

Rare Disease Research: Where Compassion Meets Commerce

The advent of a new set of potential acquirers has heightened venture capital's interest in rare diseases, resulting in the creation of a new cohort of drug developers that are using cutting edge technologies to treat and in some cases cure grave illnesses.

Rarum carum. The wisdom in the Latin proverb “rare things are prized” is increasingly being embraced by investors and executives, researchers and regulators. Beyond private foundations, growing numbers of companies are pursuing treatments for rare medical disorders affecting fewer than one in 2,000 people. Even Big Pharmas are establishing expertise in this arena. In 2010 both **Pfizer Inc.** and **GlaxoSmithKline PLC** established dedicated rare disease divisions, signing deals to access the assets of smaller firms, while **Sanofi's** greater than \$20 billion takeout of **Genzyme Corp.** validated the concept on an entirely different level. (See “*Sanofi/Genzyme: Emblematic of What Big Pharma's Buying Now,*” IN VIVO, March 2011.)

A number of factors have resulted in this embrace of “orphan” indications, including new technologies to tap intractable targets, lower regulatory hurdles, and financial incentives stemming from the Affordable Care Act. But perhaps the most persuasive argument is the cold hard cash generated by niche medicines – at a time when launches of traditional primary care medicines such as **Bristol-Myers Squibb Co.'s Onglyza** (saxagliptin) and **Eli Lilly & Co./Daiichi Sankyo Co. Ltd.'s Effient** (prasugrel) have fallen short of blockbuster status.

Biotech companies like **Genzyme** carried the flag for rare diseases in the 1980s, and later **BioMarin Pharmaceutical Inc.** and **Actelion Pharmaceuticals Ltd.** proved the market has merit for small players. Then mid-sized UK player **Shire PLC** acquired **Transkaryotic Therapies** in 2005, and turned it into the successful stand-alone subsidiary **Shire Human Genetic Therapies Inc.** (See “*Shire: Remodeling Specialty Pharma,*” IN VIVO, April 2006.) In addition to **Pfizer**, **GSK**, and **Sanofi**, **Novartis AG** is also pushing the concept in an attempt to replicate the strategy it has pursued so ably with its chronic myelogenous leukemia medicine **Gleevec** (imatinib). Since its initial approval for CML in 2001, the novel medicine has been approved for nine more indications, generating more

than \$4 billion in revenue in 2010 alone. (See “*Orphaned No Longer; Big Pharma Embraces Drugs For Niche Markets,*” IN VIVO, February 2010.)

Large companies have been willing to acknowledge big ambitions linked to rare disease research, perhaps because stockholders demand as much. Management at **Novartis** has said explicitly that the firm perceives work on rare diseases as a way to advance understanding, and generate compounds that may prove valuable in much larger markets. It hopes **Ilaris** (canakinumab), developed for a rare inflammatory condition caused by a rogue gene that over-produces interleukin-1, will go on to treat up to 30 indications including gout, rheumatoid arthritis and type 2 diabetes.

By contrast, rare disease start-ups mostly emphasize wanting to help neglected people. Such prudent positioning won't limit the upside of high-potential research, but it can help start-ups gain the support of patient groups and foundations and perhaps win sympathy from regulators.

The Human Genome Project deserves much credit for rousing interest in rare disease research. Although certain disorders have been known for centuries by their clinical symptoms, and have been recognized as occurring within families, it is public troves of sequencing data that have at last helped scientists see where specific genes are missing or mutated.

Charles Darwin described seeing “the toothless men of Scinde” in the late 1800s in travels through what is now known as Pakistan. He learned that 10 men across four generations had the disorder, but no women in the family, although they were known to carry it. Darwin had no way of knowing that the inherited genetic disorder is caused by a mutated or missing gene on the male chromosome. The disease, now classified as X-linked hypohidrotic ectodermal dysplasia (XLHED), is caused by a deficiency in the **EDA-A1** protein, which plays a vital role in the development of teeth, hair and skin. Peo-

ple with the disorder develop only very sparse hair and just a few, pointy teeth, but the most serious symptoms stem from impaired formation of glands for sweat and saliva.

Now scientists believe they can leverage not only their knowledge of the gene encoding the essential protein, but also their understanding of the precise time it must be present to assure normal development. **Edimer Pharmaceuticals Inc.**, profiled in this issue, expects to begin the first human trials of a protein-replacement therapy for XLHED this year. Although the start-up founded in July 2009 is planning to test its therapy first in adults, Edimer's ultimate goal is to permanently correct the disorder by treating developing fetuses in utero.

Edimer's founder Neil Kirby, PhD, describes the company's lead compound as "a first-in-class signaling protein replacement molecule." It was designed to cross the placental barrier, so that it can bind an endogenous receptor and trigger normal fetal development. Kirby does not deny that this lead candidate, or related therapies, could go on to serve much bigger markets, such as helping to grow hair or teeth, restore salivary glands damaged by radiation and heal wounds.

Like Edimer, and Genzyme and BioMarin before it, many rare-disease research organizations now aim to replace substances, whether proteins, enzymes or sugars that are missing because of genetic flaws. Typically, firms aim to achieve continuous or chronic replacement, but the goals are a function of the science. Edimer, for instance, aims for *timely* replacement just once.

The companies attracting the most money are those capable of convincing investors their methods will work not just in one disease, but serially, essentially creating a platform that in rapid fashion can generate new therapies – or at least targets – for multiple rare diseases. **bluebird bio LLC**, also profiled here, is a case in point: the company has taken in \$65 million in

venture capital over the past year, thanks to encouraging studies with two different kinds of lentiviral vectors that transfer new copies of genes into patients' own stem cells. Given that vectors have different properties – one integrates into the DNA coding region, the other does not – the company might eventually be able to mix and match therapeutic gene "fillings" to vectors as needed. **bluebird bio's** CEO Nick Leschly is convinced that "the time is

now" to commercialize gene therapies for serious genetic disorders. A different crop of executives said the same 20 years ago, but none managed to turn experimental therapies into products. Then again, 20 years ago clinicians were only just beginning to harvest bone-marrow transplants and manipulate stem cells. By now, both disciplines are fairly standard.

Medicine *can* leap forward when the proper forces align, and the federal government has been acting on that recognition to strengthen regulatory and financial

incentives for rare disease research. The Orphan Drug Act has since 1983 granted seven years marketing exclusivity to treatments for diseases affecting fewer than 200,000 patients in the US annually. Though some critics complain the protections have unduly enriched companies for products they would have developed anyway, the incentives remain in place. Updates in 2009 and 2010 do more: they exempt orphans from certain fees, including the Prescription Drug User Fee companies agreed to pay in 1992. Orphans also stand to be spared from federally funded comparative-effectiveness trials, and from rebates commanded by revenue-limiting provisions. (See "Valuing

Genzyme: A Health Care Reform Premium, The RPM Report, October 2010.)

Some Health Care Reform initiatives are benefiting companies by influencing practices at federal entities that serve and provide resources to the medical industry. The **National Institutes of Health** (NIH) is itself pitching in by conducting more preclinical research on drug candidates that might interest industry. Since Francis Collins, MD, PhD, took the helm in August 2009, NIH has launched two new programs to spur clinical research in the field including a collaboration with regulators that will assist in evaluating unusual clinical trial designs. Collins has also promised to create a National Center for Advancing Translational Sciences by October 2011, to speed research assets from academia to industry. FDA is likewise getting more active, launching in September 2010 a database of drug candidates it considers ripe for "repurposing" as orphans.

Even with all the government initiatives currently underway, rare-disease advocacy groups are pushing for more, better and faster assistance. The Kakkis EveryLife Foundation created in 2009 employs several professional advocates, and has signed up over 200 partner organizations to campaign for "increased predictability of the regulatory process for rare disease treatments." Among other things, the group wants FDA to consider approving therapies based on surrogate markers, and to establish a new Office of Drug Evaluation specifically to review treatments for genetic and biochemical disorders.

Rare disease foundations often help patients and families learn about their disorders and communicate with each other, and the advent of social media has been a boon. Yet start-ups cannot assume they will quickly connect with patients through the Internet or pricey advertising in popular media. It takes time to build awareness and trust. "You can't just rely on patients to self-identify on a web site. You need to go through doctors to connect with patient groups," says Emil Kakkis, MD, PhD, founder of both the Kakkis EveryLife Foundation and **Ultragenyx Pharmaceutical LLC**, profiled in this issue.

Increasingly, foundations are funding research directly. The **Cystic Fibrosis Foundation** was among the first to steer cash to

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companies, and continues to do so – with good results. Having worked with Vertex Pharmaceuticals Inc. since 1998, in early April 2011, the CFF agreed to give \$75 million over the next five years to support ongoing R&D on “correctors” of the most common forms of the disease. Vertex recently reported positive data from two Phase III trials of a compound meant to help CF patients with at least one copy of the G551D mutation. (See “With Capital Scarce, Charities Emerge As A Stronger Force On Start-Up Scene,” *START-UP*, February 2009.) Because the science enabling new understanding of rare diseases can be so complex, foundations make sure they get expert guidance before dispersing cash. Amy Hewitt, executive director of the Scleroderma Research Foundation, observes, “Having an Advisory Board comprised of some of the nation’s most highly regarded scientists allows us to invest our resources only after they have researched each proposal. We believe the best way to help people living with scleroderma is to fund the research that will result in improved therapies and a cure.”

Philip Reilly, MD, an internist and clinical geneticist who represents Boston-based VC firm Third Rock Ventures on the boards of both bluebird bio and Edimer, says, “It is so important to be in trusting and close relationships with families and foundations. No one knows better than the families. No one is more committed. We always want to make family groups our allies and full partners.”

The need to identify individual patients, and to develop personal relationships with them and their families, are only two of the challenges unique to building a business based on rare disease research. For companies developing therapies in the lysosomal storage disease area, for instance, that challenging task is further complicated by the fact that stand-bys such as Genzyme and Shire have developed savvy commercial organizations that help with a variety of services from education to patient assistance. The outsized price tags for some rare diseases also present reimbursement challenges; companies must be prepared to negotiate directly with insurers on behalf of patients in many cases.

Where traditional pharmaceutical firms are accustomed to operating in a “push” market that calls for aggressive selling, companies planning to grow in

the rare disease sector need to recognize they are in a “pull” market that requires a soft-sell approach in hopes of inspiring loyalty. Each style of marketing calls for a completely different skill set. Recognition of the discrepancies caused Shire PLC’s CEO Angus Russell not to integrate the specialty genetics business it acquired and instead to let it stand independently as Shire HGT. Russell recently spoke with Elsevier about these dynamics, explaining that HGT’s close involvement with rare disease patients is prompting Shire the parent to now also seek more understanding of how its mass-market drugs affect patients’ lives. The insights are helping Shire build stronger cases for the pharmacoeconomic value of its attention deficit hyperactivity disorder products. (See “Shire CEO Angus Russell On The Value Proposition Of Drugs,” “The Pink Sheet,” April 18, 2011 and “Seeking Value: How Lower Prices Can Make Sense,” The IN VIVO Blog, March 15, 2011.)

Reimbursement is a matter that rare-disease drug developers sometimes have to negotiate directly with insurers on behalf of patients. Doing so could bring a company a customer for life, when a single developer offered the only therapy for a particular disease. Going forward, the advent of biosimilars and pricing pressures could undermine long-term relationships, much as Genzyme’s manufacturing troubles pushed patients formerly loyal to Cerezyme (imiglucerase) into the arms of Shire and Vpriv (velaglucerase alpha) – which happens to be priced 15% lower.

With cost pressures and competition growing, it’s possible that the pricing structures and business models relied on thus far in the rare disease space may not work so well going forward. The high prices granted to small companies may not be paid out as readily to pharmaceutical behemoths. Third Rock’s Reilly says he is not overly worried about insurers denying reimbursement for rare diseases. Although the state of Arizona has recently decided to reduce funding for organ transplants, he figures “rare disease treatments will be among the last to succumb to price pressures.”

Surely Reilly and his colleagues at Third Rock, like other investors in the space, have been, and will continue, poring over pharmacoeconomic data. Any-

one investing in drugs that could have breakthrough potential in diseases where therapies are nonexistent or clearly inadequate has to be prepared to make a good case to insurers. Reilly avers that he does not anticipate much argument, and not only because “the costs of rare disease errors are little more than rounding errors on our total national health care expenditures.” He figures health care plans will use their reimbursement of rare disease treatment for bragging rights: “I can see the billboard advertising now: ‘We helped little Jimmy beat a rare disease.’”

Still, in an economic climate where all comers feel entitled to challenge the “fairness” of incentives and subsidies, and clawbacks are commonplace, even if regulators approve rare drugs for sale, insurers may start keeping closer watch on drugs that begin life as orphans. Treatments priced at a premium may not spark much argument if they are only serving niche markets. But companies planning to escort orphans out into expanded indications as Novartis did with Gleevec may find it hard to grow a blockbuster this way.

Developers of drugs for rare diseases are clearly tackling unique challenges, and getting some special incentives for doing so, but the bottom line remains the same: drugs have to be safe and effective and the higher the price, the better the data have to demonstrate clinical utility.

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– DEBORAH ERICKSON

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Edimer Pharmaceuticals Inc.

Aiming to treat, perhaps even genetically correct, a rare disorder

Edimer Pharmaceuticals Inc. aims to do something that has never been accomplished before: permanently correct a genetic disorder with a pharmaceutical. The start-up based in Cambridge, MA is tapping the talents of local as well as international experts in rare disease research to treat X-linked hypohidrotic ectodermal dysplasia. This disorder, which impacts the development of teeth, hair and skin, is caused by mutations in the gene encoding the protein ectodysplasin-A1 (EDA-A1). It is estimated to affect about one in 17,000 people worldwide. Phase I clinical trials that give patients lacking the normal protein a modified form of EDA-A1 are expected to begin in the fourth quarter of 2011. The protein's function suggests that modulating the EDA/EDAR pathway could lead not only to a treatment for XLHED but also to products for much bigger markets, including hair loss, regenerating salivary glands and wound healing. For now, Edimer is downplaying the commercial potential of such indications and focusing on XLHED.

People born without functional ectodysplasin-A1 suffer a spectrum of disorders that can manifest at variable times. One of the most serious disabilities is the inability to sweat, one of the body's means of regulating its internal temperature. XLHED infants face the risk of being swaddled to death, while children with the disorder have to refrain from playing sports, particularly in hotter climates, to avoid hyperthermia, which can cause seizures and death. Patients also suffer physical deformities, the most grievous of which is abnormal tooth formation: just a few, usually pointy. The lack of teeth makes their faces change shape, and people with XLHED often require reconstructive surgery of the

jaw just to build up enough bone mass there to receive implants.

Neil Kirby, Edimer's president and CEO says "there are no hard numbers" for how many people are presently living with XLHED. But he estimates approximately 500 to 1,000 new patients are diagnosed annually with the disorder between the US and EU. The disease has orphan status in both territories; in the EU it has been designated a "severe and life-threatening disorder."

Dealing with uncertainty about the potential size of the patient population is par for the course for companies intent on treating rare diseases. Kirby can speak with authority on the subject, having participated in development of such therapies at both Genetics Institute and **Shire PLC's Shire Human Genetic Technologies Inc.**, formerly Transkaryotic Therapies. He says it was only after **TKT** and **Genzyme Corp.** (now part of **Sanofi**) started pursuing drugs for Anderson-Fabry disease, one of the 40 or so lysosomal storage disorders that previously had no treatment, that patients and clinicians started finding their way to the companies. "At that point the estimated numbers shot up," Kirby notes. Both companies had treatments for that disorder approved in the EU in August 2001: **TKT's** (now **Shire's**) *Replagal* (α -galactosidase), and **Genzyme's** *Fabrazyme* (β -galactosidase). *Fabrazyme* then beat its competitor to the market in the US, winning approval in April 2003.

Edimer, formed in July 2009, is betting it can help XLHED patients with a rationally designed version of EDA-A1 now dubbed EDI200. The start-up acquired the compound from a small Swiss company called Edimer Biotech, created to hold the research assets of Professors Jürg Tschopp,

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Business: Treatment for XLHED

Founded: July 2009

Founder: Neil Kirby

Employees: 5

Financing to Date: \$22 million

Investors: Third Rock Ventures; VI Partners

Board of Directors: Diego Braguglia, PhD (VI Partners); Neil Kirby; Philip Reilly, MD, PhD (Third Rock Ventures); Cary Pfeffer, MD (Third Rock Ventures)

Scientific Advisors: Margret Casal, PhD (University of Pennsylvania); Joy Cavagnaro, PhD; Rebecca Dabora, PhD; Olivier Gaide, MD (University of Geneva School of Medicine); Paul Goldenheim, MD; Emil Kakkis, MD, PhD (Kakkis EveryLife Foundation and Ultragenyx Pharmaceutical); Marja Mikola, PhD (Academy of Finland, Institute of Biotechnology at the University of Helsinki); Pascal Schneider, PhD (University of Lausanne); Irma Thesleff, PhD (Academy of Finland, Institute of Biotechnology at the University of Helsinki)

PhD, Pascal Schneider, PhD, and Olivier Gaide, PhD, all biochemists at the **University of Lausanne**. This compound was also owned for a time by the Swiss biotech **Apoxis SA**, which was acquired in 2007 by Danish drug developer **TopoTarget AS**.

Tschopp, Schneider and Gaide experimented to see which of three basic components of the normal EDA-A1 protein had the most effect on its function. Their data indicated that the collagen domain of the naturally occurring protein was particularly important, and was informed in part by assay data where the domain was found to be required for proper signaling. The scientists also noted that many XLHED patients have point mutations or in-frame deletions in the collagen domain, and this too made them think that it must be important to enzyme functioning.

Despite the domain's importance, the Swiss researchers realized this complex structure would likely be difficult to pro-

duce from a manufacturing point of view. So they figured out how to replace it, and still maintain the enzyme's function, by swapping it for the so-called Fc component of human immunoglobulin, which acts as a more generalized modulator of immune activity by binding to certain structures.

The scientists bet that the substitution would help this modified form of EDA-A1 bind to the native receptor and do what it is supposed to do: trigger formation of skin appendages such as hair and teeth. It appears they were right.

Kirby says this sophisticated bit of biochemistry will not only allow the modified EDA-A1 protein to stand in for the mutated version caused by flawed genes, but also allow it to be produced in quantity and, importantly, also cross the placental barrier. Theoretically, the modified protein given to a human mother would be able to reach a fetus at the precise time it is needed to bind the receptor and enable normal development. The trick worked in the mouse version of XLHED, the company says.

Edimer anticipates beginning a Phase I trial to test the safety of EDI200 in adult XLHED patients in the fourth quarter of 2011. "We're unlikely to show true efficacy, but we might get lucky and see a signal of biological activity," Kirby declares. The start-up's next goal is to test the protein in affected newborns, within the first two weeks of life, potentially as soon as the first quarter of 2012. No one has ever been able to correct a developmental disorder after birth. But if the company's neonatal trial yields positive results, Edimer will then seek to test its treatment in pregnant women known to be carrying affected children.

"This is not gene therapy, but it has similarities, in that we'd be making a change that potentially lasts for life," Kirby declares. Unlike most gene therapies, which are meant to continuously replace a needed substance, he believes EDI200 only needs to be at the right place, at the right time, just one time. "It's a first-in-class, signaling protein replacement molecule," he states, emphasizing that the therapy's value depends on the *time* at which the EDA-A1 protein flawed by inheritance of a bad gene is replaced.

Kirby says the company is encouraged by studies in animals lacking the gene for

EDA-A1, whose physical appearance is similar to humans diagnosed with XLHED. Administering EDI200 to pregnant mice corrects the disorder in the babies, he says, and "dogs that are corrected postnatally stay corrected for the rest of their lives." XLHED patients and their families get excited when they see the dog data, Kirby says, "but it's a long road to showing efficacy in humans, so we are very careful not to over-promise."

Kirby says he did the due diligence on EDI200 himself, after joining the Boston-based venture capital firm Third Rock Ventures as an entrepreneur-in-residence, and scouting for rare disease opportunities with venture partner Philip Reilly, also an expert in the area. Third Rock was the lead investor in a \$22 million Series A round raised coincident with Edimer's founding. The investment firm VI Partners, from Zug, Switzerland, also participated in the round. Kirby insists the financing was based only on the potential of EDI200 for XLHED, not any of the other potential indications: "Yes, the science is interesting and yes, we are looking at other ways to stimulate the protein's receptors, but the investors came in because they see, as we do, real unmet medical need among XLHED patients."

As intriguing as the science behind EDI200 may be, Kirby acknowledges that Edimer faces significant commercial challenges. The company and its scientific advisors have a pretty good handle not just on dosing, but also the proper timing for delivery of the therapy, he says: "We know when appendages form and therefore what the window of opportunity for therapy is." But how to identify and treat newborn patients? And what kind of price is suitable for a short course of therapy that is life-changing? Kirby notes that a commercial diagnostic test exists; it's offered by GeneDx but seldom ordered. And there is no easy link from the medical professionals who now see people with XLHED, mostly pediatric dermatologists and dentists, to the neonatologists who would use a drug in newborns or during pregnancy.

Like other executives and investors focused on treating rare diseases, Kirby says he also intends to press regulators to accept surrogate markers of clinical efficacy and data from smaller data sets than the agency usually requires. "There simply are

not many rare disease patients available to test potential therapies," he asserts, adding that the numbers alone, let alone clinical complexities, make it difficult for rare disease companies to achieve the full statistical rigor that FDA demands. Kirby says the conundrum has turned him into "a big advocate of Fast Tracking, using surrogate markers of approval."

Edimer presented data suggesting that noninvasive testing of sweat-gland function could serve as a disease biomarker for XLHED and potential treatments in November 2010, at the annual meeting of the American Society of Human Genetics. There could be an important precedent: people suspected of having cystic fibrosis are typically tested via a sweat test first. Then, if the results come back positive, a more expensive blood test to see if the patient has CF mutations is carried out. However, using a marker for diagnosis is a different matter than using one as a clinical endpoint; no one has established how much the measure would need to change to indicate that an experimental therapy was actually helping a patient or not.

Kirby says Edimer is aware of no other organization seeking to treat this ultra-rare disorder, and so it is taking the lead in reaching out. "As with almost all of the rare diseases, working with the patient associations is very important. They are your customer as well as your strongest advocate," he declares. Because there was no XLHED patient registry anywhere in the world when Edimer started up, the company provided funding to the **National Foundation for Ectodermal Dysplasias** to initiate such a registry. That registry "just hit 1,000 patients," Kirby says, and the company has been taking other steps to broadcast its interest in helping XLHED patients. Edimer has established the XLHED Network to keep patients, families and clinicians informed of its progress, and also maintains a Facebook page. It recently donated to a fund to help defray costs associated with its annual family conference. "But nothing beats going out and meeting with patients," Kirby declares. "That's where we get to see and hear how much of a difference our therapy could make, and that's where patients and families get to know we care and are trying to help."

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