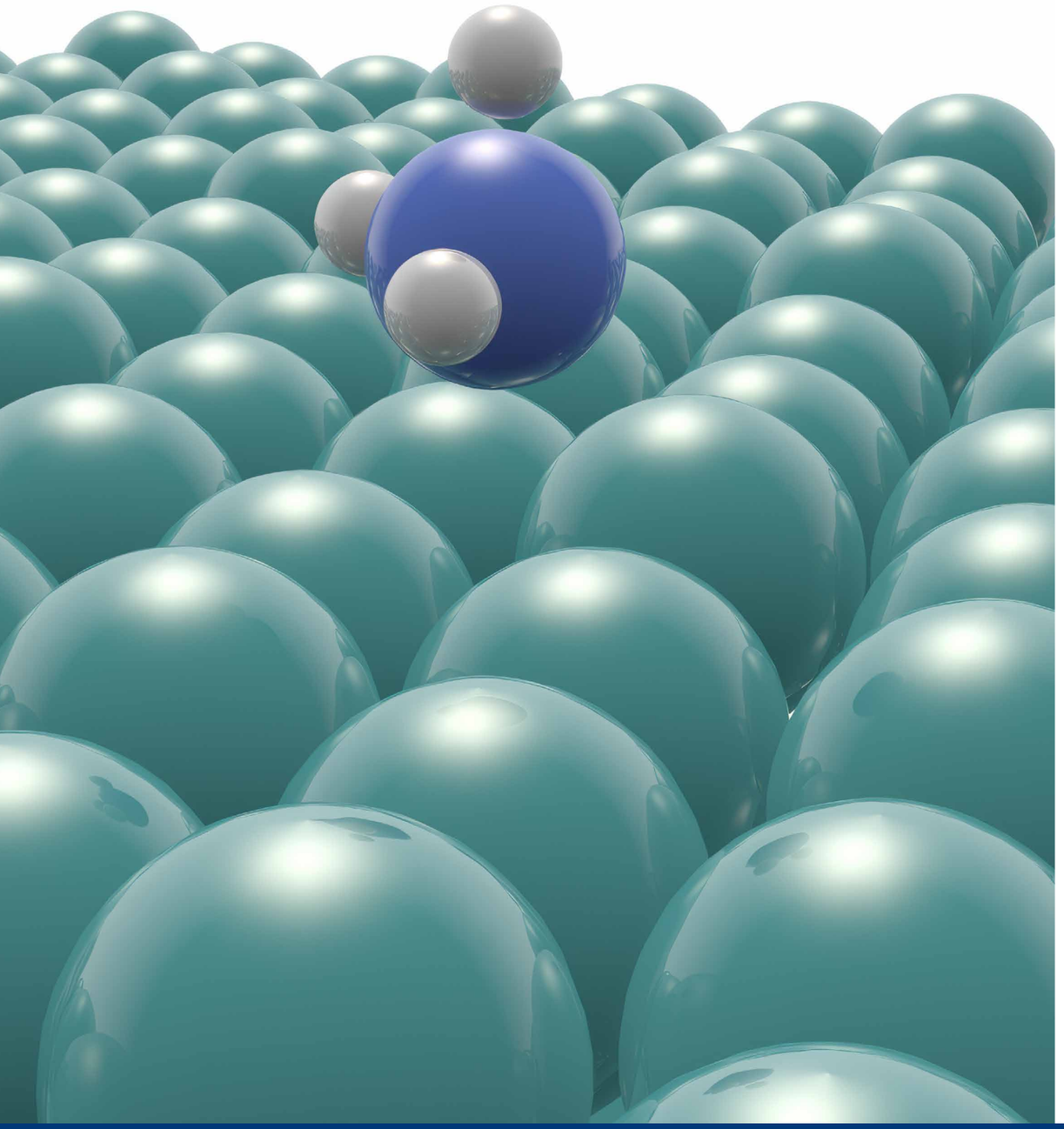


Case studies

CS1: Profiling drug-target interaction landscapes by chemical proteomics

On January 17th, 2016, at a French academic hospital, a phase 1 clinical trial volunteer died, and four others were hospitalised with serious neurological adverse effects after being given BIA 10-2474, an experimental drug that inhibits fatty acid amide hydrolase (FAAH). The cause of the clinical trial disaster was unknown, leading the American and European drug agencies to order a hold on all human studies involving FAAH inhibitors. Although the death of a healthy participant in a clinical trial is rare, the failure of clinical trials is not uncommon, as nine out of ten experimental drugs tested in humans will not reach the market due to a lack of efficacy or unexpected toxicity. Understanding and improving the protein interaction landscape of drugs in the human body is one of the key challenges in contemporary drug discovery.

The Leiden Institute of Chemistry (LIC), in collaboration with three other research institutes of the Faculty of Science (*i.e.* the LED3 hub), private companies (such as Hoffman-LaRoche), and (inter)national groups, including the Erasmus MC, Netherlands Institute of Neuroscience, the Scripps Research Institute, and the National Institutes of Health, USA, aims to develop and apply new concepts, such as chemical proteomics, to improve the drug discovery process. The first chemical proteomics study with BIA 10-2474 was performed by Leiden PhD candidates Annelot van Esbroeck, Anthe Janssen, and Marc Baggelaar to study its off-target effects in human cells and tissue. Marc and Anthe developed chemical probes that Annelot used to quantify enzyme activities in human brain tissue and human cortical neurons derived from inducible pluripotent stem cells. They found that BIA 10-2474 was not selective for FAAH and inhibited several other lipases, disrupting lipid homeostasis in cortical neurons. Ilse Baak, a bachelor student supervised by Annelot, confirmed the off-target profile using recombinant overexpression systems. The results were published in Science, JACS, and Nature Protocols and were instrumental in the decision-making process to resume clinical trials with other FAAH inhibitors by pharmaceutical companies. The Science study received (inter)national press coverage (*e.g.,* NOS, Volkskrant, NRC and Le Figaro) and commentaries in Chemistry World, F1000, Nature Reviews Drug Discovery, and Science.

The study is now incorporated into a bachelor course in the Life Science & Technology program where students learn about drug discovery and perform activity-based protein profiling experiments with BIA 10-2474. The LIC works with pharmaceutical companies to perform prospective chemical proteomics studies to guide their drug discovery programs, leading to the identification of a new experimental drug that was successful in a phase 1 clinical trial. The chemical probe facility of the LIC is part of Oncode-PACT, an awarded national growth fund initiative to improve the drug discovery process in the field of oncology.

Marc Baggelaar defended his PhD thesis *cum laude* on April 18th, 2017. He won the Best PhD thesis Award of the Medicinal Chemistry section of the Royal Dutch Chemistry Society 2017-2018. He also received a Marie Curie fellowship and VENI award and is currently an assistant professor at Utrecht University. Annelot van Esbroeck and Anthe Janssen won several national and international presentation awards and are currently assistant professors in Erasmus MC and Leiden University, respectively.

CS2: Density functional theory for molecule–metal surface reactions: When does the generalized gradient approximation get it right?

While density functional theory (DFT) is perhaps the most used electronic structure theory in chemistry, many of its practical aspects remain poorly understood. For instance, DFT at the so-called generalized gradient approximation (GGA), in which only the electronic density and its gradient are used to compute energies, tends to fail miserably at describing gas-phase reaction barriers. However, GGA-DFT performs surprisingly well for many molecule-metal surface reactions, which are important to an accurate description of heterogeneous catalysis. GGA-DFT also fails for many molecule-metal surface reactions, and up to now it has not been clear when one may expect it to work. Kroes and co-workers have recently shown[7] that GGA-DFT tends to work well if the difference between the work function of the metal and the molecule's electron affinity is greater than 7 eV, and to fail if this difference is smaller, with sticking of O_2 on Al(111) being a spectacular example (see Figure 11[7]). Using dynamics calculations, we have also shown that, for this system, the DFT problem may be solved as done for gas-phase reactions, i.e., by resorting to a hybrid functional, but using screening of the so-called exact exchange at long-range to obtain a correct description of the metal. This last result points the way to a possible solution for the "hard" dissociative chemisorption problems, where the stated difference is less than 7 eV, and which are of high relevance to sustainable chemistry.

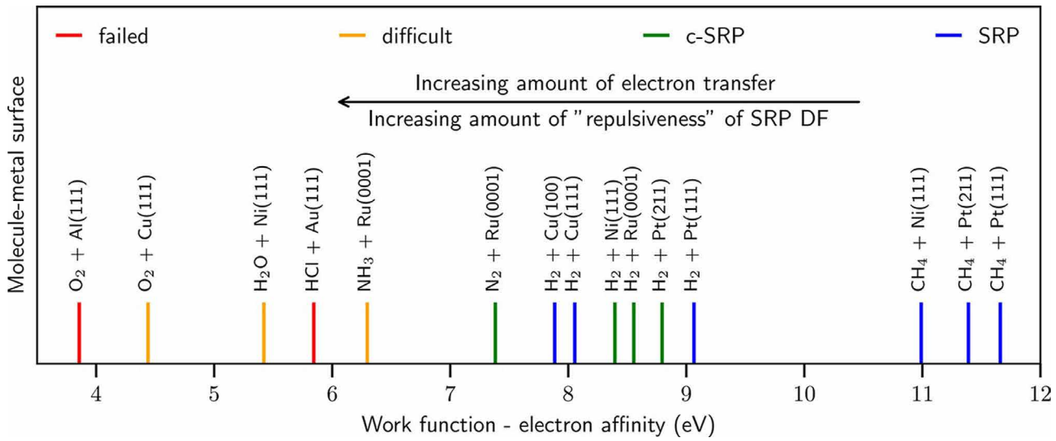


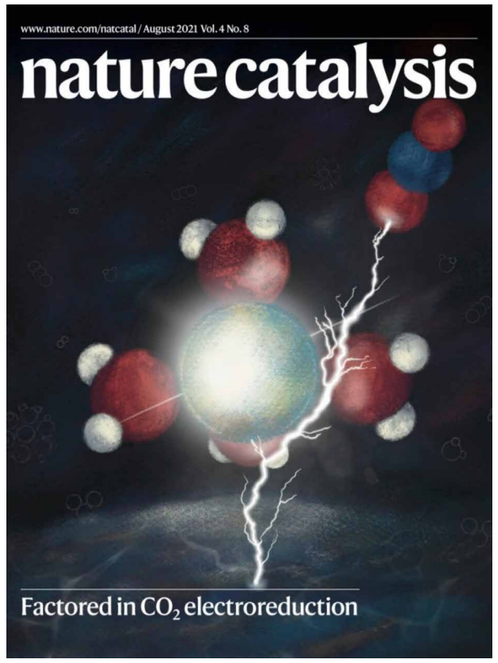
Figure 11. Correlation between the difference of the work function of the metal surface and the electron affinity of the molecule (eV) with the ability of GGA exchange-based DFs to accurately describe barrier heights to DC in the systems described. Red and orange on the one hand ("failed" and "difficult"), and green and blue on the other hand ("c-SRP" and "SRP") indicate whether efforts to compute chemically accurate reaction barriers using GGA exchange for a molecule–metal surface reaction have failed or succeeded, respectively.

7 N. Gerrits, E.W.F. Smeets, S. Vuckovic, A.D. Powell, K. Doblhoff-Dier and G.-J. Kroes
Density functional theory for molecule–metal surface reactions: When does the generalized gradient approximation get it right, and what to do if it does not
J. Phys. Chem. Lett. 2020, 11, 10552–10560 10.1021/acs.jpclett.0c02452

CS3: Electrolyte effects on electrocatalytic CO_2 reduction

The conversion of renewable electricity, CO_2 and water into fuels and chemical building blocks using CO_2 electrolysis is promising to be one of the cornerstones of future renewable energy storage and chemical production. Understanding and improving how CO_2 can be electrochemically reduced most efficiently is one of the fundamental challenges of contemporary electrocatalysis.

Within the European Initial Training Network (ITN) "ELCOREL", the Leiden Institute of Chemistry collaborated with four other research institutes (in Czech Republic, Spain, Denmark, and Finland) and two private companies (Avantium in the Netherlands, and DeNora in Italy) to find better catalysts and optimal electrolyte compositions to enhance electrocatalytic performance. Mariana Monteiro was one of the Leiden PhD candidates who performed a fundamental study on how electrolyte composition impacts CO_2 reduction on model electrodes. To this end, she developed an ultrasensitive micro-electrode probe to measure (small amounts of) carbon monoxide that may be formed as a (first) product of CO_2 reduction. She used this probe to study how cations in the electrolyte influence the first step of CO_2 reduction to CO, on copper, silver, and gold electrodes (the three most used CO_2 reduction electrocatalysts). She observed that in dilute acid solution, in the absence of any irreducible (alkali) cations, these electrocatalysts do not produce any CO. This experiment was definite proof that cations are crucial for the efficient activation of CO_2. She also showed that Cs^+ is a much better "promoter" for CO_2 reduction than Li^+. In collaboration with her colleague PhD candidate Federico Dattila at the ICIQ in Tarragona (Spain), they showed that cations lead to a significant stabilization of the negatively charged CO_2 intermediate at the electrode. Cs^+ is a better promoter than Li^+ as Cs^+ is less strongly solvated and hence has a higher tendency to accumulate at the electrode-electrolyte interface. To show that the concept of cation-coupled CO_2 reduction also applies in a real device, Mariana performed a research internship at Avantium to prepare high surface-area gold-based gas-diffusion electrodes, in collaboration with her colleague PhD candidate Matthew Philips. She tested these electrodes at high current density in Li^+- and Cs^+-containing electrolytes, to show that the Cs^+-containing electrolyte exhibited ca. 90% efficiency towards producing CO, and the Li^+-containing electrolyte 0%. It was the first report of such a dramatic effect of the electrolyte composition for CO_2 electroreduction on a technical electrode.

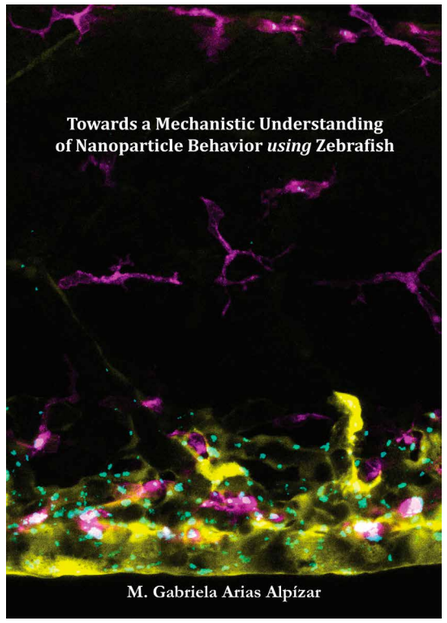


In follow-up work, Mariana and Federico scanned many multi-valent cations, both experimentally and computationally, showing how multivalent cations tend to promote H2 evolution more than CO_2 reduction, and hence Cs^+ remains the most potent metallic cation promoter that has been identified thus far. The three collaborative papers (in Nature Catalysis, Nature Communications, and JACS) describing this work have had an enormous impact on the field of "electrolyte engineering" in CO_2 electrolysis, and on fundamental electrocatalysis in general.

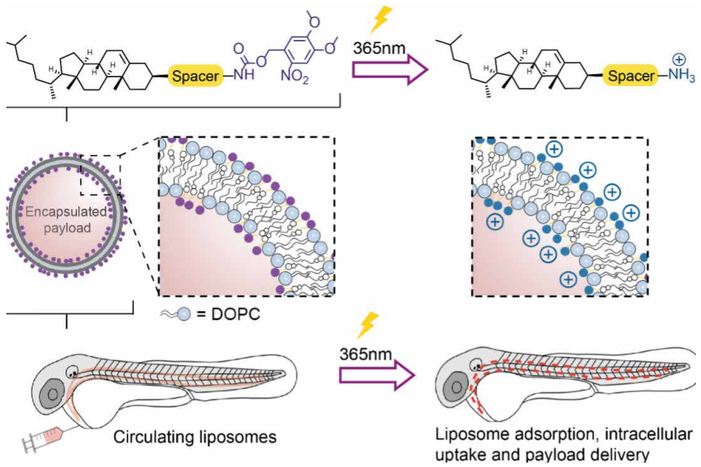
Mariana Monteiro defended her PhD on 15 February 2022 *cum laude*. Her PhD has been awarded with the Dutch Catalysis Society Best PhD Award 2021-2022 and with the Amcel (Amsterdam Centre for Electrochemistry) PhD Award 2023. She is currently a junior group leader at the MPG Fritz-Haber-Institute in Berlin.

CS4: Towards a mechanistic understanding of nanoparticle behaviour in vivo

The Kros group is interested in obtaining curiosity-driven and fundamental molecular-level insights into transport phenomena related to drug delivery. One of the long-standing grand challenges in the nanomedicine field is the delivery problem, which can be better understood and potentially solved when (*in vivo*) transport phenomena are understood at the molecular level. To achieve molecular insight, as part of her PhD-studies Dr. Gabriela Arias-Alpizar studied how surface charge is a key determinant of nanoparticle fate *in vivo* and can drastically affect the efficiency of nanoparticle-encapsulated drug delivery to target cells in the body[8].



Upon systemic administration, (near) neutral nanoparticle surface charges are optimally required to prolong circulation lifetimes and maximise nanoparticle exposure within target tissues. In contrast, cationic surface charges are optimally required to promote intracellular uptake of nanoparticles and, therefore, maximise encapsulated drug delivery. Dr Alpizar-Arias visualised in real time, light-triggered switching of liposome surface charge, from neutral to cationic, *in situ* and *in vivo* using zebrafish. Upon *in situ* irradiation and surface charge switching, however, liposomes rapidly and non-specifically adsorb to, and are taken up by, endothelial cells and/or are phagocytosed by blood resident macrophages. These two distinct cellular fates are the result of two competing interactions of cationic liposomes occurring simultaneously *in vivo*, namely non-specific cellular adsorption and aggregation in serum. The respective extent of liposome uptake within these two cell types is dependent on surface charge density and, as such, we are able to preferentially direct liposome uptake to either endothelial cells or blood resident macrophages by adjusting applied light doses. Crucially, surface charge switching does not compromise the structural integrity of the liposome, ensuring encapsulated and membrane impermeable payloads are successfully transported across target cell membranes following light activation. As a compositionally simple system that successfully couples complete external control of nanoparticle targeting together with the intracellular delivery of (encapsulated) membrane impermeable cargos, these photoactive liposomes represent a significant technological advance in comparison to existing stimuli-responsive drug delivery systems and are proof that advanced nanoparticle function does not necessarily require increased design complexity.



8 *Nature Communications* **2020**, *11*, 3638 10.1038/s41467-020-17360-9

CS5: Junior Science Lab

In 2006 a number of staff members of the Leiden Institute of Chemistry (LIC) organised a lab visit for a group of primary school students (~11-year-olds) to the LIC, including a short 'lecture' and 'practical course' related to chemistry. The visit was successful and in 2009 funding was acquired for a formal start of the 'Junior Science Lab' (JSL). The JSL is run by a coordinator (0.5 fte) and a pool of student assistants from the Science Faculty. Over the years JSL has evolved and now includes several activities:

- Programme for primary school (~3 h)
- Offers lab space for practical courses for high schools
- Offers assistance with and the use of equipment for high-school student projects (*profielwerkstukken*)
- Organisation of special activities (Faculty 'open house' for public)
- Programme for refugee students (occasionally)

The visits of classes of primary-school students form a major part of the activities. In pre-corona years the number of visits exceeded 60 per year, reaching more than 1200 children in the age range of 10 – 12. Teachers can request a visit through the website (see below) and have a choice of 'research themes' for the 'practical course', such as 'acids and bases', 'water and soap', 'food and drinks', or 'electricity and magnetism'. A team of 10 staff members from the LIC, but also the Leiden Institute of Physics and the Leiden Observatory sign up to take care of the mini lectures. These visits are highly successful, leading to happy faces of the children, who often show unexpected knowledge of science and ask good questions, and energise staff members who enjoy spending some time with our 'future scientists'.