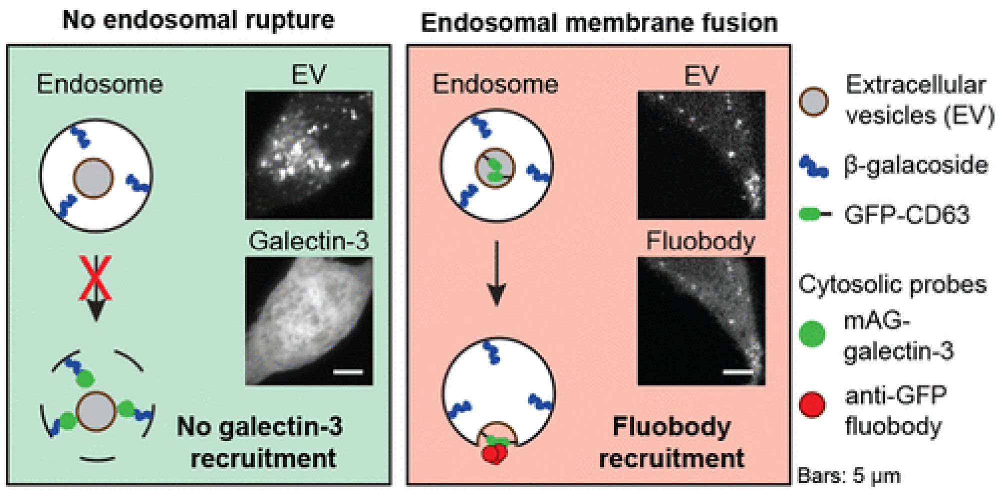
Dr. Inge Zuhorn

Scientific case study 1 / Nanomedicine
Researcher: Inge Zuhorn

The encapsulation of therapeutic molecules, e.g. chemotherapeutics, in nanoparticles improves their chemical and biological stability, and may promote delivery to the target site, while reducing off-target effects. A major challenge that needs to be overcome for the clinical translation of nanomedicine is their undesired clearance by the liver, resulting in poor accumulation at the target site. Exosomes are vesicles that are naturally secreted by cells that play a role in cell-cell communication. Through the transfer of lipids, proteins, and nucleic acids, exosomes are known to induce phenotypic changes in recipient cells. Exosomes are non-immunogenic and show excellent targetability, which makes them interesting candidates for use as nanocarriers. However, the mechanism of cargo delivery into recipient cells is largely unknown and needs to be elucidated in order to assess aspects such as the efficacy and safety of exosomes in drug delivery.

To elucidate the mechanism of cargo delivery by exosomes, their interaction with cells needs to be studied. Since exosomes are very small (~30-100 nm), i.e., below the diffraction limit of light, conventional approaches using (confocal) light microscopy do not provide sufficient resolution. Through the use of correlative light and electron microscopy (CLEM) the intracellular localization of exosomes can be revealed.

With the use of correlative light and electron microscopy (CLEM) together with molecular probes (GFP fusion protein; anti-GFP fluobody) we pinpointed the intracellular site at which exosomes release their cargo. In this way we revealed that exosomal cargo release occurs from endosomes[1]. This information will help to develop strategies to improve exosome-mediated drug delivery or inhibit exosome-mediated spreading of disease.



[1] Endocytosis of Extracellular Vesicles and Release of Their Cargo from Endosomes. Joshi BS, de Beer MA, Giepmans BNG, Zuhorn IS. ACS Nano. 2020,14(4):4444-4455. doi: 10.1021/acsnano.9b10033.

This study involved a collaboration between Inge Zuhorn (KOLFF-NanoBioMed) and Ben Giepmans (KOLFF-BRIDGE) to combine their respective expertise in nanocarrier-cell interactions and correlative light and electron microscopy (CLEM).The work was published in ACS Nano, a highly respected journal in the nanotechnology field with a broad readership. Upon publication we have received and replied to many requests to share our molecular probes with colleagues, which is expected to initiate new collaborations. Moreover, Dr. Zuhorn is in demand as a speaker at many conferences (such as NLSEV2020, ASEMV2020, ISN2A2022, Endoscape2022), which also helps to disseminate the findings. Subsequent research based on super resolution microscopy is planned, for which grant applications are being written.

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Scientific case study 2 / A holistic model to improve health
Researcher: Bart Verkerke

Prosperity has led to a relative increase in cardiovascular diseases, cancer, diabetes and stress-related conditions. Lifestyle factors, not only smoking, obesity, excessive alcohol consumption, mental overload and lack of movement, but also the social and physical environment (living, working, learning) are seen as major causes of this situation. An unhealthy lifestyle and living environment are more common in people with low Social Economic Status (SES), who therefore on average live 6 years shorter and 15 years in worse health than people with high SES. Much research has been done and many solutions have been tried out, but these often fail because they have focused on only a limited set of problems and solutions and did not account for the dependency between problems. Moreover, there has been no attention on motivating people to start changing their lifestyle and living environment.

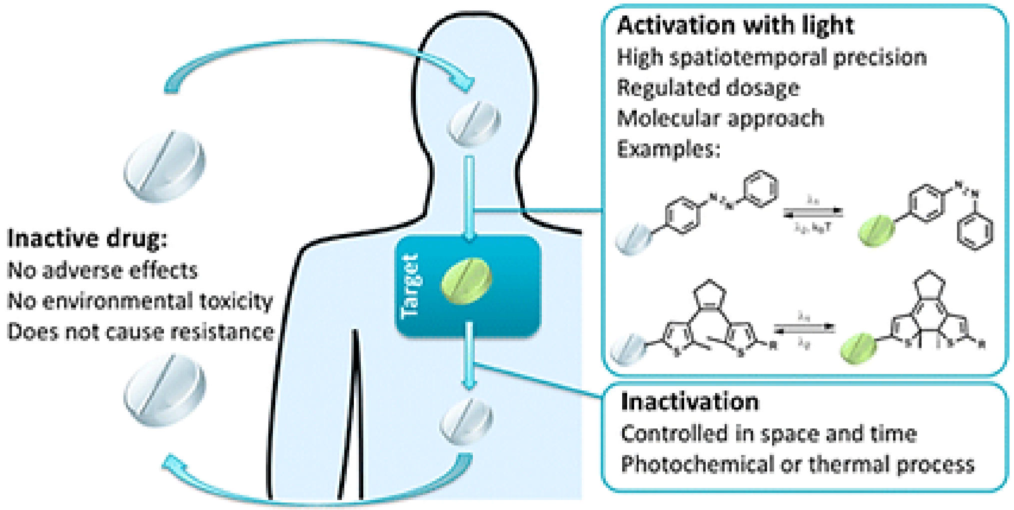
Inclusiveness of all citizens, also those with low SES, is essential to realize a solution that be effectively applied. Inclusiveness requires complying with and implementing strategies that empower and

motivate citizens to adopt a healthier lifestyle. These changes will be implemented by using existing learning communities (field labs) that include (low-SES) citizens, companies, researchers from the natural sciences, social sciences and humanities and government agencies and public bodies (quadruple helix). This ensures co-creation with all stakeholders and co-design with all required expertise.

The project presents a holistic model to improve low-SES citizens' health conditions, from high school students to people up to 65 years old (employed and unemployed). The model includes wearable and nearable sensors and domotica, AI for monitoring and analysis of the sensor data to create a picture of their current health condition, living environment and social status. The model also advises citizens on improving their lifestyle, living environment and social integration at home, work, and school. The model includes new strategies to motivate and keep motivating citizens, with collaborations beteem behavioral scientists and the creative sector. Central to this project is our interdisciplinary approach involving citizen participants, companies, researchers from the sciences and humanities and government agencies (known as the quadruple helix) with expertise ranging from Art via History (of Architecture and Urbanism) to AI.
To ensure structural embedding in society, an impact plan has been defined involving employers, health insurers, instructors and citizens. Sustainability will be investigated via the four learning communities in G2020 of our university. The results will be used to improve our theoretical model. The project will ideally result in a system of sensors, AI tools and interventions to benefit smart, motivated and health-responsible citizens in social, supportive and motivating communities that live in smart buildings.

Scientific case study 3 / Photopharmacology
Researcher: Wiktor Szymanski

Most current medical treatments rely on the use of bioactive compounds. These compounds evoke a pharmacological response by interacting with molecular targets in the human body, such as enzymes, receptors, ion channels, and carrier molecules. The selectivity of this interaction is crucial, and the lack of selectivity leads to potentially severe short-term, mid-term and long-term side effects in the human body, and limits increased dose efficacy at the site of action. Furthermore, the activity of drugs outside the patient's body (in the environment) leads to toxicity (hormonal pills) and emergence of resistance (antibiotics). Especially the latter is posing one of the greatest threats to humanity in the 21st century. Photopharmacology (Figure) aims at solving the problem of off-target activity and severe side effects by establishing an external modality for controlling the action of the drug. To achieve this, photopharmacology relies on the design, synthesis, study, and use of drugs whose activity can be regulated with light.



The use of such drugs in treatment could prevent systemic and environmental side effects through the selective activation of biological activity/toxicity. The photoactivation can be achieved either extrinsically (from outside the body) or intrinsically (from inside the body or at the site of action) by activated fluorescent compounds.

In our work, we build molecular bridges between light and clinical treatment. We pioneered photopharmacology in 2013 with the first report on light-controlled antibiotics (Nature Chem., 2013, 5, 924–928) and then provided the field-defining perspective in 2014 (J. Am. Chem. Soc., 2014, 136, 2178–2191). Later, we published proofs-of-principle for using deep tissue penetrating red light in drug activation (J. Am. Chem. Soc 2017, 139, 17979–17986) and using photopharmacology in the context of cancer chemotherapy (Chem. Eur. J., 2015, 21, 16517-16524). Finally, working together with the UMCG Surgery Dept, we defined future directions for using light-based technologies in the clinic (Angew. Chem. Int. Ed. Engl. 2016, 55, 10978-10999, Chem. Sci., 2020, 11, 11672-11691). In parallel, we have been working on developing new molecular tools for photopharmacology, to enable selective, personalized therapies (Nature Commun. 2019, 10, 2390).

After photopharmacology entered the research landscape of UMCG in 2015, we have entered many successful collaborations at the Medical Imaging Center, Surgery, Cardiology, and other departments, already leading to joint publications. UMCG researchers recognize the possibilities offered by the use of light in research and treatment. It has also been one of the most successful collaborations between the FSE and UMCG. Finally, this new approach has been also publicized outside academia (major article in Het Parool, interview on BNR radio for the Wetenschap Vandaag program)

Societal impact case study 1 / Valorization

Name
Patrick van Rijn et al.

Program
NanoBioMed

Theme
Nanotechnology & Biophysics in Medicine

A core interaction in medicine is the interaction between tissues, cells, and materials, which include macroscopic implants, biosensing platforms, and drug delivery systems. As cells and tissues are highly dynamic and are able to respond to their microenvironment, any introduction of materials will trigger an event. This is something universal and has been only recognized in terms of clinical potential in the last 15 years. Material-induced stimulation of tissue cells may elicit a similar effect as pharmaceuticals. As a result, implants and nanostructures are not only able to restore primary function of a tissue or deliver a drug, physicochemical stimulation by these implants or nanomaterials can also provide additional therapy that previously could be achieved only with pharmaceutical intervention. The challenge here is to understand which physicochemical material properties are needed to actually elicit the desired response.

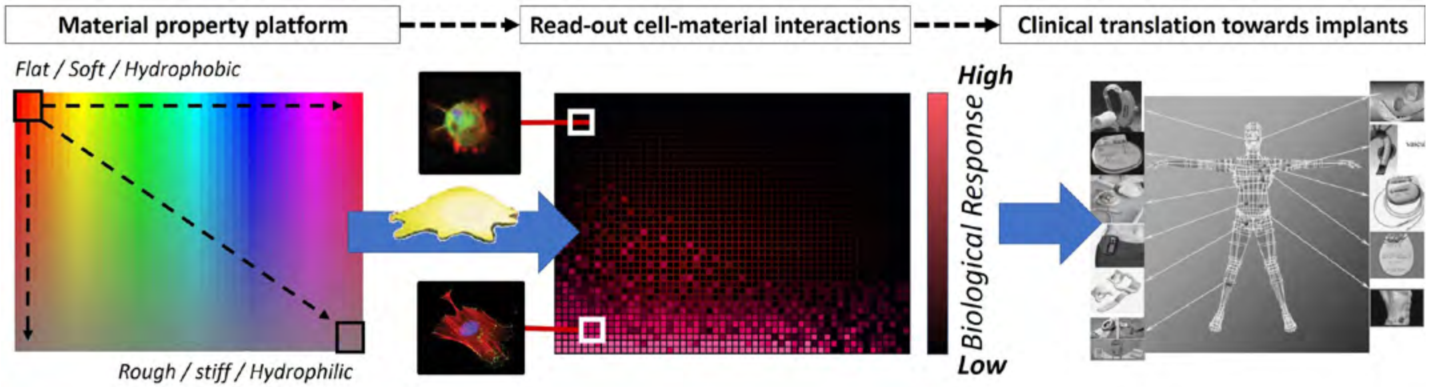
To address this the challenge, the corresponding knowledge gap must be filled. However, there are many of possibilities when it comes to material properties, and the biochemical environment also needs to be taken into account because it can significantly influence the impact of the physicochemical material properties. Additionally, various cell types or combinations of cells respond differently to the aforementioned interactions. To identify the many possibilities, new technologies need to be developed to provide insight into optimum material characteristics. The group of Dr. van Rijn at KOLFF has developed such a new technology and implemented it in the form of high-throughput screening for cell-material interactions. Known as Biomaterial Advanced Cells Screening (BiomACS), this technology enables thousands of combinations of material parameters and their influence on cells to be studied in a single experiment.

The new technology is the result of collaboration between material scientists, chemists, cell biologists, and clinicians. In particular, the department of Biomedical Engineering and Medical Biology, with scientists from NanoBioMed and REGENERATE, has been involved. The platform is composed of functional surface gradients that are cleverly combined to form a cell culture platform that provides key insights into cellular behaviors. The collaboration with clinicians from the departments of Orthopedics and Surgery (UMCG) helped formulate relevant clinical questions that would enhance the currently clinical materials for specific applications such as osteogenic materials (bone ingrown implants) and bioactive cardiovascular stents

The connection with med-tech companies such as Polyvation (specialized in polymers), Bentley (specialized in stents), VDL Wientjes (specialized in 3D printing), Bether Encapsulates (specialized in controlled delivery) on enhancement of medical products has provided clear insight into many translational aspects. To translate the findings to clinical products and applications, a spin-off company on the patented key platform technology has been established – BiomACS B.V. – which operates on a commercial level, while the current basic science research is performed by van Rijn's research group. The fundamental aspects platform are still being developed.

Teaming up with the local consultancy company EmpowerMi and assistance from CDI (Center for Developments and Innovations of the UMCG) helped with the commercialization of the patented technology. Currently, in collaboration with BiomACS BV, the department of Biomedical Engineering and Surgery, and implant manufacturer companies, innovation projects (improved aortic stents and bone ingrown implants) are being developed. In the long term, our innovative implants will not only improve patients' quality of life, but also reduce costs due to a decrease in reconstructive surgeries, medical follow-ups and hospitalizations.

Establishing a spin-off company from the research group is not only beneficial for ultimately reaching patients, highly trained and skilled fundamental researchers also have the possibility to participate in a med-tech company. As a result, pool of broadly educated professionals is created, thus impacting the regional level in technology-driven healthcare approaches.



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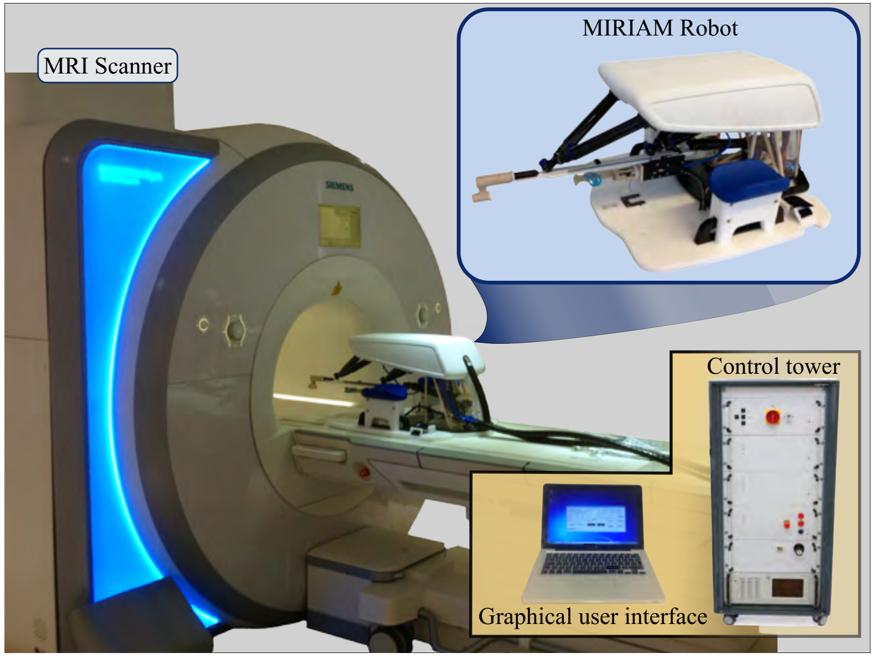
Societal impact case study 2 / Technology into the clinic

Name
Sarthak Misra et al.

Program
ROBOTICS

Theme
New techniques for robotically-steering surgery



Open surgery is a traumatic experience for most patients. It is highly invasive and results in significant recovery time. Minimally invasive surgery aims to reduce these disadvantages. Needle insertion is one of the most common procedures during minimally invasive surgery. Needles are used for both diagnosis (e.g. biopsies) and therapy (e.g., brachytherapy). In all cases, the needle must reach specific locations within the body. But the needle often deviates from its intended path due to tissue deformation, anatomical obstructions and physiological processes. One of the ways to mitigate needle targeting errors is by using robotically-steered needles.

Needles with asymmetric/bent tips naturally bend in tissue. In recent years the ***Surgical Robotics Lab*** led by Prof. Misra has developed techniques in needle design and steering methods. This is done by pre-operative planning of the procedure with intra-operative control techniques to steer the needle. Pre-operative planning involves developing models of needle-tissue interaction and obtaining images of the patient prior to the procedure. The resulting pre-operative plan is essentially a roadmap for the surgical procedure, while intra-operative control techniques involve taking real-time images (ultrasound, CT or MR) and using the pre-operative plan to insert and steer the needle to its target within the body.

The unique position of Prof. Misra's research at ***Surgical Robotics Laboratory*** comes from its dual focus on exploring experimental robotic technologies for minimally invasive surgery and as on the refinement of more established techniques into products capable of clinical deployment. Such an approach is inherently linked to a broad expertise, which ranges from the very frontier of robotics research all the way to the development of mature solutions that meet the needs of clinicians. As a result, the ***Surgical Robotics Laboratory*** generates multiple promising innovations, with its position established with groundbreaking research in needle steering, continuum robotics and medical microrobotics. This research is linked not only to a track record of highly-cited publications, but also to a variety of pre-clinical solutions for prostate biopsy, endovascular surgery and robotic ultrasound imaging in various stages of commercialization.

Prof. Misra is interested in robot-assisted minimally invasive surgery to understand and reduce the invasiveness of surgery, improve accuracy of treatment, and help push back the frontiers of inoperable disease. With his research, he can expand and accelerate the field and revolutionize the way minimally invasive surgery is currently performed.

Early prostate cancer detection and treatment is crucial to reduce the mortality rate. Magnetic resonance (MR) imaging provides images of the prostate whereby an early-stage lesion can be visualized. The use of robotic systems for MR-guided interventions in the prostate enables us to improve the clinical outcomes of procedures such as biopsy and brachytherapy.

The Surgical Robotics Lab (in collaboration with Radboudumc, Demcon Advanced Mechatronics, Siemens and Xivent Medical) has developed a novel MR-conditional robot for prostate interventions. The minimally invasive robotics in a magnetic resonance imaging environment (MIRIAM) robot has 9 degrees-of-freedom used to steer and fire a biopsy needle. Prof. Misra was the project coordinator and PI for the project. The evaluation studies with the MIRIAM robot were done at the UMCG. The technology on MR-guided robots has also resulted in robots that can be used in the CT-scanner.

Some papers and videos of the topic:

- ***Website Surgical Robotics Lab***
- ***Article*** on The MIRIAM robot
- ***Video*** on MR-guided needle steering for prostate intervention
- Segment on the television news program ***EenVandaag***
- Article on Computed tomography (CT)-compatible remote center of motion needle steering robot: Fusing CT images and electromagnetic sensor data ***https://pubmed.ncbi.nlm.nih.gov/28512000/***)

Societal impact case study 3 / Translational Research & Societal Relevance

Name
Andor Glaudemans et al.

Program
BRIDGE

Theme
Translating knowledge on the efficacy of PET scanning into guidelines

For earlier and more specific diagnosis, as well as for therapy prediction and monitoring of various diseases such as cancer, cardiovascular diseases or infection diseases, clinicians and researchers at the UMCG use molecular imaging techniques. One of the most frequently used procedures is the PET (positron emission tomography) scan where radioactive tracers are injected into patients to make specific diseases visible or to monitor current therapies.

Clinicians within the BRIDGE program are involved in translating their knowledge on the efficacy of PET scanning into guidelines that can be used all over Europe and result in the best possible diagnosis and therapy predictions. These freely available guidelines have been adopted as standard of care by a wide range of clinical and imaging societies involved, and all centers using the PET technique should adhere to these standards. For this purpose, Prof. Andor Glaudemans was the chair of the Inflammation and Infection Committee (I&I) of the European Association of Nuclear Medicine where he was involved in developing guidelines, recommendations and diagnostic flowcharts for the optimal use of nuclear medicine imaging in I&I (***https://www.eanm.org/publications/guidelines/inflammationinfection/***).

To ensure the use and uptake of these guidelines and recommendations, he and his colleagues provide education and training for nuclear medicine physicians and organize scientific and educational sessions at conferences on imaging and at international clinical conferences. Courses, workshops and webinars are given in collaboration with the European school of multimodality imaging and therapy (ESMIT, ***https://www.eanm.org/esmit/***).

To monitor and ensure the correct uptake of guidelines, Prof. Glaudemans is also involved in quality audits of multiple centers in the Netherlands and is a reviewer for various journals to ensure that new studies use the standard.

Although a great deal of effort already went into the translation of these guidelines into practice, no data is yet available to indicate its actual use. Prof. Glaudemans: “Using these techniques according to guidelines will enable us to improve diagnosis and therapy of various diseases on an European level. Currently, we are working on a survey in which we will ask all centers in nuclear medicine across Europe whether they adhere to guidelines and to which guidelines.”

To demonstrate the impact of these guidelines on the clinic, prospective studies will be needed. One of these studies in which Prof. Glaudemans and his team are involved is the EANM guideline on peripheral bone infection (Glaudemans et al, 2020, ***https://doi.org/10.1007/s00259-019-4262-x***),
which is based on research conducted in the BRIDGE program (***https://doi.org/10.1016/j.injury.2018.03.018*** and ***https://doi.org/10.1007/s00259-018-4218-6***).
Based on this guideline, prospective studies comparing the imaging techniques are now being conducted (IFI trial, ***https://doi.org/10.1136/bmjopen-2018-027772***).