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## From the Education Committee

### Need of Closer Alliances for Turning Nucleic Acids into Nanomedicines

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#### Abstract

Recent advances in the exploration of physiological processes at the molecular level and the complete characterization of the human genome and the subsequent emergence of proteomics have given great hope for turning nucleic acids into therapeutics for the treatment of severe and debilitating diseases, which are not adequately treated with conventional small molecular weight and protein drugs. The success of nucleic acid-based therapeutics will be greatly enhanced if we would apply nanoscience and nanotechnology principles to overcome numerous biological barriers from the site of administration to the site of action. In this article, we highlight these issues and address the need for closer alliance among academia, pharmaceutical industries and scientific societies.

#### Introduction

After mission to the moon, human genome project has been one of the largest projects undertaken by the scientific community. Sequencing of the human genome along with significant advances in our understanding of molecular biology and disease pathophysiology, has led to the evolution of new therapeutic possibilities – whose development is a 21st century challenge to the pharmaceutical scientists. Most diseases are due to the absence or overproduction of a specific protein, leading to clinical manifestations depending upon the function of a particular protein in normal physiology. While most low molecular weight drugs act by modulating the function of some cellular proteins or DNA by specific binding; gene therapy approaches provide the patient's somatic cells with the genetic information necessary to produce specific proteins needed for treatment. The use of proteins as drugs presents problems with respect to unfavorable pharmacokinetic profiles, need for frequent administrations, poor oral bioavailability, physico-chemical instability, inappropriate concentration in the body and rapid hepatic metabolism and renal clearance. Although significant improvements in protein therapy can be made with nanotechnology, synthesis of a desired protein, or inhibition of an aberrant protein production, in the vicinity of diseased cells would be much more desirable specially for long-term therapy. Nucleic acid medicines fall under the two broad categories of *gene expression and gene silencing*. While the former is involved with plasmid and virus-based gene delivery to desired cells and tissues, the latter is involved with silencing gene expression – which may be achieved by inhibiting transcription (antigene) or translation (antisense and siRNA). Nucleic acid drugs are high molecular weight, hydrophilic compounds with

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### Pharmaceutical Sciences Graduate Education in the Era of Nanotechnology, Pharmacogenomics, and Proteomics

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Advances in nanotechnology, pharmacogenomics, and proteomics are bringing new frontiers to pharmaceutical research and posing new challenges in providing a strong educational and scientific foundation to graduate students enrolled in the colleges of pharmacy, especially pharmaceutical sciences departments. After briefly defining the scope of these emerging disciplines, the purpose of this article is to share my personal opinions about the emerging trends in pharmaceutical science education and where we can potentially strengthen our graduate programs. I have not provided any clear resolutions to these issues because each graduate program has to utilize its own resources, and visions for the future to ensure that its graduate students are well trained. Although this article is written for graduate education in pharmaceutical sciences departments, several other programs including biomedical engineering and chemical engineering programs focusing on drug delivery also face these challenges. The opinions expressed in this article are mine and may not reflect those of the colleges I have been affiliated with over the years.

#### Emerging Technologies

Currently, there are at least three high-technology driven areas of research that are likely to make revolutionary contributions to the field of medicine. These include nanotechnology, pharmacogenomics, and proteomics. All these areas are driven by micro- and nano- machining technologies and computational science. While pharmacogenomics and proteomics rapidly advance the understanding of human biology by providing new diagnostic techniques and clinical targets for the treatment of diseases, nanotechnology is more products oriented and it is making advances in several non-pharmaceutical areas as well as in the pharmaceutical sciences.

*Nanoscience:* Nano- is currently among the most attractive prefixes, and it has been used to define many areas of science and technology – nanoscience, nanotechnology, nanoengineering, nanomedicine, nanobiology, and nanoimaging, to mention a few. If this trend is an indication of where this technology is headed, there will be nanopharmaceuticals emerging in the near future. While the inclusion of the prefix nano- is currently paramount to the new wave of nanotechnology, related pharmaceutical research on nanoparticles has been ongoing for at least the past 3 decades, with the usual slow progression to the clinic. The quantum leap in nanotechnologies has been primarily in the fields of inorganic materials including the fabrication of 90 nm transistors that can

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poor cellular permeability, and suffer from rapid inactivation, degradation and clearance *in vivo*. Thus, the use of nucleic acids as drugs requires special considerations for their effective delivery.

### Evolution of Nucleic Acid Nanomedicines

The progress of molecular biology in uncovering the genetic information of the nucleic acids, which form core of the central dogma of information transfer in living systems, has been catalyzed by the progress in information technology and evolving high-throughput, automated systems like the microarray analysis and DNA sequencing (Fig. 1). The rapid development and applications of the internet and computers has made possible widespread research at the speed of thought, in various applications of this information. Despite this unprecedented speed of progress, the clinical success in converting nucleic acids into prescribable pharmaceuticals has not been realized yet. Effective delivery of the genetic material into the cell and translocation into the nucleus, without causing immunostimulation is a major barrier. These problems can be effectively addressed by applying the principles of nanoscience and nanotechnology. This calls for a proactive role of the pharmaceutical scientists to take up this responsibility. Nanotechnology has been applied for delivery of small molecular weight drugs by encapsulation or reversible bonding on the surface of 10-100nm particles. The use of such nanoparticulate systems have been used for site-specific drug delivery to the desired disease target by passive or active targeting. The use nanoparticulate systems are limited for hydrophilic nucleic acid drugs due to their large size, strict conformational requirements and inherent instability. Nanoscale manipulation of these macromolecules must not adversely affect their stability and biological activity. Such manipulations are done through interaction with inactive, polymer, lipid and peptide-based carrier molecules, leading to significant alterations in the physico-chemical properties of the resulting systems. Additionally, small size of these complexes enables them to cross many physiological barriers that would otherwise hinder their access to their targets. Both biotechnology-derived and conventional small molecular weight drugs have their unique place in modern medicine. In some disease states, nucleic acid based therapeutics remains the best option, while in other cases one may be superior to another. An example of the former case is the modulation of insulin-secreting pancreatic islets for transplantation in type-I diabetes patients.

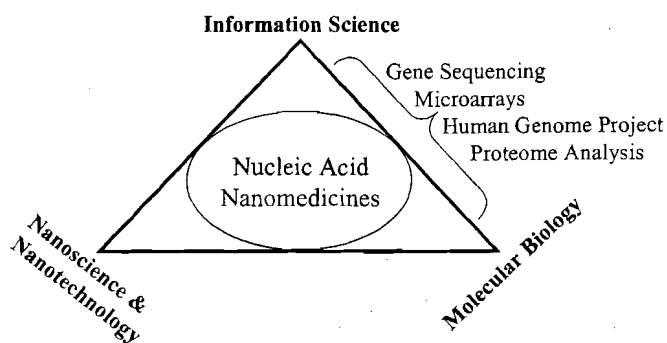


Figure 1. Evolution of nucleic acid nanomedicines from the research domains of molecular biology and nanoscience, catalyzed by the rapid progress in information science and technology.

### Can Nanotechnology Make Gene Medicines a Reality?

The promise of nanotechnology to overcome physiological barriers to drug movement alter physico-chemical properties of the molecules, facilitate targeted delivery to the desired tissues,

and to stabilize and prevent rapid clearance paves the way towards the desired systems for nucleic acid-based therapeutics. For efficient transfection to occur, vectors must be capable of condensing DNA into particles small enough to be taken up by the cells (typically <200 nm), protecting DNA from hydrolytic and enzymatic degradation; and delivering the DNA to the nucleus of the cell in a transcriptionally active form.<sup>1</sup> For example, we have been working on lipopolymers, which enhance the stability and delivery of plasmid DNA *in vitro* and *in vivo*.<sup>1,2</sup> These gene carriers bind to the multiple anionic charges on the duplex DNA by electrostatic interactions to form condensed, positively charged complexes, that provide enhanced stability from endogenous nucleic acid-degrading enzymes, and increase cellular internalization by interactions with the anionic cell surface.

Mother nature exemplifies the ideal nanoscale encapsulation and protection of nucleic acids and their specific targeting in the form of viral vectors. These vectors have been used extensively and are being evaluated in clinical trials. One good example of their application is type-I diabetes, where the insulin-producing pancreatic islet cells do not function properly. Islet transplantation can replace body's delicate machinery for glucose metabolism, but the transplanted islets are often fail to vascularize and are rejected by the host due to immune responses. Gene transfer to the islets for secretion of protective and vascular proliferative cytokines would help in better engraftment of the transplanted tissue so that physiological level of insulin can be produced.<sup>3</sup> We are working on adenoviral vectors for gene delivery to human islets. We have used recombinant adenoviral vectors with very high transfection efficiency.<sup>4</sup> We are currently working on surface modifications of these systems to incorporate enhanced targeting capabilities and reduced immunogenicity.

### Commercial Challenges

Development as well as commercialization of nucleic acid-based nanomedicines is a daunting task. The transfer of these technologies from the academia to the industry and the clinic involves many challenges. Current gene expression and gene silencing technologies do not balance well on the two most fundamental requirements: safety and efficacy. Non-viral vectors are relatively safe but they are not efficacious while viral vectors provide high efficiency but with significant safety concerns. The eventual success of nucleic acid nanomedicines will require patient acceptance and careful consideration of their social and economic consequences. Efforts are needed to develop novel systems that are efficacious, while also being safe and cost effective. In my laboratory at the University of Tennessee Health Science Center, we are working towards this end by generating hybrid systems of adenoviruses using nonviral technologies, to overcome their safety concerns.

Nucleic acid nanomedicines are being developed in the era of enhanced appreciation of the value of intellectual property – resulting in every technological advancement being patented. Scientific publications as well as patents have grown exponentially in these fields over the years. While this growing body of public knowledge provides an impetus to the development of science, complex intellectual property issues often hinder the commercial exploitation of emerging technologies. For example, patenting of different aspects of polymers, gene, gene delivery and gene expression systems, techniques for encapsulation etc by different groups working in multiple disciplines hinders the development of an integrated delivery system that utilizes these different features. Furthermore, rapid scientific advancements, although welcome in all aspects, tend to make the existing technology obsolete at a very rapid rate – sometimes faster than the industry may be able to recover and benefit from its investments in research and development. This creates a disincentive for the private companies to invest in fast growing, emerging technologies.

### Strengthening Industry Academia Alliance

The development of nucleic acid nanomedicines will also depend on the understanding and fostering of multidisciplinary intellectual environments in academic and corporate settings. While the academicians focus on developing the basic concepts and the science behind the technological advances, industrial scientists focus on technological development, with the goal of commercialization. American companies have been leaders in technological advances, in part by swiftly applying new leads from basic research in the universities, through collaborative projects as well as through the hiring of students and post-doctoral scientists. Collaborative alliances between the industry and the academia will play a key role in the development of these new therapeutic modalities. New developments need to be communicated and transferred rapidly across industry and academia to derive maximum benefit. As illustrated in Fig. 2, the Controlled Release Society, Inc. (CRS) can play a key role in enhancing scientific interaction between the two communities, by providing common meeting grounds, thereby acting as catalysts to scientific growth and technological advancement. Another important role for the CRS is to interface scientific and technological developments with the public at large, so that the laymen and young scientists and students develop a better understanding and appreciation of these newer avenues. This has an important role in helping not only to mobilize public support and young talent to the exciting new developments, but also in generating acceptance and enthusiasm in the public towards these new technological advances.

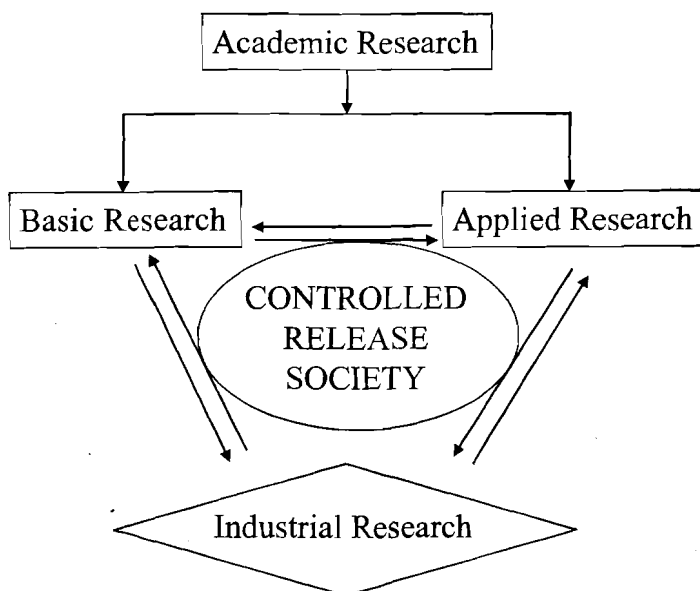


Figure 2. Interrelationship among academia, pharmaceutical industries and the Controlled Release Society, Inc.

### Gearing-up Pharmaceutical Education

The United States faces the daunting challenge of attracting enough of the best graduate students to pharmaceutical sciences.<sup>5</sup> Development of nucleic acid nanomedicines requires technical knowledge and understanding of different fields that have traditionally grown independent of each other. While pharmaceutical sciences, by its very nature, encompasses the principles of a multitude of basic sciences; these emerging technologies require people with additional expertise in the newly developed and evolving disciplines, like molecular techniques and gene cloning, that have traditionally not been in the purview of pharmaceutical scientists. Such multi-disciplinary nature of discovery as well as development of these systems poses a bottleneck in the availability

of broadly trained manpower for leading such projects. The current trends in the development of nucleic acid nanomedicines require some fundamental changes in our educational system. There is an urgent need to achieve the right balance between pharmaceutical specialization and interdisciplinary training in emerging nanoscience and nanotechnology disciplines. Education of students and budding pharmaceutical scientists towards a significant role in the development of molecular medicines of the future requires them to be trained in various disciplines.

There is an urgent need to prepare workforce for it by training budding pharmacists to learn more about molecular biology and pathophysiology. The CRS can play an active role in this evolution of pharmaceutical education by important role in addressing tremendous educational challenges by communicating the excitement and recent developments of nucleic acid nanomedicines, which will become a major factor in reinvigorating the nation's youth for careers in pharmaceuticals and drug delivery. Educational development of graduate students in our laboratory at the University of Tennessee Health Science Center in Memphis is geared towards their multidisciplinary exposure.

### Concluding Remarks

Despite early setbacks, there is no doubt that nucleic-acid based nanomedicines will eventually be prescribed as pharmaceuticals. In fact, there are already two marketed products: one is an antisense phosphorothioated oligonucleotide for the treatment of rhinitis (Vitravene<sup>®</sup>, Isis Pharmaceuticals, Inc.); and the other is an adenovirus encoding p53 gene for the treatment of cancer patients (Gencicine<sup>®</sup>, Shenzhen SiBiono GeneTech Co., Ltd., China). The inherent complexities of these systems provide an opportunity for multidisciplinary collaboration and co-operative efforts across industry and academia. The nucleic acid based medicines present enormous potential that has not yet been well utilized. The success of these emerging technologies heavily depends on the close alliance among academia, industry and scientific communities like the CRS, American Association of Pharmaceutical Scientists (AAPS), American Society of Gene Therapy (ASGT) and American Chemical Society (ACS). We hope that this review would provide an impetus to collaborative efforts between industry and academia, and will motivate young scientists and students to consider the most challenging and fast developing aspects of biomaterials and their use in turning nucleic acids into nanomedicines as their research careers.

### Acknowledgements

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