Opening the door to backroom biologics

What would a world look like in which biohackers had access to automated drug-production platforms?

At last month's Biohack the Planet conference in Las Vegas, Nevada, talk centered on the need for biohackers to "grow up" and move beyond live-streamed self-experimentation. It was even suggested that practitioners place greater emphasis on standardizing processes and protocols—something of a departure for a counterculture movement largely defined by its opposition to regulatory oversight. One of the pilot projects discussed at the conference—a bootleg version of the gene therapy Glybera for lipoprotein lipase deficiency—encapsulates both the problem and promise of DIY drug making. On the one hand, the homebrew 'gene therapy' looks nothing like a finished pharmaceutical product. On the other, with only a shoestring budget, biohackers actually made a prototype of a commercial product. The question is whether such a prototype molecule can be turned into a product with the necessary assurance of quality, consistency and safety for human therapy.

Biohackers are a movement of enthusiasts who seek to use technology and bioengineering to enhance biology. Many have little biological training; some are PhDs with deep expertise; all view homebrew therapies as a means to liberate products from the rapacious grip of pharmaceutical corporations. Pharma sees them as a reputational threat.

In recent years, several DIY drug-making efforts to create homebrew biologics have attracted headlines. In 2017, Tristan Roberts, who is HIV-positive, injected himself with a DNA minicircle encoding a neutralizing antibody (N6) targeting HIV gp120 protein. The same year, Josiah Zayner, CEO of The ODIN and supplier of DIY CRISPR kits, also gained notoriety by livestreaming the injection of CRISPR–Cas9 and a guide RNA targeting myostatin into his arm. Elsewhere, the Open Insulin Project has been working toward an open protocol for insulin manufacture.

The recent effort to create biohacked Glybera (dubbed Slybera by its developers) was accomplished "in a shed in Mississippi, a warehouse in Florida, a bedroom in Indiana, and on a computer in Austria," according to Gabriel Licina, one of the four biohackers involved. The entire project—from DNA construct design and oligonucleotide synthesis (by an outside provider) to preliminary characterization and expression of the minicircle in a mammalian cell line—cost less than $7,000.

The problem is, of course, that Slybera is not a gene therapy. There are no preclinical data on its pharmacokinetics, pharmacodynamics or toxicity; no data on its bioequivalence or clinical comparability to Glybera; no good production strain; and no assurance of product purity, quality, consistency and safety. Slybera is more plasmid prep than product.

And the inability of the biohacker community to make this type distinction is what has led the US Food and Drug Administration (FDA) and the American Society for Gene Therapy to release statements warning of the dangers of homebrew treatments. In 2020, a California bill will become law that prohibits sales of DIY CRISPR kits unless they carry a notice "stating that the kit is not for self-administration."

To the drug-development establishment, biohackers look like misfits—or worse, dangerous pariahs. Is there a scenario in which their ingenuity and endeavor could be harnessed for drug development?

Biohackers are not the only ones chipping at the pharmaceutical monolith. Several medical centers are starting to produce limited batches of drugs for patients at the bedside through either magistral pharmacies or non-profit companies serving networks of participating hospitals. These initiatives are being driven by shortages in the supply of drugs and spiraling pharmaceutical prices. In the Netherlands, the University of Utrecht has established a network of hospitals capable of manufacturing and distributing magistral products across Europe and beyond. Similarly, in the United States, hospital systems such as Advocate Aurora Health are banding together and forming non-profit companies capable of manufacturing and distributing drugs for participating institutions. Commercial efforts in autologous chimeric antigen receptor (CAR) T-cell therapies have already moved the therapeutic frontier away from bulk to small-scale production.

Automated benchtop systems are beginning to integrate oligonucleotide synthesis and protein production. Last month, San Diego biotech SGI-DNA raised $25 million to invest in the global commercial launch of its BioXp 3200 system, an automated benchtop oligo-assembly platform for protein production, antibody library generation and cell engineering. Kilobaser advertises its portable, low-scale oligo synthesizer as the "Nespresso machine for DNA primers" for the research market.

Given economic pressures to innovate in drug manufacture and the potential of platform production technologies to enable decentralization, we may imagine a future in which the brand manufacturers' monopoly on biologics could be broken. The first charge will come from biosimilar manufacturers. Small-scale magistral production for patients at the bedside would add a flanking maneuver. And biohacking might execute a final sharp pincer movement.

In such a scenario, biohackers could conceivably contribute by discovering new agents for the thousands of rare and ultra-rare diseases with no therapeutic options that drug companies dismiss because markets are too small. Contract services could provide pharmacokinetics and toxicology testing. And if automated production platforms become more widely available—perhaps in magistral production hubs—together with an adapted regulatory approval or registration system, biohackers might be able to plug their homebrew therapeutics into them.

This remains a thought experiment for now—an experiment that would require magistral-accreditation programs, new regulatory patient recruitment schemes, and trial designs using multimarker composite assessment to build statistical power on smaller patient cohorts. But for many families with children suffering from a fatal rare disease, homebrew biologics manufactured as above look like a better option than their current situation: no therapeutics at all.

Rare disease is an open door waiting for drug developers to push on it. The question is whether changes in distributed product manufacture can push biohackers into the drug development fold. ❐

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