In particular, it will be important to strike an appropriate balance between the basic research needed to progress these ideas and the required industrialization of the techniques. As an example of this balance, European researchers have just been granted funds from the European Union to pursue the development of laser-driven electron accelerators into the GeV energy regime, with a view to creating reproducible monochromatic beams. Alongside this, a demonstration proton oncology laser system known as “ProPulse” is being pursued by a team led by the Laboratoire d’Optique Appliquée (LOA) in France, with the goal of raising the energy of the proton beam to the required 70- to 250-MeV level. These two ambitious projects will help demonstrate whether laser acceleration of particles is a viable route for fundamental physics studies and clinical applications.

Looking further into the future, an exciting new proposal is being developed by a consortium of researchers led by Mourou (at the LOA) for ultrarelativistic particle beam lines based on exawatt-class laser technology. This project, known as Extreme Light Infrastructure, is currently under consideration as part of the European Research Infrastructure roadmap process (10). Its goal is to provide multiple accelerator beam lines delivering high-brightness electron, gamma, and proton sources for a wide range of user applications. It is clear that we are still a number of years away from exploitation of these laser-driven accelerators, but this should not detract from the major advances demonstrated over the past few months. Unprecedented research attention is being paid to this area, which is already paying dividends as demonstrated by the innovative techniques reported here. This is definitely a field to watch.

References and Notes
1. T. Toncian et al., Science 312, 410 (2006); published online 16 February 2006 (10.1126/science.1124414).
10. For information on the European Strategy Forum on Research Infrastructures, see (www.cordis.lu/esfri/home.html).

10.1126/science.1126051

Self-Assembly of Unusual Nanoparticle Crystals

Orlin D. Velev

The crystallization of matter on any length scale, from atoms and ions to biomolecules to nano- and microparticles, has long been a major thrust in science and technology. On page 420 of this issue, Kalsin et al. (1) report the cocrystallization of equally sized metallic nanoparticles into large crystals with diamond-like symmetry. The oppositely charged gold and silver nanoparticles attract each other at very short distances and assemble into unusual lattices. This work provides new insights into crystallization on the nanoscale, and fills in a gap in the overall picture of particle and biomolecule crystallization.

It has been known for decades that micrometer- and submicrometer-sized spheres suspended in liquids readily form “colloidal crystals” during sedimentation or drying. The spheres crystallize when their free volume is restricted below a certain threshold, but this occurs only when the interactions between the spheres are repulsive, which allows their rearrangement. Such closely packed colloids allow facile fabrication of materials with controlled porosity and long-range organization (2). Volume-restricted repulsive spheres, however, always crystallize in a trivial lattice of hexagonally close-packed layers. This limits the range of their application as other types of crystal symmetries are required for photonic, optoelectronic, and memory storage applications.

The formation of colloidal crystals with other symmetries can, in principle, be achieved if the particles are assembled by attractive interactions. Two seemingly simple ideas for crystallization by particle attraction have been considered, yet they have proven notoriously difficult to realize experimentally. The first idea is to use binary mixtures of oppositely charged particles that could cocrystallize in a manner broadly similar to crystallization of ionic solids from liquid solutions. The problem with this system is that strongly attractive particles rapidly and irreversibly stick to each other, forming gel-like aggregates. Only recently have Leunissen et al. designed a procedure whereby micrometer-sized colloidal spheres having small positive or negative charges are synthesized and cocrystallized in density-matched organic liquids (3). The particles, whose attractive interaction energies are estimated to be on the order of a few \( k_B T \) units (where \( k_B \) is Boltzmann’s constant and \( T \) is temperature), come together in mixed CsCl-type lattices of alternating positive and negative charges. A variety of crystals of other symmetries and particle compositions have been assembled, and the method could be versatile enough to be used in the routine synthesis of nano- and microparticles.

A second idea for particle crystallization by attractive interactions that has also found difficult to realize is the crystallization of particles by functionalizing them with complementary DNA strands. DNA hybridization locks the particles together when they come into contact; however, the strong irreversible “snapping” into place does not allow crystallization. The key to making this idea work has been to reduce the strength of the interactions by adjusting the temperature of the suspension very near the melting point of DNA, where hybridization is weak and reversible (4). Thus, colloidal crystallization may be achieved by various attractive forces, but only when the interaction energy is precisely adjusted within a certain small range (see the figure).

Systems of nanoparticles 1 to 10 nm in size provide a natural link between the areas of molecular and colloidal crystallization. Crystals from such particles can find applications in nanoelectronics, plasmonics, high-density data storage, catalysis, and biomedical materials. The formation of binary crystals from nanoparticle mixtures as a likely result of cocrystallization under restricted volume conditions was reported some time ago (5). Only recently has the role of electrostatics in the formation of nanoparticle crystals emerged as a parameter that can be controlled in order to assemble various crystals of new symmetry and composition (6). The report by Kalsin et al. conclusively proves that large crystals can be produced by controlled electrostatic self-assembly. The crystallization has been achieved by precise adjustment of the attraction between the oppositely charged nanoparticles, but the data also point to the existence of unusual effects of electrostatic screening of the larger particles by the smaller ones that do not scale up to interactions between microparticles.
Packing together. The crystallization of colloidal particles and biomacromolecules is intrinsically related to the interactions between the particles, which often can be controlled by their charge (graph at left). Repulsive spheres can easily be crystallized by restricting their volume. Proteins and binary mixtures of oppositely charged particles can be crystallized by precise adjustment of the interactions into a weakly attractive regime. However, if the interactions between the particles are strongly attractive, rapid precipitation of amorphous aggregates occurs. The micrograph images are of colloidal crystals assembled by restricting the free volume of repulsive latex spheres (left), crystals of the protein lysozyme obtained under slightly attractive interactions (center), and a nanoparticle crystal assembled under controlled electrostatic attraction (2) (right).

Interestingly, the idea that the key to crystallization is achieving a precise balance among weak attractive interactions has been actively explored in the field of protein crystallization for more than a decade. Proteins are large, complex molecules of nonuniform shape and charge, which have been shown to crystallize only under conditions of slightly attractive interactions when both positively and negatively charged groups are present on their surfaces (7). The intricate fundamentals of the attractive electrostatic interactions between nanoparticles in a crystal are still not understood in depth. It seems that the concepts developed for proteins may now provide a roadmap for nanoparticle crystallization.

Future research in nanoparticle assembly may bring closer the areas of biomacromolecule and nanoparticle crystallization. Could a similar charge-balancing approach be applied to binary mixtures of proteins, or mixtures of proteins and nanoparticles? A large variety of nanoparticles of special shape and properties have been synthesized in the past few years, but little is yet known about their self-assembly. New “zwitterionic” particles, having patches of negative and positive charges on their surfaces, could soon be synthesized and crystallized by adjustment of the interactions in a manner similar to the crystallization of proteins. Thus, nanoparticle crystallization and assembly may not only yield new nanomaterials, but could also provide insights into how to control colloidal forces on the nanoscale.

References
1. A. M. Kalsin et al., Science 312, 420 (2006); published online 23 February 2006 (10.1126/science.1125124).
10.1126/science.1125800

PHARMA COL OGY

Hitting the Hot Spots of Cell Signaling Cascades

John Joseph Grubb Tesmer

Transient protein-protein interactions are hallmarks of intracellular signaling cascades triggered by heterotrimeric guanine nucleotide-binding proteins, or G proteins (1). Hundreds of cell surface receptors for hormones and other extracellular factors activate G proteins, thereby regulating nearly all aspects of cell physiology. These receptors are the targets of a large fraction of the pharmaceutical drugs being used today. Thus, small molecules that negatively or positively modulate the protein-protein interactions of G proteins could likewise be powerful therapeutic agents (2, 3). However, drugs that target protein-protein interfaces are harder to develop than those that target the active sites of enzymes, which are often found in deep, well-defined pockets on the protein surface. Many of the protein-protein interfaces found in signaling cascades are comparatively flat and expansive. They also tend to be adaptive, meaning that a signaling protein can use the same surface to bind to a structurally diverse set of targets (1, 2, 4). This renders it difficult to find a drug that can turn one particular signaling pathway on or off without affecting the others.

One way to overcome at least some of these hurdles is to identify compounds that target the so-called “hot spot” of the protein-protein interface (5). In many transient protein-protein interactions, a majority of the binding energy is contributed by only a few amino acid residues within the interface. These “hot” amino acids tend to cluster together in a relatively small, central region surrounded by a ring of less energetically important and more water-accessible residues (6–8). Thus, small molecules can disrupt a comparatively large protein-protein interface by binding to the hot spot or, alternatively, to an allosteric site that alters its conformation (2).

On page 443 of this issue, Bonacci et al. (9) use a computer-based “virtual” screen of only 1990 structurally diverse compounds (available from the U.S. National Cancer Institute) to identify molecules that bind to the β2 subunits of a G protein (Gβγ). G proteins consist of three subunits. In the classic G protein signaling cascade, Gβγ subunits are released as a complex from the α subunit (Gα) after activation of an associated receptor at the cell surface. The Gβγ complex can subsequently
Self-Assembly of Unusual Nanoparticle Crystals
Orlin D. Velev

Science 312 (5772), 376-377.
DOI: 10.1126/science.1125800

ARTICLE TOOLS
http://science.sciencemag.org/content/312/5772/376

RELATED CONTENT
http://science.sciencemag.org/content/sci/312/5772/420.full

REFERENCES
This article cites 7 articles, 1 of which you can access for free
http://science.sciencemag.org/content/312/5772/376#BIBL

PERMISSIONS
http://www.sciencemag.org/help/reprints-and-permissions

Use of this article is subject to the Terms of Service

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title Science is a registered trademark of AAAS.
© 2006 American Association for the Advancement of Science