Frontiers of Scientific Discovery: Protein Evolution, Spatial Transcriptomics, and Antibody Research

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Abstract

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1. Rapid in silico directed evolution by a protein language model with EVOLVEpro

By K. Jiang *et al.*

EVOLVEpro is a novel protein engineering method that combines protein language models (PLMs) with active learning to improve protein functions more efficiently than traditional directed evolution or standalone in silico methods. The approach leverages PLM-derived sequence representations, interpreted through a regression model, which iteratively refines predictions based on experimental data. With only 10 experimental data points per round, EVOLVEpro enables rapid multi-objective optimization for enzymes, antibodies, and gene-editing tools. The method achieved remarkable results, such as a 40× increase in binding affinity for antibodies and a 100× improvement in transcription fidelity for RNA polymerases. EVOLVEpro significantly outperformed zero-shot PLM predictions, demonstrating that experimental iteration is crucial for enhancing in silico models. This approach opens new avenues in protein design, providing faster and more precise optimization for biotechnological and medical applications.

This article was previously published in Science, Volume 387, Issue 6732, on November 21, 2024.

Read the full article here

2. Highly multiplexed spatial transcriptomics in bacteria

By Ari Sarfatis *et al.*

A novel method called bacterial-MERFISH combines up to 1000-fold volumetric expansion with image-based single-cell transcriptomics to investigate bacterial behavior within complex native environments. This technique overcomes the challenge of the high density of bacterial RNAs, which previously limited the ability to resolve individual RNA molecules using conventional microscopy. By expanding bacterial cells and utilizing multiplexed error-robust fluorescence in situ hybridization (MERFISH), researchers were able to profile up to 80% of the transcriptome in single E. coli cells. The method revealed heterogeneous responses to environmental changes, such as carbon source shifts, and unveiled spatial patterns in transcriptome organization. Additionally, bacterial-MERFISH was used to study *Bacteroides thetaiotaomicron* in the mouse colon, demonstrating its capability

to map gene expression at a subcellular resolution. This technique promises to significantly advance the study of bacterial phenomena, including biofilm specialization, antibiotic resistance, and host-microbe interactions, providing a powerful tool for exploring a wide range of microbiological questions.

This article was previously published in Science, Volume 387, Issue 6732, on January 24, 2024.

Read the full article here

3. A bite of expertise

By L. Childress

The humorous writing of Childress reflects the harsh reality of the working environment of academic life. The author describes how he used the opportunity of eating with his superiors and working colleagues in order to build up a professional and personal relationship. This reflects the professional segregation of different academic positions and the difficulty that many young researchers experience when it comes to connecting to their working environment. This small lunch break made Childress realize that important investigators are also humans just as young researchers. His final conclusion is that instead of getting intimidated by the academic structure and the hierarchy that it imposes, one has to know the best bistros around the office and try them out with her/his colleagues.

This article was previously published in Science, Volume 387, Issue 6732, on January 23, 2025.

Read the full article here

4. Affinity maturation of antibody responses is mediated by differential plasma cell proliferation

By Andrew J. MacLean *et al.*

Antibodies, which are produced by plasma cells derived from B cells, are essential in adaptive immunity. Recent studies have focused on understanding how B cells producing high-affinity antibodies dominate the plasma cell population after vaccination. In this study, MacLean et al. used mouse models to show that B cells capable of producing high-affinity antibodies proliferated more than those

producing lower-affinity antibodies after immunization. This higher proliferation was associated with greater assistance from T follicular helper cells, but interestingly, it was not dependent on sustained cell-cell interactions. Instead, high-affinity plasma cells retained their ability to proliferate outside of germinal center structures, with cytokine interleukin-21 (IL-21) playing a crucial role in promoting cell division. The study sheds light on how the differentiation of B cells into plasma cells, and their subsequent expansion, contributes to the process of affinity maturation and the production of high-affinity antibodies.

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Read the full article here

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