Abstract

Inactivating SMARCA4 mutations have been shown to be the sole genetic driver event in small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), a rare and aggressive cancer affecting mostly young women. SCCOHT is also characterize by concomitant loss of SMARCA4 and SMARCA2 where SMARCA2 is epigenic silenced. Dual loss of SMARCA4/2 also define a subset of non-small cell lung cancers (NSCLCs) associated with very poor patient outcome. However, loss of SMARCA4/2 is not directly druggable and the precise mechanisms by which SMARCA4/2 loss drives tumorigenesis are not well understood. While conventional chemotherapies are rarely effective for treating SMARCA4/2-deficient cancers, rationalized and targeted treatment options are lacking for these aggressive diseases.

We discovered that the loss of SMARCA4/2 represses the expression of the glucose transporter GLUT1, leading to reduced glucose uptake and glycolysis in SCCOHT and NSCLC cells. As a result, these cancer cells are highly dependent on oxidative phosphorylation (OXPHOS). To adapt to this change, SMARCA4/2-deficient cells rely on elevated glutamine import to fuel OXPHOS. This increased reliance makes SMARCA4/2-deficient cells and tumors highly sensitive to inhibitors that target OXPHOS or glutamine metabolism both *in vitro* and *in vivo*. Furthermore, using a functional genetic screening, we uncovered a synthetic lethal interaction between SMARCA4 loss and the mitochondrial isoleucyl-tRNA synthetase 2 (IARS2) inhibition. Mechanistically, we uncovered a non-conical function of IARS2 independent of its catalytic activity in the maintenance of mitochondrial DNA (mtDNA) expression. Thus, inhibition of IARS2 but not other mitochondrial tRNA synthetases, suppresses both mitochondrial mRNA expression and translation resulting in marked decrease in expression of electron transport chain (ETC) complexes components. Consequently, IARS2 inhibition causes strong inhibition of OXPHOS and selectively induces death of SMARCA4-deficient cancer cells both *in vitro* and *in vivo*. Overall, our findings reveal potential therapeutic strategies for SMARCA4/2-deficient cancers by exploiting their mitochondrial dependency.

McGill University

Graduate and Postdoctoral Studies

Final Oral Examination
for the Degree of
Doctor of Philosophy
of **Zheng FU**

of the Department of Biochemistry**, on April 17, 2023 @ 9:00 am** Via Zoom.

COMMITTEE:

Guojun Chen	(Pro Dean)
Biomedical Engineering	
Professor Katie Cockburn	(Deputy Chair)
Professor Sidong Huang	(Thesis Supervisor)
Professor Lawrence Kazak	(Internal Examiner)
Professor Natasha Chang	(Internal Member)
Professor Chong Sun	(External Member)
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Dr. Josephine Nalbantoglu
Dean

Members of Faculty and Graduate
Students are invited to be present

CURRICULUM VITAE

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ACADEMIC BACKGROUND:

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PUBLICATIONS:

- Xianbing Zhu*, **Zheng Fu***, Shary Yuting Chen*, Dionzie Ong, Giulio Aceto Rebecca Ho, Jutta Steinberger, Anie Monast, Virginie Pilon, Eunice Li, Monica Ta, Kyle Ching, Bianca Adams, Gian Luca Negri, Luc Choiniere, Lili Fu, Kitty Pavlakis, Patrick Pirrotte, Daina Zofija Avizonis, Jeffrey Trent, Bernard E. Weissman, Ramon Klein Geltink, Gregg B. Morin, Morag Park, David G. Huntsman, William D. Foulkes, Yemin Wang and Sidong Huang. Alanine supplementation exploits glutamine dependency induced by SMARCA4/2-loss. (co-first author,***Nature Communication***, **Accepted**)
- **Zheng Fu***, Xianbing Zhu*, Jack Collier, Michael Tarry, Yibo Xue, Azadeh Arabzadeh, Howard Li, Mark Liao, Kangning Yang, Anie Monast, Virginie Pilon, Morag Park, Heidi Mcbride, Martin Schmeing, Sidong Huang. SL2 induces vesicular release of mtDNA to target SMARCA4-determined oxidative phosphorylation dependence. (**In preparation for submission**)
- **Zheng Fu***, Xianbing Zhu*, Azadeh Arabzadeh, Mark Liao, Anie Monast, Virginie Pilon, Sidong Huang. Exploiting HRI inhibition for inducing ferroptosis in SMARCA4-deficient cancers. (**In preparation for submission**)
- Xianbing Zhu*, **Zheng Fu***, Jutta Steinberger, Leora Witkowski, Audrey Astori, Nicklas Bassani, Yibo Xue, Étienne Coyaud, Amber Yasmeen, Geneviève Morin, Anie Monast, Virginie Pilon, Nelly Sabbaghian, Lili Fu, Walter H. Gotlieb, Marie-Christine Guiot, Kitty Pavlakis, W. Glenn McCluggage, Alexander J. R. Bishop, Morag Park, Brian Raught, William D. Foulkes, Sidong Huang. Loss of SMARCA4 leads to RNA polymerase II pausing and blocks BRCA1 repair in small cell carcinoma of the ovary hypercalcemic type. (**In preparation for submission,** co-first author)
- Yibo Xue*, Jordan L Morris*, Kangning Yang*, **Zheng Fu**, Xianbing Zhu, Fraser Johnson, Brian Meehan, Leora Witkowski, Amber Yasmeen, Tunde Golenar, Mackenzie Coatham, Geneviève Morin, Anie Monast, Virginie Pilon, Pierre Olivier Fiset, Sungmi Jung, Anne V. Gonzalez, Sophie Camilleri-Broet, Lili Fu, Lynne-Marie Postovit, Jonathan Spicer, Walter H. Gotlieb, Marie-Christine Guiot, Janusz Rak, Morag Park, William Lockwood, William D Foulkes, Julien Prudent and Sidong Huang. SMARCA4/2 loss inhibits chemotherapy-induced apoptosis by restricting IP3R3-mediated Ca(2+) flux to mitochondria. ***Nature Communication.*** 2021, 12(1), 5404.
- Tim Kong, Ryuhjin Ahn, Rachel Bramley, Nikki Caitlin Cliffe, **Zheng Fu**, Geneviève Morin, Yibo Xue, Hellen Kuasne, Sungmi Jung, Anne Valerie Gonzalez, Sophie Camilleri-Broet, Marie-Christine Guiot, Morag Park, Josie Ursini-Siegel and Sidong Huang. CD44 Promotes PD-L1 Expression and Its Tumor-Intrinsic Function in Breast and Lung Cancers. ***Cancer Research***. 2020, 80(3), 444-457.
- Yibo Xue, Brian Meehan, **Zheng Fu**, Xue Qing D. Wang, Pierre Olivier Fiset, Ralf Rieker, Cameron Levins, Tim Kong, Xianbing Zhu, Geneviève Morin, Lashanda Skerritt, Esther Herpel, Sriram Venneti, Daniel Martinez, Alexander R. Judkins, Sungmi Jung, Sophie Camilleri-Broet, Anne V. Gonzalez, Marie-Christine Guiot, William W. Lockwood, Jonathan D. Spicer, Abbas Agaimy, William A. Pastor, Josée Dostie, Janusz Rak, William D. Foulkes, and Sidong Huang. SMARCA4 loss is synthetic lethal with CDK4/6 inhibition in non-small cell lung cancer. ***Nature Communication***. 2019, 10(1), 557.
- Tim Kong, Yibo Xue, Regina Cencic, Xianbing Zhu, Anie Monast, **Zheng Fu**, Virginie Pilon, Veena Sangwan, Marie-Christine Guiot, William D. Foulkes, John A Porco, Morag Park, Jerry Pelletier and Sidong Huang. eIF4A inhibitors suppress cell cycle feedback response and acquired resistance to CDK4/6 inhibition in cancer. ***Molecular Cancer Therapeutics***. 2019, 18(11), 2158-2170.