THE FRONT ROW
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The choreography of life: What a protein's "dance" says about health and disease

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ABOUT THE LECTURE

Proteins are the molecular machines that run every process in the human body, but the static, freeze-frame images most of us have seen don't tell the full story. In this Front Row lecture, Scripps Research professor Dorothee Kern shared how her lab captures proteins in motion, revealing that their constant movement isn't just background noise, but rather the key to how they function. By studying these dynamics, Kern's team has uncovered a new approach to designing highly selective drugs that can target cancer while preserving healthy tissue. Her lab is also developing new enzyme therapies that could one day allow people with gluten intolerance to eat without restriction, and an artificial intelligence model that fills the critical gap in predicting protein movement.

TOP TAKEAWAY POINTS

- Proteins don't hold still, and that movement is essential to life. Every biological process in the body, from fighting infection to energy production, depends on proteins constantly shifting between different shapes. Kern's lab uses a technique called nuclear magnetic resonance (NMR) spectroscopy, the same physics underlying MRI, to capture these movements at the level of individual atoms and in real time, under normal physiological conditions.

- The conformational changes a protein undergoes after a drug binds are as important as where the drug lands. Drug discovery has long focused on fitting molecules into protein binding pockets, but Kern's research revealed a broadly overlooked step: After initial binding, some proteins undergo a slower structural change that locks the drug in place. Designing drugs that trigger this secondary step is what produces potent, selective therapies with fewer side effects.

- Understanding protein dynamics enabled the development of cancer drugs that spare healthy tissue. Kern co-founded Relay Therapeutics to translate these principles into the clinic. By exploiting structural differences in a region away from the drug-binding pocket of a kinase, a protein that helps control how cells communicate and grow, the company developed a selective inhibitor for a form of pancreatic and bile duct cancer. One patient who had been previously taken off a non-selective drug due to toxicity has been cancer-free for three years on the new molecule, and a second program targeting a kinase mutated in solid tumors is currently in phase 2 clinical trials.

- Kern's lab is also applying principles of protein dynamics to develop an oral enzyme therapy for gluten intolerance, a condition affecting roughly 10% of the population for which no treatment currently exists. The goal is a protease, an enzyme that breaks down proteins, capable of cleaving gluten into harmless fragments before it triggers an immune response in the stomach. Because modern enzymes proved too unstable and slow for this environment, the team took an unconventional approach: using computational methods to reconstruct an ancient enzyme from billions of years ago, then refining it through a trial-and-error process that mimics natural selection guided by artificial intelligence. The result was a 700-fold increase in enzymatic speed over just four rounds of optimization.

- Targeting two distinct sites on a protein simultaneously can prevent cancer cells from developing drug resistance. One of the most persistent challenges in cancer treatment is that tumors frequently mutate to evade therapy. Kern's lab demonstrated that combining a conventional cancer drug with a second molecule designed to attach to a different region of the same protein makes it far less likely for a cancer cell to develop resistance to both at once. In preclinical studies, this approach, called double drugging, reduced the chemotherapy dose needed for equivalent tumor suppression by 20-fold while significantly improving selectivity.

- Kern's team developed an artificial intelligence model, called Dyna-1, that can predict where a protein moves. Training such a model has been limited by a shortage of experimental data, but the team found a creative workaround: amino acids that move on the biologically important millisecond time scale simply vanish from the NMR data, and those absences are themselves a signal of motion. By mining 10,000 existing NMR studies on proteins for these missing signals, the team assembled a training dataset large enough to build a reliable model. Dyna-1 has already identified key dynamic regions in KRAS, whose mutations drive some of the most difficult-to-treat cancers, including those of the pancreas and lungs, making it one of the most consequential targets in oncology.

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