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Protein engineering with roPROTix: an AI-powered platform for drug discovery

Perspix Biotech's roPROTix platform combines artificial intelligence, robotics, and wet biology in a closed-loop feedback system for the discovery of next-generation multi-targeting biological therapeutics.

The challenge of treating complex, multifactorial diseases like cancer and chronic inflammatory conditions with mono-specific therapies, including monoclonal antibodies (mAbs), has raised interest in multi-specific biological therapies that combine the functional activities of two or more mAbs into a single biological entity. Yet to date, the development of multi-targeting biological therapies has been expensive and time consuming—with candidates showing a high rate of attrition.

Perspix, a new biotech headquartered in Frankfurt, Germany, aims to turn this around. The company is developing the roPROTix platform for the rapid design and synthesis of next-generation multi-targeting agents with a higher likelihood of advancing through the pipeline to clinical trials.

roPROTix utilizes validated technologies for end-to-end automation of protein-engineering processes pioneered by Perspix's co-founder and CSO, Joerg Birkenfeld[1], and outputs data on the biophysical and functional characteristics of tens of thousands of synthesized multi-targeting agents simultaneously. The physical production and analysis stages of roPROTix are in turn connected in a closed loop to artificial intelligence (AI) that uses these data to uncover design principles for creating multi-specific biologicals with higher efficacy and improved developability thanks to superior biophysical properties.

A key challenge to using AI for developing multi-specific agents is a lack of appropriate data to train systems. Although the biophysical and functional properties of multi-specific agents are interrelated and influence each other in multiple dimensions, standard approaches to optimizing them tend to do so serially, one at a time—creating one-dimensional datasets, long development times, and frequent 'optimization dead-ends'.

The roPROTix advantage

roPROTix, by contrast, analyzes multiple properties simultaneously, producing unique multi-dimensional datasets that fill the current data gaps for training AI systems to identify principles for designing multi-specific drugs with high efficacy, good biophysical features, and a higher likelihood of success. "With its unprecedented data-generation capabilities, I am convinced that Perspix will be at the forefront of AI-based innovation in the area of next-generation multi-specific antibody therapeutics design and development", said Hartmut Michel, Nobel laureate and Perspix scientific advisor.

roPROTix begins with the format- or modality-agnostic in-silico design of multi-specific biological drug entities, which can create not only multi-specific antibodies but also any other kind of multi-specific protein therapeutic. In roPROTix, the output of the in-silico 'digital design' stage is connected to the physical wet-lab stages of cloning, expression, and analysis in an automated end-to-end process, with all multidimensional experimental and metadata captured in a gapless fashion. As such, roPROTix sits at the intersection of three big trends: the move towards multi-specific drugs, flexible biotechnology platforms, and AI/machine learning (ML)-powered biological drug design.

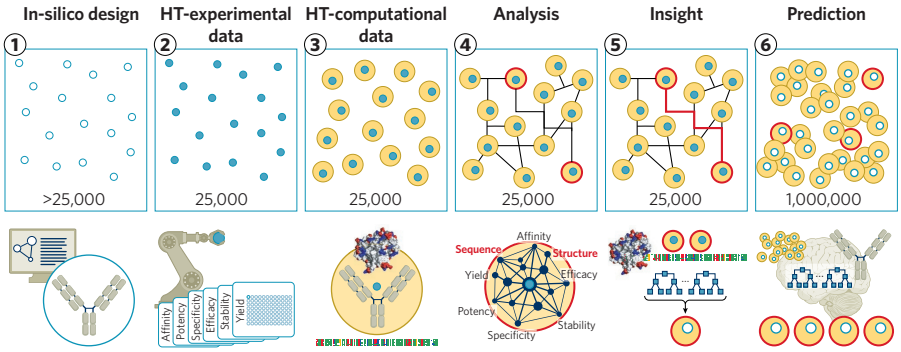

Fig. 1 | The roPROTix process. Multi-targeting molecules are designed in a format-agnostic manner (**1**), and then produced in mammalian hosts and analyzed in multiple dimensions (**2**), providing data on molecules that are further enriched with in-silico data (**3**). Deep analytics identifies variants with favorable developability properties (**4**), and their structural and sequence features build AI models that can predict the developability of in-silico-designed molecules (**5**), as well as screening large in-silico-design spaces or being used to design molecules with favorable drug-like properties de novo (**6**). HT, high throughput.

With roPROTix, up to 25,000 individual molecules of any kind—mono-, bi-, tri-, tetra- or penta-specific—can be produced in a parallelized process. Each molecule is expressed in its soluble drug-product format in an isolated mini-bioreactor-like compartment, which allows for the unbiased determination of multiple functional and biophysical properties—such as yield, potency, stability, and specificity—for each molecular design. And unlike other approaches such as display-based optimization, which enrich only positive variants, roPROTix preserves data on all variants, including those that perform poorly, providing information on what works and what doesn't (Fig. 1).

Translating the data

The huge sets of contextualized, multidimensional experimental data produced on both positive and negative variants are collated in machine-readable form and fed back to AI models to improve in-silico design. Crucially, the flexibility of roPROTix means that experimental designs can be adapted to generate the specific data required to improve AI models.

The experimental data are augmented by a wealth of in-silico data that, when combined, are used to identify sequence–structure–activity (SSA) relationships—which are the design principles of the multi-specific biological drug-entity of interest. These SSA/design principles can then be used in the short term to train AI for enhanced in-silico screening, and in the longer term to create a solid basis for the de-novo design of multi-specific agents. And as the roPROTix process emulates the final industrial drug-production process, identified candidates are de-risked for progression into large-scale production and through development to commercial manufacturing.

Perspix is currently focused on multi-specific antibodies and aims to develop a portfolio of internal and partnered oncology programs based upon novel combinations of targets with strong clinical evidence. Looking ahead, Perspix's vision is to decipher the design principles of next-generation multi-targeting biological drugs to reduce attrition and development costs and make them more affordable. The company welcomes discussions with investors or partners about the game-changing potential of roPROTix.

1. Furtmann, N. et al. *mAbs* **13**, 1955433 (2021).

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