

Nanotechnology Aims to Improve Drug Synthesis

Discovering a new drug to fight cancer is a major accomplishment, but figuring out how to synthesize that drug in large quantities and in pure form can often be as much of a challenge. A new generation of nanoscale catalysts are giving chemists the tools they need to develop less costly — and less wasteful — ways of creating complex drug molecules.

➤ To Cornell University chemist Tyler McQuade, Ph.D., one fact about the way pharmaceuticals are made worries him. "For every kilogram of pure drug molecule that gets made, the pharmaceutical industry generates 25 to 100 kilograms of waste, and since most of that waste originally comes from oil refining, I'm concerned that the cost of making life-saving pharmaceuticals could soar with the price of oil. As a chemist, I feel that's a potential problem that I can help solve."

Chemist Bing Zhou, Ph.D., vice president and chief technology officer at Headwater Nanokinetix, based in Lawrenceville, NJ, sees another serious problem with the way many pharmaceuticals are synthesized today. "Almost all chemical reactions involve the use of metal catalysts," he explained. "That's an expensive waste of the metal catalyst."

What ties these concerns together is that each of these chemists believes that nanotechnology can provide the tools needed to radically improve the chemical synthesis

of pharmaceuticals. "As we gain control over the structure of catalysts at the atomic level, we gain better control over the chemical reactions we use to make complex drug molecules," said Zhou.

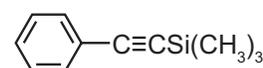
A Recognized Problem

The U.S. Food and Drug Administration (FDA) has recognized the effect that inefficient chemical synthesis has on the production of life-saving pharmaceuticals. Indeed, one of the three areas of emphasis in the FDA's Critical Path Initiative is to encourage the development of new tools for characterizing and manufacturing pharmaceuticals with the aim of producing drugs in a consistent and less costly manner.

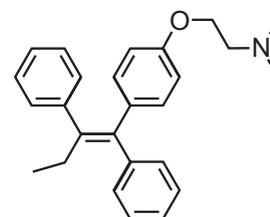
In its 2004 report "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," the FDA states, "The industrialization challenges posed by the demands of physical product design, characterization, scale-up, and manufacturing are often little understood outside of FDA and the

pharmaceutical...communities. It is crucial that...improved methods for design, characterization, and product manufacture are available to improve predictability in this area."

To understand what nanotechnology can contribute to the effort to improve drug manufacturing, it is important to have a general idea of how chemists make complex organic molecules, the active ingredients of many pharmaceuticals. The vast majority of drugs are what are known as new chemical entities — they do not exist in nature and thus must be invented by a chemist. To make such molecules, chemists start with some simpler chemical that they can purchase in bulk or isolate from a natural source. Then, just like nature does, they use catalysts to enable chemical reactions, each performed separately, that add groups of atoms to the starting material. For example, the process for making the anticancer drug tamoxifen starts with a relatively simple molecule known as phenyl (trimethyl silyl) — acetylene [compound A]. Eleven different chemical reactions are then used to build this starting molecule into tamoxifen.



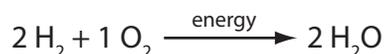
Compound A



Tamoxifen

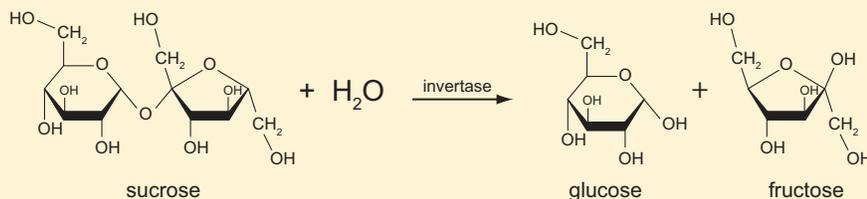
A chemical reaction is what chemists call the process of making new bonds between atoms or breaking existing ones, and all chemical reactions require energy to make them happen. For example, molecules of oxygen and hydrogen will mix together and nothing will happen. Add energy, in the form of a spark of electricity or a

flame, and two molecules of hydrogen will react with one molecule of oxygen to make two molecules of water. In this case, hydrogen and oxygen are called the reactants, and water is called the product.



A fire is a good source of energy, but not a very useful or controllable one when it comes to triggering chemical reactions. That's where a catalyst comes in — it interacts with reactants in a way that lowers the energy needed to trigger a chemical reaction. For example, sucrose, or table sugar, is made of one molecule of glucose and one molecule of fructose linked together. Dissolve it in water and all that happens is that crystalline sugar dissolves. Now, add the enzyme invertase and sucrose is broken apart into glucose and fructose — the enzyme binds sucrose and lowers the energy needed to break the chemical bond that held glucose and fructose together.

While nature uses enzymes as its catalysts, chemists use a variety of simpler chemicals, many of which include metals such as



platinum, palladium and rhodium. Unfortunately, these chemical catalysts are not as specific as their enzymatic counterparts, and as a result, none of the 11 chemical reactions (in the case of tamoxifen's synthesis) is perfect — each chemical step produces the desired chemical and various byproducts that must be removed subsequently; in contrast, enzymes rarely generate byproducts. Removing these byproducts, as well as any catalysts and other reagents used in each chemical reaction, is known as "purifying chemical intermediates." Often, developing the best purification routine is as difficult as optimizing each chemical reaction.

This inefficiency creates opportunity, and researchers are seizing on this opportunity to design new catalysts that are more efficient and easier to remove from the reaction mixtures. At NanoKinetix, for example, Zhou and his colleagues are creating tethered, nanoscale catalysts that both improve the selectivity of certain chemical catalysts and make it simple to recover all of the catalyst once the chemical reaction is complete. Zhou explained that chemical catalysts have always been nanoscale entities, but what is new is that chemists can now control the exact makeup of the catalyst at the atomic and molecular levels.

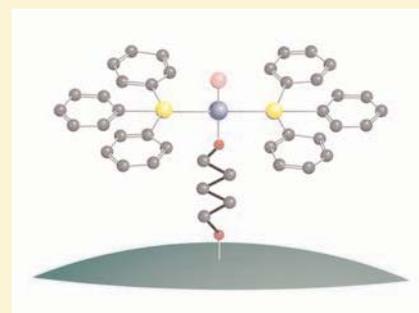
"We now have much finer control over the chemical nature of the catalyst, and that allows us to make much better catalysts."

In particular, he said, the composition of every catalytic nanoparticle produced using NanoKinetix's new technology is exactly the same, which means that every nanoparticle will behave exactly the same. "With older technology, you generate particles that have an average chemical composition, not the exact one you want to make a particular chemical reaction occur in the way you want it to proceed," he explained. With every particle of the new

nano-designed catalysts being exactly the same, the expectation is that the production of byproducts should be reduced.

A second advantage of these new catalysts is that they also contain a proprietary tethering agent. This chemical linker attaches the nanoscale catalyst particles to a larger particle than can be easily filtered after the chemical reaction is complete. In addition, the tethering process allows the individual nanoparticles to remain as discrete entities. "Without tethering, the nanoparticles tend to clump together, and that changes their catalytic behavior," Zhou added.

Courtesy: NanoKinetix.



A NanoKinetix nanoscale catalyst includes a tether that attaches the active catalyst to a solid support material.

Mimicking Enzymes

Isolating catalytic nanoparticles is also the key idea behind the work of chemist Richard M. Crooks, Ph.D., and his colleagues at Texas A&M University. Crooks' approach is to use dendrimers — spherical, nanometer-sized polymer particles — to keep catalyst particles separate from one another, as well as to fine tune important physical and chemical properties.

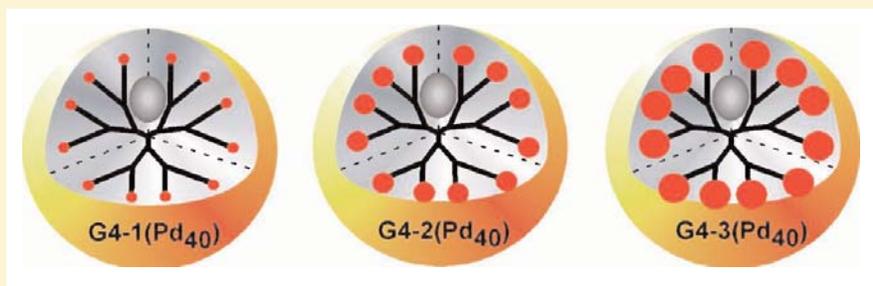
"From a chemist's viewpoint, dendrimers should make excellent templates for forming discrete, well-defined, nanometer-sized catalyst particles," explained Crooks.

"Since the chemical composition and structure of each dendrimer particle is well-defined and uniform, the resulting catalyst particles should also be well-defined and uniform."

Indeed, Crooks and his team have created catalysts that can promote some of the most useful chemical reactions for drug synthesis. Some of these catalysts contain more than one active metal atom, greatly extending the catalysts' versatility.

Moreover, the exact arrangement of the metal atoms within the catalyst can be controlled by varying the dendrimer's composition and the conditions used to assemble the catalyst. For example, the Texas A&M team has created a catalyst particle that has a gold core and a platinum shell, all trapped within the confines of the dendrimer. The activity of this novel particle is significantly enhanced compared to traditional catalysts when catalyzing a widely used chemical reaction known as hydrogenation.

Courtesy: Richard M. Crooks, Ph.D., Texas A&M University.



A nanocrystalline catalyst trapped inside a dendrimer. The makeup of the dendrimer determines how accessible the catalyst is to reactants in solution.

Another interesting property of dendrimer-encapsulated nanoparticle catalysts is that the dendrimer's structure can also influence the type of chemistry that occurs within its milieu. "In a way, these structures are like enzymes," said Crooks. "You've got the dendrimer itself, which is a 5 nanometer-diameter organic molecule," — that's the size of a typical enzyme — "with a catalytic nanoparticle as the active site."

In addition, a dendrimer, like an enzyme, is held together by what are known as amide bonds, giving the dendrimer key chemical characteristics known to play an important role in how enzymes function. As a result, a dendrimer, like nature's enzymes, can act as a nanofilter that will only allow molecules of a certain shape or size to reach the active catalytic sites within its structure. Indeed, experiments have shown that these dendrimer catalysts are capable of discriminating among many possible chemicals to selectively promote one chemical reaction over another.

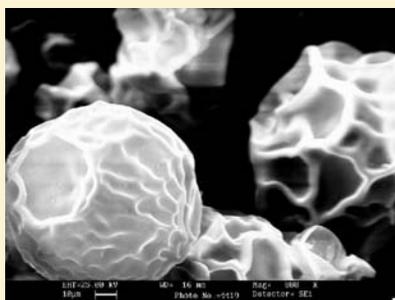
Combining Nanotechnologies

Taking a chemical approach to mimicking enzymes appeals to Cornell's McQuade, too. "For the most part, nature uses enzymes, and particularly groups of

enzymes, so much more efficiently than we [chemists] use traditional catalysts to build up complex molecules, and so if we can take some cues from nature, we should be able to improve our ability to do chemistry more efficiently," he said.

One trick that nature uses so effectively, he explained, is to separate the molecules undergoing a chemical reaction from all the other molecules in their surroundings. To achieve this effect in a synthetic system, McQuade's group traps catalytic nanoparticles inside porous polymer shells made of a material known as polyamide.

Courtesy: Tyler McQuade, Ph.D., Cornell University.



Electron micrograph of a nanoscale porous polymer shell. The active catalyst is attached to the inside of the shell.

Making these constructs starts by attaching a catalyst to a water-soluble polymer and then anchoring that polymer inside the porous polyamide shell. "This way, the catalyst retains its chemical properties, but the shell acts to restrict what molecules can reach the catalyst," he explained.

With these catalysts in hand, the McQuade group is now attempting to take another step toward the way nature does chemistry by making use of another nanoscale technology platform — microfluidic devices. "When a cell makes a complex molecule, it does so by organizing its enzymes physically so that the product of one enzymatic

reaction then moves along to the next enzyme, and so on," he said. "What we're trying to do to mimic nature's brilliance is to take different encapsulated catalysts and put them in sequence within the channels of a microfluidics device." Crooks' group has already demonstrated that microfluidics and nanoparticle-bound catalysts are a useful combination of nanotechnologies.

One enticing aspect of this approach is that once the right catalysts are developed and put on a microfluidics device, it should be possible to produce as much or as little of a drug as needed simply using more or fewer catalytic microfluidic devices. "This could then eliminate the often difficult problem of adapting chemistry as the production scale grows, because instead of changing reactor dimensions, which can have a huge effect on how your reaction proceeds, you're merely adding more reactors of the same dimension," said McQuade.

Eager to test this system, McQuade would welcome suggestions from the cancer research community regarding potential drug molecules that he and his team could try to synthesize. "This kind of science works best when you have a real target to work on," he explained. <

— Joe Alper

References

- U.S. Food and Drug Administration. "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." Washington, DC. 2005.
- Price KE, McQuade DT. A cross-linked reverse micelle-encapsulated palladium catalyst. *Chem Commun (Camb)*. 2005 13:1714-1716.
- Scott RWJ, Wilson OM, Crooks RM. Synthesis, characterization and applications of dendrimer-encapsulated nanoparticles. *J Phys Chem B*. 2005 109: 692-704.
- Seong GH, Crooks RM. Efficient mixing and reactions within microfluidic channels using micro-bead supported catalysts. *J Amer Chem Soc*. 2002 124:13360-13361.