IMMUNEHEALTHXL

IHXL strategic plan

Public version, 2025

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Preface

In 2013, Prof. Frits Koning delivered a powerful call to action during his Van Loghem Award honorary lecture: to prioritize collaboration and disease-overarching research in Immune-Mediated Inflammatory Diseases (IMIDs). Unlike cancer, which benefits from unified efforts in fundraising and research & development, these diseases lack cohesive attention despite their obvious commonalities and significant societal impact. He advocated for a dedicated, long-term fund to explore the differences and commonalities to tangible patient outcomes.

This call inspired the Samenwerkende Gezondheidsfondsen, the Nederlandse Vereniging Voor Immunologie (NVVI), and Health~Holland to fund three groundbreaking public-private partnerships in 2016. With a shared budget of €~17 million, researchers, clinicians, and companies collaborated to study a diverse set of IMIDs in a disease overarching approach. These projects—TIMID, DC4Balance, and Target-2-B—uncovered shared and disease-specific pathways, identified therapeutic opportunities and diagnostic markers, and developed tools and technologies to understand disease variability. Inspired by patient needs, and guided by their experiences, the established projects ensured a focus on patient impact. The established network of experts and connected infrastructures of patient materials of a wide range of IMIDs already proved invaluable during the COVID-19 pandemic, addressing urgent questions about SARS-CoV-2 infection and vaccine responses in IMID patients. Thereby providing critical insights, benefiting both patients and society.

Building on these successes, a follow up, ImmuneHealthSeed, project was launched in 2022 to drive findings forward and sustain the momentum of the disease-overarching approach. Crucially, the project also serves as a bridge, its partners aim to establish a long-term, financially sustainable national platform for disease-overarching research. This platform will connect experts across disciplines, provide essential tools, expertise and funding, guided by patients experiences all focused to deliver patient impact.

1. Executive summary

ImmuneHealthXL (IHXL) is a new initiative, established with a singular mission: to transform the landscape of immune-mediated inflammatory diseases (IMIDs). It achieves this by advancing disease-overarching research and delivering new research insights that have the potential to be translated into tangible impacts for the millions of patients whose lives are affected by these debilitating conditions. As a dedicated research initiative, IHXL is uniquely positioned to drive this mission forward through its commitment to cross-disease immunological research, collaboration, valorisation, and patient-centred approach.

IHXL creates impact by collaborating with patients, to ensure their perspectives are integral to research, valorisation and decision-making. This commitment strengthens IHXL's ability to deliver outcomes that directly benefit patients, enhancing their quality of life and advancing the IMID field as a whole.

A unique approach: IHXL represents the first step towards an important cultural shift in addressing IMIDs. While traditional approaches have primarily investigated and treated IMIDs as distinct conditions based on their clinical manifestations, IHXL adopts a disease-overarching perspective, recognizing these diseases as interconnected by a shared root cause: an unbalanced immune system.

Stakeholders from a broad range of disease areas will be united within IHXL, such as health foundations, basic researchers, clinicians, patients, and private entities. These stakeholders recognize the potential of this perspective and support the drive towards a cultural shift that redefines how IMIDs are understood and addressed. By exploring both the similarities and differences in the immunological processes of these diseases, IHXL creates opportunities to develop novel therapeutic and diagnostic solutions with potential applications across multiple IMIDs, ultimately impacting patient lives.

IHXL's strategy is built around ambitious, patient-centred objectives captured in four moonshots, which form the cornerstones of the initiative. All future research activities within the IHXL ecosystem will be designed with the aim to contribute to achieving these moonshots. To ensure maximal patient impact, IHXL will established structures that embed collaboration, patient involvement, and access to expert valorisation support, thereby helping to drive the broader cultural shift necessary to improve the lives of patients worldwide.

An independent organisation: IHXL will be established as an open initiative, designed to promote, drive and support cross-disease IMID research. With a mission to foster impactful research, IHXL will be able to support, provide expertise and participate in research efforts that align with its mission. Given that IHXL brings together the priorities of a broad range of stakeholders, it is essential that IHXL operates independently and with full transparency. To best serve this purpose, IHXL will be established as a foundation, a legal structure that fits the role as an independent, enabling, not-for-profit organization.

Robust governance structures within the foundation will ensure impartial decision-making focused on advancing high-quality research. These structures are essential for balancing stakeholder interests and prioritizing patient benefit. Through transparent processes, IHXL ensures all its activities align with its mission and strategic goals.

Five dedicated health foundations have demonstrated foresight in recognizing the potential of disease-overarching research and have taken the bold step to help shape the IHXL strategy and

provide IHXL with essential financial support. Their investments not only enable IHXL to establish its operations and serve as a powerful catalyst to promote collaboration, drive new initiatives and attract new (competitive) financial resources. Building on this foundation, IHXL is well-positioned to secure competitive government grants, collaborate with not-for-profit organizations, and engage in selective partnerships with for-profit entities—key steps in transforming the research, development, and clinical application landscape for IMIDs.

2. Vision, mission and strategy

Our vision

Our vision at ImmuneHealthXL is to achieve immune health for all individuals, across all sexes, ethnicities, and stages of life.

Our mission

ImmuneHealthXL aims to improve immune health and enhance quality of life for all individuals affected by immune mediated inflammatory diseases through innovative, cross-disease research that drives the development of innovative approaches cross disease research.

Our strategy

Introduction: Chronic Immune-Mediated Inflammatory Diseases (IMIDs) impact 5%–7% of people in developed countries and encompass around 80 increasingly prevalent conditions. Some examples of well-known organ specific IMIDs are rheumatoid arthritis (RA), vasculitis, type I diabetes (TID), inflammatory bowel disease (IBD), and multiple sclerosis (MS). Moreover, immune mediated inflammation contributes to vascular and neurodegenerative diseases such as atherosclerotic Cardiovascular Disease (CVD), leading to myocardial infarction and stroke and dementia. Given the central role for the immune system and inflammation in the pathophysiology of atherosclerosis, IHXL expands the focus to not only include IMIDs but also CVD caused by atherosclerosis. IMIDs are often accompanied by common comorbidities, such respiratory diseases, anxiety and depression, which further exacerbate the burden on patients and healthcare systems. In the Netherlands, more than 1 million individuals experience the daily challenges of IMIDs, dealing with impairments, pain, fatigue, medications—and their side effects, even when the disease is considered to be in clinical remission. The combined cost of care of IMIDs in the Netherlands is estimated to be 1.5 billion euro annually[1]. While major advances have been made in the targeted treatment of several IMIDs (through e.g., TNF-α inhibitors, IL-6 cytokine blockade, or B-cell depletion), most therapeutic interventions do not repair the defective immunological networks to induce long-term drug-free clinical remission. Hence, IMID patients still experience chronic disease and are kept from participating in society without limitations. The personal and societal impact of IMIDs weighs heavily on patients, their relatives, and society at large.

Historically, IMIDs have primarily been investigated and treated within their own specific niche of medical specialties, since each IMID manifests differently in each patient or patient population in terms of: affected tissues and organs and treatment response. rheumatoid arthritis, for instance typically causes joint pain and swelling, while inflammatory bowel diseases cause abdominal pain and impaired intestinal function, and multiple sclerosis can lead to neurological symptoms such as weakness, numbness and loss of vision. While the differences in clinical presentation and manifestations and differential diagnosis initially set the various IMIDs apart, their shared causative and defining commonalities beg to rethink and reshape our current approach towards this group of diseases. All IMIDs are caused by immunological derailment, display clinical heterogeneity within patient populations, often arise in genetically predisposed individuals, and have shared comorbidities. In addition, environmental and lifestyle factors, as

[1] This number is likely a significant underestimate, as it is based only on data for the most prominent IMIDs, with no comprehensive data available for less prevalent or 'orphan' IMIDs—let alone for the indirect costs associated with co-morbidities.

well as ageing, play a significant role in IMID development and progression. Most importantly, therapeutic solutions for IMIDs primarily target the derailed immune system. Therefore, in recent years both scientists, clinicians and the Association of Health Foundations (Samenwerkende GezondheidsFondsen, SGF) have started to approach IMIDs in a more holistic manner. Rather than focusing on a single disease, they saw and see the benefit of investigating the underlying immunological processes. This approach is guided by treatments that are effective in multiple IMIDs, thereby indicating commonalities in underlying pathways rather than differences. This 'disease overarching' perspective has the strong potential to lead to novel insights into IMID development and progression and find new ways to tackle the heterogeneity in the patient populations. Furthermore, this approach provides the opportunity to efficiently translate new diagnostic and therapeutic solutions across diseases, thereby accelerating development of novel approaches in diagnosis, monitoring, patient-tailored treatment, and the eventual cure of IMID patients.

IHXLs legacy projects: The 'disease-overarching' approach to IMIDs was first implemented in three projects, with a total budget of ~€17M, initiated by the Dutch Society for Immunology (NVVI), the SGF, and the Top Sector Life Sciences & Health (Health Holland). Each project focused on one of the main immune cell types that play a role in IMIDs: dendritic cells (DC 4 Balance), T-cells (TIMID), and B-cells (Target-2-B). Together, these cell types form a crucial part of the immune system, providing a fundamental perspective on the immunological processes driving IMIDs. Based on the success of these projects (see box 1 - 4), upon completion in 2022, the stakeholders involved unified once more to ensure the continuation of the disease-overarching approach in one follow-up project: "Immune Health Seed." This initiative not only continued to drive innovation, but importantly also served as a bridge toward establishment of a long-term, nationwide initiative: ImmuneHealthXL (IHXL).

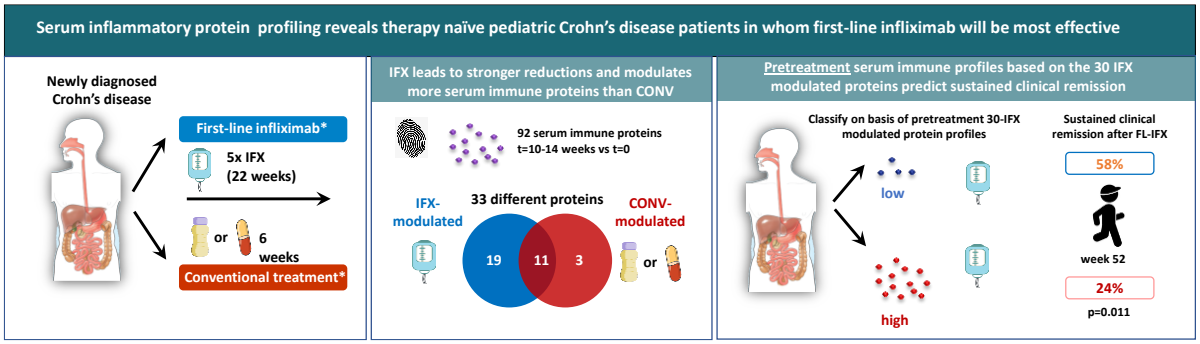
Box 1: Succes story of IHXL legacy projects
Immune profiling to decide who receives treatment and when to stop?

Within the ***TIMID project*** differences in serum immune profiles between children with Crohn's disease (pCD) were explored to improve treatment strategies.

Findings: In moderate to severe pCD, infliximab (IFX; anti-TNFα) treatment directly after diagnosis modulated a larger number of proteins and induced stronger suppression compared to conventional therapy. Crucially, stratification on pre-treatment profiles of IFX-modulated proteins directly related to maintenance of remission without treatment escalation. **Reference**: https://pmc.ncbi.nlm.nih.gov/articles/PMC10441564/pdf/jjad049.pdf

Potential Benefit for Patients: These findings can lead to better, more personalized treatment choices for children with Crohn's disease, reducing unnecessary treatments and improving long-term outcomes.

Applicability across diseases: The study identified immune profiles that can predict treatment response, a concept that will be explored in other IMIDs, such as rheumatoid arthritis, Psoriasis disease and multiple sclerosis .



These legacy projects have demonstrated the power of the disease-overarching approach, establishing a robust, nation-wide network of experts, knowledge, technology, and infrastructure—creating the solid foundation on which IHXL will be built.

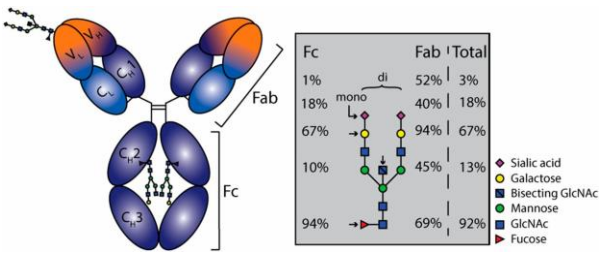
Towards our unified vision: The combined efforts outlined in this strategic plan are designed to drive us closer to our vision and mission. A unifying aspect of IHXL is rooted in the determination that its initiators want to ignite a fundamental culture shift within the entire array of IMIDs. This shift requires for all stakeholders to recognise the spectrum of IMID as one entity, with general overlapping but also unique pathways that determine disease development and predict response to treatments. For scientists and clinicians, this means broadening their expertise beyond a single disease and collaborate to elucidate the commonalities that link different IMIDs. For companies, it involves developing treatments that target shared immunotypes rather than focusing narrowly on specific disease pathologies. Regulators will need to adapt and become more agile, facilitating the approval of therapies that can be applied or repurposed across multiple diseases. Health foundations are encouraged to prioritize and fund research that target pathological commonalities of multiple diseases and lastly, patient organizations will play a crucial role in helping patients understand the commonalities among their conditions, fostering a sense of unity and shared purpose.

Box 2: Succes story of IHXL legacy projects
New roads towards improved diagnostics and treatment options across diseases

Researchers of the ***Target2B project*** investigated the differences in IgG autoantibody modifications to better understand the role of these modifications across IMIDs.

Findings: Unique autoantibody modifications were found across several chronic IMIDS. These modifications are not just random effects but may play a role in how these diseases develop and persist. **Reference**: https://www.jacionline.org/article/S0091-6749(23)00091-X/fulltext

Direct impact: The identified antibody modification has led to a patent, and valorisation with a diagnostic company is underway. Additionally, these findings has resulted several publications and additional follow-up funding including an ERC Synergy Grant (total budget €10M).



Potential Benefit for Patients: These findings pave the way towards **a)** improved diagnostic tools for earlier and more precise detection of autoimmune diseases in general and **b)** new possibilities for treatments that target these specific immune system alteration.

While IHXL will initially be established as a national initiative, its vision and ambition transcend borders. The cultural transformation we aim to ignite within the IMID community should reach beyond national boundaries in the future. By engaging with international peers, IHXL can accelerate progress, share knowledge and resources. This international perspective will be crucial in amplifying the impact of IHXL's work and setting new standards in IMID research and treatment.

By setting this cultural transformation in motion, IHXL will not only advance scientific discoveries but also create a more cohesive, efficient, and effective approach in tackling IMIDs, ultimately improving the lives of millions of patients around the world.

Health foundations: The realization of IHXL represents a significant leap forward in advancing our common goals. After their involvement in the IXHL legacy projects via SGF, multiple health foundations—Diabetes fonds, De Nederlandse Hartstichting, MDL Fonds, Stichting MS

Research, Princess Beatrix Spierfonds and ReumaNederland—have now taken the first crucial steps in further embracing the disease-overarching concept. These organizations have shown the foresight by moving beyond traditional disease-specific boundaries and prioritize the shared challenges of IMIDs. They have helped to shape the IHXL strategy and provided essential financial means to establish the IHXL foundation thereby showing that they have not only recognized the potential of this approach but have also played a pivotal role in bringing it to life. The unmet medical needs of the patient populations represented through these health foundations will play a central role in the execution of the IHXL strategy.

A key factor in IHXL's success will be harnessing the momentum created by these health foundations to inspire additional health foundations to join the cause. By spreading the IHXL approach, we can build the essential critical mass needed to unify patient needs across an even broader spectrum of IMIDs.

Box 3: Succes story of IHXL legacy projects
Paving the way for nanotherapeutics as broadly applicable treatment option for IMID patients

Nanomedicine presents a promising strategy for modulating immune responses by targeting dendritic cells (DCs), pivotal players in immune regulation. Within the ***DC4Balance project***, the effects of liposomes loaded with vitamin D3 (VD3) was investigated on DC function and subsequent immune modulation.

Findings: The study demonstrated that VD3-loaded liposomes effectively primed DCs to induce regulatory T cells, which in turn suppressed inflammatory responses. Building on this, the DC4Balance investigators incorporated vitamin D3 with selected autoantigens and allergens into nanosystems for targeted treatment of autoimmunity and inflammation. The team successfully loaded both rheumatoid arthritis-related autoantigens and allergen-derived antigens into these nanosystems, offering a promising approach for therapeutic intervention. **Reference** https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1137538/full

Potential Benefit for Patients: These studies support the development of VD3-based nanotherapeutics for autoimmune diseases and allergies, offering a targeted approach with the potential to treat, prevent, and possibly cure a broad range of IMIDs while avoiding widespread immunosuppression.

Applicability across diseases: The developed strategy shows great potential for applicability across disease, within the DC4Balance project already multiple important antigens for atherosclerosis were detected in a subset of atherosclerosis patients, and the project has received follow-up funding from the 'Diabetes fonds' for development towards redirection of the aberrant immune response in type 1 diabetes.

Academic partners: The realization of IHXL is deeply rooted in the contributions of its academic partners (Amsterdam UMC, Erasmus MC, UMC Groningen, Leiden UMC, Maastricht UMC, Radboud UMC, Sanquin Research, UMC Utrecht), who, much like the health foundations, have been instrumental in shaping IHXL. Building on their involvement in IHXL legacy projects, these partners have been key instigators of the disease-overarching concept within their academic institutes and beyond.

These institutes not only house the scientists and clinicians driving IHXL's research but also provide critical infrastructures and expertise essential to its success. Moving forward, academic partners will remain pivotal in executing IHXL's strategy, leveraging their research capacity, resources, and critical co-financing to advance cutting-edge science. Their continued involvement will be crucial in uniting diverse stakeholders and building momentum to address the shared challenges of IMIDs.

IHXL strategy: IHXL will be set up as an **independent organization** which aspires to serve as **central connecting national platform** and **key enabler** of disease-overarching research in the field of IMID research and treatment. At its core, IHXL serves to unite all relevant stakeholders within a central virtual initiative, ensuring alignment on a collective strategy focused on the critical themes detailed in this strategic plan. This shared approach will accelerate progress by fostering collaboration and innovation across the IMID landscape. As a connecting platform, IHXL not only facilitates collaboration but also ensures that the unique and critical research infrastructures, expertise, tools, and technologies established through its stakeholders and its legacy projects become accessible to a wider audience committed to the IHXL mission. By unlocking these resources, IHXL creates opportunities for transformative research that might otherwise remain out of reach.

In addition, IHXL will aim to access essential financial means, which will enable it to fund priority research projects aligned with its strategic goals. Such financial means positions IHXL to drive the initiation of large (inter)national research initiatives within competitive funding schemes, ensuring that IHXL's core themes—such as patient engagement, valorisation, and interdisciplinarity—are deeply integrated into such initiatives and the envisioned culture change inspires an ever expanding group of stakeholder. Moreover, IHXL want to closely collaborate with existing and emerging initiatives, thereby granting access to its extensive network, research infrastructures, technologies and expertise in areas. Through this collaborative framework, IHXL strengthens its role as a catalyst for advancing disease-overarching research while creating a unified approach to tackling the challenges of IMIDs.

Central to IHXL is its **disease-overarching approach**, which guides all of IHXL's actions and is intertwined with all elements of its strategy. Additionally, IMIDs confront us with complex challenges that push us to go beyond the competitive model of science and innovation and collaborate across therapeutic and scientific disciplines. For this reason, **collaboration** is also centrally placed in the IHXL strategy. IHXL will therefore be set up as a multi-disciplinary,

Box 4: Succes story of IHXL legacy projects

Patient involvement & representation

All IHXL legacy projects integrated various forms of patient involvement and representation into their project plans, ensuring alignment with patient experiences and needs.

Findings: In the Target2B and DC4Balance projects, Patient Advisory Boards (PABs) were established. Scientists regularly engaged with these PARs to discuss research plans and present findings. The TIMID project fostered connections with patient organizations. Across all projects, patient-inclusive consortium meetings were held, featuring dedicated patient-accessible sessions and opportunities for direct interactions between scientists and patients.

Benefits for Patients and Scientists: IHXL legacy projects' commitment to patient involvement significantly benefitted both patients and researchers. These efforts fostered mutual understanding, directly influencing research design. PAR members disseminated project knowledge within their networks, while patient organizations co-developed accessible materials, including infographics, a glossary, and online dissemination tools. This enhanced the projects' impact across a broader, non-scientific audience.

Applicability to IHXL: Lessons from the legacy projects have been embedded in IHXL's patient strategy. The established patient network remains engaged with the scientific IMID community. Additionally, patient representatives from a PAR in one of the legacy projects actively contributed to the IHXL steering group alongside representatives from patient organisations, helping shape IHXL's patient strategy.

collaborative initiative in which the combined efforts of knowledge institutions, patients (and their organizations), health foundations, industry, and government ensure that we can collectively achieve more than the sum of individual parts. These central themes guide our actions and are embedded in all our activities, which are concentrated around three pillars: 1) research, 2) patient involvement, and 3) valorisation.

These pillars form the backbone of our initiative, ensuring a comprehensive approach to tackling the challenges of IMIDs. IHXL's **Research strategy,** outlined in chapter 3, focuses on deepening our understanding of the underlying mechanisms that drive individual IMIDs as well as translating our findings across these diseases with the aim to improve diagnostic and therapeutic approaches. The **Patient involvement strategy,** outlined in chapter 4, describes IHXL ambitions to integrate patient perspectives and experiences throughout the research and development process, and the governance of IHXL, ensuring that IHXL activities are directly aligned with their needs and challenges. Lastly, the **Valorisation strategy**, outlined in chapter 5, centres around supporting the translation of IHXL's knowledge and research findings towards practical applications for social and economic benefits. This to ensure that scientific discoveries lead to real-world benefits for patients and society.

3. ImmuneHealthXL foundation,

Independent enabler of disease overarching research

To realize its ambitious mission, IHXL's founders recognized the necessity of establishing a dedicated legal entity to effectively implement its strategy. The creation of the IHXL foundation marks a pivotal step in ensuring the initiative's long-term success and sustainability. As an independent foundation, IHXL is uniquely positioned to become the recognized leader within the ecosystem, offering the flexibility to initiate, drive, or participate in new projects that align with its objectives, all while maintaining its operational autonomy and ensuring unbiased decision-making.

Within this structure, IHXL fosters collaboration across the healthcare and research ecosystem, connecting researchers, clinicians, patients (organisations), industry, and policymakers. By serving as a neutral enabler, it cultivates an environment that drives innovation while respecting diverse perspectives. This model of independence, openness, and strategic adaptability positions IHXL as a trusted partner and a catalyst for transformative, disease-overarching research.

3.1 IHXL structure

IHXL foundational structures: The IHXL organization will establish the foundational structures necessary for its operations, as indicated in orange in figure 1. IHXL will set up as an **open platform**. This includes building an **engaged community of stakeholders**, such as academic researchers, patients (organisations), clinicians, industry partners, governmental policymakers, and health foundations. These efforts support the fulfilment of IHXL's **research strategy** (section 4) and ensure that through its involvement the patients are represented as described in its **patient involvement strategy** (section 5). Additionally, IHXL will promote **thematic valorisation** in collaboration with strategic partners (section 6).

***IHXL building blocks*:** With its foundational structures in place, IHXL has the ability to build out its initiative through various building blocks, as indicated in blue in figure 1. These include:

- **Promoting** new projects: By directing funding toward research applications aligned with the scope of IHXL moonshots or by securing investments in the management and accessibility of critical infrastructures of IMID patient cohorts.
- **Drive** the initiation of new initiatives: IHXL will drive the creation of new collaborative initiatives aimed at securing large-scale (inter)national funding. IHXL will not fund these projects but will participate alongside its research partners as an active collaborator to advance shared objectives.
- **Facilitate** public-private partnerships: Through establishing connections between industrial research questions and academic expertise, technologies, and infrastructures. IHXL will promote both one-on-one collaborations and larger multi-partner translational research projects.

- **Support** existing projects: IHXL's network, knowledge, and infrastructure will be connected to existing and operational projects which align closely to IHXL mission and vision. IHXL will provide access to its patient involvement expertise, valorisation strategies, and other resources to maximize the impact of such projects.

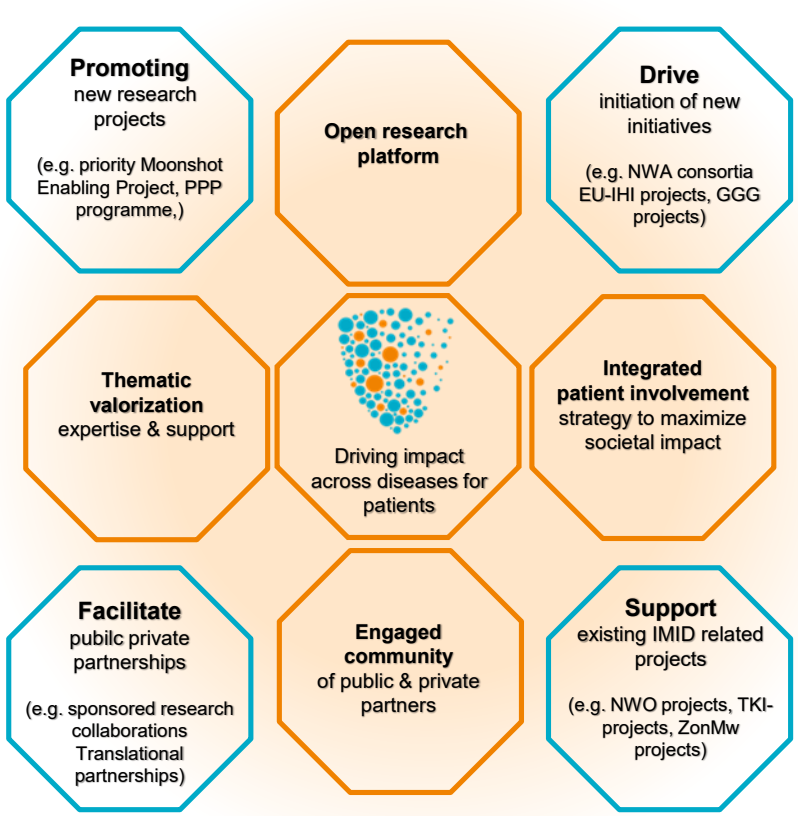


***Figure 1**: Schematic representation of the IHXL initiative, with its foundational structure in orange and its building blocks in blue.*

3.2 IHXL financial flow structure

The IXHL organisation will be the driving force to execute the strategy outlined in this document. To achieve its ambitions, IXHL will depend on a mixed funding model, in which IHXL-core funding, provided by founding health foundations and academic institutions, is supplemented by IHXL-leveraged funding which is to be secured from various resources in the coming years. This mixed funding approach provides IHXL with a stable financial base, enabling the organization to establish the foundational building blocks required to fulfil its strategy while simultaneously building out activities through new funding opportunities.

***IHXL-core funding*:** IHXL-core funding will support the central IHXL organisation, which will act as the driving force to promote, facilitate and support disease overarching research. IHXL-core funding ensures funding opportunities are matched to IHXL's research and patient strategies (see sections 4 and 5). Critically it will facilitate the creation of a cohesive community to foster collaboration and visibility.

IHXL aims to expand its group of core funding partners to ensure sustained growth and momentum in its mission. Firstly, strategic industry partners are invited to join this foundational group, contributing to IHXL's stable financial base while benefiting from a shared commitment to

transformative research. Additionally, IHXL will seek to extend the group of health foundations with new health foundations focused on other IMIDs, broadening its scope and fostering collaboration across a wider array of patient populations.

IHXL-leveraged funding: Leveraged funding greatly amplifies IHXL's ability to fully harness the potential of the ecosystem in which IHXL operates. IHXL will actively pursue funding opportunities required to fulfil its mission. Some of these funds provide the opportunity to be deployed internally within the IHXL framework, examples of such opportunities are; Health~Holland's Publiek Private Samenwerkingen (PPS)-programme call, Thematische Technolgy Transfer call from the Rijksdienst voor Ondernemend Nederland (RVO) and the Lange Termijn Projecten from the Nederlandse Wetenschap Organisatie (NOW). In addition IHXL will positioning itself as a driving force to secure medium to large-scale research funding in which the IHXL organisation and its research partners participate in collaborative research initiatives such as Nationale Wetenschaps Agenda – consortia, Innovative Health Initiative calls as well as medium sized projects in coordination with strategic partners, such as the Treatmeds foundation, and Goed Gebruik Geneesmiddelen programma from ZonMw. This dynamic funding strategy ensures that IHXL can scale its efforts effectively, fostering innovation and delivering on its mission.

4. Research strategy

In recent decades, the field of IMID research has witnessed remarkable technical, therapeutic and immunological advancements which have transformed our understanding of the emergence and development of IMIDs, subsequently resulting in new approaches for diagnosis and treatment. Key breakthroughs such as targeted biologic therapies, like anti-TNF-α agents, have immensely improved and revolutionized management of conditions like rheumatoid arthritis, multiple sclerosis, and Crohn's disease. In addition, our understanding of IMIDs through recent technical advancements in molecular and genetic research have increased our comprehension of shared signalling pathways among the various IMIDs, revealing that these diseases often involve common immune system dysregulations.

IMID definition: Within IHXL, we define IMIDs as chronic conditions in which tissue pathology is caused by chronic immune-mediated inflammation. This ranges from classic organ specific pathology (e.g. rheumatoid arthritis, type I diabetes, multiple sclerosis, inflammatory bowel disease) to contribution of inflammation to vascular and neurodegenerative diseases (e.g. atherosclerotic CVD and dementia). Most cardiovascular diseases, including myocardial infarction, stroke, and peripheral arterial disease, are caused by atherosclerosis, which is a chronic inflammatory disorder of the arterial wall.

IHXL promotes a comprehensive research strategy that emphasizes the commonalities among different IMIDs. We believe that this 'disease overarching' research approach is crucial for further deepening our understanding of the shared, but also uniquely distinct mechanisms underlying these conditions and for developing more effective, broadly applicable, diagnostic, and therapeutic strategies across diseases.

IHXL's research strategy exists of multiple activities and is built on a solid foundation of our four legacy projects (Target2B, DC4Balance, TIMID and IH seed), in which the 'disease overarching' research approach was first established and shown to be hugely impactful (see boxes 1-4).

4.1 IHXL knowledge and infrastructure platform

IHXL builds on the foundation of its legacy projects, which pioneered disease overarching research in IMIDs, fostering the integration of multidisciplinary research and launching cross-disease clinical studies. The success of these projects can be attributed to two key factors:

1. **Collaboration across fields**: These projects brought together experts from diverse disciplines and disease areas, generating new knowledge, tools, and technologies that have become readily applicable for advancing IMID research.
2. **Utilization of patient resources**: The projects leveraged the collective strength of existing IMID patient registries and biobanks. They effectively mapped existing patient cohorts, harmonized and enriched datasets, and made them accessible for (re)use by the research community. The selfless contributions of patients have proven to be an invaluable asset, enabling critical advancements in research and treatment of IMIDs.

IHXL is committed to ensuring that the knowledge, infrastructure, and technologies developed through these legacy projects—and their future extensions within IHXL — is maintained and will be accessible to the broader research community, hereafter referred to as the IHXL knowledge and infrastructure platform. By doing so, IHXL ensures that past investments continue to generate impact and drive progress. The maintenance and accessibility enable the use of these valuable

resources to address a wide range of scientific, technological, patient-centered, or industry-driven questions, fostering innovation.

Implementation: IHXL aims to become the 'go-to' initiative for IMID-related research by serving as an enabling partner that connects its knowledge and infrastructure platform with the IHXL community and external public and private partners.

Furthermore, IHXL is committed to ensuring the management and accessibility of critical patient infrastructures by supporting their maintenance and accessibility. This openness ensures that patient registries and biobanks are maintained and supported to be readily available for research efforts.

IHXL will ensure utilization of the knowledge and infrastructure platform through:

- **Community building:** IHXL will host a wide range of meetings where ideas, knowledge, and expertise can be shared (see section 7.2). These events will be inclusive, welcoming participants from across the broader ecosystem.
- **Facilitating collaboration:**
    - IHXL fosters collaboration by making it a prerequisite in its funding calls, ensuring project partners engage with owners of technologies and infrastructures. It also promotes the use of existing infrastructure and technologies through its knowledge and infrastructure platform, avoiding redundant investments and maximizing impact.
    - IHXL further acts as a linking pin within its community, connecting public and private partners with specific research questions to the right experts or patient infrastructures. This ensures the platform remains a dynamic hub for IMID research and innovation.

4.2 IHXL moonshots

Central to the IHXL research strategy are the IHXL-moonshots. Within these four interconnected moonshots, ambitious objectives have been formulated which require long term vision and

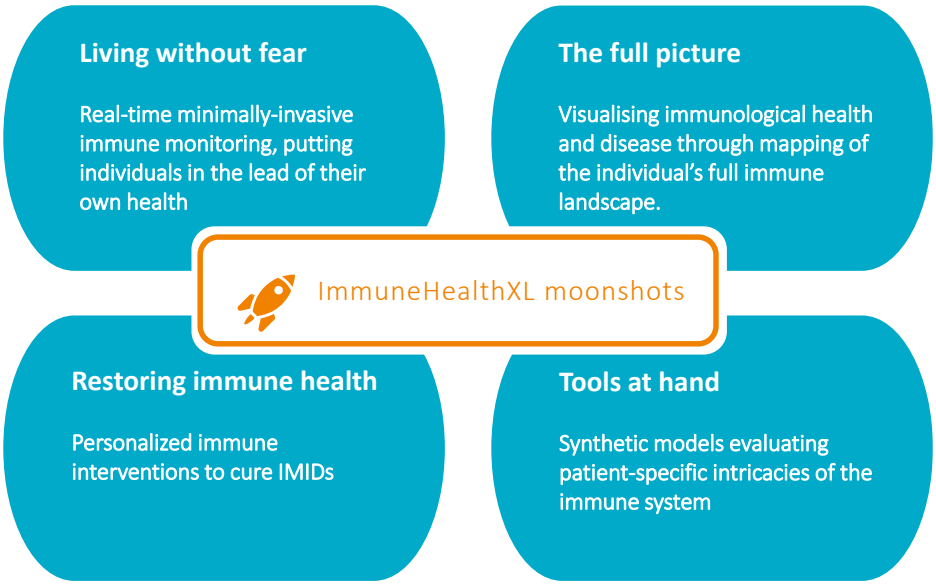


***Figure 2**: The four interconnected IHXL moonshots.*

commitment to achieve the envisioned impact for patients and society at large. The IHXL moonshots have been developed through a collaborative process involving a diverse array of stakeholders including: patients (organisations), scientists and clinicians of all medical universities in the Netherlands, Sanquin Blood Supply Foundation and the National Institute for Public Health and the Environment (RIVM), health foundations, industry partners, and governmental representatives. The moonshots were established through an extensive formulation process with exploratory discussions, in-depth interviews with a broad stakeholder base, and a series of roundtable sessions where ideas were continuously shaped, refined, and redefined based on collective input. The moonshots help to guide the IHXL activities with a clear direction towards common, shared objectives, underpinned by clear intermediate outcomes.

Set up: Each moonshot is structured to achieve a long-term objective over a 15-year period, aiming for 2040. The setup begins with a clearly described background section, including a version in layman's terms (in Dutch), to ensure accessibility. The 15-year timeline is divided into 5-year intervals (fig. 3), with clearly defined intermediate milestones. These milestones help track progress, provide benchmarks for performance, and allow for adjustments if needed. Connections and interdependencies between the different moonshots are clearly indicated within the moonshot description.

The 5-year intermediate milestones are described in a structured way, which includes:

- Background: Context and rationale for the milestone.
- Involved Stakeholders: The contributions and roles of potentially relevant stakeholders (outlined below).
- Expected Outputs: Specific deliverables tied to the milestone.

The first intervals are described in the most detail, later intervals are intentionally less detailed. This reflects the dynamic nature of the initiative, accommodating changes both within IHXL and the external environment.

Guiding Framework: To remain at the forefront of innovation, IHXL prioritizes flexibility and inclusivity in how it executes its moonshots. Therefore, the moonshots provide a structured

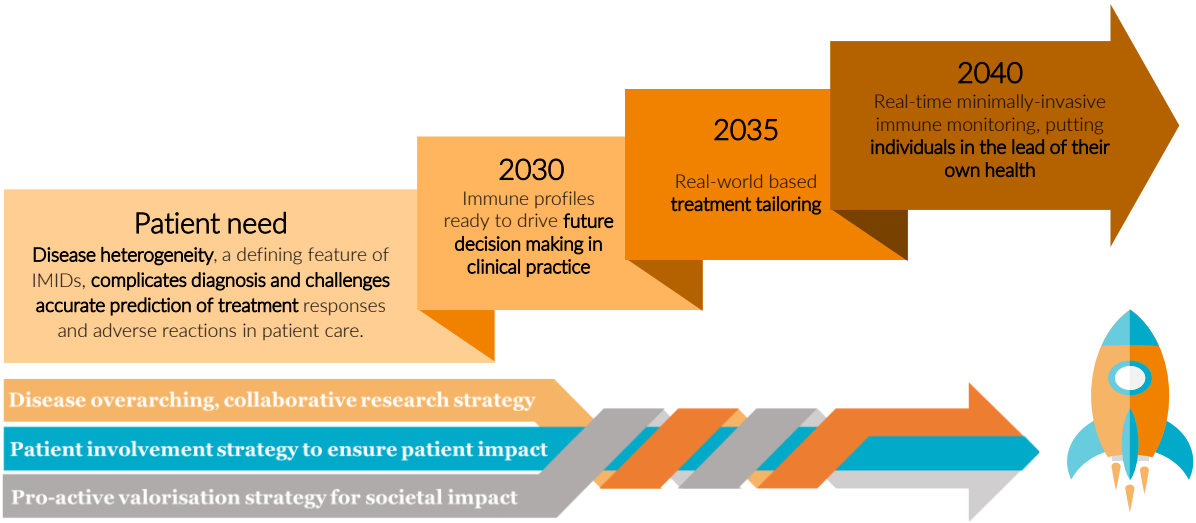


***Figure 3**: Simplified representation of the Moonshot 'Living without fear'. Each moonshot is defined from a specific patient/clinical need and accompanied by a 15 year development plan with 5 year intervals. Within the activities of each moonshot, IHXL will integrate its disease overarching, patient involvement and valorisation strategies to ensure maximal impact.*

framework to guide IHXL's strategic activities and achieve its long-term objectives. Rather than prescribing a fixed path, they allow flexibility by focusing on clear milestones and objectives. IHXL will seek out funding opportunities and match these to projects that contribute to the moonshot goals. This approach strikes a balance between clear direction and adaptability, enabling IHXL to remain responsive to evolving needs.

Involved stakeholders: To achieve the long-term strategic objectives of the moonshots, it is essential to identify the appropriate stakeholders and expertise needed throughout the development path of both projects and moonshots. IHXL will actively promote research teams to consider such development paths from the outset of a project. While the route to the end goal may vary depending on the projects technology, knowledge, or lead being developed, IHXL has structured its moonshots with a broad understanding of the types of stakeholders likely to be required.

Below a range of the anticipated stakeholder groups are listed. These serve as examples and may evolve with future technological advancements or if specific project needs emerge. Stakeholders may range from:

- **Academic researchers in immunology and technology development:** basic immunology and clinical expertise across IMIDs, with expertise in translational patient-driven research, pharmacology, medical immunology, clinical chemistry. Technical academic expertise in areas such as A.I. & machine learning, biostatistics, data management, multiparameter analyses techniques.
- **Industry partners:** Biotech and pharmaceutical companies focused on translating basic research into clinical applications or focused on the development of new technological advancements.
- **Good Manufacturing Practice (GMP) Facility and Expertise:** Dedicated GMP-certified facilities which are critical to produce immune-modulating therapeutics. Such facilities ensures that pilot productions meet the stringent quality and safety standards required for clinical trials.
- **Patients and patient advocacy groups:** Individuals contributing to research through participation in trials, and/or provide input on study designs, patient experience and practical implementation. Advocacy groups can provide input on patient needs and perspectives, and help to disseminate outcomes to larger patient populations.
- **Valorisation expert support:** Business development experts in protecting intellectual property rights, (industry) contracts negotiations, academic development pathway opportunities. As well as experts in topics such as clinical trial design, HTA and regulatory processes.
- **Public funding agencies and private investors:** public organizations (grant funders) and private entities (venture capitalists, pharmaceutical investors) that provide the financial resources for development.
- **Healthcare Providers and Clinical Stakeholders:** general practitioners, treating academic physicians, clinical societies who develop guidelines, pharmaceutical industry.
- **Government authorities and Payers:** Government entities that create policies affecting regulatory approval and patient access through the integration of new therapies into healthcare systems.

Figure 4 provides an example of the involvement of different stakeholders throughout the development pathway within a specific project. Please note that this just one example of how stakeholders can be involved, and the type of stakeholders and their involvement will vary from project to project.

Stakeholders involved	2025 – 2030 **Milestone:** Definition of age, sex and tissue critical immune networks as targets for precise immune intervention	2030 – 2035 **Milestone:** Spatially resolved immune landscapes & first full human immune atlas	2035 – 2040 **Milestone:** Immuno-characterisation as the new standard clinical practice
Academic researchers	- Scientist/Clinician scientist acts as study lead - Clinical experts support study with expertise and infrastructure	- Clinician acts as clinical study lead, for validation in relevant environment - Technical innovators develop algorithm	- prototype demonstration in a clinical environment
Industry partners	- Industry partners support study with (unique) technology	- Prototype development - In kind/cash support of development	- Validation of device/test/AI-based model in patients
Patients, & advocacy groups	- Involved in defining research question - As contributors to patient cohorts	- Involved in defining study set up - Provide input in prototype usage	- Part of clinical study - Patient groups help to disseminate outcomes to larger patient population
Valorisation expert support	- Provides BD guidance - Potential early patenting	- IP protection / launch spin off - Establishing collaboration agreement with industry - Support initiation of regulatory discussion	- Supporting expertise for trial design, regulatory pathways
Healthcare Providers & stakeholders	- early shaping of research question - definition of medical need	- Initiation of regulatory considerations	- monitoring trials, granting approvals - Incorporation in clinical guidelines
Public funding agencies, private investors	- Research grants from public funding agencies	- Collaborative public private research grants. - Proof of Concept grants for prototype development	- In kind industry contribution for clinical study - Raise capital for spin off
Governmental authorities & Payers			- Engage to determine reimbursement & healthcare integration

***Figure 4**: An example of stakeholder involvement of the development of a project over a 15 year period. Please note, that stakeholders and their involvement can vary from project to project.*

Implementation: IHXL will actively promote the formation of research teams capable of attracting funding for projects that can contribute to the moonshot objectives through innovative research with clear clinical application potential. These projects can encompass a wide spectrum of activities, ranging from explorative basic research, validation, and translation of scientific and clinical concepts, technologies, interventions, or therapeutic products across a variety of disease areas. IHXL will support or participate in projects which are:

- **Disease overarching:** IHXL is guided by the 'disease overarching' concept and thus research questions must be centred around evaluation of immunological disbalance and immunological health (both innate and adaptive) and modulation thereof across multiple diseases and additionally have the potential to be translated across more diseases.
- **Collaborative**: IHXL believes in the added value of collaboration and will always promote and drive disease overarching, multidisciplinary research.
- **Patient involvement:** To ensure that IHXL activities are aligned with the real-world needs and challenges faced by individuals with IMIDs, IHXL will always promote and drive projects where patients are not merely participants, but recognized as integral partners in the research process. IHXL will promote patient involvement at critical stages of the research, including:
    - Co-design of research questions and objectives: Where relevant, patients will provide input on the formulated research questions, thereby ensuring alignment with patient priorities and concerns.

- Active role in study implementation: Patients can provide invaluable input during the execution of research, helping to refine methodologies and ensure the research remains patient-centred.
- Dissemination and Implementation of Results; To bridge the gap between research and real-world application, patients-organizations can play a key roles in disseminating the findings and in strategizing their implementation.

Moonshot, Living without fear

Nederlandse samenvatting: Momenteel is het bij veel chronische immuun-gemedieerde ontstekingsziekten (IMIDs) niet mogelijk om te voorspellen hoe de ziekte zich in de loop van de tijd zal ontwikkelen. Het is onzeker of een behandeling zal aanslaan, of een patiënt nieuwe klachten zal krijgen en hoelang de ziekte rustig blijft wanneer deze goed onder controle is. Ook veel patiënten met hart- en vaatziekten krijgen deze doordat ze risicofactoren hebben, zoals hypertensie, hypercholesterolemie, overgewicht of diabetes. Voor patiënten is beangstigend dat echt ook als deze risicofactoren goed zijn behandeld, een groot percentage toch opnieuw hart- en vaatziekten krijgt. Een aanzienlijk deel van deze patiënten heeft bovendien helemaal geen typische risicofactoren. Dit zorgt voor onzekerheid bij patiënten en kan leiden tot onder- of overbehandeling. Bij onderbehandeling blijft de ziekte actief, met mogelijk aanhoudende klachten en weefsel-, en orgaanschade als gevolg. Bij overbehandeling kunnen onnodige bijwerkingen van medicatie ontstaan, wat weer nieuwe klachten veroorzaakt. Daarom is het van groot belang om tijdig de best passende behandeling te vinden—voordat klachten en weefselschade optreden—en voortdurend te controleren of de gekozen behandeling effectief blijft.

Het beter kunnen voorspellen van het ziekteverloop en het effect van een behandeling kan helpen om onzekerheid bij patiënten te verminderen. Dit is echter lastig, omdat IMIDs complex zijn, in de tijd veranderen en per patiënt verschillen. Veel huidige voorspellingen zijn gebaseerd op een combinatie van klinische symptomen en meetwaarden van de ziekte. IMIDs ontstaan door verstoringen in het immuunsysteem. Bij veel van deze ziekten zijn afwijkingen in het immuunsysteem al meetbaar voordat ernstige klachten of weefselschade optreden, of voordat de ziekte opnieuw actief wordt tijdens of na een behandeling. Op dit moment zijn er echter weinig testen beschikbaar om deze afwijkingen goed te meten. Deze moonshot richt zich op de ontwikkeling van testsystemen die het gedrag van het immuunsysteem nauwkeuring kan meten en bij individuele patiënt in kaart kunnen brengen. Hiermee kunnen artsen en patiënten in de toekomst sneller en beter grip krijgen op de ziekte, waardoor blijvende weefselschade zoveel mogelijk kan worden voorkomen.

In deze moonshot van ImmuneHealthXL willen we nieuwe diagnostische testen ontwikkelen door de immunologische status van patiënten met verschillende IMIDs te vergelijken. Alle IMIDs ontstaan doordat het immuunsysteem uit balans raakt, en bij aanhoudende ziekte blijft deze disbalans bestaan. Door ziekte-overstijgend onderzoek kunnen we testen ontwikkelen om immunologische disbalans beter te meten. Door de immunologische activiteit van grote groepen patiënten met verschillende IMIDs en uiteenlopende ziekte-ernst te vergelijken, kunnen we ontrafelen welke immunologische kenmerken van belang zijn: welke gedeeld worden tussen verschillende IMIDs en welke uniek zijn voor specifieke IMIDs of een bepaald ziektestadium. Daarnaast kan dit ziekte-overstijgend onderzoek bijdragen aan de ontwikkeling van betrouwbare

testen voor zeldzamere IMIDs. Voor deze ziekten is het aantal beschikbare patiënten vaak te klein om afzonderlijk goede testen te ontwikkelen. Door onderzoek te combineren met andere IMIDs kunnen we betere diagnostische mogelijkheden creëren.

Alle projecten binnen deze moonshot richten zich op het ontwikkelen van nieuwe manieren om het afweersysteem beter in de gaten te houden (*immuunmonitoring*). Dit helpt artsen om de ziekte eerder op te sporen, te volgen hoe goed een behandeling werkt en te bepalen wanneer een behandeling moet worden aangepast of gestopt.

Met geavanceerde technologieën, zoals *genomics* en *proteomics*, kunnen we nauwkeurig stoffen en andere kenmerken in het bloed en cellen meten. Zo kunnen we beter vaststellen wanneer het immuunsysteem uit balans is. Het doel is om testen te ontwikkelen die op verschillende manieren gebruikt kunnen worden: door artsen in het ziekenhuis om de juiste behandeling te kiezen, maar ook als eenvoudige thuistesten waarmee patiënten zelf hun ziekte kunnen volgen. Dit kan helpen om de zorg beter af te stemmen op de individuele patiënt en ziekte-opvlammingen zoveel mogelijk te voorkomen. Ons uiteindelijke doel is hiermee minder actieve ziekte te krijgen en de onzekerheid van de patiënt over mogelijke ziekte-opvlammingen te kunnen verminderen.

Long term objective moonshot:

Real-time minimally-invasive immune monitoring, putting individuals in the lead of their own health

Background: Disease heterogeneity, a key feature of IMIDs, translates into diagnostic challenges and causes difficulty to predict treatment response and adverse reactions when choosing the appropriate treatment for individual patients. Alternatively, lack of biomarkers to measure Immunological Disease Activity (IDA) is often hampering clinicians to provide individually tailored treatment options. Moreover, a significant portion of patients with cardiovascular diseases do not have typical risk factors. For these patients in particular, it is crucial to investigate the role of the immune system in the development of their disease and to identify immunological biomarkers to predict their risk. The current incapacity to predict has direct consequences for patients who fear for insufficient disease control, therapeutic side-effects and irreversible damage to their affected organ. Although the need for personalized medicine based on tailored treatment strategies has long been acknowledged, the parameters required for tailoring such treatment options are insufficiently known and defined. It is likely that no universal biomarkers exist and separate immune parameters will be needed to capture the various treatment challenges, like disease diagnosis, disease severity, response to treatment, risk for co-morbidity and disease reactivations. With the rapid expansion of immune therapeutics, the health care system is challenged to develop better knowledge-based treatment choices. As such, there is an urgent need for a new strategy to approach these problems and develop immune monitoring to fit the patient's and clinicians needs.

Immune monitoring for the treatment of IMIDs can be grouped in three phases:

Phase 1: Diagnostic work-up and assessing disease severity before treatment to guide a treatment choice.

Phase 2: Assessing response to treatment by measuring disease activity to prevent disease flares, avoid over/undertreatment and monitor co-morbidities.
Phase 3: Determine how to change or stop treatment.

Traditionally, each of these three phases of IMID decision making may involve a combination of clinico-pathological parameters that reflect inflammation and degree of macroscopic and histological damage to the affected organ/tissue. Very few immune parameters that show the specific type of pathological immune disbalance and the severity thereof are routinely used in IMID diagnoses. Therefore, patients invariably receive standardized immunosuppressive or immunomodulatory therapy. Unfortunately, the treatment choice is often dictated by consensus stated in treatment guidelines based on evidence collected from studies showing efficacy on a group level without patient-specific immune evaluation within the group. Also, there is selection bias in the data since patients participating in these studies need to fulfil the inclusion and exclusion criteria. Currently, multiple treatments have shown to be efficacious in more prevalent IMIDs, but choosing the appropriate treatment (phase 1; diagnosis or phase 3; stopping/changing treatment) for an individual patient targeting his/her specific derailed immunopathologic pathways is yet not possible. Similarly, during phase 2; treatment follow-up, assessing therapy efficacy and disease activity is mainly based on patient reported clinical symptoms and surrogate markers of tissue damage or inflammation (clinical assessments, imaging, laboratory parameters) but also here use of immunologic biomarkers is very limited. In this moonshot, we will therefore develop multiparameter immune monitoring for individual patients for application in IMID diagnosis, prediction of therapeutic response and co-morbidities, and allow future precision treatment.

Approach: To achieve this, we will leverage both established and novel technical approaches, including serology, unbiased immune-omics techniques such as genomics, proteomics, and multiparameter cytometry, as well as more complex assays, such as microparticle detection and functional immune cell assays. By applying these analyses across different IMIDs, we aim to develop a unified IMID immune monitoring strategy that encompasses all stages—from discovery (current stage) to development, regulatory approval, and clinical implementation. This strategy will guide the design of immune tests that can be applied across multiple IMIDs where possible, while also accelerating the development of disease-specific tests by enabling technology sharing. This is particularly relevant for rare diseases with less common immunotypes or disease-specific complications unique to a single condition.

IHXL envisages that this approach will help identify subgroups of patients with specific immunotypes that can be used for; diagnosis (phase 1), monitoring during treatment (phase 2), and treatment adjustment (phase 3). IHXL anticipates that the final immune monitoring tools will vary in complexity and their method of clinical implementation. Some will be best suited for routine use in hospital diagnostic settings, as they require advanced technology, data analysis, and clinical interpretation. However, omics techniques can also help identify key biomarkers that reflect critical immunological processes during a particular disease phase. These individual or small sets of biomarkers could then be integrated into self-monitoring tools, enabling IMID patients to track their condition at home.

This cross-disease approach will fundamentally transform the field, as current immune monitoring initiatives are largely confined to individual IMIDs, leading to fragmented knowledge and slow progress. In alignment with IHXL's vision, earlier and more effective immune monitoring will drive precision medicine (see moonshots '*Tools at hand'* and '*The full picture'*), enabling early

and optimized patient-specific diagnoses of immune health status. This will be followed by tailored treatment strategies (see moonshot '*Restoring immune health*') and ongoing immune monitoring, ultimately reducing disease flares and preventing comorbidities.

Consistent with IHXL's mission, the development strategy for immune monitoring follows a multidisciplinary approach. The expertise and stakeholders involved will vary depending on the type of immune monitoring and its stage of development, as outlined in section 4.2 under Involved Stakeholders and illustrated in Figure 4.

Milestone, 2030:

Immune profiles ready to drive future decision making in clinical practice

Background: Several techniques—including plasma proteomics, serology, multiparameter cytometric analyses, and functional assays—have shown promise for immune profiling in IMID patients. In cross-sectional, retrospective, and prospective discovery cohorts, immune profiles were shown to be associated with/ predict severity of disease course and/or better characterize clinical disease severity. The next critical step is to refine relevant immune profiles and replicate existing findings in standardized, harmonized, clinically certified prospective studies that integrate relevant clinical data and biomaterials. In the Netherlands, multiple IMID cohort studies are already available and will be leveraged to assess the technical quality, diagnostic accuracy (sensitivity, specificity), responsivity, cost-effectiveness, and cross-IMID feasibility of implementing new immune profiling assays. Ideally, these replication studies will be investigator-initiated.

The ultimate goal is to establish immune profiles as a clinical tool to guide treatment decisions.

Input: This step requires a) academic researchers in immunology and technology development; b) industry partners; c) patients and patient advocacy groups; d) IP and legal experts; e) public funding and private investors; f) health care providers and clinical stakeholders. The exact role of each expertise group will vary in composition and in time depending on

- The type of test. For instance, a cellular assay will require different expertise compared to a test with two or three biomarkers.
- The future application. For instance, an 'in-hospital test' with 24 biomarkers for use across 5 IMIDs would require more complex data analyses but also involvement of several clinical fields, patient groups etc, while a home test with two biomarkers requires earlier involvement of engineering and device development.
- The target IMIDs. For instance, designing tests across multiple IMIDs needs data harmonisation, while designing a test based on the same approach and strategy for separate IMIDs does not.

Output: In 2030, we expect to have selected five candidate biomarker profiles/assays applicable to any of the three IMID treatment phases.

Milestone, 2035:

Real-world based treatment tailoring

Background: Once the initial immune monitoring approaches have been extensively tested in clinical IMID studies, the next step is to collect real-world data on their effectiveness. Unlike clinical studies, which include patients based on specific criteria, real-world data will capture the full spectrum of patient variation across all disease stages.

Input: This step requires a) academic researchers in immunology and technology development; b) industry partners; c) patients and patient advocacy groups; d) IP and legal experts; e) public funding and private investors; f) health care providers and clinical stakeholders; g) government authorities and payers.

Output: Immune monitoring is implemented in Dutch healthcare for at least five diseases and is integrated into dedicated IMID inception cohorts, where patients are followed longitudinally. Efforts are ongoing to incorporate immune monitoring into (European) clinical guidelines and to routinely document it in electronic IMID patient records. Implementation in international guidelines is a time-consuming process and depends on the specific characteristics of each IMID.

Milestone, 2040:

Immune monitoring is implemented in hospital settings in at least five diseases for either of the three treatment phases. Next to this, self-monitoring tools are generated to capture actionable immune events preceding or associated with relapse and Quality of Life (QoL) perception.

Background: IMID patients frequently suffer from fear of disease reactivation or worsening of disease, which can hinder their societal participation and increase the risk of additional tissue damage. At this stage in the moonshot, hospital-based immune monitoring will be implemented. Moreover, self-monitoring could provide patients with direct insight into their immune status, enabling early detection of immune activity changes before they lead to relapse and organ damage. Potential self-monitoring tools include wearables, finger-prick tests, or rapid tests using alternative body fluids such as saliva, urine, or faeces.

Input: This step requires a) academic researchers in immunology and technology development; b) industry partners; c) patients and patient advocacy groups; d) IP and legal experts; e) public funding and private investors; f) health care providers and clinical stakeholders; g) government authorities and payers. This outcome has strong emphasis on selecting a minimal number of biomarkers that can be monitored at home (usually proteins), development of technical devices with industrial technology developers and means for effective electronic conversation between patients and treating physicians.

Output: Reliable tests which are simple to perform, minimally invasive and affordable. Immune responses will be measured in easily accessible body fluid (for instance saliva, urine, blood, faeces). IHXL will contribute to all phases of development and implementation.

Examples of applicability to IMIDs: For this moonshot, we will investigate and target the patient populations of the more frequent IMIDs, like IBD, RA, Atherosclerotic CVD and MS, as these IMIDs affect many people, form a large burden on patients and society and allow inclusion of large, well-defined patient cohorts. Initial Immune Disease Activity (IDA)-related studies in IBD that already have been executed form the initiation of this moonshot and follow-up studies in IBD will stay a focus in IHXL. Also, in MS IDA-related studies have been executed in the past and can see a strong follow-up in IHXL. We will also investigate and target the patient populations of Chronic Inflammatory Demyelinating Polyneuropathy, Myasthenia Gravis, Myositis, Vasculitis, Systemic Lupus Erythematosus, scleroderma, pemphigus, and other rarer IMIDs by including smaller, well-defined cohorts, as these IMIDs also carry severe disease burden. Initial IDA-related studies in CIDP have already been performed, forming a solid basis for further research.

The comparison of large IMIDs and smaller IMIDs together will allow 1) generation of novel insights by investigating large patient groups, 2) identification and targeting of key immune mediated vascular diseases such as like Atherosclerotic CVD, 3) transfer of knowledge and therapy success between IMIDs and 4) setting up diagnostics assays that can be applied across IMIDs (containing both broad markers for immunological health/disease and IMID-specific biomarkers).

Moonshot, The full picture

Nederlandse samenvatting: Deze moonshot heeft als doel beter te begrijpen hoe het immuunsysteem gezond blijft en waarom het soms leidt tot immunologische ziekten (IMIDs), door de onderliggende immuun mechanismen in kaart te brengen. We onderzoeken welke processen ziekte veroorzaken en hoe deze per persoon verschillen, bijvoorbeeld tussen mannen en vrouwen, tussen jongeren en ouderen, en tussen mensen met verschillende genetische achtergronden en/of culturele factoren. Daarnaast kijken we naar hoe ziekte zich ontwikkelt in verschillende delen van het lichaam, zoals organen, lymfeklieren, beenmerg en bloedvatwand in vergelijking met de cellen en moleculen in de bloedbaan. Ook willen we beter begrijpen hoe ziekteprocessen in de loop van de tijd veranderen en welke lichaamseigen en externe prikkels hier invloed op hebben.

Door deze inzichten te verkrijgen, willen we beter begrijpen of de mechanismen die ziektevoortgang of ziekte-opvlamming veroorzaken dezelfde zijn als de mechanismen die in vroege stadia van de ziekte worden waargenomen. Daarnaast onderzoeken we hoe chronische ontstekingen in IMIDs leiden tot schade aan organen en weefsels, wat uiteindelijk onherstelbare schade kan veroorzaken.

IMIDs omvatten ongeveer 80 verschillende aandoeningen die steeds vaker voorkomen. Uit onderzoek blijkt steeds duidelijker dat veel van deze ziekten vergelijkbare biologische processen delen. Dit komt naar voren uit studies naar de basismechanismen van het immuunsysteem, de

manier waarop patiënten reageren op behandelingen, en gegevens uit bevolkingsonderzoek. Zo is bijvoorbeeld aangetoond dat medicijnen die dezelfde ontstekingsstof blokkeren, zoals anti-TNF-therapieën, effectief kunnen zijn bij meerdere IMIDs, waaronder reumatoïde artritis, de ziekte van Crohn en psoriasis. Toch werkt deze behandeling niet bij alle patiënten met deze ziekten.

Dit komt deels doordat IMIDs sterk kunnen verschillen tussen patiënten. In plaats van één op zichzelf staande (moleculaire) ziekte is een IMID vaak een complex immuun syndroom, waarvan we de exacte oorzaak nog niet goed begrijpen. Daarnaast veranderen immuuncellen wanneer ze zich in een orgaan vestigen, waardoor metingen in het bloed niet altijd een volledig beeld geven van wat er in het lichaam gebeurt. Omdat we deze processen nog onvoldoende begrijpen, krijgen veel patiënten niet de juiste behandeling of ervaren ze bijwerkingen. Dit kan ertoe leiden dat de ziekte verergert en dat patiënten langer moeten wachten op een passende behandeling. Daarnaast brengt dit hoge maatschappelijke kosten met zich mee, omdat dure medicijnen niet altijd bij de juiste patiënt op het juiste moment terechtkomen.

In deze moonshot kijken we op een nieuwe manier naar ziekten en immunologische gezondheid. In plaats van ziekten afzonderlijk te bestuderen, richten we ons op de gemeenschappelijke, ziekte-overstijgende mechanismen in immuuncellen die bijdragen aan ziekte. Immuuncellen spelen een centrale rol in het ontvangen, verwerken en doorgeven van signalen uit het lichaam en de omgeving. Hierdoor vormen zij een communicatienetwerk dat het immuunsysteem aanstuurt. In de moonshot is het doel om beter te begrijpen welke immunologische processen een rol spelen bij verschillende IMIDs. Dit doen we door uitgebreide immuunmetingen van patiënten te combineren met klinische gegevens en biomarkers, die worden gevolgd gedurende het verloop van de ziekte en de behandeling. Dit helpt om een compleet beeld te krijgen van de “basale” biologische processen die ziekte veroorzaken en hoe deze in de loop van de tijd veranderen. Met deze inzichten kunnen artsen, wetenschappers en patiënten beter begrijpen welke mechanismen bij een specifieke patiënt bijdragen aan ziekte en hoe deze veranderen bij chronische ziekte. We bestuderen hoe immuuncellen communiceren met andere cellen en moleculen in het lichaam en hoe dit wordt beïnvloed door zowel interne factoren (zoals leeftijd, geslacht, culturele achtergrond, erfelijkheid en stofwisseling) als externe factoren (zoals voeding, medicijngebruik, veranderingen in het microbioom en infecties). Deze factoren bepalen samen of het immuunsysteem in balans blijft of ontregeld raakt.

Uiteindelijk moet dit mechanistische onderzoek leiden tot een standaard klinische praktijk waarin de immunologische mechanismen van ziekten nauwkeurig in kaart worden gebracht (zie ook moonshot ‘*Tools at hand*’) en behandelingen beter worden afgestemd op de individuele patiënt (zie moonshot ‘*Living without fear*’), waardoor behandelingen gerichter en effectiever worden. Met deze benadering verwachten wij meer precisie in het begrijpen van de mechanismen van IMIDs en het ontwikkelen van behandelingen die specifiek inspelen op de verstoring van het immuunsysteem bij elke patiënt (zie moonshot ‘*Restoring immune health*’). Uiteindelijk zal dit bijdragen aan een betere immunologische gezondheid en een hoger welzijn voor de patiënt.

Long term objective moonshot:

Defining immunological health and mechanisms of disease through mapping of the immunological pathways driving pathogenesis in IMIDs.

Background: IMIDs encompass around 80 conditions, with their prevalence on the rise. Evidence that common pathways play a role across the spectrum of IMIDs comes not only from epidemiological data and basic research but also from clinical treatment responses. As an example: Anti-TNF therapies, introduced over 25 years ago, have proven effective across multiple IMIDs, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis. Moreover, in the last decade it has been shown that anti-inflammatory drugs, such as canakinumab and colchicine, used for autoimmune diseases or gout, can also significantly lower the risk for atherosclerotic CVD. Over the years, additional targeted therapies have been approved, but within each IMID a significant proportion of patients still fails to respond to individual targeted treatments. This can be attributed to the fact that each clinically defined IMID is a complex heterogeneous immunological syndrome (see also moonshot '*Living without fear'*) rather than a distinct molecular disease entity. In addition, for each individual patient, multiple factors, such as age, sex, genetic ancestry or infection influence and modulate disease onset, presentation, and progression.

This clinical heterogeneity reflects the complexity of pathogenic immune responses, which remain poorly understood. Across and within IMIDs, inflammatory responses involving T cells, B cells, and innate immune cells show similarities but are not identical. Subtle differences in disease initiation, tissue adaptation, and antigen specificity may contribute to disease heterogeneity and the variability in response to immune-modulating therapies. To address this challenge, it is essential to gain a deeper understanding of the immune mechanisms driving disease in individual IMID patients, in relation to the affected organ. By adopting a disease-overarching approach, we aim to decipher shared pathogenic processes in IMID patients and identify factors that determine whether a patient responds to a particular therapy.

In current clinical practice, physicians define immunological diseases and assess immune dysfunction based on a limited set of parameters or biomarkers. These markers are used across patient groups to diagnose disease and evaluate inflammatory activity. However, they fail to capture the full complexity of the immunological processes that drive and sustain disease (addressed in this moonshot) and do not adequately align these processes with individual patient characteristics (see moonshot *Living without Fear'*). As a result, response rates to costly treatments remain unpredictable, with many patients experiencing treatment failure and frequent side effects. The current *trial-and-error, one-size-fits-most* approach often leads to delays in finding an effective treatment, increasing the risk of disease progression and long-term damage. The societal burden is significant, as the right drug does not always reach the right patient at the right time. A major gap remains in our understanding of the '*full picutre'* of immunological mechanisms that contribute to disease. Equally unclear is how these mechanisms are influenced by *internal* factors (such as age, sex, genetic predisposition, and metabolism) and *external* factors (such as nutrition, medication, and infections). Addressing these gaps is essential to improving treatment precision and patient outcomes.

In this moonshot, we will focus on deciphering disease mechanisms in individual patients by mapping interactions between human cells and immunological molecules that underlie IMID pathogenesis. This will enable the development of novel targeted approaches (see moonshot '*Tools at hand'*)' tailored to individual patients (see moonshot '*Living without fear'*) using personalized treatment strategies (see moonshot '*Restoring immune health'*). Immune cells are the crucial recipients, integrators, translators and communicators of external signals to internal immune function and pathology, thereby forming the central communication network in each patient that we need to understand to guide optimal treatment. Our long-term vision is to create and implement a 'Human Disease Mechanism Atlas' for IMIDs. This atlas will integrate detailed immunological and clinical data from individual patient biomaterials to uncover key mechanistic insights. These insights will help define immunological treatment targets (evaluated in '*Tools at hand*') and implement targeted treatment strategies in clinical settings (see '*Restoring immune health*'). We expect this approach to bring unprecedented granularity to understanding a patient's unique immune profile (see '*Living without fear*"), enabling patients and physicians to see the 'full picture' of immunological disease and determine the best treatment course.

As the most mechanistic moonshot, '*The full picture*' studies pathogenesis at the individual patient level. Many discoveries from this moonshot will require *'Tools at Hand'* to fully elucidate mechanisms and translate them into simplified models for future targeted therapies. Findings from **'***The full picture'* will generate novel targets for *'Restoring immune health'* and new diagnostic methods for *'Living without fear.'*

Approach: As a crucial component on the road to Immunological Health, we will probe and characterize the function of immune cells and their interactions associated to various IMIDs. This will include the integration of the diversity caused by internal and external factors. The approach will integrate existing data on how internal factors (e.g. gender, age, genetic *genetic ancestry*, metabolism, organ/tissue-specific responses) influence immune functions with existing and emerging data of immune cell function. This approach will be initiated with a limited number of IMIDs. Results will be stepwise integrated with novel studies that elucidate the influence of external (*nutrition, medication, infection*) factors on immune functions in an expanded set of IMIDs, eventually developing towards a setting in which 'the full picture', i.e. immuno-characterization of disease based on immunological landscapes is the new standard in clinical practice.

Consistent with IHXL's mission, the development strategy for mechanistic studies involves a multidisciplinary approach. Depending on the type of mechanistic study and the stage of development different categories of expertise and stakeholders will be required, as outlined in section 4.2 under Involved Stakeholders and illustrated in an example in Figure 4.

Milestone, 2030:

Definition of how internal factors such as sex and age relate to critical immune networks and targets for precise immune intervention.

Background: Classical IMIDs such as RA, IBD, MS affect approximately one in ten individuals, with the inclusion of Atherosclerotic CVD this number dramatically increases. Furthermore, the burden of these diseases is increasing over time at varying rates across the various diseases. On

average, 65% of adult IMID patients are female, though some IMIDs show even greater disparities—for example, 80% of systemic lupus erythematosus patients are female contrastingly women experience Artherosclerotic CVD ten years later than men) Disease incidence is also inversely correlated with high economic status and varies across ethnicities. Despite the predominance of females in IMID prevalence and susceptibility, gender differences exist in disease severity and progression. Male sex, for instance, is a well-characterized risk factor for severe systemic sclerosis. Similarly, the age of IMID onset influences disease development, severity, and therapeutic response. In younger patients, genetic predisposition is often considered a key driver of early and severe disease, though hormonal changes during puberty may also play a role. This is reflected in paediatric IBD, which is more common in boys, while the prevalence shifts toward females in adulthood. Conversely, in postmenopausal and elderly IMID patients, altered immune homeostasis—referred to as 'inflammaging'—is believed to contribute to disease progression, though its role remains understudied. A deeper understanding of how age and sex shape pathogenic immune responses in IMIDs is needed to decipher the underlying mechanisms. Ultimately, this knowledge will help determine whether age- and sex-tailored treatment strategies should be developed.

Input: To unravel how sex and age influence IMID incidence and outcomes, IHXL will focus on prototypical IMIDs where these factors play a critical role. Achieving this goal requires input from a multidisciplinary team, including immunologists, bioinformaticians, clinical researchers, and systems biologists. The key input areas include:

- Large, well-defined datasets on immune network function, requiring expertise in data analysis and integration. These datasets will include amongst others:
    - Immune cell phenotyping (network compositions, activation, and differentiation status)
    - Plasma/serum immune (phospho-)proteomics
    - Immune transcriptomics

- Cohort data from young and elderly males and females, analysed at the single-cell level, to construct a comprehensive age- and sex-specific immune cell atlas. This will involve single-cell analysts and computational biologists to interpret complex datasets.

By combining these analyses with mechanistic studies in vitro (see moonshot '*Tools at hand*'), detailed clinical parameters on disease severity, disease course and response to therapy effects of sex and age modulation on disease pathogenesis can be dissected.

Output: In 2030, we expect to have generated a first/prototype diagram uncovering the mechanisms driving sex/age-based differences in immunity and disease vulnerability over the lifespan.

Milestone, 2035:

Common spatially resolved immune landscapes identified integrating immune pathways driving disease in a cross IMID approach.

Background: Initiation and maintenance of innate and adaptive immune responses is tightly regulated by cellular location in the body, a phenomenon denoted as compartmentalization. For example, primary lymphoid organs such as the bone marrow and the thymus are the major sites where immune cells are produced, while secondary lymphoid organs like spleen and lymph nodes filter the lymph for pathogenic treats, thereby forming the key location for antigen-driven B and T lymphocyte proliferation and differentiation. Once differentiated, lymphocytes can travel through the blood to affected organs and exert host defense in concert with cells within the tissue environment. After elimination of the pathogenic threat lymphocytes with memory will be maintained in the tissue. This compartmentalization allows for structured integration of signals provided by cellular interactions and soluble factors. As a result, the immune system can very precisely tailor immune responses to the degree of threat while avoiding extensive tissue damage. Current IMID therapies hardly take immune compartmentalization into account. Traditionally, the IMID nomenclature and classification is based on the affected organ, i.e. RA being a disease of the joint, MS being a disease of the central nervous system, IBD being a disease of the intestine and ASCVD being a disease of the vessels. However, a wealth of data demonstrates that IMIDs have shared immune features with similarities in pathogenic innate and adaptive immune responses that have adapted to the environment of the inflamed organ. Because of the organ-based classification, research on disease pathogenesis most often happens within each IMID separately while cross-disease research has the great potential to uncover key disease drivers. In this milestone, IHXL will uncover tissue specific drivers of detrimental innate and adaptive immune responses across IMIDs and assess the mechanisms of cellular interaction that drive initiation and maintenance of IMIDs in the various compartments.

Thereto, IHXL has the aim to spatially map and functionally analyze the antigen-specificity and dynamics of key immune pathways in blood, lymph nodes, spleen, bone marrow, and IMID target tissues. With this, IHXL aims to dissect shared and non-shared pathogenic immune pathways across IMIDs in individual patients and assess how compartmentalization relates to immune adaptation. Understanding such effects of compartmentalization will also allow to demonstrate the role of exogenous disease triggers such as microbiota, diet, medication and infections. To achieve this aim, a wealth of existing single cell immune data and their functional status can be used as well as novel techniques such as advanced spatial imaging techniques. This mechanistic understanding of IMIDs is key to identify targets for more effective therapeutics (moonshot '*Restoring immune health*') and to understand which immune compartment should be monitored with diagnostic tests to quantitate immune disease activity (moonshot '*Living without fear*'). Collaboration with the moonshot '*Tools at hand*' is imperative to decipher whether immune adaptations have a causal role in disease pathogenesis and to define targets for therapeutic correction of immunological mechanisms of disease.

Input: Achieving this requires a long-term, structured collaboration between physicians, basic scientists who study disease mechanisms and cellular functions, and patients who can offer

valuable insights into what matters to them, while also donating critical biological samples. Significant investments in computational biology and artificial intelligence are crucial to analyse and integrate these complex data, and to predict protein structures and biological pathways that could serve as potential therapeutic targets.

Output: By 2035, IHXL expects to have mapped the spatially resolved immune cell landscape, integrating key antigen-specific pathways driving disease across IMIDs. This includes understanding how immune responses adapt across compartments and interact with external inflammation triggers. While clear and often similar associations between environmental factors and disease have been postulated across IMIDs, the complete picture remains unresolved for all.

Milestone, 2040:

Immunological basis of irreversible tissue damage and fibrosis in IMIDs identified.

Background: Irreversible tissue damage is a fundamental consequence of chronic immune inflammation in IMIDs. Tissue remodeling and fibrosis lead to organ dysfunction and severe comorbidities, which can be fatal when vital organs are affected. Chronic immune inflammation of the endothelium also drives atherosclerotic CVD. Ideally, targeted treatment tailored to individual IMID patients, combined with effective disease activity monitoring, would prevent such tissue damage. However, current IMID treatments are not yet capable of achieving this. As a result, strategies to prevent tissue remodeling, fibrosis, and atherosclerotic CVD in IMID patients will be essential in the coming decades. In healthy individuals, tissues undergo controlled remodeling as part of homeostatic tissue turnover and repair. In IMIDs, however, connective tissue formation and degradation are dysregulated, tightly linked to immune cell activation and extracellular matrix deposition. Our understanding of tissue remodeling and fibrosis in IMIDs remains limited, largely because the interaction between organ-specific immune responses and structural tissue cells is rarely studied in the affected IMID organs.

This milestone aims to mechanistically understand inflammation-induced tissue remodeling, and fibrosis and identify therapeutic targets to intervene in these processes. A key step toward this goal is leveraging insights from spatially resolved immune landscapes across different IMIDs. This approach will allow to decipher shared and distinct inflammatory immune cascades that interact with structural cells to drive tissue remodeling and fibrosis.

Input: This milestone requires a multidisciplinary cross-IMID approach. Existing data will need to be integrated and novel in depth omics analyses need to be performed of tissue specific responses. In combination with novel functional assays as described in the moonshot 'Tools at hand', a mechanistic understanding can be obtained on the causal relationships between immune activation, local tissue environment and tissue remodeling and fibrosis across IMIDs.

Output: In this phase, we expect to have identified putative therapeutic targets to intervene in tissue remodelling and fibrosis across IMIDs

Examples of applicability to IMIDs: As described above, the three milestones in this project have different approaches on how IMIDs will be used to perform initial studies. We strive for broad

ethnic diversity in all cohorts. For milestone 2030, we will make use of IMIDs that have a strong sex and or age bias, including systemic lupus erythematosus, multiple sclerosis and systemic sclerosis, while other IMIDs like inflammatory bowel disease, rheumatoid arthritis and type I diabetes will be subsequently integrated. For milestone 2035, IMIDs (including rarer IMIDs) will be selected based on richness in immune and clinical data, variability in target organ and capacity to study disease over time. For milestone 2040, studies will be initiated with IMIDs that have a high incidence in tissue remodeling, fibrosis and IMIDs with a high incidence in vasculitis and atherosclerotic CVD. Subsequent cohorts should cover a broad variety in IMID target organs. Importantly, these choices are made for reasons of focus, scientific considerations and guidance.

Moonshot, Tools at hand

Nederlandse samenvatting: De oorzaak van de meeste immuun-gemedieerde ontstekingsziekten (IMIDs) is nog onbekend. Daardoor begrijpen we vaak niet waarom ontstekingsremmende medicijnen bij de ene patiënt goed werken en bij de andere niet, of waarom ze na verloop van tijd hun effect kunnen verliezen. Dit komt onder andere doordat afweerreacties verschillen tussen patiënten en ook tijdens het beloop van de ziekte veranderen. Dankzij nieuwe innovatieve technieken en vooruitgang in bio-informatica kunnen we nu beter meten hoe de immunologische balans per patiënt verschilt (zie moonshot '*Living without fear'*). Daarnaast onderzoeken we welke immunologische processen verantwoordelijk zijn voor deze verstoringen bij IMIDs (zie moonshot *'The full picture'*). Dit helpt om nieuwe afweermechanismen en moleculen te ontdekken die mogelijk bijdragen aan het ontstaan van ziekte of aanknopingspunten bieden voor behandeling van ziekte op maat. Ook voor atherosclerotische cardiovasculaire ziekten is een beter begrip van de rol van het immuunsysteem van groot belang. Chronische ontstekingsprocessen in de vaatwanden dragen bij aan de vorming van atherosclerotische plaques, wat kan leiden tot ernstige complicaties zoals hartinfarcten en beroertes.

Om te bepalen of deze nieuw ontdekte afweerprocessen en moleculen geschikt zijn als aangrijpingspunt voor therapieën (zie moonshot '*Restoring immune health*'), moeten we ze testen in modellen die de werkelijkheid zo goed mogelijk nabootsen. Deze moonshot richt zich op het ontwikkelen van zulke modellen van immunologische processen in zowel ziekte als gezondheid. Hiermee kunnen we in het laboratorium beter onderzoeken en begrijpen welke factoren bijdragen aan immunologische disbalans en welke moleculen deze balans kunnen herstellen. Het bestuderen van deze factoren met behulp van deze modellen heeft grote gevolgen voor patiënten en draagt bij aan het succes van andere moonshots. Zo kunnen nieuwe ziektemodellen helpen bij het ontwikkelen van betere diagnostische testen en methoden om ziekteactiviteit te monitoren. Ook zijn ze essentieel voor het testen van nieuwe medicijnen voordat deze in klinische studies worden onderzocht (zie moonshot '*Restoring immune health*'). Uiteindelijk draagt dit bij aan de ontwikkeling van behandelingen die het ontstaan van IMIDs na de eerste klachten kunnen voorkomen of ziekte-opvlammingen snel onder controle kunnen brengen – idealiter met een eenmalige behandeling.

Bij mensen met een IMID veroorzaken immuuncellen chronische ontstekingsreacties, wat vaak leidt tot onomkeerbare schade aan aangetaste organen en weefsels. Hoe immuuncellen dit doen, hangt af van hun communicatie met andere (immuun)cellen en immunologische signaalstoffen. Deze interacties veranderen over tijd en zijn afhankelijk van de locatie van de cel in het lichaam. Om deze dynamische processen na te bootsen en te onderzoeken hoe we kunnen ingrijpen in afweermechanismen die immunologische disbalans en ziekte veroorzaken, zijn verschillende goed toegankelijke modellen van immunologische ziekte en gezondheid nodig. Dit kunnen bijvoorbeeld celkweken, weefselkweken, organs-on-a-chip en computermodellen zijn. Elk model heeft zijn eigen (technische) voordelen en beperkingen en is specifiek voor bepaalde immunologische processen, daarom is de ontwikkeling van meerdere modellen noodzakelijk.

In deze moonshot van IHXL ontwikkelen we laboratoriummodellen die de immunologische reacties bij IMIDs zo nauwkeurig mogelijk nabootsen. Deze modellen houden rekening met verschillende immuun profielen bij patiënten en maken het mogelijk om met nieuwe, gerichte moleculen ongewenste immuunreacties in IMIDs te stoppen. Om meerdere ziekteprocessen te

simuleren, combineren we geavanceerde kweek- en analysetechnieken, zoals zogeheten ‘organoïden’, ‘weefsel-explants’ en ‘single-cell’ technieken. Het gebruik van deze modellen zal ook bijdragen aan de vervanging van proefdieronderzoek. Door preciezere laboratoriummodellen te ontwikkelen, kan het gebruik van proefdieren worden verminderd en gerichter worden ingezet. Daarnaast kunnen deze modellen ook een rol spelen bij het onderzoeken van immuungemedieerde mechanismen bij hart- en vaatziekten. Zo kunnen organoïden en organ-on-a-chip systemen helpen om in detail te begrijpen hoe immuuncellen bijdragen aan vaatwandontsteking en plaquevorming. Uiteindelijk zullen deze nauwkeurige modellen artsen en patiënten helpen om beter inzicht te krijgen in de oorzaak van IMIDs en sneller effectieve behandelingen te ontwikkelen en testen.

Binnen deze moonshot richten alle projecten zich op de ontwikkeling van nieuwe methoden en technologieën om precieze modellen van immunologische ziekteprocessen bij IMIDs te creëren. Door geavanceerde technieken te combineren, zoals zogeheten ‘organ-on-a-chip’, ‘organoïden’, ‘single-cell’ technologie en bioinformatische analyses, streven onderzoekers ernaar nauwkeurige modellen van ziekteprocessen te ontwikkelen. In eerste instantie worden deze modellen ingezet om betere medicijnen te ontwikkelen die niet alleen gericht zijn op IMIDs, maar ook op immuungemedieerde mechanismen bij atherosclerotische ziekten. Uiteindelijk is het doel dat artsen deze modellen in het ziekenhuis kunnen gebruiken om per patiënt te voorspellen welke behandeling het meest effectief zal zijn. Ons einddoel is om genezing voor elke patiënt een haalbaar perspectief te maken.

Long term objective moonshot:

Develop and apply precise models of immunological processes in IMIDs, to identify key disease regulators and enable therapy development that achieve drug-free remission.

Background: IMIDs are driven by immunological disease activity (IDA), and the mechanisms of IDA are variable between IMIDs, patients and disease phases (see moonshot ‘Living without fear’). Beyond IMIDs, chronic IDA also play a key role in atherosclerotic CVD. A growing body of evidence suggests that immune mechanisms contribute to the formation and progression of atherosclerotic plaques, increasing the risk of heart attacks and strokes. The recent ‘omics’ revolution allows us to capture this huge IDA variation providing us with new immune pathways and molecules that are putatively involved in IMID pathogenesis (see moonshot ‘*The full picture’*) and/or offer new targets for therapeutic strategies (see moonshot ‘*Restoring immune health’*). Current laboratory (*in vitro)* models often lack the precision to determine the value of these new insights for understanding IMID disease pathogenesis and therapeutic potential in the general IMID population and in individual patients. In parallel, within the field of drug-development, we have seen a growing success of immunotherapies in the treatment of IMIDs, while there is still limited insight in the mechanisms mediating drug effectivity or lack thereof. Until now, it is often not known why treatments retain or lose their effect. The ultimate goal to develop treatments that can cure or prevent IMIDs in all affected patients is still out of reach. Elucidation of how newly identified molecules control the immunological mechanisms involved in IMIDs in such in vitro models has significant consequences for patients and will help to achieve the other moonshots. For example, novel precise models can expedite the development and testing of novel therapeutics that target key mechanisms of immune disbalance in IMIDs. This allows

identification of novel therapeutics for clinical evaluation (see moonshot '*Restoring immune health*'). Alternatively, novel models of disease processes may yield better tests for IMID diagnosis or for monitoring disease activity (see moonshot '*Living without fear*').

Various models of immunological processes that are affected by IMIDs exist that each mimic certain aspects of IMID pathogenesis. These can be grouped into 3 broad categories:

- 2D/3D co-culture systems (e.g. in vitro cocultures of immune cells with/without non-immune cells, organ-on-a-chip, organoids),
- tissue explant systems,
- *In silico* models.

Different models focus on distinct immunological processes and different immunological interactions, with some models containing more immunological players than others. Each model type offers unique technical advantages as well as limitations. This is in part because of the choices made based on the desired balance between achieving biological realism and acceptable throughput capacity. Therefore, each of these models can study disease processes only to a limited extent. Multiple *in vitro* models are therefore needed. To take the next step towards curation and prevention of IMIDs it is required to improve models of immunological processes underlying IMIDs and to test in an early phase whether immunological disease process models, alone or combined, can replicate the diverse immune profiles (IDA, see moonshot '*Living without fear*') observed in IMIDs. This will give insight in the existence of disease-overarching IMID subtypes and the underlying mechanism causing disease (see moonshot '*The full picture*') and allow evaluation of novel therapeutics that will lead to better and more precise treatments based on causative mechanisms. Such models need to incorporate or model the interaction of multiple cell types, molecules and tissues involved in the pathology of IMIDs. This will require development of new culture and analytical techniques and combinations thereof. The development of such models will result in a reduction in the need for animal models, and allow steering the use of animal models towards answering research questions that cannot otherwise be answered. Ultimately, precise *in vitro* models will assist future physicians and patients to gain more insight in the cause of their disease and to treat it adequately and swiftly. Some of these treatments will be effective in multiple IMIDs and in rare IMIDs. In this moonshot we will therefore develop in vitro models of immunological processes that underly IMIDs that alone or in combination precisely mimic IMID immune mechanisms in patients, and that are able to demonstrate in each individual which treatment will be most effective.

Approach: All projects executed within this moonshot will focus on leveraging novel methods and technologies to develop and implement precise models of immunological processes underlying IMIDs, ultimately contributing to more targeted and effective treatment strategies. These models will be refined through the development and integration of advanced culture and analytical techniques. Examples of innovative culture techniques include organoids and organ-on-a-chip systems. Ideally, mechanistic questions will be analysed in both space and (real) time, capturing different molecular mediators that can restore immunological balance. To achieve this, analytical tools must be further improved for use as readouts, with examples including single-cell and spatial techniques.

Developing models of immunological disease processes across IMIDs and other chronic inflammatory diseases such as atherosclerotic CVD will enable the creation of a unified IMID process model strategy. This strategy will span all stages, from discovery (current stage) to development, regulatory approval, and clinical implementation. It will be used in early phases to

assess whether models of immunological processes, individually or in combination, can replicate the diverse immune mechanisms driving IMIDs and other chronic inflammatory diseases. Additionally, it will accelerate the development of disease-specific models by facilitating technology sharing, particularly for rare diseases with uncommon immunotypes.
Our approach integrates models in a complementary manner, allowing us to address specific questions with both precision and efficiency. Initially, the focus will be on implementing models to support the development of improved treatments. In later stages, these models could be applied in hospital settings to help physicians predict the most effective treatment for individual patients—similar to current precision medicine approaches in oncology. Ultimately, our goal is to make personalized treatment and, eventually, cure attainable for every individual with an IMID.

In line with the mission of IHXL, the development strategy of immunological models underlying IMIDs will involve a multidisciplinary approach. Depending on the type of model of disease processes and the stage of development different categories of expertise and stakeholders will be required. *as outlined in section 4.2 under Involved Stakeholders and illustrated in an example in Figure 4.*

Milestone, 2030:

In vitro models for immunological disease processes that drive multiple IMIDs developed, enabling early prediction of candidate drug efficacy for these IMIDs

Background: In recent years the development of several new immunological models for IMIDs have shown promise in predicting the efficacy of targeted immunosuppressive drug candidates from the pharmaceutical industry. These include, minimalistic 2D/3D co-culture systems, 3D organoids, organ-on-a-chip platforms, tissue explants, and in silico models. While these models show great potential advances need to make these more widely applicable across IMIDs and towards translational application. A key next step to develop their technology readiness level is to tackle a number of technical and translational challenges. These consist of further integration of the following components into such models:

- Novel immune cell sources (e.g., gene transfer in cells, improved long-term culture, stem cell-like cells)
- Optimized tissue components (e.g., refined matrix and flow conditions, synthetic growth and retention factors)
- Advanced read-outs (e.g., single-cell phospho-proteomics, real-time functional assays)
- Enhanced analysis pipelines for processing large datasets (e.g., spatiotemporal processes, multi-modal sources)
- Benchmarking model systems to assess translational value (e.g., imaging, multiparameter cytometry, scRNA-seq data, digital biobanks, and disease atlases)

Inputs: The successful development of immunological models with high translational value for IMIDs relies on effective collaboration across multiple disciplines. Clinician-scientists provide access to clinically selected, relevant biomaterials; molecular and cell biologists, along with immunologists, design and construct models tailored to immunological objectives; biochemists develop and test model components; and bioinformaticians design, validate, and computationally analyse data from multi-parameter spatiotemporal read-out systems.

IHXL views model development as a dynamic R&D process, where intermediate models are iteratively improved and replaced in a stepwise manner. Ideally, project funding is balanced between low-risk, readily implementable tools and high-risk, high-gain initiatives that address fundamental and technical challenges. As projects progress, insights gained from more immediately applicable models can be validated and refined in more advanced models developed over time.

Outputs: in 2030 IHXL expects to generate immunological models for IMIDs that alone or in combination truthfully recapitulate critical components of at least 2 types of IMID or other chronic inflammatory diseases such as atherosclerotic CVD immune responses. These will be validated and available for implementation by pharma to enable select adaptive immune directed drug candidates for further development.

Milestone, 2035*:*
Models for IMIDs developed for multi-step immune processes, to enable discovery, evaluation and validation of potential novel immunotherapeutics.

Background: Once in vitro models for IMIDs have been developed that alone or in combination mimic critical components of IMIDs, in vitro models will be developed that mimic multi-step immune processes.

Models that mimic multi-step immune processes are aimed to be used alone or together with AI-driven tools to be used by academia and pharma to perform target discovery and validation for increasingly precise immuno-therapeutics, that can subsequently be evaluated in the clinics (see moonshot 'Restoring immune health'). Some models will have diagnostic and/or prognostic value for certain IMID (subtypes). To achieve this the following critical steps are required:

- Expansion of models to model complex multi-step processes (e.g. interactive networks of immune cells, chronicity, tissue imprinting and residence, affinity maturation, immune development and aging).
- Expansion of the models to model interactions between multiple types of stromal cells, innate and adaptive immune cells.
- To progress the developed complex models through the final stages of technology readiness level towards market introduction (e.g. benchmarking against therapeutic agents in pre-clinical and ex vivo studies).

Inputs: Similar to the milestone 2030 IHXL expects that inputs of a collaborative multi-disciplinarily team of scientists are required to further design and construct models tailored to multi-step immune process objectives. More emphasis will be placed on the involvement biochemists developing and testing multi-step processes models, engineering specialist for platform development and bioinformaticians involved in expanded and refined validation, and computationally analysis of data from multi-parameter spatiotemporal read-out systems.

In this phase we expect that work from different projects will need to start to integrate. As it is expected that expenses and complexity grows an increased effort is expected from commercial partners including small to medium biotech and MedTech companies specialized in model development and testing. Furthermore, as we work towards market introduction, timely

involvement of regulatory and compliance experts is required as well as valorization expertise to assess the demand, identify target users (pharma, biotech, CROs), and develop a business model.

Outputs: progress towards market introduction for at least 2 IMID disease process models, that can be marketed to pharma. Application of at least one disease process model in clinical care for diagnosis and/or prognosis.

Milestone, 2040:
Precise disease process models that predict the effects of immune modulation in each individual.

Background: In this phase we expect to have operationalized and marketed a number of in vitro models to study complex IMID immune processes and predict and analyse therapeutic candidates. Critical next steps are:

- Continued development towards more precise models of disease processes towards market introduction.
- Develop integrated combinations of ex vivo and in silico systems with real-time spatiotemporal read-outs (e.g. integrated analyses of interactions between multiple tissues, individualized treatment algorithms, sequential tolerogenic and regenerative treatment protocols).

Input: In this phase we expect the systems to become more oriented towards patients with difficult-to-detect, or rare clinical manifestations, or with e.g. a very high or young age. These models will be useful for pharma R&D but also for clinical and shared decision making in clinical practice for individual patients (personalized medicine). An important role is envisioned for patient advocates to mobilize stakeholders and regulators to stimulate development and implementation of patient-oriented disease models in clinical care and pharma R&D pipelines.

Output: Clinically and commercially available models for prevalent and rare IMIDs that can contribute to development of curative and preventative IMID treatments and transform healthcare for individual patients.

Examples of applicability to IMIDs: We aim to investigate, develop and validate tools for all IMIDs, as the disease-overarching approach to tackle IMIDs is central to IXHL. We anticipate that the variety of models will stem from the variety in the pathogenic immune mechanisms that are shared and non-shared between IMIDS. As such, we will develop models mimicking B-T cell interactions, that best reflect IMIDs in which B cells contribute to pathology (large IMIDs like rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, atherosclerotic CVD but also other IMIDs, like vasculitis, pemphigus, myasthenia gravis, Graves' disease and systemic sclerosis). Furthermore, we anticipate to have models of antigen presenting cell-T cell interactions that mimic responses in T cell mediated IMIDs like type I diabetes, inflammatory bowel disease, Celiac Disease and atherosclerotic CVD. Crucially, modelling is also required to

understand complex disease features and inflammation induced co-morbidities such as vascular dysfunction.

Moonshot, Restoring immune health

Nederlandse samenvatting: Voor patiënten met immuun-gemedieerde inflammatoire ziekten (IMIDs) zoals reumatoïde artritis, diabetes type 1, multiple sclerose en slagaderverkalking die hart- en vaatziekten kunnen veroorzaken, zijn bestaande behandelingen vaak gericht op het onderdrukken van symptomen die voortkomen uit weefselschade. IMIDs ontstaan door een ontregeling van het immuunsysteem, wat leidt tot chronische ontstekingen. Bij veel van deze ziekten blijft de onderliggende immunologische 'disbalans' aanwezig, zelfs wanneer symptomen tijdelijk onder controle zijn. Dit komt doordat bestaande therapieën zich niet specifiek richten op de mechanismen die deze ontregeling veroorzaken, waardoor patiënten risico lopen op nieuwe opvlammingen en verdere weefselschade.

Momenteel is het voorkomen van opvlammingen bij de meeste IMIDs het hoogst haalbare behandeldoel, vaak met een levenslange afhankelijkheid van medicatie. Sommige patiënten reageren niet of onvoldoende op bestaande therapieën, of verliezen na verloop van tijd respons, wat regelmatige wisselingen van behandeling noodzakelijk maakt. Dit brengt niet alleen een verhoogde ziektelast met zich mee, maar vergroot ook het risico op over- of onder behandeling, bijwerkingen en complicaties. Momenteel ontbreken behandelingen die gericht zijn op het effectief aanpakken van immunologische fouten die de ziekte veroorzaken en het herstellen van een gezonde immunologische balans.

Binnen deze moonshot richt IHXL zich op een toekomst waarin patiënten toegang hebben tot een breed arsenaal aan effectieve behandelingen. Dit omvat enerzijds het identificeren van nieuwe toepassingsgebieden voor bestaande geneesmiddelen en anderzijds het stimuleren van de ontdekking en ontwikkeling van een nieuwe generatie immuunmodulerende therapieën die het immuunsysteem kunnen herstellen.

IHXL hanteert hierbij een tweeledige strategie:

- Bestaande medicijnen voor nieuwe toepassingen inzetten ('drug repurposing en/of uitbreiding van de indicaties voor gebruik'): Sommige medicijnen die nu voor één specifieke ziekte worden gebruikt, kunnen ook effectief zijn bij andere IMIDs doordat deze worden veroorzaakt door overeenkomende onderliggende immunologische processen. Door het gebruik van dergelijke 'repurposing' strategieën wordt bredere toepassing van effectieve behandelingen versneld en wordt onnodige ontwikkeling van geneesmiddelen vermeden, wat kosten en tijd bespaart.
- Nieuwe behandelingen ontwikkelen die de oorzaak van IMIDs aanpakken en het immuunsysteem in balans brengen. Dit omvat:
    - **Nanogeneesmiddelen,** die werkzame stoffen aan de juiste cellen in het lichaam afleveren, bijvoorbeeld via kleine vetbolletjes (liposomen) om de immuunbalans te herstellen.
    - **Celtherapieën**, waarbij bepaalde cellen uit het lichaam van de patiënt worden aangepast en teruggeplaatst om het immuunsysteem opnieuw af te stemmen.

- **Antilichaambehandelingen**, die ongewenste immuunreacties verminderen door de activiteit van bepaalde eiwitten in het lichaam te verminderen of juist te versterken.
- **Kleine moleculen**, die kunnen binden aan lichaamseigen stoffen en eiwitten en daarmee signalen in het immuunsysteem beïnvloeden om ziekteprocessen te vertragen of te stoppen.

Veel van deze geneesmiddelen worden momenteel ontwikkeld voor 1 specifieke ziekte, terwijl ze mogelijk in meerdere ziekten toegepast kunnen worden. Binnen IHXL zal deze aanpak versneld en verbreed worden om de beschikbaarheid van effectieve behandelingen te vergroten, zodat mensen met IMIDs betere zorg krijgen. Dit gebeurt in nauwe samenwerking met andere moonshot-projecten. De moonshot '*Living without fear*' draagt hieraan bij door immuun monitoring te benutten, zodat behandelingen beter worden afgestemd op de ziekteontwikkeling bij individuele patiënten. Binnen de moonshot '*The full picture*' worden immunologische ziekteprocessen ontrafeld, waardoor therapieën gerichter kunnen inspelen op de specifieke ontsporing van het immuunsysteem. Tegelijkertijd zorgen de ontwikkelingen binnen '*Tools at hand´* voor nauwkeurige ziektemodellen, waarmee nieuwe therapieën of bestaande medicijnen gericht getest en geoptimaliseerd kunnen worden. Samen versnellen deze moonshots de ontwikkeling van gepersonaliseerde en effectievere behandelingen voor patiënten met IMIDs.

Long term objective moonshot:

Develop drug repurposing and/or label extension strategies and innovative immune-based interventions across diseases to effectively treat, cure, or prevent aberrant immune responses in patients with IMIDs.

Background: IMIDs, such as rheumatoid arthritis, type 1 diabetes, and atherosclerotic CVD, are characterized by chronic inflammation and immune system dysregulation. Current treatments often focus on symptom management and long-term suppression of the derailed immune system. This can result in insufficient disease control, development of insensitivity to therapy and occurrence of disease flares, significant side effects and increased tissue damage, yielding a huge disease burden and high healthcare costs. Despite these therapies, many patients, thus, remain at risk of disease flares or disease complications. This highlights the urgent need for novel approaches that directly address the root causes of IMIDs - immune dysregulation.

Innovations in immune modulation including nanomedicine, advanced cellular therapies, novel generations of therapeutic (bi- or tri-specific) antibodies, and small molecules offer opportunities to revolutionize IMID treatment. For instance: Nanomedicines, small biodegradable particles designed to deliver targeted signals to the immune system, enable precise modulation of immune cells and pathways. Cellular therapies such as tolerogenic dendritic cells (DCs) that promote antigen-specific tolerance. Bi- and tri-specific antibodies engage specific membrane molecules on immune cells, enhancing the specificity of their function and small molecules target aberrant signalling pathways in IMIDs. These technologies are currently mainly being developed in the field of oncology. Applications to the immunology field are slow while these approaches have potential to correct aberrant immune responses, reduce inflammation, and prevent future disease flares. The identification of aberrant immune responses, as determined in

moonshot '*Living without fear'*, that drive reactivation of inflammation and subsequent disease flare is crucial for developing preventive/curative novel immune modulatory interventions.

In addition to these innovative approaches, repurposing existing drugs offers a promising avenue to accelerate the availability of effective treatments which are already in clinical practice. Many drugs approved for a single IMID could be beneficial across multiple conditions/patient populations due to shared underlying aberrant immune mechanisms. For instance, TNF-alpha inhibitors, originally developed for rheumatoid arthritis, have also proven effective in treating Crohn's disease, demonstrating the potential for broader therapeutic application. IHXL will promote the exploration of such opportunities and leveraging disease-overarching immunological insights and profiles, we can identify new indications for existing therapies. This not only expedites the implementation of effective therapies but also bypasses the lengthy and costly process of new drug development, ultimately expanding treatment options and reducing patient burden.

In this moonshot, we will build a support framework through which innovative immunomodulatory therapies and drug repurposing and/or label extension strategies can be explored and developed. Initially, IHXL will scope its ecosystem for projects which have the potential to be developed into interventions which can prevent, delay, or correct aberrant immune responses in single IMIDs and support such projects in progressing their development. In the subsequent step towards the second milestone, IHXL will focus on further advancing high potential projects in their development trajectory and importantly promote and support the translation of such projects across diseases, ensuring that new innovative therapeutic options will become available for broad groups of IMID patients, all the while exploring valorisation routes. In the final phase of this moonshot, IHXL will focus on supporting projects towards clinical implementation by building strategic partnerships, gaining access to key infrastructural, technological and financial capabilities, and collaboratively exploring regulatory pathways and health economic impacts.

By integrating emerging innovative technologies, alongside strategic drug repurposing and/or label extension efforts within such a support framework, we aim to create more effective, personalized treatment options. This disease-adaptable approach has the potential to significantly improve patient outcomes by reducing over- and undertreatment, minimizing side effects, and decreasing the need for lifelong therapy.

Milestone, 2030:

Establishment of a disease-overarching translational framework by identifying and advancing high-potential projects across different therapeutic modalities.

Background: The development of effective immunomodulatory therapies for IMIDs and drug repurposing and/or label extension strategies is hindered by the complexity and heterogeneity of immune dysregulation across different conditions. Despite advances in nanomedicine, cellular therapies, antibody-based treatments, and small molecules, translating these therapeutic modalities into broadly applicable interventions remains a challenge. Historically, most therapies have been developed for individual diseases, resulting in fragmented research efforts, high costs, and slow clinical translation. A more integrated approach is needed to accelerate the discovery,

development, and application of immune-based therapies that can be adapted for multiple IMIDs.

We are now equipped with a diverse range of therapeutic modalities, each offering unique mechanisms of action to target specific aspects of immune dysregulation. While some approaches, such as nanomedicines, enable precise delivery of immune-modulating agents, others, like cellular therapies, allow for active reprogramming of immune responses and antibody-based treatments selectively engage immune receptors, providing targeted intervention to modulate immune activity. Furthermore, due to our growing knowledge of underlying immune regulations (moonshot 'the full picture'), we are now able to better grasp and explore the broader applicability of already available treatments in a broad set of IMIDs. Harnessing the strengths of these different modalities and our growing knowledge of the immune regulatory pathways allows for a more tailored and effective approach to restoring immune balance in patients.

The IHXL ecosystem holds significant untapped potential, with a broad range of promising candidate therapies at various stages of discovery and development (e.g., nanomedicine-based approaches, with initial focus applications in T1D, RA, or ACDV). To harness this potential, IHXL aims to establish a translational framework that supports the discovery, development, and validation of high-potential therapeutic candidates. By providing expert support, access to an extended network, and targeted research funding, IHXL will drive the advancement of multiple projects in parallel. Additionally, IHXL will ensure that routes to repurpose already approved drugs for other indications are actively explored, further accelerating the availability of effective treatments. This approach ensures that innovations across different therapeutic modalities and development phases contribute effectively to the overarching goal of restoring immune balance in IMIDs.

Input: To achieve this milestone, IHXL will provide its research community with a translational framework that equips them with the necessary expertise, network, support, and resources to advance candidate therapies. Thereby empowering research teams to take the lead and accelerate their innovations toward clinical application. Key input for this effort includes:

- Provide expert-led support which can aid in the identification and evaluation of high-potential projects that can support the advancement of therapeutic candidates towards the next stage of development and/or broader applicability across IMIDs.
- Regular consultation with patient representatives/patient organisations to ensure patient needs and challenges are taken into account where possible during project development.
- Build interdisciplinary collaborations integrating expertise from immunology, biotechnology, regulatory science, and clinical research to support efficient translation from discovery to clinical application.
- Alignment with the moonshots '*Living without fear'* for identification of novel therapeutic targets, moonshot '*Tools at hand'* for most optimal models mimicking diverse aspects of IMIDs and *'The full picture'* for biomarker-driven patient stratification, ensuring that therapies are developed with precision medicine principles to maximize efficacy across diverse patient populations.

Output: By 2030, IHXL will have supported at least four high-potential therapeutic projects at various stages of advancement. Their progression towards clinical applicability in a single disease will serve as proof of concept, demonstrating the effectiveness of IHXL's translational framework in advancing IMID therapies for a specific IMID. These projects will encompass diverse

therapeutic modalities—such as nanomedicine, cellular therapies, antibody-based treatments, small molecules—ensuring flexibility and broad applicability within the framework. For drug-repurposing projects proof of concept for broader applicability will be provided, laying the foundation for continued translational validation and regulatory pathway determination.

Milestone, 2035:

Continued development of most promising immune-modulatory interventions, with therapeutic potential and applicability across multiple IMIDs established.

Background: Novel interventions are needed for the treatment of IMIDs that focus not only on symptom management but also on disease modulation. Historically, most therapies have been developed for individual diseases, resulting in fragmented research efforts, high costs, and slow clinical translation. A more integrated approach is needed to accelerate the discovery, development, and application of immune-based therapies that can be adapted for multiple IMIDs. In the previous milestone IHXL will deliver various high potential projects for new drug candidates. These candidates need further analysis and development to obtain insight in the mode of action, insight in the strength and duration of the modulation, and importantly, their applicability across multiple IMIDs. Simultaneously, high potential drug repurposing and/or label extension strategies will need further studies to confirm the drug's mechanism of action in the new indication and assess whether dose adjustments are needed. Biomarker identification (see moonshot '*the full picture*') can help optimize patient selection. Additionally, regulatory agencies will need to ben engaged early on to determine the most efficient approval pathway, such as label expansion, an expedited approval process, or off-label use supported by real-world data.

Through the IHXL ecosystem this moonshot will have access to the most optimal IMID models reflecting different stages of disease to obtain this knowledge (see moonshot *'Tools at hand')*. From the earlier supported candidates, two high-potential strategies will be selected for further development this can including small-scale Phase 1 trials and supporting Proof of Concept studies demonstrating therapeutic applicability across diseases.

Input: To achieve this milestone an integrated network of basic scientists with different expertise, translational scientist and clinicians, and clinical trial experts is needed. Furthermore, IHXL will support timely valorisation support to ensure accessibility for patients through commercial and non-commercial routes. In addition, the following inputs are expected to be required:

- Engage in preliminary discussion with regulatory (e.g., EMA) and health technology assessment bodies early in the process to define optimal pathway approval and market access of disease-overarching immunotherapies, also in the case of drug repurposing and/or label extension projects.
- Build strategic partnerships with initiatives and organizations who can aid in funding and/or co-development of high-potential projects. Thereby also unlocking infrastructural needs, access to specific knowledge and/or technologies.
- Access to the models being developed in the moonshot '*Tools at hand'*, to assess translatability across diseases.
- Access to knowledge generated within the moonshots '*The full picture'* and '*Living without fear*' for biomarker-driven patient selection and immune monitoring tools

Output: By 2035 IHXL will have two lead novel immune-modulating interventions/drug repurposing and/or label extension strategies that are suitable for the treatment in a disease-overarching manner in various IMIDs. At least one of these leads will have been tested in a single IMID Phase 1 trial.

Milestone, 2040:

Apply immune modulatory interventions across multiple IMIDs.

Background: To explore the broader applicability of immune modulatory interventions across multiple IMIDs, disease-specific trials or basket trials will be conducted. This will help determine therapeutic efficacy in diverse patient populations and assess the drug's potential as a universal therapeutic approach for IDA-related immune-mediated diseases. Lessons learned from the previous milestones, including insights from early-stage trials, translational models developed in the moonshot '*Tools at hand'*, and biomarker-driven patient selection from '*The full picture'* moonshot, will be critical in designing effective large-scale clinical trials. In particular, leveraging basket trials—where therapies are tested across multiple IMIDs sharing common immunological pathways—could streamline the regulatory approval process and provide robust evidence for broad applicability. Regulatory approval pathways for disease-overarching therapies (including drug repurposing and/or label extension strategies) remain underdeveloped, requiring close collaboration with regulatory agencies to establish frameworks that support their evaluation, approval and implementation.

To ensure clinical impact, collaborations with industry partners will be essential. Pharmaceutical and biotech companies bring expertise in large-scale clinical trials, critical financial capabilities and commercialization-, and market access strategies. Additionally, engagement with regulatory agencies such as the EMA and health technology assessment bodies will be necessary to define optimal pathways for approval and reimbursement, ensuring accessibility of these interventions to a broad patient population.

Input: To successfully apply immune-modulatory interventions across multiple IMIDs, a coordinated effort is required to bridge the gap between early-phase successes and broad clinical implementation. Since funding capabilities within IHXL are limited to support clinical implementation, IHXL will focus its efforts on building relationships, providing expert support, and engaging with relevant stakeholders in support of the research teams driving the projects. This phase therefore focuses on establishing the necessary clinical, regulatory, and industry collaborations to ensure the effective translation of these therapies into standard patient care. IHXL foresees that the following inputs are required:

- **Establish strategic partnerships** with industry leaders, biotechnology companies, and clinical research organizations to fund and facilitate phase 2 and 3 trials.
- **Co-development and execution large-scale clinical studies with relevant partners**, including disease-specific and basket trials, to validate the efficacy of immune-modulatory interventions across IMIDs.
- **Work closely with regulatory agencies (CCMO/EMA)** to ensure that novel approval pathways for disease-overarching therapies are explored and refined.

- **Expand real-world evidence generation** by integrating patient registries, long-term follow-up studies, and health economic assessments to demonstrate the cost-effectiveness of these therapies.
- **Leverage insights from previous moonshots**, ensuring that patient selection criteria and biomarker-driven stratification are optimized to maximize therapeutic impact.
- **Engage with patient communities and healthcare providers** to prepare for real-world implementation and adoption of these therapies.

Output: By 2040, IHXL will have at least one immune modulatory intervention or drug repurposing strategy and/or label extension that is suitable for broad application for the treatment of various IMIDs. New immune modulatory interventions have been tested in a Phase 2 clinical trial.

Examples of applicability to IMIDs: Here we aim to develop and validate tailored immune modulatory interventions that contain relevant information that can be applied for the treatment of IMIDs, such as rheumatoid arthritis, type 1 diabetes, multiple sclerosis, or atherosclerotic CVD. These novel therapeutic strategies will serve as a prototype that can be adjusted for the treatment of other or rarer IMIDs that have shared/similar underlying immune dysfunction and immune pathogenic mechanisms.

4.3 Collaboration in research

The complex and multifaceted challenges presented by IMIDs forces us to foster collaboration across clinical, scientific, and technological disciplines. By working together, we can create synergies, strengthen our efforts, explore new directions, and connect with new fields of expertise, all with the goal of driving innovation and breakthroughs in both science and clinical practice. IHXL will be established as a multidisciplinary, collaborative research initiative, where the combined efforts of patients (organizations), knowledge institutions, government, and industry partners enable us to achieve more collectively than any individual party could accomplish alone.

The collaborative spirit of IHXL will be built upon the strong foundation established by our legacy projects, where scientists and clinicians from various therapeutic and scientific backgrounds, collaborated with patient (organizations) and industry partners. IHXL will expand and strengthen this collaborative community, ensuring that cooperation becomes the standard and is intertwined in all our activities.

Furthermore, by collaborating with external partners, IHXL has the ability to instill the ‘disease overarching’ approach within its collaborations and set in motion the culture shift in the broader research ecosystem.

Implementation: IHXL's ability to achieve its strategic objectives depends on effective and creative collaboration. To this end, IHXL will actively promote and facilitate collaboration within the following framework:

- **Prioritizing collaborative projects:** To maximize the impact of IHXL activities, collaboration will be a key criterion for projects which IHXL drives/supports. IHXL

recognizes that collaboration is not an end in itself, but a powerful means to more effectively address the challenges posed by IMIDs.

- **Community building**: IHXL builds on the strong foundation established by its legacy projects and will further expand and enrich this community by engaging new partners. Through regular meetings, workshops, and conferences, IHXL will create a cohesive and dynamic environment where stakeholders from diverse backgrounds are welcomed, new collaborations can be formed, existing relationships strengthened, and innovative ideas can flourish. (See section 7)
- **Patients (organizations)**: IHXL views patients and patient organizations as essential collaborators within our research. As experienced experts, they provide valuable inputs for the design, evaluation, implementation, and dissemination of the research (see section 5).
- **National initiative:** Within the Netherlands, a broad spectrum of research and research-related initiatives are actively contributing to scientific progress. IHXL will pursue strategic collaborations with initiatives whose research strategies align with-, or complement those of IHXL, offering opportunities to expand research beyond IHXLs current scope. Examples of such initiatives include RegMed-XB, the Dutch Cardiovascular Alliance (DCVA) Oncode Institute, the Centre for Animal-Free Biomedical Translation (CPBT), and Health-RI.
- **Industry:** IHXL is committed to translating its research findings into treatments and diagnostics for IMID patients. To achieve this, IHXL actively promotes collaboration with industrial partners and will invest in cultivating long-term relationships and identifying new opportunities for partnerships through the activities of its valorisation team (see section 6.1).
- **International**: The collaborative spirit which runs through IHXL is not limited by borders. It is IHXL belief that international collaboration is an essential means to creating meaningful synergies. IHXL will actively promote and facilitate international collaboration opportunities whether with international academic institutes, NGOs, private organizations, or within large public-private consortia.

5. Patient strategy

Patient involvement and representation have become increasingly central to shaping research initiatives that aim not only to produce scientific breakthroughs but also to impact patient lives. As the primary beneficiaries of therapeutic solutions, patients provide invaluable insights that can enrich research at every stage—from defining research questions and objectives to the implementation and execution of studies, and ultimately, to the dissemination of findings and integration of results into practice[2]. From its inception, already in the IHXL legacy projects, engaging patients and patient organizations has been an important value of IHXL. Patients have served as a key stakeholder group, helping to shape and refine the IHXL moonshots, which are central to IHXL's research strategy, thereby aligning research objectives with patient needs. Furthermore, patients and patient organizations have been valued experts in the IHXL steering group during its set-up phase. It is important to note that in the context of IHXL's patient strategy, patient involvement and representation can be provided either directly by individual patients or through patient organizations. Therefore, whenever we refer to 'patients,' this encompasses both individual patients and patient organizations.

For IHXL, engaging and involving patients in both research endeavours and decision-making is far from symbolic. When executed effectively, patient involvement and representation have the potential to elevate the quality of research and foster innovations that are more likely to succeed in the real world. To ensure patient involvement is thoroughly embedded and implemented across IHXL's activities, it will integrate patient representation throughout its governance in a balanced way. This will ensure that patients are not only present at the decision-making table ,but ideally also have a genuine influence on IHXL's direction at various levels of its governance structure.

IHXL recognizes that while patient involvement can significantly enhance the relevance and impact of research, this potential will only be realized if the inherent challenges of patient involvement and representation are properly addressed. Effective patient engagement requires more than token efforts; it demands a thoughtful and structured approach that integrates patients as equal partners throughout the research process. To achieve this, IHXL is committed to ensuring that dedicated human and financial resources will be allocated in funding opportunities to support patient involvement in a way that is both sustainable and impactful.

A key aspect of this commitment is building and fostering close collaborations with various IMID patient organizations and expert bodies such as INVOLV, which provide invaluable guidance and frameworks for effective patient engagement. By partnering with such organizations, IHXL aims to leverage their expertise to enhance its patient involvement and representation strategies.

Through these efforts, IHXL ultimately seeks to drive innovations that are more likely to improve patient outcomes and succeed in the real world.

[2] https://pmc.ncbi.nlm.nih.gov/articles/PMC11503179/

5.1 Patient involvement in IHXL research activities

Patient involvement is essential to ensure that research reflects the real needs of those it seeks to serve. By promoting collaboration with patients at critical stages, IHXL wants to enhance the relevance and applicability of its research, leading to more impactful outcomes for patient care. IHXL sees patients not just as participants but as equal partners whose unique perspectives help shape the direction and implementation of research.

IHXL aims to promote that research teams involve patients throughout the research process, from defining research questions to disseminating results, ensures that projects address the practical concerns and priorities of the patient communities. This approach fosters innovations that are both patient-centered and more likely to succeed in the real world.

Implementation: To ensure that patient involvement is consistently integrated into research projects, IHXL will follow a structured framework:

- **Promoting involvement throughout the research process:**
  - Co-design of research questions and objectives: Where relevant, patients will provide input on the formulated research questions, thereby ensuring alignment with patient priorities and concerns.
  - Active role in study implementation: Patients will provide input during the execution of research, helping to refine methodologies and ensure the research remains patient centred.
  - Dissemination and Implementation of Results; To bridge the gap between research and real-world application, patients' organizations can play a key role in disseminating the findings and in strategizing their implementation.
- **Ensuring sustainability and support:** IHXL will aim to ensure that patients are provided with the necessary resources, both financial and logistical, to support patient involvement. This includes compensating patient representatives for their time and expertise, ensuring that patient participation is sustainable.
- **Selection process**: IHXL can support selection of patient representatives, based on their relevant experience required a project. Like other members of a research team, they will be chosen for their ability to constructively contribute to discussions and the project.
- **Balanced representation**: IHXL will aim to ensure patient representation in research projects will be balanced avoiding tokenism. This will foster an environment where patients are empowered to influence decision-making and are recognized as equal contributors alongside other stakeholders.
- **Accessible**: IHXL provide research teams with guidance to ensure that patient representatives can partake in all required meetings. Encouraging research teams to provide meeting materials in clear and comprehensible language, and efforts will be made to ensure that patients can participate in the meetings discussions by safeguarding that patients are provided with opportunities to voice their perspectives, fostering a supportive environment where all contributions are valued.
- **Training and capacity building**: Where possible IHXL will aim to attract funding to enable training programs focused on research processes, governance responsibilities to ensure that patient representatives can fully engage research projects.

5.2 Collaboration with Patients

The success of IHXL's ambition for meaningful patient involvement and representation, as well as its broader objective to foster a widely supported culture shift within the IMID ecosystem, hinges on strategic collaborations with leading organizations and initiatives in the field of patient engagement. These partnerships are vital to ensuring that IHXL's efforts are informed by those with established expertise, knowledge infrastructures, broad networks, and extensive experience in working with patient populations. By collaborating with such initiatives, IHXL gains access to specialized training programs for researchers and patients, support for policy development and advocacy, and the ability to engage with large and diverse patient communities. Critically, this also provides IHXL with the opportunity to demonstrate the potential of its disease-overarching approach and set in motion the culture shift we aim to achieve across the broader IMID landscape, ensuring sustained impact and stakeholder buy-in.

IHXL will prioritize collaboration in the following type of organizations:

- **Patient organizations across IMIDs**: These organizations provide IHXL with essential access to a broad patient population, ensuring diverse perspectives are integrated into our outreach and communication strategies. By involving these organizations in advisory and feedback processes, IHXL ensures that patient voices are central to strategic decisions and public engagement efforts.
- **INVOLV (formerly PGOsupport)**: INVOLV brings expertise in training and education, supporting IHXL by equipping patients and researchers with the skills needed to actively participate in research evaluation and execution and governance.
- **Patient federation Netherlands:** Through its extensive network, Patient federation Netherlands provides IHXL with crucial support in outreach, policy development, and advocacy. This organization can guide IHXL in shaping effective communication strategies, while also helping to influence decision-makers in other organizations and within governmental policies.
- **International Initiatives**: Collaborating with initiatives like EUPATI, the European Patient Forum and the PARADIGM project will allow IHXL to adopt global best practices in patient education, ensuring patients are empowered to take active roles in healthcare and policy discussions. Furthermore, disease-specific European patient organizations are of interest to IHXL.
- **Research organizations and initiatives:** IHXL can learn from research organizations and initiatives experienced in integrating patient perspectives into governance, patient involvement in research assessment and/or specialized patient engagement activities (e.g. Patient perspective program of Oncode institute).

By fostering these collaborations, IHXL can ensure that patient involvement is sustainable, impactful, and truly embedded across all levels of its operations.

6. Valorisation Strategy

IHXL recognizes the need to ensure maximal societal and economic impact of the research activities withing the ecosystem, making collaboration to ensure knowledge valorisation a key element of its strategy. IHXL recognizes knowledge manifests itself as intellectual assets in various forms, including scientific publications, research tools, patentable inventions, educational materials, software, clinical guidelines and applications, and in public outreach efforts, amongst others. IHXL will build and foster strong relations with the Technology Transfer Offices (TTO) to align strategies and ensure that the results emanating from IHXL research projects receive the necessary support to translate their work into societal and economic benefits. This strategy builds on several critical elements:

- **Collaboration**: IHXL will work closely with its partner institutes, national valorisation initiatives and organizations to promote the accessibility of new therapies (section 6.1). Additionally, IHXL will set up interdisciplinary collaboration with industrial partners, investing in long-term relationships and identifying new opportunities for cooperation (section 6.2).
- **Expert support:** When possible IHXL will; a) through collaborations, provide its research teams with access to expert support in research, development, and valorisation and b) ensure that within research grants, funds are allocated which can be dedicated towards the translation and valorisation of research findings.

6.1 Collaboration in valorisation

Collaboration is crucial for the effective valorisation of IMID-related research. IHXL will engage with a wide range of stakeholders to ensure that research outcomes have the best chance of reaching patients. Through this strategy, IHXL aims to:

- increase visibility and awareness of the potential of IHXL research, both within research institutes and across broader societal, clinical, and industry domains;
- strengthen the translation of research by connecting with expert partners in valorisation, gaining access to the knowledge, tools, and networks needed to bring innovations to patients;
- foster a disease-overarching culture shift within partner organization , encouraging a new way of thinking and working that aligns with IHXL's vision for unified, cross-disease research and innovation.

Partner institutes: As the employers of IHXL researchers and the owners of intellectual property (IP), partner institutes are critical to the success of our valorisation efforts. IHXL will foster strong collaborations with partner institutes thereby promoting disease-overarching translation of research outcomes. Additionally, partner institutes possess invaluable knowledge of past and ongoing IHXL-funded research, serving as a critical link in ensuring the seamless translation of findings into patient impact across various IMID diseases.

National initiatives: IHXL will collaborate with national initiatives thematic technology transfer initiatives such as Biotech Booster, RegMed XB, the DCVA and Oncode Institute to align valorisation activities and strategic priorities and amplifying our collective impact. By tapping into partners expertise, we can create synergies that accelerate the development and commercialization of IMID-related innovations.

Furthermore, the pre-seed investment activities of such national initiatives lie the FIRST fund[3], Oncode Bridge Fund[4] and the Biotech Booster[5] program provide the IHXL research community with connections to specialized tools and expertise which can support the creation and growth of new ventures by providing early-stage financing to translate innovative research into impactful solutions.

NGO collaboration: Ensuring innovations are accessible and affordable to patients is a priority for IHXL. Within the life sciences and health ecosystem, various NGOs operate who prioritize accessibility and affordability over private revenues. IHXL will collaborate with initiatives such as the FAST initiative and the TreatMeds foundation. By working closely with such initiatives, IHXL will aim to embed affordability and accessibility considerations early in the innovation process. Additionally, IHXL will actively participate in advocacy and policy initiatives that promote equitable access to advanced therapies.

International collaboration: IHXL recognizes that international collaboration is essential for maximizing the global impact of IMID-related research. To achieve this, IHXL will forge connections with international research institutions, valorisation initiatives, and private parties. We will actively participate in international research consortia and funding programs, leveraging diverse expertise and resources from across the world.

6.2 Industry collaboration

Industry collaboration is essential for ensuring that IHXL's innovative research is effectively translated into therapeutic solutions that reach patients. Industry partners come in various forms, each offering unique strengths: Innovative and agile spin-offs and startups bring fresh ideas and flexibility; Technology developing companies contribute specialized expertise and cutting-edge tools; While biotech and large pharmaceutical companies provide the resources, experience, and infrastructure necessary to scale and commercialize therapies. By engaging with industry partners, IHXL researchers can collaborate with industry peers to shape, improve, and further develop IHXL innovations, while also aiding in achieving IHXL's objectives by bridging the gap between research and market readiness, making sure that our scientific advancements are not only impactful but also accessible to those who need them.

We envision setting up industry engagement through a multi-faceted approach. By **strengthening existing collaborations**, IHXL will focus on deepening relationships with the current industry collaborators of the IHXL research community. By building on established trust and shared goals, we aim to identify new opportunities for collaboration. Furthermore, IXHL will organize **industry-focused meetings and workshops** through which IHXL researchers, patients, and other stakeholders can engage with industry peers. These events will serve as platforms for knowledge exchange, fostering connections that could lead to new partnerships, and collaborative projects. Lastly, IHXL will **actively engage with industry** by reaching out to potential new industry partners. Matching IHXL's needs with industries expertise and technologies, ensuring that collaborations are mutually beneficial and aligned with our mission.

IHXL envisions three main types of industry collaborations:

[3] https://biogenerationventures.com/en/about_us/first
[4] https://oncodeinstitute.nl/valorisation/for-researchers/oncology-bridge-fund
[5] https://www.biotechbooster.nl/program/

- **Core industry partners**: These partners are integral to IHXL projects, where they work closely with our IHXL researchers to provide essential knowledge, technical expertise, or infrastructures. Core industry partners contribute either in-kind or financially to these projects, and they operate under standard terms and conditions of the various funding frameworks. Their involvement is critical to the success of specific projects where their input is highly valued.
- **Strategic industry partners**: Typically suited for larger biotech or pharmaceutical companies, these partners engage with IHXL in a more distal manner. While these partners will not be directly involved in research execution, they can stay closely connected to the cutting-edge work through annual subscription fees. Such subscriptions grant them access to IHXL meetings, conferences, and exclusive partnering sessions, ensuring they remain informed about the latest advancements in IHXL-funded research.
- **Contract research collaborations**: In this model, industry partners collaborate with one or more IHXL researchers to execute specific activities, apply particular methods, or gain access to IHXL technologies and innovations. These contract research collaborations will be governed by terms and conditions that are tailored to the type of research while remaining consistent with IHXL's values and mission.

Through these structured approaches to industry engagement, IHXL aims to create a robust ecosystem where innovation thrives and leads to significant therapeutic advancements.

6.3 Expert support

IHXL is dedicated to maximizing the impact of its funded activities by aligning them with its core objectives and patient needs. To achieve this, IHXL is committed to promoting that its research community is provided with tailored expertise that addresses the specific needs of each research project. With this approach IHXL encourages researcher team members to look beyond the immediate scope of a project, ensuring that the research and development process is aligned with future development pathways from the outset. And routes for translation and valorisation are taken into account when writing project proposals. This mean, where possible, allocating dedicated 'valorisation' budget for future activities that ensure sustainability of research findings. Additionally, IHXL will, through its collaboration partners, gain access to closely connected network of external experts and consultants who are readily available to support IHXL projects. By incorporating the diverse perspectives of experts, IHXL ensures that research and valorisation projects are strategically aligned with its objectives, regulatory requirements, patient-, and market needs, thereby enhancing the potential for successful development and patient benefit. To promote this approach, IHXL has set up its moonshots in a similar way, taken into account the different expertise's which are potentially required during the various stages of the projects executed within a moonshot.

7. Communication and Community & Collaboration

IHXL aims to drive a culture shift within the broader IMID ecosystem by promoting a disease-overarching understanding of IMIDs. To successfully bring about this culture shift, it will be essential for IHXL to communicate effectively on the power of its disease-overarching approach and ensure that its collaborations are built on a shared belief in and commitment to disease-overarching principles. It is for this reason that Communication and Community & Collaboration are two key elements of IHXL strategy. This chapter outlines IHXL's approach to establishing effective communication practices and creating a collaborative community that supports its objectives.

7.1 Communication

IHXL's communication strategy will be designed to ensure both effective and transparent internal communication and engaging, impactful external communication. Clear and consistent communication will help to maintain focus on shared goals while promoting understanding of IHXL's approach and progress.

Internal communication: Effective internal communication is essential for ensuring alignment across IHXL's governance structures and among its stakeholders. This includes fostering clear communication between boards and committees and with key stakeholders such as health foundations, partner institutes, strategic industry partners and governmental organisations. Formal and informal reporting mechanisms will be implemented to ensure timely updates on progress, alignment on strategic goals, and resolution of emerging issues.

As part of its Patient strategy (section 5), IHXL has the ambition to ensure communication is suitable for a broad audience. Therefore, communication with patients will be a dedicated focus of IHXL ensuring that communication is accessible, clear, and understandable to patients. This approach underscores IHXL's commitment to meaningful patient involvement across all aspects of its work.

External communication: IHXL's external communication will focus on ensuring impactful dissemination of its achievements, driving recognition of its disease-overarching approach, and building credibility among a wide range of stakeholders. To achieve this, IHXL will utilize a range of tools and strategies to ensure ample exposure of its progress and impact, including:

- an engaging website with up-to-date content on key developments and achievements and targeted content towards IHXL's different stakeholder groups;
- social media presence on relevant channels to connect with a broad range of stakeholder groups and amplify IHXL's achievements;
- regular newsletters targeted towards different stakeholder groups to deliver highlights of IHXL's milestones and scientific breakthroughs;
- participation in conferences and events to showcase IHXL's work and provide opportunities to engage with a wider (inter)national audience.
- ensuring regular visibility through national media coverage, celebrating major achievements and enhancing public awareness.

It will be key for IHXL external communication efforts to build strong collaborative ties with the communication teams of health foundations, partner institutes, and strategic industry partners. This approach will ensure cohesive and well-aligned messaging, strengthening IHXL's ability to amplify its achievements, raise awareness, and foster trust and engagement with stakeholders and the broader community. Additionally, leveraging the extensive networks and complementary

expertise of partners will significantly enhance IHXL's reach and impact, expanding its influence beyond its own capacities. Patient organizations will also play a vital role in tailoring communication efforts to effectively address the needs and interests of specific patient populations.

7.2 Community & Collaboration

Achieving a lasting culture change within the IMID ecosystem requires establishing a strong foundation of shared ambitions and ideas among IHXL stakeholders. This sense of community is vital for advancing IHXL's vision and creating an environment where its principles are embraced and championed. Moreover, for this culture change to extend beyond IHXL's immediate influence, IHXL will engage in strategic collaborations that transcend boundaries, engaging with (inter)national initiatives and organizations, thereby opening avenues to knowledge, expertise, perspectives, and infrastructures required to achieve our strategic goals.

To support this transformation, IHXL will focus on building a cohesive and dynamic network of researchers, clinicians, patients, and industry partners. By nurturing this community, IHXL aims to inspire collaborations that naturally emerge and thrive, emphasizing openness and mutual support. The initiative will actively promote partnerships that extend beyond traditional frameworks. IHXL will do this through the following elements:

Collaboration as an integral part of its strategy:

- Collaboration is embedded as a cornerstone of IHXL's approach. Conducting disease-overarching research inherently requires collaboration across boundaries and therefore entwined in the IHXL's DNA. IHXL will also actively promote patient involvement throughout the lifecycle of projects—from design to execution and conclusion—thereby building new ties between researchers and patients.

- Collaborations with strategic initiatives play a critical role in IHXL's efforts, since they expand its network and capabilities while also providing its community with access to expertise, perspectives and resources that may not be available internally. These collaborations create synergy and shared purpose. Each of IHXL's central strategic pillars include a section that reflects the central role of collaboration with like-minded initiatives and organizations that aid in achieving our objectives.

Meetings and events:

To foster collaboration and build an interactive community, IHXL will organize a variety of events that provide opportunities for stakeholders to connect and work together. Annual community meetings will serve as platforms for discussing progress, sharing success stories, and addressing challenges. Smaller workshops and events held throughout the year will focus on specific (moonshot related) scientific topics, patient engagement, innovative research methodologies, and valorisation strategies.

These events will be inclusive, welcoming participants from the broader ecosystem to ensure diverse perspectives. IHXL aims to ensure that, where appropriate, meetings are accessible to patients and include dedicated program elements designed to foster openness and engagement with patient communities. This approach will foster networking opportunities and encourage stakeholders from various disciplines to connect, exchange ideas, and form collaborative relationships.

Platform for sharing:

IHXL is committed to facilitating the sharing of knowledge, materials, and technologies through the creation of an open research environment. By becoming the connecting initiative in a large array of research projects, IHXL is able to identify possibilities for sharing and will promote the establishment of connections between stakeholders interested in sharing data, tools, and patient materials. Additionally, IHXL's will specifically drive the financing of the management of critical infrastructures, such as patient biobanks which ensures materials can be shared effectively across and beyond the IHXL community (see section 4.1). By fostering this culture of openness, IHXL aims to strengthen community bonds and accelerate research and innovation.

To ensure alignment and continuity, IHXL will integrate its community-building efforts with its broader communication strategy. This alignment will help maintain a unified focus on IHXL's mission while enhancing the initiative's ability to address the challenges of IMIDs effectively.

Glossary of Acronyms

CVD – Cardiovascular Disease

GMP – Good Manufacturing Practice

HTA – Health Technology Assessment

IBD – Inflammatory Bowel Disease

IHXL – ImmuneHealthXL

IMID – Immune-Mediated Inflammatory Disease

IP – Intellectual Property

MS – Multiple Sclerosis

NVVI – Nederlandse Vereniging Voor Immunologie (Dutch Society for Immunology)

NWO – Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Dutch Research Council)

PAB – Patient Advisory Board

PPS – Public-Private Partnership (Health~Holland funding program)

RA – Rheumatoid Arthritis

RVO – Rijksdienst voor Ondernemend Nederland (Netherlands Enterprise Agency)

SGF – Samenwerkende Gezondheidsfondsen (Association of Health Foundations)

TID – Type I Diabetes

TTO – Technology Transfer Office

ZonMw – Netherlands Organization for Health Research and Development