SMARTNANO

NEWSLETTER

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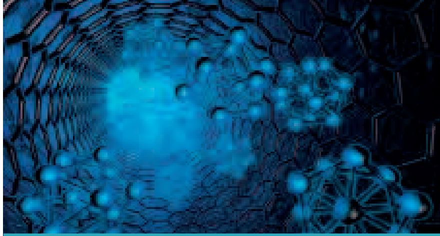


SmartNano project - newsletter n° 4

only for project dissemination activities

Monthly Interview

Daniel Lyons
Ruđer Bošković Institute, partner institution of the Smartnano project

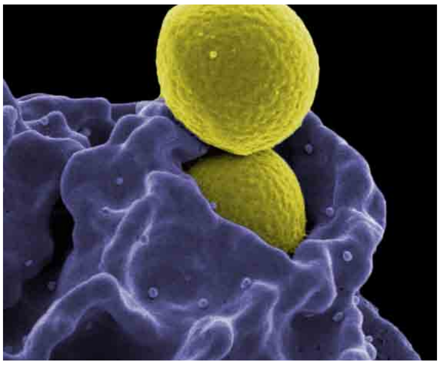
Could you give us a brief overview about RBI and its role in European research?
The Ruđer Bošković Institute Institute is regarded as Croatia's leading scientific institute in the natural and biomedical sciences as well as marine and environmental research, owing to its size, scientific productivity, international reputation in research, quality of its scientific personnel and research facilities. Today, the Ruđer Boškovć Institute Institute has over 300 staff scientists and researchers in more than 80 laboratories who participate in higher education in 78 undergraduate, 245 graduate and doctoral studies, thus making the RBI an equal partner to universities in the Republic of Croatia and abroad.

Due to its manpower and a large number of instruments, which comprise 50% of all scientific equipment in Croatia, the Institute is able to maintain its activities at the highest level, benchmarking itself against the very best in the European Union and forming an essential part of the European Research Area.

The Institute is the leading and internationally most competitive Croatian institute by virtue of its participation in international research projects. The RBI project portfolio comprises 33 FP7 projects funded by the European Commission, several HORIZON projects, 2 ERC grants, as well as many others funded by agencies such as the IAEA, NATO, NSF, SNSF, DAAD.

What have been your main focuses and findings in the past years? What about your next research goals?
Previously I have worked on developing methods for creating nano-structured architectures to improve the properties

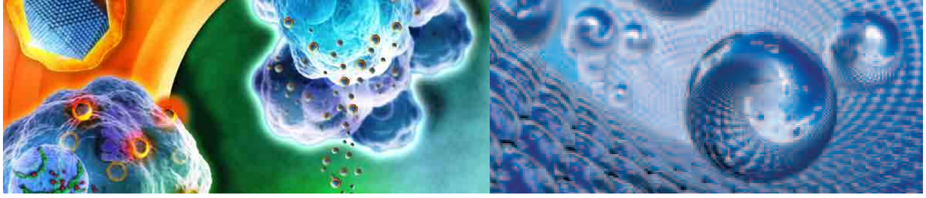
Nanoparticles toxicology and safety



Nanoparticles represent a class of materials that is continuously expanding and that involves an extraordinarily high number of examples and ideas.
Engineered nanoparticles (ENPs) are becoming increasingly frequent in consumer products, industrial applications and medical systems. Naturally occurring nanoparticles, or men-made nanoparticles in the nano scale, have always been present.
However, since more and more ingredients, products and by-products containing nanoparticles are becoming more common, concerns are being raised about their safety and possible toxicity.
Truth is, many researchers agree that our knowledge of the effects of materials in the nano scale is still incomplete. Substances often display different properties when engineered in the nano scale, mostly because of the extremely different surface to volume ratio. ENPs can be absorbed by living beings from a wide range of environmental sources. More nanoparticles may be willingly administrated in vivo/in biota for several applications. Medical applications on the nano scale have been especially researched over the past years, since they present some amazing opportunities.
We need to study the effects of these new materials on living beings extensively, in order to guarantee their safety without renouncing the exceptional benefits and opportunities they create. So, to put it simple, we know that we need to understand more.

About Ruđer Boškovć Institute

Due to its participation in many international research projects in natural and biomedical sciences, as well as marine and environmental fields, the Ruđer Bošković Institute is Croatia's leading and most competitive research institute.
The secret of this success is the multidisciplinary and "making science work for business" approach, that made it always possible to ensure high-quality scientific support to the industries and academia.
One of the most promising challenges of the institute is the development of strategies for environmental protection, that includes applied oceanographic research and the detection of toxins, pollutants and also nanomaterials in marine ecosystems.



of catalytically important materials, and to develop nanowire-based composites for applications in optoelectronics. However, over the past number of years my focus has begun to shift a away from pure materials science, and I have started to look at the environmental effects of the materials we were creating. Gradually I began to look at the marine environment through the prism of nano-science, with an approach encompassing two specific areas - investigating the behaviour, toxicity and fate of nanomaterials in the marine environment and applying our nanomaterials for solving contemporary issues related to the marine environment, e.g. food quality and safety. In this direction we have recently developed a relatively simple mix-and-shake solution chemistry approach to detecting the presence of biotoxins in shellfish using fluorescence nanoparticles which might ultimately be applied on site as a rapid and cheap method for initial field testing of mariculture products. Our aim would be to further develop this system as a multi-parametric sensor for simultaneously detecting a range of different biotoxins which may be present in shellfish.

Would you give us an overview of your research concerning the in vivo and in biota effects of nanoparticles?

With the increasing use of nanomaterials in a range of consumer products, there is growing interest in understanding their behaviour in the environment. However most of that research is focused on the freshwater environment. With more than half the world's population living in near-coastal areas and the increasing realization that freshwater systems are not necessarily the final sink for nanomaterials but that they may enter estuarine and coastal waters, questions regarding their behaviour in the marine environment are only now, somewhat belatedly, being asked. Our research has focused on the impact of nanoparticles on the embryonal development of sea urchins, particularly as the urchin immune system is also considered a model for the functioning of the human immune system. We have found that silver nanoparticles are teratogenic at extremely low concentrations but the effects are species-specific and depend on moment of first exposure. Further, we have tracked nanoparticles bioaccumulation in various organisms and subsequent trophic transfer to higher levels in the food web which is relevant, and may have consequences, for human health based on consumption of, for example, fish.

What is the driving force that brought you in Smartnano Project?

With respect to the environment, advanced techniques are available that allow the imaging of individual nanoparticles in localised areas of sediment, in organisms or tissues. Unfortunately, this gives no information about the overall ensemble of nanoparticles present in the sample, hence the application of a bulk technique is required. However, a major problem which prevents the use of such bulk techniques is that the nanoparticles are bound in complex matrices and cannot be easily freed to allow measurement, and there is a risk that aggressive methods for extracting the nanoparticles will change their structure. Such a scenario would result in measuring nanoparticles that are not actually the same as when they were in the matrix. The technology and techniques to be developed within the Smartnano Project directly address this bottleneck for the first time, so when we heard about the project we became extremely excited at the prospect of not only finally being able to carry out bulk analysis of nanomaterials in our complex environmental matrices, but to also be involved from the start in the development of a technology platform that will enable a powerful new type of analysis and as a consequence open up a huge new area of research.

What is the specific role RBI plays in the project?

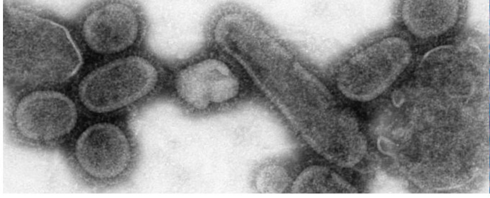
The tasks assigned to RBI as an applications partner are based on our current research topics on complex matrices in aquatic environments, with a focus on developing protocols and methods to allow the application of the technology platform to the detection and characterisation of nanoparticles in (i) salt and fresh water, (ii) marine and riverine sediments and in (iii) biological tissue of selected organisms. We are developing appropriate sample preparation methods to interface with the new technology platform, we are carrying out module testing and critically the validation the new technology platform with real, non-ideal complex inorganic and organic environmental matrices.

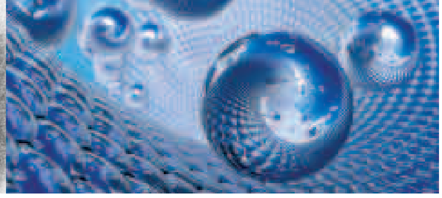
What findings raised your interest during your contribution to the project?

There had been a general feeling among the research community working in the field of nanomaterials in the environment that freshwater systems and wastewater treatment plants represent the end-of-life sinks for nanomaterials. However, over the past number of years there has been some evidence that nanoparticles can be transported as far as estuarine systems. We have unexpectedly found that even after this, in the harsh marine environment with very high electrolyte concentrations, nanoparticles can continue to exist either discretely or as small agglomerates for a significant period of time due to the stabilizing effect of marine dissolved organic carbon. This proves that the behaviour and fate of nanoparticles is equally a matter of concern for estuarine and coastal area, particularly in terms of toxicity towards living organisms, and we have found just such toxicity at extremely low, environmentally-relevant concentrations. Of course, there remains a huge amount of research in this area to be done based on the huge diversity of nanoparticles being used in various industrial and consumer applications and that are finding their way into the environment.

The effect of nanoparticles in vivo and the related applications are becoming an increasingly important focus point for biological and medical sciences. What effects can be expected from the related studies and research over the next years?

There has been an explosion of interest in using nanoparticles in biomedicine due to being able to functionalise their surfaces enabling the targeting of specific organs and cells in the human body. Not only do they show promise for direct therapeutic action based on their intrinsic properties, such as discriminate thermal destruction of cancer cells, but also as delivery vehicles for pharmaceuticals or as in situ agents which enhance the sensitivities of various diagnostic techniques such as, for example, CT. It is likely over the coming years that the targeting ability of such nanoparticles will be more finely tailored to allow even greater specificity regarding site of action and new nanoparticle functionalisation strategies will be developed to mitigate potentially unwanted toxic side effects due to nanoparticle reactivity. For continued research in this area it is clear that tracking and analyzing nanoparticles in biological matrices will be key component. Indeed, it is foreseen that the technology platform being developed in the Smartnano project will enable the extraction of nanoparticles





from these complex biological matrices and subsequent analysis. As a practical example, nanoparticle debris generated from mechanical wear of implants within the body, and which have recently been found to cause significant toxic effects, could be isolated and analysed from a drop of patient's blood, or patients may be easily and cheaply monitored for presence of such debris over long time periods.

Could you give us some practical examples of applications and collateral research that could spawn in this area?

Photodynamic or magnetic hyperthermia therapies, using gold or iron oxide nanoparticles respectively, involves the absorption of light or radiofrequency energy by the nanoparticles which then heat up and destroy the surrounding cells.

Albumin nanoparticles are being used as delivery agents for the drug paclitaxel in treating pancreatic, breast and lung cancers.

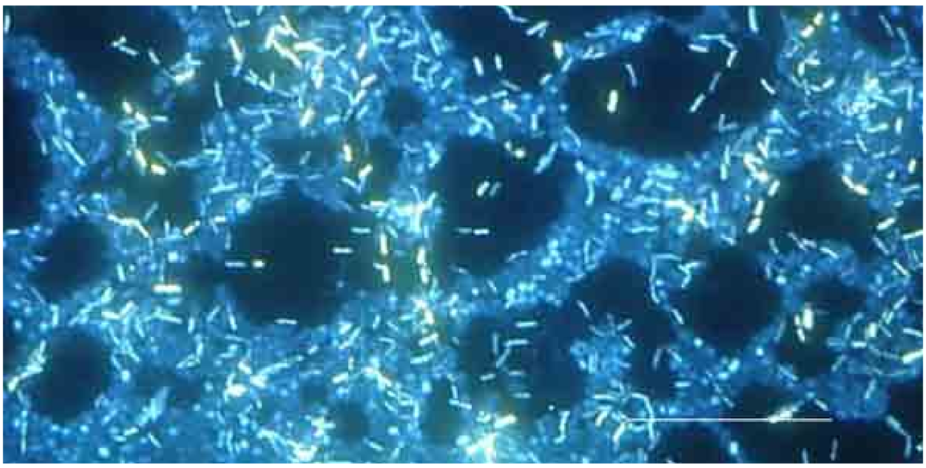
Contrast agents based on gold or lanthanide nanoparticles are being used to enhance the resolution of in vivo imaging techniques such as CT or MRI, respectively.

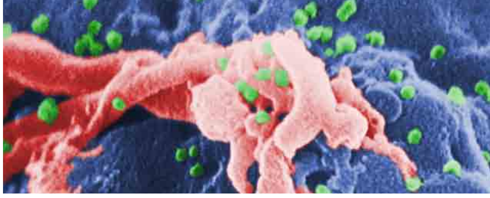
Biosensors based on fluorescent quantum dots or metallic nanoparticles may be used in microarrays for the detection of a wide range of targets, including bacteria, viruses, microRNA or specific markers such as prostate specific antigen or circulating tumour cells.

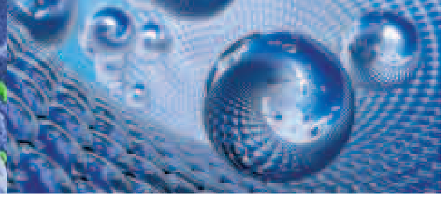
Nanoparticle-infused matrices such as wound dressings incorporate silver nanoparticles for their biocidal properties; molybdenum di-sulfite nanoplatelets have been used to improve the mechanical properties of biodegradeable polymeric composites used in bone tissue engineering.

Nanoparticles for (nano)medicine

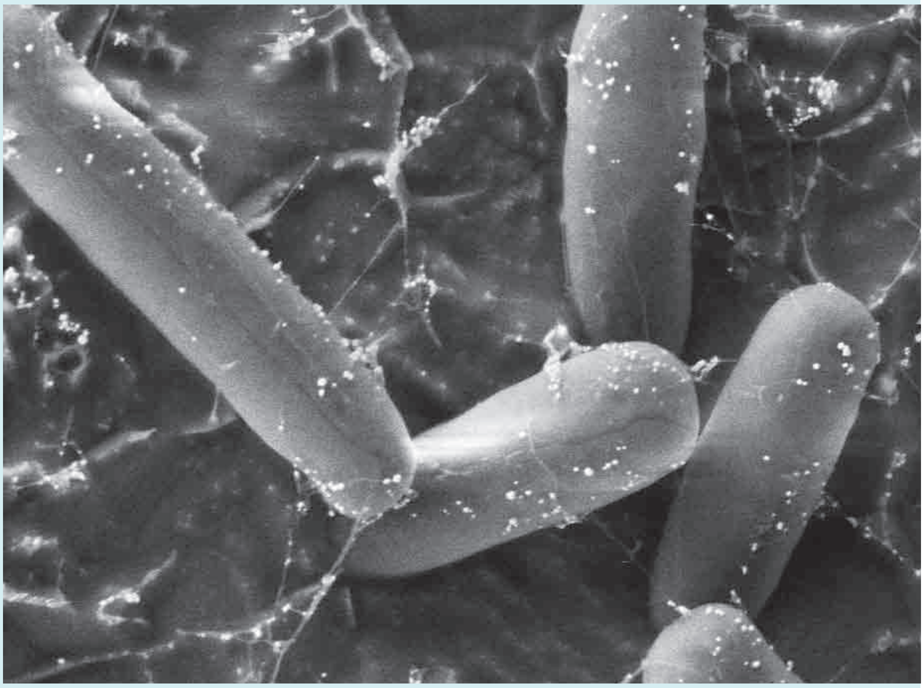
Next generation medicine will rely on innovative nanoparticles capable of unprecedented performance. Nanoparticles have indeed potential applications in diagnostics, imaging, tissue engineering, gene and drug delivery and other types of therapy. The expectations are high, among which a personalized and efficient treatment with lower side effects.
But which ones are the most promising candidates for the next generation medical applications? Iron oxide nanoparticles, gold nanoparticles and quantum dots have all generated substantial interest and their properties and applications have been thoroughly studied.
One of the key focuses is nano-imaging: the use of nanoparticles, often coated with biological molecules, in order to target and identify specific biological systems and conditions. Gold nanoparticles and quantum dots are providing extremely useful tools for in vivo imaging. Imaging techniques opened the way to nanoparticles targeting, which in turn is used for medical applications in diagnostic or to deliver drugs to specific areas of the body. Nanoparticles can be engineered and coated with biological molecules to specifically target organs, cancer tissue or other specific areas and release drugs only where needed, instead of throughout a living body. Thus, drugs that would normally cause collateral damage in the host can be targeted only where needed. This is especially useful for chemotherapy drugs that would otherwise cause relevant side effects.
However, ENPs raise biodistribution and biosafety concerns, as they can easily penetrate the living tissues due to their scale. ENPs for skin care or external applications can penetrate the skin and reach the blood and lymphatic circulation; circulating nanoparticles can be absorbed by the reticuloendothelial system; nano scale materials can be breathed and enter the blood flow through the lungs. Their fate once they enter a living organism may widely vary. Some are cleared from the body without really interacting with it. Some may accumulate in target organs, and can later be discarded through several pathways. The interaction of nanoparticles with the immune systems and the reaction they can cause in the innate and adaptive immune response also need further characterization. Following nanoparticles in vivo administration, the systemic circulation can distribute them to every body organ and tissue.
The nanoparticles currently used and studied for medical applications of course undergo severe tests to guarantee their safety and efficacy. Precise characterization of nanoparticles distribution and accumulation in the different body parts in preclinical models is required before any application in humans. The biodistribution of inorganic nanoparticles has been analysed in different preclinical models.
Nonetheless, understanding the effects of nano scale materials and ENPs in vivo would relevantly increase the number of tools available for future medicine.







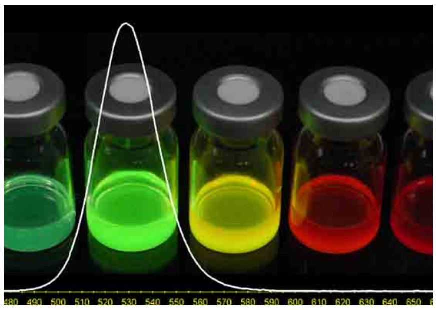
Biocides



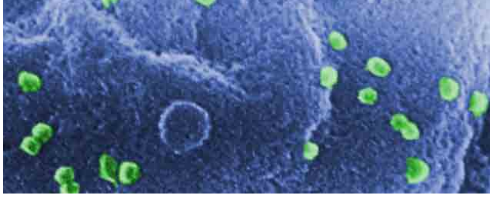
Silver nanoparticles are becoming increasingly common as a biocide. Applications include spraying silver ENPs solutions on fruit to protect it from bacteria.
Such antibacterial properties have been extensively applied by incorporating these particles in apparel, footwear, paints, wound dressings, appliances, cosmetics, and plastics. However, the same antimicrobial properties are raising some concerns: if silver ENPs can kill bacteria, what is their effect on the cells of other organisms?
By now we know that silver ENPs are toxic for green algae.
The effects of these particles on plankton and other life forms is also being studied extensively, but the behavior of these materials can be affected by a large number of variables, including coatings, aggregation, pH, temperature, and more.
Due to the increasing prevalence of silver nanoparticles in consumer products, there is a large international effort underway to verify silver nanoparticle safety and to understand the mechanism of action for antimicrobial effects.
Colloidal silver has been consumed for decades for its perceived health benefits, but detailed studies on its effect on the environment are still ongoing.

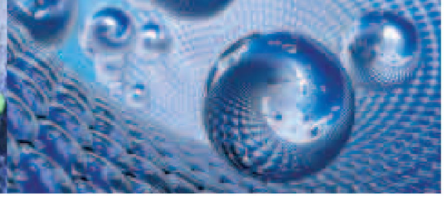
Endogenous nanoparticles

Some medical applications or devices can actually produce and release nanoparticles directly inside the body. The most common way for this to happen is through the wear of prosthetic devices. Friction between prosthetic articular surfaces can gradually produce particles in the nano scale over the years, or antimicrobial particles used to prevent biofilm formation can be released through the body. For instance, silver nanoparticles tested in thrauma implants, or reinforced nanoparticle polymers used in dentistry. Although for the most part these materials are perfectly characterized and safe on the larger scale, some of them show a different behavior in the micro and nano scales.
Recently the characterization of the release of metal nanoparticles from prosthetic device has provided results concerning the safety of these materials.
Although there are promising results with in vitro studies, the analysis of metal or polymer prosthetic implants that failed for other reasons led the medical society to better evaluate the safety threshold for metal nanoparticles in vivo, providing insights and safety thresholds for a wide range of materials, including chromium, cobalt, molybdenum, titanium, polyethylene and more. This threshold are extremely valuable in evaluating the safety of



ENPs in vivo, and prove the need for medical and scientific communities to interact on a wider scale to understand nanotoxicity. Future studies will be required to explore further the possible side effects associated with this kind of nanoparticles, to ensure their use in an effective and biocompatible way.





In vivo/in biota nanoparticle and the Smartnano project

In vivo and in biota detection and characterization of ENPs is one of the key focus of the Smartnano project.
The project system is designed to identify, quantify and characterize nanoparticles in a wide range of complex matrices.
Among these, biological matrices are of course of great interest. Furthermore, as part of the EU FP7 on nanoparticles, the Smartnano project is part of a larger effort to evaluate the safety of new nanomaterials and provide accurate systems to monitor their presence.

Closing notes

The Smart-Nano project is approaching completion.

*In the coming months, the **Smartnano partners** will validate their research, complete testing the device and the related samples and standards that were created for nanoparticles in complex matrices.*

*This issue of the **Smartnano newsletter** also completes the general overview of our target matrices for ENPs studies, and the general stage of the scientific diffusion.*

In the oncoming issues, the Smartnano newsletters will discuss the results of the project and provide some technical insights based on the experience and results obtained in the past years.

*The overall advancement of the **Smartnano project** was very satisfactory, and positive feedback was received.*

The consortium is also starting to presents its results through international conferences and publications.

*Please visit the **Smartnano official website** to check our latest publications and our presence in oncoming events, or to register for the project's newsletter.*

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