

**15 June 2009**

**PRESS RELEASE**

**NOVEL DISCOVERY IN DENDRITIC CELL SIGNALLING  
PATHWAYS PAVE THE WAY FOR NEW THERAPEUTIC  
TARGETS**

*Independent activation of CD14 through the NFAT pathway potentially heralds new ways to treat related conditions such as sepsis, heart failure and lessen side effects of immunosuppression*

1. Scientists from A\*STAR's Singapore Immunology Network (SIgN) and the University of Milano-Bicocca, Italy, have discovered another signaling pathway for the activation and apoptosis, or programmed cell death, of dendritic cells<sup>1</sup>. This discovery was published in the advanced online publication of *Nature* on 15 Jun 2009.
2. Led by Prof Paola Castagnoli, Scientific Director of SIgN and Associate Prof Francesca Granucci of the University of Milano-Bicocca, the team discovered that the well-studied immune receptor called CD14 in dendritic cells could be independently activated by bacterial fragments called liposaccharides or LPS. Once activated, the CD14 would initiate the NFAT<sup>2</sup> or nuclear factor of activated T-cells pathway, which would then activate the dendritic cells to trigger off the body's immune response. The scientists also discovered that the entire activation by CD14 was necessary to cause apoptosis.

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<sup>1</sup> Dendritic cells (DCs) are immune cells and form part of the mammalian immune system. Their main function is to process antigen material and present it on the surface to other cells of the immune system, thus functioning as antigen-presenting cells.

<sup>2</sup> NFATs are a family of transcription factors that have been shown to be the effectors in the immune response. They are involved in activities such as cell expansion and the release of immunological-related molecules from immune cells.

3. Dendritic cells are the frontline sentinels in the body's defence mechanisms and they are potent inducers of an immune response against invading pathogens. Activated dendritic cells have a short life span, and scientists have observed that they undergo apoptosis in order to protect the body from the over-stimulation of the immune system, which could result in autoimmunity. This behaviour is supported by Prof Castagnoli and Associate Prof Granucci's findings.

4. "What is exciting is the link between CD14 activation and the NFAT pathway," explained Prof Castagnoli. "These findings have identified novel potential targets for the development of therapeutics against diseases that are involved with the CD14-NFAT pathway. For example, overexpression of CD14 has been associated with sepsis and chronic heart failure. New drugs that can modulate the CD14-NFAT pathway could provide treatments for such serious medical conditions."

5. Said Prof Philippe Kourilsky, Chairman of SIgN, "Prof Castagnoli has been contributing greatly to the area of dendritic cell regulation and this latest finding has contributed towards the growing body of knowledge on immunology. I am confident that the continued efforts by the team in SIgN and their partners in the University of Milano-Bicocca would spawn more innovative discoveries in the field of dendritic cell immunology."

6. The knowledge gleaned through the findings could also contribute to the creation of immunosuppressive agents that target NFAT activity. Currently, drugs<sup>3</sup> such as cyclosporine A and FK506, which are widely used in organ transplantation, work by shutting off a protein called calcineurin, which is needed for triggering the immune response and activating the NFAT pathway. However, these drugs also cause adverse side effects such as kidney damage. Agents that

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<sup>3</sup> Datamonitor report (2006): Market value for immunosuppressants used in transplantation is set to grow to US\$4.3 billion by 2015.

interfere with NFAT specifically in lymphocytes but not in dendritic cells could potentially have yield immunosuppressive activity but with reduced side effects leading to prolonged graft survival.

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## AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH

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### About the publication:

The research findings described in the press release can be found in the article **“CD14 regulates the dendritic cell life cycle after LPS exposure through NFAT activation”**, as an advanced online publication in Nature, 15 June 2009.

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### **About the Singapore Immunology Network (SIgN)**

[www.sign.a-star.edu.sg](http://www.sign.a-star.edu.sg)

SIgN, officially inaugurated on 15 January 2008, is a research consortium under A\*STAR's Biomedical Research Council aimed at building on the strengths of the existing immunology research groups at A\*STAR, as well as expanding and strengthening the immunology research expertise in Singapore. SIgN's objectives include coordinating basic, translational and clinical research needed to establish immunology as a core capability in Singapore; establishing productive links with local initiatives within Biopolis and across Singapore; obtaining international recognition while establishing relationships with leading institutions in the world; and building up a strong platform in basic human immunology research for better translation of results into medical applications.

### **About the Agency for Science, Technology and Research**

[www.a-star.edu.sg](http://www.a-star.edu.sg)

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### **About the The University of Milano-Bicocca**

[www.unimib.it](http://www.unimib.it)

The University of Milano-Bicocca strongly believes in the potential of its students and in combining studies with active social involvement. The University has eight faculties covering humanities and science subjects, as well as a School of Medicine, which offer undergraduate and graduate programmes for students to acquire specialised skills. The University of Milano-Bicocca has a significant role in the international scientific community and has actively participated in European exchanges and research projects, as well as organised international PhD programmes in collaboration with foreign universities and research centres.