This Week's Citation Classic®

Waterfield M D, Scrace G T, Whittle N, Stroobant P, Johnsson A, Wasteson Å, Westermark B, Heldin C H, Huang J S & Deuel T F. Platelet-derived growth factor is structurally related to the putative transforming protein p28^{sis} of simian sarcoma virus. *Nature* 304:35-9, 1983.

[Imperial Cancer Research Fund Labs., Lincoln's Inn Fields, London, England; Inst. Medical and Physiological Chemistry and Dept. Pathology, Univ. Uppsala, Sweden; and, Depts. Medicine and Biological Chemistry, Washington Univ. School of Medicine, Jewish Hospital of St. Louis, MO]

Progress in understanding the role of oncogenes in the causation of cancer was suddenly put into an easily understandable context by the observation, described in this *Nature* article, that an oncogene could encode a growth factor and thus trigger cell division by subversion of a normal growth regulatory pathway. [The *SCI*® indicates that this paper has been cited in more than 1,140 publications.]

An Oncogene Can Function as a Growth Factor

M.D. Waterfield
Ludwig Institute for Cancer Research
University College
London
England

Much of our current understanding of the genetic changes that may cause cancer sprung from major advances in our ability to determine and analyze protein and DNA sequences compiled in databanks. This is shown by the discovery of the function of the sis oncogene.

Several labs studied growth factors produced by transformed cells, some of which appeared to be functionally related to platelet-derived growth factor (PDGF). PDGF, a factor released into serum from platelets during blood clotting, appeared to be needed in lesser amounts by transformed cells than normal cells in culture—a situation suggesting that autocrine stimulation might take place in certain cancer cells. What was needed was a systematic purification and amino acid sequence analysis of growth factors. This was undertaken at the Imperial Cancer Research Fund (ICRF) using PDGF purified by colleagues in Sweden and the US.

Employing newly developed HPLC methods and high sensitivity gas phase protein sequence equipment, we were able to deduce partial sequences for PDGF and show that it was a heterodimer. Meanwhile, the introduction of molecular cloning techniques into retrovirology had led to the determination of the genomic sequences of several viral oncogenes and the prediction of the amino acid sequences of their putative transforming proteins, including sis.[1]

The sequences were stored in the database of the National Biomedical Research Foundation (NBRF) and in personal databases, such as that of Russell Doolittle who generously allowed us access. Peter Stockwell helped us to ascertain if PDGF was related to any known protein by coaxing the newly installed ICRF computer to read and digest the databases. I vividly remember the excitement generated by the discovery that one chain of PDGF (the B chain) was virtually identical to the predicted sequence of the transforming protein encoded by the oncogene sis of simian sarcoma virus. The entire discovery could be encapsulated in the simple phrase "sis is PDGF," conveying to all those working in cancer research the concept that oncogenes could act by subversion of growth factor function—a seemingly logical, simple, and easily understood mechanism. While we wrote the *Nature* paper, we were amazed to see a paper[2] that contained very similar, though not identical, sequence data of PDGF. The authors had used it to search the NBRF database, but failed to find the identity with sis. When Doolittle typed the data into his computer, his diligence was rewarded by his finding of the same result—PDGF is sis! Our *Nature* article and that by Doolittle and coauthors in *Science*[3] were published extremely quickly, causing an immense flurry of scientific and media interest.

Using similar sequence-based strategies, my lab, with collaborators, was able to show that the erb-B oncogene could subvert receptor function by encoding a truncated epidermal growth factor receptor, thus obviating the need for the factor.[4] Such subversion of the growth factor-triggered pathways is now known to take place at all levels from growth factor to transcription factor.[5] Being the first paper to find the function of a cancer-causing gene, it has been cited many times in the cancer research literature.

1. **Devare S G, Reddy P, Law J D, Robbins K & Aaronson S A.** Nucleotide sequence of the simian sarcoma virus genome; demonstration that its acquired cellular sequences encode the transforming gene product p28sis. *Proc. Nat. Acad. Sci. USA* 80:731-5, 1983. (Cited 220 times.)
2. **Antoniades H N & Hunkapillar M W.** Human platelet-derived growth factor (PDGF): amino terminal amino acid sequence. *Science* 220:963-5, 1983.
3. **Doolittle R F, Hunkapillar M W, Hood L E, Devare S G, Robbins K C & Aaronson S A.** Simian sarcoma virus onc gene, v-sis, is derived from the gene (or genes) encoding a platelet-derived growth factor. *Science* 221:275-7, 1983. (Cited 980 times.)
4. **Downward J, Yarden Y, Mayes E, Scarce G, Totty N, Stockwell P, Ullrich A, Schlessinger J & Waterfield M.** Close similarity of epidermal growth factor receptor and v-erb-B oncogene protein sequences. *Nature* 307:521-7, 1984. (Cited 1,390 times.)
5. **Bishop J M.** Molecular themes in oncogenesis. *Cell* 64:235–48, 1991.

Received June 17, 1991