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nimbus

How Computational Chemistry with Structural Biology is Enabling Drug Discovery

Scott Edmondson, Nimbus Therapeutics

ACS Webinar Series, 24-June-2021

Confidential
Computational Chemistry in Drug Discovery

- Computational chemistry can support most of the discovery process
- Today's presentation will focus on how to improve hit-to-lead and lead optimization

Drug Discovery Funnel for Hit-to-Lead and Lead Optimization

- After each tier, compounds are assessed for progression
- Early cascade designed to rapidly identify potent/selective compounds
  - Biochemical assays assess potency at target and 'antitargets'
- If compounds are unsuitable to progress, new compounds are designed and synthesized to overcome their liabilities
  - Compound synthesis and testing are expensive and time-consuming
- Cycle is often called “Design, Make, Test, Analyze” (DMTA)
- How can we improve the DMTA cycle?
How can we improve the DMTA Cycle?

- After each tier, compounds are assessed for progression
- Early cascade designed to rapidly identify potent/selective compounds
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  - Compound synthesis and testing are expensive and time-consuming
- Cycle is often called “Design, Make, Test, Analyze” (DMTA)
- How can we improve the DMTA cycle?
  - Better designs that leverage target and antitarget potency predictions

A. Assess compound efficacy in vivo in parallel to primary potency
B. Synthesize more compounds
C. Use computational methods to improve designs
D. Skip the assay cascade and only make the development candidate
Tyrosine Kinase 2 (TYK2)
Allosteric Inhibition to Address Autoimmune Disorders

TYK2 Modulates Signaling Downstream of Cytokines Important to Autoimmune and Inflammatory Diseases

- TYK2 is a signal-transduction kinase for IL-23, IL-12 and Type-I interferon receptors
- Human TYK2 loss of function variant confers protection from autoimmune disease risk (e.g. psoriasis, RA, SLE, etc…)
  - Selective TYK2 inhibitors should phenocopy the risk profile of patients with LoF mutations
- TYK2 functions as heterodimer paired with JAK1 or JAK2
  - Inhibition of either member of the dimer blocks receptor signaling

Targeting TYK2 May be Safer than JAK Inhibitors… but Challenging to Achieve Selectivity

- JAK inhibitor medicines such as tofacitinib carry black box warnings
  - Enhanced risk of venous thromboembolism (VTE), serious infections, malignancy, cytopenias, lipid abnormalities
- High binding site homology between orthosteric (catalytic) binding sites of TYK2 and JAK1/2/3 kinases
  - Important to achieve high selectivity vs JAK family
- Allosteric TYK2 inhibition at the JH2 site may achieve high selectivity vs other JAK members


Poor Prospects of Achieving Selectivity vs JAKs in Catalytic Binding Pocket

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>TYK2 catalytic domain</th>
<th>JAK1 catalytic domain</th>
<th>JAK2 catalytic domain</th>
<th>JAK3 catalytic domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>489</td>
<td>15</td>
<td>77</td>
<td>55</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>61</td>
<td>4</td>
<td>7</td>
<td>787</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>2,600</td>
<td>363</td>
<td>2,400</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>4,690</td>
<td>47</td>
<td>120</td>
<td>2,304</td>
</tr>
<tr>
<td>PF-06700841</td>
<td>23</td>
<td>17</td>
<td>77</td>
<td>6,494</td>
</tr>
<tr>
<td>PF-06826647</td>
<td>17</td>
<td>383</td>
<td>74</td>
<td>&gt;10,000</td>
</tr>
</tbody>
</table>

In contrast to the catalytic site inhibitors, allosteric JH2 inhibitors have been described with excellent biochemical selectivity vs JAK catalytic sites (e.g. BMS-986165 = deucravacitinib, >10,000-fold selective vs JAK1/2/3 catalytic domains)

- Deucravacitinib exhibits 17-fold selectivity over JAK1 JH2 site: TYK2 JH2 $K_i = 0.02$ nM; JAK1 JH2 $K_i = 0.33$ nM

X-ray Crystal Structures of Ligands Bound to JH2 Allosteric Site Used to Build a Computational Model for TYK2 Potency Predictions

Predicted vs Experimental Potency at TYK2
(representative graph)

- Early in Hit-to-Lead, biochemical binding data + X-ray crystal structures used to build TYK2 JH2 potency prediction model
- Physics-based free energy perturbation (FEP) model was applied to a wide range of chemotypes
- ≥ Dozens of compounds assessed in a DMTA cycle
- Improved ability to prioritize compounds for synthesis with best predicted potency and selectivity
- Compounds more likely to progress down assay cascade

Med Chem Design/Ideation (dozens/hundreds of cpds)

Preliminary triage: high throughput docking, properties, etc...

FEP potency predictions at TYK2; selectivity vs JAK catalytic sites

TYK2 IC<sub>50</sub> < 10 nM, JAK1-3 > 100-fold

Compound Synthesis

More extensive in vitro and in vivo cascade

TYK2 IC<sub>50</sub>
JAK 1-3 IC<sub>50s</sub> / K<sub>d</sub>

Single Amino Acid Difference at Allosteric Binding Pocket Confers Excellent TYK2 Selectivity for Nimbus Clinical Compound

Deucravacitinib (BMS-986165)
Also Binds in the JAK1 *Allosteric* Pocket

Nimbus Clinical Candidate
Prohibited from Binding in JAK1 Allosteric Pocket

Source: Nimbus proprietary structure based computational modeling; TYK2 has a valine in the JH2 binding pocket
1\textsuperscript{st} and 2\textsuperscript{nd} Generation JAK Inhibitors Are All Multi-JAK Inhibitors

- As agents reach clinically relevant doses/concentrations ($C_{\text{max}}$ and $C_{\text{av}}$), they inhibit multiple JAK family members ($IC_{20-50-80}$)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/Regimen</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>5mg BID (Pfizer, Xeljanz\textsuperscript{R}, Catalytic Inhibitor)</td>
<td>Internal Nimbus analysis of publicly available information. For approved agents, approved dose regimen used. Maximum concentration at steady state ($C_{\text{max}}$) and average concentration ($C_{\text{av}}$) in human plasma (both unbound) and cellular potency ($IC_{50}$).</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>2mg QD (Lilly, Olumiant\textsuperscript{R}, Catalytic Inhibitor)</td>
<td></td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>15mg ER QD (AbbVie, Rinvoq\textsuperscript{R}, Catalytic Inhibitor)</td>
<td></td>
</tr>
</tbody>
</table>

**Legend**
- Denotes $IC_{50}$
- [50% inhibitory concentration, the amount which clinical activity is routinely demonstrated]

Nimbus Clinical Candidate Demonstrates Exquisite TYK2 Selectivity vs. Catalytic TYK2 Inhibitors

- By targeting the allosteric (JH2) domain, selectivity just for TYK2 can be achieved
- Nimbus' high selectivity allows clinical exploration of greater TYK2 inhibition (e.g. $IC_{70-80-90}$) while still avoiding JAKs & off-targets
- Ph 2b for psoriasis planned in 2H2021

**Legend**
- Denotes $IC_{50}$
- [50% inhibitory concentration, the amount which clinical activity is routinely demonstrated]
Hematopoietic Progenitor Kinase 1 (HPK1)
Key Regulator of T cell, B cell, and Dendritic Cell-mediated Immune Responses

HPK1 Inhibitors for the Treatment of Cancer

- Negative Regulator of T cells and Dendritic Cells
- HPK1 inhibitors may allow immune cells to break tolerance and evade immunosuppressive mechanisms conferred by tumor cells

HPK1 Inhibitor Designs Enabled by Advances in Crystallography

- Proprietary crystal structures of HPK1 and other MAP4K family members such as GLK
  - Co-crystals of the off-targets applied to design out undesired activities
- Protein/ligand structures guided SBDD and FEP+ to improve HPK1 potency and selectivity
- Further synthesis and optimization yielded novel ligands
- Improved biochemical specificity resulted in robust immune activation responses

NMBS-2 is a Potent HPK1 Inhibitor with Excellent Selectivity Against MAP4K Family Members and Immune Cell Kinases

<table>
<thead>
<tr>
<th>Assay</th>
<th>NMBS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPK1 Caliper IC_{50} @ 1mM ATP</td>
<td>&lt;1 nM</td>
</tr>
<tr>
<td>pSLP-76 Cell IC_{50}</td>
<td>42 nM</td>
</tr>
</tbody>
</table>

- Assessed against broad panel of >300 kinases; highly selective for HPK1 only
- High selectivity required for robust immune cell activation
Robust Tumor Growth Inhibition Observed in the Mouse CT-26 Model in Combination with Anti-PD1

CT-26 Syngeneic Mouse Model (Day 19)

Kaplan-Meier Survival Analyses

- NMBS-2 as a single agent, and combined with anti-PD-1, exhibits efficacy in multiple mouse syngeneic models
- NMBS-2 is currently in preclinical development with Ph 1 initiation planned in 2H2021
Multiple Promising Targets For Nimbus’ SBDD Approach

Werner Syndrome Helicase (WRN)
Casitas B lymphoma-B E3 Ligase (Cbl-b)
CTP Synthase 1 (CTPS1)

Selectively Targeting a Synthetic Lethal Dependency of Microsatellite Instable Tumors

Multiple Promising Targets For Nimbus’ SBDD Approach

Werner Syndrome Helicase (WRN)
Casitas B lymphoma-B E3 ligase (Cbl-b)
CTP Synthase 1 (CTPS1)

A Negative Regulator of Anti-tumor Immune Responses as a Target for Immuno-oncology
Multiple Promising Targets For Nimbus’ SBDD Approach

Key Enzyme in the Pyrimidine Synthesis Pathway as a Target For Autoimmune Disease and Cancer

- Werner Syndrome Helicase (WRN)
- Casitas B lymphoma-B E3 ligase (Cbl-b)
- CTP Synthase 1 (CTPS1)

Multiple Promising Targets For Nimbus’ SBDD Approach

- Computational chemistry and SBDD enable improved med chem designs → differentiated clinical candidates
  - TYK2 and HPK1 inhibitors
- Currently expanding our approach to non-kinase targets: CTPS1, Cbl-b, and WRN

Med Chem Design/ideation (dozens/hundreds of cpds)

Preliminary triage

FEP potency and selectivity predictions

Compound Synthesis

Primary Target IC50 or EC50
Antitarget IC50 or EC50

Target IC50 < 10 nM, Antitarget >100-fold

More extensive in vitro and in vivo cascade
Which of these spaces in the discovery continuum can computational chemistry enable and/or improve?

A. Target selection
B. Hit generation
C. Hit-to-Lead and Lead Optimization
D. Early preclinical development
E. All of the above

Which of these spaces in the discovery continuum can computational chemistry enable and/or improve?

A. Target selection
B. Hit generation
C. Hit-to-Lead and Lead Optimization
D. Early preclinical development
E. All of the above
Next Steps for Computational Chemistry in Drug Discovery

- Incorporation of molecular dynamics into affinity predictions
- Physicochemical property and DMPK predictive tools
- Improved ability to impact target selection and hit generation

**How can we Continue to Improve Drug Discovery?**

The ‘Old-Way’
Repeat, Repeat, Repeat…

The ‘Nimbus Way’
Breakthroughs by design

Enabling technologies allow for incremental steps towards this goal
We Design Breakthrough Medicines

- **Medicines are our mission**
  - Targets with highly validated disease roles
  - Couple structure-based expertise with cutting-edge computational tools
  - Progress key programs into clinical development

- **Track record of success – propelling us forward**
  - Multiple programs to the clinic:
    - ACC inhibitor for NASH
    - TYK2 inhibitor for psoriasis
  - Discovery engine has produced a pipeline of desired, difficult to drug targets, progressing to the clinic, including HPK1
  - Next generation of targets already on the horizon

TYK2 and HPK1 Acknowledgements

Beth Browning
Rebecca Carazza
Samantha Carreiro
David Ciccone
Alan Collins
Scott Edmondson
Abbas Kazimi
Neelu Kaila
Silvana Leit
Christine Loh
Joshua McElwee
Angela Toms
Peter Tummino

Mark Ashwell
Heather Blanchette
Byron DeLaBarre
Rosana Kapeller
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Sayan Mondal
Dan Severance
Shawn Watts
Shunqi Yan

Dryad

Anya Avrutskaya
Matthew Benson
Mike Briggs
Bethany Bowers
Thi Bui
Erica Goldsmith
Victoria Hughes
Marielle Lamers
Vad Lazari
Phil Leonard
Ian Linney
Natalie Lyall-Varnas

Sarah L Martin
Anthony Middleton
Nick Pearson
Adam Ringrose
Stuart Ward
Yvonne Walker
Ben Whittaker
Douglas Weitzel
Grant Wishart
Eddie Wood
Benno Van El
Back-ups

Research Triage Funnel for Hit-to-Lead and Lead Optimization

- Computational chemistry and SBDD enable improved designs
  - Accelerating the identification of highly potent and selective compounds
  - TYK2 and HPK1 inhibitors
- Expanding our approach to non-kinase targets: CTPS1, Cbl-b, and WRN
- Next frontier(s) for computational chemistry
  - Physicochemical property predictions
  - Molecular dynamics incorporation into potency predictions
  - Target selection

Med Chem Design
SBDD Guided Potency and Selectivity Predictions

Predicted Target $IC_{50} < 10$ nM, Predicted Antitarget selectivity >100-fold

Compound Synthesis

Primary Target $IC_{50}$ or $EC_{50}$
Antitarget $IC_{50}$ or $EC_{50}$

Primary Target $IC_{50} < 10$ nM, Antitarget selectivity >100-fold

Timeline

- Solubility
- In vitro safety assays
- In vitro DMPK assays
- Lipophilicity
- In vivo rodent pharmacokinetics (PK)
- Off-target panel
- In vivo PD and efficacy
- Mechanistic DMPK studies
- In vivo non-rodent PK
- Rodent and non-rodent toxicity studies
- Development Candidate
How Computational Chemistry is Accelerating Drug Discovery

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VOLUME 54
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