### Growth Factors / Receptors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Clone</th>
<th>Source</th>
<th>Isotype</th>
<th>Works in</th>
<th>Epitope</th>
<th>Quantity</th>
<th>Cat. No.</th>
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<tbody>
<tr>
<td>TGFα</td>
<td>213-4.4</td>
<td>Mouse</td>
<td>IgG2a</td>
<td>Human</td>
<td>Residues 34-50</td>
<td>100 μg</td>
<td>GF10</td>
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<tr>
<td>TGFβ3</td>
<td>236-5.2</td>
<td>Mouse</td>
<td>IgG1</td>
<td>Human</td>
<td>Not Known</td>
<td>100 μg</td>
<td>GF16</td>
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<tr>
<td>bFGF</td>
<td>236-5.2</td>
<td>Polyclonal</td>
<td>IgG</td>
<td>Human</td>
<td>Residues 40-63</td>
<td>100 μg</td>
<td>PC16</td>
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<tr>
<td>EGF</td>
<td>236-5.2</td>
<td>Polyclonal</td>
<td>IgG</td>
<td>Human</td>
<td>Not Known</td>
<td>100 μg</td>
<td>PC08</td>
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<tr>
<td>PDGF</td>
<td>528</td>
<td>Rabbit</td>
<td>IgG2a</td>
<td>Human</td>
<td>Residues 101-116</td>
<td>100 μg</td>
<td>PC01</td>
</tr>
<tr>
<td>EGFR (c-neu)</td>
<td>3B5</td>
<td>Mouse</td>
<td>IgG1</td>
<td>Human, Murine</td>
<td>C-Terminal</td>
<td>100 μg</td>
<td>GR01</td>
</tr>
<tr>
<td>Insulin R</td>
<td>29B4</td>
<td>Mouse</td>
<td>IgG2b</td>
<td>Human, Rodent</td>
<td>Internal</td>
<td>100 μg</td>
<td>GR07</td>
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<tr>
<td>PDGFR</td>
<td>3B5</td>
<td>Mouse</td>
<td>IgG1</td>
<td>Human</td>
<td>Not Known</td>
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<td>GR14</td>
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<td>IGFR</td>
<td>2B2A6</td>
<td>Mouse</td>
<td>IgG1</td>
<td>Human</td>
<td>Not Known</td>
<td>100 μg</td>
<td>GR11</td>
</tr>
</tbody>
</table>

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In 1971, after pursuing a long-standing interest in tumor regression, Alastair Currie drew together in Aberdeen, Scotland, a small team to study the biology of cell death in a number of mammalian systems. This issue's cover of Cancer Research focuses on this group, which includes Dr. Currie, his Ph.D. student Andrew Wylie, and John Kerr, a visiting fellow from Brisbane, Australia, who had already described the ultrastructure of a form of single cell death sometimes observed in tissues exposed to low concentrations of xenobiotics or to mild hyperthermia. The result of their interaction was the description of a distinctive series of structural changes that appear coordinately when the death of vertebrate cells appears to be triggered by internal stimuli, rather than merely by major perturbation of the environment. In their paper (Br. J. Cancer, 26: 239–257, 1972), they named this widespread mode of cell death “apoptosis.” The footnote from that paper is worth reproducing because it describes both the origin of the word and the suggested pronunciation:

We are most grateful to Professor James Cormack of the Department of Greek, University of Aberdeen, for suggesting this term. The word apoptosis is used in Greek to describe the “dropping off” or “falling off” of petals from a flower or leaves from a tree. To show the derivation clearly, we propose that the stress be placed on the penultimate syllable, the second half of the word being pronounced like “pōsōs” (with the “p” silent), which comes from the same root “to fall” and is already used to describe the drooping of the upper eyelid.

The concept and significance of apoptosis were slow to be accepted, and only a handful of papers in the 1970s cited this seminal work. In 1980, these same authors published a review in the International Review of Cytology (68: 251–306), in which they commented about this lack of interest in the subject:

The possibility that such “normal cell death” might involve active self destruction rather than passive degeneration has been virtually ignored; most regard the changes that take place in all dying cells as being akin to the postmortem autolysis of a corpse, a process hardly likely to stimulate enthusiastic investigation.

Back in Brisbane, Kerr continued to document the ultrastructure of apoptosis in a variety of circumstances, among them the death of tumor cells exposed to chemotherapeutic agents and immunological attack. The Scottish group, now in Edinburgh, Scotland, and led by Wyllie from the mid-1980s, described much of the underlying cell biology, including intranucleosomal chromatin cleavage, a specific glycan recognition system; the occasional dependence of the process on protein and RNA synthesis; the potential role of intracellular calcium; and most recently, the significance of c-myc and p53 in the initiation of the process.

Since 1990, there has been an explosion of interest in apoptosis. Probably the major reason for excitement in this area arose from studies focusing on the genetics of the process. New genes have been identified which can either turn on apoptosis or prevent it, and of perhaps greatest interest is the fact that oncogenes and tumor suppressor genes appear to be regulators of the process. If any one observation can be credited with stimulating this interest, it is probably the observation made in Stanley Korsmeyer's laboratory in St. Louis, MO, that the bcl-2 gene isolated from the breakpoint in follicular B-cell lymphoma could prevent cells from undergoing apoptosis (Nature (Lond.), 346: 334–336, 1990). However, inasmuch as citations to this paper could not have appeared until 1991, it is evident that this paper was not the only impetus for the resurgence of interest in apoptosis.

It has subsequently been demonstrated that bcl-2 can elicit resistance to many anticancer agents and, therefore, has a major impact on therapeutic efficacy. bcl-2 is one of a family of proteins with conserved sequence motifs; the other proteins include the ced-9 gene of the nematode Caenorhabditis elegans, the 19-kilodalton E1B protein of adenovirus, the BHRF-1 protein of the Epstein-Barr virus, and the mcl-1 protein expressed during myeloid cell differentiation. The function of these proteins remains elusive. Other proteins, such as ras and raf, which are involved in intracellular signal transduction, can also prevent cells from undergoing apoptosis. In contrast, expression of c-myc or wild-type p53 can induce apoptosis under certain circumstances. Identification of the involvement of these genes represents only one aspect of studies in apoptosis. The AACR has organized a Special Conference on Cell Death in Cancer and Development to be held in Chatham, MA, in October 1993 to discuss the multiple directions that this area of research is now taking. Andrew Wyllie will be presenting the Keynote Address.

Alastair R. Currie (right) graduated in science in 1941 and in medicine in 1944 from the University of Glasgow, Scotland. He led in succession the Division of Pathology at the Imperial Cancer Research Fund Laboratories, Oxford, England; the Department of Pathology at Aberdeen University Medical School; and the Department of Pathology at the University of Edinburgh. Through chairmanship of major scientific committees in the United Kingdom, including the Medical Research Council's Cell Board and the Scientific and Executive Committees of the Cancer Research Campaigns, he exerted a profound influence on the priorities of cancer research in Great Britain. His distinguished service to medical sciences led to many honors, including a knighthood in 1979. He is currently president of the Royal Society of Edinburgh, and although in retirement from university life, he continues to be a source of inspiration to his many students. John Kerr (left) graduated in medicine from the University of Queensland, Australia, in 1958. From 1962 to 1966 as Sir Roy Cameron's Ph.D. student in London, he first observed the characteristic ultrastructure of injured cells that was later to be recognized as apoptosis. In 1965, he returned to Queensland as Senior Lecturer, Reader, and since 1974, he has served as Professor of Pathology at the University of Queensland and adjunct Senior Principal Research Fellow at the Queensland Institute of Medical Research.

Andrew H. Wylie (center) graduated in medicine from the University of Aberdeen in 1967 and completed his Ph.D. under Professor Currie. Following postdoctoral training at Cambridge, England, he became Senior Lecturer, Reader, and in 1992, Professor of Experimental Pathology in the Department of Pathology, University of Edinburgh. A search of the Science Citation Index (bottom) was made to determine the citation frequency of the original 1972 paper defining apoptosis, and of the 1980 review on the subject. The bar graph displays the number of papers containing the word “apoptosis” or “apoptotic” in its title as determined from the Science Citation Index. Although there are many other papers that used different descriptors for this process, the papers retrieved by this search provide an accurate reflection of the interest in apoptosis since the term was first introduced.

We thank Andrew Wyllie for his contribution to the information presented in this legend.

Alan Eastman