Despite what the overcrowded, overpriced shelves of your pharmacy might suggest, pharmaceutical companies struggle to find new drugs these days. The low-hanging fruit is long gone, and the main discovery method that served so well in past decades is generating far fewer hits today. But a fresh strategy, focused on a property called allosterism, is now invigorating many investigators. Some predict it will revolutionize drug discovery and could deliver treatments for diseases that so far remain intractable.

Historically, scientists have developed drugs by finding molecules that mimic the behavior of our body’s signaling molecules, such as hormones and neurotransmitters. The pharmaceutical doppelgangers of such endogenous substances latch onto cell-surface receptor molecules exactly where the native substances bind. If a mimic fits snugly into the binding pocket, known as the “active” site, it will activate the receptor, triggering a biochemical cascade within the cell. If the mimic has a slightly different shape, it will do the opposite, impeding the cascade. Most drugs on the market today—allergy medicines, beta blockers, antipsychotic drugs—act in one of those ways.

Problem is, such drugs have an all-or-nothing effect. They stimulate or repress physiological pathways, leaving no room for normal fluctuations in activity. And because the body has evolved to use the same chemicals for multiple purposes, one endogenous molecule often binds to a range of receptor subtypes, each responsible for different tasks—so drugs intended to replicate the action of, say, a given neurotransmitter on just one subtype may end up affecting many subtypes, leading to side effects. These limitations have made it impossible for scientists to find safe therapies for some diseases.

Thanks to a few serendipitous discoveries arising from an upgrade in technology, pharmaceutical companies are now moving beyond mimicry drugs. They are on the hunt for agents...
THERAPEUTIC AGENTS known as allosteric ("other site") modulators take aim at targets outside of where classic drugs, and the body’s own substances, normally hit selected molecules in the body.

that interact with receptor regions that are geographically distinct from where a body’s chemicals bind. These allosteric drugs, as they are called—allosteric means “other site”—can interact with unique domains on receptor subtypes, thus limiting side effects by affecting only a narrow set of receptors possessing those domains. And the new agents are not mere on-off switches; they can have nuanced effects, ramping up or down the activity of a signaling pathway as needed.

Spearheading the allosteric effort is Swiss biotechnology firm Addex, the first company to devote its entire pipeline to allosteric drugs. In collaboration with several pharmaceutical makers, Addex is testing certain of its drugs in patients. Other companies are pursuing the approach, too: allosteric drugs made by Pfizer and Amgen have earned approval from the U.S. Food and Drug Administration to treat HIV and chronic kidney failure.

Order from Chaos
Allosterism is not a new concept. Since the early 20th century scientists studying enzymes, proteins that drive biochemical reactions forward,
When one of the body’s own molecules, such as a neurotransmitter, attaches to the so-called active site of its receptor on a cell (right)—something like a key fitting into a lock—the receptor sets off an intracellular signaling cascade that ultimately causes the cell to change its activity. Many drugs inhibit or enhance such signaling.

**NORMAL CELLULAR ACTIVITY**

<table>
<thead>
<tr>
<th>Body's own signaling molecule</th>
<th>Receptor for signaling molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal into cell</td>
<td></td>
</tr>
</tbody>
</table>

Typical pharmaceuticals bind to the active site in place of the native substance and either block the endogenous molecule’s signaling (left) or mimic its effects (right).

**HOW CLASSIC DRUGS ACT**

<table>
<thead>
<tr>
<th>Inhibitory drug</th>
<th>Mimic of native signaling molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signal</td>
<td>Signal into cell</td>
</tr>
</tbody>
</table>

**HOW ALLOSTERIC DRUGS ACT**

<table>
<thead>
<tr>
<th>Body’s own signaling molecule</th>
<th>Inhibitory allosteric drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced signal</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Body’s own signaling molecule</th>
<th>Stimulatory allosteric drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced signal</td>
<td></td>
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</tbody>
</table>

Allosteric drugs do not go to the active site. Instead they bind to other areas, altering the receptor’s shape in a way that decreases (left) or increases (right) the receptor’s response to the native substance. Allosteric agents might, for instance, cause the active site to grasp a neurotransmitter less or more effectively than usual.

Weave through the cell’s membrane seven times, initiating intracellular responses to events that occur outside the cell. When a ligand, a molecule that targets a receptor, binds to the active site of a GPCR on the outside of the cell, the receptor changes shape to activate a second molecule known as a G protein, which in turn initiates a biochemical cascade inside. The body produces more than 800 types of GPCRs, and about 100 types sit on any cell’s surface. But drugs on the market target only one eighth of all our GPCRs. “We’re only still touching the tip of the GPCR iceberg,” says Arthur Christopoulos, a pharmacologist at Monash University in Australia.

In the 1980s and early 1990s pharmacologists hunted for new GPCR drugs by using what were called radioligand assays. They identified the receptor they wanted to affect—perhaps a receptor linked to a disease pathway—and bound it to a known ligand that had been labeled radioactively. They then flooded the bound receptors with potential drug candidates to see which ones knocked the labeled ligands off. The more ligands a drug candidate kicked off, the better the “hit.”

These assays were designed to find drugs that bound to the active site, which is also known in the business as the “orthosteric” site. They did not find allosteric drugs that affected the receptor’s function in other ways, but at that point, scientists had no interest in doing so—orthosteric drugs were the obvious first choice. Unfortunately, for reasons not entirely clear, that approach stopped yielding good numbers of promising drug candidates after a while.

As a response, in the mid-1990s companies began trying a new, more physiological approach. They used “functional” assays that monitored how drug candidates affected the behavior of real, intact cells bearing receptors of interest, rather than looking at receptor binding alone. “This is where the interesting stuff started to happen,” Christopoulos says. Sometimes a molecule increased a receptor’s function; other times it inhibited the receptor. Orthosteric drugs should have been consistent in this regard. Some investigators realized that allosterism was responsible for the varied effects, but most saw allosterism not as a boon but as problematic.

Then, in 1999, a small La Jolla, Calif.—based biotechnology company called SIBIA Neurosciences, in collaboration with Novartis, reported discovering one of the first selective allosteric modulators: a molecule that toned down the activity of the metabotropic glutamate 5 recep-
natural ligand is present. “If you put it on the receptor, it does nothing,” Mutel explains. If a disease develops because a chemical is produced normally but does not bind as well as it should to its receptor, an ideal drug would help it bind better—but just when the chemical is around. Only an allosteric drug can do that; an orthosteric drug would activate the receptor as soon as it entered the body, which would not conform to natural dynamics.

The tendency to induce an effect only in the presence of the natural ligand could also make allosteric drugs safer than some orthosteric drugs. Although no one understood how Valium worked when it was discovered, scientists now know it is an allosteric modulator that “turns up” the activity of the receptor for GABA, the body’s main inhibitory neurotransmitter. Other central nervous system depressants, such as phenobarbital, are deadly if taken in large quantities, but Valium “just sits on the receptor and does nothing until the brain releases GABA, and then when GABA binds, its actions are boosted five- to 10-fold,” Christopoulos explains. Typically a person who takes too much Valium simply sleeps it off, he says.

On the “can do” side of the ledger, the ability of allosteric molecules to interact with receptors beyond the active site means they can bind specifically to individual subtypes. Many receptors evolved to respond to the same orthosteric ligand, explains Darryle Schoepp, a senior vice president at Merck & Co. One neurotransmitter might act on a dozen receptor subtypes, each responsible for initiating a different biochemical cascade. Nature, though, has not had a strong need to keep other parts of the receptors identical. Consequently, an allosteric modulator might bind to a nonorthosteric spot on subtype mGlu2 but not find any anchor in mGlu3 or other subtypes—thereby avoiding acting unnecessarily on receptor variants whose altered activity could potentially cause side effects.

These drugs can also have nuanced effects because they can influence a receptor’s shape in a number of ways. Administering them would be akin to replacing on-off light switches with dimmer switches, allowing for a range of outcomes—

Small Changes, Big Payoffs

Allosteric drugs may have an edge over traditional orthosteric molecules because of what they cannot do as well what they can do. When allosteric molecules bind, they subtly change the receptor’s shape, which changes how easily the natural ligand can connect to the active site. This helping role means that allosteric modulators usually do not have a noticeable effect unless the natural ligand is present. “If you put it on the receptor, it does nothing,” Mutel explains. If a disease develops because a chemical is produced normally but does not bind as well as it should to its receptor, an ideal drug would help it bind better—but just when the chemical is around. Only an allosteric drug can do that; an orthosteric drug would activate the receptor as soon as it entered the body, which would not conform to natural dynamics.

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Melinda Wenner is a science writer in Brooklyn, N.Y. Her latest feature for Scientific American addressed efforts to develop taste enhancers [“Magnifying Taste,” August 2008].
Allosteric drugs may have an edge over traditional drug molecules because of what they cannot do as well as what they can do.

A receptor could be tuned to be barely active, mostly active or highly active. Because so many diseases are marked by subtle disruptions in biochemistry or signal processing, notes Terry Kenakin, a principal research investigator at GlaxoSmithKline, it would be very useful to drug developers to be able to “tweak” the body back to normalcy.

From Concept to Clinic
With so many advantages, allosterism is now a common word among pharmacologists. “The area now has just expanded tremendously,” Conn says.

Addex has 60,000 potential allosteric modulators in its library and is screening them for effects on a number of GPCRs as well as on other types of receptors and ion channels. Its compound ADX10059, which tones down the ability of the mGlu5 receptor to bind glutamate, is now in human trials for efficacy in migraine and heartburn associated with gastrointestinal reflux disorder (GERD). Another of Addex’s mGlu5 antagonists, intended to treat involuntary movements resulting from Parkinson’s disease, has recently completed safety tests in patients. The company is also collaborating with Merck and Johnson & Johnson to develop allosteric modulators for schizophrenia and anxiety disorders.

[ALLOSTERIC ADVANTAGE]

A WAY TO LIMIT SIDE EFFECTS

If a receptor comes in multiple forms, a classic drug aimed at the active site of one subtype will also likely affect its kin, because the subtypes of a given receptor have a similar active site. An inhibitor delivered to shut down one subtype (left in top panel), then, may also inhibit relatives needed by a patient (top center and right), potentially causing side effects. But an allosteric drug can bind to a site that is specific to a single subtype (left in bottom panel), leaving other subtypes unaffected (bottom center and right) and thereby potentially limiting side effects.

TYPICAL DRUG AFFECTS TOO MANY RECEPTORS

ALLOSTERIC DRUG CAN ACT ON A SPECIFIC RECEPTOR SUBTYPE
The two allosteric drugs that have already made it to market are Amgen’s cinacalcet (sold in the U.S. as Sensipar), which was approved in 2004 to activate calcium receptors as a treatment for chronic renal failure, and Pfizer’s maraviroc (marketed as Selzentry), which was approved in 2007 for the treatment of HIV. Maraviroc gains access to cells by attaching to a receptor called CCR5, which normally binds an immune chemical called a chemokine; CCR5 likewise grasps HIV and helps it into the cell. Selzentry changes the shape of the CCR5 receptor in a way that bars HIV from binding to it. Unfortunately, Kenakin says, the drug also blocks the chemokine from binding, and chemokines help cells fight HIV. Future compounds, he says, may be able to block HIV without impeding the chemokine.

Allosteric agents do present challenges. What initially frustrated scientists about them—that they have one effect in one experiment and another in a second experiment—is still a major headache. GPCRs “are in every cell type, and they couple to G proteins, and there are lots of different types of G proteins,” Christopoulos says. A single GPCR can have multiple ligands and be paired to different biochemical pathways in the body, depending, among other things, on which tissue the receptor is in. Scientists therefore have to test allosteric drug candidates in multiple assays and tissue systems to make sure the compounds are doing the right things in the right places.

Finally, Mutel points out, “a chemical is a chemical, and it will have a certain toxicity.” Allosteric drugs may, on average, be safer than orthosteric drugs because they can be taken in smaller concentrations—they do not have to compete with the natural ligand—because most do not affect a receptor unless the natural ligand is already present. Even so, not all allosteric drugs will be safe, and some could have side effects by binding to and affecting unrelated receptors.

Nevertheless, pharmaceutical scientists are confident that allosterism has far-reaching promise for future drug development. “There’s a lot of negative press out there about inefficiency in drug discovery and how things aren’t going very well,” Merck’s Schoepp says. Allosterism breathes new life into the field. “We can do things that we couldn’t do before,” he notes. “This approach could really transform drug discovery.”

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**Allosteric Examples**

Two new allosteric drugs entered the market in the past few years, and a number of others are in, or close to, human testing for a range of disorders; the list below offers a sampling. All the agents below that are under study affect receptors for neurotransmitters and are in relatively early phases of trials (phase I or phase II, as opposed to very large phase III tests).

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>AGENT (MAKER)</th>
<th>ACTION</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney failure</td>
<td>Cinacalcet (Amgen)</td>
<td>Enhances activity of calcium receptors</td>
<td>On the market</td>
</tr>
<tr>
<td>Cognitive deficits of Alzheimer’s disease</td>
<td>XY4083 (Xytis)</td>
<td>Enhances activity of alpha7 subtype of nicotinic acetylcholine receptor</td>
<td>First human trial expected to start this year</td>
</tr>
<tr>
<td>Cognitive deficits of schizophrenia</td>
<td>GSK729327 (GlaxoSmithKline)</td>
<td>Enhances activity of AMPA-type ionotropic glutamate receptors</td>
<td>In early trials</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>ADX10059 (Addex); AZD2066 (AstraZeneca); AFQ056 (Novartis)</td>
<td>Inhibit metabotropic glutamate receptor 5</td>
<td>In early trials</td>
</tr>
<tr>
<td>HIV</td>
<td>Maraviroc (Pfizer)</td>
<td>Acts on CCR5 receptor to interfere with HIV entry into cells</td>
<td>On the market</td>
</tr>
<tr>
<td>Pain</td>
<td>Xen2174 (Xenome)</td>
<td>Inhibit norepinephrine transporter</td>
<td>In early trials</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>ADX48621 (Addex); AFQ056 (Novartis)</td>
<td>Inhibit metabotropic glutamate receptor 5</td>
<td>In early trials</td>
</tr>
</tbody>
</table>


**MORE TO EXPLORE**


