

Design of antiviral drugs for bronchiolitis virus using a novel therapeutic target

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Respiratory syncytial virus (RSV), which is responsible for bronchiolitis and pneumonia, represents an important cause of hospitalization and mortality of young children¹. However, there is no vaccine nor efficient treatment against this virus². Therefore developing new specific and cost-effective anti-RSV therapeutics would cover a real medical need. In this context, several viral cycle steps are targets for the development of antiviral drugs. Most antiviral molecules in preclinical or clinical studies are targeting the entry of the virus into the host cell. They are aiming at blocking the fusion step with the cell membrane via two surface proteins, F and G. Our approach is different as we are targeting the viral RNA polymerase responsible for the synthesis of viral mRNA during transcription and genomic RNA during replication³. For this purpose, we suggest inhibiting the interaction between two RSV proteins by small molecules, i.e. the interaction between the nucleoprotein (N) and the phosphoprotein (P). This interaction is required for the formation of the viral RNA polymerase complex and essential for the viral cycle. This complex is virus specific, and there are no counterparts in non-infected cells. We have previously obtained structural data at high resolution for this interaction and identified a compound able to inhibit it⁴. In order to identify new anti-RSV candidates, we suggest developing three complementary strategies in parallel: pharmacomodulation of the first hit, a peptidomimetic approach and *de novo* exploration on the target. To evaluate the capacity of a compound to inhibit the N-P interaction, we have developed and optimized an *in vitro* test based on the concept of fluorescence anisotropy⁵, by the competition for the binding site on N by a fluorescent P analog. Our aim is to use this tool to screen molecular libraries and test newly synthesized molecules in order to find a lead compound.

¹ Griffiths, C.; Drews, S. J.; Marchant, D. J. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. *Clin Microbiol Rev* **2017**, *30* (1), 277–319.

² Cockerill, G. S.; Good, J. A. D.; Mathews, N. State of the Art in Respiratory Syncytial Virus Drug Discovery and Development. *J. Med. Chem.* **2019**, *62*(7), 3206–3227.

³ Fearn, R.; Deval, J. New Antiviral Approaches for Respiratory Syncytial Virus and Other Mononegaviruses: Inhibiting the RNA Polymerase. *Antiviral Res* **2016**, *134*, 63–76.

⁴ Ouizougoun-Oubari, M.; Pereira, N.; Tarus, B.; Galloux, M.; Lassoued, S.; Fix, J.; Tortorici, M. A.; Hoos, S.; Baron, B.; England, P.; Desmaele, D.; Couvreur, P.; Bontems, F.; Rey, F. A.; Eleouet, J. F.; Sizun, C.; Slama-Schwok, A.; Duquerroy, S. A Druggable Pocket at the Nucleocapsid/Phosphoprotein Interaction Site of Human Respiratory Syncytial Virus. *J Virol* **2015**, *89* (21), 11129–11143.

⁵ Shapiro, A. B.; Gao, N.; O'Connell, N.; Hu, J.; Thresher, J.; Gu, R. F.; Overman, R.; Hardern, I. M.; Sproat, G. G. Quantitative Investigation of the Affinity of Human Respiratory Syncytial Virus Phosphoprotein C-Terminus Binding to Nucleocapsid Protein. *Virology* **2014**, *11* (1), 191. <https://doi.org/10.1186/s12985-014-0191-2>