Prevention and Treatment of Type 2 Diabetes with Melatonin Supplementation in High-Risk Carriers of Loss-of-Function Mutations within the Melatonin 1B Receptor Gene – A Swiss-Wide Project

Background

There is an urgent need for safe, effective and moderately priced new ways to prevent and treat Type 2 Diabetes (T2DM), which is becoming a major health problem worldwide. Over the past decade, we and others have contributed to the discovery of unequivocal associations between T2DM and common single nucleotide polymorphisms within the gene encoding the 1B receptor for melatonin, a pineal gland hormone involved in sleep homeostasis and used as supplements for jet lag and various conditions [1]. Recently, a variety of loss-of-function (i.e. null) mutations have been observed in this gene, which in aggregation amount to 0.7% variant carriers among diabetics, and which are associated with a severely increased risk of this disease [1-8]. These observations validate MNTR1B as a pharmacological target and open up the possibility to reposition melatonin for this indication[9], i.e. for the prevention and treatment of this rare, Mendelian form of T2DM.

Hypothesis

Here, we hypothesize that supplementation of exogenous melatonin (or a more specific MNTR1B agonist) shall compensate for the loss of activity in 50% of its 1B receptor in carriers of MTNR1B null mutations and that partial restoration of this pathway shall 1) improve glucose homeostasis, 2) improve glycemic control in T2DM patients and 3) prevent the development of this disease in these individuals.

Goals of the project

To test the three aspects of this hypothesis, we have assembled a outstanding Research Team with senior experts in various aspects of this project (see below).

Briefly, we plan to use a three-stage approach. First, we will investigate the effect of acute, single-dose administration of melatonin or MTNR1B agonists on glucose homeostasis in prediabetic or diabetic carriers of MNTR1B null alleles. This will allow us to identify the optimal agent, and adequate dosage for Stages 2 and 3. In Stage 2, we will examine the impact of repeated doses of the optimal agent over a four-week period of administration on fasting plasma glucose. If positive, Stage 3 will consist of a full six-month prevention trial on prediabetic individuals.

For these purposes, we will identify pre-diabetic (with HbA1c > 6.0%) or diabetic MNTR1B heterozygous null carriers (i.e. the probands) by accessing four reservoirs of individuals, for whom we have the information on diabetes, DNA samples biobanked and the proper consent to
recontact them, with a total of 30,000 participants, including 2500 pre-diabetic or diabetic individuals:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Location</th>
<th>Total number of participants</th>
<th>Number of diabetics or prediabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIL*</td>
<td>Lausanne</td>
<td>14000</td>
<td>Approx 1700</td>
</tr>
<tr>
<td>CoLaus</td>
<td>Lausanne</td>
<td>6000</td>
<td>Approx 360</td>
</tr>
<tr>
<td>Bus Santé</td>
<td>Geneva</td>
<td>4000</td>
<td>Approx 250</td>
</tr>
<tr>
<td>Sapaldia</td>
<td>8 centers</td>
<td>6000</td>
<td>Approx 360</td>
</tr>
</tbody>
</table>

** BIL : Lausanne Institutional Biobank, data as per July 15th, 2015

Probands will be contacted, and permission will be asked to contact their first-degree relatives. These will be recruited by the SCTO-associated CTU center the closest to the place they live in and will be genetically screened (through a central laboratory) for the presence of the mutation (expected prevalence 50%). Carriers will be invited to participate in Stage 1 study, which will be performed in the Department of Physiology at CHUV/UNIL, and in Stage 2 study, which will be Swiss-wide, with coordination by the SCTO.

** Specific aims (SAs) **

1. Recruitment of probands: Identify carriers of MTNR1B null mutations by sequencing the exons of approx 3000 participants in CoLaus, BIL, Bus Santé and Sapaldia with diabetes or pre-diabetes.
2. Recruitment of carriers among first-degree relatives: Contact the probands and obtain their permission to contact their first-degree relatives in order to identify additional carriers through genotyping of specific MTNR1B mutations.
3. Stage 1 - Investigate and compare the acute effect of single-dose 5 mg melatonin, a more specific MTNR1B agonist or placebo in a cross-over clamp study on glucose homeostasis in 10 T2DM carriers of MNTR1B null mutations. Finalize the optimal regimen for Stage 2 studies.
4. Stage 2- Evaluate the effect of optimal agent once-a-day over a four-week period in a randomized, double-blind, placebo-controlled, cross-over trial, SCTO-coordinated multicentric study on fasting plasma glucose levels on 30 carriers of MTNR1B null mutations.
5. Stage 3 - If positive, i.e. if melatonin improves glucose homeostasis in SA-3 or if fasting plasma glucose levels decrease by > 0.5 mmol/L in SA-4, examine the effect of a 6-month 5 mg melatonin once-a-day administration of fasting plasma glucose levels, HbA1C, body weight, plasma lipid levels and blood pressure, using a randomized, placebo-controlled, double-blind design, SCTO-coordinated, multicentric study on 50 carriers of MTNR1B null mutations.
**Expected deliverables, timelines and budget.**

The capabilities to perform the experiments described above are all available in Switzerland, so the project can start immediately. Sequencing \( MNRT1B \) exons within the 3000 participants of CoLaus, BIL, Bus santé and Sapaldia already diagnosed with T2DM or pre-diabetes (SA-1) shall identify 25 (TBC) carriers of \( MNTR1B \) null mutations and shall take 8 months. Contacting these individuals, their first-degree relatives and genotype them shall take an additional 8 months and shall allow identifying approximately 100 carriers. Performing the acute administration study (Stage 1) in Lausanne and the SCTO-coordinated one-month trial (Stage 2) shall take 18 months. The stage-3 study shall take 2 years.

**Conclusion**

If successful, the proposed series of experiments described here shall pave the way to an innovative, safe, cheap and effective way to prevent and treat a rare, monogenic form of T2DM, and shall be seen as a highly visible outcome of genomic and precision medicine and a new paradigm for genomic-medicine enabled drug repositioning. All the capabilities required to perform the experiments described here are available in Switzerland, so that chances to successfully complete these highly innovative experiments are very high. This project shall also capitalize on the power of SCTO to coordinate and bring to completion multicentric trials on subjects with rare conditions.

**Composition of the Research Team:**

- PI : Prof Marc Froissart, new Head of the Lausanne CRC and medical director of the Clinical Research Support Platform @ CHUV/UNIL
- Prof Gérard Waeber : Head of Internal Medicine, co-PI of CoLaus
- Prof Pedro Marquès-Vidal : Service of Internal Medicine CHUV
- Prof Jacques Philippe : Head Service of Endocrinology, HUG
- Prof Nicole Probst-Hensch : PI Sapaldia
- Prof Luc Tappy, Department of Physiology CHUV/UNIL

  **To be confirmed :**
  - Prof Gregor Zuend, President SCTO =???
  - Prof Marc Donath, Head Endocrinology Service, Basel.
  - Prof Stettler, Head Endocrinology Service, Bern

**Partners :**

- Prof Vincent Mooser, PI BIL
- Prof Idris Guessous, PI Bus Santé
- Dr Fabienne Maurer, Service of Genetics CHUV
- Dr Isabelle Guilleret, PSRC
- Dr Evrim Jaccard, Service Internal Medicine CHUV


