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Inside Omega Therapeutics' Epigenomic Controllers™

By Erin Harris, Editor-In-Chief, Cell & Gene
Follow Me On Twitter @ErinHarris_1

Omega Therapeutics is developing novel engineered and modular therapeutics, called Omega Epigenomic Controllers™, that are designed to target with high specificity and downregulate or upregulate the level of expression of any of the 25,000+ human genes, individually or collectively, with controlled durability, to treat and potentially cure disease. The foundation of Omega's platform lies within the three-dimensional architecture of the human genome and its accompanying regulators, which are organized into distinct and conserved structures called Insulated Genomic Domains (IGDs). Omega's technology exploits the topology and functionality of these IGDs as druggable targets to activate the genome's innate ability to treat and cure disease. Omega's medicines are being developed to be dosed only as frequently as therapeutically necessary by intervening at the pre-transcriptional level and function without altering the native human genetic code or nucleic acid sequences.

Omega leverages the foundational, breakthrough work on epigenetics by Richard Young, Ph.D., Professor of Biology at MIT, and Member of the Whitehead Institute, who first described how genomic activity is controlled by 3D closed-loop structures of DNA, or Insulated Genomic Domains (IGDs), that contain one or more genes and their regulatory elements. I caught up with Dr. Young to learn more about Omega's epigenomic programming platform and what it means for the future of gene therapy.

Omega describes their epigenomic programming as working towards a new class of medicines – what does this mean?

Young: Through Omega's Epigenomic Programming platform, we can understand how genes are regulated in a healthy state, and how they are dysregulated in diseased states. By understanding how genes are organized into 3D looping structures called Insulated Genomic Domains, or IGDs, and their role in gene regulation, we have set out to design a new class of medicines using IGDs as drug targets to treat and potentially cure disease.

IGDs can either be dysregulated genetically due to a mutation in the DNA sequence, or epigenetically by a change in the chemical modifications to the DNA or its associated proteins (histones) in a disease state. The beauty of epigenomic programming is that unlike gene editing and gene therapy approaches, we are not looking to replace a gene or to make cuts in the DNA. The real elegance of this platform is that we are able to control gene expression without making any changes in the native DNA sequence.

By using nature's own language, we simply change the lexicon of chemical marks and modifications on top of the DNA and the structures within chromatin to affect how genes are regulated. We ultimately believe that epigenomic programming will be a highly efficacious and potentially much safer way to treat the genetic and epigenetic basis of a broad range of diseases across therapeutic areas. That is how we create a new class of drugs and transform the practice of medicine.

How have your discoveries opened doors to tap into the control room of biology?

Young: The human genome is packaged into the cell with a precise architecture, and my research has led to a better understanding of how this architecture contributes to the control of each gene and how it might be exploited to modify or tune the level of gene output for therapeutic benefit. Together with my colleagues, we've shown that genes and their regulatory elements are folded into architectural domains (IGDs), but more importantly, that gene regulation could be selectively tuned to modify the architecture of specific IGDs by using epigenetic modulation.

Omega's founders recognized that these IGDs, nature's "operating system" of genomic control and regulatory elements, could be tuned without altering the genetics of an individual. We are now applying that understanding to develop a new class of genomic medicines to treat and potentially cure a broad range of serious, complex multi-genic diseases for which there are currently no therapeutic options.

What makes epigenomic controllers different from current gene therapy and editing approaches, and what can this approach achieve that established gene therapy cannot?

Young: Omega's platform and epigenomic controllers offer a completely new therapeutic option to physicians and patients. On one hand, our epigenomic controllers are able to **tune** gene expression individually or collectively, up or down, whereas gene editing or gene therapy have a binary and generally permanent effect, causing genes to remain all the way "on" or "off". Through Precision Genomic Control™, we are able to bring the gene(s) back to the correct level of biological expression needed to treat or cure disease.

Another dimension to consider is **specificity**, or our ability to target specific DNA binding domains, IGDs, and their sub-elements and regulators, because we understand their genomic addresses. Through computational techniques including Artificial Intelligence, we have been able to map the genomic "zip codes" of IGDs and have identified hundreds of thousands of potential intervention points for our Omega Epigenomic Controllers™ to target for therapeutic benefit.

In addition to specific targeting and tunable expression, we have achieved controllable **durability** of effect through our use of nature's own durable epigenetic mechanisms. We can tailor the therapeutic response of our Omega Epigenomic Controllers to last for a few days, a few weeks, or even a few months. That completely differentiates us from anything else that we know of, from a therapeutic standpoint.

What disease spaces are predicted to be the most affected by this breakthrough in epigenomic programming?

Young: All human diseases involve dysregulation of gene expression at some level, and so our platform is applicable to almost any disease across therapeutic areas, from regenerative and metabolic medicine to inflammation, oncology, rare diseases and beyond. Unless a gene is mutated to complete loss of function and has no other compensatory genes, which is fairly rare, we can very likely target it for therapeutic benefit. While we can certainly treat monogenic diseases, which is effectively "table-stakes" for gene-based therapies, our real differentiation lies in areas like oncology, where we can go after very difficult to treat and difficult to drug oncogenes and growth factors, as well as tumor suppressor genes.

To our knowledge, Omega is the only company that can regulate multiple genes to effectively control multigenic and complex diseases with a single therapeutic intervention. Our platform can also reprogram developmental genes that are normally shut down at some stage to restore cellular and organ/tissue level function, which can be applied in the regenerative medicine space. Each of these represents an area of significant unmet medical need where we believe we can bring tremendous benefit to patients.

Does this form of genomic engineering open up to new ethical considerations and dilemmas?

Young: No, not at all — in fact, we believe that our new modality represents a safer and less ethically fraught therapeutic option for treating the genetic or epigenetic basis of disease. As mentioned before, the beauty of epigenomic programming is that unlike gene editing and gene therapy approaches, we are able to control gene expression without making any permanent changes to the native DNA sequence. We are using nature's own language of epigenomics (chemical marks and modifications on top of the DNA and the structures within chromatin) to restore genes to their correct level of biological expression in order to treat or cure disease. Because we are not changing the sequence of a patient's genome and our therapeutic effects, while tunable and durable, are not permanent, we believe that epigenomic programming will be a highly efficacious and potentially much safer way to treat a broad range of diseases than current gene therapy and gene editing approaches.

Comments