～最新のScience Technologyを有する英米３社の特別講義・CBI学会スポンサー企業企画～

『次世代GPUシミュレーションと iPS疾患モデルが融合する創薬イノベーション』

Innovative drug discovery platform combining next generation GPU simulation and disease modelled iPS cells.

2018年10月9日（火）14:00～15:30　CBI学会2018年大会会場　3階 303室

座長 Chairman	池田和由　氏 Dr Kazuyoshi Ikeda Email:	慶應義塾大学薬学部 Keio University ikeda-kz@pha.keio.ac.jp
主催	BIOSPIRE株式会社 (www.biospire.jp) ライフマティックス株式会社 (www.lifematics.co.jp)	

創薬におけるスピードと手法が、iPSと、AIに代表される革新的なコンピューター技術(GPU)の進歩によって、大きな変化点を迎えています。本セミナーでは、英国と米国から講師を招き、計算化学における最先端の技術を２件、iPS創薬に関する技術を１件ご紹介します。

英Cresset社からは、昨年リリースされた最新のSBDDツール～Flare～を中心に全く新しい分子設計の方法をご紹介いたします。XED力場によるCressetソフト特有の精密な計算モデルを分子間相互作用に適用することで、インシリコによるヒット同定・拡張から、リガンド相互作用エネルギー論にもとづく残基の抽出、相互作用に関わる水分子の解析を高精度に行うことが可能です。

米SilcsBio社からは、小分子プローブを導入したマイクロ秒アンサンブル MD法をコア技術にしたヒットtoリードにおける創薬探索研究の事例をご紹介いたします。これからの計算化学において、必要不可欠なGPU高速化シミュレーションの先駆けとしてリアルタイムMDの最新技術、及びPharmacoporeの作成、ポケット発見、バーチャルスクリーニングの手法についてフォーカス致します。

英DefiniGEN社からは、ゲノム編集とiPS分化誘導を組合わせた新たな疾患モデル細胞作製に関する技術情報とグローバルファーマを中心とした受託プロジェクトの概要が説明されます。同一のiPS細胞を出発点とし、一方をゲノム編集により疾患化、一方を健常人細胞として同一の分化誘導プラットフォームに乗せた、疾患の有無のみが異なるisogenicコントロールが提供できるようになり、既に希少疾患を中心とした探索プログラムとフェノタイプスクリーニングに広く活用されはじめています。

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事業概要	ソフトウェアのライセンス販売 (Flare, Spark, Blaze, Forge, Torch) 分子設計受託サービス	分子設計受託サービス	iPS由来細胞の販売 (肝細胞・膵β細胞・小腸オルガノイド) 疾患モデルカスタム設計

Predicting biological activity using the electrostatic complementarity of protein-ligand complexes

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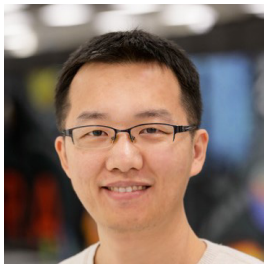
Electrostatic interactions between small molecules and their respective receptors are a key contributor to the free energy of binding. Assessing the electrostatic match between ligands and binding pockets provides therefore important insights into why ligands bind and what could be changed to improve binding. The polarizable XED force field is an excellent base for calculating electrostatic properties due to its description of anisotropic atomic charge distributions and relatively modest computational costs. By computing electrostatic potentials for both ligand and protein with XED, the Electrostatic Complementarity™ of complexes can be assessed via (1) inverse correlation of the respective local electrostatic potentials (Pearson or Spearman rho rank tests) or (2) calculating a normalized surface complementarity integral, yielding electrostatic complementarity scores. The latter approach also allows visualization of the local electrostatic matching on the van der Waals surface to identify electrostatic clashes and inform ligand design. We present the theoretical background of our electrostatic complementarity descriptors along with several case studies showing the practical application of the scores to the prediction of activity and of the visualization to ligand design.



Site Identification by Ligand Competitive Saturation (SILCS) Enables Rational Inhibitor Design for Glucocorticoid Receptor

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Glucocorticoid receptor (GR) has therapeutic relevance in autoimmune and inflammatory diseases. However, its deeply buried binding site offers significant challenges for explicit solvent molecular simulation-driven drug design campaigns. These challenges stem from difficulty in exchanges of water and other small molecules from the surrounding solution with its binding site. Additionally, recent evidence suggests significant conformational changes at the binding pocket leads to additional transient cavities not detected in most crystal structures but are nevertheless occupied by some high affinity lead candidates. Site identification by ligand competitive saturation (SILCS) is a multiple solute-solvent simulation strategy that accurately characterizes functional group affinity patterns, called FragMaps, throughout the protein, including deeply buried sites. Using a hybrid Grand Canonical Monte-Carlo/Molecular Dynamics (GCMC/MD) strategy, SILCS drives efficient sampling of chemically diverse probes and water molecules into even deeply buried pockets such as those found in the GR. SILCS FragMaps correctly recapitulated functional group patterns of previously known ligands. Additional pocket cavities driven by conformational changes to N564, Q570 and Q642 in the binding site have been characterized through the simulations and functional group affinities in these sites have been correctly identified. FragMap-based Ligand Grid Free Energy (LGFE) is a scoring metric that rapidly rank-orders ligand favorability to a defined binding site on the protein. LGFE scoring enabled rapid evaluations of virtual substitutions to previously known lead candidates with a large library of fragment-like modifications. LGFE scoring correctly rank-ordered high-affinity candidates along with identifying geometric growth vectors in lead candidates. SILCS thereby is an attractive solution to identify functional group requirements for flexible binding pockets as well as efficiently driving hit-to-lead optimization campaigns.

Validating novel determinants of metabolic disease using an integrated CRISPR/Cas9 iPS differentiation platform technology approach

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To validate the new therapeutic target candidate outputs from disruptive AI approaches and a range “omic” technologies: genetic, epigenetic and transcriptomic, proteomic, and metabolomic, next generation phenotypic screening platforms are required. DefiniGEN platform combines CRISPR/Cas9-gene editing, Nobel prize winning Yamanaka iPS stem cell and GMP-compatible directed differentiation to generate predictive disease models for metabolic disease which are reflective of the in vivo state. The platform can generate models for complex diseases such as NAFLD/NASH in which disease implicated loci are systematically modified alongside isogenic control lines which are identical to the disease variant apart from the introduced mutation. This enables us to determine the contribution of a particular gene variant to the disease state. This approach is particularly powerful for complex diseases where multiple genes and variants impact on the severity of disease progression.