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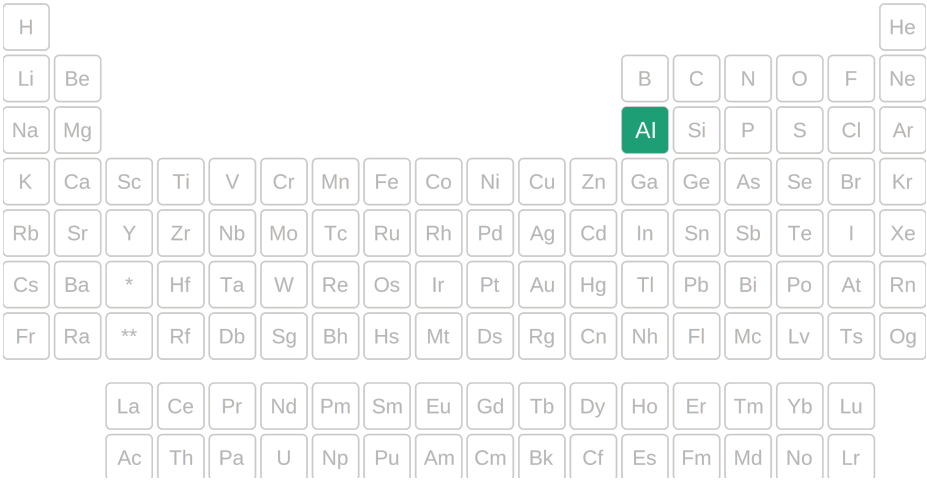
JCUP XIII

September 17–18, 2026 · Tokyo



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Agenda

Thursday, September 17

10:00 – 10:30 Registration

Morning Session:

10:30 – 10:45 Opening remarks – **Jeff Grandy,** *VP Sales at OpenEye, Cadence Molecular Sciences*

10:45 – 11:15 Looking to the horizon: Scientific Roadmap – **Jeff Grandy,** *VP Sales at OpenEye, Cadence Molecular Sciences*

Molecular Representations & Prediction:

11:15 – 11:45 Conformation-sensitive property prediction model and its applications – **Tomoyuki Miyao,** *Nara Institute of Science and Technology*

11:45 – 12:00 Break

Platform Advances:

12:00 – 12:30 DEMO: Orion Interactive Molecular Search for Chemists – **Koji Oda,** *Application Scientist at OpenEye, Cadence Molecular Sciences*

12:30 – 13:00 Break

13:00 – 13:30 Triage Hits like a Pro – **Paul Hawkins,** *Product Marketing Evangelist at OpenEye, Cadence Molecular Sciences*

Molecular Representations & Prediction:

13:30 – 14:00 Multi-Conformer 3D Molecular Fingerprints for Predicting Perceptual Odor Similarity – **Yusuke Ihara,** *Ajinomoto*

Hit Identification:

14:00 – 14:30 Find your Next Hit with AI-driven ROCS X: Beyond Trillion-scale Search – **Matthew Geballe,** *Group Director, Scientific Research and Development at OpenEye, Cadence Molecular Sciences*

Poster Session:

14:30 – 16:00 Poster Session

Lead Discovery & Optimization:

16:00 – 16:30 Computational design of radioligand therapies: From hits to low-picomolar binders – **Dusan Petrovic,** *Novartis*

16:30 – 17:00 Are modeling predictions your new bottleneck? Free Energy Prediction for Drug Discovery with Speed at Scale – **Chris Neale,** *Leader Affinity Group at OpenEye, Cadence Molecular Sciences*

17:00 – 17:30 From Molecules to Medicines: The Role of Chemical Toxicology at Takeda – **Takafumi Takai,** *Takeda Development Center Americas, Inc.*

17:30 – 17:45 Free Energy Wrap-up – **Chris Neale,** *Leader Affinity Group at OpenEye, Cadence Molecular Sciences*

Reception:

18:00 – Banquet

Friday, September 18

9:30 – 10:00 Registration

AI-Enabled Drug Discovery:

10:00 – 10:30 AI in Drug Discovery – **Paul Hawkins,** *Product Marketing Evangelist at OpenEye, Cadence Molecular Sciences*

10:30 – 11:00 Applications of AI-Based Non-Linear Morphing for Conformational Changes in Proteins – **Naoyuki Miyashita,** *KINDAI University*

11:00 – 11:30 Agentic DMTA with JedAI – **Matthew Geballe,** *Group Director, Scientific Research and Development at OpenEye, Cadence Molecular Sciences*

11:30 – 13:00 Break

Target Exploration:

13:00 – 13:30 Unleashing the Potential in Modern Structural Biology Data Using Weighted Ensemble Simulation – **David LeBard,** *Head of Scientific Development, Target Exploration at OpenEye, Cadence Molecular Sciences*

13:30 – 14:00 Ligand Screening and Modeling in the Post-AlphaFold Era: From Predicted Structures to Cryo-EM Maps – **Daisuke Kihara,** *Purdue University*

14:00 – 14:30 Dynamics and AI-Enabled Target Assessment: Advancing the Right Targets – **David LeBard,** *Head of Scientific Development, Target Exploration at OpenEye, Cadence Molecular Sciences*

14:30 – 15:00 Break

Hydration & Molecular Recognition:

15:00 – 15:30 gr Predictor and Deep GIST: Deep-Learning Models for Protein Hydration Analysis – **Takashi Yoshidome,** *Tohoku University*

15:30 – 16:00 SDOVS: A Solvent Dipole Ordering-Based Method for Virtual Screening (Revisited) – **Naoya Nagata,** *RIKEN*

Closing:

16:00 – 16:15 Closing remarks

Conformation-sensitive property prediction model and its applications

Tomoyuki Miyao
Nara Institute of Science and Technology

Molecular representations play a key role in machine learning (ML)-based property (activity) prediction models. They are categorized as two-dimensional (2D) or three-dimensional (3D) based on the molecular information required to derive them. 2D representations require connections between atoms (covalent bonds), whereas 3D representations depend on molecular conformations. It is widely believed that 3D representations are superior to 2D, yet several benchmark calculations have demonstrated otherwise. It remains difficult to draw a general conclusion about the superiority of 3D representations over 2D ones, let alone determine which 3D representation should be used for property (activity) prediction.

In this talk, I will review molecular representations and focus on 3D representations that effectively capture molecular conformation for property prediction.[1] To that end, datasets were intentionally designed to test conformer-(in) sensitive properties for diverse conformers, and both conventional ML and neural network models were evaluated. In this benchmark, Uni-Mol,[2] a neural network architecture using a geometric distance-information-incorporated attention mechanism, achieved high accuracy for conformation-sensitive property prediction only when using the conformers yielding the property values.

Based on this finding, applications using Uni-Mol-based models will be presented. One focuses on predicting nucleophilic and electrophilic sites and their strengths in neutral molecules for polar organic reactions: methyl cation affinity (MCA) and methyl anion affinity (MAA) prediction. MCA (MAA) is defined as the energy difference (negative of the energy) for the virtual reaction of a methyl cation or methyl anion with a substrate. Molecules with higher MCA (MAA) are more nucleophilic (electrophilic) because the corresponding products are more stable. These thermodynamic energy differences at atomic sites could be effectively predicted using a neural network consisting of a Uni-Mol encoder block and a feed-forward network.[3] Furthermore, extracted atom-wise contributions for a reaction site on the attention map align with researchers' knowledge of the reaction, supporting the validity of the neural network model.

References
[1] Y. Hamawaka, T. Miyao. J. Chem. Inf. Model. 2025, 65, 7, 3388–3404
[2] Zhou, G.; Gao, Z.; Ding, Q.; Zheng, H.; Xu, H.; Wei, Z.; Zhang, L.; Ke, G. 2022. https://openreview.net/forum?id=6K2RM6wVqKu
[3] Y. Iwasaki, A. Sato, T. Miyao. J. Phys. Chem. A 2026, 130, 26, 5016–5029

Multi-Conformer 3D Molecular Fingerprints for Predicting Perceptual Odor Similarity

Yusuke Ihara
Ajinomoto

Predicting odor perception directly from molecular structure remains a challenging problem in chemoinformatics. Odor quality is influenced not only by the presence of specific functional groups but also by three-dimensional molecular shape, spatial arrangements of chemical features, and conformational flexibility. Molecular representations that capture these properties are therefore needed to distinguish subtle perceptual differences among structurally related odorants and to develop quantitative structure–odor relationship models.

In this study, we investigated a set of 23 odorants comprising eugenol, vanillin, and their structural analogs. These compounds occupy a relatively narrow region of chemical and perceptual space but span a continuous perceptual gradient from eugenol-like to vanillin-like odor quality. This gradient was quantified by sensory evaluation as an eugenol-similarity score ranging from 0 to 1.

For each odorant, an ensemble of low-energy conformers was generated, and three-dimensional shape and pharmacophore similarities were computed relative to a reference library of 941 odorants. Each query compound was represented by a 941-dimensional similarity fingerprint, in which each dimension corresponded to its maximum similarity to one reference odorant across the evaluated conformer ensembles. Hierarchical clustering of the reference-odorant similarity matrix revealed chemically meaningful structure in the resulting molecular space, including a broad

separation between aromatic and aliphatic compounds and local clusters of structurally related molecules.

An XGBoost regression model trained on the multi-conformer similarity fingerprints predicted the eugenol-similarity score with an R^2 of 0.514 on the validation set. Feature-importance analysis identified reference odorants whose similarity values contributed substantially to the predictions, thereby providing an interpretable connection between three-dimensional molecular similarity and perceived odor quality.

For comparison, a regression model based on experimentally measured olfactory receptor activation profiles achieved an R^2 of 0.687 on the validation set. These results show that multi-conformer 3D similarity fingerprints provide predictive information about subtle perceptual differences from molecular structure alone. The higher predictive performance of the receptor-based model suggests that olfactory receptor activation profiles provide an intermediate, biologically informed representation of odorants that is more closely aligned with perceptual odor similarity than structural similarity alone. Integrating structure-based and receptor-based representations may therefore offer a promising strategy for improving the generalizability and predictive accuracy of future models of odor perception.

Find your Next Hit with AI-driven ROCS X: Beyond Trillion-scale Search

Matthew Geballe
OpenEye, Cadence Molecular Sciences

ROCS X was built for searching larger and larger chemical spaces. As we move beyond the realm of libraries that can be searched exhaustively, the Bayesian optimization approach at the center of ROCS X enables intelligent 3D similarity search across massive combinatorial spaces at fractions of the cost of exhaustive search. In this presentation we will review the ROCS X approach to combinatorial search and cover the advances in the method since our initial presentation last year including options for directed search, larger validation studies, and future plans for new features.

Computational design of radioligand therapies: From hits to low-picomolar binders

Dusan Petrovic
Novartis

Radioligand therapy (RLT) is a rapidly developing approach that couples radioactive isotopes to targeted ligands, allowing selective delivery of radiation directly to tumor cells. This combination of specificity and radiotoxicity opens new possibilities for cancers that are resistant to conventional treatments. In this talk, I will present how physics-based modeling supports the development of RLT compounds. By combining quantum mechanical (QM) methods, molecular dynamics (MD) simulations, and free energy perturbation (FEP) calculations it is possible to quickly progress from early hits to low-picomolar binders with favorable in vivo behavior. I will also discuss the unique modeling challenges posed by radioligands and how these can be addressed in practice. These efforts demonstrate how modern CADD approaches can help accelerate the development of innovative cancer therapies.

Are modeling predictions your new bottleneck? Free Energy Prediction for Drug Discovery with Speed at Scale

Chris Neale
OpenEye, Cadence Molecular Sciences

Selecting which compounds to synthesize is a central challenge in lead optimization, yet rigorous binding-affinity calculations are often applied only after extensive triage has narrowed the set of design options. OpenEye's free energy nonequilibrium switching (FE-NES) method in Orion® can now evaluate hundreds of compounds within hours, enabling physics-based affinity prediction to guide hypothesis selection rather than merely validate late-stage designs.

We demonstrate this approach by revisiting a published Tyk2 lead-optimization campaign. For one substitution site, BROOD generated 200 analogs intended to replace a dichlorophenyl group with less lipophilic alternatives. FE-NES correctly predicted that this strategy would reduce potency, enabling the hypothesis to be deprioritized before synthesis. For a second hypothesis, our reaction/reagent-based Floes enumerated 5,000 aminopyridine analogs designed to form an additional hydrogen bond with Val981. Property, docking, and MD-based filters reduced this collection to approximately 700 candidates for affinity prediction. Rather than reserving rigorous free-energy calculations for a handful of finalists, FE-NES was used to evaluate hundreds of compounds within a single design hypothesis, identifying 59 unsynthesized analogs predicted to outperform the published lead.

By evaluating hundreds of analogs within hours (and thousands overnight), FE-NES allows rigorous physics-based calculations to guide hypothesis selection early in lead optimization, helping teams reject unproductive hypotheses earlier, explore broader chemical space, and focus synthesis on the most promising compounds.

From Molecules to Medicines: The Role of Chemical Toxicology at Takeda

Takafumi Takai
Takeda Development Center Americas, Inc.

There are many challenges along the drug discovery and development journey—from advancing a molecule to delivering a safe and effective medicine to patients. Among these, toxicity remains one of the most critical hurdles, as it can determine the success or failure of a promising program.

At Takeda, chemical toxicologists play a pivotal role, particularly in the early stages of drug discovery. Working closely with toxicologists, medicinal chemists, and other cross-functional partners, we help identify potential safety liabilities early, guide molecular design, and support informed decision-making throughout the discovery process.

In this presentation, I will provide an overview of Takeda's drug discovery workflow and highlight how chemical toxicology is integrated into

the process. Through selected examples from drug discovery programs, I will illustrate how in silico and in vitro approaches can be leveraged to identify, investigate, and mitigate toxicity risks—ultimately helping to advance safer and more successful drug candidates toward patients.

AI in Drug Discovery

Paul Hawkins
OpenEye, Cadence Molecular Sciences

This talk will address the three key foundations for agentic AI in drug discovery: the predictive models that agents call, the molecular featurizations the models use, and the data upon which the models are trained.

Data - high-quality data is a necessity when building good models. Very sophisticated models built upon poor quality data will fail, while simpler modeling methods can work very well when built upon relevant, carefully curated data. This talk will exemplify the impact data quality has on model performance using ML models for protein binding pocket detection.

Featurization – agentic workflows require human-in-the-loop (HitL) oversight at key decision points. Once the human operator enters the workflow it is very important that the operator be able to clearly understand and interpret the models that the agent is using. This talk will show how models built upon featurization with shape and electrostatics can provide transparent, intuitive models that HitL operators can easily and quickly interpret.

Models – in agentic AI workflows a model's ability to estimate the uncertainty in its predictions is almost as important as the accuracy of its predictions. While a model continues to return high confidence predictions to its agent the agent can continue to work productively, but when a model begins to return low confidence predictions the agent should stop and request guidance from its human operator. Reliable estimation of model uncertainty therefore enables agents to request intervention from their operator only when that intervention has maximal value.

Applications of AI-Based Non-Linear Morphing for Conformational Changes in Proteins

Naoyuki Miyashita
KINDAI University

Understanding large-scale conformational changes in enzymes, transporters, pumps, and other functional proteins is essential for elucidating their cyclic mechanisms and for applications in drug discovery. Experimentally determined structures provide important snapshots, and transition pathways are often inferred using morphing or enhanced simulation methods. Linear morphing tools such as Morphit Pro are useful to demonstrate the conformational changes between two states [1], but they do not necessarily describe physically plausible domain motions. More rigorous approaches, including the string method [2], transition path sampling [3], and PaCS-MD [4], have advanced transition-path analysis, but they may require specialized implementations, or substantial computational cost.

To demonstrate conformational transition pathways with moderate accuracy at low computational cost, we developed Morphing method for Observing and Visualizing Essential Dynamics via Deep Neural Networks and Molecular Dynamics Simulations (MOVE-DM), an AI-based nonlinear morphing method [5]. MOVE-DM learns all trajectories from short MD simulations of two states and demonstrates structural changes along the connecting pathway. This method can also be applied to standard MD simulation trajectories to extract and visualize their essential dynamics.

I will present one of application of MOVE-DM to the dynamics of monoamine oxidase B (MAO-B), a dopamine-metabolizing enzyme and pharmacological target. Our results revealed that interactions with lipids are directly involved in the opening and closing of the drug-entry gate.

References:

[1] R. Veevers and S. Hayward, J. Mol. Graph. Model. 82, 108–116 (2018).
[2] W. E, W. Ren, and E. Vanden-Eijnden, Phys. Rev. B 66, 052301 (2002).
[3] C. Dellago et al., J. Chem. Phys. 108, 1964–1977 (1998).
[4] R. Harada and A. Kitao, J. Chem. Phys. 139, 035103 (2013).
[5] N. Miyashita et al., Biophys. J. 124(3), Suppl 1, 219A (2025)

Agentic DMTA with JedAI

Matthew Geballe
OpenEye, Cadence Molecular Sciences

The Agentic approach to leveraging AI has been the catalyst to rapid change in many fields and has resulted in immense interest and pressure for all of us to evaluate the usefulness and potential impact of applying these approaches. In this talk we will talk about the principles of building agentic systems, the experience and resources we have at Cadence Molecular Sciences to build agentic systems for drug discovery, and our plans and progress on building a prototype for an agentic system for DMTA.

Unleashing the Potential in Modern Structural Biology Data Using Weighted Ensemble Simulations

David LeBard
OpenEye, Cadence Molecular Sciences

The "resolution revolution" in Cryo-electron Microscopy (cryo-EM) has been underway for about a decade, allowing routine high-resolution structural characterization of proteins and complexes that have eluded crystallization; with the advent of laser phase plates, this revolution may soon accelerate further. Cryo-EM has the unique advantage of capturing native compositional and conformational ensembles, yet much of the heterogeneous information contained in the massive datasets routinely collected by industry remains unexplored. The OpenEye Structural Biology Floes are designed to make full use of this information, leveraging Weighted Ensemble simulation sampling to guide exploration while remaining grounded in experimental data. The Best Structure Search Floe matches conformations explored in simulation to maps from 3D classification or conformational variability analysis, while the Eigen-map Exploration Floe uses eigen-maps from tools such as 3DVA, RECOVAR, and SOLVAR to project simulated dynamics onto motions measured at the microscope. This talk will discuss recent applications of these methods, including fitting the GLP-1R

into low-resolution cryo-EM maps, identifying continuous transition pathways connecting large-amplitude antibody-complex motions in HER2, and recovering dynamic inhibitor pockets and experimentally consistent ensembles for CAK from AlphaFold starting structures. Together, these studies demonstrate how simulation can transform heterogeneous cryo-EM datasets into experimentally grounded structural ensembles, providing a practical framework for understanding biomolecular dynamics, mechanism, and function.

Ligand Screening and Modeling in the Post-AlphaFold Era: From Predicted Structures to Cryo-EM Maps

Daisuke Kihara
Purdue University

The emergence of AlphaFold and related methods has dramatically expanded access to protein structures, ushering structure-based drug discovery into a new era. However, predicted structures are not always sufficiently accurate at ligand-binding sites, and modest conformational differences can substantially reduce the performance of conventional docking and virtual screening. Meanwhile, cryogenic electron microscopy (cryo-EM) is increasingly being used in drug discovery, creating a need for reliable methods to identify and model ligands in experimental density maps.

In this talk, I will present two complementary approaches developed for this post-AlphaFold landscape. PatchSurfer3 (Shin et al., J. Cheminformatics, 2026) is a structure-based virtual screening method that evaluates ligand–pocket surface complementarity using molecular shape and physicochemical properties encoded by rotationally invariant three-dimensional Zernike descriptors. Its surface-based representation is less sensitive to local structural inaccuracies than conventional atom-based scoring. Consequently, PL-PatchSurfer3 provides robust ligand-screening performance with apo, modeled, and AlphaFold-predicted receptor structures and is superior or competitive with conventional docking and recent deep learning methods.

I will also introduce Emap2lig, a deep learning framework for detecting and building ligands directly in cryo-EM maps (Li et al., bioRxiv, 2026).

Without prior knowledge of ligand locations, Emap2lig identifies ligand-associated density and then combines map-derived spatial information with chemical constraints to generate the bound ligand structure using a diffusion model. The method remains effective at resolutions near 5 Å, with generated ligand structures achieving a mean deviation of 1.57 Å from native poses.

Together, these studies demonstrate how robust molecular representations and state-of-the-art generative models can expand the use of predicted structures and cryo-EM data in drug discovery.

Dynamics and AI-Enabled Target Assessment: Advancing the Right Targets

David LeBard
OpenEye, Cadence Molecular Sciences

Alternative protein conformations can reveal hidden ligand-binding sites and expand chemical space by enabling recognition of diverse ligands, but these therapeutically relevant states are often discovered serendipitously. To systematically explore rugged protein conformational landscapes, we developed a normal mode-guided enhanced sampling strategy in a water-xenon mixed-solvent environment that efficiently captures motions ranging from side-chain rearrangements to large-scale domain and protein-protein interface dynamics. Starting from apo structures, the method samples pockets within 2 Å of known holo conformations in 57% of cases, while xenon probes detect transient pocket formation with frequencies ranging from 46% to 92%. To prioritize the most promising pockets, we developed Target X, a machine learning-based ligandability model trained on Groovy, a rigorously curated, truly non-redundant dataset that eliminates redundancy and training-validation leakage through pocket-level similarity metrics. The Target X machine learning model for pocket ligandability was trained on Groovy and shows strong predictive performance across both static structures and conformational ensembles. Together, dynamics-driven pocket discovery and ligandability-based pocket assessment provide a scalable, unbiased framework for enriching known binding sites among top-ranked pockets and identifying ligandable sites for early-stage drug discovery.

gr Predictor and Deep GIST: Deep-Learning Models for Protein Hydration Analysis

Takashi Yoshidome
Tohoku University

We present two deep-learning models, gr Predictor [1] and Deep GIST [2], for analyzing protein hydration. The former predicts the hydration structure, and the latter predicts the hydration free-energy distribution, both in approximately one minute. The prediction results are in good agreement with those obtained using conventional methods, including 3D-RISM theory and molecular dynamics simulations. These models are particularly useful for analyzing large numbers of protein structures.

[1] K. Kawama, Y. Fukushima, M. Ikeguchi, M. Ohta, and T. Yoshidome, J. Chem. Inf. Model., 62, 4460 (2022).
[2] Y. Fukushima and T. Yoshidome, J. Chem. Inf. Model., 66, 1429 (2026).

SDOVS: A Solvent Dipole Ordering-Based Method for Virtual Screening (Revisited)

Naoya Nagata
RIKEN

Solvent dipole ordering (SDO), originally introduced by Higo et al., describes the spatial organization and orientation of water molecules around proteins. We found that high-SDO regions in the ligand-binding site of FKBP overlap well with experimentally observed ligand structures, suggesting that SDO captures key features of preferred ligand shape and binding mode.

Based on this concept, we generated SDO-mimetic pseudo-molecules and used them as shape-based screening queries. We first evaluated this approach using a kinase target in redocking and cross-docking studies and successfully reproduced the binding modes of known inhibitors. We then developed SDOVS, which combines SDO-derived pseudo-molecules with

shape-similarity screening. Across four representative drug targets, SDOVS showed lower RMSDs and higher ROC-AUCs than FRED.

Finally, we applied SDOVS to CK2 and successfully identified novel hit compounds. These results highlight SDOVS as a promising approach to practical drug discovery.

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