Journal of Nanomedicine & Biotherapeutic Discovery

Foldvari, J Nanomedine Biotherapeutic Discov 2014, 4:2
DOI: 10.4172/2155-983X.1000e135

Editorial Open Access

Nanopharmaceutics Innovations in Gene Therapy: Moving Towards Non-Viral and Non-Invasive Delivery Methods

M. Foldvari*

School of Pharmacy and Waterloo Institute of Nanotechnology, University of Waterloo, Canada

Gene therapy, the targeted insertion of DNA coding for a therapeutic gene into the nuclei of diseased cells or tissues followed by its expression, is one of the most promising new therapies for a host of diseases and conditions [1]. The first gene therapy product, Gendicine (adenoviral vector-based) was approved in China in 2003 for head and neck cancer. On July 24, 2012 the European Medicines Agency approved the adeno-associated viral (AAV) gene therapy, Glybera by uniQure, for lipoprotein lipase deficiency, an orphan disease. Recent progress towards patient use indicates that there is still more work ahead for developing approved products for other indications. More than 1,800 gene therapy clinical trials have been carried out in the past 25 years, including the currently in-progress of about 400 studies [2].

As recent reports of encouraging progress are emerging with viral vector-based therapies, the field is developing more confidence in gene therapy applications. For example, uniQure is developing the GDNF (glial cell derived neurotrophic factor) gene in their AAV-2 delivery vector (NCT01621581) and Oxford Biomedica reported Phase 1/2 clinical trial results with ProSavin, a tricistronic lentivirus-based vector encoding tyrosine hydroxylase, L-amino acid decarboxylase (AADC), and cyclohydrolase 1, both aimed at restoring dopamine production in patients with advanced Parkinson's disease [3]. MYDICAR®, an AAV-based sarcoplasmic reticulum calcium ATPase (SERCA2a) gene therapy, being developed by Celladon to restore SERCA2a enzyme levels, is currently in clinical trials for evaluating its efficacy in improving left ventricular function and remodeling in NYHA class III or IV chronic heart failure patients [4]. This study received 'breakthrough therapy designation' from U.S. Food and Drug Administration (FDA) through the FDA Safety and Innovation Act of 2012 (FDASIA) to expedite drug development and review of innovative new medicines that address certain unmet medical needs for serious or life-threatening diseases or conditions. The administration of these treatments is not trivial and involves bilateral, convection-enhanced delivery through an implanted catheter to the putamen, intrastriatal injection or intracoronary infusion, respectively.

In spite of the tremendous progress, future challenges in gene therapy treatments include the development of gene delivery vectors with targeting ability, controllable, high and prolonged transfection efficiency, improved safety and less complicated or non-invasive administration methods. Novel *non-viral delivery systems* represent options for gene therapy that could fulfill these mentioned requirements. However, non-viral systems are not yet effective and specific enough for clinical applications and improvements in both the structure and function of these systems are required. Non-viral gene delivery vectors are an extensive class of man-made complexes or nanoparticles (NPs) composed of a nucleic acid cargo, typically a plasmid, with one or more soft matters such as cationic lipids (DOTAP, DOTMA), surfactants, biologicals (gelatin, chitosan), metals (gold, magnetic iron) and synthetic polymers (PLG, PEI, PAMAM). This engineering flexibility provides several key advantages over viral delivery vectors, principally reduced immunogenicity resulting from their biologically inert material composition and reduced production costs. Moreover, this "bottom-up" design allows researchers to customize their composition and incorporate specific moieties to suit a wide range of applications.

Development of nano-sized delivery systems requires the understanding of a comprehensive set of parameters and the construction of fine-tuned particles capable of significantly more "intelligent" functions compared to traditional dosage forms. Among the many important properties, morphology and internal structure of nanoparticles play a significant role in their functional performance. *At the cellular level*, a multitude of parameters are of interest for fine-tuned customization. Important considerations in individual nanoparticle design for enhanced cellular interaction and drug delivery are size, surface charge, surface area, shape, surface coatings, stability and structure of particles. An interesting consideration in NP design is the size and shape of particles. Smaller particles less than 150 nm are typically taken up to a greater extent into cells, which has been shown for NPs made from various biomaterials. Until recently, all delivery systems studied were mostly spherical. The structure of lipoplexes has been the focus of both theoretical and experimental studies that examine the relationship between the morphological characteristics of lipoplexes and their functional activity. These various structural forms have been revealed in numerous studies using diffraction or magnetic resonance methods; however, the lack of understanding of the relationship between transfection and the nature of complexes has also necessitated determining other physical characteristics using various methods. A non-spherical particle shape (filament, ellipsoid, cube, rod, triangle, pentagon, disc) may provide significantly improved interactions with cells [5-10]. The relationship between the structure of DNA complexes and gene delivery has been of considerable interest in the past few years from both theoretical and experimental standpoint. The importance of the thorough understanding of particle properties is widely recognized [11,12], however, in practice there is still much to be done to fully detail out all relevant characteristics of old and new systems. NP biocompatibility, including pharmacokinetics of absorption, targetability, clearance and toxicity, is the direct result of the sum of the physicochemical features carefully designed under established dosage form design and newly developing nanopharmaceutics principles.

For selected applications, the *route of administration* can be

***Corresponding author:** M. Foldvari, School of Pharmacy and Waterloo Institute of Nanotechnology, University of Waterloo, Canada, Tel: 519-888-4567-21306; E-mail: foldvari@uwaterloo.ca

Received July 25, 2014; **Accepted** July 28, 2014; **Published** July 30, 2014

Citation: Foldvari M (2014) Nanopharmaceutics Innovations in Gene Therapy: Moving Towards Non-Viral and Non-Invasive Delivery Methods. J Nanomedine Biotherapeutic Discov 4: e135. doi:10.4172/2155-983X.1000e135

needle-free [13-16], although in most cases gene delivery systems are administered by injection. In the next few years new technologies will allow non-invasive administration methods, especially into the skin, eye, and mucus membranes, which will provide more effective treatment modalities, patient acceptance and potentially self-administration.

References

1. Seymour LW, Thrasher AJ (2012) Gene therapy matures in the clinic. Nat Biotechnol 30: 588-593.
2. Ginn SL, Alexander IE, Edelstein ML, Abedi MR, Wixon J (2013) Gene therapy clinical trials worldwide to 2012 - an update. J Gene Med 15: 65-77.
3. Palfi S, Gurruchaga JM, Ralph GS, Lepetit H, Lavisse S, et al. (2014) Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease: a dose escalation, open-label, phase 1/2 trial. Lancet 383: 1138-1146.
4. Greenberg B, Yaroshinsky A, Zsebo KM, Butler J, Felker GM, et al. (2014) Design of a phase 2b trial of intracoronary administration of AAV1/SERCA2a in patients with advanced heart failure: the CUPID 2 trial (calcium up-regulation by percutaneous administration of gene therapy in cardiac disease phase 2b). JACC Heart Fail 2: 84-92.
5. Champion JA, Katare YK, Mitragotri S (2007) Particle shape: a new design parameter for micro- and nanoscale drug delivery carriers. J Control Release 121: 3-9.
6. Gratton SE, Napier ME, Ropp PA, Tian S, DeSimone JM (2008) Microfabricated particles for engineered drug therapies: elucidation into the mechanisms of cellular internalization of PRINT particles. Pharm Res 25: 2845-2852.
7. Gratton SE, Ropp PA, Pohlhaus PD, Luft JC, Madden VJ, et al. (2008) The effect of particle design on cellular internalization pathways. Proc Natl Acad Sci U S A 105: 11613-11618.
8. Chithrani BD, Ghazani AA, Chan WC (2006) Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. Nano Lett 6: 662-668.
9. Perry JL, Herlihy KP, Napier ME, Desimone JM (2011) PRINT: a novel platform toward shape and size specific nanoparticle theranostics. Acc Chem Res 44: 990-998.
10. Galloway AL, Murphy A, Rolland JP, Herlihy KP, Petros RA, et al. (2011) Micromolding for the fabrication of biological microarrays. Methods Mol Biol 671: 249-260.
11. Gentleman DJ, Chan WC (2009) A systematic nomenclature for codifying engineered nanostructures. Small 5: 426-431.
12. McNeil SE (2011) Challenges for nanoparticle characterization. Methods Mol Biol 697: 9-15.
13. Elsabahy M, Foldvari M (2013) Needle-free gene delivery through the skin: an overview of recent strategies. Curr Pharm Des 19: 7301-7315.
14. Foldvari M, Kumar P (2012) Recent progress in the application of nanotechnology for prevention and treatment of human papillomavirus infection. Ther Deliv 3: 1005-1017.
15. Alqawlaq S, Huzil JT, Ivanova MV, Foldvari M (2012) Challenges in neuroprotective nanomedicine development: progress towards noninvasive gene therapy of glaucoma. Nanomedicine (Lond) 7: 1067-1083.
16. Badea I, Virtanen C, Verrall RE, Rosenberg A, Foldvari, M (2012) Effect of topical interferon-gamma gene therapy using gemini nanoparticles on pathophysiological markers of cutaneous scleroderma in Tsk/+ mice. Gene Ther 19: 978-987.