We showed that an oncogene, v-erb-B, from an acutely transforming retrovirus, avian erythroleukemia virus, encoded a truncated version of the receptor for epidermal growth factor, establishing that dominant oncogenes were often mutationally activated components of intracellular growth signalling pathways. [The SCF indicates that this paper has been cited in more than 1,675 publications.]

Oncogene Encodes EGF Receptor

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I joined Mike Waterfield’s laboratory at the Imperial Cancer Research Fund (ICRF) in London in October 1982. In the mid-1970s Mike had been a postdoctoral fellow in Lee Hood’s lab at Caltech, where he had worked on the development of the gas phase protein sequencer. He had returned to London with a prototype sequencer built in a garage in Pasadena and a determination to continue developing the technology of sequencing peptides at the sub-nanomole level. At the ICRF he was fortunate to find Nick Totty, who rapidly became an expert at sequencing peptides. He had returned to London with a prototype gas phase machine, thereby improving its sensitivity by more than 100-fold.

Mike changed the direction of the lab at the beginning of the 1980s from working on influenza hemagglutinin to characterising peptide growth factors and their cell surface receptors at the level of their primary structure. Stanley Cohen’s work1 at Nashville had already identified these proteins as likely to be critical in the control of cellular growth; however, their structures were a mystery and their role, if any, in human malignancy could only be guessed at.

Half the laboratory was working on the purification and sequencing of platelet derived growth factor (PDGF). In the summer of 1983 this led to its identification as the product of the c-sis proto-oncogene. My task was to join Elaine Mayes in attempting to purify and obtain sequence from the receptor for epidermal growth factor (EGF). This sequence would then be used to obtain cDNA clones, giving the full structure of a growth factor receptor for the first time. My attempts at purification proceeded slowly, initially using human placenta as a source. Later, after Elaine had moved to a different project, I took over from her the cell line A431, which massively overexpresses the EGF receptor. As well as mercifully keeping me out of the delivery room at Queen Charlotte’s Maternity Hospital, this speeded up the purification such that by the autumn of 1983 we had half a milligram of homogenous EGF receptor. We were considerably helped in this by Yosi Yarden (from Yosi Schlessinger’s lab at the Weizmann Institute), who had visited the ICRF for a few months in the summer.

This amount of protein was quite inadequate for sequencing by the conventional methods then in use in most labs. However, using Mike’s two prototype gas phase machines we were rapidly successful in obtaining extensive protein sequence from peptides from the EGF receptor. Though the use of computers in the identification of sequence similarities was only in its infancy, I immediately began to search protein sequence databases for homologies to these peptides, spurred on by the recent success with PDGF. Initially I found little of significance, but late one night in mid-December 1983 I searched a new update of the protein sequence database, compiled in the lab by Geoff Scrase, for homologies to our peptides. I was amazed to see peptide after peptide align perfectly with the product of v-erb-B, an oncogene from the acutely transforming avian erythroblastosis retrovirus.

The implications were obvious: The EGF receptor, a component of normal cellular growth signalling pathways, was capable of transforming cells to a malignant state when it was hijacked and mutated by a retrovirus. This, together with the observation that v-sis encoded a form of PDGF, led to the acceptance of the idea, now regarded as almost self-evident, that dominant acting oncogenes are capable of causing tumours because they encode mutationally activated components of normal cellular growth control mechanisms.3,4 These achievements were in large part due to the pioneering use of the gas phase sequencer and computer homology searching.

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