

Why discuss CLL ?

- **Common: 40% of US leukaemia**
 - approx 100 pa in SJH / MWHB
 - 3 inpatients in SJH at any time
- **Median age of dx is 65 (30s....**
- **Incurable, survival 2-20 years**
 - Require ongoing supportive care
 - Some need very intensive treatment
- **Active area of research**
 - Stratify patients by prognostic profile
 - Profile directs therapy

Chronic Lymphocytic Leukaemia

“Acquired clonal lymphoproliferative disorder of late adulthood leading to accumulation of small, uniform, immunologically incompetent lymphocytes (usually) of B cell lineage”*

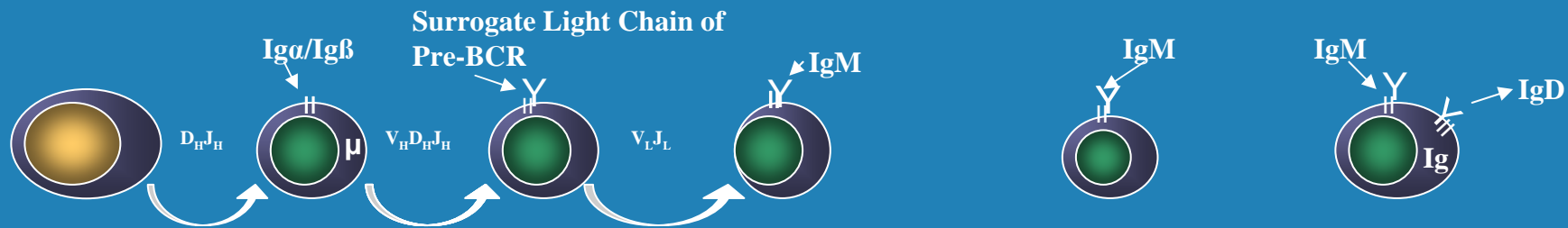
- Galton - CMAJ, 1966
- Dameshek - Blood, 1967

*Jandl, Blood Textbook of Hematology

B Cell Development



Stem Cell Pro-B Cell Pre-B Cell Immature-B Cell Naïve-B Cell Mature-B Cell



Pan B Cell Antigens CD19, CD20

CD38

CD22, CD23, CD40

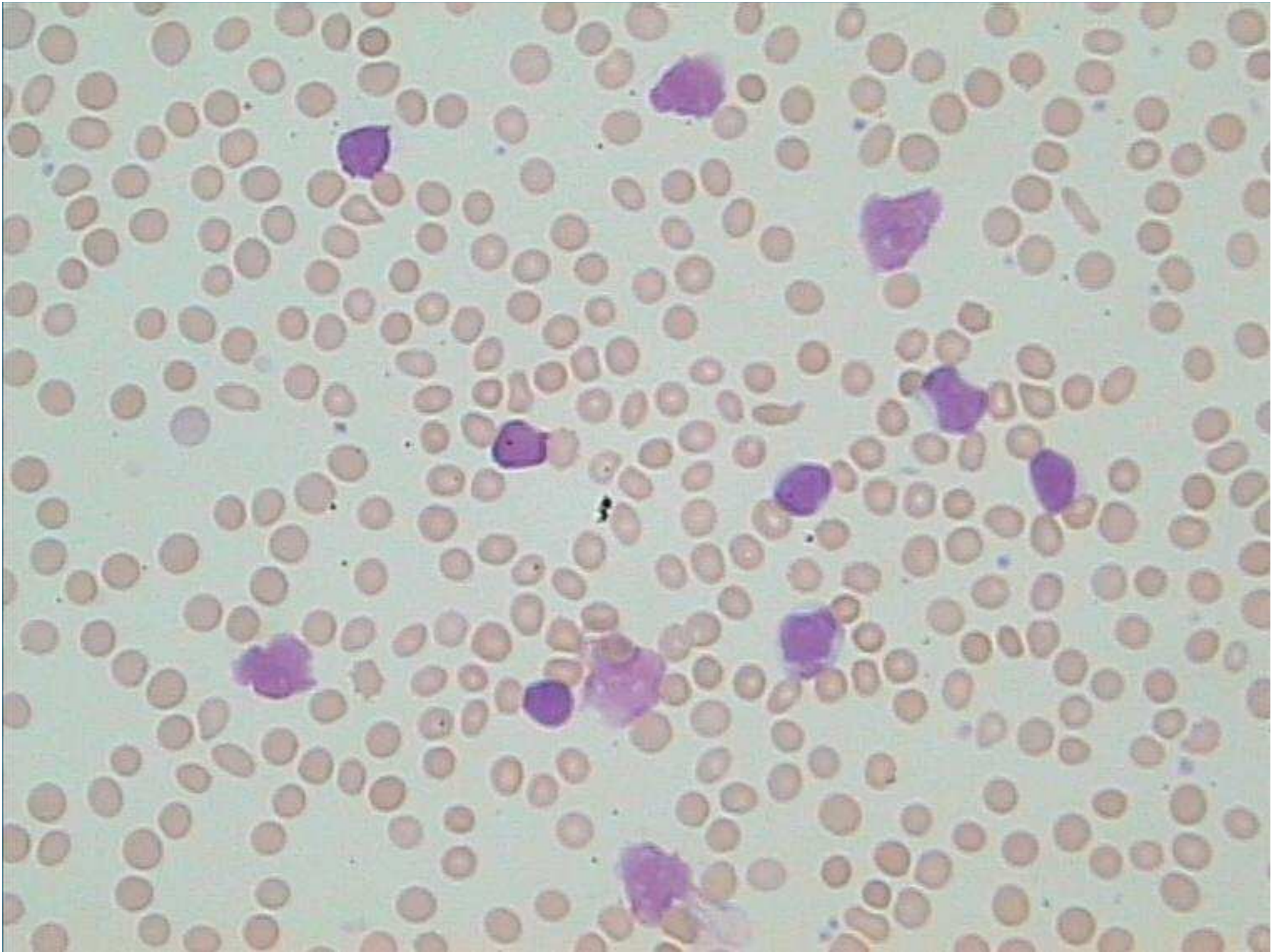
Ig gene rearrangement: -ive and +ive selection

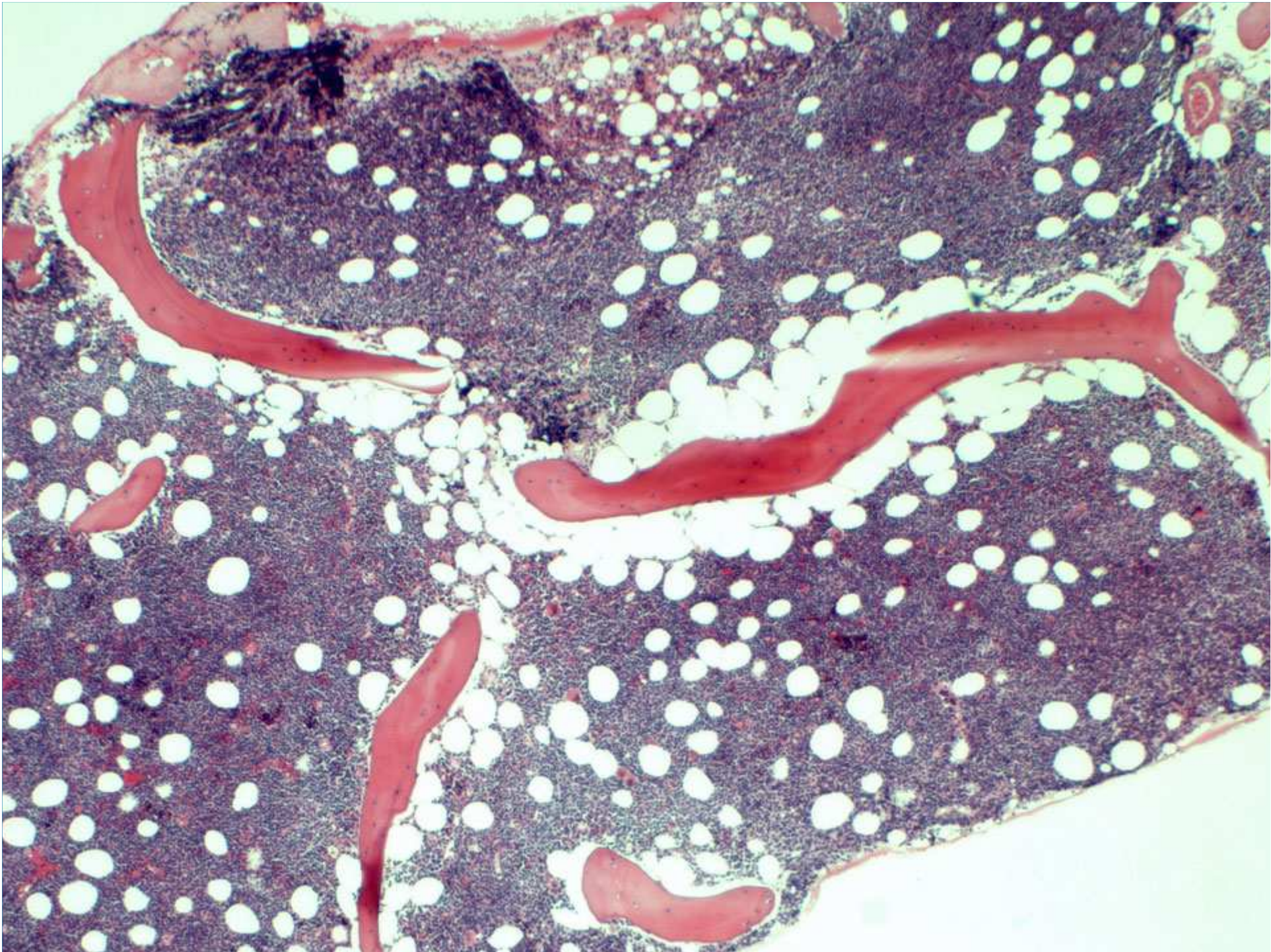
Somatic Hypermutation

Chronic LymphocyticLeukemia

Clinical presentation

- **Medi-screens**
- **Bone marrow failure**
 - anaemia, bleeding
- **Infections**
 - viral, bacterial
- **Lymphadenopathy**
- **Consequences of splenomegaly**
- **B symptoms, anergia**
- **Auto-immune presentation: AIHA**





Immunophenotype in CLL

FLOW CYTOMETRY REPORT:
GATE: Lymphocytes, representing 93% of all cells

EARLY CELL	%	B CELL	%
CD 10	<1	CD 19	97
		CD 5/ CD19	97
		CD 20	98
		CD 22	85(weak)
		CD 79b	92
		CD 23	97
T CELL	%	FMC 7	10
CD 2	3	IgM	97(weak)
CD 3	2	kappa	72
CD 5	98	lambda	24
CD 7	8	CD19/CD38	23

CLL: traditional conventional markers

Binet

Survival

10 y

A: < 3 node bearing areas

B: > 3 node bearing areas

1.5 y

C: Anaemia <10gms
+/-Thrombocytopenia
<100

Other factors

LDH

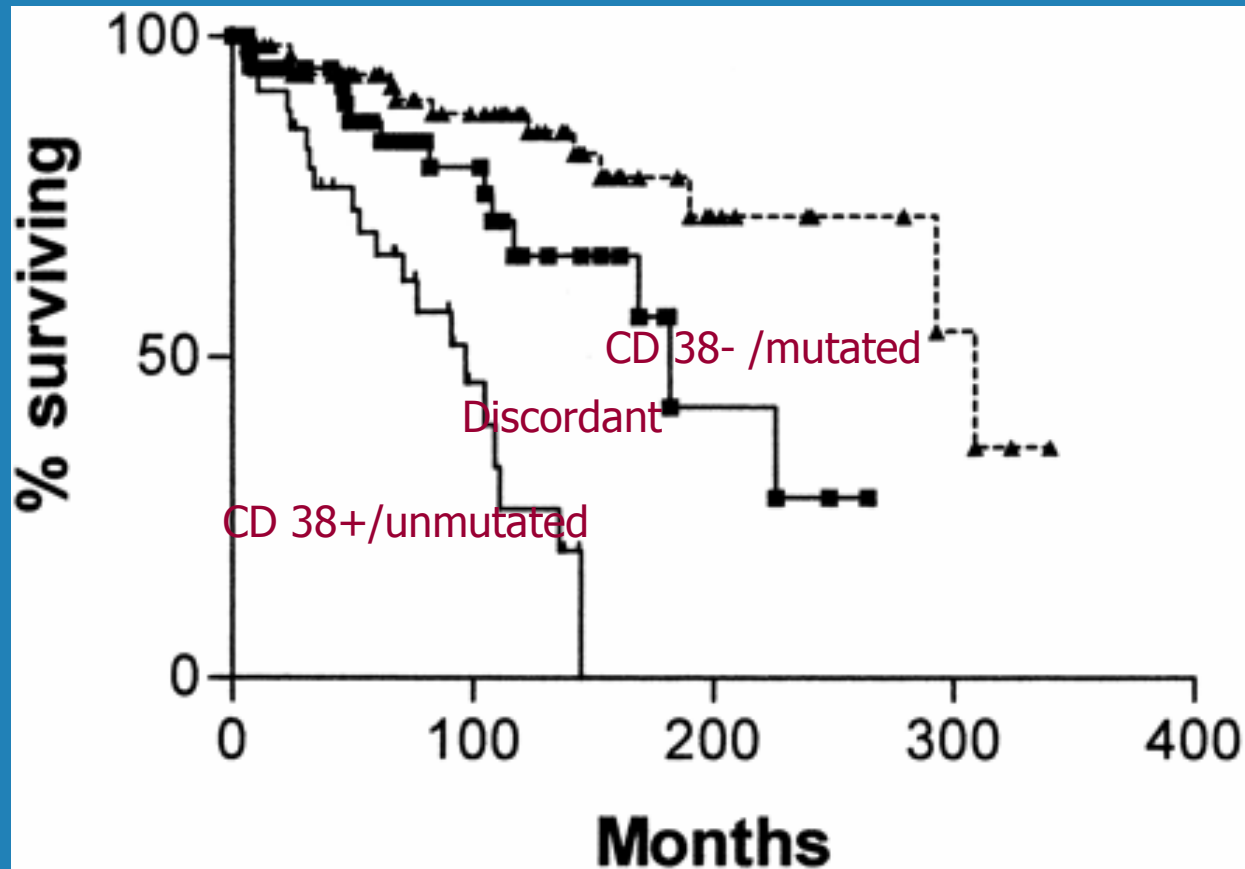
Lymphocyte doubling time

Newer prognostic factors

- **Cell surface markers**
 - **CD38 expression and pattern**
 - **CD20 expression level**
- **Cytogenetics**
 - **FISH technique**
- **Somatic hypermutation status**

Survival for 145 Stage A CLL patients by V_H gene and CD 38 expression

Hamblin et al, Blood 2002



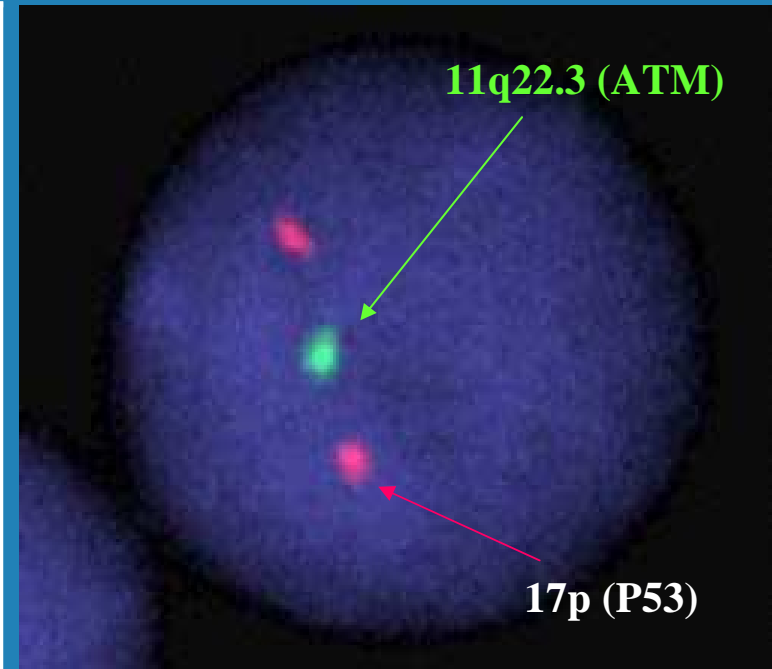
Molecular cytogenetics (FISH)

	no (%)	OS	RxFS
Del(13q)	117(36)	133	92
Normal	57(18)	119	49
Del(11q)	56(17)	79	13
+12	47(14)	114	33
Del(17p)	23(7)	32	9
Others	25(8)		

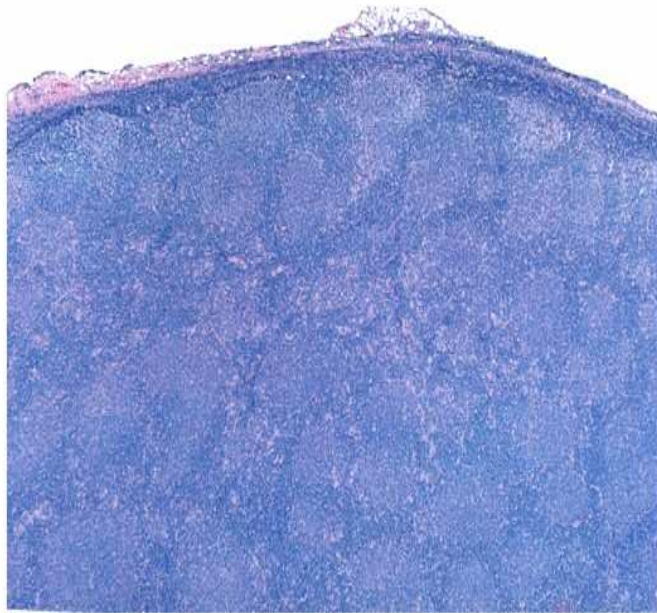
• *Dohner et al, N Engl J Med 2000*

Incidence of Chromosomal abnormalities in 77 Patients With CLL

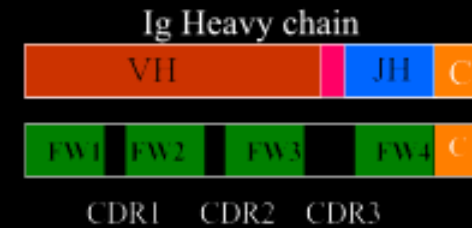
Aberration	No of Pts(%)
Normal	23 (30)
del 13q	44 (57)
Trisomy 12	8 (10)
del 11q	6 (8)
del 17p	3(4)
Total Clonal abnormalities	54(70)



The germinal centre



Clonal expansion
Apoptosis
Isotype switch

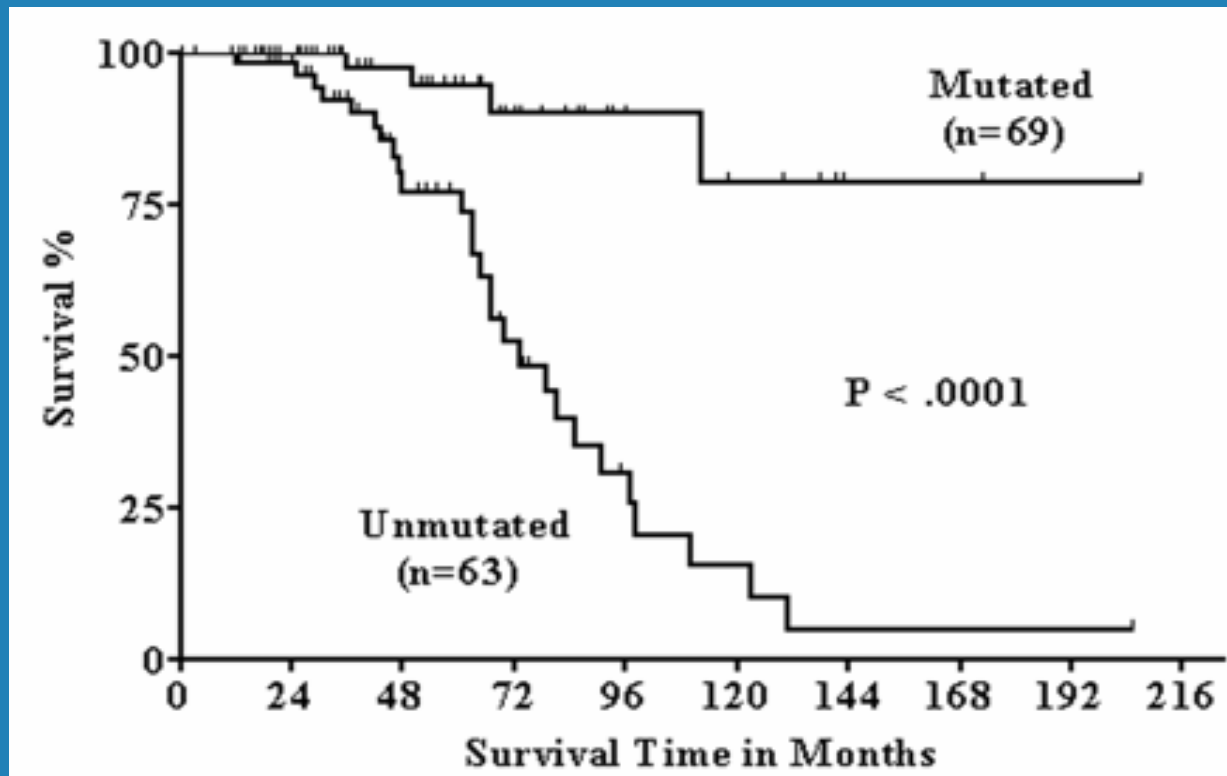


SHM: change in CDR3
homology by $\geq 2\%$

DNA PCR, sequence
and match

Marker of GC education

OS mutated vz unmutated VDJ CLL (Binet A)



Management

- **Watch and wait**
- **Supportive care**
- **Chemotherapy**
 - alkylating agent
 - purine analogues
- **Antibody therapy**
 - Rituximab
 - Campath IH
- **Transplantation**

Indications for treatment

- **Know your end-point**
- **Progressive disease (LDT)**
- **Bulky disease**
- **Bone marrow failure (Binet C)**
- **B symptoms**
- **Auto-immune disorders**

Supportive therapy

- **Prompt treatment of infections**
 - GP
 - Chiropodist and dentist
 - Other hospital services
- **Avoidance of secondary cancer**
- **Avoid re-investigation**
- **Education of patient and families**

Patients <65

- **Watch and Wait**
- **FCR chemotherapy @ SJH**
 - 39 patients (26 pup)
 - 27 patients achieved CR (mrd-ve)
 - 24 patients maintained CR @ 20m
 - Rx naïve patients <65, no NRM
- **Campath IH if 17p deletion**
 - Consider NST to consolidate

Patients <65 at relapse

- **Length of remission important**
- **FCR, FMCR or Campath**
- **Conventional intensive therapy**
 - **CHOP, ESHAP**
- **Consider NST to consolidate**
 - **Must have chemo-sensitive disease**
 - **5/6 in CR, with toxicity**
 - **4 being considered for SCT**

Patients >65

- **Tailor to co-morbidity and px**
- **Chlorambucil**
- **Rituximab if CD20 expression high**
- **Fludarabine, FC**
- **FCR**
- **Steroids**

Natural history

- **Bone marrow failure**
- **Infection**
 - **Viral infection**
 - **Fungal infection**
 - **PC pneumonia**
- **Richter transformation**
- **Second malignancy**

Unusual infections



cryptosporidium



PCP pneumonia

Unusual infections

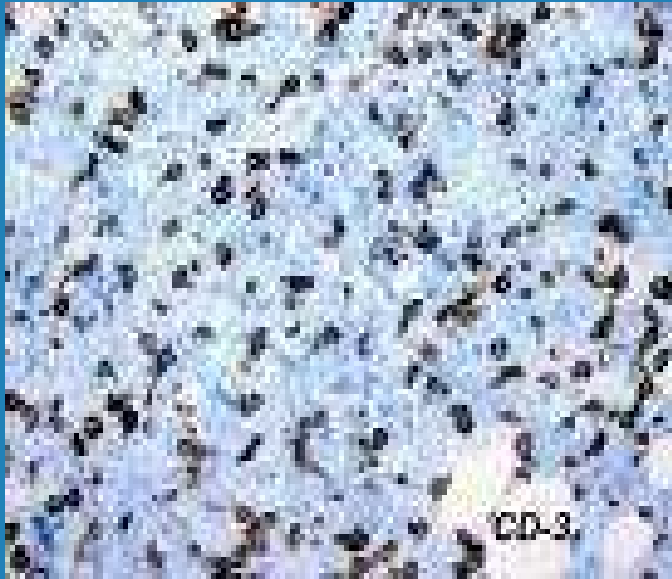


Herpes Simplex



Aspergillus

Natural history of CLL



Richter transformation



Skin cancer