CeSAM

Center for Sustainable Antimicrobials

Join us to fight antimicrobial resistance

NOTHING TOPS GRONINGEN

city of talent

CAMPUS GRONINGEN

Tackling the Antimicrobial Challenge

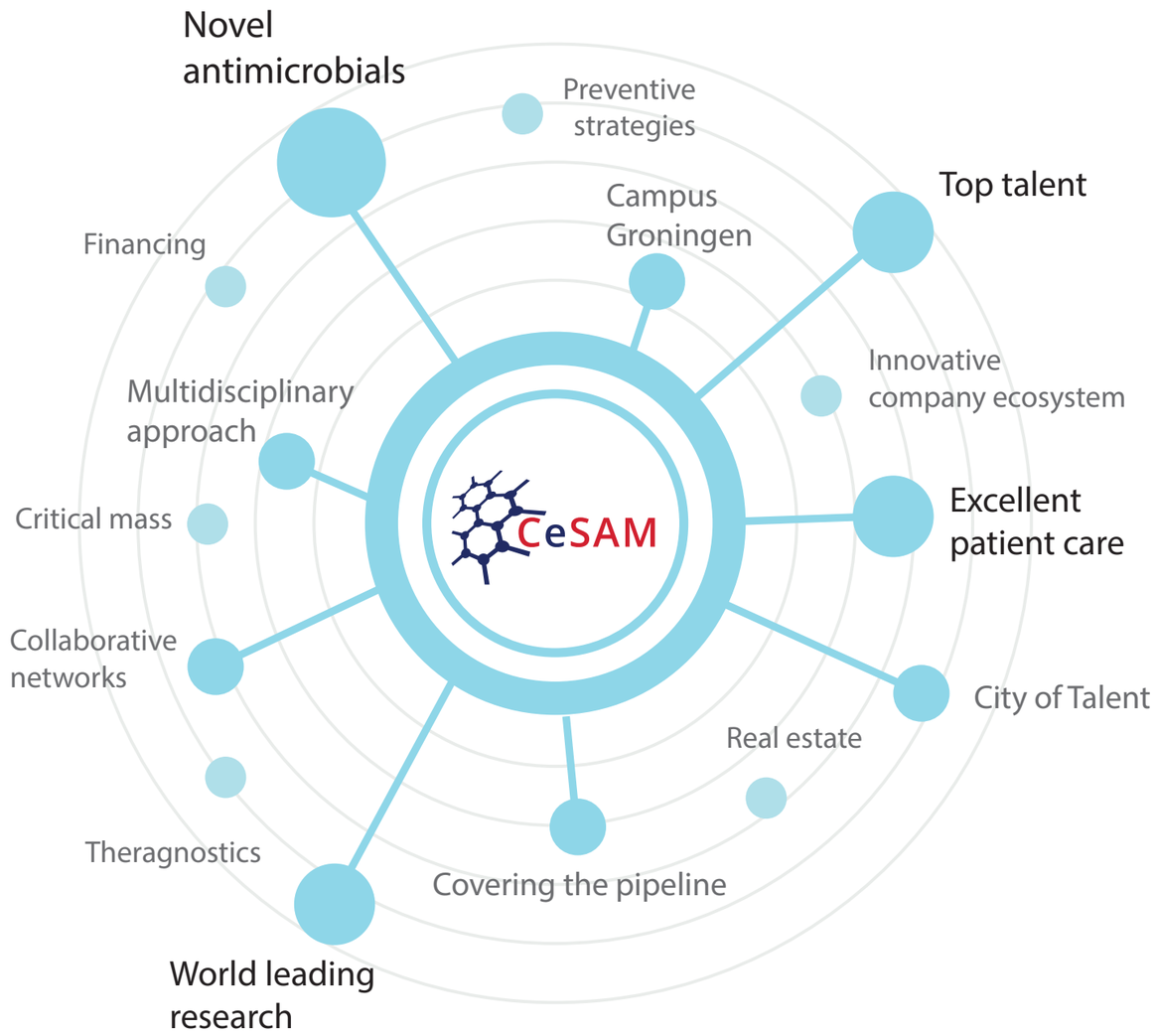
Accelerating antimicrobial development has a very high priority since antimicrobial resistance rapidly increases, with large numbers of annual deaths projected in 2050. The urgency to tackle this emergent societal concern is widely acknowledged, but yet bears on the establishment of integrative academic, public, and private partnerships.

For more than two decades researchers at the University of Groningen and University Medical Centre Groningen have focused on addressing many scientific questions to discover, synthesize, develop and apply antibiotics in combatting infectious diseases.

Now gaining in critical mass and united in the Center for Sustainable Antimicrobials (CeSAM) an extensive interdisciplinary academic hub has been formed within a vibrant innovative environment, Campus Groningen. CeSAM and Campus Groningen are suited to fight antimicrobial resistance, provide novel concepts and solutions to treat infections, and tackle the antimicrobial challenge. If our ambitions appeal to you or your organization, join our campaign.

Prof. dr. Oscar P. Kuipers
Scientific director CeSAM

T: +31 (0)50 3632093
E: o.p.kuipers@rug.nl



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Antimicrobial Resistance

a Growing Threat

Reading guide

1 Antimicrobial Resistance - a Growing Threat
2 Center for Sustainable Antimicrobials (CeSAM)
3 CeSAM - Part of Campus Groningen

1.1 Antimicrobial Resistance - a Global Challenge

Antibiotics are one of the most important therapeutic discoveries in medical history. They enable us to treat once life-threatening bacterial infections and are used in advanced medical interventions. However, the increased and unchecked use of antibiotics leads to resistant bacterial species, causing many antibiotics to become ineffective. The growth of antimicrobial resistance (AMR) risks undoing nearly a century of medical progress and poses a serious threat to both the health and wealth of nations.

As the world population grows older the need for invasive health care increases, leaving more patients susceptible to microbial infections. The situation gets worse by the lack of new antimicrobials that are discovered and developed.

AMR does not keep to national borders and therefore global action is needed. To fight AMR we have to develop new and better antibiotics and improve our diagnostic and therapeutic concepts. In addition, we have to work on improved preventive strategies and find economically affordable ways that agree with a conservative use of current and new antibiotics.

> **Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill,"**
> - Dr. Keiji Fukuda, Assistant Director-General for Health Security, World Health Organisation.

An antibiotic with an 'on' switch

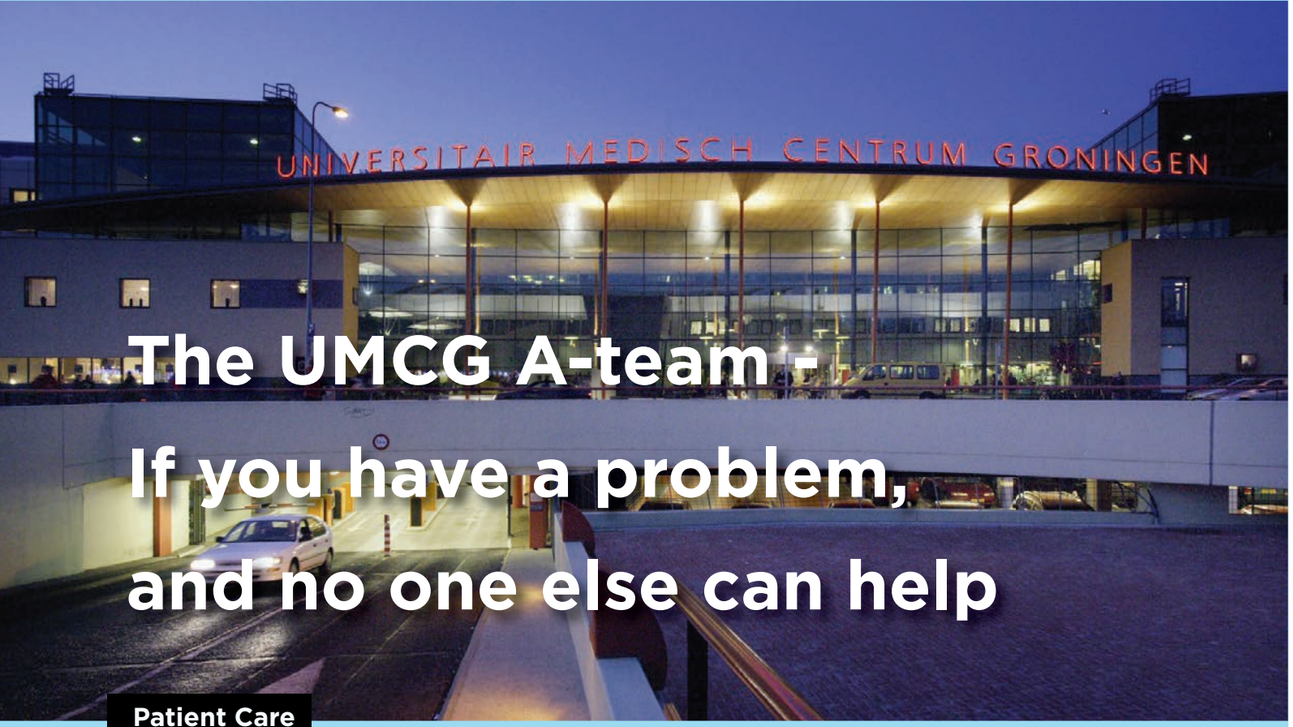
Smart Antimicrobials

Prof. dr. Ben Feringa, 2016 Nobel Prize Laureate in Chemistry

CeSAM scientists have developed an antibiotic whose activity can be controlled using light. It is possible to 'switch on' the antibiotic with light before use, after which it will slowly lose its activity. Just as most medication the compound will eventually end up in the environment. But because of its inactive state it will not promote the development of resistance in free-living bacteria.

In the long run, there are interesting medical applications as well. "You could take an inactive antibiotic for a skin infection and then activate it at the site where it is required. No useful bacteria in the intestines will be killed this way" says Ben Feringa.

Currently the researchers use ultraviolet light to 'switch on' the antibiotic, but if the switch could be tuned to near-infrared light – which can penetrate deep into human tissue – more applications become available. "That is a whole new way of thinking about drug research."



The UMCG A-team - If you have a problem, and no one else can help

Patient Care

Prof. dr. Bhanu Sinha, Medical Microbiology & Infection Prevention

To control the spread of antimicrobial resistance, the Dutch government has made an antimicrobial stewardship team mandatory for every hospital. The main objective of these so-called A-teams is to stimulate appropriate antimicrobial use. The A-team of the University Medical Centre Groningen has a special feature: the face-to-face day 2 case-audit.

The aim of the case-audit is to streamline therapy as early as possible. 48 hours after the start of antimicrobial therapy an A-team member discusses the patient's therapy with the bed-side physician. Together they decide on further treatment based on available diagnostics and local guidelines. In the near future, A-teams will exist in the entire Northern healthcare region connecting best practices and knowledge from all healthcare institutions within the regional AMR-prevention network (www.remis-plus.net).

The A-team approach immediately adds value. A study on A-team effectiveness showed a significant reduction in the number of antimicrobial prescriptions and the average length of hospital stays for patients without severe underlying diseases. "Our A-team appeared to have a major impact on healthcare sustainability and quality of care. Their proactive and preventive approach even led to a positive return on investments due to cost savings ", according to Bhanu Sinha.

1.2 The Dutch One Health Approach

Bacteria are everywhere, in humans, animals and the environment. The overuse of antibiotics in the clinic and the animal industry, and the presence of residual antibiotics in our food and ecosystems all contribute to the development of AMR. Therefore, fighting AMR requires a holistic approach that integrates the stakeholders involved in human, animal and environmental health into a One Health approach.

The Dutch Ministry of Health, Welfare and Sport has embraced the One Health approach, paying special attention to international collaboration and innovation. To boost innovation the government supports the recently established Netherlands Antibiotic Development Platform (NADP), of which the core mission is to bring public and private parties together for the development of new antibiotics and alternative therapies.

The Center for Sustainable Antimicrobials (CeSAM) in Groningen is an important partner in the NADP and contributes to the One Health approach by strongly focusing on the development of new antimicrobials and personalized diagnostic and therapeutic (theragnostic) concepts, while further improving prevention and antimicrobial stewardship.

> **All governments and a large part of the industry see the urgency for developing new antibiotics."**
> - Drs. Edith Schippers, former Dutch Minister of Health, Welfare and Sport in a letter to the Dutch House of Representatives

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Center for Sustainable Antimicrobials

(CeSAM)

2.1 Our AMR Focus

CeSAM is a recognized national centre of expertise, uniting more than 40 internationally renowned scientists. To address the AMR challenge we firmly work together in international networks with governments, knowledge institutes and industrial partners.

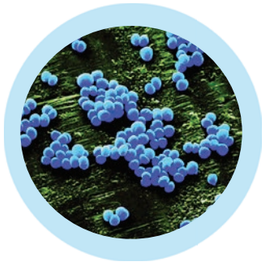
Within CeSAM we focus on two mutually reinforcing goals:

1. The development of novel intelligent antimicrobials to fight AMR
2. The development of innovative personalized theragnostic approaches and preventive strategies

CeSAM facts

- **>40** principal investigators working on AMR and antimicrobials
- **100** fte of CeSAM associated research input
- **5** participating research institutes
- **12** consortia programmes as lead partner
- **4** ERC Advanced Grants

We want to make a difference at the bedside of infected patients. To do so we concentrate on the AMR bacteria that pose the highest bacterial threat, the so-called 'Big 6':



Staphylococcus aureus

Streptococcus pneumoniae

WHO priority pathogens list

Acinetobacter baumannii

Pseudomonas aeruginosa

Enterobacteriaceae

Enterococcus faecium

Staphylococcus aureus

Helicobacter pylori

Campylobacter spp.

Salmonellae

Neisseria gonorrhoeae

Streptococcus pneumoniae

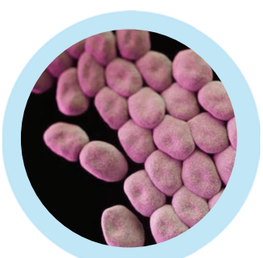
Haemophilus influenzae

Shigella spp.

Mycobacterium tuberculosis

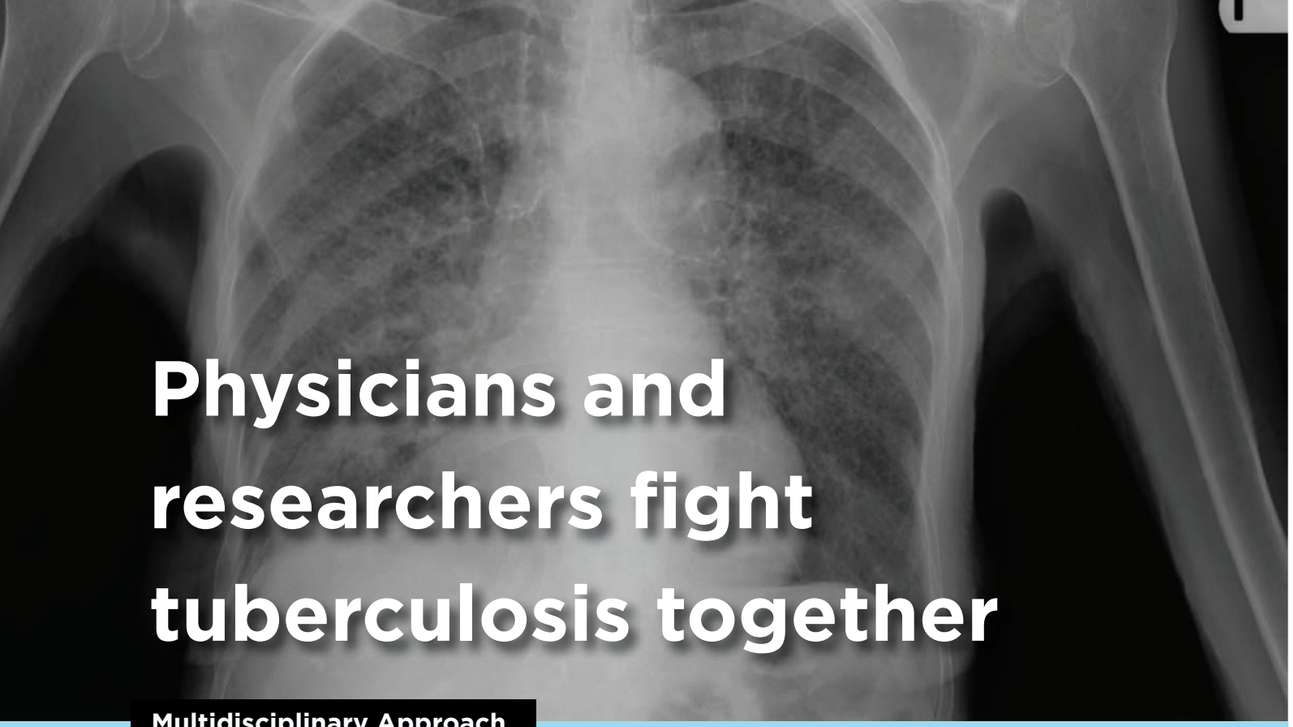
Enterobacteriaceae

Mycobacterium tuberculosis



Acinetobacter baumannii

Pseudomonas aeruginosa



Physicians and researchers fight tuberculosis together

Multidisciplinary Approach

Prof. dr.ir. Adri Minnaard, Director of the Stratingh Institute for Chemistry

The Tuberculosis Center Beatrixoord is state of the art. It has to be to fight the rapid growing number of multidrug resistant tuberculosis (MDR-TB) infections. The treatment team uses a dedicated approach, which includes drug susceptibility testing, fast molecular genetic tests, antibiotic combinations, dosage adjustments, and long-term therapy. And the approach is working. Worldwide, 50% of patients affected with MDR-TB experience treatment failure. The physicians at Beatrixoord are able to bring this number down significantly. No wonder they recently received a "centre of expertise" designation from the Dutch Government.

In addition to excellent clinical care, researchers are looking into new ways to tackle MDR-TB infections. Methods range from targeted proton therapy to pulmonary drug delivery. One approach is a new TB vaccine. Within the responsible international consortium CeSAM, affiliated researchers are in the lead to make the required molecules for such a vaccin. This is where their world class expertise in stereospecific synthesis really shines. As a synthetic chemist, Adri Minnaard is excited about working on an applied project like this. "It shows what an important part synthetic chemistry plays in developing new drugs, including vaccines and antibiotics."

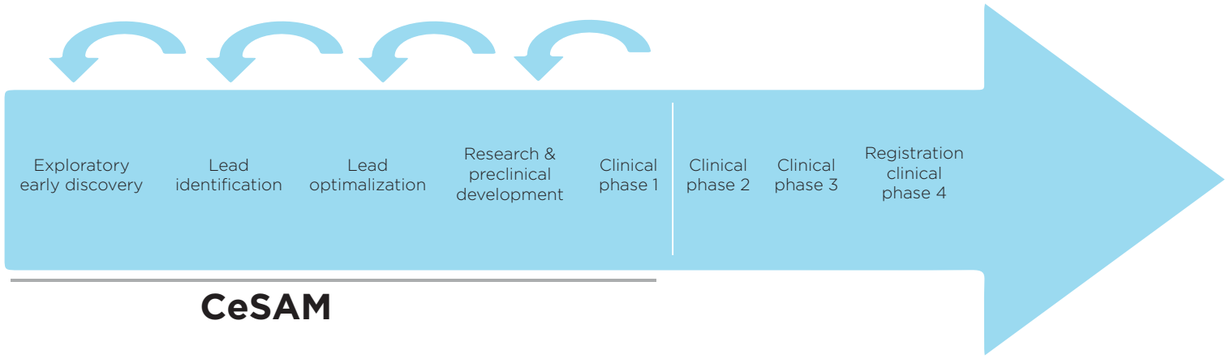
2.2 How We Make a Difference

Working together
At CeSAM we believe in the power of cooperation. We have created a unique and large cluster of AMR expertise by bringing together researchers and clinicians. Together with private and public partners we work on antibiotic development from new compounds to preclinical translational studies, new treatments, patient care, and AMR prevention. We act across disciplinary, institutional and national borders and participate actively in regional, national and international networks.

Multidisciplinary approach
We fight AMR by approaching the challenge from multiple angles. Within CeSAM we actively bring complementary researchers and disciplines together in joint projects. This results in a push and pull model, as fundamental researchers think about better antimicrobial drugs and clinicians approach researchers for input on specific clinical challenges. Decades of experience has led to a substantial critical mass; at present over 40 principal investigators are working on topics related to AMR and antibiotic development.

> **While most universities have two or three research groups working on the development of new antibiotics, we have closer to twenty"**
> - Prof. dr. Oscar Kuipers, Head of Molecular Genetics, CeSAM Scientific Program Director

Covering the entire drug development pipeline
CeSAM brings together, for the first time, the whole spectrum necessary for developing new antimicrobials and theragnostic concepts. By working together with regional Life Science companies CeSAM covers the entire drug development pipeline, from compound discovery and synthesis all the way to the clinical phases. CeSAM uses an iterative stage-gated approach to maximize success and minimize resistance development to newly discovered compounds.



Excellent patient care
CeSAM includes medical microbiologists from the leading University Medical Center for difficult-to-treat AMR bacterial infections. Foreign patients specifically come to this hospital for treatment, often as a last resort. Well-functioning and cost-effective preventive measures ensure patient safety, the careful and limited use of antibiotics, and the containment of AMR species. CeSAM focuses on highly personalized clinical management and rapid tailor-made diagnostic approaches.

Empowering antibiotic development

Spin-off

Dr. Andreas A. Bastian, Co-Founder and CEO at AGILeBiotics B.V.

To fight the continuous emergences of multi-drug resistant bacteria, the society needs constantly novel antibiotics. Until the 1980s twenty new antibiotic classes were discovered, but in the last 40 years only two new classes have been introduced. Now, we are running out of treatment options.

The most successful strategy to bring novel antibiotics to the patient is still the chemical modification of known antibiotic classes to create new variants overcoming bacterial resistance. However, the chemical synthesis of these variants takes time, a lot of time, especially for structurally complex natural product based antibiotic classes.

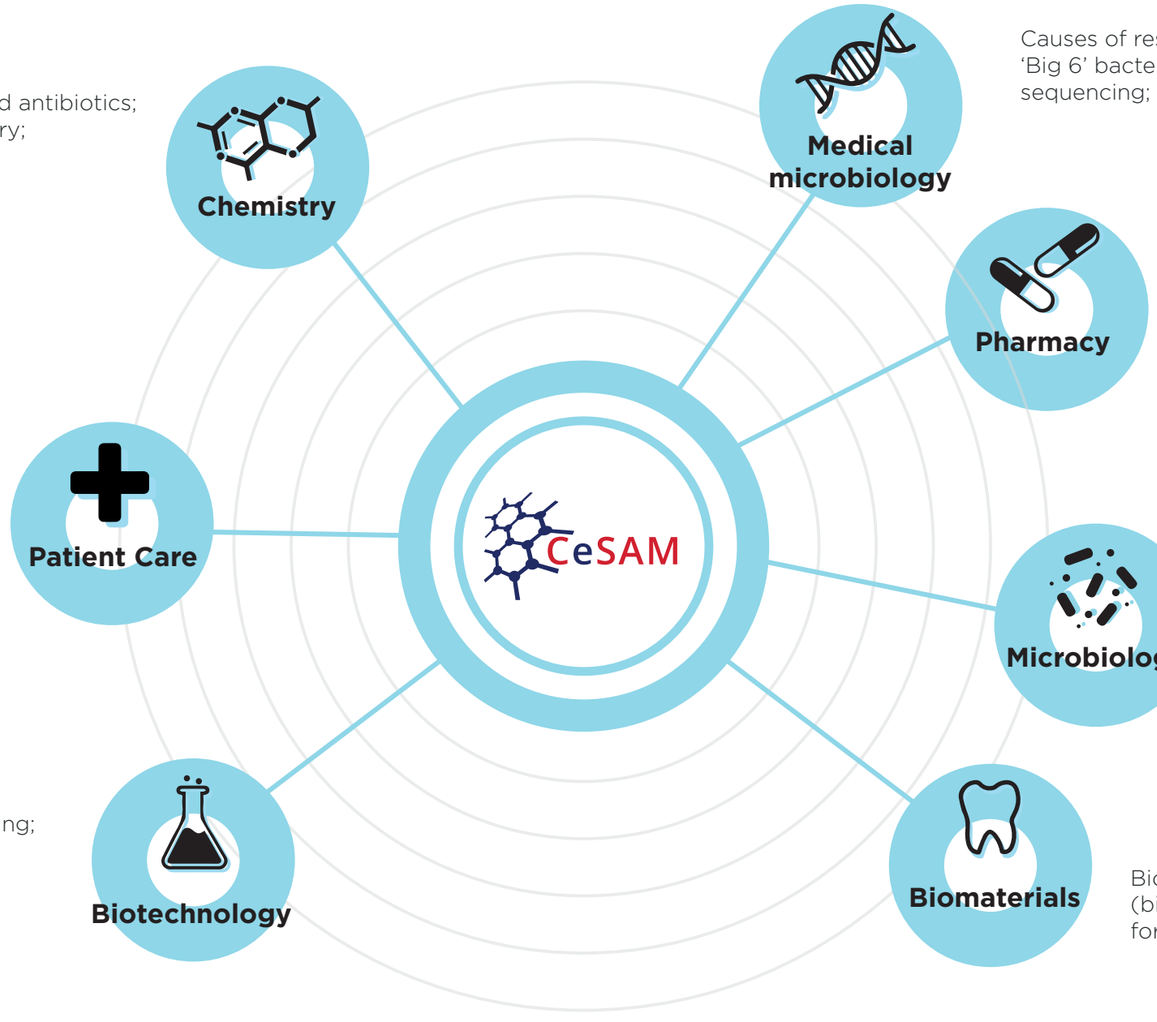
This is where AGILeBiotics comes in. This recent university spin-off is working on modifying the structurally complex aminoglycoside class of antibiotics. By using a known antibiotic class as a template the resulting new variants have less safety issues and potential toxicity, and consequently a higher chance to pass clinical trials and enter the market.

"Our patented technology platform brings one years' worth of synthesis time back to just two days", says Andreas Bastian. Due to this acceleration, the company is able to create a library of novel antibacterial compounds within a few months. This dramatically increases the chances of finding a promising clinical candidate for clinical development.

2.3 World Leading Research

Within CeSAM more than 40 principal investigators and their teams work hard each day to fight AMR. Many of them are world-leading in their field. Their backgrounds range from chemistry, biology, and pharmacy to medical microbiology and direct patient care. By working together their innovative potential has increased drastically.

2016 Nobel Prize for Chemistry, functionalised antibiotics; synthetic chemistry; natural product chemistry; bioconjugates; structure-based design;



Causes of resistance and virulence; characterization of ‘Big 6’ bacteria; resistome-database; whole genome sequencing; pathogen host-interactions

Preclinical and user studies; bioanalytical method development; therapeutic drug monitoring; drug design, delivery, dosage form & formulation, pharmacoeconomics, pulmonary delivery

Prevalence screening; personalised diagnostics; infection prevention; non-invasive analysis; complicated infections

Novel natural antibiotics; high throughput screening; quorum sensing; systems biology; high resolution imaging; secretome analysis

Advanced protein, enzyme and cell engineering; industrial production platforms; membrane engineering; molecular mechanism of AMR; molecular dynamics; cellular nanopores;

Bioengineering of antimicrobial complexes; functionalised (bio)polymers; infection resistant materials; biofilm formation, bacterial adhesion

2.4 Driving Collaborative Networks

The current innovation environment is a result of joining forces. CeSAM is in the position to drive (inter)national networks to share knowledge, tackle challenges, and create added value. The 'triple helix' model of collaboration between companies, governments and knowledge institutes is commonplace. CeSAM researchers are leading partners in a number of interregional clinical care and prevention networks and in national and international networks focused on developing new AMR drugs and therapies.

Regional Prevention Network Northern Netherlands as national example

Since 2013 multiple microbiological laboratories and health care institutes from the Northern Netherlands have joined forces to prevent the spread of AMR. Their main activity is a monthly Regional Microbiological Symposium (REgionale Microbiologisch Infectiologisch Symposium, REMIS) where professionals from all relevant backgrounds share knowledge, receive training, analyse AMR data, and coordinate joint actions. In addition, the affiliated organisations support each other during outbreaks of AMR bacteria. The partners organise prevention, diagnostics, and treatment in a regional and interdisciplinary setting.

Working together on cross-border innovations

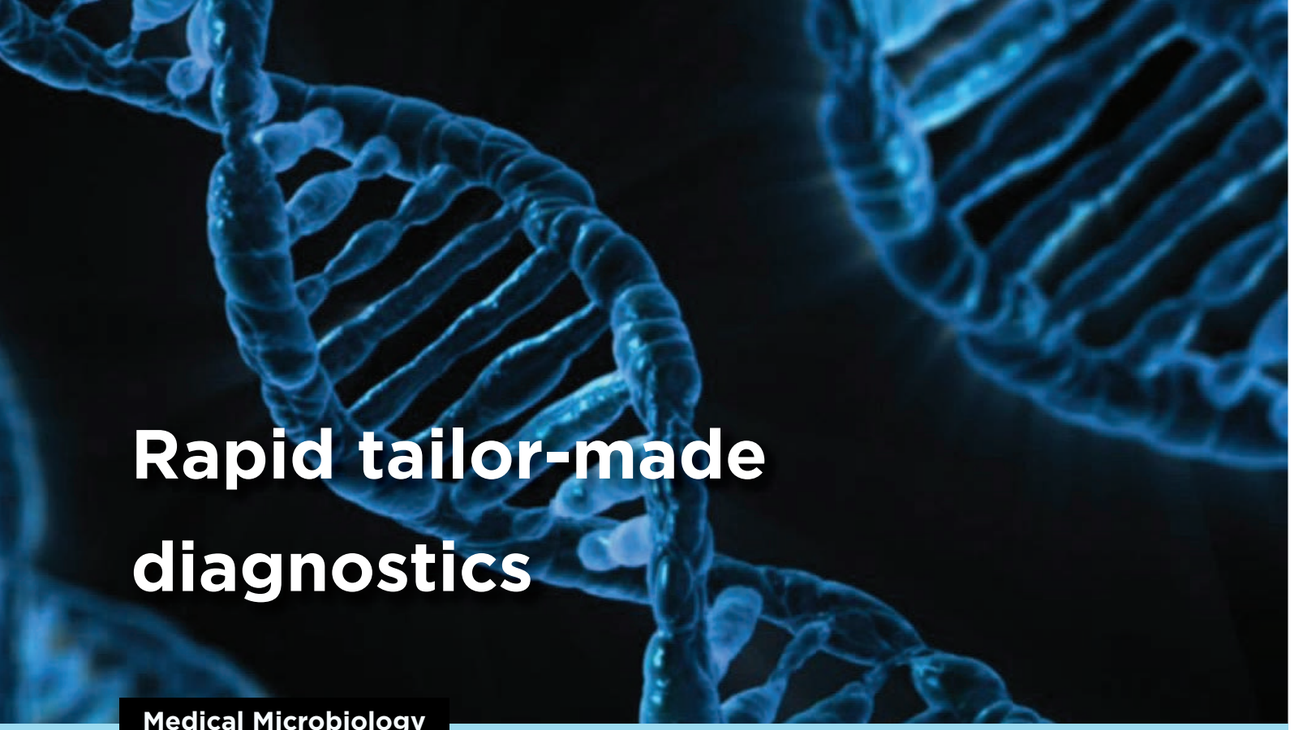
Innovative Companies

Prof. dr. Alex Friedrich, Head of Department of Medical Microbiology

In the new health-i-care project more than 30 Dutch-German innovation consortia work together on new products, technologies and health care services related to infection control, AMR prevention, and personalised diagnostics. Close collaboration between small and medium sized enterprises and health care institutes from both countries ensures smooth testing of prototypes and enables innovators to take into account the rapidly changing health care market.

The University Medical Center Groningen, a CeSAM partner, has the lead in the health-i-care project. Project leader Alex Friedrich says that "For the first time we have an active forum with professionals from companies, health care, and science. Here the right people from both countries and from different sectors meet. This ensures that what is being developed can actually be implemented".

Companies are the driving force behind the innovations, which range from diagnostic devices to digital solutions and medical technologies to new therapies. Some examples are game-based learning tools, invisible gloves, chloride-based disinfectants, and self-cleaning nanocoatings. During biannual symposia and separate investor meetings the companies present their innovations.



Rapid tailor-made diagnostics

Medical Microbiology

Dr. John Rossen, Head of Molecular Unit Medical Microbiology

Bacteria species consist of multiple comparable strains, each containing their own unique DNA fingerprint. John Rossen and his colleagues have been busy mapping the exact genetic composition of different pathogenic strains. The result is an immense database. John Rossen explains that "By comparing new bacterial strains to those that we have already mapped we can find their genetic differences and similarities. We use this knowledge to quickly identify bacteria and optimize countermeasures and treatment accordingly."

Armed with this genetic knowledge, CeSAM affiliated researchers are able to create tailor-made diagnostic tests for specific bacterial species and strains. As a result the diagnostic timeframe has been reduced from the standard 5 days down to 2. This time gain is important for the treatment of infected patients, but also for the prevention of new infections.

"By distributing the tailor-made diagnostic test to other hospitals in the region we quickly screen patients for a specific bacterial strain, hereby containing their spread, preventing future infections and saving costs."

2.5 Excellent Patient Care

The University Medical Center affiliated to CeSAM works every day on achieving a single common goal: building the future of health. And always with the patient as central point of focus. To achieve this we combine research with clinical innovations and excellent patient care. In the fight against AMR this is reflected in the role of the medical microbiologists. By combining diagnostics, treatment, clinical research and prevention we are able to give the best care to each specific patient.

To ensure excellent patient care a continuous antimicrobial stewardship programme is active in the clinic. Run by a multidisciplinary team, this programme promotes the reserved and appropriate use of antimicrobials to improve patient care, reduce AMR, and decrease the spread of AMR infections. This is supplemented with microbiological, epidemiological and clinical surveillance.

Dedicated analysts in specialised on-site laboratories use both traditional techniques and modern sequencing approaches on a multitude of patient samples. To determine potential AMR, results are compared to the largest pathogenic strain collection in the world, counting over 6,000 AMR strains.

CeSAM

Part of Campus Groningen

3

3.1 Campus Groningen - Driver of Innovation

CeSAM is part of Campus Groningen, a meeting place for students, entrepreneurs and researchers. Campus Groningen is the Northern Netherlands' driver of innovation. Its partners focus on the societal impact fields of Healthy Ageing, Sustainable Society, and Energy, with smart data and advanced materials as important enablers.

At Campus Groningen, entrepreneurs, knowledge institutes, local government and investors work together on innovations. The central aim is to link research with entrepreneurship, and hereby create impact for society. Campus Groningen provides an ideal environment by combining forefront knowledge and research with access to an ecosystem of innovative life science companies, high quality education, top talent, state-of-the-art facilities, financing resources and space for development.

181
Companies

44%
Highly educated inhabitants

> 19,000
Jobs

72
Shanghai Ranking UG

3,300
FTE academic staff

>55,000
Students

Fluorescent antibiotics detect implant infections

Theragnostics

Prof. dr. Jan Maarten van Dijl, Medical Microbiology
Prof. dr. Gooitzen van Dam, Surgical Oncology

A bacterial infection of an implant is the worst and most feared complication when implanting a prosthesis, such as an artificial knee or hip. Around five per cent of patients receiving a prosthetic bone implant get such an infection. These infections are difficult to detect and treat, and often result in replacement of the implant. Fast, non-invasive diagnostic techniques are therefore crucial for the patient's wellbeing and to prevent additional health care costs.

The team led by Jan Maarten van Dijl and Gooitzen van Dam has found an innovative solution for this problem. By injecting an infrared-fluorescent dye linked to the antibiotic vancomycin they were able to visualize *staphylococcus aureus* bacteria on an implanted prosthesis via a special infrared camera. Such an approach could allow the detection of bacterial infections at an early stage, even before the formation of a biofilm on the implant makes the bacteria unreachable for antibiotic treatment.

Breaking the biofilm

Biomedical Engineering

Prof. dr. ir. Henk Busscher, Head of Department of Biomedical Engineering

As early as the 17th century, Dutch scientist Antoni van Leeuwenhoek wrote about the inability of antimicrobials to penetrate infectious biofilms, saying that "the vinegar I use to clean my teeth only kills the creatures on the surface, but does not reach the creatures living in the deeper layers". Biofilms consist of multiple layers of bacteria embedded in a protective matrix, which can form anywhere in the body and can cause an infection.

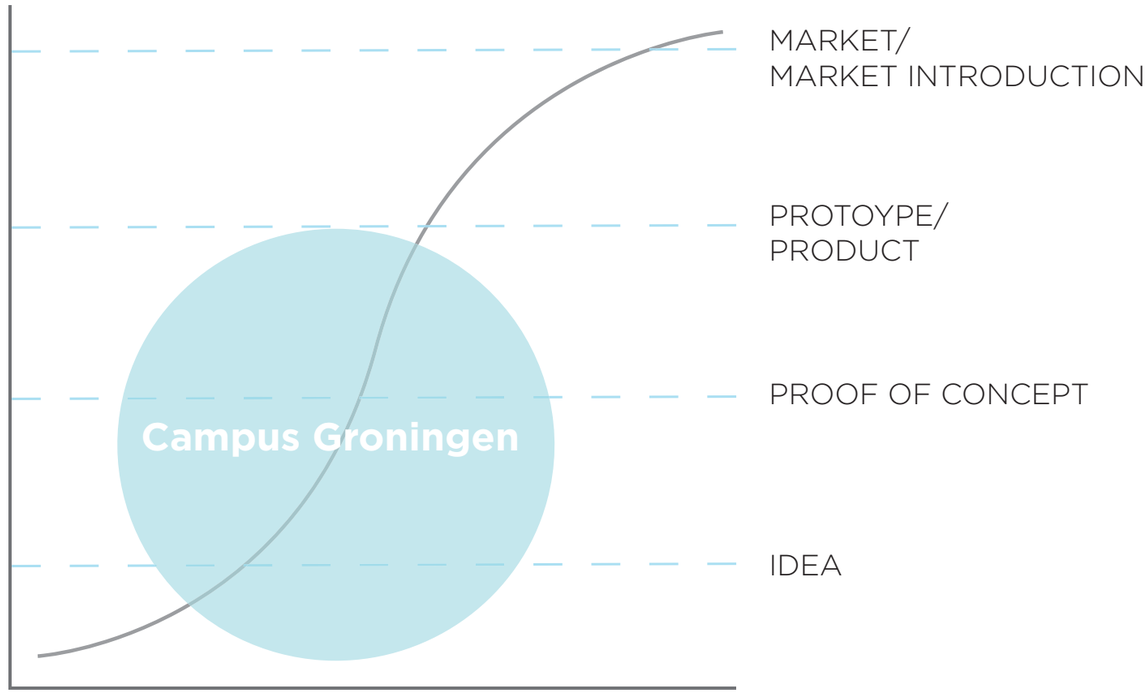
Henk Busscher, scientific director of Biomaterial Development Center, has developed a method for packaging antimicrobials so that they can penetrate deep into a bacterial biofilm. The packaging, which is made of micelles, is able to find its own way into an infection and penetrate the biofilm. The bacteria themselves open the packaging, releasing the antimicrobial and sealing their own fate to cure an infection.

In recent years little progress has been made in making biofilms more susceptible to antimicrobial treatment. This new approach represents a huge step forward in developing alternatives to the currently used methods for administering antimicrobials. The next step is to test the method in vivo before looking towards potential clinical trials.

The characteristics of Campus Groningen

- **Excellent knowledge,** easily accessible
- **Cooperative attitude,** let's roll up our sleeves together
- **Entrepreneurial mentality,** we do what we say
- **An environment** designed as a Living Lab
- **Transparency** as the key to innovation

Campus Groningen's strength is in the initial phases of the innovation chain. Due to the optimal mix of knowledge institutes, small and medium-sized life sciences companies and a large University Medical Center, new ideas smoothly mature from lab-scale to real life. Extensive experience with public-private partnerships and the management of intellectual property speeds up the innovation process. The emphasis on open innovation, collaboration and knowledge sharing ensures an extensive ecosystem of spin-offs and start-ups.



3.2 Groningen - City of Talent

Imagine finding yourself in a city with 200,000 inhabitants, of which half is younger than 35 years, with all its associated talent, creativity, innovation and industrious bustle. No less than 44% of all inhabitants have a higher education, which is 10% more than the national average.

What's more, this vibrant city is also one of the happiest cities in Europe. This is not just because of excellent facilities, infrastructure and living conditions, it is also a matter of giving space to those who are talented, to do what they are good at.

Groningen is crammed with start-ups and scale-ups that are afforded all the room and opportunities they need, thanks to effective partnerships between public authorities, the business community, Hanze University of Applied Sciences, University of Groningen, University Medical Center Groningen and other initiatives.

This is proving successful: the Deloitte Fast50, a ranking of fastest growing technology companies, consists for 10% of businesses from Groningen, whilst the city only contains 1,2% of the Dutch population. This makes Groningen a **City of Talent**.

> **There is a good business climate in Groningen. And that is not only attributable to the university, but also to the companies and entrepreneurs that work so well in this town"**
> - Drs. Neelie Kroes, ambassador StartUp Delta

*This list of companies is not exhaustive

3.3 An Entrepreneurial Life Science Ecosystem

Campus Groningen and the surrounding Northern region contains a booming life science ecosystem. An ecosystem that covers the entire drug discovery, synthesis & development pipeline, from idea generation all the way to clinical trials. The companies are diverse and include start-ups, university spin-offs, innovative biotechnology and pharmaceutical companies, equipment manufacturing companies, and international contract research organisations, all focused on drug development, drug delivery and/or clinical testing.

LIFE Cooperative
Northern Netherlands small and medium enterprises (SMEs) active in the fields of Life Science and Medical Technology have joined forces within the LIFE Cooperative. The aim is to develop solutions for shared challenges and achieve a twenty to thirty percent growth in the sector. Together, the cooperative SMEs established research-, development- and supply-chains that result in efficient innovations and a stronger competitive position.

Metabolic pathway engineering for antibiotic production

Biotechnology

Prof. dr. Arnold Driessen, Molecular Microbiology

Finding new antibiotics is important, but to cure patients the antibiotics must be produced in economic quantities. This up scaling of production is often a bottleneck. Over the years CeSAM associated researchers have gathered extensive biotechnological experience in this area, partly through standing relationships with private partners. To further improve the production of antibiotics CeSAM researchers use CRISPR-CAS technology for targeted genome editing of industrial fungi.

In addition to improving production, the CRISPR-CAS technology is also a tool for antibiotic discovery. CeSAM researchers attempt to find new antibiotics by activating sleeping gene clusters in fungi. These sleeping clusters produce secondary metabolites, which are normally only produced by the fungus under specific circumstances.

Arnold Driessen explains that “each species of fungi produces on average 40 secondary metabolites, some of which are antibiotics. Targeted metabolic pathway engineering helps us find them.” As there are a lot of fungal species, this means a high number of undiscovered antibiotics for researchers to find.

3.4 Top Talent

For more than 400 years, the Northern Netherlands is known as a source of first-rate knowledge and expertise: Nobel Prize Laureates, the first female teacher, the first female physician, the first Dutch astronaut, and the first president of the European Central bank were all trained in the Northern Netherlands.

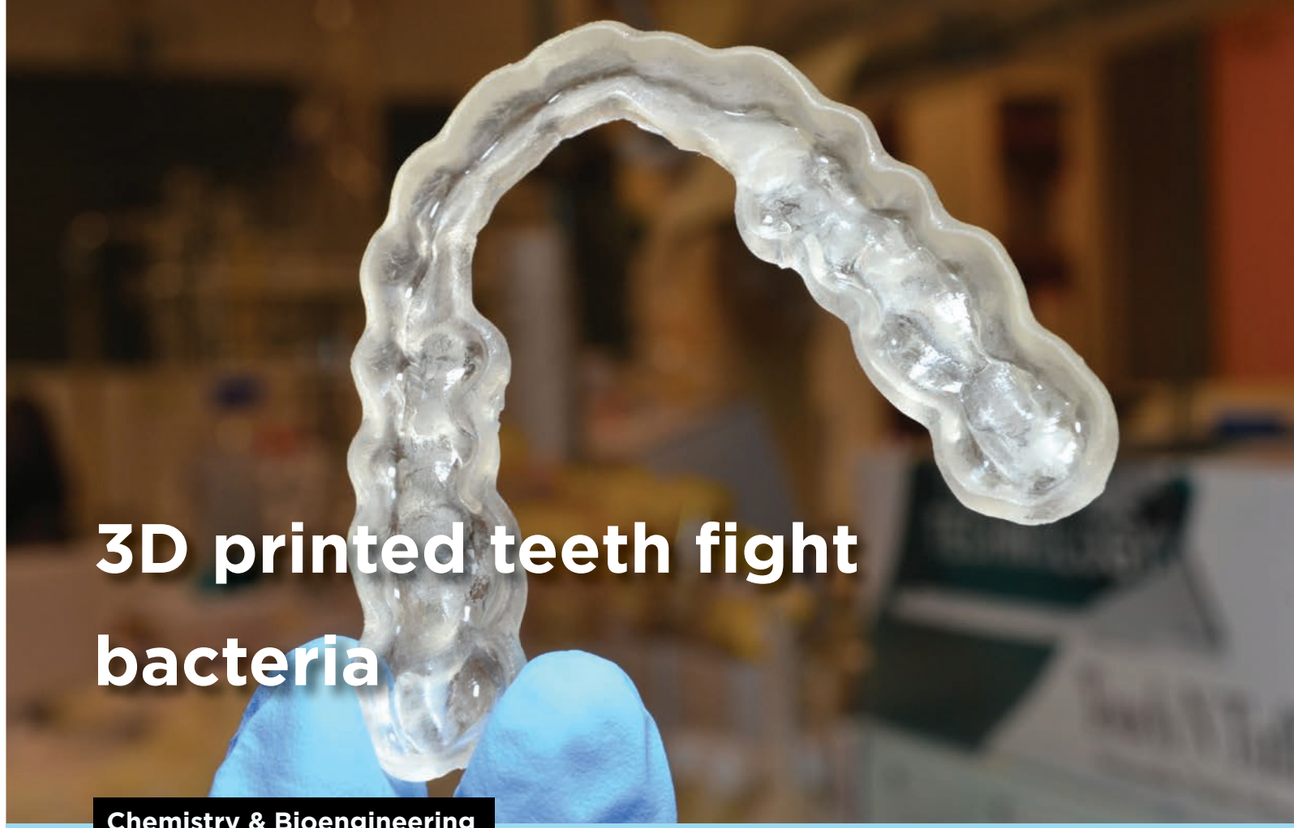
CeSAM educates the next generation of AMR professionals on Campus Groningen. Master and PhD students and postdoctoral fellows work on developing novel tailor-made antimicrobials and delivery strategies, under the supervision of top scientists. They focus on the entire pipeline, from discovery and synthesis to clinical application. Additionally, many medicine and PhD students concentrate on AMR-related hospital care, infection prevention, and improved diagnostics.

AMR education at Campus Groningen is fully integrated in a broad range of disciplinary educational programmes, at multiple levels. Talented students can enrol in special excellence programmes such as Research Masters and extracurricular Honours Programmes. The excellent curriculum combined with the open research environment attracts motivated (inter)national top talent. This provides organisations with opportunities to recruit motivated and well-educated top talent.

> **The colleagues, the unrivalled facilities at the (...) Campus and the opportunities available here make that we have a strong competitive edge across the world.”**
> - Prof. dr. Ben Feringa, Nobel prize winner for Chemistry, 2016.

At Campus Groningen businesses can come into direct contact with students by actively contributing to educational programmes. There are options to provide guest lectures, bring in case assignments, offer research internships, or support theses. Employees can also continue their learning journey by following relevant courses or taking part in open activities, such as lectures and conferences. These options for interaction create a win-win situation for businesses, students and institutes.

Educational institute	Department	Education	Education programmes related to life science
Noorderpoort	School for Laboratory & Process Engineering	Secondary vocational education	Laboratory technician, Biological Analyst, Chemical Analyst, Process Operator, Process Engineering
Hanze University of Applied Sciences Groningen	Institute for Life Sciences & Technology	Higher professional education	(Bio)informatics, Chemistry & Chemical Technology, Biology & Medical Laboratory Research, Medical Diagnostics
University of Groningen	Faculty of Science and Engineering	Scientific education	Biology, Biomedical Engineering, Biomedical Sciences, Biomolecular Sciences, Chemistry, Chemical Engineering, Molecular Biology and Biotechnology, Nanoscience, High Tech Systems & Materials, Medical and Pharmaceutical Drug Innovation, Clinical and Psychosocial Epidemiology, Medicine, Medical Pharmaceutical Sciences, Pharmacy
	Research institutes	PhD	Individual doctoral thesis



3D printed teeth fight bacteria

Chemistry & Bioengineering

Prof. Andreas Herrmann, Polymer Chemistry & Bioengineering

Material scientist Andreas Herrmann, orthodontist Yijin Ren, and their colleagues have made 3D printed antimicrobial teeth. The major breakthrough was the creation of a 3D printing substrate which kills bacteria on contact. To create the substrate the team took monomers which are routinely used in dentistry, and set out to add quaternary ammonium ions. These positively charged molecules interact with the negatively charged bacterial membrane and puncture a hole in it, killing the microbes.

“The trick in our approach was to get the mixture right to enable 3D printing and minimize any leakage of the antimicrobial ammonium ions. You don’t want these ions to enter the mouth and thus the intestines, where they could kill off healthy gut microbes”, Andreas Herrmann explains.

This innovation could solve a major problem in dentistry, as bacterial colonisation of dental implants causes billions of dollars in costs each year. But the process of 3D printed antimicrobial medical devices has even wider applications. “All implants in medicine suffer from biofilm formation, so giving them antibacterial properties would be beneficial.”

3.5 State-of-the-art Facilities

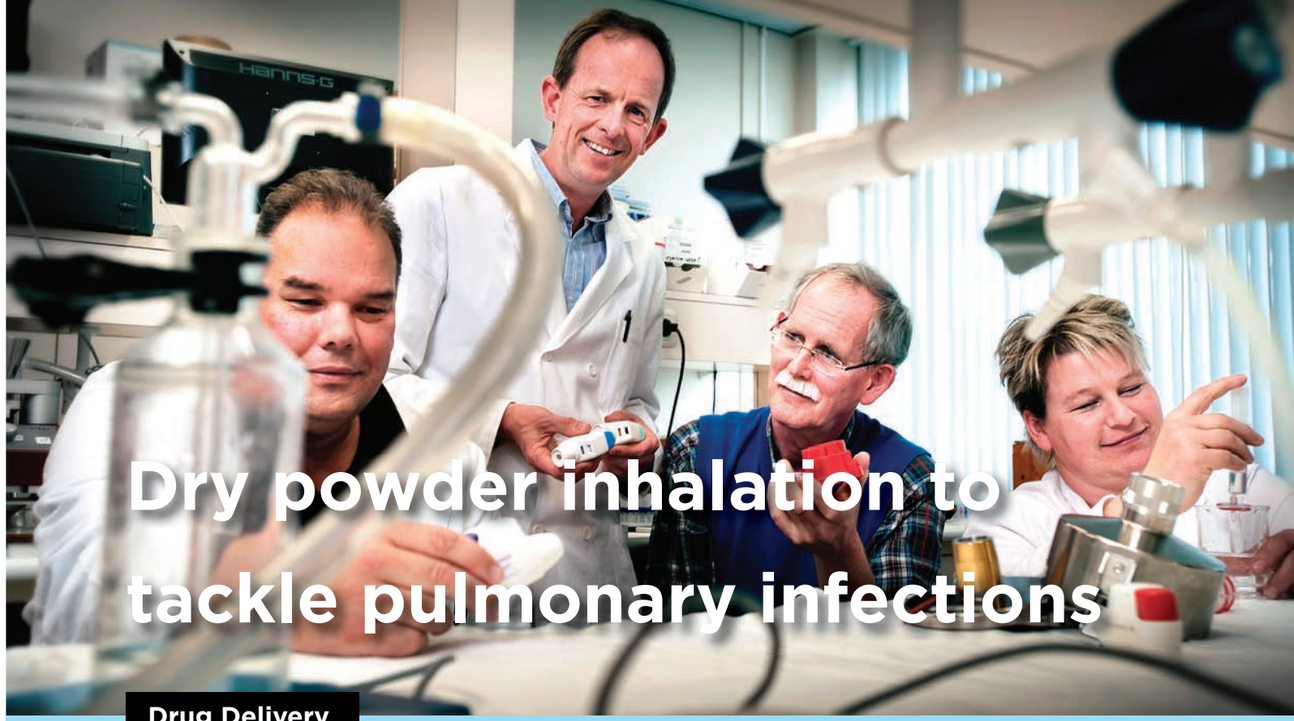
We believe in the power of collaboration to find innovative solutions. By providing access to state-of-the-art research facilities we are able to work together with our partners on joint projects.

Access to key technologies
CeSAM has access to an extended range of research techniques and state-of-the-art equipment. Examples are modern proteomics, metabolomics and genomics technologies; advanced and high resolution imaging; chemical synthesis and characterisation; high-power computational approaches; protein, metabolic and cell engineering methods; and biotechnological expertise. Through collaborations, partners can gain access to both the available equipment and knowledge.

Clinical trial facilities
A dedicated clinical trial phase I facility for studying novel antibiotics will be established in the near future. The current Trial Coordination Center (TCC) provides full-service clinical project management. The TCC has extensive experience in coordinating international single- and multicentre clinical studies . In addition, the contract research organisations QPS Netherlands and PRA Health Sciences have dedicated clinical pharmacology units located on Campus Groningen.

Clinical pharmacy and pharmaceutical services
A pharmacy that is fully equipped to support clinical studies is available and an advanced infrastructure for bioanalysis, therapeutic drug monitoring, and PK/PD modelling has been running for over a decade. Specific experience is present to optimize the use of antibiotics in different infectious diseases, such as tuberculosis. All activities are supervised by scientists that are highly experienced in the field.

GMP Manufacturing Unit
The GMP unit is a multi-purpose facility set-up for the development and GMP manufacturing of biologicals and Advanced Therapy Medicinal Products for (pre)clinical manufacturing and phase I/II clinical trials.



Dry powder inhalation to tackle pulmonary infections

Drug Delivery

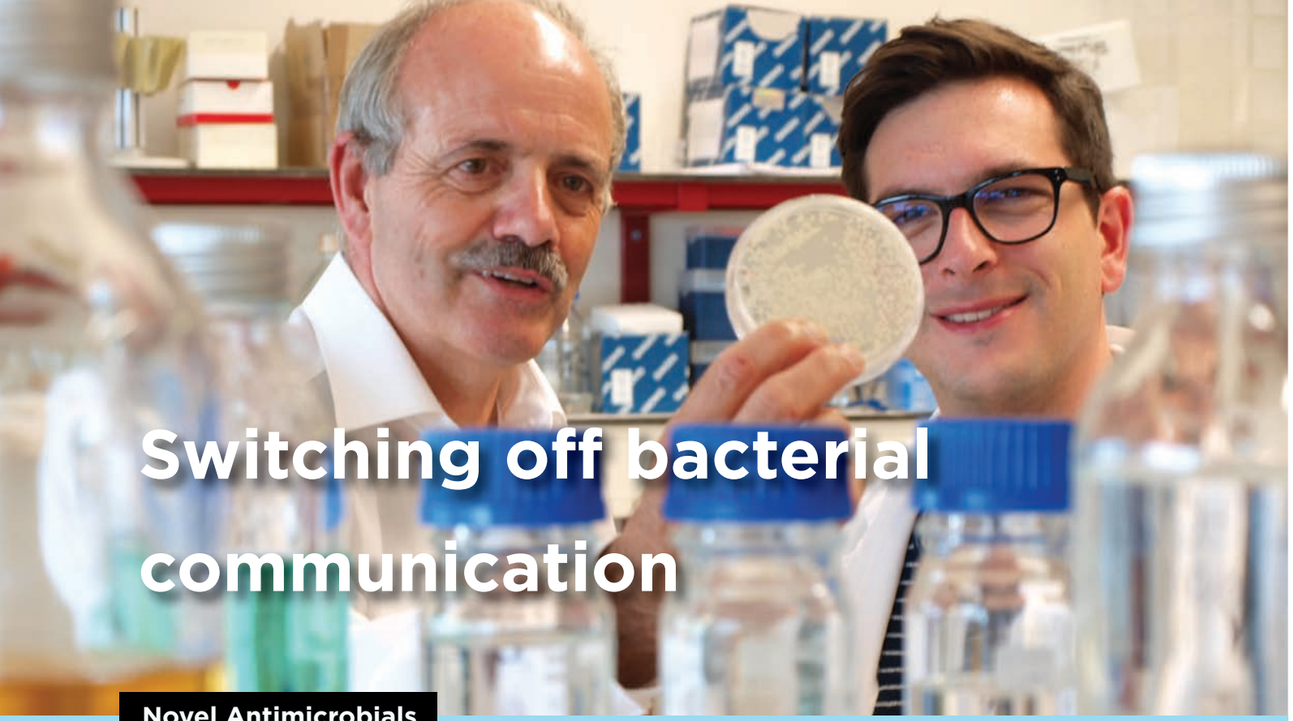
Prof. dr. Erik Frijlink, Director of the Groningen Research Institute of Pharmacy

Treating lung diseases such as tuberculosis and cystic fibrosis is notoriously difficult, especially when (multi) drug resistant bacteria are involved. The problem is that via conventional drug delivery routes only a small portion of the administered antibiotics penetrates into the lungs. The result is a partial removal of the pathogenic bacteria, while promoting antimicrobial resistance in those that survive. To overcome this problem CeSAM-affiliated researchers from the Pharmaceutical Technology group have developed an innovative dry powder inhaler platform with inhalers such as the Twincer® and Cyclops®.

Twincer® is ideal for administering high doses of antimicrobial drugs to the respiratory tract. In addition, its disposable character, short administration time, minimal environmental exposure, and long shelf life make it cost efficient and easy to handle. An initial pilot study with colistin (a "last resort" antibiotic) administered to cystic fibrosis patients resulted in excellent clinical data and enthusiastic reactions from the patients.

The Pharmaceutical Technology group has ample experience in the development of dry powder inhalers with the Novolizer® and Genuair® inhalers already on the market. The success of the Twincer® and Cyclops® platform turned the attention of CeSAM's dry powder inhalation experts to the pulmonary delivery of antibiotics. "The Twincer® platform could become an essential toolin the future treatment of pulmonary infections with resistant bacteria", says Erik Frijlink.

Photo: Stijntje de Olde



Switching off bacterial communication

Novel Antimicrobials

Prof. dr. Wim Quax, Head of Department Chemical & Pharmaceutical Biology

Although bacteria are simple single-celled organisms, they are capable of communicating with each other through a process called 'quorum sensing'. By exchanging hormone-like signal molecules groups of bacteria can synchronize their behaviour and respond to their environment. The result can be the simultaneous production of certain toxins, hereby overwhelming a human's immune system. Furthermore, quorum sensing allows groups of bacteria to coordinate the formation of impenetrable biofilms, rendering them resistant towards antibiotic treatment.

"In our search for novel antimicrobials and new treatment strategies we focus on developing effective 'quorum quenchers'. These compounds allow us to interfere in bacterial communication systems and deprive the bacteria of their most dangerous weapons" says Wim Quax. "By crippling the bacteria, normal antibiotics and the host immune system can eliminate the infection."

CeSAM-affiliated researchers focus on quorum sensing in the bacterium Pseudomonas aeruginosa, the most important pathogen in cystic fibrosis. These bacteria often create large, almost untreatable, biofilms in the lungs of patients. The research team has been able to determine the structure of specific quorum quenching enzymes and hereby have the key to design novel antimicrobial compounds to disturb bacterial communication processes. This is a large step forward for developing a new kind of antibacterial therapy.

Biosafety laboratory level 3
A new Level 3 biosafety laboratory is under construction at the University Medical Center to enable CeSAM and its partners to perform research on highly contagious material, such as extensively drug-resistant tuberculosis isolates.

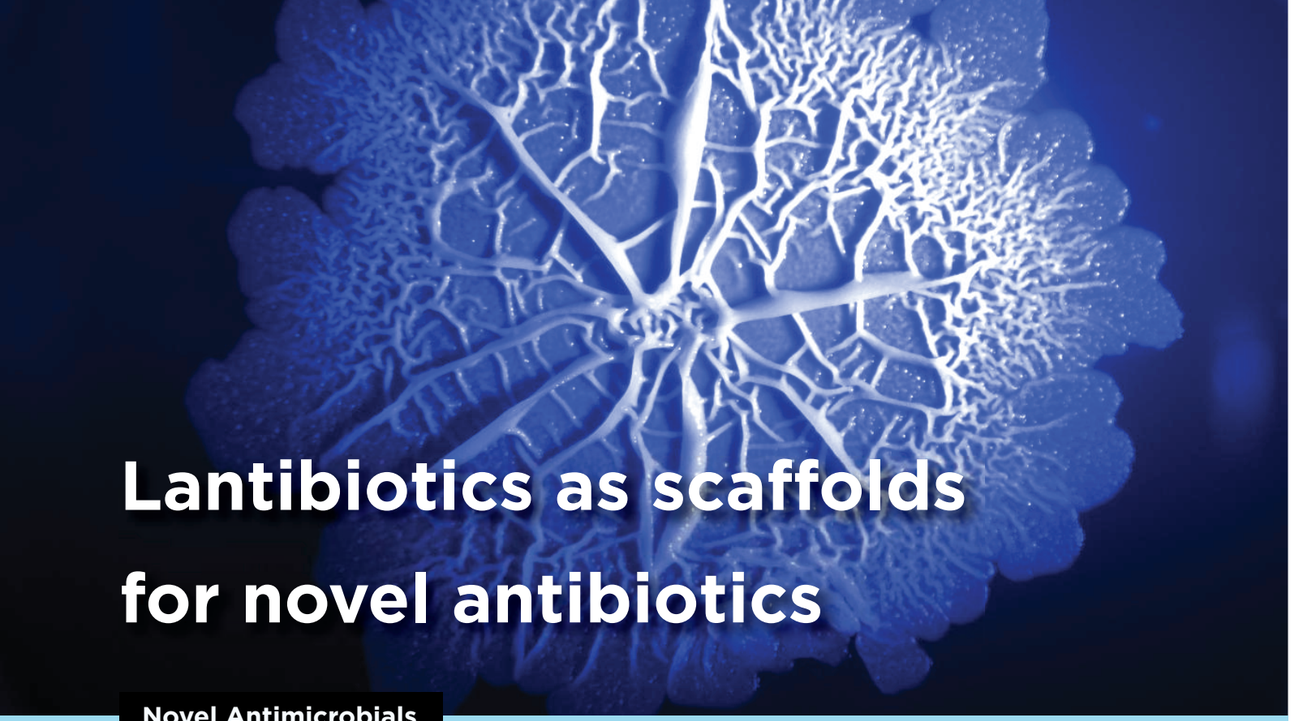
Animal testing facilities
There are modern animal facilities to perform host-microbe studies, which enables the study of novel antimicrobials in specific infection models.

Pathogenic isolate databank
This databank is the largest collection of virulent pathogenic bacteria isolates in the world, including over 6,000 isolates originating from 31 countries.

Pharma Portal and Pharma Connect Capital
The Pharma Portal offers professional support to early phase Life Science projects. The Pharma Portal combines the available public and private expertise in the Northern Netherlands to speed up and improve early phase drug development according to pharmaceutical industry standards. The Pharma Portal works closely with the Pharma Connect Capital to finance the early stages of drug development.

Innolab Chemistry Groningen
Innolab offers (starting) businesses in the chemical and life sciences sector flexible laboratory facilities and office space. This is an excellent location to work on pre-commercial development stages in close proximity to CeSAM researchers and the facilities on Campus Groningen.

Biomaterials Development Center (BDC)
The BDC coordinates and aligns the development of infection-resistant biomaterials from bench to bed. By combining the extensive knowledge, facilities and resources of the BDC together with the market knowledge, engineering skills and resources of proven medical device and material companies the BDC is working on jointly developing new infection-resistant materials for clinical application.



Lantibiotics as scaffolds for novel antibiotics

Novel Antimicrobials

Prof. dr. Oscar Kuipers, Head of Molecular Genetics, Scientific Program Director CeSAM

Lantibiotic are stable peptidic compounds, produced by bacteria to fight other bacteria. They contain modified amino acids, most notably lanthionines, from which their name originates. As lantibiotics have a dual mechanism of action they are effective against diverse (multidrug resistant) bacteria and have a low tendency to induce bacterial resistance.

Their properties make lantibiotics a promising new class for antibiotic drugs. And new drugs are badly needed Oscar Kuipers explains. “In the last 20 years or so no really new antibiotics have been developed. As bacteria become resistant to the existing antibiotics, we may reach a point where many infections are untreatable.”

Kuipers uses state of the art genome mining tools to identify novel lantibiotic gene clusters in bacterial genomes. Through synthetic biology approaches 100,000s of variant molecules are produced and subjected to high-throughput screening technologies.

By testing the variants against a panel of bacterial pathogens, antimicrobial leads are identified for further study. The goal is to end up with several promising clinical candidates.

3.6 Campus Real Estate

Campus Groningen offers innovative companies working on AMR and related themes the perfect base for settling because of the access to research, talent and entrepreneurship combined with a broad range of real estate options. These options include current office and lab facilities and future developments spread across the two Campus Groningen locations; the Healthy Ageing Campus and the Zernike Campus Groningen.

The **Healthy Ageing Campus** has various options for business accommodation. Laboratory and office space is available in the R&D Hotel, the Meditech Center and the Biotech Center. In the coming years the development of the north side of the University Medical Center, with the European Research Institute on the Biology of Ageing and the new Proton Therapy Center, will gain further shape.

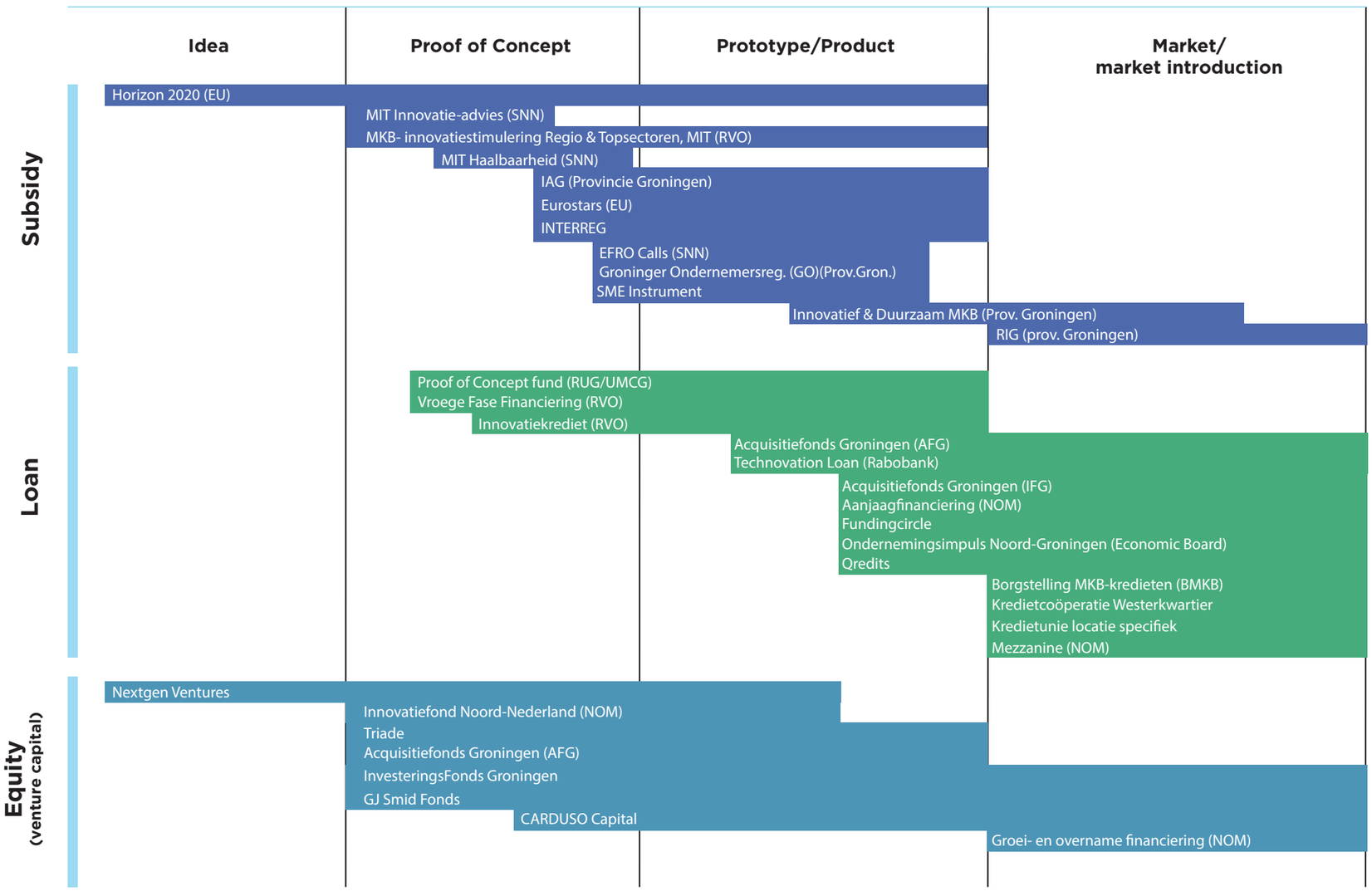
The **Zernike Campus Groningen** will undergo significant growth over the next few years. Various developments will gain further shape, including the new Innovation Centre with space for R&D companies. Also, Start-Up City provides a flexible community containing a mix of entrepreneurial educational programmes, university start-ups and established companies. The new Feringa Building, a research and education facility for chemistry, physics, astronomy, and industrial engineering, will be constructed over two phases between 2017 and 2022.

3.7 Access to Funding

Access to funding is essential for growth. Campus Groningen and the Northern Netherlands have various options and facilities to this end. Suitable solutions can be found for most financing requirements. Collaborating with CeSAM through a public private partnership or a joined research programme can also serve as a starting point for attracting (inter)national funding.

Funding of innovations can also occur through investments, by using various funds and via (regional) subsidies. The options range from small sums at the start of the development chain to million-euro investments for production scale-up. Unique in the Netherlands is the Regional Investment Support Groningen (Regionale Investeringssteun Groningen). This investment support is specifically for companies that aim to locate their activities on the Zernike Campus or at the Chemical Park in the Eemsdelta. Companies can receive up to 30% investment subsidy upon purchasing land, buildings and company equipment.

Financial Ecosystem



*This figure is not exhaustive

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NOM	nom.nl

Join us to fight antimicrobial resistance.

CeSAM and Campus Groningen aim to fight antimicrobial resistance by working on novel antimicrobials, personalized theragnostic approaches, preventive strategies, and excellent patient care, in an environment that promotes innovation and collaboration, educates top talent, and fosters world leading research. Antimicrobial resistance is a worldwide challenge, and to tackle it we need to work together. If our ambitions appeal to you or your organization, we invite you to join our campaign.

Contact

Engel Vrieling
Managing Director
Center for Sustainable Antimicrobials
T: +31 (0)50 363 4180
M: +31 (0)6 8103 2142
E: e.g.vrieling@rug.nl

Oscar Kuipers
Scientific Director
Center for Sustainable Antimicrobials
T: +31 (0)50 363 2093
M: +31 (0)6 5149 6392
E: o.p.kuipers@rug.nl

Ronald Hesse
Business Developer
Campus Groningen
T: +31 (0)50 361 0336
M: +31 (0)6 131 111 13
E: ronald@campusgroningen.nl

Rogier van der Stijl
Business Developer
Campus Groningen
T: +31 (0)50 361 0006
M: +31 (0)6 250 307 10
E: rogier@campusgroningen.nl

cesam-nnl.com

campus.groningen.nl