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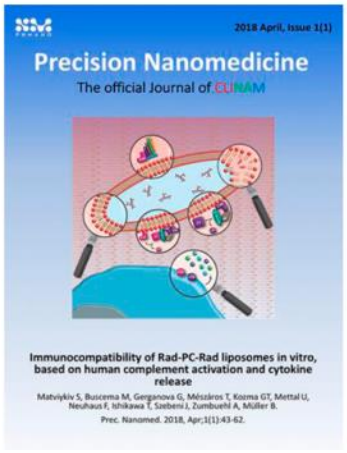

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Preamble

The Story of Precision Nanomedicine – the Journal

Lajos P Balogh
Editor-in-Chief, Precision Nanomedicine

Prec. Nanomed. 2018, Apr; 1(1):1-4. DOI: 10.29016/180328.1

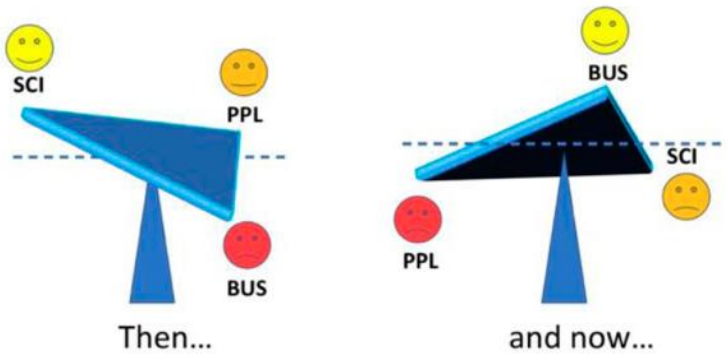
There is a growing need for responsible publishing and sharing reliable results. This means not just publishing for the sake of having one more publication, but sharing information which, in addition to basic science, educates about research and development (R&D) knowledge, and how to turn knowledge into practice. Forced to chase originality and novelty, many investigators now pursue only novel materials and complicated approaches to fulfill the criteria to make their manuscripts acceptable. *Originality and novelty are like designs and prototypes at a fashion show: they reveal a new concept but most of them could not be worn on the streets*. Without in-depth and *reproducible studies* and R&D knowledge, it is impossible to develop practical (nano)medicines for everyday use. While many societies hire for-profit publishers to run their media, we have decided to create our own publishing company. In January 2018, and with the support of the European Foundation for Clinical Nanomedicine (CLINAM) and the International Society for Nanomedicine (Basel, Switzerland) we founded our own publishing organization in New England – in one of the traditional hubs for medicine and materials science.

Editorial

Balancing Interests of Science, Scientists, and the Publishing Business

Lajos P Balogh
Editor-in-Chief, Precision Nanomedicine

Prec. Nanomed. 2018 Apr; 1(1):5-14. DOI:10.29016/180418.1



In the closely coupled system of diverse interests of science, those of scientists (authors, reviewers, and readers), and their organizations (universities, research institutions, and publishers) every component is undergoing major changes in the digital era. In reality, these interests are deeply interconnected and long-term dominance of any one of these could hinder progress in many different ways. For science, originality and novelty do not have merit

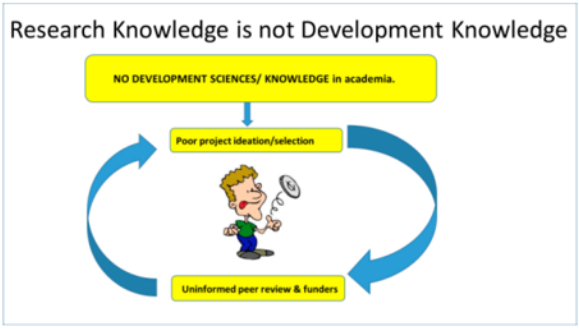
without reproducibility; for scientists, quantity is not a substitute for quality, and if businesses focus only on profit, it will suppress the value of their publications. Science, scientists, and organizations not only coexist, but cannot exist without each other, therefore all participants must adjust their actions to avoid devaluation of the whole. Many efforts are underway to regain this balance, and one possible approach – ours at *Precision Nanomedicine* – is described here.

Opinion

Improving Innovation in Nano-Healthcare Funding

Mike Eaton
ENATRANS

Prec. Nanomed. 2018 Apr;1(1):15-17 DOI:10.29016/180108.1



"…the transition from research to development requires informed debate and high-quality data and is a very challenging milestone. Researchers often say they are developing a new drug, when they are in fact doing research – funders also use the terms (R or D) interchangeably - an unfortunate consequence of their academic training. A simple test is if you don't know actually what you are developing - you are in research."

From the Clinical Editor: The author here describes the importance of R&D knowledge and its necessary funding. This is often a neglected aspect by many researchers and funding agencies, as the ultimate aim of carrying out research is creating products to bring benefits to clinical patients.

Reviews

Origins to Outcomes: A Role for Extracellular Vesicles in Precision Medicine

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Extracellular vesicles (EVs) are of great interest in biological research, and though they are a relatively recent discovery, they have rapidly shown great potential for use in clinical applications. The various techniques used in EV isolation along with their respective strengths, weaknesses, and potential for downstream applications are outlined here. A brief description of the different approaches in exosome characterisation are subsequently described. It has been highlighted that despite the recent developments in these processes, there is still a great deal of refinement to be made. EVs are produced by almost all cell types, found in many biological samples, and are implicated in multiple biological processes including cargo trafficking, cell-cell communication, and signal transduction. The presence of these EVs and their varied cargo in a biological sample can be indicative in disease diagnosis, and guide precision medicine-based approaches to disease management. EVs have been reported to act in the benefit of the cell through moderating repair and regeneration, but they can also act to the detriment of the cell through increased tumorigenesis and metastasis. This duality is intriguing as it can allow for the use of EVs in distinct therapeutic approaches and displays their versatility in potential downstream applications. In this review, examples of the cellular roles of EVs and their applications in pathological and regenerative contexts are explored. In reviewing some of the developments made in recent times, EVs are shown to be very promising both in diagnostic and therapeutic approaches.

From the Clinical Editor: Extracellular vesicles (EVs) are involved in various biological processes such as cargo trafficking, cell-cell communication, and signal transduction. The advances in nanotechnology have enabled researchers to utilize EVs for potential use in clinical applications, within the so-called precision medicine

approach. In this review article, the authors discuss the techniques used in EV isolation in length, together with their applications in clinical diagnosis and therapeutics.

A porcine model of complement activation-related pseudoallergy to nano-pharmaceuticals: Pros and cons of translation to a preclinical safety test

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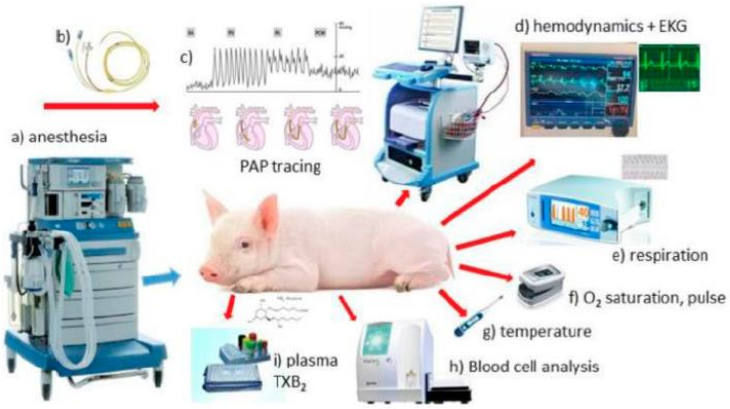
Prec. Nanomed. 2018 Apr;1(1):63-75, DOI: 10.29016/180427.1



Pigs provide a sensitive and quantitative animal model of non-IgE-mediated (pseudoallergic) hypersensitivity reactions (HSRs) caused by liposomes and many other nanoparticulate drugs or drug-carrier nanosystems (nanomedicines). The rapidly arising symptoms, including cardiopulmonary, hemodynamic, hematological, blood chemistry and skin changes, resemble the clinical picture in man undergoing infusion reactions to reactogenic nanoparticles. In addition to summarizing the basic features of the pig CARPA model, the review considers some of the advantages and disadvantages of using the model for preclinical evaluation of nanomedicine safety.

From the Clinical Editor: Due to potential hypersensitivity reactions to nanodrugs, thorough testing is required before these drugs can be used in the clinical setting. Here the authors provide a succinct review on the use of pigs as a reliable in-vivo model for pre-clinical drug testing.

Communication

Discrepancies in the in vitro and in vivo role of scavenger receptors in clearance of nanoparticles by Kupffer cells

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Nanoparticles are recognized and cleared by Kupffer cells (KCs) in the liver. This process complicates the development of targeted nanoparticles because of significant reduction of number of nanoparticles that can reach target tissues. Macrophage scavenger receptor SR type AI/II is the central phagocytic receptor that has been shown to promote *in vitro* uptake of many nanoparticle types. In this paper, the authors set out to clarify the role of SR-AI/II in the *in vivo* liver clearance of 10kDa dextran superparamagnetic iron oxide (SPIO) Feridex-IV® and 20kDa dextran-coated SPIO nanoworms (SPIO NWs). Feridex showed efficient SR-AI/II-dependent uptake by isolated KCs *in vitro*, whereas SPIO NWs showed no uptake by KCs. Both Feridex and SPIO NWs showed a very short and nearly identical circulation half-life and efficient uptake by KCs *in vivo*. The SR-AI/II inhibitor, polyinosinic acid, prolonged the circulation half-life of both Feridex and SPIO NWs, but did not reduce the KC uptake. The circulation half-life and KC uptake of Feridex and SPIO NWs were identical in SR-AI/II-deficient mice and wild-type mice. These data suggest: (1) there is a limited correlation between *in vitro* and *in vivo* uptake mechanisms of nanoparticles in KCs; and (2) redundant, SR-AI/II independent mechanisms play a significant role in the

nanoparticle recognition by KCs *in vivo*. Understanding the complexity of nanoparticle clearance assays and mechanisms is an important step to improving the design of "stealthy" nanoparticles.

From the Clinical Editor: One of the ways that nanoparticles are cleared in the body is via Kupffer cells. In this paper, the authors tested the role of scavenger receptor SR-AI/II in the clearance of dextran superparamagnetic iron oxide (SPIO) Feridex-IV® and dextran-coated SPIO nanoworms (SPIO NWs). Results here show that multiple pathways and mechanisms exist in nanoparticle clearance. Thus, further understanding of nanoparticle clearance would be required to prolong in vivo half-life.

Research Article

Immunocompatibility of Rad-PC-Rad liposomes in vitro, based on human complement activation and cytokine release

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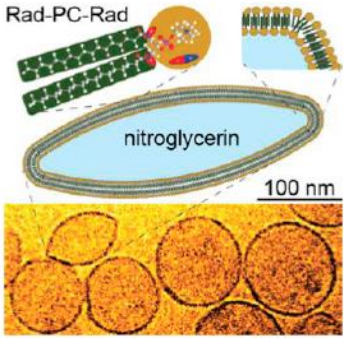
Prec. Nanomed. 2018 Apr;1(1):43-62. DOI: 10.29016/180419.2

Graphical Abstract: The mechano-responsive Rad-PC-Rad liposomes, designed to deliver a vasodilator drug to stenosis, are stable even at elevated body temperatures. The question is whether these nano-containers with a specific shape present adverse effects similar to liposomal drugs *in vitro* or they don't.



Liposomal drug delivery systems can protect pharmaceutical substances and control their release. Systemic administration of liposomes, however, often activate the innate immune system, resulting in hypersensitivity reactions. These pseudo-allergic reactions can be interpreted as activating the complement system. Complement activation destroys and eliminates foreign substances, either directly through opsonization and the formation of the membrane attack complex (MAC), or by activating leukocytes and initiating inflammatory responses via mediators, such as cytokines. In this study, we investigated the *in vitro* immune toxicity of the recently synthesized Rad-PC-Rad liposomes, analyzing the liposome-induced complement activation. In five human sera, Rad-PC-Rad liposomes did not induce activation, but in one serum high sensitivity via alternative pathway was detected. Such a behavior in adverse phenomena is characteristic for patient-to-patient variation and, thus, the number of donors should be in the order of hundreds rather than tens, hence the present study based on six donors is preliminary. In order to further prove the suitability of mechano-responsive Rad-PC-Rad liposomes for clinical trials, the production of pro-inflammatory cytokines was examined by human white blood cells. The concentrations of the pro-inflammatory cytokines, IL-6, IL-12p70, TNF- α, and IL-1 β, induced by Rad-PC-Rad liposomal formulations, incubated with whole blood samples, were smaller or comparable to PBS (negative control). Because of this favorable *in vitro* hemocompatibility, *in vivo* investigations using these mechano-responsive liposomes should be designed.

From the Clinical Editor: Although liposomes have been used in clinical practice for some years, this delivery system often result in significant systemic effects due to hypersensitivity reactions, via the activation of the complement system. The authors here showed good biocompatibility of Rad-PC-Rad liposomes in terms of complement activation and pro-inflammatory cytokines production in-vitro.