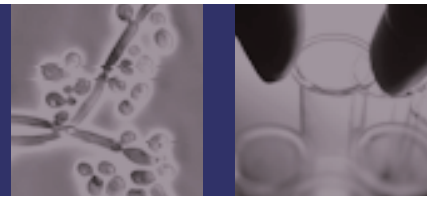


# PAC-G31P

## A NOVEL COMPOUND TO TREAT INFLAMMATORY DISEASES



### PAC-G31P: A POTENTIAL ANTI-INFLAMMATORY AGENT

ILT Therapeutics Inc. (ILT) is conducting a number of preclinical studies with PAC-G31P, a novel recombinant protein, to evaluate its potential in the prevention and the treatment of a number of acute and chronic inflammatory diseases characterized by non-beneficial neutrophil recruitment. This is a dominant feature of disease pathology in each of these conditions.

### PAC-G31P: AN IMMUNO-REGULATORY RECOMBINANT PROTEIN

#### Target Indications:

ILT is evaluating PAC-G31P for its potential to treat inflammatory diseases characterized by non-beneficial neutrophil recruitment. Indications include: acute respiratory distress syndrome, acute lung injury, neutrophilic asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia and various ischemia-reperfusion injury conditions.

#### Status:

The company projects completion of preclinical development and intends to file an IND in 2010.

#### Technology:

PAC-G31P is a novel protein that is a synthetic analogue of the human cytokine, Interleukin-8 (IL-8), the key chemokine involved in neutrophil recruitment / activation in inflammatory conditions. Based on SAR understanding of the IL-8 protein, amino acid substitutions were made to IL-8 to create a PAC-G31P compound with higher binding affinity to the target receptors for IL-8, but with antagonist (instead of agonist) activity.

#### Mechanism of Action:

PAC-G31P acts by binding to two specific cell surface receptors, CXCR1 and CXCR2. Interaction with these receptors blocks the action of a range of chemokines / cytokines that elicit neutrophil migration, activation, and de-granulation, thus restoring an appropriate neutrophil response to lung injury.

The cytokines known to be involved in neutrophil migration in ARDS include IL-8, GRO- $\alpha$ , and NAP-2. The biological response of neutrophils to these cytokines is modulated by the occurrence of receptor down-regulation. In Tikhonov et al. (2001) the CXCR1 and CXCR2 receptor number was shown to be reduced by exposure to heat killed *S. aureus* (SAC) or by exposure to *E. coli* lipopolysaccharide (LPS). The SAC effect was shown to be mediated by the induction of TNF- $\alpha$ ; the LPS effect was independent of TNF- $\alpha$ . It is interesting to note the competing effects of SAC: it induces IL-8 and simultaneously down-regulates the neutrophil receptors for IL-8. In human cases of severe sepsis, Cummings et al. (1999) examined neutrophils for receptor expression levels (by immunofluorescence) and chemotactic response (migration assay). They reported 50% down regulation of CXCR2 but only a slight change in the expression of CXCR1. Concomitantly there was a marked reduction, but not elimination, of migration response to the cytokines GRO- $\alpha$ , GRO- $\beta$ , GRO- $\gamma$ , and ENA-78 (all of which only bind with high affinity to CXCR2). The response to IL-8 was only slightly reduced. These data demonstrate down regulation of the receptors in vivo with humans, but also illustrate that as a drug target, both receptors must be inhibited to ensure maximal efficacy.

PAC-G31P binds with high affinity to both the CXCR1 and CXCR2 receptors and has negligible agonist activity. It is therefore a strong candidate for the treatment of neutrophilic inflammatory disorders.

### MEDICAL AND SCIENTIFIC ADVISORY BOARD

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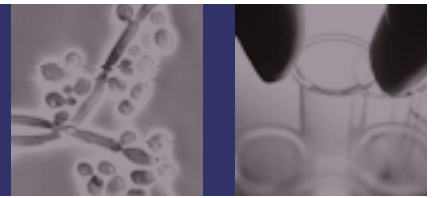
### PAC-G31P PRECLINICAL RESULTS

#### IN-VITRO

- \* Prevention of Neutrophil(PMN) degranulation
- \* Prevention of PMN stimulation by inflammatory chemokines
- \* Prevention of chemokine-induced PMN anti-apoptosis
- \* Prevention of chemokine-induced PMN chemotaxis
- \* Lack of impact on T or B cell responsiveness

#### IN-VIVO

- \* Efficacy in guinea pig aspiration pneumonia model
- \* Efficacy in rat ischemia/reperfusion injury model
- \* Efficacy in mouse benzopyrene-induced airway neutrophilia
- \* Efficacy in guinea pig LPS-induced lung inflammation model
- \* Efficacy in mouse gene-therapy-induced hepatic inflammation



## PRECLINICAL EFFICACY

### **PAC-G31P inhibits neutrophil recruitment:**

PAC-G31P modulates ELR-CXC chemokine neutrophil-recruitment factors by its ability to act as a high affinity antagonist of ELR-CXC receptors. PAC-G31P inhibited chemotaxis in isolated neutrophils treated with either IL-8 or endothelial neutrophil-activating peptide-78. These studies suggest PAC-G31P has potential as a therapeutic to modulate neutrophil recruitment.

### **PAC-G31P protects against acute lung inflammation:**

Bacterial lipopolysaccharide (LPS) induces significant peripheral blood, pulmonary and airway neutrophilia similar to those observed in acute lung injury. Treatment of guinea pigs with PAC-G31P significantly reduced neutrophil infiltration into lung airways and tissues. PAC-G31P at 250µg/kg significantly reduced or prevented lung tissue hemorrhage. These studies suggest PAC-G31P has potential to reduce neutrophil recruitment to the injured lung and lung hemorrhage in acute lung injury.

### **PAC-G31P modulates pyrexia and endogenous pyrogen expression:**

PAC-G31P was shown to influence fever and the fever response in experimental endotoxemia. Bacterial lipopolysaccharide also stimulates whole body responses including an increase in body temperature (pyrexia) and expression of endogenous pyrogens such as IL-1, IL-6, and tumor necrosis factor (TNF). Treatment with PAC-G31P inhibited increased body temperature and expression of endogenous pyrogens. These studies suggest PAC-G31P may have potential to treat various systemic effects of acute lung injury.

## PAC-G31P DEVELOPMENT

Several additional acute and chronic animal models will be evaluated to determine if the benefit provided by blocking the interaction of IL-8 with CXCR1 and CXCR2 would prove clinically beneficial in specific indications. These models include COPD, smoke inhalation, cystic fibrosis, sepsis, reperfusion ischemia, and acid aspiration and will also provide guidance on the dose and regimen as well as determining the timing of the treatment (eg. demonstrating that the PAC-G31P will be effective after ARDS has been established). In addition a standard battery of toxicology tests, receptor binding studies and pharmacokinetic studies will be conducted. Manufacture of clinical grade material is being outsourced.

### **Development Plans:**

ILT has not yet made a decision as to which indication it will pursue as the first clinical target. The development program for PAC-G31P will be very complex and will address multiple acute and chronic market opportunities. For that reason, ILT expects to seek to partner this program at an earlier stage of development than its other programs.

## MARKETS - MULTI BILLION DOLLAR POTENTIAL

### **Pneumonia:**

61,777 deaths in U.S. in 2001

### **ARDS:**

Mortality is 30% to 40%  
no approved drugs for prevention or treatment

### **Severe Asthma:**

1.8 million emergency room visits in 2004  
Total cost to the U.S. in 2004 was \$16.1 billion

### **COPD:**

4th leading cause of death in the U.S.  
the cost to the U.S. in 2004 was in excess of \$37 billion

### **Crohn's Disease:**

1 in 544 will be diagnosed in the U.S.  
The cost to the U.S. in 2004 was in excess of \$12 billion

### **Ulcerative Colitis:**

Worldwide therapeutic market in 2004 was >\$1.88 billion

### **Ischemia/Reperfusion Injuries:**

U.S. therapeutic market in 2000 was >\$3 billion

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