**A Novel Method for Increasing Protein and Peptide Based Drugs Half-Life:**

**Engineered Prolonged-Acting Prodrugs via Albumin-Binding Probes**

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| **Project Number:** | #1555 |
| **Principal Investigator:** | Prof. Yoram Shechter  Prof. Matityahu Fridkin |
| **Patent Status:** | Pending |

**Overview**

**A novel method for increasing the half-life of protein and peptide therapeutics.**

**Background and Unmet Need:**

Therapeutics based on proteins and peptides are an important class of medicines serving patients most in need of novel therapies. Recently, approved recombinant protein therapeutics have been developed to treat a wide variety of clinical indications. However, most protein and peptide based drugs, in particular those lacking specific chemical modifications (e.g. glycosylation) and under a specific size (molecular mass < 50 kDa), are short-lived when introduced to the bloodstream. **Therefore, there is a clear need for a method to extend the half-life of protein and peptide based therapeutics that minimally interferes with its pharmacological activity.**

**The Innovation**

The groups of Profs. Shechter and Fridkin have designed a set of probes capable of extending the half-life of any short-lived drug containing either an amino or mercapto group.

**The Technology**

The joint teams of Profs. Shechter and Fridkin have developed a set of novel probes capable of binding human serum albumin (HSA) with high affinity (Ka = 105), sufficient to turn short-lived molecules into long-lived species *in vivo*. The probes are comprised of long-chain fatty acids (LCFA)-like sulfonated derivatives and are capable of selectively reacting with any drug containing an amino and/or mercapto group (e.g. protein or peptides containing a free lysine or cysteine residue). Thanks to the high versatility in ligation sites on the target drug, drug-probe conjugates can be generated that are likely not to interfere with the pharmacological activity of the target drug. Testing done at Profs. Shechter’s and Fridkin’s labs demonstrated that all conjugates prepared using these probes exhibited considerably extended *in vivo* half-lives compared to non-conjugated drugs, and were pharmacologically active.

***Advantages and Applications***

* Up to a 6-fold increase in peptide/protein drug residence time in the blood.
* Generally does not interfere with target drugs pharmacological activity.
* Has potential application in extending the life-time of amine and/or cysteine containing molecule such as proteins, peptides, amino acids and other drugs containing amine and/or mercapto groups.

**Development Status**

A number of protein and peptide drug conjugates such as insulin and Exendin-4, have been prepared and tested. The joint team performed numerous *in vitro* work to characterize the biophysical aspects of the probe ligated target protein and their capacity to bind with albumin. Additional animal model work in mice was performed to show that the conjugated-proteins exhibited extended *in-vivo* half-lives compared to the native proteins without negatively affecting their pharmacological activity.

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**For additional information please contact:**

Orly Savion, PhD.

Director of Business Development

Tel: +972.8.9344374

Email: Orly.Savion@weizmann.ac.il