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APPLICATION TO ACT AS SUPERVISOR AND  
RESEARCH PROJECT PROPOSAL

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**PROJECT**

**Supervisor:** Giulio Frontino  
**Title:** Exploring Diagnostic and Therapeutic Opportunities in  
Wolfram Syndrome's Audiological Manifestations  
**Curriculum:** Experimental and clinical medicine

Link to the personal page of  
the University or relevant  
hospital site website: <https://www.hsr.it/dottori/giulio-frontino>

**Description of the Project (max 3,000 characters including spaces)**

**Background/gap of knowledge**

Wolfram Syndrome (WS) is a rare, autosomal recessive, multisystemic neurodegenerative disorder caused by mutations in the WFS1 gene, and more rarely in CISD2<sup>1</sup>. These mutations lead to dysfunction of wolframin, an endoplasmic reticulum (ER) transmembrane protein involved in calcium homeostasis, ER stress regulation, and cellular survival, particularly in metabolically active tissues such as pancreatic  $\beta$ -cells, retinal ganglion cells, neurons, and cochlear structures<sup>2</sup>. The resulting progressive degeneration manifests clinically as early-onset diabetes mellitus, optic atrophy, sensorineural hearing loss (SNHL), and various neurological and urological complications.<sup>3-6</sup>

Audiological impairment is a major but underrecognized component of WS, affecting over 80% of patients. It often presents in childhood and progresses, contributing significantly to reduced communication abilities, learning challenges, and impaired quality of life. Despite its clinical burden, hearing loss in WS currently receives only supportive therapy, such as hearing aids or cochlear implants, with no disease-modifying options available. Moreover, audiological outcomes are rarely prioritized in clinical trials.<sup>7-9</sup>

**Rationale and hypothesis**

Given the high prevalence and early onset of hearing loss in WS, improving diagnostic accuracy and longitudinal monitoring is critical. Within our institution, significant clinical and research experience has already been established in managing diabetes and progressive vision loss due to optic atrophy in Wolfram Syndrome, with active follow-up and therapeutic studies underway.<sup>10</sup> However, hearing impairment remains a relatively unexplored area, despite its substantial impact on patients' communication abilities, learning, and quality of life. This project aims to extend our multidisciplinary expertise to the audiological domain, addressing a key but often overlooked aspect of WS. We hypothesize that focused clinical follow-up, combined with translational modeling using patient-derived iPSCs, will enable a deeper understanding of auditory dysfunction and support the development of targeted, potentially disease-modifying interventions—such as GLP-1 treatment and gene therapy.

**Objectives and specific aims**



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- To perform detailed audiological phenotyping and radiological follow-up in a cohort of pediatric and adult WS patients already enrolled at our center.
- To correlate hearing function with genetic data and treatment exposure (e.g., ongoing clinical trial with GLP-1 receptor agonists) to identify clinical markers of disease progression and potential therapeutic responses.
- To generate an in vitro inner ear model using patient-derived iPSCs and differentiate these into otic lineages, including sensory hair cells and supporting cells.
- To explore the feasibility of gene therapy in WS-related hearing loss, leveraging insights from successful AAV-based approaches in other hereditary deafness models.

**Expected outcomes**

The project is expected to:

- Enhance clinical management through improved hearing assessment protocols and genotype-phenotype correlations.
- Provide preliminary data on the effects of GLP-1 treatment on hearing loss progression.
- Establish a patient-specific iPSC-derived model of the inner ear as a platform for disease modeling and drug screening.
- Contribute to the conceptual groundwork for future gene therapy targeting WFS1-related SNHL.

**Skills that the student should acquire** (max. 600 characters including spaces):

The student will gain experience in clinical research methodology, audiological testing and interpretation, basic stem cell culture and differentiation techniques, data analysis, and translational research strategy in rare genetic diseases.

**References** (max. 15)

1. Amr S, Heisey C, Zhang M, et al. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. *Am J Hum Genet.* 2007;81:673-683. doi:10.1086/520961
2. Takei D, Ishihara H, Yamaguchi S, et al. WFS1 protein modulates the free Ca<sup>2+</sup> concentration in the endoplasmic reticulum. *FEBS Lett.* 2006;580:5635-5640. doi:10.1016/j.febslet.2006.09.007
3. Cremers CWRJ, Wijdeveld PGAB, Pinckers AJLG. Juvenile diabetes mellitus, optic atrophy, hearing loss, diabetes insipidus, atonia of the urinary tract and bladder, and other abnormalities (Wolfram syndrome). A review of 88 cases from



the literature with personal observations on 3 new patients. *Acta Paediatr Scand.* 1977;66.

4. Page MM, Asmal AC, Edwards CRW. Recessive inheritance of diabetes: The syndrome of diabetes insipidus, diabetes mellitus, optic atrophy and deafness. *QJM.* 1976;45:505-520. doi:10.1093/oxfordjournals.qjmed.a067477

5. Tranebjærg L, Barrett T, Rendtorff ND. WFS1 Wolfram Syndrome Spectrum Disorder.; 1993.

6. Urano F. Wolfram Syndrome: Diagnosis, Management, and Treatment. .

7. Jung J, Jang SH, Won D, Gee HY, Choi JY, Jung J. Clinical Characteristics and Audiological Profiles of Patients with Pathogenic Variants of WFS1. *J Clin Med.* 2024;13(16). doi:10.3390/jcm13164851

8. Karzon R, Narayanan A, Chen L, Lieu JEC, Hershey T. Longitudinal hearing loss in Wolfram syndrome. *Orphanet J Rare Dis.* 2018;13(1). doi:10.1186/s13023-018-0852-0

9. Esteban-Bueno G, Berenguel Hernández AM, Fernández Fernández N, Navarro Cabrero M, Coca JR. Neurosensory Affection in Patients Affected by Wolfram Syndrome: Descriptive and Longitudinal Analysis. *Healthcare (Switzerland).* 2023;11(13). doi:10.3390/healthcare11131888

10. Frontino G, Delvecchio M, Prudente S, et al. SID/SIEDP expert consensus on optimizing clinical strategies for early detection and management of wolfram syndrome. *J Endocrinol Invest.* Published online March 1, 2024. doi:10.1007/s40618-024-02495-z

11. Torchio S, Siracusano G, Cuozzo F, Zamarian V, Pellegrini S, Manenti F, Bonfanti R, Frontino G, Sordi V, Chimienti R, Piemonti L. Liraglutide treatment reverses unconventional cellular defects in induced pluripotent stem cell-derived  $\beta$  cells harboring a partially functional WFS1 variant. *Diabetes.* 2025 Apr 9;db240720. doi: 10.2337/db24-0720. Epub ahead of print. PMID: 40202504.