and the pharmaceutical industry produce the safest drugs possible in the ideal dosage range. However, more can be done. It is recognized that many drugs are safe for some people, but can produce serious side effects in others. It is also recognized that the recommended dosage is either too small or too large for some people. These remain significant areas of drug development that are as much an art as a science.

We really do not understand fully how drugs activate receptors, or what the optimal drug dosage is for each patient. Many believe that the future will bring a better understanding of these problems, but the future is a vast realm of information that needs interpretation and perspective. Often, our perspectives on the tough scientific questions concerning drug development are based on intuition, experience and perception. We want the best drugs but we spend billions of dollars on projects that get us no closer to a basic understanding of the underlying biophysical processes. Frequently, this is because we have failed to ask the right questions. How can we design safer, more fault-tolerant medications? What are some of the side effects we can prevent? What produces the response when a drug contacts its cellular receptor? Some partial answers to these questions are that we could prevent drug–receptor desensitization with the right approach [4] and, thereby, enhance the safety and efficacy of many drugs [5]. Conventional wisdom might not want to recognize some of these problems because it wants people to believe that they are receiving the best drugs. Ironically, this is true, but to make progress, we must take a hard look at those areas in which progress needs to be made, and develop creative alternatives to the conventional wisdom.

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Dendrimers and protein cages as nanoparticles in drug delivery

The recent overview by Sanjeeb Sahoo and Vinod Labhasetwar, entitled 'Nanotech approaches to drug delivery and imaging', [1] summarizes efforts in this area well. The article is organized by type of nanostructure and provides examples of polymeric biodegradable nanoparticles, ceramic nanoparticles, polymeric micelles, liposomes, dendrimers, nanocrystals and ferrofluids.

Because the focus of my research group is on multivalent cell-surface recognition processes using dendrimer frameworks, I read this article with much interest. The review cites an example in which dendrimers coated with phospholipids are used as delivery vessels for 5-fluorouracil [2]. This is one of the best examples of dendrimers that encapsulate therapeutic agents. In my research laboratory, we use a variety of isothiocyanates to functionalize dendrimers heterogeneously through thiourea linkages to surface residues [3,4]. Although our work is primarily basic research and quite academic, one of our goals is to use surface groups on the dendrimer framework both for targeted delivery and for linking the prodrug to the dendrimer. A nice example from another group demonstrating the use of heterogeneously surface-functionalized dendrimers for targeted imaging describes ^{153}Gd-folate dendrimers [5]. Because the synthetic routes are relatively straightforward and heterogeneously functionalized dendrimers are readily attained, dendrimer surface patterning has enormous potential for targeted drug delivery.

When considering nanoscale frameworks for drug delivery, the heart of the issue is clearly the biocompatibility of the frameworks. The nanoparticles and macromolecules might effectively solve many problems such as targeting drug delivery, extending product lifetime and increasing aqueous solubility, but these improvements often come at a cost because of size. The clearance rate of the nanomaterials might be high, and the likelihood of the nanoparticle lodging in certain organs such as the liver could make adoption of nanoparticles impractical in many instances. In addition, some frameworks might be too large to fit through small capillaries. One of my concerns is that many researchers who develop nanoparticle drug delivery systems might be overlooking the potential immunogeneity of the frameworks when they are considering them for clinical use. Luckily, those of us whose research is focused on the development of nanoparticles can draw from reports of polymer–drug conjugates [6]. Although the nanoparticles are often smaller and less polydisperse than the polymers, problems with the toxicity of the framework might be similar.

Like Sahoo and Labhasetwar, I feel that nanoparticles do play an important

role in drug delivery. In cases in which the advantages afforded by multivalency are crucial components for enhancing affinity and selectivity, the appropriate framework can be chosen from the many highlighted in their review to minimize biocompatibility problems. Indeed, several groups are currently developing new nanoscale frameworks that hopefully will see use in the area of drug delivery.

Another nanoscale framework that our group is using is a protein cage. In a highly multidisciplinary research effort as part of the new Center for Bioinspired Nanomaterials at Montana State University (www.chemistry.montana.edu/nano/), we are tethering small dendrimers to ferritin and viral protein cages. These protein cages assemble from a single subunit, and their architectures define a cavity in which small molecules and nanomaterials can be sequestered. The small dendrimers on the protein cages will ultimately be used for multivalent molecular recognition. Our focus is on the development of protein cages with interesting magnetic properties, which can be coupled to targeted drug delivery.

The description by Sahoo and Labhasetwar of a variety of frameworks that are currently being developed for use as nanoscale drug delivery and imaging devices suggests exciting possibilities in this area. The role and scope of nanoparticles in drug delivery is growing. I would like to hear from the readership of *Drug Discovery Today* about which biological systems and targets they feel are most likely to benefit from nanoparticle frameworks in drug delivery.

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