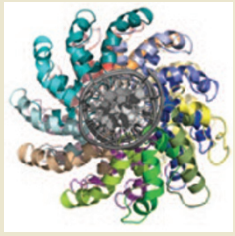
TAL effector–DNA structure



TAL effectors, a recently discovered set of DNA-binding proteins, have been embraced by genome engineers because of the simplicity and specificity of their nucleotide binding code. This family of proteins is composed of a set of 34-amino-acid-long repeating units, in which resides the key to their specificity in the form of two variable residues (residues 12 and 13, dubbed repeat variable di-residue). Now, two groups have uncovered the basis of their binding specificity through crystallographic studies. Working in one case with a naturally occurring TAL effector from a rice pathogen and a sequence from the rice genome, and in the other, with a totally synthetic TAL effector–DNA combination, they both find that the repeating units form two nearly identical alpha helices, with the variant two residues in the middle. A set of 11.5 repeating units (the most commonly occurring number of repeats), complexed with DNA, makes a complete turn of a helix, which tracks along the major groove of DNA. Both groups observed that residue 13 interacts with the protein itself, conferring stability to the structure, whereas residue 14 binds nucleotides. Working with some of the most commonly occurring di-residues, the groups identified the specific interaction between residue 14 and a nucleotide. Although there exist some binding interactions yet to be revealed, this information will assist in the design and implementation of novel TAL effectors. (*Science* published online, doi:10.1126/science.1216211, doi:10.1126/science.1215670, 5 Jan. 2012) *LD*

True colors of genome variation

Detecting variation in genomes from bacteria to man can now be accomplished during genome assembly using an application named Cortex, according to Iqbal *et al.* Cortex can assemble, *de novo,* sequence data from multiple genomes simultaneously without the need for a reference genome. The method uses de Bruijn graphs, which provide a visual picture of regions of variation in compared sequences. Any sequence read length can be combined from short reads to fully assembled genomes. One key feature of this new approach reported by Iqbal *et al.* is that although regions that are variable are clearly delimited, information specific to each individual in an analyzed population can also still be accessed by associating a color with that individual. To demonstrate the versatility of Cortex, Iqbal *et al.* present four case study applications of Cortex, including the detection of simple and complex variations in a high-coverage genome and variation among ten chimpanzee genomes. Cortex is currently the only assembler that can assemble multiple eukaryotic genomes. It doesn't use vast computational resources and can assemble 1,000 *Saccharomyces cerevisiae* samples in less than 64 GB of random-access memory (RAM). Cortex could be used to detect changes between highly related genomes, for example, cancer genomes during carcinogenesis. (*Nat. Genet.* advance online publication, doi:10.1038/ng.1028, 8 January 2012) *SJ*

Improving glycoconjugate vaccines

Bacterial glycans coat such bacterial pathogens as *Haemophilus influenzae* and Group B streptococci. Covalent coupling of glycans with proteins to produce glycoconjugates form the basis of successful vaccines, but these vaccines can have variable efficacy in different populations. Avci *et al.* now investigate immune responses to glycoconjugates with a view to throwing light on such variation. They used the type III glycan of group B streptococci (GBSIII) linked to one of three different carrier proteins and a murine model. A combination of experiments demonstrated that the processed GBSIII ($glycan_p$) is actually presented by MHCII when conjugated to a carrier protein or peptide. It was previously thought that only a processed peptide was presented by MHCII. The authors translate their findings into implications for vaccinologists, predicting that a processed GBSIII glycan-peptide with one peptide per eight repeating units of polysaccharide would increase the number of processed GBSIII glycan-peptides that could be presented from each molecule compared with an industry standard glycoconjugate. They go on to show that a GBSIII glycan vaccine rationally designed for greater efficacy elicits improved protection of mice from lethal streptococcal infection. This research could pave the way for rational design of glyco-polymers in other next-generation vaccines. (*Nat. Med.* **17**, 1602–1609, 2011) *SJ*

Mapping chromatin regulators

Although genome-wide profiling of chromatin modifications by chromatin immunoprecipitation (ChIP) has become a widespread technique, similar experiments for chromatin regulators have proven difficult, mainly due to the paucity of antibodies of requisite quality. Ram *et al.* now present ChIP-grade antibodies for 29 chromatin regulators and perform a genome-wide analysis of their localization in human K562 erythroid and embryonic stem cells. The authors screened 145 antibodies in a pilot experiment based on the readout from 487 genomic locations with different chromatin environments using an adaptation of the nCounter technology for DNA analysis. Only 39 of the antibodies passed the initial screen of which 34 proved to be useful for genome-wide experiments. The analysis of localization maps revealed that chromatin regulators bind in distinct combinations—termed chromatin regulator modules—that are associated with specific modification patterns or genomic elements such as promoters or transcribed regions. The modules often combine proteins with opposing enzymatic activities, presumably to allow rapid dynamic regulation of chromatin structure. (*Cell* **147**, 1628–1639, 2011) *ME*

Drug partners for antibiotics

Antibiotic-resistant bacterial pathogens could be treated with combinations of drugs—if only we knew which combinations would work. Two studies from the same group have identified promising compounds that warrant further exploration. In a recent study, Shakya *et al.* focused on kinase inhibitors as bacterial kinases confer resistance to two important classes of antibiotics, aminoglycosides and macrolides. The researchers screened 80 kinase inhibitors against 14 bacterial kinases *in vitro*, identifying several active compounds including quercetin, a flavonoid found in many fruits and vegetables. Quercetin and the other top hits increased antibiotic efficacy *in vivo*. In an earlier paper (Ejim *et al.*), the authors screened a library of previously approved drugs for the ability to increase the potency of a known antibiotic, minocycline. They found that loperamide (Imodium), an over-the-counter treatment for diarrhea, increases bacterial uptake of minocycline and other antibiotics, thereby increasing efficacy. The authors note the compounds they identified can serve as starting points for further optimization. (*Chem. Biol.* **18**, 1591–1601 (2011); *Nat. Chem. Biol.* **7**, 348–350 (2011)) *JK*

Written by Laura DeFrancesco, Markus Elsner, Susan Jones & Jason Kreisberg