Gene Therapy: Opportunities for Pharmacy in the 21st Century

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PROLOGUE
Throughout the history of the profession, pharmacy has adopted technologies which have eventually become recognized responsibilities of the pharmacist. Genetic technologies, which to date, have primary application for diagnostics and industrial production will soon offer the ability to routinely introduce genes into patients for therapeutic purposes. For the profession, it is important to discuss the impact of this technology and encourage involvement of pharmacists in the application of molecular genetics to therapeutics. An overview of current technology and a futuristic vision of the possible duties of a pharmacist in gene therapy is appropriate.

INTRODUCTION
As a pharmacy student in the early 70’s, I can remember few community pharmacies were involved with the preparation of IV admixtures. However, I was amazed to find laminar flow hoods in community pharmacies within a decade. Within the same time period, computers were rare in pharmacies, but now considered to be an indispensable part of every pharmacy. My purpose here is not to discuss the “good old days,” but simply indicate that our profession has demonstrated the ability to adopt technology, not simply as a sideline, but as an integral part of the responsibilities of the pharmacist. Genetic technologies, in my opinion, offer similar opportunities. Rapid developments in molecular genetics offer the ability to understand not only the molecular basis of disease, but the ability to monitor the response to drug therapy. In the 21st century, genetic technology will be readily available for the treatment of disease. However, much needs to be done at present in order for pharmacy practitioners to be prepared to adapt to as well as adopt elements of the technology as integral players in gene therapy.

THE PIVOTAL ROLE OF PHARMACOGENETICS
Although the primary focus of this discussion is gene therapy, the influence of pharmacogenetics upon this emerging field is very important for pharmacy. Most of the current interest in pharmacogenetics has focused upon the genetic basis of drug response from the perspective of inherited traits and ethnic differences. Among these are inherited differences in drug response due to differences in drug metabolism. Specifically, they include butyrylcholinesterase variants (associated with succinyl choline apnea), acetylation polymorphism, ethnic differences in glucuronidation, and the impact of cytochrome P-450 isoforms(1-3). Ethnic differences in response to drugs not specifically related to drug metabolism include agents used in anti hypertensive therapy and several classes of CNS drugs as well as adverse reactions to specific drug classes(1,4). Genetic markers for these traits are under active investigation in several laboratories. Examples include the use of restriction fragment length polymorphisms (RFLPs) to determine allele association with different drug response traits as in the case of acetylation polymorphism and markers for cytochrome P-450 isoforms(1,5). Since most pharmacy practice environments currently do not have access to resources which utilize molecular techniques to investigate pharmacogenetic markers, most practitioners must primarily rely upon the use of family history, racial and ethnic background as a guide to assist the pharmacist as a pharmacogenetic consultant when necessary. Automation of genetic probe testing is rapidly approaching. Theoretically, it may be possible to do this in an outpatient setting in a manner similar to glucose and lipid testing at present. In view of the complexity of this information, computer assisted searching and retrieval of this information is compatible with the use of computers by the pharmacist. In the simplest case, this information may be profiled on the patient record and the pharmacist should be ready to interpret the meaning of this information and the implications of the profile to patient’s response to certain drugs. Techniques used to detect the presence of certain genes is essential for not only for advancing clinical applications in pharmacogenetics, but successful targeting of genes to specific tissues for a therapeutic response. The reasons for this are numerous and the importance of several genes working in concert to modulate a physiological and pharmacological response is obvious. A clinician would need to know if a specific gene (or genes) is (are) absent or defective (a diagnostic application) before introducing the replacement gene(s) to the appropriate tissue (a therapeutic application). For many diseases, addition of new genes may lead to a therapeutic response. A brief examination of current technologies for therapeutic applications is appropriate background in a discussion of a role for pharmacy.

CURRENT TECHNOLOGIES FOR GENE TRANSFER.
Once a defective gene or genes are found to be crucial for the cause and/or progression of a disease, introduction of replacement genes into the cell types is warranted. Selected examples are presented in Table I. Retroviruses, of which human immunodeficiency virus-I (HIV-I) is an example, deliver RNA to target cells. Reverse transcriptase synthesizes complementary DNA which is destined for incorpor-

Table I. Examples of gene transfer technology

| Retroviral vectors |
| Adenovirus and adeno-associated viral vectors |
| Mammalian artificial chromosomes (MAC) |
| Cationic lipids and liposomes |

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parasitic infection may be valid. Figure II is a highly simplified summary illustration of a transient or abortive transduction. In this case, once DNA or RNA is delivered to the cell, genes are not incorporated into the host genome, nor are they replicated. They may eventually be eliminated (abortive transduction) in the presence or absence of cell division(18).

PREPARATION OF GENE DELIVERY SYSTEMS

One of the most attractive opportunities for the pharmacist in the 21st century may be in the preparation of gene delivery systems. In the case of liposomal systems, this may be as routine as reconstitution of a freeze-dried plasmid and mixing of a cationic lipid prior to sterile filtration. A more technically demanding task may be the preparation of an unstable virus for parenteral administration. Before discussing such a scenario for a pharmacist, elements of current technology which may be incorporated into such a scenario should be reviewed. An example of such a preparation is a therapeutic retrovirus. In many cases, preparation of a therapeutic retrovirus requires a two-component system(13). The first is a packaging cell line which is used to prepare sufficient copies of the viral particle. A viral vector is used as a template for the production of the therapeutic gene(s) incorporated into the particle. Within the cellular genome of the packaging cell line is an incomplete viral genome. Missing from this genome is the genes necessary for assembly of the viral genome inside a viral envelope. Therefore, the cell line can produce structural components of the viral particle, but cannot assemble an infectious virus. The second component, a retroviral vector, contains replication and the missing “encapsulation” signals along with a therapeutic gene (or genes). Upon addition of the retroviral vector to the cell line, therapeutic genes are replicated inside the packaging cell line and “packaged” into new particles which lack the genes necessary for producing new viruses. After collection, the therapeutic viral particles can be used for the intended

APPLICATIONS OF GENE THERAPY

Table II lists several examples of diseases for which gene therapy is considered. Applications of gene therapy are reported on the basis of clinical trial, selected cases, studies in humans or other animals. Due to the rapid advances in this field, it is not practical to be exhaustive. The intent of this list is to illustrate the diversity of diseases for which this technology may be useful.

STABLE VERSUS TRANSIENT TRANSDUCTION

In the course of gene therapy, introduction of a gene into a target cell may result in a transient response or a semipermanent one. Figure I is a highly simplified summary illustration of a stable or complete transduction. In the case of a retrovirus which incorporates genes indirectly into a host genome, the genes which are integrated may be replicated and expressed semipermanently(13). However, it may be sufficient to induce the cell to produce a missing protein or an RNA without the risk of insertional mutagenesis or other hazards associated with gene incorporation. The temporary use of transduction to overcome a viral, bacterial, fungal or other parasitic infection may be valid. Figure II is a highly simpli-

Table II. Selected applications of gene therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Adenosine deaminase (ADA) deficiency</td>
<td>12</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>13</td>
</tr>
<tr>
<td>Acquired immune deficiency syndrome (AIDS)</td>
<td>14</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>15</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>16</td>
</tr>
<tr>
<td>Acquired immune deficiency syndrome (AIDS)</td>
<td>17</td>
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Gene therapy opens a new frontier in pharmacy from the perspective that genes will be commonly used as drugs. As indicated above, lack of success for gene therapy at present is in part due to the fact that simple introduction of a replacement or therapeutic gene at a target tissue may not be sufficient to yield an effective therapeutic response. However, these barriers will eventually be overcome and will yield therapies with the potential to cure pathologies which are currently only modulated pharmacologically. At present, the technologies associated with these new therapies appear far from a routine associated with pharmacy. In much the same way that IV admixtures and sterile product preparation is now an important service in pharmacies, the opportunity for pharmacists to extemporaneously prepare patient-specific gene delivery formulation from multi-component systems in a pharmacy may not be technically far in the future. To gain an appreciation for the technology involved, curricula must include a discussion of the current use of viral vectors in gene therapy as well as other mechanisms for transduction of cells. These systems will become relatively reproducible for in vivo use and exhibit a reasonable selectivity for therapeutic targets (tissue specificity). As a result, component systems must be designed for routine clinical application. From this perspective, one can clearly associate the future of pharmacy practice with gene therapy and related advances in molecular medicine.


References