PANCREATIC CANCER RESEARCH IN EUROPE
Multistakeholder Brainstorming Meeting
Brussels, Wednesday12 April 2017

REPORT

Participants to the meeting are listed in the Annex.

Pancreatic Cancer at a Glance

- Pancreatic cancer (PC) is the deadliest cancer worldwide with an overall 5-year survival rate of approximately 7%.

- In a 10 years' perspective PC will rank second in cancer-related mortality.

- It has been estimated that there will be more deaths from pancreatic cancer than breast cancer in the EU by 2017.

- PC suffers from lack of profile. The degree of unawareness in the society is relatively high: 70% of UK population cannot identify where the pancreas is

- PC is a heterogeneous molecular tumour*stroma entity.

- PC aetiology is complex and very little can be done to decrease the risk of getting this cancer due to the limited knowledge on its risk factors.

- Precursor lesions are not well-characterized.

- Early-stage PC is a silent disease: non-specific symptoms hinder its diagnosis at an early stage of the disease, and for most patients, it is too late for an action with curative intent when PC is diagnosed.

- There is a lack of early-diagnosis biomarkers/imaging tests.

- Early-stage PC diagnosis is still difficult with a too high grade of uncertainty.

- Only a small proportion (15-20%) of patients benefit of radical resection. Half of them having already metastatic disease.

- PC is chemotherapy resistant. No medical treatment exists to cure the disease.

- There are inequalities in access to treatment and clinical trials exist all over Europe.

- Survival is too short: 6-month mean survival and <7% of 5-year survivors.

- Because there are only a limited proportion of survivors, there is no social pressure to control PC. Therefore, PC could be considered an orphan disease.

Challenges in Pancreatic Cancer Research

- The lack of social, medical, and politics awareness of PC leads to poor support of PC research.

- PC small incidence and limited prevalence explains that most studies are underpowered.

- Difficulties in PC diagnosis carries misclassification of the phenotype in the studies.

- Direct data collection from patients is arduous because PC patients are too sick.

- Because only a small proportion of PC patients undergo surgery, there is a shortage of PC tumour and normal tissue samples. In addition, these may be inappropriate due to PC tissue characteristics.

- There is a deficit of PC *omics* data generation following the shortage of samples.

-There is a strong need to integrate combinatorial, genetic, stromal and immunological markers and to link them to clinical and precision research in PC.

-It is essential to convince pharmaceutic companies to develop newly designed research in PC for rapid evaluation of innovative drugs.

- The still poor data sharing culture in the scientific community impacts on PC research.

- There is inadequate investment in well annotated biobanks.

- There is an important shortfall in PC funding both by public and private initiatives in EU.

- There are no targeted EU policies on pancreatic cancer

A global scale analysis of PC research unmet needs to assess the actions needed to be done in Europe was undertaken during the EUPancreas-PCE Multistakeholder Brainstorming Meeting.

The **objectives** of the meeting were to:

1. Identify, debate, select and prioritize the main aspects to address in pancreatic cancer (PC) research in Europe in accordance with the international scenario.
2. Lobby to increase awareness on PC research needs and funding in Europe.
3. Report the conclusions of the meeting with a prioritized list of PC research areas and actions and distribute the report to the European Commission, National Research Programmes and Scientific Societies.

To facilitate the **debate** and identify the gaps in pancreatic cancer research in Europe, the discussion was structured in 4 blocks each one corresponding to primary, secondary, tertiary pancreatic cancer prevention, and actions to conduct, respectively (See the Annex). Each block was introduced by the discussion conductor and a list of topics to address in pancreatic cancer research was presented to the participants who were asked to prioritize them, first by voting the most important during the meeting and, after the meeting they were asked to rank the priority of each area of research from 0 to 5 and deliver tier punctuations to the meeting organizers. Below please find the results of this effort.

Block 1. Defining a pancreatic cancer high-risk population for primary and secondary (screening) prevention

Some of the current challenges in PC prevention regards the identification of a high-risk population to whom prevention could be targeted in a more efficient way. Few risk factors of the disease have been identified but their association with PC risk is modest, making it difficult to identify a high-risk group of the disease. There is, therefore, a need to integrate *omics* with non-*omics* factors in PC risk scores. Family history is, so far, the only factor that determines a group at high risk of developing PC; however, screening programs have not proved to be successful. All attendees perceived that research should also focus on the 90% sporadic PC, while also considering Familial Pancreatic Cancer FPC/HPC (10%). The further characterisation of precursor lesions (cystic tumours) on the basis of available guidelines and new imaging data, as well as patient's characteristics, is an area of increasing interest. These lesions are regarded as precancerous or premalignant, but little is known regarding their molecular, pathological and clinical features, their malignancy risk, as well as regarding their optimal management towards PC prevention. The study of new-onset diabetes as a PC risk group was also

emphasized with the possibility to join efforts between EU and US in establishing prospective cohorts. It would be premature to apply Artificial Intelligence to build risk prediction algorithms though state-of-the-art biotech platforms and bioinformatics/biostatistics approaches are needed.

Prioritized Topic: Diagnosing and accurately classifying precursor lesions (cystic tumours, IPMN, and PanINS) according to imaging (MRI) features and biomarkers.

Block 2. Identifying and validating markers/tests for early diagnosis

Early detection is the key issue for improving the prognosis of PC. The time from the initiating mutation in the pancreas to development of metastatic PC takes several years and this provides a window for early detection of PC. It is challenging to identify potential new biomarkers. While devoting efforts to this endeavour, it is important to further characterize the potential markers that have already been identified. There have been some promising achievements in early diagnosis of PC based on genomic and metabolomics results, but larger scale and rigorous validation is required before their application in the clinic. In addition, more effective and specific biomarkers of PC are urgently needed.

Prioritized Topic: Defining the real "window of opportunity" for PC screening.

Block 3. Searching for efficient treatments for PC

PC patients should be managed in reference centres that should be ranked according to a set of agreed criteria. The Netherlands provides an example of the efficient reduction on PC mortality after the government established the PC reference centre policy with at least 5 referral centres managing PC patients at present. A European network of PC reference centres may boost PC research by pooling resources towards the implementation of precision medicine in PC with cross-border and adequately designed clinical trials.

USA is leading the field of innovative drugs development and only a few international clinical trials on PC having been coordinated from Europe. USA, however, is investing not only for science but also in policy development, advocacy, training for healthcare professional and high risk population, all of them being crucial aspects in the field.

Besides chemotherapy, radiation therapy should be taken into account in combination with new immunotherapeutic drugs in both curative and advanced settings. It was raised the need to screen the molecular immunogenic profile of the patients at the baseline, before starting with the first therapeutic approach. Also, the importance of being flexible and dynamic in offering the patients with further drugs according to their disease evolution or response/resistance to therapy may justify the establishment of small but well-designed clinical trials. Inequalities of access of patients should also be tackled

Prioritized Topic: Identifying markers for response prediction towards PC "personalized treatment"

Block 4: Actions to be conducted/invested on PC research in Europe

A more holistic approach should be applied in PC research, translating *omics* techniques and *omics* data into prediction and early diagnosis of PC. More effective and specific biomarkers based on *omics* information, epidemiological and clinical data for patients with early-stage PC are critically needed to allow a timely and curative treatment of the disease. These approaches request a long-term investment in building research networks and large-scale multicentre studies, collecting comprehensive, detailed and accurate information and linking the information collected with biobanks and medical records. The need to facilitate the structures to conduct cross-border clinical trials under the umbrella of public-private partnerships was raised.

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Prioritized Topic: Establishing multistakeholder cooperative teams including multidisciplinary research and health professional teams, private sector representatives, patients, health economics professionals and policy makers.

Funding opportunities in PC Research

US Government defined PC as a "Recalcitrant Cancer" and approved "The Pancreatic Cancer Action Network" toward improving cancer survival, on the 113th Congress to give current and future PC patients a fighting chance by:

- Providing $5.26 billion for the National Cancer Institute for FY 2015;
- Continuing to include PC in the Department of Defence (DoD) Peer-Reviewed Cancer Research Program (PRCRP) and providing continued funding of at least $25 million for the program;
- Ensuring that the provisions of the Recalcitrant Caner Research Act are fully implemented
- Joining the Congressional Caucus on the Deadliest Cancers

Non-governmental initiatives in the US includes a recent call by AACR-Stand Up to Cancer- Lustgarten Foundation Pancreatic Cancer Interception Dream Team with a 7M US$ budged for one project.

In **EU**, applying for funding for PC research is nowadays a cumbersome and complicated procedure; there is a lack on dedicated calls for cancer search. Funding organizations belong mostly to the public sector in Europe, where the EC but also the national funding bodies are the main funding sources.

- FP6 and FP7 funded a few number of PC research projects compared to other cancer sites. EC prioritized funding cancer research based on high-incidence cancers rather than on their survival rates.
- H2020 has no cancer-specific funding topics, PC having to compete with a broad range of diseases.
- National funding agencies could represent an opportunity (e.g. France call on PC). There is a need to increase PC research needs awareness at the national level.
- Charities (e.g. Cancer Research UK) could play a pivotal role in funding PC research as well.

Funding opportunities in H2020 new calls- By Dominika Trzaska, Scientific Officer, EC.

Research is a long-term EU priority and investment, enabling the rise of personalized medicine. The rational of EC view is that research and investment is increasingly complex, interdisciplinary, and costly, requiring critical mass and collaboration. The EU programme for research and innovation for 2014-2020 has a capital budget of €79 billion. Horizon 2020 offers different programmes serving different communities and purposes.

Since 2007, the EC has dedicated around €2.1 billion to cancer research using a variety of funding mechanisms tailored to address the different needs, such as collaborative research, frontier research, public-private partnerships such as Innovative Medicine Initiative (IMI), coordination of national activities and international partnerships. The bulk of the efforts has been devoted to collaborative research with a total of €1.2 billion, of which €650 million in Horizon 2014-2016 (15% overall funds of health programme calls).

The challenge approach of Horizon 2020 fits the multidisciplinarity nature of cancer research. Within H2020, the budget is being allocated differently (as compared to FP7): collaborative research has witnessed a considerable reduction in funds at the expense of other research programs; for instance, €559 million represent investments from the ERC. Marie-Sklodowska Curie Actions (ITNs) received €276 million and were devoted to training the new generation of cancer scientists.

The work programme for 2018-2020 is currently under preparation with a budget of €1.8 billion and it will provide multiple opportunities to support cancer research. Headlines for 2018-2020 in the realm of health, demographic change and wellbeing challenge will address "better health and care, economic growth and sustainable health systems" i.e. personalised medicine. Big data will be among the priorities as well.

Recommendation by the European Commission representative:

- Consider looking at broader calls than just "cancer", for instance non-communicable disease topics.
- Ask for support from European Parliament: involve MEPs (for instance Members against Cancer MAC) who call for specific areas to be funded.
- Contact the National Contact Points for the definition of future topics within H2020 and the next framework.
- Consider contacting DG Santé (allocated funding: 6 million € 2014-2017) as they have some stakeholder consultations and might be more prone to evaluate "groups of diseases"
- Consider applying to ERC and Marie Curie actions, as well as COFUND, IMI, RISE, etc.
- Consider building public-private partnership consortium to apply to IMIs research calls
- Consider joining forces with other PC-related cancers/illnesses and teaming up with global partners (ICGC, NIH, etc.).

Requests addressed to the European Commission

The areas beyond financing, including PC, in which the EU should be looking at are:

- Engagement of Patient Organizations, increasing awareness of cancer patients towards new therapies and personalized medicine.
- Harmonization of laws and regulations that affect multinational trials in terms of the transport of tumour and biological samples.
- Establishment of networking among foundations and platforms to encourage cross-border collaboration.
- EU should take a leading role to help raise awareness about the importance of supporting PC research by setting up targeted policies, encouraging research to overcome unmet needs in PC, and dedicating funds for PC research.

Conclusions

On the basis of the gaps and challenges mentioned throughout the report, researchers and stakeholders attending the meeting suggest the following issues as recommendations for future European activity, at national and international level, on PC research:

- Prioritize research into diagnosis and accurately classifying precursor lesions (cystic tumours, IPMN, and PanINs) according to imaging (MRI) features and biomarkers
- Prioritize research to define the real "window of opportunity" for PC screening
- Prioritize research into identification markers for response prediction towards PC "personalized treatment".
- Prioritize the establishment of multistakeholder cooperative teams including multidisciplinary research and health professional teams, private sector representatives, patients, health economics professionals, and policy makers.

The discussant also considered important to break up silos and to foster collaborative cross-border research to avoid duplication of efforts towards a more efficient research.

This meeting also revealed the need for strengthening and implementing targeted research policies that enhance PC control efforts across the European Union. PC continues to be a leading cause of cancer-related death and, consequently, there is a need for increasing funding for PC research in an effort to contribute to an overall reduction of its incidence and mortality.

This demand requires of the political commitment both at the EC and the national levels and should be supported by a multinational and multistakeholder approach, including patient organizations. To this end, the European Union should prioritize targeted research on PC "all-level" prevention (primary, secondary and tertiary) and direct more efforts towards the establishment of networks or programs that encourage solid cross-border collaboration for PC research, promote public-private partnership favouring convergence of research interests, provide more funding opportunities for independent academic research and for translational research to place latest discoveries into health practice and PC control, and, last but not least, implement effective policies that promote behaviours that are conductive to disease prevention.

Actions to be taken

In the foreseeable future, it is crucial to:

- Engage EC and national policy makers at the high level as well as other key stakeholders, both public and private, to set up targeted PC research policies.
- Develop a Europe-wide strategic research plan (not only EC-based), with short (adapt research goals to current research calls), medium (lobby for PC research at the national level) and long-term targets (next EC framework) under the topic of "Short Survival Diseases". Contact the National Contact Points with this purpose.
- Disseminate the meeting´s report among relevant actors of scientific research and funding organizations, including the European Commission, National Research Programmes and Scientific Societies.
- Provide list of funding opportunities to the PC research community.
- Elaborate a list of potential "consultants" of PC research in Europe, covering from basic translational to clinical researchers, established funding bodies, patient advocacy groups and decision makers.

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ANNEX

Prioritized Research Topics

* In grey, key points taken by the U.S. Congress "Pancreatic Cancer Research and Education Act"

Block 1. Defining a pancreatic cancer high-risk population for primary and secondary (screening) prevention.

1. Diagnosing and accurately classifying precursor lesions (cystic tumours, IPMN, and PanINs) according to imaging (MRI) features and biomarkers.
2. Focusing on the 90% sporadic PC, while also considering FPC/HPC (10%).
3. Integrating established risk factors with biomarkers (omics) towards a "personalized prevention" of PC.
4. Understanding the biological relationship between diabetes mellitus and PC (US RCR Act 2014).
5. Exploring the role of microbiome in PC risk and prevention.

Block 2. Main topics to address in pancreatic cancer research: Identifying and validating markers/tests for early diagnosis.

1. Defining the real "window of opportunity" for PC screening.
2. Evaluating screening protocols for biomarkers for early detection of pancreatic cancer and its precursors (US RCR Act 2014).
3. Listing and prioritizing biomarkers, upon the availability of evidences, for their validation in well-characterized common resources (population, samples, data).
4. Understanding the catastrophic progression of PC.
5. Estimating cost/efficient screening interventions in high-risk populations.

Block 3. Main topics to address in pancreatic cancer research: Searching for efficient treatments for PC.

1. Identifying markers for response prediction towards PC "personalized treatment".
2. Exploring the effect of combinatorial therapeutic schemes in PC survival including radiotherapy, surgery, immunotherapy, and standard/new chemotherapy drugs.
3. Developing new treatment approaches that interfere with RAS-oncogene signalling pathway (US RCR Act 2014).
4. Identifying prognostic markers for PC.
5. Studying new therapeutic strategies in immunotherapy.
6. Exploring the role of cachexia and its metabolic pathways in PC progression and treatment opportunities.
7. Identifying synthetic lethality combinatorial approaches leading to PC extinction
8. Searching for second-line chemotherapy drugs for PC patient management.
9. Understanding the impact of aging and co-morbidity processes in PC progression and treatment opportunities.

Block 4. Actions to be conducted/invested on pancreatic cancer research in Europe

1. Establishing multistakeholder cooperative teams including multidisciplinary research and health professional teams, private sector representatives, patients, health economics professionals, and policy makers.
2. Promoting cooperative work through the collection of longitudinal data and sample collection (PancreOS + Biobank) linked to e-medical records.
3. Building large cohorts of high-risk populations (new-onset diabetes mellitus, PC precursors: IPMN and PanINs) with detailed information and annotated biobank.
4. Facilitate the structures to conduct cross-border clinical trials under the umbrella of public-private partnerships.
5. Conducting EU large (huge) standardized (ongoing) epidemiological studies linked to clinical annotated biobanks. Apply novel "smart" technologies to characterize exposures.
6. Networking with already established registries of Familial/Hereditary Pancreas Cancer linked to family-based biobanks.
7. Supporting long-term investment.
8. Standardizing omics data generation and next-generation database platforms. Developing algorithms allowing omics and non-omics data integration.
9. Building large well annotated (clinical-pathological-follow up) biobank network applying the same procedures (SOP)
10. Strengthening the application of a "systems thinking" approach.

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