Pharm Res (2017) 34:1149–1151
DOI 10.1007/s11095-017-2156-9

PERSPECTIVE

Insights and Lessons from a Scientific Conference on Non-Invasive Delivery of Macromolecules

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Received: 22 March 2017 / Accepted: 31 March 2017 / Published online: 6 April 2017

ABSTRACT A growing share of the pharmaceutical development pipeline is occupied by macromolecule drugs, which are primarily administered by injection. Despite decades of attempts, non-invasive delivery of macromolecules has seen only a few success stories. Potential benefits of non-invasive administration include better patient acceptance and adherence and potentially better efficacy and safety. Greater interdisciplinary dialogue and collaboration are integral to realizing these benefits.

KEY WORDS blood-brain barrier · drug delivery · *in vitro* models · macromolecules · permeation enhancers

The Catalent Applied Drug Delivery Institute hosted a new scientific conference, the 'Non-Invasive Delivery of Macromolecules Conference', from Feb. 21–24, 2017, at the Rancho Bernardo Inn, San Diego, California. The four-day meeting was jointly chaired by: Dr. Randy Mrsny from the University of Bath and Chair of the Catalent Institute's Non-invasive Macromolecule Delivery Consortium; Dr. Kinam Park, Showalter Distinguished Professor of Biomedical Engineering and Professor of Pharmaceutics at Purdue University; Dr. Isabelle Aubert, Professor, Laboratory Medicine and Pathobiology and Faculty of Medicine, University of Toronto, Sunnybrook Research Institute; and Dr. Ronak Savla, Scientific Affairs Manager, Catalent Pharma Solutions.

The interdisciplinary meeting brought together 80 experts from the fields of biology, chemistry, material science, engineering, and drug delivery. Scientists and leaders from renowned academic institutions and major pharmaceutical companies were among those in attendance. This conference is the first to comprehensively address the challenges of non-invasive macromolecule delivery and examine alternate routes of delivery, whether oral, pulmonary, ocular, or transdermal. The conference included sessions on blood-brain barriers, which is normally not associated with the other delivery routes. Research groups focused on overcoming the blood-brain barrier have been tackling similar challenges that we face in non-invasive delivery by oral, pulmonary, and other routes of administration.

The interdisciplinary scope of the conference allowed scientists to understand common challenges and how approaches can be applied across disciplines. In addition to the thematic sessions, the conference incorporated poster and open discussion sessions. Attendees came away with a greater knowledge of novel technologies and approaches and greater appreciation for the requirements to bring a product to the clinic.

HARD QUESTIONS NEED TO BE ANSWERED

Despite nearly 100 years of effort, there are only a few macromolecule drugs that are administered without an injection (1). The field of oral macromolecule delivery has been mired by failure in late stage clinical trials. Because of their large size and hydrophilic nature, macromolecules are notorious for not being able to pass biological barriers (2). These spatial barriers include the skin, blood-brain barrier, and gastrointestinal tract, and of course, the target cells. Beyond spatial factors/

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barriers, scientists need to understand the temporal constraints, formulations factors, molecular characteristics, disease factors, and develop proper test and evaluation methods.

The pulmonary route is a great example of the spatial and temporal constraints faced by scientists. Dr. Ralph Niven presented that a particle delivered to the alveoli would need high solubility (>250 mg/ml) in alveolar fluid. This is even more absurd given that the lungs are dynamic and known to have highly active clearance mechanisms. This shows that scientists may need to take a step back and lay a stronger foundation for drug delivery.

The general consensus of the conference participants was that the current technology platform approaches for macromolecules are likely to be very difficult due to the hydrophilic, macromolecular nature. Most companies work on a singular approach to deliver a macromolecule drug. This makes it even more difficult to compare across different approaches and analyze past failures.

Classification systems and 'Rules of Thumb' such as the Developability Classification System (DCS) (3) and Lipinski's Rule of Five (4) help guide the development of small molecule oral drugs. However, there is a lack of successful examples of oral macromolecule drugs and concerted efforts to use or extrapolate these tools by the macromolecule community.

EMERGING TECHNOLOGIES AND APPROACHES PRESENTED AT THE CONFERENCE

There were several emerging themes at the conference such as the need for a more uniform and concerted effort, practical considerations, lack of appropriate pre-clinical models, strategies to modify biologicals, and looking to nature for inspiration.

The biggest question facing *in vitro* models is whether they give a reflection of the integrated whole system that can be translated not only into animals but also into humans. Studies using monolayers of single cell types dominate in the laboratory setting because of the ease of use and high throughput capability. This approach persists despite realization that results do not translate well *in vivo*. Three dimensional co-cultures are emerging as tools with better physiological translation. Prof. Claus-Michael Lehr of Helmholtz Institute for Pharmaceutical Research has developed such a model for inflamed intestinal mucosa. The co-culture of Caco-2 cells with macrophages and dendritic cells are indicative of the mucosa seen in patients with inflammatory bowel disease. Dr. Birgit Obermeier presented Biogen's Brain Therapeutics Initiative's research on developing a "human blood-brain barrier (BBB) on-a-chip," which has direct physiological relevance compared to current gold standard transwell assays. By trying to mimic the unique anatomy and function of the BBB and allow for real-time analysis, Biogen hopes to use the newer microfluidic-based assay to develop therapeutics with more than 5X higher exposure of therapeutics to brain targets than unmodified therapeutics.

Many of the presentations focused on looking at nature and how organisms and natural macromolecules are able to cross biological barriers. Prof. David Brayden presented on the gold standard of permeation enhancers, sodium caprate, and compared it to some recent permeation enhancers, sucrose esters and 1-phenyl piperazine. Studies showed comparable results using sucrose laurate and sodium caprate as admixtures with insulin in rat instillation. The pharmacology of newer permeation enhancers such as 1-phenyl piperazine tends to be more complex and only seen in isolated tissues. This makes their use more risky. Toxins are emerging as potential vehicles for delivering macromolecules. Dr. Nicole Fay of Applied Molecular Transport presented on fusing a truncated exotoxin from cholera onto IL-10 for treatment of inflammatory bowel disease and Dr. Joseph Nicolazzo of Monash University shared his results for alternative routes to deliver scorpion and sea anemone toxins. The safety and immunogenicity of these approaches are the top concerns with these approaches. Other approaches looked at viruses for inspiration: Virus-Inspired Polymer for Endosomal Release (VIPER) and self-assembling DNA nanoparticles. Speakers in the blood-brain barrier session presented on the promising approach of focused ultrasound to pass through perhaps one of the toughest biological barriers.

Lipinski's Rule of Five is a rule of thumb to determine if a drug is likely to be orally active. A drug is likely to be orally active if it violates no more than one rule. By definition, macromolecules violate the rule that the molecular weight is less than 500 Da. The peptide/protein or oligonucleotide structures make it highly likely that the macromolecule has more than 5 hydrogen bond donors and/or more than 10 hydrogen bond acceptors. There are plenty of examples of orally active drugs that violate the Rule of Five. Formulation is one approach. Another approach is to make macromolecule conjugates. Central to this approach is to increase the low or non-existent permeability of macromolecules. Some examples presented at the conference included guanidinylated conjugates, complexation with cell penetrating peptides, and fusion with bacterial exotoxins.

CONCLUSION

Non-invasive delivery of macromolecules is perhaps the greatest challenge in the field of drug delivery. The conference demonstrated the benefits of a forum for scientists to exchange ideas. The attendees were able to have a greater appreciation for how different areas of science are interconnected and interdependent. The dialogues and discussions served as a springboard

for further collaboration and potentially better therapies for patients. Given the overall success of this new conference bringing together biologists, chemists, pharmaceutical scientists and clinicians, leading to novel insights into how to better tackle this major issue limiting new therapies in the future, the Non-invasive Delivery of Macromolecules conference will continue in the future, with the ultimate aim of translating basic research outputs into clinically-relevant therapeutic approaches.

ACKNOWLEDGMENTS AND DISCLOSURES

RS and CS are employees of Catalent Pharma Solutions.

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