

All information regarding future IHI Call topics is indicative and subject to change. Final information about future IHI Calls will be communicated after approval by the IHI Governing Board.

Topic 3 : Decode the Immuno-science of age-related mediated diseases

Expected outcomes

The action under this topic must contribute to all of the following outcomes:

- Researchers will benefit from a **better understanding of the potential causal links between chronic inflammatory diseases and biological aging**, and the predictiveness of the accompanying biomarkers could allow for the definition of precise risk profiles for age-associated immune disease onset and exacerbations through biomarker identification.
- Patients will benefit from **new early detection strategies as well as new diagnostic approaches to differentiate disease onset in elderly people from onset in younger adults**. This will inform a personalised medicine approach to treatment and will in turn help to prevent disease progression.
- Patients and healthcare professionals will benefit from the **repurposing or development of novel therapies for aging populations with chronic inflammatory diseases** and precision medicine approaches that prevent health decline while reducing healthcare costs.
- Researchers and industry will benefit from **the establishment of systematic collaborative approaches for the use of available biobanks across age-ranges**, immune diseases and comorbidities to adopt innovative approaches (by integration of multi-omics, immunophenotyping, digital biomarkers, aging clocks, and AI with comprehensive patient information).
- Patients and healthcare professionals will benefit from **deeper insights into treatment response** and the evaluation of the impact of aging on treatment effectiveness.
- Industry and researchers will benefit from **the establishment of regulatory pathways for novel intervention strategies and biomarkers** leading to faster clinical development of drugs that improve age-associated disease exacerbations, ultimately enabling the translation of research findings into therapeutic solutions for vulnerable patient populations. The focus is the establishment, validation, and differentiation of digital biomarkers monitoring activity, strength and fatigue as potential regulatory endpoints in a prospective study.

Scope

The global population is undergoing an unprecedented demographic shift, with the number of individuals aged 65 and older projected to double by 2050, presenting one of the most significant public health challenges of our time. The transition to an aging society is accompanied by a parallel rise in the prevalence of chronic diseases, multimorbidity, and years lived in poor health, placing immense strain on healthcare systems worldwide [1]. Central to this phenomenon is the progressive decline of immune function with age which not only increases susceptibility to infections and malignancies but also drives chronic low-grade inflammation, known as "inflammaging" [2].

The age-related and profound changes to the immune system are collectively termed immunosenescence. These changes include thymic involution, reduced naive T-cell production, expansion of memory T-cells with limited repertoire diversity, increased inflammatory cytokine production (inflammaging), and broad dysregulation of innate immunity [3] [4]. In parallel, senescent cells accumulate and secrete SASP cytokines—such as IL-6, IL-1 β , and TNF—which further amplify inflammaging and contribute directly to age-related immune dysfunction [5] [6]. Concurrently, there is a rising incidence of immune-mediated diseases with initial onset in elderly populations, including late-onset rheumatoid arthritis [7], elderly-onset inflammatory bowel disease (IBD) [8], late-onset systemic lupus erythematosus (SLE) [9] and late-onset respiratory diseases [10] [11].

Critically, advanced age is associated with the increased incidence of autoimmune and inflammatory diseases [12]. Moreover, older adults exhibit heightened vulnerability to immune-mediated pathologies ranging from late-onset autoimmune disorders to vaccine hyporesponsiveness and impaired tissue repair [13] [14]. Despite the clear clinical burden, the mechanistic underpinnings of how aging reshapes immune homeostasis and disease susceptibility, and concomitantly, of how diseases reshape the aging-process and the immune system, remain incompletely understood. A comprehensive understanding of the bidirectional relationship between immune system dysfunction and the aging process is therefore imperative to develop targeted interventions that can prevent, delay, or reverse age-associated immune diseases and ultimately extend health span. The action funded under this topic therefore aims to elucidate the key biological determinants that drive healthy aging and immune-mediated disease, with a particular focus on how age-associated immune system remodelling shapes these outcomes.

Despite their clinical significance, elderly-onset immune diseases remain poorly understood compared to their younger adult-onset counterparts. Evidence suggests that they may represent distinct disease entities with unique pathogenic mechanisms, clinical presentations, and treatment responses [15] [16]. The intersection of immunosenescence with pathological immune dysregulation presents both challenges and opportunities for targeted interventions.

Industry, regulators, researchers, and other stakeholders will address the critical gap in the understanding of how aging-related immune changes contribute to disease pathogenesis in the elderly. New evidence-based findings will help in elucidating the molecular drivers of both elderly-onset immune diseases as well as immune disease exacerbations during aging. In addition, these findings will help to identify predictive biomarkers, leading to age-appropriate therapeutic and prevention strategies accounting for the unique immunological context of older patients, and ultimately reducing the socio-economic burden for society.

Applicants are expected to address all of the following objectives of the topic in their proposal:

Understanding molecular and clinical differences between younger adult-onset and elderly-onset diseases: The focus of the action should be on immune-mediated diseases with a peak of onset in elderly patients, like for inflammatory bowel disease and respiratory diseases, and specifically directed to diseases with mainly elderly onset.

Therefore, in summary the proposal should cover immune mediated:

- Gastroenterological diseases: IBD like Crohn's Disease, Ulcerative Colitis
- Respiratory diseases: like asthma, Chronic Obstructive Pulmonary Disease, Immune-mediated Interstitial Lung Disease
- Rheumatoid diseases: like Rheumatoid Arthritis, Giant Cell Arteritis, Polymyalgia Rheumatica, Sjögren's Disease, SLE

The focus and the combination of these disease types would limit the risk of dispersion but still reflect different organ systems and enable crucial cross-disease comparisons.

Identify drivers of elderly-onset immune diseases: Determine the specific cellular and molecular mechanisms that trigger immune dysregulation uniquely in elderly populations.

Characterise factors driving disease exacerbations with aging: Investigate how age-related physiological changes influence disease progression and flare frequency/severity.

Evaluate biological age as a driver of disease: Distinguish chronological from biological aging in disease pathogenesis and identify predictive biomarkers for onset and exacerbations, including the influence of comorbidities.

Discriminate the molecular phenotypes and associated patient characteristics between chronologically aged versus biologically aged adults and elderly-onset disease patients. Understanding patient heterogeneity in elderly-onset disease, both in regard to treatment response and molecular signatures.

Define the relevance of immunosenescence on biological and chronological aging and whether there is a **causal link between age, senescence and chronic inflammatory diseases** including treatment response.

Identify common immunosenescence signatures across elderly-onset immune diseases: Elucidate shared pathways that might represent universal therapeutic targets.

Evaluate how **vaccination history can contribute to reducing disease onset and/or exacerbation** in older populations. Moreover, assess the translatability of system serology or other immunological endpoints as senescence markers.

Pathway identification and validation: AI/ML-assisted identification of underlying biological pathways and biomarkers from the gathered data sets. Evaluation of the impact of aging on treatment effectiveness. Assessment of the predictiveness of identified biomarkers in aging populations independent of underlying chronic inflammatory diseases.

Applicants should envisage the following activities as part of the action funded under this topic:

1. Applicants are expected to define a strategy to assess age-related disease phenotypes and related biomarkers, incorporating a modelling perspective alongside AI-assisted data mining, appropriate statistical methodologies, and prioritisation approaches for the exploration of mechanisms of action (MoA).
2. Applicants should also detail their methodological approach and data collection procedures, providing preliminary data to show potential for success and strategies for mitigating the main methodological risks and limitations.

The action should leverage both the wealth of existing cohorts, as well as the data from new targeted observational cohort, which is expected to be set up by the consortium, and to include appropriate age-ranges and disease onset groups. Observational cohorts should also evaluate the impact of standard of care treatments on the chosen diseases to define a path forward towards precision medicine and understanding age-dependent impacts of therapy response.

The analysis of existing and new bio-specimens (Peripheral Blood Mononuclear Cells, white blood cells, stool, saliva, urine, diseased tissues and exhaled breath condensate) will allow for the conduction of deep molecular profiling of the targeted chronic inflammatory diseases across various age ranges with appropriate age-matched control groups.

The wealth of data (both existing as well as newly created via the observational cohort), including participant clinical characteristic and health records (e.g. disease, comorbidities, frailty assessment, vaccination and infection history) gathered through state-of-the-art methodologies and technologies will enable the comprehensive analysis of chronological aging, biological aging markers, and immune signatures through:

- Immunological profiling: systems serology, immunophenotyping, T/B cell repertoire analysis, Immunoepitome
 - Molecular profiling (systemic and organ-specific) including RNASeq, scRNASeq, spatial transcriptomics, proteomics, metabolomics, epigenome
 - Evaluating and comparing multiple aging clocks e.g. IMM-AGE, iAge, proteomic, somatic DNA mutations e.g. CHIP associated mutations, epigenetic (DNAm), RNA, and metabolic clocks
 - Metagenomic: Microbiome/Virome. The gut, lung and tissue-resident microbiomes are key modulators of immunosenescence and inflammaging and influence the onset and exacerbation of elderly-onset immune diseases. Integrated metagenomic and metabolomic profiling will be combined with immunophenotyping, aging clocks and digital biomarkers to identify microbiome-driven signatures of biological aging and disease risk. Incorporating host–microbiome interaction modelling will enable identification of modifiable pathways to support targeted prevention and early intervention strategies in aging populations.
 - Leveraging population-wide electronic health records with vaccination history, viral/bacterial infection data, and immunogenicity profiles as functional metrics to define immunosenescence.
 - Applying AI-driven computational approaches to integrate multi-omics data with electronic health records and population-based disease registries to identify potential disease-agnostic senescence pathways and reveal both disease-agnostic as well as disease-specific mechanisms by which immunosenescence may drive the onset and progression of autoimmune diseases in elderly populations. The action should link identified changes with patient characteristics including disease severity, treatment response, comorbidities, age and age at onset of disease.
 - Applying digital biomarkers (e.g. wearables, in-soles, hand grip, sleep monitoring) to assess physical function, track sleep and to correlate with molecular markers.
3. Applicants are expected to consider the potential regulatory impact of the results and, as relevant, develop a regulatory strategy and interaction plan for generating appropriate evidence as well as engaging with regulators in a timely manner. Additionally, applicants should anticipate engaging regional healthcare systems and authorities to prepare for clinical implementation and outcome acceptance when necessary.
 4. Applicants should include in their proposal a strategy to ensure sustainability of the outputs of the project beyond the funding period.
 5. Applicants should leverage experience from the European Research infrastructures (ERICs) already working on the areas mentioned in this call to avoid overlaps and increase the impact of results.

The actions are expected also to consider and contribute co-funded health partnerships that work on the areas of interest mentioned in this call.

Expected impacts

The action under this topic is expected to achieve the following impacts:

- **Accelerate EU access** to more cost-effective interventions in an increasingly aging population by identifying personalised treatment approaches for elderly-onset immune diseases
- **Decrease disease risk** later in life by defining specific prevention strategies based on aging biomarkers and risk factors
- **Halt age-associated disease exacerbation** by the identification of predictive and digital biomarkers that can stratify patients for early intervention
- **Improve quality of life** for healthy individuals and patients by preventing further health decline, avoiding escalating care costs, and properly stratifying individuals earlier in the diagnostic pathway
- **Accelerate adoption** of innovative diagnostic, preventative, and therapeutic strategies, strengthening EU positioning as a healthcare innovator
- Evaluate **digital biomarker as potential regulatory endpoints** in the ultimate goal to develop medicines for “healthy aging”
- **Integrate fragmented research efforts** by bringing together health industry sectors and stakeholders to develop clinical and multi-omics data integration capabilities
- **Enable new data-driven research** by building AI infrastructure on existing data and cohorts that no single organisation could develop independently

Patients and citizens will benefit from improved medical practice and healthcare solutions, new targeted prevention strategies and ultimately healthier aging.

The action will support EU political priorities including the European Health Data Space Regulation (EHDS) and the EU Artificial Intelligence Act, while contributing to European competitiveness in addressing one of society's major challenges.

Why the expected outcomes can only be achieved by an IHI JU action

Elucidating the complex relationships between aging and chronic inflammatory diseases requires a multi-disciplinary approach that transcends traditional research boundaries. The interconnected nature of immunosenescence and age-related disease onset or exacerbations demands collaboration between academic researchers with expertise in aging biology, epigenetics, immunometabolism, and multi-omics approaches, and private companies pursuing therapeutic options in chronic inflammatory diseases.

Unique IHI Advantages:

Cross-sectoral Collaboration: The project requires unprecedented collaboration between disease expertise, aging and immunology research, communities that traditionally do not overlap. IHI's model facilitates this essential partnership between academic and industry expertise.

Data Access, Integration and federated Analysis: The greatest advantage of the IHI model is increased access for all ecosystem players to:

- Existing research cohorts and biobanks
- Electronic health records and real-world evidence

- Digital biomarker data and computational resources
- Large genetic consortia and validation datasets

Resource Pooling: No single organisation possesses the comprehensive resources needed, including:

- Multi-disease expertise across inflammatory conditions
- Advanced multi-omics capabilities (immunoproteomics, spatial transcriptomics, metabolomics)
- AI/ML computational power for complex data integration
- Regulatory expertise for novel (wet lab and digital) biomarker development
- Patient recruitment capabilities across multiple age groups and diseases

Timeline Feasibility: Traditional research structures would require decades to achieve these outcomes. The IHI model enables parallel execution of data mining (existing cohorts & data) and prospective cohort preparation/recruitment making translational outcomes feasible within the project timeframe.

Sustainability and Impact: The collaborative framework ensures sustainability beyond the funding period through established industry-academic partnerships and shared data infrastructure that will continue to generate insights for the aging population's healthcare needs.

Pre-Identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI JU project is composed of the following pharmaceutical and medical technology industry beneficiaries ('constituent or affiliated entities of private members').

Indicative budget

- The maximum financial contribution from the IHI JU is up to EUR 9 000 000. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***
- The indicative in-kind and financial contribution from industry beneficiaries is between EUR 9 000 000 to 10 000 000 (target). ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities (IKOP) from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry beneficiaries most likely includes in-kind contributions to additional activities (IKAA).

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage and the predefined industry consortium may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium

The pre-identified industry consortium expects to contribute to the IHI JU project by providing the following expertise and assets:

- Expertise in target discovery, biomarker identification, AI-driven analysis, regulatory sciences and therapeutic development
- Expertise and scientific resources in the disease areas of interest – Rheumatology, Gastroenterology, Respiratory – of immune mediated origins, as well as in immunology, aging and translational science and medicine
- Enabling access to retrospective data sets, e.g. FinnGen UK Biobank, OpenTarget incl. federated analysis opportunities
- Proprietary data sets of related patients or control cohorts (baseline, placebo data)
- RWE datasets
- Computational analysis support
- Support with (digital) biomarker expertise
- Molecular Analytical support with certain technologies like CHIP

Applicant consortium

The first stage applicant consortium is expected, in the short proposal, to address the scope and deliver on the expected outcomes of the topic, taking into account the expected contribution from the pre-identified industry consortium.

This may require mobilising the following expertise and/or resources:

- Academic research capabilities in aging biology and immunosenescence
- Clinical expertise in gastroenterology and pulmonology and rheumatology
- Expertise in aging biomarkers, immunophenotyping and immunogenetics and epigenetics
- Omics expertise, generation and analysis
- Clinical trial set-up and conduct, including multi-omics analytics
- Cohorts and registry analysis available and accessible for this type of PPP
- AI- and Big Data development and handling / data management
- Expertise on digital biomarkers
- Project management experience for large multi-stakeholder European public-private partnerships.

Furthermore, the applicant consortium is expected to provide resources of the type below:

- Biobanks (systemic as well as tissue datasets) including longitudinal cohorts (for example Milieu Interieur, INSPIRE-T, NutriNet, SNAC-K and EHDEN) combined with epidemiology data and broad patient information database including disease mentioned above, treatment history, comorbidities
- Registries like UK IBD registry, Initiative on Crohn and Colitis registry, FranceCoag registry, REMISMA registries, SNDS health records
- Broad multi-omics capacities across immunology, epigenetics, microbiome, metabolism and spatial technologies
- Data inventories and strong IT, AI and bioinformatics expertise to integrate datasets and build data infrastructure
- Bio-sample handling and storage
- Clinical trial logistics

At the second stage, the consortium selected at the first stage and the predefined industry consortium will form the full consortium. The full consortium will develop the full proposal in partnership, including the overall structure of the work plan and the work packages, based upon the short proposal selected at the first stage.

Dissemination and exploitation obligations

The specific obligations described in the conditions of the calls and call management rules under 'Specific conditions on availability, accessibility and affordability' do not apply.

INDICATIVE TEXT

References

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Glossary

ACRONYM	MEANING
AI	Artificial Intelligence
EC	European Commission
ERICs	European Research Infrastructures
EU	European Union
IKAA	in-kind contributions to additional activities
IKOP	in-kind contributions to operational activities
MoA	Mechanisms of Action

INDICATIVE TEXT