7 Public Summary

The Stratingh Institute for Chemistry is a leading research institute in the area of (molecular) chemistry, which is embedded in the Faculty of Science and Engineering of the University of Groningen. Making molecules and studying their properties are the core of the institute's research activities and the molecular component in the research of all Stratingh staff members allows them to speak the same language. As 'the central science' chemistry has an overarching impact on the biological and physical sciences, with our research being uniquely positioned to address many of today's major societal challenges, such as enabling the energy transition, combating diseases, and fighting climate change through developing sustainable processes.

Our overarching mission is to perform excellent research and provide excellent education in molecular and supramolecular chemistry. Specifically, the Stratingh Institute is a discipline-oriented institute that aims to cover the full breadth of molecular chemistry, with research activities being clustered into three general research areas, which are Chemistry of Life, Chemical Conversion, and Chemistry of Materials. Over the evaluation period, the institute has to a large extent realized its strategic aims. The quality and impact of its research is excellent and Stratingh's scientific staff members not only count an active Nobel laureate in their ranks, but also a number of mid-career researchers who have assumed world-leading positions in their respective fields. Additionally, the institute has further strengthened its position by hiring talented young staff members, albeit the low gender balance being an urgent point of improvement. The scientific output of the institute is excellent as is illustrated, among others, by the fact that ~25 % of its papers published in the leading chemistry and general science journals. This culture of focus on quality also translates in high visibility and impact of its publications.

The Stratingh Institute currently also has an excellent funding position through its participation in several large programmes and the successes of its principal investigators in obtaining prestigious personal grants. With respect to societal relevance, the institute's broad research programme is well poised to address important challenges in the areas of energy transition, sustainability, health, and disease. The societal relevance of Stratingh's research is further attested by its involvement in large collaborative programmes with academic and industrial partners, its engagement with society through the national science agenda, and its numerous outreach activities.

Combined, the research results and developments over the evaluation period, the high level of our scientific staff, the quality and (societal) relevance of our research, and the quality of our facilities and support staff allows one to conclude that the Stratingh Institute for Chemistry is as a center of excellence for molecular chemistry in Europe and is well-positioned to retain, or further enhance, this status.

Towards the synthesis of Life 2.0: Self-replicating molecules that metabolize and evolve

FIGURE 1

The synthesis of life requires the functional integration of life's key features: replication, metabolism and compartmentalization. If such system is maintained away from equilibrium and undergoes Darwinian evolution a new synthetic form of life should ensue.



The question how life can emerge from inanimate matter is one of the biggest mysteries in science. It features prominently in the Dutch National Science Agenda (NWA) and has led to many initiatives worldwide directed at the origin of life and the synthesis of a synthetic cell. Prof. Sijbren Otto and his group are tackling this question in a different way, by attempting to synthesize life from completely abiotic components. They discovered a new class of completely synthetic molecules that are capable to catalyze the formation of copies of themselves (self-replication).¹ These self-replicating molecules have unique properties: they assemble into structures that shape catalytically active sites. The self-replicators were found to be highly promiscuous: they catalyze a remarkably large range of different reactions (currently the same replicator systems can catalyze five very different chemical transformations). This includes transformations that result in the production of the precursors of the replicators, amounting to a protometabolism. These systems are the first instances outside biology where replication and metabolism are integrated.^{2.3} The challenge is now to integrate the one remaining key feature of life (compartmentalization; see Figure 1), maintain the systems away from equilibrium and enable Darwinian evolution. Substantial steps in these directions have been made: out-of-equilibrium replication has been achieved mediated by a chemical fuel⁴ and Darwinian evolution, in rudimentary form, has also very recently been implemented.⁵ Thus, the research is now approaching the end game, involving the integration of compartmentalization (first successes have been achieved) and conducting more advanced evolutionary experiments. The origins of Life 2.0 may well be at the Stratingh Institute of the University of Groningen...

FIGURE 2

Outreach YouTube videos available via the Otto group website: www.otto-lab.com



Engagement with the public

The question of "The origin of life on earth and in the universe" was identified as one of the most important current scientific questions by the general public, featuring prominently in the National Science Agenda. This has led to the foundation of the multidisciplinary "Origins Centre". Prof. Otto has been one of the driving forces behind this Centre and currently is, together with Prof. ten Kate (UU), "trekker" of this initiative. The Otto lab is constantly reaching out to the general audience through several videos and animations in which their work is

explained in lay-man terms, made available through different online channels. Otto frequently explains his work in the more traditions printed media, including several substantial articles in the main national newspapers (<u>Volkskrant, NRC, Trouw</u>). Finally, Otto has given many public lectures in person, not only about his group's work, but also about the origin of life in general, to audiences ranging from (primary and secondary) school children, learned societies throughout the country and recently even a "theologisch disputt".

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New catalytic concepts for sustainable synthesis

Catalysis is at the core of chemistry and the current push towards a more sustainable synthesis of organic compounds, both in the laboratory and the chemical and pharmaceutical industry, critically depends on novel catalytic methodologies. Prof. Syuzanna Harutyunyan and her group have built an excellent international reputation for the development of fundamentally new concepts and strategies in catalysis, thereby often defying conventional wisdom ("textbook knowledge") about what is feasible and what not, to achieve unprecedented new chemical transformations.

FIGURE 1

Dearomatization of heteroaromatic compounds into complex chiral optically pure 3D heterocyclic building blocks



One such example is the groundbreaking work on the use of Lewis acid (LA) and Grignard reagent combinations, providing access to medicinally attractive chiral heteroaromatic compounds unobtainable before (published in *Science*¹ and *Nat.Commun.*²). Up until recently, LA and bases were considered incompatible in a reaction. But the group's chemical intuition and drive to make an unlikely solution work gave rise to a unique approach, which is based on the use of two highly reactive classes of reagents of opposing reactivities (Grignards and LA) that, in combination with a chiral copper catalyst, makes possible the efficient and stereoselective conversion of otherwise unreactive molecules (e.g. carboxamides and carboxylic acids, *JACS*³).

This concept was extended by Harutyunyan to another challenging reaction class, i.e. catalytic enantioselective dearomatization. (Hetero)Aromatic compounds are ubiquitous in nature and potentially are important building blocks for drug discovery. The challenge is to dearomatize them, to give the corresponding heterocyclic compounds, which is an energetically uphill and, hence, unfavorable process. Using LA with Grignard reagents and copper enables to dearomatize heteroaromatic compounds into complex chiral optically pure three-dimensional heterocyclic building blocks that otherwise require many synthetic steps (*JACS*⁴ and *Angew. Chem.*⁵).

Another game-changing research by the Harutyunyan group is the recent discovery of catalytic activation of H-P bonds (*JACS*⁶ and *Chemical Sciences*⁷). This enables the modular and cost-efficient synthesis of chiral phosphine ligands, which are the most commonly used chiral ligands in asymmetric catalysis, but their application was always hindered by the often-prohibitive costs of their synthesis.

FIGURE 2

Late-stage modifications of complex drugs molecules using Mn-catalyzed activation of H-P bonds



The key to success of this discovery is in the use of earth-abundant manganese catalysts that allow H-P bond activation to prepare phosphine ligands in more sustainable way. This methodology also provided an enanti-oselective catalytic alternative to the text book Wittig reaction, giving to access the highly demanded complex chiral functionalized Z-alkenes (*Science Advances*⁸), common motives in natural products and drugs, in just 1-2 steps in contrast to previous methodologies that require multi-step synthesis.

These discoveries have created important new opportunities for more sustainable synthesis as well as allow access to previously unattainable compounds, that are of great promise for medicinal chemistry and drug discovery. A fact that is illustrated by the long-standing collaboration with Janssen Pharmaceutica.

These achievements have established prof. Hartyunyan as one of the world's key players in asymmetric catalysis as evidenced by the *Royal Chemical Society Homogeneous Catalysis Award* (2017), by grants including *ERC Consolidator* (2017) and *NWO VICI* (2017), plenary talk invitations, including at '*Bürgenstock*' in 2022 and an invitation from the *American Chemical Society* (ACS) to serve as associate editor for one of the most prominent catalysis journals, *ACS Catalysis* (since 2020).

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Tuberculosis research: Total synthesis to the rescue

Tuberculosis is worldwide the deadliest bacterial infectious disease, whereas an effective vaccine and efficient, low-cost diagnostics are lacking. There is a massive research effort, in particular in the United States, to improve this situation, and over the past twenty years, it has become clear that the cell wall lipids of the bacterium play a crucial, yet poorly understood, role in the host immune response. Reliable immunological studies on the role of these cell wall components of *M. tuberculosis* are only possible using chemically prepared compounds. Natural isolates are not sufficiently pure, as even traces of biological contaminants significantly blur the assay outcome. The group of Prof. Adriaan J. Minnaard has over the years developed synthetic routes to a series of complex glycolipids that are found in the cell wall, found in the cell wall of *Mycobacterium tuberculosis*¹. This work has been supported by NWO TOP-grants and, in an international collaboration, funded by the Gates Foundation "Vaccine Accelerator" program and is currently supported by the Tuberculosis Research Unit of the NIH (USA). The synthetic compounds are available for researchers outside these projects from the so-called Gates Foundation Lipid Bank. His lab, who received an NWO Team Science Award, is the only supplier worldwide.

FIGURE 1 Synthesis of 1-TbAd



In order to actually make these compounds, in the first phase the molecular structure of the compound has to be elucidated, which is carried out by mass spectrometry, and the preparation of fragments and model compounds. Subsequently, the compound is prepared, for which often new synthetic methodology has to be developed. In Figure 1, an impression of the synthesis of tuberculosinyl adenosine (1-TbAd) is presented². The key step is a novel enantioselective and diastereoselective Diels-Alder reaction. It turns out that this compound plays a key role in the survival of tuberculosis bacteria in white blood cells³. This phenomenon had been observed decades ago but remained unexplained until now.

FIGURE 2

Molecular structure of PAT-1



The structure elucidation of cell wall components can be very complicated and mistakes can stay hidden for decades. The important cell wall lipid Penta-Acyl Trehalose (PAT-1) has been subject of intense study in tuberculosis microbiology. In particular its biosynthesis has been unraveled, at least, this was the *communis opinio*. Upon total synthesis of the compound by the Minnaard group, which took 5 years and over 70 synthesis

steps, it turned out the structure of PAT-1 had been incorrectly assigned. The correct structure is provided in this case study and it is clear that the molecules can be so complex that it is difficult to depict them on a page. This structure elucidation answers several of the outstanding issues in the biosynthesis of PAT-1⁴.

Based on these lipids, several of which been prepared on multigram scale, Minnaard became one of the founders of the company TBCertain in 2019. The company has developed a diagnostic device which currently is in its accreditation phase. This valorisation is carried out in collaboration with the UMCG (Tuberculosis Center at Beatrixoord).

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The CBBC's Groningen Hub - investing in the future to greenify chemistry

The Advanced Research Center Chemical Building Blocks Consortium (ARC CBBC) is a collaboration between academia and industry with the goal to develop greener methods for the chemical industry and ultimately target a fully recyclable model with zero net CO_2 emission. This public-private consortium was founded in 2016 in response to a call from the Dutch government to reduce the country's carbon footprint. By collaborating with the R&D departments of key industry players such as AkzoNobel, Shell, Nouryon and BASF, the CBBC allows academic researchers to create an impact right where it matters most. With a budget of > €100 million for the first ten years, and contributions from both top tier academics and industry leaders, the CBBC aims to become a National Center for Innovation and a key player in a more sustainable future.

In the Groningen hub of the CBBC, which is embedded in the Stratingh Institute for Chemistry and involves several of its PIs, the main research lines are Electrochemistry, Flow & Photochemistry and Synthesis of New Building Blocks. The Groningen labs are fitted with state-of-the-art equipment. The hub has further profiled itself by hosting the annual CBBC event in April 2022, aiming at creating a dialogue between academia, industry and society.

FIGURE 1





Coating research is a particular strength of the Groningen CBBC hub. Coatings are everywhere in our daily life: durability and properties of numerous products are enhanced by a layer of paint or varnish. Coatings are based on polymers and resins, which are traditionally derived from petrochemical building blocks. With global demand for coatings increasing yearly, there is an urgent need for the development of more sustainable materials and production methods. The coatings of the future should be derived from renewable resources and synthesized using waste free and low energy conversion, while retaining excellent material properties.

To address this challenge, the group of Prof. Ben L. Feringa in collaboration with AkzoNobel targeted acrylates, a class of high performing polymers. Currently, these acrylates are produced in a two-step, high temperature, process from oil-derived propylene. In their alternative method, Feringa's team starts from a monomer derived from lignocellulose, an abundant biomass source. Using only light, oxygen and a simple catalyst, the monomer is converted to various alkoxybutenolides, cyclic compounds resembling acrylic acid. These monomers can be polymerized using UV light, and the resulting materials display properties comparable to current industry standards.

This research line has been highly productive, yielding publications in *Science Advances*¹ and *Angewandte Chemie*² as well as five patents.³ In addition, it has proven to capture the imagination of the general audience. A large number of articles highlighting this project has appeared on platforms such as <u>NRC Handelsblad</u>, the official website for the Dutch '<u>Klimaatakkoord</u>', <u>C2W</u> and the <u>Reformatorisch Dagblad</u>. Initially the project involved one PhD student, but its success has induced the industrial partner to fund two more PhD positions to

expand this research line. Further collaborations with AkzoNobel will target coatings with improved qualities, and bringing the technology closer to industrial application.

While the initial impulse by the Dutch government has kickstarted this initiative, success stories such as our biobased coatings will ensure the viability of the Groningen CBBC hub. Since the start in 2016, the consortium has already attracted a new industrial partner (Nobian). New funding rounds ensure regular additions to the team, but the future of the CBBC hub extends beyond the original ten-year funding period. Two CBBC-funded tenure track assistant professors (Dr. Michael Lerch and Dr. Sebastian Beil) are embedded in the Stratingh Institute, and will ensure its continued position as a key player in the *greenification* of the chemical industry. And continued investment by the chemical industry could sustain this fruitful collaboration between academia and industry.

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Automation and artificial intelligence in chemistry

One of the new frontiers in chemistry will be automatization and robotization of experiments coupled to AI and machine learning approaches, which promises to revolutionize the development of new reactions and materials.¹ The Stratingh institute has the ambition to be at the forefront of these developments and has made it an integral part of its future research focus. One tangible action of the institute towards achieving this ambition is the new tenure track position "computation aided organic chemistry" for which we attracted Dr. Robert Pollice, who already made important contributions to this field while working with one of the leading groups in the area.²

FIGURE 1

Selection and optimization process that can be improved by automation of certain steps



Since joining the Stratingh Institute in 2022, the Pollice group seeks to implement automatization and machine learning in the realm of organic chemistry to design new, more sustainable and more efficient catalysts. Moreover, Dr. Pollice will introduce AI into the BSc and MSc chemistry education, ensuring that our students will get basic knowledge and expertise in this rapidly emerging technology that will be very important for their future careers.

A second major development towards realizing this ambition is the participation of (part of) the Stratingh Institute in a National Growth Fund (NGF) program called "The revolution of self-thinking molecular systems". <u>The National Growth Fund</u> is an initiative of the Dutch Government, managed by the Ministry of Economic Affairs and Climate Policy. Its mission is to stimulate projects with the highest potential of contributing to the national earning capacity, or in other words, to durable economic growth. Among other things, the National Growth Fund invests in research, development and innovation projects. The NGF "The revolution of self-thinking molecular systems", is an ambitious research program (96 M€ over 7 years, \approx 20 PIs) that aims to automatize chemistry in chemical formulation procedures, with a special focus on formulation in water. It originates from the <u>National research center "functional molecular systems"</u>, a highly successful consortium of groups from the Stratingh Institute, the TU Eindhoven and the Radboud University in Nijmegen working in the area of supramolecular and systems chemistry.

This new initiative is a collaboration between aforementioned research institutions, supplemented with the <u>Fontys University of Applied Sciences</u> and the <u>AMOLF Institute</u>. From the government side, the Ministry of Education, Culture and Science and <u>NWO</u> (the Dutch Research Council) are directly involved. The main drive is the acceleration of discovery: automation reduces the time required to perform repetitive and time-consuming tasks, which goes alongside more effective screening and optimization procedures. As automation also ensures

the consistent application of procedures, it becomes easier to compare results, and further this large amount of reliable data can be fed to algorithms or machine-learning techniques to gain new data-driven insights. For this purpose, a fully automated "robot lab" will be established in Nijmegen, which will work with industry to unravel the complexity of aqueous mixtures, such as paints, adhesives, beverages, vaccines and cosmetics, with the expectation that the formulation process will become more efficient, but also more sustainable and environmentally friendly. At the Stratingh Institute, Prof. Katsonis directs a local hub of the NGF program, including automated setups, where the workflow for the robot lab can be developed and tested. Moreover, a significant number of study cases, in the form of PhD and postdoc projects, will be performed which in the first phase of the program will focus on novel approaches to catalysis and self-assembly, in line with the established research strengths of the institute.

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Stratingh & Sustainability - Our chemistry labs are going green!

To a layman, entering a chemistry lab can be an overwhelming experience. The first impression: a chemistry lab is buzzing! But not necessarily with activity, but rather from the noise that fume hoods, various instruments, and pumps make. The second impression: solvent bottles, waste containers, and plastic consumables everywhere! Not surprisingly, chemistry is thus often regarded as wasteful and energy-consuming, a view that is shared by the majority of chemists. Yet, only a selected few choose to take a closer look, question the status-quo, and implement meaningful improvements.

The Stratingh Institute has a rich history for being at the forefront of sustainability. Reaffirming the drive to enable a sustainable future, the Stratingh Sustainability Committee was founded in January 2022. From the get-go the committee that is composed by PhD students, postdocs and junior staff members, started asking critical questions and set out to change habits that have been engrained in chemists for generations. Why is the fume hood sash left half open, when this increases energy consumption by 50%? Why is the freezer for biological samples set to -80°, when -70° suffices and uses 50% less energy? Why are we using single-use plastic pipettes and weighing boats if we have reusable ones made from glass? Indeed, minor adjustments already would guarantee a more sustainable approach to chemistry research.

Beyond raising awareness for actions that significantly reduce the carbon footprint without impacting the quality or safety of chemical research, the Stratingh Sustainability Committee has taken actions that have led to a cultural change within the institute. For example, a <u>lab guide</u> was developed that lists tips and tricks to improve sustainability practices is now shared with everyone who starts working at the institute. Furthermore, the committee adapted the Laboratory efficiency assessment framework (LEAF) criteria, which was initially developed for biological research, for chemical research. <u>LEAF</u> provides a quantitative measure for a more sustainable approach to research and Stratingh labs were the first within the Faculty of Science and Engineering to receive a bronze or silver accreditation. By now, all labs have received at least a bronze ranking or are in the process of implementing the necessary changes. That the actions of the committee resulted in a real cultural change can be seen from the ideas that are brought up by staff members, students and postdocs and which are discussed openly within the institute and beyond. Examples include, turning off boilers that are not used for hot water or filling half-empty fridges with cooling elements as this lowers the energy consumption.

FIGURE 1

The efforts from the Stratingh Institute are not only recognized by the faculty but also represent a pioneering initiative in the Netherlands



Chemistry labs are going green: 'The drive is in the young generations'

Eoin Gallagher - 21 November 2022

Thomas Freese

People at the Stratingh Institute are working hard to make its laboratories greener. And it has paid off: three chemistry labs were awarded a...







Coinciding with the founding of the Stratingh Sustainability Committee, the faculty initiated the *FSE is going green* programme. These two initiatives quickly joined forces with the Stratingh Sustainability lab being incorporated and taking charge of one of the four faculty-wide working groups, focusing on Green Labs.¹ The pioneering approach of this group and the Stratingh institute's commitment to real change have attracted the attention of <u>news outlets</u> as well as the Dean of the faculty, who visited the institute to congratulate labs for their LEAF bronze accreditation!

Under the leadership of Stratingh members, the *Green Labs* working groups shows no signs of slowing down any time soon. More labs from different institutes have joined LEAF in the quest for a coveted bronze/silver/gold accreditation. This also includes the teaching labs, which will mean that every generation of students that is educated will be taught a more sustainable way to perform chemical research. Having established a flourishing community that is driven by the young generation that wants change, the working group and institute are set on further engraining principles of sustainable research within Stratingh, the university and the Netherlands.

- 1. Stratingh staff members involved in the 'FSE is going green' programme:
 - Green Labs working group: Schaeffer (chair), Freese (faculty-wide LEAF coordinator), de Roo (leading the subgroup on waste), Weber, Böllersen & Pollice (out of 11 members in total)
 - FSE is going green steering committee: Beil, Schaeffer (out of 9 members in total)