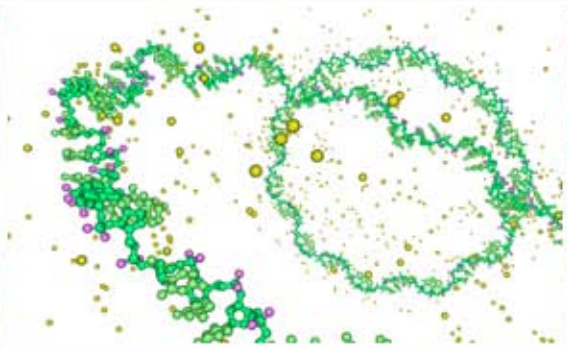
Pharmaceutical Chemistry: Drug Development Goes Deeper Into the Genome



A white paper addressing the genomic and molecular research being used by the pharmaceutical industry to develop the newest generation of targeted medicines.

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Pharmaceutical Chemistry: Drug Development Goes Deeper Into the Genome

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ABOUT THIS REPORT

I. EXECUTIVE SUMMARY

Ten years after the first completed sequences of the human genome, the promise of genomic medicine seems to many to have fallen short.[1] But the progress of pharmaceutical chemistry in that time period tells a different story, one in which an explosion of knowledge and data since 2001 has led drug discovery and development in some unexpected directions.

Protein-based and small molecule drug candidates are more selective and varied than ever, thanks to massive, genome-era databases that R&D scientists rely on for screening and design. Drug delivery and testing have benefited from similar data and an increasingly detailed picture of how disease operates at a molecular level. The genome revolution has also brought new "characters" to R&D operations, such as gene silencing molecules that function as both therapies and exploratory tools.

However, there remains a problematic lag between the information gathered about the molecular basis of disease and its translation into new drugs or drug targets. While there is a proliferation of drug candidates and drug targets, the U.S. Food and Drug Administration has approved very few new medicines in the past decade. Researchers and pharmaceutical companies expect that the next 20 years will be marked by the advance of personalized medicine, in which individual genome and proteome screening will be paired carefully with drugs specifically targeted to a person's molecular makeup. But progress in the search for biomarkers that would provide an individualized profile of disease has been slower than expected. At the same time, the more complex landscape of disease revealed by molecular research has made it more difficult and costly to design and test treatments, further slowing the appearance of new medicines. New technologies and new economic realities—from a global recession to the end of the current era of blockbuster drugs—are bringing together new partnerships in drug discovery. The future of drug discovery and development has already been profoundly affected by a weaker economy and it remains to be seen how the industry will respond to the "patent cliff" affecting the blockbuster drugs of the 1980s and 1990s.

II. Underlying Trends in 21st-Century Drug Discovery and Development

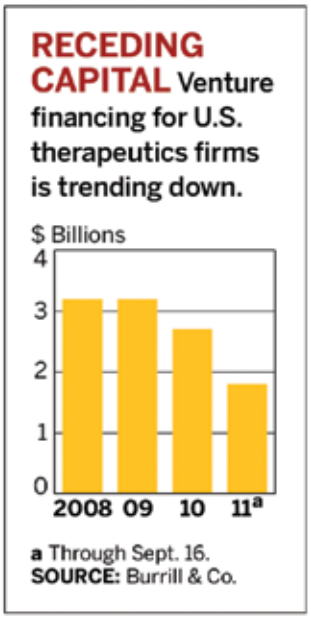
Patient need, advances in technology and commercial constraints are always among the drivers of drug discovery and development, but the form that these drivers take today is shaped by the worldwide economic downturn and the rise of genomic, personalized medicine.

After a relatively slow period over the past decade, the number of drug approvals by the U.S. Food and Drug Administration increased in 2011. The increase, however, was mainly due to the agency's work to clear a backlog of approvals rather than an industry-wide uptick in productivity. The FDA approved 35 new medicines in fiscal year 2011, including most notably more drugs paired with diagnostic testing to "personalize" and match them to specific patient groups, and new drugs for orphan diseases. Last year's approval rate was the second-highest in the decade, surpassed only by the 37 medicines approved in 2009.[2]

REVAMPING THE DIRECTION OF DISCOVERY

But the so-called "patent cliff" looms large for many large pharmaceutical companies, who are facing or will soon face the expiration of patents for some of the best-selling drugs of all time. In 2012 alone, Merck and Co. will lose patent protection for its asthma drug Singular, its biggest seller, while Bristol-Myers Squibb/Sanofi Pharmaceuticals will lose protection for its widely-prescribed blood-thinner Plavix. Pfizer's cholesterol drug Lipitor, the top-selling medicine of all time, went off-patent in late 2011.

Looking for ways to restructure after these losses, larger pharmaceutical companies are making substantial purchases of promising biotechnology start-up companies to refill their discovery and development pipelines. These buyouts are beginning to energize an industry at an R&D crossroads, battered by a weak global economy.[3]



Even as they purchase smaller companies and their products as a whole, big pharma companies are cutting back on their own costly R&D operations, preferring instead to rely on outside partners for the early stages of drug discovery and development. These outside partners include contract

research organizations (CROs) including academic labs, government agencies and even patient advocacy and disease foundations. They do much of the work that used to belong to the R&D arm of larger companies, including compound screening, synthetic development and clinical trials support.[4]

Rising health care costs and a national debate over health care reforms have also made translational research a policy priority. In practice, this means that pharmaceutical companies will be outsourcing this role to some extent as the U.S. government becomes more heavily involved in ensuring that translational research takes place. The National Institutes of Health's National Center for Advancing Translational Sciences, which made its debut in 2011, announced in May of 2012 that it would be partnering with large pharma companies such as Pfizer and Eli Lily & Company. Under the proposed partnership, government-funded researchers would be available to test promising compounds generated by commercial R&D.[5]

PUSH FOR PERSONALIZED MEDICINE

As medicine moves toward a more personalized, patient-driven model, the impetus and specific goals of drug R&D are increasingly the result of a partnership between pharmaceutical companies, patient advocacy groups and insurance companies. This partnership can identify where drug development and delivery problems exist, and bring insight into how therapies affect individual patients. At the same time, treatments are moving away from doctors' offices and hospitals into homes and workplace clinics, and new technologies are needed to ensure that therapy is portable and personal.

In part due to the concerns of patient advocacy groups, the National Institutes of Health has announced that it would refocus some of its genomic sequencing efforts with an eye to specific medical applications. Under the new plan, the National Human Genome Research Institute will direct about $100 million between 2012-2014 to three new priority areas: sequencing to find the causes of rare inherited diseases, evaluating the ethical and societal impacts of sequencing, and finding new ways to access and interrogate the huge and growing databases created by sequencing efforts.[6]

Insurers looking for drug alternatives, especially as generics expand a formerly narrow medicine market, have driven some pharmaceutical companies to focus their discovery operation on best-in-class instead of first-in-class drugs. This strategy of drug development relies on several new tools of the genomic era revolution to succeed, including screening tools like the mass spectrometer (see Chapter VII) that can reveal small differences within the molecules of a certain class of drugs.[7]

INTERNATIONAL TRENDS IN R&D

Companies outside the United States, particularly in China and India, are also joining the ranks of CROs. But many of these companies, already established as reliable generics manufacturers, have sought to make a separate name for themselves in drug R&D.

In particular, the new epicenter of R&D startups is shifting to China, where experienced researchers (often trained in the United States or Europe), available capital, and a population in need of new medicines and therapies has combined to make the nation a logical place for new R&D.[8]

The trend is well-illustrated by firms like HEC Pharm in China, which doubled its technical workforce to 1200 researchers at its R&D complex from 2011 to 2012.[9]

As part of its lab buildup, HEC Pharm has equipped a liquid chromatography area that it calls its HPLC forest

It plans to introduce its new drugs in the China market before moving on to other developed markets. In part, this strategy is used because under Chinese regulations, the approval for a new drug in China is not dependent on the new medication being superior to an existing drug. HEC Pharm's development pipelines as of 2012 include compounds for cardiovascular, antiviral, antitumor, and neurological compounds.

III. New Pathways for Drug Discovery in the Genome Age

Some analysts have seen a perfect storm in the world of drug discovery over the past two to three years. The pace of discovery has lagged, at the same time that the blockbuster drugs of the past decade have come to the end of their patent life and a worldwide economic recession has made R&D investment more tenuous.

Hidden inside the storm, however, is the lightning-strike potential of genome-based drug discovery. More than ten years after the first human genomes were sequenced, researchers have substantially advanced our understanding of the molecular basis of disease and the potential molecular targets for therapy.

At the same time, there remains a lag between the information gathered about the molecular basis of disease and its translation into new drugs or drug targets. The lag may exist simply because drug discoverers in the pharmaceutical genomics age have the challenge of finding therapies for which no suitable treatments have been discovered, by exploring molecular pathways that were unknown just a decade ago. [10] But researchers have also discovered the broad term "molecular medicine" encompasses a variety of potential targets in the genome, the proteome, the epigenome, among others. Designing a drug or drugs to be efficacious with few side effects in the midst of this complexity has proved more challenging than the direct targeting of genes that was envisioned in the earlier days of molecular medicine.

HUNT FOR BIOMARKERS AND OTHER MEANINGFUL MOLECULES

The cost of sequencing a human genome is plummeting, hovering over a fabled $1000 mark, but the analyses of these data continues to be costly. The wealth of data mean that a wealth of analysts, from a variety of expertise and background, are needed to interpret the raw data in ways that are meaningful for human health. The main challenge facing researchers is to determine what types of molecular variation are medically meaningful.[11]

For instance, the hunt for disease biomarkers in blood and urine is still in high gear, but the results so far have been less than inspiring. Several recent studies have found that associations between these protein biomarkers and diseases, including most prominently ovarian cancer, are not as strongly predictive as earlier studies suggested. These biomarkers, urgently needed to guide drug development, are being considered in new discovery studies that take into the account the molecular attributes that would make a molecule a good biomarker.[12]

In-depth studies of the genome continue to turn up new surprises, even within the core understanding of how the genome is constructed. This year, on the frontiers of genetic research, researchers isolated a mostly-unknown base pair from brain and stem cells. This nucleic acid base, a modified cysteine, is being analyzed for its role in everything from cancer to cognition[13] and its functions remain uncertain.

THREE-DIMENSIONAL SOLUTIONS

Crystal structure studies offer a glimpse at the "lock and key" nature of potential drug targets, which could guide database analyses that seek likely interactions between protein configurations and small molecules. They might also aid researchers who would like to custom-design therapies that are specific to disease-causing targets. While these design studies may not directly reveal new potential drugs, they can help hone current drug structures in increasingly rational ways.

Many researchers are mapping the crystal structure of complex proteins, protein-protein interactions, and the various parts of the genome's packaging, transcription and translation. Often performed as basic rather than applied research, crystal structure studies nonetheless have considerable relevance for drug discovery.

As an example, 2011 saw the determination of the crystal structure of the yeast Mediator complex. The protein complex is critical in determining gene expression through their transcription into RNA. A better understanding of Mediator could help researchers design drugs that interfere with gene expression.[14]

Similarly, an influx of crystal structure studies on G protein-coupled receptors (GPCRs) could aid drug discovery, particularly since many current drugs target these signaling proteins. Up to 40% of marketed drugs, from blood thinners to allergy medicines, control GPCRs.[15]

X-ray structures of the key cytochrome P450 enzyme were completed in 2012, [16] giving researchers a glimpse at how two drugs target the enzyme in the treatment of prostate cancer. The drugs, Janssen Biotech's approved abiraterone (Zytiga) and Tokai Pharmaceuticals' TOK-001 in clinical trials, bind to the enzyme in an unexpected way. The researchers think the new information could help in the design of drugs that are more selective in inhibiting activity and lead to fewer side effects.

THE EXPLORATION OF MOVING TARGETS

The decade of discovery after the first human genome sequence has also revealed the dynamic nature of the genome, and researchers are now beginning to explore how this "moving target" might be related to disease and therapy pathways. R&D scientists may now consider "metabolomics," for instance, searching for druggable targets among the full range of unique chemical byproducts left by a cell's normal functioning at any given time. Some researchers have gone so far as to characterize the entire transcriptome, or the entire set of genes expressed in a cell over a period of time. Transcriptome data from a single neuron, for example, have revealed hundreds of receptor and ion channel targets.[17]

Genetic medicine has also expanded to include epigenetic targets. Epigenetic changes, gene modifications that occur as a result of changes in the chromatin and histone packaging of genes, are of particular interest in cancer drug development. Epigenetic-based drug development is one area where smaller biotechnology companies and academic laboratories have taken the lead in research. As a result, large pharmaceutical companies have sought out these smaller partners to bring epigenetic-based drug candidates into their R&D pipelines. In 2012, for example, Genentech and Massachusetts-based biotechnology start-up Constellation Pharmaceutical began a partnership to uncover epigenetic targets for cancer drug development.[18]

The realization that the genome is a shifting rather than static construction can lead to a host of other considerations in drug development. For instance, researchers must now explore how any given drug candidate performs against an ever-changing backdrop of transcriptome, metabolome and epigenetic alteration. New research that considers treatment efficacy in relation to circadian cycling, for example, notes that certain proteins are only active at particular times of day. In both humans and other animals, it is possible that promising drug candidates were excluded from further consideration because they were tested at the "wrong" time of day, when levels of the protein targets were naturally low.[19]

TOOLS FOR EXPANDING THE REPERTOIRE

The genomic revolution has also meant that unprecedented amounts of data are now pouring into multiple databases that are just beginning to be explored by drug developers. Several efforts at drug repositioning, or applying established compounds to new therapeutic indications, are in play. In one recent example, researchers searched for potential ways to match approved drugs with targets suggested by human genome databases, and identified 435 targets that could be mediated by the approved drugs.[20]

There is also rising interest in "polypharmacology," or the use of a single drug to hit multiple molecular targets. Researchers are examining the possibilities of polypharmacology in the cancer and antibiotic pathways, and researchers anticipate that the technique could be used to find new uses for older drugs and to tease out the reasons for some drugs' unwelcome side effects.[21]

IV. Trends in Protein-Based Drug Discovery

Drug discovery rooted in protein-based therapeutics and targets has benefited from an ever-evolving understanding of molecular mechanisms in the genome era. And yet the opportunities for protein-based research are still vastly unexplored. A 2011 study suggested that more than 75% of current protein research still focuses on the 10% of proteins that were identified before the first human genome maps.[22] Researchers are expanding the repertoire of proteins and amino acids considered as therapeutics, along with experimenting with new ways to increase the impact of known protein-based therapeutics and learning more about the proteins that are intimately involved in high-profile disorders such as cancer and Alzheimer's Disease.

INTENSE INTEREST IN ANTIBODIES

Market research company Datamonitor has estimated that growth in the sale of antibody therapeutics will outpace any other therapeutic class. They estimated that sales will increase by 8.2% from 2010 to 2016, with overall sales expected to push past $65 billion by 2016.[23]

Antibodies have been of particular interest in drug developers looking for new anticancer agents or anticancer adjuvants. As in many other areas of pharmaceutical R&D, larger companies have looked to smaller firms to fill their development pipelines in this area. In early 2012, for instance, Amgen acquired Rockville, Maryland-based Micromet for $1.2 billion, on the strength of its antibody technology.[24] Micromet's bispecific T-cell engager technology (BiTE) uses antibodies to both kill cancer cells and encourage the proliferation and activity of the body's own immune T-cells at the site of a cancer. Micromed's products included blinatumoma, an antibody targeted to acute lymphoblastic leukemia that is in Phase II clinical trials.

In other cases, researchers have looked for new ways to use antibodies as drug delivery systems, taking advantage of their targeting capabilities to send drugs directly to specific cell types. In 2011, the Food and Drug Administration approved Seattle Genetics' Adcetris, the first antibody-drug conjugate used to treat Hodgkin's lymphoma and a rare cancer called systemic anaplastic large cell lymphoma.[25] The conjugate uses the antibody to direct an anticancer agent directly to CD30 lymphoma cells while sparing healthy cells.

Others have found new ways to target and increase the levels of natural antibodies that can have an anticancer effect. University of Wisconsin researchers, for example, have developed a two-headed small molecule that attracts antibodies to attack prostate cancer cells.[26]

In some cases, the drug design focuses on ways to activate the body's immune system and destroy cancer cells by provoking antibody action. These immunotherapy or cancer treatment vaccines have seen some mixed success in the past two years, with the introduction of Bristol Myers Squibb's Yervoy for the treatment of melanoma and Dendreon Corporation's Provenge for advanced prostate cancer. As of mid-2012, clinical trials were underway for immunotherapy products to treat lung, liver, breast, prostate, pancreatic, ovarian, head, neck and brain cancers.[27] Although the two approved drugs and many of those making their way toward approval do provoke a specific anticancer response, more research is needed to determine whether these drugs might work best in tandem with another antitumor drug or another immunotherapy product. One further avenue under consideration to improve cancer treatment vaccines would be strategies to boost the ability of carbohydrate-based vaccines to mount an effective immune response against cancer.[28]

PEPTIDES, UNNATURAL AMINO ACIDS AND BIOLOGICS

Peptide-based drug development continues to mature. Larger pharma companies are now showing interest in the small biotech firms that have gone through extensive peptide screening and now have products that are close to the clinical trial stage.[30]

TOXIC ORIGINS

Several successful peptide drugs have their roots in venoms

DRUG	MOLECULE	ORIGIN	DISEASE	COMPANY
Aggrastat (tirofiban)	Peptidomimetic	Saw-scaled viper	Angina/heart attack	Medicure
Byetta (exenatide)	Peptide	Gila monster	Type 2 diabetes	Amylin/Eli Lilly & Co.
Capoten (captopril)	Peptidomimetic	Brazilian lancehead snake	Hypertension	Bristol-Myers Squibb
Integrilin (eptifibatide)	Cyclic peptide	Southeastern pygmy rattlesnake	Ischemic stroke	Millennium Pharmaceuticals
Prialt (ziconotide)	Miniprotein	Magician's cone snail	Chronic pain	Elan/Azur Pharma

SOURCES: Bachem, Atheris Laboratories

San Marino, California-based Viral Genetics, for instance, is nearing the clinical trial stage for its peptide drug candidate to treat Lyme Disease, and other companies are nearing trial stage on peptides for conditions like osteoporosis.

Peptide drug developers have been challenged to find ways to produce peptides in clinical and commercial quantities. Their search has benefitted from the field's maturation, as synthesis has improved to the point where large-scale peptide production is becoming more prominent, expanding the field of viable peptide therapies.[31]

Another avenue of growing interest to drug developers is the use of unnatural amino acids. These synthetic amino acids, encoded for by different base pair combinations outside of

nature's varieties, are being inserted into a variety of protein-based drug candidates. The technique, which allows researchers to control the design of these candidates through precise chemical modifications, has found uses in a growth hormone treatment and multiple sclerosis treatments. Both of these drugs are in clinical trials, but some analysts have expressed concern that the regulatory climate for these new amino acids may be different than for natural protein-based drugs.[32]

Many pharma and biotechnology companies, particularly in Asia, have invested heavily in the development of biosimilars, or generic versions of biologic drugs. The ramp-up in biosimilars R&D has come as developments in the United States and Europe indicate that the regulatory climate for these drugs will be soon become more clear.[29]

PATHWAYS TO GREATER POTENCY

Several trends in drug development to improve upon the impact of established compounds, or increase a drug's potential targets, are finding traction in small molecule and protein-based drug discovery. The renewed interest in covalent drugs [33], which form an irreversible bond with their protein targets, has resulted in some candidates for clinical trial. Although some researchers have been reluctant to pursue covalent drug candidates, fearing their permanent bond might be too toxic, this fear has been calmed in some more recent candidate drugs that are weakly reactive. The covalent drug AVL-292, which blocks a enzyme involved in lymphoma, was one such candidate of interest for Celgene when it acquired its developer Avila Therapeutics in early 2012. Covalent compounds are being considered for treatments for other cancers, hepatitis C and obesity, among other conditions. The current generation of potential covalent compounds are very selective, suggesting smaller doses than with usual drugs are needed to see clinical effects.

Interest is also growing in developing multivalent drugs, which use multiple copies of their bioactive chemical group to inhibit multiple targets at once. Multivalency can significantly increase a drug's potency, specificity and duration of action. One route to multivalency in future drug design may include techniques for adding short peptide nucleic acids to DNA strands. [34] The artificially synthesized polymers have already shown some promise in anticancer, antiviral and gene silencing applications.

As the crystal structure and molecular details of more proteins are revealed, drug designers are exploring the possibilities of therapies that address protein-protein interactions. The multiple targets involved in these interactions were previously thought to be intractable.[35] But researchers now see the variety and versatility in protein-protein interactions as offering a

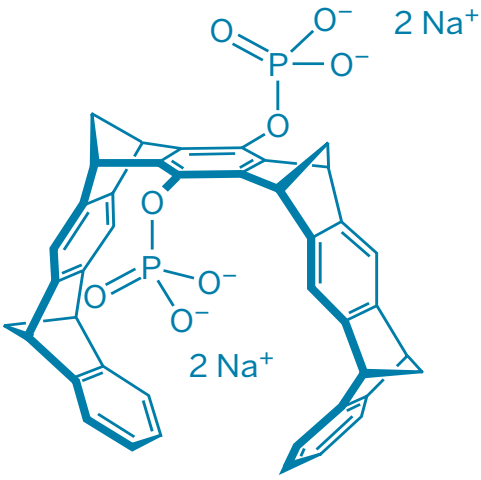
wealth of targets that can be addressed by drugs that offer subtle alteration—rather than blunt inhibition—of protein activity.

Protein profiling and screening for drug candidates and targets remains a key challenge in drug discovery, one that researchers are finding new ways to accelerate and fine-tune. Competitive activity-based protein profiling, for instance, could make it possible to identify small molecule inhibitors that work across multiple enzymes with similar functions. In early 2012, the technique was used to identify potential inhibitors for serine hydrolases, one of the largest and most diverse classes of enzymes.[36] Other screening techniques under development include new ways to profile protein oxidative stress and to create new networked maps of similar enzymes.[37]

INNOVATIONS IN PROTEIN RESEARCH: EXAMPLES FROM ALZHEIMER'S

As basic research reveals more about the amyloid protein plaques that are one of the hallmarks of Alzheimer's disease, researchers in drug discovery can begin to piece together potential targets within the disorder. As with many similar diseases in the genomic era, the molecular characterization of the disease is inspiring creative ways of considering its diagnosis and therapy.

For instance, there have been steps to create a reagent that can identify the early stages of neurodegenerative protein tangles, before they become full-blown amyloid fibrils.[38] Molecular "tweezers" may soon find a place in fighting Alzheimer's disease, with the discovery of a molecule that can disrupt the formation of and unglue existing amyloid protein plaques.[39]



CLR01

A better understanding of Alzheimer's also may come through a new method of creating a synthetic version of the tau protein,[40] implicated in these toxic protein "tangles" of the disease. The synthetic tau molecule can be more easily labeled with chemical groups such as phosphates, allowing researchers to study the protein's individual and group interactions.

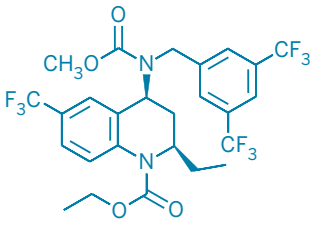
V. The Rise of Small Molecules: Inhibitors, Silencers and Viruses

Drug discovery's small molecule toolkit continues to expand, with inhibitors, strands of gene-silencing nucleic acids and viruses playing evolving roles as both therapeutics and production agents. The field has matured to the point where large pharma increasingly selects promising candidates from smaller biotechnology companies that have been busy screening thousands of such molecules in the past decade.

Small molecule treatments, with their potential for specificity and variety, are on the frontier of treatments that can be called "personalized medicine." Drugs like Vertex Pharmaceuticals' Kalydeco, a small molecule that repairs a protein defect found in a rare form of cystic fibrosis, are illustrative of the potential of small molecule drugs to correct underlying genetic defects that have come to light in the genomic era.[41] As the pipeline of blockbuster drugs with wide applications continues to shrink, these narrow-focus drugs will become increasingly important in the pharmaceutical industry's portfolio.

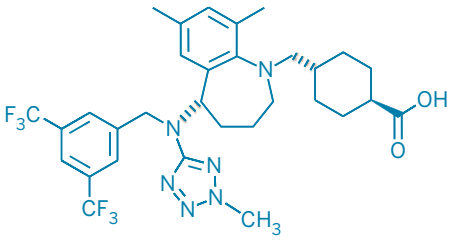
STANDOUT SMALL MOLECULES

One of the more intriguing possibilities for small molecule inhibitors has been the "comeback" story of CETP (cholesteryl ester transfer protein) inhibitors to control cholesterol levels.[42] The molecules were synonymous with failure for some industry analysts after Pfizer ceased testing the CEPT inhibitor torcetrapib in late 2006, after reporting an increased number of death and cardiac events in a 15,000 patient clinical trial.

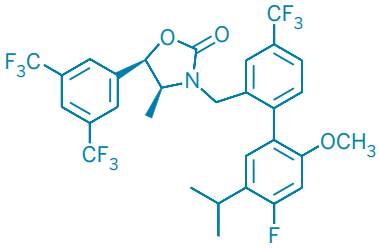


Torcetrapib

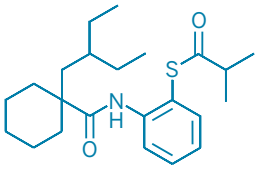
But the molecules, which may raise levels of beneficial high-density lipoproteins (HDL), are getting a second look. As of early 2012, Merck & Co.'s anacetrapib, Roche's dalcetrapib, and Eli Lilly & Company's evacetrapib are all in late-stage clinical trials. The new studies have looked carefully for off-target effects of the molecules that may raise blood pressure, cause electrolyte imbalances, and other changes seen in some torcetrapib patients[43]. The new molecules are also being examined for their efficacy in replacing and working alongside established cholesterol drugs such as statins.



Evacetrapib



Anacetrapib



Dalcetrapib

The PI3K pathway has also reemerged as the subject of intense interest from smaller biotech firms searching for small molecule inhibitors of the pathway. Key molecular nodes in the PI3K pathways have been implicated in a variety of cancers, including sarcomas and solid tumors in the brain, lung, breast and colon. These nodes have long been tantalizing targets for drug discovery, but earlier clinical studies of PI3K inhibitors had suggested they might be of limited therapeutic use against cancers.

More recent work, however, has focused on ways to alter the inhibitors to increase their effectiveness and to explore new molecular pathways connected to PI3K that might be of therapeutic interest.[44]

At the end of 2011, several large pharma companies acquired biotechnology firms pursuing this work to build their own anticancer pipelines.[45]

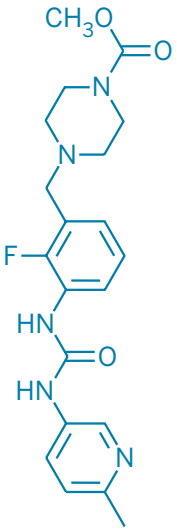
RUSH TO CLINIC

Many big pharma and biotech firms have PI3K inhibitors in clinical trials

	DRUG	DEVELOPMENT PHASE	MECHANISM
Bayer	BAY806946	Phase I	Dual mTOR/PI3K
Exelixis/Sanofi	XL765	Phase I	Dual mTOR/PI3K
Genentech/Roche	GDC0980	Phase I	Dual mTOR/PI3K
GlaxoSmithKline	GSK2126458	Phase I	Dual mTOR/PI3K
Novartis	BEZ235	Phase I/II	Dual mTOR/PI3K
Novartis	BGT226	Phase I/II	Dual mTOR/PI3K
Pfizer	PF04691502	Phase I	Dual mTOR/PI3K
Pfizer	PKI587	Phase I	Dual mTOR/PI3K
Semafore	SF1126	Phase I	Dual mTOR/PI3K
Exelixis/Sanofi	XL147	Phase I/II	PI3K
Genentech/Roche	GDC0941	Phase I	PI3K
Novartis	BKM120	Phase I/II	PI3K
Oncothyreon	PX866	Phase I/II	PI3K
Zenyaku Kogyo	ZSTK474	Phase I	PI3K
Novartis	BYL719	Phase I	PI3Kα
Amgen	AMG319	Phase I	PI3Kδ
Calistoga Pharma	CAL101	Phase I/II	PI3Kδ
Genentech/Roche	GDC0032	Phase I	PI3K[a]

a Mechanism not yet disclosed. **SOURCES:** Semafore, ClinicalTrials.gov

Although anticancer small molecules are dominant in drug discovery, other promising small molecules are being tested for conditions beyond cancer. For instance, researchers have made some preliminary but hopeful findings with the small molecule inhibitor JM6, which appears to prevent and reverse some symptoms of neurodegenerative diseases such as Huntington's and Alzheimer's in animals.[46] The small molecule omecamtiv mecarbil may be used to treat



Omecamtiv mecarbil

cardiac disease, as it activates cardiac myosin to revive poor heart muscle contraction.[47] And in early 2012, Gilead Sciences Inc. acquired Princeton, New Jersey-based Pharmasset to obtain PSI-7977, a uracil nucleotide analog in Phase II clinical trials for treatment of the hepatitis C virus.[48]

THE NEW SOUNDS OF SILENCING

Researchers have been testing ways to trigger gene silencing in human cells since 2001, hoping to find a use for gene silencing in treatments for cancer, high cholesterol treatment and more. The tools of choice have been naturally occurring and in some cases synthetic short strands of RNA called small interfering RNAs (siRNAs) and microRNAs(mRNAs).

But growth in this field has been slowed somewhat by poor progress in finding ways to target and deliver gene silencing molecules[49], as well as the development of unwanted immune side effects in testing.[50] RNAi drug development has proved more difficult than some investors would like, and developments such as Roche closing its entire RNAi research ventures have made some wonder whether the field has a future.[51]

PIPELINE PROGRESS

Several companies have RNAi drugs that are undergoing human testing

COMPANY	STATUS
Alnylam	Initiating Phase I trial of ALN-TTR01 in third-quarter 2011
Alnylam	Initiating Phase I trial of ALN-PCS in second-half 2011
Alnylam	Filing INDA for two drug candidates by end of 2011
Calando	Completing Phase I trial of CALAA-01 and selecting indication for Phase II trial
Marina Biotech	Continuing enrollment of Phase I trial of CEQ508
RXi	Filing INDA for RXI109 in second-half 2011
Silence Therapeutics	Completing Phase I trial of Atu-027 in second-half 2011
Tekmira	Reporting data from Phase I trial of TKM-PLK1 in second-half 2011

INDA = Investigational New Drug Application. **SOURCE:** Companies

As with other small molecule research, the prospects for gene silencing within drug discovery have focused on ways to create new RNA strands with increased target specificity. For instance, nanobiologists have introduced synthetic DNA and RNA structures called polyvalent nucleic acid nanostructures that can enter cells and alter gene expression. Their creators at Northwestern University see them as potential therapies for cardiovascular and neurological conditions, psoriasis and wound healing, as well as resistant cancers such as glioblastomas with a genetic basis.[52]

Other researchers have moved away from RNAi as therapy and instead see it as a unique tool to probe molecular targets and other potential drug candidates. MicroRNA signatures unique to certain tumor mutations, for instance, are increasingly used for cancer diagnosis and prognosis testing.[53]

The biochemical process of DNA methylation, which can include gene silencing in its repertoire of gene expression alterations, has found some uses in oncology. In tumor cells where DNA methylation has caused abnormal gene silencing, small molecule methylation inhibitors such as azacitidine and decitabine can revive the expression of key genes that arrest tumor growth.[54]

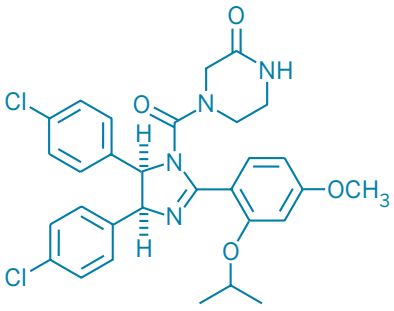
NEW APPLICATIONS FOR VIRUSES

While viruses have long held a valued position as delivery systems for other therapeutic agents, there is a small trend in using viruses themselves as the drug agent. In 2011, several anticancer viruses made their way closer to clinical testing, as research shows them to be selective and effective against specific tumors.[55]

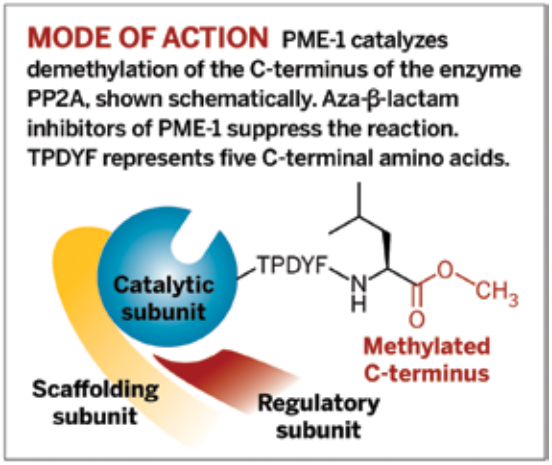
Viruses may also find new roles in the techniques used to search for and design small molecule drug candidates. For instance, researchers at Harvard reported a new system that uses bacteriophages to speed up the directed evolution of biomolecules for use as therapeutic agents.[56]

PRODUCTION POTENTIAL FOR SMALL MOLECULES

Just as with protein-based drug discovery, small molecule discovery and design are benefiting from substantial and growing molecular databases and detailed explorations of molecular structure. A new method for producing specific enantiomers of the anticancer agent nutlin-3, for instance, illustrates the potential for accessing similar anticancer drug candidates in the nutlin family.[57]



Nutlin-3



In another recent study, a molecule synthesized for the purpose of synthetic chemical testing and subsequently included in a molecular library, proved to be a highly potent inhibitor for PME-1, an enzyme involved in some cancers and neurodegenerative diseases. Although this sort of "hit" from a compound library, using molecules that were developed for a different purpose, is not yet common, it may be more prevalent in the future.[58]

VI. Inspiration from Nature

Natural products research, as a source for new drug discovery, has come back into vogue after a long period of reliance by pharma companies on automated discovery. In 2011, nearly half of all small molecule drugs approved by the Food and Drug Administration were products obtained from natural sources or derivatives of those natural products.[59]

Genetic sequencing and the ever-growing databases that are the result are making it easier for researchers to examine the "raw material" of natural organisms with an eye to discovering new therapeutic compounds and effective delivery systems for drugs. These in silico searches can help identify new metabolites, new molecular targets and in the case of genomic surveys of whole environments, even entirely new microbial organisms that might be overlooked in more costly and time-consuming traditional lab methods.[60] Companies like Cambridge, Massachusetts-based WarpDrive Bio have built a business model around "genomic search engines" that look for the molecular signatures of medically relevant chemical compounds in the genomes of microbes.

Pharmaceutical companies that abandoned their natural compound libraries in the past are finding ways to revisit these compounds in collaboration with academic laboratories and other repositories such as the National Products Discovery Institute. Established in 2011, the Institute opens up access to the combined microbe and plant samples curated by Merck & Co. and Schering-Plough. The Institute, which offers access to the collection for a fee, has already seen interest from academic researchers and small biotech firms.

Natural products have always had a built-in constraint, in that the products are often difficult to collect, cultivate or procure in large enough quantities to be commercially and clinically viable. But technique breakthroughs such as "collective total synthesis," the ability to produce multiple synthetic drugs from a common molecular starting point, could soon make it easier to develop drugs from natural products.[61]

The success of some natural products has prompted researchers to search for synthetic versions as well. German researchers this year reported, for instance, a new continuous-flow procedure to synthetically produce the powerful antimalarial medication artemisinin.[62] The highly effective drug can be extracted from its plant source, but its seasonal growth has created some volatility in its manufacture and sale.

Another recent example of a natural product once again on the rise comes from the bryostatin family of molecules. Since their discovery 40 years ago, their efficacy (mostly against cancer) has proved to be low to mixed, and any further considerations for exploring their use was complicated by the fact that they were hard to harvest and even more difficult to synthesize. Now, new synthetic techniques have shrunk the number of steps needed to produce bryostatins, and the compounds have been tapped as potential HIV and Alzheimer's treatments.[63]

Bryostatin Time Line

1968 First samples of Bugula neritina screened for anticancer activity

1976 A compound that would come to be known as bryostatin 1 identified for the first time in extracts from B. neritina collected from the California coast

1982 Structure of bryostatin 1 reported

1990 First total synthesis of bryostatin 7 in 79 steps by Satoru Masamune and coworkers at Massachusetts Institute of Technology

1991 18 g of bryostatin 1 extracted from 14 tons of B. neritina collected off the California coast

1998 First total synthesis of bryostatin 2 in 72 steps by David A. Evans and coworkers at Harvard University

2000 First total synthesis of bryostatin 3 in 88 steps by Shigeru Nishiyama, Shosuke Yamamura, and coworkers at Japan's Keio University

2008 First total synthesis of bryostatin 16 in 42 steps by Barry M. Trost and Guangbin Dong of Stanford University

2011

> First total synthesis of bryostatin 1 in 58 steps by Gary E. Keck and coworkers of the University of Utah

> First total synthesis of bryostatin 9 in 43 steps by Paul A. Wender and Adam J. Schrier of Stanford University

> Total synthesis of bryostatin 7 in 36 steps by Michael J. Krische and coworkers at the University of Texas, Austin

Discoveries of new natural products were given some guidance in 2010 with the introduction of The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the United Nations' Convention on Biological Diversity. The Nagoya protocol spells out how researchers should access biological materials (including natural compounds from plants and animals), along with their genetic or molecular materials in the nations of the developing world. The protocol explains how some countries should be compensating these bio-diverse nations if explorations of these biological materials produce profitable medical compounds.[64]

VII. Technology's Frontiers in Drug Testing, Delivery and Monitoring

Partnerships with medical technology companies are increasingly part of the portfolio of major pharmaceutical companies. Medical technologies continue to advance in materials while shrinking in size and cost, making them more viable as "add-on" products for big pharma to consider. These new products and services, the pharmaceutical companies feel, may help to staunch losses incurred during the global economic downturn and the coincident patent expirations for a cohort of best-selling drugs.

At the same time, technological advances have provided pharma companies with a host of new tools for drug development, ranging from devices used in basic discovery to mobile networks that are already helping some companies efficiently market to their to select patient groups.

TESTING TECHNOLOGIES EVOLVE

Researchers are refining their data mining techniques to use large databases more efficiently in discovery and toxicity testing processing. New statistical tools, in particular, are making it easier to glean information about genomic responses to chemical compounds and to screen hundreds of small molecules against hundreds of proteins.[65]

Data mining is also entering a new era in which large consortiums are building central and open databases to collect information that would normally be scattered among individual journal articles. The European Bioinformatics Institute's ChEMBL, a database of bioactive small molecules, illustrates the drug discovery potential in such collections.[66]

These databases are often used in conjunction with technologies that have been refined to focus on molecular structures and single-cell dynamics:

- Liquid chromatography-mass spectrometry (LC/MS) is becoming another standard tool in drug development. Mass spectrometry, in conjunction with in vitro cellular assays, are being used alongside more traditional techniques to predict drug toxicity.

- New methods such as atomic force microscopy are being tested for their ability to explore the structural properties of diseased cells, or cells under the influence of specific therapies. Atomic force microscopy, according to a recent report, can be used to examine

how ovarian cancer cells are altered when treated with cisplatin and may help fine-tune this treatment.[67]

- Microfluidics-based diagnostic tests also are beginning to come into their own. Columbia University's mChip, for instance, was found to perform as well as lab-based tests in a recent study of HIV and syphilis detection.[68] The high-throughput technologies present on these "lab-on-a-chip" devices are expected to be a boon to immunoglobin antibody production, and may also be of use in the production of new peptides and plasma.[69] As these products evolve, they are expected to reduce testing costs and improve the portability of testing, particularly in developing countries.

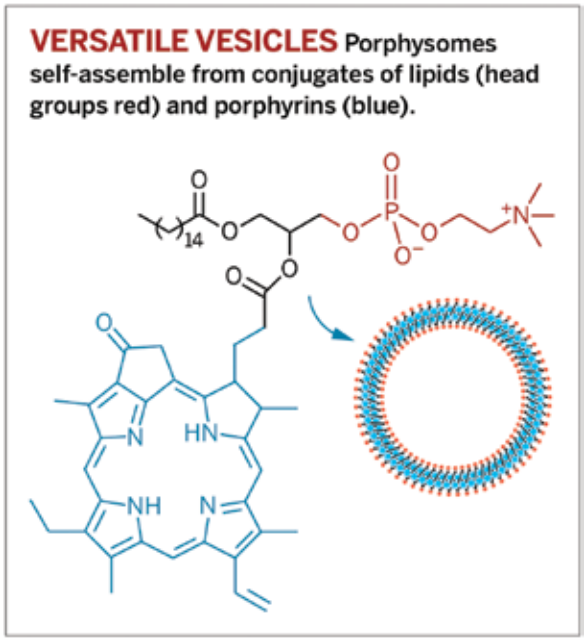
At the same time, advances in technologies such as mass spectrometry have revived older methods such as dried blood spot testing as useful samples for clinical analysis. Some experts predict that dried blood spots will become widely useful in drug development as they are analyzed with increasingly sensitive technologies.[70]

SPECIALIZED DELIVERIES

Protein crystal structure studies have been particularly helpful in inspiring drug design, but they may also prove useful in designing delivery strategies for therapeutic proteins and small molecules. Crystal structure studies reveal how nature has "solved" this problem in shielding and delivering molecular cargo, as in the recent unraveling of the crystal structure of the botulism toxin bound to a protein shield [71] for instance, could inspire new oral delivery methods for protein pharmaceuticals. In this example, the toxin and its shield demonstrate different electrostatic interactions at different pH. This type of information, which may explain why the toxin is protected in the gut but released in the bloodstream, could prove more widely useful in the design of oral and time-release medications.

Viral systems have been the delivery workhorses of vaccines and gene therapy, but researchers are exploring other vehicles for delivery that may be less likely to provoke unwanted immune responses as is sometimes the case for viral carriers. In 2011, for instance, a team of bionanomaterial scientists synthesized helical charged peptides to deliver gene therapy to cells.[72]

Tests continue on a variety of nanoparticle systems, using both biological and inorganic materials. Just as therapeutic compounds are becoming more narrowly focused and developed over a wide spectrum in the service of personalized medicine, experts say it is likely that nanoparticle delivery vehicles will be similarly customized.[73]



The field of "theranostics"—agents that both monitor and treat a disease—are a major target of nanoparticle delivery researchers. Some potential drug candidates work toward this goal by combining nanoparticles in a one-two punch, finding ways to intensify a cancer treatment by sending one type of therapeutic nanoparticle in to fight the tumor and following that with a delivery nanoparticle that carries a second drug.[74] The future should hold more examples of these coordinated therapies, experts suggest.

Porphysomes are another new entry in the world of theranostics. The nanostructures can be designed to image, heat, destroy and deliver drugs to cancer cells. Porphysomes also demonstrate the move toward therapeutic nanoparticles in which all these functions are intrinsic to the nanoparticle and not added in further manufacturing steps.[75]

PERSONALIZED MONITORING MOVES FORWARD

One particularly bright spot in drug development is the advance in personalized monitoring technologies, which can be used during clinical testing and routine medication as a way of learning more about how drugs impact health on a near-instantaneous basis. The field of monitoring and diagnostics has benefited from the miniaturization of technology, particularly microchip technology, and the widespread adoption of mobile technologies like the smartphone and tablet computers.

Take the example of Proteus Biomedical. The Redwood City, California start-up has partnered with Novartis to develop applications for its unique sensor: a biodegradable digital device that can be attached to a pill and transmit information on the pill's interactions.[76]

The device, like many others envisioned, will take advantage of new mobile apps and technologies to transmit information via smart phone or similar handheld devices. Sanofi and blood glucose monitor manufacturer AgaMatrix are collaborating on a connection between the device and the iPhone, to deliver information to patients and their physicians. Their project and others also highlight the growing importance of personalized medicine in driving drug delivery and monitoring development.

Researchers are also looking for ways to modify established readers, such as glucose monitors, to detect a variety of substances, from illegal drugs to heavy metals and biomolecules like interferon. Re-outfitting these devices will be a boon to the biosensors field, which is expanding to keep pace with the call for personalized and genomic medicine.[77]

Even further on the reaches of "Fantastic Voyage"-style technologies, researchers have devised a method for detecting bacterial infection (via detection of endotoxins) using a liquid crystal monitor[78], and nanotechnology researchers have devised "microrockets" that can cruise through human blood serum and detect isolated tumor cells and antibodies.[79]

These technologies and others like them have become as critical to the advance of medicine as the approval of new drugs. In recognition of this fact, the Food and Drug Administration launched the Medical Device Innovation Initiative[80] in 2011, as a way to help speed pioneering medical technologies through its approval process.

VIII. Conclusion

New directions in pharmaceutical chemistry will come both from new insights in human biology and new commercial realities for pharmaceutical companies. Molecular and genetic research has expanded over the past decade in unexpected ways, making it difficult to predict which discoveries eventually may have the greatest impact on drug R&D. Researchers are already using the wealth of "-omic" data that has been collected to find new drug targets and new drug compounds. But many of these early "hits" may end up being more important as teaching tools--to learn more about the dynamics of medicine at the level of the genome--rather than as specific products for development and manufacture.

The new R&D approaches may also prove to be useful test cases when it comes to clinical testing and regulation, as agencies attempt to define how new drugs and devices may fit into the marketplace. Genome sequences from a plethora of organisms will be under special scrutiny as they become more common tools in drug discovery.

The personalized and narrowly targeted nature of medicine in the 21st century, along with a shifting financial outlook for large pharmaceutical companies, will also be a significant shaper for the near future of drug R&D. As patients look for treatments tailored to their personal health profiles--as revealed by the -omics revolutions, drug discovery must shift toward a search for a variety of differing therapies rather than a broadly-applicable "blockbuster" drug. As bigger companies have found, partnerships with smaller biotechnology firms, academic labs and even patient advocacy groups may be better suited to this multi-faceted, individualized approach to discovery.

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