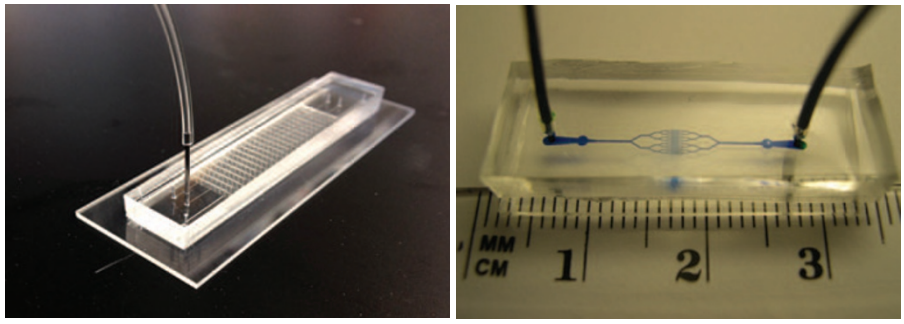
# Microfluidic chips promise better diagnosis for sickle cell disease




John Higgins, Massachusetts General Hospital (left), Wilbur Lam, Emory University School of Medicine (right)

**Blood brothers:** Microfluidic chips from the Boston (left) and Atlanta (right) teams.

As part of routine newborn screening programs, babies are checked for signs of the debilitating blood disease sickle cell anemia. Existing blood tests can accurately diagnose the disease by checking for the hallmark crescent shape of the red blood cells. But they cannot reliably predict how severe an individual's illness will be, which makes it hard for doctors to identify which infants will benefit most from early and intensive therapies and which ones can forego unnecessary treatment and expect to be relatively healthy despite their genetic condition.

"Everyone who has this disease has exactly the same genotype, but the range of clinical phenotypes is huge," explains David Wood, a bioengineer at the Massachusetts Institute of Technology in Cambridge. "Right now, there are no molecular markers to warn a physician where on that spectrum he can expect a patient to fall."

A new generation of microfluidic chips promises to change that. Two independent research groups have created experimental devices that, by measuring the flow of blood through tiny tubes thinner than the width of a human hair, can predict the likelihood of clot formation, a dangerous complication of sickle cell disease.

In one design, reported on 29 February in *Science Translational Medicine* (**4**, 123ra26, 2012), Wood, together with colleagues at Harvard University in Cambridge, Massachusetts, measured blood flow after suddenly depleting oxygen in the chip. Studying blood samples from 29 people with sickle cell disease, they found that individuals with more severe disease symptoms, as measured by the number of medical interventions required over the course of a year, typically had slower blood flow under low oxygen levels. In other words, sluggish blood predicted doctor visits.

"Microfluidic devices are good tools for discovering biomarkers for sickle cell disease, in part because the diseased cells have such a distinct morphology that affects how the blood flows or clots," notes Aaron Wheeler, a microfluidics expert at the University of Toronto who was not involved in developing the new systems.

## A waning crescent

The other new setup, designed by Wilbur Lam, a hematologist and bioengineer at the Emory University School of Medicine in Atlanta, and his colleagues, features channels lined with the same kind of endothelial cells that make up the walls of blood vessels. "To make an ideal model of small blood vessels, we wanted to recreate the blood vessel environment as closely as possible," says Lam. Reporting in the January issue of the *Journal of Clinical Investigation* (**122**, 408–418, 2012), Lam's team showed that this 'microvasculature-on-a-chip' model could be used to study blood dynamics in samples taken from people with sickle cell disease and another blood disorder called hemolytic uremic syndrome. "The next step is to gather clinical samples and see whether our flow data correlates to anything clinically relevant," he says.

Microfluidic devices could also have utility as a drug discovery platform. For example, Lam and his colleagues used their chip to show how a chemotherapy agent called hydroxyurea helps prevent many of the complications of sickle cell disease. Meanwhile, Wood's group plans to use its system to screen potential treatments for the illness under the assumption that the same flow metrics that predict disease severity should also predict response to drug therapy.

Notably, drug companies have begun to express interest in the devices, says Antigoni Alexandrou, a bioengineer at the École Polytechnique near Paris. Two years ago, Alexandrou and his colleagues reported one of the first microfluidic chips for characterizing blood cell sickling (*Lab Chip* **10**, 2505–2512, 2010). His team hasn't published any clinical results using the system yet, but those data are coming soon. Then, he notes, "we expect the response to intensify as we obtain more tangible applications for sickle cell disease patients."

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molecule drugs can simply be tested for so-called 'bioequivalence'—basically that the active ingredients act the same way pharmacologically in the body as do the name brand drugs—generic versions of biologics, also known as biosimilars, are likely to require more extensive testing. Under the FDA's draft guidance for biosimilars released in February, the agency recommended that copycat biologics seeking approval pass a number of checkpoints to compare them to their branded versions, including *in vitro* functional assays, animal toxicity tests and human clinical trials. These extra hurdles are needed to ensure safe and effective medicines, experts say. But the increased development costs will inevitably be passed on to consumers, meaning that biosimilars will probably not save the healthcare system as much as their generic small-molecule counterparts.

Whether generic NBCDs will be held to the same standards as biosimilars is still up in the air—and experts who were at last month's meeting remain divided. "The important measure for complex drugs, whether they are biological or not, is clinical efficacy," says Huub Schellekens, a biostatistician at Utrecht University in the Netherlands who thinks that NBCDs should be classified as biologics whether they are generic or not.

But Beatriz Silva-Lima, a pharmacologist at Lisbon University in Portugal, says the real problem in evaluating NBCDs is the current lack of good laboratory tests. As such, she argues that better preclinical assays might be sufficient to evaluate the bioequivalency of generic NBCDs. "What we need are new ways—better ways—to test the pharmacokinetic interactions of complex drugs with their targets," she says.

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