The power of nanopharmaceutics to cure deadly diseases

Professor Salette Reis’ group develops nanodelivery systems designed to overcome the limitations of conventional treatments for a variety of diseases, from rheumatoid arthritis to tuberculosis, as well as for theranostic and nutraceutical purposes.

Why did you become interested in nanodelivery systems?

My interest in nanodelivery systems was a natural progression. I started my research in membrane biophysics, using membrane mimetic models of different dimensionalities to assess drug-membrane interactions and unveil additional drug mechanisms of action. In this context, I extensively used liposomes. I am able to tune their composition and know the type of chemical bonds that reinforce drug binding. Some of my research has shed light on the side effects that arise from direct interplay with membranes, which can also be correlated with their wide biodistribution.

How do the nanocarriers developed in your lab lend themselves to use as nutraceuticals?

Polyphenols have numerous benefits in the prevention and treatment of cancer, vascular and degenerative diseases, diabetes and also in obesity. Of those, resveratrol, curcumin and epigallocatechin gallate are very promising as nutraceuticals. The development of nanoparticles that can load these compounds for application as nutraceuticals is being implemented in our group to take advantage of health benefits similar to those currently attributed respectively to red wine, curry and green tea.

Could you summarise your theranostics approach to rheumatoid arthritis?

Treatment monitoring is crucial for controlling the progression of rheumatoid arthritis. Thus, the idea of a nanocarrier that can both monitor and treat disease is of great interest. In particular, one of our rheumatoid arthritis strategies takes advantage of gold nanoparticles as imaging and therapeutic agent in combination with methotrexate, the standard current therapy. We have recently shown that incorporating gold nanoparticles and methotrexate in polymeric nanospheres results in controlled drug release triggered by hyperthermia. Our theranostic nanospheres lead to significant reduction in inflammatory cytokines in vitro.

What potential do hydrogels and lipid nanocarriers have to target conditions such as psoriasis?

Lipid nanoparticles, as solid lipid nanoparticles and nanostructured lipid carriers (NLCs), are frequently used to incorporate and deliver lipophilic drugs. In terms of topical administration, formulations of NLCs are characterised by their occlusive ability in creating a monolayered lipid film on the skin, thereby avoiding water evaporation and increasing skin moisture and hydration and, consequently, drug permeation. These are all great characteristics for psoriasis topical therapy, where skin hydration and drug absorption have a crucial role.

We have developed a nanocarrier able to cross the stratum corneum barrier, based on lipid nanoparticles enriched with hydrogel. So far, we have successfully produced NLCs loaded with methotrexate able to improve drug skin permeation in vitro. The incorporation of these nanocarriers into hydrogels is under optimisation. Their biological efficacy will be assessed in human psoriatic skin in collaboration with dermatology clinicians from a nearby hospital.

Can you outline the progress made towards developing nanocarrier systems for treatment of tuberculosis and Helicobacter pylori infection?

The main weaknesses of existing nanocarrier systems for tuberculosis include expensive technology, difficulties in scaling up and an invasive route of administration. Our lipid nanoparticles are designed to be administered non-invasively via inhalation. They are inexpensive to produce and easy to scale up. However, current barriers to market entry include difficulties in accessing animal models and dealing with tuberculosis in clinical trials.

Regarding H. pylori, the main cause of peptic ulcer and gastric cancer, eradication rates are currently distant from those proposed by the World Health Organization (WHO) and far from desirable. This is a consequence of current therapy drawbacks, including lack of therapeutic compliance and degradation of antibiotics at gastric pH and their consequent insufficient retention in the stomach. Our research group is exploring the limitations of current therapy in biophysical studies of the interaction between the most-used antibiotics and biological membranes (the gastric mucosa and the H. pylori membrane) in lipid model systems. We are using this work towards our goal of developing a drug delivery system.
Drug delivery systems for theranostic relief

Predictive biophysical studies of drug-lipid membrane interactions at the University of Porto underpin the rational design of integrated nanoscale systems for highly targeted delivery of diagnostic and therapeutic compounds.

In the last decade, nanoparticles have started to rise in importance in the minds of researchers in many fields of science, especially medicine. Part of this increase in interest is due to the special qualities these particles display. For example, as their surface area-to-volume ratio increases significantly when scaled down to nanosize, the physical properties of materials can change dramatically, enabling them to penetrate cell walls and interact with specific atoms and molecules. Used as nanocarriers, nanoparticle-scale materials can thus deliver diagnostic and therapeutic agents with high specificity.

The benefits of the approach include boosting the potency of low drug concentrations through raising their bioavailability and solubility, targeting particular dysfunctional molecules to reduce drug wastage, and obviating the unwanted side effects that arise from conventional scattergun drug treatment. Nanoparticle surface modification with hydrophilic polymers that react to certain physical stimuli can also extend the time over which a diagnostic or therapeutic agent is released in the body. Dr Salette Reis, head of the Molecular Biophysics and Biotechnology group at the University of Porto in Portugal, has dedicated her career to unveiling membrane dependant drug mechanisms. More recently, Reis has been rationally designing nanosystems for treating a wide range of conditions from psoriasis to tuberculosis.

TARGET OR TRIGGER
The central theme of the laboratory’s work is that designs should overcome the severe practical limitations often present with even the most highly effective conventional treatments, ranging from invasive means of administration to cumbersome or unpleasant treatment regimes that reduce compliance rates. A further consideration that frames the group’s activities is the economic viability of the solution, especially where a disease is particularly widespread or can rapidly attain epidemic proportions.

To overcome these challenges, Reis develops drug delivery systems (DDS), where the nanoparticle surface is functionalised to target or trigger specific pathological conditions, such as the chronic inflammatory processes in psoriasis. Additionally, Reis shares: “Our DDSs are typically based on liposomes and lipid nanoparticles, as the US Food and Drug Administration recognises these as safe ingredients, and they are designed according to the disease in question. My lab also seeks to ensure that our creations are easy to scale up, do not involve the use of solvents and have low production costs.”

A recent example is a liposome based DDS for rheumatoid arthritis. Twenty-one million people worldwide suffer from this incurable disease, many of which must take long-term therapeutic courses with nasty, systemic side effects. DDSs focused on treating rheumatoid arthritis are showing great promise in laboratory testing, and may one day circumvent current treatments. “The DDS’s design is based on pH-sensitive nanosystems coupled with active targeting for synoviocytes and loading of prednisolone and methotrexate,” notes Reis, pointing out that the formulation meets the European League Against Rheumatism recommendations that these drugs should be combined in treatment for early-stage rheumatoid arthritis. “In addition, this pH-sensitive strategy is being applied to develop a site-specific DDS to improve pulmonary tuberculosis treatment,” reveals Reis.

GUIDING BIOPHYSICAL STUDIES
A major issue impeding the efficacy of many drugs is the biological membrane. “Before reaching their targets and during body distribution, DDSs must cross biological membranes,” Reis explains. “Therefore, it is of utmost importance to evaluate the interaction of drugs and nanocarrier systems with membranes.” Therefore, her laboratory is utilising knowledge obtained via biophysical drug-membrane studies to direct rational design of system composition, type of drug and drug release structuring.
NOVEL DRUG DELIVERY SYSTEMS

OBJECTIVE
To develop nanopharmaceutics (liposomes, lipid and polymeric nanoparticles) as drug delivery systems to create new and more efficient therapies for a range of diseases and infections.

KEY COLLABORATORS
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PROFESSOR SALETTÉ REIS has focused her academic career investigating biophysics and pharmaceutical chemistry. Since she earned her PhD in Analytical Chemistry from the University of Porto in 1995, she has risen to acclaim in the nanopharmaceutical and biomimetics communities and is currently Associate Professor at the University of Porto, where she also directs the Chemistry Department.

For example, Reis is currently working on a DDS for Helicobacter pylori infection. As H. pylori resides between the mucus gel layer and the epithelial cells of the stomach, high concentrations of antibiotics need to cross the gastric mucosa to reach the infection. However, infection rates remain extremely widespread. This is due to a range of reasons, including a lack of therapeutic compliance due to side effects such as nausea, as well as growing bacterial resistance and insufficient antibiotic resilience to stomach acid processes. This trend has the medical community worried because if inadequately treated, H. pylori infection can result in peptic ulcers and lead to stomach cancer.

The idea behind the DDS that Reis and her team are creating is simple, even if the execution is not. It is made up of three parts. One is a core that will carry an antibiotic. It will be hidden inside a shell that has a phospholipid bilayer and contains an antacid to enable the DDS to selectively bind to H. pylori. Finally, the structure will be covered in a pH-sensitive coating that will prompt the antacid to release when the stomach conditions are perfect.

To improve the functionality of this system, the team is performing studies into phospholipid shell interactions and the pharmacokinetic properties of the antibiotics throughout the whole development process. It is also using membrane mimicking systems to model the pH gradient of gastric mucosa and the nature of the H. pylori bacterial membrane. The pharmacokinetic properties of both the antibiotics and the nanodrug formulations will then be evaluated against these model systems, and then against cell lines in vitro to observe the interactions between the nanosystem and different H. pylori strains, as well as evaluate the gastric cytotoxicity of the nanosystem.

In addition to her work with H. pylori, Reis is also working on a topical DDS formulation for psoriasis, a chronic autoimmune disorder of the skin that affects upwards of 5 per cent of the population worldwide. Her aim is to improve patient compliance with treatment, in particular, Reis’ group has examined how the mechanisms of resveratrol affect the biophysical properties of the membrane lipid bilayer at the molecular level: “The results indicate that resveratrol influences membrane structure and lipid raft organisation, which may explain its pharmacological activities,” she states. “We are certainly excited to see where this line of research will take us in the future.”

In particular, Reis’ group has examined the content of bioactive compounds on the nanosystem production on an industrial scale: “Given their high potential, the use of nanodelivery systems for nutraceuticals is of great interest worldwide”.

At present, Reis’ laboratory is focusing on producing nanocarriers containing resveratrol, curcumin or epigallocatechin gallate. Resveratrol is the ingredient in grapes to which the cardiovascular health benefits of red wine are attributed. Curcumin and epigallocatechin gallate are the active compounds in turmeric and green tea. They have antioxidant properties and are thought to deliver a range of benefits, from reducing cholesterol and preventing cancer to inhibiting the development of Alzheimer’s disease.