A class-based approach to drug discovery: mining the pharmacotherapeutic potential of the ABC transporter superfamily

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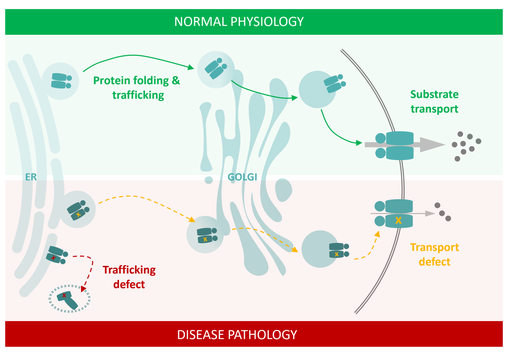
Abstract

ATP-binding cassette (ABC) transporters are a large, phylogenetically conserved gene family with broad physiological and pathological relevance. At present, the cystic fibrosis transmembrane conductance regulator (CFTR) is the only ABC transporter targeted by approved drugs. These CFTR-targeted pharmacological compounds can directly address the underlying genetic defects driving CF and reestablish chloride transport to dramatically improve pulmonary function. Deepening understanding of the molecular mechanism of action (MoA) of these transformative CF therapies suggests a broader potential of the ABC family as therapeutic targets, opening the door for the development of new first-in-class drugs for the treatment of human disease.

At Rectify, we have established a class-based approach to drug discovery that leverages understanding across the ABC transporter superfamily to drive the identification of novel drug-like molecules. Here we describe the components of our discovery platform and illustrate how these have been applied to identify positive functional modulators (PFMs) and establish the druggability of key targets across the ABC-T proteome. These enabling discovery tools include a custom synthesized, proprietary compound library (RectifyER), which has been designed based on chemical motifs previously shown to enhance ABC transporter expression, trafficking and transport function. The RectifyER library, as well as large diversity libraries, are screened using a versatile, high-throughput screening approach that can be rapidly implemented for any ABC transporter target, including wild-type transporters as well as transporters harboring key patient mutations. An additional suite of assays characterizes drug effects on transporter function, as well as drug MoA. A cryo-EM gene-to-structure pipeline has also been established to generate high-resolution structures for key liganded complexes, in near real-time, to drive scaffold prioritization and chemical design. Finally, development of predictive translational models, both cellular and animal models, is critical for program advancement and development candidate selection. We will provide examples from multiple ABC transporter drug discovery programs, focusing primarily on rare monogenic ABC transporter diseases of unmet need.

Pharmacotherapeutic potential of the ABC proteome

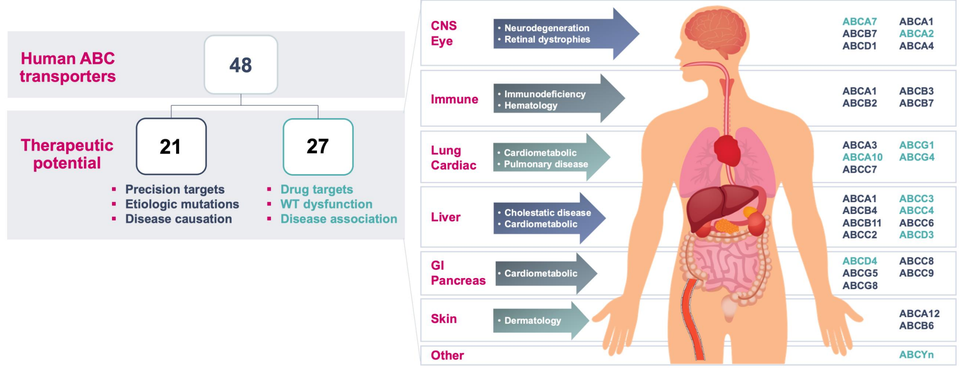
ABC transporter dysfunction cause monogenic disease and is relevant to many common diseases



- ABC transporters are folded in the ER and trafficked to lipid membranes where they transport diverse substrates
- Genetic mutations can cause:
  - **Protein trafficking defects**
  - **Substrate transport defects**
- ABC transporter protein are associated with multiple human diseases:
  - Etiological causes of **rare monogenic diseases**
  - Predispose to symptoms & severity of **complex disease**
  - Mechanistic association to pathways implicated **in common disease**

ABC transporter are biologically rationalized drug targets

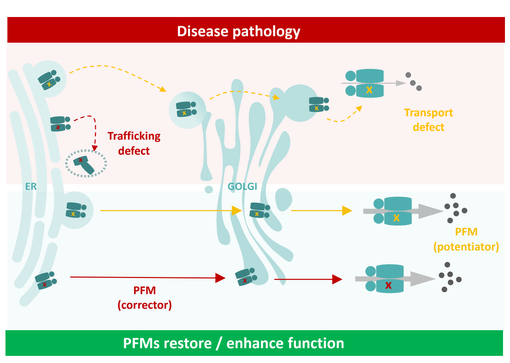
Broad therapeutic opportunity to impact rare genetic and large common diseases



Comprehensive assessment of monogenic and common disease associations across the ABC-T proteome

The Rectify approach

Rectify is developing Positive Functional Modulators (PFMs) to restore ABC transporter function in rare and common disease

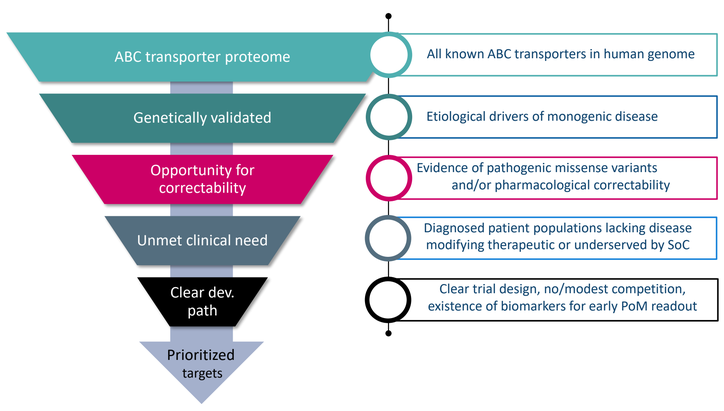


- **Positive Functional Modulators (PFMs):**
  - Small molecule compounds that rescue mutant ABC transporter function
  - **PFM correctors** can rescue mutant protein **trafficking** to reestablish membrane localization
  - **PFM potentiators** can rescue mutant protein functional activity to reestablish substrate **transport**
  - PFMs also have potential to **enhance WT ABC transporter biology**

PFMs can be disease-modifying for ABC transporter monogenic disease and represent an attractive intervention for common diseases

Target prioritization

Prioritized platform targets are selected based on a rationalized assessment of disease contribution, feasibility, opportunity and medical need



Rectify drug discovery platform

Building a breakthrough ABC transporter product platform

RectifyER Chemistry Library

Privileged screening library defining a unique chemistry space targeting ABC transporters

ABC-T Assay Suite

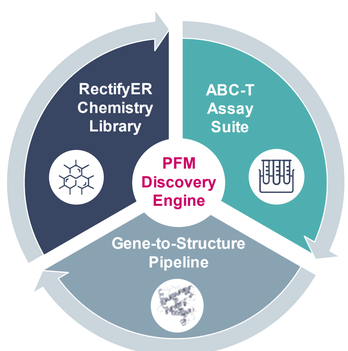
Target-focused, information-rich primary, mechanistic and functional assays for rapid insights into ABC transporter small molecule druggability

Gene-to-Structure Pipeline

Structural and computational optimization driven by cryo-EM platform and knowledge aided ligand design across ABC transporter proteome

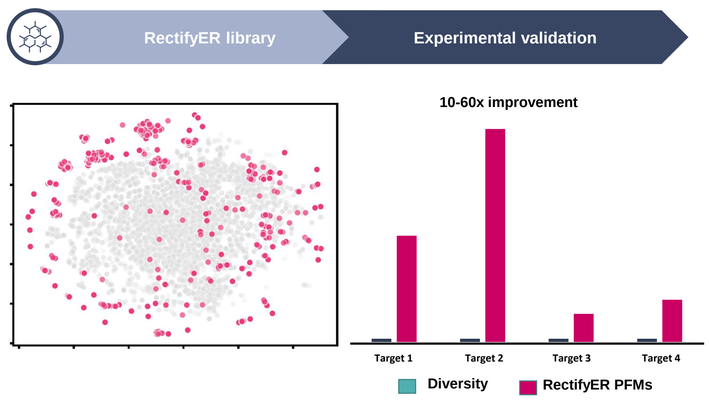
Proprietary translational models

Measuring clinically relevant transport and trafficking in vitro and in vivo to enable rapid POM



RectifyER ABC-focused screening library

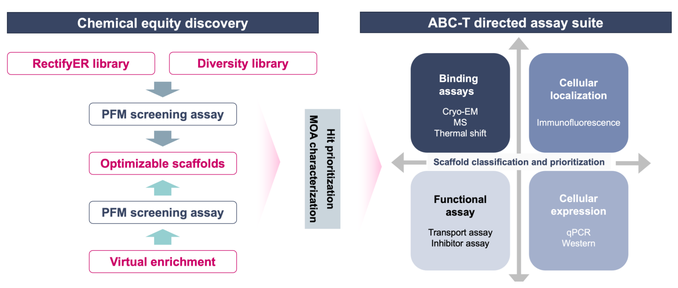
- Rich collection of lead-like compounds enabling pan-ABC transporter drug discovery
- Deep structural and computational mining generates novel and diverse privileged scaffolds annotated by MOA
- In-built initial SAR to enable rapid iterative optimization of potent and selective PFMs
- Rationalized library design and iterative buildout enables ABC-T target hopping



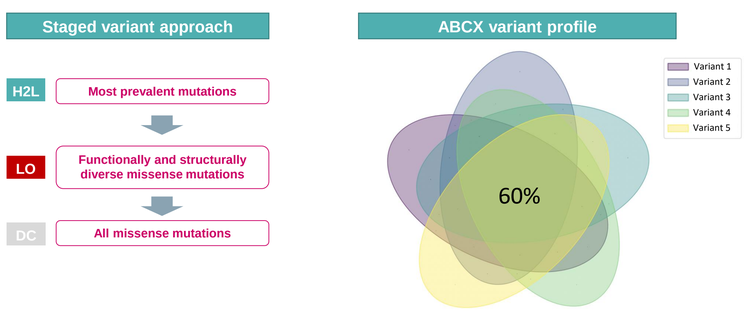
Consistent enrichment of hits from the REctifyER library efficiently drives PFM discovery

Rectify drug screening funnel

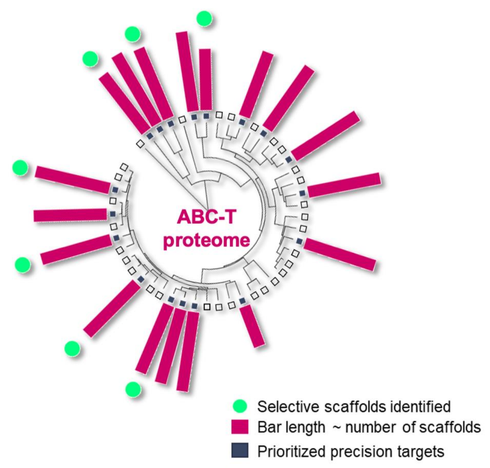
Rectify platform enables rapid hit ID & classification of PFMs



Rectify approach to variant screening and emerging data



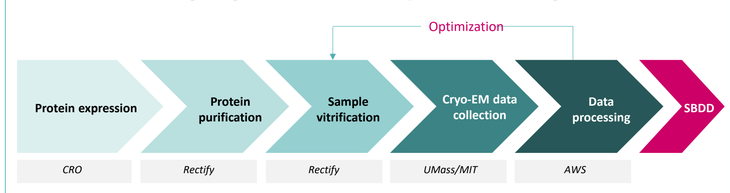
Pan-ABC proteome druggability screening



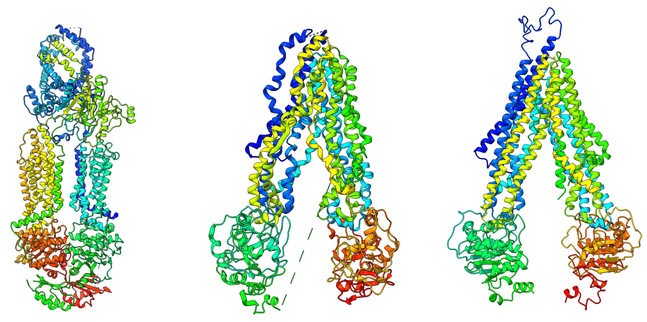
- Parallel hit identification across ABC proteome target space
- Rapid potency and selectivity data for scaffold prioritization and downstream MoA analysis
- Broad understanding of target druggability
- Integration of hit pharmacology, with MoA insights and structural biology expertise informs scaffold-based target hopping and seeds drug discovery

Gene-to-structure pipeline

Iterative structure-based drug design for challenging membrane protein targets



- Expression/purification pipeline for high quality protein samples
- Access to advanced microscope technology at academic institutions/CROs
- Computational infrastructure (virtual GPU cluster) @AWS



ABCA4 ABCB4 ABCB11