DUTCH NATIONAL PROGRAM RESPIRATORY RESEARCH P4O2

JOIN THIS PUBLIC PRIVATE INITIATIVE FOR PRECISION MEDICINE FOR MORE OXYGEN

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Prof. Dr. A.H. Maitland-van der Zee


J.J.M.H. van Bragt, PharmD, MSc


Prof. Dr. H.J. Bogaard


Prof. Dr. I.H. Heijink


Dr. S.D. Pouwels


Prof. Dr. A. Schols

WELCOME

We would like to offer you this brochure of 'P402 - Precision Medicine for more Oxygen'. Scientists of the Dutch National Program Respiratory Research of the Netherlands Respiratory Society aim to submit this research proposal at the Matchcall of Health~Holland which stimulates public private partnerships. The aim of P402 is to prevent the onset and progression of lung disease and to treat patients with lung disease better and earlier. This multidisciplinary project focusses on risk factors for developing lung disease in the exposome, mechanisms of tissue damage and repair, biomarkers for early detection of lung damage, interventions, and new therapeutic targets. Data that is already available will be integrated with data obtained with novel technologies. Advanced experimental models will be designed, and a new cohort of healthy, middle-aged individuals with and without a high risk of developing lung disease will be followed-up for five years in the long-term. Research centers, private partners, participants in the cohort, and others will join forces to make a real difference in this societal problem. We would like to get in contact with you if you are interested in joining this initiative. Please visit the website www.P402.org for more information, or contact us via nrs@nrs-science.nl. We hope to welcome you as a collaborator!

With kind regards,
Prof. Dr. A.H. Maitland-van der Zee, PI P402


Dr. R.C.J. Langen


Dr. R. Beijers


Dr. F. Mohamed Hoesein


Prof. Dr. R. Vermeulen


Dr. G. Downward


M. van den Heuvel, MSc

THE DUTCH NATIONAL PROGRAM FOR RESPIRATORY RESEARCH

In 2012, the Netherlands Respiratory Society developed a scientific program for lung research together with researchers, caregivers, health funds, governance, private partners and patients. The mission of the National Program for Respiratory Research named ‘Life Long Lungs’ is to contribute to the improvement of the quality of research, to strengthen the (inter)national position and strength of this research, and to prevent and optimally treat lung diseases. The next years, the program focusses on the following three topics:

- Fatigue in chronic diseases including lung diseases (Fatigue)
- Prevention of lung diseases in early life (HALO)
- Precision Medicine for more Oxygen (P4O2)

In the program ‘Fatigue’, a strategic program for fatigue in chronic diseases (including lung disease) will be developed, as fatigue is an important problem that is indicated by patients with chronic disease. Causes and interventions will be further examined. The program ‘HALO’ focusses on the prevention of lung diseases (with a focus on asthma) early in life. It is a multi-center cohort study where interventions such as lifestyle coaching of pregnant women and administration of biologicals and bacterial lysates to neonates will be examined. The P4O2 program aims to contribute to prevention of progression of early lung damage and to reverse established lung damage. It will focus on identification of treatable traits and innovative personalized therapeutic strategies. More information on this program can be found in this brochure.

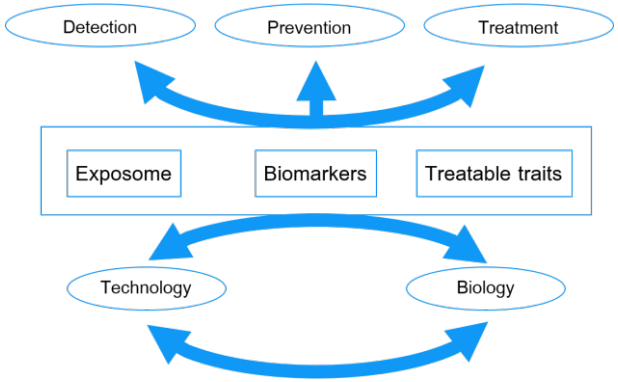

Fig.1 P402 - Novel technologies and methods to study the biology of tissue damage and repair, together with analysis of the exposome will lead to discovery of biomarkers and treatable traits for early lung damage and lung disease.

RESEARCH IN THE NETHERLANDS

For many years lung disease have been relatively fatal and treatment has been largely symptomatic or palliative. Because of an exceptional research infrastructure and tradition, the Dutch respiratory field is uniquely positioned for a leading role in transitioning to better outcomes. Various patient cohorts are already available, and Dutch lung research is rather unique in the fact that in many cases also tissue data (basic research) of these patients is available. Furthermore, the Netherlands is one of the main players in eHealth and big data and has experience in combining basic science with eHealth. The PRIL-cohort will be a unique addition, as it is the first to follow a population of healthy, Dutch patients (for at least one year within this project, but for five years in the long-term), to examine determinants of early lung damage.

P402

According to the World Health Organization, lung diseases are the number one cause of death worldwide. Lung diseases almost without exception lead to extremely debilitating symptoms and loss of quality of life and productivity. Therefore, the Precision Medicine for more Oxygen (P402) program aims to identify treatable traits and innovative personalized therapeutic strategies to both prevent progression of early stage damage and to reverse established lung damage by stimulating repair.

P402 is a national multidisciplinary collaborative program to innovate, reinforce and display the current know-how and physical infrastructure for biomarker and data acquisition, storage and analysis. The program will identify risk factors in the external exposome, gain novel insights in tissue damage and repair and will develop and combine cutting edge imaging with analysis of different patient materials (tissues, cells, blood samples, exhaled air). In a later stage the acquired insights will be used to create tailored strategies for prevention and treatment of individual subjects. With our combined effort, we aim to integrate traditional phenotypic data (e.g. demographics and lung physiology) with analysis of innovative biomarkers (e.g. molecular imaging, radiomics, breathomics, (epi)genomics, proteomics, metabolomics).

The scale and ambition of the P402 program empowers fundamental improvements in quality of life, perspectives and societal participation of patients with chronic lung diseases by 2030. P402 will provide unique opportunities for universities and business enterprises in the Netherlands to remain in the driver's seat of respiratory research.

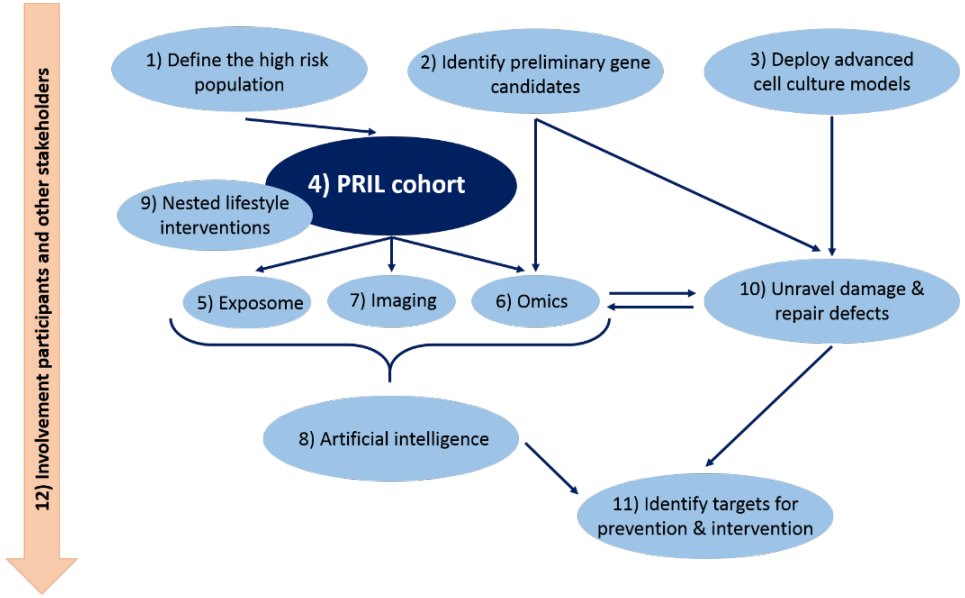

Fig.2 P402 consists of twelve work packages. A high risk population for the development of lung disease will be identified. This information will be used to set up the PRIL-cohort. Genes for tissue damage and repair will be analyzed in existing cohorts. These genes will later be analyzed in multiomics and in new experimental models that will be set up. The exposome of participants in the PRIL-cohort will be examined, and is expected to lead to the discovery of biomarkers for early lung damage together with multiomics approaches and imaging by using artificial intelligence. Lifestyle interventions will be tested in the PRIL-cohort, and other interventions that target pathways of damage and repair that were identified in an earlier stage will we tested in novel experimental models.

OVERVIEW OF THE WORK PACKAGES

WP1 - Populations at high risk for respiratory disease
Identifying populations at risk by combining established individual risk factors with information on the external exposome.

WP2 - Gene candidates in damage and repair responses
Analyzing the effects of smoking on pathways for lung damage and repair in existing cohorts.

WP3 - 3D lab-on-a-chip culture models for tissue damage and repair
Setting up advanced lab-on-a-chip models to improve the usability of experimental models.

WP4 - The PRIL (Persons at high RIsk for Lung disease)-cohort
Setting up and follow up (5 years) a cohort of participants without lung disease at the start to obtain samples that could detect early lung disease.

WP5 - The exposome in the PRIL-cohort
Development of data management systems, wearable devices, tools and apps to integrate data, and sampling the PRIL-cohort.

WP6 - Multiomics in the PRIL-cohort
Performing breathomics, (epi)genomics/transcriptomics, metabolomics, and microbiomics on a great variety of PRIL-cohort samples.

WP7 - Imaging in the PRIL-cohort
Designing an automatic method to measure pulmonary and extra-pulmonary features on chest CT of PRIL-cohort participants.

WP8 - Combining exposome, multiomics, and imaging data
Analyzing 'big data' with bio-informatics and bio-statistical tools.

WP9 - Personalized lifestyle interventions in the PRIL-cohort
Goalsetting on smoking, physical activity level, dietary quality and cognitive performance.

WP10 - Mechanistic studies into repair defects
Including identification of extra-pulmonary tissue derived protective and damaging features of the metabolic milieu.

WP11 - Intervention studies for lung repair in lung disease
Modulation of identified therapeutic targets using (repurposed) pharmacological inhibitors and/or CRISPR/(d)CAS *in vitro*.

WP12 - Initiatives to involve stakeholders and disseminate findings
Initiation of various communication initiatives.

WP1 -

Defining populations at high risk for respiratory disease in the Netherlands, combining risk factors and the external exposome

Currently, we have limited insights into how environmental and personal risk factors contribute to lung disease risk within Dutch populations and how areas where specific risks factors or 'at risk' populations can be identified. Exploring the exposome will help to define those populations. The exposome refers to the combination of external environments (buildings and urban space, food, lifestyle, social, and physico-chemical) which are encountered by individuals and populations. Combining a-priori established individual risk factors for respiratory disease (e.g. age, smoking, occupation) with information on the external exposome (e.g. maps of ambient air pollution or pollen density) will identify individuals with an individual predisposition to lung disease residing in areas likely to contribute to lung disease and so will be extra at risk.

The aim of this WP is to identify candidate areas and populations in the Netherlands which are at (relatively) increased risk of developing respiratory disease. As a second method to define risk factors and at-risk populations, we have requested a partnership with the EPIC (European Prospective Investigation into Cancer and Nutrition)-cohort.

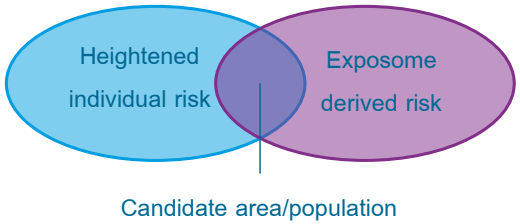

Fig.3 Identifying an area/population that is extra at risk by combining information on individual risk factors with data on exposome derived risk.

WP2 -

Identifying gene candidates and pathways involved in aberrant damage and repair responses to cigarette smoking in existing cohorts

Although we know that smoking is unhealthy and it is the major risk factor for the development of COPD, not all smokers develop COPD (15-20% does). This indicates that besides environmental factors, (epi)genetic factors are involved in the susceptibility for the disease. We need better insights into the mechanisms involved in the development of aberrant repair and lung damage in response to smoking.

The first aim of this work package is identification of candidate genes and signaling pathways that are differently expressed in the airway epithelium upon acute cigarette smoke exposure. The second aim is identification of cigarette smoke-influenced COPD susceptibility genes by identifying which candidate genes identified in aim 1 are also differently expressed in lung tissue of COPD patients compared to (non-)smoking controls. The third aim is validation of previously identified COPD susceptibility genes, and identify whether these are influenced by acute cigarette smoke exposure. This will lead to the identification of novel therapeutic targets for cigarette smoke-induced lung damage.

WP3 -

Setting up novel 3D lab-on-a-chip culture models for tissue damage and repair

There is a need for complex 3-dimensional cell and tissue models that recapitulate the local complexity of the lung, and the capacity of intercellular communication by the lung epithelium. The first aim of this work package is to transfer established co-culture models of air-liquid interface (ALI)-differentiated airway epithelial cells and mesenchymal stromal cells and/or alveolar organoids (including 3D matrix environment) into dynamic lab-on-chip systems. The second aim is to transfer precision-cut lung slices (human and animal) to such chips to prolong *ex vivo* viability of the tissue. These models will be used for real-time monitoring to provide insight in the optimal timeframe to study repair responses upon different environmental exposures, including cigarette smoke extract (CSE), air pollutants (e.g. particulate matter, diesel exhaust) and occupational exposures.

These models will enable us to gain insight in abnormal damage and repair responses in lung disease and to test novel therapeutic strategies.

WP4 -

Building the PRIL-cohort for detection of early lung damage

Not everybody living in high risk areas or belonging to high risk populations will develop lung disease, so there is a need for a method to distinguish those people that will develop lung disease from those that will not. Easy to measure biomarkers to diagnose lung damage at an early stage could be of great importance. Once a patient develops complaints the disease process usually has already proceeded beyond the point of no return. However, it is likely that treating early lung damage may halt the progression to lung disease.

The first aim of this work package is to inventorize the prevalence of a high risk profile in the Netherlands using questionnaires on the exposome and respiratory complaints of 5000 middle-aged people. The second aim is setting up the PRIL-cohort of 350 subjects (250 subjects with high risk on developing a lung disease, and 100 with average risk). Within P402, the third aim is a follow-up of at least one year for all participants of the PRIL-cohort. A five-year follow-up is planned in the long-term. This will provide information on physical function, muscle function, cognitive function, body composition, lung function, and exhaled breath, and will provide multiple biological samples (e.g. blood, urine, feces, nose swabs). Also information on lifestyle characteristics, psychosocial function, and health status will be available.

WP5 -

Analyzing the exposome in the PRIL-cohort

The exposome is likely to play a role in the development of lung disease. However, current methods to analyze the exposome are largely insufficient. The wish to non-invasively monitor one's personal health status and to assess the quality of the environment is increasing, leading to new opportunities and avenues of study. The exposome of PRIL participants will be explored through examining a combination of pre-existing data and the generation of new data via wearable devices. This leads to a wealth of data which will be used to understand differences between individuals that do develop lung disease and those that do not, despite having the same level of risk.

The first aim of this work package is to develop advanced data management techniques, including the development of software machine learning algorithms. The second aim is to develop and deploy non-invasive devices, minimally invasive diagnostic tests and simple environmental sensors for the day-to-day use of healthy subjects and patients with respiratory conditions. The third aim is to develop tools and apps to integrate population level data with personalized data and generate lifestyle and medication advice. The last aim is to generate data on the exposome of participants in the PRIL-cohort.

WP6 -

Multiomics in the PRIL-cohort

Lung diseases are detected at a late stage, when it is no longer possible to cure disease, instead the only option is to reduce symptoms and optimize quality of life as good as possible. Treatment early in disease is likely to be more successful. We expect that multiomics will help identifying signs of early damage as they provide insight into an enormous number of different molecules.

The aim of this working package is to analyze samples of the PRIL-cohort and to compare biological markers of patients who are showing early signs of lung damage (and after some years of follow-up subjects who developed a lung disease) to markers of participants who do not show early signs of lung disease (and those who did not develop lung disease in a later stage of the project). We will perform breathomics, (epi)genomics/transcriptomics, metabolomics, and microbiomics from a great variety of PRIL-cohort samples.

WP7 -

Imaging of the lungs, extra-pulmonary tissue, and body composition in the PRIL-cohort

Lung diseases have traditionally been diagnosed and assessed simply by spirometry. This reliance on spirometry has led to modest advances in our understanding of underlying pathophysiology of many lung diseases. Detection of early stage disease in the PRIL-cohort is not only possible with wearable devices and multiomics, but also by imaging modalities.

It is increasingly recognized that the development of many lung diseases is complex. Many lung diseases are heterogeneous. Recent advances in CT of the chest have enabled extensive phenotyping by allowing morphologic characterization of parenchymal and airways disease, and provide important information on body composition and vasculature.

The aim of this work package is to detect lung damage at an early stage using CT, and to develop an automatic method to measure pulmonary and extra-pulmonary (body composition and vasculature status) features on chest CT. Also artificial intelligence by deep learning will be performed on the CT scans to provide an unbiased analysis.

WP8 -

Combining exposome, multiomic, and imaging data using artificial intelligence to identify phenotypes of groups at-risk for developing lung diseases

It has become clear that the complexity and heterogeneity of lung diseases cannot be encompassed by single biomarkers and that the exposome is an important factor in the development of lung diseases. A combination of the data collected in the other work packages will allow us to maximize the information we can retrieve from this data. This ‘big data’ approach introduces the need for sophisticated bio-informatics and bio-statistical tools.

Conventional statistical methods will be used for correlations of single layer omics biomarkers between the subjects that have early signs of disease versus disease-free subjects despite a similar high-risk exposome at start. Artificial Intelligence (AI) incorporating approaches, including deep learning techniques such as artificial (convolutional) neural networks and decision tree algorithms will be used for supervised analyses. These techniques will improve the classification of patients at-risk to develop lung diseases.

WP9 -

Personalized lifestyle interventions in the PRIL-cohort

Smoking is an important risk factor for development of lung diseases such as COPD and lung cancer, but there is increasing evidence that also other lifestyle characteristics including physical inactivity and poor dietary quality, in combination with smoking, are involved.

The aim of this work package is to test the modulating potential of lifestyle interventions to counteract or decrease the development of lung disease and associated extra-pulmonary manifestations as well as to modify overall health and well-being. In a nested study of the PRIL-cohort, a lifestyle intervention by lifestyle counseling based on preset goalsetting on smoking, physical activity level, dietary quality and cognitive performance will be set up. This will lead to the development of strategies to counteract or decrease the development of lung disease and associated extra-pulmonary manifestations and will modify health and well-being.

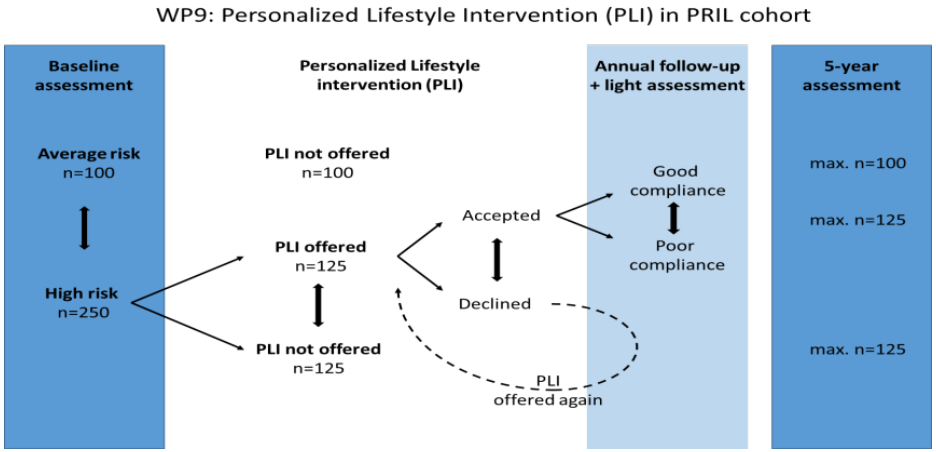

Fig.4 Set up of work package 9.

WP10 -

Mechanistic studies into repair defects in chronic lung disease using advanced models and analyzing biomarkers identified in the PRIL-cohort

There is a need to gain more insight in abnormal damage and repair responses to environmental exposures in lung disease. Advanced models developed in P402 will be used to examine the role of biomarkers identified in P402 on lung damage and repair.

The first aim of this work package is to provide novel insight in abnormal repair responses in lung disease upon environmental exposures using advanced models. The second aim is identification of extra-pulmonary tissue derived protective and damaging features of the metabolic milieu in these models. We will monitor real-time secretion profiles of cytokines/danger signals, growth factors and other markers for damage/repair. We will collect RNA from our co-culture models and lung slices to study for next generation RNA sequencing (RNASeq). Also, metabolic interaction between extra-pulmonary tissue (including skeletal muscle) and lung cells will be assessed.

WP11 -

Intervention studies for lung repair in lung disease

Once treatable targets have been found in P402, these will be modulated *in vitro* using (repurposed) pharmacological inhibitors and/or CRISPR/(d)CAS.

We will study consequences of damage (cellular stress responses, cell death by immunodetection/flow cytometry) and repair responses using scratch wounding, wounding by electroporation using real-time electric cell-substrate impedance sensing (ECIS) and organoid cultures to study regenerative responses. Pharmacological inhibitors will subsequently be tested *ex vivo* in the precision-cut lung slices.

The second aim is to evaluate soluble mediators (metabolites, growth factors, cytokines) derived from extra-pulmonary tissue sources identified in WP6/7/10 as potential determinants of lung damage and repair responses as candidates for therapeutic intervention. Using the *in vitro* models outlined in WP10, the aberrant secretome of skeletal muscle associated with an unhealthy lifestyle, will be modulated with targeted genetic (causality) and dietary/activity (translational) interventions, followed by evaluation of the protective or stimulatory effects on lung damage or repair.

WP12 -

Initiatives to involve stakeholders and disseminate findings

P402 was set up to help the general society by preventing development of lung disease at an early stage and preventing its progression towards severe disease. Therefore, the involvement of the general society and patients is of great importance. Furthermore, it is a multi-disciplinary project, with many different stakeholders and collaborators. Optimal communication between the different stakeholders requires a communication plan.

The aim of this work package is to initiate multiple initiatives to involve the different stakeholders in P402. We will set up a cohort participation board, we will send newsletters every 6 months, and we will organize a symposium for professionals and one for participants, patients and the general public. This will lead to a strong and active network of participants, researchers, collaborators and the general public, to make use of different visions and to empower the effect that the study will have on the goal to fundamentally improve quality of life, perspectives and societal participation of patients with chronic lung diseases by 2030.

TIMELINES

On the 9th of October 2019, we hope to submit P402 to the PPP allowance call of Health~Holland, an organization that stimulates interdisciplinary R&D in public private partnerships. Does your company have experience in artificial intelligence, big data, bioinformatics, pharmaceutical industry, diagnostics, or another related field, and are you interested in collaborating and investing (both in cash or in kind) in P402? Please let us know, we would be happy to meet you in July or August to discuss opportunities. After that we would like to invite you and the person from your organization responsible for collaborations to one of the meetings we organize to make the collaboration official.

Please visit us at one of our meetings

- Evening of 17 September

Stadskasteel Oudaen, Utrecht, NL (more info to follow)

- Evening of 29 September

ERS meeting Madrid (more info to follow)

Visit the website (www.P402.org) or contact the secretary (nrs@nrs-science.nl) for more information about the project.

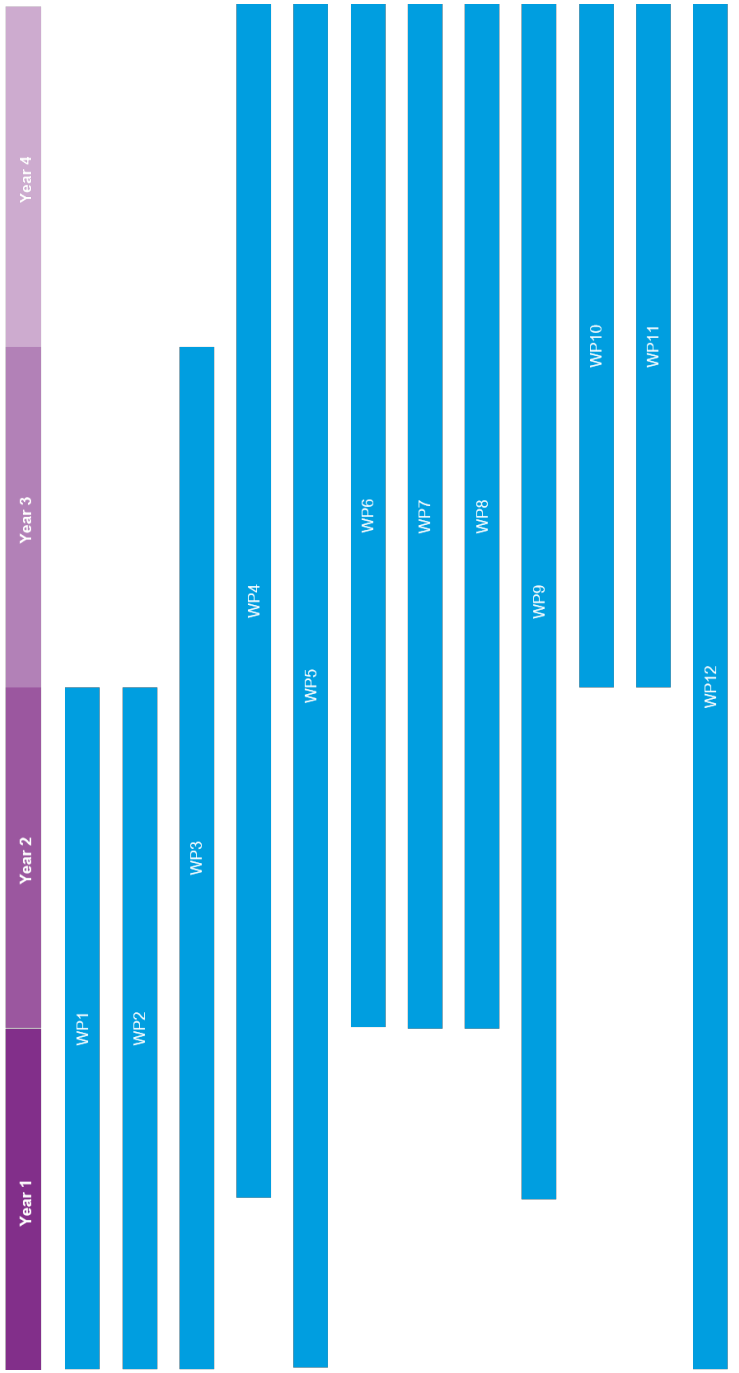

Fig.5 Timelines work packages in P402.

PARTNERS

Amsterdam University Medical Centers (Amsterdam UMC)
University of Amsterdam
Prof. Dr. A.H. Maitland-van der Zee
J.J.M.H. van Bragt, PharmD MSc
VU University
Prof. Dr. H.J. Bogaard

University Medical Center Groningen (UMCG)
Prof. Dr. I.H. Heijink
Dr. S.D. Pouwels

Maastrich University Medical Center (Maastricht UMC+)
Prof. Dr. A. Schols
Dr. R.C.J. Langen
Dr. R. Beijers

University Medical Center Utrecht (UMC Utrecht)
Dr. F. Mohamed Hoesein
Prof. Dr. R. Vermeulen

Utrecht University
Prof. Dr. R. Vermeulen (IRAS)
Dr. G. Downward

Tecknoworks/Breathomix
M. van den Heuvel, MSc

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