IMMUNOMETABOLISM OF INSULIN RESISTANCE, ALESSANDRA PETRELLI

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

Few groups around the world focus on the immunology of insulin resistance (IR) in obesity/T2D. Frequently immunologists of T1D, experts of a specific immune cell subset, report findings on the role of that subset in the context of obesity and insulin resistance. Some examples are Agnès Lehuen for MAIT cells (https://www.institutcochin.fr/la-recherche/emd/equipe-lehuen) and Diane Mathis for Tregs.

The role of insulin resistance in T1D is often neglected as causative for the disease, as it is rather considered a consequence of hyperglycemia. Retrospective epidemiological studies have been conducted to assess whether IR associates with the development of symptomatic T1D with contradictory results. TrialNet investigators are definitely interested in the topic and are willing to jump on my current JDRF project.

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

JDRF-APF: to determine the presence and immunological mechanisms of IR in subjects at risk to develop T1D

GR-19: to test the hypothesis that IR has an autoimmune underlying mechanism by assessing T cell Ag-specificity/clonality in the visceral fat of T2D

PAD-project: to determine T1D-endotypes, including excess body weight/IR-associated endotypes

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

- novelty of the concept of IR as an autoimmune disease
- accessibility of biological material, such as VAT and PB, from obese patients, lean individuals, T1D transplanted patients; and PB from paediatric and adult T1D, pre-symptomatic T1D, healthy donors and patients with other autoimmune diseases.

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

- Highly risky project as IR is likely to be present in some T1D patients but not to contribute to disease pathogenesis. Furthermore, immune cells may only partially/weakly be involved in the development of IR in T2D as immunomodulators do not appear to have dramatic effects on T2D or weight loss.
-the collaboration with the Pediatric Unit is sustained by the presence of fundings coming from the PAD project (end date: Jan 2023). The collaboration with the bariatric surgery, which provided VAT samples from obese patients, lean subjects and T1D patients just stopped as Carlo Socci resigned. The collaboration with INNODIA was no longer resumed after march 2020.
-collaborations that should be implemented: 1. with clinicians to perform clinical trials on the effect of immunomodulatory drugs in T2D; 2. with pharmaceutical companies providing funding to perform basic research; 3. with anatomia patologica to access biopsies of insulin sensitive tissues of patients with and without IR/T2D; 4. with EU networks to catalyze European fundings.

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

M1. Determine if IR is involved in the pathogenesis of T1D
D1. assess the presence of IR in pre-symptomatic T1D
D2. assess the role of IR at the transition between stages
D3. assess whether IR is associated with the development of symptomatic T1D
D4. Assess whether excess body weight and IR are associated with a T1D-endotype

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

M1. Determine if IR has autoimmune underlying mechanisms
D1. study clonality of the TCR of VAT-infiltrating T cells
D2. study the interplay between adipocytes and VAT-derived T cells
D3. assess if and how VAT-T cells modulate IR

M2. Assess antigenicity of adipocytes in T2D
D1. Define the VAT-derived HLA Class I peptidome
D2. Explore identity and specificity of VAT-derived antigen-specific T cells.

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

M1. Build the Diabetes and Obesity research Program (DORP)
The project aims to generate new therapeutic options for obesity and diabetes through the collaboration of researchers, nutritionists, dieticians, surgeons, endocrinologists, psychologists, statisticians and bioinformaticians. The DORP will include clinical/surgical teams from GSD and will collaborate with EAT.

Specific aims are:
1. Study the role of the immune system in the development of obesity and diabetes

2. Study the relationship between intestinal microbiota, obesity and diabetes

3. Determine triggers of obesity and diabetes

4. Develop new therapeutic options to halt obesity and diabetes
D1. Set up clinical trials with immunomodulatory drugs in obese individuals with T2D undergoing bariatric surgery with the aim to prevent T2D relapse
D2. Study the effect of a psycho-alimentary and motor education model on IR
D3. Set up clinical trials in stage 1 T1D using diet and/or metformin to modulate IR

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

-research nurse available “24/7” for sample collection
-technician dedicated to sample processing, storage and database management
- an office for the PI (I really need it!)
-1 postdoc and 2 research fellows or PhD students to work on research projects
-one lab with 2 benches and a hood dedicated for sample processing and experiments
-stable collaboration with the clinic: 1 reference pediatrician and 1 adult endocrinologist dedicated to sample collection; collaboration with other hospitals of the GSD for the collection of biological material from patients undergoing bariatric surgery and at follow-up visits; collaboration with Ospedale Niguarda for the collection of VAT and PB from T1D patients undergoing pancreas transplantation and lean kidney donors