# Nanoparticles and the Immune System

## Safety and Effects

Diana Boraschi
Albert Duschl

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# Nanoparticles and the Immune System

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# PREFACE

This book has the objective to provide a reference text for toxicologists, materials scientists, and regulators by covering the key issues that define interaction of nanomaterials with the immune system. Altering immune responses can lead to many kinds of pathologies; therefore, it is important to make adequate assessments before new nanomaterials are introduced in the market. On the other hand, negative perception and excessive concerns, based on incomplete or misleading results, need to be avoided by communicating existing knowledge and by defining in the future clear endpoints and thresholds for immunosafety regulations.

Nanotoxicology investigations often focus on toxicity leading to death of cells or organisms, while important immune parameters can be affected much earlier and at much lower doses. Some aspects of immunity, for example allergic sensitivity and heightened danger for risk persons with a frail immune system, are usually not covered at all. This gap in nanosafety assessment needs to be filled, not only from a scientific point of view but also for a better implementation of relevant safety regulations. A friend and nanotoxicologist, Jan Mats, told us once: "if we do not consider immunity, we keep studying the mouse without seeing the elephant in the room." To increase the awareness of the importance of immunity in nanotoxicology, several years ago we started the Immunosafety Focus Group within the Working Group "Hazard" of the EU-supported NanoSafety Cluster, and this book intends to disseminate knowledge gained by the research community in this field.

The book covers several issues that all stakeholders in nanotechnology should be aware of: identification of endpoints that are relevant for assessing hazard, evaluating impact on immunologically frail populations, considering allergic responses, and how to evaluate chronic/cumulative effects. In addition, the book addresses a very important issue, that is, how to shape and turn the immunomodulating properties of nanomaterials to our advantage for preventive strategies (such as vaccination) or for therapeutic approaches in diseases where immunostimulation is

desired (infections, tumors) or where immunosuppression in needed (inflammatory diseases, allergies, autoimmunity).

Our goal is to raise awareness about the effects of nanomaterials on our immune system, in order to ensure a safe design or safe use of such materials. We also want to emphasize an especially useful role of the immune system: it has been optimized by evolution to identify whether or not specific foreign materials are dangerous to the body. Finding that out is also the key question in nanosafety, so knowing the opinion of the professional immune cells should be of particular interest to us.

**Diana Boraschi and Albert Duschl**

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# CONTENTS

CHAPTER 1

# How Innate and Adaptive Immunity Work

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## 1.1 THE IMMUNE SYSTEM: PROTECTING THE BODY FROM DAMAGE

The human body exists in a hostile environment. Besides macroscopic dangers, the body needs to defend its integrity from the invisible attacks by infectious agents (bacteria, viruses, unicellular and multicellular parasites), poisons, and contaminants in air, water, and food. Other dangers come from within, those posed by the senescence, damage, or anomalous behavior of the body's own cells and tissues.

The survival and integrity of our body relies on a very sophisticated system of recognition of danger and of reaction to it, the immune system [1]. The immune system is a complex of cells and soluble factors, scattered throughout the entire body, which has the function of surveilling the body's well-being, by detecting and eliminating potentially dangerous events/agents. The immune cells patrol the body, and in particular the areas more exposed to the external environment (skin, mucosal surfaces of lung, gut, and reproductive organs). Molecules or agents that pass the mechanical barriers (mucus, keratinized epithelium, mucosa) are sampled by immune cells, which decide whether the foreign element may represent a danger or not, and act consequently. If the nonself element is considered to be a threat, the immune system mounts a defensive reaction to destroy the agents that are considered as potentially dangerous.

Which are the optimal characteristics of an effective immune response? Two are particularly important:

1. *Rapidity*: The immune reaction must be fast, leaving no time to the dangerous agent to multiply and gain access to the inner body and cause serious damage.

2. *Specificity*: The immune system must be able to discriminate between what is dangerous and what is not, so as to target the dangerous agent only and spare the surrounding cells and tissues.

How can the immune system reach the opposing goals of being both rapid and specific? In fact, being quick means having no time for developing sophisticated specific weapons, it is like firing cannonballs, which may well destroy the target but also cause substantial collateral damage. On the other hand, being specific means that some time is required for designing and building the right tools, but the risk is that during this time the dangerous agent may further invade the organism and endanger its survival.

This is why, in higher vertebrates including man, **two immune systems are active in parallel**. The innate immune system is the more primitive, rapid, and nonspecific system, with prebuilt weapons always ready to be fired. The adaptive immune system on the other hand is the sophisticated and highly specific system that, each time a dangerous agent comes in, builds new weapons specifically targeting that agent. The adaptive immune system has an additional characteristic, it can learn. This means that after having encountered a foreign agent and having designed and built the specific weapons, the cells of the system keep memory of what they have done and, if the same agent is encountered again (for instance an infective virus), the system can rebuild the specific weapons much faster and get rid of the infection much quicker.

The innate immune system is the defensive system that is already present in plants and lower animals (insects, worms, sponges, etc.). Adaptive immunity developed as consequence of a single molecular event in bony fish and, due to its evolutionary advantage for larger and long-lived species, it has been maintained and expanded into highly sophisticated system in higher vertebrates. Thus, man possesses both immune systems acting in concert. Table 1.1 summarizes the main characteristics of innate and adaptive immunity.

## 1.2 INNATE IMMUNITY

The innate immune system (see Chapter 2 for full details) is the more primitive defense system and is based primarily on phagocytosis [1]. Foreign agents and particles, as well as damaged cells of the own

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