A toxin with a useful twist: Diphtheria fragment merges lipid vesicles at neutral pH

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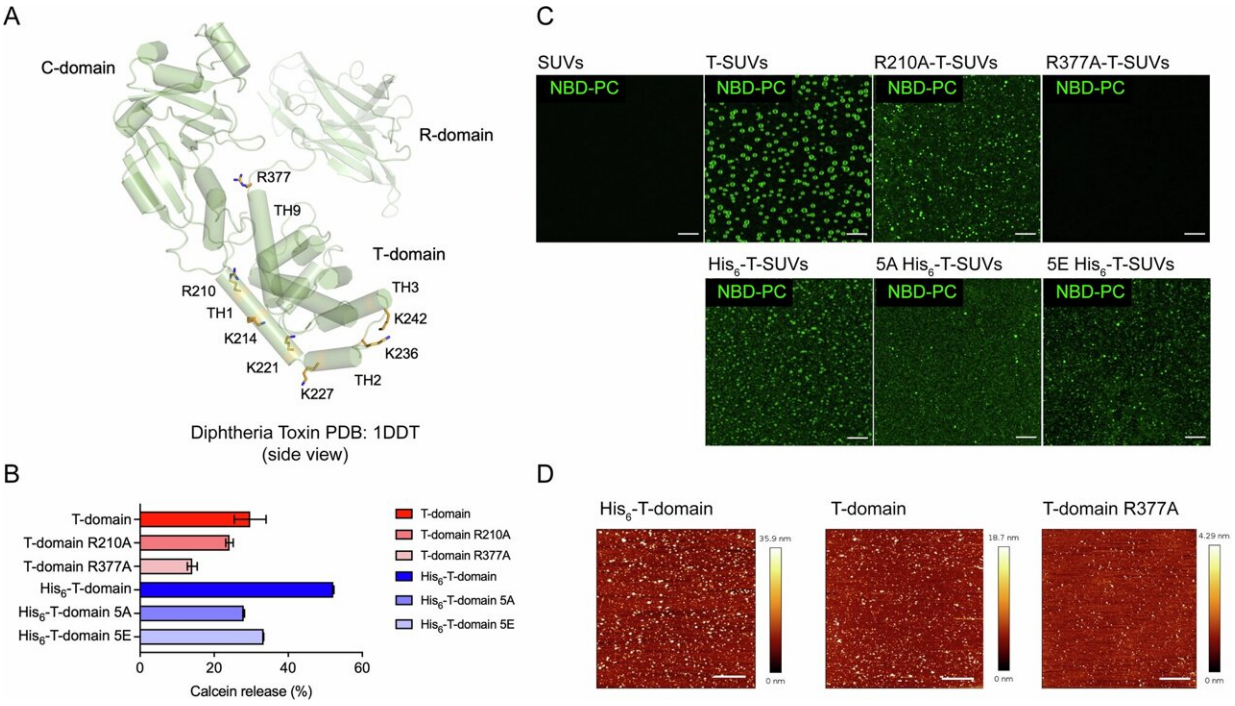


Role of basic amino acid residues in T-domain mediated vesicle fusion. Credit: *Communications Chemistry* (2025). DOI: 10.1038/s42004-025-01738-1

Researchers from the SNI network have discovered a novel way to fuse lipid vesicles at neutral pH. By harnessing a fragment of the diphtheria toxin, the team achieved vesicle membrane fusion without the need for pre-treatment or harsh conditions. Their work, recently published in *Communications Chemistry*, opens the door to new applications in lab-on-

a-chip technologies, biosensors, and artificial cell prototypes.

Lipid vesicles—tiny spheres enclosed by membranes—are important tools in medicine and nanotechnology. They can transport pharmaceutical agents to specific cells and tissues or contain contrast agents for diagnostic examinations. On the other hand, they can serve as versatile building blocks in synthetic biology, where controlled fusion enables the creation of larger compartments that mimic the complexity of living cells by sharing and combining their contents.

There are several ways to make larger vesicles, such as electroporation or microfluidic production. Another attractive strategy, inspired by biology, is to let smaller vesicles fuse into bigger compartments. Fusion is particularly compelling because it mimics natural processes and allows compartments to grow and connect dynamically.

Yet, achieving well-controlled membrane fusion in the laboratory, especially without vesicles pre-treatment, has long been a challenge. To pave the way for applications in a real-world setting, researchers are investigating the use of specific proteins to control and target the fusion of vesicles.

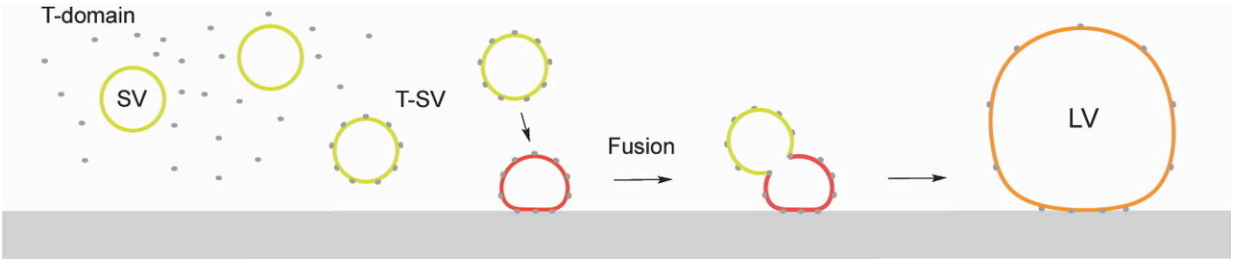
Diphtheria toxin enables membrane fusion

A research team led by Prof. Dr. Cornelia Palivan at the Department of Chemistry, University of Basel, and Dr. Richard A. Kammerer at the Paul Scherrer Institute (PSI) has now achieved a breakthrough in protein-driven membrane fusion in the laboratory using diphtheria toxin.

"A specific part of the diphtheria toxin, known as the T domain, can induce membrane fusion even at neutral pH—without the need to functionalize the vesicle membranes during production. It is unique because normally this toxin works under acidic conditions in cells,"

explains Piotr Jasko, first author of the study and doctoral student at the Swiss Nanoscience Institute.

"In our experiments, we were able to show how the binding of the toxin's T domain leads to membrane fusion without compromising the integrity of the membrane," he adds.



Specific positively charged amino acids of the diphtheria toxin domain (gray dots) bind to negatively charged vesicle membranes (T-SVs - T-domain-associated smaller vesicles). The vesicles then adhere to a glass surface. This leads to asymmetric tension in the membrane (red). When other free-floating vesicles in the solution fuse with an adhering vesicle, the membrane tension is reduced and larger vesicles (LVs) are formed. Credit: P. Jasko, University of Basel and PSI

Positively charged amino acids are critical

Certain positively charged amino acids in the diphtheria protein play a role in fusion at neutral pH. The amino acids bind to the negatively charged vesicle membrane and then enable adsorption of the vesicles to a glass surface.

The resulting asymmetric tension in the membrane is the trigger that then leads to the fusion of attached and free-floating particles, which is

accompanied by a reduction in membrane tension. The vesicles that do not adhere to the glass plate and float freely in the solution do not fuse among each other.

"Depending on the strength of the positive charge on the T domain or amount of negatively charged lipids, the fusion produces many small or fewer large vesicles, which in all cases retain their spherical shape," explains Kammerer.

"Targeted membrane fusion at neutral pH is of great interest to us because it can be used for numerous applications. It provides the basis for various lab-on-a-chip technologies, biosensors, and possible use with synthetic analogs of liposomes—polymersomes to produce more chemically advanced and stable cell mimics," comments Palivan.

More information: Piotr Jasko et al, Diphtheria toxin T-domain as a tool for inducing lipid vesicle fusion, *Communications Chemistry* (2025). DOI: 10.1038/s42004-025-01738-1

Provided by University of Basel