Our Cellarity platform has a single purpose: **creating transformative medicines for patients.** This example illustrates how we used our platform to design a differentiated drug candidate to treat sickle cell disease and provide new hope to patients.

Sickle cell disease (SCD) is a devastating inherited blood disease affecting over 5M patients globally. SCD is the most common inherited blood disease and manifests with systemic complications and shortened lifespan. A mutation in the β-globin gene leads to a shape change in red blood cells when oxygen levels are low resulting in rupture of these cells (hemolysis), anemia, and blockage of small blood vessels. The blockage of small blood vessels causes ischemic damage to all organs including spleen, liver, kidneys, heart, lungs and brain and leads to excruciating pain crises called vaso-occlusive crises (VOCs).

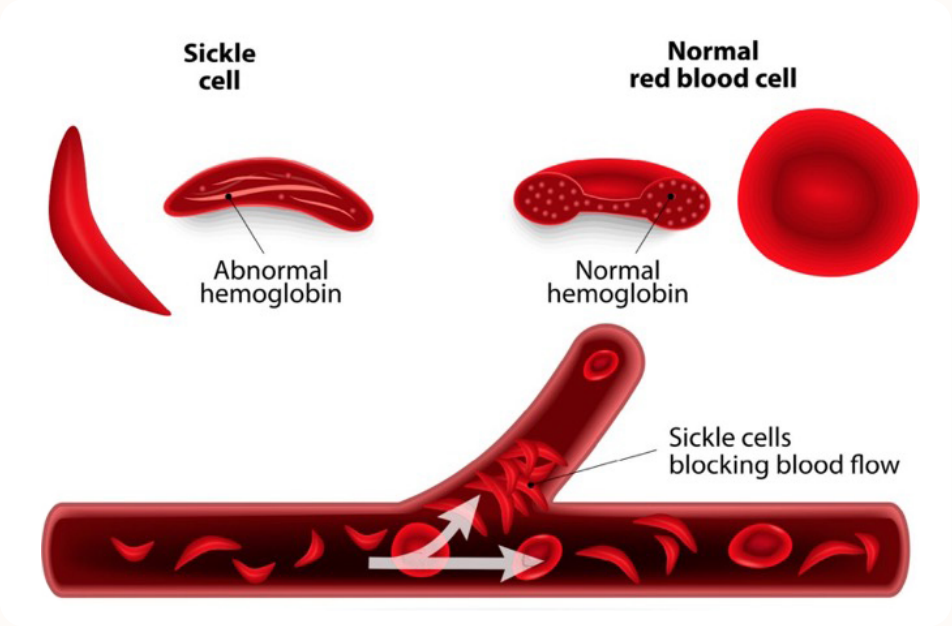


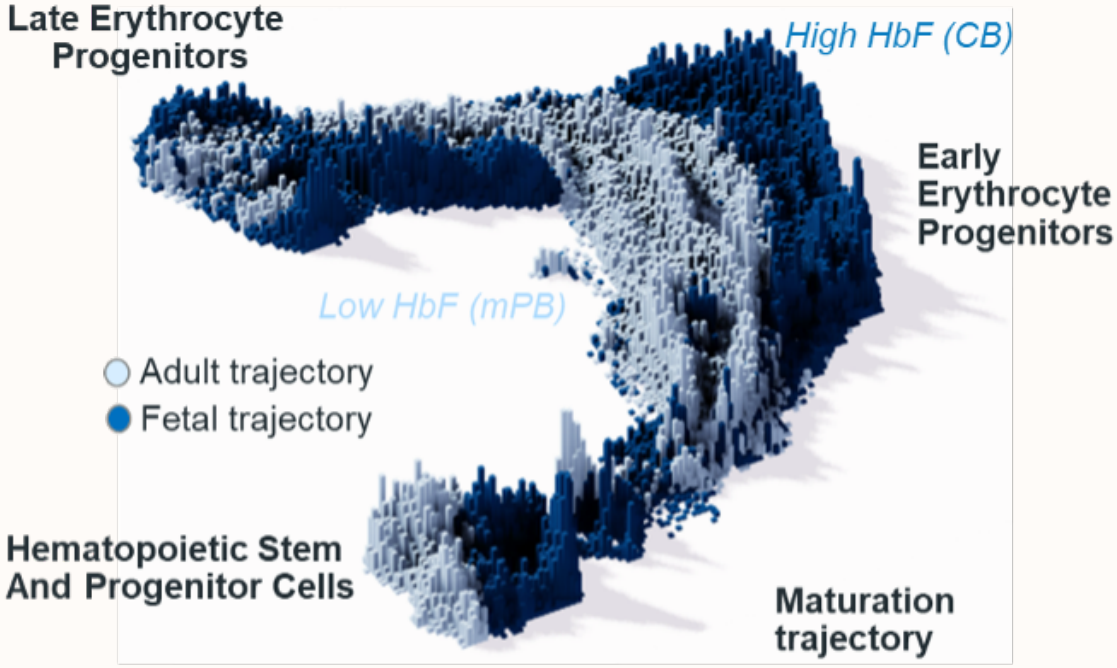
Image source: Georgia Research Alliance (www.gra.org)

If a patient with SCD makes enough fetal hemoglobin (HbF) - genetically or through a therapy - they have fewer or no SCD complications. Cellarity is aiming to address SCD complications with an oral therapy to drive sufficient HbF to minimize or eliminate further damage and complications of the disease and transform patients' lives.

While any increase in HbF is beneficial for patients with SCD, many hematologists aim for 20-30% HbF to fully protect from the disease. Even 8.6% HbF has been shown to improve mortality in SCD.[1] Hydroxyurea can move patients to ~15%[2] but individual patient responses vary and dosing is limited by toxicity causing low white blood cell counts and risks of infection.

As Hbf is validated by human genetics as a therapeutic approach in sickle cell disease, there are two primary questions for therapies: how much HbF can you induce and how safely can your mechanism of action increase HbF. HbF increase is the mechanism of action of Casgevy and hydroxyurea. Our goal is to mimic the gene switching mechanism of BCL11A knockdown, but without the complexity, cost and risks to patients including infertility and potential malignancy. We have found a novel approach to induce high levels of HbF without the dose-limiting neutropenia of hydroxyurea and other therapies that induce HbF as a side effect of their bone marrow toxicity.

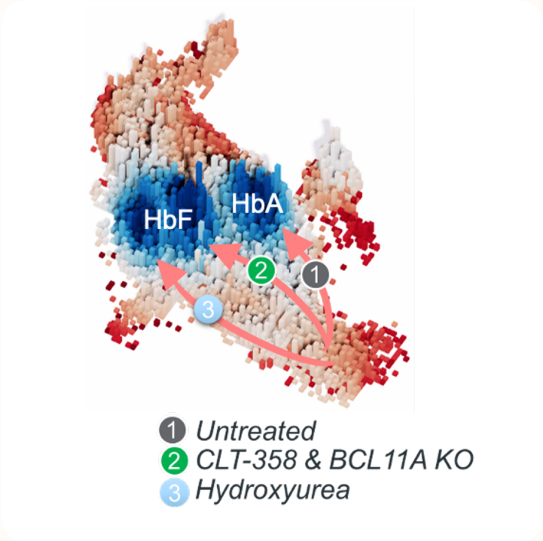
How Cellarity approached HbF induction in SCD

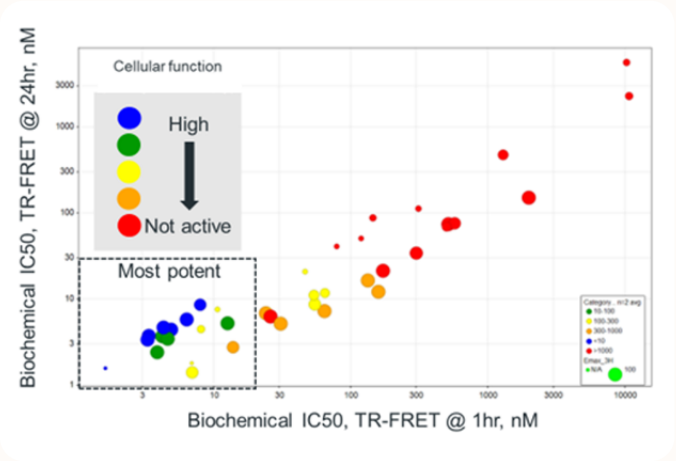


At Cellarity we set out to discover a novel compound to induce high levels of HbF safely. Many drugs (including hydroxyurea) induce HbF as a side effect of their cytotoxicity. We took a different approach than traditional phenotypic screening to achieve a differentiated safety profile to avoid this dose-limiting cytotoxicity. Guided by single cell transcriptomics, we applied our Intervention Library to find novel chemical matter that increased HbF production by influencing erythroid differentiation favoring a fetal transcriptional signature that included an increase in HbF.

Our predicted compounds were then validated in an *in vitro* human hematopoietic stem cell differentiation experiment. By applying our platform during stem cell differentiation, we were more likely to predict compounds involved in a high potency globin switching mechanism of action. One example of these validated compounds in CLT-358.

As we further studied our predicted compounds transcriptionally, we characterized two distinct pathways to increasing HbF. CLT-358 mimics the globin-switching mechanism of action of BCL11A gene-editing and is distinct from cytotoxic approaches like hydroxyurea. We are hopeful to avoid dose-limiting cytotoxicity, supported by both in vitro and in vivo data that CLT-358 does not impair hematopoietic differentiation or proliferation. As we worked to elucidate this biology, we uncovered a novel target responsible for potent induction of HbF. This is an example of how our target-agnostic approach to drug discovery may derive a specific pharmacologic target though exploration of novel biologic insights.





Our lead optimization campaign has progressed efficiently and has generated several potent binders which are cell permeable and affect downstream biology of our novel target. These compounds not only bind potently (nanomolar range in TR-FRET @ 1h on x-axis), they stay bound at 24h (y-axis). Our most potent compounds also demonstrate our highest cellular function, a composite readout of cell permability, binding and influence on downstream biology.

Our lead compounds do not have hematopoietic cytotoxicity or genotoxicity in *in vitro* experiments. Further, our mechanism of action does not have risk of oncogenesis or teratogenicity. We are rapidly progressing our lead compound into IND-enabling studies and to clinic, aiming to submit our first IND early in 2025.

We have presented our latest data at the J.P. Morgan Healthcare Conference in January 2024 and are planning to present these data at an upcoming medical conference. We plan to include these exciting data here after that presentation and/or publication.

REFERENCES:
1. Platt OS, et al. N Engl J Med. 1994; 330:1639-1644.
2. Charache S, et al. Blood. 1992; 79(10):2555-65.