Metalen en licht: sleutels naar een gezondere wereld

Bonnet, S.A.

Prof.dr. S. Bonnet

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Universiteit Leiden

Bij ons leer je de wereld kennen

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Oratie uitgesproken door

Prof.dr. S. Bonnet

bij de aanvaarding van het ambt van hoogleraar in de

PhotoBioAnorganische Chemie

aan de Universiteit Leiden

op 8 September 2023

Universiteit
Leiden

Mevrouw de Rector Magnificus,
zeer gewaardeerde toehoorders,

Most of you might have come to this inaugural lecture thinking about metals as something hard, shiny, particularly useful for making solid objects such as pieces of a train, nails, jewels, cooking pans, or swords. For many, metals still unconsciously remind us of the Bronze and the Iron ages in prehistory, when men learned how to smelt and melt gold, copper, bronze, and iron. Already at that time, metals were used to make weapons, and metal chemistry was one of the most important skills to have to stay ahead of competitors. Metals bring power and fascination since the bronze age till today, where we still make tanks and planes, but also bikes or surgery scalpels, out of hard metals such as steel or titanium.

However, these kinds of metals are not the ones I want to discuss with you today. Though access to metal ores and mastering the chemistry of metallic elements still represents an important source of power in modern societies, there is a more peaceful, natural aspect to metals that you might ignore: their ubiquitous presence in the living world, and their widespread use in medicine.

In contrast to the metallic objects mentioned before, metals in life appear in a form that is difficult to grasp for the untrained human eye: they are engulfed into molecules. In fact, metal-containing molecules are everywhere in our body. Proteins containing iron transport dioxygen in my blood while I am talking to you; copper enzymes ensure that my articulations remain flexible and move quickly, but also that you survive the radical species you produce when listening to my inaugural lecture... Calcium controls our muscles, while magnesium stabilizes DNA in our cells; zinc is central to the communication between neurons in our brains, so that you can make sense of what I say. Other metals are not used by humans directly, but they are still essential to human health. For example, nickel is needed by bacteria growing in our digestive track. Too much nickel in our food and our immune system goes berserk; too little nickel in our guts, and good bacteria such as *Bifidobacterium bifidum* cannot survive, thereby destabilizing our microbiome. Green plants also need metals; manganese and molybdenum allow them to extract electrons from water or nitrogen from the air. Overall, understanding the chemistry of the so-called biometals forms half of the research domain covered by my professorship. It is the main topic of one of the courses I currently teach to the students of our Chemistry and Life Science and Technology Master programmes, called " Metals and Life". The fact that 30% of the proteins in our body rely on biometals for their structure or function, remains to me one of the most fascinating aspects of biology. Understanding why an enzyme needs iron and not copper, or manganese and not zinc, is both exciting and challenging.

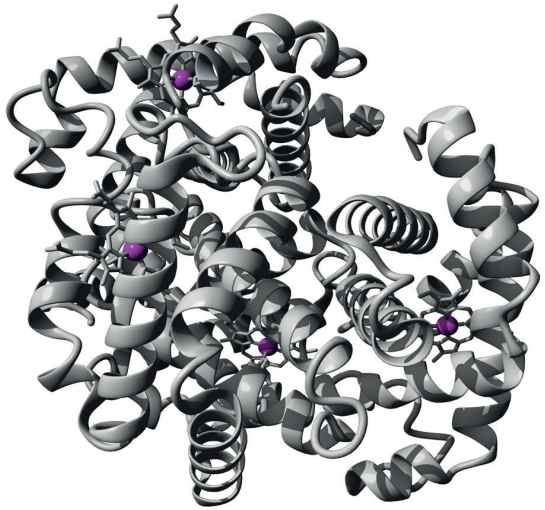

Figure 1. X-ray structure of haemoglobin, the red-coloured, iron-containing protein that transports dioxygen in our blood. The four Fe^{2+} ions of the protein appear as magenta spheres; the rest of the protein backbone is shown in grey (PDX: 1GZX).

In all metal-containing proteins, the metal atom is not in its metallic form. In fact, a metalloprotein is neither shiny nor hard, but soluble in water, and coloured. Also, unlike in an iron dust particle where thousands or even millions of iron atoms are close to each other like soldiers in a Roman legion, in proteins metal atoms are usually found in small numbers. For example, one molecule of haemoglobin in our blood contains only four iron (Fe) atoms, while the protein as a whole is made of 4765 other atoms (*Figure 1*). Still, without these four iron atoms haemoglobin could not transport dioxygen to our muscles and brain. These four iron atoms are not only further away from each other than in metallic iron; but also, each Fe atom has lost 2 electrons, to form an Fe^{2+} ion. Because of its positive charge, each Fe^{2+} ion likes to be bound by 5 electron-rich nitrogen atoms that hold the metal centre to the protein. While the iron element allows haemoglobin to bind dioxygen, the protein in return modifies the chemical properties of each iron ion, which cannot do much else than binding or releasing the O_2 molecule. If the Fe^{2+} ion could escape the protein backbone, it would become highly toxic to our cells by reacting with O_2 to form radical species that cause both ageing and cancer. As you can see, in enzymes the metal centre defines the property of the enzyme - haemoglobin cannot transport O_2 without iron – but the protein also modifies the chemical properties of the metal centre. Iron in haemoglobin does not perform the same biological function than iron in cytochrome P450, one of the enzymes involved in drug metabolism.

The other half of my research is dedicated to another aspect of metals in life that is central to my research: the use of metal-containing chemicals in medicine. Because of their importance in technology and weaponry, the mastership of metal ores, their transformation into metal containing products and tools, has put human into contact with metal-containing compounds since thousands of years. While the handling of iron ores and objects is usually considered as chemically safe, copper ores for example often contain large amounts of a toxic metal called arsenic (As, see *Figure 2*). Preparing pure copper therefore requires knowing how to stay away from arsenic. In fact, arsenic was even added deliberately to metallic copper to make bronze between 4000- and 2000-years BC in Mesopotamia, ancient Egypt, and in Northern Italy, from which it travelled further to Europe and China. These techniques have spread arsenic all over the world, following the route of bronze objects and of the humans who made them. Arsenic compounds are toxic to nerves, and lame smiths were not uncommon in ancient times. The Greek god of blacksmiths and metallurgy, Hephaestus, was lame as well. Gold workers, on the other hand, extracted the precious metal using mercury (Hg), another toxic metal. Because of mercury toxicity, artisanal gold miners were also subject to many neurological disorders. The same applies to felt hatters in 15th century England, who were using mercuric nitrate in their felt production. Throughout history, heavy metals have gathered a bad reputation. Still today, mercury traces in fish or cadmium (Cd) in industrial waste waters, cigarette smoke, chocolate, or phosphate-containing fertilizers, make the headlines in national and international newspapers.

The limits between the toxicity and a medical use of a chemical compounds, are thin. Humans have discovered throughout history that "toxic" could also mean "biologically active", and that the general toxicity of a compound for the organism, when properly understood, could be turned into a very specific and medicinally useful action. For example, arsenic and mercury were the first metals in history to be deliberately used in human medicine. Hippocrates already developed arsenic-containing preparations to treat ulcers, and Chinese and Indian traditional medicine advised arsenic-containing herbal preparations as early as 200 BCE. Paracelsus, a professor of medicine in Padua in Italy in the 16th century, or Thomas Fowler, a British physician from the late 18th century, perfected the therapeutic use of arsenic to treat syphilis, malaria, or skin cancer, in times when no other human preparation could do that. The arsenic-containing drug called Salvarsan, which was co-developed by Sahachiro Hata in Japan and Paul Ehrlich in

Germany, saved many people from syphilis. In this drug, the toxicity of arsenic was fine-tuned to be targeted more towards the syphilis bacteria than to its human bearer. Closer to our times, in the early years 2000, arsenic trioxide, a very simple arsenic compound, was approved by the FDA as anticancer drug for the treatment of leukemia. What a success for an element with such a bad reputation!!!

Nowadays, not only arsenic, but many other metallic elements of the periodic classification, are used in medicine. Platinum anticancer compounds are added to almost half of cancer patients receiving chemotherapy, while 45% of patient undergoing MRI diagnosis receive a gadolinium-containing contrast agent. Other techniques to treat cancer involve metals: radioactive actinium (^{225}Ac) is used in internal radiotherapy of metastatic prostate cancer, while radioactive ruthenium (^{106}Ru) is the standard-of-care in The Netherlands for the treatment of uveal melanoma, a rare form of cancer appearing in the eye.

One of the most common misconceptions in my field is coined with the term "heavy metal": I am not talking about music here, but about metals with a high specific weight. The idea was that all elements being heavier than, say iron, would share a common toxicity to the human body. This idea is widespread, but completely wrong. All metals are different! For example, platinum (Pt) and gadolinium (Gd), both classified as heavy metals, are as different from arsenic (As) and mercury (Hg) as nitrogen differs from carbon or hydrogen. While many may think that gadolinium or ruthenium are necessarily radioactive, they are not! Most elements of the classification exist in different isotopes, some of which are radioactive and some others are not. Carbon or hydrogen are no metals but yet can be strongly radioactive. In my lab, we work with ruthenium-containing compounds that are not radioactive at all. In fact, the difference in chemical properties between different metal ions, is one of the most fascinating aspects of my research. We discovered throughout the years that

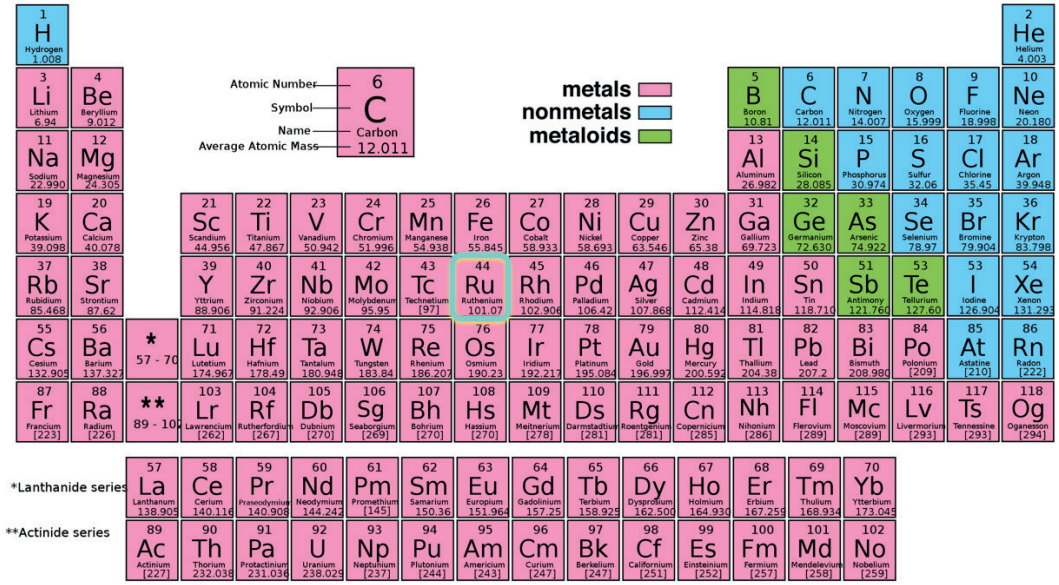

Figure 2. Periodic classification of the elements. Metal elements are coloured in pink (CC-BY-SA-4.0).

compounds that contain heavy metals are not necessarily very toxic; in fact, their toxicity strongly depends on the organic ligands that are bound to the metal ion. Ruthenium (Ru) is a large metal element situated in the same column as iron in the periodical classification (*Figure 2*). While Ru chemically speaking belongs to the family of heavy metals, many ruthenium-containing compounds made in my lab, are in fact non-toxic.

So why use ruthenium for making new anticancer medicines? As you all know, most chemotherapy cocktails have strong side effects for the patient. These effects are not only cosmetic such as hair loss, or limited to the short time of the therapy like fatigue. Chemotherapy side effects also include pain, severe disruption of the digestive tract, and can have life-threatening effects. In fact, many chemo treatments have to be tuned down to what a patient can bear, which may limit the antitumour efficacy of the treatment. My research group develops new ruthenium-containing compounds to solve this problem: We want to develop anticancer drugs that do not provoke these nasty side-effects. We use ruthenium compounds because of their unique combination of three properties: they are stable in the dark, they absorb light very well, and they are photochemically active. Let me explain these three ideas.

First, their stability in the dark. When an anticancer drug, for example one containing platinum, is injected in a patient, the chemical clock starts ticking: the different organic molecules bound to the platinum ion, upon facing the complex environment of our blood, start to detach. In fact, they are replaced by biomolecules from the biological environment, such as our DNA, amino acids from our proteins, or other small molecules present in the cell. The binding of these molecules to the platinum centre starts, in fact, the cascade of events that lead to the biological action of the drug. Of course, as long as these reaction occurs in or near the tumour, the patient and doctor are happy. The problem arises when these reactions also take place in healthy tissues: then, toxicity to the patient's liver, gut, or nerves, start as well. With ruthenium it is possible, by careful molecular engineering, to make prodrugs that are particularly stable chemically: they will not exchange their ligands with other biomolecules, they will not start killing cells before we do something to the molecule from the outside. In other words, they will essentially do nothing: we call them "prodrugs".

The second reason why ruthenium compounds are so special are their light absorption properties. Ruthenium is not magic, but it is placed right at the good place in the periodic classification. Go one column to the right or to the left: the rhodium (Rh), iridium (Ir), or rhenium (Re) compounds you will obtain will be poorly coloured because they mostly absorb light in the UV region of the spectrum. By contrast, it is possible to make ruthenium prodrugs that absorb green, red or even near-infrared (NIR) light. These types of light are best suited for phototherapy in the treatment of cancer: NIR light penetrates up to 1-2 cm in biological tissues and can be used for larger tumours, while green light penetrates a few millimetres in human flesh, which can be used to treat thinner tumours with great precision.

These last explanations lead me to my third point: the specific photochemical properties of the ruthenium compounds made in my group. Upon absorption of visible light, they become "excited". Like each of you would become sharper, run faster, or hit stronger when faced to an enemy on the battlefield because of the exciting action of adrenaline, a molecule that has absorbed a visible photon become much more reactive. To lose this excitation, the molecule will react : this is called a photoreaction. In fact, many photoreactions can occur upon light absorption. We fine-tune our ruthenium-containing molecules so that they split in two fragments when absorbing light. This reaction, when it takes place in a molecule that does not react in the dark and absorbs visible light, allows us to build photoactivated chemotherapy compounds. In a nutshell, we follow this receipy: we take a toxic chemotherapy drug that contains a nitrogen or sulfur atom that likes binding to metal ions. We then attach this molecule to ruthenium

by heating a ruthenium-containing precursor chemical and the chemotherapy drug. By doing so you obtain a so-called "photocaged" chemotherapeutic drug, or "prodrug": a compound that cannot do much harm in the body, unless it is activated by light. It does not do much in the body because the anticancer mechanism that was carefully built in the chemotherapy agent by medicinal chemists, is blocked by the presence of the large ruthenium fragment now attached to it. The unactive ruthenium-based prodrug is introduced in the patient, where it will reach the tumour without any toxicity. In a second step, the oncologist will use a green, red, or NIR laser to shine light onto the tumour in the operating room. By doing so, the surgeon will activate the prodrug by cleaving the link between ruthenium and the chemotherapy agent, thereby releasing the chemotherapy locally, only at the tumour location. This local release will kill the tumour cells and destroy the tumour as would do a dose of compound directly injected in the tumour. However, the toxicity of the treatment to the patient will be minimal, because the prodrug is only activated in the tumour, and remains inactive in the rest of the body. This is the principle of photoactivated chemotherapy – a principle abbreviated as PACT and schematized in Figure 3.

[Demonstration of shining light onto the tumour of a mock patient with the public]

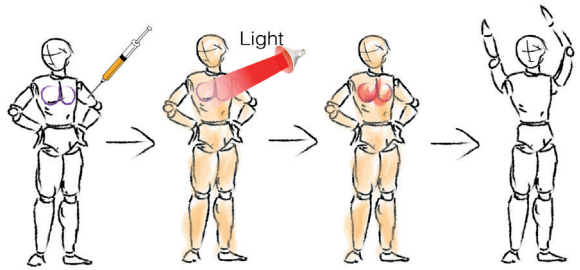

Figure 3. The principle of anticancer light-activated prodrugs. The tumour is shown in purple, the prodrug in orange, and the light-activated prodrug in red.

I should probably say here that I did not invent the idea of using light to activate a prodrug in a tumour. There is another technique to do that, which is called photodynamic therapy and abbreviated PDT. PDT is already approved for clinical use to fight bacterial infections or certain forms of cancer. For oncology only a handful of light-sensitive PDT prodrugs are approved by the FDA or EMA. They are used in a range of cancers such as non-melanoma skin cancer, prostate cancer, lung tumours, oesophagus cancer, or head-and-neck cancer. All these approved PDT molecules work by a mechanism that is completely different compared to that of our ruthenium-based PACT compounds. In PDT, upon absorbing a photon the molecule transfers the light energy to a molecule of dioxygen, which generates radical species that are highly toxic to cells. Any compound that is not irradiated with light remains non-toxic, while cells irradiated with light but in which no compound is present, remain unaffected. If you can target such compounds to tumour by chemical engineering, and if you shine light only on a tumour, you can hence obtain quite fascinating antitumour effects with particularly low side effects for the patient. New applications of PDT in the fight against bacteria and parasites are currently emerging, with here as well particularly promising results.

In the last years I have travelled to Brazil, to the USA, and to Finland, to international conferences that have convinced me of the power of the PDT approach. I have seen photos of a 16-year-old Brazilian girl devastated by a genital infection for which the standard of care in Western countries is surgery. When performed at 16, this treatment means no sex life, no children, strong psychological disorders, and a very hard life overall. Brazilian doctors did a series of photodynamic treatments of this patient, which led to eradication of the infection without a need for surgery, avoiding the horrible side effects that I just mentioned. Older Caucasian women affected by a form of skin cancer of the genitals called Paget's disease of the vulva, are treated by PDT as well in a clinical trial performed in the North of France. Here as well, the western

standard of care involves highly debilitating and painful surgery. Thanks to PDT, surgery could be avoided. I have seen cancers at the tip of the penis, treated with PDT with similar success in men. I have seen face tumour photographs that I would not dare to show you today; here as well PDT treatment has shown to be extraordinary efficient, and led to much less side effects than radiation therapy , chemotherapy or surgery. In the veterinarian world, I have seen tumours on a cats' face: when removed by surgery, the cat's moustache had disappeared and the nice animal had been transformed in a healed but scary tiny monster; after PDT treatment, the tumour was simply gone, without any change of the cute face of the feline companion. PDT also does wonders for small eye tumours called retinoblastoma in 2-year-old children, or recurrent bladder tumours. In the latter case, standard of care often leads to the removal of the bladder, with the side effects and low quality of life that you can imagine. When PDT is successful, the therapy is efficient, and causes much less side effects for the patients.

Though impressive, PDT cannot treat every kind of cancer. There are more than 100 identified forms of cancers in humans, and 18 million cancer patients worldwide in 2020, each of whom with individual specificities. Like any forms of anticancer treatment, PDT fails in many cases. PDT with currently approved molecules also has some side effects for the patient, such as photosensitivity, tissue necrosis, or pain. Also, in many tumours, it is simply not efficient. Several problems can arise that explain the lack of efficacy of PDT. For example, some tumours in the brain or liver are poorly oxygenated. As PDT relies on the activation of dioxygen, it will not work in such tissues. Other tumours offer specific resistances to the PDT effect, for example eye melanomas, in which melanin protects the tumour against the radical species generated by PDT. These cases where PDT does not work, are precisely the ones for which we develop new ruthenium-based PACT molecules. In these molecules, the activation of the drug is oxygen independent, so it will still work when there is little or no oxygen in the tumour tissue, or when the tumour tissue is too rich in melanin. In my lab, we grow cancer cells in low oxygen conditions, and test our molecules specifically in such conditions. We have seen and published evidence showing that our molecules still work when PDT fails. We have seen antitumour efficacy in black melanin-rich eye tumour models in mice. I am convinced PACT can lead to new anticancer treatment with low side-effects for the patient.

Of course, we have no time today to discuss the details of how to design, synthesize, and test new PACT compound. I will only mention that within my group we are only busy with the beginning of drug development. We start with the design of a chemical formula on paper, move to the chemistry lab to perform the synthesis and characterization of the ruthenium compound, and then go to the Cell Observatory, our biology laboratory. Here we test our compounds in cancer cells, both in the dark and upon irradiation with different sources of light, from blue to green, from red to infrared. We also test what happens in cancer cells deprived of dioxygen. 3 years ago, we even started testing our molecules in mice tumour models using the animal facility of the Faculty of Science, as it is currently impossible to convince industrial partners of the efficacy and safety of a medicinal compound without mice studies. Recently, we obtained funding from the European Commission to develop one of our PACT compounds for the treatment of eye cancer towards the clinic. This translational research is more applied than what we are used to. We do it in collaboration with a start-up who is in charge of the commercial development of the prodrug, and two major medical hospitals for the treatment of eye cancer in patients: the LUMC in The Netherlands, and the Institut Curie in Paris. The path towards clinical trials is long and risky, but specific funding can help to at least try. I would like to mention here that, though very exciting, this translational opportunity is only one of our projects. Other people in my group are busy with more fundamental aspects of light-activated drugs, from improving their synthesis, to the challenge of delivering them

to tumours of different kinds. But we always keep an eye on possible clinical applications of our research.

In fact, our research on light-activated ruthenium compounds is quite special. While many colleagues in chemistry focus on a sole discipline, such as organic or inorganic synthesis, spectroscopy, or theoretical modelling, in my group all PhDs and postdocs do interdisciplinary research. They surf between synthetic work to make their molecules, spectroscopy to study what shining light on them does in a glass tube, biology to check whether they work in cells, and sometimes theory as well, to understand with quantum mechanics why their molecules react with light the way they do. Not all the people in my group are chemists, some of them are biologists and theoretical chemists. This necessary combination of expertise is both a blessing and a challenge. A blessing, because some people truly like to see with their own eyes what a molecule they have prepared in the lab can do. They don't want to send their molecule to a collaborator, wait for 3 months, and see numbers in a graph. They want to prepare a solution of their compound, put it on cancer cells, shine light of different colours, and see what happens. These people are in fact precisely the people who are attracted by my research group. But this combination is also a challenge, because working at the interface between many disciplines bears the danger to miss excellence in any given topic, and to exhaust students with too many experiments to do. This is a catch 22. To resolve it, my approach is based on two pillars: collaborations and training. Collaborations, because keeping discussing details with pure biologists, pure theoretical chemists, or medical doctors outside the group, keeps us aware of our limits, and allows us to sharpen our questioning. Training, because people in the group train each other – chemists teach biologists how to look at a molecule; biologists train chemists to be sharper with errors and statistics, and better at pipetting. For me, there is nothing more valuable than hiring a young scientist on a question that I don't really know how to solve, and through extensive discussions in the group and experience sharing, to see the beginning of a solution, and sometimes an unexpected discovery, in a nice-looking booklet. We call this process "training by research"; this is where I want to be in the next 20 years of my professorship.

I will leave for a while the safe paths of Shakespeare's language, to address my Dutch colleagues and guests. For the others, my speech is translated in the booklet you have in your hands. Let me start by confessing two things to you: First, when coming to the Netherlands I was not planning to stay. In the French mind of the young French researcher I was, being a postdoc was a necessary moment in life to increase my publication list and my experience in research, to perfect my English, and an obligatory step to apply for a CNRS position in France. Second, I will be honest: I have never applied to such a position; I even refused an offer made by a renowned French institute a few years ago. Why did I stay in Leiden? A special love for bitterballen? A passion for the cantine of the Faculty of Science? These are certainly unexpected discoveries, but they did not help me stay in Leiden. Did I stay because of a steady, secure, and abundant funding for my research? Those who think this may raise their finger in the room… I have been quite successful in acquiring research funding, but it was neither steady nor secure; you can think about it as a bumpy road, or a wavy, windy ocean: you better catch the wave, or it will pass over you, or hit you hard. A good friend of mine working at Shell once said that academia was "a bad business model". Shell managers invest in new projects when their chance of economic reward is 60-70%. In the academia, most calls we apply for have between 5 and 10% of success rate: we spend a lot of time writing excellent projects that will never be funded. The direct consequence of this system remains the main burden on my shoulders as professor: The difficulty to keep a steady number of co-workers in my research group, and not to lose our own expertise. Every PhD student or postdoc who leaves the group is an important part of our knowledge that goes away. The only way to keep our expertise is to organize training of young ones by more experienced

researchers. In a group where the turnover is limited to 3-4 years, this knowledge transfer is a major endeavour. I keep using my time avoiding my group to become empty when funding is not successful, and managing overcrowding when it is. In fact, Dutch researchers like me do not need more money for research, but we do need more equally distributed money, and more secure funding.

Then, you might ask again, why did I stay? Maybe the intertwining between teaching and research, which forms the core of our university, is both productive and powerful for me. Maybe the freedom to develop my research wherever I can acquire funding, is just what I need. Maybe the constant operational support from my institute, since the first day of my tenure track position, has played a critical role in my success in acquiring funding, and in my international recognition. Maybe the unique research environment in Leiden combining physically close institutes working on drug development, the LUMC, the BioScience Park, and the nearby NKI, was just the right place to be for me to develop PACT. Maybe the overall positive and energizing relationship of the Dutch people towards France, has made my personal life easier than in other foreign countries. Maybe the possibility for women in general and for my wife in particular to build a career in The Netherlands while working part-time, has prevented me from moving anywhere else. Maybe all these reasons together have simply cancelled little by little all professional reasons I would have had to come back to France.

The Leiden environment is a particularly good one to perform our research on light-responsive metal complexes in cells and animals: it provides a pool of excellent undergraduate students from our Master programmes; the international fame to attract excellent international PhD candidates and postdocs; and the academic freedom to perform timely innovative chemical research at the interface with biology. I think our group's ancient and more recent successes have shown my community and my institute that our group was able to publish excellent multidisciplinary science at the highest international level.

To be able to do so I profited from the constant support of my Institute; I would like to wholeheartedly thank my three institute directors: Jaap Brouwer for having hired me and supported me during the early days of my independent career, Hermen Overkleeft for demonstrating how short answering an email can be, and for letting himself convince that I had the right stuff to become full professor; and Marcellus Ubbink, for his renewed support since he became director of our institute. My thanks also go to my three Deans, Geert de Snoo, Michiel Kreutzer, and Jasper Knoester, for their enthusiasm throughout the years, their support in my career development, and their ear to the feedback of young colleagues from the Faculty of Science. A special mention goes to my two mentors at the LIC: Jan Reedijk, who has left me the freedom I needed during my postdoc in his group to develop my research on spin-switching iron molecules. This research has set a few seeds that became particularly important, 10 years after, for the making of new ruthenium-based PACT molecules. I would also particularly like to thank here Lies Bouwman, my second mentor in Leiden and our up to now unique female full professor in chemistry. She has faithfully and critically supported me since my hiring and to this day without interruption: by her active mentoring in learning the Dutch language, by her sharp and honest feedback, both on our differences in management styles, but also when reading my students' PhD theses, we have all tremendously profited from her incredible analytical eye on language clarity and logical ordering of ideas. Like Jan, Lies gave me the freedom I needed to develop an independent research line, always keeping her name out of my PhD student's papers in spite of the time she had spent to read their thesis. Her support, like her friendship, are invaluable to me.

Let me zoom out of the institute a bit, and mention a few names: Michal Heger and Antoinette Killian from Utrecht University, Sylvia Le Dévédec from LACDR, and Ewa Snaar-Jagalska from IBL, have taught me a large part of the biology I know today. Their lessons have always been friendly and productive, and I am proud to have published excellent papers with them. Martine Jager, Khanh Vu, and Ellen Kapiteijn, from

the ophthalmology and oncology departments of LUMC, who have introduced me to the challenging but fascinating world of eye cancer, and allowed me to successfully apply to my first translational EU grant. I look forward to working with you in the years to come. My thanks go to my PhD and postdoctoral mentors: first, Gerard van Koten from Utrecht University, who has attracted me to the Netherlands, and taught me a few management lessons on how to run a large group. Then Bert Klein Gebbink, who taught me how to write a scientific paper, and how the Dutch research system was working. And of course my thanks go to my PhD supervisor Jean-Pierre Sauvage from Strasbourg University. He has shown me first that it was possible to be demanding with your PhD students and never sacrifice anything on scientific novelty and quality. Second, his daily practice showed that one could be a top-notch scientist while respecting your co-workers on the work floor, respecting their working times, and respecting their need for a private life. My own private life has been filled with love and care by my two children Marie-Lou and Max and my wife Wiebke; they bring me the stability I need to be productive professionally, and the necessary occasions to breathe and think about something else, when more professional successes always call for more work to do. I would like to also thank my parents and my two brothers, who taught me how to discuss, how to read, how to share, and how to play. Though I probably don't tell them often enough, I owe them a lot.

Last but not least, I would like to thank all my group members, from bachelor and master students to PhD students and postdocs still in my group or who have left several years ago: you are the cornerstone of my research, your scientific and personal development fills me with pride and joy. When I had the honour to have my toga be made, I decided to decorate it with one molecule per student I supervised during my independent career. I could unfortunately not involve molecules made by undergraduates, because I have had 52 BSc and 92 MSc interns since 2009… I would have needed to be much taller, and have many more arms than two, to accommodate them all. I decided hence to go for 1 molecule per PhD student and postdoc who have worked in my group between 2009 and 2020. I even have one under my hat! A metal-containing molecule interacting with a protein, a prototypical example of the research we do in the group. This silk print, more than anything else, puts in drawing my core interest on metal-containing molecules. However, it is also a physical symbol that my professor position, which we celebrate today, is based on the contribution of each individual young researcher who has worked in my group in the last 14 years. I hereby want to thank them all, and I hope many more will come.

Ik heb gezegd.

Prof.dr. Sylvestre Bonnet

After undergraduate studies in physical chemistry in Lyon and Strasbourg Sylvestre Bonnet obtained his PhD in 2005 on light-activated molecular machines with Jean-Pierre Sauvage at the University of Strasbourg, France. He then moved to The Netherlands to work as a postdoc with Gerard van Koten, Bert Klein Gebbink, Antoinette Killian (Utrecht University), and Jan Reedijk (Leiden University). He completed a Tenure Track position at Leiden University (2009-2014), where he recently became full professor. He received several prestigious grants from The Netherlands Organization for Scientific Research (VENI, VIDI, VICI), from the European Research Council (Starting Grant, Proof-of-concept), and from the European Innovation Council (Transition). He is a Fellow of the Young Academy of Europe, of which he was Board Member from 2017 to 2020. His expertise lies at the crossing road between bioinorganic chemistry, photochemistry, and liposomes. He mostly studies how metal-containing molecules interact with light in biological and biomimetic systems. His current research interests are light-activated anticancer metallodrugs, upconversion, and biomimetic photocatalysis.

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