IN brief

FDA okays IT-powered trial

In December, the US Food and Drug Administration cleared the way for Transparency Life Sciences (TLS) to conduct a virtual clinical trial using telemonitoring to collect data from patients' homes. The phase 2 trial will test a long-used blood pressure medication, lisinopril, repurposed for multiple sclerosis (MS), employing a commonly used set of metrics that can be communicated by digital media, such as smartphones and tablets. TLS, located in New York, is the brain child of former Novartis executive Tomasz Sablinski, who has been banging on the idea of reducing the cost of drug development since founding TLS in 2010. The company incorporates crowdsourcing into clinical trial design and will have patients monitoring their progress for all but the first and last assessments to reduce costs. As much as 60% of costs come from data collection, according to TLS's COO and co-founder Marc Foster. The MS trial, which will start once funding is secured, will demonstrate whether TLS can succeed where others have failed. A much touted Pfizer virtual phase 4 trial for a drug for overactive bladder, which employed online recruitment and self-monitoring, was suspended due to low patient enrollment. In its first trial, TLS will "keep it simple," says Foster, a notion endorsed by Carolyn Compton, president of the Critical Path Institute of Tucson, Arizona, which is developing tools for improving efficiencies of trials. Compton believes that "citizen scientists" are set to revolutionize clinical science, but points to the need for validated, rigorous methods for collecting patient-reported data. *Laura DeFrancesco*

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IN their words

"We are in what I call an awareness moment."

Eric D. Green, director of the National Human Genome Research Institute at the US National Institutes of Health, comments on a demonstration that

individuals could be identified using publically available genome data, combined only with age and country of origin. (*The New York Times*, 17 January 2013)

"That is why we are in the trouble we are in."

Dennis J. Cotter, a health policy researcher, who studies the cost and efficacy of dialysis drugs. January's "fiscal cliff" bill is viewed by some as a gift to Amgen because it carves out exceptions as far as Medicare pricing restraints for kidney dialysis drugs. (*The New York Times*, 19 January 2013)

Personalized, sequencing-based immune profiling spurs startups

Seattle-based Adaptive Biotechnologies and S. San Francisco, California-based Sequenta made a splash at December's American Society of Hematology annual meeting, in Atlanta, with over a dozen posters demonstrating how in-depth, sequencing-based analysis of lymphocyte receptor repertoires can improve detection of blood cancer recurrence. Both companies are poised to enter the clinical marketplace in 2013 with assays for diagnosing lingering leukemia and lymphoma in patients.

Several other startups are also gearing up to use next-generation sequencing (NGS) platforms to read immune system footprints present in cancer, infection or autoimmune disease. "For most human diseases, something is damaged or something is growing—and our immune system has already made the diagnosis for us," says Jian Han, a group leader at the Hudson Alpha Institute of Biotechnology and founder of the immune cell-profiling company iRepertoire, both based in Huntsville, Alabama.

The speed and accuracy of NGS platforms combined with sophisticated bioinformatics can provide detailed snapshots of the immune system's repertoire. The diversity of such sequences is staggering. Even sequencing experts like Robert Holt, who cut his teeth sequencing the human genome at Celera, see the immune repertoire as daunting. "We read 35 million clones to do the first draft assembly of the human genome, but you would have to do as much or even ten times as much to get a reasonably deep analysis of the same person's immune repertoire," says Holt, now at the British Columbia Cancer Agency Genome Sciences Centre in Vancouver.

T-cell receptors (TCRs) and B cell-derived antibodies are composed of different combinations of variable (V), diverse (D) and joining (J) gene segments that undergo extensive somatic recombination. The diversity resulting from these recombination events is enhanced by enzymatic insertion of additional nucleotides between these loci. The complementarity determining regions (CDRs) of TCRs and antibodies establish their affinity and specificity for particular antigens; CDR3 is the region that contains the recombined VDJ products, and is generally recognized as the most variable segment.

Until recently, scientists made do with spectratyping, a PCR-based technique for characterizing CDR3. This approach enables repertoires to be categorized by CDR3 fragment length, but yields no sequence data. The advent and rapid maturation of NGS technology brought this challenging target within reach, and 2009 saw a flurry of studies from several groups—including Holt's—which have applied NGS to characterize CDR3 repertoire diversity with a thoroughness that would have been previously unimaginable. Several companies promptly emerged with business models centered around 'immunogenomic' analysis for clinical diagnostics or research applications. "This was very much a case of convergent evolution," says Sequenta co-founder and CEO Tom Willis.

Blood cancers will be the first to benefit from the prognostic potential of immune profiling. People with lymphocyte malignancies, such as acute lymphoblastic leukemia, have a highly skewed immune repertoire. "The most abundant T-cell clone a healthy person will have in their blood will

represent 5–6% of their T cells," says Harlan Robins, a researcher at the Fred Hutchinson Cancer Research Center and co-founder of Adaptive Biotechnologies. "If I take someone with cancer, it might be 98% of this one clone—it's an overwhelming signal." Successful therapy will largely eradicate these defective lymphocytes, but doctors must remain vigilant for small numbers of

Adaptive Biotechnologies' founding brothers, Dr. Harlan Robins (left) and Chad Robins (right).

Adaptive Biotechnologies