Computational Discovery of Liposomal Drugs: From in silico predictions to in vivo validation

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Abstract

The FDA approval of the first nano-drug Doxil® [1] encouraged the development of new nano-liposomal drugs. These benefit from the enhanced permeability and retention effect leading to a better biodistribution for treating cancers, neurodegenerative, inflammatory, and infectious diseases. The use of nano-liposomes requires reaching high drug concentration per liposome (described as high drug-to-lipid mole ratio). The interplay between liposome membrane composition, drug physico-chemical properties and liposome medium will determine drug-to-lipid mole ratio and loading stability.

We propose to use computational modeling to predict whether drug candidates can achieve these objectives. We developed models with Iterative Stochastic Elimination (ISE) [2] and k-Nearest Neighbors (kNN) [3] approaches to predict liposomal drug loading efficiency (high vs. low). Both chemical and formulation descriptors were employed and the resulting statistically validated models [4] were used for virtual screening of the Comprehensive Medicinal Chemistry (CMC) database. The included figure compares the predicted ISE index and kNN category score for all compounds in the CMC database. Hits identified by both models as positives are found in the upper right quadrant. Negative hits are found in the lower left quadrant. Three drugs were selected for our own experiments and experimental data for ten additional molecules were taken from the literature. Results showed that the prediction accuracy of the models was 92% [5]. Red squares are molecules tested in this study and green squares are molecules found in the literature

With additional ISE modeling of the loading stability, we found 133 new candidate molecules for the development of novel liposomal drugs. One of these mupirocin, when further tested as Nano-mupiricin in a *necrotizing fasciitis* mice model showed significant superiority over non liposomal mupirocin.

References

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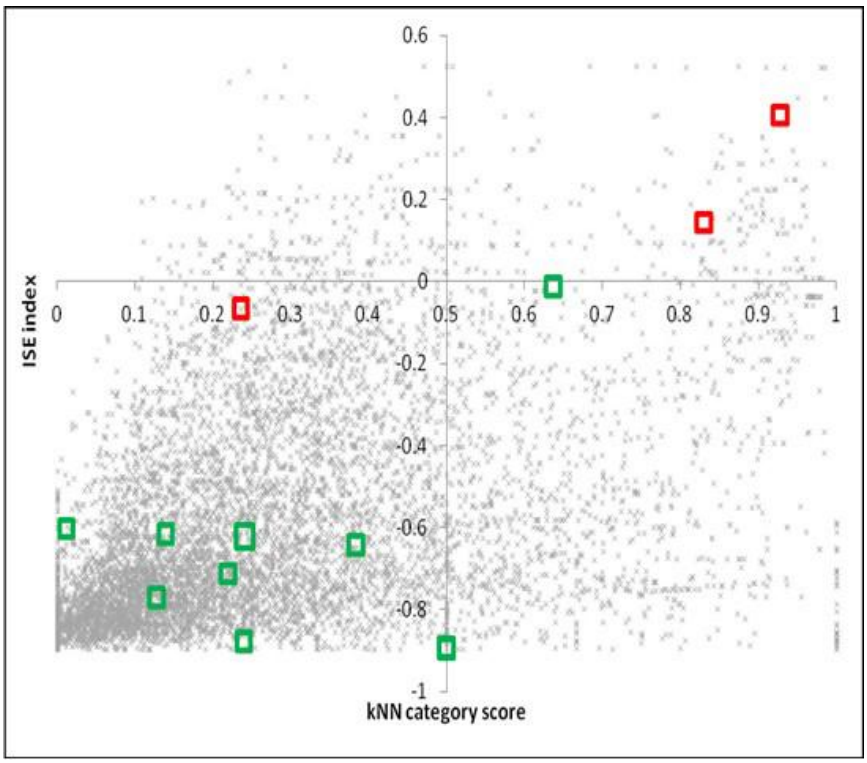
Figures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0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
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0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
ISE index
kNN category score

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