Non-Confidential Disclosure

Immune Disease Institute	Office of Technology Development 3 Blackfan Circle, 3rd Floor Boston, Massachusetts 02115 www.idi.harvard.edu

IDI 00-004, 06-004	FULLY HUMAN ANTI-LFA-1 ANTIBODY TREATING INFLAMMATION AND AUTOIMMUNE DISEASE

Key Words: LFA-1, fully human antibody, anti-inflammatory, immune suppression, psoriasis, rheumatoid arthritis, transplant rejection, and ischemia/reperfusion injury.

Application: Human therapeutics, drug target.

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Invention Summary:

Integrins are cell surface molecules that mediate important cellular interactions and are selectively expressed on specific cells in the body. The activity of integrins is dynamically up-regulated by structural changes from the low- to the high-affinity conformation. One such integrin is LFA-1 that mediates leukocyte-to-leukocyte and leukocyte-to-endothelial cell adhesions essential for immune and inflammatory response. The drug Raptiva is an anti-LFA-1 antibody.

Native LFA-1 is in a default low-affinity closed conformation; however, aberrant activation evoked in chronic inflammation would induce the high-affinity conformation persistently. Using an engineered disulfide bond, the LFA-1 ligand-binding domain was locked in the high-affinity open conformation as a drug target. Through phage display techniques, the fully human monoclonal antibody AL-57 was developed. AL-57 targets the open conformation of the LFA-1 ligand-binding domain, thereby discriminating among active and inactive LFA-1. When bound to LFA-1, the AL-57 inhibits the interaction between LFA-1 and ICAM. Therapeutics could selectively suppress aberrant inflammatory reactions while preserving immune competency to avoid unwanted immune defects. Potential applications include several autoimmune and inflammatory diseases, such as psoriasis and rheumatoid arthritis, and may also treat transplant rejection and ischemia/reperfusion injury.

Publications:

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Cell. 2003. 112: 99-111.
Proc Natl Acad Sci U S A. 2001. 98:6009-14.
Nat Struct Biol 2000. 7:674-8.

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Availability:

Exclusive license for therapeutic human antibody AL-57; Nonexclusive license for drug targeting.

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