Elucidation of epigenetic mechanisms underlying normal and disease biology

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Introduction

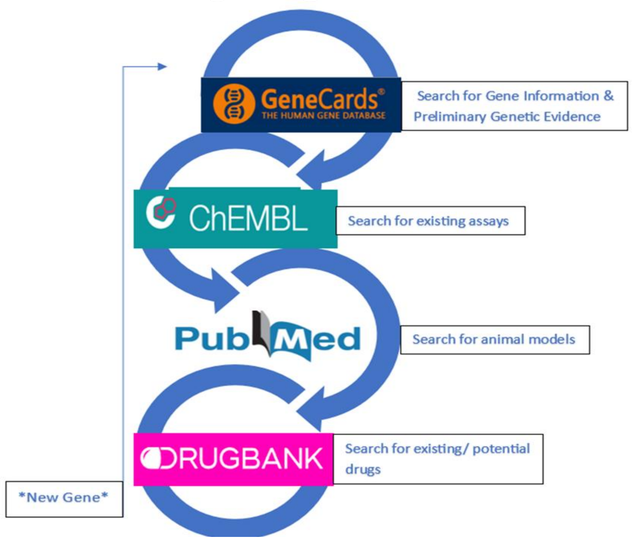
Epigenetics is defined as the study of heritable alterations in gene function that occur without underlying changes in DNA sequence[1]. Biologically, aging is linked with a gradual increase in molecular and cellular damage eventually leading to a decline in physiological reserves and an increased risk of developing diseases[2]. It is now well established that a vast number of epigenetic changes, notably DNA methylation occur during the aging process[3]. Epigenetic changes offer the potential for maintaining health or reversing diseases by modulating the function of druggable proteins coded by genes with dynamic and reversible methylation changes.

Methods

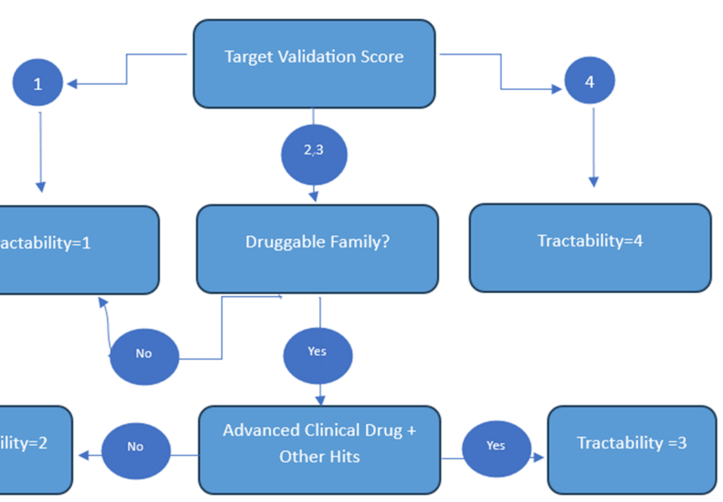
We developed an algorithm that analyses large DNA methylation datasets from genomic DNA sequences which allows for the calculation of "biological age" for any individual. This parameter when considered with other measurements such as BMI, blood profile and lifestyle can serve as a health indicator.

Subsequently, we identified and ranked the genes, protein targets and compounds that are associated with the epigenetic changes. This exercise was performed on in healthy and specific disease cohorts.

Ranking Target Validation:



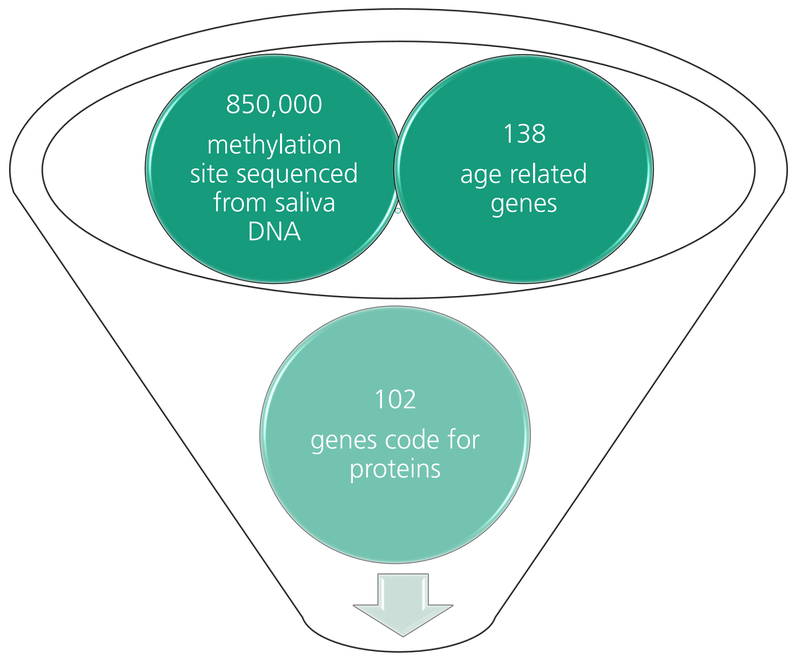
Ranking Target Tractability:



Results

Our LASSO and subsequent stepwise regression analysis method for the calculation of "biological age" had improved accuracy with Mean Absolute Error (MAE) of 1-2 years in comparison to previously reported methods (Horvath clock 3.6 years; Hannum clock 4.9 years)[4].

Prioritisation of the genes associated with the epigenetic changes yielded 4 proteins (SIRT7, PDE4C, PANK1, and FURIN) which are druggable by small molecules.



30 prioritised druggable age related proteins

High priority: SIRT7, PDE4C, PANK1, FURIN
Medium priority : PRKCZ, ELOVL2, GRIA4, PRKCH, CACNA1D, DAP, TRPV3, ACACA, SLC1A2, NCOR2, EPAS1, USP4, KCNS1, NDUFA10, RXFP3, ISPD, INPP5A
Low priority: MAP4, ST7, GNAI1, GNG2, GNAQ, POLG2, GMPS, SINHCAF, TDRD1

Natural compound databases are currently being evaluated to search for substances that can potentially modulate the epigenetic status in a manner that improves the health status of any individual.

Conclusions

We have identified the key epigenetic changes that take place during the normal aging process and deviations thereof in specific diseases. We are currently searching for natural substances that can potentially modulate these epigenetic changes in a meaningful manner that offer health benefits.

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[2]Baker III, G.T. and Sprott, R.L. 1988. Biomarkers of aging. Experimental Gerontology, 23, 223-239.
[3]Li, D., Ju, F., Wang, H., Fan, C., Jacob, J.C., Gul, S., Zaliani, A., Wartmann, T., Polidori, M.C., Bruns, C.J. and Zhao, Y. 2023. Combination of the biomarkers for aging and cancer? - Challenges and current status. Translational Oncology, 38:101783.
[4]Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biology, 14, 1-20.