

# Trending 2018: Pipeline Disrupters

Pipeline disruptors are innovative therapies that impact current therapies with significant competition and alter the course of treatment. Industry leaders take a look at three hot areas — regenerative medicine, RNA technologies, and immunotherapies — and their potential impact on the future of medicine.



In recent years, several therapeutic disruptors have hit the market, pushing aside current standard treatment protocols. From hepatitis C cures to immuno-oncology therapies, recent approvals have upended how diseases are treated, providing patients with significant advances.

Pharmaceutical, biotech, and biopharma companies are working on tomorrow's disruptors. With more than 7,000 medicines in development around the globe, the pipeline is filled with potential first-in-class therapies.

"We currently find ourselves on the cusp of the next therapeutic revolution: the use of cells as medicine," says Ross Macdonald, Ph.D., managing director and CEO, Cynata Therapeutics, which is one of several companies pursuing stem cell and regenerative medicine. "The approval of Novartis' Kymriah was a turning point in the validation of cell-based therapies, an area now in the midst of an innovation windfall."

## Stem Cell and Regenerative Medicine

This past summer, the Food and Drug Administration approved the first gene therapy for the treatment of patients with B-cell precursor acute lymphoblastic leukemia (ALL). Novartis' Kymriah is an immunocellular therapy that is a one-time treatment to enhance cellular expansion.

More recently, a second CAR-T therapy was approved. In October, the FDA approved Kite/Gilead's Yescarta, a cell-based gene therapy, to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment.

Gene and stem cell therapies are the cornerstone of the next wave of regenerative medicine, industry leaders say.

The field of regenerative medicine is an emerging one, aimed at regeneration, repair,

or replacement of damaged tissue and organs. Regenerative medicine is defined by the National Institutes of Health as the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects.

At the close of 2016, there were 804 clinical trials under way involving cell therapy; further, there are a number of approved and/or marketed products worldwide, according to the Alliance for Regenerative Medicine.

Scott Gottlieb, M.D., commissioner of the FDA, said in a statement in August 2017 that regenerative medicine is one of the most promising new fields of science and medicine.

Regenerative medicines are developed by using translational research techniques such as molecular biology, tissue engineering, and gene engineering. Stem cells and tissue scaffolds have effective therapeutic potential, which is increasing the adoption of regenerative medicine.

"These new technologies, most of which are in early stages of development, hold significant promise for transformative and potentially curative treatments for some of humanity's most troubling and intractable maladies," Dr. Gottlieb said in the statement.

Dr. Macdonald explains that the advent of regenerative, cell-based medicine has the potential to empower people's bodies to heal themselves and defend against illness and injury.

"This could translate into a healthier population and allow patients to lead fuller lives, while also extending their ability to productively contribute to society," he says.

Cynata's Cymerus technology platform addresses a critical hurdle in the application of mesenchymal stem cells (MSCs) as therapeutic agents, by enabling the production of large-scale and consistent MSCs based on a single blood donation from one adult donor.

Athersys is another company working in the emerging field of regenerative medicine.

## FAST FACT

WITH MORE THAN 7,000 MEDICINES IN DEVELOPMENT AROUND THE GLOBE, THE PIPELINE IS FILLED WITH POTENTIAL FIRST-IN-CLASS THERAPIES.

The company is developing MultiStem, an adult-derived “off-the-shelf” stem cell product platform, for multiple disease indications in the areas of neurological, cardiovascular, inflammatory, and immune disease areas, as well as other indications where there is unmet medical need.

“In the next several years, we’re going to see the approval of therapies that will reshape medicine in some very powerful ways — in fact, it’s already happening with cell therapies like CAR-T,” says Gil Van Bokkelen, Ph.D., CEO of Athersys. “This is exciting; these new therapies have the potential to address some of the areas that are driving healthcare costs, not just now but well into the future.”

Dr. Van Bokkelen says the company’s technology is demonstrating powerful biological activity.

“In situations where there is an injury or some form of tissue damage, the body starts to send out signals and when these cells are administered they respond to those signals,” Dr. Van Bokkelen explains. “The cells home to the site of tissue damage or inflammation, or other relevant organs, and can dynamically regulate what is happening to help promote recovery and repair.”

MultiStem is a biologic product that is manufactured from human stem cells obtained from adult bone marrow. Unlike other cell types, after isolation from a qualified donor, MultiStem consists of a special class of human stem cells that have the ability to express a range of therapeutically relevant proteins and other factors. These cells exhibit a drug-like profile in that they act primarily through the production of multiple factors that regulate the immune system, protect damaged or injured cells, promote tissue repair and healing, and are subsequently cleared from the body over time.

In contrast to other cell therapy technologies or procedures, MultiStem is simple to prepare and administer, using a three step process that takes only a few minutes. First, a vial of product is removed from the freezer. Second, the vial containing the frozen cells in liquid is thawed.



Cell therapy is maturing as a field, and the indications and markets we are addressing are growing because much of the field is working to address diseases associated with aging.

**DR. KARINE KLEINHAUS**  
Pluristem

Third, using a syringe, the cells are then transferred to an IV bag of saline, and then administered to the patient.

Athersys currently has six clinical-stage programs, including a pending Phase III study in ischemic stroke that has already been given fast track status, an ongoing Phase II clinical study for the treatment of damage from acute myocardial infarction, and an ongoing exploratory clinical study in acute respiratory distress syndrome.

“In addition to their therapeutic properties, there are two other important characteristics of MultiStem,” Dr. Van Bokkelen says. “First, we can administer these cells just like type O blood with no tissue-matching or immune suppression required. Second, we can manufacture the cells that make the MultiStem product in a highly scalable way, meaning we can generate millions of doses using a small amount of material from a single, healthy, consenting donor. That’s a huge advantage, and one of the things that will make these types of therapies a widespread clinical reality.”

Experts say the field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves.

“The cell therapy market is coming into its own,” says Karine Kleinhaus, M.D., divisional VP, North America, Pluristem. “There are a lot of cell therapy trials happening, which

## Pipeline Trends



**NEZAM AFDHAL, M.D.**  
Chief Medical Officer, Spring Bank Pharmaceuticals

### HEPATITIS B

Toward the end of 2016, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver organized the Hepatitis B Treatment Endpoints Workshop, with the goal of assembling key leaders in the field of hepatitis B to discuss the current state of the field, as well as the future of hepatitis B treatment. From this meeting, a consensus was formed about the definition of a hepatitis B cure. Eradication of cccDNA was felt to be unachievable, and a functional cure was defined as loss of hepatitis B surface antigen, which will likely require a combination of therapies including direct-acting antivirals and immune stimulators.

We believe that with this consensus on the definition of a functional cure for chronic hepatitis B virus infection, we will begin to see significant innovation in the field in 2018. A functional cure will require collaboration among pharmaceutical companies, and we believe that collaboration inspires innovation.

At Spring Bank, we will begin a collaboration with Gilead in 2018 to tackle this functional cure. We will initiate Phase II combination studies of our lead candidate inarigivir, which is novel with both antiviral and immunomodulating capabilities, with Gilead’s Viread and Vemlidy, in addition to potential planned novel combinations with capsid inhibitors and siRNAs.

### NAOMI AOKI

Head of Corporate Communications, Syros Pharmaceuticals

### NON-PROTEIN CODING

Targeted drug discovery and development in oncology to date has focused largely on mutations in regions of the genome that code for proteins. While that approach has and continues to yield new therapies that make a difference for patients with certain cancers, we believe that the growing understanding of non-protein coding, regulatory regions of the genome provides a new lens for identifying drug targets and segmenting patients that has been largely unexploited for drug discovery and development.

We have built the first platform solely focused on analyzing regulatory regions of the genome to develop medicines to control the expression of disease-driving genes.

In AML, for example, using our approach to analyze super-enhancers profiles in healthy and diseased cells from AML patient tissues, we identified new subsets of AML patients



In the immuno-oncology research space, there's been a lot of progress, but tumors mutate in response to and as a result of different treatments, which is why continual research is needed to find new ways to overcome this.

**GEERT KERSTEN**  
Cel-Sci

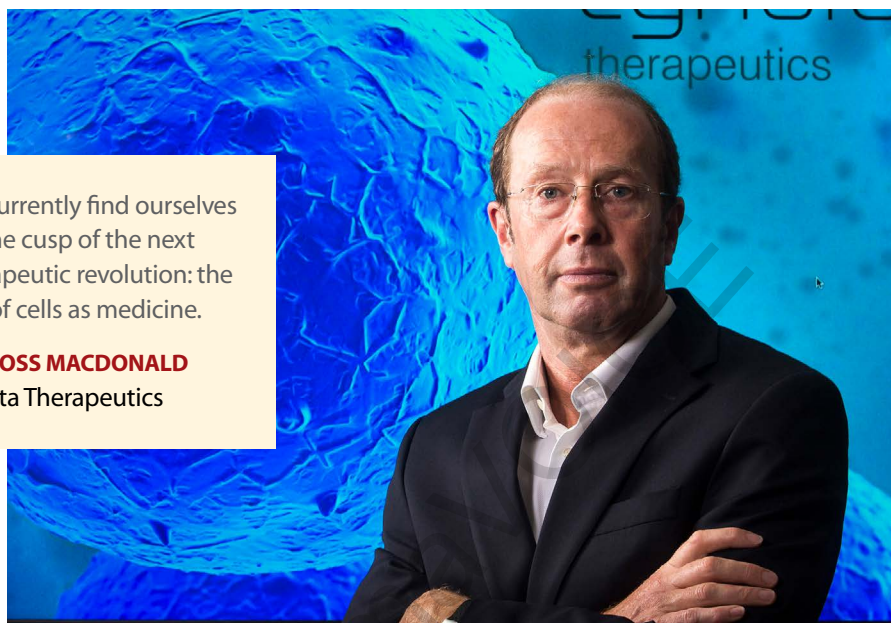
reflects the interest and excitement about cell therapy."

Pluristem is using donated placental cells and a proprietary, 3D technology platform to develop cell therapies for conditions such as inflammation, ischemia, muscle injuries, hematological disorders, and exposure to radiation.

"We grow cells from the placenta in large bioreactors, and while they're expanding and growing, we change the environment in order to train them to do more of one particular function or another," Dr. Kleinhaus explains. "For example, if the cells are exposed to low oxygen environments, they'll pump out proteins that push the body to grow blood vessels to bring oxygen to ischemic tissues. We can add in different types of substances that represent inflammation, for example, which triggers the cells to modify and reduce inflammatory response and scarring."

Pluristem is currently recruiting patients for a Phase III clinical trial for a therapy for critical limb ischemia, a disease where cholesterol blocks blood flow to the legs, which can lead to non-healing sores, gangrene, and a high risk of amputation and death.

Another program addresses recovery after hip fracture where there is soft tissue and muscle breakdown and there's a need for new blood



We currently find ourselves on the cusp of the next therapeutic revolution: the use of cells as medicine.

**DR. ROSS MACDONALD**  
Cynata Therapeutics

vessels, muscle regeneration, and for reducing inflammation and scarring. Pluristem has received positive feedback from the FDA and European Medicine Agency for its Phase III program, and is waiting for protocol approval for this program.

A third program is focused on acute radiation syndrome to treat patients after high-dose radiation exposure, which can damage the bone marrow's ability to produce blood cells and platelets. The U.S. National Institutes of Health has supported and completed the equivalent of a Phase II trial in this area, which produced very positive results; treatment with Pluristem's cells resulted in a 70% improvement in survival as compared with placebo.

Osman Kibar, Ph.D., CEO of Samumed, predicts that regenerative medicine and tissue regeneration will have an enormous impact on the future generation of "restorative" drug research and development, i.e. therapeutics that target the underlying cause of disease progression, and thereby, restore the health of the diseased or damaged tissue.

"Being able to regenerate healthy tissue or prevent the formation of unhealthy tissue would reverse the course of disease and have a curative effect on the patient," Dr. Kibar says. "This is the ultimate goal, but packaging that faculty into a safe and efficacious drug is a challenge for most technologies."

Samumed is developing a drug platform that targets a pathway known as the Wnt pathway, which is a key regulator in stem cell differentiation and proliferation, maintaining and/or restoring the health of numerous tissues and organs.

Samumed has had success with this approach evidenced by its progress with its Phase II clinical trial in osteoarthritis, the compa-

## FAST FACT

**GLOBALLY, THE REGENERATIVE MEDICINE MARKET WAS PEGGED AT \$2.5 MILLION IN 2012, AND IT IS PROJECTED TO ACHIEVE \$6.4 MILLION BY THE END OF 2019, EXPANDING AT A CAGR OF 12.8%.**

Source: Transparency Market Research

ny's most advanced program. In this trial, SM04690 improved function and reduced pain on the WOMAC scale, by leveraging the ability to modulate the Wnt pathway.

"The same promise of this platform in OA can be used across a wide range of disease areas, validating its potential to change the way drug developers approach disease modification," Dr. Kibar says.

Within the next year or two, Adi Mohanty, co-CEO, BioTime, predicts that more human data will come out for stem cell therapy clinical trials, which will dramatically increase the comfort level with the technology. He acknowledges that there are still some remaining concerns that cells will migrate and form carcinomas and teratomas, or only have short-term effect.

BioTime has two cell platform technologies: one is a pluripotent cell platform where the company can make almost any kind of cell in the human body. The other platform

## Regenerative Medicine Achievements

### YESTERDAY

- ▶ Transplantation of bone, soft tissue, and corneas took place in the 20th century.
- ▶ Real progress in organ transplantation began in 1954 with the first successful kidney transplant.
- ▶ During the 1960s, successful transplantation of pancreas/kidney, liver, isolated pancreas, and heart occurred.
- ▶ Transplant surgery success continued into the 1980s with successful heart-lung, single lung, double lung, living-donor liver, and living-donor lung transplants.

### TODAY

- ▶ The rapid development of transplant medicine along with the aging of the baby boomer generation has caused an increased demand for tissues and organs far exceeding the available donor organs.
- ▶ About 500,000 Americans benefit from a transplant each year.
- ▶ Tissue-engineered skin has been used for skin replacement, temporary wound cover for burns, and treatment for diabetic leg and foot ulcers.
- ▶ Tissue-engineered bladder, derived from a patient's own cells, can be grown outside the body and successfully transplanted.
- ▶ A material developed from the small intestines of pigs is increasingly used by surgeons to restore damaged tissues and support the body's own healing processes
- ▶ Tissue-engineered products are used to induce bone and connective tissue growth, guide long bone regeneration, and replace damaged knee cartilage.
- ▶ Tissue-engineered vascular grafts for heart bypass surgery and cardiovascular disease treatment are at the preclinical trial stage.

Source: National Institutes of Health

- ▶ Stem and precursor cells are available from a wide variety of sources (e.g., embryos, gestational and adult tissues, and reprogrammed differentiated cells).

### TOMORROW

- ▶ Imagine a world where there is no donor organ shortage, where victims of spinal cord injuries can walk, and where weakened hearts are replaced. This is the long-term promise of regenerative medicine, a rapidly developing field with the potential to transform the treatment of human disease through the development of innovative new therapies that offer a faster, more complete recovery with significantly fewer side effects or risk of complications.
- ▶ Insulin-producing pancreatic islets could be regenerated in the body or grown in the laboratory and implanted, creating the potential for a cure for diabetes.
- ▶ Tissue-engineered heart muscle may be available to repair human hearts damaged by attack or disease.
- ▶ The emerging technique of organ printing utilizes a standard ink jet printer modified with tissue matrix material (and possibly also cells) replacing the ink. "Made-to-order" organs of almost any configuration could then be cast and implanted.
- ▶ Materials science meets regenerative medicine as "smart" biomaterials are being made that actively participate in, and orchestrate, the formation of functional tissue.
- ▶ New approaches to revitalizing worn-out body parts include removing all of the cells from an organ, and infusing new cells to integrate into the existing matrix and restore full functionality.

is a delivery matrix that can deliver cells or molecules.

In the near term, BioTime is focused on aesthetics and ophthalmology. One of the company's lead products is OpRegen, which is in a Phase I/II trial for the dry form of

age-related macular degeneration (dry AMD). Currently, there are no FDA approved therapies for dry AMD, the most prevalent form of AMD and one of the major diseases of aging.

OpRegen consists of retinal pigment epithelial (RPE) cells that are delivered subret-

associated with survival and predictive of response. These subsets were found to be independent of known mutations in AML and, thus, would not have been identified using conventional genome sequencing approaches. One of these patient subsets, defined by the presence of a super-enhancer associated with the RARA gene, was found to be predictive of response to SY-1425, a selective RAR $\alpha$  agonist, in preclinical studies and is now in a Phase II clinical trial for defined subsets of patients with a biomarker for the RARA super-enhancer.



**RALPH KERN, M.D.**  
Chief Medical Officer and  
Chief Operating Officer,  
BrainStorm Cell Therapeutics

### CNS SCIENCE AND TECHNOLOGY

We are at an inflection point in the CNS space. CNS science and technology is coming of age. Our technology, NurOwn, has been developed and advanced for more than 10 years, and we're now conducting a pivotal multicenter Phase III trial at six sites in the United States. The support of this clinical trial by the California Institute of Regenerative Medicine highlights the critical need for novel approaches, such as stem cell therapy, to address ALS beyond current therapies, which slow disease progression but do not maintain or restore function.

The CNS disease states is currently where cancer was 20 years ago. When we look at what cell therapy has started to do in cancer, it's exciting to imagine how the CNS space can benefit from similar technological advances and results. Where others have ended with mesenchymal stem cells (MSCs) is where we began and we are continually refining our technology, seeking new solutions, and finding additional areas of unmet need in neurodegenerative disease such as Parkinson's disease, multiple sclerosis, and autism.



**DAVID NICHOLSON, PH.D.**  
Executive VP and Chief R&D  
Officer, Allergan

### ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is currently the sixth-leading cause of death in the United States and represents a major and growing global public health problem, for which very few approved treatment options are available. Fewer than 1% of drugs developed for AD have successfully advanced to FDA approval, and many people living with AD are not using the treatments that are currently available on the market. While there is no cure for AD, current treatments have been shown to help slow the worsening of symptoms.

Late last year, Allergan completed the acquisition of Chase Pharmaceuticals. This

RNA interference, such as gene therapy or gene editing, is a paradigm shift in terms of changing the way patients can be treated for various conditions.

**DR. MARK MURRAY**  
Arbutus Biopharma



cord injury, and is funded in part through a \$14.5 million grant from the California Institute for Regenerative Medicine.

The other lead product for the company leverages the platform for cosmetic or reconstructive surgery purposes. The product Renevia has completed a pivotal study in the EU with top line data that appears to be twice as good as a typical fat transfer and also helps validate the ability for this platform to deliver cells locally. This prod-

uct could be commercial in Europe next year and is already starting to treat patients in the United States through a clinical trial.

### RNA Technologies

Another area of therapeutic excitement and disruption is the use of RNA in potential therapies. Biopharma researchers are making significant progress toward this goal. Ribonucleic acid, or RNA, is one of the three major biological macromolecules essential for all known forms of life. For many years RNA was believed to have only three major roles in the cell — as a DNA photocopy (mRNA), as a coupler between the genetic code and the protein building blocks (tRNA), and as a structural component of ribosomes (rRNA). But researchers have begun to realize that the roles adopted by RNA are much broader.

In 2006, the American scientists Andrew Fire and Craig Mello were awarded the Nobel Prize in Medicine for their research of RNA interference. They discovered a fundamental mechanism for controlling the flow of genetic information. In 1998, the two published their discovery of a mechanism that can degrade mRNA from a specific gene. This mechanism, RNA interference, is activated when RNA molecules occur as double-stranded pairs in the cell. This activates a biochemical machinery that degrades mRNA molecules. When such mRNA molecules disappear, the corresponding gene is silenced and no protein of the encoded type is made.

Since this discovery, researchers have been studying this mechanism to develop potential therapeutics. In the last decade, RNAi has become an important innovation in the field of drug discovery and development. RNAi has the potential to generate a new

class of therapeutics that take advantage of the body's own natural processes to silence genes.

"RNA interference, or RNAi, is a natural mechanism that all cells use to eliminate unwanted proteins," says Mark Murray, Ph.D., president and CEO of Arbutus Biopharma. "For example, during the course of the development of an organism, cells want to turn off and eliminate proteins for various reasons."

Arbutus has been able to harness this mechanism to eliminate proteins from cells that are associated with disease. For example, the company is using its technology to eliminate or to reduce a protein called hepatitis B surface antigen, which is produced by the hepatitis B (HBV) virus in infected patients.

Arbutus' Lipid Nanoparticle (LNP) technology allows RNAi drugs to be encapsulated in tiny particles made of lipids (fats or oils). These tiny particles travel through the bloodstream to target tissues. They are designed to stay in the circulation long enough to accumulate at disease sites, such as in the liver or cancerous tumors.

Through a process called endocytosis, cells take up the LNPs, which allows them to migrate into the cell. The LNPs then undergo an interaction within the cell and the RNAi trigger molecules are released.

The company is conducting Phase II trials of an RNAi therapy using LNPs for patients with chronic hepatitis B.

"We have used this agent in multiple cohorts of patients and we have been able to demonstrate that we can reduce surface antigen levels in HBV patients," Dr. Murray says. "Depending on the dosing, the dosing frequency, and so forth, we can significantly reduce patient's surface antigen levels."

Alnylam Pharmaceuticals has licensed Arbutus' LNP technology for use with its patisiran RNAi therapeutics program. In September, Alnylam and its partner Sanofi announced positive results of a Phase III trial of patisiran, an investigational RNAi therapeutic being developed for patients with hereditary ATTR amyloidosis with polyneuropathy. Patisiran uses the body's natural processes to lower the levels of the TTR protein that causes TTR amyloidosis, an inherited, progressively debilitating, and often fatal disease. Patisiran is designed to target and silence specific messenger RNA, potentially blocking the production of TTR protein before it is made. This may help to enable the clearance of TTR amyloid deposits in peripheral tissues and potentially restore function to these tissues.

"RNAi has now emerged as a powerful, clinically validated approach with the potential to transform treatment for patients with limited or inadequate options," says Yvonne

inally during an intraocular injection. RPE cells are essential components of the back lining of the retina, and perform many functions including to help nourish the retina, including photoreceptors. OpRegen is designed to be an "off-the-shelf" allogeneic (non-patient specific) product. Unlike treatments that require multiple, frequent injections into the eye, it is expected that OpRegen would be administered in a single procedure.

"We're giving patients new cells made in a factory and, if they attach and grow and the graft survives, then it's likely the cells are going to do what they normally do," Mr. Mohanty says. "This makes it more like a transplant than a therapeutic and could likely have a higher probability of success."

Early human data show after 12 months after the transplant, patients' cells appear to be increasing in thickness in the retina for both the RPE and photoreceptor layer.

The company's subsidiary Asterias is using the same technology for a therapy for spinal cord injury. The company's lead product, AST-OPC1, is now in a Phase I/IIa clinical trial in patients with complete cervical spinal

Very soon we will be able to both sequence the entire genome of a patient's cancer and get a complete picture of the immune response against that cancer. By understanding that complete picture, we can understand how immunotherapies might work.

**DR. BRIGGS MORRISON**  
Syndax



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We are using a form of RNA interference-inducing drug molecules that can be administered by a simple injection underneath the skin releasing a small amount of a drug.

**DR. DOUGLAS FAMBROUGH**  
Dicerna

Greenstreet, MBChB, chief operating officer of Alnylam.

“Medicines based on our RNAi therapeutics platform have the potential to overcome some of the key shortcomings of current therapies, with features including infrequent, low-volume, subcutaneous dosing; durable drug effect; potential for improved efficacy with sustained drug activity; and room temperature stability,” Dr. Greenstreet says.

Beyond Alnylam’s lead candidate patisiran, the company is currently advancing givosiran, a subcutaneously administered therapy that targets ALAS1 for the treatment of acute hepatic porphyria, including acute intermittent porphyria. Givosiran has the potential to be a novel treatment approach for the prevention of recurrent attacks and is on an accelerated path to approval.

Alnylam is also developing a next-generation platform to improve the specificity of RNAi-based therapies. This Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-siRNA conjugate platform is being applied to all the company’s preclinical programs and has shown successful translation of potency from rodents to non-human primates.

Dicerna is another company researching potential RNAi therapeutics. The company’s GalXC technology platform advances the development of next-generation RNAi-based therapies designed to silence disease-driving genes in the liver.

Compounds produced via GalXC are intended to be broadly applicable across multiple therapeutic areas, including rare diseases,

## FAST FACT

**THE U.S. REGENERATIVE MEDICINE MARKET IS EXPECTED TO GROW AT 23.5% CAGR FROM 2017 TO 2021.**

Source: TechNavio

chronic liver diseases, cardiovascular diseases, and viral infectious diseases. GalXC molecules are structured to be processed by the enzyme Dicer, the initiation point for RNAi in the human cell cytoplasm.

Dicerna’s RNAi platform is designed to enable subcutaneous delivery and does not involve lipid nanoparticles (LNPs) or other formulation components that facilitate drug delivery. Instead, the molecules are stabilized by chemical modifications.

“We are using a form of RNA interference inducing drug molecules that can be administered by a simple injection underneath the skin releasing a small amount of a drug,” says Douglas Fambrough, Ph.D., president and CEO of Dicerna. “Our particular technology is specific to disease states that involve problems with liver cells.”

The company’s most advanced program is DCR-PHXC, for the treatment of a rare, but serious, family of diseases called primary hyperoxalurias, genetic diseases where there’s an in-born error of metabolism. In patients with this disease, the liver makes too much of the chemical oxalate and that excess oxalate damages the kidneys.

Studies in animals show the potential therapeutic can eliminate that excess production of oxalate, bringing it back down toward normal. The company expects to begin clinical trials this year.

Quark Pharmaceuticals is also focusing on innovative therapeutics based on the RNAi mechanism. Quark has focused its drug discovery and development efforts on a new class of drugs called small interfering RNAs, or siRNAs.

The company’s two products, QPI -1002 and QP -1007, are in global Phase III pivotal clinical studies for delayed graft function following kidney transplants and for nonarteritic anterior ischemic optic neuropathy, or NAION. Orphan designation has been granted to QPI-1007, and for the delayed graft function of QPI-1002.

QPI-1002 is designed to temporarily inhibit the expression of the pro-apoptotic gene, p53. The temporary inhibition of p53 inhibits

acquisition added a new Phase III ready program for AD to our CNS portfolio and built on our commitment to developing innovative approaches to improve the lives of millions of patients suffering from this devastating illness.

Allergan also entered into an agreement with Heptares Therapeutics, a subsidiary of Sosei Group, to license exclusive global rights to a broad portfolio of novel subtype-selective muscarinic receptor agonists in development for the treatment of major neurological disorders, including AD. Cognitive impairment and psychosis are progressive and debilitating symptoms associated with many CNS diseases.



**CHRISTOPHER RANDOLPH, PH.D.**  
Chief Scientific Officer,  
MedAvante-ProPhase

### ALZHEIMER’S DISEASE

There has been a complete paradigm shift in Alzheimer’s disease clinical trials. There are now multiple ongoing trials that are designed to prevent the onset of AD in clinically normal individuals who are at risk for the disease. Instead of the typical six- to 12-month trials designed to detect a clinically relevant change in a subject’s symptoms, these new trials can last five years or longer, and are designed to detect subtle neurocognitive decline in asymptomatic subjects.

There are currently six such prevention trials under way, all of which involve the use of novel neurocognitive composites as primary endpoints. These composites include neuropsychological tests that are relatively complicated and error-prone. These studies are powered to detect relatively small differences between treatment arms on the composites, and require precise administration and scoring.

To improve signal detection, most of these new studies are collecting their source data using personal tablet computers rather than paper. This technological innovation allows additional clinical guidance to be programmed into the electronic forms, improving the reliability of test administration and scoring.

This shift from collecting clinical endpoints on paper to tablet computers, generating electronic source data, has been demonstrated to reduce scoring errors by about 50% to 85%, depending on the scale, and has been adopted for both prevention trials and those involving subjects with symptomatic AD.



**GUY SEABROOK, PH.D.**  
VP, Scientific Innovation,  
Neuroscience, Johnson &  
Johnson Innovation

### ALZHEIMER’S DISEASE

While unmet need exists in several therapeutic areas, I believe we’re heading toward a



In the next decade, we will see the growth of the siRNA business; this will be similar to the market shift that took place 20 years after the discovery of monoclonal antibodies, when the first therapy hit the market.

**DANNY ZURR**  
Quark

There is a growing need to innovate, especially in the areas of aggressive and treatment-resistant cancers. The first generation of those innovative agents are anti-VEGFs and TKIs, but tumors find other ways to grow.

**DR. DROR HARATS**  
VBL Therapeutics



### Next-Generation Immunotherapies

Cancer continues to be one of the most complex and far-reaching diseases that researchers focus on. It is estimated that 1.6 million Americans will be diagnosed with some form of cancer this year. As researchers and drug developers continue to gain a better understanding of the immune system and how to better target cancer, immuno-oncology will continue to be a key area of

programmed cell death, allowing time for cellular damage repair to preserve tissue and organ integrity and function.

In July 2017, Quark completed a Phase II trial exploring efficacy of QPI-1002 in prevention of acute kidney injury, or AKI, following cardiac surgery, which met the primary and multiple secondary endpoints.

QPI-1007, an siRNA targeting the gene Caspase 2, is a neuroprotective drug candidate in development for NAION and other optic neuropathies. Following a type C meeting with the FDA, Quark initiated a global Phase II/III pivotal clinical study for the treatment of NAION.

“One of the problems with kidney transplantation has to do with the immune response and another has to do with rejection due to the fact that the kidney of the donor was under ischemia and then reperfusion,” says Daniel Zurr, Ph.D., CEO, Quark.

He says the company’s drug has been shown to reduce the severity of delayed graft function (reduce the number of dialysis sessions needed after transplantation).

“A lot of kidneys that are harvested from donors are not used because the surgeons are scared about the possibility of a delayed graft function,” he says.

anticancer drug development.

Over the last few years, researchers have found that the immune system has the capability to detect and destroy abnormal cells, but cancer cells, at times, are able to avoid detection and destruction. There is exciting research that is leading to a new generation of immuno-oncology agents that target different immune players responsible for tumor growth, effectively combatting cancer cells’ ability to avoid eradication. Effective cancer approaches are taking into consideration multiple arms of the immune system to coordinate an effective antitumor response.

“We are witnessing the advancement of never-before seen approaches to addressing cancer with immunotherapy,” says Dominique Costantini, CEO and director, OSE Immunotherapeutics. “Technological advances in healthcare that allow drug developers to harness the power of the natural immune system, i.e. immunomodulatory agents, are proving to be useful therapeutics and the most promising immunotherapies to date.”

A new report released in June 2017 by the Pharmaceutical Research and Manufacturers of America in partnership with The American Cancer Society Cancer Action Network finds there are more than 240 immuno-oncology

medicines and vaccines currently in development.

The advancing field of cancer immunology has produced several therapies for treating cancer that increase the strength of immune responses against tumors. There are several areas of research, including checkpoint inhibitors, chimeric antigen receptor t-cell therapies (CAR-Ts), and novel therapeutic vaccines.

Checkpoint inhibitors have gained the most attention with Merck’s Keytruda and Bristol-Myers Squibb’s Opdivo being the leading products available in this category. Recent research has shown that cancer cells often use immune checkpoint molecules to suppress and evade an immune system attack. T-cells, deceived by these normal-looking proteins, may allow the tumor cell to go undetected. Checkpoint inhibitors block these normal proteins on cancer cells, enabling the T-cells that respond to them.

Matt Coffey, Ph.D., president and CEO of Oncolytics Biotech, says immuno-oncology research in coming decade will focus on how to expand the 20% or 25% of patients who derive meaningful benefit from immune checkpoint inhibitors and other immuno-oncology classes, and predicts that at least 50% or 55% of patients can realize a benefit.

“There will also be efforts to target and personalize these immune therapies in the next 10 years,” he says.

Oncolytics Biotech is researching a new class of immuno-oncology agents that aim to create a vaccination effect against cancer. The company is developing Reolysin, a variant of the reovirus, a shortened form for Respiratory Enteric Orphan Virus. Reovirus is a naturally occurring virus that affects the gastrointestinal system or respiratory tract.

Reolysin is based on lysis or the destruction of the tumor cell. The reovirus infects the tumor cells and then alerts the immune system that the tumor cells are foreign or strange, Dr. Coffey explains.

“We generate an adaptive response so that the infected cells start releasing chemical signals, chemokines and cytokines, that warn the body that there’s a pathogen present,” he says. “The natural killer cells will look for infected cells whether they are bacteria, viruses, any form of pathogen, and they will start destroying those cells, turning an immune desert ‘cold’ tumor to an immune-responsive ‘hot’ tumor. This causes a secondary wave releasing tumor epitopes, neoepitopes, viral epitopes.”

Studies of Reolysin have shown a long-term memory response, which gives the patients long-term immunity. In a randomized breast cancer study, Reolysin resulted in a seven-month improvement in overall survival for patients with stage IV breast cancer —

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17.4 months compared with standard of care, which was paclitaxel that resulted in 10.4 months of median overall survival.

Oncolytics Biotech recently had a positive end of Phase II meeting with the FDA, and the agency confirmed that the company would only need a single registration study for approval in stage IV breast cancer in luminal disease — targeting HR+/HER2-patients, which is almost 75% of breast cancer patients. Dr. Coffey says they are now seeking European guidance, and they would hope to have this study initiated by mid-2018.

The company plans to conduct research to determine if the vaccination effect of Reolysin will help prevent metastasis from establishing. Oncolytics Biotech also has a collaboration with Celgene looking at the virus in multiple myeloma in conjunction with Revlimid, essentially looking at the impact Reolysin has on up-regulating NK cells to enhance or prolong the effect of Revlimid.

Dr. Coffey says when newer classes of immuno-oncology therapeutics such as Reolysin are used in conjunction with checkpoint inhibitors, there can be a stronger immune response.

“Each oncolytic virus acts in a distinct way, while at the same time acting in concert with immune checkpoint inhibitors,” he says. “We see the field moving to combine new immuno-oncology therapies with immunomodulatory drugs.”

Briggs Morrison, M.D., CEO of Syndax Pharmaceuticals, says today, we can sequence the entire genome of a patient’s cancer and that will tell us what specific mutations exist in cancer.

“In the future, we’ll also be able to get a complete picture of the immune response against cancer, and we will be able to better understand the characteristics of the cancer; therefore the ability to tailor therapy to specific patients will just increase over time,” he says.

Syndax is working on a small molecule drug candidate that has direct effects on both cancer cells and immune regulatory cells, potentially enhancing the body’s immune response to tumors. Syndax received breakthrough therapy designation from the FDA based on the results of a randomized Phase II trial looking at the ability of the lead molecule, entinostat, to overcome resistance to anti-estrogens. The trial looked at exemestane plus or minus entinostat. A Phase III for that

## The Biopharmaceutical Pipeline — Innovative Therapies in the Pipeline

- ▶ **74%** of medicines in clinical development are potentially first-in-class medicines, meaning they represent a possible new pharmacological class for treating a medical condition.
- ▶ **822 projects** — defined as unique molecule-indication combinations — are designated by the U.S. Food and Drug Administration (FDA) as orphan drugs, which is critically important given only 5% of rare diseases have an approved medicine.
- ▶ A range of novel scientific approaches are being pursued, including cell and gene therapies, DNA and RNA therapeutics, and conjugated monoclonal antibodies.

## FIRST-IN-CLASS MEDICINES IN CLINICAL DEVELOPMENT FOR SELECTED THERAPEUTIC AREAS

Therapeutic Areas	Percentage of Projects that are Potentially First-in-Class
Alzheimer's Disease	86%
Psychiatry	75%
Cancer	79%
Neurology	74%
Cardiovascular	73%
Diabetes	73%

Source: PhRMA

specific indication for patients with hormone receptor positive/HER2 negative breast cancer is now under way.

Syndax is also conducting separate Phase II trials of entinostat in combination with Keytruda, Tecentriq, and Bavencio with the aim of enhancing the effect of these immunotherapies. By blocking the immuno-suppressive effects of myeloid-derived suppressor cells, and regulatory T cells, company leaders believe entinostat could enhance the body’s immune response to tumors.

“There’s been some interesting preclinical work that shows that entinostat could overcome resistance to PD-1 and CTLA4 checkpoint inhibitors,” Dr. Morrison says. “Preclinical work shows the addition of entinostat can suppress the two different cell types in the tumor microenvironment — the myeloid-derived suppressor cells and regulatory T cells. Both of those seem to be inhibited by our drug.”

Ziopharm Oncology is working to de-

Renaissance in terms of our understanding of Alzheimer’s disease. Subsequently, I predict over the next five to 10 years we will see a burst of innovation in the area.

The first factor driving innovation in this area is our growing understanding of the underlying cause of AD. Knowing risk factors could enable earlier detection and earlier interventions. Armed with this knowledge, one day we may treat Alzheimer’s similarly to how we detect and treat heart disease today — we predict risk by measuring cholesterol regularly and then prescribe a preventive medication, statins.

In parallel to our increased scientific knowledge, key stakeholders are working together to create an environment that fosters breakthroughs. Investments are being made to advance promising research or therapeutic approaches, and we are seeing collaborations forming between academia, government institutions, the pharmaceutical industry, and/or philanthropic organizations.



**LYNN SEELY, M.D.**  
President and CEO, Myovant Sciences

## WOMEN’S HEALTH

A quiet transformation is taking place in women’s health. Women make up 50% of the U.S. population, are the primary consumers of healthcare, and make most healthcare decisions for their families. These same women often suffer silently, sidelined by common diseases specific to women, which are not discussed.

About 10% of premenopausal women have endometriosis. In one survey, 50% of women with endometriosis reported spending on average 17.8 days per year in bed from pain over the preceding 12 months. Endometriosis can take seven to 10 years to diagnose and is characterized by pelvic pain, painful intercourse, and infertility. Three million women in the U.S. suffer from heavy menstrual bleeding and uterine fibroids.

More than 350,000 hysterectomies are performed each year in the United States for uterine fibroids or endometriosis. Effective medical therapies are limited. Fortunately, change is expected with the approval of new medicines in 2018. New drug applications for marketing approval have been filed with the FDA and more are expected in the next two to three years.

As the biopharma industry better appreciates the size and impact of these underserved areas of women’s health, research spending is increasing resulting in progress toward new medical treatments. Successful IPOs in 2016 and 2017 for companies focused on women’s health suggest investors are also noticing the potential and need for innovation and transformation in these marketplaces and are once again investing.





Having the ability to regenerate healthy tissue or prevent the formation of unhealthy tissue would reverse the course of disease and have a curative effect on the patient.

**DR. OSMAN KIBAR**  
Samumed

velop CAR-T and other cell and gene therapies. In collaboration with its partner, The University of Texas MD Anderson Cancer Center, the company is employing novel cell engineering techniques and multigenic gene programs to develop next-generation patient- and donor-derived cellular therapies based on designer cytokines to target hematologic malignancies and solid tumors.

“For years, companies as well as academics, have tried to harness the potential and power of a cytokine called interleukin 12 or IL-12,” says Laurence Cooper, M.D., Ph.D., CEO of Ziopharm. “IL-12 has been shown in many model systems to eradicate solid tumors. But the problem, up until now, has been that nobody has known how to control IL-12 in the patient. While IL-12 works in the tumor to drive an immune response against the malignancy, it is also active outside the cancer and activates the body’s own immune system against normal cells.”

Dr. Cooper says the company has figured out how to control IL-12 by using an adenovirus. The virus triggers transcription of the IL-12 from the brain tumor.

“Not only have we figured out how to put IL-12 under control of a switch, we’ve done it with medically fragile patients who have glioblastoma that has recurred,” he says.

Ziopharm is about to begin recruiting for a Phase III trial of its lead program for Ad-



Technological advances in healthcare that allow drug developers to harness the power of the natural immune system are leading to useful therapeutics and the most promising immunotherapies to date.

**DOMINIQUE COSTANTINI**  
OSE Immunotherapeutics

## FAST FACT

**GENE AND STEM CELL THERAPIES ARE THE CORNERSTONE OF THE NEXT WAVE OF REGENERATIVE MEDICINE.**

RTS-hIL-12 plus veledimex in glioblastoma. The company’s Phase I trial was able to almost double patient life to about 12.5 months in those with recurring glioblastoma.

Additionally, Ziopharm is working in partnership with Intrexon and The University of Texas MD Anderson Cancer Center, to advance a portfolio of adoptive cell therapies using multiple effector cells, including CAR-T, T-cell receptors, and natural killer (NK) cells.

“CD19 or CD33 are two of our targets for liquid tumors,” Dr. Cooper says. “In these situations, the patient can die within days. We’ve developed a technology not only to redirect the specificity of T-cells, but do so with real-time manufacturing and to get the cost down.”

Dr. Cooper says it has taken 10 years to develop the three major technologies to accomplish these goals. The first technology is the so-called *Sleeping Beauty* system, which uses a DNA plasmid not a virus to genetically modify cells. The second system is another cytokine called membrane-bound interleukin 15 or mbIL-15, and the third is a switch similar

to what the company uses with its glioblastoma therapy.

“When all the switches are coordinated in their behavior, we can do the gene transfer in real time,” he says. “In other words, we can put the DNA plasmid into the T-cells, the codes for the switch, codes for the CAR, and codes to the IL-15, and then we can immediately infuse those cells without any further manipulation. This is a big step forward for the field. Right now, if a patient needs CAR-T therapy it can take two to three weeks to make those cells and costs — according to current numbers — can approach \$400 million to \$500 million.”

Costs are high, he says, because companies in this space have tried to scale-up academic research, which is designed to test hypotheses and not necessarily be commercialized.

“At Ziopharm, we’ve looked at the costs to manufacture these cell therapies and we’ve engineered solutions to design around these issues related to scaling up,” Dr. Cooper explains. “When there is no need for the virus to genetically modify T-cells, there is no need for big manufacturing facilities, and we can start thinking about another world — a world in which the expenses are simply related to the cost of DNA, which is a lot less expensive.”

Another immunotherapy company is Cel-Sci, which is developing Multikine, an investigational immunotherapy currently in Phase III development for the treatment of head and neck cancer.

## Innovation in HEMATOPOIETIC CELL TRANSPLANTATION AND GENE AND CELLULAR THERAPIES Drive Results in Pediatric Oncology

**T**his is an exciting time in medicine, providing more novel treatments for patients with cancer blood disorders. Scientists are learning more about the human genome and its role in disease. This knowledge allows investigators to develop new diagnostic tools and therapeutic interventions to more specifically treat individual diseases. We are now identifying ways to correct disorders characterized by single gene mutations.

### Innovations in Clinical Development Yield Promising Results

New technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR), allow scientists to excise a mutated gene and replace it with a non-mutated gene. Equally important, we are learning to harness the power of the immune system to treat cancer. We have learned that the human immune system can, in some cases, be tolerized to a patient's malignant cells, so that it does not mount an immune response

**A deeper understanding of the human genome and its role in disease is driving the development of novel therapies. Today we are seeing dramatic improvements in outcomes for many pediatric cancers.**

against the cancer, allowing the cancer cells to escape detection (and subsequent destruction) by the body's immune system.

New agents such as checkpoint inhibitors are showing promise in activating the patient's immune response against the cancer. In addition, we are now developing new therapies that enhance the immune system response against cancer. Investigators are studying ways to alter hematopoietic cell grafts to alter the immunologic power of the grafts, leading to reduction of graft-versus-host disease or enhancement of anti-leukemia effects. In addition, cytotoxic T-cell therapies are increasingly utilized to treat post-transplant viral infections such as EBV and adenovirus. Natural killer (NK) cell infusions are being explored for their leukemia cell-killing abilities, especially in AML when the donor and recipient are killer immunoglobulin-like receptor (KIR)-ligand mismatched.

### CAR-T cell Therapy for Patients with ALL and NHL

Finally, CAR-T cells, T-lymphocytes from a patient are genetically modified to express a leukemia-specific antigen, are showing great promise in patients with ALL and NHL. The first CAR-T cell products are projected to be approved by the FDA later this year. As we learn more about each of these technologies, they can be expanded to other cancers. With all of these new therapies, physicians will need to learn how to best identify which patients will benefit, how to identify and treat the new toxicities, and how to incorporate those active agents into current treatment guidelines. Taken together, these novel immunotherapy interventions expand our armamentarium of weapons against cancer, complementing or replacing existing therapies, with the ultimate goal of reducing acute and long-term toxicities and increasing survival. ●

Multikine is a mixture of cytokines that essentially activates T-cells to break tumor tolerance, says Geert Kersten, CEO of Cel-Sci. Multikine creates a change in the CD4/CD8 ratio in favor of the CD4 cells in the tumor microenvironment.

"Essentially, a major defense mechanism of a tumor is to make itself invisible to the immune system," he says. "Our drug changes the type of cells that infiltrate a tumor. In the process of doing so, the tumor becomes visible to the immune system so that it can 'see' and attack the tumor."

Multikine is currently being studied and is administered for three weeks as the first treatment a cancer patient gets before surgery.

"Immuno-therapies are still being developed the old-fashioned way: patients receive chemotherapy after they've failed surgery, radiation, and/or chemotherapy," Mr. Kersten says. "Think about what a patient's immune system looks like at that point. Patients would have a better chance if we gave a cancer immunotherapy while the patient still has an intact immune system."

Mr. Kersten says for its Phase III study, the last patient was enrolled last year, and the company is waiting for 298 events before the final data are available.

Industry leaders say there is a growing need to innovate, especially to address aggressive and treatment-resistant cancers. The previous big shift was from non-targeted chemotherapy and radiation, to targeted treatments. The first generation of these therapies were the anti-VEGFs (vascular endothelial growth factor receptors) and TKIs (tyrosine kinase inhibitors). Unfortunately, even with these advances tumors find other ways to grow.

"We are finding that selective targeting of just one element or one pathway supporting tumor growth is often not enough," says Dror Harats, M.D., CEO at VBL Therapeutics. "We have to come at the cancer from a few different directions to really make a big difference."

VBL's therapy, VB-111, in Phase III development for glioblastoma multiforme, was designed using advances in targeted gene therapy technology to deliver a genetic mechanism that stops tumor-supportive blood vessels from growing, while activating the immune system. VB-111 works through a dual mechanism to combine a viral immune oncology action, which brings the immune system — the CD8+ T cell response — to the tumor, with a targeted gene therapy technology, that eliminates the cells responsible for the tumor blood supply.

"We are stopping tumor growth by cutting off the blood supply, and recruiting the immune system to fight the tumor, in a single therapeutic," Dr. Harats says. "So far in the clinic this has translated to meaningful overall and long-term survival benefits in patients with advanced solid tumors, including recurrent glioblastoma multiforme, for which the current standard of care, the anti-VEGF drug Avastin, does not provide a benefit of overall survival."

Also part of this next wave of breakthrough therapies in immuno-oncology will be therapies targeting myeloid-derived suppressor cells (MDSC) in the tumor microenvironment, which help the tumor evade the body's natural immune response, and are associated with a poor prognosis. Blocking the suppressive functions of myeloid cells could restore the anti-tumor response of T-lymphocytes, which is a novel immune target for cancer.

OSE Immunotherapeutics' preclinical asset, OSE-172, is being developed to do just this, and the company is expected to complete preclinical studies at the end of 2018.

"Our program studying OSE-172 is guided by the paradigm that therapies regulating the immunosuppressive effects of MDSCs will allow effective engagement of the body's natural immune responses against tumors," Ms. Costantini says. ●