EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Brussels, 25 May 2021

COST 057/21

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action "Converting molecular profiles of myeloid cells into biomarkers for inflammation and cancer" (Mye-InfoBank) CA20117

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Converting molecular profiles of myeloid cells into biomarkers for inflammation and cancer approved by the Committee of Senior Officials through written procedure on 25 May 2021.

COST Association AISBL
Avenue du Boulevard - Bolwerklaan 21, box 2 | 1210 Brussels, Belgium
T +32 (0)2 533 3800 | office@cost.eu | www.cost.eu

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MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA20117
CONVERTING MOLECULAR PROFILES OF MYELOID CELLS INTO BIOMARKERS FOR INFLAMMATION AND CANCER (Mye-InfoBank)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to better define and understand the role of myeloid cells in diseases associated with chronic inflammation (DACI) and their potential as markers and therapeutic targets in clinical trials, bringing together myeloid immunologists, clinicians, and bioinformaticians to create a competent, multidisciplinary network. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
Myeloid immune cells are important mediators in the pathology of many diseases, especially in **diseases associated with chronic inflammation** (DACI). Recent advancements in molecular profiling technologies have led to the generation of large data sets, many of those not fully explored yet, but accessible to the entire scientific community via public data repositories. It is the aim of this COST Action to repurpose those data sets, retrieve and curate myeloid cell-specific information, and apply this information to develop novel biomarkers for DACI. To this end, Mye-InfoBank will utilise COST networking tools to enable the interaction of molecular biologists, bioinformaticians, immunobiologists, biobank coordinators and clinicians. The concerted activity of these experts on myeloid cell biology (either basic or clinical research) **MYE**, bioinformatics **INFO**, and bio-banking **BANK**, will transform complex molecular information into standardised and applicable biomarkers, which have the potential to improve clinical decision making in a number of socio-economically important diseases.

Areas of Expertise Relevant for the Action	**Keywords**
● Basic medicine: Biological basis of immunity related disorders ● Clinical medicine: Oncology ● Basic medicine: Transcriptomics ● Basic medicine: Innate immunity ● Basic medicine: Databases, data mining, data curation, computational modelling	● Myeloid cells ● Molecular profiling ● Biobanking ● Diseases associated with chronic inflammation ● Biomarkers

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Exploit molecular profiling data in order to identify and develop novel myeloid cell associated functional biomarkers with potential relevance in diseases associated with chronic inflammation (DACI).
● Develop SOP-like protocols for application of novel myeloid cell-associated biomarkers.
● Ensure sustainable and interoperable use of existing biosample collections.

Capacity Building
● Mobilise the expertise and resources of three independent groups of investigators, myeloid cell researchers (either basic or clinical) MYE, bioinformatics specialists INFO, and biobank experts BANK, all of which share a common focus on fundamental aspects of chronic inflammation, to expedite and expand Action's knowledge on myeloid cells across DACI.
● Transfer knowledge and skills between MYE and INFO groups: Close the well-known existing gap between biological expertise and bioinformatics expertise, presently hosted and contained in different scientific communities.
● Develop a workflow that links omics data on myeloid cells and their functionally related molecules, with experimental investigation of Mye-Signatures on cells and tissues.
● Broaden a cooperation between MYE and BANK groups: Foster the interaction between experimental researchers and clinicians in order to overcome gaps that currently hinder reverse and forward translational research in the field.

● Establish robust and clinically testable myeloid cell-centric protocols for application in retrospective or prospective clinical settings.
● Connect and expedite interaction between MYE, INFO and BANK groups within the ERA: Promote a list of myeloid cell-associated markers that can improve the diagnosis and treatment of DACI.
● Facilitate the development of senior and junior “Mye-Leaders” that will consist of established investigators fully acquainted via the Mye-Community network with high throughput screening methods, and ECIs trained to implement bioinformatics technology in the myeloid field.
● Develop databases and web-based analysis tools for enabling system biologists to apply this knowledge on patient samples, and biobankers and clinicians to test novel and most promising myeloid cell-associated markers across DACI.
● Enhance the career perspectives of ECIs by providing intersectoral activities that span more than one theme (through involving ECIs in the three-theme programme): 1. MYE- 2. INFO- 3. BANK.
● Enable pan-European, region- and gender-balanced collaboration to integrate and strengthen research on myeloid cells in the fight against DACI.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1 Soundness of the Challenge

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

Diseases associated with chronic inflammation (DACI) are a significant health problem in Europe and pose a significant challenge to its population. DACI (including cancer, autoimmune, infectious, and cardiovascular diseases) are the leading cause of mortality and morbidity in Europe, representing approximately nine million or 86% of all deaths – with a disease burden of around 120 million DALY (disability-adjusted life year). Mechanistically, inflammation is a process of acute or chronic immune activation, originally intended to contribute to host protection and reparative processes. However, under pathological conditions, inflammation can also contribute to disease progression. The immunological mechanisms contributing to DACI are complex. In a nutshell, chronic inflammation is caused by the continued and unwanted sensing and triggering of effector mechanisms of the immune system. **Myeloid immune cells (i.e. monocytes/macrophages, granulocytes and dendritic cells) are central elements of this pathological cascade and often control the activity of other immune cells.**

Recent technological developments have improved researchers' understanding of the role of immune and non-immune-mediated pathological processes in disease. Much of this recently acquired knowledge has been realised through the advent of next generation sequencing technologies and their application to the study of the myeloid cell diversity during health and disease in humans. Bioinformatic approaches, such as transcriptome analysis, SNP genotyping analysis and high dimensional proteome analysis have revealed important intrinsic features of myeloid cells in healthy volunteers as well as their prominent role(s) in distinct DACI. Specifically, population level and single cell resolution transcriptome analysis, which by now has been widely applied to most myeloid cell subsets with the exception of eosinophils, has revealed the cellular heterogeneity and the core transcriptomic programmes relevant for the establishment of key functionalities in monocytes, macrophages and dendritic cells. In addition, it has paved the way for the discovery of myeloid-based disease pathobiology, assigning major roles for these cells in DACI such as various forms of cancer, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), neurodegenerative diseases and cardiovascular diseases. Current state of the art bioinformatic workflows enable researchers to normalise, batch correct, analyse their own dataset, and to some extent, compare and integrate them to other data sets. These analysis strategies, in the case of the transcriptome data, both at the population level and single cell resolution, allow researchers to gain insights into differentially or communally expressed gene modules, their time-dependent expression, and the usage of transcription factor motifs overrepresented in these data. It furthermore allows for the prediction of functionalities associated to the aforementioned features by using pathway enrichment and gene ontology analysis strategies. Therefore, it enables researchers to lay down a solid, data-driven hypothesis, which can then be followed up experimentally. However, as both bulk and single cell transcriptome approaches become more accessible to many researchers, a vast amount of data is stored in repositories, which encompass a wide array of diseases studied. Nevertheless, this amount of data is convoluted and difficult to interpret, particularly if different technologies or analysis strategies were utilised. Hence, the promising potential for uncovering novel roles for myeloid cells and other immune cells during disease remains untapped and will be addressed by this Action.

Next to transcriptomic data, also other omics data such as proteomics, metabolomics, epigenomics and others are of great importance and potential interest. Nevertheless, **this Action will prioritise both population level and single cell transcriptomic data sets, as those ones are presently the most advanced, most common and therefore most feasible in the context of this COST network.** However, in the long-term perspective and apart from feasibility issues, integration of those other

"omics" data will undoubtedly be essential to fully unravel the role of myeloid cells in DACI and their potential in diagnosis and treatment.

Well-preserved, clinically annotated and catalogued human biosamples (e.g. plasma, tissue, cells) are of central importance for the translation of experimental findings to the clinic. This material plays a significant role in the identification of biomarkers or new therapeutic modalities. Unfortunately, in the past, biosamples collected in the course of clinical trials and linked to rich clinical information were often not available for further research after termination of the initial project due to the absence of governance structure and because of suboptimal organisation of storage of samples and data. In recent years, various funding initiatives have been launched on national levels and across Europe to enable sustainable use of biosamples and data by establishing high quality centralised biobanks, which follow harmonised procedures and interconnect to create interoperability and sustainability. This has been supported by the introduction of harmonised guidelines for standardised collection, processing and storage of biosamples and corresponding data, along with ethical and data protection aspects. By setting-up biobank IT networks ("Sample Locator") and consolidated catalogues ("Directory"), queries for appropriate biosamples and data collections across various countries and many biobanks have become more feasible. One of the largest compilations in this respect, and a suitable potential Mye-InfoBank collaborative partner, is the BBMRI-ERIC Directory, which covers more than 500 European biobanks with more than 100 million samples of various diseases.

The above-mentioned development of such biobank registers and directories has, however, not yet been completed. Many inquirers find the existing categorisations and directories not yet sufficient. The current focus of the registers and biobank sample locator on diseases and the type of material as central query parameters is not applicable for all research questions. For immunological network projects, such as this COST Action, information on cell composition would be decisive for the collective compilation. An intensive exchange within the Mye-InfoBank network between clinicians, pathologists, researchers and biobanks will contribute to closing this gap.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The above-described technical and analytical progress in molecular profiling techniques (so-called "omics") has generated large data sets and advanced analytical algorithms to describe the diversity of cells and mechanisms in disease. Sophisticated functional models (e.g. genetic manipulation of cells, genetic animal models) have generated deep insights into the functional biology of cells. Large infrastructural efforts have achieved great improvement with respect to the sampling, processing and biobanking of biosamples from patients. Nevertheless, it remains a great challenge to bring together these diverse areas of biomedical research in a synergistic manner. Aside from technical issues, cell biologists, molecular biologists, bioinformaticians and clinicians not only work in independent areas, but also have their own "language" and challenges.

With the concrete aim to better define and understand the role of myeloid cells in DACI and their possible usage as markers and therapeutic targets in clinical trials, Mye-InfoBank will bring together myeloid immunologists, clinicians, and bioinformaticians to create an open, competent and multi-disciplinary network termed Mye-Community.

This approach is because myeloid cells are well recognised as important mediators of disease progression and potential targets in most inflammatory diseases. At the same time, myeloid cells can also mediate therapeutic effects and thus serve as beneficial components of the immune system. Nevertheless, it is currently unclear which exact molecules or molecular signatures contained in particular subsets of myeloid cells are most useful as prognostic or predictive biomarkers in DACI. Hence, Mye-InfoBank will employ multi-disciplinary approaches in order to:

- Improve the (pre)clinical evaluation and usage of existing myeloid cell-associated biomarkers, targets, and immune-targeted therapies, so as to improve their translation for patient benefit.
- Help to develop new myeloid cell-associated research grade biomarker tests.

Better utilisation of existing databases will be a first step in this direction. At present, transcriptomic data related to the role of myeloid cells during DACIs is dispersed in various broad bioinformatic repositories.

Consequently, a comprehensive search and analysis effort in order to establish fully the role of myeloid cells across DACIs is not feasible.

In order to overcome this limitation, a major aim of Mye-InfoBank is the **creation of an expertly curated database of myeloid cell transcriptome data** related to DACIs. Algorithms like NICHE NET or regulatory network analysis on single cell data sets will be used in order to identify disease-relevant interactions between myeloid cells and other immune cell subsets. These data will be further integrated with a constantly updated **text mining enabled myeloid cell-centric literature portal** in order to integrate published results into existing transcriptome and proteome data on myeloid cells in DACIs. The literature portal will use established and publicly available text mining tools (for clustering of articles, concept discovery, tagging of biological entities etc.). Where possible, measures will be implemented to critically review published work for research quality criteria. Altogether, this approach will aid the identification of novel myeloid cell related biomarkers and therapeutic cellular targets for DACI. Comparing these new findings with the respective molecules and pathways that are known to play an important role for DACI will help to uncover the role of myeloid cells for the aforementioned diseases.

The availability of human tissue material and/or blood samples is of key importance for achieving the aims mentioned above. However, in current biomedical research, the standardised and high-quality sampling of this material in daily clinical settings is a major challenge for clinicians and pathologists. Despite many countries having made efforts to install centralised biobanks, more professional workflows and improved technical standards for sample processing and storage are desirable. Across the European Research Area (ERA), biobanks will benefit from enhanced possibilities to search for samples and data via registers, sample locators and directories, to better exploit this huge data resource. Connecting molecular & cellular immunologists, pathologists and clinicians, who tend to operate in different “work environments” will be instrumental to improve information and documentation, such as cell composition of the biosample in question (for example, information on the leukocytic infiltrate in neoplastic tissues). In order to better utilise and clinically translate the data-derived biomarkers within this Action, Mye-InfoBank aims to a) develop searchable parameters for better characterisation of biosamples at the cellular level, b) consolidate and standardise the presentation of existing sample and data collections, c) harmonise the work-flows for sample preparation and storage, and d) develop protocols for data analyses and storage.

1.2 Progress beyond the state-of-the-art

1.2.1 APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE-OF-THE-ART

Bioinformatic and data repository challenge:

At present, transcriptome (and other molecular profiling) data are organised in large repositories, which do not always allow for the specific extraction of disease and cell type-related data sets, provide only limited amounts of meta data, and harmonisation between different dataset remains challenging. Quality and optimisation of data deconvolution is also of critical importance, especially when extraction of myeloid-cell specific information from data sets such as bulk and single-cell RNA sequencing of complex tissues is intended. The same holds true for transcriptomic data on other immune cell types that potentially interact with myeloid cells, providing a rationale to integrate this information into a draft of the myeloid cell-interactome in various DACI in order to foster biomarker discovery. Therefore, the Action will build a unique catalogue of curated data sets from these available repositories, in order to uncover the unappreciated roles of myeloid cells in DACIs and their interaction with other immune cell types such as T-, B- and NK cells. The molecular profiling approaches will be facilitated by advanced text mining, expert data curation and enlistment in a user-friendly searchable database organised according to disease. This will then allow for the further analysis of the data sets within WG 1 and inter-connected with WG 2 and WG 3.

Biomarker development and application challenge:

Published molecular profiling studies and analyses in functional model systems strongly support an important role of myeloid cells in DACI. However, the clinical translation and exploitation of this

knowledge faces hurdles and has not been systematically addressed. This Action will use the catalogue of curated data sets (for molecular profiling data) and databases generated from advanced text mining (for published literature) to identify myeloid-cell associated signatures, molecules or cellularsubsets that represent disease overarching “myeloid marks” in DACI. This information will be integrated with signatures of myeloid cell-interacting immune cell types, providing a detailed insight in the myeloidcell immune context in various DACI. Depending on the type of those “myeloid marks”, biomarker panelswill be generated, tested and technically standardised into a format applicable to archived tissue material. The (when possible retrospective) testing of these biomarker panels on tissue samples of defined and well-annotated patient cohorts will enable this Action to transfer new molecular-biological findings on myeloid cells into a clinical context.

Biobank and tissue archive challenge:

Most studies (research or clinical studies) produce a large number of biosamples, which are usually not completely used during the initial project. Under pre-defined conditions, these samples could be used for further studies. In the context of this COST Action, this collection of biosamples via a specifically designed registry (Mye-Register) will be presented to a broad pan-European research community and be made accessible for the exploration of immune biomarkers in DACI. Search criteria and search masks will be optimised and amended to contain (immuno) biological information wherever possible. Bioinformatic experts, molecular immunologists, cellular immunologists, biobank experts, pathologists and clinicians will discuss and provide parameters and search criteria, which will improve the future selection of tissues and patient material based on (immune) biological parameters. Members of this Action will also collect requirements and legal issues associated with the use of potential biosamples in order to facilitate utilisation in pan-European studies. Within WG 3 and in close cooperation with the experts from the other WGs, the group members will compile the various requirements with regard to sample quality, sample characterisation and standardised documentation for later second usage. Guidelines will then be formulated to support the conception of future biosample collections.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

Mye-InfoBank has the following major research coordination objectives:

1. **Exploit existing molecular profiling data in order to identify and develop novel myeloid cell-associated functional biomarkers with potential relevance in DACI.**

This objective is **specific** and **measurable**, because the Action will extract testable biomarkers from existing complex data sets. This will be done by the identification of suitable transcriptome data sets (single cell and bulk) in ArraysExpress and GEO by database survey and followed by the extraction, homogenisation and organisation of data sets related to DACIs and myeloid cells from those repositories by manual curation and text mining when applicable. **Achievable** by the coordinated activity of bioinformatics experts, immunologists and molecular biologists. Dataset normalisation and exploratory analyses shall be conducted using mainstream tools and techniques to predict gene signatures for the involvement of myeloid cells in DACI. **Relevant** and **timely** considering the large potential of existing molecular profile databases, the importance of DACI and the relevance of myeloid cells.

2. **Develop SOP-like protocols for application of myeloid cell-associated biomarkers in DACI**.

This objective is **specific** and **measurable** as the Action will develop, test, distribute and apply those biomarkers. Potential novel (objective 1) biomarkers will be designed and, together with already known existing biomarkers, translated into applicable flow cytometry-based protocols (for circulating myeloid cells) or immunostaining protocols (for tissue-based markers). Whenever possible, protocols should be suitable for multi-centre studies. **Achievable** given the expertise of the consortium members in monitoring immune cells and molecules in the circulation and in tissue. Immunomonitoring experts will collaborate with Action members overseeing the participating biobanks and with associated clinical partners. **Relevant** and **timely** considering the strong potential of myeloid cells as targets or biomarkers in DACI, together with the need for better prognostic and predictive biomarkers in these diseases.

3. **Ensure sustainable and interoperable use of existing biosample collections.**

This objective is **specific** and **measurable** as the Action will sort biobank samples into (myeloid) cell type composition, determine the sample quantities, define the processing specifications, exclusion criteria and requirements for clinical data, and finally design the documentation required for characterisation. **Achievable** given the current biosample infrastructure among Action members in the ERA and the access to already existing biosamples that are immediately available for research use without initiating expensive and slow new collection activities. **Relevant** and **timely** as biological information is sparse in existing biobanks and biobank directories.

1.2.2.2 Capacity-building Objectives

In the context of DACI, myeloid cells are critical components of immunopathology and thus are attractive therapeutic targets. However, phenotypic and functional complexity of myeloid cells requires:

i. A critical mass of investigators dedicated to combating DACI through targeting myeloid cells.
ii. Novel approaches that would exploit the full potential of omics data and biobank-stored clinical material to better understand involvement of these cells in different pathological states.

The expertise and resources of three independent groups of investigators, myeloid cell researchers (either basic or clinical) **MYE**, bioinformatics specialists **INFO**, and biobank experts **BANK**, all of which share a common focus on fundamental aspects of chronic inflammation, will be mobilised to expedite and expand the Action's knowledge on myeloid cells across DACI. The involvement of partners with complementary research activity areas who would team up with groups from regions with less capacity in one or more of these areas has a strong capacity building aspect, as detailed below.

Mye-InfoBank will promote capacity building through the following strategy:

I. Transfer knowledge and skills between MYE and INFO groups

- Close the well-known existing gap between biological expertise and bioinformatics expertise, presently hosted and contained in different scientific communities.
- Develop a workflow that links omics data on myeloid cells and their functionally related molecules, with experimental investigation of Mye-Signatures on cells and tissues.

II. Broaden a cooperation between MYE and BANK groups

- Foster the interaction between experimental researchers and clinicians in order to overcome gaps that currently hinder reverse and forward translational research in the field.
- Establish robust and clinically testable myeloid cell-centric protocols for application in retrospective or prospective clinical settings.

III. Connect and expedite interaction between MYE, INFO and BANK groups within the ERA

- Promote a list of myeloid cell-associated markers that can improve the diagnosis and treatment of DACI.
- Facilitate the development of senior and junior "Mye-Leaders" that will consist of established investigators fully acquainted via the Mye-Community network with high throughput screening methods, and ECIs trained to implement bioinformatics technology in the myeloid field.
- Develop databases and web-based analysis tools for enabling system biologists to apply this knowledge on patient samples, and biobankers and clinicians to test novel and most promising myeloid cell-associated markers across DACI.
- Enhance the career perspectives of ECIs by providing intersectional activities that span more than one theme: 1. MYE- 2. INFO- 3. BANK.
- Enable pan-European, region- and gender-balanced collaboration to integrate and strengthen research on myeloid cells in the fight against DACI.

2. NETWORKING EXCELLENCE

2.1. Added value of networking in S&T Excellence

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

To fully unravel and exploit the important role for myeloid cells in DACI requires an unsupervised view of the related (transcriptomic) data landscape. This COST Action will address this gap by mining the treasure trove of existing data in public repositories for relevant data sets, using text-mining approaches coupled to subsequent expert curation of the data sets, thereby building a unique catalogue of data sets related to DACI. This will then enable a more detailed interrogation of the role of myeloid cells in disease, not yet studied for their involvement up to now. To integrate this effort to existing initiatives, this Action will approach consortia such as the European Flagship Initiative LIFETIME (which elucidates disease mechanisms using single cell technologies), the BLUEPRINT Epigenome consortium (which catalogues the cellular epigenome during health and disease) or the Human Cell Atlas (which aims to produce a single cell resolution transcriptomic map of the human body in order to validate and integrate their analysis and data). Their work will be integrated with the work of the Mye-InfoBank Action, thereby further enhancing researchers' understanding of the role of myeloid cells in the pathology of DACI. In contrast to other initiatives, Mye-InfoBank will connect already published data from multiple OMICS layers with clinical available phenotypes, thereby generating a multi-modal dataset, which will be the basis for a faster discovery of DACI biomarkers that are associated with myeloid cells and their biology. Secondly, Mye-InfoBank will bring together bioinformatic,experimental and clinical expertise to fully exploit available datasets, which synergises with the aforementioned initiatives, such as BLUEPRINT. Furthermore, Mye-InfoBank will integrate well with other ERA initiatives as it will utilise datasets generated within other European initiatives and apply them across disease entities to generate further synergism between various funding initiatives.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

Mye-InfoBank brings together several groups of investigators with different expertise (myeloid cell, inflammatory disease and biobank experts, as well as experts on transcriptomics (incl. single-cell RNA sequencing) and bioinformatics specialists). Moreover, it involves academic laboratories and clinicians (many of them with links to industry and involved in clinical trials). Mye-InfoBank is an open, inclusive network, which at the moment integrates European leaders in the field with less- advanced groups from countries with a history of significant collaborative interactions as well as less research-intensive countries. This creates a critical mass of researchers exploring myeloid cells in DACI, single cell and population level transcriptomics / bioinformatics alongside clinical fellows facilitating the take-up of knowledge and expertise generated from this Mye-Community network. However, the current integration between partners often only spans one out of three activities of Mye-Info-Bank. Therefore, further integration across these disciplines is highly needed. The network will be open to experts involved in one or more research themes of Mye-InfoBank from all regions of the ERA. The emphasis will be placed on recruitment of geographically- and gender-balanced interdisciplinary range of new members, especially with underrepresented expertise, complementary DACI models or at early stage of scientific career. Recruitment of new members will be achieved by advocating Mye-InfoBank within European academia, biotech and healthcare industry, through websites, conferences, workshops and publications. To strengthen the network further, Mye-InfoBank leaders will regularly review and discuss emerging challenges in DACI during WG meetings, and actively seek desirable collaboration partners through several available communication/research channels, such as single cell expression atlas, repositories of RNA-Seq datasets etc. The involvement of transcriptomic and bioinformatic researchers with both expertise in single cell and population level analysis in Mye-Community activities will be a game changing solution for defining specific myeloid cells across DACI and providing new avenues of exploration. This can be accomplished by re-analysis of already available big data sets that provide information to Mye-Community investigators about myeloid-specific biomarkers and/or signatures. On the other hand, the involvement of biobanking experts is important for the future translation of this work to the clinic by enabling translational testing of myeloid cell-related markers in DACI, using vast biobank resources. Such a multi-disciplinary and comprehensive approach requires a pan-European networking effort. Innovative networking activities, such as hackathons of biologists and bioinformaticians, organised by Mye-InfoBank, will introduce technological challenges to the participants and will create a

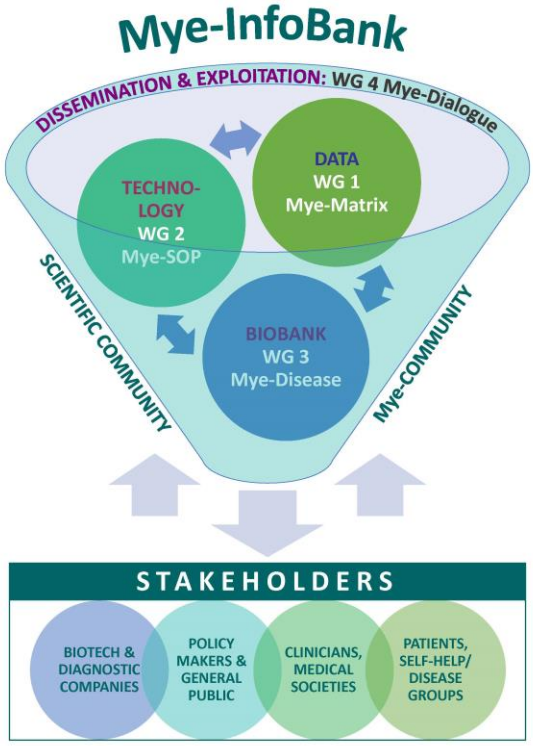

Figure 1: Mye-InfoBank's interactive structures

favourable environment for the development of novel and additional solutions not yet included at this point in time (compare Figure 1).

2.2.2. INVOLVEMENT OF STAKEHOLDERS

Mye-InfoBank will have an impact on several stakeholders (see Figure 1), including biotechnology companies (for the immunomonitoring, to generate kits and antibodies), clinicians, patients, health insurances, patient associations (European Patients' Forum as well as disease-specific organisations), scientific and clinical societies, self-help groups, clinical trial networks (TREAT- AID, AID-NET, EORTC,IBD clinical trial network, ITNs), other COST Actions etc. Thus, WG 4 will be created and a central task will be to facilitate continual stakeholder contact throughout the Action's lifetime. As from day one, Mye-InfoBank will conduct an in-depth stakeholder analysis, and representatives of all these identified stakeholder groups will be actively approached through the personal network of Action participants, social media, and flyers at conferences (e.g. ESCI meetings, ESMO, Keystone meetings, Neutrophil Meeting, COST Connect Meetings), and by the selected search and personal invitation of individuals. Specific workshops will be held to involve, attract and communicate with stakeholders.

Companies will be invited to presentations of the Mye-InfoBank concept and, at a later time point, the exploitable results of the COST Action. Selected technology transfer and IPR officers from participating institutions will be invited to chaperone the discussions. Based on the recent experiences during the COVID-19 pandemic, in-person meetings will be supplemented by cost-effective virtual or hybrid meetings, if applicable.

During these workshops translatable and applicable data sets, biomarkers and laboratory protocols will be discussed with potentially interested companies that are active in this market segment. Technology transfer and IPR offices of participating institutions will be consulted prior to those meetings to ensure that there are no conflicts of interest.

The members that apply to the Mye-InfoBank Action will join the WG(s) of their choice. Clinicians will be actively approached and invited to guide the discussions on patient cohort selection and the usage of biobanked material. The results of biomarker studies will be distributed to clinical societies and presented at the respective national and European society meetings. WG 4 will liaise between all WGs and the stakeholders. Mye-InfoBank will have an impact on several stakeholders (see Figure 1), including biotechnology companies (for the immunomonitoring, to generate kits and antibodies), clinicians, patients, health insurances, patient associations (European Patients' Forum as well as disease-specific organisations), scientific and clinical societies, self-help groups, clinical trial networks (TREAT- AID, AID-NET, EORTC, IBD clinical trial network, ITNs), other COST Actions etc. Thus, WG 4 will be created and a central task will be to facilitate continual stakeholder contact throughout the Action's lifetime. As from day one, Mye-InfoBank will conduct an in-depth stakeholder analysis, and representatives of all these identified stakeholder groups will be actively approached through the personal network of Action participants, social media, and flyers at conferences (e.g. ESCI meetings, ESMO, Keystone meetings, Neutrophil Meeting, COST Connect Meetings), and by the selected search and personal invitation of individuals. Specific workshops will be held to involve, attract and communicate with stakeholders.

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Potential members that apply to the Mye-InfoBank Action will be assigned to the WG of their choice. Clinicians will be actively approached and invited to guide the discussions on patient cohort selection and the usage of biobanked material. The results of biomarker studies will be distributed to clinical societies and presented at the respective national and European society meetings. WG 4 will liaise between all WGs and the stakeholders.

2.2.3. MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

The NNC Georgia acts as a secondary proposer of this Action. Additional NNCs have expressed interest and will be actively approached in order to widen the cooperative network. It is anticipated that colleagues and institutions from these countries will specifically benefit from the multi-disciplinary approaches planned for this network. Since the planned research activities of this Action are built on existing and available data bases and on existing biobankedpatient specimens, they are less cost-intensive than many current biomedical research activities.

The Action's founding members have multi-lateral connections to key scientific opinion leaders in International Partner Countries. These experts will be approached and invited to join as members throughout the Action. Since opportunities for networking and standardisation is less frequently available in the American or Asian biomedical research area, there is mutual benefit for this type of interaction.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

Scientific impact: Recent research has provided compelling evidence for the claim that myeloid cells modulate disease progression and therapeutic response in cancer as well as non-neoplastic DACI. However, it has been difficult to translate this evidence into beneficial clinical scenarios. Due to their substantial functional plasticity, myeloid cells can help to either fight disease or worsen the pathology. Beneficial and protective roles in acute infections and regenerative inflammation are contrasted by disease-promoting and therapy-limiting roles in cancer and other DACI. All these properties are associated with distinct functional subtypes of myeloid cells. Recent efforts in molecular profiling of immune cells in various diseases have generated large data sets, which have not yet been fully exploited. Despite important insights into the complex biology of myeloid cells, the identification of potential novel subsets or discovery of potential new therapeutic targets, very few of these findings could yet be exploited therapeutically. Using text mining and bioinformatic analysis tools this Action will re-

analyse those publications and data to identify transcriptomic signatures, proteins or myeloid cell subsets with a potential role in DACI. Most importantly, Mye-InfoBank will extract from these analyses applicable biomarkers. Ideally, the researchers will identify and develop “easy-to-use” antibody-based staining panels, which can be applied to standard biobanked material under SOP-like conditions. The application of biomarker panels will then provide the Action’s members with information regarding the potential of myeloid cells or their functional molecules to predict disease progression or therapeutic response. It is therefore the aim of this COST Action to go beyond existing specialised studies and publications, reduce complex data and make them applicable to archived tissue material and finally link this biological information to existing tissue material in European biobanks. This COST Action will generate a major scientific breakthrough and innovation by linking publicly available high-endmolecular profiling data sets with archived tissue material from patients with DACI.

Technological impact: This initiative will provide considerable technological impact as it will utilise myeloid cells as a prototype to link and practically exploit two large existing research infrastructure resources (that is biologic data sets and biobanked patient specimens) in a synergistic manner. This impact will be achieved by several innovations and breakthroughs. Firstly, the COST Action will generate a comprehensive user-friendly, graphical user interface driven portal in which these data sets will be catalogued by disease. Furthermore, data sets will be bioinformatically deconvoluted to reveal gene signatures affiliated to myeloid cells, which will allow the prediction of biomarkers and gene modules associated to myeloid cells during the pathogenesis of DACI. Additionally, text-mining approaches will be applied to biomedical literature to further identify publications that link new molecular pathways operating in myeloid cells to DACIs. These data will then be cross-analysed with the deconvoluted transcriptomic data allowing a stringent prediction of biomarkers followed by biological validation. Moreover, the COST Action will provide in depth online tutorials on how to access the information presented in this newly curated database alongside webinars that aim for knowledge dissemination by meetings and the exchange of researchers in the field of differential expression analysis, transcriptomic data deconvolution and biomarker analysis.

Interoperability and sustainability are important issues not only at the data level, but also for biosamples and biobanking. Considering the growing biobanking infrastructure in the ERA, the efficient use of existing archived materials must be given high priority in the future. In addition to ethical and data protection aspects, the standardised recording and description of biosamples is of relevance. In most cases, clinical and translational studies have a disease-specific focus and the biosample documentation is mostly limited to classical pathological and clinical parameters of the donating patients. By incorporating additional (immune) biological parameters the searchability of biobanks for specific biofunctional studieswould be greatly improved. Therefore, a major innovation of this Action will be to facilitate the inclusionof additional (myeloid cell-related) biological features of biosamples into biosample catalogues and related search masks. This way this Action will create an operational channel that optimises the use of biobanked material by implementation of additional immunobiological properties of the specimens. This channel will also motivate pathologists and biobank operators to participate in this Action as it offers substantially improved opportunities for participation in translational and clinical (biomarker) studies.

Socio-economic impact: According to recent statistics, nine out of ten deaths within Europe are caused by DACI. Cancer is by far the main cause of death with an average of 261 deaths per 100 000 inhabitants, while ischaemic heart diseases accounted for 127 deaths per 100 000 inhabitants, and respiratory diseases were the third most common cause of death with 88 deaths per 100 000 inhabitants in 2015 (across the EU28, source Eurostat). There is a clear east-west disparity in the standardised death rates per 100 000 inhabitants per country, reflecting that in the Eastern European area cancer caused up to as many as 300 deaths, ischaemic heart diseases up to 400 deaths, while in the Western Europe area the average for respiratory diseases was higher than the European norm, with over 100 deaths. Hence, through its pan-European and collaborative nature, this Action will contribute to the counterbalancing of geographical differences in disease burden and morbidity. In addition, the development of new e-tools and an enrichment of biobank catalogues that will emerge from the Mye-InfoBank network have a potential to be more universally exploited in other research projects. This is likely to have economic benefit, for example through driving scientific output and competitiveness in the ERA. Moreover, given that omics-technologies represent one of the most cost-effective and timely ways

to analyse cell identity and alterations in different pathophysiological contexts, the e-approach-driven Mye-InfoBank network can provide an excellent environment for empowering new and high potential actors towards future leadership in omics technologies. Several members of this initiative have previously been successful in founding spin-off companies based on the discovery of novel potential targets for immunotherapy and related biomarkers. An analogous approach is envisioned for this Action, thus generating additional direct economic benefit from this network.

3.2 MEASURES TO MAXIMISE IMPACT

3.2.2. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

DACI is an umbrella term spanning a vast range of disorders that constitute by far the highest disease burden in Europe. Chronic disease is strongly affected by immunological mechanisms, which in turn are highly influenced by myeloid cells. While there are huge bioinformatic and data repositories at biomedical researchers' disposal, the extraction of data, the meta data status, and the generation of meta data sets between different studies is currently difficult and overwhelming for non-bioinformaticians. Similarly, myeloid cell-focused biobank catalogues and registries are presently lacking. Here, Mye-InfoBank aims to contribute towards:

Knowledge creation by:

- Closing the large gaps between the different disciplines through concerted, specifically defined collaborations using the COST Action inclusiveness framework to achieve this.
- Establishing bioinformatic profiles for myeloid cells for basic and clinical application (Mye- Matrix).
- Identifying and testing biomarkers and molecular signatures ("Mye-Signatures").
- Verifying new SOP-like protocols.
- Data curation in biobanking and Mye-Matrix generation.

Transfer of knowledge by:

- Collaborative workflow and sharing of expertise between the WGs.
- Creation of a user-friendly Mye-Matrix portal (including tutorials).
- Action collaboration with selected companies based on their core technological expertise.
- Strongly focused ECI training on bioinformatic tools and techniques, the detection of biomarker genes and proteins, biomarker analysis in tissues and digital pathology, and SOP application.
- Harmonised protocol and guideline publication.

Career development by:

- Implementing the COST inclusiveness policies within the pan-European area when creating Mye-Community, especially with regard to ITC, ECI and gender balance.
- Creation of next-generation young experts specifically trained to meet Mye-InfoBank's interdisciplinary DACI challenge.
- Encouraging the use of ITC Conference Grants for personal career development and high-profile international conference networking.

3.2.2 PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

A common pitfall of classical dissemination and dialogue policies in science is that the non-basic research players are often excluded from research initiatives until the more advanced stages where results are presented and the stakeholders are informed of or are invited to participate or invest in these results (deliverable-exclusive dialogue). However, this strategy often denies both primary and secondary stakeholders the potential to influence research at an early stage. Thus, Mye-InfoBank will involve these target groups early on in order to positively impact the research process right from the start (deliverable-inclusive dialogue). Hence, Mye-InfoBank shall establish a Working Group for communication and outreach (WG 4) whose direct task will be to cultivate and maintain regular stakeholder and public awareness of COST Mye-InfoBank's network, activities, events and achievements throughout the Action's lifetime, and facilitate dissemination and exploitation of results. To this end, in addition to scientists, the Mye-InfoBank WG 4 will be open to PR officers, technology transfer and IP experts, as

well as regulatory and ethics committee members from participating centres. Furthermore, through its close contact to stakeholders, WG 4 will have a strong drive to facilitate the successful exploitation of the Action's deliverables and support the establishment of spin-offs.

Target audiences and channels: The stakeholders shall be concertedly approached as defined in chapter 2.2.2. **At the start of the Action**, a stakeholder analysis will be conducted, and the contact persons within relevant companies and associations will be identified and approached. Hackathons will be organised to draw attention to Mye-InfoBank's goals and to initiate contact and involvement with the target groups. Webinars will be offered for the same purpose. A short PR film will be created highlighting and explaining the aims of the network to raise awareness amongst the diverse stakeholder communities. A large European immunology meeting will be used as a key platform for dissemination of this network's activities and attracting collaborating members. **During the Action**, Mye- InfoBank's website will be used as a central communication and information platform with specially prepared information sections for the different target groups, the contents being continuously updated and expanded. Newsletters with contents specially tailored to the individual target groups will be sent out quarterly. Key messages will be sent out for sharing with already established target networks by nurturing contact with the relevant communication officers, a strategy to achieve dialogue on a broad, European-wide basis. At appropriate time points during the Action's lifetime, meetings with specific groups will be held e.g. with industry and SMEs and other potential investment partners with a view to the targeted further development and establishment of research cooperation; with regulatory bodies regarding the SOPs; with patient organisations to share clinical insights. The platforms available at international and national conferences will be used to draw attention to the Action's work, as will round table discussions, media interviews, and all Action publications. **At the end of the Action**, a final conference will highlight the COST Action's achievements, as will the final publication. In all these outreach activities, close attention shall be given to adhering to the requirements for the communication, dissemination and valorisation of COST Action results and outcomes.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

WG 1 Mye-Matrix

In order to build the Mye-Matrix data framework, publicly available databases will be mined for single cell and population level transcriptome data sets related to myeloid cells and DACIs. Data and meta data will be extracted, quality controlled, expertly curated and organised in a user-friendly database to allow easier access to the available landscape of data by the broader research community. Use of algorithms such as NicheNet or regulatory network analysis on single cell data sets will be used in order to identify potential cellular interactions between myeloid cells and lymphocytic immune cell subsets with potential relevance in DACI. In a second step, transcriptomic data sets will be linked to existing literature, mined by advanced text mining approaches from public databases, e.g. PubMed.

Working Group 1 has the following specific tasks:

1. Enumerate, extract and organise the fragmented transcriptome and meta data about the role of myeloid cells in DACI from various repositories (ArrayExpress, GEO, Human Cell Atlas etc.) and convert it into biologically and clinically meaningful biomarkers and data sets.
2. Integration of novel generated transcriptomic data sets from other partners (wet lab collaborators) into the newly curated database.
3. Establish a text mining based database of biomedical literature related to myeloid cells and DACIs and link it to a user-friendly database encompassing the aforementioned information in order to determine the role of myeloid cells in DACI.

4. Prediction of **novel** and informative biomarkers (gene signatures or proteins), for myeloid cells associated with various DACI through bioinformatic data analysis approaches.

These tasks will be achieved by the following activities and networking tools:

1. WG 1 will establish a bioinformatic pipeline in order to automatically mine the data repositories to extract transcriptomic data sets related to myeloid cells and DACIs.
2. Following data mining, WG1 will generate a compendium of DACI related transcriptomic data sets and develop strategies to normalise, explore and validate (in cooperation with WG 2) these approaches.
3. WG 1 will setup tutorials, training schools and STSMs to enable the largest possible dissemination of bioinformatic tools and techniques to the myeloid and DACI research community. This will be achieved through dissemination of webinars, virtual meetings and hands on demonstrations at dedicated Mye-InfoBank workshops.
4. At the end of the project, the created database will be published in a peer-reviewed journal and made publicly available.

WG 2 Mye-SOP

WG 2 will focus on the validation and standardisation of **existing** myeloid-related biomarkers. These biomarkers will be extracted from literature mining utilising the expertise of Action members also active in WG 1. Those candidates are thus mostly derived from wet lab experiments, but (i) have not yet been properly validated due to a lack of adequate tools for their detection, or (ii) have only been validated in one or a limited number of diseases. Hence, in the first instance WG 2 will establish the standard operating procedures (SOPs) for the evaluation of existing biomarkers, and, as WG 1 gradually makes progress, intensify interaction with WG1 to explore additional novel biomarkers. WG 2 will finally test the principal applicability of these signatures and markers on real-life clinical samples and for this purpose collaborate with WG 3.

Working Group 2 has the following specific tasks:

1. Existing, but as yet not fully explored signatures and biomarkers should be validated at the protein level on circulating cells or in tissues of various DACI, when applicable. Detecting proteinexpression will in the first instance require an assessment of the (commercially) available antibodies, their use in published literature and, if needed, the generation of novel antibodies (eventually in collaboration with companies).
2. Novel antibody panels will be designed for the detection of DACI-associated myeloid cells via appropriate technology such as multi-colour flow cytometry, multiplexed immunohistochemistryor FISH. These panels will undergo a first validation through exploratory staining on material from patients with DACI.
3. Constitute a task force of groups willing and capable of pre-testing potential biomarker panels on an exploratory level.
4. Develop standardised SOP-like protocols for myeloid-associated biomarkers.
5. Train ECI Action members with a special interest in translational biomarker research to conduct biomarker staining and perform analysis.
6. Translate SOP-like protocols onto archived tissue material obtained from patients with DACI.

These tasks will be achieved through the following activities and networking tools:

1. WG 2 members will have frequent meetings, in person or online, with WG 1 members to discuss which biomarkers and signatures are promising, starting with existing biomarkers but gradually moving to newly discovered biomarkers. Such markers should be withheld for the subsequent testing in wet-labs. This includes important decisions on whether similar biomarkers can be used for various DACI, or whether disease-specific biomarkers/signatures will be needed.
2. WG 2 will identify companies with whom to collaborate for the development of antibodies not presently available on the market. Companies will be selected based on their core technological expertise (generation of tools, methods, technologies).
3. WG 2 will organise workshops with individual companies to assess the company's suitability and willingness to collaborate on this project and to generate an antibody suitable for immunostaining.

4. If possible, the same samples will be shared between the different WG 2 laboratories to independently evaluate the suitability of the selected biomarkers. Markers will then be discussed with WG 3 members to relate these markers to clinical information and to determine their suitability for testing on biobanked material.
5. A smaller number (3-5) of expert labs will join forces to develop SOP-like protocols byexchanging and testing protocols, by web-conferencing and by engaging in STSMs.
6. A training school on biomarker analysis in tissues and digital pathology will be held. Companies providing (hardware or software) products in this field will be invited to participate and present their solutions; also as a means of reaching out to private sector stakeholders. STSMs will be organised to train ECIs in SOP application. It is envisioned that 50% of the ECIs will be recruitedfrom ITC countries.
7. Action members trained under task 6 will apply biomarker candidates via SOP-like protocols on DACI tissues in collaboration with clinical and biobank experts from WG 3.

WG 3 Mye-Disease

The first main task of WG 3 is to provide clinical expertise and high-standard clinical samples from patients with DACI for the testing of myeloid cell-associated biomarkers. The second main task of this WG is the further enrichment of current biobank catalogues with searchable information on immunobiological features of archived biosamples.

Working Group 3 has the following specific tasks:

1. Definition of those DACI that are most appropriate for analysis in the context of this Action.
2. Identification of feasible existing sample collections with the parameters defined under 1 and with a governance that allows the use of samples and data in the context of this Action.
3. Conception of a questionnaire for a comprehensive query in already existing registers (such as BBMRI-ERIC) regarding the re-use or second use of biosamples outside the original context inthe absence of broad consent.
4. Parallel compilation of the parameters used in existing biobank registers for characterisation and search for biosamples. Based on this, creation of an adapted catalogue for the characterisation of biosamples with regard to myeloid cells. Identification of biobanks within theBBMRI-ERIC Directory, which have biosamples with immunological characterisation and information on the cellular composition in their inventory and query the utility of this material.
5. Identification of critical meta-information and guidelines for data curation together with other WGs.
6. Establishment of a register for existing biosample and data collections.
7. Preparation of a guideline for the future conceptualisation of biosample and data collections with immunological characterisation.
8. Hosting of a training school with focus on the standardised collection and documentation/processing of biosamples and the use of these samples for biomarker development and validation.

These tasks will be achieved through the following activities and networking tools:

1. In a joint effort with members from WG 1 text mining tools and published literature will be used to generate a knowledge background on the role of myeloid cells in DACI. Next, together with clinical colleagues, a prioritisation of diseases will be done. Relevant clinical experts within the Action will be identified or newly recruited. Once novel data from database work of WG 1 becomes available, additional DACI may be considered.
2. With the other WGs, potential network members with biosamples collections will be identified and collections must be evaluated. As a mandatory requirement for integration into Mye-Register the ethical (consent, governance) and data protection requirements are reviewed, applied for and obtained, if necessary.
3. Conception of a questionnaire regarding the re-use or second use of biosamples in close cooperation with national or European biobank nodes.
4. Screening of European consortia (such as BBMRI-ERIC), various national solutions and commercial providers of biosamples with respect to their search catalogues and their usability in the Mye-Community context. Development of a practical catalogue for the characterisation of

biosamples with regard to myeloid cells.
5. Identification of biobanks with relevant biosamples for DACI questions via existing directories. Alternative providers will also be taken into account, if necessary.
6. Selection of several experts (clinicians, pathologists, immunologists, biobankers, IT experts) to create a catalogue of material descriptions.
7. Query within the Action network whether and to what extent biosamples and data collections are available that can be made available for broader use.
8. Examination of ethical and data protection aspects for the establishment of a register. The involvement of representatives from the ethics committee, data protection experts and patient representatives in this process should help to establish processes that will enable the broad use of samples and data outside the original study in the future.
9. Standardisation of data from retrospective collections.
10. IT implementation of the registry.
11. Based on the work of WG 1 and WG 2, guidelines for the standardised and characterisation of biosample collections with an immunological focus will be developed.
12. In collaboration with all other WGs, a training school on the technical and theoretical issues of biobanking, biomarker development and biomarker validation will be organised.

Leaders of WG 2 and 3 will attend conferences on DACI to present the Action and recruit clinicians with the interest, expertise and capacity to transfer the clinical testing of SOPs and biomarkers.

WG 4 Mye-Dialogue

The task of WG 4 is to coordinate and execute the communication, dissemination and outreach activities as well as identifying cross-sectional topics that require the participation of WG 1 - WG 3. To this end, WG 4 will execute “classical” dissemination strategies and channels (see below) to contact stakeholders, disseminate Action outcomes, and engage with the general public. In addition, WG 4 will organise in-person workshops and virtual meetings to engage specifically with selected stakeholder groups in order to facilitate strong interaction on both research and development.

Working Group 4 has the following tasks:

1. To identify stakeholders and interest groups clearly and specifically.
2. Creation and maintenance of the Action website, ensuring the website is an up-to-date central communication tool publicly sharing the latest presentations, findings, papers and other communications produced by the Action.
3. Creation of information material for distribution by the Action members at different type of events to increase the number of ECIs and female researchers.
4. To establish and maintain the Mye-InfoBank member directory online.
5. To initiate and nurture contact with communication representatives of the industry, policy makers, clinicians and patient groups as well as within the Action’s network (at the COST Country and institutional level) in order to facilitate the achievement of Mye-InfoBank aims and the exploitation of results.
6. To maintain public awareness of the Action through (bundled) social networks.
7. To enlist professional advice on and support for Action spin-offs (lab-to-market).

These tasks will be achieved through the following activities and networking tools:

1. An in-depth stakeholder analysis and background search will be undertaken to define the pertinent target groups and contact persons precisely.
2. Implementation of a strong innovation strategy to guide and support Action spin-offs.
3. Meeting with intellectual property (IP) experts from Mye-InfoBank member institutions in order to establish a framework and the criteria relevant for later exploitation of results.
4. Formation of an IP committee that regularly oversees potential of Action outcomes for commercial exploitation.
5. Workshop with venture patent attorneys, technology transfer officers, IP commercialisation experts etc. to consult and guide Mye-InfoBank researchers on this topic.
6. Workshop with regulatory experts to support WG 3 in setting up the framework for effective utilisation of existing biobanked samples for secondary use.

7. Liaison with potential researchers from NNC and ITC countries.
8. Dialogue with representatives from medical societies related to DACI covered by Mye-InfoBank.
9. Support WG 2 in dialogue with companies potentially interested to develop biomarker kits commercially.
10. Organise disease-specific virtual meetings between self-help groups and clinical experts in Mye-InfoBank.
11. Serve as contact point and moderator between basic research scientists and stakeholders.
12. Organise workshops on scientific writing with additional input from journalists.

Further, WG 4 will prepare project templates for internal communication and publications, coordination of outreach events for promoting Mye-InfoBank topics. Target audiences are those mentioned in Figure 1 as well as reaching out to wider audiences such as e.g. next-generation youth at high schools through participation in science festivals. This will be achieved by seeking direct contact with PR departments and communication officers of Mye-InfoBank member institutions and greater stakeholder network. In addition, a dedicated website and regular group-specific newsletters will be utilised.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

Through the collaborative activity of experts in the fields of bioinformatics, biostatistics, molecular biology, immunobiology, pathology, biobanking, and clinical treatment of DACI the Mye-InfoBank Action will be able to provide the following deliverables:

- Reports on identified myeloid cell-associated biomarkers with the potential to serve as prognostic orpredictive biomarkers in DACIs.
- Developed SOP-like protocols for myeloid cell-associated biomarkers, which can be tested on archived biobanked samples in participating centres.
- Publications of developed SOPs and provision to the scientific community.
- Reports on performed translational studies that apply the above-mentioned biomarkers via SOP-like protocols.Scientific publications on obtained data and presentations for conferences.
- Compiled training material and manuals on tissue analysis methods, digital pathology and associated statistical methods.
- Reports on existing workflows amended by the network for collecting and cataloguing biosamples through the definition of novel biological parameters that will ease and foster the utility of stored biosamples.
- Target group specific information material and Action Fact-Sheets for distribution among professional stakeholders and for communication with the general public.

For the detailed timeframe, please see chapter 4.1.4. (GANTT DIAGRAM at the end of the document)

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

General COVID-19 pandemic restrictions

Risk: Travel is restricted, and larger physical meetings and/or Training Schools and STSMs are suspended.
Contingency: WG and MC meetings will be conducted virtually. Wherever possible, Training Schools and STSMs will be organised according to the specific pandemic situation in the individual countries and considering travel regulations.
Risk: Mye-InfoBank's planned timeline cannot be implemented as envisaged.
Contingency: The GANTT and Action's schedule will be re-organised accordingly. Mye-InfoBank shall focus on the data analyses aspects in the earlier phases of the Action, moving on to physical meetings, workshops, Training Schools and STSMs at later stages.

WG 1 Mye-Matrix

Risk: Data normalisation and harmonisation across different data sets can be a major challenge, leading to the identification of non-stringent biomarkers or gene signatures.
Contingency: In order to mitigate these risk factors, various data normalisation strategies will be benchmarked on the assessed data sets and the results will initially be validated by WG 2 on an exploratory data set.

WG 2 Mye-SOP

Risk: The most interesting novel biomarkers and signatures identified by WG 1 at the transcriptional level contain genes that are hard or impossible to assess at the protein level (genes with unknown function, low abundant genes, etc.)

Contingency: The concerted discussions between WG 1 and WG 2 should lead to a list of approachable targets. Some of these markers may not be the perfect markers (solely based on expression pattern), but should at least be markers that provide relevant information and can be tested in an assay. Gene expression signatures will also be considered for testing.

Risk: WG 1 & 2 develop a biomarker for which no antibody is commercially available.

Contingency: COST Action members will (directly or through collaboration) generate such antibodies in house. If necessary, new partners with this expertise will be approached.

Risk: Staining patterns and quality differ between centres.

Contingency: STSMs will be organised to further harmonise the procedure and train the investigators.

WG 3 Mye-Disease

Risk: Criteria for sample characterisation are too specific and complex for integration in routine biobanking.

Contingency: Already during the elaboration of the characterisation parameters, it must be checked whether these parameters can be analysed and documented as part of clinical routine examination.

Risk: In the Mye-Community, insufficient sample-related data exist for efficient interdisciplinary use and establishment of a registry.

Contingency: Inclusion of working groups that have not yet been strongly represented in the Mye-Community. Selection may be based on the results of WG 1. Optimisation of sample-related data (sample quality, patient characteristics, clinical documentation).

Risk: Use and access of existing sample collections does not yet allow usage with Mye-InfoBank.

Contingency: Dialogue with responsible regulatory and ethics authorities to broaden applicability.

WG 4 Mye-Dialogue

Risk: An initial scepticism or lack of interest of the desired stakeholder groups.

Contingency: A contact-friendly, individually focused approach to establish a good rapport and basis of interaction with each target group.

Risk: A conflict of interests between the various groups hinders the communication, dialogue and/or development of spin-off process.

Contingency: A mediation process enabling the parties to express their varying or conflicting interests and to find new common ground for continued collaboration.

4.1.4. GANTT DIAGRAM

Milestones and Deliverables	Year 1				Year 2				Year 3				Year 4			
Action Annual Quarter	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Core Activities																
Kick-Off Meeting	■															
MC Meeting		■			■				■				■			
WG Meeting (all WGs)		■			■				■				■			■
Workshop		■			■				■				■			
Publications															■	■
Progress Report				■				■								
Final Assessment																■
Final Conference																■
FAD																■
WG 1: Mye-Matrix																
Establishment of bioinformatic pipeline	■	■	■													
Data information retrieval	■	■	■													
Integration of novel data sets			■	■	■	■	■	■	■	■	■	■				
Generation of compendium					■	■	■	■	■	■	■	■				
Text mining	■	■	■	■												


Biomarker & signature prediction
Establishment of Mye-Matrix
WG 1 + 2 joint meeting
WG 1 Meeting
Tutorials
Training school
STSM
WG 2: Mye-SOP
Link data mining and biology
Obtain signatures and markers
Identify biomarkers
Prediction of biomarker candidates
Pre-testing of biomarker panels
Validation of biomarkers with existing tools
Development and translation of SOP-like protocols
Generation of novel tools for biomarker detection
Exploratory stainings with novel tools
WG 1 + 2 joint meeting
WG 2 Meeting
WG 2 + 3 joint meeting
Company workshop
Training school
STSM
WG 3: Mye-Disease
Define appropriate DACI for analysis
Identify, collect and provide biosamples
Analysis of biobank catalogues
Biobank screening
Creation of Mye-Catalogue
Establishment of register
Guideline publication
WG 2 + 3 joint meeting
WG 3 Meeting
Training School
STSM
WG 4: Mye-Dialogue
Stakeholder analysis
Website set-up
Website and target group updates
Stakeholder relations, inclusion, consultation
Mye-InfoBank member directory
IP meeting and committee establishment
Implementation of innovation strategy
Workshops
Virtual meetings (outreach and exploitation)
Capacity Building Objective
Establishment of Mye-Community