Power of Rare Diseases: Found in Translation

Mark C. Fishman

Aside from established genetic evidence, the best proof of a model for disease pathogenesis rests on predicted perturbation via targeted medicines in clinical trials. Here, I discuss the strategy of performing exploratory first-in-human clinical studies on mechanistically homogeneous populations (often small groups of patients with rare diseases) as a routine entrance to full-registration clinical trials. Over the past decade, this approach has proved some pathogenic theories, disproved others, and guided investigators in new scientific directions. The immediate advantages have been smaller trials and provision of new treatments for rare diseases. Later, indications often can be expanded to subsets of more common diseases.

Using a two-by-two chart, consultants have been known to define “strategy” as whatever puts a client in the upper right corner. Define the ordinate as “unmet medical need” and the abscissa as “scientific tractability” and, voilà, you have a strategy for drug discovery and development (Fig. 1A). If patients need a drug (unmet need), and there is a shot at developing one (tractability), that’s a logical starting point.

A main corollary to this strategy is a focus on rare diseases, which are often neglected from a drug discovery vantage point because of the small potential market. But rare diseases—especially those with a genetic basis—often have well-defined biological mechanisms. Because of the homogeneity of rare genetic disorders and (hopefully) precise molecular targeting of medicines made possible by strong underlying science, small clinical trials can reveal whether we are correct about the pathogenesis of a disease and the effectiveness of a potential new medicine.

At Novartis Institutes for BioMedical Research (NIBR), we refer to such small, precisely targeted first-in-human clinical studies as proof-of-concept (PoC) trials. The goal of our PoC trials is to show whether a drug is effective in a defined set of patients. This moves beyond finding a safe drug dose in healthy volunteers (classical phase 1) or proving that the drug target is engaged in the patient (pharmacodynamics). The patient must show a defined clinical response for a PoC trial to be considered successful. The clinical response is frequently assessed using one dose, the highest tolerable one, which often was determined in a typical phase 1 study of healthy volunteers or subjects with a disease. PoC trials are smaller than full phase 2 trials—their start is more likely within the range of safety and efficacy established by phase 1.

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FROM RARE TO SUBSETS OF COMMON DISEASES

Muckle-Wells and IL-1. One guiding premise is that fundamental pathways disrupted in rare disorders are the same as those in subsets of patients with common diseases (Fig. 1B). In evaluating ACZ885, a monoclonal antibody (mAb) to interleukin-1β (IL-1β), we focused on the Muckle-Wells syndrome. This rare autosomal-dominant cryopyrin-associated periodic syndrome (CAPS) is caused by gain-of-function mutations in the NALP3 gene, which encodes a component of the inflammasome. The genetic defect results in constitutive activation of caspase-1, which generates excess IL-1β cytokine (2). Patients suffer from rash, fevers, and arthralgias; preventing IL-1β from activating its receptor with an IL-1β mAb has been shown previously to improve symptoms (3). Traditional market research would not pinpoint such a rare disease as a sensible indication over more prevalent inflammatory disorders such as rheumatoid arthritis (RA). But RA is a far more heterogeneous disease, and the mechanistic link to IL-1β is far more tenuous. Testing treatments for such conditions necessitates large and long clinical trials.

The first Muckle-Wells patient treated with the IL-1β mAb (ACZ885) was a 33-year-old woman who had suffered daily urticarial rash, malaise, arthralgias, and fatigue since childhood. Hours after a single...
injection her inflammatory markers normalized, and within 48 hours she experienced a complete clinical remission that lasted 169 days. After treating three patients, all with similarly robust responses, we declared the PoC trial a success and moved on to registration trials for CAPS (including Muckle-Wells syndrome and familial cold autoinflammatory syndrome), which became the first approved indication for the drug (termed Ilaris).

Rather than the standard approach of pursuing regulatory approval of a drug in a large-market indication and returning later for testing in rare diseases—the results of which are often reported only as case reports in small trials from academic institutions—the PoC approach quickly provides approved therapies to patients suffering from rare diseases. Can such findings be expanded to subsets of patients with more common diseases (Fig. 1B)? During the registration trials for the drug ACZ885 in Muckle-Wells patients, evidence appeared that the cryopyrin pathway is activated by uric acid crystals and thus may function in the development of gout, the most common inflammatory arthritis in the developed world (4).

There is a medical need for better gout therapies, especially for the subset of patients for whom standard therapies—colchicine, steroids, and nonsteroidal anti-inflammatory drugs—are contraindicated. Hence, we explored the effect of the IL-1β mAb in a PoC trial of six patients with acute gout flares, three who received the mAb and three controls who received corticosteroids. All three patients responded well to mAb therapy, confirming the pathogenic role of this pathway and indicating that the drug may be effective in treating gout. Thus, we proceeded to full registration trials for gout, which led to the drug’s approval in Europe for this indication. We are now investigating additional indications in which stimulation of the cryopyrin inflammasome pathway is implicated, such as systemic juvenile idiopathic arthritis.

**Tuberosus sclerosis and mTOR.** Conserved from yeast to humans, the mammalian target of rapamycin (mTOR) pathway is an essential growth-regulatory pathway that responds to nutrients and growth factors. The tuberosus sclerosis genes TSC1 and TSC2 encode tumor growth suppressors that negatively regulate the mTOR pathway; mutations in these genes activate mTOR and lead to tissue overgrowth. In humans, mutations in TSC1 or TSC2 cause the rare autosomal-dominant disorder tuberous sclerosis, which is marked by benign, tumorlike growths in many tissues, including skin, kidney, heart, and brain (often causing seizures). Twenty-eight patients with tuberous sclerosis were enrolled in a PoC trial in Cincinnati, Ohio, to examine the effect of RAD001, a rapamycin derivative that inhibits mTOR. The study focused on subependymal giant cell astrocytomas (SEGA), which are benign brain ventricular tumors that occur in 5 to 20% of patients with tuberous sclerosis and require surgical removal. The effect of RAD001 was clear: None of the treated patients developed new lesions or required surgery, many had a decline in seizure frequency, and 21 had a reduction of 30% or more in their tumor size (5). These findings confirmed the role of mTOR in SEGA development and suggested that RAD001 might be used to prevent seizures. Although the medicine has side effects, notably stomatitis, the patients’ quality of life improved. The drug was approved for the treatment of astrocytomas in tuberous sclerosis patients, and investigational studies are under way to examine effects on other aspects of the disease, such as renal tumors (6), epilepsy, and cognitive impairment.

Expansion of investigational studies to malignant cancers is a logical step, as aberrations in the mTOR pathway are associated with a variety of tumor types. For example, combination with an aromatase inhibitor has been observed to improve progression-free survival in postmenopausal women with hormone-positive advanced breast cancer (7).

**CHALLENGING HYPOTHESES**

Not all PoC trials are successful, no matter how apparently airtight the underlying scientific hypothesis is. Strong experimental evidence suggests that many autoimmune disorders depend on the cytokine IL-17, which is released from the Th17 population of effector T lymphocytes (8). One way to test the IL-17 hypothesis is with the use of targeted medicines. In a series of PoC trials, patients were treated with AIN457, an inhibitory mAb to IL-17, which was found to ameliorate psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis (9). Crohn’s disease is a relapsing remitting inflammatory disease of the gastrointestinal (GI) tract characterized by pain, diarrhea, and, in some patients, GI obstruction and extraintestinal pathology such as joint inflammation. IL-17 concentrations are increased in the vicinity of inflammation, and some patients with Crohn’s disease carry polymorphisms in genes that encode components of the IL-17 inflammatory pathway. However, in a PoC trial, AIN457 did not reduce the Crohn’s disease activity index in patients with Crohn’s disease (and the incidence of infections was higher than placebo) (10). These results suggest that Crohn’s disease pathology is less dependent on IL-17 than are other autoimmune disorders.

**CHANGING INDICATIONS**

PoC trials can also quickly redirect use of a new lead compound. For example, in seeking an antihypertensive drug for patients with primary hyperaldosteronism, we designed the small molecule LCI699 to reduce aldosterone levels by blocking 11-β-hydroxylase, an enzyme in the adrenal cortex that converts 11-deoxycortisol to cortisol. LCI699 reduced blood pressure in a PoC trial but also reduced adrenocorticotropic hormone–stimulated cortisol release, which could make it less attractive for the treatment of hyperaldosteronism. However, another endocrine disorder, Cushing’s disease, results from excess cortisol release triggered by ACTH-secreting tumors of the pituitary. The excess cortisol causes diabetes, dyslipidemia, obesity, and depression. There are no approved medications for Cushing’s disease, and surgery is required for relief. In another PoC trial, LCI699 consistently reduced urinary free cortisol in all nine patients; hence, we have redirected the drug toward further investigational studies on Cushing’s disease.

**REFINING TARGET POPULATIONS**

Genetic uniformity does not guarantee consistency of response because epigenetic modifications may alter gene expression. Fragile X syndrome is caused by a single-gene defect, an expansion of a CGG repeat in the 5’-untranslated region of the *FMR1* gene. This defect is associated with autism and other behavioral and intellectual disorders. The pathogenesis of fragile X syndrome is under debate but is speculated to result from up-regulation of proteins normally kept under control by the fragile X gene product, including the metabolotropic glutamatergic receptor mGluR5 (11). A PoC trial with an mGluR5 blocker, AFQ056, was conducted in 30 patients with the fragile X syndrome. Initially, no statistically significant evidence of a response was detected.
However, we knew that the FMRI gene is not silenced directly by the CGG repeat, but rather by epigenetic suppression of gene expression, and epigenetic modifications are not equally evident in all individuals who bear the CGG repeat expansion. When we analyzed the response of a subset of seven patients with full methylation of the fragile X gene, there was evidence of a positive behavioral response to AFQ056 in all (12). Further investigational trials are being conducted to examine both genetic and epigenetic characteristics of the fragile X gene so as to define a precise responder population.

**INTERPRETATION OF POCT TRIALS**

Statistical analyses of small clinical trials may be facilitated by a variety of trial designs (13), including an adaptive trial design and Bayesian approaches (14), but we often find that the robustness of response in a few patients is to be convincing with respect to the clinical hypothesis. Certainly, many important fields have been launched by trials with dramatic responses in just a few patients. James Lind’s 1753 trial of nutritional therapies for scurvy included only two patients in the oranges and lemons arm (15). The first intracoronary thrombolitic therapy included two patients with one success (16). Cancer chemotherapy began in 1942 with Goodman, Gilman, and Lindskog’s administration of nitrogen mustard to a single patient with refractory lymphosarcoma. The results could not be published until World War II ended (17) because of concerns about the chemical warfare implications of nitrogen mustard, but the success quickly led to exploration of this agent at Yale University and other institutions.

In the oncology field, PoC trials are becoming more standard, even if not so designated. Drugs are tested early in patients rather than in healthy volunteers because of the low therapeutic ratio of many cancer therapies, and patient populations are rendered more homogeneous with genetic characterization of tumors.

**POCS AND R&D**

Drug discovery and development has been described as an inefficient and flawed process, with an average of 20 to 30 new medicines approved each year by FDA, only a handful of which are novel with respect to target and clinical need (18, 19). There are many reasons for this paucity, and a lack of well-validated drug targets is high on the list. Therefore, when evaluating agents that are truly new in terms of target or medical need, or when disease pathogenesis is not well understood or has not been manipulated in human patients, clinical trials that yield negative results can readily redirect R&D efforts before deeper resource investments are committed. The traditional graveyard of new medicines is early discovery through phase 2 clinical trials, where success rates have declined now to 7% across the industry (20). Since instituting successful PoC as a routine entry criterion to a larger clinical development program and registration trials, Novartis has seen a 50% increase in early-development success rates (now 21%). We believe this is at least in part because of the PoC approach. More precise genomic stratification of common disorders should further increase our opportunities to use PoC trials to probe disease pathogenesis in homogeneous populations and deliver effective targeted medicines to patients with rare and common diseases.

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Acknowledgments: I thank T. Wright, E. Beckman, B. Weber, and J. Spector for helpful commentary on the manuscript. Competing interests: The author is president of the NIBB. The opinions are those of the author and not those of any of the Novartis Group of companies. All statements regarding any indications for or use of compounds for which regulatory approval has not been granted are investigational only (safety and efficacy have not been established).

10.1126/scitranslmed.3006800

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Sci Transl Med 5, 201ps11
DOI: 10.1126/scitranslmed.3006800

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