PRESS RELEASE

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Scientists construct a synthetic yeast genome

The yeast genome contains redesigned chromosome sequences that can shed light on the impact of genetic variations on individual traits and potentially be used to reveal the causes of genetic diseases

Singapore, 18 December 2023— It all begins in the chromosomes.

Chromosomes are long DNA molecules that collectively form a genome, containing all the genetic material of an organism. Advances in technology have allowed scientists to redesign and construct different chromosomal sequences, facilitating the study of the link between gene variations and traits.

Notably, yeast is an important model organism for the understanding of basic cellular processes, owing to its similarity to plants and animals at the cellular level while being considerably simpler to manipulate and study. Therefore, redesigning and synthesising a yeast genome can help scientists to understand the impact of genetic variations on individual traits, potentially elucidating the mechanisms of genetic diseases.

With this goal in mind, scientists from the NUS Synthetic Biology for Clinical and Technological Innovation (SynCTI), the Synthetic Biology Translational Research Programme (Syn Bio TRP) and the Department of Biochemistry at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), have synthesised a redesigned yeast—chromosome XV, that comprises 1.05 million base pairs—the largest synthesised chromosome in Asia.

The scientific team, led by Associate Professor Matthew Chang, is part of the Synthetic Yeast Genome Project (Sc2.0), an international consortium comprising labs all over the world working together to redesign and construct from scratch all 16 yeast chromosomes. The work of A/Prof Chang's team is seen as a major milestone in the field of synthetic biology.

In creating the synthetic Chromosome XV (synXV), the NUS Medicine team extensively redesigned the original DNA to incorporate various changes that resulted in a sequence which is distinctively unique and different from the natural one. In order to streamline the assembly process of synXV, the team developed a groundbreaking technology, called CRISPR/Cas9-mediated mitotic recombination with endoreduplication (CRIMiRE). This innovative technology significantly speeds up the exchange of large chromosomal DNA segments at specific sites, hence enabling multiple synthetic chromosome segments to be assembled concurrently and stitched together into a complete synthetic Chromosome XV. The work is published in *Cell Genomics*.

Upon generating the synthetic yeast chromosome, CRIMiRE further allows for the intentional mixing and matching of synXV with another yeast chromosome. This generates different genetic combinations for studies, which illuminates the association between genetic variations and individual traits.

Given the challenges of working with extremely long DNA sequences, the traditional approaches are unable to change the sequences efficiently. However, the use of CRIMiRE has simplified the process, shortening it tenfold, potentially revolutionising the way larger synthetic chromosomes are built for more complex organisms.

“This achievement opens the door to understanding basic questions about biological processes,” said A/Prof Matthew Chang.

"Our journey to complete the construction of the synthetic yeast chromosome has been remarkable. We have not only showcased our technical prowess in creating synthetic chromosomes but are now able to rapidly reconfigure them into different designs for further studies. These synthetic chromosomes are our key to unlocking answers to fundamental biological questions, offering the potential for groundbreaking advancements that can ultimately benefit humanity in profound ways,” he added.

“The achievements from this work hold the promise of paving the way for future advancements in synthetic genomics, especially with larger and more complex chromosomes. This approach can be beneficial in deciphering the mechanisms of and understanding genetic diseases better, and potentially devising treatments,” added Dr Foo Jee Loon, Research Assistant Professor from SynCTI, Syn Bio TRP and the Department of Biochemistry, NUS Medicine, the first author of the paper.

For media enquiries, please contact:

Natalie TAN
Senior Executive, Communications
Yong Loo Lin School of Medicine
National University of Singapore
DID: +65 9011 1459
Email: nat_tan1@nus.edu.sg

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2024 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2023).

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