Nanomedicine
Uniting medicine and technology

“Nanomedicine” has become a popular term in the media today. A Google search turns up nearly 35,000 hits for the German “Nanomedizin” while the English term racks up nearly 264 million entries. In this article, we want to explain what nanomedicine means and discuss the many ways in which the Swiss Nanoscience Institute is contributing to the field’s wide-ranging applications.

The term nanomedicine is frequently used to describe nano delivery systems and cancer therapies that rely on nanoparticles and nanocarriers. In this article, we use the term to refer generally to the use of nanotechnologies in the field of healthcare, or more specifically, the application of nanotechnological methods in medical diagnostics and treatment.

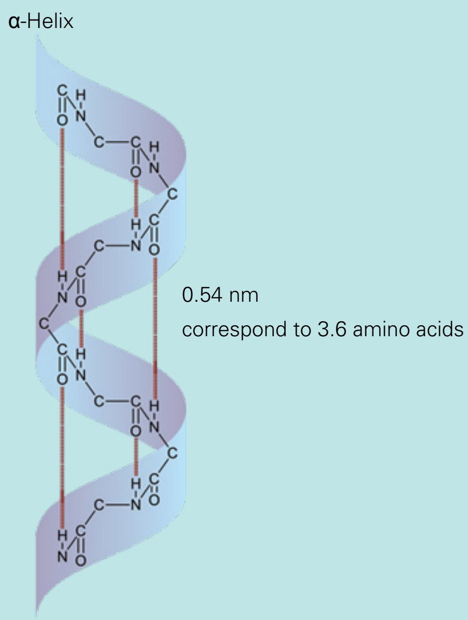
Nanomedicine is concerned with molecules and materials ranging in size from 1 to 100 nanometers. Materials of this size exhibit novel properties that do not occur in the macro world as we know it. For this reason, many past discoveries are now subject to renewed study from this fresh perspective.

In modern research, new milestones in medical science often hinge on technical advancements related to phenomena at the level of the micrometer or the nanometer. This is no real surprise, since the miniscule components that make up the machinery of our bodies operate at these tiny scales.

Nanotechnology methods and instruments can be used to study proteins and other tiny structures. Researchers in the field investigate the molecular causes of disease and develop new therapies that target these causes instead of simply treating the symptoms. For instance, they may study new biomaterials for implants and prosthetics or develop nano

Proteins

Proteins play a central role in the way our bodies work. We need them to live, and they are the primary components of every cell in our bodies. Proteins transport materials, provide structural support, navigate, and regulate processes. They are made up of vast amino acid chains that vary in length and have different three-dimensional structures. Hydrogen bonding determines the secondary structure of the protein – in this case, an alpha helix, which, with a diameter of 2 nanometers, falls within the nano range.



The «alpha helix» is a common protein structure produced by hydrogen bonding (indicated by the dotted lines). These structures have a diameter of 2 nanometers. Each amino acid contributes 0.15 nanometers to the overall length of the helix, and each twist of the helix, with a length of 0.54 nanometers, is made up of 3.6 amino acids. (Image: Shutterstock) delivery systems designed to transport pharmaceutical substances and release them exactly where they are needed.

Combining nanotechnology and medicine has also produced new diagnostic methods with improved sensor systems. Researchers are developing both miniature laboratories that fit on tiny chips and help simplify the study of cellular processes as well as novel contrast agents that sharpen medical imaging results.

Nanotechnology for implants and prosthetics

Surgery, orthodontics and dental medicine have all benefitted dramatically from advancements in nanomedicine. Current work on medical implants illustrates this point very clearly. Nanotechnology methods are being implemented to optimize the materials used to make medical implants, as these devices must comply with a lengthy list of requirements. On the one hand, they must be capable of effective force distribution, while on the other hand, they must demonstrate high biocompatibility, as they will make direct contact with the host's bone and soft tissue cells. In addition, the material must be non-toxic, sterilized, and engineered with submicrometer precision. Most implants are made from metallic substances; titanium and titanium alloy implants are particularly well suited to these applications, as they exhibit the properties listed here.

To guarantee a lasting bond between the titanium implant and the bone, bone synthesizing cells (osteoblasts) must adhere to the surface of the titanium. These osteoblasts form new bone cells and ensure that the implant gradually fuses with the bone tissue. To promote bone growth on the surface of the implant and help the implant fuse to the bone, researchers coat these implants with hydroxyapatite, a calcium phosphate compound that is also a central component of organic bone tissue.

As part of the Nano Argovia project NanoCoat, an interdisciplinary team of scientists have developed a cost-effective method to further optimize the surface properties of conventional titanium dental implants. The newly developed process involves taking the conventional microstructure of the surface and adding nanotexturing and a calcium phosphate coating that serves as a kind of synthetic bone tissue. The team is currently planning additional comprehensive studies

Sources:

Nanomedizin

https://link.springer.com/content/pdf/10.1007/s12285-010-0192-0.pdf

Nanomedizin – Chancen und Risiken

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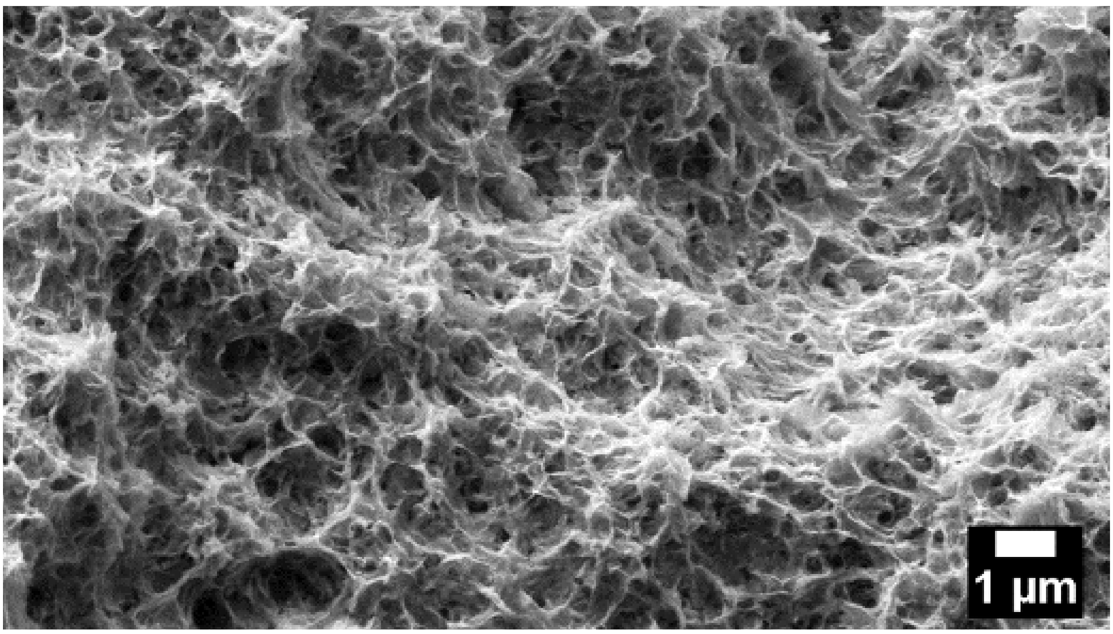
nanomedicines

https://doi.org/10.1016/j.jconrel.2019.10.020

More information about the projects:

NanoCoat

Project description



Nanostructured and calcium phosphate coated NanoCoat surface. (Image: Medicoat)

Dental implant (Image: Shutterstock)

More information:

Promucola

Project description

3D Cellophil

Project description

CIS Pharma Technology

Website

SLActive®

Website

Perionano

Project description

investigating the biocompatibility of these surfaces and the way they fuse to the surrounding bone tissue. Once the studies begin, it will be at least three years before patients can benefit from the optimized implant technology.

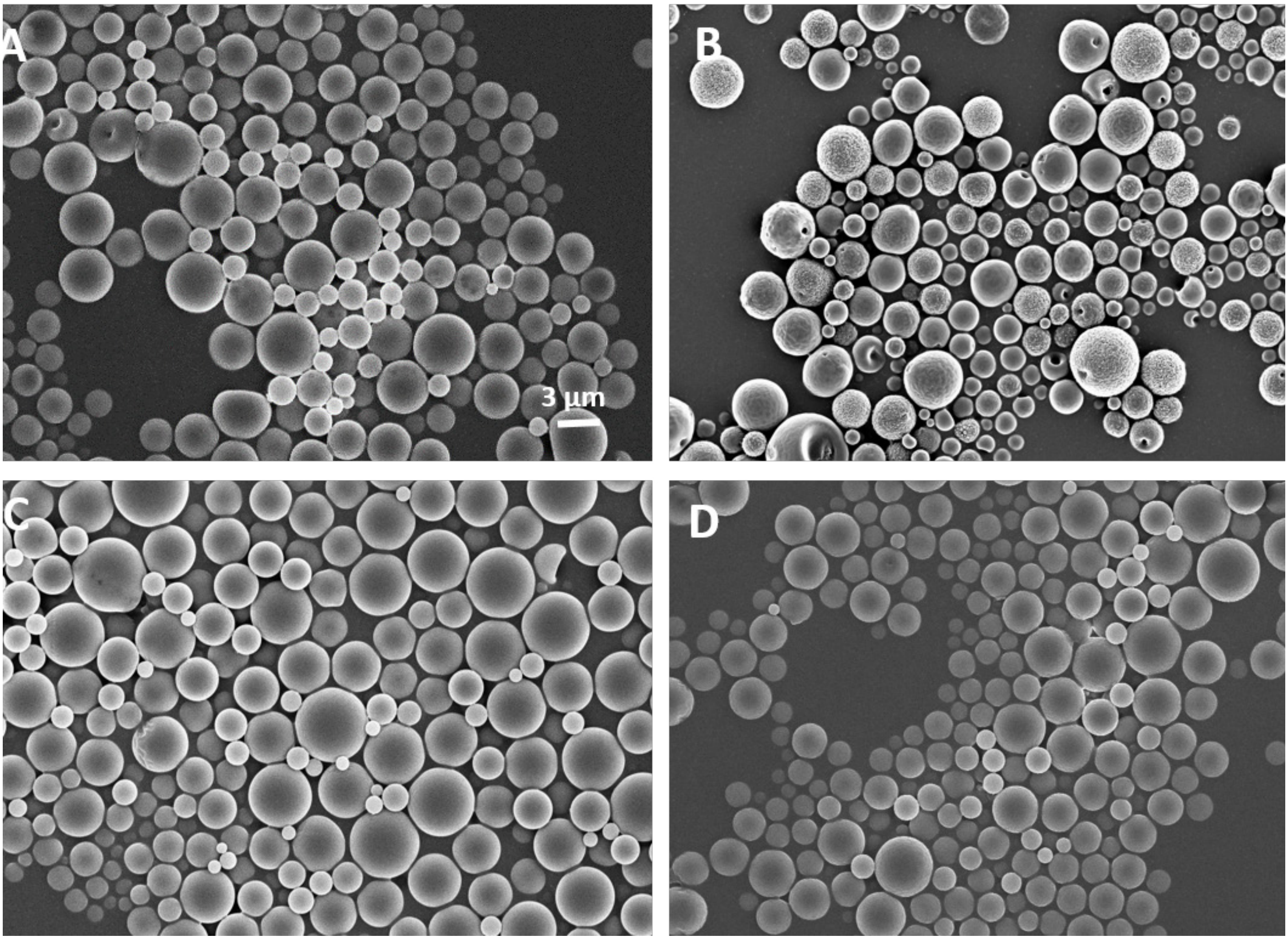
There is a second project in the Nano Argovia program that focuses on coating titanium implants. The Promucola project is slightly different in that its main objective is to minimize wear on the titanium implants. In collaboration with Orchid Orthopaedics Switzerland GmbH, the researchers use a plasma spray procedure to apply a ceramic coating that protects the implant from premature wearing. By applying a controlled coating of this new, complex, biocompatible powder mixture, researchers create a multi-component layer that vastly increases the implant's hardness and resistance to abrasion. The team is currently studying how to optimize the procedure and apply these additional coatings on an industrial scale.

Nanostructures promote early bone-to-implant integration

The field of dental implantation is also witnessing dramatic innovations. In the Nano Argovia project 3D-Cellophil, scientists have developed a triple-layered, biocompatible polymer membrane based on the Cellophil® technology pioneered by CIS Pharma. Cellophil is a combination of various natural amino acids linked by an acrylic backbone and characterized by a high degree of biocompatibility.

After exposure to UV light, the membrane layer polymerizes within seconds. The porosity of the membranes varies based on the intensity of the irradiation. With the help of this technology and an additional layer of nano hydroxyapatite crystals embedded in the membrane, this membrane meets the needs of both soft and hard tissues, thus supporting the tissue regeneration process. Although each of the three layers has a different structure, these layers can be manufactured and cross-linked one after another in a kind of stacking process. Using a 3D printer, it is possible to customize the size of the membrane to suit the needs of each individual patient.

The superhydrophilic, nanotextured surface technology SLActive® developed by Institut Straumann also helps implants fuse to the jawbone as it heals. Dental implants are coated in nanostructures made of Roxolid® (titanium-zirconium alloy) that increase the surface area of the implant. This aids in protein absorption



In the PERIONANO project, researchers studied particles loaded with antimicrobial agents (A + B) or with substances of plant origin (C + D).
(Image : FHNW Muttenz)

and fibrin scaffold formation as well as bone cell mineralization. These properties are key to promoting early healing in dental implant procedures.

Using peptide scaffolds and integrated particles to fight peri-implantitis

Dental implants are frequently affected by bacterial inflammation of the surrounding tissue (peri-implantitis). Failure to treat this condition may result in the loss of the implant. To prevent major bone defects that could result in implant loss, this inflammation must be remedied early on and any lost tissue promptly regenerated.

As part of the Nano Argovia project Perionano, an interdisciplinary team of scientists is working to develop a therapy to both combat the inflammation caused by bacterial infection and regenerate damaged tissue. In this approach, peptides are used to create a nanofiber scaffold containing tiny nano- and microscale particles that gradually release pharmaceutical substances to combat pathogenic bacterial strains at a local level. The peptide fiber scaffold also helps promote regeneration of damaged soft tissue and bone tissue.

Antibacterial and antiviral surfaces

During surgical procedures and in the case of implants, it would be practical to simply prevent the spread of the bacteria responsible for causing these problems in the first place. That is why researchers are developing antibacterial surfaces designed to prevent bacterial growth.

Preventing bacterial growth

Nano Argovia's TiSpikes project is dedicated to just this approach: The team aims to prevent biofilms – or a layer of bacteria – from forming, as biofilms are extremely difficult to treat using antibiotics. This idea originally stemmed from observations of natural phenomena. The surfaces of a cicada's wings are covered in myriad tiny pillar-like structures and a gecko's skin is equipped with nanostructures; each of these adaptations prevents the formation of biofilms. TiSpikes's interdisciplinary research team developed a process that allows surfaces made from titanium and titanium alloys to be textured in different ways. They are now working to determine which of these surface textures most effectively inhibits the growth of bacteria of various sizes.

Binding viruses using silver chloride microparticles

Coated surfaces can imbue many materials with a range of new properties. In light of current events, antibacterial and antimicrobial materials have become a subject of intensive study. Components such as silver or cell-like structures known as liposomes can be used to bind and destroy viruses. HeiQ Viroblock NPJ03, developed by the Swiss firm HeiQ, a spin-off from ETH Zurich, is an example of this type of application: Positively charged silver chloride microparticles attract the negatively charged viruses and bond to them. The specially formulated liposomes extract the cholesterol from the viral envelope, depriving the virus of the protective membrane it needs to survive. This paves the way for the silver particle, which attacks the viral DNA on a chemical level, ultimately destroying the virus. The principle is currently being broadly implemented in face masks designed to protect the wearer from infection by SARS CoV-2.

Many companies are now embracing the idea of using silver as an antiviral product. In addition to producing antiviral textiles, they are also developing specialized silver coatings for common surfaces such as door handles, work surfaces and medical devices.

Detecting antibiotic resistance

Bacteria that have become resistant to a range of antibiotics present a major threat to public health. When treating bacterial infections, medical specialists need fast access to information about resistant strains in order to make the right decisions as quickly as possible. Normally, bacteria are cultured and then tested for antibiotic resistance, a process which can take between 48 and 72 hours. Some strains of bacteria, however, are very difficult to culture. Molecular biological PCR tests produce rapid results, but they are not equally effective for all types of bacteria.

More information:

TiSpikes

Project description

HeiQ Viroblock

Website

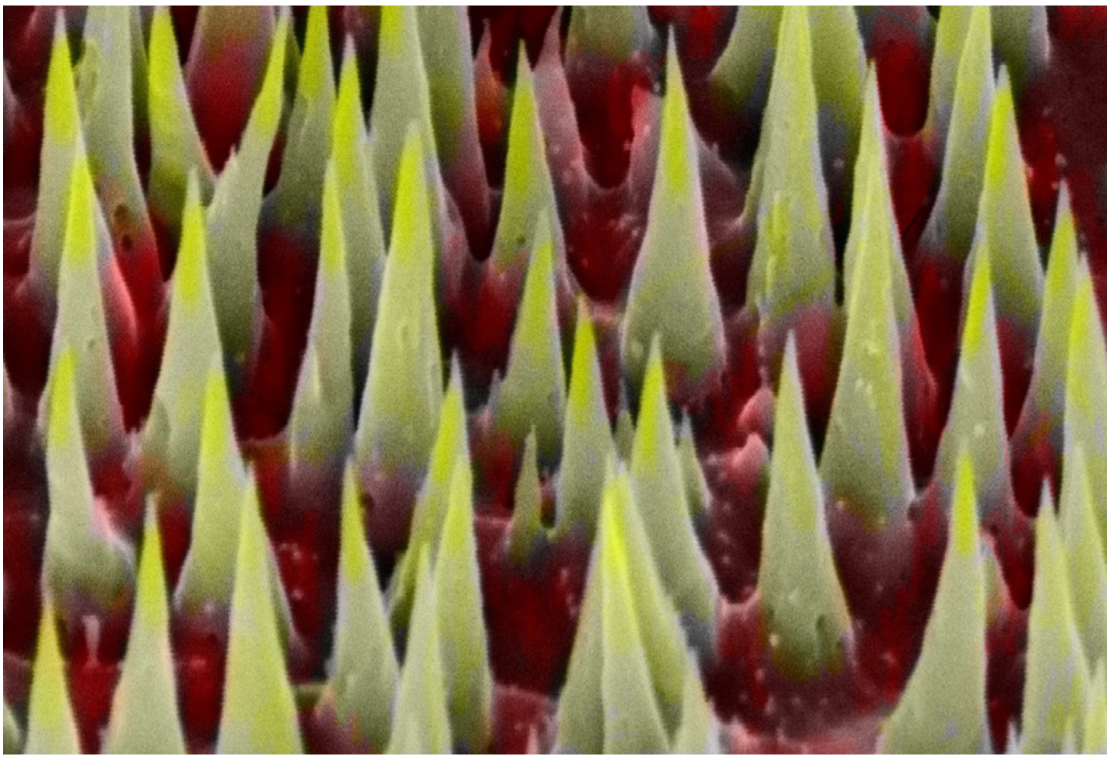
Test system for antibiotic resistance

Project description

Video

Resistell

Website



Nanostructures on titanium surfaces are being used in the TiSpikes project to mimic the wing surface of cicadas in order to keep bacteria at bay. (Image: D. Mathys, F. Sanchez, University of Basel)

Now, researchers at the University of Basel have developed a highly sensitive testing system capable of detecting bacterial antibiotic resistance quickly and effectively. The system is built around tiny cantilevers designed to bend as they bind to sample material. This type of test requires a sample size of only 1 to 10 bacterial cells to detect antibiotic resistance.

The idea pioneered by start-up Resistell is based on a very similar principle. First, a so-called nanomotion detector is used to determine whether a bacterial cell is viable. This method is based on the assumption that all living cells, such as bacteria, exhibit at least some amount of motion due to their metabolic processes. Using a technique similar to atomic force microscopy, Resistell's technology determines how bacterial pathogens respond to a specific antibiotic.

Unlike conventional antibiotic diagnostics, the technology developed by Resistell can detect antibiotic resistance within just a few hours, allowing doctors to select an effective antibiotic to treat their patients. Resistell plans to have its products on the market by September 2021. The company aims to decrease mortality rates associated with sepsis, reduce the use of broad-spectrum antibiotics and prevent the development of dangerous antibiotic-resistant bacteria.

Diagnostics

The sooner a disease can be diagnosed, the better the patient's chances for recovery. That is why it is important to identify the molecules or genes that signal the presence of different diseases. Diagnostic methods based on nanotechnology require only miniscule sample sizes, therefore allowing these so-called biomarkers to be detected more quickly using less invasive procedures.

Lab on a chip

Normally, when doctors take blood and cell samples, they send them to a laboratory for analysis since not every doctor's office is equipped with a fully stocked laboratory. Using the lab-on-a-chip technique, doctors' offices can assay tiny samples on-site.

To do this, they need a microfluidic chip attached to a pump and a sensor and software to analyze the results. The pump delivers nanoliter-scale doses of the sample material while the sensor records the necessary parameters, and the software evaluates the results. In the future, this type of technology could be used to carry out multiple assays using the same sample without requiring laborious preparation prior to testing. The smaller sample sizes reduce strain on patients, and diagnoses can be made more quickly and cost-effectively.

This device, developed by Resistell, can detect bacterial sensitivity to various antibiotics (Image: Resistell).

Digital pocket diagnostics

Some diseases require continuous monitoring; diabetes, for example, requires frequent blood glucose testing, and the spread of coronavirus can be tracked with the now familiar rapid tests. These types of diagnostics, referred to as point-of-care testing (POC), require no specialized diagnostic equipment and can be conducted wherever patients are being treated. POC testing also allows patients to monitor key markers independently from the comfort of their own homes. Moreover, it provides medical personnel with fast, easy-to-administer tests that lead to safe, more efficient treatment. In areas where personnel have limited access to specialized diagnostic facilities, these types of POC tests, which do not require any additional laboratory equipment, have enormous potential to offer.

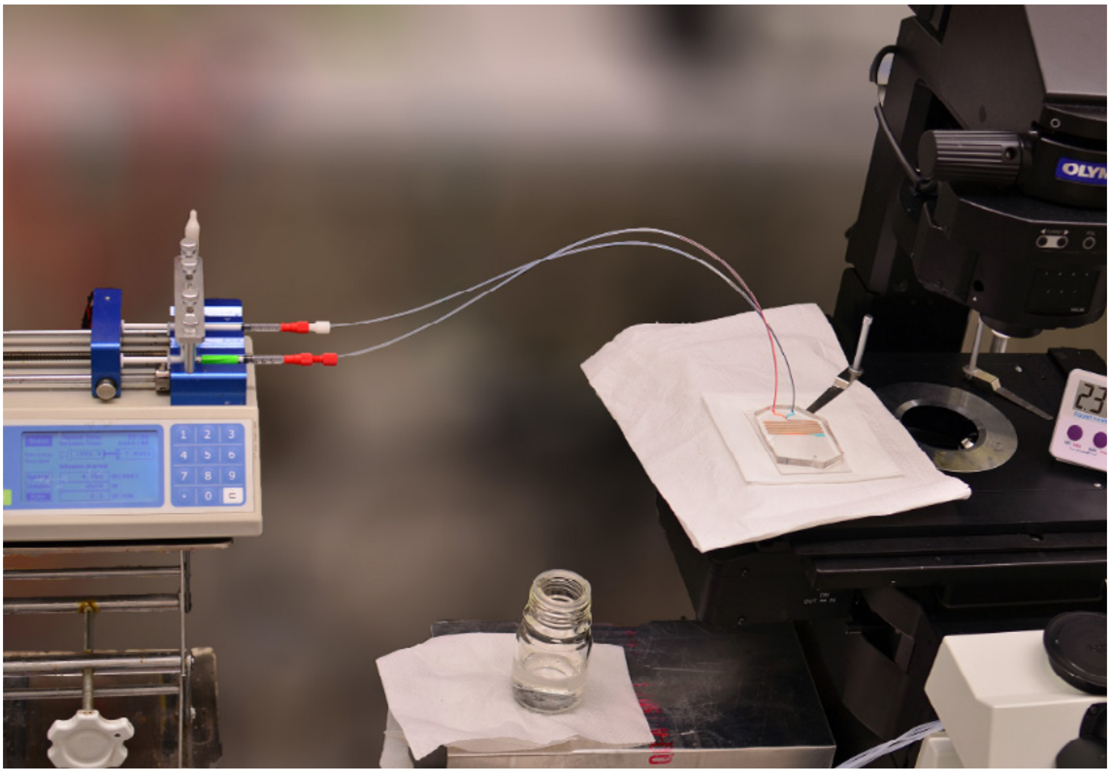
As part of the Nano Argovia project PEPS, an interdisciplinary research team is currently developing a digital POC device equipped with an electrochemical sensor designed to detect specific protein biomarkers.

The novel aspect of the approach selected for the PEPS project is the team's plan to use affordably manufactured, conductive nanocomposite electrodes. The combination of high electrical conductivity and strong antifouling properties could prove to be the key to producing highly sensitive electrochemical POC tests.

Cell-on-a-chip

Researchers at the University of Basel have developed a precisely controllable system for mimicking biochemical reaction cascades in cells. Using microfluidic technology, they produce polymeric vesicles equipped with the desired properties. Researchers can control the exact size and composition of the vesicles to allow different biochemical reactions to

Highly sensitive electrochemical sensor, which is being developed in the PEPS project (Image: CSEM).



Lab on a chip: A microfluidic chip connected to a pump and sensor and the appropriate software to analyze the sample (Image: Shutterstock).

More information:

PEPS

Project description

Cell on a chip

Project description

Video

Artidis

Project description

Website

Contrast agents

Project description

occur inside each one without affecting any of the others – just like in the different organelles of a cell. This technology can be used for in-depth study of specific mechanisms involved in metabolic disease.

Nanomechanical biomarkers help diagnose cancer and optimize treatment methods

The company ARTIDIS, a spin-off from the University of Basel with deep roots at the SNI, has developed a platform capable of analyzing nanomechanical biomarkers for tumor diagnosis and optimized cancer therapy. The technology uses an atomic force microscope to probe individual cells. Metastatic tumor cells are much softer and more pliable than the cells of normal tissue and benign tumors.

Unlike conventional assays, which can take up to two weeks, the ARTIDIS method is capable of analyzing biopsy samples within just a few hours, sparing patients tense waiting times of days or even weeks before they receive their diagnoses. On top of that, the ARTIDIS platform paves the way for personalized cancer treatment.

Researchers have successfully completed a clinical trial in which this approach was used to treat breast cancer. Now the diagnostic method is being broadened to include lung and pancreatic cancer and is ready for clinical implementation. The dedicated team at ARTIDIS is planning to build on this nanotechnology platform, expanding beyond tumor biopsies and applying the approach to the analysis of all types of tissue.

Novel contrast agent for medical imaging procedures

Contrast agents improve the visibility of bodily structures in medical imaging techniques such as X-rays, magnetic resonance imaging (MRI) and ultrasounds. Conventional contrast agents do not always produce sufficient contrast to allow medical practitioners to identify diseases in their earliest stages. Moreover, they make it difficult to recognize the biochemical environment. Researchers at the University of Basel's Department of Chemistry have developed nanoparticles that serve as "smart" contrast agents for MRI.

Many contrast agents are based on the metal gadolinium, which is injected into the bloodstream. From there, it enters the body's tissues, boosting the visibility of the internal organs. However, gadolinium is toxic and must be chemically bonded to a carrier substance so that it is safe for humans. In a major improvement to this diagnostic technique, the newly developed contrast agent can function with far lower concentrations of gadolinium. Researchers at the University of Basel have developed nanoparticles composed of heparin-modified polymers with gadolinium ions and functionalized peptides. Trials indicate that nanoparticles consisting of these components produce a tenfold amplification of the MRI signal compared with conventional contrast agents. In addition, due to the functionalized peptides, they are able to respond to their environment, therefore allowing researchers to image inflamed or malignant tissue. The trials showed no evidence that the nanoparticles possess cell damaging or anticoagulant properties.

Nano delivery systems

One promising area of nano medical research involves nano transport systems designed to deliver pharmaceutical substances to different parts of the body. These systems employ a range of materials, such as polymers, metallic nanoparticles and liposomes. Polymers in particular are the subject of extensive study, as they demonstrate numerous beneficial properties: They are easy to manufacture, highly biocompatible and biodegradable. In addition, it is easy to load them with different substances. Some approaches undergoing study in the SNI network were described in detail in an article on plastics published in the December 2020 issue of SNI INSight.

Nano delivery systems such as these can be used for both diagnostic and therapeutic purposes. The recent trend toward combining diagnostics and therapy has gained the moniker "theranostics" and is

More information:

ForMeL

Project description

Cancer therapy with virus

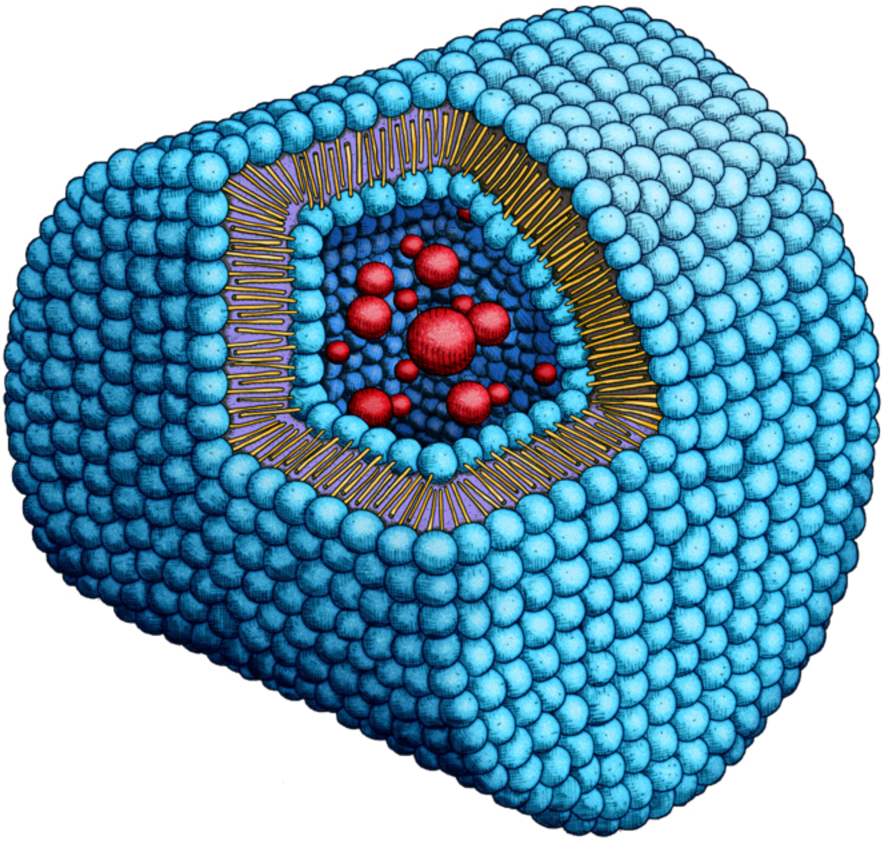
Project description

NCTNano

Project description

SNI INSight December 2020

https://nanoscience.ch/wp-content/uploads/sites/8/2020/12/en_sni-insight_dezember_2020.pdf



Artistic representation of a mechanoresponsive liposome loaded with an active ingredient (in red). (Image: Moser Graphic Design) sometimes referred to as "personalized medicine." Some of the main components of this approach include testing for genetic predispositions, characterization of the stage of disease, and monitoring of the healing process. One of the aims of theranostics is to determine whether a particular pharmaceutical agent is suitable and effective for treating a particular disease in a specific patient.

Liposomes – reinventing the membrane

Liposomes are vesicles made of a double layer of phospholipid molecules designed to resemble a natural membrane. These phospholipid molecules have both a hydrophobic pole and a hydrophilic pole. This property causes them to self-organize in a double layer, with the hydrophobic parts facing inward and the hydrophilic parts facing outward.

Liposomes can be used to study the biophysical properties of organic membranes. And they are also the focus of intensive study in the field of drug targeting.

The Nano Argovia project ForMeL aims to develop stable, drug-loaded, mechanoresponsive liposomes for use in preclinical studies and to design a manufacturing process capable of producing these liposomes at the scale needed for a pilot project.

Mechanoresponsive liposomes respond to pressure changes in the patient's blood vessels, for example in the case of atherosclerotic vasoconstriction. Liposomes of this kind could be used to directly target blood clots in vessels affected by arteriosclerotic narrowing without flooding the patient's entire body with anticoagulants. In the first stage, the team will investigate different liposome formulation technologies and develop targeted analytic methods to characterize the liposomes. Subsequently, in the second stage, the researchers will design and optimize the loading process. The objective of this Nano Argovia project is to develop a complete proposal for the formulation and storage of mechanosensitive liposomes.

Cancer therapies using nanotechnologies

Over the past few years, researchers have developed numerous new and effective therapies for treating different forms of cancer. The success of tumor cells can often be attributed to their ability to outwit the immune system and the body's built-in defenses. Researchers have discovered that immune system activation may prove to be a key tactic in the fight against cancer. That is why immune activation is central to many modern cancer therapies. Some approaches combat cancer cells using antibodies while others focus on developing therapeutic or prophylactic vaccines. One international research group led by scientists at the University of Basel, for instance, has formulated a promising therapeutic cancer vaccine. Two different weakened viruses are used as vehicles to enable the immune system to identify the cells that cause tumors, thereby prompting it to attack against tumor tissue. The approach is currently being tested in clinical studies.

Many of these therapies have already met with a measure of success but results still vary widely based on the individual patient. Another limiting factor is the process of transporting the necessary proteins to the target cells. The proteins must be protected from enzymatic degradation en route to the target cell. Once they have reached their destination, they must be absorbed by the target cell and release their cargo in the right organelle to achieve the desired effects.

Using nanoparticles to defeat cancer

TargImmune Therapeutics is currently developing a nanotechnology platform in the field of immuno-oncology. Nanoparticles are loaded with a specific cargo substance designed to mimic a viral infection, ultimately destroying tumor cells while simultaneously stimulating the body's immune system to fight the cancer. Using a chemical vector ensures that the cargo is selectively absorbed by the cancer cells.

The main objective of this research is to optimize the formulation of the nanoparticles used to carry the cargo substance. The Nano Argovia project NCTNano is focused on identifying the optimum physiochemical properties of such nanoparticles – characteristics such as size, shape and surface tension – as they are key to the safety and efficiency of the delivery system. Furthermore, various microscopy techniques have helped to reveal how these particles form molecular bonds and deliver their cargo into the target cells.

Another significant factor is understanding exactly how the pharmaceutical cargo works. The SNI-funded project was able to employ cutting-edge sequencing methods to investigate the activity of the innovative nanoparticles in numerous different cell lines. In addition, researchers have continued development on the pharmaceutical used by TargImmune Therapeutics so that the agent can soon be approved for implementation in the first phase of a series of clinical trials.

Nanoparticles for safe and efficient gene therapy

Gene therapy is one of the methods used to treat genetic disorders, tumors or other diseases. The process involves taking some of the affected cells from the patient's body and inserting specific nucleic acid sequences (RNA or DNA). The modified cells are then cultured and injected back into the body. Depending on the type of gene therapy and technique used, the nucleic acids may either be fully integrated into the cell's genome or simply remain inside the cell for a period of time.

For gene therapy to be successful, DNA fragments need to be delivered to the target cells. A research team at the University of Basel and ETH Zurich has successfully designed a peptide-based delivery system capable of transporting DNA fragments of up to 100 nucleotides in length.

Peptides are short chains consisting of roughly 50 amino acids. It is their size alone that distinguishes them from proteins. Peptides make excellent nanocarriers because they are highly biocompatible and simply biodegrade in the body. Moreover – and even more fascinating from a biochemical perspective – they can be constructed and modified using countless different combinations of amino acids. These peptides serve as a scaffold for self-assembling nanostructures that can subsequently be used as therapeutic and diagnostic delivery systems. Peptides are also capable of carrying out functions, such as identifying and targeting molecular sequences that researchers can use to build the desired nanostructures.

In the Nano Argovia project KOKORO, the interdisciplinary project team is developing a novel three-dimensional heart model. A cellulose paper is used for this purpose, which is intended to serve as an ideal scaffold for heart muscle cells due to its nanostructure. (Image: M. Gullo, FHNW)

These micelle-like, multi-element nanoparticles retain a stable size and structure for five months when stored at 4°C. The individual components degrade at body temperature, releasing the DNA cargo.

Nanomedicine aims to reduce animal testing

For many research projects, it can be a long time before human patients to enter into the equation. And not least because once a suitable agent has been identified, the approval process can take years. Following initial testing in the laboratory, animal trials are often conducted to determine the efficacy of the pharmaceutical agent in a complex organism. Among their other objectives, nanotechnology projects also aim to reduce the number of animal tests.

As part of an original Nano Argovia research project, researchers at the University of Applied Sciences Northwestern Switzerland (FHNW), the Department of Biomedicine (DBM) at the University of Basel and Omya International AG are developing a novel, three-dimensional heart model made of cellulose paper. The model's specialized design and nanostruc-

More information:

Gene therapy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7435460/

https://doi.org/10.1039/C9SM01990A

KOKORO

Project description

ture make it the ideal scaffold for biological cells. A 3D bioprinter is used to print fine layers of cardiac muscle cells onto the paper. These layers of cardiac tissue are then folded just like origami. This folding process allows the model to expand and contract in the manner of a biological heart.

The cells on the model are then cultured in a bioreactor and subjected to mechanical and electrical stimulation. The aim of the project is to use this model to test the efficacy of pharmaceuticals, ultimately reducing the need for animal testing.

Wide-ranging advancements in the field of nanomedicine

These projects showcase the diversity of the research currently taking place in the field of nanomedicine.

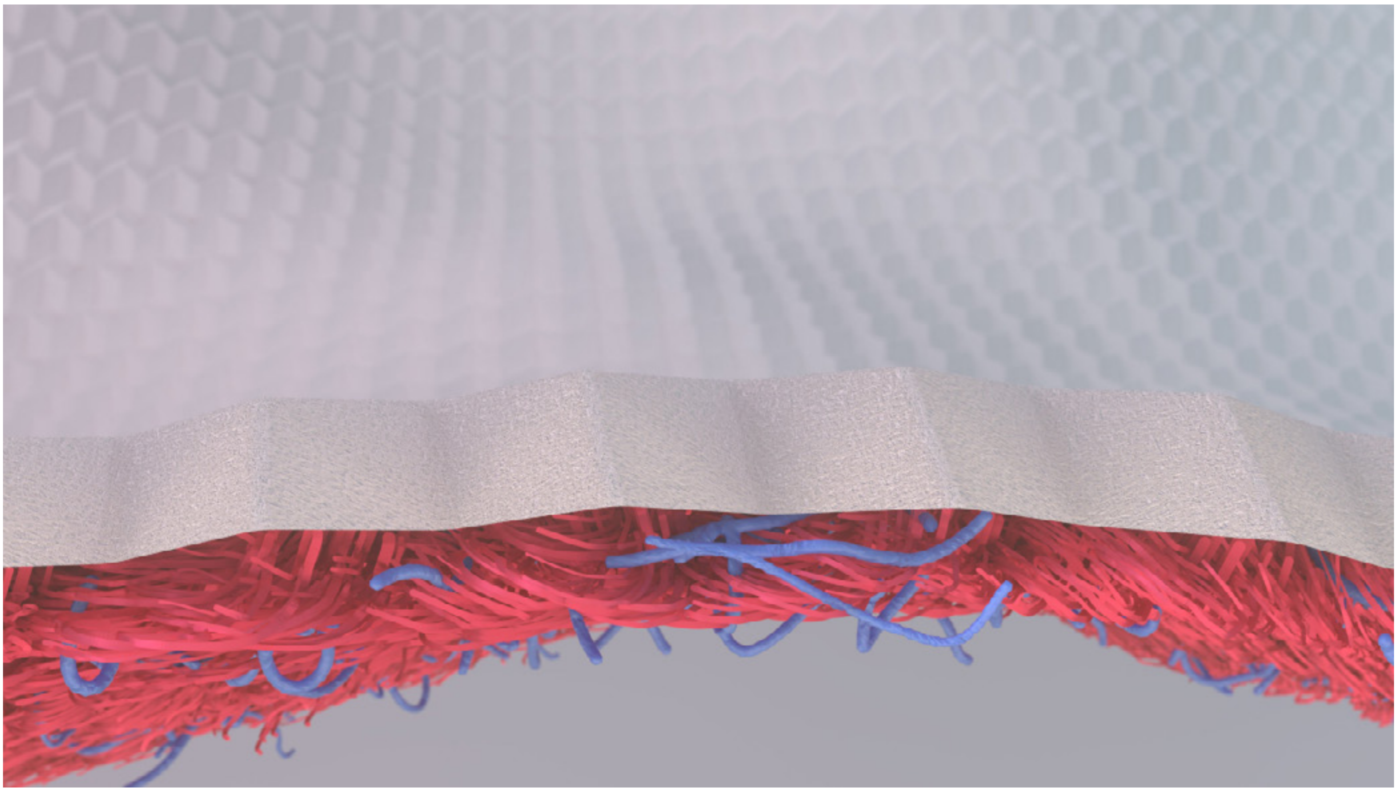
Technological progress has made it possible to produce prosthetics and implants that are more biocompatible with the body, therefore reducing costly complications. Specialized surfaces can curb the spread of bacteria and viruses, and new methods are being developed to combat the problem of antibiotic resistance.

There are also a range of approaches in the field of diagnostics that are based on developments in nanotechnology. Microfluidics is a key component of many of these breakthroughs – from the lab-on-a-chip all the way to the rapid antigen tests for COVID-19, microfluidic chips dramatically reduce diagnostic costs. Advances in nanotechnology have also significantly improved the quality of medical imaging. Atomic force microscopy, for example, delivers fast results for tumor identification, enabling medical practitioners to begin treatment promptly. Research on nano delivery systems has uncovered new insights for treating tumors and the diseases the produce them.

Researchers in the field of medical nanotechnology are currently developing other systems, such as the cell-on-a-chip or the origami heart, that precisely mimic the conditions inside the body with the aim of reducing animal testing in future pharmaceutical trials.

Before these and other innovations are actually applied, there is still a lot to be done, as not only scientific aspects play a role, but regulatory requirements must also be met.

Researchers in the interdisciplinary SNI network are using their research to ensure that the nanomedical applications described and others can be used for the benefit of patients.



Artist’s impression of origami cellulose sheets (white) with cardiac muscle cells (red) and a network of vessels (blue). (Image: SiVU ©)