

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

Dr. Oreola Donini



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Dr. Oreola 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.

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.

I received my PhD in chemistry from Queen's University and went on to complete a post-doctoral fellowship with one of the leading computational chemists, Dr. Peter Kollman of the University of California, San Francisco. After completing my fellowship, I moved into biotechnology, attracted by the cross-disciplinary research and the desire to apply my skills to developing drugs to improve patients' lives.

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 peptides (essentially small molecules) which we call 'innate defence regulators' (or IDRs). These peptides interact with and activate a specific component of our immune system, known as the innate immune system, which comprises a number of first-line cells and molecules that

instantly respond to infections. IDRs basically harness our body's innate immune responses to control infection.

Most of us are familiar with antibiotics as the most common treatment for bacterial infections, so what is the difference between innate defence regulators and conventional antibiotics?

Antibiotics kill bacteria directly, while IDRs engage your body to use its normal mechanisms to kill and clear bacterial infections. This is extremely important to understand because there have been no other attempts to develop drugs with this type of mechanism. IDRs do not kill or even interact with the bacteria directly, but rather they change the innate immune response so that more bacterial killing mechanisms operate at the site of infection, while reducing inflammation.

Why are new approaches for emerging and antibiotic resistant diseases so important?

Antibiotics are probably the most powerful drugs known to mankind, and have greatly reduced illnesses and deaths due to infections over the past six decades. However, with the wide-scale use of antibiotics to treat varieties of infections, a growing number of bacterial species and strains have evolved mechanisms to adapt to antibiotic toxicity. It is not a myth to think of a coming era when antibiotics are no longer effective against bacterial diseases. There is a wide consensus among medical and public health communities on the pressing need to develop potential alternatives to antibiotics.

Throughout the stages of the SGX94 development, has Soligenix collaborated with any academic research groups? If so, what has been their role and how did they contribute to the progress of the research?

Innate immunity has been a very under-appreciated aspect of our immune system for many years and it is only with the ground-



breaking work of our collaborators, as well as others in the field, that a treatment approach like SGX94 is possible. The original idea of modulating the innate immune system instead of directly targeting the bacteria was developed at the University of British Columbia by Dr. Brett Finlay and Dr. Robert Hancock. As the program advanced, other collaborators lent their expertise in molecular biology (Dr. Leonard Foster, University of British Columbia) as well as specific animal models of infection (Dr. Steve Opal, Brown University; Dr. Lisa Morici, Tulane University). As with any scientific endeavour, the outcome is always built upon the efforts of many individual scientists and this is true of the SGX94 program as well.

Is there anything else you would like to add?

While we believe that the impact of IDRs in the treatment of antibiotic resistant and emerging infectious disease is a breakthrough, we cannot lose sight of the fact that the innate immune responses to both pathogenic invasion and tissue damage has applicability in many other indications. Given the broad applicability of IDRs, we are also investigating the utility of IDRs in oral mucositis and other indications such as macrophage activation syndrome. At Soligenix, we pursue these and other indications as part of our overarching goal to develop treatments for rare diseases, where there remains an unmet medical need.

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

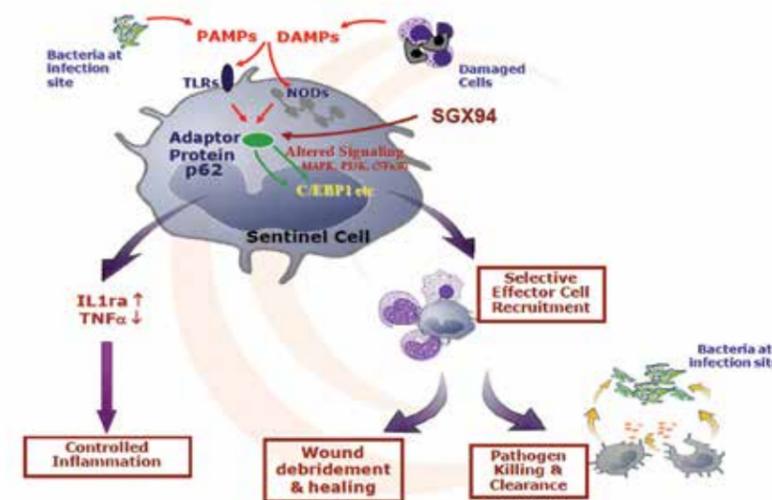
Antibiotic resistant and emerging diseases represent an alarming public health problem, with a growing number of diseases being difficult to treat with conventional antibiotics and anti-infectives. Innate defence regulators constitute a late-stage technology that offers promising therapeutic alternatives to antibiotics for the treatment of a variety of infections and inflammatory conditions.

THE ALARMING THREAT OF ANTIBIOTIC RESISTANCE

Antibiotic resistant and emerging infectious diseases represent constant and growing threats to public health, both in the developed and the developing countries. A number of the world's most dangerous diseases are caused by pathogens that are not only difficult to treat, but also antibiotic resistant, making the treatment options very limited. Antibiotics have been the gold standard in the treatment of infectious diseases and since their discovery in the 1940's they have greatly reduced illnesses and deaths due to infections. However, with the wide use of antibiotics over the past decades, an increasing number of bacterial species and strains have become adapted to their action. According to the US Center of Disease Control and Prevention, approximately two million people become infected with bacteria that are resistant to antibiotics each year, with at least 23,000 annual deaths occurring as a direct result of these infections. Therefore, with the gradually diminishing efficacy of the currently used antibiotics, and with only few discoveries being made on new antibiotic generations, the importance of identifying alternative methods to treat infections has been highlighted by the World Health Organization (WHO) and major American public health bodies including Centers for Disease Control and Prevention, the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Agency (BARDA). Moreover, the US White House released a 'National Action Plan for Combating Antibiotic-Resistant Bacteria' in March 2015, with the search for new treatment alternatives being a key goal.

INNATE IMMUNITY TO COMBAT INFECTIONS

The immune system is the biological system that defends our body and organs against invading pathogens and microbes. The protection provided by the immune system is achieved through two functional components, termed adaptive and innate immunity. The



former involves the production of antibodies and killer cells that are specifically generated to neutralize or destroy a certain individual microbe, while the latter comprises a set of killer and scavenger cells that recognize common factors among microbes and thus reacts generically to all of them. Activation of innate immunity typically involves inflammation, the reaction in which innate immune cells aggregate at the site of infection to destroy and clear the causative microbe. The generation of adaptive immunity requires days or weeks as it involves a sequence of time-consuming processes. 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 to adaptive immunity 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 immunity, 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 fellows discovered a clinical candidate in a novel class of small molecules known as innate defence regulators (IDRs), which have the potential to selectively modulate infection-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 SGX94 AS AN ANTI-INFECTION

SGX94 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, SGX94 has been shown to improve the disease outcome in mouse models of both local

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.

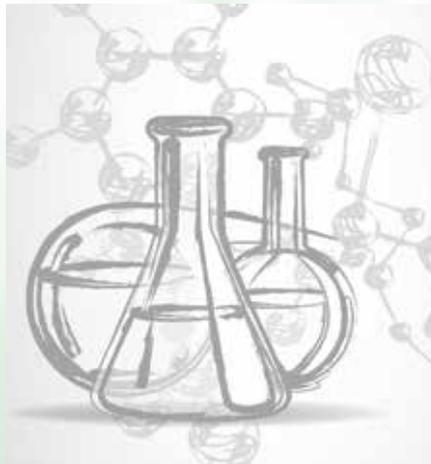
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Innate defence regulators (IDRs) offer a promising alternative to antibiotics for treatment of antibiotic-resistant infections, for prevention of infections in highly susceptible individuals, and for empirical treatment of yet-undiagnosed infections.

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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 SGX94 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 bioterror agent.

Researcher Profile

Dr. Oreola Donini
Chief Scientific Officer
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Dr. Donini has more than 15 years experience in drug discovery and preclinical development with start-up biotechnology companies and has been instrumental in leading early stage development of several novel therapies into the clinic. She is an inventor of Soligenix's SGX94 innate defence regulator technology, which is currently undergoing a phase II clinical study in oral mucositis. Since the discovery of the IDR technology, Dr. Donini has been responsible for overseeing all aspects of SGX94 development, including its manufacture and preclinical testing, which demonstrated efficacy in combating bacterial infections and mitigating the inflammation and tissue damage caused by trauma or infections.

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PARTNERSHIPS

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