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DBOARD summary
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Publishable summary

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Please provide a summary description of the project context and the main objectives. The length of this part cannot exceed 4000 characters. Our contribution to DBOARD was to assess the potential of SIRT1 to serve as a biomarker for OA predisposition. As such, we attempted to analyse the various variants of SIRT1 in spent media of human chondrocyte cultures, mouse models of OA and human sera (WP1). As part of WP1, we additionally tested the activity of lysosomal cathepsins, which are responsible for SIRT1 cleavage in cartilage, using activity based probes. Another aim of our research contribution to D-BOARD was to assess if SIRT1 variants are involved in metabolic OA models, including mice subject or a high fat diet and human cohort of obese females (PROOF). As such, we analysed fat tissue and serum samples for Sirt1 variants and visfatin, which is an adipokine secreted from fat tissue but additionally capable of modulating SIRT1 activity.

Please provide a description of the work performed since the beginning of the project and the main results achieved so far. The length of this part cannot exceed 4000 characters. The results for WP1, showed that 75SIRT1 is detectable in culture media of cells exposed to pro-inflammatory stress. We additionally observed an increase in a particular SIRT1 variant (cleavage variant "a"; clSIRT1_a) in sera of mice bearing age or trauma related OA. As part of WP1, we analyzed human cohorts and found that they show a similar increase in clSIRT1_a when comparing non-OA to early OA donors.

Analysis of cathepsin activity in cell lysates, conditioned media explants and DC sections showed enhanced enzymatic activity of cathepsins B and S. Further histological analysis revealed that cathepsin activity was higher in superficial zones of

degenerating cartilage vs intact cartilage. Examining serum and SF revealed that cathepsin B is significantly elevated with OA severity in serum and SF, yet levels of cathepsin S are more correlated with synovitis and RA.

Results from WP2 related research, revealed another SIRT1 variant (cleavage variant "b"; clSIRT1_b), which rose in mice fed with a high-fat diet. The increase in clSIRT1_b, was also apparent in individuals with metabolic syndrome within the PROOF cohort, but did not associate with OA severity based on KL scoring.

Please provide a description of the expected final results and their potential impacts and use (including socio-economic impact and the wider societal implications of the project so far). Overall, it appears that SIRT1 serum variants are not robustly correlated with OA severity, since there are aberrant SIRT1 variants appearing in metabolic OA vs. age or trauma-related OA. More specifically, the results point that confounding factors, such as aging, metabolism, diet and post-trauma, leading to OA, may individually alter Sirt1 variants in sera through tissues unrelated to cartilage, which is gradually tarnished during the disease. For this reason, it appears that SIRT1 fragments are beneficial for **stratifying OA types** and confounding risk factors, such as in metabolic, inflammatory or age related OA.

These results preclude our conclusion of SIRT1 variants being prognostic, diagnostic or relevant to efficacy of intervention, or relevant to Burden of disease, based in BIPED criteria. Rather, this biomarker is still INVESTIGATIVE and EXPLORATORY, based on BIPED criteria, until the exact physiological and pathological chain of events, can explain its altering trends in the circulation during OA. It should be noted, that these Sirt1 variants may rise in sera under different pathophysiological conditions which are related or un-related to OA. As such, a particular variant could be included in a panel of biomarkers related to numerous diseases, with similar confounding criteria and risk factors.

In summary, the results support that SIRT1 variants can help in stratifying types of OA, but not as a stand-alone prognostic or diagnostic means for OA development. It is expected that the tools developed during D-BOARD will provide a ground for

further assessment SIRT1 variants relevant to other diseases bearing common confounding risk factors as OA.

Beyond the scientific novelty and impact of the D-BOARD project, the tools developed in this program will undoubtedly provide a foundation for industrial development and assessment of these variants as biochemical measures for other disorders and/or pathophysiological conditions, which will have a significant socio economic impact and commercial potential.