



## **MEDIA RELEASE FOR IMMEDIATE RELEASE**

**18 JULY 2016**

### **SINGAPORE SCIENTISTS DISCOVER NEW PATHWAYS LEADING TO CANCER PROGRESSION**

**SINGAPORE** – Scientists from A\*STAR’s Genome Institute of Singapore (GIS) and the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore came together to understand how EZH2, a cancer-promoting gene which is known to be involved in many types of cancers, is activated in breast cancer and lymphomas. The collaborative discoveries have been published in the journals, *PNAS* and *Blood*, respectively. The new findings pave the way to develop more effective treatment strategy for aggressive cancers associated with EZH2.

#### **Identifying new pathway of tumour-promoting EZH2 may lead to targeted therapies for aggressive breast cancer**

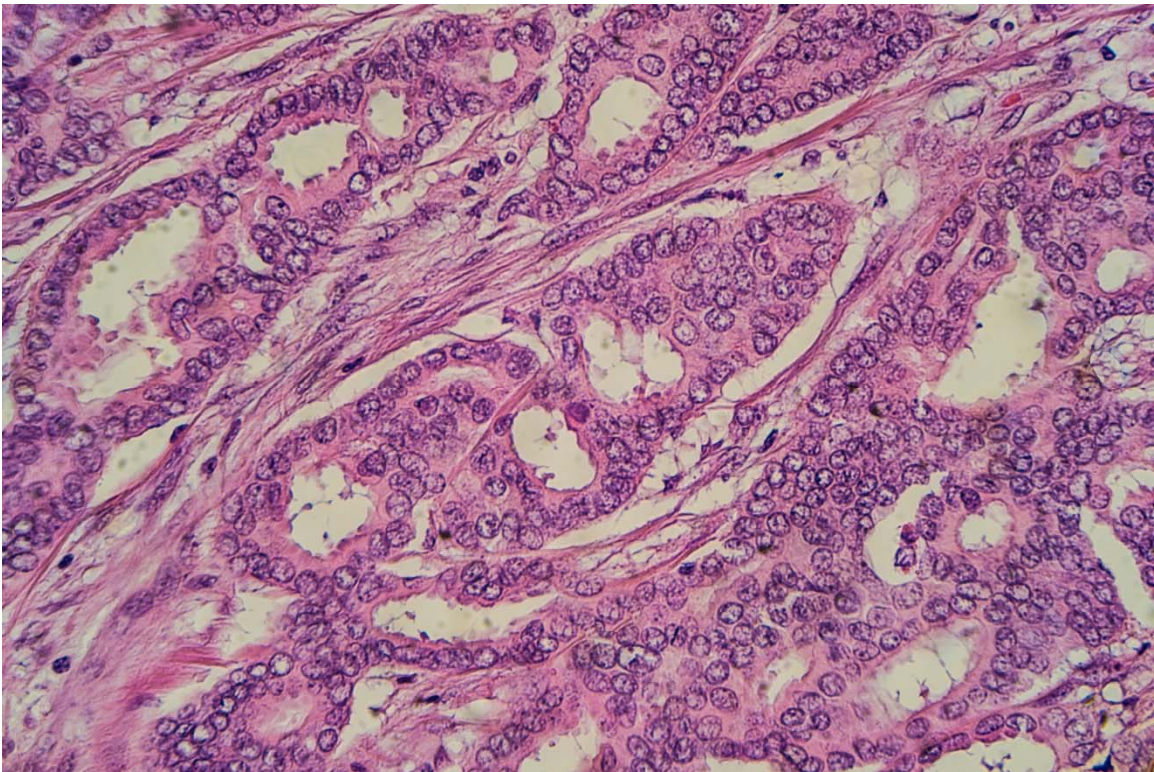
It is known that Polycomb repressive complex 2 (PRC2) and its catalytic component EZH2 are often overexpressed in multiple human malignancies, which promotes cancer. Interestingly, EZH2 or PRC2 also has a protective role against tumour formation in certain cancer types, including solid tumours and blood cancers. However, it is unclear how this paradoxical role of EZH2/PRC2 – as a tumour-promoting and tumour-suppressing gene – is regulated in cancer.

Researchers at the GIS, led by Prof Qiang Yu, found that the paradoxical role of EZH2/PRC2 in breast cancer can be switched when tumour cells are in hypoxic condition, a situation when fast growing solid tumour cells have been deprived of oxygen. The researchers found that when the tumour cells are supplied with sufficient oxygen, EZH2/PRC2 acts as a tumour suppressor to inhibit some of the genes involved in cancer invasion. However, this protective function against cancer progression is attenuated by hypoxia-inducible factor 1- $\alpha$  (HIF1- $\alpha$ ), which is activated during hypoxia. Instead, EZH2 engages another well-known tumour-promoting gene, FoxM1, to promote breast cancer invasion and this function no longer needs the catalytic function of EZH2. This study was published in *PNAS* in June 2016.

“Interestingly, this phenomenon seems to be more common in triple negative breast cancer (TNBC), as compared to other types of breast cancer,” said Prof Yu, the study's co-corresponding author and Senior Group Leader, Cancer Therapeutics & Stratified Oncology at the GIS. “We were among the first in the world to show a non-catalytic function of EZH2 in cancer a few years ago. Now that we identified a new pathway of EZH2 in promoting TNBC invasion, this finding may lead to a new treatment strategy to target TNBC, a disease in which effective treatments are currently lacking.”

Prof Wee Joo Chng, co-corresponding author of the study, and Deputy Director and Senior Principal Investigator at CSI Singapore, added, “The study fundamentally changes our understanding on the role of EZH2 in breast cancer. Apart from providing molecular insights into how EZH2/PRC2 is regulated in the tumour microenvironment, it also provides therapeutic implications: without a proper patient stratification, the catalytic inhibitor of EZH2 treatment may exacerbate the disease progression.”

## IMAGE



Invasive breast cancer cells

## Gaining deeper insights into the role on EZH2 in lymphomas

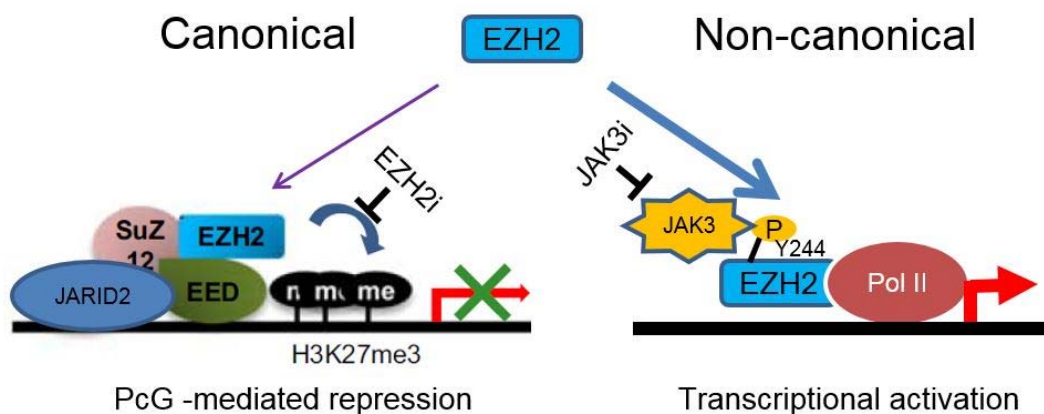
In a separate study on natural killer/T-cell lymphoma, a relatively rare lymphoma that is more common in Asia, the researchers found that EZH2 activity is regulated by a protein kinase called JAK3. Phosphorylation of EZH2 by JAK3 leads to dissociation of EZH2 from PRC2 complex, leading to a non-catalytic activity of EZH2 to promote cancer cell proliferation. Published in *Blood* in June 2016, the study was led by Prof Chng, whose team focuses on hematological oncology.

“As JAK3 is often mutated and activated in natural killer/T-cell lymphoma cells, this finding is particularly intriguing as it suggests a predominant non-catalytic function of EZH2 in JAK3 mutant natural killer/T-cell lymphoma. Our study also suggests that various oncogenic mutations may modify the function of EZH2, explaining the complex roles of EZH2 in cancer,” said Prof Chng, who is also Director of the National University Cancer Institute, Singapore (NCIS).

Together, these studies in both solid tumours and blood cancers raise concerns on the therapeutic application of EZH2 catalytic inhibitors, which are currently under active clinical development. Prof Chng added, “Moving forward, a biomarker strategy might be needed to ensure appropriate application of EZH2 inhibitors. This will help to identify tumours where EZH2 requires its catalytic activity or actually acting through non-catalytic function. At the same time, we need to develop therapies that can target the non-catalytic function of EZH2.”

GIS Executive Director Prof Huck Hui Ng said, “Findings like these highlight the importance of sustained collaborative research efforts within our community. Deeper insights into these aggressive cancers associated with EZH2 will help us better understand their progression, and in turn, open up new possibilities for more targeted therapies for the patients.”

### IMAGE



(Image Credit: Cancer Science Institute of Singapore at NUS)

Switch in EZH2 function in natural killer/T-cell lymphoma (NK lymphoma). JAK3 activation leads to phosphorylation (a type of protein modification) of EZH2. This phosphorylation event shifts EZH2 from its normal function of suppressing the expression of genes to a new function of activating genes which lead to the development of NK lymphoma. This study suggests that the use of JAK3 inhibitors can block EZH2 phosphorylation in NK lymphoma and lead to the killing of NK lymphoma cells.

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### Notes to Editor:

The research findings described in this media release can be found in the journals:

1. *PNAS*, under the title, “HIFI- $\alpha$  activation underlies a functional switch in the paradoxical role of Ezh2/PRC2 in breast cancer” by Sylvia Mahara<sup>a,b</sup>, Puay Leng Lee<sup>a</sup>, Min Feng<sup>a</sup>, Vinay Tergaonkar<sup>c,d,e</sup>, Wee Joo Chng<sup>b,f,g,1</sup>, and Qiang Yu<sup>a,h,i,j,1</sup>

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The *PNAS* paper can be accessed online from:

<http://www.pnas.org/content/early/2016/06/13/1602079113>

2. *Blood*, under the title, “EZH2 phosphorylation by JAK3 mediates a switch to non-canonical function in natural killer/T-cell lymphoma” by Junli Yan<sup>1</sup>, Boheng Li<sup>2</sup>, Baohong Lin<sup>3</sup>, Pei Tsung Lee<sup>1</sup>, Tae-Hoon Chung<sup>1</sup>, Joy Tan<sup>1</sup>, Chonglei Bi<sup>1</sup>, Xue Ting Lee<sup>1</sup>, Viknesvaran Selvarajan<sup>4</sup>, Siok-Bian Ng<sup>1,2,4</sup>, Henry Yang<sup>1</sup>, Qiang Yu<sup>5</sup>, Wee-Joo Chng<sup>1,2,3</sup>

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The *Blood* paper can be accessed online from:

<http://www.bloodjournal.org/content/early/2016/06/13/blood-2016-01-690701>

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### **About the Genome Institute of Singapore (GIS)**

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A\*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS

will pursue the integration of technology, genetics and biology towards academic, economic and societal impact.

The key research areas at the GIS include Human Genetics, Infectious Diseases, Cancer Therapeutics and Stratified Oncology, Stem Cell and Regenerative Biology, Cancer Stem Cell Biology, Computational and Systems Biology, and Translational Research.

The genomics infrastructure at the GIS is utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact.

For more information about GIS, please visit [www.gis.a-star.edu.sg](http://www.gis.a-star.edu.sg).

### **About the Agency for Science, Technology and Research (A\*STAR)**

The Agency for Science, Technology and Research (A\*STAR) is Singapore's lead public sector agency that spearheads economic oriented research to advance scientific discovery and develop innovative technology. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit society.

As a Science and Technology Organisation, A\*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by contributing to societal benefits such as improving outcomes in healthcare, urban living, and sustainability.

We play a key role in nurturing and developing a diversity of talent and leaders in our Agency and Research Institutes, the wider research community and industry. A\*STAR oversees 18 biomedical sciences and physical sciences and engineering research entities primarily located in Biopolis and Fusionopolis.

For more information on A\*STAR, please visit [www.a-star.edu.sg](http://www.a-star.edu.sg).

### **About Cancer Science Institute of Singapore**

CSI Singapore is a state-of-the-art university research institute affiliated with, and hosted at the National University of Singapore. It was established in 2008, with a "Research Centre of Excellence" grant, one of only five in Singapore, by the National Research Foundation and the Ministry of Education. Professor Daniel G.

Tenen, MD, a leader in the field of transcriptional regulation, hematopoiesis, and cancer, was named its founding director.

The institute is an anchor for research expertise in three broad programmes; Cancer Biology & Stem Cells, Experimental Therapeutics, and the RNA Biology Centre; these programmes form expansive platforms for CSI Singapore's focus on key cancer disease cancers in gastric, liver, lung and leukemia which are endemic in Asian populations. CSI Singapore aims to position Singapore as a global-leader in the field of Biomedical Sciences. Its mission: to conduct a multifaceted and coordinated approach to cancer research, extending from basic cancer studies all the way to experimental therapeutics and in so doing improve cancer treatment.

For more information on CSI Singapore, visit [www.csi.nus.edu.sg/ws](http://www.csi.nus.edu.sg/ws)