Opinion Paper **Open Access**

Tore Skotland*

How organizers of scientific meetings and journal editors could facilitate transfer of nanomedicine into the clinic

DOI 10.1515/ejnm-2015-0048
Received November 13, 2015; accepted December 1, 2015

Abstract: This opinion paper contains views on how organizers of scientific meetings and journal editors can facilitate transfer of new nanomedicine into the clinic. The need for interdisciplinary discussions at such meetings are emphasized, as well as the importance of learning from the regulatory authorities and large pharmaceutical companies about what is needed to bring new products into clinical use. The importance of improving the review process of translational studies published by the main nanomedical journals is pointed out as very important for bringing the field forward and to increase the level of scientific discussions in general.

Keywords: approval process; biosimilars; cross-disciplinary; nanomedicine; scientific meetings.

Introduction

During recent years there has been an extensive research on new nanoparticles (NPs) for delivery of drugs or contrast agents for imaging of various diseases. There is no doubt that there is a large potential for such use of NPs. Although some NPs have been approved for clinical use, and many more are in clinical trials, approvals of new NPs are going slower than many researchers in the field expected some years ago. The present thoughts about how organizers of scientific meetings could help to bring nanomedicine more rapidly into clinical use appeared during the CLINAM Meeting in Basel 2015.

***Corresponding author: Tore Skotland,** Centre for Cancer Biomedicine, Institute for Cancer Research, Faculty Division Norwegian Radium Hospital, University of Oslo and Department of Molecular Cell Biology, The Norwegian Radium Hospital, Oslo University Hospital, 0379 Oslo, Norway, Phone: +47 22 78 19 33, Fax: +47 22 78 17 98, E-mail: tore.skotland@rr-research.no

Scientific meetings

Cross-disciplinary participants

Development of new NPs for clinical use has to include collaborations between experts in many different areas, such as (a) synthesis and manufacturing of NPs; (b) physiochemical characterization of NPs; (c) in vitro cell studies; (d) in vivo preclinical studies, including efficacy, safety, biodistribution, metabolism and excretion studies; (e) in vivo imaging studies; (f) and clinical studies. Thus, it is important for organizers of meetings/conferences to promote discussions between scientists from all these disciplines. Moreover, when scientists from many different disciplines are participating it is essential to have sufficient time for questions and discussions after each presentation and during poster sessions and breaks.

Research and development of new drugs were some years ago mainly ongoing within pharmaceutical companies. There is now a clear trend that many companies are reducing internal research activities and looking for opportunities to take over development of drugs after the early research work has been carried out at universities or hospitals. Most scientists know very little about what is needed to bring products into clinical use, and NPs are in general more complicated in such respect than low molecular weight drugs with a well described structure. Thus, it is important that meetings focusing on translational research with NPs include time for presentations by regulatory authorities of what is needed of documentation studies to obtain market approval. I believe that it would be of great help for many researchers to understand how the time needed for development studies and the cost of such studies may differ for various types of products. What do the authorities expect to receive of documentation for different types of new NP-based therapeutics, contrast agents, or the combined products called theranostics? Also, what do they require for biosimilars,

i.e. products to be marketed when the original products have gone off patent (similar to generics)? Such knowledge may help investigators in choosing among several product candidates and not selecting a candidate for which it is almost impossible to obtain regulatory approval. We have recently discussed some of these issues and also the risk/benefit analysis one can expect pharmaceutical companies to perform before they start expensive developing studies (1). One challenge in the field of drug development is that there are many regulatory authorities with partly different views on what is needed to bring new drugs to the market. Meetings like CLINAM obviously have contributed to bringing several of the major regulatory authorities together, and representatives from several of these authorities stated during the last CLINAM meeting that they are making progress in their discussions regarding collaboration and harmonization. Despite that, one should not expect a very rapid progress in such a harmonization process. Nevertheless, it is important that organizers of meetings continue to invite participants from the regulatory authorities in order to stimulate further discussions between the authorities and between them and scientists. The regulatory authorities should be asked to contribute with lectures about which hurdles scientists can expect to meet if they want to bring new products into clinical use. It would also be beneficial to invite large pharmaceutical companies to tell about their experience with the drug approval process. The industry should be interested in doing so, because it would increase the likelihood that they in the future will get access to more interesting products for their development.

Presentations and discussions

At CLINAM this year it was very clear in a session about biosimilars that there is a challenge about what to present and discuss at such meetings. A couple of presentations could be selected to discuss issues related to information given by companies that have products on the market or are close to bringing new products to the market. I have chosen to illustrate this with the case of Abraxane as I have followed the information about that product closely for several years (because I have myself been involved in bringing an albumin-based product to the market). First, I would like to state that I fully understand that people who have developed a new and interesting product have to be very careful about what they are telling outside the company. However, that means that we cannot expect that they are presenting the complete story about their products. Several years ago Abraxane was said to consists of nanoparticles of 120 nm that were taken up by caveolae, which seemed very unlikely since caveolae should not be expected to take up particles larger than 80 nm (2). Later, company people told us that the Abraxane particles are rather rapidly solubilized following intravenous injection, and this year it was stated that the product was designed to be solubilized shortly after injection. Also, we heard for the first time that the albumin is cross-linked, giving a specific ratio of albumin monomer/dimer/trimer/tetramer. The cross-linker or the ratio of different albumin forms in Abraxane have to my knowledge not been published and was not mentioned at the meeting. The reason that the company now released this new information seemed obvious; they would like to make it more difficult for other companies to make a similar (i.e. biosimilar) product. Thus, they showed data for four other biosimilar products of Abraxane and stated that they all were different from Abraxane without showing the Abraxane data. Several questions come to my mind regarding this example. Should companies be allowed to show comparing data for biosimilars and state that they are different from their own product without showing data for their own product? Should companies be allowed to market an albumin-based product without stating that the albumin molecules have been cross-linked and which cross-linker that is used? This information may be very important regarding possible immunological reactions against the cross-linked structures.

Approval of biosimilars

How similar must a biosimilar be compared to the original product? For traditional drugs with a well described structure it is obvious how the generic structure must be, but, e.g. for NPs it might even be that the company marketing the drug is not producing exactly the same product in different batches. When using albumin as a raw material, it would not be surprising if albumin delivered by various suppliers may result in different products. As mentioned, I have myself been involved in developing an albumin-based product where we after screening albumin batches delivered by many different suppliers were able to manufacture the product in a reproducible way only when using albumin from one single supplier [(3) and references therein].

What criteria should then be used for approval of biosimilar NPs? I believe that such approvals have to focus on the biological similar effects as it might be impossible to make products identical to the original. Furthermore, it is not given whether the biosimilar has a biological

effect similar to, or being better or worse than the original product; only the studies of the biological effects can answer that question.

Journal editors and reviewers

A PubMed search (November 12, 2015) with the search term "nanoparticles" revealed that close to 120,000 articles have been published, with 14,600 articles published so far in 2015. Using the search term "nanomedicine" the corresponding numbers were 11,430 and 2455. Thus, an amazing number of articles are published and the number published per year is increasing every year. In my opinion too many of these articles are not of the quality needed in order to bring this field forward in an optimal way. This is worrisome because young scientists read and may believe in what is published. We probably have to accept that there may be new journals with less than the wanted quality in a rapidly increasing new field like nanomedicine. It worries me more to see how often "high impact journals" in the field publish articles where the data do not support the conclusions drawn. We have published a couple of articles where we have commented upon some issues that are important to improve (1, 2, 4). I have tried a couple of times to comment on articles in high impact journals, but my experience is that editors often seem to enter into a defense position, and I wonder if they will not like to visualize for everybody the lack of quality during the review process. It looks like many editors especially have problems in obtaining reviewers with the needed competence for cross-functional translational research. I am sure that editors do their best in the review process, but my point is that it is extremely important that at least editors of high impact journals before accepting a paper claiming to demonstrate important new information for development of new drugs should include expert reviewers of all disciplines relevant for that article. This is extremely important for bringing the field forward and to increase the level of the scientific discussions at meetings/congresses.

Acknowledgments: This author was supported by the Research Council of Norway through its Centre of Excellence funding scheme (project number 179571) and the NANO2021 project "Biodegradable nanoparticles in cancer diagnosis and therapy" (project number 228200/O70).
Conflict of interest statement: The author states no conflict of interest. He has read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirms that he complies with all its parts applicable to the present scientific work.

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Bionote

Tore Skotland
Centre for Cancer Biomedicine, Institute for Cancer Research, Faculty Division Norwegian Radium Hospital, University of Oslo and Department of Molecular Cell Biology, The Norwegian Radium Hospital, Oslo University Hospital, 0379 Oslo, Norway,
tore.skotland@rr-research.no

Tore Skotland, received his PhD in Biochemistry from the University of Bergen, Norway in 1980. He moved to pharmaceutical R&D in 1983 (Nycomed, Oslo), where he stayed for 26 years in one of the world leading companies developing contrast agents for medical imaging (Nycomed was bought by Amersham in 1997 and Amersham was bought by GE Healthcare in 2003). For 20 years he was heading work to describe the biodistribution, metabolism and excretion of all types of contrast agents for CT, MRI, ultrasound, SPECT, PET and optical imaging. He has been involved in bringing five products to the market (including two particle-based) and another five products into clinical trials. Since 2009 he is a senior researcher at the main cancer hospital in Norway.