

From DEPARTMENT OF ONCOLOGY AND PATHOLOGY  
Karolinska Institutet, Stockholm, Sweden

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

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**Karolinska  
Institutet**

Stockholm 2021

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Published by Karolinska Institutet

Printed by US-AB

ISBN 978-91-8016-202-9

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

THESIS FOR DOCTORAL DEGREE (Ph.D.)

In light of the global pandemic the dissertation will be held online. The meeting information will be published prior to the defence on the KI-website.

**Friday, April 23rd, 2021, 13:00**

By

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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 the dependence on reductive glutamine metabolism using a combined treatment of eIF4A and glutaminase inhibitors revealed an exciting therapeutic treatment strategy for PDAC that did not affect healthy cells.

In **Study 3**, we investigated the effects of insulin on gene expression in malignant and non-malignant cells. This revealed that malignant cells modulate total mRNA levels differently 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

**Oertlin Christian** , Lorent Julie , Murie Carl , Furic Luc , Topisirovic Ivan & Larsson Ola. (2019). Generally applicable transcriptome-wide analysis of translation using anota2seq. *Nucleic acids research*. 47. 10.1093/nar/gkz223.

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<sup>†</sup>Equal contribution.



## Other publications or works

Hipolito Victoria , Diaz Jacqueline , Tandoc Kristofferson , **Oertlin Christian** , Ristau Johannes , Chauhan Neha , Saric Amra , McLaughlan Shannon , Larsson Ola , Topisirovic Ivan & Botelho Roberto. (2019). Enhanced translation expands the endo-lysosome size and promotes antigen presentation during phagocyte activation. PLOS Biology. 17. e3000535. 10.1371/journal.pbio.3000535.

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

**Oertlin Christian**, Watt Kathleen, Ristau Johannes and Larsson Ola. Anot2seq for transcriptome-wide studies of mRNA translation. Methods in Molecular Biology. *in review*.