Title: Old Drugs for JAK-STAT Pathway Inhibition in COVID-19 Patients:

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Abstract:

The pandemic threat of COVID-19 with more than 37 million cases in which about 5 percent entering critical stage characterized by cytokine storm and hyperinflammatory condition, the state more often leads to admission to intensive care unit with rapid mortality. Janus kinase enzymes of Jak-1, Jak-2, Jak-3, and Tyk2 seem to be good targets for inhibition by medications to control cytokine storm in this context. In the present work, the inhibitory properties of different analgesic drugs on these targets are studied to assess their ability for clinical application from different points of view. Our docking results indicated that naproxen, methadone, and amitriptyline considering their higher binding energy, lower energy variance and higher hydrophobicity, seem to express more inhibitory effects on Janus kinase enzymes than thats for approved inhibitors i.e. baricitinib and ruxolitinib. Accordingly, we suggest our wide list of candidate drugs including indomethacin, etodolac, buprenorphine, rofecoxib, duloxetine, valdecoxib, naproxen, methadone, and amitriptylin for clinical assessments for their usefulness in COVID-19 treatment, especially taking into account that up to now, there is no approved cure for this disease.

Keywords: COVID-19, Janus Kinase, Cytokine Storm, Naproxen, Methadone, Amitriptyline
**Introduction:**

Janus kinase (JAK) is a family of intracellular tyrosine kinase enzymes that participate in signal transduction through cytokine receptors in the JAK-STAT pathway. There are two types of cytokine receptors: type-1, and type-II. Both of these receptors have no kinase activities and so they dependent on JAK enzymes for phosphorylation and signal transduction. The family of JAK is comprised of tyrosine kinase-2 (Tyk2), JAK-1, JAK-2, and JAK-3 enzymes. This enzyme Tyk2 is the first described member of this family. The enzyme collaborates with cytoplasmic domains of cytokine receptors (type I and II) for signal transduction induced by IL-6, IL-11, IFN-α, IFN-β, and IFN-γ cytokines. The JAK-1 enzyme uses the gamma chain of type-I receptor and participates in signal transduction from IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 cytokines and also mediates signals through type-II receptor posed by IFN-α, IFN-β and IFN-γ.

The JAK-2 enzyme facilitates signal transduction through a type-I receptor that is induced by IL-3, IL-5, IL-6, IL-11, GM-CSF, EPO, TPO, GH, G-CSF and also signals through type-II receptor exerted by TFN-α, IFN-β and IFN-γ cytokines [3-6]. Unlike the other Janus kinase enzymes, JAK-3 only mediates signals through type-I receptor that is induced by IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 cytokines [7-12]. In contemporary medicine, Janus kinase inhibitors are used as medications to interfere with JAK-STAT signaling pathways and to manage and control hyperinflammatory states or cytokine storms in severe diseases such as cancer and autoimmune diseases [13-14]. Among JAK inhibitors some are approved for clinical use including ruxolitinib, against JAK1/JAK2, oclacitinib, against JAK1, baricitinib, against JAK1/JAK2, peficitinib, against JAK3, fedratinib, against JAK2 inhibitor and upadacitinib, against JAK1 pathways [15-18]. There are also some JAK inhibitors, e.g. filgotinib, cerdulatinib, gandotinib, lestaurtinib, momelotinib, pacritinib, and abrocitinib which are in clinical trials for future applications [19-21].

The newly emerging disease of COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease causes a pandemic threat with more than 37 million cases and more than 1 million deaths by October 2020 [27-28]. It is well documented that COVID-19 patients experience a dramatic increase in plasma levels of different kinds of inflammatory cytokines that in server cases lead to profound infiltration of immune cells in the lungs with ultimate alveolar damage and death [22-26].
Increasing the cytokines of IL-2, IL-6, IL-7, IL-10, G-CSF, GM-CSF, and IFN-γ in accordance with increasing different chemokines comprises the main cause for COVID-19 mortality, the state primarily mediated by JAK-STAT pathway [28-30].

There are increasing efforts performed to control hyperinflammatory state in COVID-19 by application of Janus kinase inhibitors. Ruxolitinib is one of the approved inhibitors used in the clinic for treatment of myelofibrosis and selectively inhibits JAK-1 and JAK-2 shows reasonable effects on mitigating hyperinflammatory state in COVID-19 patients [27-32]. Baricitinib is the next example of JAK inhibitors that is prescribed as anti-rheumatic drug for rheumatoid arthritis and significantly blocks both JAK1 and JAK2 decreases fever, breathlessness, cough and improves pulmonary function in COVID-19 patients [33-34].

There are also miscellaneous reports indicating the benefits of JAK inhibitors in COVID-19 treatment that encouraged us to search for new candidates among old analgesic or pain relief drugs for their ability in this context from a bioinformatics point of view [35-37].

Methods and Materials:

Coordinate structures for JAK enzymes:

Coordinate structures of JAK-1, JAK-2, JAK-3, and TyK2 enzymes with PDB IDs’ of 4I5C, 2W1I, 3LXK, and 4GVJ, respectively were retrieved from protein data bank (https://www.rcsb.org/). These structures were obtained by the X-ray diffraction and refined at the resolutions of 2.1Å, 2.60Å, 2Å, and 2.03Å, respectively. These structures were energy minimized in separate rectangular boxes with dimensions of 9.79×9.98×6.84nm, 7.87×7.62×9.27nm, 5.62×5.73×6.87nm, and 5.67×7.18×6.18nm dimensions respectively. The boxes were filled with SPCE water. The algorithm of the steepest descent algorithm, neutral pH, 37°C temperature, 1atmosphere of pressure, and total energy of 200kj/mol was used as minimization criteria [38-39].

Drugs coordinate structures: The coordinate structures of candidates drugs (selected from analgesics or pain relief drugs including almotriptan, amitriptyline, amlodipine, baricitinib, buprenorphine, celecoxib, diclofenac, duloxetine, ergotamine, esomeprazole, etodolac, famotidine, fentanyl, indomethacin,
lansoprazole, lasmiditan, methadone, nalbuphine, naloxone, naproxen, naratriptan, oxycodone, piroxicam, remifentanil, rimegepant, rofecoxib, ruxolitinib, sufentanil, sulindac, tofacitinib, ubrogepant and valdecoxib) in SDF format were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and converted to PDB format with Open Babel software (http://openbabel.org/). The structures then were energy minimized in ArgusLab software (http://www.arguslab.com/) [40].

**Enzymes Active Sites:** The active sites of JAK enzymes were extracted using Computed Atlas of Surface Topography of proteins server (http://sts.bioe.uic.edu/castp/).

**Docking experiments:** In order to study the potential ability of studied drugs in binding to the JAK enzyme active sites we have performed blind docking experiments in Hex 8.0.0 (http://www.loria.fr/~ritchied/hex/) [41]. The setting of sahpe+electrostatic and macro sampling method, optimized structures of JAK enzymes as receptor and drugs as ligands were used for docking experiments. The best 100 docking pose and their binding energies were recorded for analysis.

**Drugs Hydrophobicity:** Partition coefficient or logP is an acceptable index for drug hydrophobicity in which a positive value means the compound has a higher affinity for hydrophobic phase. The server of the Virtual Computational Chemistry Laboratory (http://www.vcclab.org/) was used to calculated logP for the studied drugs [42].

**Data Handling and Analysis:** All the numerical data were exploited in Excel and SPSS software. P-value under 0.05 was considered as the significance level.

**Results and Discussion:**

Figure 1-a represents sequence alignment results for Janus kinase enzymes. As it is clear, there are high sequence similarities between these enzymes in such a way that the overall structures and their binding site motifs indicate structural similarities (Figure 1-b). However, the ligand binding properties of the enzymes are somewhat different that lead to different results seen in our docking experiments.
Figure 1: a- Multiple sequence alignment for Jak-1, Jak-2, Jak-3, and TyK-2 was performed on CLUSTAL (www.ebi.ac.uk/Tools/msa/clustalo/). b- Binding site predicted using Computed Atlas of Surface Topography of proteins server (http://sts.bioe.uic.edu/castp/) for Jak-1, Jak-2, Jak-3, and TyK-2 used for analysis of docking results.

Table 1 represents the docking results obtained for the studied drugs used as ligands and Jak-1, Jak-2, Jak-3, and TyK2 as receptors. The drugs with higher binding energies, lower variances, higher logPs', and higher degree of binding site occupancies seem to be better candidates for enzyme inhibition.
Table 1: Average binding energy in kJ/mol (as Mean±SD) as well as variance in their binding energy calculated for the best 100 poses for Janus kinase enzyme and the logP values of the drugs calculated on [http://www.vcclab.org/](http://www.vcclab.org/) website.

|        | JAK-1     |        | JAK-2     |        | JAK-3     |        | TYK2     |        |
|--------|-----------|--------|-----------|--------|-----------|--------|----------|--------|
|        | Mean±SD   | Variance | Occupancy | Mean±SD | Variance | Occupancy | Mean±SD   | Variance | Occupancy | Mean±SD   | Variance | Occupancy | logP   |
| amlopiptine | -344.5±8  | 67.8 ± 100 | -299.1±8 | 38.41  | 59        | -323.4±9 | 92.07    | 100      | -322.9±8 | 63.46    | 91        | 2.04    |
| buprenorphine | -389.4±14 | 206.8 ± 100 | -349.9±14 | 50.94  | 20        | -391.1±14 | 51.84    | 68        | -372.3±9 | 90.68    | 98        | 1.08    |
| celecoxib | -538.6±13 | 179.3 ± 0 | -444.1±8 | 68.44  | 47        | -530.0±15 | 246.3    | 21        | -426.5±14 | 211.4±8  | 25        | 4.53    |
| diclofenac | -391.7±2 | 82 ± 0 | -328.13±10 | 113.12  | 0        | -392.19±8 | 74.11    | 39        | -304.8±9 | 94.61    | 0        | 4.98    |
| etodolac | -332.8±11 | 124.6 ± 100 | -310.25±8 | 71.65  | 60        | -301.5±9 | 98.96    | 93        | -299.41±8 | 70.77    | 87        | 4.72    |
| famotidine | -299.9±5 | 28.37 ± 100 | -264.9±8 | 79.29  | 91        | -266.5±8 | 74.12    | 86        | -274.5±17 | 55.7 ± 95  | 95        | 1.66    |
| indomethacin | -373.6±10 | 113.49 ± 100 | -346.3±13 | 178.68  | 80        | -358.8±10 | 119.69   | 16        | -322.9±6 | 71.17    | 96        | 4.25    |
| lansoprazole | -567.4±12 | 146.08 ± 100 | -52.15±10 | 100.99 | 25        | -53.8±24 | 243.78   | 67.4±11  | 134.44 | 11      | 2.84    |
| naproxen | -276.4±7 | 57.86 ± 100 | -252.06±6 | 40.54  | 80        | -250.6±6 | 39.86    | 86        | 288.3±5 | 32.65    | 80        | 1.47    |
| piroxicam | -327.6±7 | 60.33 ± 100 | -291.07±8 | 68.25  | 75        | -294.2±11 | 130.14   | 100       | -298.19±6 | 41.28    | 74        | 2.2     |
| remifentanil | -368.4±11 | 136.09 ± 100 | -322.15±7 | 49.44  | 70        | -305.5±8 | 64.79    | 94        | -335.0±2 | 89.36    | 94        | 1.75    |
| riluzole | -301.8±5 | 29.01 ± 100 | -275.29±6 | 38.81  | 58        | -274.3±8 | 69.14    | 89        | -285.5±2 | 34.76    | 95        | 2.32    |
| ruxolitinib | -331.57±8 | 79.9 ± 100 | -302.82±12 | 152.08 | 0        | -287.1±8 | 77.19    | 90        | -309.28±7 | 58.25    | 95        | 2.94    |
| sufentanil | -364.0±8 | 78.92 ± 100 | -336.96±11 | 133.74  | 39        | -330.0±10 | 102.77   | 95        | -350.9±12 | 146.58   | 100       | 2.4     |
| valdecoxib | -299.6±5 | 60.1 ± 100 | -275.96±6 | 39.86  | 40        | -281.0±5 | 34.15    | 98        | -288.5±7 | 55.06    | 95        | 3.32    |
In order to optimize the calculated variables in table 1 and to obtain a reliable and cumulative index for comparing the studied drugs from their inhibitory potency point of view, we converted the values of binding energies, 1/variances (as stability index), percent of binding site occupancies and the logP values to normalize absolute values in 0 to 1 range and then summate them in a total cumulative index for this purpose (Table 2). It is of prime importance to note that, in these calculations we take the same contribution effect for all variables on the total effects of drugs, the assumption that could be under question quantitatively.

Table 2: The total cumulative index for each drug calculated based on normalized values for binding energies, 1/variances, binding site occupancies, and logP as described in the text.

| Drug          | Jak-1 | Jak-2 | Jak-3 | Tyk2 | Total |
|---------------|-------|-------|-------|------|-------|
| fentanyl      | 2.23  | 1.72  | 1.68  | 1.84 | 7.47  |
| amlodipine    | 1.87  | 1.93  | 1.96  | 1.84 | 7.60  |
| buprenorphone | 1.98  | 1.34  | 2.12  | 2.30 | 7.74  |
| ubrogepant    | 1.63  | 2.37  | 1.41  | 1.68 | 7.82  |
| ruxolitinib   | 2.45  | 1.40  | 1.53  | 2.68 | 8.06  |
| diclofenac    | 1.94  | 1.93  | 2.52  | 1.93 | 8.32  |
| lasmiditan    | 2.32  | 1.66  | 2.61  | 1.87 | 8.46  |
| lansoprazole  | 2.67  | 2.05  | 2.11  | 1.79 | 8.62  |
| rimegepant    | 2.42  | 1.84  | 1.63  | 2.75 | 8.64  |
| sulindac      | 1.64  | 1.56  | 3.03  | 2.43 | 8.66  |
| naltobutine   | 2.52  | 2.38  | 2.04  | 1.93 | 8.86  |
| naloxone      | 2.04  | 2.22  | 2.10  | 2.58 | 8.96  |
| celecoxib     | 1.92  | 2.75  | 2.18  | 2.18 | 9.02  |
| tofacitinib   | 2.14  | 2.32  | 2.00  | 2.62 | 9.08  |
| naratriptan   | 2.62  | 2.02  | 2.13  | 2.39 | 9.17  |
| remifentanil  | 2.14  | 2.40  | 2.35  | 2.32 | 9.21  |
| baricitinib   | 2.35  | 2.12  | 2.41  | 2.46 | 9.34  |
| esomepazolate | 2.43  | 1.93  | 2.52  | 2.50 | 9.38  |
| piroxicam     | 2.41  | 2.28  | 2.21  | 2.50 | 9.41  |
| oxycodone     | 2.70  | 2.19  | 2.04  | 2.52 | 9.44  |
| ergotamine    | 1.61  | 2.62  | 2.51  | 2.74 | 9.49  |
| famotidine    | 2.76  | 2.37  | 2.12  | 2.38 | 9.62  |
| almatriptan    | 2.36  | 2.50  | 2.34  | 2.45 | 9.65  |
| sufentanil    | 2.60  | 1.99  | 2.53  | 2.61 | 9.73  |
| indomethacin  | 2.67  | 2.53  | 1.91  | 2.88 | 10.00 |
| etodolac      | 2.54  | 2.46  | 2.63  | 2.56 | 10.19 |
| buprenorphone | 2.66  | 1.98  | 2.69  | 3.00 | 10.33 |
| rofecoxib     | 2.87  | 2.48  | 2.32  | 2.84 | 10.52 |
| duloxetine    | 2.69  | 2.64  | 2.73  | 2.84 | 10.89 |
| valdecoxib    | 2.59  | 2.47  | 3.13  | 2.74 | 10.92 |
| naproxen      | 2.56  | 2.82  | 2.77  | 2.93 | 11.07 |
| methadone     | 2.60  | 2.75  | 2.89  | 3.04 | 11.29 |
| amitriptyline | 2.85  | 2.78  | 3.42  | 3.16 | 12.21 |
**Conclusion:**

Based on our finding and as indicated in table 2, indomethacin, etodolac, buprenorphine, rofecoxib, duloxetine, valdecoxib, naproxen, methadone, and amitriptyline with higher total effects seem to be good candidates for further studies in JAK-STAT pathway blockage and cytokine storm control in chronic and severe disease of cancer, autoimmune and COVID-19 disease via clinical trials assessments.

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References:

[1] Rodig SJ, Meraz MA, White JM, Lampe PA, Riley JK, Arthur CD, King KL, Sheehan KC, Yin L, Pennica D, Johnson EM, Schreiber RD (1998). "Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses". Cell. 93 (3): 373–83. doi:10.1016/S0092-8674(00)81166-6. PMID 9590172.

[2] Christian Nordqvist. "Protein JAK Makes Cancer Cells Contract, So They Can Squeeze Out Of A Tumor". Medical News Today.

[3] Ungureanu D, Wu J, Pekkala T, Niranjan Y, Young C, Jensen ON, Xu CF, Neubert TA, Skoda RC, Hubbard SR, Silvennoinen O (August 2011). "The pseudokinase domain of JAK2 is a dual-specificity protein kinase that negatively regulates cytokine signaling". Nature Structural & Molecular Biology. 18 (9): 971–976. doi:10.1038/nsmb.2099. PMC 4504201. PMID 21841788.

[4] Neubauer H, Cumano A, Müller M, Wu H, Huffstadt U, Pfeffer K (May 1998). "Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis". Cell. 93 (3): 397–409. doi:10.1016/S0092-8674(00)81168-X. PMID 9590174.

[5] Brooks AJ, Dai W, O'Mara ML, Abankwa D, Chhabra Y, Pelekanos RA, et al. (2014). "Mechanism of activation of protein kinase JAK2 by the growth hormone receptor". Science. 344 (6185): 1249783. doi:10.1126/science.1249783. PMID 24833397.

[6] Morgan KJ, Gilliland DG (2008). "A role for JAK2 mutations in myeloproliferative diseases". Annual Review of Medicine. 59 (1): 213–22. doi:10.1146/annurev.med.59.061506.154159. PMID 17919086.

[7] Degryse S, de Bock CE, Cox L, Demeyer S, Gielen O, Mentens N, Jacobs K, Geerdens E, Gianfelici V, Hulselmans G, Fiers M, Aerts S, Meijerink JP, Tousseyn T, Cools J (November 2014). "JAK3 mutants transform hematopoietic cells through JAK1 activation, causing T-cell acute lymphoblastic leukemia in a mouse model". Blood. 124 (20): 3092–100. doi:10.1182/blood-2014-04-566687. PMID 25193870.

[8] Henkels KM, Frondorf K, Gonzalez-Mejia ME, Doseff AL, Gomez-Cambronero J (January 2011). "IL-8-induced neutrophil chemotaxis is mediated by Janus kinase 3 (JAK3)". FEBS Letters. 585 (1): 159–66. doi:10.1016/j.febslet.2010.11.031. PMC 3021320. PMID 21095188.
[9] Mishra J, Verma RK, Alpini G, Meng F, Kumar N (November 2013). "Role of Janus kinase 3 in mucosal differentiation and predisposition to colitis". The Journal of Biological Chemistry. 288 (44): 31795–806. doi:10.1074/jbc.M113.504126. PMC 3814773. PMID 24045942.

[10] Mishra J, Kumar N (June 2014). "Adapter protein Shc regulates Janus kinase 3 phosphorylation". The Journal of Biological Chemistry. 289 (23): 15951–6. doi:10.1074/jbc.C113.527523. PMC 4047368. PMID 24795043.

[11] Mishra J, Verma RK, Alpini G, Meng F, Kumar N (December 2015). "Role of Janus Kinase 3 in Predisposition to Obesity-associated Metabolic Syndrome". The Journal of Biological Chemistry. 290 (49): 29301–12. doi:10.1074/jbc.M115.670331. PMC 4705936. PMID 26451047.

[12] Mishra, Jayshree; Das, Jugal Kishore; Kumar, Narendra (2017). "Janus kinase 3 regulates adherens junctions and epithelial mesenchymal transition through β-catenin". Journal of Biological Chemistry. 292 (40): 16406–16419. doi:10.1074/jbc.M117.811802. PMC 5633104. PMID 28821617.

[13] Kontzias A, Kotlyar A, Laurence A, Changelian P, O'Shea JJ (August 2012). "Jakinibs: a new class of kinase inhibitors in cancer and autoimmune disease". Current Opinion in Pharmacology. 12 (4): 464–70. doi:10.1016/j.coph.2012.06.008. PMC 3419278. PMID 22819198.

[14] Norman P (August 2014). "Selective JAK inhibitors in development for rheumatoid arthritis". Expert Opinion on Investigational Drugs. 23 (8): 1067–77. doi:10.1517/13543784.2014.918604. PMID 24818516.

[15] Vaddi K, Sarlis NJ, Gupta V (November 2012). "Ruxolitinib, an oral JAK1 and JAK2 inhibitor, in myelofibrosis". Expert Opinion on Pharmacotherapy. 13 (16): 2397–407. doi:10.1517/14656566.2012.732998. PMID 23051187.

[16] Zerbini CA, Lomonte AB (May 2012). "Tofacitinib for the treatment of rheumatoid arthritis". Expert Review of Clinical Immunology. 8 (4): 319–31. doi:10.1586/eci.12.19. PMID 22607178.

[17] Gonzales AJ, Bowman JW, Fici GJ, Zhang M, Mann DW, Mitton-Fry M (August 2014). "Oclacitinib (APOQUEL®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy". Journal of Veterinary Pharmacology and Therapeutics. 37 (4): 317–24. doi:10.1111/jvp.12101. PMC 4265276. PMID 24495176.
[18] Kivitz AJ, Gutierrez-Ureña SR, Poiley J, Genovese MC, Kristy R, Shay K, Wang X, Garg JP, Zubrzycka-Sienkiewicz A (April 2017). "Peficitinib, a JAK Inhibitor, in the Treatment of Moderate-to-Severe Rheumatoid Arthritis in Patients With an Inadequate Response to Methotrexate". Arthritis & Rheumatology. 69 (4): 709–719. doi:10.1002/art.39955. PMID 27748083.

[19] Liu D, Mamorska-Dyga A (July 2017). "Syk inhibitors in clinical development for hematological malignancies". Journal of Hematology & Oncology. 10 (1): 145. doi:10.1186/s13045-017-0512-1. PMC 5534090. PMID 28754125.

[20] Shabbir M, Stuart R (March 2010). "Lestaurtinib, a multitargeted tyrosine kinase inhibitor: from bench to bedside". Expert Opinion on Investigational Drugs. 19 (3): 427–36. doi:10.1517/13543781003598862. PMID 20141349.

[21] Hart S, Goh KC, Novotny-Diermayr V, Hu CY, Hentze H, Tan YC, Madan B, Amalini C, Loh YK, Ong LC, William AD, Lee A, Poulsen A, Jayaraman R, Ong KH, Ethirajulu K, Dymock BW, Wood JW (November 2011). "SB1518, a novel macrocyclic pyrimidine-based JAK2 inhibitor for the treatment of myeloid and lymphoid malignancies". Leukemia. 25 (11): 1751–9. doi:10.1038/leu.2011.148. PMID 21691275.

[22] Y. Zhou, B. Fu, X. Zheng, D. Wang, C. Zhao, Y. Qi, et al., Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients, Natl. Sci. Rev. 7 (2020) 998–1002.

[23] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.

[24] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (2020) 420–422.

[25] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (2020) 727–733.

[26] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, Intensive Care Med. 46 (2020) 846–848.
[27] Swamy Yeleswaram, Paul Smith, Timothy Burn, Maryanne Covington, Ashish Juvekar, Yanlong Li, Peg Squier, Peter Langmuir (2020) Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment. Clinical Immunology 218 (2020) 108517

[28] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

[29] Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients With coronavirus disease 2019 (COVID-19). JAMA Cardiol. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017

[30] Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020;130(5):2202-2205. doi:10.1172/JCI137647

[31] Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-2629. doi:10.1172/JCI137244

[32] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. Published online March 3, 2020. doi:10.1007/s00134-020-05991-x

[33] Favalli EG, Biggioggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment?. Lancet Infect Dis. 2020;20(9):1012-1013. doi:10.1016/S1473-3099(20)30262-0

[34] Cingolani A, Tummolo AM, Montemurro G, et al. Baricitinib as rescue therapy in a patient with COVID-19 with no complete response to sarilumab [published online ahead of print, 2020 Jul 8]. Infection. 2020;1-5. doi:10.1007/s15010-020-01476-7

[35] Spinelli FR, Conti PF, Gadina M. (2020) The potential role of JAK inhibitors in the management of COVID19. Science Immunology:5(47),eabc5367. doi: 10.1126/sciimmunol.abc5367

[36] Rehman M, Tauseef I, Aalia B, Shah SH, Junaid M, Haleem KS. Therapeutic and vaccine strategies against SARS-CoV-2: past, present and future. Future Virol. 2020;10.2217/fvl-2020-0137. doi:10.2217/fvl-2020-0137
[36] Mehta P, Ciurtin C, Scully M, Levi M, Chambers RC. JAK inhibitors in COVID-19: need for vigilance regarding increased inherent thrombotic risk [published online ahead of print, 2020 Jul 6]. *Eur Respir J*. 2020;2001919. doi:10.1183/13993003.01919-2020

[37] Schett G, Manger B, Simon D, Caporali R. COVID-19 revisiting inflammatory pathways of arthritis. *Nat Rev Rheumatol*. 2020;16(8):465-470. doi:10.1038/s41584-020-0451-z

[38] Sheng C, Ji H, Miao Z, Che X, Yao J, Wang W, et al. Homology modeling and molecular dynamics simulation of N-myristoyltransferase from protozoan parasites: active site characterization and insights into rational inhibitor design. *J Comput Aided Mol Des*. 2009; 23(6) : 375 -89

[39] Macindoe G, Mavridis L, Venkatraman V, Devignes MD, Ritchie DW. HexServer: an FFT-based protein docking server powered by graphics processors. *Nucleic Acids Res*. 2010; 38 -9 [DOI][PubMed]

[40] Abdelouahab C, Abderrahmane B (2008) Docking Efficiency Comparison of Surflex, a Commercial Package and Arguslab, a Licensable Freeware. *J Comput Sci Syst Biol* 1: 081-086. doi:10.4172/jcsb.1000007

[41] Accelerating Protein-Protein Docking Correlations Using A Six-Dimensional Analytic FFT Generating Function, D.W. Ritchie, D. Kozakov, and S. Vajda (2008), *Bioinformatics* 24(17), 1865-1873

[42] Tetko, I. V.; Gasteiger, J.; Todeschini, R.; Mauri, A.; Livingstone, D.; Ertl, P.; Palyulin, V. A.; Radchenko, E. V.; Zefirov, N. S.; Makarenko, A. S.; Tanchuk, V. Y.; Prokopenko, V. V. Virtual computational chemistry laboratory - design and description, *J. Comput. Aid. Mol. Des.*, 2005, 19, 453-63