**A)** Pathogenesis of Fabry fibrosis

a) **Conventional view:** Fibrosis is a consequence of ischemic injury secondary to glycolipid accumulation inside endothelial cell lysosomes in the microvasculature

   **Therapeutic implication:** ERT clearance of endothelial deposits as sole approach

b) **Novel concepts:**
   1. accumulated glycolipids promote the release of secondary mediators of injury from target cells that include parenchymal cells
   2. ischemia promotes the release of secondary mediators of injury

   **Therapeutic implication:** a correct understanding of the molecular mechanisms involved may provide new add-on therapeutic approaches

**The conceptual framework**

<table>
<thead>
<tr>
<th>Accumulated metabolite</th>
<th>Target cells</th>
<th>Secondary mediators of injury</th>
<th>Consequences</th>
</tr>
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</table>

**Diabetic nephropathy**

- **Glucose**
  - Podocytes, tubular cells, endothelial cells...
  - Many, including TGFβ1, MIF/CD74, TNF...
  - Fibrosis, inflammation

**Fabry nephropathy**

- **Lyso-Gb3?**
  - Podocytes, VSMC, others?
  - TGFβ1, CD74?
  - Fibrosis, inflammation

New potential add-on therapeutic targets:
- Lyso-Gb3 receptor or lyso-Gb3-activated intracellular signaling pathways
- TGFβ1 receptor or intracellular signaling pathways

**B)**

- **ERT**
- **SRT**
- **Receptor blocker?**
- **Antiproteinuric therapy**
- **Mediator targeting**