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 α_4β_7
- Proprietary examples: CDC7, Wee1, MALT1

**Our Platform: Future Capabilities — Robert Abel**

**Business Outlook and Opportunities — Geoff Porges**

**Q&A**
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**Q&A**
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.
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

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

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.

“**All**” synthesizable molecules

Select **THE** best molecule

- Potency ✓
- Selectivity ✓
- Solubility ✓
- Bioavailability ✓
- Clearance / Half-life ✓
- Permeability ✓
- Drug-Drug Interactions ✓
- Synthesizability ✓
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

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?

2. Rigorous first principles physics-based modeling
   - Requires deep understanding of the physics underlying highly complex molecular interactions

\[ i\hbar \frac{d}{dt} \Psi(t) = \hat{H} \Psi(t) \]
\[ i\hbar \frac{\partial}{\partial t} \Psi(r, t) - \left[ \frac{\hbar^2}{2m} \nabla^2 + V(r, t) \right] \Psi(r, t) \]
Machine Learning Can Only Interpolate Within the Training Set

Train

Predict

Cat
Machine Learning Can Only Interpolate Within the Training Set
Machine Learning Can Only Interpolate Within the Training Set
How Does This Apply to Prediction of Molecular Properties?
Machine Learning Can Only Interpolate Within the Training Set
Machine Learning Can Only Interpolate Within the Training Set

- **Train**: Cat
- **Predict**: Cat ✓, Dog ✗

- **Train**: Potent
- **Predict**: Potent ✓
Machine Learning Can Only Interpolate Within the Training Set

- **Train**
- **Predict**

Cat: ✓
Dog: ×

Potent: ✓

Machine Learning Can Only Interpolate Within the Training Set
Machine Learning Can Only Interpolate Within the Training Set

- 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


\[ \Delta G_{\text{bind}} = \Delta G(1) + \Delta G(2) + \Delta G(3) + \Delta G(4) + \Delta G(5) \]
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.

\[ \text{IC}_{50} = 2 \ \mu\text{M} \]

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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Q&A
Physics & Machine Learning Are Complementary

Machine Learning / Artificial Intelligence

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

Physics-based Methods

✓ No training set required
✓ Can extrapolate into novel chemical space
✓ Accurate
X Slow
Physics & Machine Learning Are Complementary

Machine Learning / Artificial Intelligence
- ✓ Effective at interpolation
- ✓ Fast
- ✓ Can handle very large datasets
- X Requires very large training set
- X Cannot extrapolate

Machine Learning + Physics
Training set for ML generated using physics
- ✓ Fast
- ✓ Accurate
- ✓ Can handle very large datasets
- ✓ Can extrapolate into novel chemical space

Physics-based Methods
- ✓ No training set required
- ✓ Can extrapolate into novel chemical space
- ✓ Accurate
- X Slow
Long Track Record of Scientific Innovation

1990: Schrödinger Founded

1994: Quantum Mechanics
Accurate calculation of small molecule solution structures

1998: Molecular Mechanics
Fast calculation of small molecule solution structures

2002: Protein Refinement
Accurate prediction of local protein structure

2012: Comprehensive Force Field
Accurate description of atomic interactions

2008: Molecular Dynamics
Simulation of molecular motion

2004: Docking
Virtual screening for Hit Identification

2016: Free Energy Calculations
Broadly applicable and accurate calculation of potency, selectivity, and solubility

2019: Active Learning
Accurate, large-scale property predictions

2022: Next Gen Protein Refinement
Enablement of proteins without experimental structures
Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy

Richard A. Friesner, Jay L. Banko, Evan D. Harder, coworkers

Volume: 58, Issue: 8, Pages: 3137 - 3141, 2012

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†, Yueji Wu†, Yueqing Du†, Daniel T. Mainz, Matthew P. Repasky

Volume: 32, Issue: 10, Pages: 3697 - 3706, 2018

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

- Target Validation
- Hit Identification
- Lead Optimization
- Preclinical Development

2000

Virtual Screening

GLIDE

JAGUAR MACROMODEL
Schrödinger Platform in Drug Discovery Process

Target Validation
- Protein Structure Determination
- Druggability Assessment

Hit Identification
- Virtual Screening

Lead Optimization
- IFD
- MAESTRO
- PRIME
- SITEMAP
- WATERMAP

Preclinical Development
- JAGUAR
- MACROMODEL
- AUTOQSAR
- CORE HOPPING
- DESMOND
- IFD
- LIGPREP
- LIVEDESIGN
- MAESTRO
- PRIME
Schrödinger Platform in Drug Discovery Process

Target Validation

- Accurate Protein Structure Determination (~10% of human genome)
- Reliable Druggability Assessment

Hit Identification

- Large-Scale Virtual Screening
- Fragment Screening

Lead Optimization

- 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

Preclinical Development

- Polymorphs Prediction
- Drug Manufacturing

Tools:

- IFD-MD
- MAESTRO
- PRIME
- SITEMAP
- WATERMAP
- OPLS4
- FEP+
- PRIMEX

- GLIDE
- CONGEN
- 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

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

- **1 billion** *De novo* molecules
- **1,000** random molecules
- **1** DAY
- **Top 5,000** molecules enriched in “good” molecules
- **~8** molecules that advance the program
- **FEP+** Compute property using physics
- **Score 1 billion** molecules using machine learning model
- **1–2 DAYS**
- **Synthesize 10** molecules
- **Train machine learning model**
Incorporating Physics-based Compound Design into Drug Discovery

Upto 100 billion idea molecules scored

100s of molecules synthesized and tested

Drug Discovery Process:
- Structural Biology
- Cellular Binding & Function
- Disease Pharmacology
- Pharmacokinetics & ADME
- Safety / Toxicology

18 – 36 Months

Development Candidate

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- Safety / Toxicology

18 – 36 Months

Development Candidate
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

**Schrödinger’s Physics-Based Platform**

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

Drug development candidate with
- Property issues
- Optimal property profile
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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

- agios
- MORPHIC THERAPEUTIC
- STRUCTURE THERAPEUTICS
- ONO
- Orexia
- nimbus THERAPEUTICS
- SANOFI
- BRIGHT ANGEL THERAPEUTICS
- Ajax THERAPEUTICS
- PETRA PHARMA

2010
2015
2020
Expanding Portfolio of Proprietary Programs

Partnered programs
Wholly-owned programs

Takeda
Schrödinger
Wee1
SGR-1505 (MALT1)
SGR-2921 (CDC7)
Bristol Myers Squibb
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
<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>Discovery</th>
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<th>Phase 1</th>
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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

<table>
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<th>PROGRAM</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
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<td>Undisclosed Neurology</td>
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<td>Protein Degraders Oncology, Immunology and Neurology</td>
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<td>Schrödinger</td>
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<td>Undisclosed Oncology</td>
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<td>Takeda</td>
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<td>Schrödinger Zai Lab</td>
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<td>Undisclosed</td>
<td></td>
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<td>Schrödinger Lilly</td>
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</tbody>
</table>

47
Novel ACC Inhibitor Collaboration
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

Challenges of Targeting ACC

- HTS gave low yields
- Poor drug-like properties

CT Domain
Highly lipophilic

BC Domain
No drug-like inhibitors

DESIGN CHALLENGE
Discover novel chemotypes to address these limitations

Crystal structure available
- 3GID (2.30 Å)

Binding site predicted to be druggable

Potential Solution to Targeting ACC

CT Domain
Highly lipophilic

- HTS gave low yields
- Poor drug-like properties

BC Domain
No drug-like inhibitors

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

DESIGN CHALLENGE
Discover novel chemotypes to address these limitations

Water Physics Revealed Unique Binding Opportunity

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

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

Red spheres represent locations of high-energy unstable waters
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
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.

Drug Design Goal

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

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

55
Selective Inhibition of TYK2 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

Use of FEP+ for TYK2 Program

Additional Proprietary Co-crystal Structures

New sub-series that takes advantage of additional interactions with non-conserved residues

~560-fold Selectivity

Number of Compounds Synthesized

- 600
- 500
- 400
- 300
- 200
- 100
- 0

TYK2 / JAK2 Selectivity

- 600
- 500
- 400
- 300
- 200
- 100
- 0
NDI-034858 Shows Desired *In Vitro* Potency and Selectivity

Selective Inhibition of TYK2 vs. JAKs

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

- 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*

*ClinicalTrials.gov Identifiers NCT04999839 and NCT05153148.
α₄β₇ Integrin Collaboration
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

Leukocyte

$\alpha_4\beta_1$

$\alpha_4\beta_7$

$\alpha_4\beta_7$ Inhibitor

VCAM-1

MAdCAM-1

Endothelial cell

Inhibiting VCAM-1 brings risk of PML

Just need to find the right molecule!

Small molecule $\alpha_4\beta_7$ inhibitors

Potent ................. Known

Selective ............ Rare

Good PK ............. Rare

Potency

Selectivity

PK

Established and proven on target biology
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
- $\sim$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

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>$\alpha_4\beta_7$ IC$_{50}^a$ (nM)</th>
<th>$\alpha_4\beta_7/\alpha_4\beta_1$ Fold selectivity</th>
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</thead>
<tbody>
<tr>
<td>MORF-057</td>
<td>1.2 nM</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>0.035 nM</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>0.166 nM</td>
<td>1-12</td>
</tr>
<tr>
<td>AJM300</td>
<td>93 nM</td>
<td>8-45</td>
</tr>
</tbody>
</table>

- MORF-057 shows dose-dependent saturation of the $\alpha_4\beta_7$ 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

- 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

*ClinicalTrials.gov Identifiers NCT05291689.

\[\text{IC}_{50}^a\]
SGR-2921: Our Selective CDC7 Inhibitor
CDC7 Kinase Is a Key Cell Cycle Checkpoint for DNA Repair

CDC7 Kinase activation resolves replication stress during DNA replication.

Healthy Cells

Following DNA repair, cell division resumes.

G2 Phase
Growth
Pre-Mitosis

M Phase
Cell Division

S Phase
Replication stress response & DNA Repair

G1 Phase
Growth
Genome Duplication

Cell Cycle
High Replication Stress Tumors Are Sensitive to CDC7 Inhibition
Synergistic with PARP and BCL2 Inhibitors

**CDC7 kinase phosphorylates** proteins involved in repair of double stranded breaks

**PARP inhibitors** cause trapping of PARP on DNA

**Stalled DNA replication fork**

**Fork collapses DNA Breaks**

**SGR-2921**

**Apoptosis and cancer cell death**

**Genomic instability**

**Replication Catastrophe**

**Replication fork instability DNA breakage**

**Physiological**
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

- ROCKY/MOK9 biochem. assay
- CDCC7/0BF4 ADP-Glo Assay
- ADME Tier 1 sol. microsome, perf.
- CDCC7/0BF4 SPR assay
- CC025, BapC-3 pMCM2 SS3 MSD assay
- Comp Chem and Modeling
- CDCC crystallography

- Cancer cell proliferation assay (CellTiter-Glo) colo-205, BapC3
- ADME Tier 2 In vivo mouse PK

- Colo205 CGX pMCM2 SS3 Pk/PD model
- Colo205 CGX tumor growth inhibition

- Human bone marrow growth inhibition assay
- Cancer cell line screening
- PDX tumor growth inhibition model
- Exploratory Biomarker discovery

- API scale up
- Acute safety in rat
- 3-strain AMES (+ SSI), MINT

- Rat and dog in vivo safety (single, multiple dose) CV safety (dog)

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

Novel tight binding core with favorable drug metabolism properties

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

Improved permeability resolves in vitro / in vivo disconnect

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

- 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

AML CDX efficacy study shows tumor regression

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

25 Months

Development Candidate
Our Wee1 Inhibitor Program
Wee1 Data Demonstrate Clinical Opportunity in 3rd Party Studies

**Breast Cancer**
26% ORR (cisplatin combination)

**Uterine Cancer**
30% ORR monotherapy

**Ovarian Cancer**
Up to 50% ORR monotherapy

**Head and Neck Cancer**
50% ORR (chemo combination)

**Lung Cancer**
Monotherapy and combo responses

**Pancreatic Cancer**
Increased PFS and OS (gemcitabine combination)

**Colorectal Cancer**
Responses and increased PFS

**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

Schrödinger Wee1 Inhibitors
Optimized Selectivity and Physicochemical Properties

<table>
<thead>
<tr>
<th></th>
<th>AZD-1775</th>
<th>Zn-C3</th>
<th>SDGR Wee1 Program</th>
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<tbody>
<tr>
<td>Wee1 Binding $K_D$ (nM)</td>
<td>3</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Efficacy in cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell viability IC$_{50}$ (nM)</td>
<td>130; 290</td>
<td>260; 210</td>
<td>100; 90</td>
</tr>
<tr>
<td>CTG assay in lung cancer and ovarian cancer cell lines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selectivity</td>
<td></td>
<td></td>
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<tr>
<td>Kinome Selectivity</td>
<td></td>
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<td>scanMAX at 1 µM</td>
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<tr>
<td>Drug Drug Interaction Liability</td>
<td>CYP3A4 TDI</td>
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<td>No CYP3A4 TDI</td>
</tr>
</tbody>
</table>

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

Protein FEP+ predictions reproduced experimental trends

Retrospective
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

Compounds proven experimentally to be highly selective for Wee1

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Cmpd B3</th>
<th>Cmpd B5</th>
<th>Cmpd B6</th>
<th>Cmpd B7</th>
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<td>&gt;1000</td>
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</tbody>
</table>

On-target Selectivity (fold): Kinase

On-target potency (IC50) [nM]:

% kinases with >100x window

Prospective Wee1 binding pocket

Compound
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
SGR-1505: Our MALT1 Inhibitor Program
MALAT1 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

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

- Computational assay established
- Early compound enabled in vivo efficacy and PK/PD
- Lead-optimization of priority series initiated
- DC compound that met TPP discovered

Target potency range

- Prior MALT1 inhibitor potency
  - 1 nM
  - 100 nM
  - 10 µM

Project Month

0 1 2 3 4 5 6 7 8 9 10

# Compounds Synthesized

0 20 40 60 80 100

Early compound enabled in vivo efficacy and PK/PD

Lead-optimization of priority series initiated

DC compound that met TPP discovered
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

~World population

A town

A street

A person
SGR-1505 Shows Well-balanced Properties

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

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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 inhibition¹,²
- SGR-1505 IND open; initiating a Phase 1 dose escalation in relapsed/refractory B-cells lymphomas in 4Q22

Yin et al. ASH 2021.

¹WO2022184716 Combination Therapy using MALT1 Inhibitor and BTK Inhibitor.
²WO2022185097 Method of treating a condition using a therapeutically effective dose of the MALT1 inhibitor JNJ-67856633.
Examples of Platform Impact Across a Growing Portfolio

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

**Best in class**
Selectivity / Properties

**First in class**
Modality Switch
Selectivity / Properties

Discovery Phase Complete
Ongoing Collaborations
Ongoing Proprietary Programs (partnered and wholly-owned)
Platform Is Producing an Expanding Portfolio

Schrödinger Cumulative Portfolio Success
Metrics Over 10 years

% Cumulative Technical Success

<table>
<thead>
<tr>
<th>Program</th>
<th>Schrödinger</th>
<th>Industry</th>
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<tbody>
<tr>
<td>HitID</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Hit2Lead</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>LO</td>
<td>82%</td>
<td>60%</td>
</tr>
<tr>
<td>IND enabling</td>
<td>76%</td>
<td>51%</td>
</tr>
<tr>
<td>Phase I</td>
<td>66%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>56%</td>
<td></td>
</tr>
</tbody>
</table>

Collaboration programs in the clinic

Expanding pipeline of partnered and wholly-owned programs

[References]


1% Technical Success is defined as the percentage of programs that advance to the next stage, which excludes problems 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

<table>
<thead>
<tr>
<th><strong>Introduction</strong></th>
<th>Ramy Farid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Our Platform: Current Capabilities</strong></td>
<td>Robert Abel</td>
</tr>
<tr>
<td><strong>Putting Our Platform to Work: Case Studies</strong></td>
<td>Karen Akinsanya and Hamish Wright</td>
</tr>
<tr>
<td>• Pipeline Overview</td>
<td></td>
</tr>
<tr>
<td>• Collaboration examples: Nimbus’s ACC &amp; TYK2; Morphic’s $\alpha_4\beta_7$</td>
<td></td>
</tr>
<tr>
<td>• Proprietary examples: CDC7, Wee1, MALT1</td>
<td></td>
</tr>
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<td><strong>Our Platform: Future Capabilities</strong></td>
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<td>Geoff Porges</td>
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<tr>
<td><strong>Q&amp;A</strong></td>
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*Image credit: Schrödinger*
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]

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

New Capability

Future Application Area

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
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<tbody>
<tr>
<td>Introduction</td>
<td>Ramy Farid</td>
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<td>Our Platform: Current Capabilities</td>
<td>Robert Abel</td>
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<tr>
<td>Putting Our Platform to Work: Case Studies</td>
<td>Karen Akinsanya and Hamish Wright</td>
</tr>
<tr>
<td>• Pipeline Overview</td>
<td></td>
</tr>
<tr>
<td>• Collaboration examples: Nimbus’s ACC &amp; TYK2; Morphic’s α₄β₇</td>
<td></td>
</tr>
<tr>
<td>• Proprietary examples: CDC7, Wee1, MALT1</td>
<td></td>
</tr>
<tr>
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</tbody>
</table>
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

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

Software Revenue

<table>
<thead>
<tr>
<th>Year</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>1H22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Software ($M)</td>
<td>$60</td>
<td>$67</td>
<td>$93</td>
<td>$113</td>
<td>$63</td>
</tr>
</tbody>
</table>

Customer Retention Rate*

<table>
<thead>
<tr>
<th>Year</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention Rate (%)</td>
<td>97%</td>
<td>96%</td>
<td>99%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Total Active Customers 2018-2021*

<table>
<thead>
<tr>
<th>Year</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Active Customers ($1,000)</td>
<td>1,000</td>
<td>1,500</td>
<td>1,800</td>
<td>2,000</td>
</tr>
</tbody>
</table>

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

Drug Discovery Revenue

- Yearly revenue from 2018 to 1H22.

Active Proprietary Programs

- Number of programs eligible for royalties on sales.

Cumulative Total Milestone Opportunity ($Billion)*

- Total milestone opportunity assuming all indications, all geographies for all partnered and collaboration programs.

# of Programs Eligible for Royalties on Sales**

- Royalties range from low single to low double-digits.

*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**

---

**SOFTWARE LICENSING**

- Steady revenue growth

**TECHNOLOGY PLATFORM**

**COLLABORATIONS**

- 12 active discovery programs
- 9 clinical programs

**PROPRIETARY PIPELINE**

- New partnership with Lilly
- 18 programs progressing to monetization

Inflecting revenue growth
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.