



Singapore  
Immunology Network

## PRESS RELEASE

9 Oct 2009

### REDEFINING THE MOLECULAR SIGNATURE OF P53

#### ***A\*STAR scientists discover widely sought molecular key to understanding p53 – the gene nemesis of cancer***

1. Scientists at A\*STAR's Singapore Immunology Network (SIgN), led by Prof Ren Ee Chee, have made a landmark discovery of how the master gene regulator, p53 could switch a gene in a cell 'on' or 'off' by recognising specific sequences of nucleotides in the gene's DNA known as 'response elements'. The switching on and off of a gene, or gene regulation, serves to activate or repress the production of proteins, which are involved in virtually every process vital to life<sup>1</sup>. In particular, since p53 undergoes mutations or deletions in over 50 percent of all cancers, the finding sheds more light on how cancer develops, and provides more intelligence in the global battle against this complex disease.

2. p53 response elements have theoretically 4<sup>10</sup> or over one million possible combinations, making them very difficult to decipher. In fact, predicting if p53 actually switched a gene on or off had been an elusive goal until this recent discovery. But the scientists at SIgN applied a systematic approach to analyse known p53 response elements and successfully identified a simpler two-nucleotide core sequence which was sufficient to provide an accurate prediction. Their findings were published this August in the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*<sup>2</sup>, and highlighted in *Nature Reviews Cancer*<sup>3</sup>, the highest-impact monthly review journal in the field of oncology.

3. Prof Sir David Lane, Chief Scientist of A\*STAR and a co-discoverer of p53<sup>4</sup> attributed the group's success to a combination of sound thinking and the right opportunities. He said, "The findings are truly intriguing. The precise interaction of p53 with its response elements has been studied for some 20 years, and while we have a good understanding of how p53 turns on genes, no clear answer as to the equally important question of how p53 turns off or 'represses' genes has emerged. The SIgN group's identification of a bona fide 'repressive' response element has

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<sup>1</sup> These processes range from catalysing biochemical reactions that break down our food and maintaining cell structure to cell signalling and effecting our immune responses.

<sup>2</sup> Bei Wang, Ziwei Xiao, Ee Chee Ren. "Redefining the p53 response element", *Proc Natl Acad Sci USA* 2009, 106: 14373-14378.

<sup>3</sup> Nicola McCarthy. "Transcription: Reaching a consensus", *Nature Reviews Cancer* 9, 689 (October 2009) AOP | doi:10.1038/nrc2743

<sup>4</sup> Arnold Levine, Sir David Lane and William Old first discovered p53 in 1979.

provided the missing piece which has eluded p53 researchers for a long time, as well as a definitive key with which to perform future studies. I expect their findings to have very positive and significant impact on the progress of biomedical research and to help define this vital tumour-fighting pathway.”

4. Interestingly, the discovery was made by a group focusing on immunology rather than molecular biology or genetics. Said Prof Ren, “We had been studying a metastasis gene which is upregulated in liver cancer called Lasp-1<sup>5</sup>. As it happened to be under the control of p53, we wanted to determine in detail the role of p53. However we quickly realised that the existing literature was not helpful enough as there were ambiguities over how p53 exerts control over specific genes.” This led to the SlgN researchers’ identification of the definitive two-nucleotide sequence, and subsequent establishment of a general set of rules to predict the roles of nucleotides within a response element, which enabled them to correct those of 20 response elements (out of 162 assessed). Added Prof Ren, “Our findings illustrate how exciting science can be, when innovative discoveries can arise from unexpected sources. They are also proof that frequently in nature, what may seem very complicated at first eventually turns out to be simple and elegant.”

5. Praising the group’s efforts, Prof Paola Castagnoli, Scientific Director of SlgN said, “This study has significant and far-reaching implications. It will allow for the confirmation of many genes involved in the complex pathways of p53 and, potentially, uncover new p53 pathways. It also clarifies our understanding of which cellular pathways are damaged by p53 mutations and points to areas where new cancer targets might be discovered. I am proud of the group’s achievements thus far, and look forward to more exciting findings from them.”

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

SlgN, officially inaugurated on 15 January 2008, is a research consortium under A\*STAR’s Biomedical Research Council. It is 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. SlgN’s objectives include coordinating basic, translational and clinical research needed to establish immunology as a core capability in Singapore. The major focus areas of research at

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<sup>5</sup> Wang B, Feng P, Xiao Z, Ren EC. “LIM and SH3 protein 1 (Lasp1) is a novel p53 transcriptional target involved in hepatocellular carcinoma”, *J Hepatol* (2009) 50:528–537.

SIgN are Infection and Inflammation, in which SIgN researchers investigate immune responses and regulation in disease-specific contexts. Through this, SIgN aims to build up a strong platform in basic human immunology research for better translation of research findings into clinical applications. SIgN also sets out to establish productive links with local initiatives within Biopolis and across Singapore, as well as to obtain international recognition as a leading immunology research hub while establishing relationships with the best institutions in the world.

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

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

The Agency for Science, Technology and Research (A\*STAR) is the lead agency for fostering world-class scientific research and talent for a vibrant knowledge-based and innovation-driven Singapore. A\*STAR oversees 14 biomedical sciences, and physical sciences and engineering research institutes, and seven consortia & centre, which are located in Biopolis and Fusionopolis, as well as their immediate vicinity.

A\*STAR supports Singapore's key economic clusters by providing intellectual, human and industrial capital to its partners in industry. It also supports extramural research in the universities, hospitals, research centres, and with other local and international partners.

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