# 大学院特別講義

（医歯学先端研究特論）（生命理工学先端研究特論）
（生命理工医療科学先端研究特論）（医歯理工学先端研究特論）

## Zoom によるオンライン講義

受講希望者は 2023 年 1 月 6 日（金）17 時までに、下記の連絡先まで問い合わせてください。なお、本学の学生については出席確認のため本講義を受ける際は本学の機関登録をした Zoom ID とパスワードでログインするようお願いします。

記

1．講　師　University of Texas Health Science Center
San Antonio, Department of Molecular Medicine
勝村　早恵

2．演　題　Deadenylase-dependent mRNA decay of hepatokines controls systemic metabolism

3．日　時　2023年１月10日（火）17：30～19：30

4．要　旨

Organokines, such as hepatokines from the liver, have been coined to indicate the group of secretory proteins that mediate inter-organelle cross-talk and maintain whole-body metabolism, such as food intake and energy expenditure. The imbalance of inter-organelle communication by dysregulation of organokines leads to metabolic disorders that increase the risk of type 2 diabetes and atherosclerosis. Although transcriptional regulation to induce organokines has been well-studied, the mechanisms underlying how organokine expression is switched off by mRNA decay are largely unknown. We demonstrated that hepatokines, such as FGF21 and GDF15, are post-transcriptionally turned off by CNOT6L, mRNA poly(A) nuclease (deadenylase), to maintain metabolic balance. The genome-wide screening of the CNOT6L targets discovered the mRNAs encoding GDF15 and FGF21, which are attractive as anti-obese drugs. To determine the molecular mechanism, we identified an inhibitor of CNOT6L deadenylase by in silico and high-throughput screenings. The inhibitor administration in mice increases hepatic Gdf15 and Fgf21 mRNAs by stabilizing these mRNAs, leading to increasing the corresponding serum protein levels. The increase in GDF15 and FGF21 dramatically suppress food intake through the hindbrain and stimulate energy expenditure and fat utilization through the communication with adipose tissues and the hypothalamus. The CNOT6L inhibition further shows the therapeutic potential for the treatment of metabolic disorders.

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