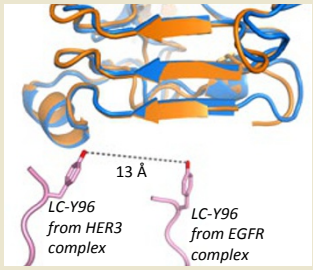
Two antibodies for the price of one



Cancer drugs that block cell signaling by means of epidermal growth factor receptors (EGFRs) have had some success in the clinic, but over time, and with certain receptor-bearing cancers, these therapies fail when used as single agents. Increasingly, drug developers are turning to combinations of drugs, which are challenging to test in trials and add to the cost of therapy. Researchers at Genentech had previously created "two-in-one antibodies" that target two common cancer targets, HER2 and VEGF, through the same binding site. Now they show that with this approach they can create other potentially clinically useful molecules with dual binding specificities. Antibodies that bind EGFR were generated by phage display, and subsequently selected for the ability to bind HER3. The researchers show through competition experiments that the resulting antibody, MEHD7945A, binds either or both ligands at the same region of the molecule. MEHD7945A inhibits receptor binding *in vitro* and was a more potent inhibitor of HER3-dependent growth in culture, as well as in 12 xenograft models, than antibodies with single specificities. Whereas most bispecific antibodies combine two distinct antigen-binding molecules, here the two specificities reside in the same binding site, which might potentiate its effects and could simplify manufacture. (*Cancer Cell* **20**, 472–486, 2011) *LD*

Multigenome analysis of variation

Structural variation in the human genome can be discovered by comparing paired-end next-generation sequencing reads from an individual to the human reference genome. Hormozdiari *et al.* improve the accuracy of discovering variants in repetitive regions of the genome through simultaneous analysis of several genomes, rather than the one-by-one approach that has been the norm. The key to discovering structural variants lies in the identification of 'discordantly mapped' paired-end reads: pairs that match regions in the reference that are further apart or closer together than expected are indicative of an insertion or deletion, respectively. Existing approaches fall short in repetitive genomic regions when there are several possible discordant mappings for a read pair, indicative of several possible variants. Hormozdiari *et al.* describe algorithms, called CommonLAW, that harness discordant read pairs from multiple genomes to determine which of the discordant mappings is most likely. Applying the new algorithms to genomes sequenced in the 1000 Genomes Project reduced the number of false-positive calls of mobile element insertions by >20-fold and provided moderate improvements to calling deletions. (*Genome Res.* published online, doi:10.1101/gr.120501.111, 2 November 2011) *CM*

Written by Laura DeFrancesco, Markus Elsner & Craig Mak

Ribosomes reveal proteome complexity

Our understanding of regulatory processes at the level of cellular RNAs lags far behind our understanding of transcriptional control at the DNA level. Ingolia *et al.* have used profiling of the position of ribosomes on RNAs to characterize RNA translation in mouse embryonic stem cells. Using the drug harringtonine to stop translation during the first rounds of peptide elongation, the authors were able to accumulate ribosomes at sites of translation initiation. Forty-four percent of the initiation sites they identified were unannotated. In many cases, they predict the production of N-terminally truncated forms of known proteins, but also the translation of parts of the 5′-untranslated region. Initiation of the upstream open reading frames was frequently observed at non-AUG codons. Which of these sites leads to productive protein production remains to be determined by alternative methods. The authors also identify sequences that cause pronounced pausing during peptide elongation and show that no substantial pausing occurs at rare codons. Small RNAs are also frequently covered with ribosomes, suggesting that they might be translated into proteins instead of, or in addition to, other regulatory functions. (*Cell* **147**, 789–802, 2011) *ME*

Sifting proteins for proteomics

Determining the identity of an intact protein by mass spectrometry without first digesting it with an enzyme is called 'top-down' proteomics. Although this approach has been applied to single proteins, the inability to separate a complex protein mixture in a way that is suitable for high-throughput analysis by mass spectrometry has limited the application of the top-down method on a large scale. Tran *et al.* report a new combination of separation approaches that allowed analysis of >3,000 protein forms produced from 1,043 genes in HeLa S3 cells, a >20-fold increase over previous top-down studies in mammalian cells. In contrast to the current dominant strategy requiring enzymatic digestion, top-down proteomics enables protein variants and complex combinations of post-translational modifications to be identified. This allowed Tran *et al.* to monitor changes in phosphorylated and methylated protein species and isoforms from splice variants over time in cells exposed to DNA damaging agents. The new separation approach appears to provide throughput and capacity superior to the gold-standard method of two-dimensional gel electrophoresis, and thus may facilitate top-down approaches to better identify biomarkers, understand modifications induced by intracellular signaling and catalog the proteome in its entirety. (*Nature* published online, doi:10.1038/nature10575, 30 October 2011) *CM*

New role for VEGF

The success of anti-vascular endothelial growth factor (VEGF) therapy has mainly been attributed to its effects on tumor angiogenesis. Beck *et al.* now show that VEGF signaling is also important for the maintenance of tumor stem cells. Working with a mouse model of squamous skin tumors, the authors show that tumor stem cells are localized close to endothelial cells and that blocking VEGF-receptor 2 not only reduced blood vessel density in the tumor but also decreased the number of cancer stem cells. In addition to promoting the formation of a cancer stem cell niche by regulating angiogenesis, VEGF also has a direct effect on the cancer stem cells, as selective deletion of the VEGF co-receptor neuropilin-1, which is normally expressed in cancer stem cells, also caused an inhibition of cancer stem cell self-renewal and differentiation. The involvement of a VEGF signaling pathway in cancer stem cell biology might provide new therapeutic avenues in the future. (*Nature* **478**, 399–403, 2011) *ME*