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Drug hunting vs. drug fishing

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The presentation will cover the difference between drug hunting and drug fishing. This will be illustrated by two drug discovery efforts aimed at identifying antiviral and antibiotic clinical agents. Namely, we have discovered azaindole-based molecule acting through a novel mechanism targeting the influenza virus, which led to a clinically effective agent VX-787. The second part will cover efforts aimed at solving medicinally relevant bio-transformations, which can limit progress of clinical molecules, as we discovered a new and pharmacologically effective class of antibiotics, VX-100.

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Adapting DNA-encoded library technology for fragment-based drug discovery

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DNA-encoded library (DEL) technology is a powerful method for rapid drug discovery. Combinatorial synthesis is used to generate large (up to billions of members) libraries of compounds, with each one tagged by a unique barcode made from DNA. A target protein is then screened with a small amount of the library. After non-binding members are washed off, hit compounds are identified by amplifying and sequencing their DNA tags. This method is becoming increasingly popular, but the core workflow has remained largely unchanged in many years. DyNAbind has developed key technologies to overhaul and modernize the DEL discovery process, while also adapting it for a fragment-based discovery approach. Our dynamic fragment libraries allow random pairing and reshuffling of library members in solution, until stabilized by protein binding, resulting in fewer but more reliable hits. Furthermore, our binding profiler technology allows validation and quantification of binding kinetics from fragment-based hits without the need for linker optimization. As a case study, these technologies were deployed to find and characterize new synergistic binders for human carbonic anhydrase 2.

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