Evaluation of Gene Expression as Trial-Level Surrogate Markers of Vaccination Across Multiple Settings

M2 Internship

Background

Direct measurement of the primary outcome in a clinical trial is often time-consuming, expensive, or infeasible. For instance, when the outcome is rare, it may take many years to observe enough events to observe a statistically significant difference between groups, even if the treatment is effective. Consequently, there is considerable interest in identifying *surrogate markers*- variables that can be observed more quickly, at lower cost, or with greater ease, and that can serve as reliable substitutes for the primary outcome to accurately infer treatment effects [1].

Surrogate markers may be classed into two general categories. *Trial-level surrogates* (TLS) are predictive of the average treatment effect in a given population, whereas *individual-level surrogates* (ILS) allow for the prediction of individual treatment effects. Surrogates from these two classes are conceptually distinct and differ in clinical utility [2]: while TLS can be used to improve the efficiency of clinical trials, ILS can be used for patient-level decision making, known as precision medicine. The former are particularly relevant in the context of vaccine development. TLS could provide evidence for the rapid selection of candidate vaccines in experimental adaptive trials, and allow for vaccine evaluation when a phase 3 trial is not feasible due to the absence of endemic disease in the target population. In addition, they can provide insight by identifying the components of the immune system characterising effective vaccines.

High-throughput technologies, such as transcriptomics data, hold great promise for informing effective vaccine design. Transcriptomic data describe gene expression- the process by which information encoded in DNA is transformed into proteins that shape phenotypes. Changes in gene expression occur in the first hours and days after vaccination and are likely to reflect early biological perturbations leading to protective immunity. Recently, we developed the *RISE* method to identify and evaluate high-dimensional surrogate markers [3]. Applying this method to a number of different vaccines, we have identified promising gene expression TLS signatures with strong biological interpretations. However, the generalisability of these signatures across multiple settings has yet to be explored. The objective of this internship will therefore be to apply the RISE method to multiple public datasets (e.g. on annual influenza vaccination [4]) to evaluate the generalisability of transcriptomic trial-level surrogate markers of vaccination.

Objectives

1. Apply the RISE method across multiple public molecular vaccinology datasets of the same vaccine to explore the generalisability of any identified trial-level surrogate signatures
2. Investigate alternative ways to apply RISE to improve power and interpretability (e.g. applying it on the level of gene-sets instead of individual genes)
3. Perform a biological interpretation of any identified TLS signatures

Required Skills

- Master 2/Bachelor/Engineering school with a major in biostatistics or similar
- Programming proficiency with R
- Interest in biomedical research and scientific curiosity
- Written and spoken English proficiency

Hosting laboratory
SISTM Team
INSERM U1219 and INRIA Sud-Ouest

Location
Bordeaux Population Health Research Center
Université de Bordeaux – ISPED
146, Rue Léo Saignat
33076 Bordeaux

Duration:
Internship of 4 to 6 month available starting from January 2025.

Compensation:
Intern gratification according to government recommendations (15% of social security ceiling, i.e. around 660€/month).

Contact:
Send a detailed CV and a motivation letter to Boris Hejblum (boris.hejblum@u-bordeaux.fr) and Arthur Hughes (arthur.hughes@u-bordeaux.fr).

References

[1] Christensen, R., Ciani, O., Manyara, A. M., and Taylor, R. S. (March, 2024) Surrogate endpoints: a key concept in clinical epidemiology. *Journal of Clinical Epidemiology,* **167**, 111242.

[2] Buyse, M., Saad, E. D., Burzykowski, T., Regan, M. M., and Sweeney, C. S. (March, 2022) Surrogacy Beyond Prognosis: The Importance of "Trial-Level" Surrogacy. *The Oncologist,* **27**(4), 266–271.

[3] Hughes, A., Parast, L., Thiébaut, R., and Hejblum, B. P. (September, 2025) RISE: Two-Stage Rank-Based Identification of High-Dimensional Surrogate Markers Applied to Vaccinology. *Statistics in Medicine,* **44**(20–22).

[4] Hagan, T., Gerritsen, B., Tomalin, L. E., Fourati, S., Mulè, M. P., Chawla, D. G., Rychkov, D., Henrich, E., Miller, H. E. R., Diray-Arce, J., Dunn, P., Lee, A., Deckhut-Augustine, A., Gottardo, R., Haddad, E. K., Hafler, D. A., Harris, E., Farber, D., Kleinstein, S. H., Levy, O., McElrath, J., Montgomery, R. R., Peters, B., Pulendran, B., Rahman, A., Reed, E. F., Rouphael, N., Sarwal, M. M., Sékaly, R. P., Fernandez-Sesma, A., Sette, A., Stuart, K., Togias, A., Tsang, J. S., Levy, O., Gottardo, R., Sarwal, M. M., Tsang, J. S., Suárez-Fariñas, M., Sékaly, R.-P., Kleinstein, S. H., and Pulendran, B. (October, 2022) Transcriptional atlas of the human immune response to 13 vaccines reveals a common predictor of vaccine-induced antibody responses. *Nature Immunology,* **23**(12), 1788–1798.