

## VIII Wilsede Symposium on Current Trends in Leukaemia Research Introduction: Differentiation-Oncogenes

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Each of the successive Wilsede Symposia has provided a fine vantage point from which to survey current progress in leukaemia research. Because of their regularity, their consistently high standard of presentation, their broad international coverage, and their informal but highly critical atmosphere they have come to be accepted as providing authoritative statements of the achievements and research agenda of the day. This is the eighth of these biennial symposia, and it conforms to the same high standards.

From this vantage point in 1988 the most striking feature is the enormous strength and breadth of molecular genetics. This starts from the now universally accepted assumption that leukaemia, in common with other forms of neoplasia, develops as a result of mutational changes in the genome of a cell. These mutational changes occur serially and embrace a fairly wide range of options, that evidently include rearrangements, deletions, and loss of DNA as well as single-base substitution. Our background thinking on this subject is deeply coloured by knowledge of the cumulative increase of cancer incidence with age, co-operation between cytoplasmic and nuclear oncogenes, and the special susceptibility to DNA transformation of partially transformed cell lines. This view now dictates the main agenda of leukaemia research, which is to elucidate the mechanisms through which these mutational

changes alter the behaviour of cells. An understanding of these mechanisms, it is confidently believed, will enable us to control and eventually eradicate leukaemia and other forms of cancer.

Not only does genetics dictate the agenda, but also in the form of recombinant DNA technology provides an immensely powerful set of tools. With these tools one felt at this symposium that almost any task can now be accomplished: sites of mutation can be located with total precision, functions identified by site-specific mutagenesis, and the interactions of a gene or its control elements with the rest of the cell can be analysed by transfection. Things move with great speed because DNA is after all just DNA: each protein confronts us with a new set of problems, but the problems posed by a gene and the methods for solving them by recombinant DNA technology are transferable. For instance this symposium includes reports on the first fruits in human leukaemia research of Cetus' new method of generating multiple copies of a short length of DNA in between oligonucleotide end-markers. The method is used by J. Rowley to study chromosome breakpoints, and by R.-A. Padua to identify *Ras* mutations.

Within the landscape defined by genetics a significant shift in emphasis is taking place, from dominant to recessive oncogenes. This is an abbreviated and somewhat misleading way of characterizing an important shift in the direction of research. The crucial point is not so much how many copies of a gene are needed for manifestation in the phenotype of a cell, but how the gene works. In general, genes that code for growth fac-

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tors, their receptors, or the cascade of messages that they trigger in the cell produce cancer through *activation*; while those that code for mechanisms of differentiation do so through *inactivation*. And, in general, since both copies of a diploid gene will need to be inactivated to prevent differentiation, the latter will behave as recessives. The new emphasis then is on genes that control differentiation, and their inactivation as differentiation-oncogenes in cancer. This emphasis goes back to the pioneering work of H. Harris in somatic genetics, where cancer cells upon fusion with normal cells generally display a normal phenotype. New experimental results to the same effect were presented in a poster by J. Wolf et al. on fusions between malignant and non-malignant B cells, and similar results in the papilloma virus system were discussed by H. zur Hausen. Over the last 2 decades this line of research became bogged down in sterile controversy about the generality of the result, and exactly what the famous Minz-Ihlmensee "suppression of malignancy by differentiation" experiments really mean. Now, thanks to molecular genetics, a way forward is open.

Leading on from the original ideas derived from work on somatic hybrids, three lines of approach to the recessive oncogene problem can be distinguished in this symposium. One is via formal genetics, and represents development of the concepts first formulated to explain the familial inheritance of retinoblastoma, Wilm's tumour, and coeliac polyposis. Another is via development, where our increasing understanding of molecular mechanisms in cell biology helps to identify situations in which recessive oncogenes able to inhibit normal differentiation might operate. And a third relates to the major growth factors that are normally associated with dominant oncogenes: research on these molecules and their receptors is beginning to identify control mechanisms that regulate their activity, and that may themselves be disrupted by recessive oncogenes.

The first of these lines of approach is represented by the contributions of J. Rowley, F. Anders, and M. Dean. In her outstanding Frederick Stohlmann Lecture, Rowley surveys the role that chromosome studies have played in identifying dominant oncogenes, and goes on to mention her current interest in monosomy of human chromosome 5 as indicative of recessive oncogene activity. As this chromosome also carries genes for growth factors and their receptors, it is possible – perhaps even likely – that closely linked recessive oncogenes may regulate the expression of these potentially dangerous molecules (at least that is what I understand her to have told me in conversation). Ander's vast effort in the genetics of congenital melanoma in fish (extended also to the genetics of carcinogen susceptibility) has revealed much about the control of dominant oncogenes by the rest of the genome. My guess is that in the future this branch of genetics will need to focus on these presumably recessive control elements, and that something like the mouse recombinant inbred lines will be needed for that task – a formidable undertaking. Dean describes an ongoing study of the long arm of human chromosome 7, often missing in myelodysplastic syndrome with all that that implies for the operation of recessive oncogenes.

The second line of approach, through development, is evident in the papers of M. Moore, T. Waldmann, N. Haran-Ghera, A. Friedenstein, T. M. Dexter, D. Mason, K. Rajewsky, and F. Melchers. Analysis of the interactions between haemopoietic cells and their surrounding stromal cells makes steady progress and the molecules involved in this binding are becoming clearer: this is an area that Friedenstein pioneered, and where Dexter is moving ahead with his studies of solid-phase-bound IL-3. Cell-bound and matrix-bound growth/differentiation functions are here to stay. Perhaps the best-characterized differentiation factor, and certainly the one where a potential for recessive oncogene activity is most

evident in its title, is D. Gearing's leukaemic inhibitory factor.

The contribution of M. Lenardo and M. Greaves take us deep into the molecular mechanisms of transcriptional control that underline differentiation.

Finally there are the studies that sketch in the way that dominant oncogenes either respond to developmental control, or escape: those of W. Ostertag,

W. Alexander, C. Moroni, and T. Ernst. The last of these provides novel and interesting evidence that enhanced levels of CSF production in leukaemic cells, and the autocrine stimulation that ensues from this, may reflect increased mRNA stability rather than increased transcription: a post-transcriptional modification, and therefore yet one more candidate site for the operation of recessive oncogenes.