DIABETES IN CHILDHOOD. BONFANTI R, FRONTINO G, RIGAMONTI A, DITONNO R, CASTORANI V, MOROTTI E, SANDULLO F, SCIALABBA F, DIONISI B, ARRIGONI F, FOGLINO R

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

The PEdiatric DIAbetes Unit (PEDIA) is a clinical research unit of the DRI with pediatric expertise. At least 50% of all patients with type 1 diabetes (T1D) are of pediatric age (18 years), and the number of new cases with (T1D) among European children younger than 5 years of age has been predicted to double between 2005 and 2020. Furthermore, about 1–6% of pediatric diabetes cases are monogenic (MD).
PEDIA focuses on translational research including: 1) collaborative efforts with other DRI Units involved in research on T1D, T2D and MD; 2) biobanking of patient samples (to assess beneficial effects of therapies, investigate biomarkers (disease onset, progression and complications), and appropriately stratify with the aim of personalized management) 3) improving diabetes outcomes by also translating clinical research regarding nutrition, lifestyle, technology, new insulins into clinical practice guidelines for children and adolescents with diabetes. A personalized educational/insulin delivery/glucose monitoring approach is applied at onset and during follow-up for all children with diabetes (T1D, T2D, and MD) with optimal results.
PEDIA is recognized as a regional and national Center of Reference for the diagnosis and treatment of pediatric diabetes and has recently received certification as an "International Clinical Center of Reference" within the SWEET Project by the International Diabetes Federation (IDF) and the International Society for Pediatric and Adolescent Diabetes (ISPAD). As such, PEDIA is part of an international collaborative effort to benchmark and optimize pediatric diabetes care worldwide.
In collaboration with DRI, PEDIA is researching mechanisms underlying T1D patient heterogeneity using genomics, immunomics and transcriptomics which may allow for patient stratification and potentially promote an ever more personalized medicine. A "Rare Diabetes Clinic" is being planned as a facility specifically dedicated to the diagnosis and management of patients with non-autoimmune diabetes such as Wolfram Syndrome. It will collaborate with DRI for biological sampling and storage thereby creating a research infrastructure to study natural history and assess biomarkers of prognosis/drug response.
PEDIA is also experienced in pediatric pharmacological clinical trials.

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

PEDIA is involved in the following collaborative projects:
1) stratifying children with T1D at onset (including those with polyendocrine autoimmunity) assessing different patient subgroups in terms of metabolic control and residual beta cell functions, with the aim of a more personalized treatment/follow-up (a "Finalizzata" project funded by the Ministry of Health in collaboration with Dr Petrelli's Lab).
2) an interdisciplinary project "Personalize new treatments for diabetes and neurodegeneration in Wolfram syndrome" involving DRI, the Departments of Neuroscience and Neurophthalmology with the aim creating a bio banking and biomolecular resource research infrastructure for Wolfram syndrome, model disease genotype and phenotype and drug repurposing using beta-cells differentiated from Wolfram disease iPSC lines, an to perform a first proof-of-principle approach of retinal gene therapy in Wfs1 mutant mice. PEDIA will be fundamental in patient and follow-up via a "Rare diabetes clinic" specifically designed to follow these complex patients (Prof. Piemonti - DRI, Dr. Broccoli – Dept. of Neuroscience, Dr Cascavilla and Barboni – Dept of Ophthalmology).
3) screening patients for prediabetes and involve them in T1D secondary and tertiary prevention studies (FID Prevention Center and INNODIA network).
4) relationship between gut microbiome and T1D in order to assess the impact of probiotics (Dr Falcone's group).
5) research on genetic determinants of T1D (Dr Fousteri's group)
6) study comparing brain MRI and neuropsychological tests in children onset of diabetes treated with sensor-augmented pumps vs multiple daily injection therapy (Department of Neuroradiology).
7) research early markers of retinal and renal complications (Dr Zerbini)
8) muticenter studies within the Italian Society for Pediatric Endocrinology and Diabetes (ISPED). We also collaborated in the creation of the ISPED card which represents a benchmarking tool for Italian centers involved in pediatric T1D follow-up.
9) several pediatric clinical intervention trial in children with T1D (Dept of Pediatrics)

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

We are recognized as a center of reference for diagnosis, treatment and follow-up T1D, T2D and monogenic diabetes at a national and European level. At our center, around 100-120 new onsets are diagnosed each year (reprenting around 50% of the region's total).
Our work for TRIALNET and INNODIA Center has contributed to a significant output of regarding the screening of families with T1D. The DRI represents one of the few environments with a close relationship between clinical, research and biobanking facilities enabling an significantly collaborative environment for efficient translational research. We believe that this represents the major strength and driving force at our Scientific Institute. Furthermore, PEDIA has developed particular experience in intervention studies with both drugs and technology (artificial pancreas).

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

The main shortcoming for PEDIA is the current absence of a formally structured organization both in terms of staff and facilities. Research activities are carried out between daily clinical activities which include a daily outpatient clinic, daily ward rounds, emergency department (both daytime, nighttime and weekend shifts). Furthermore, protocol visits and sample collections are often carried out without the aid of a dedicated research nurse and in the already congested outpatient clinic where freeing an office for clinical trial visits is ever more difficult. This determines a significant challenge in carrying out clinical trials efficiently. Moreover, the lack of a data manager also makes our data analysis and output less proficient. Another limitation may be the absence of a clinical geneticist experienced in non-autoimmune diabetes especially for what concerns the follow-up of patients in which NGS analysis has shown variants of uknown significance.

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

1)- study heterogeneity of new onset type 1 diabetic children and their effect of the short-medium term follow-up.
2)- develop a precision medicine approach using data from heterotypes as a guideline: a different approach to each diabetic children
3)- develop new approach of treatment for Wolfram syndrome

4)- develop best application of hybrid closed loop in children and adolescents
6)- plan a trial for the prevention of DKA at onset of type 1 diabetes: actually the percentage of DKA at onset is very high (>40%) and increasing during last years. Antibodies screening trial both at familiar and general population levels have demonstrated the capacity of a great reduction (from 30% to 3%). The Idea is to develop a trial at the Lombardy Region in collaboration with Prof Bosi and Innodia Unit

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

in the medium term:
1) we carry on all previously mentioned points
2) we would like to develop studies in the secondary and tertiary prevention of type 1 diabetes in children and adolescents
2) we would like to participate to works planned in the bio-depository of HSR-DRI in Milan
3) carry on clinical trial of new drugs in children and adolescents with diabetes

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

we would like to be able to bring to the clinic the cellular therapy for type 1 diabetes in children and adolescents developed by the Diabetes research Institute

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

We suggest the institution of an upgrade of the Clinical approach dedicated to Type 1 diabetes (House of Diabetes), involving two dedicated unit one from pediatric and one from adult diabetologists, working together for the best clinical outcomes, facilitating the transition and allowing the cure of type 1 diabetes from birth to elderly, equipped by the best software applications and with the support of industry.
Of course the development of these infrastructure is a benefit for all the research groups of Diabetes Research Institute for the capacity of patients engagement.
Moreover we suggest an investment in the structure of a clinical trial center facility in order to simplify the carry on of clinical trials in children with type 1 diabetes.