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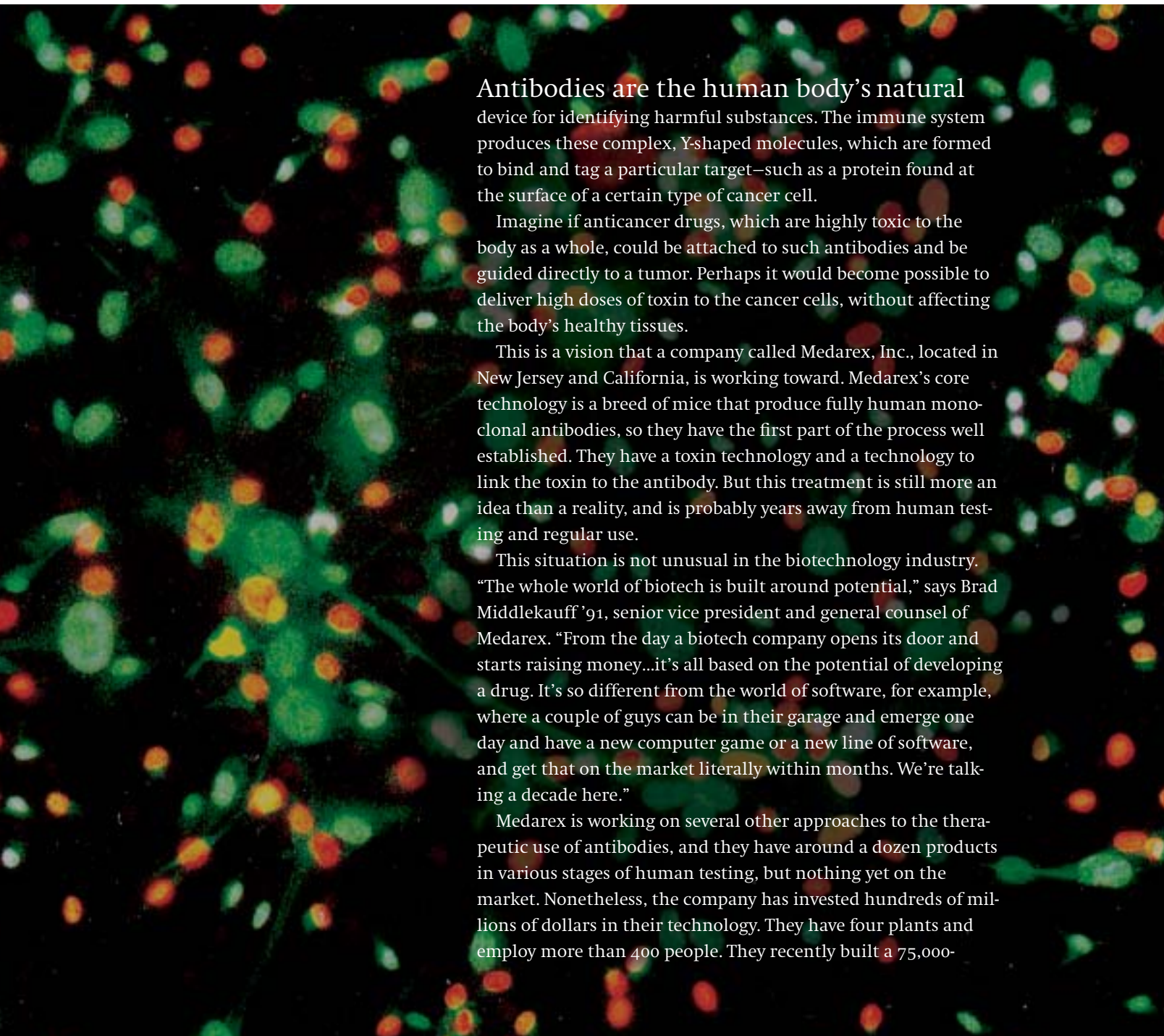
YALE LAW SCHOOL ALUMNI WORKING IN THE BIOTECHNOLOGY INDUSTRY BALANCE LAW, TECHNOLOGY, BUSINESS, AND ETHICS CONCERNS, WHILE HOPING TO USHER LIFE-SAVING TREATMENTS TO THE MARKETPLACE.

LAWYERING THE FRONTIER OF SCIENCE



Antibodies are the human body's natural device for identifying harmful substances. The immune system produces these complex, Y-shaped molecules, which are formed to bind and tag a particular target—such as a protein found at the surface of a certain type of cancer cell.

Imagine if anticancer drugs, which are highly toxic to the body as a whole, could be attached to such antibodies and be guided directly to a tumor. Perhaps it would become possible to deliver high doses of toxin to the cancer cells, without affecting the body's healthy tissues.

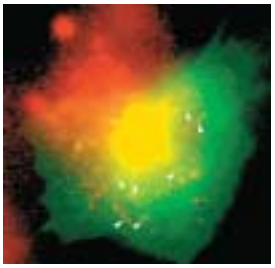
This is a vision that a company called Medarex, Inc., located in New Jersey and California, is working toward. Medarex's core technology is a breed of mice that produce fully human monoclonal antibodies, so they have the first part of the process well established. They have a toxin technology and a technology to link the toxin to the antibody. But this treatment is still more an idea than a reality, and is probably years away from human testing and regular use.

This situation is not unusual in the biotechnology industry. "The whole world of biotech is built around potential," says Brad Middlekauff '91, senior vice president and general counsel of Medarex. "From the day a biotech company opens its door and starts raising money...it's all based on the potential of developing a drug. It's so different from the world of software, for example, where a couple of guys can be in their garage and emerge one day and have a new computer game or a new line of software, and get that on the market literally within months. We're talking a decade here."

Medarex is working on several other approaches to the therapeutic use of antibodies, and they have around a dozen products in various stages of human testing, but nothing yet on the market. Nonetheless, the company has invested hundreds of millions of dollars in their technology. They have four plants and employ more than 400 people. They recently built a 75,000-

square-foot facility on 106 acres in Bloomsbury, New Jersey, with dozens of labs, as well as administrative offices—and the potential to expand further in the future.

But Middlekauff says that this investment remains something of a "crap shoot," since they haven't yet gotten a drug through the FDA approval process. "When you put a drug into the clinic [for human testing], nobody knows if it's going to work. It's just one of these things where the best science testing this drug in mice, monkeys, or whatever, is not going to correlate with whether it's going to work in humans or not. So you've got to put them in the clinic and roll the dice."



A dendritic cell, part of the immune system. Photograph by Amy Chow and Derek Toomre, courtesy of *Yale Medicine*. (Opposite) Rat stem cells, nuclei stained red. Photograph by Jeffery Kocsis, courtesy of *Yale Medicine*.

In today's system, a promising medical treatment doesn't have any chance of reaching patients without lawyers stationed along the way.

Henry T. Greely '77, the C. Wendell and Edith M. Carlsmith Professor of Law at Stanford Law School, studies the social and legal implications of new technologies, particularly biotechnology. He also teaches a regular course at Stanford, called Biotechnology Law and Policy, in which he walks students through the life cycle of a hypothetical biotech firm. He points out the many places where lawyers become involved: A scientist at a university comes up with a new idea. The university patents it, bringing in patent lawyers. They then license it to a start-up company, which requires careful licensing agreements. The company secures funding, bringing in lawyers from many sides. The firm allies with another company with a complementary technology, meaning more contracts and licenses. You can see how this is going, and the company hasn't even gotten a product into testing, with all the FDA regulations that involves, or to the market, where its manufacture and marketing will be subject to reams of regulation.

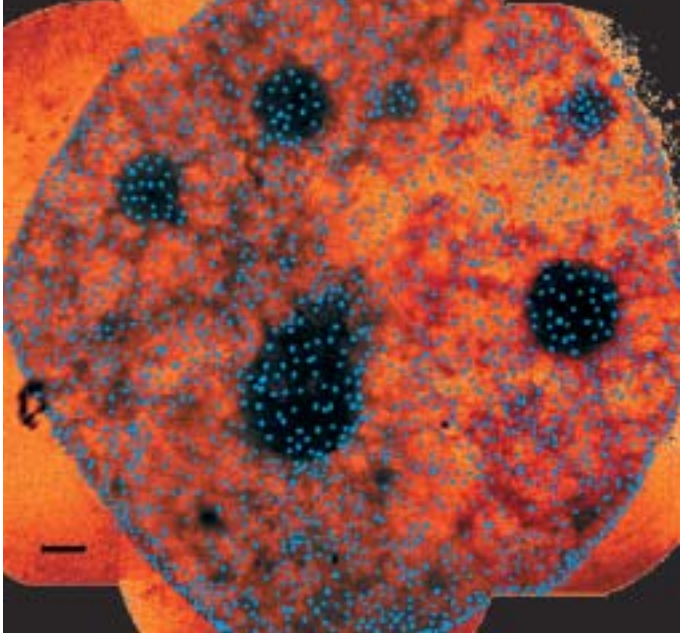
"Every step of the way there are legal questions, business questions, ethical questions, all intertwined," says Greely. He speculates that there is so much legal involvement in this industry for two reasons: First, patents are vital in biotech. "[Patents are] much more important than they are in software—software changes too fast; you can write around things....But with biotech, usually your big asset for a long time is a patent or even a patent application." Second, the final product, if it's realized, will enter the highly regulated healthcare market.

As general counsel at Medarex, Middlekauff deals with all facets of the business. Patents and intellectual property are a big part of his duties, although a chief patent counsel who reports to him carries a lot of the responsibility. Middlekauf also deals regularly with corporate governance and securities issues, partnerships and licensing, and employment law, as well as playing a strategic role as part of the company's senior management.

Middlekauff says he is required to make decisions that balance law, business, and science—but the science always has a primary place. For instance, even though Medarex is a for-profit company, looking to produce medicines that will have a large market, the decision to pursue a particular line of investigation is driven by the research possibilities. "If you work from the perspective of 'What are the large markets out there?' by the time you get there, the market might not be so large, because somebody's come out with a strong drug.... It's more often than not driven by the science and looking at promising targets from an antibody perspective. And then we begin to factor in things like the size of the market and the competitive landscape."

Medarex is developing some treatments on its own, but conducts a lot of its research through partnerships with other companies—either fifty-fifty arrangements in which Medarex provides its antibody technology and the other company provides intellectual property around a particular target, or an agreement in which Medarex licenses out its technology in exchange for royalties. In crafting these sorts of licensing agreements, Middlekauff says, he needs to understand the science in order to practice effective law. "In the context of a contract, always in the back of my mind is the fact that this contract could someday wind up in litigation and you want the description of the science for purposes of the contract, for describing what I'm licensing to you and what you're licensing to me, to be something that will be intelligible to either a judge or an arbitrator or a jury." At the same time, the contract has to be specific enough to protect the company's intellectual property. "You've got to have one foot on the science side of things and one foot on the layperson understanding of things."

The same rule applies in the company's SEC filings, which focus on the potential and risk surrounding Medarex's approach to science. Says Middlekauff, "Whereas with much of corporate America, there are certain basic ways that you can judge whether this is a good company or not—what are their earnings per share, are they increasing over time... that's not the metric by which people judge most biotech companies. So the issues related to disclosure are different."



Neal Roach ’87 is a vice president and head of global licensing at Roche Diagnostics, a division of the pharmaceutical giant F. Hoffmann-La Roche, Ltd, that develops and manufactures diagnostic products for medical laboratories, patient use, and research. “I’m in charge of all licensing in and out of intellectual property for the entire division,” says Roach. He points out that this is actually not a legal position—he reports to the head of business development—but like Middlekauff he works in a business-science-legal milieu.

Roach’s department supports the research and development side of the business by “mak[ing] sure that whatever products the company wants to develop, that we are free to use them. So we find who has intellectual property that we need access to and we negotiate access.” He can become involved in the development of a new product at any point from its conception until after it’s on the market. “Preferably, very early,” he says. “On occasion you get that letter, ‘You just launched this product and...’”

Roche also licenses out its technologies, particularly a process called polymerase chain reaction, which Roach calls “a standard tool in the molecular biologist’s toolbox.” PCR allows scientists to amplify small samples of DNA, making it easier to work with. In all areas, the company depends on intellectual property rules, and with its global activities, Roach is able to compare the patent systems in different countries and how they affect a company’s activities. “In the Far East there’s still not a lot of respect for patent rights. Therefore your incentive to innovate may be less, because you’re not able to protect [a patent]. With respect to the U.S. and Europe, with the way the patent structures have evolved, you could probably argue it either way, that it’s a check on innovation or it’s not. It’s just a structure that we’ve lived with for so long that it’s a part of the landscape.”

Roach does see one challenge arising in the near future, as diagnostic technologies bore toward the molecular level. “It’s becoming more and more difficult to say one invention is separate and distinct and stands alone. And even when you can do that, there are so many filings out there that it also becomes very difficult to sell a product.” Roach provides the example of a test for hepatitis C. There are several forms of the virus that causes the disease, as well as numerous mutations. Various entities own the patents on these different gene sequences. “The fundamental intellectual property is the chip technology, the testing technology, but then there may be several owners of what we call content, the genetic sequences you’re trying to test for. You could have to negotiate rights with a bunch of people just to get access to sell this one chip.... If you’ve got to pay one percent to a hundred and two different guys, there goes all your profit.”

Hank Greely sees this as a problem that will solve itself in time. “There have been a lot of fights within the patent industry, within the biotech and research community, about whether genes should be patentable,” says Greely. “The internal argument has revolved more around utility than anything else.” But he thinks the argument is somewhat misplaced. Take a patent on the gene for insulin in humans, for instance. “You patent it, twenty years from date of filing... the patent’s gone. ...Twenty years is a long time in my lifetime, but it’s not a very long time in the lifetime of the human genome.”

For the time being, though, the growing complexity of the patent terrain is a challenge for lawyers working in the biotech industry. Says Roach, “We’re responsible for insuring that...what we do with intellectual property is aligned with the company’s strategy.” But because of the number of people involved and the number of patents the company owns or has a stake in, “It’s sometimes unclear what we actually own and why we own it.”

The rapid advances of the science that biotech companies can actually perform has brought the industry a lot of attention. Patenting genes, cloning mammals, drug pricing, and genetic engineering have all become part of a broader debate that measures scientific progress against other cultural standards. Wiliam Stempel ’78 is the vice president, general counsel, and secretary of Geron Corporation, a biopharmaceutical company in Menlo Park, California. Like Medarex, Geron doesn’t yet have a treatment on the market, but is pursuing several lines of development. The company is working on cancer treatments that target telomerase, an enzyme that essentially allows cancer cells to reproduce indefinitely, rather than being subject to the normal limits on how many times each cell can reproduce itself. Geron is also developing a suite of treatments based on

A human mammary cell. Photograph courtesy of U.S. Department of Energy Genomes to Life Program.

human embryonic stem cell technology. The hope here is to turn stem cells—which are the precursors to all other types of cells—into replacement tissues, such as heart cells or nerve cells, which could then be transplanted into people to replace or bolster damaged tissues. Geron has successfully induced stem cells to take on several different forms, and is currently conducting animal tests. In animals with induced heart attacks, for instance, transplanted heart cells appear to engraft to the heart and improve cardiac function.

Work on embryonic stem cells has become controversial, however, because they are produced, as the name implies, from human embryos. In 2001, President Bush ordered that no federal money could be used to support embryonic stem cell research, unless the research used one of a limited number of already established cell lines. This regulation doesn't affect Geron, as a private company, but future laws could affect the course of their work. "We pay attention to that," says Stempel. "We try to follow and, in some cases, participate in the debate about how these things should be regulated. ...We try to focus on what's going on now; what's going on soon rather than the blue sky of regulations in some other country in ten years."

Furthermore, Stempel points out, "The stuff we're doing, even though it's extremely innovative and novel, isn't wholly different from other things that are being done." He says that stem cell therapies are a form of cellular therapy, for which the FDA has already established regulations. "A lot of the controversy that's swirling around this stuff is important as a public policy matter without being terribly important to us as a business."

Middlekauff says he watches the policy debate for any shifts that might affect the business. Biotech is particularly susceptible to changes in intellectual property rules, because as many as ninety percent of drugs that reach clinical testing don't make it to the market. "I can see this in decisions we make at Medarex all the time," he says. "If you lower the amount of recovery by shortening the patent term, or having price ceilings, or whatever, that's going to change the equation on the number of drugs that a company is willing to put into the clinic." The fewer drugs going into the clinic, the fewer effective treatments being developed.

But Middlekauff emphasizes that good companies will be agile enough to adjust to any small changes in the regulatory environment, "as long as a couple of core sets of rules are maintained." Although the patent landscape is constantly evolving, the basic strength of patent protection is one of these core rules. Another is "a level of certainty and cooperation from the Food and Drug Administration," says Middlekauff. "We can't control the science.... But what we do need is some certainty about, if I achieve this kind of result, then I can get the drug approved."

Hank Greely points out that the role of business interests in drug development also raises the fundamental question of how large a role market forces should play in decisions that ultimately affect people's health. But he also argues that

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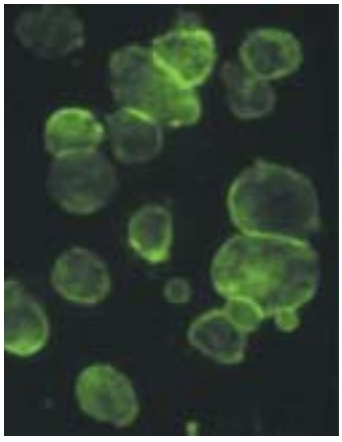
while individual biotech companies operate for-profit, the medical and scientific enterprise as a whole has a public component. The U.S. government, primarily through the NIH, spent around twenty-five billion dollars supporting basic biological research in 2002. "We recognize that drugs are to some extent public goods, in an economist's sense, and as a result we spend public money to try to encourage research that will lead to their development," says Greely.

Middlekauff sees a similar blending of public-mindedness and self-interest in the functioning of his company. And he calls it a "healthy mix of motives." He continues, "A lot of us are here at a place like Medarex because we would like to be somehow involved in drugs that can treat cancer and other life-threatening diseases.... But at the same time, we have a fiduciary responsibility to our shareholders to make money and be profitable." Both sides of the equation drive the people at Medarex to produce better drugs.



Medarex drug attacking cancer cells. Photograph courtesy of Medarex, Inc.

Understanding both sides of the equation at once is part of Middlekauff's job. Thinking of Medarex's potential again, Middlekauff foresees a tension in the mix of motives when deciding how to price a drug. If and/or when one of the company's drugs makes it through the clinical trial process, he wonders, "How do you make the profit you need to make in order to provide support for your research and development pipeline, but at the same time make a drug that is going to...save as many lives as we can, or improve the quality of as many lives as we can?" Y