

Haematology

WITH OUR INCREASED UNDERSTANDING of the molecular mechanisms of haematological disorders, it has become possible to target therapy precisely to the underlying defect. Targeted therapy can increase safety and potency, while causing fewer side effects than standard treatment. "Smart" drugs and gene therapy have recently shown great promise in a wide range of malignant haematological and coagulation disorders.

Chronic myeloid leukaemia.¹ Since the Philadelphia chromosome was recognised over 40 years ago, the genetic changes that lead to chronic myeloid leukaemia (CML) have been progressively unravelled. A reciprocal translocation between chromosomes 9 and 22 creates a unique hybrid gene, *BCR-ABL*, which encodes a protein with tyrosine kinase activity. The abnormal gene is found in almost all patients with CML and can be detected routinely on cytogenetic analysis using fluorescent markers (Figure). The *BCR-ABL* protein confers on its host cell extended life span, disregard for marrow inhibitory signals and inevitable progression to a more malignant phenotype, clinically recognised as blast crisis.

Imatinib is a specifically designed, highly targeted drug that blocks *BCR-ABL* tyrosine kinase action. At well tolerated oral doses, it eliminates the abnormal Philadelphia clone and dramatically normalises blood counts in almost all chronic-phase patients, as well as in most of those with advanced disease (accelerated phase and blast crisis). Remissions appear durable, although long term data are unavailable. While imatinib is not yet believed to cure CML, it could become initial therapy for all patients, including those who would otherwise have proceeded immediately to allogeneic stem-cell transplantation.

Gene therapy in haemophilia.² Much is already known about the genetic abnormalities, laboratory measurement and clinical course of haemophilia. This condition is an excellent model to demonstrate the feasibility of human gene transfer, as large clinical benefits can follow even small improvements in the level of clotting factors (eg, from less than 1% to 5% of factor VIII or IX).

Factor VIII or IX genes have been successfully transferred in at least 29 people with haemophilia, using either skin, blood, muscle or liver cells transformed by various carrier vectors. All studies have demonstrated some clinical efficacy, with sustained improvement in factor level over a period, and reductions in bleeding symptoms and use of clotting-factor concentrate. However, concerns remain about the potential of the technique to alter the individual's genetic code, leading to cancer and transmission of changed genes to the next generation.

"Magic bullet" therapy in non-Hodgkin's lymphoma.³ The CD20 antigen is a specific protein expressed in virtually all malignant B-cell lymphomas, but not non-lymphoid cells, normal early B lymphocytes or plasma cells. This antigen is the target for the monoclonal antibody rituximab, which has shown great clinical benefit in patients with non-Hodgkin's lymphoma. Around half of patients

with relapsed or refractory low-grade, non-Hodgkin's lymphoma have a

response to rituximab, which can last for over a year (median, 12 months). Because of its specificity, rituximab has side effects that are milder than and differ from those of other forms of chemotherapy. The main, but uncommon, problem is infusion-related fever, chills or wheeze. When rituximab is used in conjunction with standard chemotherapy as initial treatment for lymphoma, it improves response with virtually no added toxicity. Further benefit is seen in patients with refractory lymphoma, when radioactively tagged anti-CD20 antibody can be used to deliver targeted local radiation treatment.

New anticoagulants.^{4,5} Anticoagulants have been designed that are more specific than standard and low molecular weight heparin. Most focus has been on factor X and thrombin, but there are new anticoagulants for almost every coagulant factor. Three direct thrombin inhibitors (hirudin, bivalirudin, and argatroban) are approved for clinical use in the United States. Four other anticoagulants (activated protein C, tissue factor pathway inhibitor, synthetic pentasaccharide, and the oral thrombin inhibitor H376/95) are undergoing or have completed phase III evaluation studies. Each drug must show a positive benefit-to-risk profile, and particularly cost effectiveness, in the face of the marginal therapeutic advantage over established agents. The new drugs are likely to avoid the serious non-anticoagulant side effects of heparin, such as thrombocytopenia, and perhaps osteoporosis. With the trend for reduced hospital stay and evidence suggesting that the risk of venous thrombosis remains high for several months after orthopaedic surgery, oral agents are likely candidates for improving care. The oral thrombin inhibitor H376/95 is arousing most interest, as it produces predictable anticoagulant response without laboratory monitoring. It is currently being evaluated in phase III trials as a possible substitute for warfarin in venous disease and atrial fibrillation.

The early completion of the Human Genome Project and advances in biotechnology will inevitably increase the number of new therapies specifically designed for the individual patient and disease.

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Figure: Cytogenetic analysis showing *ABL* probe (red) on chromosome 9, *BCR* probe (green) on chromosome 22, and both probes on the Philadelphia chromosome, indicating the abnormal hybrid *BCR-ABL* gene.

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2. White GC. Gene therapy in haemophilia: clinical trials update. *Thromb Haemost* 2001; 86: 172-177.
3. Schnipper LE, Strom TB. A magic bullet for cancer — how near and how far? *N Engl J Med* 2001; 345: 283-284.