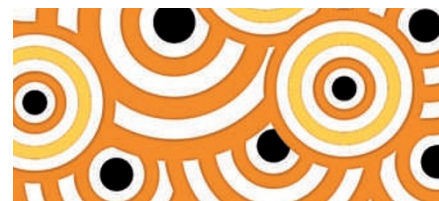


Drug discovery targeting apoptosis

As part of this month's special focus on apoptosis, two researchers in the field discuss their role in the development of therapeutic strategies to target apoptosis.



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Two decades ago, a link between apoptosis and cancer was recognized, following the discovery that the protein BCL-2 specifically blocked apoptotic death of B cells in follicular lymphoma. Now, there is widespread interest in anticancer agents that trigger the apoptosis of tumour cells, and the BCL-2 family is among the most prominent targets, says David Huang, Principal Research Fellow at the Walter and Eliza Hall Institute of Medical Research (WEHI), Melbourne, Australia.

"We are focused primarily on elucidating how the interactions between the proteins of the BCL-2 family determine whether a cell lives or dies, how this is deregulated in diseases such as cancers and exploiting our knowledge of the BCL-2-regulated pathway for developing better

therapeutics," he says. Complementing this research in cellular and molecular biology, he also works extensively with Peter Colman, who leads a team at WEHI that is focused on applying structural biology and medicinal chemistry to identify and investigate agents targeting the BCL-2 pathway as potential anticancer drugs (see page 989).

Huang first became involved in the oncology field in the 1980s as part of his specialist training following his undergraduate medical degree at the Royal Free Hospital School of Medicine, University of London, UK. Attracted by the possibility of basic research that could make a difference for patients with cancer, he then studied Ras signalling with Chris Marshall at the Institute of Cancer Research, London. This experience convinced him to continue with research in academia, and in 1994 he moved to WEHI for a postdoc with Suzanne Cory — now Director of WEHI — who, together with Jerry Adams, David Vaux and Andreas Strasser, made the pioneering discovery of the importance of BCL-2 in cancer.

Here, his previous experience has proved valuable in exploiting the therapeutic potential of this discovery, and led him to establish the

group he leads now at WEHI. "I anticipated that our knowledge of this pathway and my clinical training in haematology and oncology would place us in an ideal position to evaluate molecules that trigger apoptosis — especially compounds that mimic the action of the BH3-only proteins, which are the physiological antagonists of BCL-2," explains Huang. "Furthermore, I thought such reagents could be useful tools for our biological studies."

This year, WEHI has also entered into a research partnership with Abbott and Genentech, which together with the collaborations that Huang has with colleagues such as Peter Colman and Andreas Strasser, is further aiding the translation of biological insights into drugs that target the BCL-2 family. "The opportunity to lead a multiparty and multidisciplinary project, and work in a team with top-rate colleagues, is something that I particularly enjoy," says Huang. And for those keen to find a position like his, he highlights the importance of such people in his career. "I have been fortunate to have outstanding mentors, both in the clinical (Lucio Luzzatto and Victor Hoffbrand) and scientific (Chris Marshall, Suzanne Cory and Jerry Adams) fields," he concludes.



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The isolation of cytolytic immunoglobulin G (IgG) antibodies against the cell-surface protein human Fas in the late-1980s was another of the pioneering discoveries in the field of apoptosis, and led to the characterization of the key role of this tumour-necrosis factor (TNF) receptor family member in the regulation of the apoptotic process. The goal of translating these findings into potential therapeutics first brought Kimihisa Ichikawa — now Director of a group focusing on therapeutic antibodies at Daiichi Sankyo — into the field of apoptosis drug discovery in the early 1990s.

"At the time, Sankyo was interested in targeting Fas as a potential therapeutic strategy for rheumatoid arthritis," recalls Ichikawa. "And in collaboration with Professor Shin Yonehara at Kyoto University, who discovered the Fas molecule, we identified agonistic

anti-human Fas IgG antibodies that were able to induce apoptosis of synovial-cell-activated lymphocytes."

This research represented a realization of Ichikawa's initial goals after joining Sankyo in 1990 following 6 years of studying the molecular genetics of yeast at the Advanced Industrial Science and Technology institute, Tsukuba, Japan. "I became very interested in the role of cell death — for example, in the immune system — and I wanted to apply my research to a cure for diseases," he explains.

Although the Fas programme did not ultimately result in a drug candidate, as agonistic Fas antibodies were found to cause safety issues, Sankyo continued with research related to the role of apoptosis in disease. For example, another collaboration in this field in which Sankyo was closely involved began in 1994 with Professor William Koopman, Chairman of the Department of Medicine at the University of Alabama, Birmingham (UAB), USA.

Sankyo sent visiting researchers to UAB to promote the collaboration, and so Ichikawa had the opportunity to continue studying the molecular mechanisms of apoptosis in the laboratory of Associate Professor Tong Zhou at the Department of Clinical Immunology and

Rheumatology from 1998 to 2000. This research pursued a strategy based on targeting another member of the TNF receptor family — DR5, a receptor for TNF-related apoptosis-inducing ligand (TRAIL). "We succeeded in obtaining an anti-DR5 antibody that had a strong ability to induce apoptosis against several cancer cells and rheumatoid arthritis synovial fibroblast cells, but without hepatocyte cytotoxicity," says Ichikawa. A humanized version of this antibody is now in early clinical trials for cancer.

After the disappointment with the Fas programme, reaching this stage with another therapeutic antibody is something that Ichikawa is particularly happy to have achieved, and he attributes this success to two key lessons: "First, we should look at the raw data without being constrained by the results of others, and second, we should not be afraid to take a risk with new challenges, such as an experimental trial," he says. "I believe that we will also be able to find useful therapeutic antibodies against other target molecules in cancer by applying these two lessons."

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