May 15, 2018

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

Last month, I covered "The Top Eight Traits an Entrepreneur Needs to Be Successful." If you missed last month's article, click here to read it. This month we'll cover "Drugs and Products to Watch in 2018."

Read on to learn more about this topic and other current news. The next newsletter will be published on June 15th, 2018.

We encourage you to share this newsletter with your colleagues by using the social media icons below, or by simply forwarding this newsletter or use the link below. Should you or your colleagues want to join my mailing list, click on the link below.

Sincerely,
Regina Au
Principal, New Product Planning/
Strategic Commercial Consultant
BioMarketing Insight

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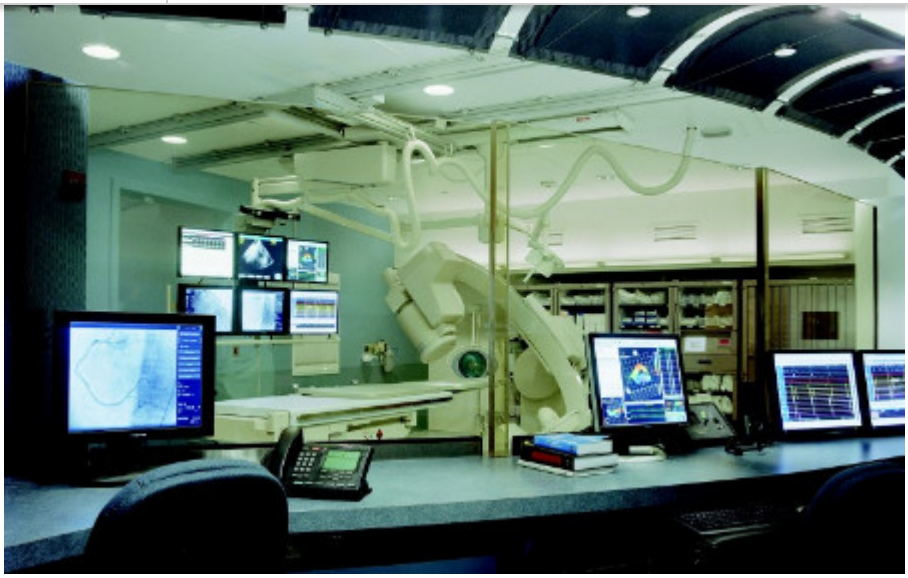

Developing a Product? Commercializing a Product?

If you are developing a product and have not conducted the business due diligence to determine commercial viability or success, contact me for an appointment. For successful commercial adoption of your product or looking to grow your business, contact me for an appointment.

For more information on our services, click on the links below:

Product Development
Market Development
Marketing Strategies

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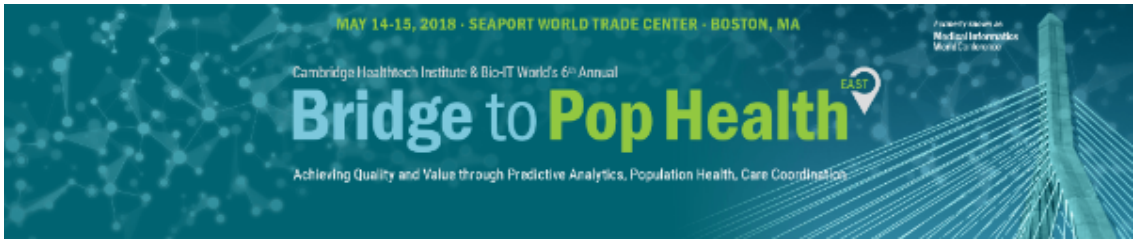

Going on Now: Bridge to Pop Health, May 14-15, 2018, Seaport World Trade Center, Boston, MA

Bridge to Pop Health in Boston provides the platform for collaborative discussion on maximizing outcomes through predictive models, population health management and clinical care innovation. Now in its sixth year, the event has become the annual meeting

50 HEALTHCARE CHANGE AGENTS SELECTED TO PRESENT CASE STUDIES & UPDATES

Here is a sample list of speakers for the conference:

- **Steven Atlas, MD, MPH**, Associate Professor, Medicine, Harvard Medical School, Director, Practice-Based Research & Quality Improvement, Massachusetts General Hospital
- **Scott Berkowitz, MD, MBA**, Senior Medical Director, Accountable Care, Office of Johns Hopkins Physicians
- **Haley Bolton**, Senior Manager, Regulatory Strategy and Value Management, Emory Healthcare
- **Matthew Burton, MD**, Assistant Professor, Biomedical Informatics, Mayo Clinic; Vice President, Clinical Informatics, Apervita, Inc.
- **Albert Chan, MD**, Chief of Digital Patient Experience, Sutter Health
- **Uli Chettipally, MD**, CTO, CREST Network, Kaiser Permanente
- **Teri Chou, PhD**, CEO, Modus Health LLC
- **Michael Fischer, MD**, Associate Professor of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School
- **Roshan Hussain, MBA**, Senior Director, Analytics & Public Reporting, Boston Medical Center
- **Craig Monsen, MD**, Medical Director, Analytics and Reporting, Atrius Health
- **Randall Moore, MD, MBA**, President, Mercy Virtual
- **Dominique Morgan-Solomon**, President, Morgan-Solomon Consulting, Population Health Subject Matter Expert, Merck
- **Janet O'Hollaren**, COO, Northwest, Kaiser Foundation Health Plan and Hospitals
- **Michael Paris**, Senior Director, Business Intelligence and Data Analytics, Banner Health
- **Jason Phibbs, CPXP**, Director, Patient Experience, TriHealth

For more information on the conference and to register, click here

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I am pleased to announce that I will be moderating a panel discussion entitled "Our Microbiome and Its Relationship to Various Diseases" under the Next Generation Biotherapeutics Track. This session is scheduled for Monday, June 4th 2018 from 1:00 PM - 2:15 PM. The location is Room 210B, Level 2 at the Boston Convention Center. The session will focus on the application and implication of our microbiome specifically looking at microbiome signatures (dominance and absence of certain species) for different diseases and it's implication in restoring symbiosis.

Please join me for a very informative and interactive panel discussion with some of the top researchers and companies working in this space. My distinguish panel of speakers:

1. **JC Gutierrez-Ramos**, CEO, Synlogic Therapeutics
2. **Matt Henn**, Executive Vice President, Microbiome Research and Development, Seres Therapeutics
3. **Philip Strandwitz**, Co-founder and CEO, Holobiome
4. **Sonia Timberlake**, VP Research, Finch Therapeutic

For more information on BIO and to register, click here.

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Why Our Microbiome is Important to Our Physiology and Diseases

Pharmacology & Pharmacotherapy. This article reviews the results of the Human Microbiome Project and the factors that affect our microbiome in relation to our healthy state and dysbiosis or disease state. To read the article, click here.

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Immunooncology: Can the Right Chimeric Antigen Receptors T-Cell Design Be Made to Cure All Types of Cancers and Will It Be Covered?

I am pleased to announce that my article on "Immunooncology: Can the Right Chimeric Antigen Receptors T-Cell (CAR-T) Design Be Made to Cure All Types of Cancers and Will It Be Covered?" has been published in Journal of Pharmaceutics. This article reviews the mechanism, design and administration of CAR-T cells, and whether payers will pay for this new technology. To read the article, click here.

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Drugs and Products to Watch in 2018

Scientists understanding of diseases have advanced tremendously in the past two decades due to the advancement of technology. The list of drugs and products to watch in 2018 would be an extensive list as there are numerous diseases that have either no treatment or the fact that not all patients will respond to one medication.

If one were to look at the trends in the market for the past six months, Immuno-oncology, gene editing and gene therapy is still "hot" for pharma and biotech, and for medical devices the trends are still around patient monitoring devices with apps for preventive measures in delivering better patient care.

However, for this newsletter and looking back for the last six months on technologies to watch, I'll be covering immuno-oncology, gene editing and gene therapy as a class rather than any specific drug for pharma/biotech in regards to advancements since these products are still in their infancy.

For medical devices, I'll be covering one specific device for heart failure (HF), a progressive medical condition that doesn't leave a lot of options once a patient exhausts all drug available. The only option is a Left ventricular Assist device (LVAD) which is limited to certain types of patients or a heart transplant which is also limited to certain patient criteria.

Immuno-oncology- Check-point inhibitors

Researchers have found that using a patient's own immune system to recognize and target cancer cells, not only needs a drug to help the immune system recognize the cancer cell, but they also need to consider the micro-environment in getting the drug to hone in to

For example, Roche's Tecentriq drug was able to have the immune system recognize and attack tumors but failed to work in about 80% of patients for their bladder cancer trial. Upon further analysis of their trial data, they discovered two biomarkers: 1) PD-L1, that drives a good response to drugs that inhibit the checkpoint PD-L1, like Tecentriq; and 2) TGF-beta, a protein that drives resistance. The TGF-beta protein levels were high in tumors of patients who did not respond well to Tecentriq.

Roche scientists discovered that non-responders were either severely lacking cancer-fighting T- cells, or T-cells were stuck to a wall made of collagen that prevented them from getting inside cancer cells. When they used a combination of anti-PD-L1 and an anti-TGF-beta therapy, it allowed more T-cells to penetrate to the center of the tumor, reducing the size of the cancerous mass. This discovery further supports the theory of combination therapy.

Other combinations to boosting immune checkpoint inhibitors are being studied such as combining checkpoints with pentoxifylline, a drug that's currently used to improve blood circulation for melanoma in mouse models at Columbia University Medical Center. The cocktail helped control the activity of regulatory T-cells (Tregs) by preventing them from suppressing cancer-killing T- cells. In addition, Memorial Sloan Cancer Center in New York found that in animal trials, an inactivated formulation of the vaccinia virus helped boost tumor-fighting T-cells when given along with checkpoint inhibitors.

Other companies have conducted trials with TGF-beta inhibitors but have had mixed results indicating that more research is needed to find better TGF-beta inhibitors.

Gene Editing - CRISPR Technology

The CRISPR technology, or gene editing is interesting because it is used both as a research tool to advance the knowledge of diseases, by discovering gene mutations specific to diseases and as a form of treatment by editing specific gene mutations.

While the CRISPR/Cas9 was developed to edit genes easier, cutting DNA into two triggers both non-homologous end joining (NHEJ) and Homology Directed Repair (HDR) where NHEJ can lead to unwanted off-target side effects that are permanent even though the HDR may be the predominant pathway that is used by scientists. This lead researchers to search for safer alternatives in avoiding a DNA break in the following methods:

1) Kill Switch - UC Berkeley and UC San Francisco, are focusing on a molecule that limits Cas9 activity once the desired editing is complete.

2) Non-viral Delivery Vehicle - Another Berkeley team is using gold nanoparticles to deliver CRISPR/Cas9 into mice to correct the genetic mutation that causes Duchenne muscular

MIT researchers used nanoparticles to snip out a certain gene that regulates cholesterol in about 80 percent of liver cells in the mice. In humans, a mutation in that gene can cause a rare disorder called dominant familial hypercholesterolemia.

The advantages of using nanoparticles over viruses as a delivery system for CRISPR/Cas9 are in patients that might have antibodies to a particular virus, resulting in the treatment being less effective or even triggering a harmful immune response. Patients could also develop antibodies to a virus once it is used and therefore, this method can't be used again.

3) RNA Edits - Scientist from the Broad Institute scientists have devised a way to edit RNA instead of DNA making edits reversible vs. DNA where cuts are permanent. The system, called REPAIR (RNA Editing for Programmable A to I Replacement) can edit single nucleosides, or the “letters” that make up the RNA helix. More, specifically, it can change the nucleoside adenosine (A) to inosine (I), which is read as guanosine (G) inside cells. This could become a treatment for diseases in which a G-to-A mutation plays a role, including Duchenne muscular dystrophy and Parkinson’s disease.

The REPAIR system is based on Cas13, an enzyme that does the same as Cas9, but for RNA. The scientists created a deactivated version of the Cas13 enzyme, PspCas13b, which binds precisely to a stretch of RNA, but does not cut it. They combined the enzyme with the protein ADAR2, which switches A to I in RNA transcripts, and then improved the tool to cut down on off-target effects.

"So far, we've gotten very good at inactivating genes, but actually recovering lost protein function is much more challenging. This new ability to edit RNA opens up more potential opportunities to recover that function and treat many diseases, in almost any kind of cell,” said Feng Zhang, core institute member at the Broad Institute, in a press release.

Scientists from UC San Diego are also working to correct mistakes in RNA in diseases that are caused by excess repeats in RNA sequences, causing the RNA to clump together in cells. The RNA-targeted CRISPR managed to clear majority of the clumps and RNA sequences errors in disease models such as Huntington’s and a type of ALS. Scientists have struggled to figure out how these toxic protein clumps cause neurons to die.

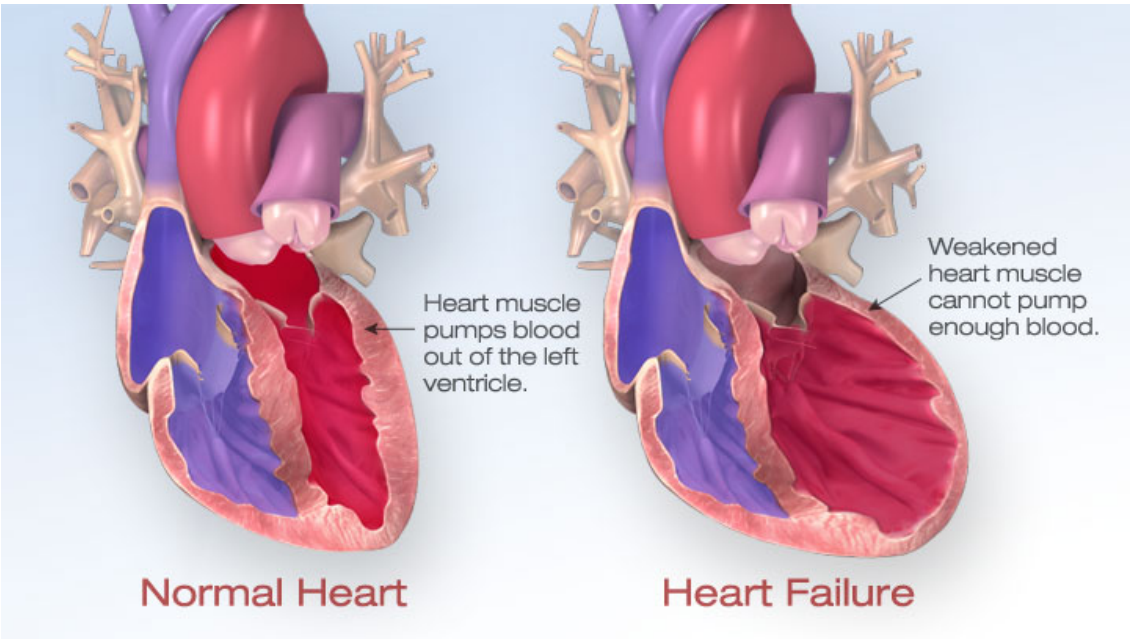
Other scientists have used the CRISPR technology to knock out every gene in the genome, allowing them to zero in on genes that protect neurons against the toxic effects of protein aggregates by being inactivated. They discovered that knocking out a gene called Tmx2 prevented cell death in mouse neurons. "If you have a small molecule that could somehow impede the function of Tmx2, there might be a therapeutic window there" for ALS, said Michael Haney from Stanford in a press release.

Gene Therapy has been found to be effective for diseases that are a one gene mutation. The challenge is to find a delivery system, such as an associated adeno viral (AAV) vector that will penetrate the cell and deliver the gene completely.

Scientists at the University of Pittsburgh School of Medicine made significant progress in their efforts to use gene therapy to reverse diabetes. They demonstrated a gene therapy approach that transforms alpha cells in the pancreas into fully functioning beta cells. Using an AAV vector, they delivered two proteins, Pdx1 and MafA instead of a gene, into the pancreas. These proteins "reprogrammed" alpha cells into insulin-producing cells and the mice maintained normal blood glucose levels for about four months.

One potential advantage of transforming alpha cells into beta cells is that alpha cells are distinct enough that the immune system is unlikely to mistake them for beta cells and attack them. The researchers compared gene expression patterns between normal beta cells and the alpha cells that they transformed into insulin producers and determined they had achieved "nearly complete cellular reprogramming," according to George Gittes lead author the study.

However, Gittes and his colleagues will need to further their research in determining how to obtain this same response in humans. They are also concerned that this gene therapy approach may be only temporary and the mice would eventually returned to a diabetic state.



Medical Device - Heart Failure

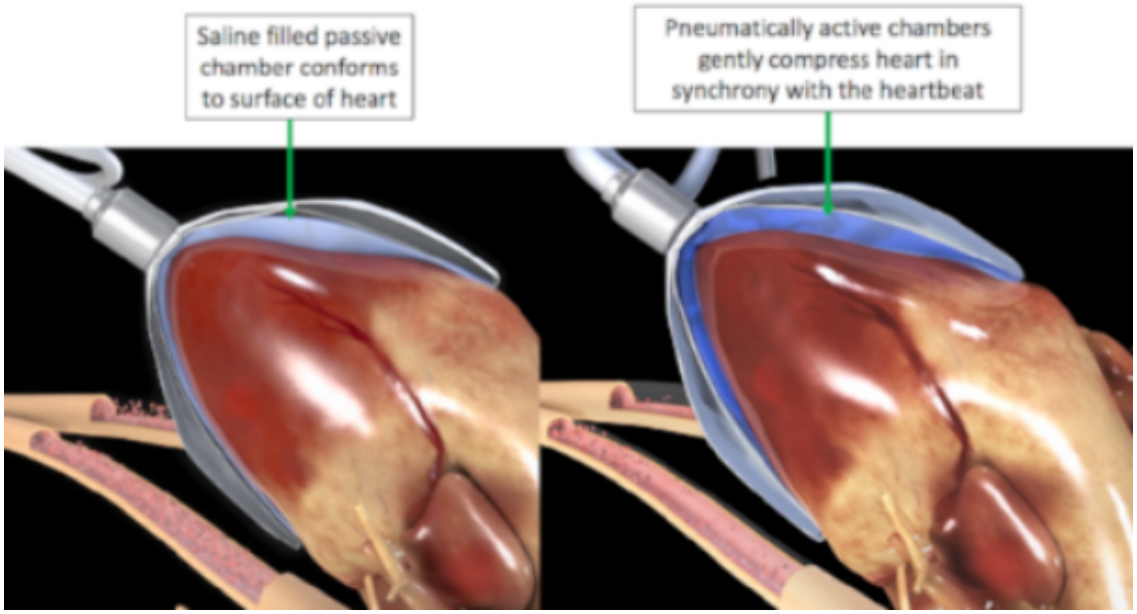
Heart Failure is a chronic, progressive condition in which the heart muscle is unable to pump enough blood through the heart to meet the body's needs for blood and oxygen.

patient will need a heart transplant.

More than 12 million people in the United States and European Union have congestive heart failure, but there are only about 4,500 hearts available each year for transplant. While a patient is waiting for a heart, a Left Ventricular Assist Device (LVAD), a device that helps to pump the heart for the patient can be used while waiting for a heart transplant or for patients who are not candidates for a transplant because they are too small or frail.

The decision to have a LVAD implanted requires open heart surgery, where the patient has an incision from the top to the bottom of his chest and chest spreaders are used to creak open the chest in providing direct access to the heart. A major surgical procedure that has a recovery time of a month and has to be repeated should the patient decide to have a heart transplant when a heart becomes available.

The challenge with the LVAD, is that the device was big and bulky and therefore uncomfortable and cumbersome for the patient because the external battery packs were also big making the patients immobile. As with all these devices the most common complications are bleeding and stroke depending on the device.



There hasn't been a lot of innovation with LVADs because of these challenges, but Corinnova, a medical device company took on this challenge and developed a device called the EpicHeart. It is a minimally invasive device that surrounds the heart with a plastic encased wire framework. The innermost of two chambers is filled with saline to conform to the shape of a patient's heart and the outermost pumps air to gently squeeze the heart to increase its output. The recovery time for this minimally invasive procedure is about a week according to the company.

The battery pack is small and portable, the size of a small briefcase enabling the patient to

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Closing Thoughts

There are a lot of technologies and products being developed today to restore the quality of life for patients in addition to reducing morbidity and mortality for a number of diseases allowing people to living longer. In the past, those diagnosed with cancer had a mortality rate of a 100% within months, but scientists have and are developing drugs that can keep a patient cancer free for years.

When I was younger watching futuristic shows such as Star Wars depicting transporters and flying cars, I always thought that it was only in one's imagination and that we would never get there. But today, in medicine, we have MRI and CT scanners, 3D images, 3D printing from these images and the technologies that I've discussed above and past topics that I've written about such as regenerative medicine and CAR-T therapy. We live in an incredible time to be so fortunate to see all these innovation come to life.

The one technology that would be interesting to see in the future if I had a crystal ball is cryogenics. Will scientists one day be able to freeze a human being and bring them back to life fully functional and live a normal life? We are on the path as scientists are already freezing human eggs but those are cells and not a human being.

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Should you have any questions or need of assistance with your business due diligence, determining your product's value proposition and economic value of your product, feel free to contact me at 781-935-1462 or regina@biomarketinginsight.com.