International Journal of
Medical Nano Research

Achilli et al. Int J Med Nano Res 2015, 2:1

Commentary: Open Access

Bnct and Nanoparticles: A Long Way to a Routine Clinical Method

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We have recently had the chance to read the editorial "Boron Neutron Capture Therapy of cancer as a part of modern nanomedicine" [1], by Alexander V. Safronov, in which the potential of nanomaterials as boron-carriers for the treatment of many types of tumors by BNCT is discusses. The author argues that "Most of the modern papers on BNCT report 'potential' BNCT agents […] and don't even include cell studies", and "In some cases the abbreviation BNCT may become a 'golden ticket' for authors who just want to public their current study without intent to continue". We agree with the first assertion, which is unequivocally verifiable by reading the recent literature about BNCT, but not with the second, that is somewhat speculative.

The study for a new drug is complex and may last ten years or more. It includes the preparation of the molecule in a pure form, the experimentation on cell lines, the animal testing, and the three phases of clinical trials on humans. In the case in which *in vitro* results already point to a possible cytotoxicity, additional *in vivo* tests on animals become inopportune on the basis of ethical principles that have been even reinforced by novel laws promulgated in some countries, such as the new European regulation (2010/63/UE), that strongly restrict inessential *in vivo* experiments. Therefore, a scientific work can be interrupted at an early stage and, unfortunately, the obtained data remain generally unpublished, staying hidden to the rest of the world.

In a field such as nanotechnology, when little differences in size, shape and chemical-physical properties of nanoparticles induce great alterations in the interaction with biological systems, the failures and the frustrating difficulties in the interpretation of the results are widespread.

A dramatic obstacle that is encountered in the application of nanomaterials for biological purposes (especially for BNCT, in which the compound must be administered as a homogeneous suspension by intravenous infusion), is their strong tendency to aggregate/agglomerate, in aqueous solvents, into large particles of micrometric size, by reason of their thermodynamic properties. These micrometric particles, besides having an elevated sedimentation rate, induce several adverse reactions to blood components (e.g. thrombi, inflammation, and hemolysis) and, most importantly, will never be internalized by target cells. The stability of nanoparticle suspensions is influenced by several parameters, including: the intrinsic properties of the nanomaterial (size, porosity, surface polarity), the characteristics of the medium (viscosity, pH, ionic strength, ionic composition, presence of molecules and/or macromolecules), and nanoparticle concentration. The addition of various molecules can partially stabilize some types of nanoparticles in suspension, but often these additives are not compatible for medical use, because toxic (e.g. alcohols, surfactants) or anyway contraindicated for intravenous injection [2,3].

Little is yet known about the interactions between nanomaterials and biological systems. The safety issues derived from nanoparticle routes of entry and their potential bio distribution are probably governed by size, surface area, shape, agglomeration/aggregation tendency, and binding to biological structures. Many types of nanomaterials display strong toxicity to cells during the *in vitro* experiments [4] and, furthermore, induce thrombotic [5], inflammatory [6] and hemolytic [7] effects during experiments with purified human blood cells. For some of these materials, however, functionalization with various organic molecules may reduce the toxicity and the unwanted biological effects, making it desirable to continue the studies in this direction [8,9]. Nevertheless, so poor is the current knowledge concerning the bio distribution, metabolism, clearance mechanism and the consequences of accumulation in the body of the new classes of nanoparticles, that the precautionary principle should discourage their use with lightness in humans [10]. It should be noted, however, that toxicity and adverse effects toward blood cells are not a phenomenon caused only by nanoparticles, in fact also non-nanostructured soluble molecules may trigger strong unwanted biological consequences [11,12].

On the basis of the above mentioned criticalities about nanomedicine, it is evident that the absence in the literature of detailed investigations, for most of the materials proposed for BNCT (and for many other biological fields of application), should not be intended as a shortcut adopted by researchers hasty to publish their results. On the contrary, it is related to intrinsic serious difficulties that slow down the development in this promising area of research, and that show how several types of nanomaterials, although theoretically valid for their application in medicine, are *de facto* incompatible with therapeutic use.

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Citation: Achilli C, Grandi S, Ciana A, Minetti G (2015) Bnct and Nanoparticles: A Long Way to a Routine Clinical Method. Int J Med Nano Res 2:007

Received: October 29, 2014: **Accepted:** January 21, 2015: **Published:** January 22, 2015

Acknowledgements

This work has been supported by FondazioneCariplo, Italy, grant n. 2011-2099.

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