Concept Paper Template

Provisional Paper Title: Genetic Markers of the Inflammatory Biomarker Soluble Urokinase Plasminogen Activator Receptor (suPAR) in a Population of Healthy Blood Donors

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P.I. Sponsor:
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Today's Date:

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

The plasma protein soluble urokinase plasminogen activator receptor (suPAR) is a non-specific biomarker for low-grade inflammation. Previously suPAR has been found to predict various negative conditions, including incident cancer, cardiovascular disease, diabetes, depression and mortality[1,2]. Though there is a wide range of negative outcomes associated with suPAR, the genetics of suPAR remain unexplored.

A recent genome-wide association analysis (GWAS) meta-analysis of the well-known inflammatory marker C-reactive protein (CRP) identified 58 associated genetic loci and consequently provided new insight into the genetic aetiology of chronic inflammation[3]. However, CRP and suPAR reflect different aspects of low-grade inflammation despite both being used as inflammatory biomarkers[4]. Additionally, unlike CRP, suPAR is a stable biomarker in the sense that circadian changes in plasma suPAR are minimal [5,6].
Therefore, performing a GWAS on suPAR in a population of otherwise healthy blood donors may reveal genetic variants that affect this inflammatory marker's systemic expression. The findings may provide new insight into the aetiology of low-grade inflammation.

We have conducted a suPAR GWAS using log-transformed suPAR values and adjusting for sex, age, smoking status, BMI and 10 principal components (N= 12,236). The results from the GWAS discovered 8 genome-wide significant loci.

We wish to replicate the findings in independent cohorts by using the suPAR measurements and genomic (SNP) data available from the Dunedin Study and the E-Risk Longitudinal Twin Study.

Data analysis methods:
Additive genetic association tests between suPAR levels and each of the available SNPs will be performed using the R package "SNPassoc". Briefly, the following model will be employed:

suPAR ~ SNP + sex + PCs1-10

SNP genotypes will be coded as number of risk alleles (0,1,2).

Variables needed at which ages:
Dunedin: suPAR and SNP data at age 38.
E-Risk: suPAR and SNP data at age 18.

Significance of the Study (for theory, research methods or clinical practice):
To our knowledge, a GWAS on suPAR has never been attempted, and datasets with suPAR measurements and genomic data are extremely limited. As we have already identified several genome-wide significant SNPs, a replication study in Dunedin and E-risk would naturally complement the GWAS and strengthen the study. suPAR is a stable biomarker for low-grade inflammation with many associated negative conditions, highlighting the potential importance of the findings from this study. Identifying genetic markers associated with plasma suPAR levels may provide essential insight into the aetiology of low-grade inflammation.

References cited:

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3 Ligthart, S. et al. Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. American journal of human genetics 103, 691-706, doi:10.1016/j.ajhg.2018.09.009 (2018).

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5 Andersen, O., Eugen-Olsen, J., Kofoed, K., Iversen, J. & Haugaard, S. B. Soluble urokinase plasminogen activator receptor is a marker of dysmetabolism in HIV-infected patients receiving highly active antiretroviral

therapy. Journal of medical virology 80, 209-216, doi:10.1002/jmv.21114 (2008).
6 Sier, C. F. et al. Presence of urokinase-type plasminogen activator receptor in urine of cancer patients and its possible clinical relevance. Laboratory investigation; a journal of technical methods and pathology 79, 717-722 (1999).

CONCEPT PAPER RESPONSE FORM

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Potential Journals	
Today's Date	
Intended Submission Date	

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B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
	Conceptualizing and collecting one or more variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
	Reviewing manuscript drafts
	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature:

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