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Are We Entering the Nano Era?

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It looks like we are entering the nano era. If you recently purchased a new laptop, it likely contains processors manufactured using 22 nm technology, which means that half the distance between identical features in an array measures only 22 nm. It probably carries a heat-assisted magnetic recording (HAMR) hard disk drive by Seagate, with a storage capacity of one terabit (TB) per square inch, which implies that each bit of information only occupies an area of $12.7 \times 12.7\ nm^2$. If you recently relaxed on a beach, you have possibly put on some sunscreens based on nanoparticles made of titanium dioxide or zinc oxide. It has been found that these tiny particles can block out harmful rays without the "clown-face" white color of many sunscreens. If you hate the unpleasant odors coming from your socks, you might have tried out the so-called "nanosilver socks", which contain silver nanoparticles that are able to kill bacteria and eradicate the unwanted odors. The same is true for some sports clothing. Slowly but surely, manmade nanomaterials are finding their ways into our everyday lives.

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The Nano Boom

The word "nano" started to shine in writing, reporting, and publishing about two decades ago, when everybody started to combine it with all possible noun: science, technology, chemistry, physics, electronics, photonics, mechanics, medicine, crystal, rod, wire, tube, cube, shell, cage … Astonishingly, there is nothing that you cannot affix "nano" to. Many new journals with "nano" in the titles also started to appear, such as *Nano Letters*, *Nano Today*, *Nano Research*, and *ACS Nano*. There are just too many to list all of them here. Luckily, I was just about to leave graduate school when this "nano boom" took place, so I was able to take advantage of this good opportunity to build a professional career in this dynamic field of research that advances every day at an amazingly fast pace.

Some people would argue that "nano" is nothing new at all. Before it became a buzzword, people had already used nanomaterials for many decades, if not centuries. Taking heterogeneous catalysis as an example, the key component of a catalyst are the fine particles, typically with physical dimensions below 10 nm. Some of the techniques have been known for centuries and are still widely used by the chemical, pharmaceutical, petroleum, and automobile industries to produce fuels, drugs, and materials needed for everyday living and to keep the environment clean (as exemplified by catalytic converters, which were commercialized in the 1970s). Another notable example is the field of "colloidal science", which has a history as old as the modern science. It primarily deals with particles with sizes of around 100 nm, which could be correctly referred to as "nanoparticles".

The biological world is also filled with remarkable examples of nanostructures. For example, cells are packed with complex, functional structures with at least one dimension on the nanoscale. These structures define the territory of life by separating the interior of a cell from the outside environment. They also define the meaning of life by replicating DNA, transcribing DNA into RNA, and making proteins and many other components of the cell. Furthermore, they help maintain the life by generating energy, sensing and reacting to the environment, recognizing pathogens, and moving the cell and its components from place to place. Some of the organisms, such as viruses, naturally only exist as nanostructures. In fact, tobacco mosaic virus (18 nm in diameter and ca. 300 nm in length) represents the most uniform and best-controlled sample of nanorods that a synthetic chemist could ever dream of. These nanostructures and their functions have been a subject of extensive research for biophysicists and biochemists long before "nano" became a kind of pet name in English. All of these facts are legitimate arguments for exploring the nanoworld but most importantly, it is the new knowledge and novel application that keep a research field alive!

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What Can Nano Offer?

The quantum effect is probably the most exciting gift from nano as it is in the nanosize range that this effect can be observed and utilized easily. In one demonstration, this effect has been used by chemists to magically turn the same solid material into nanoparticles (so-called quantum dots) capable of emitting light of different colors. The trick is to tune the electronic structure of a nanoparticle by controlling its size. In many other demonstrations, the quantum effect has led to the discovery of phenomena such as the Coulomb blockade, single-electron tunneling, and metal–insulator transition; all of these phenomena could serve as the basis for the design and fabrication of future electronic or photonic devices. These phenomena based on the quantum effect do not follow the rules we have learnt from the ordinary macroscopic or microscopic world, and we should refer to the relevant applications as being "disruptive".

On the other hand, moving from micro- into the nanoscale regime may only result in "continuous" changes to the properties of a material. These changes may seem to be less exciting or only incremental, but many of them can also have significant impacts on applications. A good example can be found in the electronic gadgets we use every day. No one would argue that laptops nowadays operate much faster, use much less power, and store far more data when compared to the products of just a few years ago. All these benefits are brought about by constantly shrinking the size of transistors and thus doubling the integration density of chips every 18 months. Although the critical dimension of a transistor has been reduced from hundreds of micrometers to 22 nanometers over the past half-century, those devices still operate under the same physical principles. In a sense, the changes are continuous rather than disruptive.

Another great example is heterogeneous catalysis, where a transition from micro- to nanosized particles means a drastic increase in specific surface area and the proportion of atoms sitting on the surface relative to those in the bulk. 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. In general, one should not expect to observe any new phenomenon, but the societal impact of such a practice of size reduction can never be overestimated.

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People always wonder about the "killer" applications or revolutions that nano will bring us. In this regard, I think we should not forget that nano could enable both disruptive and continuous changes. For the reasons discussed above, both changes could be used to significantly improve the quality of our daily life. We simply have no reason to bet our future on just one of them. At the moment, the notion of continuous changes seems to prevail in most research that has immediate impact on our society. One such example is nanomedicine, which refers to the use of highly specific medical intervention at the molecular level for the diagnosis and treatment of diseases, as well as for the repair of damaged tissues or organs. It has emerged as one of the most exciting new playgrounds for chemists, materials scientists, physicists, biologists, and biomedical engineers. From early on, the US National Institutes of Health (NIH) recognized the promise of nanomedicine for both basic and applied biomedical research, and included it as a priority area in the Roadmap for Medical Research in the 21st century. In some cases, the new developments are causing a paradigm shift for biomedical research.

The power of nanomedicine lies in its ability to operate on the same molecular scale as the intimate biochemical functions involved in the growth, development, and aging of the human body. It will provide a new platform for the diagnosis, treatment, and prevention of diseases. The ultimate goal in relation to cancer is to have highly efficient therapeutics that can overcome biological barriers, distinguish between malignant and benign cells, and selectively target the cancerous tissues. The enablers of all these applications are nanomaterials whose physicochemical properties can be synthetically engineered by tailoring their compositions, sizes, shapes, structures, morphologies, and surface properties. Again, this research was already started long before nano became a buzzword. After two to three decades of technological developments, engineered nanomaterials have started to become conspicuous, with a great promise in cancer theranostics. A large number of drug delivery systems have been approved for cancer therapy in clinics, with many more in the pipeline currently under clinical trials or preclinical evaluations. Nanomaterial-based therapeutics are poised to greatly improve the outcomes of many clinical procedures, transforming the basic research discoveries into tangible benefits for people.

Nanomedicine will provide a new platform for the diagnosis, treatment, and prevention of diseases.

In searching for the new applications of a nanomaterial, we have to be flexible and open-minded. In many cases, the original target may not be the best choice or the wisest bet. A recent example can be found in the field of conducting polymers. In the early days, essentially everybody in this field was working on the doped, metallic form of conjugated polymers in an attempt to chase the highest electrical conductivity compared to a metal. That is why these materials have the nickname of "synthetic metals". The original goal was to replace copper with a cheaper, lighter, and easily processable conducting polymer, but this goal is yet to be achieved. Later, it was found that the undoped, semiconducting form of conjugated polymers was more useful, but for the manipulation of photon absorption and emission rather than the conduction of electrons. In the late 1990s, people working in this field redirected their research to this new direction. After about one decade of research, commercial products started to appear for applications in display and photovoltaics. This and other examples tell us that the same shift or transition in terms of direction may also occur for each single type of nanomaterial we have developed. So don't just bet on the original target, even though it is the initial motivation or driving force that led you to develop that nanomaterial in the first place.

Riding the Nano Wave

As a chemist in the nano era, what should I do? First of all, I should take advantage of this opportunity to expand the knowledge base and scope of synthetic chemistry. After all, every one of the applications is based on the availability of nanomaterials with controlled sizes, shapes, compositions, structures, and many other properties. It is of critical importance to establish the logic of nanomaterial synthesis. If someone needs a particular type of nanomaterial, I wish I could tell that person exactly what the best synthetic route is and what experimental conditions and procedures should be used. Ultimately, I hope we will have the same level of mechanistic understanding and experimental control for the synthesis of nanomaterials as we have accomplished for organic synthesis. That day may never come, but we should never give up. At the moment, people tend to take nanomaterials at hand that were developed for other purposes or for no reason at all and seek to apply them to an application. Ideally, I would prefer to have a different option—that is, starting from a specific application to come up with the best nanomaterial for that application. That may represent the ultimate goal (or dream) of a synthetic materials chemist.

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Secondly, I think I should collaborate more with people in other fields. Taking nanomedicine as an example, the scale and complexity of such applications demand that scientists move beyond the confines of their own disciplines and work together in synergic teams. As a truly interdisciplinary field, it must engage researchers from chemistry, physics, engineering, biology, genetics, proteomics, radiology, oncology, and public health, among others. One of the major challenges that nanomedicine has faced from the outset is to bring together all these different people and ask them to work in true collaboration. Personally, I view collaboration as a natural vehicle to broaden the scope of my own research and help me quickly move into new fields. A fruitful collaboration will not only creates a new research direction for the principal investigator but also train a new generation of graduate students and postdocs capable of tackling interdisciplinary problems. If there is a constant theme for research in nanotechnology, it is broad collaboration!

Although the potential of nanotechnology is tremendous, questions remain about the long-term safety of nanomaterials and the risk–benefit characteristics of their usage. Along with the birth of nanomedicine, a new field known as nanotoxicology has also emerged, which refers to the study of interactions between a nanomaterial and a biological system. In this case, an understanding of the relationship between the intrinsic properties of a nanomaterial and its in vivo and in vitro behaviors would provide a fundamental basis for assessing the toxicity. Specifically, studies with animal models will identify the organs of interest, in turn, leading to identification of the best cell types for in vitro cytotoxicity studies to further understand how these cells response to the nanomaterial on the molecular level. In spite of the tremendous effort in recent years, a reliable database of the toxicologic tests still needs to be constructed in order to provide a materials safety data sheet (MSDS) for each nanomaterial, and a basis for risk assessment and management. Not surprisingly, the technical challenges in nanomedicine and nanotoxicology also represent additional opportunities for chemists, materials scientists, physicists, biologists, and biomedical researchers.

> ***Nanotoxicology refers to the study of interactions between a nanomaterial and a biological system***

Filling the Gap

Research in nanomaterials is moving ahead with a tremendous speed. With each passing year, we are able to greatly expand our inventory of nanomaterials. Despite the many applications reported in the literature, there still exists a big gap that impedes moving nanomaterials from academic studies to industrial applications. Taking noble-metal nanocrystals as an example, the last decade has witnessed their successful syntheses, with well-controlled sizes, shapes, and other properties. However, most of their industrial applications such as catalysis are still based on nanoparticles with poorly controlled sizes and shapes. The gap can be attributed to the lack of an ability to produce well-controlled nanocrystals at an industrially relevant scale while still maintaining their uniformity. The protocols originally developed for the syntheses are based upon batch reactors, typically, small flasks or vials.

While such syntheses can always be finely tuned to obtain high-quality products, they cannot meet the requirements for quantity and batch-to-batch reproducibility. Taking the synthesis of Pd nanocubes as an example, it often takes 4–6 hours to obtain just 0.05 grams of solid products for a batch-based synthesis conducted in a 50 mL flask. This amount is barely enough for one single test on their catalytic properties. As a major technical issue, it is impractical to scale up the production of noble-metal nanocrystals with controlled sizes, shapes, and structures by simply employing more reagents in increasingly enlarged reactors. First of all, it is very difficult, if not impossible, to obtain high-quality products. Both nucleation and growth involved in a synthesis of nanocrystals are very sensitive to experimental details such as the way reagents are added and mixed, the heat management, as well as spatial variations in temperature and chemical composition. None of these parameters correlates with the volume of reaction solution in a linear fashion. As such, any increase in reaction volume will inevitably result in a degradation of the product quality because of the inhomogeneity arising from a large volume of reaction solution. Secondly, it is economically disadvantageous to optimize the experimental conditions of a synthesis in a large reactor. If such a synthesis fails, it not only wastes a lot of resources but also generates a huge amount of waste. For the purpose of manufacturing colloidal nanocrystals, we need to develop a linearly scalable platform that can be operated at both small (for the optimization of reaction parameters) and large (for high-volume production) scales.

As we and other groups have recently demonstrated, the new approach based on a continuous flow of droplet reactors in a fluidic device can serve as a practical platform for the scalable, reliable, and cost-effective production of nanomaterials with uniform and controlled shapes, sizes, and structures. The use of small droplets with a volume typically below 1 mL and the linear relationship between the total volume of production and the duration of a synthesis will allow people to consistently achieve good control of the nanomaterials without compromising the quality and reproducibility. By operating multiple, identical fluidic devices in parallel, it is highly feasible to increase the volume of production in a linear fashion to a scale at tens of kilograms per day.

The purpose of this special issue of *Angewandte Chemie* is to present a series of Review articles by the leading experts to provide an overview of recent developments and issues related to nanoparticles. The Review articles include: "Nanosafety Research—Are We on the Right Track?" by Harald Krug; "Formation of Nanoparticles and Nanostructures—An Industrial Perspective on $CaCO_3$, Cement, and Polymers" by Jens Rieger et al.; "The Many Faces of Soot: Characterization of Soot Nanoparticles Produced by Engines" by Reinhard Niessner; "Spot the Difference: Engineered and Natural Nanoparticles in the Environment—Release, Behavior, and Fate" by Frank von der Kammer et al.; together with "Engineered Nanoparticles for Drug Delivery in Cancer Therapy" by me and my co-workers. From this special issue, the readers can quickly learn about the multiple faces of nanomaterials. It is hoped that all readers will find that the work presented in this special issue is beneficial to their current research projects and will begin to venture into this exciting field if they have not already done so.

In conclusion, as our synthetic capabilities for nanomaterials continue to evolve, we should not forget to channel those new creations into commercial applications. From electronics to photonics, information storage, communication, catalysis, energy, medicine, homeland security, environment protection, cosmetics, and even building construction, every one of them could be powered by nanomaterials. Only when this relatively new and still seemingly bizarre realm of nano is able to make a positive and long-lasting impact on every aspect of our society, can we finally declare the arrival of the nano era.

