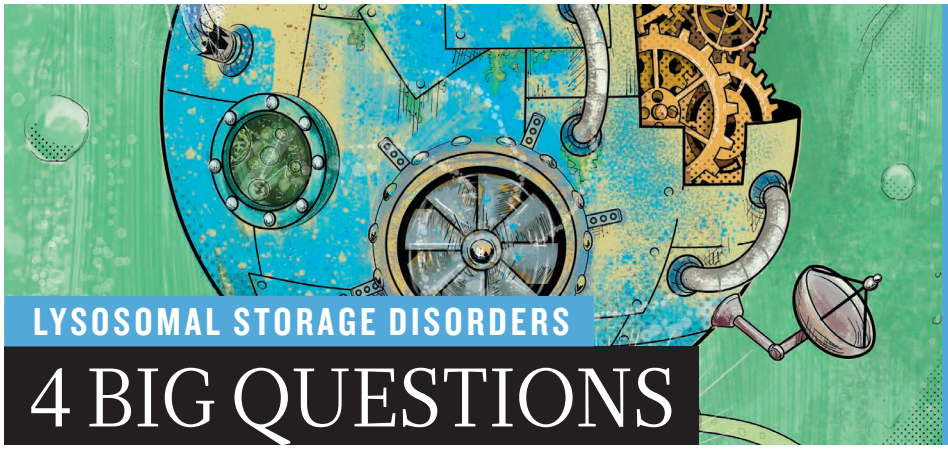
NIK SPENCER



LYSOSOMAL STORAGE DISORDERS

4 BIG QUESTIONS

The quest to understand lysosomal storage disorders (LSDs) has left researchers grappling with questions that have implications for other diseases too.

BY MICHAEL EISENSTEIN

	QUESTION	WHAT WE KNOW	WHY IT MATTERS	CURRENT STRATEGIES
1	***How can the neurological deficits associated with LSDs be treated?***	Many LSD therapies, especially enzyme replacements, which work well in many tissues of the body, either cannot cross the blood–brain barrier or fail to do so reliably.	Neurological deficits, including cognitive problems and loss of motor control, are among the most debilitating symptoms of many LSDs. Once neurological damage has occurred, it is extremely difficult to undo.	Small-molecule drugs are being developed to cross the blood–brain barrier, although none yet reliably reaches the brain. Gene therapies that directly target the central nervous system hold promise.
2	***What is the relationship between LSDs and other neurodegenerative diseases?***	The pathology of LSDs overlaps that of other brain disorders. Mutation in the *GBA* gene causes Gaucher's disease and is the main risk factor for Parkinson's. The brains of people with Niemann–Pick type C can exhibit hallmarks of Alzheimer's.	Common neurodegenerative conditions have so far proved resistant to most treatments. The cellular processes that malfunction in LSDs could offer new targets for the treatment of more complex diseases.	Data show that drugs that boost *GBA* activity could eliminate toxic aggregates of α-synuclein from Parkinsonian cells. Researchers are now exploring autophagy as a possible target to treat currently incurable neurological disorders.
3	***What is the lysosome's role as a mediator of cellular signalling?***	The lysosome is more than a mere 'recycling bin'. It actively communicates with the nucleus through an extensive gene network to coordinate a wide variety of metabolic functions.	Appreciating the interplay between lysosomes and the nucleus opens up research that could reveal insights into LSD pathology and more general cellular physiology.	Researchers are trying to understand all the effects of this lysosome-led metabolic regulation, including strong effects on ageing and longevity.
4	***How can the design of clinical trials be improved to accelerate drug development for ultra-rare LSDs?***	Designing clinical trials for the LSDs with the lowest incidence is difficult because disease pathology and natural history, which are normally required to devise clinical-trial endpoints, are poorly understood.	Many potentially fatal LSDs occur in fewer than 1 in 100,000 births. Without better clinical-trial endpoints, it is almost impossible to develop drugs for these conditions.	The US Food and Drug Administration has been flexible about endpoints — trials of Pfizer's taliglucerase alpha for Gaucher's disease used shrinkage of spleens and livers. But the process for biomarker approval is still poorly defined.

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