Targeted Delivery

Nanoparticle drug delivery systems present exciting opportunities for safer and more effective anti-cancer drug therapy. In the Shoichet Lab, we are engineering intelligent biomaterials for these applications, giving rise to a platform technology that can be used to target and destroy more cancer cells, and with greater specificity. Toxic chemotherapeutics given in their free form distribute broadly throughout the body, but by redirecting more of the drug dose towards tumour sites, we aim to reduce systemic side effects to make anti-cancer treatment safer. Our expertise in drug delivery, chemistry, materials science, and engineering allows us to create innovative solutions to deliver a variety of bioactive molecules to diseased cells.

With our innovative nanoparticle technology, we aim to target the delivery of a variety of active compounds to destroy cancer cells, including chemotherapeutic drugs, antibodies, and siRNA.

Conventional chemotherapy can cause severe side effects in patients because these approaches exploit rapid cell division in cancer cells; however, rapid cell division is not limited to diseased cells. As a result, many healthy cells are also killed, causing suppression of the immune system, irritation in the digestive tract, and accelerated hair loss.
Conventional chemotherapy kills rapidly dividing cells indiscriminately. This can cause severe toxicity in healthy tissues. Resulting side effects are commonly seen in blood (anemia, immune suppression), the digestive tract (nausea, vomiting), and hair follicles (hair loss).

Nanomedicine uses a completely different approach to cancer targeting. As tumours grow, they develop new blood vessels to provide nutrients to rapidly dividing cancer cells. These blood vessels, however, are poorly formed and leave abnormal gaps in the vessel walls. Consequently, large molecules that would ordinarily be contained by healthy blood vessels can cross these gaps. These abnormal tumour blood vessels are also called leaky vasculature, and this is the feature of cancer that we target using nanoparticles. While free drugs are small enough to pass through healthy blood vessels, packaging these same drugs in nanoparticles channels a greater portion of the drug dose through leaky vasculature into tumour tissue. This size-based method is called passive targeting, and is our approach to targeting cancer on a tissue level.

Additionally, tumour cells have subtle differences compared to healthy cells, as certain genes are turned down (tumour suppressor genes) and others are turned up (oncogenes). Selected oncogenes result in increased expression of markers on the cancer cell surface. Binding these markers is called active targeting, and it allows us to target cancer on a cellular level. Through these combined approaches, our nanoparticles offer better cancer specificity than traditional chemotherapy, which we hope will translate into improved tumour remission rates and lower toxic side effects for patients.
Our nanoparticles target cancer in two ways: firstly, leaky tumour blood vessels allow nanoparticles to pass through, targeting the tumour on a tissue level; secondly, attached antibodies recognize and bind cancer cell markers for targeting on a cellular level. By directing more of the drug dose to the tumour, our technology has the potential to kill more cancer cells for greater treatment efficacy, while sparing healthy cells for lower toxic side effects.

To take advantage of leaky tumour vasculature, we synthesized a novel biodegradable polymer to form drug-loaded nanoparticles and engineered several key features into this our material to make it useful for anti-cancer drug delivery. Two segments comprise our polymer: one is hydrophobic (water-fearing) and the other is hydrophilic (water-loving), and this dual behaviour allows polymer strands to come together and form nanoparticles through self-assembly in water. We have shown that the core-forming hydrophobic segments entrap hydrophobic anti-cancer drugs, and the outer hydrophilic shell facilitates the long circulation in the bloodstream needed to achieve passive targeting. As a result, we also observed enhanced retention of the drug at tumour sites over equal doses of the same free drug.

To actively target cancer cells, we also designed our polymer to be easily modified with antibodies to bind known markers present on the surface of cancer cells. Cancer cell binding is intended to increase nanoparticle uptake, where the encapsulated drug load can have the largest toxic impact. Our innovative use of Diels-Alder chemistry allows us to use mild reaction and processing conditions, better preserving the binding activity of the antibodies during nanoparticle attachment, and further enhancing...
our platform’s ability to target cancer cells. We have demonstrated active, specific, and tunable binding of our antibody-modified nanoparticles to cancer cells in culture, and also verified their uptake and increased toxicity against targeted diseased cells. We have also improved the uniformity of our nanoparticle size by reducing variation in the length of our polymer strands through advanced synthesis methods, and shown that these nanoparticles are stable in biologically relevant media. Through a combination of passive and active targeting approaches, our platform technology has the potential to transform anti-cancer drug therapy into a safer and more effective treatment strategy.

Our novel polymer self-assembles in water to form nanoparticles. We engineered this material for simple modification with antibodies for active targeting. Our innovative use of Diels-Alder chemistry allows us to use mild reaction conditions, preserving antibody activity and enabling recognition and binding of target cancer cells.

We are continually looking for ways to improve our material and expand the range of drugs we can deliver. To learn about our work in greater detail, please consult our research publications:

**POLYMER SYNTHESIS, NANOPARTICLE PREPARATION, AND DIELS-ALDER AND CLICK CHEMISTRY**


NANOPARTICLE BINDING, UPTAKE, AND CYTOTOXICITY IN CANCER CELL CULTURE


NANOPARTICLE STABILITY IN BIOLOGICAL MEDIA


NANOPARTICLE CIRCULATION AND DRUG ACCUMULATION IN TUMOURS


WE THANK OUR COLLABORATORS AND FUNDING SOURCES