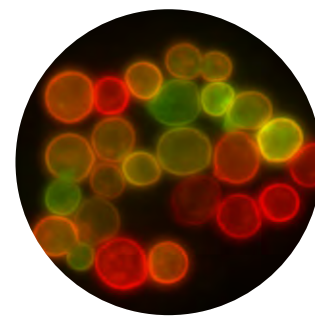


Hitchhiker's Guide to building life from the genome up

A decade of trial and error reveals the hidden complexity of rewriting life's genetic code



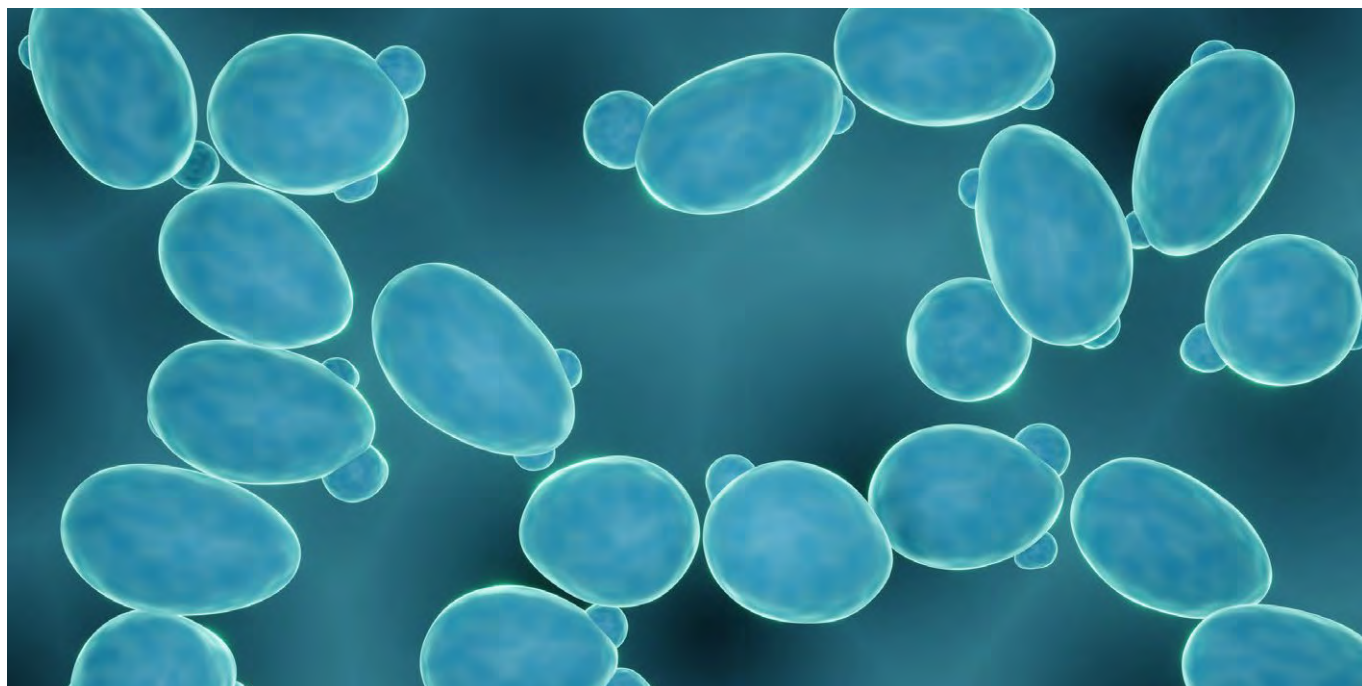
By Fran Molloy

After 10 years and countless setbacks, scientists who completed the world's first synthetic yeast genome have published a troubleshooting guide for building microbes from scratch.

To build the world's first synthetic eukaryotic genome, more than 200 scientists followed a standardised set of design principles to construct all 16 chromosomes. But every research team found some common challenges; and a new review of these shared failures has turned up valuable lessons for future progress in synthetic biology.

Dr Paige Erpf is lead author of a paper published in *Nature Biotechnology* which catalogued these hard-won lessons from the decade-long Synthetic Yeast Genome Project (Sc2.0).

'We've assembled a comprehensive overview of how to build a synthetic microbe, reviewing what went right and wrong,' says Dr Erpf, who is a postdoctoral researcher at the ARC Centre of Excellence in Synthetic Biology at Macquarie University.





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The Sc2.0 project involved researchers from more than 10 institutions worldwide, led by Professor Jef Boeke. This international consortium jointly redesigned and chemically synthesised all 16 chromosomes and 12 million base pairs making up baker’s yeast, *Saccharomyces cerevisiae*.

Unlike traditional genetic engineering methods involving tweaks to existing genomes, Sc2.0 rewrote an entire genome from the ground up.

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Each chromosome followed the same blueprint: remove unstable genetic elements, introduce molecular watermarks to distinguish synthetic from natural DNA, and add a gene-shuffling system called SCRaMbLE.

Tiny DNA watermarks, designed to be genetically silent, occasionally disrupted gene function in unexpected ways. Genes flagged as non-essential caused significant growth problems when removed. Deleting certain tRNA (transfer RNA) genes prompted unanticipated compensatory changes, while removing others damaged mitochondria, those cellular powerhouses that yeast cannot regenerate from scratch.

‘Much of the redesign at a genetic level was done manually and it caused a lot of headaches,’ Dr Erpf says.

Dr Hugh Goold, who led work on synXVI (one of the two synthetic chromosomes developed at Macquarie University) for the NSW Department of Primary Industries and Regional Development, says the challenges were both technical and psychological.

‘The long haul of a decade-long project where progress could feel painfully slow, combined with the difficulty of working with cells that were unfit and difficult to grow, made morale hard to manage,’ Dr Goold says.

‘However, the “learning by building” approach gave us incredible insights into genetics that we may not have fully grasped had we taken historical step-by-step approaches.’

Distinguished Professor Ian Paulsen, who jointly led the Macquarie University SC2.0 team with Professor Sakkie Pretorius, says: ‘This is a landmark achievement and a heroic effort by all the researchers in our team. We started with one scientist in 2014 and it took the combined efforts of more than 20 researchers at Macquarie University to build two synthetic chromosomes.’ ■