Successful interdisciplinary collaboration
Combined knowledge of cell biology and biofunctional polymers

For many years, Argovia Professor Roderick Lim from the Biozentrum at the University of Basel has studied the molecular mechanisms that control transport into and out of the cell nucleus. In 2019, Lim's team concluded a successful interdisciplinary collaboration with the group led by Professor Cornelia Palivan from the Department of Chemistry. The two professors brought together their expertise in the fields of nuclear pore complexes and biofunctional polymers. This excellent collaboration has led to the development of a highly selective system for delivering artificial cargoes directly into the nuclei of cells.

Targeting the nucleus

A key objective in nanoscience is to understand and emulate Nature's design principles for bio-inspired applications in healthcare and beyond. In nanomedicine for instance, it remains formidable to encapsulate and deliver drugs directly to specific organelles such as the cell nucleus. This is beneficial as it prevents exposing the drugs to other parts of the cell and would be advantageous in chemotherapy or gene

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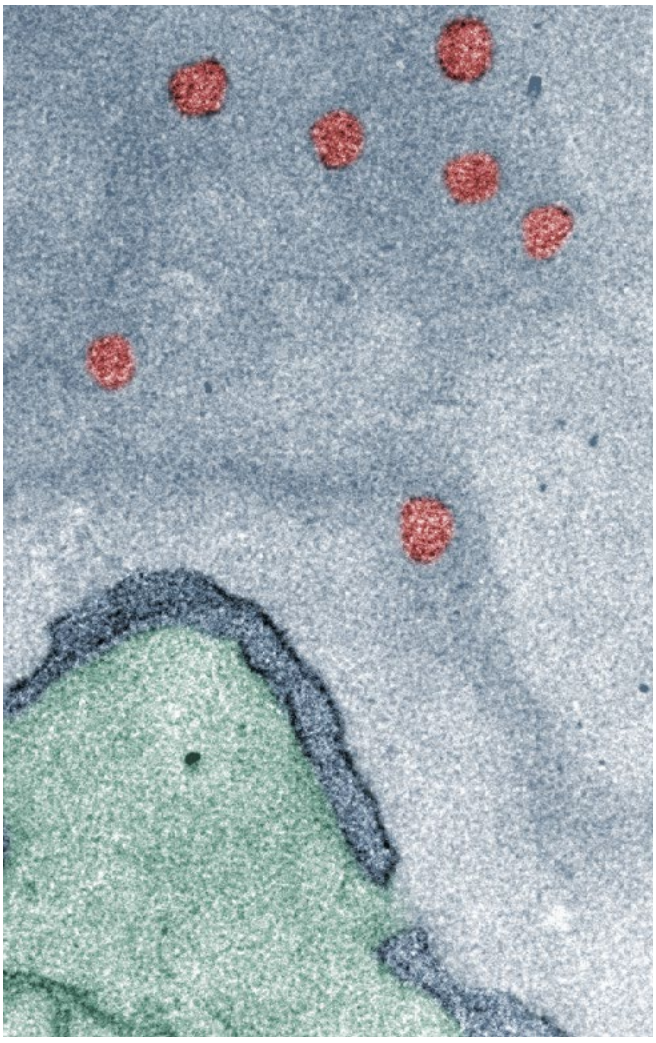
therapy. Drugs introduced into the nuclei of tumor cells could stop the further proliferation of cancer cells. Desired genes introduced into the nucleus could replace non-functional genes. Before this type of nanotechnology can be applied in medicine, there are a number of hurdles to overcome. A method for tackling the first step in this process was recently published in the journal Proceedings of the National Academy of Sciences of the United States of America by the team led by Argovia Professor Dr. Roderick Lim in collaboration with the group led by Professor Dr. Cornelia Palivan.

Biocompatible, polymer vesicles

In order to address the problem, Lim and Palivan jointly submitted a project proposal to the SNI PhD School in 2014. The proposal was approved the same year, and Christina Zelmer, whom Lim and Palivan selected for the project, began her doctoral research work in 2015.

Step by step, she developed biocompatible, flexible polymer vesicles (also known as polymersomes) that can trick cells into allowing their transport through the protective nuclear pore complexes in a highly selective manner so that they can introduce cargo into the nuclei.



To enter into the cell nucleus (grey), the polymersomes (red) selectively translocated across the nuclear membrane (dark blue) via the nuclear pore complexes (gaps in the membrane). (Image: C. Zelmer, University of Basel, and E. Bieler, Swiss Nanoscience Institute)

For this, Christina initially worked in Cornelia Palivan's laboratory to produce flexible vesicles from polymers whose structure mimic natural membranes. As larger molecules can only enter the nucleus through pores in the nuclear membrane (nuclear pore complexes), the vesicles are subject to some highly specific requirements. They must not only be below a certain size but also have recognition molecules on their surface that allow them to pass through the nuclear pore complexes.

The first task was therefore to produce polymer vesicles with a uniform diameter of about 60 nanometers. In addition, the vesicles, which self-assemble from triblock copolymers, needed to exhibit short-chain peptides – known as nuclear localization signals – on their surfaces.

Entry ticket into the nucleus

Once the polymersomes were constructed, Christina then moved to Roderick Lim's laboratory to study how the polymersomes interacted with the key transport proteins. "We postulated that the nuclear localization signals would allow the polymersomes to trick the cellular transport mechanism, which imports the cargo into the nucleus through the nuclear pore complexes. This mechanism involves karyopherins, which regulate passage through the pore barrier, as well as Ran guanosine triphosphate, which releases the polymersomes inside the nucleus. The same strategy is used by a number of viruses," explains Roderick Lim.

The researchers were able to track the path of the polymersomes by marking them with two different dyes and observing them using various microscopic techniques. Ruthenium red served both as a dye and as cargo for the vesicles. The positive results were successfully confirmed not only *in vitro* using a biosensor and isolated cell nuclei but also *in vivo* using live cell cultures.

Towards precision nanomedicine

Together the team has succeeded in developing biocompatible polymersomes that have a nuclear localization signal and are therefore able to deliver artifical cargo into the nucleus in a highly selective manner. Conversely, vesicles without this marker cannot be detected in the nucleus. "It was only thanks to our combined knowledge of biofunctional polymers, cell biology, and how nuclear pore complexes operate that we were able to complete this work successfully," comments Roderick Lim.

In subsequent trials, the dyes that were initially used will be replaced with therapeutic agents. Another option is to alter the size of the vesicles in order to increase the vesicle concentration in the nucleus. This work will also be conducted as an ongoing collaboration between the two groups, providing a beautiful demonstration that the SNI's interdisciplinary network offers an ideal platform for this kind of cooperation.