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2024: research in review

Nature Biotechnology **editors pick their favorite research articles from 2024.**

There has been plenty to talk about in biotechnology and clinical research in 2024. The year started with the development of a new class of antibiotics that are currently in clinical trials, and artificial intelligence (AI) once again took center stage with updates to AlphaFold and RoseTTAFold. Advances in T cell and mRNA therapies also made our list of favorite articles for the year.

Generalizing biomolecular interactions with AI

Researchers continued to build better AI-based models for protein structure prediction and design, notably Alphafold3[1] and RoseTTAFold All-Atom[2]. Last year's versions could model how peptides could fold into their final shapes, but these new models can show how folded proteins bind and interact with other small molecules, including DNA, RNA and other proteins. As training data continue to grow and improve, these models will perform even better, leading to better prediction of protein functions and possible drug design.

Engineering 'smart' insulin

People with diabetes need to adjust insulin doses daily to account for changing glucose sensitivities, which are difficult to predict. Researchers have tried for over 40 years to engineer an insulin that can modify its own bioactivity in response to varying glucose levels, but with little success. This year, a group created a new insulin conjugate that demonstrated glucose-concentration-dependent and reversible bioactivity[3]. In addition to avoiding the risk of hypoglycemia, the insulin also outperformed conventional insulin injections in animal models. Other groups are also developing smart insulin drugs.

Engineered T cell therapy for soft-tissue cancers

The US Food and Drug Administration granted an accelerated approval this year for the first use of an engineered T cell therapy to treat a solid tumor, unresectable or metastatic synovial sarcoma[4]. The therapy combines aspects of chimeric antigen receptor (CAR) T cells and tumor-infiltrating lymphocytes (TILs), engineering a patient's T cells to express a receptor that recognizes the MAGE-A4-peptide–HLA complex found on the tumor. More approvals may come soon, if we look ahead in the clinical trials pipeline.

Finding new antibiotics

Antibiotic-resistant bacteria pose major threats to human health, and new antibiotics are desperately needed. Two studies published early this past year develop a new class of antibiotics that target the lipopolysaccharide transport machinery on the outer membrane of the hard-to-target gram-negative bacterium *Acinetobacter baumannii*[5,6]. The two studies show that new antibiotics can be discovered by thinking outside the traditional box of how to target and destroy bacteria.

Mining microbiomes for AMPs

Antimicrobial peptides (AMPs) are short peptide chains that could be used as an alternative to antibiotics because they are less likely to induce bacterial resistance. In a recent study, researchers looked at over 444,000 peptides from the Human Microbiome Project, validating 55 candidate AMPs that had strong activity against pathogens but no effect against commensals[7]. Another group created a catalog of over 800,000 peptides from the global microbiome, finding 63 that targeted pathogens[8].

mRNA-LNPs for enzyme replacement

There have been proof-of-concept studies for mRNA-based therapies in mouse models of propionic acidemia, a rare, inherited metabolic disorder that is caused by a deficiency in propionyl-CoA carboxylase enzymatic activity. This year the positive results of a phase 1/2 clinical trial were published[9]. A lipid nanoparticle (LNP) encapsulating two mRNAs encoding normal human propionyl-CoA carboxylase protein subunits was intravenously administered to people with propionic acidemia, restoring natural enzyme activity. This approach proves that mRNA can be used for more than just vaccines.

Spatial biology translates into the clinic

Spatial 'omics methods have improved substantially over the last few years, showing single-cell-level details of tissue organization and cellular interactions. In an exciting clinical step forward, researchers used deep visual proteomics to functionally validate targeted small-molecule inhibitors for rapid therapeutic intervention in severe cutaneous adverse drug reactions[10].

Foundation models for biological applications

Foundation models are AI-based models that can perform well across a range of different problems, by pretraining on very large, unannotated datasets. In biology, many machine learning and deep learning algorithms are focused on specific tasks, using specific training data, but foundation models are providing alternative ways to interrogate biology. For example, scGPT uses a vast amount of single-cell data to capture gene–gene interactions[11]. Companies are also taking note.

Shielded HSCs

A major limitation for treating hematopoietic cancers is that healthy hematopoietic stem cells (HSCs) and cancerous cells are equally affected by chemotherapy, leading to attempts to shield healthy cells from antigen-specific therapies. A study this year replaced the immune system using a CD45-targeting antibody–drug conjugate that targets leukemic cells in vivo while simultaneously transplanting HSCs that were edited to be resistant to the therapy[12]. Similar work is being done with CD33 as a target.

Merging biotechnology with art and design

This year biotechnology was inspired by art, and artists were inspired by biotechnology. A mass-market video game was designed to improve microbial phylogeny estimations[13]. The art of paper cutting and 3D folding, kirigami, was used to develop an electrical recording platform that can record from neural organoids[14]. Bacteria were engineered to produce their own pigments, which can be used for textiles[15]. Bacteria have been engineered to produce polyhydroxyalkanoates, which are

flexible and biodegradable and are being made into shoes and fabrics.

Of course, these are only a snapshot of the articles that the *Nature Biotechnology* editors read with interest this past year. Please also see the list of our top ten news stories, also published in this issue.

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