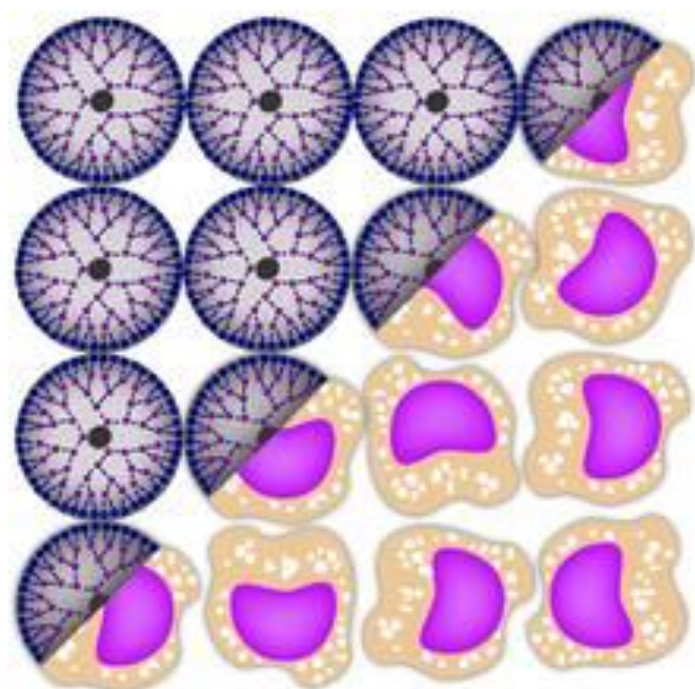




RESEARCH CONFERENCES



ESF-EMBO Conference

Interaction between the immune system and nanomaterials: safety and medical exploitation

4 – 9 October 2015
Pultusk, Poland

Chaired by: Diana Boraschi
Co-chaired by: Albert Duschl

<http://nanomaterials.esf.org/>

ESF-EMBO Interaction between the immune system and nanomaterials: safety and medical exploitation - Scientific Report

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Highlights & Scientific Report

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Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

It is inevitable that nanoparticles and the immune system meet. A major task of the immune system is to recognise foreign entities that are present within the body, and to decide whether they are dangerous and warrant defensive action. Most of such entities are not dangerous (think about food, clothes, commensal bacteria, etc.), so being recognised as foreign by the immune system does not mean that an inflammatory defensive reaction is automatically triggered. The default response of the immune response is in fact tolerance. Only when there are clear signs of danger, like toxins or materials released from necrotic cells, defensive actions start.

Engineered nanoparticles are foreign entities, so we would expect that the immune system recognises them as such. The question is now whether immune cells consider these entities dangerous or harmless. Since this is the same question that nanosafety researchers are trying to answer, the immune system should have direct relevance for us: immune cells are professional in evaluating risk and safety! Still, the contacts between mainstream immunology and nanotechnology are not very well developed. In an attempt to improve this, the **ESF-EMBO Symposium on Interaction between the immune system and Nanomaterials: safety and medical exploitation** took place at Polonia Castle, Pultusk, Poland from 4th to 9th October 2015.

It was chaired by Diana Boraschi (chair of the sub-group on immunosafety within the WG2 “Hazard” of the European NanoSafetyCluster) and co-chaired by Albert Duschl (WP leader for case studies within the FP7 EU project NanoValid). About 40 experts attended the meeting, from all career levels and from different fields, including immunology, nanotechnology, nanomedicine, materials sciences, pharmacology, biochemistry, biotechnology, law and business. The event was very international; in terms of continents only Australia was not represented.

In four days of presentations and discussion, younger and older scientists interacted lively and examined several aspects of the concepts and methodological approaches to understanding the features and outcomes of the interaction between nanomaterials and the immune system. Future perspectives in the scientific area, applicability of results in nanomedicine and nanosafety, regulatory, legal and economical aspects, education and job perspectives were also examined and discussed. But possibly the most striking result of the entire meeting was the easy and rapid establishment of a network of interaction among the participants, which will facilitate exchange, understanding, collaboration, and progress in the area.



I hereby authorise ESF – and the conference partners to use the information contained in the above section on ‘Conference Highlights’ in their communication on the scheme.

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Scientific Report

Executive Summary

(2 pages max)

While it is not possible to summarize a 4-day meeting in a brief note, some aspects that were discussed should be mentioned, to give a flavour of what types of questions are hot in this interdisciplinary field.

The meeting opened with talks by Albert Duschl and Ineke Malsch on the job market in nanotechnology, an aspect of obvious interest to the younger participants, but important also to senior scientists, who should provide training that is in line with job skill requirements.

Dose emerged – as so often – as crucial factor. Diana Boraschi pointed out that cell death is a normal event and immune cells like neutrophils or monocytes die normally within a few days or less. For this reason, cytotoxicity induced by nanoparticles in such short-lived cells is not necessarily damaging, unless it occurs at a massive scale. Moein Moghimi emphasized risks associated with nanodrugs, like adverse reactions up to anaphylactic episodes. The response is triggered by innate immune receptors like those of the complement system, which interact with particle surface, so surface characteristics have to be controlled to prevent them. Victor Puentes focused on trafficking and recycling of NPs, in which size is an important factor that can determine routes and uptake, and thus influences persistence and effective dose in the body. Albert Duschl called for more studies on nanoparticles that are not clean and thus closer to factory or consumer products, citing three studies from NanoValid, that used on-site collected materials, and particles intentionally mixed with allergens or with bacterial compounds. Only the last of these three studies gave data mostly as expected.

Cornelia Keck contributed to highlighting the importance of complement, pointing out that coating with opsonins or dysopsonins (*i.e.*, proteins that activate or suppress complement) can be used in targeting nanocrystals to the brain. Related to targeting, but also to toxicity, Donald Tomalia introduced the concept of the “periodic table” of nanomaterials, which, like the periodic table of elements, allows predictions about elements in advance. This concept, which he has developed originally for dendrimers, but which was now extended to include other particle types, has been successfully applied to engineer efficient “stealth” coatings to nanodrugs that escape immune detection. Moein Moghimi further elaborated the concept of “stealth”, pointing out that pathogenic bacteria use nanosized protein structures to escape the immune system, so they provide an example that facilitates targeting of nanodrugs especially to liver and spleen. Coming up in several talks was targeting to the brain, still the most challenging goal in nanomedicine, with several good approaches but generally low efficiencies.

Diana Boraschi discussed *in vivo* vs. *in vitro* models. It is a general consensus that all models have weaknesses, but they have different ones and thus can complement each other. Selection of appropriate endpoints is critical, as illustrated by her for a model of induction and resolution of inflammation in the gut. Laura Canesi presented a less familiar model, which is the marine mussel *Mytilus*. Since many responses of the body, including central parts of innate immunity, are conserved in invertebrates, these organisms can be compared to humans. Mussel hemocytes may thus be used

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to compare environmental impacts with effects in human monocytes. Lea Ann Dailey talked about her work on nanodrug delivery to the lung, highlighting the critical role of hydrophobicity, which correlates with local lung toxicity, as shown for different experimental nanoparticle carrier models. In-Hong Choi presented studies on mouse models of atopic dermatitis and of allergic asthma. While nanosilver had an influence on the phenotype of the dermatitis model, nanosilica had no effect during the acute phase of allergic asthma in the mouse. Rob Vandebriel addressed the issue of crystal structure of titania nanoparticles in determining effects on inflammasome activation and on the capacity of dendritic cells to present antigen, using both *in vitro* cell cultures and *in vivo* inhalation models. The bottom line is that, while both anatase and rutile particles increase allergic inflammation *in vivo*, anatase nanoparticles are more active in augmenting dendritic cell maturation and specific IgE production. It was underlined that, since the mouse model used (BALB/c mice) is genetically prone to developing Th2 responses, these data do not imply that titania nanoparticles can induce allergic reactions in humans.

Within the round table that concluded the meeting, Shadi Farhangrazi, an expert in economics of nanotechnology, introduced the participants to the nanomedicine market and explained the ways and rules of business in this area. She provided many tips and suggestions for those who plan to create a company. The round table continued with a series of issues and discussion that will be reported below, in the section dedicated to the Forward Look.

Forward Look

(1 page min.)

- *Assessment of the results*
 - *Contribution to the future direction of the field – identification of issues in the 5-10 years timeframe*
 - *Identification of emerging topics*
-

Assessment of the results

Moein Moghimi led the Forward look discussion, which defined a series of issues that the participants considered worth of an in-depth analysis. These included three major issues:

1. the **application context** of the nano-immune interaction studies. The participants have identified pharmaceuticals, diagnostics, vaccination, and environmental exposure (accidental, work-place related, on both humans and environmental biota) as central issues. The analysis of nanomedicine-related issues should include materials' choice, complexity, manufacturing feasibility, regulatory and approval suitability, product development.
2. the **structure-activity relationship** in nanoparticles in relation to their immune-targeted effects. Again, as already mentioned during the scientific programme, dose was identified as a central issue, as well as accurate characterisation of the particles, evaluation of bioactive contaminants such as endotoxin and the feasibility of their removal after synthesis, and the types and suitability of the analytical models (*in vivo* vs. *in vitro*, simple vs. integrated, systems approach, relevance to disease/diseases progression/therapeutic course).
3. the need of **progressing beyond what is already known**. The senior experts in the faculty underlined the important fact that most of the studies currently performed seem to ignore a wealth of studies and data of 30-50 years ago that had practically already described and analysed in great detail many of the problems addressed. The general recommendation of the senior faculty members to the younger researchers was that reading and studying the data of the past will allow them to move forward their research, rather than staying blocked and re-inventing the wheel. The problem with many new journals, also those that are heavily

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cited and have high impact factor, is that in many instances the editors do not seem to be able to find reviewers that are sufficiently knowledgeable to identify the lack of novelty of the submitted manuscripts.

Contribution to the future directions

The foresight discussion focused on the possible future directions in which research on nano-immune interaction should go. The audience identified two major focus areas, human diseases and environment, in which studies on nano-immune interaction would find applicability and exploitability in the future. The discussants underlined the necessity of introducing the issue into the more general context of safety and efficacy of nanomedicine and nanotechnology at large, and examined the various possibilities of obtaining dedicated funding. All agreed that global networking is required, and immediately started to discuss possible collaborations, exchange of materials, and harmonisation of characterisation procedures. The audience also discussed on the feasibility of founding a European Nano-Immune Characterisation Lab, based on the US experience of the NCL but specifically focussing on the nano-immune interaction. While everybody thought the concept is excellent and exciting, the participants entered into a lively discussion on various aspects of its practical implementation.

Identification of emerging topics

In general, the entire topic of nano-immune interaction can be considered as an emerging topic. The fact that the meeting has gathered a limited number of participants, although such participants come from all over the world, underlines the fact that the topic is acknowledged everywhere but still overlooked by the majority of the scientific community. The raising in awareness attained with this meeting, and the enthusiasm of the participants in the wish of increasing their knowledge and pursuing the issue more in depth, testify the importance of the topic and the intellectual investments that the scientific community is willing to deploy in it.

- Is there a need for a foresight-type initiative?

A foresight initiative would be important, as the present one has been, for better focusing on the future perspectives and developments of the topic, as well as for defining and harmonising methods and procedures in order to provide the relevant scientific and technical support to the nanomedicine and nanosafety business.

Business Meeting Outcomes

- *Election of the Organising Committee of the next conference*
- *Identified Topics*
- *Next Steps*

Some of the members of the faculty (Boraschi, Duschl, Moghimi, Puntès, Tomalia, Dailey) have met and discussed the possibility of running other conferences like this one in the future. Since it appears that ESF has no intention of continuing organising such conferences (which is a real pity, given their great expertise and the general success of their initiatives), we did explore the possibility of approaching other funding agencies and scientific organisations. Everybody agreed that, given the excellent outcome of this first meeting, the conference should be maintained and should become a regular appointment (every two years) for continuous education and updating.

Given the expected lack of support from ESF in the future, the faculty members did not go too much into the details of the next organising committee, topics and practical procedures. Boraschi and Duschl

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were available for doing it again, with the help of the other members, and the agreement was that a format similar to the first one could be successful, with emphasis on the participation and involvement of the younger participants, with a good blend of scientific concepts, technical issues and “collateral” topics such as career development, regulatory and marketing considerations. In any case the first and key issue is that of identifying a funding agency willing to take over the conference.

Atmosphere and Infrastructure

▪ *The reaction of the participants to the location and the organisation, including networking, and any other relevant comments*

The participants seemed particularly satisfied with the location. The idea of having a meeting in a secluded place was very effective, as it avoided the risk of having the participants leaving the venue for touristic reasons or other business. The drawback was the difficulties in reaching the place (2-3 h drive from the Warsaw Chopin airport). The difficulty was increased by the fact that, for budget reasons, the organisation reduced the shuttle buses from Chopin-Pultusk and Pultusk-Chopin from three to one. This has forced many of the participants either to wait long hours at the airport, or to organise alternative transportation at their own expenses.

The atmosphere of the entire meeting was very informal and friendly, encouraged by the room sharing, the common meals and the many occasions for meeting and interacting. The on site organisation was superb, with Marie-Laure Schneider always present to organise every single detail and to help solving also the smaller problem. The local collaborators were also excellent in supporting Marie-Laure and the scientific chairs.

Networking took place naturally and very fast. The senior participants were glad to see that the junior fellows were actually seeking their advice, while on the other hand discussion with the junior fellows has opened new interests and perspectives also to the senior scientists. The interdisciplinary aspect was also particularly stimulating for all, as many lab scientists were exposed for the first time to issues of economics, training, marketing and regulatory.

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Date & Author: September 10, 2015 Diana Boraschi