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Spotlight article

Spotlight on Oligo Pools and Protein Engineering

Nobel Prize Winner Dr. David Baker's focus on engineered mini-binder proteins and their applications

The 2024 Nobel Prize in Chemistry was recently awarded for pioneering work in computational protein design and protein structure prediction. This research has enabled scientists to predict three-dimensional protein structure and folding with remarkable precision and has opened the possibility for design of novel proteins with specific, unique functions.

Computational approaches to protein design

A computational approach to protein design provides a rational, more direct and faster approach to generating protein-binders than large scale, random library selection methods. When trying to explain the difference between old and the new computational approaches, one article[1] uses an analogy of a climber having to ascend a wall with just a few of the most reliable footholds or handholds which happen to be very far away from each other. This approach might fail in finding a way to the top because there is no easy or obvious way to connect the reliable footholds and handholds together into a successful route.

The new approach involves identifying and including every potential handhold and foothold, regardless of their quality. Next, numerous climbers attempt to ascend the wall using various routes or combinations of these holds. The most promising routes are then identified, and subsequently, a different group of climbers examines these routes thoroughly.

From analogy to algorithms

This research is advancing quickly, and while it is possible to design high-affinity binding proteins using only the structural information of the target, the success rate has been low.[2] Recent developments in machine learning and artificial intelligence have augmented the design and prediction processes though. Using data from AlphaFold2 or RoseTTAFold, researchers saw a 10-fold increase in design success rate when combining probabilities of monomer structure sequence adoption with the probability of the structure binding to the target as designed.[2]

From the digital world to the laboratory

Taking the design out of the computer and into the laboratory to confirm that the predicted 'minibinders' have the desired functionality is a big task. In one study, they experimentally tested ~20,000 designs[2] per target, and another study reports up to 100,000 designs being tested per target.[1]

Each one of these starts with an oligo pool manufactured by Agilent on the SurePrint Oligo Library Synthesis platform. Baker lab protein design software generates DNA sequence files that can be directly uploaded to the SurePrint platform for the rapid production of completely custom oligo pools. As Baker Lab member Dr. Brian Coventry once said, "We have ordered enough DNA sequences for at least two million proteins from Agilent. They are a lot less expensive than people would think."[3]

Applications of minibinders

Minibinders have a wide range of applications due to their high selectivity, stability, and ease of production. These proteins can be tailored to fit their targets much more tightly than traditional monoclonal antibodies. The list of applications of minibinders grows rapidly--here are a few examples:

- Neutralization of the SARS-CoV-2 spike protein, showing promise as antiviral agents.[4]
- Targeting of pattern recognition receptors for improving the performance of vaccines.[5]
- Neutralization of toxins from botulinum toxin and *Clostridioides difficile* toxin B.[6]
- Used as scaffolds for drug development, providing a platform for creating new therapeutics with high specificity and stability.[7]

Agilent's contribution to the success of protein engineering

Agilent's SurePrint oligo pools deliver cost-effective sequence diversity allowing researchers to screen thousands of sequence variants and perform low-cost gene assembly processes.

- **Length:** Minibinders typically require DNA sequences encoding for around 65 amino acids, which translates to 195 nucleotides. Additional sequence content for assembly and amplification bring the total length to 230 nucleotides.
- **High fidelity:** Agilent is renowned for its ability to produce long oligonucleotides with low error rates. This precision is crucial for research that demands accurate and reliable starting material for complex protein designs.
- **Customization and quality:** Agilent's SurePrint platform provides high-quality completely custom oligonucleotide libraries with no restrictions on sequence content.
- **Exceptional uniformity:** High-throughput functional genomics screening and protein engineering with fewer false positive or false negatives from over or under-represented sequences.
- **Efficiency and scalability:** Rapid turnaround times enabled by our high capacity continuously operating production facility keep your research on track and at scale.

The utilization of Agilent oligo pools in Nobel Prize-winning research highlights the importance of high-quality, custom oligonucleotide libraries in scientific investigations.

For researchers in protein, antibody, and genome engineering, Agilent's SurePrint oligo pools offer a valuable resource for achieving high fidelity, exceptional uniformity, and rapid turnaround times in all of their scientific endeavors.

Nobel Prize 2024, Chemistry laureates John Jumper, David Baker and Demis Hassabis. © Nobel Prize Outreach. Photo: Clément Morin.

Collection of articles

Explore a collection of articles from Nature highlighting the groundbreaking research and contributions of the awardees and their significant advancements in the field of protein design and engineering.

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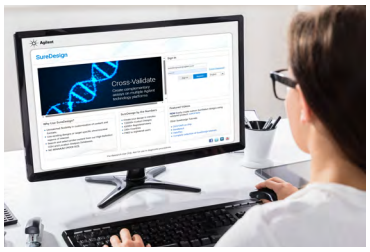

SureDesign

The SureDesign custom design tool creates custom designs for NGS, CGH, CRISPR, and FISH.

SurePrint HiFi Oligo Pools

High Fidelity Oligo pools made for applications requiring the highest quality starting material.

ProteoAnalyzer System

Automated SDS capillary electrophoresis system separates 12 protein samples in parallel.

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PR-7001-4261

Published in the USA, May 10, 2025
5994-8367EN

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