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Virtual screening and drug repurposing: together against worm-borne diseases

Chaired by DR. ALFREDO BERZAL-HERRANZ;
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pharmaceuticals MDPI

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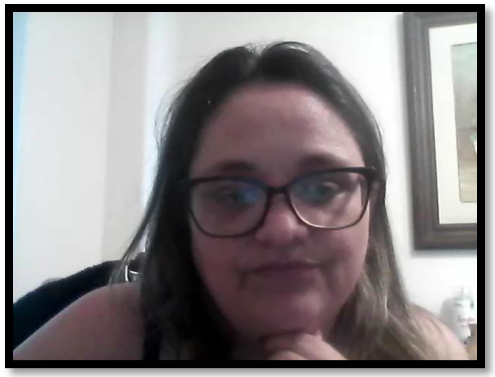

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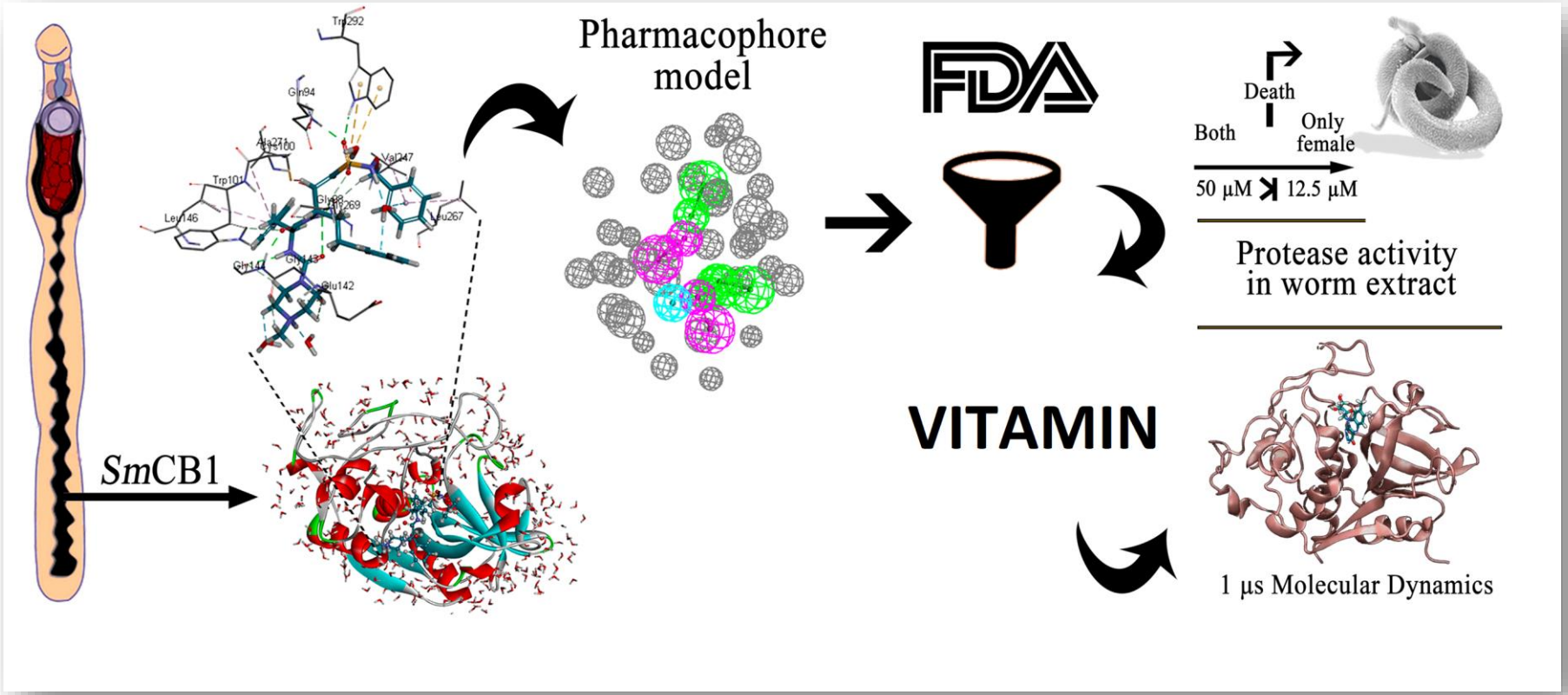
Virtual screening and drug repurposing: together against worm-borne diseases



Virtual screening and drug repurposing: together against worm-borne diseases

Worm-borne diseases cause a huge impact on human health and economics since they can also affect livestock animals. For these reasons, our research group has been employing simple rational-designed approaches to fight them. Here we present the results of combining the Virtual Screening approach and drug repurposing to find, among the drugs on the market, fast and cheap therapeutic alternatives. Starting from the top 10 pharmacophore models, validated through the ROC curve, we screened the FDA-approved drugs library to find any compound that fulfils the pharmacophore requirements. We were able to select a vitamin which was submitted to molecular dynamics simulations and in vitro experimental assays. We found out that the compound really seems to keep stable in the enzyme's active site, but it first needed to accommodate to perform a higher number of interactions inside the site. Once accommodated, the vitamin seems to be able to close the active site denying access to the original substrate. Experimental in vitro data corroborate that the vitamin is able to inhibit worm growth and induces 100% of females' death after 72 h when used at 12.5 micromolar. In vitro tests with digestive extract of the worms, prepared to predominantly measure CatB1 activity, showed that the vitamin was able to inhibit the substrate consumption closer to 10 micromolar when using the specific CatB1 substrate but when the experiment employed a non-specific substrate, the vitamin was effective only at higher doses (up to 2000 micromolar) suggesting the potential selectivity of it toward cathepsins B1.

Virtual screening and drug repurposing: together against worm-borne diseases

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Introduction

WORMS – helminths from Phyla:

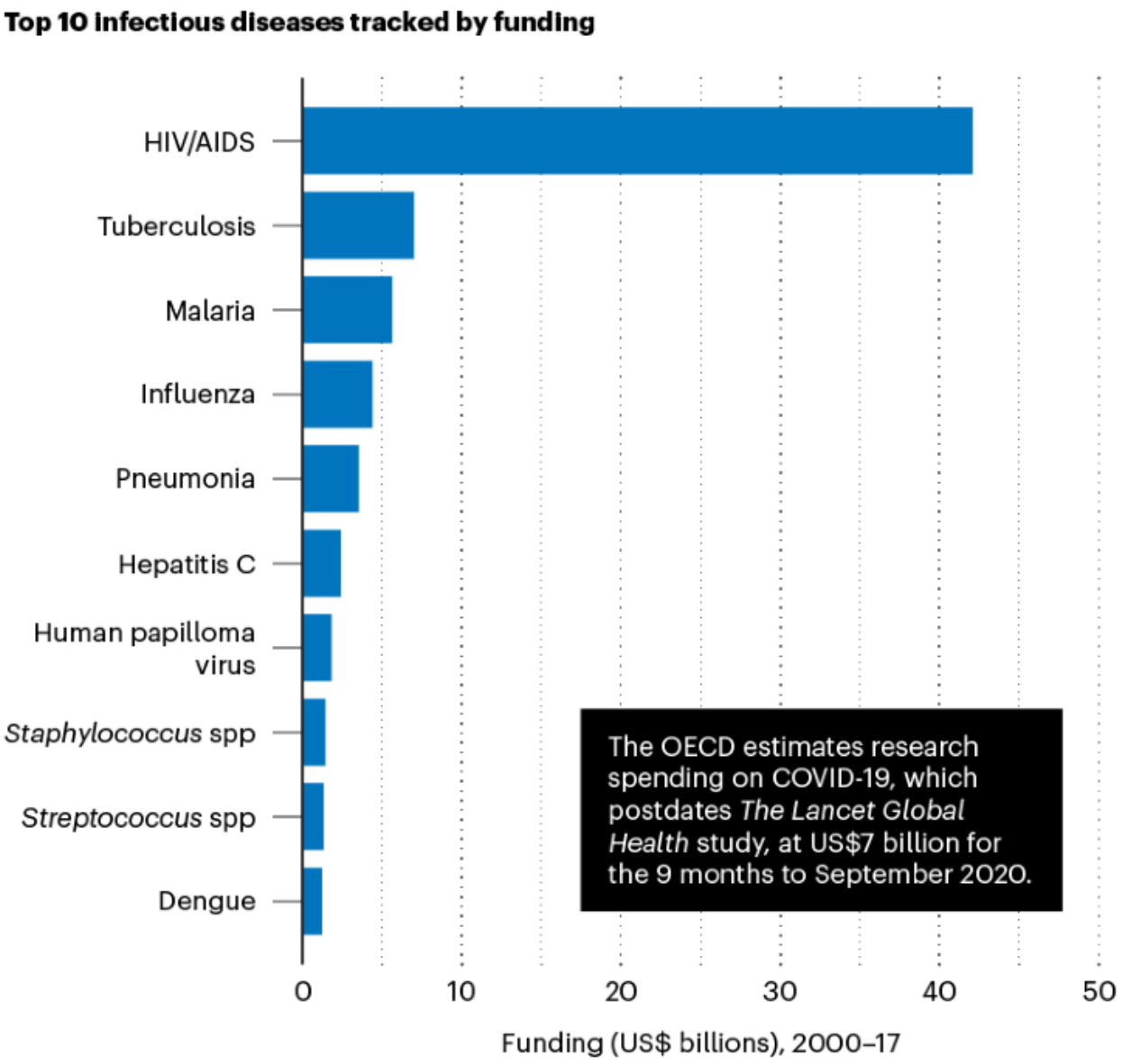
- Plathelminth (flat)
- Nemathelminth (round)

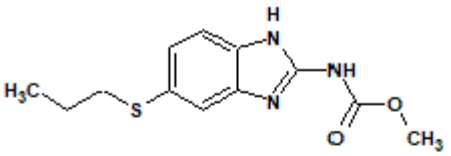
Great impact in health:
Human
Other animals
pets - dog/cats
livestock – cattle

PARASITE	DISEASE	EPIDEMIOLOGY
Ascaris lumbricoides	Ascariasis	819 million
Ancylostoma duodenal *Necator americanus*	Ancylostomiasis	438 million
Trichuris trichiura	Trichuriasis	464 million
Schistosoma spp.	Schistosomiasis	800 million
Plasmodium spp.	Malaria	216 million
Leishmania spp.	Leishmaniasis	12 million
Trypanosoma spp.	Trypanosomiasis	10 million

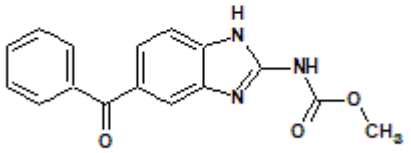
1,5 billion STH
25% world's population

Introduction





Albendazole



Mebendazole

Abdominal ache
Nausea/vomit
Diarrhea

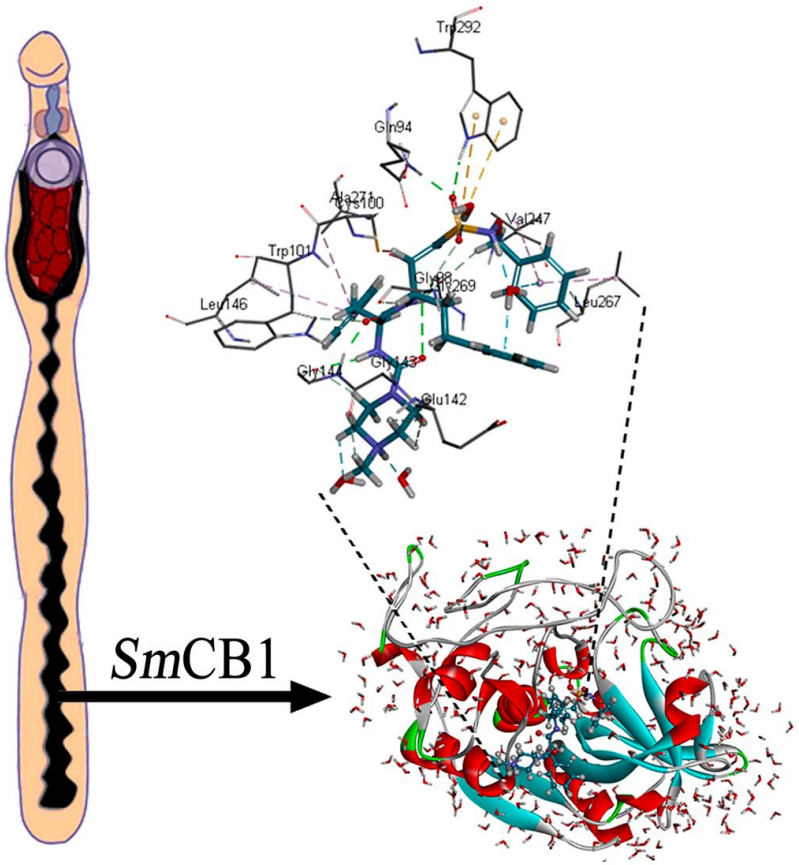
Allergic reactions

Neglected among the neglected?

APPROACH:

VS + DRUG REPURPOSING

Potential inhibitors of helminths cathepsin B1



Cathepsin B1: *S. mansoni* nutrition
blood protein digestion

Validated target:
worm do not growth and/or put new eggs

Known Inhibitors:

Peptidemimetics – vinylsulfones - Covalent ligands

Collateral effects

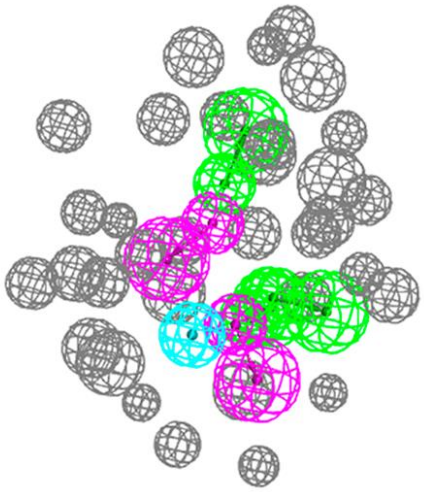
mimic an inhibitory protein domain
exclusive of the SmCB1

APPROACH:

VS + DRUG REPURPOSING

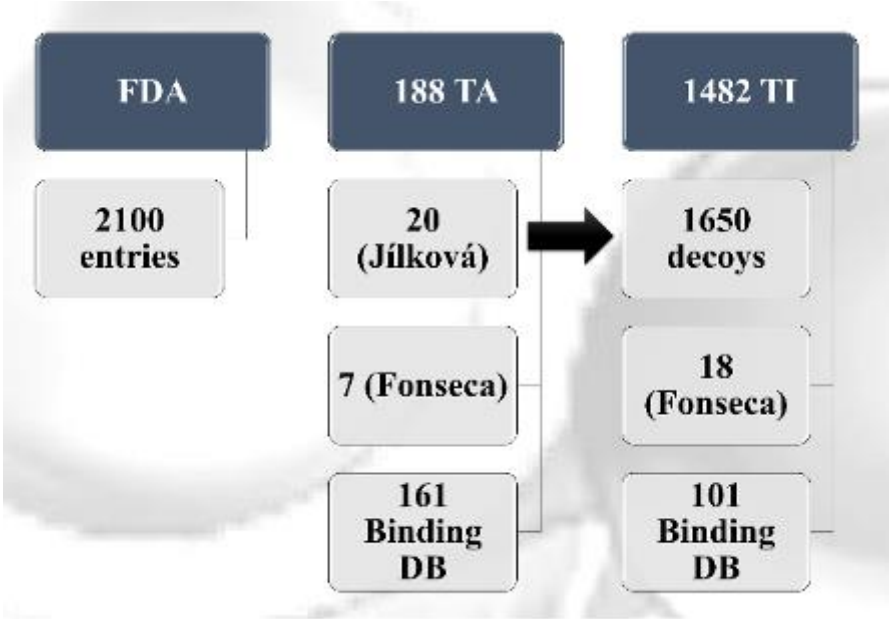
Potential inhibitors of helminths cathepsin B1

Pharmacophore model



FDA

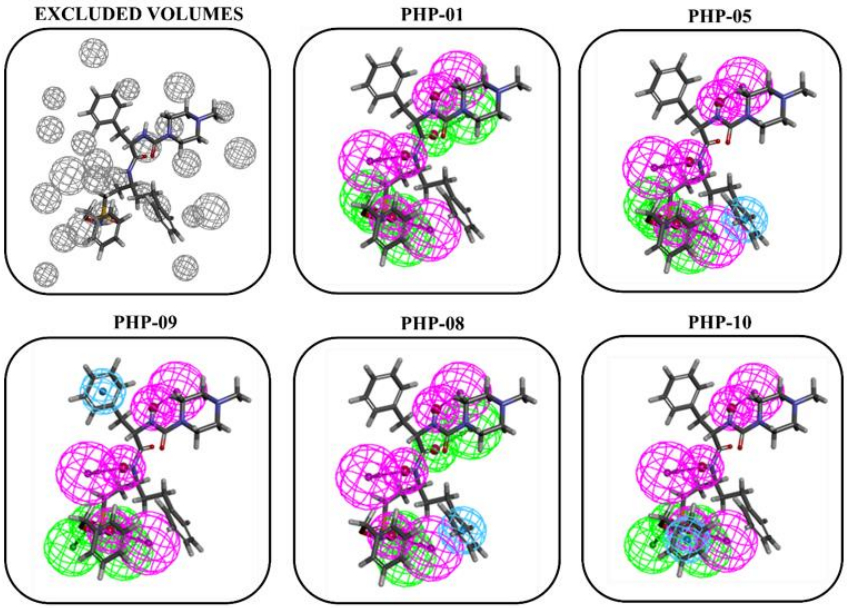
Pharmacophore modeling and validation by ROC curve



Results and discussion

Model	Total Actives	Total Inactives	True Positives	True Negatives	False Positives	False Negatives	Sensitivity	Specificity	AUC ROC
PHP_01	188	1482	159	922	560	29	0,84574	0,62213	0.823
PHP_02	188	1482	157	913	569	31	0,83511	0,61606	0.816
PHP_03	188	1482	150	1029	453	38	0,79787	0,69433	0.807
PHP_04	188	1482	153	1039	443	35	0,81383	0,70108	0.810
PHP_05	188	1482	154	1012	470	34	0,81915	0,68286	0.815
PHP_06	188	1482	153	930	552	35	0,81383	0,62753	0.798
PHP_07	188	1482	154	953	529	34	0,81915	0,64305	0.808
PHP_08	188	1482	158	928	554	30	0,84043	0,62618	0.816
PHP_09	188	1482	151	1038	444	37	0,80319	0,7004	0.809
PHP_10	188	1482	154	1045	437	34	0,81915	0,70513	0.812

Results and discussion



5 best selected ligands and filtered by:

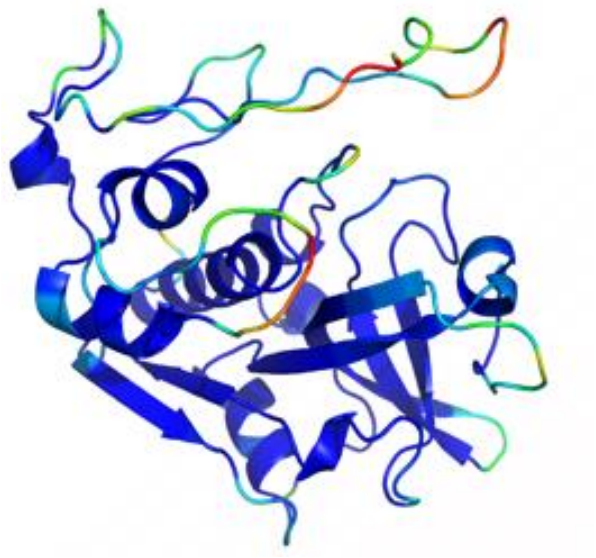
- Consensus analyses
- Suitable toxicity profile
- Commercial accessibility

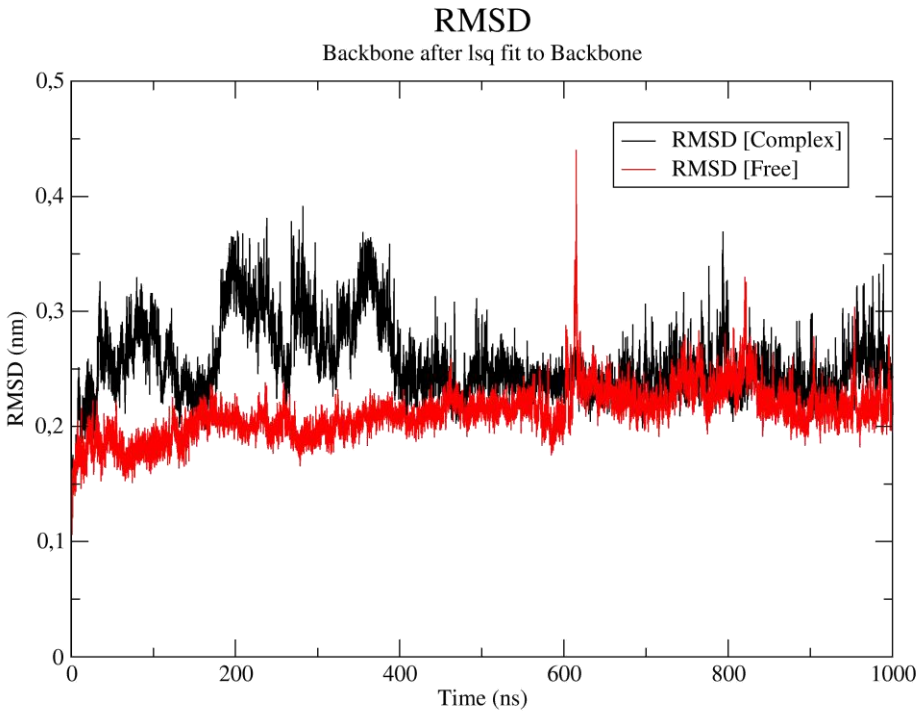
VITAMIN

DOCKING FOLLOWED BY DINAMICS

Results and discussion

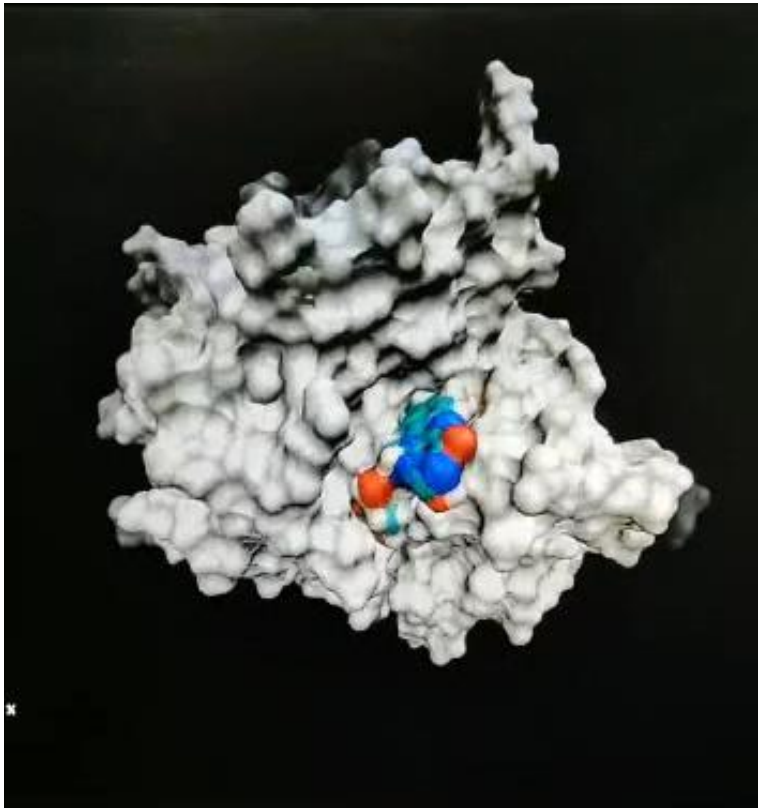
DOCKING FOLLOWED BY DINAMICS

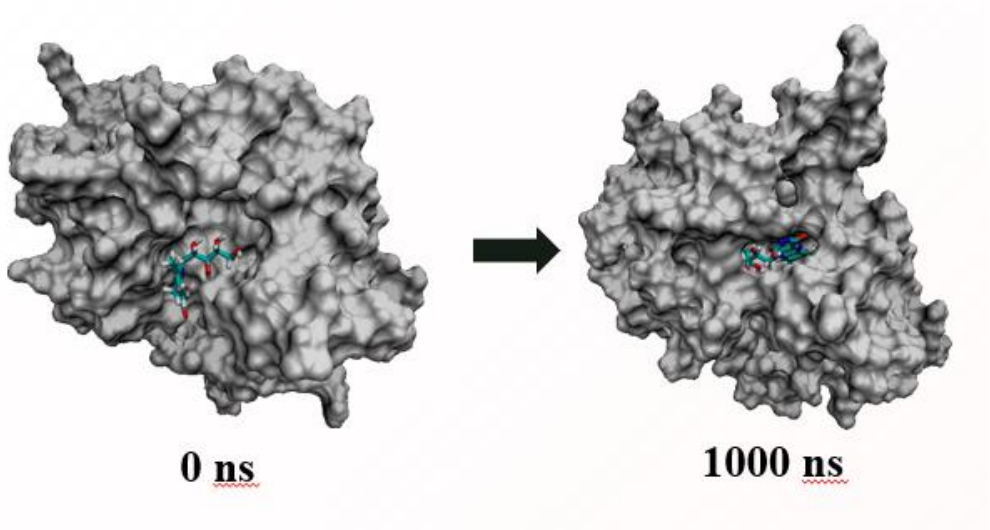




Results and discussion

DOCKING FOLLOWED BY DINAMICS





Results and discussion

EXPERIMENTAL DATA IN VITRO

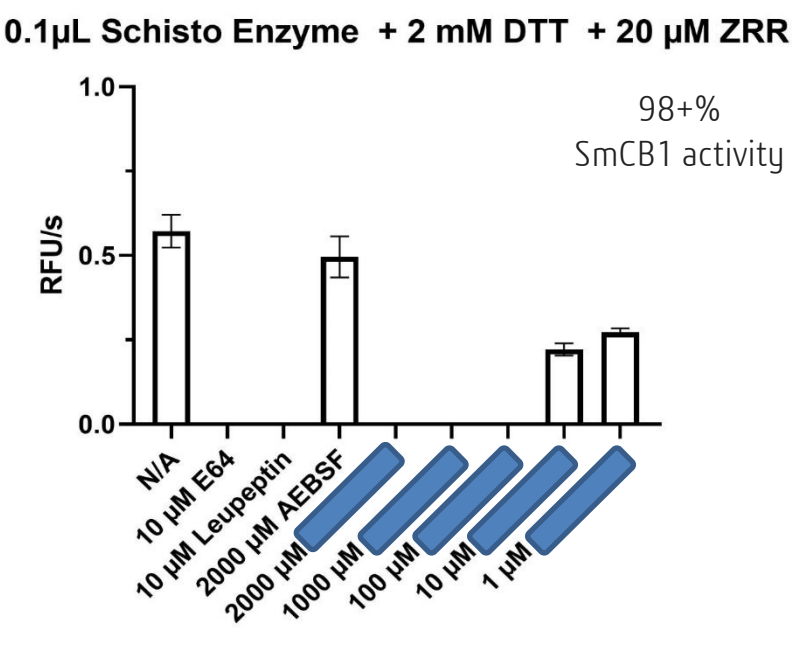
Group	infection (h)	(%) [a]					
				Slight		Significant	
		M	F	M	F	M	F
Control	Immediate	0	0	0	0	0	0
	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
0.5% DMSO	Immediate	0	0	0	0	0	0
	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
Praziquantel 2 µM	Immediate	100	100	0	0	100	100
	24	100	100	0	0	100	100
	48	100	100	0	0	100	100
	72	100	100	0	0	100	100
VITAMIN 50 µM	Immediate	0	0	0	0	0	0
	24	100	100	0	0	100	100
	48	100	100	0	0	100	100
	72	100	100	0	0	100	100
VITAMIN 25 µM	Immediate	0	0	0	0	0	0
	24	30	100	0	0	30	100
	48	60	100	0	0	60	100
	72	60	100	0	0	60	100
VITAMIN 12.5 µM	Immediate	0	0	0	0	0	0
	24	30	60	0	0	30	60
	48	30	100	0	0	30	100
	72	30	100	0	0	30	100

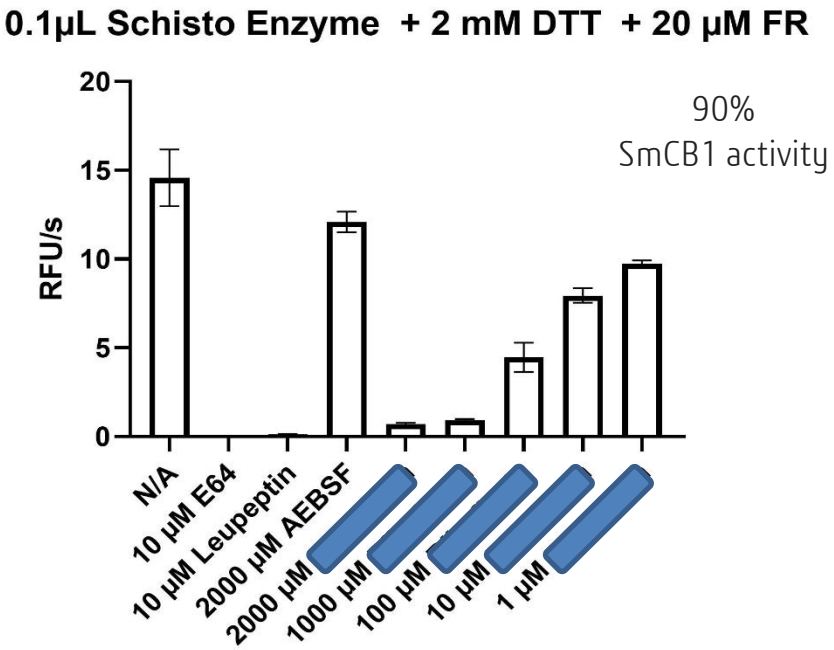
Results and discussion

EXPERIMENTAL DATA IN VITRO

Digestive Extract prepared to predominantly measure CatB1 activity

Two amino-methyl coumarin (AMC) substrates were used, Z-RR-AMC (selectively degraded by catB under the assays conditions used) and Z-FR-AMC (degraded by a number of cathepsins, incl B and L).





Conclusions

VS + DRUG REPURPOSING

The study was able to point potential ligands to SmCB1

The MD revealed that the obtained pharmacophores described more the interactions to a ligand approximation

After MD, we could see the stabilization of the complex in one set of conformations

Active site seems to be non-accessible to the substrate
experimental data
simulation data

The in vivo tests are under performance - **if ok**, the repurposing could easily be studied

This approach could be employed to many other worm-borne diseases Toxocara spp
Babesia spp

HUMAN AND VET HEALTH

Acknowledgments

GPQFfesp

To collaborators

NPDN NÚCLEO DE PESQUISA EM DOENÇAS NEGLIGENCIADAS

CDIPD RESEARCH EDUCATION AWARENESS
CENTER FOR DISCOVERY AND INNOVATION IN PARASITIC DISEASES

LMMBEC Laboratório de Modelagem Molecular e Biologia Estrutural Computacional

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