MASTER « *In Silico* Drug Design »

1ère année

PROPOSITION DE STAGE

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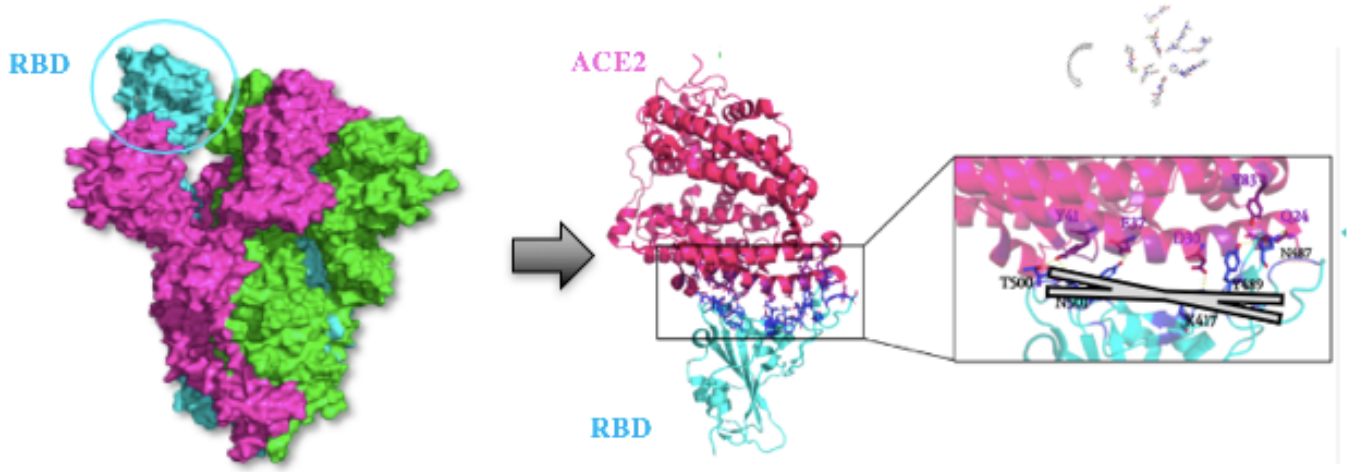
Titre du stage : Identification of inhibitors against SARS-CoV-2 spike protein.

Description du sujet (quelques lignes):

Year 2020 has been marked by the emergence of the highly pathogenic coronavirus SARS-CoV-2. SARS-CoV-2 is rapidly and internationally spreading causing a serious global public-health emergency, hence the importance of developing new drugs to inhibit the virus mechanism and reduce global infection [1,2]. The Spike protein, which is the key element for SARS-CoV-2 viral attachment, fusion and entry, is the main target for development of antibodies, entry inhibitors and vaccines [1,2]. The RBD (Receptor Binding Domain) which is located on the S1 subunit of the Spike protein mediates viral entry through ACE2 (Angiotensin Converting Enzyme 2) recognition [1,2,3,4]. In our previous work, the interaction between RBD and ACE2 receptor have been vigorously studied through MD (Molecular Dynamics) simulations (GROMACS) [5] using 6M0J and 6LZG PDB structures, MM/PBSA analysis in order to identify interesting key hotspots at the interaction surface [6,7], and PockDrug to spot druggable pockets in RBD [8]. Our study helped us to identify interesting druggable pockets and contributing key residues for the RBD-ACE2 interaction. Thus, the aim of this study is to determine interesting inhibitory molecules in order to disturb the complex interaction [9,10]. A preliminary virtual screening study with the ZINC database [11] has been screened on identified druggable pockets from our different MD trajectories.

The student will have to gather a lot of bibliographic records on the SARS-CoV-2 in order to understand the virus mechanism and catch up with the regularly updated news [12]. The goal is to finalize our research by identifying interesting inhibitors for the SARS-CoV-2 RBD-ACE2 interaction using a virtual screening program called Smina [13]. The results can be refined with AutoDock docking program [14] and verified with MD simulations [5]. The MD step will allow us to see if the SARS-CoV-2 complex along with the selected inhibitor(s) is (or are) stable. Through the MD simulation, many analyses can be done to study the complex (stability, flexibility, MM/PBSA, interaction…).



SARS-CoV-2 Spike protein **SARS-CoV-2 RBD-ACE2 complex**

References:

[1] Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., Lu, G., Qiao, C., Hu, Y., Yuen, K.-Y., Wang, Q., Zhou, H., Yan, J., & Qi, J. (2020). Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. *Cell*, *181*(4), 894-904.e9. https://doi.org/10.1016/j.cell.2020.03.045

[2] Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., & Wang, X. (2020). Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, *581*(7807), 215–220. https://doi.org/10.1038/s41586-020-2180-5

[3] Othman, H., Bouslama, Z., Brandenburg, J.-T., da Rocha, J., Hamdi, Y., Ghedira, K., Srairi-Abid, N., & Hazelhurst, S. (2020). Interaction of the spike protein RBD from SARS-CoV-2 with ACE2: Similarity with SARS-CoV, hot-spot analysis and effect of the receptor polymorphism. *Biochemical and Biophysical Research Communications*, *527*(3), 702–708. https://doi.org/10.1016/j.bbrc.2020.05.028

[4] Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H., Geng, Q., Auerbach, A., & Li, F. (2020). Structural basis of receptor recognition by SARS-CoV-2. *Nature*, *581*(7807), 221–224. https://doi.org/10.1038/s41586-020-2179-y

[5] M.J Abraham, D. van der Spoel, E. Lindhal, B. Hess, and the GROMACS development team, GROMACS User Manual Version 2019, http:/www.gromacs.org

[6] https://rashmikumari.github.io/g_mmpbsa/

[7] Spinello, A., Saltalamacchia, A., & Magistrato, A. (2020). Is the Rigidity of SARS-CoV-2 Spike Receptor-Binding Motif the Hallmark for Its Enhanced Infectivity? Insights from All-Atom Simulations. *The Journal of Physical Chemistry Letters*, *11*(12), 4785–4790. https://doi.org/10.1021/acs.jpclett.0c01148

[8] Borrel,A., Regad,L., Xhaard,H.G., Petitjean,M. and Camproux,A.-C. (2015) PockDrug: a model for predicting pocket druggability that overcomes pocket estimation uncertainties. J. Chem. Inf. Model., 10.1021/ci5006004.

[9] Cao, L., Goreshnik, I., Coventry, B., Case, J. B., Miller, L., Kozodoy, L., Chen, R. E., Carter, L., Walls, A. C., Park, Y.-J., Strauch, E.-M., Stewart, L., Diamond, M. S., Veesler, D., & Baker, D. (2020). De novo design of picomolar SARS-CoV-2 miniprotein inhibitors. *Science*, *370*(6515), 426–431. https://doi.org/10.1126/science.abd9909

[10] Gopinath, K., Jokinen, E. M., Kurkinen, S. T., & Pentikäinen, O. T. (2020). Screening of Natural Products Targeting SARS-CoV-2–ACE2 Receptor Interface – A MixMD Based HTVS Pipeline. *Frontiers in Chemistry*, *8*, https://www.frontiersin.org/articles/10.3389/fchem.2020.589769/full. https://doi.org/10.3389/fchem.2020.589769

[11] http://zinc.docking.org/

[12] Molecular dynamic simulation reveals E484K mutation enhances spike RBD-ACE2 affinity and the combination of E484K, K417N and N501Y mutations (501Y.V2 variant) induces conformational change greater than N501Y mutant alone, potentially resulting in an escape mutant. (in press). *BiorXiv*.

[13] Koes DR, Baumgartner MP, Camacho CJ. Lessons learned in empirical scoring with smina from the CSAR 2011 benchmarking exercise. J Chem Inf Model. 2013;53: 1893–1904. pmid:23379370

[14] Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S. and Olson, A. J. (2009) Autodock4 and AutoDockTools4: automated docking with selective receptor flexiblity. *J. Computational Chemistry* 2009, **16**: 2785-91.

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