



Genome Sciences Seminar

Wednesday, 1.6.21 | 3:30 | held remotely

<https://depts.washington.edu/gstrestrc/remote.htm>



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“Tormenting Genomes”

Rapid advances in DNA synthesis techniques have made it possible to engineer diverse genomic elements, pathways, and whole genomes, providing new insights into design and analysis of systems. The synthetic yeast genome project, Sc2.0 is well on its way with the 16 synthetic *Saccharomyces cerevisiae* chromosomes now >99% completed by a global team. The synthetic genome features several systemic modifications, including TAG/TAA stop-codon swaps, deletion of subtelomeric regions, introns, tRNA genes, transposons and silent mating loci. Strategically placed loxP sites enable genome restructuring using an inducible evolution system termed SCRaMBLE which can generate millions of derived variant genomes with predictable structures leading to complex genotypes and phenotypes. The fully synthetic yeast genome provides a new kind of combinatorial genetics based on variations in gene content and copy number. Remarkably, the 3D structures of synthetic and native chromosomes are very similar despite the substantial number of changes introduced.

We recently completely engineered the yeast karyotype, by systematically fusing pairs of telomeres and deleting single centromeres, thus generating an isogenic series of yeast ranging from $n=16$ to $n=2$. These strains show reproductive isolation and a massively altered 3D genome structure, but are surprisingly “normal” and show high fitness. We have also developed a method that allows us to move megabase segments to distant locations in the genome in a single step, again, with surprisingly little impact on fitness.

Yet another form of genome tormentation is switching up the protein packaging of DNA. The substitution of human for yeast nucleosomes leads to a number of unexpected transcriptional and other phenotypes.

Finally, we have automated our big DNA synthesis pipeline (the *GenomeFoundry@ISG*), opening the door to parallelized big DNA assembly, including assembly of human genomic regions of 100 kb along with multiple designer synthetic variants thereof. We can precision deliver such segments to stem and cancer cells, and use these methods to dissect genomic “dark matter”, perform transplants of specific human genomic regions to animal genomes, and endow human cells with new capabilities.

www.thedarkmatterproject.org

www.yeastart.org

<https://med.nyu.edu/research/boeke-lab/>

Questions? Contact Brian Giebel at bgiebel@uw.edu or visit the Seminar website at <http://www.gs.washington.edu/news/seminars.htm>

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