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TNO report | draft

TNO Biomedical Health
Research program 2021
Topsector Life Sciences & Health

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1 VP Biomedical Health

Program 2021

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1.1 Summary

BMH supports the Mission driven Innovation approach of Topsector Life Sciences & Health ('LSH') and the Dutch Ministry of Health, Wellbeing and Sports ('VWS'). – **the central mission aiming for Dutch citizens living 5 year longer in good health and reducing the health differences between the higher and lower social classes.** More specifically we will contribute to: **reducing health issues that are a consequence of unhealthy lifestyle or exposure to unhealthy environment (Mission I), and we will also help to prevent chronic diseases and increase the proportion of people with a chronic illness or lifelong disability who can participate in society as desired (Mission III).**

We aim to achieve this by developing new technologies for efficient drug development, thus enabling faster access to the right drugs for the chronically ill, and by developing knowledge on mechanisms of metabolic and immune health diseases and use those to develop and help citizens to adopt tailored lifestyle changes that will help them maintain or restore their metabolic and immune health. The new technologies and knowledge will be implemented in collaborations with academic and industrial partners as well as health professionals in field labs.

By 2023 we want to have achieved the following:

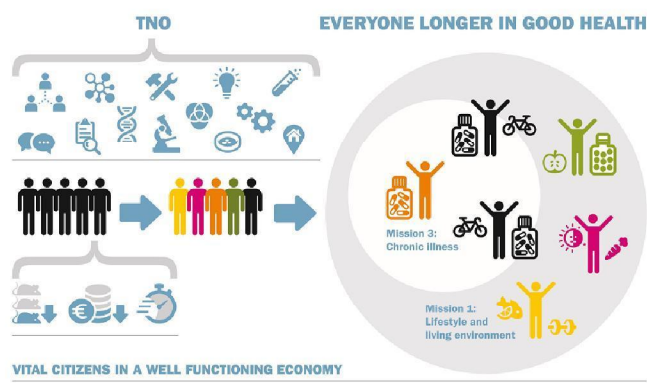
Enable lower attrition rates and more efficient development of innovative drugs and other health intervention development:

1. Demonstrate in practice that current pre-clinical trajectories can be improved (reducing costs, time and animal use) when new approaches and technologies are employed (Mission III)
2. Demonstrate that smaller clinical trials for a novel therapy can be achieved by targeting the right patient population through novel tools for stratification (Mission III)
3. Demonstrate that determination of accurate dose of new drugs for young children can be determined directly in children, using advanced (safe) microtracer approaches (Mission III)

4. Demonstrate that a fairer pricing of innovative medicine is possible by applying the right technology and integrated discussions with pharmaceutical industry and public stakeholders (Central Mission).

Help improve metabolic and immune health:

5. Demonstrate metabolic and immune health improvement by (combination of) food, lifestyle or medication therapy in stratified groups of patients; right drug and intervention for the right patient (Central Mission, Mission I and II)
6. Prove that tailored interventions contribute to vitality of the citizens as well as the quality of health care and cost management (Central Mission, Mission III)
7. Demonstrate that tailored interventions for the lower SES are more effective in improving healthy lifestyle than one size fits all interventions (Central Mission)



To progress towards these above goals, in 2021 we will:

- Continue the discussions with TNO as one of the opinion leaders and facilitators of discussions on fairer pricing of innovative medicines in NL, in strategic discussions with public and industrial stakeholder representatives
- Develop advanced microtracer techniques that will help to personalize the development of novel drugs, such as antibody-drug conjugates
- Develop combined in-vitro and in-silico methods for mechanism based drug target selection, a better and faster choice in drug development.
- Continue the co-development of animal free tests for drug development, such as advanced in-vitro and ex-vivo techniques.
- Validate a blood test for early detection and prediction of NASH /fibrosis in humans, as an alternative for liver biopsy.
- Evaluate, together with care providers, the 360° tool for diagnosis in which various aspects of health and vitality are integrated (metabolic health, mental health, socio-economic environment, activity); define personalized interventions in prevention, cure and care for different SES groups in the society to match the diagnosis.
- Develop an integrated approach where the health (immune) impact of new interventions (compounds) can be predicted in-silico, screened and optimized in vitro and result in a study design in humans or in-vivo animal models.

- Develop new strategies to detect, prevent and reverse inflammation (in infants and adults), one of the main underlying processes in chronic illness, focus areas are COPD and overweight (young) children.
- Generate a first assessment of gender differences in muscle health deterioration (with age) that can serve as basis for personalized intervention development.
- Develop a translational model for diabetic nephropathy that will enable testing of new drugs for this chronic disease in a relevant model.
- Develop new in-vitro platforms to test interventions for individuals with underlying chronic inflammation e.g. skin-health improvement
- Evaluate and test strategies for metabolic health improvement as a support for stronger immune health in relation to pandemics such as Covid-19.

1.2 Description

1.2.1 *VP Biomedical Health*

The global healthcare industry grapples with an unsustainable cost trajectory. Most economies face increased demand for healthcare services by an expanding population of consumer/patients and by growth in costly chronic disease management. We are confronted with a pandemic that affected the entire population, but especially the health of chronically ill citizens. Furthermore, high attrition rates in drug development contribute to expensive medication and to higher health care costs. Innovations in several areas may offer solid solutions for structurally improving the drug development process, for increasing the quality of care and population health while containing costs.

Our program is founded with the firm believe that through development and application of advanced tools and technologies and knowledge on models and mechanisms of disease (onset) in metabolic and immune health, we can enable more efficient development of personalized treatments for prevention of these diseases, delay or cure the onset of (chronic) diseases and thus reduce healthcare costs. In personalized treatments, we recognize that every individual is unique, not only with respect to their physiological and genetic background, but also related to their mental status and social context.

In the last years we have shown that we are an active contributor to innovation in the healthcare in collaboration other knowledge institutes, industry and government bodies. In 2021-2024, through specific regional collaborators (area of the Hague, also including citizens with a low socio-economic status) we plan to strengthen the active participation of patients and citizens in improvements of their health.

1.2.2 *Goals for 2023*

The overall goal of this program is to help professionals and industry to efficiently develop (personalized) treatments to maintain health and wellbeing and to prevent or cure diseases with main focus on metabolic and immune health. In addition we aim to help professionals to bring the developed approaches in prevention and cure directly to the citizens that need them, through field labs.

The knowledge we develop together with partners will enable earlier detection of metabolic and immune diseases, help their prevention and also improve the efficacy of their (drug or vaccination) treatment. The novel tools and technologies developed by TNO and partners will also contribute to efficient drug development, lower the

attrition rates and help to achieve a more efficient clinical study design and thus help to bring the right drugs to the right patient faster.

More specifically we will:

Enable lower attrition rates and more efficient development of innovative drugs and other health intervention development by:

1. Development of translational, mechanism based, better predictive models (in-vitro, ex-vivo, in-vivo, in-silico), development of advanced measurement methods, increase the information density of early clinical trials, by enabling the first in man studies much earlier in the development (Personalized medicine, LSH Mission III)
2. Development of advanced in-silico tools for risk and safety assessment of new targets and treatments as well as biomarker discovery (LSH Mission III)

Help improve metabolic and immune health by:

3. Better understanding of metabolic and immune health and disease mechanisms, thus enabling the development of better predictive models and improved diagnostics (LSH Mission III)
4. Identification and validation of (novel) translational biomarkers for early detection and better stratification of the medical status, combination of blood biomarkers with multimodal parameters for a personalized analysis of metabolic and immune disease including complications (LSH Mission III)
5. (co-)Development and (co-)implementation of tailored (lifestyle) intervention strategies for improvement and maintenance of metabolic and immune health in different communities, based on advanced biomarkers and health assessment tools including multimodal aspects of health (LSH Central Mission, Mission I and Mission III)

Tools and models for efficient innovative drug and other intervention development

Within this research line we will **address the need for better predictive, translational models and tools for efficient drug and other intervention development**. We will focus on development of validated, highly predictive translational models (in-vitro, ex-vivo, in-vivo and in-silico) that assess the efficacy, kinetics and toxicity of various interventions (drugs, foods, lifestyle) in humans, applicable in the entire product development trajectory. We will contribute to innovations towards animal free testing (e.g. 'organs-on-a-chip', candidate selection directly in humans using microdosing and AMS). We develop tools and models that predict biological outcomes of the modulation of a biological process or protein target in-silico (risk assessment) and better mimic (personalized aspects of) physiological and disease processes in humans. The development of the tools and models is based on **better understanding of the mechanisms of onset of inflammation, metabolic and immune health dys-regulation (including chronic complications)**. Data mining tools and systems biology approaches will be developed for **identification and risk assessment of targets and identification and efficacy assessments of treatments and biomarkers**.

Improvement of metabolic and immune health through personalized interventions

Within this research line we will focus on **identification of (dynamic) biomarkers for early detection of metabolic& immune disease and corresponding**

(chronic) health complications, identifications of new targets for treatment of metabolic and immune disease. Systems biology methods will be used to identify biomarkers based on genes, proteins, metabolites, specific microbiome compositions or specific lifestyle aspects. The biomarkers can be used for **stratification of patients in clinical trials** and for development and implementation of personalized intervention strategies. A logical follow-on application for patient profiles and biomarkers is the ability to provide health care professionals with concrete advices on what preventive measures or therapeutic interventions fit best with the biological profile of their patient. We aim to have these advices laid down in standards of care for the various diseases.

We will develop **personalized interventions for maintenance and improvement of metabolic & immune health and well-being. We will help to implement personalized and stratified interventions in specific target groups**, children (immune and metabolic health and pediatric microdosing), (chronically ill) adults (immune and metabolic health) and (pre)obese persons, (immune and metabolic health) and elderly (metabolic decline of skeletal muscle with age), but also cancer patients which might benefit from metabolic and immune health improvement. This line is closely connected to TNO's research program Digital Health Technologies.

1.3 Results 2021

We have a strong position in bringing together parties from different industrial sectors (pharma, nutrition, diagnostics, retailers) and develop PPP projects with several industrial partners. End of 2019 and 2020 we started four new PPP projects. We also participated in several NWA grant submissions. In 2021, we will continue to expand our activities in public-private partnerships and shared research program(s) in which we will (co) develop the technologies and knowledge necessary to achieve the set program goals.

selection of (planned) collaborations	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	contribution to program BMH goals	main deliverable	Roadmap LSH	Mission LSH
Tools, models for efficient drug development																					
PPP Animal free drug development																		1,3	better translational models	5	III
PPP In silico target discovery tools efficacy																		1	animal free pre-clinical tools	5	III
PPP microtracers in Antibody drug conjugates for cancer																		1	advanced analytical tools	5	III
PPP microtracers in Pediatric drug dosing																		1	advanced analytical tools	5	III
PPP microbiome personal care																		1	better translational models	5	III
NASH biomarker panel validation in human cohorts																		3	metabolic health biomarkers, NASH	1	III
PPP ADMET on a chip (UMCU)																		1,3	better translational models	5	III
PPP translational model diabetic Nephropathy																		1,3,4	insight in mechanisms metabolic health	1,5	III
Metabolic and immune health improvement																					
PPP NASH Biomarkers																		3	metabolic health biomarkers, NASH	1	III
PPP Phenflex 2, phenotypic flexibility in prevention																		3,5	novel biomarkers metabolic health	3,8	C, I
PPP Microbes and immune health																		3,5	biomarkers and targets immune health	7	III
PPP Muscle health and gender differences																		1,3,4	mechanisms and translational models	7	III
PPP 360 Health Diagnostic																		4,5	tailored interventions metabolic health	7,8	C, I, II
PPP Personalised nutrition in cure																		1,3,5	tailored interventions metabolic health	7	III
PPP Pro Liver, targets for NASH treatment																		1,3,4	insight in mechanisms metabolic health	1,5	III
PPP Identification of dietary factors in inflammatory diseases																		3,4,5	insight in mechanisms, immune health	1,5	C, I, II
PPP-TAOH Oral Health																		3,4,5	insight in mechanisms, personalised prevention	1,5	C, III
PPP Global, Organ cross talk in metabolic health improvement																		1,3,4	mechanisms and translational models	1,8	C, III
PPP just signed and started PPP planned PPP already in execution PPP in preparation/submitted PPP extended with RQ and/or partners																					

Figure 1: Selection of current and planned PPP collaborations and their contribution to the Biomedical Health research program goals and the roadmaps and missions of Topsector LSH. BMH program goals: (1) Development of translational and better predictive models and measurement methods, (2) Development of advanced in-silico tools for drug discovery, (3) Better understanding of disease mechanisms, (4) Identification and validation of (novel) translational biomarkers, (5) Development and (co-)implementation of tailored intervention strategies for improvement of metabolic and immune health. LSH roadmaps: (1) Molecular Diagnostics, (3) Homecare and self management, (5) Pharmacotherapy, (6) One Health, (7) Specialised Nutrition, health and disease, (8) Health technology, assessment, individual functioning and quality of life. Missions: C, Central Mission, I reduction of negative effects of lifestyle and environment, III (Enabling increased participation in the society of the chronically ill).

To align with the KIA missions, Just as in 2020, extra focus will be on development of PPP projects that will test and implement the developed technologies in field labs.

In figure 1 several examples of existing and planned public-private collaborations that are planned to start in 2021 are shown, as well as their contribution to the program goals and the LSH mission-driven innovation. In the course of 2021, new ideas/ technology needs will be identified that will be used for the setup of new collaborations. The activities within these PPP's will lead to achievement of several knowledge and technology deliverables. Each PPS contributes to one or more program goals. The table also indicates the LSH roadmaps to which the newly developed knowledge and technology will contribute.

The knowledge and technology developed within this program will also contribute to developing PPP collaborations in the area of Do-it-yourself measurements, eg.

smart toothbrush, smart incubator. These PPP projects will be a collaboration between Biomedical Health, Digital Health Technologies, Child Health and Semiconductor equipment.

Program line tools and models for efficient drug and other intervention development

- Demonstrator microdosing in pediatrics with FDA (BMH goal 1).
- (Semi-) automated AI-based in-silico platform for mechanism based target, drug and biomarker discovery combined with in-vitro models for verification of the findings (BMH goal 2).
- Proof of concept of ex-vivo perfused human kidney model as an alternative for animal experiments for application in pharmaceutical industry (BMH goals 1 and 3).
- 3D liver-function (NASH/Fibrosis) model on a chip coupled to human intestine model on a chip, for studies of drug efficacy and drug metabolism (BMH goals 1 & 3).
- Democase for microtracer use in research of metabolic dysregulation mechanisms (fluxomics, de-novo lipogenesis in the liver) (BMH goal 1)
- Analytical platform for functional microbiome analysis extended with interpretation of health effects (BMH goals 1 and 3).
- Relevant biomarker analysis methods enabling analysis of several biomarkers in low sample volumes, applicable in child cohorts. (BMH goal 1).
- Protocol for analysis of microbial skin metabolome on skin applicable in testing the health effects of probiotics and other ingredients on skin (BMH goals 1 and 3)
- In-vitro gut IBD model for testing beneficial interventions for IBD (BMH goals 1 and 3)
- In-silico and in vitro pipeline for identification and biological evaluation of antifungal compounds for new antifungal treatments (BMH goals 1, 2 and 3)
- Established position of TNO as one of the opinion leaders and facilitators of discussions on fairer pricing of innovative medicines in NL, achieved by active participation in strategic discussions with public and industrial stakeholder representatives. (all BMH goals)

Program line Improvement of metabolic and immune health

- Protocol for metabolic health improvement interventions as a support to increase the efficacy of standard drug treatments for e.g. gut cancer (BMH goals 4 and 5)
- In-silico model for risk-benefit assessment of immune health interventions in early life and adults (BMH goals 2 and 3)
- Evaluation of the 360° tool, which integrates multimodal data (from different domains, amongst others socioeconomic status) in addition to plasma bio markers, tested in collaboration with caretakers (BMH goals 4 and 5).
- Automated tool to generate personalized health reports (BMH goal 5, in collaboration with VP Digital Health Technologies).
- Description of gender differences in (deterioration of) muscle health based on which gender specific interventions can be developed for elderly or chronically ill (BMH goal 3)
- Translational NASH model validated with clinically relevant compounds, which will be used for development of new NASH interventions (BMH goals 1&3)
- New translational model for studying prevention (with supplement or drug interventions) of muscle atrophy in obese (BMH goals 1, 3 and 4)

- First prototype of optical sensors to monitor health status, stress and other triggers of (chronic) inflammation in infants (BMH goals 4 and 5)
- Insights into consequences of maternal obesity on health risks in offspring (BMH goal 5)
- Testing of the non-invasive 'health patch' in a COPD cohort. Prediction models for loss of lung function based on the acquired data (BMH goals 3 and 5).
- Interventions for 360 degrees dimensions 'thinking and feeling', 'behaviour' and 'socio-economic situation' to enable personalised lifestyle advice (BMH goal 5)
- Personal health advice system (PHAS): advice on reduction of medication in T2D (BMH goals 4 and 5)
- Validated biomarkers of metabolic age and metabolic stress that will enable applications in further personalization of health interventions (BMH goals 4 and 5)
- 1st subtyping of obese subjects based on health status of different organs, this will enable personalized interventions.

Internal collaboration:

Several of the deliverables listed above will be realized in close collaboration with TNO early research programs and development, testing and in the future also implementation of deliverables related to empowerment of patients and citizens will be done together with research program Digital Health and those focused on young children will be developed and implemented together with research program Child Health (part of Prevention, work and Health).

In order to achieve the set goals we will develop new interventions, knowledge, tools and technology in two program lines which will be interacting with other research programs and TNO early research programs, shown in figure 2.

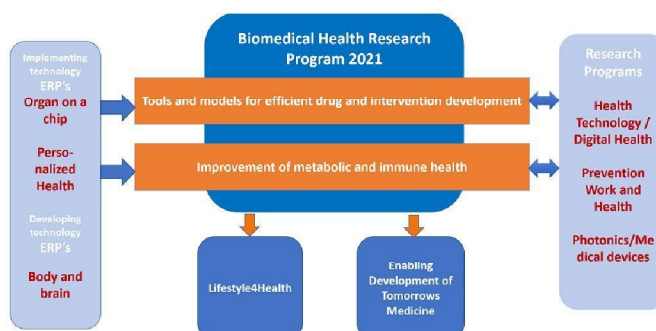


Figure 2: Program lines of research program Biomedical Health. Connection to three early research programs (Organ on a Chip, Personalized Health, Body and Brain) and strong collaboration with research programs Digital Health Technologies, Prevention, Work and Health, Photonics/medical devices. In 2021 Biomedical Health is supporting 1 shared research program (Lifestyle4Health) and new discussions with private and public partners around drug development.

This program will only be successful if we succeed in realizing further (project based) collaboration with the experts also from other Units within TNO, specifically from:

Unit Industry: Photonics, Holst Center, Nano-instrumentation, Materials and Solutions for Organs on chips technologies for **development of novel materials that will be used in better translational in-vitro and ex-vivo models**. For detection of low-grade inflammation, collaboration is needed with the Photonics group to develop advanced non-invasive sensors.

Unit Defense, Safety & Security: Distributed Sensor Systems, Human Behavior and Organizational, Innovations Training & Performance Innovations, Modeling, Simulation & Gaming, for knowledge and approaches in **personalized interventions**.

Unit Circular Economy and Environment: Environmental sensing, modelling and analysis for collaboration in development of non-invasive sensing technologies.

In many cases collaboration has already been realized, through collaborative projects and early research program 'Personalized Health', early research program 'Organ-function-on-a-Chip'. For these two programs, technology implementation in BMH needs to be achieved in 2021. Early research program 'Body and Brain' started as full ERP in 2021 and will deliver important knowledge for the Metabolic and Immune line.

External collaborations and connections.

This program is directly connected to the mission, ambition and objectives of topsector LSH (**Knowledge and Innovation Agenda 2020-2023** (see section 1.3). The results of this program will directly contribute to the tackling of the societal challenge: **vital citizen in a well-functioning economy**.

Our PPP projects will continue their contribution to the roadmaps of Topsector LSH:

1. Molecular Diagnostics
3. Homecare and self-management
5. Pharmacotherapy
6. One Health
7. Specialized Nutrition, Health and Disease
8. Health technology assessment, individual functioning and Quality of Life

The program is linked to the following NWA routes:

- NWA route Personalized Medicine
- NWA Gezondheidszorgonderzoek, preventie en behandeling
- NWA route Kwaliteit van de omgeving
- NWA route Regenerative medicine

Examples of operational strategic PPP's collaborations that are supported by LSH include:

Netherlands Institute for Lifestyle4Health this collaboration with TNO and LUMC in the lead aims at reversing or curing lifestyle related diseases by changing lifestyle. The initial focus is on type 2 diabetes with the aim to cure this disease within 10 years..

With the technology and knowledge (to be) developed with will effectively contribute to the mission driven innovation as described in the Knowledge and Innovation agenda of LSH and supported by the **Ministry of Health, Wellbeing and Sports, Health and Care**.

This program also has a number of strategic collaborations with academia, such as University Medical Center Utrecht in the area of immune and metabolic health, Wageningen University and LUMC in the area of metabolic health and physiology, ACTA metabolic and dental health, University of Nijmegen for links between metabolic health and healthy brain development as well as pediatric research. We are setting up a collaboration with VUMC for microtracers and PET imaging. In addition to academia we also have strategic collaboration with several companies that are often partners in PPP projects, such as BioFortis, PRA, CHDR (Human studies) and Nordic Biosciences (biomarker measurements). In discussions on more efficient drug development, we are a partner in **HollandBIO**, we participate in **BRIDGE** discussions.

We participated in several consortia applying for NWA funding in 2019 and 2020 (rebuttals) and will be participating in the projects, depending on the outcome.

Apart from being linked to the Knowledge Agendas of topsector LSH, this program also links to **hdMT** (a strategic PPS, national initiative in the area of organ-on-chip technologies, TNO became partner in 2016), has good connections with policy makers at ZonMW. We align with **One Health**, **Humane Meettechnieken** (3/4V) and **Animal free innovations** and are currently strengthening our links to the **European Medicine Agency (EMA)**. We will also align and participate in the PPS in development, **FAST** (Affordable Future Therapies). We work together with several patient organizations and foundations, such as MLDS, Diabetes Foundation.

1.4 Dynamics

E-health, digital health and partially also medical devices (collaboration with the Van 't Hoff program and Holst Center) have shifted from the roadmap Biomedical Health to Digital Health Technologies in 2018. The collaboration between Biomedical Health and Digital Health Technologies is very strong and the programming of the two research areas is coordinated.

We steer the knowledge development within this program based on societal needs and changes. As of 2018 we collaborate with LUMC and co-fund projects that are part of the Netherlands Innovation Center LifeStyle4Health.

For efficient drug development, we believe that the use of the right innovations in the private sector and joining forces in the public & private sector, innovative medicines will become available to patients faster and the (high) development costs and prices of new medicines can be more contained. We actively participate in the discussions with industrial and public stakeholders. In Leiden Bioscience park we are building new laboratories with advanced unique technology Accelerator Mass Spectrometer (as of 2020 two instruments available) to meet the high demand of our pharma and biotech partners. In Q4 2021, all TNO Health laboratories will be a part of the TNO location at Leiden Bioscience park.

We will further align our technology development with the needs of pharma industry by connections to HollandBio (and BRIDGE program), EMA and EATRIS. In 2021 we will further actively interact with VWS and other public bodies in the discussions on affordable medicines.

During the 2020 pandemic we actively participated in maintenance of safety measures by setting up methods to measure the safety of protective materials. In discussions with VWS we lead consortia on development of fast methods for Covid-19 detection.