About a journey from basic science to societal impact

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Prof.Dr. Matthias Barz

Prof.dr. Matthias Barz heeft een achtergrond in polymeerchemie en organische chemie. Hij studeerde scheikunde aan de Johannes Gutenberg-Universiteit Mainz (Duitsland) en Seoul National University (Zuid-Korea) en promoveerde in de polymeerchemie aan de Johannes Gutenberg-Universiteit Mainz in 2009, waarna hij in laboratoria in Spanje en de Verenigde Staten werkte. In 2013 startte hij zijn eigen lab in Mainz en begon hij aan zijn habilitatie (een wetenschappelijke promotie die na de eerste promotie volgt), die hij eind 2016 afrondde. In het voorjaar van 2020 trad hij toe tot de Universiteit Leiden als hoogleraar Biotherapeutics delivery binnen LACDR. Momenteel verhuist hij zijn onderzoeksgroep van Mainz naar Leiden.

Universiteit Leiden
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About a journey from basic science to societal impact

Dies lecture given by

Prof.dr. Matthias Barz

Professor for Biopharmacy

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Esteemed Rector Magnificus, thank you for your introduction, Excellencies, d*istinguished audience,*

I would like to sincerely thank our rector magnificus, Hester Bijl, and everyone involved in the organization of this event for the amazing chance and great honor to speak to all of you today and present a personal view on collaborative science and pharmaceutical research in particular.

Once again, my name is Matthias Barz and I am since 2020 professor for Biopharmacy at the Leiden Academic Center for Drug Research (LACDR).

First of all, I would like to start with a confession; when I started my career as a chemist, I never imagined I would become a professor one day. But as I became intimately involved in research, and fortunately being allowed significant freedom by my supervisor, I came to realize that I really enjoyed raising my own research questions and trying to find answers; I appeared to have some aptitude for performing independent research, and I felt that I could be creative in finding solutions for existing problems, and thus, I took the chance to become an academic researcher. Although I worked fairly independently, I nevertheless benefited enormously from inspirational mentors. These scientists supported me, taught me to think independently, and encouraged me be creative and innovative. In the end, they prepared me to realize interesting findings and to take the chances to explore them.

At the Center for Drug Research, my team and I are doing just that. We are are working in the field of nanomedicine at the interface of chemistry and pharmaceutical science.
I am sure the current COVID 19 pandemic has raised awareness for the importance of nanomedicine for our society, since both approved mRNA vaccines are based on nanosized delivery systems. They use lipids, comparable to the ones in cell membranes, to shield mRNA and deliver it inside antigen presenting cells, where the vaccine induces immunity against the spike protein of the COVID 19 virus, protecting us from severe or even deadly disease progression. These nanoparticles are 1000-10000 times smaller than the diameter of human hair. On a different note, the development of mRNA vaccines is an excellent example of the importance of fundamental science for our society.

In the area of nanomedicine, we specialize in using tiny polymer particles of 10 to 200 nanometers made from naturally occurring amino acids as vehicles to deliver drugs. In contrast to conventionally administered drugs, which often fail to distinguish between diseased and healthy tissues, we design our systems to become active specifically at the side of disease and thus reducing adverse effects. Moreover, several potent drug molecules, like mRNA, fail to reach their target, which requires specialized carrier systems to deliver them.

As I am a synthetic polymer chemist by training, my research focus was initially on designing polymer materials for biomedical applications. For the last 5 decades polyethylene glycol, or in short PEG, has been the most widely used polymer in this area. It is used to reduce undesirable interactions of the drug molecules or carrier systems with blood components, e.g. proteins or lipids, to enlarge the size of active molecules, as well as to stabilize these particles to enable their injection, like in the case of mRNA vaccines. A consequence of these effects is to enhance the residence times of drugs in the blood stream and thus prolong their time of activity in the body. Therefore, PEGylation, the attachment of PEG to drug molecules, was and is a widely applied strategy in pharmaceutical science.

My first review article in 2010 raised a series of questions and outlined possible drawbacks of using PEG:

“Overcoming the PEG-addiction”

Robert Luxenhofer and I, we discussed potential alternatives, such as pHPMA, Polyoxazolines, polypeptides, and -as you will see later- the polypeptoid polysarcosine.

The potential drawbacks of PEG are the non-degradable nature and an increasing number of patients showing immune responses towards this material. Although it showed very limited interactions with proteins, the immune system of many patients seems to recognize PEG nowadays. For example, an accelerated blood clearance of PEGylated protein therapeutics and liposomal drugs has been reported, which can be also attributed to the recognition of PEG by our immune system and the formation of antibodies against it. Antibodies against PEG were shown to account for efficacy loss due to accelerated blood clearance and hypersensitivity reactions entailing severe allergic symptoms with occasionally fatal anaphylaxis. The reasons for the observed phenomena have not yet been answered consistently and may remain under debate for a couple more years, but since PEG and PEGylated surfactants and emulsifiers are broadly used in cosmetics and detergents it is very likely that our immune system has been in touch with these artificial materials and was trained to recognize them. Despite these drawbacks, PEG is still a very useful and important material, since it is an integral part of the lipid formulation used in mRNA vaccines against Covid 19 and it has contributed to changing the life of billions of people around the world. Although these novel vaccines are among the best tolerated ones ever, adverse effects still do occur in a small number of patients, and these may relate to the use of PEGylated lipids. These findings generated again a broader interest in the search for PEG alternatives, especially in pharmaceutical industry.

Ours was one of several research groups that started searching for possible alternatives to PEG. But while many scientists were interested in using polymers that are non-degradable, I was only interested in using materials that are completely based on natural amino acids to construct novel drug delivery systems. Eventually polysarcosine caught my attention, a polymer based on the natural and body-own amino acid sarcosine (N-methyl-glycine), which is part of our glycine metabolism. We later discovered that polysarcosine actually behaves like PEG in water, which could make it an ideal substitute for it. Since some of the properties of PEG are highly desirable, I felt we could maintain them, but maybe have a chance to improve the downsides of using PEG everywhere. Already in 2013 we started working on polysarcosine as an alternative to PEG and applied it to the synthesis of various nano-sized drug delivery systems. Interestingly, we observed that polysarcosine had less pronounced adverse-effects than PEG in mice and primary human cells. In contrast to PEG, in mice polysarcosine can also reduce the undesired immunogenicity of mRNA lipid nanoparticles, comparable to the current mRNA vaccines. These results are for sure promising at this stage and underline the importance of academic research, however, the final proof of any therapeutic benefit takes place in patients.

To move forward towards a clinical proof for our hypothesis, one needs a partner from the pharmaceutical industry, ideally working on PEGylated nanosized drugs. We were fortunate that we have had the opportunity of working together with BioNTech on mRNA delivery systems at that time. This collaboration originated in 2013 from a joint research project with Prof. Peter Langguth and Prof. Ugur Sahin on the next generation of mRNA based immune therapies at the center for nanoparticle-based tumor immune therapy (CRC 1066) funded by the German Research Foundation (DFG). This initial project provided the seed for the collaboration with BioNTech, which hopefully leads to a clinical trail supporting our preclinical findings and improve mRNA vaccines a bit

further. In a more general sense this example emphasizes the importance of connecting scientists at universities with industry to allow basic science to make advances available for our society. Often researchers cannot do this on their own.

From my point of view, such collaboration between universities and industry should be fostered and supported, for example with joint research infrastructures, as is currently planned with the Pharma NL initiative. The PharmaNL program, co-founded by both Leiden University and LUMC and currently under review by the Dutch Growth Funds, aims to give a substantial impulse to translational drug research and the local production of pharmaceuticals, goals that can only be achieved with strong public-private partnerships. We have seen that many solutions to societal problems, such as the current pandemic, are based on translating basic science into applied therapies. And while justifiably paying our tribute to the scientists who developed the COVID19 vaccines, our society and our political leaders need to understand that in most cases this is not possible without connecting academic with industrial research, for example by shared, well-equipped infrastructure.

We will hear in the next talk by Prof. Meta Roestenberg that in some areas of infectious diseases even more demanding public efforts will become necessary when diseases are rare, poverty-related or simply out of the current focus of pharmaceutical industry, as is the case concerning the development of new antibiotics.

In conclusion, I strongly believe that private public partnerships can be, and indeed need to be, much more than just contract research. Research institutes and universities should clearly not become a cheap alternative to R&D divisions in companies and must be allowed to maintain their academic freedom. In pharmaceutical science, however, only the collaboration between academic researchers and industry can enable our society to directly profit from fundamental science and advances stemming therefrom. Since the final proof of all therapeutic concepts is in patients, we can only know if our ideas and visions can evolve into therapies after clinical translation has been achieved. When scientists team up across disciplines and institutions, they can enable curiosity driven science to provide solutions to societal problems and enable their application quicker than ever anticipated, although these solutions may initially not even have been developed specifically for a therapeutic application, they can end up being useful for it. I have learnt that life -and science- is about realizing chances and taking them. We need to establish a research environment in the Netherlands enabling scientists to innovate and connect, to join efforts in order to provide a valuable return for all the major investments our society makes in universities and research institutes. Moreover, a collaborative mindset in the life sciences will for sure be an integral part of the thinking of the generations of researchers to come, who will consider collaborations between scientific disciplines and institutions as the new normality.

Finally, I would like to wish the University on this 447th Dies a Happy Birthday.

I have spoken.