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P222 - DISCOVERING THE BINDING AFFINITY OF REPURPOSED DRUGS TO TLR4

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Resumen

Introduction: The dramatic increase in rheumatic diseases incidence is causing a severe impact on the population's welfare. The pharmacologic treatment of systemic rheumatic diseases like rheumatoid arthritis, has been revolutionized recently by the development of novel biologics and small molecules that directly inhibit specific molecular or cellular targets. Nonetheless, other rheumatic diseases are yet to find an efficient treatment. Furthermore, novel drug workflow from bench to bed requires decades of millionaire investments until a single drug is approved. Therefore, drug repurposing is an appealing approach to find new treatments for these diseases in a shorter period of time. It has been suggested that different drugs like amitriptyline and naloxone might bind and block the toll like receptor 4 (TLR4), a known receptor that has been associated to mayor rheumatic diseases like osteoarthritis. Here we present a new *in silico* approach capable of determining whether these candidate drugs could potentially bind to TLR4.

Objectives: Determine the binding affinity of amitriptyline and naloxone to TLR4 using a new in silico approach.

Methods: A customized configuration of several target proteins was developed for Autodock - Vina and Lasergene protein - Novadock (DNASTAR inc.) was used for binding affinity analysis.

Results: To determine the reliability and efficiency of our customized docking analysis, several commercialised drugs (tofacitinib, dexamethasone...) had their binding affinity tested towards their targets (JAK1, GR...). Similarly, innate immune factors (IL6, IL1β, LPS), relevant in rheumatic diseases, were also analysed. Results were represented in docking score which means the more negative the results are, the stronger the binding is. All of them were found to strongly bind their known targets (-5.8 to -32.99 kcal/mol). Next, naloxone and amitriptyline were tested against TLR4 receptor and both were able to strongly bind to TLR4. In fact, their binding score was even stronger than LPS, opening the possibility to a binding competence dynamic. Results were visualised in 3D imaging to determine the atom position and pocked topology of the binding.

Controls	... binds to ...	Time of analysis
Tofacitinib	JAK1 (-7.4 kcal/mol)	< 15 min
	JAK2 (-7.9 kcal/mol)	< 15 min

Dexamethasone	GR (-12.9 kcal/mol)	< 15 min
Diclofenac	COX-2 (-8.1 kcal/mol)	< 15 min
Ibuprofen	COX-2 (-6.8 kcal/mol)	< 15 min
IL6	IL6R (-32.99 kcal/mol)	< 5h
IL1β	IL1R (-24.8 kcal/mol)	< 5h
LPS	TLR4 (-5.8 kcal/mol)	< 15 min
Novel/repurposed drugs		
Naloxone	TRL4 (-7.8 kcal/mol)	< 15 min
Amitriptyline	TLR4 (-6.3 kcal/mol)	< 15 min

None/unlikely binding: 0 to -2 kcal/mol. Binding:< -2 kcal/mol. The more negative the results are, the stronger the binding is.

Conclusions: As a prove of our docking analysis methodology we validated the binding of currently commercialized drugs and known inflammatory factors to their targets. More importantly, we were able to show the binding affinity of potential repurposed drugs amitriptyline, and naloxone to the key receptor TLR4, which have been involved in key inflammatory processes. We suggest that both compounds could be used as TLR4 blocking drugs.