

X2 CTLA4-based SCORPION™ Therapeutics

The Future of Multi-Specific Therapeutics

PLATFORM OVERVIEW: SCORPION THERAPEUTICS

Trubion introduces a novel platform for the development of multi-specific protein therapeutics – SCORPION therapeutics. SCORPION therapeutics are single chain proteins comprised of an N-terminal binding domain, an effector domain based on immunoglobulin Fc regions, and a C-terminal binding domain, which are produced as disulfide-linked dimers by standard eukaryotic manufacturing cell lines. This proprietary molecule class leverages Trubion’s clinically proven SMIP™ (Small Modular ImmunoPharmaceutical) product format by combining single-chain binding and effector domain libraries and adding additional C-terminal binding moieties. We utilize human protein sequences selected for stability, manufacturability, spatial optimization of the binding domains, and low immunogenicity.

SCORPION Therapeutics leverage Trubion’s clinically validated SMIP product format and offer:

- **Dual Targeting:** unique structure enables simultaneous multi-valent engagement of two or more different soluble or cell-surface targets, providing the capability for differentiated signaling events
- **Desirable Pharmacodynamic Properties:** retains immunoglobulin effector functions such as long *in vivo* half-life and Fc-dependent cellular cytotoxicity (FcDCC) activity, if desired
- **Rapid Development of Multiple Product Candidates:** provides for a multitude of product candidates by utilizing binding domains in a variety of target combinations
- **Reliable Manufacturing:** stable, homogeneous products with a robust manufacturing profile
- **Broad Therapeutic Application:** autoimmune and inflammatory diseases (AIID), transplant, oncology, and other high unmet need areas

PROGRAM OVERVIEW: X2 CTLA4-BASED SCORPION THERAPEUTICS

Trubion’s X2 SCORPION therapeutics are a family of molecules combining the CTLA-4 ectodomain with selected single chain moieties to address the deficiencies of CTLA-4Ig therapy. CTLA-4Ig (abatacept and belatacept) in humans has proven efficacy and safety in rheumatoid arthritis and is in Phase II or III trials in solid organ transplantation, ulcerative colitis, Crohn’s disease, and lupus nephritis. Although CTLA4-based molecules are active in humans, the potency of these molecules can be increased. We have generated a series of SCORPION molecules that combine CTLA4 and other immune modulators (e.g., IL-10) to increase the immunosuppressive activity and to target the inhibition to antigen-presenting cells to reduce potential safety risks.

PROGRAM RATIONALE: X2 SCORPION THERAPEUTICS

Initial molecules of the program combine the CTLA-4 ectodomain with the IL-10 cytokine. IL-10 is an excellent candidate to combine with CTLA4 since IL-10 has been demonstrated to be tolerogenic in the context of CD80/86+ antigen presenting cells and can enhance indoleamine 2,3-dioxygenase (IDO) production, a known immunosuppressant, by APCs. In addition, genetic analyses have linked IL-10 to human inflammatory diseases (e.g., ulcerative colitis). The role of IL-10

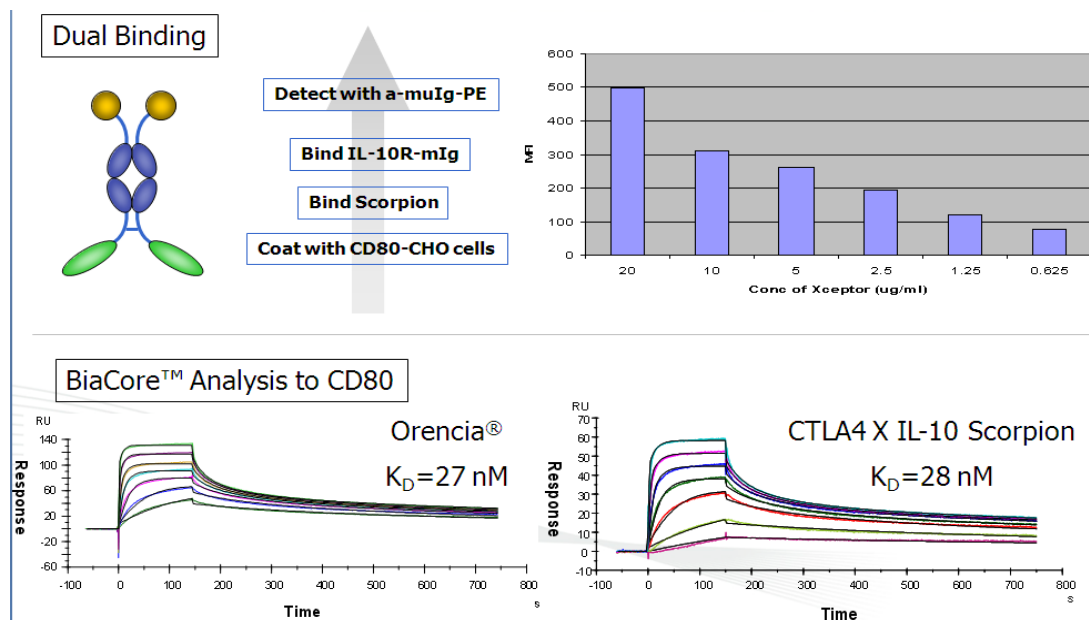
in inflammatory bowel diseases has also been observed in preclinical studies (e.g., IL-10 deficient mice spontaneously develop colitis and administration of IL-10 prevents colitis in some preclinical animal models). Since the CTLA4 and IL-10 moieties are physically linked in the SCORPION format, the X2 molecules will potentially deliver IL-10 to where it is needed most, the APC. Initial *in vitro* results with the CTLA4 X IL-10 molecules demonstrate significantly enhanced activity in comparison to Orenicia[®] and belatacept.

PROGRAM RESULTS TO DATE: X2 SCORPION THERAPEUTICS

Demonstration of Dual Targeting activity:

Candidate SCORPION therapeutics were tested *in vitro* for simultaneous binding to cell surface expressed CD80 and IL-10R. The SCORPION molecule was clearly capable of binding both targets. In addition, the binding activity for CD80 was measured via BiaCore[®]. The SCORPION therapeutic and Orenicia[®] had similar binding to CD80.

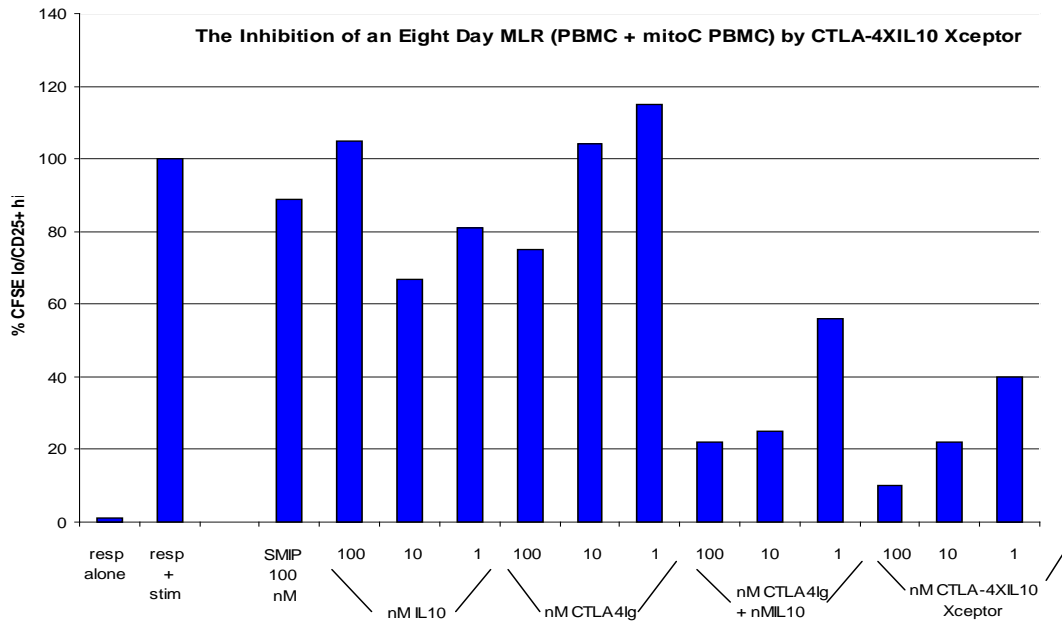
Significant Binding Activity for Both CD80 and IL-10R



Desirable Pharmacodynamic Properties:

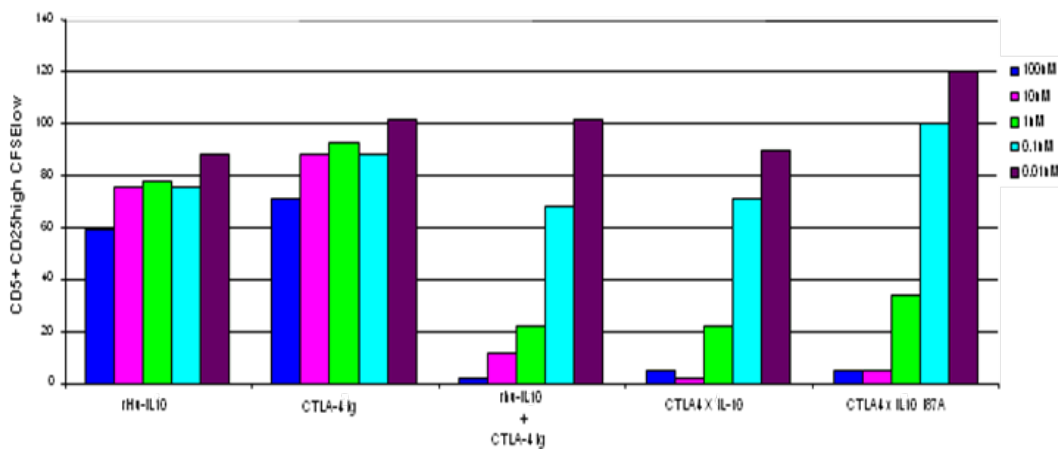
The CTLA4 X IL-10 SCORPION demonstrated enhanced immunosuppressive activity *in vitro*. Utilizing a human mixed lymphocyte response (MLR), the CTLA4 X IL-10 SCORPION molecule was significantly more potent than Orencia[®] alone.

CTLA4 X IL-10 SCORPION Inhibits a Human Primary MLR



Rapid Development of Multiple Product Candidates:

Multiple potential product candidates can be generated from the SCORPION technology. The potential number of CTLA4-based SCORPION product candidates was increased by utilizing additional binding domains in combination with CTLA4 or anti-CD86. SCORPION candidates containing modified IL-10 molecules have been generated and shown to inhibit biologic activity *in vitro*. The modified IL-10 molecules, containing the I87A mutation, retained immunoinhibitory activity but reduced immunostimulatory activity.



• IL 10(I87A)
based Scorpion
retains
significant MLR
inhibitory
activity

Reliable Manufacturing:

SCORPION therapeutics can be expressed in transient or stable systems at levels which are comparable to SMIP™ (Small Modular ImmunoPharmaceutical) therapeutics. SMIP proteins have been manufactured at large scale (multi-thousand L vessels) and are produced at >g/L titers. SCORPION molecules can demonstrate biophysical properties consistent with clinical and commercial development.

MARKET OPPORTUNITY

The autoimmune and inflammation (AIID) therapeutic market is >\$16.0B and rapidly growing with many significant unmet needs in efficacy improvement, ease of administration, and safety. The worldwide therapeutics market for solid organ transplant rejection was over \$3.0B in 2008 despite having just a few approved therapeutics that have significant safety/tolerability issues. The unmet needs in both AIID and solid organ transplant areas represent large market opportunities for X2 CTLA-based SCORPION therapeutics.

TRUBION ALLIANCE OPPORTUNITIES

Trubion is in the process of constructing alliances with a select group of technology and development partners. Our alliance strategy is focused on alliances that develop Trubion product candidates for commercialization in high-value indications, or that identify and develop differentiated products against targets of mutual interest using our SMIP™, SCORPION™ and TRU-AdhanCe™ technology platforms.

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Target	Product Candidate	Disease Indication	Development Stage				
			Design	Pre-Clinical	Phase I	Phase II	Phase III
CD20	TRU-015	Rheumatoid Arthritis (RA)	█	█	█	█	
CD20	SBI-087	Rheumatoid Arthritis (RA)	█	█	█	█	
CD20	SBI-087	Systemic Lupus Erythematosus (SLE)	█	█	█		
CD37	TRU-016	Chronic Lymphocytic Leukemia (CLL)	█	█	█		
CD37	TRU-016	Non-Hodgkin's Lymphoma (NHL)	█	█			
CD37	TRU-016	Autoimmune and inflammatory Disease (AIID)	█				