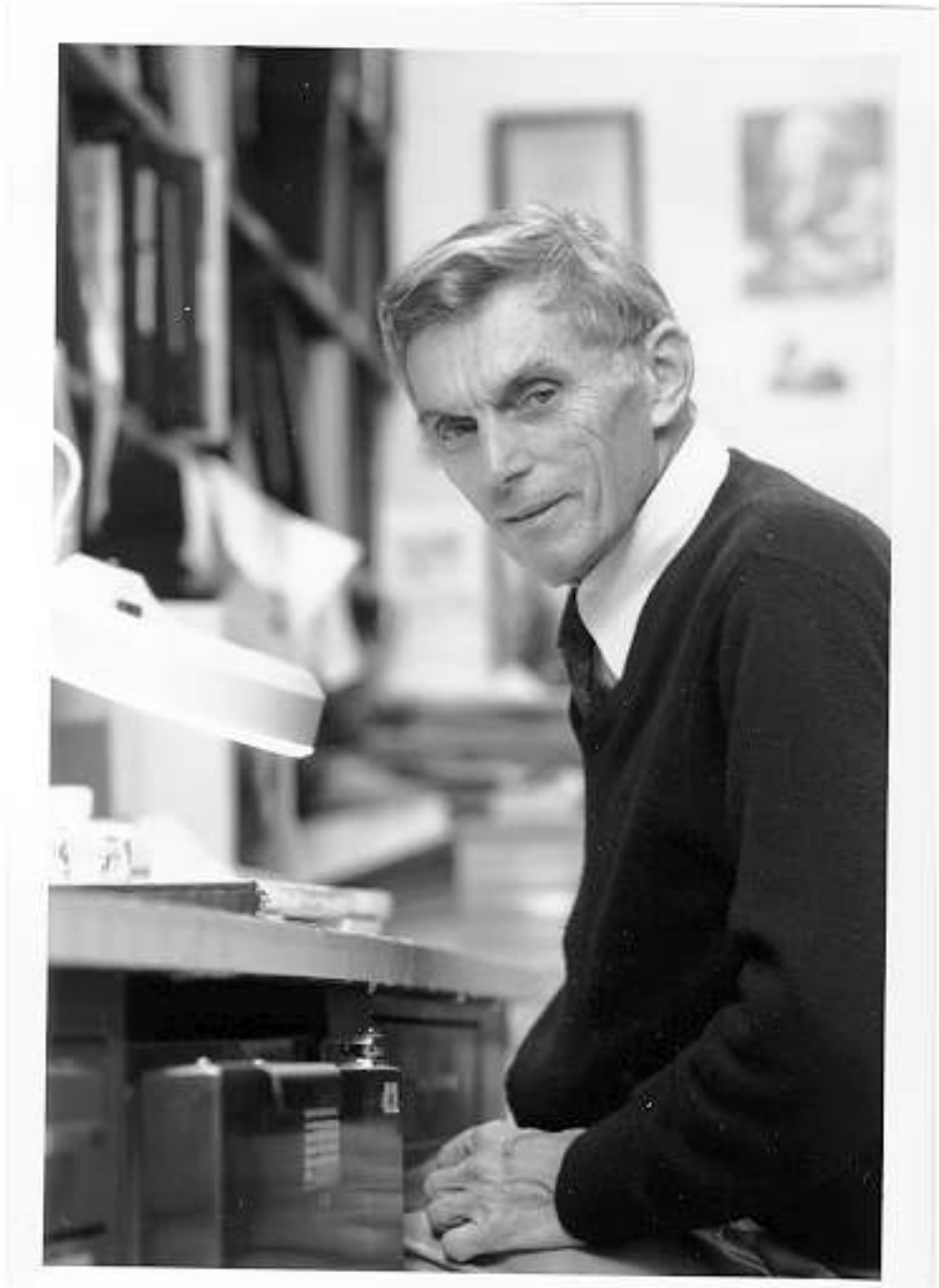
Molecular pathogenesis of plasma cell MGUS and MM

Michael Kuehl
National Cancer Institute

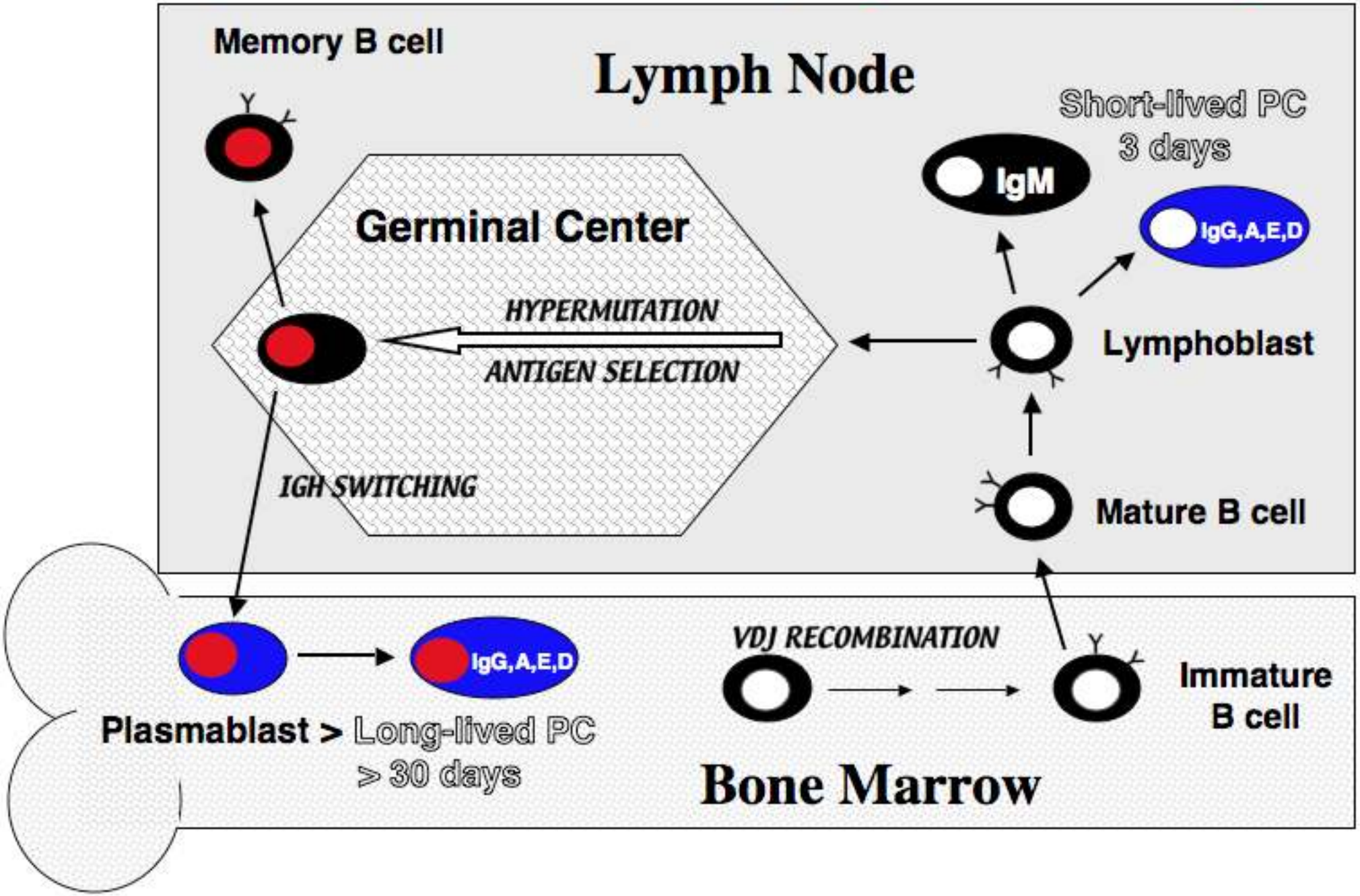
13th International Myeloma Workshop



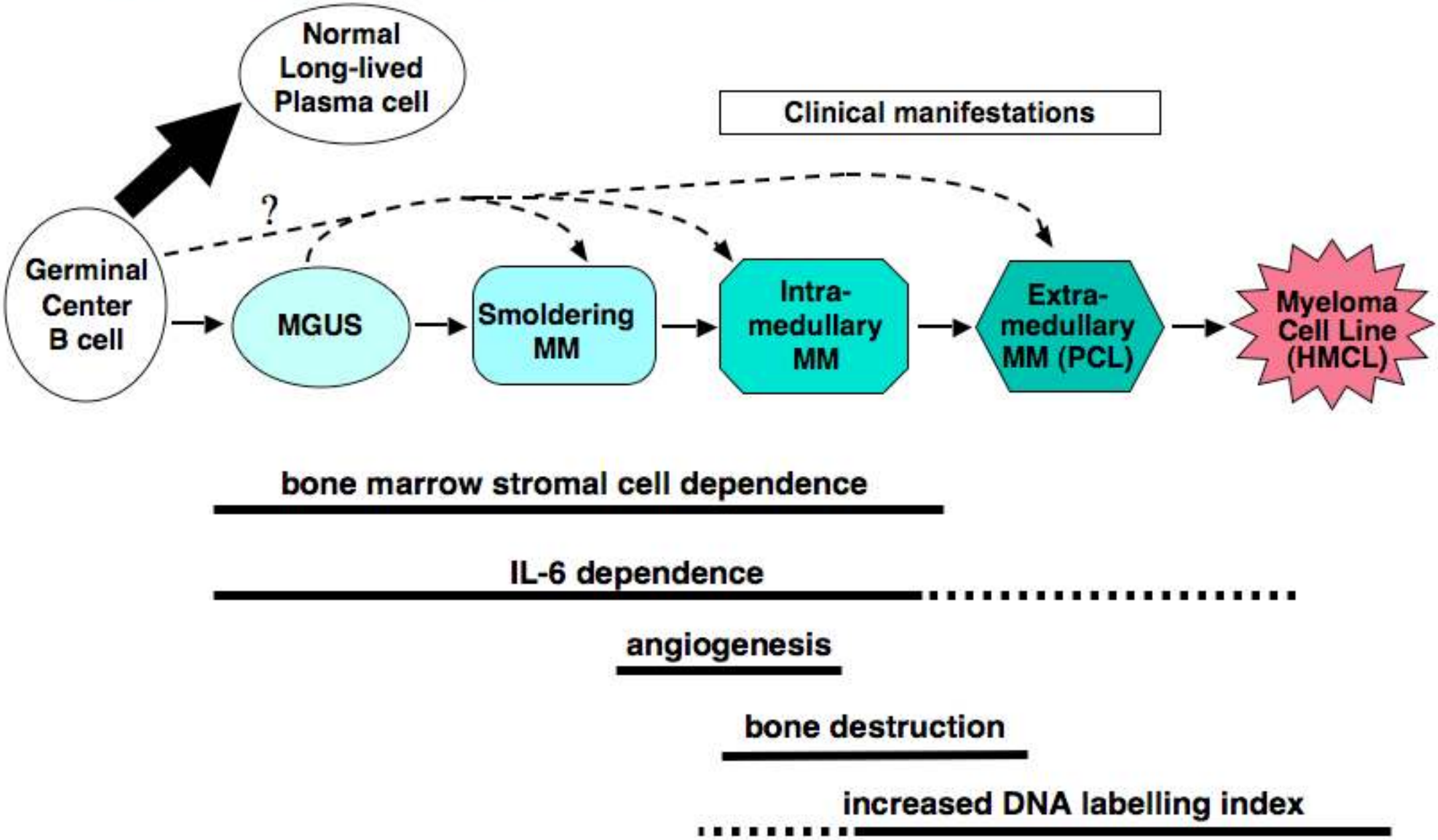
Michael Potter

Leif Bergsagel
1988

Two kinds of plasma cells: short-lived and post-germinal center long-lived

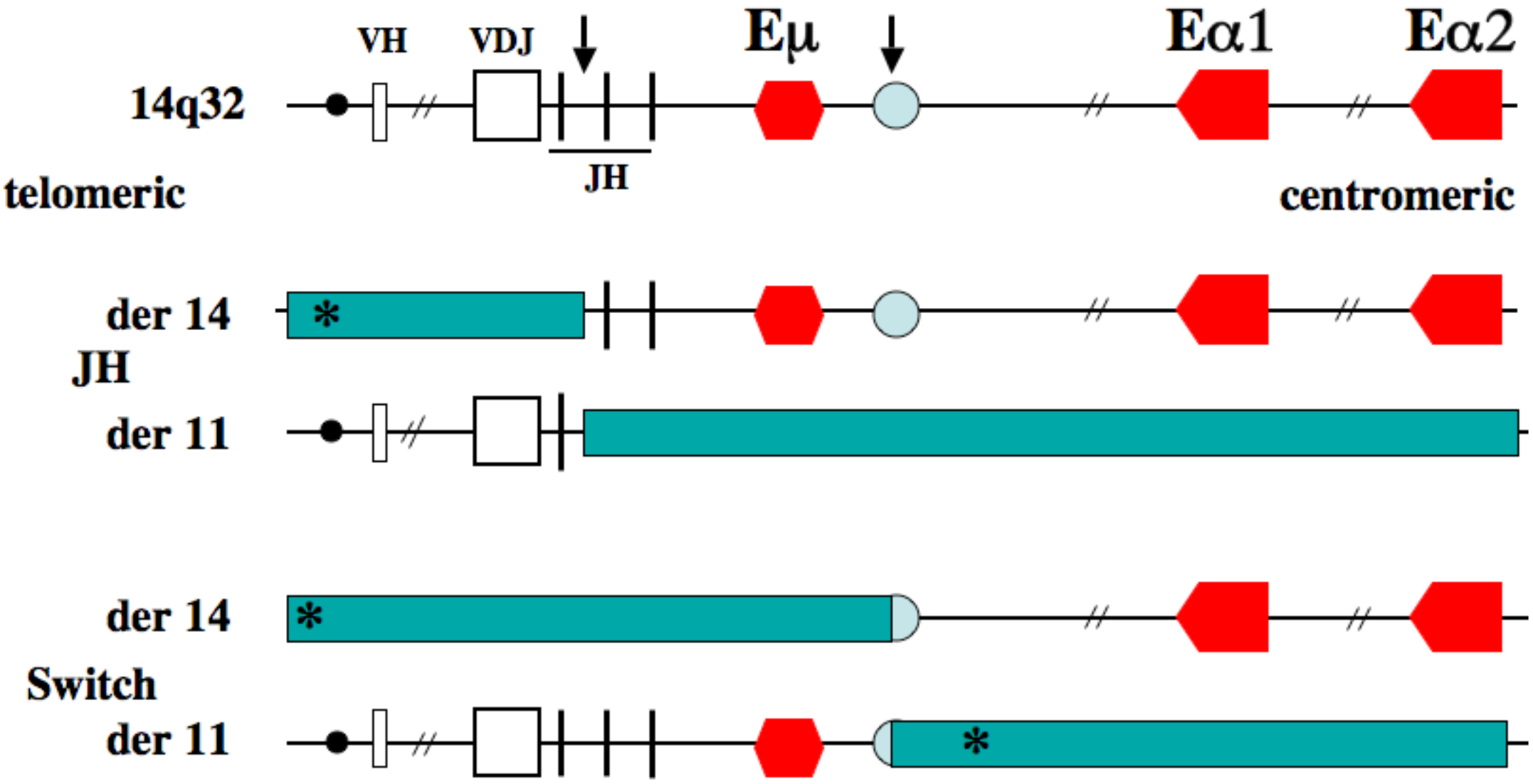


Stages: pre-malignant MGUS > MM > EMM > HMCL



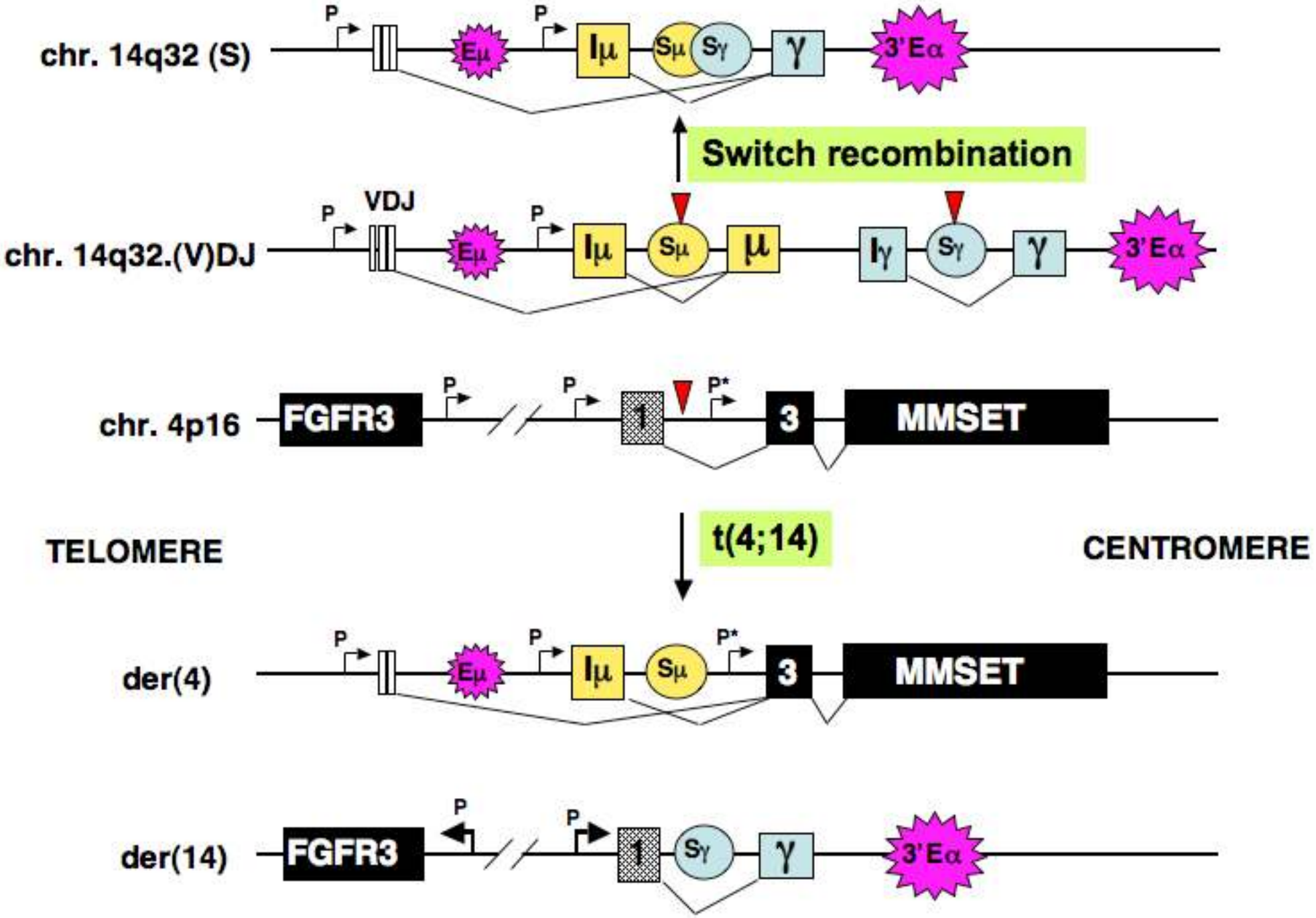
Phoenix, Arizona November 2010

14q32 translocation breakpoints: JH vs SWITCH



*** Oncogene dysregulated by Eμ and/or Eα ***

Figure 3. Anatomy of t(4;14)(p16;q32) chromosome translocation



Marta Chesi

Three primary IgH translocation groups In MGUS and 40% of MM tumors

CYCLIN D group		**18%**
11q13 (CYCLIN D1)	15	
6p21 (CYCLIN D3)	3	
12p13 (CYCLIN D2)	< 1	
MAF group*		**7%**
16q23 (c-MAF > CYCLIN D2)	4	
20q11 (MAF B > CYCLIN D2)	2	
8q24.3 (MAF A > CYCLIN D2)	< 1	
MMSET/FGFR3 (4p16)		**15%**

* MAFs are transcription factors for Cyclin D2

Rafael Fonseca

Chromosome content indicates 2 pathogenic pathways, each occurring in ~50% of both MGUS and MM tumors

Hyperdiploid (HRD) (48-75 chromosomes)

- **multiple trisomies selectively involving 8 chromosomes (3, 5, 7, 9, 11, 15, 19, 21)**
- **primary IgH translocations in ~10%**

Non-hyperdiploid (NHRD) (<48 and/or >75 chromosomes)

- **primary IgH translocations in ~ 70%**

MYC locus complex rearrangements in MM: a late progression event

- Selective expression of L-MYC, N-MYC or one parental MYC allele (11) in all 13 informative HMCL

- MYC rearrangements by FISH
  - 84% HMCL
  - 48% advanced MM
  - 15% newly diagnosed MM
  - rarely - if ever - in MGUS or SMM

- Heterogeneity of MYC rearrangements frequent in MM

Progression by secondary (Ig) translocations

What translocations are secondary?

MYC: c- >> N- >> L-

OTHER secondary translocations

IgH(non-recurrent or rare partner)

IgL (κ >> λ)

rarely IgH with one of seven recurrent partners

	PRIMARY	SECONDARY
TIMING	very early	anytime*
B CELL SPECIFIC MECHANISM	yes**	no (off in PC)
STRUCTURE	simple	complex
PREVALENCE	70%NHRD;10%HRD	NHRD = HRD
HETEROGENEITY	no	sometimes

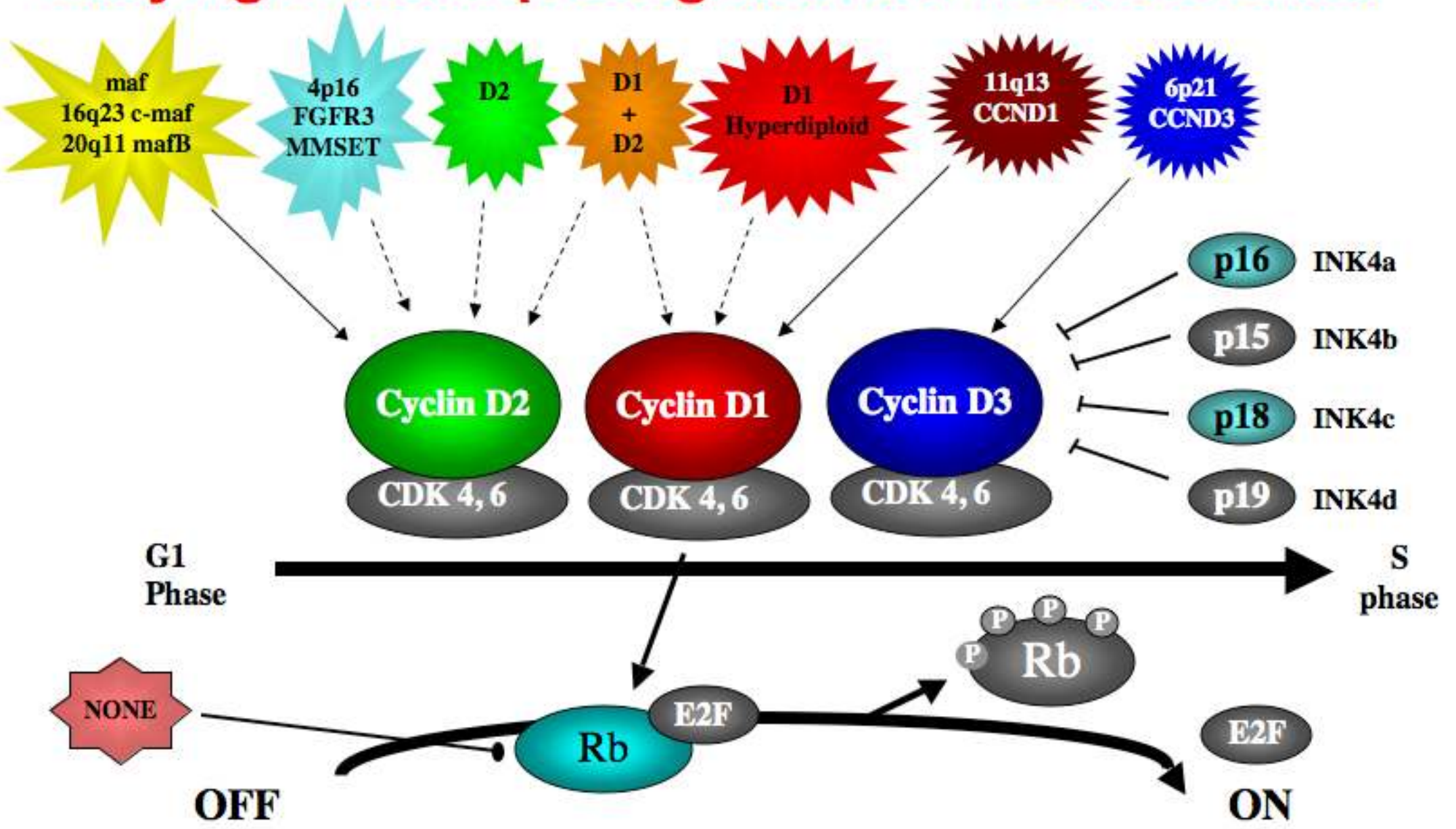
* MYC rare in MGUS but OTHER 2° TLC not rare in MGUS

** mostly IgH switching; sometimes somatic hypermutation

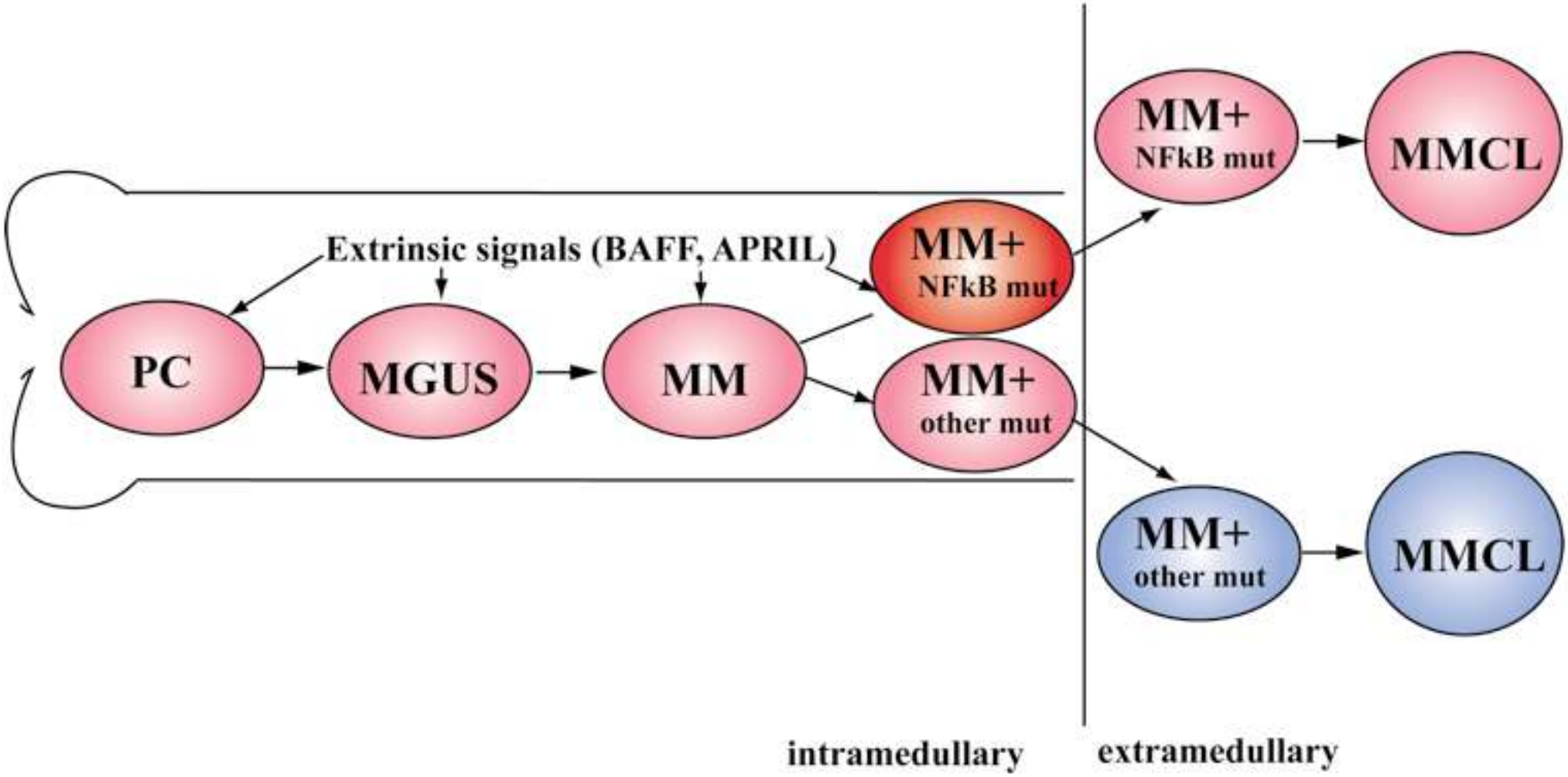
John Shaughnessy

Bart Barlogie

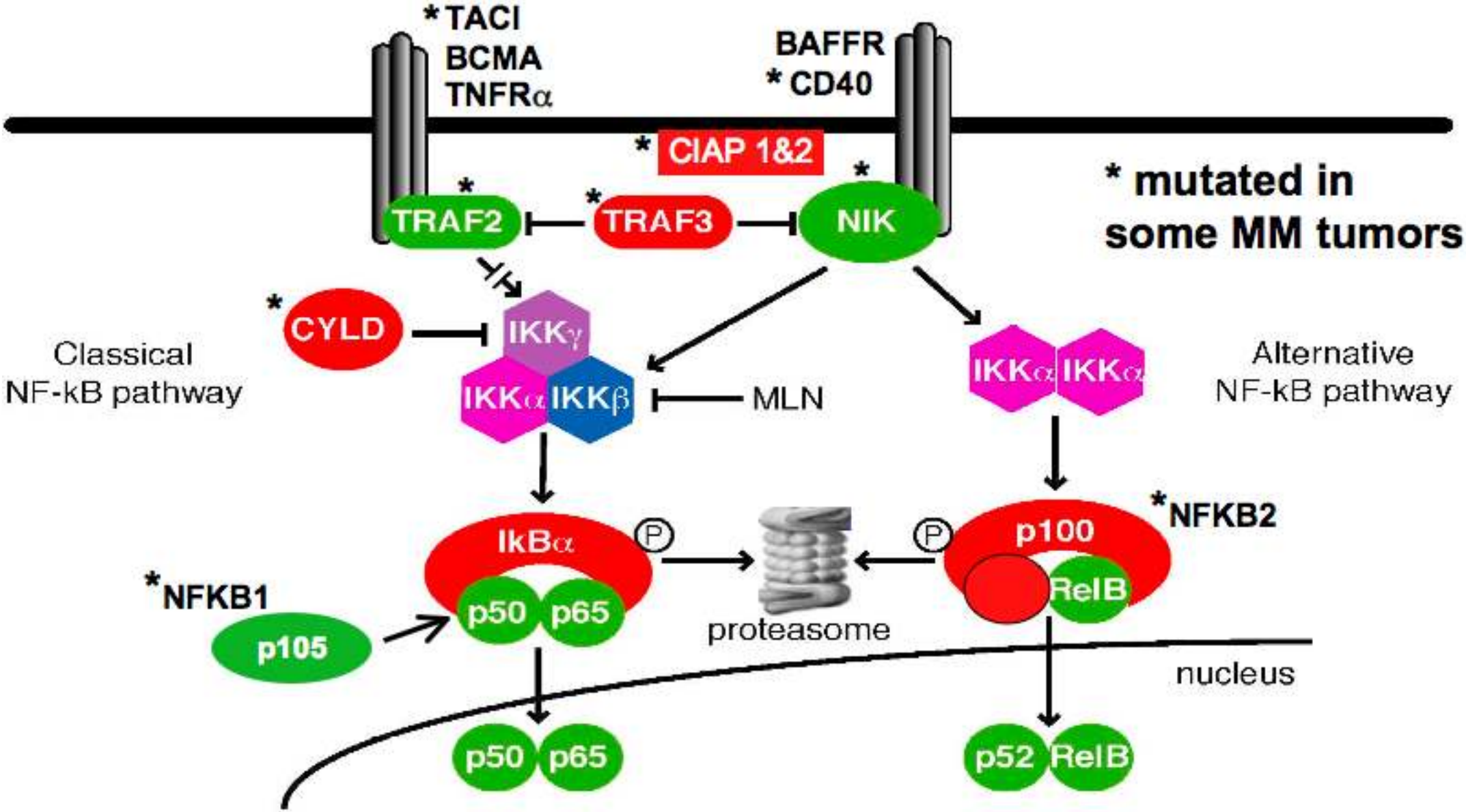
Dysregulation of a CYCLIN D gene is early, and unifying event in pathogenesis of MGUS and MM



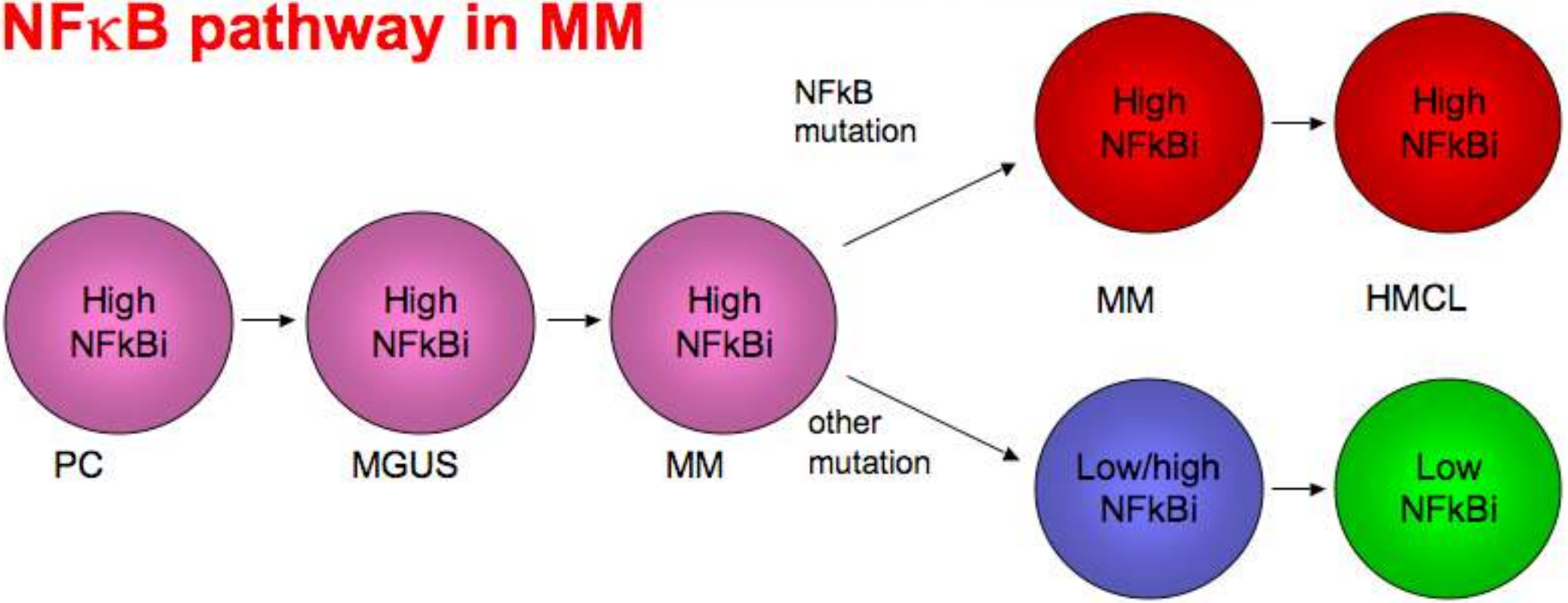
NFkB pathway is activated by extrinsic signals in PC, MGUS, MM: activating mutations during progression contribute to less dependence of MM tumor cells on bone marrow microenvironment



Mutations activate classical and/or alternative NFkB pathway in 45% MMCL and >17% MM tumors



Extrinsic and intrinsic agents to target the NFκB pathway in MM



Extrinsic activation of NFkB

BAFF,APRIL > BCMA,TACI, BAFF-R > NFkB activation

BCMA-Fc
TACI-Ig

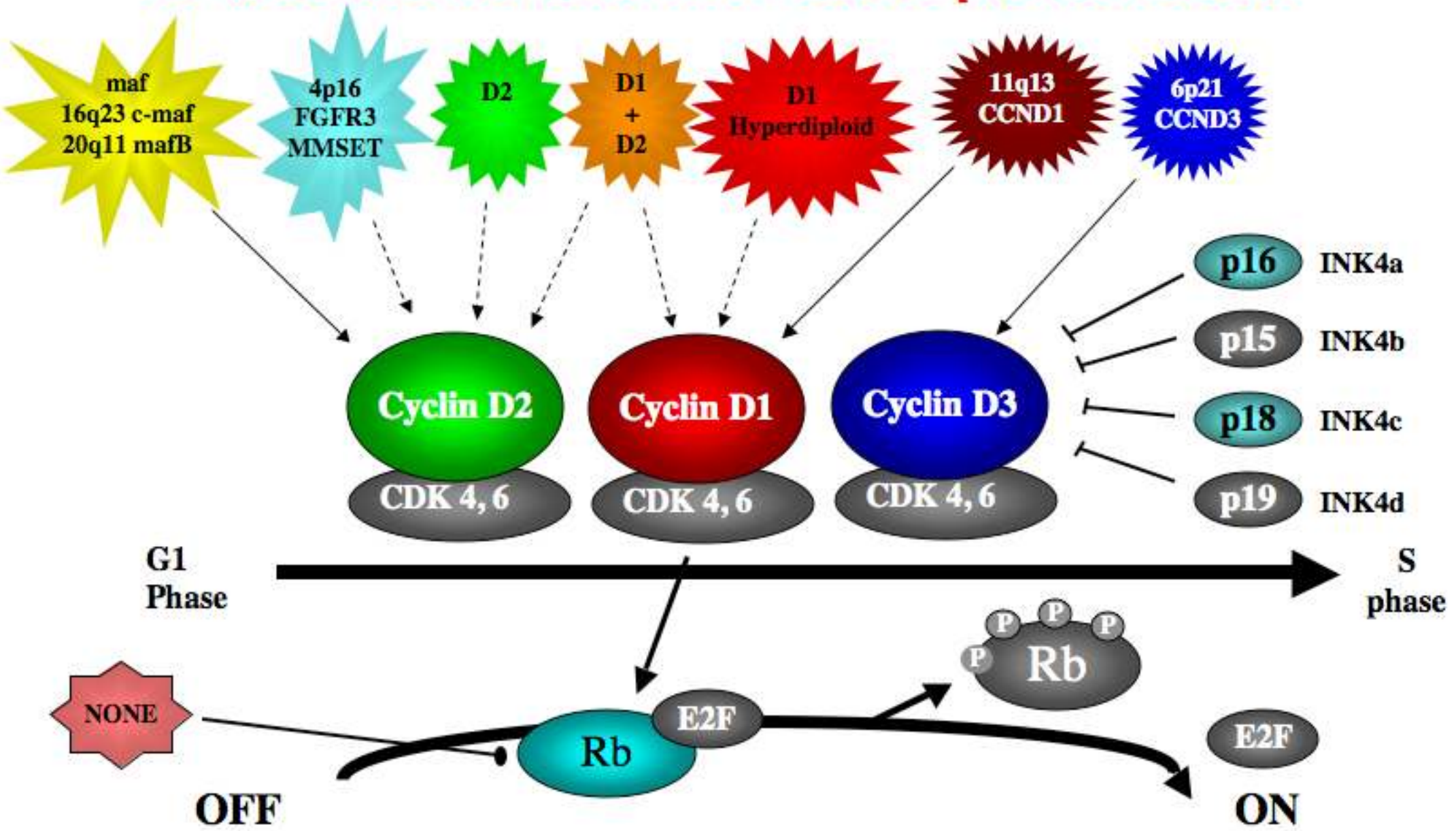
Bortezomib
IKKß inhibitor
NIK inhibitors

The p18INK4C PARADOX: increased p18 RNA / insensitivity to p18 in most HMCL & proliferative (PI > 2) MM

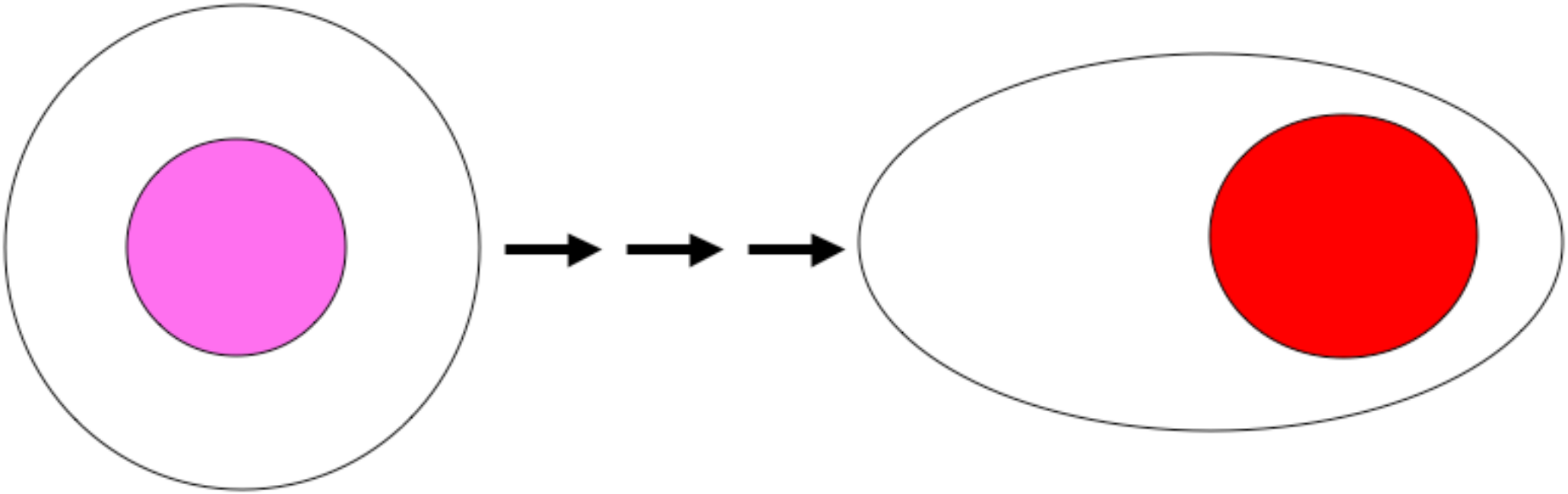
CELLS	PI	% HIGH p18
NL PC	<1	0
HMCL	>2	59
MM	<1	3
	1-2	13
	>2	60

Increased E2F -> increased proliferation and increased p18 RNA

Sequential disruption of the RB pathway is associated with increased proliferation



Memory B cell that shares clonotype and primary IgH translocation but not K-RAS mutation is a premalignant precursor but not a tumor propagating/cancer stem cell



Memory B cell
CD138- CD19+
IgH translocation
K-RAS NOT mutated

Myeloma tumor cell
CD138+ CD19-
IgH translocation
K-RAS MUTATION

Bob Kyle

MGUS mostly/?always precedes MM

- Monoclonal Ig is detected at least 2.5 years prior to diagnosis of MM in most patients

  Weiss et al: 27/30 patients (90%)

  Landgren study: 75 patients (>95%)
- Four (13%) light chain only MM evolved from light chain only MGUS, both detected only by sFLC

  Consistent with Dispenzieri et al that there is a similar fraction of light chain only MGUS and MM

K-RAS mutations in 17% of MM, but not detected in MGUS

	No.	N-RAS	K-RAS	N+K-RAS
MGUS	51	0.08	0*	0.06
MM	248	0.14	0.17	0.31

*$P<10^{-7}$

N-RAS: 21% CYCLIN D1 but only 4% CYCLIN D2 MM
K-RAS: 17% CYCLIN D1 and CYCLIN D2 MM

? Overlapping but non-identical roles for K- and N-RAS mutations in MGUS/MM

Kathy Giusti
MMRF > MMRC

MYC dysregulation during MM pathogenesis

FISH: MYC-Ig rearrangements occur late in pathogenesis
0% MGUS
6% untreated MM
27% advanced MM
50% MM cell line

CGH: MYC locus rearrangements in MM
- Discordant with MYC-Ig rearrangements detected by FISH
MM, 35% in newly diagnosed and 42% in relapsed
- Prevalence is 16% with t(11;14) but 55% for hyperdiploid

MYC RNA expression:
MMR > MMNR > MGUS
HMCL: mono-allelic with MYC locus rearrangement
bi-allelic without rearrangement

MYC dysregulation occurs both early and late in MM pathogenesis

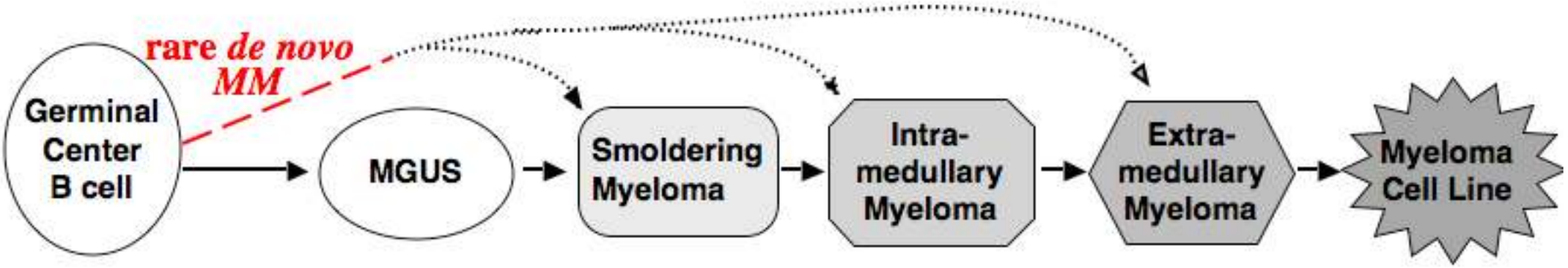
EARLY

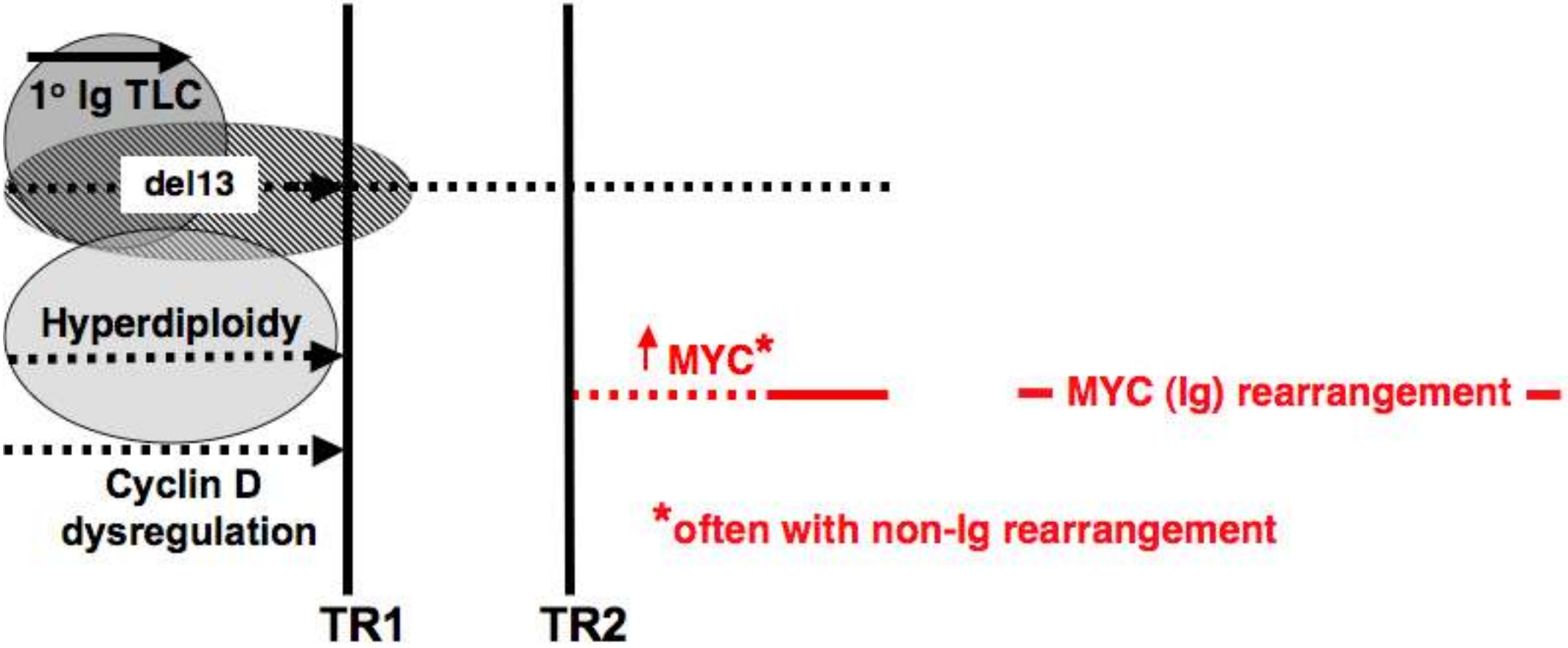
- Increased MYC RNA in MM compared to MGUS (?SMM)
- Cryptic rearrangements detected by CGH
- MYC-Ig rearrangements are rare

LATE

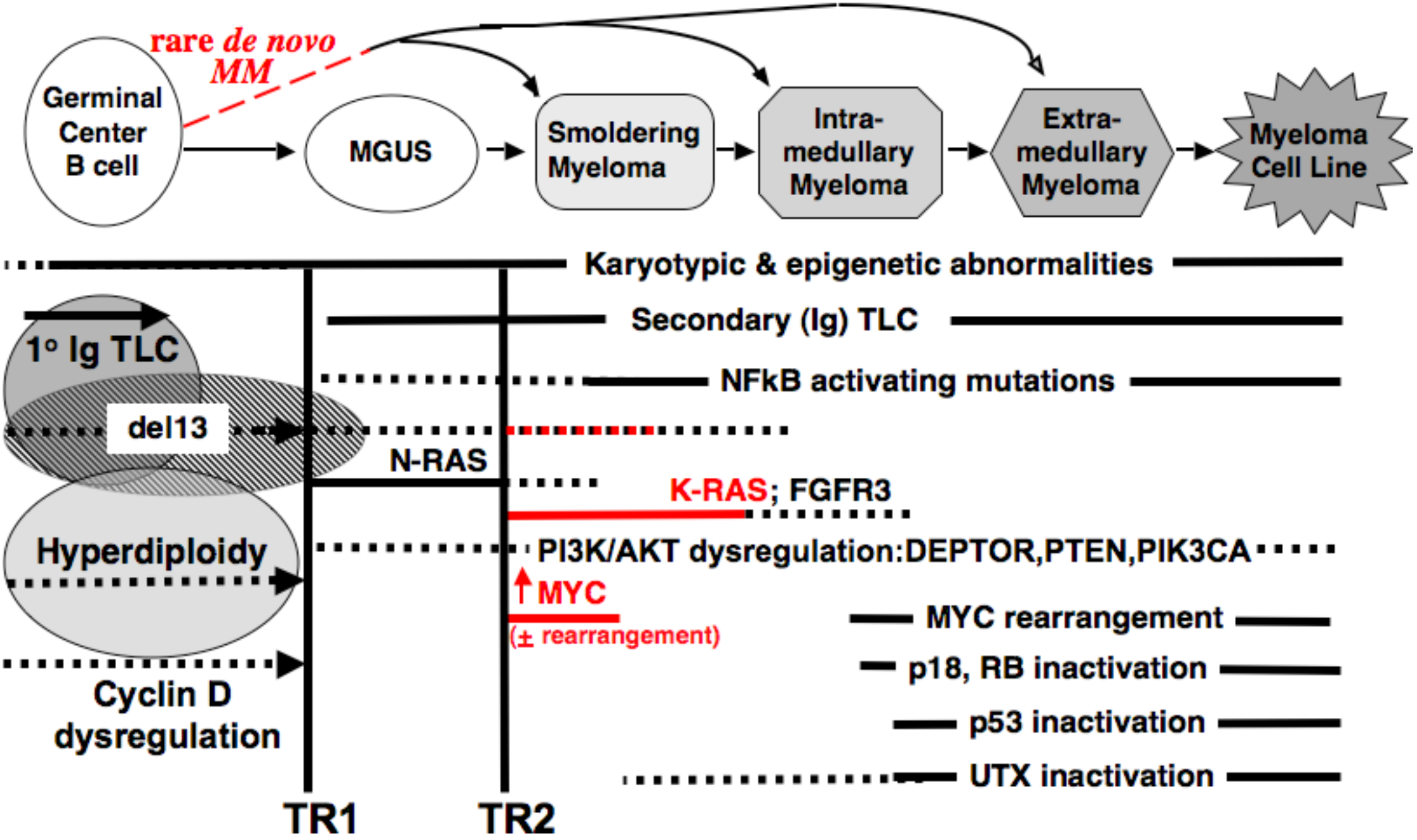
- MYC rearrangements often involve juxtaposition of MYC near an Ig locus (IgH>IgL>IgK)
- Associated with increased prevalence of p53 mutations
- Associated with increased proliferation and stromal cell independence, i.e., extramedullary

MYC dysregulation: 2 stages of MM pathogenesis





Molecular pathogenesis of MM



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