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Insights from Bcl-2 and Myc: Malignancy Involves Abrogation of Apoptosis as well as Sustained Proliferation[1]

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It is indeed an enormous honor and pleasure to introduce Drs. Suzanne Cory and Stanley Korsmeyer, this year's winners of the Mott Prize.

I think no one would question the view that their seminal experiments radically changed the way we think about the process of cancer. If we look back about 10 or 15 years, programmed cell death was a very interesting phenomenon, but we had no idea what this meant in terms of cancer, although suggestions were made. It was certainly interesting in terms of development, but we had no idea about the mechanisms involved.

Of course, all this has changed enormously over the last decade, and in terms of cancer particularly, through the seminal contributions of Suzanne Cory and Stan Korsmeyer and their colleagues. Now we know that not only do cancer cells have to escape proliferation controls, they also have to abolish cell death pathways. Not only is this incredibly important for our understanding of the mechanisms underlying cancer, but the way we think about therapy has been radically altered.

And as was said already, it is very exciting and a great coincidence, perhaps, that the Sloan Prize this year is awarded to Bob Horvitz who has used very elegant genetics to dissect cell death pathways in C. elegans. And, of course, what is particularly exciting is the convergence of the studies on bcl-2 in humans and mice with those in C. elegans to show these pathways are conserved. What an exciting combination of studies.

So, now, to introduce Dr. Suzanne Cory. Suzanne has made many seminal contributions over the years, and I would say one thing that has typified her approach has been to use pioneering transgenic experiments to dissect gene interaction in cancer—together with her collaborator over many years, Dr. Jerry Adams, who is here in the audience.

Suzanne got her degree at the University of Melbourne in Australia and then made a very visionary and wise choice in coming to Britain to do her Ph.D. I wasn't going to crack any jokes, just a slight one. . . to do her Ph.D., as she says, in the Department of One Called Francis Crick.

She survived that experience and came out with a very important paper on sequencing transfer RNA which was a breakthrough at the time.

After a productive post-doctoral period in Switzerland, Suzanne then set up a joint laboratory with Jerry Adams in the Walter and Eliza Hall Institute in Melbourne. First, they concentrated on normal B cell development and identified immunoglobulin gene clusters, showed that deletions were important in rearranging those clusters in B cells to bring about the formation of the immunoglobulin genes, and then they moved to pathology and made a very important observation, that in mouse plasmacytomas and Burkitt's lymphoma, the myc gene is deregulated by translocations.

However, they went one step further than that. They actually recreated the myc rearrangements in transgenic animals which then developed lymphomas, proving causality which is a very important thing we all have to do.

The next move that they made was to use transgenic approaches to look at the interaction of different oncogenes and how they cooperate in oncogenesis in mice. Then, in terms of this particular prize, the seminal finding, after the isolation of the bcl-2 oncogene by Stan Korsmeyer and other groups, was the study published in Nature in 1988. Together with David Vaux and Jerry Adams, Suzanne Cory showed that the introduction of bcl2 into B-cells in culture increased their survival. This was, of course, a very, very important observation.

Suzanne then went on to pursue aspects of the biology of bcl-2, showing for example that bcl-2 can cooperate with myc in oncogenesis in transgenic animals, and has continued to study the function of bcl-2 and interacting partners.

Suzanne is now the director of the Walter and Eliza Hall, a very famous, wonderful institute in Melbourne, and she has had many honors over the years, including election to the Royal Society in London in 1992, and foreign membership of the National Academy of Sciences in 1997. She has also won the Burnet's Medal and shared the 1998 Australia Prize of the Australian Academy of Sciences.

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Abstract

The chromosome translocations typifying Burkitt's lymphoma and follicular lymphoma deregulate very different oncogenes, *myc* and *bcl-2*. Transgenic mouse models have illuminated how each contributes to lymphomagenesis. Constitutive *myc* expression provokes sustained cell proliferation and retards differentiation. However, the resulting expansion in cell number is self-limiting, because the cells remain dependent on cytokines and undergo apoptosis when these become limiting. In contrast, *bcl-2* is the prototype of a new class of oncogene that enhances cell survival but does not promote proliferation. Coexpression of these genes leads to the rapid transformation of lymphocytes, probably because each can counter an antioncogenic aspect of the other. Several close homologues of Bcl-2 also enhance cell survival and are thus potential oncogenes; each is essential for maintenance of particular major organs. More distant Bcl-2 relatives instead promote apoptosis and can be regarded as tumor sup-

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[3] Co-recipient of the Mott Prize along with Stanley Korsmeyer, whose article can be found on pages 1693s–1700s of this supplement.

Introduction of Suzanne Cory

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