Developing Light-Responsive Drug Carriers and Diagnostic Sensors

Dr Xiaoqiang Chen





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DEVELOPING LIGHT-RESPONSIVE DRUG CARRIERS AND DIAGNOSTIC SENSORS

Delivering drugs to their target site and conducting medical diagnostics non-invasively are two major goals of biomedical researchers across the globe. **Dr Xiaoqiang Chen** and his team of scientists at Nanjing Tech University in China are developing advanced materials and procedures that can keep drugs protected before they reach their target site in the body. The group is also developing materials that can be used to detect certain substances in the body, towards providing non-invasive diagnostic tools for clinicians.



Drug Delivery and Diagnostics

Developing new ways of administering drugs to where they are required in the body is a challenging pursuit. For instance, drug molecules not only need to reach their target site, but must also be protected in order to survive the body's natural defences along the way. The search for new materials that can transport drugs safely to their target is thus an active field of research.

Similarly, countless researchers are also attempting to develop non-invasive medical sensors for a range of different applications. For example, a sensor that could non-invasively measure levels of the neurotransmitter acetylcholine would allow clinicians to easily identify and monitor the development Alzheimer's disease, allowing for timely diagnosis, and offering a simple way of measuring treatment effectiveness.

Dr Xiaoqiang Chen and his team at Nanjing Tech University are making substantial leads in both areas of research. They are designing 'prodrugs' that release the active drug molecule in a more controlled manner at its intended site. At the same time, the team is also developing biological sensors that can monitor cell activity in a non-invasive manner.

Central to Dr Chen's research is the study of how light interacts with molecules. In his drug delivery research, he employs UV as an energy source to break molecular bonds, allowing drug molecules to be released on cue. In his team's diagnostic research, they utilise excited light to cause biological molecules to emit visible light signals – or 'fluorescence'. Such fluorescence can be recorded accurately with an external sensor, providing key information about the levels of the molecule of interest.

Molecules that Glow

Zinc ions are vital to the survival of all living organisms. In humans and other animals, zinc is involved in immune system and brain functions. Therefore, finding reliable ways of detecting and replenishing zinc levels at the cellular level is of great significance.



Dr Chen's team investigated how current light-based sensors, some of which have limited detection ranges, could be improved. The team investigated how a class of molecules called 'benzothiazoles', which can bind to zinc ions, responds after irradiation with UV light. They found that in the absence of zinc, the benzothiazole molecules emitted a yellow fluorescence, but when bound to zinc, they emitted a blue signal. Importantly, the researchers were able to view these colour signals from outside cells, allowing for non-invasive monitoring.

After these experiments, Dr Chen's team then realised that the concentration of zinc ions was related to the intensity of the fluorescence signal. Their new



detection system allows them to determine the concentration of zinc by simply analysing the colour of the sample. Furthermore, the team was able to detect concentrations as low as approximately one ten-billionth of a gram of zinc per litre of solvent.

Releasing Drugs from Their Cage

Following these studies, Dr Chen and his colleagues then set about designing drug candidates that could potentially replenish zinc levels. To do this, the team designed what they refer to as 'photocages', which can carry zinc ions or other therapeutic substances. When irradiated with UV light, these photocages open and release their contents. Such cages can protect the zinc ions from the surroundings as they travel to the target site, where they can be irradiated with a beam of UV beam.

There are several known photocages that can carry zinc to a target site in cells. However, these compounds require high levels of UV exposure before they will open, ultimately meaning that experimental samples would need to be subjected to prolonged UV exposure in order to release the zinc, which can be dangerous.

Dr Chen's photocage is based on a derivative of a chemical known as Sanger's reagent, which opens much more easily when irradiated with UV. His team was also able to identify the breakdown products resulting from the decomposition of the photocage, which is an important requirement in the development of new drugs.

In order to demonstrate the effective release of zinc in a more realistic situation, Dr Chen's team tested the photocaged zinc against an enzyme which has an activity that is accelerated by high levels of zinc ions. They found that as the irradiation time increased, the activity of the enzyme increased, indicating that zinc was being released. The researchers were also able to control how much the enzyme was activated by precisely controlling the UV parameters. The above-mentioned research was performed outside of cells, so the team was keen to demonstrate the release of zinc inside cells. To do this, they incubated cells with caged zinc ions at 37°C. Upon irradiating with UV irradiation, the cages released their zinc ions. Fortunately, the caged zinc compounds showed little to no toxicity before and after UV irradiation.

After this success, Dr Chen proceeded to investigate a molecule that slows down an enzyme called acetylcholinesterase. Acetylcholinesterase is located in the gaps between nerve cells and muscle cells, which breaks down the neurotransmitter acetylcholine after it transmits a signal, thereby stopping the signal. The introduction of an 'inhibitor' molecule, which slows down acetylcholinesterase, would subsequently prevent the breakdown of acetylcholine, thus maintaining signal transmission.

When tested out on heart cells, which pulse upon signal transmission, the team found that their photocage efficiently protected the inhibitor of



acetylcholinesterase. Using UV irradiation to interact with the caged inhibitor, they were able to control when the pulse of the cells returned. This shows that the inhibitor was released from its cage and was able to block the action acetylcholinesterase enzyme.

Furthermore, the researchers found that neither UV light nor the caged inhibitor alone influenced the pulse rate, demonstrating that both were needed to elicit a response. 'These successful proof-of concept examples open a new avenue for using Sanger's reagent-based photolabile compounds in the exploration of the complex cellular functions and signalling pathways,' says Dr Chen.

Molecular-Assisted Imagery

In dissipative structure theory, once some parameters of an open system reach a certain threshold far from the equilibrium state, mutations will take place in the system by increasing and decreasing, from non-order to order. In this research area, Dr Chen's team apply their knowledge of light-sensitive materials to trace dissipative structures during the evaporation of organic solvent. This work also helps other research groups to build efficient methods to observe thermal field distributions and flow patterns on the surface of fluids. In addition to designing methods, the team's research is also helpful in understanding the fundamental mechanism involved in other industrial processes, including the growth of crystals, droplet evaporation and microfluidics.

Understanding how temperature induces fluid motion and vice versa is important in several fields. However, it is quite difficult to precisely map the temperature distribution of fluids and observe fluid motion on the surface when the fluid is evaporating. Currently, researchers can observe fluids using infrared cameras. However, the precision of these images could be improved.

Dr Chen and his team studied a class of molecules, known as 'spiropyrans', which can reversibly change between two different chemical states. Like photocages, when UV light is shone on a spiropyran molecule, some of the bonds break, leading to a change in its chemical structure. This new 'isomerisation structure' is temporary and causes the spiropyran to appear green. Dr Chen's team demonstrated how the green form of spiropyran then reverts back to its original, colourless state. Knowing this, the team then conducted an extensive study showing the behaviours of the surface of a solvent containing spiropyran as it evaporates. When the solvent evaporates, the molecules at the surface aggregate spontaneously due to the surface tension.

Prior to evaporation, the spiropyran molecules were distributed randomly in the test solvent. The team found that irradiation with UV resulted in a uniformly spread green colour, with no discernible pattern. When evaporation had occurred and the temperature was in a suitable range, the researchers observed an ordered temperature distribution on the surface of the evaporating solvent. The spiropyran molecules then congregated in the colder area and were no longer randomly distributed, instead forming an ordered and green coloured pattern when the solvent was subjected to UV light. Dr Chen's findings also agreed with infrared images taken at the same time but, as intended, his technique achieved a much higher resolution.

In their study, Dr Chen's team used photo-stimulated spiropyran as a tool to observe the temperature distribution and flow pattern on the surface of fluids; however, they now hope that their results can be applied to other contexts where there is a need to understand the patterns formed on a surface of volatile solvent in a special container. Indeed, there are probably more exciting discoveries ahead for Dr Chen's team, as they continue to apply their expertise to solve diverse scientific problems.



Meet the researcher

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Dr Xiaoqiang Chen received his PhD in Applied Chemistry from Dalian University of Technology, China, in 2007, under the supervision of Dr Xiaojun Peng. Upon graduating, he joined Dr Juyoung Yoon's group at Ewha Womans University in Korea as a postdoctoral fellow in 2008. In March of 2010, Dr Chen moved to Nanjing Tech University, China, where he is currently a Professor at the College of Chemical Engineering. His current research interests mainly focus on the development of dyes for sensing, imaging and controlled drug delivery. Dr Chen has published more than 100 academic papers in this field, which have been cited more than 10000 times by others.

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FURTHER READING

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