On behalve of The Netherlands Society for Biochemistry and Molecular Biology (NVBMB), together with Prof. Dr. Dirk-Jan Slotboom from RuG, Armagan Kocer will host

prof. Dr. Jef Boeke

(New York University School of Medicine, Institute for Systems Genetics, USA)
He is the NVBMB Speaker of the Year 2018.

Engineering genomes, karyotypes, and dark matter of the human genome

Date and time: Fri Oct 12, 2018 13:30-14:30
Place: Boeringzaal, UMCG

Abstract
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 six synthetic Saccharomyces cerevisiae chromosomes 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 loxPsym sites enable genome restructuring using an inducible evolution system termed SCRaMbLE (Synthetic Chromosome Rearrangement and Modification by LoxP-mediated Evolution). SCRaMbLE 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 structure of synthetic and native chromosomes are very similar despite the substantial 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.

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 intend to 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.

Dymond et al. 2011 Synthetic chromosome arms function in yeast and generate phenotypic diversity by design. Nature, 477:471-6.
Annaluru et al. 2014 Total synthesis of a functional designer eukaryotic chromosome. Science. 344:55-8.
Richardson et al. 2017 Design of a synthetic yeast genome, Sc2.0. Science 355:1040-1044.
Mitchell et al. 2017 Synthesis, debugging and effects of synthetic chromosome consolidation: synVI and beyond. Science, 355 pii: eaaf4831.

Mercy et al. 2017 3D organization of synthetic and scrambled chromosomes. Science, 355 pii: eaaf4597.
Luo, Sun, Cormack and Boeke 2018 Karyotype engineering: chromosome fusion leads to reproductive isolation. Nature, in press.