

## Summary Groningen Research Institute of Pharmacy SEP research quality assessment (2015-2020)

The Groningen Research Institute of Pharmacy (GRIP) performs multidisciplinary research at the frontiers of knowledge in the pharmaceutical sciences. The institute is part of the Faculty of Science and Engineering (FSE) and its research programmes are embedded in the Groningen University Institute for Drug Exploration (GUIDE), home also to researchers from the medical sciences. The central position of the institute allows it to bridge the gap between the fundamental sciences (e.g. chemistry, biology or physics) and the more applied medical sciences. The research focusses on platform technologies used in the research and development of new drugs and therapies. It is the mission of the institute to perform ground-breaking research in the field of medicinal products that contribute to the discovery and development of innovative therapeutics. Furthermore, the institute wishes to contribute to social and economic wellbeing by exploiting the results of its research, thereby improving the quality of life of patients and stimulating (regional) economic development. Finally, we aim to integrate top-notch research with education in order to ensure the availability of qualified professionals and scientists.

Over the review period, the organisational structure of the institute was streamlined by two mergers of research groups and several shifts of research activities among the research groups. Importantly, one of the mergers has resulted in a new research group, PTEE (*PharmacoTherapy, -Epidemiology and -Economics*) which is now part of the GUIDE programme *PharmacoEpidemiology, -Genetics, -Economics, &-Therapy (PEGET)*. The new research group also strengthens GRIP research on personalized therapy. Over the review period, the number of employees in the institute remained stable. However, in light of the ambitions of the institute and the increasing demands on employees, it should aim to grow significantly in the future.

Over the review period, the total research input remained stable. In spite of this fact, the output increased significantly, especially the number of peer-reviewed publications (+20%) and theses (+30%) increased. Moreover, the quality of the papers could be maintained at a high level or even be somewhat increased. The results clearly show that GRIP's researchers successfully exploit the collaborative potential that stems from the central position of the institute in the University's organisation. Participation in the Molecular Life and Health programme of the FSE and in two multidisciplinary EU funded projects with UMCG researchers, further strengthened the collaborative character of GRIP's research, creating additional links to both science and engineering on the one hand, and the medical sciences on the other.

The institute's research has a high societal impact, which is apparent from an increased interaction with stakeholders such as patient organisations or charities. Furthermore, the high number of patents, the frequent collaboration with industry and funding from industry, the formation of 6 start-up companies and significant royalty income of the institute demonstrates the industrial and economic relevance of GRIP's research. Sources of external funding have become more balanced, though at the same time yearly variations in funding and sources are high.

The institute has adopted a culture of open science and is successfully improving the gender balance in the institute. This last aspect may be helped by the fact that in the near future a significant number (5) of male senior scientists will retire, offering the opportunity to introduce early- to-midterm-career female scientists to the institute's management.

### **Case study scientific quality: World-leader in human precision-cut tissue slices**

Over the past years the institute has become a world-leader in the field of human precision-cut tissue slices (PCTS). Complementary to organoids, the human tissue slices are of immense value in the translational phases of drug research and development. Prof Peter Olinga's group has set-up the logistics to acquire different human surgical excess tissue from normal and diseased human organs in collaboration with UMCG. It allows the evaluation of therapeutic concepts and drug candidates in human (diseased) tissue already in early phases of the R&D process. At this moment at least 6 research groups in GRIP use PCTS in their research. The groups of the Profs. Olinga, Gosens, Melgert, Poelstra, Salvati, Schmidt and Dolga apply slices from a variety of organs, such as liver, kidney, lung, intestines and brain. The in-house availability of the technology forms the basis of a significant number of collaborations both inside and outside the UG/UMCG. The technology plays a central role in many collaborations with UMCG research groups working on topics such as gastro intestinal genetics and immunology (3GI), liver, digestive and metabolic diseases (CLDM), as well as asthma and COPD (GRIAC). Moreover, it resulted in more than 10 collaborations with external academic partners and at least eight industrial collaborations. Furthermore, the availability of the technology was of pivotal importance for several research groups (in GRIP and GUIDE) in their endeavour to become a major player in fibrosis research. A major grant of ZonMW was awarded to Prof Olinga in 2014 (988 k€), with the main aim to develop human organ fibrosis models to conquer the quest for anti-fibrotic compounds as no pharmacological treatment solutions exists for this disease. Absence of relevant animal models is the main reason that no drugs are currently available to treat organ fibrosis. This project has led to some landmark papers ([10.1007/s00204-019-02611-6](https://doi.org/10.1007/s00204-019-02611-6), [10.1152/ajpgi.00209.2019](https://doi.org/10.1152/ajpgi.00209.2019), [10.1016/j.bcp.2019.113633](https://doi.org/10.1016/j.bcp.2019.113633)) and Boehringer models in their drug discovery research. Furthermore, as a follow up of the previous grant, a new grant, also including Boehringer Ingelheim, was awarded by ZonMW in 2017 (625k€) specifically investigating non-alcoholic steatohepatitis (NASH), one of the main diseases of the liver that leads to liver fibrosis and cirrhosis, and primary liver cancer. NASH also dramatically increases the risk of overt type 2 diabetes and cardiovascular morbidity and mortality. Again, the research field is currently hampered by the lack of adequate models, animal or human, that recapitulate the complex interplay between host and environmental factors in the human disease.

Olinga's group succeeded to develop a human ex vivo liver model that mimics the onset of non-alcoholic steatohepatitis (NASH), a subject on which several publications are currently in preparation. These novel models have also been used in collaborations with the pharmaceutical industry (contracts in a total of 630 k€) and the already mentioned academic partners.

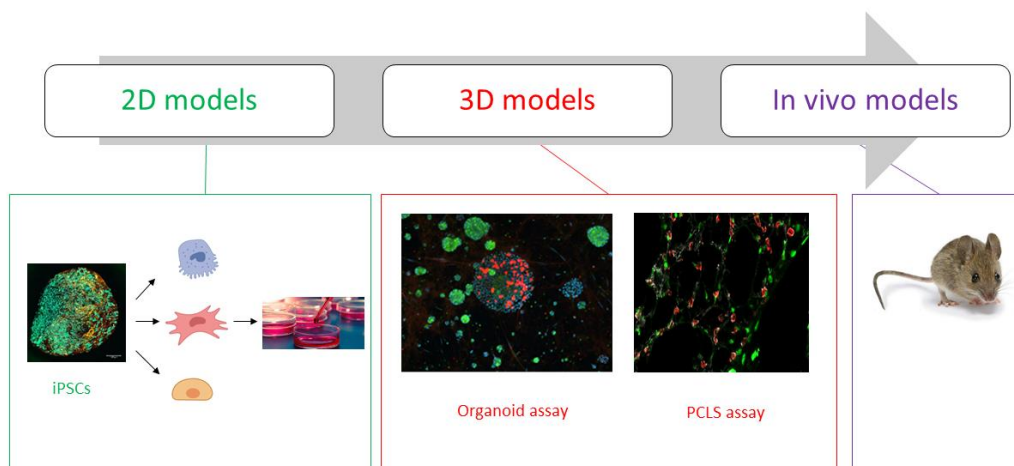
### **Case study societal impact: start-up companies making use of GRIP IP**

The excellent contacts and collaborations with the industry and the establishment of a series (6) of start-up companies remain a stronghold of the institute and they demonstrate the high societal relevance of the institute's research activities. This success is the direct result of the institute's research strategy, which focuses on platform technologies that can be widely used in pharmaceutical R&D. Over the past 6 years, income from industrial contracts was in excess of 25 million Euro, approximately 5 million of which could be invested in unfettered research and support for tenure track researchers. This money allowed us amongst others to have a PharmD programme for awarding PhD positions to excellent master students in Pharmacy and Medical and Pharmaceutical Sciences, and to pay for the fourth year of a PhD in some EU granting schemes.

Aquilo is a start-up company that may serve as a good example of how knowledge can lead to mutual benefit for both the institute and the company. The contract research organisation Aquilo was founded in 2015 as a spin-off company from the department of Molecular Pharmacology at GRIP. Led by Dr. Loes Kistemaker, former PhD candidate and postdoc at GRIP, it is Aquilo's mission to support clients with drug development in respiratory research. Aquilo does this by performing efficacy analyses of existing and novel therapies using pre-clinical disease models, by developing novel models for lung diseases and by acting as a core lab for laboratory analyses in clinical trials. Being a spin-off company from the University of Groningen, Aquilo benefits from close interaction with the GRIP and the University Medical Center Groningen. In turn, GRIP benefits from Aquilo by shared participation in studies, by shared publications and by partnering in grant applications. For example, Aquilo and Prof. Reinoud Gosens from GRIP teamed up in the EU sponsored PROMINENT programme, and in the ZonMW sponsored More Knowledge with Fewer Animals (Meer Kennis met Minder Dieren) programme. These grants allowed us to develop shared human disease modelling technology, including the lung organoid and stem cell-derived neurons, both of which are key to the research programme of Prof. Reinoud Gosens at GRIP and to the portfolio of Aquilo.

Since Aquilo was founded in 2015, it has delivered 49 studies for 20 unique international clients, ranging from small biotech companies to big pharmaceutical companies such as Novartis. Furthermore, Aquilo collaborates

with other Life Science SME's in the region via the Life Cooperative. Aquilo has grown steadily each year since its establishment in 2015. At present, Aquilo employs 5 search staff.



The figure depicts various models, ranging from models based on stem cells (2D), organoids and precision cut tissue slices (3D), and animal models (in vivo), where the 2D and 3D models aim to significantly reduce or ultimately replace the need for animal studies.

### Case study scientific quality: PharmLines

#### *Big data labs to understand and improve pharmacotherapies in the North of the Netherlands*

Since the inception of the Lifelines cohort study, one of the largest population-based studies worldwide, Prof. Eelko Hak aimed to combine this databank with data from our widely researched in-house community pharmacy database IADB.nl. In 2018, he started the PharmLines Initiative with partners from UMCG, Lifelines and colleagues from GRIP to link the databases with the help of the Third Trusted Party National Statistics Netherlands (CBS in Dutch). Currently, 80,000 "Lifeliners" can be tracked with regard to their drug prescriptions. Combined with clinical, demographic, genetic, and, in a smaller group metabolic data, the first unique projects have been set up to support personalized pharmacotherapies. Projects range from anti-infective therapies in immigrants, to feedback on the RIVM guidelines, and to gender disparities in statin therapy effects to fill the knowledge gap between genders, to name a few. All outcomes of the project are widely advertised by Lifelines communications (e.g. Instagram, Facebook, YouTube movies). Importantly, cardiologist Dr. Van der Harst showed that feedback on the presence of risk factors directly improved the uptake of preventive cardiovascular therapies in Lifelines-participants, with an estimated 160+ prevented CVD events in five years; an immediate improvement for patients reported from the PharmLines Initiative.

### Case study scientific quality: Green Production

Chiral  $\gamma$ -aminobutyric acids (GABAs) are widely prescribed as anticonvulsants, antidepressants and for the treatment of neuropathic pain. Because the global population is expected to increase in the coming decades, there is a pressing need to develop and produce pharmaceutically active GABAs and similar drugs for increasing numbers of consumers. This requires the cost-effective synthesis of GABAs and their analogues via greener, more sustainable, and more step-economic synthesis routes, which is of high societal and economic interest.

To address this challenge, the research group of Prof. Gerrit Poelarends intends to manufacture GABAs via multi-enzyme catalysis, using simple and inexpensive precursors, and avoiding (de-)protecting steps and intermediate purifications which would be unavoidable using conventional synthetic chemistry routes. By using a ground-breaking chemomimetic biocatalysis approach that draws from organocatalysis, Poelarends' group successfully developed unique enantioselective enzymes (known as 'Michaelases') for the production of optically pure  $\gamma$ -nitroaldehydes, which are essential in the production of the target GABAs and their precursors from simple and inexpensive starting materials (see Nature Communications and ACS Catalysis). This discovery has resulted in additional international attention for Poelarends' research and has enhanced his standing in the scientific community, which is evident from invitations to chair prestigious biocatalysis

conferences (Biotrans 2019, GRC Biocatalysis 2022, Amine Biocatalysis 2022) and the contribution of review papers to high-ranking journals.

This productive research line, amply funded by an ERC-PoC grant (2016-2017), followed by an NWO-VICI grant (2017-2022), has yielded many publications in high-impact journals, as well as a patent entitled “Means and methods for synthesizing precursors of  $\gamma$ -aminobutyric acid (gaba) analogs”. New collaborations with industrial partners as part of a recently funded H2020-MSCA-ITN project (2021-2025) will further explore these novel enzymes and multistep enzymatic cascades for the greener and more sustainable synthesis of an important class of pharmaceuticals and their precursor. This will enable the further development of these novel enzymatic synthesis routes, bringing the technology closer to industrial application.

This process is currently ongoing through collaborations with several industry partners (e.g. Enzymicals AG, Germany; Prozomix Limited, UK). Enzymicals is interested in validating the technology developed in Poelarends' group in industrially relevant settings by working together on upscaling and demonstration studies, which are essential in optimising this novel technology for selected commercial applications. The collaboration with Prozomix Limited is crucial, affording access to numerous oxido- and nitroreductases with different substrate specificities, thus supporting Poelarends' efforts in developing efficient fully enzymatic cascades for synthesis of GABAs and their precursors (see collaborative paper in ACS Catalysis).

The efficient biosynthesis of GABAs will help bring new generics to the market, using greener, more sustainable, more step-economic, and cost-effective production routes. The rapid synthesis of GABAs and their analogues should also facilitate the development of new pharmaceuticals, e.g. suitably improved replacements for currently prescribed GABAs. Finally, through close contacts with several academic and industrial partners, collaborations are in place to develop new industrial processes based on a C-C bond-forming enzyme platform (H2020-supported CC-TOP project). As part of this international consortium, the building blocks are in place to overcome the hurdles to developing new industrial processes based on biocatalysis and understanding the key practical issues in synthetic biology.

### **Case study societal impact: Pharmaco-economic evaluation methods to support health care policy**

In The Netherlands, new medicines which claim added value compared to existing care, after approval for market access by the EMA, will undergo assessment and appraisal to support decision making concerning coverage. This holds for outpatient medicines, as well as inpatient medicines that are financed via add-ons. Talitha Feenstra supports policy makers in various ways in this process.

As a researcher, she has worked on several projects to improve the methods available for the model-based cost-effectiveness study that is part of the assessment process. This involves studies in real options, uncertainty analysis, and model validation. In 2016, she joined in the committee that worked on the revision of the Dutch guidelines for economic evaluation, which was published by the Dutch Healthcare institute. She co-authored the additional module on uncertainty analysis and contributed to the overall guideline.

She developed a model validation reporting tool (Advise), that is now part of the Dutch- and Australian guidelines for economic evaluation, and has been used by numerous modelers to report on their validation work. From 2013 to 2021 she was a member of the scientific advisory committee (WAR) of the Dutch Healthcare Institute (ZIN) which discusses medicine reimbursement dossiers in monthly meetings and supports the assessment process. She also taught an in-house course for ZIN regarding survival modeling and patient level simulation models.

In 2019 she won a European tender organized by ZIN to develop a blue-print for multiple-use disease models and produce a Diabetes Mellitus model.

In the area of mental health, she has worked with a multidisciplinary team and a consortium consisting of mental healthcare providers, a health insurer and patient representatives next to academia to allow safe and respectful use of observational data in mental health. This project has clinical impact with the I-shared tool, which allows clients and care providers in depression to discuss choice of treatment in a structured and personalized way, using observational data-fed models as well as the individual's own measurements to provide advice concerning what might work well.

As a researcher at RIVM since 2001 she has produced more than 25 reports supporting the Dutch Ministry of Health, mostly concerning healthy lifestyle and non-communicable disease prevention.