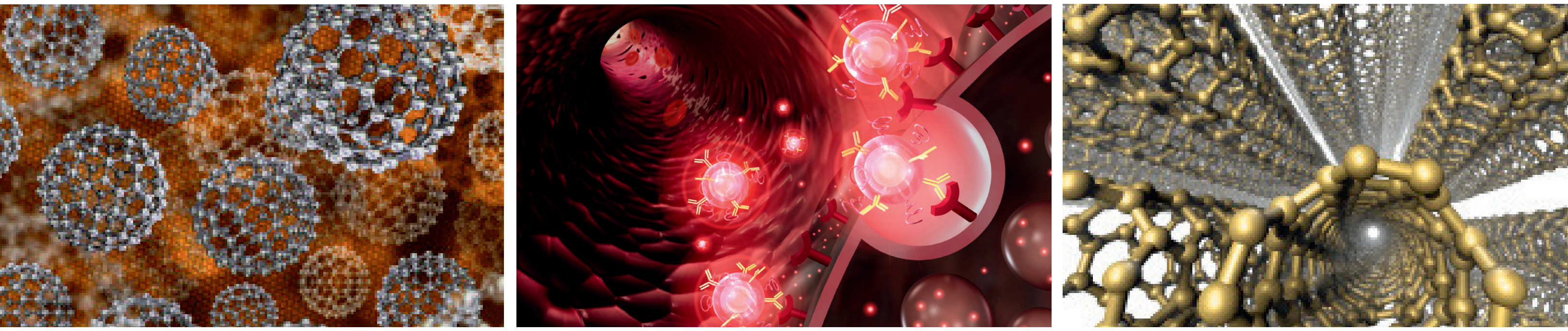
Nanotechnology: The Promises and Pitfalls of Science at the Nanoscale



A white paper examining the emerging science, applications, and controversies of chemistry at the nanometer scale

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I. INTRODUCTION

In the nearly 15 years since the federal National Nanotechnology Initiative (NNI) was launched, "nanotechnology" has transitioned from buzzword to reality. The United States government alone has dedicated some $20 billion to nanotech research in that time, and there have been many billions more in foreign and private investment.

According to a 2014 report by Lux Research Inc., "Total spending on nanotechnology research and development (R&D) and start-ups by governments, corporations, and venture capital (VC) investors reached $18.5 billion in 2012, an 8% increase over 2010, with $6.6 billion of this spending from the U.S."[1]

In the U.S., interest in nanotechnology remains high. The Obama Administration's 2016 budget for the NNI requests $1.5 billion, down slightly from $1.57 billion in 2014.[2] In September 2015, the National Science Foundation announced some $81 million in new funding for nanotech research, according to a report in *Chemical & Engineering News (C&EN)*.[3] And according to a June 2015 report in *C&EN*, the White House has announced "that nanotechnology will be at the core of its newest grand challenge."[4]

Today, the fruits of that research are all around us. There are nanotech-based cosmetics, and coatings, electronics, diagnostics, therapeutics, and even clothes, with nanotechnology promising "water-resistant and dirt-free clothes, odor-less socks, and intelligent clothes that can perform climate control for you."[5] In one recent example, Aamir Patel, a San Francisco-based student and "aspiring entrepreneur," raised nearly $300,000 on Kickstarter in 2013 to fund development of Silic, a "self-cleaning" fabric "layered with billions of silica particles, preventing most liquid molecules from attaching to it."[6] According to Lux Research, revenue from "nano-enabled products" jumped from $339 billion in 2010 to $731 billion 2012.[1] One 2015 report counts some 1,814 nanotechnology-derived products on the market.[7]

The NNI defines nanotechnology as "science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers."[8] The term is fuzzy, as that size range also includes such materials as polymers, proteins, viruses, and subcellular components, which are not usually categorized as nanotech. But generally speaking, when researchers speak of nanotechnology, they mean those materials and processes that take advantage of the unique behaviors and properties that are found only at the nanoscale: The nanoscale is the size regime at which material properties are governed largely by quantum effects, according to the NNI web site.[9]

Unlike bulk materials, the behaviors of nanomaterials vary with size. For instance, semiconductor quantum dots – nanoscale crystals of semiconducting material such as cadmium-selenide – fluoresce like organic dyes. But their emission spectra – that is, the color that they emit upon excitation – varies sharply with particle size, a feature that is not true of the bulk material.[10]

In a 2013 feature in *C&EN*, Chad A. Mirkin, director of the International Institute for Nanotechnology at Northwestern University, said of nanotechnology:

> *The general idea that everything when miniaturized is new is an incredibly powerful concept. If you take any bulk material and you shrink it down to a sub-100-nm-length scale, then you will have a material with new properties—new chemical properties and new physical properties.*[11]

The nanoscale also is the size range of biology, Mirkin says[12], meaning it is relatively straightforward to interface chemistry and biology by working at that size range. Mirkin, for instance, has coupled nanomaterials and DNA to develop an entirely new, third form of DNA, called "spherical nucleic acids" (SNAs; the other two being linear and circular molecules), which can be used to drive both diagnostic and therapeutics applications.

"You take the most important molecule ever discovered by scientists – DNA – [and] ever synthesized by a chemist, and you use nanoscience and the concept of a nanoparticle to arrange the same strand of DNA into a spherical form, and on a sequence-for-sequence basis, you get a completely different material. And it's different in every way, including the way it interacts with living systems."[12]

Others are developing nanoparticles as agents for biomedical testing, drug delivery, and even vaccines.[13] Joseph DeSimone at the University of North Carolina at Chapel Hill, recently described in *Molecular Pharmaceutics* "a versatile vaccine delivery platform based on PRINT hydrogels" that target the lymph nodes and induce a strong immune reaction comparable to traditional adjuvants.[14] Nanoparticles also support some decidedly more mundane uses, too. For example, in forming the foundations of such products as sunscreens containing nanoparticulate titanium dioxide or zinc oxide, paints, and antimicrobial coatings.

SNAs, nanoparticles, and quantum dots are just a few of many kinds of nanomaterials researchers study. There are also buckyballs, carbon nanotubes, and graphene, as well as inorganic nanoparticles. Each of these possess properties that have induced considerable excitement in the nanotechnology community and among investors – though that excitement has not often been matched by commercial success.

One class of nanomaterial that has spurred considerable widespread research and commercial interest is graphene. Discovered in 2004 (and earning its discoverers a Nobel Prize just six years later), graphene is a hexagonal lattice of pure carbon just one atom thick. With exceptional electrical conductivity, strength, and flexibility, among other properties, graphene is being explored for use in transparent electronics displays and solar panels, in batteries and medical scaffolds, and even for sopping up radioactive elements.

One measure of that interest is the number of patents researchers have filed to protect their discoveries; according to a feature on graphene in *The New Yorker* magazine, there has been "a worldwide proliferation of graphene-related patents, from 3,018 in 2011 to 8,416 at the beginning of 2013."[15]

Whichever nanomaterials are to be studied, researchers need methods at hand to do just that. Today, there exists a robust and growing suite of tools that researchers can use to study and examine nanomaterials, bridging the gap between the nanoscale and macroscopic worlds. This includes old standbys like the scanning tunneling microscope, atomic force microscopy, and electron microscopy. But it also includes newer developments, such as super-resolution optical microscopes, dip-pen nanolithography, and others.

Still, despite all the advances, nanotechnology remains very much a field in its adolescence, and one in which researchers are still grappling with issues of safety and environmental impact. A Perspective published in *Science* in 2015, entitled "How safe are nanomaterials?" noted a lack of consensus on the safety of nanomaterials and the need for further studies.[16] Yet when the U.S. Environmental Protection Agency put forth rules under the Toxic Substances Control Act for collecting information on the manufacturing and safety of new nanomaterials, industry groups expressed concern, with one representative calling the rule "highly subjective and arbitrary" and creating "an uneven playing field for nanomaterial manufacturers and processors."[17] Nevertheless, nanotechnology appears set to remain an area of active interest and funding for some time to come, for both researchers and manufacturers alike.

II. WHAT'S 'NANO': A NANOTECHNOLOGY PRIMER

Etymologically speaking, "nanotechnology" refers to any material or engineering occurring at the nanometer scale. Yet according to Paul Weiss, Editor-in-Chief of *ACS Nano* and Distinguished Professor of Chemistry and Biochemistry and of Materials Science and Engineering at the University of California, Los Angeles, the term typically is construed more narrowly. Nanotechnology, he says, refers to any material "where a key dimension is [on the] 1–100 nm scale."[86] Naturally, a great many materials fall into that category, many of which would not be considered true "nanotechnology," such as synthetic polymers and protein complexes. Some "natural" (that is, not engineered) materials also would qualify, such as the colloids found in soot.[18]

In the 2013 *C&EN* feature, staff writer Bethany Halford captured the difficulty in describing nanotechnology by quoting a well-known US Supreme Court decision on pornography: "I know it when I see it."[11] Today, the evidence of nanotechnology in the world around us is plain to see.[19] There are nanotechnology-enabled fabrics and toothpastes, coatings and batteries, tennis balls and solar panels, televisions and patches and diagnostics – the list goes on and on. The most recent data from the Nanotechnology Consumer Products Inventory, a joint project of the Woodrow Wilson International Center for Scholars and the Project on Emerging Nanotechnologies, lists 1,814 products, the majority (42%) in the "health and fitness" category.[20] These products are built from such materials as organic and inorganic nanoparticles, ceramics, polymers, quantum dots, and more, including different forms of nano-structured carbon, such as carbon nanotubes, "buckyballs," and graphene.

Whatever the material, what makes the nanoscale world so exciting is that materials in that size regime often acquire new and unexpected physical properties, according to educational resources at the NNI web site.[9] Take nanoparticulate gold, for instance:

> *Nanoscale gold particles are not the yellow color with which we are familiar; nanoscale gold can appear red or purple. At the nanoscale, the motion of the gold's electrons is confined. Because this movement is restricted, gold nanoparticles react differently with light compared to larger-scale gold particles. Their size and optical properties can be put to practical use: nanoscale gold particles selectively accumulate in tumors, where they can enable both precise imaging and targeted laser destruction of the tumor by means that avoid harming healthy cells.*

Furthermore, the web site explains, properties on the nanoscale often exhibit the property of tunability – that is, of changing with the size of the nanoparticles themselves. Thermo Fisher Scientific's QDot® nanocrystal reagents, for instance, are quantum dots that are made of the same basic semiconductor materials — cadmium-selenide or cadmium-telluride coated in a layer of zinc sulfide. Yet when excited with light at the same wavelength, these materials fluoresce at wavelengths from 525 nm to 800 nm, depending on the particle size.

So, too, do quantum dots built of the hexagonal carbon lattice known as graphene. James Tour, the T. T. and W. F. Chao Professor of Chemistry at Rice University, and his team demonstrated in a recent paper in *ACS Applied Materials and Interfaces* that by synthesizing graphene quantum dots at different temperatures, they could produce particles that fluorescence anywhere from green to red based on the diameter of the resulting materials.[21]

Materials at the nanoscale have far greater surface areas than corresponding bulk materials, which also leads to new or at least amplified properties for coatings and surfaces. In the introduction to a recent special issue of *Angewandte Chemie International Edition* on nanotechnology, Younan Xia, the Brock Family Chair in Nanomedicine at the Georgia Institute of Technology, explained why that might be:

> *In this case, a nanoparticle may have essentially the same properties as a microparticle, or even a bulk single-crystal substrate; only the efficiency of utilizing the material is remarkably increased. However, such an increase can enable us to greatly reduce the cost of a device (e.g., a catalytic converter) and the achievement of resource-saving use for some of the scarcest precious metals (e.g., Pd, Pt, and Rh) that only exist in the earth's crust at the parts-per-billion level. Of course, when the size of a particle is reduced, it can also increase the proportion of atoms at vertices and edges relative to the faces, which may change the activity and selectivity of a particle too.*[18]

One example, says Anthony Schiavo, a Research Associate on the Advanced Materials team at Lux Research, Inc., are nanoparticle-based "superhydrophobic" or "lotus leaf" coatings, highly water-repellant materials that can be used to create self-cleaning surfaces, water-repellant goggles, efficient heat exchangers, and more.[23]

Nanostructured materials can exhibit novel absorptive properties, as well. In 2013, Sheng Dai of Oak Ridge National Laboratory, and colleagues reported the development of a nanoporous polymer material that could be used to rapidly and efficiently absorb uranium ions from seawater.[24]

Nanocomposites built of ferric or aluminum oxyhydroxide are being used in West Bengal, India, to eliminate arsenic and bacteria from drinking water. As reported in *C&EN*, the success of this material seems to be due to surface area improvements at the nanoscale: "The team boosted their metal oxyhydroxide's activity by reducing the particle size to nanoscale, thereby increasing the surface-to-volume ratio, and anchoring the material within a network of chitosan."[25]

Nanoscale catalysts are often more efficient than their bulk counterparts. But that's not only because of their size: In a 2012 review, University of Central Florida researcher Beatriz Roldan Cuenya demonstrated that platinum nanoparticles of comparable size (0.8–1 nm) but different shape vary in their ability to catalyze the oxidation of 2-propanol. "A correlation between the NP shape and the onset reaction temperature was observed," she reported.[26]

Perhaps most exciting, though, is that nanotechnology operates at the scale of biology. Thus, researchers can develop materials to interface with biological systems, such as nanoparticles that are capable of directly engaging proteins or entering cells and tissues. One 2014 review lists 10 nanoparticulate anticancer therapies currently approved for use in humans, including Abraxane (a nanoparticulate form of paclitaxel developed by Abraxis Biosciences and used for treating breast cancer), as well as more than a dozen other materials in clinical trials.[27] "Compared with traditional chemotherapeutics, the delivery of anticancer drugs through a nanoparticle-based platform offers many attractive features," the authors write, such as improved delivery of water-insoluble compounds and increased dosing, improved pharmacokinetics and maintenance in the circulation, options for multi-drug delivery and controlled drug release, and more. Plus, by controlling nanoparticle shape, researchers can extract other desirable properties, as well. Teri Odom, the Charles E. and Emma H. Morrison Professor of Chemistry at Northwestern University and Executive Editor of *ACS Photonics*, is exploring the applications of gold structures called "nanostars." Nanostars, Odom explains, are branched gold structures that taper to "well defined" points measuring about 2 nm, about the size of a protein. "So you can have one protein in essence bind to the point of the star."[28]

In one recent study, Odom's team used gold nanostars conjugated to a HER2-targeting aptamer – what Odom calls a "chemical antibody"[28] – to enhance the killing of cultured cancer cells. In this case, the team exploited the fact that nanoparticles often become sequestered within intracellular compartments called lysosomes to increase the degradation of the cancer cell receptor HER2, leading to cell death by apoptosis.[29]

The primary focus of Odom's lab, though, is nanophotonics, the application of nanotechnology to manipulate light. In one 2015 study, she and her team demonstrated the ability to turn an array of gold nanoparticles into a tunable plasmonic laser (from 858–913 nm), based on the refractive index of the dye solution surrounding the nanostructures.[30] In a traditional macroscale system, Odom explains, the only way to tune a laser is by changing the distance between the mirrors in the laser "cavity." "But in our case, our cavity is the same; the array of nanoparticles is not changed. You've just changed the local refractive index around the particles, and you get all this amazing tunability."[28]

In a subsequent study in *ACS Nano*, the team showed that by mounting the array on what essentially is a kind of mirror, they could direct the laser energy in a single direction.[31] According to Odom, such lasers could be used to miniaturize components for optical communications and to drive high-precision photolithography, among other applications.[28] Another recent study from Odom's lab demonstrated the ability to use engineered nanostructures called "lattice opto-materials" (essentially arrays of nanometer holes in a solid substrate) to manipulate light into desired patterns – a strategy that could be used to produce a nanoscale lens or for high-resolution biological imaging.[32]

III. IMAGING AT THE NANOSCALE

To study materials at the nanoscale, researchers must be able to access that domain. But they cannot use standard microscopy techniques. Materials on the nanoscale are, for the most part, invisible to traditional light microscopy, as they are smaller than the so-called diffraction limit (which holds that a microscope cannot distinguish two particles separated by less than about half the wavelength of the light used to view them). There are, however, dedicated instruments that researchers can use instead, and several fall under the category of "scanning probe microscopy."

One of the first tools for visualizing the nano-world in this class was the scanning-tunneling microscope (STM).[33] Developed in 1981 by Gerd Binnig and Heinrich Rohrer at IBM in Zürich, the STM is a kind of electron microscope featuring an extremely sharp tip (just one atom in diameter) at the end of a long arm (called a "cantilever"). When the stylus is positioned above an electrically conductive sample at a distance of about two atomic diameters, an electrical current can flow between tip and sample, a quantum-mechanical process called "tunneling."

STM provides a mechanism for measuring sample topology. Essentially, as the tip is moved across a surface, the system adjusts to maintain a constant tunneling current. As the sample elevation "rises" – say, because of an atom on a surface – so too does the stylus. Likewise, the stylus dips when there is a "hole" in the sample, and the system records these changes by bouncing a laser off the end of the cantilever arm and measuring its deflection. In an alternative operating mode, the STM tip height is held constant to record differences in current. The resulting system features angstrom to sub-angstrom resolution both horizontally and vertically, allowing researchers to map the structure of a surface atom by atom. For instance, the cover image of a 2013 feature on nanotechnology in *C&EN* features an STM image of carbon monoxide molecules arranged on a copper substrate to spell out "1nm," complete with two arrows separated by that distance.[11]

Binnig and Rohrer were awarded half of the 1986 Nobel Prize in Physics for their discovery of STM, splitting it with Ernst Ruska, who developed the electron microscope. In the press release announcing the award, the Royal Swedish Academy of Sciences alluded to the rising field of nanotechnology they helped usher in:

> *The scanning tunneling microscope is completely new, and we have so far seen only the beginning of its development. It is, however, clear that entirely new fields are opening up for the study of the structure of matter. Binnig's and Rohrer's great achievement is that, starting from earlier work and ideas, they have succeeded in mastering the enormous experimental difficulties involved in building an instrument of the precision and stability required.*[33]

Yet according to Chad Mirkin at Northwestern University, STM suffers from one fundamental limitation: It requires an electrically conductive sample to work.[12] Five years after STM's invention, however, atomic force microscopy (AFM) overcame that barrier.[34] As described by its authors, which included Binnig and Calvin Quate at Stanford University and Christoph Gerber at IBM San Jose Research Laboratory, "The atomic force microscope is a combination of the principles of the scanning tunneling microscope and the stylus profilometer. It incorporates a probe that does not damage the surface."

Essentially, Mirkin explains, the system uses a tip on a cantilever "as a feeler," measuring "the repulsive interactions between the atoms on the surface and the tip." As with an STM, the result is a contour map of a sample, only with the added bonus of being able to image insulating surfaces, including biological samples.[12]

In 1999, Mirkin and his team developed a method to turn an AFM, which essentially reads a surface, into a nanoscale "writer," a technique they called dip-pen nanolithography (DPN). Using such a system, researchers are no longer limited to visualizing objects on the nanoscale, they also can build materials and devices from myriad materials that can be deposited from tips onto surfaces with nanoscale precision.

In a proof-of-principle study in *Science*, Mirkin's team used an AFM tip coated in 1-octadecanethiol to pattern that material on a gold surface via a water meniscus, creating lines, arrays of dots, and a grid.[35] Mirkin formed NanoInk in 2002 to commercialize the technology, but the company shut down in 2013. Among other problems, Mirkin says, was throughput: to scale up, DPN requires large arrays of cantilevers, and that number can become unmanageable if researchers wish to write nanoscale features over micrometer- or millimeter-sized areas.

More recently, Mirkin's lab has developed newer nanolithography techniques to ramp up the throughput, including polymer-pen lithography and beam-pen lithography. In polymer-pen lithography (PPL), the AFM cantilevers are replaced with an array of inverted pyramids built of a soft elastomer such as polydimethysiloxane.[36] Those tips act as an array of styluses, and Mirkin's team has generated arrays of up to 11 million operating in tandem. The array is dipped into an "ink" (such as 16-mercaptohexadecanoic acid) and then "written" onto gold. In one proof of principle, the team traced 15,000 copies of the Beijing 2008 Olympics logo on a 1-cm^2 surface, each comprising some 24,000 "dots."

Beam-pen lithography (BPL) uses that same pyramidal architecture, but coats each pyramid (except its tip) in gold. That configuration allows the pens to be used to guide a beam of light for sub-diffraction-limited photolithography applications, such as patterning features on a photoresist.[37] In its original incarnation, each BPL pen wrote in unison, allowing users to create thousands of copies of the same pattern. More recently, Mirkin's team interfaced the system with a "digital micromirror device," providing a mechanism for addressing each pen independently. Among other things, the team used that configuration to create a millimeter-scale global "map" with nanosized features.[38]

As described in the research article,

> *… [an] 8,100 pen array was used to generate a mosaic map of the world wherein each tile of the world image was a bitmap depicting the structure of a unique molecule from the PubChem database. Importantly, this pattern was chosen to highlight the multiscale nature of patterning as the macroscale pattern (the map of the world) is composed of microscale objects (chemical formulae) which are in turn entirely composed of nanoscale dot features. The final pattern consists of 1.3 million dot features arranged to define 900 molecular structures in a 9 × 9 mm2 area.*

Both BPL and PPL technologies are being commercialized by another Mirkin start-up, TeraPrint, creating what he calls “the first ‘desktop fab’ based upon scanning-probe lithography capable of making macroscopic prototypes with sub-100 nm resolution.”[12]

IV. SUPER-RESOLUTION MICROSCOPY

To actually view nanomaterials, researchers can and do use transmission and scanning electron microscopy (SEM). SEM is particularly useful, as it can reveal both sample topography and elemental composition. For example, when coupled to an energy-dispersive x-ray spectroscopy detector). But until recently, light microscopy was of little value for nanotech research, as nanoscale materials by definition are smaller than the resolution capabilities of these instruments.

The resolving power of light microscopes is constrained by the so-called diffraction (or Abbe) limit, which dictates the ability of a microscope to resolve two adjacent objects. Basically, a microscope cannot distinguish two objects that are separated by less than half the wavelength of the illumination light. In other words, even with a very high-end microscope, researchers cannot resolve (nor closely examine) objects smaller than about 200 nm.

But since 2000, a series of new so-called “super-resolution” microscopy techniques have opened up the nanoscale world to light-microscopy examination. One such super-resolution method is STED (stimulated emission depletion). In this method, a fluorescently labeled sample is raster-scanned by two overlapping lasers; the first excites the fluorophores within a diffraction-limited spot, while the second essentially shrinks down the excitation volume to under the diffraction limit by deactivating fluorophores at the spot periphery using stimulated emission.[39]
STED was developed in the 1990s by Stefan Hell of the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, and described in a pair of papers in 1999 and 2000, by which point, it had achieved a resolution of just under 100 nm.[39] According to Leica Microsystems, which has commercialized the technology, the system can now resolve objects smaller than 50 nm in size.[40]

In 2006, Eric Betzig of the Howard Hughes Medical Institute Janelia Research Campus, and colleagues described an alternative super-resolution strategy. Called PALM (photoactivated localization microscopy), the approach relies on a special fluorescent protein that initially is “off.” After irradiation at one wavelength of light, the protein is activated to fluoresce, and after a brief period of excitation, it photobleaches and turns off. To use the technique, a researcher activates a relatively small number of fluorophores and records their positions with an area detector; these then spontaneously turn off, another set of fluorophores is activated, and the process repeats. Because only a few fluorophores are on at any one time, it is possible to localize them to better than 25-nm resolution; then, by consolidating the different collected images, a picture of the total dataset can be generated.[41]

Today, PALM is just one of several localization-based super-resolution microscopy techniques; others include STORM, dSTORM, F-PALM, and GSDIM.[42] Among other things, these methods can be used to characterize nanoscale catalysts. One 2015 review showed how the techniques could be used to study how reaction rates vary across a nanoparticle surface.[43] Betzig and Hell shared the 2014 Nobel Prize in Chemistry for their discoveries, alongside William Moerner of Stanford University, who also worked on a PALM-like method.

A third type of super-resolution microscopy is SIM (structured illumination microscopy). In SIM, a sample is illuminated with specific structured patterns of light from different angles. By capturing the interaction of these patterns within the sample, SIM systems can essentially back-calculate the sample's starting architecture. The Nikon N-SIM, a commercial implementation of this approach, promises 115-nm resolution in the x-y (i.e., sample) plane.[44]

One limitation of all these approaches is that they require a fluorescent sample. In 2013, researchers at Purdue University developed a super-resolution strategy that sidesteps that requirement.[45] As explained in a Purdue University press release announcing the study,

> *The imaging system, called saturated transient absorption microscopy, or STAM, uses a trio of laser beams, including a doughnut-shaped laser beam that selectively illuminates some molecules but not others. Electrons in the atoms of illuminated molecules are kicked temporarily into a higher energy level and are said to be excited, while the others remain in their "ground state." Images are generated using a laser called a probe to compare the contrast between the excited and ground-state molecules.*[46]

The team used their approach to achieve super-resolution imaging of unlabeled graphite nanoplatelets measuring 100 nm in size.

V. GRAPHENE

There exists a wide array of synthetic materials that fall under the umbrella of "nanotechnology." One of the most exciting is a form of elemental carbon called graphene. Discovered by Andre Geim and Konstantin Novoselev at the University of Manchester, UK, in 2004, graphene is a two-dimensional sheet of pure carbon in which the atoms are arranged in a flat hexagonal lattice, just one atom thick.[47] Geim and Novoselev were awarded the Nobel Prize in Physics in 2010 for the discovery. Graphene is just one member of a larger class of ultrathin materials exhibiting remarkable properties, including transition-metal dichalcogenides[48] and borophene.[49] But graphene is by far the best studied.

Like an unrolled single walled carbon nanotube – narrow graphene ribbons actually can be created in that fashion[50,51] – graphene possesses several extraordinary properties, says Tour, who has published more than 100 papers on the material and holds a number of patents on its many applications.[52] Among other things, graphene is an excellent electrical conductor – moving electrons up to 75-to-100-times faster than silicon[15]– and it is exceptionally strong for its weight, flexible, non-toxic, and stable. The material can be used to create organic quantum dots and batteries, transparent and flexible displays and solar cells, scaffolding for splitting water and repairing damaged tissue, and more.

That's not to say the material can do everything. Among other limitations, pure graphene does not function as a semiconductor, and at least traditionally, it has been hard to produce in a way that makes it useful for electronics manufacturing.[53] But researchers have demonstrated that by introducing impurities into the material, or by introducing "wrinkles,"[54] it may be possible to overcome the former problem; and in 2014, researchers at the Samsung Advanced Institute of Technology and Sungkyunkwan University in South Korea announced a potential solution to the latter issue as well.[53] As explained in a Samsung press release, researchers have previously created large pieces of graphene by allowing smaller pieces to grow and fuse into one another. But that process has tended to degrade the material's properties. "The new method … synthesizes large-area graphene into a single crystal on a semiconductor, maintaining its electric and mechanical properties. The new method repeatedly synthesizes single crystal graphene on the current semiconductor wafer scale."[55]

Still, big-time commercial applications have yet to arrive. As Tour notes, it takes probably 15 years to translate a new discovery to market, and though "graphene is moving much faster than that pace," many of them are not there yet.[52] What makes graphene so good for these different tasks and applications? According to Tour, it's because of the way that graphene is built. Graphene is composed of pure carbon-carbon bonds, "one of the strongest bonds" known. And not just single bonds, he points out: Because each carbon is bonded to only three other atoms (rather than four), each bond is actually about 30% stronger than a standard carbon-carbon single bond.[52]

Furthermore, Tour says, the graphene lattice is full of "*sp2*-hybridized carbons, which means that it has delocalized electrons that can move through the sheet … very, very rapidly." Indeed, whereas silicon has an electron mobility of about 2,000 cm_2/V-sec, graphene's mobility is on the order of 150,000 cm_2/V-sec. That suggests the material could be used to create ultra-fast electronics, among other applications.[52] Combine those features with the fact that the material is abundant, inexpensive, easy to work with, and stable in air, and it's easy to see why researchers have embraced the material so enthusiastically. "I don't know of a material that has been exploited any more than graphene in its short lifetime," Tour says.[52]

Graphene Quantum Dots

One exciting application for graphene is as quantum dots. Traditional quantum dots are built of inorganic semiconductor materials, such as cadmium-selenide or cadmium-sulfide. But these materials are both toxic to humans and expensive – about $1 million per kg, according to Tour – limiting their applications.[52] In 2013, Tour and his team demonstrated that tunable graphene quantum dots (GQDs) can be created in 20% yield from coal, a material that costs just $10 to $100 per ton.[56]

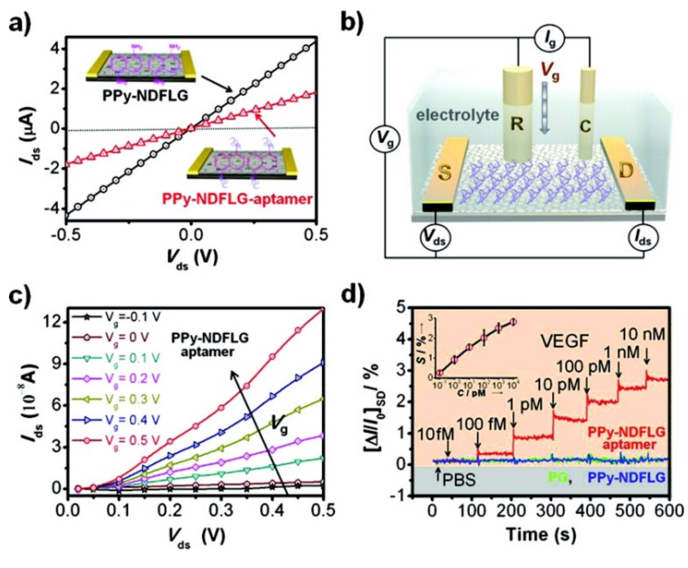
The procedure couldn't be simpler: "The GQDs derived from bituminous coal were obtained by sonicating the bituminous coal in concentrated sulphuric acid and nitric acid, followed by heat treatment at 100 or 120 °C for 24 h."[56] The size of the resulting material (and its corresponding fluorescent properties) can be changed by changing the temperature at which GQDs are treated: GQDs created at 100 °C measure about 3 nm in diameter, whereas those made at 120 °C measure about 2.3 nm, corresponding to fluorescent emission at 500 nm and 460 nm, respectively. In a subsequent study in *ACS Applied Materials and Interfaces*, Tour's team created GQDs from anthracite coal, producing particles of different size via either "cross-flow" filtration or by controlling reaction temperature.[21]

Among other things, quantum dots can be used as alternatives to organic fluorescent dyes for biomedical research, and also as light sources for digital displays. Both Apple[57] and Samsung[58] have made strides towards the latter application, with Apple filing multiple patents for "quantum dot-enhanced" tablet displays in 2014. Tour has licensed his GQD intellectual property to a startup called Dotz to develop commercial applications.

Graphene-Based Biomedical Applications

Graphene, and its derivatives, also have multiple applications in biomedical research, as reviewed by Byung Hee Hong and Dal-Hee Min of Seoul National University, Korea, in *Accounts of Chemical Research*.[59]

In one 2012 study in *ACS Nano*, Jyongsik Jang of Seoul National University, Korea, and colleagues used "polypyrrole-converted nitrogen-doped few-layer graphene" functionalized with an aptamer that recognizes the protein called vascular endothelial growth factor (VEGF) to build an "aptasensor," in which VEGF binding results in a measurable change in current through a circuit.[60]



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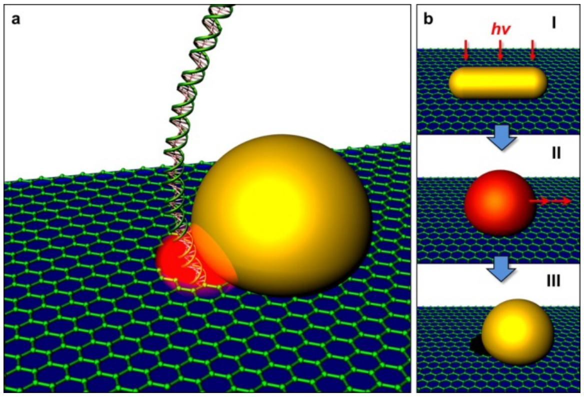
(a) Current–voltage curves of PPy-NDFLG on the PEN film before and after aptamer immobilization in air (V_{ds} = –0.5 V to +0.5 V and scan ratewas 10 mV s^{-1}). (b) Schematic diagram of a liquid-ion gated FET using aptamer-conjugated PPy-NDFLG (Ag/AgCl reference electrode, R; platinumcounter electrode, C; source and drain electrodes, S and D). (c) I_{ds}–V_{ds} output characteristics of PPy-NDFLG-aptamer at different Vg from –0.1 to 0.5 V in a step of 0.1 V in phosphate-buffered solution (V_{ds}, 0 to 0.5 V in a step of 50 mV). (d) Real-time responses and a calibration curve (*S* in the inset indicates $\Delta I/I_0$)of aptasensor with various vascular endothelial growth factor concentrations.

Another study exploited the ability of graphene oxide to bind single-stranded nucleic acids and quench fluorescent probes to build a multiplexed sensor for regulatory transcripts called microRNAs.[61] Chaoyong James Yang of Xiamen University, China, and colleagues bound fluorescent DNAs complementary to three different microRNAs to graphene oxide, dousing their fluorescence and protecting them from nuclease activity. In the presence of an appropriate miRNA, the miRNA and ssDNA form a double-stranded duplex, releasing the probe from the graphene surface, yielding a fluorescent signal.

Sunitha Nagrath of the University of Michigan, and colleagues developed a graphene derivative-based microfluidic chip to selectively capture circulating tumor cells (CTCs) from blood. The team attached graphene oxide sheets to 58,957 "flower-shaped gold patterns with dimensions of 100 mm x 100 mm" on a silicon substrate within a flow chamber.[62] The graphene was then functionalized with polyethylene glycol, a linker, and an antibody to the cell surface receptor EpCAM. When blood samples containing CTCs were flowed through the resulting chamber, the CTCs were captured, at which point they could be counted or cultured.



Schematic drawing of graphene nanopore with self-integrated optical antenna. (a) Schematic illustration of DNA translocation event through graphene nanopore with self-integrated optical antenna (gold) and enhanced optical signal (red) at the junction of nanopore and optical antenna. Nanoscale optical antenna functions as optical signal transducer and enhancer. (b) Illustration of photothermal sculpting process of graphene nanopores: (I) Light (*hv*) is illuminated on a gold nanorod on a graphene membrane, (II) the gold nanorod is melted and reshaped into a hemispherical nanoparticle (red color indicates a high surface temperature), and (III) the heated gold nanoparticle subsequently oxidizes the graphene surface to create a nanopore.

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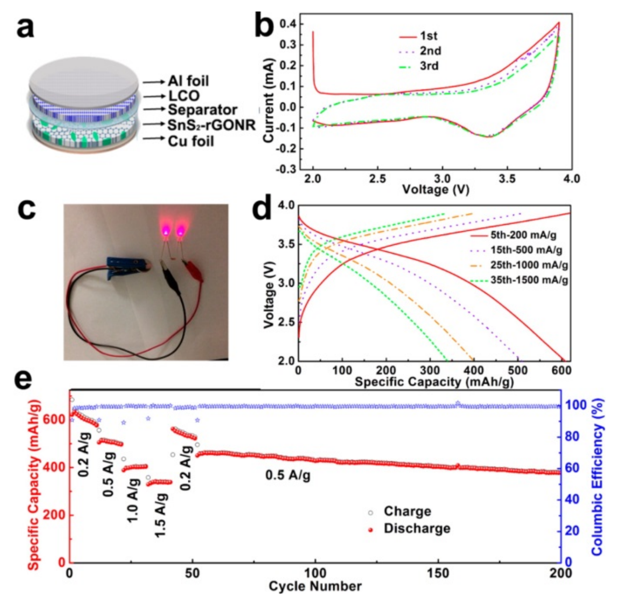
Other researchers are exploiting graphene to create next-generation DNA-sequencing devices. In one recent study, Luke Lee of the University of California, Berkeley, and colleagues describe a method for creating a nanopore in a graphene sheet by placing a gold "nanorod" on the sheet and heating it.[63] The result is a pore of controllable size with a "self-integrated optical antenna" (the gold particle) attached that amplifies a fluorescent signal as DNA passes through the pore.

"The dimensions of the nanopores and the optical characteristics of the plasmonic antenna are tunable, with the antenna functioning as both optical signal transducer and enhancer," explains a news story at *phys.org* describing the study.[64] "The atomically thin nature of the graphene membrane makes it ideal for high resolution, high throughput, single-molecule DNA sequencing. DNA molecules can be labeled with fluorescent dyes so that each base-pair fluoresces at a signature intensity as it passes through the junction of the nanopore and its optical antenna."

Still others are using graphene as a drug-delivery vehicle. Zhen Gu of the University of North Carolina, Chapel Hill, and North Carolina State University, and colleagues, recently described a compact "flying carpet"[65] of graphene conjugated to an anti-cancer drug (doxorubicin) and pro-apoptotic cytokine (TRAIL) to deliver a "one-two punch" that can kill cancerous cells in culture and in vivo.[66] The team developed a graphene oxide nanoribbon to which the TRAIL protein was attached via a polyethylene glycol-peptide linker, while doxorubicin associated with the graphene oxide itself. When the structure binds to targeted cells, a membrane-associated enzyme (furin) digests the peptide, releasing TRAIL to initiate apoptosis while the graphene/doxorubicin complex is internalized. When administered intravenously to nude mice bearing a human lung tumor, the drug complex concentrated in the tumor and rapidly slowed tumor growth relative to controls.[66]

Graphene-Based Consumer Products

Researchers and companies are also pursuing consumer applications of graphene. According to the Nanotechnology Consumer Product Inventory's most recent survey, only a handful of nanotech-related products currently on the market are based on graphene.[20] But more are likely coming.



(a) Schematic illustration of a SnS_2-rGONR/LCO full cell. (b) CV of the first three cycles for the SnS_2-rGONR/LCO full cell. (c) Digital photograph of two tandem LEDs lit by a SnS_2-rGONR/LCO full cell. (d) Representative discharge/charge voltage profiles at various rates for the SnS_2-rGONR/LCO full cell. (e) Capacity retention of the full cell at various rates from 0.2 to 1.5 A/g and then kept at 0.5 A/g for 200 cycles.

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Tour's team, for instance, has published a dozen papers exploring the application of graphene to building better lithium-ion batteries, licensing the technology to a company called Tubz. The most recent is a study in *ACS Applied Materials and Interfaces* describing a "nanocomposite material made of layered tin disulfide (SnS_2) nanoplates vertically grown on reduced graphene oxide nanoribbons (rGONRs)," which functions as an efficient anode in lithium ion batteries.[67] "When SnS_2-rGONRs are applied as an anode material in half cells, they deliver a high specific capacity (1033 mAh/g at 0.1 A/g) with a high-rate capability and excellent cycling stability even after 800 cycles," Tour wrote. "More importantly, the full cell of SnS_2-rGONRs/[$LiCoO_2$] was successfully fabricated and showed a high capacity of 642 mAh/g at 0.2 A/g and a high capacity retention of 82% after 200 cycles."

Others are exploring applications of graphene in creating graphical displays. In 2014, researchers from the Cambridge Graphene Center at the University of Cambridge, working with a company called Plastic Logic, demonstrated "a flexible display incorporating graphene in its pixels' electronics … the first time graphene has been used in a transistor-based flexible device."[68]

As explained in a press release announcing the development, "The new prototype is an active matrix electrophoretic display, similar to the screens used in today's e-readers, except it is made of flexible plastic instead of glass. In contrast to conventional displays, the pixel electronics, or backplane, of this display includes a solution-processed graphene electrode, which replaces the sputtered metal electrode layer within Plastic Logic's conventional devices, bringing product and process benefits."[68]

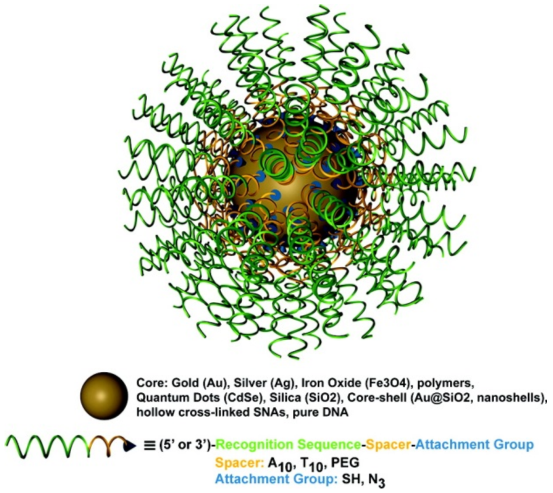
More recently, a University of Manchester team, led by K.S. Novoselov, described the development of flexible, two-dimensional light-emitting diode-based displays, also derived from graphene.[69] As a press release announcing the development explains, "The new research shows that graphene and related 2D materials could be utilised to create light emitting devices for the next-generation of mobile phones, tablets and televisions to make them incredibly thin, flexible, durable and even semi-transparent."[70]

And there are other, more pedestrian applications, including graphene-enhanced tennis racquets,[96] condoms,[71] and even light bulbs. In a news article on the latter development, *popsci.com* wrote, "Instead of running current through the traditional tungsten filament found in an incandescent bulb, this newly designed method instead uses a graphene-coated LED shaped into a filament to provide light."[72] The design "could be up to 10 percent more efficient than traditional LED lights …. [and is] expected to be priced competitively to current LED models when it goes on sale later this year."

VI. DNA-BASED NANOMATERIALS

Another exciting class of nanomaterials is based on DNA.[73] But in this case, the DNA often is acting not as a carrier of genetic information per se, but as a configurable binding reagent whose characteristics can be altered by tweaking its length and sequence.

One such material, first described by Chad Mirkin in 1996, is the spherical nucleic acid (SNA), traditionally a 13-nm gold nanoparticle core studded with multiple copies of the same piece of DNA, all oriented in the same direction.[74] As explained in a 2012 review in the *Journal of the American Chemical Society*, that configuration imparts some extraordinary features on nucleic acids: "They have higher binding constants for their complements than free strands of the same sequence, exhibit cooperative binding and subsequent sharp melting transitions, are resistant to nuclease degradation, and are capable of transfecting cell lines without the need for ancillary physical or chemical transfection methods."[74]



The anatomy of SNA nanostructures. An inorganic core is densely functionalized with oligonucleotides containing three segments: a recognition sequence, a spacer segment, and a chemical-attachment group. Additionally, other functional groups such as dye molecules, quenchers, modified bases, and drugs can be attached along any segment of the oligonucleotide.

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According to Mirkin, SNAs represent "one of the best examples of how architecture on the nanoscale can make a difference. And how both nanoscience and chemistry in this case can completely change the properties of what's arguably the most important molecule ever discovered and synthesized by chemists."[12]

In particular, Mirkin notes, SNAs' ability to freely enter cells is especially powerful, and the technology has been licensed for both research and medical applications. EMD Millipore SmartFlare reagents, for example, exploit SNAs to measure the abundance of RNAs in living cells. A SmartFlare is an SNA in which each DNA molecule on the SNA is duplexed to a short fluorescently labeled complementary sequence called a "flare." Interaction of the SNA with its target RNA in the cell causes the flare to release and fluoresce, producing a signal easily seen under fluorescence microscopy.

Mirkin's team recently described a variant of this technology, called a Sticky-flare.[75] In a SmartFlare (which Mirkin's team calls Nano-flares[76]), RNA binding causes release of a short fluorescently labeled oligonucleotide. But as that "flare" is no longer associated with the transcript, the technology cannot be used to track its subcellular localization. The Sticky-flare design rectifies that shortcoming: the presence of the target RNA causes the flare to dissociate from the SNA and hybridize to the transcript, such that RNA subcellular localization can be tracked in live cells microscopically.

Another company called Exicure is developing therapeutic applications for SNAs, harnessing their ability to disrupt gene-regulatory circuits via antisense- or siRNA-mediated approaches. According to the company's web site, an SNA called AST-005, targeting tumor necrosis factor, is currently in clinical development for treatment of mild to moderate psoriasis.[77]

An alternative DNA-based nanotechnology strategy is DNA origami. As explained in a 2015 review,

> *The premise of DNA origami is to fold a multithousand-base circular single-stranded DNA "scaffold," obtained from a viral genome, by using short helper or "staple" oligonucleotides into desired nanoscale shape. Because each staple strand is different, some can be designed to present DNA sticky ends at programmed locations on the periphery of the final assembled object, allowing these structures to act as scaffolds with spatially prescribed DNA bonds that capture and organize other nano-objects.*[73]

Originally conceived in 1996 by Nadrian (Ned) Seeman, DNA origami uses carefully designed hybridization of branching DNA molecules to create everything from rigid two-dimensional lattices and three-dimensional "wireframes" to more complex structures and scaffolds – all via molecular self-assembly.[73] In 2012, for instance, Harvard University geneticist George Church and colleagues described "an autonomous DNA nanorobot" – a hexagonal barrel measuring 35 nm x 34 nm x 45 nm – that they could load with cargo and open in response to different protein signals.[78] That same year, a research team led by Tim Liedl at Ludwig-Maximilians-Universität in Munich, Germany, exploited DNA origami to create precise helical arrangements of metal nanoparticles, which exhibited predictable and tunable optical characteristics.[79]

A DNA-Based Periodic Table

Though SNAs were originally made with a gold nanoparticle core, they don't have to be. Indeed, SNAs can be built with any number of core materials, or without a core at all.[74] That flexibility opens the door to using SNAs as the basis for new kinds of designer material, the so-called "programmable atom equivalent," Mirkin says.[80]

In traditional chemistry, researchers' abilities to develop new materials are limited by the valences and atomic properties of the elements they use. Thus, some desired combinations simply are not practical or possible. But by exploiting SNAs, Mirkin explains, that limitation can be circumvented. Essentially, by carefully coupling the desired cores (functioning as "atoms") to the oligonucleotides needed to link them in the right way ("bonds"), researchers can explore the materials landscape in a way not previously possible, Mirkin says. "You can begin to assemble hierarchical materials where you can build structures that didn't exist in nature before, and have properties by virtue of the type of architectural control afforded by that concept." And, by building SNAs with hairpin structures on the attached nucleic acids, it even becomes possible to open and close those bonds, affording even greater flexibility in material design assembly. The result, he says, should be a new kind of chemistry: "materials-by-design." "We are building a whole table of elements, a new table of elements, where the particles are the entries. But the elements are not just defined by composition; they're defined by particle size …. They're defined by the shape and they're defined by the composition," he says.[12] Mirkin explored this idea of a new periodic table in a 2013 essay in *Angewandte Chemie International Edition*.[80]

VII. ENVIRONMENTAL & ENERGY APPLICATIONS

As described above, nanomaterials such as graphene can be leveraged to build better batteries. But nanotechnology has greater potential for impact in the energy sector than that. A 2009 article in *Renewable and Sustainable Energy Reviews*, notes that "According to the 'Roadmap Report Concerning the Use of Nanomaterials in the Energy Sector' from the [European Union's] 6th Framework Program, the most promising application fields for the energy conversion domain will be mainly focused on solar energy (mostly photovoltaic technology for local supply), hydrogen conversion and thermoelectric devices."[81]

There are absolutely multiple intersection points between nanotechnology and the energy sector – building better catalysts for refining biofuels and hydrogen, better solar harvesters, better batteries and energy storage devices, better power lines, and more.[82] The NNI specifically supports solar energy research as part of its Nanotechnology Signature Initiatives (NSI), "Nanotechnology for Solar Energy Collection and Conversion: Contributing to Energy Solutions for the Future." Among other things, that particular NSI seeks to exploit nanotechnology and nanomaterials to "improve photovoltaic solar electricity generation," "improve solar thermal energy generation and conversion," and "improve solar-to-fuel conversions."[83]

Ken Silverstein, a contributing writer at *Forbes.com* who covers energy, provided a few concrete examples of other potential applications of nanotechnology in the energy sector:

> *Carbon nanotubes, for example, are the most conductive materials known and could be used to modernize the transmission system to save a lot of power. However, mass-producing those nanotubes for such purposes is still problematic. Improvements, though, are forthcoming.*
>
> *… Wind power, meantime, could be transformed. The wing span of turbines is much bigger and is now 120-150 feet. The kind of forces and mechanical stresses put on those turbines is incredible. By putting nano-composites into the design, such wind mills can get higher performance. And, solar cells that turn sunlight into electric currents could become more efficient and diminish the global need for carbon-based fuels.*[84]

Naturally, work on many of these fronts is moving ahead. In a 2015 article in Nature Communications, Tour and his team described "an electrocatalyst for hydrogen generation based on very small amounts of cobalt dispersed as individual atoms on nitrogen-doped graphene."[84]

The catalyst, the authors conclude, "represents the first example of SAC [single-atom catalysis] achieved in inorganic solid-state catalysts for HER [hydrogen evolution reaction]. This excellent catalytic performance, maximal efficiency of atomic utility, scalability and low-cost for the preparation makes this catalyst a promising candidate to replace [platinum] for water splitting applications." Tour's team has also developed methods to create boron-doped graphene for building flexible "microsupercapacitors," a kind of energy-storage device.[85]

On the solar energy side, Paul Weiss of UCLA notes that, in order for solar energy to be practical for many purposes, it must be "as cheap as paint." As a result, there's been considerable excitement in the field around a highly efficient, inexpensive material called perovskite.[86]

One issue with perovskite has been the challenge of fabricating large pieces of the material of uniform and high efficiency. In one recent study, researchers at the National Renewable Energy Laboratory in Golden, Colorado, reported a potential fix: "a solution-based synthetic route … for the formation of uniform, large-grain, and high-crystallinity planar $MAPbI_3$ [that is, $CH_3NH_3PbI_3$] perovskite films."[87] Using that method, the team built planar perovskite solar cells (PSCs) measuring up to 1.2 cm^2. "Over 15% stabilized PCE [power conversion efficiency] has been achieved for large-area (1.2 cm^2) PSCs, while a small area 'champion' PSC (0.12 cm^2) has a PCE of 18.3%, with a stabilized PCE output at ≈17.5%," the authors note, concluding, "The solution-processing route demonstrated here paves the way for further development of the much needed large-area PSCs."

Perovskite structures are also relatively unstable. But in late 2015, Yang Yang, of the University of California, Los Angeles, and colleagues reported a method for stabilizing these structures.[88] As described in a press release announcing the results, perovskite solar cells normally are coated with an organic layer that fails to protect the cells from moisture for extended periods. Yang's team eliminated that layer, instead sandwiching the perovskite between layers of metal oxide. "The difference was dramatic. The metal oxide cells lasted 60 days in open-air storage at room temperature, retaining 90 percent of their original solar conversion efficiency."[89]

VIII. SAFETY CONSIDERATIONS

Clearly, there's vast potential for nanomaterials and other nanotechnology-enabled products. But that potential must be balanced against the safety of the researchers that study nanomaterials, the workers that produce them, and the consumers that use them. Nanoparticles, as has been previously stated, exhibit unique properties, structures, and behaviors. They also exist on the scale of biological systems. It is likely, therefore, that many of these materials will exhibit different toxicities and environmental impacts than the bulk materials to which they are related, and testing is required to work that out.

A 2015 *Science* Perspective on nanomaterial safety notes that nanoparticles may be safe when intact, but become toxic over time. That can pose particular problems in the human body, if that degradation occurs after the materials have been taken up into the cells – a concept called a "Trojan horse."[16]

As explained in a 2014 study by researchers at the Chinese Academy of Sciences in Beijing regarding the toxicity of nanoparticulate silver,

> *"'Trojan horse' means a vehicle or carrier to transport ions/particles or other toxic substances through membrane barrier, and then releases these substances inside cells or organisms. In the field of nanoscience, nanomaterials such as ZnO and CuO nanoparticles could enter cells through endocytosis, and nanomaterials inside cells could undergo dissolution and release their corresponding ionic species. In contrast, the ionic forms of these materials could not enter the cells freely due to the presence of membrane barrier. The 'Trojan horse' model therefore delineates the potential mechanisms and possible sources responsible for the cytotoxicity of nanomaterials.*[90]

Among other things, the study demonstrated that silver nanoparticles are themselves toxic, with the ability to bind and inhibit RNA polymerase, and that when mammalian cells are exposed to nanosilver, both free ions and intact particles exist in the cells.[90]

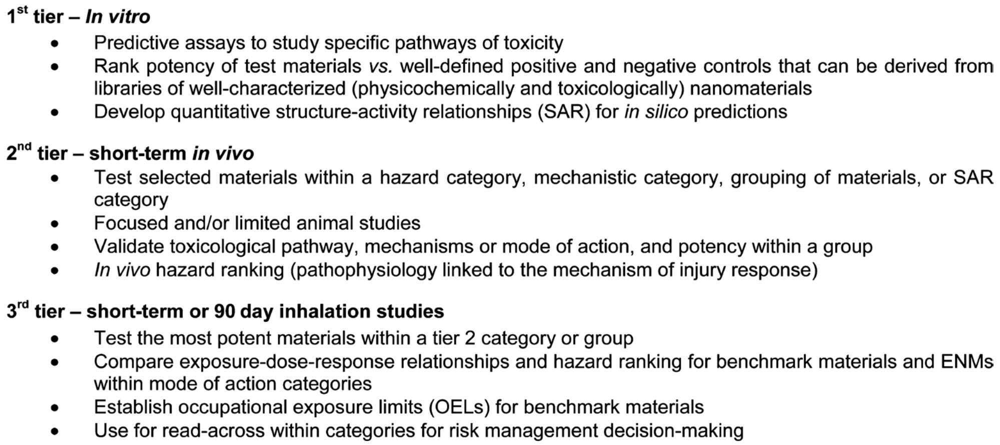
According to one 2014 analysis by Harald Krug of Empa in St. Gallen, Switzerland, nearly 11,000 studies on the environmental and health impact of nanomaterials (nanoEHS) have been published since 2001.[91] A review of 1,000 such studies concluded that, though engineered nanomaterials can clearly enter the body via the lungs or gastrointestinal tract, the toxicologic data are simply not yet there to say whether, as a class, they pose a significant risk.

> *Currently, an overview of the many thousands of publications which have appeared to date leads to the clear conclusion that, despite great efforts by many working groups, no unexpected results that give cause for concern have been shown for technical nanomaterials, with a few not very surprising exceptions such as quantum dots containing cadmium, soluble zinc oxide and copper oxide particles, and fibrous carbon nanotubes (including associated metal catalysts). The uncertainty remains as to whether hazardous effects possibly exist which have not yet been found or whether such effects are in fact absent in the ENMs investigated to date.*[91]

The article goes on to make recommendations to funding agencies and others to close the knowledge gap by supporting and promoting nanotoxicology studies and the standardization of methods. "If we do not insist on employing comparable methods and similar dosing techniques in future experimental work, we will once again be confronted with some results that, whilst generating shocking headlines, are not based on sound fundamentals and which yet again will need to be disproven by new studies," Krug wrote.[91]

The U.S. Environmental Protection Agency has been conducting research of its own into the safety of such nanomaterials as nano-silver, carbon nanotubes, and titanium dioxide.[92] And in 2015, according to a *C&EN* report, the agency issued a new rule requiring nanomaterial manufacturers to report to "data on production volume, manufacturing methods, and health and safety, among other information."[17] Chemical manufacturers, though, contend the rule is "highly subjective and arbitrary and would create an uneven playing field for nanomaterial manufacturers and processors." For its part, the U.S. Food and Drug Administration issued in June 2014 voluntary guidelines on the use of nanomaterials in food and cosmetics, as well as draft guidelines covering their use in animal food.[93]

One issue confounding the collection of data on nanomaterial safety is simply the sheer number of materials to be tested and the nature of analyses required to profile them. Among other things, traditional toxicological testing requires animal testing, but some researchers advocate for a transition to "alternative test strategies," including both in vitro and in silico assays. In a recent Perspective in *ACS Nano*, Andre Nel of the University of California, Los Angeles, and colleagues present a case study in the use of alternative testing strategies to evaluate the safety of carbon nanotubes.[94] The article advances a three-tiered testing strategy comprising in vitro and short- and long-term animal studies as a way to streamline and prioritize analyses:



1st tier – *In vitro*

- Predictive assays to study specific pathways of toxicity
- Rank potency of test materials *vs.* well-defined positive and negative controls that can be derived from libraries of well-characterized (physicochemically and toxicologically) nanomaterials
- Develop quantitative structure-activity relationships (SAR) for *in silico* predictions

2nd tier – short-term *in vivo*

- Test selected materials within a hazard category, mechanistic category, grouping of materials, or SAR category
- Focused and/or limited animal studies
- Validate toxicological pathway, mechanisms or mode of action, and potency within a group
- *In vivo* hazard ranking (pathophysiology linked to the mechanism of injury response)

3rd tier – short-term or 90 day inhalation studies

- Test the most potent materials within a tier 2 category or group
- Compare exposure-dose-response relationships and hazard ranking for benchmark materials and ENMs within mode of action categories
- Establish occupational exposure limits (OELs) for benchmark materials
- Use for read-across within categories for risk management decision-making

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Another recent study suggests a strategy for homing in on toxicity pathways. In a 2014 article, Hilary Godwin of UCLA and colleagues used a library of 4,159 bacterial gene mutants to map toxicity pathways in response to different forms of nanoparticulate silver.[95] "Although there are some common pathways involved in how bacteria respond to silver stress, there are other pathways that appear to correlate with nanoparticle-related stress. Reactive oxygen production and impairment of flagellar activity were observed for a broad range of silver species. By contrast, effects on cell outer surface lipopolysaccharides appear to be nanoparticle-specific," the authors concluded.

IX. CONCLUSION

Fifteen years and billions of dollars later, there's no denying the nation's investment in nanotechnology research and development has led to some remarkable outcomes. Nanotechnology today is seemingly everywhere – it's in our electronics and diagnostics, our solar panels and coatings, in our food and cosmetics, and even our clothing.

Yet despite the rapid development and subsequent applications in nanotechnology, the field is in a sense still very much in its adolescence. Using graphene as an example, the substance has induced considerable excitement, reams of research, and thousands of patents. Yet no products leveraging that material's remarkable capabilities have yet to hit the market. In part, that's simply a function of time: transitioning a new technology from bench to product can take 15 years, says Tour, and graphene was only isolated in 2004.[52]

But it also could be a function of what makes nanomaterials so exciting in the first place. Materials at the nanoscale take on new and sometimes unexpected behaviors and properties. As a result, while the materials can sometimes simply be slotted to existing industries, the real disruptive opportunities may lie elsewhere, and it can take time and serendipity to find them, as stated by Anthony Schiavo of Lux Research Inc.[23] In other words, stay tuned: when it comes to nanotechnology, the best is likely yet to come.

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