Bio-bites!

Semisynthetic organism with unnatural base pair shows stable growth

Three years ago, a team of scientists at The Scripps Research Institute introduced a synthetic base pair into the *Escherichia coli* genomic script.

Known as the unnatural base pair, this semisynthetic organism (SSO) replicated DNA containing the unnatural base pair dNaM-d5SICS UBP.

In a recent follow-up publication, the scientists were able to achieve stable growth and prevent loss of the additional base pair by engineering the transporter, use of a more chemically optimized UBP, and by using Cas9 to eliminate DNA that had lost the UBP. The optimized SSO grows robustly, constitutively imports the unnatural triphosphates, and is able to indefinitely retain multiple UBPs in virtually any sequence context. This newly created semisynthetic organism is thus a form of life that can stably store genetic information using a 6-letter, 3-base-pair alphabet.

Zhang Y, Lamb BM, Feldman AW, Zhou AX, Lavergne T, Li L, Romesberg FE. A semisynthetic organism engineered for the stable expansion of the genetic alphabet. Proc Natl Acad Sci U S A 2017 Feb 7; 114(6):1317-1322.

Chimeric embryos created

An international team of researchers led by Dr. Belmonte, Salk Institute for Biological Studies, reported successful creation of both chimeric mouse-rat and human-pig embryos. In their report published in *Cell*, the establishment of a versatile blastocyst complementation platform based on CRISPR-Cas9-mediated zygote genome editing is described. Successful enrichment of rat pluripotent stem cell derivatives in several tissues of gene-edited organogenesis-disabled mice is presented, together with engraftment of naïve and intermediate human pluripotent stem cells into pig and cattle pre-implantation blastocysts.

Wu J, Platero-Luengo A, Sakurai M, Sugawara A, Gil MA, Yamauchi T, Suzuki K, Bogliotti YS, Cuello C, Morales Valencia M, Okumura D, Luo J, Vilarino P, Parrilla I, Soto DA, Martinez CA, Hishiha T, Sanchez-Bautista S, Martinez-Martinez ML, Wang H, Nohalez A, Azinaw Z, Martinez-Redondo P, Ocampo A, Reddy P, Roca J, Maga EA, Esteban CR, Berggren WT, Nuñez Delicado E, Lajara J, Guillen L, Guillen P, Campistol JM, Martinez EA, Ross PJ, Izpisua Belmonte JC. Interspecies Chimerism with Mammalian Pluripotent Stem Cells. Cell 2017 Jan 26; 168 (3):473-486.e15.

Genetic Basis of Tomato Flavor revealed

In a study published in *Science*, an international team of researchers report the results of a comprehensive study unravelling the genetic basis of tomato flavor. The team analyzed 398 modern, heirloom, and wild accessions by whole genome sequencing. From that pool, they selected 160 tomato samples representing about 100 varieties, and grew them in the laboratory. These laboratory-grown tomatoes were tasted by a panel of a hundred people, who rated them according to taste.
By comparing that information with their genetic analysis, the researchers were able to understand which genes are associated with flavors that people enjoy. According to the study authors, these results provide an understanding of the flavor deficiencies in modern commercial varieties and the information necessary for the recovery of good flavor through molecular breeding.

Tieman D, Zhu G, Resende MF Jr, Lin T, Nguyen C, Bies D, Rambla JL, Beltran KS, Taylor M, Zhang B, Ikeda H, Liu Z, Fisher J, Zemach I, Monforte A, Zamir D, Granell A, Kirst M, Huang S, Klee H. A chemical genetic roadmap to improved tomato flavor. Science 2017 Jan 27; 355 (6323):391-394; https://doi.org/10.1126/science.aal1556.

We now have the genetic recipe for making tomatoes taste like tomatoes again. Alessandra Potenza, Jan 2017. The Verge, available from http://www.thverge.com/2017/1/26/14398882/tomato-genetics-flavor-science-study

Successful mRNA-based Zika-Vaccine

Zika virus has recently emerged as a pandemic associated with severe neuropathology in newborns and adults. There are no ZIKV-specific treatments or preventative. Therefore, the development of a safe and effective vaccine is a priority. A recent study, published in Nature, describes the design of a potent anti-Zika virus vaccine in which pre-membrane and envelope glycoproteins encoded by mRNA contain the modified nucleoside 1-methylpseudouridine (m1Ψ). The use of modified mRNA prevents innate immune sensing and increases mRNA translation in vivo. Nucleoside-modified mRNA was encapsulated in lipid nanoparticles for vaccination. A single, low-dose intradermal immunization with this vaccine was protective in both mice and rhesus macaques.

Pardi N, Hogan MJ, Pelc RS, Muramatsu H, Andersen H, DeMaso CR, Dowd KA, Sutherland LL, Searce RM, Parks R, Wagner W, Granados A, Greenhouse J, Walker M, Willis E, Yu JS, McGee CE, Sempowski GD, Mui BL, Tam YK, Huang YJ, Vanlandingham D, Holmes VM, Balachandran H, Sahu S, Lifton M, Higgs S, Hensley SE, Madden TD, Hope MJ, Karikó K, Santra S, Graham BS, Lewis MG, Pierson TC, Haynes BF, Weissman D. Zika virus protection by a single low-dose nucleoside-modified Mrna vaccination. Nature. 2017 Mar 9; 543 (7644):248-251; https://doi.org/10.1038/nature21428

Bacterial Biosensor to Detect Estrogenic Activity Developed

Endocrine disrupting compounds are detected in increasing amounts in our environment. Although the full impact of these compounds is still under study, they have already been implicated in diseases such as obesity, diabetes, and cancer. In a recent publication, an electrochemical detection strategy for estrogenic chemicals was reported. A native estrogen receptor α construct was expressed on the surface of freeze-dried Escherichia coli cells. In the presence of estrogenic activity, the bacterial cells bind to modified electrodes.

Furst AL, Hoeperke AC, Francis MB. Quantifying Hormone Disruptors with an Engineered Bacterial Biosensor. ACS Cent Sci. 2017 Feb 22; 3(2):110-116; https://doi.org/10.1021/acscentsci.6b00322

Engineered Salmonella typhimurium as a Cancer Therapy

A Korean Team report a method of cancer immunotherapy using an attenuated Salmonella typhimurium strain. To boost immunogenicity, the team engineered the S. typhimurium strain to secrete Vibrio vulnificus flagellin B (FlaB) in tumor tissues. Engineered FlaB-secreting bacteria effectively suppressed tumor growth and metastasis in mouse models and prolonged survival to the end of the 4-month observation period. Tumor microenvironment colonization by engineered Salmonella appeared to induce the infiltration of abundant immune cells, such as monocytes/macrophages and neutrophils, via TLR4 signaling. Subsequent secretion of FlaB from colonizing Salmonella resulted in phenotypic and functional activation of intratumoral macrophages with M1 phenotypes and a reciprocal reduction in M2-like suppressive activities.

Zheng JH, Nguyen VH, Jiang SN, Park SH, Tan W, Hong SH, Shin MG, Chung JJ, Hong Y, Bom HS, Choy HE, Lee SE, Rhee JH, Min JJ. Two-step enhanced cancer immunotherapy with engineered Salmonella typhimurium secreting heterologous flagellin. Sci Transl Med 2017 Feb 8; 9(376); https://doi.org/10.1126/scitranslmed.aak9537

Aflatoxin-free Transgenic Maize

Aflatoxins are potent carcinogenic metabolites produced by the Aspergillus species Aspergillus flavus and Aspergillus parasiticus. These fungi infect a wide range of crops and are responsible for massive agricultural losses worldwide. In a recent study, host-induced gene silencing (HIGS), which involves the expression of double-stranded RNA
molecules in plants, to silence genes expressed by pests and pathogens, was used in maize kernels to reduce aflatoxin contamination. While there was variability from plant to plant in the extent of toxin accumulation in the nontransgenic control samples, the results of the study consistently show that null plants became contaminated with aflatoxin concentrations higher than 1000 ppb, whereas aflatoxins were not detected in any of the transgenic lines.

Thakare D, Zhang J, Wing RA, Cotty PJ, Schmidt MA. Aflatoxin-free transgenic maize using host-induced gene silencing. Sci Adv 2017 Mar 10; 3(3):e1602382; https://doi.org/10.1126/sciadv.1602382.