FINAL PUBLISHABLE SUMMARY REPORT

- **Executive summary**

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human malignancies and a major health problem. It has been estimated that PDAC causes 34000 deaths per year in the EU alone. Despite considerable research efforts in the past decades, conventional treatment approaches, including surgery, radiation, chemotherapy, and combinations of these, have close to no impact on the course of this aggressive neoplasm. Therefore, virtually all of the patients diagnosed with PDAC develop metastases and die.
Given this scenario, the search for new drugs to combat PDAC progression and thus increase patient life expectancy and quality of life has been given high priority (Philip PA et al. Consensus Report of the National Cancer Institute Clinical Trials Planning Meeting on Pancreas Cancer Treatment. J Clin Oncol. 2009 Nov 20;27:5660-5669). In particular, the National Cancer Institute's Gastrointestinal Cancer Steering Committee has recently placed major emphasis on:

- the enhancement of "research to identify and validate the relevant targets and molecular pathways in PDAC, cancer stem cells, and the microenvironment";
- the "establishment of high-throughput assay systems to accelerate target identification and validation";
- the "use of preclinical tumor models that are better predictive of human PDAC", particularly of genetically engineered mouse models;
- well-designed pilot studies with survival as a primary endpoint.

To achieve these goals, it was recommended that "communication between the academic community and the pharmaceutical industry is improved to benefit patients with this deadly disease", as "developing research partnerships that involve academic investigators, pharmaceutical industry, and patient advocacy will best accomplish the goals of decreasing the morbidity and mortality from this disease".
Our understanding of the biology of PDAC is improving thanks to efforts to identify the mutations and genetic alterations that lead to pancreatic carcinogenesis. A comprehensive genetic analysis has recently shown that PDACs harbor on average more than 50 genetic alterations, mostly represented by mutations and, to a lower extent, by deletions and amplifications of fragments of genomic. These abnormalities, in turn, are responsible for the aberrant pattern of protein expression/activity that characterizes PDAC and that determines its invasive phenotype. The emerging genetic landscape of PDAC is thus a complex one where deregulation of key cellular processes and signalling pathways (DNA repair, apoptosis, invasion, neoangiogenesis, Hedgehog signaling, etc.) can be achieved by different genetic alterations that act, at least to some extent, in an interchangeable fashion. Based on this evidence, it was suggested that new therapeutics should target downstream mediators or key nodal points of a pathway rather than aiming to specific mutated genes. Pathways that should be targeted include those causing "metabolic disturbances, neoangiogenesis, misexpression of cell surface proteins, cell cycle alterations, cytoskeletal abnormalities, and an impaired ability to repair genomic damage". In addition to the above-mentioned features, PDAC owes its aggressiveness to the capacity to escape immune surveillance. Among the mechanisms invoked in this context is the upregulation of the tryptophandegrading enzyme indoleamine 2,3-dioxygenase-2 (IDO2), which inhibits T lymphocyte responses possibly by reverting tumor-infiltrating antigen presenting cells to a less immunogenic mode. In addition, immune escape was reported to be due to anergy induction in T cells by the β-galactoside-binding protein galectin-3 (Gal-3) expressed by the tumor. Pharmacological strategies that will nullify the tumor immune escape mechanisms and, more in general, new therapeutic approaches aimed to boost anticancer immunity are deemed important in the fight to this form of cancer.

- **Summary description of project context and objectives**

The PANACREAS project proposed to build a team composed of clinicians, translational cancer researchers, chemists, and one pharmaceutical enterprise (an SME), to synthesize, implement and test new drugs for PDAC. These drugs were meant to work through diverse and novel modes of action, targeting oncogenic pathways, mutated tumor suppressors and aberrant biological functions which still lack clinically applicable inhibitors. The most promising structures identified during the project have been validated for

their therapeutic potential in the Feldmann laboratory [Center for Integrated Oncology (CIO) Cologne-Bonn, UKB] using an established genetically engineered PDAC mouse models and orthotopic PDAC xenografts. Leading groups in their respective fields have developed and tested drugs to

- inhibit the Hippo signalling pathway [a signaling cascade originally recognized as playing a central role in organ size control, which is now emerging as crucially involved in carcinogenesis in mammals;
- reverse immune escape in PDAC [IDO2 inhibitors and galectin-3 (Gal-3) inhibitors];
- disrupt the cytokine pattern of PDAC (SIRT6 inhibitors);
- trigger the apoptotic machinery in PDAC cells via extrinsic death receptors/endoplasmic reticulum stress (edelfosine and its analogues), and by reversing the anti-apoptotic effect of Gal-3 by inhibitors;
- inhibit metastasis using glycosidase inhibitors (α-mannosidase inhibitors) and Gal-3 inhibitors;
- target PDAC exploiting its synthetic lethal genetic interactions.

Dr. Feldmann's laboratory at UKB has coordinated the efforts of the beneficiaries in the consortium, monitored the development of the most promising new compounds and evaluated their efficacy in preclinical *in vitro* and *in vivo* experiments.

- **Main S & T results/foregrounds**

The main S&T results are described below for each RTD WPs:

WP1: A kinase inhibitor that interferes with YAP ability to activate TEAD-mediated transcription has been identified through a small scale compound screen approach. Ongoing efforts aim to characterize its precise mode of action and to assess its therapeutic potential. Meanwhile strong evidence for the ability of the identified compound to counter epithelial to mesenchymal transition in pancreatic cancer cells has been obtained.

WP2: the first effective IDO2 inhibitors have been identified.

WP3: This work package has achieved the goal of identifying the first chemical SIRT6 inhibitors, which are currently evaluated in PDAC models. Interestingly, a double-faced role for SIRT6 in PDAC has been identified, with this protein countering aerobic glycolysis (Warburg effect) in PDAC cells, but also promoting cell migration and resistance to DNA damaging agents (see final Scientific Report). Remarkably, effective NAD^+ lowering agents (NAMPT inhibitors) that could also be used for treating PDAC were identified within this WP, too (patent filing ongoing). *In vivo* testing of these compounds is currently been performed.

WP4: Numerous studies have been performed to elucidate edelfosine mode of action and the activity of edelfosine has been confirmed in several PDAC models. Several compounds with potential to act as edelfosine analogues were also found, with one of them being active *in vivo* against PDAC xenografts.

WP5: Several alpha-mannosidase inhibitors have been synthesized and they were tested for their antiproliferative activity in PDAC models. However, due to their poor specificity, these compounds were no further pursued and the activities of this WP were stopped.

WP6: Numerous new galectin inhibitors were synthesized and their efficacy in PDAC models is currently being assessed.

WP7: Many chemical-genetic screen for the identification of compounds with synthetic lethal activity in PDAC were performed. However, due to the very few hits that were identified and to their very small therapeutic index, this work package has been also interrupted.

- **Potential impact and main dissemination activities and exploitation of results**

<u>Potential Impact</u>

Medical and Social impact: the identification of new treatments for PDAC is going to have a major social impact by improving the physical and psychological status of the patients affected by PDAC and of their families. Moreover, the discovery of drugs that are finally able to counter the natural history of PDAC would represent a milestone in the history of this disease. This would increase reliance on cancer research performed in Europe and on its capacity to find treatments for diseases that are traditionally regarded as incurable.

Economical impact: by reducing disease-related complications and by improving patient performance status and quality of life, potential new drugs identified by PANACREAS will help reduce the burden of health costs that affects the EU. Moreover, our work will open new avenues for scientific and technological innovation and prompt the development of new drugs by European pharmaceutical industries.

Dissemination activities

Since the beginning of the project, the dissemination activities were aimed at enhancing visibility of the consortium and of the project, mainly for informing the scientific community and stakeholders and for communicating the value of the research funded by the European Community through FP7.
The main dissemination approaches from the project start included:

- **Development of a Project website**

The project website was created with its own domain: www.panacreas.eu. The homepage summarizes the main focus and structure of PANACREAS. Using the menu of the home page it is possible to access the main sessions of the **public area**:

The **partners** page describes the composition of the PANACREAS consortium and contains email address of the scientists involved and a link to their organization.

The **publications** page list all the papers derived from the PANACREAS project.

The **reserved area** is intended as a tool of information and updating for scientists; the access is restricted with a password in order to protect and dedicate to internal project communication. The project website has been updated periodically.

- **Development of Project information material**

A Brochure of the project was prepared by beneficiary 12-ALTA, that was distributed to partners in the occasion of project meetings.

ALTA has also designed the logo that visually identifies the project and that has been used in occasion of meetings, posters, and communication activities.

- **Wikipedia page** http://en.wikipedia.org/wiki/PANACREAS

- **Participation at scientific events**
  see list in A2.

- **Publications/chapter of books/reviews**
  See A1 for publications.

Exploitation activities

Several of PANACREAS deliverables lend themselves clearly to successful exploitation. Namely:
1. Knowledge of new therapeutic targets for PDAC: this will become an invaluable resource to researchers in the field of oncology and cancer research. Such a deliverable will also have high dissemination impact.
2. Development of novel therapeutic compounds for PDAC treatment: it will have a major social impact by improving the physical and psychological status of the patients affected by PDAC and of their families.
3. Development of high throughput assays to be used in the drug discovery process for the identification of original chemical entities with potential therapeutic efficacy in the clinical treatment of PDAC.

The main goal of PANACREAS was to identify and validate new compounds to be used for treating PDAC. Specifically, a main focus of this initiative was the identification of Hippo signaling inhibitors (WP1), IDO2 inhibitors (WP2), SIRT6 inhibitors and NAMPT inhibitors (WP3), edelfosine analogues (WP4), alpha-mannosidase inhibitors (WP5),galectin-3 inhibitors (WP6), and of synthetic lethal therapeutics for PDAC (WP7).

We have obtained important results (particularly in our WP3 - SIRT6 and NAMPT inhibitors - and WP6 - Galectin-3 inhibitors), which we anticipate could find applications in PDAC, but also in other types of solid and hematologic cancers.

8 patents (already granted or filing ongoing) have been produced within PANACREAS.

Project website and relevant contact details
www.panacreas.eu

Contractors involved:

- Universitaetsklinikum Bonn (GERMANY)
- Università degli Studi di Genova (ITALY)
- Agencia Estatal Consejo Superior de Investigaciones Cientificas (SPAIN)
- Ecole Polytechnique Federale de Lausanne (SWITZERLAND)
- Hospices Cantonaux CHUV (SWITZERLAND)
- Universidad de Sevilla (SPAIN)
- Università degli Studi di Trento (ITALY)
- Swiss Institute of Bioinformatics (SWITZERLAND)
- Lunds Universitet (SWEDEN)
- Debiopharm SA (SWITZERLAND)- (terminated 31 August 2014)
- Apointech S.L. (SPAIN)
- ALTA Ricerca e Sviluppo in Biotecnologie Srlu (ITALY)

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