

# SMIP<sup>™</sup> Therapeutics vs. mAbs

## Trubion's Competitive Advantage

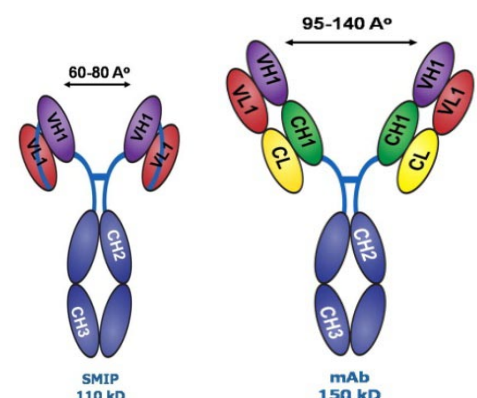
Trubion's custom Small Modular ImmunoPharmaceutical (SMIP<sup>™</sup>) drug assembly technology was designed to specifically address the limitations of monoclonal antibodies (mAbs). SMIP therapeutics, which have been clinically validated, are single chain polypeptides comprising a binding domain, a hinge domain and an effector domain designed in an effort to meet predetermined therapeutic criteria for specific diseases. SMIP proteins are mono-specific therapeutics — a drug that recognizes and attaches to a single antigen target and initiates biological activity. SMIP therapeutics have unique structural design characteristics and are significantly smaller than whole antibodies, which allows for better *in vivo* penetration.

SMIP technology enables us to design and develop differentiated product candidates for a range of targets and biological activities that have the following advantages:

- **Unique Structural Characteristics:** When engaging cell surface targets, SMIP proteins are capable of co-approximating cell surface molecules in unique ways. The binding domains of SMIP product candidates have a different geometry than the binding domains of conventional mAbs – that is, the binding domains are closer together. The structural format of SMIP proteins permits engineering a range of distances between the binding domains. SMIP proteins are also capable of binding and neutralizing soluble molecules, if so desired.
- **Differentiated Product Candidates:** SMIP product candidates can be engineered to deliver the desired cellular signaling responses. These unique properties can be used to generate biological responses not observed with mAbs. In addition, SMIP proteins can be engineered to balance target signal induction, complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) mediated activity. The ability to customize this balance of biological activities can result in safer and more effective immunopharmaceuticals.
- **Improved Biodistribution.** SMIP product candidates have a particle size that is approximately one-half the size of mAbs. Smaller molecules have been demonstrated to penetrate tissues more readily, a feature we believe will provide increased therapeutic benefits.
- **Reliable Manufacturing.** SMIP product candidates can be produced at large scale in mammalian cell expression systems from readily available materials.
- **Broad Therapeutic Application:** SMIP product candidates have potential application in diabetes, solid organ transplant, oncology, and other high unmet need areas.

## UNIQUE STRUCTURAL CHARACTERISTICS

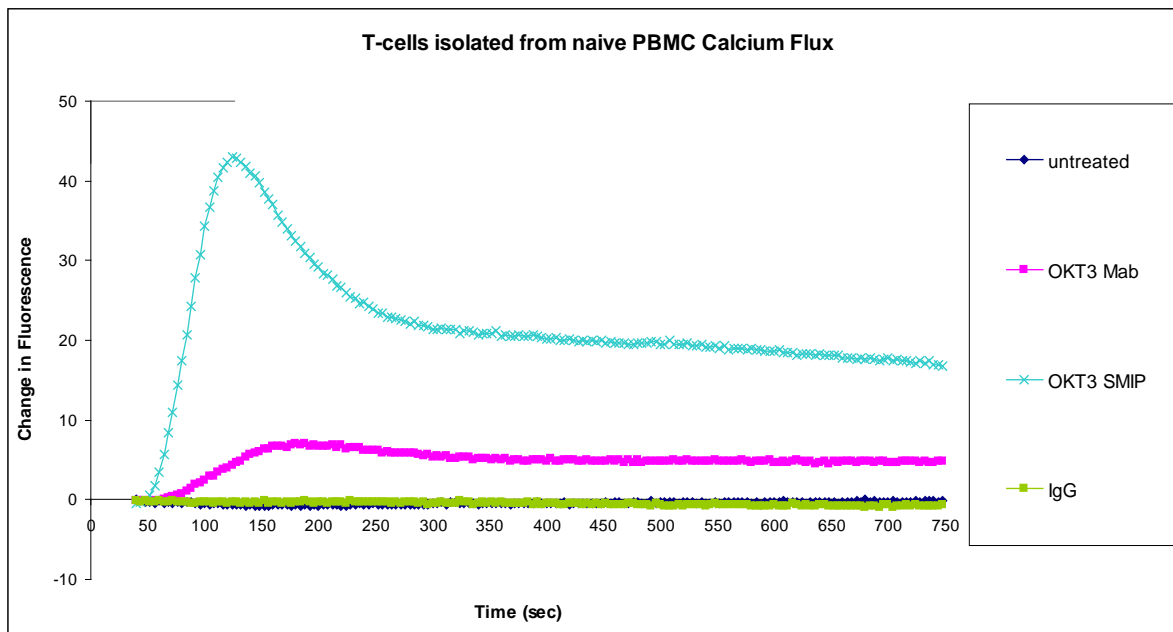
SMIP product candidates have binding domains with a different geometry as compared to conventional mAbs. SMIP proteins utilize scFvs as binding domains and do not contain the CH1 and CL domains present in conventional antibodies. Based on molecular modeling studies conducted at Trubion, the scFvs in SMIPs can be in significantly closer approximation than conventional mAbs. Trubion has developed an array of hinge sequences to modulate the

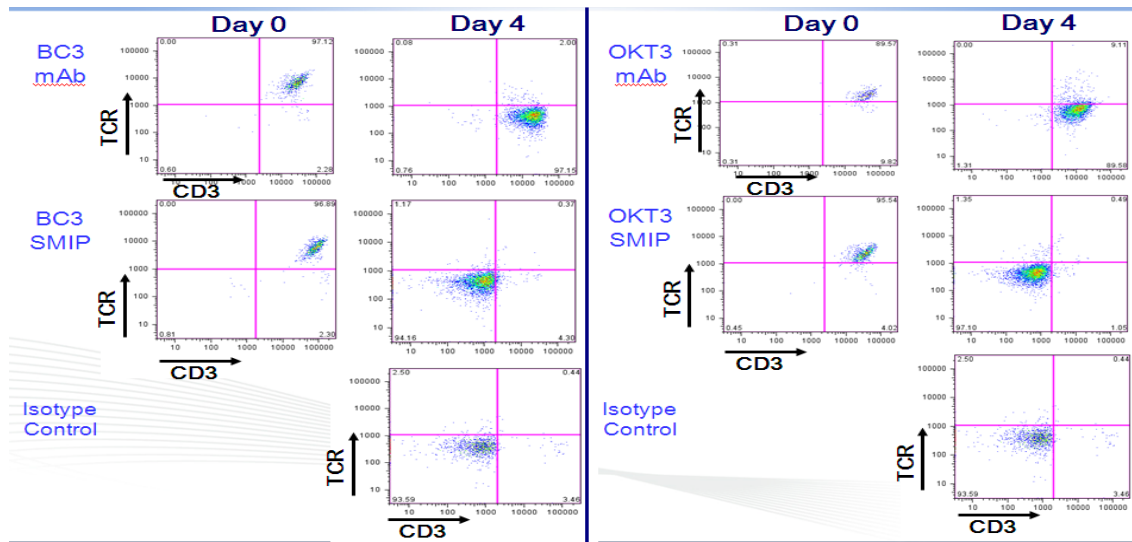


distances between binding domains. This engineering capability generates SMIP product candidates with unique pharmacologic properties.

### DIFFERENTIATED PRODUCT CANDIDATES

SMIP molecules are capable of delivering unique signaling responses. For example, binding domains to CD3, part of the T cell receptor complex, were presented to human T cells in either the SMIP or mAb product format. The human T cells responded by generating a Ca<sup>++</sup> flux. The anti-CD3 binding domains in SMIP format induced a significantly higher level of Ca<sup>++</sup> which persisted at higher levels for an extended period of time. The amount and duration of Ca<sup>++</sup> flux can be controlled by altering the composition of the hinge (data not shown). Thus, the biologic activity of SMIP product candidates can be designed to fit the desired product profile.





### IMPROVED BIODISTRIBUTION

SMIP product candidates have a particle size that is approximately one-half the size of mAbs. It has been demonstrated that size is a critical component of the ability of protein molecules to penetrate into tissues (see Jain, RK. Cancer Research (Suppl). 50: 814-819, 1990). Smaller molecules have been demonstrated to penetrate tissues more readily, a feature we believe will provide increased therapeutic benefits for SMIP product candidates.

### RELIABLE MANUFACTURING

SMIP product candidates have been produced at large scale (multi-thousand liter reactor volumes) in standard mammalian cell expression systems from readily available materials. SMIP therapeutic expression levels (> g/L), biophysical profiles and stability characteristics are consistent with a robust manufacturing profile for clinical and commercial development.

### BROAD THERAPEUTIC APPLICATION

SMIP therapeutics have broad therapeutic application in many high unmet need areas including diabetes, solid organ transplant, and oncology. The diabetes therapeutic market is estimated at over \$23.0B and rapidly growing world-wide. The world-wide solid organ transplant rejection therapeutics market was over \$3.0B in 2008 despite having limited approved therapeutic options with significant safety/tolerability issues. The world-wide oncology therapeutics market is approaching \$70.0B with an estimated 1.5M<sup>1</sup> new cases in the U.S. yearly with significant unmet needs in the majority of cancer types for improved survival, safety, and administration.

<sup>1</sup> NCI, Cancer Facts and Figures, 2009

**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)	[Red bar spanning Design, Pre-Clinical, Phase I, and Phase II]				
CD20	SBI-087	Rheumatoid Arthritis (RA)	[Red bar spanning Design, Pre-Clinical, Phase I, and Phase II]				
CD20	SBI-087	Systemic Lupus Erythematosus (SLE)	[Red bar spanning Design, Pre-Clinical, and Phase I]				
CD37	TRU-016	Chronic Lymphocytic Leukemia (CLL)	[Red bar spanning Design, Pre-Clinical, and Phase I]				
CD37	TRU-016	Non-Hodgkin's Lymphoma (NHL)	[Red bar spanning Design and Pre-Clinical]				
CD37	TRU-016	Autoimmune and inflammatory Disease (AIID)	[Red bar spanning Design]				