PI: Asfar Azmi

Funding Source: SKY Foundation (funds received on June 9th 2019)

In the last report we mentioned that (a) we are working on a combination therapy involving PAK4-NAMPT dual inhibitor in pancreatic neuroendocrine tumors and (b) we secured a grant from National Cancer Institute and National Institute of Health.

Progress: Substantial amount of new and clinically relevant data was generated using SKY foundation Inc. funds. We published several articles and acknowledged SKY Foundations Inc. in these papers.

Detailed report: I would like to thank the SKY Foundation for generously supporting my research on the p21 activated kinase 4 (PAK4) and Nicotinamide Phosphoribosyltransferase (NAMPT) dual inhibitors. We used the funds to work aggressively over the last several months on this project. COVID-19 did stop our work for few months. However, we resumed the experiments with additional zeal once our laboratories were allowed to function. New data in animal tumor models was obtained. See below.

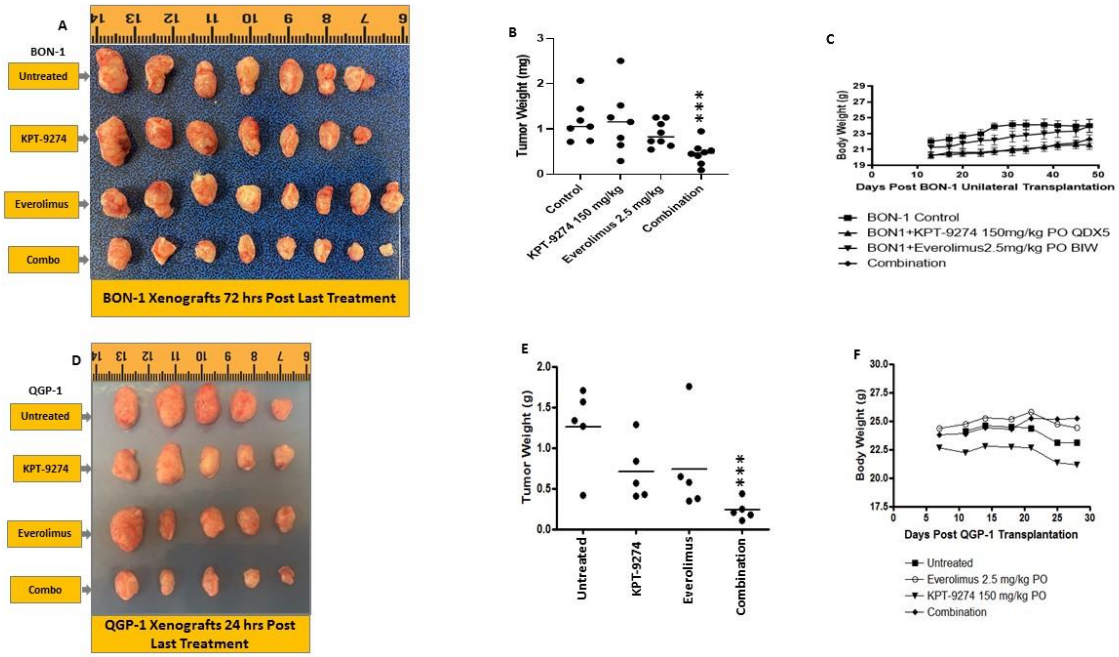

Figure 1: KPT-9274-everolimus attenuates BON-1 and QGP-1 growth *in vivo*. BON-1 and QGP-1 cells were grown as subcutaneous xenografts in ICR-SCID mice. **[A, and D]** Gross visualization of excised tumors. **[B, and E]** Graphical representation of tumor weight post-treatment. **[C, and F]** Animal body weight at the indicated days during the treatment. Five mice per group were used in the QGP-1 experiment and eight mice per group were used in the BON-1 experiment. Treatment in the BON-1 experiment was extended to 12 weeks to track eventual toxicity. **[A]** In the control group, one mouse developed malocclusion and was euthanized; in the KPT-9274 single-agent group, one mouse did not develop tumors. (*** representing $p<0.05$).

We Showed one combination study last year (lower panel of the above figure). This year we tested the same combination in another cell line derived tumor xenograft (upper panel). As can be seen in the results of **Figure 1**, KPT-9274-everolimus treatment led to superior inhibition of tumor growth in PNET xenograft. Additional mechanistic work was done to understand the mechanism of synergy between these two drug. The clinical protocol was written and is under consideration for approval. We anticipate to initiate this clinical study in the second quarter of 2021.

More significantly, we have now been funded by National Institute of Health/National Cancer Institute on this project that already started in April 2020.

Title: A novel therapy for pancreatic neuroendocrine tumors

Project Period: 04/01/2020 - 03/31/2025

PI: AZMI, ASFAR SOHAIL (PD/PI)

Publications: The following publications came out of this study that cited SKY Foundation.

1. Mpilla GB, Philip PA, El-Rayes B, **Azmi AS**. Pancreatic neuroendocrine tumors: Therapeutic challenges and research limitations. World J Gastroenterol. 2020 Jul 28;26(28):4036-4054. PMID: 32821069
2. Sexton RE*, Mpilla G*, Kim S, Philip PA, Azmi AS. Ras and exosome signaling. Semin Cancer Biol. 2019 Feb;54:131-137. doi: 10.1016/j.semcancer.2019.02.004. Epub 2019 PMID: 30769101
3. Nagasaka M, Li Y, Sukari A, Ou SI, Al-Hallak MN, **Azmi AS.** KRAS G12C Game of Thrones, which direct KRAS inhibitor will claim the iron throne? Cancer Treat Rev. 2020;84:101974. PMID: 32014824 (Tweeted 17 times and discussed as a hot paper by ASCO Monthly Blog)

The research article with data has been written and currently undergoing editing. We will submit this research article in one week.

Budget status and closure: The entire budget has been used up. We thank the SKY Foundation for helping us by providing seed funds that have helped us secure a 5 year grant.