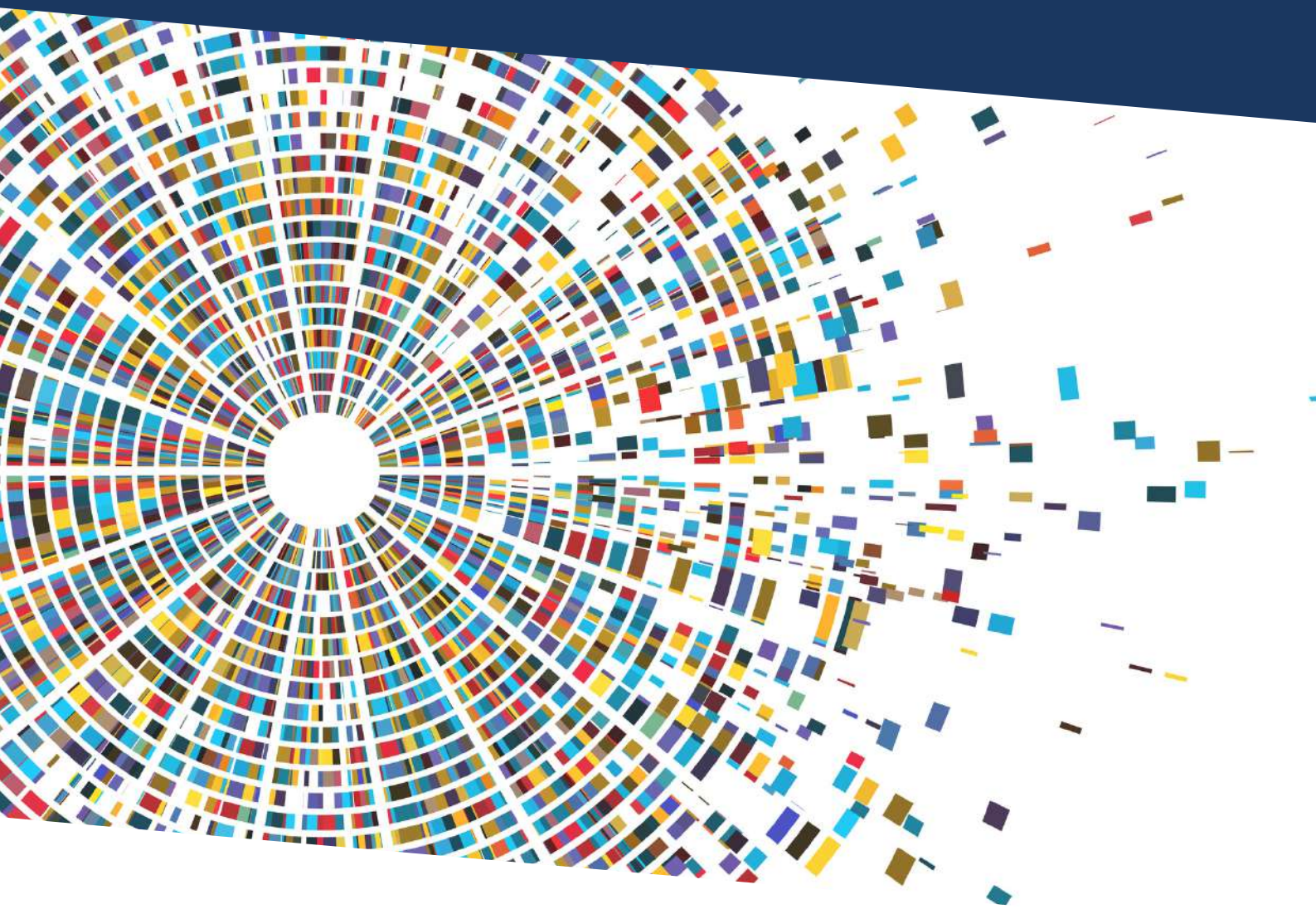
Industry Focus



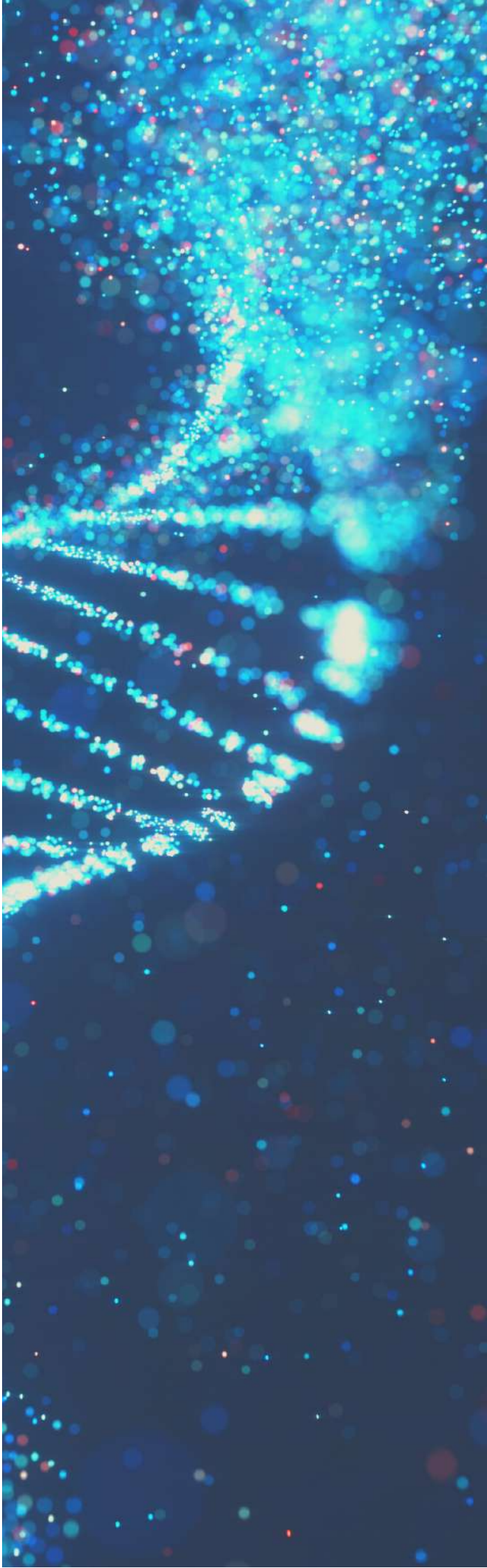
2021-22

Genetics & Genomics

A curated collection of top articles, Thought Leaders and Insights from Industry

NEWS MEDICAL LIFE SCIENCES
AZO LIFE SCIENCES

TABLE OF CONTENTS



Tracking a Pathogen through its Genome: the challenges and opportunities of the global governance of genomic surveillance

Interview conducted by Danielle Ellis, B.Sc.

In this interview, News-Medical speaks to Henry Fingerhut, Senior Policy Analyst for Science & Innovation at the Tony Blair Institute for Global Change, about genomic surveillance and its associated opportunities and challenges. In collaboration with Professor Derrick Crook of Oxford's Nuffield Department of Medicine, Henry recently published Global Governance of Genomic Pathogen Surveillance, a paper outlining the recent history and future opportunities at the international level.

Please can you introduce yourself and tell us about your professional background and your current role at the Institute for Global Change?

I'm a Senior Policy Analyst for Science & Innovation at the Tony Blair Institute for Global Change. I come from an interdisciplinary background. At TBI, I work on a range of technology policy issues, including health, biotechnology, and UK innovation policy, with the aim to help governments leverage technology for social good.

Most recently, I completed my Ph.D. in Technology, Management, and Policy at MIT with research on how healthcare providers use Evidence-Based Practice and incorporate new technologies into clinical care.

As part of The Global Health Security Consortium, the Institute for Global Change advocates for a comprehensive approach to genomic surveillance. Could you explain the process of genomic surveillance, its importance, and how it aids global public health security?

Genomic pathogen surveillance systematically identifies and tracks pathogens to understand how they develop, mutate, and spread. This process includes all the steps from the swab—when a sample is taken from an infected individual—to public health decisions. It incorporates 1) sampling potentially infected individuals, 2) sequencing that sample to get the underlying pathogen's genome, 3) a series of systematic data analysis steps to isolate the pathogen's genome, remove personally identifiable information about the patient, and compare it to other pathogens, 4) and storing and sharing that data among labs and public health officials to generate public health insights.

Genomic surveillance complements the current public health infrastructure to help public health officials quickly identify and evaluate new pathogens and variants of concern. A comprehensive global network with sequencing and data analysis capabilities worldwide, as well as the governance standards to ensure the data is analyzed consistently and shared ethically, would help alert officials at the national and global levels about new outbreaks and variants. It would also help researchers and pharmaceutical companies understand pathogen dynamics and develop effective treatments.

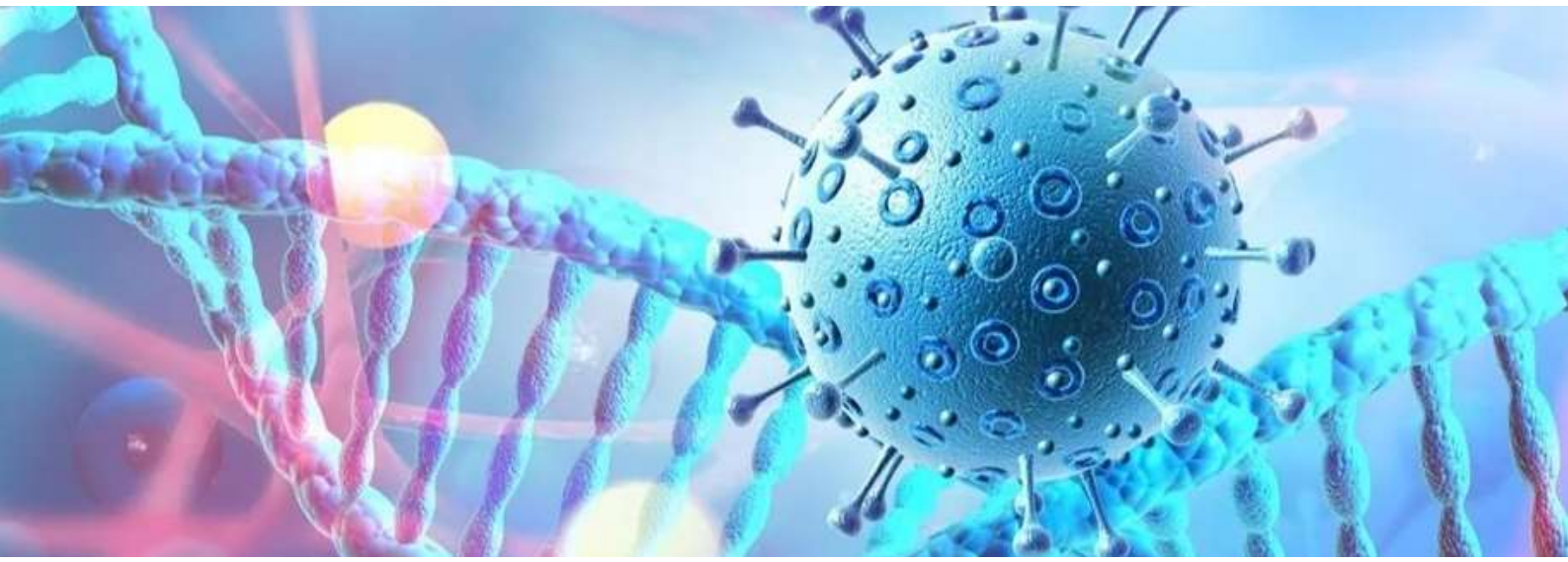


Image Credit: Explode/Shutterstock.com

Genomic surveillance has been an integral part of managing the COVID-19 pandemic. How has genomic surveillance and its associated technologies/sequencing methods changed since the start of the pandemic?

The COVID-19 pandemic helped call global attention to this need and rapidly advanced global initiatives. There has been a range of philanthropic initiatives to build out genomic sequencing capacity in low- and middle-income countries during COVID-19, and the WHO's new Berlin Hub for Pandemic and Epidemic Intelligence and 10 year strategy for global genomic surveillance, both launched in the past year, will help build out this critical infrastructure post-pandemic to monitor other pathogens and related concerns like TB and anti-microbial resistance.

In your study entitled "Global Governance of Genomic Pathogen Surveillance," you discuss the opportunities and challenges within this field. What are the current challenges of the global governance of genomic pathogen surveillance, and how may these challenges be overcome in the future?

We outline three challenges in the paper: governing the ethical and geopolitical concerns around genomic data sharing, setting and adopting technical standards, and scaling capacity across the globe. These each require global cooperation and trust-building, particularly to ensure technical providers or beneficiaries of data sharing, often from high-income countries, respond to the concerns of low- and middle-income countries who contribute data to the network. But as we highlight in the paper, structures like the new WHO Hub will play an important convening role in bringing together an effective and responsible global network.

Related Stories

- A genome-wide catalog of rare copy-number variant associations for 54 disease phenotypes
- Researchers report genomic profiling from more than 110,000 tumors
- SARS-CoV-2 variant-specific polymerase chain reaction assay for SARS-CoV-2 genomic surveillance

Global public health security includes proactive approaches to minimize public health disasters like pandemics. How can genomic pathogen surveillance help healthcare professionals in their pandemic preparedness.

Genomic pathogen surveillance can help public health officials and healthcare professionals in pandemic preparedness. For public health officials, a well-designed genomic surveillance network will help quickly identify new pathogens and variants of concern, track their population dynamics within and across countries, and—when linked securely and anonymously to routine clinical data—monitor their virulence and symptomatology.

Image Credit: Blue Planet Studio/Shutterstock.com

For healthcare professionals, this data could also help inform diagnosis and treatment decisions, both by access to that public health data and hopefully by developing precision treatments targeted to a specific pathogen variant.

Generally, the COVID-19 pandemic indicated how important it is to coordinate and collaborate across the research, clinical, policy, and public health spheres to improve health outcomes – to do so requires the infrastructure to share data securely and anonymously. Genomic pathogen surveillance is one piece of that puzzle and could help to establish best practices for cross-sector collaboration broadly.

The COVID-19 pandemic highlighted patterns of global health inequality. How can health innovation policies improve health inequalities, especially regarding scaling genomic sequencing worldwide?

As we highlight in the paper, the global genomic surveillance community has been responsive to valid concerns of health inequality in the past decade, raised especially by low- and middle-income countries—most notably Indonesia in 2008.

It is essential that vulnerable populations be represented in data collection to enable us to learn how pathogens spread among different groups and how their symptoms develop.

But it is also important that this data collection and sharing be done responsibly, with attention to their autonomy, engagement as partners, and benefit-sharing. The 2010 Nagoya Protocol secures many of these principles of fair and equitable benefit-sharing, but it will be essential to develop mechanisms to build local capacity and share benefits effectively.

You work in collaboration with the Ellison Institute for Transformative Medicine and the University of Oxford. How important is collaboration between partners when addressing global public health issues?

The COVID-19 pandemic demonstrated how important collaboration is in global public health – including across the academic, policy, and private sectors and at the local, national, and global levels. The GHSC is a new kind of partnership, bringing together political, scientific, and technological expertise to drive progress in global health - and with this paper, we wanted to highlight the need for such cooperation in global genomic surveillance.

Of course, collaboration at this scale brings challenges. Still, we hope this paper helps identify some ways forward for a critical modern infrastructure that can not only future-proof us against pandemics but can also build far greater capabilities in the fight against communicable diseases and help revolutionize microbiology.

What are the next steps for The Global Health Security Consortium and its ongoing work within genomic pathogen surveillance?

We have a handful of initiatives in this area, ranging from thought leadership to facilitating cross-sector partnerships to move forward global genomic surveillance efforts. This includes looking at how national governments can build genomic surveillance capabilities and engage in effective, mutually beneficial data sharing. But it also includes engagement at the international level to ensure momentum does not slow as political and public focus on the pandemic subsides.

We've come a long way in accelerating digital infrastructure in response to COVID. Still, there is a significant opportunity to build 21st-century technology that cannot only help us fight against future variants and pandemics but has much wider potential impacts, including in areas like TB. It is an opportunity we need to take: the health and economic benefits of doing so will likely be substantial in the future.

Where can readers find more information?

You can find more information about the Global Health Security Consortium and current initiatives here. And the Tony Blair Institute is also working on a range of policy issues more broadly, including health and biotech, available here.

About Henry Fingerhut

Henry is a Senior Policy Analyst for Science & Innovation at the Tony Blair Institute for Global Change. He comes from an interdisciplinary background at the intersection of science and policy. In particular, he focuses on how social and political factors impact scientific projects (like the genomic pathogen surveillance initiatives) and how technical details can impact policy outcomes. At TBI, he works on a range of technology policy issues, including health, biotechnology, and UK innovation policy, with the aim to help governments leverage technology for social good.

Prior to joining TBI, he completed his Ph.D. in Technology, Management, and Policy at MIT with research on how healthcare providers use Evidence-Based Practice and incorporate new technologies into clinical care.

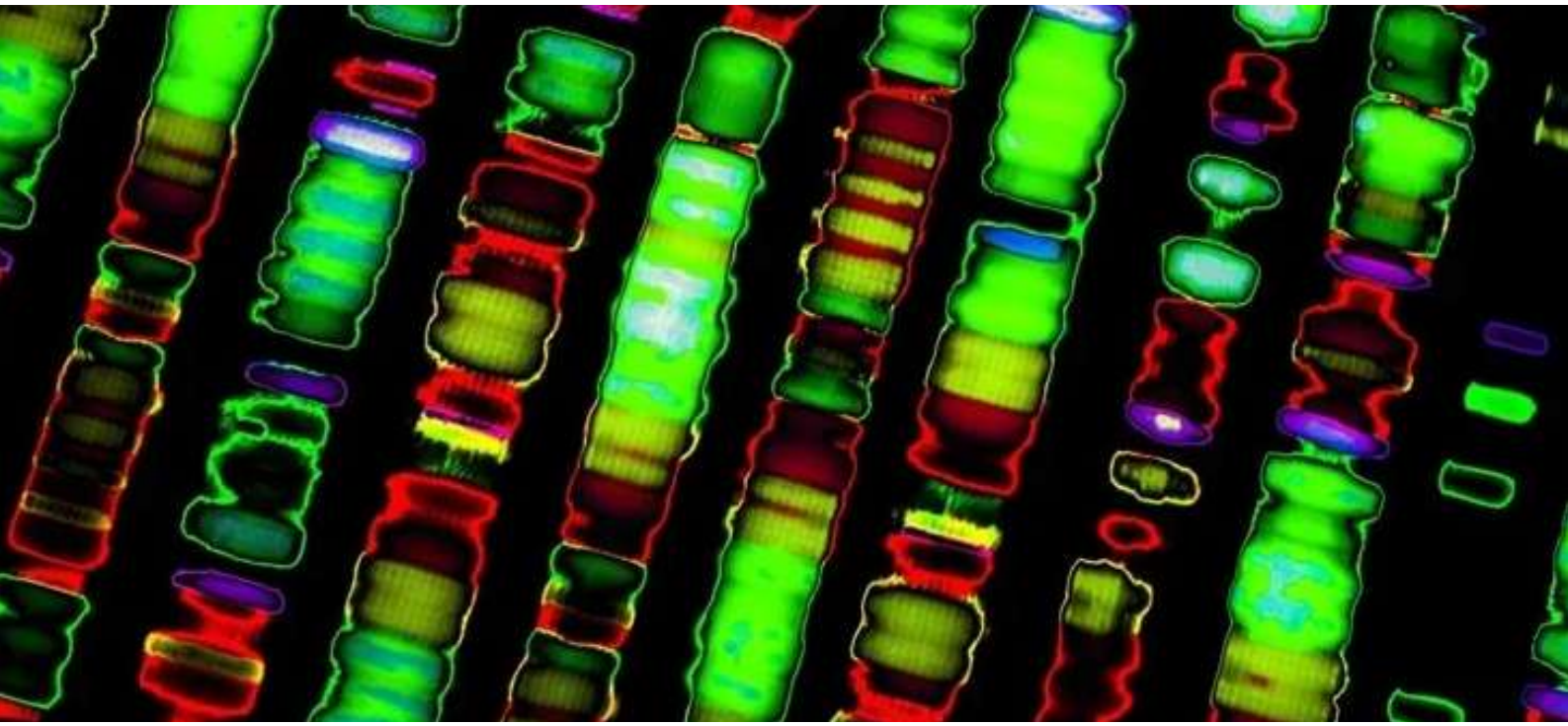
Written by
Danielle Ellis

Danielle graduated with a 2:1 in Biological Sciences with Professional Training Year from Cardiff University. During her Professional Training Year, Danielle worked with registered charity the Frozen Ark Project, creating and promoting various forms of content within their brand guidelines. Danielle has a great appreciation and passion for science communication and enjoys reading non-fiction and fiction in her spare time. Her other interests include doing yoga, collecting vinyl, and visiting museums.

Human genome sequenced in its entirety for the first time

By Dr. Tomislav Meštrović, MD, Ph.D.
Reviewed by Emily Henderson, B.Sc.

An international team of almost one hundred scientists has uncovered the complete, gap-free human genome by deciphering the remaining and hitherto unknown sequences – opening the door for novel approaches to treat various diseases. This seminal, historical study is published in the renowned journal Science.



The complete sequence of a human genome. Image Credit: Gio.tto / Shutterstock

All the way back in 2003, the historic Human Genome Project was able to sequence 92% of the human genome. These were essentially codes to human euchromatin, which contains many loosely packaged genes that code for many essential proteins with pivotal roles in our physiology.

However, for almost two decades, researchers were struggling to decipher the remaining 8%, which is a smaller and tightly packaged segment of the genome known as heterochromatin. Its salient characteristic is that it is not responsible for producing proteins.

This was one of the reasons why scientists initially chose to prioritize euchromatin, but also due to the fact that sequencing heterochromatin is extremely demanding. In other words, we needed much more advanced genomic tools to take a deep dive into this part of the genome.

This means that for a long time, we had a massive gap in our knowledge regarding certain basic cellular functions. If we look at the reference genome, there are many long runs of unknown bases, and not even all of the euchromatic genome has been adequately sequenced, as many errors have been noticed (such as duplications).

That now changed in this flagship study that was conducted by the Telomere-to-Telomere (T2T) Consortium, which joined the researchers from different academic institutions and the National Institutes of Health (NIH) in the United States.

Using Merfin and long-read methods

With state-of-the-art techniques and renewed determination, this group of researchers has been able to help in finalizing what the Human Genome Project has successfully started by revising errors found in euchromatic regions but also providing a full display of heterochromatic regions.

One of the most important tools they have used for that quest is Merfin, which conveniently cleans up some of the most difficult sequences found in the human genome. More specifically, this tool enables sequence accuracy testing and finding a potentially misaligned code, subsequently correcting those mistakes.

Furthermore, in this study, researchers have also leveraged the complementary aspects of PacBio HiFi and Oxford Nanopore ultralong-read sequencing, which are both used to resolve large and complex genomes with almost 100 percent precision. Both of these methods are known as long-read methods.

A gapless human DNA blueprint

In short, the work in this study includes gapless telomere-to-telomere assemblies (i.e., from one end of the chromosome to the other) for all 22 human autosomes and chromosome X, resulting in 3,054,815,472 base pairs of nuclear DNA – alongside a 16,569-bp mitochondrial genome.

The completed and sequenced regions now include all centromeric satellite arrays, short arms of acrocentric chromosomes and recent segmental duplications, which unlocks these previously unknown regions to complex functional and variational studies.

In a way, this is the first meticulous view of our human DNA blueprint. The aforementioned long-read methods opened the door to understanding the most cumbersome, repeat-rich segments of the human genome.

Towards personalized medicine

We are still a long way from complete genome sequencing on an individual level, but this will now inform studies on diseases linked to the heterochromatic genome, primarily cancer associated with centromere abnormalities (centromere being a constricted chromosome region that separates it into a short and long arm).

> *"This 8% of the genome has not been overlooked because of a lack of importance but rather because of technological limitations", the research group states in their groundbreaking Science paper.*
> *"High-accuracy long-read sequencing has finally removed this technological barrier, enabling comprehensive studies of genomic variation across the entire human genome, which we expect to drive future discovery in human genomic health and disease," they add.*

In any case, this study (and accompanying research endeavors) will substantially impact genome analysis and are a salient step toward assembly models that represent the genetic code of humanity. Benefiting all of us will also open the door for personalized medicine and genome editing in the future.

Journal reference:

- Nurk S et al. (2022). The complete sequence of a human genome. Science. https://doi.org/10.1126/science.abj6987, https://www.science.org/doi/10.1126/science.abj6987

Written by

Dr. Tomislav Meštrović

Dr. Tomislav Meštrović is a medical doctor (MD) with a Ph.D. in biomedical and health sciences, specialist in the field of clinical microbiology, and an Assistant Professor at Croatia's youngest university - University North. In addition to his interest in clinical, research and lecturing activities, his immense passion for medical writing and scientific communication goes back to his student days. He enjoys contributing back to the community. In his spare time, Tomislav is a movie buff and an avid traveler.

Gene Identification Tools in Bioinformatics

By Dr. Priyom Bose, Ph.D.
Reviewed by Emily Henderson, B.Sc.

Identification of genes has rapidly evolved with the advancements in molecular biology techniques and increased accessible data on genomics and functional genomics information. Bioinformatics helps identify genes within a long DNA sequence. This technique locates a gene simply by analyzing sequence data using a computer (in silico).

Image Credit: bluesroad/Shutterstock.com

One of the most essential aspects of bioinformatics is gene prediction. Gene prediction involves locating regions of genomic DNA that encode genes (protein-coding genes). Gene prediction or gene identification is extremely important because it helps scientists to distinguish between coding and non-coding regions of a genome, explain genes in terms of their function, conduct research related to detection, treatment, and prevention of genetic disorder diseases, etc.

Genes are identified broadly via two methods, i.e., a) similarity-based searches and b) Ab-initio prediction. These methods are briefly discussed below.

Similarity-based Searches

As the name suggests, this method of gene identification is based on sequence similarity searches. Similar genetic sequences are found between ESTs (expressed sequence tags), proteins, or other genomes and unknown genomes. This method assumes that exons (functional regions) are conserved evolutionarily than introns (nonfunctional regions).

The commonly used bioinformatics tool that is based on the similarity search method is BLAST. Other commonly used software are PROCRUSTES and GeneWise. This software predicts genes by using the global alignment of a homologous protein to translate open reading frames (ORFs) in a genomic sequence. However, CSTfinder is a software that uses pairwise genome comparison to identify genes.

Ab-initio Prediction

This method of gene identification is based on gene structure and signal-based searches. Ab initio gene predictions use known gene structure as a template to determine unknown genes. This method is based on two types of sequence information, namely, signal sensors and content sensors. Signal sensors include short sequence motifs, for example, start codons, stop codons, splice sites, and branch points.

On the other hand, content sensors rely on patterns of a codon that are unique to a species or in other words major distinct features present in the gene. This allows coding sequences to stand out from the surrounding non-coding sequences by statistical detection algorithms. Researchers use this method for the detection of an exon.

What is Bioinformatics?

Many algorithms are being used for modeling gene structure, e.g., linear discriminant analysis, dynamic programming, hidden Markov model, linguist methods, and neural networks. These models have helped develop many ab initio gene prediction programs such as FGENESH, GeneID, GeneParser, GENSCAN, GlimmerM, etc.

Bioinformatic Tools Used for Gene Identification

CRAIL: It is one of the most commonly known computational tools used for ORF identification. This tool provides important information such as splice junctions, translation start points, and non-coding scores of 60 base regions on both sides of the putative exon.

GLIMMER: Glimmer is a software used for finding genes in microbial DNA, especially the genomes of bacteria and archaea. Gene Locator and Interpolated Markov Modeler (Glimmer) uses interpolated Markov models (IMMs) to recognize the coding regions and differentiate them from noncoding DNA.

GenScan: This tool is used for the identification of complete gene structures in genomic DNA for various organisms. It can predict exon-intron structures of genes as well as locations in genomic sequences.

Genie: This gene finder is based on generalized hidden Markov models. Genie was developed as a collaborative project by the University of California's Computational Biology Group, Lawrence Berkeley National Laboratory's the Human Genome Informatics Group, and the Berkeley Drosophila Genome Project.

Gene Finder: This tool is used to predict splice sites. It can also identify protein-coding exons, construct gene models, and recognize the promotor and poly-A region.

ORF Finder: This is a graphical analysis tool that can detect open reading frames along with their protein translation from sequences already in the database. This program is used to search new DNA sequences for potential protein-encoding segments.

Easy Gene: This tool is used to identify genes in prokaryotes, the current version of which includes 138 different organisms. Each gene identified by Easy Gene is attributed with a significant score (R-value), which reveals the probability of a sequence to be a non-coding open reading frame rather than a real gene.

Gene Publisher: This program performs automated data analysis from gene expression experiments on several different platforms. This tool also accepts Affymetrix CEL files or gene tables as inputs and conducts detailed numerical and statistical analysis. It connects its result with the available data across various databases and finally produces a cumulative report of the result.

ORPHEUS: This software is used to predict genes from large genomic fragments or complete bacterial genomes.

HMMgene: This program is based on the hidden Markov model and is used to predict genes in anonymous DNA. It can predict whole or partial genes as a result of which it can identify exons and can splice precisely. It can also predict start/stop codon and splice genes. It is used to identify the genes of vertebrates.

Promoter: This software is based on neural networks and genetic algorithms. It can predict transcription start sites of vertebrate PolII promoters in DNA sequences.

Sources

- Chavali, A.K. and Rhee, S.Y. (2018). Bioinformatics tools for the identification of gene clusters that biosynthesize specialized metabolites, Briefings in Bioinformatics, 19(5), pp. 1022–1034, https://doi.org/10.1093/bib/bbx020
- Ghorbani, M. and Karimi, H. (2015). Bioinformatics Approaches for Gene Finding. International Journal of Scientific Research in Science and Technology, 4(1), pp. 12-15.
- Wang, Z. et al. (2004). A brief review of computational gene prediction methods. Genomics, proteomics & bioinformatics, 2(4), pp. 216–221. https://doi.org/10.1016/s1672-0229(04)02028-5
- Koonin, E.V., and Galperin, M.Y. (2003). Sequence - Evolution - Function: Computational Approaches in Comparative Genomics. Boston: Kluwer Academic. Chapter 4, Principles and Methods of Sequence Analysis. [Online] Available at: https://www.ncbi.nlm.nih.gov/books/NBK20261/

Further reading:

- All Bioinformatics Content
- Circular RNA profiles could serve as a biomarker of ovarian cancer
- Potential biomarker for lung cancer prognosis revealed
- Study reveals significant neighborhood preferences of tumor cells in Hodgkin lymphoma
- Bioinformatics in Research

Written by

Dr. Priyom Bose

Priyom holds a Ph.D. in Plant Biology and Biotechnology from the University of Madras, India. She is an active researcher and an experienced science writer. Priyom has also co-authored several original research articles that have been published in reputed peer-reviewed journals. She is also an avid reader and an amateur photographer.

Novel anti-inflammatory drug target identified by CRISPR

Interview conducted by Danielle Ellis, B.Sc.

In this interview, News-Medical speaks to Dr. Jeffrey Rathmell about his recent research into how metabolic pathways impact immune function.

Please can you introduce yourself and tell us what inspired your recent research into how metabolic pathways impact immune function?

I direct the Vanderbilt Center for Immunobiology and have been interested in the field of immunometabolism for more than twenty years. A major focus in this field is to explore metabolic enzymes as potential drug targets to selectively inhibit specific immune cell populations. Our work has focused on the metabolism of T cell subsets in a variety of settings, including inflammatory diseases and cancer.

The metabolic pathway you studied is the one-carbon metabolism. What is a metabolic pathway, and why is the one-carbon metabolism pathway important?

A metabolic pathway is a series of very specific reactions that convert a nutrient into energy and/or building blocks that the body's cells can use for their daily functions. The one-carbon metabolism pathways are a set of pathways that are required for maintaining the building blocks of DNA and RNA, as well as the markers that regulate the DNA. In our study, we found that these pathways also have signaling roles in T cells that can determine whether the immune response is pro-inflammatory or anti-inflammatory.

In your study, you used CRISPR technology. Why did you choose to use this technology, and how was it applied to your research?

In our study, we used CRISPR technology to screen genes for potential drug targets. We used this approach because of the versatility of this system and its effectiveness compared to earlier approaches. This approach is unbiased and allows us to rapidly assess a long list of genes whether each gene has certain qualities that make a good drug target. CRISPR screening can be applied to many different types of cells and culture conditions. In our study, we used primary T cells and an in vivo lung-inflammation model to identify the most relevant targets for anti-inflammatory therapy.

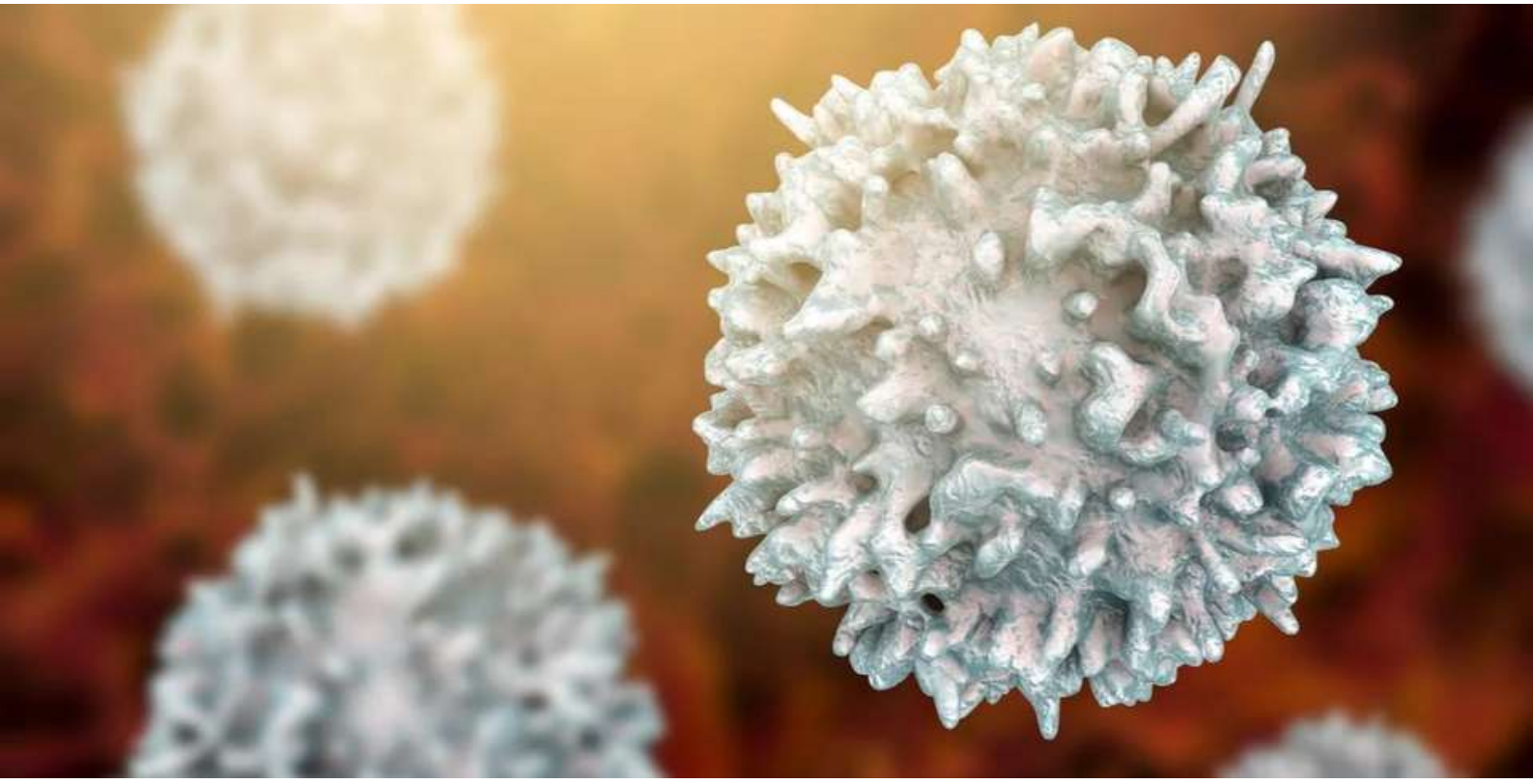


Image Credit: Kateryna Kon/Shutterstock.com

MTHFD2 was identified as a gene of interest. Can you tell us about this gene and its role in T cell function?

MTHFD2 is an enzyme within the one-carbon metabolism pathways. It is located in the mitochondria and is highly expressed upon T cell activation. It is required for the synthesis of DNA and RNA building blocks. We found that MTHFD2 is critical for T cell proliferation and for promoting the pro-inflammatory function of T cells.

What did you discover about MTHFD2? Were there any particularly surprising findings?

We discovered that blocking MTHFD2 leads to less disease-causing pro-inflammatory T cells and more anti-inflammatory T cells. This was particularly surprising because we were able to alter T cell identity by altering a metabolic pathway. When applied to mouse inflammatory disease models, blocking MTHFD2 led to decreased severity of delayed-type hypersensitivity, multiple sclerosis, and inflammatory bowel disease-associated colitis. In the multiple sclerosis model, in particular, the mice showed significantly fewer symptoms of paralysis, fewer immune cells were invading the spinal cord, and less damage to the protective sheaths surrounding the brain cells.

Related Stories

- CRISPR-based diagnostics for SARS-CoV-2 detection
- Study identifies risks in the use of CRISPR therapeutics
- Using CRISPR technology to successfully prevent and treat SARS-CoV-2 infections

Overall, what do your findings suggest?

Overall, our findings show that MTHFD2 may be an effective drug target for anti-inflammatory therapy for a wide range of inflammatory and autoimmune diseases. Many of the drugs currently in use can completely suppress the immune system and have many adverse side effects, including susceptibility to infections. Our studies indicate that MTHFD2-targeted therapy may potentially have fewer adverse effects and be effective without being broadly immune suppressive.

Collaboration is of great importance when trying to make new scientific and medical advancements. How important is collaboration in the progress of this research?

Many of our key experiments were performed by our collaborators. Many of our ideas were generated by discussing data with collaborators. Good research is absolutely a collaborative effort. Bringing together many people with diverse expertise and exchanging ideas and skills allows for meaningful progress in research.

How might these findings be applied to treating diseases, such as an inflammatory cancer like colorectal cancer?

In colorectal cancer, inflammation driven by a type of immune cell called Th17 cells is associated with poor survival. Our study specifically found that blocking MTHFD2 not only dampens the activity of Th17 cells but confers anti-inflammatory properties to these cells. Additionally, it promotes the production of a type of anti-inflammatory immune cell called a regulatory T cell.

How has CRISPR screening impacted anti-inflammatory drug target identification, and what role do you see CRISPR having in drug discovery in the future?

CRISPR screening has made it possible to take a systematic and unbiased approach to drug target identification. We can now perform CRISPR screens in specific conditions that better predict a particular gene's potential performance as a drug target. For example, we performed our screen in an inflammatory disease model to identify an anti-inflammatory drug target. The same paradigm works for many other applications, such as using a cancer model to identify anti-tumor drug targets.

Image Credit: vchal/Shutterstock.com

Historically, chemical compounds used as drugs are discovered first, and then their targets are identified. More and more, we are seeing the reverse process, where the drug targets are being identified first, and drugs specific for these targets are being designed. This gives the advantage of having better control of on-target and off-target effects.

What is next for you and your research into the identification of anti-inflammatory gene targets?

We have a wide range of projects ongoing in our lab ranging from studying cancer immunology to inflammatory and autoimmune diseases. The common theme is harnessing the power of cellular metabolic pathways to alter immune cell functions. We are applying the CRISPR screening approach to a variety of projects and hope to identify more effective gene targets for anti-tumor and anti-inflammatory therapy in different types of immune cells.

Where can readers find more information?

- https://www.sciencedirect.com/science/article/abs/pii/S1074761321004489
- https://news.vumc.org/2021/11/11/crispr-screen-identifies-anti-inflammatory-target/

About Jeffrey Rathmell, PhD

Dr. Rathmell is the director of the Vanderbilt Center for Immunobiology, associate director of the Vanderbilt Institute for Infection, Immunology and Inflammation, Professor of Pathology, Microbiology and Immunology, and associate director of the Molecular Pathology & Immunology Ph.D. Program at Vanderbilt University Medical Center and Vanderbilt University School of Medicine. He holds the Cornelius Vanderbilt Chair of Immunobiology.

Dr. Rathmell studies mechanisms by which extracellular cues influence lymphocyte death and differentiation in efforts to control inflammatory diseases and leukemia. His group showed that the metabolism of T cells is highly dynamic and that specific metabolic programs are essential for each functional T cell subset. These fundamental metabolic distinctions may now allow modulation of selective populations of lymphocytes in inflammatory diseases and anti-tumor immunity.

Written by

Danielle Ellis

Danielle graduated with a 2:1 in Biological Sciences with Professional Training Year from Cardiff University. During her Professional Training Year, Danielle worked with registered charity the Frozen Ark Project, creating and promoting various forms of content within their brand guidelines. Danielle has a great appreciation and passion for science communication and enjoys reading non-fiction and fiction in her spare time. Her other interests include doing yoga, collecting vinyl, and visiting museums.

Researchers develop the smallest CRISPR to date for genome editing

Reviewed by Emily Henderson, B.Sc.

A compact and efficient CRISPR-Cas system, named CasMINI, could be broadly useful for cell-engineering and gene-therapy applications because it is easier to deliver into cells. The findings appear in a study publishing September 3 in the journal Molecular Cell.

> *"This is a critical step forward for CRISPR genome-engineering applications. The work presents the smallest CRISPR to date, according to our knowledge, as a genome-editing technology. If people sometimes think of Cas9 as molecular scissors, here we created a Swiss knife containing multiple functions. It is not a big one, but a miniature one that is highly portable for easy use."*
>
> *Stanley Qi, Senior Study Author, Stanford University*

The development of CRISPR-Cas systems for human cells has revolutionized genome engineering. These systems offer opportunities for the development of gene therapies for a variety of genetic diseases. But their large sizes often restrict delivery into cells and thus impede clinical applications. For example, adeno-associated virus (AAV), a vector widely applied for in vivo delivery, has limited packaging capacity of the payload (less than 4.7 kb), and many Cas fusion proteins are beyond this limit. As a result, there is a need to engineer highly efficient, compact Cas systems to facilitate the next generation of genome-engineering applications.

One potential solution is Cas12f, also known as Cas14. Ranging between 400 and 700 amino acids, the protein is less than half the size of currently used CRISPR systems such as Cas9 or Cas12a. But until now, it was not clear whether this compact protein could be used in mammalian cells. "Recent years have identified thousands of CRISPRs, which are known as bacteria's immunity defense system," Qi explains. "More than 99.9% of discovered CRISPRs, however, cannot work in human cells, limiting their use as genome-editing technologies."

In the new study, Qi and his team applied RNA and protein engineering to the Cas12f system to generate an efficient miniature Cas system for mammalian genome engineering.

Derived from archaea, the natural Cas12f protein and its single-guide RNA showed no detectable activity in mammalian cells. By optimizing the single-guide RNA design and performing multiple rounds of iterative protein engineering and screening, the researchers generated a class of Cas12f variants named CasMINI.

The engineered Cas12f protein variants combined with engineered single-guide RNAs exhibited efficient gene-regulation and gene-editing activity. The researchers demonstrated that CasMINI can drive high levels of gene activation comparable to those associated with Cas12a and allows for robust base editing and gene editing. Moreover, it is highly specific and does not produce detectable off-target effects.

"Here we turn a non-working CRISPR in mammalian cells, via rational RNA engineering and protein engineering, into a highly efficient working one," Qi says. "There were previous efforts from others to improve the performance of working CRISPRs. But our work is the first to make a non-working one working. This highlights the power of bioengineering to achieve something evolution has not yet done."

The size of the engineered CasMINI molecule is only 529 amino acids. This small size makes it suitable for a wide range of therapeutic applications. For example, the CasMINI fusion proteins are well suited for AAV packaging. In addition, CasMINI mRNA can be easily packaged into lipid nanoparticles or other RNA-delivery modalities, potentially enhancing its entry into cells. Its small size and non-human pathogen source might make it less likely to produce immune responses than large protein payloads would be.

More work is needed to further optimize the efficiency of CasMINI for base editing and gene editing and to test the performance of the system in vivo with different delivery modalities. The researchers plan to test the system for in vivo gene-therapy applications.

"The availability of a miniature CasMINI enables new applications, ranging from in vitro applications such as engineering better tumor-killing lymphocytes or reprogramming stem cells to in vivo gene therapy to treat genetic diseases in the eye, muscle, or liver," Qi says. "It is on our wish list that it will become a therapy to treat genetic diseases, to cure cancer, and to reverse organ degeneration."

Source: Cell Press
Journal reference:
Xu, X., et al. (2021) Engineered Miniature CRISPR-Cas System for Mammalian Genome Regulation and Editing. Molecular Cell. doi.org/10.1016/j.molcel.2021.08.008.

What does the Future of Gene Therapy Look Like?

By Dr. Priyom Bose, Ph.D.
Reviewed by Emily Henderson, B.Sc.

Gene therapy is one of the most exciting areas of biotechnology, with respect to the current signs of progress as well as future possibilities. The advancements in technology, which have allowed the alteration of the immune system, control of nucleic acid delivery, and defined the manipulation of the human genome, have inspired whole new areas of medical research. The recent developments in gene therapy have paved a path for next-generation technologies. This article focuses on the future of gene therapy.

Image Credit: Visual Generation/Shutterstock.com

Scientists are currently investigating gene therapies extensively to develop an effective methodology and minimize the risks and side effects of treatment. They opine that the past five years have brought about a renaissance in the field of gene and cell therapy. During this time, many therapies have been approved by global regulatory bodies. This includes the introduction of the first oligonucleotide-based therapies and two in vivo gene therapies, with many more in the pipeline.

These therapies could cure multiple diseases, such as neuromuscular disease, inherited blindness, and cancer. Scientists and clinicians emphasized that these therapies have been life-changing for many affected patients.

An Overview of the Present and Future of Gene Therapy

As the name suggests, gene therapy involves modifying or manipulating gene expression to treat or cure diseases. Human genes contain DNA that controls every form and function of the body. A faulty gene causes disease, and this condition can be altered via gene therapy by replacing a faulty gene with a new gene to cure the disease or enhance the ability to fight against it. Scientists have suggested that gene therapy has the potential to treat a broad spectrum of diseases, such as cystic fibrosis, cancer, heart disease, hemophilia, diabetes, and AIDS.

Several mechanisms are involved in gene therapy, for example, replacing a disease-causing gene or mutated gene with a copy of a healthy gene. It also involves introducing a new or modified gene into the body that could cure diseases. Additionally, this technique is also associated with inactivating a faulty gene that is not functioning appropriately or fixing a mutated gene so that it can function normally.

Scientists have determined the potential risks associated with gene therapies and are working to alleviate them. For instance, a new gene cannot be directly inserted into a cell, instead, it has to be delivered via a carrier called a vector. Researchers have engineered various vectors to carry therapeutic genes into human cells, such as plasmid DNA, viral vector, and bacterial vectors. Additionally, the development of new technologies has aided gene therapies. These new technologies include human gene-editing technology and patient-derived cellular gene therapy, i.e., removing cells from patients, genetically modifying them, and replacing them in the body.

Some of the common risks associated with gene therapies include unwanted immune system reactions, especially while using bacterial or viral vectors, where the body's immune system recognizes it as an intruder and attacks it. This may cause severe inflammation or even organ failure. Adverse effects could also occur if a viral vector carrying a mutated gene targets the wrong cells. Additionally, when these viruses are introduced into a body, they can sometimes regain their ability to cause infection.

Future of Gene Therapy

One of the approved gene therapies is in vivo AAV gene transfer to the human retina and central nervous system for Leber's congenital amaurosis (retinal dystrophy) and spinal muscular atrophy, respectively. This therapy has laid a foundation for developing AAV-based therapies for liver issues, hemophilia, skeletal muscle dystrophy, and Duchenne muscular dystrophy.

Additionally, the development of technology, such as ex vivo lentiviral and retroviral gene transfer to T cells, has paved the way for adoptive cell immunotherapy and therapies for inherited disorders (e.g., sickle cell disease and beta-thalassemia). Gene therapy for beta-thalassemia has been recently approved in the European Union and is under review in the US.

Although AAV-based gene therapies have proved to be highly successful, 50% of patients have to be excluded from this therapy owing to pre-existing immunity to the viral capsids. Therefore, scientists are currently working on next-generation technologies for the treatment of many human diseases while minimizing the risk of inducing immune responses.

Researchers believe that advancements in the engineering and profiling of non-viral nanoparticles for gene delivery and the recent approval of siRNA-based drugs would have a tremendous impact on future gene therapies. One of the key advantages of using nanoparticles in gene delivery is that they can evade the body's immune responses.

The first-generation technologies, such as gene-editing technologies, have laid the foundation for an entirely new treatment modality based on a precise modification of human genome sequences. The success of CRISPR-based gene editing for sickle cell disease and beta-thalassemia has demonstrated that these technologies could also be applied for other diseases. Previous results have made scientists optimistic about the ongoing clinical trials of in vivo genome editings, such as AAV-based gene editing in the retina (EDIT-101) and a planned trial for non-viral nanoparticle-based delivery of CRISPR to the liver (NTLA-2001).

In the future, some of the high-cost therapies for targeted disorders need to be replaced with affordable therapies. The rate of technological innovation of genes has significantly outpaced the ability to assess the safety profiles of the treatment. According to current regulatory models, a large number of patients are required to establish the safety and efficacy of treatment. In the future, new genetic therapies will be developed for both common as well as rare diseases. Researchers stated that similar to biologics, gene therapies are also expected to see significant advances in the coming years.

Sources

- Jensen, L.T. et al. (2021). Current and Future Prospects for Gene Therapy for Rare Genetic Diseases Affecting the Brain and Spinal Cord. Frontiers of Molecular Neuroscience. 14. DOI=10.3389/fnmol.2021.695937
- Dorholt, M. (2021) We're on the Verge of a Breakthrough for Gene Therapies. [Online] Available at: https://www.evernorth.com/articles/the-history-and-future-of-gene-therapy
- Daley, J. (2021) Four Success Stories in Gene Therapy. [Online] Available at: https://www.scientificamerican.com/article/four-success-stories-in-gene-therapy/
- Bulaklak, K., and Gersbach, C.A. (2020). The once and future gene therapy. Nature Communications. 11, 5820. https://doi.org/10.1038/s41467-020-19505-2
- What is Gene Therapy? (2018) [Online] Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

Written by

Dr. Priyom Bose

Priyom holds a Ph.D. in Plant Biology and Biotechnology from the University of Madras, India. She is an active researcher and an experienced science writer. Priyom has also co-authored several original research articles that have been published in reputed peer-reviewed journals. She is also an avid reader and an amateur photographer.

'Switching on' Sight using Gene Therapy

Interview conducted by Emily Henderson, B.Sc.

To help raise awareness for World Sight Day, AZoLifeSciences speaks to Dr. Raymond Wong about his latest research into eye health and we could potentially 'switch on' sight using gene therapy.

Please could you introduce yourself and tell us about what inspired your career into eye health?

My name is Dr. Raymond Wong. I'm a stem cell biologist by training, and I run a lab at the Centre for Eye Research Australia studying how we can use stem cell technologies to study and treat degenerative diseases affecting the eye.

I was always fascinated by the biology of the eye – the eye basically acts like a camera to capture images and send them to our brain for interpretation. Also, being based at the Royal Victorian Eye and Ear Hospital, I see many patients suffering from different eye diseases.

Often I ask myself the same question: Can we help these vision-impaired patients? I think that is the key motivation for me to continue our research in the hope that we can make a difference in the life of vision-impaired patients.

Research states that nearly everyone on the planet will experience an eye health issue in their lifetime. Other than this fact, why is research into eye health so critical?

Image Credit: Inside Creative House/Shutterstock.com

Blindness is one of the most feared disabilities and regular check-up to monitor our eye health is important so we can detect any potential problem early on.

Eye research is critical because it can potentially offer better ways to monitor our eye health, detect diseases earlier or more accurately, understand eye diseases and develop better treatment for them.

More than a billion people worldwide currently do not have access to eye care services. Why is this and what more could be done to help provide equal access to eye health?

As part of CERA's role as a WHO Collaborating Centre for the Prevention of Blindness, we aim to help address the global inequalities that lead to millions of people missing out on eye care services because of a shortage of eye care specialists and equipment.

Working with our many partners, we are involved in several projects including the development of new artificial intelligence technology to screen for the detection of eye diseases such as diabetic retinopathy and empower health care workers to deliver eye care services, particularly in low to middle-income countries.

What can our eyes tell us about our general health and wellbeing?

Besides vision, the eye can also provide other indicators to our health, including the brain and cardiovascular system. For example, recent research shows that imaging the eye can offer diagnosis to many neurological diseases, such as multiple sclerosis or stroke.

The teams at the Centre for Eye Research Australia are working on using eye imaging for the detection of Alzheimer's disease, providing a non-invasive diagnostic method to detect Alzheimer's disease early and artificial intelligence screenings to detect those at higher risk of stroke.

The theme for this year's World Sight Day was #LoveYourEyes. The message aims to ensure people are aware of their own eye health. Why is this message important and what can people do to love their eyes and ensure their eyes are in good health?

Raising public awareness to look after their own eye health is a very important point. Many eye diseases can be avoided or treated if we detect them early on. We talk about the 4 Ps to 'love your eyes' – Prevent, Protect, Preserve and Prioritise, and the International Agency for the Prevention of Blindness offers some great tips for doing that (www.IAPB.org). You can also check out the Centre for Eye Research Australia website for tips on keeping our eyes healthy (https://www.cera.org.au/eye-health-resources/).

For example, many eye diseases can be prevented by adopting a healthy lifestyle, for instance eating a balanced diet, cutting down on smoking and drinking, maintaining a healthy weight, and exercising. For 'Protection', we can wear protective eyewear such as sunglasses that protect us from harmful radiations, cut down on screen time, and take regular breaks to avoid eye strain.

To 'preserve' our vision, we should get a regular eye examination. This will ensure that any eye problem can be detected early on and deal with medically.

What can our eyes tell us about our general health and wellbeing?

Finally, we should ‘prioritize’ our eye health, putting eye exams as part of our routine medical check-up, and don’t ignore any warning signs that indicate any potential vision problems. Also, we need to spread the message and tell your family and loved ones to care for their eye health.

How does irreversible vision loss and blindness occur?

The retina is a complex tissue at the back of our eye that consists of many retinal cells with different roles in vision. For instance, the photoreceptors are the light-sensing cells that pick up light signals and convert them into electrical signals, which are then transmitted to other neurons and eventually the optic nerve relay these signals to our brain, and we interpret that as an image.

Image Credit: puhhha/Shutterstock.com

Degeneration of any retinal cells involved in this process will cause a problem and lead to irreversible vision loss. This occurs in rare inherited retinal diseases like retinitis pigmentosa or Stargardt's disease and also more common conditions, with a more complex genetic profile, such as age-related macular degeneration (AMD).

Currently, there is no cure once these photoreceptors are lost. Why is this?

Many cells in our body don’t replenish following an injury or degeneration in diseases. This includes the photoreceptors which are the critical cells in the retina that sense light and once they are lost currently there is no cure to blindness.

In this regard, regenerative medicine is an exciting approach to address this problem, by regenerating and replacing the lost photoreceptors to improve or restore vision in patients.

New groundbreaking research aims to reprogram stem cells and turn them into photoreceptors, restoring sight. How would this work and what research is currently being carried out?

Yes, there is some exciting research development in this area. Using a Nobel Prize-winning technology called cell reprogramming, we can now turn one cell type into another cell type by switching on a set of genes. Cell reprogramming has been applied in eye research.

Recent research showed that cell reprogramming can stimulate the stem cells in the retina (called the Muller glia cells) to regenerate other retinal cells in preclinical models, including the photoreceptors and the optic nerve cells.

Related Stories

- Gene expression analysis helps identify genes that cause endocrine resistance in breast cancer
- Study reveals that gene variant regulates protein level to prevent blood clots in the lungs
- Study highlights retrotransposition in CRISPR gene therapy clinical trials

My research aims to develop cell reprogramming technology to turn Muller glia cells into photoreceptors by switching on the right set of genes.

We are currently testing this technology in preclinical models to translate our findings to the clinic. If successful, this could be available as a new gene therapy as an injection to the patient's eye which stimulates retinal regeneration and improves/restore sight.

Do you believe that this research will hopefully lead to gene therapies that have the potential to treat blindness?

Yes, that is certainly the goal of our research. Gene therapy to treat blindness is a reality now, in recent years Luxturna become the first clinically approved gene therapy for inherited retinal diseases. This supports the potential and safety for gene therapy to treat blindness, and there is a lot of excitement in developing new gene therapies to treat other retinal diseases.

We are hoping that our research can lead to a new gene therapy to stimulate regeneration of the retina in order to treat blindness.

The ongoing COVID-19 people has shown that when people work together, scientific and medical advancements can be made quickly. How could this level of collaboration be applied to eye research and what benefits would this bring?

The problems that we address in eye research nowadays are often highly complex and requires many groups with different expertise to work together to come up with innovative solutions. Collaboration is a key to speed up research and different experts often provide new perspectives and ideas to solve the problem.

My lab collaborates with many groups in Australia, Europe, the US, and Singapore with a range of expertise in molecular biology, system biology, stem cell biology, and ophthalmology. We are fortunate to have fantastic collaborators helping us and this is certainly very important for our ongoing research.

Image Credit: Natali _ Mis/Shutterstock.com

Where can readers find more information?

Please check out the Centre for Eye Research Australia (www.cera.org.au) for more information on our Hope in Sight Giving Day.

For tips to keeping our eyes healthy, please check out the websites for the Centre for Eye Research Australia website (https://www.cera.org.au/eye-health-resources/) and the International Agency for the Prevention of Blindness (www.IAPB.org).

To find out more about the research in my lab, please check out (https://www.cera.org.au/research/cellular-reprogramming-research/).

About Dr. Raymond Wong

Dr. Raymond Wong is a Principal Investigator at the Centre for Eye Research Australia (CERA), the University of Melbourne, and a Guest Professor at Shenzhen Eye Hospital (China). He is a stem cell biologist specializing in cell reprogramming and stem cells in eye research.

He completed his Ph.D. in stem cell biology at Monash University and was awarded a California Institute of Regenerative Medicine Fellowship to pursue overseas postdoctoral training at the University of California Irvine (USA), and a Visiting Fellow Award to train at the National Institutes of Health (USA).

In 2013, Dr. Wong joined CERA with the support of a Cranborne Foundation Fellowship and subsequently established the Cellular Reprogramming Unit with the support of a MAWA Fellowship and a New Investigator Grant from the National Health and Medical Research Council.

Currently, Dr. Wong's research focuses on understanding the genetic signals that define retinal cells and using cell reprogramming and stem cell technologies to study and treat retinal degenerative diseases.

Written by

Emily Henderson

During her time at AZoNetwork, Emily has interviewed over 300 leading experts in all areas of science and healthcare including the World Health Organization and the United Nations. She loves being at the forefront of exciting new research and sharing science stories with thought leaders all over the world.

New computer program can read any genome sequence and decipher its genetic code

Reviewed by Emily Henderson, B.Sc.

Yekaterina "Kate" Shulgina was a first year student in the Graduate School of Arts and Sciences, looking for a short computational biology project so she could check the requirement off her program in systems biology. She wondered how genetic code, once thought to be universal, could evolve and change.

That was 2016 and today Shulgina has come out the other end of that short-term project with a way to decipher this genetic mystery. She describes it in a new paper in the journal eLife with Harvard biologist Sean Eddy.

The report details a new computer program that can read the genome sequence of any organism and then determine its genetic code. The program, called Codetta, has the potential to help scientists expand their understanding of how the genetic code evolves and correctly interpret the genetic code of newly sequenced organisms.
"This in it of itself is a very fundamental biology question," said Shulgina, who does her graduate research in Eddy's Lab.

The genetic code is the set of rules that tells the cells how to interpret the three-letter combinations of nucleotides into proteins, often referred to as the building blocks of life. Almost every organism, from E. coli to humans, uses the same genetic code. It's why the code was once thought to be set in stone. But scientists have discovered a handful of outliers -; organisms that use alternative genetic codes – exist where the set of instructions are different.

This is where Codetta can shine. The program can help to identify more organisms that use these alternative genetic codes, helping shed new light on how genetic codes can even change in the first place.

> *Understanding how this happened would help us reconcile why we originally thought this was impossible... and how these really fundamental processes actually work."*
>
> *Yekaterina "Kate" Shulgina*

Already, Codetta has analyzed the genome sequences of over 250,000 bacteria and other single-celled organisms called archaea for alternative genetic codes, and has identified five that have never been seen. In all five cases, the code for the amino acid arginine was reassigned to a different amino acid. It's believed to mark the first-time scientists have seen this swap in bacteria and could hint at evolutionary forces that go into altering the genetic code.

The researchers say the study marks the largest screening for alternative genetic codes. Codetta essentially analyzed every genome that's available for bacteria and archaea. The name of the program is a cross between the codons, the sequence of three nucleotides that forms pieces of the genetic code, and the Rosetta Stone, a slab of rock inscribed with three languages.

The work marks a capstone moment for Shulgina, who spent the past five years developing the statistical theory behind Codetta, writing the program, testing it, and then analyzing the genomes. It works by reading the genome of an organism and then tapping into a database of known proteins to produce a likely genetic code. It differs from other similar methods because of the scale at which it can analyze genomes.

Shulgina joined Eddy's lab, which specializes in comparing genomes, in 2016 after coming to him for advice on the algorithm she was designing to interpret genetic codes. Until now, no one has done such a broad survey for alternative genetic codes.

"It was great to see new codes, because for all we knew, Kate would do all this work and there wouldn't turn out to be any new ones to find," said Eddy, who's also a Howard Hughes Medical Investigator. He also noted the potential of the system to be used to ensure the accuracy of the many databases that house protein sequences.

Image Credit: Immersion Immagery/Shutterstock.com

"Many protein sequences in the databases these days are only conceptual translations of genomic DNA sequences," Eddy said. "People mine these protein sequences for all sorts of useful stuff, like new enzymes or new gene editing tools and whatnot. You'd like for those protein sequences to be accurate, but if the organism is using a nonstandard code, they'll be erroneously translated."

The researchers say the next step of the work is to use Codetta to search for alternative codes in viruses, eukaryotes, and organellar genomes like mitochondria and chloroplasts.

"There's still a lot of diversity of life where we haven't done this systematic screening yet," Shulgina said.

Source:
Harvard University
Journal reference:
Shulgina, Y & Eddy, S.R., (2021) A computational screen for alternative genetic codes in over 250,000 genomes. eLife. doi.org/10.7554/eLife.71402.

Biotechnology vs Genetic Engineering

By Eve Navin, BSc
Reviewed by Emily Henderson, B.Sc.

By harnessing the cellular and biomolecular processes of an organism, researchers can develop biotechnological tools such as the infamous CRISPR-Cas system. Tools such as these can be used in genetic engineering, an area of biotechnology, to directly manipulate or modify the genome of an organism such that it possesses the desired phenotype.

Image Credit: PopTika/Shutterstock.com

Biotechnological Tools as Old as Bread

The application of tools derived from living organisms is a practice dating as far back as the Mesopotamian people. More than 7,000 years ago, civilizations were fermenting yeast with grape juice to produce wine, a drink with hedonic and preservative properties. Some 3,000 years later, Egyptians began using yeast to make their bread. Though yeast was recognized as playing a role in fermentation, the process was not understood.

It took roughly 3,000 more years before the work of Antonie Van Leeuwenhoeck and Louis Pasteur revealed the role of yeast in fermentation. Writing in the 17th century, Leeuwenhoeck described the first observation of yeast “globules” under a microscope. Building on this, in the 19th century Pasteur established the groundwork of processes involved in alcoholic fermentation.

Beyond elucidating its role in fermentation, food-grade yeast (Saccharomyces cerevisiae) has long been studied for its applications in biological research. In 1996, S. cerevisiae was the first eukaryotic organism to have its whole genome sequenced, establishing it as a fundamental model organism. To date, yeast remains a popular biotechnological tool for studying human genetics and health.

A Tool for Genetic Engineering

In addition to harnessing the innate processes of yeast, biotechnology can utilize genetic engineering to create transgenic organisms with applications in the biosynthesis of various products. While different species of yeast have specific applications in biotechnology, S. Cerevisiae is the most widely used cell “factory” for the production of biofuels, biocontrol agents, probiotics, flavoring agents, and various other products.

Biotech in 2022: A Good Place to be?

By modifying the genome of yeast, researchers can develop biosynthetic factories that produce desired products. The clustered regularly interspaced short palindromic repeat (CRISPR)-Cas system is popular biotechnology derived from prokaryotic adaptive immune systems, with various applications in genome editing. Readily programmed for targeting, the CRISPR-Cas system contains a guide RNA that is easy to design and express in the host.

Complementary base pairing of this guide RNA to DNA, as well as the presence of upstream protospacer adjustment motif, directs CRISPR accessory protein to target sites in the genome.

The CRISPR-Cas system has helped to revolutionize the field of genetic engineering beyond directly manipulating the genomic sequence. This biotechnological tool efficiently targets genes to modulate their activity. By enabling activation and repression of gene transcription in yeast, the CRISPR system can be utilized to carry accessory proteins with desired functions to target sites in the genome.

By constructing a catalytically deactivated Cas9 (dCas9), CRISPR systems can be used to modulate gene expression. As part of interference systems, CRISPR/dCas9 inhibits transcription by binding to target genes or promoters and preventing RNA polymerase binding. To upregulate select genes, dCas9 can be fused to transcriptional activators or activation domains.

Fusing dCas9 with various effectors can enable precise genome regulation. Without altering the genetic sequence of its host, this tool could improve crop production. In plants, the CRISPR/dCas9 system has been used to enhance stress tolerance, improve immunity against RNA viruses and regulate metabolites critical to growth and development. In this way, bioengineering can be used to enhance the desirable characteristics of an organism.

Applications of Bioengineering

Developed by either directly editing the genome or altering the expression of genes, bioengineered organisms are becoming increasingly prevalent in agriculture. In response to this, the U.S Department of Agriculture expanded its regulation of bioengineered foods in 2016. Alongside this, the Standard defined the new term for bioengineered foods as “those that contain detectable genetic material that has been modified through certain lab techniques and cannot be created through conventional breeding or found in nature”.

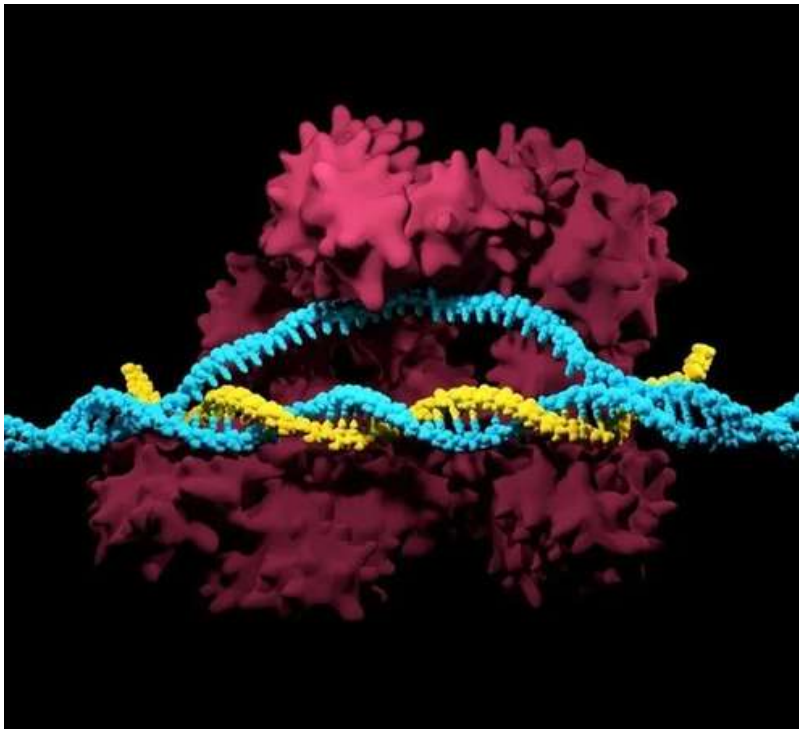


Image Credit: Meletios Verras/Shutterstock.com

While the potential applications of CRISPR/dCas9 systems are still being explored, it is clear this could be a powerful tool to support plant genome engineering. However, putting this tool into practice is still often limited by a concern of the public; namely the possible hazards due to the consumption of crops that have been engineered.

To ensure proper and adequate regulations of these foods, the U.S Agricultural Marketing Service compiled a list of crops or foods are available in a bioengineered form, as well as guidance on testing methods and validation for detecting modified genetic material.

Sources:

- Walker RSK, Pretorius IS. Applications of Yeast Synthetic Biology Geared towards the Production of Biopharmaceuticals. Genes (Basel). 2018;9(7):340. Published 2018 Jul 6. doi:10.3390/genes9070340
- Pretorius IS. Solving yeast jigsaw puzzles over a glass of wine: Synthetic genome engineering pioneers new possibilities for wine yeast research. EMBO Rep. 2017;18(11):1875-1884. doi:10.15252/embr.201745231
- Using yeast in biology. [Online] Your Genome. Available at: https://www.yourgenome.org/stories/using-yeast-in-biology (Accessed on 15 December 2021)
- Ding W, Zhang Y, Shi S. Development and Application of CRISPR/Cas in Microbial Biotechnology. Front Bioeng Biotechnol. 2020;8:711. Published 2020 Jun 30. doi:10.3389/fbioe.2020.00711
- Karlson CKS, Mohd-Noor SN, Nolte N, Tan BC. CRISPR/dCas9-Based Systems: Mechanisms and Applications in Plant Sciences. Plants. 2021; 10(10):2055. https://doi.org/10.3390/plants10102055
- The history of yeast...[Online] Explore yeast. Available at: https://www.exploreyeast.com/article/the-history-of-yeast (Accessed on 15 December 2021)
- List of Bioengineered Foods. [Online] Agricultural Marketing Service. Available at: https://www.ams.usda.gov/rules-regulations/be/bioengineered-foods-list (Accessed on 15 December 2021)