**Master-2 Bioinformatique | Année 2023-2024**

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**Titre du sujet de stage :**

Structural analysis and classification of T4SS: leveraging Foldseek and AlphaFold

**Nom et adresse de l’Unité d’accueil :**

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**Superviseur(s) :**

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**Résumé du Sujet de stage proposé :**

The Type 4 Secretion System (T4SS) found in bacteria is a sophisticated machinery that facilitates the transport of DNA and proteins directly into target cells, including other bacteria and eukaryotic host cells. Its significance in biology is undeniable, with notable roles in Horizontal Gene Transfer (HGT), bacterial pathogenesis (including cancer), and genetic engineering, exemplified by the creation of the first genetically modified plants.

T4SS classification has traditionally relied on functional criteria, distinguishing between conjugation systems (T4ASS) primarily involved in DNA transfer and effector secretion systems (T4BSS) responsible for delivering virulence factors and proteins into target cells. However, this approach is showing its age, as recent high-throughput genome sequencing has revealed a wealth of novel T4SS variants across various bacterial species, highlighting the limitations of the old-school classification.

Harnessing the AI revolution, we are enthusiastic about applying state-of-the-art technologies like AlphaFold and Foldseek to revolutionize our understanding of T4SS. This internship will involve using AlphaFOLD/Foldseek to differentiate between T4SS types and unlock hidden structural mysteries. Moreover, the internship will involve using coevolution and AlphaFold to propose a substrate recruitment mechanism model, this approach will also facilitate the identification of potential new effectors through comparative structural analysis.

This internship offers an exciting opportunity to explore the latest advances in structural bioinformatics and contribute to the understanding of the molecular mechanisms underlying bacterial secretion systems. With AlphaFold and Foldseek, we're not just redoing T4SS classification; we're pushing the boundaries of what we can achieve. It's akin to exploring uncharted territories, where each discovery opens up new possibilities in microbiology and biotechnology.

**Technologies utilisées :**

AlphaFOLD2, Foldseek, Blastp, Uniprot

**Mots clés:**

T4SS, biology structural, AlphaFOLD, Foldseek,

**Publications d’intérêt:**

G. Waksman. From conjugation to T4S systems in Gram‐negative bacteria: a mechanistic biology perspective. EMBO reports (2019) [doi:10.15252/embr.201847012](https://doi.org/10.15252/embr.201847012)

K. Macé\*, A.K. Vadakkepat\*, N. Lukoyanova, N. Braun, A. Redzej, M. Ukleja, F. Lu, T.R.D. Costa, E.V. Orlova, D. Baker, Q. Cong, and G. Waksman. Cryo-EM structure of a type IV secretion system. Nature (2022) [doi:10.1038/s41586-022-04859-y](https://www.nature.com/articles/s41586-022-04859-y)

C. Noroy, T. Lefrançois, DF. Meyer. Searching algorithm for Type IV effector proteins (S4TE) 2.0: Improved tools for Type IV effector prediction, analysis and comparison in proteobacteria. PLOS Computational Biology (2019) [doi:10.1371/journal.pcbi.1006847](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1006847)