THE FRONT ROW
at Scripps Research



Accelerating evolution to create new medicines

Christian Diercks PhD
Assistant Professor, Department of Chemistry

ABOUT THE LECTURE

Evolution is slow. Over millions of years, random mutations alter organisms' characteristics, and traits that help them survive and reproduce stick around. But the immune system has a fascinating capacity to fast-track evolution when it produces antibodies. Inspired by this system, Scripps Research assistant professor Christian Diercks described a synthetic biology platform called T7-ORACLE in his Front Row lecture, which he co-developed to accelerate the evolution of other proteins, such as enzymes, with therapeutic potential. Diercks explained how his lab is using the system to evolve enzymes to selectively break down or modify disease-related molecules—a strategy that could help make new medicines for gout and chronic pain.

TOP TAKEAWAY POINTS

- Natural evolution takes an astonishingly long time. Humans and chimpanzees diverged from a common ancestor around 6.5 million years ago, and despite that time, our genome sequences only differ by about 1.2%. Diercks described how the chimpanzee gene for cytochrome c—a small protein involved in programmed cell death—contains only 4 DNA base changes compared to the human gene, all of which are considered "silent" since they produce the same building blocks and functionally identical proteins.

- The immune system contains an exception. The antibody-improvement process, called "affinity maturation," has a mutation rate that can be up to 1 million times faster, allowing for rapid evolution of antibodies against specific pathogens or other molecules. This approach has been harnessed by drug developers to produce therapeutic antibodies, which account for around 25% of recently approved drugs.

- For enzymes and other non-antibody proteins with therapeutic potential, there's no comparable natural system for accelerating their evolution. So Diercks co-developed a synthetic one: a platform called T7-ORACLE. It's engineered to continuously mutate a selected gene within Escherichia coli (E. coli) bacteria using machinery borrowed from T7 bacteriophages (which are small E. coli-infecting viruses). The researchers can then select which evolved proteins best perform the intended function.

- For people with refractory gout, painful uric acid crystals build up and cause inflammation in the joints. This is because humans have lost activity of the uricase enzyme (which breaks down uric acid) in recent evolutionary history. Diercks described how his lab used T7-ORACLE to evolve human-like uricases from ancestrally reconstructed genes, providing a potentially viable strategy to treat the disease.

- While effective at relieving pain, the highly addictive nature of opioids has led to an overdose crisis in the United States—highlighting the need for alternative, non-addictive pain medications. Diercks described work from his lab using T7-ORACLE to repurpose an enzyme from botulinum neurotoxin type A (the substance used in Botox) to selectively inactivate a sodium ion channel called $Na_v1.7$ (which is involved in pain signaling). If successful, the evolved toxin could be delivered locally to suppress pain while avoiding activation of brain reward pathways that lead to addiction.

Learn more and register for upcoming lectures at frontrow.scripps.edu.

SUPPORT SCRIPPS RESEARCH