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ALY 6080: Integrated Experiential Learning

Annotated Bibliography II

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*I. Introduction*

The purpose of this annotated bibliography is to review/ summarize a paper based on our group project’s selected disease for research, “Leukemia”. It is a group of blood cancers that usually begin in the bone marrow and result in high numbers of abnormal blood cells. These blood cells are not fully developed and are called blasts or leukemia cells. Symptoms may include bleeding and bruising, feeling tired, fever, and an increased risk of infections. These symptoms occur due to a lack of normal blood cells (Leukemia 2020). The paper is based on Merging of ruxolitinib and vorinostat leading to highly potent inhibitors ofJAK2 and histone deacetylase 6 (HDAC6). Acetylated histone and non-histone proteins are pharmacologic targets for both solid and hematological cancers including myeloproliferative neoplasms (MPNs), a group of clonal hematological malignancies driven by aberrant JAK2/STAT signaling. MPNs are characterized by epigenetic alterations, including aberrant acetylation, which makes this disease particularly interesting for targeting with HDAC inhibitors (Sharma et al., 2019). Making the paper extremely important for us to understand the how this small molecule “ruxolitinib” can be effective as a drug.

*II. Summary*

Current cancer treatment ordinarily requires mixes of more than one medication in carefully designed dosing regimens. Despite good progress with this methodology in numerous sickness signs a solid need for better therapies actually exists for example in drug resistant disease. Where a medication is controlled along with a second operator careful scheduling is normally needed to streamline viability with satisfactory toxicity. However, it is resource intensive and time consuming to identify the best doses and schedules and minimizing problems such as drug-drug interactions. Another approach to achieving multi-target inhibition, which may alleviate some of the problems associated with combination therapy, is to design molecules capable of selectively inhibiting multiple targets. The so called ‘multi-component ligand’ requires judicious choice of biological targets known to be important when inhibition is combined in disease pathways while having complimentary pharmacophores to enable design of a single molecule able to bind both targets. Combination inhibition of JAKs and HDACs could provide multiple blockage of the JAK-STAT pathway (et al., 2018). In this paper they focus their studies on new combination molecules based on the smaller JAK1/2 inhibitor ruxolitinib. Known SAR of reference compounds ruxolitinib and vorinostat indicates solvent exposed areas of each inhibitor which can be used to as connection points for combination compounds. Preservation of key hydrogen bonding groups ensures important binding interactions are maintained at each target. From different combination molecules we find clearly the pyrazole substituent is a very influential tuning point for potency and selectivity. Continuing the investigation, they explored even larger substituents. Phenoxypropy experienced a drop in JAK2 potency and when the carbon chain was extended no significant change in the data was seen for either target enzyme. This could reflect the ability of long flexible pyrazole side chains to adopt a conformation toward solvent. Finally, methylsulfone also had single digit nanomolar potency for JAK2and HDAC6 but with less selectivity over HDAC1. They next evaluated selected compounds for their ability to inhibit proliferation in a panel of 4 solid tumor cells lines including breast, colorectal, and prostate cancer. Of the new compounds, the most potent enzyme inhibitor, pyrazole substituent, was also the most potent in each of the cell lines. This activity is most likely reflecting the potent HDAC activity of pyrazole substituent version.

In conclusion, this preliminary work describes small molecules with highly potent sub-nanomolar inhibition of two different enzyme classes, exemplified by JAK2 and HDAC6, both strongly implicated in serious diseases such as cancer and immuno-inflammatory diseases (et al., 2018).

*IV. References*

1. Leukemia. (2020, September 30). Retrieved October 04, 2020, from https://en.wikipedia.org/wiki/Leukemia
2. Sharma, V., Yue, L., Horvat, N., Christodoulidou, A., Akuffo, A., Beatty, M., . . . Epling-Burnette, P. (2019, November 13). Selective Targeting of Histone Deacetylase 11 Disables Metabolism of Myeloproliferative Neoplasms. Retrieved October 04, 2020, from <https://ashpublications.org/blood/article/134/Supplement_1/474/426424/Selective-Targeting-of-Histone-Deacetylase-11>
3. L., MurugappanRamanujuluab, P., Poulsenc, A., Ohlsond, S., & W.Dymocka, B. (2018, June 19). Merging of ruxolitinib and vorinostat leads to highly potent inhibitors of JAK2 and histone deacetylase 6 (HDAC6). Retrieved October 04, 2020, from https://reader.elsevier.com/reader/sd/pii/S0960894X18305250?token=30F64762728FBA4EEBB5B2397C2C6ED9F6A38E7945A189EC1A22230A2D59EDEC41D37F2B19F6F910065483417448BDBF