



Innovative Medicines Initiative

IMI2 T1DM Call Topic Text: Translational approaches to disease modifying therapy of T1DM

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efpia*

General T1DM disease facts



Facts

- Type 1 diabetes mellitus (T1DM) is a chronic disease affecting worldwide around 17 Million people.
- The incidence rate is high in Europe affecting ~ 22 / 100.000 per year, with major regional differences.
- The peak onset of the disease is at puberty, but may occur at any age.
- The incidence of childhood T1DM is rapidly on the rise, especially in the under 5 year old age group.

Diagnosis

- T1DM is typically characterized by hyperglycemia due to destruction and loss of insulin producing pancreatic beta cells and function over time.
- The earliest detectable change in biomarkers is the occurrence of one or several autoantibodies directed towards antigens of the endocrine pancreatic islets (e.g. IAA, IA-2, GAD, ZnT8).
- The disease T1DM is generally seen today as an autoimmune disease.
- The precise cause of type 1 diabetes is unknown and believed to be caused by one or more of the following: genetic susceptibility, diabetogenic trigger(s) and/or exposure to a driving antigen.
- Longstanding diagnosed T1DM patients vary in their residual pancreatic beta cell status independent of their insulin deficiency and active autoimmunity status.

Therapy

- The disease is currently not preventable and no cure is available.
- The only available pharmacotherapy for T1DM patients is the lifelong injection of insulin.
- An alternative approach to subcutaneous insulin replacement therapy is pancreas or pancreatic islet cell transplantation. Both methods acquire immunosuppression and are time limited in their effectiveness.



Problems in T1DM therapeutic development



- The current limited success in T1DM prevention or intervention trial settings using therapeutic approaches to induce
 - Immune tolerance to known islet autoantibodies (GAD65, Insulin)
 - Immune suppression through T cell modifying therapies (e.g. anti CD3)
 - anti-Inflammatory Abs (eg IL1b)
- The gaps in understanding the „at-risk“ patients and the diagnosed T1DM patients in their heterogeneity / individuality.
- The need in „read-outs“ to improve the
 - understanding of the beta cell status and the immune phenotype
 - to improve the patients disease staging
 - to allow improved, individualised therapy dosing
 - to find new end point measurements in clinical trials.
- Realistic understanding in the translatability of data sets obtained from preclinical models.



Why do we need a T1DM Call within IMI2



Current Facts:

- Standard insulin therapy for T1DM is associated with the risk of drug-induced hypoglycaemia.
- Rational disease modifying therapeutic approaches to address T1DM are lacking.
- Scientific insights to the triggering events of the disease susceptibilities and the subsequent pathophysiological events leading to drop in β -cell function & beta cell number are limited today.
- Improved understanding of the interaction between the immune system and the pancreatic beta cells in high risk and diagnosed T1DM humans is urgently needed to be able to address the opportunity to develop therapies that could lead to prevention, modification or ultimately cure of the disease in the future.

Opportunity:

- IMI projects bear the excellent, unique opportunity **to tackle complex scientific questions efficiently in a cross functional team of experts from different disciplines** and background.
- Pharmaceutical industry, represented through EFPIA, decided to play a leading role in **establishing the widest possible cross-functional consortium** with representatives from patient advocacy groups, health authorities, diabetes care givers, innovators, and industrialists to address the obstacles faced today in T1DM prevention & treatment.



Overall description



Program:

- The T1DM program in IMI2 invites applicant consortia **to build a cross-functional research initiative** with the objective to launch a program that **could lead to prevention as well as T1DM disease modifying and ultimately to a curative therapy** in the future.
- To achieve this ambitious goal **deeper insight to the heterogeneous, phenotypical characteristics of people either at risk of developing T1DM or having manifest disease** is required.
- Using state of the art technologies it is envisioned that the successful consortium will **focus on a complete mapping of interactions between the immune system and pancreatic beta cells** in humans and on the **environmental changes** that has led to increased disease incidence.
- The programs should embrace a strong focus on **translational medical activities initiated at the bedside, refined at the workbench, and then finally brought back to the bedside for clinical validation** of potential therapeutic approaches aiming at fundamentally preventing, halting, and reversing the β -cell destructive course of T1DM.



Objectives of the T1DM call



Objective I

Expand existing patient registries and prospective cohorts and the establishment of new cohorts to allow

- Systematic retro- & prospective collection and characterization (→ “full-Omics” approach) of human biological samples from children/ adolescents at risk of developing diabetes as well as new onset T1DM patient cohorts undergoing standard glucose controlling therapy.
- Phenotypical characterization (in silico based on medical records as well as through experimental clinical studies).
- The establishment of systematic large-data and biobank repository enabling extensive cross functional data mining and modelling of disease incidence and progression.
- Long term glucose control status (HbA1c) monitoring in recent onset patients.
- Leukocyte characterisation for immune cell target identification
- Beta cell status and functional measurement

Exploration in

- imaging technology for improved patient stratification and as a surrogate end point in clinical studies
- novel diagnostic(s) and device opportunities to improve disease handling



Objectives of the T1DM call



Objective II

Development and characterization of the most suitable translatable preclinical T1DM models for discovery of novel clinical therapies.

- Representative for distinct stages of the human disease
- Animal models / human cell models

Objective III

To apply the newly acquired molecular knowledge to facilitate the development of improved standardized clinical T1DM trials and to evaluate novel mono & combination treatment approaches.

- Generation of a EU network of clinical and translational research centers for conducting clinical trials for T1DM.
- Development of standardized entry criteria and end points for T1DM trials.
- Clinical data documentation to allow most comprehensive data analysis options.
- Evaluate novel mono & combination treatment approaches addressing T1DM.



Envisioned Consortium



To address the complex tasks of the T1DM Call, a pan-European clinical trial network should be established in collaboration with clinical centers in the US and with participants from patient advocacy groups and regulatory authorities.

- The network will include:
 - Academic endocrine clinics and associated supporting departments
 - Basic researchers from the fields of autoimmunity and β -cell biology
 - Drug discovery and medical staff from Pharmaceutical Industry (and presumably Biotech)
 - Patient advocacy groups and regulatory authorities
- The applicant consortium is expected to address all objectives and make key contributions on the deliverables in synergy with the industry consortium.

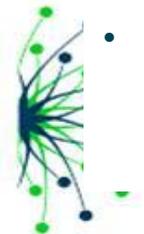


Consortium Applicants & their Organisation

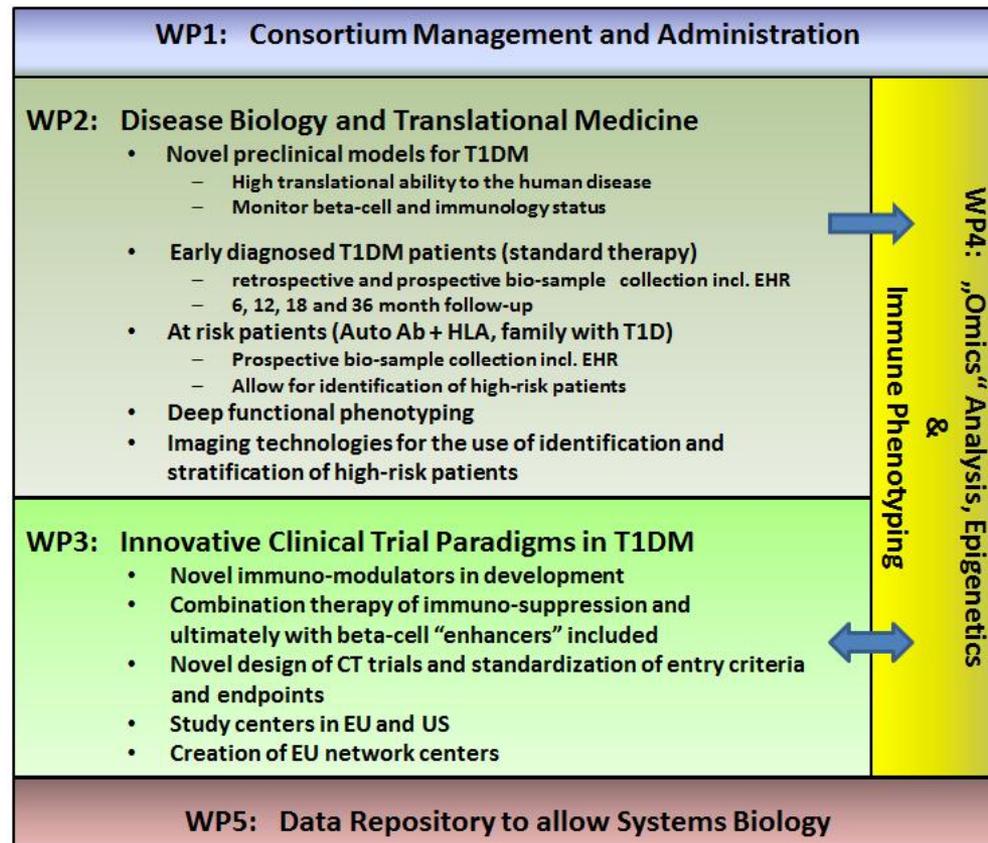


A network of following experts is envisioned:

- research physicians (pediatric endocrinologists, immunologists),
 - basic researcher in the fields of immunology and β -cell biology,
 - biomarker specialists
 - bioinformaticians and statisticians,
 - chemists and biologics specialists,
 - Device and imaging experts
 - hand-on data base specialists and big data managers,
 - regulatory science and health technology assessment representing european health authorities,
 - clinical trialists,
 - translational medicine experts,
 - patient organisations / representatives.
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- The cross functional expert team should work together in smaller work packages addressing the different call aspects most efficient.
 - Each work package team is recommended to consist of academic and industry members with regular interaction to ensure knowledge exchange.
 - Interwork package knowledge transfer must be ensured at all times through a common used data repository and via regular management board meetings.



Suggested architecture of the project



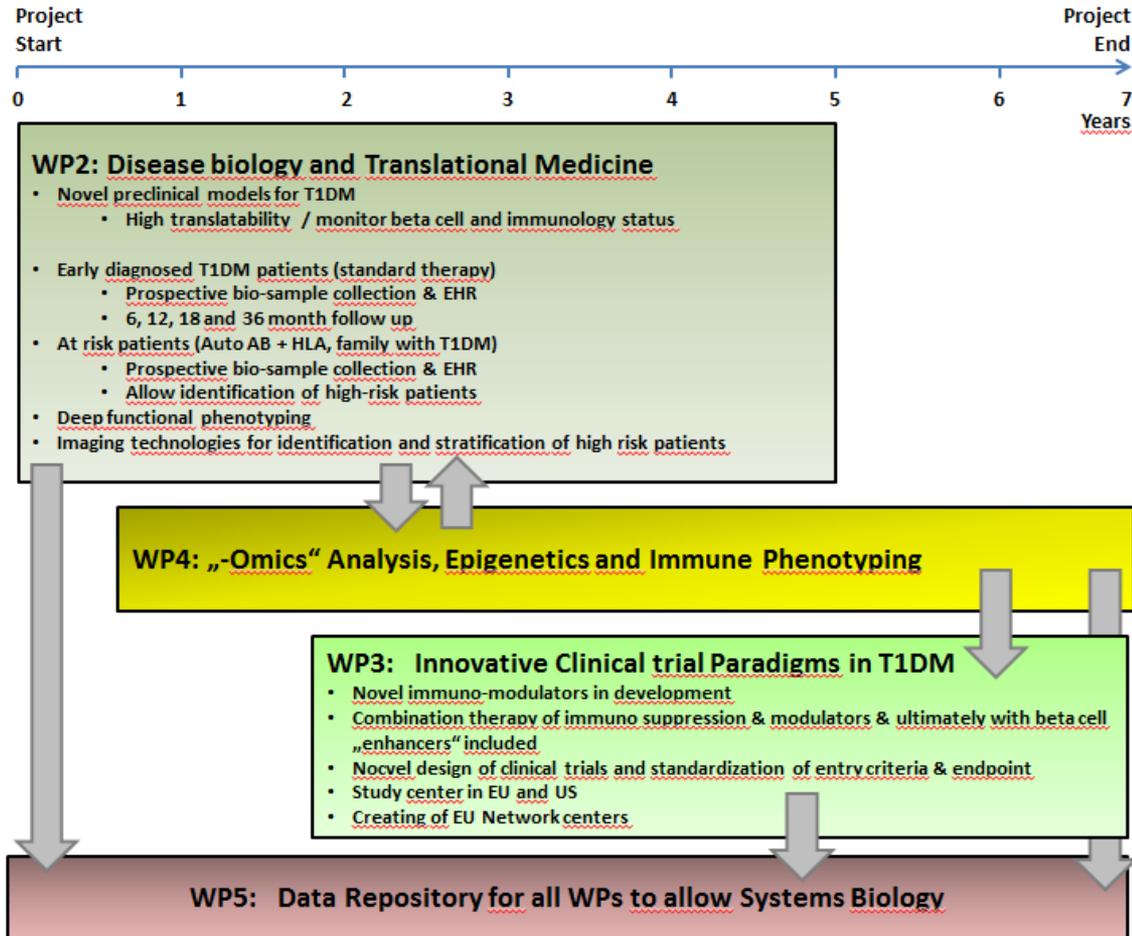
Expected project duration



- The indicative duration of the project is 84 month (equals 7 years). This time frame should allow
 - to perform “full-Omics” profiling to gain in depth systematic molecular analysis and immune phenotyping data of retro- and prospective collected biological samples from at risk and from established T1DM patient cohorts.
 - to develop and characterize translatable preclinical T1DM model(s) for discovery of novel clinical therapies.
 - to establish the opportunity to apply the newly integrate molecular knowledge in to be defined prospective clinical trials



Suggested project time line and WP connectivity



Committed EFPIA companies & associated partners



EFPIA participation:

- Sanofi (coordinator), Juvenile Diabetes Research Foundation (JDRF) (co-coordinator), Helmsley Charitable Trust, GSK, Novo Nordisk, Eli Lilly.
- The EFPIA partners have invited the JDRF and the Helmsley and Charitable Trust to participate as equal partner in the steering group formulating this T1DM focused call.
 - JDRF: <http://jdrf.org>
 - Helmsley Charitable Trust: <http://helmsleytrust.org>

Budget

- The current budget encompass € 35.260.000 equally shared by the EFPIA companies & associated partners with the IMI2 Joint Undertaken (JU).
 - Equals 17.630.000 € IMI JU funding to beneficiaries of the selected consortium.



Key deliverables of the full project



- Improved understanding of the heterogeneous disease T1DM in their immunological and beta cell biology aspects in children/adolescents at risk of developing diabetes as well as on early diagnosed T1DM patient cohorts undergoing standard glucose controlling therapy.
- Complex clinical & standardised molecular “real world data” obtained from T1DM patients and the application of novel bio-statistical methodologies will result in compositions of relevant endpoints & readouts for T1DM clinical trials.
- The pre-clinical T1DM models in their translational value will be improved.
- Improved understanding of the complex human T1DM disease offers the opportunity to test novel mono- and combination approaches in an optimised clinical trial setting.



Synergies with existing Consortia



- **IMI_IMIDIA:** “Innovative Medicines Initiative in DIAbetes”, has the goal to “Improve beta cell function and identification of diagnostic biomarkers for treatment and monitoring in (T2) Diabetes”.
- In the frame of IMIDIA a unique standardised human biorepository on biofluids (plasma, serum), pancreatic tissue and pancreatic islets / beta cells has been established also from non-diabetic control subjects, characterised beside others by their islet-autoantigen and their blood glucose status. In addition to clinical parameters, the samples have been comprehensive molecular and functional characterised and system biology been applied.
- → IMIDIA bears valuable information
 - On human pancreatic islets of a continuously growing collection of biosamples obtained from non-diabetic control subjects.
 - On how to integrate different data types to allow Systems Biology
- **IMI_DIRECT:** “Diabetes Research on Patient Stratification”
- Is focusing on the improved understanding of the heterogeneous disease T2DM via the assessment of patient samples from comprehensive cohorts.
- → DIRECT bears valuable information
 - On a comprehensive collection of biosamples and clinical information on non-diabetic control subjects
- In addition to, synergy to FP7 consortias in the field of T1DM can be seen, like e.g. to BIOSID, DIABIL_2, DIABIMMUNE, DIAMAP, DIAPREPP, NAIMIT, PREPOBEDIA.



Where do we stand & What are the next steps



- ✓ **Launch of the IMI2 T1DM call topics text:** 9th July, 2014
http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/IMI2_C1_S0_TEXT_DRAFT%2023%20May%202013.pdf

- **Anticipated Timelines for the time to come:**
 - Submission of Expression of Interest (Eoi; academic consortia).
 - *9th July thru November 2014*
 - Eoi review by independent experts and selection of top ranked academic consortium (in-house evaluation):
 - *November 2014 thru February 2015*
 - Preparation of Full Project Proposal:
 - *February thru May 2015*
 - Project Start
 - *July 2015*



What's in it for Applicants?



- Explain the benefits of this particular project for:
 - Academic researchers: *interconnectivity improved between beta cell biologist & immunologists; deep knowledge about the molecular & clinical characteristics of the human disease; improved understanding in the heterogeneity of the human T1DM disease; information on the translatability of the pre-clinical T1DM models; which preclinical model fits best to which status of the human disease; connectivity between basic scientists and clinicians; improved understanding of the need of the T1DM patients when living with the disease;*
 - SMEs: *Develop /obtain new emerging biomarkers that are indicative for the disease progression & for disease modification will ultimately optimise patient selection and treatment monitoring; Development of standardized entry criteria and endpoints for T1DM trials will improve their performance; Opportunity to test novel mono- and combination approaches in an optimal clinical trial setting as a result of the improved understanding in the T1DM disease & patient;*
 - Patients organisations: *Gaining deep insight into the heterogeneity of the disease will result in a more personalised treatment opportunity; Availability of new emerging biomarkers indicative for the disease progression & for disease modification will improve the understanding of the disease status of each patient
→ will ultimately improve the treatment understanding and outcome;*



Questions?



- Contact the **IMI Programme Office**

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