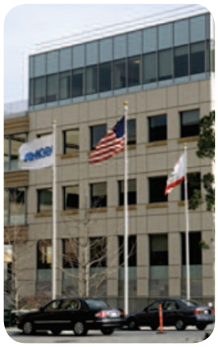
IN brief

Amgen to shut key plant

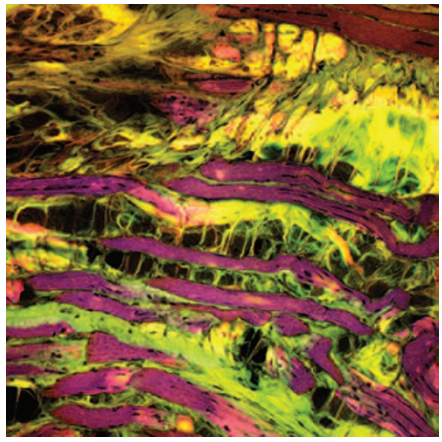


AP Photo/Reed Saxon

Thousand Oaks, California–based Amgen is shuttering its Epogen (epoetin alfa) manufacturing facility in Longmont, Colorado, a sign that the 20-year anemia drug's dominance has ended. Declining US sales of the erythropoietin stimulating agent (ESA) and its pending patent expiration are likely factors in the decision. Epogen accrued roughly $40 billion in sales since the drug was approved for treating anemia in kidney patients on dialysis. But in 2011 sales of Epogen were $2 billion, down from $2.6 billion in 2009. Amgen also reported a 28% fall in demand during the first half of 2012. Sales may have never recovered from the safety issues that emerged in 2010 when high doses of Epogen and its sister product Aranesp (darbepoetin alfa) were linked to serious adverse effects, including death, prompting labeling changes. But analysts say falling sales are mostly due to bundling rules introduced by Medicare in 2011, whereby a single payment covers all dialysis services including drugs and diagnostics. "Since Epogen is one of the more expensive drug treatments for dialysis patients, it is a logical place for utilization cuts, particularly since it was widely believed that dosages had increased in recent years partly due to more favorable reimbursement rather than pure medical necessity," says Morningstar analyst Karen Andersen, based in Chicago. Amgen faces competition from Affymax's newly approved Omontys (peginesatide), a once-a-month PEGylated synthetic dimeric form of erythropoietin (*Nat. Biotechnol.* **30**, 377–379, 2012). And Epogen's imminent patent expiry in 2013 could see biologically similar drugs such as Novartis' Binocrit (epoetin alfa) and Roche's Mircera, a PEGylated epoetin beta, gaining ground. Amgen has taken steps ahead of its rivals by signing contracts earlier this year with dialysis providers DaVita, of Denver, and Fresenius Medical Care, of Waltham, Massachusetts, that together account for two-thirds of US dialysis patients. The Longmont plant's doors will still close in 12–15 months, but until then Amgen intends to ramp up production at the 485-employee facility. "This way, Amgen is simultaneously prepared for best- and worst-case scenarios and able to quickly shutter the facility entirely or ramp up production, depending on the strength of these emerging threats," Andersen says. "Epogen will certainly be one of the first test cases for the traction of biosimilars in the US market." *Karen Carey*

Big players jostle for pole position in muscular dystrophy

At the end of June, Biogen Idec of Cambridge, Massachusetts, obtained rights to a preclinical program targeting myotonic dystrophy type 1 (DM1) from Isis Pharmaceuticals of Carlsbad, California, in a deal worth $271 million. In July, South Plainfield, New Jersey startup PTC Therapeutics raised $30 million in financing to develop a small molecule for treating Duchenne's and Becker's muscular dystrophies. The recent deals and some positive clinical data are sparking interest among investors, big pharma and large biotechs. Companies, such as Shire of Dublin and GlaxoSmithKline (GSK) of London, have also inked deals on compounds for several disorders related to muscular dystrophies, for which there are no meaningful treatments.



Patrick Landmann/Science Photo Library

This muscle tissue shows adipose metaplasia, where muscle (purple) is being replaced by fat (black)—a characteristic symptom of muscular dystrophy.

More than two decades of research into these rare neuromuscular disorders is shaping up to deliver returns. The technologies range from small molecules and stem cells to antisense and gene therapy (**Table 1**). All are underpinned by a growing understanding of the specific molecular pathology underlying each disease. This knowledge "gives you a handle," believes Frank Bennett, senior vice president of research at Isis. "Our technology can modulate splicing, so with this information we are in a unique position in developing targeted therapies."

Since the discovery in 1987 that mutations in the dystrophin gene cause Duchenne's muscular dystrophy (DMD), more than 100 genes have been identified that are involved in muscle-wasting and neuromuscular conditions. DM1, for instance, is an inherited trinucleotide repeating disorder, whereby three nucleotides on the dystrophia myotonica protein kinase gene prompt the production of overlong RNA. The defect leads to RNA buildup and prevents the formation of normal skeletal muscle cells.

Although it is the most common muscular dystrophy in adults, DM1 represents a small market, affecting 40,000 people in the United States. If that appears to limit the commercial potential, it is at least the case that the Isis therapy could be used for all patients. That is not so with DMD, where the leading products in development are tailored to treat small subsets of the 1 in 3,500 boys afflicted with this condition.

Strictly speaking, DMD is caused by a single-gene defect. But as the largest gene in the human genome, dystrophin is prey to a range of different mutations that can occur along its length. Many of these are frameshift mutations located between exons 45 and 53. The most advanced product in development, PRO-051 (also known as GSK2402968), which is currently in a phase 3 trial, uses a 2′-O-methyl antisense RNA oligonucleotide to skip over a single one of these mutations, at exon 51, restoring the reading frame. If approved, that would provide a therapy for the 13% of DMD patients with this particular defect.

PRO-051, discovered by Prosensa Therapeutics of Leiden, The Netherlands, was licensed to GlaxoSmithKline of London, in a $670 million deal agreed on November 2009. This was extended in September 2011, with GSK taking up options on products skipping exons 44, 45 and 53. Between them, these three address a further 24% of the DMD population.

Luc Dochez, chief business officer and senior vice president of business development at Prosensa, says the issue of whether it will be necessary to replicate each stage of development for each exon has been broached with the European Medicines Agency. Regulators are of course data driven, and Dochez believes any concessions would depend on the outcome of the current PRO-015 phase 3 trial. "There could be potential to shorten the development pathway," he says.

Another company working on exon skipping, Sarepta Therapeutics, of Cambridge, Massachusetts (formerly AVI BioPharma), hopes to persuade the US Food and Drug Administration (FDA) that it should not be necessary to take each product through full clinical development if its lead product