

## Soligenix Inc. SGX94 (DUSQUETIDE) EXECUTIVE SUMMARY

### INVESTMENT HIGHLIGHTS

1. Dusquetide is a fully synthetic, water soluble, 5-amino acid synthetic peptide that is the lead clinical candidate in a new class of compounds called Innate Defense Regulators (IDRs).
2. IDRs modulate the innate immune system, targeting an integration point in the intracellular signaling network directly downstream of most innate immune receptors (e.g., TLRs, NODs) and upstream of the cytokine and chemokine response (e.g., TNF $\alpha$ , IL-1). IDRs interact directly with the intracellular adaptor protein p62 or sequestosome-1.
3. New paradigm for treatment of Tissue Injury and Infection:
  - a. Ameliorates mucositis induced by cancer therapies;
  - b. Enhances tissue healing by preventing inflammatory damage;
  - c. Controls infection even during immune suppression;
  - d. Augments antibiotic therapy against all bacteria; and
  - e. Addresses the growing problem of antibiotic resistance.
4. Redirects the host innate defense cascade, leading to enhanced resolution of infection and tissue injury - *NOT* an antibiotic.
5. Extensive *in vivo* data in broad range of bacterial infection models and models of mucositis, colitis & skin injury.
6. Enhances antibiotic activity without increasing inflammation.
  - a. Adjunctive efficacy demonstrated in an acute model of infection with the Category B biothreat agent *Burkholderia pseudomallei*, the cause of melioidosis.
7. Dusquetide is administered IV over 4-minutes every second or third day. It has a rapid half-life (minutes) but an enduring pharmacodynamic response (days).
8. Safe and well tolerated in placebo-controlled Phase 1 trial in 84 healthy volunteers.
9. Positive preliminary efficacy and safety demonstrated in an exploratory Phase 2 double-blind, dose-ranging, placebo-controlled trial in 111 head and neck cancer patients treated with chemoradiation therapy: reductions in duration of severe oral mucositis and incidence of infection observed.
10. Fast-track designation in oral mucositis; orphan designation for treatment of acute radiation syndrome; fast-track and orphan designation for the treatment of melioidosis (bacterial infection); and orphan designation for treatment of macrophage activation syndrome.
11. Composition of Matter patents granted in multiple jurisdictions.
12. Substantial market potential.

### OVERVIEW

Soligenix Inc.'s IDR platform represents a novel and innovative approach to therapeutically modulating the immune system by targeting the innate immune system, to treat infection and tissue damage. Preclinical data indicate that IDRs are active in models of a wide range of therapeutic indications including life threatening bacterial infections as well as the severe side-effects of chemo- and radiation-therapy.

Dusquetide, the most advanced in the company's IDR library, is a fully synthetic, 5-amino acid peptide with high aqueous solubility and stability. Extensive *in vivo* preclinical studies have shown that dusquetide reduces tissue damage associated with chemotherapy, radiation, trauma and inflammation. Although dusquetide is not directly antimicrobial, it accelerates pathogen clearance and increases host survival in a broad spectrum of bacterial infections including Gram positive and negative bacteria, and both drug sensitive and resistant strains, occupying either intracellular or extracellular niches, by directly targeting the host innate immune system. IDRs have the potential to provide adjunctive or stand alone therapies for the broader antimicrobial/antibiotic (US\$22B)<sup>1</sup>, antiviral (US\$22B)<sup>2</sup>, anti-inflammatory (US\$58B)<sup>3</sup> and anti-cancer (US\$50B)<sup>4</sup> markets.

SGX942 is the first drug product in this class and contains dusquetide as the active ingredient. Soligenix recently reported positive preliminary results from an exploratory Phase 2 clinical study in oral mucositis in 111 head and neck cancer patients where the median duration of severe oral mucositis was reduced by 50% in the 1.5 mg/kg group (p=0.099) and 67% in patients receiving the most aggressive chemo-radiation therapy (p=0.040). The p-values surpassed the prospectively defined statistical threshold of p<0.1 in the study protocol. Additional observations included reduction in the incidence of infection, particularly bacterial infection, and increased "complete response" of tumor status at one-month follow-up visit. Other dose groups tested (3.0 and 6.0 mg/kg) were also well-tolerated but did not provide additional benefit. Long-term follow-up of the patients is continuing. There are currently no approved therapies for mucositis in patients with solid tumors.

SGX942 has previously demonstrated safety and tolerability in an 84 subject healthy volunteer Phase 1 clinical trial.

The Company has a strong worldwide intellectual property position on SGX94 and related IDR analogs including composition of matter.

## TECHNOLOGY

IDRs provide a novel approach to the control of infection and tissue damage via highly selective binding to an intracellular adaptor protein, sequestosome-1, also known as p62, which has a pivotal function in signal transduction during activation and control of the innate defense system.

### *Innate Immunity is:*

The immune system is constantly exposed to pathogenic microorganisms (i.e., bacteria, virus, fungi, and parasites) but has evolved a powerful response to deal with these threats to our health with a two-tiered response involving innate and adaptive immunity. Innate immunity is the "first responder" component of the immune system that is immediately activated to destroy invading microorganisms and trigger inflammation that contributes to blocking their assault. If microorganisms breach the innate immune system, adaptive immunity is activated. Adaptive immunity uses T and B cells to produce antibodies and killer cells to destroy infected cells. The two components of the immune system provide excellent protection against infections but they

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<sup>1</sup> Taken from Business Communications Company Inc. report (Antibiotic Resistance: New Products and Strategies)

<sup>2</sup> 2010 estimated market from MarketResearch.com "Market Research Forecasts Antiviral Market at \$30 Billion by 2017" May 7, 2012.

<sup>3</sup> Anti-Inflammatory Therapeutics Market to 2017 - Respiratory Diseases and Arthritis Continue to Dominate, Nov. 8, 2011

<sup>4</sup> 2009 worldwide sales estimate from "Leading Anti-Cancer Drugs: World Market Prospects 2011-2021", February 2011.

also pose a risk. If the activation threshold of either component is too low, or if activation is excessive, inflammatory disease may follow.

The innate immune system is a highly integrated system of cells protecting us from pathogens at all body surfaces that interface with the external environment: skin, mouth, gastrointestinal tract and lung. Innate immunity is dependent on rapidly sensing infection or damage and responding quickly with both inflammation and host repair or anti-infective functions. When excessive activation of innate immunity causes inflammation, modulation of the activated innate immune system can re-direct the system to decrease inflammatory responses and increase the anti-infection or healing responses. The innate immune system responds quickly by sensing non-specific molecules released by the process of infection and damage through its Toll-like receptors and associated receptors. One of the key molecules in transmission of the sensing information is an adaptor protein called sequestosome-1 or p62. The p62 protein integrates and regulates the signals sensed by these receptors and can re-direct the response of the innate immune system in a benign way without perturbing the function of the adaptive immune system.

***Sequestosome (p62) is:***

- expressed in most cell types;
- downstream of pattern recognition receptors (e.g., TLR, NOD);
- a “signal integrator” in innate defense signaling pathways; and
- a recently identified target for modulation of innate defenses.

Since IDRs target the host (and not the pathogen), IDRs do not engender resistance and are active against resistant pathogens. *In vitro* data indicate that the endothelium plays a significant role in dusquetide activity and animal studies show that IDRs selectively promote monocyte and macrophage recruitment to disease sites and accelerate resolution of disease. Though IDR action depends on monocytes and macrophages, there is no dependence on either the adaptive immune system (e.g., T cells and B cells) or neutrophils. This suggests that IDRs may be effective in immunosuppressed patients. Moreover, p62 functions downstream of signaling receptors (TLRs, NODs) responsible for sensing both infection and tissue damage – giving it a role in innate immune modulation relevant to a wide range of diseases from infection (pathogen sensing) to colitis and mucositis (damage sensing).

***Preclinical Studies:***

Soligenix’s extensive animal dataset points to high potential for successful development of a broad spectrum of IDR products based on the following established product attributes:

- ameliorate injury;
- reduce inflammation;
- fight both antibiotic sensitive and resistant infections;
- complement antibiotics; and
- protect immune-compromised animals.

More specifically:

- Dusquetide ameliorates tissue damage in models of chemotherapy- or radiation-induced mucositis as well as DSS-induced colitis and has shown accelerated healing in a murine model of skin infection and injury.
  - Dusquetide is not a growth factor and does not promote tumor growth or protect tumors against treatment in a breast cancer xenograft model using the MCF-7 cell line.

- Studies in murine models of bacterial infection have shown activity against a broad range of pathogens including methicillin-resistant *S. aureus* (MRSA), *K. pneumoniae*, *E.coli*, *P. aeruginosa* and *B. pseudomallei*.
- Dusquetide enhances the activity of antibiotics administered at sub-optimal doses.
- Studies in a model of MRSA bacteremia indicate that dusquetide is effective both therapeutically and prophylactically.
- Dusquetide is most potent when administered by IV injection and has a very short plasma half-life (~10 minutes).
- When administered prophylactically in the MRSA model, a single dose of dusquetide is protective when injected up to 5 days before bacterial challenge, indicating a prolonged pharmacodynamic effect despite rapid plasma clearance.

### ***Clinical Studies:***

**Phase 2** – A Proof-of-Concept multi-center, dose-ranging, double-blind, placebo-controlled trial in 111 patients to treat oral mucositis in patients with head and neck cancer undergoing chemoradiation treatment. Oral mucositis in this patient population is very prevalent, with >90% of patients experiencing ulcerative oral mucositis and two-thirds of patients experiencing severe oral mucositis, compromising their ability to talk, swallow, eat and/or drink. The study is ongoing with preliminary results indicating a significant reduction in the duration of severe oral mucositis, as well as reductions in the rate of infection in the dusquetide treated patients, entirely consistent with the preclinical experience with dusquetide.

This exploratory study achieved all objectives, including identifying a best dose of 1.5 mg/kg. The study enrolled patients across three SGX942 dose groups (i.e., 1.5, 3.0, and 6.0 mg/kg administered IV over 4 minutes) and a placebo group and evaluated patients undergoing chemoradiation therapy for head and neck cancer. In the 1.5 mg/kg treatment group, the median duration of severe oral mucositis was decreased by 50%, from 18 days to 9 days ( $p=0.099$ ), meeting the prospectively defined statistical threshold of  $p<0.1$  in the study protocol. Further, patients receiving the most aggressive chemoradiation in this dose group had even more striking reductions in their median duration of severe oral mucositis of 67%, from 30 days to 10 days ( $p=0.040$ ).

Additional observations included, increased incidence of “complete response” of tumor at the one month follow up visit (47% in placebo versus 63% in SGX942 at 1.5 mg/kg), decreases in mortality and infection rate. SGX942 was found to be generally safe and well tolerated at all dose levels.

**Phase 1** – SGX942 (dusquetide for injection) has been evaluated in a double-blind, placebo-controlled Phase 1 clinical trial in 84 healthy volunteers with both single ascending dose (0.15 – 8.0 mg/kg administered IV over 4 minutes) and multiple ascending dose (0.5 – 6.5 mg/kg/day administered IV over 4 minutes for 7 days) stages. Dusquetide showed a strong safety profile in both stages. Drug clearance in humans is rapid and similar to results seen in preclinical studies. Inflammatory and anti-inflammatory markers, evaluated in the blood of both SGX942 and placebo treated subjects, indicated that treatment with SGX942 (0.15-2.0 mg/kg) resulted in a more anti-inflammatory response compared to the placebo subjects. Subjects receiving higher doses of SGX942 (3.0-8.0 mg/kg) were indistinguishable from placebo subjects.

Drug Substance and Drug Product manufacturing processes have been established in accordance with current Good Manufacturing Practices (cGMPs).

## MARKET OPPORTUNITY

The dusquetide platform offers a new way to address serious infections and injury by enhancing the host response without increasing inflammation. Positive clinical activity in the Phase 2 study provides important Proof-of-Concept for the IDRs. Soligenix' technology has the potential to provide adjunctive or stand alone therapies for the broader antimicrobial/antibiotic (US\$22B)<sup>1</sup> antiviral (US\$22B)<sup>2</sup>, anti-inflammatory (US\$58B)<sup>3</sup> and anti-cancer (US\$50B)<sup>4</sup> markets.

### ***Mucositis:***

Mucositis is the clinical term for damage done to the mucosa by anticancer therapies. It can occur in any mucosal region, but is most commonly associated with the mouth, followed by the small intestine. Mucositis affects 500,000 people in the US per year and occurs in 40% of patients receiving chemotherapy. Mucositis almost always occurs in patients with head and neck cancer treated with radiation therapy (>80% incidence of severe mucositis<sup>5</sup>) and is common (40-100% incidence) in patients undergoing high dose chemotherapy and hematopoietic cell transplantation, where the incidence and severity of mucositis depends greatly on the nature of the conditioning regimen used for myeloablation<sup>6</sup>. Mucositis can be severely debilitating and can lead to infection, sepsis, the need for parenteral nutrition and narcotic analgesia. The gastrointestinal damage causes severe diarrhea. These symptoms can limit the doses and duration of cancer treatment, leading to sub-optimal treatment outcomes. Direct and indirect consequences of mucositis have been estimated to add ~\$18K per patient to cancer treatment costs<sup>7</sup>.

The mechanisms of mucositis have been extensively studied and have been recently linked to the interaction of chemotherapy and/or radiation therapy with the innate defense system<sup>7</sup>. Bacterial infection of the ulcerative lesions is now regarded as a secondary consequence of dysregulated local inflammation triggered by therapy-induced cell death, rather than as the primary cause of the lesions.

### ***Bacterial Infections:***

Bacterial infections such as acute bacterial skin and skin structure infections (ABSSSI) are increasing dramatically, with treatment days in the US projected to rise from 20 to 30 million 2009-2015<sup>8</sup>, with ~75% of cases are caused by *S. aureus* (MSSA or MRSA). Additional infection indications include prevention of infection in chemotherapy patients, as well as the treatment of ventilator associated pneumonia, tracheobronchitis, bacteremia, and endocarditis. As more and more pathogens become antibiotic resistant and the number of elderly and immunocompromised patients increases, the demand for existing and new therapies is expected to rise. For example, the global anti-infectives market is forecast to expand at a compounded annual growth rate (CAGR) of 5.7% through 2013 according to *Business Insights*<sup>9</sup>.

## FURTHER INFORMATION:

Further information on IDRs are available at the following links:

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<sup>5</sup> Elting et al. 2008 *Cancer*, 113(10), 2704-2713

<sup>6</sup> Murphy. 2007. *J Supportive Oncology*, 5(9) supplement 4, 13-21.

<sup>7</sup> Sonis. 2010. *Current Opinions in Supportive and palliative care* 4, 29-34

<sup>8</sup> Cowen Report March 2011: "Infectious Disease"

<sup>9</sup> An Industry Analysis of the Anti-Infectives Market Outlook to 2013: Examine the Competitive Landscape, a Pipeline Analysis & Growth Opportunities, Business Wire, Sept 26 ,2008

1. European Pharmaceutical Review overview of IDR:  
<http://www.europeanpharmaceuticalreview.com/41002/news/blog/soligenix-idr-technology-sgx942/>
2. Dusquetide Phase 2 clinical trial publication:  
<http://dx.doi.org/10.1016/j.jbiotec.2016.03.032>
3. Dusquetide in infectious disease publication:  
<http://dx.doi.org/10.1016/j.jbiotec.2016.10.010>
4. IDR mechanism of action publication:  
<http://www.jbc.org/content/284/52/36007.full.pdf>