Advanced 3D-Pharmacophores for Drug Discovery and De-Risking Neurotoxicity

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3D-pharmacophores are widely used in pharmaceutical research for design, discovery and selection of promising molecules targeting versatile therapeutic areas, such as, neurodegeneration, cancer, antimicrobials, antivirals, cardiovascular, and others [1,2]. LigandScout advanced pharmacophore models are abstractions of the molecular chemical-features needed to achieve pharmacological outcomes of interest [3]. Therefore, they enable key decisions and address critical issues in drug discovery including, adverse-effect/toxicity prediction, SAR, hit finding, lead optimization, target prediction [4], drug repurposing, phenotypic screening analysis, druggability of allosteric sites [5], irreversible binding events, and off-target selectivity, as exemplified in more than 3000 publications. They are highly suitable for virtual screening, demonstrating high computational speed, and scaffold diversity, as shown in performance comparison studies [6]. Furthermore, they have been applied in artificial intelligence and machine learning paradigms [7].
Recently we used LigandScout pharmacophores to develop the NeuroDeRisk Toolbox [NeuroDeRisk Project (821528)] [8,9]. Current preclinical studies poorly predict the adverse effects of pharmaceuticals on the nervous system and do not mitigate risk by influencing chemical structure design. The Toolbox addresses this unmet need with validated 3D-models to identify chemicals with potential risk. Early assessment of risk for neurotoxicity benefits volunteers and patients through safer clinical candidates and approved pharmaceuticals.

References:

[1] Langer, T. Pharmacophores in Drug Research, *Mol. Inf.* **2010**, 29, 470.

[2] Gallego, R.A., Bernier L., et al., Design and Synthesis of Functionally Active 5-Amino-6-Aryl Pyrrolopyrimidine Inhibitors of Hematopoietic Progenitor Kinase 1, *J. Med. Chem*. **2023,** 66, 7, 4888.

[3] Wolber, G. & Langer, T. LigandScout: 3-D pharmacophores derived from protein-bound ligands and their use as virtual screening filters. *J. Chem. Inf. Model*. **2005**, 45, 160.

[4] Bryant, S.D. & Langer, T. *Data Mining Using Ligand Profiling and Target Fishing* in Data Mining in Drug Discovery, Hoffman, Gohier, Pospisil, Eds, Wiley-VCH, **2013**, pp. 257.

[5] Tomašič, T., Durcik, M., Keegan, B.M., Skledar, D.G., Zajec, Ž., Blagg, B.S.J., Bryant, S.D. Discovery of Novel Hsp90 C-Terminal inhibitors using 3D-pharmacophores derived from molecular dynamics simulations. *Int. J. Mol. Sci.* **2020**, 21, 6898.

[6] Karaboga A.S., Planesas, J.M., Petronin, F., Teixido, J., Souchet, M., Perez-Nueno, V. Highly specific and sensitive pharmacophore model for identifying CXCR4 antagonists. Comparison with docking and shape-matching virtual screening performance. *J.Chem.Inf. Model.* **2013**, 53, 1043.

[7] Yoshimori, A., Asawa, Y., Kawasaki, E., Tasaka, T, Matsuda, S., Sekikawa, T., Tanabe, S., Neya, M., Natsugari, H., Kana, C. Design and Synthesis of DDR1 Inhibitors with a Desired Pharmacophore Using Deep Generative Models. *ChemMedChem.* **2021**, 16, 955.

[8] Bryant, S.D., Ibis, G., Seidel, T., Kohlbacher, S., Heider, J., Ernst, M., Langer, T. The NeuroDeRisk toolbox: DeRisking chemical structures for neurotoxic adverse outcomes.

Toxicology Letters. **2022**, 368, S82.
[9] The NeuroDeRisk Toolbox [https://neuroderisk.eu/in-silico-toolbox/].