BIOMARKERS OF ORGAN SPECIFIC AUTOIMMUNITY FOR DISEASE PREDICTION AND MONITORING

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

Historically, our research activity is focused mostly on type 1 diabetes (T1D) autoimmunity. T1D is a predictable disease and immunological interventions have already proven that T1D can be delayed or transiently arrested if not outright prevented. Currently, autoantibody measurement and genotyping of susceptibility genes are used to screen for subjects at risk of T1D. Recently, novel technologies have led to improved T1D autoantibody immunoassays and to the establishment of T1D genetic risk scores, based on the genotyping of selected SNPs.
Current research/development goals include the further development of high throughput, low cost immunoassays and genotyping assays to make practical, financially sustainable and extremely accurate the screening programs for T1D of the general populations.
However, despite the identity of the major targets of the major T1D autoantibodies being known since decades, the causes, process and modulators of the development of T1D autoantibodies remain obscure. In fact, while autoantibodies are essentially a universal feature of bona fidae T1D, obvious differences exist across patients, pre-diabetic and at-risk subjects with regards to the timing of appearance of autoantibodies, the number of antigens targeted in each patient, and the level of the autoantibody response. Understanding which mechanisms gives rise to a given antibody "phenotype" might provide insight into the pathogenetic mechanism of T1D and in turn suggest actionably targets for therapeutic interventions.
Finally, all lessons learned in T1D can find a likely application in the study of other autoimmune diseases with which T1D can be associated with and/or partially shares genetic determinants, circulating biomarkers and immunological mechanisms.

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

The main activity of the Autoimmunity Biomarkers unit is focused on the development and validation of immunoassays for antibodies (mostly but not exclusively autoAbs). This involves the design and expression of modified recombinant antigens aimed at reducing unwanted aspecific binding of non-disease associated antibodies while preserving recognition by bona fidae autoantibody reactivities. All the implemented immunoassays have been used in trying to address questions pertaining the natural history of disease, the ability to predict future disease development and to stratify patients according to the phenotype of autoAbs profile.
A second activity includes the implementation of the measurement candidate biomarkers of pancreatic endocrine tissue damage on high sensitivity digital PCR platforms. These biomarkers consist of nucleic acids (microRNA and differentially methylated DNA) of beta cell origin released in the bloodstream.
A third activity is focused on the implementation of T1D genetic risk scores on medium to high throughput genotyping platforms.
A fourth activity currently on hold is the search for B lymphocytes specific for T1D autoantigens.

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

The autoimmunity biomarkers unit is a recognized world class laboratory in the field of T1D autoantibody measurement. We design, clone, mutagenize, and express recombinant protein antigens and use them to set-up state of the art liquid phase T1D immunoassays. Moreover, we transferred the acquired expertise to the measurement of other antibodies (e.g. viral antibodies in COVID-19) demonstrating our ability to rapidly and independently move from prototyping to medium throughput application of our novel immunoassays. Furthermore, our know-how regarding digital PCR platforms and circulating nucleic acid biomarkers is strong and has already found application in clinical trials.
The unit has also acquired a considerable expertise in the management and analysis of data based on the concept of "reproducible science". In fact, we have implemented analysis pipelines based on the R software for the all the data generated over the past four years both in house and externally (e.g. data from international standardization workshops for the T1D autoantibody measurement). This expertise is likely to become necessary in light of the current movement towards making mandatory the publication of the raw data and analysis pipelines underlying all papers.

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

Our activity in T1D immunoassays development is positioned in a niche of T1D research in which several major international groups and commercial players are now operating. Crowding for funding for assay development is likely to make more difficult to access the resources required to set-up and mature alternative assay format approaches that we would actually wish to explore to improve immunoassays.
A big "area of disappointment" regards the unresolved scientific issue of the "origin" of T1D (and other diseases') autoantibodies. Relevant expertise in some fields (e.g. B cell analysis and manipulation) is missing from our unit
Among our most relevant systemic weaknesses we count instead the access to relevant biological samples and the administrative management of ongoing research projects and grant applications.
Regarding biological samples, the development and implementation of T1D biomarkers assays requires access to samples from new onset T1D sera and pre-diabetic individuals. While collaborations with external institutions have provided a partial solution to this issue, we currently don't have a regular and "organic" access to this type of samples.
With regards to administrative issues, we suffer from a chronic inability to receive rapid and punctual support in the management of currently active grants and grant applications. A negotiation with external partners takes on average one year or more, deadlines for the financial reporting and administration of international grants are routinely missed. This has caused repeated delays in finalizing standard administrative procedures which are linked to basic but fundamental activities related to grant activation, subcontracts signatures and activation, financial reporting and allocation to international partners of budget resources.

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

1)LIPS immunoassays for the measurement of additional antigens (ongoing development for non T1D autoantibodies),
2)establishment of recombinant monoclonal antibody standards of the IgG and IgM class for classical T1D autoantibodies.
3)Application of circulating nucleic acid biomarkers to the study of "beta cell" damage in vitro and in vivo models
4)definition of a pilot screening algorithm for T1D risk based on genetic and autoantibody biomarkers
5)expression of multimeric fluorescently tagged autoantigens for flowcytometric or immunofluorescence detection of antigen specific B cells

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

1)Validation of in house selected genetic and autoAbs algorithm for T1D risk prediction in small-scale pilot screening programs based on family studies plus subjects from the general population
2)Validation of a circulating nucleic acid signature of beta cell damage in samples from T1D family studies
3)Pilot application of fluorescently tagged antigens to the detection of antigen specific B cells

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

1)selection of a high throughput platform for population based screened for T1D
2)study of the antibody immune response development using models reconstituting in vitro key players of the immune reaction: the pancreatic endocrine tissue and lymph nodes

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

1)Essentially, our business model has been “translational”, bringing the output of the development phase directly to fruition into medium/high throughput testing/screening program(s). Currently, while the demand to implement the “fruits” of our development phase is invariably rising, this model is under strain because of a lack of manpower, space, obsolescence of equipment and overall reduction of financial resources with a direct impact on our ability to further pursue innovation and development activity and then sustain a positive cycle of activity.
2)Regarding the goal of start to clarify the basis for the T1D b cell response this would require skills that our unit lacks although they might be partially available within the DRI or at DIBIT. However, one of the lessons learned over the last years is that a successful and coherent research program likely requires a single direct supervision. This might be more promising and potentially successful compared to fleeting collaborations based on ad hoc agreements between units already heavily stretched to pursue their own main research activities. This implicitly requires the recruitment of additional personnel possibly with relevant skills or to be instructed via stages in other labs.
3)“If the mountain will not come to Muhammad, then Muhammad must go to the mountain” The administrative model according to which the DRI devolves to OSR offices the management of grants and grant applications is dysfunctional. Could a single (person) channel of communication/interaction with administrative offices be identified? And facilitate this work? Can it be conceived that a single person could be selected in agreement with the grant office to be associated with the management of DRI administrative issues? Alternatively, could a financial/administrative (ok centrally supervised by someone outside the DRI) activity be performed by DRI paid personnel?