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

Anke M. Schulte, Sanofi-Diabetes

30.09.2014 • IMI Open Info Day 2014 • Brussels, Belgium

General T1DM disease facts

Disease prevalence

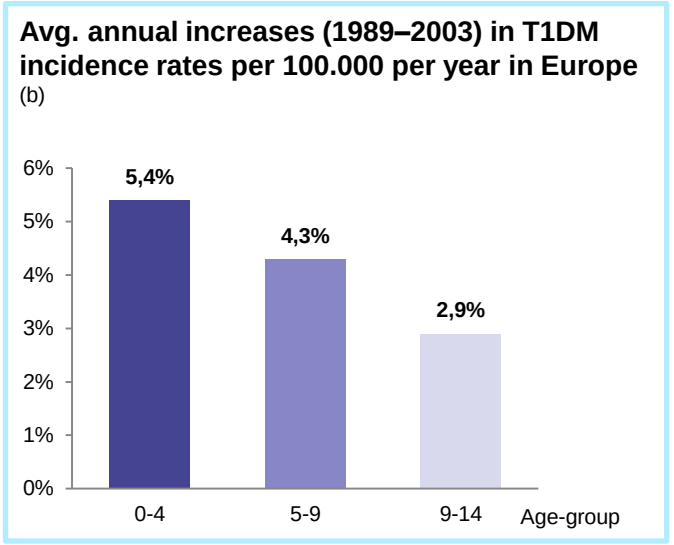
- Chronic disease affecting worldwide ~ 17 Million people.
- Incidence rate in Europe: ~ 39 / 100.000 per year.
- Rapidly on the rise, especially in the under 5 year old.

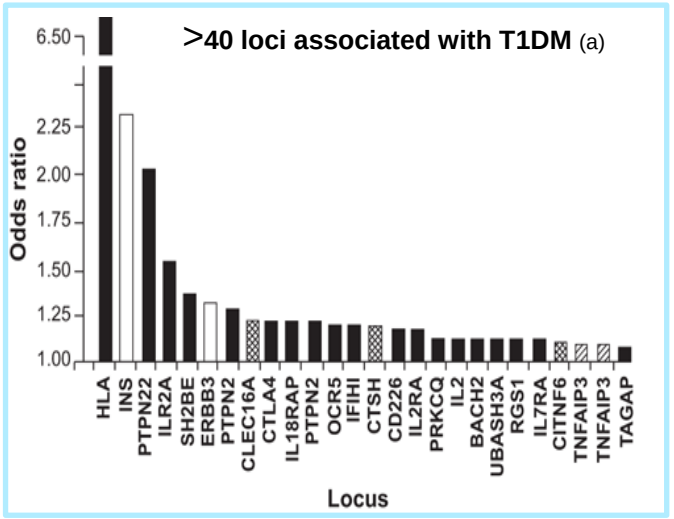
Diagnosis

- Hyperglycemia due to functional beta cells loss.
- Islet cell autoantibodies ….the earliest known biomarkers.
- Autoimmune disease.
- Heterogeneity of the disease (beta cell / immune status).

Disease cause

- Unknown → not preventable
- Driven by e.g. genetic susceptibility, diabetogenic triggers, exposure to antigen(s), dysfunctional immune tolerance.





Adapted from (a) Zhank & Eisenbarth 2011, (b) Patterson CC et al. (2009), Herold et al., 2014

Therapy options

- **Only pharmacotherapy is lifelong injection of insulin.**
- >150,000 injections per patient life
- Major life-style adaptation

- **Insulin therapy does not cure**
  - and sets the risk for hypoglycemia
  - & uncontrolled blood glucose episodes lead to vasculature complications

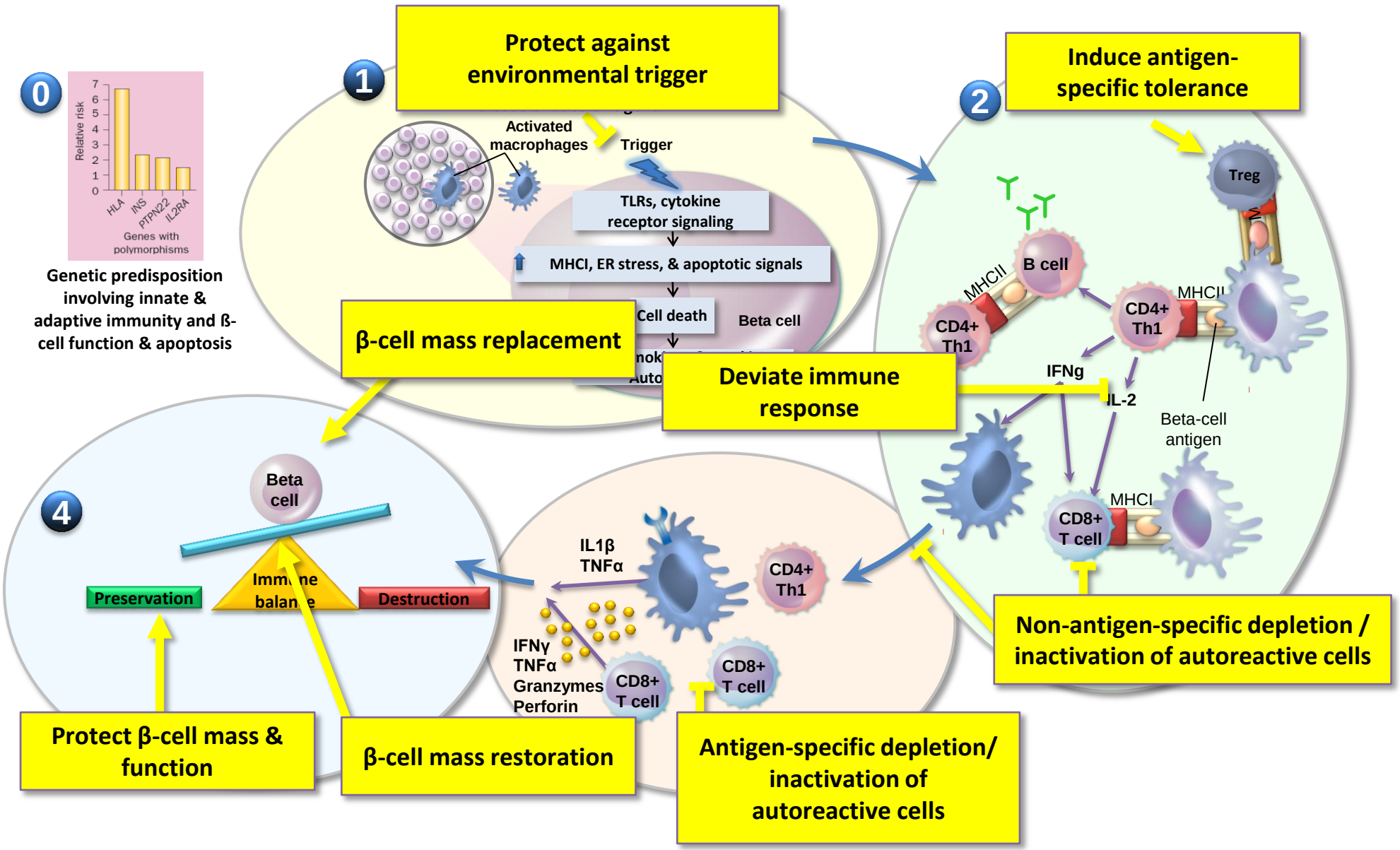
"I have to check my blood sugar 8 -10 times a day; everything I eat is counted for carbohydrates. Too much exercise or forget eating can be dangerous ***Jonathan, 8 years***

- **Alternative option is organ/islet transplantation; limited in its usability**

→ **Define disease modifying, even curative therapies –** preserving, restoring endogenous insulin secretion in immune tolerance setting **– is the eager goal**

imi innovative medicines initiative

Knowledge of T1DM pathogenesis provides multiple opportunities to intervene



Source: Modified after Peakman, M. et al. (2012) Nature Reviews Endocrinology: Type 1 Diabetes Mellitus 2012 / Rotenstein LS et al. (2011) diaTribe

Status in T1DM therapeutic development

- **Limited lasting success in T1DM prevention or intervention trial settings using different therapeutic approaches**
  - Immune tolerance to known islet autoantibodies (e.g. GAD65, Proinsulin)
  - Immune suppression therapies (e.g. anti CD3, -CD20)
  - anti-Inflammatory Abs (eg IL1b)
- **Gaps in understanding the „at-risk“ people, the T1DM patients, the responders & non responders in their difference(s)…**

- **We need to obtain „read-outs“ to increase our knowledge**
  - about the „at risk“ patients
  - in the disease taxonomy (beta cell status / immune phenotype)
  - in evidence based entry & end point parameters
- **Realistic understanding in the translatability of data sets obtained from preclinical models.**

Why do we need a T1DM Call within IMI2

- **Addressing complex scientific questions efficient in a cross functional team of experts of multiple disciplines.**

- Lack in lasting T1DM disease modifying therapeutics.
- Limited insight on the disease triggering events leading to failing β-cell functionality.
- Limited understanding of the patients heterogenous disease status.
- Need in standardized clinical trial settings with reliable read outs.

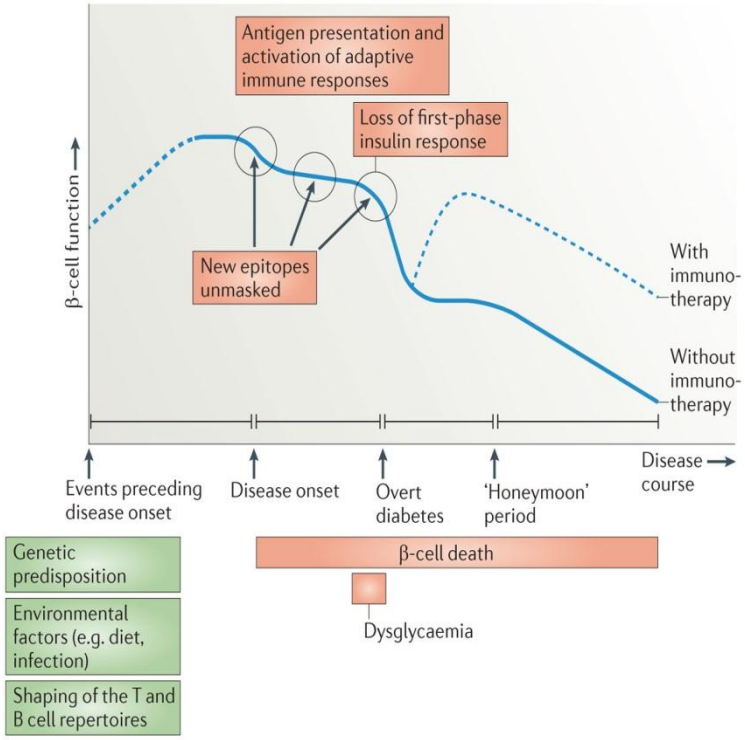
Solid progress in the understanding of the complex pathophysiology of T1DM.

Allow mono- & combination therapies to be tested in innovative clinical trail settings with evidence based new entry & end point criteria.

innovative medicines initiative

Overall project description

- Build a cross-functional clinical & research initiative tackling T1DM comprehensively.
- Gain deeper insight to the heterogeneous, phenotypic characteristics of people either “at Risk” of developing T1DM or with disease manifestation.
- Map the interactions between the immune system and pancreatic beta cells as well as on environmental changes that lead to increase in disease incidence.



- Build a European clinical trial network testing novel approaches under standardized new entry & endpoint criteria.

imi innovative medicines initiative

Objectives of the T1DM call

Objective I

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

- Retro- & prospective collection and characterization (broad “–Omics” approach) of human biological samples from
  - Newborn/infants/children/adolescent/adults at risk of developing diabetes
  - early diagnosed T1DM patient cohorts under standard therapy
- In depth phenotypic characterization (HER, functional tests)
- Systematic large-data repository enabling cross functional data mining & integrated analysis
- Elucidate novel pathways for the interaction of autoimmune response and beta-cell function
- To explore imaging technology, novel diagnostic(s) and device opportunities.

Objectives of the T1DM call

Objective II

Development and characterization of preclinical T1DM models with better translational ability for the human disease

Objective III

Apply the new knowledge to set up improved future trial settings to test novel therapeutic assets in mono &/or combination therapy.

- Build an EU network of clinical and translational research centers conducting clinical trials for T1DM.
- Apply evidence based standardized entry & end point parameters.
- Comprehensive data collection & “state of the art” analysis to define new biomarkers for disease status, progression and modification.

Key deliverables of the full project

- Improved understanding of the heterogeneous disease T1DM in their immunological and beta cell biology underlying pathophysiology.
- Integration of complex clinical & standardised molecular “real world data” from at risk and T1DM diseased patients will support identification of new disease relevant entry & end point readouts.
- Understanding in the translational value of pre-clinical T1DM models.
- An European clinical trial & translational research network has been established.
- Facilitate improved, standardized clinical trial settings applying the new read out criteria for evaluation of novel mono & combination treatments.

innovative medicines initiative

Envisioned Consortium

Build a pan-European clinical & translational research network including a clinical registry of eligible people with T1DM / at risk.

The consortium should include :

- Academic endocrine clinics & supporting departments.
- Basic, translational and clinical researchers from the fields of T1DM autoimmunity and β-cell biology.
- Drug discovery & medical staff in Pharmaceutical Industry and Small & Medium size Enterprises.
- Hands-on data base specialists and big data managers.
- Patient advocacy groups.
- Experts in regulatory science and health technology assessment preferably representing European health authorities.

imi innovative medicines initiative

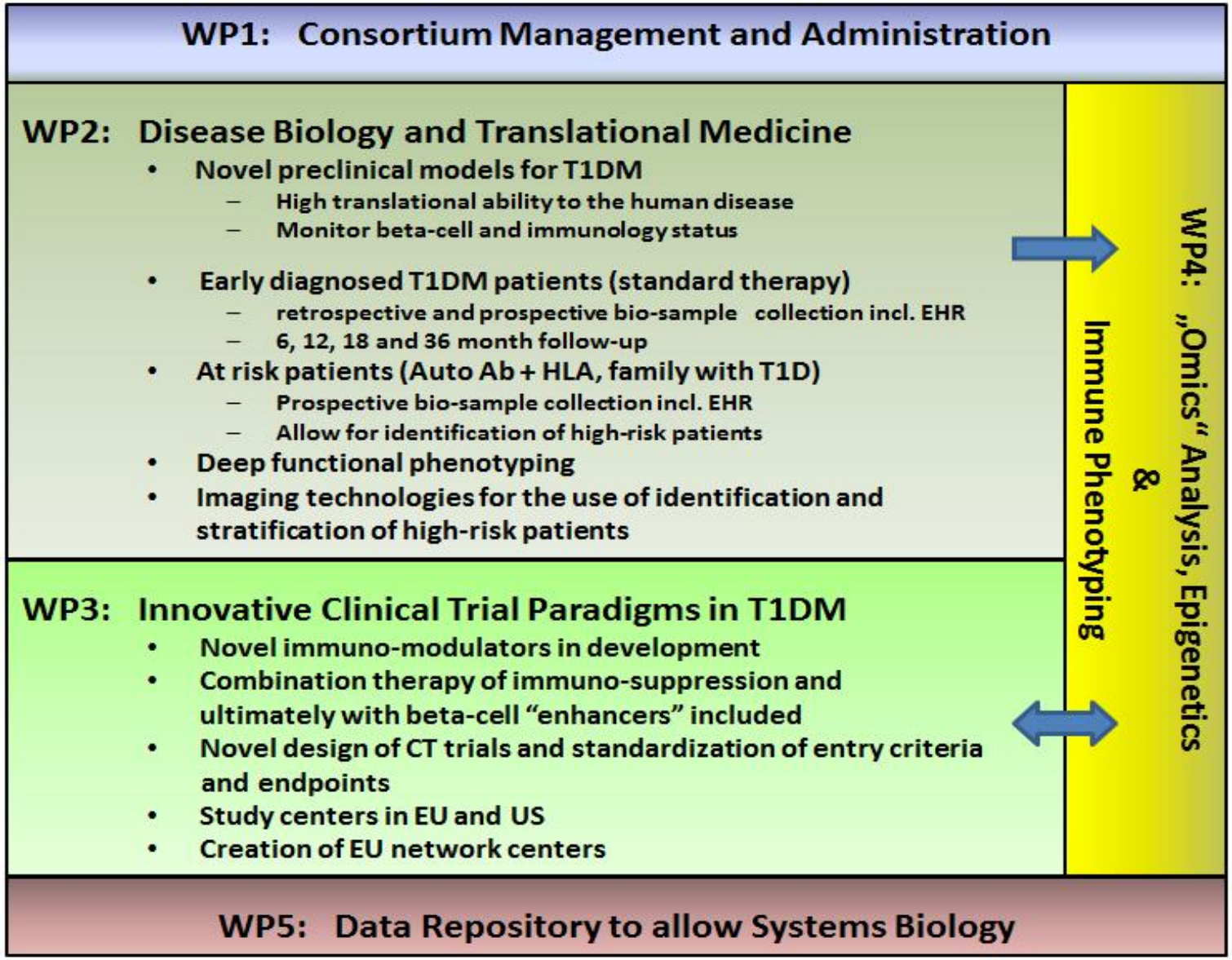
Recommended Modus operandi

- The cross functional team of experts should be sub-organised in work packages.
- Each work package should consist of academic, clinical & industry members with regular exchange.
- Interwork package knowledge transfer must be ensured at all times.

Cross fertilization within this team of experts is key for the success of the initiative.

innovative medicines initiative

Suggested architecture of the project

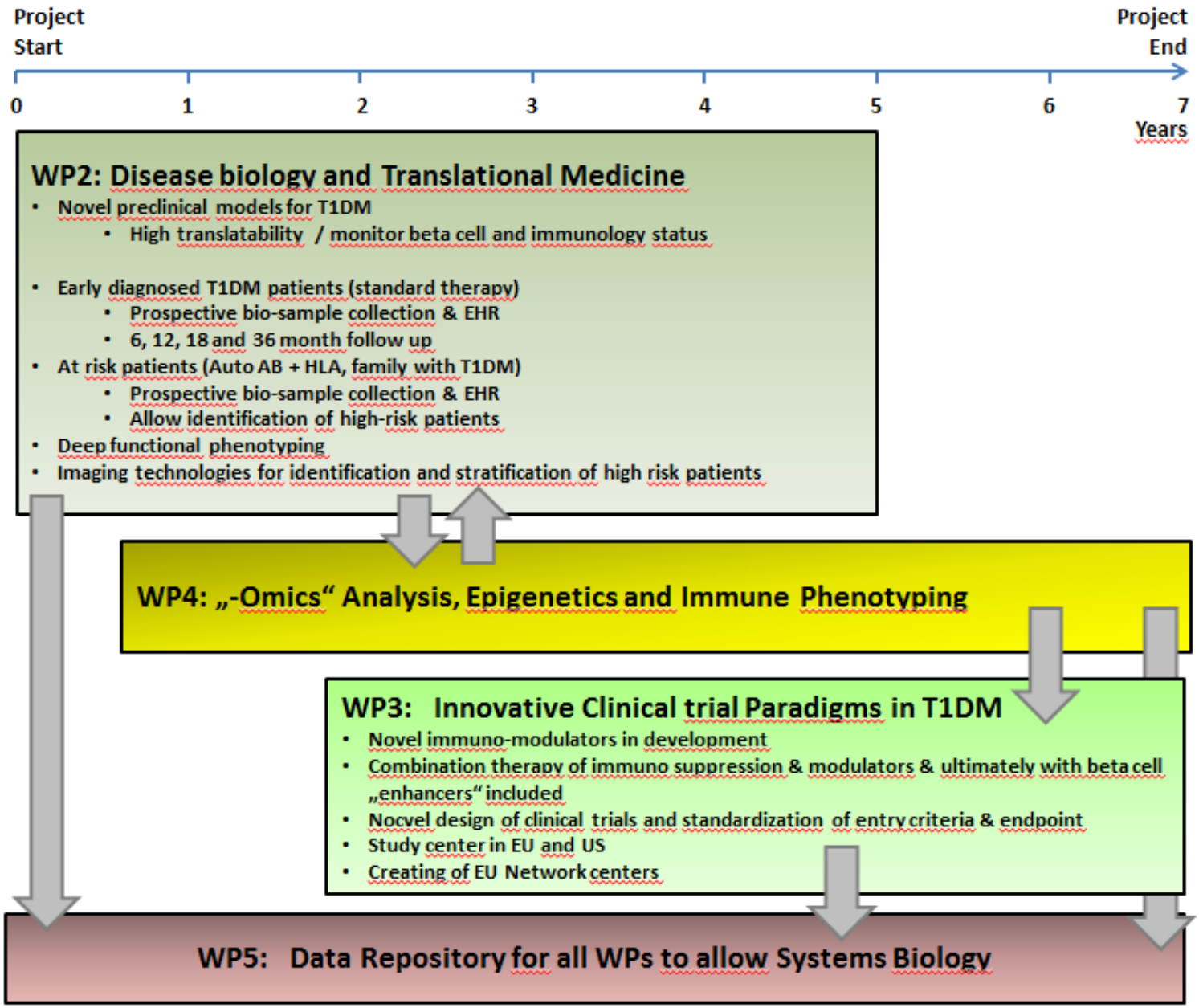


innovative medicines initiative

Expected project duration

- The indicative duration of the project is 84 month (7 years).

Suggested time lines 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.
  - JDRF and the Helmsley Charitable Trust participate as equal partner in the steering group.

- **Budget**
  - € 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.

innovative medicines initiative

Where do we stand & What are the next steps

✓ **Launch of the IMI2 T1DM call topic text: 9th July, 2014**

Timeline to come:

- Submission of Expression of Interest (EoI; academic consortia).
  - until the **12th of November 2014**
- External EoI review by independent experts and selection of the winning academic consortium: (IMI JU driven)
  - until **end of February 2015**
- Preparation of Full Project Proposal: (EFPIA/consortium driven)
  - until **end of May 2015**
- Project proposal evaluation: (IMI JU driven)
  - until **July 2015**
- Project start: **July 2015**

innovative medicines initiative

Questions?

- Contact the IMI Programme Office

  E-mail: infodesk@imi.europa.eu

  Website: www.imi.europa.eu

innovative medicines initiative

Thank you

Anke M Schulte • Head of Islet Biology Department •
Sanofi-Diabetes Frankfurt, Germany

www.imi.europa.eu
@IMI_JU

Back Up

What's in it for Applicants?

Clinicians & academic researchers & SMEs

- improved interconnectivity
- improved understanding the heterogeneity of the human T1DM disease;
- translatability of the pre-clinical T1DM models improved ;
- Better connectivity between basic scientists and clinicians;
- improved understanding of the need of the T1DM patients when living with the disease….
- new emerging biomarkers 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

- Gain personalised treatment opportunities;
- New emerging biomarkers indicative for the disease progression & for disease modification will improve the understanding of the disease status of each patient
- ultimately improvement in the treatment options

innovative medicines initiative

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".

- IMIDIA bears valuable information
  - On human pancreatic islets of a continuously growing collection of bio-samples obtained from non-diabetic control subjects.
  - On how to integrate different data types to allow Systems Biology

IMI_DIRECT: "Diabetes Research on Patient Stratification"

- DIRECT bears valuable information
  - On a comprehensive collection of bio-samples and clinical information on non-diabetic control subjects
  - On how to integrate different data types to allow Systems Biology

In addition to, synergy to FP7 consortia in the field of T1DM can be seen, like e.g. to BIOSID, DIABIL_2, DIABIMMUNE, DIAMAP, DIAPREPP, NAIMIT, PREPOBEDIA.

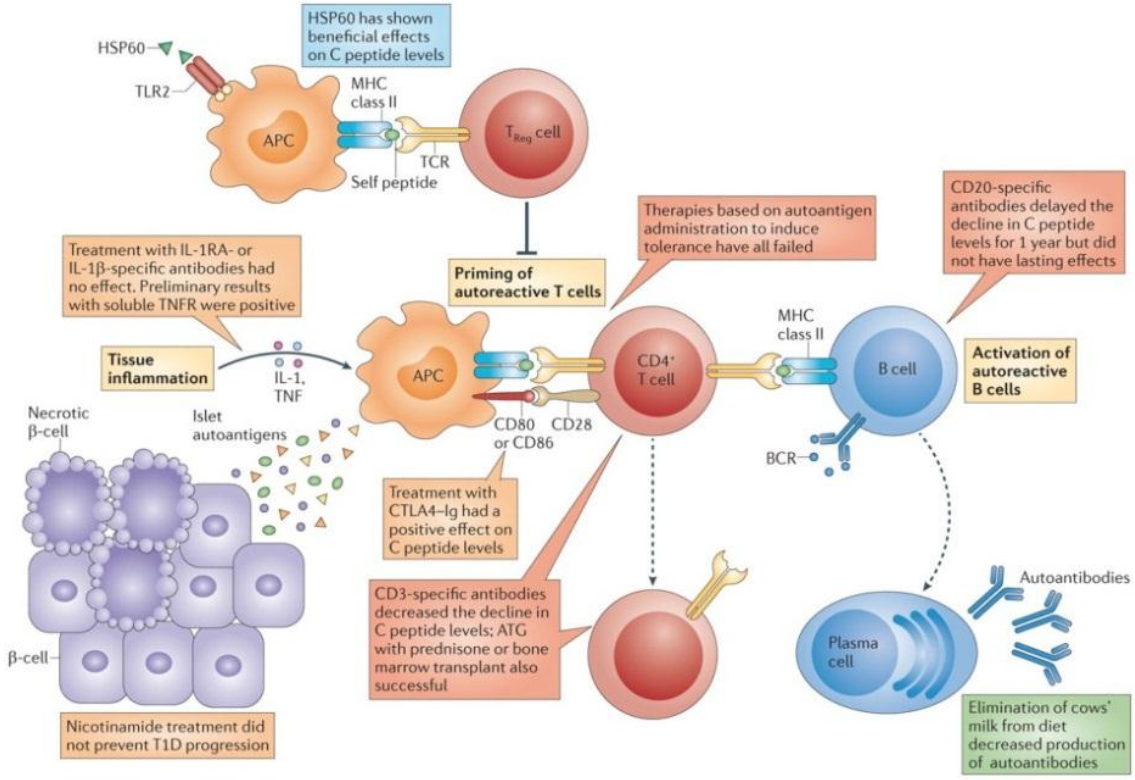
imi innovative medicines initiative

Addressing T1DM at different MoA-classes

MoA class

Ag-specific Desensitization
T-cell antigen-/target-specific inactivation
Tissue-/ antigen-specific inactivation
T/B-cell non-specific depletion/ inactivation
Co-stimulatory pathway inhib. / Cell-spec. activ. block
Cell migration blockade
Induce replication of beta cells
Induce transdifferentiation to beta cells
Secretagoges
Stem cells (hESC, iPSC, …)
Devices
Human islet transplantation
Xenotransplantation (islet)
Vaccination against viruses

Reality check



Adapted from Herold et al., 2013 Nature Review Immunology

innovative medicines initiative