Tumor Biology and Experimental Therapeutics Program

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Transcription Factors

Transcription factors are central nodes in multiple oncogenic signaling pathways and represent attractive targets for development of new cancer therapeutics. However, very few pharmacological inhibitors of transcription factors are currently available. Efforts in this area can lead to more effective anticancer therapies.

Available Projects:
- Novel inhibitors of the transcription factor STAT3: from drug design to preclinical testing.
- Molecular determinants of sensitivity to STAT3 inhibitors in human cancers.
ETS Transcription Factors in Prostate Cancer

ETS Transcription Factors
ETS proteins constitute one of the largest family of transcriptional regulators and play important roles in cell differentiation and carcinogenesis.

ETS proteins share a highly conserved DNA binding domain but individual ETS factors have distinct biological functions.

Specific ETS factors (ERG, ESE3/EHF) with oncogenic or tumor suppressor functions are highly deregulated in human prostate cancers.

Available Projects:
- ESE3/EHF control of epithelial differentiation and acquisition of cell stemness
- ERG orchestrated epigenetic network in cancer progression.
- Therapeutic targeting of ERG oncogenic functions.
Epigenetic Effectors

Extensive reprogramming of the epigenetic landscape occurs during cancer development and progression. Epigenetic processes contribute to cancer pathogenesis and impact on disease progression. Proteins involved in epigenetic networks are emerging as promising targetable elements in cancer cells for developing novel epigenetic therapies.

Available Projects:
- BET bromodomain proteins: epigenetic readers and cancer therapeutic targets.
- Histone demethylases inhibitors for cancer therapy.
Epigenetic Networks in Cancer: noncoding RNAs

Noncoding RNAs
Epigenetic reprogramming in cancer cells involves new classes of noncoding RNA molecules with distinct regulatory functions. Understanding these processes and the mechanisms involved may provide new information on the pathogenesis of cancers and opportunities for new therapeutic strategies.

Available Projects:
- Rewiring of epigenetic landscape in cancer: role of novel regulatory noncoding RNAs.
MicroRNA in Prostate Cancer

MicroRNA
microRNA are small non-coding RNA that regulate post-transcriptionally gene expression. microRNA may exert their functions in cell autonomous and non-cell autonomous manner. microRNA can be secreted by donor cells into extracellular vesicles or exosomes and influence recipient cells in the surrounding microenvironment. Specific microRNA are highly deregulated in prostate cancer subtypes and may contribute to tumor progression.

Available Projects:
- ETS regulated microRNA networks in prostate cancer.
- Exosome-secreted microRNA in tumor progression.
Cancer Stem Cells

Rare stem-like tumor cells within the bulk tumor mass are the likely culprits of metastasis, disease recurrence and treatment failures. Drugs targeting the stem-like tumor cells within the bulk tumor cell population may have a relevant impact on disease control and clinical outcome.

Available Projects:
- Epigenetic reprogramming of cancer stem cells.
- Metabolic plasticity and mitochondrial dynamics: new targets for cancer stem cell-directed therapeutics.
Main research projects:
- Characterization of the mechanism of platinum resistance in Epithelial ovarian cancer.
- Analysis of serum miRNA expression and circulating tumor DNA (ctDNA) mutational profile.
- Mode of action of Trabectedin in mixoid liposarcomas.
Main research projects:
- Strategies to target tumors with activated PI3K and K-RAS pathways.
- Targeting KRAS mutations in NSCLC through LKB1 co-vulnerability
- Role of epithelial to mesenchimal transition and stemness in resistance to chemotherapy of ovarian carcinoma
- Inhibition of Chk1 and Wee1 as a new therapeutic approach in aggressive non-Hodgkin lymphomas.
- New combination strategies for the treatment of human solid tumors in immunodeficient mice.
Main research projects:
- Thrombospondin-1, translating biological insights into the design of novel antiangiogenic approaches.
- Identification of selective markers on tumor associated endothelium as possible therapeutic targets.
- Preclinical development of novel angiogenesis inhibitors and their optimization in combination with conventional therapy.
- A bio-bank of patient derived ovarian carcinoma xenografts (PDX) to develop new pharmacological intervention.
- Identification of stroma related biomarkers for early diagnosis and risk assessment of pancreatic cancer.
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- We are an integrated Basic-Clinical Science Unit with different translational and applied approaches
- Because of the strong interaction with the clinical Oncology Department, we specifically work on pre-clinical in vitro research with the aim to study and clarify the results arising from clinical trials on new anticancer drugs in Breast Cancer (BC) and/or Solid tumors
- In parallel we develop in vitro new strategies of treatment to be applied in clinic
- Different field of activity

Pharmacology
Immunology
Diagnostics
**Pharmacology**

**PROJECT1**

Starting from the results of Clinical trial NAPHER2 (Neo-Adjuvant Treatment with Palbociclib (CDK4/6 inhibitor) / Fulvestrant/ Trastuzumab/ Pertuzumab combination in HER2+, ER+ Breast Cancer) *Gianni L. Lancet 2018*

- The *in vitro* preclinical study will investigate the activity of the novel Cyclin-Dependent Kinase 4/6 Inhibitor Palbociclib and its efficacy (synergism) in association with anti-HER2 antibodies and hormone therapy in breast cancer cell lines. The immuno-modulatory implications of palbociclib treatment were also studied.
- Cytotoxicity (MTT), Cell cycle and Apoptosis (Cytofluorimetry), Modulation of intracellular pathways (Western Blotting), Immuno-markers (Cytofluorimetry) will be studied.

**PROJECT2**

In the contest of Project 1 we are planning to study the combination of Palbociclib and Fulvestrant with new generation anti-HER2 antibodies

- **DS-8201a (Daiichi Sankyo)**: antibody-drug-conjugate (ADC) which links the activity of the anti-HER2 antibody to the topoisomerase I inhibitory activity of the conjugate molecule (exatecan derivative)
- **ZW-25 (Zymeworks)**: bispecific antibody which target two distinct HER2 epitopes (same domains of trastuzumab and pertuzumab)

The same experimental approaches of Project 1 will be applied
**Immunology**

**PROJECT3**
Starting from the results of Clinical trial NeoSphere (Neo-Adjuvant Trastuzumab /Pertuzumab/ chemotherapy (Docetaxel) combination treatment in locally advanced/early stage HER2 positive breast cancer) Bianchini et al. Ann.of Onc.2015

- Since the response to treatments was inversely correlated to basal expression of MHC1 and CTLA4, we wont to study the implication of the antibody dependent cell cytotoxicity (ADCC) in this effect and the contribution of epigenetic alteration to immuno-escape in breast cancer.
- ADCC (Grantoxilux and LDH test), Granzyme-B (ELISA) and expression of ligands of NK activator receptors (CD155, MICA,HLA,β2 microglobulin: Cytofluorimetry) will be evaluated.

**Diagnostics**

**PROJECT4**
Starting from the Clinical Need: determination in patient’s tissues of **EGFR and HER2 phosphorylation status** by IHC to establish the tyrosine kinase receptor activation

- The research will focus on the question of how to preserve the phosphorylated sites during fixation and inclusion procedures. The addition of phosphatase inhibitors in the fixative and the use of fast method of inclusion will be studied in cell pellets and tissue biopsies from patients
Vesicle-mediated protein transport and neurodegeneration

- One pathway of cell-to-cell communication is by extracellular membrane vesicles (exosomes)
- Exosomes may contribute to the brain spreading of pathological protein forms associated to neurodegenerative disorders

from http://www.latrobe.edu.au

from https://scienceofparkinsons.com
The aim of the study is to elucidate

a) which subcellular compartment within recipient cells is the target for exosomal protein cargo release

a) how this process is affected by the presence of pathological protein forms associated to neurodegenerative disorders
TRPs in neurodegenerative diseases

AIM of the project
Protein signatures correlation with phenotype/genotype
**ProLyPALS**

Two-dimensional electrophoresis

**AIM of the project**
Identification of specific PD/ALS protein signatures

**Parkinson**

**ALS**

**Now verification step!!**
DinaMoParD

**AIM of the project**

*Generation of a dynamic model of the altered mitochondrion in PD*