COMPLICATIONS OF DIABETES (NEURODEGENERATION AS COMMON BACKGROUND AND PHARMACOLOGIC TARGET OF DIABETIC RETINOPATHY AND NEPHROPATHY) GIANPAOLO ZERBINI

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

Despite huge research efforts and the development of new therapeutic approaches, a final cure for diabetic retinopathy (DR) and nephropathy (DN) has not yet been identified. Tight glycemic control (in both types of diabetes) remains the key target but it only allows to delay, not to avoid the development of DR and DN. As a consequence, the two complications still remain (respectively) the first cause of blindness at working age in Western Countries and the first cause of end stage renal disease on a worldwide basis.
Calls to identify new pathogenic mechanisms that might explain the development and, at the same time, that could represent a novel pharmacologic target for both complications have been repeatedly made during the last National and International research meetings focused on diabetes.
DR and DN are tightly related, being DN always preceded by the development of DR. This peculiar temporal sequence has always suggested the endothelial cell as the target of diabetes common to both retina and renal glomerulus.
However, the recent evidences that 1) retinal microaneurisms (the first clinical sign of DR) are preceded and, possibly, caused by the degeneration of a specific type of neurons known as retinal ganglion cells and 2) podocytes, the glomerular cells in charge of size selectivity of the renal filtration (sharing with neurons specific characteristics including the presence of active synapses) are lost still alive with urine during the early phase of DN, have suggested the alternative hypothesis that neurodegeneration may represent the very first dysfunction for both complications. Based on these premises, the future of the research area will consist, on one hand, in confirming the above described hypothesis and, on the other, in verifying the possibility to prevent the development of both complications by interfering directly in the pathogenesis of diabetes-driven neurodegeneration.

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

Diabetic retinopathy: the connection between diabetes-driven neurodegeneration, DR and predisposition to develop cognitive impairement (in particular Alzheimer's disease) is presently investigated at DRI taking advantage of a clinical and pre-clinical H2020 European grant (Recognised). This four-years long project will allow not only to clarify the role of diabetes-driven neurodegeneration in the onset and progression of DR but also if this dysfunction involves the brain, thus possibly explaining the increased risk to develop cognitive impairment that has always been associated to diabetes.

Diabetic nephropathy: that neurodegeneration may be involved also in the pathogenesis of DN comes from the evidence that the loss of podocytes (the neuron-like cells responsible for the size-selectivity of the renal filtration) characteristic of end stage renal disease induced by diabetes is not caused, as previously believed, by the (diabetes-driven) death of podocytes but by their detachment from the glomerular basement membrane, a phenomenon that is preceded and paralleled by the shedding with urine of neuronal proteins such as nephrin. Quantification of the podocytes lost with urine (podocyturia) could represent a specific marker of podocyte neurodegeneration and, as a consequence, of early diabetic nephropathy. Aim of our research in this field is to set up, in collaboration with Menarini, of a precise and reproducible methodology to count urinary podocytes in both type 1 and type 2 diabetes. Future clinical studies aimed at preventing/curing DN by neuroprotecting the podocyte will take major advantage on the possibility to quantify the podocyturia.

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

Beside the tight and continuous connections between the Complications of Diabetes Unit of DRI and the Departments of Ophthalmology and Nephrology of OSR, strengths of the research area are based on the National and International connections of the Complications of Diabetes Unit: member (and founder) of the RIACE. Renal Insufficiency And Cardiovascular Events group, member of the European Network for Pre-Clinical and Translational Eye Research, and member of the GEnetics of Nephropathy an International Effort (GENIE) Consortium.
The Complications of Diabetes Unit of DRI is also in charge of the Murine Ophthalmic Facility (located inside the Experimental Imaging Facility) of OSR. This facility is unique in Italy and allows to perform in vivo ophthalmic examinations in mice and rats including fundus oculi, fluorescein angiography, optical coherence tomography (OCT), tonometry and also treatment with photocoagulation laser.
Finally, the Complications of Diabetes Unit has developed along the years a specific expertise in the analysis of biomarkers (nucleic acids and proteins) both in whole blood and at tissue level taking also advantage of immunofluorescence and immunohistochemistry techniques.

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

Weaknesses of the research area are the direct consequences of the ongoing Covid-19 pandemics. The rate of enrollment of diabetic patients in studies aimed to verify the possible connection between DR and cognitive impairement (Recognised) as well as in studies aimed to verify the potentiality of urinary excretion of podocytes (podocytura) as a novel marker of DN (Menarini) is significantly slowed down because of the impact of the pandemia on the patients' attendance to the outpatient clinic.

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

Diabetic retinopathy:
Milestones.
6 months: end of patients enrollment in the clinical cross-sectional Recognised study, start of the in vivo retinal examination of mice predisposed to Alzheimer's disease (5xFAD), basic Recognised study.
12 months: start of the clinical longitudinal Recognised study, start of the in vivo retinal examination of diabetic mice (akita), basic Recognised study.
Deliverables.
18 months: results (ophthalmic and neuropsychological) of the clinical cross-sectional Recognised study, results of the retinal examination of mice predisposed to Alzheimer's disease

Diabetic nephropathy:
Milestones.

6 months: set up of the methodology to identify and quantify podocyturia by flow cytometry (in collaboration with Silicon Biosystems).
12 months set up of the methodology to identify and quantify podocyturia by CellSearch (Menarini study).
Deliverables.
18 months: podocyturia measured by flow cytometry and CellSearch: results of the comparison analysis.

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

Diabetic retinopathy:
Milestones.
24 months: start of behavioral tests of mice predisposed to Alzheimer's disease (5xFAD), basic Recognised study
30 months start of behavioral tests of diabetic mice (akita), basic Recognised study
Deliverables.
24 months: results (FDG-PET/MRI) of the clinical cross-sectional Recognised study, results of the in vivo retinal examination of diabetic mice (akita).
30 months: results of the behavioral tests of mice predisposed to Alzheimer's disease (5xFAD), basic Recognised study
36 months: results of behavioral tests of diabetic mice (akita), basic Recognised study

Diabetic nephropathy:
Milestones.
24 months: set up of the methodology to identify and quantify podocyturia by means of ddPCR.
36 months: Flow cytometry vs CellSearch vs ddPCR definition of the best methodology of use to quantify podocyturia
Deliverables
30 months: podocyturia measured by flow cytometry, CellSearch and ddPCR: results of the comparison analysis

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

Diabetic retinopathy:
Milestones.
42 months: end of the clinical longitudinal and of the basic Recognised studies
48 months: If the results of the Recognised studies will confirm that DR is characterized by retinal neurodegeneration, we will apply for a clinical study aimed to verify whether DR can be prevented and/or treated by specific neuroprotection
Deliverables.
36 months: results of the behavioral tests of diabetic mice (akita), basic Recognised study
42 months: results of the clinical longitudinal Recognised study

Diabetic nephropathy:
Milestones.
40 months: end of the Menarini study
42 months: If the results of the Menarini study will confirm that podocyturia can be quantified, we will apply for a clinical study aimed to verify whether podocyturia is affected by the current treatment for DN
48 months: Application for the first clinical study aimed to verify whether podocyturia can be prevented and/or treated by specific neuroprotection

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

To safely achieve the different goals of this project It would be of great help if the Diabetes Research Institute could support Dr. Silvia Galbiati (co-author of this document) in her targeted effort to access the OSR career paths for research.