SUPERBUGS & SUPERDRUGS 2017 INTERVIEW SERIES

An Interview with Dr. Joe Sliman, MD, MPH, Chief Medical Officer, Synthetic Biologics, Inc.

1. About you – what is your role and what perspective does your company bring to the conference?

I am the Chief Medical Officer for Synthetic Biologics, Inc. We are a late-stage clinical company developing therapeutics designed to preserve the gut microbiome to protect and restore the health of patients.

The unique perspective that we as a company bring to this meeting is based on our focused approach to identify superbugs that specifically impact the gut microbiome, identify the specific processes by which that impact is made, and interdict that process. Our focused approach limits the possibilities for off-target activities and increases the likelihood of success. For example, Methanibrevibacter smithii is the primary producer of methane in the gut, which in turn is the mechanism that induces constipation in IBS-C patients. By using a specially-formulated version of lovastatin lactone that remains in the intestinal tract, we are attempting to interdict the methane-producing pathway of this Superbug, and therefore alleviate the symptoms of IBS-C.

2. Can you speak briefly about your lead microbiome-focused programs and how they target the microbiome utilizing very distinct mechanisms of action to influence therapeutic outcomes?

Our lead programs are both microbiome-based, but use entirely different concepts to adapt and utilize the gut microbiome to maintain the body's own unique ecosystem.

Our first program is SYN-004, also referred to by its generic name "ribaxamase". Ribaxamase is a beta-lactamase designed and formulated to be orally co-administered with intravenous beta-lactam antibiotics. Harnessing the power and design of nature, we have formulated this beta-lactamase to survive the stomach and remain in the intestinal tract, where it has been shown to meet and destroy the beta-lactam antibiotic that is excreted after circulating and fighting the infection it is intended to treat. In this way, we intend to prevent the unintentional destruction of our sensitive microbes, preserve the body's existing gut microbiome and reduce the rate of dysbiosis, which should prevent the emergence of antibiotic-resistant organisms and the resultant disease states such as antibiotic associated diarrhea and, for example, C difficile infection. In addition, the

reduction in selective pressure on the microbiological ecosystem in the gut should significantly reduce the emergence of antimicrobial resistance. We believe that for this reason, ribaxamase could be an important public health tool, in that prevention of antibiotic resistance and the resultant reduction in the spread of antibiotic resistant organisms is a benefit that accrues to the public as well as the individual.

Our second program is SYN-010, a specially formulated version of lovastatin lactone, which is also designed to survive the stomach and remain in the intestinal tract. SYN-010 is intended to reduce the amount of methane gas in the small intestine, which has been identified as the primary causal factor of constipation in patients diagnosed with Irritable Bowel Syndrome. SYN-010 targets the enzymatic mechanism of the gut archaeon, M. smithii, that produces methane and is designed to do so without eradicating the microorganism from the gut, thereby improving the symptoms of IBS such as bloating and pain, while improving the number of bowel movements in these patients.

3. With the 2 lead drugs in your pipeline impacting the microbiome in very different ways, talk to us about how you ultimately ended up with these 2 very different approaches in drug development within the microbiome space?

As a company, we decided that the microbiome is the new frontier, so to speak, in medicine. It has become clear that we live in a symbiotic state with the thousands of species of microbes that live on and in us, and make up 90% of our body mass and genetics, and much of our metabolism and homeostasis systems. But the regulatory guidance hasn't caught up with the science yet, although it is on its way. So, we deliberately sought out any potential drug candidates that leveraged our microbiome in some way, whether that's use of our own microbes, or elimination of an imbalance or something similar, but that could also be adapted to existing clinical development and regulatory pathways. So, while our two lead candidates use very different approaches, they share one important characteristic: they leverage existing regulatory guidance and pathways, which enables us to proceed in a scientifically valid and developmentally sound way. So, while both of our lead drugs offer a distinctly unique mode of action, they each target specific mechanisms that result from the disruption of the gut microbiome.

4. What do the findings from your most recent clinical trial suggest about the role the gut microbiome plays in preserving human health and protecting against AMR? In referencing your most recent clinical trials, can you speak to how ribaxamase was shown to protect the gut microbiome and how it may prevent the development and proliferation of AMR?

Our study strongly suggests that disruption of the gut microbiome due to the unintended effects of antibiotics leads to adverse clinical outcomes and directly results in the emergence of antibiotic resistance. Conversely, preservation of the gut microbiome, through mechanisms as simple as inactivation of the antibiotic before it can impact the organisms, can result in clinically significant reduction in the emergence of antibiotic

resistance. Ribaxamase may prevent the emergence of antimicrobial resistance genes and antibiotic-resistant organisms by preserving the native gut microbiome. By preventing the unintentional killing of the "normal" gut organisms, there is far less selective pressure for resistant organisms, which remain suppressed. In this way, ribaxamase may prevent the emergence of antimicrobial resistance.

5. You referred to ribaxamase as a "public health" drug. What does that mean to Synthetic Biologics and what role should government play in the development of new antibiotics and/or strategies designed to limit the proliferation of AMR?

When we refer to public health drugs, we are really referring to drugs, biologics, and vaccines that benefit everyone, even those who are not prescribed the product. Vaccines confer "herd immunity" when enough members of the community are vaccinated, and the target pathogen no longer can spread due to being denied a path through the population. We believe that a similar effect could be accomplished with resistant organisms and genes in a community, hospital, or lab. If enough people taking antibiotics can avoid dysbiosis and the effects of dysbiosis, the emergence and spread of antibiotic resistance could be interdicted. This could also enable the use of broader spectrum, cheaper antibiotics where they are indicated, without fear of causing dysbiosis or unleashing a resistant organism. Government agencies including FDA, CDC, BARDA, USAID, and NIH, among others, have historically cooperated to produce or enable the development of such public health products. By providing funding, expertise, and partnerships in preclinical and clinical development, as well as enacting public health policies, various government agencies have often contributed to development of products that will benefit society as a whole.

6. Are new antibiotics the answer to the AMR question? What are the merits and shortcomings to this approach?

There is a clear need for more antibiotics, and new classes of antibiotics. As one of the most important medical and public health innovations of all time, antibiotics and other antimicrobials will always have a very important part to play in human health. As the battle among organisms for survival continues and escalates, new antibiotics will undoubtedly become necessary to treat new types of infections and organisms that adapt to resist existing antibiotics. However, as a practical approach to health care, treating infections with the simplest and most effective antibiotics is the preferred method. To that end, new antibiotics should be applied judiciously to minimize, if not outright eliminate, the selective pressure on infectious organisms to become resistant. Treatment of infectious diseases can become a vicious cycle of escalating resistance necessitating more powerful antibiotics, and this cycle should be broken as early as possible to minimize the emergence of resistance.

7. How far do you think we have advanced in recent years with regard to combating the global threat with antimicrobial resistance?

The identification of the importance of the native human microbiome and its impact on human health is perhaps the seminal advance in medicine of our lifetimes. Recognition that those organisms are not simply "commensal" and are actually supposed to be there, performing vital functions and helping maintain health and homeostasis, is the first step towards a deeper understanding of human health and more effective treatment of diseases. But in terms of combating the global issue of antimicrobial resistance, the need to treat potentially life-threatening infections overrides other concerns. We have, however, taken the first and most important step towards combating antimicrobial resistance and that is recognizing that it is a real problem requiring real solutions and prevention where possible. The FDA and EMA have begun addressing these issues of AMR but it is clear that we will need more than just new antibiotics. Infection control and antibiotic stewardship programs are extremely useful, but they don't address the root cause. Prevention of selective pressure is the key to preventing resistance from emerging in the first place.

8. What are the biggest challenges facing microbiome-oriented discovery and clinical stage companies and what impact might this have on the development of AMR-related products? What specific challenges has Synthetic Biologics encountered with your lead compound, ribaxamase?

Specific challenges would include, primarily, creation of a viable regulatory pathway. That is, can the FDA, for example, create a set of guidances that will apply to at least some of the potential approaches? For example, how does the FDA regulate development of specific organisms or microbial components when we haven't yet established what "normal" or "healthy" means? For us, the beauty of our approach is that we don't seek to modify the microbiome. Our goal is to prevent disruption. Our challenge, therefore, will be establishing what constitutes a clinically relevant change, and how much prevention is adequate. Prevention by definition requires one to "prove the negative", so to speak, so preservation must result in less diarrhea, for example. That's not necessarily hard to demonstrate, but it requires a study that is properly designed and executed.

--- end ---

Superbugs & Superdrugs 2017
17th Annual Conference: 20th & 21st March
Copthorne Tara Hotel, London UK
www.superbugssuperdrugs.com