Schrödinger Japan
Drug Discovery Summit 2024
Abstract

July 2024

The Predict-First paradigm: How Digital Chemistry is Shaping the Future of Drug Discovery

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Digital chemistry offers a modern paradigm for enabling rapid in silico testing of design ideas using highly accurate computational assays of key properties, accessible across whole project teams. This shift from design strategies based largely on experimental trial and error towards a 'predict-first' approach to drug discovery allows teams to dramatically expand the chemical space that can be explored and results in a highly interactive, computationally-driven design-model-make-test-analyze (DMMTA) cycle. Chemists are empowered to test hypotheses through predictive modeling and iteratively improve designs prior to compound synthesis. Teams can confidently explore novel, and often more complex designs while sending only the top scoring molecules for synthesis therefore improving efficiency and cost of the discovery process.

In this talk we describe a predict-first approach using prospective physics-based computational models to advance two of our wholly owned oncology programs through successive rounds of chemical space exploration, filtering, and compound optimization to generate clinical-stage compounds. We will also present the discovery and optimization of selective aV family integrin family inhibitors driven by computational methods and structural biology advancements from collaborative work with Morphic Therapeutic.

Our MALT1 inhibitor SGR-1505 was discovered in 10 months from project initiation and shows potent inhibition of MALT1 enzymatic activity and anti-proliferative activity in the activated B-cell (ABC) subtype of diffuse large B cell lymphoma (DLBCL) cell lines. In combination with approved agents, SGR-1505 demonstrates strong combination potential with Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib in ABC-DLBCL cell lines. SGR-1505 has recently been characterized in human clinical trials. In our WEE1/Myt1 inhibitor program, Free Energy Perturbation (FEP) and Protein FEP were deployed to identify novel, potent, and highly selective nanomolar WEE1/Myt1 co-inhibitors that demonstrate superior kinase selectivity compared to existing WEE1 clinical compounds in a broad kinase panel with >450 kinases (ScanMAX) and desirable ADME, CYP3A4 TDI properties, and PK profiles in preclinical species. SGR-3515 demonstrates dose-dependent target engagement, tumor growth inhibition, and tumor regression at high doses and improved therapeutic index after intermittent dosing.

Inhibitors of integrins αvβ6 and αvβ1 have the potential to treat fibrotic disease through blockage of the TGFβ pathway. In collaboration between Morphic Therapeutic and Schrodinger, we investigated a series of zwitterionic alpha amino acid αvβ6 inhibitors in a structurally enabled program. Efficient DMMTA cycles driven by FEP+ for potency and selectivity predictions and QM pKa calculations for permeability optimization enabled rapid identification of potent and selective αvβ6 inhibitors. These efforts resulted in identification of αvβ6 selective development candidate MORF-627. We were able to use FEP+ to identify αvβ1 selective inhibitors quickly within the same zwitterionic alpha amino acid chemical series.

創薬研究の初期における、
タンパク質立体構造を核とした戦略的アプローチ

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これまでに上市された医薬品の多くは、生体内で機能するタンパク質を標的としていることは周知の事実である。セントラルドグマの最下流であるタンパク質は、その複雑な立体構造と物理化学的性質に基づいた固有の機能を有している。それらを標的として医薬品を選択的に作用させることによって、望まれる薬理活性を発揮しつつ、副作用を低減させることができる。従来の低分子や抗体医薬品の多くは、標的とするタンパク質を阻害あるいは活性化してその薬理活性を発揮しているが、近年では、抗体薬物複合体のように特定の組織をターゲティングする目的として生体内のタンパク質を利用するような医薬品も上市されている。さらに最近では、標的タンパク質分解誘導キメラ分子（PROteolysis TArgeting Chimeras; PROTACs）の研究開発が急速に進展している。PROTAC は、生体内の E3 ユビキチンリガーゼが持つ機能を利用して標的タンパク質を分解することができ、次世代医薬品の一つとして期待されている。タンパク質を標的とする、あるいは利用するモダリティを開発する初期段階においては、対象とするタンパク質に対して特異的に結合する分子を取得することが共通の目標となる。特に、低分子化合物を同定することは、合成展開が容易である点、細胞内外を問わず作用できる点、さらに ADC、PROTAC など次世代医薬品に応用できるといった点から、その後の研究開発を大きく進展させるための重要なステップである。

我々のグループでは、研究対象とするタンパク質の選定から低分子化合物のスクリーニング、最適化合成に至るまで、タンパク質立体構造に基づいて研究を進めている。特にスクリーニングにおいては、実験的アプローチと in silico アプローチを組み合わせることで、より確実かつ迅速に候補化合物を同定することを実現している。その際に鍵を握るのは、早期にタンパク質－リガンド複合体構造を決定することである。それにより、精度の高いバーチャルスクリーニング、FEP 解析が可能となる。本講演では、早期に複合体構造を取得することを目的とした化合物スクリーニングの方法や、構造解析の手法、in silico アプローチの詳細について、可能な範囲で実例を交えながら紹介したい。

Leveraging Physics-based Computational Approaches for the Discovery of Highly Novel and Potent NLRP3 Inhibitors

Andrew Placzek, PhD
Principal Scientist, Schrödinger

The NLRP3 Inflammasome is a very attractive therapeutic target for addressing a wide variety of inflammatory and autoimmune diseases. High therapeutic momentum stemming from positive preclinical and clinical data with NLRP3 inhibitors has given rise to a highly competitive area of drug discovery involving many biotechnology and pharmaceutical companies. In this talk, I will describe the use of our physics-based computational platform, allied with machine learning techniques, enabling the rapid identification of several unique and potent NLRP3 inhibitors capable of targeting both peripheral and CNS diseases. A range of functional and mechanistic cellular assays, in vivo pharmacodynamic and human disease models have been used to explore NLRP3 pathway inhibition by these small molecules.

Leveraging the Ongoing Revolutions in Machine Learning and Physics-Based Modeling to Expanded Impact in Small Molecule and Biologics Drug Discovery

Matt Repasky, PhD
Senior Vice President, Schrödinger

At Schrodinger, the multi-year mission of scientific development has three components, (1) to increase the number and types of targets our platform can progress, (2) to improve the effectiveness and efficiency of discovery program progression, and (3) to expand the applicability of our platform to new, high value areas. To provide insight into the types of challenges that are currently under investigation, a few not-yet-released active scientific projects will be discussed covering small molecule and biologics development. These projects employ a mixture of physics-based modeling and machine learning to advance the three high-level goals of scientific development.

In Silico Enabled Hit Identification with the Schrödinger Platform: Case Studies in EGFR and DLK Inhibitor Drug Discovery Programs

Hideyuki Igawa, PhD
Director, Therapeutic Group, Schrödinger

In this talk, we will present examples of ultra-large scale *in silico* chemical space exploration using AutoDesigner, a synthetically-aware *de novo* design method, coupled with highly accurate physics based FEP$^+$ calculations. We will outline the application of this approach to successful and rapid hit identification in two drug discovery programs within Schrödinger's therapeutics group. In the epidermal growth factor receptor (EGFR) triple mutant program, we will detail a discovery of a novel chemical series with a unique hinge binding motif and identification of a WT-sparing lead compound with dose-dependent tumor growth inhibition in a Ba/F3 EGFR del19/T790M/C797S CDX model. In the dual leucine zipper kinase (DLK) program, a novel energy of solvation method (E-sol) will also be highlighted to identify brain-penetrant advanced lead molecule (KAI-11101) which showed neuroprotective properties in an *ex vivo* axon fragmentation assay and demonstrated dose-dependent p-c-Jun reduction in *in vivo* mouse cerebellum PK model.

Exploiting Computational Tools in the Design of First-in-class Small-molecule Inhibitors of SARS-CoV-2 NSP14 Guanine-N7 RNA Cap Methyltransferase

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The global impact of the COVID-19 pandemic necessitated the development of new therapeutics targeting the causative agent, SARS-CoV-2, to reduce hospitalizations and deaths by lessening the severity of the disease. Disruption of the RNA-capping machinery of SARS-CoV-2 represents a novel therapeutic approach via a mechanism important for viral RNA translation and evasion of the host innate immune response. The first step in this process is mediated by the viral guanine-N7 methyltransferase (MTase) activity of NSP14. Here, we report the development of a highly-potent, non-nucleoside, small-molecule inhibitor of NSP14 MTase activity. High-throughput screening identified a sulfonamide-carboxamide pyrrole scaffold exemplified by TDI-012992. We exploited a range of computational tools during hit-to-lead optimization of this series. Prior to structural enablement, we used large-scale enumeration to efficiently explore chemical space. Compound data analysis, ideation, and modelling were coordinated through Schrödinger's Live Design platform. In addition, we worked with Schrödinger to implement third-party tools for exploration of commercially-available chemical space and retrosynthesis planning into Live Design. Using the crystal structures that became available during the project, we then utilized Schrödinger's Glide docking and FEP+ calculations to drive compound potency into the subnanomolar range. Design efforts resulted in the identification of TDI-015051 with a KD of 39 pM and an EC50 of 11 nM in a cell-based viral replication system. TDI-15051 also inhibited viral replication in a mouse model with efficiency comparable to the FDA-approved protease inhibitor nirmatrelvir. This finding represents the first validation of NSP14 as a drug target for SARS-CoV-2 and the first example of a methyltransferase inhibitor as an antiviral. Inhibition of viral cap methylases as an antiviral strategy should also be applicable to other viruses of pandemic concern.

武田薬品における
AI/ML を利用した創薬化学研究の事例

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創薬プロセスのもっとも大きな課題の一つは長い研究期間と膨大な研究開発費用を必要とすることである。そのため、一連の創薬プロセスの各ステップにおいて、効率化や成功確率の向上を目指す検討がなされている。なかでも創薬化学研究は膨大なケミカルスペースから期待する生物活性を有する医薬品候補化合物を探索するプロセスであり、効率化や成功確率の向上の余地があると考えられる。このため、AI/ML を利用してこのプロセスを効率化することへの期待が高まっており、武田薬品においても創薬化学研究への AI/ML の活用をすすめてきた。本講演では、有用な外部技術を取り入れながら実際の創薬研究プログラムに AI/ML を適用した弊社におけるいくつかの事例について紹介し、これらの経験に基づいた創薬化学研究におけるＡＩ/ML の可能性および課題について議論したい。