ALS in the absence of riluzole [without Rilutek]," says Donald S. Wood, director of science technology for the Muscular Dystrophy Association (Tucson, AZ).

Sanofi Recherche (Paris), for instance, has reported positive phase II results with its orally available small molecule drug, SR57746A, a growth factor-like compound. It is now running a phase trial in Europe (and soon also in the US) where the control study uses Rilutek alone, while the test arm uses SR57746A with Rilutek.

There are several other ALS studies under way, too. Amgen is conducting a phase I trial with glial cell derived neurotrophic factor (GDNF) delivered via catheter directly into the brain. Cephalon's (West Chester, PA) insulin-like growth factor (IGF-1) drug Myotrophin is available to ALS patients in the US under a treatment-IND protocol, and the company will soon apply for drug approval in both the US and in Europe. A phase III trial of Myotrophin is running in Japan through Cephalon's marketing partner, Kyowa Hakko Kogyo (Tokyo). Cephalon and RPR are discussing a possible combination trial with IGF-1 and Rilutek.

CytoTherapeutics (Providence, RI) is delivering nerve growth factors to the central nervous system of ALS patients through ex vivo gene therapy (*Nature Medicine* 2:696–699, 1996). In a phase I study, encapsulated cells, genetically modified to produce CNTF implanted within the lumbar intrathecal space, produced measurable levels of the neurotrophic factor in the cerebrospinal fluid for at least 17 weeks. CytoTherapeutics is also applying the same approach to deliver Genentech's (S. San Francisco, CA) growth factors, neurotrophin-4/5 and cardiotropin-1 to ALS patients.

But despite all this activity in ALS treatment, the disease causes and thus the appropriateness of any treatments are still uncertain. "ALS continues to baffle," says the Muscular Dystrophy Association's Wood. Environmental triggers, genetic causes, or combinations of the two may be responsible.

One pessimistic view suggests that ALS symptoms may emerge too late for nerve growth factors to be effective. Wood says that motor neurons aren't simply dysfunctional in ALS, they are destroyed. He suggests that "the nerve growth factors may come too late in the course of the disease." Rothstein agrees: "Trophic factors affect only 'sick' motor neurons and not those that are moribund." These conclusions reflect data from experiments in superoxide dismutase (SOD) knockout mice: These animals develop ALS-like symptoms at about 4.5 months of age and are dead at 5 months.

Rilutek is effective in the SOD mouse model and in ALS patients carrying mutations in the SOD gene—10% or less of the total ALS population. However, says Wood, "the biotechnology companies developing neurotrophic drugs for ALS have not, in general, publicized the results of studies in SOD mice, leading one to conclude that the drugs have not been effective in this model."

Failure of a nerve growth factor to have an effect in ALS should not condemn the drug (or the company), says Rothstein. "These are potent drugs," he adds, that could prove effective in other neurodegenerative diseases, and they should remain in the clinical pipeline. Smith Barney's Reijer Lenstra agrees: "We believe that nerve growth factors could become as successful in the marketplace as blood growth factors [such as Epogen and Neupogen] have already become." BDNF, CNTF, GDNF, and IGF-1, all being tested in ALS, are also in development to treat diseases that have much larger potential markets, such as peripheral neuropathies (including diabetic neuropathy), Parkinson's disease, Huntington's disease, and perhaps Alzheimer's disease.

Vicki Glaser

Monsanto swallows Calgene whole

Monsanto's (St. Louis, MO) offer to acquire the remaining 46.4% of Calgene (Davis, CA) that it did not yet own for $218 million ($7.25 per share) in early February would, if accepted by the shareholders, mark the completion of an acquisition that began in June 1995. Calgene's somewhat checkered year—composed as it was of significant successes offset by some pressing losses—may have made the directors more amenable to the unsolicited proposal to acquire the remaining stock.

Late last year, Calgene was awarded a number of significant US patents covering carotenoid production, control of triglyceride production in plant oils, and plastid transformation. In November 1996, it forged an important agreement with Kirin (Tokyo) in which it cross-licensed its Flavr Savr gene for Kirin's carotenoid biosynthesis genes to improve the nutritional properties of human and animal foods. In December, it also agreed with Canada's Saskatchewan Wheat Pool (SWP) to produce its bioengineered canola oil in Canada using SWP's germplasm (Canada is the world's largest producer of canola). This last agreement had as its foundation Calgene's oilseed cross-licensing agreement with Monsanto.

Monsanto's acquisition of Calgene accounts for one piece in a strategic plan that has not been articulated to the public.

However, during that same period, Calgene also reported a substantial net loss—$17 million—compared with $10 million for the same period in 1995, due to the poor performance of its tomato and strawberry crops, one part of its tripartite business of oils, cottonseed, and produce. Although Calgene's response was to try to cut overheads, it was also in the process of expanding its R&D program in plant oils—a major reason for making its May 1996 strategic cross-licensing agreement with Monsanto.

Monsanto's acquisition of Calgene accounts for one piece in a strategic plan that has not been articulated to the public, but is part of a dizzying buying binge that began in February 1996 with a 10-year R&D collaboration primarily for corn and soybean seed, and cross-licensing agreement for corn products with DEKALB Genetics (Dekalb, IL). In April 1996, Monsanto acquired Agracetus' (Middleton, WI) plant biotechnology assets, mostly for cotton and other plants, for $150 million in cash (*Nature Biotechnology* 14:554, 1997). In early February 1997, it bought the soybean company Asgrow Agronomics (Kalamazoo, MI) for $240 million. And a few days later, it acquired Holden's Foundation Seeds (Williamsburg, IA), and its corn germplasm technology for $1.02 billion.

Clearly, Calgene's stock was tempting for Monsanto after its crops' failure. Although Monsanto has not made any specific statement about the proposed acquisition, saying only that it "needed a closer relationship and greater sharing of technologies only possible with total ownership." No doubt the acquisition is part of its new program announced in December, to "create a new life sciences company that will combine its existing agricultural, food, and pharmaceutical businesses and seek to develop new businesses that capture synergies among these fields." To that end, Monsanto spun off its chemical businesses and created two new separately traded companies—one in life sciences encompassing agriculture, food, and health care, and one for chemicals.

Vicki Brower