Brussels, 19 May 2025

COST 026/25

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Innate lymphoid cells – the European quest for innovative cancer prognosis and immunotherapy” (ILCquest) CA24117

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Innate lymphoid cells – the European quest for innovative cancer prognosis and immunotherapy approved by the Committee of Senior Officials through written procedure on 19 May 2025.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA24117
INNATE LYMPHOID CELLS – THE EUROPEAN QUEST FOR INNOVATIVE CANCER PROGNOSIS AND IMMUNOTHERAPY (ILCquest)

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 drive innovation in therapeutic cancer research by understanding the role of innate lymphoid cells in cancer pathogenesis, enabling their wider use in cancer research by defining unique phenotypic determinants, and developing standardized protocols for their isolation and in vitro propagation. 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
Since their discovery in the early 2010s, innate lymphoid cells (ILC) have been increasingly recognized for their roles in cancer pathogenesis, exhibiting both pro- and anti-cancer activities. However, the inconsistent use of phenotypic markers for their identification has hindered progress in utilizing ILC for cancer prognosis and therapy. ILCquest aims to overcome this obstacle by standardizing methodologies for the identification, isolation, and cultivation of ILC, thus enabling accurate and reproducible quantitative and qualitative assessment of ILC during cancer pathogenesis, and design of novel ILC-targeting drugs.

Leveraging a comprehensive pan-European network of experts in basic and clinical immunology, systems biology, synthetic chemistry, biochemistry, computational modelling, medical biotechnology and clinical oncology, this initiative will create a unique collaborative platform - the European ILC Network. This network will facilitate consortia creation for joint research proposal applications and serve as a hub for training and capacity-building, promoting best practice, and elevating ILC research quality and reproducibility, that way ensuring sustained impact beyond the project's lifespan. Through close communication and dissemination of ILCquest results to policymakers, R&D professionals, and biotechnology and pharmaceutical companies, the use of ILC in cancer prognosis and therapy will be significantly advanced.

By integrating diverse expertise and embracing the fresh perspectives of early-career investigators and innovators, ILCquest aims to deepen our understanding of ILC in cancer. This systemic approach will pave the way for future clinical trials and support the development for novel cancer diagnostic tools and immunotherapies, addressing a critical and growing global health challenge.

Areas of Expertise Relevant for the Action	**Keywords**
● Basic medicine: Innate immunity ● Basic medicine: Cell differentiation, physiology and dynamics ● Clinical medicine: Oncology ● Basic medicine: Systems biology ● Basic medicine: Biological basis of immunity related disorders	● Innate lymphoid cells ● Cancer ● Immunotherapy ● Prognostic markers ● Tumor organoids

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

Research Coordination
● To precisely delineate the signature markers of ILC in blood and across various healthy and tumor tissues of mouse and human origin and develop panels for their accurate identification.
● To summarize existing approaches for isolation and expansion of ILC from blood and tissues of human and mouse origin and recommend SOPs.
● To develop novel approaches for ILC isolation and expansion from solid tumors.
● To model/develop ILC-containing tumor organoids/spheroids for in vitro drug testing.
● To validate standardized panels for the ILC identification, ILC isolation and propagation through engagement of multiple research centers.
● To identify novel ILC-based prognostic and therapeutic targets in cancer.
● To plan and initiate a clinical trial for ILC prognostic use in cancer.

Capacity Building

● To create Open Access data storage system and repository comprising ILC information.
● To create an Open Access ILC Atlas.
● To kick-start European ILC Network and expand it beyond the ILCquest borders.
● To enhance and support communication between clinicians and basic scientists.
● To initiate development of ILC-related R&D products (antibody panels and toolkits) and ILC-modulating drugs.
● To create steady communication channel between the basic scientists, and industry, regulatory and legislative bodies, cancer patients organizations and general public.
● To establish new consortia for joint research proposal applications.
● To attract ECIs and innovators in the ILC-related research and foster their career progress through trainings, mobility and participation in the scientific projects.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

ILCquest aims to provide innovative concepts for cancer prognosis and immunotherapy centred on type 1, type 2 and type 3 innate lymphoid cells (ILC). However, the use of ILC as predictors of disease or drug targets is severely hampered by the lack of precise identification of specific ILC subsets. Due to their variable identification markers influenced by tissue origin and inflammatory status, the definition of ILC subsets presents a challenging task. Since their discovery in the early 2010s, studies on their roles, functions, and modulation have resulted in over 8000 papers, according to PubMed data[1]. **Recognizing the increasing significance of ILC in cancer pathogenesis, global attention is focusing on investigating their involvement in cancer initiation and progression**. The importance of ILC has been acknowledged by establishment of the annual International ILC Conference. However, a unified network of investigators focused on ILC is still missing and this lack of communication and ILC markers standardization pose significant obstacles to advancements in ILC research, particularly concerning comparative immunological studies, the use of ILC as prognostic biomarkers, ILC-targeted drug design and synthesis, and the potential translation of acquired knowledge into clinical applications. To avoid repetitive and incomparable studies, this initiative seeks **to standardize ILC identification, isolation and propagation** and to drive research into their **prognostic and therapeutic implications in cancer** leveraging a pan-European network of experts in immunology, systems biology, biochemistry, synthetic chemistry, computational modelling, medical biotechnology and clinical oncology.

- **Function and nomenclature of ILC**

ILC are primarily located in mucosal membranes, where they play crucial roles in maintaining tissue homeostasis, response to infections, and tissue repair. They integrate signals from neighbouring stromal and immune cells, thereby significantly influencing the regulation of both local and systemic immune responses[2,3]. ILC encompass several subpopulations, including ILC1, ILC2, ILC3, lymphoid-tissue inducer (LTi) cells and natural killer (NK) cells, each with distinct roles in immune responses. As NK cells have already been thoroughly investigated in the cancer field and their phenotype precisely determined, the focus of this Action will be on the other ILC. ILC1, ILC2, and ILC3 exhibit cytokine and transcriptional profiles akin to helper CD4+ T cell subsets, namely T helper (Th)1, Th2, and Th17/22 cells, respectively. LTi are either considered as a specific subgroup of ILC3 or as a separate ILC subset. These cells are pivotal in the development of secondary lymphoid organs during embryogenesis, but also in the formation of tertiary lymphoid structure during carcinogenesis[2-4].

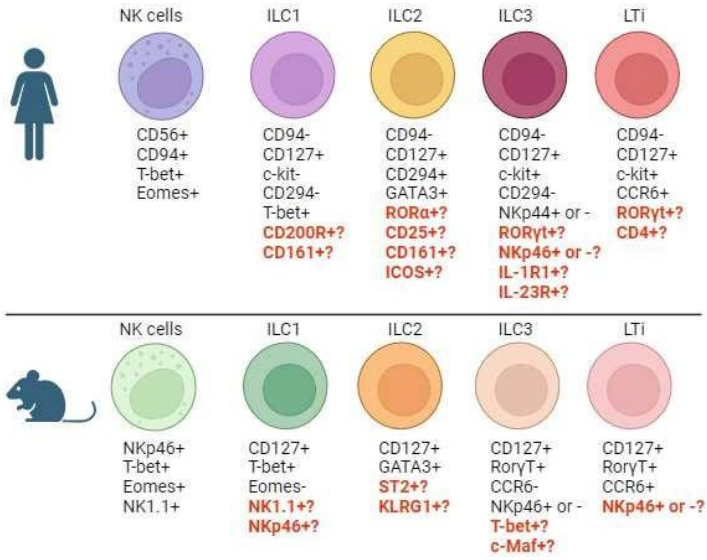

Figure 1. Proposed markers for identification of human and mouse ILC. Red coloured markers are ambiguous. ILC are CD45+ and hematopoietic lineage markers negative (Lin-). For mice, Lin- designates cells negative for CD3, CD5, CD19, Ly6G, Ter119 and FceRI, while for human, cells negative for CD2, CD3, CD14, CD16, CD19, CD56, CD235a. Created by BioRender.com

Although the markers for ILC identification differ between mice and humans, signature cytokines are shared between human and mouse ILC subsets. ILC1 are characterized by IFN-γ production[2,5], ILC2

secrete IL-5 and IL-13, while ILC3 produce IL-17A and/or IL-22[6]. In mice, ILC are categorised as hematopoietic lineage-negative populations expressing CD127 (IL-7 receptor)[2]. However, these basic features do not suffice for precise subset identification. Various potential signature markers must be considered in phenotypically characterizing ILC populations (Figure 1). Additionally, while transcription factors serve as identification markers for mouse cells, human ILC employ different designation markers (Figure 1); for instance, RORγt is not used for phenotyping human ILC3[7,8]. The standardization of both mouse and human ILC is important for the appropriate correlations between results obtained on animal studies and their translation to human diseases.

Currently, **discrepancies in markers utilized for identifying ILC populations** complicate the comparison and the interpretation of results across different studies[2,3,7]. Adding to this complexity, the distinct gene modules are expressed in migratory versus tissue-resident ILC populations[9]. Furthermore, ILC residing within specific tissues acquire tissue-specific markers. For instance, salivary gland ILC1 lack CD127 expression but express CD49a, CD49b, and CD103[10]. Mature ILC, particularly in inflammatory contexts, often exhibit mixed or interchangeable properties of multiple subsets instead of adhering strictly to discrete ILC1, ILC2, and ILC3 phenotypes[10,11].

➢ ILC in cancer research

Although immunotherapies have revolutionized the treatment of cancer over the last two decades, the field of cancer investigation requires a reassessment as there is rising prevalence of cancer patients worldwide with an estimated annual economic impact of over €100 billion in Europe alone (data from Europe's Beating Cancer Plan). The European societal burden is reflected by 2.74 million cancer cases reported in 2022. The 2.4% increase in cancer-related deaths between 2020 and 2024 highlights the critical importance of addressing this issue for human health (data from European Cancer Information System). Despite the unprecedented success of the first wave of cancer immunotherapies based on immune checkpoint inhibitors and chimeric antigen receptor T cells, many people fail to benefit from such treatments, or alternatively, the benefit is not permanent[12,13]. There is thus a need to expand next-generation cancer immunotherapeutics. As T cells depend on signals from innate cells to guide their responses, ILC have been identified as promising candidates and the future focal point of cancer-related research[1] (Figure 2). With the exception of NK cells, the contribution of individual ILC subsets to immune responses during early tumour development has been poorly defined so far. The role of ILC in cancer initiation and progression can either be **disease-restricting or promoting**. For instance, ILC1, similar to NK cells, serve to destroy cancer cells in renal cell carcinoma, and limit development of acute myeloid leukemia or colon cancer[14,15]. However, emerging findings indicate pro-tumour roles of ILC1, either through provoking chronic inflammation or angiogenesis[16]. Further, ILC2 create colon and lung cancer-permissive microenvironment by inhibiting T cell activation[17,18], but also can protect from melanoma and pancreatic cancer[19]. While aberrant activation of ILC3 precipitates colon cancer[20], the presence of ILC3 in the breast cancer tissue correlates with increased metastatic potential[21].

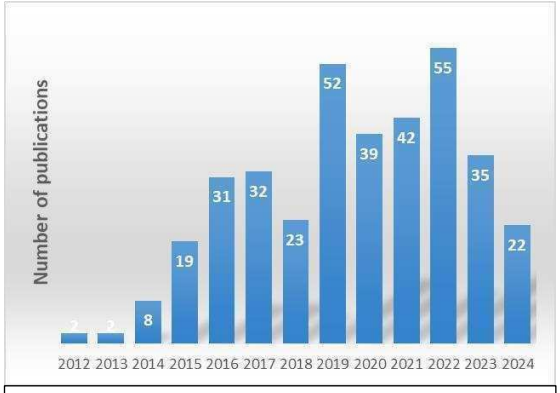

Figure 2. Annual distribution of scientific articles on ILC and cancer (PubMed, 2024).

ILC hold potential **as predictive markers for** various types of **cancers**, but this potential has yet to be fully validated. Although in human peripheral blood ILC represent a minute fraction of CD45+ lymphoid cells, literature suggests that elevated ILC1 proportions are associated with favourable prognosis in breast, colorectal cancer and metastatic seeding of the liver[22-24]. Higher ILC3 numbers in breast cancer tissue and in the lungs of squamous cell lung carcinoma patients correlate with poorer prognosis[25], whereas elevated ILC2 numbers indicate favourable diagnosis in melanoma or colorectal cancer[19,23,26].

Research into **ILC targeting is still in its nascent stages**. ILC can be targeted using specific cytokines, anti-cytokine antibodies, glucocorticoids, immune checkpoint inhibitors, lipid mediators (particularly short-chain fatty acids - SCFA), aryl hydrocarbon receptor (AHR) ligands and β2-adrenergic receptor agonists[27]. An important point here is that ILC are radio-resistant[28], thus allowing their manipulation in parallel with radiotherapy. The future of drug testing on ILC depends upon **standardized protocols for ILC purification from blood and tissues.** There are ongoing disputes on the use of specific methodologies such as flow cytometry sorting, magnetic beads purification, and conditions for *in vitro* propagation of ILC[7]. Furthermore, the cultivation of ILC in tumor organoids or spheroids to mimic tumor environment will offer new insights in ILC behaviour during tumorigenesis, an area completely unexplored thus far.

In summary, ILCquest aims to drive innovation in cancer research by fostering collaboration, defining unique phenotypic determinants of ILC, and developing standardized protocols for their isolation and *in vitro* propagation. This will pave the way for novel interventions for the treatment of cancer and introduce ILC-related immune indicators for improved cancer prognosis.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The main aim of ILCquest is to drive innovation in therapeutic cancer research by understanding the role of ILC in cancer pathogenesis, enabling their wider use in cancer research by defining unique phenotypic determinants of ILC, and developing standardized protocols for their isolation and *in vitro* propagation. The rising prevalence of cancer worldwide and still limited therapeutic modalities justify the exploration of ILC involvement in various types of cancers and the formulation of novel prognostic approaches related specifically to ILC. To achieve the ultimate goal of reducing the mortality of cancer patients and severity of cancer pathologies through improvement of ILC-related research, ILCquest will address the following challenges:

CH1: The lack of uniform ILC phenotyping impairs the comparison between different studies and the implementation of ILC-related data. Fifteen review papers focusing on ILC detection variability (PubMed, 2022-2024) identify ILC standardization as a major academic concern worldwide. Depending on the markers that researchers use for ILC identification, the identity of specific ILC can be often misinterpreted and therefore potentially misleading. In these vague circumstances, ILC isolation and propagation are often inaccurate, while the comparison of data obtained in different studies is usually impossible. This leads to the global increase in research expenditure. The results of this Action will provide a precise definition of ILC identification markers, minimizing redundant research efforts and facilitating more effective translational research.

CH2: Unstandardized ILC isolation and propagation protocols hinder *in vitro* drug testing. To progress the field of cancer immunotherapy, the interrelations between ILC and cancer cells, and the response of ILC to therapeutics has to be thoroughly investigated. The best option for doing so is the *in vitro* approach, either on purified ILC or combined ILC and tumor cells in the form of organoids/spheroids. ILC isolation and propagation protocols from blood and tissues differ depending on the laboratory where they are examined and uncertainties still exist about their behaviour *in vitro* under variable cultivation conditions[7,29,30], while the quality of the ILC culture depends upon the exact ILC identification and purification process. Therefore, to remove the main barrier for *in vitro* drug testing on ILC, ILCquest aims to provide recommendations for the standardization of the protocols for isolation and propagation *in vitro* and their cultivation in 2D cultures or 3D tumor organoids/spheroids.

CH3: ILC utilization as prognosis indicators or as druggable targets in cancer remains underexplored. As pointed out in the section 1.1.1, the cancer prevalence and the mortality increase validates a search for the new prognostic indicators that will allow patient stratification and timely introduction of adequate therapy, thereby reducing the cost of the treatment and cancer-associated mortality. As ILC are present in solid tumors and aid T cell response[2,3,7], they represent a logical, yet underexplored target for development of novel immunotherapies. ILCquest will systematize the existing knowledge and propel pre-clinical and clinical research in ILC-cancer area.

CH4: International network of researchers from diverse backgrounds with the focus on ILC does not currently exist. This is the first initiative that will bring together researchers with expertise in immunology, biomedicine, systems biology, molecular biology, clinical oncology, synthetic chemistry, bioinformatics, mathematical modelling and drug development. It aims to unify ILC identification and isolation protocols and therefore create fertile ground for ILC targeting or their use as immune indicators for cancer progression. The initiative from ILCquest to form the European ILC Network as a Study group under the auspice of the European Federation of Immunological Societies (EFIS) will increase Europe's competiveness in this field of research. Finally, inclusion of early-career investigators (ECIs) and innovators in the proposed network and allowing them to join high-ranking ILC research groups (those within the ILCquest network and beyond), through short-term scientific missions (STSMs) will bring the fresh perspective in ILC field and simultaneously improve their career prospects.

CH5: Dissemination and communication of ILC-related research and data is insufficient. Although significant efforts in dissemination of ILC-related research to the scientific peers have been initiated by the establishment of annual International conference on ILC, the interest of industry, patients and policy makers for the use of ILC in cancer therapy, despite their potential, is generally lacking. ILCquest aims, through dedicated Meetings, to attract R&D, Biotech and Pharma companies and small/medium enterprises (SMEs) and generate a fertile ground for the evolution of ILC-related therapeutics, antibody panels and toolkits, with the support of civil society, investors and legislators.

At present, ILC are underrepresented as prognostic indicators and cellular targets in cancer therapy. Considering the significant body of ILC knowledge accumulated over the past decade, launching this Action is both timely and highly appropriate as it will solve the critical issue of non-comparable ILC-related data and therefore establish a solid foundation for the scientific and industrial progress in the field of cancer prognostic indicators and drug design, ultimately benefiting cancer patients and reducing overall research and healthcare costs.

1.2. PROGRESS BEYOND THE STATE OF THE ART

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

To respond to the stated challenges, this Action will establish cooperative network across Europe and beyond, utilizing knowledge in biomedicine and oncology, together with the expertise in flow cytometry and microscopy, big data analysis and *in silico* tissue modelling to provide instructions for the most precise phenotypical characterization of ILC in humans and mice, and suggest optimal methods for their isolation and propagation. Networking among scientists with the background in 2D and 3D cultures, animal models, drug design and development, clinical oncology, together with R&D, Biotech and Pharma companies, regulatory bodies and cancer patient groups will galvanize establishment of novel ILC-based prognostic protocols and therapeutic approaches for cancers, which are still unexplored areas. Innovative ILC-based drug targets will secure progress in the cancer therapy for the benefit of cancer patients. ILC research field surely requires a fresh perspective which will be obtained through enrolling new students and empowering ECIs to advance to leading positions or to transfer and use their knowledge in industry. ILCquest is going to address all mentioned challenges through the activities organized by specific Working groups (WG).

As a response to CH1, **WG1** will be dedicated to **Standardization of ILC phenotypic identification.** In order to enable comparison between different research groups that investigate ILC, and for the benefit of utilizing ILC as specific immune indicators for cancer development, WG1 activities will result in the development of uniform and standardized panels for phenotypic identification of ILC according to the personal research experience of the participants and the existing literature data. Flow cytometry data across various tissues will be harmonized and systematized in the form of ILC Atlas, an Open Access repository. A uniform ILC phenotypic identification will enable creation of upgraded antibody panels in cooperation with R&D companies. Application of panels for ILC identification will not only facilitate data comparison but also reduce redundant studies and improve the possibility of translation of animal cancer research to human settings. This will pave the way for clinical trials, ultimately benefiting cancer patients and reducing the costs associated with their usually long-term treatment.

To address **CH2, Standardization of ILC isolation and propagation protocols** will be performed through the activities of **WG2**. WG2 will systematize the existing protocols for ILC isolation/enrichment and propagation primarily from blood, but also from other accessible tissues rich in ILC such as animal lungs, intestines and tumors, and human tonsils and intestinal biopsies. ILCquest will pioneer the development of ILC isolation protocols for human tumors, a previously unaddressed area of research. By integrating this new knowledge with the expertise in organoid/spheroid culture, the modelling of cancer environments will be enabled (*in silico* and *in vitro*). This approach will advance the testing of ILC-based cancer therapeutics. ILCquest Participants will reach consensus on the optimal conditions for ILC isolation and propagation and suggest standard operating procedures (SOPs) for each tissue of interest, and design toolkits for possible commercialization.

As a response to **CH3, WG3** will pursue any relevant information about **Prognostic and therapeutic exploitation of ILC in cancer.** WG3 will systematize existing knowledge and provide statistical analysis and mathematical modelling of data, leading to predictions regarding the quantitative and qualitative assessment of specific blood ILC. Combined with the standardized identification markers, these results will support the use of ILC as prognostic bioindicators for cancer progression, encouraging clinical oncologists to initiate studies on ILC. Further, *in silico* predictive analysis using computational models will identify known and derive new compounds (e.g. modifications of AHR and FFAR ligands) that can modulate specific ILC populations. Recommended drugs will be tested on tumor organoids and spheroids *in vitro*, with promising lead compounds evaluated in cancer animal models, thereby minimizing animal use in research. This WG will move forward the field of cancer prognosis and treatment through discovery of novel ILC-related biomarkers and therapeutic options.

In order to respond to **CH4, WG4** will be dedicated to **Networking, training and mobility**. Establishment of the European ILC Network as formal entity will aid communication of ILC-related results and perspectives even beyond the project lifetime. The Network will also aim to expand globally, beyond participants from Europe, China and Japan that are already involved in the ILCquest, achieving a long-term goal of establishing formal International ILC Society. Networking through in person Meetings and online will facilitate the creation of consortia of participants with the matching expertise that will

apply for grants provided by Horizon Europe (HE) and other funding bodies to finance the research activities. The global perspective outlook on new cancer treatments will be increasingly shifted towards ILC by cultivating a new generation of researchers proficient in ILC biology. These training initiatives will also strengthen the management skills of ECIs, equipping them for leadership positions. To inspire ECIs to pursue scientific careers in ILC and cancer, ILCquest will provide opportunities for mobility and collaboration with renowned research institutes through COST framework and other HE initiatives.
Extensive **Dissemination and communication** will be covered by **WG5** as a response to **CH5.** Data management plan will encompass measures for data exchange through online storage system (Dropbox), Open Access web data repositories (Zenodo and the Open Science Framework) and preprints repositories bioRxiv or medRxiv (in accordance to the FAIR principle). In addition to the usual dissemination and communication tools used for reaching scientific peers (biannual WG Meetings, conferences, publications, social networks and website), ILCquest will promote the results of the Action through the ILC Atlas (archived in one of the indicated repositories) and submit an improved panel of identification markers for human ILC to Human Cell Atlas to ensure wider dissemination. The potential of ILCquest results commercialization will be explored during the dedicated Meetings with R&D, Pharma and Biotech companies. The exchange in knowledge about ILC coming from different areas (research, clinic, pharmacology) will facilitate developing new research agendas, primarily in cancer prediction and treatment, which will be discussed with the European Medicine Agency (EMA) and the local Committees for National Guidelines and Ministries of Health of each country participant. Cancer patients will be involved through promotional material, dedicated Meetings and through the capacity of the European Association for Cancer Research (EACR) for information dissemination. Patients' opinion and awareness of new ILC-related cancer therapies will be assessed through a web-based survey. General public will be informed *via* social networks and during outreach events such as Researcher's nights and Science Fairs.

The response of the ILCquest to the posed challenges will drive the progress of science, technology and community welfare through several aspects:
- ✓ Up-scaling excellence in ILC-related research
- ✓ Fostering *in vitro* drug testing on tumor organoids/spheroids instead on animal models
- ✓ Raising awareness of clinical oncologists about the new ILC-based therapeutic avenues
- ✓ Establishing closer connection between preclinical researchers and medical doctors
- ✓ Moving forward translation to ILC-based clinical studies
- ✓ Developing new R&D products
- ✓ Directly involving the society in shaping the future cancer therapy roadmaps
- ✓ Improving career prospects for ECIs and innovators.

1.2.2. OBJECTIVES

1.2.2.1. Research Coordination Objectives

ILCquest aims to unify and standardize ILC phenotyping, isolation and propagation protocols and increase the knowledge about the prognostic value of ILC and their modulation for the benefit of cancer treatment. ILCquest Participants are highly motivated to achieve these goals as the future of the ILC-related research depends on the precision of ILC identification that will allow accurate comparisons between the scientific data obtained by different research groups. The appropriate comparisons will strengthen the value of the obtained knowledge, avoid repetitive studies and instigate patient-oriented investigations. This unification and standardization will ultimately lead to novel prognostic and therapeutic modalities that will overcome limitations of the current approaches and enable cancer patient stratification, and timely and more efficient therapy of various cancers. All this will benefit society by introducing new potential for cancer prognosis and immunotherapy as well as through economical use of research funding and healthcare resources. To address the challenges identified in 1.2.1, this project sets the specific objectives, each of them covered by a specific WG:

- RO1: To precisely delineate the signature markers of ILC in blood and across various healthy and tumor tissues of mouse and human origin and develop panels for their accurate identification (WG1).
- RO2: To summarize existing approaches for isolation and expansion of ILC from blood and tissues of human and mouse origin and recommend SOPs (WG2).
- RO3: To develop novel approaches for ILC isolation and expansion from solid tumors (WG2)
- RO4: To model/develop ILC-containing tumor organoids/spheroids for *in vitro* drug testing (WG2).
- RO5: To validate standardized panels for the ILC identification (WG1), ILC isolation and propagation (WG2) through engagement of multiple research centres.
- RO6: To identify novel ILC-based prognostic and therapeutic targets in cancer (WG3).
- RO7: To plan and initiate a clinical trial for ILC prognostic use in cancer (WG3).

1.2.2.2. Capacity-building Objectives

To maximise the impact of the research objectives, the main ILCquest capacity-building objective is to establish an efficient international network of basic research and clinical oncology centres, strengthening Europe's competitiveness in the ILC field. The dissemination of new knowledge acquired through ILCquest will enhance the research capabilities of institutions in the field of cutting-edge ILC-related science. Additionally, it will strengthen the capacity of industry stakeholders by driving the development of innovative R&D products and advancing immunotherapy solutions. An equally important focus will be placed on a class of ECIs and innovators that will be empowered to pursue scientific careers and leadership positions. To achieve all this, the following capacity-building objectives are set:

- CO1: To create Open Access data storage system and repository comprising ILC information (WG5)
- CO2: To create an Open Access ILC Atlas (WG1)
- CO3: To kick-start European ILC Network and expand it beyond the ILCquest borders (WG4).
- CO4: To enhance and support communication between clinicians and basic scientists (WG3)
- CO5: To initiate development of ILC-related R&D products (antibody panels and toolkits) (WG1, WG2) and ILC-modulating drugs (WG3).
- CO6: To create steady communication channel between the basic scientists, and industry, regulatory and legislative bodies, cancer patients organizations and general public (WG4 and WG5).
- CO7: To establish new consortia for joint research proposal applications (WG4).
- CO8: To attract ECIs and innovators in the ILC-related research and foster their career progress through trainings, mobility and participation in the scientific projects (WG4).

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

ILC-related research is greatly expanding over the last years as evidenced by the increase in the number of publications, but uniform identification of ILC remains a persistent issue that halts further progress in utilizing compiled data on ILC for new research avenues, specifically in cancer prognosis and therapy. The added value of this Action lies in standardizing ILC phenotyping, isolation, and cultivation techniques, which will drive advancements in ILC-related anti-cancer immune responses - an area expected to grow significantly in the coming years.

ILCquest will explore new potential targets for the cancer treatment, that way **synergizing with the Cancer mission of EU Commission**, and specifically with the suggested area of intervention “Health promotion and cancer prevention” in EU4Health agenda. This Action aims at organizing Meetings/panel discussions with the Cancer mission representatives and publication of common “ILC and cancer” white paper.

The importance and attractiveness of ILC research is depicted by the **Horizon Europe-approved funding** for several grants. Two ERC Advanced grants were awarded in 2015 and they focus on “Targeting innate lymphoid cells” and “Biological determinants of ILC reactivity for immune responses in health and disease”, and one Marie Skłodowska-Curie Actions (MSCA) Individual Fellowship in 2016 “Metabolic characterization of ILC under homeostatic or stress conditions”. Additionally, the anticipated outcome of ILCquest, which involves evaluating ILC as prognostic markers or druggable targets for cancer therapy, can be leveraged by stakeholders from two other ongoing COST actions “Modelling immunotherapy response and toxicity in cancer” (IMMUNO-model - CA21135) (2022-2026) and “Converting molecular profiles of myeloid cells into biomarkers for inflammation and cancer” (Mye-InfoBank - CA20117) (2021-2025). The results of BM0907 “European Network for Translational Immunology Research and Education (ENTIRE): From immunomonitoring to personalized immunotherapy” (2009-2013) will complement and guide ILCquest efforts in the determination of ILC-related prognostic biomarkers and drugs.

Globally, ILCquest aligns with the efforts of the **National Institutes of Health (NIH)** in the USA, which is currently funding 16 projects related to ILC, three of which focus specifically on the interplay between ILC and cancer. Furthermore, international efforts in ILC research are depicted by the establishment of the annual International conference on ILC. ILCquest will add to all these efforts by establishing European ILC Network with the mission to disseminate and share new data on ILC and their use for interference with cancer. Such activity is proposed for the first time in Europe and in the global scientific community as well. This innovative collaborative research agenda will unite clinical oncologists and basic science investigators to harness existing ILC-related data for developing new immunotherapies and utilizing ILC as predictive immune indicators for cancer development and severity, in alignment with the targets outlined in Goal 3 of the United Nations (UN) Sustainable Development Agenda 2030.

ILCquest will also **promote the reduction of animal models in scientific research** by adhering to the 4Rs principle. By advancing new methods for the testing of ILC-based drugs using organoids/spheroids, this Action aims to enhance the Europe's competitiveness in ethical use of animals for the research.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS, EXPERTISE AND GEOGRAPHICAL BALANCE WITHIN THE COST MEMBERS AND BEYOND

Efforts of the European scientific community together with International partners will be unified to generate a gold standard of common protocols and harmonize guidelines for the analysis and clinical monitoring of ILC and their prognostic or therapeutic value that will result in efforts to translate such studies to the clinical practice. The Action Participants possess highly complementary expertise, which will be further enriched by welcoming additional experts in synthetic chemistry, big data analysis and oncology, together with patient groups and industry stakeholders (companies and SMEs). During recruitment of new participants, special attention will be given to the inclusion of participants from ITC to bridge gaps in research infrastructure and resources, thus promoting equal opportunities for all. While ILCquest involves total of 26,5% of young researchers, additional initiatives tailored to ECIs needs will be implemented to encourage their greater participation. ILCquest will strive to achieve gender balance in leadership roles among young researchers. However, the primary criterion for the participant and awardees selection will be the excellence of the participants, regardless of gender.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

Scientific community. The ILC research community is rapidly growing. The findings developed during ILCquest will be presented to the scientific community by organizing two ILCquest conferences (mid-term and final) and eight WG Meetings, as well as by participating at four International Conferences on ILC, and on at least eight relevant scientific Meetings organized by the third parties (European Congress of Immunology - ECI, EACR, European Society for Medical Oncology - ESMO Congress) (T5.6). Further, the scientific community will benefit from unified ILC identification and SOPs dissemination, in terms of research accuracy and standardization. This will facilitate precise comparisons of results enabling the formulation of accurate conclusions. Various complementary research groups will be attracted to join ILCquest (through the activity of the Management Committee), thus expanding the Action expertise spectrum and impact.

ECIs and innovators. They will be given the opportunity to enhance their career prospects and attain leadership positions through Summer School trainings in ILC research and managerial skills (T4.4). The interest in the scientific career by young investigators will be nurtured through dedicated STSMs and VMs (T4.4), through the possibility of acquiring postdoc positions through MSCA Postdoctoral Fellowship granting scheme (T4.5) and through media coverage of their achievements (T5.5).

Potential new COST framework applicants. WG5 activities under the T5.8 will be dedicated to providing help to potential new COST framework applicants in their journey towards successful application through organization of seminars and in person Meetings.

Oncologists and other related health practitioners. Specific Meetings clinical oncologists will be organized by the Management Committee (on the occasion of WG Meetings) in each participants' country, to raise their awareness about the importance of ILC-related research in human diseases.

Patients, patient organizations. Introducing ILC-related research to cancer patients and their organizations will be one of the central activities of ILCquest mission. This will be achieved by attending patient organization Meetings and inviting their representatives to dissemination events organized by ILCquest (T5.9). A special session dedicated to the discussion with the representatives of cancer patient and advocacy groups will be organised by the Management Committee at each biannual WG Meeting.

Policymakers. Each partner will be responsible for planning the Meetings with the Ministry of Health representatives to present objectives and results of the Action, to emphasize the importance of ILC-related cancer prognosis and to discuss possible ways for ILC-based drug development (T5.11).

Local, national and European Regulatory Bodies. Meetings with the relevant governmental agencies, such as the Committees for National Guidelines and EMA will be organized to discuss possible ways for introducing ILC-based prognosis and immunotherapy into the clinical practice (T5.11).

R&D, Biotech and Pharma companies. Advertising the new products in the form of antibody panel for ILC determination to R&D companies will be organized under the T5.10. Although one SME for drug development is already involved in ILCquest, efforts will be made to advertise commercialization of ILC-related products to Pharma and Biotech companies that are leaders in producing and developing cancer therapeutics (Roche, Celgene, Bristol-Myers Squibb, Pfizer, AstraZeneca, Merck, Novartis…). This will be achieved by attending the indicated conferences (T5.6), creating and sharing special brochures with companies, organizing Meetings and extending invitations to the companies of interest.

Society and Media. Joint publication of the white paper between representatives of Cancer Mission and ILCquest will ensure better public outreach. Additionally, ILCquest will ensure publication of articles in newspapers and non-scientific journals, giving interviews for TV and creating podcast to reach the broader society and advertise new approaches for cancer treatment (T5.5). A brochure with ILC related information for the general public will be published (T5.3) along with the YouTube clips (T5.5). All Action Participants will advertise ILC-based research and novelties within the field in social media (LinkedIn, Instagram and X) under the coordination of the Science Communication Officer (T5.4).

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

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

ILCquest will be the first international and multidisciplinary network that will enrol experts from diverse scientific fields to steer future ILC research and clinical implementation, thus leading to significant innovations in the diagnosis and treatment of cancer patients. The main expected impacts are:

Impacts on research and EU competitiveness

● Establishment of a multidisciplinary ecosystem will result in the formation of the European ILC Network (T4.1), a platform for close communication and collaborative research that will ensure ongoing exchange of knowledge and expertise from project inception, facilitating the identification of common patterns for ILC and the development of innovative therapeutic strategies (WG1-3). The network's expansion over time by at least ten new research groups dealing with ILC and two R&D SMEs, will be accompanied by tailored arrangements to ensure its sustainability, serving as a robust foundation for at least three collaborative project proposals spanning cancer research (T1.4, T2.7, T3.6). Providing a solid foundation for small-scale production of ILC will opportune for using ILC as advanced therapy medicinal products for the treatment of cancer, as a long-term possibility beyond the project lifetime. Finally,
ILCquest will contribute to shaping future research agendas and roadmaps, leveraging scientific advancements in the ILC field, with the potential of breakthrough innovations in cancer therapy and extreme benefit for the cancer patients (T5.11).

● Financial support for mobility and trainings will result in increased interest among the younger population in the ILC-cancer field and science as a whole (T4.4, T4.5). Leveraging the established network of high-ranking scientists involved in this Action will enable the participation of ECIs and innovators in high-quality research endeavours thereby advancing their professional trajectories. In addition to fostering global mobility, ILCquest will facilitate the retention of ECIs within Europe by providing the MSCA fellowships and including ECIs in the project proposal consortia (T4.5). ILCquest will support and motivate (through organized webinars) at least one ECI or innovator to engage as entrepreneur (expected to occur beyond the project duration).

● Provision of advisory support to colleagues preparing new COST scheme proposals will facilitate the development of impactful new research initiatives and thereby increase the EU scientific competitiveness (T5.8).

Establishment of a roadmap for clinical translation

● By elucidating the potential of ILC composition as a marker of cancer progression, we aim to uncover and validate panels for detection in peripheral blood (T1.1, T1.2, T3.1) and initiate clinical trials (T3.5).

● Continuously disseminating project achievements to the industry stakeholders will facilitate the development of an innovative state-of-the-art platform for the next-generation products, such as antibody panels and toolkits (WG1, WG2, T5.10).

● Identifying ILC as potential therapeutic targets will contribute to the definition of ground-breaking ways for the preparation of safe and accessible products, offering companies or SMEs new avenues for ILC-based theranostics for cancer, suitable for translation into the clinical practise (WG3).

Socio-economic impacts

● Impacts on patients: It is estimated that lives lost to cancer are set to increase by more than 24% by 2035 (https://gco.iarc.fr/tomorrow/en/.), making it the leading cause of death in the EU. Cancer patients will benefit from the insights gained through ILCquest, which will establish ILC as viable targets for the treatment of various cancer types (T5.5, T5.7, T5.9). This advancement holds promise for long-term benefits through prediction of cancer severity and improved therapeutics possibly tailored to individualized therapeutic approaches. Investment in this unexplored approach for cancer therapy will provide a chance to restrain cancer-related mortality at a steady level.

● Impacts on research funding: EU4Health programme and other EU instruments will provide €4 billion to Member States in their efforts to increase readiness of their health systems in addressing cancer.

ILCquest will mitigate redundant research efforts across different research groups and thus reduce the overall cost of ILC-related research in cancer by introducing standardized ILC determinants and SOPs. Ultimately, this initiative will lead to cost savings for healthcare systems in Europe and worldwide.
● Impacts on collaboration with the industry sector: By offering new avenues for the development of cancer prognosis tools and immunotherapeutics, ILCquest will influence the global R&D and pharmaceuticals market (WG1-3).
● Impacts on ecology. ILCquest will minimize the carbon footprint by organizing WG Meetings together with the other satellite Meetings dedicated to industry and patient stakeholders.

3.1. MEASURES TO MAXIMISE IMPACT

3.1.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

ILC-related knowledge creation. The integrated and complementary expertise of the network will provide new experimental and clinical data on ILC, thus opening new research pathways and contributing in the definition of a future research agenda and roadmap on the topics tackled by the project, for the benefit of the international research community. To this end, ILC Atlas will be created (T1.3) and appropriate studies and designs published (T1.4, T2.6, T2.7, T3.6), enabling future ILC research to be comparable, reproducible and to avoid study duplications.

Transfer of knowledge. ILCquest Data management plan will ensure that the project outcomes will be shared with the identified key stakeholders (T5.2). Data will be shared internally via Dropbox, and made available to the scientific community through open data repositories (Zenodo, Open Science Framework) adhering to international publication standards and guidelines. Presentation of results at WG Meeting and conferences (T5.6) will further facilitate internal and external knowledge transfer. Also, strategic plan for knowledge transfer to crucial non-scientific stakeholders (in particular industry, policy-makers and patient organizations) within Dissemination and Communication agenda, will be adopted at the Kick-off and subsequently implemented through dedicated Meetings to ensure that a significant number of representatives acquire ILCquest results (T5.1, T5.9, T5.10, T5.11). Furthermore, participation at the COST Action Chairs' forum will enable the spread and transfer of the gathered knowledge. STSM, VM and Summer Schools will ensure the exchange of knowledge within the Network and beyond (T4.3, T4.4). Advisory sessions with the colleagues who want to pursue COST framework funding will be also arranged to upgrade their possibilities in gaining funding (T5.8).

Career development. Training events for expertise development and career progression will target master students, PhD, early-career postdocs and medical doctors. Training events will include: four Summer Schools in total, and at least four webinars per year. Two Summers Schools will be dedicated to "Standardization of ILC nomenclature and isolation protocols" and "The role of ILC in cancer". The other two will include trainings for upscaling managerial skills of young researchers "How to manage my scientific career?" and "Hands-on training in project proposal writing" that will empower ECIs and innovators for leadership positions and entrepreneurship. Webinars will follow similar topics as Summer Schools. Special attention will be given to the fair and equitable distribution of funds for Schools and STSMs, encouraging participants from Inclusiveness Target Countries (ITC) to apply. We anticipate to accommodate 30 students per Summer School (120 students in total), and at least 100 viewers per webinar (T4.3, T4.4). Engagement of at least two Action Participants in a postdoc position through MSCA Postdoctoral Fellowships programme will enable young investigators/innovators to become ILC experts (T4.5). Also, webinars and STSMs created for clinicians/oncologists will increase their knowledge in ILC-related fields and through gaining new skills and know-how enable them to pursue their academic career as true physician scientists (T4.3, T4.4).

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

Dissemination of results. It will be carried out continuously by all members and coordinated by the Science Communication Officer. Dissemination and Communication Agenda will be adopted at the Kick-off Meeting and updated once a year. It will contain description of activities, the timeline, target groups, indicated Action Participants that are responsible for certain dissemination activities, key performance indicators (KPI) and channels for dissemination of key aspects of the Action efforts and results.
Key channels of dissemination:
Website (T5.4). It will be initiated at the beginning of the Action, and it will be updated regularly with information on the Action Members, aims, activities and results of the Action. All information will be brief, clearly visible and attractive to the readers. Links to the ILC Atlas, repositories, Instagram, X and LinkedIn profiles will be displayed. The website will target both the scientific and general population. KPI

will be the number of website visits (more than 2,000 by the end of the first year, and more than 5.000 by the end of the project).
Articles and Videos (T1.4, T2.6, T2.7, T3.6, T5.13). To disseminate the ILCquest findings to the scientific community seven specific-topic articles, 60 topic-related articles and six videos will be published in international peer-reviewed journals (or video journal) adhering to Open Access policy. Papers and SOPs will be made available as preprints on bioRxiv or medRxiv and in Open Access repositories. White paper will be published in collaboration with the Cancer Mission representatives.
Conferences and events**.** ILCquest mission and results will be presented at four annual International ILC conferences and at least 12 oncology-related conferences (EACR, ESMO) or immunology conferences (ECI) using ITC conference grants and Dissemination grants (T5.6). During the project implementation ILCquest will organize two ILCquest scientific conferences: mid-term (as a satellite to International ILC conference) and final conference at the end of the project (T5.6). All participants will be encouraged to promote ILCquest mission and results on the occasion of World Cancer Day, Day of Immunology and other events open to general public (European Researchers' Night, Science Fairs) (T5.9). Therefore, ILCquest will target both the scientific and general public. KPI: five experts from different fields attracted to COST Action after advertisements of ILCquest mission, five more countries involved in the COST Action, at least 12 scientific Meetings (organized by the third parties) attended.
Connection with other funded projects. Members of the Core Group will actively monitor all new HE funded projects that have similar or complementary aims and will approach the project coordinators for arranging at least four Meetings and discussions and inviting them to join ILCquest.
Newsletters, brochures, internet clips, podcasts (T5.3, T5.4, T5.5). Newsletters and brochures for the general public will be issued regularly during the project implementation, one per year. Also, specific newsletters will be created for impacting policy makers when relevant achievements are being made. One brochures for the industry stakeholders will be created. Two YouTube clips for the general public will be posted. Media participation (TV, podcast, radio and newspapers interviews) will be organized.
Social media (T5.4). LinkedIn, Instagram and X pages will be created for the advertisement of ILCquest results and announcements appropriately tailored for all stakeholders. Total views of these social media is targeted to be over 2,000 for the first year, and over 10,000 until the end of the project.

Exploitation of results. Results of the ILCquest will be exploited by different stakeholders: basic scientists and clinical oncologists (including ECIs and innovators within the field), R&D, Biotech and Pharma companies, oncology patients and eventually healthcare systems. The cost of the research will be decreased through the creation of uniform panel for ILC identification (ILC Atlas) which will prevent redundant and repetitive studies and therefore lower the financial burden taken by EU taxpayers. Further, the ILC Atlas can be exploited by Biotech companies that will bring the six different antibody panels for ILC and six toolkits for prognostic analysis of cancer to the market, especially if the results of this Action will identify the possibility of patient outcome prediction by quantitatively and qualitatively assessing specific ILC (WG1 and WG3, T5.10). Establishing ILC as a therapeutic target for cancer and identifying at least 20 ILC-modulating compounds can be exploited by Biotech companies/SMEs to develop adequate drugs and for Pharma companies to initiate clinical trials (WG2 and WG3, T5.10, T3.5). IP protection for the results that can be commercialised will be provided through Technology Transfer Office of each participant. Other results of the project and training materials will be made publicly available in accordance with the FAIR principle to increase the global knowledge about ILC. To exploit the capacity of European ILC Network, ILCquest will actively promote the formation of consortia for at least one new collaborative grant proposals targeting HE and other funding agencies.

Dialogue with the public and policy makers. To ensure that the general public is acquainted with the Action results and the possibilities that ILC-related research may provide, the participants of ILCquest, guided by Science Communication Officer, will produce newsletters and brochures, and make announcements on Instagram, LinkedIn and X, attend different media, produce YouTube clips adjusted to layperson language, and distribute promotional material with an opportunity for feedback at Science Fairs and occasions accompanying European Researcher's night events (T5.3, T5.4, T5.5, T5.9). Also, to investigate the general opinion in large cohorts on ILC-based research, web-based questionnaires on the knowledge and availability of new cancer treatments will be disseminated through Social networks and to patient organizations (T5.7). Dialogue with the policy makers will be in the form of arranged Meetings with the Health Ministry of each country participant and through attendance at public disputes related to health and cancer in particular (T5.11). Through Meetings with EMA, ILCquest will ensure the sharing of knowledge about the novel possibilities for targeting ILC (T5.11).

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The Network will be organized in five WGs, with WG1 focused on the uniformity of ILC identification and development of corresponding antibody panels. WG2 will establish consensus on existing protocols for ILC isolation and propagation, develop new protocols for isolating ILC from solid tumors, and assess the feasibility of using ILC-containing tumor organoids/spheroids. WG3 will concentrate on identifying specific ILC subsets as prognostic indicators in cancer, evaluating their translational value, and assessing ILC as viable druggable targets for cancer treatment using *in vitro* and *in vivo* tools. WG4 will aim for capacity building objectives including European ILC Network creation, trainings and mobility, while WG5 will circle out all WG activities through achieving dissemination of obtained results (Figure 3). Two bodies will be constituted to continuously oversee Action activities and ensure the implementation according to the tasks and deadlines that are proposed. The **Management Committee** will consist of one representative from each COST Full Member Country, each possessing one voting right. It will convene biannually at the occasion of WG Meetings, either in person or remotely. The responsibilities will include: monitoring project implementation in collaboration with Core Group, monitoring distribution of finances, creating channels for internal communication, provide relevant information for the mid-term and final report. The **Core Group** will monitor implementation of WG activities and dissemination of Action results. Also, the Core Group will approve of the mid-term and final reports which will be compiled by the Action chair in cooperation with WG leaders. The Core Group will meet at least 10 times per year, either on the occasion of official events organized by the Action or online. The Core Group members will take advantage of COST Academy trainings in order to strictly follow COST framework rules and regulations regarding the management, budget eligibility, dissemination and communication. It will be composed of the Action chair, Vice-chair, WG leaders, Science
Communication Officer (role: in charge of ensuring that all project outcomes and results, suitable for communication and dissemination activities, are appropriately shared with the relevant target groups, WG5 member), Grant Awarding Coordinator (role: gathers STSM, VM and ITC Conference grants applications and acts in cooperation with the WG leaders to ensure appropriate management of mobility, WG4 member), Gender Equality Officer (role: to arrange that gender balance is adopted when appointing Action Participants for managerial roles and STSM and VM approvals, WG5 member) and Data Management Officer (role: responsible for Data management plan implementation, WG4 member). Appointing Participants to the proposed duties will be in accordance to the COST framework Mission and Policy
(favouring the balance between ITC and non-ITC participants).

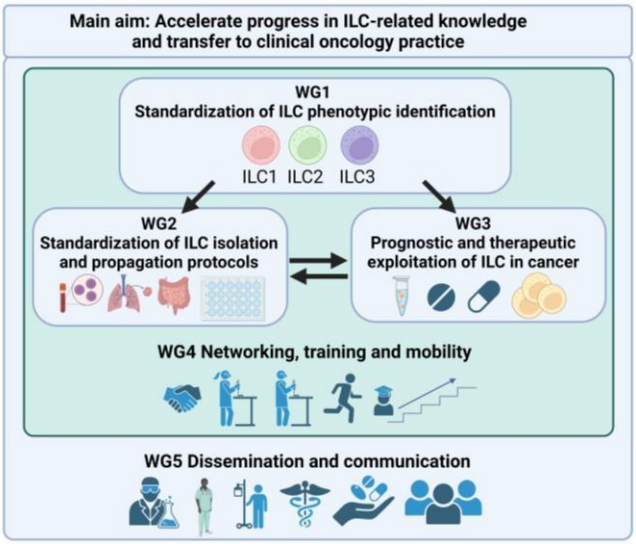

Figure 3. Pert chart of WG interrelations.

WG1	Standardization of ILC phenotypic identification (M4-M48)
OBJECTIVES The objectives of WG1 are: **a)** to collect and critically evaluate data on the phenotypic characterization of ILC in various mouse and human tissues; **b)** to reach a consensus on the phenotypic characterization of ILC; **c)** to discuss and disseminate the WG findings.	
TASKS T1.1 Review of the existing literature on ILC identification in various tissues of human and mouse origin (M4-M12); T1.2 Organization of the multicentre study for the quality check of the minimal standardized panel for ILC identification (M13-28). T1.3 Creation of the Open Access ILC Atlas (M13-M28); T1.4 Drafting scientific papers (M13-M44). T1.5 Organization of WG Meetings (M4-M48).	

ACTIVITIES WG1 participants will be allocated to three groups ILC1, ILC2 and ILC3+LTi dedicated to the literature review on the specific ILC subtype. Intra- and inter-group discussions will be organized during regular WG biannual Meetings, and complemented by intensive online interaction using Dropbox. This will lead to the consensus on the biomarkers for ILC phenotyping in mouse (blood, lungs, the intestines) and human (blood, tonsils, intestinal biopsy) followed by the multi-centre study that will validate the proposed panels and adjust them if necessary. ILCquest participants together with other invited research groups will be the members in this study that will be partly organized by making use of STSMs (WG4). **WG1 outcomes**: ILC Atlas, one systematic review paper, one position paper, 20 topic-related scientific articles, one project proposal, six antibody panels for ILC identification, dissemination of the results employing WG5 activities.	
Milestone (MS1) Antibody panels for ILC identification created (M28).	
WG2	**Standardization of ILC isolation and propagation protocols (M4-M44)**
OBJECTIVES The objectives of WG2 include: **a)** collecting and critically evaluating data on the ILC isolation from various mice and human tissues; **b)** to reach a consensus on the minimal surface markers necessary for successful and pure ILC isolation **c)** to reach a consensus on optimal ILC propagation conditions in 2D and 3D cultures; **d)** discussions and dissemination of the WG findings.	
TASKS T2.1 Review of the existing literature on ILC isolation and propagation protocols (M4-M32); T2.2 Development of SOPs for isolation and propagation from healthy tissues (M9-M32); T2.3 Development of SOPs for ILC isolation from tumors (M9-M32); T2.4 Modelling and development of ILC-tumor organoids/spheroids (M21-M32); T2.5 Organization of multicentre study and development of specific toolkits (M21-M40); T2.6 Filming video articles (M25-M44); T2.7 Drafting scientific papers (M25-M45); T2.8 Organization of WG Meetings (M4-M48).	
ACTIVITIES WG2 will have three thematic groups dedicated to ILC isolation, ILC propagation and organoid modelling. All groups will systematize and exchange their findings during WG Meetings and *via* Dropbox. Consensus on optimal methodology for ILC isolation from healthy tissues and tumors and conditions for their propagation (2D or 3D cultures) will lead to recommendation of SOPs. These recommendations will be distributed to ILCquest participants, including invitations to other ILC research groups, for quality check (multi-centre study) of SOPs by making use of STSMs under the coordination of WG4. **WG2 outcomes**: three SOPs for isolation from the mouse blood, lungs and intestines, four SOPs for isolation from the human blood, tonsils, intestinal biopsies, solid tumors, 12 SOPs for ILC propagation (three for mouse and three for human ILC1, ILC2 and ILC3 and six for various tumor organoids), at least six toolkits for ILC isolation and propagation (containing medium, growth factors, serum), advertisement of SOPs (WG5), four position papers, 20 topic-related articles and six video articles, one project proposal, dissemination of the results employing WG5 activities.	
MS2 Toolkits for ILC isolation and propagation developed (M40).	
WG3	**Prognostic and therapeutic exploitation of ILC in cancer (M3-M48)**

OBJECTIVES The objectives of WG3 include: **a)** collecting and critically evaluating data on existing published results on the correlation of ILC with cancer severity or development; **b)** collecting and critically evaluating data on the ILC as a druggable target for cancer; **c)** discovery and testing new potential ILC-based drugs in animal models/organoids; **d)** planning clinical trial on ILC prognostic value **e)** discussions and dissemination of the WG findings.	
TASKS T3.1 Review of the existing literature and identification of ILC as prognostic markers (M4-M32); T3.2 In-depth analysis of possibilities for ILC modulation (M4-M30); T3.3 *In silico* generation of new ILC-focused drugs for cancer treatment (M13-M33); T3.4 Initiation of preclinical studies in the animal models/organoids (M34-M46); T3.5. Clinical trial planning for evaluation of ILC prognostic capacity (M38-M46); T3.6 Drafting scientific papers (M19-M46); T3.7 Organization of WG Meetings (M4-M48).	
ACTVITIES Group dedicated to prognostic ILC will systematize the existing knowledge and provide statistical analysis of data that is going to result in predictions about ILC use as prognostic bioindicators for cancer. Group for targeting ILC will systematize the existing knowledge and perform *in silico* predictive analysis (computational models) to identify already known and derive new compounds for modulation ILC populations for the benefit of cancer treatment. Extensive exchange of gathered data by the two groups will be achieved on biannual Meetings and by sharing data on the Dropbox. Evaluation of new drugs for targeting ILC will be performed through initiation of preclinical studies in cancer animal models and tumor organoids. **WG3 outcomes**: identification or synthesis of at least 20 new compounds for ILC modulation, initiation of at least four preclinical studies on potential drugs that modulate ILC activity in the animal models/organoids and four preclinical studies on ILC use for cell-based therapy, initiation of at least one clinical study for cancer prognosis, two position papers, 20 topic-related papers, dissemination of results employing WG5.	
MS3 Specific ILC as prognostic indicators identified (M30)**. MS4** Panel of drugs for ILC modulation compiled (M33).	
WG4	**Networking, training and mobility (M1-M48)**
OBJECTIVES The objectives of WG5 are: **a)** to create a secure communication channel for networking; **b)** to establish the European ILC Network; **c)** to ensure adequate expertise development especially towards ECIs, innovators and clinical practitioners.	
TASKS T4.1 Launching of web-based communication platform (M4-M48). T4.2 Formal establishment of European ILC Network, continual admission of new members and consortia creation for joint project application (M13-M48). T4.3 Annual organization of Summer Schools and webinars (indicated on the Gantt chart) (M1-M48); T4.4 Coordination of international mobility of PhD students and postdoc researchers and innovators, pertinent to activities in WG1-3, across the network and beyond through STSM or VM (calls for STSM or VM application indicated on the Gantt chart) (M1-M48); T4.5 Application for MSCA fellowships (M13-M36). T4.6 Organization of WG Meetings (M4-M48).	
ACTIVITIES Communication channel (WhatsApp) will be created. After establishment of the European ILC Network (constituted of ILCquest participants), the membership will be extended by at least ten new research groups investigating ILC and other interested parties, including industry stakeholders, patient groups, drug developers and legislative offices, providing opportunity for consortia creation for new funding acquisition. Training a new generation of researchers proficient in ILC biology will be accomplished by offering Master, PhD students and early postdocs and young innovators to approach ILC research from different angles (basic immunology, clinical immunology and oncology, computational models and drug design) by using STSMs, VMs or MSCA fellowship. Two Summer Schools will be dedicated to basic ILC knowledge, while the other two to the upgrading of management skills of ECIs that will enable them to pursue leadership positions. Webinars will follow Summer Schools and represent similar topics. **WG4 outcomes**: One collaborative project submitted, 120 students attended four Summer Schools (30 students per event), 1200 participants in 16 webinars (4 per year), at least 20 students utilized STSMs and least 10 students VMs (budget dependent), at least two ECIs applied for MSCA programme.	
MS5 Communication channel and data storage created (M4). **MS6** European ILC Network established (M16).	
WG5	**Dissemination and communication (M1-M48)**
OBJECTIVES The objectives of WG4 are: **a)** to guarantee the widest dissemination of the knowledge gathered within the Action to the scientific community; **b)** to communicate the Action findings to the target patient groups and larger public; **c)** to communicate the Action results to the industry, policy makers and regulatory bodies.	
TASKS T5.1 Dissemination and Communication agenda creation (M1); T5.2 Data Management plan creation (M1); T5.3 Project promotional materials printing (M1-M2, M13-M14; M25-M26; M37-M38); T5.4 Creating the Website, social network groups, Dropbox community (M1-M48); T5.5 Media	

representation (TV, podcasts, YouTube clips, radio, newspapers) (M1-M48). T5.6 Organisation of mid-term (M22) and final (M47) ILCquest conference, promotion of the Action results on the annual ILC conference, and other oncology/immunology related conferences (M1-M48); T5.7 Preparation and conducting of the questionnaire and analysis of the public feedback (M25-M36); T5.8 Advisory sessions with prospective COST framework applicants (M5-M48); T5.9 Organization of Meetings with patient groups and participation in the events for the general public (M5-M48); T5.10 Meetings with R&D, Pharma and Biotech companies (M13-M44); T5.11 Meetings with the Ministry of Health representatives, representatives of regulatory bodies, attending public discussion forums (M13-M44); T5.12 White paper drafting (M29-M44). T5.13 Organization of WG Meetings (M4-M48).
ACTIVITIES Widespread communication will be achieved through creation and continuous maintenance of the Action website, creation of ILC Atlas, social networks, dedicated Meetings with identified stakeholders and public events. Data Management plan will organize data storage and handling in the cloud (Dropbox) and repositories (Zenodo, Open Science Framework). ILCquest will foster knowledge exchange through organization of two Action conferences, through attending at least 16 third-party conference, coordination of eight WG Meetings, as well as through assistance to new COST framework applicants. Dissemination through EACR that encompasses 13,000 members worldwide (cancer researchers, medical doctors and patient groups) will be employed. Local cancer patient groups will be also attracted to join the special sessions of WG Meetings that will be designed for the general public. General public will be informed via social networks, YouTube clips and during European Researcher's night and Science Fair (events held once a year). Also, a web-based survey will be conducted to assess the patient's awareness of new ILC-based cancer therapies. Dedicated Meetings with the industry stakeholders, EMA, the local Committees for National Guidelines (responsibility of each participant), local Ministries of Health of each country participant. Meetings with "Cancer Mission" representatives will be organized and joint white paper "ILC and cancer" will be published. **WG5 outcomes**: Anticipated outcomes are presented in the Section 3.1. Additional outcomes are: Public opinion on ILC-related discoveries, one white paper, two SMEs attracted to participate in the Action, raising awareness of industry, regulatory and legislative bodies to new possible drugs/targets for cancer therapy.
MS7 Dissemination and Communication agenda created (M1). **MS8** Data Management plan created (M1). **MS9** Website/social networks launched (M4).

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

WG1 deliverables	**Month**
D1.1 Report on the consensus on ILC determinants	15
D1.2 ILC Atlas open repository	28
D1.3 Systematic review, position paper, topic-related papers	44
WG2 deliverables	
D2.1 Report on ILC isolation and propagation consensus	32
D2.2 Report on the multicentre study for validation of ILC protocols	40
D2.3. Video articles	44
D2.4 Position papers on ILC isolation/expansion, topic-related papers	45
WG3 deliverables	
D3.1 Report on ILC-related prognostic indicators/ILC modulation in cancer	30
D3.2 Report on *in silico* generated ILC-targeted drugs	33
D3.3 Report on pre-clinical and clinical trials	46
D3.4 Position papers on ILC and cancer	44
WG4 deliverables	
D4.1 Web platform for communication	4
D4.2. Reports on European ILC Network (applications for joint projects)	24,36,48
D4.3 Annual report on organized Summer Schools and webinars	12,24,36,48
D4.4 Annual report on participant mobility (STSMs and VMs)	12,24,36,48
WG5 deliverables	
D5.1 Dissemination and Communication agenda	1
D5.2 Data management plan	1
D5.3 Reports on dissemination and communication activities	11,23,35,47
D5.4 Reports on Meetings with the industry, policy makers and reg. bodies	20,32,44
D5.5 White paper compiled with "Cancer mission" representatives	44
D5.6 Reports on Kick-off and biannual WG Meetings	12,24,36,48

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

- **Risk:** WG members do not reach consensus on ILC phenotype. **Risk level/Impact:** Medium/strong. **Mitigation:** Active moderation based on reestablished selection criteria.
- **Risk:** Withdrawal from the organization of Summer School. **Risk level/Impact:** Low/medium. **Mitigation:** Inviting other participants to organize the Summer School, offering the help of CG.
- **Risk:** Industry stakeholders are not participating at Meetings. **Risk level/Impact:** Low/medium. **Mitigation:** Consider adjusting Meeting times to accommodate the availability of industry stakeholders (companies and SMEs). Implement feedback mechanisms to gather input from industry stakeholders about Meeting scheduling and content. Stimulate industry stakeholder's participation through ensuring that Meeting agendas prioritize relevant topics, or require their input. Enable remote participation.
- **Risk:** Conflicts between members. **Risk level/Impact:** Low/strong. **Mitigation:** Promoting clear communication, defining roles and responsibilities clearly, establishing procedures for mediating and resolving conflicts, encouraging constructive feedback, active listening, and a willingness to compromise when necessary. Maintaining transparency in all activities and addressing any emerging issues promptly.
- **Risk:** Lack of funding to support the multicentre quality check of the proposed ILC detection panel and ILC isolation and propagation. **Risk level/Impact:** High/strong. **Mitigation:** Organizing consortium members to apply for joint project grants that will enable the performance of the quality check.
- **Risk:** Policy makers are not responding to the ILCquest invitation to partake in Meetings. **Risk level/Impact:** Medium/medium. **Mitigation:** Send polite and personalized follow-up messages to remind the policy makers of the invitation and emphasize the importance of their participation. Provide options for meeting times or formats (virtual Meetings) that accommodate their busy schedules. Reach out to intermediaries or contacts who have connections with the policy makers and ask for their assistance in encouraging participation. Communicate the benefits of participating, such as access to valuable information and networking opportunities.

4.1.4. GANTT DIAGRAM

Tasks	Year 1			Year 2			Year 3			Year 4		
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36	37-40	41-44	45-48
WG1 Standardization of ILC phenotypic identification												
T1.1 Review of the existing literature on ILC identification				D1.1								
T1.2 Organization of the panel quality check - multicentre							MS1					
T1.3 Creation of ILC Atlas							D1.2					
T1.4 Scientific papers preparation											D1.3	
T1.5 WG1 Meetings	Kick-off											
WG2 Standardization of ILC isolation and propagation												
T2.1 Lit. rev. on ILC isolation and SOPs preparation												
T2.2 SOPs for isolation and propagation								D2.1				
T2.3 Development of SOPs for ILC isolation from tumors								D2.1				
T2.4 Model and develop ILC-tumor organoids/spheroids								D2.1				
T2.5 Validation of SOPs										D2.2, MS2		
T2.6 Filming video articles											D2.3	
T2.7 Scientific papers preparation												D2.4
T2.8 WG2 Meetings	Kick-off											
WG3 Prognostic and therapeutic exploitation												
T3.1 Lit. rev. on ILC as prognostic markers for cancer								D3.1, MS3				
T3.2 In-depth analysis of ILC modulation for cancer th.								D3.1, MS3				
T3.3 *In silico* generation of new ILC-focused drugs									D3.2, MS4			
T3.4 Pre-clinical studies in animal modesl/organoids												D3.3
T3.5 Clinical trial planning												D3.3
T3.6 Scientific papers drafting											D3.4	
T3.7 WG3 Meetings	Kick-off											
WG4 Networking, training and mobility												
T4.1 Launching of the communication channel	D4.1, MS5											
T4.2 Coordination of the European ILC Network/consortia				MS6		D4.2			D4.2			D4.2
T4.3 Organization of Summer Schools and webinars			D4.3			D4.3			D4.3			D4.3
T4.4 STSM and VM coordination (*open submission)			*, D4.4		*	D4.4		*	D4.4	*		D4.4
T4.5 Application for MSCA PF												
T4.6 WG4 meetings	Kick-off											
WG5 Dissemination and communication												
T5.1 Dissemination and communication agenda	D5.1, MS7											
T5.2 Data Management plan	D5.2, MS8											
T5.3 Project promotional materials												
T5.4 Website, social networks, Dropbox	MS9		D5.3			D5.3			D5.3			D5.3
T5.5 Media representation			D5.3			D5.3			D5.3			D5.3
T5.6 Organization of conf./participation on third party conf.			D5.3			D5.3			D5.3			D5.3
T5.7 Questionnaire and analysis of the public feedback									D5.3			
T5.8 Advisory sessions with new COST framework applicants			D5.3			D5.3			D5.3			D5.3
T5.9 Meetings with patient groups, events for general public			D5.3			D5.3			D5.3			D5.3
T5.10 Meetings with R&D, Pharma and Biotech					D5.4			D5.4			D5.4	
T5.11 Meetings with the leg., reg. bodies, Cancer mission					D5.4			D5.4			D5.4	
T5.12 White paper drafting											D5.5	
T5.13 WG5 Meetings	Kick-off, D5.6		D5.6			D5.6			D5.6			D5.6

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