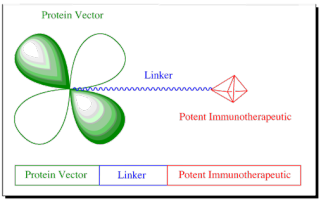
Targeted Immunotherapeutics



Specific Targeting and Half-Life Extension

Proteins as Vectors

While there are many proteins (including antibodies) currently used as vectors to target diseases, albumin is proving to be a versatile protein vector for drug targeting and for improving the pharmacokinetic profile of attached drugs, due to its a long circulation time (17 days in humans) and increased accumulation in tumors and inflammatory tissues. It simultaneously steers clearance pathways away from the kidneys and GI tract and prevents penetration of the blood-brain barrier – all major sources of drug toxicity.

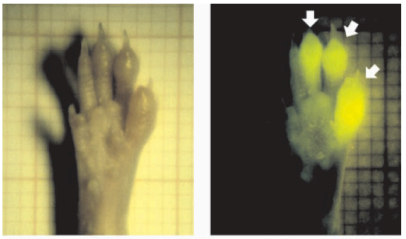


FIGURE 1. Uptake of human serum albumin labeled with aminofluorescein (AFLc-HSA) by inflamed toes of a mouse with CIA as determined by laseroptical imaging. The figure shows white light and fluorescence images taken of an inflamed paw with three arthritic toes (indicated by arrows) 3 h after i.v. injection of AFLc-HSA. Only toes affected by arthritis showed strong fluorescence when illuminated with laser light at 488 nm, demonstrating the high rate of albumin accumulation in inflamed toes.

Utilizing the best design practices in linking technology, peptide chemistry, and protein conjugation, our team has created conjugates that greatly extend the biological half-life of well-known and potent immunotherapeutic agents. Albumin is attractive not only for half-life extension, but also because HSA selectively accumulates in inflamed tissues (*J Immunol 2003; 170:4793-4801*), such as the joints of rheumatoid arthritis patients. This allows albumin to effectively target diseased tissue over normal tissue. Thus, an albumin-immunotherapeutic conjugate optimizes both specific disease targeting and biological half-life extension, providing a significant improvement in pharmacokinetic and drug toxicity profiles over small molecule immunotherapeutics given alone.

The concept of using albumin to target tissues of interest is well known, as evidenced by the many albumin conjugates in various stages of regulatory approval. The clinical indications vary, with most being in oncology and very few treating RA.

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Lead Compound Development

Conjugation techniques developed over 15 years have resulted in multiple proprietary methods of attaching potent small molecules to proteins, peptides, and macromolecules with stable linkers primed to cleave to fully biologically active immunotherapeutic derivatives in the target. Various linker technologies attempt to achieve this goal by different means; however, we have developed a class of linker that works for a variety of immunosuppressive agents. The technology is tunable, allowing the degree of biological stability to be increased or decreased based on desired outcomes. In addition, the technology to connect the immunosuppressive agent/linker to the protein has achieved >90% yield.

The final conjugate targets a highly potent immunosuppressive directly to the site of inflammation and greatly extends its half-life. Targeting a potent immunosuppressive to the affected tissue with reduced toxicity is highly desirable in clinical medicine.

The Peptide Research Lab at Tulane University has proven successes in designing pharmaceutical products with two peptide drugs marketed worldwide, decapeptyl (IPSEN) and lanreotide (IPSEN). This success brings with it a great deal of technical know-how and expertise, reducing many risks inherent in a pharmaceutical development project.

Tulane is seeking interested parties to further develop these novel ADC-like molecules as therapeutics for rheumatoid arthritis and other inflammatory conditionsstochastical optical reconstruction microscopy (dSTORM).

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