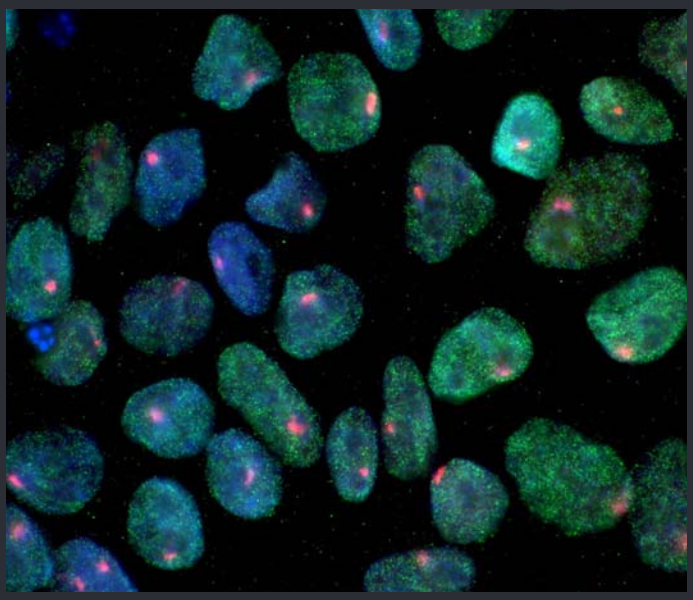

Left: Induced pluripotent stems cells (iPSC) derived from skin. Licensed from sciencesource.com.

DIVIDE AND CONQUER

Using iPSC stem cells to model two distinct phenotypes of X-ALD

BY KATHARINE H. HENDRIX

There is a saying that there are two ways to spend one's life—digging a lot of shallow wells in many areas, or digging a single deep well in one place. It can safely be said that **Inderjit Singh, Ph.D.**, a scientist specializing in neurodevelopmental and neurodegenerative disorders who serves as Scientific Director of the Charles P. Darby Research Institute at MUSC Children's Hospital, falls into the latter category. He has devoted over three decades to the study of X-adrenoleukodystrophy (X-ALD)—a genetically determined metabolic disorder depicted in the 1992 film *Lorenzo's Oil*. His persistence has paid off in the application of a novel research technique developed elsewhere[1] to the creation of much-needed diagnostic and therapeutic tools for this deadly disease.

X-ALD is a progressive, inherited disorder that primarily affects the adrenal cortex and nervous system white matter by promoting the accumulation of saturated, very-long-chain fatty acids in these tissues. Although the two primary ALD phenotypes are characterized by the same mutations in the *ABCD1* gene, their clinical course is quite distinct. The most common and aggressive type—fatal inflammatory childhood disorder (cALD)—presents in children younger than eight and leads to death by the age of twelve. A second, less aggressive variant—adrenomyeloneuropathy (AMN)—progresses more slowly, enabling many patients with this phenotype to survive into their fifties or sixties.

Thirty years ago, Singh was part of the team at Johns Hopkins that first described how peroxisome dysfunction—not mitochondrial dysfunction, which had been the prevailing theory—drives the impaired fatty acid metabolism seen in X-ALD.[2] Despite this leap forward, there was still no way to study each phenotype separately because there was no mouse or other model that could reproduce the two phenotypes.

Singh and his team, which includes **Mauhmad Baarine, Ph.D.**, and **Navjot Shah, Ph.D.**, recently overcame this barrier by harvesting skin cells from patients with the two disease types, reverse-engineering them to induce pluripotent stem cells (iPSC), and then re-differentiating those into neuronal cells. Using this method, Singh and his team identified differences in the two disease types not only by directly comparing neuronal cells but also by studying the differing epigenetic mechanisms triggered by excessive very-long-chain fatty acid accumulation.

Early results suggest that the load of very-long-chain fatty acids is higher in cALD and leads to an often lethal inflammatory response, whereas in AMN the lower load of very-long-chain fatty acids causes only oxidative insult.

"This is the first time we have been able to see the differences between two phenotypes of X-ALD," says Singh. "This could facilitate diagnosis early in childhood. We can predict which children will require more aggressive treatment."

Most exciting, this technique will allow researchers to develop and test potential mechanism-based agents to reduce fatty acid accumulation in human cells with the phenotype of interest, as they recently did for suberoylanilide hydroxamic acid.[3]

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