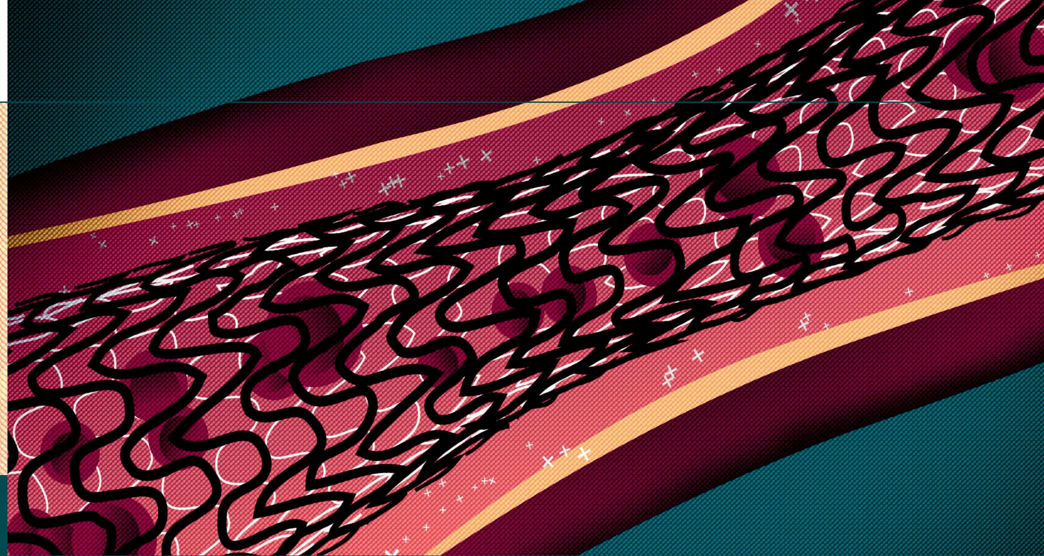

Spotlight on the surface

With a background in supramolecular chemistry and chemical biology, **Professor Dr Pascal Jonkheijm** is currently exploring surface modification techniques using biomaterials and cell biology. He discusses how his fundamental research is paving the way for innovative clinical applications

You are head of the Bioinspired Molecular Engineering Labatory at the MESA+ Institute for Nanotechnology. Can you introduce your group and its aims?

We are an interdisciplinary group focused on research based in chemistry that interfaces with organic, physical organic, cell biology and biomaterials investigations. Broadly speaking, our main long-term goal is to combine supramolecular chemistry and materials science with cell biology to study a range of complex processes related to cell behaviour, develop bioanalytical tools for various biotechnologies, and create and employ biomaterials for regenerative medicine applications.

A major focus of your work is on improving chip-printing technologies and techniques. How would you describe your group's research in this field?

We have created a completely unique technique to print arrays so that we can have a high number of different biomolecules dotted into the wells of the chip. One novel aspect of our technique is that we place proteins in a water-based hydrogel, and are thus able to keep it in the environment in which it thrives. Moreover, the dots that our techniques produce are smaller than in conventional cases. The advantage of this is that we can increase the amount of information a chip contains. Additionally, we have scaled down the wells in which we do the analysis, enabling us to increase the number of analyses that we can complete per chip area. This is of interest for upscaling and in the diagnosis of diseases.

Your group is also deeply invested in improving the outcomes of individuals undergoing coronary artery stenting. How does your improvement in coating technology play into these activities?

Our dynamic coatings can be applied to bioabsorbable polymers that are composed of polyesters and polyetheresters or biostable polymers such as polyurethane-based elastomers. The key is that all of these polymers have been approved for human applications and are already used in numerous marketed biomedical implants – such as coronary artery stents – and pharmaceutical sustained release formulations.

Since it is mostly unclear which component of the surface of implanted biomaterials is responsible for the unwanted biological response, we often take such biomaterials that are commonplace in the clinic and simply modify the surface. By trying to keep as close as possible to what is already out there, we do not have to make new polymers. Instead, we take the stents and apply our chemistry to the surfaces.

Do you facilitate the translation of your biomaterials from the laboratory to the real world?

At the moment we are evaluating our approaches in detail and, similarly, our partner in Amsterdam is planning to validate our techniques using animal models. In addition, we receive detailed feedback on how our coating technologies are applied from our clinical partners, allowing us to carry out in-depth and extensive evaluations on our products. That is essentially our limit as an academic group – from there, if our results are positive, we are able to reach out to biomaterials companies where they can apply our chemistry to real-world products.

In what ways have collaborations with industry and other academics aided the progress of your research on biomaterials?

There is no doubt that collaboration has immensely aided our progress. Going forwards, there is of course much work to be done to improve biomaterial products.

As academics, we are constantly studying and applying new surface chemistry approaches. For us, it is hugely inspirational to see how the results of our research can address really important medical problems. By working with industry professionals, we aim to eliminate some of the problems they encounter. Essentially, these collaborations allow us to respond to real-world medical challenges through the means of a simple solution.

A cutting-edge coating

A group of researchers based in the **Bioinspired Molecular Engineering Laboratory** at the **University of Twente** in Enschede, Netherlands, is using innovative supramolecular chemistry techniques to design a special coating for stents that enables optimal interaction between the device and the patient's cells

AS THE NUMBER one cause of death globally, cardiovascular diseases represent an enormous burden to public health. One of the most common life-threatening problems is the abnormal narrowing of the coronary artery, which restricts blood flow and can eventually lead to a heart attack. In order to prevent this, coronary artery stenting is a frequently performed clinical procedure involving the implantation of a small mesh tube that supports the inner walls of the artery. Although this intervention saves countless lives every year, it is not without problems. In the Netherlands, for instance, approximately 3 per cent of the 30,000 patients who are stented each year experience clinical complications within six months of the insertion, causing enormous social and economic costs.

Historically, complications as a result of stent insertion occurred due to the body rejecting the stent, thus triggering the proliferation of scar tissue and causing the artery to re-narrow. In more recent years, this problem has been curbed by the development of advanced drug-eluting stents coated with anti-inflammatory polymers that are released slowly to prevent the growth of cells from blocking the artery. Worryingly, however, in some cases these stents can lead to the formation of deadly blood clots that may block blood vessels. Scientists have observed that these clots tend to occur where the stent coating is damaged, implying that contact between the bare metal and the blood is causing these complications. Preventing such problems would improve the quality of life of many patients, as well as saving a significant amount of time and money.

In response, a group of researchers – the Superdices Consortium, which was officially established in November 2010 – is attempting to develop safer stents by designing a natural, self-healing coating for stent surfaces. "Our coating will enable the optimal interaction between the implant and the patient's cells, thus preventing restenosis, or the recurrence of abnormal narrowing of an artery or valve after corrective surgery," states Professor Dr Pascal Jonkheijm, the project leader.

Based in the Bioinspired Molecular Engineering Laboratory at the University of Twente, Jonkheijm is motivated by a fascination with the dynamic self-assembling properties of biomolecules and the prospect of translating his fundamental research into practical, life-saving clinical applications. His extensive expertise in surface modification and self-assembling molecules is contributing to the success of the project.

INNOVATIVE APPLICATIONS

In addition to their work on improving the coating of stents, Jonkheijm and the other members of the Superdices Consortium are also involved in the following activities:

- They are collaborating with InnoCore, a Netherlands-based company, on the creation of an ophthalmic drug-delivery particle. Together, they are creating these small polymer nanoparticles and then coating them with the Consortium's dynamic interface.
- A project on diabetes, whereby they are creating a carrier material with small pits in which they pack and transport islets of Langerhans – groups of specialised cells in the pancreas that make and secrete hormones. Their aim is to increase the number of islets that they can transport into a patient's body.

EMPHASIS ON ENDOTHELIALISATION

When it comes to remedying problems with implant materials, many scientists attempt to synthesise entirely new polymers that interact better with the host's cells, tissues and organs. However, the problem with this approach is that certain important chemical and biological properties can be lost when the polymers are changed. As a result, Jonkheijm and his team are using a different, innovative technique for implant improvement; instead of replacing the polymer, they are seeking to modify its surface by means of a simple chemical adjustment.

This alteration involves manipulating the endothelial cells in the artery wall so that when they coat the surface of the stent, they prevent the fast-growing smooth muscle cells from proliferating around it. To attach the endothelial cells to the stent's surface, the researchers have used dynamic chemistry strategies to create a type of 'glue' made from proteins found in the human body. With their

SUPERDICES CONSORTIUM

OBJECTIVES

- To develop dynamic coating strategies for biomaterials for improved integration with surrounding cells, tissue and organs
- To provide a proof of concept for cell attachment to stent surfaces using supramolecular chemistry
- To develop dynamic chemical strategies to understand, direct and manipulate cellular processes with temporal and spatial control

KEY COLLABORATORS

Professor Luc Brunsveld, University of Technology Eindhoven, Netherlands

Professor Marcel Karperien, University of Twente, Netherlands

Professor Jan de Boer, University of Maastricht, Netherlands

Dr Aart van Amerongen, Wageningen University, Netherlands

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PASCAL JONKHEIJM completed his PhD on supramolecular chemistry with Professor Bert Meijer before continuing on to a postdoctoral position at the Max Planck Institute of Molecular Physiology, Germany, with Professor Herbert Waldmann. There, he gained experience in chemical biology before beginning as Assistant Professor at the University of Twente, Netherlands. Currently, he is heading the Bioinspired Molecular Engineering Laboratory at the MESA+ Institute for Nanotechnology.

specially engineered 'arms', these proteins can simultaneously grasp the stent and attract endothelial cells. Then, by addressing the clusters of receptors in the membranes of endothelial cells, the researchers can induce the cells to spread themselves over the stent surface until it is completely covered. The idea is that this will stop blood clots from forming by preventing contact between the mesh and the blood. "The cell membrane that we are trying to imitate with our glue is a very dynamic interface," Jonkheijm outlines. "Essentially, you could say that we are tricking the endothelial cells into protecting the stent surface by creating a coating that they like."

As well as investigating which peptides and growth factors appeal most to the receptors in endothelial cells, the scientists are also seeking to determine the optimum locations in which to apply them and which densities give the best results. Interestingly, they have observed that the endothelial cells seem to grow better and move more freely over the stent if the glue is applied in specific patterns rather than uniformly. Going forwards, as Jonkheijm and his colleagues continue forging a better understanding of these dynamic cellular interactions, they will be able to further enhance their smart coating.

FUTURE ADVANCES

The Superdices Consortium has undoubtedly made significant advances to date. For instance, it has successfully developed novel supramolecular surface chemistry to systematically study cell adhesion and migration. It has also completed an *in vitro* evaluation of controlled interactions between supramolecular platforms and endothelial cells in a fluidic environment. At present, the Consortium is in the process of establishing a preclinical evaluation of one of its supramolecularly modified stent surfaces; excitingly, once the principle is demonstrated in animal models the next logical step is translation to the clinic.

Looking ahead, there is enormous scope for the Consortium's work on biomaterials to extend to multiple applications beyond treatments for stenosis. Indeed, as a modular concept for enhancing the interface between cells and foreign bodies such as stents, it has the potential to be translated to other biomedical and bioanalytical surfaces. Furthermore, with interest burgeoning in the field of smart materials, Jonkheijm and his collaborators are planning to continue applying their knowledge and ingenuity to fundamental research with novel applications.

Jonkheijm is motivated by a fascination with the dynamic self-assembling properties of biomolecules and by the prospect of translating his fundamental research into practical, life-saving clinical applications

PROBING CELLULAR PROCESSES

Cell membranes are extremely complex and dynamic. They are covered with multiple enzymes, receptors and growth factors that play a pivotal role in transferring signals between cells and the external environment. To achieve a deeper understanding of these dynamic cellular processes, Jonkheijm has replicated cell membranes on a multiplexed array entitled MULTICHIP.

This innovative tool contains miniscule circuits and fluid channels that enable him to determine exactly how the biomolecules on the artificial cell membranes communicate with living cells. Importantly, the knowledge gained as a result of applying these techniques could fuel research into biomaterials for regenerative medicine.

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