mission bio

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RESEARCHER SPOTLIGHT

Catherine Smith, MD

UCSF

Dr. Catherine Smith is a physician-scientist and an Assistant Professor in the Department of Medicine at UCSF. Her lab in the Division of Hematology/Oncology is focused on a subtype of AML (acute myeloid leukemia) characterized by mutations in FLT3, a gene that is mutated in a large proportion of AML cases. Her translational approach to AML research, utilizing samples from patients enrolled in clinical trials, yields information on how tumors adapt to the selective pressure of therapy and enables her lab to devise ways to circumvent and forestall these adaptations for improved patient outcomes.

Beyond Bulk Sequencing: Single-Cell DNA Analysis in Cancer Research and the Potential of Dynamic Therapy

We recently had an opportunity to speak with Dr. Smith about her research, her use of the Tapestri™ Platform, and her thoughts on the clinical potential for routine, high-throughput single-cell DNA analysis.

Q: What can you tell us about your research approach to AML?

Catherine Smith, MD (CS): My background is in targeted therapeutics. I believe that by using non-cytotoxic, targeted therapies, we can treat cancer more effectively and with less toxicity. The challenge is, we don't actually understand which mutations are real drivers of a cancer versus ones that are just passengers or contributors. What my research program hopes to answer is, which genetic lesions are true genetic drivers of leukemia, and how best to target those driver lesions to produce the best outcome for the patient.

Q: What is the role of single-cell DNA sequencing in your research?

CS: From previous genomic studies, we know that secondary mutations that occur in FLT3 or in off-target genes are major mechanisms of resistance that arise in patients. But we also know that with individual patients, these mechanisms are highly polyclonal. Single-cell DNA sequencing allows us to research the co-occurrences of these mutations and determine what combination of mutations could potentially be mediating a resistance mechanism.

Q: How has the Tapestri Platform contributed to your research?

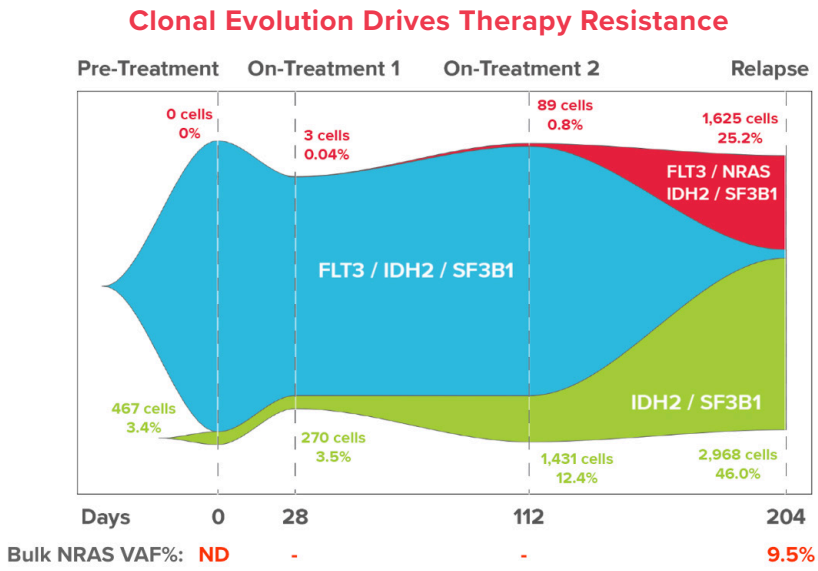
CS: In collaborative work with my colleague at the University of Pennsylvania, Dr. Alexander Perl, we discovered that RAS mutations were a common mechanism of resistance to the FLT3 inhibitor Gilteritinib. The Tapestri Platform has enabled us to determine that those RAS mutations co-occur in the same cells as the FLT3 mutations and establish that as a mechanism of resistance in patients who relapse on Gilteritinib.

This finding has huge implications clinically because it means that we might actually predict resistance mechanisms prior to overt relapse, and prevent relapse, with the appropriate targeted therapy. We could add that therapy as soon as we saw the mutation occurring at a low level.

Q: What do you see in the future for routine single-cell DNA analysis?

CS: In the study that showed us co-occurrence of RAS and FLT3 mutations, we were also able to show that in some cases, the RAS mutation pre-existed treatment. This is something we had not been able to see in bulk sequencing data. In addition to allowing us to start effective, targeted therapy earlier, this high level of sensitivity, and the ability to resolve clonal composition, could represent a tractable way to assess minimal residual disease.

Cancer is "smart" and it is continually adapting to treatment. Cancers are also genetically heterogeneous and there are different clones at any time that could be driving the cancer population. Single-cell DNA analysis allows us to actually observe the clonal composition of cancer, instead of guessing at it. This opens up the possibility of being able to make dynamic changes in treatment. As we see the clonal composition of the cancer change, we can change our therapy and potentially allow the patient to have the most effective therapy at any given point in time.



Single-cell DNA analysis can inform dynamic therapy

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