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BioMarketing Insight Newsletter

Creating Markets and Marketing Strategies

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

Last month I covered "Genetically Modified Organisms (GMO) Food: Good or Bad?" If you missed last month's article, click here to read it. This month is part 2 of a two part series and I will cover "Today's advances with genome engineering, and What is the Impact of Genome Engineering on the Future of Agriculture and Medicine?"

Read on to learn more about this topic and other current news. On the right are quick links to the topics covered in this month's newsletter. The next newsletter will be published on February 15th.

We encourage you to share this newsletter with your colleagues by using the social media icons at the top left, or by simply forwarding the newsletter via email.

Please email me, Regina Au, if you have any questions, comments, or suggestions.

Sincerely,
Regina Au
Principal, Strategic Marketing Consultant
BioMarketing Insight

In This Issue

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Regulatory Challenges - Rapid Response

I'm pleased to announce that my article on regulatory challenges entitled "Rapid Response" has been published in the October 2014 issue of European Biopharmaceutical Review. To read an electronic version, please click here. To learn more about EBR, click here.

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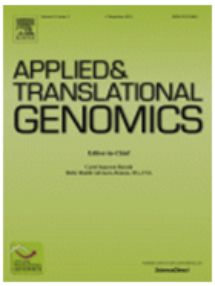
The Paradigm Shift to an "Open" Model in Drug Development

I'm pleased to announce that my article "The Paradigm Shift to an 'Open' Model in Drug Development" was published in the December 1st, 2014 issue of Applied and Translational Genomics. To read an electronic version, please click here.



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Save the Date: Medical Informatics World Conference - May 4-5, 2015

At the Medical Informatics World Conference, I will present "Designing Your Wearable Technology with Mobile Apps: What is Needed for Successful Product Adoption and Impact."

Wearable technology with mobile apps will become the norm in monitoring patients' vital signs at home or at work for diagnoses, alerts, management, or treatment of diseases. Getting product adoption from all stakeholders (patients, physicians, other healthcare professionals etc.) involved with these devices can be difficult unless the device meets their needs and demonstrates significant benefits to them. Learn the rationale behind what motivates each stakeholder and the attributes to incorporate into a product for successful product adoption.

I invite you to hear more details on the subject on Tuesday, May 5th at 9:25 am under Track 5,

Leveraging mHealth, Telehealth and the Cloud. For more information on this track click here. For conference details, click here.

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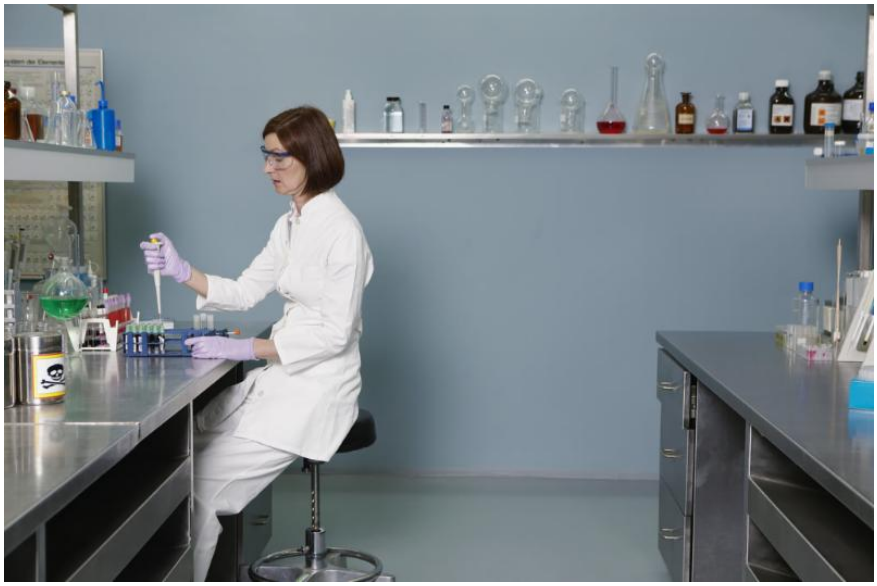
Developing a Product?



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, contact me for an appointment.

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Today's Advances with Genome Engineering

Genome engineering is a definite improvement over genetic engineering (insertion of a gene and hoping the host will acquire the trait) when trying to achieve more specificity in its target, ease of gene editing and identifying off-target outcomes as well.

DNA Structure
Source: National Institue of Health

Genome engineering started with the deletion or insertion of a DNA sequence at a specific location, increasing its accuracy through a technique called homologous recombination. This technique was a long and random process, because the desired recombination events occur extremely infrequently (1 in 106-109 cells), presenting enormous challenges for large-scale applications of gene-targeting experiments and has been limited in most organisms.

Today, genome engineering is based on the use of engineered or programmable nucleases composed of sequence-specific DNA-binding domains bound to a nonspecific DNA cleavage module. These nucleases are guided to a specific sequence within the genome to induce a double-strand DNA break (DSB). When a DSB is generated, the cell's intrinsic DNA repair system is activated and the genome is modified during the repair of the DSB. DSBs are typically repaired by either nonhomologous end joining (NHEJ) or homology-directed repair (HDR). There are four main DNA-binding proteins that have been engineered. The first three have issues with specificity, or flexibility and adaptability of gene editing.

1) Meganucleases derived from microbial mobile genetic elements

2) Zinc-finger nucleases (ZFNs) based on eukaryotic transcription factors
3) Transcription activator-like effector nucleases (TALENs) from Xanthomonas bacteria
4) Clustered regularly interspaced short palindromic repeats CRISPR/Cas9 endonucleases-RNA-guided DNA endonuclease Cas9 from the type II bacterial adaptive immune system

According to experts in the field, meganucleases have not been widely adopted, due to a lack of clear correspondence between meganuclease protein residues and their target DNA sequence specificity. They are rarely used for genome modification because their DNA specificity requires an extensive network of up to 50 amino acids, making redesign difficult. It is a biotechnological challenge to accomplish extensive reprogramming molecular recognition across such a complex interface, therefore meganucleases are used here as a model system for the development of an efficient approach to alter their specificity.

ZF domains have not been widely used because assembly of functional ZFPs with the desired DNA binding specificity remains a major challenge that requires an extensive screening process. ZFNs can be purchased or (with effort) engineered using publicly available resources, but often display measurable off-target activity.

TALENs still suffer from context-dependent specificity and their repetitive sequences render construction of novel TALEN arrays labor- intensive and costly. In contrast, TALENs and CRISPRs can be more easily reprogrammed to a wider range of DNA sequences, but their lengthy reading frames may complicate packaging and delivery in certain contexts and applications.

In the CRISPR/Cas9 system, the protospacer-adjacent motif (PAM) is the critical element located at the 3' end of the DNA target site and dictates the search mechanism for the DNA target with Cas9. Several studies have demonstrated that PAM is involved in the binding of the Cas9 to the target and the DSB. Target sequences without PAM do not induce DSB. Cas9 (formerly known as Cas5, Csn1, or Csx12) is the only enzyme within the cas gene cluster that facilitates target DNA cleavage.

The CRISPR/Cas9, type II system is emerging as the sequence-specific nucleases of choice for genome engineering for three reasons: 1) Cas9 is guided by a single guide RNA (gRNA) that is easily engineered. The gRNA targeting sequence consists of 20 nucleotides (nt), which is homologous to the DNA target site and can be ordered as a pair of oligonucleotides and rapidly cloned; 2) The modular features of the CRISPR-Cas9 system and short 20 nt length of the targeting gRNA makes these components advantageous in being able to target and cleave multiple target sequences simultaneously (multiplexing); and 3) the CRISPR-Cas9 system enables efficiency and high specificity with minimal off-target effects of unwanted chromosomal translocations when well designed gRNAs are used.

The Cas9 requires precise homology between the gRNA and the targeted DNA sequence but it does allow a few mismatches of base pairs in the target sequence when a DSB is generated. Depending on the number, position and distribution of mismatches, this could affect specificity and the desired application. These off-target effects and the long-term consequences of these effects are the current concerns with the CRISPR systems. Scientists are working on various methodologies, such as Cas9 nickase, to target single-strand breaks on opposite sides of the targeted DNA, or choosing unique target sequences and optimizing gRNA and Cas9 to minimize this phenomenon.

CRISPR/Cas9 shows definite promise but even with the current advances, scientists have just started to scratch the surface with gene editing that would ultimately enable correction of genetic disorders in humans, with minimal side effects.

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What is the Impact of Genome Engineering on the Future of Agriculture and Medicine?

Using the CRISPR/Cas9 technology will certainly advance the field of genome engineering. But will it resolve public concerns regarding long-term safety and will it change our way of living?

GMO foods

Genome sequencing with the CRISPR can help, due to its specificity in editing desired traits, which results in potentially fewer off-target effects. But the problem remains that when an unexpected negative outcome happens, outcrossing could spread to non-altered crops, by nature or by man. Outcrossing could impact hundreds of millions, or even billions, of people in our global economy. Measures can be taken to minimize the occurrence of mishaps, but precipitating incidents would be nearly impossible to control on a large scale.

A recent survey conducted by North Carolina State University and University of Minnesota polled 1,117 U.S. consumers nationwide about their preference for choosing nanotech foods and GMO foods with qualifiers such as price, nutrition and taste. Survey responses showed that in general, consumers are willing to pay more to avoid these technologies in their food. However, they are more willing to buy these foods if there are health and safety benefits.

When we alter our foods, will we encounter the same issues with wheat (gluten), where we have difficulty digesting the grain completely? This partial digestion triggers the release of the protein Zonulin, that opens the tight junctions of our intestinal lining and leads to a leaky gut, which may affect our immune system.

Research and developing new drugs

This is an area where genome engineering could advance basic research and our understanding of disease tremendously and promote the development of more effective drug therapies. Developing the right models for researching diseases and evaluating various drug therapies with speed and accuracy are the biggest hurdles in the pharmaceutical and biotech industry. Being able to knock-in or knock-out genes in mice with accuracy and speed and limit off-target effects with well- designed gRNA, are the ultimate goals. The mouse model is not a human model, but perhaps genome editing can get us a little closer.

Gene editing in curing single genetic disorders

It may be a while before we advance to gene editing in humans and we should proceed with extreme caution. Diseases involving more than one gene are so complex, implementation may require more advanced technology.

Life scientists are mindful that once gene editing is done, it's permanent and can't be undone. We can't predict with certainty the long-term effects. Should an unexpected negative outcome happen, we may not know how to correct it and this altered gene will be passed down for generations until scientists can figure out how to correct it.

When we cure diseases, patients live longer. The rising cost of healthcare would be reduced, but the financial burden would shift to the already cash-strapped social security system. Today, Americans are living longer and retirees are collecting social security payments for a longer period of time than originally anticipated. If the retirement age is raised, will there be enough jobs to sustain all the people entering the work force each year? For several years now, it has been documented that recent college graduates are having difficulty finding gainful employment. We must anticipate and plan for the impact that scientific discoveries might have on society.

Medicine will change. Physicians will learn more efficient methods of diagnosing and treating diseases and many now common diseases might be eliminated. Prevention would be defined as editing a gene for a particular disease once it is diagnosed. Insurance providers will be more likely to pay for

reimbursement of this new and highly specific preventive medicine because once a disease is cured, expenses will drop both short-term and long-term. The one area that science won't be able to change anytime in the extended future is the normal aging process.

Regenerative Medicine

With the introduction of 3D bioprinting using stems cells, the area of regenerative medicine has advanced significantly and scientists have been able to print tiny living kidneys, blood vessels, and livers in hopes of making organs available for transplant. Bioprinting organs from a person's own stem cells will eliminate the risk of organ rejection and render organ transplant waiting lists obsolete.

But when we perfect the technology, at what point do we cross the line from practicing medicine to printing organs as if they are consumer goods? Currently, 3D models are used to strategize the best approach for repairing a defected heart or knee. Will the mindset of practicing medicine change from repair to replacement? If so, would surgeons still need specialized training?

Researchers at the University of Toronto have discovered that the Sox2 gene, an on-off switch for a stem cell gene, is critical for determining the fate of the cell when it matures in mice. A major discovery for regenerative medicine. Could we get to the point where we can generate our own body parts should we lose a limb due to an accident, or regenerate damaged tissue in the heart? Scientists at the Gladstone Institute have found a way to transform non-beating cells into heart muscle cells after a heart attack with assistance from three genes, known together as GMT, in mice.

If technology eventually enables us to regenerate our own body parts, the impact on human life would be enormous but there could be negative consequences in tandem with the positive. The positive impact is that we could replace lost or damaged limbs or organs. But will the mindset of how we currently care for our bodies change? Will we still be cautious about not touching a hot stove or an electric saw to avoid getting burned or cutting off our fingers if we can regenerate? I think there will be those who would avoid getting burned and those who won't.

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Closing Thoughts

The take away message is, while advancing technology is essential for curing diseases and improving crop yields, we must proceed with extreme caution. Scientists have the best intentions, as they work diligently to advance research in the life sciences, but there are always consequences to everything we do.

Where do we draw the line when great technology may have greater negative consequences than positives ones? Similar to drug approval where regulators have to weigh the benefits against the risk. Can we anticipate the repercussions and have defensive measures in place to help avoid the negatives?

If we all live longer and healthier lives, what are the consequences, good and maybe not so good? Over-population or population control? Would we feel compelled to eliminate more forests to build more single-family housing for a growing population, or choose to build more multi-unit high-rises, referred by some as concrete or glass-walled jungles? What will happen to wildlife and the environment?

Sometimes we get so enamored with technology that we may forget about the possibility of unforeseen consequences to society. What have we learned from our experience with GMO foods? Future generations will likewise be impacted by consequences rooted in today's technology. Life is a cascade or domino effect, everything is related to and affected by everything else, much like systems biology.

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About BioMarketing Insight

We help companies de-risk their product development process by conducting the business due diligence to ensure that it is the right product for the right market and the market opportunity for the product meets the business goals of the company. We can then develop marketing strategies to drive adoption for the product.

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