Setting the Scene

Dr Faith Davies

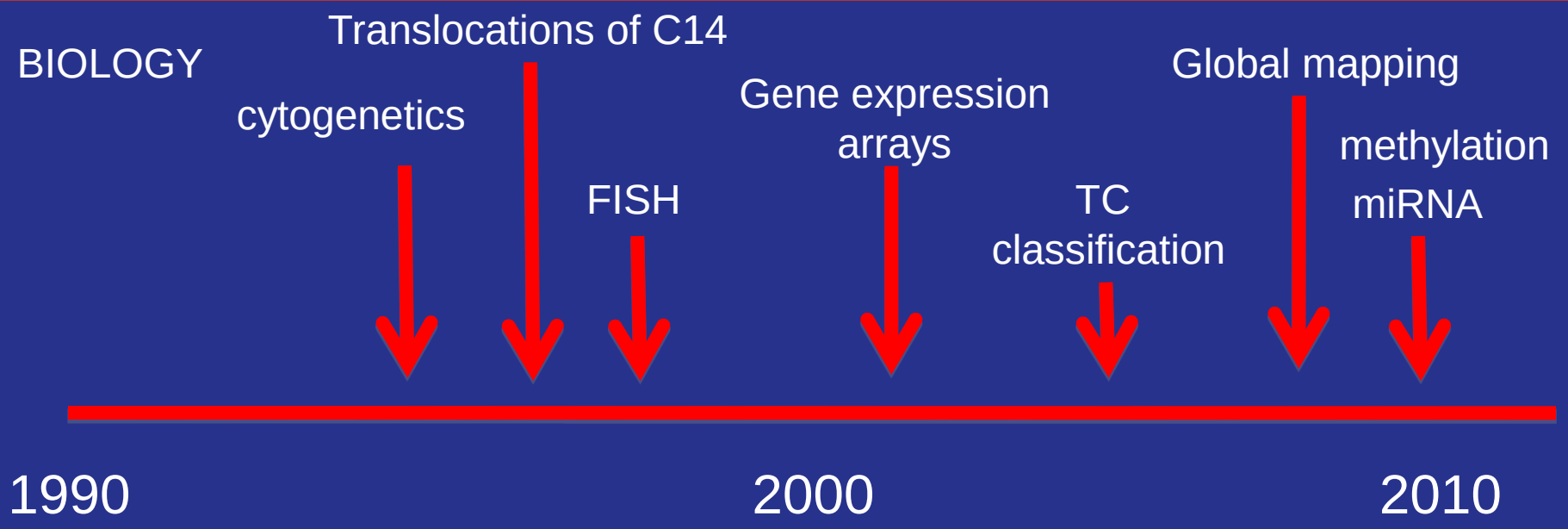
Royal Marsden Hospital and Institute of Cancer Research

Genetic Abnormalities

3 main areas:-

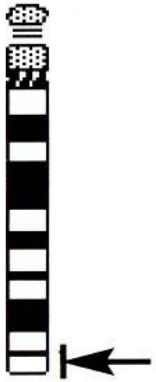
- Biology
- Prognosis
- Directing therapy

Driven by advances in technology



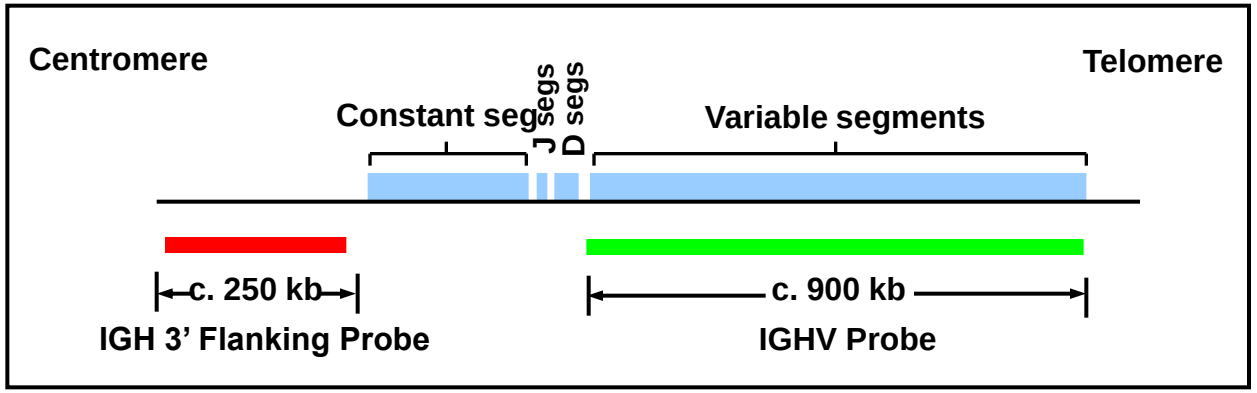
Chromosome 14 FISH - translocation

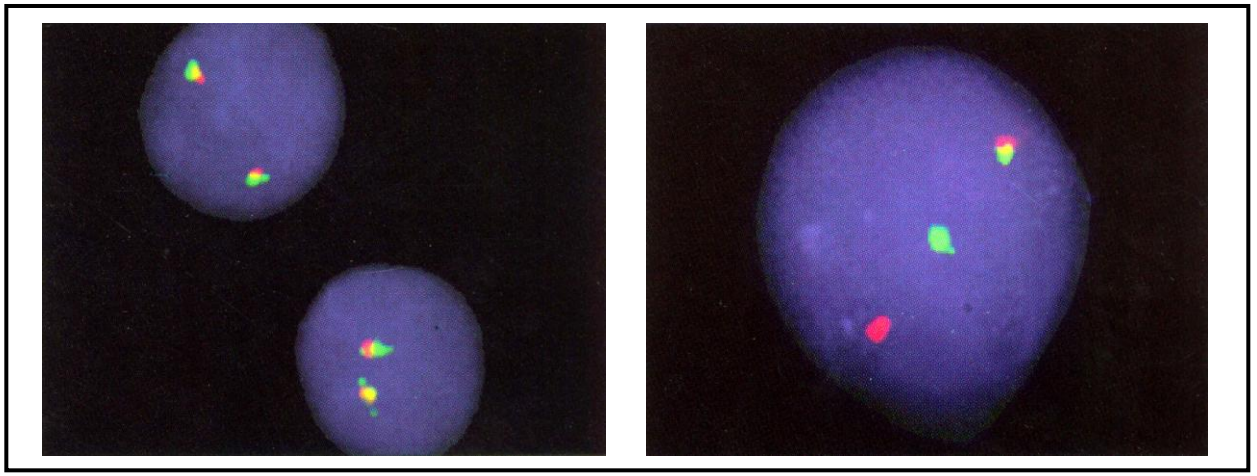
14q32 region



Immunoglobulin heavy chain locus

Dual, Break Apart probe



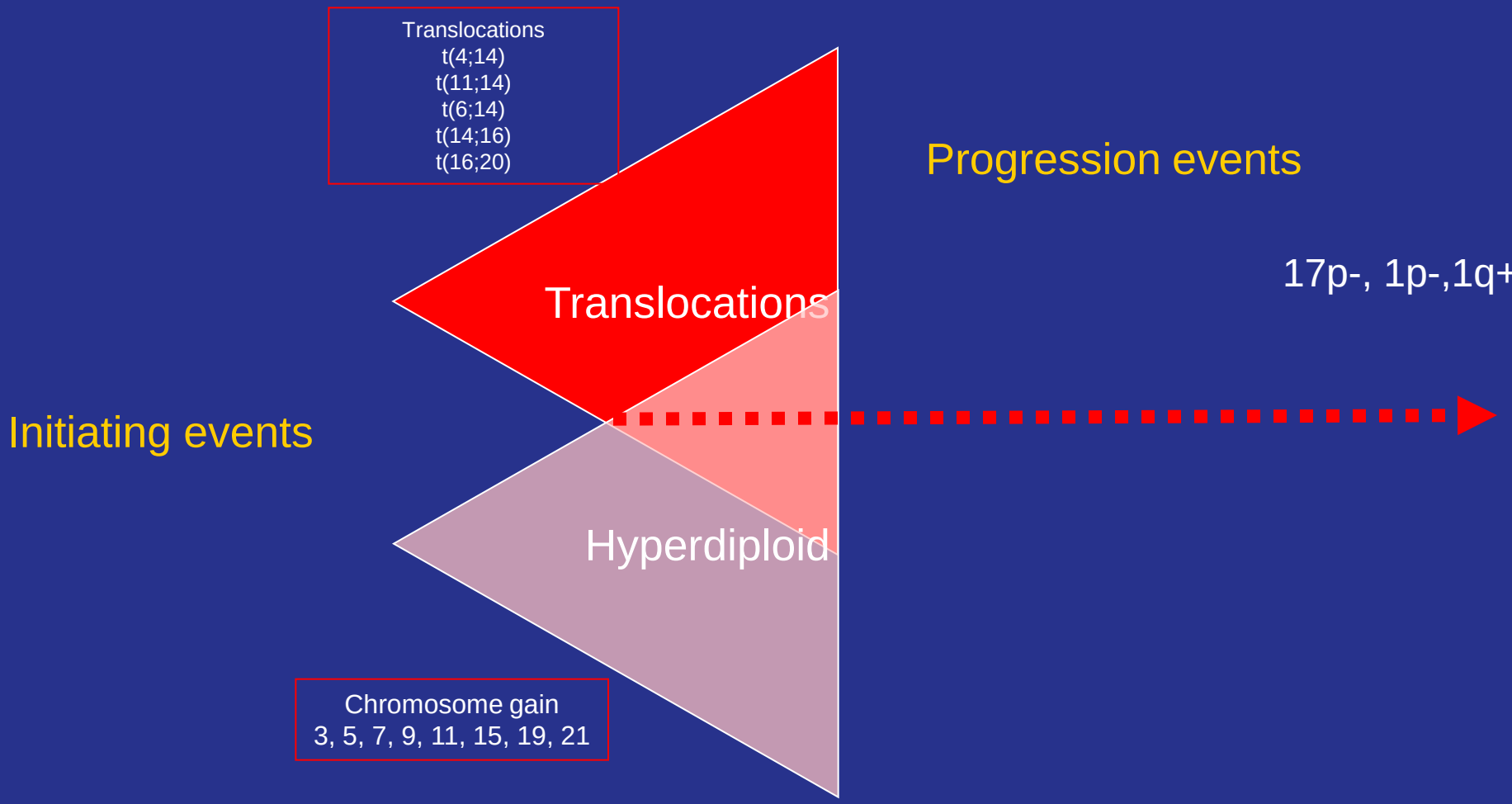


Also copy number FISH

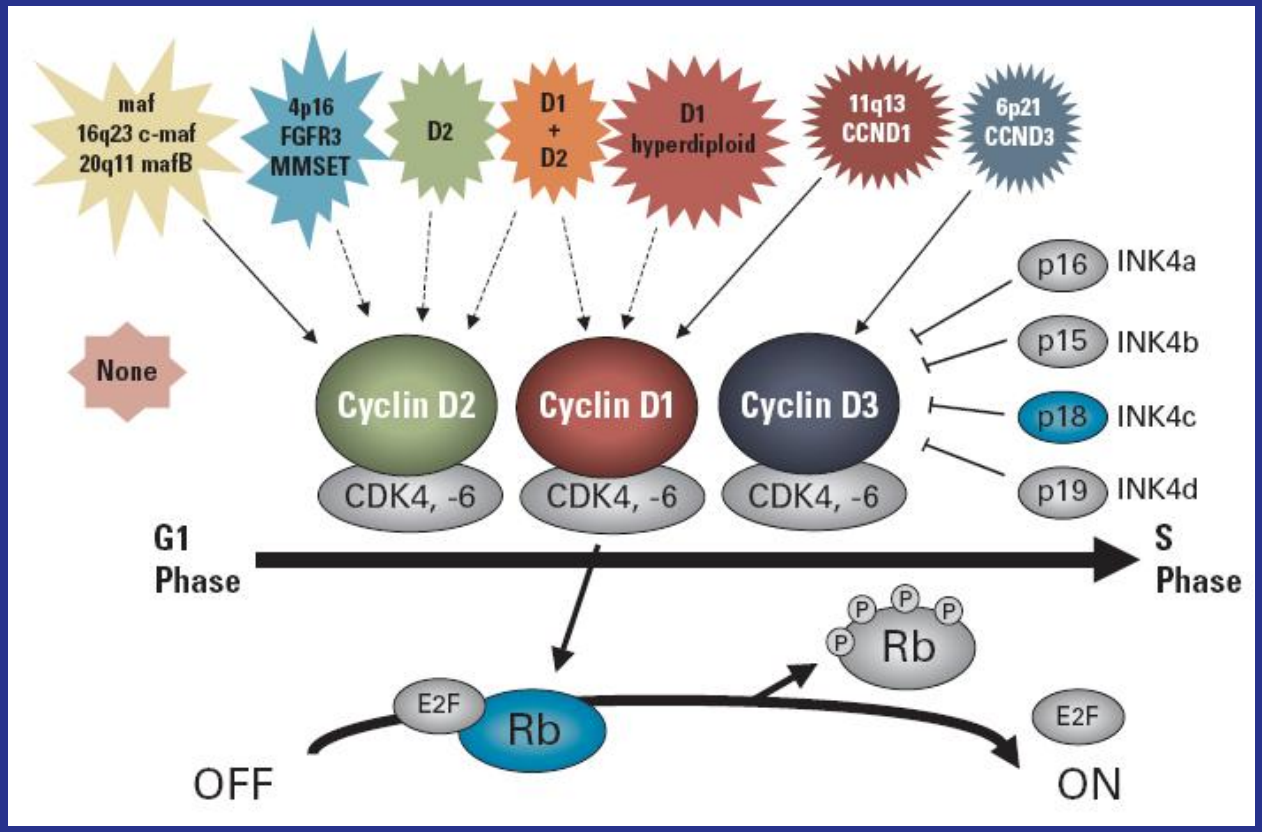
Kindly provided by Dr Fiona Ross, Wessex Regional Cytogenetics Laboratory

Classification Based on Initiation Events

Myeloma divided into 2 subgroups: hyperdiploid and non-hyperdiploid

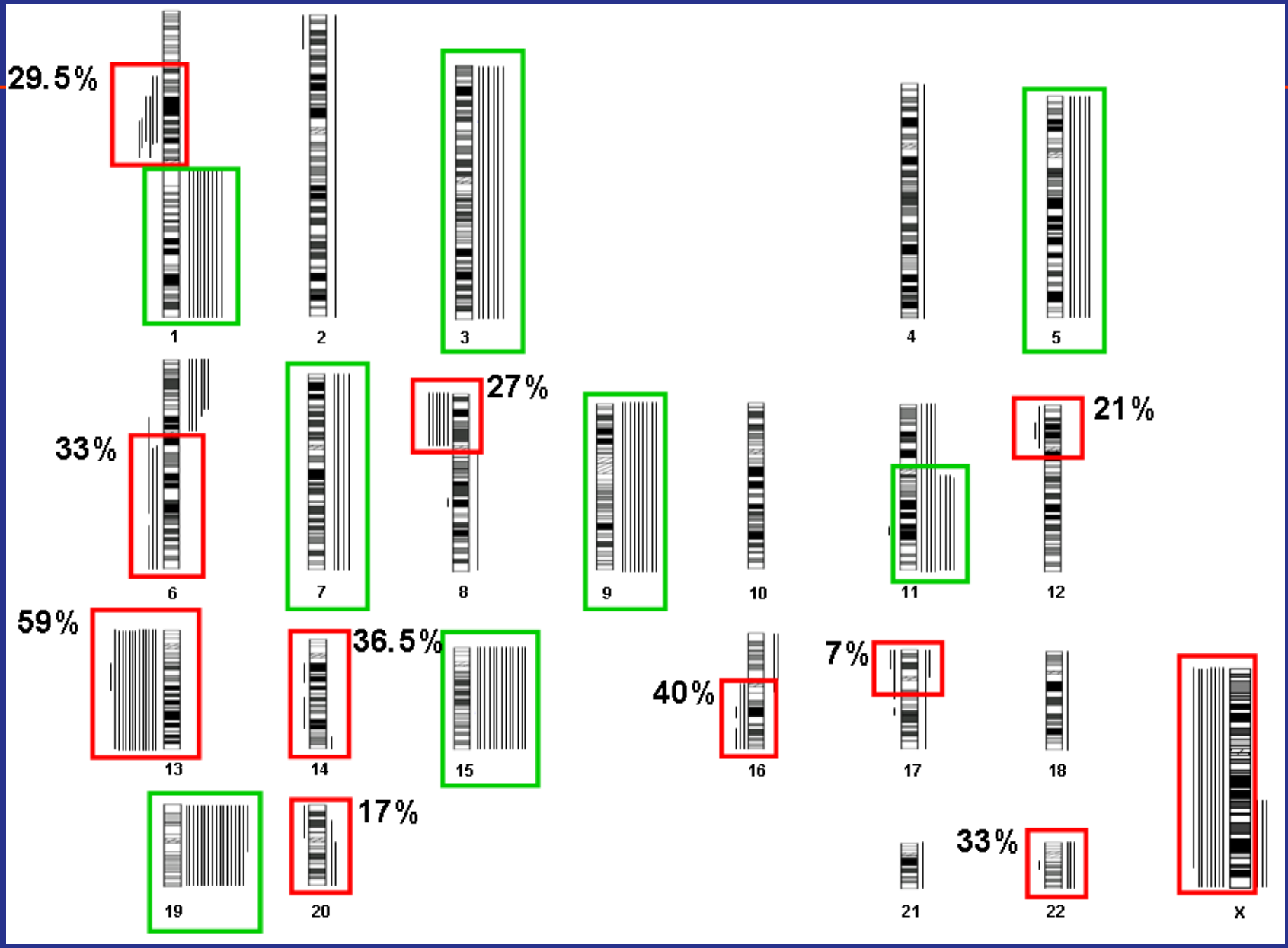


TC Classification



Bergsagel *et al.* 2005

Copy Number Changes by SNP Array

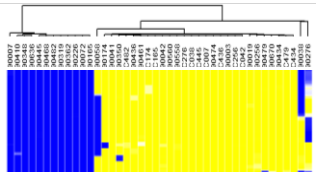


Walker et al Blood 2006, Dickens et al Clin Can Res 2010, Walker et al Blood 2010

Integration of SNP and Expression Data to Detect Tumour Suppressor genes

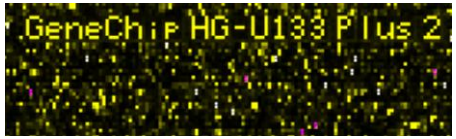
Collect SNP array data

Cluster samples by DNA copy-number/LOH difference



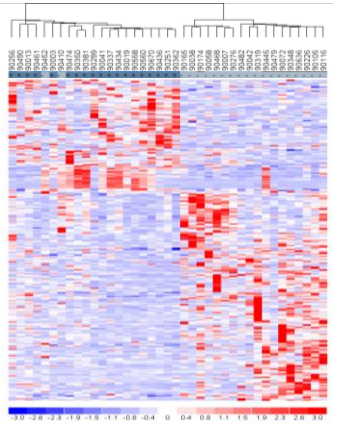
Define genomic regions driving subclusters

Homozygous deletions

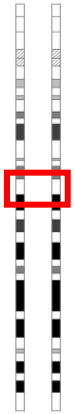


Collect gene expression data

Integrate with SNP array data



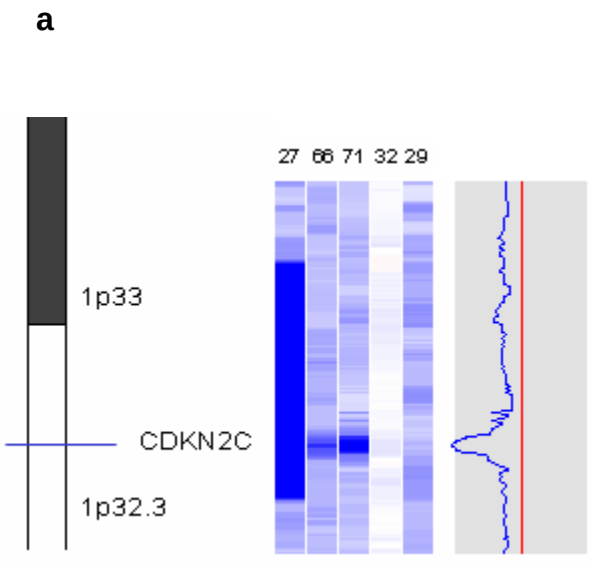
Perform supervised analysis of subclusters

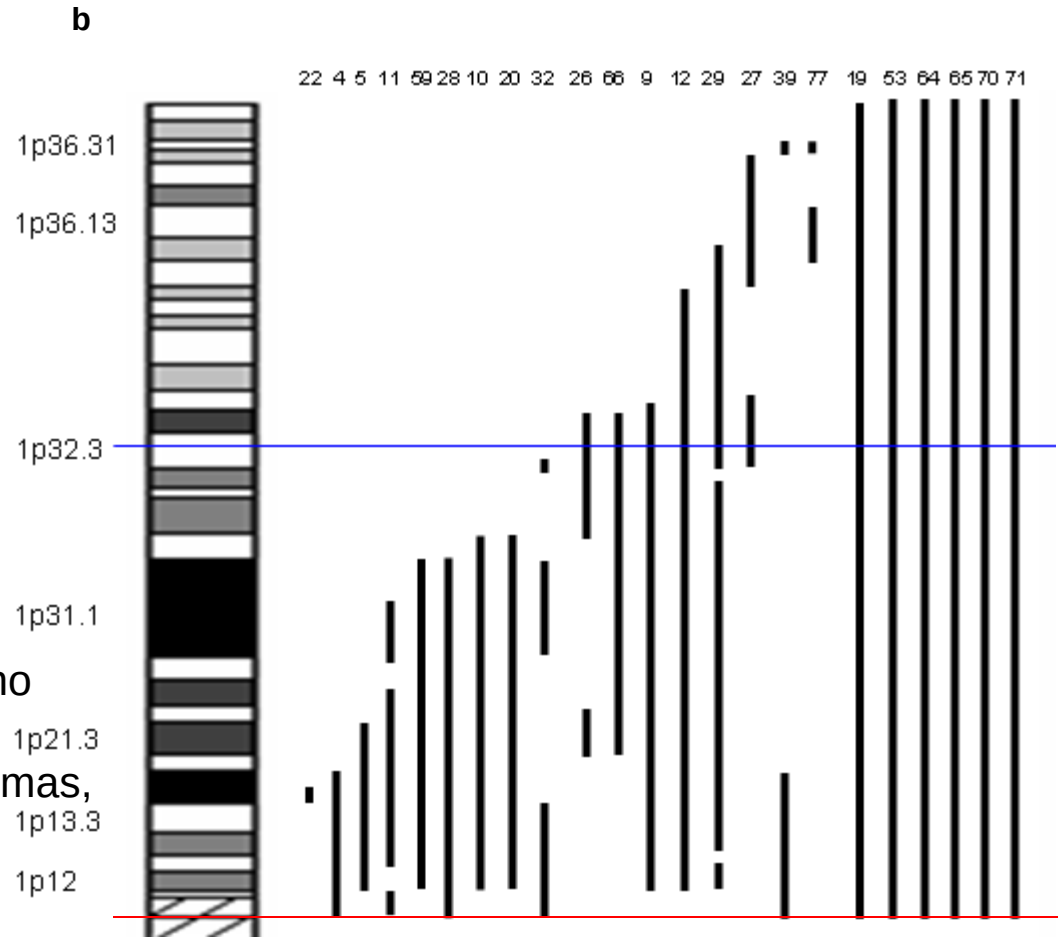


Map significant genes to genomic locations and identify candidate genes within genomic alterations

Experimental validation of candidate cancer genes

Homozygous deletion of 1p – CDKN2C

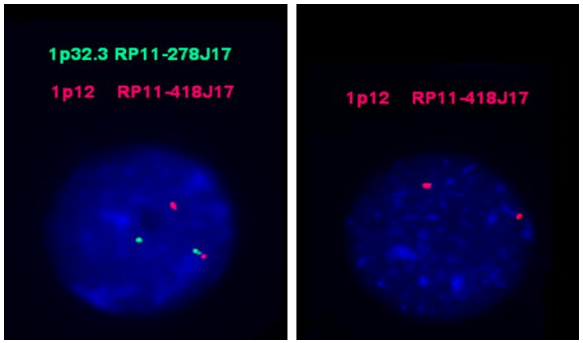


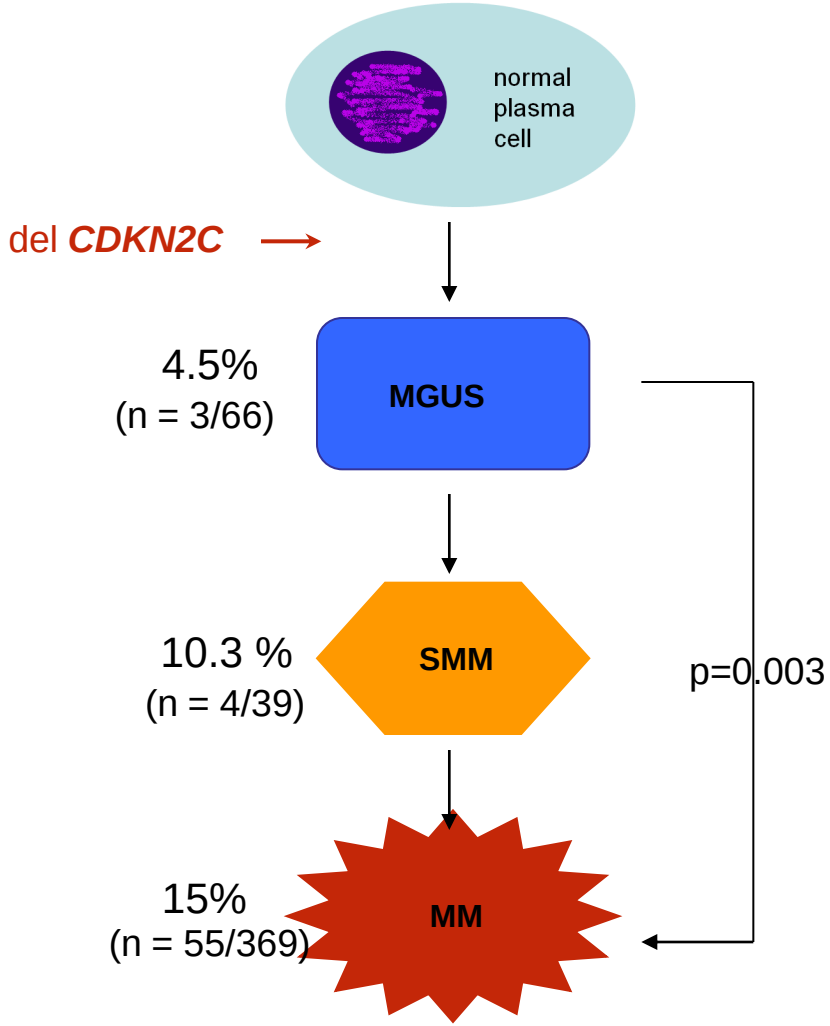


Identified a series of cases with homozygous deletion of 1p23.3 and no CDKN2C gene expression.
These cases were proliferative myelomas, defined by an expression-based proliferation index,
consistent with CDKN2Cs biological function as a cyclin-dependent kinase inhibitor (negative regulator of cell cycle progression).

Leone *et al* Clin Can Res 2008

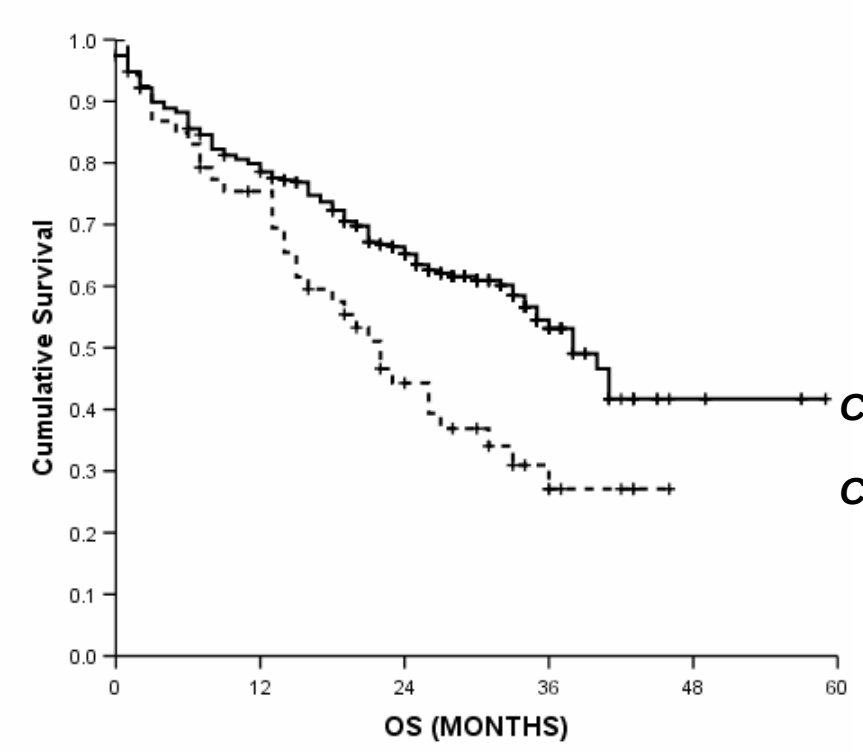
CDKN2C: MGUS-SMM-Myeloma





Leone *et al* Clin Can Res 2008

CDKN2C Prognostic significance



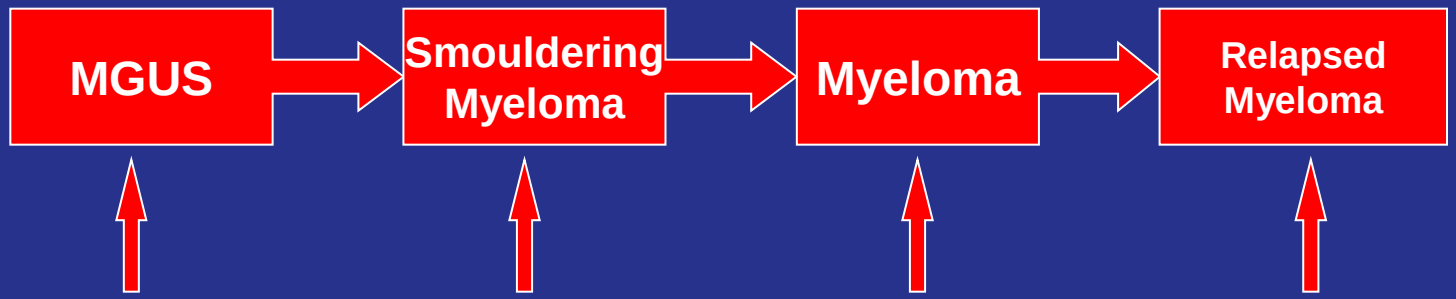
p=0.003

***CDKN2C* normal (n=308)**

***CDKN2C* deleted (n=53)**

Leone *et al* Clin Can Res 2008

The Multistep Progression Model of Myeloma



INITIATION EVENTS

IgH Translocations
- -t(4;14) FGFR3/ MMSET
- -t(11;14) Cyclin D1
- -t(6;14) Cyclin D3
- -t(14;16) c-maf
- -t(14;20) mafB

Hyperdiploidy

PROGRESSION EVENTS

Allelic gain
- Amplification of genes on 1q (*CKS1B*)

Deletion / Loss of Heterozygosity
- Dysregulation of NF-*K*B (*TRAF3, BIRC2, BIRC3, CYLD*)
- Deletion 17p (*TP53*)
- Deletion 1p (*FAF1, CDKN2C*)
- Deletion 13q

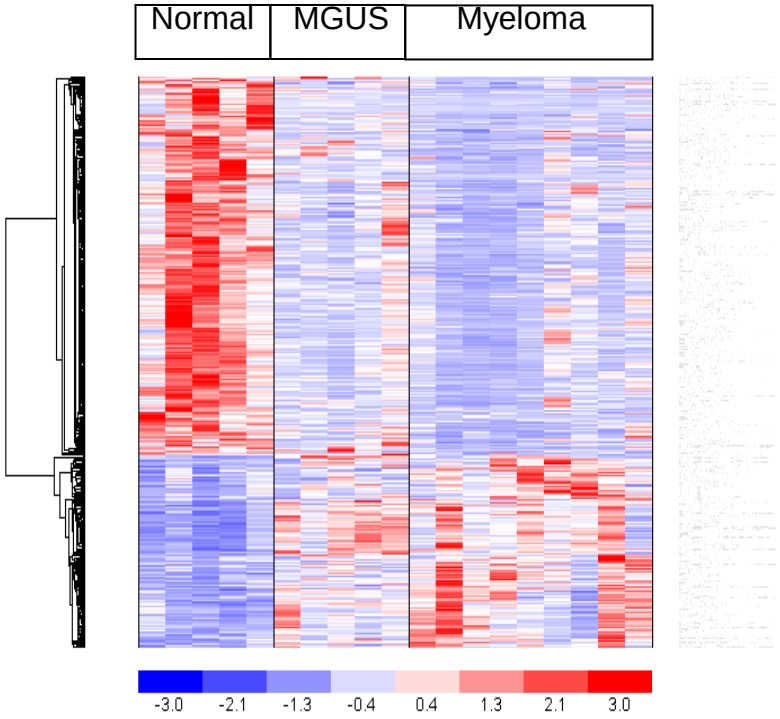
Epigenetic Phenomena
- Methylation of Promoter Regions of Tumour Suppressor Genes
- MicroRNAs

Secondary Translocations
- t(8;14) *MYC*

Mutations
- *N-RAS, K-RAS*
- *TP53*
- *CYLD; TRAF 3 , NIK, NFKB1, NFKB2,*

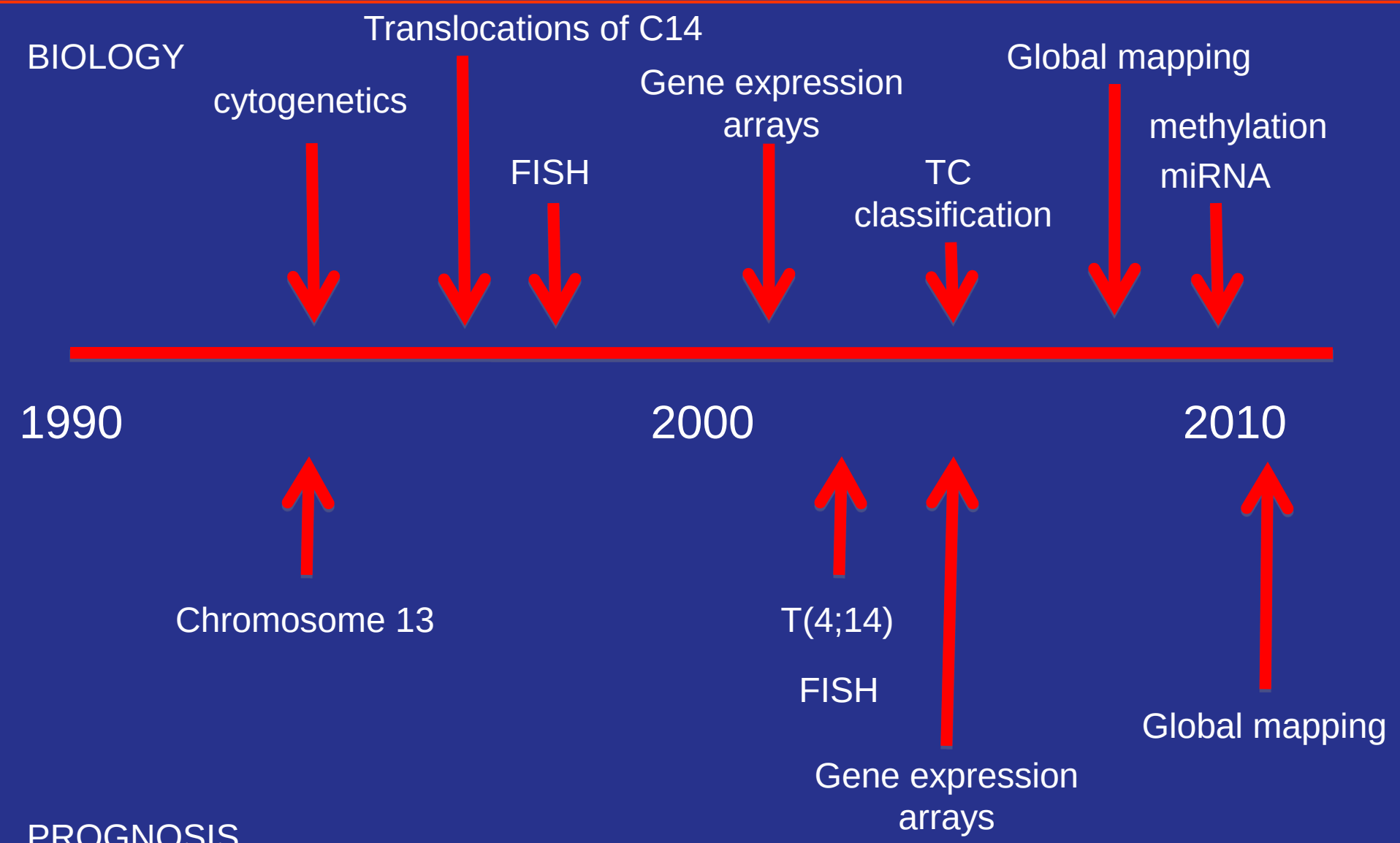
Identification of new therapeutic targets

- Use technology to identify genetic target
- Number of criteria for a good drug target
  - Central to the disease process
    - Over expression results in the disease phenotype
    - Knockdown results in cell death
  - Important in patients
    - Prognostic significance
  - Druggable
    - Design a small molecule that can inhibit the targets expression or function



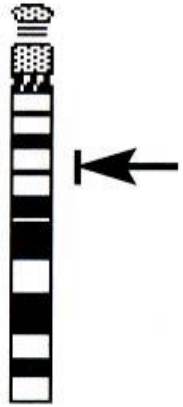
Davies *et al* Blood 2001, Dring *et al* Clin Can Res 2004, Bagratuni *et al* Blood 2010, Ali *et al* EMBOJ 2011

Timelines

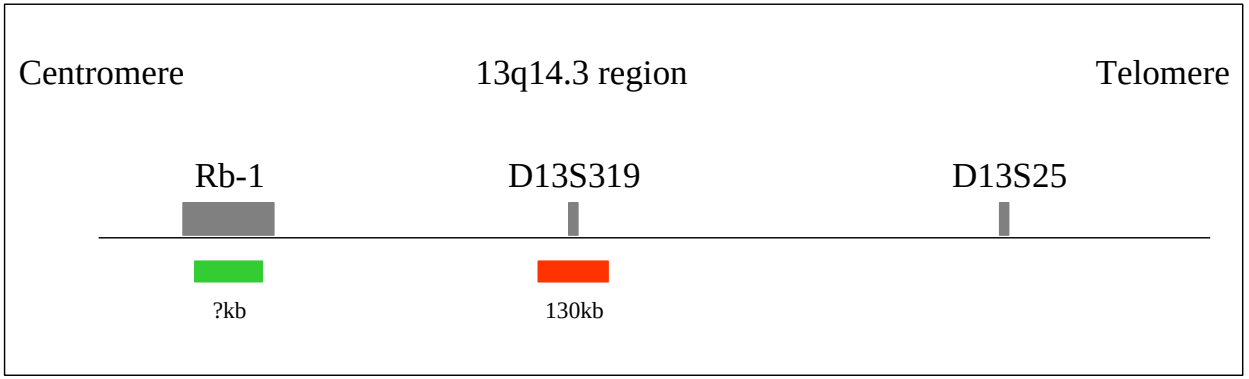

BIOLOGY
cytogenetics
Translocations of C14
FISH
Gene expression arrays
TC classification
Global mapping
methylation
miRNA
1990
2000
2010
Chromosome 13
T(4;14)
FISH
Gene expression arrays
Global mapping
PROGNOSIS

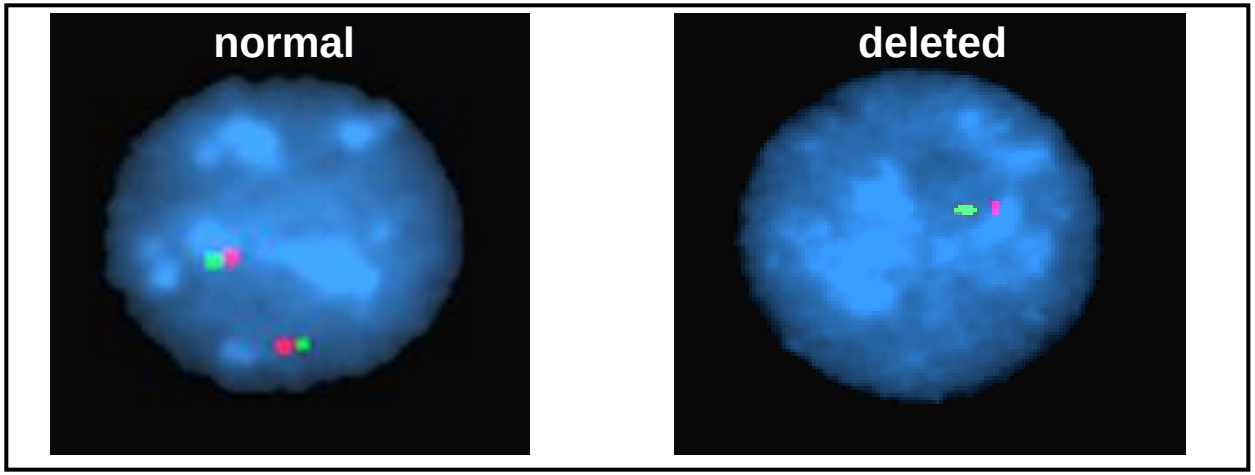
Chromosome 13 FISH – copy number

13q14 Region



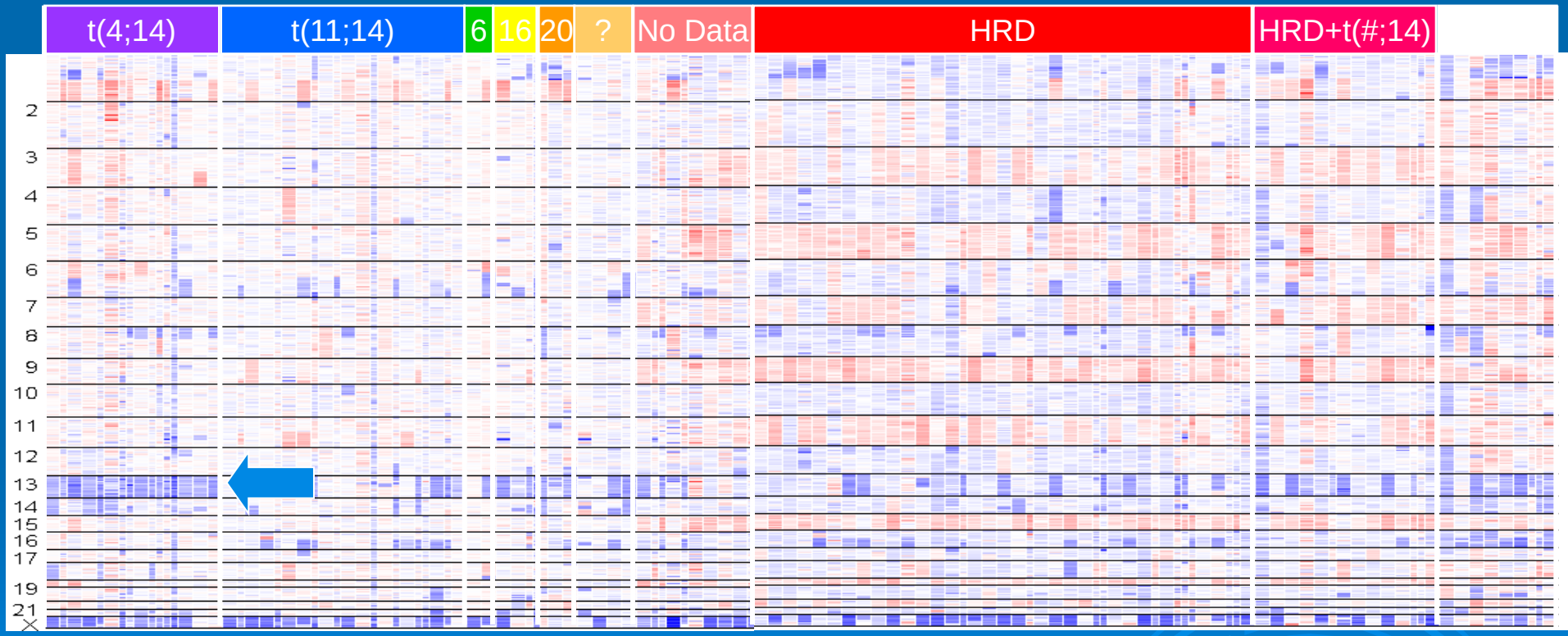
Retinoblastoma locus and distal area





Kindly provided by Dr Fiona Ross, Wessex Regional Cytogenetics Laboratory

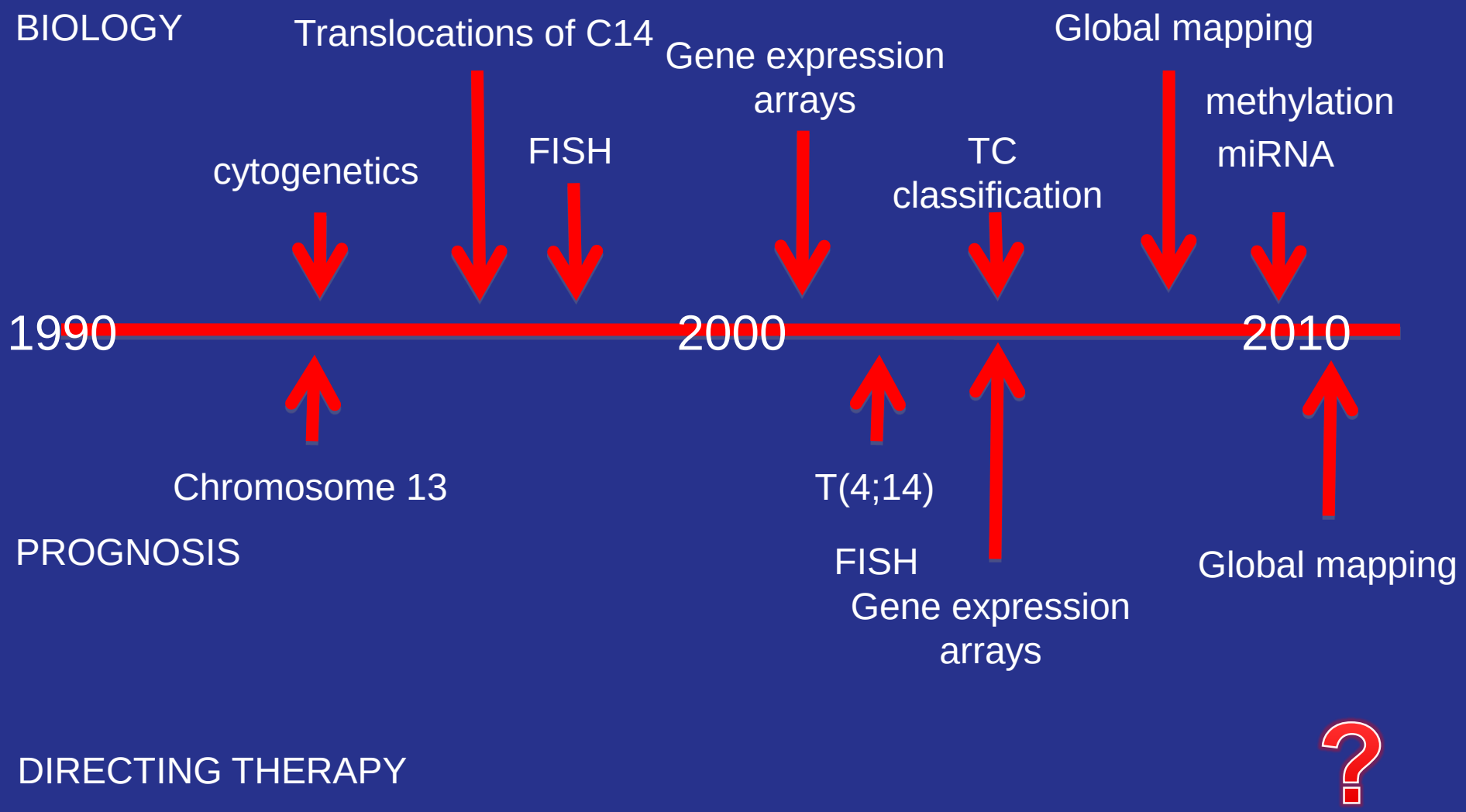
Inter relationship of genetics



All t(4;14) have del(13)

Kindly provided by Dr B Walker

Timelines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FISH
Gene expression arrays
Global mapping
DIRECTING THERAPY
?

Outstanding Questions

Have we identified all of the important lesions and do we know what they mean?

How do we integrate all the information from all of the different techniques?

What does it mean to our patients…….

- Can we identify any other new therapeutic targets?
- Do we know which markers we should use to predict prognosis?
- Should we be using genetic markers to lead our treatment decisions?
- Can we translate the technology into cost effective routine practice?

Acknowledgements

MRC Myeloma IX

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