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Gene-expression profiling to classify soft-tissue sarcomas

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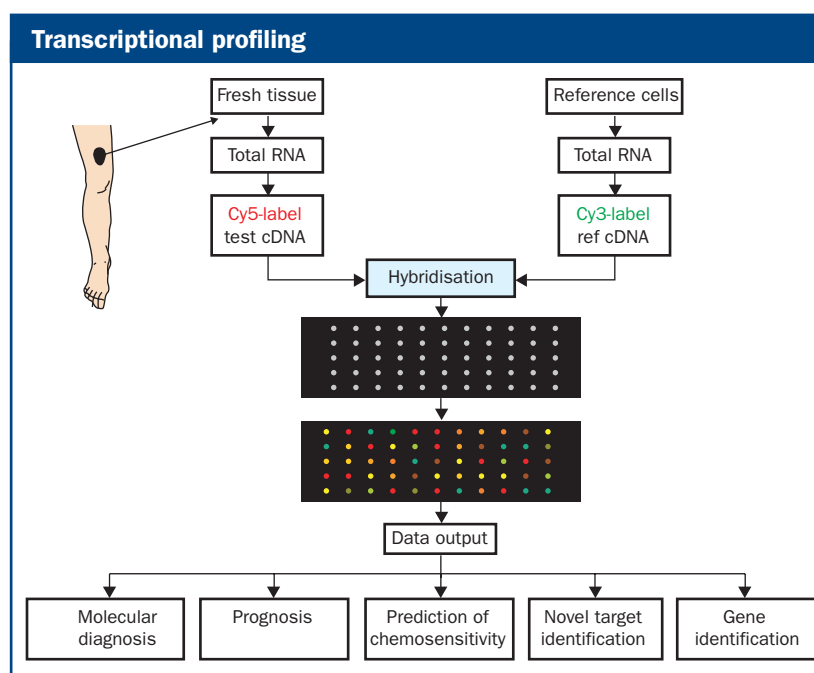
Soft-tissue sarcomas are heterogeneous, with several histotypes that all share a putative common mesenchymal origin. Prognosis is determined clinically (size, location, resection-margin status) and pathologically (mitotic activity, necrosis), and the histological subtype is only sometimes a consistent independent prognostic factor. For the common soft-tissue sarcomas, (leiomyosarcomas, liposarcomas, synovial sarcomas, malignant fibrous histiocytomas, malignant peripheral-nerve-sheath tumours), predictable histotype-specific behaviour remains illusive. The clinical course ranges from slowly growing localised tumours to highly aggressive, rapidly metastatic tumours. These cancers are rare (<1% of all cancers) and studying large groups of individual tumour types is difficult. Wide surgical resection with irradiation ensures optimum local control. Only doxorubicin and ifosfamide are active as chemotherapy.¹

In this issue of *The Lancet*, Torsten Nielsen and colleagues report the use of transcriptional profiling with cDNA microarrays. Transcriptional profiling can help diagnosis, explain and predict

differences in biological behaviour, predict responsiveness to treatment, and may identify new molecular targets (panel). Routine immunohistochemistry can be considered as a single-gene expression study; expression profiling gives a holistic view, while lacking topographical information.

Nielsen and colleagues analysed 41 soft-tissue tumours, which gave over 1.5 million data points. These profiles were obtained with two different microarrays. Bias from the two arrays was successfully removed by a method known as singular value decomposition. This mathematical technique allows the recognition of the dominant gene (eigengene) and the corresponding array expression (eigenarray), which will facilitate the comparison of data from different arrays. Against the gene-expression profile of 5520 well-measured genes, displaying predefined variation across the different specimens, the 41 sarcomas could be separated into five distinct groups: gastrointestinal stromal tumours, synovial sarcomas, the benign peripheral-nerve-sheath tumours, half the leiomyosarcomas, and a broad group containing all the malignant fibrous histiocytomas, the liposarcomas, and the other leiomyosarcomas. This separation of half of the sarcomas, classified morphologically as leiomyosarcomas, into a cluster characterised by 24 highly expressed genes, gives at least three groups previously grouped together: the gastrointestinal stromal tumours, and the calponin-positive and the calponin-negative leiomyosarcomas.

Most gastrointestinal stromal tumours have a gain-of-function mutation in the proto-oncogene *KIT*, which activates tyrosine kinase. This observation led to the molecular therapy, imatinib mesylate, a *KIT*-kinase inhibitor.² In the Nielsen study a cluster of 125 genes were highly expressed, which separated the gastrointestinal stromal tumours from the other sarcomas. These results and others³ strengthen the case for separating gastrointestinal stromal tumours from other leiomyosarcomas, and support the hypothesis of phenotypic resemblance between gastrointestinal stromal tumours and the interstitial cells of Cajal.³ A *c-KIT* mutation was thought to indicate a more aggressive, worse prognosis gastrointestinal stromal tumour, but more recent data suggest that *c-KIT* mutation occurs early in the development of the tumour and that many lack a *c-KIT*



mutation but have increased *KIT* mRNA levels and expression of CD117 protein.^{3,4} The study by Nielsen and colleagues suggests that, because gastrointestinal stromal tumours relatively underexpress proliferation genes, the finding of *c-KIT* activation is not itself a hallmark for aggressive clinical behaviour. The striking presence of genes counteracting the function of *KIT* and the homogeneous expression profile observed in Nielsen's study suggest that gastrointestinal stromal tumours are, as the investigators conclude, "low-grade and of low limited complexity", which contrasts with the genetic instability in most common epithelial cancers.

The synovial sarcomas account for some 10% of adult soft-tissue sarcomas and they have a monophasic and biphasic subtype, most having a characteristic translocation, t(X; 18) (p11;q11), that results in the fusion of the proximal portion of the *SYT* gene at 18q11 to the distal portion of, primarily, one of two genes, *SSX1* or *SSX2*. The type of gene fusion is clinically important.⁵ The type of spotted microarray was not developed to identify these differences. A "sarcomachip", by analogy to the "lymphochip", might be developed taking this into account. The observation that a cluster of 104 genes was identified that included retinoic-acid pathways and the epidermal-growth-factor receptor is more important, because it suggests a role for retinoids in this disease and a role for the epidermal-growth-factor receptor as an active growth-promoting pathway. These pathways were apparently unrelated to glandular differentiation because all eight synovial sarcomas in Nielsen's study were monophasic. Other reports⁶ have suggested increased *c-KIT* and *SCF* mRNA in most synovial sarcomas, but Nielsen and colleagues did not find this. This difference might highlight another limitation of these arrays: their relative insensitivity for minor upregulations compared with RT-PCR.

Malignant fibrous histiocytoma was until recently considered the most common soft-tissue sarcoma among adults. Histologically, karyotypically, and clinically, this is by far the most heterogeneous group of sarcomas, and the concept of malignant fibrous histiocytoma as a histogenetically separate entity became questioned. An alternative hypothesis considered that malignant fibrous histiocytoma is a poorly differentiated sarcoma and might present as a common endpoint for various other sarcomas. Fletcher and colleagues⁷ suggested that, in over 80% of cases, a line of differentiation is found. In Nielsen's microarray analysis the group of malignant fibrous histiocytoma did not separate from the liposarcomas and the calponin-negative group, which strengthens this alternative view of malignant fibrous histiocytoma.

The results in Nielsen and colleagues' report are a first step towards a molecular pathology of soft-tissue sarcoma. The limited data provided in Nielsen's report and in other expression-profiling studies suggest that primary tumours and their metastases seem to be more alike than once expected.⁸ New drugs aimed at specific targets (eg, signal-transduction inhibitors at the receptor for vascular epidermal growth-factor) will hopefully be evaluated in patients with tumours known to have this activated pathway. This approach should lead to patient-tailored treatment based on tumour-tailored microarrays. In the meantime, correct sampling, processing, and storage of fresh-frozen tumour tissue will need to become routine.

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Tobacco industry and EC advertising ban

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In today's *Lancet*, Mark Neuman and colleagues analyse in detail the way in which the tobacco industry worked against an advertising ban within the European Community (EC). The revelations in this cautionary tale may startle public-health workers. Using documents from the tobacco industry brought into the open by court cases, Neuman and colleagues report on how the industry works and exemplify its comprehensive approach to achieving its market-expanding objectives—of which mortality expansion is a by-product.

The industry had lobbied at the highest political level in Europe to try to prevent the EC passing a directive to ban tobacco advertising and sponsorship. When the directive was adopted in 1998, the industry continued to lobby against it and a suit brought by the German government at the European Court of Justice succeeded in overturning the directive in 2000, as anticipated in tobacco-industry strategies. Neuman and colleagues show that the tobacco industry has attempted to use as part of its blocking strategies the principle of subsidiarity, in which the EC cannot over-rule individual member states. A watered-down directive, largely limited to cross-border activities, is now being discussed. It will always be difficult to achieve public-health objectives in this environment and a total advertising ban probably lies beyond the EC's present powers.

Cross-border advertising on satellite television is potent and ubiquitous. In a single afternoon watching television in India I saw tobacco-industry sponsored: cricket from India, motor-car racing from Europe and Macau, motor-bike racing from Europe, golf from Indonesia, and soccer played before an empty stadium emblazoned with tobacco advertising (country unknown).

Complete bans on tobacco advertising work.¹ Legislation providing such bans required a single act in Norway and Finland, but a 30-year battle in Australia (which is also a federation). However, no such ban is ever complete, because the ultimate advertisement still exists—a teenager offers a cigarette from an attractively branded packet to a friend. Because of skilful marketing, cigarettes still have a strong general appeal as a product, especially to