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## Developmental cell lineage dynamics in Bicuspid Aortic Valve disease

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STELLINGEN BEHORENDE BIJ HET PROEFSCHRIFT GETITELD:

## **Developmental cell lineage dynamics in Bicuspid Aortic Valve disease**

**Joshua Peterson**

1. Both the right and non-coronary cusp of the aortic valve develop from the septal cushion; the classical theory that the intercalated cushion gives rise to the non-coronary cusp should be discredited. (*this thesis*)
2. BAV disease is lesser a consequence of absolute cell number reductions rather than a consequence of regional deviations in the positioning of the cells. (*this thesis*)
3. Current genetic cell lineage tracing studies should always be complemented with detailed RNA expression profiles of each cell within the studied cell lineage to differentiate between cellular subtypes. Wagner DE, Klein AM. *Nat Rev Genet* 2020; 21: 410–427. doi: 10.1038/s41576-020-0223-2.
4. Given the observed relation between aortopulmonary angulation and the incomplete penetrance of BAV in *Nos3* mutants, a ranked framework to assess congenital predisposed aortopulmonary variation in humans should be constructed from screenings of all relatives of - and patients with any form of thoracic aneurysms with or without BAV. (*this thesis*)
5. Translating the gene expression profiles of individual cells into the complex dynamics observed within a multicellular environment should be the next milestone for developmental biologists. Mittnenzweig M, et al. *Cell*. 2021; 184(11): 2825-2842.e22. doi: 10.1016/j.cell.2021.04.004.
6. The pathogenesis of BAV is derived from disruptions in extracellular matrix components. Kern CB. *J Cardiovasc Dev Dis*. 2021; 8(8): 92. doi: 10.3390/jcdd8080092
7. The hemodynamic effects of BAV cannot be studied independent of genetic context. Kimura N, et al. *Ann Vasc Dis*. 2022; 15(1): 37-44. doi: 10.3400/avd.oa.21-00116
8. Whenever digital image analysis is performed within a study, all underlying data and scripts should be made publicly available to facilitate reproducibility. (*this thesis*)
9. Placing publicly funded scientific outputs behind a publisher's paywall should be considered unethical academic behavior.
10. Science should attempt to disprove a theory rather than attempt to continually support a hypothesis. **Karl Popper 1902 - 1994** Current academic incentives do not reward good scientific practices.