DEPARTMENT SEMINAR

日時：1月7日（火）17:00-18:00
場所：工学部3号館8B04

演者：**Dr. Yuma Ishigami**
(Postdoctoral fellow, Krainer lab., Cold Spring Harbor Laboratory)

Specificity, synergy, and mechanisms of small-molecule/antisense-oligonucleotide splice-modifying drugs

Activation of pre-mRNA splicing by drugs holds great therapeutic potential and is an emerging target for drug discovery, but the quantitative understanding of how these drugs work is limited. Here we introduce mechanistically interpretable mathematical models to describe how splicing-modifying drugs affect specific RNA sequences. Using massively parallel splicing assays, RNA-seq experiments, and dose-response curves, we obtain quantitative models for splicing activation by two small-molecule drugs, risdiplam and branaplam, developed for treating spinal muscular atrophy. The results quantitatively characterize the specificities of these drugs for 5’ splice site sequences and contradict the prevailing two-site hypothesis for risdiplam activity at *SMN2* exon 7. The results also show that multi-drug synergy is widespread in multiple gene contexts, among small-molecule drugs and antisense-oligonucleotide drugs that promote exon inclusion. Our quantitative models thus clarify the mechanisms of existing treatments and provide a basis for the rational development of new therapies.

References:
M. S. Wong, J. B. Kinney, A. R. Krainer. Quantitative Activity Profile and Context Dependence of All Human 5' Splice Sites. Mol Cell. (2018)
Y. Ishigami, M. S. Wong, C. Martí-Gómez, A. Ayaz, M. Kooshkbaghi, S. M. Hanson, D. M. McCandlish, A. R. Krainer, J. B. Kinney. Specificity, synergy, and mechanisms of splice-modifying drugs. Nat Comm. (2024)

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