to be prelabeled perfectly for any reactions to happen at all. But it also allows for more finely tuned control over the design and composition of the library and for some quality-control features. And Ensemble's collection still—although not as gigantic as purely barcoded libraries—consists of over 10 million macrocycles, large circular molecules that can have high affinity and selectivity for protein targets. As such, it still dwarfs high-throughput libraries, which typically contain a few hundred thousand to 2 million compounds.

Philochem, based in Zurich, follows an entirely different strategy. Whereas the other biotechs end up with small molecules that are each attached to single DNA tags, Philochem's 'dual-pharmacore' approach uses DNA as a means to co-display and co-label pairs of chemical fragments, essentially combining fragment-based drug discovery and DNA-encoding technology.

DiCE's platform now adds a directed-evolution approach into the mix, as outlined by Pehr Harbury, of Stanford University (*Annu. Rev. Biochem.* **76**, 331–349, 2007). As in other methods, DiCE attaches a unique DNA linker to every compound that it creates. After screening the DNA-encoded library against the target, DiCE fishes out the target along with any small molecules that have bound to it, and reads the attached DNA tags to identify the best binders. But whereas competitors would treat these results as hits, DiCE re-synthesizes all the best binders and runs another screen. Repeating this process three or four times amplifies the signal from genuine binders far above the background noise. "In one example, we went from a billion-compound library to a highly enriched collection of 10,000 hits, broken into about a dozen distinct families, that were the best binders," Judice says.

And then the directed chemical evolution comes into play. The company designs a new, more focused DNA-encoded library to generate large amounts of chemical diversity just around the best hits. If a family of binders includes a tyrosine building block, for example, they'll use dozens of variants of tyrosine to grow that family in the hopes of finding even better hits. Because they tweak several different elements of a family at the same time, they expand each family up to around 50 million compounds. "That's where the true power of the evolutionary algorithm comes in," says Judice. "It's like doing medicinal chemistry on a very, very large scale."

Sanofi and DiCE will be working on 12 targets in total, though the companies did not disclose the indications. Judice anticipates potentially striking a similar deal with another pharma partner, and says the company will also work on developing drugs against its own targets.

While industry scientists await results from this experiment with directed chemical evolution, they are also continuing to work out the kinks from the first iterations of DNA-encoding technologies. "Quite a few of the top 10 pharma are still in the process of figuring out how well the technology works," says Jin Li, CEO of HitGen. "But they are also figuring out which company is the right partner from a cultural perspective."

HitGen, founded in 2012, is a recent entrant into the DNA-encoded library space. The company takes a similar approach to GSK and X-Chem, but uses single-stranded pieces of DNA in the library construction that it then turns into double-stranded DNA fragments, whereas its competitors use double-stranded DNA all along. HitGen has signed 12 partnerships in 2015, including three deals with top 10 pharma companies. Two of these deals have already been extended this year, says Li, who expects more deals to follow.

In addition to the rampant partnering activity, most of the DNA-encoded library companies are also working on drug discovery programs of their own. Most of the biotechs work on these projects directly in house, but X-Chem is spinning out therapeutic-area startups to move their candidates forward. Their first spin-out, X-Rx, based in Wilmington, North Carolina, for example, is focused on oncology, autoimmunity and fibrosis targets. Li likens the situation to what happened with fragment-based drug discovery companies. While big pharma was working through its skepticism for the emerging technology platform, fragment-based drug discoverers used in-house projects as a means to speed up acceptance.

A similar situation may be starting to unfold with DNA-encoded libraries, as big pharma starts to take more DNA-encoded library work in house. Novartis has secured a technology transfer deal with Nuevolution so that it can modify the biotech's DNA-barcoding approach for internal use. "The technology is well advanced and recent literature from academia and industry proves the validity of the technology," says Johannes Ottl, a senior investigator at Novartis, Basel, Switzerland. Novartis is now improving the robustness of library chemistry, fine-tuning the quality-control elements and experimenting with new screening processes. Roche, too, is working with DNA-encoded libraries in house, following an approach similar to those from the GSK and X-Chem platforms, although the pharma declined to provide any details of their strategy.

"What happens next with DNA-encoded library companies depends on the science, on each company's vision for its own future, and on the view of their investors," says Li.

Asher Mullard *Ottawa, Canada*

Merck, Ionis prevail in Gilead HCV suit

A federal jury in March sided with Kenilworth, New Jersey–based Merck and its co-inventor Ionis Pharmaceuticals (formerly Isis Pharmaceuticals) to uphold two patents owned by the companies relating to the treatment of hepatitis C virus (HCV). The jury in the US District Court of the Northern District of California said that Foster City, California–based Gilead Sciences had infringed US Patents 7,105,499 and 8,481,712, covering methods and compounds used to develop medicines for the treatment of patients with HCV and HCV-related infection. The medicines include Gilead's blockbuster drugs Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir). Gilead had filed suit in 2013 seeking a declaratory judgment that Sovaldi did not infringe the two patents. The jury ordered Gilead to pay Merck $200 million in damages as compensation for infringement of the HCV drug patents through 31 December 2015—an amount far less than the $2 billion demanded by Merck. Gilead said in a statement that it will appeal the decision if the judge maintains the jury's verdict. "Since Merck made no contribution and assumed none of the risk in the discovery and development of sofosbuvir, we do not believe Merck is entitled to any amount of damages. We will continue to believe the Merck patents are invalid." Ionis, of Carlsbad, California, will receive 20% of the damages awarded to Merck, including future payments and excluding litigation costs.

"Cutting-edge science thrives where the power of diversity is advanced, not when it is weakened. Individuals cannot reach their full potential when they have to spend time focusing on whether they are at risk for their beliefs, sexual orientation, gender identity or expression." Biogen CEO George Scangos on North Carolina's law that bans lesbian, gay, bisexual and transgender people from anti-discrimination protection. Biogen has had operations in North Carolina since 1995, employing over 1,300 employees, according to its website. (*The News and Observer*, 26 March 2016)

"You can only do that once. After that, it's game over." Richard Evans, an analyst at Sector & Sovereign Research (Stamford, Connecticut), referencing some pharma companies' (read Valeant's) penchant for raising prices on common drugs. *STAT*, 29 March 2016.

"The pharmaceutical industry is under such public scrutiny now that any arrangement that's kept secret is going to be presumed to be evil. [All companies should know that transparency matters]." Erik Gordon, a business and law professor at the University of Michigan, comments on the aftermath of Valeant's sales and marketing scandal. (*STAT*, 29 March 2016)