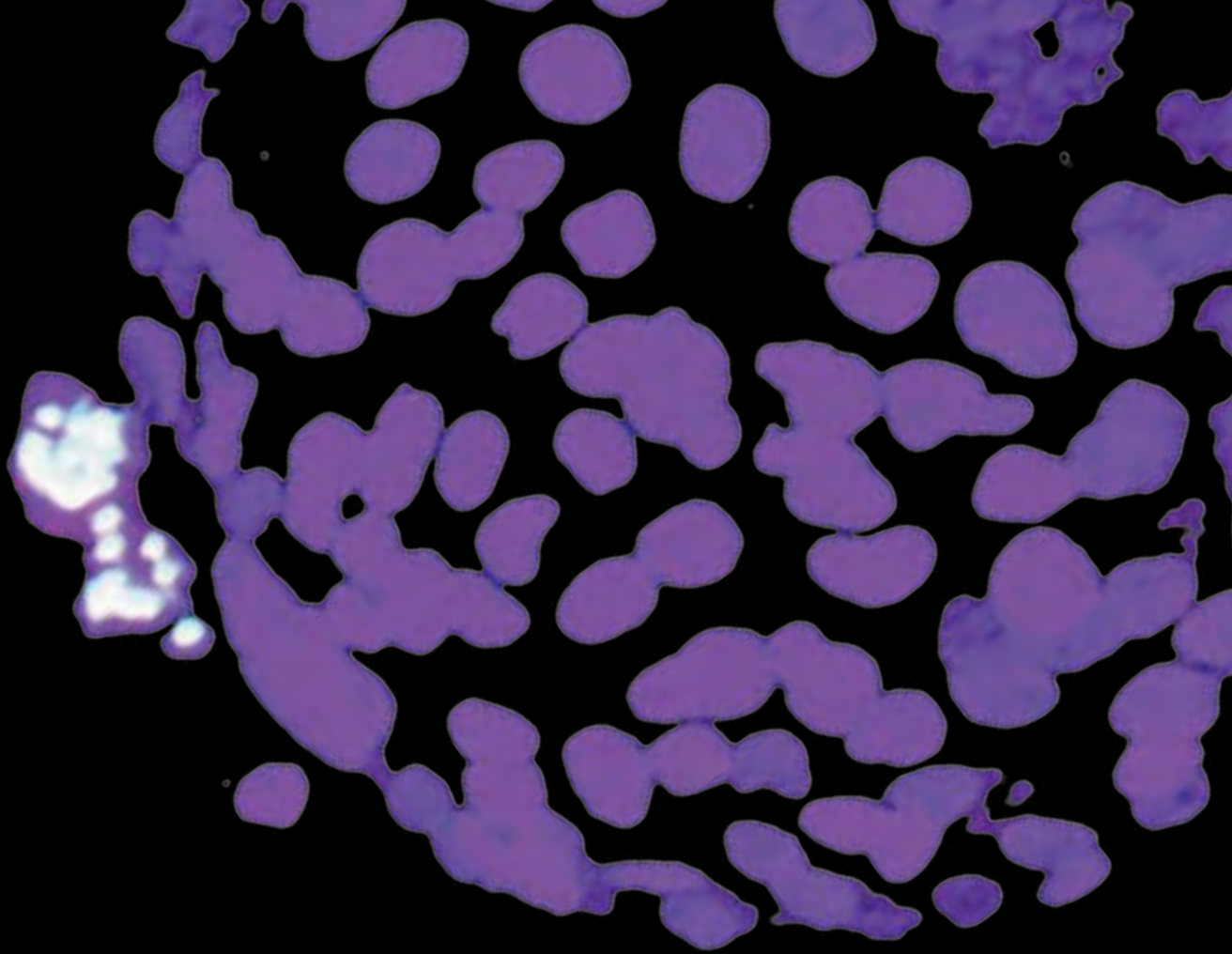


TRANSFORMATION OF AN ICON

ATCC and the New Business Model for Science

TABLE OF CONTENTS

“ The specter of irreproducibility damages the credibility of science and the people who practice it, and ultimately hurts society. A society can ill afford to lose its trust in science and its practitioners.”

RAYMOND H. CYPESS, DVM, PHD

PROLOGUE

On an early spring morning in 1993 as his plane descended for landing in Washington, D.C., Raymond Cypess could look out the window to see the Washington Monument and other memorials on the National Mall, the budding cherry trees across the Potomac, and directly below, the river's waters rising to meet the plane. The white caps approached closer and closer; once they were just yards away, it seemed the plane would tumble into the river. At the last moment, the runway appeared and the plane landed safely.

Cypess had arrived from Memphis for a short visit: a drive out Interstate 270 to Rockville, Maryland. He had come for an interview at the American Type Culture Collection (ATCC), a nonprofit little known to the public but familiar to anyone who, like Cypess, had spent a career in biological studies. ATCC's history stretched back to the 1920s, when it was established as a public treasure in the burgeoning science of microbiology. For nearly seven decades since then, the world's leading biologists had pooled their resources to create an unparalleled, open-access trove of living organisms. ATCC's service to biological science had set a new standard.

Yet, once he stepped inside the Rockville facility, Cypess experienced a letdown. The offices were cramped and the laboratories were far from state of the art. The venerable institution was in crisis. The staff member who gave Cypess his tour of the facility, a senior leader named Frank Simione, led the way to the freezer room where the collection resided. By the time they reached the windowless room that held the comprehensive collection of microscopic bacteria, flora and fauna, Cypess was almost depressed.

Later, as he read further into the organization's financial documents, the depth of the crisis became clearer still. Government grants for ATCC's mission had dried up, and the fees it collected for services didn't cover expenses. The staff was divided among small fiefdoms that were poorly coordinated. Furthermore, employees had little motivation to look ahead into the dismal future for publicly funded science.

ATCC was not alone. Across the country and internationally, science institutions faced threats to their very existence. The threats were both internal and external, as breakthroughs in chemistry, engineering and biology led disciplines in directions that many institutions were not equipped to follow. As ATCC looked to hire a new CEO, those threats loomed large.

The challenges to science are even more pronounced today. Leading institutions and landmarks in science face unprecedented cutbacks. University research libraries and public museums struggle to stay open and vital. In early 2016, the National Science Foundation, which supported research collections and museums for decades, suspended funding for all natural history collections. State governments are also pulling funding. One example is the temporary shuttering of the Illinois State Museum, which put at risk millions of artifacts and evidence of past climates and biomes (Conniff, 2015). Staff numbers at many publicly funded institutions have shrunk, with a resulting loss of analytical and creative capacity. The crisis is global. Institutions in Europe feel the budget squeeze, as biological and natural history collections across the continent have merged; some have closed their doors in the wake of the Great Recession.

The challenges that science faces have life-and-death consequences, even if those consequences unfold beyond the view of the laboratories and collections themselves. In countries that contend with old and new scourges like tuberculosis and Zika, public health agencies and laboratories must find new resources to accomplish their mandates. The United Nations Secretary-General has warned that the fight against tuberculosis, which has seen important gains, could falter without sustained support. In Vietnam, for example, hospitals' tuberculosis wards are dangerously overcrowded, and hard-to-reach populations harbor the disease beyond the reach of the health care system (McNeil, 2016). Vietnam's very effective TB program needs nearly three times its current budget to reach the goal of eliminating tuberculosis as a public health threat.

It is conceivable that a vigorous public dialogue could lead to a renewed commitment by the public to invest in these collections and institutions. For now, however, many institutions essential to science, health and research must grapple with these formidable challenges with limited resources and renewed creativity.

For scientists of all stripes, and for nonprofits internationally, the story of ATCC's survival and transformation to a secure, forward-looking and invigorated scientific institution in the two decades following Raymond Cypess' first visit to the Rockville facility offers an important hope and a new self-sustaining nonprofit business model.

The microbe collection at ATCC, like the world's great natural history museum collections, began as an investment in solving problems of the future. Its thousands of samples represent a small slice of life's diversity, assembled long before tools of DNA testing emerged. Yet that technology, unimagined then, now extends the value and potential of those samples for creating new treatments and new avenues for improving human life.

More importantly, this story addresses why science matters. Through the commitment and dedication of people to the cause of the scientific process for improving quality of life and our understanding of it, we as readers experience the considerations that scientists face — not just the research questions but the dilemmas of making careers and institutions work. These dilemmas and their outcomes have consequences far beyond the laboratory, extending through education and economies to our daily lives and health in the world's most remote communities where, for example, malaria still haunts children with fever dreams and limits their lives and horizons. For all these reasons — health, livelihood and the pursuit of a better quality of life — this is a story for our time.

CHAPTER

1

The Dawn of BIORESOURCING

Mycobacterium tuberculosis

Lore Rogers transported a valuable collection of microbes in a suitcase from New York to the Army Medical Museum in Washington, D.C.

The year was 1922. A collection of microbes that had been curated for over a decade at the American Museum of Natural History in New York needed a new home. The Society of American Bacteriologists (SAB) had agreed to take responsibility for the collection. Lore Rogers, the president of SAB and a bacteriologist with the U.S. Department of Agriculture, had found a place for the collection of microbial strains, but it was 250 miles away, at the Army Medical Museum in Washington, D.C.

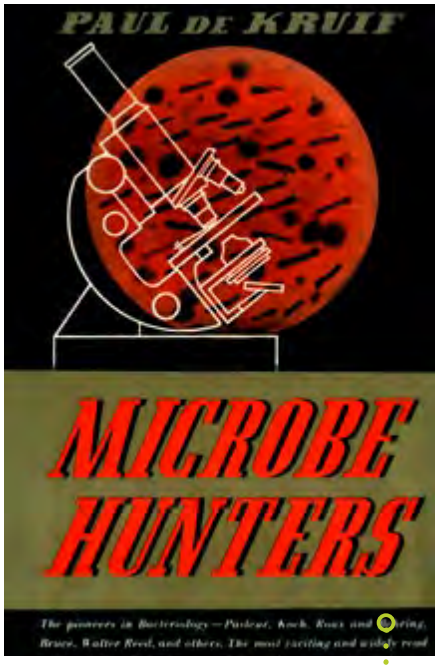
Rogers greatly valued this collection and what it represented — a collaborative resource for science. The collection, which consisted of cultures in tubes stoppered with cotton to allow aeration, had been assembled from contributions from scientists across the country, and now amounted to 175 strains. The question was: How could he safely transport his valuable but fragile cargo from New York to Washington?

Rogers came up with an unorthodox solution for his unorthodox problem. With few other options, he placed the entire collection in a suitcase, which he carried from New York to Washington by rail. For the last part of the trip, he hauled the valise across the grassy National Mall to the museum's brick building on the Mall's south edge.

Rogers' journey paved the way, three years later, for a handful of scientists to formally establish the American Type Culture Collection for the study of microorganisms and their potential.

Public awareness of bacteriology was growing. A bacteriologist, Jules Bordet, had received the Nobel Prize in Physiology or Medicine a few years before. But public esteem was mixed with a vague fear of the dangers that microbes could pose, in deadly tuberculosis, yellow fever and other epidemic diseases.

Few of Rogers' fellow passengers on the train would have understood the tools of cell science, such as sampling, reagents and experimental analysis, but Americans were still intrigued by the idea of microorganisms. Newspaper accounts painted a picture of an invisible frontier that could hold benefits for human life. "Scientists are of increasing significance, and they increasingly need interpretation to the man in the subway," the *New York Times* observed. The statement came in a review of the bestseller that helped to make bacteriology famous across the United States, *Microbe Hunters*. Paul de Kruif's 1926 book described the pioneers who were venturing beyond what the eye could see and bringing back keys to age-old mysteries of health and illness, and possibilities for better life. The book recounted Walter Reed's triumph against yellow fever in the Western Hemisphere, and the advances against malaria made by Ronald Ross and Giovanni Battista Grassi, along with others. "They only had one thing in common, originality. In other words, they were artists," the *New York Times* stated. The article painted these pioneers in romantic tones (its title: "Adventurers with Test Tube and Microscope") and hailed de Kruif's book for showing the very human side of science.



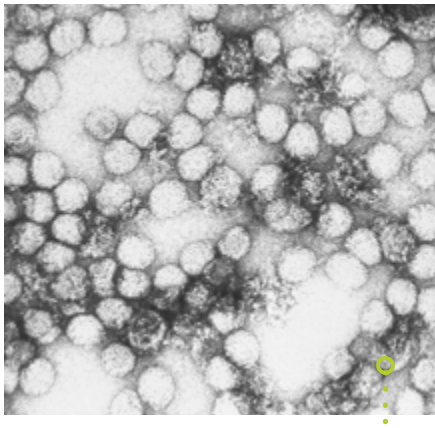
The book *Microbe Hunters* was influential in changing public perceptions of biomedical science.

"Culture collection" had a special meaning for biologists and chemists. If *Microbe Hunters* documented what happened when scientists engaged on the invisible frontier, then culture collections provided the tools to support those adventures.

Representatives from a variety of scientific disciplines had been working toward establishing ATCC for decades. The first cell culture collection accessible to researchers was most likely the collection started by Frantisek Král at the German University of Prague in 1890. Another important collection was started in the Netherlands in 1904, with a catalog of its holdings published in 1907. Japan, too, established a culture collection in 1904.

In 1911, bacteriologist and public health pioneer C.E.A. Winslow started the first culture collection in the United States at the American Museum of Natural History.

American scientists grappled with how to keep up with these international initiatives. In 1911, C.E.A. Winslow, a charter member of SAB at the College of the City of New York, sent out a notice to laboratories across America. A bacteriologist trained at the Massachusetts Institute of Technology (MIT), Winslow was curious about everything from septic sore throat to tuberculosis, from taxonomy to health surveys and the cost of medical care. He sowed the seeds for his nationwide invitation by giving presentations at SAB's annual meetings.



Yellow fever, pictured here, was among the epidemic diseases that had sparked public fears about dangerous microbes. However, growing curiosity about cell science helped people see the potential for microorganisms to combat illness.

Winslow's passion roused others to his cause. He said that SAB "was founded as a protest against . . . necessary but dangerous specialization, to bring together workers in all fields for a consideration of their problems in the light of the underlying, unifying principles of bacteriology. . . . It is this ideal which distinguishes our society from any other organization in America" (*Science*, 1914).

Winslow's 1911 bulletin to laboratories announced the establishment of the Bacteriological Collection and Bureau for the Distribution of Bacterial Cultures at the American Museum of Natural History:

> The Department of Health at the Museum of Natural History has equipped a laboratory to serve as a central bureau for the preservation and distribution of bacterial cultures of both pathogenic and non-pathogenic organisms. . . . It is hoped that . . . those engaged in biochemical work of all sorts will furnish the museum with cultures at present in their possession. The laboratory is ready to receive and care for such cultures (Clark and Geary, 1974).

The American Museum of Natural History in New York housed the first culture collection.

The response was resounding. Researchers across the country sent their cell cultures to the new repository. The Museum of Natural History's collection in New York flourished, growing to include more than 500 donations by 1912. Winslow, a seminal figure in public health, produced a 10-page catalog of the holdings in 1913.

However, the museum collection's experience also underscored a question: How do you sustain such efforts for the long term? A collection of cultures was not like a book repository. Without a champion and constant care, it would languish. By 1922, the collection Winslow started had shrunk to only 175 viable strains (Stern, 2004).

CREATING THE CATALOG

Rogers was born into a farm family in 1875 in rural Maine, where his mother's interest in the natural world fueled his own love of life science (Alford, 1975). As an undergraduate at the University of Maine, he gravitated toward the new field of bacteriology even though it appeared in only one course. (That course, he observed later, "wasn't much of a course.") He could see, nonetheless, that bacteriology was the future.

The field was making national news even then. In 1899, the *Washington Post* reported that philanthropists' fortunes were going to fund fellowships and research grants in bacteriology, "an unusual but extremely valuable avenue . . . for a rich man's millions," allowing scientists to investigate in a systematic way the causes of disease. After graduate study at the University of Wisconsin and a stint at the New York

Experiment Station in Geneva, New York, Rogers took a job in 1902 with the U.S. Department of Agriculture (USDA) in Washington, D.C., to explore dairy bacteriology (Alford, 1975).

In 1902, Rogers also attended his first SAB meeting. As a young scientist, he was overwhelmed by the number of distinguished professionals in attendance: Theobald Smith, the pioneering pathologist considered America's first major international medical researcher; William Thompson Sedgwick, a key figure in public health at MIT; Erwin Smith, who would discover the cause of crown galls in a bacterium a few years later; William Welch, founder of the country's first school of public health, at Johns Hopkins; and George Sternberg, the first American bacteriologist (Alford, 1975). Three years later, Rogers was elected to be a member of SAB with them.

During his highly productive career at the U.S. Department of Agriculture from 1902 to 1942, Lore Rogers led groundbreaking research on butter spoilage, cheese production and freeze-drying of cultures.

Friends described Rogers as an "inventive Maine Yankee who would contrive gadgets at the least suggestion," and his co-workers held him in esteem as a man of few words who had great energy and integrity. At USDA, Rogers had an office next to the machine shop and was often next door crafting a solution to some problem. In 1914, he embarked on studies in pursuit of better cell culture preservation, work that paved the way for the freeze-drying technique that is still used today. Later, he would collaborate with the National Geographic Society on a device designed to capture spores of plant disease in the atmosphere; the trap passed its first test dangling from a blimp miles above the U.S. Capitol. Rogers contributed to the device's ingenious use of a small parachute that jerked open a sterile tube, allowing high-altitude air to stream into the tube and capture spores "like flies on fly paper" (*Washington Post*, 1935).

Besides technical ability, Rogers had an eye for the institutional issues that could hamstring scientists. When he became the 24th president of SAB in 1922, he devoted his presidential address not to lofty abstractions but to the question, "What constitutes efficiency in research?" For Rogers, human and institutional problems were the choke points of science.

"It is safe to say that the greatest difficulties which the average investigator has to overcome," he wrote, "are not involved in his problem itself, but are those thrown in his way by man-made organizations." *American Society for Microbiology News* urged the speech "be read by science administrator and bench scientist" (Alford, 1975).

That same year, 1922, was the year that SAB took responsibility for the collection that would become the American Type Culture Collection (ATCC), and Rogers brought the collection by hand to the Army Medical Museum's brick building.

The John McCormick Institute for Infectious Diseases in Chicago served as ATCC's first home from 1925 to 1937.

The museum provided the space and supplies for the collection, and the Agriculture Department arranged for staffing, with a bacteriologist in Rogers' laboratory, W.R. Albus, serving as acting curator on his own time. Under that arrangement, the collection continued to offer cultures to scientists at no charge.

The Army Medical Museum was an odd place, with exhibits consisting mainly of pathological specimens from World War I, including 15,000 autopsy protocols and 10,000 specimens ranging from large to microscopic, on tissue, bacteriology, X-ray and histology. Museum visitors included medical students attending the conference of the American Congress of Internal Medicine. This hodgepodge of exhibits did not seem like the best long-term home for an active resource of cell cultures.

On October 23, 1924, a committee of the National Academy of Sciences met to figure out a more durable arrangement for the culture collection. With a grant from the Rockefeller Foundation, the committee formally established ATCC a few months later in 1925. ATCC's first home would be the John McCormick Institute for Infectious Diseases in Chicago.

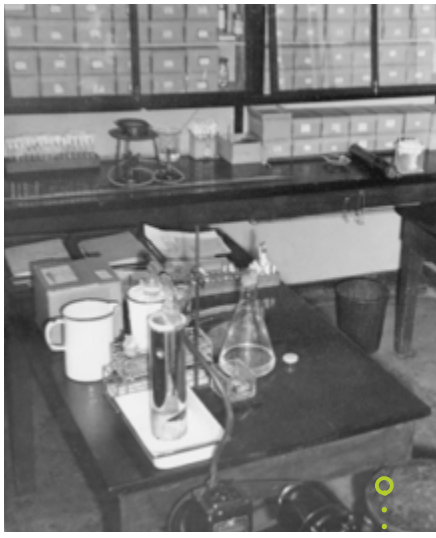
In Chicago, the collection grew rapidly. The McCormick Institute had long ties with the Rockefellers, and the story of its origin was a poignant tale of the hopes for such research. Edith Rockefeller McCormick's son John died of scarlet fever in 1901; the next year she and her husband established the Institute. While early ATCC clients

The first ATCC catalog was published in 1927.

were big Midwestern food companies and universities, medical researchers saw that microorganisms in ATCC's collection held promise for health advances.

The first ATCC catalog came out in 1927, with entries appearing in alphabetical order from *Absidia coerulea* Bainier to *Zygosaccharomyces priorianus* Klöcker. The curators announced that the catalog reflected improvements brought about by new management in just two years. The second edition two years later showed ATCC's emphasis on quality control, noting that around 130 cultures had been lost or "found atypical" and another 650 new cultures had been added, with extensive cross-referencing for more complete information. "Those who describe new species or make studies of older ones are urged to send cultures together with such history as is available," the catalog noted.

During its first dozen years in Chicago, ATCC grew to house more than 2,000 strains despite the financial straits of the Great Depression. The Rockefeller Foundation provided an additional $10,000 in 1930, and ATCC started to charge for cultures to cover costs. However, by 1937 the financial pressures proved too great for the McCormick Institute and the collection needed to move again. ATCC moved back to Washington, D.C., this time to Georgetown University's School of Medicine. Mario Mollari, a professor of bacteriology and preventive medicine, took on the duties of curator. ATCC hired Katherine Alvord as secretary, managing its day-to-day functions and eventually serving as secretary-manager until 1960.



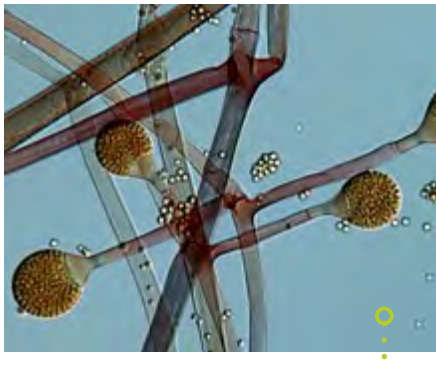
ATCC's quarters at Georgetown University's medical school consisted of a shared laboratory and a small room that housed the fungi collection.

SUSPENDING TIME WITH NEW TECHNOLOGIES

The techniques of freezing and freeze-drying microorganisms advanced in the decades after Rogers' first experiments. The basic concept was simple: By placing a microorganism in a liquid and lowering the temperature to freezing, cell activity could be suspended, allowing a pure culture to endure for years and then be thawed and used again when needed. Furthermore, a cell could be frozen at a particular phase of its development, creating a snapshot of that phase.

Freeze-drying, or lyophilization, is similar to freezing except that it goes one step further, using the low pressure of a vacuum to remove moisture content as freezing occurs. While under low pressure, the container is torch-sealed. To revive cells later, a technician hydrates them and places them in a liquid nutrient medium. Both freezing and freeze-drying were game-changing techniques that allowed researchers to compare cells' reaction to a drug, for example, at set periods after exposure.

Both technologies would eventually form an iconic image of ATCC: the large liquid-nitrogen freezers for cultures that resemble brewers' giant vats, where a frozen mist rises when opened. (Today, ATCC's main facility has about 100 of these liquid-nitrogen freezers, plus another 100 mechanical freezers that resemble household



***Absidia coerulea* was one of the early specimens listed in ATCC's first catalog.**

Before the collection could be moved to its new facility in 1947, ATCC staff had to complete extensive renovations of the two-story building at 2029 M Street N.W. in Washington, D.C.

freezers, but much colder.) Debates continued on what genetic changes might occur in preserved microbes; for decades, new technologies would continue to spur questions and rigorous assessments of the materials used for culture collections.

ATCC adapted during tumultuous times. By 1940, it maintained 90 percent of its bacterial stocks using freeze-drying; for distribution, it used duplicate cultures in test tubes. As the United States emerged from the Great Depression, the organization provided more services to the reviving private sector. The growing antibiotics industry relied on ATCC; culture sales to commercial firms grew by 35 percent in 1942. As the United States entered World War II, ATCC also contributed to the war effort. At the Surgeon General's request, ATCC became a central depository for cultures isolated during epidemics (Clark and Geary, 1974). With the Allies' victory in 1945 came another pulse for institutional growth. By 1947, with nearly 3,000 strains, ATCC was again swelling beyond the capacity of its home institution.

CHANGING ENVIRONMENT FOR CULTURE COLLECTIONS

America's infrastructure for scientific and medical research was growing in tandem with rapid breakthroughs. As tools for public health improved, public institutions had a mandate to provide them, on a scale far beyond what scientific associations and private foundations could provide.

Government agencies devoted to medical research were growing. The tiny agency that began as Public Health Services in 1922 with an initial focus on cancer emerged after World War II as the National Institutes of Health (NIH). The Communicable Disease Center (later the Centers for Disease Control and Prevention) was established in 1946 in offices on Peachtree Street in Atlanta that had housed a wartime malaria control effort. The CDC had a simple but breathtaking primary mission: to control communicable diseases with field investigation and training. As scientists' understanding of biology and diseases advanced, they forged a basis and mandate for a fuller infrastructure for public health. As the 20th century progressed, public and private investment in research would make the United States a world leader in public health and disease prevention.

The *Washington Post* reported that philanthropists' fortunes were going to fund fellowships and research grants in bacteriology, "an unusual but extremely valuable avenue . . . for a rich man's millions."

By 1947, ATCC's collection had outgrown its facility at Georgetown University. Rogers and his colleagues needed to find an independent solution to avoid the constant shuffling between institutions. Their search led to a small two-story building on M Street Northwest in Washington, less than two miles from ATCC's Georgetown home. "It was in poor condition and required extensive re-modeling," one staff member recalled later. "Lore Rogers and the staff of nine did most of the work themselves" (Clark and Geary, 1974).

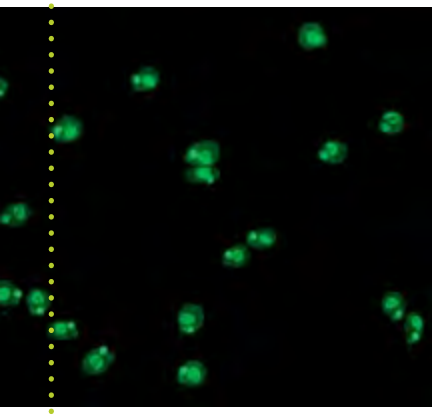
Julius Youngner was a member of the team of scientists who developed the first effective polio vaccine in 1952.

ATCC's new home opened in September 1947 under the curatorial care of Ruth Gordon, with assistance from laboratories at USDA and the National Institutes of Health. It included an office, a media room, and laboratories for chemistry, bacteriology and mycology. The growing staff included 18-year-old Marion T. Alexander, who would in time become ATCC's Chief of Facilities and Microbiological Services.

After 24 years supporting ATCC, Lore Rogers retired as chairman in 1949. "Had it not been for the devotion, foresight, executive ability, ingenuity and manual dexterity of Lore Rogers," a colleague later declared, "I am sure that the collection would not have survived" (Clark and Geary, 1974).

PROVING ITS WORTH

The importance of cell cultures and the potential benefits for the public captured the attention of researchers and policymakers. In 1949, Julius Youngner, a young virologist who had just arrived in Pittsburgh, began working with Jonas Salk. Scientists had recently proved that polio could grow in cell culture, but Salk's team relied on growing it only in monkeys, a slow process. Youngner brought cell culture into the Salk lab, developing a technique for culturing animal cells on a large scale known as trypsinization. It used trypsin, an enzyme found in the digestive tract, to break down cells' proteins and allow the cells to be held in suspension. This method exponentially increased the amount of polio virus that Salk's team could grow in the lab. Youngner's innovation transformed the potential of tissue culture studies.



Scientific breakthroughs sometimes come from unusual places. The green bottle fly, top, contained the protozoa *Crithidia luciliae*, above, which led to the development of a diagnostic tool for systemic lupus.

Amid such advances, the ATCC catalog continued to grow. A generation of scientists who grew up reading *Microbe Hunters* saw in the ATCC catalog something more than a library — it was a tool chest for discovery. More and more, scientists drew on its vast range of microorganisms and in turn contributed their own. A growing consensus on the need to preserve and distribute important virus strains led to the creation of the Viral and Rickettsial Registry in 1949, a subset of ATCC's work with added production capacity and authentication of most viruses. ATCC's Virology Program ensured that reference strains of viruses were available to scientists or teachers who needed them. ATCC also started a collection of plant viruses.

As ATCC's collections expanded, the research based on the collections expanded as well. From 1951 to 1966, the number of published papers involving cell culture more than tripled every year (Skloot, 2010). The national system for medical research was also becoming more consistent and comprehensive. In 1962, the National Institute of Allergy and Infectious Diseases (NIAID) transformed what had been a piecemeal approach to clinical vaccine studies into a nationwide network for clinical research.

Many scientists deposited strains with ATCC not knowing what benefits might result, or when. Important findings might emerge only decades later. In 1958, a researcher deposited a sample of *Crithidia luciliae*, a protozoan isolated from a green bottle fly, which became ATCC 14765. Nobody at the time knew if it would have any use. Years later, that entry helped to detect lupus, an immune system disorder that affects more than 1 million Americans (Cypess, 2003).

Breakthroughs came in different forms. One strain deposited in 1983 was *Thermus aquaticus* (ATCC 25104), a heat-stable bacterium that can survive at up to 80 degrees C (176 F). Later, chemist Kary Mullis used *Thermus* in the lab to develop a method for detecting tiny quantities of genetic material, called Polymerase Chain Reaction (PCR).

DISASTER ON THE HORIZON

Despite a growing collection and growing acceptance of its role in scientific inquiry, ATCC saw signs of disaster looming. Just as Lore Rogers had warned that institutional bottlenecks held more dangers than scientific issues, financial hurdles had threatened ATCC's existence from the start. With no permanent or dedicated funding source, it was nonetheless expected to maintain a high-quality facility that scientists anywhere could access. ATCC had weathered a series of financial crises, but how many more could it survive?

There was a larger risk to science itself. The integrity of the growing body of cell culture research hinged on the expectation that the materials used were exactly those cited in the studies. However, ATCC had no means for authenticating its culture materials beyond the point of delivery to a buyer, revealing a serious vulnerability in the practice of collaboration among scientific colleagues. As Youngner once explained, researchers might obtain a cell line or a bacteria line from a colleague who may have originally

SAVING LIVES WITH THE FLU VACCINE

ATCC's Influenza Reagent Resource provides public health labs around the world with reagents, tools and information to help develop seasonal flu vaccines. Advances during the 20th century helped make pandemic flu (such as the Spanish flu, which filled wards and killed millions in the late 1910s) a thing of the past.

One of the many ways that ATCC touches people's lives comes in their annual flu shot. The selection of the influenza viruses for inclusion in the vaccine each year relies on surveillance of viruses circulating and forecasts about which strains are most likely to proliferate during the coming season, based on results from use of diagnostic kits provided by ATCC. The World Health Organization then recommends specific viruses for inclusion in the vaccine. Each country makes its own decision about which viruses to include. In the United States, the Food and Drug Administration (FDA) determines which strains will be represented in the vaccine.

What does that mean for public health? In 2015, a report by the CDC estimated that in a nine-year period between 2005 and 2014, seasonal flu vaccine prevented more than 40,000 deaths in the United States (Foppa et al., 2015).

sourced it from ATCC, thinking that the ATCC imprimatur carried over. But changes occur in cell cultures and their properties. Contamination by mycoplasma, for example, can change a strain's characteristics. Such contaminations can occur invisibly during the course of sharing cultures. "So there's not uniformity when other scientists try it," Youngner said. "That's a problem."

In 1959, presentations at three high-profile conferences showed that important cell cultures contained widespread contamination and admixtures. The papers called into question the scientific validity of studies across a range of fields that were conducted using cultured animal cells. The National Cancer Institute called for a national collection that would contain reference standards of characterized animal cell strains, and it funded a committee of experts to formulate policies for certifying cell lines that satisfied those standards (Clark and Geary, 1974). The scientific community would need to police itself on quality control.

ANOTHER HOME

ATCC had become a respected, centralized repository in a field that was mushrooming. With funding from NIH and the National Science Foundation (NSF), ATCC set about building a permanent laboratory in Rockville, Maryland. It broke ground on March 15, 1963. The chief of NIH Health Research Facilities Branch, Francis Schmehl, called

Having outgrown its building on M Street N.W. in Washington, D.C., ATCC constructed its first permanent laboratory in Rockville, Maryland, in the early 1960s. The facility served as ATCC's home from 1964 to 1998.

the new facility "the first real home for one of our nation's most precious resources" (Clark and Geary, 1974). Designed specifically for ATCC's comprehensive range of microorganisms and cell lines, the 35,000-square-foot building opened on February 23, 1964. The 8,496 cultures rolled out from Washington, D.C. — this time in a van, not a suitcase.

More than 300 microbiologists and assorted others attended the dedication of the Rockville facility on May 2, 1964. ATCC had moved only about a dozen miles, but in another sense, the frontier of biology was moving much further and faster, and ATCC faced tremendous challenges in keeping up. It needed to attract expert staff to expand the knowledge of culture preservation and systems. It also needed to maintain high-quality conditions for the growing number of strains in its collection (nearly doubling again to 16,000 by the 1970s), and it needed the capacity to meet the global and ever-increasing demand for cultures. Most orders came from universities, hospitals and companies. Industrial uses of ATCC strains involved everything from developing antibiotics to testing flavoring agents and perfumes for quality. Research and government requests were also soaring.

By the 1970s, ATCC published three catalogs every other year: the *Catalogue of Strains* (including bacteria, fungi, plant viruses, algae and protozoa), the *Registry of Animal Cell Lines*, and the *Registry of Viruses, Rickettsia and Chlamydiae* (Clark and Geary, 1974). ATCC had an annual budget of $1.1 million. Half of that came from fees and sales of cultures, while the other half relied on grants and contracts from NIH, NSF and USDA.

In 1971, the federal government signaled in clear terms that it would not subsidize ATCC forever. NIH reduced its annual support for ATCC and announced it would be

phasing out funding in the coming years. ATCC eliminated a dozen staff positions and was forced to search for additional ways to cut costs. It would have to find new revenue sources to make up for declining federal support.

As the collection approached its half-century mark, Lore Rogers was corresponding with his ATCC colleagues while managing a dairy in Maine. He had seen bacteriology advance far beyond what he might have dreamed as an undergraduate student in Bangor. Born the year that Ferdinand Cohn published the first classification of bacteria that used the genus name *Bacillus* and established bacteriology, Rogers had joined a scientific community that had pushed the boundaries of human understanding to the moon's surface and to the subatomic realm of quarks at the foundation of matter. Rogers' honors ranged from the first Borden Award for his achievements in dairy science (it was noted that "there is not a branch in our industry that has not felt the helping hand of his genius") to others from professional associations and institutions including SAB and his alma mater, the University of Maine. Perhaps the tribute that came closest to reflecting his contribution to science was the enduring service of ATCC, the organization he helped to birth. Rogers passed away in March 1975, in his hundredth year.

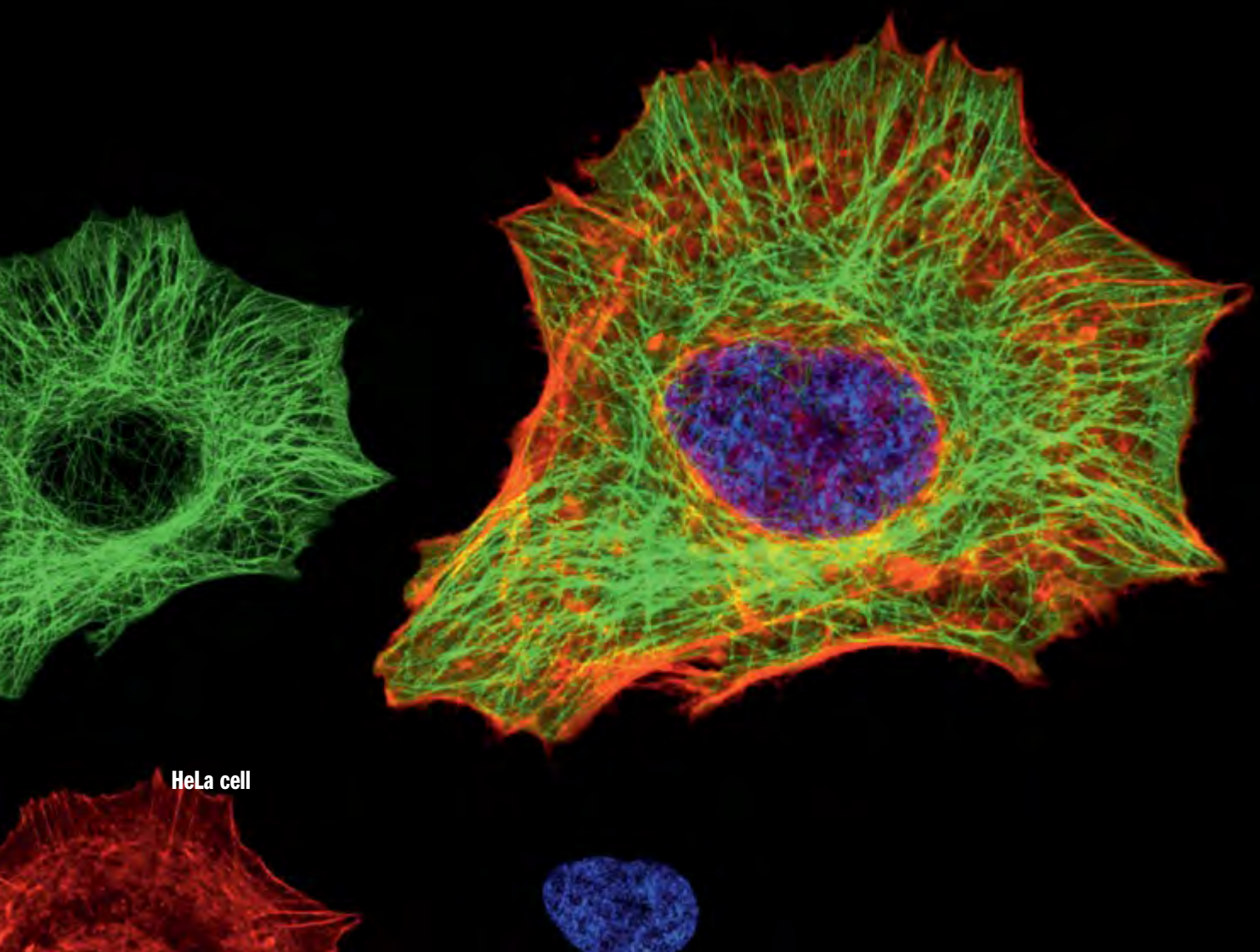
In the 1980s, ATCC pursued more contracts with the World Health Organization (WHO), NIH, and USDA, including government support for the plant virus collection. However, the era of government support was waning. ATCC had seen phenomenal growth. Now it would need a new model to survive.

CHAPTER

2

Crossroads

A MANDATE WITHOUT MEANS



HeLa cell

As ATCC entered the 1990s, everything looked fine on the surface. The organization continued to provide a vital service to the scientific community. Orders were still increasing and researchers still contributed to the collection, which contained more than 53,000 strains of everything from algae and bacteria to fungi, plant tissues, protozoa, seeds, viruses and recombinant DNA materials from vectors, hosts and clones. The 1991 annual report noted a growth in acquisitions. ATCC's shipping unit sent out more than 134,000 orders, including 50,281 cell cultures, more than 17,000 recombinant DNA orders, and more than 47,000 bacteria cultures.

EVERYTHING'S GOING GREAT

Internationally, ATCC had set a standard for authenticating strains and providing high-quality products. In 1976, P.H.A. Sneath, a bacteriologist at the University of Leicester in England, hailed ATCC's valuable functions, remarking that its work "is especially important in the present climate of economic and ecological thought. . . . Without culture collections, microbiology would soon be strangled: like libraries, they are most needed when the need is unexpected" (Sneath, 1976).

As a bench scientist at NIH in the 1980s, Mindy Goldsborough often used ATCC cultures, purchasing cell line reagents as a graduate student in cell biology. In her research, she discovered a significant oncogene that she knew other scientists would be interested in studying. Suddenly she had the opportunity to make a contribution to this repository that all the scientists she knew relied upon. She found that prospect so exciting that she hand-carried her deposit to ATCC's Rockville, Maryland, location. "It was like visiting a hall of fame," she recalled later (Goldsborough interview, 2015).

[ATCC's] work "is especially important in the present climate of economic and ecological thought. . . . Without culture collections, microbiology would soon be strangled: like libraries, they are most needed when the need is unexpected."

Scientists like Sneath and Goldsborough knew the value of culture collections, but nobody had systematically documented the benefits to science, either in economic terms or in the knowledge shared. At that point, scientists merely suspected what research would later show: that one value of premier culture collections was the imprimatur they gave to research that was linked to them. Science is a dialogue, with ideas set forth in one study getting reinterpreted, critiqued and ideally validated in later publications, like a long-running exchange of letters. A study published by the Brookings Institution would later compare citations linked to ATCC deposits with others, looking at the same journals and same time frames for comparability. A paper linked to ATCC had more than 200 percent greater likelihood of being cited later. That advantage increased with the passage of time (Stern, 2004).

Amid this growing academic visibility, a 1986 survey of plant virology researchers revealed their high regard for ATCC, as well. "Many investigators emphasized that the services ATCC provides are essential, and that the values of these collections cannot be overestimated," the article concluded.

Even as scholarly peers acknowledged the high value of the work ATCC was performing, continuing this work of a public repository was becoming harder. In the survey, researchers reported depositing materials with ATCC less frequently, and some voiced dissatisfaction with the ordering process. Still, they looked to ATCC for information and new offerings — for example, requesting a referral service and serological protocols and procedures (Hill, 1988).

A CHANGING LANDSCAPE

Despite the positive signs, a deeper look at ATCC revealed troubling trends. What had been a vital institution in the red-hot center of science at mid-century had become almost marooned — financially vulnerable, technically outdated, and on the verge of being left behind by drivers of scientific change. Fields involving cell biology and microbiology were expanding with developments in molecular and synthetic biology and genomic research, making culture collection itself less important. Some questioned privately whether ATCC would survive into the 21st century.

A stable financial base had eluded ATCC from the start. Total revenue had grown from just over $1 million in 1971 to $14.45 million in 1991, but that growth masked a continued dependence on federal subsidy. For 20 years, NIH and other federal agencies had warned that they would be ending their support. NIH and NSF were struggling to maintain their own funding levels against congressional pressure for reductions in the age of smaller government heralded by the election of President Ronald Reagan. However, the ATCC director in 1971 had insisted on the necessity of public funding, stating in the annual report, "It is impossible to operate a national culture collection solely on self-generated income." He reported that increases in culture fees pushed order levels down, and his statement reflected the view that ATCC's leaders had held since Lore Rogers: that the cultures were a shared resource that should be widely available.

ATCC's board changed leadership in 1972, and the new director, Richard Donovick, sought new revenue streams. Capital campaigns yielded corporate donations from Eli Lilly, Pfizer, Schering-Plough and others, but ultimately came up short of the need.

Donovick had tried new initiatives. Nature-based discoveries were one area that was expanding, and ATCC pursued them with support from the U.S. Department of Agriculture. By 1989, ATCC had over 24,000 strains of living fungi, representing 5,000 species. Nature-based medicines held potentially high benefits to human

Richard Donovick

health: Looking at a sample representing less than 1 percent of those ATCC fungi holdings, Donovick noted that 518 strains yielded 207 antibiotics (Jong and Donovick, 1989). How much more potential lay in all 24,000 strains?

These steps notwithstanding, the real challenges came from larger shifts in the scientific landscape — significant changes in innovation and what motivated researchers, along with technical changes in how biologists worked and discoveries that were driving advances in chemistry and biology.

The shifts became marked in the late 1970s, when the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure brought a new regime for intellectual property to the core of ATCC's work: cells and cell lines. Signed by 79 countries, the Budapest Treaty spelled out how researchers could obtain patents for innovations involving microorganisms — bacteria, fungi, plant spores, eukaryotic cell lines, viruses and more. The territory of microorganisms, previously terra incognita for patenting, was being charted.

For generations, this change had been unimaginable, yet in the context of scientific advances, a new map of the terrain and incentives was inevitable. Universities gained the means to protect more and more types of innovations and intellectual property that their research generated. Previously, patents were the only kind of intellectual property that university systems managed, and very few even had patent policies (Slaughter and Rhoades, 2010). After 1980, that changed dramatically.

Around that time, a debate was heating up about bioprospecting and the question of who benefits from scientific discoveries from nature. Inventors and companies were beginning to reap financial benefits from plant-based products, often using knowledge of their properties from indigenous groups. Yet the indigenous group at the plant's source typically gained nothing in return. By the early 1990s, advocates for these groups labeled this "biopiracy." Refining the framework for intellectual property rights involving nature would require addressing the claims of marginalized groups and making scientific discovery more equitable.

Keith Bostian

As a research faculty member at Brandeis University, Keith Bostian was studying genetic circuits in yeast and cloning techniques in the early 1980s — basic research involving gene expression. Later in the decade, he started working with

pharmaceutical companies on developing applications that helped people. He recalled the disruption across disciplines that occurred as research faculty members adapted to the changes and moved to applied research and entrepreneurial approaches. "We were not yet sequencing genomes, but biogenetic and cloning applications were on the way through the use of microorganisms," he said (Bostian interview, 2015).

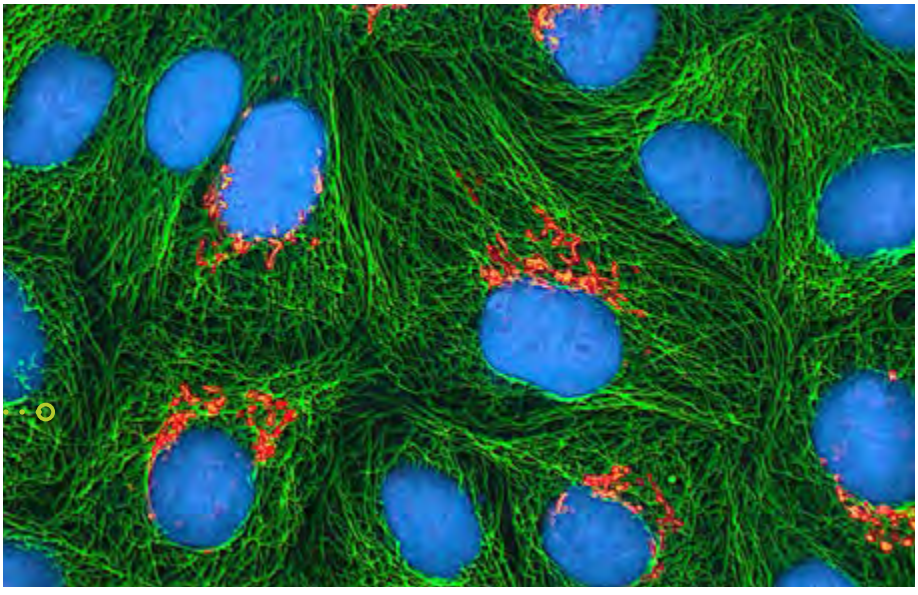
Lydia Villa-Komaroff

The change in intellectual property rights had the effect of dampening the widespread sharing of material that had been common for nearly a century and on which ATCC was founded. Universities did not want researchers giving away resources for inventions, and income streams that could replace the federal grants that were drying up. On the other hand, the new intellectual property regime created an opportunity for institutions like ATCC to play a new role: as a depository of record, recognized by the international patent system, for accepting the materials submitted for patents. ATCC had long had a small role supporting patent deposits in the U.S. patent system, but items from nature had not been patentable. Now, by depositing patented material with one recognized depository, a researcher's patent application could cover all countries that signed the Budapest Treaty (*ATCC Quarterly Newsletter* No. 1, 1981). ATCC's patent depository grew to 11,731 holdings by 1991.

Integral to that institutional shift as a trust organization for intellectual property in the United States was the Bayh-Dole Act, a law that took effect in 1980. More than $75 billion per year in inventions were created with federal support; the act essentially created a model of patent ownership by U.S. academic institutions to channel that return on investment to feed the university research system (Loise and Stevens, 2010). Over time, university policies became more nuanced, but the law's first effect was to push universities to corral the potential of their researchers' inventions and reduce contributions to public repositories like ATCC (Villa-Komaroff interview, 2015).

In the long term, all branches of the federal government would continue to look for ways to cut back. The consequences of the Budapest Treaty and Bayh-Dole would continue to unfold, and researchers like Bostian adapted to the new climate.

ATCC faced other shifts as new fields of genetic research, bioengineering and synthetic biology advanced. Synthetic biology, described as combining biotechnology, evolutionary biology, molecular biology, biophysics and computer engineering with genetic engineering, boomed following the discovery of restriction enzymes, which could slice a DNA molecule at precise points. (That discovery won the 1978 Nobel in Physiology or Medicine for Werner Arber, Daniel Nathans and Hamilton O. Smith.) The new field, focused on design and construction of new biological devices and even redesigning biological systems, drew on an eclectic range of disciplines and promised remarkable new directions. The biological and ethical ramifications of redesigning natural systems were still unknown.



When scientists discovered that HeLa cells interfered with biological research, ATCC helped to isolate and identify contaminated cell lines.

NEW DANGERS AND CONTAMINANTS

Another emerging issue in science at the time was the continuing problem of cell line contamination. Since the 1960s, the problem of cell lines being overwhelmed by a particularly aggressive cell line known as HeLa cells had pervaded research and corrupted many experimental results. HeLa cells, human epithelial cells originally taken from the cervical cancer cells of a Baltimore woman named Henrietta Lacks, were the first human cells successfully cloned, in 1955. Their exceptional ability to grow in tissue culture made them a kind of laboratory "weed" that interfered with cells they were meant to help study. HeLa contamination threatened not just the integrity of ATCC's lines but the reproducibility at the heart of the life sciences. As ATCC board member John Child put it, "If you were making a cake and couldn't repeat it, how usable is that recipe?"

Elliot Levine

ATCC became deeply involved in the vast effort to isolate and identify the contaminated cell lines. Staff members assembled a list of known HeLa-contaminated cell cultures and updated the list regularly. The Cell Culture Department characterized cell lines in ways to reduce the chance of contamination between and within species.

There was another type of risk that would grow in importance in the years ahead: would-be purchasers who posed threats to public safety and security. This was signaled by an episode in 1984, when two men with an Upstate New York address tried to order potentially dangerous bacteria: tetanus and botulism (Associated Press, 1984). When ATCC staff learned that the men had faked their authorization for the order, they notified federal law enforcement. By the time the men placed a second order for the two bacteria, the FBI and ATCC were ready. ATCC shipped a package to the Federal Express branch in Cheektowaga, outside Buffalo, substituting harmless solutions for the requested strains. When the suspects arrived to sign for the package

from FedEx, FBI agents arrested them. They were convicted and sentenced to prison for fraud and attempting to order deadly agents. The case garnered headlines that put ATCC in an unwanted public spotlight: Even though ATCC responded appropriately and coordinated with authorities, headlines of "deadly bacteria" made skeptics ask how potentially dangerous materials could be mail-ordered (Durcanin, 1984).

THE WRITING ON THE WALL

In addition to external threats, warning signs were emerging within ATCC's facilities, which were approaching 30 years old. Annual reports downplayed the issue, noting only that space was a continuing problem, but board members observed that the issue was deeper than mere space constraints. Equipment and facilities were pushed to capacity and nearing obsolescence. Cell biologist Elliot Levine had first heard about ATCC when he was a graduate student in the 1960s. He had been amazed to learn that he could get so many strains of bacteria from a single source. "You mean they have *all* of these, frozen?" he remembered asking his mentor. She smiled and answered, "Yes, you should see. They're working out of a house in downtown Washington." In 1990, representing the Society for In Vitro Biology to the ATCC board of directors, Levine finally visited ATCC in Rockville. He found the facility and staff divided among three buildings, and an infrastructure stretched to the limit. They could not buy any new equipment without sacrificing existing equipment or disrupting the power supply. There was no margin for growth. "It was amazing they were able to do anything," he recalled later (Levine interview, 2015).

Bob Stevenson

Yet Levine marveled how the staff soldiered on. "Look at how they're working under these conditions," he thought. For staff members like Trish Slaski, a cell biologist who joined ATCC in 1977, the working conditions reflected the organization's origins: an organization that was run by scientists who were each focused on their collections, like fiefdoms of bacteriology, mycology, virology, cell biology and other disciplines. The focus was not on the organization as a whole, but each on their section's acquisitions and maintenance (Slaski interview, 2015).

Trish Slaski

Other problems emerged because of ATCC's governing structure. Its board of directors consisted of more than 30 members, representing different scientific associations, with more experience debating scientific issues than overseeing operations. None had business management experience. John Child, who joined the board in 1992 at the invitation of director Bob Stevenson, found it an unwieldy group. As the first board member without a Ph.D., Child often felt like an outsider at an old boys' club where scientists assessed microbes, not organizational performance. Coming from the financial world, Child felt that the board viewed business and enterprise with considerable distrust and fear.

In 1991, Stevenson announced his plans to retire. He worked with the board to create a list of the skills that the next director would need in order to revitalize the institution: science administration, research and business management expertise. The resulting

Julius Youngner

Raymond Cypess

job description struck Levine as nearly impossible to fill. The board was looking for change, but the search for a new director would be difficult. From a field of scientist scholars, prospects for finding an entrepreneurial candidate looked bleak.

AN UNEXPECTED DIRECTION

Like Levine, Julius Youngner was an ATCC board member who had come to understand the organization's importance along with its vulnerabilities. Youngner knew the value of cell culture better than anyone: He had brought the technique to the historic milestone of a successful polio vaccine with his development of trypsinization, which transformed cell culture's prospects. Youngner also was asked to serve on the ATCC board in the early 1990s and found that he was quickly discouraged by the same limitations Levine described: a decaying facility, tired leadership and a paralyzing organizational structure. Youngner believed deeply in ATCC's mission, but he wondered if the organization was up to achieving that mission anymore. The facility needed major improvements and fresh ideas. "It was a declining institution," he said.

One day in April 1992, Youngner received a visit in Pittsburgh from longtime colleagues Raymond Cypess and his wife, Sandra Cypess, a professor of Latin American culture and literature. Youngner had known the couple since he was chairman of the University of Pittsburgh's Microbiology Department and Ray Cypess had joined the School of Public Health. Youngner invited Cypess to give lectures on parasitology to medical students, and a friendship developed. Cypess' comparative approach to medicine and his willingness to search broadly for diagnostic solutions made him a popular lecturer at universities nationwide. In Youngner's office that day, the job description for ATCC director lay on the desk between them. Youngner urged his friend to take a look (Youngner interview, 2015).

Cypess dismissed the job announcement with barely a glance, insisting his career was in universities and research, not nonprofit administration. Youngner persisted, suggesting it could be an opportunity. Sandra, too, urged her husband to take another look.

Cypess was then vice provost and dean at the University of Tennessee's College of Graduate Health Sciences, where he was also teaching and overseeing the university's research portfolio. He took satisfaction in building institutions that responded to societal needs. At Tennessee, he created the university's Department of Comparative Medicine, which was committed to development of models for research. He responded to changes as medicine integrated elements of engineering, and started the Department of Biomedical Engineering. He recognized the growing importance of nursing's role in health care and fought to create a Ph.D. program in nursing well before the growth of nurse practitioners.

Cypess held a broad view of medicine — not carved among dividing lines of human medicine or veterinary medicine but within the lines of the One Health or One Medicine

By the early 1990s, ATCC's future growth was inhibited by cramped, outdated facilities in Rockville and a siloed organizational structure.

concept, which looks across disciplines for public health synergies and solutions. In that view, microbe interactions form a core dynamic for addressing health care for people, animals and the environment. Growing up in a working-class neighborhood of Brooklyn, Cypess had come to love the beauty and scope of biology and biological systems while spending summers with his parents on farms in the Catskills. As a boy he had been inspired by the book *Microbe Hunters*, with its real-life heroes and adventures with the natural world. He pursued a master's degree in entomology at the University of Illinois, studied medical entomology (including the role played by fleas in the spread of plague), and received his doctorate there in veterinary medicine.

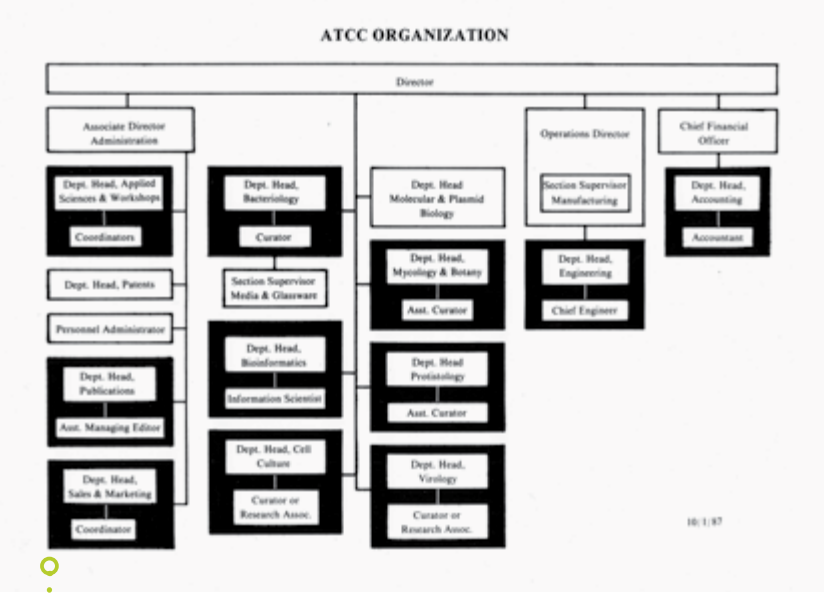
His curiosity paved the way for a wide-ranging career that combined academic structures with opportunities for real-world applications. He practiced veterinary medicine in Illinois and North Carolina in the late 1960s, and as head of New York's veterinary diagnostic center at Cornell University he was responsible for diagnostic laboratories that combined bacteriology, endocrinology, parasitology, immunology, toxicology and virology for greater diagnostic capacity. Later that decade, he managed the state's system for drug-testing racehorses. He had witnessed races at Saratoga in the era of Secretariat and came to understand the dynamics of horse racing and what that industry shared with human sports industries. He was forming a wider view of medicine, health and management. At Cornell, he designed and created the Department of Preventive Medicine, with strengths in epidemiology and public health, and as a New York state-certified medical microbiologist he was responsible for Cornell's Student Health Center microbiology laboratory.

Cypess was also steeped in the research world. He had published widely in parasitology and understood the grant review process at NIH from the inside, having participated in panels that awarded research grants in a number of fields, including parasitology, comparative medicine and veterinary medicine. These

elements of a dynamic dialogue advancing medicine were not qualities he saw in the job description on Youngner's desk.

There's no way I'm going to take that job, Cypess thought during that April visit to Pittsburgh. *Why leave a tenured academic position to head an institution that's essentially a library?* At the same time, the possibilities for a repository to do more percolated in his mind. Previously in his career, he had seen solutions that were missing from institutions and built departments to address those gaps. Could that be true also with ATCC? Maybe an institution founded on little more than scientific goodwill had hidden assets that could make it vital again.

Despite his misgivings, Cypess felt drawn to the challenge. Like anyone who worked with microbial strains, he knew and respected ATCC's mission. It occupied a junction of many important fields. Standing at a life juncture himself, where he had to decide between finishing out a career in university administration or taking on a new challenge, Cypess decided to apply for the position at ATCC.



Before Cypess arrived at ATCC, the organization was siloed, hampering efforts to move beyond a maintenance mindset.

A DISCOURAGING INTRODUCTION

When Cypess received an invitation to visit Rockville for an interview, he made the trip from Tennessee with tempered expectations. Frank Simione, the staff member who escorted the job candidates on their tours of the facility, showed Cypess the main building housing the laboratories and freezers, and the other two buildings with warehouse space and administrative offices. He ushered Cypess into the secure, windowless freezer room where they observed technicians checking strains, with wisps of condensation mist rising from an open liquid nitrogen container and quickly vanishing.

As they returned to the main office, Cypess pulled Simione aside, looked him in the eye and asked a question that had been turning in Cypess's mind through the day: What was his estimation of the ATCC staff situation? Not wanting to prejudice a candidate's impressions, Simione replied cautiously, saying he did not think they realized their own potential. Cypess thanked him for the tour and they parted.

Cypess completed the interview and came away depressed. "It was terrible," he recalled later. He saw the same declining facility the others had. "It was cramped. It was cluttered with all kinds of things. It was siloed." Where was the funding for development, for growing staff capacity and research?

"You had all of the -ologies distributed all over the institution," he said. ATCC scientists were still focused on taxonomy and systematics because those were fields that had always been the purview of culture collections. The mentality was a mindset of preservation and maintenance, poorly suited to the challenges that faced biology and other fields where researchers used ATCC products. ATCC had pioneered methods for growing cell lines indefinitely and how to share them, but it lacked a vision of where to go next.

Cypess phoned Youngner afterward and asked, "Juli, do you realize what a mess that place is?"

"You're telling me?" Youngner replied. "I'm on the board!"

Cypess talked over the challenges with his wife. The task would be supremely difficult, and they would need a lot of luck to succeed, he said. Sandra listened to his concerns, and they talked into the night. Then ATCC called, asking him to come back for another interview.

In his second interview, Cypess allowed himself to show impatience. "I was a little angry at them for letting this very noble institution deteriorate," he said later. He spoke in more direct terms of how he would approach the problems he saw: the need to create a standards institution that answered the problems of contamination, and the need to capitalize on the incredible storehouse of information that ATCC possessed in this collection of microbes that had been assembled since 1925. New technologies and approaches were extracting more forms of information from those microbes, and ATCC could be part of those discoveries. By improving the quality of its information and the skills of its staff, ATCC could boost the value inherent in its products and perhaps become financially sustainable.

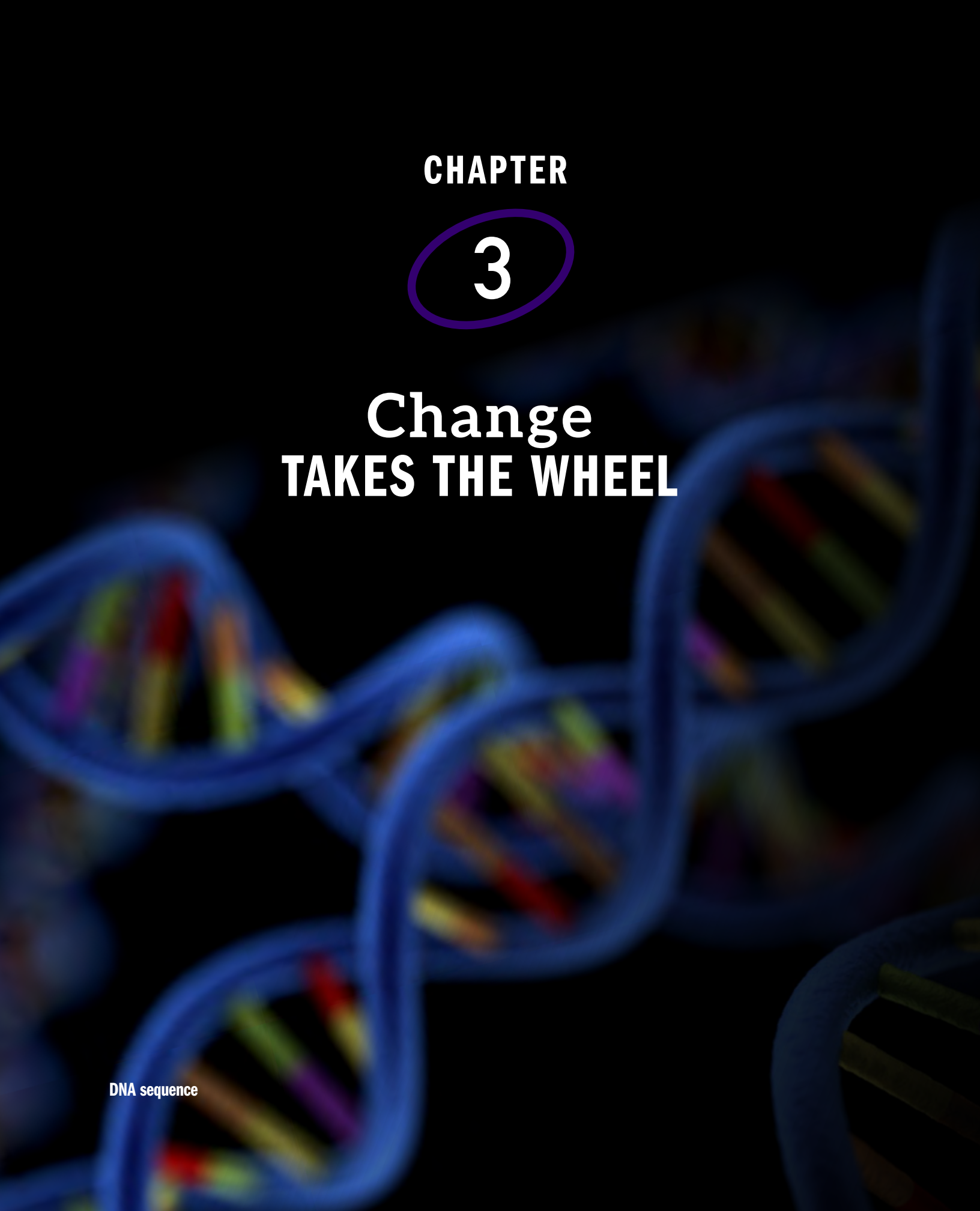
Cypess's notion that their collection represented containers of information, vessels of knowledge that could move science forward and expose the organization as a resource of standards, captured the board's interest. They offered him the job. But he still had reservations. "The calculation in my mind was: *Give me a five-year contract. If I don't get it figured out in three years, I'm probably not going to get this thing done.*"

To move forward, the ATCC board had demanded a new set of skills and vision for the institution. Cypess brought great experience and skill without necessarily knowing exactly how he would deploy them. The next phase would prove critical, with more fundamental change than the repository had seen in its nearly 70 years. Finding a new facility was merely the most urgent step. ATCC needed a new blueprint.

CHAPTER

3

Change TAKES THE WHEEL



DNA sequence

Raymond Cypess knew he had to immediately address major organizational challenges when he succeeded Bob Stevenson as director of ATCC in 1993.

Raymond Cypess accepted the ATCC board's offer of the director position. The question of who would wrangle the transitions facing the organization had been answered. The new challenge was that Cypess had to make the changes that he had proposed. At the start of 1993, everyone involved was headed for a tumultuous period.

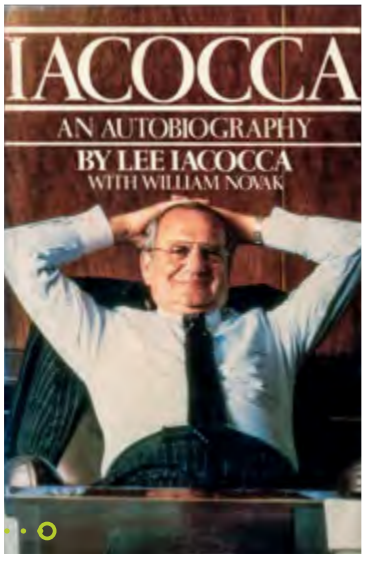
"The work is not glamorous and doesn't get much recognition," Bob Stevenson observed in his last Director's Note in the ATCC annual report. Stevenson acknowledged leaving major problems unsolved for ATCC, including finding a new home and resolving deep-seated financial problems. He likened ATCC to a football team's manager: They weren't out on the field making touchdowns, but they cared for the team equipment, tended to the players and suggested gear improvements to manufacturers. Unfortunately, this analogy widened the divide between research and support that Cypess wanted to bridge.

Wrapping up his work in Memphis as he prepared for the move to Rockville, Cypess faced serious questions. The biggest challenge was going to be changing attitudes within ATCC: The organization needed to lose its rearguard mentality and adopt a forward-looking approach. Still, Cypess knew that if changes happened too fast, it would cause panic; he couldn't afford to have the entire staff leave, or risk a mutiny from the board. To avoid inciting fear, the changes needed to take place at a measured pace.

The board had concerns about the transition and its risks. They were bringing in a new kind of CEO at a key juncture. Board member Elliot Levine appreciated the risk that Cypess was taking, leaving a tenured university leadership position for an institution that people likened to an equipment manager. "Our perspective was: It better work," Levine said later. A number of middle-management staff members who had been hired under Stevenson had become accustomed to Stevenson's style. "We foresaw that most of those people were going to leave on their own because Ray Cypess was such a different personality," Levine said.

One of the most formidable issues Cypess faced was the financial problem, for which ATCC had few potential solutions. Other culture collections had a parent organization that could shield them from financial hardship. Still other institutions, like the Coriell Institute for Medical Research, had boards composed of high-net-worth individuals who could endow a position or bequeath a legacy gift; by contrast, ATCC's board members were, in Levine's words, "a bunch of scientists who were probably making less than the ATCC director's executive secretary. Fundraising through the board was a nonstarter."

Facing the challenges head on, Cypess began to map out his approach. First, he surveyed the situation. "You landscape what your problem is," he said. "Then, after you landscape your problem, you figure out your plan, your strategy." Notwithstanding his wide-ranging experience managing varied staffs and institutions, Cypess realized that he had no formal management training for this kind of organization. So he did his homework, drawing inspiration from public- and private-sector leaders like Lee Iacocca,



Organizational management books like Lee Iacocca's bestselling autobiography helped Cypess prepare for his new role at ATCC.

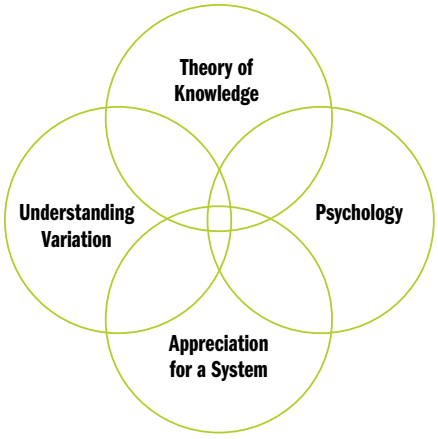
the longtime automotive business leader and Chrysler CEO whose 1984 autobiography was a national bestseller. Iacocca wrote, "In the end, all business operations can be reduced to three words: people, product, and profits. People come first. Unless you've got a good team, you can't do much with the other two" (Iacocca, 1984).

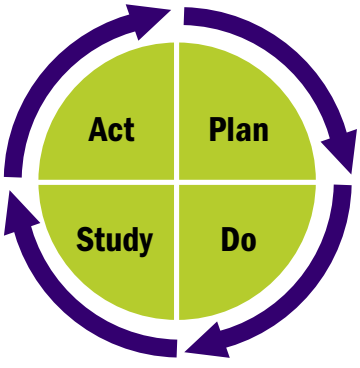
As a youth, Cypess went to work for his father at the bakery he ran. The elder Cypess introduced his son to the workers and what they did. When they encountered a baker who claimed "I've never burnt my fingers," Cypess' father would say, "Then you've never baked." The son absorbed his father's approach to management and an appreciation for the value of communicating with customers. "You have to understand where they're coming from, what their concerns are, what their budgets are, what their next purchase is going to be," he said. Customer attitudes should guide the business strategy for growth.

A bakery, for example, would sell various breads at a low price, even at cost, to gain a customer's trust. After establishing that relationship, you could sell them cake. From a first cake, the baker would then guide the customer toward a specialty cake, maybe an anniversary or a birthday cake. At that level, a bakery could have a larger profit margin.

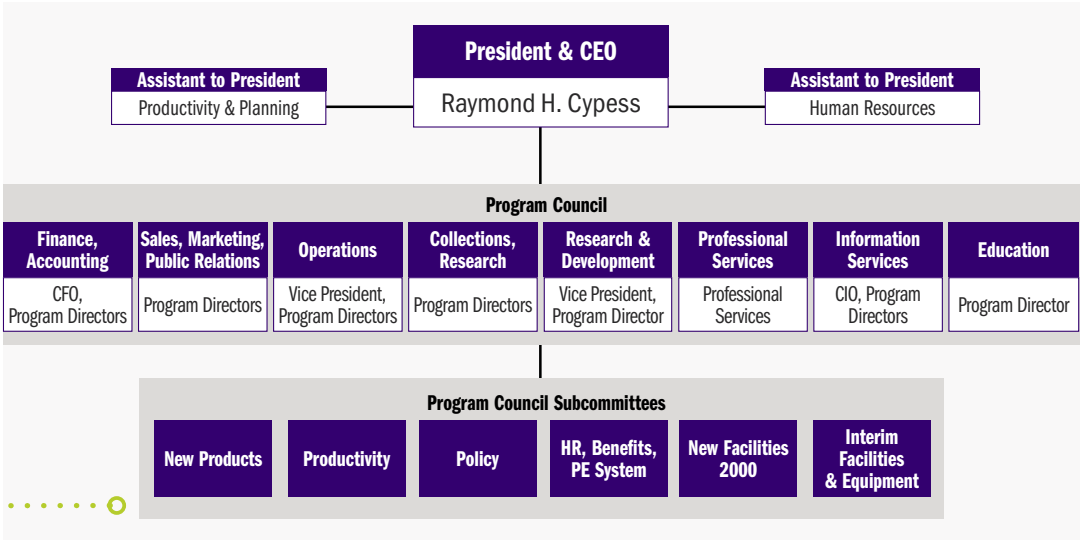
ATCC was not entirely different. Its catalog had more than 122,000 items and 4,000 cell lines, but most orders drew on only a small portion of that — roughly 10 percent. A for-profit enterprise would gradually remove many non-selling items, but from the start ATCC had a mandate to keep everything in the catalog available. What services could ATCC offer to cover the costs of the entire repository of "long-tail" catalog entries that were rarely ordered?

For another guide to this landscape, Cypess drew on W. Edwards Deming, the American engineer and process expert responsible for the principles of quality control that helped transform Japan's manufacturing economy in the 1950s. Deming's message was that with a focus on improving quality, organizations could reduce expenses and boost their productivity and market share. Quality was not necessarily an intuitive focus for a support institution in a setting where demand appeared fixed and inelastic, but quality control was what ATCC needed to do better. With improved service, it could create value in a space where clients did not expect it.





W. Edwards Deming's System of Profound Knowledge and Plan-Do-Study-Act Cycle provided inspiration for business leaders to transform organizations by reducing costs while increasing quality, customer loyalty, employee satisfaction, market share and profitability.



Supported by Nancy Wysocki, Cypess immediately began to transform ATCC's organizational culture and structure.

THE WORK CULTURE CHANGES

When he arrived in Rockville, Cypess addressed the pressing issue of human resource development. Even a bakery needed a plan for developing its human resources and the skills of its workers, yet ATCC had not been investing in its staff or team-building in that way. Cypess cites a key passage in a *Training* magazine article as particularly influential: "The principle of re-engineering, also called process redesign, holds that organizations must be reconfigured to do business more efficiently. Hierarchy is out, and empowered work teams are in" (Geber, 1993).

Cypess immediately put that principle into practice. In drawing up corporate goals for ATCC, he wrote: "Flatten the organization — encourage a team approach." In his first days on the job, Cypess made what he called the most important first move he could. "The first employee I hired was my head of HR, because we're dealing with human capital. It's all about human capital." Nancy Wysocki, a human resources expert previously with American Medical Laboratories, accepted the job.

Wysocki and Cypess set about asking basic questions concerning ATCC's work and its customers that would guide the new approach to human resource development. From the start, Cypess said this would involve a spotlight on productivity. He prepared to move people among ATCC's program areas "as needs arise," breaking down silos that had separated individual programs. This approach allowed management, for example, to shift a promising employee like Trish Slaski from the cell biology section, where she developed and documented cell lines, over into quality assurance and standards. Cypess also announced a productivity project to "not only increase our level of customer service and hone our competitive edge, but . . . eventually serve as a source for internal capital." These initiatives would mark a step toward less hierarchy and more of a team atmosphere (ATCC Annual Report, 1993).

Management did not sugarcoat these changes, emphasizing that making ATCC into a self-sustaining enterprise would require self-reflection and hard work, not vague hopes for outside help. "Stop looking for divine intervention or saviors from industry, agencies or scientific societies," Cypess told the staff. "You've got to help yourselves, so let's roll up our sleeves and get it done" (Mukhopadhyay, 2015). The implication was clear: *And if you won't do that, go! Because that's the new expectation here.*

This was not an easy message for staff to hear. For Slaski, a single parent commuting to ATCC's headquarters from Philadelphia, the prospect of big changes and reorganization at a time when ATCC staff already felt stretched was difficult. Everyone knew that changes were necessary. Slaski knew that ATCC had to find a way to become self-sustaining in order to expand and achieve financial stability. Even with that recognition, the first months with the new CEO were turbulent. "He was disrupting our little worlds," she said.

These changes hit hard for some of the science staff. For one thing, they now had to justify their budgets and plans for the coming year. One scientist told Simione, "Just give me a budget number and let me do my work." Simione replied that maybe a job in the government or academia would be a better fit. (Eventually that staffer took the suggestion.) Others balked at the notion of assessing return on investment for new acquisitions. In other words, ATCC would now consider whether a new strain would make the collection more useful to researchers. Some staff members had colleagues outside who wanted to deposit their microbes with ATCC and they resented having to apply this market standard to their friends' work. The plan for a new centralized unit that would consolidate similar production tasks across the divisions also caused friction; some insisted that only a trained mycologist, for example, could handle materials related to fungi, and they couldn't be handled by bacteriologists. In another policy change, staff scientists could no longer trade microbes with colleagues in other repositories.

Wysocki's most pressing task was to design a way to reclassify all the jobs in a system that included titles, position descriptions, compensation and a new performance appraisal methodology. The goal meshed with the strategy that Cypess outlined: to make ATCC's organizational structure more horizontal, "so that future promotional opportunities would be based on acquisition of skills and job duties, as opposed to time in service," she said. Wysocki's team achieved this reclassification by implementing a "broad banding" system for jobs: a job-grading structure with wider salary "bands" than a typical salary structure. In other words, the new system widened the view across departments to bring disparate salary levels into a shared frame. Broad banding would streamline ATCC's hierarchy, add transparency, and with its clarification of skills and terms across departments, promote movement within the organization. Wysocki also established performance reviews based on staff members' annual goals and 360-degree feedback, meaning that an employee's immediate circle of colleagues contributed to the assessment.

Meanwhile, management had to define the HR skills that ATCC needed in order to accomplish its priorities. Wysocki worked on creating an integrated HR/payroll computer system for collecting, tracking and reporting on progress. All of this represented a vast organizational leap forward. When Wysocki arrived, the only HR tools were paper records and spreadsheets.

Wysocki's team integrated new training and development goals into the annual performance goals. For example, staff members with management responsibilities would receive mandatory training, which Wysocki developed and presented. All new employees received a formal orientation, which reinforced the mission and vision of ATCC along with training in key policies.

One visible element of the productivity effort summed up the new atmosphere. It was a small lapel button that each staff member received: light blue with a capital Y followed by a question mark. It signaled constant questioning of the status quo, reminding everyone to ask themselves on a daily basis: Do I need to do this task in this way? Why? Could this task be done better?

The "Y?" lapel button reminded ATCC to constantly question existing organizational practices and seek better solutions.

These changes met with much resistance. Wysocki responded by holding quarterly meetings where she provided progress reports and answered questions for staff members. Some of them voiced concerns that became familiar: science staff felt they should be dedicated solely to research and not concerned with business issues, or as they said, "the company's profit and loss." They considered ATCC's mission to be a public service of science. They wanted continued government funding and didn't accept the shift. Wysocki "slowly chipped away at this mentality by hiring from the business world," she said.

THE LANGUAGE CHANGES: INTRODUCING A BIOLOGICAL RESOURCE CENTER

Coming to ATCC, Cypess recognized how much the language of different scientific disciplines reinforced restrictive silos and the mindset of a static repository. Disciplines need specialized terms for internal precision, of course, but scientists also needed a vocabulary that crossed disciplinary lines for talking about shared objectives. Cypess knew that language had the power to inspire action or cause paralysis. Growing up, he was stirred by radio dramas and comedies, from *The Green Hornet* to comedian Jack Benny, who had moved millions of listeners to laughter. Benny's timing and precision were a bright spot for Americans even in the darkest hours of World War II. Yet in the workplace, this power often remained unacknowledged.

Cypess realized that to engage people's energies fully during this period, management had to adjust the language at ATCC. For too long, the staff had accepted outsiders' description of ATCC as a "germ library." Cypess focused on a term at the core of ATCC's identity as a place to start: *culture collection*. "I had to get rid of that term [culture collection] pretty quickly because it has a negative connotation to me and to a lot of other people in the world of science," he said. With Judy Vaitukaitis, then the head of the National Center for Research Resources at NIH, Cypess adopted the term *biological resource center* to emphasize a more dynamic institution — not simply a repository but a resource for sourcing, authentication, preservation, manufacturing and standards (Mukhopadhyay, 2015). The new term replaced the narrower technical term "culture" with the broader frame of biology. In short, a biological resource center was a place for problem-solving in science.

Some board members immediately grasped the change and embraced it. John Child regarded the new term as an important shift. "*Biological resource center* is a broader term that says, 'Instead of a passive process of maintaining a freezer full of cultures, we're addressing the international community and developing the organization's capacity.'" The new term represented a more proactive outreach process. Keith Bostian agreed; later, it struck him that Cypess was among the first to use the term. "It was not a prevalent notion at the time and didn't resonate with many in the field at first," Bostian said. "Now it's much more recognized." For David Gillece, who served as the company's relocation consultant, *biological resource center* meant growth and transformation with an expanded view of the services ATCC could provide for the scientific community. "*Collection* feels like a museum," Gillece said. "The new term feels like a university."

David Gillece

To reinforce the focus on solutions and client needs on a daily basis, Cypess preferred to speak of ATCC as the "company," unusual for a nonprofit. "It didn't go down well," Slaski said. "There was resistance. Change is always threatening." Some managers felt protective of their units and didn't want to see them "distorted" by business calculations. "Some feared that we would lose our mission," she added.

Cypess and Wysocki weeded out other vague or outmoded terms in the workplace, especially in job titles. Cypess bristled at the title "curator," which reflected a role that harked back to C.E.A. Winslow. By the 1990s, the terms *curator*, *culture collection* and *repository* were regarded among biological researchers as passive terms. To spell out the distinction between *culture collection* and *biological resource center*, Cypess developed what he called a "new DNA" for ATCC — a shorthand statement of its core features, articulated as AAPPDD.

A – Acquisition
A – Authentication
P – Production
P – Preservation
D – Development
D – Distribution

Each letter represented a business unit within the organization. *Authentication* involved the science of standards. The first D — *Development* — was crucial, Cypess said: "If you don't do development, you don't get any respect. If you want respect and you want to attract people, you have to have an R&D activity in science." The DNA-like articulation spelled out both what was retained and essential since

the organization's founding, and what was a new emphasis. Development and distribution were essential functions that had previously been implicit or simply ignored. In the new era they would be valued.

THE BOARD CHANGES

Soon after Cypess arrived, John Child noticed that board meetings began to follow a different structure. As someone who felt like an outsider on the board for not having a Ph.D., Child was mindful of these changes. "If you change too much too fast in an organization like that, it just dissolves," he said. However, the board struck him as a necessary starting point for progress, so he agreed to work with Cypess to make the board more manageable, in line with boards of other organizations. They created a scientific advisory board as a way to keep certain board members engaged but reduce the core size. They also created a fiduciary responsibility board. These changes helped to bring the governing board's size down to what Child considered a manageable one for tackling operational issues.

John Child

The board was distilled from more than 30 members to a dozen. Members no longer had to represent the various professional societies that had established ATCC. The new body would be made up of qualified people from different parts of the scientific community, both public and private. "So we'd have business people, scientists, insurance people, HR people — a real board, with terms," Cypess said. He identified a core group of people who understood the organization's needs along these lines, and together they worked to get the changes passed by majority vote.

The philosophy of taking a wider view for diagnostics and problem-solving helped to steer the group away from the narrow debates that previously could sidetrack the board's discussions. Cypess liked to tell people, "Operate at a height of about 10,000 feet so you can really get the big picture. But when you land, land hard. Get very analytical, focus in on what you have to do." Like Lore Rogers before him, he knew the risk that people could get lost in details, in becoming "a specialist on small molecules on the head of a pin." ATCC had to think more nimbly to grasp the changes that were driving the bigger picture.

THE SCIENCE CHANGES

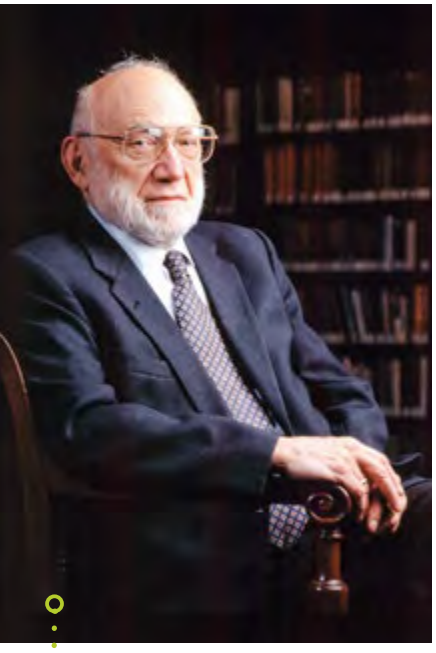
With the rise of genetic fingerprinting and rapid advances in biogenetics, DNA sequence information and computational analysis were growing more important than

In the mid-1990s, ATCC's board of trustees was reorganized to better meet the needs of governance, scientific oversight, planning and fundraising for the organization.

cell lines for discoveries in biology. In the early 1990s, gene therapy and genetically modified foods were becoming more common. James D. Watson, the Nobel-winning decoder of DNA structure, headed up the Human Genome Project for NIH in 1993. That project had a goal of identifying the many thousands of human gene sequences and detailing their makeup with breathtaking speed. The target for completing this feat, the year 2005, was as bold as President John F. Kennedy's pronouncement in his inaugural address that an American would be on the moon by the end of the 1960s.

Rapid advances in microbiology and ambitious new projects like the Human Genome Project forced ATCC to reevaluate its business model and goals.

Keith Bostian began attending ATCC annual meetings as a representative of the American Society for Microbiology in the early 1990s. Since moving from basic research to pharmaceuticals work in the late 1980s, he had worked to introduce industrial innovations and analytical methods to the Society's approach to research. Breakthroughs in the lab were changing processes for developing new products. He wrote in *ASM News* that culture collections had made valuable contributions to microbiology over the decades, but now those collections needed to face a new, ever-more-powerful era. That era integrated genome science with ecology, systematics, molecular evolution and microbial chemistry. The changes could be devastating or they could spell



Joshua Lederberg

opportunities. To determine which side of that line they came down on, collection managers needed to consider fundamental questions: Should they shift their goals to another objective, such as inventorying and ensuring biodiversity? What would happen to smaller collections like the one assembled by Selman Waksman, whose work led to the discovery of important antibiotics like Streptomycin? What about the soil fungi collection gathered by Martha Christensen (Bostian, 1994)?

Cypess found these changes in biology compelling. He had seen them coming in the years he served on review panels for NIH research proposals, a task that demanded a lot of time but rewarded panelists with a window on the scope of research being conducted across the country. Furthermore, experience in entrepreneurial research at Cornell gave Cypess a sense of how the changes might be navigated. As a consultant to companies in diagnostics and microbiology, he saw how the opportunities for integrating public and private research could prove fruitful at ATCC. But addressing the questions posed by Bostian required changes in the organization's capacities. The state of practice in culture collections had fallen behind the state of the art, and in areas such as authentication, development of new lines and thorough characterization, ATCC had some catching up to do.

TAKING A CUE FROM SPORTS BUSINESS

In 1993, Washington, D.C., newspaper headlines bubbled with provocative statements from the sports team owner and entrepreneur Jack Kent Cooke. He was threatening to move the Washington Redskins to a new home outside the city. For decades, the team's home had been the Robert F. Kennedy Stadium in Southeast Washington. The public viewed any move as betrayal. Cooke was creating headaches with his talk about finding a less expensive team home in the suburbs. Cypess followed the story as it unfolded, fascinated by what he considered an "extraordinary battle" between Virginia and Maryland to win with the Redskins. "I said, 'This is interesting that they're fighting so hard for the Redskins. Would they fight for something else if they felt it was important?'" It planted the seed of an idea that would take time to explore.

Many questions remained for ATCC's future, and the stakes were high. Around this time, Cypess was haunted by an exchange he had with Joshua Lederberg, the Nobel-winning molecular biologist and a member of ATCC's board. In one of their frequent meetings, Lederberg looked at the new CEO. "ATCC is essential to the scientific community," he said. "Don't let it fail, Ray."

FROM CELL CULTURE TO A POST-GENOMIC ERA

Genomic biology emerged in the early 1990s as the path toward faster medical advances, at a time when culture collections were struggling to find new relevance. It was like a new age dawning, with epic-scale questions. "Genetic engineering has raised more ethical concerns than any other technology before it," the *Chicago Tribune* warned (Gorner and Kotulak, 1990). Researchers were rushing to patent genes as soon as they decoded their chemistry, even when, as the *Washington Post* wrote, they didn't "have any idea of what role most of the genes play in the body or how they might be useful in fighting disease" (Herman, 1992). Scientists saw perils in this patenting rush, asking, "Where is the boundary between fundamental knowledge and those useful inventions that patent law properly protects?" In other words, how did new genetic information compare to the categories of information already subject to intellectual property?

Through the 1990s, the confluence of genomic sequencing (with genotypic and phenotypic analysis and chemical synthesis) and advances in informatics and analytical power yielded a new order of tools for understanding biology at the subcellular level. It was a "renaissance in comparative and population genomics, evolutionary biology, global biodiversity, and environmental sciences," wrote Keith Bostian. That renaissance opened doors across science and business: not just new vistas for the pharmaceutical and biotech industries, but also for chemistry, energy, agriculture, and the environment sectors. This sea change was fundamentally redefining the role of biological resource centers (Bostian, 2003). Looking across species and taxa, ATCC's leadership saw that genomic research made possible the ability to predict molecular functions through computational analysis with unprecedented scope.

Twenty years later, big-data computational analysis accelerates the process of identifying new drugs. Gene sequencing is common. "It's a complete paradigm shift, that computational shift to a meta-genomic space," said Bostian, now dean of the New Jersey Center for Science, Technology and Mathematics and the Office of Technological Commercialization at Kean University.

Genomic sequencing together with advances in informatics led to a renaissance across science and business that redefined the role of biological resource centers.

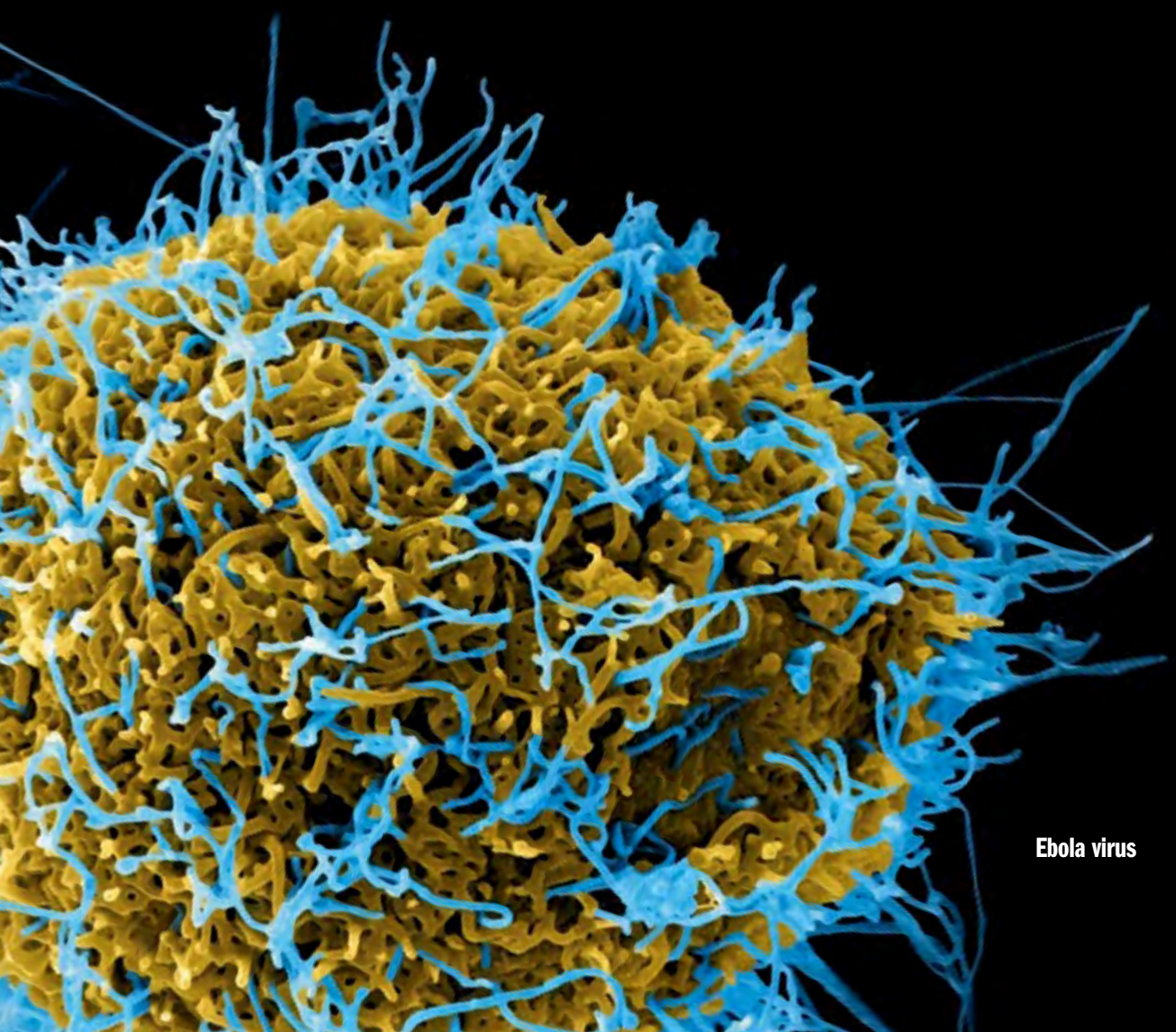
Take the discovery of natural product drugs, for example. Previously, biological research explored genetic and biochemical mechanisms using a reductionist approach of isolating new compounds one at a time (Bostian, 2003). Sequence-based biology created a dramatically more efficient framework where large-scale data analysis runs in parallel, followed by targeted experimentation. Today, a researcher can sequence thousands of organisms and predict a novel metabolite. The genomic approach and DNA sequencing facilitates design for novel organisms. The bottleneck is no longer the search process but the analysis of sequence information (also called annotation).

The challenge now is to create analytical approaches so streamlined that a bench scientist who wants to design a new experiment for discovering a compound can access those tools and use them. For resolving the analytical bottleneck, Bostian says, centers like his at Kean University are working with ATCC to move from a decision to sequence to the curation of organisms annotated in just one or two weeks.

CHAPTER

4

Shifting Winds
OF SCIENTIFIC ENTERPRISE

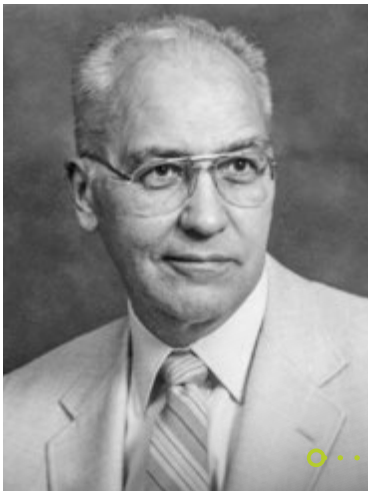


Ebola virus

Anne Vidaver

The American economy was emerging slowly from recession in the mid-1990s, but culture collections continued to struggle with financial instability. In March 1995, several dozen representatives of these repositories gathered in Washington, D.C., at the National Academy of Sciences (NAS) for some soul-searching.

"The future of collections is not yet in a state of crisis, but we share a concern," said Anne Vidaver of the University of Nebraska. She and her colleagues, including ATCC managers, made the case that culture collections were important for the future of biodiversity — as important as field research, which was considered far sexier. Roger Goos of the University of Rhode Island grumbled that policymakers who were slashing budgets were overlooking the value these collections had demonstrated over the past 70 years: "Something seems inconsistent to fund initiatives for global biodiversity if we can't find money to preserve the microbial biodiversity we already have in hand" (ASM News, 1995).



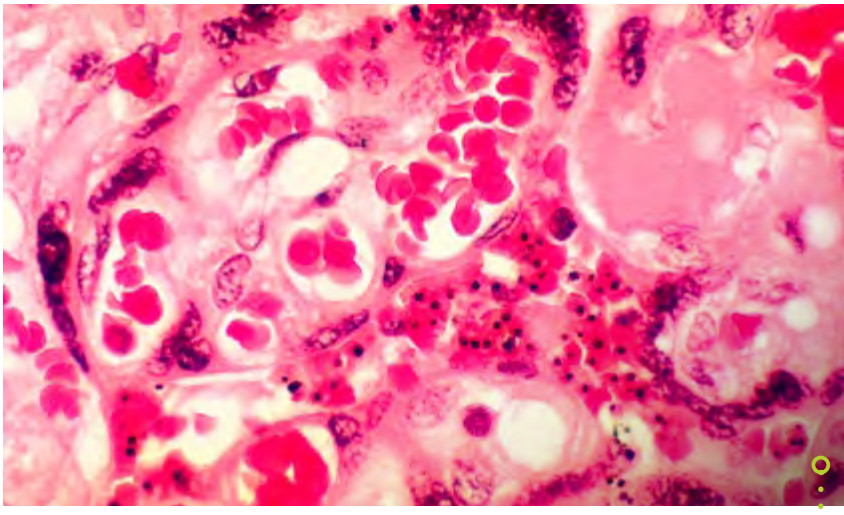
Roger Goos

Even advocates for culture collections at that NAS meeting acknowledged the challenge of crafting a winning strategy in the face of indifference to scientific infrastructure funding from Congress and the public. "There's no petting zoo, no feeding time for the rickettsiae, no rides on the amoeba," Joan Bennett of Tulane University said despairingly. "The proverbial guy on the street just doesn't have a clue . . . making it extremely difficult to translate what we're trying to do for the people who provide funding." As universities and federal agencies tightened their belts, they often regarded collections as organizations not utilizing cutting-edge science and technology. Private companies as well as scientific societies were reluctant to directly support specialized collections financially. Furthermore, as Raymond Cypess observed at that 1995 NAS gathering, the tradition of sharing through donation of biological materials to collections had ended with the change in commercial value of biomaterials. The shifting attitude toward donating to nonprofit collections was undermining their efficacy and, more broadly, the authentication system. "Now there is a black market for biological materials as, increasingly, non-standardized materials are being exchanged," Cypess said (ASM News, 1995).

Joan Bennett

In this unpredictable environment, change at ATCC could not succeed using small, incremental, methodical steps. Board member Elliot Levine watched the approach evolve gradually. ATCC attempted new arrangements to uncover a deeper pool of resources and clarify ATCC's value proposition. Not all of these new efforts bore fruit, but the experimentation was essential. "This willingness to experiment, to try things

that others wouldn't try — the ability to be eclectic and to connect this field to other fields — was very, very important," Cypess said. "Equally important, financial models for collections suggested that public resources could not fully serve their mission without being subsidized," he added.



***Plasmodium falciparum* in placental tissue.**

AN OPENING WITH MALARIA

One opportunity appeared in an unlikely corner of international health: malaria. The National Institutes of Health had long partnered with the World Health Organization and other countries on global health, an area supported by ATCC's collection. Cypess, with his experience as a post-doc in the School of Public Health at the University of North Carolina and as a faculty member in the School of Public Health at the University of Pittsburgh, regarded himself as "a public health guy," with a perspective that focused on the population level. One of the leading problems in global health for generations was the scourge of malaria, which killed millions every year and remained stubbornly resistant to efforts to control it. Decades of work on a vaccine had been maddeningly ineffective. WHO categorized malaria as a neglected tropical disease, one of 17 bacterial and parasitic infections that sickened more than 1 billion people worldwide yet were under-researched because their sufferers lived mainly in developing countries. Like the other neglected diseases, malaria had an impact on families that perpetuated a cycle of poverty and was far more devastating than the accumulation of individual cases (Malaria Consortium, 2015).

Malaria's intricate life cycle and tendency to mutate had stymied treatment efforts and work on vaccines. The complex dynamics involve, to a larger and lesser extent, the four species of malaria — *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium ovale* and *Plasmodium malariae* — and the female *Anopheles* mosquitoes that deliver it to humans. The complexities of the disease cycle hampered efforts to use computer simulation modeling to grasp the disease's patterns (Taylor, 2011). One problem was the state of the global research infrastructure, both in countries where the disease was no longer endemic, especially the United States, and countries where the disease was epidemic. Researchers needed materials to work with: the mosquitoes that transmitted the disease, the life cycle stages, reference samples and more. But because malaria had been eradicated in most developed countries, the medical community didn't have ready access to those tools and reagents. As a result, nearly half the world's population was vulnerable to malaria, with young children and pregnant women the most susceptible. And in the 1990s, the disease was becoming still more difficult to control (Varmus, 2014).

***Anopheles* mosquito**

When Harold Varmus became director of NIH in 1993, he brought a commitment to global public health. Varmus, who had won the Nobel Prize for discovering the cellular

John LaMontagne led research efforts to combat malaria, HIV/AIDS, and tuberculosis in Mali.

origin of retroviral oncogenes saw that just as biological systems followed universal laws that crossed borders, research was essentially international, too, and multi-country collaborations should pursue the goals of disease prevention and treatment shared by all. To grow a cohort of skilled malaria specialists in Africa, NIH co-sponsored a meeting in West Africa. There, Varmus found a dynamic dialogue among scientists from Africa and Western countries who engaged on an equal footing to consider ways to defeat the disease together. The trip allowed Varmus to visit a malaria research center in Bamako, the dusty capital of one of the world's poorest countries, where Malian researchers who had grown up in villages without electricity worked hard to build a scientific effort to combat one of the world's most difficult diseases. Varmus returned home committed to supporting their effort (Varmus, 2014).

Around that time, Cypess proposed a model for creating a U.S.-based malaria research center with the Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases (NIAID). NIAID program officer John LaMontagne saw the benefits of the model and having ATCC participate in this important effort. With LaMontagne's encouragement, Cypess teamed up with the CDC and assembled a proposal. Their plan offered the global research community access to certified materials and systems for studying malaria. "The hypothesis was if you did that, you would attract researchers to the field who couldn't enter the field before because they didn't have the materials," Cypess said. Also, at that time the Clinton administration was looking for a way to demonstrate to the international community that the United States was serious about tackling a top priority in global health. The timing for the proposal was perfect.

MR4 logo

The result was the Malaria Research and Reference Reagent Resource Center, known as MR4, an $11 million NIAID initiative. MR4 acquired the parasite, vector and host cell materials needed for malaria research; ensured they were characterized and authenticated; and provided malaria researchers with the malaria reagents, information and training. ATCC authenticated more than 175 reagents using data from donors and publications, and shipped materials requested by malaria scientists worldwide. MR4 charged only shipping costs and helped scientists far from well-stocked libraries to find outlets for sharing their research findings (ATCC Annual Report, 1999).

In the partnership, the CDC provided the mosquitoes, a critical link in the malaria life cycle; and NIH provided the community of researchers. MR4 reached scientific

GROWING MALARIA RESEARCH TO BEAT A SCOURGE

Malaria culture — growing malaria parasites in an ex vivo setting — eluded scientists much longer than most diseases. Researchers tried to culture malaria as early as 1912, but they could not sustain the microbes beyond a few life cycles. Malaria resisted successful culturing until 1976. Even that breakthrough, however, did not yield a vaccine. Moreover, the illness was entrenched in many geographies by the difficulty involved in changing the behaviors that made people vulnerable. By using a mosquito net for sleeping, parents could drastically reduce children's vulnerability to contracting malaria. However, in many tropical countries, generations had suffered chills and had died of malaria — so it was understandable when people asked: How could a flimsy mosquito net change that history?

With MR4, ATCC fostered greater understanding of the Plasmodia and the other links in malaria through its training and documentation of how to cultivate isolates and freeze them for identification and study (Ljungström et al., 2004). Then in 1999, another NIAID-led effort yielded the first high-resolution genetic map of the *Plasmodium falciparum* parasite.

When MR4 began, there had been approximately 200 researchers worldwide actively engaged with malaria studies and the ATCC collection. Within a decade, that figure quadrupled proving the hypothesis underlying the model. The boost in malaria research was a factor in one of the most important world health stories of the past 20 years: the reduction of malaria deaths worldwide (WHO/UNICEF, 2015). Between 2000 and 2015, the rate of new malaria cases fell by 37 percent globally, and malaria death rates dropped by a stunning 65 percent among children under the age of 5. In 2015, WHO estimated that the effort has prevented some 6.2 million malaria deaths globally. That includes saving the lives of about 5.9 million children (WHO, 2015).

communities in regions of the world where malaria was the leading killer of children under the age of 5. "The program was a world resource, which was very important," Cypess said, "and a model for integration of infrastructure from government agencies and nonprofit organizations."

CREATING A NEW LEVEL OF SERVICE

The contract with the CDC and NIAID on malaria research led to other opportunities for collaboration and a much-needed expansion of ATCC's network and value. ATCC signed agreements to distribute DNA with the Integrated Molecular Analysis of Genome Expression (IMAGE) consortium. It also received a four-year NIH grant to develop a course on the genetics of disease (ATCC Annual Report, 1995).

By 1997, government subsidies for core collection activities had decreased to 9% of ATCC's total revenue (ATCC Annual Report, 1997). The organization needed

"When Republicans took control of Congress in 1995, they skeptically scrutinized the institutes' budget and told scientists to expect substantial cuts. . . . But Speaker Newt Gingrich and other Republicans have become strong supporters of the agency, in part because they see it as an engine of economic growth."

"BUILDING BOOM AT INSTITUTES OF HEALTH," THE *NEW YORK TIMES*, NOVEMBER 1, 1998

The five-year contract to manage the CDC and ATSDR Specimen Packaging, Inventory, and Repository (CASPIR), pictured here, jump-started ATCC's biorepository management services program.

capital from other sources, and it needed to build its business not just on its products, but on the quality of its services, information and staff. An example came in a phone call that Cypess received from a CDC colleague, concerned about a particular collection that the agency maintained in Atlanta. There were questions about what the collection held, its authentication, and even how to catalog it.

Cypess traveled to Atlanta to have a look. He indeed found problems in the documentation, in the process, and in the facility. After a competitive review process, the CDC engaged with ATCC to put in place a system for consolidating and managing all the materials at a facility in Lawrenceville, Georgia. The contract was to manage specimen packaging and inventory for the collection that the CDC shared with the Agency for Toxic Substances and Disease Registry, an effort involving nearly 200 liquid nitrogen freezers and two cold rooms (ATCC Annual Report, 1997).

The arrangement took months to finalize, but the $4.6 million contract with the CDC was ATCC's first agreement for repository management at an external site in its history. This milestone marked a new level of capacity for the organization. "Clearly this contract heralds new opportunities available to ATCC in the area of management services," Cypess said in the ATCC newsletter, in praise of the team that had won the contract (ATCC Connection, 1997).

THE PERILS OF BIOSAFETY REDUX

Four biosafety levels (BSL) exist for handling biological agents such as microbes in the laboratory, from safe BSL-1 to contagious and untreatable BSL-4. (BMBL, 2009). ATCC handles microbes in the first three levels. In the United States, the CDC determines the levels and accompanying precautions. Class 3 includes West Nile virus and Hantavirus, a deadly dustborne virus first detected in the American Southwest in 1993. Class 4 includes Ebola, smallpox, hemorrhagic fever virus and chikungunya virus. By 1995, ATCC had worked with more than 3,500 customers that had Class 3 compliance; it had holdings of 33 viruses, nine bacteria and two fungi in that class, plus 11 rickettsia.

In 1995, ATCC experienced an echo of the 1984 botulism episode when unauthorized buyers had attempted to purchase cultures illegally. This time, a man in Columbus, Ohio, named Larry Wayne Harris placed an order for *Yersinia pestis*, the bacterium that causes the deadly bubonic plague. When the order was delayed, he telephoned ATCC, where a technical services representative tracked the order. While they were on the phone,

Larry Harris claimed that he needed *Yersinia pestis* cultures for experiments on kangaroo rats.

Harris described his research: It involved the kangaroo rat of California, which Harris thought carried an avirulent strain of *Yersinia*. He wanted to test his theory by infecting some kangaroo rats with the virulent strain from ATCC.

***Yersinia pestis* bacteria**

The purchase order had come on letterhead from an accredited registry and an Ohio EPA approval number, with a certificate from the American Academy of Microbiology. But Harris' story raised red flags for the technician on the phone, and the technician reported the conversation to his supervisor. On that Wednesday, ATCC went to the CDC with concerns about Harris' research; the next day, an official with the Plague Section of the Division of Vector-Borne Infectious Diseases at the CDC's Fort Collins branch in Colorado determined that Harris' scenario of plague among kangaroo rats in the Southwest was a fiction. Follow-up calls revealed that Harris' "lab" was a room in his basement (and occasionally at the water-quality lab where he worked). Harris seemed to know enough about the microbiology to grow the cultures in his home, a potentially hazardous situation. An ATCC representative faxed the documents to authorities; it turned out the certificate and EPA number were fraudulent. Meanwhile, FedEx had delivered the package Thursday morning.

Frank Simione received a call late that Thursday afternoon, informing him that police in Ohio were examining the case. A few hours later, Simione's pager buzzed. Soon, a captain with the Ohio Police Department was explaining that the state prosecutor had probable cause to execute a search warrant and wanted advice about the plague cultures they were going to retrieve. What might they find when they got to Harris' basement? Simione described the cylinder containing three small vials of freeze-dried specimens of bubonic plague strain, and explained that the specimens would require specific reconstitution measures and time before they could become a health hazard. The next day, Simione's pager buzzed again from ATCC's emergency voice mail system. The Ohio Public Health Department had sent a hazardous materials team to the house and they had seized the cultures, still in the unopened metal cylinder. Should they be looking for anything else?

Under a plea agreement, prosecutors arranged for Harris to receive a sentence of up to six months in prison. But that agreement was dismissed by a U.S. District Court judge, so the case went to trial. In the end, Harris was sentenced to 18 months of probation and 200 hours of community service. But as in the 1984 case, the episode stirred questions in the press: Why wasn't the punishment more severe? How could someone unauthorized order a dangerous microbe? The case led the CDC to re-examine the domestic regulation of human pathogens.

At the board's request, ATCC staff developed a risk management program and created a more robust program for managing and shipping materials with appropriate safeguards. The team proposed extra measures to ensure that ATCC was not providing potentially dangerous materials to unqualified individuals. The Material Safety Data Sheets for all products would be bolstered with written warnings spelling out in greater detail their potential hazards, dangers and illegal uses. Screening procedures for new clients were codified. The consistent issue was how to balance two competing interests: preventing unauthorized shipments and serving legitimate customers with speed and courtesy (*ATCC On the Move*, 1995).

LEVERAGING A LIABILITY INTO A BIDDING WAR

Finding a strategy for capitalizing ATCC's infrastructure was a priority for Cypess from his first days in Rockville. But with a board largely made up of academic scientists who were unable to drive fundraising, where would the capital come from?

There were few examples in the realm of nonprofit science. Instead, inspiration came from news headlines. Intrigued by the elaborate negotiations involved in relocating the home of the Washington Redskins, Cypess decided to put out feelers to see if a similar bidding process could possibly work for a much less attractive public asset, such as a biotechnology facility. Was there a precedent? What were the risks? The exploration could backfire and leave a bad taste in the mouths of local officials and dig an even deeper hole for the organization. Yet ATCC board member David Gillece agreed that the first step was to test the market and see if a state or county would be willing to contribute to the costs of building a new facility.

In a first volley, local officials in Montgomery County prematurely claimed a victory, announcing the county had kept ATCC's 225 jobs from leaving (Montgomery County Business View brochure, 1994). But then discussions with the county stalled, and in July 1994 Gillece approached Maryland's Division of Business Development to see if the state could provide more substantive resources than the county had. Gillece wrote, "Reluctantly and regrettably, I am left with the unavoidable conclusion that ATCC is more likely to find a home that makes financial sense elsewhere" (Gillece letter, 1994).

To make the case that ATCC was an asset to any local economy, the leadership team emphasized the forward-looking appeal of biotech and life sciences and their prospects for attracting a highly skilled work force and raising the county's profile. "I sold smoke and mirrors," Cypess said of his marketing efforts with Maryland, Virginia and several other states. "They didn't know how bad the situation [involving ATCC's finances] was. The future was bright if you could turn it around."

As with the MR4 proposal, the timing was perfect. With a 1994 statewide election in Maryland heating up, legislator and gubernatorial candidate Ellen Sauerbrey saw she could gain support for her campaign as a job creator if she kept ATCC in the state.




Virginia Govenor George Allen (left), George Mason University President George W. Johnson, Prince William Board of County Supervisors Chairman Kathleen Seefeldt, and Secretary of Commerce and Trade Bob Skunda persuaded ATCC to relocate to Virginia.

In November, as Sauerbrey campaigned in the final sprint of a tight race, Cypess received a letter from her that stated, "When I ultimately am declared Governor please be assured of my pledge to do all that I can to assist in retaining the ATCC in Maryland" (Sauerbrey, 1994).

However, Sauerbrey lost the election and the new incoming governor, Parris Glendening, showed up at ATCC's board meeting two days after the election. By then, other states had come forward with more competitive offers. Michigan and Virginia appeared the most promising. Cypess visited Virginia's capital several times to make his case to the state's top officials. He gradually persuaded Governor George Allen, along with Secretary of Commerce and Trade Bob Skunda and George Mason University President George W. Johnson, that ATCC would be an attractive win for the state.

"I recognized an opportunity for Virginia to build a strong biotechnology component to our overall economy as I became involved in the recruitment of ATCC to Virginia," Allen wrote later. The state would provide ATCC and the county "substantive assistance because they were a tremendous national leader and prize employer. ATCC is a world-class organization with an exemplary safety record and a history of being a good corporate citizen" (Allen, 2005). In the process of negotiation with Allen and his state and local team, a personal chemistry developed between Allen, his team and Cypess, which has endured.

In December, the Washington Post reported that ATCC had decided to relocate to Prince William County in Virginia, declaring that the move "opens a new realm of corporate recruitment opportunities to a county starved for white-collar jobs. . . . In one leap, ATCC becomes Northern Virginia's largest biotech employer" (Hsu, 1994).

Prince William County approved a package of $950,000 for a 26-acre site and architectural plans to lure ATCC across the Potomac. Local politicians voiced the hope that ATCC's presence would boost jobs around Manassas and improve the

technology capacity of nearby George Mason University. Other incentives directly from the state brought the subsidy deal up to a reported $16 million (*ATCC Quarterly Newsletter* No. 3-4, 1994). The investment proved to be correct. Through the years, ATCC added significant jobs and served as a flagship catalyst for Innovation Park in Prince William County and as an active contributor to the local community.


ON THE MOVE

The Manassas Relocation

A new internal newsletter kept employees abreast of the move.

FROM THE FRYING PAN

The announcement resolved a major dilemma in ATCC's survival. It opened the way to a growth strategy and a business plan that focused on four major areas: collection research services, information services, professional services and education services. Revenue from the sale of the old facility in Rockville could go toward expanding the growth areas of microbiology and cell, molecular and developmental biology. A new, more efficient facility would make ATCC more competitive on several levels. In that description of the deal, too, the language was starting to change, in describing ATCC as "the world's most diverse collection resource" (*ATCC Quarterly Newsletter* No. 3-4, 1994).

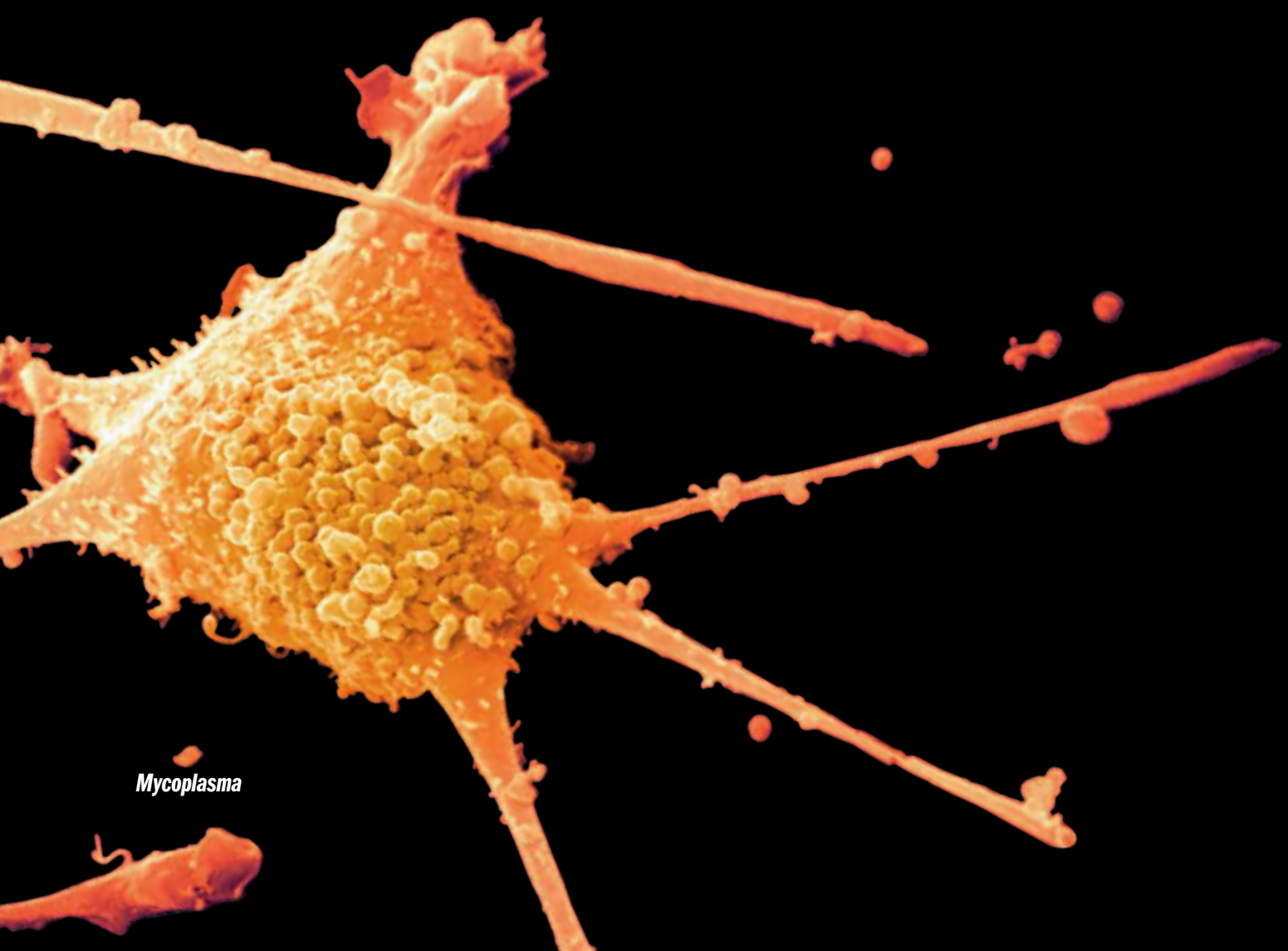
The move to Virginia would be the largest relocation in ATCC's history. From the start, the prospect created anxiety for everyone involved. To quell the buzz of nervous rumors, management started an internal newsletter devoted to news about the move. "While it is natural for employees to be anxious about how the move will affect them," the newsletter's first issue cautioned, "you are urged not to take every rumor at face value." Wysocki installed a question box for staff members' use. Future newsletter issues would contain responses (*ATCC On the Move*, 1995).

Planning for the move took months. As moving day loomed, even the most sanguine board members confessed to nerves. The days when Lore Rogers could pack the entire collection in a suitcase were long past, and even that had posed hazards. Elliot Levine, familiar with the challenges of maintaining the freezer in a small lab's collection, knew enough to be scared. "I was shaking in my boots about ATCC," he said. "They're going to put these things on a truck? Then they're going to travel from Rockville to Manassas? I expected to see headlines: Biohazards Spilled All Over Virginia."

CHAPTER

5

Bioresourcing
IN AN ERA OF TRANSFORMATION



Mycoplasma

As ATCC prepared to leave its Rockville facility in 1997, new technologies were adding to the array of tools that could help the organization grow in new ways. Biogenetics was evolving, and ATCC was beginning to probe the information encoded in the biological materials of its collection. These new technologies would come into play in the shift to its new location.

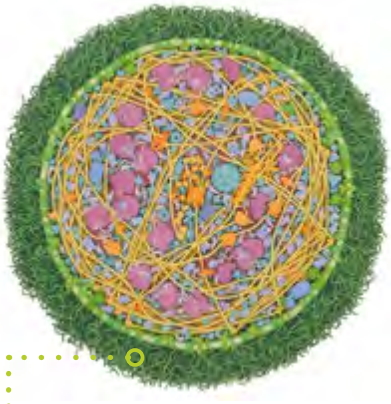
For example, ATCC's mycology program with the U.S. Department of Agriculture was using high-resolution DNA fingerprinting to compare cultures. Using DNA identification to distinguish individual strains was vital for quality control. DNA fingerprinting methods based on the polymerase chain reaction (PCR), which amplifies very tiny quantities of DNA tested, could identify a strain's genotype (Molina et al., 1995). ATCC mycologists tested these new methods and developed improved protocols to avoid contamination of its cell lines.

Robert Hay

PROBLEMS OF CONTAMINATION

By 1995, Cypess' team had expanded its tools for quality control and authentication and offered new kits using PCR methods to identify widespread sources of contamination such as mycoplasma (*ATCC Quarterly Newsletter* No. 3, 1995). As Julius Youngner and Elliot Levine noted, contamination by the mycoplasma bacteria could occur invisibly when scientists shared a strain. Levine had watched this contamination grow over the years. He and his research team were finding more and more lines contaminated with mycoplasma; chromosomal mapping showed many cell lines had a different gene map than the one predicted by their documentation. Levine and others had advocated that the professional societies for microbiology, plant science and virology should compel authors who submitted journal articles for publication to prove that the strains in their studies were authenticated. Those societies resisted for decades.

Robert Hay joined ATCC in the 1970s to take over leadership of the cell biology program. His efforts led to growth of the cell culture collection and more widespread usage, as well as a greater awareness and focus on the problems of contamination and misidentification of cells. He played a role in teaching others in the global community about preservation and authentication of cells, and he supported the efforts of his colleagues to reduce the problem of cell culture contamination.



***Mycoplasma mycoides* cell**

Years later, Levine's lobbying effort scored a partial victory: The *Journal of Cell Biology* and the *Journal of Microbiology* instructed authors that they should include the provenance of their cells and the results of a mycoplasma assay — but these elements were still not required. "The thing about mycoplasma is it's so small: just one-fifth the size of *E. coli*. So it doesn't refract light in the medium. It's not big enough to do that. A standard technique when you're inspecting a culture is to hold it up to the light to see if it's cloudy. But there could be plenty of mycoplasma in there and it won't be cloudy," Levine said.

With the risk of misidentification, mycoplasma contamination brought the risk of unpredictable reactions in the lab. Studies of cellular senescence using materials that were purportedly the same could yield conflicting results. To minimize the risk in their own studies, Levine's lab personnel included a scientist who was devoted to mycoplasma testing.

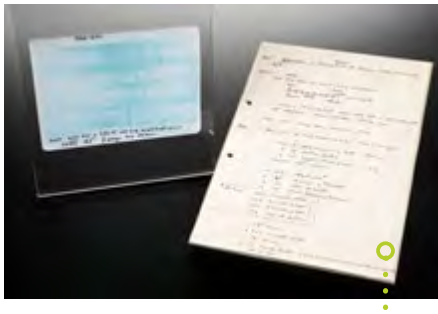
The phenomenon of contamination by HeLa cells, the first "immortal" line of cancer cells noted in Chapter 2, also was a continuing threat to the validity of findings throughout the research system. Misidentification across experiments and contamination of other lines stemmed from the outdated cell-line practices of the 1950s, before equipment like laminar flow hoods enclosed experimental benches. In 1962, ATCC became the repository for animal cell lines. By the 1980s, researchers documented cross-species contamination by HeLa cells. Later studies showed that fewer than half of researchers regularly verified the identities of their cell lines (Buhering et al., 2004). The consequences to research included the loss of cell lines, squandered research funds and effort, and the spread of misinformation.

Yvonne Reid

Yvonne Reid, a staff cell biologist who started working at ATCC in 1980 on human and animal cell lines, was keenly aware of the dangers of contaminated lines. She found that "immortal" lines were essential for creating hybrids that ensured that desired lines could be propagated indefinitely, but they required repeated screening to ensure that the lines retained the properties for which they were intended. Reid, who was pursuing a doctorate at Howard University while working at ATCC, learned from the pioneering work of Steve O'Brien, a research geneticist at the National Cancer Institute in Frederick, Maryland. O'Brien was among the first to use DNA fingerprinting technology in the late 1980s, and Reid helped lead cell biology in that direction.

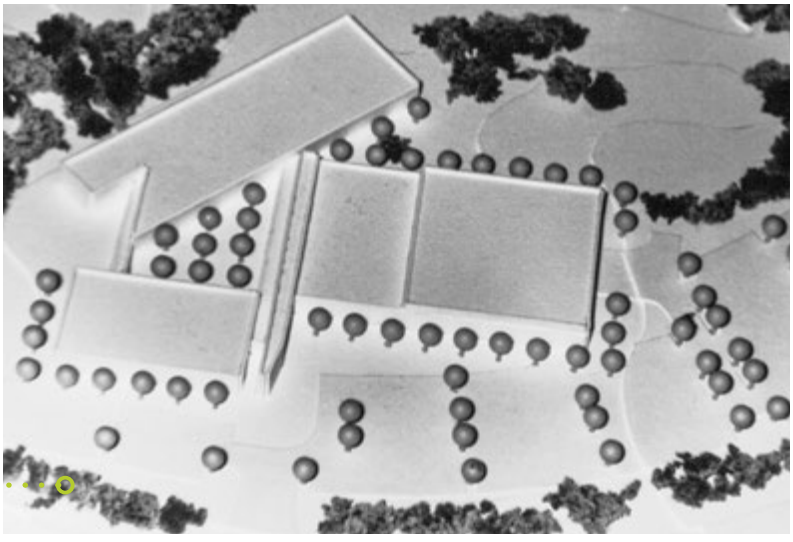
DNA fingerprinting technology changed ATCC's control methods immediately. "It was more sophisticated than any other tool for distinguishing human cell line identification. We were at the forefront," Reid said. She began showing other scientists the DNA fingerprinting method and its results. In the 1990s, the method led to a further development with short tandem repeat (STR) screening, which brought even greater ability to distinguish cell lines and reduce contamination (Reid interview, 2016).

ATCC developed new kits to detect contamination by mycoplasma bacteria.



British geneticist Alec Jeffreys created an autoradiograph of the first genetic fingerprint in 1984. DNA fingerprinting helped scientists to better distinguish cell lines.

The Internet opened up new distribution and communication channels for ATCC in the 1990s.



ATCC's new headquarters in Manassas were designed by renowned architect Hal Davis.

The steps for reducing contamination included better labeling of flasks, working on one cell line at a time in a biological safety cabinet, and allowing at least five minutes between cell lines at a work bench.

New information technology brought other changes. ATCC launched a website in 1993 and soon made its catalog available on the Internet, which was on the brink of changing research networks. "You can connect directly to ATCC's Gopher server by pointing your Gopher client at the address 'culture.atcc.org,'" the newsletter announced. Cell culture entered the Internet age.

DESIGNING A NEW SPACE

Amid great advances in technology and process, ATCC also pursued a fresh vision for how a culture resource center looked, felt and functioned. To design its new home in Virginia, ATCC engaged a top architect. Hal Davis, a partner in the architecture firm Metcalf Tobey Davis, had studied under Louis Kahn, one of the most influential architects of the 20th century, and had worked with Kahn on designs for the Salk Institute in La Jolla, California. The ideal design would balance Cypess' aim of an institution that fostered learning and openness with the need for secure and safe systems. Cypess and Davis discussed the various combinations of public access space and secure lab facility. Visiting the Scripps Research Institute in San Diego, Cypess was impressed by the common space where scientists could gather and talk informally. He wanted ATCC to have a similar environment, as well as space for interaction with George Mason University colleagues nearby. In time, the team settled on a design with three wings — Laboratory, Operations and Administration — arranged around a central courtyard. Cypess made sure the laboratory would include large interior windows so that visitors in the hall could see the freezer room ("watch them make pizza," as Frank Simione recalled) without the encumbrance of biosafety procedures.

THE INTERNET AND BIOLOGY RESEARCH

The Hybridoma Data Bank has provided scientists with a comprehensive digital directory of information on hybridomas and their products since 1985.

The same issue of *ATCC Quarterly* that announced ATCC's new home in Virginia contained a note about training on how to use the Internet. Universities and researchers had already been using the Internet to share information, but it was still new enough that explanation was needed for why ATCC was offering training, citing "the dramatic growth of the Internet, its value as a communications tool and archive of resources and its increased use by our clients."

Knowledge management efforts had led the way toward that recognition, beginning in the 1980s with the Hybridoma Data Bank (HDB), managed by ATCC, along with other databanks initiated in Europe and the United Kingdom. Data resources initiated in the days before the World Wide Web used commercial networks such as Dialcom and DIMDI for distribution. High fees for data transfer put these databases out of reach for most organizations and scientists, but they opened the way for new forms of data management and exchange (Blaine, 2003).

The Internet's growth increased expectations for biological resource centers like ATCC, which scientists expected would provide validated and up-to-date information about their holdings. The main challenge in meeting these expectations, ATCC researcher Lois Blaine noted, was a lack of standards in the community of biological research (Blaine, 2003).

Beyond its communications value, the Internet harnessed computational power that made analysis on a new scale possible, as Keith Bostian noted in *Biological Resource Centers: Their Impact on the Scientific Community and the Global Economy*. The advances — in tandem with genome sequencing and other advances in phenotypic analysis, chemical synthesis and other fields like microfluidics used in automation and high-throughput screening — paved the way for ever-faster discoveries in pharmaceuticals and other industries (Bostian, 2003).

Construction proceeded, and the new facility was completed in the spring of 1998. But nothing about the move would be simple. Public awareness of the risks inherent in the transport of dangerous microbes was heightened based on a tense international situation. President Bill Clinton had recently announced that Saddam Hussein's chemical arsenal in Iraq posed a threat to the world. On February 18, the nation's top security advisors held a town hall meeting on the possibility of war with Iraq. A week after that meeting, a state delegate from Prince William County raised concerns about ATCC's arrival. "It's like the West Coast steel manufacturers shipping stuff to Japan just before World War II. Then that came back to us as bullets and bombs," said Del. Robert G. Marshall of Virginia. "I'm concerned for anybody this stuff could be shipped to" (McKay, 1998). However, several years later, Marshall sent a complimentary letter to Frank Simione praising ATCC as an outstanding organization.

Accompanied by police, movers transported liquid nitrogen vats filled with 2 million vials of cultures from Rockville to Manassas.

ATCC's chief of operations acknowledged that the timing was unfortunate. For the most part, though, public reaction to the planned move was minimal, and Prince William County officials reminded the press of the economic benefits of having ATCC as a neighbor. Prince William County Fire Chief Mary Beth Michos worked to calm any nerves, saying, "I know ATCC has gotten a lot of focus recently, but a lot of companies have chemicals and biohazards. Our department is ready" (Cramer, 1998).

Every possible hazard, human-caused and natural, had to be anticipated: tornadoes, earthquakes, washed-out bridges. Even more likely than a hazardous material spill was the possibility that parts of the collection would heat up too fast during the journey. Typically, the drive from Rockville to Manassas took one hour, but traffic around the Beltway was notoriously hard to predict. A delay could be devastating.

THE BIG MOVE

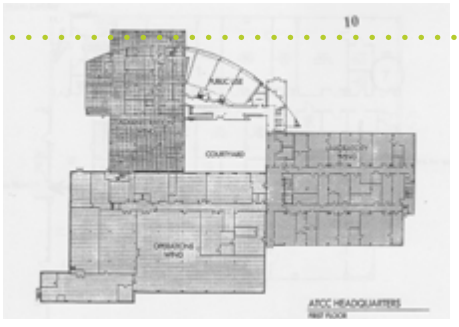
The day of the move — Friday, March 13 — passed uneventfully. As the staff parking lot gradually emptied at the end of the workday, Cypess and the moving committee were busy with final arrangements — from calling state officials to double-checking generators. Liquid nitrogen vats holding 85,000 strains in roughly 2 million vials were loaded onto more than a dozen Office Movers trucks. For security, only the transfer team knew the details of the 45-mile route and its timing.

"With relatively few headaches, American Type Culture Collection, a microorganism repository, completed its long-awaited move."

***WASHINGTON POST*, MARCH 29, 1998**

ATCC waited until after nightfall to hit the road, when light traffic posed fewer risks.

Despite the complexities of transport, the convoy set off according to schedule. The trucks were escorted by police from Rockville south on Interstate 270 to the Capital Beltway and the state line at the Potomac River. At the American Legion Memorial Bridge, Maryland troopers handed off duties to Virginia police. A hazardous-materials team rode alongside the whole way, as well as a backup truck with a generator in case any materials began to thaw.



Left: Front view of the main entrance to ATCC's new headquarters.

Right: The two-story building is made up of laboratory, operations and administration wings as well as a public use area.

Left: The laboratory wing initially housed 24 state-of-the-art labs.

Right: The operations wing provided space for 65 vapor-phase liquid nitrogen refrigerators and 55 ultra-low-temperature mechanical freezers.

Another team was on standby, prepared to shut down the entire six-lane highway, one of the busiest in the country, in just two minutes in case an accident or hijacking occurred.

"It was like moving Noah's ark," Cypess said (Gamerman, 1998). "This sort of move had never been done before. It was a logistics nightmare." The move involved thousands of planning hours over two years and cost more than $200,000. Yet by dawn the next day, the operation was complete. Some of the ATCC staff members, exhausted, chose to sleep at the new facility to be on hand in case a freezer malfunctioned or a generator failed.

Finally, Cypess sent word early Sunday to all staff and board members: "Noah's ark has landed; all species intact."

That still did not mean that all was smooth sailing. Such a massive move involved new systems, such as inventory management, and those new systems needed to be debugged. "It was a little crazy when we got there," Trish Slaski said. "It had its elements of bedlam." Simply unpacking the lab after arrival was challenging. "It's a tremendous feat to move all the freezers," she noted. Plus, there was a series of inexplicable wind tunnels: from time to time, a strong wind would blow through the building, and nobody really understood why.

NEW SYSTEMS AND CHANNELS

The Manassas facility included new systems for customer service and maintenance as well as state-of-the-art equipment for cell culturing that could produce much

Former Governor George Allen, Kathleen Seefeldt, Walter Dowdle and Raymond Cypess celebrated ATCC's successful move to Manassas at a dedication ceremony on November 5, 1998.

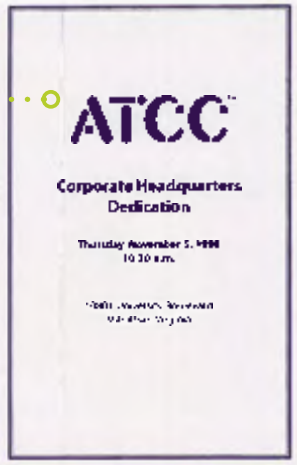
larger lots, bringing the organization advantages of scale. Still, many staff members did not want to be uprooted from Maryland. Nancy Wysocki said that the relocation team prepared to lose nearly half the staff with the move. Management announced a retention bonus to smooth the pace of staff transition, rewarding those who stayed at least through the end of the year (Levine interview, 2015).

In November, after working out the kinks of the new systems, a dedication ceremony put the final touches on this transition. The event attracted local and state officials who had helped bring ATCC to Virginia, including former Virginia Governor George Allen and Kathleen Seefeldt, the Prince William County supervisor. The keynote speaker was Dr. Walter Dowdle, a former University of North Carolina (UNC) colleague of Cypess' who had led the infectious diseases program at the Centers for Disease Control and Prevention as well as national task forces for child development and polio eradication.

At the dedication, Dowdle called ATCC a national treasure, valuable both for preserving essential biological information and for being a standards institution (ATCC Annual Report, 1998). The event concluded with a symposium on biodiversity and bioinformatics, which demonstrated that ATCC was not simply a repository — it was a place where public-sector leaders like the head of genomic diversity at the National Cancer Institute could exchange ideas with counterparts from the private sector and academia.

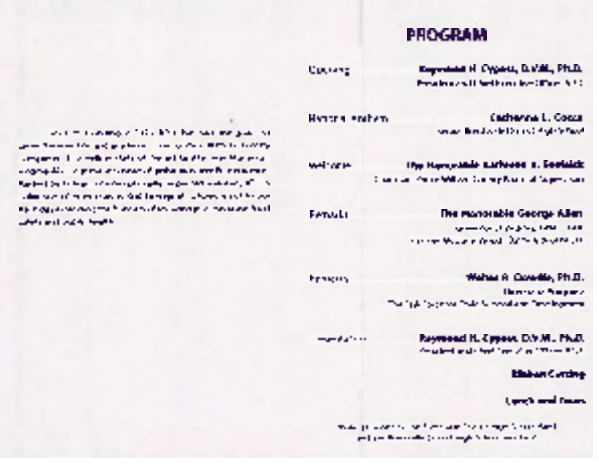
The journey to Manassas was another evolution for Cypess. He had come a long way from the immigrant, working-class Brooklyn neighborhood where he grew up. He had made a big leap from his part-time, house call veterinary practice and Ph.D. program in North Carolina to the medical center in Pittsburgh (where he was a member of a basic and clinical sciences faculty) to his leadership position at Cornell (where he

The establishment of ATCC's corporate headquarters in 1998 was a culmination of team effort and dedication.


ATCC

Corporate Headquarters Dedication

Thursday November 5, 1998
10:30 a.m.


PROGRAM

had learned to deal with a new range of clients in the racing industry, dairy farmers, pet owners and pharmaceutical executives accustomed to private corporate jets). He had learned the languages of business and philanthropy, and how to deal with people who wore power as comfortably as a tailored shirt. His experiences in state capitols, alumni meetings and as a consultant to industry prepared him for fundraising and negotiation at a new level. This was essential for growing an organization like ATCC, and for participating in the public dialogue about the sciences, as the smallpox debate would show.

SPACE FOR THE BIG QUESTIONS

With ATCC positioning itself to become a leader in information-sharing as well as microbiology and cell biology, a new level of dialogue emerged internally. Board meetings became heated as the stakes rose in the war on smallpox.

One of the deadliest scourges ever known, smallpox had been contained and prevented since the first vaccine was developed in 1798. In 1977, epidemiologists tracked down the last cases in Somalia and focused vaccinations in the areas around them, ending the spread of the disease (Altman, 1999). By the 1990s, the disease had been eradicated among humans for nearly two decades. The question arose: Should scientists keep the remaining smallpox samples in repositories? Or could the world's leading science organizations decide to consign smallpox to oblivion?

In a paper he wrote for the American Society for Microbiology, Youngner argued that all smallpox strains should be destroyed. The disease was highly contagious and unlikely ever to be used as a weapon of bioterrorism, so preserving it for counterterrorism purposes didn't make sense. "It's a terrible bioterrorism agent," Youngner said. "A country planning to deploy smallpox would have to vaccinate its population first or risk decimating its own people." Such a large-scale vaccination effort for a disease long eradicated would immediately signal to international observers a plan for biological attack. There was nothing to be gained from preserving smallpox, and only benefits from its extinction. ATCC didn't hold smallpox strains in its facility — it had placed its holdings with the CDC in 1979 — but as a key player in the scientific community, its voice mattered.

On the other side of the debate was a colleague of Youngner's at Duke University, an expert on the Vaccinia virus related to smallpox. He and others who opposed destroying smallpox cited the potential future uses of the virus, and the principle that humans did not have a right to eliminate any form of life. "That was the philosophical argument, and people really felt very strongly about that," said Elliot Levine. Some extinction opponents agreed with the Vaccinia expert, expressing the view that ATCC was established as a repository for all living things. Others took a stance rooted more in pragmatism. ''Everyone can envision situations in which you might want to take the virus from the freezer,'' said Harold Varmus, then the head of the NIH (Altman, 1999).

The difference between Youngner and his friend at Duke proved irreconcilable. "It actually cost us our friendship, believe it or not," Youngner said. "That's how strongly he felt that they should not destroy smallpox because it would be useful in the future. . . . People felt very strongly about this issue. And the people who said not to destroy it won out."

Stepping back from the impassioned arguments, Cypess was struck by the stakes of the debate and the rigorous thinking on both sides. "The question was a real one," he said. "And the exchanges were like a high-level tennis match at Wimbledon." The board compromised by giving the CDC permission to determine the ultimate fate of the ATCC samples. After the board reached its decision, Cypess traveled to Scotland and communicated the decision to international colleagues.

The World Health Organization (WHO) took up the issue and came down on the same side as the ATCC board. In May 1999, WHO announced the appointment of a committee to decide the virus's fate. WHO requested that Russian and American scientists map the complete genetic sequence for three strains of the virus and considered that sufficient for future research (Altman, 1999). In the end, that review allowed the virus a reprieve and authorized "further temporary retention of the existing stocks of live virus on the understanding that all approved research would remain outcome-oriented and time-limited, and its accomplishments and outcomes would be periodically reviewed" (WHO, 2004).

ATCC itself still stood at the juncture of public purpose and private sustainability. Its management had to consider again: What does success look like? It was not simply more cell culture lines in the repository. It was not simply revenue growth. Value-chain growth was part of the answer. What was the rest?

The answers involved, in part, absorbing the transformation in our understanding of biology. Sustainability also meant sorting through the continuing aftershocks from changes that shook up intellectual property rights more than a decade before. Beyond changing revenue flow and ownership, the rules filtered through university departments and were altering the dynamics of the scientific community itself.

INTELLECTUAL PROPERTY REVISITED

ATCC had adjusted its approach to the landscape of intellectual property that began shifting after the Bayh-Dole Act opened the door for patenting biological products. Yvonne Reid saw the dramatic consequences of these shifts. Besides making scientists less willing to deposit their materials for sharing, the new rules also made colleagues less willing to share ideas at conferences. "Now that things are becoming patented, you go to meetings and no one wants to talk about their work because they're looking to patent it," she said. Scientists looked to build partnerships with private enterprises for a better return on investment. Patent rules even affected

how ATCC could propagate antigens that were not directly restricted. In other words, before distributing a cell line, ATCC had to get patent clearance not only for that cell line but also for the plasmids used in the hybrid form that made the distributed version durable (Reid interview, 2016).

These cascading effects of the intellectual property machinery in the 1990s required continued tweaking of the mechanisms and agreements used with scientists depositing materials with ATCC as well as patent applications. In the 1998 annual report, five years into his tenure, Cypess revisited the assessment of ATCC's role in a new era:

> In 1993, I stated to the Board that ATCC was an information and standards company and its future would be guided by that vision. As we approach the year 2000 and our 75th anniversary, we reaffirm and expand upon that vision in which ATCC positions itself as one of the world's preeminent bioresource centers by providing reference standards for the research and industrial communities; serving as a "trust company" for patent depositors; supporting knowledge management for the scientific enterprise; and providing research resource development.

"Intellectual property in biological systems is a minefield," Cypess admitted frankly years later. "It raises the cost of doing business." Still, owners of intellectual property, including universities, looked to royalties to pay for further research and development and other costs. ATCC adapted to the new terrain. In consultation with legal advisors, the organization developed new agreements that allowed exchanges in biological research to continue. Those agreements served as templates for other groups and consortia. Approaching its 75-year mark, ATCC was again pioneering ways to facilitate research and raise the standard.

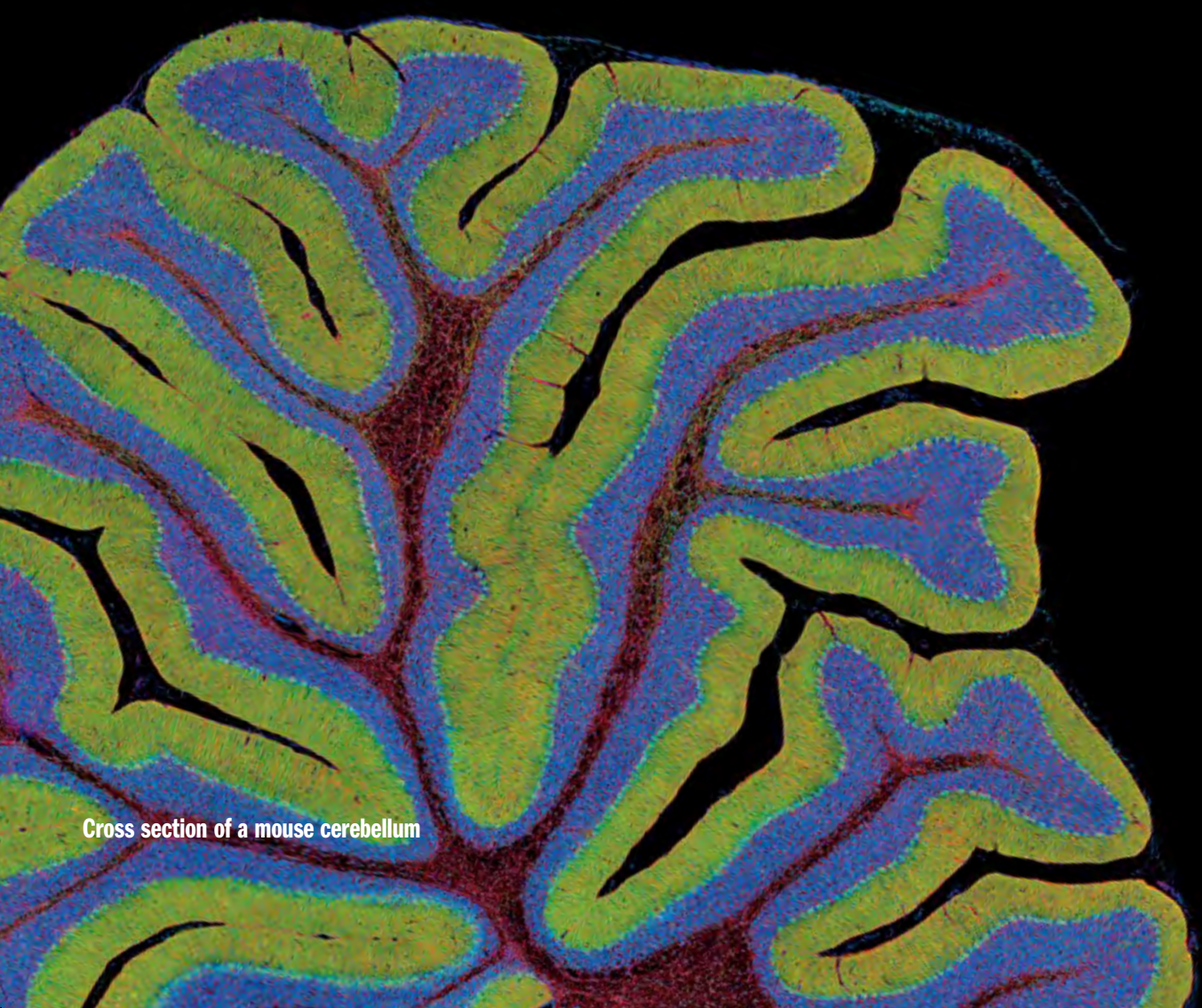
Even as ATCC was challenging the status quo, however, it had to grapple with the effects of change on scientific attitudes, especially a change in the value of sharing. Open sharing of ideas and advances had been a cornerstone of ATCC's foundation. "The complexity of making a deposit or an exchange — it's fed the problem of sharing in science," Cypess said. "We've lost that tradition of sharing in science. And it's very bad for the community."

The CEO had his champions and critics, but the changes were crystallizing. "What became apparent quickly to me in that process was that Dr. Cypess was as visionary an entrepreneur as I have encountered," board member David Gillece said. "It's a larger view of the organization, not merely as a repository but in creating value-added science, adding to the distribution functions and diagnostics." ATCC had a map for its direction in a new century. However, nobody could predict the dramatic events that the coming years held in store.

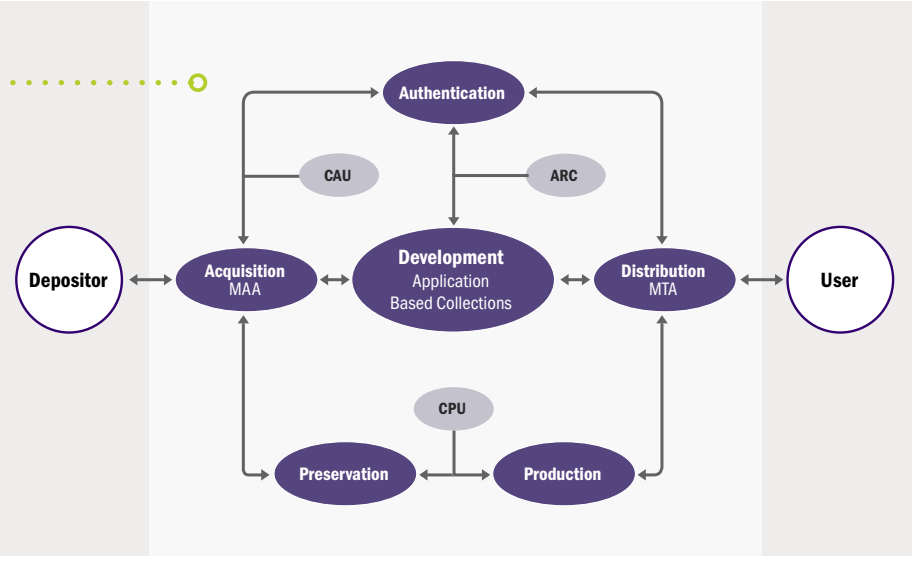
CHAPTER

6

A NEW MODEL EMERGES



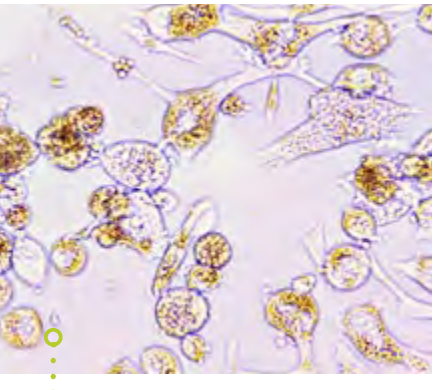
Cross section of a mouse cerebellum



Reorganizing ATCC around its six core functions (acquisition, authentication, preservation, production, development and distribution) allowed the organization to evolve from managing a supply chain manufacturing enterprise into a knowledge-based research institution.

Even before ATCC moved into its new home, Raymond Cypess had been working on a new business model based on the organization's growth, as an information and standards organization and as an applied research institution. Individual units developed their own marketing strategies as ATCC accepted contracts to provide curatorial services for the Centers for Disease Control and Prevention and other agencies. By addressing clients' demands, these strategies could point to an overall direction for the organization.

Looking at the organization's DNA signature that he had formulated (AAPPDD), Cypess began to center his larger strategy on the units for authentication, production, development and distribution. "Whenever you use the word DNA in science, everybody gets excited," Cypess said jokingly. The idea, he said, was to link ATCC's work to a higher purpose for science, and climbing the value chain for its commercial stakeholders. For example, correctly identifying cell lines not only verified the quality in ATCC's work, it also addressed a growing problem. A new business model would help ATCC grow as it addressed larger needs in the scientific community.



Recurring problems in biological research such as strain contamination by mycoplasma and HeLa cells (pictured) demonstrated a need for higher standards.

The issues that cell biologist Yvonne Reid witnessed among her colleagues — strain contamination by mycoplasma and HeLa cells, problems of misidentification, and increasing reluctance to exchange information — suggested the need for higher standards. Cypess had watched the fields of chemistry and engineering move ahead of biology in grasping the need for shared standards. In the absence of a central authority for biology, ATCC prepared to take a greater role, fostering dialogue about key issues, using its collective experience across disciplines to address gaps, and developing diagnostic kits and other products as appropriate. But that didn't constitute a business model.

A COUNTERPART IN EXPERIMENTAL RESEARCH

In surveying comparable business models, Cypess found very few organizations that served science clients the way that ATCC did. One of the few nonprofit biological

resource centers in the United States with independent standing was the Jackson Laboratory (TJL). As the *New York Times* playfully described, "The modern mecca, or at least the Club Med, of mice is the Jackson Laboratory on Mount Desert Island in Maine. There, some half million mice live in leisure, protected from cats, disease and all other nuisances by assiduous human attendants" (Wade, 1998). Jackson was both a leading supplier of laboratory mice for genetic research and a research institution with a focus on genetic studies with mice. It had been launched in the 1930s and survived its own hard times; 60 years later, it was distributing over 1.6 million mice every year (Berns et al., 1996).

In addition to serving as a leading supplier of laboratory mice, the Jackson Laboratory conducts scientific research in six major areas: cancers, computational biology and bioinformatics, developmental and reproductive biology, immunology, metabolic diseases, and neurobiology.

Cypess had met Jackson scientists at a 1996 meeting organized by the National Research Council on Resource Sharing in Biomedical Research. The presentation of the laboratory's history, mission and business approach impressed him. Jackson's board included nonscientists as well as scientists, and its mission had clear resonance with ATCC's mission, particularly in its goals to provide essential research resources to the scientific community and to educate scientists on how to conduct research better. At the meeting, Muriel Davisson-Fahey outlined Jackson's solid operating budget ($45 million annually in the 1990s) and financial base, which combined funding from the federal government and large organizations like the American Cancer Society with its enterprise in laboratory mice sales and services. Fees paid by the large associations for mouse strains helped to lower costs for smaller customers (Berns et al., 1996).

Jackson had taken a firm position on intellectual property. When researchers wanted to deposit material, they had to transfer the rights surrounding that deposit to Jackson. If a strain's originator requested royalties, that researcher had to bear the costs involved in the process for distribution such as those for re-deriving the strain and cryopreservation. As the National Research Council workshop summary noted:

> One of the reasons this approach works at TJL is that individuals have an incentive to contribute their genetically modified animals to the laboratory because it assumes responsibility for the distribution of animals; gives credit to the contributors in all TJL publications, including a reference to the investigator's work; and sees that the animals are shared with fellow scientists (Berns et al., 1996).

Muriel Davisson-Fahey

Yet clouds loomed on the horizon as technical transfer offices at universities caused longer and longer delays in deposits.

The Jackson Laboratory made a profit from its wide range of test mice: strains with impaired immune systems that would accept various grafts, for example, as well as the large variety of "knockout" mice — mice lacking a specific gene that are useful for researchers studying that particular gene. Jackson had also created an endowment to

Laboratory mice generated a consistent revenue stream that enabled the Jackson Laboratory to advance its research agenda and expand its product line.

ATCC's *Mycoplasma* Detection Kit offered a quick test to detect mycoplasma contaminants in cell culture using a nested PCR reaction to amplify rRNA spacer regions from *Mycoplasma* and *Acholeplasma*.

support research, training and its library, among other purposes. By 1998, the lab was charging from $8 to $100 for each experimental mouse. The question was: Did the laboratory's experience hold lessons for ATCC's direction?

Like ATCC, the Jackson Laboratory faced two problems: only a small portion of the strains in its collection were commercially viable, and other suppliers had developed their own businesses selling the most popular strains.

To explore the parallels, Cypess made the trip to Maine's coast. The laboratory's director, Kenneth Paigen, would tell visitors, "It's amazing how important mice are and how little people understand them" (Wade, 1998). At Jackson, Cypess found a lab where research bolstered the product line, with new mutations and better methods for preserving germplasm, while simultaneously raising the organization's scientific stature. The lab was helping to advance bioinformatics by publishing the Mouse Genome Database, which provided genetic mapping information to the scientific community, in addition to publishing its price and stock lists, data sheets and newsletters.

"Jackson and ATCC were the only two true biological resource centers in the U.S.," Cypess said. "The major difference was that Jackson started as a research center and developed a commercial enterprise through the sale of rodents that they developed. In contrast, ATCC started as a repository whose holdings were donated by the community and then expanded its research and development activities." For ATCC's expansion of research and development, the Jackson experience reinforced the notion that it must develop as a standards institution and partner for researchers. In his discussions with the Jackson Laboratory's management, Cypess proposed collaboration on a shared interest: cryopreservation of biological materials, an important area of research for both, but one that was often neglected.

PARTNERS IN RESEARCH

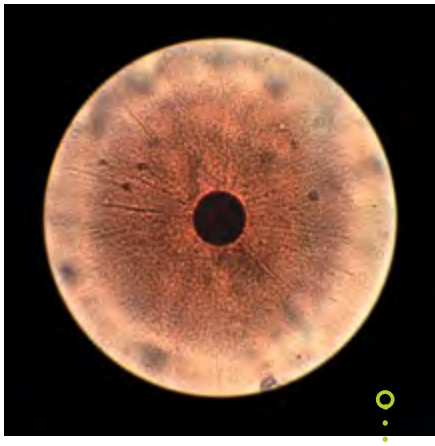
Beyond the nonprofit sphere, Cypess' team looked for other research partnerships that would leverage ATCC's strengths. One step toward that came in packaging its *Mycoplasma* Detection Kit, which used the polymerase chain reaction method; the kit was the third patent held by ATCC (ATCC Connection, 1997). The kit allowed scientists to test their own cell lines and get accurate results in one day. ATCC also offered researchers mycoplasma testing services at their facility using a combination of methods. The kit, like ATCC's medium and serum products, adapted what the organization used in its own labs for use by research clients.

Another development that drew on the organization's strengths was an initiative to create a universal virus database. Under the auspices of the International Committee on Taxonomy of Viruses (ICTV), and with research funding from the National Science Foundation, ATCC took the lead in making the new database available

on the Internet. Working with research partners in Australia, ATCC Director of Bioinformatics Lois Blaine developed software tools to help researchers identify virus strains, obtain information on viruses and integrate data across different virus taxa. The database built upon a standardized description and taxonomy of viruses created by the ICTV and provided an environment where virologists could contribute data (Blaine, 1997). This initiative paved the way for better taxonomy and a greater shared understanding of virology.

ATCC and other biological resource centers, Blaine wrote, were poised to become the points where repositories, innovative data management, and tools for data analysis and discovery would bring together the power of bioinformatics (Blaine, 2003).

The universal virus database served as an example of the future of professional journals, according to Blaine. "Computerized databases will progressively replace the journal literature as the primary legacy of science," Blaine wrote. "The cost of well-curated, reliable, and stable databases must eventually be borne by the users, just as is the cost of the reagents and equipment used for scientific research. The goal, however, is to continue the quest to provide these data at reasonable cost" (Blaine, 2003). What the appropriate burden-sharing looked like remained an open question.



Acholeplasma laidlawii

GROWING STAFF CAPABILITIES

Making ATCC a stronger research partner required investment to increase the number of staff members as well as their skills and capabilities. That was easier than before with the internal systems that Nancy Wysocki had put in place, including an educational assistance policy for staff members pursuing postgraduate degrees, with the assistance based on service, financial need, approval and a commitment to remain with ATCC for a period of time. In addition to this policy, the organization started hiring more experienced scientists. In time, more than one-third of the staff had advanced degrees. As Cypess has emphasized repeatedly, the essence of a science organization should be its science.

"You don't need a high proportion [of advanced degrees] if you're just running a freezer farm," said Mindy Goldsborough, who witnessed the evolution of ATCC into a true product development organization. "But such a high level of degreed employees pays off if the goal is to develop and deliver products and services that anticipate the needs of the scientific community." A high-caliber staff enables ATCC to explore, invent and use technology to benefit our customers and enhance careers (Goldsborough interview, 2015).

Finding the right talent is always a challenge. Cypess asked a core set of questions of job candidates: What has been your most important professional mistake? What was the last book you read? What makes you angry, and how do you express that? These questions, and others focused on science, were designed to gauge a person's self-awareness, reflective capacity and curiosity.

Lois Blaine

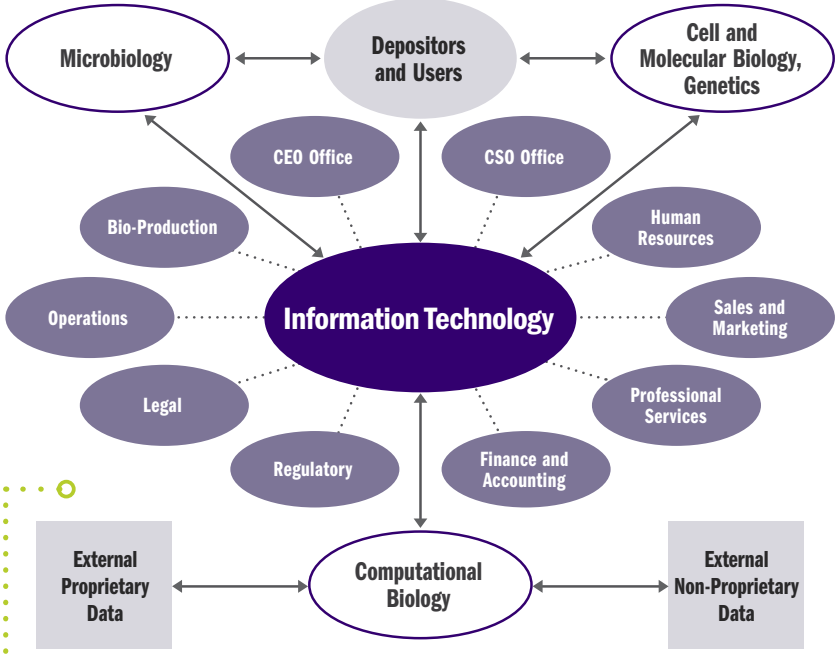
ATCC raised its profile internationally in the 1980s and 1990s by hosting annual hands-on laboratory workshops and patent and licensing conferences.

On the international stage, ATCC expertise became more recognized. In 1983, ATCC initiated a workshop program that brought attendees to ATCC from all over the world for the next 17 years. In addition to the hands-on laboratory workshops, ATCC conducted an annual patent and licensing conference in collaboration with patent attorneys and other intellectual property experts. Alumni from ATCC's education programs later established themselves in other areas of the world, including Taiwan and other Asian countries and became friends of ATCC.

DECISION POINTS

While ATCC had come a long way from the financial precipice of the 1980s and early 1990s, debate still churned internally over just how entrepreneurial its future would be.

By 1999, internal discussions to clarify its business model were coming to a head. At a strategic planning retreat in May, held at its brand new home in Manassas, the steering committee considered recommendations from a business analysis of changes in ATCC's assets and exposure, and alternative paths. Keith Bostian posed the question: What will ATCC look like in five years? In response, Cypess suggested that ATCC will have increased application-based R&D and offer expanded professional services in addition to being a world-renowned repository. The key to success, the meeting notes observed, would be the ability to integrate ATCC's assets horizontally to meet market demand. By "horizontal integration," Cypess meant dissolving the silos within the organization that divided the science from the business side. "We finally broke science up and distributed it across the whole company," Cypess said.



Dissolving organizational silos enabled ATCC to integrate assets horizontally and strengthen the connection between science and business.

Pooling the operations pieces from the different science divisions for cell biology, mycology, virology and other units allowed integration and synergy between the collections and opened new business opportunities. In all developmental plans, the framework of standards was the compass for direction.

Board members still had their differences. Some wanted to preserve ATCC's traditional repository focus, and others recommended new directions aligned with market forces. Should they create a for-profit entity to keep the "pristine" objective of repository maintenance separate from the "higher-risk" business opportunities? How would they decide what products and services might be better served with a for-profit spinoff enterprise? Should ATCC create a national endowment for biological resources? Should they consider outsourcing product development? And if they did that, would staff capacity decline? There were no easy answers.

SEEING A BUSINESS MODEL IN BIOTECH

After nearly two decades of growth, many were looking to the biotechnology sector for a new business model for science. Biotech had attracted hundreds of billions in capital investment, *Harvard Business Review* noted, "based on the belief that biotech could transform health care. The original promise was that this new science, harnessed to new forms of entrepreneurial businesses that were deeply involved in advancing basic science, would produce a revolution in drug therapy" (Pisano, 2006). A few biotech leaders had commercial success, but most firms did not make a profit. Many observers debated whether the shift to a business-based model for basic science was limiting access to discoveries and slowing the advance of science. Some said that the funding mechanism for businesses was at odds with the longer time frames needed for creating effective new drugs.

Harvard Business School professor Gary Pisano demonstrated that biotechnology companies engaged in basic science needed to find new business models and build long-term collaborations.

By contrast, the very long back catalogs of collections like those of the Jackson Laboratory and ATCC implicitly valued a long timeline in which the less popular strains shared equal stature with the most popular of the day. Underused strains held the same potential to yield effective products eventually, but holding open that long-term opportunity had a cost. "Before the emergence of biotech, businesses did not engage in basic science, and scientific institutions did not try to do business," wrote technology strategist Gary Pisano. The biotech industry's approach did not by itself improve research and development for drugs, although it did enlarge the toolkit for that process with molecular biology, cell biology, genetics and other emerging disciplines. Observers like Pisano were seeing that the science sector needed a variety of business models and forms. It needed closer and longer-term collaborations. Collaboration would become a watchword for ATCC's evolving model.

STRUCTURAL CHANGE FOR MANAGING RISK: A HOLDING COMPANY

ATCC had improved its fiscal standing by increasing revenue from fees from its services, keeping a close eye on reducing expenses, and leveraging public funds for infrastructure in the move to its new facility. With this improved financial stability, the organization took another step to manage risk: It created a holding company called International Bioresources Group (later called ATCC Global). This was a very unusual action for a nonprofit but, as proposed to the board in 1999, it made two things possible. First, it allowed safe placement of cash assets in an umbrella entity, protecting them against a sudden drain on ATCC's resources. As ATCC had become profitable, its cash assets had grown. That fact, along with its initiatives in biosafety after 2001, had combined to raise ATCC's profile and exposure to potential risk from lawsuits, regardless of how groundless they might be. Second, a holding company created a flexible structure for spinning off subsidiaries as the organization grew and became more responsive to the market.

With the formation of ATCC Global, the nonprofit was becoming a more industry-facing entity. This shift involved balancing its public mission and its growing need for private, sustainable growth. Lydia Villa-Komaroff, a molecular and cell biologist who later served on ATCC's board of directors, saw nonprofits like ATCC face the demand for more testing and diagnostic tools, as well as the competition from private companies. She compared ATCC's situation to that of hospitals and universities: "It's a constant tension between the public mission of the institution and the need to make money to support that mission."

Helping to set a higher standard for science practices served as one way for the organization to get more involved in the scientific community. "Standards is a perfect area for ATCC. It suits its brand and is much needed in biology," Villa-Komaroff said. Working to promote standards would involve a great deal of collaborative advocacy. Partnerships with academic researchers and international support agencies, such as the creation of the universal virus database, provided avenues for exploring how collaborations on standards might proceed — with academia, with professional associations, with government agencies and with industry.

Together with George Mason University, ATCC built a hub of bioinformatics and computational biology in the Washington, D.C., area.

Cypess viewed ATCC's new neighbor, George Mason University, as one prospective partner in this process. Months after ATCC settled into its new home, the university established a new, larger space for its Institute for Biosciences, Bioinformatics and Biotechnology (IB3). It was a vast 88,000-square-foot building, intended to serve as a place where scientists from the university and ATCC could work together on subjects like decoding DNA and improving research equipment (McKay, 1998).

IB3 started with an annual budget of $1 million from the university, and up to 20 ATCC staff members would teach classes. The hope was to foster the kind of incubator atmosphere that North Carolina achieved in the biotech and environmental sphere with Research Triangle Park, situated near major academic institutions in Raleigh, Durham and Chapel Hill. Yet as time passed, collaboration proved difficult. "It's sometimes hard to find common ground," said Miles Friedman, who served as chairman of Prince William County's Economic Development Council. "Businesses assume the university isn't into actually applying its research to anything practical, and universities think the private sector is only out to make money" (McKay, 1998).

PARTNERING WITH INDUSTRY IN THE DISCOVERY PROCESS

Another way to approach the intersection of nonprofit and for-profit was to address the obstacles of infrastructure and process that proved too large for any single actor to tackle. The private sector increasingly used ATCC collections in controls for testing, diagnostics and for cell lines, to make vaccines and do basic discovery work for drug development, and to create cell assay systems for toxicity before products could be used by people. Toxicity testing alone was expensive for the pharmaceutical industry.

Taking a step back, Cypess and his team considered how the entire process for drug development might better manage risk. "It takes $1.2 billion to make a drug in this country and at least 10 years," Cypess said. "You enter something called the 'valley of death' before you hit success, and the success rate is about 3 or 4 percent. So as you're going through this process and you get to this valley of death, which is between phase II and III, you've got to do drug testing."

They needed to look more closely at that stage of the process. To see if ATCC could help reduce the risks of that phase, Cypess began talking with more industry scientists. If they could improve risk management for those clients, he reasoned, they could offer a good value and serve science at the same time.

Just as ATCC was on the cusp of something new, however, the pharmaceutical industry was on the verge of its own big changes. As Gautam and Pan noted in *Drug Discovery Today*, big pharma's model in the 1990s involved large, diversified companies, while the coming years would find it moving toward leaner, more focused companies with smaller research clusters (Gautam and Pan, 2015). ATCC approached its 75th anniversary with the myriad benefits of a new and improved facility, a capable staff, and a range of partners in research. It had expanded its customer base and product offerings, and it had become a respected voice on issues in science that were becoming more and more urgent.

Fine-tuning the business models for ATCC and its holding company would require several more years. By 2005, the leadership shared a vision for ATCC to become the global leader in supply chain management of biomaterial standards. Managing the flow of materials from bench scientist to other researchers had been at the core of ATCC's strengths ever since C.E.A. Winslow tapped his fellow scientists to create a library of microbes. ATCC would continue to address the mature markets for cell lines, microbes and cell culture reagents, and it would take on an important role in supporting patent applications.

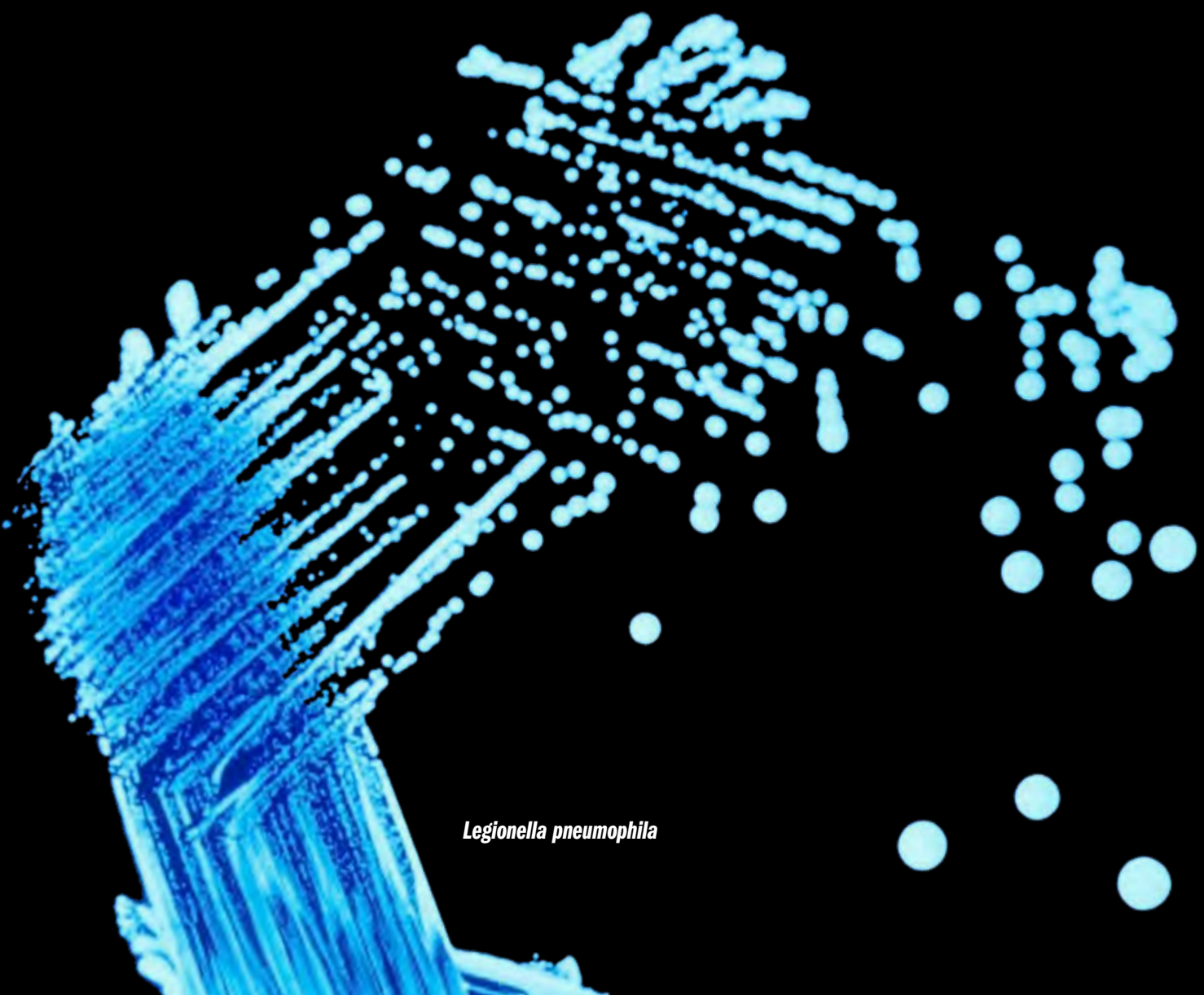
For ATCC, the emerging field of translational science — the middle phase that links basic research to its commercial applications, often in medicine — would be a key path to new markets. The highly interdisciplinary field was proving a good match for ATCC's reach across biological disciplines: Its name embodied its aim of "translating" basic research findings into meaningful health practices and results.

However, ATCC would still have to address the shift toward genomics and more comprehensive analytical tools. Thousands of science institutions internationally faced the same pressure. In the atmosphere of reduced government funding and competition, nonprofits needed to find new hybrid forms. ATCC was gaining expertise for navigating those changes; it remained a nonprofit but with an eye toward market solutions. With its holding company structure, it could even launch new businesses from its more successful innovations. Cypess and his team had earned a moment to catch their breath and look ahead.

CHAPTER

7

BLACK SWAN EVENTS



Legionella pneumophila

Since ATCC's beginnings, microbe libraries have walked a delicate line in regard to public perception, reflected in the drawing on the cover of the 1954 paperback edition of the bestseller *Microbe Hunters*, which showed a ghastly specter rising from a microscope. The artist had captured people's uncertainty about organisms they couldn't see. Oftentimes, the public only learned of these repositories when something went wrong, such as incidents involving safety lapses and laboratory accidents, biological weapons or the re-emergence of microbial disease agents (e.g., measles and tuberculosis). Known as collections, repositories, germ banks and bioresource centers by the end of the century, these libraries were often central to the response to such outbreaks, providing reference tools for field and clinical diagnoses to contain them. As the *New York Times* noted in 1998:

> Standardized germ banks played a major role in helping scientists find public health improvements and make vaccines and antibiotics. Today more than 1,500 microbe banks around the world work hard to maintain the purity and accessibility of a million or so strains of microorganisms, many deadly (Broad, 1998).

Amid a growing understanding of the benefits of these libraries, the public registered only the fact that many of the microorganisms caused disease and death. In the 1990s, that impression began to harden.

NATURAL OUTBREAK OR BIOTERRORISM?

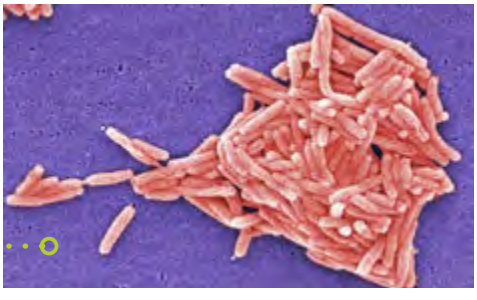
One factor that contributed to public confusion was the difficulty in distinguishing natural outbreaks from human-caused attacks. In July 1976, more than 2,000 people attended the national convention of the American Legion at the Bellevue-Stratford Hotel in Philadelphia. Soon after the event ended, five of the attendees died, all of apparent heart attacks. By August 1, six more had died. All had complained of fatigue, chest pains, fever and congestion. Within another week, more than 130 people were hospitalized, and the death toll rose to 25. Was this some kind of attack? State and federal law enforcement searched for clues but lacked a system for coordination across jurisdictions and agencies. The investigation dragged on.

The Centers for Disease Control and Prevention launched its own investigation into the deaths that focused on the hotel and its environment. In January 1977, the bacterium was finally identified and named *Legionella* based on the fact that its discovery was prompted by the Philadelphia outbreak. Investigators isolated the bacterium and found it reproducing in the hotel's air-conditioning system. The outbreak left 34 dead, and pointed up the need for an effective communication system and protocols for such an investigation. An unfortunate byproduct of this event (compounding other factors such as drug pricing concerns and public awareness of unethical research practices in the infamous Tuskegee Syphilis Study) was a loss of confidence in public health agencies.

CDC and ATCC scientists studied the Legionnaires' disease bacterium for years after the 1976 incident put it on the map. In keeping with the tradition of sharing microbial

American Legion representatives attended a 1977 hearing before the U.S. Senate Subcommittee on Health and Scientific Research.

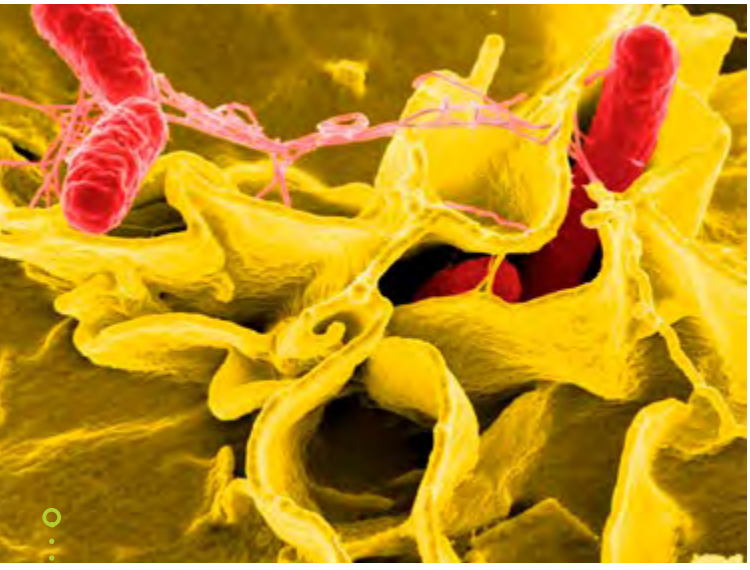
samples, strains of the bacterium were deposited with ATCC and managed as a Biosafety Class 2 material. Environmental studies found *Legionella* species in more than one-third of ground, drinking and whirlpool water sources tested, and scientists discovered an association with amoebae (Fields et al., 1990). Research using new strains of amoebae and their links to *Legionella* showed how microbe collections like ATCC's contribute to the advancement of public health knowledge.



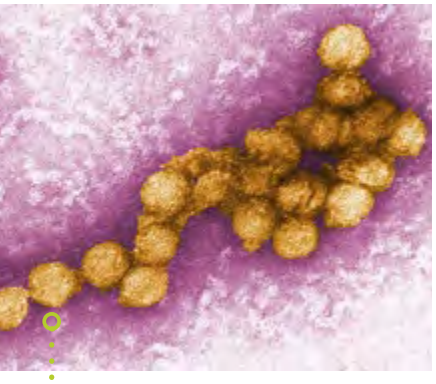
The CDC launched an unprecedented investigation into the 1976 outbreak in Philadelphia and isolated the disease carrier, a bacterium they named *Legionella pneumophila*, within a few months.

An actual biological attack could be as hard to decipher as the emergence of Legionnaires' disease. Biological warfare's long history stretched back to the 6th century B.C., when Assyrian forces poisoned the wells of their enemies with a fungus that caused delirium. In colonial America, the 1763 siege of Fort Pitt became infamous for the British army's use of smallpox-infested blankets, presented as gifts to Native American emissaries with the aim of spreading the disease. In 1984, an outbreak of salmonella in Oregon proved to be an unexpected, targeted attack by a cult known as the Rajneeshees. The cult had obtained a strain of salmonella from a supply house and poisoned a series of restaurant salad bars in one Oregon town, attempting to arouse public fears and reduce voter turnout for a local election. The episode caused over 750 cases of salmonella.

Regardless of whether an outbreak's source is natural or human-caused, the public health response requires lab analysis and the involvement of epidemiologists.



In 1984, a religious cult in Oregon used a strain of salmonella, shown here in red, to perpetrate the largest bioterrorist attack in U.S. history.



The 1999 outbreak of West Nile in New York City marked the first time that this encephalitis virus had been identified outside of the Eastern Hemisphere.

Another case in which the origin of an outbreak was initially unclear came in 1999. Some FBI officials theorized that the West Nile virus was released into New York by terrorists; CDC investigators had to explain to the FBI investigators that the mosquito vectors and case distribution were consistent with a natural outbreak. (Three years later, the question of bioterrorism as a source of West Nile was raised again, through the lens of the 9/11 attacks and an impending U.S. invasion of Iraq. CDC biologists compared strains from the 1999 outbreak with strains sent to Iraq in 1985 and confirmed they were different.) The book *Deadly Outbreaks* notes the West Nile virus episode showed that investments in bioterrorism preparedness could be especially effective when the resources they produced could be applied to any public crisis (Levitt, 2013).

Chemical attacks and biological attacks have very different effects. Chemical weapons, which first became used on a large scale in World War I with the deployment of mustard gas in Europe, act more quickly than biological weapons. Attacks such as the mustard gas attacks in the trench warfare of World War I, typically involve massive burning or suffocation; biological weapons act more slowly. Despite the differences, the two types of attacks often trigger similar fears among the public. Even though ATCC never handled chemical materials, it occasionally had to reckon with the public concerns from this common conflation of biological and chemical threats.

TERROR IN TOKYO

A chemical attack on the Tokyo subway system galvanized fears internationally. During rush hour on the morning of March 20, 1995, members of the cult Aum Shinrikyo placed 11 plastic bags containing the deadly chemical sarin on subway trains and punctured them, dispersing the deadly toxin on three major train lines, including those that served many Japanese government ministries and the National Police Agency. The gas spread invisibly, killing a dozen people and injuring 5,500 (Broad, 1998).

Investigators discovered that the cult had experimented with biological weapons before turning to sarin. The group's chief of biological weapons, Seiichi Endo, had the task of finding and testing lethal germs for attacks. At the cult's base near Mount Fuji, he worked in the lab with botulism, anthrax and other biological agents and learned what most experts already knew: Toxic biological agents make relatively clumsy weapons (Broad, 1998).

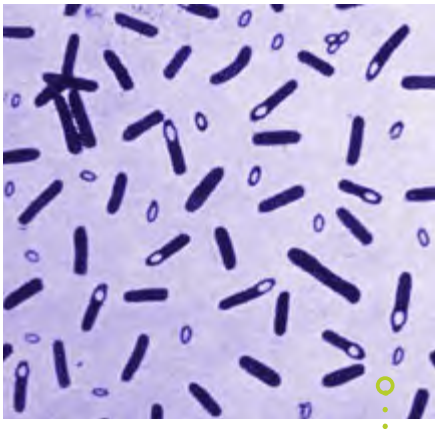
Endo tried using the microbe that causes botulism, *Clostridium botulinum*, as a weapon, with a botulinum starter found in the wilderness in northern Japan. His team produced enough to launch an attack: In 1990, cult members drove three trucks through the streets of downtown Tokyo, spraying poisonous mists of botulism as they

headed toward the U.S. Navy base at Yokohama and the headquarters of the U.S. Navy's Seventh Fleet at Yokosuka. After several days, it was clear the attack didn't work — no illnesses were reported.

Next, the cult tested *Bacillus anthracis*, which causes anthrax. Under certain conditions, the spores can cause an epidemic of fever, coughing and death. A cult member with a medical license allegedly obtained anthrax from a university northeast of Tokyo, and when the guru ordered an anthrax attack in mid-1993, cult members sprayed a cloud of liquid anthrax from the roof of an eight-story building in eastern Tokyo. Once again, the attack failed. These repeated failures led to the cult's decision to use sarin for its deadly 1995 attack (Broad, 1998).

Writer Haruki Murakami interviewed survivors for a book about the subway attack and its impact on the Japanese psyche. One survivor's account paints a portrait of disorientation:

> I turned to look and saw something about the size of a notebook. . . . 'Ah, so that's what's making the place smell,' I thought, but I still just sat there. . . . I heard the announcement, 'Next stop, Roppongi,' and I thought to myself, 'I really must be anemic today.' The symptoms were pretty much the same: a little nauseous, can't see so well, breaking out in a sweat. Still, I didn't connect it at all with the smell. I was utterly convinced it was anemia. Lots of my relatives are doctors, so I'm familiar with the smell of medicinal alcohol or cresol. . . . But when I tried to stand I couldn't get up. My legs had gone. I grabbed the hand strap and sort of dangled from it. . . . Then I blanked out (Murakami, 2001).

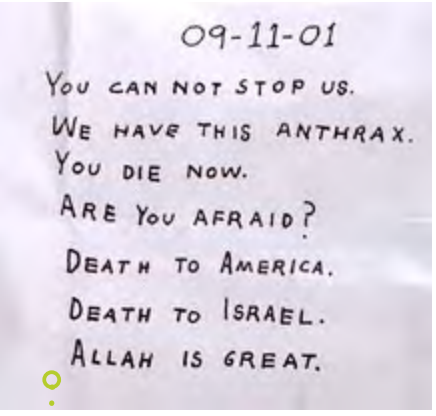


The *Clostridium botulinum* bacterium causes botulism, a rare but serious paralytic illness.

The *Bacillus anthracis* bacterium causes anthrax, a lethal disease that can be transmitted from livestock to humans.

Two months after the Tokyo chemical attack, Larry Wayne Harris, a microbiologist from Ohio, was arrested in the United States for the unauthorized purchase of bubonic plague bacteria (Chapter 4). Following these events, Congress passed tough rules on the transfer of dangerous germs and any threats to use such microbes as weapons. The bill was signed into law in April 1996 and praised by ATCC. Previous federal rules governing biosafety had not been able to prevent episodes such as the Rajneeshee attack in Oregon. Cypess viewed the new law as a corrective that could forestall such episodes in the future.

Later in 1996, Cypess called on the World Federation for Culture Collections (WFCC) to adapt U.S. law for international use, but the WFCC did not take action. "The international community has failed to address this issue in a meaningful way," Cypess told the *New York Times* in May 1998. (Broad, 1998)



Letters containing spores of the Ames strain of *Bacillus anthracis* were mailed to several news media offices and two U.S. senators in the weeks after 9/11, killing five people and infecting 17 others.

9/11 AND ANTHRAX

Weeks after 9/11 came a series of anthrax attacks that prompted public health officials and lawmakers to make biodefense a top national priority. A first batch of anthrax-laced letters postmarked in Trenton, New Jersey, arrived via U.S. Postal Service at media outlets in New York and Florida just a week after the World Trade Center disaster. Two more letters containing anthrax went to the U.S. Capitol mailroom, addressed to two senators. Five people died from inhaling anthrax, and at least 22 people developed anthrax infections. Analysts identified the strain used in the attacks as the Ames strain of anthrax, isolated from a sick heifer in Texas in 1981 but not deposited with ATCC. Bruce Ivins, a microbiologist who worked at the government's biodefense labs at Fort Detrick in Frederick, Maryland, was the chief suspect in the attacks. He died in July 2008 from an overdose of acetaminophen.

The anthrax incident highlighted once again the gaps in experts' understanding of how biological agents were controlled and distributed, and the channels for coordination among federal agencies. Representatives of the American Society for Microbiology testified before Congress that measures to restrict biological exchanges to ensure public safety had to be balanced with the need for legitimate research and development of medical treatments (Cypess, 2003).

Following the 2001 anthrax scare, ATCC gleaned a handful of policy recommendations based on its experience. These included the need for a database on the availability and legitimate distribution of key biological materials; a centralized system with regional facilities for storage, production and use of select agents; and better citation of sources and strains in publications. In the five years after the 2001 attacks, the federal government invested more than $10 billion in biodefense (Bush, 2006). Amid this growing commitment to standards as well as heightened public safety, the world also needed an international system for registering and monitoring the labs and repositories that worked with select microbes; up until then, no international body had a mandate for that monitoring (Cypess, 2003).

WHERE BIOSAFETY MEETS GLOBAL HEALTH

ATCC worked with federal agencies to emphasize the importance of policies that establish standards, along with the technical regulations needed for biosafety and materials exchange. ATCC's close relationship with NIH continued, with a shift. In the same way that the CDC had tapped ATCC's expertise to improve its own collection in Lawrenceville, Georgia, five years before, NIH leaders consulted with Cypess. How could ATCC support the National Institute of Allergy and Infectious Diseases (NIAID) in its work on biodefense and emerging infections as it addressed new demands in the wake of 9/11?

First, the agency consulted with Cypess on direction. It was unusual for NIH to engage with a CEO as principal investigator, but these were unusual times and ATCC was not a conventional research organization. The discussions with Cypess provided an overview

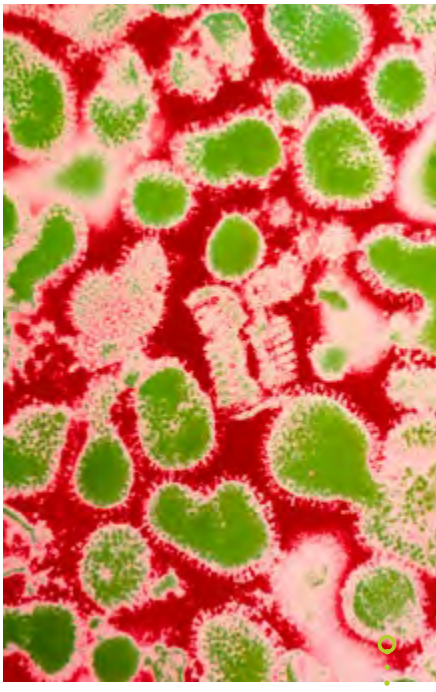
of how NIAID could improve its process for creating tools and reagents for diagnostic and environmental monitoring. Then, NIAID held a meeting with expert organizations in April 2002 to explore how those ideas could be executed. By the end of the year, the agency requested proposals for moving ahead. ATCC studied its own position compared with other firms likely to apply, saw that its advantage lay in its experience in sourcing and managing a collection and its in-house supply chain and manufacturing, and research capacity, and submitted its proposal in March 2003. The competition was fierce, including leaders like the Battelle Memorial Institute, the world's largest nonprofit research and development organization. In the end, NIAID chose ATCC. The result was a seven-year, $120 million contract establishing a repository for biodefense and emerging infections research that became known as BEI Resources.

BEI Resources studied and developed reference reagents for priority pathogens and emerging infectious diseases, and produced the reagents crucial for diagnostic tests, disease detection, vaccines and treatments. As part of its contract with NIH, ATCC shipped these resources to NIAID-registered researchers worldwide; the qualified researchers and their institutions had to pay only shipping charges. The work of BEI Resources made distribution of reagents more secure and better authenticated, which in turn allowed the government to identify public health threats more quickly and reliably. This contract, which was renewed twice, would prove its worth against another outbreak in a few years' time.

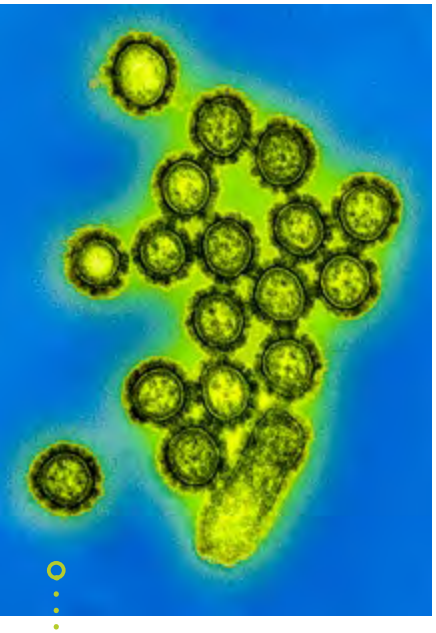
During this same period, a little-known 2005 incident involving the CDC highlighted the government's deepening partnership with ATCC. Proficiency testing assesses the quality of laboratories' analytical performance by comparing the analytical results from different labs testing the same materials. A non-circulating strain of the H2N2 influenza virus was accidentally distributed to more than 4,500 laboratories worldwide by four independent proficiency testing programs, using kits from a commercial manufacturer. The problem came to light when a lab in Canada detected live H2N2 microbes in the kit it received. The discovery raised two questions for the CDC: 1. How did the H2N2 get into the kits? and 2. Was H2N2 classified and handled at the proper safety level?

A spokesperson for the kit manufacturer claimed that the H2N2 strain had come from ATCC, although ATCC had not distributed the strain to anyone for over 20 years. Most likely the placement was simply a mistake, but the episode required corrective measures. This close call underscored the need for standardized methods of transfer among laboratories, as well as clearer standards in proficiency testing and the need for independent verification of samples among labs.

After a CDC analysis revealed the gaps in the proficiency testing process, the agency held a meeting in Atlanta on June 14, 2005, to bring together experts to determine how to avoid similar mistakes in the future. Frank Simione attended with ATCC's vice president for standards, Joe Perrone. At the meeting, Perrone proposed to CDC officials that ATCC



After test kits that had been accidentally contaminated with the H2N2 influenza virus were distributed around the world, ATCC set up a standards program in partnership with the CDC in 2005.



Despite the rapid response by health officials, the new influenza virus, which scientists named H1N1, quickly spread around the world and killed more than 18,000 people.

set up a standards program as a voluntary licensing system, so that test providers and manufacturers could obtain verified strains from ATCC. The CDC saw the seriousness of the issue and agreed. "We were looked upon as a friend of the agency," Cypess said.

ATCC's role as a federal partner, and not just a grant recipient, was maturing. The successful analysis and response with the CDC led to discussions with officials at the Department of Health and Human Services (HHS), where ATCC impressed upon officials the need to address gaps in standards governing production and distribution of cell lines. "Aside from ATCC's material transfer agreements and security policies for distribution of material, few other restrictions apply to the transfer of material between organizations. Microbes currently used in proficiency test panels may not be traceable," ATCC told HHS officials in a 2005 presentation at the agency. Using a PowerPoint deck, ATCC illustrated those vulnerabilities and proposed a program for standards that would strengthen labs' capacity to trace materials to their origins. The program based on that proposal is still used by providers of proficiency tests today.

BUILDING A CASE THROUGH DIAGNOSTIC KITS

ATCC's successful collaborations with government agencies reinforced its reputation for quality services and capacity-building in biosafety and response. These contracts in turn led to a new program, stemming from the awareness that new viruses were emerging globally and moving from one host species to another with increasing frequency and risk. To provide labs and health teams worldwide with the tools they needed to detect new varieties of influenza virus, the CDC created the Influenza Reagent Resource (IRR).

The capacity for malaria research globally had improved with better access to quality samples and diagnostic tools; in a similar way, IRR would provide scientists worldwide with quality tools for tackling influenzas. The project would supply the needed ingredients for improving diagnostic kits and creating vaccines that could defuse the growing influenza threats. Given the speed of the flu outbreaks, researchers placed a premium on fast distribution and high-quality tools. Centralizing these functions in IRR answered both needs. In September 2008, the CDC contracted with ATCC starting on a year-by-year basis, with renewal of up to 10 years.

Then came the spring of 2009. Early that year, a flu strain swept through scores of countries. Global health officials had been bracing for an outbreak of avian influenza, known as H5N1, which was endemic in poultry on several continents and had occasionally caused human deaths. ATCC was working with the CDC to create an influenza reagent resource. Then in April, an unprecedented combination of influenza virus genes emerged in the United States. Initially, its resemblance to swine flu viruses caused early reports to call it swine flu, but investigators found no exposure to pigs among the sufferers. They soon suspected it was a new virus altogether. Lab samples from a 10-year-old patient in California went to the CDC, which confirmed this was a virus unknown to humans. They dubbed it H1N1.

ENSURING A DURABLE RESPONSE

Cypess and ATCC's board of directors knew that in addition to instituting biosafety practices for handling the individual microbial strains in the collection, they needed to implement a disaster management plan that covered the whole collection. Ever since the first backup of the inventory in 1979, ATCC had maintained a reserve against the possibility of a disaster at its main facility. With the 1998 relocation to Virginia, the company shifted the backup function to a facility located 60 miles west of the Manassas, Virginia, campus. It also put in place a business continuity disaster plan to ensure that if a calamity occurs, ATCC can continue to support clients and supply its main products (Simione, 2011).

Samples taken from patients were soon coming from clinics in Texas and Mexico. On April 23, CDC officials held a press briefing to provide information about the widening outbreak. The following day, the CDC uploaded the complete gene sequences of the H1N1 virus to an international database so that colleagues worldwide could compare the genome with other viruses (CDC, 2010). On April 25, the director-general of the World Health Organization (WHO) declared the 2009 H1N1 outbreak a public health emergency of international concern. By late June, all 50 states, the District of Columbia, Puerto Rico and the U.S. Virgin Islands had reported cases, along with more than 70 countries. That summer and fall, the CDC revised its surveillance methods and eventually developed a new methodology based on the data, which helped to make public health responses to disease outbreaks faster and more comprehensive.

Throughout the crisis, ATCC responded with support for the CDC and WHO, delivering flu diagnostic kits quickly and securely to laboratories in 133 countries. "Disease knows no boundaries. We had to get kits into countries far and wide, including some with special sensitivities," Cypess said. "The speed of our response and the fact that we made no mistakes were significant." WHO reported that ATCC's effort was the fastest response to a global disease outbreak it had ever experienced.

A national vaccination campaign began in October. By December, federal agencies launched a nationwide public awareness campaign that encouraged Americans to get vaccinated. By mid-December, 100 million doses of the vaccine were available. Based on the number of people vaccinated, it was estimated that hundreds of thousands of cases of the disease were averted. The characterization of the virus and production of a vaccine in record time were notable successes, according to the HHS report on the pandemic. This public recognition of ATCC's capacity highlighted the value of biological resource centers in public health response.

TAKING A LEADERSHIP ROLE

In the years after 9/11, Cypess had seen ATCC's work with federal agencies on technical issues of biosafety improve crucial parts of the public health system. However, he also saw the need to engage more deeply on the issue of biosafety at a policy level. In the atmosphere of heightened public fears, ATCC had experience that could inform a higher-level discussion of the public health threat from biological agents. Advocates for an active community of biological researchers needed to speak up and communicate clearly. ATCC embraced the role of public authority on the safe handling of materials and the larger issue of standards.

A singular opportunity came in April 2006, when ATCC convened and hosted a gathering of experts to talk about biodefense standards. At the Panel on the Development of Standards for Biodefense, President George W. Bush addressed the participants in a letter that said, "This event is an opportunity to establish important standards in the development and deployment of cutting-edge defenses against a biological attack" (Bush, 2006).

At the Hay-Adams Hotel in Washington, D.C., Cypess welcomed the group of about 90 experts from government agencies, universities and the private sector. After noting the advances that standards make possible in science and technology, he homed in on the need for standards in biodefense:

> This meeting marks a launching point for a process that will eventually lead to useful consensus-based standards for biodefense. The process of developing standards is best accomplished through a transparent, consensus-based process that incorporates the participation of all materially interested stakeholder groups.

Cypess issued a challenge to the attendees: "While the United States is still a worldwide leader in scientific research and innovation, our foreign counterparts are ahead of us in the development of biological standards" (Cypess, 2006).

The blue-ribbon group reviewed responses to the anthrax scare and the monitoring of strains by the CDC and WHO. Together they assessed the state of the art in forensic science and found two types of standards in use: materials/components-based standards and performance-based standards. They found a lack of robust and flexible systems and too much variation in validation methods. In academia, the lack of standard labeling of microorganisms posed a particular problem. Another obstacle was a lack of shared standards for biodefense among defense agencies.

The topic of terminology came under scrutiny (not surprisingly, given Cypess' interest in language). Differences in terms were highlighted in the meeting summary:

> Common terminology allows the community of interest to work precisely and consistently with any given standard. . . . The Process work-group created a list

Leading biodefense research and development experts established a foundation for voluntary consensus standards for critical materials in biodefense during the summit at the Hay-Adams Hotel in Washington, D.C.

of terms that would likely be used in process standards relating to their list of potential standard categories and sub-categories. The group recommended that a similar lexicon should accompany all new standards.

The panel of experts forged a consensus on categories for new standards. In addition to starting a shared lexicon, participants called for standardizing key characteristics of biodefense materials and the methods for creating them. For a short, high-level event that involved many agencies and disciplines, it proved surprisingly productive (ATCC, 2006).

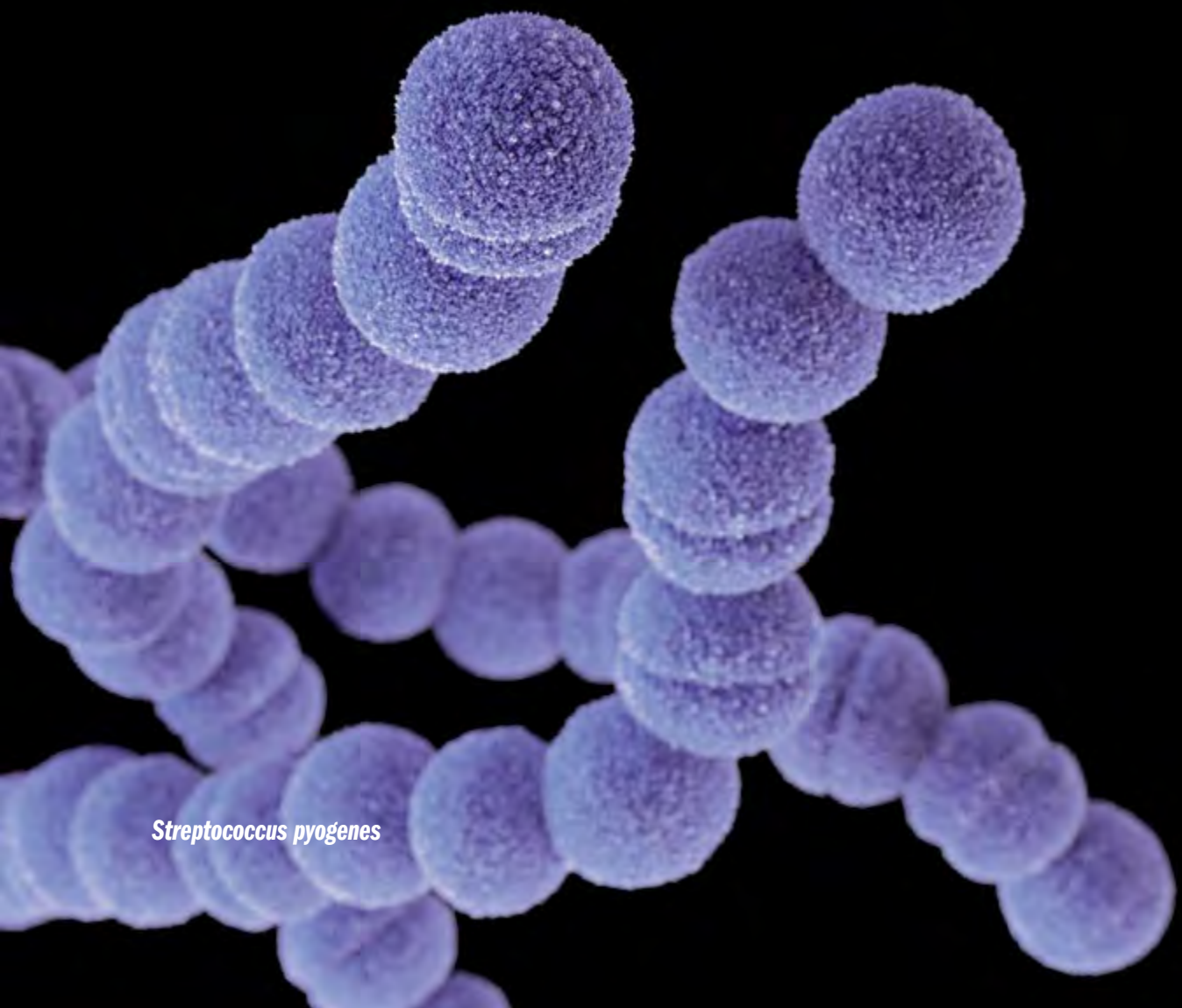
Bioterrorism fears and shrinking government budgets for research support were making the climate for public scientific exchanges more daunting, just as the need for scientists to work together was becoming more pronounced. From the threat of Legionnaires' disease in the 1970s to the national anthrax scare 25 years later, ATCC had worked with researchers and investigators to improve the process for understanding outbreaks and improving biosafety. Collaboration was a key part of the organization's strategy through the 1990s in order to shift its posture from a passive collection to an active partner in research and governance. But impressions seeded decades earlier would take time to shift. "Very few scientists really understand the changes that have occurred at ATCC," said board member Lydia Villa-Komaroff. "Most still think of it as selling cell lines and reagents."

There was still more work to do. The years ahead would bring public vindication for some of the changes that Cypess had initiated and the decision to move assertively away from what was once a supporting cast role.

CHAPTER

8

The Model Matures
FROM RED TO BLACK



Streptococcus pyogenes

As a senior fellow at the Brookings Institution, economist Scott Stern began to investigate the economic value of science in the early 2000s.

Vladimir Volkov, a Russian scientist who worked with human pathogenic bacteria, was among the scores of researchers whose jobs were threatened after the Soviet Union collapsed in 1991. This upheaval revealed how quickly the Soviet Union's large investment in biological repositories could be jeopardized. The State Research Center for Applied Microbiology and Biotechnology in Obolensk, Russia, where Volkov worked, had grown into an enormous national resource during the Cold War: More than 3,000 researchers there studied biological materials (and weaponized some, although that was illegal under the Biological Weapons Convention). In the decade after the fall of the Berlin Wall, the Obolensk center's budget was slashed. It hit rock bottom in early 2002, when the threat of power outages put Obolensk's entire collection at risk. The funding cutbacks had pushed managers to suspend utility payments for 14 months (Chase, 2001).

The story of Volkov and the Obolensk center's decline intrigued Scott Stern, an economist at the Massachusetts Institute of Technology (MIT), because it highlighted the public investment and the perils of its loss, the economic dynamics of biological resource centers (BRCs) that employed thousands of people, and the changing public discourse about their value. Stern had been fascinated by innovation and entrepreneurship since he began his career at MIT. As a junior faculty member, he saw the unexamined relationship of science to a country's economic progress as a fundamental problem.

People accepted the notion that scientific advances drove economic growth; this was understood to result from the cumulative nature of science knowledge. (The computer industry became an economic engine in this way.) The scientific method and the literature that supported it evolved to build improved understanding into the system: Every generation of researchers built on lessons documented in the literature by previous researchers. Stern liked to quote Isaac Newton on this element of the scientific culture: "If I have seen further, it is by standing on the shoulders of giants."

In economics, this accrual of the work of previous scientists had only been described qualitatively. Nobody had found a way to analyze with clarity how this understanding of economic growth worked. How do we measure the economic benefits of science? Stern also wanted to know what kinds of policy and market environments made scientific innovation accelerate and what environments dampened innovation. During the accumulation of knowledge, certain institutions must be important, he thought, even if they might be nearly invisible to the nonscientist. At the start of the 21st century, as he started a research stint at the Brookings Institution in Washington, D.C., Stern had an idea about how he might study this fundamental notion of the economic value of science.

"I was on the hunt for an institution that would satisfy a few conditions: one was that most people hadn't heard of it, but that to people in the field of study, it was completely obvious that the institution was important," Stern said. He was looking for an organization that was obscure to the person in the street but essential to a working biologist. In a way, he was looking for the elephant in the room — an institution that was

practically unseen and yet essential to biological advances.

Around the same time, Raymond Cypess had lunch in New York with Joshua Lederberg, a Nobel Prize winner and member of the ATCC board. Over a meal in the cafeteria of Rockefeller University, where Lederberg taught, Cypess spoke of the challenges of declining subsidies for ATCC's work. For nearly a decade, he had been building an argument for the value of repositories and higher standards in biological research, based mostly on evidence from health and agricultural research.

"Ray, if you want subsidies, you have to show an economic benefit," Lederberg said. "And you have to do it in Washington, where they decide on those subsidies." So Cypess set about looking for a study that would show the economic value of ATCC's work.

Cypess mentioned his search to an acquaintance, Robert Litan, a senior fellow at the Brookings Institution. Cypess asked Litan how an economic analysis of the impact of biological resource centers might proceed. Cypess recalled Litan saying, "I have this young associate professor from Boston. Maybe he can help." The young professor was Stern. As Stern recalled it, the Brookings scientist said, "That's a little outside of Brookings' main areas of competence, but we've got this young guy who's pottering around a few topics in that area. Maybe there's a match."

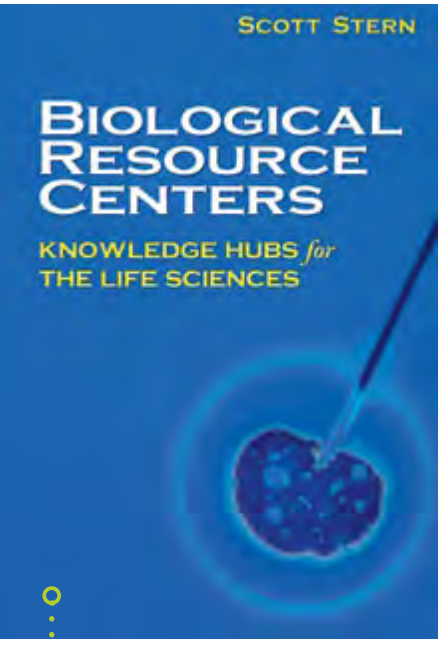
Stern, with the support of Jeffrey Furman, began examining the economic and policy dynamics of biological resource centers to assess their role as knowledge hubs in innovation. Stern met with Cypess and Frank Simione at the Brookings offices as he started his research. "I found Ray Cypess to be, from the start, inspiring and insightful and open to the idea of an independent study that would allow us to investigate the economic consequences of biological resource centers," Stern said.

ATCC provided Stern and Furman with access to board members, staff and scientific peers as they conducted their research. Stern came to see ATCC as a prime example of the kind of institution that he called a "knowledge hub." Knowledge hubs help peers to acquire, authenticate and gain access to knowledge and materials needed to foster innovation. The term covers everything from open-access libraries and science journals to standards groups. Stern and Furman's study led them on a path through biology that would unfold over a decade, with strands that extended to the story of the Obolensk center and its fate in post-Soviet Russia. At the end of that 2002 Obolensk episode, the Russian government had provided emergency funding to pay the electric bill. Yet the episode showed how an electric utility could hold the upper hand in national biosafety and research (Stern, 2004).

A knowledge hub could be for-profit or nonprofit, although Stern found that for-profit hubs were less likely to provide some benefits, such as long-term preservation of materials or pricing that allowed the widest access to knowledge and material. His findings, first published by Brookings in 2004, broke new ground in establishing a

When asked by Cypess about existing research on the economic impact of biological resource centers, economist Robert Litan (pictured) recommended contacting his Brookings colleague Scott Stern.

Jeffrey Furman joined Stern in investigating the economic and policy dynamics of ATCC and other biological resource centers to assess their role as knowledge hubs for the sciences.



Stern's seminal study, first published in 2004, established a method to measure how biological resource centers foster cumulative knowledge.

method to measure how biological resource centers foster cumulative knowledge.

"It was a challenge, but in ATCC they could directly measure that there's a passing between one generation of research to another. Moreover, when we were talking with people at ATCC we came to understand a real fundamental insight," Stern said. That insight came in seeing that a depositor to ATCC's collection might publish knowledge about that material at the same time, or there may be a gap between publication and material deposit. Where there was such a gap in time, that created a research opportunity to study the knowledge diffusion essentially in two different eras: "You could trace the impact of the article during an era where the materials underlying that knowledge were in a more closed environment, and one where they were associated with this institution of cumulativeness."

That method opened a new door for analyzing an institution's role in the scientific process. The work of Stern and Furman became the center of a larger body of research on science and technology as well as the economics of innovation. "That methodological breakthrough was very much grounded in our ability to see it so vividly in ATCC," Stern said. "ATCC is the purest example of an institution that served to facilitate this fundamental function of science."

Stern confirmed what ATCC had experienced: Advances in biological research increased scientists' ability to build on previous findings, but mechanisms for validating materials in the research were slow to catch up. Filling that gap in authentication of materials was vital for biological resource centers to ensure their continued relevance and existence. "Perhaps more than any other action, BRCs' efforts to address the problem of misidentification and to restore trust in biomaterials exchange established the importance of their role in life sciences research," Stern's Brookings study stated (Stern, 2004).

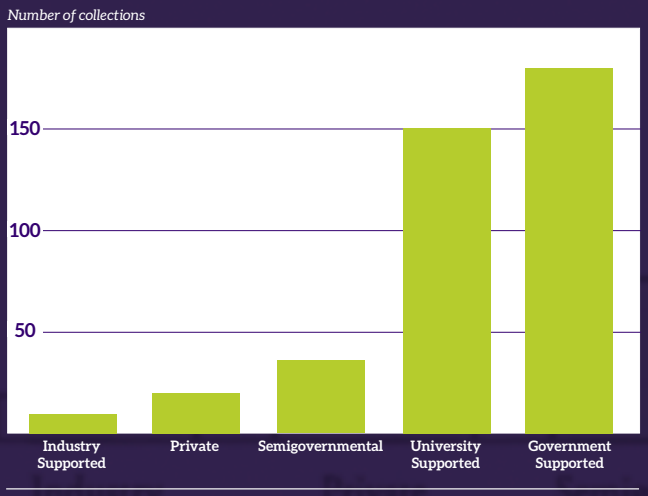
The economists also outlined other large challenges that BRCs faced: changing research structures and technologies as well as the way that the threat of bioweapons had shifted the debate about safe sharing of sensitive bioorganisms. Their study showed that despite such challenges, biological resource centers made the whole research infrastructure more cost-effective.

The work of Stern and Furman captured the attention of analysts of science and enterprise policy. "It's interesting in terms of the magnitude of the effects," said Josh Lerner, a fellow economist at Harvard Business School who studied innovation and entrepreneurship. "I think BRCs have not been that visible to people outside the biological research academy, so to see how significant they are is striking" (MIT News, 2012).

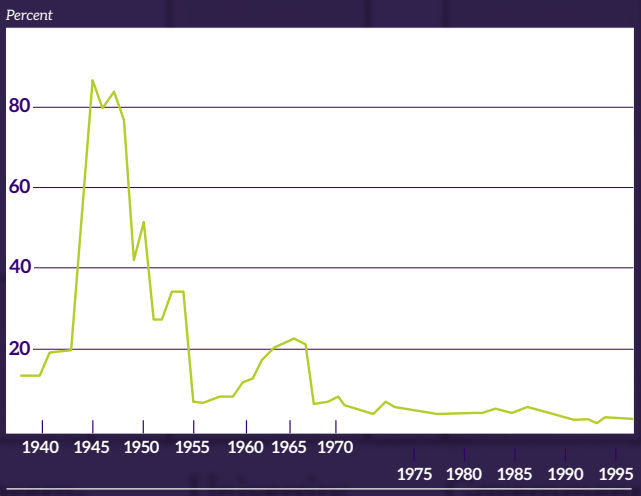
The service that ATCC had provided to biology for nearly a century embodied what Lore Rogers and the other founders of the collection had hoped it would: Independent of patent or intellectual property, the collection provided a vehicle for sharing knowledge and best practices. Stern's analysis confirmed that a scientific paper linked to ATCC was more

CHARTING SEA CHANGE IN THE FUNDING OF LIFE SCIENCES

The early 21st century confirmed a trend in resources dedicated to biological research. By 2004, ATCC received less than 10 percent of its budget from direct government grants; most of its funding came from fees for patent depository services and product sales and distribution, along with contracts. This reflected the larger trend in federal government funding — a decline from over 80 percent in the 1940s to under 10 percent by 2000, as seen in this figure from Scott Stern's Brookings study.



Source of funding for culture collections, 2004



Percentage of Federal Life Sciences Research Funds, 1938–2000

than twice as likely to be cited by other scientists than a paper published with no ATCC affiliation. Furthermore, that significant benefit increased over time as the literature grew. Stern and Furman continued to highlight these findings for years afterward. "BRCs are suppliers of public goods that are essential to supporting the rate of scientific progress," Furman told *Nature* in 2014.

The methods that he and Stern developed extended into other fields and policy thinking. Their MIT colleague Heidi Williams, an economist who received a MacArthur "Genius Grant" in 2015, adapted the approach to examine the role of the patent system in innovation. Another colleague explored how public investment in satellite imagery of Earth, such as Landsat, had spurred growth in sectors as unexpected as gold mining and the discovery of new gold deposits.

An analysis of public investment in ATCC that appeared in the *American Economic Review* in 2011 featured a cost-effectiveness index. This addressed the issue that had long bedeviled ATCC's directors in seeking government funding: Congress had always preferred to fund new research instead of a microbe repository. The 2011 study showed that the assumption that it was better for government to invest in a research study rather than the infrastructure that supported research was mistaken. "In asking whether we

Applying Stern and Furman's approach to the patent system, MIT economist Heidi Williams investigated how patent policy affects follow-on scientific research and product development.

Left: The BACPAC Resources Center at Children's Hospital Oakland Research Institute reduced its collection of artificial chromosomes and disposed of backup materials due to declining revenue.

Right: Changes in federal funding for living collections forced the Fungal Genetics Stock Center to relocate its 75,000 strains to a center at the Department of Plant Pathology at Kansas State University in 2014.

spend the last dollar of federally allocated funds on enhancing BRCs — making sure results are accessible — or doing additional research, there's been a bias to fund more research that nobody can use," Stern noted. "Basically this study became one of the pieces of evidence that people used to justify much more investment in open data, open access and funding investments to make research more accessible."

This analysis was validating for Cypess. Still, it did not stop many BRCs from feeling the pinch from genetic technologies and a chilly funding environment made chillier by intellectual property restrictions and the effect that bioterrorism fears had on the sharing of microbes. The bind that the Fungal Genetics Stock Center at the University of Missouri (later Kansas State University) faced was typical. The National Science Foundation (NSF) had supported the center's effort to make more than 25,000 fungal strains available to researchers, but then the NSF grant was not renewed in 2013. "They want us to become self-sustainable, but then you have to raise your fees so much that you impact the ability to use your resources," said Kevin McCluskey, the collection's curator. Another collection highlighted in *Nature* offered a cautionary tale: The BACPAC Resources Center in California held a large collection of artificial chromosomes for gene-sequencing projects, but it got bypassed when cheaper sequencing technologies came along. As user fee revenues declined, the center had to cut the number of its freezers in half and dispose of backup materials, limiting future access to important material (Baker, 2014).

Addgene, a startup repository for plasmids, adapted to the changing scientific environment by leveraging underused material.

Another library of biological material that started as a small startup in Cambridge, Massachusetts, managed to adapt and thrive. Addgene, a repository for plasmids (packets of DNA used to put genes into cells), grew in 10 years to ship more than 90,000 plasmids a year. It found itself well positioned with the advent of CRISPR, the gene-editing tool. Like ATCC, Addgene's managers found they needed to capitalize on

the "long tail," as they discovered that about one-third of the plasmids in their collection never got requested. But they knew that could change. There had to be a way to leverage that underused material (Baker, 2014).

NEW USES FOR A LONG TAIL

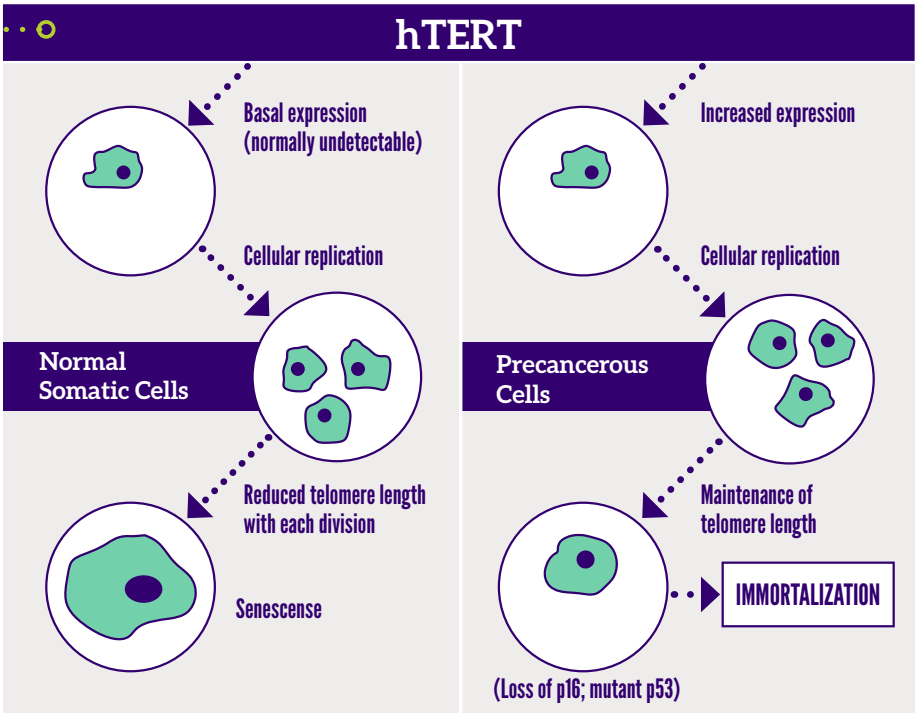
Two researchers in systems biology saw a way for genetic research to provide the needed leveraging of underused microbes. In particular, they saw knowledge of the better-known strains in a collection as a way to advance understanding and use of the many lesser-known species in the "long tail" (Wang and Lilburn, 2009). Systems biology was a good area for such an insight: the field emphasizes a holistic view, with the understanding that an organism or system is greater than the sum of its parts.

Yufeng Wang and Timothy Lilburn noted in *Bioscience* magazine that the genome sequences of ATCC's better-known strains (totaling nearly 500 species in 2009) were relevant for the nearest relatives of those strains. Using knowledge of evolutionary relationships among bacteria, those sequences could be used to inform research on lesser-known relatives. Phylogenetic transfer involves building robust metabolic network models for the "data-rich" species and extrapolating those models to the lesser-known relatives. In that way, the less than 1 percent of organisms that were "data rich" could help expand the scope of use for another 5 to 10 percent (Wang and Lilburn, 2009). This approach suggested that advances in genetics offered new ways to mine information from centers like ATCC and get it shared more widely.

With greater diversification based on staff capacities aligned with the research community's needs, ATCC felt a boost in its bottom line. In 2005, the board had reviewed the strategy and mission for several proposed offshoots under the holding company's umbrella. These included BioNexus™, a subsidiary created to protect and grow the equity assets of ATCC Global. BioNexus in turn created the Global Biological Standards Institute (GBSI), which was formally established in 2013 with three purposes: provide thought leadership in the articulation of viable standards for biological research, inform policy that supported that direction, and provide training to scientists in best practices for authentication.

Launched in 2013 with funding from ATCC's BioNexus Foundation, the Global Biological Standards Institute provides thought leadership to improve the quality and reproducibility of life science research through standards and best practices.

Around that same time, ATCC's expansion continued with the creation of the Cell Derivation Unit (CDU). That unit starts with non-embryonic tissues approved by the Institutional Review Board, a group designated by the Food and Drug Administration to review and monitor biomedical research involving human subjects. The CDU takes



ATCC's newly created Cell Derivation Unit used telomerase reverse transcriptase (hTERT) to develop new "immortalized" cell lines.

those tissues and develops cell lines that can be manipulated with gene editing into more specialized forms for use in drug development. "A first goal of the CDU was to develop new cell lines that were not readily available to the scientific community," said ATCC's Yvonne Reid. "The unit would use new technology such as hTERT (which is a subunit of the enzyme telomerase that is useful in RNA editing) to 'immortalize' cells so that they would retain the characteristics of the original tissue. These cell lines would have significant value for use in basic and applied research, as *in vitro* models and as standard references in the life sciences." Another reason for creating the CDU flowed from the success of the effort to improve malaria research: by addressing gaps in available cell materials and by making scarce materials for cancer studies more accessible to researchers, ATCC could help to recruit research talent for tackling priorities such as lung cancer (Cypess, 2016).

Developed in 2012, ATCC's Cell Derivation Unit (CDU) provides specialized cell lines for scientific research.

Cypess saw the CDU as a big step up on the value chain of research. He had pursued an hTERT license with Geron Corp. because he envisioned the impact this technology would have on new product development. ATCC had long

EMPLOYEE COMPENSATION AND CAREER DEVELOPMENT

In an environment influenced by government contracts and an emerging biotech employment environment, ATCC found that it needed to enhance its programs for attracting and retaining new talent.

Companies in the D.C. area, known for its high cost of living, compete for federal contracts with a workforce that demands higher wages than those in other parts of the country. The culture and workforce structure at ATCC that Cypess inherited lacked creativity, innovation and urgency. Nonprofits do not have the same ability as profit-making companies to offer incentives to employees, such as stock options, bonuses and relocation subsidies.

With a need to better manage personnel costs, and in order to overcome the obstacles in attracting and retaining new talent, Cypess restructured the ATCC compensation program for the first time in 1994. A corporate bonus program was introduced for all employees as well as a competitive total rewards program based on a hybrid model. Since then, employees have consistently received merit increases, and bonuses have been awarded for 21 consecutive years. To address the issue of employee productivity, ATCC established a pay-for-performance system as well as continued internal and external training programs. Career development for management, science and technology tracks were also established.

been a pre-clinical business, supporting researchers in the early phases of their work. What he envisioned was a kind of vertical integration, taking the knowledge embedded in ATCC's cells and moving that information closer to translational medicine and medical applications. With the Cell Derivation Unit, ATCC could mobilize a greater portion of its collection's vast assets toward Phase 1 clinical trials. "We supplied elements for all levels of the value chain, but we were at the bottom," Cypess said. "My analogy was: We were a lumber company. We had to become a furniture maker." If ATCC kept on simply providing cell lines, it also faced intense competition from nonprofits and startups like Addgene. With the CDU creating cell lines with greater demand, ATCC moved toward being a furniture maker, capturing a greater portion of the end product's value in revenue.

Pursuing the development of cell lines from tissues provided a way around some of the encumbrances ATCC was experiencing and also provided a mechanism for developing new and better quality materials. For example, the CDU has reduced the problems of availability, technology transfer and delays in getting materials from depositors. Unhindered by these, the process for technology transfer and distribution becomes more efficient. The development of cells from tissues also addresses gaps in the available cell and organ systems, especially from those diseases currently lacking tools and reagents. Built around a set of criteria for standards, these items become reference standards and quality control is built in from the beginning.

Now ATCC was generating cell lines that the community needed and wanted. Looking back, Cypess saw this as an organic business growth path. ATCC's success in making materials available for malaria research contributed to greater capacity for that research. On the strength of that experience, ATCC performed a similar service with the National

At the 2013 Biotechnology & Standards Conference, over 80 biologists, biopharma executives, economists, legal and standards experts, and policymakers discussed the challenges and opportunities in establishing standards as an efficient, cost-effective driver of high-quality research and reproducibility in the life sciences.

Cypess developed a new non-governmental model for ATCC by mobilizing a greater portion of its vast collection assets, investing in research and development, and building new business relationships higher up the value chain.

Institutes of Health for biosafety and emerging infectious disease research, with the BEI Resources contract. That contract in turn paved the way for ATCC's expansion into providing diagnostic kits with the Influenza Reagent Resource (IRR) and providing new cell lines for neglected diseases and for gene editing with the CDU. The investment in the organization's research and development was yielding new business relationships higher up the value chain.

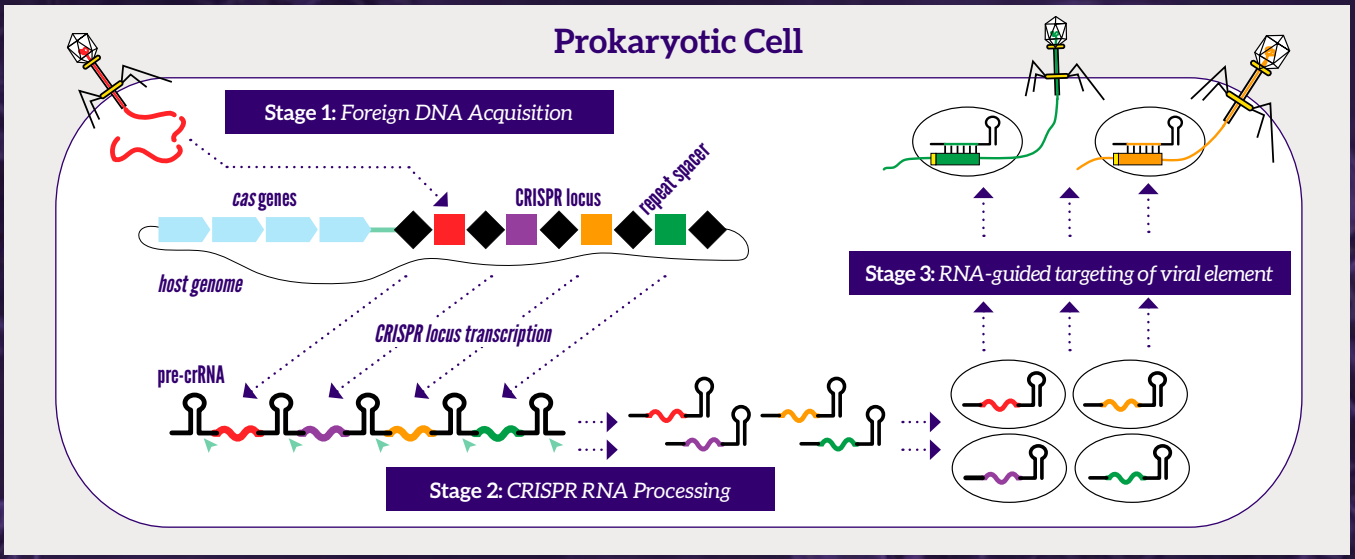
The growth showed in the bottom line. ATCC's revenue from grants and contracts had more than doubled in the decade since Cypess' arrival, from $15.7 million in 1992 to $36.3 million in 2003. With the organization's increased R&D capacity and business diversification, revenue more than doubled again in the next decade, to $87.2 million in 2013, with $100 million projected for 2016. Overall, ATCC's compound annual growth rate (CAGR) is more than 9 percent in the past decade, which is two times the rate of its industry peers. ATCC has experienced 21 years of unqualified financial audits, has had many audits by regulatory agencies without any major findings, and has a flawless safety record.

In 2012, Cypess met with Scott Stern again in Boston, and they made initial plans for a conference on biotechnology and standards, supported by the new Global Biological Standards Institute and the MIT Sloan School of Management. The conference the following year would serve as another example of how ATCC fostered the cumulative knowledge-building essential to science that Stern had studied a decade before. His research had shaped the agenda for economists in the area of science policy for the past decade. Now he gave credit to the biological resource center that had inspired it: "a great organization, one of the most interesting places that I've had the opportunity to explore as a social scientist."

ATCC's business model had matured substantially. As economists were at last quantifying the long-term economic benefits of biological resource centers and ATCC's original purpose to serve science, the organization had evolved from a nonprofit venture vulnerable to declining government budgets into a hybrid that incorporated new, more enterprising approaches to public science.

In an age of declining public budgets for science worldwide, Cypess and his colleagues had created a new non-governmental model for working with researchers. However, their work wasn't done. They still needed to address an emerging problem in the scientific community, where research results themselves were at risk of losing credibility.

CRISPR: GENE EDITING FOR SPEEDIER SOLUTIONS

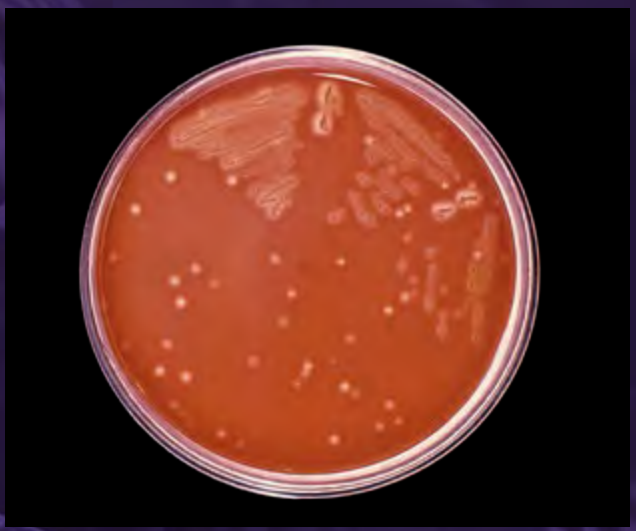


CRISPR allows scientists to create segments of prokaryotic DNA with unprecedented precision, efficiency and flexibility, using the Cas9 nuclease enzyme as a snipping tool.

In recent years, a technique called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has emerged as a foundational tool of genetic research. CRISPR uses an enzyme for gene editing like very precise DNA snippers to cut a genome at any desired point and activate a variety of genetic changes in the Cas9 mouse, a lab mouse variety engineered using the Cas9 enzyme.

"CRISPR is the Model T of genetics," one researcher explained in *The New Yorker*. "The Model T wasn't the first car, but it changed the way we drive, work, and live. CRISPR has made a difficult process cheap and reliable" (Specter, 2015). CRISPR will likely make it easier to model the genetic dynamics of major illnesses like cancer and Alzheimer's disease, at a speed exponentially faster than the animal models that have long been standard practice. CRISPR techniques allow study of the many possible responses of a cancer cell to treatment, for example. It allows work that once took a decade to be compressed into just months. So far, one of CRISPR's main uses is that it allows scientists to quickly reconfigure the genomes of many plant and animal species.

In January 2016, ATCC licensed CRISPR technology to develop a portfolio of new products and services to support basic and translational research. The first ATCC product developed using CRISPR is a cell line known as a workhorse for lung cancer research. The product is expected to be critical for drug discovery and molecular diagnostics of non-small cell lung cancer, which can spread to other parts of the body and which make up 85 to 90 percent of lung cancers.

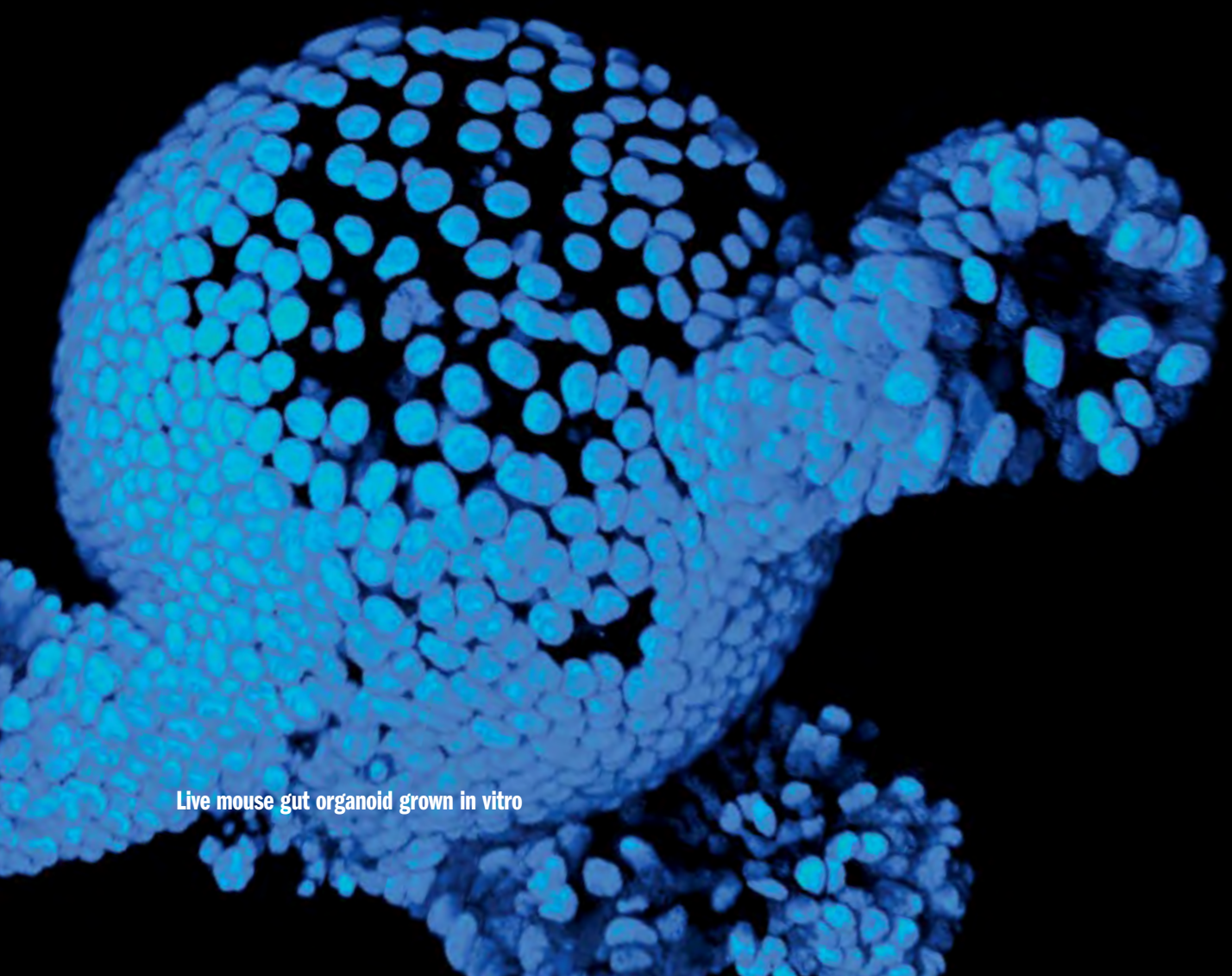


The Cas9 enzyme, derived from *Streptococcus pyogenes* bacteria (pictured), can snip DNA sequences 20 bases long at specific locations.

CHAPTER

9

Superior Quality
FOR THE NEXT 100 YEARS



Live mouse gut organoid grown in vitro

By 2012, it was clear that ATCC had solved a problem that many public science organizations around the world were still grappling with: how to survive in an environment where the public investment in science was shrinking. Raymond Cypess and his team had fashioned a revised strategy derived from market analysis, the execution of which was dependent on breaking down the silos that separated the science units from the business and manufacturing operations within ATCC; expanding the organization's capacity as a research partner; growing the products and services that the organization provided to the regulated industry and regulatory agencies; and offering higher-value tools, other products, and other services that responded to researchers' current and anticipated needs. In addition, ATCC was creating primary, immortalized and gene-edited cell lines from both normal and diseased tissues. To support its mission as a biological resource center (BRC), ATCC developed new policies and tools to address the changes in intellectual property laws and practices concerning biological materials that had constrained the tradition of depositing biomaterials in public collections since 1984. These new policies and tools included material transfer agreements, licensing structures and royalty agreements, and the creation of the Biomaterial Contributor Network (BCN).

Mindy Goldsborough, vice president and manager of ATCC Cell Systems, began to see a change in how people regarded ATCC when she started in 2012. "Science clients who visit our facility are often struck by the range of work ongoing. ATCC has internal R&D on issues that support the scientific community and the drive for authentication and standards," Goldsborough said. "They see us more as a scientific peer than just a repository. ATCC is an organization that has the future of science always in the foreground."

TAKING ON LARGER ISSUES

Now, having fine-tuned its approach, ATCC began providing greater service by sharing it worldwide. From its limited global distribution base, it grew to include 12 distributors worldwide. Its global business model was a solution to a problem many science organizations faced, i.e., sustainable growth in an increasingly competitive global environment.

The economic analyses by Scott Stern and his colleagues confirmed that scientific infrastructure benefited researchers substantially. Stern showed that BRCs provide an essential function in their distribution and authentication of quality inputs in a way that enhances the scientific literature and the entire field of biology. The value of the organization went back to the notion Cypess touched upon when he called ATCC a standards and knowledge company. Nevertheless, despite Stern's groundbreaking analysis, ATCC still faced the challenge of educating the lay public about the link between this "essential infrastructure" and its vital connection to solutions in health care and disease control.

For decades, ATCC's relationship with the press was a source of tension for the organization. Reporters called whenever there was a biological disaster, and their articles typically labeled ATCC with the disparaging term of "germ library" or a similar term that

THE BIOMATERIAL CONTRIBUTOR NETWORK

The Biomaterial Contributor Network (BCN) emerged in 2012 as a way to foster collaboration between academic and government agencies in the new intellectual property environment. Modeled on the patent deposit system, BCN would provide a standardized channel for faster movement of nonpatentable materials among participating institutions. The network achieved critical mass when four major government agencies embraced it: the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Agriculture (USDA). BCN represented a new tool for navigating the challenges of technology transfer, and a step toward sharing non-patentable materials, comparable to what the Budapest Treaty did for patentable biomaterials (Cypess, 2016).

sounded vaguely dangerous. A *Washington Post* article in 1997 described ATCC bleakly: "a supply house for academic and government researchers, the ATCC is housed in a faded, two-story Rockville office building with a cramped basement that was home to some of the most deadly bacteria and viruses known" (Smith, 1997). The article also stated incorrectly that ATCC had purchased a hazardous agent and then "swiftly advertised it for sale." Cypess responded with a letter to the editor, objecting to the mischaracterization, pointing out the errors, and affirming that ATCC does not buy biological materials.

To help change the dominant thinking in the public and the press that ATCC was just a "germ bank," ATCC published a company brochure in 2001 that explained the connection between ATCC's biomaterials and a number of key products that affected the well-being of the public at large, e.g., the PCR process; supplements for infant formula derived from an ATCC microalga; and agro-bio and food safety products (ATCC Products That Touch People, 2001). Despite this initial public relations effort, it would not be until 2006 that ATCC could address this dominant perception in an updated company brochure (ATCC Touching People's Lives, 2006).

Gradually, between 2006 and 2010, ATCC's contributions to successful efforts against worldwide emerging and re-occurring diseases — including SARS, swine flu and tuberculosis — together with its stewardship of key contracts, facilitated a new public stance. ATCC's media communications became more proactive alongside the organization's structural changes. Around 2010, in a board discussion of ATCC's mission, a board member suggested that ATCC should become "a beacon of light to the scientific community." Management determined that advocacy would be most effective through a disinterested entity such as GBSI, unencumbered by service contract ties to government or potential conflicts of interest. GBSI thus became a hub for communications, training and public policy events, including the BioPolicy Summit. This was consistent with Cypess' concern that "the specter of irreproducibility damages the credibility of science and the people who practice it, and ultimately hurts society. A society can ill afford to lose its trust in science and its practitioners."

To change the public perception of ATCC as a mere "germ bank," the organization published a brochure in 2001 that highlighted the multifaceted functions it performs in the scientific community as a standards and knowledge company.

The Massachusetts Life Sciences Center received advice from Cypess on how to leverage its repository more effectively.

Increasing public awareness of the need for standards required that ATCC's leadership look beyond its experience with the press and willingly interact with journalists in a new way. Since 2010, GBSI has embraced opportunities to educate the media and the public. A 2015 report on National Public Radio's All Things Considered addressed the cost of irreproducible research results. The path toward changing the culture of research and building the public's trust in science will involve many more such stories.

Yet even bigger issues loomed. For Cypess, one was the problem that HeLa and mycoplasma contamination highlighted: flawed research practice due to both inadequate authentication and adventitious agent contamination along with the failure to incorporate other material and process standards. Addressing these issues effectively required that ATCC take a more public role in influencing policy and thinking about biological research — a spotlight that ATCC had avoided for decades. The professional societies that had created and supported ATCC had long served as advocates on policy and legislation, including the American Society for Microbiology, which had counseled Congress in 1999 on regulation and biosafety (Atlas, 1999). Now it was time for ATCC to participate more actively in the public dialogue.

The future of science was central to ATCC's new initiative on standards. Everything from drug testing to development of an Ebola vaccine relied on the fundamental soundness of the materials and methods used in experimental research. "One of the most important things in science today is repeatability in testing," said board member John Child. "ATCC was on the front line of developing those standards."

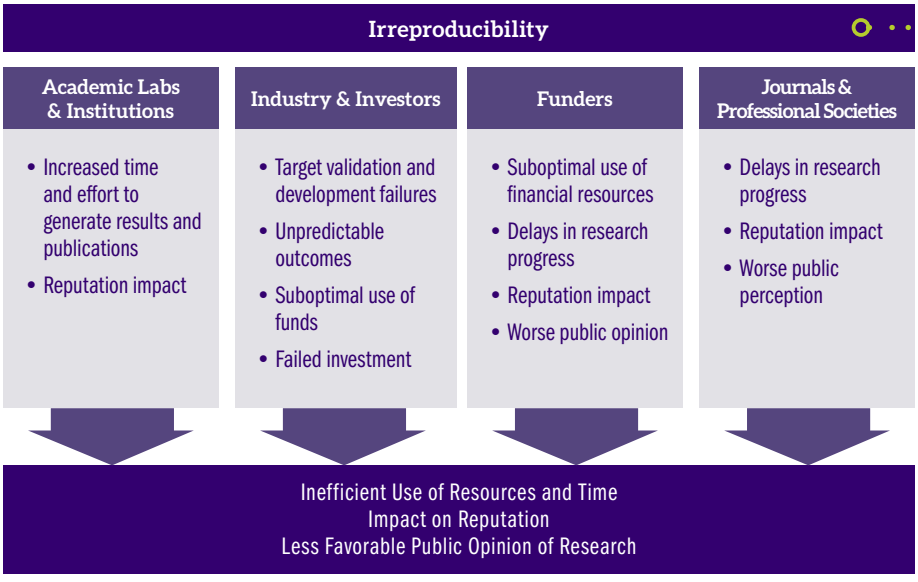
With its 100th birthday on the horizon, and following the re-organization of its board structure, ATCC enjoyed a greater wealth of expertise among its advisors than ever. Cypess, marking two decades at the organization's helm, recalled the treasury of wisdom he had received from board members over the years, from Nobel winner Joshua Lederberg to virology legend Julius Youngner. Years after Youngner stepped down from ATCC's board, Cypess continued to draw upon Youngner's insights as he developed new initiatives for the


CERTIFICATE OF ACCREDITATION

American Type Culture Collection

ANSI

In 2007, ATCC became the first biological resource organization to become accredited by the American National Standards Institute as a Standards Developing Organization.



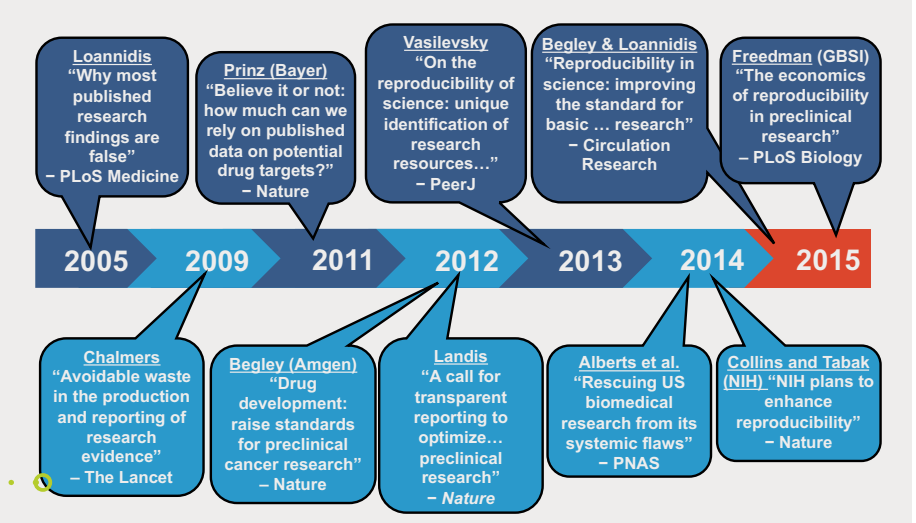
Irreproducibility can lead to negative organizational, financial, reputational and legal consequences for scientific research.

organization. "I felt very good that he valued my advice or used me as a sounding board, so I could always be the devil's advocate," Youngner recalled with a laugh.

Newer board members brought new experiences and energy, too. Lydia Villa-Komaroff, affiliated with MIT, Harvard and several biotechnology companies, had known about ATCC since she was a postgraduate student in the 1970s and had used its collection for her research. She had seen how ATCC had lost its pre-eminence in the world of microbiology when recombinant DNA approaches changed the landscape in biology research. At that time, government research budgets were shrinking and universities created technology transfer offices to seek intellectual property royalties to fill the gap; sometimes, those offices overreached and slowed the research process.

As those technology transfer offices matured in their approach to intellectual property, however, the dynamics began to improve. Villa-Komaroff met Cypess at the Massachusetts Life Sciences Center when he helped the center think through issues involving its repository. She found that Cypess approached problems much as she did: with pragmatism and a desire for solutions. At Cypess' invitation, she joined ATCC's board in 2010 and served as another advocate for better standards. In 2014, Villa-Komaroff was appointed chair of the board's executive committee; in that capacity, she worked closely with Cypess on a further restructuring of the board and its committees, including the addition of term limits.

Villa-Komaroff knew that cutting through the background noise to get attention for ATCC's new direction was a challenge, even within the scientific community. She recalled an MIT colleague who said, "I had forgotten about ATCC." Villa-Komaroff thought that if ATCC spoke more publicly on important issues, it would have the added benefit of reminding scientists of its existence and role. She also applauded ATCC's shift toward a more active research profile, with staff giving more presentations at scientific gatherings.



Left: In his keynote address at the 2013 Biotechnology & Standards Conference, Cypess emphasized the need for a "continuum of standards" in an increasingly complex research environment.

Right: The scientific community started to recognize irreproducibility as a major issue in the mid-2000s.

Having aligned its business model closely with the research enterprise, ATCC prepared to take on an initiative that would span generations — and that would require a bigger platform. Cypess was coordinating with the American National Standards Institute, which had promoted voluntary consensus standards for U.S. industries since 1918. ANSI recognized ATCC officially as a Standards Developing Organization (SDO) and the first such organization with the authority to create standards for biological materials. This put ATCC on par with groups like the Society of Automotive Engineers in terms of stature for building consensus among researchers, policymakers and manufacturers in related disciplines. This ANSI certification led to the development of the groundbreaking consensus standard for STR-based cell authentication by ATCC. ATCC's status as a flagship global standards organization was enhanced further when it achieved ISO status (ISO 9001; ISO 13485; ISO/IEC 17025; ISO Guide 34). Both of these corporate developments reflected Cypess' strategy to seek external certification as a non-government global standards organization.

Continuing this strategy, the establishment of the Global Biological Standards Institute (GBSI) in 2012 set the stage for meaningful advocacy for biotech and biology standards. This advocacy ramped up with the publication of a white paper, "The Case for Standards in Life Science Research," and the Biotechnology & Standards Conference in Boston, arranged in collaboration with Scott Stern and held at MIT's Sloan School of Management. Researchers and industries were voicing increasing concerns over the issues of standards and the lack of reproducibility in many research findings. The steps ATCC had championed for a decade — consistent materials authentication, process standards, better training, high-quality research support — received a brighter spotlight.

A second publication, following the white paper, made clear the cost of irreproducibility: roughly $28 billion a year spent on preclinical research in the United States alone. That

represented almost 25 percent of the total estimated $114.8 billion spent on life sciences research annually, most of that funded by the pharmaceutical industry (61.8 percent), and nearly a third funded by the federal government (31.8 percent). The paper also provided a historical frame for viewing the issue:

> The concept of standards is not new, nor specific to the life sciences. Standards have, in fact, served as the foundation of progress throughout millennia. Many advancements that we take for granted every day, including language, lightbulbs, bridges, Wi-Fi, and the internet, would not be possible without the development and adoption of global standards within their respective industries. But unlike other fields of endeavor, life science research has very few broadly implemented standards (Freedman et al., 2015).

The authors acknowledged the negative connotations that "standards" conjured for many biologists: bureaucracy, stifling regulation, and pages of obscure and rigid rules. However, estimates of the extent that misidentification and contamination affected cancer cell lines ranged from 15 to 36 percent. These issues fueled the loss of public trust: "Researchers must confront a small but growing negative public perception of scientists and the scientific method" (Freedman et al., 2015). It was determined that most standards proposed for biology would be voluntary and more effectively managed by researchers themselves, and would improve the quality of their studies. With these arguments, the policy paper crystallized the appeal to scientists themselves.

ATCC's advocacy for biotech and biology standards culminated in the creation of the Global Biological Standards Institute and the publication of the influential white paper "The Case for Standards in Life Science Research."

GBSI, led by President Leonard Freedman, has embraced new forms of advocacy to increase public awareness of the need for standards in the life sciences.

In his keynote talk at the conference, Cypess described the causes of irreproducibility, the rise in misidentification of experimental materials and the increasing cost of poor research performance. He explained that the problem grew from the growing complexity of biological systems and multi-team science, coupled with the increase in competition to publish research findings, as well as a de-emphasis in materials-handling, statistical training and standard operating procedures. The procedures of adhering to proper identification and validation of materials "were not on the scientists' to-do lists" and not explicitly required by most publications or grant-making organizations.

The problem, Cypess said, was important far beyond the billions lost directly to the

Frank Simione played an integral role in ATCC's transformation from a culture collection to the premier global biological materials resource and standards organization.

faulty research results. Flawed experiments had a domino effect, he explained: "Mistakes you make early on in the process in basic research will have an effect on translational research and clinical research. You have to have a continuum of standards."

Solving the problem will require more than simply establishing a process for better research. It requires acknowledging the behaviors and environment that had led to the problem — coping with an increasingly complex research situation and the temptation of shortcuts.

> Culture is not always as appreciated as it should be. We're going to have to bring the social scientists into some of this work that we're talking about. Not only the economists, but also the sociologists and anthropologists. Guess what? We're dealing with behavior. A lot of what we're talking about is behavior (Cypess, 2013).

The new tools and processes dedicated to improving use of material and process standards would need to reckon with individual and institutional behavior, and that meant professional training and education.

From the stage, Cypess also acknowledged his longtime colleague, Frank Simione, as "Mr. ATCC." The two had worked together for 20 years and had weathered financial crises, creating a new facility and moving the entire collection there, and addressing threats resulting from the increased focus on bioterrorism in the early 2000s (Cypess, 2013). Simione was an early acolyte for the new vision. In addition, during his presidency of the International Society for Biological and Environmental Repositories (ISBER) and his trusted relationship with the World Intellectual Property Organization (WIPO), he represented ATCC in important domestic and international governing bodies. His familiarity with regulations for shipping biomaterials, and his relationships with government agencies such as the USDA and the Department of Commerce (DOC), were critical in facilitating the task of distributing biomaterials worldwide.

PROGRESS IN THE HALLS OF SCIENCE

Board member Keith Bostian saw how ATCC's work on standards was starting to change institutions: "Ray Cypess' argument for the need for standards has been taken up by others in the science community," he said. "The cost of irreproducible research results has become clearer and more widely recognized." Getting institutions to change — including the professional societies that had come together at ATCC's earliest days — was not easy. But gradually associations began to change their editorial guidelines for publication in their journals. ATCC board member Elliot Levine recalled the hard work and advocacy that were needed in order to inch forward those changes in editorial policy:

> Several journals — the *Journal of Cell Biology*, the *Journal of Microbiology* and maybe the *Journal of Virology* — now have a statement in the instructions to authors that say they should — they don't say must — they *should* include the provenance of the cells [used] and the results of a mycoplasma assay.

Eventually, other journals such as *Nature* also adopted that policy in their checklists for authors. However, only about 10 percent of scientists who submit papers check that box, so far (GBSI, 2014).

Getting grant-making agencies to require grant applicants to authenticate their materials was also an uphill battle. The cause gained champions like Howard Soule, a senior fellow with the Milken Institute, an independent economic think tank. At a summit on policy sponsored by GBSI at the Newseum in Washington, D.C., Soule described how the Prostate Cancer Foundation requires the scientists it funds to test their cells, and he challenged NIH to do the same.

In time, NIH took up the challenge. As Larry Tabak, NIH principal deputy director, explained:

> Nothing could be more important to our enterprise than research rigor, assuring that the results of our work are reproducible. . . . In 2014, NIH worked alongside journal editors to develop a set of common principles to guide how research results are reported. In 2015, NIH published a series of videos as a resource intended to stimulate conversation in courses on experimental design.

The agency also highlighted ways researchers could strengthen experiments by incorporating gender as a variable, and ways to improve cell line authentication. In 2016, NIH added review criteria for applications and outlined its expectations for scientists about the rigor of research in their applications.

> These changes will prompt applicants and reviewers to consider issues, which — if ignored — may impede the transparency needed to reproduce key results. . . . It is this strong foundation upon which research going forward relies, and we are confident that these changes will be embraced as an important step in lifting the entire research enterprise to even greater heights (Tabak, 2015).

NEW DIRECTIONS IN RESEARCH

Cypess always reminded colleagues that "the essence of a science organization is its science." To that end, he put a great emphasis on recruiting competitive scientists who preferred to work at the nexus of basic and applied research. This also meant seeking collaborations and partnerships with leading research organizations and laboratories, including the University of Virginia (UVA), the University of Maryland-College Park (UMD), the Massachusetts Institute of Technology (MIT) and Johns Hopkins University (JHU). The conversations between ATCC and MIT were especially fruitful and evolved with the participation of MIT's Weiss Lab for Synthetic Biology. As noted in Chapter 2, the young field of synthetic biology — combining biotechnology, evolutionary biology, molecular biology and genetic engineering — had broadened horizons with the technological ability to edit DNA with precision.

Larry Tabak

ATCC deepened its relationship with MIT by funding a postdoctoral scholarship at MIT's Weiss Lab for Synthetic Biology.

Left: Together with the Institute for Life Science Entrepreneurship, ATCC co-founded the Center for Translational Microbiology in 2015.

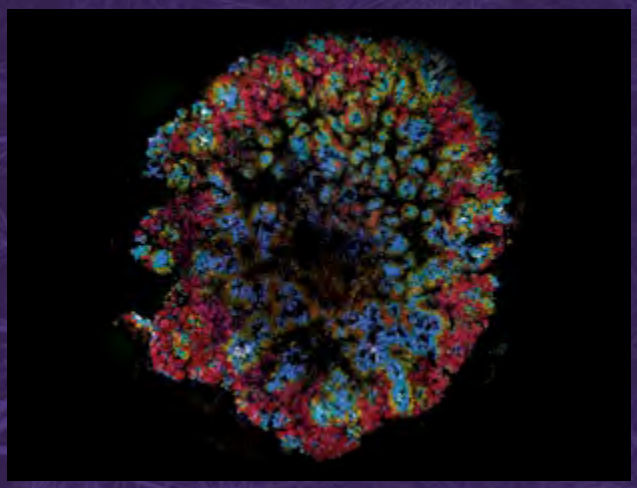
Right: The center's state-of-the-art labs are located in the New Jersey Center for Science, Technology & Mathematics at Kean University.

In 2015, ATCC took a step further into synthetic biology by arranging to support a postdoctoral research post at the Weiss Lab. Deepak Mishra, whose work focused on the design principles of synthetic biology networks and systems, became one of the first postdoctoral researchers supported by ATCC funding. In his work, Mishra looked at making circuits created by synthetic biology as predictable as electronic circuits. More predictable synthetic biological circuits for biosensing, for example, could create cells to track specific molecules in the environment — for example, they could detect indicators of cancer and then trigger the release of molecules targeted to kill the cancer cells (Chandler, 2014).

The prospects were exciting. Still, why should ATCC, as a research and inorganic growth paths support organization, get actively involved in basic research? Cypess based his answer to that question on an old hockey adage: "Go where the puck is going." ATCC could leverage its work in biological science more by getting to new developments faster through key partnerships like the one with the Weiss Lab. Equally importantly, ATCC was advocating the incorporation of standards as early as possible in the research and development process. Failure to incorporate standards early in the process would result in downstream consequences in clinical applications (Boonstra et al., 2010).

In May 2015, ATCC took another decisive step toward translational and inorganic growth paths research when it applied its Buy-Build-or-Partner business strategy to team up with the Institute for Life Science Entrepreneurship (ILSE), a nonprofit organization for incubating translational science research, and established the Center for Translational Microbiology (CTM) in Union, New Jersey. The concept for the CTM had been sketched on a napkin at a 2013 lunch meeting in Philadelphia involving Cypess, Bostian and Goldsborough. The center works on key challenges in translational microbiology, including synthetic biology and antimicrobial resistance, microbial bioinformatics, and the microbiome, which is the ecosystem of microorganisms found in animals or humans.

INFRASTRUCTURE FOR KEY CANCER RESEARCH



Organoids, three-dimensional organ-buds grown in vitro, enable scientists to simulate diseases in order to better identify their causes and identify treatments.

Recognizing ATCC's leadership role in the development of standards, the National Cancer Institute (NCI) awarded ATCC a contract in September 2016 to support a global consortium focused on the development of the next generation of cancer models using three-dimensional cell systems such as organoids. The consortium is comprised of Hubrecht Organoid Technology (The HUB) in the Netherlands, the Wellcome Trust Sanger Institute, and Cancer Research UK, in collaboration with NCI. ATCC's role is to provide the infrastructure for storage, manufacturing and distribution of organoids for cancer research within the framework of standards.

The center's laboratories and staff work in state-of-the-art facilities at the New Jersey Center for Science, Technology & Mathematics, dedicated to fostering a new generation of teachers and researchers in science and technology, located at Kean University, New Jersey's third-largest public university. The multimillion-dollar partnership has laid groundwork for deeper collaborations. It also allowed for sharing of revenues from products and licensing fees that emerge from the center's research, along the lines of ATCC's model (ILSE press release, 2015). As Cypess observed at the opening:

> [The center's structure served the unifying strategy:] to bring together basic researchers from academia with applied scientists from industry, entrepreneurs and business concerns, in an environment that facilitates the translation of early innovation in microbiology into successful outcomes. The center seeks to become a world-class research organization centered on cutting-edge technologies shaping the future of microbiology.

Using approaches from systems biology and in big data analytics, for example, the center was poised to explore microbial ecosystems and metabolomics, which is the study of metabolites found within an organism. Cypess took a century-long view at the center's launch in Union: "We see this as an opportunity to expand our footprint into the talent- and resource-rich New Jersey region and develop new research tools and technologies that will enable the execution of 21st-century microbiological R&D."

Short tandem repeat analysis, a method that compares specific loci on DNA from different samples, could reduce the cost of irreproducible research by 15 percent.

ATCC had gathered a formidable team. With Cypess at the event were Goldsborough; Bostian, representing ILSE and Kean University; and Maryellen de Mars, senior director of ATCC's Standards Resource Center.

With the widening of its research capabilities, ATCC keeps an active eye on emerging fields for opportunities, including cellular therapy, precision medicine, organoids and "organ on a chip." In cellular therapy, patients receive injections of cell material, such as T cells, that can fight cancer. Precision medicine is an approach for treating disease that looks at individual variability in genes, environment and lifestyle; practitioners envision a future in which medical researchers, providers and patients work together toward more individualized care (NIH, 2015).

Organoids and "organ on a chip" are two similar areas of emerging medicine. Researchers, who use stem cells to shape balls of neural cells that then organize themselves into functioning structures, look at processes that mimic the cellular formation of human organs.

Organoids exist for thyroid, intestine, pancreatic, gastric, epithelial, lung, kidney and even brain growth. These structures offer ways to simulate a disease to foster better understanding of its causes and identify treatments. In the same way, an "organ on a chip" is a three-dimensional microfluidic chip designed to simulate the function of an entire organ or organ system. Coming out of cell biology, these fields involve biomedical engineering research and new models of multicellular organisms. These breakthroughs could eventually end the need to use animals in the development and testing of new drugs. Most importantly, all these fields will need standards.

ATCC's participation in these advances to the frontiers of health and medicine was very different from ATCC's stewardship role of the past. It was now funding research and collaborating actively on innovative basic studies. These new fields approached the vision of holistic medicine that Cypess had championed in his previous career as a research manager in academia. Since the 1990s, when biological research shifted further into genomics with new analytical tools, the organization had to chart a new path. But even Cypess did not know how much that would alter the nature of ATCC itself. Now, as a research partner, ATCC could glimpse the horizon of its second century, in the words of Isaac Newton, "by standing on the shoulders of giants."

WHAT SUCCESS LOOKS LIKE

On the cusp of a renaissance in biology, the coming years could bring either extraordinary advances or a tragic erosion of that promise, if the trend in irreproducibility continues.

Much of the discussion of irreproducibility looks at the costs of current failure — the $28 billion a year lost in the United States alone. The reverse image shows what would be gained through use of best practices already available. Improving the reproducibility rate would amplify the benefits of research.

> [T]he return on investment from taxpayer dollars would be in the billions in the U.S. alone. . . . Although any effort to improve reproducibility levels will require a measured investment in capital and time, the long-term benefits to society that are derived from increased scientific fidelity will greatly exceed the upfront costs (Freedman et al., 2015).

In 2015, NIH funded roughly $3.7 billion in research that used cell lines. Using the estimate that one-quarter of those projects suffered from misidentified or contaminated cell lines, and the knowledge that wider use of "short tandem repeat" analysis could reduce that damage from 25 to 10 percent, that single improvement would save nearly $750 million. Furthermore, a more reliable research system would speed the development of new treatments for cancer and other illnesses. Immediate improvements in two areas — study design, and biological reagents and reference materials — would yield significant benefits quickly (Freedman et al., 2015).

Cypess' legacy at ATCC did not emerge from years of single-minded planning, just as Lore Rogers had not devoted himself to long-range strategic plans. For Rogers, innovation came through daily practice and visits to the laboratory where he examined the questions that arose. Cypess and his team similarly found long-term solutions to ATCC's directional challenge through a continuous, iterative process of incremental changes, innovation and transformation using the tools at hand, partnerships and his perpetual drive of wide-ranging curiosity and eclecticism.

By incorporating entrepreneurial concepts to revitalize ATCC, the organization's stewards discovered a vocabulary that could be applied to larger challenges, even to examine the health of the scientific enterprise at large. Far beyond keeping a biological repository afloat, these stewards created an environment for renewing the prospects of advances in life sciences for decades to come.

In that evolution, ATCC's story has itself become a source of authority and strength. Its ups and downs for nearly a century offer lessons for the many hurdles faced by scientific organizations large and small. This narrative is testimony to the many scientists who dedicate their lives to advancing human understanding through the scientific method, and to the challenges and satisfactions that that mission entails.

ACKNOWLEDGMENTS

This book is the result of a team effort, and we would like to thank everyone who played a role in bringing the remarkable history of ATCC to life.

We would like to thank the ATCC staff, board and alumni who went above and beyond to make this book possible, especially Keith Bostian, John Child, David Gillece, Mindy Goldsborough, S.C. Jong, Elliot Levine, Yvonne Reid, Trish Slaski, Lydia Villa-Komaroff, Nancy Wysocki and Julius Youngner. They and others gave of their time in answering many rounds of questions and participating in group and individual interviews; to them we extend our sincerest thanks.

We would also like to acknowledge David Taylor for undertaking the daunting task of distilling nearly a century of ATCC's achievements into a unified narrative.

A special note of appreciation is extended to Sandra Cypess for her review and critical comments during the writing and editing process.

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This list is not exhaustive. Dozens more people helped us capture this story and put it in context. In honor and respect for the thousands of scientists who have contributed to a shared pool of biological resources for advancing medicine, agriculture and quality of life — we sincerely hope we succeeded in rendering your story with authenticity.

Raymond H. Cypess, DVM, PhD
Frank P. Simione

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IMAGE CREDITS

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BOOK COVER

Front cover, Co-culture of ATCC CCL-185 and ATCC CRL-1593.2: Crabbe, A et al. 2010. Alveolar epithelium protects macrophages from quorum sensing-induced cytotoxicity in a three-dimensional co-culture model. Cellular Microbiology. 13(3), 469-81, fig. 4-B1.

Back cover, First minute of EGF endocytosis in a duodenal adenocarcinoma: Arola Fortian

CHAPTER 1

CDC/James Archer

Army Medical Museum: Courtesy of the U.S. National Library of Medicine

Winslow: Fisher IF, Fisk EL. 1916. How to Live: Rules for Healthful Living Based on Modern Science. 9th ed. New York: Funk & Wagnalls, XXXVI.

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McCormick Institute: HathiTrust/John McCormick Institute for Infectious Diseases. 1915. Brief History and Description. Chicago, n.p.

Absidia coerulea: Courtesy of Alena Kubátová

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Congressional hearing: Associated Press

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Salmonella: CDC/Sherif Zaki, Elizabeth White

West Nile virus: CDC/ P.E. Rollin, Cynthia Goldsmith

Clostridium botulinum: CDC

Bacillus anthracis: CDC/Laura Rose

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