Hits discovery on the Androgen receptor: *in silico* approaches to identify agonist compounds

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The androgen receptor (AR) is a transcription factor involved in various physiological processes including the reproduction, the musculoskeletal and the cardiovascular systems development and maintenance [1-2]. Naturally, the AR can be directly modulated through a ligand-dependent manner via the binding of androgenic hormones such as testosterone and dihydrotestosterone that act as agonist compounds. The AR activity is associated with several pathological processes including prostate, testicular and ovarian cancer, impaired reproduction system development and neuromuscular diseases [3].

AR can be modulated by exogenous compounds such as pharmaceuticals or chemicals present in the environment, and particularly by AR agonist compounds that mimic the action of endogenous agonist ligands and whether restore or alter the AR endocrine system functions [3-4]. Worldwide initiatives have been launched to identify the risky compounds and to propose alternative solutions to their industrial or agricultural use.

The elucidation of AR three-dimensional structures in an agonist-bound state and the availability of numerous binding and activity data (NRLiSt BDB[5], NR-DBIND[6], Tox21[7]) provide a good framework for understanding agonist ligands binding modes and for developing rational *in silico* hit prediction models. These models have been long time dedicated to therapeutic research and are now increasingly used for non-desired interaction prediction, to help prioritizing compounds for further toxicological assay.

Herein, we propose and compare AR agonism prediction models derived from docking and pharmacophore modeling approaches that both benefit from experimentally validated active and inactive data for training and selection. All models were trained on the NR-DBIND [6] that provides high quality binding data and annotations for nuclear receptors and tested on AR-agonist activity assays from the Tox21 initiative [7]. We showed that very high performances are reached from a therapeutic research point of view, nonetheless, the discussed models still need data feeding to be used as large scope undesired effect prediction models.

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