PLANT & LIFE SCIENCES COMPANIES

APT THERAPEUTICS INC.
Drug discovery and optimization

DR. ERIC LEIRE, APT therapeutics Inc.

Dr. Eric Leire, M.D. President & CEO
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“"A biotech company in the Midwest has to be very good to attract people, so your proposition has to be very interesting.”

Historic overview: President and CEO Eric Leire, who’s an M.D. with an M.B.A., was with bioStrategies Group in Washington, D.C. when he was approached about joining APT Therapeutics Inc., formed in 2001 in St. Louis. “Initially, I was moderately interested, but when I looked at the details of the technology I became very excited,” he says. “I found the diamond in the rough”—a biopharmaceutical company driven by knowledge-based, computer-aided drug discovery engines leading to accelerated development and optimized therapeutics. Based in the Nidus Center, APT has six employees, including five Ph.D.s or M.D.s. “We design drugs for pharmaceutical and biotech companies and for ourselves,” Leire says.

Products and services: APT uses protein engineering, protein informatics and cheminformatics software to the study of the function and expression of proteins, in order to understand disease mechanisms at the protein, cell and cell pathway levels. As a result,
APT is able to shorten drug development cycles, rescue failed drugs and improve existing ones. At the moment APT’s leading drug candidate, APT102, is a promising protein drug for treating acute ischemic stroke. Now in pre-clinical development, APT102 is expected to offer a safer, more potent and more convenient treatment alternative than current treatments. With more than one-half million American stroke victims annually, the market opportunity for APT102 is estimated at more than $1 billion. APT is negotiating with pharmaceutical partners to develop it commercially.

**Distinguishing characteristics:** “Usually it takes three to five years and a team of 30 people to develop a new drug candidate. But six of us developed APT102 in a year,” Leire says. “Instead of the long process in the lab with test tubes, doing multiple experiments, we just do that a couple of times and we modelize on the computer, which goes faster and allows us to make predictions. That saves a lot of time and money and the bottom line is we have a very interesting drug candidate.” APT also is moving forward with a second drug candidate.

**Regional benefits:** Leire believes Midwest capital firms like CID Equity and Prolog Ventures “are doing a fantastic job.”

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**CHEMIR ANALYTICAL SERVICES**
Contract research and synthesis services

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▲ **SHRI THANEDAR**, Chemir Analytical Services

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“Our expertise is finding quick solutions to unusual problems.”

**Historic overview:** In 1990, Shri Thanedar was working for a huge corporation and realized he “wanted to be somewhere to make a difference, but that was hard to do in a large company set in its ways,” he says. Thanedar decided to buy a company of his own, so he opened the Yellow Pages to look for small chemical companies. He ended up first working for, then purchasing Chemir. The company had two employees and $150,000 in sales when he bought it. Now Chemir employs 45 and expects $7 million in sales for 2003, a growth rate of 300 percent since 1996.

**Products and services:** Chemir solves unusual performance and quality problems found in most industries, offering practical solutions for non-routine materials identification, deformation, and chemical analysis. The company offers a wide range of analytical and testing services (organic, inorganic and polymer) for difficult problems like failure analysis, customer complaints and legal issues. “People frequently come to us in a crisis situation,” Thanedar says. “There’s a lot of variety in our work.”

**Distinguishing characteristics:** “Most testing labs do more routine work, like water samples. Only a handful of others do what we do. It’s
Chemir’s impressive record of problem solving has been profiled in Time magazine.

What’s new since last year: The company established Chemir Synthesis Services to provide custom synthesis for the chemical, pharmaceutical, agricultural and polymer industries. Also, the company officially changed its name to Chemir Analytical Services from Chemir Polytech Laboratories Inc.

Regional benefits: “St. Louis has enough high-tech companies here that we don’t have any trouble attracting high quality people locally. It’s a good source of talented people from Washington University,” Th nedar says.

Looking ahead: Chemir plans to grow internally and through acquisitions. “We’d like to acquire some companies on either or both coasts,” Th nedar says, “as well as doing more pharmacological analysis, helping companies bring out new drugs.”

The name: Th nedar says he inherited the name when he bought the company. It stood for the infrared technology the company used for analysis. “Now of course we use infrared and several other investigative tools,” he says.

CORETECH HOLDINGS, LLC
Laboratory products and product solutions

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"We knew we’d never be satisfied just having a job."

Historic overview: In 1999, Doug Martin and Jim Unnerstall were working at Rockwell International and looking for a business they could own. “We did a lot of market research and studied trends and identified a market segment where we could limit our risk,” Unnerstall says. That turned out to be the life sciences. Martin says, “We wanted to become a full-blown manufacturing facility for research instrumentation.” They hired scientists with Ph.D.s, put together a scientific board and created Coretech Holdings, LLC. The company has 21 employees and provides the highest quality laboratory products and product solutions for biotechnology research all over the world.

Products and services: Coretech Holdings actually is four companies. Vibratome has been a leading supplier of histology equipment for tissue sectioning since 1980. GlasswoRx is a leading manufacturer of precision tools used to produce glass micro-instruments. myNeurolab.com provides online access to a comprehensive selection of laboratory equipment-instrumentation suppliers and also offers online or telephone answers to researchers’ applications questions. Med-Core is a medical instrument and research company currently working on several NIH-funded projects to develop brain injection systems for surgical procedures.

What’s new since last year: Coretech received Ernst & Young’s Entrepreneur of the Year Award in the Life Sciences for the state of Missouri. Also, the company was included in the “Killer Applications” category in Inc. magazine’s annual Internet awards.

Regional benefits: “The region offers advantageous global transportation and a fantastic employee base,” Unnerstall says. “We’re fortunate to be able to collaborate with Washington University School of Medicine and Saint Louis University.” Martin adds, “The region is focusing on life sciences now, so we can integrate with others in the field. We get good feedback from the Donald Danforth Plant Science Center.”
DIVERGENCE INC.
Nematode research and control

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"There are tens of thousands of nematode species and some of them are pretty creepy."

Historic overview: CEO Derek Rapp explains, as a doctoral candidate at Washington University, Divergence founder James McCarter gathered a lot of information about the C. elegans nematode, the first multi-celled organism whose genomes were mapped. "He saw there were opportunities to come up with safe applications to control parasitic nematodes in plants, animals and humans," Rapp says. As a result, in 1998, Divergence was created to develop products to fight nematodes, which cause an estimated $80 billion in crop damage annually worldwide and pose major health risks to humans (pinworms, for example) and animals (e.g., heartworms). The company already has 15 employees.

Products and services: "All the mainstream nematode control products on the market today in plant protection are harmful to humans and the environment or ineffective. No product is selective regarding activities toward nematodes," Rapp says. In addition, resistance to current drugs is increasingly a problem in livestock parasites. Using genomics, bioinformatics, nematode genetics and parasite biology, Divergence has developed a discovery platform identifying new and innovative ways to control these important parasites.

The big news: "The EPA has already banned several products from the marketplace and others are slated to be banned in 2005-2007. Most are restricted or soon will be," Rapp says. "The bottom line is new products are needed and with bioinformatics and genetic information, we expect we can succeed where others have failed."

What’s new since last year: "We have some candidates we think offer very exciting opportunities to become commercial products," Rapp says. "They have shown very good activity against nematodes in plants and also very favorable toxicology results. Initial field trials confirm product performance we’ve seen in the greenhouse. So we think our basic research approach has been borne out by the progress we’ve seen in a number of areas."

Regional benefits: "We’ve been able to hire people out of strong academic institutions," Rapp says. "Also being across the street from the Donald Danforth Plant Science Center and being in the supportive atmosphere of the Nidus Center is very important."

Looking ahead: "We will continue product development and work to find the right relationships with third parties to optimize the commercialization of the products, but the actual commercialization of products is still years from now," Rapp says

Interesting fact: There’s a 50 percent genomic overlap between humans and C.elegans nematodes.
ISTO TECHNOLOGIES INC.
Tissue engineering research

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“The idea that you can actually grow cartilage is quite amazing.”

Historic overview: Isto Technologies was created as the result of research by former Barnes Jewish Hospital scientist David Adkisson. He developed a way to grow cartilage in vitro to replace cartilage that’s been damaged or diseased—a major discovery since cartilage does not heal on its own. Barnes Jewish licensed the process and Mid-America Transport Services, the regional tissue and organ bank, helped establish Isto Technologies in 1997 to commercialize its tissue engineering technology, explains Isto President Joe Feder. The company has 22 employees.

Products and services: Isto Technologies develops technology to repair, replace and regenerate human tissue that has been injured or destroyed by trauma or disease. The company’s lead technology is a process to produce neocartilage. "Using donor cells, we can make a piece of tissue that has the potential to integrate into a cartilage lesion," Feder explains. Isto also is working on a natural tissue glue that makes a biological seal during surgery; an angiogenesis inhibitor that can be used in arthritis treatment; and a tissue-based bone matrix material or BAM to repair bone voids and spinal fusions.

The big news: All of Isto’s products are in or about to be in preclinical testing (animal studies). The neocartilage technology may move to clinical (human) studies at the end of 2004.

What’s new since last year: In 2002, the company moved into larger, custom-designed facilities, added staff and equipment and expanded its research and development activities.

Regional benefits: “St. Louis is a major center for scientific and medical research. Consequently, it has the potential for providing new scientific discoveries, which are the basis for entrepreneurial opportunities in the biotech area. St. Louis also offers a few new venture capital firms, which are critical for the creation of new start-up companies, and area universities are a source of trained personnel,” Feder says. He adds reasonable housing costs and excellent suburban school systems are attractive to potential employees. “These advantages need to be exploited to attract companies to the St. Louis area,” he says.

Looking ahead: “We feel we’re in the forefront of the science to grow a viable piece of cartilage tissue, and we believe our agreement with Zimmer, a major orthopedic company, provides an excellent opportunity for marketing, sales and distribution of the neocartilage product,” Feder says.

The name: Isto derives from a Greek word for tissue and reflects the company’s focus on tissue healing.

LINCO RESEARCH INC.
Research diagnostics for metabolic diseases
"We work with key researchers to develop innovative and robust assays."

**Historic overview:** Rick Ryan, Linco president, explains in 1994, Linco founder Ron Gingerich left the Department of Pediatrics at Washington University School of Medicine, where he did research on diabetes and managed an analytical core laboratory that developed and performed assays for other diabetes researchers at the university. "He had a basement business for many years, but then it became a serious venture," says Ryan, who joined the company in 1999. Today the company consists of two divisions: Linco Research Inc. manufactures and sells test kits; Linco Diagnostics Inc. does contract assays for pharmaceutical and academic research. The company employs 62 people and sells its products directly to laboratories and research institutions worldwide.

**Products and services:** Linco develops assays for scientists working in metabolic disease (diabetes, obesity, cardiovascular) research. The company offers several unique kits and bioanalytical services not commercially available elsewhere. The LINCOplex line uses a new technology from Luminex Corp., Ryan says, which allows researchers to do multiple assays simultaneously in the same test tube.

**The big news:** "Our hot newer products are things not really recognized by the lay population, unless they follow the medical press," Ryan says. "With the revolution in genomics and proteomics, many new proteins are being discovered, and one involved in obesity appears to be Ghrelin, the Hunger Hormone. What we do is develop innovative assays that help provide new knowledge in the area of metabolic disease."

**What’s new since last year:** "Basically we’ve been executing our business plan. We’ve added people in development and manufacturing, and we’re in a phase of organic growth that’s strong," Ryan says.

**Regional benefits:** "There certainly are good benefits being associated with researchers at Washington University We have several collaborations there," Ryan says.

**Looking ahead:** "We expect to grow organically in the categories we work in and with the new multiplexing technology," Ryan says. "Estimates are over the next five to 10 years up to 5,000 new drug targets will be discovered through genomics and proteomics. Many of those will be proteins related to metabolic disease, and we see a pipeline that will continue to grow."

**Interesting fact:** "A new protein may be discovered, but until there’s a reproducible way to measure it, the literature will be cluttered with conflicting data. So we make sure and work with researchers early on and then help to get results published. With consistent data a clearer picture of the new protein function can emerge," Ryan says.
“Our employees are literally world renowned players in this field.”

**Historic overview:** MetaPhore is the result of technology discovered at Monsanto (now Pfizer) over a 10-year period, starting in the late 1980s. The technology is a mimic of a natural enzyme found in your body. MetaPhore is developing drugs for the treatment of diseases associated with free radical damage and inflammation with this technology. The company employs 28 people.

**Products and services:** Specifically, MetaPhore scientists have developed compounds that mimic the function of superoxide dismutase, beneficial enzymes that serve an important protective role in the body by removing superoxide, a toxic free radical that can damage cells and tissues. The compounds have broad therapeutic potential in treating pain, rheumatoid arthritis, inflammatory bowel disease, fibrosis, septic shock and asthma, just to name a few. “What I hear from investors and collaborators is the breadth and depth of the pipeline and the ability to address various disease conditions is a huge benefit,” says Alan W. Dunton M.D., president & CEO. “Our investors only back things showing an extremely high level of promise, so their commitment confirms the science and potential of the company.”

**The big news:** One of the compounds, M40403, is now in human clinical trials. “We just completed a Phase II clinical trial relating to pain,” Dunton says. “While getting to human clinical trials is an important developmental milestone for us, demonstrating human efficacy with our compounds is a pivotal event.” Another compound, M40419, is in safety trials.

**Regional benefits:** “There are great intellectual abilities here. A great work force is available,” says Phillip J. Cooper, senior vice president. “The research and development coming out of St. Louis is excellent, coupled with strong university support.”

**Looking ahead:** Cooper says MetaPhore will team up with a major pharmaceutical company or large biotech firm when indications require it. “Imagine a huge market like rheumatoid arthritis,” he says. “It would be difficult for us to handle every aspect of development, production, distribution and marketing without collaboration.” The company may also open other locations to have a presence near some of the large pharmaceutical companies on the East Coast, “though the core crux of what we do is here,” Cooper says.

**The name:** “We work with a mimic of a natural enzyme, a metaphor for the real one,” Dunton says.

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**ORION GENOMICS**
Cancer diagnostics and life science research

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“We’re a genomics company that employs novel technologies to understand the genetic basis of disease.”

**Historic overview:** After participating in the Human Genome Project and a leading genomics research group at Millennium Pharmaceuticals in Cambridge, Mass., Nathan Lakey and his partners realized “we could leverage our genomics experience in a business,” he says and that was the beginning of Orion Genomics in 1998. “Our original idea was to develop and market novel genome technologies in agriculture. Because two of our founding scientists were at Washington University’s School of Medicine and St. Louis was in the heart of ag country, we decided to locate here.” By obtaining a complete and computerized inventory of the genetic parts that make up a plant, you understand how it survives and can come up with product concepts that improve plants.” The company has 22 employees at the Center for Emerging Technologies.
Products and services: Orion Genomics has a series of patents that exploit DNA methylation to elucidate the gene-rich regions of plants. DNA methylation is a “code printed on top of the DNA sequence that helps you distinguish between junk and genes in a plant,” Lakey says. Exclusively licensed from scientific founders based in Cold Spring Harbor Labs in New York, Gene Thresher™ methylation filtering technology threshes the “junk DNA” from plants, leaves behind only the genes and allows Orion and its strategic partners to sequence plant genomes up to 10 times faster and cheaper than competitors. Orion is sequencing five plant genome sequences with funding from strategic partners or federal agencies including Philip Morris, the Department of Energy, the National Science Foundation through the Donald Danforth Plant Science Center and Via Lactia, a subsidiary of the New Zealand Dairy Board.

The big news: “Orion has expanded its methylation-based technology platform into human health,” Lakey says. “It’s fortuitous for us that the central technology of our company’s focus is so fundamentally important to life that our newest invention happens to work over the tree of life, not just the branch that includes plants.” He’s referring to Orion’s latest MethylScope™ technology, which can be used to detect new cancer biomarkers, leading to breakthrough diagnostic tests, earlier cancer detection and more effective treatment. “We think MethylScope technology is the first that allows methylation profiling of an entire genetic landscape on a single DNA microchip,” Lakey says. MethylScope™ technology also has research applications in obesity, diabetes, psychiatric disorders and aging, as well as in homeland security and biodefense.

Regional benefits: “While the region’s venture capital base has historically lagged behind the two coasts, recently St. Louis has made tremendous strides with the formation of several high quality venture funds led by quality managers,” Lakey says.

The name: Lakey explains, “Orion, the character outlined by the Greek constellation, is a hunter. Orion Genomics hunts for the genetic basis of disease. And Rick Wilson, one of our founders, is an amateur astronomer.”

SIGMA-ALDRICH
Life science and high-technology research products

DAVID R. HARVEY, Sigma-Aldrich

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2001 Spirit of St. Louis Award

“We have more scientific knowledge here than any other company in the world.”

Historic overview: The biochemicals company Sigma of St. Louis
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Back then the company had a turnover of about $40 million and initially doubled its size every five years,” says Chairman, President and CEO David Harvey, Ph.D. Today Sigma-Aldrich is the global leader in life science and high-technology research products, with 6,000 employees (1,700 in St. Louis) in 34 countries and sales of more than $1.2 billion.

Products and services: Sigma-Aldrich supplies more than 85,000 biochemicals and organic chemical products and kits for scientific and genomic research, biotechnology, pharmaceutical development, the diagnosis of disease and chemical manufacturing. Customers include life science companies, university and government institutions, hospitals and industry.

Distinguishing characteristics: Harvey says there are three drivers behind Sigma-Aldrich’s success. “We don’t just mouth these,” he says. “We really believe them.” The first is “an absolute commitment to leadership in life science and high technology. We have unrivaled scientific knowledge at Sigma-Aldrich with the broadest range of biotechnical capabilities in the world. And we list more products and actually make more products, 40,000 of them, than anyone else.” Second, the company has “an obsession with service,” Harvey says. “The whole company is geared toward service.” And third, “we have a passion for process improvement. That really does mean making the best possible use of the company’s resources.”

What’s new since last year: Early this summer St. Louis Mayor Francis Slay helped Sigma-Aldrich officials open the company’s new production campus on DeKalb Street.

Regional benefits: “In recent years, it has become easier to hire top level people, especially scientists, because there is a developing biotech corridor here and local involvement with the human genome project,” Harvey says. “Also the St. Louis Science Center is a tremendous asset to the community and an excellent way to encourage young scientists.”

Looking ahead: “Sigma-Aldrich will continue its commitment to research and development, spending more than $40 million annually, to remain the world’s leading supplier of quality research products,” Harvey says.

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**TRIPOS INC.**
Life science chemistry research products and services

![Image of TRIPOS INC.](image)

▲ JOHN MCALESTER III, TRIPOS INC.

John McAlister, III, Ph.D., President & CEO
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"We are the only company that has fully integrated chemistry and software in an effort to accelerate the drug discovery process.”
Historic overview: Tripos Inc. was founded in 1979 by Professor Garland Marshall at Washington University based on technology developed there, was purchased in 1987 by a simulation hardware company and was "spun off" as a public entity in 1994, says President and CEO John McAlister, III. "The inspiration for the company was the discovery of computational methods and three-dimensional modeling and visualization for the successful design of new pharmaceutical entities. It was a scientific and technological drive for more efficient discovery of new therapeutics that motivated the founding of the company." When McAlister joined Tripos as a consultant in 1982, the company employed six people. Today there are 350 employees, with 150 based in St. Louis and the remaining 200 in offices around the globe.

Products and services: Tripos has two areas of expertise. Tripos Discovery Informatics provides software products and consulting services to develop, manage, analyze and share critical drug discovery information. "For example, when a pharmaceutical company decides on a particular disease target, one of the first things they do is look for an analysis of what kind of compounds might be effective against it. Our software is effective in that early exploration," McAlister says. Tripos' Discovery Research integrates state-of-the-art, high-throughput and medicinal chemistry operations with proprietary and commercial informatics and knowledge-management capabilities enabling the company to rapidly transform clients' research "ideas" and program objectives into tangible, novel chemical entities with potential medicinal properties. "Where we stop our work is the point at which the compounds are tested in clinical trials," McAlister says.

What's new since last year: Tripos recently launched its SYBYL® and UNITY® lines of computational chemistry software on Linux. This makes Tripos' industry-leading computational chemistry applications available in a PC environment for the first time, reducing hardware costs for customers and making the technology more accessible to a broader market. "This gives us a great deal of growth opportunity," McAlister says. The company plans to release up to eight additional offerings this year, delivering industry advancements in operational and strategic research informatics. Tripos also is continuing on track with its $100 million strategic chemistry collaboration with Pfizer, which was announced early in 2002.

Regional advantages: McAlister says St. Louis is "a growing area of interest for the biotechnology industry with world renown expertise already present in agriculture, plant and animal biotechnology." He adds, "St. Louis also is a nice place to live and the cost of living is reasonable. This helps us attract new employees."

Looking ahead: "We are certainly planning to grow," McAlister says. "This year we went from 140 to 220 people in our chemistry operations, mostly driven by the Pfizer contract. And we have added software engineers in St. Louis, too. The remarkable thing is despite generally poor economic news, we continue to grow."

The name: McAlister explains, the software produced by Tripos is used to predict the behavior of compounds in therapeutic use. Because of the many variables involved in biological systems, this prediction is subject to many constraints and ambiguities. In a similar way, the Greek seers called Sibyls were known for providing useful if ambiguous predictions as they sat on a three-legged stool called a Tripos. "From this mythology, we have taken the name of our principal line of software, SYBYL and the name of our company on which this product rests, Tripos," McAlister says.