From DEPARTMENT OF ONCOLOGY AND PATHOLOGY

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DEVELOPING ANALYTICAL TOOLS TO INVESTIGATE THE ROLE OF TRANSLATION IN HOMEOSTASIS AND DISEASE

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Developing analytical tools to investigate the role of translation in homeostasis and disease

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Abstract

Transcriptome-wide studies of translation efficiencies are required to improve understanding of translational regulation and its role in homeostatic mechanisms. In **Study 1**, we developed an algorithm for analysis of translation efficiency, called anota2seq. We show that anota2seq outperforms current methodologies and, due to its unique analytical approach, it is the only method to statistically distinguish important modes for regulation of gene expression, i.e translation and translational buffering.

Pancreatic cancer is a lethal malignancy with very limited treatment options. In **Study 2**, we evaluate the impact of using an eIF4A inhibitor, CR-31, on mRNA translation in pancreatic cancer. eIF4A is a component of the eIF4F translation initiation complex. We show that inhibiting eIF4A in murine and human pancreatic ductal adenocarcinoma (PDAC) models induces an energy crisis by impacting translation of mRNAs related to oxidative phosphorylation and glycolysis. This leads to the shift of metabolic dependency of PDACs towards reductive glutamine metabolism. Exploiting this dependence using a combined treatment of eIF4A and glutaminase inhibitors revealed an exciting therapeutic treatment strategy for PDA that did not affect healthy cells.

In **Study 3**, we investigated the effecs of insulin on gene expression in malignant and non-malignant cells. This revealed that malignant cells modulate total mRNA levels differerenly in response to insulin compared to non-malignant cells, whereas in both translation was dependent on mammalian/mechanistic target of rapamycin (mTOR). However, mTOR inhibition during insulin stimulation in malignant cells lead to translational offsetting of alterations in total mRNA levels. Comparing the effects of mTOR inhibition in malignant cells to that of hypoxia in stem cells revealed that these vastly different cell types share the ability to translationally offset mRNAs.

Collectively, these studies improved analysis of translational efficiencies and

contributed to advanced understanding of the role of translational dysregulation in cancer.

List of publications

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†Equal contribution.

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Oertlin Christian, Watt Kathleen, Ristau Johannes and Larsson Ola. Anota2seq for transcriptome-wide studies of mRNA translation. Methods in Molecular Biology. *in review*.