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Structural characterisation and inhibition of Arenavirus replication complex elements : assembly, function and inhibition of embedded nucleases.

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Arenaviruses, belongs to a family of emerging enveloped segmented and ambisens RNA viruses associated with neurological and hemorrhagic diseases in humans. Arenavirus transcription and genome replication are cytoplasmic ensured by a ribonucleoproteine replicase complex NP-L. After penetration, L protein initiates transcription to produce NP and L mRNAs[1]. The priming of transcription is the result of a *cap-snatching mechanism* ensured by an endonuclease domain associated to the L polymerase. As the concentration of NP in the cell increases, genome segments are replicated, to produce full-length copies (cRNA). cRNAs are now templates for transcription of GPC mRNA (from the S segment) and Z mRNA (from the L segment). The NP carries an *exonuclease* in charge of clearing out from the cytoplasm dsRNA triggering innate immunity response. Both nucleases have a similar *two metal ion catalytic mechanism*, with the particularity of transitioning ion brought by the RNA substrate. Any alteration of the remaining ion impairs greatly these activities[2]. We present a global study aiming to characterize the assembly of the NP[3], through flexible domains[4], a step critical for vRNA packaging and the positioning of L for vRNA replication, as well as using a combined approach of biophysical screening, *crystallography* and *in silico* docking, identifying active compounds against both nucleases[5]. Crystal structures of the nucleases domain complexed with several compounds were obtained[67]. By developing specific compounds to alter both transcription and innate immunity shadowing, our strategy is to give the cell a fighting chance to clear the infection. Combining structure, enzymology, rational synthesis, hit-To-lead optimization, *in cellula* evaluation, and screening methods, we are presenting the results of a 2nd generation of molecules paving the way to the design of a 3rd generation increasing specificity towards Arenaviral nucleases in the context of the replication complex[8].

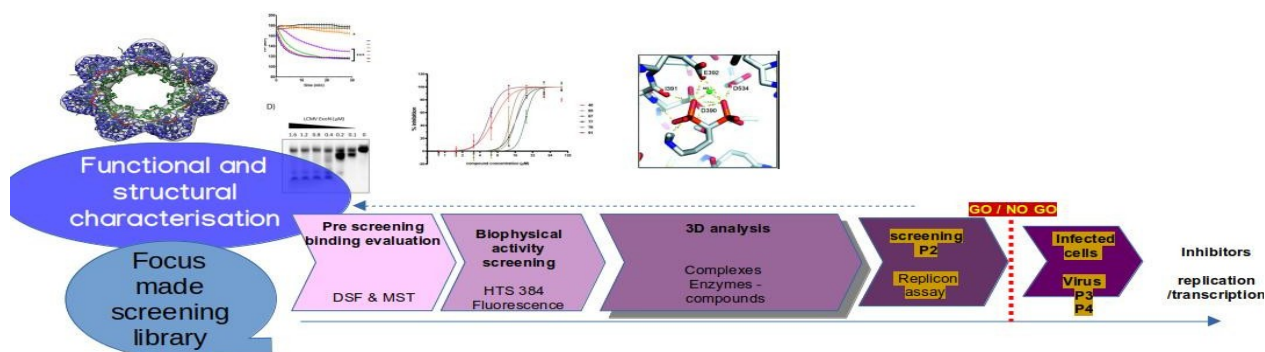


Figure 1. Experimental pipeline from characterisation to inhibitor.

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