Challenges in Developing Therapies for Rare Diseases Including Pachyonychia Congenita

Roger L. Kaspar
Transderm and SomaGenics, Inc., Santa Cruz, California, USA

The ability to attract sufficient resources to effectively develop therapeutics for rare diseases is a daunting task. This review summarizes existing resources for rare diseases and discusses some of the challenges and strategies associated with developing therapies for small patient populations with an emphasis on pachyonychia congenita.

Key words: orphan disease/pachyonychia congenita/rare disease

A rare (orphan) disease is defined under the United States Orphan Drug Act amendment (Orphan Drug Act, P.L. 97–414 (1983); Health Promotion and Disease Prevention Amendments, P.L. 98–551 (1984)) as a disorder that generally affects less than 200,000 individuals ( ~ 0.07% of the US population). The definition is extended to disorders that affect greater numbers of individuals for which drug development is not likely, due to the expectation that the sales of such a drug would not be sufficient to recover development costs. Similar rare disease definitions are used by other countries including the European Community, Japan, Singapore and Australia (see the websites, http://www.rare-cancer.org/rare-diseases.html and http://www.europarl.eu.int/stoa/publi/167780/chap5_en.htm).

Approximately 6,000 rare diseases have been identified and a list is maintained by the Office of Rare Diseases (ORD) at the National Institutes of Health (NIH) (http://ord.aspen.sys.com/asp/diseases/diseases.asp). Some of the listed rare diseases are well-known, such as sickle cell anemia, Huntington disease, cystic fibrosis, Lou Gehrig disease, and Tourette syndrome, whereas most are less familiar including pachyonychia congenita (PC). Many rare diseases have patient populations of fewer than a hundred (http://www.fda.gov/fdac/features/2003/603_orphan.html).

Although the incidence of an individual rare disease is small, cumulatively the 6,000 known rare diseases affect 25 million Americans or nearly 10% of the US population (Rados, 2003). The majority of rare diseases, including PC, have a genetic origin component, have little or no treatment options, and are not rigorously studied. The number of PC patients worldwide is currently unknown, but is likely to be on the order of 1,000–10,000 patients (Sancy Leachman, personal communication; see also http://www.emedicine.com/derm/topic812.htm).

Abbreviations: FDA, Food and Drug Administration; NIH, National Institutes of Health; ORD, Office of Rare Diseases; PC, pachyonychia congenita

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Costs of Developing Therapeutics

According to a widely accepted study performed by DiMasi et al (2003), the estimated average out-of-pocket cost for bringing a new drug to market is $403 million (year 2000, US dollars). When investment and capitalization costs are included this estimate rises to $802 million. A more recent study by Bain & Co. put the costs at $1.7 billion (Gilbert et al, 2003; Mullin, 2003). Regardless of the actual costs, these impressively large numbers, coupled with the observation that only 21% of drugs that enter phase I clinical trials make it to the marketplace, underscore the difficulty of enticing the investment community to fund research for rare diseases for which recovery of development costs seems unlikely. In a marketplace where the business model has historically been on blockbuster drugs that generate over a billion dollars in annual sales, there has been reluctance among large pharmaceutical companies and the investment community to pursue small market therapeutics.

Resources Available to Stimulate Rare Disease Research

Perhaps the most important governmental act that stimulated research and development of rare disease therapeutics was passage of the 1983 Orphan Drug Act. This program provided financial incentives to develop treatments for rare diseases, including a guarantee of a 7-y period of market exclusivity, tax credits for clinical research, and waiver provisions for license fees. The Orphan Drug Act has been successful in stimulating development of rare disease drugs (Fig 1) by small and medium-sized biotechnology companies—more than 200 drugs and biological products for the treatment of rare diseases have been brought to market since its passage in 1983. In contrast, in the 10 y prior to its passage, fewer than ten rare disease products came to the market (Rohde, 2000; Lichtenberg and Waldfogel, 2003; see also http://www.fda.gov/orphan). European
Orphan Medicinal Drug Product legislation similarly provides financial incentives (Milne et al, 2001).

Recognizing the need to address the 25 million Americans afflicted with a rare disease, the US Congress established the ORD in 1993 to promote research and collaborative efforts. H.R. 4014 (2002) gave statutory status to the ORD at the NIH. The ORD provides information on rare diseases, and links investigators with research subjects and patients, and supports rare disease research (Rados, 2003). In addition, the ORD funds research into rare diseases directly or in combination with other NIH Institutes. Furthermore, in 2003 a Rare Diseases Clinical Research Network was established, which includes seven Rare Diseases Clinical Research Centers spread throughout the United States (see website: http://rarediseases.info.nih.gov/html/resources/extr_res.html). This Network maintains a database of clinical trials for rare diseases and refers rare disease patients to appropriate medical care.

Other organizations have been formed to facilitate information flow and research and development of rare disease therapeutics. The National Organization of Rare Diseases (NORD) is a federation of approximately 125 voluntary health organizations and over 60,000 patients (http://www.rarediseases.org/). The International Rare Disease Support Network (IRDSN) offers support groups for over 1200 diseases (http://www.raredisorders.com/). OrphaNet provides information on rare diseases (http://www.orpha.net/consor/cgi-bin/home.php?Lng=GB). The European Rare Disease Therapeutic Initiative (ERDITI, http://www.erditi.org/) is a coalition of patient organizations fostering interactions between academic institutions working on rare diseases and the pharmaceutical industry to bring new therapeutics to the marketplace. Similarly, the Office of Orphan Products Development (OOPD, http://www.fda.gov/orphan/progovw.htm) at the US Food and Drug Administration (FDA) and Public Health Programme (formerly The EU Programme on Rare Diseases, http://europa.eu.int/comm/health/ph_overview/previous_programme/rare_diseases/rarediseases_en.htm) facilitate orphan drug development through guidance and financial assistance (see Fig 2). The National Center For Study of Orphan Disease (CSOD, http://www.csod.us/) bridges various organizations to facilitate rare disease therapeutic development.

Justification of Research Dollars for Rare Diseases

Given the current high cost of bringing a new drug to market (see above), the difficult question arises regarding at what level it becomes financially feasible to fund research that benefits a relatively small group of patients with a given rare disease. If the costs of developing a therapeutic to treat a disease that afflicts 10 million people is approximately the same as a distinct therapeutic that would treat 100,000 (or 100), how can the high cost of developing a therapeutic for a rare disease be justified?

A study by Love and Palmedo (Consumer Project on Technology, (see website: http://www.cptech.org/ip/health/orphan/irdsdata9798.html) challenges the reported high development costs associated with rare disease drug discovery. Taking into account the amount US taxpayers received as tax credits (50% credit allowed) for orphan disease clinical development ($141 million for 1997 and 1998, the most recent data available), they calculated the cost for clinical development, testing and marketing of the 36 orphan products approved during the same time period to be $7.9 million per orphan product ($283 million/36 products) before tax, and $3.9 million with the benefits of the orphan drug tax credit.

A number of biotechnology companies have taken advantage of the Orphan Drug Act financial incentives to specifically develop and market therapeutics for the rare disease market. Several companies have profitably targeted this niche market. Approximately half of Genzyme's 2003 revenue came from $740 million in sales of Cerezyme (Genzyme, Cambridge, MA). This is an enzyme replacement therapy for Gaucher disease, a potentially deadly genetic disorder.
disorder that causes anemia and enlarged organs (http://
www.genzyme.com). Gaucher disease affects less than
10,000 people worldwide and about 40% are treated with
Cerezyme. Although the 7 y marketing exclusivity of Cere-
zyme has long since ended, the drug remains entrenched in
the marketplace and highly profitable. Much of the remain-
der of Genzyme’s sales comes from other therapeutics with
current orphan drug status including Fabrazyme (for Fabry
disease), Aldurazyme (for Mucopolysaccharidosis I), and
Thyrogen (for thyroid cancer). Other companies including
Transkaryotic Therapies (Cambridge, MA), Oxford Glyco-
Sciences (Brussels, Belgium), and Orphan Medical (Minne-
tonka, MN) have also taken a similar approach to seek niche
markets for specific rare diseases, taking advantage of the
Orphan Drug Act. Many current blockbuster drugs
(sales over $1 billion per year), including Amgen’s Epo
gen and Neupogen, were originally introduced as orphan drug
products and were later extended to larger markets.

Societal Benefits of Rare Disease Research

Why treat rare diseases, particularly diseases in which very
small numbers of patients are involved? There are several
answers to this question, not the least of which is that these
are real people with families and employers that are also
affected by the loss of quality of life and productivity. Fur-
thermore, science is replete with examples of esoteric re-
search that has led to unintended discoveries that benefit
society at large. Basic research is funded with the expec-
tation that investigation in one area will have benefits in
many related as well as unrelated and unexpected areas.
The study of rare diseases has often yielded great amounts
of information, completely out of proportion with the
number of patients suffering from the disorder. William Har-
vey, the English physician and discoverer of blood circu-
lation, stated in a letter dated 1657, “Nature is no where
accustomed more openly to display her secret mysteries
than in cases where she shows traces of her workings apart
from the beaten path; nor is there any better way to ad-
vance the proper practice of medicine than to give our
minds to the discovery of the usual law of nature, by careful
investigation of cases of rarer forms of disease. For it has
been found in almost all things that what they contain of
useful or applicable, is hardly perceived unless we are de-
prived of them, or they become deranged in some way
(Willis, 1847; Zelzer and Olsen, 2003).”

The majority of rare diseases are due to genetic muta-
tions. In many cases, these mutations affect a single gene
and cause perturbations in a metabolic pathway. This rare
disease datasource has been a rich resource from which a
great deal has been learned about normal human metab-
olism, since the study of aberrant metabolism (i.e., blockage
of a single step in a metabolic pathway due to the absence
of a functional gene) teaches a great deal regarding how
normal pathways function. These “natural” experiments are
similar to carefully controlled knockout animal experiments
in which the function of single genes are analyzed and often
give major insights into metabolic pathways.

There are numerous examples in which rare disease re-
search has led to insights into more general disease proc-
esses. For instance, it would have been difficult to predict
that study of kuru, a mental illness in a New Guinea tribe,
one symptom of which is uncontrollable laughter, would
lead to the discovery of a new class of contagion and result
in a Nobel prize for Stanley Prusiner (Prusiner, 1984). The
discovery that the disease-causing prions were passed
along by consumption of the brains of deceased relatives
allowed the discovery of the disease-causing prions of other rare
diseases including Creutzfeldt–Jakob and Gersmann–
Straussler–Scheinker (GSS) syndrome, as well as recognizing
that bovine spongiform encephalopathy (BSE), was
caused by ingestion of contaminated beef. This pioneering
work likely resulted in an epidemic being averted and thou-
sands of lives spared. Another example is α-1-antitrypsin
deficiency, a rare genetic emphysema lung disease that
develops 10–30 y before the occurrence of the more com-
mon form found in smokers. The earlier onset has allowed
researchers to study the disorder in the absence of com-
pounding factors due to smoking and aging, leading to in-
sights into emphysema (Rados, 2003).

Leveraging Existing Resources

PC is an excellent example of a rare disease that could
serve as a model for a multitude of other skin disorders and/
or autosomal dominant disorders. As discussed above and
in other reports in this issue, the specific mutations in ker-
atin genes K6a/b, K16 and K17 responsible for PC have
been identified (Munro, 2001; Terrinoni et al, 2001; Smith,
2003). Furthermore, the skin cell type involved (keratinocyte)
is known and is readily accessible. Therefore, this disorder
could serve as a paradigm for many other keratinocyte skin
disorders, including psoriasis and epidermolysis bullosa
(Porter and Lane, 2003; Sawamura et al, 2003). Technolo-
gies including siRNA, ribozymes, and antisense have been
shown to specifically block expression of target genes in
many systems (see Lewin et al, this issue) including kera-
tinocytes (Mehta et al, 2000; Arts et al, 2003; Barbieri et al,
2003; Seo et al, 2004). The main remaining hurdle for clinical
application is efficient delivery to the appropriate cells. De-
velopment of a skin delivery system in an “easy to work
with” system would be a boon to treatment of other skin
disorders. PC may represent one of the “most straightfor-
ward” genetic disorders for treatment due to the accessi-
bility of the skin. Furthermore, complete blockage or
removal of a mutant keratin gene may not be necessary
as a partial reduction may be sufficient to give a therapeutic
effect (see discussion of K10/K14 in Chen and Roop, this
issue). Unlike psoriasis, which involves multiple cell types
including keratinocytes and immune cells (Kirby and
Griffiths, 2002; Barry and Kirby, 2004), PC appears to be
limited to keratinocytes. Finally, the difficulty of discrimina-
tion between mutant and wild-type genes, likely to be nec-
essary for most genetic diseases, does not appear to be a
requisite for an effective PC treatment. Reduction of both
the wild-type and mutant keratin gene products is likely to
give a therapeutic effect as other “redundant” keratin pairs
will likely compensate for the missing mutant keratin gene
pair (see Lewin et al, in this issue).
Bringing Together Existing Expertise and Resources for Rare Disease Therapeutic Development

The Pachyonychia Congenita Public Charity was formed with the aim to develop an effective therapeutic for the relatively small number of patients suffering from PC (http://www.pachyonychia.org/index.html). To this end, a consortium of investigators was brought together with medical and scientific expertise in various areas related to PC and technology that may be useful in developing PC therapeutics. The Public Charity has provided seed funding to allow targeted research that should facilitate progress towards PC therapeutic development (see Introductory PC article in this issue). The collaborative nature of the consortium is essential to prevent wasteful redundant research and allow efficient use of limited resources. Furthermore, the breadth of the expertise of the consortium membership will allow continual monitoring of scientific and medical progress of related skin disorders, ideally taking advantage of and building on breakthroughs including new skin delivery systems.

In addition to the Pachyonychia Congenita Public Charity, other private organizations and philanthropic individuals, public resources are available for rare diseases research and clinical development and testing including the NIH R21 Exploratory and Development (http://grants1.nih.gov/grants/guide/pa-files/PA-03-171.html) and U54 (http://grants.nih.gov/grants/guide/ra-files/RFA-RR-03-008.html) grant mechanisms. Furthermore, the FDA administers a program to fund clinical trials for drugs that have achieved orphan drug status (see website: http://www.fda.gov/orphan/grants/2004RFA.htm).

Other Considerations

As discussed in other reports in this PC JID edition, the ideal solution for a permanent cure for PC would be a gene therapy replacement procedure in which the defective PC gene would be replaced with a corrected version that would be regulated in identical fashion to the wild-type gene. This “gold standard” gene replacement therapy has not been approved for any disorder to date and will likely be initially applied to acute, life threatening, “no alternative” diseases. The amount of development and testing required, as well as its non-life threatening nature, makes PC an unlikely early candidate for gene therapy. On the other hand, PC is a straightforward dominant-negative genetic skin disorder in which diagnosis of overexpressed genes involved in rare diseases is readily translated into designer molecular medicines that specifically target these problem genes. If the delivery issue can be solved, theoretically any gene can be targeted and its protein product blocked or reduced, providing a therapeutic effect. Specifically targeting problematic single nucleotide mutations in disease-causing genes will likely prove more difficult and may require improved technology. Some diseases, such as PC, however, may not suffer from this discrimination difficulty as concomitant reduction of the wild-type gene is unlikely to affect the therapeutic outcome as other keratin gene pairs may compensate as a result of redundancy in the system (Wong et al, 2000; Wojcik et al, 2001; Wong and Coulombe, 2003). This advantage, coupled with relatively easy access to the diseased cells (skin keratinocytes), makes PC an excellent candidate disorder for treatment with specific and robust nucleic acid therapeutics such as siRNA.

Conclusions

Personalized molecular medicine: the end of rare diseases? With the advent of new technologies including microarray chips that can detect steady-state levels of tissue mRNA including single nucleotide mutations, the era of personalized molecular medicine appears imminent (Jain, 2002, 2004). Powerful technologies continue to be developed that can specifically target and block expression of specific genes (the latest being RNA interference or siRNA (Dave and Pomerantz, 2003; Alisky and Davidson, 2004; Caplen, 2004; see also Lewin et al, in this issue). As progress continues in the arena of specific and safe delivery vectors for correcting genes or delivering siRNA or other gene-specific inhibitors directly, one can envision a scenario in which diagnosis of overexpressed genes involved in rare diseases is readily translated into designer molecular medicines that specifically target these problem genes. If the delivery issue can be solved, theoretically any gene can be targeted and its protein product blocked or reduced, providing a therapeutic effect. Specifically targeting problematic single nucleotide mutations in disease-causing genes will likely prove more difficult and may require improved technology. Some diseases, such as PC, however, may not suffer from this discrimination difficulty as concomitant reduction of the wild-type gene is unlikely to affect the therapeutic outcome as other keratin gene pairs may compensate as a result of redundancy in the system (Wong et al, 2000; Wojcik et al, 2001; Wong and Coulombe, 2003). This advantage, coupled with relatively easy access to the diseased cells (skin keratinocytes), makes PC an excellent candidate disorder for treatment with specific and robust nucleic acid therapeutics such as siRNA.

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Address correspondence to: Roger L. Kaspar, Transderm, 2161 Delaware Ave., Santa Cruz, CA 95060, USA. Emails: rkaspar@somagenetics.com

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