FID-INNODIA CLINICAL RESEARCH CENTER FOR TYPE 1 DIABETES PREVENTION AT THE SAN RAFFAELE UNIVERSITY HOSPITAL, MILAN. AUTHORS EMANUELE BOSI, SABINA MARTINENGHI, RICCARDO BONFANTI, PAULINE GROGAN, ELEONORA BIANCONI

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

Prevention of type 1 diabetes (T1D) is a major goal of contemporary biomedical research. The riskof developing symptomatic T1D in unaffected individuals can be assessed using a number of biomarkers, where islet autoantibodies hold the highest predictive value. Nearly all patients are
positive for one or more autoantibodies at the time of T1D diagnosis, being these detectable well before the onset of symptomatic disease. Accumulated evidence indicate that positivity for two or more autoantibodies in asymptomatic people predicts at nearly 100% future T1D. Therefore, autoantibody screening represents the most powerful tool for risk assessment and staging T1D prior to symptomatic disease and provides the opportunity to intervene to delay and ultimately prevent the onset of clinical symptoms.
At San Raffaele, a site denominated JDRF-TrialNet International Clinical Center was established in 2004 and has been operating until mid 2020, with the uninterrupted support through capitated reimbursement form TrialNet (NIH) and dedicated grants from JDRF. In early 2020, substantial US Government budget cuts to NIH and a financial crisis of JDRF following Covid pandemic, have resulted in the discontinuation of the financial support to the JDRF-TrialNet Center at San Raffaele. In the meanwhile, the San Raffaele research group entered INNODIA, a European Consortium with activities similar to those of TrialNet, funded by the EU and other European partners, with the same mission of contributing to the understanding of pathogenesis of T1D, creening for at risk individuals, conduct clinical trials to prevent or delay clinical T1D. In early 2021, Fondazione Italiana Diabete (FID) took the place of JDRF as funding agency with a dedicated grant supporting the Center, which was renamed as FID-INNODIA. The main activity is screening for autoantibodies
in order to identify individuals at risk for T1D, eligible for intervention trials aimed at preventing their progression to clinical diabetes.

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

The FID-INNODIA San Raffaele Center, maintaining the status of TrialNet International collaborating Center (meaning the maintained possibility of participating to TrialNet trials), is pursuing its mission along three lines:

Screening.
a. Currently, screening is conducted in 1st and 2nd degree relatives in the INNODIA screening program, in continuity with TrialNet TN01 Pathway to Prevention. In 2021, 301 relatives have been screened for islet autoantibodies.
b. The FID-INNODIA Center is considering projects to conduct autoantibody screening campaigns for T1D in the general population. The rational has recently been reinforced by the demonstration of prevention of diabetic keto acidosis (DKA) as modality of T1D clinical presentation in individuals previously identified as at risk, with subsequent clinical improvement. This evidence supports screening in the general population as an ethical and cost-effective procedure within public health programs.

Clinical trials.
Secondary prevention (i.e. in at risk asymptomatic people).
- TrialNet TN22. Hydroxychloroquine in relatives with two or more autoantibodies (nearly 100% T1D risk). Trial currently re-approved by AIFA and the San Raffaele Ethics Committee. Tertiary prevention (i.e. preservation of β-cell function in new onset T1D)
- INNODIA Impact (Co-sponsor Imcyse). S.q. IMCY-0098 protein (Imotope). Ongoing, 16 patients screened, 7 randomized
- INNODIA Ver-A-T1D. Oral Verapamil, calcium channel blocker. Trial approved.
- INNODIA Iscalimab (Co-sponsor Novartis). I.v. and then s.q. CFZ533 monoclonal antibody anti-CD40: ongoing, one patient screened.
- INNODIA MELD-ATG. I.v. Anti-Thymocyte Globulin (ATG). Trial approved.
3) Ancillary studies.
The unique biological material obtained during screening activity is precious for studies on pathogenesis of T1D. As in the past, the FID-INNODIA Center is willing to provide useful material to interested scientists also outside INNODIA, first within DRI and San Raffaele

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

The type 1 diabetes research group at San Raffaele is known within the scientific community as a reference in the field of pathogenesis, prediction and prevention. Many scientists in the group gained international reputation, in the past (Ezio Bonifacio, Manuela Battaglia) as well as in the present (Emanuele Bosi, Vito Lampasona, Lorenzo Piemonti). The screening activity within families has been uninterrupted since 1990s, initially in the San Raffaele Family Study, then within TrialNet and currently in INNODIA. Numerous clinical trials on T1D prevention have been conducted over the years, with TrialNet (Mycophenolate Mofetil and Daclizumab, Oral Insulin, Abatacept, Hydroxychloroquine), pharmaceutical sponsors (anti-CD3 Otelixizumab, Albiglutide, Ladaraxin), academically (MITO) and with INNODIA (Imotopes, Iscalimab anti-CD40, Verapamil, ATG). The FID-INNODIA Center pools high expertise in the clinical, regulatory and administrative conduction of trials in T1D. The clinical connections with adult and pediatric diabetes clinics of San Raffaele Hospital warrant a large access to patients and families, with remarkable figures (e.g. more than 130 new onset T1D cases in 2021) and advanced expertise in the use of T1D applied technologies. The FID-INNODIA Center takes also advantage by the scientific environment of the DRI, and the whole San Raffaele, incorporating top levels scientific know how in the neighboring fields of immunology and autoimmunity, molecular and cell biology, islet and cell transplantation, stem cell research and therapy.
A further strength of the FID-INNODIA Center is the support by the communication activity of FID.
All the dissemination, education and promotion activities, especially through the social media, carried out by FID with the objective of strengthening the knowledge and sensitization towards T1D, ultimately enhance the overall recruitment capability of the FID-INNODIA Center.

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

A weak aspect of FID-INNODIA is the difficult interaction with clinicians (both adult and pediatric diabetologists) due to lack of physical contiguity and dispersion through the San Raffaele of the different clinical units (outpatient adult and pediatric diabetes clinics, inpatient diabetes units, Day Hospital, laboratories, offices) and lack of full

time committed physicians. The interaction with the research laboratories is also difficult, due to physical distance, lack of shared protocols and meeting opportunities. In particular, a re-establishment of a close collaboration with the autoantibody research laboratory led by dr. Vito Lampasona would be advisable. Finally, there is a general lack of assistance by the San Raffaele Institution in trial administrative follow up and management of regulatory affairs.

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

Completion of the approved and ongoing clinical trials (TN22, Impact, Ver-A-T1D, Iscalimab and MELD-ATG). Implementation of any other trial proposed through INNODIA, TrialNet and others, considered interesting and compatible with the FID-INNODIA conduction abilities. Expansion of screening activities in relatives, with the involvement of centers around Italy using the established procedures for remote screening. Connections and collaboration will be facilitated by FID through interactions with local patient associations, families, doctors and other health care providers. Start and conduction of screening campaigns in the general population. Although a general planning is to be completed, some pilot trials are already at an advanced stage of definition.

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

The same goals of 0-18 months.
In addition, a major focus will be on the implementation of large screening programs for the identification of people at risk to T1D in the general population, particularly children and adolescents. Opportunities will probably come from INNODIA or other international consortia; however, efforts will be also made to develop campaigns in Italy. The model to follow is the Fr1da
study currently ongoing in Germany, using local blood capillary sampling and central laboratory measurement of islet autoantibodies for risk assessment.

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

Not reported

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

None in the short term.
Not applicable at present in the medium-long term, depending on future relationships between FID-INNODIA center and the DRI