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Peptone

Peptone: unlocking the therapeutic potential of intrinsically disordered proteins

Biophysics company Peptone is developing Oppenheimer, a protein-modeling platform that can transform undruggable intrinsically disordered proteins (IDPs) into developable drug candidates.

Around a third of the proteins in the human body—including many that are crucial in health and disease—are IDPs and are structurally labile in whole or in part, assuming different shapes and forms depending on their cellular context. With no fixed structure when isolated, they are not amenable to classical drug discovery methods, and their underlying genetic sequences cannot accurately predict their structural properties. Consequently, efforts to find and develop rigidly designed drugs that will target and bind these proteins are likely to fail.

The translational biophysics company Peptone is changing all that. By combining experimental biophysics, atomic-level experimental approaches, high-performance supercomputing (HPC) and machine learning (ML), Peptone is unlocking the potential of IDPs and pioneering the development of novel therapeutics against this entirely new class of high-value and previously undruggable targets.

Bringing order to disorder

Founded in 2018 and born out of 30 years of academic research at the universities of Cambridge, Oxford, ETH Zurich and Groningen, Peptone provides end-to-end capability in understanding the structure and dynamics of IDPs and how to target them as therapeutics.

Peptone is developing an automated protein-modeling and engineering platform, Oppenheimer, which integrates biophysical experimental data, artificial intelligence (AI) and ML to understand the structural dynamics of these difficult-to-drug IDPs. Through Oppenheimer, Peptone is able to build a profound understanding of the behavior and heterogeneity of IDPs, accurately model their structures under relevant conditions, establish the optimal target binding sites, and determine the best therapeutic modalities against them (Fig. 1).

Initially, nuclear magnetic resonance (NMR) and hydrogen/deuterium-exchange mass spectrometry (HDX-MS) are used to analyze IDP behavior, determining what the protein looks like under conditions that differ in terms of factors such as pH, temperature and the presence of membrane-mimicking excipients—in certain environments, IDPs may assume a more stable structure that is potentially druggable. Data from these experiments are used in silico to identify the most plausible drugging sites and regions. AI and ML are then used to generate compact but diverse libraries of high-quality IDP variants that may have drug-like properties or are easy-to-manipulate targets for high-affinity protein-binder development. Subsequently, Peptone performs lead selection and end-to-end testing in its advanced biophysical laboratory and through third-party engagements.

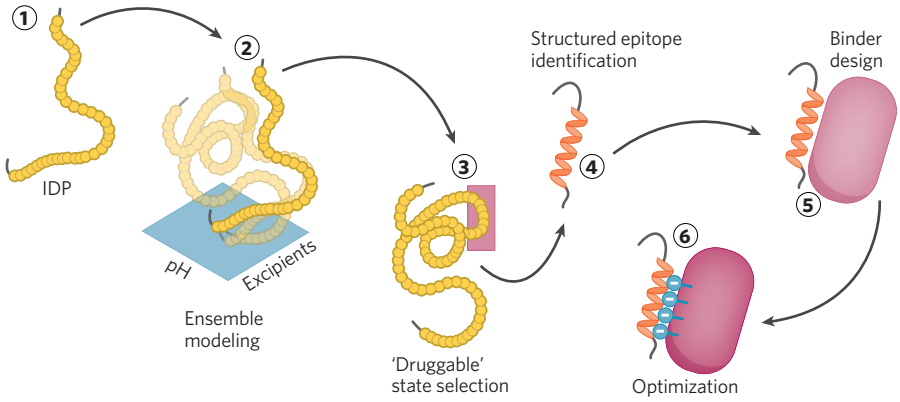

Fig. 1 | High affinity protein binder design process for an intrinsically disordered protein target using the Oppenheimer platform.

End-to-end capability

The platform has already been tested through successful proof-of-concept studies on novel disordered proteins with major pharmaceutical companies. By utilizing Oppenheimer, for instance, Peptone helped with unlocking the therapeutic potential of an orphaned IDP that is in development to become a recombinant protein drug, and addressed the aggregation issues of a therapeutic monoclonal antibody (mAb) that targets a folded protein with a prominent disordered region.

Peptone's internal platform, however, is designed to ultimately deliver therapeutic molecules. The company, which has plans for its own portfolio of unique targets in a range of indications, including inflammation, cancer, fibrosis and diabetes, plans to develop structurally dynamic drugs based on disordered proteins—a completely novel class of biologic medicines.

Peptone recently raised $40 million in Series A financing to build a scalable business with cutting-edge supercomputing capabilities and advanced research and development (R&D) laboratory in Switzerland. Future financings will enable development through late stage drug discovery towards new drug filing and into early human clinical studies.

Considerable potential

With disordered epitopes abundant across the human proteome, and IDPs often involved in signaling and cell-cycle regulation, the IDP target landscape is very broad and continues to expand. "Peptone's technology can be scaled to many hundreds of disordered and partially unstructured proteins of high medical relevance," said Bojana Popovic, Peptone's CSO. Moreover, in addition to the huge potential for developing therapeutics to treat many major diseases, the technology has wide-ranging potential applications that extend to industries beyond pharmaceuticals, where understanding, engineering and controlling IDP function may provide novel and valuable approaches.

Peptone is pursuing two major routes in deploying its technology platform. The first is via internal preclinical pipeline development of therapeutic assets based on the rigorous understanding of IDP biophysics. The second is via select external co-development partnerships with pharmaceutical and biotech companies to unravel the complexities of some of their most challenging targets—in many such cases the disordered nature of the target is not known, let alone understood, added Benjamin Owens, Peptone's Chief Strategy Officer.

"IDPs are abundant, challenging to work with, and represent highly attractive targets and potential therapeutics that are largely unexplored. We are building a category-defining company that has the capability to unlock not only a new landscape of protein targets but also a new class of biologics that contain intrinsically disordered regions themselves," said Kamil Tamiola, Peptone's CEO. "Our Oppenheimer platform can transform an undruggable and scientifically unknown disordered protein into a developable drug candidate—potentially game-changing technology that has vast potential for creating novel therapeutics to treat diseases with significant need.

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