Project 5

Long-term pharmacological interventions to increase longevity is becoming popular among big pharma and research community. These interventions are based on repurposing known therapeutical drugs to the longevity setting. For example, interventions based on long-term use of low-dose Metformin – a drug for treating type 2 diabetes - have shown promising results in mice and humans. Another example is the use of resveratrol, a compound found in red wine, which extends lifespan in mice by activating the SIRT1 pathway.

Imagine that a drug company intends to invest in the longevity market and wants to know whether Metformin can be used alone or in combination with a SIRT1 activator. The company previously ran a hypothetical phase 0 clinical (proof-of-concept) trial where mice received a standard diet, a low dose (0.1%) of Metformin administered from middle age (n=4), and followed a 40% calorically restricted diet (as reported in Martin-Montalvo et al, 2013). Gene expression data in liver and muscle tissues from these mice are available in the GEO database (https://www.ncbi.nlm.nih.gov/gds) under the accession number GSE40936. The objective of the data analysis is to advise the company whether a low-dose (0.1%) Metformin is sufficient to induce SIRT1 activation (i.e., to increase the respective gene expression levels). In other words, the company needs to know whether there is a need to include SIRT1 activator in the formulation of the new drug. They also want to know whether there are some major pathologies associated with the long-term administration of low-dose metformin.

In this project, prepare a presentation where you present the problem and answer the following questions:

1. Is there any evidence of increased SIRT1 expression overall or in the liver/muscle tissues when comparing the Metformin group to the standard diet or the caloric-restricted group?
2. Is there any evidence of increased toxicity (i.e., increase frequency of adverse events) in the 0.1% Metformin group comparing to the standard diet group (data from Supplementary Table S3 of Martin-Montalvo et al)?
3. What is the statistical power of detecting the observed differences in prevalence of lung tumor or spleen enlargement between 0.1% Metformin group and the standard diet group? Use data from Supplementary Table S3 of Martin-Montalvo et al.
4. What are the eventual problems of running a phase II/III clinical trial in this setting?

Some Useful R packages: GEOquery, Table1, pwr.

Reference:

Martin-Montalvo A, Mercken EM, Mitchell SJ, et al. Metformin improves healthspan and lifespan in mice. Nat Commun. 2013;4:2192. doi:10.1038/ncomms3192