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GENETICS

Superbaby Serum

A brawny infant's mutation has set off a hunt for a muscular dystrophy drug.

By Matthew Herper



THE CHILD WAS THE TALK OF THE NEONATAL WARD at Charité Hospital in Berlin, Germany. His biceps and thighs were twice as thick as a normal newborn's despite typical height and weight. He looked like he'd been lifting weights in the womb.

This was in 2000. The child's doctor called in pediatric neurologist and geneticist Markus Schuelke. He thought the boy might have had a muscular disease but then remembered that Se-Jin Lee, a Johns Hopkins University geneticist, had produced overly buff mice by knocking out the gene for a protein called myostatin, which is supposed to slow muscle growth. Schuelke thought here was the first evidence of a myostatin mutation in a human.

Four years later the world heard about the boy for the first time, when a group of researchers including Schuelke and Lee proved the boy had a myostatin mutation. By then the child could hold a 7-pound dumbbell in each of his outstretched hands. One writer to the *New England Journal of Medicine* speculated that the mythical Hercules was a myostatin mutant, too.

The news about this rare mutation precipitated an intensive effort to design drugs—call them myostatin blockers—that

would let muscles flourish without onerous side effects. The work holds the most promise for patients with Duchenne muscular dystrophy, a debilitating and deadly disease diagnosed in 600 American children, almost all boys, every year. Corticosteroids and heart-failure drugs have allowed some patients to survive into their 40s, but they are still strapped to ventilators and require round-the-clock care.

"This is like a bright light in a fairly dark tunnel," says Patricia Furlong, founder of Parent Project Muscular Dystrophy. She lost two teenage sons to Duchenne. The research also offers hope for patients with Lou Gehrig's disease and age-related weakening.

Myostatin was discovered in mice in 1992 in Lee's Johns Hopkins lab. In 1996 he proved its importance by showing that mice without the myostatin-producing gene got twice as big. The next year he discovered that the bulging Belgian Blue cow was a myostatin mutant, the first of eight prized cattle breeds later found to have the mutation. The company he had cofounded, MetaMorphix, is working on manipulating myostatin to beef up livestock. Wyeth picked up the rights to develop a drug for humans. Its experimental antibody drug produced bulked-up mice in 2002, and results of a trial in adults with muscular dystrophy are expected as early as March.

Already there are concerns that the drugs might be used by athletes as a kind of supersteroid, and dietary-supplement companies have introduced knockoffs made from sea algae for that purpose. "They don't work," says Schuelke.

Schuelke and Lee still see room for failure. Side effects could crop up, and Lee's work shows that real muscle growth may require a broader attack than the Wyeth drug's targeted approach, because there are a host of mysterious myostatin-like proteins that also dampen muscle growth. Lee doesn't know how many. Acceleron Pharma is set to begin human trials on a drug that mimics a cell receptor that could disable many of the myostatin-like proteins. The Cambridge, Mass. firm has raised \$56 million from venture funds, including Polaris Venture Partners and OrbiMed Advisors.

Schuelke continues to see the muscular boy he found in Berlin seven years ago. Though there were fears that his heart might get too thick, the boy is completely healthy. He's strong but no longer abnormally so. It may be that myostatin's effects are most dramatic during fetal development, but that's one of many guesses in this genetic mystery.

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