Flagship Project – Competence Center for Personalized Medicine

The Intra-Tumor Heterogeneity Census Project — Decoding Mechanisms of Intratumor Heterogeneity for Precision Medicine

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**Background and challenges:** Many, if not all tumors share the characteristic of being phenotypically heterogeneous as manifested by the existence of genomically distinct subclones within a tumor that feature diverse malignant properties. Intratumor heterogeneity is now recognized as being responsible for the development of aggressive and metastatic disease, polygenetic therapy resistance and poor overall survival. Clonal intratumor heterogeneity poses not only a major therapeutic challenge but also confounds the development of companion diagnostics and implementation of clinically qualified biomarkers.

**Project goals:** The Intra-Tumor Heterogeneity Census Project will tackle the enormous challenge posed by intratumor heterogeneity through establishing an experimental/technological framework aimed at (i) assessing quantitatively the genetic, epigenetic and cellular diversity of primary and drug resistant tumors, (ii) defining the molecular processes underlying clonal intratumor heterogeneity and their dynamic evolution during therapy and resistance, (iii) exploring the signaling influence perpetrated by the tumor microenvironment on heterogeneity and (iv) validating tumor subclonal-specific molecular targets and biomarkers for their therapeutic, prognostic and predictive power in clinical studies. Initially, the project will focus on primary and therapy-resistant melanoma but will expand, in a subsequent phase, towards other cancers.

**Team and experimental/technological framework:** World-leading experts from the fields of clinical oncology, computational genomics, cancer cell biology and cell signaling will provide unique complementary expertise and apply advanced cell/tissue systems and technologies including single-cell/ultra-deep genomic sequencing, computational modeling, high-throughput screening, genome engineering, 3D tumor microtissues, mouse cancer models and clinical material.

**Output:** The anticipated output of this project will be validated, novel prognostic and predictive tools to assess risk of metastasis, treatment responses and early markers for therapy resistance and subpopulation specific molecular targets for therapeutic interventions. This knowledge will directly impact on clinical decision making and guide precision medicine.

**International impact and visibility:** The Intra-Tumor Heterogeneity Census Project complements ongoing global cancer genome sequencing projects with efforts on knowledge generation of the genomic and molecular mechanisms underlying intra-tumor heterogeneity and the clinical implications and the therapeutic challenges posed by diversity within tumors. The focus and integration of the project into a larger framework of interactions between clinicians, biomedical scientists and engineers, creates a project of international scale and visibility.