THE UNIVERSITY OF TEXAS
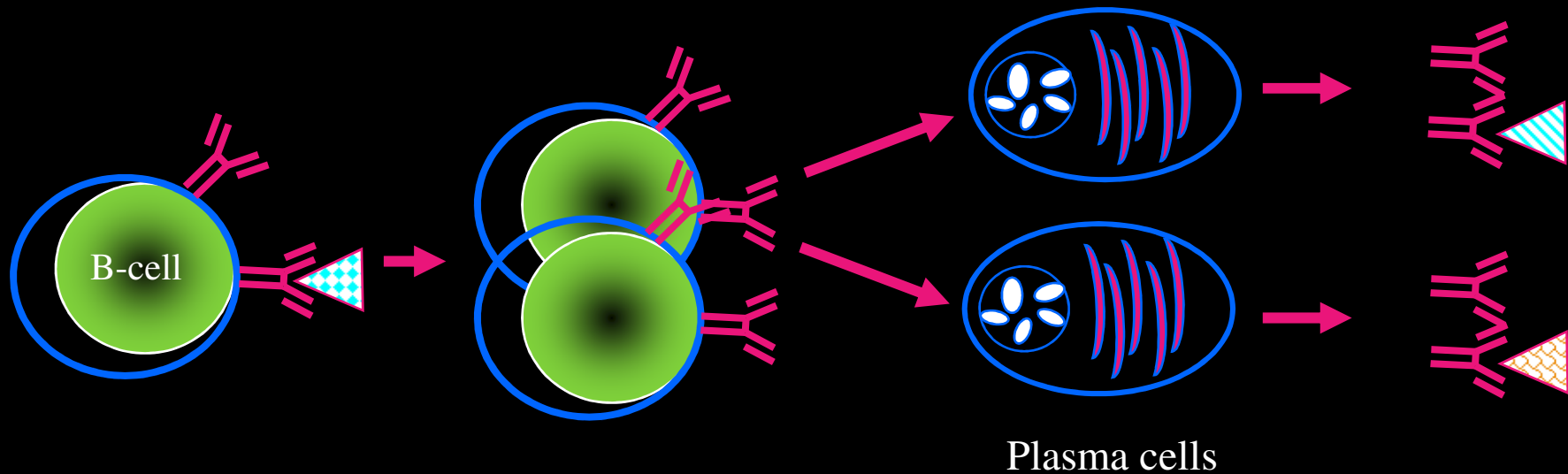**MD Anderson**
Cancer Center
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Role of Immunoglobulin Gene Expression in Acute Myeloid Leukemia

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Department of Hematopathology
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Cancer Center

Immunoglobulin (Ig) has been presumed to be produced only by B-cells and plasma cells
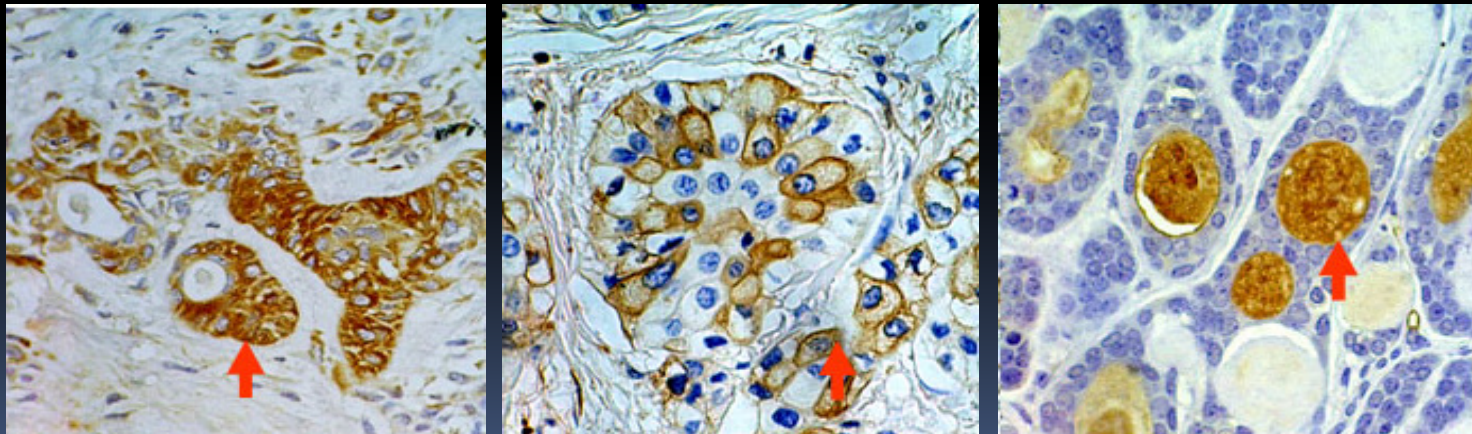

B-cell

Plasma cells

- Consists of 2 heavy chains and 2 light chains
- Function as antibodies to identify and neutralize pathogens
- Ig diversity generated by several mechanisms
- Only produced by B-cells and plasma cells
- Ig gene rearrangement used for the diagnosis of B-cell lymphomas
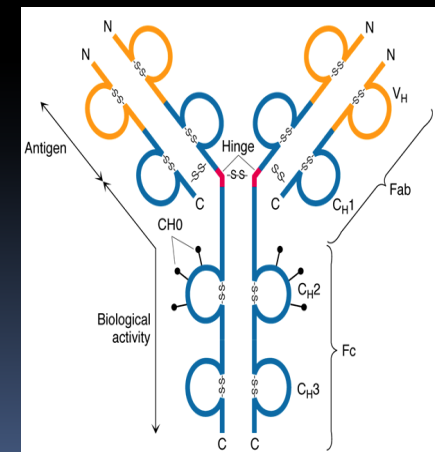
Discovery of non-B-cell-derived Ig

- 1989, IgG-like immunostaining was found incidentally in breast cancer cells (Qiu *et al*.)

- 1996, first report of IgG-like molecule in epithelial cancer cells (Qiu *et al. Chinese J Immunol*. 1996)

- 2003, first report of IgG-like molecule with growth factor-like activity (Qiu *et al. Cancer Res*. 2003)

Non B-lineage cells could also produce Ig

B-cells

Ig
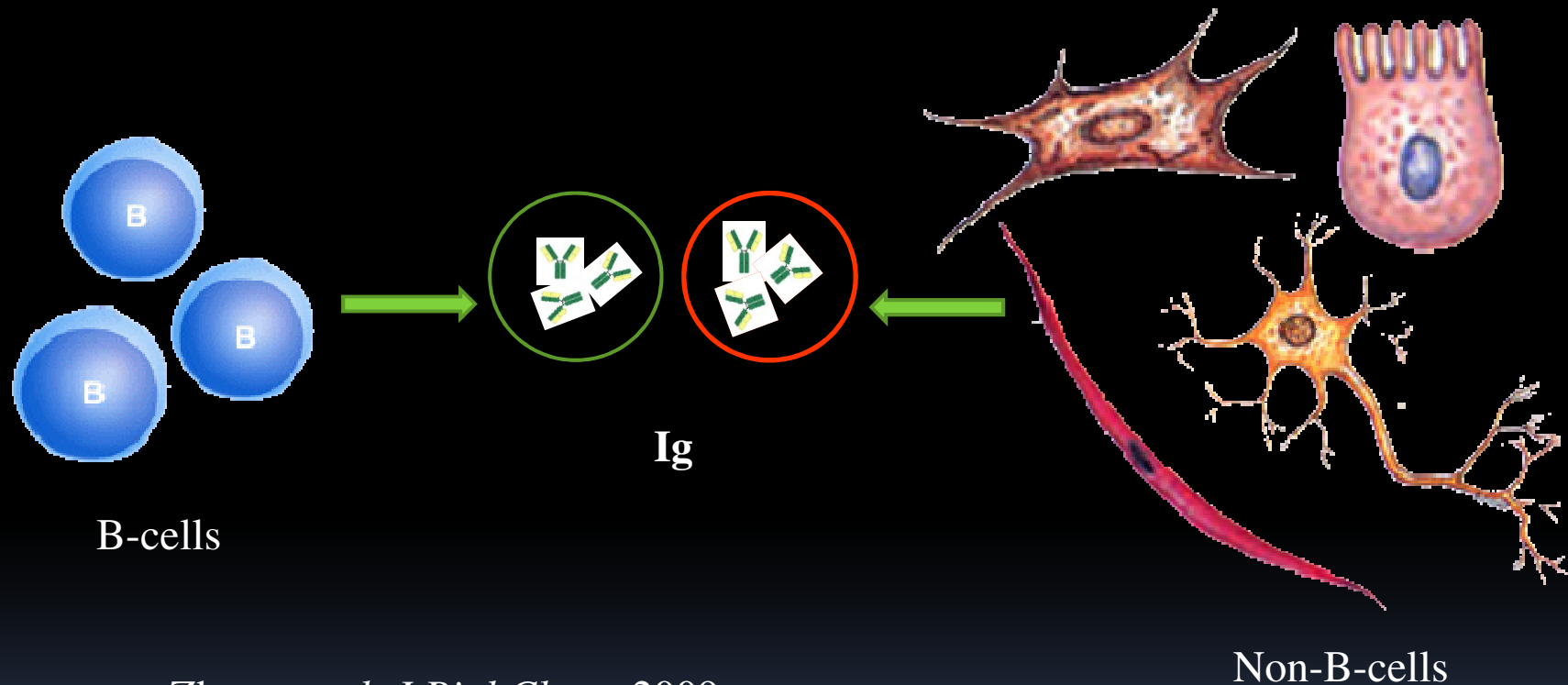
Non-B-cells

Zheng *et al. J Biol Chem.* 2009
Zhang *et al. Cell Mol Life Sci.* 2010
Zhu *et al. Cell Mol Immunol.* 2010
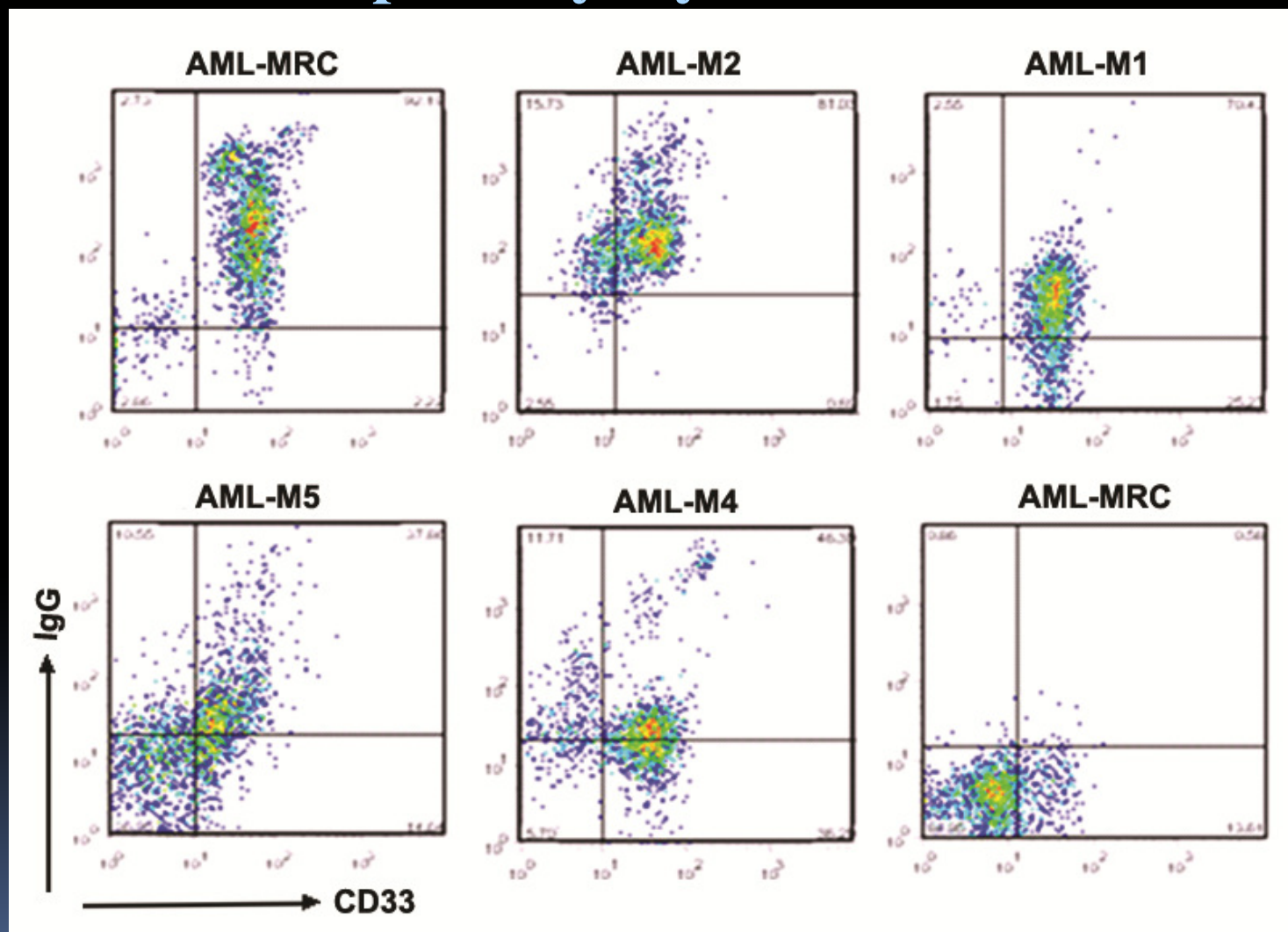Hu *et al. Plos One.* 2012

Key questions on non-B-cell-derived Ig

- Is it expressed in AML cells?

- Is it transcribed by AML cells or due to non-specific binding of B-cell-Ig? How about normal myeloid cells?

- What is the mechanism of rearrangement? Does it have diversity?

- What is the biological function and significance?
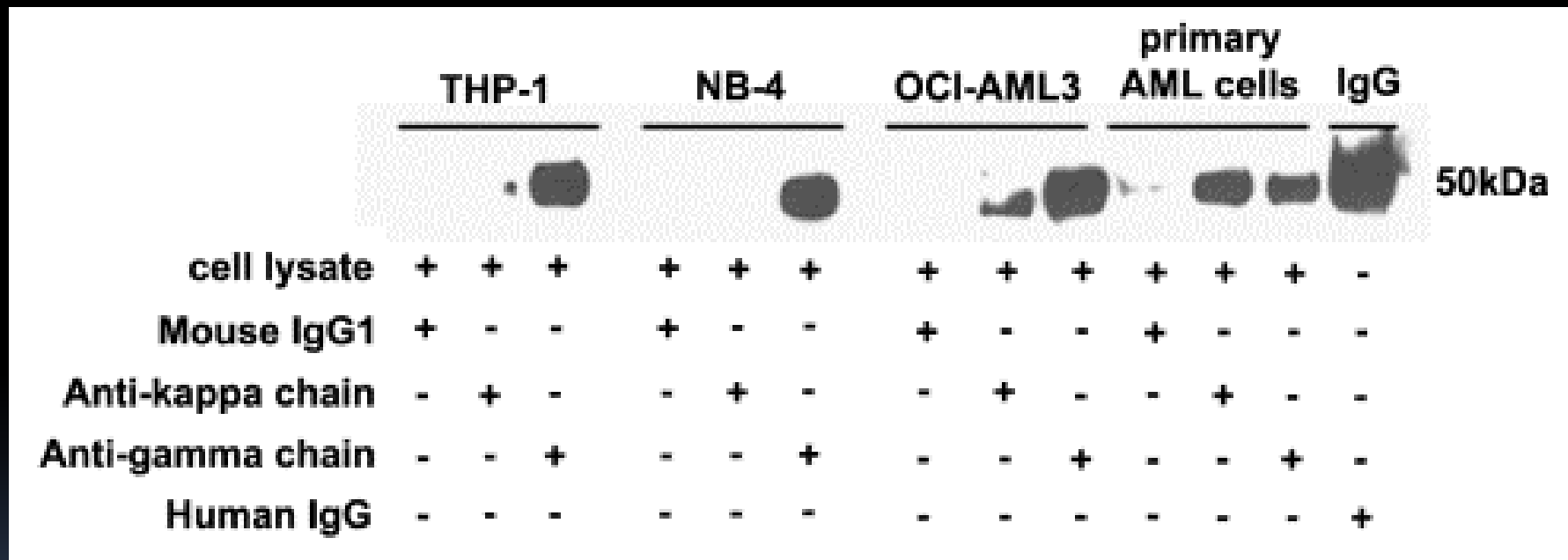
- What is its clinical implication?

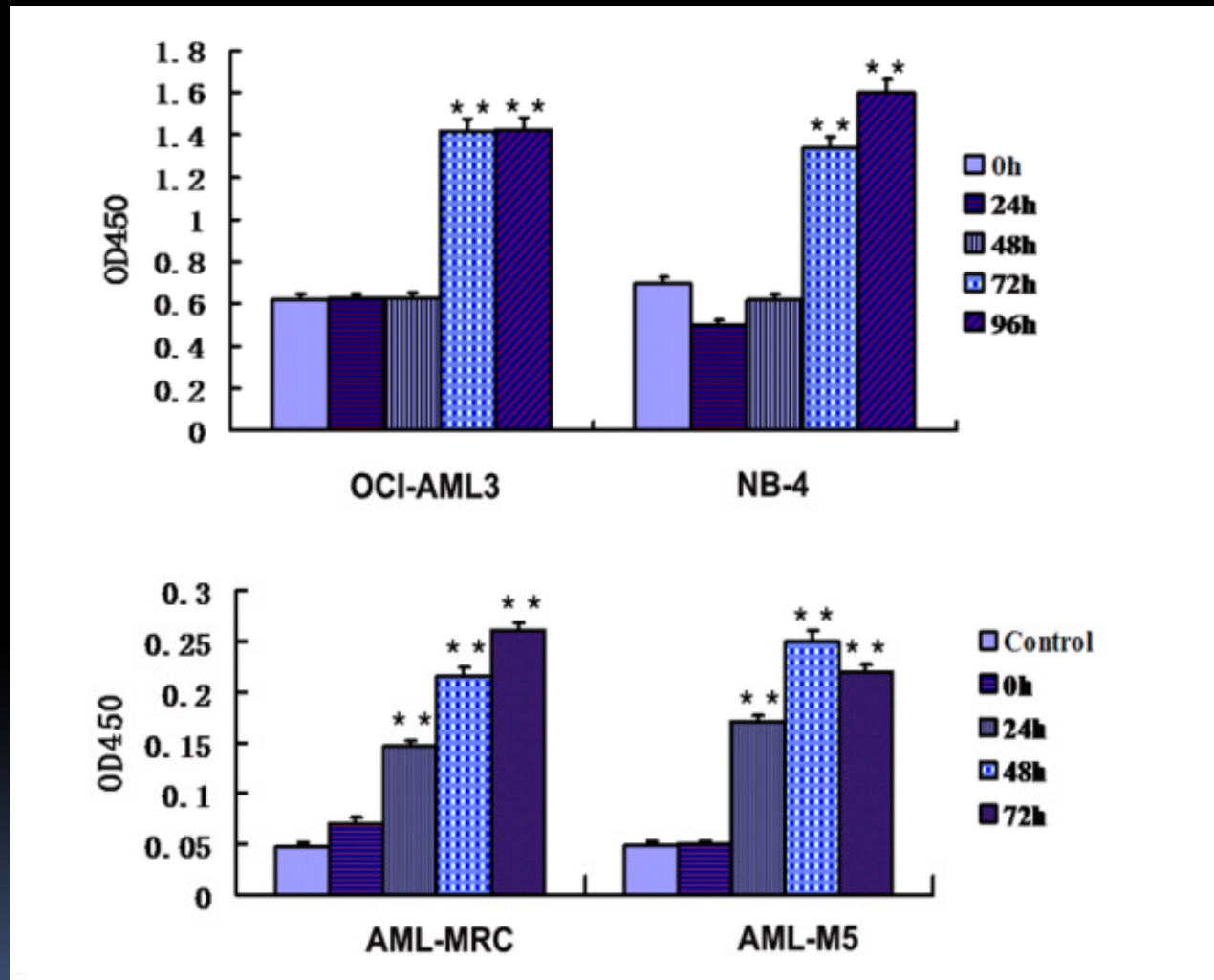# IgG is expressed at a high frequency and level in AML cell lines

Qiu *et al. Leukemia* 2013
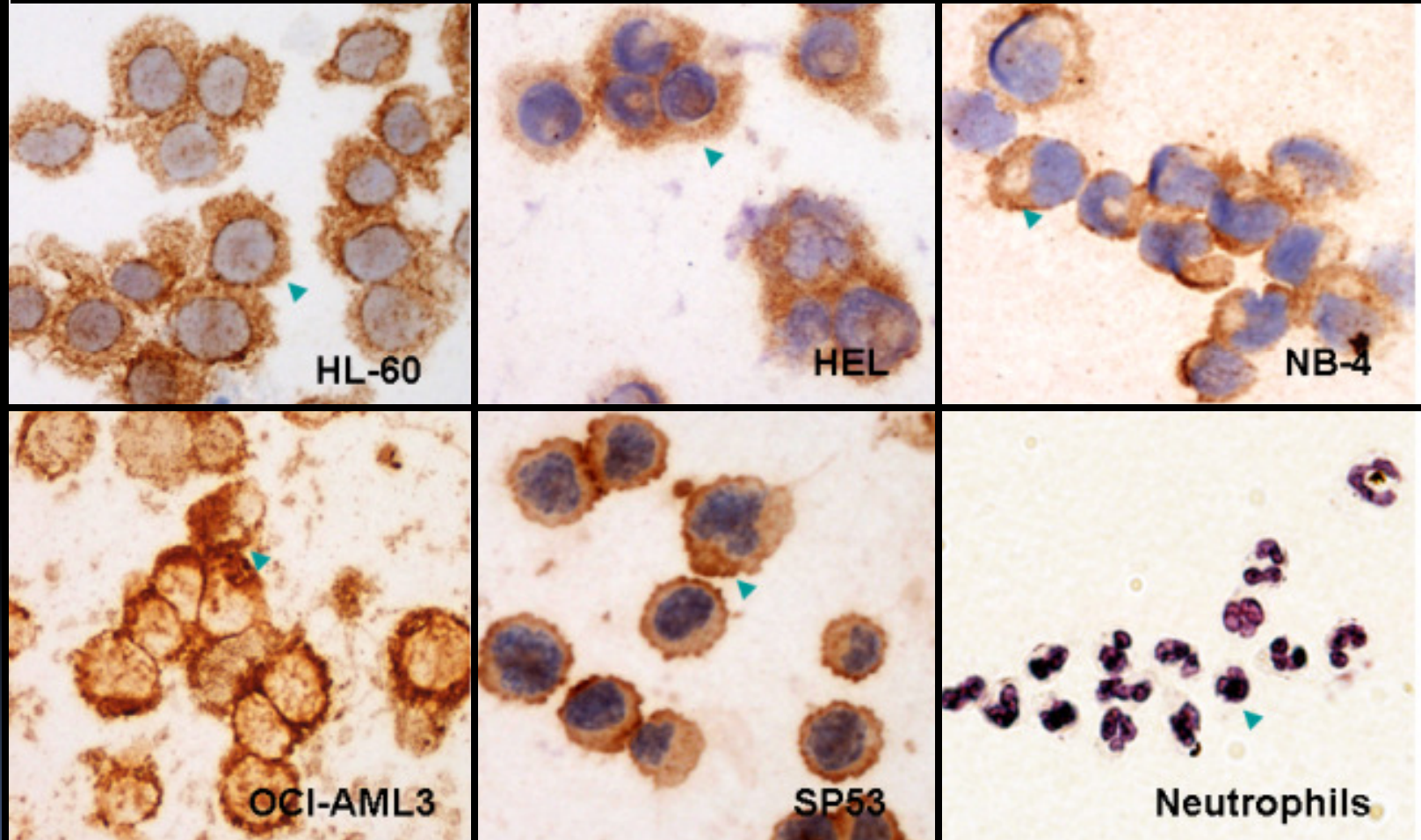
IgG is expressed at a high frequency and level in primary myeloblasts

Qiu *et al. Leukemia* 2013

AML-IgG has the same molecular weight as B-cell-IgG

Qiu *et al. Leukemia* 2013

AML-IgG is present both as membrane and secreted forms

Qiu *et al. Leukemia* 2013
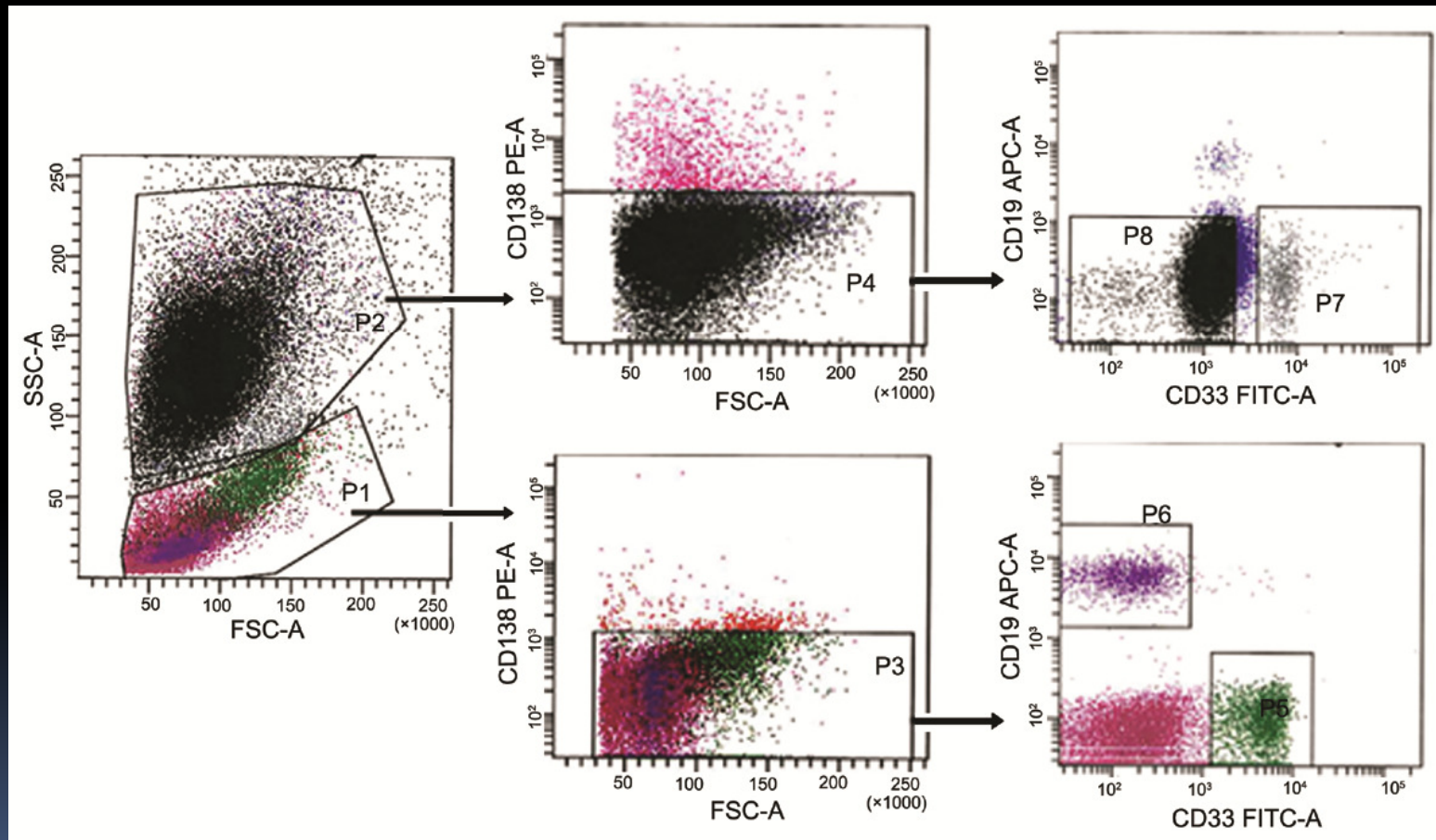
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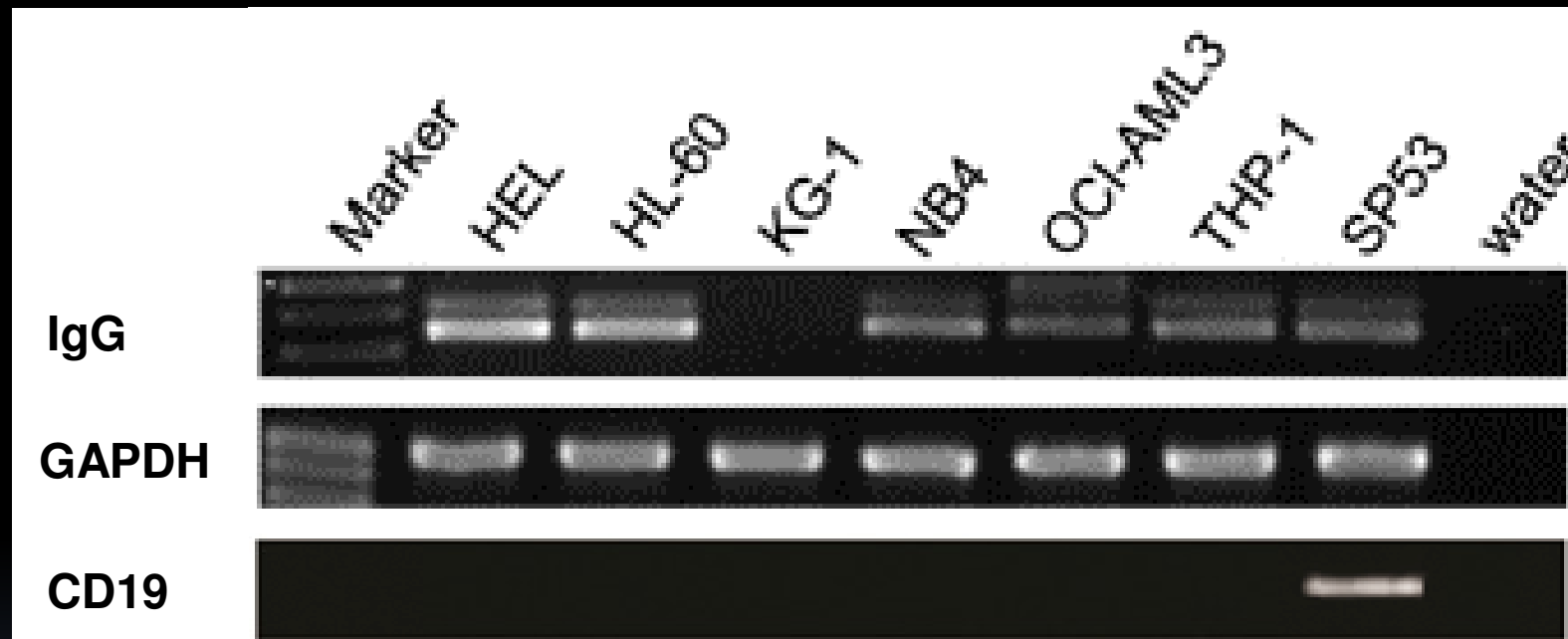
Flow cytometry cell sorting of CD33$^+$CD19$^-$ CD138$^-$ myeloblasts
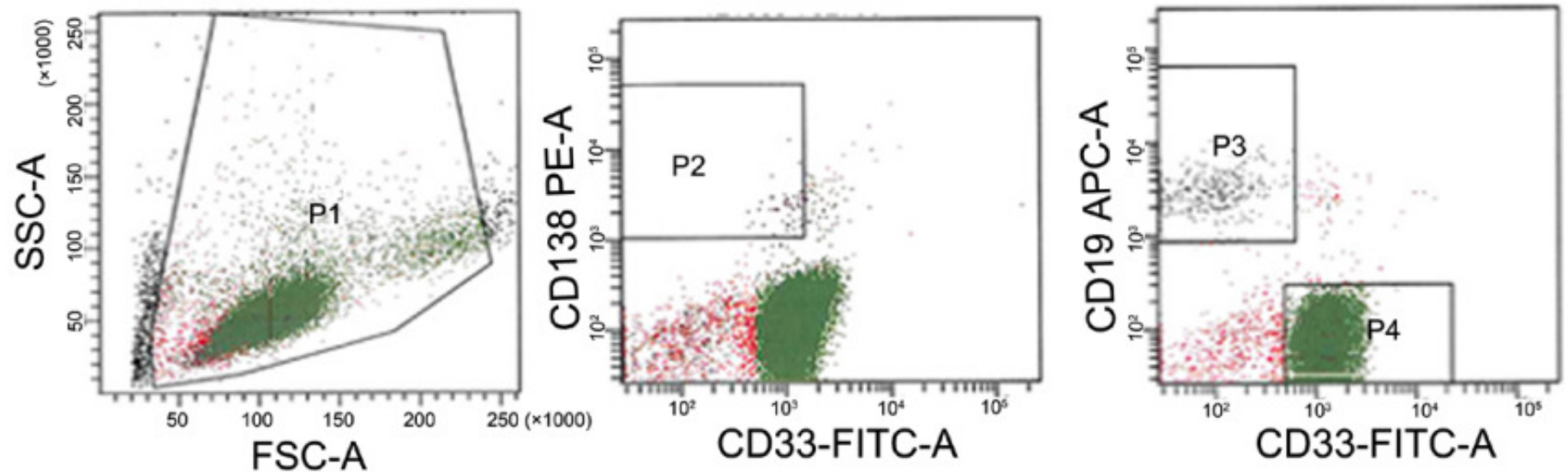
Flow cytometry cell sorting of CD33⁺CD19⁻ CD138⁻ neutrophils and monocytes

Qiu *et al. Leukemia* 2013

IgG $V_H DJ_H$ transcript is detected in AML cell lines

IgG is indeed produced by AML cells

Qiu *et al. Leukemia* 2013

IgG $V_H DJ_H$ transcript is detected in primary myeloblasts but not in non-neoplastic monocytes and neutrophils
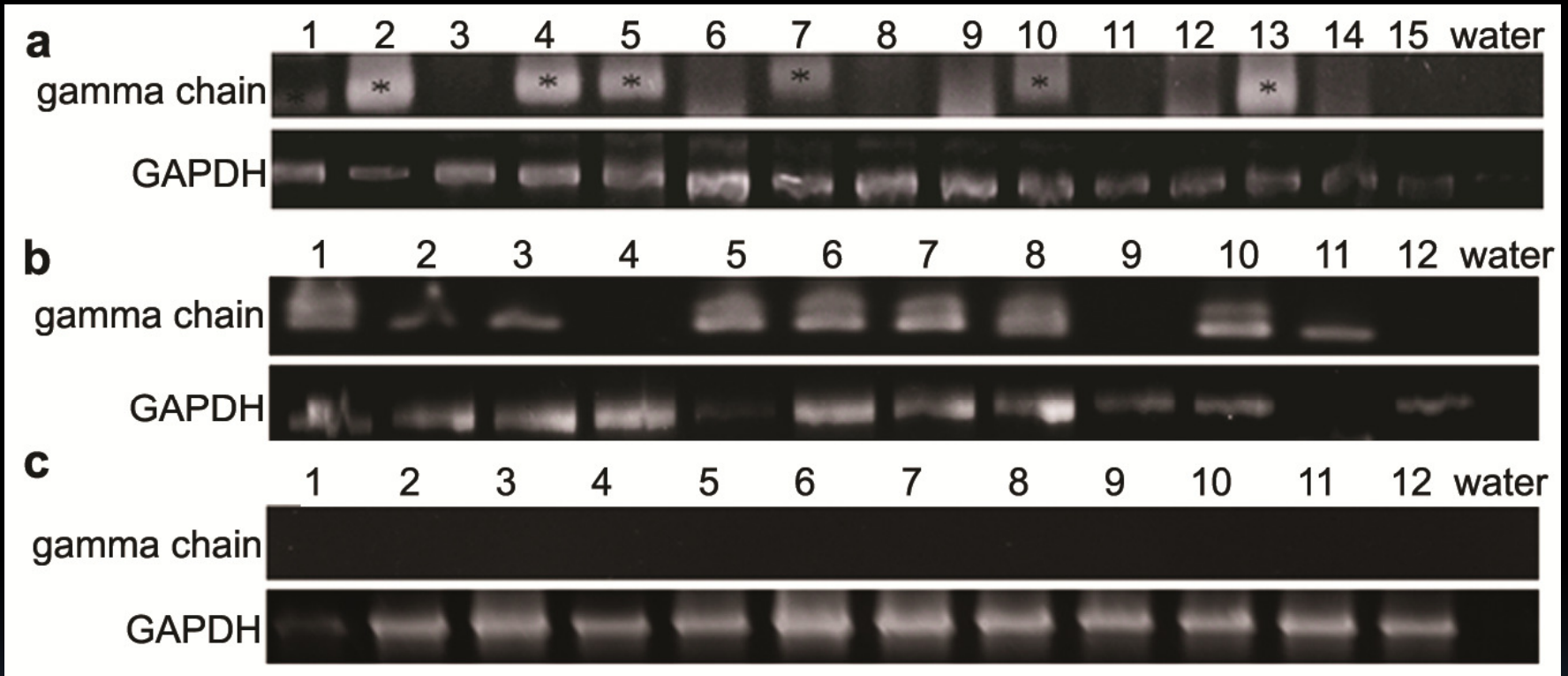
a. CD33+CD19-CD138- myeloblasts from AML patients
b. CD19+ B-cells for the patients with non-hematopoietic neoplasms
c. Monocytes and neutrophils from patients with non-hematopoietic neoplasms

Qiu *et al. Leukemia* 2013

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Classical B-cell-Ig shows high diversity

Ig H chain Locus

Chr. 14q32.2 — $V_H(39)$ $D_H(27)$ $J_H(6)$ $C_H(9)$

Ig κ chain Locus

Chr. 2q1.2 — $V_\kappa(40)$ $J_\kappa(5)$ $C_\kappa(1)$ κde

Ig λ chain Locus

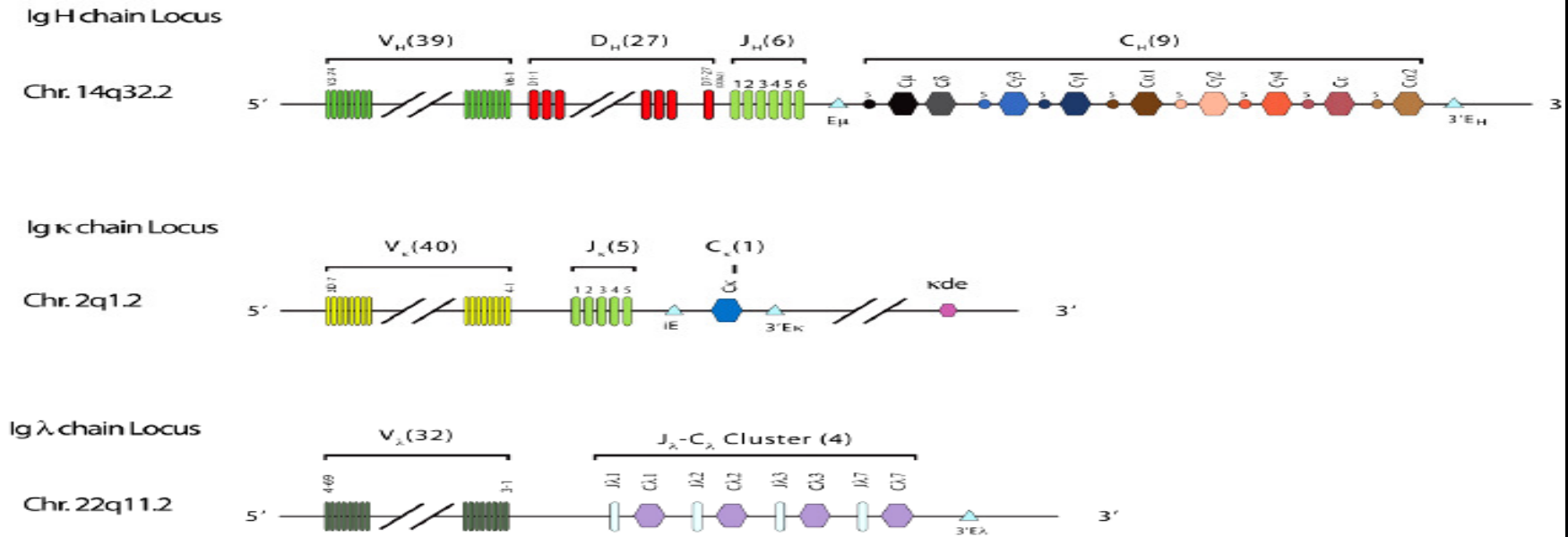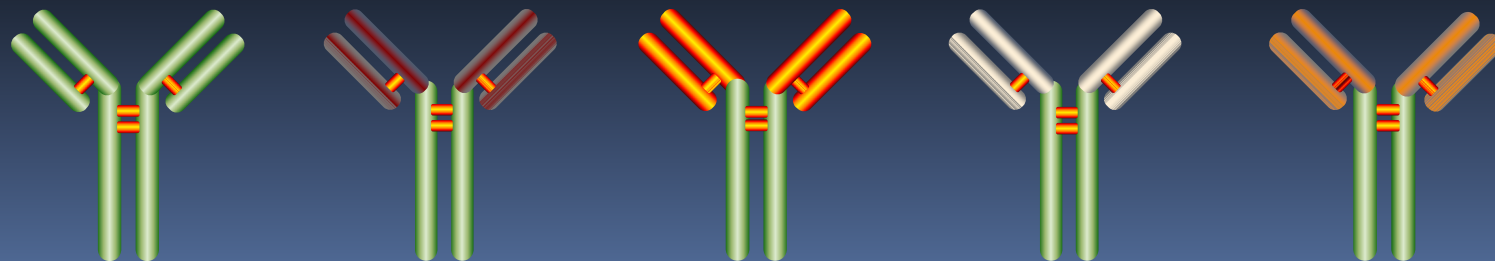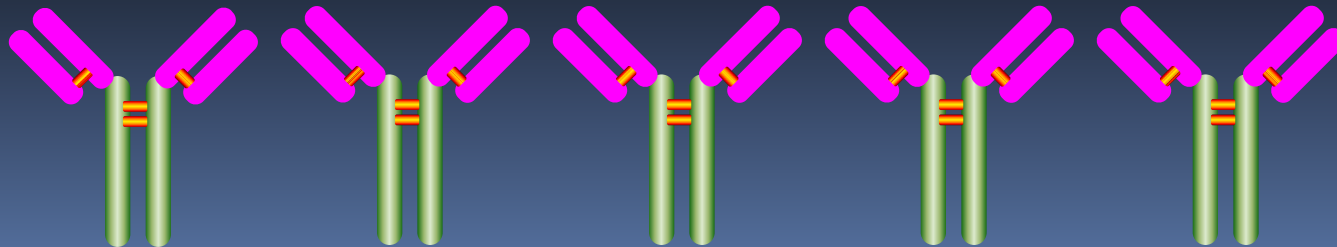Chr. 22q11.2 — $V_\lambda(32)$ J_λ-C_λ Cluster (4)

FIG 3. Representation of the chromosomal organization of the immunoglobulin H, κ, and λ gene clusters. The typical numbers of functional gene segments are shown. The κ gene cluster includes a κ-deleting element that can rearrange to sequences upstream of Cκ in cells that express λ chains, reducing the likelihood of dual κ and λ light chain expression.
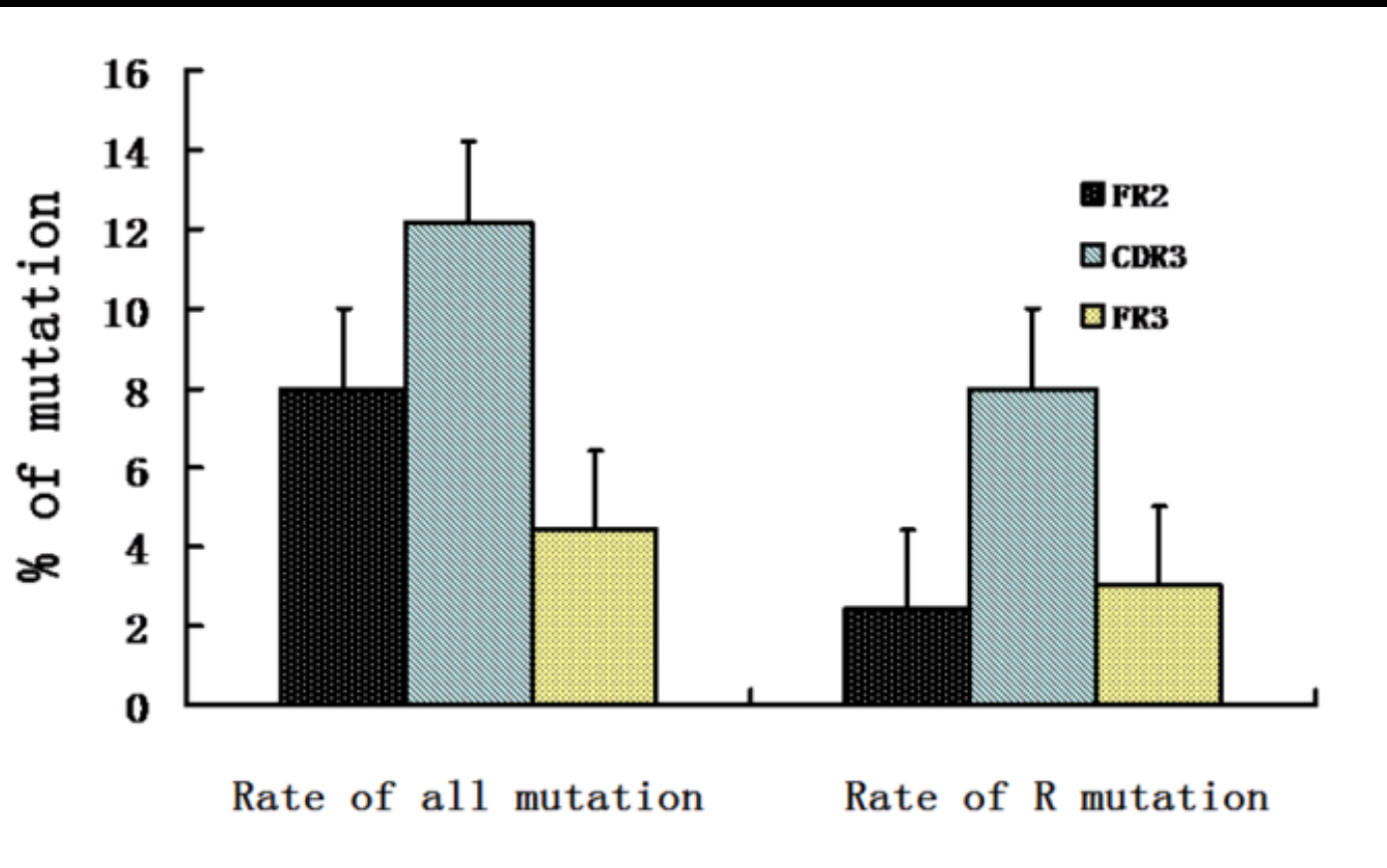
AML-IgG V_HDJ_H rearrangements demonstrate restricted or biased V region usage

VH3-48/D4-7/JH4

AML-IgG usually undergoes somatic hypermutation

Qiu *et al. Leukemia* 2013

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Anti-human IgG reduces cell viability and induces apoptosis in AML cell lines
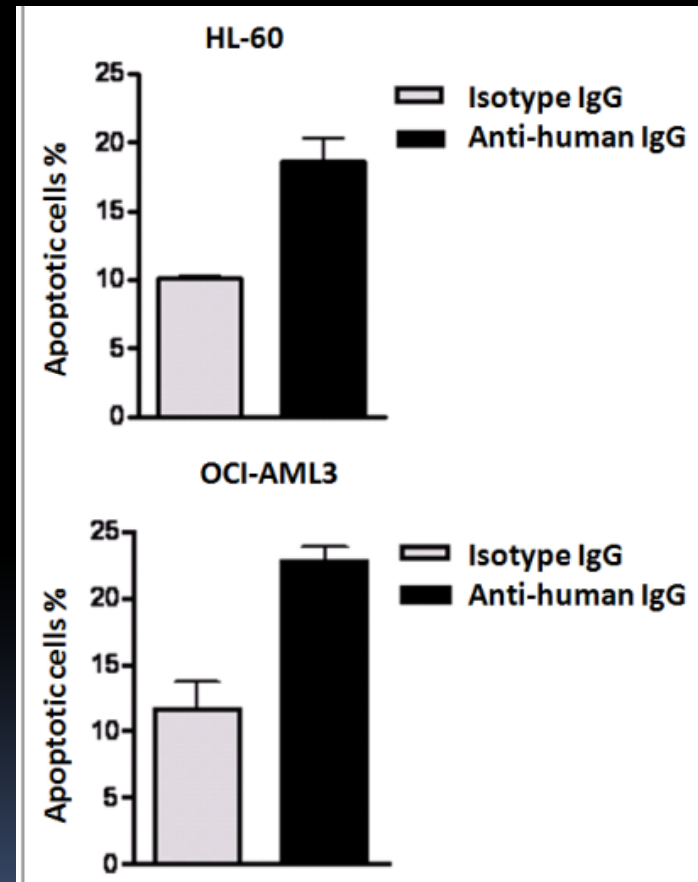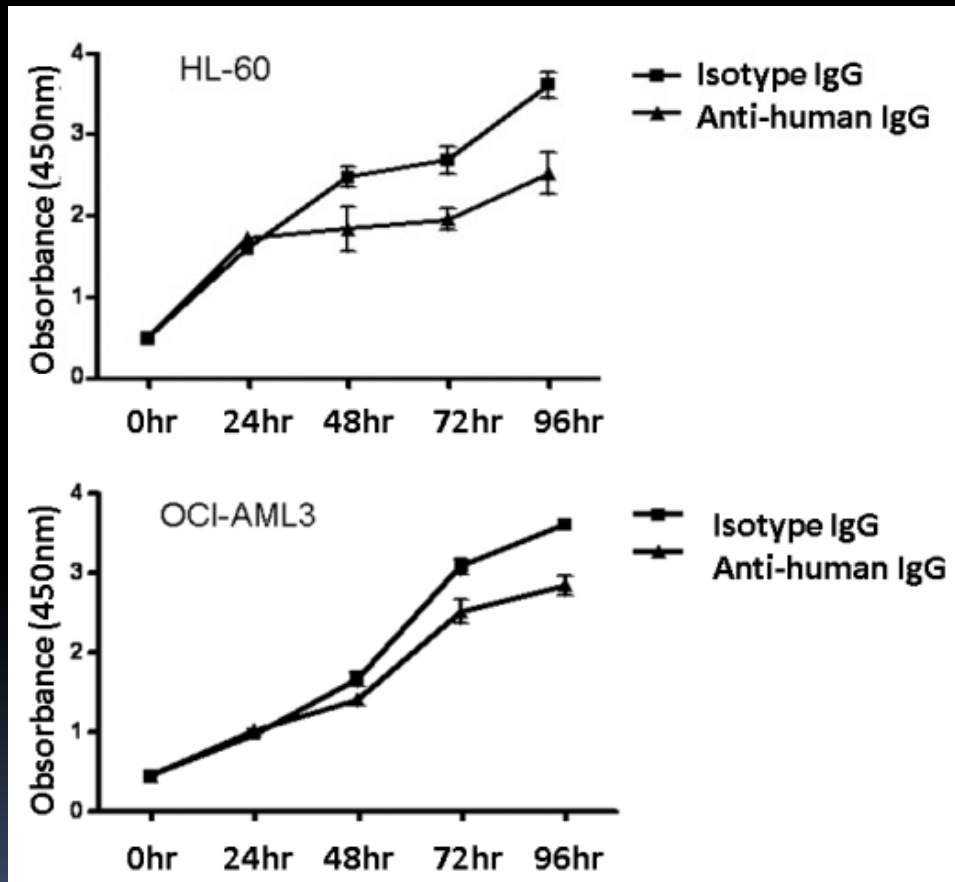
IgK expression promotes cell migration and chemotaxis in AML cell lines
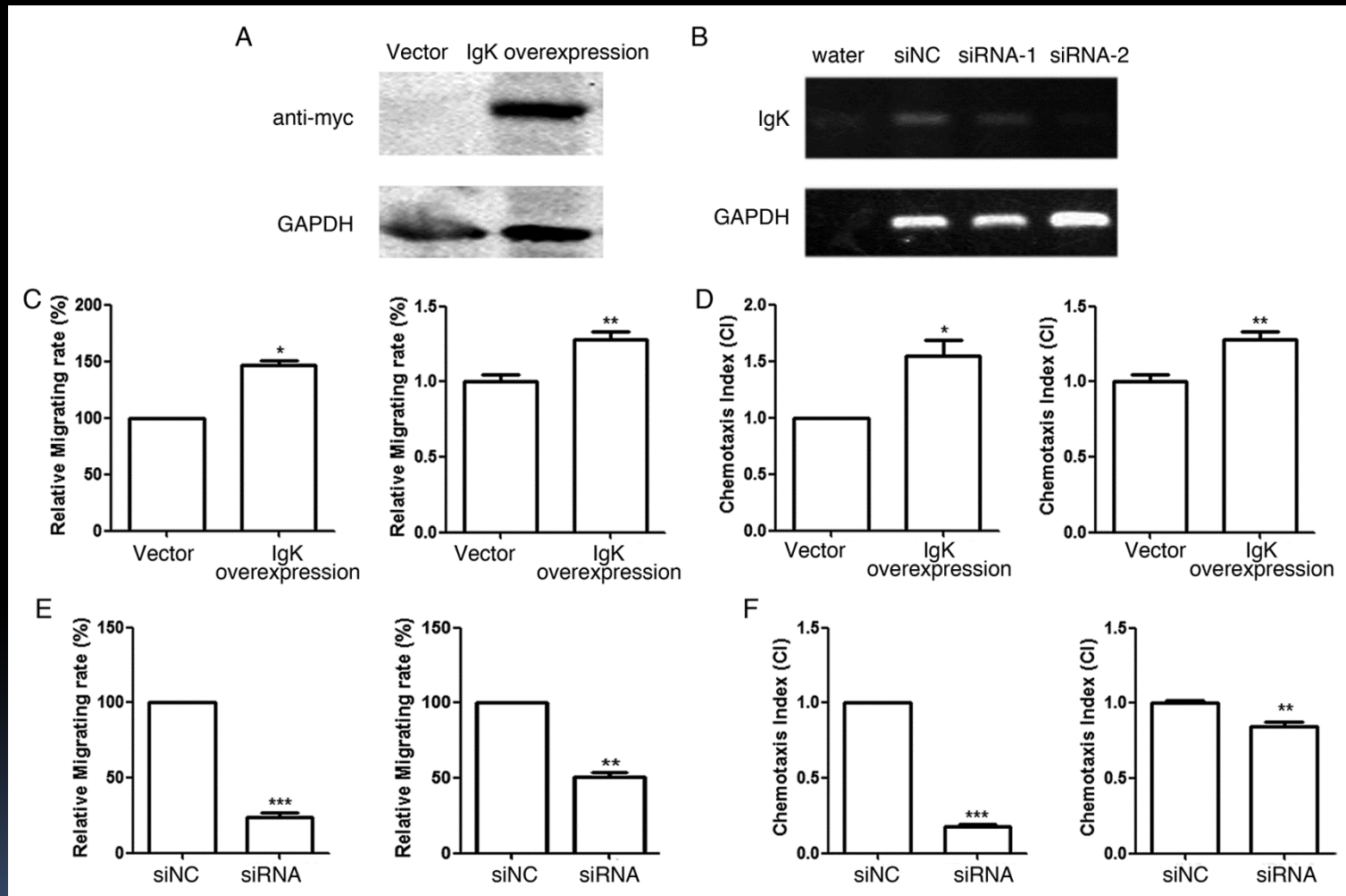
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High level of IgG expression is correlated with overall survival of lung adenocarcinoma

Liu *et al. Histopathol.* 2015
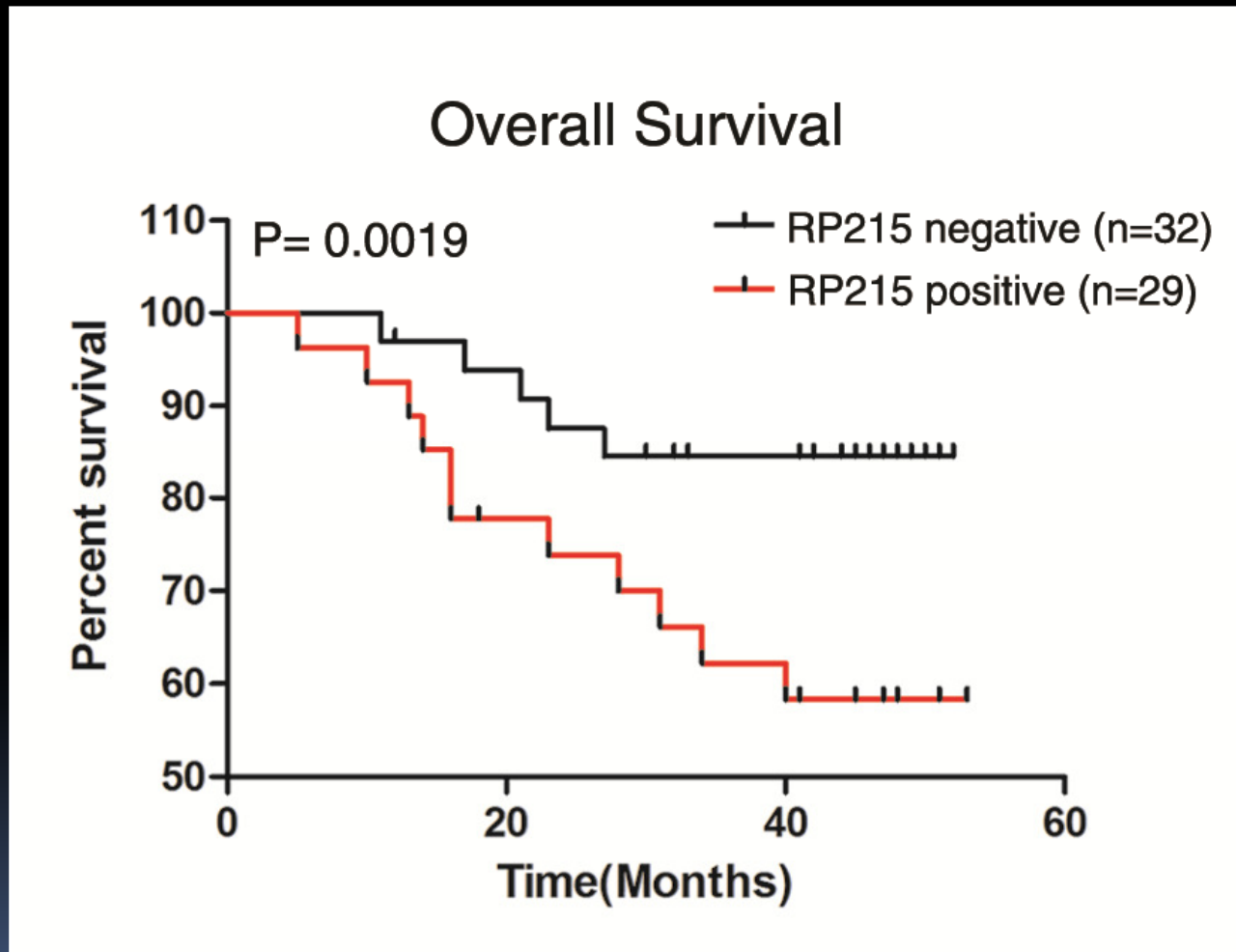
Clinical and laboratory findings

	IgG+ (n=18)	IgG- (n=7)	p value
Age	65 (26-87)	56 (25-79)	0.4544
Gender	8M/10F	6M/1F	0.0900
WBC	82.6 (1.1-620.4)	26.4 (0.1-152.8)	0.3654
Hgb	9.0 (4.6-11.8)	10.8 (8/62)	0.0706
Platelet	71 (10-374)	26 (8-62)	0.0950
PB blast	64 (8-96)	72 (0-91)	0.9514
PB monocytes	1.35 (0-48.88)	0.09 (0-1.52)	0.1093
LDH	1405 (199-10571)	570 (427-1782)	0.1702

Bone marrow findings

	IgG+ (n=18)	IgG- (n=7)	p value
BM blast	60 (24-90)	80 (45-93)	0.1178
Dysplasia	10	3	0.6728
Classification			0.3654
M4/M5	8	3	1.0000
MRC	7	0	0.1326
M1	1	1	0.4900
t(8;21)	1	0	
M0	0	1	
Unclassifiable	1	1	

28-gene NGS analysis

	IgG+ (n=18)	IgG- (n=7)	P value
FLT3	6/18	3/7	0.6729
DNMT3A	7/17	1/7	0.3521
PTPN11	6/17	0/7	0.1300
NPM1	5/17	3/7	0.6466
NRAS	5/17	0/7	0.2721
IDH1	5/17	0/7	0.2833
IDH2	3/17	3/7	0.3068
RUNX1	3/17	0/7	0.5296
TET2	3/17	2/7	0.6080
ASXL1	2/17	1/7	1.0000
JAK2	2/17	0/7	1.0000
WT1	2/17	1/7	1.0000
KIT	1/17	0/7	1.0000
TP53	0/17	1/7	0.2917
CEBPA	1/17	1/7	0.5072
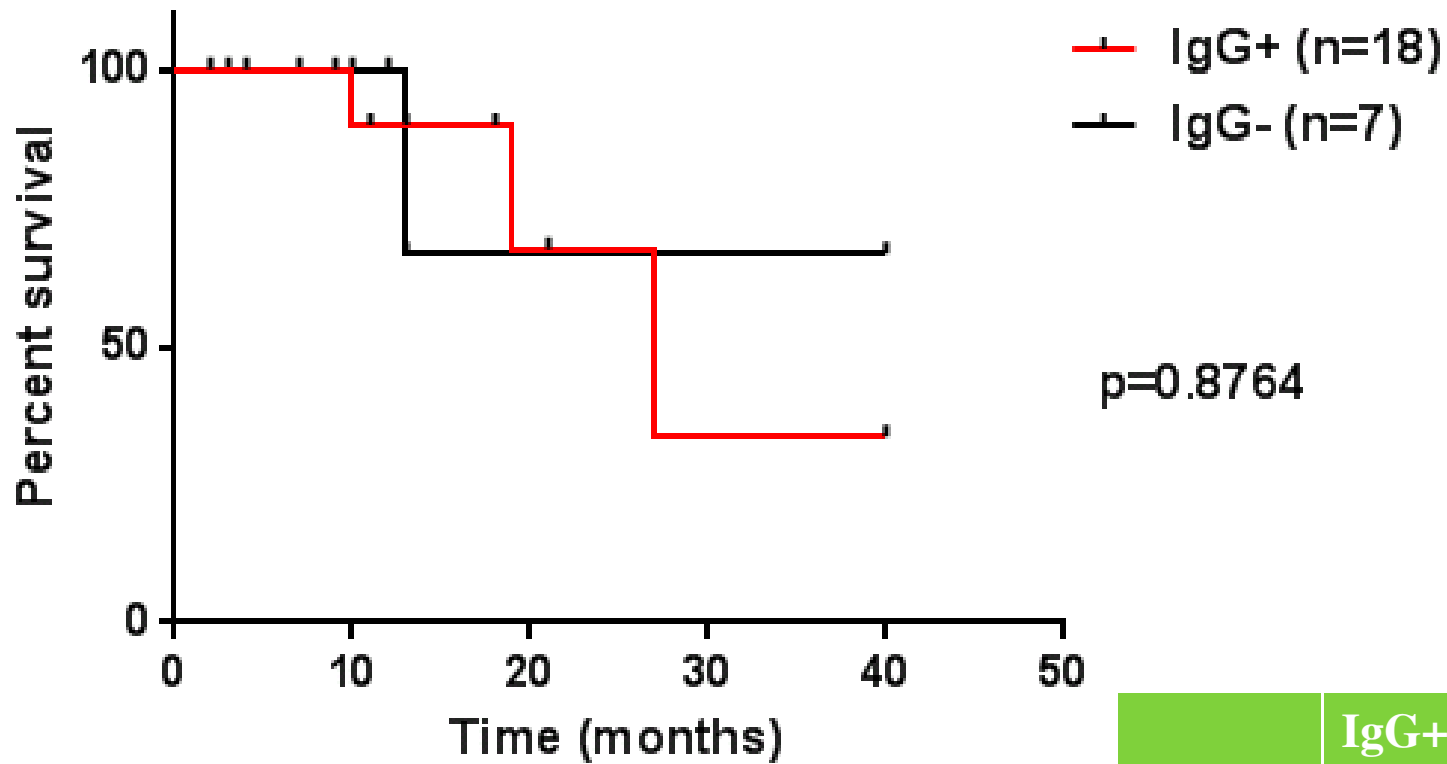
	IgG+ (n=18)	IgG- (n=7)
F/U (m)	11 (0-40)	12 (3-40)
CR	3	2
pAML	11	4
Died	4	1

Conclusions

- IgG gene is transcribed, expressed and secreted at a high frequency and level in AML cell lines and primary myeloblasts.

- AML-IgG V_HDJ_H rearrangements have undergone somatic hypermutation and display restricted or biased usage of V segments.

- Anti-human IgG reduces cell viability and induces apoptosis in AML cell lines.

- AML-IgG may be a novel AML-related gene that contributes to leukemogenesis and AML progression.

- AML-IgG may serve as a useful molecular marker for monitoring MRD or designing target therapy

- A large scaled study is needed to evaluate the prognostic implication of AML-IgG.

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