SANOFI

INTERNSHIP

SUBJECT

Experimental designs and analysis for detecting synergy and antagonism between compounds with in vitro experiments: method when the maximum effects are not shared or/and the relative potency is not constant and method for combination of at least 3 compounds

CONTEXT

In therapeutic areas such as oncology, there is an increasing interest in the development of drug combinations. These combinations are selected because of a biological and mechanistical rational. They can increase efficacy or maintain it at lower doses with reduced adverse events.
The first step of the development of a combination is to characterize the interaction between two compounds from in vitro experiments. The aim of these experiments is to determine the nature of the interaction between both compounds: synergistic, additive or antagonistic.
An additive effect corresponds to a noninteraction situation in which the effect of a combination is that expected from the dose-response curves of the single compounds. A synergistic combination is commonly defined as a combination with an effect greater than an additive effect and an antagonistic combination as a combination with an effect lower than an additive effect.
The dose-effect relation is commonly modelled by a 4-parameter logistic model considering a saturation process. Therefore, the idea of simply adding the effects of single compounds and to compare this result to the effect of the combination is not accurate.
In this context, several models and methods have been developed to demonstrate synergy. One of the main reference models to express synergy is the Loewe additivity model (Loewe and Muischnek, 1926).
Although the Loewe model is widely used, two strong constraints must be met before using it: both compounds should have the same maximum effect and a constant relative potency. At least one of these constraints is very often non respected, in this case the validity of the model is questionable.

MISSION

The first aim of this internship will be to make an overview of the current statistical methods to analyze compounds combination with in vitro experiments. This work will be focused on:

- the management of the cases where the maximum effect is not shared between compounds or where the relative potency is not constant
- the analysis of combinations of at least 3 compounds

Improvements of Loewe model as well as new models/methods will be explored.
In parallel, the R packages available for the analysis of in vitro combination experiments will be studied and compared.
From this review of the bibliography and of R packages, a method will be selected and implemented in R and/or SAS.

PROFILE

Level BAC + 5 with Biostatistics option (ENSAI, ISUP, Master 2 University, …)
Good knowledge of R and SAS
Good level of English

Duration: 6 months (beginning between February and April)
Location: Vitry-sur-Seine (94)

Contact:

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References

- Berenbaum M C – What is Synergy? - Pharmacological Reviews (1989)
- Straetemans R et al. - Design and Analysis of Drug Combination Experiments - Biometrical Journal (2005)
- Foucquier J., Guedj M. - Analysis of drug combinations: current methodological landscape – Pharmacology Research and Perspectives (2015)
- Tallarida R J - An Overview of Drug Combination Analysis with Isobolograms – The Journal of Pharmacology and Experimental Therapeutics (2006)