PRECISION MEDICINE IN TYPE 1 DIABETES: ACCURATE DIAGNOSIS, ENDOTYPES AND BIOMARKERS OF RESPONSE TO THERAPY, GEORGIA FOUSTERI

State-of-art and future development/perspectives of the research area at international level (max 2000 characters):

Successful treatment of type 1 diabetes (T1D) continues to be a major unmet clinical need accounting for a considerable portion of healthcare expenditure. Insulin replacement offers long-term relief of symptoms but doesn't cure the disease, making it increasingly clear that new approaches are required to halt its progression during its early stages or sustain beta cell replacement after disease onset. One of the barriers to successful treatment is the heterogeneity of the disease that includes different phenotypes (cluster of "visible" properties, for example, age, sex, race, disease onset, symptoms, C-peptide) and endotypes (compilation of disease mechanisms underlying disease expression). Delineating the precise genetic and molecular elements that discriminate T1D from other forms of diabetes and defining disease endotypes is the first step to precision medicine. What we envision is the development of T1D-specific diagnostic tests for accurate disease diagnosis, classification, and individualized targeted treatments.

Actual lines of research (as is) of the Diabetes Research Institute (max 2000 characters):

We propose lines of research that take into account a "holistic" approach to solving the conundrum of T1D diagnosis, prediction, and heterogeneity.
We propose longitudinal collection of clinical and biological data and a polyomics approach (big data) for their analysis. Phenotypic data (collected via an App by the clinician and/or the patient [TIME4CS]) together with biologic markers (reliably-measurable indicators in serum/plasma/blood, e.g. autoantibodies, complete blood count, micro RNA, and gene expression signature), and genotypic (HLA, SNP, next-generation sequencing of transcriptomic and genomic data) will be translated into pathway-specific diagnostic tests for T1D diagnosis, classification, and individualized targeted treatments (collaborative efforts between Drs. Piemonti, Lampasona, Carrera, Bosi, Petrelli). The successful implementation of precision medicine in T1D will require the adoption and development of computational approaches and tools (artificial intelligence systems) and real-time databases where clinical and molecular data will be managed (collaboration with Omics center). Further studies will include analyses on specific genes and mechanisms involved in isogenic systems (in collaboration with Piemonti, Sordi).

Strengths of the research area (as is) of the Diabetes Research Institute (max 2000 characters):

A revised diagnosis and "taxonomy" of T1D based on precision medicine and endotype profiling will stimulate targeted research for the identification of the therapeutic protocols and biomarkers that predict patient response to treatment. In addition, early endotyping in at-risk patients might provide more insight into disease mechanisms. Studies on the specific genes and mechanisms involved will provide potential new therapeutic targets. It is important to emphasize that there are many clinical studies planned and ongoing with biologicals that target single or multiple pathways (combination therapies) in individuals at different stages of the disease. Possible, additional ad-hoc analyses using the same principles could provide a wealth of data on disease profiles and response to therapy that will allow better patient stratification in future clinical trials.

Weaknesses of the research area (as is) of the Diabetes Research Institute (max 2000 characters):

Diagnosing different forms of T1D and developing treatment faces multiple challenges that need to be addressed. Currently, most of the endotype research is conducted in a discordant mode, by individual labs; however, this effort needs to be undertaken by joining forces and expertise between clinical and research centers at a national and international level. A huge amount of data will need to be rationally analyzed in-depth with cooperation between biologists, data scientists, computer engineers, and health professionals. The sustainability of an endotype is another major issue. Changes of an endotype may occur over time, depending on external, environmental, and psychological triggers that we still can't comprehend. Translational bioinformatics (deep learning and artificial intelligence) and the configuration of ad-hoc machine-learning algorithms will need to be developed and tested before being used as a guide for diagnostic and therapeutic decisions and that would require additional time.

Short-medium term OSR/UniSR goals (0-18 months): milestones and deliverables (max 1000 characters):

Development of App (questionnaire) for the collection of clinical and biological (historical) data from patients and clinical records. Integration of other info, for example, interactome (environment, other illnesses, family history, pollution). A questionnaire (especially to high-risk individuals) will be implemented to include longitudinal information and psychological influences. Generation of Open database. Development of tools for biological testing (isogenic systems) and data analysis and prediction (machine learning).
f2. i) Production of human and murine Treg avatars (with Magnani, Bonini, Gaipa, Brusko)
• HLA-A2-specific +/- CXCR5 CAR Tregs with the bidirectional LV system.
• Islet-specific TCR +/- CXCR5 Tregs with the bidirectional LV or RV system.
• CD19 and CD22 CAR Tregs using the SB transposon system.
ii) In vitro phenotypic and functional analysis of Tregs, optimization of transduction, and culture conditions.
iii) Testing of culture protocols (with Dr. P. Monti)
iii) Development of protocols for iPSC-derived Tregs (with Dr. Themeli)
iv) Testing of xeno Treg isolation, transduction, and culture protocols (with Piemonti, Citro).

Medium term OSR/UniSR goals (18-36 months): milestones and deliverables (max 1000 characters):

i) Automation of biological testing. ii) Collection of data and Open database curation. iii) Validation of artificial intelligence tools for data analysis. Iv) Elucidate the specific genes and mechanisms involved, providing potential new therapeutic targets.

Long term OSR/UniSR goals (36-60 months): milestones and deliverables (max 1000 characters):

Development of: i) accurate diagnostic model for T1D and other forms of diabetes, ii) development of a diagnostic model of T1D endotypes, iii) development of biomarker-based /model that predicts responders from non-responders to therapy, iv) development of a predictive model of T1D progression in at-risk individuals

(possibly apply from birth?), v) design of early, from-birth, interventions to halt T1D.
Possible commercialization and company spin-off.

Investments of the Diabetes Research Institute (e.g. personnel, space, technology) to achieve the short-medium-long term goals (max 2000 characters):

Successful implementation of aim 1 will require:
1. Launch of a special diabetes Program for accurate T1D diagnosis, prediction, and prognosis ("T1D bio-digital health program")
2. Crowdfunding initiative for sustained funding, access to funding opportunities by non-profit VC
3. Financial advisors, perhaps hiring project managers
4. Foster training and career development for young investigators
5. Hiring of molecular biology scientists, technicians, statisticians
6. Hiring of supportive/administrative personnel (secretary, reporting, IACUC, IRB protocol support, public engagement and communication, web page and social media curators, fundraising)
7. Space for lab and offices for scientists, bioinformaticians, and administrative personnel
8. Engagement of public and private healthcare systems along with the territory and, if possible, the entire country
9. Development of a free, friendly-to-use app for data collection
10. Design and development of affordable molecular diagnostic platforms (autoantibodies, genetic tests, serum metabolites, RNA signatures), perhaps with the assistance of industry experts-automation.
11. Generation of real-time open databases and hiring of curators
12. Bioinformaticians to develop a machine-learning algorithm
13. Development of facility for isogenic system testing (immunology and beta-cell)