

## Topic: Assessment of the uniqueness of diabetic cardiomyopathy relative to other forms of heart failure using unbiased pheno-mapping approaches

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### Topic details

Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

### Specific challenges to be addressed

Diabetes contributes to the development of Heart Failure (HF) indirectly by promoting the progression of coronary artery disease and directly through the development of cardiomyopathy. Thus, diabetic patients have a 2.5-fold greater risk for HF as compared to those without diabetes. Epidemiological studies have reported a 4-fold higher prevalence of diabetes mellitus in HF patients (20%) compared to age-matched populations without HF (5%) which rises up to 40% in hospitalised HF patients. Over last decades it became clear that there is a relationship between diabetes and HF although not all patients with diabetes develop cardiomyopathy or evolve toward HF.

Traditionally, heart failure is divided into two types based on ejection fraction:

- 1) Heart failure with reduced ejection fraction (HFrEF) or systolic heart failure caused by left ventricular systolic dysfunction which manifests when the ejection fraction is less than 40%.
- 2) Heart failure with preserved ejection fraction (HFpEF) also known as diastolic heart failure or heart failure with unaltered ventricular contractility and normal ejection fraction. In this type the ventricle fails to adequately relax and, therefore, does not fill completely with blood in the relaxation phase.

Diabetic cardiomyopathy is considered as a distinct form of heart failure that occurs in diabetic patients in absence of coronary artery disease, long standing hypertension, valvular or familial heart disease. It relies on a diagnosis of exclusion based on the presence of symptomatic cardiomyopathy, a long history of diabetes with many exclusion criteria as referred above. The main feature of diabetic cardiomyopathy is left ventricular diastolic dysfunction with impaired relaxation that impedes the efficiency of passive filling during diastole, preserved left ventricular contractility, increased filling pressure with or without cardiac hypertrophy. It is more frequent in obese females with poor glycaemic control. Diabetic cardiomyopathy shares many commonalities

with HFpEF and Hypertrophic CardioMyopathy (HCM). Although its pathogenesis is yet to be clearly defined, diabetic cardiomyopathy is increasingly recognised as a clinically relevant entity.

Therefore the overall objective of this call is to determine how unique and distinct diabetic cardiomyopathy is relative to other forms of heart failure such as HFpEF or HCM by performing unbiased statistical clustering analysis from a dense phenotyping of these patient populations. Similar methodology has recently been used to identify phenotypically distinct and more homogeneous HFpEF segments. This approach would facilitate a molecular taxonomy of diabetic cardiomyopathy which is widely accepted in the scientific community and could be applied in the clinics for differentiation from other forms of heart muscle disorders already at disease onset, thereby enabling an optimised and individualised treatment of patients.

Furthermore, a better comprehension of the underlying mechanisms and clinical manifestations of diabetic cardiomyopathy will also allow the development of more translatable and predictable preclinical models to support target and drug discovery.

## Need and opportunity for public-private collaborative research

The purpose of this topic is to bring a sufficient level of funding and multi-stakeholder commitment to comprehensively and definitively address the compilation of a set of jointly agreed phenotype criteria enabling the classification and new definition of diabetic cardiomyopathy. The leading edge of this IMI2 initiative is to make use of extant heart failure cohorts with or without diabetes and then prospectively access clinical and imaging data, as well as samples that meet carefully considered criteria. This unprecedented effort will be transformative for the field and is the type of effort needed to gain consensus acceptance by those carrying out basic research into diabetes and heart failure and clinical investigators.

The magnitude of the issue is such that it can only be addressed by a major Public-Private-Partnership involving a variety of stakeholders, including those primarily involved in understanding the clinical parameters and molecular mechanisms of disease, who have a complementary experience and expertise, as well as regulators. This is a programme which cannot be successfully administered by an individual research group or company but will require a broad consortium to be successful:

- Pharmaceutical companies contribute expertise in diabetes and cardiovascular drug discovery and development, including understanding of regulatory, economic, and logistical challenges facing drug development for disease prevention and modification. They bring unique expertise in biomarker discovery, data analysis, assay development, and prospective clinical trial design. Furthermore, companies may provide biological samples from control and standard therapy arms of clinical trials.
- Small- and Medium-sized Enterprises (SMEs) are expected to contribute specific methodologies or technical platforms to foster efficiency and innovation within the project.
- Academic investigators contribute expertise in a range of methods to discover and validate molecular phenotypic biomarkers from human tissues and bio-fluids e.g. by multi-omics and genetics/epigenetics analyses, to assess clinical and imaging phenotypes, and to analyse the relationship of molecular phenotypic biomarkers with clinical/imaging evaluation of disease development and progression.
- Hospitals, clinical research centres, and practicing physicians with access to patients with diabetes and heart failure will allow prospective assessment of these patients and contribute to the understanding of epidemiology, pathophysiology, clinical, imaging and biochemical phenotypes and provide bio-banked samples that may be used in combination with novel molecular biomarkers to discriminate patients with diabetic cardiomyopathy from other heart failure forms.
- The taxonomy and new classification will need to find acceptance by global regulators and other public bodies including payers. It will be crucial for the success of the project to interact and integrate these stakeholders as early as possible. This can be achieved by integrating them as participants into the project or if appropriate within advisory bodies.

## Scope

The overall goal of the proposed call is to assess the uniqueness of diabetic cardiomyopathy and to unveil the underlying mechanisms of cardiomyopathy in diabetic patients and the impact on cardio-vascular mortality in this population, which may finally allow the clustering of patients into an independent cohort. In consequence, this improved understanding of the clinical manifestations and diagnosis of diabetic cardiomyopathy as well as the linkage between the onset and disease progression with a specific signature will enable patient stratification at an early stage of the disease by clustering of patients into an independent cohort. The scope of the collaborative research for diabetic cardiomyopathy can be envisioned to ideally encompass objectives, outlined below:

- Definition of the inclusion criteria for patients with preserved ejection fraction (EF > 50%) and diastolic dysfunction of four different origins including:
  - Non-ischemic diabetic cardiomyopathy;
  - Non-diabetic HFpEF;
  - Idiopathic HCM;
  - Type 2 Diabetes Mellitus (T2DM) with no HF or cardiomyopathy.

- Enrollment of patients according to pre-defined inclusion criteria into the four different patient groups.

A cohort of patients shall be enrolled from registries and prospective clinical trials running at academic centers or EFPIA partners according to the pre-defined and jointly agreed inclusion criteria. Deep phenotyping of patients will be done prospectively at baseline. Additionally, blood, plasma and urine samples will be taken for multiple omics and genetics/epigenetics analysis.

It is estimated that approx. 1000 patients per patient group need to be investigated at baseline in order to achieve statistical significance of cluster discrimination. Since the initiation of the sample analyses is dependent on a phenotype overlap of less than 10 % across the different clusters (see below), study recruitment and deep phenotyping shall be completed within three years.

- Application of non-invasive imaging technologies (transthoracic echocardiography, Speckle Tracking Echo-cardiography (STE), doppler echocardiography and Magnetic Resonance Imaging (MRI)) to detect subclinical myocardial dysfunctions;
- Assessment of cardiac, endothelial and metabolic functions in all patient groups;
- Unsupervised machine learning applied to the dense phenotypic data with the goal to identify more homogeneous and differentiated clusters;
- Analysis of patients' lipidomic, metabolomic, proteomic and transcriptomic profiles in blood, plasma or urine samples, if pheno-mapping of the different clusters shows discriminative phenotypes.

A phenotype overlap of less than 10 % is being considered as criterion for the initiation of multi-omics and genetics/epigenetics analyses of baseline samples. A go/no go decision will be taken during the course of the project based on the ability to significantly differentiate and cluster newly defined diabetic cardiomyopathy from other patients in the cohort. The expectation of the multi-omics/genetic analysis is to discover a panel of novel biomarkers that (i) predicts cardiac function decline in T2DM patients, (ii) allows for early preventative life style changes, (iii) facilitates tailored therapies to slow disease progression and (iv) enables the discovery of new pathophysiological pathways responsible for diabetic cardiomyopathy or heart failure and complications. Traditional biomarkers associated with cardiomyopathy and heart failure will be monitored to determine whether the novel biomarkers offer greater predictive value for each newly defined cluster.

- System biology data analysis for disease modelling;
- Compilation of existing pre-clinical models for diabetic cardiomyopathy which will serve as a "state-of-the-art" reference;
- Translation of clinical results back into pre-clinical settings to improve the knowledge on translatable preclinical models for diabetic cardiomyopathy and develop relevant and reliable *in silico*, *in vitro* and *in vivo* models based on disease modelling.

## Expected key deliverables

The expected deliverables concentrate on those to be achieved during the five years of funding described in this Call.

Through a network of clinical databases and laboratories, efforts to enable the classification of diabetic cardiomyopathy and validation of relevant biomarkers and imaging modalities, in addition to parallel efforts towards pathway/target identification for future therapeutics development shall be initiated. These will include the following aspects:

- Definition of jointly agreed inclusion criteria/parameters that will be used for initial patient enrollment;
- Successful patient enrollment into the four groups (1000 patients/group) to ensure successful deep phenotyping and prospective assessment of phenotyping markers including clinical, imaging and biological ones;
- Applied unsupervised machine learning algorithms to deep phenotyping in order to identify patients with diabetic cardiomyopathy and distinguish them from other heart failure populations;
- Identification of causal mechanisms and pathways responsible for diabetic cardiomyopathy resulting from the comparative evaluation of the four clusters;
- Better understanding of the disease biology of diabetic cardiomyopathy based on disease modelling that will lead to the development of more translatable and predictive preclinical models;
- Paving the way for implementing this new classification by communicating value proposition to target audiences (i.e. Global Regulators, Patients, Healthcare Practitioners and Payers).

## Expected impact

In terms of Research and Development (R&D), clinical, regulatory, healthcare practice and patient's management:

- Proposals are expected to define and assess key phenotypes that characterise diabetic cardiomyopathy and could serve to establish patient diagnosis and ultimately prognosis.
- The stratification of patients into the diabetic cardiomyopathy cluster based on pheno-mapping, supported by biomarkers specific for this group will be transformative for the clinical management of these patients.
- Furthermore, novel pre-clinical models with improved knowledge on the translatability to humans will profoundly enable drug development for the treatment of diabetic cardiomyopathy beyond blood glucose control.

Overall, a better comprehension of the mechanisms and clinical manifestations of diabetic cardiomyopathy will allow the development of more translatable and predictable preclinical models supporting target and drug discovery in academia and industry. The molecular taxonomy of diabetic cardiomyopathy to be developed will enable innovative and individualised treatment options for patients.

## Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Currently, there are no synergies with completed or ongoing IMI projects.

Consortia like **DIRECT** (<http://www.direct-diabetes.org>), **RHAPSODY** (<https://imi-rhapsody.eu>) and **BEAt-DKD** (<https://www.imi.europa.eu/content/beat-dkd>) are also investigating T2DM patients. However, their scientific

goals are addressing different aspects of research. The focus of DIRECT and RHAPSODY is the identification of novel biomarker panels predictive for glycaemic deterioration / disease progression of pre-diabetes and early onset of T2DM, and treatment response that can be applied for patient stratification, whereas the BEAt-DKD consortium is assessing biomarkers for diabetic kidney disease.

## Industry Consortium

The industry consortium will contribute the following expertise and assets:

The industry consortium will bring expertise in methodologies for the merging, harmonisation and meta-analyses of existing clinical, imaging and biomarker data as well as systems biology and disease modelling. This will include expertise in biomarker evaluation, bioinformatics and statistical expertise and possibly technology for measuring specific biomarkers when appropriate. Additional contributions will include diabetes and heart failure clinical trial and regulatory expertise. Furthermore, it is envisaged that data, results and samples from control arms of ongoing clinical trials may be provided to the Consortium.

EFPIA participants have also indicated interest in providing in-kind contributions that will entail efforts at 'back-translation' into preclinical models to help in validating appropriate animal model(s) and biomarkers of diabetes cardiomyopathy.

## Indicative duration of the action

The indicative duration of the action is 60 months.

This duration allows in-depth systematic evaluation of collected clinical parameters for pheno-mapping and molecular analysis of biological samples from registries and prospective patient cohorts. Further, the obtained insights will be integrated into novel to-be-established and existing pre-clinical models.

## Applicant Consortium

The academic applicant consortium will be selected on the basis of submitted short proposals. The academic applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected academic applicant consortium in preparation of the full project proposal for stage 2.

To address the ambitious objectives of the topic adequately, the project is expected to establish a multidisciplinary network that will include scientists, physicians and imaging specialists who are recognised experts in heart failure and diabetes and contribute expertise in developing and maintaining the clinical database that is relevant to an in-depth characterisation of the patients enrolled into the four cluster groups. Furthermore, expertise in clinical research recruitment including access to clinical research centres with registries and ongoing prospective trials shall be given.

Such a network shall include applicants with the following capabilities to make the following types of contributions:

- Access to clinical cohorts of heart failure patients with or without diabetes from registries or prospective clinical trials to ensure the enrolment of 1000 patients per group within the first phase of the project;
- Availability of key non-invasive imaging technologies to assess subclinical myocardial dysfunctions;
- Development of a structured database that allows the joint analysis of complex datasets;
- Strong experience in unsupervised machine learning;
- Capability of systems biology analysis by vertical integration of phenotype, clinical, multi-omics and genetics/epigenetics datasets;
- In-depth expertise in pre-clinical models relevant to diabetic cardiomyopathy;

- Experience in communication with Global Regulators, Patients, Practitioners and Payers, who may be members of a to be established Advisory Board.

Consequently, partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI IP and legal framework. Consideration should also be given to any additional information that may be introduced after the start of the project but is not listed as project background at start date.

The applicants need also to take into consideration that the sharing of data and samples within the consortium should be allowed and in conformity with the applicable data privacy laws and laws regarding ethical matters.

## Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/Health Technology Assessment Bodies with relevant milestones and resources allocated should be proposed to ensure e.g. qualification advice on the proposed methods for novel methodologies for drug development.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

### **Work package 1 – Consortium management, administration, integration and dissemination**

#### **Work package 2 – Clinical study**

- Definition of inclusion criteria for the different patient groups;
- Enrollment of patients according to pre-defined inclusion criteria from registries and prospective clinical trials.

#### **Work package 3 – Imaging technologies**

- Application of non-invasive imaging technologies to detect subclinical myocardial dysfunction in diabetic cardiomyopathy patients.

#### **Work package 4 – Data management and machine learning**

- Data centralisation in a unique, scalable and secured database for data analysis;
- System biology approach for data analysis using data from multiple sample analysis (work package 5);
- Unsupervised machine learning for clustering on phenotypic differences beyond diabetes.

#### **Work package 5 – Multiple sample analysis**

- Proteomics, lipidomics, metabolomics, transcriptomics and genetics/epigenetics analyses;
- Analysis starts after go/no go decision depending on a phenotype overlap of less than 10% across the different clusters.

#### **Work package 6 – Disease modelling**

- Systems biology analysis based on imaging and omics data generated in work packages 3 and 5.

#### **Work package 7 – Preclinical models**

- Identify existing pre-clinical models for diabetic cardiomyopathy;
- Development of relevant and reliable *in silico*, *in vitro* and *in vivo* models based on disease modelling.