iCASE Project / AY 2025 -2026

Probing the evolvability of enzymes for biocatalysis by deep mutational scanning and machine learning

Project Reference: ICS-BIO-FH

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Industrial Partner: Merck & Co. Inc. (via its UK arm: Merck Sharpe and Dome, MSD)

BBSRC DTP main strategic theme: Understanding the rules of life

BBSRC DTP secondary strategic theme: Transformative technologies, Bioscience for renewable resources and clean growth

Project outline:

The use of sustainable biocatalysis in the synthesis of pharmaceuticals is desirable, beginning in early stage development, but enzymes with useful activity and specificity do not always exist. Directed evolution is the method of choice for generating such enzymes, but can take a long time and is not always successful. We have developed a powerful combination of ultrahigh-throughput screening in microfluidic droplets (see Chem Rev (2023) 123(9):5571-5611; doi: 10.1021/acs.chemrev.2c00910) and deep learning that accelerates the timescale of biocatalyst improvement to a few weeks. Datasets based on screening >10e7 mutants provide the input for deep learning, which is able to improve the hits arising of the experimental screen by orders of magnitude. The powerful combination of experimental and computational approaches will be applied to imine reductases (IREDs), versatile enzymes for imine reductases, IREDs synthesis of chiral amines.