Taken together, the findings by Li et al. as published in this issue of *Chemistry & Biology* are exciting and offer new mechanistic insight and potential therapeutic strategies for PD. At the same time, these results in conjunction with the above discussed findings give rise to a number of questions that need to be addressed. For example, what are the chemical and quarternary structure(s) of the α-synuclein oligomers that are potentially stabilized by rifampicin, baicalein, or dopamine? What is the morphology and what are the biochemical, biophysical, and cell viability-associated properties of these species? Are they neurotoxic oligomers or are they nontoxic oligomers? Are the oligomers that are stabilized by rifampicin (or the other compounds) via interaction with soluble α-synuclein different from the oligomeric species that are generated from fibril disaggregation? If β sheet-rich α-synuclein oligomers or protofibrils were in fact neurotoxic [8, 9] and the stabilized oligomers had properties similar to them, this would possibly result in a rifampicin-/baicalein-/dopamine-enhancing effect on α-synuclein-associated neurotoxicity. On the other hand, if the "fibril disassembly" oligomers and the stabilized partially ordered oligomers were noncytotoxic and because conditions of oxidative stress promote α-synuclein fibrillization and neurotoxicity by rifampicin, baicalein, and related compounds would offer a reasonable perspective for the development of drugs to combat PD and, possibly, AD and other protein aggregation diseases [16, 17].

Finally, for the potential long-term use of rifampicin and related compounds in a novel disease situation, i.e., its use as a therapeutic in cell degenerative diseases, it appears important to find out if and how efficiently these compounds may unwantedly modify cellular proteins other than the amyloidogenic proteins. However, these potential drawbacks could well be counter balanced, because the medical use of rifampicin is long established in principle from its application in infectious diseases.

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Microbe Manufacturers of Semiconductors

Synthesis of cadmium sulfide (CdS) semiconductor nanoparticles within a prokaryotic organism is reported for the first time by Sweeney et al. [1]. This paper demonstrates the utility of microorganisms to perform chemistries outside the scope of their "normal" metabolism and offers an environmentally benign synthesis of CdS nanoparticles.

Semiconductor nanoparticles are an extremely important class of materials with properties that can be finely tuned through composition, size, and particle morphology. This is illustrated by the technological drive toward the single electron transistor and in the use of semiconductor nanoparticles for bioimaging. It is well known that the properties of semiconductors change as a function of size, shape, and crystallinity. Cadmium sulfide (CdS) is a semiconductor material that has been used for such applications as fluorescent labels and optoelectronic transistor components, where particles of approximately 4–5 nm in diameter behave as so-called quantum dots (QD) [2, 3]. These particles when embedded within an appropriate matrix act as potential wells that confine and stabilize electrons in discrete energy levels. The technologically useful properties of CdS QDs are due in part to the fact that the band-gap is tunable over a range of 1.5–3.5 eV (i.e., visible to UV).

Many synthetic routes to semiconductor nanoparticles involve highly toxic solvents, explosive precur-

sors, high temperatures (~250°C–230°C), and anoxic conditions [4–6]. Although methods that utilize less hazardous precursors can also be used, these methods still require high temperatures [4]. An advantage of current synthetic methods for the production of CdS nanoparticles is the ability to control particle morphology by varying conditions. Tunable synthesis results in monodisperse CdS nanoparticle populations of particular shape (dots, rods, tetrapods), size (2–25 nm), and luminescent properties [7]. Using mild biomimetic synthetic conditions, CdS, ZnS, CdSe, and ZnSe nanoparticles have also been synthesized using biological molecules as templates, including fatty acids, polyphosphates, amino acids, and small thiol-containing glutathione-like peptides [1, 7, 8]. In addition, supramolecular protein assemblies including viral protein capsids have served as nanometer-scale templates for directed synthesis of CdS [10, 11]. In many of these syntheses, the size and crystallinity of the QD is determined by the biotemplate as the CdS (or other) nanoparticles nucleate and grow. Biosynthesis of CdS nanometer-sized crystallites has been described previously in eukaryotes, where two yeast species, *Candida glabrata* and *Schizosaccharomyces pombe*, produced CdS nanoparticles when cultured in the presence of cadmium salts [8, 9].

In this issue of *Chemistry & Biology*, Sweeney et al. [1] present the first CdS nanocrystals synthesized within a prokaryotic organism. This "green chemistry," microbial culture approach, demonstrated within *Escherichia coli*, is strikingly different from current synthetic approaches to the synthesis of semiconductor nanoparticles. Bacteria were grown in rich medium, at 37°C, supplemented with $CdCl_2$ and Na_2S prior to isolation and characterization of the intracellularly produced CdS nanoparticles. The CdS nanoparticles produced within *E. coli* bacteria range in diameter from 2–5 nm. Although moderately polydisperse, it is estimated that each bacterium generated greater than 10,000 CdS nanoparticles! In this work, the capability of biological systems for materials synthesis was harnessed prior to understanding *how* the organisms control CdS crystal formation. The genetic, and in turn biochemical, basis of CdS formation within *E. coli* is currently being investigated. Interestingly, only two of the four *E. coli* strains tested produced CdS nanoparticles. Having bacterial strains with different phenotypes will prove useful in the investigation into the mechanism behind CdS biosynthesis. *E. coli* genetics are well understood; genes can be easily replaced, overexpressed, and/or introduced utilizing routine molecular biological methodologies. Therefore, elucidation of the mechanism of CdS nanoparticle formation in *E. coli* might enable researchers to "genetically tune" properties, including size, shape, and crystal structure, to match the technological requirements for these materials.

One approach to understanding the role of the *E. coli* genes and proteins involved in CdS nanoparticle formation is to look for *E. coli* homologs of particular genes known to be important to the processes of heavy metal uptake, efflux, and sequestration in other microorganisms [12]. While some organisms tolerate cadmium in their environment, no organisms known to date require cadmium for life, and most organisms (including humans) are sensitive to its toxic effects. Previous research in the fields of plant physiology, microbial ecology, and bioremediation has led to the characterization of cadmium-resistant organisms (both prokaryotic and eukaryotic). Investigations into the molecular and genetic factors responsible for heavy metal tolerance have uncovered some interesting pieces of the puzzle, but the entire story varies in different organisms and there is a lot of work to be done in this field. The importance of unraveling the complex set of events leading to CdS nanoparticle formation in bacteria, yeast, and plants reaches beyond the immediate goals of nanotechnologists to produce CdS nanoparticles in a cost-effective manner. These organisms have great potential for effective bioremediation of cadmium-contaminated sites, particularly those associated with mining.

Metals such as Mn^{2+}, Co^{2+}, and Zn^{2+} enter Gram-negative bacteria (including *E. coli*), archaea, and yeast cells through fast metal inorganic transport (MIT) systems [12]. These pathways are nonspecific, and thus it is probable that Cd^{2+} enters microorganisms via MIT systems [12]. Bacteria usually deal with cadmium toxicity through elimination via efflux pumps, whereas yeasts usually sequester cadmium in nanocrystals [8, 12]. Sequestration is a more "energy expensive" process requiring 16 molecules of ATP (adenosine triphosphate) in order to generate one sulfide (from reduction of sulfate) which complexes one cadmium. While sequestration may involve a large energy expenditure, efflux systems require only about one ATP for every one Cd^{2+} effluxed [12]. Energetic expenses are more crucial when cells are growing quickly or exponentially, as they are in log phase growth of *E. coli*. Consistent with this analysis, Sweeney et al. [1] only observed significant CdS nanoparticle formation during stationary growth phase (when *E. coli* are replicating at a much slower rate). However, this energetic argument must be tempered by the fact that in these experiments the *E. coli* are provided with sulfide directly, perhaps bypassing normal metabolic requirements for sulfide production. It might be possible that the two *E. coli* strains that form CdS nanoparticles are deficient in proteins required for Cd^{2+} efflux. On the other hand, these strains of *E. coli* may have acquired the genes encoding proteins necessary to sequester cadmium. Definitely, further genetic analysis of these strains will prove to be very interesting.

As mentioned by Sweeney et al. [1], glutathione (a tripeptide consisting of cysteine, glutamic acid, and glycine) has been shown to be important for cadmium tolerance in organisms including yeast, plants, and animals [13]. For example, phytochelatins are composed of glutathione-like peptide repeats and are known to bind and sequester heavy metals including Cd^{2+}. While Sweeney et al. did find an increased thiol concentration in stationary phase cultures (correlating with abundant CdS nanoparticles), they did not find differences in thiol content between the *E. coli* strains that do and do not produce CdS nanoparticles. In order to investigate other cellular components that may be important to CdS nanoparticle formation within *E. coli*, the authors visualized nanoparticles within bacterial cells embedded in resin (60 nm slices) by transmission electron microscopy (TEM). Energy dispersive spectroscopy (EDS) was used for elemental analysis of areas around CdS nanoparticles. This analysis showed colocalization of phosphorus, nitrogen, iron, and oxygen, possibly implicating phosphates in the mechanism of CdS mineralization.

In conclusion, it will be important to establish the mechanism of CdS nanoparticle synthesis in bacteria. The results of this work will undoubtedly prove useful to many fields, including bioremediation and nanotechnology. In addition, it will be interesting to see if the bacterial proteins responsible for CdS biomineralization bear any sequence resemblance to the CdS binding peptide sequences discovered via phage display techniques [11].

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Finding Their Groove: Bifunctional Molecules Arrest Growth of Cancer Cells

In this issue, Dickinson et al. describe an exciting advance in the search for inhibitors of transcription that function well in cells [1]. The authors screen for small molecules that selectively damage DNA and identify a histone gene as a potential new target for cancer therapeutic development.

Many human diseases exhibit altered patterns of gene transcription [2–4]. Overexpression of the human transcriptional inhibitor Mdm2, for example, has been correlated with a number of human cancers [5–7]. These altered patterns are a signature of a particular disease, they are useful for characterization and diagnosis, and they further offer an opportunity for targeting therapies specifically to diseased cells. One exciting approach is to home in on the affected genes themselves and interrupt or promote their transcription by using molecules that interact with specific DNA sequences [8–11]. So, for example, a triplex-forming oligonucleotide that prevents the transcription factor Sp1 from binding to DNA effectively inhibits the transcription of the *Src1* gene regulated by that protein in cell culture [12]. Among the historic difficulties with identifying small molecules that can accomplish this task is that such molecules must not only be cell and nuclear permeable but also must compete for DNA binding sites with a wide range of proteins in order to exert their function. An additional hurdle is that the molecules must interact with only a minimal number of binding sites within the genome in order to avoid affecting numerous biological processes. The most common approach taken to develop transcriptional inhibitors relies upon designing a molecule to target a specific DNA binding site associated with the gene of interest. The designed molecule is then tested first in vitro and subsequently in cell culture. However, it is often difficult to predict the behavior of the molecule in the complex environment of the cell based upon in vitro results due to issues of cell and nuclear permeability as well as the accessibility of the cognate DNA binding sites in the context of chromatin.

The approach taken by Gottesfeld and Dervan in this issue of *Chemistry & Biology* circumvents some of the difficulties outlined above and represents a departure from the typical mechanism of transcriptional inhibitor discovery [1]. Instead, the authors synthesized a small group of molecules and screened for activity in human colon cancer cells before investigating the origin of the observed effects. The molecules themselves are bifunctional, containing a sequence-specific DNA binding module and a functional group that damages DNA (Figure 1). The DNA binding module is a hairpin polyamide, a minor groove binding agent composed largely of heterocyclic amino acids that mediate sequence-specific interactions with the functional groups present in the minor groove. The mode of binding for hairpin polyamides is such that pairs of heterocycles bind side-by-side in the minor groove recognizing a specific base pair in a predictable manner—G•C versus C•G, for example—and it is thus possible to design a structure that recognizes a particular sequence. The authors prepared five polyamide-based structures for screening, each with a distinct