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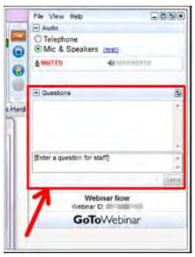
Have Questions?



Type them into questions box!

"Why am I muted?"
Don't worry. Everyone is muted except the presenter and host.
Thank you and enjoy the show.

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Learn how to write better abstracts, deliver more engaging presentations, and network to your next dream job. Brush up on your soft skills and set a new career path by mastering what can not be taught in the lab.

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Why does food taste better when it is grilled or what molecular compounds make a great wine? Discover the delectable science of your favorite food and drink and don't forget to come back for a second helping.

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Business & Entrepreneurship

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How do ideas make it from the lab to the real world? Discover the ins and outs of the chemical industry whether you are looking to start a business or desire a priceless industry-wide perspective.

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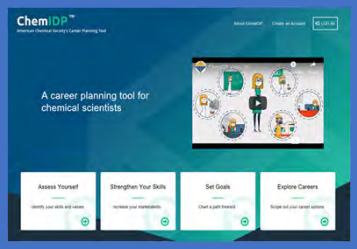

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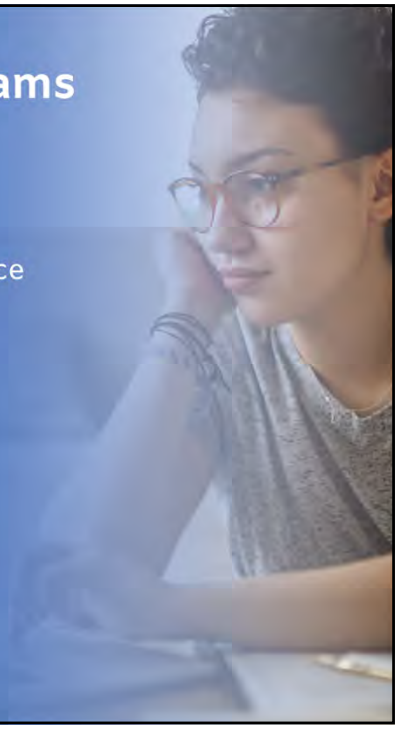

ACS Career Navigator: Your Home for Career Services

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Whether you are just starting your journey, transitioning jobs, or looking to brush up or learn new skills, the **ACS Career Navigator** has the resources to point you in the right direction.

We have a collection of career resources to support you during this global pandemic:


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A Career Planning Tool For Chemical Scientists

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https://chemidp.acs.org

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- **Resources to help write competitive grad school applications and connect you with mentors, students, and industry partners!**

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Email us at bridge@acs.org

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ACS Department of Diversity Programs

Advancing ACS's Core Value of Diversity, Inclusion & Respect

We believe in the strength of diversity in all its forms, because inclusion of and respect for diverse people, experiences, and ideas lead to superior solutions to world challenges and advances chemistry as a global, multidisciplinary science.

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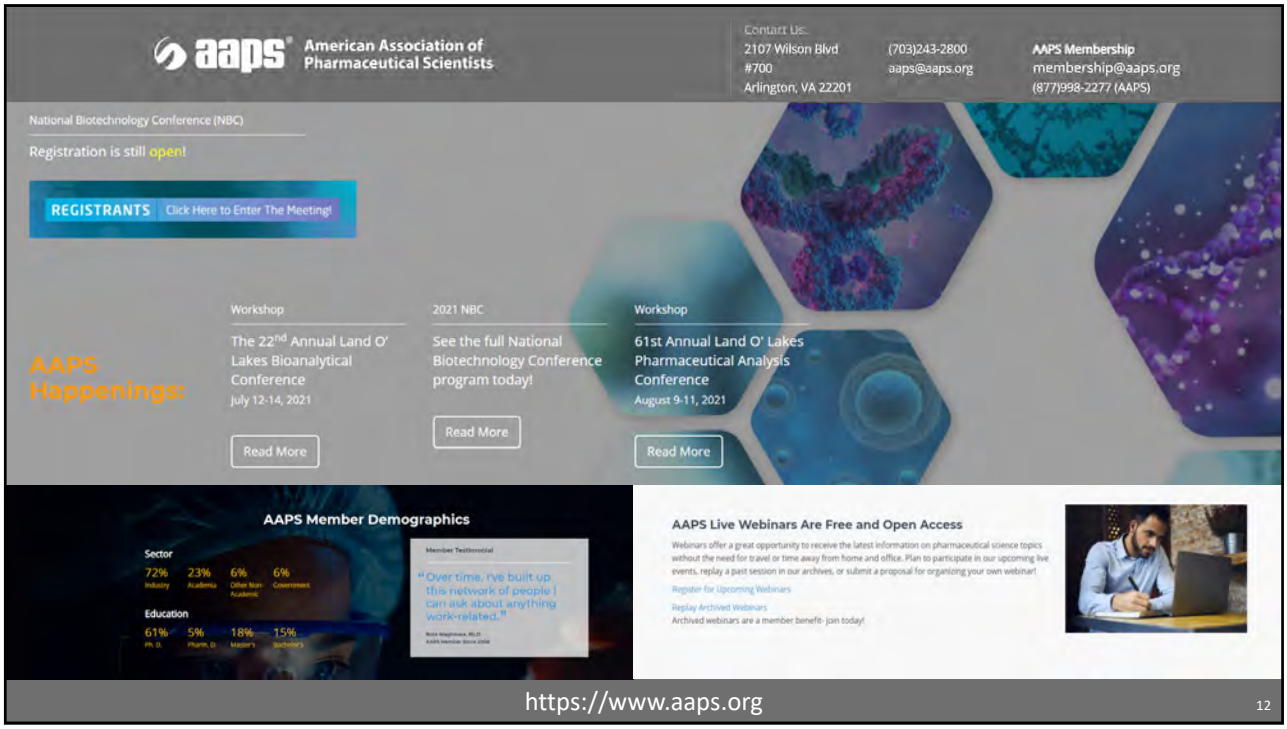

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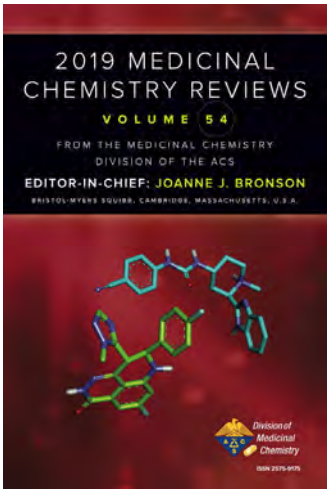

For $25 membership ($10 for students)**, You Will Receive:**

- A free digital copy of our annual medicinal chemistry review volume (over 680 pages, $160 retail price)
- Abstracts of MEDI programming at national meetings
- Access to student travel grants and fellowships

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ACS Publications


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Bristol-Myers Squibb


John Morrison
The Janssen Pharmaceutical Companies of Johnson & Johnson


Nurulain Zaveri
Astraea Therapeutics

2021 Drug Design and Delivery Series

We are continuing the theme of last year's symposium and will feature more of the most innovative and revolutionary ideas in drug design and delivery. **This year we have decided to increase the duration of each broadcast for an additional 30 minutes in the hope to dive deeper into each topic as well as answer more of your questions.** The details for upcoming broadcasts will be posted as they are finalized.

CO-PRODUCED WITH

ACS Technical Division Medicinal Chemistry (MEDI)

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ACS Webinars
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Artificial Molecular Machines

Going from Solution to Surfaces

ACS President H.N. Cheng Presents:

FRONTIER FRIDAYS

Featuring 2016 Nobel Laureate in Chemistry Sir Fraser Stoddart

Date: Friday, June 25, 2021 @ 2-3:30pm ET
Speaker: Sir Fraser Stoddart, 2016 Nobel Laureate in Chemistry, Board of Trustees Professor of Chemistry, Northwestern University and H.N. Cheng, ACS President
Moderator: Young-Shin Jun, Washington University in St. Louis

Register for Free!

What You Will Learn:

- How mechanically interlocked molecules (MIMs) are easily made and how they can be used inn the construction of artificial molecular machines (AMMs)
- How AMMs operate under kinetic control using energy ratchets in a manner similar to that employed by our many biomotors and are at odds with how machines operate in the macroscopic world: the difference could not be more stark!

Co-produced with: ACS Committee on Science

Chemistry on Capitol Hill

2021 Emerging Policies

Date: Wednesday, June 30, 2021 @ 2-3pm ET
Speakers: Caroline Trupp Gil, American Chemical Society / Karen Garcia, American Chemical Society / Carl Maxwell, American Chemical Society
Moderator: Lauren Posey, American Chemical Society

Register for Free!

What You Will Learn:

- How the Biden Administration and 117th Congress are shaping up in terms of its STEM priorities
- Which specific pieces of legislation or federal policies will be likely to impact ACS members
- How members can become involved

Co-produced with: ACS Government Affairs

Designing Bio-Sourced Polymers

that Enable Recycling

Date: Thursday, July 1, 2021 @ 2-3pm ET
Speaker: Stefan Mecking, University of Konstanz
Moderator: Mark Jones, Dow Chemical (retired)

Register for Free!

What You Will Learn:

- What is solvolysis and how it can enable plastics recycling
- How renewable polycarbonates and polyesters with a low density of in-chain functional groups as break points in a polyethylene chain can be recycled chemically
- How long-chain building blocks for polycondensation can be created from common plant oil feedstocks or microalgae oils

Co-produced with: ACS Division of Polymer Chemistry

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How Computational Chemistry is Accelerating Drug Discovery

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How Computational Chemistry is Accelerating Drug Discovery

SCOTT EDMONDSON
Sr. Vice President and Head of Chemistry,
Nimbus Therapeutics

NICHOLAS MEANWELL
Vice President,
Bristol-Myers Squibb

Presentation slides available now! The edited recording will be made available as soon as possible.

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This ACS Webinar is co-produced with the ACS Division of Medicinal Chemistry, American Association of Pharmaceutical Scientists, and ACS Publications.

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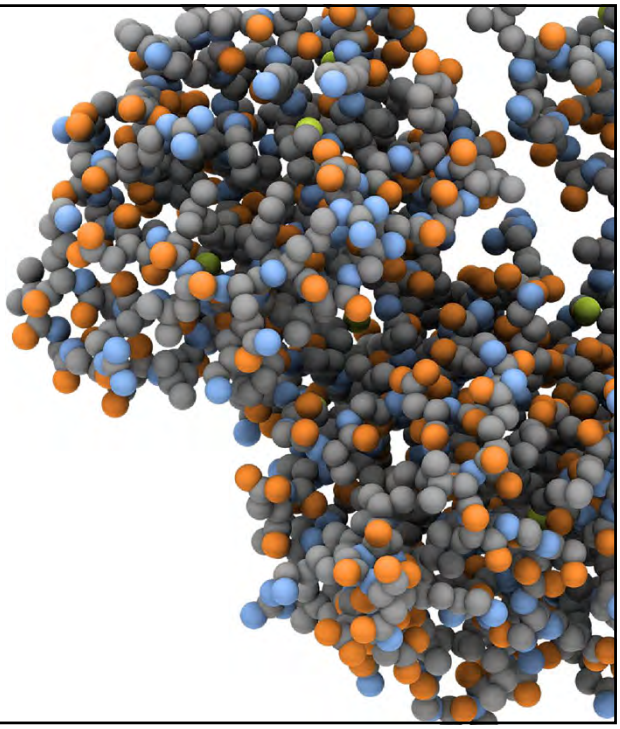
THERAPEUTICS

How Computational Chemistry with Structural Biology is Enabling Drug Discovery



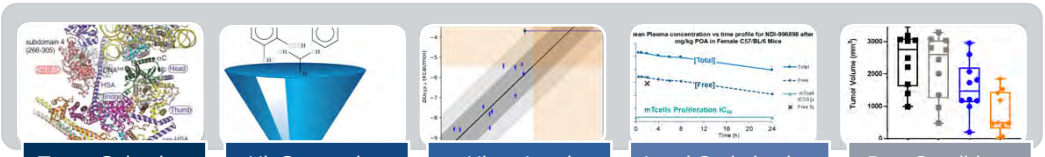
Scott Edmondson, Nimbus Therapeutics

ACS Webinar Series, 24-June-2021

0 | 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



Target Selection | Hit Generation | Hit-to-Lead | Lead Optimization | Dev. Candidate → IND …and beyond

- Ligandability assessment
- Homology models

- Virtual screening
- De novo design
- Pharmacophore maps
- Docking
- Hit expansion

- De novo design
- **Structure-based drug design (SBDD)**
- Mol. dynamics
- **Quantum mech**
- Quantitative structure-activity relationships (QSAR)

- Cheminformatics
- **Quantum mech**
- **Off-target models**
- QSAR / machine learning (ML)
- Property predictions
- SM crystal predictions

- Modeling / simulation for PK/PD/efficacy
- Salt selection
- Route dev. software

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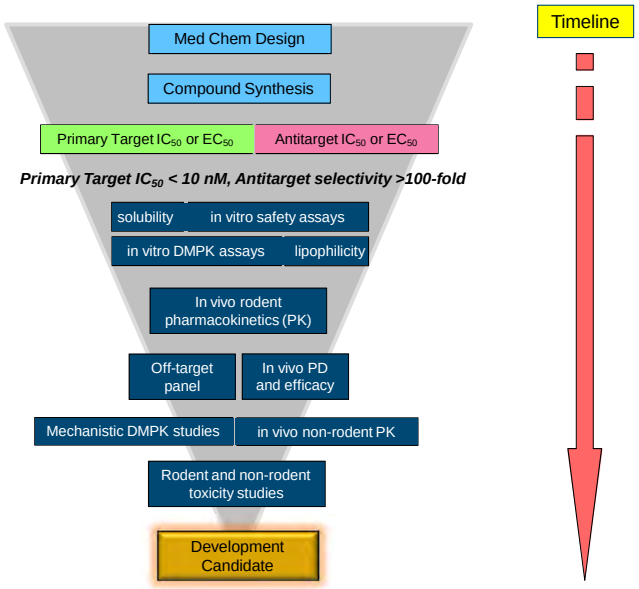
Drug Discovery Funnel for Hit-to-Lead and Lead Optimization

- 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?



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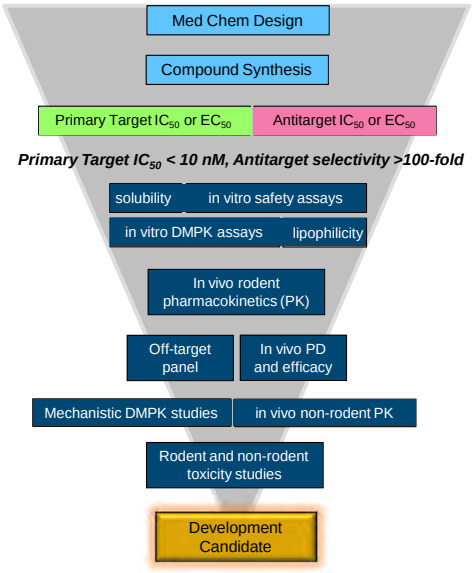

A. Assess compound efficacy in vivo in parallel to primary potency

B. Synthesize more compounds

C. Use computational methods to improve designs

D. Skip the assay cascade and only make the development candidate

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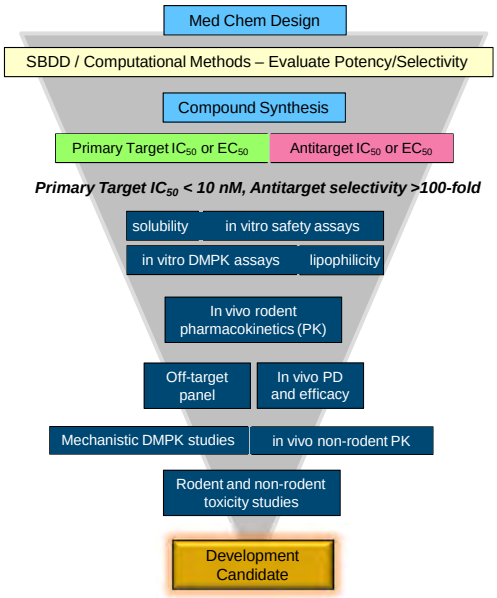
  - Compound synthesis and testing are expensive and time-consuming
- Cycle is often called "Design, Make, Test, Analyze" (DMTA)
- How can we improve the DMTA cycle?
  - **Better designs that leverage target and antitarget potency predictions**



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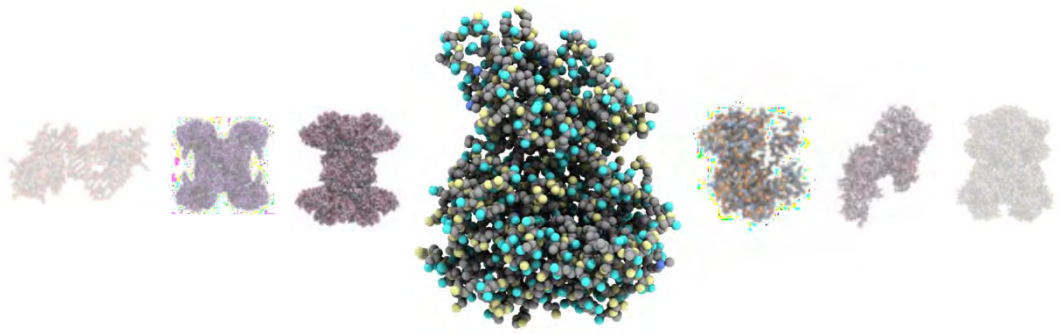

Tyrosine Kinase 2 (TYK2)

Allosteric Inhibition to Address Autoimmune Disorders

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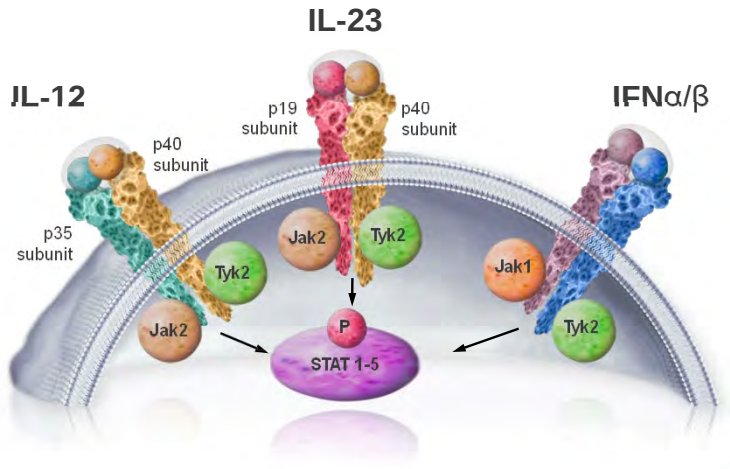
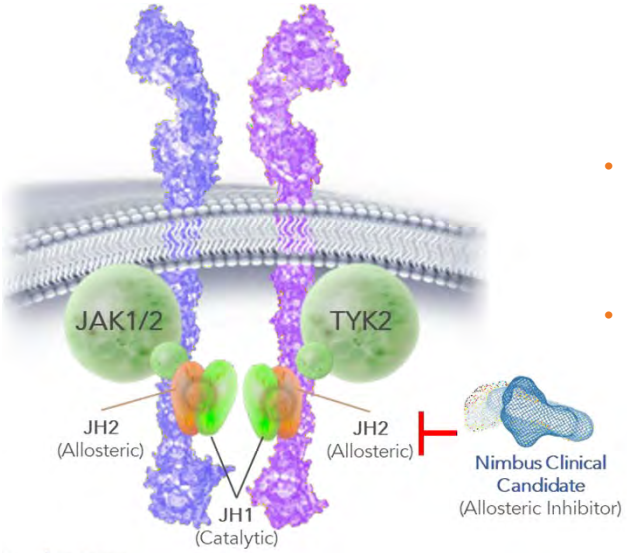
TYK2 Modulates Signaling Downstream of Cytokines Important to Autoimmune and Inflammatory Diseases



- 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*…)[1]
  - 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

1) Dendrou, et al., (2016) Sci. Transl. Med. 8, 363 ra149

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[1]
- 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***

1. K.L. Winthrop, *et al. Nat. Rev. Rheumatol.* **2017**; 13; 234-243.

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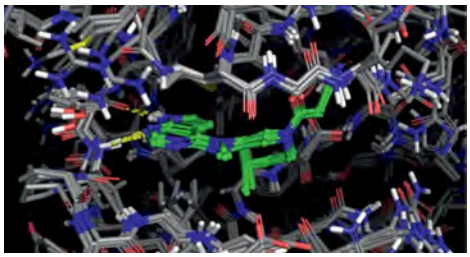
Poor Prospects of Achieving Selectivity vs JAKs in Catalytic Binding Pocket

Biochemical IC_{50}s (nM) of Inhibitors of the Catalytic (JH1) Sites of TYK2 and JAK1-3[1]

Inhibitor	TYK2 catalytic domain	JAK1 catalytic domain	JAK2 catalytic domain	JAK3 catalytic domain
Tofacitinib	489	15	77	55
Baricitinib	61	4	7	787
Filgotinib	2,600	363	2,400	>10,000
Upadacitinib	4,690	47	120	2,304
PF-06700841	23	17	77	6,494
PF-06826647	17	383	74	>10,000



Crystal structures of TYK2, JAK1, JAK2, and JAK3 with tofacitinib in catalytic JH1 site[2]
Very Similar Binding Pockets

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)[2,3]

- Deucravacitinib exhibits 17-fold selectivity over JAK1 JH2 site: TYK2 JH2 K_i = 0.02 nM; JAK1 JH2 K_d = 0.33 nM[3]

1. S.T. Wrobleski, *et al. J. Med. Chem.* **2019**; 62; 8973-8995.
2. R. Abel, *et al Curr Opin Structural Biology* **2017**, 43: 38-44.
3. J.R. Burke, *et al. Sci. Transl. Med.* **2019**; 11; eaaw1736.

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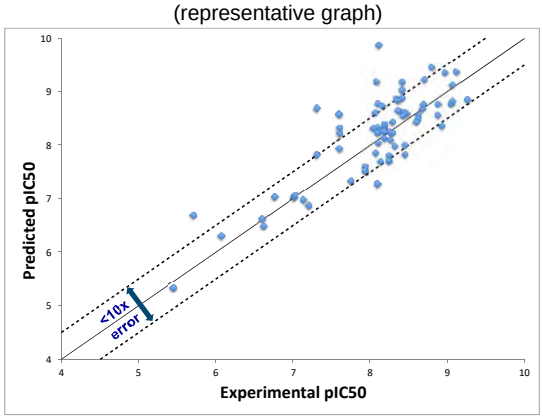
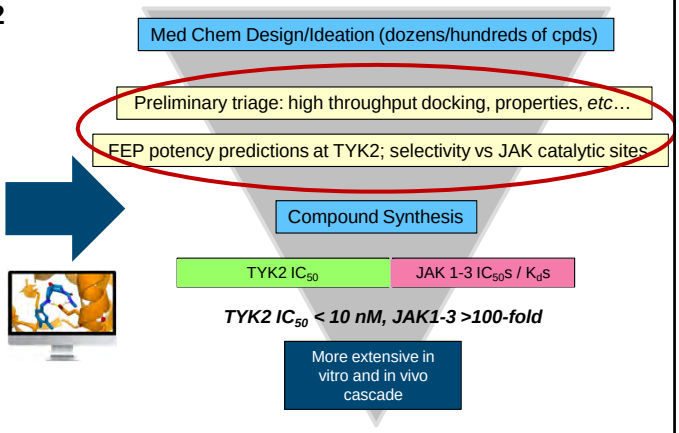
X-ray Crystal Structures of Ligands Bound to JH2 Allosteric Site Used to Build a Computational Model for TYK2 Potency Predictions

Predicted vs Experimental Potency at TYK2
(representative graph)

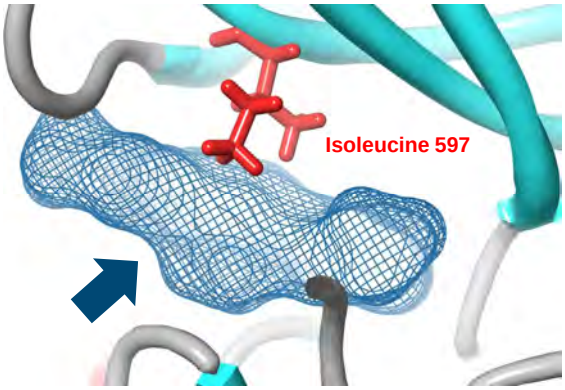




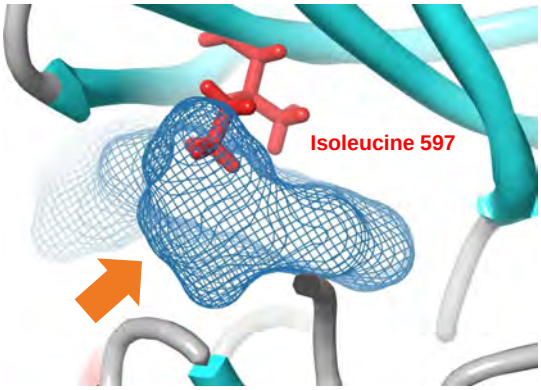
- Early in Hit-to-Lead, biochemical binding data + X-ray crystal structures used to build TYK2 JH2 potency prediction model
- Physics-based free energy perturbation (FEP) model was applied to a wide range of chemotypes
- ≥ Dozens of compounds assessed in a DMTA cycle
- Improved ability to prioritize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

R. Abel, et al Curr Opin Structural Biology 2017, 43: 38-44 (doi: 10.1016/j.sbi.2016.10.007)
L. Wang, et al Biomolecular Simulations 2019, 201-232 (DOI: 10.1007/978-1-4939-9608-7_9)

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

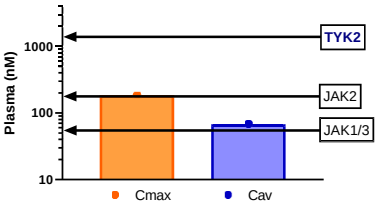
Source: Nimbus proprietary structure based computational modeling; TYK2 has a valine in the JH2 binding pocket

1st and 2nd Generation JAK Inhibitors Are All Multi-JAK Inhibitors

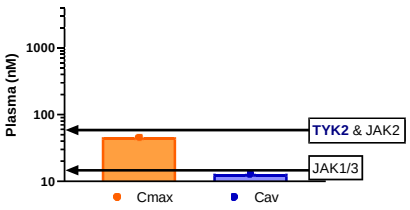
- **As agents reach clinically relevant doses/concentrations (C_{max} and C_{av}), they inhibit multiple JAK family members ($IC_{20-50-80}$)**

Legend
JAK1/3, JAK2, TYK2
Denotes IC_{50} [50% inhibitory concentration, the amount which clinical activity is routinely demonstrated]

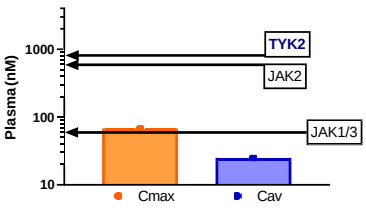
Tofacitinib, 5mg BID
(Pfizer, Xeljanz(R), Catalytic Inhibitor**)**



Baricitinib, 2mg QD
(Lilly, Olumiant(R), Catalytic Inhibitor**)**



Upadacitinib, 15mg ER QD
(AbbVie, Rinvoq(R), Catalytic Inhibitor**)**



Source: Internal Nimbus analysis of publicly available information. For approved agents, approved dose regimen used. Maximum concentration at steady state (C_{max}) and average concentration (C_{av}) in human plasma (both unbound) and *cellular* potency IC_{50}s.

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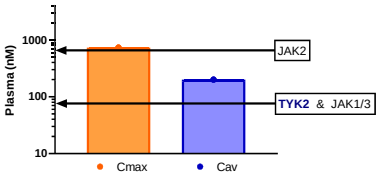
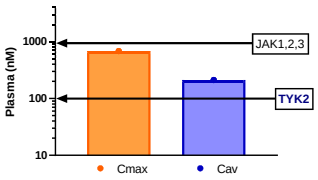
Nimbus Clinical Candidate Demonstrates Exquisite TYK2 Selectivity vs. Catalytic TYK2 Inhibitors

PF-06700841, 30mg QD
(Pfizer, Catalytic Inhibitor**)**

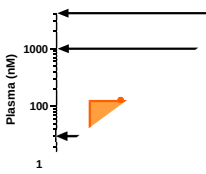


PF-06826647, 100mg QD
(Pfizer, Catalytic Inhibitor**)**

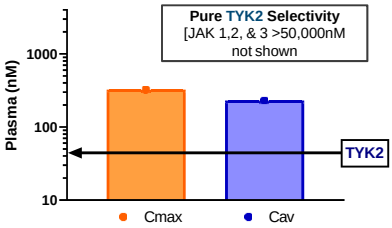


Catalytic Site Inhibitors

Deucravacitinib, 6mg QD
(BMS, BMS-986165, TYK2 Allosteric Inh



Nimbus Candidate
(Nimbus, TYK2 Allosteric Inhibitor**)**



Allosteric Site Inhibitors

Legend
JAK1/3, JAK2, TYK2
Denotes IC_{50} [50% inhibitory concentration, the amount which clinical activity is routinely demonstrated]

- 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**

Source: Internal Nimbus analysis of publicly available information. For approved agents, approved dose regimen used. Maximum concentration at steady state (C_{max}) and average concentration (C_{av}) in human plasma (both unbound) and *cellular* potency IC_{50}s.

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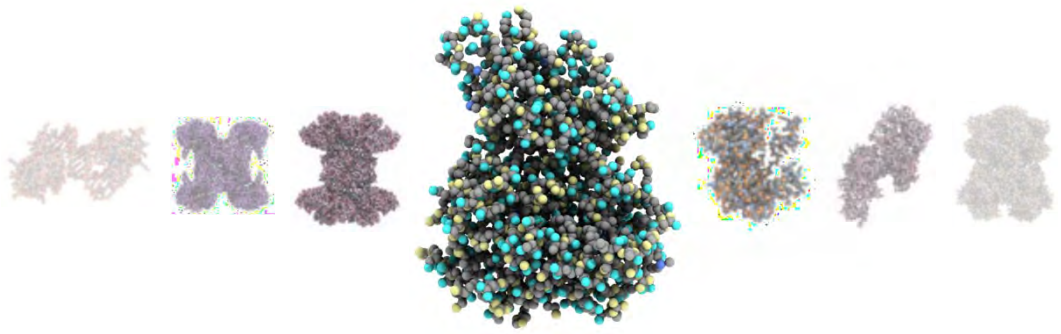

Hematopoietic Progenitor Kinase 1 (HPK1)

Key Regulator of T cell, B cell, and Dendritic Cell-mediated Immune Responses

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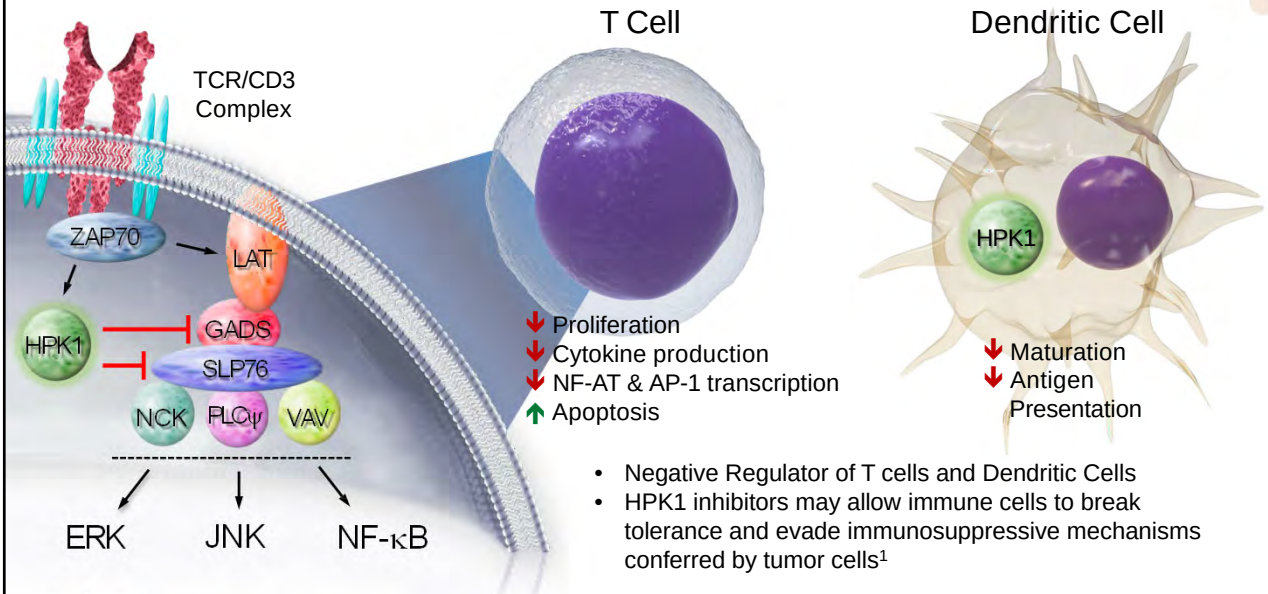
HPK1 Inhibitors for the Treatment of Cancer



- 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[1]

1) Alzabin S. Cancer Immunol Immunother (2010); Hernandez S. Cell Reports (2018)

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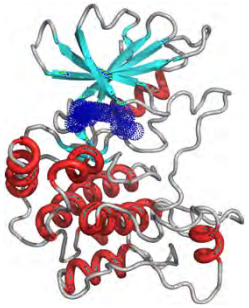
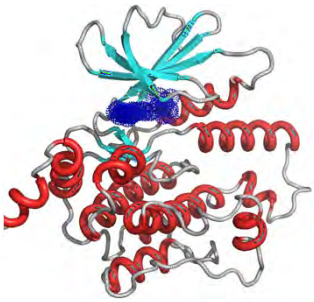
HPK1 Inhibitor Designs Enabled by Advances in Crystallography

HPK1 Co-Crystal



GLK Co-Crystal



- 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

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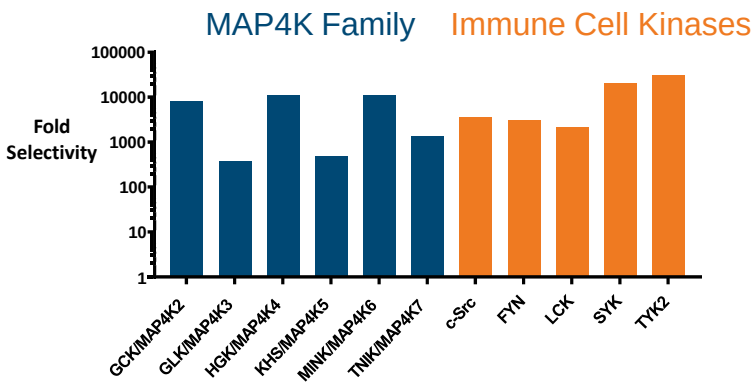
NMBS-2 is a Potent HPK1 Inhibitor with Excellent Selectivity Against MAP4K Family Members and Immune Cell Kinases

Assay	NMBS-2
HPK1 Caliper IC_{50} @ 1mM ATP	<1 nM
pSLP-76 Cell IC_{50}	42 nM



- Assessed against broad panel of >300 kinases; highly selective for HPK1 only
- High selectivity required for robust immune cell activation

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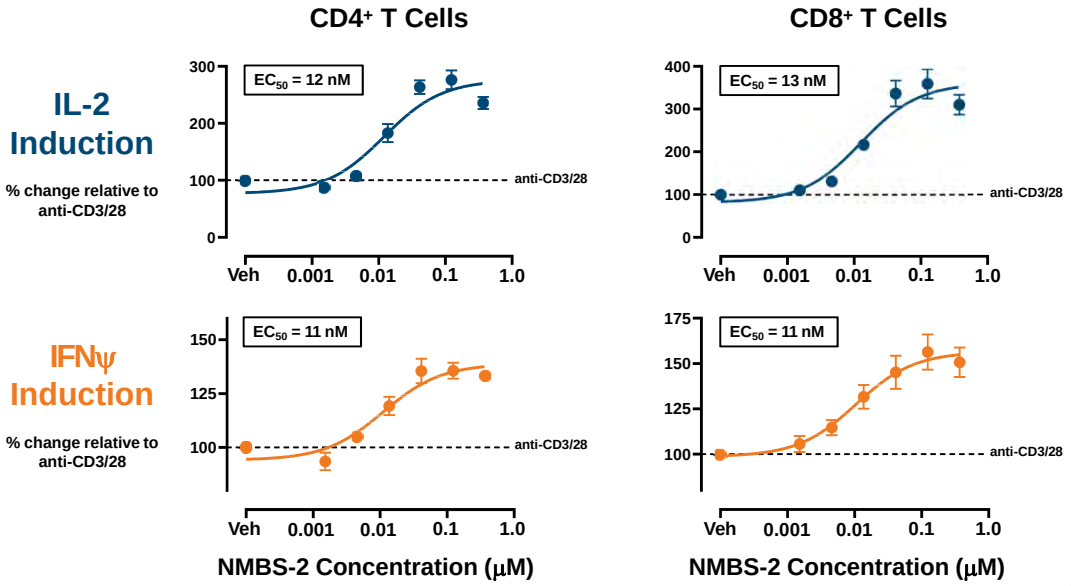
HPK1 Inhibition Enhances IL-2 & IFNψ Production from Human T Cells



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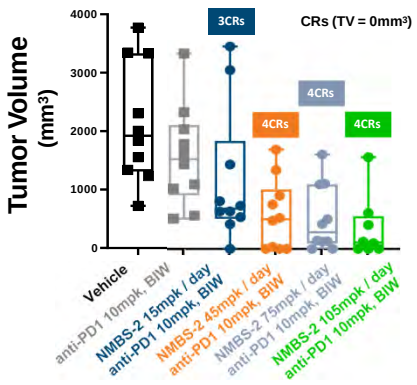
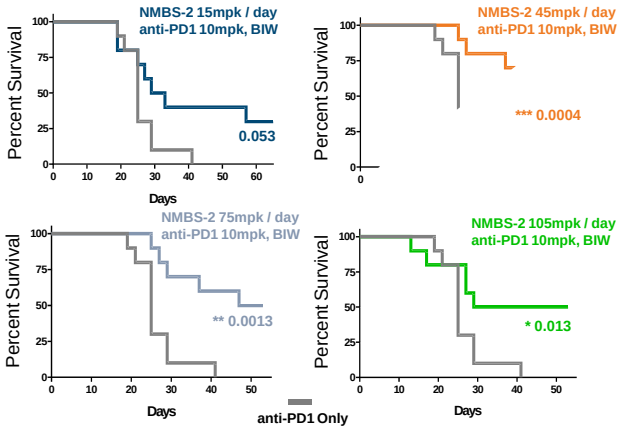
Robust Tumor Growth Inhibition Observed in the Mouse CT-26 Model in Combination with Anti-PD1

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**

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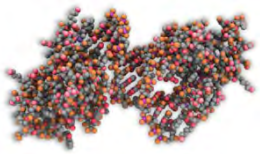
Multiple Promising Targets For Nimbus' SBDD Approach



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

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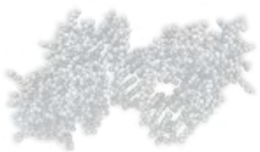
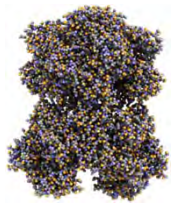
Multiple Promising Targets For Nimbus' SBDD Approach



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

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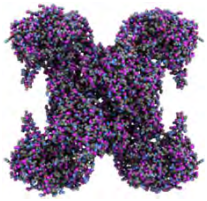
Multiple Promising Targets For Nimbus' SBDD Approach

Werner Syndrome Helicase (WRN)

Casitas B lymphoma-B E3 ligase (Cbl-b)



CTP Synthase 1 (CTPS1)

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

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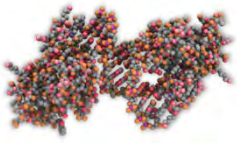
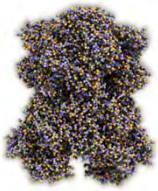
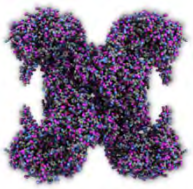
Multiple Promising Targets For Nimbus' SBDD Approach



Werner Syndrome Helicase (WRN)

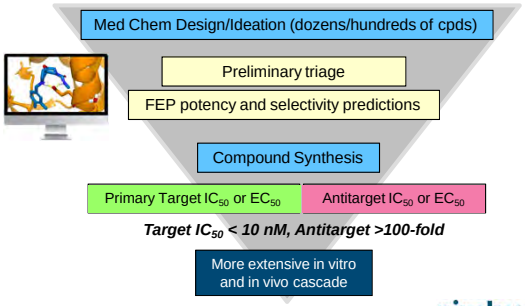


Casitas B lymphoma-B E3 ligase (Cbl-b)



CTP Synthase 1 (CTPS1)

- 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



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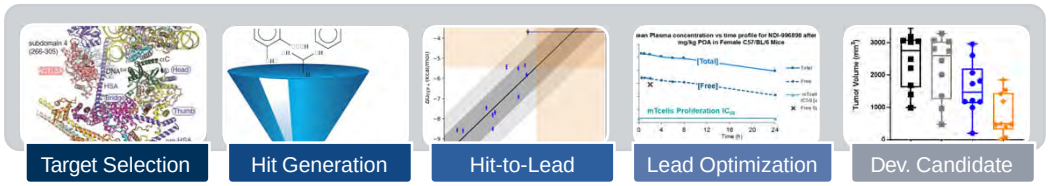
Which of these spaces in the discovery continuum can computational chemistry enable and/or improve?



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

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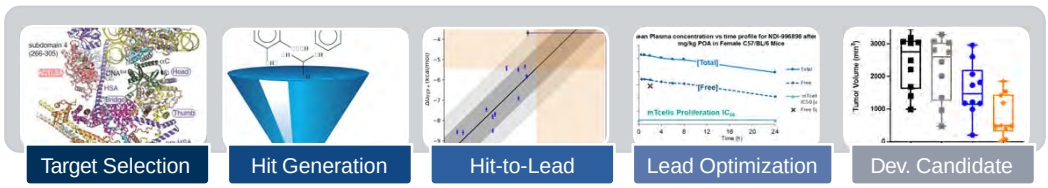
Which of these spaces in the discovery continuum can computational chemistry enable and/or improve?



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

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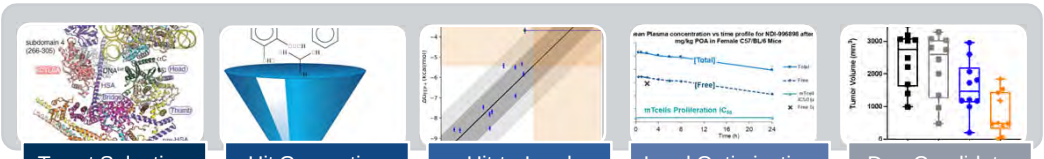
Next Steps for Computational Chemistry in Drug Discovery

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



Target Selection | Hit Generation | Hit-to-Lead | Lead Optimization | Dev. Candidate → IND …and beyond

Target Selection
- Ligandability assessment
- Homology models

Hit Generation
- Virtual screening
- De novo design
- Pharmacophore maps
- Docking
- Hit expansion

Hit-to-Lead
- De novo design
- Structure-based drug design (SBDD)
- Mol. dynamics
- Quantum mech
- Quantitative structure-activity relationships (QSAR) / ML

Lead Optimization
- Cheminformatics
- Quantum mech
- Off-target models
- Cheminformatics
- QSAR / Property predictions / ML
- SM crystal predictions

Dev. Candidate
- Modeling / simulation for PK/PD/efficacy
- Salt selection
- Route dev. software

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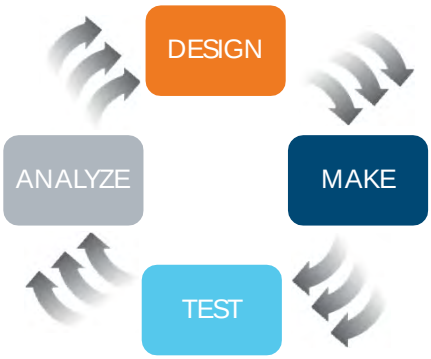
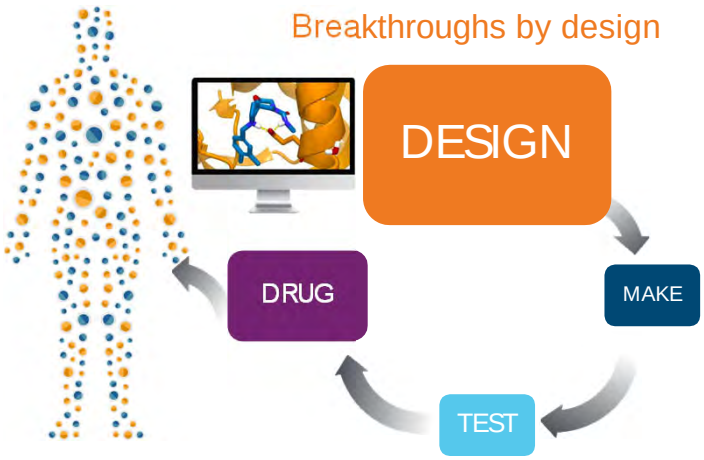
How can we Continue to Improve Drug Discovery?

The 'Old-Way'
Repeat, Repeat, Repeat…



The 'Nimbus Way'
Breakthroughs by design



Enabling technologies allow for incremental steps towards this goal

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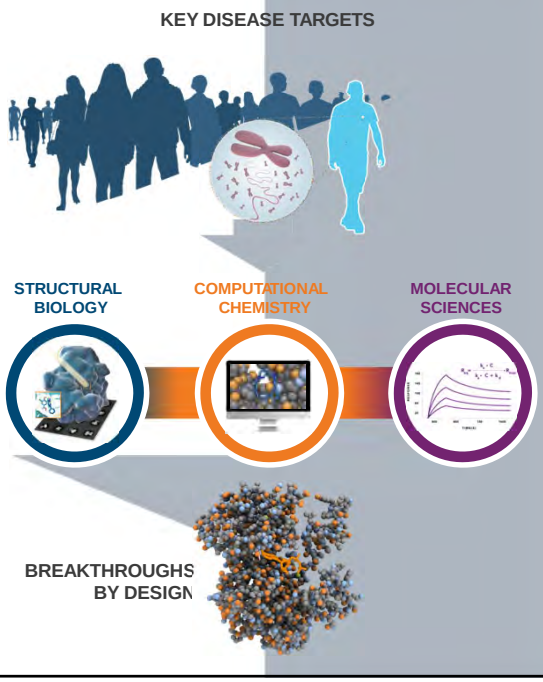
We Design Breakthrough Medicines

- **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

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Sayan Mondal
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Back-ups

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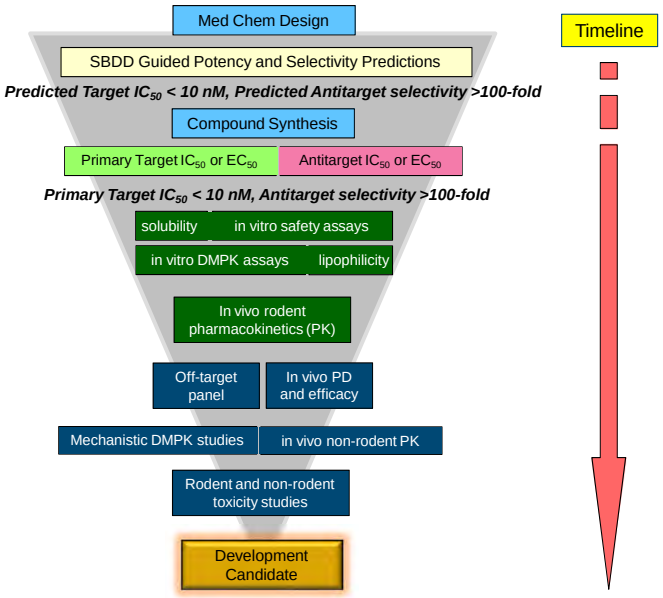
Research Triage Funnel for Hit-to-Lead and Lead Optimization

- 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



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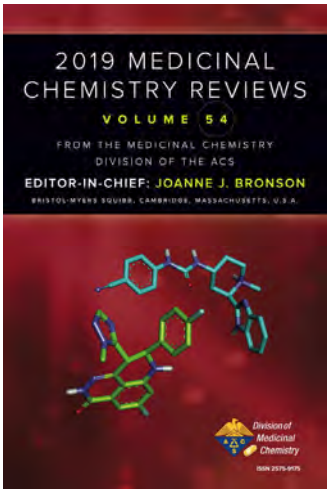

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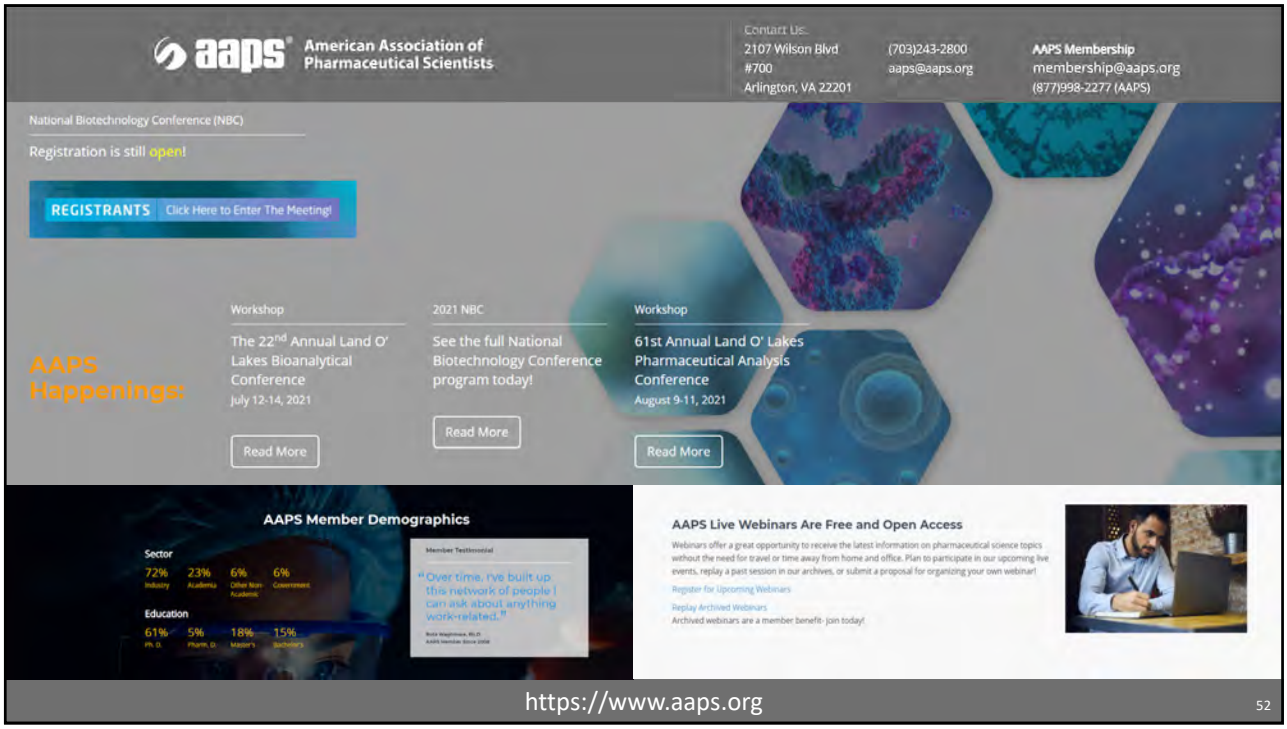

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Date: Friday, June 25, 2021 @ 2-3:30pm ET
Speaker: Sir Fraser Stoddart, 2016 Nobel Laureate in Chemistry, Board of Trustees Professor of Chemistry, Northwestern University and H.N. Cheng, ACS President
Moderator: Young-Shin Jun, Washington University in St. Louis

Register for Free!

What You Will Learn:

- How mechanically interlocked molecules (MIMs) are easily made and how they can be used inn the construction of artificial molecular machines (AMMs)
- How AMMs operate under kinetic control using energy ratchets in a manner similar to that employed by our many biomotors and are at odds with how machines operate in the macroscopic world: the difference could not be more stark!

Co-produced with: ACS Committee on Science

Date: Wednesday, June 30, 2021 @ 2-3pm ET
Speakers: Caroline Trupp Gil, American Chemical Society / Karen Garcia, American Chemical Society / Carl Maxwell, American Chemical Society
Moderator: Lauren Posey, American Chemical Society

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What You Will Learn:

- How the Biden Administration and 117th Congress are shaping up in terms of its STEM priorities
- Which specific pieces of legislation or federal policies will be likely to impact ACS members
- How members can become involved

Co-produced with: ACS Government Affairs

Date: Thursday, July 1, 2021 @ 2-3pm ET
Speaker: Stefan Mecking, University of Konstanz
Moderator: Mark Jones, Dow Chemical (retired)

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What You Will Learn:

- What is solvolysis and how it can enable plastics recycling
- How renewable polycarbonates and polyesters with a low density of in-chain functional groups as break points in a polyethylene chain can be recycled chemically
- How long-chain building blocks for polycondensation can be created from common plant oil feedstocks or microalgae oils

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