An Interview with Jiahao Chen

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1. What is the most important take-home message readers should get from your work?

7. What is the best piece of advice you could offer trainees interested in establishing a successful research career?

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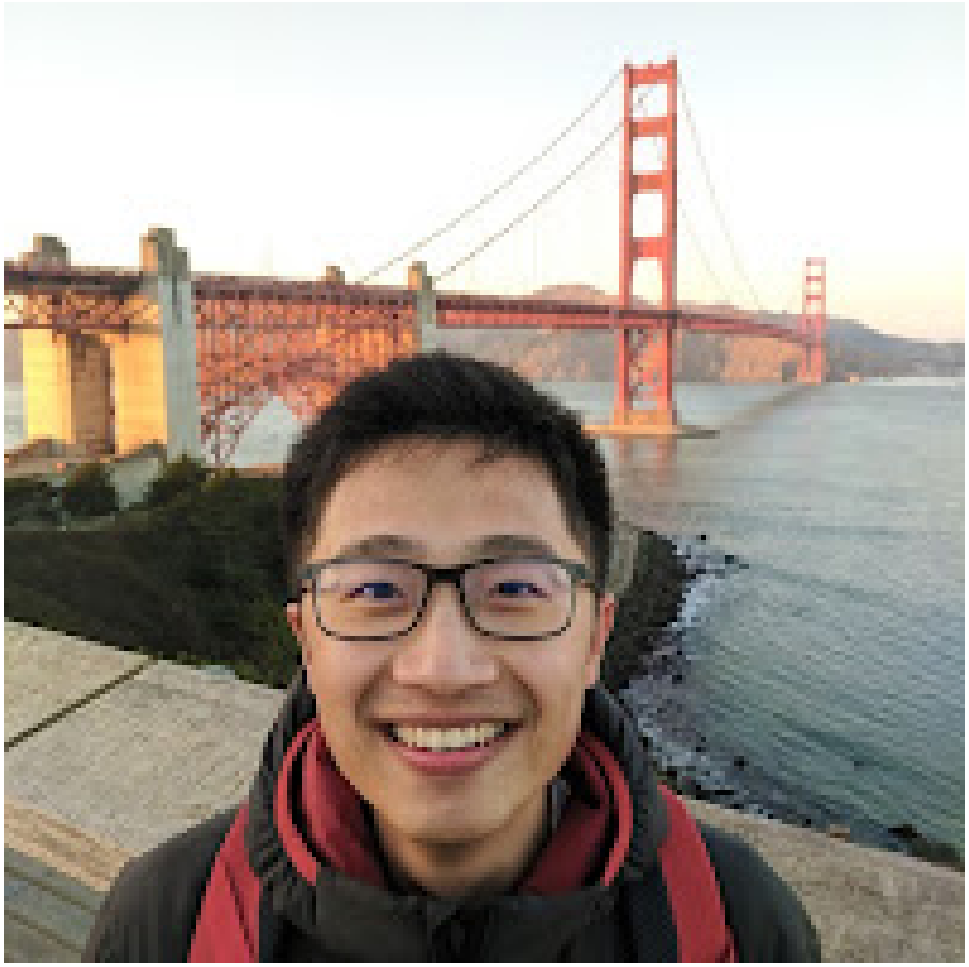

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A widely known fact is that patients diagnosed with myelodysplastic syndrome (MDS) are at a significantly increased risk for developing subsequent acute myeloid leukemia (AML). However, how these clinical entities are related at a clonal level has not been well elucidated, let alone studied at the single-cell-level in comparing stem and blast cell populations from the same individual over time. At last year's ISEH 2018 meeting in Los Angeles, I met Jiahao Chen, the first author of a recently published paper from Dr. Ulrich Steidl's lab at Albert Einstein College of Medicine who addressed these knowledge gaps (Chen et al. 2019). Here are answers to a few follow-up questions about his work that was first reported at the annual meeting.

I would say that the most important message from our work comes from our demonstration that stem cells within MDS and AML have a much higher level of clonal heterogeneity than their corresponding blast cells. Secondly, we found that somatic mutations present in rare MDS stem cell subclones, but not detectable in MDS blasts, gained significant

representation in the subsequent AML profile in 3 out of the 7 patients with MDS who had later progressed to secondary AML, which points to these rare MDS stem cell clones having a potentially critical role in the progression this disease. Importantly, our work here provides a rationale for using targeted genetic screening approaches in MDS stem cells to ultimately guide and help better design therapeutic approaches for patients in the future.

2. What do you think are some of the evolutionary pressures that may be driving these complex clonal and subclonal patterns?

While our finding that MDS stem cells have a complex clonal architecture aligns with other recent studies showing that the number of clones in normal hematopoietic cells – including stem and progenitor cells – is increased in adulthood overall (Lee-Six et al., 2018; Liggett et al., 2018), it was interesting for us to find in our work that mutation analysis of both MDS and AML stem cells revealed an association with aging as well as DNA damage repair related signatures. This may indicate that both processes may play an important role in driving these patterns (at least for the mutational acquisition process) seen during clonal evolution and if so, could warrant further study to determine what exact mechanisms drive clonal selection and MDS progression into AML. It is still unclear what the exact role of the mutations in subclonal competition and cancer initiation and progression are, and what roles non-genomic mechanisms and also likely cell-extrinsic factors play in these processes.

3. What are your thoughts on emerging data that suggest drivers of clonal hematopoiesis may not be present in therapy-related AML (i.e. Kartal-Kaess et al. 2018)?

The data surrounding the PPM1D mutation has been interesting for us to follow as it provides a focused example of a type of mutated clone found in both clonal hematopoiesis and MDS, that when exposed to chemotherapy, develops a competitive advantage relative to other cellular counterparts. However, whether or not this mutation directly contributes to the progression of MDS to AML remains to be determined. Although our own study sample size here is significantly smaller than related previous work, we did not find a PPM1D mutation in our paired MDS-AML samples.

4. What is the most interesting question and/or next step this work raises for future studies?

I think it will be very interesting to investigate the clonal architecture of HSCs in aged individuals - HSCs in clonal hematopoiesis cases that eventually progressed to hematological malignancies versus those cases that didn't progress. In addition, it will be promising to study the potential mechanisms that drive the very dramatic clonal dynamics in some patients and to determine whether these findings are due to the identified mutations themselves, or if alterations at other levels of regulation (e.g. transcriptional, epigenetic, and

cellular extrinsic factors, etc.) are responsible for such phenomena.

5. What was the most challenging aspect to overcome during this work?

Our work here was made possible by acquiring paired MDS and AML samples from patients – this aspect was made possible through a very close collaboration with Dr. Amit Verma, who has been able to establish a sample bank storing precious longitudinal samples of MDS and AML patients. Apart from having these samples, I spent a lot of time troubleshooting and optimizing protocols for sequencing preparations from very few cells in ways that ensured we could uphold several quality indices that included good DNA quality, verifying unbiased amplification steps that would not distort mutation frequencies, and to then apply these steps at the single cell level and with the very high recovery rate necessary for this project.

6. How did you celebrate when the paper was accepted for publication?

I was writing my PhD thesis and preparing for my defense when we received notification of the paper's acceptance, so while we didn't do much to celebrate then, it was great news for sure! After my thesis defense, we had a combined celebration and I received a really nice poster display of this story as a gift from my lab mates to commemorate this achievement.

I would encourage trainees to realize and explore different labs/research areas if they're not yet sure of what they want to do – rotate in different labs, figure out if they really want to pursue a PhD (it's not an easy path, especially if you don't like what you're doing in the lab!), and then find projects that you're really interested in and/or excited about that will keep you going. Talk to senior students and post-docs to get some idea of what to expect in the following 3-5 years and learn a variety of techniques well. Your relatively "undifferentiated" status at these stages can be an advantage to being able to train in various directions!