SPEAKER: In recent years, we have also become aware that it's not only the intracellular accumulation of Gb3 but that also accumulation of lyso-Gb3 both inside and outside the cells contributes to pathogenesis. So this is what takes place inside the podocyte. Podocytes, they accumulates this huge amount of Gb3 inside the lysosomes, and they try to get rid of the Gb3.

So lysosomes start degrading Gb3. However, they get stuck at the level of our secondary metabolites, which is lyso-Gb3. And lyso-Gb3 relates to a much higher level than Gb3. And it is more highly soluble, so it circulates in the circulation for free. And it is a soluble mediator of kidney injury in fabry disease. Indeed, when you expose normal podocytes to lyso-Gb3 levels found in the circulation in fabry patients, this elicits a podocyte stress response very similar to the podocyte stress response we find in cells exposed to high glucose levels.

So again, the analogy, Fabry nephropathy, diabetic nephropathy. Fabry nephropathy will have this soluble mediator, lyso-Gb3, which causes podocyte distress. Diabetic nephropathy will have the soluble mediator that causes podocyte distress, which is high glucose levels.

And both high glucose and lyso-Gb3 will induce the podocyte to secrete fibrogenic cytokines, such as T [INAUDIBLE] 1, secrete extracellular matrix giving rise to fibrosis, and secrete inflammatory mediators. So one target of therapy for fabry disease is to keep lyso-Gb3 levels as low as possible because we now know that independently from the presence of glycolipids inside cells, the presence outside of the cell of lyso-Gb3 will be injurious to cells and specifically to podocytes.