Schrödinger

Platform Day

October 6, 2022



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This presentation contains certain "forward-looking statements" within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this presentation, including, without limitation, statements regarding the potential advantages of our computational platform, our strategic plans to accelerate the growth of our software licensing business, our research and development efforts for our proprietary drug discovery programs and our platform, the initiation, timing, progress, and results of our proprietary drug discovery programs and the drug discovery programs of our collaborators, the clinical potential and favorable properties of our CDC7, MALT1, and Wee1 inhibitors, including SGR-1505 and SGR-2921, and other compounds discovered with our platform, the timing of potential IND applications as well as initiation of clinical trials for our proprietary drug discovery programs, the clinical potential and favorable properties of our collaborators' product candidates, including Nimbus Therapeutics and Morphic Holding, our ability to realize milestones, royalties, and other payments from our collaborative, partnered and proprietary programs, our plans to discover and develop product candidates and to maximize their commercial potential by advancing such product candidates ourselves or in collaboration with others, our plans to leverage the synergies between our businesses, our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our existing cash, cash equivalents, and marketable securities, and our expectations related to the key drivers of our performance, are forward-looking statements. The words "aim," "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "goal," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "will," "would" or the negative of these words or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements reflect our current views about our plans, intentions, expectations, strategies and prospects, which are based on the information currently available to us and on assumptions we have made. Actual results may differ materially from those described in the forward-looking statements and are subject to a variety of assumptions, uncertainties, risks and important factors that are beyond our control, including the demand for our software solutions, the reliance upon our third-party drug discovery collaborators, the uncertainties inherent in drug development and commercialization, such as the conduct of research activities and the timing of and our ability to initiate and complete preclinical studies and clinical trials, uncertainties associated with the regulatory review of clinical trials and applications for marketing approvals, the impacts of the ongoing COVID-19 pandemic on our business and other risks detailed under the caption "Risk Factors" and elsewhere in our Securities and Exchange Commission ("SEC") filings and reports, including our Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2022, filed with the SEC on August 4, 2022, as well as future filings and reports by us. Any forward-looking statements contained in this presentation speak only as of the date hereof. Except as required by law, we undertake no duty or obligation to update any forward-looking statements contained in this presentation as a result of new information, future events, changes in expectations or otherwise.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys, and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this presentation involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. We have not independently verified such third-party data, and we undertake no obligation to update such data after the date of this presentation.

Today's Agenda

Introduction — Ramy Farid

Our Platform: Current Capabilities — Robert Abel

Putting Our Platform to Work: Case Studies — Karen Akinsanya and Hamish Wright

- Pipeline overview
- Collaboration examples: Nimbus's ACC & TYK2; Morphic's $\alpha_4\beta_7$
- Proprietary examples: CDC7, Wee1, MALT1

Our Platform: Future Capabilities — Robert Abel

Business Outlook and Opportunities — Geoff Porges

Q&A



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Chief Executive Officer,
Board Member



Robert Abel, Ph.D.
Executive Vice President,
Chief Computational Scientist



Karen Akinsanya, Ph.D.
President of R&D,
Therapeutics



Hamish Wright, Ph.D.
Vice President,
Translational Science



Geoff Porges, MBBS
Chief Financial Officer

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Schrödinger Overview

SOFTWARE LICENSING

- Life Sciences
- Materials Science

TECHNOLOGY PLATFORM

Industry-leading physics-based platform: enables discovery of novel molecules faster, at lower cost, with a higher likelihood of success compared to traditional methods

Schrödinger Overview



SOFTWARE LICENSING

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- Materials Science



COLLABORATIONS

- Drug Design
- Materials Design

TECHNOLOGY PLATFORM

Industry-leading physics-based platform: enables discovery of novel molecules faster, at lower cost, with a higher likelihood of success compared to traditional methods

Schrödinger Overview



Industry-leading physics-based platform: enables discovery of novel molecules faster, at lower cost, with a higher likelihood of success compared to traditional methods

Unique Commitment to Scientific Innovation and Software Development



30+ years of innovation in computational chemistry research



Over 800 employees worldwide; >40% Ph.D.



More than 50% of the company dedicated to research and development



Large scientific support & education teams offer expertise and guide in knowledge transfer



Quarterly software releases with new functionality and performance improvements

More than $800 million invested*

*Amount invested is the estimated aggregate total of revenue and capital raised since inception, net of cash resources on hand.

Designing Drugs Is Extremely Hard!

Lengthy, Capital-intensive, and Subject to High Failure Rates

Need to identify a molecule that balances a large number of anti-correlated properties:

- Potency
- Selectivity
- Solubility
- Bioavailability
- Clearance / Half-life
- Permeability
- Drug-drug interactions
- Synthesizability

Designing Drugs Is Extremely Hard!

Lengthy, Capital-intensive, and Subject to High Failure Rates

Need to identify a molecule that balances a large number of anti-correlated properties:

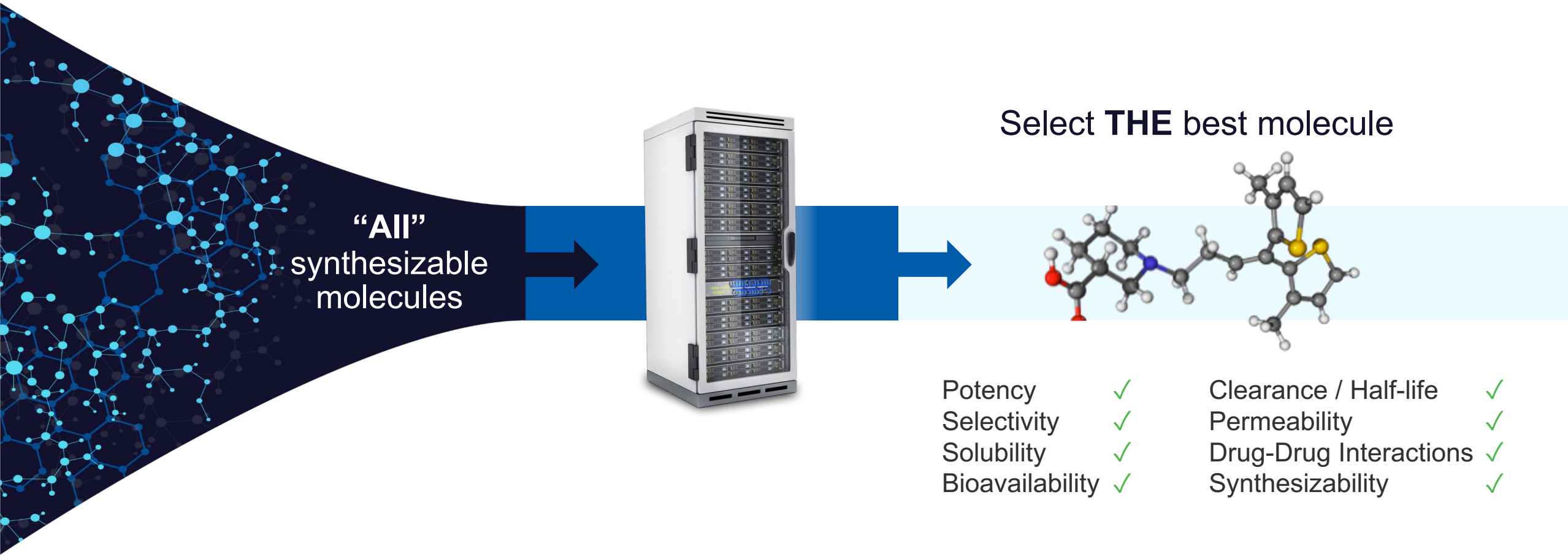
• Potency	✓	✗	✓	✗	✓	✓
• Selectivity	✗	✓	✓	✓	✗	✓
• Solubility	✗	✗	✗	✓	✓	✗
• Bioavailability	✗	✗	✗	✗	✗	✗
• Clearance / Half-life	✗	✗	✗	✗	✗	✗
• Permeability	✗	✗	✗	✗	✗	✗
• Drug-drug interactions	✗	✗	✗	✗	✗	✗
• Synthesizability	✗	✗	✗	✗	✗	✗



*Paul, S.M., Mytelka, D.S., Dunwiddie, C.T. et al. "How to improve R&D productivity: the pharmaceutical industry's grand challenge." *Nature reviews Drug discovery*

Vision for the Future of Drug Discovery

If all properties can be calculated with perfect accuracy, designing drugs would have a much **higher success rate**, be much **faster** and **cheaper**, and would produce much **higher-quality** molecules.



Potential Solutions to Accurately Predicting Drug Properties

Decades-long Challenge – Two Major Approaches

1 **Knowledge-based machine learning (often referred to as AI)**

If AI can:

- beat humans at chess and Go
- recognize faces in photos
- autonomously drive cars

Can it be used to design drugs?

Potential Solutions to Accurately Predicting Drug Properties

Decades-long Challenge – Two Major Approaches

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If AI can:

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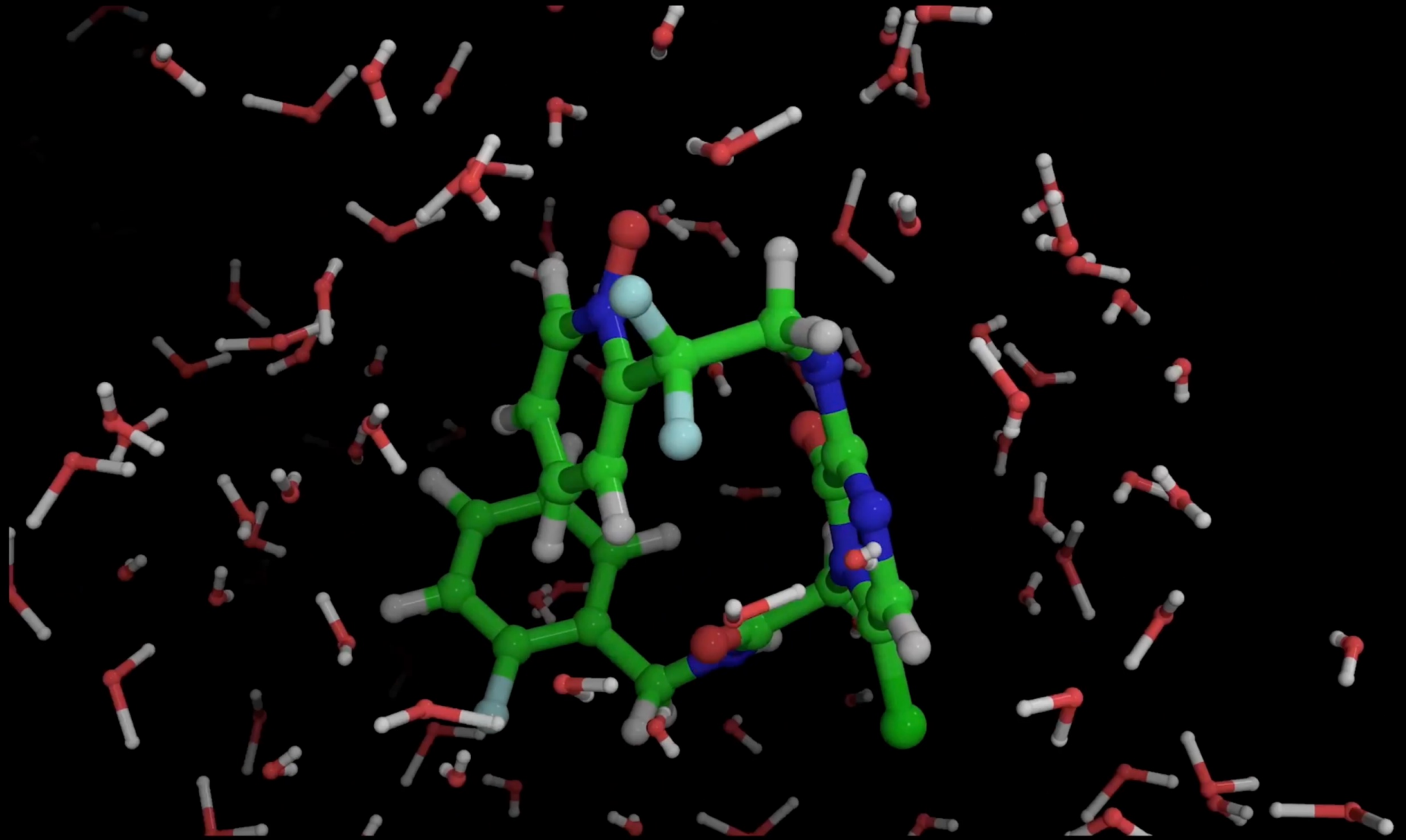
Can it be used to design drugs?

2 Rigorous first principles physics-based modeling

Requires deep understanding of the physics underlying highly complex molecular interactions

$$i\hbar\frac{d}{dt}|\Psi(t)\rangle = \hat{H}|\Psi(t)\rangle \qquad i\hbar\frac{\partial}{\partial t}\Psi(\mathbf{r},t) = \left[\frac{-\hbar^2}{2m}\nabla^2 + V(\mathbf{r},t)\right]\Psi(\mathbf{r},t)$$



Machine Learning Can Only Interpolate Within the Training Set



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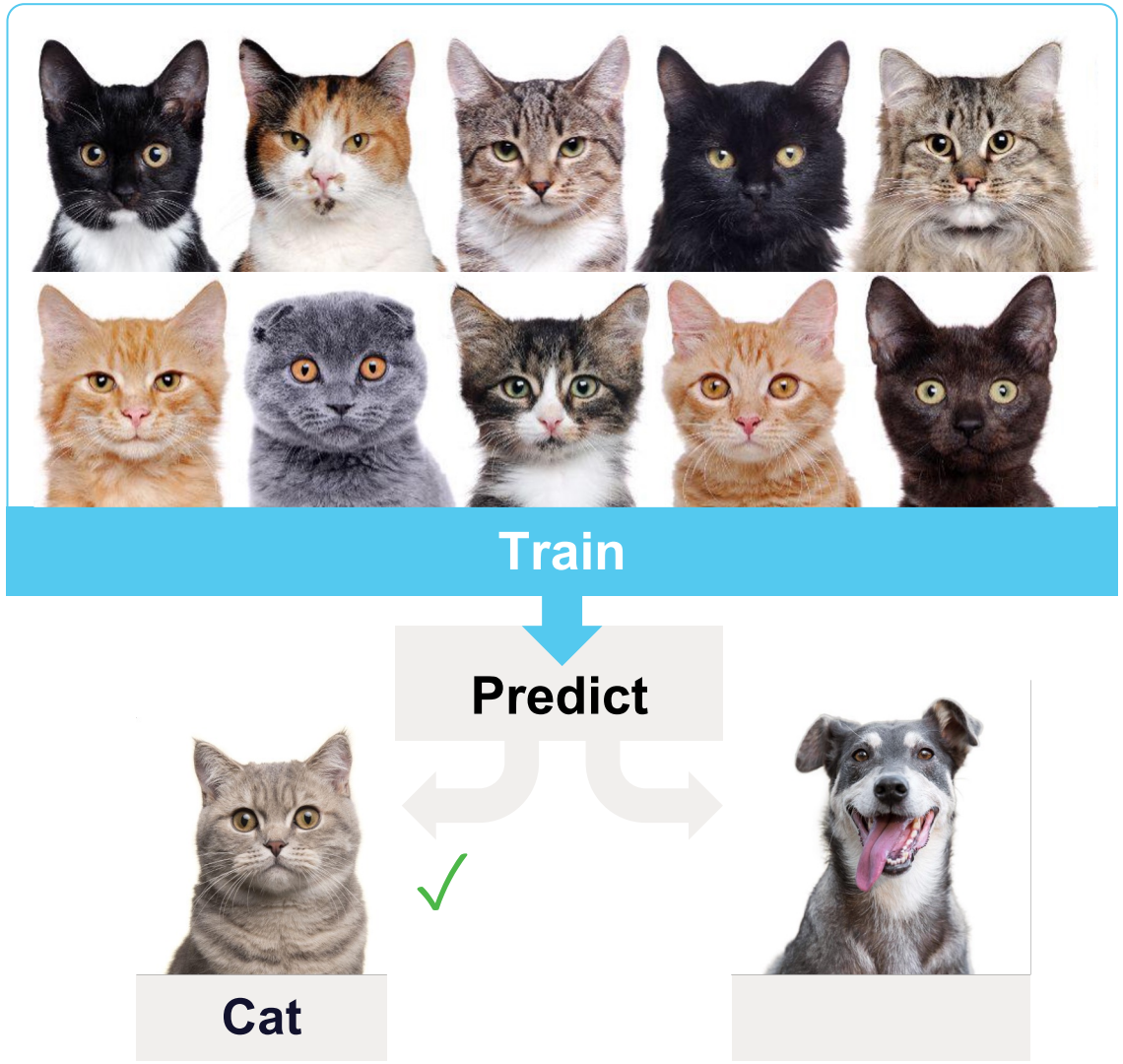

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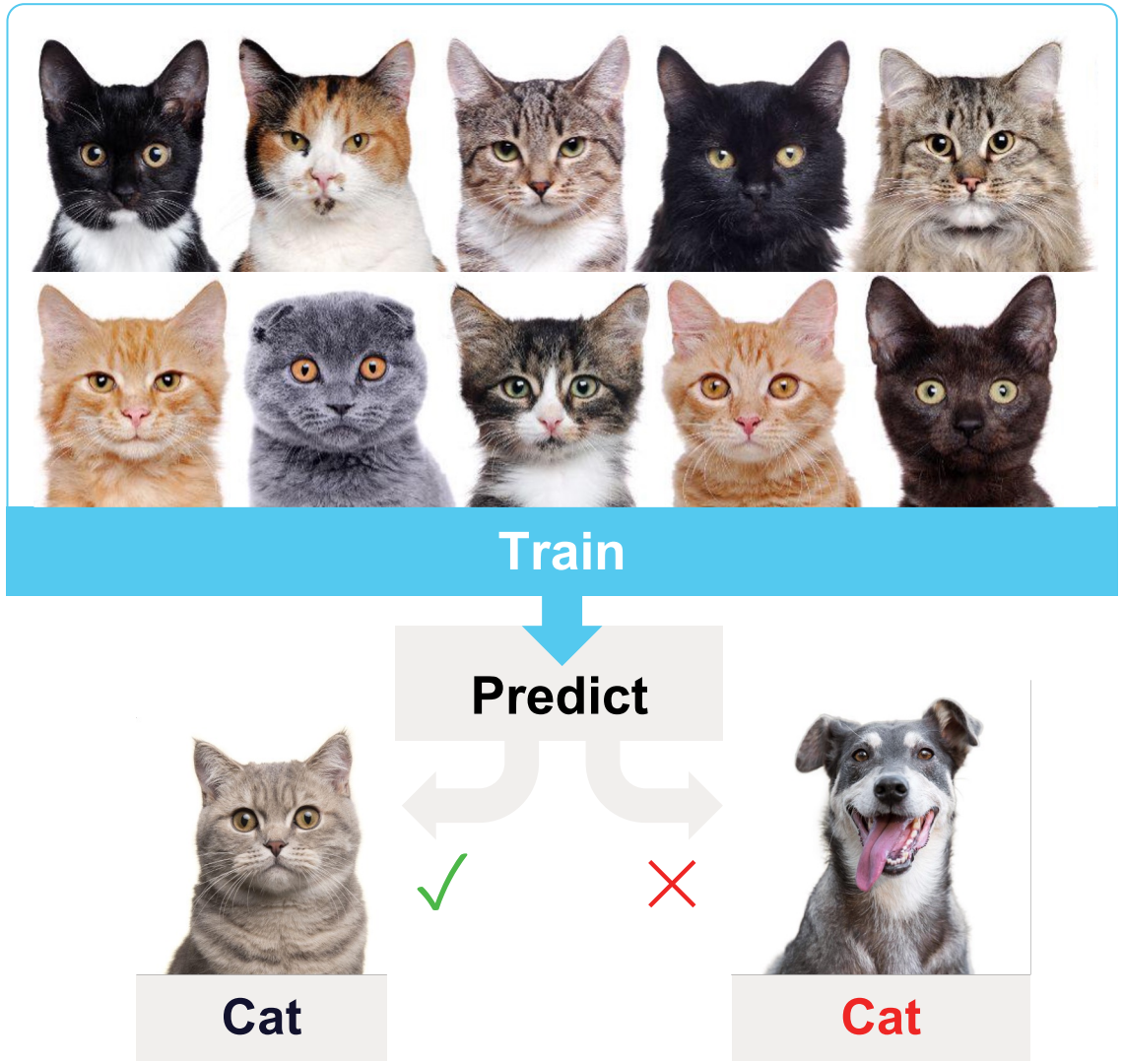
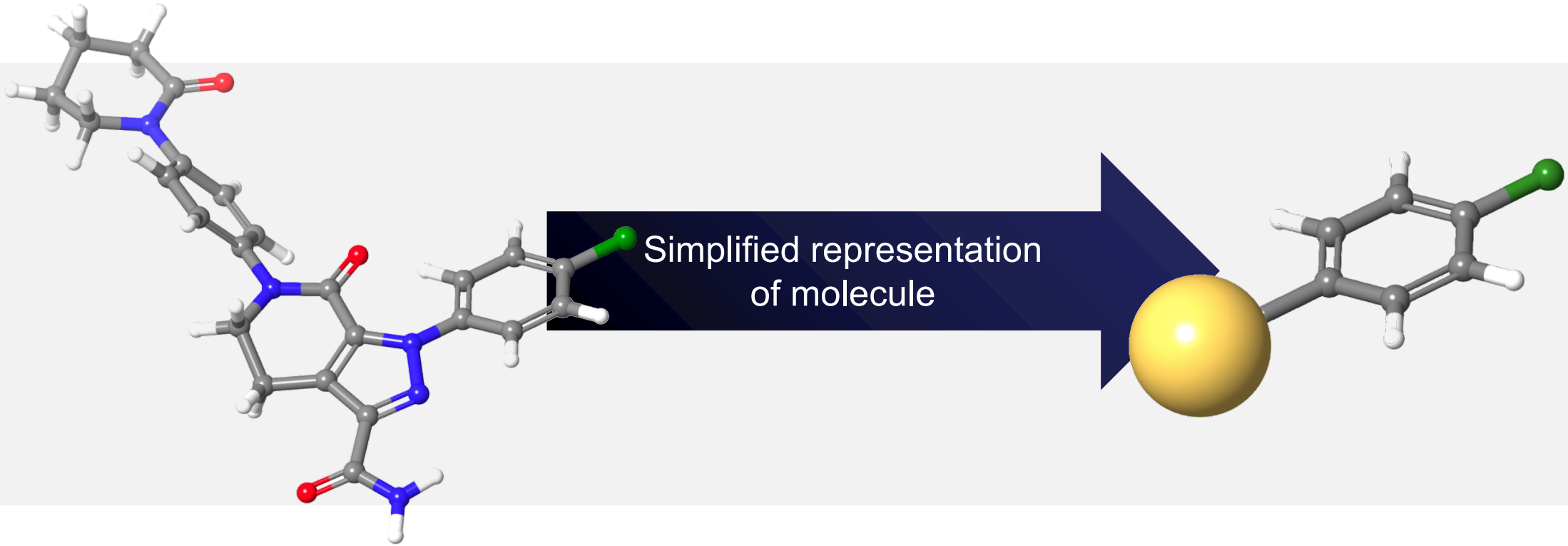


How Does This Apply to Prediction of Molecular Properties?



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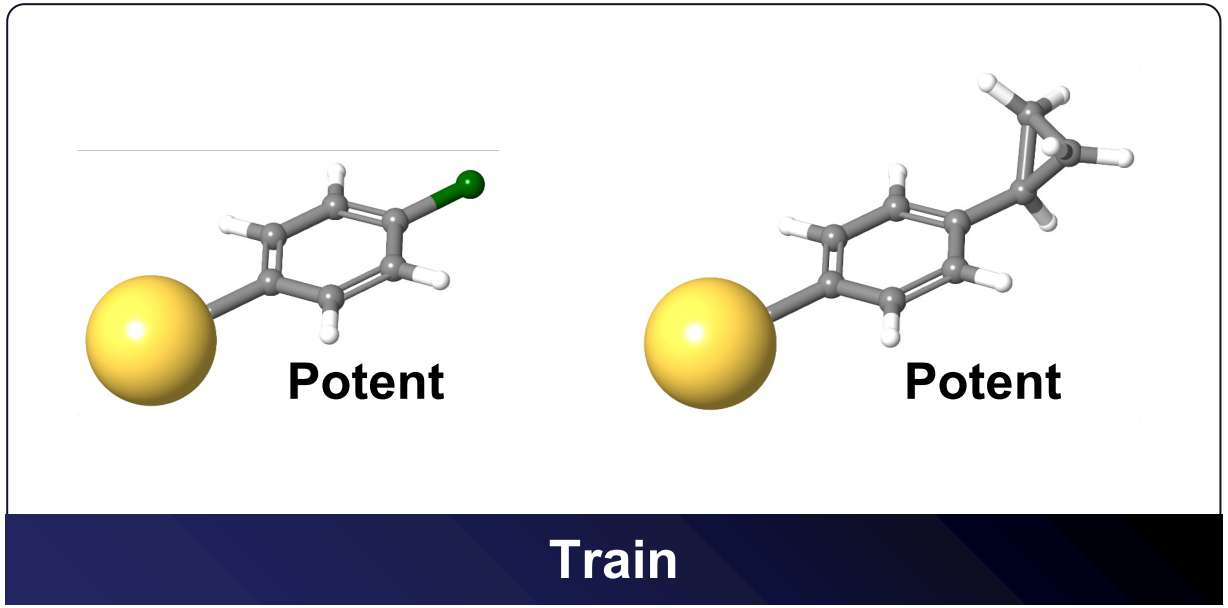

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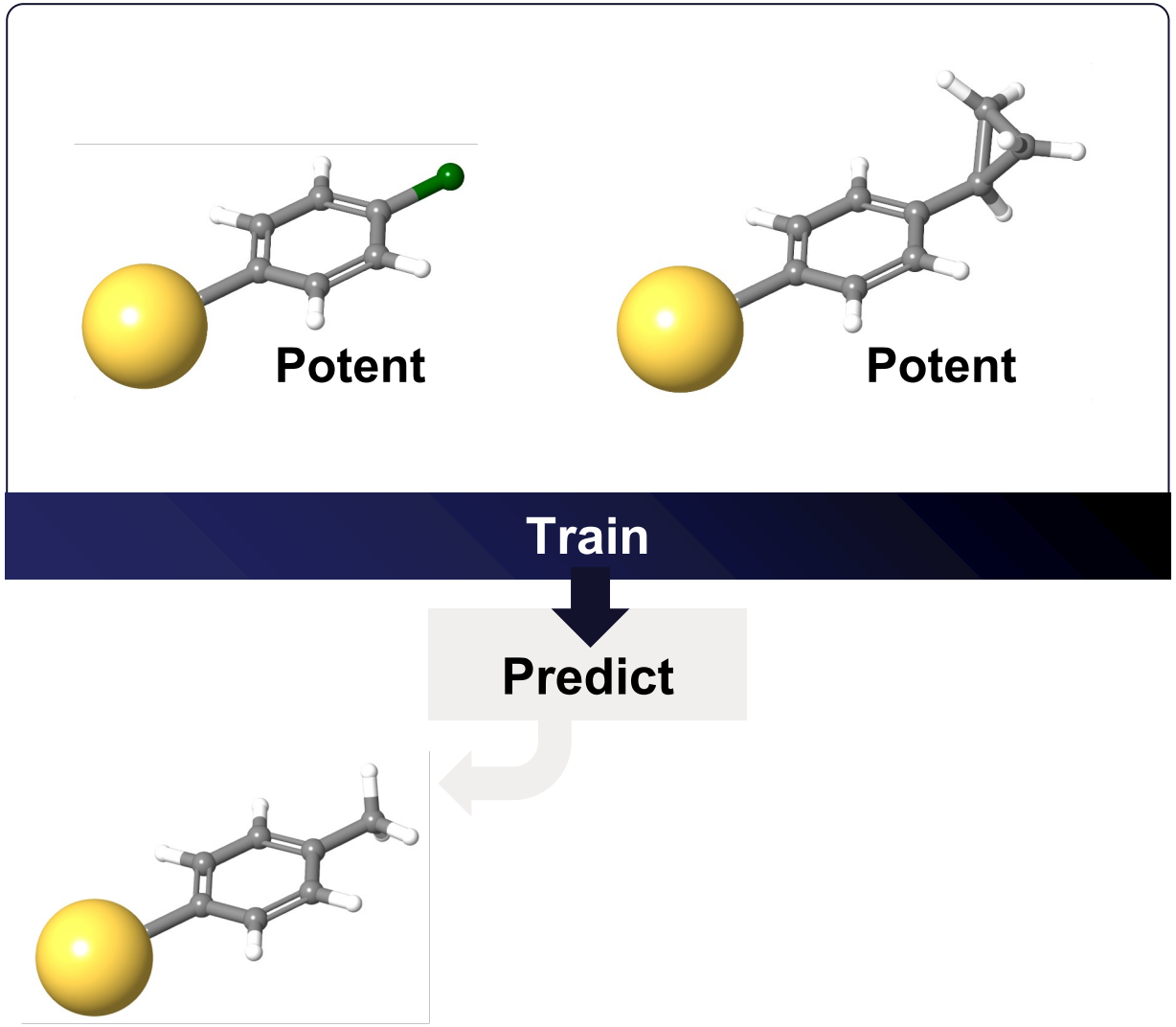

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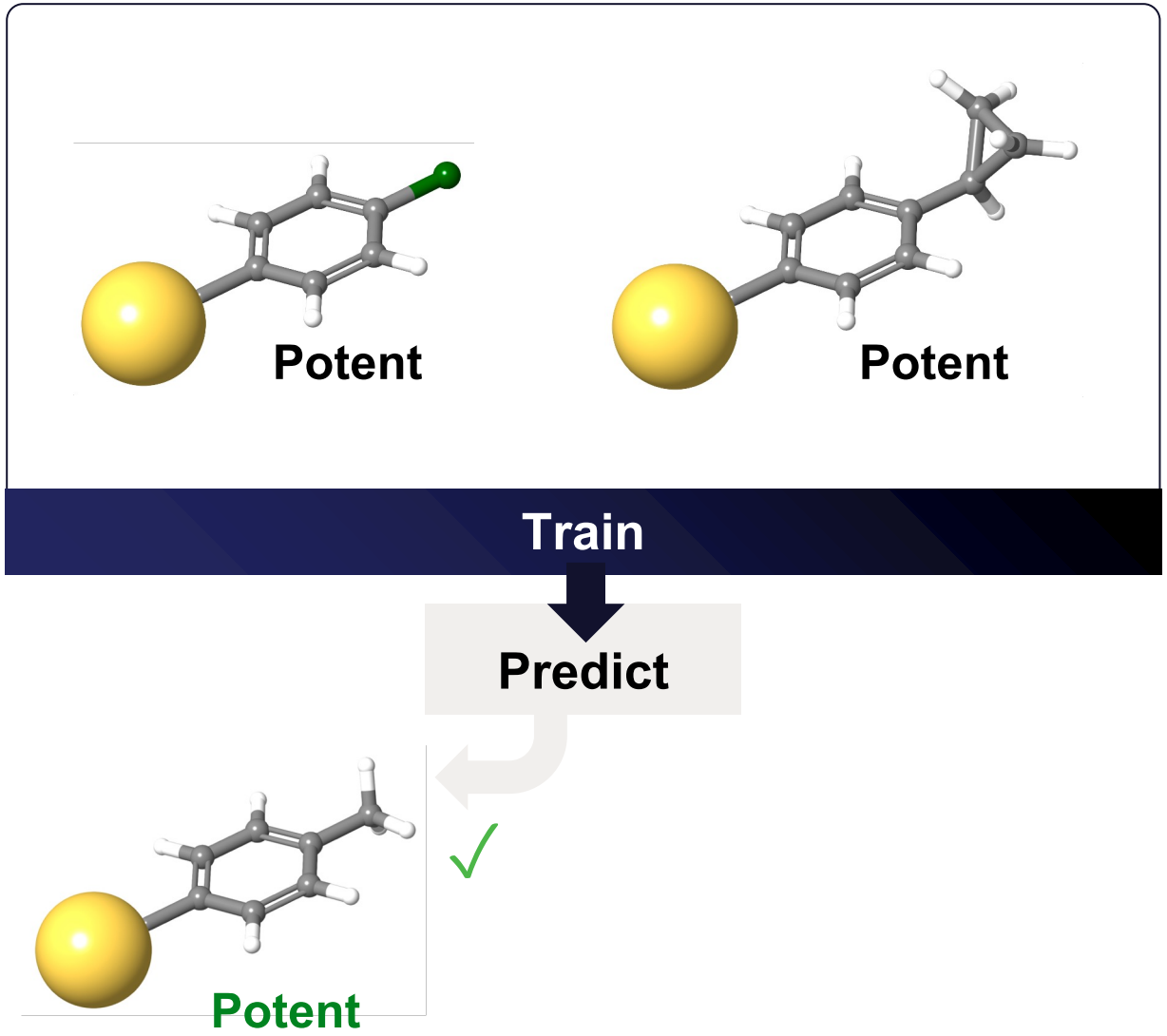

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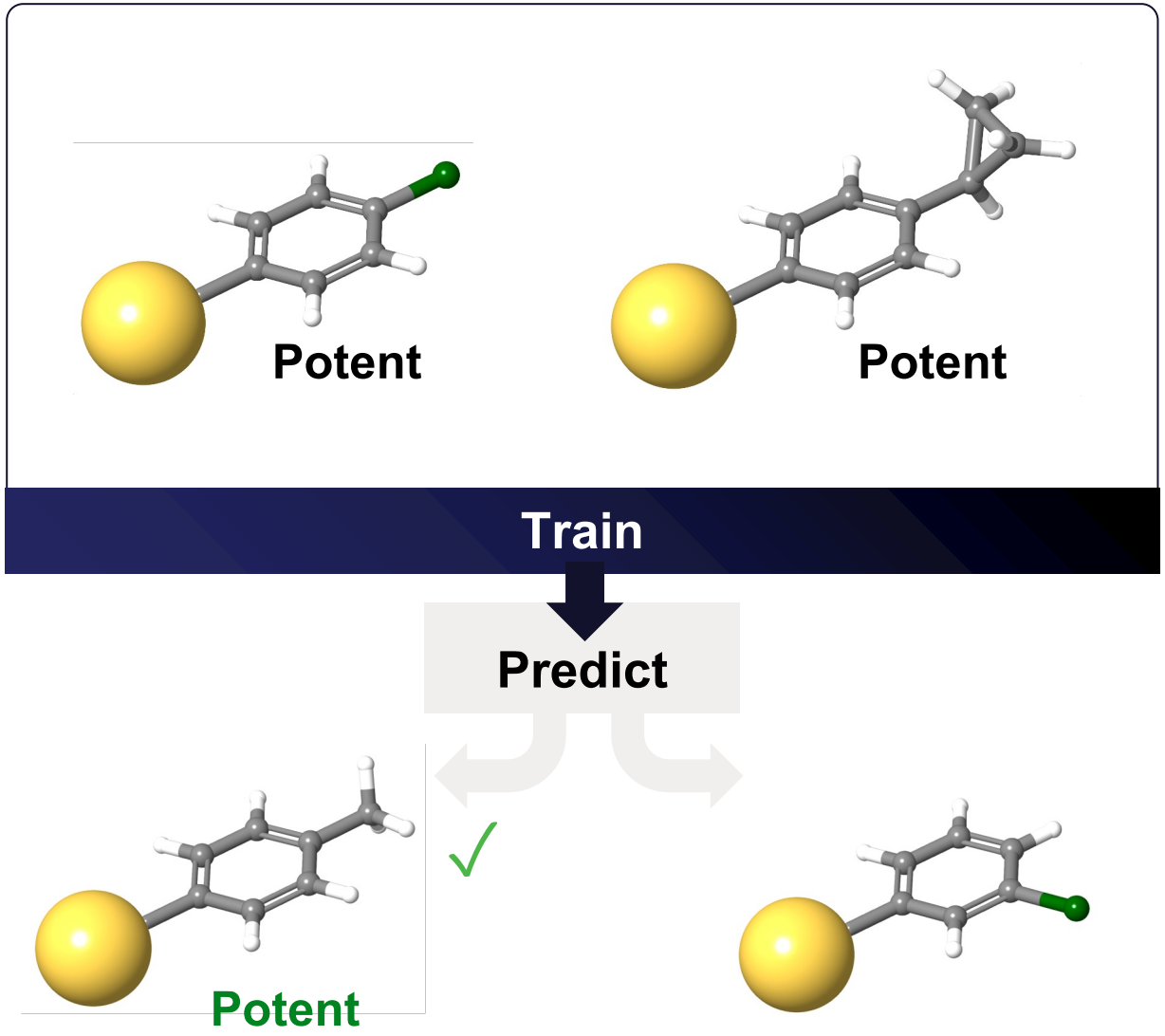

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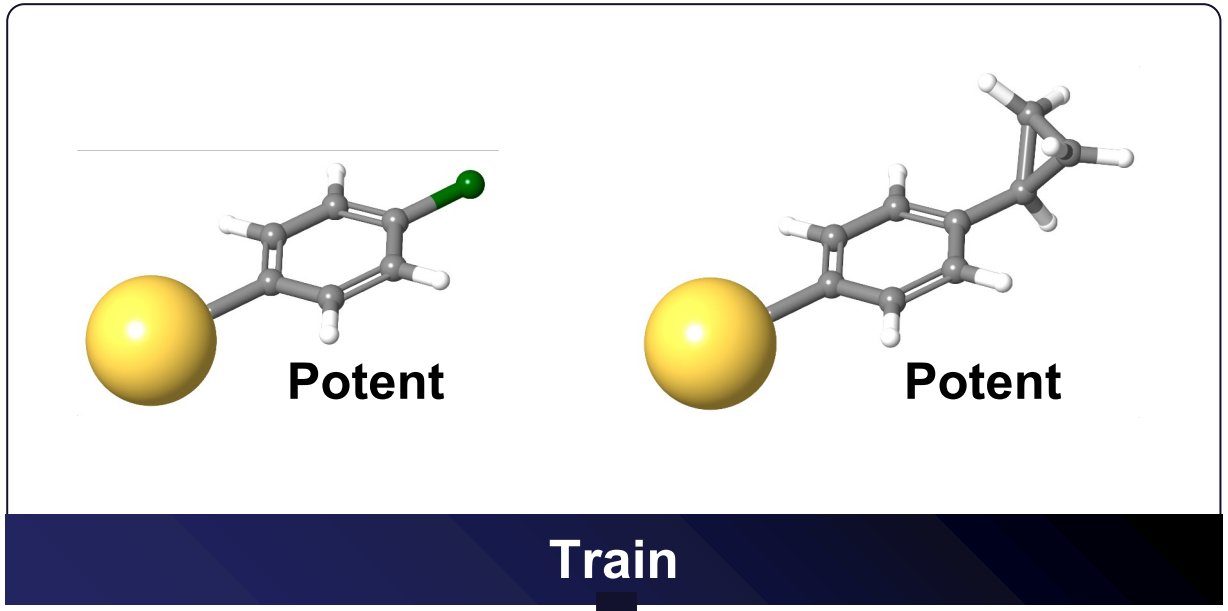
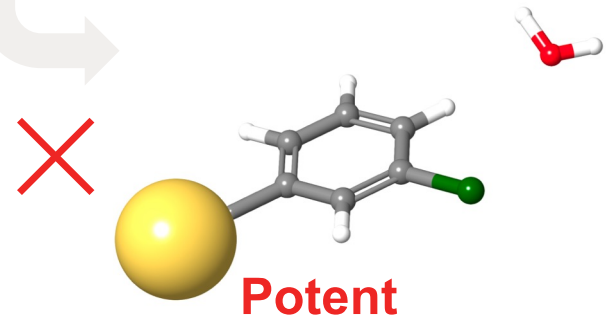
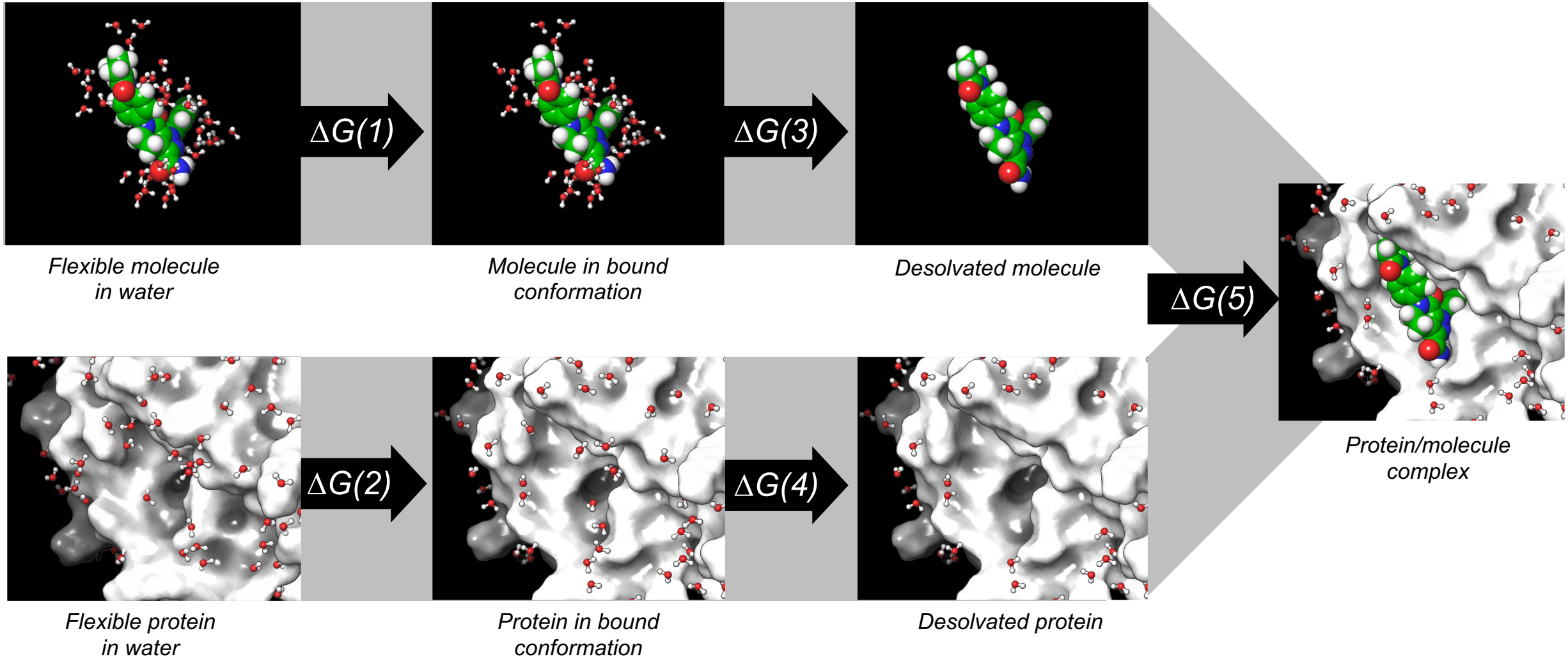


- Seemingly minor change has profound impact on protein binding site (un-displaced water)
- Impossible for the ML model to know about



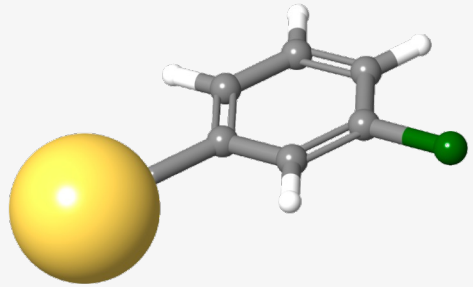
Rigorous Simulation of Full Thermodynamic Cycle Required to Accurately Predict Binding Affinity of a Molecule to a Protein



$\Delta G_{bind} = \Delta G(1) + \Delta G(2) + \Delta G(3) + \Delta G(4) + \Delta G(5)$

Physics-Based Methods Can Extrapolate Into New Chemical Space

Only physics-based methods can accurately predict properties of new “species” of molecules using first-principles, as no training is required



IC_{50} = 2 μM

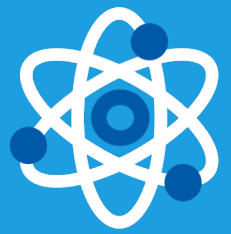
Not Potent

Physics & Machine Learning Are Complementary



Machine Learning / Artificial Intelligence

- ✓ Effective at interpolation
- ✓ Fast
- ✓ Can handle very large datasets
- ✗ Requires very large training set
- ✗ Cannot extrapolate



Physics-based Methods

- ✓ No training set required
- ✓ Can extrapolate into novel chemical space
- ✓ Accurate
- ✗ Slow

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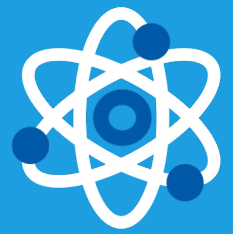

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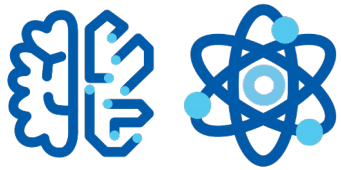
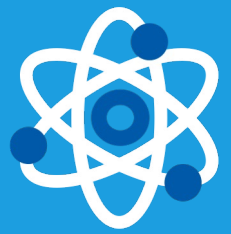


Machine Learning + Physics

Training set for ML generated using physics

- ✓ Fast
- ✓ Accurate
- ✓ Can handle very large datasets
- ✓ Can extrapolate into novel chemical space



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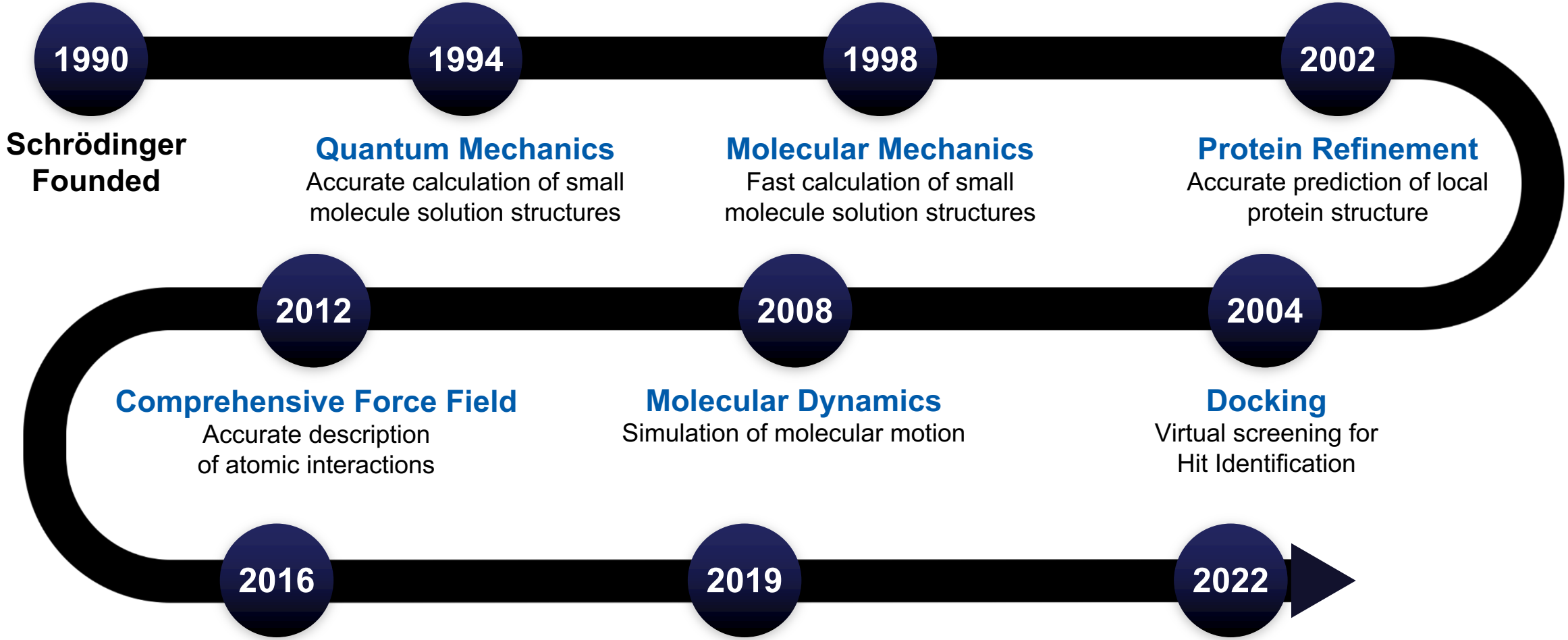
Long Track Record of Scientific Innovation



1. Abel, R.; Bhat, S., Annual Reports in Medicinal Chemistry, 2017, 50, 237 - 262
2. Abel, R.; Mondal, S.; Masse, C.; Greenwood, J.; Harriman, G.; Ashwell, M.A.; Bhat, S.; Wester, R.; Frye, L.; Kapeller, R.; Friesner, R.A., Curr. Opin. Struct. Biol., 2017, 43, 38-44
3. Abel, R.; Salam, N.K.; Shelley, J.; Farid, R.; Friesner, R.A.; Sherman, W. , Chem Med Chem , 2011, 6, 1049-1066
4. Abel, R.; Wang, L.; Friesner, R. A.; Berne, B. J. , J. Chem. Theory Comput. , 2010, 6, 2924-2934
5. Abel, R.; Wang, L.; Harder, E.D.; Berne, B.J.; Friesner, R.A., Acc. Chem. Res., 2017, 50, 1625-1632
6. Abel, R.; Wang, L.; Mobley, D.L.; Friesner, R., Curr Top Med Chem., 2017, 17, 1-9
7. Abel, R.; Young, T.; Farid, R.; Berne, B.J.; Friesner, R.A., J. Am. Chem. Soc., 2008, 130(9), 2817–2831
8. Albanese, S.K.; Chodera, J.D.; Volkamer, A.; Keng, S.; Abel, R.; Wang, L., bioRxiv, 2020, Pre Print, 1-35
9. Baik, M. H.; Friesner, R. A., J. Phys. Chem. A, 2002, 106, 7407–7412
10. Baik, M.; Crystal, J. B.; Friesner, R. A., Inorg. Chem., 2002, 41, 5926–5927
11. Baik, M.; Friesner, R. A.; Lippard, S. J., Inorg. Chem., 2003, 42, 8615–8617
12. Bell, J. A.; Cao, Y.; Gunn, J. R.; Day, T.; Gallicchio, E.; Zhou, Z.; Levy, R.; Farid, R., International Tables for Crystallography, Volume F: Crystallography of biological macromolecules, 2012, 18, 534-538
13. Bell, J. A.; Ho, K. L.; Farid, R., Acta. Crystallogr. D Biol. Crystallogr., 2012, 68(Pt 8), 935-952
14. Beuming, T.; Che, Y.; Abel, R.; Kim, B.; Shanmugasundaram, V.; Sherman, W., Proteins, 2011, 80, 871-83
15. Beuming, T.; Farid, R.; Sherman W. , Protein Sci., 2009, 18(8), 1609-1619
16. Bhachoo, J.; Beuming, T., Methods Mol Biol., 2017, 1561, 235-254
17. Bochevarov, A. D.; Watson, M. A.; Greenwood, J. R.; Philipp, D. M., J. Chem. Theory Comput., 2016, 12 (12), 6001–6019
18. Bochevarov, A.D.; Friesner, R.A.; Lippard, S.J., J. Chem. Theory Comput., 2010, 6, 3735–3749
19. Bochevarov, A.D.; Harder, E.; Hughes, T.F.; Greenwood, J.R.; Braden, D.A.; Philipp, D.M.; Rinaldo, D.; Halls, M.D.; Zhang, J.; Friesner, R.A., Int. J. Quantum Chem., 2013, 113(18), 2110-2142
20. Breiten, B.; Lockett, M.R.; Sherman, W.; Fujita, S.; Al-Sayah, M.; Lange, H.; Bowers, C.M.; Heroux‖, A.; Krilov, G.; Whitesides, G.M., J. Am. Chem. Soc., , 2013, 135(41), 15579–15584
21. Cao, Y.; Hughes, T.; Giesen, D.; Halls, M.D.; Goldberg, A.; Vadicherla. T.A.; Sastry, M.; Patel, B.; Sherman, W.; Weisman, A.L.; Friesner, R.A., J Comput Chem., 2016, 37, 1425-1441
22. Cappel, D.; Dixon, S.L.; Sherman, W.; Duan, J., J. Comput. Aided Mol. Des., 2015, 29(2), 165-182
23. Cappel, D.; Hall, M.L.; Lenselink, E.B.; Beuming, T.; Qi, J.; Bradner, J.; Sherman, W., J. Chem. Inf. Model., 2016, 56 (12), 2388–2400
24. Cappel, D.; Jerome, S.; Hessler, G.; Matter, H., J. Chem. Inf. Model., 2020, 60 (3), 1432-1444
25. Cappel, D.; Sherman, W.; Beuming, T., Curr Top Med Chem., 2017, 17 (23), 2586-2598
26. Cho, A. E.; Guallar, V.; Berne, B.; Friesner, R. A., J. Comput. Chem., 2005, 26, 915–931
27. Chris Croshaw, Levi Hamernik, Lina Ghanbari, Andrea Browning, Jeffrey Wiggins, Polymer Degradation and Stability, 2022, 200,
28. Clark, A.J.; Gindin, T.; Zhang, B.; Wang, L.; Abel, R.; Murret, C.S.; Xu, F.; Bao, A.; Lu, N.J.; Zhou, T.; Kwong, P.D.; Shapiro, L.; Honig, B.; Friesner, R.A. , J. Mol. Biol., 2016, 16, 30516-2
29. Clark, A.J.; Negron, C.; Hauser, K.; Sun, M.; Wang, L.; Abel, R.; Friesner, R.A., Journal of Molecular Biology, 2019.
30. Crystal, J.; Zhang, L. Y.; Friesner, R. A.; Flynn, G., J. Phys. Chem. A, 2002, 106, 1802–1814
31. Dajnowicz, S.; Ghoreishi, D.; Modugula, K.; Damm, W.; Harder, E.D.; Abel, R.; Wang, L.; Yu, H.S., J. Chem. Theory Comput., 2020, X, X-X
32. Dana Katz, Michael A. DiMattia, Dan Sindhikara, Hubert Li, Nikita Abraham, Abba E. Leffler, Marine Drugs, 2021, 19(7), 367
33. Dixon, S.L.; Duan, J.; Smith, E.; Von Bargen, C.D.; Sherman, W.; Repasky, M.P., Future Med. Chem., 2016, 8 (15), 1825-1839
34. Dukovic, G.; White, B. E.; Zhou, Z. Y.; Wang, F.; Jockusch, S.; Steigerwald, M. L.; Heinz, T. F.; Friesner, R. A.; Turro, N. J.; Brus, L. E., J. Am. Chem. Soc., 2004, 126, 15269–15276
35. Evansa, D.R.; Kwak, H.S.; Giesen, D.J.; Goldberg, G.; Halls, M.D.; Oh-ee, M., Organic Electronics, 2016, 29, 50-56
36. Fox J.M.; Kang K.; Sherman W.; Héroux A.; Sastry G.M.; Baghbanzadeh M.; Lockett .M.R.; and Whitesides G.M., J. Am. Chem. Soc., 2015, 137 (11), 3859–3866
37. Fratev, F.; Steinbrecher, T.B.; Jónsdóttir, S.O., ACS Omega, 2018, 3(4), 4357–4371
38. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shaw, D. E.; Shelley, M.; Perry, J. K.; Francis, P.; Shenkin, P. S., J. Med. Chem., 2004, 47, 1739–1749
39. Friesner, R. A.; Dunietz, B. D., Accounts of Chemical Research, 2001, 34, 351–358
40. Friesner, R.A.; Murphy, R.B.; Repasky, M.P.; Frye, L.L.; Greenwood, J.R.; Halgren, T.A.; Sanschagrin, P.C.; Mainz, D.T., J. Med. Chem., 2006, 49, 6177–6196
41. Gary Tresadern, Kanaka Tatikola, Javier Cabrera, Lingle Wang, Robert Abel, Herman van Vlijmen, and Helena Geys, JCIM, 2022, 62(3), 703-717
42. Ghanakota, P.; Bos, P.; Konze, K.; Staker, J.; Marques, G.; Marshall, K.; Leswing, K.; Abel, R.; Bhat, S., ChemRxiv, 2020, Preprint, xx-xx
43. Gherman, B. F.; Dunietz, B. D.; Whittington, D. A.; Lippard, S. J.; Friesner, R. A., J. Am. Chem. Soc., 2001, 123, 3836–3837
44. Goldberg, A; Kwak, S; Hall, M.D.;.Matsuzawa, N.N.; Sasago, M; Arai, H; Fujii, E, Org. Electron., 2019, 105571, In Press
45. Greenwood, J. R.; Begtrup, M., Theor. Chem. Acc., 2003, 109, 200–205
46. Greenwood, J. R.; Calkins, D.; Sullivan, A. P.; Shelley, J. C., J. Comput. Aided Mol. Des., 2010, 24, 591-604
47. Guallar, V.; Gherman, B. F.; Miller, W. H.; Lippard, S. J.; Friesner, R.A., J. Am. Chem. Soc., 2002, 124, 3377–3384
48. Guido Scarabelli, Eliud O. Oloo, Johannes K.X. Maier, Agustina Rodriguez-Granillo, JMB, 2022, 434(2
49. Guo, Z.; Mohanty, U.; Noehre, J.; Sawyer, T. K.; Sherman, W.; Krilov, G., Chem. Biol. Drug Des., 2010, 75, 348-359
50. Hadi Abroshan, H. Shaun Kwak, Yuling An, Christopher Brown, Anand Chandrasekaran, Paul Winget, and Mathew D. Halls, Frontiers in Chemistry, 2022, ,
51. Haifeng Tang, et al., Journal of Medicinal Chemistry, 2022, 65(9), 6775-6802
52. Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L., J. Med. Chem., 2004, 47, 1750–1759
53. Hall, M.L.; Calkins, D.; Sherman, W.B., J. Chem. Inf. Model., 2016, 56 (11), 2216–2224
54. Halls, M.D.; Djurovich, P.J.; Giesen, D.J.; Goldberg, A.; Sommer, J.; McAnally, E.; Thompson, M.E., New J. Phys., 2013, 15, 105029
55. Halls, M.D.; Yoshidome, D.; Mustard, T.J.; Goldberg, A.; Kwak, H.S.; Gavartin, J.L., Journal of the Imaging Society of Japan, 2015, 54(6), 561
56. Harder, E.; Damm, W.; Maple, J.; Wu, C.; Reboul, M.; Xiang, J.Y.; Wang, L.; Lupyan, D.; Dahlgren, M.K.; Knight, J.L.; Kaus, J.W.; Cerutti, D.S.; Krilov, G.; Jorgensen, W.L.; Abel, R.; Friesner, R.A., J. Chem. Theory Comput., 2016, 2 (1), 281–296
57. Higgs, C.; Beuming, T.; Sherman W. , ACS Med. Chem. Lett., 2010, 1, 160-164
58. Horbert, R.; Pinchuk, B.; Johannes, E.; Schlosser, J.; Schmidt, D.; Cappel, D.; Totzke, F.; Schächtele, C.; Peifer, C., J. Med. Chem., 2015, 58(1), 170–182
59. Hughes, T. F.; Harvey, J. N.; Friesner, R. A., Phys. Chem. Chem. Phys., 2012, 14, 7724-7738
60. Hughes, T.F.; Friesner, R.A., J. Phys. Chem. B, 2011, 115, 9280-9
61. Jacobson, L., Bochevarov, A., Watson, M., Hughes, T., Rinado, D., Ehrlich, S., Steinbrecher, T., Vaitheeswaran, S., Philipp, D., Halls, M., Friesner, R., J. Chem. Theory Comput., 2017, 13 (11), 5780–5797
62. Jennifer L. Knight, Karl Leswing, Pieter H. Bos, and Lingle Wang, Free Energy Methods in Drug Discovery, 2021, 1397, 205-226
63. Junko Habasaki, The American Ceramic Society, 2022 ,
64. Kalid, O.; Warshaviak, D.T.; Shechter, S.; Sherman, W.; Shacham, S., J. Comput. Aided Mol. Des., 2012, 26, 1217–1228
65. Kaminski, G. A.; Friesner, R. A.; Zhou, R., J. Comput. Chem., 2003, 24, 267–276
66. Kaminski, G. A.; Stern, H. A.; Berne, B. J.; Friesner, R. A., J. Phys. Chem. A, 2004, 108, 621–627
67. Kaminski, G. A.; Stern, H. A.; Berne, B. J.; Friesner, R. A.; Cao, Y. X.; Murphy, R. B.; Zhou, R.; Halgren, T. A., J. Comput. Chem., 2002, 23, 1515–1531
68. Kamps, J.J.A.G.; Huang, J.; Poater, J.; Xu, C.; Pieters, B.J.G.E.; Dong, A.; Min, M.; Sherman, W.; Beuming, T.; Bickelhaupt, F.M.; Li, H.; Mecinović, J., Nat. Commun., 2015, 6, doi:10.1038/ncomms9911
69. Kannan Sankar, Kyle Trainor, Levi L. Blazer, Jarrett J. Adams, Sachdev S. Sidhu, Tyler Day, Elizabeth Meiering, Johannes K. X. Maier, Mol Inform, 2022, ,
70. Katz, D.; Sindhikara, D.; DiMattia, M.; Leffler, A.E., Toxins, 2021, 13(3), 193
71. Kaus, J. W.; Harder, E.; Lin, T.; Abel, R.; McCammon, A.; Wang, L., J. Chem. Theory Comput., 2015, 11(6), 2670–2679
72. Keränen, H.; Pérez-Benit, L.; Ciordia, M.; Delgado, F.; Steinbrecher, T.B.; Oehlrich, D.; van Vlijmen, H.; Trabanco, A.A.; Tresadern, G., J. Chem. Theory Comput., 2017, 13, 1439-1453
73. Klicic, J. J. ; Friesner, R. A.; Liu, S. Y.; Guida, W. C., J. Phys. Chem. A, 2002, 106, 1327–1335
74. Ko, C.; Malick, D.K.; Braden, D.A.; Friesner, R.A.; Martínez, T.J., J. Chem. Phys., 2008, 128, 104103-104111
75. Konze, K.; Bos, P.; Dahlgren, M.; Leswing, K.; Tubert-Brohman, I.; Bortolato, A.; Robbason, B.; Abel, R.; Bhat, S., J. Chem. Inf. Model., 2019, 59, 9, 3782–3793
76. Krishnendu, P.; Al-suraih, F.; Gonzalez-Rodriguez, G.; Dutta, S.K.; Wang, E.; Kwak, H.S.; Caulfield, T.R.; Coffer, J.L.; Bhattacharya, S., Nanoscale, 2017, 9, 15622-15634
77. Kuhn, B.; Tichy, M.; Wang, L.; Robinson, S.; Martin, R.E.; Kuglstatter, A.; Benz, J.; Giroud, M.; Schirmeister, T.; Abel, R.; Diederich, F.; Hert, J., J. Med. Chem., 2017, 60 (6), 2485–2497
78. Leah Frye, Sathesh Bhat, Karen Akinsanya, Robert Abel, Drug Discovery Today: Technologies, 2021, 39, 111-117
79. Leger, P.R.; Hu, D.X.; Biannic, B.; Bui, M.; Han, X.; et. al., J. Med. Chem., 2020, 63 (10), 5398–5420
80. Leif D. Jacobson, James M. Stevenson, Farhad Ramezanghorbani, Delaram Ghoreishi, Karl Leswing, Edward D. Harder, and Robert Abel, JCTC, 2022, 18(4), 2354-2366
81. Lenselink, E.B.; Louvel, J.; Forti, A.F.; van Veldhoven, J.P.D.; de Vries, H.; Mulder-Krieger, T.; McRobb, F.M.; Negri, A.; Goose, J.; Abel, R.; van Vlijmen, H.W.T.; Wang, L.; Harder, E.; Sherman, W.; IJzerman, A.P.; Beuming, T., ACS Omega, 2016, 1, 293-304
82. Leung, S.S.F.; Mijalkovic, J.; Borrelli, K.; Jacobson, M.P., J. Chem. Inf. Model., 2012, 52(6), 1621-1636
83. Li, J.; Schneebeli, S. T.; Bylund, Farid, R.; Friesner, R.A., J. Chem. Theory Comput., 2011, 7, 3829–3845
84. Liao, C.; Selvan, M.E.; Zhao, J.; Slimovitch, J.L.; Schneebeli, S.T.; Shelley, M.; Shelley, J.C.; and Li, J., J. Phys. Chem. B., 2015, 119 (33) , 10390–10398
85. Liu, M.; Bender, S.A.; Cuny, G.D.; Sherman, W.; Glicksman, M.; Ray, S.S, Biochemistry, 2013, 52, 1725-1736
86. Liu, S.; Wu, Y.; Lin, T.; Abel, R.; Redmann, J.P.; Summa, C.M.; Jaber, V.R.; Lim, N.M.; Mobley, D.L., J. Comput. Aided Mol. Des., 2013, 27(9), 755-770
87. Lockett M.R.; Lange H.; Breiten B.; Heroux A.; Sherman W.; Rappoport D.; Yau P.O.; Snyder P.W.; Whitesides G.M., Angew. Chem. Int. Ed., 2013, 52(30), 7714-7717
88. Lorena Zara, Francesca Moraca, Jacqueline E. Van Muijlwijk-Koezen, Barbara Zarzycka, Robert Abel, and Iwan J. P. de Esch, ACS Medicinal Chemistry Letters, 2022, 13(6), 904-910
89. Loving, K.; Alberts, I.; Sherman, W., Curr. Top. Med. Chem., 2010, 10, 14-32
90. Loving, K.; Salam, N.K.; Sherman, W., J. Comput. Aided Mol. Des., 2009, 23, 541–554
91. Lupyan, D.; Abramov, Y.A.; Sherman, W., J. Comput. Aided Mol. Des., 2012, 26, 1195-1205
92. Lyman, E.; Higgs, C.; Kim, B.; Lupyan, D.; Shelley, J. C.; Farid, R.; Voth, G. A., Structure, 2009, 17, 1660-1668

93.Mattelaer, F.; Van Daele, M.; Minjauw, M.M.; Nisula, M.; Elliott, S.D.; Sajavaara, T.; Dendooven, J.; Detavernier, C., Chem. Mater., 2020, 32 (10), 4152–4165
94.Michael J. Robertson, Justin G. Meyerowitz, Ouliana Panova, Kenneth Borrelli & Georgios Skiniotis , Nature Structural & Molecular Biology, 2022, 29, 210-217
95.Migues, A.N.; Muskat, A.; Auerbach, S.M.; Sherman, W.; Vaitheeswaran, S., ACS Catal., 2015, 5, 2859-2865
96.Miller, E.; Murphy, R.; Sindhikara, D.; Borrelli, K.; Grisewood, M.; Ranalli, F.; Dixon, S.; Jerome, S.; Boyles, N.; Day, T.; Ghanakota, P.; Mondal, S.; Rafi, S.B.; Troast, D.M.; Abel, R.; Friesner, R.A., ChemRxiv, 2020, Preprint, 1
97.Minuesa, G.; Albanese, S. K.; Xie, W.; Kazansky, Y.; Worroll, D. et al., Nature Communications, 2019, 10, 2691 (2019)
98.Mohammad Atif Faiz Afzal, Kristin Lehmkemper, Ekaterina Sobich, Thomas F. Hughes, David J. Giesen, Teng Zhang, Caroline M. Krauter, Paul Winget, Matthias Degenhardt, Samuel O. Kyeremateng, Andrea R. Browning, and John C. Shelley, Molecular Pharmaceutics, 2021, 18(11), 3999-4014
99.Mondal, S; Tresadern, G.; Greenwood, J.; Kim, B.; Kaus, J.; Wirtala, M.; Steinbrecher, T.; Wang, L.; Masse, C.; Farid, R.; Abel, R., ChemRxiv., 2020, preprint, https://doi.org/10.26434/chemrxiv.10263077.v1
100.Moraca, F.; Negri, A.; de Oliveira, C.; Abel, R., J. Chem. Inf. Model., 2019, 59(6) , 2729-2740
101.Myrianthopoulos, V.; Kritsanida, M.; Gaboriaud-Kolar, N.; Magiatis, P.; Ferandin, Y.; Durieu, E.; Lozach, O.; Cappel, D.; Soundararajan, M.; Filippakopoulos, P.; Sherman, W.; Knapp, S.; Meijer, L.; Mikros, E.; Skaltsounis, A.L., ACS Med Chem Lett, 2013, 4(1), 22-26
102.Newman, A.H.; Beuming, T.; Banala, A.K.; Donthamsetti, P.; Pongetti, K.; LaBounty, A.; Levy, B.; Cao, J.; Michino, M.; Luedtke, R.P.; Javitch, J.A.; Shi, L., J. Med. Chem., 2012, 55(15), 6689–6699
103.Oliveira, C; Yu, HS; Chen, W; Abel, R; Wang, L, J. Chem. Theory Comput., 2019, 15 (1), 424-435
104.Osguthorpe D.J.; Sherman, W.; Hagler, A.T., J. Phys. Chem. B, 2012, 116(23), 6952-6959
105.Osguthorpe, D.J.; Sherman, W.; Hagler, A.T., Chem. Biol. Drug Des., 2012, 80(2), 182-193
106.Pearlstein, R. A.; Hu, Q. Y.; Zhou, J.; Yowe, D.; Levell, J.; Dale, B.; Kaushik, V. K.; Daniels, D.; Hanrahan, S.; Sherman, W.; Abel, R. , Proteins, 2010, 78, 2571–2586
107.Pearlstein, R.A.; Sherman, W.; Abel, R., Proteins, 2013, 81(9), 1509-1526
108.Philipp, D., Watson, M., Yu, H., Steinbrecher, T., Bochevarov, A. , Int. J. Quantum Chem, 2018, DOI: 10.1002/qua.25561, preprint
109.Pieter H. Bos, Evelyne M. Houang, Fabio Ranalli, Abba E. Leffler, Nicholas A. Boyles, Volker A. Eyrich, Yuval Luria, Dana Katz, Haifeng Tang, Robert Abel, and Sathesh Bhat, JCIM, 2022, 62(8), 1905-1915
110.Plenge, P.; Shi, L.; Beuming, T.; Te, J.; Newman, A.H.; Weinstein, H.; Gether, U.; Loland, C.J., J. Biol. Chem., 2012, 287, 39316-39326
111.Podvinec, M.; Lim, S. P.; Schmidt, T.; Scarsi, M.; Wen, D.; Sonntag, L.; Sanschagrin, P.; Shenkin, P. S.; Schwede, T., J. Med. Chem., 2010, 53, 1483–1495
112.Rao, S.; Sanschagrin, P. C.; Greenwood, J. R.; Repasky, M. P.; Sherman, W.; Farid, R., J. Comput. Aided. Mol. Des., 2008, 22, 621-627
113.Rebecca T. Haber, Andrea R. Browning, Bayleigh R. Graves, William P. Davis, and Jeffrey S. Wiggins, Polymers, 2022, 14(6), 1219
114.Rim, K.T.; Muller,T.; Fitts, J.P.; Adib, K.; Camillone, N.; Osgood, R.M.; Batista, E. R.; Friesner, R. A. ; Joyce, S. A.; Flynn, G. W., J. Phys. Chem. B., 2004, 108, 16753–16760
115.Robertson, M.J.; van Zundert, G.C.P.; Borrelli, K.; Skiniotis, G., Structure, 2020, 28(6), 707-716.e3
116.Robertson, M.J.; van Zundert, G.C.P.; Borrelli, K.; Skiniotis, S., bioRxiv, 2019, 750778, Preprint
117.Robinson, D. D.; Sherman, W.; Farid, R., Chem. Med. Chem., 2010, 5, 618– 627
118.Rombouts, F.J.R.; Tresadern, G.; Buijnsters, P.; Langlois, X.; Tovar, F.; Steinbrecher, T. B.; Vanhoof, G.; Somers, M.; Andrés, J.; Trabanco, A. A., ACS Med. Chem. Lett., 2015, 6(3), 282–286
119.Roos, K.; Wu, C.; Damm, W.; Reboul, M.; Stevenson, J.M.; Lu, C.; Dahlgren, M.K.; Mondal, S.; Chen, W.; Wang, L.; Abel, R.; Friesner, R.A.; Harder, E.D., J. Chem. Theory Comput., 2019, 1863–1874,
120.Rossini, E., Bochevarov, A., Knapp, E., ACS Omega, 2018, 3 (2), 1653–1662
121.Ruvinsky, A.M.; Aloni, I.; Cappel, D.; Higgs, C.; Marshall, K.; Rotkiewicz, P.; Repasky, M.; Feher, V.A.; Feyfant, E.; Hessler, G.; Matter, H., ChemMedChem, 2018, ,
122.Salam, N.K.; Nuti, R.; Sherman, W., J. Chem. Inf. Model., 2009, 49, 2356–2368
123.Sastry, G.M.; Inakollu, V.S.; Sherman, W, J. Chem. Inf. Model., 2013, 53, 1531-1542
124.Scarbath-Evers, K.; Cappel, D.; Weiser, J., Nachrichten aus der Chemie, 2020, Jul (68), 34-36
125.Schindler, C.; Baumann, H.; Blum, A.; Böse, D.; Buchstaller, H-P.; Burgdorf, L.; et al. , J. Chem. Inf. Model., 2020, Preprint, xx-xx
126.Schneebeli S.T., Hall M.L., Breslow R., Friesner R., J. Am. Chem. Soc., 2009, 131, 3965-3973
127.Shah, B.; Sindhikara, D.; Borrelli, K.; Leffler, A.E.;, Toxins, 2020, 12 (10), 652
128.Shah, F.; Jiri, G.; Legac, J.; Shivakumar, D.; Sherman, W.; Rosenthal, P.J.; Avery, M., J. Chem. Inf. Model., 2012, 52(3), 696-710
129.Shelley, J.C.; Cholleti, A.; Frye, L; Greenwood, J.R.; Timlin, M.R.; Uchimaya, M., J. Comp. Aided Mol. Des., 2007, 21, 681-691
130.Shelley, M.Y.; Selvan, M.E.; Zhao, J.; Babin, V.; Liao, C.; Li, J.; Shelley, J.C, J. Chem. Theory Comput., 2017, 13 (8), 3881–3897
131.Shivakumar, D.; Harder, E; Damm, W.; Friesner, R.A.; Sherman, W., J. Chem. Theory Comput., 2012, 8(8), 2553-2558
132.Shivakumar, D.; Williams, J.; Wu, Y.; Damm, W.; Shelley, J.; Sherman, W., J. Chem. Theory Comput., 2010, 6, 1509–1519
133.Sindhikara, D. and Borrelli, K., Nature, Scientific Reports , 2018, 8 (6585)
134.Sirin, S.; Kumar, R.; Martinez, C.; Karmilowicz, M.J.; Ghosh, P.; Abramov, Y.A.; Martin, V.; Sherman, W., J. Chem. Inf. Model., 2014, 54(8), 2334-2346
135.Sirin, S.; Pearlman, D.A.; Sherman, W., Proteins, 2014, 82(12), 3397-409
136.Snyder. P.W.; Mecinovic, J.; Moustakas, D.; Thomas, S, III.; Harder, M.I.; Mack, E.; Lockett, M.; Héroux, A.; Sherman, W.; Whitesides, G., PNAS, 2011, 108, 17889-17894
137.Steinbrecher, T.; Abel, R.; Clark, A.; Friesner, R., J. Mol. Biol. , 2017, 429 (7), 923–929
138.Steinbrecher, T.; Zhu, C.; Wang, L.; Abel, A.; Negron, C.; Pealman, D.; Feyfant, E.; Duan, J.; Sherman, W., J. Mol. Biol. , 2017, 429 (7), 948-963
139.Steinbrecher, T.B.; Dahlgren, M.; Cappel, D.; Lin, T.; Wang, L.; Krilov, G.; Abel, R.; Friesner, R.; Sherman, W., J. Chem. Inf. Model., 2015, 55 (11), 2411–2420
140.Tang, L.; Papish, E. T.; Abramo, G. P.; Norton, J. R.; Baik, M.; Friesner, R. A.; Rappé, A., J. Am. Chem. Soc., 2003, 125, 10093–10102
141.Tian L., Friesner R.A., J. Chem. Theory Comput., 2009, 5, 1421-1431
142.Tianchuan Xu, Kai Zhu, Alexandre Beautrait, Jeremie Vendome, Kenneth Borrelli, Robert Abel, Richard Friesner, Edward Miller , ChemRxiv, 2022, Preprint,
143.Toledo Warshaviak, D.; Golan, G.; Borrelli, K.W.; Zhu, K.; Kalid, O., J. Chem. Inf. Model, 2014, 54(7), 1941–1950
144.Tony, H.; Baik, M.; Bridgewater, B. M.; Shin, J. H.; Churchill, D. G.; Friesner, R. A.; Parkin, G. F., Chemical Communications, (British Royal Society), 2002, 22, 2644–2645
145.Tran, Q.T.; Williams, S.; Farid, R.; Erdemli, G.; Pearlstein, R., Proteins, 2013, 81(2), 291-299
146.Tubert-Brohman, I.; Sherman, W.; Repasky, M.; Beuming, T., J. Chem. Inf. Model., 2013, 53(7), 1689-1699
147.van Zundert, G.CP; Moriarty, N.W.; Sobolev, O.V.; Adams, P.D.; Borrelli, K.W., Structure, 2021, ,
148.Wang T., Friesner R.A., J. Phys. Chem. C, 2009, 113, 2553-2561
149.Wang, L; Chambers, J; Abel, R, Biomolecular Simulations, 2019, 2022, 201-232
150.Wang, L.; Berne, B. J.; Friesner, R. A., Proc Natl Acad Sci U S A., 2012, 109(6), 1937-1942
151.Wang, L.; Deng, Y.; Knight, J.L.; Wu, Y.; Kim, B.; Sherman, W.; Shelley, J.C.; Lin, T.; Abel, R., J. Chem. Theory Comput., 2013, 9, 1282-1293
152.Wang, L.; Deng, Y.; Wu, Y.; Kim, B.; LeBard, D.N.; Wandschneider, D.; Beachy, M.; Friesner, R.A.; Abel, R., J. Chem. Theory Comput., 2017, 13 (1), 42–54
153.Wang, L.; Friesner, R. A.; Berne, B. J., J. Phys Chem B., 2011, 115(30), 9431–9438
154.Wang, L.; Wu, Y.; Deng, Y.; Kim, B.; Pierce, L.; Krilov, G.; Lupyan, D.; Robinson, S.; Dahlgren, M.; Greenwood, J.; Romero, D.; Masse, C.; Knight, J.; Steinbrecher, T.; Beuming, T.; Damm, W.; Harder, E.; Sherman, W.; Brewer, M.; Wester, R.; et al., J. Am. Chem. Soc., 2015, 137, 2695-2703
155.Wang, L.; Wu, Y.; Deng, Y.; Kim, B.; Pierce, L.; Krilov, G.; Lupyan, D.; Robinson, S.; Dahlgren, M.K.; Greenwood, J.; et al., J. Am. Chem. Soc., 2015, 137 (7), 2695–2703
156.Wang, S; Mondal, S; Zhao, C; Berishaj, M; Ghanakota, P; Batlevi, CL; Dogan, A; Seshan, VE, Abel, R; Green, MR; Younes, A; Wendel, H-G, JCI Insight, 2019, 4(12), e127566
157.Wang, Y.; Haze, O.; Dinnocenzo, J. P.; Farid, S.; Farid, R. S.; Gould, I. R., J. Phys. Chem. A, 2008, 112, 13088–13094
158.Wang, Y.; Haze, O.; Dinnocenzo, J.P.; Farid, S.; Farid, R.S.; Gould, I.R., J. Org. Chem., 2007, 72, 6970-6981
159.Watson, M.A.; Yu, H.S.; Bochevarov, A.D., J. Chem. Inf. Model., 2019, 59(6), 2672-2689
160.Watts, K.S.; Dalal, P.; Murphy, R.B.; Sherman, W.; Friesner, R.A.; Shelley, J.C., J.Chem. Inf. Model., 2010, 50, 534-546
161.Weldon, D.J.; Shah, F; Chittiboyina, A.G.; Sheri, A.; Chada, R.R.; Gut, J.; Rosenthal, P.J.; Shivakumar, D.; Sherman, W.; Desai, P.; Jung, J.C.; Avery, M.A., Bioorg. Med. Chem. Lett., 2014, 24(5), 1274-1279
162.Yildiz, M.; Ghosh, S.; Bell, J. A.; Sherman, W.; Hardy, J. A., ACS Chem. Biol., 2013, 8(12), 2744-2752
163.Young, T.; Abel, R.; Kim, B.; Berne, B.J.; Friesner, R.A., Proc. Natl. Acad. Sci. U S A., 2007, 104, 808-813
164.Yu, H. S.; Deng, Y.; Wu, Y.; Sindhikara, D.; Rask, A. R.; Kimura, T.; Abel, R.; Wang, L., J. Chem. Theory Comput., 2017, 13(12), 6290–6300
165.Yu, H., Watson, M., Bochevarov, A., J. Chem. Inf. Model., 2018, 58 (2), 271–286
166.Yu, HS.; Modugula, K.; Ichihara, O.; Kramschuster, K.; Keng, S.; Abel, R.; Wang, L., J. Chem. Theory Comput., 2021, 17 (1), 450–462
167.Zhou, Z.; Brus, L.; Friesner, R. A., Nano Letters, 2003, 3, 163–167
168.Zhou, Z.; Friesner, R. A.; Brus, L., J. Am. Chem. Soc., 2003, 125, 15599–15607
169.Zhou, Z.; Steigerwald, M.; Hybertsen, M.; Brus, L.; Friesner, R. A., J. Am. Chem. Soc., 2004, 126, 3597–3607
170.Zhu, K.; Borrelli, K.W.; Greenwood, J.R.; Day, T.; Abel, R.; Farid, R.S.; Harder, E., J. Chem. Inf. Model., 2014, 54, 1932−1940

93.Mattelaer, F.; Van Daele, M.; Minjauw, M.M.; Nisula, M.; Elliott, S.D.; Sajavaara, T.; Dendooven, J.; Detavernier, C., Chem. Mater., 2020, 32 (10), 4152–4165
94.Michael J. Robertson, Justin G. Meyerowitz, Ouliana Panova, Kenneth Borrelli & Georgios Skiniotis , Nature Structural & Molecular Biology, 2022, 29, 210-217
95.Migues, A.N.; Muskat, A.; Auerbach, S.M.; Sherman, W.; Vaitheeswaran, S., ACS Catal., 2015, 5, 2859-2865
96.Miller, E.; Murphy, R.; Sindhikara, D.; Borrelli, K.; Grisewood, M.; Ranalli, F.; Dixon, S.; Jerome, S.; Boyles, N.; Day, T.; Ghanakota, P.; Mondal, S.; Rafi, S.B.; Troast, D.M.; Abel, R.; Friesner, R.A., ChemRxiv, 2020, Preprint, 1
97.Minuesa, G.;
98.Mohammad A
M. Krauter, Pa
Pharmaceutics
99.Mondal, S; Tr
R., ChemRxiv.
100.Moraca, F.;
101.Myrianthopo
Soundararajan
2013, 4(1), 22-
102.Newman, A.
Luedtke, R.P.;
103.Oliveira, C;
104.Osguthorpe
105.Osguthorpe,
106.Pearlstein, R
Abel, R. , Prot
107.Pearlstein, R
108.Philipp, D.,
preprint
109.Pieter H. Bo
Katz, Haifeng
110.Plenge, P.; Shi, L.; Beuming, T.; Te, J.; Newman, A.H.; Weins
39316-39326
111.Podvinec, M.; Lim, S. P.; Schmidt, T.; Scarsi, M.; Wen, D.; So
Chem., 2010, 53, 1483–1495
112.Rao, S.; Sanschagrin, P. C.; Greenwood, J. R.; Repasky, M. P
22, 621-627
113.Rebecca T. Haber, Andrea R. Browning, Bayleigh R. Graves,
1219
114.Rim, K.T.; Muller,T.; Fitts, J.P.; Adib, K.; Camillone, N.; Osgoo
W., J. Phys. Chem. B., 2004, 108, 16753–16760
115.Robertson, M.J.; van Zundert, G.C.P.; Borrelli, K.; Skiniotis, G.
116.Robertson, M.J.; van Zundert, G.C.P.; Borrelli, K.; Skiniotis, S.
117.Robinson, D. D.; Sherman, W.; Farid, R., Chem. Med. Chem.,
118.Rombouts, F.J.R.; Tresadern, G.; Buijnsters, P.; Langlois, X.;
Andrés, J.; Trabanco, A. A., ACS Med. Chem. Lett., 2015, 6(3),
119.Roos, K.; Wu, C.; Damm, W.; Reboul, M.; Stevenson, J.M.; Lu
Friesner, R.A.; Harder, E.D., J. Chem. Theory Comput., 2019, 18
120.Rossini, E., Bochevarov, A., Knapp, E., ACS Omega, 2018, 3
121.Ruvinsky, A.M.; Aloni, I.; Cappel, D.; Higgs, C.; Marshall, K.;
G.; Matter, H., ChemMedChem, 2018, ,
122.Salam, N.K.; Nuti, R.; Sherman, W., J. Chem. Inf. Model., 200
123.Sastry, G.M.; Inakollu, V.S.; Sherman, W, J. Chem. Inf. Model
124.Scarbath-Evers, K.; Cappel, D.; Weiser, J., Nachrichten aus der Chemie, 2020, Jul (68), 34-36
125.Schindler, C.; Baumann, H.; Blum, A.; Böse, D.; Buchstaller, H-P.; Burgdorf, L.; et al. , J. Chem. Inf. Model., 2020,
xx-xx
126.Schneebeli S.T., Hall M.L., Breslow R., Friesner R., J. Am. Chem. Soc., 2009, 131, 3965-3973
127.Shah, B.; Sindhikara, D.; Borrelli, K.; Leffler, A.E.;, Toxins, 2020, 12 (10), 652
128.Shah, F.; Jiri, G.; Legac, J.; Shivakumar, D.; Sherman, W.; Rosenthal, P.J.; Avery, M., J. Chem. Inf. Model., 2012,
710
129.Shelley, J.C.; Cholleti, A.; Frye, L; Greenwood, J.R.; Timlin, M.R.; Uchimaya, M., J. Comp. Aided Mol. Des., 2007,
691
130.Shelley, M.Y.; Selvan, M.E.; Zhao, J.; Babin, V.; Liao, C.; Li, J.; Shelley, J.C, J. Chem. Theory Comput., 2017, 13 (
3897
131.Shivakumar, D.; Harder, E; Damm, W.; Friesner, R.A.; Sherman, W., J. Chem. Theory Comput., 2012, 8(8), 2553-2558
132.Shivakumar, D.; Williams, J.; Wu, Y.; Damm, W.; Shelley, J.; Sherman, W., J. Chem. Theory Comput., 2010, 6, 1509–1519
133.Sindhikara, D. and Borrelli, K., Nature, Scientific Reports , 2018, 8 (6585)
134.Sirin, S.; Kumar, R.; Martinez, C.; Karmilowicz, M.J.; Ghosh, P.; Abramov, Y.A.; Martin, V.; Sherman, W., J. Chem. Inf. Model., 2014, 54(8), 2334-2346
135.Sirin, S.; Pearlman, D.A.; Sherman, W., Proteins, 2014, 82(12), 3397-409
136.Snyder. P.W.; Mecinovic, J.; Moustakas, D.; Thomas, S, III.; Harder, M.I.; Mack, E.; Lockett, M.; Héroux, A.; Sherman, W.; Whitesides, G., PNAS, 2011, 108, 17889-17894
137.Steinbrecher, T.; Abel, R.; Clark, A.; Friesner, R., J. Mol. Biol. , 2017, 429 (7), 923–929
Zhu, C.; Wang, L.; Abel, A.; Negron, C.; Pealman, D.; Feyfant, E.; Duan, J.; Sherman, W., J. Mol. Biol.
963
; Dahlgren, M.; Cappel, D.; Lin, T.; Wang, L.; Krilov, G.; Abel, R.; Friesner, R.; Sherman, W., J. Chem.
(11), 2411–2420
E. T.; Abramo, G. P.; Norton, J. R.; Baik, M.; Friesner, R. A.; Rappé, A., J. Am. Chem. Soc., 2003,
R.A., J. Chem. Theory Comput., 2009, 5, 1421-1431
Zhu, Alexandre Beautrait, Jeremie Vendome, Kenneth Borrelli, Robert Abel, Richard Friesner, Edward
022, Preprint,
k, D.; Golan, G.; Borrelli, K.W.; Zhu, K.; Kalid, O., J. Chem. Inf. Model, 2014, 54(7), 1941–1950
; Bridgewater, B. M.; Shin, J. H.; Churchill, D. G.; Friesner, R. A.; Parkin, G. F., Chemical
ritish Royal Society), 2002, 22, 2644–2645
ns, S.; Farid, R.; Erdemli, G.; Pearlstein, R., Proteins, 2013, 81(2), 291-299
.; Sherman, W.; Repasky, M.; Beuming, T., J. Chem. Inf. Model., 2013, 53(7), 1689-1699
D.; Borrelli, K.W., Structure, 2021, ,
561
9, 2022, 201-232
A., 2012, 109(6), 1937-1942
.; Shelley, J.C.; Lin, T.; Abel, R., J. Chem. Theory
eider, D.; Beachy, M.; Friesner, R.A.; Abel, R., J. Chem.
, 115(30), 9431–9438
yan, D.; Robinson, S.; Dahlgren, M.; Greenwood, J.;
; Damm, W.; Harder, E.; Sherman, W.; Brewer, M.;
yan, D.; Robinson, S.; Dahlgren, M.K.; Greenwood, J.; et
evi, CL; Dogan, A; Seshan, VE, Abel, R; Green, MR;
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Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy

Richard A. Friesner, Jay L. Bank
Daniel T. Mainz, Matthew P. Rep
Perry Francis, and Peter S. Sher

J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Accurate and Reliable Prediction of Relative Ligand Binding Potency in Prospective Drug Discovery by Way of a Modern Free-Energy Calculation Protocol and Force Field

Lingle Wang†, Yujie Wu†, Yuqing De
Dmitry Lupyan†, Shaughnessy Rob
Donna L. Romero‡, Craig Masse‡,
, Wolfgang Damm†, Ed Harder†, Wo
, Leah Frye†, Ramy Farid†, Teng Lin
, Richard A. Friesner§, and Robert A

JCIM
JOURNAL OF CHEMICAL INFORMATION AND MODELING

Combining Cloud-Based Free-Energy Calculations, Synthetically Aware Enumerations, and Goal-Directed Generative Machine Learning for Rapid Large-Scale Chemical Exploration and Optimization

Phani Ghanakota, Pieter H. Bos, Kyle D. Konze, Joshua Staker, Gabriel Marques, Kyle Marshall , Karl Leswing, Robert Abel, and Sathesh Bhat*

Schrödinger Platform in Drug Discovery Process

2000

Target Validation	Hit Identification	Lead Optimization	Preclinical Development
	Virtual Screening		
	GLIDE	JAGUAR MACROMODEL	

Schrödinger Platform in Drug Discovery Process

2010

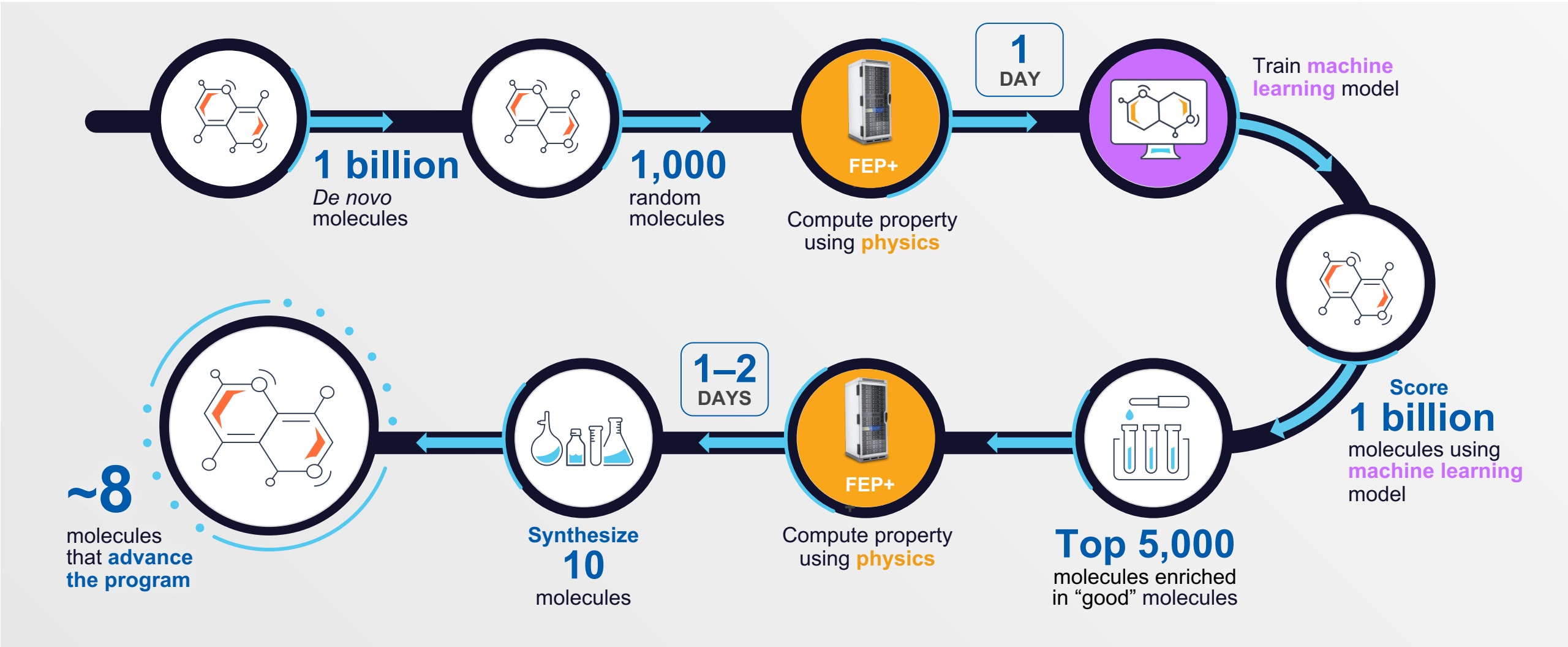
Target Validation	Hit Identification	Lead Optimization	Preclinical Development
Protein Structure Determination Druggability Assessment	Virtual Screening		
IFD MAESTRO PRIME SITEMAP WATERMAP	GLIDE CONFGEN CORE HOPPING EPIK LIGPREP MAESTRO PHASE PRIME	JAGUAR MACROMODEL AUTOQSAR CORE HOPPING DESMOND IFD LIGPREP LIVEDESIGN MAESTRO PRIME	

Schrödinger Platform in Drug Discovery Process

TODAY

Target Validation	Hit Identification	Lead Optimization	Preclinical Development
Accurate Protein Structure Determination (~10% of human genome) Reliable Druggability Assessment	Large-Scale Virtual Screening Fragment Screening	Large-Scale Compound Enumeration *In silico* assays for • Potency • Selectivity (Off Targets) • Solubility Prediction of • Membrane Permeability • hERG Inhibition • Cyp Inhibition / TDI • Cyp Induction (DDI) • Site of Metabolism • Brain Exposure	• Polymorphs Prediction • Drug Manufacturing
IFD-MD MAESTRO PRIME SITEMAP WATERMAP OPLS4 FEP+ PRIMEX	GLIDE CONFGEN CORE HOPPING EPIK LIGPREP MAESTRO PHASE PRIME ACTIVE LEARNING AUTOQSAR FEP+ IFD-MD LIVEDESIGN OPLS4 SHAPE SCREENING	JAGUAR MACROMODEL AUTOQSAR CORE HOPPING DESMOND IFD-MD LIGPREP LIVEDESIGN MAESTRO PRIME ACTIVE LEARNING AUTODESIGNER FEP+ MEMBRANE PERM OPLS4 WATERMAP	POLYMORPH MS SUITE DEEPAUTOQSAR DESMOND FEP+ JAGUAR JAGUAR PKA

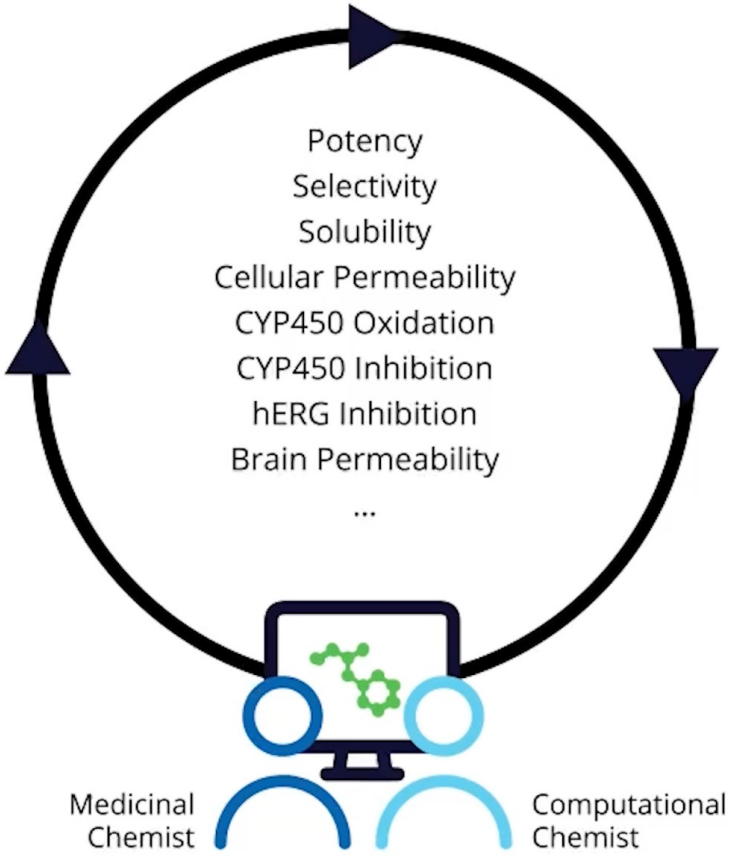
Combining Accuracy of Physics with Speed of Machine Learning Enables Ultra-Large Scale Exploration of Chemical Space

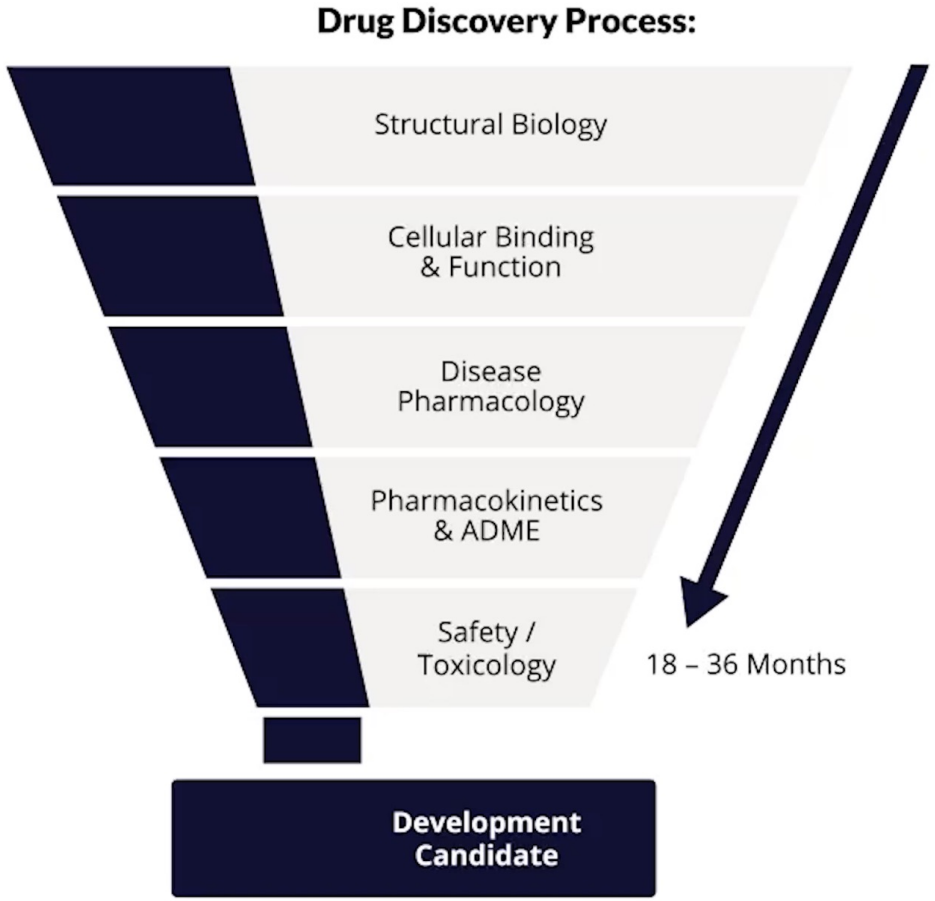


Incorporating Physics-based Compound Design into Drug Discovery

Upto **100 billion** idea molecules scored

100s of molecules synthesized and tested





Demonstrated Benefits of Schrödinger Drug Discovery Platform

Reduces time and cost, and increases quality vs. traditional drug design

Traditional Drug Design

- **Manual** molecule design
- **~5,000** molecules synthesized and tested over **~4 – 6 years**

Hit Discovery → **Hit-to-Lead** → **Lead Optimization** → **!**

Drug development candidate with **property issues**

Schrödinger's Physics-Based Platform

Hit Discovery → **Hit-to-Lead** → **Lead Optimization** → ✓

Drug development candidate with **Optimal property profile**

- **Billions** of molecules tested in computational assays
- **<1,000** molecules synthesized and tested over **~1.5 – 3 years**

Today's Agenda

Introduction — Ramy Farid

Our Platform: Current Capabilities — Robert Abel

Putting Our Platform to Work: Case Studies — Karen Akinsanya and Hamish Wright

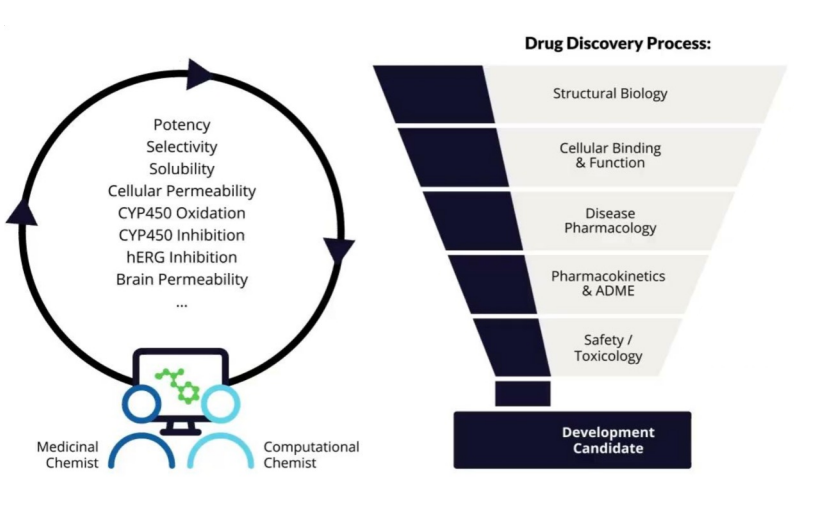
- Pipeline Overview
- Collaboration examples: Nimbus's ACC & TYK2; Morphic's $\alpha_4\beta_7$
- Proprietary examples: CDC7, Wee1, MALT1

Our Platform: Future Capabilities — Robert Abel

Business Outlook and Opportunities — Geoff Porges

Q&A

Application of Powerful Design Platform to a Growing Portfolio of Collaborations and Proprietary Programs



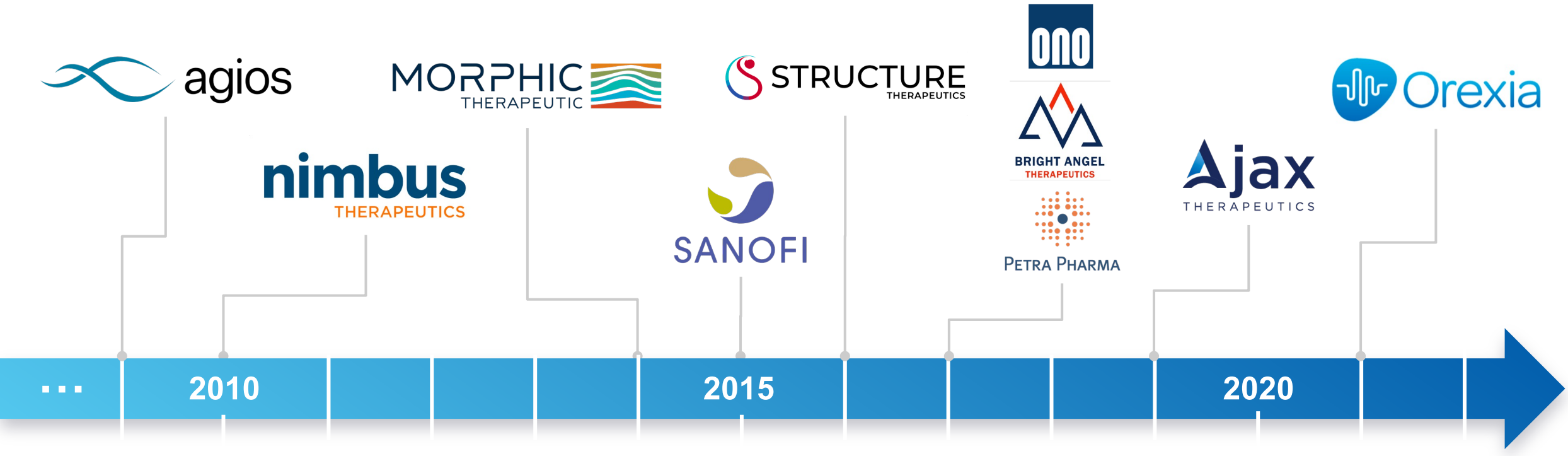
COLLABORATIONS

- Drug Design
- Materials Design

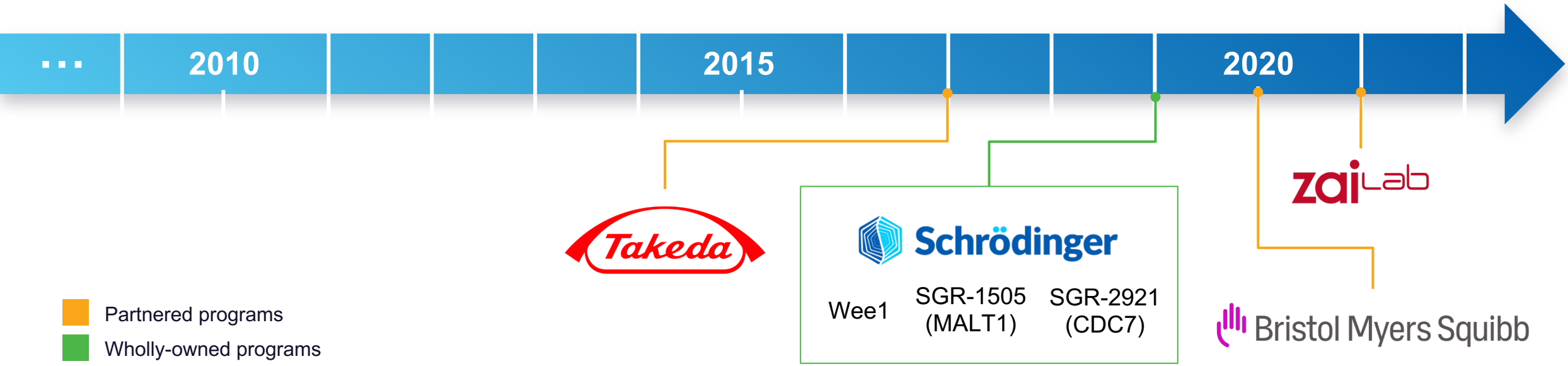
PROPRIETARY PIPELINE

- Drug Discovery & Development
- Wholly-owned & Partnered

Expansive Portfolio of Drug Discovery Collaborations



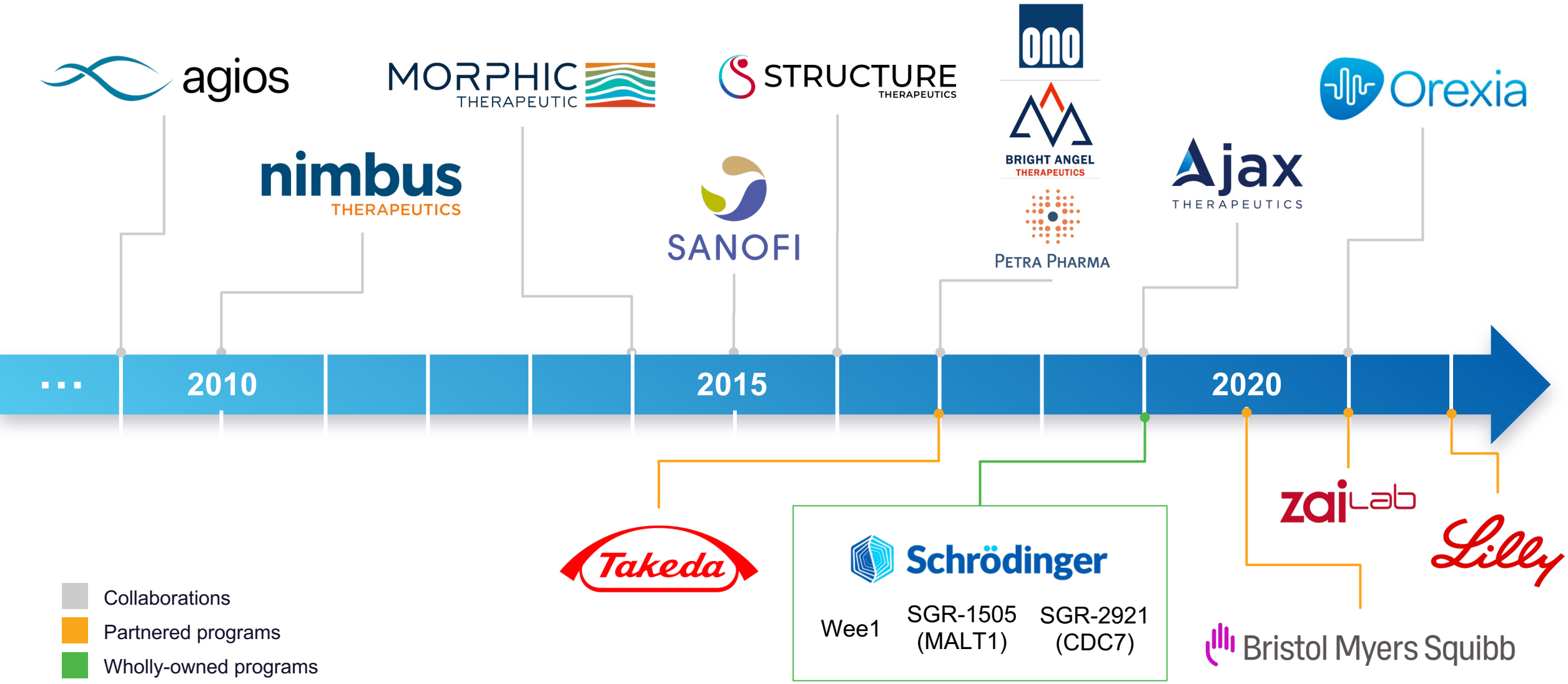
Expanding Portfolio of Proprietary Programs



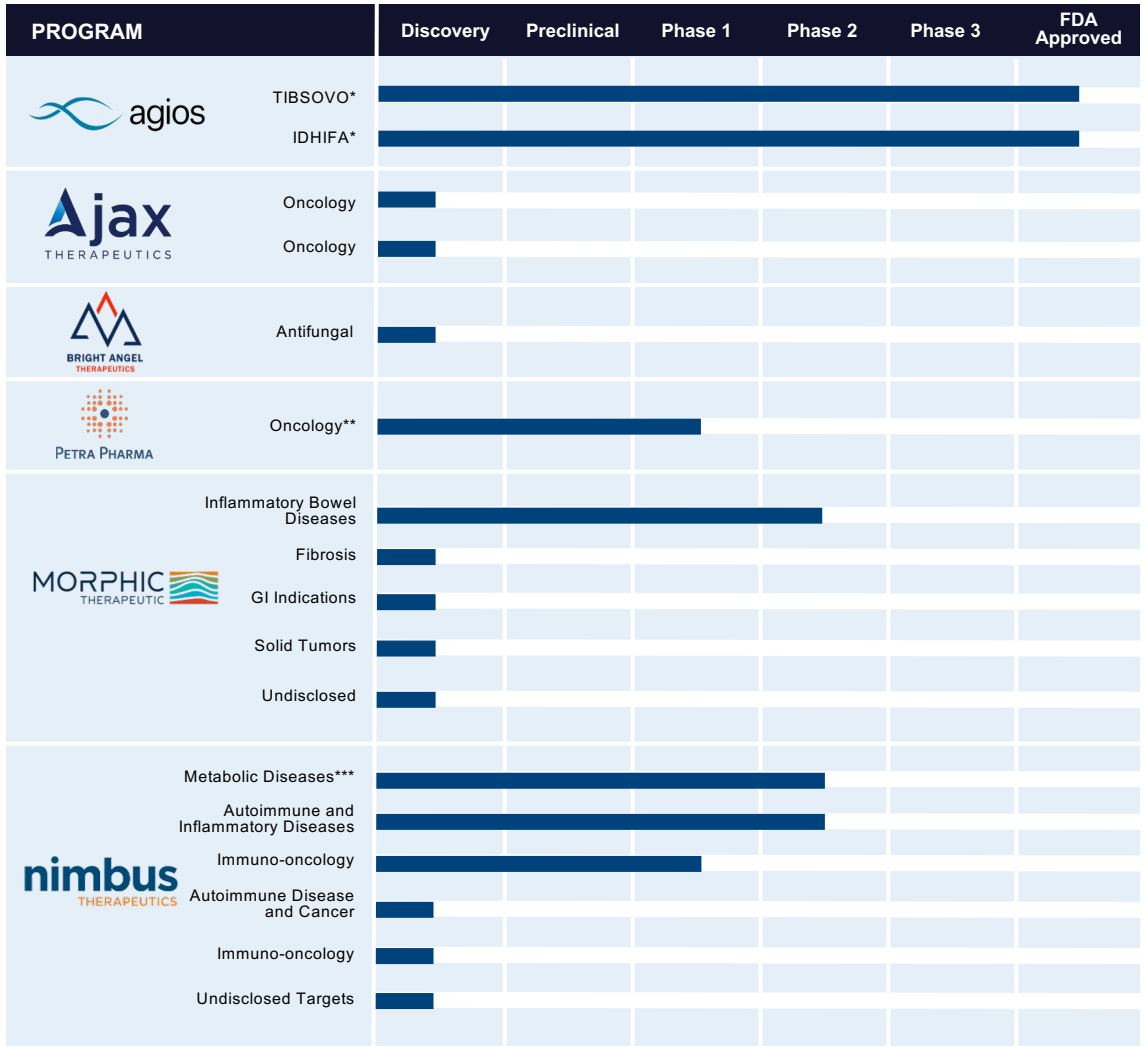
New Partnership with Lilly

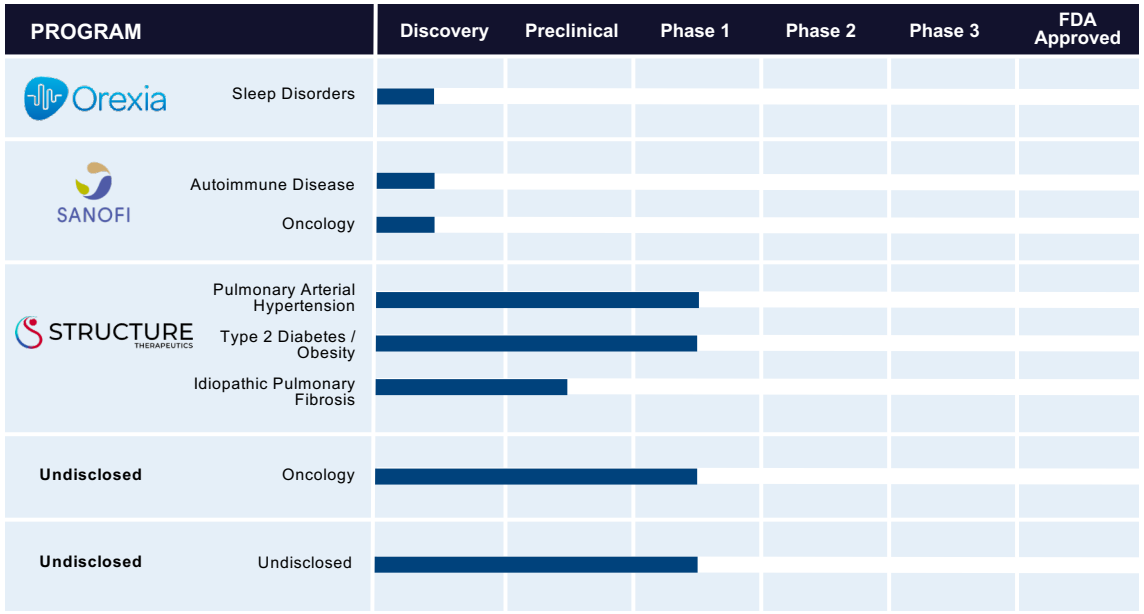
- **Small molecule program**
- **Economics**
  - Undisclosed upfront payment
  - Eligible for $425M in discovery, development and commercial milestones
  - Royalties ranging from low single-digit to low double-digit
- **Responsibilities**
  - Schrödinger responsible for the discovery and optimization of small molecule compounds
  - Lilly responsible for the completion of preclinical development, clinical development and commercialization

Collaborations, Proprietary Programs, and Partnerships



Platform Validated by Advancing Collaboration Programs[1][2]





9 programs currently in the clinic

[1]As of October 2022. Based on publicly available information or information disclosed to us. [2]All of the programs being pursued under these collaborations are owned and controlled by each respective collaborator.
*Acquired by Servier **Acquired by Lilly ***Acquired by Gilead

Our Proprietary Drug Discovery Programs

PROGRAM	DISCOVERY	PRECLINICAL	PHASE I
SGR-1505 (MALT1) Relapsed / Resistant Non-Hodgkin's Lymphoma			
SGR-2921 (CDC7) Hematological Cancers and Solid Tumors			
Wee1 Gynecological Cancers and other Solid Tumors			
Multiple Oncology Programs			
Multiple Immunology Programs			

PROGRAM	DISCOVERY	PRECLINICAL	CLINICAL	RIGHTS
SOS1 / KRAS KRAS-Driven Cancers				Schrödinger, Bristol Myers Squibb
Undisclosed Oncology				
Undisclosed Oncology				
Undisclosed Immunology				
Undisclosed Neurology				
Protein Degraders Oncology, Immunology and Neurology				
Undisclosed Oncology				Schrödinger, Takeda
DNA Damage Response Oncology				Schrödinger, Zai Lab
Undisclosed				Schrödinger, Lilly

Novel ACC Inhibitor Collaboration

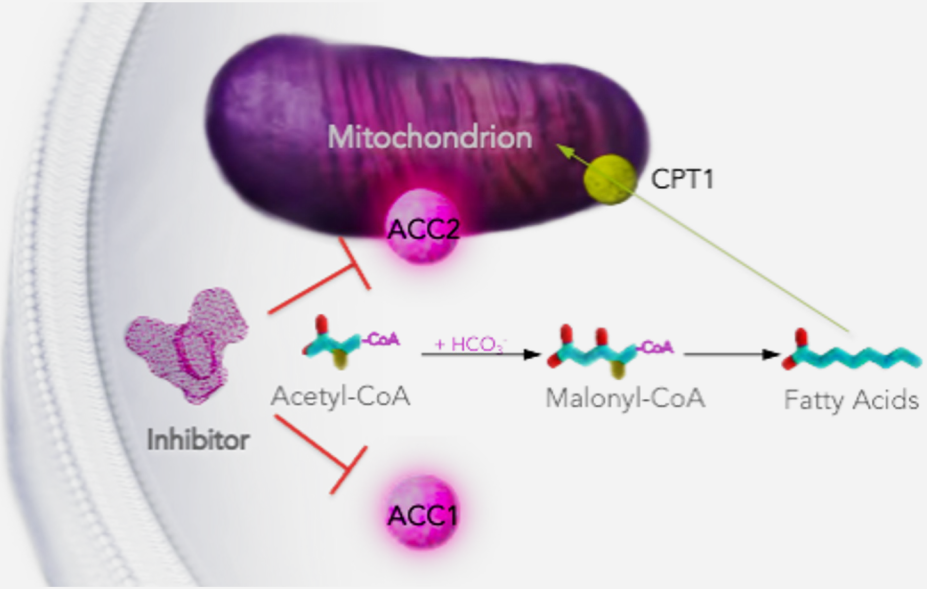
nimbus THERAPEUTICS



Best-in-Class ACC Inhibitor Program with Nimbus

Addressing Lipid Production Through ACC Inhibition Has Implications Beyond the Liver

ACC inhibition → elicits beneficial effects on lipids, blood glucose and body weight → which show promise for disease modification



- ↓ Fatty acid synthesis
- ↓ Tissue triglycerides
- ↓ Body fat and weight
- ↑ Fatty acid oxidation
- ↑ Insulin sensitivity


Liver Disease

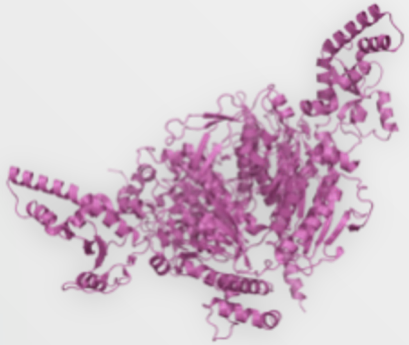

Type 2 Diabetes


Dyslipidemia

https://www.nimbustx.com/wp-content/themes/nimbustx/pdf/acetyl-coa-carboxylase-inhibition-by-nd-630-inhibits-fatty-acid-synthesis-and-stimulates-fatty-acid-oxidation-in-cultured-cells-and-in-experimental-animals.pdf
https://www.nimbustx.com/wp-content/themes/nimbustx/pdf/liver-directed-allosteric-inhibitors-of-acetyl-coa.pdf

Challenges of Targeting ACC

ACC



CT Domain
Highly lipophilic

- HTS gave low yields
- Poor drug-like properties

DESIGN CHALLENGE

Discover novel chemotypes to address these limitations

BC Domain
No drug-like inhibitors

- Crystal structure available – 3GID (2.30 Å)
- Binding site predicted to be druggable

Stiede, K. et al. *Hepatology* (Baltimore, Md.) vol. 66,2 (2017): 324-334. doi:10.1002/hep.29246.

Potential Solution to Targeting ACC

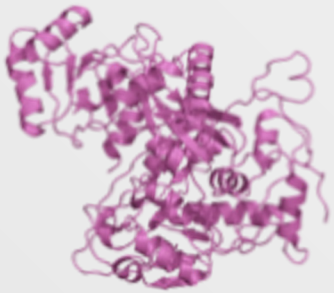
ACC

CT Domain
Highly lipophilic

- HTS gave low yields
- Poor drug-like properties

DESIGN CHALLENGE

Discover novel chemotypes to address these limitations



BC Domain
No drug-like inhibitors

- Crystal structure available
  - Soraphen (2.30 Å)
- Binding site predicted to be druggable

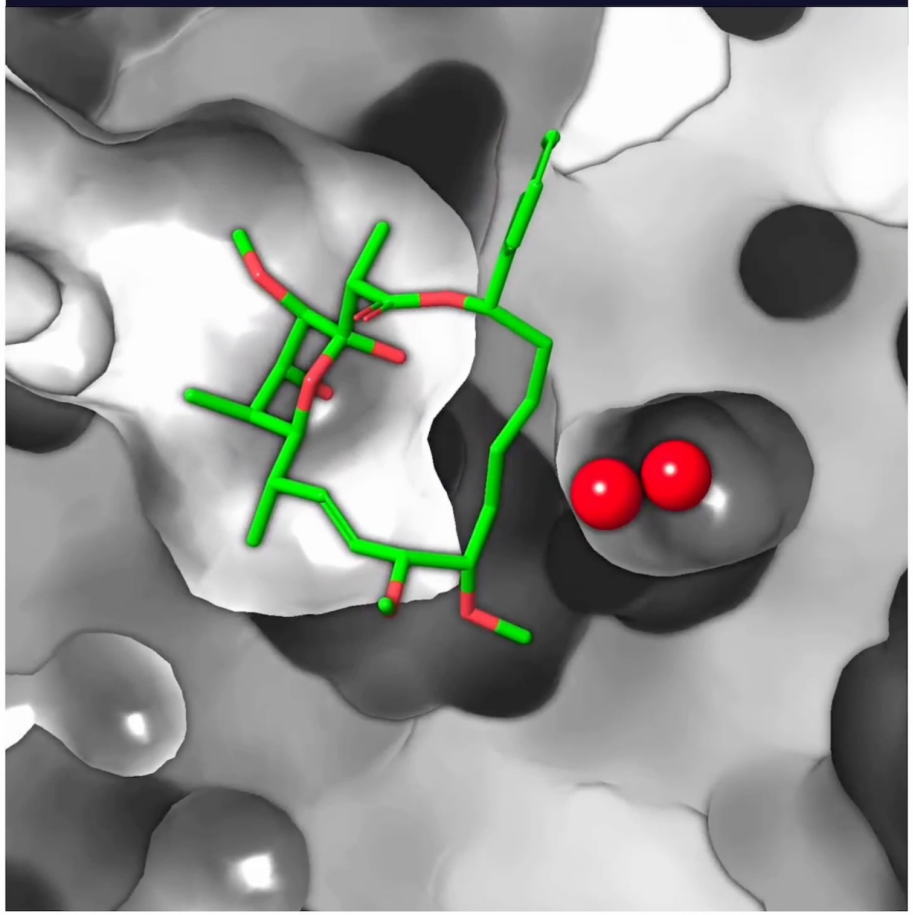
Schrödinger

Stiede, K. et al. *Hepatology* (Baltimore, Md.) vol. 66,2 (2017): 324-334. doi:10.1002/hep.29246.

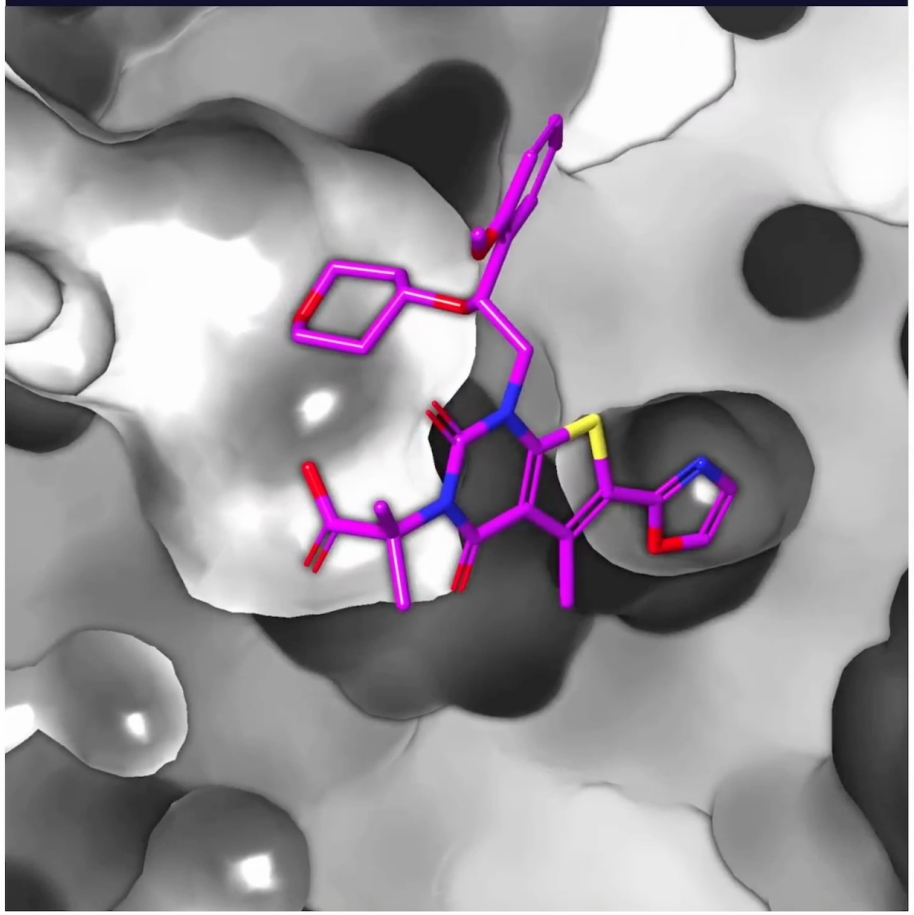
Water Physics Revealed Unique Binding Opportunity

Red spheres represent locations of high-energy unstable waters

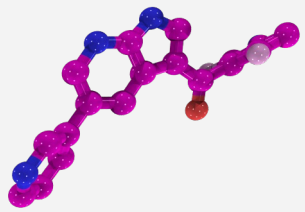
Soraphen does not displace high-energy waters — provides an opportunity to improve potency



Potent ACC inhibitor displaces high-energy waters and captures additional potency

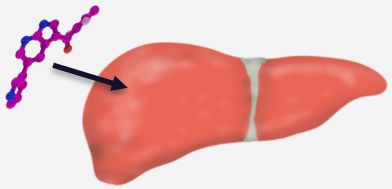


Summary



First-in-Class ACC Inhibitor

- NDI-976 exhibits a unique MoA — allosteric BC domain inhibition
- Dual ACC1/2 inhibition for maximum impact on reversing lipid accumulation



Liver-Directed Biodistribution

- Biodistribution optimized to improve hepatic glucose and lipid utilization
- Minimizes effects on non-target tissues



Current Status

- Gilead acquired the program (2Q16)
- GS-0976/Firsocostat progressing in Ph2b trial*

*ClinicalTrials.gov Identifier: NCT04971785; NDI-976 became GS-0976 following acquisition by Gilead.

Selective TYK2 Inhibitor Collaboration

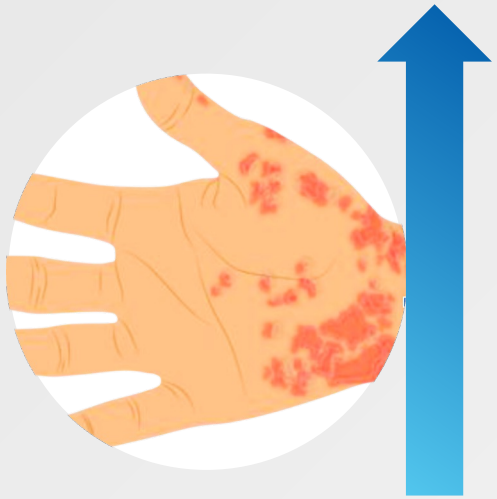
nimbus
THERAPEUTICS



JAK/TYK Kinases Are Key Signaling Molecules in Inflammation

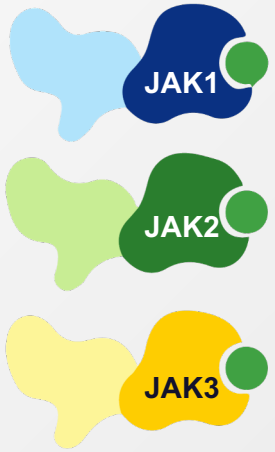
Including Psoriasis, Rheumatoid Arthritis, Crohn's and Lupus Disease

Psoriasis

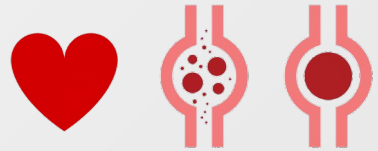


Inflammation in psoriasis is driven by increased interferon and cytokine release, which is regulated by the JAK/TYK family of proteins

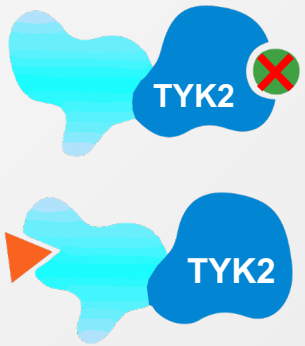




Approved JAK inhibitor drugs hit multiple JAKs and have side effect safety warnings



Drug Design Goal



Avoid the kinase domain

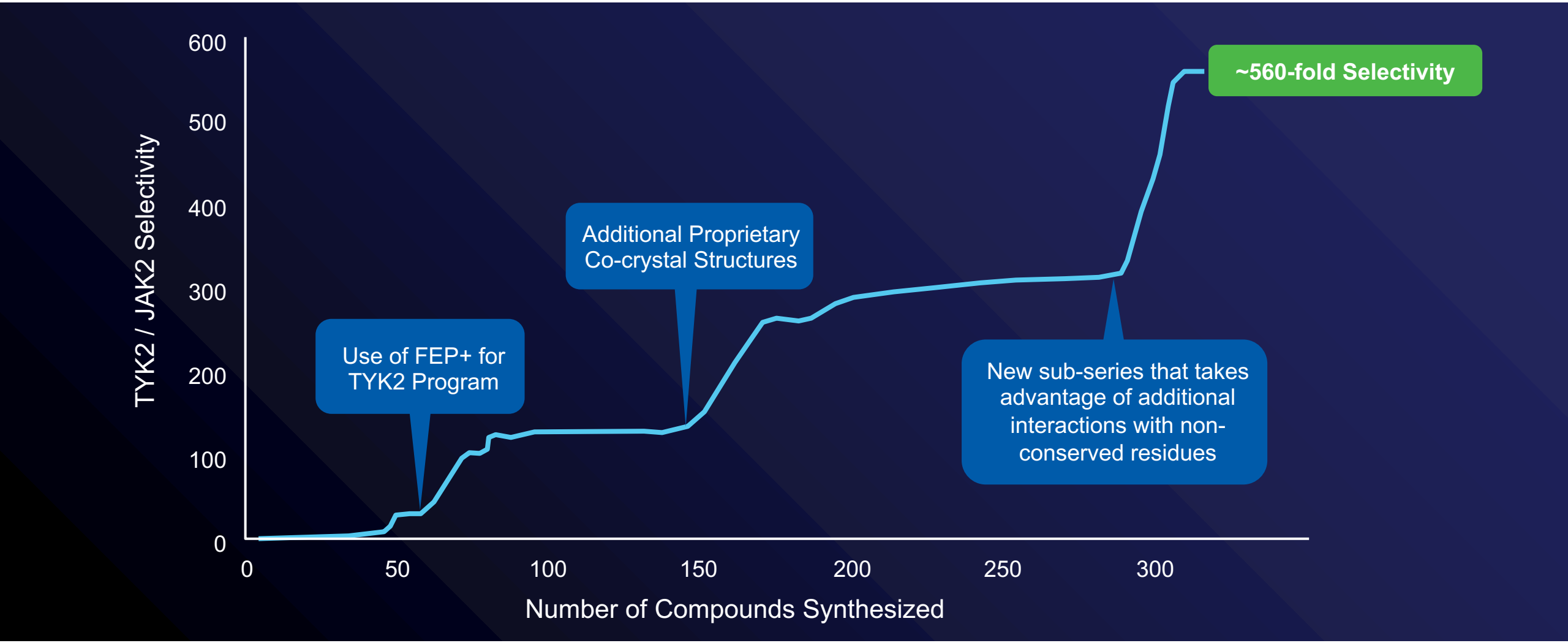
Focus on allosteric inhibitors that bind the regulatory domain and disrupt kinase activity

Selective Inhibition of TKY2 Is Highly Challenging

TYK2, JAK1, JAK2, JAK3 superimposed in complex with tofacitinib shows extremely high similarity in the active site — to achieve selectivity required accurate modeling of ligand binding to all 4 proteins



Free Energy Calculations Enabled Breakthroughs in Achieving Selectivity



NDI-034858 Shows Desired *In Vitro* Potency and Selectivity

Selective Inhibition of TYK2 vs. JAKs

In vitro potency / selectivity	NDI-034858
TYK2 JH2 Potency	0.0038 nM
TYK2 Function: IL-12 Inhibition	8.4 nM*
Interferon inhibition in human blood	51 nM*
Interferon inhibition in mouse blood	347 nM*
Interferon inhibition in rat blood	91 nM
JAK 1-3 kinase activity	>30,000 nM
JAK1 inhibition	5,000 nM
JAK2 inhibition	23,000 nM
JAK2 Function	>50,000 nM*
JAK1/3 Function	>50,000 nM*
PDE4 inhibition	>10,000 nM
hERG inhibition	>30,000 nM
87 target panel of enzymes, ion channels, receptors @10,000 nM	<50% inh for 85 targets**



- Highly potent and selective TYK2 allosteric inhibitor
- Nimbus Therapeutics' clinical data indicate compound is well-tolerated
- NDI-034858 shows desired target engagement in humans
- Phase 2b trials in moderate to severe psoriasis are ongoing*

Leit S. ACS Fall 2022 Conferences.

*ClinicalTrials.gov Identifiers NCT04999839 and NCT05153148.

$\alpha_4\beta_7$ Integrin Collaboration

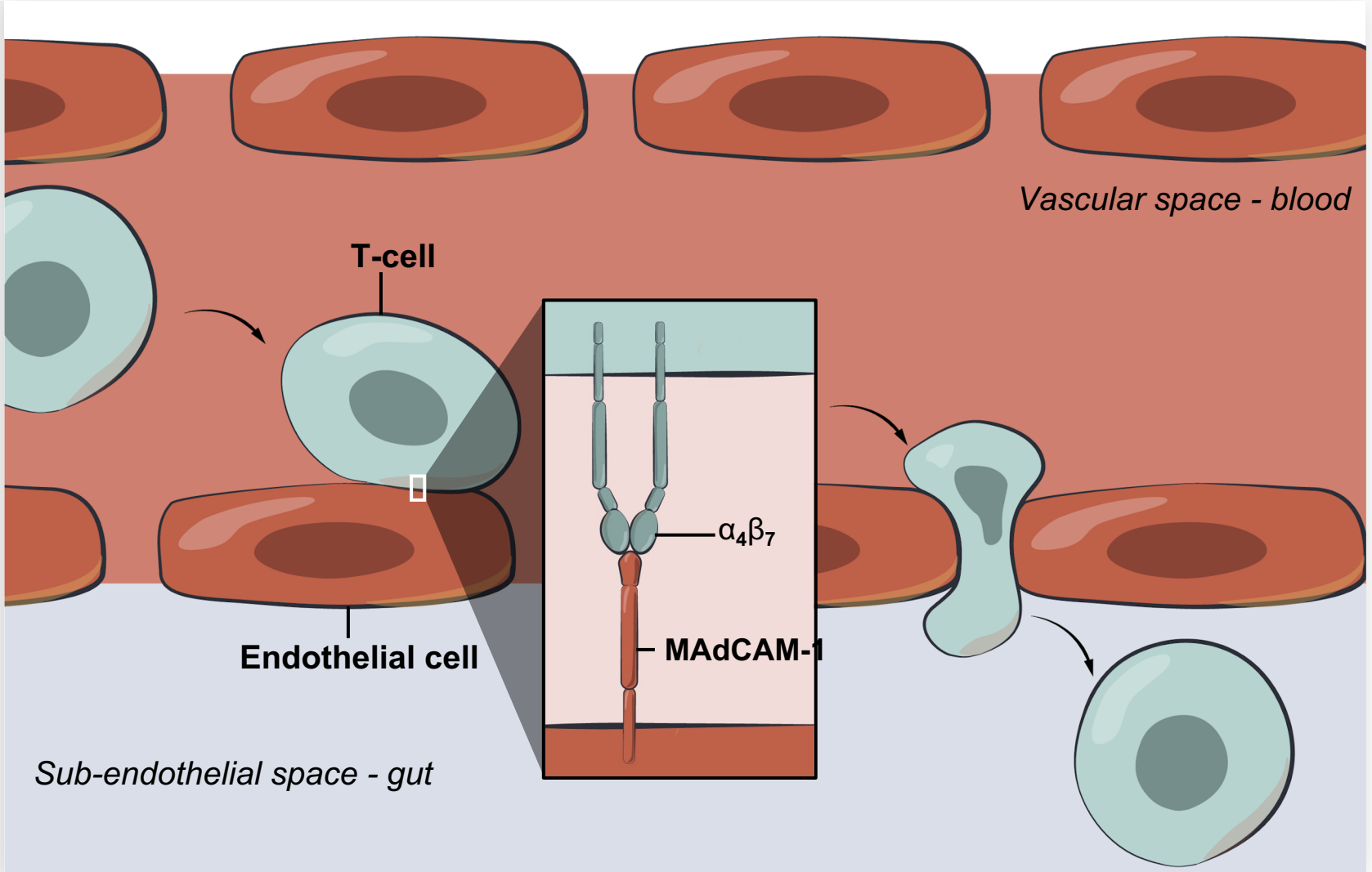
MORPHIC THERAPEUTIC



$\alpha_4\beta_7$ Inhibition Is a Proven Mechanism to Treat IBD

Approved antibody Entyvio® (vedolizumab)

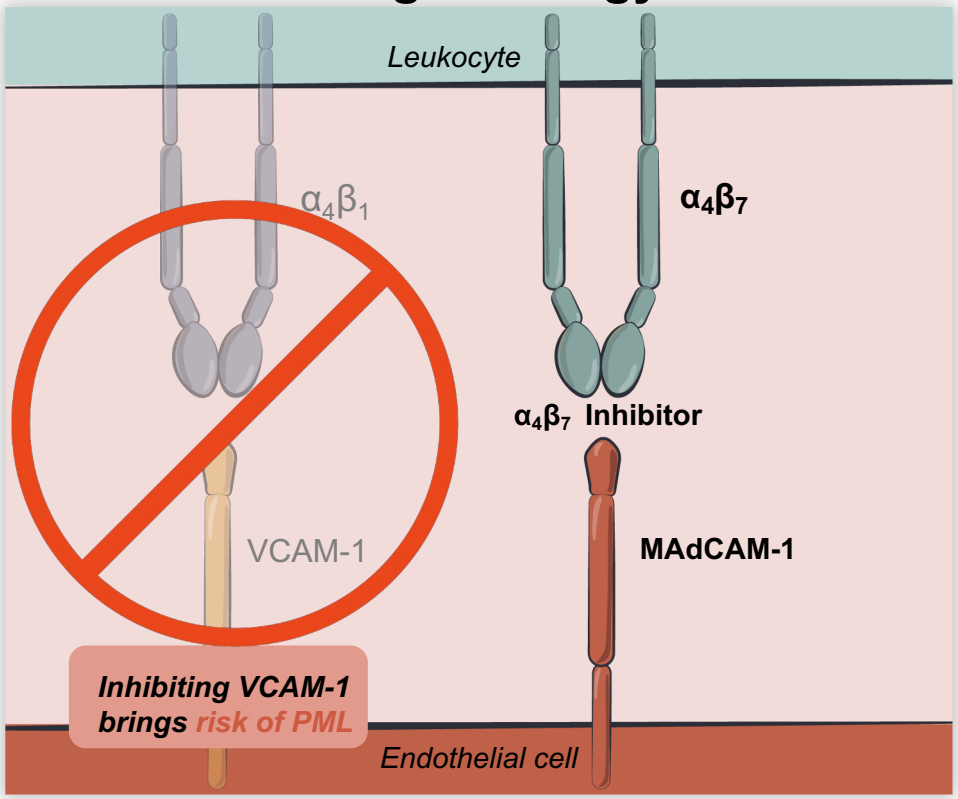
- **Vedolizumab** (an anti-$\alpha_4\beta_7$ antibody): inhibits T-cell trafficking via well validated mechanism to treat both UC and Crohn's disease
- **MAdCAM-1**: homing receptor that plays a central role in leukocyte trafficking into the mucosal immune compartment; **vast majority expressed on gut-associated endothelial cell**
- Since approval, > 150k patients have received vedolizumab



Vedolizumab is an approved monoclonal antibody medication developed by Millennium Pharmaceuticals for the treatment of ulcerative colitis and Crohn's disease.

Developing Oral Small Molecule $\alpha_4\beta_7$ Inhibitors

Established and proven on target biology



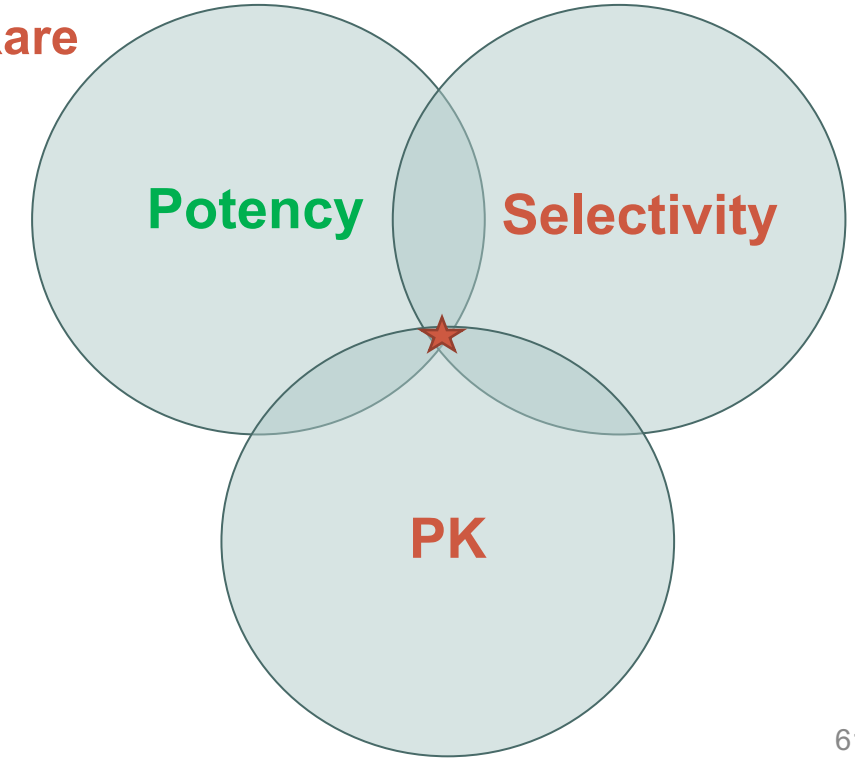
Just need to find the right molecule!

Small molecule $\alpha_4\beta_7$ inhibitors

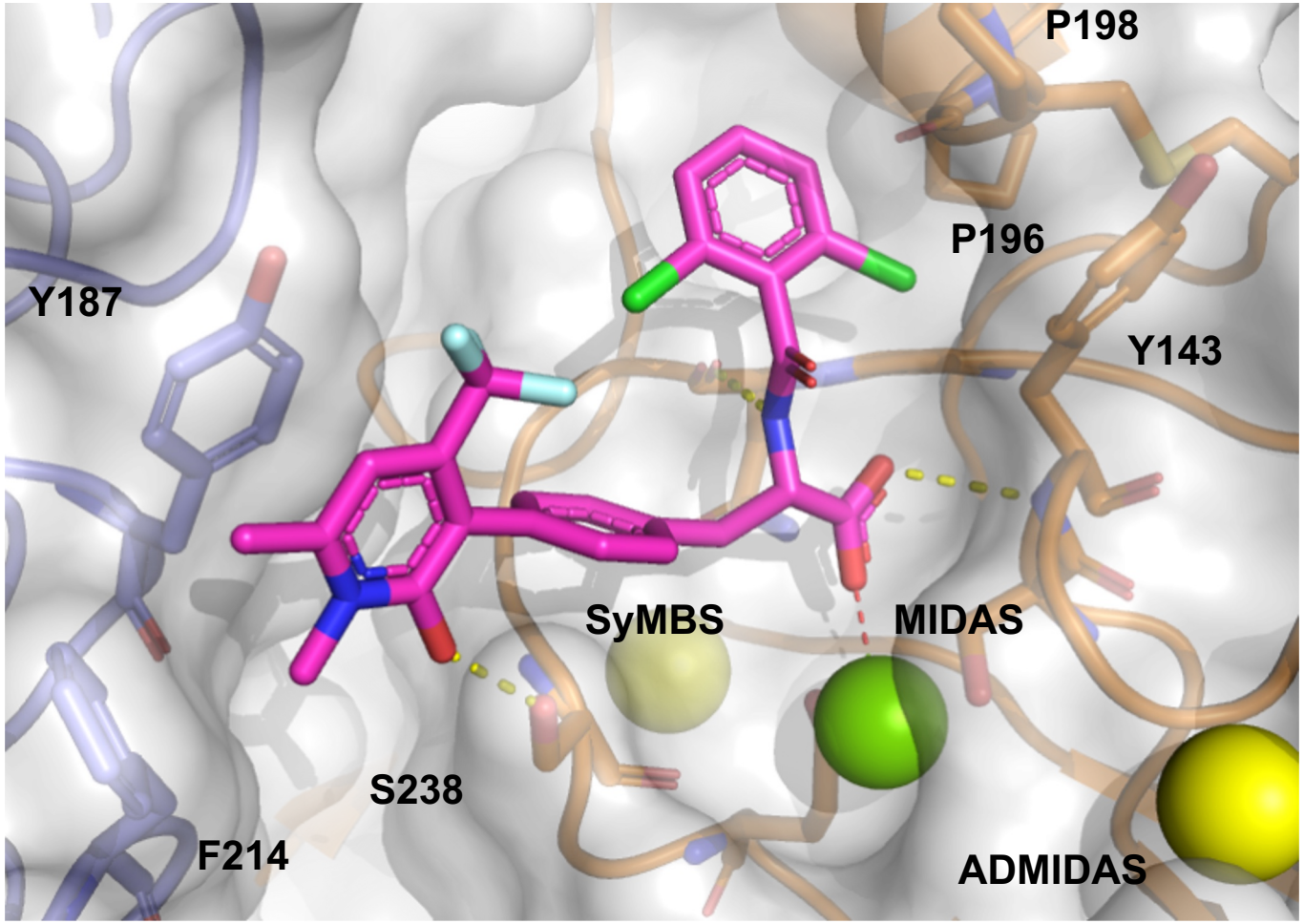
Potent …… **Known**

Selective …… **Rare**

Good PK …… **Rare**



Structural Biology and Computational Chemistry

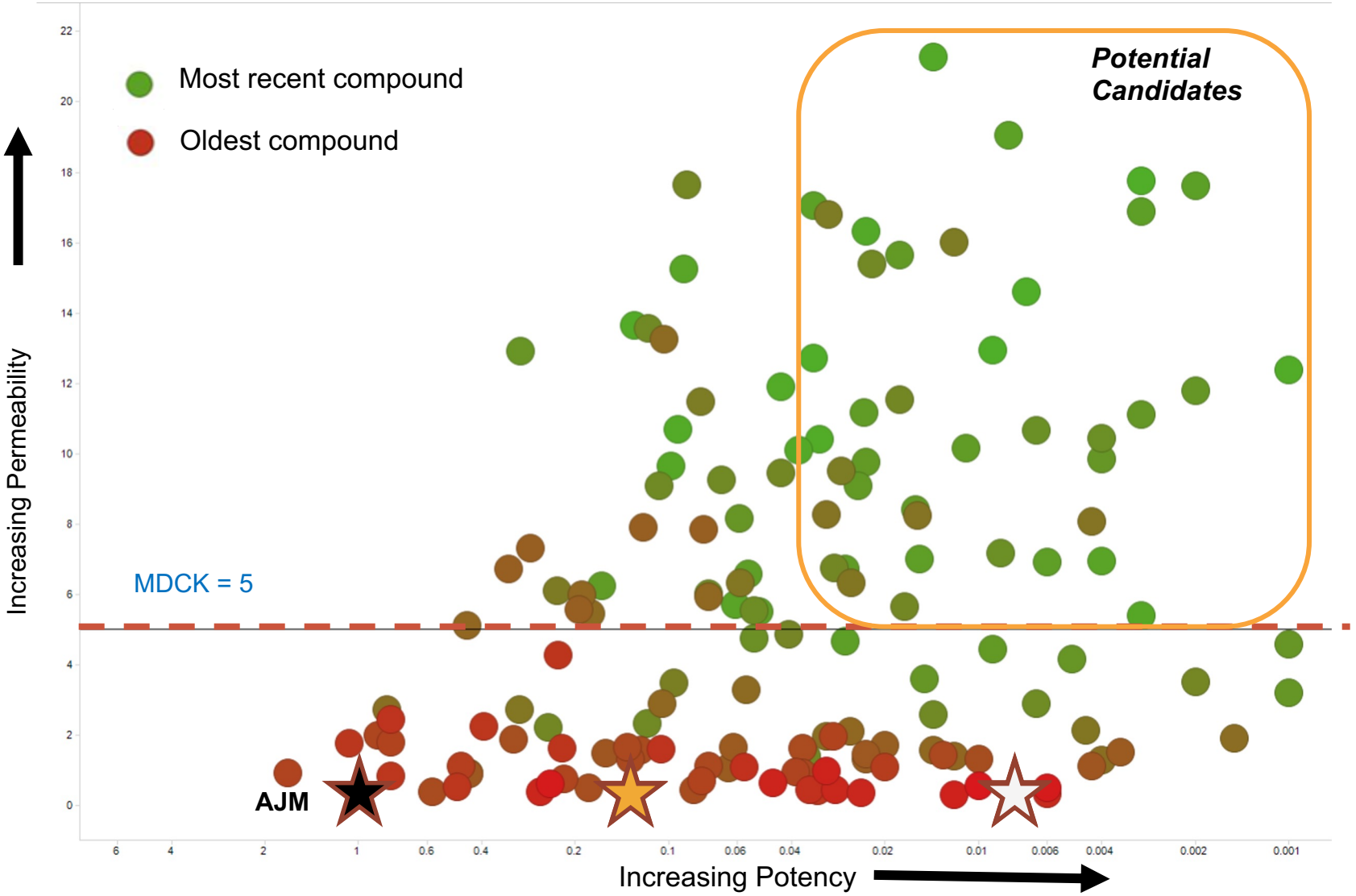


3V4V: Springer & co-workers. JCB. 2012. 196, 131-46. 2012

Roche's RO-0505376
Potent $\alpha_4\beta_7$ inhibitor
No $\alpha_4\beta_1$ selectivity

100+ $\alpha_4\beta_7$ Proprietary MT Crystal Structures

Combining Permeability and Cellular Potency



- 100 $\alpha_4\beta_7$ crystal structures
- ~8,500 Free Energy Perturbations (FEP) to predict $\alpha_4\beta_7$ potency
- Multi-parameter optimization (MPO) to improve permeability

MORF-057 Shows Desired *in Vitro* Potency and Selectivity

Inhibitor	$\alpha_4\beta_7$ IC_{50}[a]	$\alpha_4\beta_7/\alpha_4\beta_1$ Fold selectivity
MORF-057	1.2 nM	**>3,000**
Vedolizumab	0.035 nM	**>3,000**
Natalizumab	0.166 nM	**1-12**
AJM300	93 nM	**8-45**

- MORF-057 is highly selective for $\alpha_4\beta_7$ over $\alpha_4\beta_1$ in cell adhesion assays
- MORF-057 has high selectivity against other integrins

- MORF-057 shows dose-dependent saturation of the α4β7 receptor in humans
- Morphic is conducting a Phase 2a trial to evaluate MORF-057 in patients with moderate to severe ulcerative colitis*
- A Phase 2b study is planned to begin in 4Q22

Schrödinger

*ClinicalTrials.gov Identifiers NCT05291689.

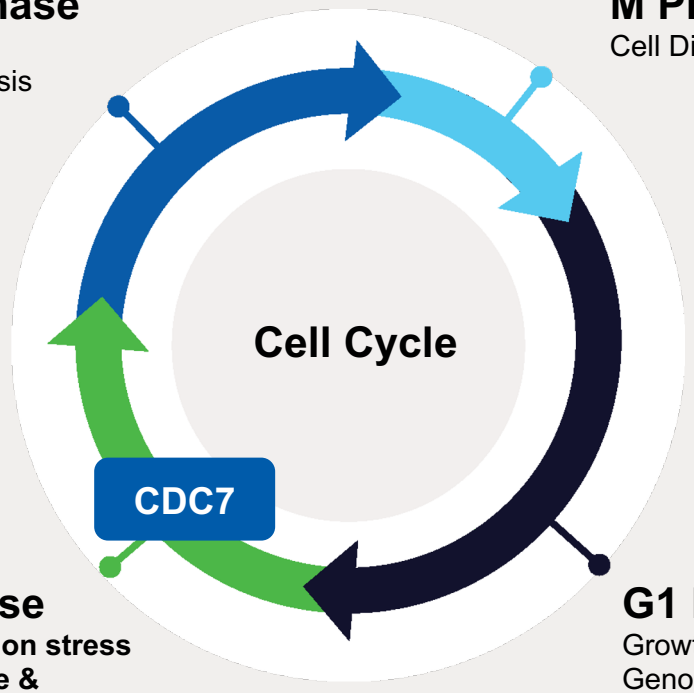
SGR-2921: Our Selective CDC7 Inhibitor



CDC7 Kinase Is a Key Cell Cycle Checkpoint for DNA Repair

G2 Phase
Growth
Pre-Mitosis

M Phase
Cell Division

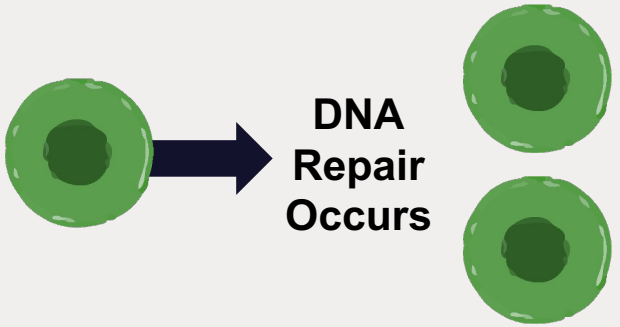


S Phase
Replication stress response &
DNA Repair

G1 Phase
Growth
Genome Duplication

CDC7 activation resolves replication stress during DNA replication

Healthy Cells

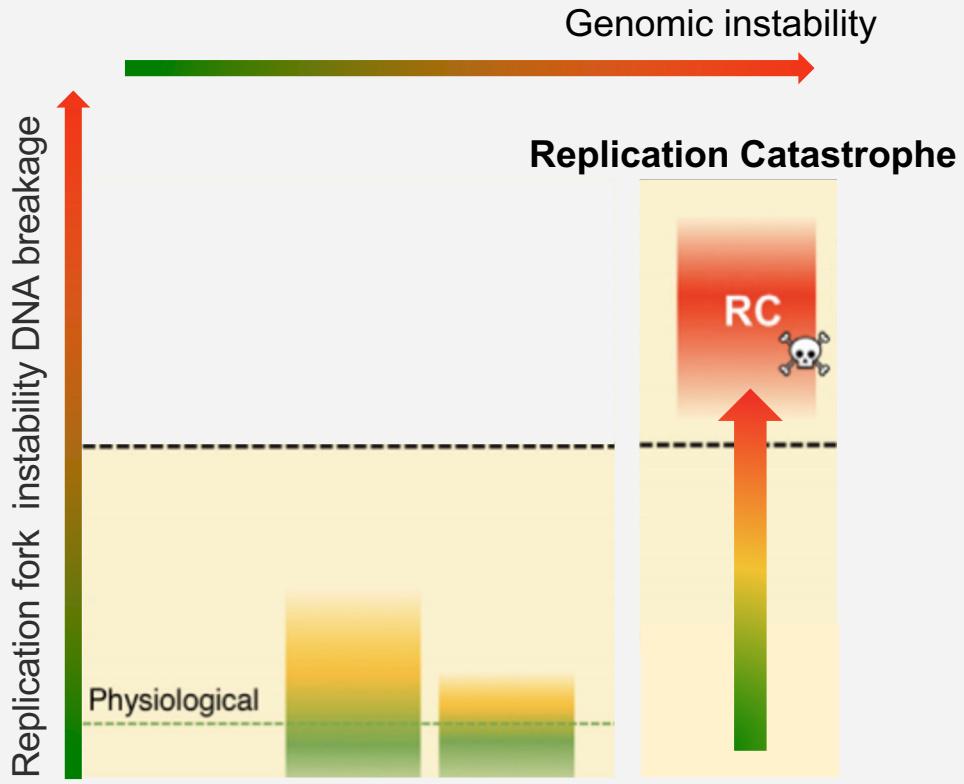


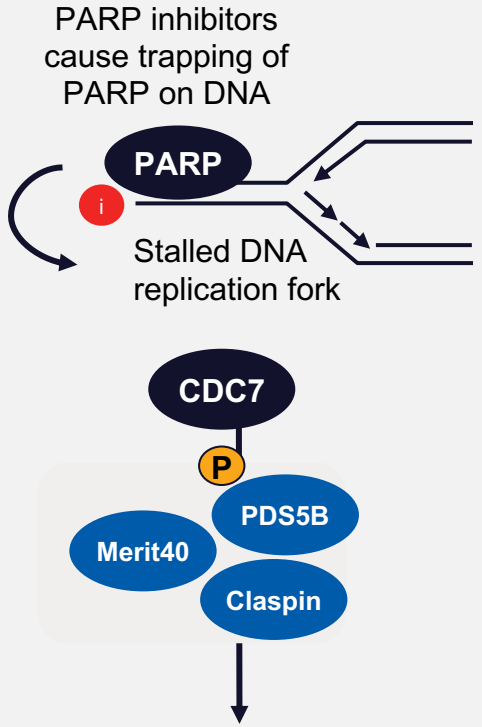
DNA Repair Occurs

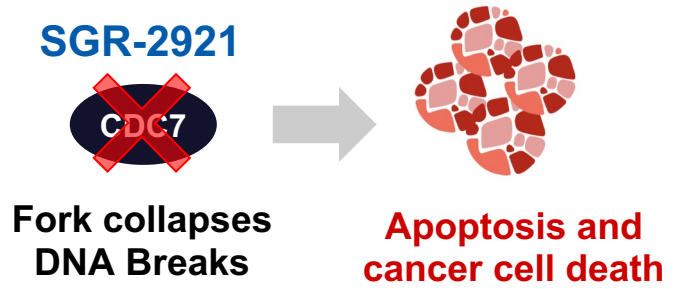
Following DNA repair cell division resumes

High Replication Stress Tumors Are Sensitive to CDC7 Inhibition

Synergistic with PARP and BCL2 Inhibitors







Designing Potent CDC7 Inhibitors Has Been Challenging for the Industry



- Potency: ~10-100 nM
- Poor PK
- Poor selectivity

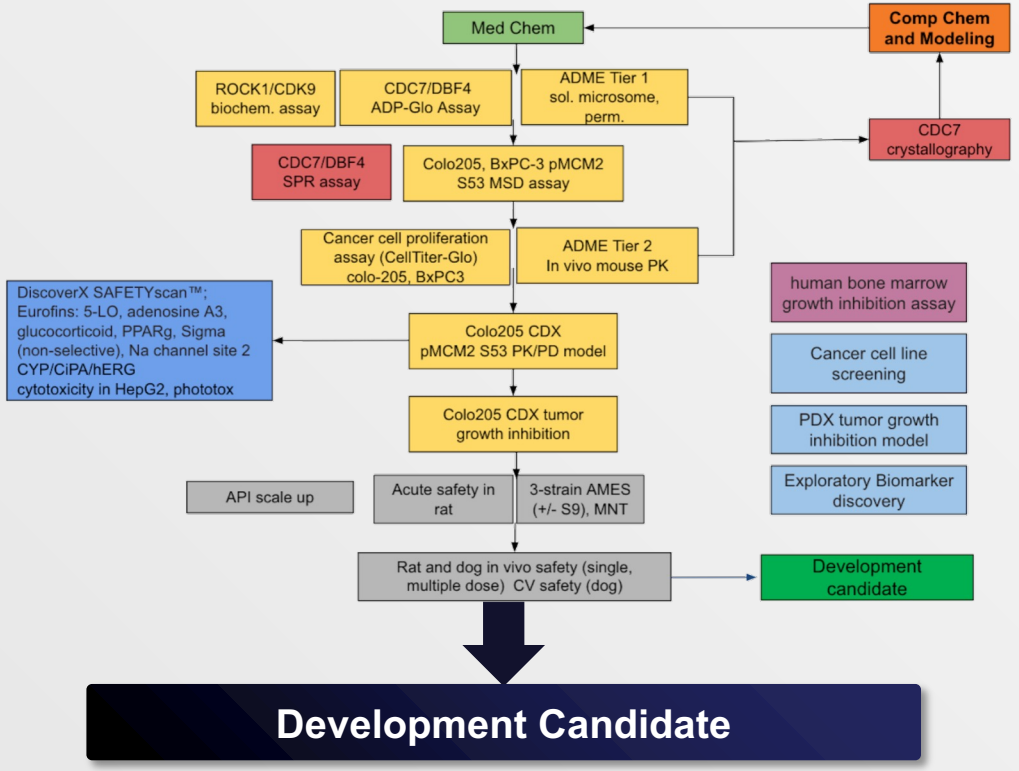
- Potency: ~1 nM
- Poor PK
- Poor selectivity

DESIGN GOAL:

- Discover **pM** inhibitors due to CDC7 low ATP K_m with improved drug-like properties
- Achieve optimal target engagement in vivo

Cross-functional Teams Leverage Accurate Modeling at Scale to Make Rapid Decisions on Chemistry, Biology and ADME

Cross-functional Program Activities



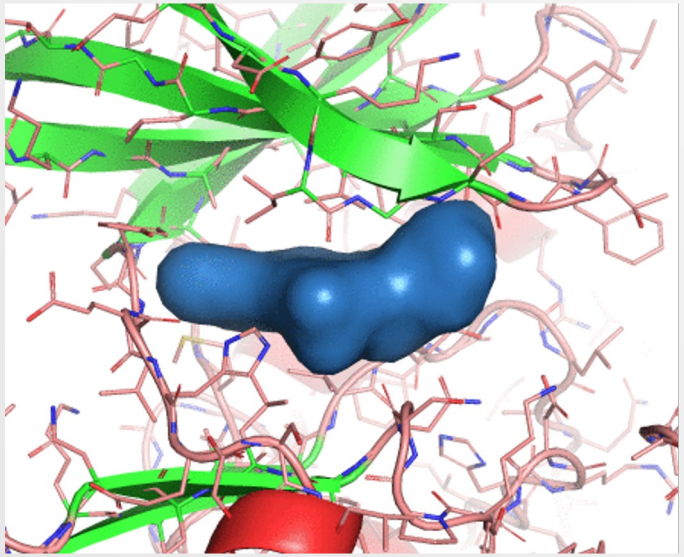
LiveDesign



Simultaneous Modeling of Potency, Selectivity, Solubility, and Permeability Achieve the Target Product Profile

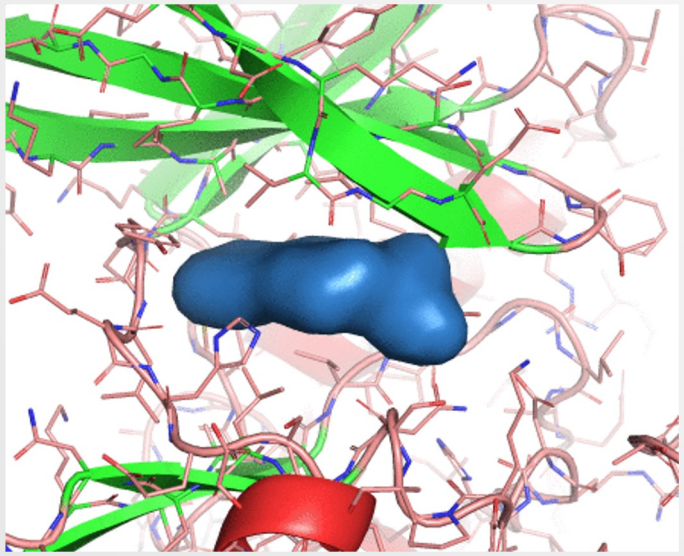
Novel tight binding core with favorable drug metabolism properties

1 nM



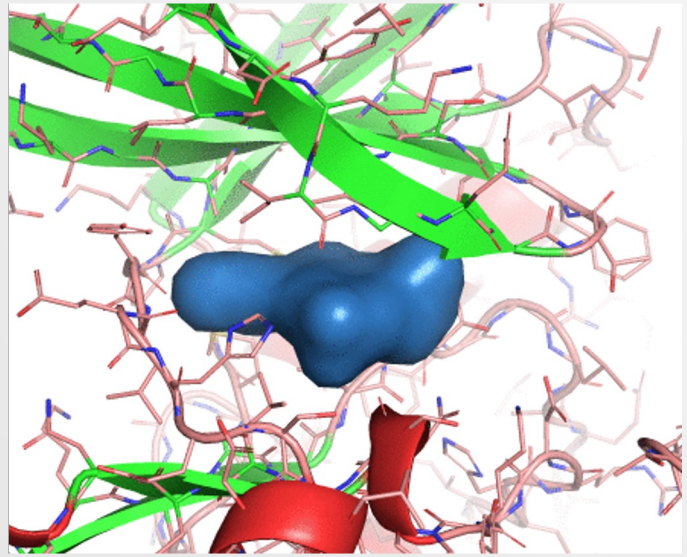
Balanced potency, selectivity, solubility properties balanced support PK/PD studies

100 pM



Improved permeability resolves in vitro / in vivo disconnect

10 pM

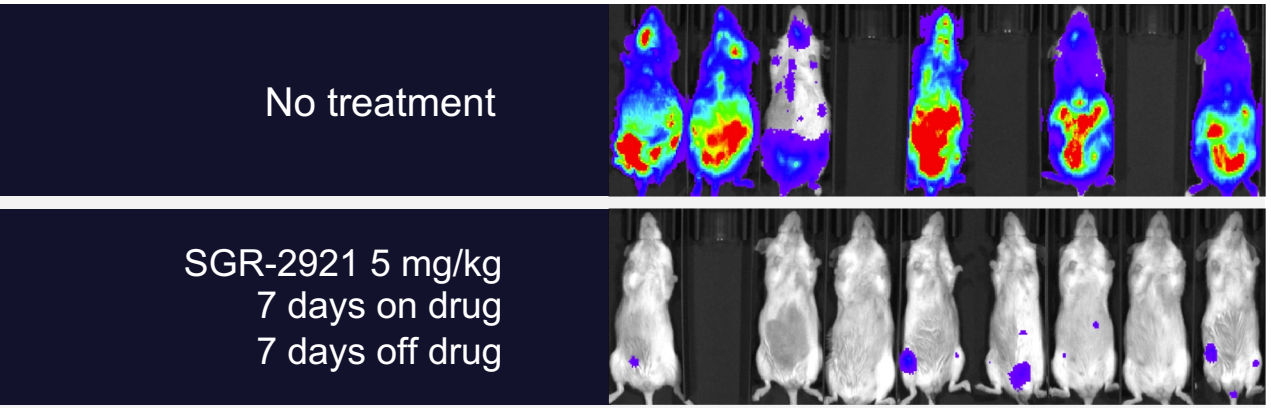


5,456 FEP+ calculations

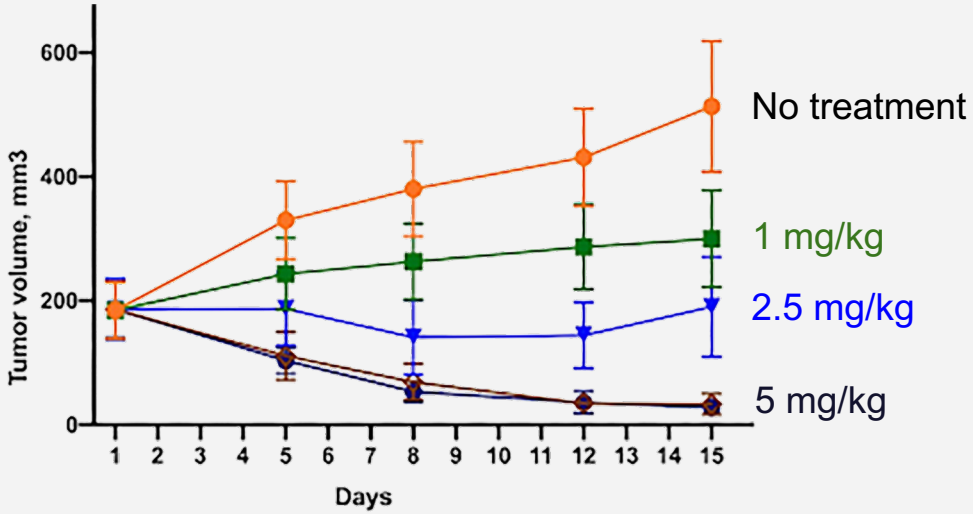
Only **20 compounds synthesized** in the chemical series that led to the development candidate

226 compounds synthesized across all series in the project

Monotherapy Tumor Growth Control with SGR-2921



AML CDX efficacy study shows tumor regression



- Superior potency and balanced drug like properties relative to prior CDC7 inhibitors
- Strong single agent anti-tumor activity seen in patient-derived AML tumor models
- SGR-2921 is in IND-enabling studies with plans to initiate a Phase I trial in 2H23 in relapsed/refractory AML

Tsvetkov et al. AACR 2021.

Achieving CDC7i TPP Required Optimization Across Multiple Series



79 billion
compounds scored with machine learning

→

24,325
compounds scored with physics

→

226
compounds synthesized

Development Candidate

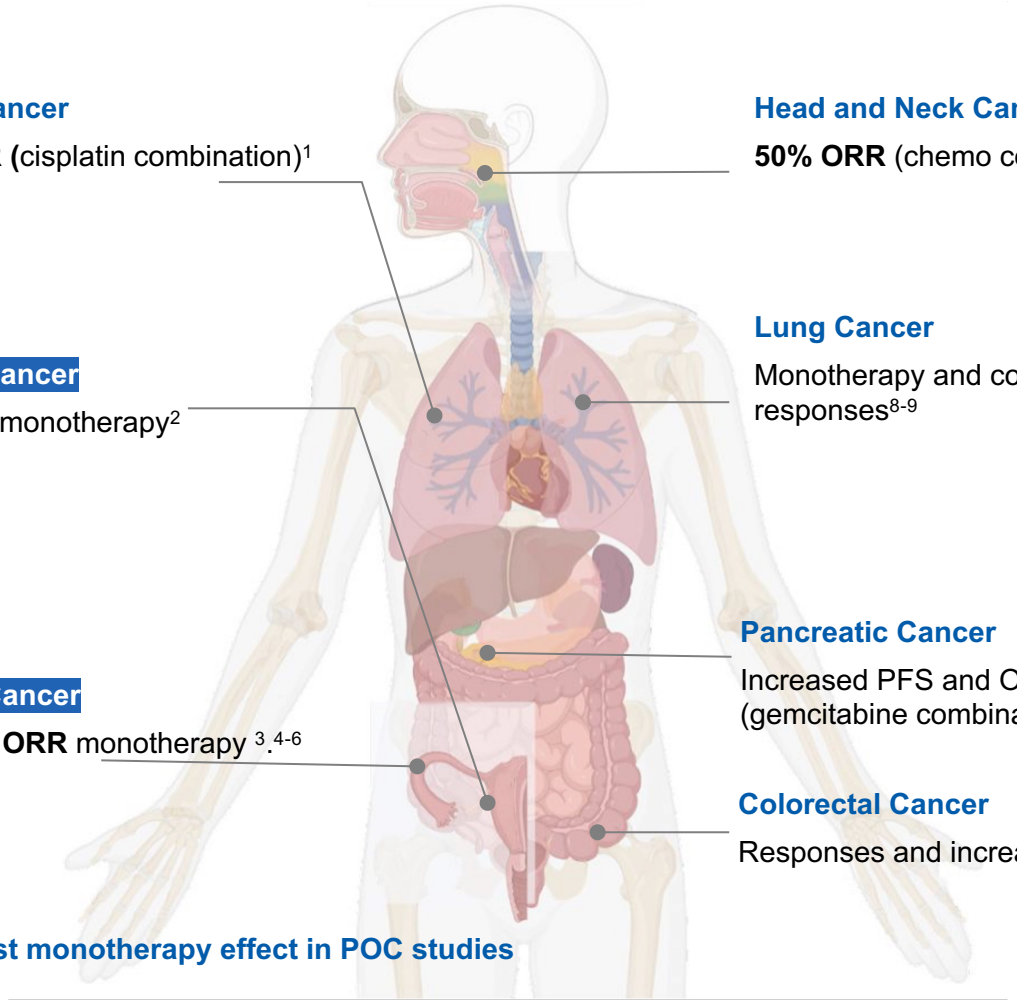
25 Months

Schrödinger

Our Wee1 Inhibitor Program



Wee1 Data Demonstrate Clinical Opportunity in 3rd Party Studies



Breast Cancer

26% ORR (cisplatin combination)[1]

***Uterine Cancer**

30% ORR monotherapy[2]

***Ovarian Cancer**

Up to 50% ORR monotherapy [3,4-6]

Head and Neck Cancer

50% ORR (chemo combination)[7]

Lung Cancer

Monotherapy and combo responses[8-9]

Pancreatic Cancer

Increased PFS and OS (gemcitabine combination)[10]

Colorectal Cancer

Responses and increased PFS[8,11,12]

***Strongest monotherapy effect in POC studies**

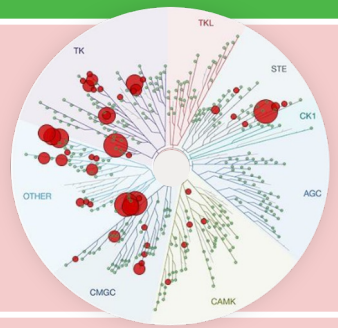
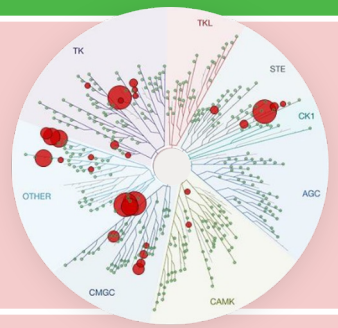
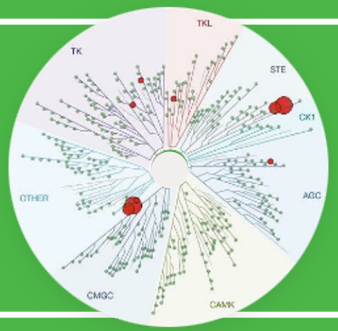
WEE1 PROGRAM DESIGN GOAL:

- Discover highly selective molecule with balanced drug-like properties
- Avoid drug-drug interactions and off-target effects

1.*Clin Cancer Res* 2021: 27(4). 2.*J Clin. Oncol* 2021: 39(14):1531-1539. 3.*J Clin. Oncol* 40, no. 16_suppl (June 01, 2022) 5515. 4.*Lancet* 2021: 398:281-92. 5.*J Clin. Oncol* 2016: 34:4354-4361. 6.*Clin Cancer Res* 2018: 24(120): 2740-8. 7.*Clin Cancer Res* 2018: 15;24(12):2740-2748. 8.Zentalis investor deck. 9.*Annals of Oncology* 2020: 31 (suppl_4). 10.*J Clin Oncol* 2019 Oct 10;37(29). 11.*Cancer Res* (2019) 79 (13_Supplement): CT02. 12.*J Clin Oncol* 2021 Nov 20;39(33).

Schrödinger Wee1 Inhibitors

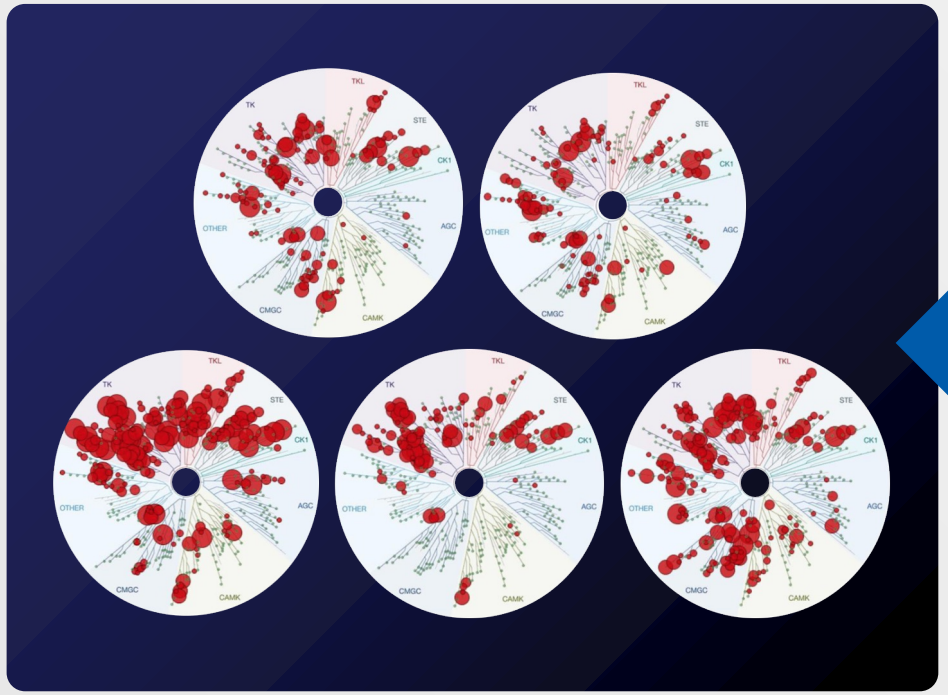
Optimized Selectivity and Physicochemical Properties

	AZD-1775	Zn-C3	SDGR Wee1 Program
Wee1 Binding K_D (nM)	3	2	4
Efficacy in cells Cell viability IC_{50} (nM) CTG assay in lung cancer and ovarian cancer cell lines	130; 290	260; 210	100; 90
Selectivity Kinome Selectivity scanMAX at 1 µM			
Drug Drug Interaction Liability	CYP3A4 TDI	CYP3A4 TDI	No CYP3A4 TDI

All competitor data is internally generated by contract research organizations using publicly available structure information.

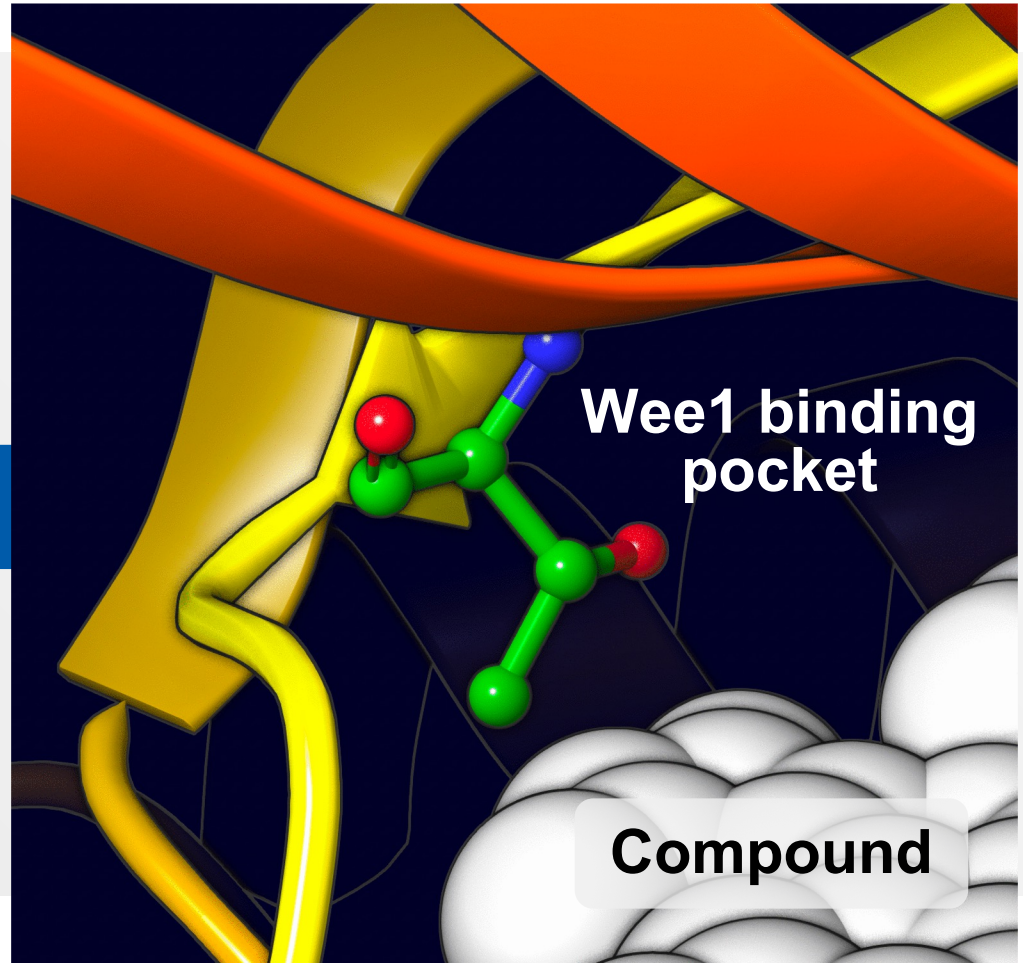
Initial Wee1 Compounds Were Unique But Too Risky to Progress

Initial project hits were not selective

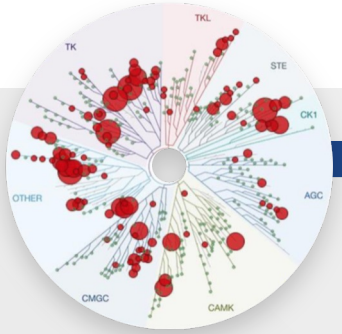


Retrospective

Protein FEP+ predictions
reproduced experimental trends



Three-month Modeling Campaign Identified Many Highly Selective Compounds



Initial project hits were not selective

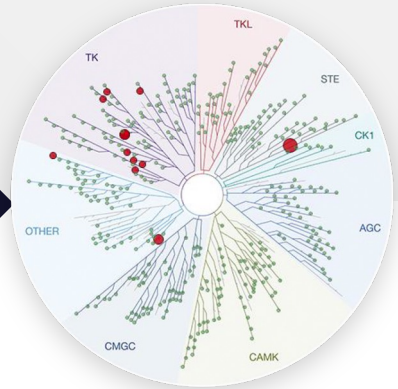
445 Million
crowd sourced, enumerated and follow-on design ideas

6,707
FEP+ potency calculations

1,500
FEP+ selectivity calculations

42
compounds synthesized

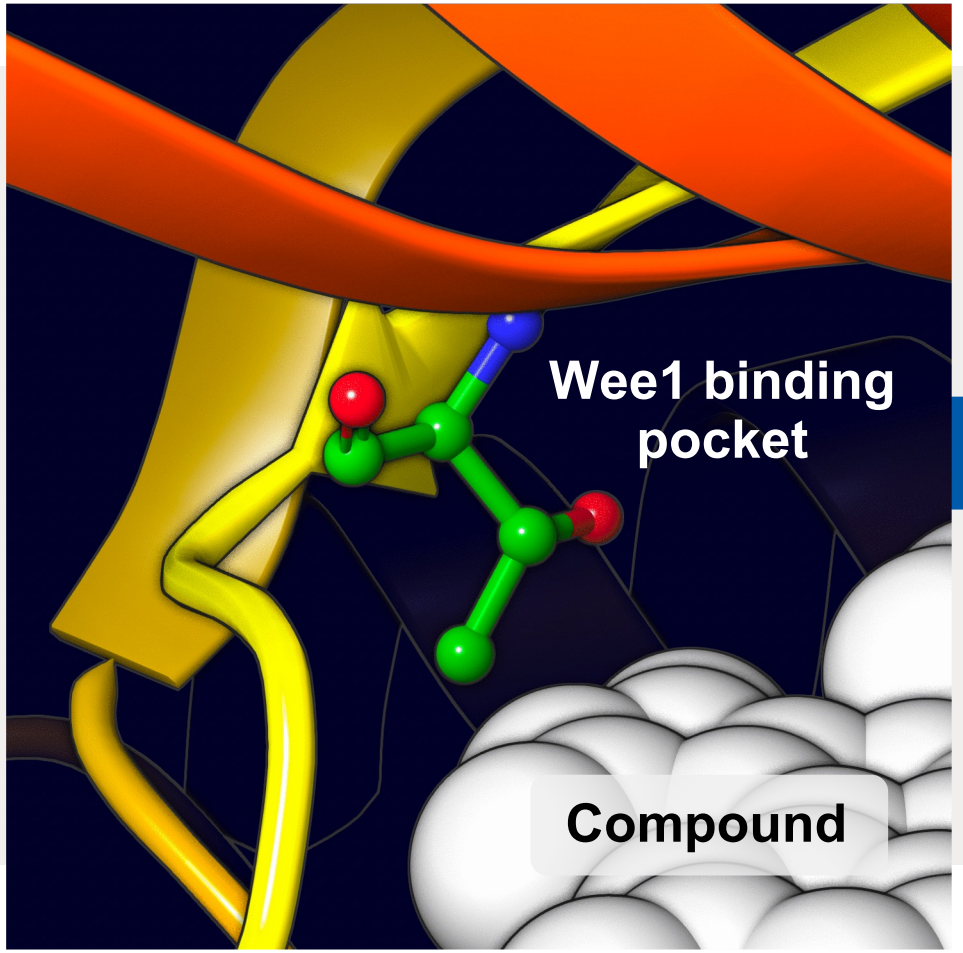
22 Compounds met project potency and selectivity goals



Sun et al. AACR 2022.

Highly Selective Compounds Were Identified Using Protein FEP to Run Thousands of *In Silico* Experiments

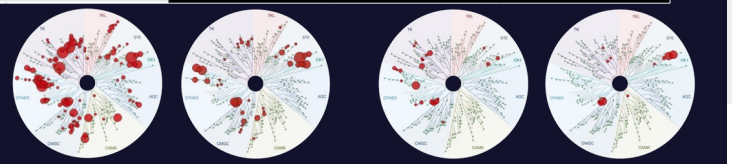
Protein FEP+ predictions identified compounds that should be highly selective for Wee1



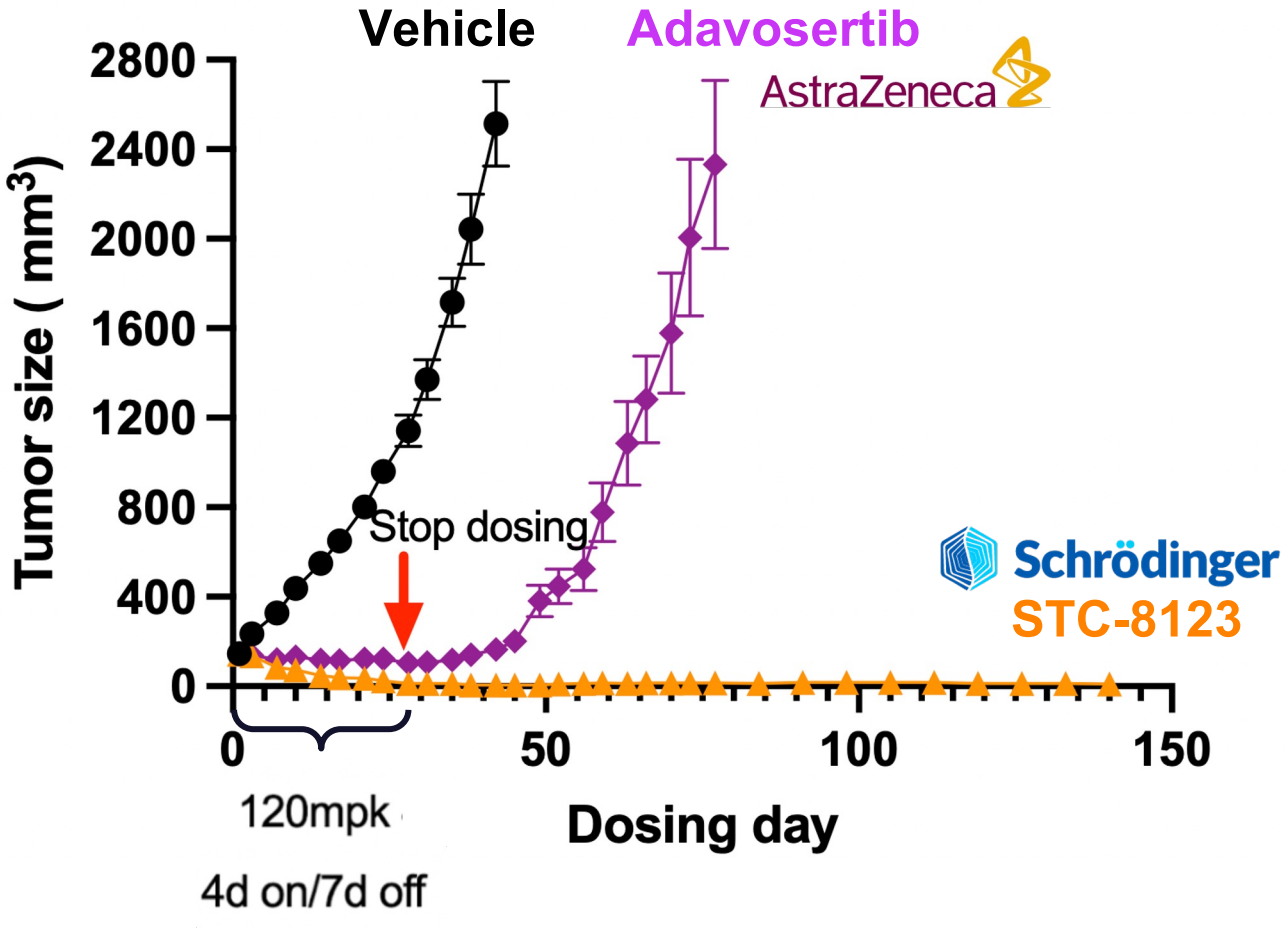
Prospective

Compounds proven experimentally to be highly selective for Wee1

On-target Selectivity vs (fold)	Cmpd B3	CmpdB5	CmpdB6	CmpdB7
Kinase1	3	430	>1000	>5000
Kinase2	6	>1000	>1000	>5000
Kinase3	10	>1000	>1000	>5000
Kinase4	11	80	>1000	>5000
Kinase5	20	550	>1000	>5000
Kinase6	23	>1000	>1000	>5000
Kinase7	23	140	>1000	>5000
Kinase8	36	70	>1000	>5000
Kinase9	46	>1000	>1000	>5000
Kinase10	70	>1000	720	>5000
Kinase11	70	570	>1000	>5000
Kinase12	90	>1000	>1000	>5000
Kinase13	100	>1000	250	>5000
Kinase14	120	>1000	>1000	>5000
Kinase15	150	>1000	>1000	>5000
Kinase16	170	600	>1000	>5000
Kinase17	>1000	>1000	>1000	>5000
Kinase18	>1000	>1000	>1000	>5000
Kinase19	>1000	>1000	>1000	>5000
Kinase20	>1000	>1000	>1000	>5000
On-target potency (IC50) [nM]	1.0	0.5	0.9	0.7
% kinases with >100x window	40	90	100	100



No Tumor Regrowth Observed After STC-8123 High Dose Treatment Was Stopped in A427 Lung Cancer Tumor Model



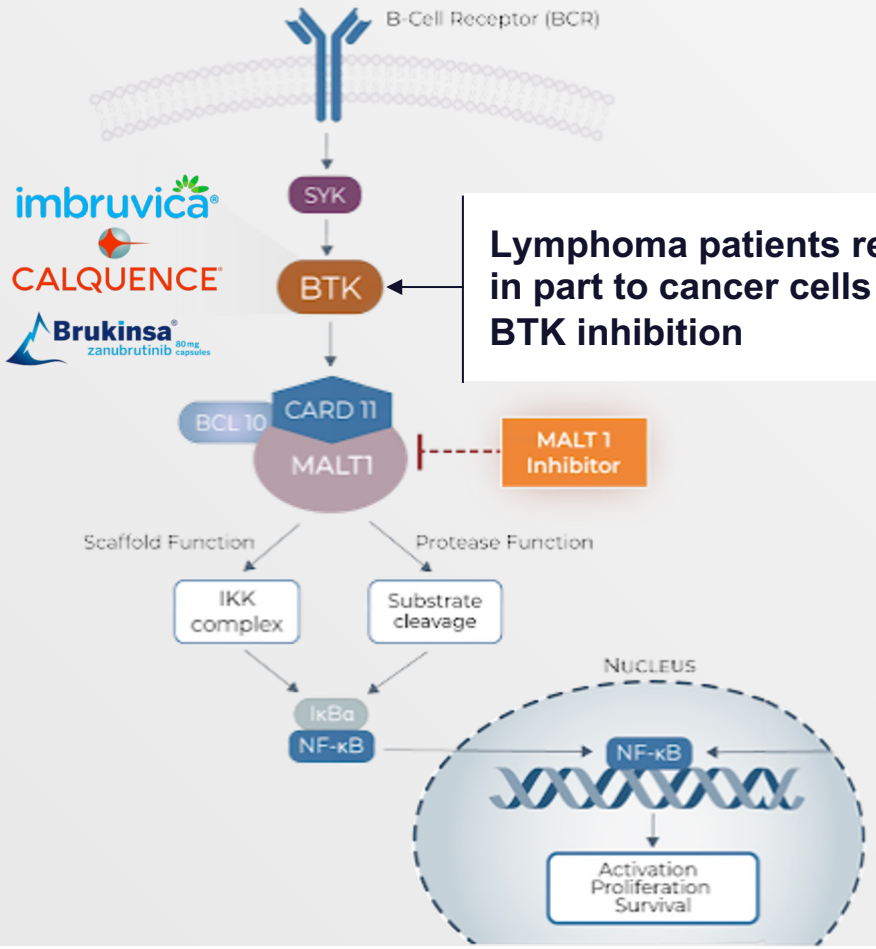
- Durable single agent activity seen in models used in development of Phase 2 Wee1 inhibitors
- Best-in-class compound preclinical characterization in progress
- Studies required for selection of DC underway – multiple candidates being investigated

Sun et al. AACR 2022.

SGR-1505: Our MALT1 Inhibitor Program



MALT1 Is a Genetically Validated Mechanism Regulating Lymphocytes



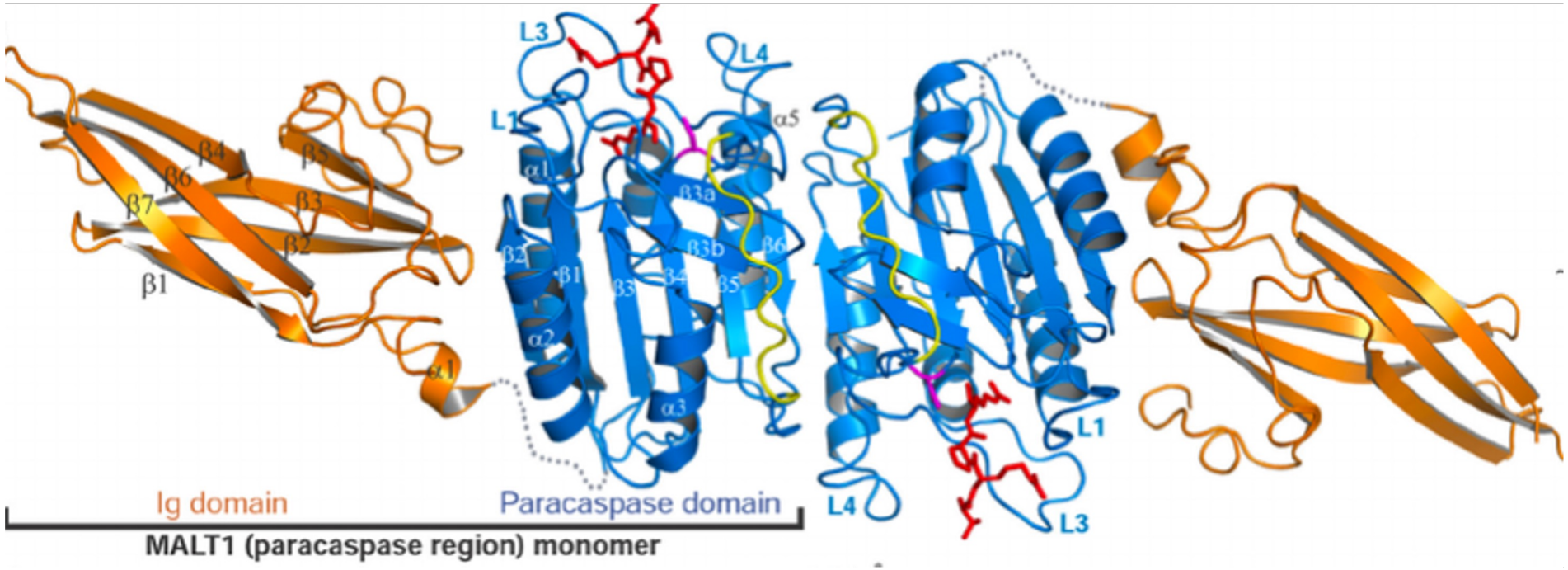
Lymphoma patients relapse due in part to cancer cells escaping BTK inhibition

Potential indications in multiple disease areas

- **B-Cell Malignancies**
- **Advanced Solid Tumors**
- **Autoimmune Diseases**

MALT1

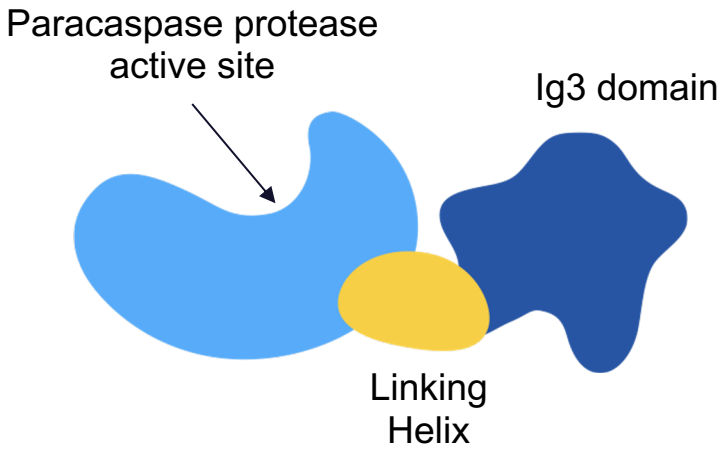
Mucosa-associated Lymphoid Tissue Lymphoma Translocation Protein 1



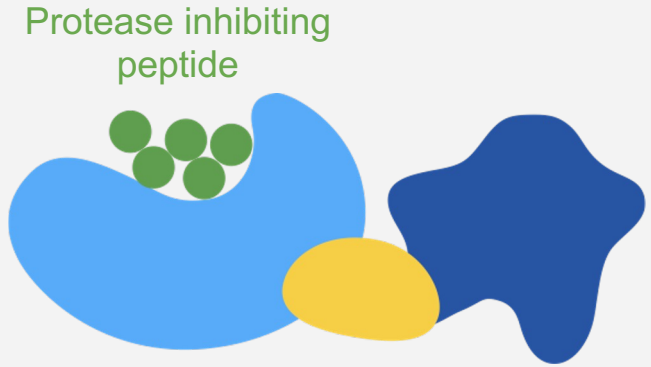
Jaworski, M., Thome, M. The paracaspase MALT1: biological function and potential for therapeutic inhibition. *Cell. Mol. Life Sci.* 73, 459–473 (2016). https://doi.org/10.1007/s00018-015-2059-z

MALT1 Inhibitor Design Challenge

MALT1 is a multi-domain protein with many functions



1st generation MALT1 inhibitors were large peptidic protease inhibitors that are short-lived in blood and have poor drug-like properties — **none entered the clinic**



2nd generation MALT1 inhibitors are allosteric. First examples were not potent or optimized. Initial allosteric compounds are currently in Phase I

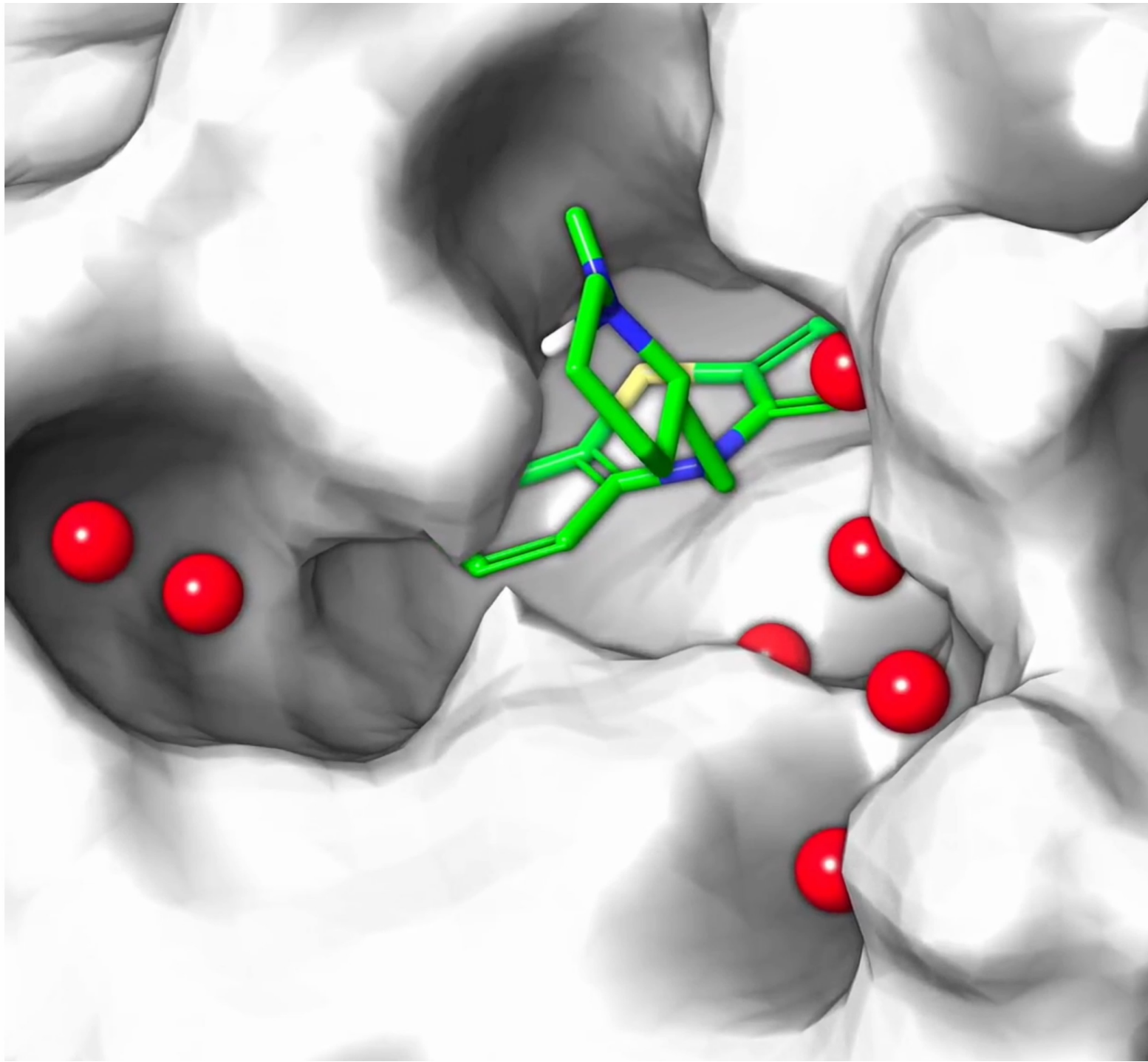


High-energy Unstable Water Molecules in the MALT1 Allosteric Site Provided Potency Improvement Opportunities

Thioridazine, an old antipsychotic, binds weakly to the MALT1 allosteric site

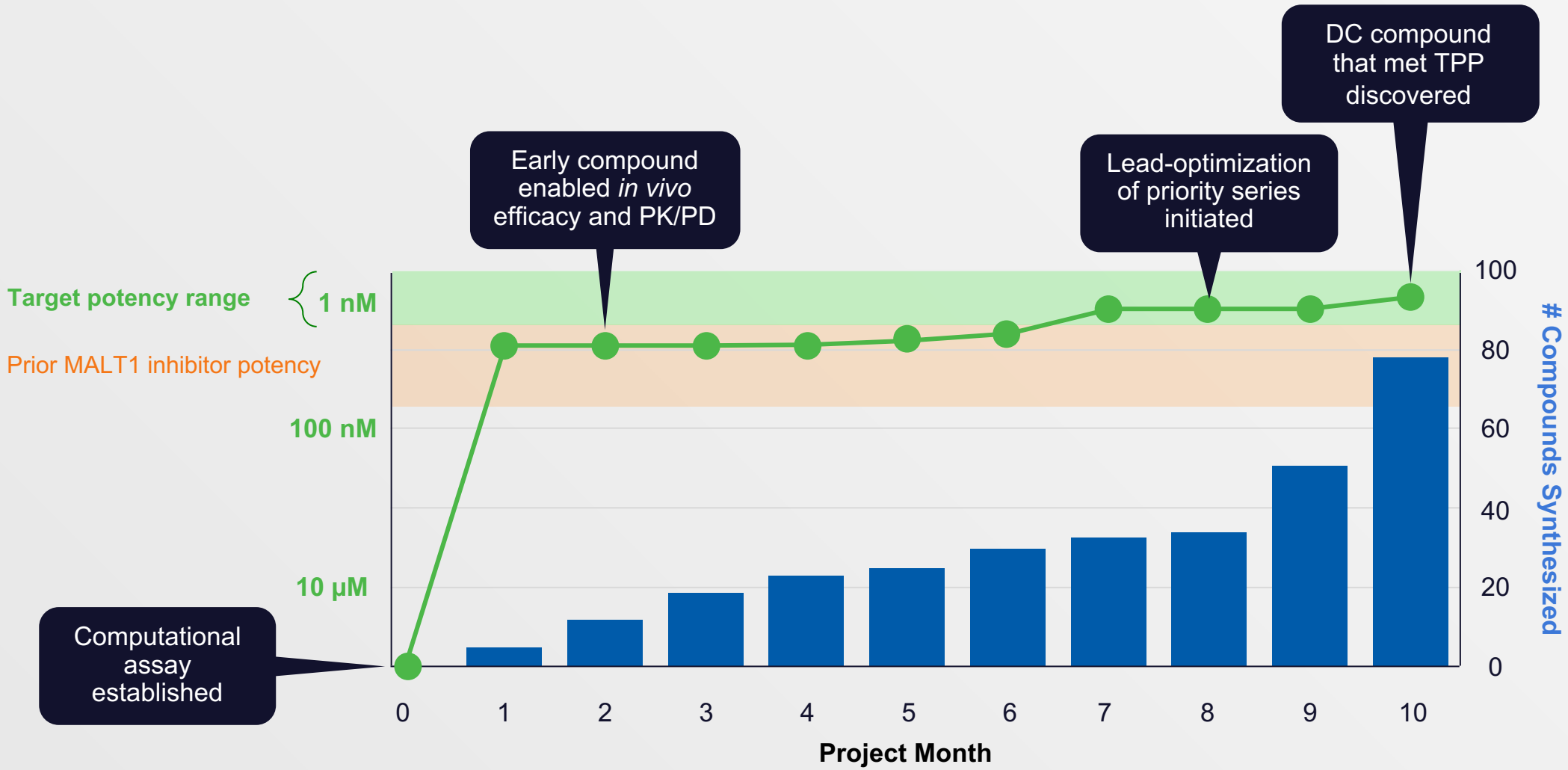
DESIGN CHALLENGE

Discover a potent MALT1 inhibitor with good overall drug properties to support combinations with standard of care agents



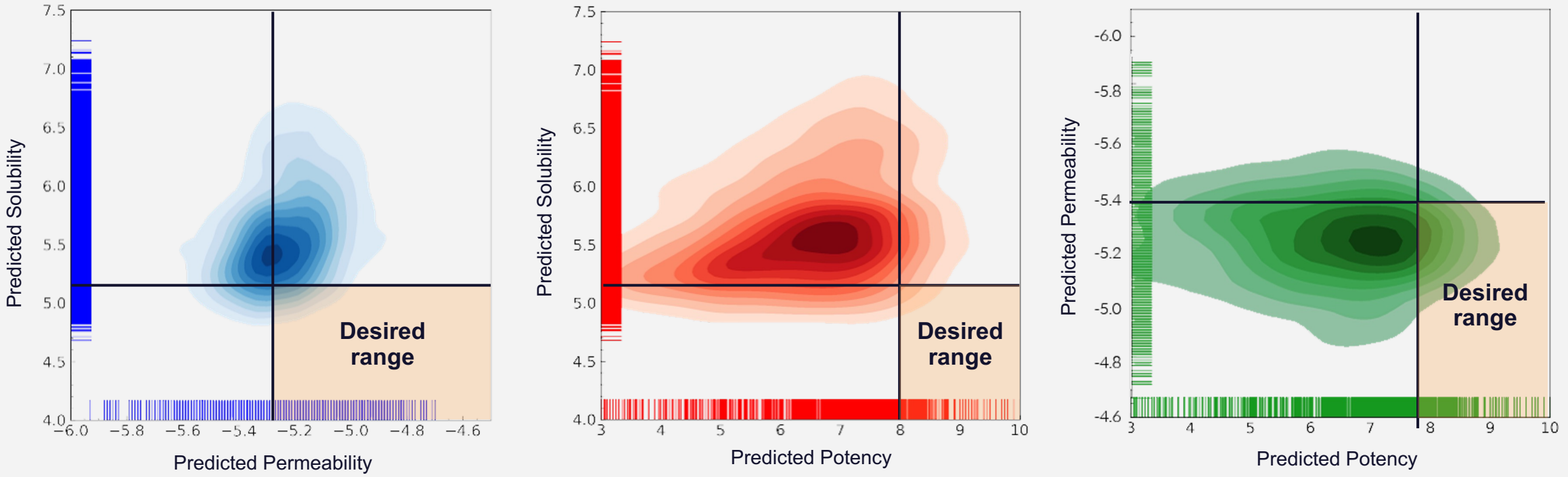
Red spheres represent locations of high-energy unstable waters

Progress Timeline to Selection of Our SGR-1505 Candidate



Optimization Challenge

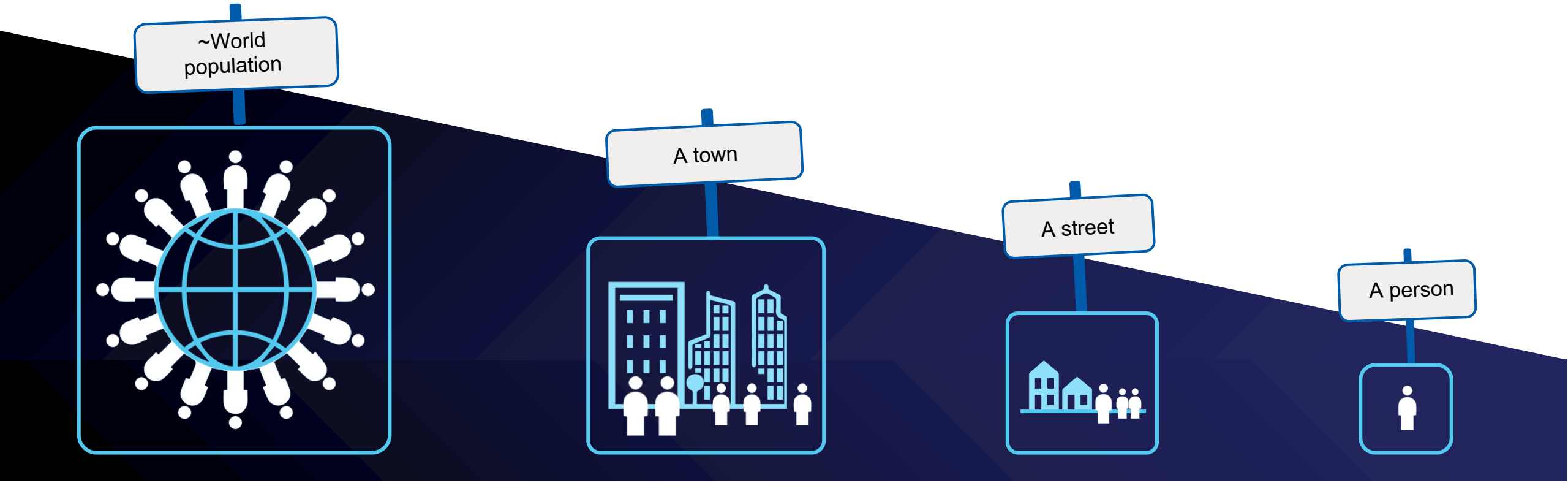
Tuning Potency, Solubility, and Permeability Simultaneously



Model-specific predictions for **~5000 idea compounds**

Only **43 designs were predicted** to meet all three criteria

Technology Platform Supported Rapid MALT1 Program Progression



8.2 billion
compounds scored with machine learning

→

12,186
compounds scored with physics

→

78
total compounds synthesized in lead series

→

Development Candidate

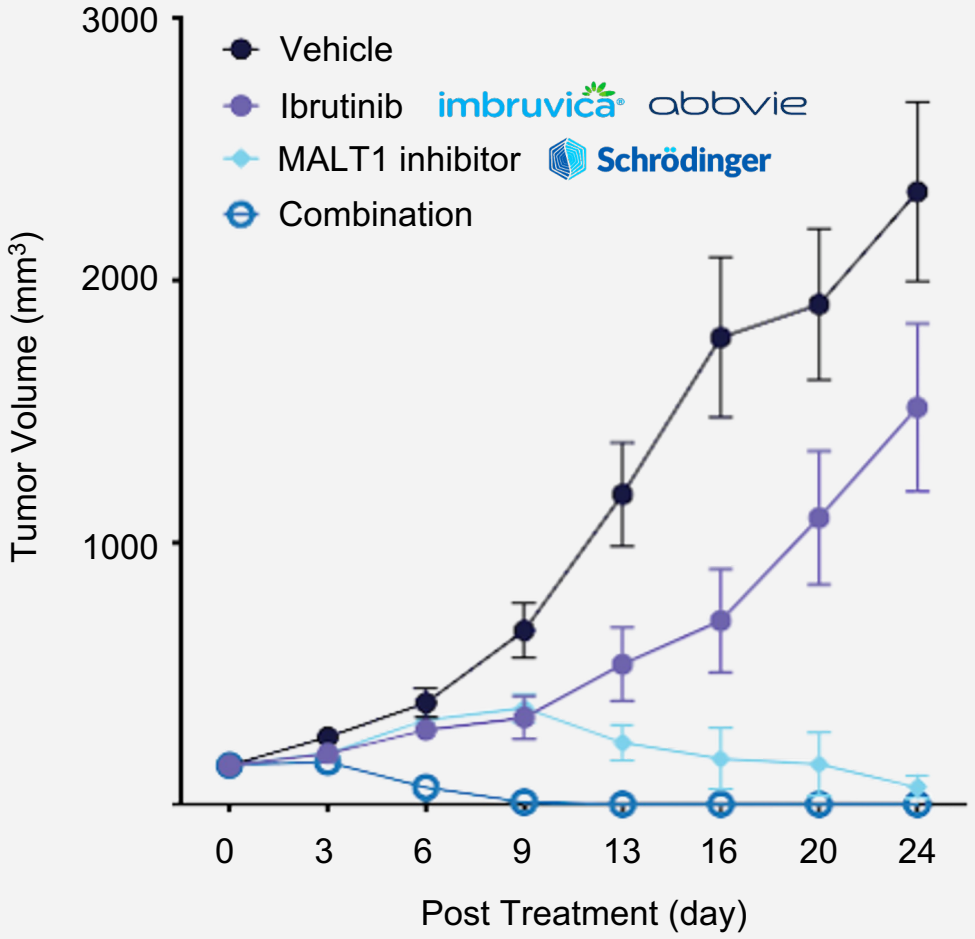
~10 Months

SGR-1505 Shows Well-balanced Properties

Criteria	JNJ-6786633 Janssen	ONO-XXXX Ono	SGR-1505 Schrödinger
MALT1 binding affinity			
Inhibition of MALT1 functional activity			
Inhibition of target engagement marker			
MALT1-mediated cell killing (potency)			
Clearance (human liver microsome)			
Plasma Clearance (mouse/rat/dog/cyno)			
Permeability/Efflux			
Solubility			Improved by formulation
Oral Bioavailability			
hERG Affinity			
Cytochrome P450 Inhibition			

All competitor data is internally generated by contract research organizations using publicly available structure information

SGR-1505 Shows Activity in ABC-DLBCL Tumor Models



- Strong single agent and combination activity seen in patient-derived B-cell tumor models
- JNJ-67856633 clinical data show responses in CLL and NHL in combination with BTK inhibition[1,2]
- SGR-1505 IND open; initiating a Phase 1 dose escalation in relapsed/refractory B-cells lymphomas in 4Q22

Yin et al. ASH 2021.

[1]WO2022184716 Combination Therapy using MALT1 Inhibitor and BTK Inhibitor.
[2]WO2022185097 Method of treating a condition using a therapeutically effective dose of the MALT1 inhibitor JNJ| -67856633.

Examples of Platform Impact Across a Growing Portfolio

Best in class
Selectivity / Properties

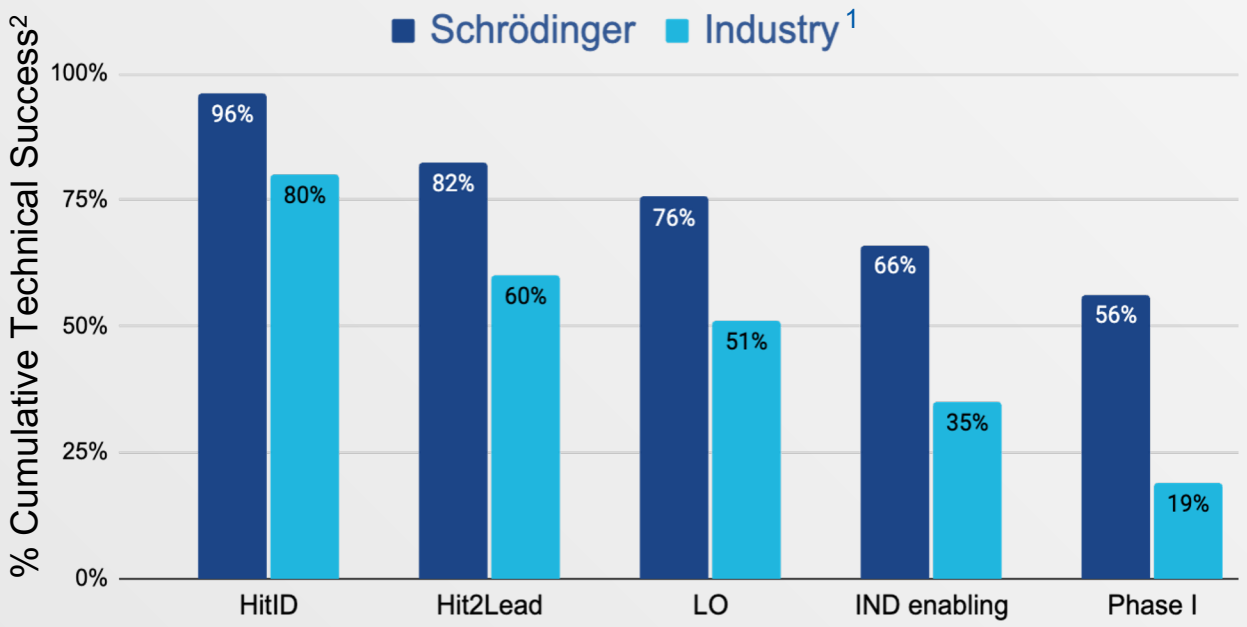
First in class
Modality Switch
Selectivity / Properties

- ACC
- TYK2
- α4β7
- CDC7
- MALT1
- WEE1

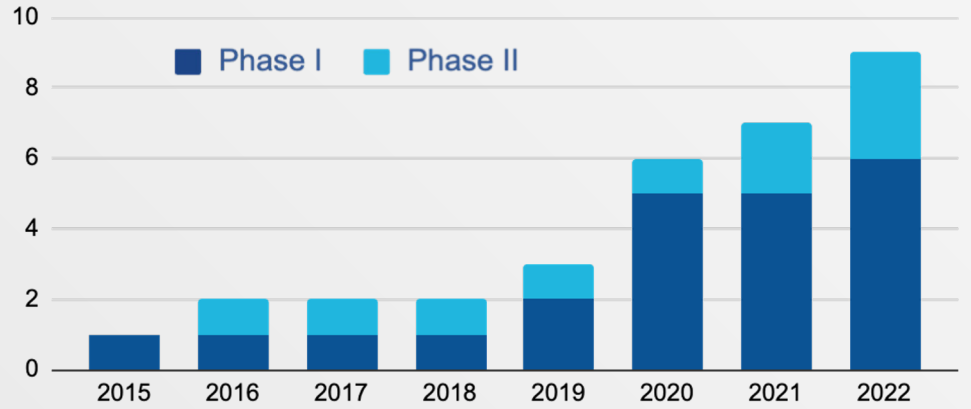


Platform Is Producing an Expanding Portfolio

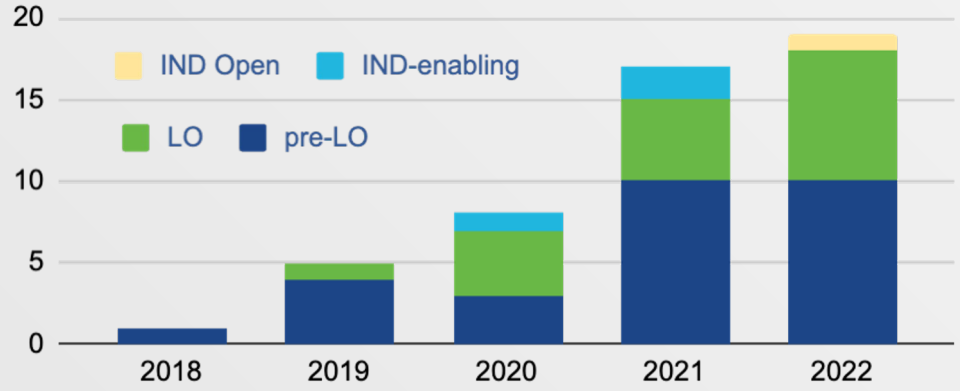
Schrödinger Cumulative Portfolio Success Metrics Over 10 years



Collaboration programs in the clinic



Expanding pipeline of partnered and wholly-owned programs



Schrödinger

[1]Paul, Steven M et al. "How to improve R&D productivity: the pharmaceutical industry's grand challenge." *Nature reviews. Drug discovery* vol. 9,3 (2010): 203-14. doi:10.1038/nrd3078

[2]% Technical Success is defined as the percentage of programs that advance to the next stage, which excludes programs that are terminated for non-technical reasons, such as a change of strategy or termination of research in a therapeutic area for scientific or commercial reasons

Today's Agenda

Introduction — Ramy Farid

Our Platform: Current Capabilities — Robert Abel

Putting Our Platform to Work: Case Studies — Karen Akinsanya and Hamish Wright

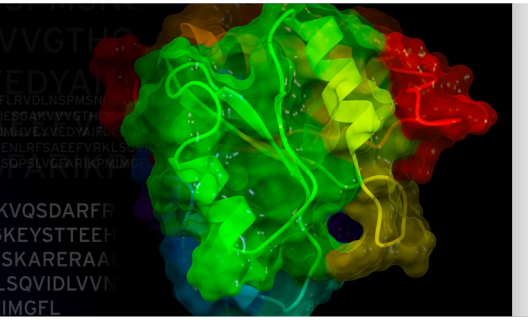
- Pipeline Overview
- Collaboration examples: Nimbus's ACC & TYK2; Morphic's $\alpha_4\beta_7$
- Proprietary examples: CDC7, Wee1, MALT1

Our Platform: Future Capabilities — Robert Abel

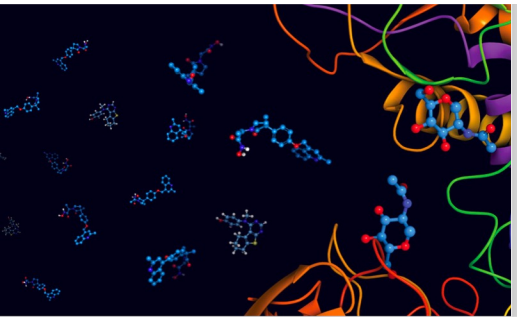
Business Outlook and Opportunities — Geoff Porges

Q&A

Increase the Number and Types of Targets Our Platform Can Progress

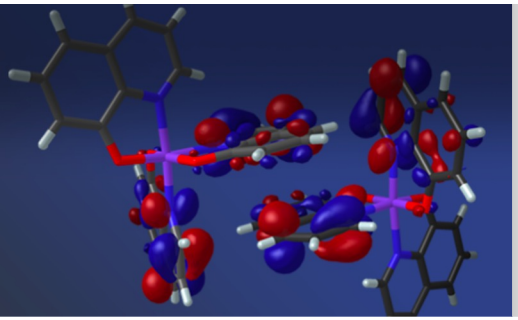


Structure-based drug discovery for nearly all targets

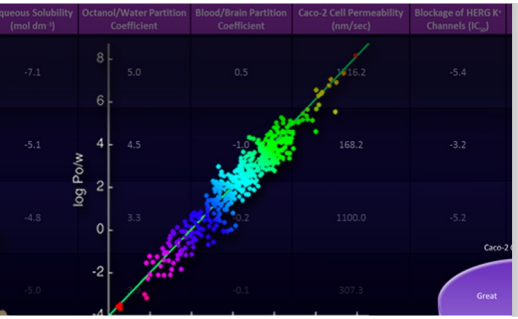


Hit ID for historically difficult and yet to be drugged targets

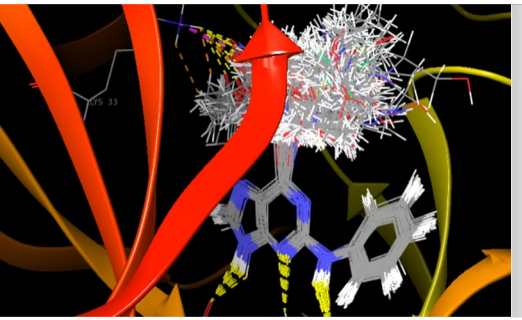
Improve the Effectiveness and Efficiency of Program Progression



Developing physics-based methods of the future:
Metals, quantum effects, hybrid methods…



More comprehensive support of ADME-Tox Optimization:
Rate of clearance, TDI, hERG…



***De Novo* Design:**
More tractably assessing the vast universe of chemical possibilities

High-Value Future Applications Emerging

Protein-Residue-Mutation FEP+ Predicts BTK Clinical Resistance

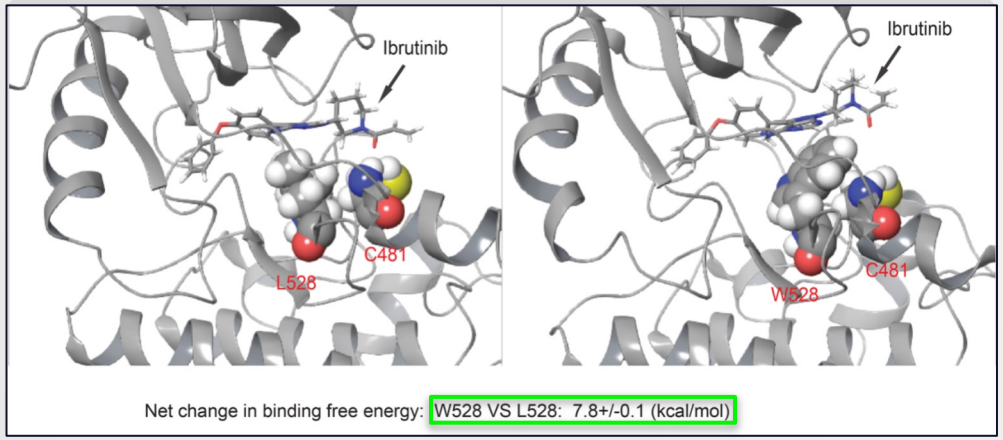
Prospective prediction of clinical resistance mutations years before clinical observation [**2019**]

JCI insight

Noncovalent inhibitors reveal BTK gatekeeper and auto-inhibitory residues that control its transforming activity

Shenqiu Wang,[1] Sayan Mondal,[2] Chunying Zhao,[1] Marjan Berishaj,[1] Phani Ghanakota,[2] Connie Lee Batlevi,[3] Ahmet Dogan,[4] Venkatraman E. Seshan,[5] Robert Abel,[2] Michael R. Green,[6] Anas Younes,[3] and Hans-Guido Wendel[1]

Published June 20, 2019 - More info



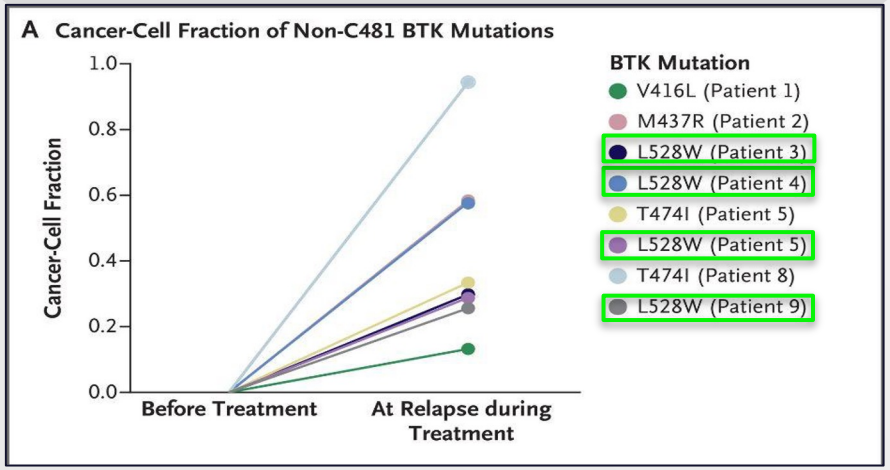
Most prevalent resistance mutation L528W predicted 3 years earlier by FEP+ analysis [**2022**]

The NEW ENGLAND JOURNAL of MEDICINE

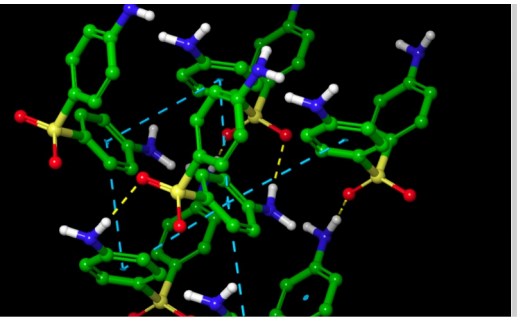
Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors

Eric Wang, Ph.D., Xiaoli Mi, M.D., Meghan C. Thompson, M.D., Skye Montoya, B.Sc., Ryan Q. Notti, M.D., Ph.D., Jumana Afaghani, B.Sc., Benjamin H. Durham, M.D., Alex Penson, Ph.D., Matthew T. Witkowski, Ph.D., Sydney X. Lu, M.D., Ph.D., Jessie Bourcier, M.D., Simon J. Hogg, Ph.D., et al.

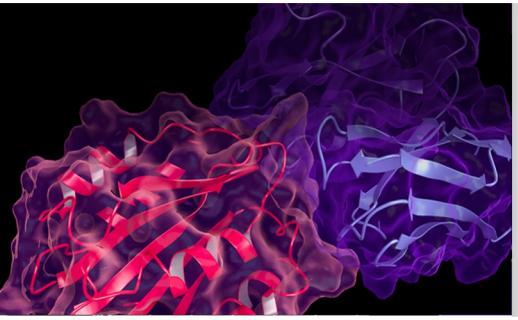
Article Figures/Media Metrics
22 References 11 Citing Articles
February 24, 2022
N Engl J Med 2022; 386:735-743
DOI: 10.1056/NEJMoa2114110
Chinese Translation 中文翻译



Expand the Applicability of our Platform to New High-value Areas



Preclinical Development and Formulations:
Solubility, excipients, process chemistry



New Modalities:
Biopharmaceuticals, protein degraders, molecular glues



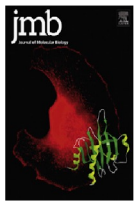
Materials:
Energy, chemical reactivity, polymers

High-Value Future Applications Emerging

Protein-residue-mutation FEP+ has potential to improve antibody design

Design and optimization of pH sensing recycling antibodies

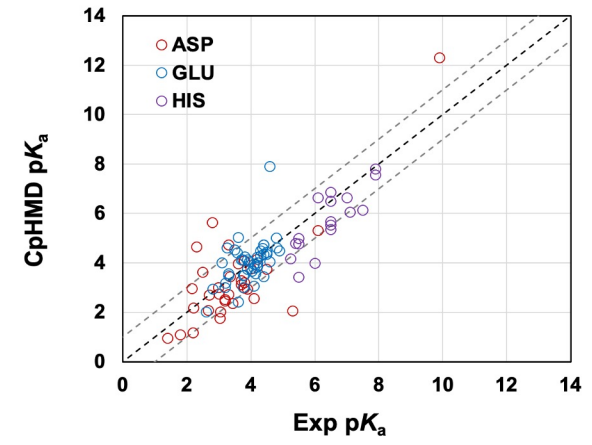
2017



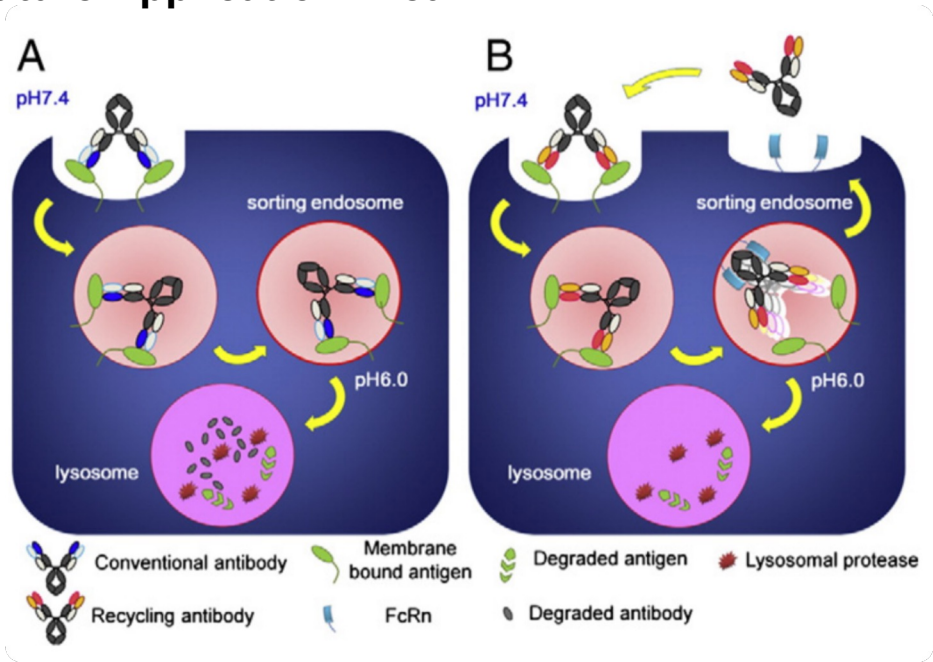
Free Energy Perturbation Calculation of Relative Binding Free Energy between Broadly Neutralizing Antibodies and the gp120 Glycoprotein of HIV-1

JMB. 429:930-947 (2017)

New Capability



Future Application Area



Igawa T, Mimoto F, Hattori K. pH-dependent antigen-binding antibodies as a novel therapeutic modality. Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics.

Today's Agenda

Introduction — Ramy Farid

Our Platform: Current Capabilities — Robert Abel

Putting Our Platform to Work: Case Studies — Karen Akinsanya and Hamish Wright

- Pipeline Overview
- Collaboration examples: Nimbus's ACC & TYK2; Morphic's $\alpha_4\beta_7$
- Proprietary examples: CDC7, Wee1, MALT1

Our Platform: Future Capabilities — Robert Abel

Business Outlook and Opportunities — Geoff Porges

Q&A

The Evolving Spectrum of Schrödinger Value Creation

SOFTWARE LICENSING

- Arm's length
- Moderate engagement/support/feedback
- No downstream value participation
- Earliest validation

COLLABORATIONS

- Conceived, driven and owned by partner
- Modeling, molecular design ± medicinal chemistry
- Computation at full-scale
- Funded by partner
- Milestones, royalties, equity stakes

PROPRIETARY PIPELINE

- Conceived and driven by Schrödinger
- Complete computation, discovery and development
- At-risk investment by Schrödinger
- Out-license as hits, leads, DCs or clinical, or retained
- Upfront payments, discovery, development and commercial milestones, royalties, commercial rights

TECHNOLOGY PLATFORM

Industry-leading physics-based platform: enables discovery of novel molecules faster, at lower cost with a higher likelihood of success compared to traditional methods

The Evolving Spectrum of Schrödinger Value Creation

SOFTWARE LICENSING

- Life Sciences
- Materials Design

~1,600 customers worldwide*

COLLABORATIONS

- Drug Design
- Materials Design

12 active projects

PROPRIETARY PIPELINE

- Drug Discovery & Development
- Wholly-owned or Partnered

18 active programs

TECHNOLOGY PLATFORM

Industry-leading physics-based platform: enables discovery of novel molecules faster, at lower cost with a higher likelihood of success compared to traditional methods

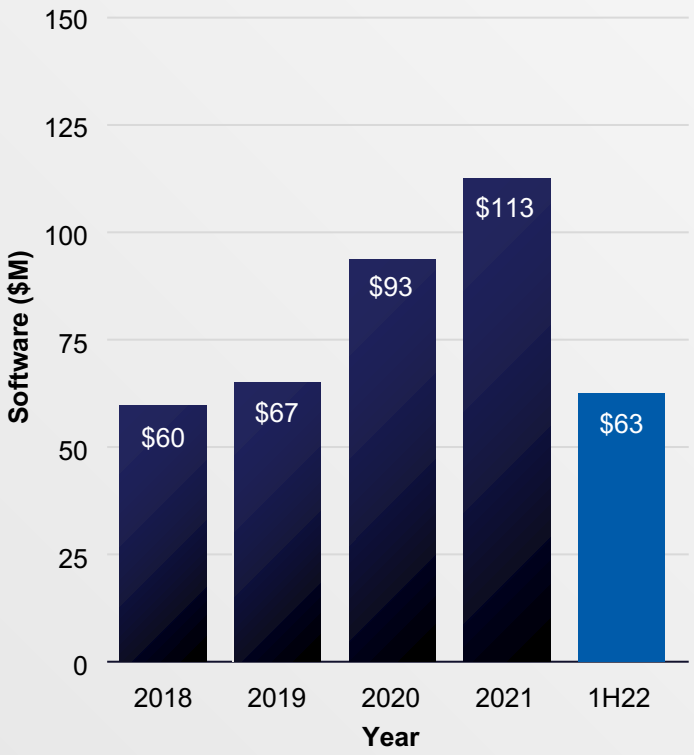
*Active Customers (# of customers who had an Annual Contract Value (ACV) >$1,000) as of Dec. 31, 2021.

Three Sources of Value Provide Balanced Opportunity for Cash Flow and Long-term Value Creation

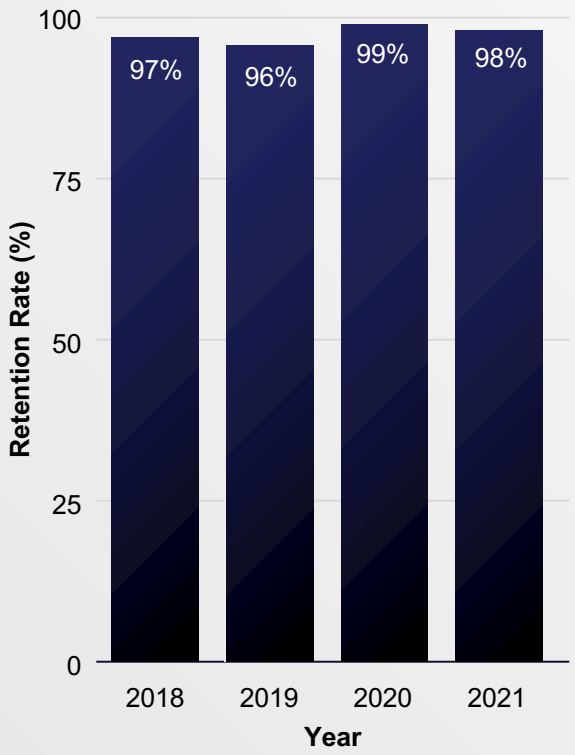
Profile	Software Licensing	Collaborations	Proprietary Programs
Timing of Value Creation	Near term	Near- & medium-term	Medium- & long-term
Profitability	Profitable	Funded by partner	Investment
Direction	Steady revenue growth	Inflecting revenue growth	
Platform	Validates platform	Deploys & develops platform	Leverages & enhances platform
Customer Universe	Extensive	Limited, curated	Targeted
Outlook	Continued growth via increased adoption	Accelerating growth in collaborations, targets, stages	Advance to monetization

Software Licensing

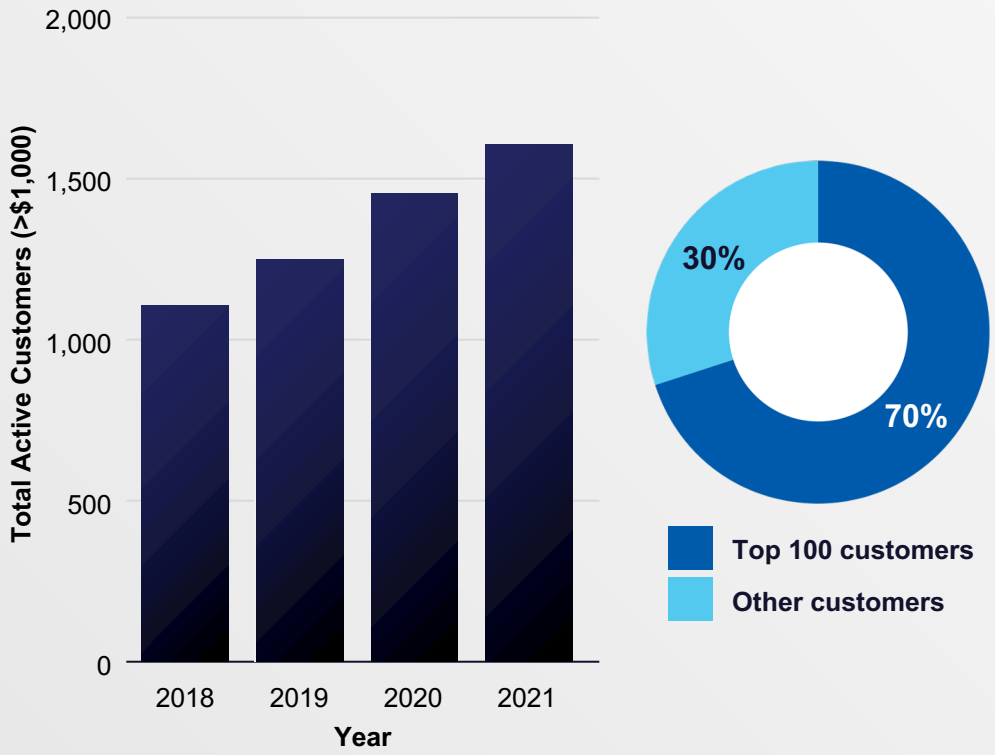
Software Revenue



Customer Retention Rate*



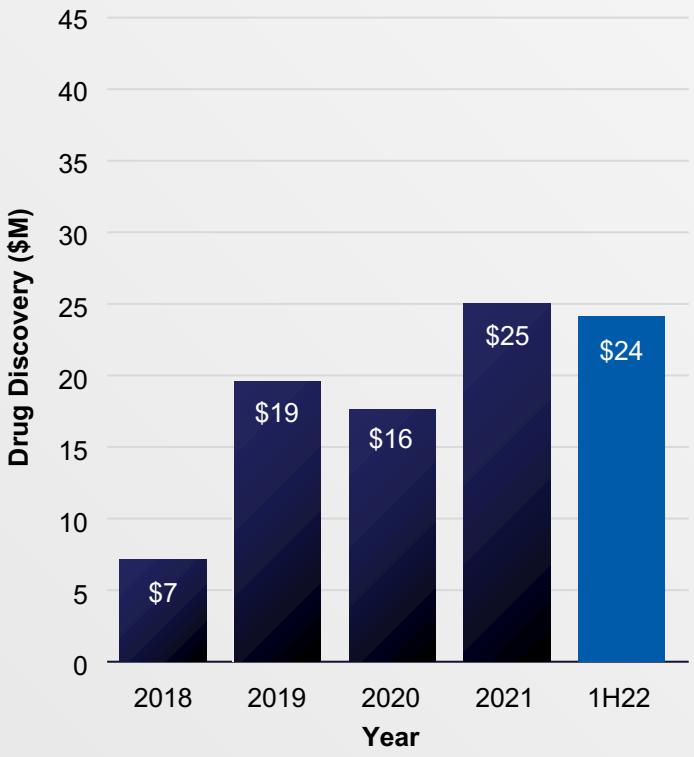
Total Active Customers 2018-2021*



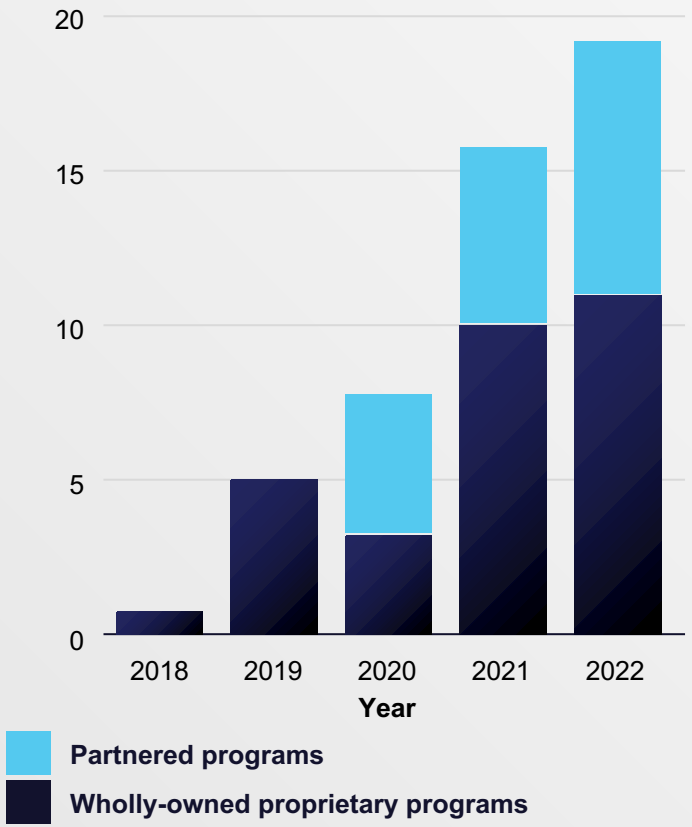
See Appendix Slide for descriptions and definitions for customer retention rate, active customers and ACV.

Collaborations and Proprietary Programs

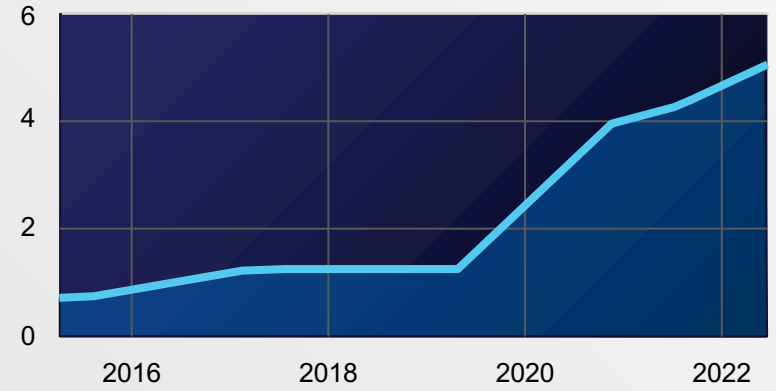
Drug Discovery Revenue



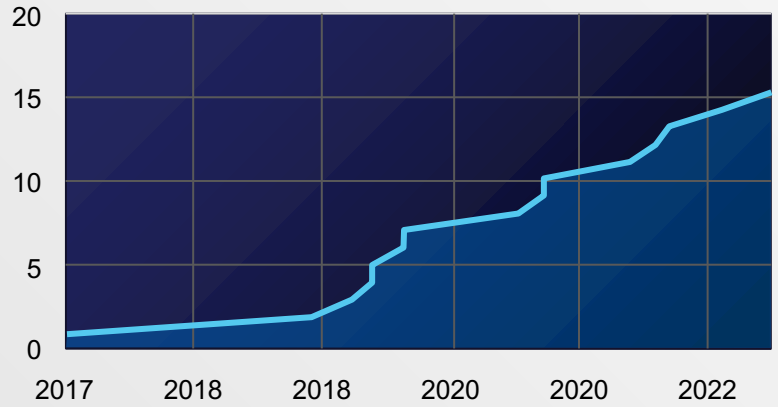
Active Proprietary Programs



Cumulative Total Milestone Opportunity ($Billion)*



of Programs Eligible for Royalties on Sales**



*Total milestone opportunity assuming all indications, all geographies for all partnered and collaboration programs.
**Royalties range from low single to low double-digits.

Summary



Summary

30+ year track record of scientific **breakthroughs** and continuing scientific **innovation**

Highly **validated** drug discovery platform

Strong financial position and balanced business model with multiple **value-creation opportunities**



Schrödinger

Q&A

Appendix: Operating Metrics

To supplement the financial measures presented in accordance with generally accepted accounting principles in the United States (“GAAP”), we also present certain other performance metrics, such as annual contract value and customer retention rate.

Annual Contract Value (ACV). We track the ACV for each of our customers. With respect to contracts that have a duration of one year or less, or contracts of more than one year in duration that are billed annually, we define ACV as the contract value billed during the applicable period. For contracts with a duration of more than one year that are billed upfront, ACV in each period represents the total billed contract value divided by the term. ACV should be viewed independently of revenue and does not represent revenue calculated in accordance with GAAP on an annualized basis, as it is an operating metric that can be impacted by contract execution start and end dates and renewal rates. ACV is not intended to be a replacement for, or forecast of, revenue.

Customer Retention for our customers with an ACV of over $100,000. We calculate year-over-year customer retention for our customers in this cohort by starting with the number of customers we had in the previous fiscal year. We then calculate how many of these customers were active customers in the current fiscal year. We then divide this number by the number of customers with an ACV over $100,000 we had in the previous fiscal year to arrive at the year-over-year customer retention rate for such customers.

Active Customers. We define an active customer as a customer that had an ACV of at least $1,000 in the fiscal year. We use $1,000 as a threshold for defining our active customers as this amount will generally exclude customers that only license our PyMOL software, which is our open-source molecular visualization system broadly available at low cost.