Individualized PaediatricCure

TUMOUR TYPE WORKING GROUPS

The iPC project focuses mainly on five different types of childhood cancer: Hepatoblastoma, Medulloblastoma, Neuroblastoma, Ewing Sarcoma and Leukaemia. The leaders of the working groups are our partners Germans Trias i Pujol Research Institute (IGTP), Deutsches Kinderkrebsforschungszentrum Heidelberg (DKFZ), Prinses Maxima Centrum voor Kinderoncologie (PMC), Institut Curie (CURIE), Universität Zürich (UZH) and Max-Planck-Gesellschaft zur Förderung der Wissenschaften (MPG). The relevance of the tumour types and what the different tumour type working groups are working on is described in more detail below.

Hepatoblastoma and hepatocellular carcinoma are the main liver cancers in childhood with a rising incidence. To date, there is no cure for aggressive tumours, usually resistant to chemotherapeutic drugs. Moreover, survivors can suffer severe lifelong adverse effects due to high doses of chemotherapy in these young patients. Although it is well-known that therapy response in oncology is associated with cancer biology, no molecular data is currently being used to guide the treatment of these patients. Therefore, during iPC, we set-up three different platforms (data, patient and in vitro pre-clinical) to be used to build a comprehensive and large omic dataset of childhood liver cancer, generate new knowledge to understand its cancer biology and identify biomarkers as well as new therapeutic targets/drugs for aggressive tumours with the final aim to provide the basis for a precision medicine in this rare disease (1.5 anual cases per 1 million).

Medulloblastoma (MB) is the most common embryonal tumour of the central nervous system. The current consensus recognizes four main molecular groups and each group shows distinct patient- related characteristics, genetic alterations, dysregulated signalling pathways and a differing clinical outcome. Current intensive, often curative therapies for medulloblastoma on the other hand impose debilitating effects on the developing child, and highlight the need for mechanism-of-action based treatments with reduced toxicity. Further, generating PDX models for some of other MB groups has been a challenge. The focus for the computational partners should therefore be ideally on these groups and much but not all of the molecular (sequencing) data is already collected and harmonised from our partners Barcelona Supercomputing Center (BSC) and Academisch Medisch Centrum bij de Universiteit van Amsterdam. The working group leader DKFZ will facilitate further data access by coordinating with BSC and the Cavatica team.

Neuroblastoma originate in the sympathetic nervous system and can present in very different ways. In a small subgroup of patients, the metastasised tumours may even disappear without treatment. However, the majority of neuroblastoma are occurring in slightly older children and have a very poor prognosis with still 40-50 % of mortality in high-risk disease. In the iPC consortium lead by PMC this tumour type is studied extensively in a collaborative effort by several groups. In a dream challenge organized within the iPC neuroblastoma compound screening data and DNA (Deoxyribonucleic acid) and RNA (ribonucleic acid) profiling of neuroblastoma organoids is currently being studied to define relations between DNA/RNA aberrations and compound efficacy.

Ewing Sarcoma is a rare type of cancer that occurs in bones or in the soft tissue around the bones. The core partner of the Ewing sarcoma working group in iPC is CURIE, with two subpartners working on this cancer type with more focus on the cancer biology and data generation and with focus on computational systems biology. The first field of transcriptomic single cell data sets for Ewing sarcomas was generated and on this basis, an analysis of the causes of epigenetic intratumoral heterogeneity in Ewing sarcomas was characterised. CURIE used a collection of publicly available multiomics molecular profiles from Ewing sarcoma inside large scale meta-analyses based on application of machine learning methods and network-based methods, which allows to distinguish tumour type-specific molecular mechanisms from common to many paediatric cancer types.

Leukaemia: Hematological malignancies figure amongst the most frequent types of childhood cancers. Within iPC the working groups focus on both the lymphoid and myeloid lineage of acute leukemias, namely acute lymphoblastic leukemia (ALL) and acute myeloid leukaemia (AML). IBM Research GmbH and UZH are working on automated processing of flow cytometry data of paediatric ALL patients. The lead of this working group UZH has collected a dataset of 3125 flow cytometry files with associated clinical parameters, whereupon IBM is developing a machine learning model to classify the immune cell repertoire. Frequency of marker expression is being correlated to risk stratification and clinical response. A single-cell atlas of multiple distinct AML blasts and the non-malignant immune compartment has also been generated and is currently being analysed using clustering and trajectory inference.

SHORT PROJECT INFO

Cancer is a very heterogeneous disease that arises in patients with a great variety of genomes, epigenomes and clinical history, and especially the treatment of paediatric cancers presents particular challenges that differ from the treatment of adult cancers. Therefore, the iPC aims to integrate high quality data sources and their analyses using knowledge-based and artificial intelligence models to increase the performance of individual datasets and improve therapeutic decision-making in paediatric cancers. The project's approach is based on the development of virtual patient models, i.e. in-silico avatars that resemble the molecular and clinical landscape of the paediatric patient and can be used for computer-assisted personalised diagnosis and treatment recommendations. iPC will therefore develop a computer-based platform that will also allow caregivers to interrogate the models to deduce the pros and cons of specific treatment combinations for each child. More information about iPC and its vision, motivation and objectives can be found on the project website.

GOOD TO KNOW: A virtual patient is the virtual analogue of a real patient and is based on a complex computer model. These virtual patients help predict drug response and related information, including possible side effects for each treatment of a given patient.

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Technical Lead

María Rodríguez- Martínez

IBM Research – Zurich
MRM@zurich.ibm.com

Scientific Lead

Hans Lehrach

Max-Planck-Institute for Molecular Genetics
lehrach@molgen.mpg.de

Project Coordinator

Klaus-Michael Koch

Technikon Forschungs- und Planungsgesellschaft mbH
coordination@ipc-project.eu

Budget

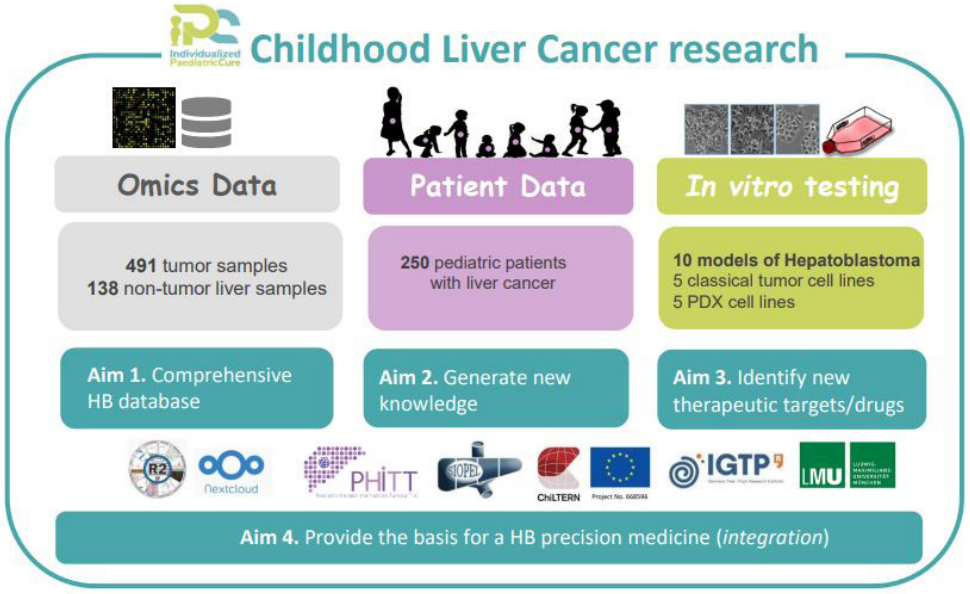
€ 15.1 Million
14.7 Million EU-funded

Consortium

21 Partners
3 Continents

Duration

53 Months
01/2019 - 05/2023



Partners

1. Technikon Forschungs- und Planungsgesellschaft mbH
Austria [Villach]

2. IBM Research GmbH
Switzerland [Rueschlikon]

3. MPIMG
Max-Planck-Gesellschaft zur Förderung der Wissenschaft EV
Germany [Berlin]

4. Institut Curie
France [Paris]

5. Technische Universität Darmstadt
Germany [Darmstadt]

6. Universita degli Studi di Napoli Federico II
Italy [Naples]

7. Universiteit Gent
Belgium [Ghent]

8. Germans Trias i Pujol Research Institute (IGTP)
Spain [Barcelona]

9. Barcelona Supercomputing Center
Spain [Barcelona]

10. XLAB
Slovenia [Ljubljana]

11. Deutsches Krebsforschungszentrum Heidelberg
Germany [Heidelberg]

12. Academisch Medisch Centrum bij de Universiteit van Amsterdam
The Netherlands [Amsterdam]

13. Prinses Maxima Centrum voor Kinderoncologie
The Netherlands [Utrecht]

14. Universitätsklinikum Heidelberg
Germany [Heidelberg]

15. Alacris Theranostics GmbH
Germany [Berlin]

16. Universität Zürich
Switzerland [Zurich]

17. Ludwig-Maximilians-Universität München
Germany [Munich]

18. Consiglio nazionale delle ricerche
Italy [Rome]

19. Baylor College of Medicine
USA [Houston, Texas]

20. The Children´s Hospital of Philadelphia
USA [Philadelphia, Pennsylvania]

21. Children´s Medical Research Institute
Australia [Westmead, NSW]

21. Charité – Universitätsmedizin
Germany [Berlin]

More information about the consortium can be found on the project website.

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