CASE STUDY

Morphic Therapeutic leverages digital chemistry strategy to design a novel small molecule inhibitor of $\alpha_4\beta_7$ integrin

Collaborative enterprise platform and physics-based digital assays empower a team of experts to tackle a challenging target — $\alpha_4\beta_7$ integrin

Performed rapid *in silico* design cycles with collaborative platform

Balanced potency, selectivity, and permeability using a structure-based design strategy

Resulted in a development candidate currently in Phase 2b

"By combining Morphic's integrin drug hunters with Schrödinger's *in silico* molecular design technologies, we were able to successfully deliver a novel small molecule with the key potency, selectivity, and PK properties for this highly validated biological target where others had previously failed."

— Matt Bursavich
VP, Head of Chemical Sciences
Morphic Therapeutic

Target	$\alpha_4\beta_7$ integrin
Program Type	Collaborative program, small molecule
Partner	Morphic Therapeutic
Indication	Inflammatory bowel diseases (ulcerative colitis, Crohn's disease)
Stage	Phase 2b clinical trial

Schrödinger MORPHIC

DESIGN CHALLENGE

$\alpha_4\beta_7$ integrin is a well validated target for the treatment of inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis. The approved biologic vedolizumab is an antibody targeting $\alpha_4\beta_7$ and is delivered via injection or infusion, severely limiting accessibility and affordability. An orally bioavailable small molecule therapeutic would represent an enormous step forward in addressing these diseases on a global scale. Despite R&D efforts for over 20 years, the design of potent and selective small molecule inhibitors of $\alpha_4\beta_7$ has been unsuccessful due in large part to the daunting task of overcoming the protein's structural similarity to other integrin family members. Furthermore, maintaining high potency while balancing optimal physical properties in the design of an oral small molecule inhibiting protein-protein interactions is a formidable challenge.

Morphic Therapeutic, experts in all things integrin, partnered with Schrödinger's drug discovery team to design an orally bioavailable drug selectively targeting $\alpha_4\beta_7$ integrin to treat inflammatory bowel disease. The goal of the program was to leverage a digital chemistry approach, using the power of physics-based predictive modeling technologies combined with Morphic's unique integrin biology and chemistry insights, to design a highly selective $\alpha_4\beta_7$ inhibitor with best-in-class properties.

Driving efficient, data-driven design cycles with LiveDesign

Dispersed teams and remote work environments can pose a significant obstacle to real-time collaboration in a drug discovery program. **LiveDesign**, Schrödinger's cloud-based enterprise informatics platform, enables project teams to design compounds, run predictive models, and analyze experimentally-generated data in one place, allowing teams to drive design-make-test-analyze (DMTA) cycles either independently or collaboratively in teams. Centralizing data access and design tools within LiveDesign was imperative to the project team's ability to tackle their $\alpha_4\beta_7$ integrin inhibitor design challenge (Figure 1).

Using LiveDesign, the Morphic and Schrödinger teams efficiently evaluated and triaged thousands of design ideas much faster than with traditional methods, with far fewer meetings required. Using LiveDesign as the data and predictive modeling platform allowed the teams to utilize a multi-parameter optimization (MPO) strategy driven by advanced data analytics, accurate biophysical modeling of potency and selectivity, and predictive models for pharmacokinetic (PK) properties. Enabled by seamless integration of data, visualization, and predictive modeling, the team rapidly prioritized molecules for synthesis and testing, which resulted in the identification of novel chemical matter that combined the key properties required to overcome all hurdles.

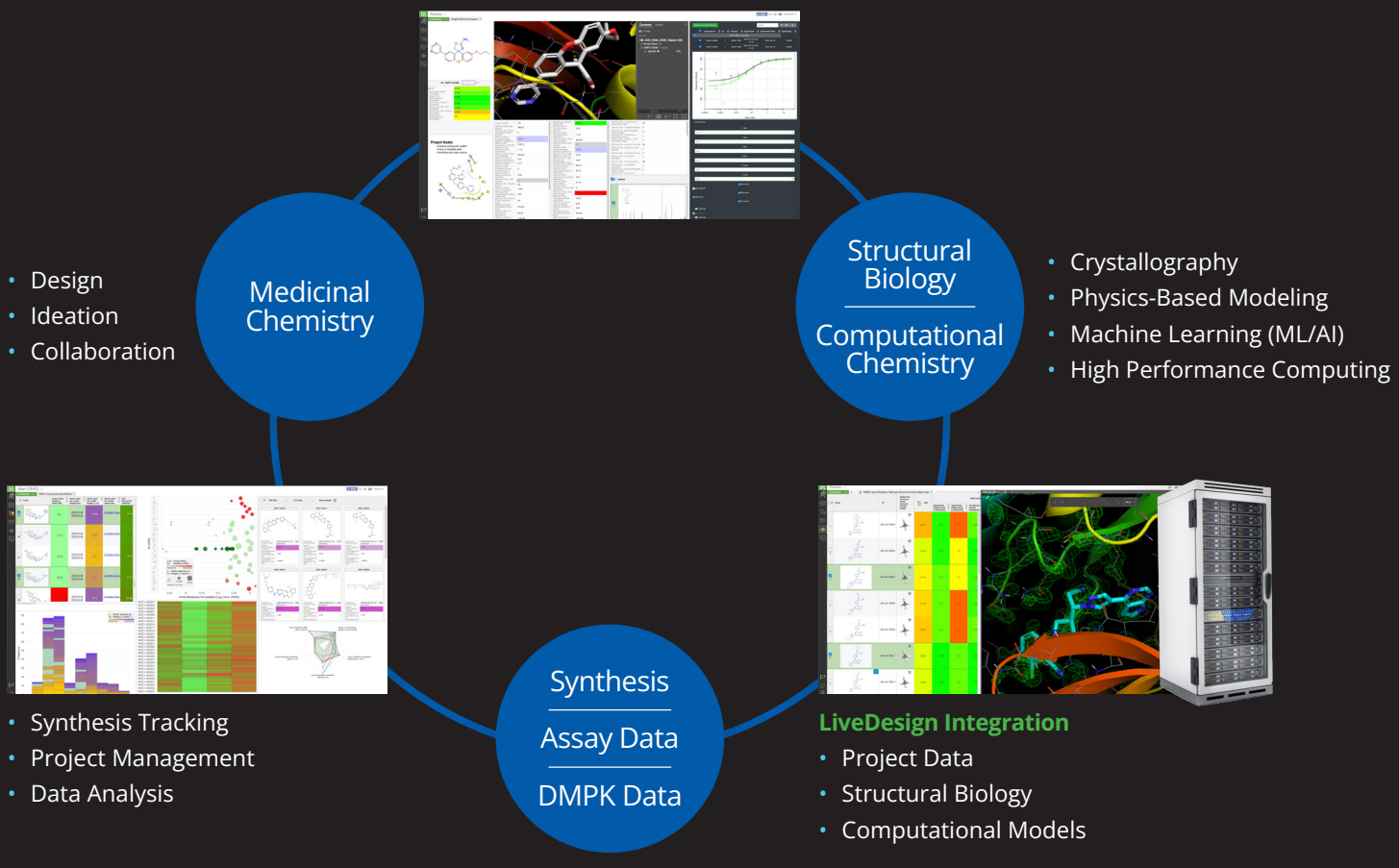


Figure 1: Modeling strategy and DMTA cycle employed in LiveDesign for the $\alpha_4\beta_7$ inhibitor program.

Gaining potency and balancing ADMET properties through rigorous computational assays

Through generation of over 100 proprietary co-crystal structures of inhibitor-bound $\alpha_4\beta_7$ as well as $\alpha_4\beta_1$ — a key off-target — the project team gained significant novel insight into the structure-activity relationships (SAR) of potency and selectivity. However, balancing PK properties with potency remained unsolved. To address this challenge the team combined advanced pK_a prediction (a parameter known to correlate with oral bioavailability) using quantum mechanics (**Jaguar**) with free energy perturbation simulations (**FEP+**) for accurate potency prediction. The accuracy and utility of FEP+ as a computational assay for the prediction of relative binding energies of molecules has been validated extensively, generating predictions within 1.0 kcal/mol of experimental values on average.[1]

Over 8,500 FEP+ calculations were performed, enabling the team to improve potency 1000-fold, while simultaneously addressing PK liabilities. In parallel, a membrane permeability prediction model was applied to each design as part of the MPO strategy. Compounds that met the computational MPO were then synthesized in the lab. All resulting data obtained for synthesized analogs — both modeled and experimentally derived — were stored and analyzed in LiveDesign. Compounds that were identified to satisfy potency, selectivity, and permeability criteria were aggressively pursued with further characterization (Figure 2). The team's efforts culminated in the design and delivery of MORF-057, a clinical candidate currently in Phase 2b development for treatment of ulcerative colitis (Figure 3).

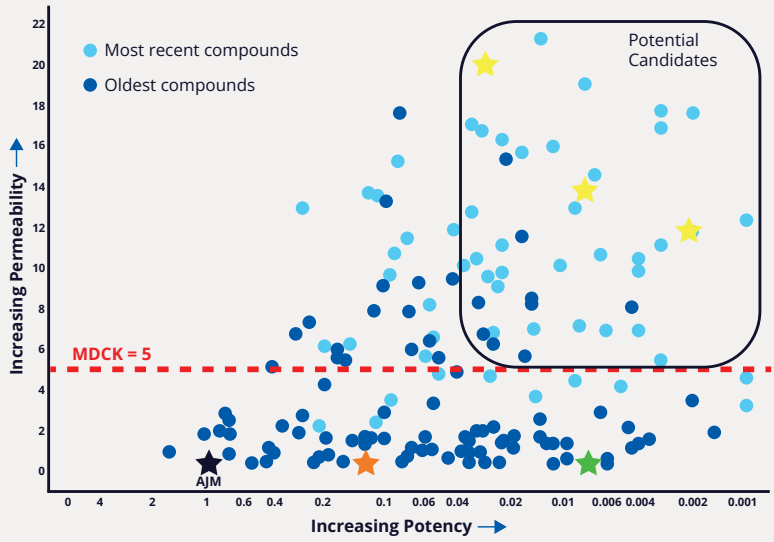
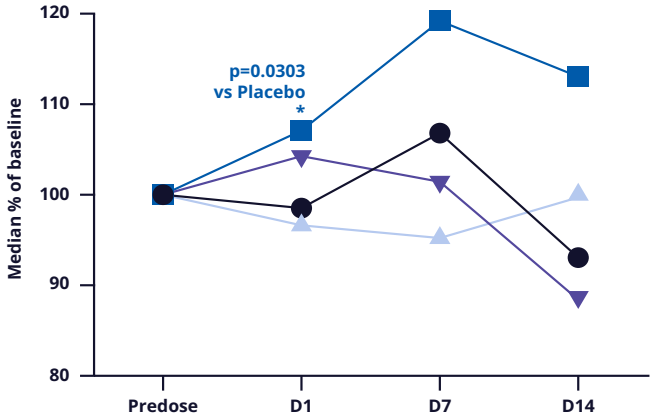


Figure 2: Improving cellular potency and permeability over time using a hypothesis-driven, property-focused computational design strategy. The data points in dark blue represent the early compounds, while the data points in light blue represent the more recently designed compounds. The red dashed line marks the MDCK value of 5; above 5 correlates to an increased absorption. AJM (black star) is a competitor compound that is approved in Japan, requires three doses per day, and is not selective between $\alpha_4\beta_7$ and $\alpha_4\beta_1$. A promising early compound designed by Morphic (orange star) was further optimized and resulted in a compound (green star) with a potency 200x greater than AJM. Additional optimization resulted in a number of potential candidates in the upper right square, including what would become MORF-057.[2]

β7 high effector memory T cells



β7 central memory T cells

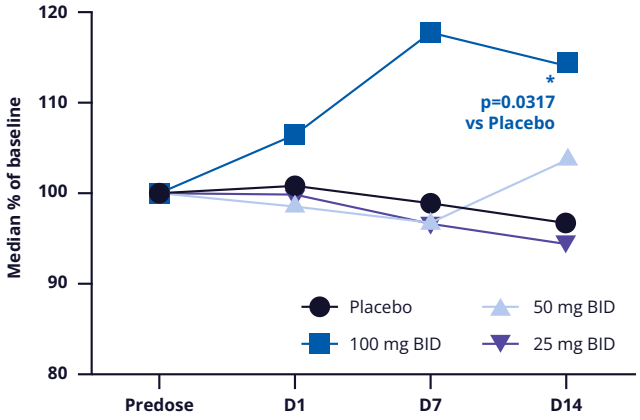


Figure 3: MORF-057 demonstrated changes in pharmacodynamic biomarkers consistent with those of approved antibody drugs.[3]

Enabling digital technologies to drive discovery programs

LiveDesign

Collaborative enterprise informatics platform for centralizing access to virtual and wet lab project data and powerful computational predictions

FEP+

Digital assay for predicting protein-ligand binding across broad chemical space at an accuracy matching experimental methods

Jaguar

High performance quantum mechanics package enabling pK_a prediction

Software and services to meet your organization's needs

Industry-Leading Software Platform

Deploy digital drug discovery workflows using a comprehensive and user-friendly platform for molecular modeling, design, and collaboration.

Research Enablement Services

Leverage Schrödinger's team of expert computational scientists to advance your projects through key stages in the drug discovery process.

Scientific and Technical Support

Access expert support, educational materials, and training resources designed for both novice and experienced users.

References

1. Advancing drug discovery through enhanced free energy calculations. Abel et al. Acc. Chem. Res. 2017, 50, 7, 1625–1632.
2. Accelerating first-in-class and best-in-class programs using a large-scale digital chemistry strategy. Bursavich et al. Endpoints Webinar.
3. MORF-057, an oral selective α4β7 integrin inhibitor for Inflammatory Bowel Disease, leads to specific target engagement in a single and multiple ascending dose study in healthy subjects. Ray et al. ECCO 2021.

Contact us: sales@schrodinger.com
Learn more: www.schrodinger.com/platform/drug-discovery

Schrödinger