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From AI to the Y chromosome (and everything in between)

Nature Biotechnology **editors pick their favorite research articles from 2023.**

Investors may have been cautious about what to support this past year; however, that didn't slow biotech research. Technology made huge gains this year with artificial intelligence (AI) and software design, and the public got on board quickly as they played with ChatGPT. Scientists have a human reference genome with fewer errors, the first CRISPR therapy has been approved to treat disease, and devices are helping patients to walk again.

Generative AI models for drug discovery

The generative AI model ChatGPT from OpenAI launched in late 2022, and now, at the end of 2023, generative AI models in biotech have shown tremendous promise for uses such as protein sequence generation and small molecule drug discovery. Generative AI models are trained on very large data sets, so they can explore vast sequences and structures much faster than existing methods, with the potential to revolutionize the fields of personalized medicine or antibody engineering. While we have yet to see the first AI-designed drugs reach the market, 2023 saw a noticeable increase in companies developing these platforms, such as Insilico Medicine, Adaptyv Bio, Absci, and Exscientia.

Diffusion models for protein engineering

While there has been progress in designing new proteins using deep learning, one of the major advances seen in 2023 was applying diffusion models to RoseTTAFold structure prediction networks[1]. The Baker lab published RFdiffusion, showing that they could generate diverse protein structures across a range of contexts, including the design of protein monomers, protein binders, symmetric oligomers and enzyme active site scaffolding.

Human reference draft represents human variation

For the last 20 years, researchers have used a single human reference genome for all studies in human genetics. This reference was a composite of merged haplotypes from 20 people, but a single person's data comprised the majority of the sequence. Over the past years, it has been shown to contain biases and errors, and it did not represent global human genomic variation. The Human Pangenome Reference Consortium was created to address these limitations, and in 2023 the consortium published the first draft of its graph-based pangenome reference[2], containing 47 phased, diploid assemblies from a cohort of diverse individuals, enabling future research into variant diversity.

Sequence of the human Y chromosome revealed

Another sequencing consortium, the Telomere-to-Telomere (T2T) Consortium, completed a major effort with the sequencing of the human Y chromosome[3]. The human Y chromosome has a complex structure that contains long palindromes, duplications and tandem repeats, and more than half of the sequence was completely missing from the GRCh38 reference. Like the pangenome reference effort, this assembly required the development of new computational methods. The original complete Y chromosome assembly was then supplemented by additional assemblies for 43 men from five continents, providing a comprehensive view of genetic variation over human evolution.

CAR-NK therapies start to be tested

CAR-T therapies have shown promise for treatment of hematological cancers, but there are limitations in these treatments. Natural killer (NK) cells are being considered as alternatives. Compared with CAR-T therapy, CAR-NK therapy could be safer, with a lower chance of immune side effects, more efficient antitumor activity and higher efficiency of production. NK cells can be derived from a variety of sources, such as human induced pluripotent stem cells, hematopoietic stem cells, cord blood and peripheral blood. CAR-NK cells are engineered in a similar way to CAR-T cells, and while there are no FDA-approved drugs for CAR-NK, this year has seen several promising clinical and preclinical trials.

Personalized RNA cancer vaccines show promise

Development of therapeutic vaccines for cancer has been disappointing over the years, but this year we are seeing a change. In May 2023, a phase 1 clinical trial was published announcing the results from delivery of individualized mRNA neoantigen vaccines to 19 patients with pancreatic ductal adenocarcinoma[4]. We also saw recent advances in nanoparticle delivery of these vaccines to tumors. In the biotech space, Moderna announced an mRNA-based skin cancer vaccine in partnership with Merck, and BioNTech and Gritstone Bio are also pushing forward with personalized mRNA cancer vaccines.

Human embryo models improved

Human embryos created from in vitro fertilization can only be grown in a lab for 14 days, so it is difficult to understand the complex processes in human development that occur after that time point. Three teams this year showed that naïve human stem cells could be grown in a dish to structures that resemble day 13 and 14 human embryos under specific chemical conditions[5–7]. The work described in all three papers is a technical achievement, although the rate of success in generation of the models is still very low.

Base editing approved to treat disease

In a huge step forward for the gene editing field, the first trial of base editing of humans from Verve Therapeutics has recently shown promising results for controlling cholesterol levels through deactivation of the *PCSK9* gene. Base editing does not cause double-strand breaks in DNA and is more precise, so it is potentially safer for use in humans. This year, base editors were also shown in preclinical research to have potential for single-dose gene therapies to correct or silence pathogenic mutations in hypertrophic cardiomyopathy[8,9], CD3δ severe combined immunodeficiency[10], and sickle cell disease and β-thalassemia[11]. We ended the year with the announcement

that the UK has approved Casgevy for the treatment of sickle cell disease, opening the door for more of these treatments to reach the public.

Wearable ultrasounds for body measurements

Traditional ultrasound probes are bulky and require cables for data transmission and power, so they are nearly impossible to incorporate into everyday life for patients. Interpretation of the data from these systems also requires medical professionals with specialized training and is labor-intensive. A new integrated autonomous ultrasonic-system-on-patch (USoP) integrates the ultrasonic probe and miniaturized wireless control electronics into a soft, wearable format[12]. Other wearable ultrasound monitors were recently developed to monitor the bladder and image the heart, allowing real-time, accurate measurements of body functions.

Neurotech for walking after paralysis

When the spinal cord is injured, the brain and spinal cord can no longer communicate, leading to paralysis. Until earlier this year, there was no strategy to recover movement in the large number of people who sustain these types of injuries every year. In a recent study[13], an implantable digital bridge was engineered and implanted in a participant with tetraplegia. The man was able to walk naturally and climb stairs at the conclusion of the study.

Of course, these are only a snapshot of the articles that the *Nature Biotechnology* editors read with interest this past year. Please also see our list of our top ten news stories, also published in this issue. We're looking forward to seeing what 2024 brings!

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