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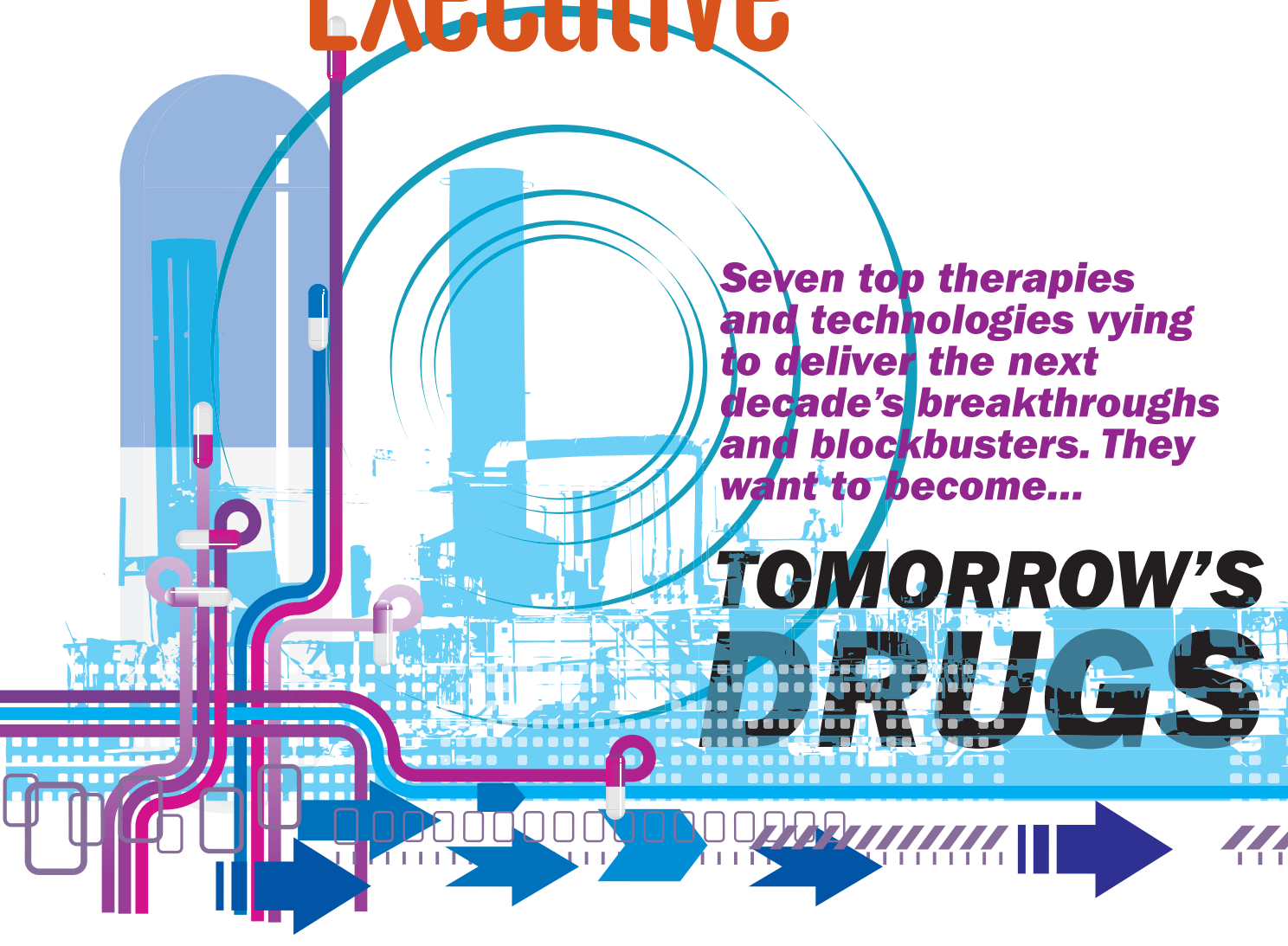

Seven top therapies and technologies vying to deliver the next decade's breakthroughs and blockbusters. They want to become...

TOMORROW'S DRUGS

Have you heard the rumors that all the drugs have already been discovered? Well, forget it. Maybe some of the low-hanging fruit is gone—but in the last few years, science has opened up thousands of new targets, while new technologies have made it possible to treat disease in unprecedented ways.

In the next few pages, the *Pharm Exec* staff profiles some of the hottest therapies and smartest technologies that have caught our eye—from RNAi therapies to genetic editing to therapies that stop disease before it starts. Taken together, they form a vision for the next generation of drugs, one that will transform the industry (and the face of healthcare) in the decades to come.

THE REAPPEARING ACT

Inhibition of BMP and GDF proteins offers a twist on the science—and a way to reverse disease

"Accentuate the positive," went the old song. "Eliminate the negative." Who knew it was describing two alternative strategies for encouraging the growth of bone and tissue?

Two key families of proteins are involved in creating the structure of the body during embryonic development and the regulation of growth: the growth and differentiation factor (GDF) and the bone morphogenic proteins (BMP). So far, there are at least 15 known types of both GDF and BMP, each with the ability to stimulate cell growth in a particular way and at a particular time.

These proteins are endlessly active and control cell growth and death. Take the case of bone: Sometimes, the molecules in BMP send a signal to the osteoblast cells, which carry out the growing of bone. Other times, BMP sends a signal to the osteoclasts, which are responsible for breaking down bone.

"The less developed area is recognizing there are also molecules that say, 'Stop, you've built enough bone.'" –Steven Ertel of Acceleron Pharma

Many companies have tried to tap into the lucrative markets of osteoporosis and cancer-related bone loss by manipulating GDF and BMP. (Currently, most treatments only slow down bone loss, rather than rebuild bone.) For example, Medtronic has a product called Infuse, which is genetically engineered BMP: when administered locally, it signals osteoblasts to get to work. It's a very effective option for a narrow slice of patients, such as those undergoing spinal-fusion surgeries.

However, successive attempts to develop drugs to treat blockbuster conditions like osteoporosis and cancer-related bone loss have failed, because companies have not been able to figure out how to develop a therapeutic that could be administered systemically. (Most recently, Ortho Biotech terminated a BMP-7 program licensed from Curis for tissue repair in renal disease.)

Part of the problem is that most companies have overlooked attempts to "eliminate the negative." "Rather than triggering osteoblasts to grow bone, the less developed area of biology is recognizing that there are also molecules that send signals to osteoblasts to say 'Stop, you've built enough bone,'" said Steven Ertel, vice president of business development at Acceleron Pharma.

Acceleron is pioneering BMP and GDF inhibition, and working on the "off" switch for osteoblasts. "Think of the two ways to move a car," said Ertel. "You can hit the gas pedal, or you can take your foot off the brake. Instead of giving a positive growth factor, you inhibit the negative growth factor."

The company's lead candidate, ACE-011, is in Phase I for postmenopausal osteoporosis, according to Wolters Kluwer. So far, the results are positive.

"The early data based on mouse models of ACE-011 are interesting—and actually quite intriguing," says Louise Perkins, research director of the Multiple Myeloma Research Foundation. "There appears to be a huge amount of bone growth. If this agent works in [humans], it could bring a change in the quality of life in multiple myeloma patients."

Acceleron is developing several other therapies based on this underlying science, including ACE-031 for muscle growth. This therapy will seek to grow muscle in patients by turning off myostatin, or GDF-8, and holds promise to treat ALS (amyotrophic lateral sclerosis) and muscular dystrophy. In this category, it will face stiff competition, with Wyeth and Amgen investing their own research muscle in these promising processes.

–JOANNA BREITSTEIN