BUSINESS AND REGULATORY NEWS

Prostate-cancer link sours IGF-1

New results from a long-term prospective study (*Science* 279:563–566, 1998) that correlate plasma levels of insulin-like growth hormone-1 (IGF-1) with a risk of prostate cancer may come as a further blow to companies such as Genentech (S. San Francisco) and Chiron/Cephalon (Emeryville, CA, and Malvern, PA), which are developing the protein as treatments for neurological conditions. The study may have implications, too, for the development of other cell-growth–promoting compounds.

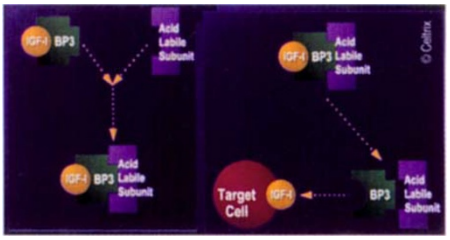
The research, from teams at Harvard University (Cambridge, MA) and McGill University (Montreal, Canada), shows that men with the highest natural levels of circulating IGF-1—but levels still within the normal range of 100–500 ng/ml—had more than four times the risk of prostate cancer compared with those in a reference group. The IGF-1 level was a much better early-stage indicator of the risk of getting prostate cancer than the presence of prostate specific antigen, the marker currently used. "The association of IGF-1 and prostate cancer risk is stronger than that of any previously reported risk factor, including steroid hormone levels," write the study's authors.

The study points to the danger of long-term exposure to high levels of IGF-1. Michael Pollak from McGill University, the study's principle researcher, now questions the long-term use of IGF-1 in a chronic disease such as diabetes where treatment apparently provides only marginal benefits. Genentech halted two well-advanced phase III diabetes trials of IGF-1 last autumn. On the other hand, Pollak considers that IGF-1 can still be useful for short-term use in life-threatening situations such as burns and postsurgical trauma.

Genentech's two trials were stopped not because of concern about prostate cancer but because the US Food and Drug Administration (FDA; Rockville, MD) had requested long-term safety data to prove the drug would not cause the ocular complication, diabetic retinopathy. "We felt the risk, cost, and extended time needed to do such long-term studies outweighed any potential value," said Genentech spokesperson Kathleen Rhinehart.

The future of Chiron/Cephalon's IGF-1, Myotrophin, as a treatment for amyotrophic lateral sclerosis (ALS) is also uncertain. Since the FDA did not recommend approval for Myotrophin in June 1997, the files on the drug have been languishing at the FDA. In November 1997, Chiron and Cephalon in effect withdrew their application for approval and resubmitted, thereby "resetting the clock" on the time the FDA had to approve the drug.

One analyst, Toni Claudio of UBS (New York), has repeatedly pointed out that more ALS patients have died on the drug than have improved (*Nature Biotechnology* 14:253, 1996). "IGF-1 is a dangerous drug with numerous serious side effects, and it has failed in many clinical trials," says Claudio. She points to side effects such as edema, dyspnea (difficult breathing), tachycardia (rapid heart beat), muscle and joint pain, and low blood pressure, which were sufficient to lead to the premature termination of an early study of IGF-1 in Type II diabetes. "These are not good side effects for ALS patients, either," says Claudio.



SomatoKine complex (IGFBP-3+IGF-1) can be used in much higher doses than IGF-1 alone.

A 1993 study of IGF-1 in osteoporosis in postmenopausal women (*J. Clin. Endocrinol. Metab.* 77:1384–1387) is no more encouraging. On the positive side, IGF-1 stimulated osteoblasts, promoting the formation of bone in a dose-dependent fashion. However, at the two highest doses (120 and 180 μg/kg/day), it caused side effects similar to those seen in diabetes trials. This study also concluded that at higher doses, the severe side effects of IGF-1 meant that it should not be used for long-term treatment.

Currently, the only side-effect–free experimental use of IGF-1 seems to be with a product made by Celtrix (Santa Clara, CA). Significantly, its drug, SomatoKine, is a recombinant version of the natural complex formed by IGF-1 and the protein that naturally binds it in the body, BP-3. Normal circulating levels of IGF-1 complexed with BP-3 are approximately 200 ng/ml in younger adults and about 100 ng/ml in the elderly. Uncomplexed IGF-1 is not found in appreciable amounts in the blood. Paradoxically, the addition of exogenous IGF-1 inhibits the production of new IGF-1.

Celtrix' SomatoKine IGFBP-3 complex can be used in much higher doses than IGF-1 alone to build bone and connective tissue—apparently without side effects. The company is testing SomatoKine in a number of short-term, acute care indications: a phase II trial for recovery from surgery for hip fracture (used for 8 weeks), and a phase II study in severe burns (intended to be used for an average of 4 weeks). Celtrix's partner is also considering testing SomatoKine for a short-term period in women with severe osteoporosis.

David Rosen, vice president of research and development at Celtrix, and Michael Pollak both note that whereas IGF-1 on its own stimulates the proliferation of both normal and cancerous cells, BP-3 and the IGFBP-3 complex both have antiproliferative effects on certain cells. In an editorial last year (*Endocrinology* 138[7], 1987) Matthew Rechler of the NIH (Bethesda, MD) points out that transforming growth factor-beta, retinoic acid, the tumor suppressor p53, and antiestrogens—all cancer-reducing agents—induce IGFBP-3. The IGF-1–prostate cancer link may soon be joined by other studies showing that high blood levels of IGF-1 are a risk factor for other cancers, including breast and colon cancer, said Pollak.

Indeed, according to Pollak, Novartis (Basel) is testing the IGF-1–cancer connection hypothesis by giving somatostatin—a known inhibitor of IGF-1—to cancer patients. Pollak has been involved in the Canadian trials. Early results indicate that somatostatin prevents recurrences of estrogen-dependent breast cancer. When used with tamoxifen, another antiestrogen, the effects are magnified. "We believe that drugs that block IGF-1 and growth hormone alone, like somatostatin, may be effective in cancer prevention and treatment," said Pollak.

Genentech has devoted a great deal of money and time to developing IGF-1—as well as growth hormone, which stimulates IGF-1—and has not abandoned it. According to Rhinehart, it is currently evaluating IGF-1 in preclinical studies for a variety of other applications in metabolic and neurological indications.

One of Genentech's indications, reportedly, is multiple sclerosis. A recent study (*NEJM*, 338:278–285, Jan. 29) implicated neuronal damage in the development of multiple sclerosis. Given this study, companies seeking to treat MS and other neurodegenerative diseases may now be more likely to try IGF-1 to treat such conditions. As *Nature Biotechnology* was going to press, Neurocrine Biosciences (San Diego, CA) announced a preclinical study (*PNAS* 95:1894–1898, Feb. 17), using IGF-1 as a neuroprotective for stroke as well as MS, Parkinson's and head trauma.

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