Short-read genome assembler

A novel algorithm lies behind recent insights into the genomes of the giant panda (*Nature*, published online 13 December 2009, doi:10.1038/nature08696), the cucumber (*Nat. Genet.*, **41**, 1275–1281, 2009) and new versions of two human genomes (p. 57–62). Wang and colleagues developed an approach, called SOAPdenovo, to assemble short sequencing reads (~35–75 bp) of large genomes into multikilobase sized chunks without needing a reference genome, a process termed *de novo* assembly. The approach combines efficient data structures for representing short reads with methods for correcting sequencing errors before genome assembly. Together, these advances enabled two human genomes to be assembled so that half of all bases are contained in stretches of sequence at least 5.9–7.4 kb long compared to 1.5 kb for the previous best *de novo* assembly methods. Although this size was smaller than the 20–100 kb achieved using Sanger sequencing (which generates longer reads), it was long enough to discover fragments containing novel coding regions of the human genome. And with the help of long-insert paired-end libraries, the sequences could be arranged into linear genome scaffolds hundreds of kilobases long, which is closer in size to assemblies derived from Sanger sequencing. As these studies suggest, *de novo* assembly of large mammalian and plant genomes from next-generation sequencing technology is now feasible. (*Genome Res.*, published online December 17, 2009, doi:10.1101/gr.097261.109) *CM*

Discrete logic models signaling

With the advent of ever more detailed maps of cellular signaling pathways, it has become apparent that sophisticated analysis methods are needed to understand the behavior of the whole system. Approaches based on differential equations require measuring or estimating a multitude of parameters. A simpler method, discrete logic modeling, which represents the signaling networks as a series of interconnected 'on' and 'off' switches, only requires knowledge of protein-protein interactions and whether they activate or inhibit each other. Although this modeling strategy has been successfully applied in some cases, so far no general approach to optimizing the model using experimental data had been developed. Now, Sorger and colleagues present an algorithm that can modify an input signaling network to optimize the fit to experimental results. By introducing a tunable parameter that balances goodness of fit with model complexity, the authors avoid overfitting and optimize the predictive power of the model. This is validated by constructing a model of HepG2 cell signaling and optimizing it with experimental data of phosphorylation cascades after different stimulations. Several predictions of the model have already been validated in the literature. (*Mol. Syst. Biol.* **5**, 331, 2009) *ME*

Taking down hepatitis C

Chronic infection with hepatitis C virus (HCV) remains a public health problem, as current therapies work in only half of the 170 million people infected worldwide, many of whom will develop serious complications. Lanford and colleagues show that in chronically infected primates, targeting an endogenous, highly expressed liver microRNA results in an enduring reduction in viral load. The target, microRNA (miR)-122, upregulates HCV replication by binding to the viral 5′-untranslated end. Four chimpanzees were given 12 weekly intravenous injections of a locked nucleic acid–modified oligonucleotide directed against that region. In animals given the highest dose, circulating virus as well as liver HCV RNA was reduced by almost three orders of magnitude. Two lines of experiments showed that resistance to treatment did not develop: there was no viral rebound during treatment and deep sequencing did not reveal any mutations in samples taken throughout and after treatment. As viral loads took several months to rebound to pretreatment levels after therapy was stopped, the approach shows therapeutic promise. (*Science*, published online December 3, 2009; doi:10.1126/science1178178) *LD*

Receptor-selective aglycosylated Abs

The ability of antibodies to bind all six members of the Fc gamma receptor (FcγR) family is essential for many aspects of adaptive immunity, including the antibody-dependent cell-mediated cytotoxicity (ADCC) response that underlies the effects of IgG-based therapeutics, such as the anticancer drug trastuzumab (Herceptin). Although the critical dependence of FcγR engagement on IgG glycosylation has restricted the manufacture of therapeutic antibodies to mammalian expression systems, Sazinsky *et al.* (*Proc. Natl. Acad. Sci. USA* **105**, 20167–20171, 2008) demonstrated the ability to uncouple FcγR binding from antibody glycosylation by mutation of the Fc region. Jung *et al.* now further demonstrate the utility of microbial systems for antibody engineering by identifying mutants of aglycosylated trastuzumab that bind the high-affinity FcγR1 receptor with affinity similar to that of their glycosylated counterparts. Importantly, however, the mutant antibodies bind none of the five other FcγRs, including the inhibitory FcγRIIb receptor that is well documented to prevent dendritic cell activation. Accordingly, mutant aglycosylated trastuzumab—but neither clinical-grade trastuzumab nor glycosylated mutant trastuzumab—potentiate the killing of HER2-overexpressing cancer cells *in vitro* by potent activation of dendritic cells. Although these effects have yet to be tested *in vivo*, they suggest that the efficacy of therapeutic antibodies might be enhanced by engineering aglycosylated variants to mediate more potent ADCC. (*Proc. Natl. Acad. Sci. USA*, published online December 18, 2009, doi:10.1073/pnas.0908590107) *PH*

Haploid genetic screens for human cells

The haploid genetic screens routinely used by yeast researchers to recognize recessive mutations have long been the envy of those working with multicellular eukaryotes. RNA interference–based strategies never silence gene expression completely and are often fraught with undesired off-target effects. Moreover, knockout strategies with diploid cells are complicated by the fact that most mammalian genes require disruption of both alleles to confer a phenotype different from the wild-type condition. To address this problem, Carette *et al.* use gene-trap retroviruses for large-scale gene disruption and tagging in a previously described derivative of the KBM7 chronic myeloid leukemia cell line that is haploid for all chromosomes except chromosome 8. Their efforts to screen gene trap–mutagenized KBM7 cells for resistance to influenza virus, cytolethal distending toxin and ADP-ribosylating toxins identify previously uncharacterized genes required for the actions of several intensively studied pathogens. This strategy should be amenable to screens that assay modulation of any reporter gene of interest. (*Science* **326**, 1231–1235, 2009) *PH*

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