PROJECT

Supervisor:	Prof. Patrizia Rovere Querini
Title:	Integrating Continuous Glucose Monitoring with Immune-Molecular Profiling for Risk Stratification in Pre-Symptomatic Type 1 Diabetes
Curriculum:	Clinical and Experimental Medicine
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/docenti/r/roverequerini-patrizia

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Clinical Type 1 Diabetes (T1D) is preceded by a pre-symptomatic phase characterized by the presence in the circulation of islet-specific autoantibodies, including anti-GAD, anti-insulin, anti-IA2 and anti-ZnT8. Positivity for ≥2 of these autoantibodies identifies pre-symptomatic T1D, staged as Stage 1 (normoglycemia), Stage 2 (dysglycemia), and eventually Stage 3 (symptomatic clinical diabetes). Staging is currently based on autoantibody status combined with glucose measurements, with oral glucose tolerance test (OGTT) as the gold standard. However, OGTT is cumbersome and poorly tolerated, especially in children. Continuous Glucose Monitoring (CGM), using wearable glucose sensors, has emerged as a less invasive and more acceptable alternative, capable of detecting early alterations in glucose homeostasis during daily life. Key studies showed that time spent above 140 mg/dl (>10% of 24 hours) predicts rapid progression to Stage 3, supporting CGM as a viable alternative to OGTT. In 2023, Italy became the first country to mandate national T1D screening in children aged 1–17 years, identifying an increasing number of individuals in the pre-symptomatic phase who require longitudinal monitoring, preferably by CGM according to expert recommendations. However, while autoantibodies define disease stage, their presence alone does not provide sufficient predictive accuracy to guide early immunomodulatory intervention. In parallel, multiple immune and molecular abnormalities have been implicated in T1D pathogenesis, including features of adaptive and innate immunity: autoantibody characteristics (type, number, titre, affinity); neutropenia and dysregulated NET formation; miRNA-mediated regulation of beta-cell survival; pro-inflammatory cytokine-driven beta-cell damage; and novel humoral responses to oxidatively post-translationally modified insulin (oxPTM-INS). Despite their biological relevance, these markers have not yet been integrated into predictive models of disease progression. Their

systematic characterization across early T1D stages, and integration with CGM-derived metrics, represents a major unmet need and an innovative opportunity to improve risk stratification.

Rationale and hypothesis

CGM captures beta-cell stress through glucose dynamics, but reflects only one dimension of a complex, multifactorial process. Immune dysregulation—both adaptive and innate—may independently contribute to disease progression and interact with early metabolic alterations. We hypothesize that integrating CGM-derived metrics with immunological and molecular markers will generate a composite predictive algorithm with superior accuracy in identifying progression to clinical T1D. Such an approach may enable risk stratification robust enough to support future precision monitoring and timely immunomodulatory intervention.

Objectives and specific aims

1. Investigate CGM profiles in pre-Stage 1, Stage 1 and Stage 2 children enrolled in the Italian national screening program, and evaluate CGM-derived metrics as predictors of progression over 3 years.

2. Characterize autoantibody patterns (number, titre, epitope specificity, affinity) using established expertise at San Raffaele.

3. Evaluate innate immune dysregulation, including circulating neutrophil counts and NET formation, across disease stages.

4. Profile circulating miRNAs as biomarkers of beta-cell identity, function and stress.

5. Measure anti-oxPTM-INS antibody levels and assess their association with CGM metrics and disease progression.

Expected outcomes

This project will: (1) validate CGM as a monitoring tool within the Italian national screening cohort; (2) define relationships between CGM-derived metrics and qualitative features of the autoantibody response; (3) provide the first integrated characterization of NETs, miRNA signatures and anti-oxPTM-INS autoimmunity in pre-symptomatic T1D; (4) generate a composite CGM–molecular predictive algorithm for stage progression; and (5) identify novel candidates for precision monitoring and early disease-modifying intervention in T1D.

Skills that the student should acquire (max. 600 characters including spaces):

- Clinical management of pre-symptomatic T1D within the national screening programme, including advanced interpretation of CGM-derived metrics and their integration with clinical and immunological data, as well as patient–family communication.

- Study management in a translational setting: protocol design oriented to biomarker discovery, patient recruitment, longitudinal follow-up, data integration and regulatory compliance.
- Biological sample collection, processing and biobank management within a multicentre network, with focus on high-quality datasets suitable for multi-layer biomarker analysis.
- Laboratory and analytical skills for biomarker characterization (autoantibodies, innate immunity markers, miRNAs), including basic data analysis and integration toward the development of predictive models.

References (max. 15)

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