**Anis Rahman, PhD**

# An introduction to the world of nanoscience and nanotechnology

## Nanotechnology that permeates every branch of modern technology

2019

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**2017–2019**

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# 1. Forewords

It is now clearly evident that sooner or later each and every technology of today will be influenced by nanotechnology for better. Many new technologies will also be created from this new world of nanotechnology. This review is targeted to introduce the main aspects of the present-day status of nanotechnology. In particular, several modern topics have been outlined referencing the use of nanotechnology and how it will play a game changing role. This is a work in progress.

# Chapter 1

# 1. An Introduction to Nanotechnology

Nanotechnology is defined as the study and use of structures between 1 nanometer and 100 nanometers in size. To give you an idea of how small that is, it would take eight hundred 100 nanometer particles side by side to match the width of a human hair.

While this is the most common definition of nanotechnology, researchers with various focuses have slightly different definitions. For a summary of these different definitions see **Definitions of Nanotechnology**.

Scientists have been studying and working with nanoparticles for centuries, but the effectiveness of their work has been hampered by their inability to see the structure of nanoparticles. In recent decades, the development of microscopes capable of displaying particles as small as atoms has allowed scientists to see what they are working with.

The following illustration titled "The Scale of Things", created by the U. S. Department of Energy, provides a comparison of various objects to help begin to envision exactly how small a nanometer is. The chart starts with objects that can be seen by the unaided eye, such as an ant, at the top of the chart, and progresses to objects about a nanometer or less in size, such as the ATP molecule used in humans to store energy from food.

## 1.1. Nanotechnology Definitions

Ref: http://www.understandingnano.com/nanotechnology-definition.html

To help one understand exactly what nanotechnology is, here we provide a definition or two.

### 1.1.1. Pinning down a definition of nanotechnology

Because nanotechnology is still evolving, there doesn't seem to be any one definition that everybody agrees on. We know that nano deals with matter on a very small scale - larger than atoms and molecules, but smaller than a breadcrumb. We know that matter at the nano scale can behave differently than bulk matter.

Beyond that, different individuals and groups focus on different aspects of nanotechnology as a discipline. Here are a few definitions of what nanotechnology is for your consideration:

- Nanotechnology is the study and use of structures between 1 nanometer (nm) and 100 nanometers in size.

This is probably the most barebones and generally agreed upon definition of nanotechnology. To put these measurements in perspective, compare your one meter (about three feet three inches) high hall table to a nanometer. You would have to stack one billion nanometer-sized particles on top of each other to reach the height of your hall table. Another popular comparison is that you can fit about 80,000 nanometers in the width of a single human hair.

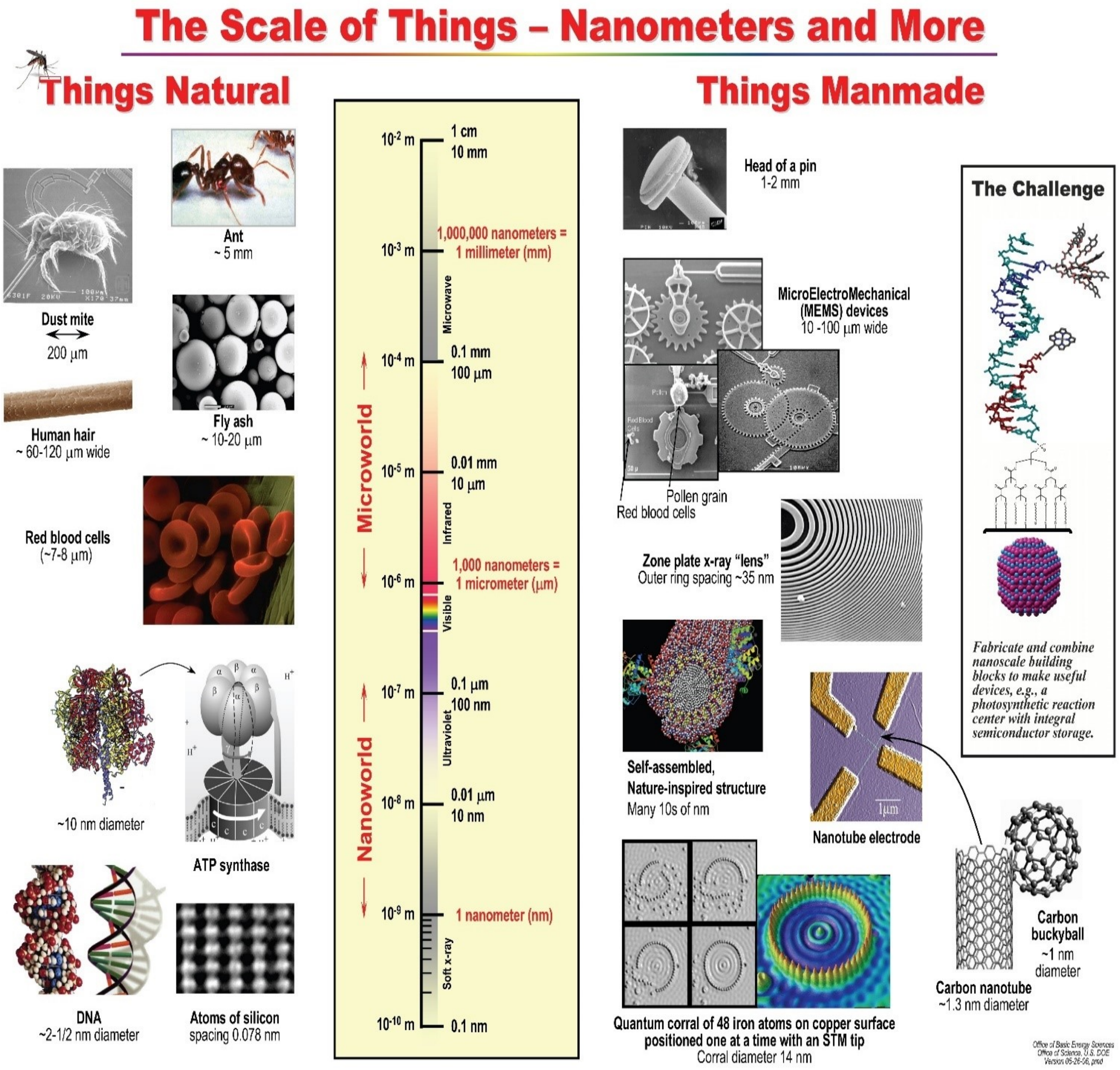

*Figure 1. The scale of things – from 1 cm to 1 Å ⇒ (=0.1 nm) [1].*

# An introduction to the world of nanoscience and nanotechnology

The word nano is a scientific prefix that stands for $10^{-9}$ or one-billionth; the word itself comes from the Greek word nanos, meaning dwarf.

- “Structures, devices, and systems having novel properties and functions due to the arrangement of their atoms on the 1 to 100 nanometer scale. Many fields of endeavor contribute to nanotechnology, including molecular physics, materials science, chemistry, biology, computer science, electrical engineering, and mechanical engineering.”

This definition from The Foresight Institute adds a mention of the various fields of science that come into play with nanotechnology.

- “Nanotechnology is the study of phenomena and fine-tuning of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale. Products based on nanotechnology are already in use and analysts expect markets to grow by hundreds of billions of euros during this decade.”

The European Commission offers this definition of what nanotechnology is, which both repeats the fact mentioned in the previous definition that materials at the nanoscale have novel properties, and positions nano vis-a-vis its potential in the economic marketplace.

> “Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale.”

This definition from the National Nanotechnology Initiative adds the fact that nanotechnology involves certain activities, such as measuring and manipulating nanoscale matter.

- “[Nanotechnology is] an upcoming economic, business, and social phenomenon. Nano-advocates argue it will revolutionize the way we live, work and communicate.”

This last one is taken from a definition of nanotechnology by Thomas Theis, director of physical sciences at the IBM Watson Research Center. It offers a broader and interesting perspective of the role and value of nanotechnology in our world.

*The above is excerpted from Nanotechnology For Dummies (2nd edition), from Wiley Publishing.*

https://youtu.be/0fKBhvDjuy0

**Commonly Used SI Prefixes**

| Prefix | Meaning | Abbreviation | Numeric value | Exponential Notation |
|---|---|---|---|---|
| exa- | Billion trillion | E | 1000000000000000000 | $10^{18}$ |
| peta- | thousand trillion | P | 1000000000000000 | $10^{15}$ |
| tera- | trillion | T | 1000000000000 | $10^{12}$ |
| giga- | billion | G | 1000000000 | $10^{9}$ |
| mega- | million | M | 1000000 | $10^{6}$ |
| kilo- | thousand | k | 1000 | $10^{3}$ |
| hecto- | hundred | h | 100 | $10^{2}$ |
| deka- | ten | da | 10 | 10 |
| n/a | one | n/a | 1 | $10^{0}$ |
| deci- | one tenth | d | 0.1 | $10^{-1}$ |
| centi- | hundredth | c | 0.01 | $10^{-2}$ |
| milli- | thousandth | m | 0.001 | $10^{-3}$ |
| micro- | millionth | µ | 0.000001 | $10^{-6}$ |
| nano- | billionth | n | 0.000000001 | $10^{-9}$ |
| pico- | trillionth | p | 0.000000000001 | $10^{-12}$ |
| femto- | quadrillionth | f | 0.000000000000001 | $10^{-15}$ |
| atto- | quintillionth | a | 0.000000000000000001 | $10^{-18}$ |

## 1.2. The Relative Size of Things

We can express the relative size of things with which we are familiar. For instance, the Figure below shows the height of a human as measured in meters, or 100 scale. We see a dust mite, measured in micrometers – $10^{-6}$ scale; and a virus, measured in nanometers – $10^{-9}$ scale. These are examples of length related to relative size and scale.

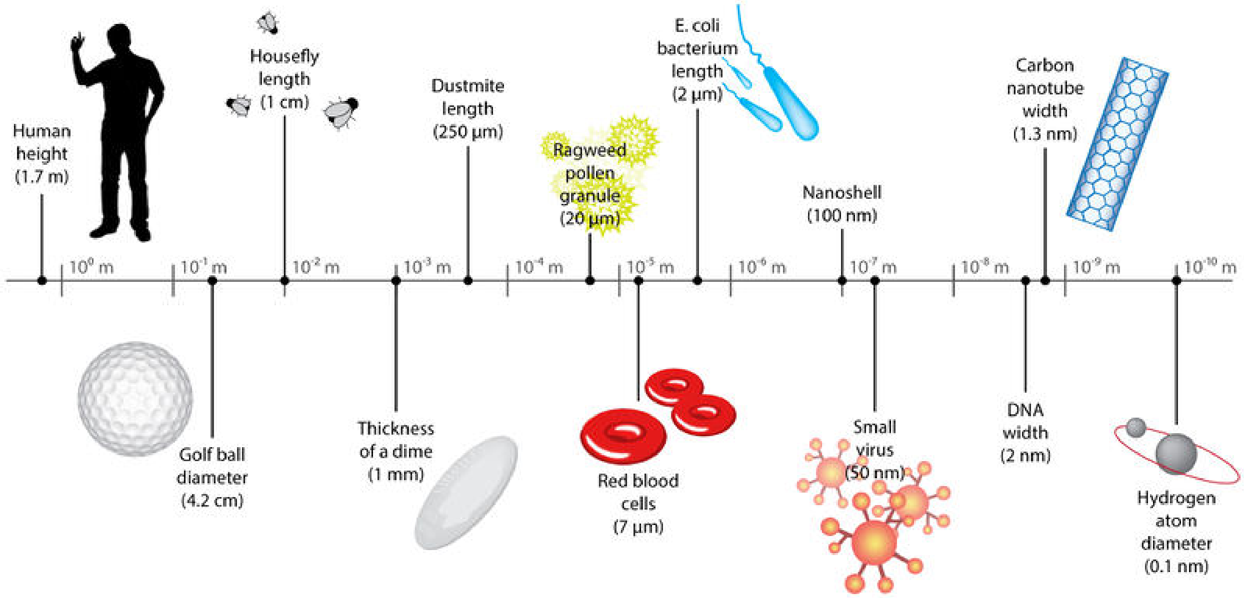

*Figure 2. Relative size and scale of things.*

Now that you have an idea of how small a scale the nanotechnologists work with, consider the challenge they face. Think about how difficult it is for many of us to insert thread through the eye of a needle. Such an image helps you imagine the problem scientists have working with nanoparticles that can be as much as one millionth the size of the thread. Only through the use of powerful microscopes can they hope to 'see' and manipulate these nano-sized particles.

However, we'll introduce another (new) technique for visualizing the nanoparticles by a relatively easy method. This is called "terahertz multispectral reconstructive 3D imaging." [?]

## 1.3. What's so special about nanoscale?

(ref: http://nano.gov/nanotech-101/special)

Nanoscale particles are not new in either nature or science. However, the recent leaps in areas such as modern terahertz imaging and microscopy have given scientists new tools to understand and take advantage of phenomena that occur naturally when matter is organized at the nanoscale. In essence, these phenomena are based on "quantum effects" and other simple physical effects such as expanded surface area (more on these below). In addition, the fact that a majority of biological processes occur at the nanoscale gives scientists models and templates to imagine and construct new processes that can enhance their work in medicine, imaging, computing, printing, chemical catalysis, materials synthesis, and many other fields. Nanotechnology is not simply working at ever smaller dimensions; rather, working at the nanoscale enables scientists to utilize the unique physical, chemical, mechanical, and optical properties of materials that naturally occur at that scale.

## 1.4. Scale at which quantum effects dominate materials' properties

*Figure 3. Computer simulation of electron motions within a nanowire that has a diameter in the nanoscale range. (Image: NSF multimedia/ Eric Heller Gallery)*

When particle sizes of solid matter in the visible scale are compared to what can be seen in a regular optical microscope, there is little difference in the properties of the particles. But when particles are created with dimensions of about 1–100 nanometers (where the particles can be "seen" only with powerful specialized microscopes), the materials' properties change significantly from those at larger scales. This is the size scale where so-called quantum effects rule the behavior and properties of particles. Properties of materials are size-dependent in this scale range. Thus, when particle size is made to be nanoscale, properties such as melting point, fluorescence, electrical conductivity, magnetic permeability, and chemical reactivity change as a function of the size of the particle.

Nanoscale gold illustrates the unique properties that occur at the nanoscale. 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.

A fascinating and powerful result of the quantum effects of the nanoscale is the concept of "tunability" of properties. That is, by changing the size of the particle, a scientist can literally fine-tune a material property of interest (e.g., changing fluorescence color; in turn, the fluorescence color of a particle can be used to identify the particle, and various materials can be "labeled" with fluorescent markers for various purposes). Another potent quantum effect of the nanoscale is known as “tunneling,” which is a phenomenon that enables the scanning tunneling microscope and flash memory for computing.

## 1.5. Scale at which much of biology occurs

Over millennia, nature has perfected the art of biology at the nanoscale. Many of the inner workings of cells naturally occur at the nanoscale. For example, hemoglobin, the protein that carries oxygen through the body, is 5.5 nanometers in diameter. A strand of DNA, one of the building blocks of human life, is only about 2 nanometers in diameter.

Drawing on the natural nanoscale of biology, many medical researchers are working on designing tools, treatments, and therapies that are more precise and personalized than conventional ones—and that can be applied earlier in the course of a disease and lead to fewer adverse side-effects. One medical example of nanotechnology is the bio-barcode assay, a relatively low-cost method of detecting disease-specific biomarkers in the blood, even when there are very few of them in a sample. The basic process, which attaches “recognition” particles and DNA “amplifiers” to gold nanoparticles, was originally demonstrated at Northwestern University for a prostate cancer biomarker following prostatectomy. The bio-barcode assay has proven to be considerably more sensitive than conventional assays for the same target biomarkers, and it can be adapted to detect almost any molecular target.[2]

Growing understanding of nanoscale biomolecular structures is impacting other fields than medicine. Some scientists are looking at ways to use nanoscale biological principles of molecular self-assembly, self-organization, and quantum mechanics to create novel computing platforms. Other researchers have discovered that in photosynthesis, the energy that plants harvest from sunlight is nearly instantly transferred to plant “reaction centers” by quantum mechanical processes with nearly 100% efficiency (little energy wasted as heat). They are investigating photosynthesis as a model for “green energy” nanosystems for inexpensive production and storage of nonpolluting solar power.[3]

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[2] For example, see C.S. Thaxton, R. Elghanian, A.D. Thomas, S.I. Stoeva, J.S. Lee, N.D. Smith, A.J. Schaeffer, H. Klocker, W. Horninger, G. Bartsch, and C.A. Mirkin. Nanoparticle-based bio-barcode assay redefines “undetectable” PSA and biochemical recurrence after radical prostatectomy. Proc. Nat. Acad. Sci. U. S. A. 106(44):18437–18442, 2009, doi:10.1073/pnas.0904719106.

[3] For more detail, see http://newscenter.lbl.gov/feature-stories/2010/05/10/untangling-quantum-entanglement/ and associated links.

## - Scale at which surfaces and interfaces play a large role in materials properties and interactions

Nanoscale materials have far larger surface areas than similar masses of larger-scale materials. As surface area per mass of a material increases, a greater amount of the material can come into contact with surrounding materials, thus affecting reactivity.

A simple thought experiment shows why nanoparticles have phenomenally high surface areas. A solid cube of a material 1 cm on a side has 6 square centimeters of surface area, about equal to one side of half a stick of gum. But if that volume of 1 cubic centimeter were filled with cubes 1 mm on a side, that would be 1,000 millimeter-sized cubes (10 x 10 x 10), each one of which has a surface area of 6 square millimeters, for a total surface area of 60 square centimeters—about the same as one side of two-thirds of a 3” x 5” note card. When the 1 cubic centimeter is filled with micrometer-sized cubes—a trillion ($10^{12}$) of them, each with a surface area of 6 square micrometers—the total surface area amounts to 6 square meters, or about the area of the main bathroom in an average house. And when that single cubic centimeter of volume is filled with 1-nanometer-sized cubes—$10^{21}$ of them, each with an area of 6 square nanometers—their total surface area comes to 6,000 square meters. In other words, a single cubic centimeter of cubic nanoparticles has a total surface area one-third larger than a football field!

One benefit of greater surface area—and improved reactivity—in nanostructured materials is that they have helped create better catalysts. As a result, catalysis by engineered nanostructured materials already impacts about one-third of the huge U.S.—and global—catalyst markets, affecting billions of dollars of revenue in the oil and chemical industries.[4] An everyday example of catalysis is the catalytic converter in a car, which reduces the toxicity of the engine’s fumes. Nanoengineered batteries, fuel cells, and catalysts can potentially use enhanced reactivity at the nanoscale to produce cleaner, safer, and more affordable modes of producing and storing energy.

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[4] As of 2003, catalyst technologies accounted for over $1 trillion of revenue in the U.S. economy and about a third of the material GDP (M.E. Davis and D. Tilley, Future Directions in Catalysis Research, Structures that Function on the Nanoscale, NSF Workshop, Caltech, June 19-20, 2003; http://www.che.caltech.edu/nsfcatworkshop/#Reports).

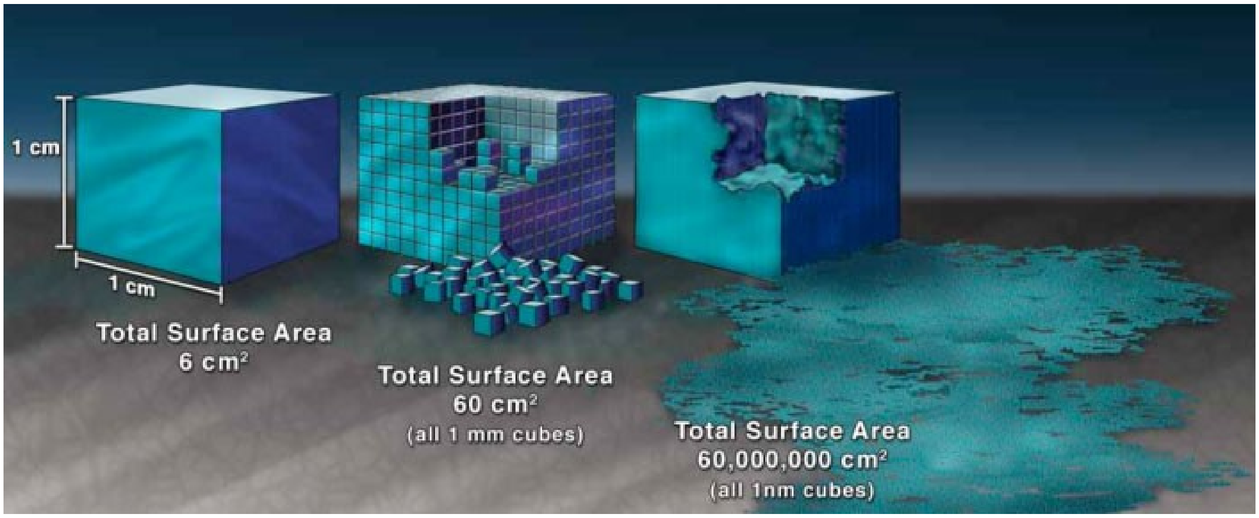

*Figure 4. Illustration demonstrating the effect of the increased surface area provided by nanostructured materials. If 1 cm$^3$ is converted in to blocks of 1 nm$^3$, the resulting blocks will cover an area of 60 million cm$^2$.*

Large surface area also makes nanostructured membranes and materials ideal candidates for water treatment and desalination (e.g., see “Self-Assembled, Nanostructured Carbon for Energy Storage and Water Treatment” in our database, NNI Accomplishments Archive), among other uses. It also helps support “functionalization” of nanoscale material surfaces (adding particles for specific purposes), for applications ranging from drug delivery to clothing insulation.

# Chapter 2

- ## Frequently Asked Questions

(Ref: http://nano.gov/nanotech-101/nanotechnology-facts#content)

## 1.6. What is nanotechnology?

Nanotechnology encompasses science, engineering, and technology at the nanoscale, which is about 1 to 100 nanometers. Just how small is that? A nanometer is one-billionth of a meter. For reference, a sheet of paper is about 100,000 nanometers thick. Nanoscale matter can behave differently than the same bulk material. For example, a material's melting point, color, strength, chemical reactivity, and more may change at the nanoscale.

Researchers seeking to understand the fundamentals of properties at the nanoscale may call their work nanoscience; those focused on effective use of the properties may call their work nanoengineering. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at the nanoscale.

## 1.7. What is a nanometer?

A nanometer is one billionth of a meter. (A meter is 39.37 inches, or slightly longer than one yard.) The prefix "nano" means "one billionth", or $10^{-9}$, in the international system for units of weights and measures. The abbreviation for nanometer is "nm."

For visual examples of the size of the nanoscale, see below. Just how small is "nano?" In the International System of Units, the prefix "nano" means one-billionth, or $10^{-9}$; therefore, one nanometer is one-billionth of a meter. It's difficult to imagine just how small that is, so here are some examples:

A sheet of paper is about 100,000 nanometers thick

A strand of human DNA is 2.5 nanometers in diameter

There are 25,400,000 nanometers in one inch

A human hair is approximately 80,000–100,000 nanometers wide

A single gold atom is about a third of a nanometer in diameter

On a comparative scale, if the diameter of a marble was one nanometer, then diameter of the Earth would be about one meter

One nanometer is about as long as your fingernail grows in one second

The illustration below has three visual examples of the size and the scale of nanotechnology, showing just how small things at the nanoscale actually are.

- ## Is nanotechnology new? Where did it come from?

Nanoscale materials have been used for over a thousand years. For example, nanoscale gold was used in stained glass in Medieval Europe and nanotubes were found in blades of swords made in Damascus. However, ten centuries passed before high-powered microscopes were invented, allowing us to see things at the nanoscale and begin working with these materials.

Nanotechnology as we now know it began more than 30 years ago, when tools to image and measure at the nanoscale became available. Around the turn of the century, government research managers in the United States and other countries observed that physicists, biologists, chemists, electrical engineers, optical engineers, and materials scientists were working on interconnected, multidisciplinary issues emerging at the nanoscale. In 2000, the U.S. National Nanotechnology Initiative (NNI) was created to help these researchers benefit from each other's insights, accelerate technology development, and foster commercialization across disciplines.

## 1.8. What are nanomaterials? Do they exist in nature?

The term "nanomaterial" refers to nanoscale materials, or materials that contain nanoscale structures internally or on their surfaces. These can include engineered (or man-made) nanometer-scale objects such as nanoparticles, nanotubes, and nanofilms, as well as naturally occurring nanoparticles such as volcanic ash, sea spray, and smoke.

## 1.9. What are nanoparticles, nanotubes, and nanofilms?

Depending on the shape, the application, or the components, nanomaterials may be called by a variety of different names, including nanoparticles, nanotubes, nanofilms, nanoshells, nanospheres, nanowires, nanoclays, nanoconcrete, nanopolymers, and much more. Other nanomaterials have distinct qualities that have led researchers to call them by other non-nano prefix names, such as quantum dots or graphene. Generally speaking, nanomaterials are objects with one or more dimension at the nanoscale. Efforts to standardize these words are currently underway, for example, by the International Organization for Standardization.

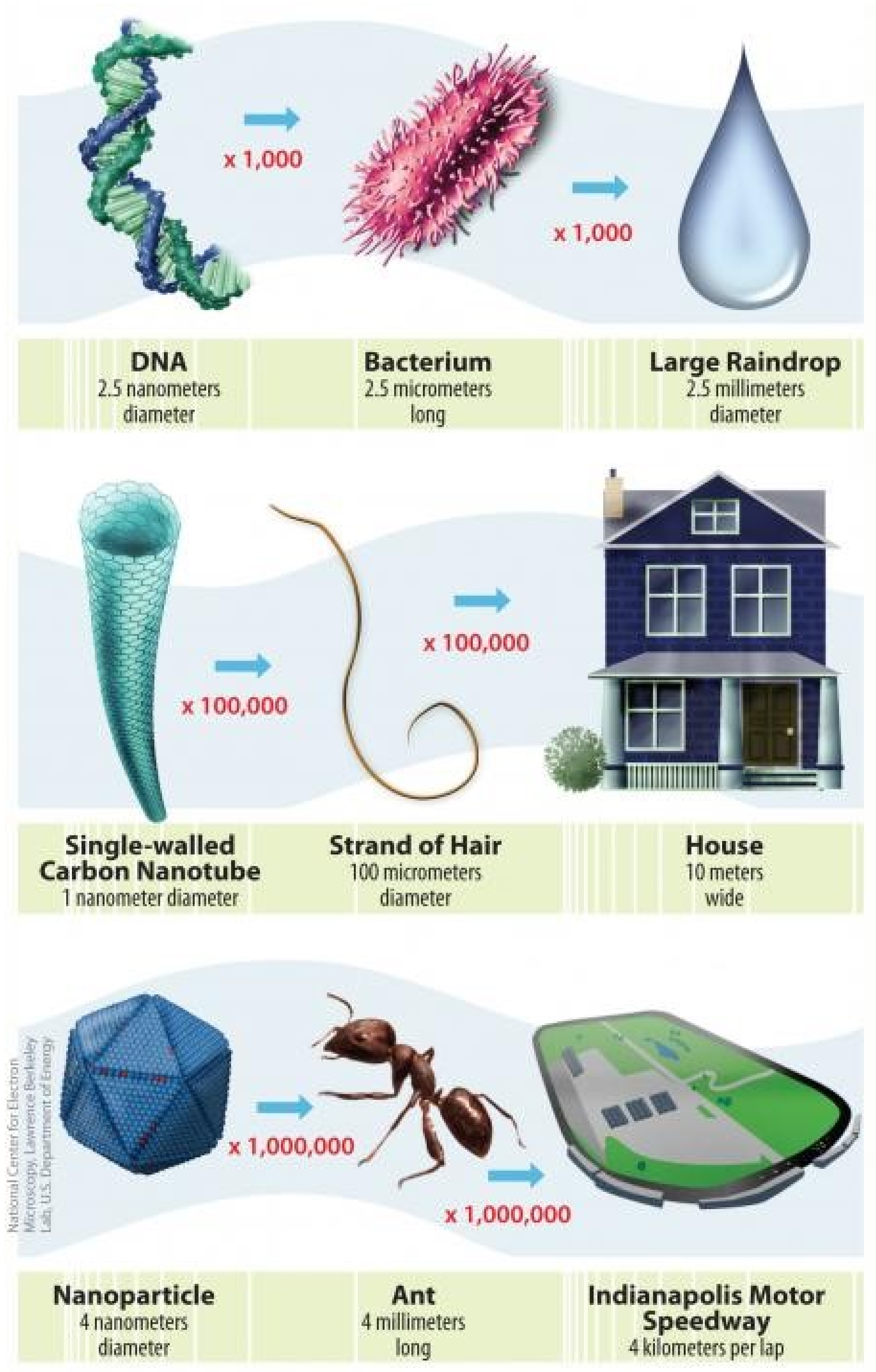

*Figure 5. The Scale of Things; from DNA (2.5 nm) to a racetrack (4 km).*

## 1.10. Are nanotechnology products available today?

# An introduction to the world of nanoscience and nanotechnology

Yes, nanotechnology is becoming ubiquitous in our daily lives and has found its way into many commercial products, for example, strong, lightweight materials for better fuel economy; targeted drug delivery for safer and more effective cancer treatments; clean, accessible drinking water around the world; superfast computers with vast amounts of storage; self-cleaning surfaces; wearable health monitors; more efficient solar panels; safer food through packaging and monitoring; regrowth of skin, bone, and nerve cells for better medical outcomes; smart windows that lighten or darken to conserve energy; and nanotechnology-enabled concrete that dries more quickly and has sensors to detect stress or corrosion at the nanoscale in roads, bridges, and buildings. By some estimates, revenue from the sale of nanotechnology-enabled products made in the United States has grown more than six-fold from 2009 through 2016.

The National Nanotechnology Initiative (NNI) is a U.S. Government research and development (R&D) initiative involving the nanotechnology-related activities of 20 departments and independent agencies. Since 2001, Federal agencies and Cabinet-level departments have invested more than $25 billion in nanotechnology research, development, and commercialization. These investments, made under the auspices of the NNI, have enabled groundbreaking discoveries that have revolutionized science; established world-class facilities for the characterization of nanoscale materials and their fabrication into nanoscale devices; educated tens of thousands of individuals from undergraduate students to postdoctoral researchers; and fostered the responsible incorporation of nanotechnology into commercial products.

The NNI community extends beyond the Federal Government and includes grantees, students, companies, technical and professional societies, foundations, and others engaged in nanotechnology research and development. This vibrant community exists in large part as a result of the efforts of the NNI agencies over the past two decades. With the expansion of scientific knowledge in nanotechnology, formal and informal collaborations have developed among researchers across a diverse range of fields and countries. These interactions and collaborations have been and continue to be facilitated by agency activities including public–private partnerships, research centers, and networks. In addition to providing fabrication, characterization, and testing capabilities, the NNI’s physical infrastructure also provides a place for researchers, industry, and ideas to mix, further expanding the community. This community has broken down the traditional disciplinary boundaries and laid the foundation for interdisciplinary discovery, which is increasingly vital to research as fields converge.

The National Nanotechnology Coordination Office (NNCO) helps to coordinate the U.S. Government’s R&D efforts in nanotechnology, serves as the central point of contact for Federal nanotechnology R&D activities, helps to foster the commercialization of nanotechnology, and provides public outreach on behalf of the National Nanotechnology Initiative. The NNCO also provides technical and administrative support to the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council, which coordinates the NNI. For more information, see the NNCO section of this website.

The cumulative NNI investment since fiscal year 2001, including the 2018 request, now totals more than $25 billion. In addition, more than $1.1 billion has been invested cumulatively since 2004 in funding for nanotechnology-based small businesses through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs of the participating Federal agencies. Nanotechnology-related environmental, health, and safety (EHS, or nanoEHS) activities have become a hallmark of the NNI, with R&D, policy, and regulation in this area extensively coordinated among Federal agencies. Cumulative NNI EHS investments surpassed $1 billion in 2015. For more information, visit the NNI Budget page.

The United States is not the only country to recognize the tremendous economic potential of nanotechnology. The U.S. National Nanotechnology Initiative's member agencies have cumulatively spent more than $23 billion since the inception of the NNI in 2001. According to a Lux Research estimate released in December 2015, “The U.S. leads in government (state and Federal) nanotechnology funding with $1.72 billion spent in 2013 and $1.67 billion spent in 2014. Europe’s collective spending (European Commission and individual country programs) was $2.45 billion in 2014, an increase of 9.8% from 2012. While some countries, such as the U.S., continue to have centralized government programs to coordinate nanotechnology activities, most countries no longer do. In fact, many countries no longer explicitly fund nanotechnology, although it may be a part of initiatives that are funded under different technology support programs. Because of this change, it is difficult to determine with certainty the level of nanotechnology funding by country or region.”

Although federally funded R&D yields hard-to-quantify benefits such as students educated, degrees conferred, companies started, patents and copyrights granted, developmental partnerships formed, and private sector investment inflows, there are many indicators of the impact of this -----investment.

For example, there are over 1,900 U.S.-based companies conducting R&D, manufacturing, or product sales in nanotechnology in 2016. Of these companies engaged in the nanotechnology sector, over 36% have participated in the Small Business Innovation Research or Small Business Technology Transfer programs funded by the Federal agencies that participate in the National Nanotechnology Initiative. The most recent Business R&D and Innovation Survey (BRDIS) conducted by the National Science Foundation (NSF) found approximately 1,500 companies engaged in nanotechnology with approximately 1,100 of these classified as small businesses (less than 500 employees). The difference in the number of companies cited above can be attributed to the year the data was collected and other methodologies.

A noteworthy impact of the NNI has been the focused investment by NNI-participating agencies in the establishment and development of multidisciplinary research and education centers devoted to nanoscience and nanotechnology. NNI agencies have developed an extensive infrastructure of nearly 100 major interdisciplinary research and education centers and user facilities across the United States. This cutting-edge fabrication and characterization equipment provides state-of-the-art nanoscience tools and expertise for research by non-profit or business organizations, whether small or large, for use-inspired research and some of the user facilities are available free-of-charge for non-proprietary work if the user intends to publish the research results in the scientific literature.

In December 2015, Lux Research estimated that nanotechnology-enabled products generated $1.6 trillion in global revenues in 2014; and that figure is anticipated to increase to $3.5 trillion in 2018.

The National Nanotechnology Initiative itself is not a funding program; funding is provided through the NNI member agencies. There are various mechanisms for funding research through these agencies. For detailed information on Federal funding programs, see Funding Opportunities. For grant information, see Current Solicitations. See also the list of Federal agency representatives to the NSET Subcommittee, who can help members of the research community find the appropriate mechanisms to apply for competitive funding programs.

Yes, nanotechnology is enabling more and more products every day, from engine catalysts to cancer medicines to stain-proof pants, and everything in between. Revenue from the sale of nanotechnology-enabled products in the United States has grown more than six-fold from 2009 through 2016.

Nanotechnology has the potential to create many new jobs across a variety of sectors. While some jobs, will require an advanced degree, a 2014 study funded by the National Science Foundation points out that 2-yr and 4-yr training with access to continuing and technical education will be sufficient for many of the future positions in nanotechnology, nanomanufacturing, and beyond.

Previous estimates stated that 6 million nanotechnology jobs will be needed by 2020, with 2 million of those jobs in the United States (Roco, Mirkin, and Hersam 2010). According to the U.S. News/Raytheon analysis, the number of STEM jobs increased 20 percent between 2000 and 2014. Looking ahead, the U.S. Bureau of Labor Statistics (BLS) projects that between 2012 and 2022, employment in occupations that NSF classifies as science and engineering (S&E) will increase 15 percent. To find out about nanotechnology programs at college and graduate levels, see College and Graduate Programs. If you are interested in 2-year degrees or training programs, see Associate Degrees, Certificates, & Job Info.

# Chapter 3

## Introduction to Nanotechnology Applications

## 1.11. Nanotechnology Applications: A Variety of Uses

The ability to see nano-sized materials has opened up a world of possibilities in a variety of industries and scientific endeavors. Because nanotechnology is essentially a set of techniques that allow manipulation of properties at a very small scale, it can have many applications, such as the ones listed below.

**Drug delivery**. Today, most harmful side effects of treatments such as chemotherapy are a result of drug delivery methods that don't pinpoint their intended target cells accurately. **Researchers** have been able to attach special RNA strands, measuring about 10 nm in diameter, to nanoparticles and fill the nanoparticles with a chemotherapy drug. These RNA strands are attracted to cancer cells. When the nanoparticle encounters a cancer cell it adheres to it and releases the drug into the cancer cell. This directed method of drug delivery has great potential for treating cancer patients while producing less harmful side effects than those produced by conventional chemotherapy.

**Fabrics**. The properties of familiar materials are being changed by manufacturers who are adding nano-sized components to conventional materials to improve performance. For example, some clothing manufacturers are making water and stain repellent clothing using **nano-sized whiskers** in the fabric that cause water to bead up on the surface.

**Reactivity of Materials**. The properties of many conventional materials change when formed as nano-sized particles (nanoparticles). This is generally because nanoparticles have a greater surface area per weight than larger particles; they are therefore more reactive to some other molecules. For example studies have show that **nanoparticles of iron can be effective in the cleanup of chemicals in groundwater** because they react more efficiently to those chemicals than larger iron particles.

**Strength of Materials**. Nano-sized particles of carbon, (for example nanotubes and bucky balls) are extremely strong. Nanotubes and Bucky balls are composed of only carbon and their strength comes from special characteristics of the bonds between carbon atoms. One proposed application that illustrates the strength of nanosized particles of carbon is the manufacture of t-shirt weight **bullet proof vests made out of carbon nanotubes**.

**Micro/Nano ElectroMechanical Systems**. The ability to create gears, mirrors, sensor elements, as well as electronic circuitry in silicon surfaces allows the manufacture of miniature sensors such as those used to activate the airbags in your car. This technique is called MEMS (Micro-ElectroMechanical Systems). The MEMS technique results in close integration of the mechanical mechanism with the necessary electronic circuit on a single silicon chip, similar to the method used to produce computer chips. Using MEMS to produce a device reduces both the cost and size of the product, compared to similar devices made with conventional methods. MEMS is a steppingstone to NEMS or Nano-ElectroMechanical Systems. NEMS products are being made by a few companies and will take over as the standard once manufacturers make the investment in the equipment needed to produce nano-sized features.

**Molecular Manufacturing**. If you're a Star Trek fan, you remember the replicator, a device that could produce anything from a space age guitar to a cup of Earl Grey tea. Your favorite character just programmed the replicator, and whatever he or she wanted appeared. Researchers are working on developing a method called molecular manufacturing that may someday make the Star Trek replicator a reality. The gadget these folks envision is called a molecular fabricator; this device would use tiny manipulators to position atoms and molecules to build an object as complex as a desktop computer. Researchers believe that raw materials can be used to reproduce almost any inanimate object using this method.

The Understanding Nanotechnology, this compilation is aimed at providing clear and concise explanations of nanotechnology applications. Some applications of interest are discussed below.

(Ref. **Nanotechnology Applications in Medicine)**

### 1.1.2. Medicine

Researchers are developing customized nanoparticles the size of molecules that can deliver drugs directly to diseased cells in your body. When it's perfected, this method should greatly reduce the damage treatment such as chemotherapy does to a patient's healthy cells.

### 1.1.3. Electronics

Nanotechnology holds some answers for how we might increase the capabilities of electronics devices while we reduce their weight and power consumption.

### 1.1.4. Food

Nanotechnology is having an impact on several aspects of food science, from how food is grown to how it is packaged. Companies are developing nanomaterials that will make a difference not only in the taste of food, but also in food safety, and the health benefits that food delivers.

### 1.1.5. Fuel Cells

Nanotechnology is being used to reduce the cost of catalysts used in fuel cells to produce hydrogen ions from fuel such as methanol and to improve the efficiency of membranes used in fuel cells to separate hydrogen ions from other gases such as oxygen. Check out our Nanotechnology Applications in Fuel Cells page for the details.

### 1.1.6. Solar Cells

Companies have developed nanotech solar cells that can be manufactured at significantly lower cost than conventional solar cells.

### 1.1.7. Batteries

Companies are currently developing batteries using nanomaterials. One such battery will be a good as new after sitting on the shelf for decades. Another battery can be recharged significantly faster than conventional batteries.

### 1.1.8. Space

Nanotechnology may hold the key to making space-flight more practical. Advancements in nanomaterials make lightweight spacecraft and a cable for the space elevator possible. By significantly reducing the amount of rocket fuel required, these advances could lower the cost of reaching orbit and traveling in space.

### 1.1.9. Fuels

Nanotechnology can address the shortage of fossil fuels such as diesel and gasoline by making the production of fuels from low grade raw materials economical, increasing the mileage of engines, and making the production of fuels from normal raw materials more efficient. Check our Nanotechnology Applications in Fuels page for details.

### 1.1.10. Better Air Quality

Nanotechnology can improve the performance of catalysts used to transform vapors escaping from cars or industrial plants into harmless gasses. That's because catalysts made from nanoparticles have a greater surface area to interact with the reacting chemicals than catalysts made from larger particles. The larger surface area allows more chemicals to interact with the catalyst simultaneously, which makes the catalyst more effective. Check our **Nanotechnology and Air Qualit**y page for details.

### 1.1.11. Cleaner Water

Nanotechnology is being used to develop solutions to three very different problems in water quality. One challenge is the removal of industrial wastes, such as a cleaning solvent called TCE, from groundwater. Nanoparticles can be used to convert the contaminating chemical through a chemical reaction to make it harmless. Studies have shown that this method can be used successfully to reach contaminates dispersed in underground ponds and at much lower cost than methods which require pumping the water out of the ground for treatment. Check out our **Nanotechnology and Water Quality** page for details.

### 1.1.12. Chemical Sensors

Nanotechnology can enable sensors to detect very small amounts of chemical vapors. Various types of detecting elements, such as carbon nanotubes, zinc oxide nanowires or palladium nanoparticles can be used in nanotechnology-based sensors. Because of the small size of nanotubes, nanowires, or nanoparticles, a few gas molecules are sufficient to change the electrical properties of the sensing elements. This allows the detection of a very low concentration of chemical vapors. Check out our **Nanotechnology Applications in Chemical Sensors** page for details.

### 1.1.13. Sporting Goods

If you're a tennis or golf fan, you'll be glad to hear that even sporting goods has wandered into the nano realm. Current nanotechnology applications in the sports arena include increasing the strength of tennis racquets, filling any imperfections in club shaft materials and reducing the rate at which air leaks from tennis balls. Check out our **Nanotechnology Applications in Sporting Goods** page for details.

### 1.1.14. Fabric

Making composite fabric with nano-sized particles or fibers allows improvement of fabric properties without a significant increase in weight, thickness, or stiffness as might have been the case with previously used techniques. For details see our **Nanotechnology in Fabrics** page.

# Chapter 4

## Nanotechnology in Cancer Treatment

The use of nanotechnology in cancer treatment offers some exciting possibilities, including the possibility of destroying cancer tumors with minimal damage to healthy tissue and organs, as well as the detection and elimination of cancer cells before they form tumors.

Most efforts to improve cancer treatment through nanotechnology are at the research or development stage. However, the effort to make these treatments a reality is highly focused. For example, The Alliance for Nanotechnology in Cancer, established by the U.S. National Cancer Institute, is fostering innovation and collaboration among researchers to resolve some of the major challenges in the application of nanotechnology to cancer. In addition, there are many universities and companies worldwide working in this area. It is possible that these efforts will result in cancer becoming being nearly eliminated in a decade or so, in the same way that vaccines nearly eliminated smallpox in the last century.

The next section provides examples of the research underway, a few of the methods discussed have reached the pre-clinical or clinical trial stage.

## 1.12. Cancer Treatments Under Development

One treatment under development involves targeted chemotherapy that delivers a tumor-killing agent called tumor necrosis factor alpha (TNF) to cancer tumors. TNF is attached to a gold nanoparticle along with Thiol-derivatized polyethylene glycol (PEG-THIOL), which hides the TNF bearing nanoparticle from the immune system. This allows the nanoparticle to flow through the blood stream without being attacked. For more details read the article at this **link**. The company developing this targeted chemotherapy method to deliver TNF and other chemotherapy drugs to cancer tumors is called **CytImmune**.

Another targeted chemotherapy treatment under development uses a nanoparticle called **CRLX101**. The company developing this targeted chemotherapy method is called **Cerulean Pharma**.

Another technique being developed works on destroying cancer tumors by applying heat. Nanoparticles called **AuroShells** absorb infrared light from a laser, turning the light into heat. The company developing this technique is called **Nanospectra**.

Cristal Therapeutics is conducting Phase 1 clincal trails using nanoparticles called **CriPec®** to deliver a drug called docetaxel to tumors.

Researchers at Massachusetts General Hospital are working on a method using **infrared light to trigger** the release of two anticancer drugs to tumors.

Researchers at the University of Georgia are working on a method to fight prostate cancer. They are using nanoparticles to deliver a molecule called IPA-3 to the cancer cells. In laboratory mice studies the IPA-3 appears to reduce the **growth of prostate cancer** cells.

Researchers at the University of Texas Southwestern Medical Center have used nanoparticles called **dendrimers to deliver nucleic acids** that suppress tumors to liver cancer tumors. The researchers have demonstrated, in lab tests, that this method can reduced tumor growth in mice.

Researchers are developing graphene strips to deliver different drugs to specific regions of cancer cells. When the **graphene strip** reaches the cancer cell one drug separates from the graphene and attacks the cell membrane while the graphene strip enters the cell and delivers the second drug to the cell nucleus.

Researchers at MIT are developing nanoparticles that carry **precise ratios** of three different drugs. They are testing the effectiveness of this approach on ovarian cancer cells.

Researchers at UCLA are investigating a method to **fight pancreatic cancer** using two different nanoparticles. The first nanoparticle removes material on the exterior of the cancer cells that block the entry of chemotherapy drugs, the second nanoparticle carries the chemothreapy drug. Testing this method on laboratory mice showed significantly faster shrinkage of the tumors than other methods.

Using **iron-oxide nanoparticles and a magnetic field** to heat up cancer tumors has been shown to stimulate the immune system to fight cancer cells in other parts of the body. Researchers believe this methodology may be useful in preventing the spread of cancer cells, while other techniques are used to fight localized tumors.

Researchers at the Institute of Bioengineering and Nanotechnology and IBM researchers have demonstrated **sustained drug delivery using a hydrogel**. The hydrogel is injected under the skin, allowing continuous drug release for weeks, with only one injection, rather than repeated injections. They demonstrated this method by injecting the hydrogel, containing the chemotherapy drug herceptin, under the skin of laboratory mice. The study showed significant reduction in tumor size.

Another targeted chemotherapy technique being developed uses polymer nanoparticles to carry the chemotherapy drug called docetaxel. The nanoparticles are attracted to a protein present on many types of cancer tumors, with the intention of increasing the rate of delivery of the chemotherapy drug to the tumors. For more details read the article at this **link**. The company developing this targeted chemotherapy method is called **BIND Biosciences.**

Researchers are testing the use of **chemotherapy drugs attached to nanodiamonds** to treat brain tumors. The nanodiamond/chemotherapy drug combination stays in the tumor longer than the chemotherapy drug by itself, which should increase the effectiveness.

Researchers are also testing the use of chemotherapy drugs attached to nanodiamonds to treat leukemia. It turns out that leukemia cancer cells can pump chemotherapy drugs out of the cancer cell, limiting the effectiveness of the drug. The cancer cell cannot pump the nanodiamond out, so **attaching the drug molecules to nanodiamonds** results in the drug staying in the cancer cell longer.

Researchers are connecting different DNA strands together into a structure they call a "**nanotrain**". They have demostrated in lab studies that these nanotrains are effective in delivering chemothreapy drugs to cancer cells, and that by using different DNA strands they can customize which type of cancer cells the nanotrains target.

Researchers are testing a nanoparticle carrying a chemothreapy drug (camptothecin) along with a antibody (herceptin) that **targets breast cancer cells**. The lab tests in mice produced very postitive results.

Researchers at UC San Diego have encapsulated an anti-cancer drug called staurosporine in liposome nanoparticles. They demonstrated the staurosporine bearing particles were effective in suppressing tumors in mice without apparent side effects.

Researchers are developing a nanoparticle that both delivers a chemotherapy drug and stimulates the immune system to attack cancer cells. They have tested the method on mice with positive results.

Researchers have developed nanoparticles containing a radioactive core with attached molecules that attach to lymphoma tumor cells. The researchers are designing this method to stop the spread of cancer from the primary tumor.

Researchers have demonstrated a nanoparticle that kills lymphoma cancer cells. They use a nanoparticle which looks like HDL cholesterol, but with a gold nanoparicle at its core. When this nanoparticle attaches to a lymphoma cell it blocks the cancer cell from attaching to real HLD cholesterol, **starving the cancer cell**.

Researchers have demonstrated a method of delivering a protein to cancer cells that destroys the cancer cells. They use a **polymer nanoshell to deliver the protein** into the cancer cells. When the protein accumlates in the nucleus of the cancer cell the protein causes the cancer cell to self-destruct.

Researchers are using a photosensitizing agent to enhance the ability of drug carrying nanoparticlesto enter tumors. First, they let the photosensitizing agent accumulate in the tumor, then illuminate the tumor with infrared light. The photosensitizing agent causes the blood vessels in the tumor to be more porous, therefore more drug carrying nanoparticles can enter the tumor.

Researchers are investigating the use of **bismuth nanoparticles** to concentrate radiation used in radiation therapy to treat cancer tumors. Initial results indicate that the bismuth nanoparticles would increase the radiation dose to the tumor by 90 percent.

A method being developed to fight skin cancer uses gold nanoparticles to which RNA molecules are attached. The nanoparticles are in an ointment that is applied to the skin. The nanoparticles penetrate the skin and the **RNA attaches to a cancer related gene**, stopping the gene from generating proteins that are used in the growth of skin cancer tumors.

A method being developed to fight bladder cancer uses nanoparticles called micelles to deliver a chemotherapy drug called paclitaxel to bladder cancer cells.

One heat therapy to destroy cancer tumors using nanoparticles is called AuroShell™. The AuroShell™ nanoparticles circulate through a patient's bloodstream, exiting where the blood vessels are leaking at the site of cancer tumors. Once the nanoparticles accumulate at the tumor the AuroShell™ nanoparticles are used to concentrate the heat from infrared light to destroy cancer cells with minimal damage to surrounding healthy cells. For a good visual illustration of this process, click **here**. Nanospectra Biosciences has developed such a treatment using AuroShell™ that has been approved for a **pilot trial with human patients**.

Targeted heat therapy is being developed to destroy breast cancer tumors. In this method antibodies that are strongly attracted to proteins produced in one type of breast cancer cell are attached to nanotubes, causing the nanotubes to accumulate at the tumor. Infrared light from a laser is absorbed by the nanotubes and produces heat that incinerates the tumor. For more details read the article at this **link**.

X-ray therapy may be able to destroy cancer tumors using a nanoparticle called nbtxr3. The nbtxr3 nanoparticles, when activated by x-rays, generate electrons that cause the destruction of cancer tumors to which they have attached themselves. Click here for more details on this **method**. This is intended to be used in place of radiation therapy with much less damage to healthy tissue. Nanobiotix has released **preclinical results** for this technique.

An intriguing targeted chemotherapy method uses one nanoparticle to deliver the chemotherapy drug and a separate nanoparticle to guide the drug carrier to the tumor. First gold nanorods circulating through the bloodstream exit where the blood vessels are leaking at the site of cancer tumors. Once the nanorods accumulate at the tumor they are used to concentrate the heat from infrared light; heating up the tumor. This heat increases the level of a stress related protein on the surface of the tumor. The drug carrying nanoparticle (a liposome) is attached to amino acids that bind to this protein, so the increased level of protein at the tumor speeds up the accumulation of the chemotherapy drug carrying liposome at the tumor. For more details read the article at this **link**.

An improved way to shield nanoparticles delivering chemotherapy drugs from the immune system has been developed by forming the nanoparticles from the **membranes of red blood cells**.

Delivery of short interfering RNAs (siRNA) is interesting because siRNA simply stops the cancer tumor from growing and there is the potential to tailor synthetic siRNA to the version of cancer in a individual patient. For more details read the article at this **link**.

A method to increase the number of cancer-fighting immune cells in cancer tumors is interesting. Nanoparticles containing drug molecules called **interleukins are attached to immune cells ( T-cells)**. The idea is that when the T-cells reach a tumor the nanoparticles release the drug molecules, which cause the T-cells to reproduce. If enough T-cells are reproduced in the cancer tumor the cancer can be destroyed. This method has been tested on laboratory mice with very good results.

Researchers have demonstrated a method of delivering a protein to cancer cells that destroys the cancer cells. They use a **polymer nanoshell to deliver the protein** into the cancer cells. When the protein accumulates in the nucleus of the cancer cell the protein causes the cancer cell to self-destruct.

Magnetic nanoparticles that attach to cancer cells in the blood stream may allow the cancer cells to be removed before they establish new tumors. For more details read the article at this **link**.

Another method that targets individual cancer cells inserts gold nanoparticles into the cells, then shines a laser on the nanoparticles. The heat explodes the cancer cells. For more details read the article at this **link**.

A method to make radiation therapy more effect in fighting prostate cancer is using radioactive gold nanoparticles attached to a molecule that is **attracted to prostate tumor cells**. Researchers believe that this method will help concentrate the radioactive nanoparticles at the cancer tumors, allowing treatment of the tumors with minimal damage to healthy tissue.

Using gold nanoparticles to deliver platinum to cancer tumors may reduce the side effects of platinum cancer therapy. The key is that the toxicity level of platinum depends upon the molecule it is bonded to (for the tech types the toxicity depends upon the oxidation state of the platinum). So, the researchers chose a platinum containing molecule that has low toxicity to attach to the gold nanoparticles. When the platinum bearing nanoparticle reaches a cancer tumor it encounters an acidic solution which changes the platinum to its toxic state, in which it can kill cancer cells. For more details read the article at this **link**.

Other researchers are taking a different approach to delivering platinum to cancer tumors. Instead of attaching platinum to nanoparticles they have used molecular building blocks to produce nanoparticles designed to deliver platinum to cancer tumors. For more details read the article at this **link.**

Using polymer nanoparticles to deliver a molecule called JSI-124 to cancer tumors. This molecule degrades the ability of the cancer cells to suppress the immune system, possibly slowing the growth of cancer tumors. For more details read the article at this **link**.

Iron oxide nanoparticles can be used to improve MRI images of cancer tumors. The nanoparticle is coated with a peptide that binds to a cancer tumor. Once the nanoparticles are attached to the tumor, the magnetic property of the **iron oxide enhances the images from the Magnetic Resonance Imagining scan**.

Sensors based upon nanoparticles or nanowires can detect proteins related to specific types of cancer cells in blood samples. This could allow early detection of cancer. T2 Biosystems uses superparamagnetic nanoparticles that bind to the cancer indicating protein and cluster together. These clusters provide a magnetic resonance signal indicating the **presence of the cancer related protein**. For another approach researchers at John Hopkins University use quantum dots and molecules that emit a fluorescent glow to detect DNA strands that are **early indicators of cancer**.

# Chapter 5

## Nanotechnology in Electronics: Nanoelectronics

How can nanotechnology improve the capabilities of electronic components?

*Nanoelectronics* holds some answers for how we might increase the capabilities of electronics devices while we reduce their weight and power consumption. Some of the nanoelectronics areas under development, which you can explore in more detail by following the links provided in the next section, include the following topics.

Improving display screens on electronics devices. This involves reducing power consumption while decreasing the weight and thickness of the screens.

Increasing the density of memory chips. Researchers are developing a type of memory chip with a projected density of one terabyte of memory per square inch or greater.

Reducing the size of transistors used in integrated circuits. One researcher believes it may be possible to "put the power of all of today's present computers in the palm of your hand".

Nanoelectronics: Applications under Development

Researchers are looking into the following nanoelectronics projects:

- Cadmium selenide nanocrystals deposited on plastic sheets have been shown to form **flexible electronic circuits**. Researchers are aiming for a combination of flexibility, a simple fabrication process and low power requirements.
- Integrating **silicon nanophotonics** components into CMOS integrated circuits. This optical technique is intended to provide higher speed data transmission between integrated circuits than is possible with electrical signals.
- Researchers at UC Berkeley have demonstrated a low power method to use **nanomagnets as switches**, like transistors, in electrical circuits. Their method might lead to electrical circuits with much lower power consumption than transistor-based circuits.
- Researchers at Georgia Tech, the University of Tokyo and Microsoft Research have developed a method to print prototype circuit boards using standard inkjet printers. **Silver nanoparticle ink**was used to form the conductive lines needed in circuit boards.
- Researchers at Caltech have demonstrated a **laser that uses a nanopatterned silicon surface**that helps produce the light with much tighter frequency control than previously achieved. This may allow much higher data rates for information transmission over fiber optics.

- Building transistors from carbon nanotubes to enable minimum transistor dimensions of a few nanometers and developing techniques to manufacture integrated circuits built with nanotube transistors.
- Researchers at Stanford University have demonstrated a method to make functioning **integrated circuits using carbon nanotubes**. In order to make the circuit work they developed methods to remove metallic nanotubes, leaving only semiconducting nanotubes, as well as an algorithm to deal with misaligned nanotubes. The demonstration circuit they fabricated in the university labs contains 178 functioning transistors.
- Developing a lead free solder reliable enough for space missions and other high stress environments using **copper nanoparticles**.
- Using electrodes made from nanowires that would enable flat panel displays to be flexible as well as thinner than current flat panel displays.
- Using semiconductor nanowires to build transistors and integrated circuits.
- Transistors built in single atom thick graphene film to enable very high speed transistors.
- Researchers have developed an interesting method of forming PN junctions, a key component of transistors, in graphene. They patterned the p and n regions in the substrate. When the graphene film was applied to the substrate electrons were either added or taken from the graphene, depending upon the doping of the substrate. The researchers believe that this method reduces the disruption of the graphene lattice that can occur with other methods.
- Combining gold nanoparticles with organic molecules to create a transistor known as a NOMFET (Nanoparticle Organic Memory Field-Effect Transistor).
- Using carbon nanotubes to direct electrons to illuminate pixels, resulting in a lightweight, millimeter thick "nanoemmissive" display panel.
- Using quantum dots to replace the fluorescent dots used in current displays. **Displays using quantum dots** should be simpler to make than current displays as well as use less power.
- Making integrated circuits with features that can be measured in nanometers (nm), such as the process that allows the production of integrated circuits with **22 nm wide transistor gates**.
- Using nanosized magnetic rings to make Magnetoresistive Random Access Memory (MRAM)which research has indicated may allow memory density of 400 GB per square inch.
    - Researchers have developed lower power, higher density method using nanoscale magnets called magnetoelectric random access memory (MeRAM).
- Developing molecular-sized transistors which may allow us to shrink the width of transistor gates to approximately one nm which will significantly increase transistor density in integrated circuits.
- Using self-aligning nanostructures to manufacture nanoscale integrated circuits.

- Using nanowires to build transistors without p-n junctions.
- Using Buckyballs to build dense, low power memory devices.
- Using **magnetic quantum dots** in spintronic semiconductor devices. Spintronic devices are expected to be significantly higher density and lower power consumption because they measure the spin of electronics to determine a 1 or 0, rather than measuring groups of electronics as done in current semiconductor devices.
- Using nanowires made of an alloy of iron and nickel to create dense memory devices. By applying current magnetized sections along the length of the wire. As the magnetized sections move along the wire, the data is read by a stationary sensor. This method is called **race track memory.**
- Using silver nanowires embedded in a polymer to make conductive layers that can flex, without damaging the conductor.
- IMEC and Nantero are developing a **memory chip that uses carbon nanotubes**. This memory is labeled NRAM for Nanotube-Based Nonvolatile Random Access Memory and is intended to be used in place of high density Flash memory chips.
- Researcher have developed an organic **nanoglue** that forms a nanometer thick film between a computer chip and a heat sink. They report that using this nanoglue significantly increases the thermal conductance between the computer chip and the heat sink, which could help keep computer chips and other components cool.
- Researchers at Georgia Tech, the University of Tokyo and Microsoft Research have developed a method to print prototype circuit boards using standard inkjet printers. **Silver nanoparticle ink** was used to form the conductive lines needed in circuit boards.

# Chapter 6

- **Role of Nanotechnology in the Semiconductor Industry**
- **Ways Nanotechnology is Impacting the Semiconductors**

Ref: https://www.advancedmp.com/post/3-ways-nanotechnology-is-impacting-semiconductors

As devices shrink, pushing Moore’s Law to its limits, the semiconductor industry has to be creative with pushing the size envelope.

NANOTECHNOLOGY
Influencing Semicontuctors

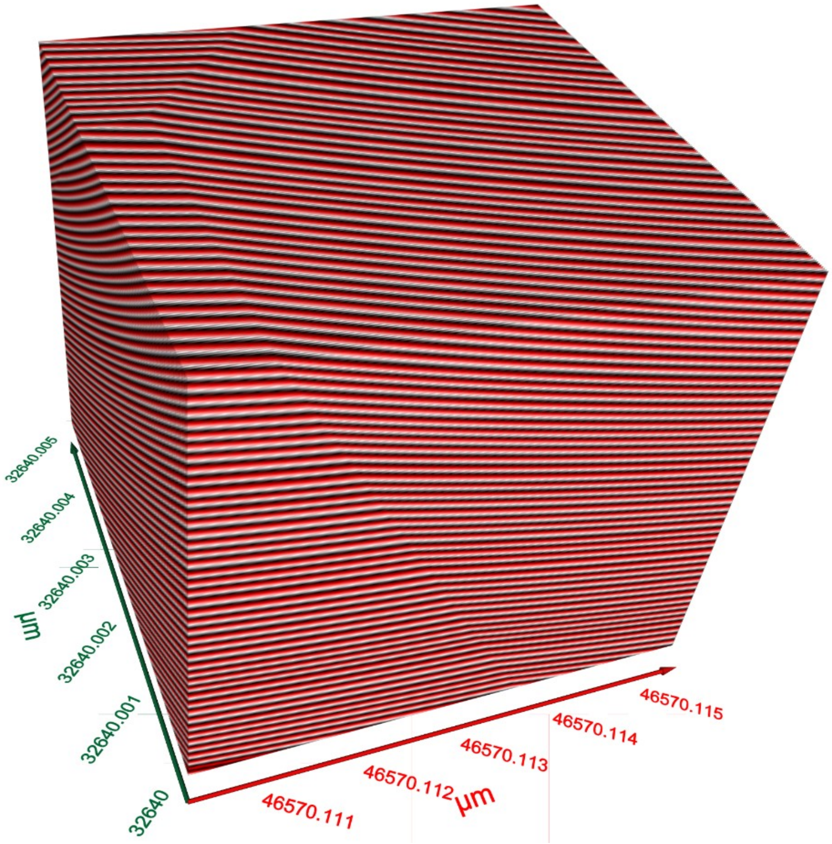

*Figure 6. Three-dimensional (5 nm x 5 nm x 5 nm) image of graphene-nanocellulose composite. Adapted from: Anis Rahman, Francis Tanzella, Aunik K Rahman, Carl Page and Robert Godes, “Lattice Dilation of Plasma Sprayed Nickel Film Quantified by High Resolution Terahertz Imaging,” (2019), Nov Res Sci. 2(4). NRS.000545.2019. DOI: 10.31031/NRS.2019.2.000545(Best paper award winner).*

# An introduction to the world of nanoscience and nanotechnology

It is crazy to think that we are now seeing feature sizes of some devices that are as small as a few atoms thick with line thickness of just one atom. There is a substantial increase in research development because manufacturing companies are continuously hitting brick walls to find solutions. Nanotechnology is taking over to be one of the most active and promising fields of technology. This technology can be applied to everything from clothing to golf balls, so of course billions of dollars are going into the research of semiconductor fabrication.

Intel defines nanotechnology as being "components below 100 nanometers." Microprocessor designer Nick Tredenick believes that nanotechnology has the potential to lead the semiconductor industry to long-term growth and eliminate the boom-and-bust cycles. Some nanotechnology developments we will likely see in the near future are:

- **CNTs** (Carbon Nanotubes): A tube-shaped material, made of carbon that is measured on the nanometer scale. They are ballistic conductors with quantum behavior and exhibit exceptionally low electrical resistance. One of the major causes of power consumption and propagation delay in semiconductor circuits is the RC time *(the time required to charge the capacitor through the resistor)* constant of interconnects; reducing R by a factor of 10 will confer significant benefits to conventional semiconductors.
- Nanotechnology may **replace gold plating** found on the connectors of virtually every plug-in card. Gold is an excellent conductor, but nanomaterials that are under development may mimic the electrical and mechanical properties of gold. This will allow for a stable and low price since nanomaterials are base metal alloys.
- **Germanium**: A method to make semiconducting nanoscale circuits from grapheme, a form of carbon only one atom thick. This was developed to revolutionize electronic circuitry by the research team from the University of Wisconsin (UW). "What we've discovered is that when graphene grows on germanium, it naturally forms nanoribbons with these very smooth, armchair edges," said Michael Arnold, an associate professor of materials science and engineering at UW-Madison. "The widths can be very, very narrow and the lengths of the ribbons can be very long, so all the desirable features we want in graphene nanoribbons are happening automatically with this technique."

Although there are few examples of commercialized semiconductor nanotechnology, there is no doubt that it offers the prospect of significant innovation by providing materials with properties outside of the current domain.

As a leading global independent electronic component distributor, Advanced MP Technology keeps close look at the latest and greatest updates in the technology field to adopt our resources and capabilities to support the most up-to-date applications and products, providing the highest level of service to our customers.

## The Role of Nanotechnology in Semiconductor Industry

Ref. Tamirat Y, Journal of Materials Science & Nanotechnology, Vol. 5, Issue 2, September 05, 2017. ISSN: 2348-9812. Review Article. J Mater Sci Nanotechnol 5(2): 202

Nanotechnology is a field of science and technology of controlling matter on a nanoscale. It is a highly multidisciplinary field, including electrical and mechanical engineering, physics, chemistry, and biosciences. Nanotechnology will radically affect all these disciplines and their application areas. It is commonly attributed for the technologies leading to produce materials at the nano-scale. To create nano-structured materials there are two commonly routine techniques can be used, top-down technique and bottom-up technique; their main difference is based on the size of primary entities applied to build nano components with or without atomic level control. In the bottom-up technique, one builds features on a wafer on a layer-by-layer sequence. One of the main applications of nanotechnology and therefore a driving force for nanoscience is the electronics industry. Over the past few decades, the transistor has been continually miniaturized. Modern integrated circuits incorporate transistors with feature as small as 22 nm. Nanotechnology broadly includes all technologies that handle nano - scale materials, and in a narrow sense, technologies that handle unique phenomena that arise in the 10 nm to 100 nm size range. Materials of these sizes have been prepared using two techniques, the top-down and the bottom-up methods.

### 1.12.1. Top-Down Approach

This approach, which leads physicists and engineers to manipulate progressively smaller pieces of matter by photolithography, Electron-beam lithography, X-ray lithography and related techniques, has operated in an outstanding way up until now. It is becoming increasingly apparent, for example, that miniaturization in computer technology, which relies on silicon-based chips, is rapidly approaching the upper limits of its capabilities. But it is very large on the scale of atoms and molecules. Therefore, “there is plenty of room at the bottom” for further miniaturization.

### 1.12.1. Bottom-Up Approach

An alternative and most promising strategy to exploit science and technology at the nanometer scale is offered by the bottom-up approach, which starts from nano- or sub-nano- scale objects (namely, atoms or molecules) to build up nanostructures. The bottom-up approach is largely in the realm of nanoscience and nanotechnology. This is the reason why chemists, being able to manipulate atoms and molecules, are in the ideal position to contribute to the development of nanoscience and nanotechnology.

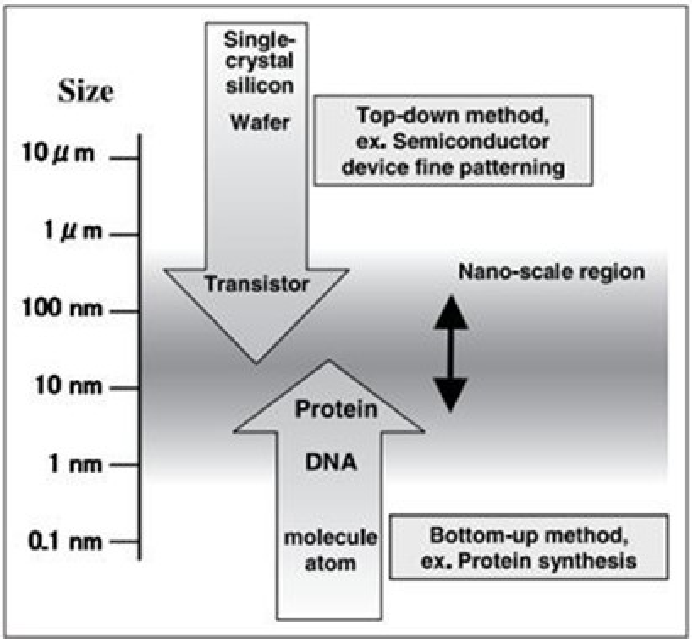

*Figure 7. Two methods of approach to nano-scale [5].*

The top-down method is applied to process just as in the semiconductor process, whereas the bottom-up method is applied to integrate molecules or atoms into nano-scale materials just as a living organism synthesizes DNA and proteins, and integrates them into a cell, and further, into a pattern (or structure).

The ability to fabricate structures with nanometric precision is of fundamental importance to any exploitation of nanotechnology. The great promise of nanotechnology is the ability to do more in the same space: to advance our current technologies through miniaturization, so that each crop of electronics is smaller, faster, and more powerful than the one before. Due to their small dimensions, nanomaterials have extremely large surface area to volume ratio, which makes a large number of surface or interfacial atoms, resulting in more "surface" dependent material properties. Nanomaterials can be classified depending on the dimensions such as (a) 0D spheres and clusters, (b) 1D nanofibers, nanowires, and nanorods, (c) 2D films, plates, and networks, (d) 3D nanomaterials as shown in Figure 7.

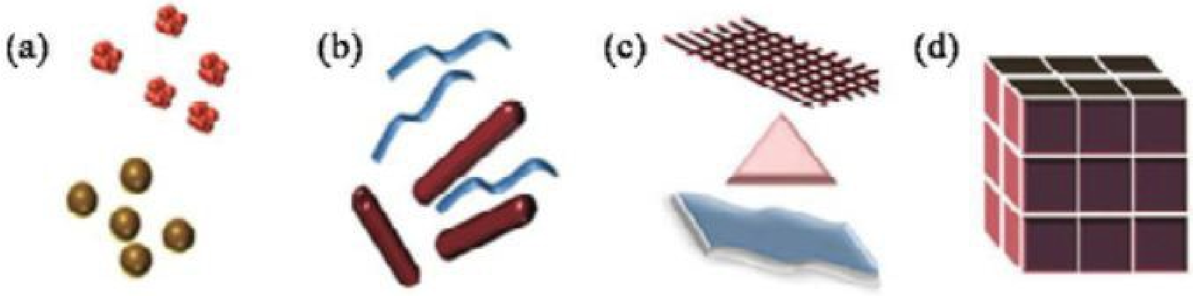

*Figure 8. Classification of Nanomaterials (a) 0D spheres and clusters, (b) 1D nanofibers, wires, and rods, (c) 2D films, plates, and networks, (d) 3D nanomaterials.*

Especially, when the sizes of nanomaterials are comparable to length, the entire material will be affected by the surface properties of nanomaterials. This in turn, may enhance or modify the properties of the bulk materials. For example, metallic nanoparticles can be used as very active catalysts. Chemical sensors from nanoparticles and nanowires enhance the sensitivity and sensor selectivity. The nanometer feature sizes of nanomaterials also have spatial confinement effect on the materials, which bring the quantum effects. The energy band structure and charge carrier density in the materials can be modified quite differently from their bulk and in turn will modify the electronic and optical properties of the materials.

Reduced imperfections are also an important factor in the determination of the properties of the nanomaterials. For example, the chemical stability for certain nanomaterials may be enhanced and the mechanical properties of nanomaterials will be better than the bulk materials. Nanomaterials have applications in the field of nanotechnology and displays different physical chemical characteristics from normal chemicals (i.e., silver nano, carbon nanotube, fullerene, photocatalyst, carbon nano).

Carbon nanotube becomes one of the most promising materials in recently developed materials on account of its superior properties of rigidity, strength, elasticity, electric conductivity, and field emission. The applications of nanotube-integrated devices include single-electron transistors, molecular diodes, memory elements and logic gates. There is great deal of interest in devising strategies to address each molecular unit individually and to interconnect them without affecting their local electronic structure adversely and also Silver nanoparticles are of interest because of the unique properties (e.g., size and shape depending optical, electrical, and magnetic properties) which can be incorporated into antimicrobial applications, biosensor materials, composite fibers, cryogenic superconducting materials, cosmetic products, and electronic components. Several physical and chemical methods have been used for synthesizing and stabilizing silver nanoparticles.

- ## Semiconductor Quantum Dot

Quantum dots are nanostructures in which electrons and/or holes are confined to a small region [26]. Quantum dots (QDs) as colloidal nanocrystalline semiconductors have unique photophysical properties due to quantum confinement effects. They emit different wavelengths over a broad range of the light spectrum from visible to infrared, depending on their sizes and chemical compositions. Compared with the traditional organic fluorophores (e.g., organic dyes and fluorescent proteins), QDs have unique optical and electronic properties, such as larger absorption coefficients, size-tunable light emission, superior signal brightness, resistance to photobleaching and simultaneous excitation of multiple fluorescence colors [27-29].

The applications of quantum dots are still mostly confined to research laboratories, but they are remarkable and often rely on the fact that quantum dots give acces to the quantum mechanical degrees of freedom of only a few carriers. Single electron transistors, the manipulation of one, or two electron spins are only some examples [30,31]. Other applications of quantum dots are related to optics: some quantum dots can confine both electrons and holes in the same region, making it possible to perform, in a solid state system, similar experiments as in atoms [32,33]. In particular, quantum dots where successfully used to produce single photons, photon pairs in an entangled polarization state and indistinguishable photons [34-36]. The combination of two or more nanostructure architectures provides another option to modulate the performance of light-harvesting devices [37,38]. The electron transport across particles is susceptible to recombination loss at the grain boundaries and charge trapping in nanostructured semiconductor films prepared from particles. The use of nanotube/nanowire support to anchor light-harvesting assemblies (e.g., semiconductor particles and dye molecules) provides a convenient way to capture photogenerated charges and transport them to electrodes. Quantum-dot-sensitized solar cells (QDSSCs) provide additional opportunities that are not available with dyesensitized solar cells (Figure 3) [39]. First, the use of quantum dots in lieu of the dye molecules provides the ability to tune the optical absorption in the solar cell through selection of semiconductor material and particle size. Second, QDSSCs can potentially exploit the recently observed multiple electron-hole pair generation per photon to achieve higher efficiencies than that predicted by Shockley and Queisser [40-43].

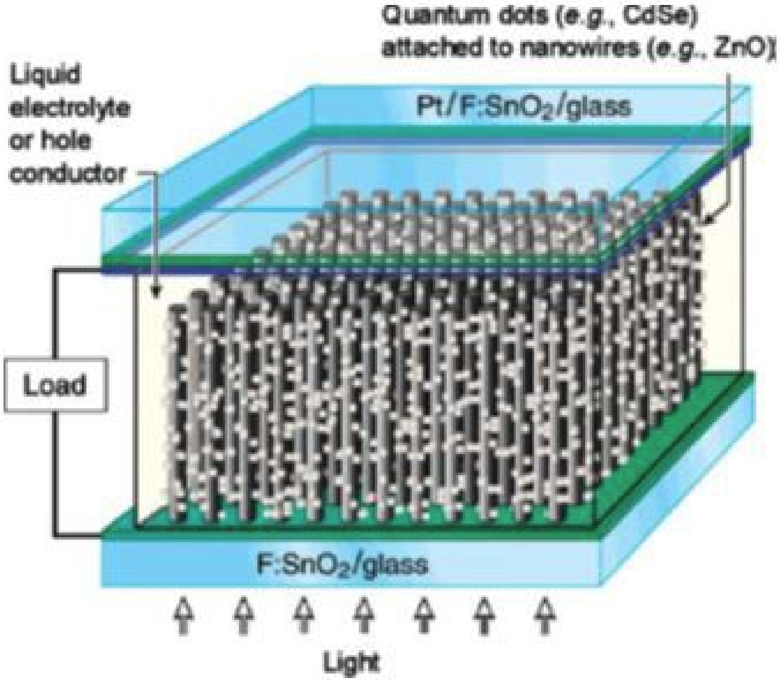

*Figure 9. Schematic diagram of a quantum-dot-sensitized solar cell (QDSSC). An array of ZnO nanowires, grown vertically from an FTO/glass substrate and decorated with CdSe quantum dots, serves as the photoanode. A second FTO/glass substrate, coated with a 100 Å layer of Pt, is the photocathode. The space between the two electrodes is filled with a liquid electrolyte and the cell is illuminated from the bottom [39,43].*

Quantum dot sensitized solar cells (QDSSCs) make use of a metal oxide electron accepting species such as TiO2. In the assembly of these devices, a layer of TiO2 is applied to a conductive material and then quantum dots are deposited. A variety of deposition methods are common, such as colloidal deposition, chemical bath deposition, SILAR (successive ionic layer adsorption and reaction), and electrodeposition [44-51]. This part of the setup constitutes the QDSSCs working electrode, which is connected via an external circuit to a counter electrode. The working electrode (also called the photoanode) and counter electrode can be brought close to one another with an electrolyte sandwiched in between them in the construction of an aptly named sandwich cell. The electrolyte serves to replenish the charge carriers as they are drawn off to produce a current. The overview for QDSSC is shown in Figure 10 [52].

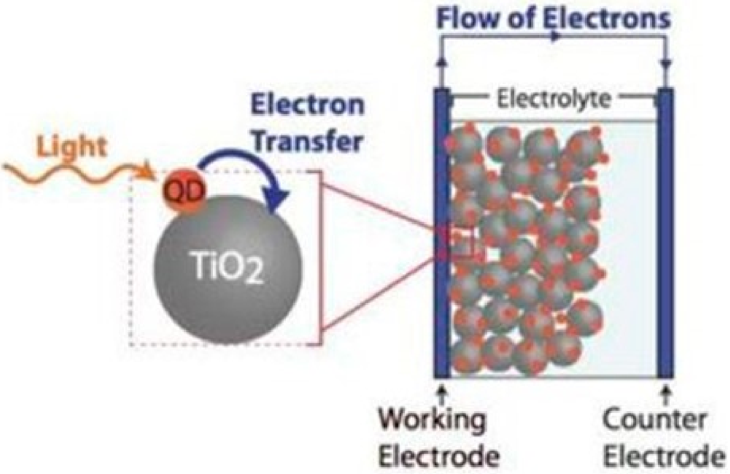

*Figure 10. Typical Schematic of a QDSSC. Light interacts with the QD, which causes electrons to be injected into TiO2 and drawn off an external circuit to generate electricity. The electrolyte then replenishes the charge carriers [52].*

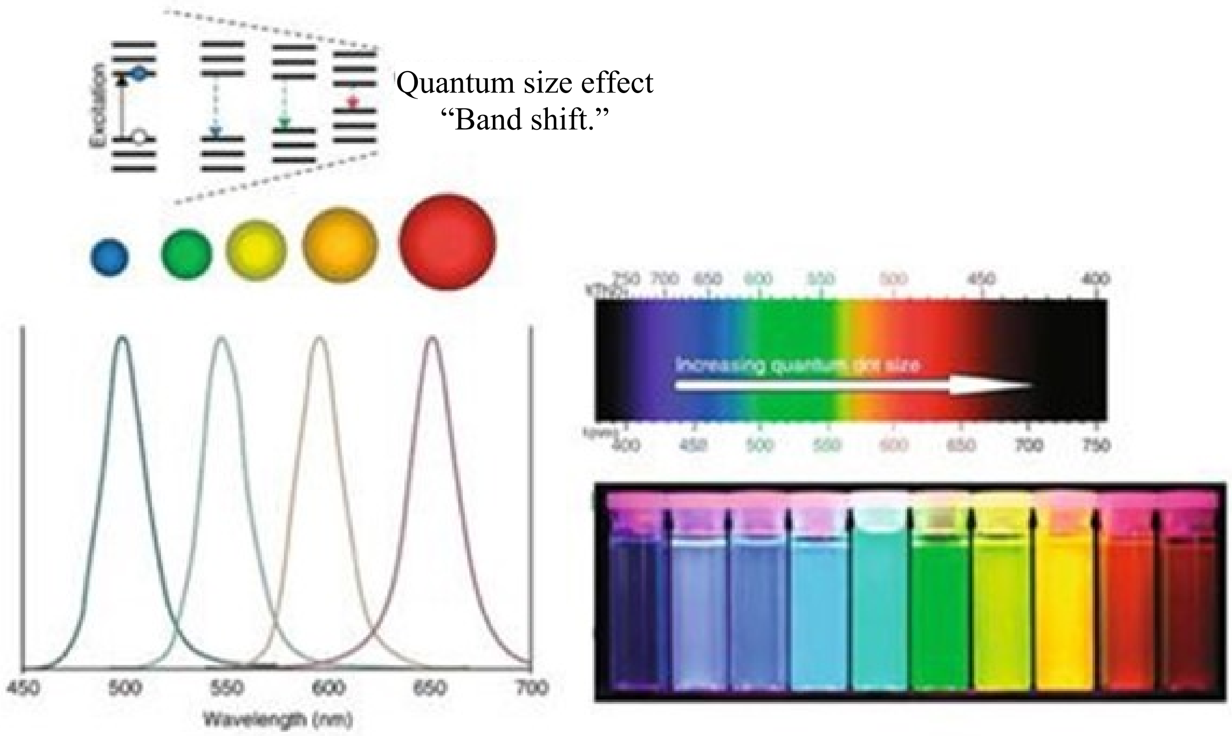

*Figure 11. Schematic drawing representing the changes on optical behavior of nanoparticles associated with their size. Top: Electronic structure of QDs with “blue shift” due to quantum confinement [53,54].*

In a bulk semiconductor, electrons can freely move within an area from a few nanometers to a few hundred of nanometers as defined by the Bohr radius. Thus, continuous conduction and valence energy bands exist which are separated by an energy gap. Contrary, in a quantum dot, where excitons cannot move freely, discrete atomic like states with energies that are determined by the quantum dot radius appear.

The effect of quantum confinement has a great technological interest from semiconductors and optoelectronics to biological applications. As depicted in Figure 11, by changing the particle size the emitting color of quantum dots can be tuned. Shorter quantum dots emit shorter wavelength of light and bigger quantum dots emits longer wavelengths of light. The energy band gap Eg is correlated with size: as the dimension of particles decreases, the energy increases [54].

## • Semiconductor Nanowire

Semiconductor nanowires (NWs) represent a unique system for exploring phenomena at the nanoscale and are also expected to play a critical role in future electronic and optoelectronic devices [55]. Over the past two decades, research in the field of semiconductor nanowires (NWs) has helped to reshape our understanding of atomic-scale crystal assembly and uncover novel physical phenomena at the nanometer scale. Compound semiconductor NWs have also been established as central components in next-generation electronic and photonic devices. This is particularly beneficial for efficient collection of photo generated carriers when core and shell segments are engineered to be thinner than minority carrier diffusion lengths. Finally, NWs are more conducive to heterogeneous integration solutions, owing to the nature of the NW geometry to accommodate hetero-epitaxially induced strain by relaxation along the NW free surface. This advantage effectively increases the critical thickness of lattice mismatched NW crystals in comparison to epi-layers having a purely planar geometry. Therefore, NW array-based architectures are attractive for multi-junction PVs, insofar as high-efficiency devices relying on the monolithic integration of III-V materials with Si technology have been envisioned [3]. Semiconductor nanowires serve as one of the most powerful platforms available today in nanoscience given that it is now possible to design structures ab-initio and synthetically realize these structures with the structure and composition controlled from the atomic scale and up. These capabilities to design and synthetically realize complex nanowire materials are unique among nanomaterials and enable systems or building blocks to be created that have predictable physical properties [56].

## • Semiconductor Nanowires with Novel Structure

Semiconductor nanowires have remarkable potential for novel nanostructures and optoelectronic devices, such as heterojunctions, crystal phase quantum dots, solar cells, LED and quantum devices [57]. Graphene 2D and 1D integrated semiconductor nanostructures are exploited as a new class of nano hybrid systems that possess outstanding electronic and optoelectronic properties. In particular, fabrication of highly orientated 1D semiconductor nanowires (NWs)/nanorods (NRs) on graphene substrates can exhibit unique characteristics. The presence of graphene layer over selective substrates may support the nucleation of NWs/NRs in preferred orientations. The extraordinary properties of graphene, such as one atom thick sp2 hybridized carbon, high carrier mobility, excellent optical transparency (97.7%) over the visible region, flexibility and high thermal conductivity allow it to integrate it with semiconducting NWs, NRs and nanoribbons (NRbs) that may exhibit exceptional properties [58-64].

- ## Nanowires with High-Quality Hetero-Junctions

The bottom-up nanowire growth mechanism allows forming hetero-junctions with high interface quality and provides a larger freedom in combining different semiconductor materials compared to the bulk. Lattice matching is a basic requirement to form a hetero junction without creating misfit dislocations at the interface. Because of this reason, it is quite challenging to grow heterojunctions without misfit dislocations in conventional thin film technology. However, in a nanowire, the stress at the interface between two different semiconductors is significantly smaller than that in a thin film. The reason is that a nanowire has a small footprint (usually less than 200 nm) allowing elastic radial compression or expansion. This means that it is possible to stack different bandgap semiconductors with much larger lattice mismatch without creating any misfit dislocations by using nanowires. For example, a InSb/GaAs hetero-structure has been demonstrated in nanowires with an extremely large lattice mismatch of 14.6% between InSb and GaAs. In addition, a large variety of III-V materials have been axially integrated in bottom-up nanowires. This is an important advancement for material growth technology, because it may solve some long-standing technical problems that have plagued the thin film community for a long time. For instance, one of the key goals in microelectronics is to integrate optoelectronics devices made from III-V materials into traditional Si based electronic devices. In nanowire technology, this can be achieved directly by III-V nanowire growth on Si. Figure 12, a, b and c show an example, where GaP and Si are epitaxially grown on top of each other within a single nanowire. Moreover, GaP can be vertically and epitaxially grown on a cheap substrate, e.g., Si, as shown in Figure 12, d, e and f [57].

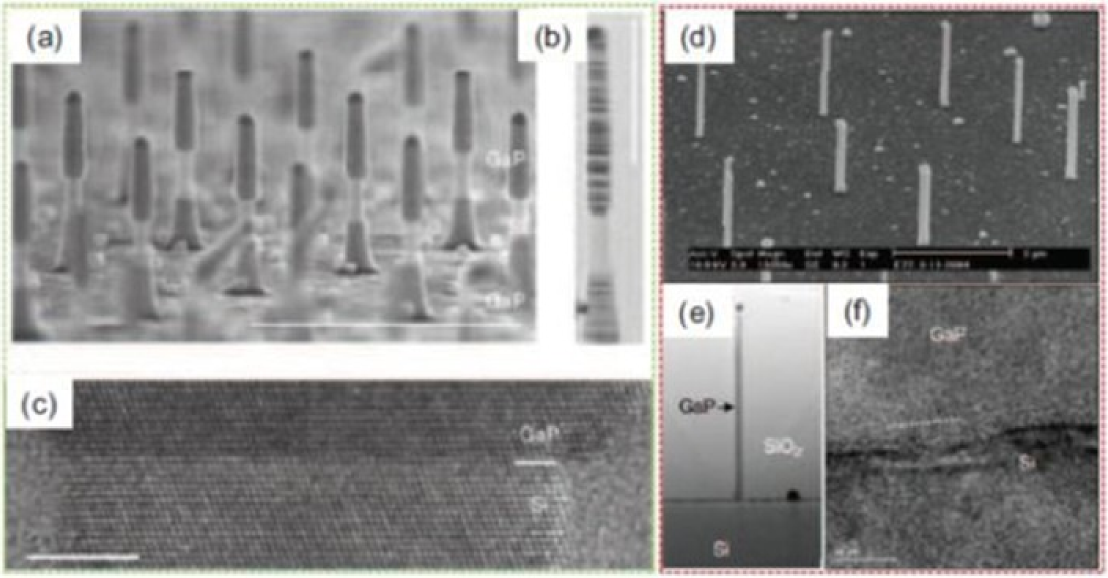

*Figure 12. 6: (a) SEM image of an array of 60 nm diameter GaP-Si-GaP nanowires with GaP, Si, and GaP segment lengths of 180, 150 and 270 nm, respectively. The sample is tilted by 80°, the scale bar is 1µm. (b) TEM image of a single GaP-Si-GaP nanowire with a diameter of 28 nm, scale bar is 200 nm. (c) High-resolution TEM picture of a Si-GaP transition, scale bar is 5 nm. (a)-(c). (d) A GaP nanowire array grown epitaxially on Si (111) by laser ablation. (e) Cross-sectional TEM image of a single GaP wire on Si and (f) a high-resolution TEM image of the GaP-Si interface, showing an epitaxy growth with a rotational twin dislocation at the interface [57]*

## Technologies Based on Solar Energy

Technologies and resources of solar energy refer to sources of energy that can be directly attributed to the light of the sun or the heat generated from the sun. In contrast, active solar energy technology refers to the harnessing of solar energy to store it or convert it for other applications and can be broadly classified into two groups: (i) Photovoltaic and (ii) solar thermal. The PV technology converts radiant energy contained in light quanta into electrical energy when light falls upon a semiconductor material by causing electron excitation and strongly enhancing conductivity. Two types of PV technology are currently available in the market: (a) crystalline silicon-based PV cells and (b) thin film technologies made from a range of different semiconducting materials, including amorphous silicon, cadmium-telluride and copper indium gallium diseline. Solar thermal technology uses solar heat, which can be used directly for either thermal or heating application or electricity generation. Accordingly, it can be divided into two categories: (i) solar thermal nonelectric and (ii) solar thermal electric. The former includes applications such as agricultural drying, solar water heaters, solar air heaters, solar cooling systems and solar cookers and the latter refers to the use of solar heat to produce steam for electricity generation, also known as concentrated solar power (CSP) [65-67]. Recent efforts to synthesize nanostructures with well-defined geometrical shapes (e.g., solid and hollow spheres, prisms, rods, tubes, and wires) and organize them as 2- and 3-dimensional assemblies have further expanded the possibility of developing new strategies for light energy conversion. Quantum dot based solar cells have drawn a lot of attention during past few years because of the possibility of boosting the energy conversion efficiency beyond the traditional Shockley and Queisser limit of 32% for Si based solar cells [68].

Three different types of solar cells that capitalize salient properties of semiconductor nanocrystals have emerged:

(i) metal-semiconductor or Schottky junction photovoltaic cell, (ii) semiconductor nanostructure-polymer solar cell, and (iii) semiconductor sensitized quantum dot solar cell (Figure 13). Specific advantages to using semiconductor quantum dots as light harvesting assemblies in solar cells exist. First and foremost, their size quantization property allows one to tune the visible response and vary the band offsets to modulate the vectorial charge transfer across different sized particles. In addition, these quantum dots open up new ways to utilize hot electrons or generate multiple charge carriers with a single photon. Multiple carrier generation in PbSe nanocrystals has shown that two or more excitons can be generated with a single photon of energy greater than the bandgap [68-75].

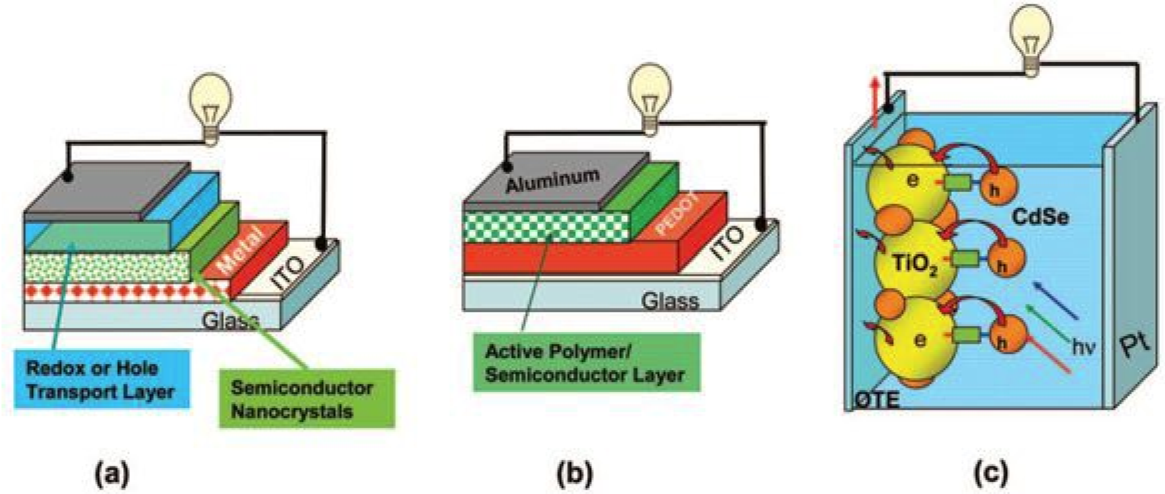

*Figure 13. Schematic diagram showing the strategies to develop quantum dot (semiconductor nanocrystal) based solar cells: (a) metal-semiconductor junction, (b) polymer-semiconductor, and (c) semiconductor-semiconductor systems*

## Thin Film Application

Thin film is a more cost-effective solution and uses a cheap support onto which the active component is applied as a thin coating. As a result, much less material is required (as low as 1% compared with wafers) and costs are decreased. Most such cells utilize amorphous silicon, which, as its name suggests, does not have a crystalline structure and consequently has a much lower efficiency (8%), however it is much cheaper to manufacture [76-78] (Figure 14).

*Figure 14. Picture of a solar cell, which utilizes nanorods to convert light into electricity [78,79]*

To coat the nanoparticles with quantum dots tiny semiconductor crystals. Unlike conventional materials in which one photon generates just one electron, quantum dots have the potential to convert high-energy photons into multiple electrons. Quantum dots work the same way, but they produce three electrons for every photon of sunlight that hits the dots. Electrons moves from the valance band into the conduction band. The dots also catch more spectrums of the sunlight waves, thus increasing conversion efficiency to as high as 65 percent. Another area in which quantum dots could be used is by making so-called a hot carrier cells. Typically, the extra energy supplied by a photon is lost as heat, but with a hot carrier cells the extra energy from the photons result in higher-energy electrons which in turn leads to a higher voltage [78,80,81].

Polycrystalline thin-film solar cells such as CuInSe2 (CIS), Cu (In, Ga) Se2 (CIGS), and CdTe compound semiconductors are important for terrestrial solar applications because of their high efficiency, long term stable performance and potential for low-cost production. Because of the high absorption coefficient ($\sim 10^5\ cm^{-1}$), a thin layer of ~2 mm is sufficient to absorb the useful part of the spectrum [67].

## • Photovoltaic Application

The past decade has witnessed a strong increase in the demand of clean electricity production based on renewable energy sources and an associated exponential growth of installed photovoltaic (PV) power capacity. The largest share of the actual PV electricity supply is still based on crystalline silicon wafer solar cells (SC) [82]. For photo-functional materials, nanoscale architectures usually exhibit unique optical and electronic properties. More importantly, the ability to control size and shape provides enhanced optoelectronic properties due to size- and shape-dependent effects and collective behaviors from the assembled building blocks. So far, numerous inorganic- and organic-based nanostructures have emerged as new building blocks to construct photocatalysis systems. However, compared to inorganic nanostructures, the organic counterparts have received special attention attributed to their considerable flexibility in molecular design, excellent tunability of the optoelectronic properties and their nice solution processability. Accordingly, the investigation of the fabrication of organic nanostructures is of great importance for photocatalytic applications [83]. One issue of particular interest is solar energy conversion using nanostructured photovoltaic devices, which can convert absorbed light into electrical energy. The use of nanowires as photovoltaic elements presents several key advantages. First, the principle of bottom-up design allows the rational control of key nanomaterial parameters, which will determine photovoltaic performance, including chemical/dopant composition, size, and morphology. Second, single or interconnected nanowire elements can be integrated with conventional electronics and/or nanoscale electronics to provide energy for low power applications. Third, single nanowire level will permit determination of the intrinsic limits, areas of improvement, potential benefits, and potentially new concepts for such nano-enabled energy conversion devices. Two unique structural motifs that can yield functional photovoltaic devices at the single nanowire level are shown schematically in Figure 15 [84-87].

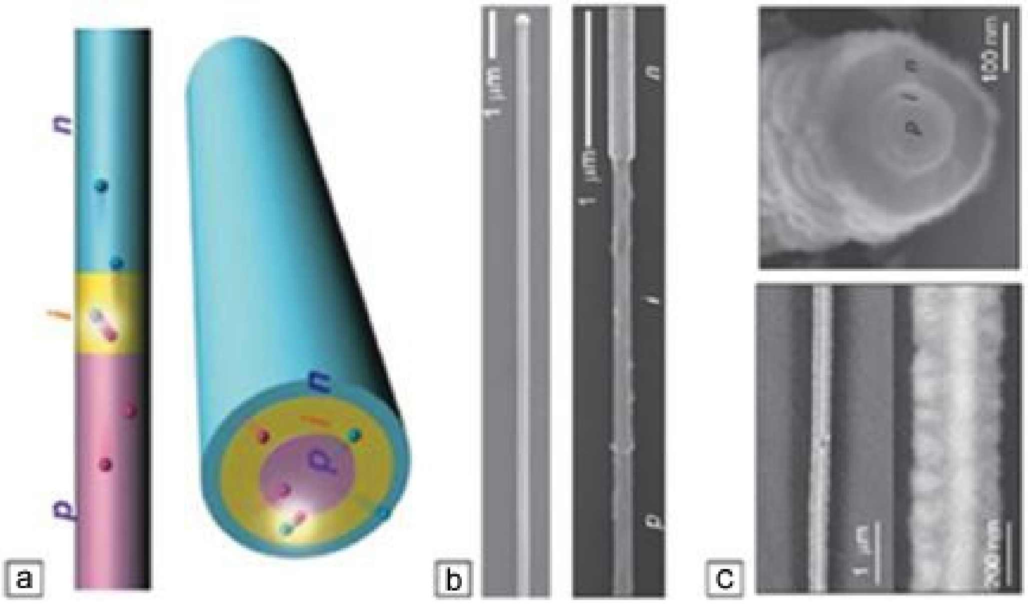

*Figure 15. (a) Schematics of two distinct motifs for nanowire photovoltaics where the single p - type/intrinsic/ n -type (p-i-n) diodes are synthetically integrated in (top) axial and (bottom) core/shell structures. (b) Scanning electron microscopy (SEM) images of p-i-n silicon nanowires. (top) As-grown nanowire with nanocluster catalyst on right tip of nanowire. (bottom) Dopant selective etched nanowire highlighting the distinct p-, i-, and n- type regions with lengths consistent with growth times. (c) SEM images of a p-i-n coaxial silicon nanowire at different magnifications. Images were recorded with the electron beam (left) perpendicular to the nanowire axis and (right) nearly end on.*

- ## PV Based on Bulk Semiconductors

PV solar cells operate by absorbing photons from incident solar radiation that have energies above the semiconductor band gap and thus create negative electrons and positive holes. Bulk inorganic semiconductors have relatively high dielectric constants, and at room temperature these photogenerated electronic particles are uncorrelated and move freely in the conduction and valence bands of the semiconductor; they are thus called free (charge) carriers. In organic semiconductors the dielectric constant is low and the photogenerated carriers are correlated and form bound electron-hole pairs that are called excitons. In the former case an internal electric field is required to efficiently separate the free electrons and holes so that they can be collected at oppositely charged electrodes and utilized in a PV cell. This electric field is most commonly produced by a p-n junction in the device; however, Schottky junctions between a semiconductor and metal or liquid contacts with appropriate work function differences relative to the semiconductor material can also be used [88].

## • Conclusion

Nanotechnology is like a toolkit for the electronics industry. It gives us tools that allow us to make nanomaterials with special properties modified by ultra-fine particle size, crystallinity, structure or surfaces [89]. So that semiconductor is one of the materials which can be produced or fabricated by nano technology with top down or bottom up approach. Currently nano technology-based semiconductor materials are becoming the basic for our modern life style due to the production of materials with extremely large surface area to volume ratio, which indicates that the electronics device we are using is small and more efficient than that we used before. Nowadays, semiconductor industry is becoming a key tool for energy harvesting with increasing its efficiency as well. One of the most important area that we used semiconductor is for solar energy harvesting, so that solar cell or photovoltaic materials are the one which is produced by nano technology with increasing its efficiency of photon trapping and converting to electric energy by making the material quantum dot, quantum wire and quantum well.

# 6.12. References

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# Chapter 7

## 7. Nanotechnology and Energy

Weary of high utility bills and gas pump sticker shock? You'll be glad to hear that nanotechnology is being used in several applications to improve the efficiency of energy generation or develop new methods to generate energy.

### 7.1. The Application of Nanotechnology to Energy Production

Here are some interesting ways that are being explored using nanotechnology to produce more efficient and cost-effective energy:

**Generating steam from sunlight.** Researchers have demonstrated that sunlight, concentrated on nanoparticles, can produce steam with high energy efficiency. The "**solar steam device**" is intended to be used in areas of developing countries without electricity for applications such as purifying water or disinfecting dental instruments. Another research group is developing nanoparticles intended to use **sunlight to generate steam for use in running powerplants**.

Producing high efficiency light bulbs. A nano-engineered polymer matrix is used in one style of high efficiency light bulbs. The new bulbs have the advantage of being shatterproof and twice the efficiency of compact fluorescence light bulbs. Other researchers developing high efficiency LED's using arrays of nano-sized structures called plasmonic cavities. Another idea under development is to update incandescent light bulbs by surrounding the conventional filament with crystalline material that converts some of the waste infrared radiation into visible light.

Increasing the electricity generated by windmills. An epoxy containing carbon nanotubes is being used to make windmill blades. Stronger and lower weight blades are made possible by the use of nanotube-filled epoxy. The resulting longer blades increase the amount of electricity generated by each windmill.

**Generating electricity from waste heat.** Researchers have used sheets of nanotubes to build thermocells that generate electricity when the sides of the cell are at different temperatures. These **nanotube sheets** could be wrapped around hot pipes, such as the exhaust pipe of your car, to generate electricity from heat that is usually wasted.

Storing hydrogen for fuel cell powered cars. Researchers have prepared graphene layers to increase the binding energy of hydrogen to the graphene surface in a fuel tank, resulting in a higher amount of hydrogen storage and therefore a lighter weight fuel tank. Other researchers have demonstrated that sodium borohydride nanoparticles can effectively store hydrogen.

Clothing that generates electricity. Researchers have developed piezoelectric nanofibers that are flexible enough to be woven into clothing. The fibers can turn normal motion into electricity to power your cell phone and other mobile electronic devices.

Reducing friction to reduce the energy consumption. Researchers have developed lubricants using inorganic Buckyballs that significantly reduced friction.

Reducing power loss in electric transmission wires. Researchers at Rice University are developing wires containing carbon nanotubes that would have significantly lower resistance than the wires currently used in the electric transmission grid. Richard Smalley envisioned the use of nanotechnology to radically change the electricity distribution grid. Smalley's concept these upgraded transmission wires, which could transmit electricity thousands of miles with insignificant power losses, with local electricity storage capacity in the form of batteries in each building that could store power for 24 hours use.

**Reducing the cost of solar cells.** Companies have developed nanotech solar cells that can be manufactured at significantly lower cost than conventional solar cells. Check out **Nanotechnology in Solar Cells** page for the details.

**Improving the performance of batteries.** Companies are currently developing batteries using nanomaterials. One such battery will be as good as new after sitting on the shelf for decades. Another battery can be recharged significantly faster than conventional batteries. Check out **Nanotechnology in Batteries** page for details.

**Improving the efficiency and reducing the cost of fuel cells.** Nanotechnology is being used to reduce the cost of catalysts used in fuel cells. These catalysts produce hydrogen ions from fuel such as methanol. Nanotechnology is also being used to improve the efficiency of membranes used in fuel cells to separate hydrogen ions from other gases, such as oxygen. Check out **Nanotechnology in Fuel Cells** page for the details.

**Making the production of fuels from raw materials more efficient.** Nanotechnology can address the shortage of fossil fuels, such as diesel and gasoline, by making the production of fuels from low grade raw materials economical. Nanotechnology can also be used to increase the mileage of engines and make the production of fuels from normal raw materials more efficient. Check out **Nanotechnology in Fuels** page for details.

Compiled by Earl Boysen of Hawk's Perch Technical Writing, LLC and UnderstandingNano.com. You can find him on **Google+**.

## 7.2. Nanotechnology in Energy

Nanotechnologies provide the potential to enhance energy efficiency across all branches of industry and to economically leverage renewable energy production through new technological solutions and optimized production technologies. Nanotechnology innovations could impact each part of the value-added chain in the energy sector. Read more: Nanotechnology in Energy

Let's look at these five areas of the energy value chain in detail (Ref. "Application of Nanotechnologies in the Energy Sector" (pdf))

Energy sources | Energy change | Energy distribution | Energy storage | Energy usage

**Regenerative**

**Photovoltaics:** Nano-optimized cells (polymeric, dye, quantum dot, thin film, multiple junction), antireflective coatings

**Wind Energy:** Nano-composites for lighter and stronger rotor blades, wear and corrosion protection nano-coatings for bearings and power trains etc.

**Geothermal:** Nano-coatings and -composites for wear resistant drilling equipment

**Hydro-/Tidal Power:** Nano-coatings for corrosion protection

**Biomass Energy:** Yield optimization by nano-based precision farming (nanosensors, controlled release and storage of pesticides and nutrients)

**Fossil Fuels**

Wear and corrosion protection of oil and gas drilling equipment, nanoparticles for improved oil yields

**Nuclear**

Nano-composites for radiation shielding and protection (personal equipment, container etc.), long term option for nuclear fusion reactors

**Gas Turbines**

Heat and corrosion protection of turbine blades (e.g. ceramic or intermetallic nano-coatings) for more efficient turbine power plants

**Thermoelectrics**

Nanostructured compounds (interface design, nanorods) for efficient thermoelectrical power generation (e.g. usage of waste heat in automobiles or body heat for personal electronics (long term))

**Fuel Cells**

Nano-optimized membranes and electrodes for efficient fuel cells (PEM) for applications in automobiles/mobile electronics

**Hydrogen Generation**

Nano-catalysts and new processes for more efficient hydrogen generation (e.g. photoelectrical, elektrolysis, biophotonic)

**Combustion Engines**

Wear and corrosion protection of engine components (nano-composites/-coatings, nanoparticles as fuel additive etc.)

**Electrical Motors**

Nano-composites for superconducting components in electro motors (e.g. in ship engines)

**Power Transmission**

**High-Voltage Transmission:** Nanofillers for electrical isolation systems, soft magnetic nano-materials for efficient current transformation

**Super Conductors:** Optimized high temperature SC's based on nanoscale interface design for loss-less power transmission

**CNT Power Lines:** Super conducting cables based on carbon nanotubes (long term)

**Wireless Power Transmission:** Power transmission by laser, microwaves or electromagnetic resonance based on nano-optimized components (long term)

**Smart Grids**

Nanosensors (e.g. magneto-resistive) for intelligent and flexible grid management capable of managing highly decentralised power feeds

**Heat Transfer**

Efficient heat in- and outflow based on nano-optimized heat exchangers and conductors (e.g. based on CNT-composites) in industries and buildings

**Electrical Energy**

**Batteries:** Optimized Li-ion-batteries by nanostructured electrodes and flexible, ceramic separator-foils, application in mobile electronics, automobile, flexible load management in power grids (mid term)

**Supercapacitors:** Nanomaterials for electrodes (carbon-aerogels, CNT, metall(-oxides) and elektrolytes for higher energy densities)

**Chemical Energy**

**Hydrogen:** Nanoporous materials (organometals, metal hydrides) for application in micro fuel cells for mobile electronics or in automobiles (long term)

**Fuel Reforming/Refining:** Nano-catalysts for optimized fuel production (oil refining, desulphurization, coal liquefaction

**Fuel Tanks:** Gas tight fuel tanks based on nano-composites for reduction of hydrocarbon emissions

**Thermal Energy**

**Phase Change Materials:** Encapsulated PCM for air conditioning of buildings

**Adsorptive Storage:** Nano-porous materials (e.g. zeolites) for reversible heat storage in buildings and heating nets

**Thermal Insulation**

Nanoporous foams and gels (aerogels, polymer foams) for thermal insulation of buildings or in industrial processes

**Air Conditioning**

Intelligent management of light and heat flux in buildings by electrochromic windows, micro mirror arrays or IR-reflectors

**Lightweight Construction**

Lightweight construction materials using nano-composites (carbon nanotubes, metal-matrix-composites, nano-coated light metals, ultra performance concrete, polymer-composites)

**Industrial Processes**

Substitution of energy intensive processes based on nanotech process innovations (e.g. nano-catalysts, self-assembling processes etc.)

**Lighting**

Energy efficient lighting systems (e.g. LED, OLED)

*Figure 16. Examples for potential applications of nanotechnology along the value-added chain in the energy sector. Ref: http://www.nanowerk.com/nanotechnology-in-energy.php*

## 7.3. Energy sources

Nanotechnologies provide essential improvement potentials for the development of both conventional energy sources (fossil and nuclear fuels) and renewable energy sources like geothermal energy, sun, wind, water, tides or biomass. Nano-coated, wear resistant drill probes, for example, allow the optimization of lifespan and efficiency of systems for the development of oil and natural gas deposits or geothermal energy and thus the saving of costs. Further examples are high-duty nanomaterials for lighter and more rugged rotor blades of wind and tide power plants as well as wear and corrosion protection layers for mechanically stressed components (bearings, gear boxes, etc.). Nanotechnologies will play a decisive role in particular in the intensified use of solar energy through photovoltaic systems. In case of conventional crystalline silicon solar cells, for instance, increases in efficiency are achievable by antireflection layers for higher light yield.

First and foremost, however, it will be the further development of alternative cell types, such as thin-layer solar cells (among others of silicon or other material systems like copper/indium/selenium), dye solar cells or polymer solar cells, which will predominantly profit from nanotechnologies. Polymer solar cells are said to have high potential especially regarding the supply of portable electronic devices, due to the reasonably-priced materials and production methods as well as the flexible design. Medium-term development targets are an efficiency of approx. 10% and a lifespan of several years. Here, for example, nanotechnologies could contribute to the optimization of the layer design and the morphology of organic semiconductor mixtures in component structures. In the long run, the utilization of nanostructures, like quantum dots and wires, could allow for solar cell efficiencies of over 60%.

## 7.4. Energy conversion

The conversion of primary energy sources into electricity, heat and kinetic energy requires utmost efficiency. Efficiency increases, especially in fossil-fired gas and steam power plants, could help avoid considerable amounts of carbon dioxide emissions.

Higher power plant efficiencies, however, require higher operating temperatures and thus heat-resistant turbine materials. Improvements are possible, for example, through nano-scale heat and corrosion protection layers for turbine blades in power plants or aircraft engines to enhance the efficiency through increased operating temperatures or the application of lightweight construction materials (e.g. titanium aluminides).

Nano-optimized membranes can extend the scope of possibilities for separation and climate-neutral storage of carbon dioxide for power generation in coal-fired power plants, in order to render this important method of power generation environmentally friendlier in the long run. The energy yield from the conversion of chemical energy through fuel cells can be stepped up by nano-structured electrodes, catalysts and membranes, which results in economic application possibilities in automobiles, buildings and the operation of mobile electronics.

Thermoelectric energy conversion seems to be comparably promising. Nano-structured semiconductors with optimized boundary layer design contribute to increases in efficiency that could pave the way for a broad application in the utilization of waste heat, for example in automobiles, or even of human body heat for portable electronics in textiles.

## 7.5. Energy distribution

Regarding the reduction of energy losses in current transmission, hope exists that the extraordinary electric conductivity of nanomaterials like carbon nanotubes can be utilized for application in electric cables and power lines. Furthermore, there are nanotechnological approaches for the optimization of superconductive materials for lossless current conduction.

In the long run, options are given for wireless energy transport, e.g. through laser, microwaves or electromagnetic resonance. Future power distribution will require power systems providing dynamic load and failure management, demand-driven energy supply with flexible price mechanisms as well as the possibility of feeding through a number of decentralized renewable energy sources.

Nanotechnologies could contribute decisively to the realization of this vision, inter alia, through nano-sensory devices and power-electronical components able to cope with the extremely complex control and monitoring of such grids.

## 7.6. Energy storage

The utilization of nanotechnologies for the enhancement of electrical energy stores like batteries and super-capacitors turns out to be downright promising. Due to the high cell voltage and the outstanding energy and power density, the lithium-ion technology is regarded as the most promising variant of electrical energy storage.

Nanotechnologies can improve capacity and safety of lithium-ion batteries decisively, as for example through new ceramic, heat-resistant and still flexible separators and high-performance electrode materials. The company Evonik pushes the commercialization of such systems for the application in hybrid and electric vehicles as well as for stationary energy storage.

In the long run, even hydrogen seems to be a promising energy store for environmentally friendly energy supply. Apart from necessary nanostructure adjustments, the efficient storage of hydrogen is regarded as one of the critical factors of success on the way to a possible hydrogen management.

Current materials for chemical hydrogen storage do not meet the demands of the automotive industry, which requires a hydrogen-storage capacity of up to ten weight percent.

Various nanomaterials, inter alia based on nanoporous metal-organic compounds, provide development potentials, which seem to be economically realizable at least with regard to the operation of fuel cells in portable electronic devices.

Another important field is thermal energy storage. The energy demand in buildings, for example, may be significantly reduced by using phase change materials such as latent heat stores. Interesting, from an economic point of view, are also adsorption stores based on nanoporous materials like zeolites, which could be applied as heat stores in district heating grids or in industry. The adsorption of water in zeolite allows the reversible storage and release of heat.

## 7.7. Energy usage

To achieve sustainable energy supply, and parallel to the optimized development of available energy sources, it is necessary to improve the efficiency of energy use and to avoid unnecessary energy consumption. This applies to all branches of industry and private households. Nanotechnologies provide a multitude of approaches to energy saving.

Examples are the reduction of fuel consumption in automobiles through lightweight construction materials on the basis of nanocomposites, the optimization in fuel combustion through wear-resistant, lighter engine components and nanoparticular fuel additives or even nanoparticles for optimized tires with low rolling resistance.

Considerable energy savings are realizable through tribological layers for mechanical components in plants and machines. Building technology also provides great potentials for energy savings, which could be tapped, for example, by nanoporous thermal insulation material suitably applicable in the energetic rehabilitation of old buildings.

In general, the control of light and heat flux by nanotechnological components, as for example switchable glasses, is a promising approach to reducing energy consumption in buildings.

# Chapter 8

## 8. Graphene Batteries

Ref. https://www.azonano.com/article.aspx?ArticleID=4326#6

## Table of Contents

### 8.1. Introduction

This Graphene Battery User's Guide, which has been created for both scientists and non-scientists, explains the working principle of graphene batteries, their benefits, and details immediate, actionable steps that can be taken to begin developing a graphene battery.

Don't miss out on the next phase of nano evolution. This guide covers four well-established graphene electrode designs of experiments (DOE) from innovative academic research, including one for a graphene-lithium-sulfur battery, the current front runner technology, and are included for reference.

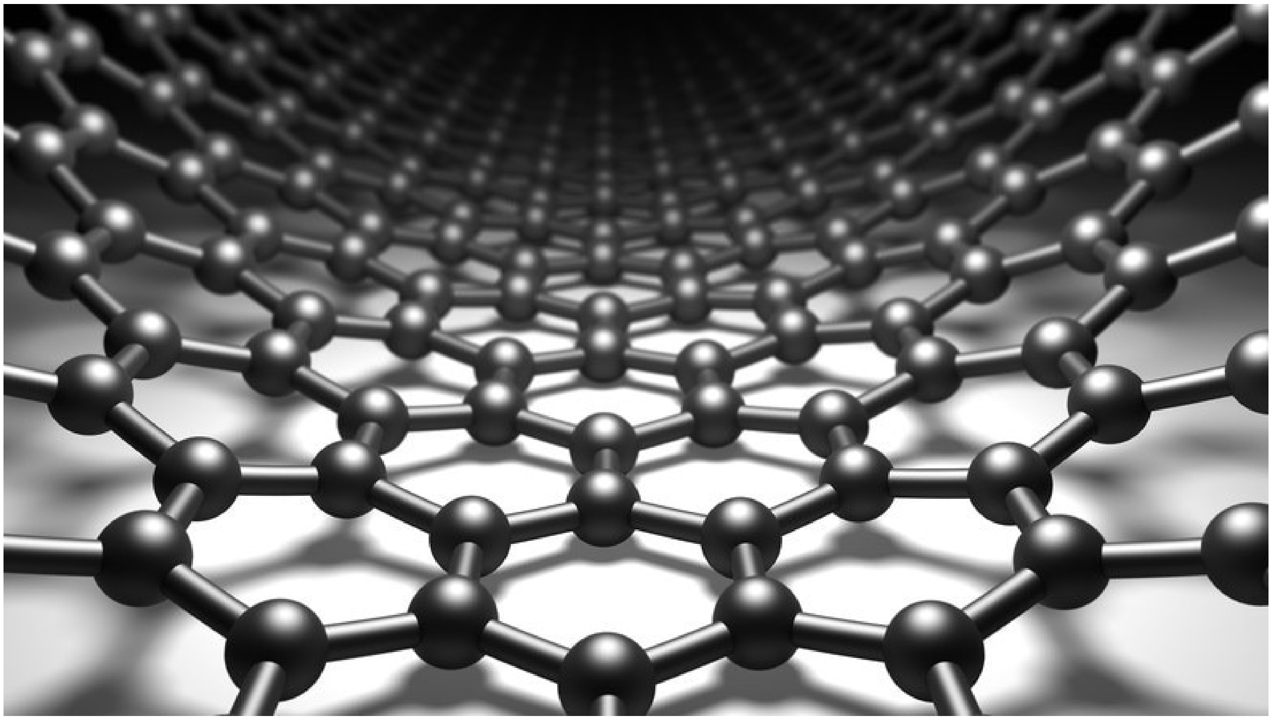


*Figure 17. The molecular structure of a graphene sheet*

Graphene-based batteries are being actively studied for a variety of commercial applications. The improved performance and life cycle benefits when developing graphene-based batteries over conventional metal-ion batteries are well worth the resource investment.

Elon Musk's Tesla Motors provides a well-known example of innovative companies actively involved in graphene battery research and commercialization.

The real graphene battery breakthroughs are expected from graphene-lithium-ion hybrid chemistries incorporated into the cathodes of lithium-sulfur cells. This kind of technology will take many years to be commercialized and intensive research is ongoing. The more advanced graphene battery technologies will need considerable R&D expenditures and will take many years to commercialize.

## 8.2. Traditional Battery Technology

*Figure 18. A cross sectional view of a traditional battery*

Lithium is the common material used in both rechargeable and non-rechargeable batteries. Although alkaline- and zinc-based batteries are available, they typically have a shorter service life because of their high charge density. Unlike lithium-based batteries, these batteries cannot operate at higher voltages.

A primary (non-rechargeable) battery is composed of two electrodes, allowing current flow in one direction only, via an intermediary electrolyte. Secondary (rechargeable) batteries still contain two electrodes, but lithium ions can flow in both directions depending on if charging or discharging.

The anode is typically a lithium-based (metal oxide) compound and the cathode is a porous carbon. Both the anode and cathode have a rigid structure with defined holes, enabling the absorption of lithium ions into the holes upon the application of current. The ions desorb into the electrolyte solution when there is no current being applied.

Absorption of the lithium ions can take place on both the cathode and the anode. The ions move towards to the cathode when a battery is being used. During charging, the current is reversed and the ions are absorbed into the anode. This process allows for many cycles to be produced, resulting in an enhanced lifespan. The material of choice for cathodes is traditionally graphite, but it can vary for anodes. The most common types include $Li_4Ti_5O_{12}$, $LiNiCoAlO_2$, $LiFePO_4$, $LiNiMnCoO_2$ (NMC), $LiCoO_2$, and $LiMn_2O_4$.

## 8.3. Graphene Battery Technology

*Figure 19. Graphene batteries can reduce the environmental impact of battery use [Ref. https://www.cheaptubes.com/resources/graphene-battery-users-guide/]*

The structure of graphene battery technology is similar to that of traditional batteries, where two electrodes and an electrolyte solution are used to facilitate ion transfer. The main difference between graphene-based batteries and solid-state batteries is in the composition of one or both electrodes.

The change primarily lies in the cathode, but it is also possible to utilize carbon allotropes in the anode. The cathode in a conventional battery is purely composed of solid-state materials, but a composite-a hybrid material containing a solid-state metallic material and graphene is used as the cathode in a graphene battery.

Depending on the intended application, the amount of graphene in the composite can differ. The amount of graphene incorporated into the electrode is usually based on the performance requirements and depends upon the existing efficiencies and/or weaknesses of the solid-state precursor material.

*Click Here to Read the Graphene Battery User's Guide*

## 8.4. Graphene Battery Breakthrough

The real graphene battery breakthroughs are the incorporation of graphene-lithium-ion hybrid chemistries into the cathodes of lithium-sulfur cells as described in this guide. Pure graphene electrodes are not used in a graphene battery, and many graphene-based electrodes are fabricated and operate in a similar way to conventional batteries.

Their performance is improved by adding graphene to the electrode formulation. Inorganic-based electrodes generally have limitations in terms of density, conductivity, surface area, capacity, capacitance, or cycle times to name a few.

Graphene is a versatile molecule possessing many unique and desirable properties, and it can be adopted in many different ways, as there is no ‘one size fits all’ solution for using graphene. Graphene is used to improve many of the benefits already present with conventional materials, but it also helps to overcome previous battery limitations, resulting in increased battery life or performance.

In electrodes, graphene works in two general ways, either as a composite/hybrid or as a support material. As a support material, graphene helps to keep metal ions in a regular order, which helps with electrode efficiency.

As a composite material in an electrode, graphene is generally involved in the facilitation of the charge itself, where its high conductivity and well-ordered structure are important attributes to provide an improvement against its non-graphene predecessors. The role of graphene in enabling certain battery applications is discussed in the following sections.

## 8.5. Lithium-Ion Batteries

Graphene-based batteries are rapidly becoming more favorable compared to their graphite predecessors. They are an emerging technology, allowing for faster cycle times and increased electrode density. They also have the ability to retain the charge longer, improving the lifespan of the battery.

Graphite batteries are a proven technology and available in many forms. Like graphite, various types of functional graphene derivative electrodes are now available and researchers are discovering many advantages over pure graphite electrodes.

## 8.6. Graphene-Metal Oxide Hybrids

Historically, graphite has been employed as the primary cathode material, where the lithium ions move into the structured holes. However, graphene lacks this capability, but it can store the lithium ions via surface adsorption and induced bonding due to its large surface area.

Induced bonding generally occurs during the presence of a graphene derivative and the lithium ions attach to the functionalized surface. In addition to possessing a large surface area, high conductivity is another key characteristic of graphene electrodes. Many metal oxides traditionally used in batteries have downsides such as low volumetric energy density, low conductivity, and the loss of contact points.

Hybridizing the metal oxide matrix with graphene can eliminate most of these problems, and the conductivity becomes greater due to vast improvement in the interaction between the interstitial ions and the hybrid matrix. To produce graphene-metal oxide nanoparticle hybrids, graphene serves as a template during the process, producing an evenly distributed matrix owing to the regular repeating structure of graphene.

This process also limits the aggregation of nanoparticles, promoting the large nanoparticle surface area during the lithium charge and discharge cycles. As such, there is an improvement in the specific capacity and cycling performance compared to pure MO-based electrodes.

Graphene-MO hybrid electrodes are capable of exhibiting up to 1100 mAh $g^{-1}$ for the first 10 cycles. The specific energy density is maintained at 1000 mAh $g^{-1}$, even after 130 cycles.

## 8.7. Graphene-Carbon Nanotube/Fullerene Hybrids

While not as widely reported, an electrode containing both graphene and either carbon nanotubes and/or fullerenes have been implemented. Electrodes consisting of 6-15 monolayers of graphene, with each layer on top of one another, exhibit a specific capacity of 540 mAh $g^{-1}$, which is considerably higher when compared to their graphitic counterparts due to their higher surface area.

Dispersing the graphene sheets with either fullerenes or carbon nanotubes increases the inter-graphene spacing. This extra spacing form extra cavities for the lithium ions to occupy, increasing the specific capacity by up to 40% compared with stacked graphene electrodes.

## 8.8. Graphene Lithium Sulfur Batteries

Lithium sulfur batteries have the potential to substitute lithium-ion batteries in commercial applications, due to their low toxicity, low cost, and the potential for possessing an energy density of 2567 W h $kg^{-1}$, which is five times higher than that of existing lithium-based batteries.

As such, they have gained a lot of interest, but have several significant shortcomings that have prevented them from reaching the commercial marketplace. The first is inorganic salt deposition at the cathode due to the presence of highly soluble reactants in the cell.

The salt deposition causes a loss in active material, low utilization of the sulfur cathode, low coulombic efficiency, and a degradation of the cycle life. The second major drawback is the inherent low conductivity of sulfur.

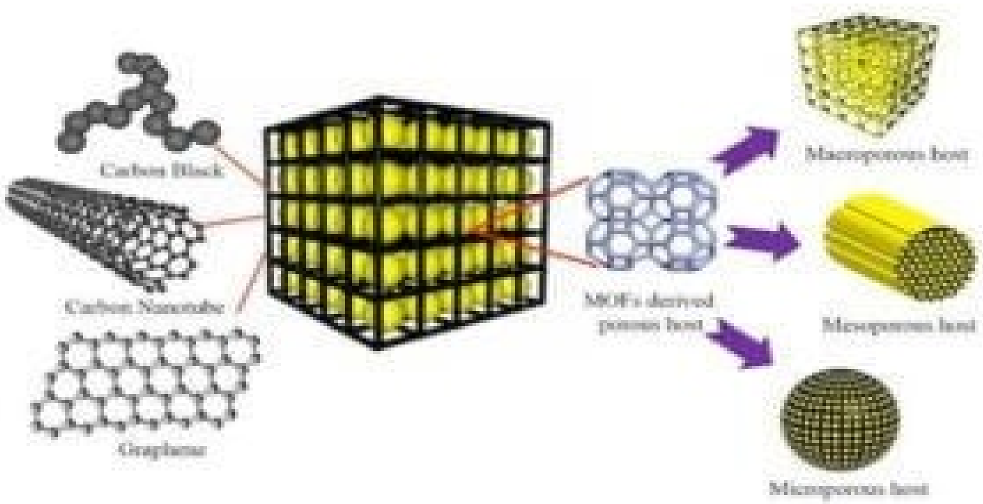


*Figure 20. A graphene-lithium-sulfur battery [ Ref. https://www.cheaptubes.com/resources/graphene-battery-users-guide/]*

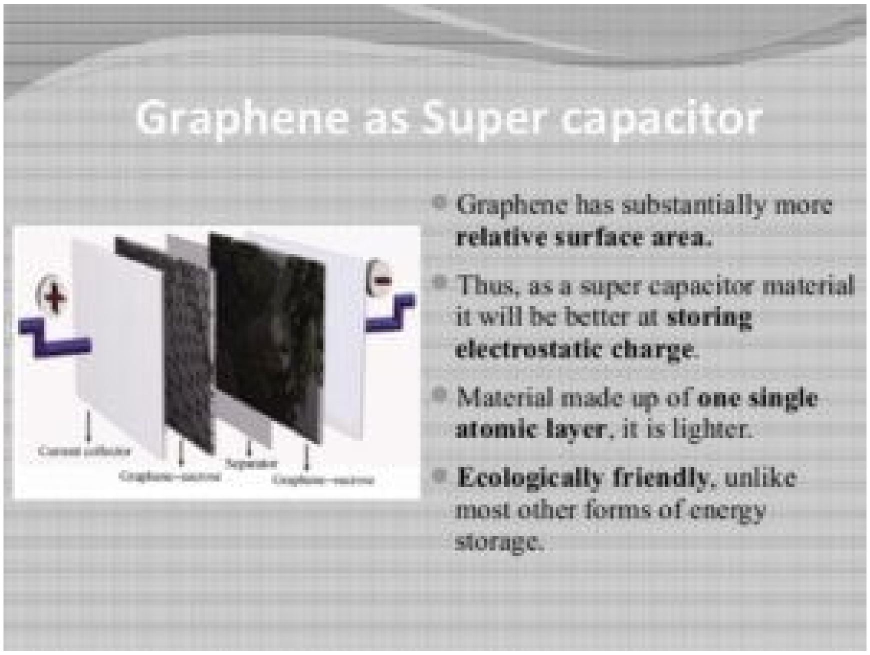
Using graphene as a support material for the sulfur ions eliminates some of the associated problems in sulfur batteries, thanks to its unique properties, such as a large surface area, high chemical/thermal stability, good mechanical strength, and high electrical conductivity.

The high surface area provides a good dispersion of sulfur, which controls the mobilization of sulfur ions and eliminates a build-up of sulfur ions on the cathode. A one-pot synthesis can also be used to produce graphene supported sulfur particles.

The performance of lithium-sulfur batteries relies largely on sulfur concentration (and effectively the graphene to sulfur ratio) in the electrode. From electrodes produced to date, electrodes containing higher sulfur content deliver the best performance. Electrodes consisting of 63 wt% sulfur have a capacity of 731 mAh $g^{-1}$, with the potential of obtaining up to 1160 mAh $g^{-1}$.

The capacity remains at 700 mAh $g^{-1}$ even after 50 cycles and is at least double the capacity of other sulfur-graphene electrodes fabricated. They are also stable under high rate cycling. Some degradation of the cell does occur because the sulfur binding has not yet achieved 100% efficiency, but graphene supported sulfur electrodes still demonstrate a vast improvement when compared with non-graphene-based sulfur electrodes.

## 8.9. Graphene Supercapacitors



Graphene as Super capacitor

- Graphene has substantially more **relative surface area.**
- Thus, as a super capacitor material it will be better at **storing electrostatic charge**.
- Material made up of **one single atomic layer**, it is lighter.
- **Ecologically friendly**, unlike most other forms of energy storage.

*Figure 21. A graphene supercapacitor design*

In the electronics field, supercapacitors are a useful device capable of storing up more than a hundred times more energy than standard capacitors. They can also work in low temperature conditions and are regularly used as a replacement for electrochemical batteries.

The ability to produce double-electric layers is one of the key properties of a supercapacitance material, and is important in electric double-layer capacitors (EDLC) supercapacitors. Supercapacitors store energy by building up charges at the electrode-electrolyte interface through polarization.

Activated carbon has been traditionally used as the electrode material, but the inability to work at high voltages is its major disadvantage. Graphene, and its derivatives, are useful due to their open-pore structure, high conductivity, high specific surface area, production potential and low cost; all of which are desirable attributes for a supercapacitor.

## 8.10. Graphene-Metal Oxide Composite Electrodes

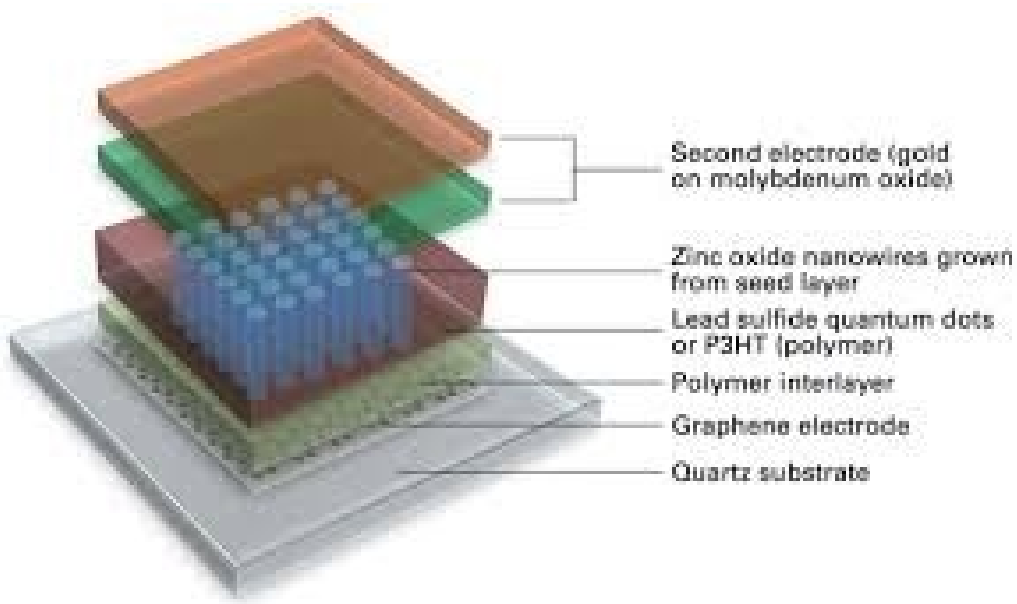


*Figure 22. Graphene molybdenum oxide electrodes*

Graphene and metal oxide composite electrodes have provided a new area wherein the capacitance is higher than that of standard capacitor electrodes. Common metal oxides are $MnO_2$, $Co_3O_4$, $SnO_2$, and $ZnO_2$. $MnO_2$ graphene composites are the most promising due to the variable oxidation states that manganese ions can adopt.

The redox reaction between the III and IV states involves the intercalation of metal ions in the electrolyte solution (e.g. $Li^+$, $Na^+$), which facilitates energy storage. In addition to the efficient ion intercalation, the graphene sheets provide a conductive network with a large surface area, which further promotes ion-electrode interactions.

Graphene-MO composites possess a high specific capacitance of 310 F $g^{-1}$, which is three times more than an electrode made of either pure graphene or metal oxide. They can retain 95.6% of its specific capacitance even after 2000 cycles.

As previously mentioned, supercapacitors are currently preferred over electrochemical batteries for certain applications. However, lower energy density is an issue with using supercapacitors.

The incorporation of graphene into the negative electrodes of supercapacitors increases the energy density, while keeping the power density high. Supercapacitors have been made using a nanowire-graphene composite as the positive electrode and graphene as the negative electrode.

This capacitor is configured asymmetrically and has been shown to deliver a high-energy density of 30.4 Wh $kg^{-1}$ at an operating voltage of 2 V. The graphene supercapacitors have outperformed other capacitors in terms of power density and energy, making them promising in the field of supercapacitors.

## 8.11. Graphene-Polymer Composite Electrodes

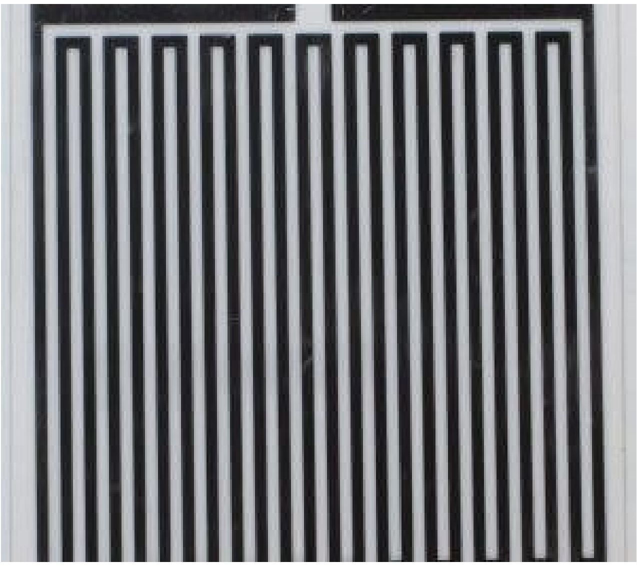


*Figure 23. A graphene-polymer composite electrode*

Graphene-polymer composites do not have high conductivity compared to other graphene-based composites, but they do possess a high doping-undoping capability, high charge/discharge rate, and flexibility. Graphene-polymer composites work by n and p doping redox reactions where electrons are lost or gained to convert and store energy.

Graphene oxide and a nitrogen containing polymer are ideal to fabricate a graphene-polymer electrode composite. Polymerization of the functional groups facilitates strong pi-pi interactions between the two components of the composite, resulting in a large surface area and a semi-flexible structure that can mechanically deform during the cycle charge-discharge processes. These graphene-polymer composites can exhibit up to 531 F $g^{-1}$ and retain up to 74% of its capacitance even after 2000 cycles.

## 8.12.Graphene-CNT Electrodes

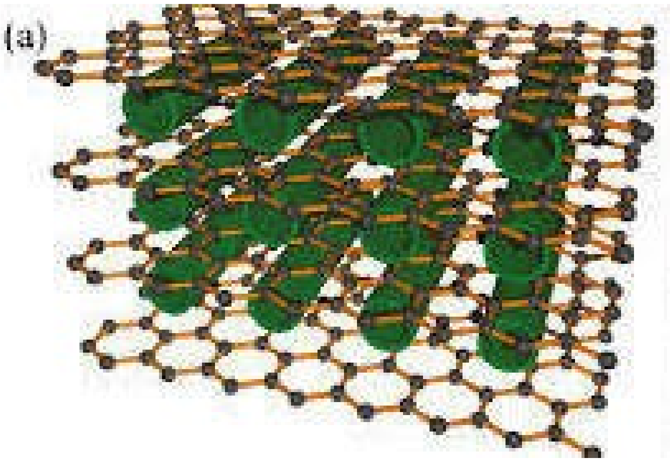


*Figure 24. A representation of aligned carbon nanotubes in between graphene sheets*

Similar to lithium-ion batteries, carbon nanotubes are used to increase the inter-graphene spacing between the different monolayers. Stacked graphene electrodes can suffer from a reduced surface area compared to monolayered graphene. The introduction of nanotubes into the electrode increases the nanopores as well as the conductivity of the electrode.

Nanotubes can be used into the graphene matrix in either two or three-dimensions, with an average specific capacitance of 120 F $g^{-1}$ and 386 F $g^{-1}$, respectively. The capacitance can even rise by up to 20% after 2000 cycles in the three-dimensional graphene-CNT, demonstrating the excellent electrochemical stability of these electrodes.

## 8.13. Graphene Fuel Cells

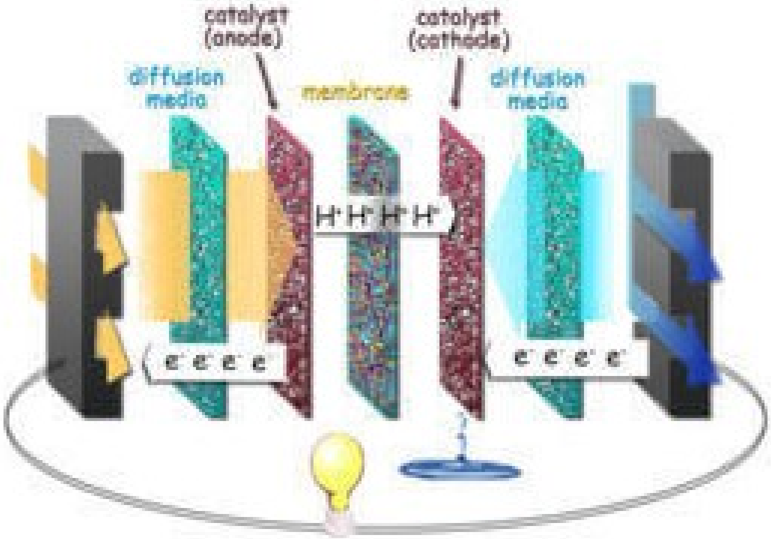


*Figure 25. A Fuel Cell Inside View.*

Unlike batteries and capacitors, fuel cells generate electricity rather than store it. Many fuel cells consist of a platinum-based catalyst, which is very expensive to produce. The cost of fuel cells can be lowered using carbon allotropes as a support for the platinum catalysts. One such catalyst support is graphene.

With a large surface area, good dispersion, and high conductivity (when reduced) of graphene oxide, the integrity and efficiency of fuel cells is improved by incorporating graphene into the composite materials used in the device.

Graphene is employed in some fuel cells to facilitate the oxidation of methanol and has been shown to be more effective when compared with other carbon allotropes, such as carbon black and carbon nanotubes. Two-dimensional graphene sheets possess a greater active surface area for electron/ion transport because both of their sides are exposed to the solution within the fuel cell.

The uniformity of the graphene surface also eliminates aggregation, promoting an even distribution of the platinum particles across the supports. Also, the surface defects in the graphene structure promote the interaction between the graphene support and the platinum particles. Platinum-graphene supported fuel cells can have a current density up to 0.12 mA $cm^{-2}$, which is at least three times more than other carbon-based supports.

Graphene can be doped with nitrogen after subjecting it to a nitrogen plasma treatment. Doped graphene possesses nitrogen-based functional groups on its surface, which enable a better dispersion and decoration by the platinum nanoparticles. Doped graphene possesses a greater conductivity and electrocatalytic activity than undoped graphene. The oxidation current of doped graphene is two times that of undoped graphene.

## 8.14. Design of Experiments- Synthesizing a Graphene-Based Battery Electrode

There are many methods available to convert graphene and metal-based inorganic compounds into usable graphene composites for electrodes. As this is an emerging field, new methods are frequently being developed and subsequently published. Some of the methods include chemical reduction, ex-situ hybridization, electroless deposition, in-situ crystallization, hydrothermal methods, sol-gel methods, thermal evaporation, electrochemical deposition, and in-situ self-assembly.

As with any method, there are multiple ways to synthesize the material itself. To cover each approach would be impractical, so here some specific ways to implement graphene into composite materials for use as electrodes in graphene battery R&D projects are discussed.

The values used are from published experiments and are used for ratio illustrative purposes only. The scale and amounts can be varied to better suit specific experiments.

The following is a DOE for graphene-lithium-sulfur batteries, a current leading technology.

*“Synthesis of the Thermally Exfoliated Reduced Graphene. Thermally exfoliated reduced graphene was obtained.*

*Preparation of Graphene-Sulphur Hybrids- The G/S hybrids were prepared by hydrothermal reduction assembly of GO with a sulfur-dissolving* $CS_2$ *and alcohol solution. In brief, 50 mL of the GO aqueous dispersion and 15 mL of alcohol were mixed, and then 3 mL of* $CS_2$ *containing 100, 150, and 200 mg of dissolved sulfur (tuning the sulfur content in the samples) was added to the GO dispersion. The mixture was stirred for 90 min and then sealed in an 80 mL Teflon-lined stainless steel autoclave for a hydrothermal reaction at 180 C for 10 h. The black cylinder of the G/S hydrogel was washed by ethanol and distilled water, and the wet hydrogel was then freeze-dried to obtain the G/S hybrids.*

*Preparation of Graphene-Sulphur Hybrids (Powder)- G/S hybrids (powder) were prepared by mixing 90 mg of intercalation-exfoliated graphene and thermally exfoliated reduced graphene with 150 mg of sulfur under the same hydrothermal conditions as the G/S hybrids.*

*Preparation of* $\text{Graphene-Sulphur}_{mix}$ *The* $G/S_{mix}$ *was prepared by mixing- 50 mL of the GO aqueous dispersion, 15 mL of alcohol, and 150 mg of sulfur under the same conditions but without* $CS_2$*.*

*Electrochemical Measurements. The G/S hybrid was cut, compressed, and shaped into a circular pellet with a diameter of 12 mm and directly used as a cathode. The mass loading of a G/S electrode was about 2 mg* $cm^2$*. The G S59 or G S60 hybrid (powder) cathode was prepared by mixing 90 wt % G S59 or G S60 hybrid (powder) with 10 wt % polyvinylidene fluoride dissolved in N-methyl-2-pyrrolidone as a binder to form a slurry, which was then coated on an aluminum foil and dried under vacuum at 70 C for 12 h. The foil was pressed between twin rollers, shaped into a circular pellet with a diameter of 12 mm, and used as a cathode. The electrolyte was 1.0 M lithium bis-trifluoromethanesulfonylimide in 1,3-dioxolane and 1,2-di- methoxyethane (1:1 by volume) with 0.5 wt %* $LiNO_3$ *additive. A 2025 type stainless steel coin cell was used to assemble a test cell. A lithium metal foil was used as the anode, and a G/S slice as the cathode. A LAND galvanostatic charge discharge instrument was used to perform the measurements. The coin-type cell was assembled in an Ar-filled glovebox (MBraun Unilab). The current density set for cell tests was referred to the mass of sulfur in the cathode and varied from 0.3 to 4.5 A* $g^{-1}$*. The charge discharge voltage range was 1.5 2.8 V. The CV was measured using a VSP-300 multichannel potentiostat/galvanostat (Bio-Logic, France) workstation in the voltage range 1.5 2.8 V (vs Liþ/Li) at a scan rate of 0.1 mV* $s^{-1}$*. The G S63 hybrid electrode was discharged to the end of the second plateau and disassembled, dried in the glovebox, and followed by transferring to the vacuum chamber of XPS for structure characterization.”*[1]

Three more types of graphene electrode DOEs are discussed in the following sections.

A pure graphene-based electrode is created by dispersing graphene oxide powder (100 mg) in distilled water (30 mL) and sonicating for 30 minutes. The resulting suspension is heated on a hot plate until it reaches 100 °C and 3 mL of hydrazine hydrate is then added.

The suspension is kept at 98 °C for 24 hours to reduce the graphene oxide to rGO. The reduced graphene oxide can be collected by filtration to leave a black powder. The filtered powder is then washed several times with distilled water in order to reduce the excess hydrazine.

The graphene powder is re-dispersed into water by sonication and the resulting solution is then centrifuged at 4000 rpm for 3 minutes to remove the larger particles. Graphene is collected by vacuum filtration and dried in a vacuum. This step can be left out if rGO is used.

To create the electrode, graphene is dispersed in ethanol until a concentration of 0.2 $mgmL^{-1}$ is achieved. The resulting suspension is filtered by vacuum filtration and then collected on the microporous filter paper. The filtered graphene is cut into 1 x 2 $cm^2$ (1 mg weight) for subsequent use. It is attached to a cell with an electrolyte buffer in order to examine the graphene electrode.

The second method explains the preparation of a cobalt-graphene hybrid electrode for use as an electrode in lithium-ion batteries. To prepare the electrode, graphene oxide (0.1 g) is added to cobalt acetate (350 mg) and deionized water (400 mL). $NH_4OH$ (3800 μL) and hydrazine (250 μL) are added to the solution and the mixture is stirred for 4 hours at 100 °C.

The resulting solution is filtered out once the reaction is complete. The solution is then re-crystallized by heating the product for 6 hours at 200 °C.

This last method involves creating a tin-graphene nanoribbon composite electrode for use in lithium-ion batteries. To create the electrode, graphene nanoribbon (GNR) (75 mg), $SnCl_2.H_2O$ (1.33g, 5.89 mmol), 2-pyrrolidinone (65 mL) and a magnetic stirrer bar are added to a dried round-bottom flask.

The solution is sonicated for 20 minutes and then refluxed for 1 hour. The vessel is cooled down to room temperature and sonicated overnight in an open-air environment. The mixture is quenched with acetone and water three times and filtered over a PTFE membrane (0.45 μm). The resulting product is dried in a vacuum (60 °C) for 24 hours and annealed in a quartz furnace (500 °C, Ar atmosphere) for 2 hours. The theoretical yield is 380 mg.

## 8.15. Graphene Products Available

Cheap Tubes Inc offers a variety of graphene-based products that can be used in electrode formulations.

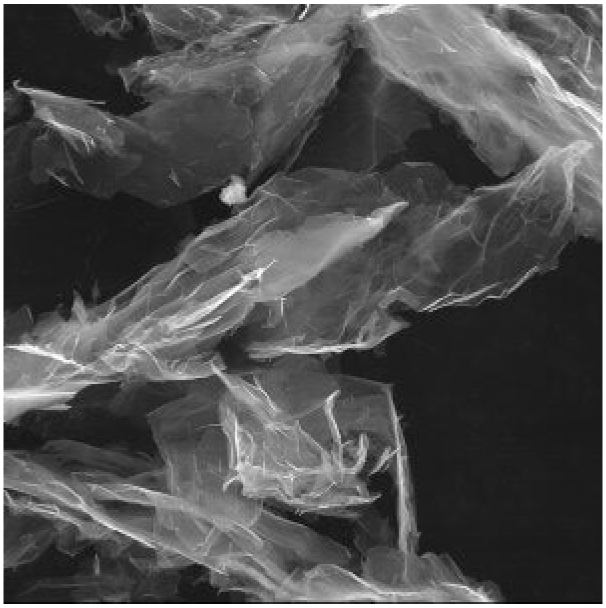


*Figure 26. Cheap Tubes' plasma exfoliated graphene nanoplatelets*

Graphene nanoplatelets (GNPs) possess some of the best properties for battery applications. They can be used as an alternative to other carbon-based materials. GNPs have outstanding thermal and electrical conductivity, mechanical stability, and the ability to provide a composite with enhanced mechanical strength, conductivities, and lower gas permeation.

Cheap Tubes produces research grade graphene nanoplatelets by plasma exfoliation. The company's plasma exfoliation process synthesizes high-grade GNPs with a higher internal conductivity and less defects. The GNPs contain several graphene layers and typically have a thickness range of 3 - 10 nm and are friable with high shear methods such as a 3 roll mill or homogenizer.

The GNPs are produced with varying functional groups, including oxygen-based, nitrogen-based, fluorine and amine groups. Non-functionalized GNPs (argon processed) are also available. As the production methods of GNPs are scalable, these materials can be implemented in large volume and larger scale applications.

Graphene oxide (and reduced graphene oxide) is supplied as a dispersion, a powder, or a spin coated film. The elemental composition of Cheaptubes graphene oxide includes 35 - 42% carbon, 45 - 55% oxygen and 3 - 5% hydrogen. The company provides dispersions in various solvents and in a range of concentrations.

It also offers graphene oxide (and reduced graphene oxide) films and coatings. A graphene oxide film composed of Cheap Tubes' single layer graphene oxide product spin coated on glass offers a final thickness of 5 - 20 nm. Its conductivity is in the range of $10^4$ - $10^5$ $\mathrm{Sm^{-1}}$ and sheet resistance in the range of $10^1$ - $10^3$ $\Omega\ \mathrm{sq^{-1}}$.

Conversely, a single (flexible) graphene sheet on a flexible organic substrate offers the same thickness and area but has a conductivity range of $10^3$ S/m – $10^4$ S/m and sheet resistance range of $10^2$ - $10^4$ $\Omega$ sq$^{-1}$.

Cheap Tubes also offers CVD graphene films grown on a range of substrates, including silicon, quartz, PET, and copper. They can also be transferred to a range of customer supplied substrates if they are compatible with the solvents employed to float the graphene off the substrate so that it can be re-deposited onto the substrate.

Conductive carbon nanotube composite additives can be used as an alternative to graphene. They have been specifically designed to enhance the efficiency of lithium-ion electrodes. They are a blend of both nanotubes and carbon black, improving the tap density (up to 10%) and capacitance retention of the electrode without decline after multiple charge/discharge cycles.

The additive consists of multi-walled carbon nanotubes blended with a proprietary carbon black and can be used in the anode as well as in the cathode within a battery cell. Typically, 1-2 wt% is used in an anode and 2-3 wt% in a cathode.

## 8.16. Summary

Graphene-based batteries are quickly becoming comparable, in terms of efficiency, to traditional solid-state batteries. They are advancing all the time and it won’t be long before they surpass their solid-state predecessors. The extra benefits associated with graphene being present in the electrodes can be useful, even if the efficiency isn’t as high. For batteries that possess a similar efficiency, graphene batteries are an ideal choice, which is why scientist are trying to further advance this class of batteries. They have started to gain traction in the commercial marketplace, and it won’t be long before they become the norm and phase-out solid-state batteries. To quote recent forecasts “the world graphene battery market is expected to reach $115 million by 2022, growing at a CAGR of 38.4% during the forecast period. The automotive industry is estimated to dominate the market throughout the analysis period. Geographically, Europe is expected to be the leading market in 2016, with a revenue contribution of around 38%.”

With increasing energy demands globally, improving energy storage devices while reducing negative environmental impacts related to consumer-based battery usage is a noble goal and one that we emphatically support. We hope that this guide has helped you to understand the current graphene battery research trends and inspired you to begin graphene battery development.

## 8.17. Conclusion

In terms of efficiency, graphene-based batteries are quickly becoming comparable to conventional solid-state batteries. Thanks to the continuous advancements in graphene-based batteries, it will not be long before they outperform their solid-state predecessors.

The additional advantages associated with graphene being present in the electrodes can be useful, even if the efficiency is not as high. Graphene batteries are an ideal option for batteries that possess a similar efficiency and because of this reason researchers are striving to further advance this class of batteries.

Graphene batteries have started to gain interest in the commercial marketplace, and it will not be long before these batteries become the norm and phase-out solid-state batteries.

To quote recent forecasts "the world graphene battery market is expected to reach $115 million by 2022, growing at a CAGR of 38.4% during the forecast period. The automotive industry is estimated to dominate the market throughout the analysis period. Geographically, Europe is expected to be the leading market in 2016, with a revenue contribution of around 38%."

With ever-increasing energy demands all across the world, developing improved energy storage devices with reduced negative environmental impacts related to consumer-based battery usage is a noble objective and one that Cheap Tubes definitely supports. Cheap Tubes hopes that this guide has helped you to know the current graphene battery research trends and inspired you to initiate graphene battery development.

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# Chapter 9

## 9. Environmental Nanotechnology

Nanotechnology is being used in several applications to improve the environment. This includes cleaning up existing pollution, improving manufacturing methods to reduce the generation of new pollution, and making alternative energy sources more cost effective.

### 9.1. The Application of Nanotechnology to Environmental Issues

In trying to help our ailing environment, nanotechnology researchers and developers are pursuing the following avenues:

Generating less pollution during the manufacture of materials. One example of this is how researchers have demonstrated that the use of silver nanoclusters as catalysts can significantly reduce the polluting byproducts generated in the process used to manufacture propylene oxide. Propylene oxide is used to produce common materials such as plastics, paint, detergents and brake fluid.

Producing solar cells that generate electricity at a competitive cost. Researcher have demonstrated that an array of silicon nanowires embedded in a polymer results in low cost but high efficiency solar cells. This, or other efforts using nanotechnology to improve solar cells, may result in solar cells that generate electricity as cost effectively as coal or oil.

Increasing the electricity generated by windmills. Epoxy containing carbon nanotubes is being used to make windmill blades. The resulting blades are stronger and lower weight and therefore the amount of electricity generated by each windmill is greater.

Cleaning up organic chemicals polluting groundwater. Researchers have shown that iron nanoparticles can be effective in cleaning up organic solvents that are polluting groundwater. The iron nanoparticles disperse throughout the body of water and decompose the organic solvent in place. This method can be more effective and cost significantly less than treatment methods that require the water to be pumped out of the ground.

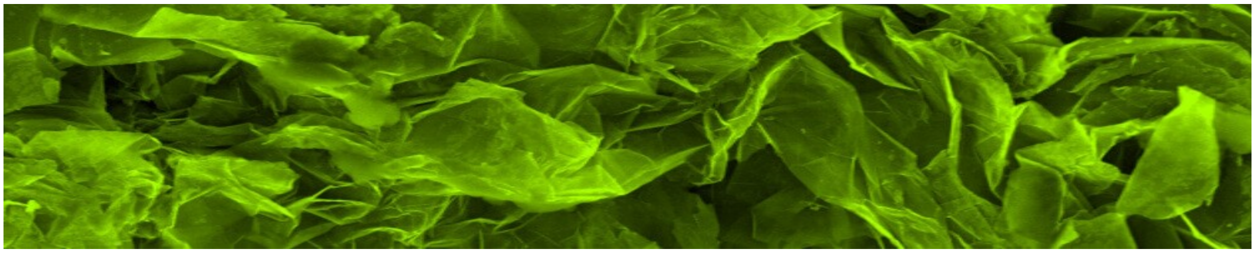
Cleaning up oil spills. Using photocatalytic copper tungsten oxide nanoparticles to break down oil into biodegradable compounds. The nanoparticles are in a grid that provides high surface area for the reaction, is activated by sunlight and can work in water, making them useful for cleaning up oil spills.

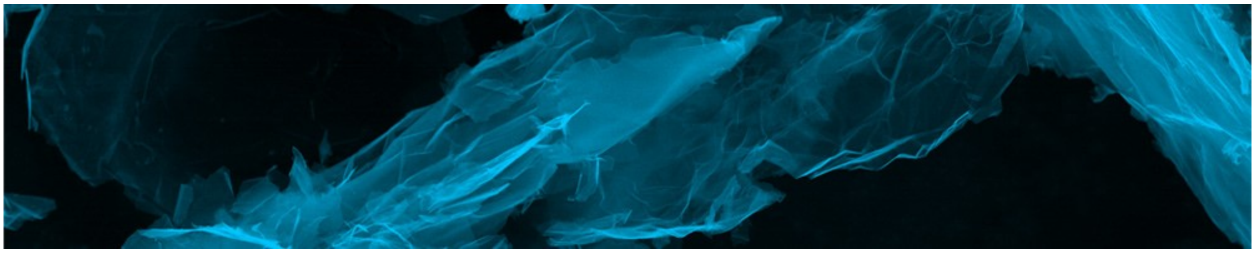
Clearing volatile organic compounds (VOCs) from air. Researchers have demonstrated a catalyst that breaks down VOCs at room temperature. The catalyst is composed of porous manganese oxide in which gold nanoparticles have been embedded.

Reducing the cost of fuel cells. Changing the spacing of platinum atoms used in a fuel cell increases the catalytic ability of the platinum. This allows the fuel cell to function with about 80% less platinum, significantly reducing the cost of the fuel cell.

Storing hydrogen for fuel cell powered cars. Using graphene layers to increase the binding energy of hydrogen to the graphene surface in a fuel tank results in a higher amount of hydrogen storage and a lighter weight fuel tank. This could help in the development of practical hydrogen-fueled cars.

Compiled by Earl Boysen of Hawk's Perch Technical Writing, LLC and UnderstandingNano.com. You can find him on **Google+**.





# Chapter 10

## 10. Nanotechnology in Medicine - Nanomedicine

The use of nanotechnology in medicine offers some exciting possibilities. Some techniques are only imagined, while others are at various stages of testing, or actually being used today.

Nanotechnology in medicine involves applications of nanoparticles currently under development, as well as longer range research that involves the use of manufactured nano-robots to make repairs at the cellular level (sometimes referred to as *nanomedicine*).

Whatever you call it, the use of nanotechnology in the field of medicine could revolutionize the way we detect and treat damage to the human body and disease in the future, and many techniques only imagined a few years ago are making remarkable progress towards becoming realities.

### 10.1. Nanotechnology in Medicine Application: Drug Delivery

One application of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells, which allows direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease.

For example, nanoparticles that **deliver chemotherapy drugs directly to cancer cells** are under development. Tests are in progress for targeted delivery of chemotherapy drugs and their final approval for their use with cancer patients is pending. One company, CytImmune has published the results of a **Phase 1 Clinical Trial** of their first targeted chemotherapy drug and another company, BIND Biosciences, has published preliminary results of a **Phase 1 Clinical Trial** for their first targeted chemotherapy drug and is proceeding with a **Phase 2 Clinical Trial**.

Researchers at the Wyss Institute are testing nanoparticles that release drugs when subjected to sheer force, such as occurs when passing through a section of artery that is mostly blocked by a clot. Lab tests on animals have shown that this method is effective in delivering drugs used to dissolve clots. Read more about their study **here**.

Researchers at the Houston Methodist Research Institute have demonstrated a targeted drug delivery method in mice using **silicon nanoparticles** that degrade inside a tumor, releasing polymer strands that form a nanoparticle containing the drug to be delivered. This polymer nanoparticle dissolves inside the cancer cell, delivering the drug to the cancer cell.

Researchers at the University of Illinois have demonstated that **gelatin nanoparticles** can be used to deliver drugs to damaged brain tissue more efficently than standard methods. This has been demonstrated in the lab, the researchers hope that this method will result in more effective drug delivery for brain injuries.

Researchers at MIT are investigating the use of **nanoparticles to deliver vaccine**.The nanoparticles protect the vaccine, allowing the vaccine time to trigger a stronger immune response as shown in lab tests with mice. Additional work needs to be done to adapt the technique to human patients.

Researchers are developing a method to release insulin that uses a **sponge-like matrix that contains insulin as well as nanocapsules** containing an enzyme. When the glucose level rises the nanocapsules release hydrogen ions, which bind to the fibers making up the matrix. The hydrogen ions make the fibers positively charged, repelling each other and creating openings in the matrix through which insulin is released. So far this has been shown to be effective in tests with lab mice.

Researchers are developing a **nanoparticle that can be taken orally** and pass through the lining of the intestines into the bloodstream. This should allow drugs that must now be delivered with a shot to be taken in pill form. The researchers have demonstrated the technique with lab mice so far.

Researchers are also developing a nanoparticle to defeat viruses. The nanoparticle does not actually destroy viruses molecules, but delivers an **enzyme that prevents the reproduction of viruses molecules** in the patients' bloodstream. The effectiveness of the technique has been demonstrated in lab tests.

## 10.2. Nanotechnology in Medicine Application: Therapy Techniques

Researchers have developed "nanosponges" that absorb toxins and remove them from the bloodstream. The **nanosponges** are polymer nanoparticles coated with a red blood cell membrane. The red blood cell membrane allows the nanosponges to travel freely in the bloodstream and attract the toxins.

Researchers have demonstrated a method to generate sound waves that are powerful, but also tightly focused, that may eventually be used for noninvasive surgery. They use a **lens coated with carbon nanotubes** to convert light from a laser to focused sound waves. The intent is to develop a method that could blast tumors or other diseased areas without damaging healthy tissue.

Researchers are investigating the use of **bismuth nanoparticles** to concentrate radiation used in radiation therapy to treat cancer tumors. Initial results indicate that the bismuth nanoparticles would increase the radiation dose to the tumor by 90 percent.

Nanoparticles composed of polyethylene glycol-hydrophilic carbon clusters (PEG-HCC) have been shown to **absorb free radicals** at a much higher rate than the proteins out body uses for this function. This ability to absorb free radicals may reduce the harm that is caused by the release of free radicals after a brain injury.

Targeted heat therapy is being developed to destroy breast cancer tumors. In this method antibodies that are strongly attracted to proteins produced in one type of breast cancer cell are attached to nanotubes, causing the nanotubes to accumulate at the tumor. Infrared light from a laser is absorbed by the nanotubes and produces **heat that incinerates the tumor**.

Read more about **nanomedicine therapy techniques**

## 10.3. Nanotechnology in Medicine Application: Diagnostic Techniques

Researchers at Worcester Polytechnic Institute are using **antibodies attached to carbon nanotubes** in chips to detect cancer cells in the blood stream. The researchers believe this method could be used in simple lab tests that could provide early detection of cancer cells in the bloodstream.

Researchers at MIT have developed a sensor using carbon nanotubes embedded in a gel; that can be injected under the skin to **monitor the level of nitric oxide** in the bloodstream. The level of nitric oxide is important because it indicates inflammation, allowing easy monitoring of inflammatory diseases. In tests with laboratory mice the sensor remained functional for over a year.

Researchers at the University of Michigan are developing a sensor that can detect a very low level of cancer cells, as low as 3 to 5 cancer cells in a one milliliter in a blood sample. They grow sheets of **graphene oxide**, on which they attach molecules containing an antibody that attaches to the cancer cells. They then tag the cancer cells with fluorescent molecules to make the cancer cells stand out in a microscope.

Researchers have demonstrated a way to use nanoparticles for **early diagnosis of infectious disease**. The nanoparticles attach to molecules in the blood stream indicating the start of an infection. When the sample is scanned for Raman scattering the nanoparticles enhance the Raman signal, allowing detection of the molecules indicating an infectious disease at a very early stage.

A test for early detection of kidney damage is being developed. The method uses **gold nanorods** functionalized to attach to the type of protein generated by damaged kidneys. When protein accumulates on the nanorod the color of the nanorod shifts. The test is designed to be done quickly and inexpensively for early detection of a problem.

Read more about **nanomedicine diagnostic techniques**

## 10.4. Nanotechnology in Medicine Application: Anti-Microbial Techniques

Researchers at the University of Houston are developing a technique to kill bacteria using **gold nanoparticles and infrared light**. This method may lead to improved cleaning of instruments in hospital settings.

Researchers at the University of Colorado Boulder are investigating the use of **quantum dots** to treat antibiotic resistant infections.

Researchers at the University of New South Wales are investigating the use of **polymer coated iron oxide nanoparticles** to treat chronic bacterial infections.

One of the earliest nanomedicine applications was the use of **nanocrystalline silver** which is as an antimicrobial agent for the treatment of wounds, as discussed on the **Nucryst Pharmaceuticals Corporation** website.

A nanoparticle cream has been shown to fight staph infections. The **nanoparticles contain nitric oxide gas**, which is known to kill bacteria. Studies on mice have shown that using the nanoparticle cream to release nitric oxide gas at the site of staph abscesses significantly reduced the infection.

Burn dressing that is coated with **nanocapsules containing antibotics**. If a infection starts the harmful bacteria in the wound causes the nanocapsules to break open, releasing the antibiotics. This allows much quicker treatment of an infection and reduces the number of times a dressing has to be changed.

A welcome idea in the early study stages is the **elimination of bacterial infections** in a patient within minutes, instead of delivering treatment with antibiotics over a period of weeks. You can read about design analysis for the antimicrobial nanorobot used in such treatments in the following article: **Microbivores: Artifical Mechanical Phagocytes using Digest and Discharge Protocol**.

## 10.5. Nanotechnology in Medicine Application: Cell Repair

Nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes. Read about design analysis for one such cell repair nanorobot in this article: ***The Ideal Gene Delivery Vector: Chromallocytes, Cell Repair Nanorobots for Chromosome Repair Therapy***

# Chapter 11

## 11. Nanotechnology in Manufacturing

Various manufacturers are using nanotechnology to make products with improved capabilities or to reduce their manufacturing cost. This page provides examples of how nanotechnology is helping manufacturers today.

A technique called **laser shock imprinting** that forms nanoscale metallic shapes such as gears has been demonstrated by researchers at Prudue University.

Researchers at Northwestern University have developed a **desktop nanofabrication tool**. The desktop tool uses beam-pen lithography arrays to create nanoscale structures.

Researchers at the University of Pennsylvania have developed a technique to make AFM tips from diamond. The **nanoscale diamond tips** last much longer than AFM tips made of silicon and the researchers envision these tips being used to etch or deposit material in nano-manufacturing processes.

MesoCoat has developed a nanocomposite coating called CermaClad™ that can be applied to pipes used in the oil industry pipes to provide resistance to corrosion. The **process for applying the nanocomposite** is faster and can be done at a lower temperature than is possible using conventional methods. The result is the production of lower cost pipes with equivalent corrosion resistance.

Researchers at Rice University have demonstrated that atomically thin sheets of boron nitride can be used as a **coating to prevent oxidation**. They believe this coating could be used for coating parts that need to be light weight, but work in harsh environments, such as jet engines.

ArcelorMital is producing a kind of steel that contains nanoparticles. This material allows them to make thinner gauge, lighter beams and plates. These steel beams and plates are about same weight as aluminum but can be produced a lower cost. ArcelorMital is marketing this light weight steel to **car manufacturers**.

Researchers have produced yarn from **carbon nanotubes coated with diamond**. They believe this material can be used in thin saw blades that reduce the waste produced when cutting high cost material, such as sawing silicon ingots into wafers for the semiconductor or solar industries.

IMEC and Nantero are developing a **memory chip that uses carbon nanotubes**. This memory is labeled NRAM for Nanotube-Based Nonvolatile Random Access Memory and is intended to be used in place of high density Flash memory chips.

Nanosolar is building solar cells using **semiconductor nanoparticles** applied in a low temperature printing process. This process results in lower cost solar cells than conventional high temperature manufacturing processes.

Hewett Packard is working with Hynix Semiconductor to bring a memory device, called a memristor to production. Memristors uses nanowires coated with titanium dioxide and are projected to have better memory density than flash memory.

Intel is producing integrated circuits with feature sizes as small as 22 nm. This process allows Intel to build more computing power into each chip.

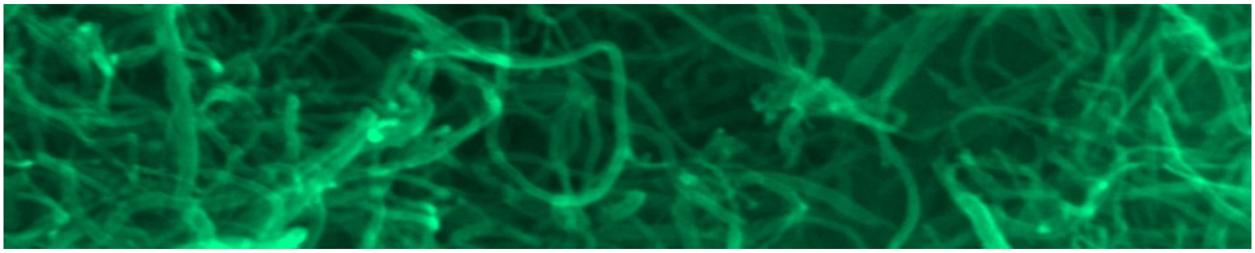
St. Croix uses an epoxy resin called NSi that contains **silica nanoparticles** in making fishing rods that are stronger than rods made with conventional material; but just as lightweight.

Yonex uses a resin containing Buckyballs (Fullerenes) to make lightweight badminton racquets with greater hitting power and stability.

Taking the longer view researchers are working on developing a method called molecular manufacturing that may someday make the Star Trek replicator a reality. The gadget these folks envision is called a molecular fabricator; this device would use tiny manipulators to position atoms and molecules to build an object as complex as a desktop computer. As **shown in this video**, researchers believe that raw materials can be used to reproduce almost any inanimate object using this method.

By building an object atom by atom or molecule by molecule, molecular manufacturing, also called molecular nanotechnology, can produce new materials with improved performance over existing materials. For example, an airplane strut must be very strong, but also lightweight. A **molecular fabricator** could build the strut atom by atom out of carbon, making a lightweight material that is stronger than a diamond. Remember that a diamond is merely a lattice of carbon atoms held together by bonds between the atoms. By placing carbon atoms, one after the other, in the shape of the strut, such a fabricator could create a diamond-like material that is lightweight and stronger than any metal.

Compiled by Earl Boysen of Hawk's Perch Technical Writing, LLC and UnderstandingNano.com. You can find him on **Google+**.



# Chapter 12

## 12. Chapter: Nanocellulose

Nanocellulose is another crystalline nanomaterial that is a light solid substance. Usually obtained from plant matter which comprises of nanosized cellulose fibrils. Cellulose is a linear polymer of glucose and is the most abundant biopolymer on Earth. This new material is a pseudo-plastic and possesses the property of specific kinds of fluids or gels that are generally thick in normal conditions. The lateral dimensions of nanocellulose range from 5 to 20 nm, and the longitudinal dimension ranges from a few 10's of nanometers to several microns.

Nanocellulose is a class of renewable nanoscale material from natural origins that has been the subject of increasing research and development (R&D) activities in many countries around the world. Current R&D in industry, academia and government laboratories suggests that it has a broad range of application potential in products and industries such as paper, building materials, polymer composites, medical, defense, electronics, automobile and aircrafts. By most accounts, nanocellulose-based products will be available in commercial quantities within five years.

Nanocellulose, originating from flora and fauna, provides a key materials platform for the sustainable production of renewable, recyclable, and environmentally preferable goods and products to meet the needs of people on a global scale. For example, these materials will allow 1) the production of improved strength to weight performance materials and thus allow light-weight products to be produced without sacrificing end use performance; 2) new generations of light-weight, hyper-performance nano-enabled structural and non-structural smart composites with unique multifunctional properties tailored to end-use requirements; 3) unique optical, electrical and mechanical characteristics of nanocellulose will enable a new generation of high performance electro-optical materials and products.

As nanocellulose can be easily dispersed in a variety of media, the processing of such additives will be considerably more facile than other nanomaterials, particularly the spectrum of carbon nanotubes that tend to aggregate or agglomerate. The immediate challenge is to develop production facilities so that the various domains of possible application can be explored. Building on initial developmental research, the mid-term effort will most probably be focused on functionalized materials that will be tailored to the material media to be enhanced. The potential of nanocellulose in such applications is very large and will likely lead to large market potential. This will in turn emphasize the need for recognized international standards to facilitate the commercial transactions that will underpin the realization of that potential.

The following content collected from: Lucie Bacakova, Julia Pajorova, Marketa Bacakova, Anne Skogberg, Pasi Kallio, Katerina Kolarova and Vaclav Svorcik, "Versatile Application of Nanocellulose: From Industry to Skin Tissue Engineering and Wound Healing," Nanomaterials, 2019, 9, 164; doi:10.3390/nano9020164.

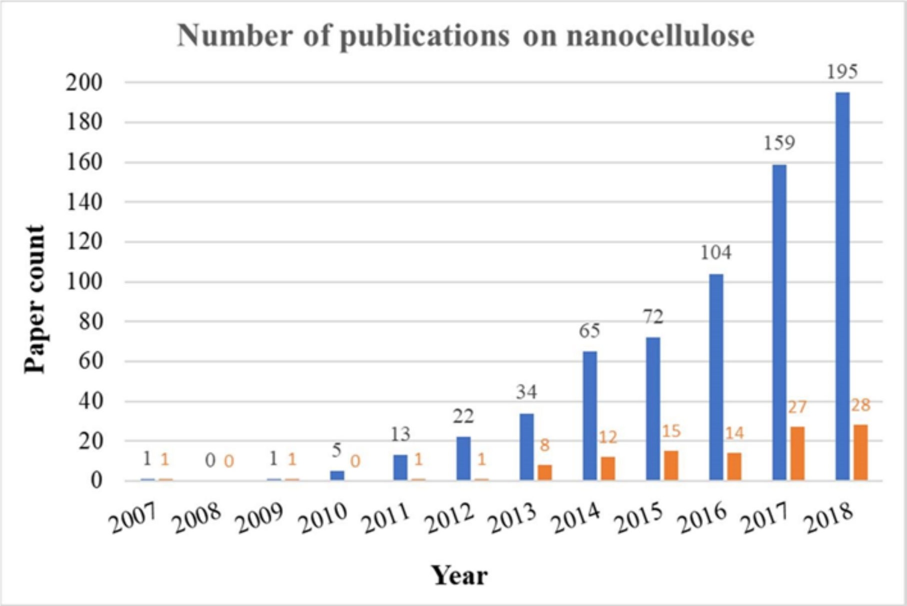


*Figure 27. The number of publications on nanocellulose found in the PubMed database from 2007 to 2018 using the search term "nanocellulose". Blue columns: total number of papers, orange columns: papers on cell-material interaction, tissue engineering and wound healing.*

## 12.1. Types of nanocellulose

| **Nanocellulose structures** | **Example** | **Dimensions** | **Reference** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Nanofibrils | In bacterial cellulose | Diameter from 70 to 140 nm, length in µm | [2] |
| | In wood-derived cellulose | Diameter 3–5 nm, length several µm, form 20–50 nm thick aggregates | [18,19] |
| Nanofibers | Created by electrospinning | Cellulose acetate: average diameter about 400 nm | [20] |
| | | Bacterial cellulose (33 wt. %) with chitosan: diameters from 80 nm to 170 nm | [21] |
| | Isolated from pineapple | Width 6.4 ± 4.6 nm, length in µm | [12] |
| Nanowhiskers | Kenaf bast | Diameter 10-15 nm, length hundreds nm | [22] |
| | Bacterial cellulose | Diameter 10–100 nm, length 100–1000 nm | [23] |
| Nanocrystals | Cotton-derived | Mean width 7.3 nm, mean length 135 nm | [24] |
| Nanorods | Grass-derived | Width 15 ± 3 nm, length 120 ± 15 nm | [16] |
| Nanoplatelets | Agave-derived | Thickness 80 nm, other dimensions in µm | [17] |

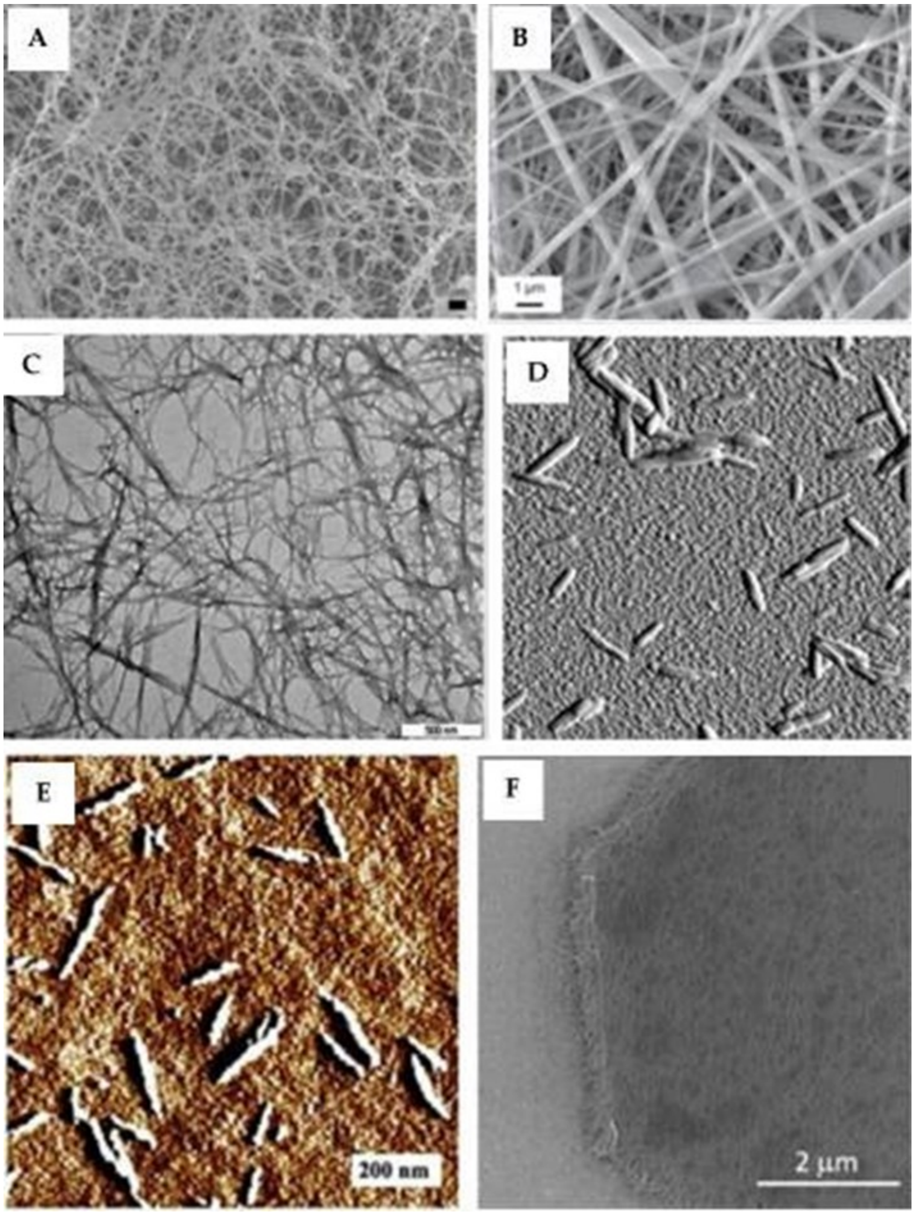


*Figure 28. Examples of various forms of nanocellulose. [*
*A: Bacterial cellulose nanofibrils synthesized by Acetobacter xylinum subsp. Sucrofermentas BPR2001 [1];*
*B: Nanofibers created by electrospinning of cellulose acetate [20];*
*C: Cellulose nanowhiskers obtained from kenaf bast, AFM image [22];*
*D: Cellulose nanocrystals obtained from cotton, AFM image 1x1 µm [24];*
*E: Cellulose nanorods in a monolayer generated from a colloidal suspension with a concentration of 0.1 wt.%, AFM image [16];*
*F: Detail of a nanoplatelet 80 nm in thickness and containing cellulose nanofibrils approx. 14 nm in diameter, SEM image [17].*

## 12.2. Properties of Nanocellulose

The following properties of nanocellulose are important:

- Lightweight
- Stiffer than Kevlar®
- Electrically conductive
- Non-toxic
- The crystalline form is transparent, and gas impermeable
- It can be produced in large quantities in a cost-effective manner
- It has a very high tensile strength - 8 times that of steel
- It is highly absorbent when used as a basis for aerogels or foams.
- The raw material - cellulose - is the most abundant polymer on earth

## 12.3. Applications of Nanocellulose

Nanocellulose has a wide range of applications, from cleaning of oil spills to usage in children's toys. Nanocellulose can be used in pharmaceutical, food and medical industries. This new material can also replace some petrochemical-based products and is very likely to be cheaper than most other kinds of high-performance nanoscale materials.

### 12.3.1. Ultimate Body Armor

Because nanocellulose is made from a tightly packed array of needle-like crystals, it's incredibly tough stuff. In fact, it has a strength-to-weight ratio that's eight times higher than stainless steel, which makes it perfect for building future body armor that's both strong and light. Because nanocellulose is transparent, light and strong, it can be used in place of plastic or glass. That's why Pioneer Electronics is experimenting with it to make some of the most insanely thin—and flexible—screens of the future.

## 12.4. High-Volume Applications

*Automotive—Body Components*: Because cellulose nanomaterials are inexpensive relative to other composite reinforcement fibers, it should be possible to use them in wide-scale structural applications.[8] In the near term, the most likely adoption will be in applications already using composite materials. CNF can be used as stable, extremely reactive raw materials for technical applications. It offers the added advantages of being renewable, biologically produced, and biodegradable. Applications include reinforcing biopolymers to create promising, environmentally safe, and lightweight construction material for the automotive industry.

*Automotive—Interiors*: CNC has been incorporated in polyethylene, polypropylene, and biopolymers, where it enhances mechanical and barrier properties, as well as abrasion resistance. CNC is envisioned as improving prospects for using bioplastics in interior automotive parts.[9] Further, the ability to create aerogels and structural foams can create lightweight decorative and interior panels such as dashboards and door panels.

*Construction—Cement and Pre-stressed and Pre-cast Concrete:* Concrete can be reinforced with a combination of cellulose nanomaterials and micro-cellulose fibrils to increase the toughness of an otherwise brittle material.[10] These fibers could provide the benefit of other micron-sized and nanofibril reinforcement systems at a fraction of the cost. The addition of up to 3% micro- and nanofibrils in combination increases the fracture energy by more than 50% relative to the unreinforced material, with little change in processing procedure. Benefits include reducing the amount of cement needed, which will lower material and labor costs and results in reduction in associated carbon emissions.

*Packaging—Fiber/Plastic Replacement*: Cellulose nanomaterial-based foams are being studied for packaging applications to replace polystyrene-based foams.[11] The advantage of using cellulose nanomaterials instead of wood-based pulp fibers is that the CNF can reinforce the thin cells in the starch foam, replacing a polymer produced from fossil fuel with a renewable material that decreases weight.

*Packaging Film*: The mechanical and optical properties of cellulose nanomaterials make them a promising material for reinforcing plastics. Cellulose nanomaterials have been reported to improve the performance of, for example, thermosetting resins, starch-based matrices, soy protein, rubber latex, and poly(lactide).[12] Such applications may be used as coatings, films, paints, foams, and packaging.

*Personal Care—Hygiene and Absorbent Products*: The super-absorbency of cellulose nanomaterials makes them an ideal biodegradable water-retention filler in incontinence pads and diapers.[13] There is likely to be high demand for lighter, thinner, and natural-product alternatives in this market.

*Textiles—Clothing*: Cellulose has long been used to make textiles. For example, rayon is made from pulp or cellulose. Recently, scientists have developed a highly processed form of cellulose nanomaterials that, once mass-produced, will provide stronger, lighter, more durable textile materials from which to make clothing.[14] The development of electrospinning techniques that produce continuous fibers can be used to develop cellulose nanomaterial composite fabrics.[15] The movement toward more natural materials from textiles creates a consumer driver, and biodegradability decreases the burden of textiles in the waste stream.

## 12.5. Nanocellulose in biotechnology and medicine

### 12.5.1. Industrial and (bio)technological applications of nanocellulose

| Application | Specification | Example | Reference |
|---|---|---|---|
| **Adsorption** | Air purification | Odor removal (in combination with zeolites) | [93] |
| | Removal of pollutants from aqueous solutions | Heavy metal ions ($Cu^{2+}$, $Pb^{2+}$, $Hg^{2+}$) | [79,94] |
| | | Toxic dyes (methylene blue, Congo Red) | [30,95] |
| | | Mefenamic acid (a nonsteroidal anti-inflammatory drug, a potential endocrine disruptor) | [96] |
| | | Oily substances | [31,84] |

| | | | |
|---|---|---|---|
| | | Insecticides (neonicotinoids in milk) | [97] |
| | Immobilization of atoms and (bio) molecules | Metal catalysts (copper) | [98] |
| | | Proteins (bovine serum albumin, lysozyme, γ-globulin, and human IgG | [77] |
| | | Enzymes (trypsin, laccase, lysozyme, lipase) | [61,99–101] |
| | | Ingested lipids (obesity management) | [102] |
| | | DNA oligomers | [103] |
| **(Ultra)filtration** | Removal of toxic dyes | Methylene blue, methylene orange, rhodamine | [104] |
| | Hemodialysis membranes | Nanofibrillated cellulose with polypyrrole | [105] |
| | Removal of viruses | Swine influenza virus | [74] |
| | | Murine leukemia virus | [106] |
| | | Bacteriophages | [78] |
| **Packaging** | Food, sensitive devices | Self-standing nanocellulose films from birch pulp | [25] |
| | | Paper sheets modified with nanocellulose and chitosan | [107] |
| **Conservation** | Historical papers, cotton canvas | Cellulose nanofibrils, carboxymethylated cellulose nanofibrils, cellulose nanocrystals | [108] |
| **Thermal applications** | Thermal insulators | Wood-derived nanofibrils with extremely low thermal conductivity | [109] |
| | Fire retardants | Wood-derived cellulose nanofibrils with silica nanoparticles | [110] |
| | | Wood-derived nanocellulose with montmorillonite clay | [59] |
| | Lithium batteries | Nanocellulose/polypyrrole | [111] |
| | | Nanocellulose/polyethylene | [112] |

| | | | |
|---|---|---|---|
| **Energy extraction and storage** | | Graphene/nanocellulose/silicon | [113] |
| | Solar cells/panels | Nanofibers from sisal with graphene oxide | [73] |
| | (Super)capacitors | Bacterial nanocellulose/carbon nanotubes/triblock-copolymer ion gels | [114] |
| | | Nanocellulose with polyaniline | [115] |
| **Acoustics** | Membranes for loudspeakers | Cellulose nanofibers with $Fe_3O_4$ nanoparticles | [71] |
| **(Bio)sensors** | Optical SERSbased | Detection of pesticides, dyes, bacteria | [116,117] |
| | Optical fluorescencebased | Detection of heavy metals | [118] |
| | | Detection of thiols | [119] |
| | | Detection of elastase | [120] |
| | Chemical | Detection of vapors ($NH_3.H_2O$, $H_2O$, HCl, acetic acid) | [16] |
| | Electrochemical | Detection of cations in biological fluids ($Na^+$, $K^+$, $Ca^{2+}$) | [38] |
| | | Detection of cholesterol | [121] |
| | | Detection of avian leukosis virus | [122] |
| | Piezoelectric | Based on bacterial cellulose | [123] |
| | | Based on plant-derived cellulose nanofibrils | [124] |
| | | Based on nanocellulose with chitosan | [125] |
| | | Tactile sensor (simultaneous sensing of temperature and pressure) | [126] |
| | | Strain-sensing protonated aerogels from cellulose nanofibrils | [127] |
| **Drug delivery** | Peroral | Paracetamol | [49] |
| | | Ibuprofen (colonic release) | [70] |
| | | Methotrexate (colonic release) | [128] |
| | Transdermal | Analgesics, antiphlogistics, corticoids, antihypertensives | [50,51] |
| | | Diclophenac | [129] |
| | | Propranolol | [130] |
| | Topical | Local anesthetics | [131] |
| | | Antiseptics | [132,133] |
| | | Antibiotics (gentamycin, ceftriaxone) | [33,43] |
| | | Antibacterial peptides | [134] |

| | | | |
|---|---|---|---|
| | | Other antimicrobial, antiinflammatory and antitumor drugs | [135,136] |

### 12.5.2. Recent use of nanocellulose in tissue engineering and tissue repair

In the last five years, i.e. **from 2014 to 2018**, the use of nanocellulose in tissue engineering and related areas, such as wound healing and cell-material interaction, has been further developed, although the proportion of these studies in the PubMed database did not exceed the value from 2013, and ranged approx. between 13% and 21%. This was due to the rapid concurrent development of applications of nanocellulose in industry and technology, including various biotechnologies, such as biosensing and controlled drug delivery (**Table 2**; for a review, see [83,157–162]. Nevertheless, research on the potential use of nanocellulose in neural tissue engineering, cartilage tissue engineering and skin wound dressings, as mentioned above, continued with several promising achievements.

*In neural tissue engineering*, it was demonstrated for the first time that SH-SY5Y neuroblastoma cells, cultured on three-dimensional (3D) bacterial nanocellulose (BNC) scaffolds, not only adhered and proliferated, but also differentiated toward mature neurons, as indicated by functional action potentials detected by electrophysiological recordings [163]. The adhesion, proliferation and formation of 3D neuronal networks on 3D BNC scaffolds can be further enhanced by cationic modification of this material, i.e. on trimethyl ammonium betahydroxy propyl cellulose, as demonstrated on PC12 cells, a widely-used model of neurons [164]. In addition to their potential use in neural tissue replacements, nanocellulose-based neural tissue-engineered constructs were designed as innovative tools for brain studies. For this purpose, an ink that contained wood-derived cellulose nanofibrils and carbon nanotubes was used for 3D printing of electrically-conductive scaffolds, which promoted the adhesion, growth and differentiation (manifested by elongation of neurites) of human SHY5Y human neuroblastoma cells [165].

*In cartilage tissue engineering*, the high water-retention capacity and the high mechanical strength of cellulose nanofibrils have led to the further development of applications of bacterial nanocellulose for *auricular cartilage* reconstruction. It was found that BNC with an increased cellulose content of 17% is a promising non-resorbable biomaterial for auricular cartilage tissue engineering, due to its similarity with auricular cartilage in terms of mechanical strength and host tissue response [2]. Other promising materials for this application were bilayered scaffolds composed of BNC and alginate, which were non-cytototoxic, non-pyrogenic and promoted the growth of human nasoseptal chondrocytes [166]. For *articular cartilage* engineering, BNC scaffolds modified by laser perforation were used as substrates for the cultivation of human chondrocytes derived from the cartilage covering femoral condyles. These novel scaffolds improved the diffusion of nutrients, the ingrowth and differentiation of chondrocytes, and the deposition of their newly synthesized extracellular matrix within the scaffolds [41]. A further novelty was the application of nanocellulose-based bioink in 3D bioprinting with living cells. A bioink consisting of wood-derived nanofibrillated cellulose and alginate, and containing human articular chondrocytes, was used for 3D printing of anatomicallyshaped cartilage structures, such as a human ear and sheep meniscus [167]. A similar bioink was used for 3D printing together with irradiated human chondrocytes and induced pluripotent stem cells (iPSC), both derived from articular cartilage [168]. An alginate sulfate/BNC bioink promoted spreading, proliferation, and collagen II synthesis in bovine chondrocytes from femoral condyle cartilage [169]. Another interesting composite material developed for cartilage tissue engineering was a double cross-linked interpenetrating polymer network of sodium alginate and gelatin hydrogels, reinforced with 50 wt% cellulose nanocrystals [170]. Nanocellulose is also promising for the treatment of intervertebral disc degeneration. Gellan gum hydrogels reinforced with cellulose nanocrystals were designed as substrates for regenerating the annulus fibrosus, i.e. the outer part of the discs [171].

From 2014 to 2018, nanocellulose has been increasingly applied in other interesting areas of experimental tissue engineering, namely in liver tissue engineering, adipose tissue engineering, vascular tissue engineering, bone tissue engineering and bone implant coating, and in reconstruction of the urethra and the *dura mater*.

*In liver tissue engineering*, the first idea was to create a 3D culture of hepatic cells, which is more physiologically relevant than the two-dimensional (2D) culture that is traditionally used to predict and estimate the metabolism, excretion and toxicity of drugs and other chemicals in the human liver. For this purpose, 3D scaffolds based on birchwood-derived nanofibrillar cellulose were generated. These scaffolds promoted differentiation and proper functioning of human liver progenitor cells of the line HepaRG, derived from a liver tumor of a female patient who was suffering from a hepatitis C virus infection and hepatocarcinoma. Specifically, the HepaRG cells formed 3D multicellular spheroids with apicobasal polarity and functional bile canaliculi-like structures. In addition, hepatobiliary drug transporters, i.e. MRP2 and MDR1, were localized on the canalicular membranes of the spheroids, and vectorial transport of fluorescent probes towards the biliary compartment was demonstrated. Cell culture in a 3D hydrogel supported the mRNA expression of hepatocyte markers (albumin and CYP3A4), and the metabolic activity of CYP3A4 in the HepaRG cell cultures [172].

*In adipose tissue engineering*, similarly, efforts were made to create a 3D *in vitro* model of adipose tissue for studies on adipose biology and on metabolic diseases, such as obesity and diabetes. For this purpose, 3D scaffolds were prepared by crosslinking homogenized bacterial nanocellulose fibrils using alginate and by freeze-drying the mixture to obtain a porous structure. When seeded with mesenchymal stem cells of the line C3H10T1/2, derived from mouse embryos and incubated in an adipogenic medium, the 3D scaffolds contained more cells with markers of adipogenic cell differentiation, i.e. growing in clusters and containing large lipid droplets, than 2D bacterial nanocellulose scaffolds. 3D scaffolds therefore have great potential not only for *in vitro* studies, but also for adipose tissue engineering, for reconstructive surgery after trauma, tumor removal or congenital defects [173]. A similar system was created in a study by Henriksson *et al.* [174] by 3D printing with the use of a bioink made of nanocellulose and hyaluronic acid, and containing adipocytes. The adipocytes showed uniform distribution throughout the scaffolds, high viability and more mature phenotype than the cells in conventional 2D culture systems.

*For vascular tissue engineering*, tubular structures were created from BNC using silicone tubes as molds. These tubes were also considered to have great potential for substituting other hollow organs, including the ureter and the esophagus [175]. In a study by Weber *et al*. [176], BNC tubes were used to replace the right carotid artery in sheep *in vivo*. After explantation, a histologic analysis revealed no acute signs of foreign body reaction, such as immigration of giant cells or some other acute inflammatory reaction, and therefore provided evidence for good biocompatibility of the tubes. However, the tubes were highly prone to thrombotic occlusion, and their implantation required antiplatelet therapy [176]. Another interesting idea was to use bacterial nanocellulose coupled with superparamagnetic iron oxide nanoparticles for coating endovascular stents, which will then attract vascular smooth muscle cells (VSMCs) for *in situ* reconstruction of the *tunica media* in blood vessels. In experiments *in vitro*, magnetic BNC coated with polyethylene glycol proved to form suitable scaffolds for porcine VSMCs, showing minimum cytotoxicity and supportive effects on cell viability and migration. This material also possessed suitable mechanical properties, and was considered to be promising for the treatment of brain vascular aneurysms [177,178]. Nanocellulose scaffolds were also applied for studies on vasculogenesis. BNC scaffolds functionalized with IKVAV peptide, i.e. a laminin-derived ligand for integrin adhesion receptors on cells, were used for studies on vasculogenic mimicry of human melanoma SK-MEL-28 cells, and appeared to provide a promising 3D platform for screening antitumor drugs [42].

BNC, even in its unmodified state, also showed a great promise for **bone tissue engineering**. BNC without additives stimulated the adhesion, multilayered growth and osteogenic differentiation of bone marrow mesenchymal stem cells (MSCs) derived from rat femur. As revealed by Second Harmonic Generation (SHG) imaging, the MSCs on BNC scaffolds produced a mature type of collagen I and showed activity of alkaline phosphatase [179]. Wood-derived nanofibrillated cellulose is also promising for the construction of scaffolds for bone tissue engineering, as proved on human MSCs grown on composite scaffolds containing this cellulose and chitin [180].

The performance of MSCs and other bone-forming cells, e.g. rat calvarial osteoblasts, on nanocellulose-based scaffolds can be further improved by biomimetic mineralization with calcium phosphates, such as hydroxyapatite and tricalcium phosphate [7,181,182]. In addition, these scaffolds can be coupled with collagen I or with osteogenic growth peptide [44]. Nanocellulose is also promising for **bone implant coating**. A hybrid coating, consisting of

45S5 bioactive glass individually wrapped and interconnected with fibrous cellulose nanocrystals (CNCs), was deposited on 316L stainless steel in order to strengthen bone-to-implant contact and to accelerate the bone healing process. This coating substantially accelerated the attachment, spreading, proliferation and differentiation of mouse MC3T3-E1 osteoblast progenitor cells *in vitro*, and also mineralization of the extracellular matrix deposited by these cells [183]. Similarly, coating 3D-printed polycaprolactone scaffolds with wood-derived hydrophilic cellulose nanofibrils enhanced the attachment, proliferation and osteogenic differentiation of human bone marrow-derived mesenchymal stem cells [27].

*Urethral reconstruction* was performed in a rabbit model using 3D porous bacterial cellulose scaffolds seeded with rabbit lingual keratinocytes [184], and in a dog model using smart bilayer scaffolds comprising a nanoporous network of bacterial cellulose and a microporous network of silk fibroin [185]. The bilayer scaffolds were pre-seeded with keratinocytes and smooth muscle cells isolated from dog lingual tissue obtained by biopsy. The nanoporous network provided good support for epithelial cells, while the microporous scaffolds supported the growth and penetration of smooth muscle cells [185].

For reconstruction of the ***dura mater***, bacterial cellulose membranes were tested as potential dural patches to prevent leakage of cerebrospinal fluid, which is a common complication after cranial and spinal surgery. These membranes supported the attachment and the viability of human dural fibroblasts [186].

Other interesting applications of nanocellulose have included connective tissue repair, repair of congenital heart defects, ophthalmologic applications, creation of protective barriers and cell transfection.

*For connective tissue repair*, softwood pulp-derived cellulose nanocrystals were injected into skin and tendon specimens, isolated from pigs and stretch-injured using a mechanical testing machine. This treatment mechanically reinforced these matrices, which was manifested by the increased elastic moduli and yield strength of the matrices. At the same time, the cellulose nanoparticles showed no cytotoxicity for rat primary patella tendon fibroblasts, as revealed by a WST-1 assay of the activity of mitochondrial enzymes. Moreover, the activity of mitochondrial enzymes in cells cultivated for 2-3 weeks in the presence of cellulose nanocrystals was significantly higher than in the control untreated cells [54].

*For the repair of congenital heart defects*, bacterial nanocellulose was used as a new patch material for closing ventricular septal defects in a pig model. This material could serve as an alternative to materials currently used in clinical practice, namely polyester, expanded polytetrafluoroethylene (ePTFE) and autologous or bovine pericardium, which are often associated with compliance mismatch and with a chronic inflammatory response [187].

*Ophthalmologic applications* of nanocellulose include the construction of contact lenses. For the construction of contact lenses, a highly transparent macroporous hydrogel was developed, consisting of poly(vinyl alcohol) reinforced with cellulose nanofibrils and containing more than 90% of water. The hydrogel exhibited high transparency with a refractive index close to that of water, very good UV-blocking properties and elastic collagen-like mechanical behavior typical for soft tissues [188].

*Creating protective barriers* involves designing materials that prevent intraperitoneal adhesions or immune rejection of transplanted cells. For example, in experimental abdominal defects in dogs, which were repaired using BNC membranes, negligible intraperitoneal adhesions were detected between the BNC and the intestinal loops in comparison with conventionally-used polypropylene meshes [47]. Modifying polypropylene meshes, and also metallic meshes, with BNC enhanced their potential applicability in hernioplasty and cranioplasty [189]. For immunoprotection of transplanted cells, a composite hydrogel consisting of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO)oxidized bacterial cellulose and sodium alginate was developed for encapsulation of cells, e.g. insulin-secreting β-cells of Langerhans islets [190]. A sophisticated nanocomposite membrane was developed for encapsulation of PC12 cells. One of the surfaces of bacterial cellulose (BC) pellicles was coated with collagen to enhance cell adhesion, and the opposite side of the BC pellicles was coated with alginate to protect the transplanted cells from immune rejection. The nanocomposite membrane was permeable to small molecules, i.e. dopamine secreted by the cells, but was impermeable to large molecules, such as IgG antibodies [191].

An interesting finding was that nanocellulose can also modulate **the efficiency of cell transfection** by its structure and electrical charge density. Nanofibrillated cellulose was prepared from birch kraft pulp in the form of films or hydrogels with low or high charge density. The films with low charge density showed a more pronounced increase in the efficiency of transfection of HeLa cells with DNA constructs, encoding the Red Fluorescent Protein, than the films with high charge density and hydrogels with both low and high charge densities [53].

The following part of this review is focused on the use of nanocellulose for skin tissue engineering and wound healing.

### 12.5.3. Nanocellulose in skin tissue engineering

#### *Bacterial nanocellulose in skin tissue engineering*

Skin tissue engineering involves reconstructing two main layers of the skin, namely the epidermis, i.e. the superficial skin layer formed mainly by keratinocytes, and the dermis, i.e. the skin inner layer formed mainly by fibroblasts. Due to its certain resemblance to natural soft tissues, including skin, bacterial cellulose is the most widely used type of nanocellulose for reconstructing these layers [192]. In fact, bacterial cellulose is a hydrogel containing nanofibrils, which mimics the fibrillar component of natural extracellular matrix. Bacterial cellulose has a great capacity to retain moisture, and it also has appropriate mechanical properties, such as strength, Young's modulus, elasticity and conformability [11,21,193]. The use of bacterial cellulose in skin reconstruction started long before the first appearance of the word "nanocellulose" in the PubMed database. It was simply called "bacterial cellulose", though it is a hydrogel containing cellulose nanofibrils. The first report of the use of bacterial cellulose in skin wound therapy came from 1990, when bacterial cellulose pellicles were proposed as "temporary skin substitutes" for treating burns, ulcers, abrasions and other skin injuries [194]. In 2006, thin films of bacterial cellulose were used as substrates for the cultivation of human transformed skin keratinocyte and human normal skin fibroblast cell lines. The films supported spreading, growth and migration in keratinocytes but not in fibroblasts, which formed clusters and detached from the films. This phenomenon was explained by relatively weak cell-material adhesion in comparison with the relatively strong cell-cell adhesion in fibroblasts, which generates a contractile force [195]. However, in a study by Kingkaew *et al*. [196], bacterial cellulose films proved to be good substrates for the adhesion, spreading and growth of both human skin keratinocytes and fibroblasts. Similarly, a surface-structured 3D network of bacterial cellulose nanofibers also provided good support for human keratinocytes and fibroblasts and stimulated the healing of experimental skin wounds in mice [10].

The adhesion and growth of skin cells on bacterial cellulose can be further improved by combining it with other biologically active molecules. For example, the adhesion of human keratinocytes on bacterial cellulose films was improved by enriching these films with chitosan [196]. Incorporation of keratin, isolated from human hair, into bacterial cellulose improved the attachment, proliferation and morphology of human skin keratinocytes of the HS2 cell line and human skin fibroblasts of the Detroit 562 cell line [197]. Composite scaffolds made of microporous regenerated bacterial cellulose and gelatin provided good support for the adhesion and proliferation of human keratinocytes of the HaCaT line, and for their penetration into the scaffolds (to a depth of 300 µm). In experiments *in vivo* performed in mice, scaffolds with gelatin showed greater wound closure efficacy (93%) than pure bacterial cellulose (63%) [198]. Electroactive composites of bacterial cellulose and conducting polymers, such as polypyrrole and polyaniline, also hold promise for skin tissue engineering [199].

The potential use of bacterial cellulose in skin regeneration and in other areas of tissue engineering has been reviewed by many authors, e.g. [9,37,40,158,193,200–202]. Novel microporous 3D scaffolds with controllable pore size were prepared from bacterial nanocellulose using paraffin microspheres. These scaffolds supported the proliferation of mouse embryonic NIH 3T3 fibroblasts, and were considered to be promising for soft tissue engineering [34].

### *Plant- and algae-derived nanocellulose in skin tissue engineering*

Like bacterial nanocellulose, plant-derived nanocellulose has repeatedly been shown to be promising for skin tissue engineering, especially after its physical and chemical properties have been modified. For example, CNFs were modified either by introducing a negative electrical charge using TEMPO-mediated oxidation, or by introducing a positive charge using glycidyltrimethylammonium chloride (EPTMAC) [203–205]. In a study by Skogberg *et al.* [203], unmodified (u-), anionic (a-), and cationic (c-) cellulose nanofibrils (CNFs), derived from hardwood kraft pulp (u-, c-CNF) or from softwood kraft pulp (a-CNF) were fabricated using an evaporation-induced droplet-casting method on glass. Atomic force microscopy showed a significantly higher degree of orientation of nanofibers along a single line on c- and u-CNF surfaces than on a-CNF surfaces. Both a-CNF and c-CNF surfaces supported the adhesion, spreading, viability and proliferation of mouse embryonic fibroblasts, though the cell performance was better on a-CNF. However, the cells on aligned c-CNF surfaces showed orientation in parallel, which could be utilized for guided cell growth. Recently, transferrable free-standing nanocellulose films have also been produced with a similar alignment of CNFs in parallel to an evaporating liquid boundary line during evaporation [206]. When an electrical charge is introduced into nanocellulose, it can be functionalized with various biomolecules, e.g. cell adhesion peptides [204] and silk fibroin [205], which improves the capacity of nanocellulose for colonization with cells and for wound healing.

In our recent experiments in collaboration with Skogberg and her colleagues, human dermal fibroblasts were cultured on cellulose meshes in a DMEM medium with 10% of fetal bovine serum and 40 μg/ml of gentamycin. Two different types of nanocellulose solutions, i.e. c-CNF, a-CNF, were applied on the surface of a cellulose mesh (obtained from Holzbecher Ltd., Czech Republic) in order to cover its microfibrous structure. Both c-CNF and a-CNF were expected to improve the surface properties of the cellulose mesh for cell adhesion and proliferation. A 0.15 wt% c-CNF solution formed a thin film on the surface of the cellulose meshes, while the 0.15 wt% a-CNF solution covered individual cellulose microfibers and filled the wide spaces between them. This may be due to a lower degree of fibrillation of c-CNF in comparison with a-CNF, which results in a solution with larger fibers in the case of c-CNF. Larger c-CNF fibers cannot penetrate into the pores of the cellulose mesh. They cumulate on the top of the mesh and form a film-like structure there. However, the smaller aCNF fibers can leak in to the pores of the cellulose mesh. Our results have shown positive effects of both types of CNF coverings on the adhesion and proliferation of dermal fibroblasts. However, we observed that a-CNF was more suitable for adhesion and growth of dermal fibroblasts than c-CNF, on which the cells were often round, less spread and proliferated relatively slowly. The morphology of human dermal fibroblasts was more physiological on a-CNF than on c-CNF. The cells on a-CNF adhered along the cellulose fibers, spread between them and formed a better-developed filamentous actin (F-actin) cytoskeleton (**Figure 30**).

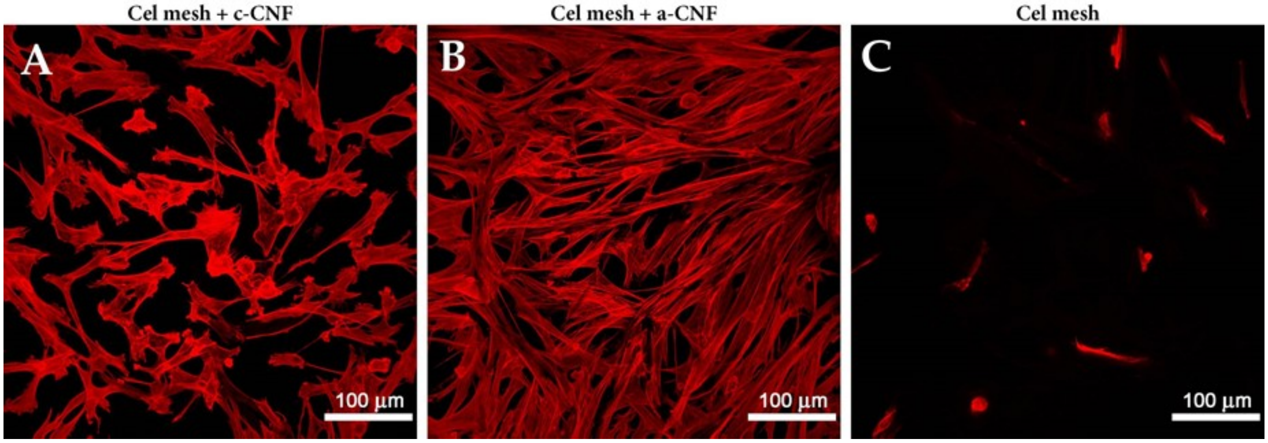


*Figure 29. Morphology of human dermal fibroblasts on day 4 after seeding on a cellulose mesh modified with cationic cellulose nanofibers (A), with anionic cellulose nanofibers (B), and on pristine cellulose mesh (C).*

Other chemical modifications of plant nanocellulose intended for skin tissue engineering include converting it to cellulose acetate or to hydroxyethyl cellulose. Conversion to cellulose acetate is known to enhance the electrospinnability of cellulose, as was demonstrated in cellulose extracted from sugar cane bagasse, and the electrospun fibrous scaffolds then supported the adhesion and growth of mouse subcutaneous fibroblasts of the line L929. The cell behavior was further improved by blending the cellulose with poly (L-lactide) or with polydioxanone [66]. Three-dimensional cellulose acetate scaffolds, produced by an electrohydrodynamic direct jet process called spinprinting, stimulated the adhesion and metabolic activity of human dermal fibroblasts to a greater extent than polycaprolactone scaffolds with a similar fibrous morphology and pore geometry [207]. Blending cellulose acetate with gelatin can modulate its applicability for skin tissue engineering or for wound dressing. The scaffolds with a lower content of cellulose acetate and a higher content of gelatin (ratio 25:75) promoted high proliferation activity of human dermal fibroblasts and adhered to a wound, showing that they were promising for skin tissue engineering. By contrast, the scaffolds with a higher content of cellulose acetate and a lower content of gelatin (ratio 75:25) appeared to be suitable for low-adherent wound dressings [208]. Other cellulose acetate-based scaffolds with potential for skin tissue engineering include composite 3D electrospun cellulose acetate/pullulan scaffolds, which promoted the adhesion and growth of mouse L929 fibroblasts [209], and composite biomimetic nanofibrous gelatin/cellulose acetate/elastin scaffolds, which promoted the adhesion and growth of human gingival fibroblasts [210]. Nanofibrous scaffolds prepared by rotary jet spinning from cellulose acetate and soy protein hydrolysate are another promising material. *In vitro*, these scaffolds promoted the migration and proliferation of dermal fibroblasts, their infiltration inside the scaffolds and their expression of $\beta_1$-integrin adhesion receptors. *In vivo*, these scaffolds accelerated re-epithelialization and epidermal thinning, and also reduced scar formation and collagen anisotropy [211].

Hydroxyethyl cellulose is another modification of cellulose that can be used for creating nanostructures. This modification of cellulose is water-soluble and, like cellulose acetate, it can be used for electrospinning of nanofibrous scaffolds. Nanofibrous scaffolds made of hydroxyethyl cellulose blended with poly(vinyl alcohol) supported the adhesion and growth of human skin fibroblasts [212]. The behaviour of the fibroblasts was further improved by adding collagen into the blend, and the antimicrobial activity of the scaffolds was established by adding silver nanoparticles without a considerable increase in the cytotoxicity of the scaffold for the fibroblasts [213].

Plant-derived nanocellulose in the form of nanocrystals can be used advantageously for reinforcing materials typically used for tissue engineering, such as degradable natural and synthetic polymers, which are relatively weak. Cellulose nanocrystals (CNCs) are produced by acid hydrolysis of cellulose fibers, employing either sulfuric acid or hydrochloric acid. Due to their structural defects, CNCs have a very large elasticity modulus (about 130 GPa), which is similar to that of Kevlar, and they have high strength (about 7 GPa). In addition, CNCs have low extension to break, high aspect ratios, high surface areas, high crystallinity, and apparent biocompatibility [13,70]. CNCs were used to reinforce collagen films, and these composites, also supporting the viability of mouse embryonic 3T3 fibroblasts, were promising for skin tissue engineering [13]. In another study, cotton-derived cellulose nanocrystals were electrospun together with poly(lactic-*co*-glycolic acid) (PLGA). The resulting scaffolds improved the adhesion, spreading and proliferation of 3T3 fibroblasts in comparison with neat PLGA nanofiber membranes [214].

Nanocellulose derived from *Cladophora* algae can also be improved for tissue engineering purposes by physicochemical modifications. The adhesion and spreading of human dermal fibroblasts were relatively poor on unmodified *Cladophora* nanocellulose films, but they increased on nanocellulose carboxylated by electrochemical TEMPO-mediated oxidation. This increase was proportional to the degree of oxidation of the material [75].

### *Limitations of the use of nanocellulose in skin tissue engineering*

In spite of all the encouraging results mentioned above, the use of nanocellulose (and cellulose in general) in skin tissue engineering is limited by its non-degradability in the human organism. The retention of non-degradable material in skin could induce scar formation. Degradability of cellulose can be induced by incorporating cellulase enzymes, as demonstrated in bacterial cellulose [215], especially in conjunction of these enzymes with β-glucosidase [216]. Degradable cellulose can also be created by introducing N-acetylglucosamine residues into the cellulose molecule during its synthesis by metabolically engineered *Gluconacetobacter xylinus*. These residues then render the cellulose molecules susceptible to degradation by lysozyme, an enzyme that is widespread in the human body [217,218]. Another approach for rendering cellulose-based scaffolds degradable, at least partially, is oxidation. Oxidized acetyl cellulose sponges, implanted subcutaneously into rats *in vivo*, showed degradation of 47% of their dry mass after 60 weeks, while in ethyl cellulose the proportion was only 18% [219]. Regenerated cellulose (methylolcellulose) and 2,3-dialdehydecellulose (DAC) have also been considered as degradable, although only at a slow rate. In addition, DAC membranes supported adhesion, growth and extracellular matrix formation in human neonatal skin fibroblasts cultured on these materials [220]. Last but not least, cellulose derived from *Styela clava* tunics is also slowly degradable. After subcutaneous implantation into rats for 90 days, the weight loss was greater in cellulose films from *Styela clava* (almost 24% of their initial weight) than in films prepared from wood pulp cellulose (less than 10%) [80].

### 12.5.4. Nanocellulose as a carrier for cell delivery into skin defects

Although there has been only limited direct use of cellulosic materials, including nanocellulose, in skin tissue engineering, these materials, even in their non-degradable forms, can be used indirectly for skin tissue engineering, i.e. as carriers for delivering cells into wounds. After the cells have adhered to the wound bed, they can be released from the scaffolds, and the scaffolds can be removed. Experiments *in vitro*, performed on a bacterial cellulose/acrylic acid (BC/AA) hydrogel colonized by epidermal keratinocytes (EK) and dermal fibroblasts (DF), showed that from day 1 to day 3 after seeding on BC/AA, about 63% of EK and 69% of DF were cumulatively transferred from BC/AA on to an ovine collagen hydrogel [192]. Experiments *in vivo* performed in mice showed that BC/AA hydrogels loaded with cells produced the greatest acceleration on burn wound healing, followed by treatment with hydrogel alone, and by the untreated group. On day 13 after wound coverage, the percentage of wound reduction for the hydrogel loaded with cells, for the pure hydrogel and for the control untreated group of animals were about 77%, 72% and 65%, respectively. The transferred cells are believed to assist in initiating the wound healing process, where the fibroblasts play a role in forming the granulation tissue and the keratinocytes help in re-epithelialization [221]. Wound healing can also be accelerated by transferring mesenchymal stem cells, seeded on nanocellulose-based carriers, into the damaged skin. For example, membranes of bacterial cellulose with gellan gum, incorporated with the antifungal drug fluconazole, were developed for delivery of human adiposederived mesenchymal stem cells (ASCs), obtained by liposuction. The membranes with ASCs were applied for covering second-degree burn wounds produced in rats. Fluorescence staining with FITC and DAPI proved that the ASCs were transferred into the wounds. The transferred ASCs can improve wound healing not only directly, by proliferating and differentiating in the host tissue, but mainly indirectly, by their paracrine secretion of a wide range of bioactive molecules, such as cell-adhesion mediating molecules, immunomodulatory molecules, growth factors and angiogenic factors [222]. Carboxymethylcellulose (CMC) combined with rat ASCs, obtained from visceral fat, was tested for treating skin lesions created by punch in a dorsal region of rats. In this model, commercially available sodium CMC at a concentration of 10 mg per 1 ml of the culture medium associated with ASCs, increased the rate of cell proliferation of the granulation tissue and the epithelium thickness in comparison with untreated lesions, but did not increase the collagen fibers or alter the overall speed of wound closure. In addition, the use of CMC was safe up to a concentration of 20 mg/ml. At a higher concentration of 40 mg/ml, the sodium CMC showed a certain genotoxicity, although this was small and transient, as revealed by an alkaline comet assay [223]. Other cellulose-based carriers for human ASCs were threads prepared from nanofibrillated cellulose, extracted from plants and cross-linked with glutaraldehyde. Cross-linked threads were not cytotoxic for ASCs and supported their adhesion, migration and proliferation *in vitro*. After intradermal suturing with ASC-decorated threads in an *ex vivo* experiment performed on porcine skin, the ASCs remained attached to the multifilament sutures without displaying morphological changes or reducing their metabolic activity [224]. In our recent study, novel cell carriers based on clinically used carboxymethylcellulose fabrics (Hcel® NaT), modified with fibrin nanofibers, were designed for potential delivery of dermal fibroblasts into skin wounds [225].

### 12.5.5. Nanocellulose in wound healing

*Bacterial nanocellulose*

*Bacterial nanocellulose without additives*

Similarly, as in skin tissue engineering, bacterial nanocellulose (BNC) is considered to be one of the most suitable materials for wound dressing. This is due to its favorable physical, chemical and biological properties, as mentioned above, such as chemical purity, favorable mechanical properties and water-absorbing capacity [11,21,48,193]. BNC itself, i.e. without any additives, showed a great capacity to stimulate wound healing, i.e. regeneration of the epidermis and dermis. For example, as mentioned above, BNC wound dressings improved the healing of full-thickness skin defects of a relatively large area (2 x 2 cm), created surgically on the back in mice *in vivo*, in comparison with the control untreated mice. At the same time, BNC-treated mice showed a lower inflammatory response, evaluated by the amount of neutrophils, lymphocytes and macrophages in histological sections. In addition, a cytotoxicity test, performed *in vitro* on NIH/3T3 fibroblasts, demonstrated that the growth rate of the cells seeded on BNC films was more than 80% of the value obtained in cells grown in standard culture wells, which indicated low cytotoxicity of BNC [37]. Similar results were obtained when bacterial cellulose membranes were applied for 15 days on second-degree burn wounds (1 x 1 cm) produced by contact with a heated metal plate. Bacterial cellulose accelerated the process of healing in comparison with a conventionally used gauze, as manifested by greater thickness of the regenerated epidermis and dermis, a higher number of newly-created blood vessels, a higher level of collagen expression and a lower number of mast cells infiltrating the damaged site. At the same time, bacterial cellulose did not show toxic effects on the liver and kidney, as revealed by the levels of alanine transaminase, aspartate transaminase, alkaline phosphatase, blood urea nitrogen, creatine and lactate dehydrogenase in the blood serum [226]. A recent study by Kaminagakura *et al.* [46] showed that bacterial cellulose membranes (Nanoskin®) promoted healing of full-thickness skin wounds in guinea pigs, created by surgical removal of skin from their dorsal region (2 x 4 cm), to a similar extent as in the control autologous skin implants. A coating of Nanoskin® with gelatin did not further improve the healing effect. However, skin wound healing can be modulated by the architecture of bacterial cellulose films. The bottom side of these films was constructed with a larger pore size, and with a looser and rougher structure than that of the top side. A microfluidics-based *in vitro* wound healing model revealed that the bottom side of the films better promoted the migration of cells to facilitate wound healing. These scaffolds are therefore also promising for skin tissue engineering. Moreover, full-thickness skin wounds in Wistar rats, covered by the bottom side of the films, showed faster recovery and less inflammatory response than the top side of these films and the traditionally used gauze [227]. Finally, an interesting application of bacterial nanocellulose was for creating transparent wound coverings, which allowed optical real-time monitoring of wound healing, and also diagnostics of the infection and inflammation in chronic wounds [228]. Another transparent wound dressing was developed by combining bacterial cellulose whiskers with a poly (2-hydroxyethyl methacrylate) hydrogel and silver nanoparticles, which endowed the dressing with antibacterial activity. At the same time, this material facilitated the growth of NIH 3T3 fibroblasts, which indicated its non-toxicity [23].

### *Bacterial nanocellulose with additives*

In order to further improve the healing effect of bacterial (nano)cellulose, this material has been combined with other biologically active molecules, such as other polysaccharides, proteins, glycosides, cytokines and growth factors, local anesthetics, and even nanoparticles. For example, combination with chitosan improved the mechanical properties and endowed bacterial cellulosebased wound dressings with antimicrobial properties [229]. The mechanical properties of composite electrospun nanofibrous mats containing bacterial nanocellulose and chitosan were further improved by adding medical grade diamond nanoparticles to the electrospinning solution. Introducing these nanoparticles facilitated the electrospinning process and reduced the diameter of the fibers. Moreover, the nanodiamond-modified mats were more hydrophilic and thus more attractive for the adhesion and growth of mouse skin L929 fibroblasts, which made them promising for skin tissue engineering [21].

An important protein for modifying bacterial cellulose is sericin, which is created by silkworms (*Bombyx mori*) as a component of silk. A silk sericin-releasing bacterial nanocellulose gel was developed to be applied as a bioactive mask for facial treatment [230]. Silk sericin diffusing from bacterial cellulose did not influence the growth of keratinocytes but enhanced the proliferation of fibroblasts, increased the cell viability and improved the production of extracellular matrix. Bacterial cellulose/silk sericin composites are therefore promising not only for wound dressing applications but also for tissue engineering [231]. A bacterial nanocellulose wound dressing with sericin and polyhexamethylene biguanide (PHMB), an antimicrobial agent, was clinically tested in volunteers [132].

An important cytokine used for bacterial cellulose modification was macrophage-stimulating protein (MSP), a cytokine highly expressed in ASCs and probably playing a critical role in wound healing. In an *in vivo* study, MSP was applied to a full-thickness skin wound with bacterial cellulose membranes, and this treatment accelerated the wound healing, probably by migration of dermal fibroblasts, which have receptors for MSP, and by enhanced synthesis and remodeling of collagen [232]. Smart membranes made of oxidized bacterial cellulose incorporated with epidermal growth factor (EGF) were developed in order to enhance the process of re-epithelialization. The release of EGF was triggered by lysozyme, an enzyme commonly found at infected skin wounds [233]. Reepithelialization of skin wounds in rats was also enhanced by bacterial cellulose membranes incorporated with vaccarin, a flavonoid glycoside known to promote neovascularisation [39]. In the field of local anesthetics, lidocaine was incorporated into bacterial cellulose in order to reduce pain, especially in burn wounds, and thus to improve the wound healing [131]. Another system developed for lidocaine delivery was based on biodegradable microneedles manufactured from bacterial cellulose and fish scale-derived collagen [28]. A further useful modification of bacterial cellulose is the introduction of glycerin. Glycerin has a characteristic moisturizing effect, which could be clinically relevant for the treatment for skin diseases accompanied by dryness, such as psoriasis and atopic dermatitis [234]. Bacterial nanocellulose usually occurs in the form of nanofibrils, but nanocrystals have also been prepared from this material. The bacterial cellulose nanocrystals were then used to reinforce regenerated chitin fibers, and these composite fibers are applicable for suturing skin wounds [235].

An important issue is that wound dressings should protect the wound from microbial infections, which are caused mainly by bacteria. Although bacterial nanocellulose is considered to be an almost ideal wound dressing, it exhibits no antibacterial properties when used by itself. Therefore, numerous studies have dealt with incorporating bacterial cellulose with various antibacterial agents, such as metal-based agents, antiseptics, antibiotics and various nature-derived antibacterial molecules. Metal-based agents used for bacterial cellulose modification include various forms of silver, such as silver sulfadiazine [236] and silver nanoparticles [237], both of which are active against *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus*. Silver nanoparticles were further combined with magnetic $Fe_3O_4$ nanoparticles in order to increase the wound healing efficiency of bacterial nanocellulose [238]. Other metal-based nanoparticles with activity against Gram-negative bacteria, combined with bacterial cellulose, were 4,6-diamino-2-pyrimidinethiol (DAPT)-modified gold nanoparticles [239]. Antiseptics used in bacterial cellulose-based wound dressings included povidone-iodine and polyhexamethylene biguanide (PHMB; [48,132]), and also octenidine [240]. Prolonged release of octenidine was achieved by incorporating it into Poloxamer micelles, which were introduced into bacterial nanocellulose [133]. Other antimicrobial drugs incorporated into bacterial cellulose were antimicrobial quaternary ammonium compounds based on fatty acids and amino acids ([EDA][DLA-Tyr]), which were active against *Staphylococcus* aureus and *Staphylococcus epidermidis* [241]. A representative of antibiotics is ceftriaxone, a third-generation cephalosporin [43]. Nature-derived antibacterial molecules used for modifying bacterial cellulose include chitosan, which exhibited bacteriostatic properties against *Escherichia coli* and *Staphylococcus aureus* [229,242]. Other antimicrobial compounds are bromelain, a protease present in pineapple tissues, which also has anti-inflammatory and anticancer properties [243], lignin and lignin-derived compounds [244], and particularly curcumin, i.e. a naturally occurring polyphenolic compound isolated from *Curcuma longa*. The application of curcumin is limited by its extremely low water solubility, which leads to its poor bioavailability. For wound dressings, curcumin was applied mainly with plant-derived and chemically modified nanocellulose, and, in rare cases, in combination with bacterial cellulose. In a recent study, curcumin was entrapped into a composite containing gelatin and ionically modified self-assembled bacterial cellulose and showed wound healing activity and antimicrobial activity [245].

In our experiments, we prepared bacterial cellulose loaded with pristine curcumin or with curcumin degradation products. As was mentioned above, pristine curcumin is almost insoluble in polar solvents. In addition, curcumin is unstable in neutral and alkaline pH, and it degrades mainly to ferulic acid, feruloylmethane and vanillin [246]. The degradation of curcumin can also be modulated by temperature. It is known that curcumin starts to degrade at a temperature of approx. 180°C [247]. In our experiments, degradation products of curcumin were therefore prepared by thermal decomposition of curcumin molecules at temperatures of 180 °C and 300 °C. Fourier transform infrared spectroscopy (FTIR) and high-performance liquid chromatography (HPLC) detected vanillin and feruloylmethane as the major product at 180 °C, and feruloylmethane at 300 °C.

Our results showed that bacterial cellulose loaded with curcumin, and particularly with its degradation products obtained at 180°C, reduced the number of growing colonies of *Staphylococcus epidermis*. Antibacterial activity against *Escherichia coli* was obtained only in samples loaded with the degradation products of curcumin obtained at 180 °C (Figure 5).

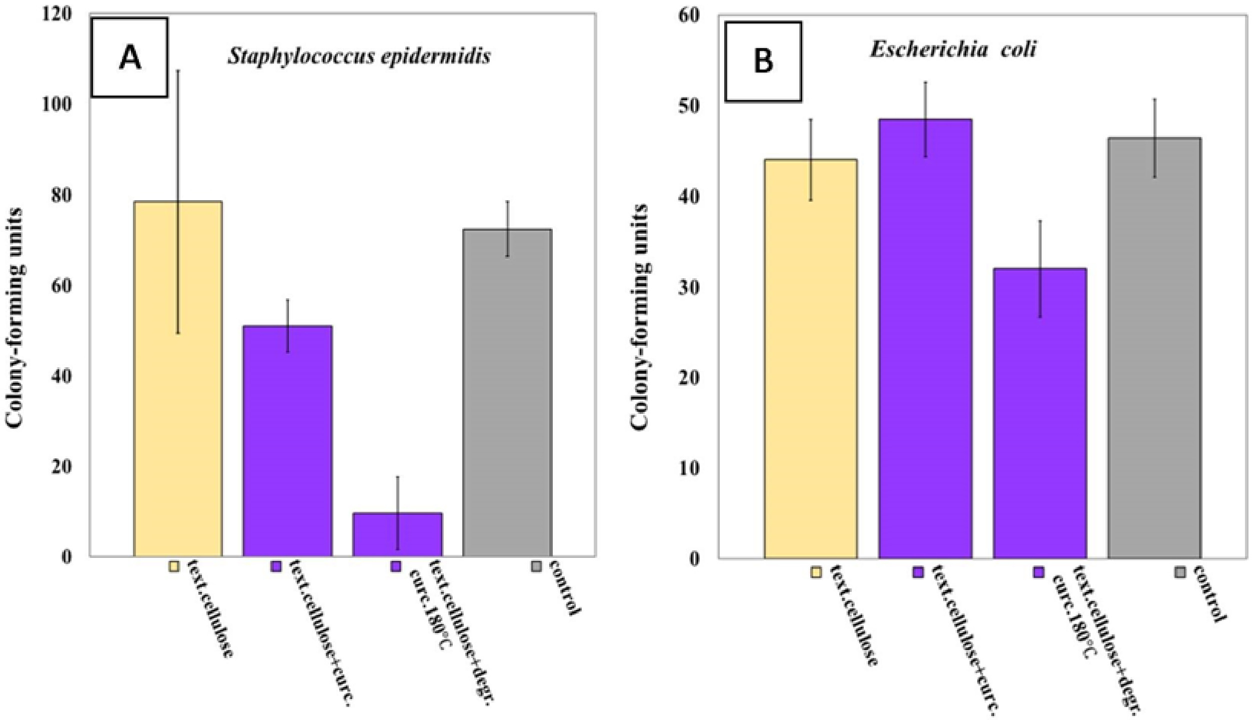


*Figure 30. Antibacterial activity against S. epidermis (A) and E. coli (B) in unmodified bacterial cellulose (text.cellulose), bacterial cellulose with curcumin (text.cellulose+curc.) and bacterial cellulose with curcumin degraded at 180 °C (text.cellulose +degr.curc. 180 °C) for 1 hour [248].*

*In vitro* tests performed on human dermal fibroblasts revealed that curcumin degraded at 180 °C showed a significant cytotoxic effect on these cells, while curcumin degraded at 300 °C supported the adhesion, spreading and growth of these cells (Figure 6). It therefore appears that vanillin - as the major degradation product at 180 °C - is cytotoxic, and feruloylmethane - as the major degradation product at 300 °C - is non-cytotoxic. However, the antimicrobial and cytotoxic effect of curcuminloaded bacterial cellulose is strongly dependent on the concentration of curcumin or its degradation products. We observed no cytotoxic effect on fibroblasts at very low doses of curcumin degraded at 180 °C, incorporated into cellulose.

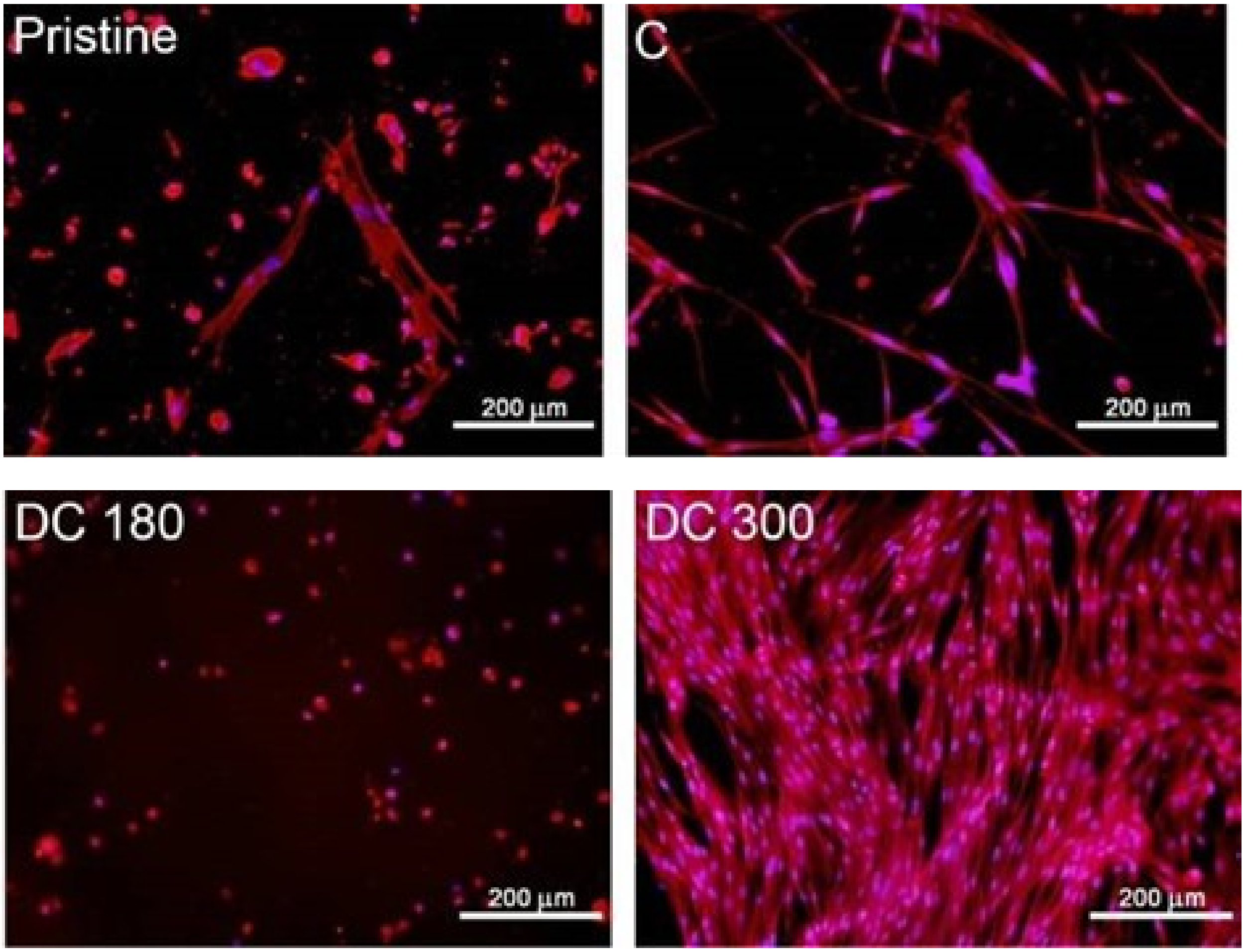


*Figure 31. Human dermal fibroblasts on bacterial cellulose in a pristine state (Pristine), loaded with curcumin (C) or with degraded curcumin at 180 °C (DC 180) or at 300°C (DC 300) after 7 days of cell seeding. The cells were stained with Texas Red C2-Maleimide (red fluorescence, cell membrane and cytoplasm) and Hoechst #33258 (blue fluorescence, cell nuclei).*

Other drugs that can be incorporated into bacterial cellulose are anticancer drugs, such as αmangostin, an antioxidant and antigenotoxic agent derived from the mangosteen tree, which suppressed the growth of B16F10 melanoma cells and MCF-7 breast cancer cells [249]. Bacterial cellulose can also be used for transdermal drug delivery, such as systemic delivery of propranolol, a non-selective β-adrenergic receptor antagonist [130] or diclophenac, a non-steroidal antiinflammatory drug [129]. Another interesting application of bacterial nanocellulose is in epidermal electronics, e.g. self-adhering bioelectronic decal monitoring of the concentration of cations (Na+, K+ and $Ca^{2+}$) in sweat as a marker of the physiological status of the organism [38].

The use of bacterial cellulose in skin tissue engineering and wound healing, including its clinical applications, has been reviewed by Fu *et al*. [37].

### 12.5.6. Plant- and animal-derived nanocellulose in wound healing

*Plant-derived nanocellulose without additives*

Like bacterial nanocelullose, plant cellulose can also appear in the form of a hydrogel containing nanofibrils. Unlike bacterial nanocelullose, however, plant cellulose can induce wound healing by itself, i.e. without any additives. Wood-derived nanofibrillar cellulose (NFC) has been tested for wound dressing applications due to its high capability to absorb liquids and to form translucent films. These properties are required for non-healing and chronic wounds, where exudates need to be managed adequately. In addition, the translucency of NFC makes it possible to evaluate the development of the wound without needing to remove the dressing [250]. The healing potential of wood-derived NFC was tested in a clinical trial on burn patients. An NFC dressing was applied to split thickness skin graft donor sites. The NFC dressing was compared with the Suprathel® commercial lactocapromer dressing (PMI Polymedics, Germany). Epithelialization of the donor site was faster when covered by the NFC dressing than when Suprathel® was used. The NFC dressing seemed to be promising for skin graft donor site treatment, since it was biocompatible, it attached easily to the wound bed, and it remained in place until the donor site had renewed. It also detaches from the epithelialized skin by itself [52].

Wood-derived NFC (obtained from commercial never-dried bleached sulfite softwood dissolving pulp), crosslinked with calcium ions, also had hemostatic potential, especially when enriched with kaolin or collagen [55]. In addition, inflammatory response studies with blood-derived mononuclear cells revealed the inert nature of NFC hydrogels in terms of cytokine secretion and reactive oxygen species production. Water retention tests showed the potential of NFC hydrogels to maintain a suitably moist environment for various types of wounds [18].

Hemostatic potential was also observed in oxidized cellulose (OC) modified in an inert argon plasma [251]. The plasma-modified OC was more acidic, and had a larger surface area and greater ability to absorb water. These factors are crucial for effective haemostasis. In addition, the acidity of plasma-modified OC increased its antibacterial activity. Plasma-modification could therefore be utilized for advantageous modification and also for sterilizing the OC haemostat in a single easy step [251].

Similarly, nanofibrillated cellulose, prepared from *Pinus radiata* pulp fibers and pre-treated with TEMPO-mediated oxidation, in the form of films, impaired the growth of *Pseudomonas aeruginosa*, a frequent wound pathogen, and led to more death of bacterial cells than Aquacel®, a commercial control wound dressing [57]. The same NFC in suspension and in the form of aerogels also showed activity against *Pseudomonas aeruginosa* PAO1. In the case of aerogels, bacterial biofilm formation decreased with decreasing porosity and surface roughness of the material [252]. Incorporating cellulose nanocrystals (derived from *Hibiscus* *cannabinus*) into chitosan/poly(vinyl pyrrolidone) composite membranes, developed for wound dressing applications, enhanced their antibacterial activity, as revealed in *Staphylococcus aureus* and *Pseudomonas aeruginosa* [64]. The antibacterial activity was further increased by coating these membranes with hydrophobic stearic acid, which hampered the adhesion of bacterial cells [253].

### *Plant-derived nanocellulose with additives*

Similarly, as in bacterial nanocellulose, the antibacterial properties of plant-derived nanocellulose can be further improved by various chemical modifications, and by adding various ions, nanoparticles and synthetic or nature-derived molecules. An example of chemical modification is carboxymethylation and periodate oxidation of nanocellulose, which was then used as bioink for preparing porous antibacterial wound dressings [254]. As concerns the ions, the antibacterial properties of softwood pulp-derived NFC were modulated by using divalent calcium or copper ions as crosslinking agents. Calcium-crosslinked hydrogels were more active against *Pseudomonas aeruginosa*, while copper-crosslinked hydrogels were more active against *Staphylococcus epidermidis* [19]. In addition, $Ca^{2+}$-crosslinked NFC hydrogels could be used for topical drug delivery applications in a chronic wound healing context [56]. Copper-containing nanocellulose materials also showed angiogenic activity. Composites of wood-derived NFC and copper-containing mesoporous bioactive glass showed not only antibacterial activity against *Escherichia coli*, but also angiogenic activity, as revealed in a 3D spheroid culture system of human umbilical vein endothelial cells, and also in cultures of mouse 3T3 fibroblasts, which upregulated the expression of pro-angiogenic genes in these cells [255]. Nanocomposite hydrogels containing carboxylated cellulose nanofibers (prepared by TEMPO-mediated oxidation), gelatin and aminated silver nanoparticles showed strong mechanical and self-recovery properties, antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, satisfactory hemostatic performance, and an appropriate balance of fluids on the bed of skin wounds created in mice [6]. Micro- and nanofibrillated cellulose incorporated with bismuth complexes was effective against *Escherichia coli*, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* [256].

Examples of synthetic and nature-derived molecules that have been incorporated into plantderived nanocellulose in order to enhance its antibacterial activity include antibiotics, antiseptics, antimicrobial peptides, alkanin, shikonin, isoliquiritigenin, coumarin and curcumin. From this point of view, nanocellulose-based materials can serve as carriers for topical and transdermal drug delivery. For example, a gentamycin-grafted nanocellulose sponge, prepared by multi-crosslinking of CNF (extracted from wood pulp), cellulose acetoacetate and 3-aminopropyl(triethoxy)silane, showed excellent antibacterial performance against *Escherichia coli* and *Staphylococcus aureus*, with bactericidal rates of over 99.9% [35]. Similarly, a hydrogel containing cellulose nanofibrils (produced by TEMPO-mediated oxidation from bleached softwood kraft pulp), and polydopamine loaded with tetracycline, was active against *Escherichia coli* and *Staphylococcus aureus*, and stimulated the healing of skin defects created in rats *in vivo* [6]. Due to the increasing resistance to antibiotics, attention has also been paid to other antimicrobial compounds. Composite films containing spherical cellulose nanocrystals and titania nanoparticles complexed with triclosan, i.e. an antibacterial and antifungal agent, showed activity against *Escherichia coli* and *Staphylococcus aureus* [257]. Another novel strategy for fighting bacterial infections involves delivering antibacterial peptides, e.g. nisin, a polycyclic antibacterial peptide produced by the bacterium *Lactococcus lactis*. This peptide was incorporated into TEMPO-oxidized nanofibrillated cellulose (TONFC) *via* electrostatic attraction between the negatively charged TONFC surface and the positively-charged nisin molecules. The capacity of TONFC to bind nisin was regulated by pH and ionic strength. The activity against *Bacilus subtilis* and *Staphylococcus aureus* was higher in nisin-TONFC composites than in free nisin [134]. In another nanocellulose-based material, i.e. nanocrystalline cellulose functionalized with aldehyde groups, also known as sterically stabilized nanocrystalline cellulose, nisin was combined with lysozyme, another antibacterial agent [101]. Other interesting molecules are alkannin, shikonin and their derivatives, which are naturally occurring hydroxynaphthoquinones with wound healing potential and antimicrobial, anti-inflammatory, antioxidant and antitumor activities. In a study by Kontogiannopoulos *et al*. [135], these agents were for the first time incorporated in electrospun cellulose acetate nanofibrous meshes for potential wound dressings. Isoliquiritigenin, a phenolic compound found in licorice, was incorporated into pH-sensitive hydroxyethyl cellulose/hyaluronic acid complex hydrogels. These composites showed antimicrobial activity against *Propionibacterium acnes*, and they were therefore considered to be promising for treating acne [258].

Other important plant-derived molecules for incorporation into wound dressings are coumarin and curcumin. These compounds have a wide spectrum of biological and pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial and anticancer activities. However, as was mentioned above, their potential therapeutic applications are hindered by the low stability and the poor water-solubility of these molecules. Attempts have been made to overcome these drawbacks and to improve the bioavailability of these compounds, e.g. using a Pickering emulsion, i.e. a kind of emulsion stabilized by solid particles located at the oil-water interface, in which aminated nanocellulose particles were used [136]. Another approach was a nanocellulose-reinforced chitosan hydrogel incorporated with Tween 20, i.e. a non-ionic surfactant, in order to improve the solubility of curcumin [259]. Other relatively simple cellulosic materials for curcumin delivery include capsules made of ethyl cellulose blended with methyl cellulose [260]. More complicated materials are polyvinyl alcohol/polyethylene oxide/carboxymethyl cellulose matrix blended with nanosilver nanohydrogels, Aloe vera and curcumin, deposited on a hydrolysed PET fabric [261], electrospun nanofibers containing PLGA, cellulose nanocrystals, curcumin and polyethyleneiminecarboxymethyl chitosan/pDNA-angiogenin nanoparticles [262], and composites made of complexes of curcumin/gelatin microspheres and porous collagen-cellulose nanocrystals [263].

Another important material with antimicrobial activity is chitosan. Chitosan and pectin with organic rectorite, i.e. a layered silicate, were used for deposition on electrospun cellulose acetate nanofibers in order to inhibit bacterial growth, which was proven on *Escherichia coli* and *Staphylococcus aureus.* At the same time, the material supported the growth of human epidermal cells. This material was considered to be suitable not only for wound dressing, but also for food packaging [8]. In a study by Vosmanská *et al.* [264], a three-step modification of the standard cellulose wound dressing was prepared. This modification included argon plasma-treatment, chitosan impregnation and AgCl precipitation. The plasma treatment oxidized the material surface, which increased the hydrophilicity of the material surface and the amount of chitosan impregnated on to the surface. In addition, plasma treatment almost doubled the amount of AgCl precipitated on the plasma-activated surface. All these factors endowed the cellulose-based wound dressing with antibacterial activity against *E. coli* and *S. epidermidis* [264].

Various antibacterial nanocellulose-based materials have been reviewed by Li *et al.* [265].

Nanocellulose in the form of nanocrystals has been widely used for delivering drugs for wound healing and for treating various skin disorders. Cellulose nanocrystals conjugated with folic acid are promising vectors for the targeted delivery of chemotherapeutic agents to folate receptor-positive cancer cells [266]. Cellulose nanocrystals (CNCs) isolated from *Syzygium cumini* leaves or bamboo, impregnated with silver nanoparticles, have been proposed for accelerated healing of acute and diabetic wounds [62,71]. Other potential wound dressings for accelerated healing of diabetic wounds are composite nanofibrous membranes containing PLGA fibres and cellulose nanocrystals loaded with neurotensin, an inflammatory modulator [267]. Cellulose nanocrystals loaded with hydroquinone, which inhibits the production of melanin, were designed for treating hyperpigmentation, a disorder occurring during pregnancy and sun exposure [268]. The use of various cellulose-based nanocarriers, such as bacterial cellulose, cellulose acetate, microcrystalline cellulose, carboxymethyl cellulose, cellulose nanocrystals, cellulose nanofibrils, etc., in drug delivery systems for cancer treatment has been reviewed in [269]. Advanced "intelligent" nanocellulose-based wound dressings were combined with biosensors, e.g. for human neutrophil elastase present in chronic wound fluid [120,270,271].

### 12.5.7. Animal-derived nanocellulose

Animal-derived nanocellulose also has potential for application in wound dressings. Cellulose membranes manufactured from *Styela clava* tunics, by themselves and in combination with alginate or selenium, stimulated healing of surgically created wounds in normal rats and in rats with diabetes induced by treatment with streptozotocin [75,83], probably through regulation of angiogenesis and connective tissue formation.

### 12.5.8. Potential cytotoxicity and immunogenicity of nanocellulose

Nanocellulose materials are often considered as materials with no cytotoxicity and immunogenicity, or with low cytotoxicity and immunogenicity. Cellulose nanofibers isolated from Curauá leaf fibers (*Ananas erectifolius*) provide an example of non-cytotoxicity. They showed no signs of cytotoxicity in direct or indirect assays for cell viability and cell morphology using Vero cells, i.e. monkey-derived kidney epithelial cells. Moreover, during an adhesion test, the cells demonstrated a relatively high affinity to the CNF surface [16]. Cotton-derived cellulose nanocrystals (mean width 7.3 nm, mean length 135 nm, concentrations from 30 to 300 μg/μl per ml of cell culture medium) are an example of non-immunogenic nanocellulose. These nanocrystals did not induce any release of pro-inflammatory cytokines, namely tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), from human macrophages derived from peripheral blood monocytes, while microcrystalline cellulose (particle size ~50 μm) induced the release of these cytokines [26].

However, several studies documenting considerable cytotoxicity and pro-inflammatory activity of nanocellulose *in vitro* and *in vivo* have also emerged. *In vitro*, five types of wood-derived nanocellulose materials (doses up to 100 μg/ml of cell culture medium) were practically non-cytotoxic for human macrophage-like THP-1 cells, when compared with multi-walled carbon nanotubes and nanomaterials based on ZnO, Ag and $SiO_2$, as revealed by an Alamar blue assay. However, multiplex profiling of cytokine and chemokine secretion indicated that nanocellulose materials induced potent inflammatory responses at sub-cytotoxic doses [272]. *In vivo*, wood-derived cellulose nanocrystals were shown to induce an inflammatory response in mice after aspiration, manifested by an increase in leukocytes and eosinophils in the lungs, recovered by bronchoalveolar lavage (BAL), and upregulation of pro-inflammatory cytokines and chemokines, such as TNF-a, G-CSF, GM-CSF, INF-γ, MCP-1, MIP-1α, MIP-1β, RANTES and various interleukins (including IL-1β), in the BAL fluid. These nanocrystals also induced oxidative stress and tissue damage, manifested by an accumulation of oxidatively modified proteins and an increase in lactate dehydrogenase activity in BAL fluid [18]. Similar results were obtained in a study by Shvedova *et al.* [4]. The exposure of mice to respirable wood-derived cellulose nanocrystals caused pulmonary inflammation and damage, induced oxidative stress, increased levels of collagen and transforming growth factor- β (TGF-β) in the lung, and impaired pulmonary functions. In addition, these effects were more pronounced in female mice than in male mice [4]. Sulphonated nanocellulose obtained from *Khaya sengalensis* seed showed renal toxicity in rats, manifested by hypernatremia, enhancement of the antioxidant status and immunohistochemical expressions of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in the kidneys [64].

The cytotoxicity and immunogenicity of nanocellulose can be modulated by its physicochemical properties, e.g. by functionalizing it with specific chemical groups or by endowing it with an electrical charge. Wood-derived nanofibrillated cellulose (NFC) modified with carboxymethyl and hydroxypropyltrimethylammonium groups elicited a lower pro-inflammatory effect than unmodified NFC in human dermal fibroblasts, in lung MRC-5 cells and in human macrophage-like THP-1 cells [273]. Anionic NFC films significantly activated THP-1 cells towards a pro-inflammatory phenotype, whereas cationic and unmodified cellulose induced only mild activation of these cells [274].

The morphology of cellulose nanoparticles can also influence their cytotoxicity and immunogenicity. Nanofibrillated cellulose (NCF) showed more pronounced cytotoxicity and oxidative stress responses in human lung epithelial A549 cells than cellulose nanocrystals (CNC). However, exposure to CNC caused an inflammatory response with significantly elevated proinflammatory cytokines and chemokines compared to NCF. Interestingly, cellulose staining indicated that CNC particles, but not NCF particles, were taken up by the cells [275]. *In vivo* experiments performed in mice also confirmed different immune responses to NFC and to CNC. Pulmonary exposure to NFC led to discrete local immune cell polarization patterns with TH1-like immune reaction, while CNC caused non-classical or non-uniform responses. However, the response to both types of nanocellulose was milder than the response to asbestos and carbon nanotubes [276]. In addition, curcumin was able to suppress, at least in part, the immune response to cationic needle-like cellulose nanocrystals, as observed by diminished IL-1β secretion in mouse J774A.1 macrophages primed with LPS [19]. The immunogenicity of bacterial, wood-based and algal nanocellulose may also be because these types of nanocellulose can contain immunogenic contaminants, such as endotoxin and (1,3)-β-d-glucan [76,277].

# Conclusions

Nanocellulose is a promising material for a wide range of applications in industry, technology, biotechnology and medicine, including tissue engineering and wound healing. However, the nondegradability of nanocellulose in the human organism is a limiting factor for its direct use in skin tissue engineering as a scaffold for skin cells, because scaffolds persisting in the skin could lead to scar formation and other complications. A more promising approach is therefore to use nanocellulose as a temporary carrier for delivering cells into wounds, which can be removed after the cells have adhered to the wound bed. However, artificial skin constructed *in vitro* could be used for experimental purposes, e.g. for studies on the biology, metabolism and vascularization of skin tissue, and for studies on the effects of various drugs, similarly as was demonstrated in artificial liver, adipose and tumor tissues. In skin applications, nanocellulose seems to hold the greatest promise as an advanced dressing material for topical, transdermal and systemic applications of various drugs, as a transparent dressing material enabling direct inspection of wounds, as a dressing material coupled with sensors, and as a material for constructing epidermal electronics.

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