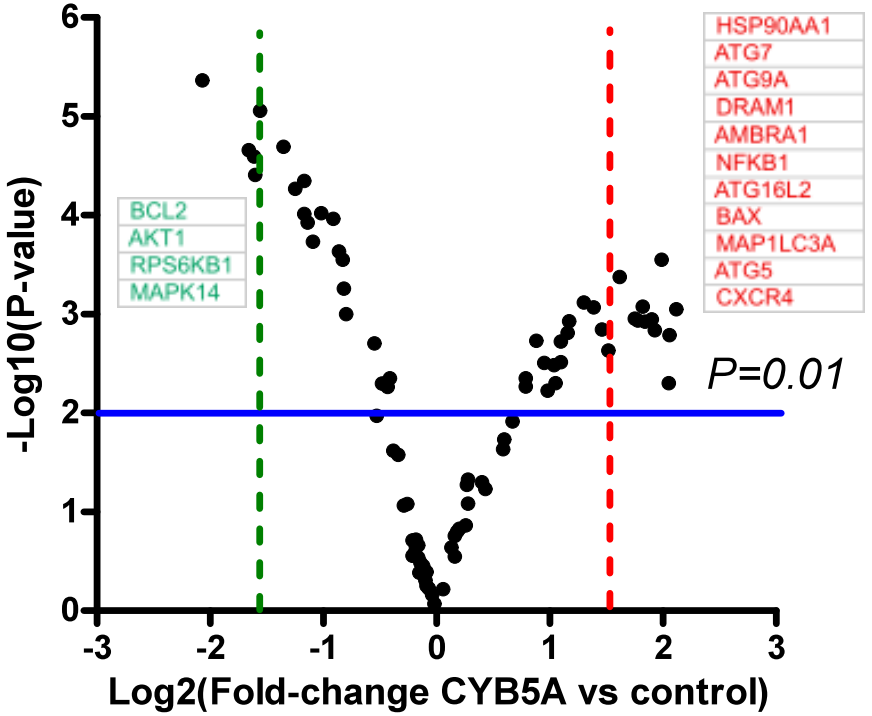




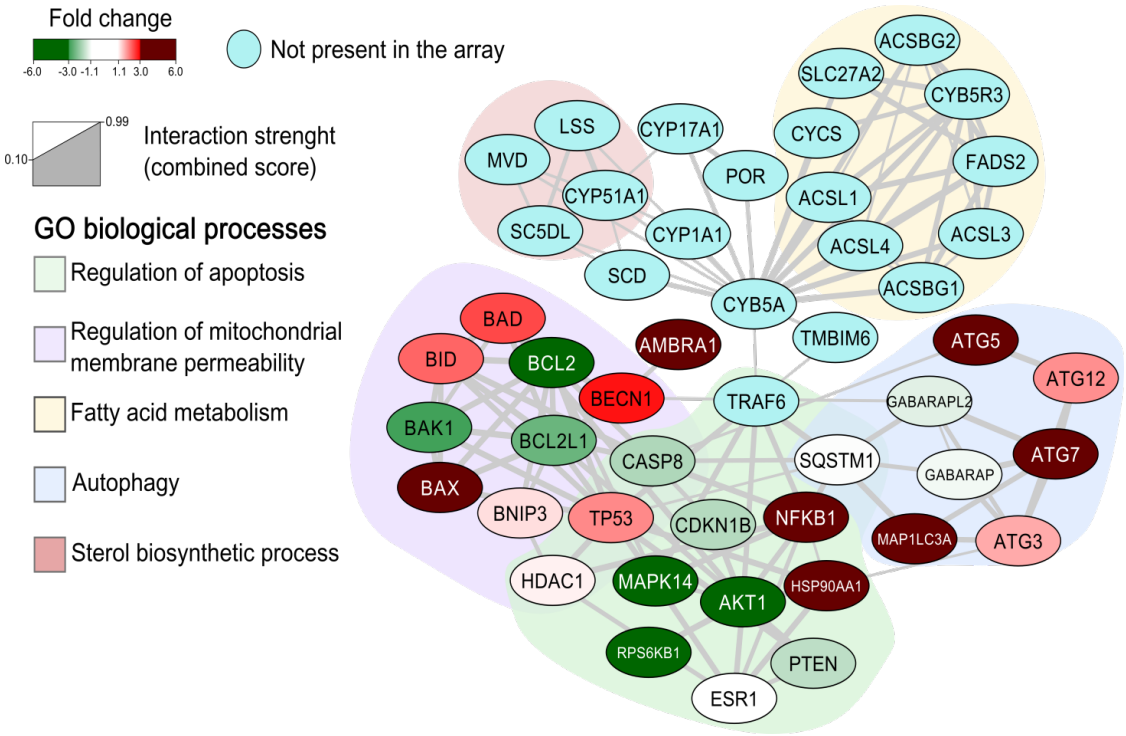
Role of autophagy

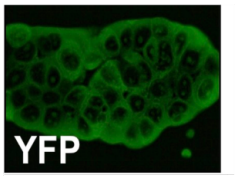


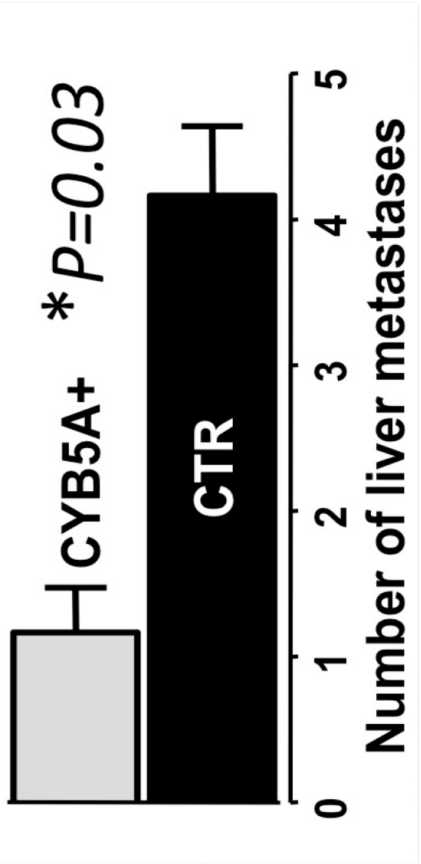


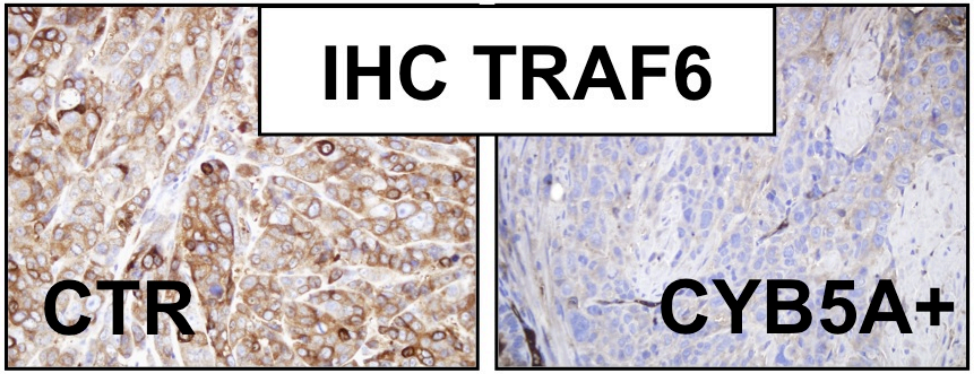


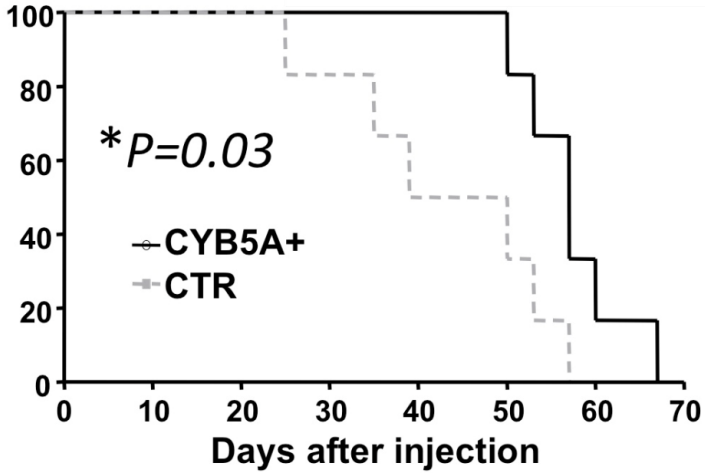
Pathways, OS and mts











Giovannetti et al., JNCI 2014

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Therapeutics, Targets, and Chemical Biology

Cancer Research

Crizotinib Inhibits Metabolic Inactivation of Gemcitabine in c-Met–driven Pancreatic Carcinoma

Amir Avan[1], Viola Caretti[3,6], Niccola Funel[7], Elena Galvani[1], Mina Maftouh[1], Richard J. Honeywell[1], Tonny Lagerweij[3], Olaf Van Tellingen[4], Daniela Campani[7], Dieter Fuchs[5], Henk M. Verheul[1], Gerrit-Jan Schuurhuis[2], Ugo Boggi[8], Godefridus J. Peters[1], Thomas Würdinger[3,9], and Elisa Giovannetti[1]

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Role of CYB5A in Pancreatic Cancer Prognosis and Autophagy Modulation

Elisa Giovannetti, Qiuyan Wang, Amir Avan, Niccola Funel, Tonny Lagerweij, Jih-Hsiang Lee, Viola Caretti, Arjan van der Velde, Ugo Boggi, Yisong Wang, Enrico Vasile, Godefridus J. Peters, Thomas Wurdinger, Giuseppe Giaccone

Manuscript received May 11, 2013; revised October 28, 2013; accepted October 29, 2013.

Conclusions… “everything is illuminated” (?)

“**co-clinical trials**” performed in several mouse models in parallel with human patients enrolled in ongoing phase I and II trials should improve the **velocity** and the outcome of personalized treatments and helps to **identify genetic and molecular determinants** mediating drug resistance

This approach should enable oncologists to **tailor novel, optimized combinatorial therapies** based on patient stratification