Lead Optimisation of Small Molecule Sulfatase Reactivators for MSD

Niama Ezzaidi,*[a] Lars Schlotawa,[b] Julia Kowal,[c] Hartmut Niemann,[c] Matthias Baud†[a]

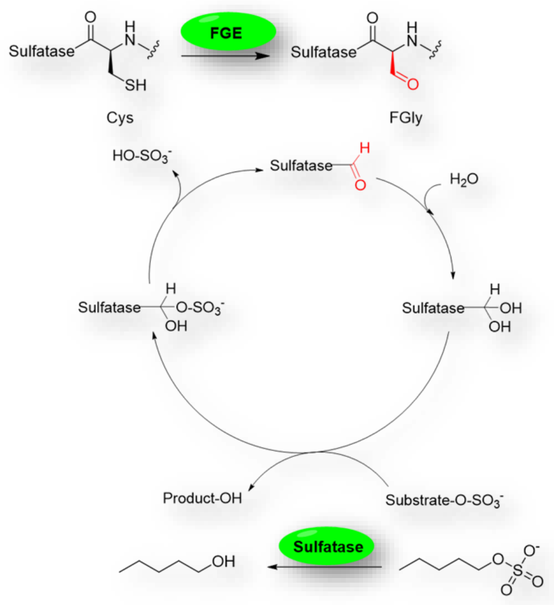
[a] School of Chemistry, University of Southampton, Southampton, UK. [b] University Medical Center Goettingen Department of Paediatrics and Adolescent Medicine, Goettingen, Germany. [c] Bielefeld University, Department of Chemistry, Bielefeld, Germany.

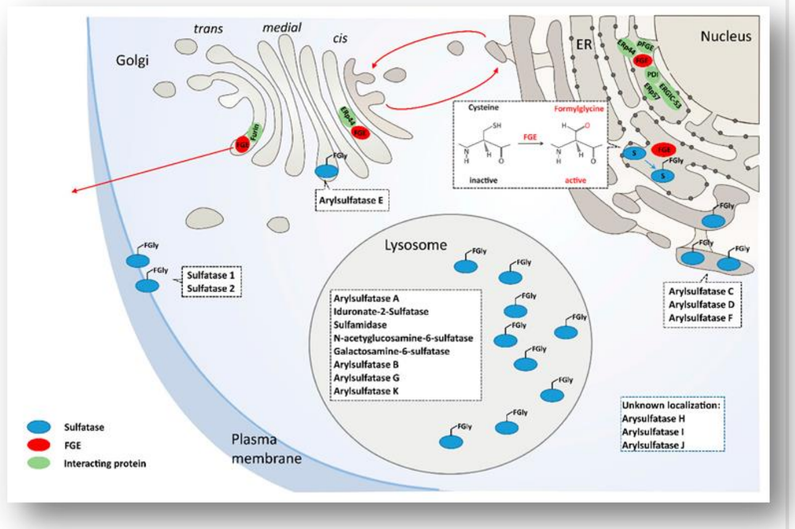
1. Introduction

Multiple sulfatase deficiency (MSD) is a rare lysosomal autosomal recessive disease. MSD results from mutations of the SUMF1 gene, which encodes for the formylglycine generating enzyme (FGE) responsible for post-translationally activating 17 cellular sulfatases.

Lack of FGE activity leads to reduced sulfate ester hydrolysis and build-up of cytotoxic by-products.

We aim to develop treatments that operate by two approaches: **(1)** activation of nuclear receptors RAR/RXR and stabilisation; **(2)** pharmacological chaperones targeting FGE directly.

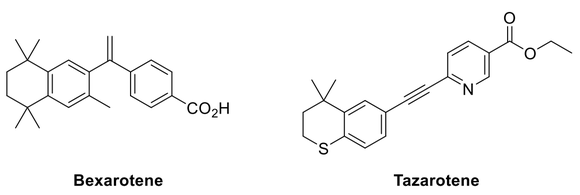


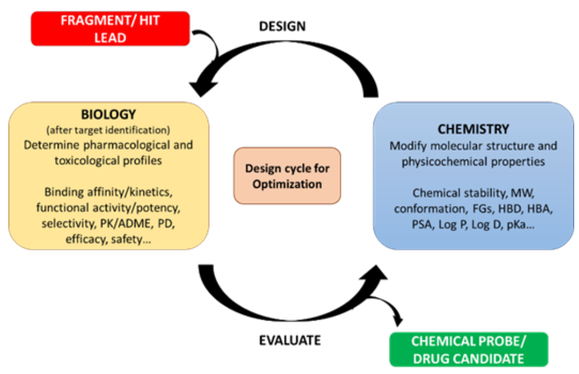


2. Drug repurposing

High throughput screen of circa **800 FDA approved drugs** (LifeArc) identified a family of structurally and functionally related molecules that are able to upregulate sulfatases activity in MSD patient derived cell lines by up to 30 %.[1]

- Third generation retinoids





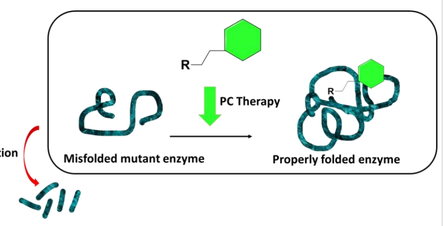
Upregulation of sulfatase activities by Taz/Bex through activation of members of the **Retinoic acid receptor** (RAR) and **Retinoid X receptor** (RXR) families.

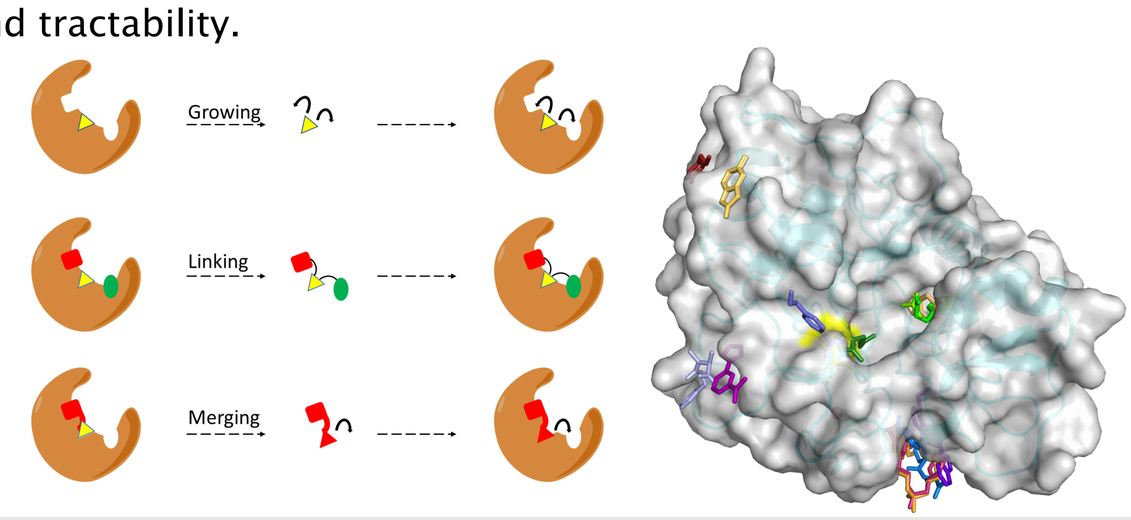
3. Fragment-based lead discovery

Identification of **novel stabilizers of FGE** using *in vitro*/*in silico* screening.

Co-crystallisation of the hits with FGE

- Fragments hits typically benefit from high ligand efficiency, solubility and tractability.





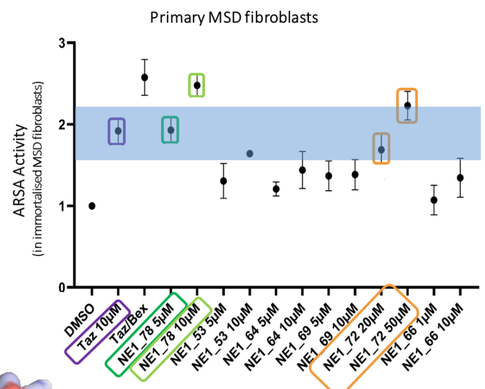
4. Objectives

- Rational SAR based design and chemical synthesis of retinoid derivatives targeting RAR/RXR receptors; development of suitable synthetic routes to access them.
- Design, synthesis and biological evaluation of novel small-molecule stabilizers of FGE using Fragment-based drug discovery (FBDD)

5. Results

Synthesis and testing of circa 20 Tazarotene analogues + testing of 77 Bexarotene analogues.

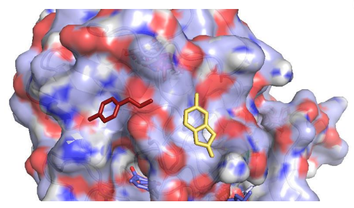
Biologic evaluation in patient-derived MSD cells: ARSA sulfatase activity assay, cell viability/proliferation.



Co-crystallisation of validated hits from primary fragment screen with FGE and identification of the fragment binding sites.

Computational docking (Glide) against specific receptor.

Synthesis and lead optimization of linked/merged fragments and their biological evaluation.



6. Future Work

Evaluation of TZ and BX analogues for SGSH/steroidsulfatase as well as glycosmainoglycan storage and lysosomal size/positioning in cell reactivation.

Synthesis and biological evaluation of linked and merged fragments towards the first small molecule FGE stabilizers.

7. References

1. L. Schlotawa, L. A. Adang, K. Radhakrishnan and R. C. Ahrens-Nicklas, International Journal of Molecular Sciences, 2020, 21, 3448. **2.** L. Schlotawa, E. C. Ennemann, K. Radhakrishnan, B. Schmidt, A. Chakrapani, H.-J. Christen, H. Moser, B. Steinmann, T. Dierks and J. Gärtner, Eur J Hum Genet, 2011, 19, 253–261. **3.** T. Dierks, B. Schmidt, L. V. Borissenko, J. Peng, A. Preusser, M. Mariappan and K. von Figura, Cell, 2003, 113, 435–444.

Author contact details
*N.Ezzaidi@soton.ac.uk
†m.baud@soton.ac.uk
Academic Poster September 2022