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Drug Delivery: Too Much Complexity, Not Enough Reproducibility?

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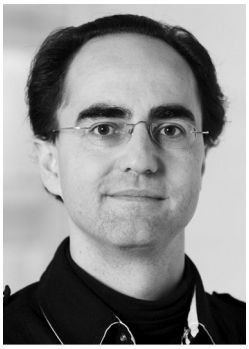

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Drug formulation and delivery is a part of the drug discovery and development process, whose goal is to transform an active compound into a stable and effective pharmaceutical product that can be administered to a patient. Until recently, this field had been confined to a relatively small research community, but has nevertheless contributed to the success of modern medicine. Several major innovations, such as sustained release oral formulations, self-emulsifying systems, biodegradable implants, transdermal patches, and liposomes, have helped improving the bioavailability, efficacy, and safety of drugs as well as treatment acceptance and compliance. Today, drug delivery is experiencing a major expansion. Recent progress in the field of molecular biology, biotechnology, and material sciences has resulted in the emergence of interesting technologies, which may hold great potential for the development of more efficient and safer pharmacological therapies. Paradoxically, the concomitant upsurge in published reports on drug-delivery systems does not correlate with therapeutic advances.

The reasons for this disappointing outcome may lie partly in the approach with which pharmaceutical scientists are tackling medical problems in academia. Over the two decades of my career as a researcher, I have witnessed a noticeable evolution in scientific practices. Reporting drug-delivery systems with exotic features and/or a high degree of complexity seems to have prevailed over the desire to treat a disease effectively with a simple, robust, and safe formulation. While it is clear that drug-delivery scientists must remain creative, and should be motivated not only by translational aspects, one could ask, for example, whether formulations based on graphene or carbon nanotubes are suited for drug-targeting applications. Are the properties of these materials in terms of drug loading, release characteristics, pharmacokinetics, biodistribution, and safety competitive enough to warrant pharmaceutical development? This is a legitimate question since clinical translation is an inherently complicated journey that should not withstand unsurmountable hurdles in its early steps. The parenteral administration of high doses of non- or poorly biodegradable materials with controversial safety profiles (e.g., graphene) would probably frighten the representatives from most pharmaceutical companies, thus precluding such materials from being developed any further. Innovation and risky research are important aspects but the progression of more delivery technologies towards the clinic is required to validate novel fundamental concepts. Given the plethora of literature available today in pharmaceutical technology, this effort is largely insufficient.

The upsurge in published reports does not correlate with therapeutic advances

One point recently raised by several scientists in our community is that innovation in pharmaceutical technology is dominated by nanosystems mainly designed to treat solid tumors (see S. Mitragotri et al., *J. Controlled Release* **2017**, *246*, 183). Indeed, a large proportion of what is nowadays published, especially in chemistry and nonspecialized journals, relates to nanosized carriers (nanoparticles, nanocapsules, drug–polymer conjugates, etc.) aimed at directing anticancer drugs to neoplastic tissues. In such systems, the tumor-targeting principle generally relies on the enhanced permeation and retention (EPR) effect. However, this constitutes the main limitation of the "nanomedicine" dogma, since the EPR effect is increasingly recognized to be much less prominent in humans than in the classical rodent models employed to demonstrate antitumoral activity. It is also quite commonly assumed that nanocarriers have the ability to cross biological barriers because of their small size. While they can be endocytosed/trancytosed under certain conditions and be endowed with membrane-destabilizing properties to escape endosomal/lysosomal organelles, nanocarriers remain much larger than their cargo, and therefore suffer from diffusion restrictions and poor access to most tissues when administered orally or systemically. For example, one could question whether the use of nanoparticles for the oral administration of protein drugs such as insulin is a reasonable approach to increase bioavailability. Issues such as the low and erratic absorption of colloidal particles remain to be addressed, especially for biological drugs whose

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plasmatic levels must be tightly controlled. Drug-delivery research definitely needs more diversity and new hypotheses, and must find original avenues to better exploit the unique characteristics of nanotechnologies.

Another important issue that is not specific to pharmaceutical sciences but contributes to the stagnation of our field is that many published findings cannot be reproduced. The roots of these problems are diverse, but may be affecting drug-delivery research more strongly than fundamental sciences. In recent years, our laboratory has experienced several situations where projects could not be conducted as planned because the initial findings on which they relied on were, in our hands, irreproducible or built on unproven assumptions. One might say that it is sometimes difficult to replicate findings from other groups as research outcomes may depend on subtle experimental conditions and certain "tricks" that are not necessarily disclosed in manuscripts. While such an argument may hold in some disciplines, it is definitely a weak one when it comes to pharmaceutical technology. In its essence, this field deals with the administration of drugs or diagnostic agents to patients whose health and physiological status differ considerably from one individual to another, thus imposing some level of robustness on the delivery system. Moreover, dosage forms with a proven added value will ultimately be produced on a large scale and they will need to withstand long storage under fluctuating conditions. If a system is so unstable that it depends on tightly controlled and "lab-specific" experimental conditions, then it is certainly not suitable for the administration of drugs and its impact in terms of knowledge gain or patient care will likely be negligible.

As discussed above, many drug-delivery systems that are now reported in the literature are relatively complex, if not overengineered, in terms of their structure and functionalities. Regrettably, complex formulations are rarely validated by independent groups, thus preventing their evolution or their definite rejection by the scientific community. In order to illustrate their wide applicability and earn the "platform" status, which is usually a desired feature to be published in top-tier journals, these rather elaborate formulations are superficially tested in different indications, often in non state-of-the-art animal models. Moreover, the controls to which they are compared to are usually chosen to amplify the claimed benefits of the novel formulation, and toxicity is minimally assessed to permit the publication of the work. For instance, routinely performed cytotoxicity assays do not inform much about the ability of a drug-delivery system to trigger a pseudoallergic reaction, a relatively common side-effect of intravenously injected colloids. I am of course not pleading for scientists to always include exhaustive toxicity testing in their study, but simply avoid claiming that a system is not toxic when its safety profile has not been examined with the appropriate tests in a relevant animal model.

Lack of reproducibility is an important issue

We should also grant more recognition to investigations that independently reproduce or fail to replicate others' work. These studies are extremely important to build on existing knowledge and make our field evolve at a faster pace. There is a crucial need for stronger research hypotheses and more reliably conducted experiments. Drug formulations disclosed in reputed journals should not simply be consigned to the archives. It is our duty to re-establish critical discussions in an open and non-anonymous fashion in order to stimulate debates around key questions. Pharmaceutical scientists should be willing to challenge their delivery systems against the best possible control systems, perform double-blinded in vivo experiments whenever possible, and avoid overrating their discoveries. Solid data obtained through carefully executed experiments have a greater weight than "platform technologies" associated with unrealistic claims.

To address reproducibility concerns and improve the traceability of raw data, journals and funding agencies are now implementing new rules and guidelines. While honorable, such measures will be largely inefficient as long as the motivation to publish overrides the simple wish to share a finding or knowledge that will ultimately benefit society.

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