令和7年度 第5回 NCNP国際セミナー
International Seminar

From Gene Discovery to Therapeutics in Profound Autism

Prof. Joseph Buxbaum

Autism spectrum disorder (ASD) is highly genetic, with many dominant, haploinsufficient risk genes. This creates opportunities for precision medicine that upregulates wild-type protein from the intact allele. Small molecules that interact with RNA (SMIRNAs) offer an oral, titratable, immune-sparing, and scalable platform. Because 3′UTRs regulate translation and mRNA stability via RNA-binding proteins and structural elements, we examined them as targets to boost expression in haploinsufficient states. Thermodynamically stable 3′UTR structures were found in most dominant ASD genes and appear amenable to small-molecule binding. Library screening and counter-screening yielded selective hits for top genes (e.g., ADNP, SHANK3, FOXP1, DDX3X). For several targets, leads increased endogenous protein in a dose-dependent manner in transformed cells and induced human neurons. Similarity searches produced active analogs, enabling preliminary SAR and a Chem-CLIP probe for target engagement. These data support 3′UTR-targeting SMIRNAs as a complementary alternative to ASOs and gene therapy, addressing dosage “Goldilocks” constraints across many ASD risk genes.

米国マウントサイナイ医科大学自閉症センター長として、世界の自閉スペクトラム症研究をリードするBuxbaum教授に、最新のゲノム解析・動物モデル解析・臨床試験などについてお話頂きます。
大変貴重な機会ですので、ぜひ多くのご参加をお待ちしております。

Selected publications:
1. Familial confounding in the associations between maternal health and autism. ***Nat Med*** (2025)
2. Identification of shared and differentiating genetic architecture for autism spectrum disorder, attention-deficit hyperactivity disorder and case subgroups. ***Nat Genet*** (2022)
3. Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. ***Cell*** (2020)

演者：Prof. Joseph Buxbaum
(Director of Seaver Autism Center for Research and Treatment, Ichan School of Medicine at Mount Sinai)

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場所：研究所3号館1階セミナールーム

担当連絡先：精神保健研究所　知的・発達障害研究部（内線：6280）
神経研究所　微細構造研究部（内線：5213）、疾病研究第２部（内線：5124）