

Q&A with Andrew J Holman, MD, CEO and Co-Founder of Inmedix Inc developing Diagnostics and Therapeutics for Immuno-Autonomics where Stress controlled within the Brain plays a role in Autoimmune Diseases such as Rheumatoid Arthritis, Lupus and Inflammatory Bowels Disease



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CEOCFO: Dr. Holman, what was the impetus for starting Inmedix?

Dr. Holman: Inmedix was founded in 2006 to commercialize discoveries I made in my Seattle rheumatology office. I worked to address chronic pain and discovered therapeutic options for patients with fibromyalgia. I published a number of studies, including a double-blind, randomized, controlled trial before

selling an international portfolio of utility patents to a major pharmaceutical company. That was the first Inmedix project. More recently, our team has begun to define immuno-autonomics: where stress, controlled within the brain by the autonomic nervous system impacts and distorts immune function in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowels disease (IBD) and other autoimmune diseases.

"Immuno-autonomics is the most overlooked component of personalized, precision medicine." - Andrew J Holman, MD

CEOCFO: What have you found out? What do you understand today that you want to share with the world?

Dr. Holman: Despite magnificent advances in biologic therapy, only 25% of our patients with RA achieve symptom-free remission. It appears that treatment fails in 75% of patients not because of the immune system, but due to the brain. The new concept is called Immuno-autonomics. Patients have been telling us for years that stress flares their autoimmune disease. We believed them, but did not know how to respond. Now, we are beginning to understand that stress affects the immune system like pouring gasoline onto a fire. More active disease is simply much harder to control.

A few other groups in the US, UK, EU and Japan are also working on this. Diagnostics able to measure stress in elite, professional athletes are being proposed as measures for patients with autoimmune disease. In pilot studies, this diagnostic strategy has correlated with RA treatment outcome, SLE flares and even who eventually develops autoimmune diseases in the first place. What makes it very exciting, in addition to understanding how stress makes such an important difference for patients, is that stress state can be addressed and potentially modified. Four different models to reduce the adverse effect of stress on autoimmune disease activity have been published. The effect has been reported to be a reduction of nearly 40%. When autoimmune disease is reduced by 40%, the rheumatology toolbox works much better.

CEOCFO: What is the science happening in the brain or in the body in general with these different scenarios?

Dr. Holman: The autonomic nervous system, or ANS, impacts and distorts immune function on many levels. The ANS is divided it into two principal branches: the sympathetic and the parasympathetic. The parasympathetic is essentially the

rest and restorative component, most prominent during sleep. The sympathetic or “fight or flight” can activate at any time and is designed to ensure survival. One mechanism related to survival is enhancement of immune function to make it more vigorous and aggressive to protect us from pathogens. Generally, this is helpful, but not for patients with an autoimmune disease characterized by an immune system bent on destroying their normal tissues. Sympathetic “fight-or-flight” stress intensifies disease to make it nearly untreatable.

Inmedix licensed arguably the best technology in the world to measure ANS state currently used by the NFL, Premier League football in the UK/EU and Olympic federations. We completed clinical studies to evaluate its utility, both as a predictor and as a guide to improve therapy for patients with autoimmune disease. We are currently working to achieve US FDA clearance and UK/EU CE mark approval to assist rheumatologists.

Three mechanisms have been described to mitigate adverse ANS state to improve RA treatment outcomes. First is treatment of obstructive sleep apnea in patients who also have RA. Japanese authors reported in 2003 that doing so reduced RA severity by 35%. Second, a pilot study reported superior outcomes combining FDA-approved medications used to treat restless legs syndrome (RLS) with a biologic therapy used to treat RA. While the strategy is not FDA approved and the study was only a pilot, it adds to our knowledge of immuno-autonomics. Third, a company called SetPoint Medical has evaluated mitigation of adverse ANS profile through vagus nerve stimulation (VNS). The vagus nerve in the neck transmits important ANS signals from the brain to attenuate immune activity. In a pivotal 2016 report, VNS reduced RA activity and did so through reduction in the same inflammatory cytokines (immune messenger molecules) targeted by the biologic agents rheumatologists currently prescribe to treat RA.

CEOFCO: *Does the medical community understand this concept or are they not aware of what can be done or what should be looked at?*

Dr. Holman: Most clinicians are fully aware that stress affects their patients. However, most physicians are not aware of the extent of this research from the US, UK, EU and Japan. The Inmedix scientific advisory board includes two former American College Rheumatology past-presidents and academic experts from Stanford, Harvard, Oxford and other prestigious institutions. They understand. The researchers in the field understand. Companies defining immuno-autonomics understand, including GSK, Inmedix, SetPoint Medical and Galvani. Immuno-autonomics is the most overlooked component of personalized, precision medicine. I suspect that in the next two to four years this is going to be well understood by the average rheumatologist.

CEOFCO: *Would you tell us about the UK subsidiary and why you have it?*

Dr. Holman: This is a unique strength of Inmedix. Immuno-autonomic strategies not only improve treatment outcomes, but may also significantly reduce cost. Marita Zimmermann, MPH, PhD, a research scientist in Health Economics and Outcomes Research in the Pharmaceutical Outcomes Research & Policy Program at the University of Washington, and her colleagues at Consultants in Global Health, LLC, presented their findings at the 2017 American College of Rheumatology Annual Meeting in San Diego. Immuno-autonomic diagnostics (Inmedix) coupled with immuno-autonomic therapeutics (Inmedix, GSK, SetPoint Medical, Galvani) were projected to significantly improve quality of life for patients with rheumatoid arthritis while also reducing biologic therapy costs to payers over ten years in the United States by \$23-28 billion. Identifying who pays the ultimate bill for treatment and disability in the US is not always clear. In the UK, it's the government. Inmedix came to the UK in 2017 to conduct studies with Profs. Peter Taylor (Oxford) and Ernest Choy (Cardiff) not only to help patients overcome the burdens of autoimmune disease, but also to explore health economic benefits of immuno-autonomics.

CEOFCO: *What is the prevalence of rheumatoid arthritis?*

Dr. Holman: RA affects 0.6% of the population, nearly two million Americans. It can occur in children, but primarily affects adults in the prime of their lives. Most patients are women who develop RA between age twenty and forty-five. The immune system attacks otherwise normal joints. We do not yet know why, but in many respects, we know how. All rheumatologists wish they could address the cause of RA. Until we can, we will continue to try to control it so those affected will get their lives back.

CEOFCO: *What have you learned as you have done your early studies? What surprised you?*

Dr. Holman: What surprised me is the extent of impact this factor has on autoimmune disease expression. Of course, rheumatologists believed patients when they related how stress flared their disease and, sometimes, preceded its onset. What's shocking is the extent that it's true. A study abstract supporting this comment will be presented at the British Society for Rheumatology meeting in Liverpool in May 2018.

CEOCFO: What is your funding like for the steps you need to take?

Dr. Holman: Much of our immuno-autonomic initiative has been funded by our first discoveries and patent sales. However, we are currently offering a \$1.5 MM seed convertible note with 6-8% guaranteed interest paid quarterly for 3 years. Interest is kept in a Debt Service Reserve Account. It's unusual to guarantee interest, but we wanted to take special care of our first investors. Currently, we are 50% subscribed and hope to close it very soon to transition to a \$4.5MM Series A with our partners Belgrave Capital in the UK. We anticipate a \$10MM Series B in 18 months for launching our diagnostic.

CEOCFO: Is that the ANS Neuroscan™?

Dr. Holman: Correct. Our diagnostic is called the ANS Neuroscan™. It is a repurposed 5-minute ECG tool with established CPT reimbursement codes. We anticipate this point-of-service diagnostic will transform care for autoimmune diseases and also allow Inmedix to participate in the discovery of immuno-autonomic therapeutics applicable to any disease adversely impacted my stress.

CEOCFO: How do you standout at conferences when you are giving presentations?

Dr. Holman: With data and with a thorough knowledge of the literature and potential applications appropriate to this new medical field of immuno-autonomics. Unlike most seed round life science companies, Inmedix has already published five studies with 243 patients. We established our IP as well as an exclusive license to what we and others believe to be is the best ANS testing technology in the world. We have payers in the UK interested in working with us. We have already had an audience with NICE. We created one of the top scientific advisory boards in the entire pharmaceutical industry. Our challenge is to share our discoveries and why this diagnostic is atypical. We believe two million Americans with RA will need our diagnostic every 3-4 months to achieve optimal treatment of RA. With current reimbursement, that equates to a \$500MM potential annually (US). Within the breadth of our IP (all autoimmune disease and fibromyalgia), analogous calculation yields a \$2.5 billion annual potential for Inmedix. And by providing payer benefits to reduce the cost of biologic care, we see strong tailwinds for our adoption and reimbursement.

CEOCFO: What should people expect from Inmedix over the next year or so? Why pay attention right now?

Dr. Holman: Today, the concept of Immuno-autonomics is far enough along as a science to attract considerable attention. It's potential impact to patients, payers and on the pharma industry is quite profound. Fundamentally, this is a new field of medicine that will develop a wide range of therapeutics applicable, not just to rheumatology, but to any disease where stress plays a role to aggravate disease. One would immediately think of cardiovascular disease, diabetes, psychiatric disease, but also, cancer. Immuno-autonomics may be the most significant breakthrough in autoimmune disease since the biologics were first discovered with Enbrel® in 1998. Stay tuned!

