Toward Better Cures for Kids With Acute Myeloid Leukemia

Soheil Meshinchi, MD, PhD, discusses developing personalized therapies for the deadliest childhood leukemia that have fewer side effects.

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Leukemias from both an adult and a child may look the same under a microscope. They may have the same name. But take a deeper look at the molecular engines that make them go, and it becomes clear that they're completely different diseases.

Understanding those distinctions, knows Dr. Soheil Meshinchi, is absolutely critical to giving patients the right treatment. The Fred Hutchinson Cancer Research Center physician-scientist has dedicated his career to developing better treatments for young people with the most deadly form of leukemia in childhood: acute myeloid leukemia.

To do this, he's led massive efforts to characterize the biology of this cancer in young patients and identify targeted new treatments that could save more lives and have fewer dangerous side effects. His vision: detailed molecular testing for each young patient with AML, followed by personalized therapy — followed by, ultimately, long and healthy lives.

This year, Meshinchi received two substantial new grants from private foundations to fund his work. We talked with him about his research and where he is on his quest.

This transcript has been edited for clarity and conciseness.

You've focused on defining unique biology of AML in children and young adults — why?

AML is really a disease of older adults, and the majority of AMLs are in 80-, 90-year-olds. Primarily because of that, all the discovery and all the therapeutic development has been in older adults — with the assumption that it's the same disease, and if you discover something and develop a therapeutic in an 80-year-old, it's simply a matter of using that information and that therapy in younger patients.

And I think that's flawed for multiple reasons. In fact, I really think that we are not treating younger patients appropriately, because we're simply using what really was intended to be used in our elderly patients. And the assumption that it's the same disease is really quite pervasive even

in the scientific community.

How have you approached this?

This is where our donor funding and family involvement became quite significant. This is part of what we called Target Pediatric AML, a philanthropically funded project. With donor resources we were able to sequence over 2,000 patients and really define the underlying biology and makeup of leukemia in younger patients. And showing that really, biologically, it is such a different disease, it's almost like comparing breast cancer to lung cancer.

This provided us an opportunity to really rethink AML. And the two grants that we're discussing are the result.

Let's talk about these new grant-funded projects. First, you have a project funded by a new grant from the American Cancer Society/St. Baldrick's Foundation to define better diagnostic and prognostic markers.

We are using the information that we have from Target Pediatric AML to determine, at the time of diagnosis, what is the likelihood that patients will respond [to treatment] vs. not, or that our patient will survive vs. not.

This grant brings together people with nonoverlapping expertise in data analysis. We have a group of folks who are entirely focused on merging the different platforms that we have [such as data on the patterns in patients' DNA and its cousin, RNA]. Now we're trying to merge all this data and integrate it so we can more robustly define outcomes.

Each of these platforms, they give us a ton of information. But we hope that by merging all of these we can come up with a single platform that outperforms anything else that exists right now.

What we are aiming to do — and what I think is a realistic goal — is at the time of diagnosis to be able to tell with high certainty that, for example, 40% of the patients are expected to have a survival of 90% and the remaining 60% are expected to have survival of 25-30% with conventional therapies. So that allows us to have a different approach, a different thinking about those patients who are high risk. It gives us an opportunity to escalate therapies for those that don't have a really good outcome.

Right now, one of our biggest problems, besides disease recurrence, is the fact that of AML patients who survive — who are potentially, theoretically cured — 20% develop clinically significant cardiac failure 15 to 20 years down the road. And that is a population we don't really take into consideration when we are treating them, because we're focused on preventing relapse. But if patients who are cured, 20 years down the road they need a cardiac transplant or they die — that is not our idea of cure.

What we hope is that with this information, we can modify therapy for the very high-risk patient, but also try to de-escalate therapy for those patients who have really good outcomes.

And then you have another new grant for a Specialized Center of Research from the Leukemia & Lymphoma Society. Tell us about this project.

This one uses that data to identify appropriate therapeutic targets in pediatric AML and then develop specific therapies. We're seeing targets forward with three different therapeutic modalities, with the plan that the best therapy will reach our patients. We set out to identify targets that are expressed [displayed] on AML cells but not expressed in normal hematopoiesis [blood/immune cell development]. So, theoretically, by delivering the therapy you're going after only leukemic cells and you're not even going to touch the normal cells.

Meshinchi described the immune-harnessing strategies his team is testing in the laboratory with this funding. One, led by Dr. Terry Fry of the University of Colorado, is testing a strategy called CAR T-cell therapy, in which an individual's own T cells, a type of immune cell, are genetically re-engineered with a molecule called a CAR to recognize and destroy leukemic cells that carry two telltale targets (since a healthy cell may have one or the other, but only leukemic cells have both). Another, overseen directly by Meshinchi and his colleague Dr. Colleen Delaney, does a similar thing, but with a different immune cell called natural killer cells that are grown out of donated umbilical cords and then re-engineered with the specialized CAR molecule. A third, led by Dr. Jim Olson of Fred Hutch, uses engineered molecules called BiTEs (for bispecific T-cell engagers) that act like high-tech double-sided tape to pull immune cells and cancer cells together.

This is more of a cooperative approach (rather than the traditional competitive process), that all three of us are pursuing the same targets, with three different modalities, with the idea that we will compare them side by side and with a plan to bring them into the clinic based on the efficacy that we see. That allows us to bring these therapies in as rapid a fashion as we possibly can.

I'm also spearheading a discovery project, in which we're continuing to evaluate new targets.

It's been 30 years or so, and children with AML have been treated mostly with the same chemotherapy. Do you feel optimistic that, after all that time, big improvements in treatment are coming?

I have never been more optimistic than I have been the last couple or three years, because we've been able to not only identify these targets in pediatric AML, we've been able to move them forward to the clinical end. Right now, we have two CAR-Ts that are poised, in a matter of months, to move into clinical space. So, yes, I'm highly, highly optimistic.

Neither of these two drugs are supported by drug companies; there is very little interest in developing anything in pediatric AML. One of the therapies is being developed for infants with very high-risk disease. And since this is a rare subset, there is virtually no interest by drug companies to support such an effort. This CAR is being developed by us as an academic institution with help from philanthropy. The second one, is a CAR T for mesothelin, a lung cancer target that is expressed in a third of AML.

Let's imagine that we fast-forward to 10 years from now: It's 2031, and there is a five-year-old

who's diagnosed with AML. Can you lead me through your vision for what would follow that child's diagnosis in treatment and outcomes?

The initial thing is making the appropriate diagnosis. A five-year-old with AML would go through a pretty thorough, well-defined diagnostic process. The critical piece is that child's marrow sample needs to be sequenced by all available modalities — RNA sequencing, DNA sequencing, making sure we know the mutation profiles, the fusion profiles [proteins that are inappropriately fused together as a result of genetic mutations].

Once we have that, then the patient would fall into two categories: low risk or high risk. If we say that you have a five-year-old whose survival is anticipated to be 80%, 90%, the approach will be substantially different. With conventional therapy we can manage them appropriately with good outcomes; we would create a path that would try to minimize toxicity. And this is where we would make a decision, whether you would require a blood stem cell transplant, or whether you require a particular targeted agent.

In the case the patient falls into the high-risk category, one thing we have learned is that blood stem cell transplant can be a great asset in managing these patients. The only problem is that we need to get them into a deeper remission before transplant. We need to do everything we can to optimize the response. … So then the question becomes, how do we approach these patients? Because we know with a standard approach, these patients' risk of relapse with the standard approach is extraordinarily high. So, then, can we interrogate and say, what are some of the targets that are expressed? If we said the patient expresses this antigen [target] on the cell surface, and we have this drug that can hit that, then theoretically we can prioritize that patient to get the drug that hits that target, for example. And that's the process for trying to get them into as deep of a remission as possible before we go to transplant.

And I'm hoping that we can get to a point where we can minimize the need for transplant more and more, because the toxicity of transplant is not trivial. We are actually at a point where we have started doing that. We've taken patients who have historically dismal outcomes, whose outcome now is substantially better. There is a group of patients who have a particular translocation [a large chunk of their genome moved somewhere else in the genome it doesn't belong] and Dr. Katherine Tarlock [a collaborator of Meshinchi's] looked at the outcome of those patients who were treated with conventional therapies 15 years ago and also at the outcomes of [recent] patients after targeted therapies and transplant. We've gone from survival of 20% to survival of 95%. So we can actually change the trajectory of that disease and outcome by how we treat these patients. The whole point is, we're not just saying, you have a high-risk disease and there's nothing we can do. The whole point is: You have high-risk disease, and we're going to quantify that for you. We're going to find out what it is that's making that leukemia tick. And we're going after that in a much more targeted fashion.

What role do donors play in your research and what do you think draws donors to support your work?

The role donors play is huge. Overall, there's a lot of funds allocated to cancer, but it's still an underfunded area. This becomes especially significant in pediatrics, and especially in pediatric AML, because it's such a rare subset of a more common disease. The funding from federal sources is in part limited because the thought is, why would anyone fund a project that looks at such a tiny fraction of AML? So, they say the funding should be directed toward a more common cancer. In fact, when I was applying for funding initially, without including adult studies, my funding would not have been approved. So I think, especially in pediatric AML, the private donor funding becomes critical.

In pediatric AML, the other limitation is that there's no interest from pharma. In adults, 60% of all research is supported by pharma. My colleagues in AML, their laboratories are sometimes entirely supported by pharmaceutical companies. That is lacking in pediatric cancer research. There is zero interest from pharma in developing therapies in children. In fact, regarding therapeutic development in childhood AML, if we don't do it, it won't get done. That's where foundation support and private support becomes absolutely critical, without their support, the research in pediatric AML and pediatric cancer in general would come to a standstill.

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