



## TECHNOLOGY BACKGROUND

Modulation of the innate immune response has the potential to impact a broad range of disease indications e.g., infection, cancer, and inflammatory disease. The innate immune response involves numerous signalling pathways and leads to a wide spectrum of biological responses. First generation technology involves stimulation or inhibition of Toll-like Receptors (TLRs) of the innate response, yielding improved vaccines and drugs to suppress allergic and asthmatic responses.

The Inimex technology platform represents the next generation of innate immune modulation. Inimex Innate Defence Regulator (IDR) peptides modulate innate immunity downstream of the TLR-ligand interaction, and thus do not suffer from limitations inherent in that therapeutic modality, in particular the stimulation of potentially harmful inflammation. As a consequence, Inimex IDRs will address unmet medical needs in the control of infectious disease and inflammation.

### BACKGROUND ON INNATE IMMUNITY

The immune system is an interactive network of cellular and molecular systems that are responsible for recognizing and eradicating pathogens and harmful foreign molecules. In general, the immune response to a threat of infection can be divided into three stages. These stages are outlined in Figure 1 below:

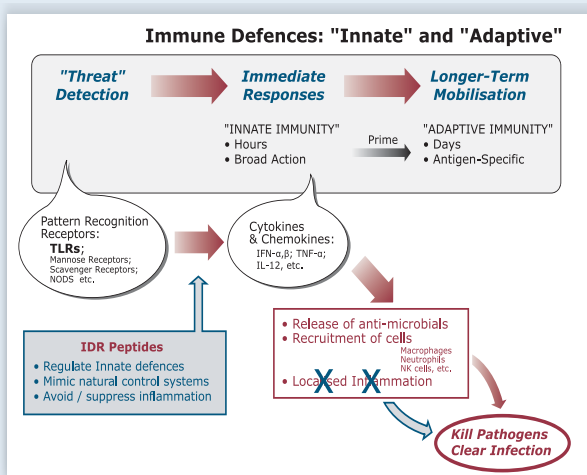


Figure 1: Immune Defences against Infection

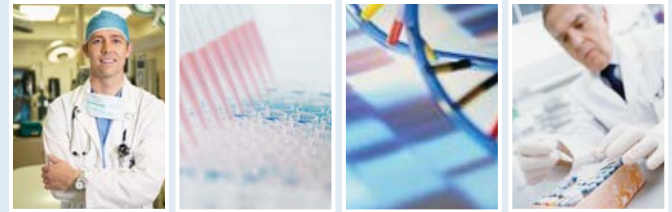
**Threat detection** mechanisms and the immediate responses to infection are highly conserved, being present in even the simplest of animals, including many that do not have an adaptive immune system. Foreign molecules are discriminated from self through pathogen-associated molecular patterns, or "signalling molecules," which are present on microbes, but not on host cells. These signalling molecules are essential to bacterial survival and are therefore highly conserved during environmental adaptation (even during the development of antibiotic resistance).

Immune responses are "triggered" partly by the binding of these signalling molecules to pattern-recognition receptors (including TLRs) on the surface of host cells. Within hours, the non-specific innate immune system is activated. Local Inflammation plays an important role in this immediate response to infection. Numerous players in the innate immune system, including neutrophils, monocytes, macrophages, complement factors, cytokines, antimicrobial peptides and acute phase proteins, are marshalled rapidly in a complex and highly regulated response to provide immediate defence against infection. These immediate responses kill pathogens and clear infection.

Over the ensuing days and weeks a more lasting immunity develops which involves specific antigen recognition and longer-term mobilisation/differentiation of T & B cells of the immune system. This evolution is the hallmark of the adaptive immune system and generates immune memory of the infection in the form of circulating antibodies and/or antigen-specific T cells. These components of immune memory generate a powerful response to future challenge by the same pathogen. Crucial differences between the innate and adaptive immune responses are summarized in Figure 2 below:

|                       | INNATE IMMUNITY     | ADAPTIVE IMMUNITY                      |
|-----------------------|---------------------|--|
| Type of Response      | Antigen-independent | Antigen-dependent                      |
| Time to Max. Response | Immediate           | Lag between exposure and response      |
| Specificity           | Broad spectrum      | Antigen-specific                       |
| Immunologic Memory    | None                | Exposure results in immunologic memory |

Figure 2: Innate vs. Adaptive Immunity



### INIMEX INNATE DEFENCE REGULATORS

Until now, a major disincentive to pharmaceutical exploitation of the innate immune system has been the knowledge that prolonged or excessive release of pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) can lead to severe inflammation and significant tissue damage.

Groundbreaking work by Professors Bob Hancock and Brett Finlay at the University of British Columbia showed that bacterial infections can be cleared without triggering inflammation through selective modulation of the innate immune response using host defence peptides lacking direct antimicrobial activity.

Inimex has extended these discoveries to develop a proprietary library of short synthetic peptides termed Innate Defence Regulators (IDRs). IDRs will be commercialized for the prevention and treatment of a broad spectrum of medical disorders.

Inimex' lead IDR product binds to a novel target that modulates the function of adaptor proteins in the TLR signaling pathways (see Figure 3). This suppresses the production of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 while activating the transcription factor C/EBP to cause induction of the chemokines RANTES, MCP-1, and MCP-3. Rapid induction of these chemokines by IDRs promotes recruitment of monocytes and macrophages to disease sites, speeding the resolution of bacterial infection without promoting the development of antibiotic resistance. Importantly, and unlike immunomodulatory drugs in development that bind to TLRs, IDRs do not cause persistent activation of NF $\kappa$ B, the central transcription factor associated with potentially harmful inflammatory responses. The scientific background on IDR-1, a prototype IDR compound, was recently published (Nat. Biotechnol. Vol. 25 No.4).

The distinct regulation of pro-inflammatory mediators from antimicrobial effector mechanisms has been independently reported by other workers (Foster et al, 2007).

IDRs are active in mice depleted of neutrophils, B cells, and/or T cells. IDRs act within hours to alter cytokine and chemokine signalling and enhance recruitment of macrophages to sites of infection. IDRs are not directly antimicrobial; rather, they selectively up-regulate the infection-clearing aspects of innate immunity without being pro-inflammatory. (See Figure 4).

### IDR PHARMACOLOGY, EFFICACY, AND SAFETY

IDRs can be administered as a single injection either prior to infection (prophylaxis) or following infection (therapy) in murine infection models, indicating a prolonged impact on the innate immune system and a wide "time-window" of treatment opportunities. IDR peptides are rapidly degraded to naturally occurring amino acids *in vivo*, but nevertheless provide a prolonged activation of host innate immunity. Hence, these agents have a "trigger effect" which alters the responsiveness of the innate system to the threat of infection without the need for continuous exposure to the drug. Importantly, local IDR administration (*e.g.* by intraperitoneal injection) provides impact at a distal site (*e.g.* in a lung infection), indicating that IDRs cause a systemic effect.

IDRs show efficacy in multiple preclinical models of bacterial disease, including models that reflect chemotherapy-associated infections, surgical site infections, and pneumonia. In addition, it has been demonstrated that when an inadequate dose of an antibiotic is administered to animals, a supplementary administration of IDRs provides a complementary effect on controlling infection.

Inimex IDRs also display anti-inflammatory activity in pneumonia and abdominal infection models, as well as in a widely used model of sepsis in mice, where the peptides are able to protect animals from the lethal effects of an endotoxin injection.

Safety studies indicate that IDR peptides are very well tolerated *in vivo* at doses at least 5-10 fold in excess of therapeutic levels. Multiple courses of IDR administration directly into the lungs of mice have revealed no toxicities or hypersensitivity responses. Further, IDRs are not pro-inflammatory or immunogenic in mice, and do not stimulate mast cell de-granulation, suggesting that they will be well tolerated in man.

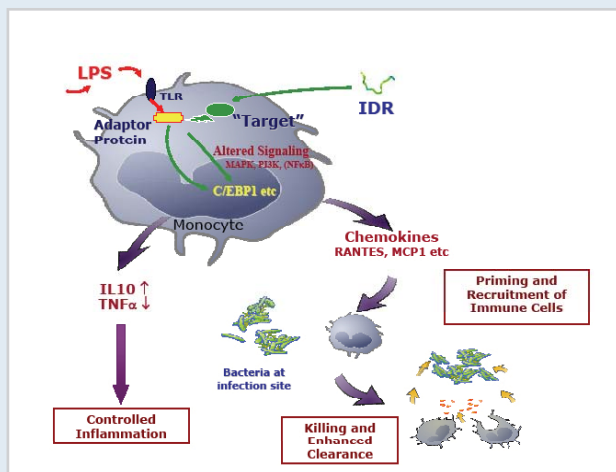


Figure 3: Mechanism of Action of Inimex IDRs

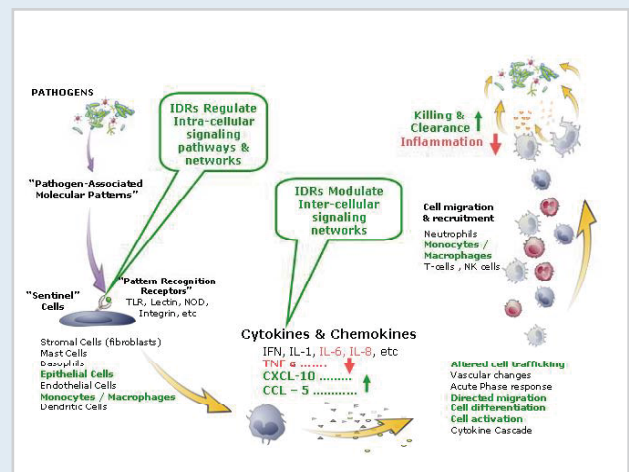


Figure 4: Impact of Inimex IDRs

# TECHNICAL LITERATURE



Inimex Pharmaceuticals Inc. is focused on the development of Innate Defense Regulators (IDRs), a novel class of innate immune modulators. Select references related to this technology are listed below.\*

## INIMEX TECHNOLOGY

Scott, MG et al. 2007. **An anti-infective peptide that selectively modulates the innate immune response.**  
Nat. Biotechnol. 25:465-472.

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## INNATE IMMUNITY

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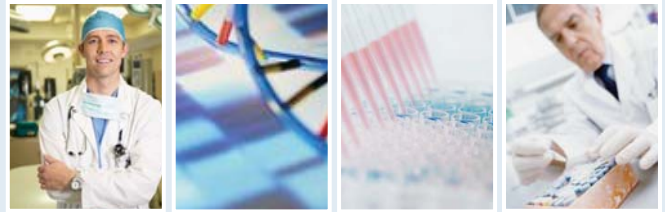
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Oppenheim, JJ & Yang, D. 2005. **Alarmins: chemotactic activators of immune responses.**  
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Brit. J. Haematol. 129:713-722.

*\* All of these articles are available upon request from Inimex Pharmaceuticals Inc.*



## INIMEX FOUNDING SCIENTISTS



### **B. Brett Finlay, Ph.D., O.C., F.R.S.C. (Chairman of Scientific Advisory Board)**

Dr. B. Brett Finlay is a cofounder of Inimex Pharmaceuticals, Inc., and also serves on several editorial and advisory boards. He is a Professor in the Michael Smith Laboratories, and the Departments of Biochemistry and Molecular Biology, and Microbiology and Immunology at the University of British Columbia. He obtained a B.Sc. (Honors) in Biochemistry at the University of Alberta, where he also did his Ph.D. (1986) in Biochemistry under Dr. William Paranchych, studying F-like plasmid conjugation. His post-doctoral studies were performed with Dr. Stanley Falkow at the Department of Medical Microbiology and Immunology at Stanford University School of Medicine, where he studied Salmonella invasion into host cells. In 1989, he joined UBC as an Assistant Professor in the Biotechnology Laboratory.

Dr. Finlay's research interests are focused on host-pathogen interactions, at the molecular level. By combining cell biology with microbiology, he has been at the forefront of the emerging field called Cellular Microbiology, making several fundamental discoveries in this field, and publishing over 300 papers. His laboratory studies several pathogenic bacteria, with Salmonella and pathogenic *E. coli* interactions with host cells being the primary focus. Dr. Finlay directed the SARS Accelerated Vaccine Initiative (SAVI), resulting in the development of two vaccine prototypes within six months which were tested on animals within one year.

He is well recognized internationally for his work, and has won several prestigious awards including the E.W.R. Steacie Prize, the CSM Fisher Scientific Award, a MRC Scientist, five Howard Hughes International Research Scholar Awards, a CIHR Distinguished Investigator, BC Biotech Innovation Award, the Michael Smith Health Research Prize, the IDSA Squibb award, the Jacob Biely Prize, the prestigious Canadian Killam Health Sciences Prize, the Flavelle Medal of the Royal Society, is a Fellow of the Royal Society of Canada and the Canadian Academy of Health Sciences, and is the UBC Peter Wall Distinguished Professor. He is an Officer of the Order of Canada and Order of British Columbia.



### **R.E.W. (Bob) Hancock, Ph.D., O.C., F.R.S.C.**

Bob Hancock is co-founder of Inimex, Professor of Microbiology & Immunology at UBC, and a Canada Research Chair holder. He was the founding Scientific Director of the Canadian Bacterial Diseases Network and currently heads the UBC Centre for Microbial Diseases and Immunity Research.

Dr Hancock's research interests include antibiotic uptake and resistance, functional genomics and the development of small cationic peptides as novel antimicrobials and modulators of innate immunity. He has published more than 380 papers and reviews, being one of ISI's highly cited authors in Microbiology, and has 21 patents awarded.

Dr Hancock has won many awards, including the Canadian Society of Microbiologists Award in 1986, Fellow of the Royal Society of Canada in 1994, the Canada 125 Silver Medal in 1995, MRC Distinguished Scientist 1995-2000, Jacob Biely Faculty Research Prize 2000, BC Biotech Alliance Innovation and Achievement Award 2001, Fellow of the American Academy of Microbiology 2002, the QEII Jubilee Medal 2002, the Aventis Pharmaceuticals Award 2003, the Zellers Scientist award and BC Innovation Council Chairman's award in 2004, the McLaughlin Medal of the Royal Society of Canada, 2005, the Michael Smith Prize, 2006 and the Killam Prize, 2007. In 2001 he was inducted as an Officer of the Order of Canada. Dr. Hancock has served as a Scientific Advisory Board Member or consultant with 21 biotech and pharmaceutical companies.

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