Innate Defense Regulators: Novel Therapeutics for Emerging and Antibiotic-Resistant Diseases

Dr. Oreola Donini
First, what has been your primary motivation as a scientist and what is your academic and professional background?

I have always been focused on the application of science at the crossroads of disciplines. For my PhD program, I joined a research group working at the interface of chemistry and neurology to understand potential treatments for epilepsy and Alzheimer’s disease. There, my interest in computational chemistry as a discipline started to grow, because it operates at this interface, integrating knowledge from many disciplines.

During my career, I have always focused on working with biotechnology companies with novel solutions to unmet medical needs. These included the former Inimex Pharmaceuticals Inc, where I and my colleagues invented SGX94, and the current Soligenix Inc, where we have established a late-stage development pipeline focused on treatments for rare diseases with unmet medical needs.

SGX94 is the name of a novel drug that you have invented as a therapy to bacterial infections. What is the nature of SGX94 and how does it work?

SGX94 is representative of a new class of small molecules known as innate defence regulators (IDRs), which have the potential to selectively modulate innate immune responses to kill and clear bacterial infections, while reducing inflammation. The generation of adaptive immunity requires days or weeks as it involves a sequence of immune responses. By contrast, innate immunity is pre-programmed to respond very quickly, constituting the first line of defence against infections. The majority of the research done on the immune system has been directed towards the production of antibodies as it constitutes the main biological target for vaccines, but recently innate immunity is gaining growing interest from the perspective of exploring a rapidly acting alternative to antibiotics. Several classes of molecules have been investigated for their ability to stimulate or enhance innate immune responses to kill and clear pathogens during infection. It is noteworthy that this anti-infective mechanism differs from that of antibiotics, which act by directly targeting and killing the bacterial cells. However, most of these innate immune stimulants are unable to differentiate inflammatory and pathogen-clearing pathways of the innate immune system, which can bias the outcome either towards aggravated inflammation (potentially harmful) with high pathogen-clearing activities or towards diminished inflammation and insufficient infection clearance. In 2004, Dr. Donini and her research colleagues discovered a clinical candidate in a novel class of small molecules known as innate defence regulators (IDRs), which have the potential to selectively modulate inflammation-clearing and inflammatory pathways so as to reduce inflammation, while enhancing the infection-clearing responses. Therefore, IDRs offer a unique and safe therapeutic approach that harnesses innate immunity to treat infectious diseases as well as other inflammatory disorders.

The IDR prototype SXG94 as an Anti-infective

The IDR prototype SXG94 is the lead representative of IDRs that binds to a highly evolutionarily conserved protein of the innate immune system known as p62. This leads to stimulation of innate immune cells like monocytes and macrophages, which engulf both bacteria and other damaged cells and clear them from the body, while mitigating the associated deleterious inflammatory responses. Since the discovery of the IDR concept, SXG94 has been shown to improve the disease outcome in mouse models of both local antibiotic resistant and emerging infectious diseases represent an alarming public health problem, with a growing number of diseases being difficult to treat with conventional antibiotics and anti-infectives. Innate defence regulators constitute a late-stage technology that offers promising therapeutic alternatives to antibiotics for the treatment of a variety of infections and inflammatory conditions.

Innate Defence Regulators as Alternative Anti-infectives: Principles and Current Status

Innate Defence Regulators: Novel Therapeutics for Emerging Antibiotic-Resistant Diseases

Dr. Ocrea Donini is the Chief Scientific Officer of Soligenix Inc, a late-stage biopharmaceutical company developing products that address unmet medical needs in the areas of inflammation, oncology and biodefence. Dr. Donini is the inventor of Soligenix’s anti-infective technology, SGX94, which offers an alternative option for treatment of antibiotic-resistant infectious diseases.
and systemic infections with a broad array of bacterial pathogens. The anti-infective power of SGX94 was evident upon either preventive or therapeutic administration (i.e. prior to or during infection), and either as a stand-alone agent or in conjunction with suboptimal antibiotic treatment. Despite these promising therapeutic effects, Dr. Donini and her research team do not propose SGX94 to totally replace antibiotic treatment, but to rather be the drug of choice in cases of antibiotic-resistant infections or in cases where antibiotic use is discouraged or contraindicated. ‘Antibiotics are true “miracle drugs” and we would not consider replacing them with IDRs, however, the latter can be the drug of choice in cases where antibiotics are ineffective or contraindicated’, said Dr. Donini. For instance, with the ongoing concerns over the growing problem of antibiotic resistance, the empirical use of broad-spectrum antibiotics to prevent infection in individuals under high risk (e.g., patients suffering immune-deficiencies) or to blindly control infections until the causative bacteria is identified in the laboratory is highly discouraged. In these cases, SGX94 can be used instead of antibiotics to prevent or treat infections. Moreover, antibiotics in many instances can increase inflammation, because as they kill the bacteria, the contents of the bacterial cells further activate the inflammatory pathways of the innate immune system. Thus, combining SGX94 to antibiotic treatment will not only enhance the infection clearance, but also mitigate antibiotic-induced inflammation. This is of significant importance, because most other anti-inflammatory approaches can delay pathogen clearance as well as tissue healing.

Innate defence regulators (IDRs) offer a promising alternative to antibiotics for treatment of antibiotic-resistant infections, for prevention of infections in highly susceptible individuals, and for empirical treatment of yet-undiagnosed infections.

THE PRESENT AND FUTURE OF SGX94

Dr. Donini and her research team have already characterized the majority of the therapeutic and pharmacological attributes of the SGX94 action in a variety of animal models, as well as in laboratory cell and organ culture systems. These studies demonstrate the value of the drug in enhancing the clearance of bacteria and increased survival after acute infections with a wide array of bacterial species. This work has led to a phase I clinical trial with SGX94 to evaluate the safety and tolerability of the molecule in human subjects. The lead clinical IDR, SGX94, was found to be well tolerated in 84 healthy volunteers under single and multiple ascending dose administration. In addition, there were no serious or severe side effects and there was no dose-limiting toxicity or maximum tolerated dose identified. Importantly, although the trial was conducted to primarily evaluate safety, secondary studies on isolated blood cells from the treated participants showed similar innate immune responses as obtained from mouse models, indicating consistency of the SGX4 action across species. SGX94 is currently being evaluated in a phase II clinical study of approximately 100 patients as a potential treatment for the reduction of oral mucositis in patients receiving combined chemo- and radiation therapy for head and neck cancer. Oral mucositis is non-infectious disease, but a condition of serious inflammation, ulceration and damage of the mouth cavity as a side-effect of chemoradiation. In such a case, SGX94 may potentially reduce the inflammation while enhancing clearance of the dead/dying cells, reducing the severity and the duration of oral mucositis in these patients.

Dr. Donini and her research team are currently pursuing the SGX94 technology platform (USAN: dusquetide) in a number of other unmet medical needs including emerging and antibiotic resistant diseases. For instance, they have been evaluating SGX94 in preclinical models of melioidosis, a disease caused by the antibiotic-resistant, gram-negative, intracellular bacterium Burkholderia pseudomallei, which is broadly endemic in areas of northern Australia and southeast Asia and is considered a high priority biothreat agent.