1. Any significant change or updates since we last spoke?

Lots of updates since we last spoke!

- We have received investment and got acceptance into UC Berkeley SkyDeck – which has an acceptance rate of less than 1.5%. We now spend a lot of time in the west coast as well, building relationships, expanding our network and initiating conversations with potential investors.
- We have generated new in vitro CIPN and CMT model data that shows disease-modification capability of our lead molecule, and superiority compared to current competitor molecules.
- We have conducted neurotoxicity studies in primary rat DRG neurons, where we showed no sign of neurotoxicity – suggesting commendable safety for neuropathies like CIPN. We have also conducted side-by-side comparison with competitor compound, and demonstrated significant improvement from the competitor.
- We are in the processing of completing the onboarding of our scientific advisory board member Dr. Ahmet Hoke, Director of Neuromuscular Division, and Professor of Neurology and Neuroscience at Johns Hopkins School of Medicine. Dr. Hoke is a key figure in the neuropathy space, both as a clinician scientist, and also as an advisory member of prior biotech companies in similar disease space with successful exists.
- We are in early conversations with two large pharmaceutical companies who are interested in HDAC6 as a target for multiple diseases, and have shown interest in both our central-acting and peripheral-acting assets.
- We have hired 1 new FTE, 2 PTE interns and 2 PTE postdoc interns in the last 3 months.
- We have been working closely with Dr. Neal Muni, who has served over 20 years in senior roles across the entire life sciences value chain, most recently serving as the CEO of Azurity Pharmaceuticals. We are in the process of onboarding him as an independent board member.
- Our CEO, Nabanita Nawar, got selected as a delegate for the Second Canadian Women-only Business Mission to Japan, organized by the Government of Canada, and Asia Pacific Foundation of Canada in Dec 2022. She represented HDAX Therapeutics in Japan, and held numerous meetings with investors (such as Shinsei Capital Partners), CROs, KOLs to expand the internationalization journey of HDAX Tx into Japan.
- HDAX Tx was selected to present at the 2023 Biotech Seed Showcase at JP Morgan in San Francisco, where we engaged with 5+ potential investors and built relationships with KOLs (Dr. Dawn Bell https://www.dawnbell.com/, Micheal Tippie https://alignmentventures.com/, Colin Foster, Ex-CEO, Bayer).
- HDAX Tx was selected as one of the five University of Toronto spinouts for a business mission to Israel in November 2022. This incredible opportunity allowed us to explore the growing biotech ecosystem in Jerusalem and Tel Aviv, and engage with biotech investors in Israel. https://www.linkedin.com/posts/utestuoft_utest-founders-dreaming-big-making-connections-activity-6998631753514987520--abL?utm_source=share&utm_medium=member_desktop

2. "They have started with HDAC6, whose knock-down also increased the lifespan of animal models in **recent literature**" -- can you please provide a citation for this?

The following key publication discusses the draggability of HDAC6 as experiments revealed that mice lacking HDAC6 are viable, fertile, and can develop normally. Moreover, it also shows that tubulin hyper acetylation is not detrimental to normal mammalian development. https://pubmed.ncbi.nlm.nih.gov/18180281/
Additionally Takeda Pharmaceuticals has demonstrated the safety of HDAC6-targetting via generation of HDAC6-knockout mice where no significant changes in body weights, development, and abnormality in behavior were observed.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8322070/

3. I did not find anything in mice, except for this paper, which actually claims that inhibiting HDAC6 is bad for fertility: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5413599/
The article goes on to link HDAC6 to DDR, implying a detrimental effect of HDAC6 inhibition. Papers from other authors also confirm a link with DDR, in cancer, but rather finding that higher HDAC6 actually helps cancer cells and lower HDAC6 makes them more vulnerable to therapy. For example: https://academic.oup.com/nar/article/44/21/10017/2282822
But what about healthy cells? Has the team an insight on HDAC6-DDR biology?

We had a look at the papers that were cited within the aforementioned paper that discussed DDR from HDAC6 inhibition. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5413599/. Unfortunately the compounds used were not actually HDAC6-selective, which was only understood in the last 3 years https://pubmed.ncbi.nlm.nih.gov/30964290/. In fact, several of the paper before 2017 have used supposed "HDAC6-selective" inhibitors, but further research in the last 5 years has highlighted that those tool compounds and drug candidates were indeed having off-target inhibition that made true interrogation of sole HDAC6 inhibition very difficult/impossible.

We have conducted genotoxicity experiments (Ames fluctuation test), to assess our compounds' ability to manipulate DNA, and have been able to show no mutagenicity concerns. We have tested our compounds for neurotoxicity, cytotoxicity and tolerability in healthy cells, primary rat DRG neurons, and in mice models- none of which showed any concerns. Upon reaching clinical candidate nomination, we aim to conduct reproductive toxicity assays to further establish the safety profile of our compound.

Unlike the other 10 HDAC protein isoforms, HDAC6 is a strictly cytoplasmic lysine deacetylase and not an epigenetic modifier (not a *histone* deacetylase!). Since its substrates are alpha-tubulin, Miro1 and cortactin, newer research (in the past 5-7 years) have shown that it is not an anti-cancer target. Its functions are primarily related to cytoskeleton, cell mobility, microtubule stabilization and misfolded protein clearance. See this recent review that clarifies a lot of the misconceptions from past literature: https://pubs.acs.org/doi/full/10.1021/acs.jmedchem.0c00830

4. I understand that the plan is to go first for CMT and test in a mice model of the disease. If this is the case and it's not confidential, I would write it and specify **which strain exactly**.

We have selected chemotherapy-induced peripheral neuropathy (CIPN) as our lead indication. We aim to show POC/efficacy in humans for CIPN, and then expand towards other neuropathies such as CMT. After deep indication evaluation, discussions with multiple KOLs in the space and discussions with big pharma, we recognize that CMT is a slow progressive disease which would make POC in humans more time- and cost-intensive in

contrast to CIPN. We have newly generated CMT data in human induced pluripotent stem cell (hiPSC)-based models of CMT2D bearing mutations in GARS1 showing that our compounds have efficacy in this model, and also demonstrated improved effects in contrast to competitor molecules. More biological investigation is required to finalize the type of CMT where HDAC6 inhibition would be the most beneficial. As we advance and prioritize our development towards CIPN, we will continue to engage experts to pursue CMT as a secondary/follow-on indication. This is in line with the development plans that potential big pharma partners have brought up.

5. "What challenges have they faced so far in securing funding for their validation studies/company?"

An overarching challenge we face is the current funding landscape. Biotech investment for preclinical stage therapeutics companies are at an all-time low. We have been extending our runway with a range of non-dilutive funding to reach our milestones without giving up considerable equity and also establishing collaboration with academic investigators. We have been benefiting from tax incentives and R&D credits from the Canadian government, which has allowed to extend our pre-seed runway.