Review 1

Application data

Project Title	Galectin-3 in the pathogenesis of type 2 diabetes: the role in ß-cell proliferation, insulin secretion and anti-inflammatory mechanisms within islets
Project title in English	Galectin-3 in the pathogenesis of type 2 diabetes: the role in ß-cell proliferation, insulin secretion and anti-inflammatory mechanisms within islets
Project number	IZ73Z0_152407
Instrument	Joint research projects (SCOPES)
Research Field	Life sciences
Main Discipline	30304 Endocrinology
Main Applicant	Bernard Thorens
Amount requested (CHF)	105000

Comments regarding the overall assessment

This is a very timely project that addresses one of the possible genes involved in low grade inflammation, leading to obesity-associated type 2 diabetes focusing on beta cell dysfunction. The use of transgenic and knock-out mice for in vivo and ex vivo experiments combined with characterization of the immune cells that infiltrate the pancreas make this application highly topical. The feasibility is very good and the collaborating groups complement each other well. The collaboration and technology transfer to the Eastern European group is promising. High priority for funding without any hesitation.

Detailed evaluation

A1. How novel is the proposed research approach and research question?

Galectin-3 (Gal-3) is a scaffolding protein, important among others, in the Wnt signaling pathway. It has been suggested to protect pancreatic beta cells from apoptosis, despite its upregulation by the proapoptotic cytokine interleukin-1 beta. Increases in plasma concentrations of Gal-3 have attracted interest as markers for cardiovascular disease and type 2 diabetes. While Gal-3 knock-out mice have been studied previously, an animal model overexpressing the gene is not yet available. The project is thus of clinical importance and of high originality.

A2. How significant could the expected results be scientifically?

Gal-3 has been studied in the context of carcinogenesis, cardiovascular disease, obesity as well as type 1 and type 2 diabetes. The results have been in part conflicting and a systematic approach investigating as well immune cells as pancreatic islets in mouse models either deficient in or overexpressing Gal-3 is an important research topic. The results should elucidate the role of Gal-3 in the development of islet inflammation, relevant to the development of both type 1 and type 2 diabetes. As there are chemical inhibitors of Gal-3, the project could clarify whether inhibition or activation of Gal-3 changes the cause of diabetes development. In addition, Gal-3 has been implicated in vascular and renal diabetic complications, which further emphasizes the importance of the proposed studies.

A3. What is the quality of the research plan and the proposed methodology?

The research plan is logical and designed to fill in the gaps in our understanding of Gal-3 action in low grade inflammation of obesity and type 2 diabetes. The eight subprojects are all important. In particular the generation of mice with targeted beta cell overexpression of Gal-3 is commendable. The comparison of this model with the knockout in terms of in vivo phenotypes, immune cell infiltration of islets and other characterization of islet function after normal and high fat diet is laudable. It should be emphasize that the effect of Gal-3 on beta cell proliferation (subproject B) should definitely be performed in primary cells. Insulinoma cells can only be used for screening

purposes, as they have been tailor-made for replication. All methods are available and the generation of the transgenic mouse represents the only unknown parameter. This will be outsourced. The feasibility of obtaining publishable results is thus high.

A4. How good is the scientific qualification and the complementarity of the teams?

Professor Lukic is an experienced experimental immunologist with a decent publication record (H index = 19). His expertise has been extended to studies on immune infiltration in pancreatic islets and his group is well placed to perform the experiments listed to be executed in Serbia. Professor Thorens is one of the world leaders in experimental diabetology, whose laboratory masters a wide range of techniques spanning from in vivo phenotyping to islet biology and genetic analyses. He has an extremely good publication record (H index = 62). The two teams complement each other well: as cellular immunology lies outside the expertise of Prof. Thorens, while all other methodology is available in Lausanne.

B.1 Could the expected results be economically and socially important for the partners in I

This project comprises training of Serbian scientists in Lausanne, transfer of technology to the Eastern European laboratory as well as regular research contacts and scientific meetings. There is thus good educational benefit.

B2. How much will the JRP strengthen the individual and/or institutional research capacit

The transfer of highly specialized methods of experimental diabetology to the Serbian University should benefit diabetes research in this country. This is of particular importance as the increase in obesity and type 2 diabetes reaches pandemic proportions world-wide.

B3. How appropriate is the plan for disseminating/exploiting the expected results?

The plan is very well designed.

B4. How adequate is the distribution of duties and responsibilities among the partners?

The distribution of tasks between the partners is well thought through and seems logical.

C1. How clearly are the objectives and expected results defined? Are adequate measures pl

The proposed sub-projects are well designed to fill in gaps in our understanding of the low grade inflammation and immune cell infiltration of pancreatic islets in obesity and aging eventually leading to diabetes. Both background and outlook are reasonable.

C2. How likely is it that the foreseen management scheme will be successful?

The feasibility of this project is high and most of the experimental goals should be accomplished by the applicants.

C3. How appropriate is the requested funding and its allocation to cost categories?

The budget is reasonable and the allocation of funds seems adequate.

D1. Ethical standards

The collaborating groups have a long-standing experience in laboratory animal experimentation and hold the requested authorizations.

Review 2

Application data

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Comments regarding the overall assessment

This is a convincing project, nicely combining expertise from two complementary partners (diabetes and inflammation). The project is ambitious and would require additional funding to be completed. Alternatively, applicants may prioritize sub-projects.
In conclusion, this project is eligible for funding pending complementary financial resources.

Detailed evaluation

A1. How novel is the proposed research approach and research question?

The co-applicant (ML Lukic) has recently reported that Gal-3 deficient mice are highly responsive to high-fat diet-induced obesity, exhibiting insulin resistance and pancreatic islet inflammation (Diabetes. 2013, 62:1932-44). The present proposal is a follow-up of this paper, extending analyses on this model, in particular at the beta-cell level, through collaboration with the main applicant (B. Thorens).

A2. How significant could the expected results be scientifically?

Inflammation in general and immune attack in particular at the level of pancreatic islets in the development of type 2 diabetes is a matter of debate. The applicants would take advantage of a pro-inflammatory mouse model to question the role of Gal-3 in beta-cell failure in the context of obesity. This project nicely combines basic science (molecular regulation of inflammation) and clinical issues (anti-inflammatory strategies against type 2 diabetes).

A3. What is the quality of the research plan and the proposed methodology?

Applicants have the expertise and most of the required tools to conduct their research.

A4. How good is the scientific qualification and the complementarity of the teams?

Both applicants are recognized experts in their respective fields. These two teams are certainly complementary (Thorens for diabetes research and Lukic for mechanisms of inflammation).

B.1 Could the expected results be economically and socially important for the partners in I

Not directly on economic and/or social aspects, more on scientific side.

B2. How much will the JRP strengthen the individual and/or institutional research capacit

The JRP should provide some financial resources to support the research programme and transfer of technology (transgenic mouse and transcriptomics).

B3. How appropriate is the plan for disseminating/exploiting the expected results?

Both applicants have long standing experience in disseminating their results in efficient ways.

B4. How adequate is the distribution of duties and responsibilities among the partners?

It looks like the work in the Swiss institution would be more time consuming (and more expensive); in particular regarding generation of transgenic mouse and transcriptomics.

C1. How clearly are the objectives and expected results defined? Are adequate measures pl

Objectives are clearly defined. Most probably, the overall project is too ambitious. However, since both applicants have long standing experience in biomedical research, it is likely that sub-projects will be prioritized in the course of the research.

C2. How likely is it that the foreseen management scheme will be successful?

Management of the project should not be an issue.

C3. How appropriate is the requested funding and its allocation to cost categories?

The project as a whole would clearly require alternative funding.

D1. Ethical standards

Not addressed.

Review 3

Application data

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Main Applicant	Bernard Thorens
Amount requested (CHF)	105000

Comments regarding the overall assessment

a) eligible for funding.

The aim of the project is very relevant for modern medicine and Type2 diabetes. It is a balanced and realistic research project.
It is important that this network also include younger scientists in central positions to make sure it is beneficial also for future research structures.

Detailed evaluation

A1. How novel is the proposed research approach and research question?

The researchers have a great track record in the same scientific field as this application. They are therefore likely to deliver.

A2. How significant could the expected results be scientifically?

They will very well focus on the mechanistic parts. If they could further test pharmacological approaches, as they have done before, it would be even more interesting.

A3. What is the quality of the research plan and the proposed methodology?

The research plan is very well written and well thought out. The proposed mechanism are well established and important for the research program.
Affymetrix chip technology need to be validated with other technologies.
I do not fully agree that this project contain “state of art” cellular techniques.

A4. How good is the scientific qualification and the complementarity of the teams?

They have both an impressive track record.

B.1 Could the expected results be economically and socially important for the partners in I

I would say the the technology transfer especially would be important for Serbia. Not the results. No IP is mentioned in the proposal.

B2. How much will the JRP strengthen the individual and/or institutional research capacit

It could be a contribution for the young scientist in the network.
Not only because of the funds but the formation of the JRP.

B3. How appropriate is the plan for disseminating/exploiting the expected results?

They have a really good track record and will, according the the proposal continue publish in respected journals.

B4. How adequate is the distribution of duties and responsibilities among the partners?

It is not very clear from the proposal.

C1. How clearly are the objectives and expected results defined? Are adequate measures pl

Yes

C2. How likely is it that the foreseen management scheme will be successful?

The PIs are very are experienced. Still, the number of scientist in the research groups are limited.

C3. How appropriate is the requested funding and its allocation to cost categories?

In detail, Budget per year, it would be appreciated if ”Travel + accommodation + Participation at international conferences and consumables” already at this stage defined that 62 000 CHF is related to consumables and not travel expenses.

Extra funding will be needed for this proposal.

D1. Ethical standards

No comments. This is not elaborated in the proposal