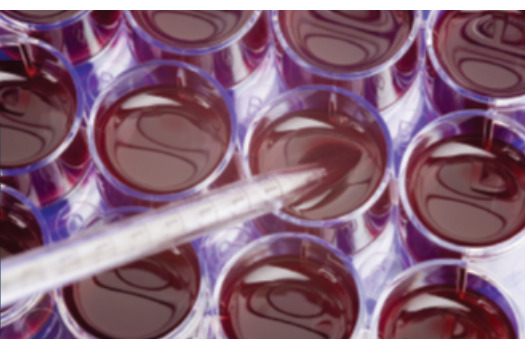


The New Pharmaceuticals: Drug Development for the 21st Century



An ACS-e! Discovery Report examining the new drug development strategies being used to manage the high risk and cost of R&D including new drug classes, stem cell technologies, proteomics, and delivery systems



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The New Pharmaceuticals: Drug Development for the 21st Century

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I. INTRODUCTION

On Jan. 7, 2015, researchers announced the discovery of teixobactin, the first new antibiotic in 25 years.¹ Although it was tested only in animal models, teixobactin could prove to be a key weapon in the ongoing war against antibiotic-resistant bacteria. But if history is any guide, teixobactin's developers face a tough road.

Hundreds of drugs have been developed over the past decade, some of them multi-billion-dollar blockbusters. The U.S. Food & Drug Administration (FDA) approved 41 new drugs in 2014, according to a report in *Chemical & Engineering News (C&EN)* – the most in 18 years.² Yet the road to success is paved with failure: One report from the Pharmaceutical Research and Manufacturers of America (PhRMA), documents the challenge of shepherding anticancer therapeutics to market. Between 1998 and 2014, the report says, just seven therapeutics won approval by the FDA for the treatment of melanoma, while 96 were “discontinued,’ suspended,’ or had ‘no development recorded.’”³ In fact, the actual number approved is eight as the FDA approved Bristol-Myers Squibb's (BMS) Opdivo in late December, after PhRMA's report was compiled.⁴ In the same time period, 10 lung cancer therapies and three brain cancer therapies were approved out of 177 and 78 tries, respectively.³

Given that low approval rate, it's no surprise that the price of successful therapies is now \$1.2 billion or more, up from an estimated \$800 million or so in the late 1990s.⁵ Drug developers spent in excess of \$51 billion on pharmaceutical research and development in 2013 – nearly double the \$26 billion spent in 2000.⁵ With the price of failure higher than ever, drug developers want to make the drug development process as efficient as possible. The result has been a fundamental and multipronged change in the way pharmaceutical research and development is done.

Drug developers are more aggressively targeting conditions they might never previously have considered. “Orphan” diseases, for example, are to some extent shaking off their orphan status, as more and more drug developers expand into the rare-disease space where few alternative therapeutics are found at the moment. As reported in *C&EN*, orphan drugs are big business for such companies as Genzyme, BioMarin Pharmaceuticals, Shire, and others.⁶ Since passage of the Orphan Drug Act in 1983, 450 medicines for rare diseases have been brought to market, according to PhRMA, and some 450 more were in development as of 2014, “focusing on rare cancers, genetic disorders, neurological conditions, infectious diseases, and autoimmune disorders.”⁵

Seventeen drugs approved in 2014, representing 41% of the total, “carried ‘orphan’ status, meaning they treat a disease that affects fewer than 200,000 people”² These include BioMarin

Pharmaceutical's Vimizim, an enzyme replacement therapy for mucopolysaccharidosis type IVA, and two anti-melanoma antibody therapeutics, BMS's Opdivo and Merck & Co.'s Keytruda, both of which inhibit the PD-1 protein, "which blocks the body's immune system from attacking melanoma tumors."⁴ As a point of reference, nine approved drugs carried the "orphan" label in 2013.

Pharmaceutical companies are also exploring novel modes of drug action. Seventeen drugs in the class of 2014 were "first-in-class" therapeutics, according to an FDA report,⁷ including Gilead Sciences' Harvoni, a combination of two hepatitis C virus (HCV) inhibitors, and "Blinicyto, an orphan drug from Amgen for the treatment of a rare form of acute lymphoblastic leukemia and the first bispecific antibody therapeutic to win FDA approval." Blincyto is the first approved drug that engages the body's T-cells, a type of white blood cell or lymphocyte, to destroy leukemia cells," according to the FDA press release announcing Blincyto's approval. "The drug acts as a connector between a protein called CD19, which is found on the surface of most B-cell lymphoblasts, and CD3, a protein on T-cell lymphocytes."⁸

In addition to novel indications and mechanisms of action, drug developers are also using new tools to identify promising compounds in the first place. One fast-growing strategy exploits the power of induced pluripotent stem (iPS) cells and genome editing technology. This method has been used to identify potential drug targets and create a platform for drug testing, especially of human cell types that are not readily available or cultured, such as neurons.⁹ Other promising strategies use mRNA expression (transcriptomics) to identify signatures of toxicity or efficacy, and chemical proteomics, both to profile the specificity of promising candidates (the better to reduce off-target effects) and identify their intended targets.

Of course, no matter how good a drug is *in vitro*, it is useless in the clinic if it cannot get to where it is needed in the body. Thus, drug developers are also exploring novel delivery strategies, such as next-generation nanoparticulate pharmaceutical drug delivery systems (NDDSs)¹⁰ and nanomaterials. Researchers at Baylor College of Medicine have created a "biodegradable polymer wafer" that could be loaded with an anti-angiogenesis agent to block blood vessel formation after injury to the eye, for instance.¹¹ And in 2013, Samir Mitragotri at the University of California, Santa Barbara, described an oral delivery system for peptides (which normally must be injected) that, extends the principle of a nicotine patch to the small intestine.¹²

Despite these and other advances, drug development continues to be a high-risk venture. In the following pages, we will break down some of the strategies drug developers are using to make that risk more manageable.

II. NEW DRUG CLASSES

When drug developers seek solutions to clinical problems, they can tweak an existing strategy, or invent a new one. In 2013, Ulrik Schulze and Michael Ringel at the Boston Consulting Group attempted to quantify the economics of these two options – that is, of being first to market with a so-called “first-in-class” drug vs. “best-in-class,” in a pre-existing market.¹³ “The data indicated that it is slightly better to be first than to be best,” Schulze and Ringel wrote. According to their analysis, a best-in-class drug that also is first-in-class should recoup 100% of its potential value. But a best-in-class drug released second will capture 88%, while a middle-tier performer that is also first, can capture 92%.

Of course, being first in class has both benefits and risks. “A first-in-class program is one that is on the cutting edge of science. It is a project that is unprecedented scientifically with the goal of generating the first type of drug of its kind,” pharma analyst John LaMattina wrote at *Forbes.com*. “Clearly, the thought of bringing a totally new therapy to patients is very appealing. But novelty doesn’t ensure success.”¹⁴ New drug classes may not work as expected, or produce unanticipated side effects. If they don’t outperform existing therapeutics, they may fail to make a dent in the marketplace.

Nevertheless, manufacturers are devoting considerable resources to first-in-class drug development. “A recent report examining innovation in the drug development pipeline found that 70% of the more than 5,000 new molecular entities being investigated are potential first-in-class medicines,” according to PhRMA.⁵ The FDA approved 113 first-in-class therapeutics between 1999 and 2013. Seventy-eight were identified using “target-based approaches” that home in on specific protein targets, while 25 were developed using “chemocentric approaches,” which start from chemicals or chemical families of known activity. Eight were the result of “phenotypic screening.”¹⁵

First-in-class therapeutics represented a third of new molecular entities approved by the FDA in 2013⁵, and 41% (17/41) in 2014². The 17 first-in-class medicines approved by the FDA in 2014 cover conditions ranging from HCV infection and ovarian cancer, to leishmaniasis and “multicentric Castleman’s disease.” According to an analysis in *C&EN*, 11 are small-molecule drugs; the remainder includes three antibody therapeutics, an enzyme replacement therapy, a peptide, and a phospholipid.² That’s a greater fraction of non-small-molecule drugs (6/17) than among all drugs approved in 2014, of which “a quarter . . . were antibodies, peptides, and enzymes.” By contrast, 24 of 27 new drugs approved in 2013 were small molecules.²

The three first-in-class antibodies approved in 2014 are Keytruda, Sylvant, and Blincyto. According to the FDA, Keytruda (Merck, pembrolizumab) is “the first approved drug that

blocks a cellular pathway known as PD-1 (programmed death receptor-1), which restricts the body's immune system from attacking melanoma cells."¹⁶ The sixth melanoma therapeutic approved since 2011, but just the seventh since 1998, pembrolizumab blocks interaction of PD-1 with its ligands. In one "multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating cohort" trial comprising 173 individuals, the drug caused otherwise unresponsive tumors to shrink in about a quarter of patients.¹⁷ The FDA approved Bristol-Myers Squibb's Opdivo (nivolumab), another PD-1-targeted antibody therapeutic for melanoma, later in 2014.⁴

Sylvant (Johnson & Johnson, siltuximab) and Blincyto (Amgen, blinatumomab) both address so-called "orphan" disorders. Sylvant targets interleukin-6 in patients with "multicentric Castleman's disease" – "a rare disorder similar to lymphoma"¹⁸ – while Blincyto targets patients with "Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL)," a rare form of leukemia.⁸ Blincyto is actually first-in-class in two ways. First, is its mechanism. According to the FDA, "Blincyto is the first approved drug that engages the body's T-cells ... to destroy leukemia cells. The drug acts as a connector between a protein called CD19, which is found on the surface of most B-cell lymphoblasts, and CD3, a protein on T-cell lymphocytes."⁸ Secondly, Blincyto is also the first bispecific antibody of any type to be approved by the FDA. Where conventional antibodies target only a single molecule, bi- or multi-specific antibodies target two or more, serving as a bridge. At least 23 other bispecific antibodies are in clinical development⁹¹, but the only other such molecule to gain regulatory approval to date has been Removab (Trion Pharma/Fresenius Biotech's catumaxomab), a "trifunctional antibody" greenlit in Europe in 2009, which links tumor cells, T-cells, and other immune system actors such as natural killer cells and dendritic cells for the treatment of tumor-associated malignant ascites.¹⁹ As reported in *Nature Reviews Drug Discovery*, blinatumomab was developed using Micromet's "bispecific T-cell engagers" (BiTE) platform, "one of the first to solve the manufacturing problems that had hampered previous efforts to produce bispecifics on a large scale."²⁰ "Micromet's approach is to link two single-chain variable fragments via a polypeptide chain, which has enabled the company to bring forward a pipeline that includes MT110, which targets CD3 and EpCAM to treat advanced solid tumors, and MT111, which targets CD3 and carcinoembryonic antigen CEA to treat advanced gastrointestinal cancers."²⁰ Amgen, which purchased Micromet in 2012, currently lists only one BiTE antibody in its pipeline besides blinatumomab: AMG 211 (MT111), now in phase 1 testing.²¹

At least one additional antibody has received regulatory clearance so far this year. The FDA approved Novartis' Cosentyx (secukinumab), an anti-inflammatory antibody to IL-17A "the first approved psoriasis medication to selectively bind to IL-17A and inhibit interaction with the IL-17 receptor" for moderate-to-severe plaque psoriasis, in January 2015.²² And still more are on the way. According to *C&EN*, the first two PCSK9 inhibitory antibodies,

Amgen's evolocumab and Sanofi/Regeneron's alirocumab, for reducing low-density lipoprotein cholesterol, are expected to receive FDA approval later this summer.⁹⁰

Two first-in-class members of the FDA's class of 2014 replace key polypeptides required for normal physiology, including Myalept (AstraZeneca, metreleptin) and Vimizim (BioMarin Pharmaceutical, elosulfase alfa). The former is an analog of the human hormone leptin "for the treatment of complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy," a rare deficiency of fat tissue.²³ Vimizim is a formulation of the enzyme N-acetylgalactosamine-6-sulfatase, which is missing or deficient in patients with another rare condition, mucopolysaccharidosis type IVA (Morquio A syndrome).²⁴

First-in-class small-molecule therapeutics to win FDA approval in 2014 include two anti-HCV formulations, including Gilead Sciences' once-a-day pill, Harvoni (ledipasvir/sofosbuvir). The drug's prescribing information describes Harvoni as a blend of inhibitors of the HCV proteins NS5A and NS5B, both of which are required for viral replication. Sofosbuvir, a nucleotide prodrug that had already been approved on its own as Solvadi, targets NS5B, the viral RNA-dependent RNA polymerase, acting as a "chain terminator."²⁵ "Harvoni is the first combination pill approved to treat chronic HCV genotype 1 infection. It is also the first approved regimen that does not require administration with interferon or ribavirin, two FDA-approved drugs also used to treat HCV infection," according to the FDA.²⁶ The *New York Times* reported, "In clinical trials, more than 90 percent of the patients treated with Harvoni had no detectable virus in their blood 12 weeks after treatment ended. Doctors say that is considered an effective cure."²⁷

And there were still other first-in-class small molecules approved in 2014, including Kerydin, a tRNA synthetase (protein synthesis) inhibitor targeting toenail fungus (Anacor Pharmaceuticals, tavaborole); Lynparza, a poly-ADP-ribose polymerase inhibitor for treatment of ovarian cancer (AstraZeneca, olaparib); and Belsomra, an orexin receptor antagonist for insomnia (Merck, suvorexant).

European regulators approved 40 new drugs in 2014. According to *Nature Reviews Drug Discovery*, that list has "considerable overlap" with the FDA's, but includes some notable differences.²⁸ One is Chiesi Farmaceutici's Holoclar, a product comprising "ex-vivo expanded autologous human corneal epithelial cells containing stem cells" for the treatment of "moderate to severe limbal stem cell deficiency (LSCD) due to physical or chemical burns to the eye(s) in adults."²⁹ In its press release announcing the approval, the European Medicines Agency (EMA) called Holoclar the "first stem-cell therapy recommended for approval" in the European Union.²⁹ Another difference in approved therapeutics is PTC Therapeutics' Translarna (ataluren), a small molecule that allows translational readthrough of mutant stop codons in Duchenne muscular dystrophy, an orphan indication.²⁸

III. ORPHAN DRUG DEVELOPMENT

As pharmaceutical firms look to expand their businesses, they are not just looking at new drug classes; they also are looking to new indications. One set of indications in which they are investing heavily is one the drug industry traditionally has overlooked: rare, or “orphan” diseases. An orphan disease is one that affects 200,000 or fewer individuals in the United States; 6,000 to 7,000 diseases meet that specification, affecting up to 30 million Americans, according to the National Organization for Rare Disorders.³⁰

Of the 41 new drugs the FDA approved in 2014, 17 (41%) target orphan diseases. “This is significant because patients with rare diseases often have few or no drugs available to treat their conditions,” the FDA noted in its annual roundup of drug approvals.⁷ Nine of the new orphan drugs are small molecules, among them Cerdelga (Genzyme/Sanofi, eliglustat), a glucosylceramide synthase inhibitor for treatment of Gaucher disease type 1, and Zykadia (Novartis, ceritinib), an anaplastic lymphoma kinase (ALK) inhibitor for late-stage non-small cell lung cancer. Zykadia was approved under the FDA’s breakthrough designation program, the fourth such therapeutic to be approved at the time, and one of nine approved in 2014.^{2,45} The remainder includes five antibody therapeutics, a polypeptide (Myalept), an enzyme replacement therapy (Vimizim), and a phospholipid (Impavido, from Paladin Labs).² Eleven of these new orphan drugs also are first-in-class therapeutics. In the classic “blockbuster” drug-development model, pharmaceutical companies target indications that affect huge numbers of potential patients – heart disease, breast cancer, impotence, and so on. The idea, of course, is that by tapping into such broad healthcare markets, companies can reap commensurate rewards. By that calculus, orphan disease drug development makes little sense. Yet drug developers increasingly have been working to address that market. As laid out in a 2013 report in *C&EN*, drug developers have found that rare-disease work can pay big dividends.⁶ “The biotechnology firm Genzyme pioneered the model for rare disease drug development that is followed today: make an impact on a previously untreated rare disease, charge high prices, and be rewarded with significant revenues and a long reign in the marketplace.”

In the United States, the Orphan Drug Act of 1983 “provides economic incentives to encourage development, such as seven years of market exclusivity for an approved product, exemptions from fees for regulatory submission and advice, as well as certain tax credits.”³¹ Similar incentives are in place in Europe and Japan.³² Orphan drug development also provides “a window into common diseases,” according to *C&EN*.⁶ For instance, “the first scientific clue in the development of cholesterol-lowering drugs like Pfizer’s Lipitor ... was the discovery of a cluster of families with a rare, genetic mutation that causes very high levels of ‘bad’ cholesterol.”

There are other potential benefits for orphan drug developers, too, such as accelerated regulatory review and (of necessity) smaller clinical trials.³³ Another benefit is that the majority (80%) of orphan diseases are genetic, and many are caused by a single genetic error, simplifying therapeutics development.^{6,33} Diseases caused by lack of a particular protein, for instance, can be addressed by supplying that protein in trans. BioMarin's newly approved Vimizim is an example of this so-called "enzyme replacement" strategy. Vimizim is a recombinant form of N-acetylgalactosamine-6-sulfatase, the enzyme missing or deficient in mucopolysaccharidosis type IVA.²⁴

Orphan indications also can give new life to seemingly played-out therapeutics. In 2012, for instance, the FDA approved Aegerion Pharmaceuticals' small-molecule drug lomitapide (Juxtapid) for homozygous familiar hypercholesteremia (HoFH), a genetic disease that affects about one in one million individuals. As reported in *C&EN*, lomitapide is a "microsomal triglyceride transfer protein" (MTP) inhibitor originally developed by Bristol-Myers Squibb as a "general-purpose cholesterol treatment."³⁴ The drug failed in Phase 1 trials, but Aegerion, working with its "pharmaceutical services partner" Aptuit, repurposed lomitapide for HoFH, pushing it across the finish line one month ahead of Isis Pharmaceuticals/Genzyme's alternative therapy, mipomersen (Kynamro).³⁴

That being said, rare-disease drug development also poses significant logistical hurdles. For instance, often so little is known about rare diseases that biomarkers of efficacy can be hard to come by, and drug developers may need to perform "natural history studies" of disease progression before they can even initiate clinical trials. And although orphan clinical trials may be small, they are often widely distributed across sites, complicating coordination.³²

Still, the pharmaceutical industry and funding agencies have embraced rare-disease drug development. According to a 2013 report in *Nature Biotechnology*, "The European Commission (EC) has allocated €144 (\$188) million among 26 new research projects, under the global banner of the International Rare Diseases Research Consortium (IRDiRC). In the US, members of PhRMA invested \$49.5 billion in rare disease research and development in 2011 alone, whereas the National Institutes of Health bestowed \$3.5 billion."³⁵

Evidence of this trend is shown in the early 2015 announcement by Shire to acquire rare disease-focused NPS Pharmaceuticals for \$5.2 billion and Meritage Pharma for \$70 million.^{36,37} And late in 2014, BioMarin Pharmaceutical acquired Prosensa, which is developing therapeutics for the orphan condition Duchenne muscular dystrophy (DMD), for as much as \$840 million.³⁸ Prosensa is developing therapeutics based not on enzyme replacement but "exon skipping." The company's drisapersen is an antisense oligonucleotide that binds the DMD pre-mRNA and causes the cellular splicing machinery to skip exon 51 of the DMD gene, restoring the proper reading frame.³⁹ Prosensa announced it had

“commenced the submission process” for a New Drug Application (NDA) for drisapersen, which targets about 13% of DMD patients, in October 2014.⁴⁰

As reported in *The Wall Street Journal*, two other companies also are racing to win FDA approval for the first DMD therapeutic in the U.S.⁴¹ Sarepta Therapeutics’ eteplirsen is a “morpholino” oligonucleotide also based on exon-skipping, while PTC Therapeutics’ Translarna (ataluren) is a small-molecule drug that apparently “enables the ribosome to read through premature nonsense top signals on mRNA and allow the cell to produce a full-length, functional protein.”⁴²

Eteplirsen and drisapersen are members of a new and growing class of pharmaceuticals, nucleic acid-based therapeutics. Along with antibodies, proteins, and cell-based therapies, these represent a rising tide of biologics in drug development overall. As reported in a *C&EN* story on small-molecule chemistry outsourcing in the pharmaceutical industry, “Biologics are hot. Sales are growing at close to 10% per year, and biologics represent nine of the top 20 pharmaceuticals by sales, according to the market research firm EvaluatePharma.”⁴³ Among other things, nucleic acid-based therapeutics can be used to regulate non-coding RNAs, alter transcript processing, and disrupt protein translation. But few oligonucleotide therapeutics have been approved to date, the last being Isis Pharmaceuticals/Genzyme’s mipomersen (Kynamro), a “second-generation antisense oligonucleotide” that inhibits apolipoprotein B100 for treatment of homozygous familial hypercholesteremia.⁴⁴

IV. THE RISE OF “OMICS” TECHNOLOGIES

Perhaps no development has been quite so transformative to life science research – including drug development – as the sequencing of the human genome. “Since 2001, most activities in biomedical research have utilized sequence information in one way or another,” Amgen’s Sasha Kamb and Sean Harper wrote in 2013. “The genome project provided valuable infrastructure—roads and bridges to facilitate and enhance the pace of discovery.”⁴⁶ Coupled with the development of exponentially faster sequencing technologies in the mid-2000s, the decoding of the human genetic blueprint has allowed researchers to identify the genetic roots of phenotype and disease, pinpoint novel drug targets, match patients to therapies, and more. Indeed, the sequencing of the human genome has made “personalized medicine” possible.

But there's more to the resulting technological revolution than genomics per se. The genomics era has ushered in a whole host of highly parallelized, genome-scale technologies, many of which also are changing the way drugs are developed.

EPIGENETICS-FOCUSED DRUG DEVELOPMENT

There is increasing awareness, that the state of DNA or histone modification, as well as expression of both coding and non-coding genes, can play a role in disease. The umbrella term for such phenomena is "epigenetics," or at the genome scale, "epigenomics."

One 2012 review, entitled "Epigenetic protein families: A new frontier for drug discovery," described the so-called "druggable epigenome" – the epigenetic analog of the "druggable genome," that subset of genes that encode enzymes or receptors, the traditional targets of pharmaceutical research.⁴⁷ The druggable epigenome includes enzymes that read, write, and erase chemical modifications to DNA and histones, such as histone deacetylases. In *Genetic Engineering & Biotechnology News*, technical editor Patricia Dimond explained how drug developers could exploit such enzyme activities: "Inhibition of histone deacetylases (HDACs) results in hyperacetylation of histones and modulates gene expression by creating an open chromatin state that leads to expression of previously silenced genes. Although the mechanism of action is not fully understood, inhibiting HDACs has been observed to result in cell cycle arrest and apoptosis of cancer cells."⁴⁸

A handful of HDAC inhibitors have been approved by the FDA to date, and still more are in development: A 2012 review in *Nature Reviews Drug Discovery* lists 16 in development and two approvals.⁴⁷ The most advanced of those then-in-development compounds was panobinostat. In February 2015, the FDA approved panobinostat (Novartis' Farydak) for treatment of multiple myeloma following a Phase 3 study of 193 patients in whom the drug extended progression-free survival from 5.8 to 10.6 months.⁴⁹

TRANSCRIPTOMICS

Researchers are also using gene-expression fingerprints – i.e., transcriptomics data – to detect potentially dangerous side effects early in development. Increasingly, such data are acquired using next-generation DNA sequencing technology, but DNA microarrays may also be used. In one recent study, researchers affiliated with Janssen Pharmaceuticals' Quantitative Structure Transcriptional Activity Relationships (QSTAR) project used some 1,600 Affymetrix DNA microarrays to measure the transcriptional impact of 757 compounds representing eight distinct pharmaceutical projects.⁵⁰

In three of the eight cases, "the data provided clear go/no-go decisions;" another three yielded "novel biological insights" but not "direct decision support." In the remaining two cases, neither of these benefits emerged.⁵⁰ In one example highlighted in the study, three

potential antipsychotics were found to adversely affect tubulin gene expression, leading to apparent genotoxicity. Though they acknowledge that such data are limited in that they do not necessarily reflect metabolite or protein abundance, the team concluded that “transcriptional profiling experiments can contribute to decision making during the lead optimization phase of drug discovery projects.”⁵⁰

CHEMICAL PROTEOMICS

Another increasingly popular “omics” strategy involves chemical proteomics. Chemical proteomics, writes Evotec’s Henrik Daub in a 2015 review in *ACS Chemical Biology*, “combines the affinity capture of small molecule targets from cell or tissue extracts with protein identification by mass spectrometry (MS).”⁵¹

Among other applications, the method may be used to assess drug selectivity – that is, to identify what other proteins a compound hits besides its intended target.⁵² In that case, Daub notes, chemical proteomics offers the benefit that it “is closely linked to the physiological environment as compounds are profiled against endogenously expressed, post-translationally modified full-length proteins in the presence of cellular cofactors and complex partners.”⁵¹

In one example, Bernhard Kuster, of Technische Universität München, and colleagues applied an “optimized chemical proteomics assay for kinase inhibitor profiling” to test nine “approved or very advanced kinase inhibitors” against the entire human kinome in cell lysates.⁵³ Some of the compounds proved far less specific than might be desired, the team found – a fact that could lead to unwanted side effects. For instance, “Dasatinib is quite unselective but still preferentially targets tyrosine kinases, whereas Sunitinib targets can be found across many families.”⁵³

Another application of chemical proteomics is identification of targets for drugs that have been identified via phenotypic screens.⁵² In December 2014, a team of French researchers used this approach to identify the parasite protein targets of the antimalarial compound, albitiozolium.⁵⁴ The team created a bifunctional derivative of albitioazolium that is both “photoactivatable and clickable” to “covalently crosslink drug-interacting parasite proteins *in situ* followed by their isolation via click chemistry reactions.”⁵⁴ They then digested the crosslinked proteins down to peptides and analyzed them via mass spectrometry, identifying 11 interacting proteins. Many of these were involved in “plasma biogenesis and dynamics,” including a putative choline/ethanolamine phosphotransferase, suggesting a potential biochemical mechanism for drug activity.

V. STEM CELL AND GENOME EDITING TECHNOLOGY

Another rapidly developing technology that is altering the modern drug development workflow is stem cells, and in particular, human pluripotent stem cells. Pluripotent stem cells are perpetually renewable – that is, they divide indefinitely – and can differentiate into any cell type in the body. They exist in two forms, embryonic stem (ES) cells, in which a pluripotent cell is removed from an early-stage embryo, and induced pluripotent stem (iPS) cells, in which terminally differentiated cells are returned to a pluripotent state via the transient expression of a handful of transcription factors.

Though both cell types elicit considerable excitement in the research community, iPS cells offer substantial benefits for drug developers.⁵⁵ For one thing, they don't require human embryos. iPS cells also allow researchers to insert genetic diversity into their development workflow, enabling what Estelle Doudement and Hirdesh Uppal of Genentech in 2014 called a "clinical trial in a dish":

*"Currently, human clinical populations are poorly represented in drug development with a lack of genetic heterogeneity in human cellular models and a limited number of human disease models. With the 2006 discovery of induced pluripotent stem cell (iPSC) technology, researchers can generate pluripotent stem cells from adult somatic cells, preserving the genetic information within those cells. As a result, new cellular models can be created from individuals with a diverse range of drug susceptibilities and resistances, offering the premise of a "clinical trial in a dish" in a field where a personalized medicine approach is becoming increasingly predominant."*⁵⁶

DISEASE MODELING

That latter point in the previous section is key for researchers and drug developers alike: Because iPS cells may be created with cells from both diseased and healthy individuals – and retain the donor's genetic profile – they provide a platform for disease modeling.⁵⁷

Rather than trying to obtain part of a precious biopsy from a diseased individual, for instance, researchers can use more easily acquired epithelial cells, reprogram them to pluripotency, and differentiate them into the cells of interest, such as motor neurons or cardiomyocytes. In this way, researchers can not only obtain a limitless supply of these cells – which often are hard to access otherwise – they can also study how a mutation or environmental conditions can cause normal cellular development to go awry. That is, they can study disease progression. A wide variety of diseases has been modeled in this way; one 2014 review lists 24, representing more than 30 genetic mutants.⁵⁷

Recently, Stanford University researcher Joseph Wu and colleagues created iPSC cells from 10 individuals with familial hypertrophic cardiomyopathy, an inherited form of heart disease. When those cells were differentiated into cardiomyocytes, the cells exhibited a phenotype consistent with the human disease, including both enlarged and multinucleated cells and “electrophysiological and contractile arrhythmia.”⁵⁸ The team’s analysis suggested that “dysregulation of calcium cycling and elevation in intracellular calcium are central mechanisms for disease pathogenesis,” and treatment of iPSC cell-derived cardiomyocytes with multiple calcium channel blockers alleviated the cellular phenotype.⁵⁸

Similarly, Ellen Sidransky and colleagues at NIH, created iPSC cells from five individuals with Gaucher disease, a lysosomal storage disease caused by a deficiency of glucocerebrosidase, which mostly affects macrophages.⁵⁹ Because patient-derived macrophages are hard to come by, the team differentiated their iPSC cells to monocytes and then to macrophages, which – like the disease itself – displayed diminished glucocerebrosidase activity and elevated glucosylceramide and glucosylsphingosine levels. The cells also exhibited deficiencies in reactive oxygen species production and chemotaxis – phenotypes that could be reversed using a previously identified “noninhibitory chaperone” (NCGC00188758), which causes the mutant enzyme to fold and function properly.⁵⁹

DRUG DISCOVERY

Such cellular models provide novel platforms for investigating disease pathophysiology, of course. But they also enable new drug discovery strategies as well. “iPSC models hold immense promise for the development of more effective drugs to better manage human diseases,” Hans Schöler, of the Max Planck Institute for Molecular Biomedicine, and colleagues wrote in 2014.⁵⁷ Schöler and colleagues identify four key applications for iPSC cells in drug discovery, including screening for new pharmaceutical compounds.

iPierian Inc., a biotechnology company that uses iPSC cells as a platform for disease research and drug development, has developed a novel antibody therapeutic targeting secreted Tau protein, which is involved in the progression of so-called “tauopathies,” a form of neurodegenerative disease. “iPierian’s monoclonal antibody program for Tau is based on novel Tau discoveries made using the company’s proprietary induced pluripotent stem cell (iPSC) technology,” the company said in a late 2013 announcement of “promising in vivo efficacy results” in a mouse model of Alzheimer’s disease.⁶⁰ The company said at the time that it planned to file an Investigational New Drug (IND) application with the FDA in 2014.⁶⁰ Six months later, Bristol-Myers Squibb acquired the company for \$175 million upfront and up to \$550 million more, assuming successful achievement of certain milestones.⁶¹

On the academic front, researchers at the Johns Hopkins University School of Medicine and NIH generated iPS cells derived from patients with alpha-1 antitrypsin (AAT) deficiency, a hereditary liver condition that can necessitate liver transplantation. The team differentiated those iPS cells into “hepatocyte-like cells” and used them to screen for new therapeutics from a library of 3,131 compounds, identifying five that reduced accumulation of the AAT protein, as measured by fluorescence intensity using a labeled antibody.⁶²

Lee Rubin, at Harvard University, and colleagues screened a 5,000-compound library against mouse embryonic stem cell-derived motor neurons, looking for molecules that increased cell survival and retained normal cell morphology in a model of amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig disease.⁶³ The screen identified the GSK-3 inhibitor kenpaullone, among other hits, as a potential ALS therapeutic, and validated those results by testing the compound on human ALS patient-derived iPS cells.

TOXICITY TESTING

Another application of iPS cells is assessing drug-induced cardiotoxicity. Existing toxicity testing platforms, such as animal models or transgenic cells, are not sufficiently accurate to reliably catch cardiotoxic compounds before they reach the clinic, Stanford’s Wu explained in a 2014 Perspective in *Science Translational Medicine*. “Numerous drugs against aches (propoxyphene), weight loss (sibutramine), inflammatory disease (rofecoxib), and gastrointestinal disease (cisapride) were recently withdrawn from the market owing to structural damage or apoptosis of cardiomyocytes, induction of arrhythmias, seizures, or sudden cardiac death.”⁶⁴

Drug developers obviously want to minimize such cases, and indeed, the FDA generally mandates that they do so: In its industry guidance for drug compound “safety pharmacology studies,” the FDA’s Center for Drug Evaluation and Research recommends developers assess drug impacts on “vital functions,” including the cardiovascular system.⁹² Yet primary cardiac tissue from patients is not easily obtained for testing, nor is it easy to grow in culture. But by using iPS cells and increasingly well-defined differentiation protocols, researchers can create as many cardiomyocytes as they like, from both normal and diseased donors, and test candidate compounds before expending the time and money to advance them into the clinic. In 2013, Wu and colleagues offered proof of principle for this idea by creating a library of patient-derived iPS cells from individuals with any of three cardiac-related genetic conditions. They then differentiated those cells to cardiomyocytes, and tested them against a panel of “drugs known to interact with different cardiac ion channels.”⁶⁵ The cells, the team reported, “exhibit distinct in vitro phenotypes associated with the ... patients from which they were derived.”

PATIENT STRATIFICATION

Other applications for iPS cells Schöler identified include identifying patients likely to respond to a therapy and pinpointing “new ‘druggable’ targets.” As an example of the former, Schöler wrote, consider Alzheimer disease (AD). AD may not be a single disease but a “collection of different disease with different causes that require different treatments.” To ensure patients receive the correct therapies, “panels of iPS cells would be generated from patients with AD, differentiated into neurons and tested for drug responsiveness. These results could then be correlated with the genotype to identify mutations that could be used to stratify patients, so that patients who are likely to respond would be selected for treatment with a drug.”⁵⁷

GENOME EDITING WITH CRISPR/CAS9

iPS cell technology dovetails nicely with another emerging technology: genome editing. Genome editing involves a suite of technologies that allow researchers to make surgical changes to genomic DNA *in situ*.⁶⁶ The earliest editing technologies – DNA meganucleases, zinc-finger proteins (ZFNs), and transcription activator-like effector nucleases (TALENs) – used engineered DNA-binding nucleases to recognize and cut specific sequences, at which point the cellular DNA-repair machinery takes over, introducing or repairing a mutation, or inserting an exogenous sequence as desired. The newer CRISPR/Cas9 system relies on the same cellular processes, but is RNA-guided: Users simply design a short RNA molecule complementary to the sequence they wish to target, and the RNA-guided Cas9 nuclease does the rest.⁶⁷

CRISPR/Cas9 is derived from a bacterial adaptive immune system. The system allows bacteria to remember infection by viruses, cleaving viral DNA with the Cas9 nuclease at a site determined by the sequence of a short RNA. Researchers have turned the system into a versatile biotechnology tool and adapted it to eukaryotic cells, allowing them to mutate and repair genes in genomic DNA, as well as (using a modified Cas9 enzyme) to control transcription.⁶⁷ Several companies are exploring applications of the technology as a direct therapeutic to “repair” defective genes or make cells resistant to pathogen infection. Others are using the technology to drive drug discovery and validation efforts, by creating cell lines with specific mutations or genetic variants.

C&EN reported in February 2015, that AstraZeneca had established collaborations with the Wellcome Trust Sanger Institute in the UK, the Broad and Whitehead institutes in Cambridge, MA, the Innovative Genomics Initiative, and Thermo Fisher Scientific, to “exploit” CRISPR/Cas9.⁶⁸ According to the report, AstraZeneca will use the technology “widely to identify and validate drug targets in preclinical disease models.” Novartis has

adopted CRISPR technology, too, according to *Nature Reviews Drug Discovery*, partnering with Caribou Biosciences to “gain access to Caribou’s CRISPR–Cas9 platform ‘to research new CRISPR-based drug target screening and validation technologies.’”⁶⁹ Naturally, CRISPR technology may be paired with iPS and other human pluripotent stem cell research, for instance to create isogenic control cell lines: cell lines that vary at only a single genetic locus.⁵⁵ Such lines are key controls for distinguishing mutations associated with a given phenotype from those that are not – a key consideration when studying complex diseases potentially involving multiple genetic loci.⁵⁷

Rudolf Jaenisch, of the Whitehead Institute, and colleagues described an example of this application in a pair of papers published in 2011 and 2013 on Parkinson’s disease. In 2011, Jaenisch’s team created pairs of isogenic cell lines by using ZFNs to repair Parkinson’s disease mutations in patient-derived iPS cells or to introduce Parkinson’s mutations into otherwise normal human embryonic stem cells, demonstrating that the cells retained the ability to differentiate into neurons.⁷⁰ Two years later, Jaenisch, with Susan Lindquist, also of the Whitehead Institute, used these same cells (as well as yeast models) to identify biochemical changes in iPS cell-derived neurons from Parkinson’s patients, and to correct them using a ubiquitin ligase-targeting N-arylbenzimidazole compound previously isolated from a yeast screen.⁷¹

VI. DRUG FORMULATION

Once a therapeutic target and active drug have been identified, development doesn’t stop there, of course. The drug also has to get to where it’s needed, and avoid (or at least minimally impact) the areas where it is not, making the therapeutic only as good as its delivery system.

DRUG DELIVERY TO THE EYE

One drug delivery approach that has received attention of late is the eye. In one recent example published in *ACS Nano*, Baylor College of Medicine researchers Stephen Pflugfelder and Ghanashyam Acharya described an “ocular drug delivery nanowafer” that could improve corneal recovery following a corneal burn.^{11,72} Current methods for drug delivery to the eye, such as eye drops, are problematic, Pflugfelder and Acharya explained in their study. Between rapid blinking, tearing up, poor drug absorption, and rapid

clearance, an indeterminate and often relatively low level of therapeutic agent will reach its target via droplet administration, thus necessitating repeated dosing and increasing the likelihood for discomfort, toxicity, and patient noncompliance.⁷²

To address those problems, Pflugfelder and Acharya developed “a tiny transparent circular disc that can be applied on the ocular surface with a fingertip and can withstand constant blinking without being displaced. It contains arrays of drug-loaded nanoreservoirs from which the drug will be released in a tightly controlled fashion for a few hours to days.”⁷² Following drug release, the wafer, made of poly(vinyl alcohol), “will dissolve and fade away,” simplifying its use.

Wafers loaded with 5- μ g of the anti-angiogenic tyrosine kinase inhibitor axitinib were used to block corneal neovascularization (which impede vision) in a mouse model of ocular damage, and compared with axitinib eye drops delivered twice a day. The results demonstrated “a strong therapeutic effect” compared to untreated or droplet-treated mice, the authors noted, as well as reduced corneal expression of angiogenic growth factors.⁷² Another recent study from researchers at Northwestern University and the University of California, Los Angeles, described a drug-infused “nanodiamond” hydrogel fashioned into a contact lens for the purpose of slowly releasing an anti-glaucoma medication.⁷³ Nanodiamonds are just what they sound like – “faceted carbon particles about 5 nm in diameter.”⁷⁴ The researchers “coated the nanodiamonds with a polymer, polyethyleneimine. Then, in the presence of the glaucoma drug timolol maleate, they crosslinked the polymer-coated nanodiamonds to the polysaccharide chitosan, trapping the drug in the resulting gel. When lysozyme, an enzyme in tears, cleaves chitosan, the gel begins to break down and the drug leaches out.”⁷⁴ The authors did not test their design on an actual eye, but the eluted compound retained efficacy on human cells, they reported.⁷³

AVOIDING NEEDLES

Other researchers have devised alternatives to injectable therapeutics, a common route of administration for biologics, which generally cannot be taken orally.⁷⁵

In a 2014 review, MIT chemical engineer Robert Langer and colleagues noted, “Intravenous, intramuscular and subcutaneous injections are currently the most commonly used ways of delivering biopharmaceuticals.”⁷⁵ But in most cases, regardless of the route of administration, these compounds are cleared rapidly from the body, “meaning that frequent injections are required.” The review described multiple strategies researchers have explored to improve biopharmaceutical drug delivery and efficacy, including microparticles, nanoparticles, “depot injections,” and transdermal delivery.⁷⁵

In one example of the latter, researchers in the lab of Joseph DeSimone at the University of North Carolina, Chapel Hill, reported in 2013 a novel method for generating flexible

arrays of dissolvable microneedles for transdermal drug delivery.⁷⁶ Microneedle arrays typically are made either of metal or silicon, which must be removed following delivery, or a biodegradable material, which can result in incomplete dosing. DeSimone's alternative is PRINT (Particle Replication in Non-wetting Templates), a method for fabricating biodegradable needles on a water-soluble backing. The PRINT process is akin to filling a microscopic ice-cube tray. "The researchers first make a perfluoropolyether mold covered with pyramid-shaped holes. Then they fill this 'ice cube tray' with a mixture of polyvinylpyrrolidone and either enzymes or nanoparticles. Finally, they add to the needles a backing layer made of water-soluble polymer and then peel the whole assembly out of the mold. When gently pressed into excised human skin or live mouse skin, the microneedle patch punctures the surface and then releases its cargo as it degrades.... The backing layer dissolves after exposure to a few drops of water."⁷⁷

In their preliminary study, DeSimone's team loaded their needles with rhodamine, a fluorescent dye.⁷⁶ At the 2014 American Chemical Society national meeting, however, DeSimone lab graduate student (and first author on the 2013 paper) Katherine Moga extended those findings, reporting that "when encapsulated in the needles, the model enzyme butyrylcholinesterase remained almost 100% active. Similarly, polymer nanoparticles stayed intact during the microneedle fabrication process, which bodes well for the tiny hypodermics one day being used to deliver vaccines and nanomedicines."⁷⁷

Boston-based Entrega is pursuing yet another approach to avoiding injections: biologics delivered via pill. As reported in the *Boston Globe*, "Entrega's approach isn't too different from the way nicotine patches work when affixed to the skin. Except Entrega is designing miniature circular patches—the company calls them wafers—that would be packed into a capsule. Once swallowed, the capsule carries its cargo of drug-infused patches through the stomach and into the small intestine, where it dissolves and releases the wafers."⁷⁸ Once released, these wafers attach to the lining of the small intestine, where their payload is released over several hours. In late 2014, *C&EN* reported that Entrega was working with Google's "Google X" laboratory to adapt its delivery mechanism into a platform for Google's newly announced remote diagnostics concept.¹²

LONG-ACTING FORMULATIONS

Long-acting formulations simplify drug delivery and dosing, reducing the number of times a patient must be injected. One company developing such formulations is Dublin-based Alkermes, whose aripiprazole lauroxil is a once-monthly injectable form of the anti-schizophrenia oral medication, aripiprazole (Bristol-Myers Squibb's Abilify). In top-line phase 3 trial data announced in April 2014, the company said, "Patients treated once monthly with either 441 mg or 882 mg of aripiprazole lauroxil demonstrated statistically significant reductions from baseline in Positive and Negative Syndrome Scale (PANSS) total scores at week 12, compared to placebo ... which was the prespecified primary endpoint in the study."⁷⁹ The company filed a new drug application with the FDA in August.⁸⁰

As reported in *Xconomy.com*, in a news report describing the phase 3 data, “long-acting injectables are gaining steam. Citing IMS Health data, for instance, Cowen & Co. analyst Anant Padmanabhan wrote in a recent research note that long-acting injectables could double in market share over the next five years due in part to an ‘increased emphasis’ in hospitals on preventing people from relapsing.”⁸¹

Another strategy Langer’s review describes is implantable pumps, which can be used, among other things, to free diabetics from their daily insulin injections.⁷⁵ One such system is ITCA 650, a once- or twice-yearly “subcutaneous osmotic mini-pump” from Boston-based Intarcia. The “matchstick-sized” ITCA 650, “which primary care physicians insert under a patient’s skin in less than five minutes, combines an approved mini-pump and an existing drug: the active ingredient in the once-weekly glucagon-like peptide-1 (GLP-1) agonist AstraZeneca’s Bydureon (exenatide).”⁸²

In October 2014, Intarcia announced top-line results from two phase 3 clinical trials of ITCA 650.⁸³ Four hundred sixty individuals with type 2 diabetes were given pumps that delivered either placebo or 40 or 60 micrograms per day of exenatide. Glycated hemoglobin (HbA1c) levels – a diabetes biomarker – decreased over 39 weeks by an average of 1.4% to 1.7% in patients with baseline levels of 7.5% to 10%, and by up to 2.1% in patients with baseline levels above 8.5%. A separate, open-label trial for “uncontrolled” patients with HbA1c baselines between 10% and 12% yielded a 3.4% decrease at 39 weeks. (Complete data will not be released until June 2015.)⁸³

These are positive results, and the company is understandably bullish.⁸³ Yet according to *Nature Biotechnology*, the innovation with ITCA 650 lies not with the drug per se but in its stabilization and formulation: “The underlying formulation technology also stabilizes other proteins, peptides, antibody fragments and small molecules at body temperature for up to 3.5 years, opening up other drug development options.”⁸²

NANOPARTICLES

Another increasingly popular delivery strategy is drug-filled nanoparticles, sometimes called “nanoparticulate pharmaceutical drug delivery systems” (NDDSs).¹⁰ According to a recent review by Vladimir Torchilin at Northeastern University, NDDSs – which include designs ranging from liposomes and metal nanoparticles to carbon nanotubes and dendrimers – “can overcome several problems that are associated with traditional drugs, such as poor aqueous solubility, low bioavailability and nonspecific distribution in the body.”¹⁰

For example, NDDSs can increase therapeutic retention time in the circulation (relative to an unpackaged drug) by coating the particles with polyethylene glycol, direct drugs to tumors or other pathologies with targeting agents such as antibodies or peptides, and

make otherwise toxic compounds usable by reducing unwanted exposure. Originally, Torchilin wrote, NDDSs “mainly aimed to address single challenges, such as the need to increase drug stability in vivo and the circulation time in the blood, or the need to target a drug to a specific tissue or pathology.” But new “multifunctional” designs have now been created, including particles that can respond to combinations of both internal and external stimuli for more precisely targeted therapeutic delivery.¹⁰

A recent study described a trifunctional nanoparticle capable of releasing precise ratios of three anticancer drugs – doxorubicin, camptothecin, and cisplatin – with three distinct triggers.⁸⁴ The research team, led by Jeremiah Johnson of MIT, used so-called “brush-first” ring-opening metathesis polymerization (ROMP) to assemble nanoparticles containing precise levels of the three therapeutics. The final particles release doxorubicin in response to UV light, camptothecin in response to an “endogenous enzyme,” and cisplatin in response to “a redox reaction induced by endogenous glutathione.”⁸⁵

The team tested their particles on OVCAR3 human ovarian cancer cells in culture dishes. “The three-drug nanoparticles, with ratios matched to maximum tolerated doses of each of the drugs, were better than corresponding one- and two-drug-loaded nanoparticles at killing cultured ovarian cancer cells.”⁸⁵ This nanoparticle design allows researchers to optimize combination therapy dosing.⁸⁵ And still more complex designs are possible. As Johnson and his colleagues noted, “This approach has no fundamental limitation in terms of the number and ratio of molecular species that could be built into particles, as long as the molecules of interest possess addressable functional groups that are compatible with ROMP.”⁸⁴

Cancer is a popular target for nanoparticle developers. Researchers at the University of Illinois at Urbana-Champaign recently described a polymeric nanoparticle called NanoVenin that’s capable of targeting scorpion venom peptides specifically to cancer cells – a strategy that potentially makes the toxins, which otherwise don’t distinguish between healthy and diseased cells, medically useful.⁸⁶

Blend Therapeutics, based in Watertown, MA, is developing nanoparticulate delivery vehicles for its antibody-drug conjugate (ADC) analogs, called “miniaturized biologic drug conjugates” (mBDCs). As described in a report at *Xconomy.com*, Blend’s therapeutics address a key limitation of current ADCs – that they are “more effective” against blood cancers than solid tumors, “because they typically have a hard time penetrating solid organs, or solid tumors very well. . . . So Blend—which was essentially making conjugated drugs anyway—figured it had the solution. Why not, according to cofounder and chairman Omid Farokhzad, use nanotechnology to create ‘an ADC specifically engineered and designed for solid tumors?’”⁸⁷ Unlike ADCs, which are based on antibody targeting, Blend’s

mBDCs (called Pentarins) use smaller targeting moieties, such as peptides or antibody fragments. The resulting construct is then encased in a “polymeric” nanoparticle to enable “tunable biodistribution of the conjugate, with enhanced accumulation in the tumor tissue.”⁸⁸ Blend’s first Pentarin, BTP-277, whose molecular target has yet to be named, will address non-small cell lung cancer, and is slated to enter clinical trials in 2016.⁸⁷

VII. CONCLUSION

Drug development is a fluid and ever-changing space. Technological and regulatory developments combine to make what once seemed impossible (or at least impractical) feasible. The Orphan Drug Act has paid huge dividends for the industry and patients alike: The FDA has approved some 450 orphan drugs since the Act’s passage, many for indications for which no alternative therapies exist.⁵ A comparable number of orphan drugs are currently in development.⁸⁹

Small-molecule pharmaceutical development has given way, at least in part, to novel therapeutics classes, such as antibody-drug conjugates, bispecific antibodies, and nucleic acids. Small molecules accounted for three-fourths of the new drugs FDA approved in 2014 – a majority to be sure, but still less than the 89% (24/27) they represented just a year before.² *C&EN* reported earlier this year that French pharmaceutical maker Sanofi “bragged recently that 72% of its drug discovery and development projects these days are in biologics.”⁴³

Those discovery efforts increasingly are being driven by novel technologies, particularly from the genomics and stem-cell spaces. Using induced pluripotent stem cells and genome editing, drug developers now have the ability to create cellular models without having to rely on precious patient samples. Should an interesting variant appear in the literature, they can simply insert it into otherwise healthy cells and see what it does. Increasingly, developers are using such cells to both enhance their understanding of disease processes and develop pharmaceuticals to block them. And thanks to genomics, they can complement such studies with chemical proteomics to identify the protein targets of the promising agents that emerge.

Even still, the development process isn't complete, because a drug is only as useful as its ability to get where it's needed. Drug developers are becoming ever more clever in their ability to tune these properties, using nanotechnology to keep drugs in the circulation and minimize side effects.

Pharmaceutical companies spent some \$51.1 billion on research and development in 2013, nearly twice the amount spent in 2000.⁵ Their investments have been rewarded with nearly 70 FDA approvals in the past two years. Nobody knows what the future will bring. But given the tools that increased funding has purchased, and the fantastic returns they have brought for both industry and their clients, it's a safe bet the innovation will continue for some time to come.

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