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Leiden
The Netherlands

Decoding tissue-specific TGF- β signaling in pulmonary arterial hypertension: from genetic predisposition to mechanobiology

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Citation

Becher, C. (2026, March 26). *Decoding tissue-specific TGF- β signaling in pulmonary arterial hypertension: from genetic predisposition to mechanobiology*. Retrieved from <https://hdl.handle.net/1887/4299423>

Version: Publisher's Version

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Propositions accompanying the thesis entitled

Decoding Tissue-Specific TGF- β Signaling in Pulmonary Arterial Hypertension: From Genetic Predisposition to Mechanobiology

1. The therapeutic potential of targeting the TGF- β pathway is governed by contextual signaling dynamics rather than the intrinsic affinities of its ligand-receptor interaction. (*This thesis*)
2. Success in PAH therapy is determined as much by the mechanical and biochemical state of the targeted tissue as by the molecular specificity of the therapeutic drug (this thesis)
3. Endothelial cell culture under static conditions is a biological artifact; shear stress is not an optional variable but a fundamental requirement for vascular relevance. (*Chapter 6 of this thesis*)
4. The emphasis on *BMPR2* mutations in PAH research has created a genetic 'tunnel vision', obscuring the role of dynamic environmental and biomechanical cues in disease progression. (*Chapter 5 of this thesis*)
5. The emergence of Activin A as a therapeutic target demonstrates that in PAH, the pathological 'over-activation' of signaling pathways is as critical as the loss of 'protective' signals. (*Adapted from Hoeper et al., NEJM. 2023*)
6. Sotatercept marks a milestone in the treatment of PAH, yet it also illustrates the limitations of global pathway modulation rather than the advent of true precision medicine.
7. The growing abundance of multi-omics data in PAH research has generated an abundance of information but a deficit of understanding; more detailed molecular maps do not necessarily tell us where to walk. (*Adapted from Simpson et al., Am J Respir Crit Care Med. 2022*)
8. Treating PAH as a single clinical entity is a convenient fiction that ignores the biological diversity of the disease and undermines the promise of precision medicine. (*Adapted from Leopold et al., Circ Res. 2020 and this thesis*)
9. A hypothesis that is proven wrong often advances scientific understanding more than a hypothesis that is proven right, yet we only celebrate the latter.

10. Academic publishing resembles a prisoner's dilemma where the most rational individual behavior leads to a collective compromise of scientific quality. (Sagartirtha Chakraborty, Leiden Madtrics, 2025)

11. The pressure of 'indicatorism' has transformed citation from an intellectual acknowledgment into a strategic tool; as Goodhart's Law suggests, when a measure becomes a target, it ceases to be a good measure." (Adapted from Hicks et al., Nature. 2015 – The Leiden Manifesto)

12. Scientific progress cannot be genuinely collective as long as access to knowledge is contingent on institutional privilege.