<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30 – 10:00</td>
<td>Welcome and opening address</td>
</tr>
<tr>
<td>10:00–10:20</td>
<td>Translational application of DNMT-interacting RNA in leukemia development Annalisa Di Ruscio, Università degli Studi del Piemonte Orientale, Novara</td>
</tr>
<tr>
<td>10:20–10:40</td>
<td>Deciphering the impact of non-coding RNA in cancer Riccardo Taulli, Università degli Studi di Torino</td>
</tr>
<tr>
<td>10:40–11:00</td>
<td>Bioluminescent pancreatic cancer mouse models from genetically characterized primary cells: a platform for drug discovery Elisa Giovannetti, Azienda Ospedaliero Universitaria Pisana</td>
</tr>
<tr>
<td>11:00–11:20</td>
<td>Mechanisms of Leukemia Immune Evasion Upon Hematopoietic Stem Cell Transplantation Luca Vago, Università Vita-Salute San Raffaele, Milano</td>
</tr>
<tr>
<td>11:20–11:40</td>
<td>Coffee break</td>
</tr>
<tr>
<td>11:40–12:10</td>
<td>Integrità nella ricerca e altre policies AIRC Lisa Vozza, Chief Scientific Officer, AIRC Peer Review Office</td>
</tr>
<tr>
<td>12:10–12:30</td>
<td>A new role of the E3 ligase UBR5 in DNA replication and damage tolerance Simone Samboneda, Istituto di Genetica Molecolare CNR, Pavia</td>
</tr>
<tr>
<td>12:30–12:50</td>
<td>The use of Raman spectroscopy in Leukemia diagnostics Anna Chiara De Luca, Istituto di Biochimica delle Proteine CNR, Napoli</td>
</tr>
<tr>
<td>12:50–13:10</td>
<td>microRNAs in most aggressive breast cancers: HER2 and TNBC Marilena Iorio, Istituto Nazionale Tumori, Milano</td>
</tr>
<tr>
<td>13:10–13:30</td>
<td>How to consolidate your new laboratory Diego Pasini, Istituto Europeo di Oncologia, Milano</td>
</tr>
<tr>
<td>13:30–14:30</td>
<td>Lunch</td>
</tr>
<tr>
<td>14:30–14:50</td>
<td>SDF1/CXCR4 axis is a novel target to block muscle wasting during cancer cachexia Rosanna Piccirillo, Istituto di Ricerche Farmacologiche &quot;Mario Negri&quot;, Milano</td>
</tr>
<tr>
<td>14:50–15:10</td>
<td>Taking aim at treatment resistance in gastrointestinal tumors Davide Melisi, Università degli Studi di Verona</td>
</tr>
<tr>
<td>15:10–15:30</td>
<td>ncRNAs and telomere regulation in human cancer Stefan Schoeftner, Università degli Studi di Trieste</td>
</tr>
<tr>
<td>15:30–15:50</td>
<td>Role of microRNAs in chronic lymphocytic leukemia Rosa Visone, Università degli Studi di Chieti</td>
</tr>
<tr>
<td>15:50–16:00</td>
<td>Closing remarks</td>
</tr>
</tbody>
</table>
Bioluminescent pancreatic cancer mouse models from genetically characterized primary cells: a platform for drug discovery

Elisa Giovannetti, MD, PhD
Azienda Ospedaliera Universitaria Pisana
“All happy families are alike; each unhappy family is unhappy in its own way”

Anna Karenina – L. Tolstoj
Why PDAC is so lethal?

- 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

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

Methods to measure orthotopic tumors

Orthotopic vs. Subcutaneous

Orthotopic
- Histopathological analysis
- MRI
- High-resolution ultrasound

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)
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

Pancreas
Spleen
Tumor
Left Kidney
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
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 dott.ssa Elisa Giovannetti ed il dott. Funel (del Cancerpharmacology lab, unica Start-Up dell’Airc in tutta la regione Toscana), insieme alle ricercatrici e specializzandi del laboratorio della prof.ssa Elisabetta (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”
Collaborations on PDAC studies

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

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

Imperial College London Dr. Frampton Prof. Liao

Dept. Gastroenterology Prof. Del Chiaro Prof. Lohr

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

Stanford University Dr. Caretti, Prof. Wurdinger

Georgetown University Dr. Wang, Prof. Giaccone
www.cancerpharmacology.org