PrECISE

Personalized Engine for Cancer Integrative Study and Evaluation

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PrECISE

Mission of PrECISE:

PrECISE aims to improve patient risk-stratification and treatment in prostate cancer by developing new computational approaches to exploit next generation molecular data. The expected outcome is the development of a predictive computational technology that can exploit molecular and clinical data to improve the understanding of disease mechanism and to inform clinicians about optimized treatment strategies.

Motivation:

Despite of their great promise, high-throughput technologies in cancer research have often failed to translate to major therapeutic advances in the clinic. One challenge has been tumour heterogeneity, where multiple competing subclones coexist within a single tumour. Genomic heterogeneity renders it difficult to identify all driving molecular alterations, and thus results in therapies that only target subsets of aggressive tumour cells. Another challenge lies in the integration of multiple types of molecular data into mathematical disease models that can make actionable clinical statements. PrECISE aims to develop predictive computational technology that can exploit molecular and clinical data to improve our understanding of disease mechanisms and to inform clinicians about optimized strategies for therapeutic intervention. We will focus on two urgent clinical needs in prostate cancer:

- distinguishing the many indolent tumours from the minority of lethal ones, and
- providing rationally chosen treatment options for patients with advanced disease.

Concept:

Recent studies have demonstrated the presence of clonal diversity in prostate cancer and highlighted the difficulties in designing diagnostic and therapeutic strategies based on morphological evaluation and single-sample biopsies. We propose an in-depth characterization of the tumour clonal architecture through deep-sequencing the state-of-the-art- quantitative proteomics. We will develop mathematical models to gain a mechanistic understanding of clone-specific lesions and predict personalized drug therapies based on individual molecular profiles.

Objectives:

The PrECISE project is a pilot project that combines hypothesis-driven strategies with data-driven analysis in a novel mathematical and computational methodology for the integration of genomic, epigenetic, transcriptomic, proteomic, and clinical data with the goal of risk-stratifying patients and suggesting personalized therapeutic interventions. We have the following specific objectives:

Development of a comprehensive computational methodology:
to integrate publicly available multi-omics datasets, well-characterized multiple-biopsies cohorts, and literature-driven knowledge powered by the Watson cognitive computer, developed at IBM.

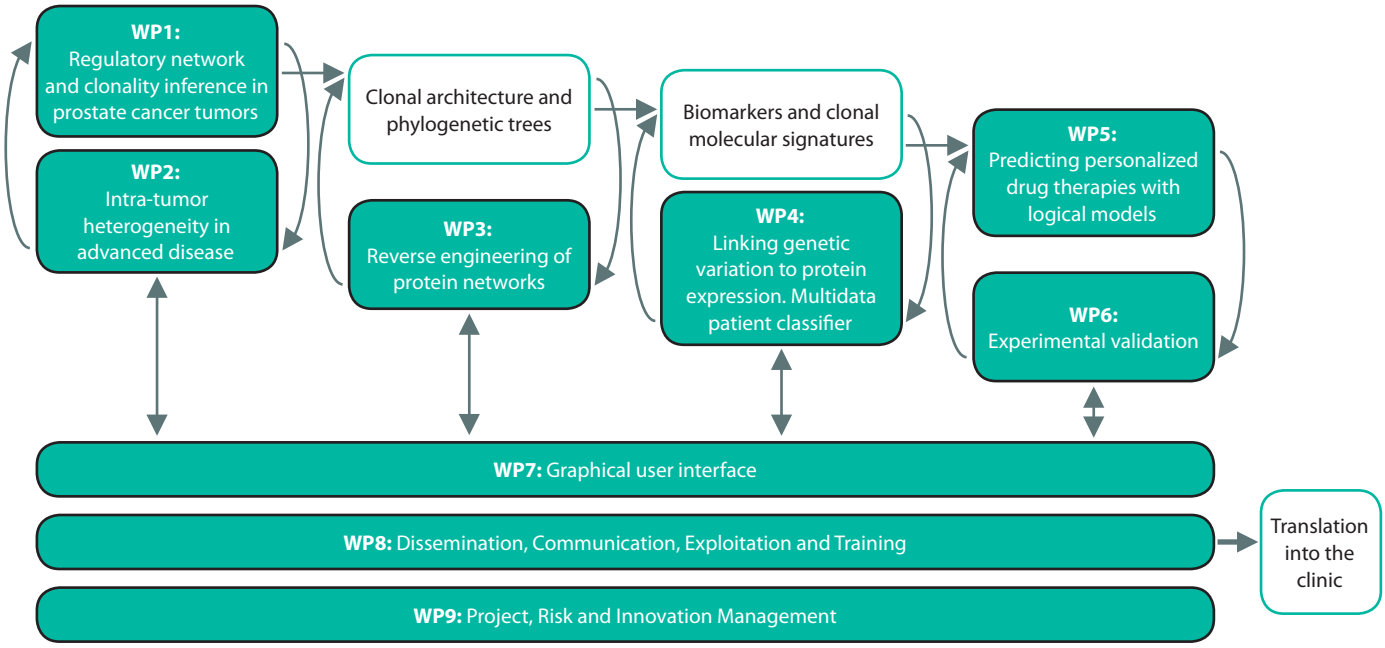
Characterization of intra-tumour heterogeneity:
We will apply PrECISE to prostate cancer molecular cohorts where multiple biopsies have been generated from each patient.

Suggestion of chemotherapy drugs and targeted therapies for each patient:
We will investigate molecular mechanisms, identify suitable intervention points for therapy and suggest personalized therapies based on patient's clonal signatures, and we will validate our predictions in a panel of prostatic cell lines.

Development of PrECISE into deployable, easy to use software tool:
We will integrate the developed computational modules with the Watson cognitive technology developed at IBM in a user-friendly interface and make PrECISE accessible to the clinical research community.

PrECISE

PrECISE structure and work packages



Technical Approach:

The PrECISE project is planned to run for 36 months. It is organized into nine work packages with significant dependencies and expected synergies between them which are described shortly in the following.

WP1: Regulatory network and clonality inference in prostate cancer tumours

WP1 provides the basis for clone identification and associated biomarkers. Therefore, regulatory networks and clonality analyses of proCOC tumour biopsies as well as public prostate genomic profiles are used.

WP2: Identification of sub-clonal genomic alterations

This WP identifies sub-clonal genomic alterations and describes intra-tumour heterogeneity in prostate cancer through protein profiling and ultra-deep sequencing in the proCOC samples and additional selected CRPC biopsies.

WP3: Reconstruction of protein interaction networks from high-dimensional proteomic maps and IBM – Watson technology

WP3 provides data-driven context-specific interaction networks out of the SWATH mass spectrometry for the proCOC samples, prostatic cell lines and public proteomic data. Another focus will be on network reconstruction algorithms that incorporate automatic text-mining capabilities through the Watson cognitive computer.

WP4: Linking genetic variation to protein expression

WP4 aims at incorporating genomic, transcriptomic and proteomic maps into a comprehensive molecular map, which is then utilized to detect clusters of proteins enriched in genomic alterations. It shall also identify key pathways and molecular mechanisms that underlie cancer progression specific clones and it shall help to develop a multi-data patient classifier to group patients in clinically meaningful groups.

WP5: Logic models of prostate cancer patients: predicting personalized drug therapies

The objective of WP5 is to develop a mathematical model that includes the key molecular players identified in upstream WPs and that can provide a qualitative understanding of cancer underlying molecular mechanisms.

WP6: Experimental validation of prognostic biomarkers and targeted drug predictions

WP6 is a validation WP that creates quantitative proteomic and genomic datasets from selected samples. These new data will be used to validate inferred biomarkers and dysregulated pathways.

WP7: Graphical user interface

This WP provides an interface for analyses and prognostic inference from molecular profiles. A dashboard is established that contains all project data in order to select, control, execute or display the analyses.

WP8: Dissemination, Communication, Exploitation and Training

WP8 focuses on communication and dissemination of scientific research results achieved within the individual WPs to outside parties as well as to participating entities. Furthermore, this WP will support the partners to exploit the achieved results and impact the European as well as the international market. Moreover, WP8 results will lead to contributions in terms of trainings.

WP9: Project, Risk and Innovation Management

Finally, WP9 ensures a successful project lifetime with respect to risk and innovation management. There are dependencies to all other work packages as this WP coordinates the tasks so that they are in line with the project work plan in order to reach the objectives of PrECISE.

PrECISE

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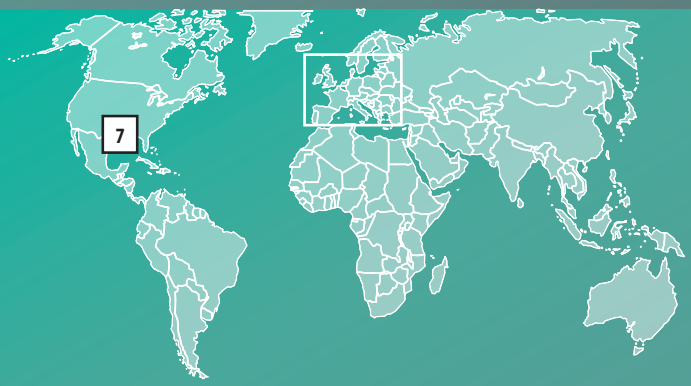

Project Partners:

1 **Technikon Forschungs- und Planungsgesellschaft mbH, Austria [Villach]**

2 **IBM Research GmbH, Switzerland [Zürich]**

3 **Technische Universität Darmstadt, Germany [Darmstadt]**

4 **RWTH Aachen University Hospital Germany, [Achen]**

5 **Eidgenössische Technische Hochschule Zürich, Switzerland [Zürich]**

6 **Universitaet Zuerich, Switzerland [Zürich]**

7 **Baylor College of Medicine Corporation – BCM, USA [Houston, Texas]**

8 **Institut Curie, France [Paris]**

9 **Astridbio Technologies KFT, Hungary [Budapest]**

Consortium:

The PrECISE consortium is well-positioned to achieve its objectives by bringing together a team of two research institutes, two research oriented SME´s, four universities and one leading industrial company from six different countries to form a complete chain stretching from basic research and service design, via applied research, up to end-user oriented service providers.