## Wellness 'omics in clinics

Providence Health & Services has joined forces with the Institute of Systems Biology (ISB) to offer clinical care focused on keeping patients healthy, using analytics to predict, prevent, or detect the onset of disease before clinical symptoms develop. In March, Providence became affiliated with the not-for-profit ISB, located in Seattle and founded by systems biologist Leroy Hood, immunologist Alan Aderem, and protein chemist Ruedi Aebersold. The partners aim to provide insights into wellness and disease by generating dense, personalized clouds of billions of data points from proteome, metabolome, and gut microbiome analyses taken from each patient and tracked over time. Hood will serve as senior vice president and chief science officer of Renton, Washington–based Providence, a not-for-profit healthcare provider, whose services include 34 hospitals and 600 physician clinics across Alaska, California, Montana, Oregon, and Washington. Providence and ISB will pursue a number of joint projects, including analyzing people at risk of Alzheimer's disease over time, helping breast cancer patients return to wellness following therapy, and uncovering new glioblastoma treatments.

**"Even with scientific evidence, the brand of the Theranos name is in trouble,"** said Joshua Rauh, of Stanford Business School, after the US Centers for Medical and Medicaid Services reportedly threatened stiff sanctions against the company in March. The proposed sanctions, which include barring CEO Elizabeth Holmes from running a laboratory for two years, come five months after the agency's inspection of Theranos' laboratory in California revealed numerous problems with the revolutionary blood-testing platform. The company's response, the agency wrote, **"does not constitute a credible allegation of compliance and acceptable evidence of correction for the deficiencies cited."** (*Wired*, 13 April 2016)

**"I feel devastated that we did not catch and fix these issues faster,"** a contrite but defensive Theranos CEO Elizabeth Holmes tells interviewer Maria Shriver on NBC's Today show. (*Today (NBC)*, 18 April 2016)

**"[Steve] Burrill spent his fund's capital on whatever he pleased, and elevated his own interests above those of investors."** Andrew Ceresney, director of the Securities and Exchange Commission (SEC) Enforcement Division, comments on allegation that Steve Burrill mishandled one of his funds. While not admitting guilt, Burrill has agreed to pay a $1 million fine and $4.78 million in restitution to institutional investors whose money he had been squirreling away into private accounts since 2007. (*Fierce Biotech*, 30 March 2016)

# DNA-encoded drug libraries come of age

DiCE Molecules, a company with a new approach to DNA-encoded chemical libraries, signed a deal in March worth $2.3 billion with French pharma Sanofi. The Paris-based drugmaker will pay DiCE an initial $50 million to access DiCE's 'directed-evolution' technology and up to $184 million in milestones per target. In January, Sanofi also inked a drug discovery deal with X-Chem, a biotech with a DNA-encoded drug discovery platform, based in Waltham, Massachusetts.

The deals show that big pharma is continuing to amp up its interest in DNA-encoded chemical libraries, even though they have so far produced only one publicly disclosed clinical-stage drug candidate. Other firms have also been forging alliances in this space, attracted by the notion that these libraries can identify leads for 'undruggable' targets, such as those involved in protein-protein interactions.

"I think DNA-encoded libraries in general have now passed the point when they were greeted with confusion and hostility. They are now being pulled into various pharmaceutical companies and being used as another tool, and that's great," says Kevin Judice, chief executive officer of DiCE Molecules, based in Redwood City, California. "But I think it's up to us to prove that directed chemical evolution will be a really useful addition."

DNA-encoded libraries were first proposed as a thought experiment in 1992 by Sydney Brenner and Richard Lerner, then at the Scripps Research Institute in La Jolla, California (*Proc. Natl. Acad. Sci. USA* **89**, 5381–5383, 1992). The idea was that by adding unique DNA fragments to each compound in a combinatorial library, researchers could create gigantic libraries containing billions of compounds that can be easily identified by sequencing their DNA 'barcode' tags.

These could offer cost, speed, and efficiency benefits over the painstaking methods used with traditional high-throughput screening libraries. DNA-encoded libraries incorporate DNA fragments into the compound synthesis, such that every compound ends up with a stretch of unique DNA attached. Because researchers can read the DNA tags with molecular biology tools—PCR or sequencing—they can easily identify the hit compounds.

For one thing, DNA-encoded libraries are much larger than HTS libraries. But because the DNA barcodes can quickly identify any given compound, researchers can run screens of billions of compounds against a target in a single vessel. This is an attractive alternative to HTS, which requires aliquoting millions of compounds into individual wells, adding a biological target to each well, and then monitoring for an interaction between the target and small molecules.

The simple experimental setup of DNA-encoded chemical screens also means that they require very little target protein, whereas HTS requires enough target to add to each well. An entire DNA-encoded library can be stored in a single freezer; HTS libraries, by contrast, need to be stored in expensive robot-filled facilities.


DiCE Molecules

Kevin Judice, CEO DiCE Molecules.

And yet pharma companies took time to warm to the concept. One of the first to test this screening technology was GlaxoSmithKline's (GSK), with its acquisition in 2006 of Waltham, Massachusetts–based Praecis Pharmaceuticals. Today, GSK has the most advanced candidate to stem from a DNA-encoded library: an epoxide hydrolase inhibitor currently in phase 1 clinical trials for chronic obstructive pulmonary disease.

DNA-encoded libraries come in two main flavors. In some, DNA is purely a barcode for identification, added on to the compounds as they are constructed. This is the case for the libraries made by GSK/Praecis, by X-Chem, by HitGen, in Chengdu, China, and by Nuevolution, in Copenhagen. These were created on a truly massive scale, sacrificing some control over composition for the benefits of scale. GlaxoSmithKline's library, the largest of this type, now exceeds 1 trillion compounds.

Other DNA-encoded screening tools, such as those of Ensemble Therapeutics, in Cambridge, Massachusetts, and Vipergen, in Copenhagen, use DNA not just as a barcode but also as a physical template that directs the synthesis of the libraries' chemical members. In the case of Ensemble, researchers prelabel a set of chemical building blocks (such as amino acids, amines, and carboxylic acids) with strands of DNA. They can then make use of base-pairing between complementary strands of DNA to force these building blocks into pre-specified proximity with one another, at which point they covalently bind the building blocks together into preplanned small molecules. Vipergen takes a similar approach, relying on the self-assembly of complementary DNA but using three-way and four-way DNA junctions to position the building blocks relative to one another. (In both cases, the DNA tags remain attached to the resulting small molecules for use as DNA barcodes.)

Both approaches require careful up-front planning, because all the building blocks need