Exploiting an immune response to alter the side effects of cancer treatment

Chemotherapy remains a powerful but unpleasant treatment for cancer patients, often causing severe side effects as it impacts healthy tissues alongside cancerous ones. At the **University of Colorado Anschutz Medical Campus** in the US, **Professor Tom Anchordoquy**, **Professor Dmitri Simberg**, **Dr Scott Tilden** and **Dr Madison Ricco** are exploring how a specific immune response can potentially reduce the damage chemotherapy causes to healthy cells. By studying this innovative approach, they hope to make cancer treatments more targeted, effective and tolerable for patients.

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Field of research
Pharmaceutical science

Research project
Reducing off-target drug accumulation by exploiting a type-III interferon response

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Talk like a ...

pharmaceutical scientist

Cationic lipid — a synthetic lipid with a positive charge that helps bind nucleic acids (e.g., mRNA) to nanoparticles

Chemotherapy — a cancer treatment that uses drugs to kill cancer cells

Epithelial cells — cells that line the surfaces of organs and tissues, acting as a barrier to protect underlying structures

Type III Interferon (IFN-λ) — a protein in the immune system that helps defend against viruses by blocking their spread (λ is the Greek letter lambda)

Lipid — a fatty compound found in the body

Nanomedicine — a branch of medicine that aims to use nanoparticles to diagnose, treat or prevent diseases with a high level of precision, with the goal of targeting only disease sites

Nanoparticles — extremely small particles that are engineered to carry drugs to specific sites within the body

PEGylation — a technique in which nanoparticles are coated with polyethylene glycol (PEG) to shield them from immune detection

Chemotherapy remains one of the most widely used and effective cancer treatments, yet it is often reserved as a last resort due to its severe side effects. Hair loss, fatigue, nausea and damage to healthy cells are common, as chemotherapy

drugs affect both cancerous and healthy cells in the body. These side effects can be intense, significantly impacting patients' quality of life during treatment. A therapeutic approach that delivers these drugs directly to cancer cells, sparing healthy tissues from collateral damage is highly sought after. This is the promise of nanomedicine – a pioneering field where tiny, carefully engineered particles transport drugs precisely to the site of disease.

Professor Tom Anchordoquy, Professor Dmitri Simberg, Dr Scott Tilden and Dr Madison Ricco, from the University of Colorado's Skaggs School of Pharmacy and Pharmaceutical Sciences, are focused on reducing the unwanted accumulation of chemotherapy drugs in healthy tissues by making use of the body's natural immune responses. Their research explores how a specific type of immune response, known as the type-III interferon response, might be used to shield healthy cells from chemotherapy's toxic effects, making treatment safer and more effective.

Why has tumour-targeted nanomedicine struggled to deliver on its promise?

For nanomedicine to successfully target only cancer cells, it needs to tell them apart from healthy cells in the body. This precision, however, has proven difficult to achieve. Current targeting strategies generally rely on two approaches. The first uses the body's natural mechanisms, which often clears particles through organs such as the liver, resulting in less precise targeting. The second approach involves engineering molecules that can bind to specific proteins found at higher concentration on cancer cells.

"It is important to recognise that cancer cells start out as normal healthy cells, and thus, they have the same proteins as every other cell, but sometimes they express more of these proteins than healthy cells," says Tom. "Even if we use a targeting molecule that binds specifically to a protein that is highly expressed on cancer cells, this molecule will also bind to healthy cells that express that protein." Consequently, even though some proteins are found in higher amounts on cancer cells, they are not usually exclusive to them. This means that targeting nanoparticles will likely interact with both cancerous and healthy cells that carry these proteins. This lack of specificity can lead to chemotherapy reaching healthy tissues, resulting in unwanted side effects.

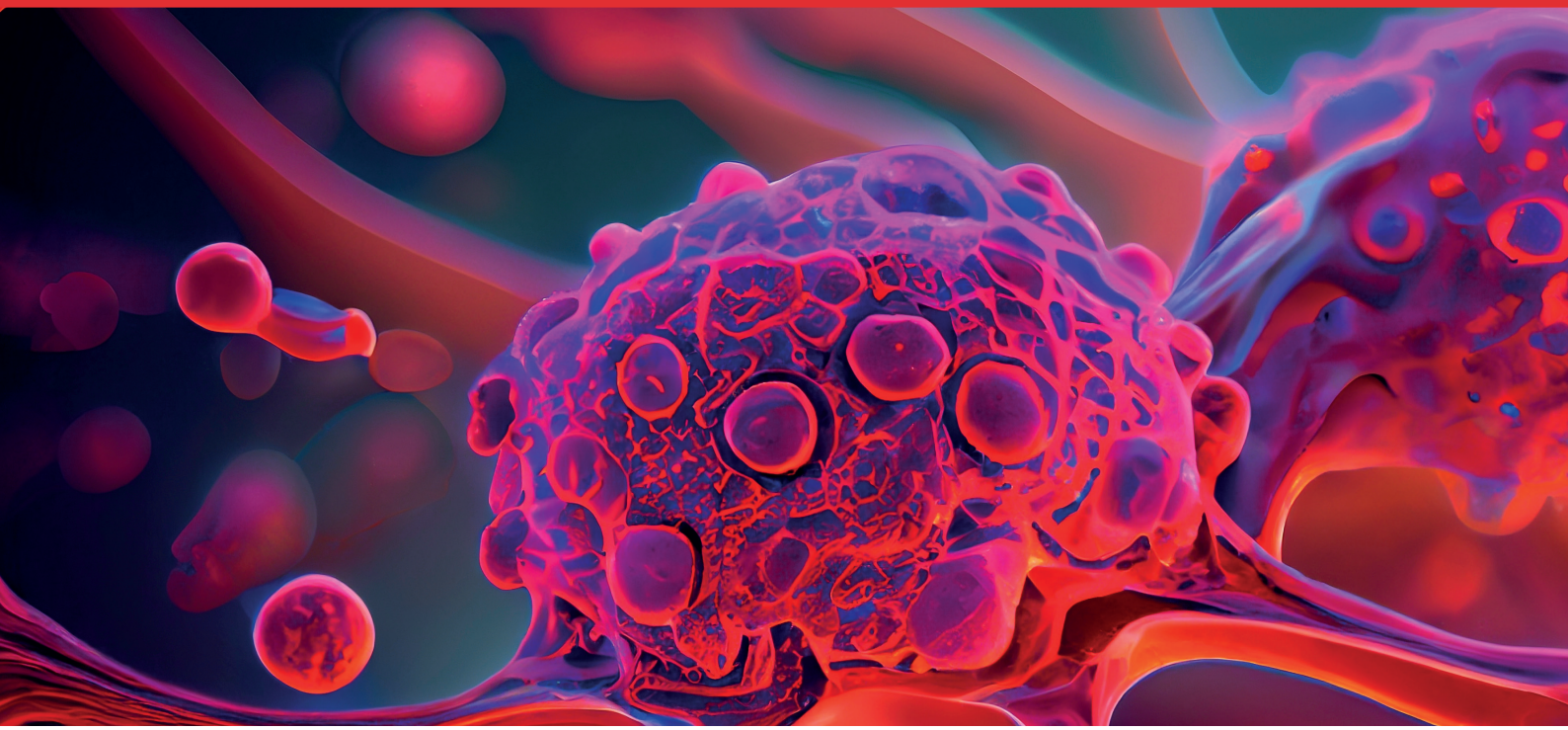
How does the immune system react to nanoparticles?

"We must recognise that our immune system has evolved to recognise small particles and eliminate them," says Dimitri. "In evolutionary time, our cells have been invaded by viruses and bacteria for hundreds of millions of years." This evolutionary history means that our bodies are particularly good at recognising small particles as potential threats. When nanoparticles are introduced for drug delivery, the immune system perceives them as invaders rather than as therapeutic agents designed to treat cancer. Before these particles can serve their intended purpose, this recognition triggers a series of responses aimed at clearing them from the body. This natural reaction presents a significant challenge in nanoparticle-mediated drug delivery. The immune system quickly activates its defences to neutralise and eliminate the nanoparticles. "The field has made progress in trying to 'hide' the particles from the immune system, but this is very difficult to accomplish," explains Scott.

How can researchers address immune recognition?

"The predominant technology that has evolved to combat recognition by the immune system is called 'PEGylation'," says Madison. "Essentially, particles are coated with a polymer (polyethylene glycol, aka 'PEG') that shields them from being recognised by the immune system." By changing how nanoparticles are coated, PEGylation makes it harder for the immune system to identify and remove these particles. This allows the nanoparticles to stay in the bloodstream longer, which increases the chances of them reaching the disease site and improves treatment effectiveness.

However, while PEGylation has shown promise, it is not without its limitations. "While the PEG shields the particle surface from the immune system, PEG itself is a foreign molecule that is recognised by the immune system," explains Tom. Some patients develop anti-PEG antibodies, which are immune proteins produced in response to the presence of PEG in the body. These antibodies can lead to adverse reactions, some of which can be severe and even life-threatening.



What are lipid nanoparticles, and how do they enable drug delivery?

Lipid nanoparticles are tiny particles composed primarily of lipids (fatty molecules) and are typically smaller than one micron in size. "While liposomes have been used for drug delivery for fifty years, the latest technology uses lipids to deliver nucleic acids (e.g., mRNA)," explains Dimitri. "The power of this technology received lots of recent attention due to its use in COVID-19 vaccines, but the basic technology has been around for decades."

One of the advantages of lipid nanoparticles is that most of the lipids used are naturally occurring, making them generally safe for human use. However, to effectively deliver mRNA, these nanoparticles incorporate cationic lipids, which are synthetic and not found in nature. These cationic lipids play a crucial role by binding the mRNA to the nanoparticle and facilitating its delivery into cells. Once inside, mRNA in the lipid nanoparticle is usually entrapped within a vesicle – a small, membrane-bound compartment that directs its contents to the degradation pathway (lysosome) within the cell. This vesicle also prevents the mRNA from accessing the cellular machinery required to produce proteins. To overcome this challenge, cationic lipids have the unique ability to disrupt the vesicle membrane, essentially 'poking holes' in it. This action allows the mRNA to escape into the cell's cytoplasm, where it can then be translated into proteins, enabling effective drug delivery.

What is a type III interferon (IFN-λ) response?

Type III interferon, known as IFN-λ, is an essential part of the immune response that mammals use to defend against viral infections. When a virus attempts to invade healthy tissues, IFN-λ triggers a process that causes the spaces between cells to tighten. This tightening effect acts as a barrier, preventing viral particles from spreading to deeper tissues and helping to contain the infection. "Unlike type I and II interferons, IFN-λ acts only on specific epithelial cells and its effects are limited," explains Scott. "This is a significant advantage when using IFN-λ therapeutically because it reduces the risk of widespread side effects that could arise from a more general immune response."

However, there is an important consideration: the tightening effect of IFN-λ is not limited to viruses alone. It can also block other particles of a similar size, including nanoparticles used in drug delivery. This characteristic allows IFN-λ to effectively keep chemotherapy-laden nanoparticles away from healthy tissues, which decreases the amount of drug that enters those tissues and, as a result, lessens the likelihood of adverse side effects experienced by patients. For reasons that are not fully understood, it appears that cancer cells are incapable of responding to IFN-λ, so the chemotherapy still accumulates in tumours, despite the reduced accumulation in healthy tissues.

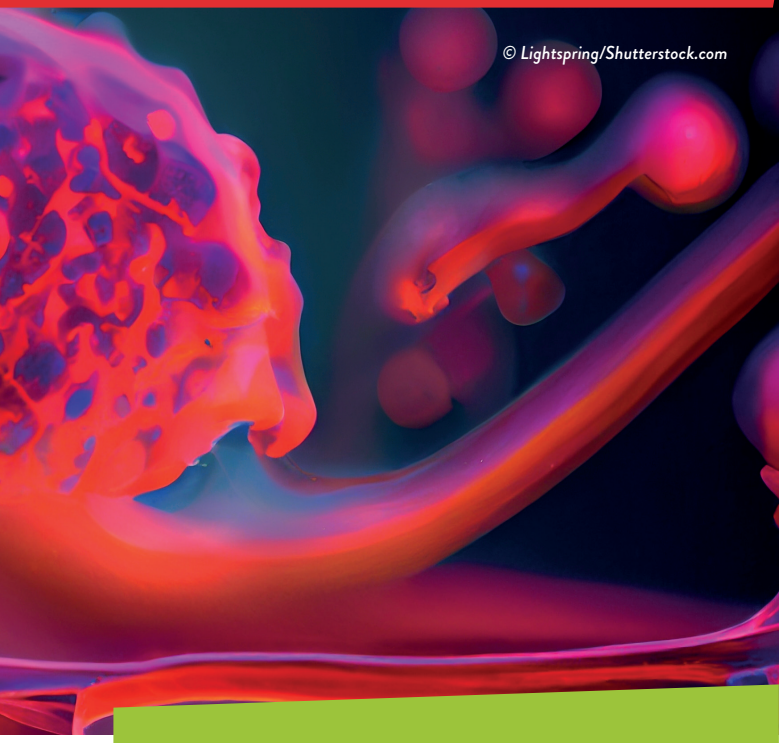
What makes the team's approach unique?

Traditionally, cancer treatment has focused on improving how well drug-carrying particles target and deposit in cancerous tissues. "This intense focus on targeting and identifying molecules that bind to specific receptors has ignored the fact that most chemotherapy is problematic due to the toxicity in healthy tissues, which limits how aggressively cancer can be treated," explains Madison. As more than 90% of the chemotherapy drug often ends up in healthy tissues, even small improvements in targeting have little impact on reducing adverse side effects.

The team's approach is unique because it uses the body's natural anti-viral response to lower the amount of drugs that build up in healthy tissues. Instead of simply trying to direct drugs to the tumour, the team is taking a counterintuitive route by reducing the amount of chemotherapy that reaches healthy cells. This strategy allows for stronger cancer treatments while reducing side effects, giving patients a better chance of recovery.

What does the future hold?

The future of cancer treatment looks promising with the use of IFN-λ. Research using mouse models has already demonstrated that pretreatment with IFN-λ significantly reduces the accumulation of chemotherapy drugs in healthy tissues, enabling more effective treatment options for cancer.



Pathway from school to *pharmaceutical sciences*

A foundation in science and mathematics is essential for pharmaceutical sciences. Biology and chemistry are fundamental for understanding drug mechanisms, human physiology and the development of pharmaceutical treatments.

Pursuing a degree in pharmaceutical sciences, biochemistry, biology or immunology is a common route. Courses in microbiology, cellular biology and immunology are increasingly important due to the expanding understanding of immune system interactions and their links to diseases like cancer and autoimmune disorders.

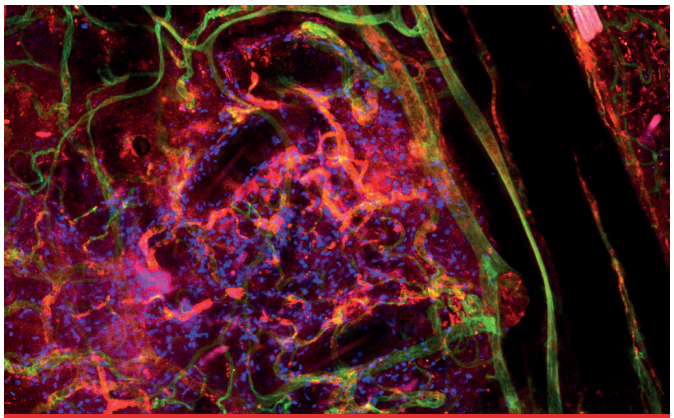
You can benefit from internships or volunteer opportunities in healthcare or research settings.

About *pharmaceutical sciences*

Pharmaceutical sciences is an interdisciplinary field, which includes areas such as drug discovery, development and delivery. “While much of academic science is purely pursued for the sake of acquiring knowledge in the hope that it will be useful at some point in the future, pharmaceutical sciences is an applied science that has direct implications for the treatment of patients,” says Tom. “It is motivating to think that what you are working on may someday help another human being.”

The field is evolving rapidly, with each new generation of researchers building upon the advancements of those who came before. Today’s pharmaceutical scientists have access to advanced tools that allow them to investigate complex biological systems in ways that were unimaginable a few decades ago. As a result, the chances of success in developing new treatments are constantly increasing.

Future researchers will find opportunities to work at the intersection of biology, chemistry and technology, exploring innovative methods for targeted drug delivery, personalised medicine, and the creation of treatments with fewer side effects. “There will always be humans suffering from disease, and there will always be a need for pharmaceutical scientists,” says Tom.



The team is focused on the accumulation of liposomal doxorubicin (Doxil in the US, Caelyx in Europe) in the skin (hand and foot syndrome). This photo shows the accumulation of doxorubicin (red) in mouse skin. Blood vessels are shown in green, and cell nuclei are shown in blue.

Explore careers in *pharmaceutical sciences*

Pharmaceutical scientists work in various sectors, including pharmaceutical companies, academic research, government agencies and biotechnology firms. Some focus on drug discovery and formulation, while others specialise in clinical research, quality control, or regulatory science

Professional organisations like the American Association of Pharmaceutical Scientists (**www.aaps.org/home**) and the International Pharmaceutical Federation (**www.fip.org**) provide resources and career guidance for future scientists.

Meet *Tom*

I have always been interested in working on applied problems at the interface between biology, physics and chemistry, but I felt like an imposter when I first arrived in the pharmacy school as a postdoc! Being trained in a biology department with a focus on biophysics, the idea of applying science to medicine had never occurred to me. At first, this was an uncomfortable fit, but as I learnt more about pharmacy and the need for people from different disciplines, I realised that this was exactly what I was looking for.

I have had several eureka moments where I realised that what I was doing could actually help other human beings who were suffering from a disease. As I grew older and watched friends and family die of various ailments, I came to understand my role in this big picture. Although the probability of any one researcher having a significant impact on human health is quite remote, in aggregate, researchers like me are the only hope of successfully treating many diseases in the future. I have had the privilege to be involved in several projects that have been tested in humans, and I feel fortunate to be in the position of potentially helping overcome disease. How many people can say this?

The barrier to repeat administration of nucleic acid-based drugs has been considered mysterious and unresolvable. We haven't solved this problem, but we are attempting to exploit this effect for improving cancer treatment, and I am proud that we arrived at this counter-intuitive approach to help people. We are the first to think of 'targeting' in this way.

I am fortunate to have bright, creative, hard-working colleagues who make my job enjoyable and motivate me to keep moving forward, even when challenges seem overwhelming. By combining the expertise and talents of multiple scientists, we increase our probability of success – and it's a lot more fun that way.

I want to see how far we can push this IFN-λ approach with the ultimate hope of testing this in cancer patients. That would be a crowning achievement to my long career.

Tom's *top tips*

1. Be bold and don't let anybody tell you that you are not good enough.
2. Don't be afraid to be wrong.
3. Pursue your interests with passion, even if nobody else seems interested.
4. Always try to think outside of the box and don't be afraid to disagree with the majority... they are often wrong and/or limited in their approach.

Meet *Scott*

I was inspired to pursue toxicology by watching the TV programme Forensic Files! There was always a forensic toxicologist who helped solve the case. Investigating toxicology careers led me to pursue my PhD.

I fell in love with learning during my undergraduate degree and subsequent research career and decided to continue my education at the prestigious pharmaceutical sciences programme at CU Anschutz. I first met Tom during my interview and instantly realised that we were kindred spirits who shared a passion for learning and discovery. After a rough patch during my first year, I turned to Tom for help, and he welcomed me into his lab with open arms. My background and love of immunology drew me to the interferon project and the rest is history.

I was the lead on this project. I did every ELISA test, animal injection, qPCR run, cell culture, and so much more! Tom was always there for support and guidance, but he truly empowered me to make the project my own and pursue the questions I wanted to answer. The highlight of this project for me is that it opens an entirely new path of research. The idea that we have just scratched the surface sends chills down my spine. I can't wait to see where this research will lead.

I approach each challenge as another opportunity to learn. If I fail or make a mistake, I treat it as a as an important lesson. The more lessons you learn, the more confident and competent you become when facing new challenges.

Earning my PhD has been my proudest moment so far. When I got to stand up and give my thesis presentation with my 90-year-old grandmother watching, I felt immensely proud.

I hope to always discover new things. Whether I stay in academia, industry or another field entirely, I will always keep learning.

Scott's *top tips*

1. Never stop asking questions! The world is an indescribably wonderful place, and the more you learn about its secrets, the more beautiful it becomes.
2. Learn to love learning, and you'll be able to achieve anything.

Meet *Madison*

I am fortunate to have had teachers and professors who have nurtured my curiosity and instilled in me a love of learning and discovery. Their encouragement and passion for science has influenced my decision to pursue pharmaceutical sciences.

I always envisioned applying my clinical education to research, rather than being a traditional pharmacist. Tom's research interests offered an ideal bridge between clinical pharmacy and basic science research. After persuading him to take a chance on a pharmacy student, I had the opportunity to collaborate with him on various projects, including this one, which has been an incredibly rewarding experience.

As a graduate student working alongside Scott, I played a dual role as a collaborator and a student. I supported his experiments by serving as a sounding board for ideas, while also contributing hands-on in the lab. There were many afternoons running assays and tag teaming experiments.

Watching this project grow from its conceptual stage to the point where it holds potential for real clinical application has been highly satisfying. The evolution of an idea into something that could eventually impact patient care is both fascinating and fulfilling to me.

Building a network of supportive mentors and peers has been my most reliable strategy for overcoming obstacles. Whether it's collaborating over a cup of coffee or troubleshooting experiments together in the lab, the support of colleagues has been key.

One of my proudest achievements has been helping to carve out a unique path for pharmacy students at the university, with a focus on integrating foundational sciences into clinical practice. I've had the privilege of sharing my experiences and inspiring a growing number of students with similar interests. I take great pride in mentoring students who are passionate about research and exploring the vital connections between science and patient care.

I hope to continue educating future pharmacists, emphasising the importance of a strong foundational knowledge in the basic sciences and its relevance to clinical practice. Additionally, I hope to encourage more clinical pharmacists to engage in research, as their clinical insights are invaluable in shaping successful research projects.

Madison's *top tips*

1. Don't be afraid to forge your own path.
2. Pharmacy and science are incredibly diverse fields, full of opportunities to discover what excites you and aligns with your passions. Be open to exploring those possibilities.

Meet *Dmitri*

One of my teachers on my pharmacy degree course was a renowned biochemist who developed a liposomal drug for cancer treatment. I have always been passionate about science, and I believed that starting in basic science with a focus on drug delivery was the perfect path for me. As a result, I joined his lab to pursue a PhD.

My interest in nanoscience began during my PhD studies, which I later continued with a postdoctoral position focused on understanding how the immune system recognises nanoparticles. After establishing my lab in Colorado, I pursued a deeper understanding of how nanoparticle drugs accumulate in various organs, including the skin.

Together with Tom, I am a principal investigator on this research. Our role is to train the students, supervise the research, design experiments, and write papers and reports.

My lab has made several important discoveries explaining how particles gather in the skin. We used a special type of fluorescent microscope in living animals to observe drug-loaded nanoparticles accumulating in the skin. This work was very rewarding and laid a strong foundation for our current collaboration with Tom on interferon and its role in drug accumulation at target sites.

My motto is that everything can be solved with a good amount of thinking and trying new approaches. Historically, things have worked out this way or another; it's just a matter of persistence and optimism.

Dmitri's *top tip*

Be passionate about your work and intrigued by the unexpected directions science can take.