



Università degli Studi di Verona
Strada Le Grazie, 15
Sala Verde

AIRC START-UP Meeting
2015

9:30 – 10:00

Welcome and opening address

10:00-10:20

Translational application of DNMT-interacting RNAs in leukemia development

Annalisa Di Ruscio, Università degli Studi del Piemonte Orientale, Novara

10:20-10:40

Deciphering the impact of non-coding RNA in cancer

Riccardo Taulli, Università degli Studi di Torino

10:40-11:00

Bioluminescent pancreas cancer mouse models from genetically characterized primary cells: a platform for drug discovery

Elisa Giovannetti, Azienda Ospedaliero Universitaria Pisana

11:00-11:20

Mechanisms of Leukemia Immune Evasion Upon Hematopoietic Stem Cell Transplantation

Luca Vago, Università Vita-Salute San Raffaele, Milano

11:20-11:40 Coffee break

11:40-12:10

Integrità nella ricerca e altre policies AIRC

Lisa Vozza, Chief Scientific Officer, AIRC Peer Review Office

12:10-12:30

A new role of the E3 ligase UBR5 in DNA replication and damage tolerance

Simone Sabbioneda, Istituto di Genetica Molecolare CNR, Pavia

12:30-12:50

The use of Raman spectroscopy in Leukemia diagnostics

Anna Chiara De Luca, Istituto di Biochimica delle Proteine CNR, Napoli

12:50-13:10

microRNAs in most aggressive breast cancers: HER2 and TNBC

Marilena Iorio, Istituto Nazionale Tumori, Milano

13:10-13:30

How to consolidate your new laboratory

Diego Pasini, Istituto Europeo di Oncologia, Milano

13:30-14:30 Lunch

14:30-14:50

SDF1/CXCR4 axis is a novel target to block muscle wasting during cancer cachexia

Rosanna Piccirillo, Istituto di Ricerche Farmacologiche "Mario Negri", Milano

14:50-15:10

Tak-ing aim at treatment resistance in gastrointestinal tumors

Davide Melisi, Università degli Studi di Verona

15:10-15:30

ncRNAs and telomere regulation in human cancer

Stefan Schoeftner, Università degli Studi di Trieste

15:30-15:50

Role of microRNAs in chronic lymphocytic leukemia

Rosa Visone, Università degli Studi di Chieti

15:50-16:00

Closing remarks



AIRC Start Up Meeting 2015
Verona, June 5th, 2015

**Bioluminescent pancreatic cancer mouse models
from genetically characterized primary cells:
a platform for drug discovery**

Elisa Giovannetti, MD, PhD

Azienda Ospedaliera Universitaria Pisana



Cancer Pharmacology Lab
AIRC Start-up Unit





Incipit

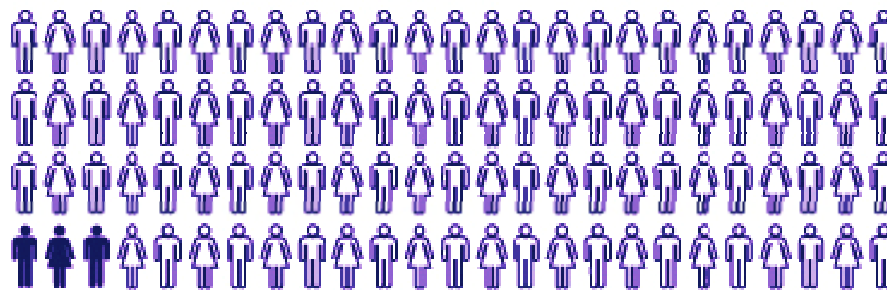


**“All happy families are alike;
each unhappy family is
unhappy in it’s own way”**

Anna Karenina – L. Tolstoj

**PANCREATIC CANCER SURVIVAL
RATES HAVE NOT IMPROVED**

IN 40 YEARS

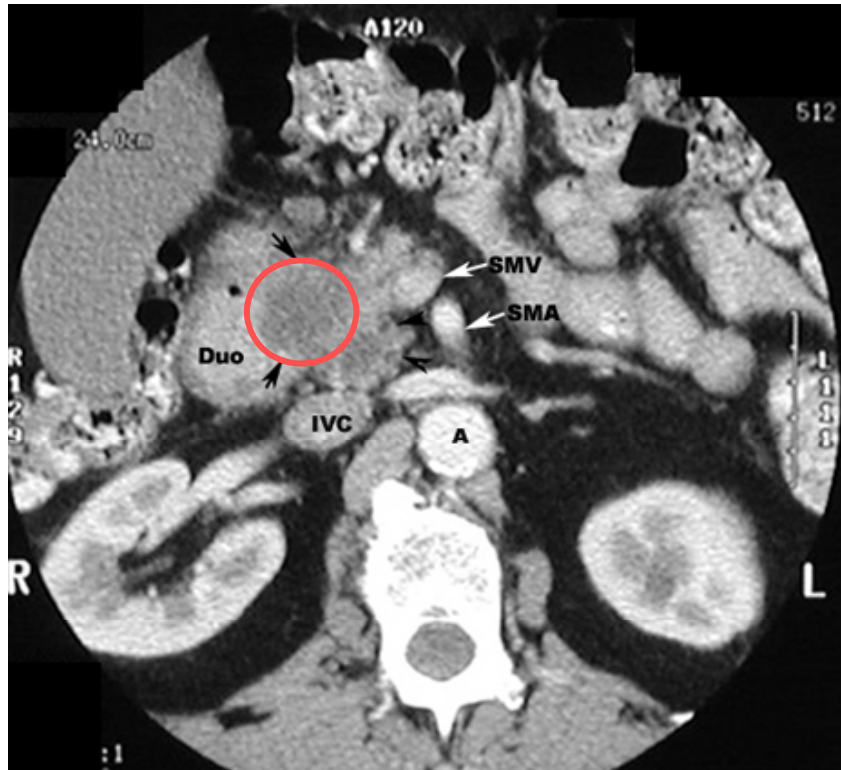


**Out of 100 patients
diagnosed**

**3 will survive beyond
five years**



Why PDAC is so lethal?



SMA: Superior mesenteric artery
SMV: Superior mesenteric vein
Duo: Duodenal sweep

- No established guidelines for prevention
- No screening for early diagnosis
- Symptoms delay
- Early metastatic spread
- Local/metastatic recurrence
- Multifactorial resistance to treatments
- Lack of biomarkers to select “targeted” treatments



Currently no proper preclinical PDAC models exist



Xenografts of established cell lines
(loss of genetic/biological properties)



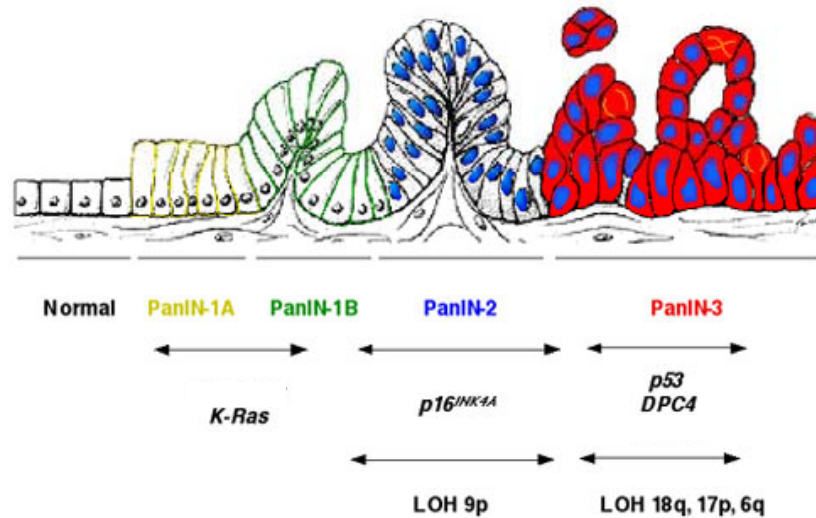
GEMM

Genetically engineered mouse models (*Tuveson et al., Cancer Cell 2010*)

Subcutaneous engrafted primary xenografts (*Hidalgo et al., JCO 2012*)

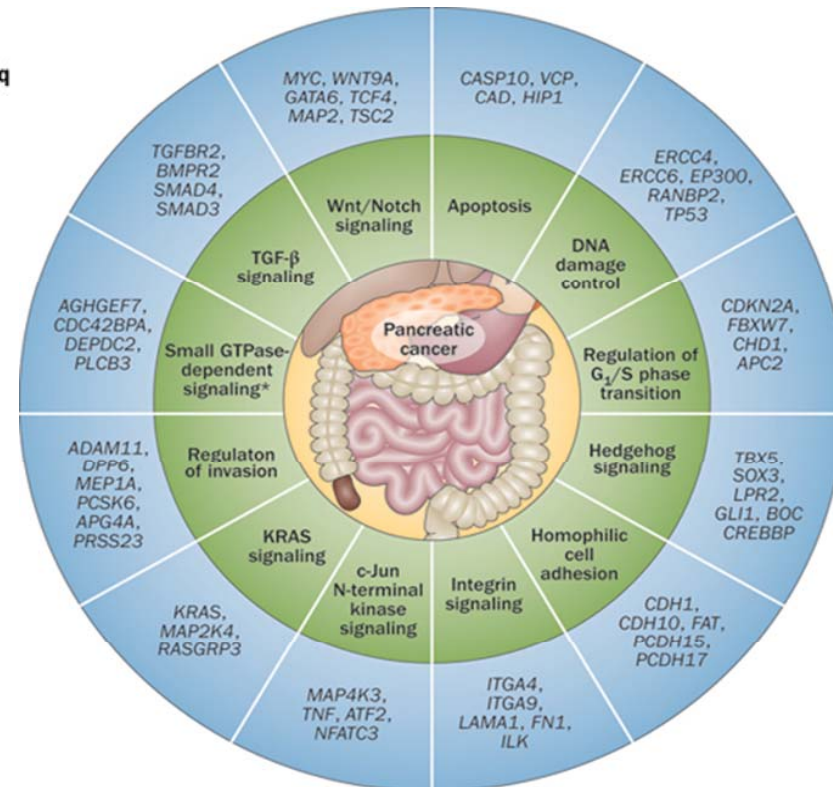


PDAC genomics - heterogeneity



Hallmark genetic changes contributing to pancreatic carcinogenesis (*Hruban et al, Clin Cancer Res 2000*)

Multiple genetic alterations that function through **core signaling pathways** (*Jones et al, Science 2009, Biankin et al, Nature 2012*)





Methods to measure orthotopic tumors



Subcutaneous

- vs.
- Histopathological analysis
 - MRI
 - high-resolution ultrasound

Orthotopic



Bioluminescence

In luminescent reactions, light is produced by the oxidation of a substrate:

- i.e., the reaction catalyzed by Firefly luciferase (FLuc)

1. Luciferin + ATP → luciferyl adenylate + Ppi

2. Luciferyl adenylate + O₂ → oxyluciferin + AMP + light

- the substrate for Gaussia luciferase is coelenterazine

Of note, GLuc is secreted by the cells and can be monitored in blood samples (Wurdinger et al., Nat Methods 2008)





The Start-Up project

Bioluminescent pancreas cancer mouse models from genetically characterized primary cells: a platform for drug discovery

AIM

To create and use our models

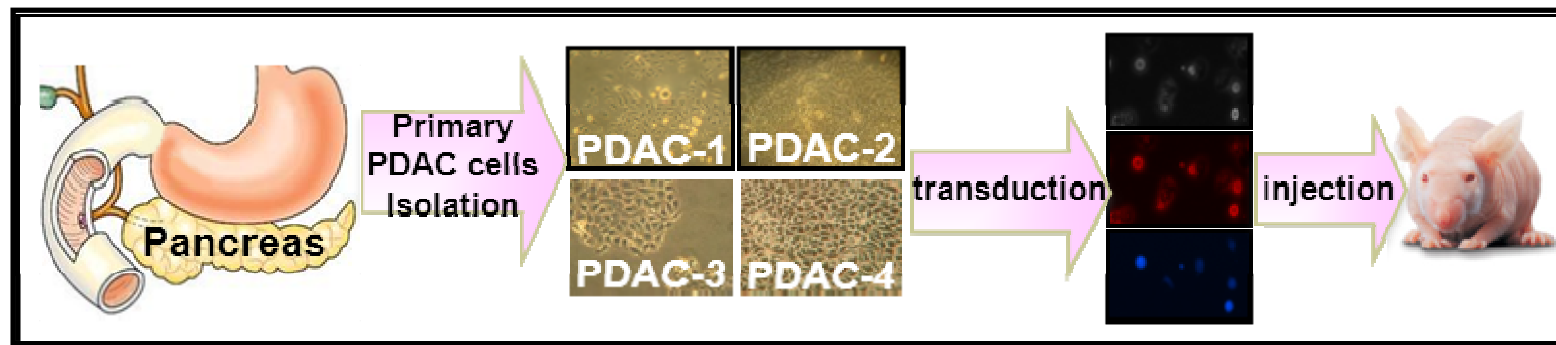
- with our unique **primary cells**
 - characterized for their genetic signature compared to the originator tumors
 - selected for cancer-stem-cell (CSC) / invasive markers
- Transduced with **bioluminescent** luciferase reporters
- Injected **orthotopically** in the pancreas of nude mice



To test **new molecular targeted agents**

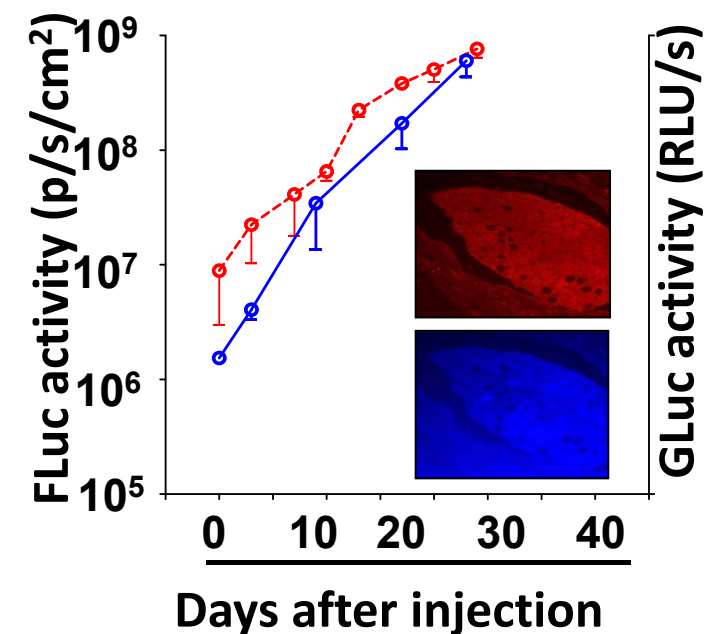


Results: Our models



Avan et al, Cancer Res 2013 - Giovannetti et al, JNCI 2014

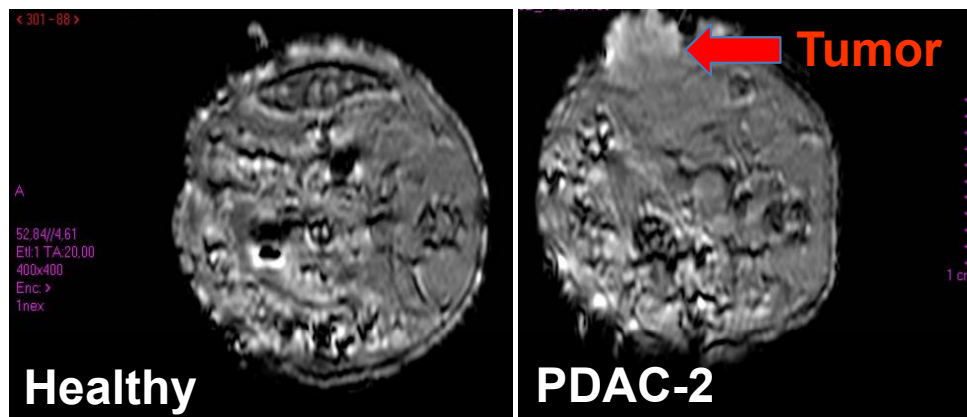
Maftouh et al, Oncotarget 2014 - Giovannetti et al, Autophagy 2014



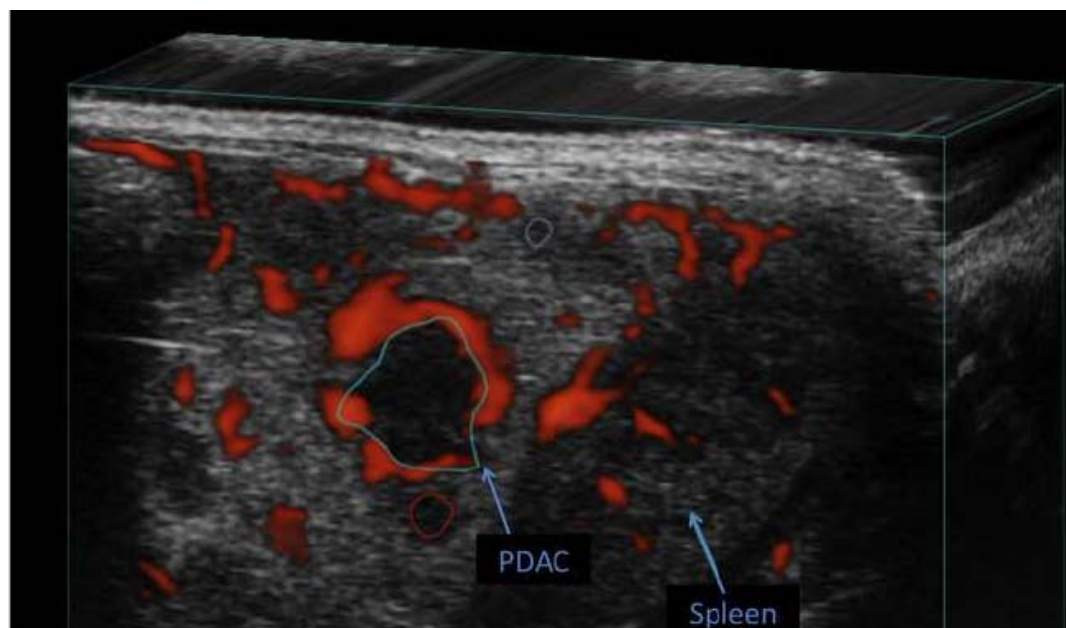


Other imaging

MRI

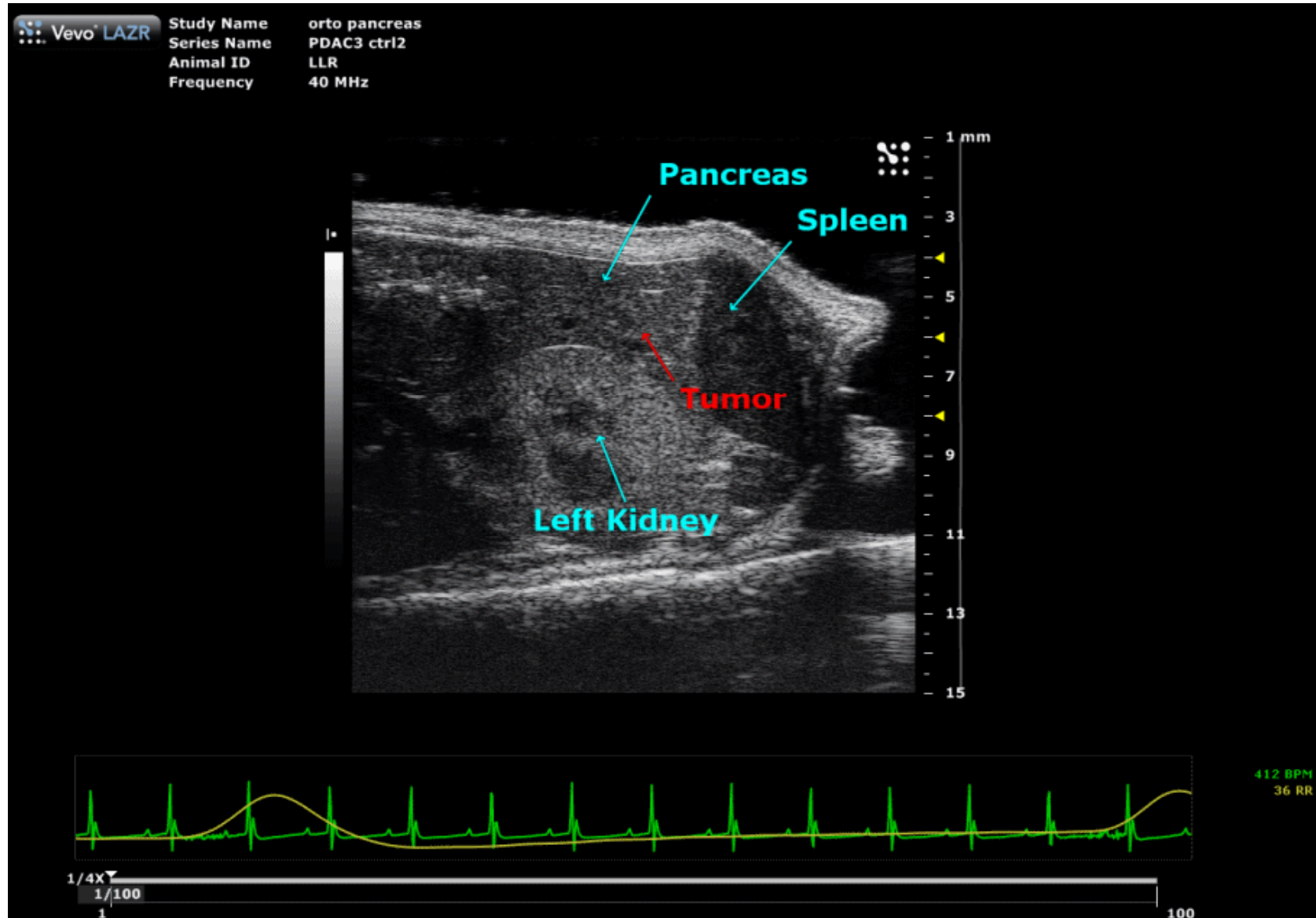


Doppler



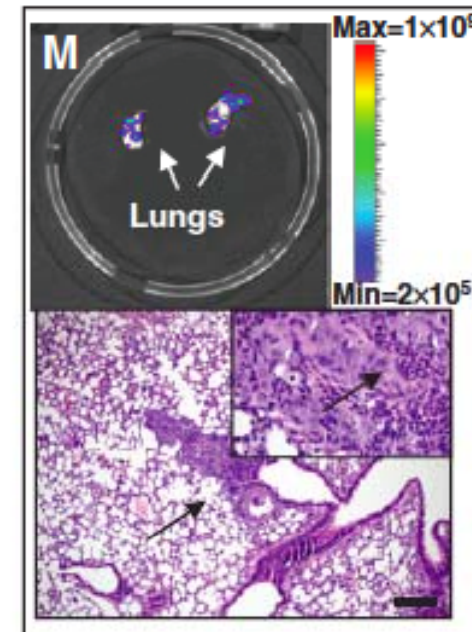
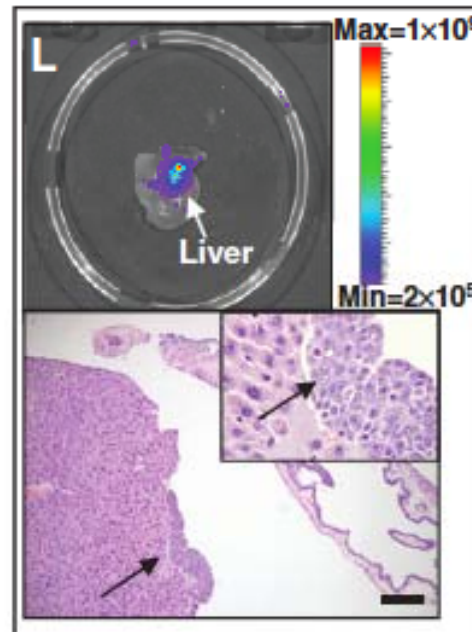
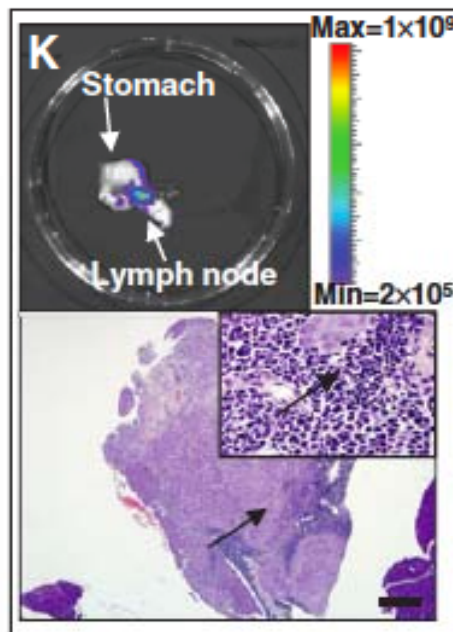
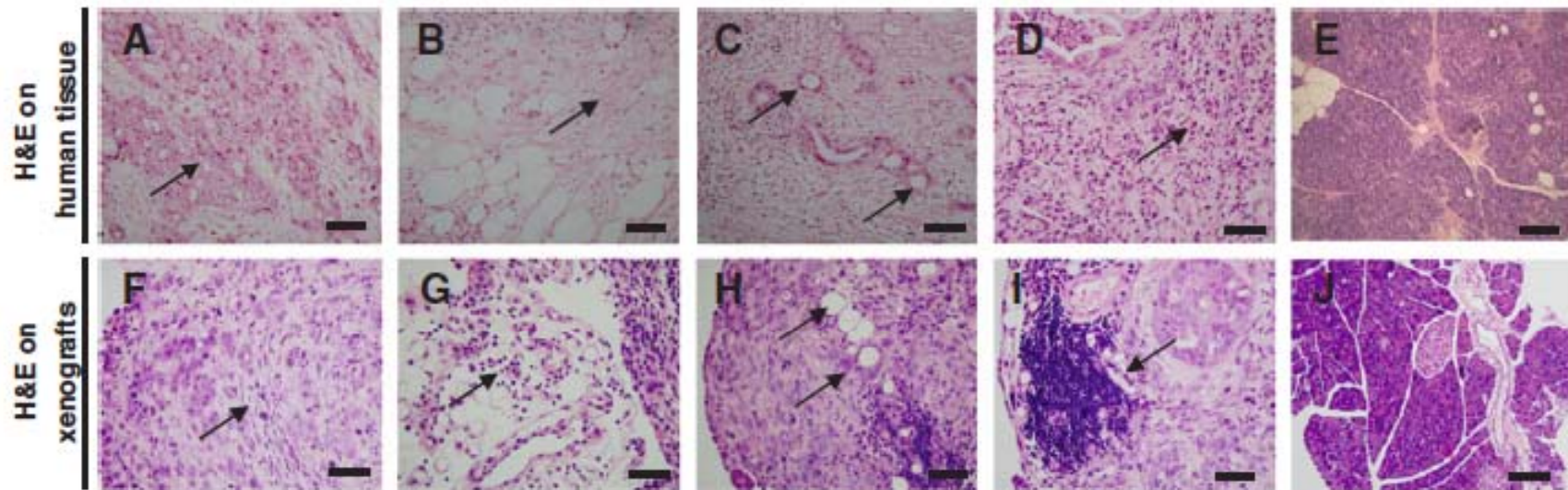


High-frequency ultrasound

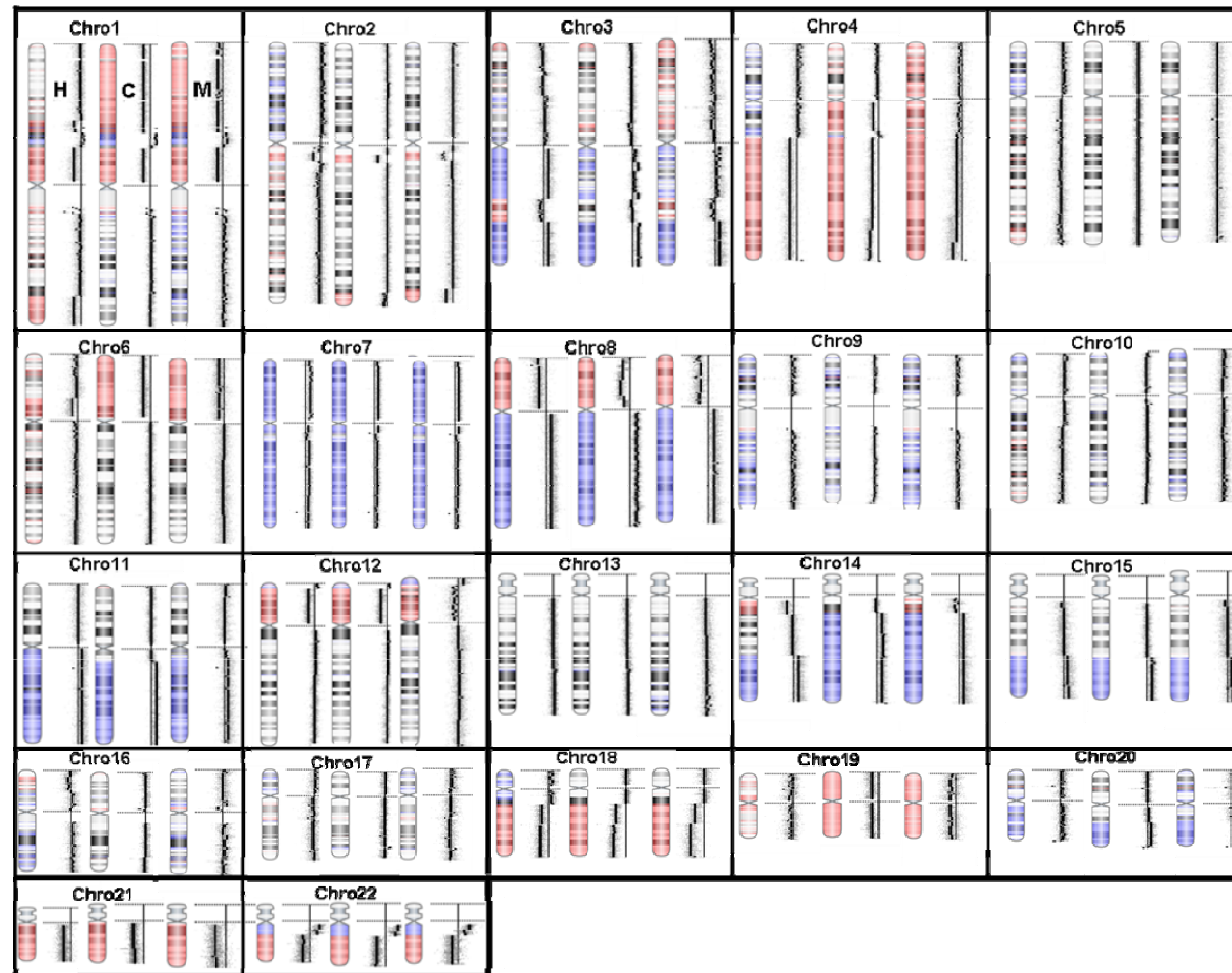
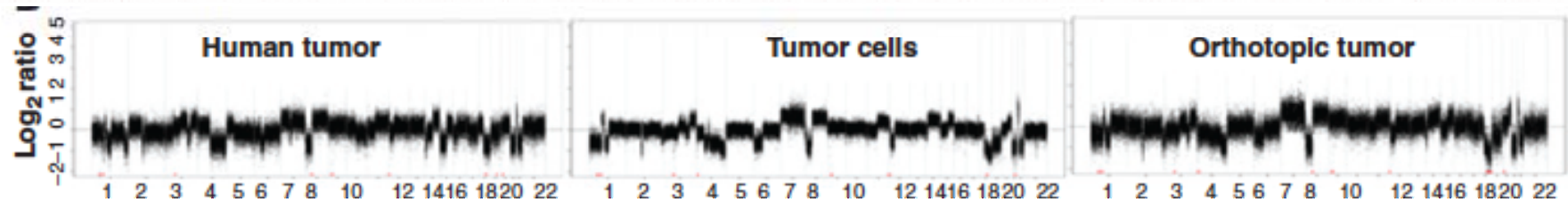




Histological features and metastases

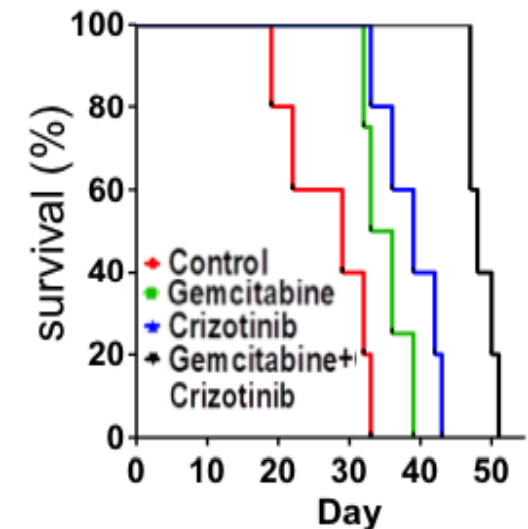
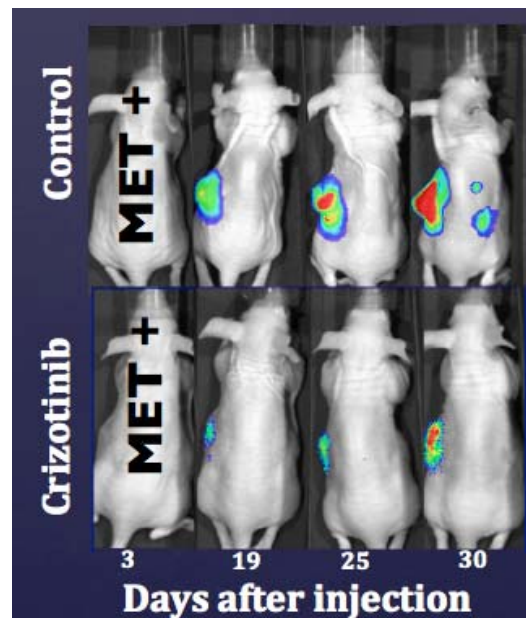
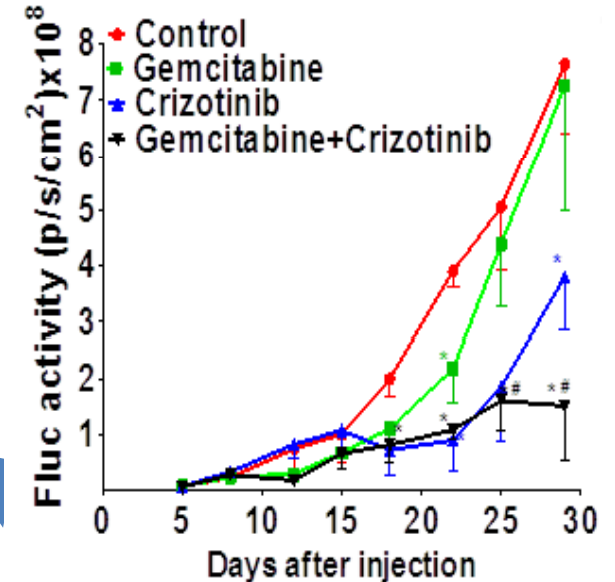
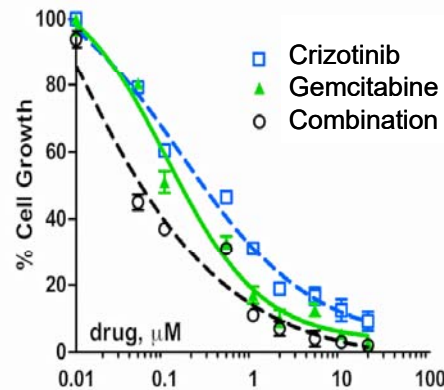
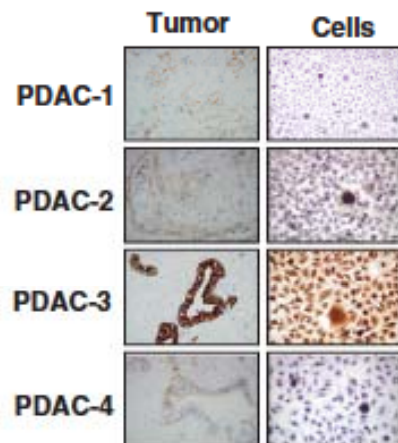
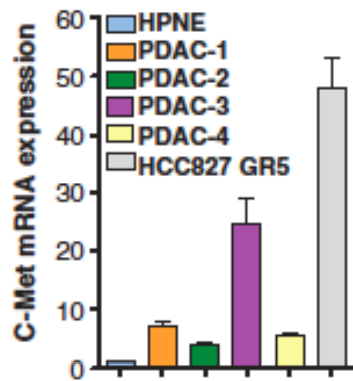
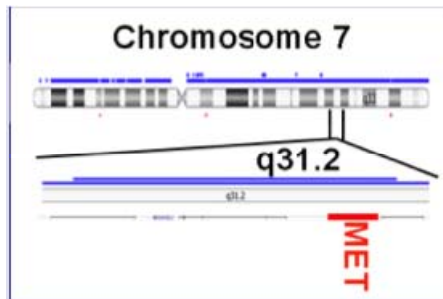


Genetic profiles: PDAC3 model





A proof-of-concept study on our models as an effective platform for drug testing





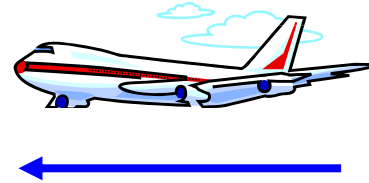
Conclusions

- Our readily imaged orthotopic PDAC models displayed genetic, histopathologic, and metastatic features similar to human tumors
- Their use pointed to c-Met as a therapeutic target and highlighted crizotinib and gemcitabine as a synergistic combination of drugs warranting clinical evaluation
- “co-clinical trials” performed in mouse models in parallel with patients enrolled in phase I/II trials should improve the outcome of personalized treatments and helps to identify molecular determinants mediating resistance
- This approach should enable oncologists to tailor novel, optimized combinatorial therapies based on patient stratification





Acknowledgements



... and back



L'INIZIATIVA

In tanti ad "Azalea della ricerca"

Domenica, in occasione dell'iniziativa "Azalea della Ricerca", i volontari dell'associazione "I Cavalieri" sono scesi in piazza per distribuire le azalee a sostegno dell'Associazione Italiana per la Ricerca sul Cancro (Airc). L'iniziativa ha riscosso un grande successo: tutte le azalee sono state vendute, ed è stata raccolta una cifra di quasi 10 mila euro, che sarà interamente devoluta a sostegno dei progetti di ricerca sui tumori femminili. Accanto ai volontari erano presenti anche i ricercatori pisani che hanno ottenuto i prestigiosi grant dell'Airc per svolgere le loro attività (nella foto). Per il secondo anno partecipavano la dottoressa Elisa Giovannetti ed il dottor Funel (del Cancerpharmacology lab, unica Start-Up dell'Airc in tutta la regione Toscana), insieme alle ricercatrici e specializzande del laboratorio della professoressa Elisei (dell' U.O. di Endocrinologia del Dipartimento di Medicina Clinica e Sperimentale). Quest'anno, inoltre, l'Airc celebra i 50 anni dalla sua fondazione.

Airc di Pisa ■ Grande partecipazione all'iniziativa per sostenere la ricerca sul cancro con i volontari dell'associazione "I Cavalieri"



GCGCTAAATATCAGGGGTACCGA
CGCGATTTATAGTCCCATGGCTA
GTAGCTAGCCATCGACTTGACTA





Collaborations on PDAC studies



Dept. Oncology – Surgery – Pathology Prof. Peters, Prof. Verheul, Prof. Kazemier



LEXOR – Surgery
Dr. Bijlma, Prof. Medema
Dr. Besselink



Dept. Surgery
Dr. Frampton
Prof. Liao



Pisa University Prof. Boggi
Prof. Falcone, Prof. Minutolo



Dept. Gastroenterology
Prof. Del Chiaro
Prof. Lohr



Dept. Oncology
Dr. Reni



Georgetown University
Dr. Wang, Prof. Giaccone



Stanford University
Dr. Caretti,
Prof. Wurdinger





Other info

www.cancerpharmacology.org

The screenshot shows a Safari browser window with the address bar displaying cancerpharmacology.org. The website header includes the logo for the Cancer Pharmacology Lab, an AIRC Start-up Unit, and social media follow buttons for RSS, YouTube, Facebook, and Google+. A navigation menu contains links for Home, Team, Projects, Presentations, Publications, News, Collaborations, Gallery, FAQ, and Contacts. The main content area features a large image of a laboratory setting with a person working at a biosafety cabinet. Overlaid on this image is a dark box with the heading "RESEARCH" and the text: "We are focusing on the study of the mechanism of action, toxicity and efficacy of anticancer agents mostly in pancreatic and thoracic cancers." Below the image, a paragraph states: "Cancer Pharmacology Lab is an 'AIRC Start-up Unit' which aims at improving cancer therapeutics either by the development/optimization of new antitumor agents and more effective drug combinations (including chemotherapy, immunotherapy and targeted therapy) or by the tailoring of existing and new therapies."