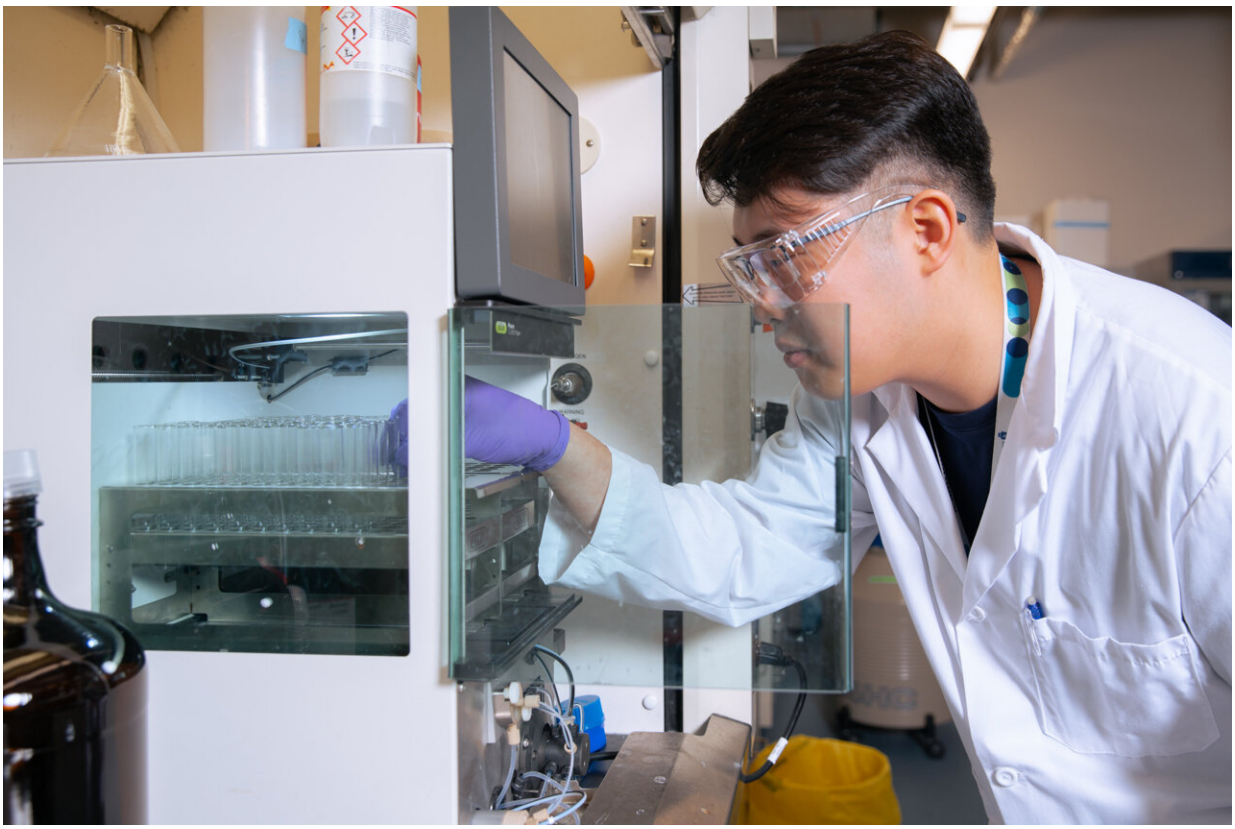
Researchers discover new lipid nanoparticle that shows muscle-specific mRNA delivery, reduces off-target effects.

December 8 2023, by Kate Richards



A team of researchers based at the University of Toronto's (U of T) Leslie Dan Faculty of Pharmacy has discovered a novel ionizable lipid nanoparticle, iso-A11B5C1, that enables muscle-focused mRNA delivery while minimizing off-target delivery to other tissues. Credit: Steve Southon, University of Toronto

A team of researchers based at the University of Toronto's (U of T) Leslie Dan Faculty of Pharmacy has discovered a novel ionizable lipid nanoparticle that enables muscle-focused mRNA delivery while minimizing off-target delivery to other tissues. The team also showed that mRNA delivered by the lipid nanoparticles investigated in their study triggered potent cellular-level immune responses as a proof-of-concept melanoma cancer vaccine.

The study, led by Bowen Li, assistant professor, Leslie Dan Faculty of Pharmacy, U of T, was published this week in *Proceedings of the National Academy of Sciences.*

Called iso-A11B5C1, the new lipid nanoparticle demonstrates exceptional mRNA delivery efficiency in muscle tissues while also minimizing unintended mRNA translation in organs such as the liver and spleen.

Additionally, study results show that intramuscular administration of mRNA formulated with this nanoparticle caused potent cellular immune responses, even with limited expression observed in lymph nodes.

"Our study showcases for the first time that mRNA lipid nanoparticles can still effectively stimulate a cellular immune response and produce robust anti-tumor effects, even without direct targeting or transfecting lymph nodes," said Li. "This finding challenges conventional understandings and suggests that high transfection efficiency in immune cells may not be the only path to developing effective mRNA vaccines for cancer."

Reducing off-target effects vital step to increase the safety of potential therapies

Lipid nanoparticles, also called LNPs, are crucial for delivering mRNA-based therapies, including COVID-19 mRNA vaccines that were used worldwide during the recent global pandemic. However, many LNP designs can inadvertently result in substantial mRNA expression in off-target tissues and organs like the liver or heart, resulting in often treatable but unwanted side effects.

The drive to improve the safety of mRNA therapies that have the potential to treat a broad range of diseases means there is an urgent need for LNPs designed to minimize these off-target effects, explains Li, who is also a recent recipient of the Gairdner Early Career Investigator Award.

The new research shows that, compared to the current benchmark LNP developed by the Massachusetts-based biotechnology company Moderna, iso-A11B5C1 demonstrated a high level of muscle-specific mRNA delivery efficiency. It also triggered a different kind of immune response than what is seen in vaccines used to treat infectious diseases.

"Interestingly, iso-A11B5C1 triggered a lower humoral immune response, typically central to current antibody-focused vaccines, but still elicited a comparable cellular immune response. This finding led our team to further explore this as a potential cancer vaccine candidate in a melanoma model, where cellular immunity plays a pivotal role," said Li.

The interdisciplinary research team that conducted the study includes Jingan Chen, a Ph.D. trainee from the Institute of Biomedical Engineering at U of T, and Yue Xu, a postdoctoral researcher in the Li lab and a research fellow with PRiME, U of T's cross-institutional precision medicine initiative.

"Although iso-A11B5C1 showed limited capacity to trigger humoral immunity, it effectively initiated cellular immune responses through

intramuscular injection," said Chen. "The substantial anti-tumor effects observed with iso-A11B5C1 underscore its promise as a viable candidate for cancer vaccine development."

New platform allows for faster, more precise lipid design

The research team identified iso-A11B5C1 by using an advanced platform developed to quickly create a range of chemically diverse lipids for further testing. This platform, newly introduced as part of the study, overcomes several challenges seen in previous research by streamlining the process of creating ionizable lipids that have a high potential to be translated into therapies.

By rapidly combining three different functional groups, hundreds to thousands of chemically diverse ionizable lipids can be synthesized within 12 hours. "Here we report a powerful strategy to synthesize ionizable liquids in a one-step chemical reaction," said Xu. "This platform provides new insights that could help guide lipid design and evaluation processes going forward and allows the field to tackle challenges in RNA delivery with a new level of speed, precision and insight."

More information: Jingan Chen et al, Combinatorial design of ionizable lipid nanoparticles for muscle-selective mRNA delivery with minimized off-target effects, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2309472120

Provided by University of Toronto—Leslie Dan Faculty of Pharmacy