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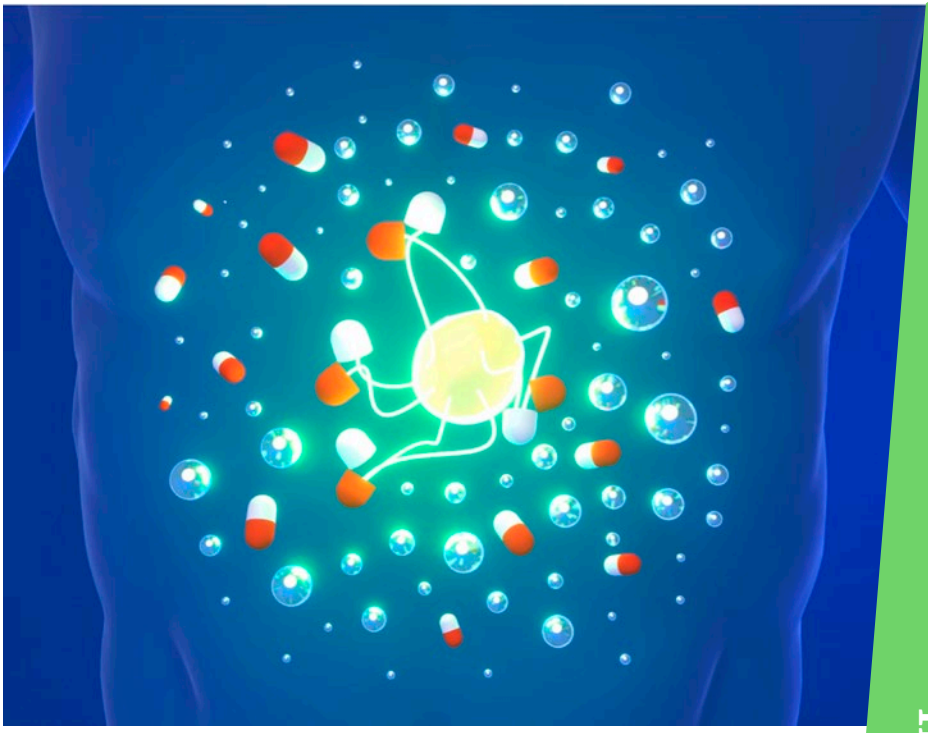

Inaugural lecture

Prof. dr. W. Szymański

Building Bridges: the magic of light and the logic of molecules

15 November 2024

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On acceptance of the post of professor of

Medicinal Chemistry, Photopharmacology and Imaging

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Faculty of Science and Engineering

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Members of the Board of the University,
Ladies and Gentlemen,

I address you as the newly appointed professor of Medicinal Chemistry, Photopharmacology and Imaging. From the extensive name of this chair alone you may expect that several bridges will have to be built between disciplines before my time here is done. And with this in mind, I would like to tell you today a tale of three bridges and three thinkers, and it will be up to you to decide if by the end I went a bridge too far.

The First Bridge

The first bridge that we will attempt to build in the coming years will be that between light and medicine, and to understand my motivation, I would like to introduce to you the dream of our first hero: Professor Paul Ehrlich.

Ehrlich was born in 1854 in Strehlin in Lower Silesia and his contributions to science and medicine are immense – we will come back to them a few times today. But his most important idea, at least for us, is that of a "magic bullet" (or *"zauberkugel"*) – a dream which he introduced in 1907 and which we are still trying to realize today.

Such a "magic bullet" would be a drug that treats only what needs treating, without harming the rest of the patient's body. To realize such a drug we would be using a molecule – a chemical – to do therapy. In other words, we would do "chemotherapy", and Paul Ehrlich not only introduced this term, but he also

invented the first antibiotic – Salvarsan – in his successful efforts to cure syphilis.

Was salvarsan the magic bullet? Unfortunately, no – it affected not only *Treponema pallidum* bacteria that cause syphilis, but also the patient body itself, leading to liver damage and even death. It was substituted in the 1940-ties with penicillin, which is also not innocent, killing many types of bacteria in patients' body non-discriminatively.

Which brings us the **key problem** that we were, are, and will be trying to solve: drugs are helping where they need to help, but also cause harm where they are acting unnecessarily. Besides treatment of infections, the most striking example of this is cancer chemotherapy, where highly toxic drugs are used to kill cancer cells, and it is practically impossible to avoid collateral damage to healthy cells, leading to side effects so severe that they sometimes result in the termination of the treatment.

So how can one target a drug to the cells in the patient's body that one wants to affect, and make it completely oblivious to other cells? For 120 years we have been struggling with this problem. The good cells and the bad cells do not differ that much, so how can we distinguish between them using a small molecule of a toxic drug? A promising idea that emerged in recent years is to take something that very specifically binds to

the cancer cells and brings drugs directly to them. Those very selective binders, given to us by nature, are antibodies – and guess who coined this term? It was the father of immunology, Paul Ehrlich! The principle is rather simple: in an antibody-drug conjugate, the antibody is attached to a drug and brigs it to the tumor, where the linker between antibody and tumor is metabolized, the drug is liberated and kills tumor cells.

This would all look very nice indeed, if it was not for the inquisitiveness of Prof. Liesbeth de Vries and her colleagues from UMCG, who once radiolabeled those antibodies to find out how much of them really ends up in the tumors and has the potential to bring toxic drugs there. Sadly, it turned out that the amount of tumor-targeted antibody that ends up in the tumor is a bit disappointing, to say the least.

So, despite all the efforts in antibody-drug conjugates, this might not always be the way to go. We seem, at least for the time being, not to be able to control what our drugs work on. We need a new idea: could we control not **what** we hit with drugs, but **where** we hit with drugs? Can we think of a magic bullet that is targeted in time and space?

This brings me to the main topic of today, and of my new department's work in general, which is Image Guided-Pharma-

cotherapy. Again – a mouthful, but this is where the medicinal chemistry, photopharmacology and imaging from our new department's name come together. And the big dream is as follows: **to use medical imaging to find out where the problem is, and then activate the drugs there and only there**.

This is a project for a lifetime of research, which is good news for someone just setting up their department at a university. Before we can establish first working systems, there will be a lot of difficult questions that need answering. And there is something relevant that we teach our students in the advanced organic synthesis classes: when you try to make a difficult molecule, do not start with making the easy parts – start with the toughest part and see if you can do it at all. With our research vision, the situation is similar – and if you look at the whole idea of using imaging to guide the local activation of a drug, the most challenging, otherworldly part seems to be: how will you precisely switch a drug on only in the place and at the time you want? Drugs usually do not come with convenient switch that you can just flip...

To answer this question, I would like to come back to the year 2010, when I was just finishing my biocatalysis postdoctoral work with Professors Dick Janssen and Ben Feringa at the University of Groningen. And professor Feringa had an idea – to use the light-controlled molecules that he was developing in

clinical applications. A few others around the World shared this dream, and so I was appointed in Groningen to help to make it happen.

And this is a perfect moment to acknowledge Prof. Ben Feringa, as my mentor or many years and my laudator on this very special occasion, a person who is never afraid to dream big and to champion fundamental research knowing very well that any application that changes the world starts from scientific curiosity. It is thanks to this attitude that in Groningen the idea of Photopharmacology was born, and our first drugs were made that could be in the future used as Paul Ehrlich's magic bullets. These drugs stay inactive, until activated with light on the spot.

This idea is not new – in fact already in ancient Egypt and India diseases were treated with sunlight. But already thousands of years ago they knew that something was needed to translate light into the cure. Today, we know that this something is a molecule that is both bioactive and photoactive, and we are at the brink of making the design of such molecules a science driven, general approach to safe and precise medicine.

And with this molecular design principle, the most important challenge of activating drugs remotely receives scientific support and our plan for image guided pharmacotherapy gets sharper, becoming: **to use medical imaging to find out**

where the problem is, and then activate the drugs only there with light.

So let us imagine this future before we can build it. If you are a photo-doctor, working in the newly created photomedicine department at UMCG in, say, 25 years, sitting next to your patient with a light source (and protective glasses), I believe you will have several questions to us, fundamental researchers.

1. Firstly: how will you know where to point your light to? Most diseases, including tumors, unfortunately tend to hide their location. Can we somehow color them for the doctors to see? Well, luckily there was a person who discovered that certain pigments can be accumulated by living organisms, which led to the discovery of cell staining. And believe it or not – this person was Paul Ehrlich! In the century that followed, we have of course learned much more on how to do it better, also without necessarily cutting the patient's body open to see where the colored cells are. In that respect, we are really lucky here in Groningen, where strong chemistry program at the Faculty of Science and engineering is matched with extensive preclinical and clinical expertise in medical imaging at the Medical Imaging Center of the UMCG, supported by initiatives such as GronsAI. This is an opportunity that we must – and will – build on, to synergize photopharmacology with medical imaging on several levels.

2. The next question might be even more obvious – how do we deliver light to the parts of the human body that require the pharmacological intervention? You do not see what is behind me, and this is simply because our bodies are not transparent to light, and even the most deeply penetrating red light only goes around one centimeter into soft tissues before it is scattered and absorbed. It might be tempting to use very thin, biodegradable optic fibers for light delivery – but this is not always feasible, and we are constantly on the lookout for less invasive options, even if this takes us to the realm of science fiction. Simply because... what if we do not deliver light to the chosen place, but try to generate light in there? One option, around which I have built a consortium of researchers from all over Europe, is to use sonoluminescence – a curious phenomenon that occurs when you hit very small bubbles of air with high intensity ultrasound, and they emit light that could activate drugs locally. We know from our work with UMCG that such high intensity ultrasound can be delivered even into the brain – making this a very promising approach. Another option is to use deeply penetrating, high energy radiation, such as the one we use in X-ray imaging, PET imaging and radiotherapy, and complement them with materials developed for CERN in Geneva to change this radiation into visible light. Another avenue that we are actively exploring is to make drugs that respond directly to this high energy radiation. This quest for the holy

grail of light delivery in human body is definitely one of the most outlandish, science-fiction and exciting work we are doing, and a quest in which the special connections between fundamental disciplines and clinical research that we find in Groningen can make a real difference.

3. For the final question, let us come back to our photo doctor, sitting there with his laser. Even if they know where and how to deliver light, they are paradoxically still blind – having no idea if the light reaches its destination and activates therapy with sufficient efficiency. So, they do not know if the treatment session is complete or should be continued, or if the light intensity is enough or should be increased. This is something that cannot be standardized – our bodies differ in their composition, pigmentation, thickness of adipose tissue, and we need to show real inclusivity in our treatments by accommodating for those differences. To do this, we need to give the doctors the possibility to see on-line how efficient the light treatment is, and again – this is something that will occupy my research group in the years to come, in collaboration with our UMCG friends working on optoacoustic and magnetic resonance imaging. And it is exactly this need for interdisciplinary research that brings me to the construction of second of the three bridges, and it is something that I cannot do without the help of many of you.

The Second Bridge

At the risk of testing your patience, I would like to come back one more time to Paul Ehrlich, who realized that his magic bullet is a bit more a bullet and a bit less magic. Specifically, it caused severe side effects such as rashes, liver damage, and something he noted down as the "risks of life and limb". He considered those effects to be caused by improper handling and administration, which made him observe that "the step from the laboratory to the patient's bedside is extraordinarily arduous and fraught with danger."

And indeed, this is a quest better not undertaken alone. Luckily for me, having worked at GBB Institute, Stratingh Institute, University Medical Center and now Groningen Research Institute of Pharmacy (in that specific order), I have made enough friends to embark on this journey. It would not have been possible without the help of Professors Rudi Dierckx and Gerrit Poelarends, the two key people who trusted me enough to give me a chance to build my group under their wings. They also realized that what a young professor needs is not necessarily direct scientific help, but rather an umbrella to shield them from faculty politics and everything else that is a distraction rather than science. To both, many thanks.

And now onto the second bridge that I will help to build - which will definitely be easier when interfaculty politics is taken away

- the bridge between the Faculty of Science and Engineering and the University Medical Center. While I have worked for both, I will approach this obvious synergy here from the fundamental research perspective of the FSE. We are different, and this difference must be celebrated and taken advantage of. At FSE, we have reaction mechanisms on our blackboards – while the doctors at UMCG experience clinical dilemmas at the bedside. We don't trust correlation coefficients less than 0.95. They are distrustful of anything above 0.8. They talk to patients, we talk to our chemical reactions (if you are a chemist and you do not talk to your reactions, I suggest you start doing it). PhD students at UMCG define the chapters of their theses in the first months of their PhD trajectory, while the PhD students at FSE are watching in disbelief. Sometimes, working for both seems like navigating between the sacred and the profane, and I refuse to say which one is which. Instead, I will help build a bridge, which is based on a simple equation: we provide solutions and seek problems. They provide problems and seek solutions. We simply need to make sure that the problems in both those sentences are in fact the same...

To showcase the solutions that the second bridge will provide, let me introduce the second of my three heroes, distinct due to the fact that she is still alive and I in fact had a chance to meet her. This hero is Tayyaba Hasan, Professor of Dermatology at Harvard Medical School. If I ever have any doubts about a scien-

tist being able to bring light-based medicines into the clinic – and the pharmacies – her example comes to the rescue. Trained as an organic chemist in Karachi, she crossed country borders and scientific disciplines and built her own bridge between chemistry and the clinic, exemplified by the discovery of Verteporfin, a medication used in photodynamic therapy. What I find the most inspiring, is her realization that such light-activated therapy can be relatively cheaply and routinely applied in third world countries, leading her to focus on diseases such as leishmaniasis, tuberculosis and infection with antibiotic-resistant bacteria. This not only aids the war against poverty but also our war against microbes, who so far are able to come up with defence mechanism against every antibiotic we can find. Inspired by this, together with our friends in the Medical Microbiology department, we will follow her footsteps to create treatments that pathogenic bacteria cannot fight against.

Coming back to Paul Ehrlich and his words about the step from the laboratory to the patient's bedside – Professor Hasan is a true hero to follow when navigating the vast sea between disciplines, and I am always taken aback by how close my scientific goals follow hers – we come from different generations, different continents, different backgrounds – and yet the dream remains the same. And if she can find the synergy of fundamental science of and the clinic at Harvard – then so should we. Will it be easy? No. Will it drive me crazy? Possibly, as everyone

who tried before can attest. Will I be alone? No, because I have friends who guard my sanity in academia, and this is a perfect moment for me to give thanks to my friend dr. Anouk Lubbe, who has played this part for many years now.

Furthermore, initiatives such as HTRIC are a step in the very good direction and will help establish Groningen even more firmly on the map when it comes to health innovation in Europe. Together, we can build this bridge, and I will tell you how – the key lies in the training of students at both faculties. I am very happy to be involved in teaching courses that show the clinical perspective to students in the chemistry master program, and courses that explain quantum chemistry to master students at the medical faculty. In the end the best way to build the bridge is to show the young generation that the bridge is in fact not needed – and that the divide is only made on paper.

The Third Bridge

If you walked with me that far, and built two bridges, let us not be shy and let's attempt the third – and the last - one. I would not be here without some very important people: my father who could not come here anymore, my mother who could and who made me who I am, my brothers and cousins who helped raise me, my wife whose dream of coming to The Netherlands I bravely followed in 2007 and who then even more bravely fol-

lowed my dream of returning to Groningen in 2008, and my amazing son. Thank you all.

And it is my son Adam, with whom I would like to introduce the last bridge of today. When I look inside his room at night, I see him quietly asleep in his bed, and I see the toy stars that he put on the wall – the kind that collect light during the day and shine it back for a half an hour after the light has been switched off. These toys likely contain strontium aluminate, doped with europium or dysprosium, giving it a long persisting phosphorescence. Light during the day brings the chemicals in the toy stars into excited state, leading to the electrons being trapped in the vacancy defects in crystal lattice that then in the dark decay to ground state emitting light. And this is the scientifically correct perspective on how they work, as good as I can explain it.

But I want to believe that these stars also work by bring peaceful dreams to my child, and this is also a correct perspective. Maybe we can agree that those two points of view are both right and yet we keep them as much orthogonal as we can. However, do we need to keep them separate, or is there indeed another bridge to be built here? With a bit of trembling heart, I support this idea with a thought from our third hero, one of the greatest philosophers and logicians of 20th century: Bertrand Russell, who wrote:

> "Metaphysics, or the attempt to conceive the world as a whole by means of thought, has been developed, from the first, by the union and conflict of two very different human impulses, the one urging men towards **mysticism**, the other urging them towards **science**.
>
> But the greatest men who have been philosophers have felt the need both of science and of mysticism: the attempt to harmonize the two was what made their life, and what always must, for all its arduous uncertainty, make philosophy, to some minds, a greater thing than either science or religion."
>
> (Bertrand Russell, "Mysticism and Logic," The Hilbert Journal 12 (July 1914), 780-803)

My friends in fundamental science and engineering, do not be alarmed by this tone – but just look at the date. This is still Russell the hopeful logician, who has 4 years earlier, together with Whitehead, published *Principia Mathematica*, trying to create a foundation of mathematics that is perfectly consistent and complete. In the process they spent almost 400 pages on proving that 1+1 equals 2, and with the typical British humour noted that this proposition is occasionally useful. This is still Russell 17 years before Gödel obliterated the hopes of reducing mathematics to a set of logical laws with his incompleteness theorems.

So, let us give Russell the benefit of the doubt and explore the bridge between science and that which made us look to the stars in the first place. As Russell outlines, these two approaches differ in several aspects that are, however, not exclusive. In scientific epistemology, certainty follows inquiry. In mysticism – certainty precedes inquiry. While science gathers knowledge through sense, reason and analysis, mysticism proceeds through the path of insight, revelation or intuition, and I challenge any scientist to deny that they have ever made a discovery through those means alone. As Russell puts it:

> "(...) the opposition of instinct and reason is mainly illusory. Instinct, intuition, or insight is what first leads to the beliefs which subsequent reason confirms or confutes; (...) Reason is a harmonizing, controlling force rather than a creative one. Even in the most purely logical realm, it is insight that first arrives at what is new." (idem)

So, what is the gap over which the bridge should be built? Where does the main line of division lie? As Russel outlines, mysticism is characterized often with the denial of any divisions (seeking "The One" behind the many), which leads directly to the denial of time and space – if all is one then the division between the past and the future, the here and the there, must be illusory. Science, on the other hand, embraces this division, recognizes space and time – and yet makes them

relative and connected. However – and this is as crazy as I will go today, so have no fear those who still read this lecture – Russell says this as a child of the West. Looking East – and I do it with Samkhya and Yoga philosophies in mind, but I am sure my more humanistically inclined friends could broaden this view – we can discover that The One and The Good of Plato were not necessarily the same. Conversely, the Eastern ontological dualism gives us access to seeing the experiencing entity as separate from the experienced, bridging the gap to the purely scientific world view.

I bring this all up because building the bridge between the science as we do it in our laboratories, and metaphysics as our philosophy friends do in their offices, as advocated by Russell, will affect how we see our duty and how we interact with our colleagues and patients. It will let us look at a molecule as a product of our chemical synthesis and as a cure or a poison for a suffering patient, whom we meet in the corridor of hospital where we work. It will let us look at it from the perspective of a physician contemplating a clinical dilemma in which the molecule can help.

And finally, seeing the human being behind the molecule, and the molecule behind the human being, will change how we see our students – who are the most important products of what we do in academia. And I as an academic am a product of them and

every moment they spend in my group. There are no words with which I can thank you all. I humbly stand on your shoulders, and I see each and every one of you. This is what happens when you stand on the shoulders of giants.

In my last words, let me come back again to Russell who concludes his assay as follows:

> "A truly scientific philosophy will be more humble, more piecemeal, more arduous, offering less glitter of outward mirage to flatter fallacious hopes, but more indifferent to fate, and more capable of accepting the world without the tyrannous imposition of our human and temporary demands." (idem)

Russell is talking here to his colleagues, philosophers. But as a representative of fundamental sciences, I took this personally and will try to meet him in the middle. It is a tall order, mister Russell. But let us see what we can do.

I have spoken. Ik heb gezegd.

Wiktor Szymański received his PhD degree from The Warsaw University of Technology, Poland, in 2008. He spent two years working on the use of biotransformations in organic chemistry with Prof. Ben L. Feringa and Prof. Dick B. Janssen at the University of Groningen. Since 2010 he has been working on the development of photopharmacology in the Feringa Labs. In 2014, he joined the Medical Imaging Center, University Medical Center Groningen, where he was appointed in 2015 as tenure track assistant professor and in 2019 as associate professor. In 2023, he became a full professor at the Groningen Research Institute of Pharmacy, where he holds the chair of Medicinal Chemistry, Photopharmacology and Imaging. In his free time, Wiktor dives and teaches classical yoga.