8th International Conference and Exhibition on

Pharmaceutics & Novel Drug Delivery Systems

March 07-09, 2016 Madrid, Spain

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Computer-aided design of liposomal drugs: *In silico* prediction and experimental validation of drug candidates

Liposomes are the most extensively clinically used drug delivery system. Since the FDA approval of the first nano-drug Doxil®, more than 12 other liposomal drugs were approved by the FDA and more liposomal drugs are under development. Doxil is based on the combination of high and stable drug loading which is also responsible for the controlled drug release as well as on the use of nano-pegylated liposomes. Pegylated nano-liposomes are important for treating cancers, neurodegenerative and inflammatory disorders, as they take advantage of the enhanced permeability and retention (EPR) effect and deliver drugs to the site of disease. Development of liposomal formulations is a time consuming process which requires major efforts. A more rational and less labor intense process is, taking advantage of computational modeling approaches capable of predicting whether an active pharmaceutical ingredient (API) could be loaded to and delivered by liposomes. Towards that end, Quantitative Structure– Property Relationship (QSPR) models were developed with iterative stochastic elimination and k-nearest neighbors approaches to predict drug loading efficiency (high vs. low) in liposomes. Chemical as well as formulation descriptors were employed and the resulting statistically validated models were used to screen a few thousand biologically active molecules from the Comprehensive Medicinal Chemistry database. Three drugs were selected for experimental testing of their loading into nano-liposomes, also taking into account challenges of nano-liposomal development. Two of the selected drugs were high-and one was low-loading, confirming the predictions. Ten other negative molecules from literature were also confirmed, to a total prediction accuracy of 92%. Screening results of CMC database were obtained by the two computational approaches (ISE and kNN). One of the tested drugs- mupirocin, was remotely loaded into pegylated nano-liposomes, and stabilized by intraliposomal hydroxypropyl-β-cyclodextrin to form nano-mupirocin, which was evaluated *in-vivo* for its therapeutic efficacy. Mupirocin, an antibiotic with a unique mode of action is currently restricted to topical administration due to its rapid degradation in the blood. Intravenous administration of nano-mupiricin to mice in *Necrotizing fasciitis* model showed significant superiority of nano-mupirocin over mupirocin. Our approach demonstrates the utility of QSPR models in screening API libraries for identifying candidates that should benefit from being administered as nano-drugs.

Biography

Amiram Goldblum is the Head of the Molecular Modeling and Drug Design and Discovery Unit at the Institute for Drug Research of the Hebrew University. Following a BSc in Chemistry and Physics and an MSc in QM Studies of Molecular Spectra, he did PhD in Organic Reaction Mechanisms (Mechoulam, Hebrew U). He completed his Post-doctoral studies of Quantum Biochemistry (Paris), QSAR and QM reaction mechanisms (California). He receieved his first award at the American Chemical Society National Meeting in Washington DC 2000 for his algorithm called "Iterative Stochastic Elimination" (ISE) used to solve extremely complex combinatorial problems and focuses in recent years on molecular discovery by chemoinformatics.

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Pharm Anal Acta
ISSN: 2153-2435 PAA, an open access journal

Pharmaceutica 2016
March 07-09, 2016

Volume 7, Issue 1 (Suppl)

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