ProThera Biologics

Harnessing the Power of Proteins

Inter-alpha Inhibitors: From Laboratory to Market

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MISSION

Developing novel products that exploit the promise of personalized medicine by leveraging on its proprietary technology of natural serine protease inhibitor proteins.

The company focuses on unmet medical needs by developing INTEGRATED *theranostic* and *therapeutic* biomolecules for serious human diseases such as sepsis and cancer.

Theranostics (*thera*py specific diag*nostics*) refer to tests specifically for predicting and assessing drug response in individual patients rather than diagnosing disease.

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Focus of Research & Funding History

Inter-alpha Inhibitors

Year	Topics	Funding Agency	Grant	Amount ($)
I. S E P S I S				
2001	Early preclinical study	RI Slater Ctr.	Seed	100,000
2002	Therapeutics *(Proof-of-Concept)*	NIH/NIGMS	SBIR I	143,000
2003	Diagnostics/Theranostics	NIH/NIGMS	SBIR I	131,000
2004	Therapeutics *(Clin. Trials I/IIa)*	NIH/NIGMS	SBIR II	1,800,000
II. C A N C E R				
2005	CNS Cancer Detection	NIH/NCI	SBIR I	140,000
III. B I O D E F E N S E				
2006*	Anthrax Intoxication	NIH/NIAID	STTR I	1,000,000

*pending

Total Funding > $ 3 Million

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Inter-alpha Inhibitor Proteins (ITI)

- Inhibit key enzymes in many disease processes:
  - Sepsis
  - Cancer metastasis/spreading
  - Anthrax intoxication
- Anti-inflammatory activity by modulating mediators/ cytokines
- Natural blood proteins; complex with multiple subunits
- In healthy individuals: relatively high concentration; In a diseased state: 'consumed' and rapidly excreted in urine - markedly drop of blood ITI level

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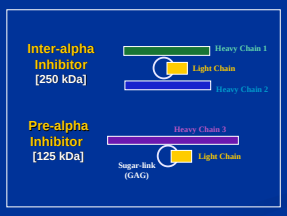
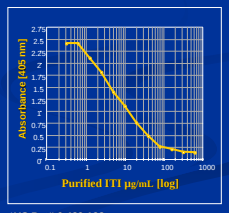
Theranostic Platform Technology: Composition and Quantitative Immunoassay of ITI in Blood

Two Complex Molecular Forms Of ITI in Blood



Competitive ELISA Test*
(Single Monoclonal Antibody 69.31)
Standard Curve



*US Pat# 6,489,128

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Unmet Medical Need: SEPSIS
('Blood Infection')

Local Infection → Overwhelmed Inflammatory Response → Multiple Organ Dysfunction → DEATH

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SEPSIS MARKET OPPORTUNITY

- 1.5 M people world-wide suffer from sepsis annually
- 700,000 new cases of sepsis annually diagnosed in the U.S. with 30-50% mortality rate*
- The leading cause of death in ICU
- Increased incidence over the next decade due to increasing number of Baby Boomers & immunosuppresive therapies
- Only one FDA approved drug (anticoagulant APC, Xigris) with a limited efficacy and indication; bleeding problems
- Estimated annual cost of sepsis treatment in the U.S.: $17 billion* ($22,100/per patient)

*Angus D, *et al.* Crit Care Med 2001; 29(7): 1303-1310.

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Altered Blood ITI Levels in Septic Patients: Potential Clinical Marker

- Significant decrease in adult septic patients; the levels inversely correlate with disease severity & mortality (Lim *et al*, J Infect Dis, 2003)
- Similar decrease also found in septic newborns; the levels increase/normalize with responsive antibiotic therapy (Baek et al, J Ped, 2003)
- Serial studies in >250 septic patients (1250 blood samples):
  - confirmed the results
  - strong inverse correlation of ITI with IL-6
  - failure of recovery of ITI levels during sepsis associated with poor outcome (Opal & Lim, *submitted*)

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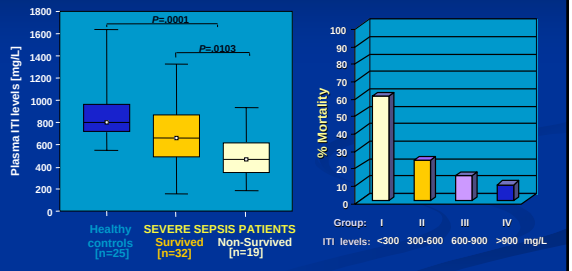
Decreased Plasma ITI Levels Correlate with Disease Severity & Mortality in Sepsis



(Lim *et al.*, J Infect Dis. 2003 Sep 15;188(6):919-26)

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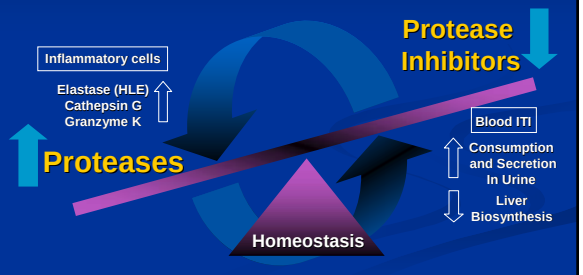
Proteases/Inhibitors Imbalance in Sepsis: Rationale for Replacement Therapy



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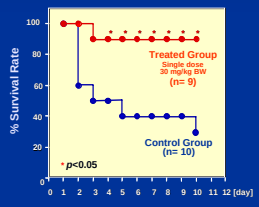
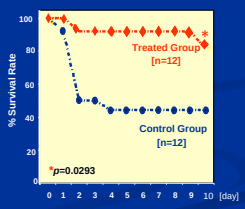
ITI Increases the Survival Rate in Adult Rat Polymicrobial Sepsis Model

ITI administered at 1 hr after sepsis



(Yang *et al*, Crit Care Med. 2002, 30(3):617-22)

...or even delayed at 10 hrs after sepsis



(Wu *et al*, Crit Care Med, 2004, 32(8):1747-52)

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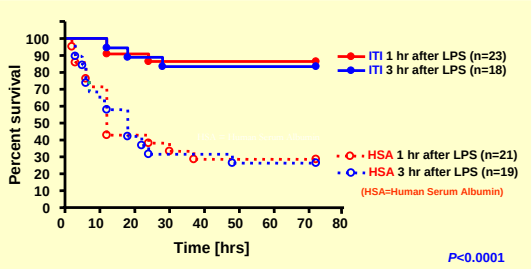
Increased Survival in Newborn Septic Mouse (Endotoxin/LPS injection in 2 days old pups)



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CONCLUSIONS

- **Useful CLINICAL MARKER in Sepsis:**
  Decreased levels in adult and neonatal sepsis; correlation with mortality and therapy
- **Beneficial THERAPEUTIC effects in Animal Studies:**
  Maintaining hemodynamic stability; modulating cytokines/ mediators (TNF-α & IL-10) and reducing sepsis-related deaths

Novel and unique personalized approach in sepsis:
ITI as an INTEGRATED *theranostic* marker and *therapeutic* agent in adult and newborn sepsis:
- to identify high risk patients
- to monitor disease progression/response to therapy
- to provide effective ITI replacement therapy.

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SUMMARY

- ProThera founded as LLC in RI in 2001
- Achieved >$ 3M non-dilutive funding (SBIRs)
- Developing unique and novel theranostic & therapeutic platform technologies targeting various unmet medical needs
- Opportunities in collaboration, strategic alliance and investment to move promising products to market

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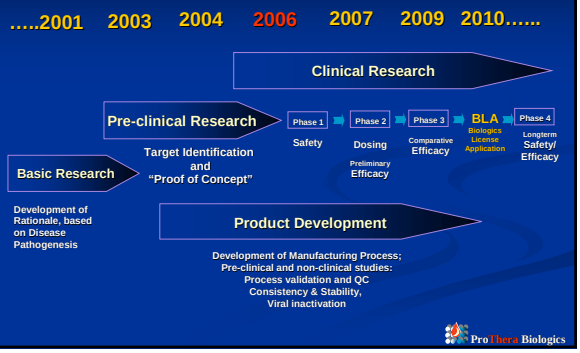
Projected Timeline



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