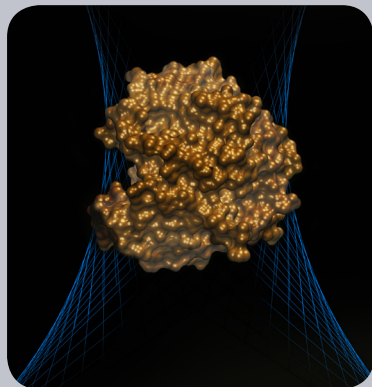


Subtilase Cytotoxin Conjugates for Cancer Therapy and other Uses



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Description of Technology

Subtilase cytotoxin, from Shiga toxinogenic *E. coli*, was discovered by the Paton laboratory (J Exp Med 2004; 200: 35-46). This toxin is an exquisitely specific serine protease, which cleaves the major endoplasmic reticulum (ER) chaperone, GRP78/BiP; no other cellular substrates have yet been discovered (Paton et al., Nature 2006; 443: 548-552). Scientists at SibTech Inc. have genetically fused the active toxin subunit A (SubA) to specific targeting molecules such as epidermal growth factor (EGF) and are developing conjugates of SubA with vascular endothelial growth factor (VEGF). Receptors for EGF are expressed at high levels on many tumours, while receptors for VEGF are expressed at high levels in tumour vasculature. Thus, targeted SubA is expected to be selectively accumulated in tumours. The resulting targeted toxins proved to be extremely cytotoxic, with IC50s in the pM range, to cells expressing the corresponding growth factor receptors at high levels. Furthermore, targeted SubA acted synergistically with drugs that induce ER stress, providing for high cytotoxicity of combination

regimens at essentially non-toxic concentrations of each component. Therapeutic experiments in animal tumour models are in progress..

Commercial Applications

The cellular chaperone GRP78/BiP targeted by the cytotoxin is critical for tumour cell self-defence and promotes metastasis and resistance to conventional chemotherapeutic agents. It is possible that targeting this cytotoxin to tumour cells, particularly in combination with other ER-stress inducing drugs, could be used in the development of new mechanism-based cancer therapies. Targeted destruction of GRP78/BiP using native Subtilase cytotoxin is also a potentially useful tool for examination of a wide variety of cellular processes.

Patent Status

There is a Patent Application, owned by the University of Adelaide on the toxin molecule and its DNA sequence filed in Australia, Canada and the USA. It has issued as US patent # 7,078, 489, and is still under examination in Australia and Canada. The University of Adelaide and SibTech Inc are joint owners of a PCT application WO 2008/014574 that claims the various uses of this toxin, and conjugates made from it.

Partnership Opportunities

The University of Adelaide and SibTech Inc are seeking development partners and licensees for the various applications of this technology.

Summary

This toxin, which is produced by certain strains of *E. coli* bacteria, can be conjugated to one of a variety of targeting molecules to give it the property of selectively killing certain cancer cells. It acts synergistically with ER stress-inducing drugs and has potential as a human therapeutic.

Key People

Dr Adrienne Paton, Senior Research Fellow, School of Molecular & Biomedical Science

Prof James Paton, Head of Discipline Micro and Immuno, School of Molecular & Biomedical Science

Dr Joseph Backer, CEO, SibTech Inc, Brookfield CT, USA

Dr. Marina Backer, Senior Principal Scientist, SibTech, Inc. Brookfield, CT, USA



THE UNIVERSITY
OF ADELAIDE
AUSTRALIA

Contact:

Dr Paul Tolstoshev
Commercial Development
Adelaide Research & Innovation

GPO Box 149, Rundle Mall
Adelaide SA 5000 Australia
Tel: +61 8 8303 5020
Fax: +61 8 8303 4355
Email: aripl@adelaide.edu.au

Dr Joseph Backer
CEO, SibTech Inc.

115A Commerce Drive
Brookfield CT 06804, USA.
Tel +1 203 775 5677
E-mail joseph.backer@gmail.com