CANCER SCIENCE INSTITUTE OF SINGAPORE

IN THE SPOTLIGHT

mid-year wrap-up

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CSI Singapore's second year...

Exhibiting at AACR

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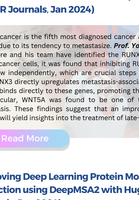
we had the honour of hosting..



EMBO Chromatin Biology in Cancer Workshop in April

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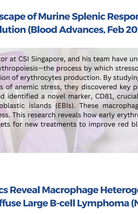
A step forward in CSI's philanthropic mission:

Diana Koh Breakthroughs in Cancer Learning Series



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Research Highlights

Aberrant Upregulation of RUNX3 Activates Developmental Genes to Drive Metastasis in Gastric Cancer (Cancer Research Communications - AACR Journals, Jan 2024)

Gastric cancer is the fifth most diagnosed cancer and the third leading cause of cancer-related deaths due to its tendency to metastasize. ***Prof. Yoshiaki Ito***, Senior Principal Investigator at CSI Singapore and his team have identified the RUNX3 protein as a key driver of this process. In gastric cancer cells, it was found that inhibiting RUNX3 reduces their ability to migrate, invade, and grow independently, which are crucial steps in metastasis. Further investigation revealed that RUNX3 directly upregulates metastasis-associated genes, including WNT5A, CD44, and VIM. RUNX3 binds directly to these genes, promoting their expression and thus aiding cancer spread. In particular, WNT5A was found to be one of the main effectors of RUNX3 in promoting metastasis. These findings suggest that an improved understanding of RUNX3 regulation of WNT5A will yield insights into the treatment of late-stage gastric cancer.

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Improving Deep Learning Protein Monomer and Complex Structure Prediction using DeepMSA2 with Huge Metagenomics Data (Nature Methods, Jan 2024)

A team led by ***Prof. Yang Zhang***, Senior Principal Investigator at CSI Singapore, reports DeepMSA2, a new pipeline that significantly improves protein structure predictions through more advanced multiple-sequence alignments (MSAs) construction. Leveraging iterative alignment searches through genomic and metagenome sequence databases, DeepMSA2 excels in balancing alignment coverage and diversity, leading to more precise predictions of protein structures. DeepMSA2's integration with the AlphaFold2 modelling approach has shown remarkable improvements. In large-scale tests, it achieved substantial gains in predicting complex protein structures, outperforming current state-of-the-art methods in the CASP15 experiment. By improving the accuracy of protein structure predictions, DeepMSA2 opens new avenues for understanding protein functions, interactions, and mechanisms, which are crucial for drug discovery and disease treatment.

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Deciphering the Regulatory Landscape of Murine Splenic Response to Anemic Stress at Single-cell Resolution (Blood Advances, Feb 2024)

Prof. Tashia Suda, Senior Principal Investigator at CSI Singapore, and his team have uncovered new molecular mechanisms behind stress erythropoiesis—the process by which stressors, such as hemolysis and bleeding, may cause disruption of erythrocytes production. By studying spleen tissue from mice subjected to different types of anemic stress, they discovered key phases in the development of early red blood cells and identified a novel marker, CD81, crucial for the function of terminal maturation of erythroblastic islands (EBIs). These macrophages help support red blood cell production during stress. This research reveals how early erythroid cells respond to stress, highlighting potential targets for new treatments to improve red blood cell production in anemia and related conditions.

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Spatially-resolved Transcriptomics Reveal Macrophage Heterogeneity and Prognostic Significance in Diffuse Large B-cell Lymphoma (Nature Communications, Mar 2024)

Led by **Asst. Prof. Anand Jeyaseharan**, Principal Investigator and Facility Head of Microscopy and Multiplex Assay (MMA) Core at CSI Singapore, his team provided new insights into the role of macrophages, which are immune cells abundantly present in the tumour microenvironment of diffuse large B-cell lymphoma (DLBCL). DLBCL is the most common subtype of non-Hodgkin lymphoma in adults, with a high relapse rate after initial treatment. By using advanced digital spatial profiling, the team identified six distinct macrophage signatures linked to specific regions within the tumour and patient outcomes. This highlights the importance of macrophages in the fight against lymphoma. Mapping these immune cells and understanding their specific roles within the tumour environment has provided a framework to further evaluate the biological and clinical relevance of macrophage subtypes in lymphoma.

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A Glycolytic Metabolite Bypasses "two-hit" Tumor Suppression by BRCA2 (Cell, Apr 2024)

Prof. Ashok Venkitaraman, Director of CSI Singapore, and ***Dr. Li-Ren Kong***, Senior Research Scientist, led a team of researchers to uncovering a novel mechanism by which the glycolytic metabolite methylglyoxal (MGO), a byproduct of glucose breakdown, can transiently disable the tumour-suppressing function of the BRCA2 protein. As such, individuals with high MGO levels—who have been found to be those with conditions like diabetes, obesity, and poor diet—may have an elevated cancer risk. This discovery also offers new insights into how cancer can develop even without the complete inactivation of both BRCA2 gene copies, traditionally thought necessary according to Knudson's "two-hit" hypothesis, which states that for a tumour suppressor gene like BRCA2 to lose its cancer-preventing ability, both copies of the gene must be inactivated. However, their latest research indicates that MGO can temporarily bypass this requirement by causing BRCA2 protein degradation, leading to cancer-associated mutations even when only one copy of the BRCA2 gene is affected. The team also found that MGO can temporarily inactivate such cancer-preventing genes, suggesting that repeated episodes of poor diet or uncontrolled diabetes can 'add up' over time to increase cancer risk. This new knowledge is likely to be influential in changing the direction of future research in the area of lifestyle habits and cancer.

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A PRMT5-ZNF326 Axis Mediates Innate Immune Activation Upon Replication Stress (Science Advances, Jun 2024)

Asst. Prof. Anand Jeyaseharan, Principal Investigator and Facility Head of Microscopy and Multiplex Assay Core at CSI Singapore has led a team, together with co-author ***Asst. Prof. Dennis Kappei***, unveiling critical findings on the role of protein arginine methyltransferase 5 (PRMT5) in mediating DNA replication stress (RS) and its implications for cancer treatment. RS, a common phenomenon in cancer development, disrupts DNA replication, causing damage and genomic instability. The research identified PRMT5 as a crucial player in activating interferon-stimulated genes (ISGs) during RS. PRMT5 also targets the zinc finger protein ZNF326, which is essential for the ISG response. This interaction involves a specific modification called symmetric dimethylarginine (SDMA), which PRMT5 applies to ZNF326 during RS. Upon RS induction, PRMT5 relocates from the cytoplasm to the nucleus, increasing SDMA levels and enhancing ISG expression. This study highlights PRMT5 as a significant regulator of immune signalling in response to DNA replication stress, opening up new avenues for cancer treatment strategies. By understanding and manipulating PRMT5 activity, there is potential to enhance the efficacy of existing therapies and develop novel approaches to combat cancer more effectively.

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