Haematological malignancies
- an introduction

Dr. Chris Poynton
Consultant and Senior Lecturer in Haematology
University Hospital of Wales,
Cardiff

All Wales Lymphoma Panel – January 2006
The Cancer League

1. Lung
2. Prostate
3. Breast
4. Colon
5. Bladder
6. Non Hodgkin Lymphoma
THE PATIENT PATHWAY

1. DIAGNOSIS

2. TREATMENT

3. FOLLOW UP
The Diagnostic Journey for lowish grade lymphoma or Hodgkin's

- Goes to GP with illness - given antibiotics
- Referral to a specialist eg surgeon
- Biopsy taken and patient discharged
- Seen in clinic, wound healed "we'll write to you"
- GP chases biopsy result
- Referral to lymphoma doctor
Referral Pathways:

Fastest to slowest.................

- Consultant to Consultant (eg ENT)
- General Practitioner
- Tertiary referral from another hospital haematologist/oncologist
- Corridor Consultation
- Friend/acquaintance at a party
THE HAEMATOLOGICAL DISEASES

1. Acute Leukaemia
   AML - 42 per million per year
   ALL - 70 per million children per year

2. Myeloma - 50 per million per year

3. Chronic Leukaemias
   CLL - 35 per million per year
   CML - 10 per million per year

4. The Lymphomas (6th commonest cancer)
   175 per million per year
The Haemopoietic Tree

The chronic myeloproliferative disorders

Acute Leukaemias

Myeloma
Conventional morphological diagnosis
Normal Blood Cells

http://medweb.cardiff.ac.uk/haemy)

- Neutrophil
- Lymphocyte
- Monocyte
- Eosinophils
THE LEUKAEMIC BLASTS OF ACUTE MYELOID LEUKAEMIA
FLOW CYTOMETRY – complex monitoring of cell populations

488 nm laser

CELL

LENS

DICHROIC MIRRORS

FL3 DETECTOR

FL2 DETECTOR

FL1 DETECTOR

SSC DETECTOR

LENS

FSC DETECTOR

UP
LEUKAEMIA AND FLOW CYTOMETRY
Human chromosomes
The Philadelphia chromosome (1962). A translocation between chromosomes 9 and 22

46XY t(9;22)(q34;q11)
FISH = Fluorescence in situ hybridisation

Blue = Chromosome 13q34 probe
Red = Chromosome 13q14 probe
Green = Chromosome 12 telomeric alpha satellite probe

Normal

Trisomy 12
Oligonucleotide arrays

• Probes for each gene are synthesized directly onto the chip as oligonucleotides of 20-25 bases on to a glass slide using photolithography and oligonucleotide synthesis (Density of 500,000 spots per 1.28 cm²)

• Can get gene expression information on an almost genome-wide scale (tens of thousands of genes)

• Limitations: at the moment requires quite a lot of RNA 2-5 µg mRNA; 107-108 cells; 1 tot 10 mg tissue for gene expression analysis
Oligonucleotide array

Typical result after data analysis by computer

Clustered gene expression

Green means less fluorescence than the reference sample

Red is more fluorescence

Black is equal expression
Multiple Myeloma
The effects of antiangiogenesis on fetal development – blockage of vascular endothelial growth factor receptors - VEGF-R
The chronic myeloproliferative disorders
The Philadelphia Chromosome

t(9;22)(q34;q11)
Mutated c-kit Signaling

- The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation.
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival.

ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.
PKC-412: Mechanism of Action

- PKC occupies the ATP binding pocket of the c-kit kinase domain.
- This prevents substrate phosphorylation and signaling.
- A lack of signaling inhibits proliferation and survival.
The annual incidence of lymphoma is increasing faster than any other cancer.
Increasing incidence of Lymphoma

SE Wales Cancer Centre (1.45 million): 175 new cases/year

1980
70 per million per year

2000
120 per million per year
Enlarged Livers and Spleens
LYMPHOMA MADE ..........