

Dalle Immunodeficienze alle neoplasie e viceversa

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SAPIENZA
UNIVERSITÀ DI ROMA

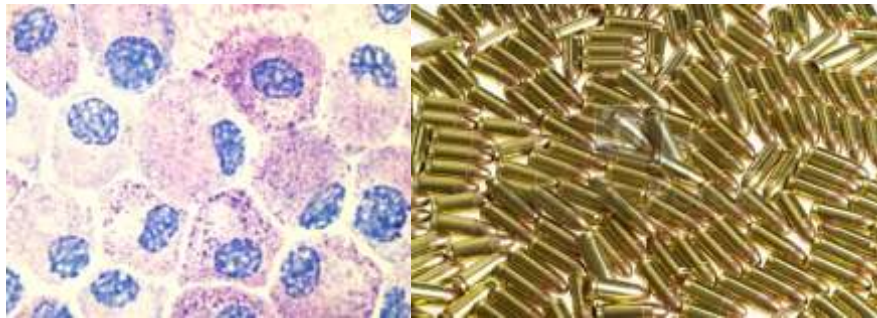
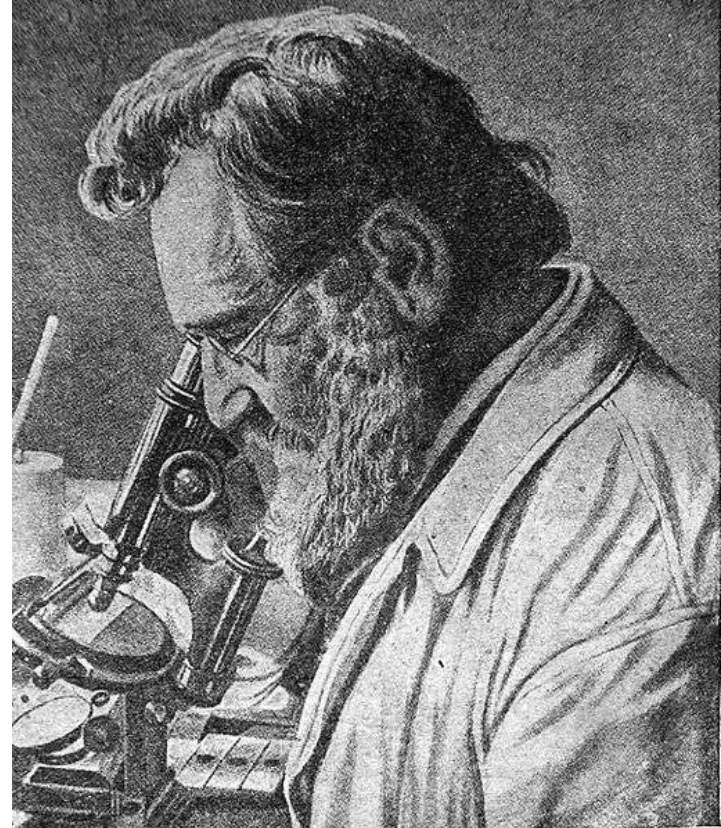




Paul Ehrlich

**Premi Nobel
1908**

Élie Metchnikoff



Magische Kugel



Ag microbici



Ag ambientali

1906

Clemens Peter von Pirquet

1963

Robert Royston Amos ("Robin") Coombs
Philip George Houthem Gell



self

Sorveglianza:
Autoimmunità
Tumori



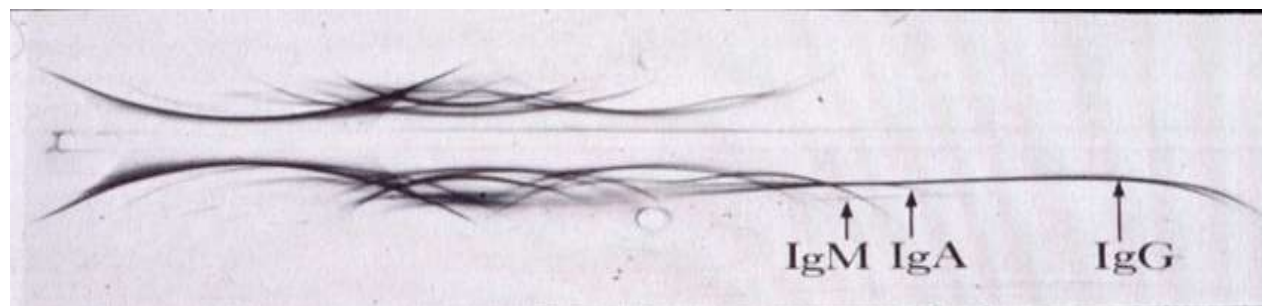
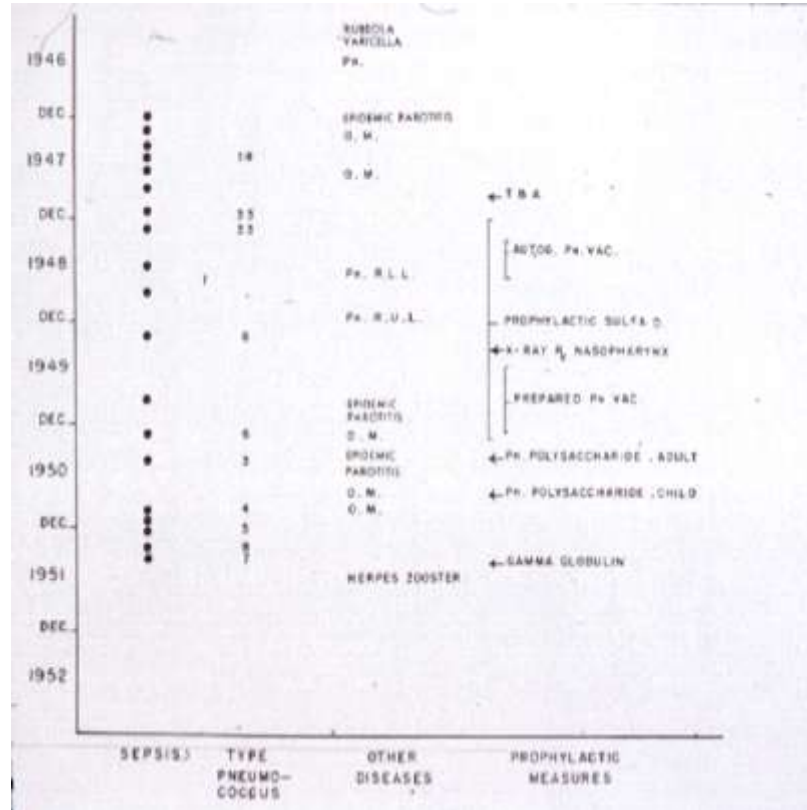
Sir Frank Macfarlane Burnet
Premio Nobel 1960

non self

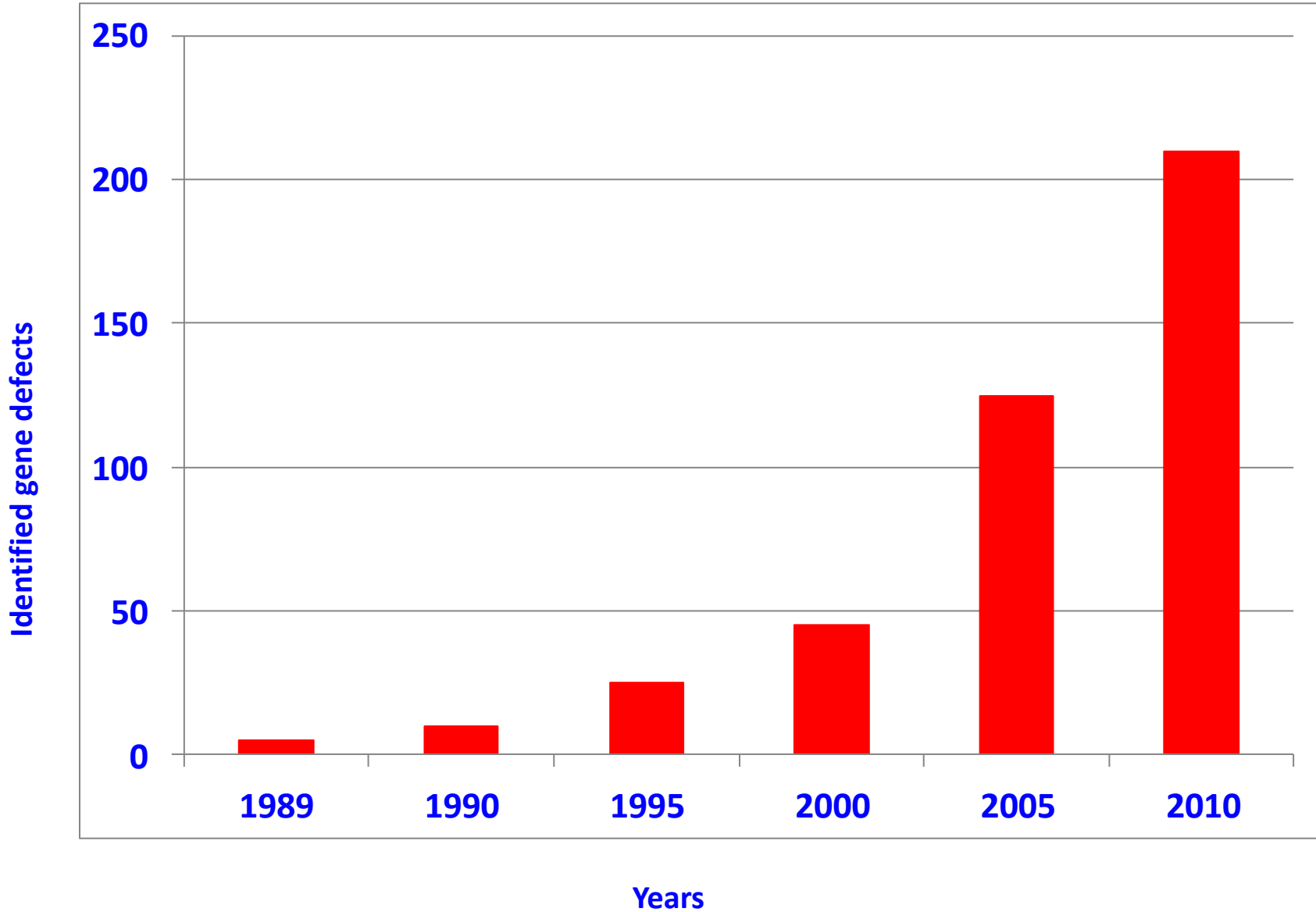
Ag microbici
immunodeficienza

ambientali
alimentari
allergia

1952



Advances in primary immune deficiencies: characterization of the molecular defect



EDITORIAL

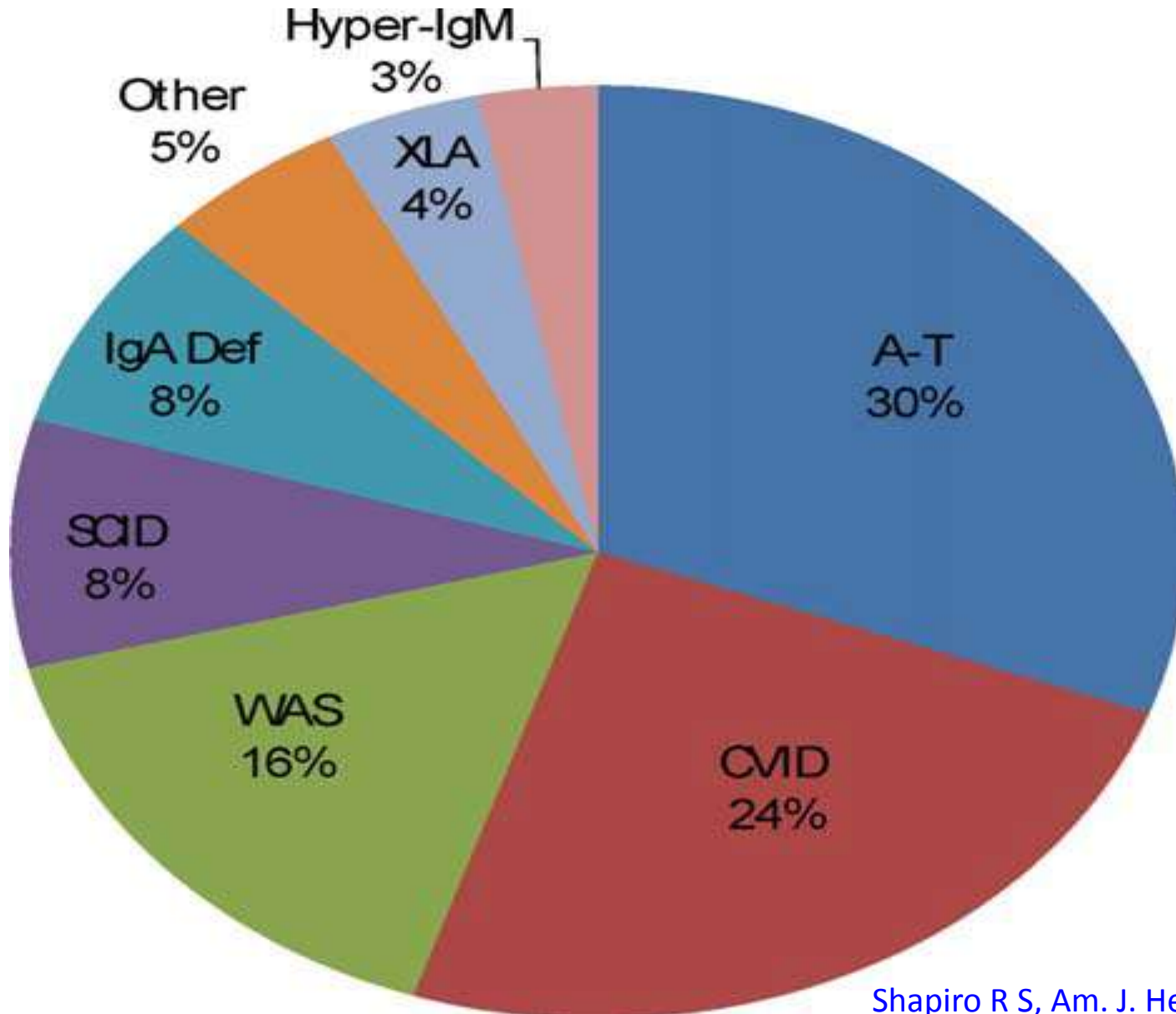
Primary immunodeficiency: a never ending story

Amos Etzioni^a and Ramsay Fuleihan^b

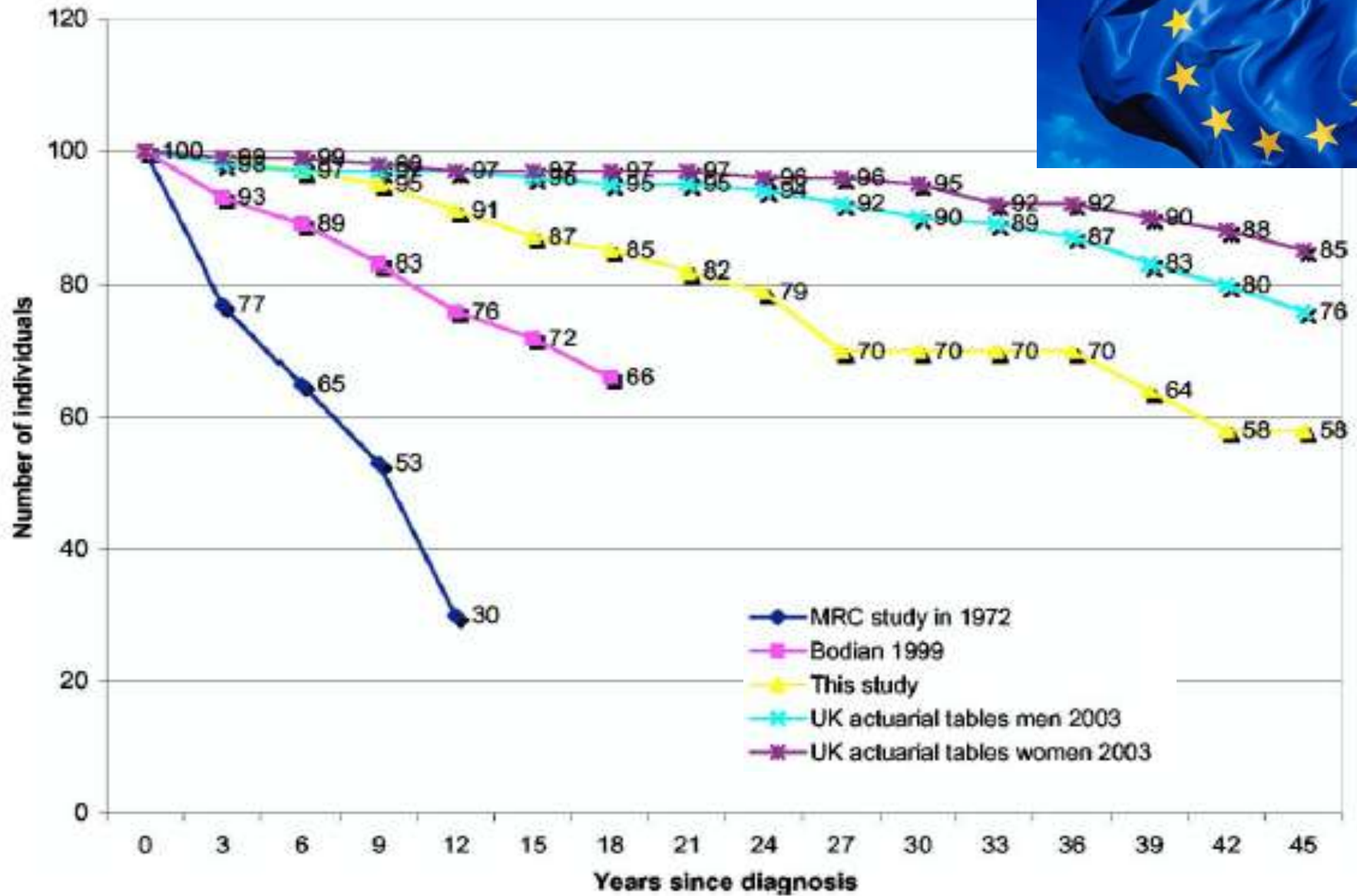
The field of primary immunodeficiency is a continuously growing field. In the 1990s, when the first genes involved in PID were discovered, some investigators believed that with these discoveries all the 'mysteries' of PID will be solved. It was the late Dr Robert Good, the father of the field, who said, 'This is not the beginning of the end, but just the end of the beginning'.



Immunodeficiencies associated with malignancy (4-25%)

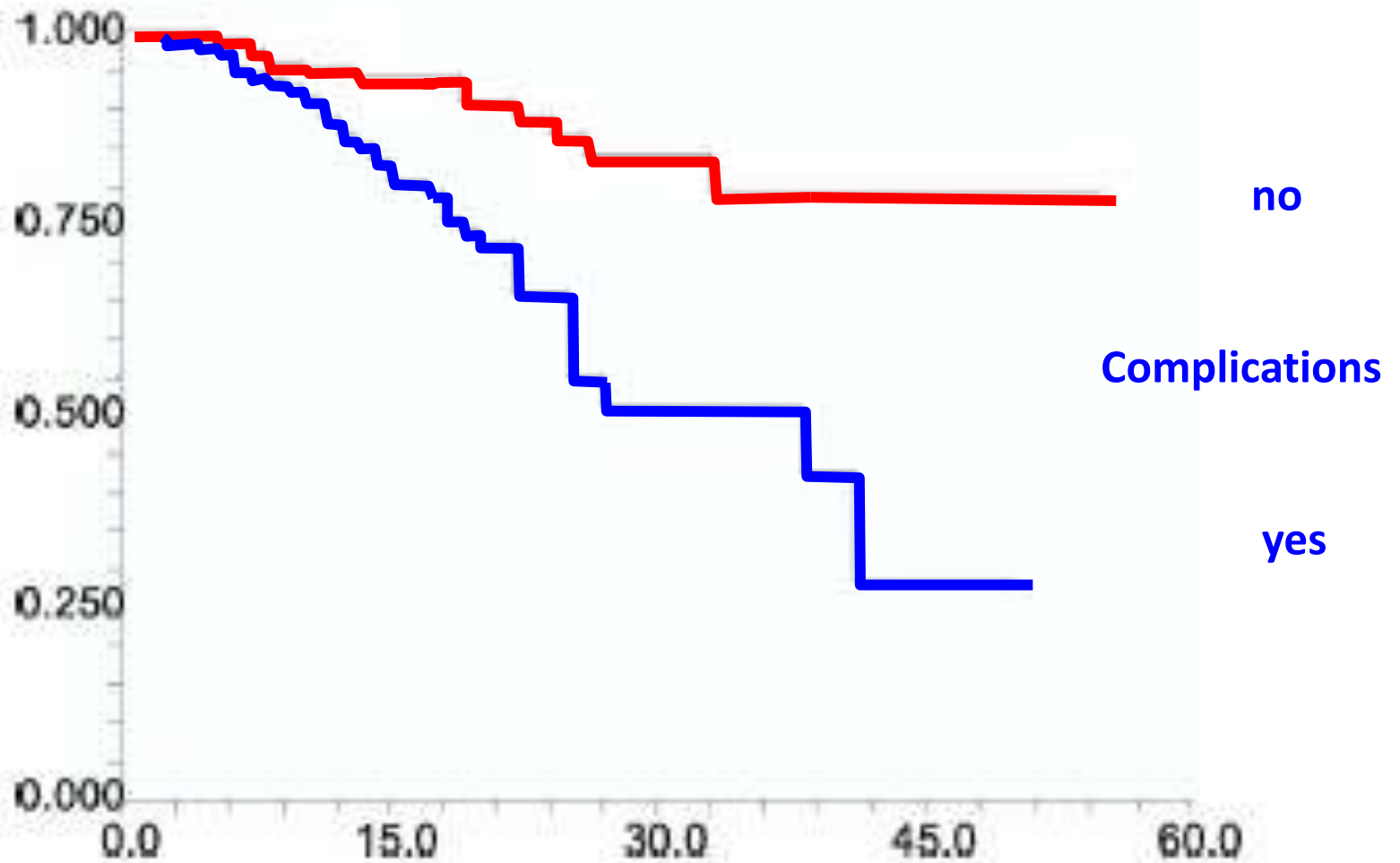


Survival



334 pt CVID

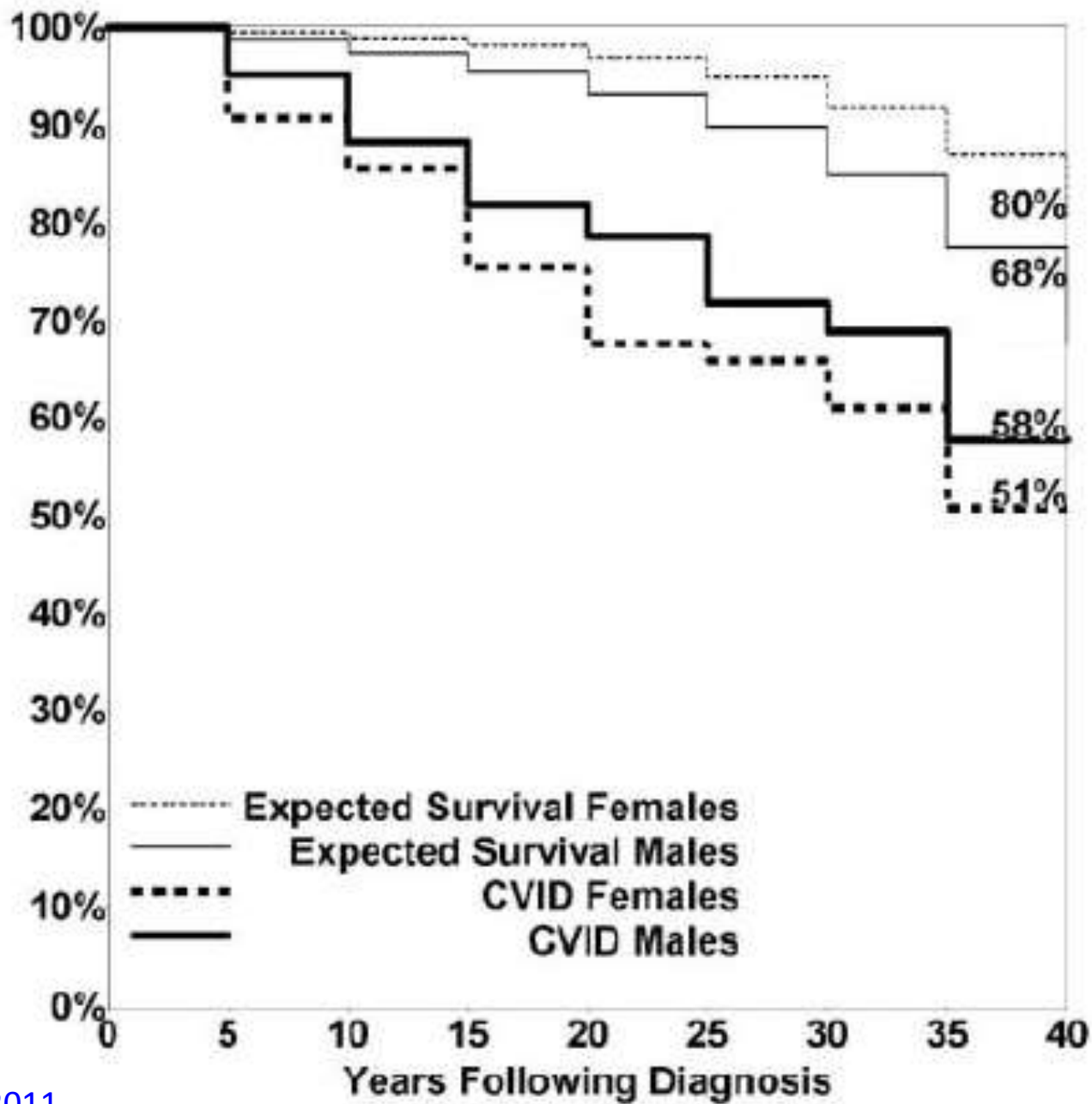
Survival Plot

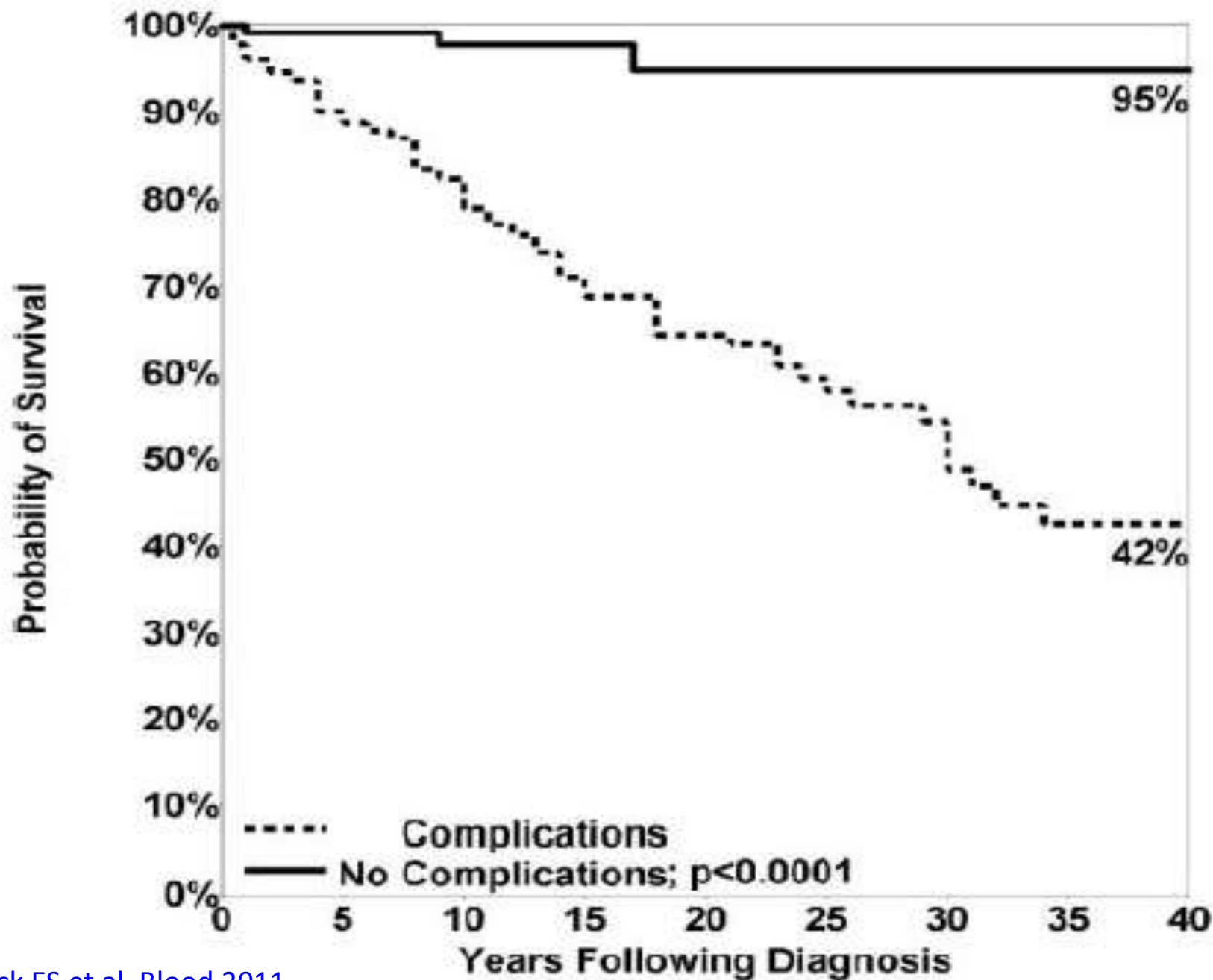




CVID
473 pt

Probability of Survival





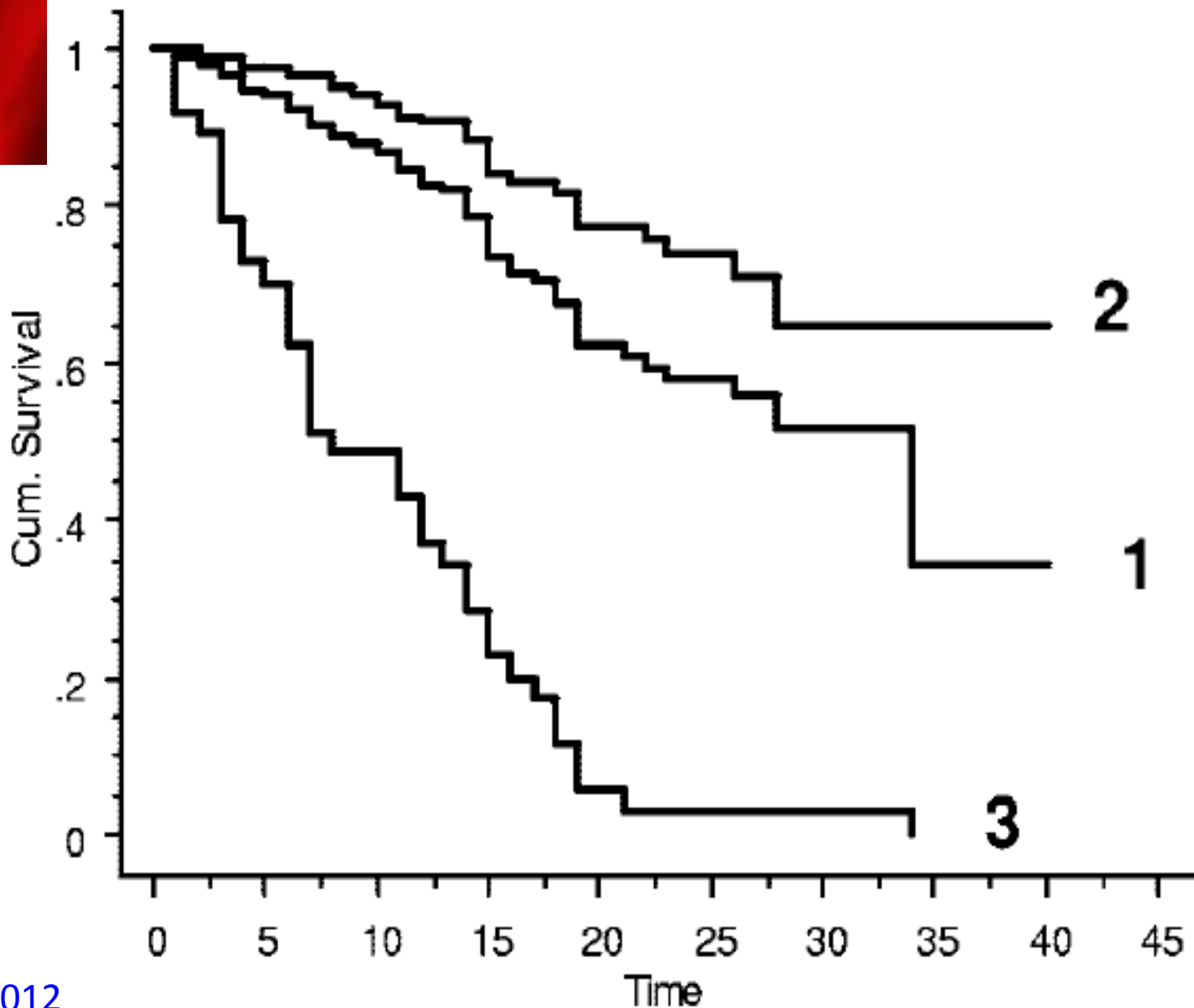
Cox proportional hazard modeling of complications

	HR	95% CI	P
Any complication	10.96	(3.46, 34.69)	< .0001*
Gastrointestinal disease	2.78	(1.44, 3.59)	.0004*
Liver disease/hepatitis	2.48	(1.51, 4.09)	.0003*
Lymphoma	2.44	(1.43, 4.16)	.0010*
Chronic lung disease (structural and functional)	2.06	(1.34, 3.16)	.0010*
Malabsorption	2.06	(1.11, 3.81)	.0218*
Splenectomy	1.69	(0.91, 3.12)	.0957
Cancer	1.51	(0.795, 2.87)	.2084
Autoimmunity	1.36	(0.87, 2.12)	.1735
Granuloma	1.27	(0.65, 2.48)	.4939
Bronchiectasis	0.76	(0.39, 1.48)	.4235

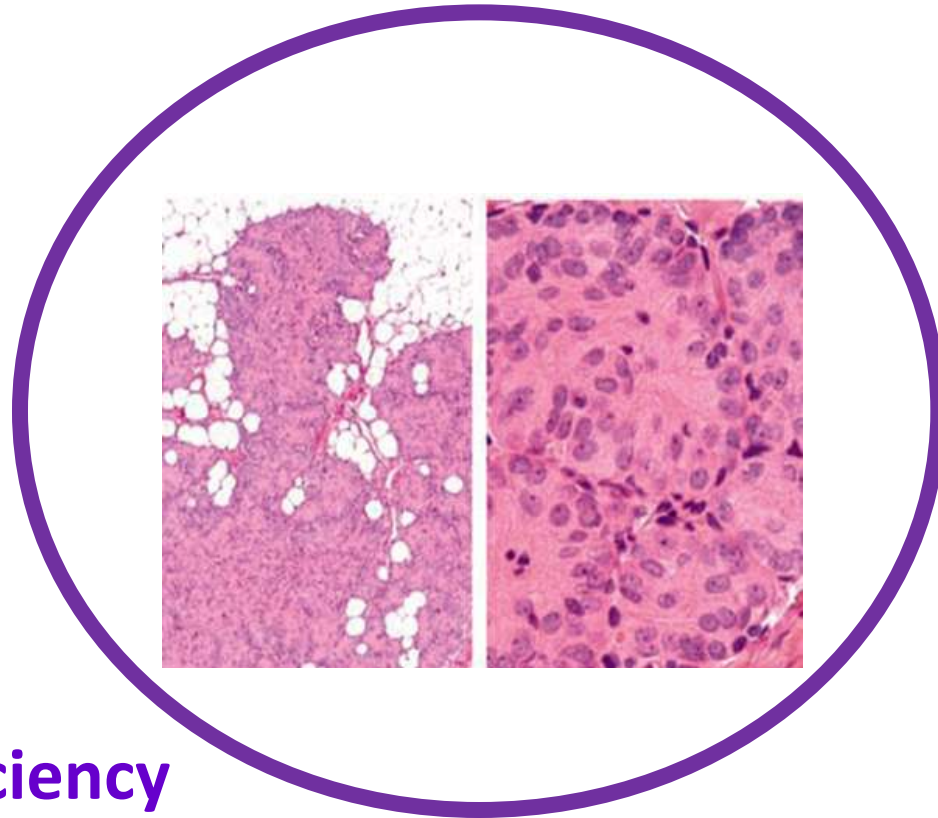


Kaplan-Maier curves for patients with CVID
1 Cumulative; 2 without; 3 with cancer complication

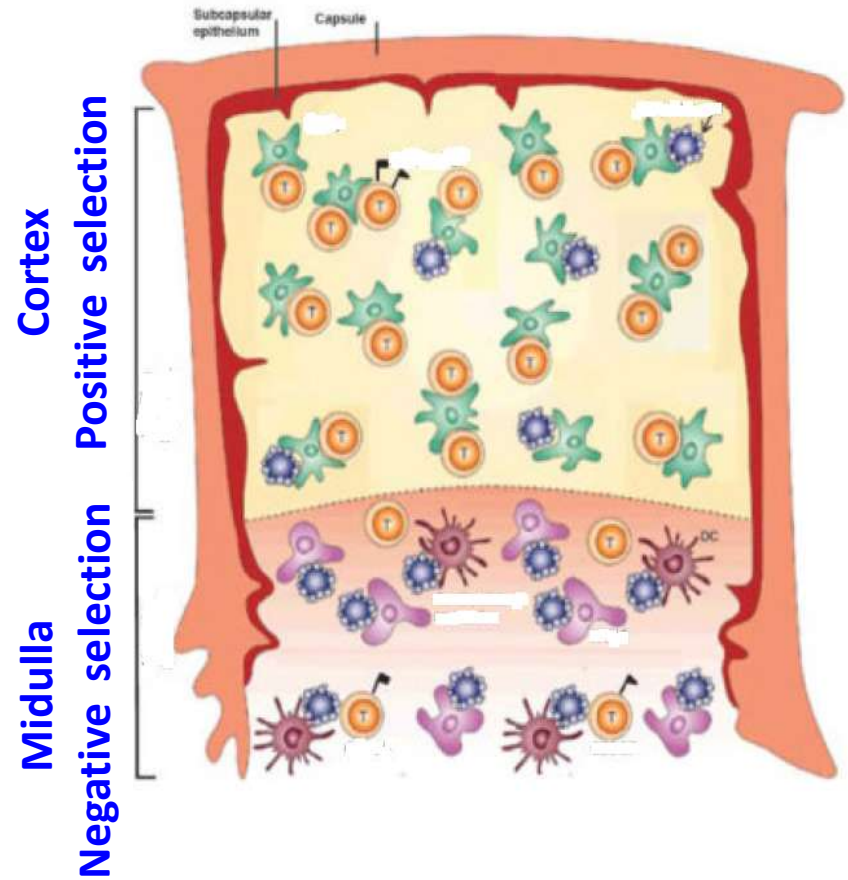
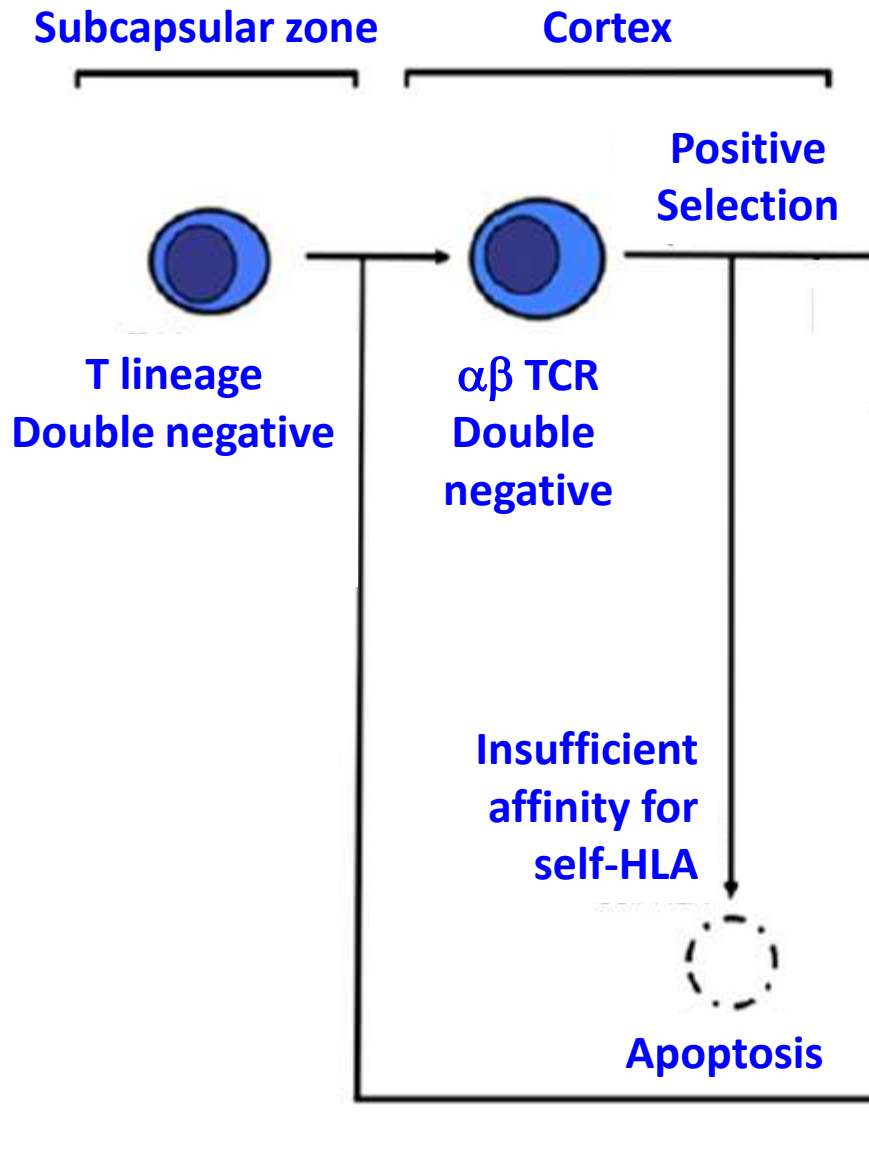
CVID
353 pt

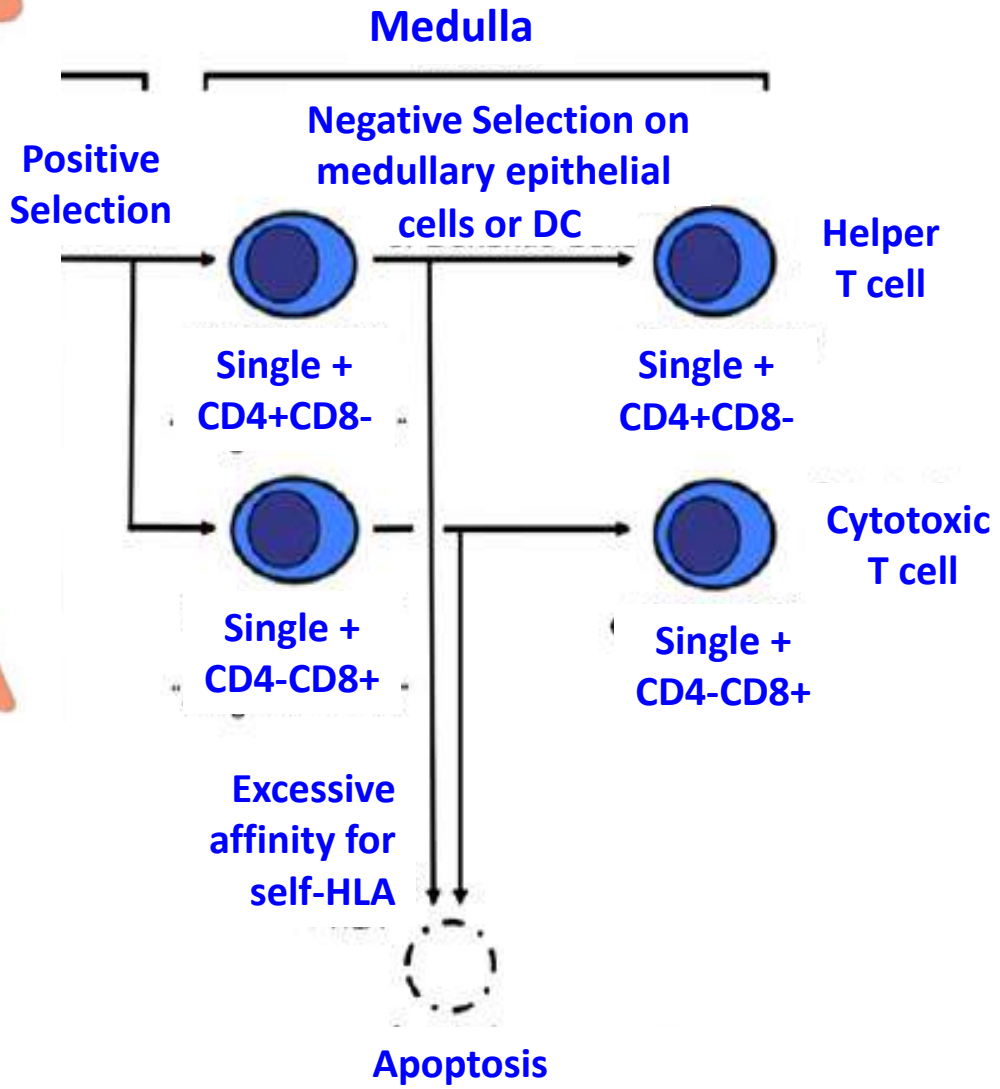


Interaction of factors contributing to cancer in PID



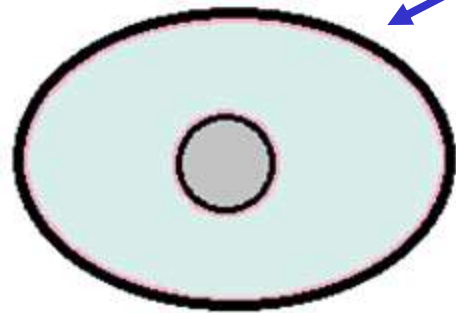
Immunodeficiency



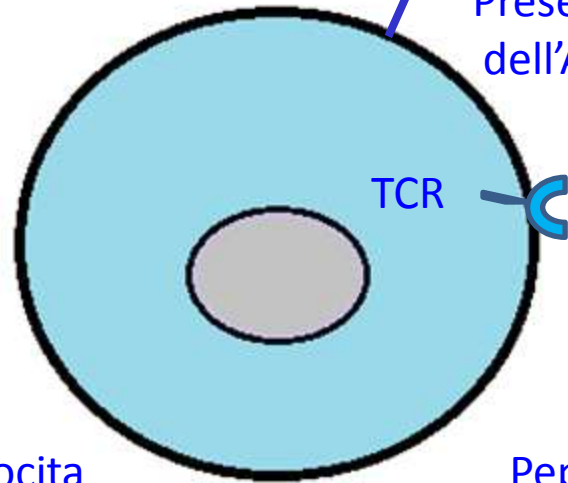


Tolleranza centrale

Eliminazione linfociti T autoreattivi



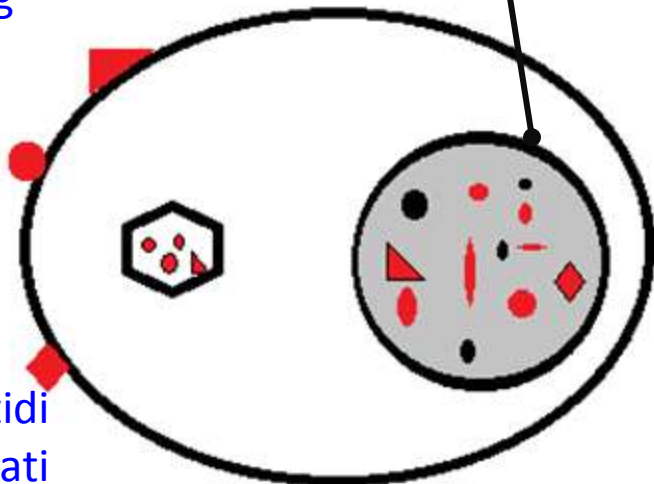
Timocita



TCR

Presentazione dell'Ag

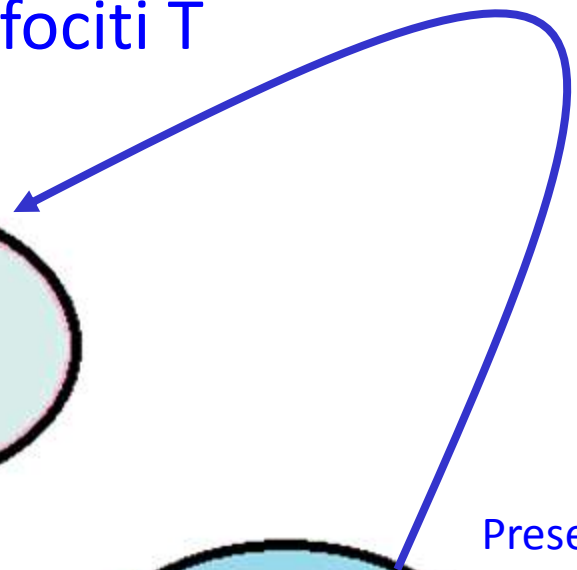
Peptidi associati a MHC I/II



Cellula epiteliale timica

AIRE

(AutoImmune Regulator)



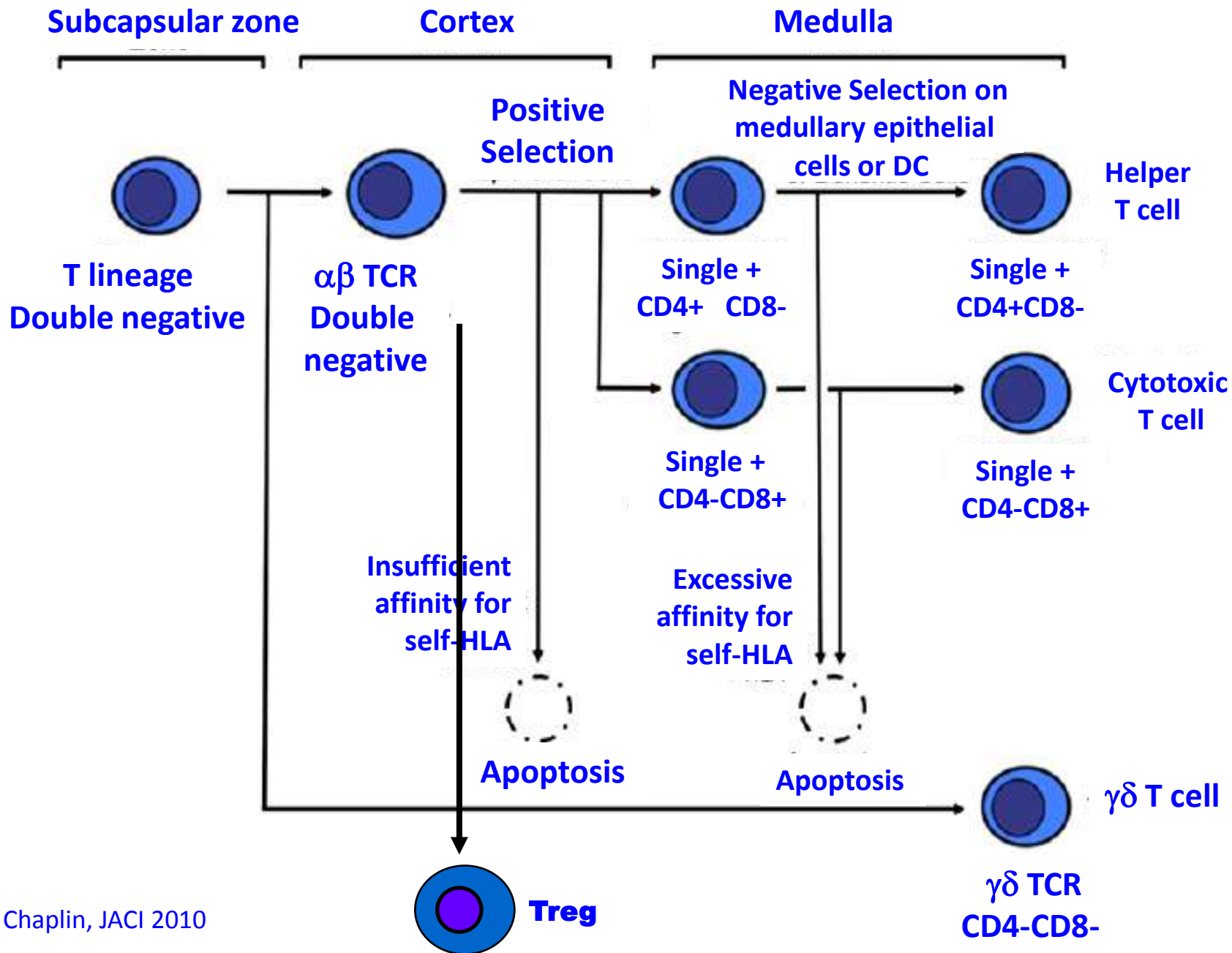
A utoimmune

L ympho

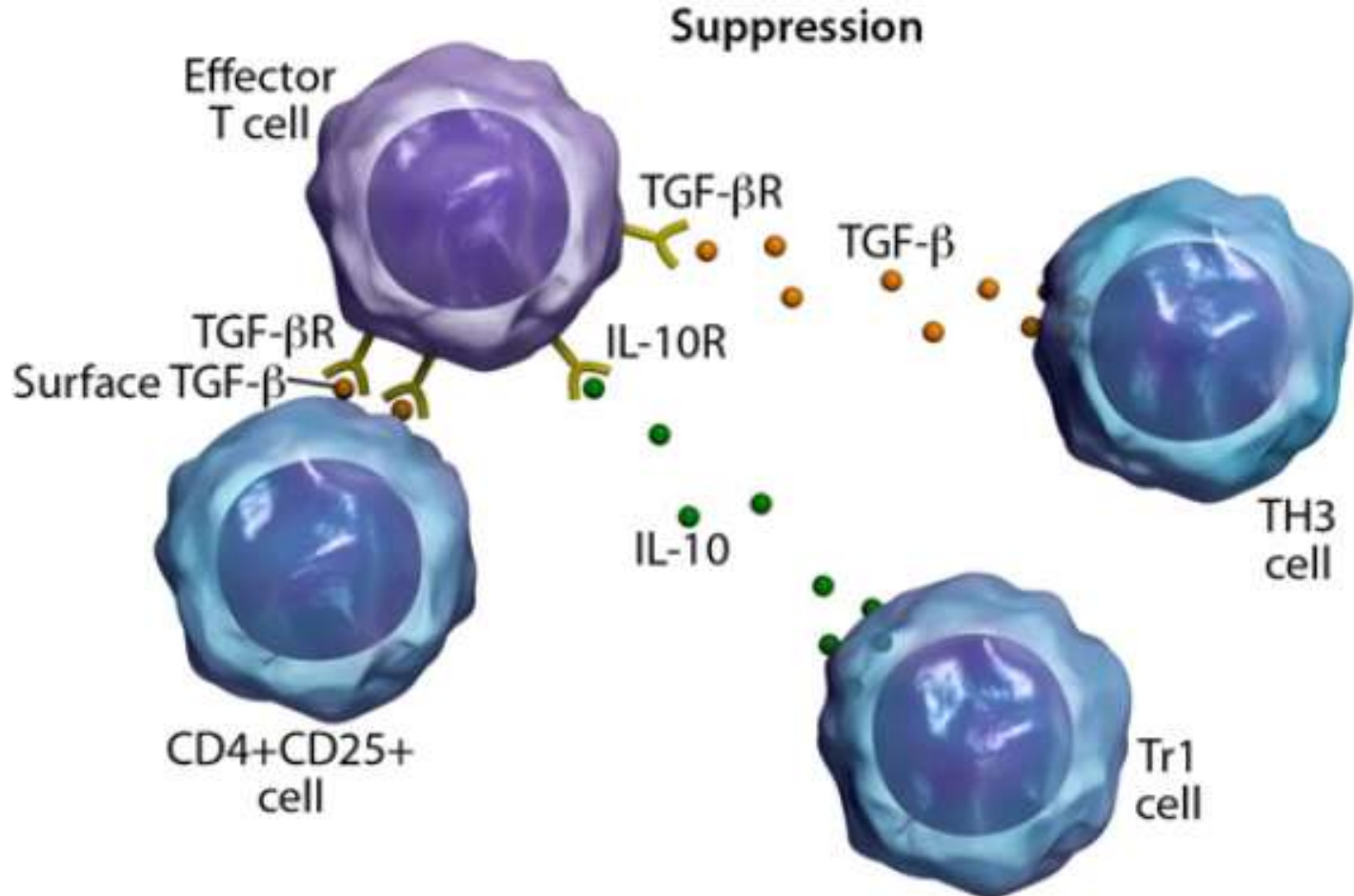
P roliferative

S yndrome

- Linfadenopatia
- Epatosplenomegalia
- Pancitopenia
- Orticaria, vitiligine
- Glomerulonefrite
- Epatite, artrite
- linfomi



Low dose tolerance



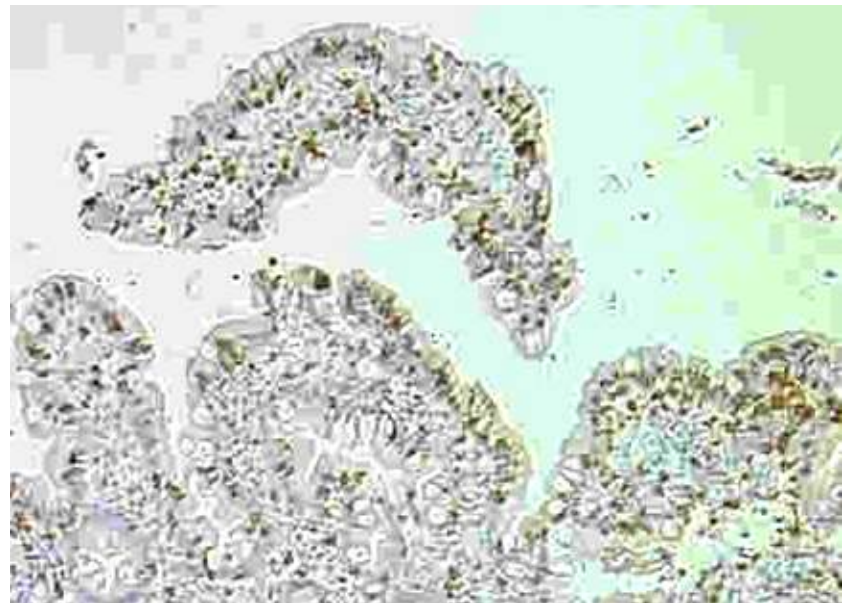
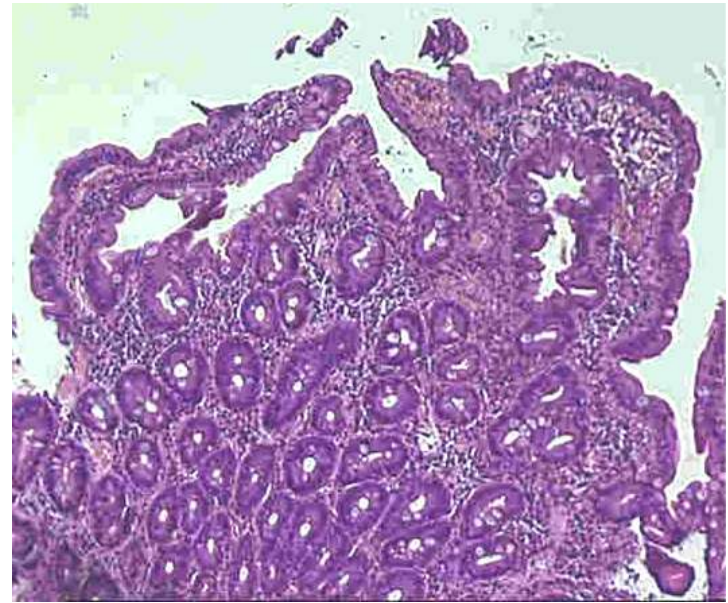
Mutazione di FOXP3

I mmunodysregulation

P olyndocrinopathy

E nteropathy

X -linked



Interaction of factors contributing to cancer in PID

Genetic alterations of oncogenic and tumor suppressor genes



Immunodeficiency

ATM & CANCER

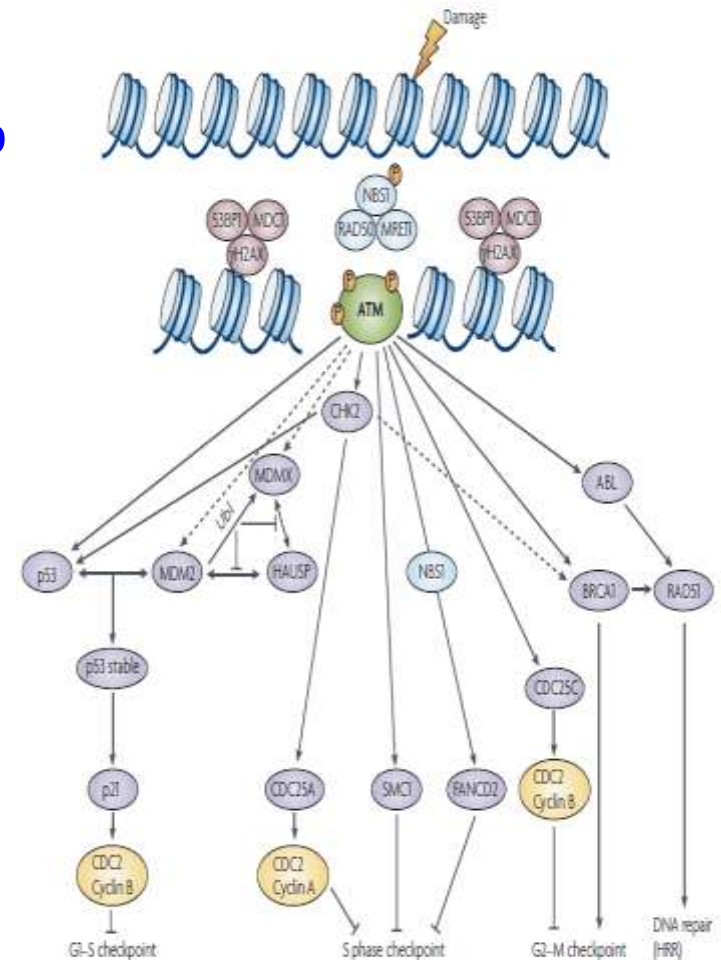
Incidence of malignancy 40%

Radiosensitivity

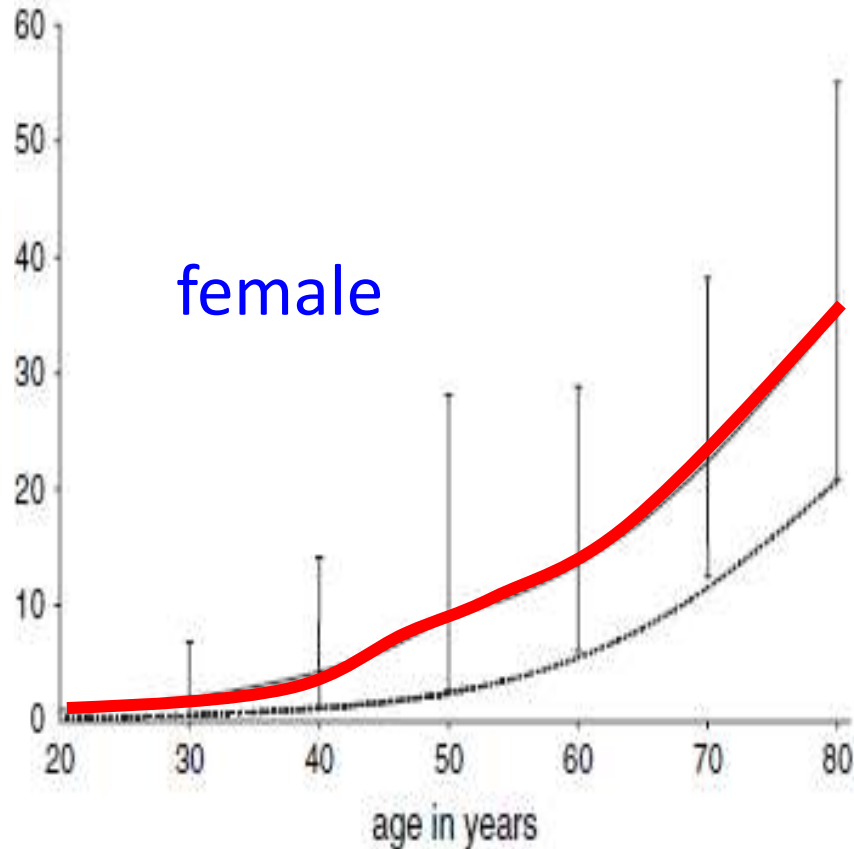
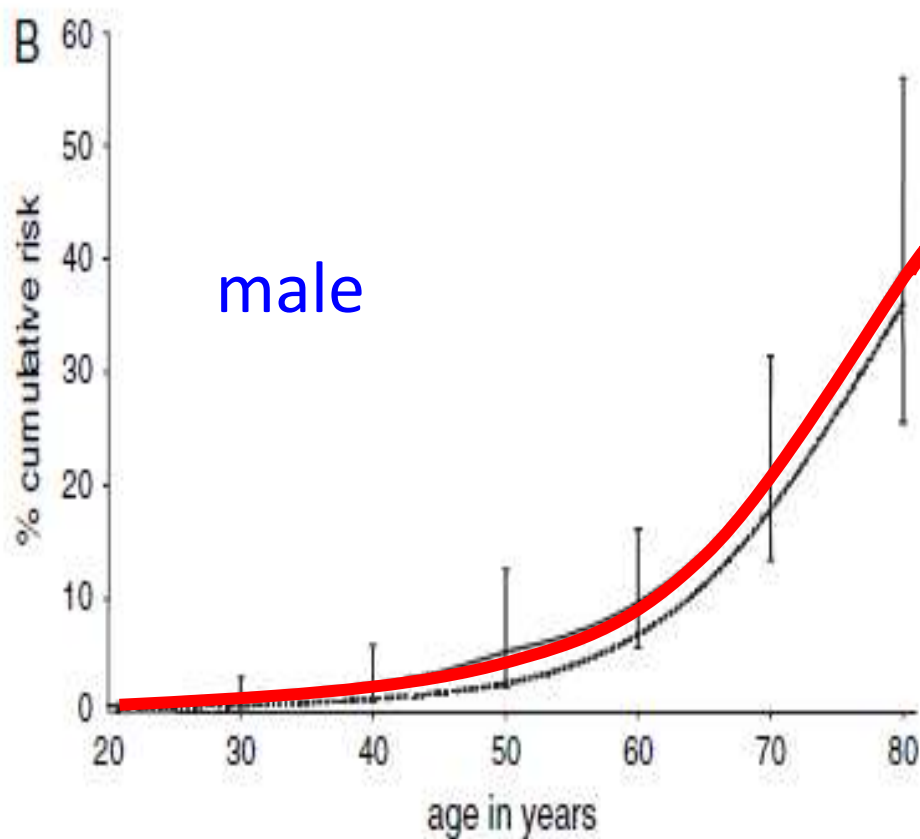
Leukemias & lymphomas

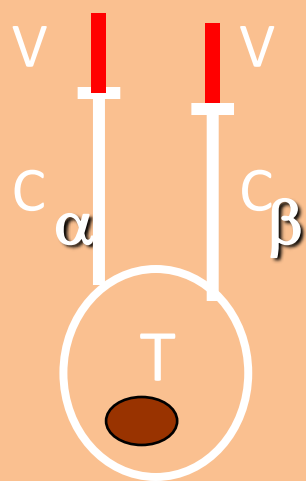
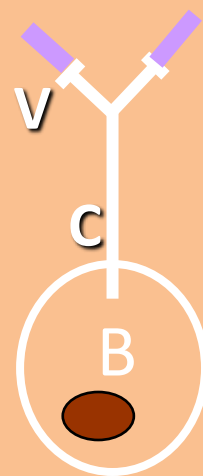
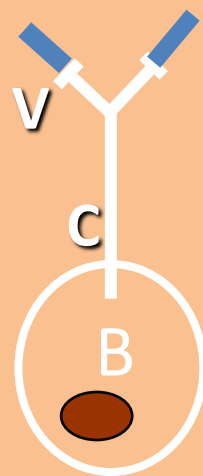
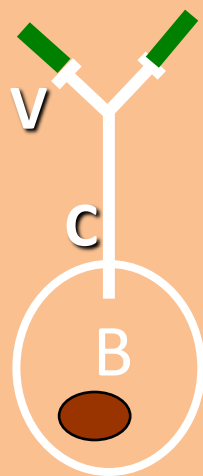
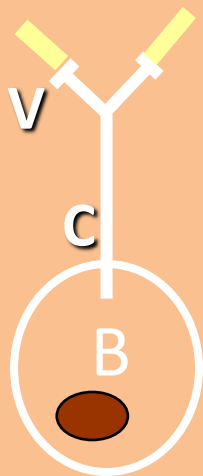
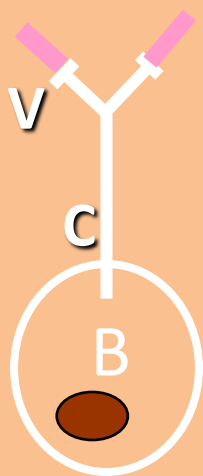
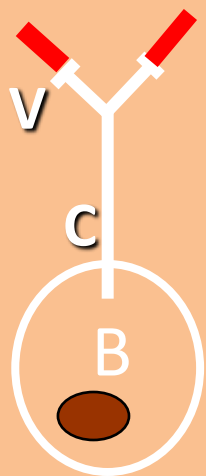
Breast cancer

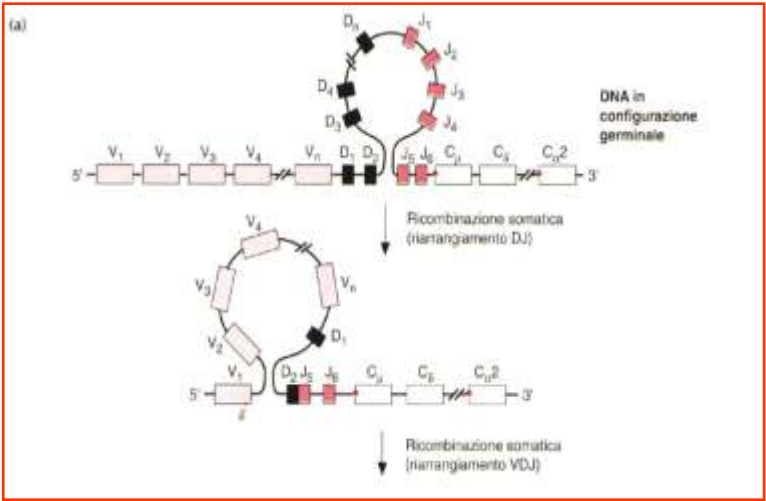
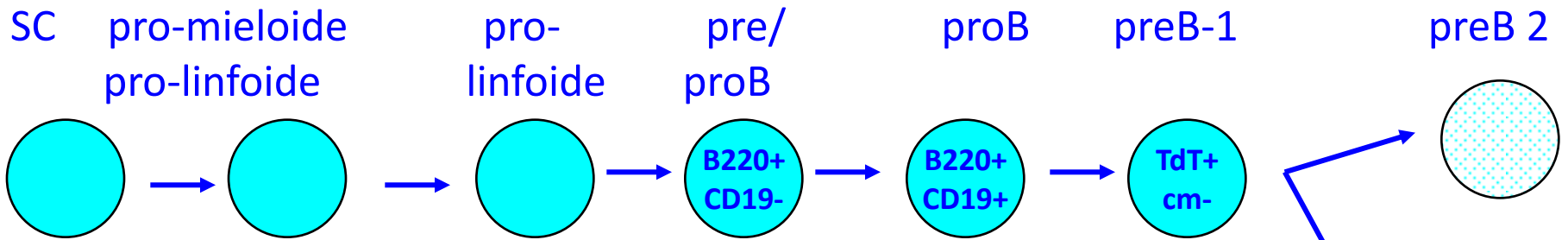
Increased risk of other cancers



Risk of cancer in heterozygous ATM mutation & general population (132 families, 1160 relatives)







Surrogate λ chain

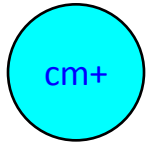
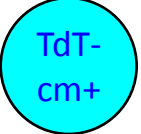
IL-7R
Rag-1
Rag-2

Sox4
IL-7
IL-2R

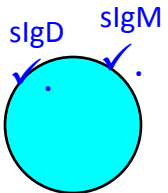
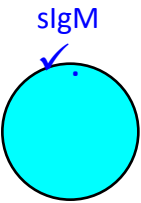
Pax-5

editing

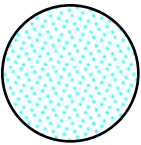
Riarrangiamento VDHJ-H



Riarrangiamento VDHJ-L

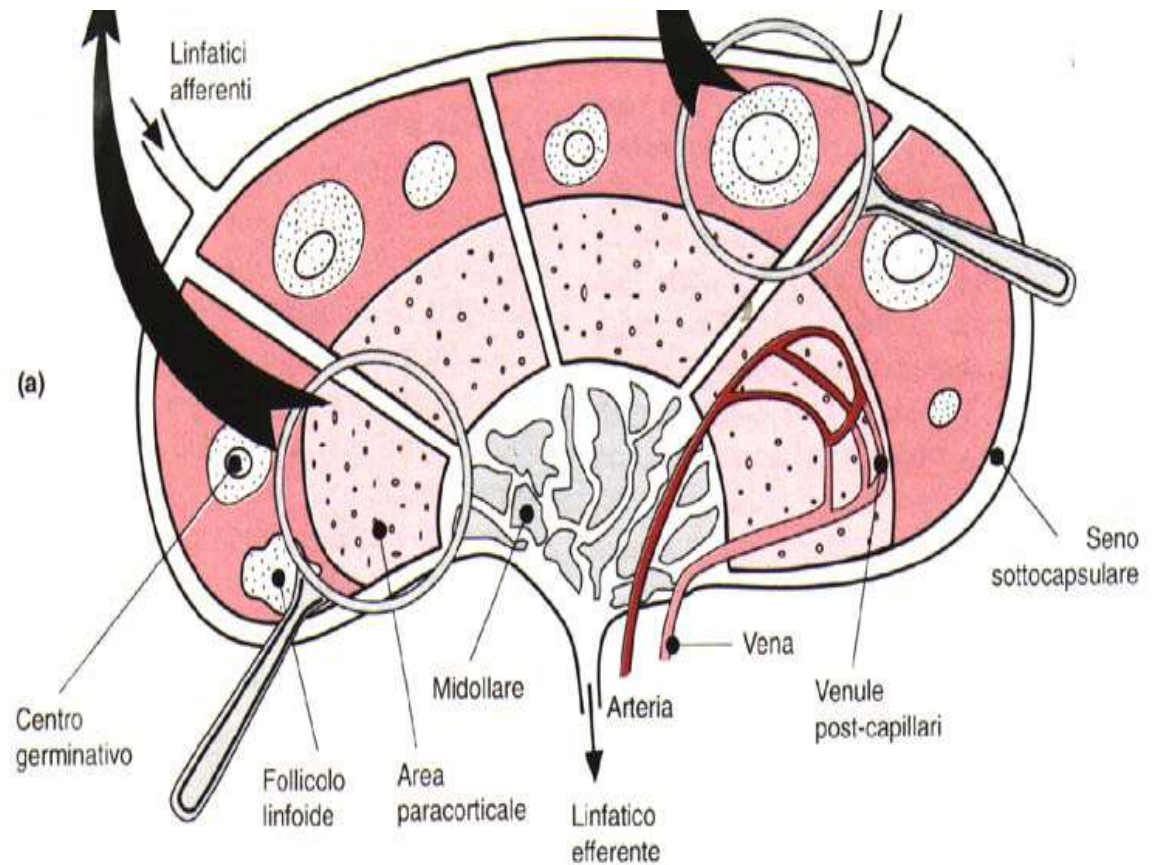


BTK CD40

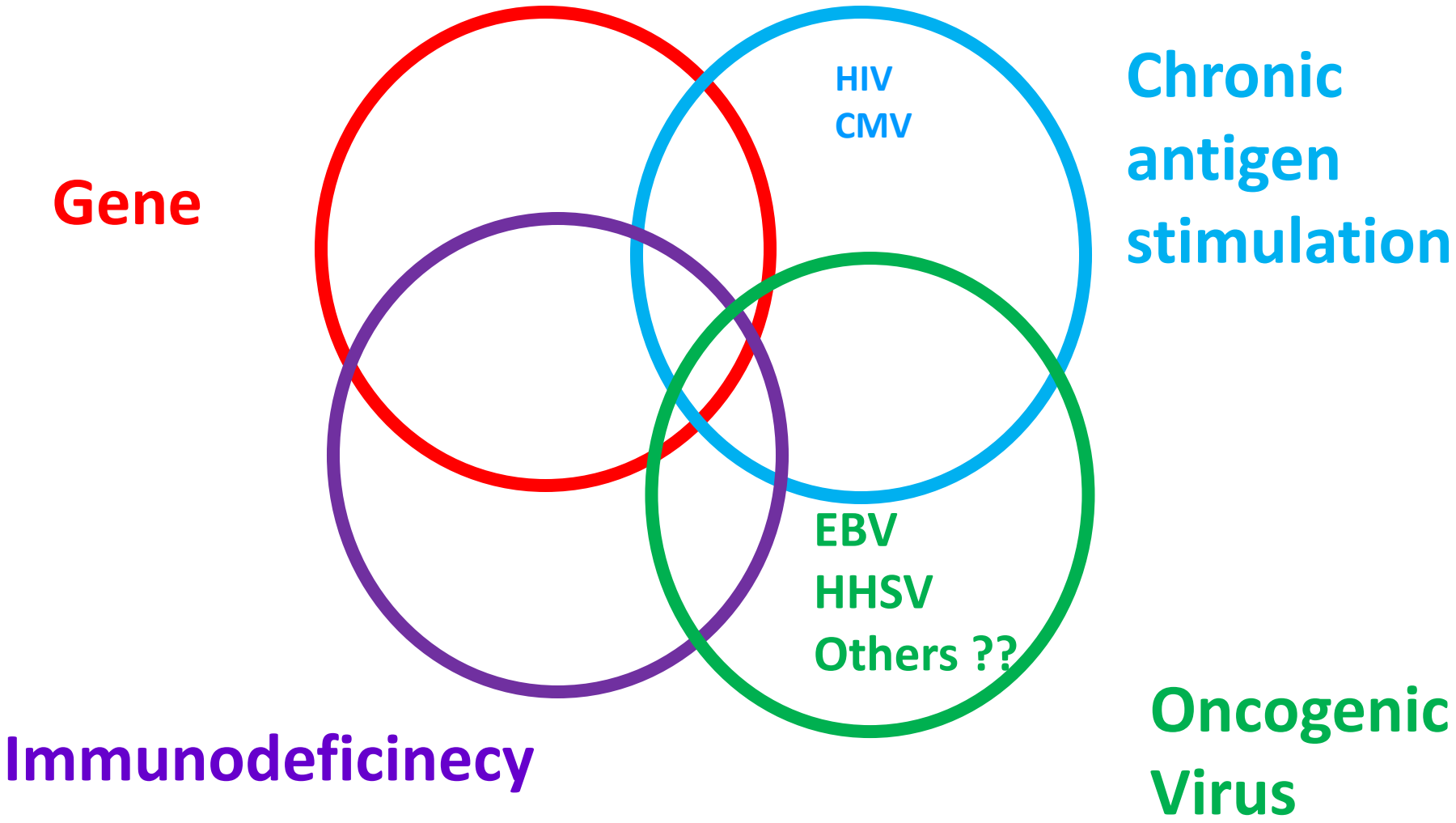


BAFF
APRIL

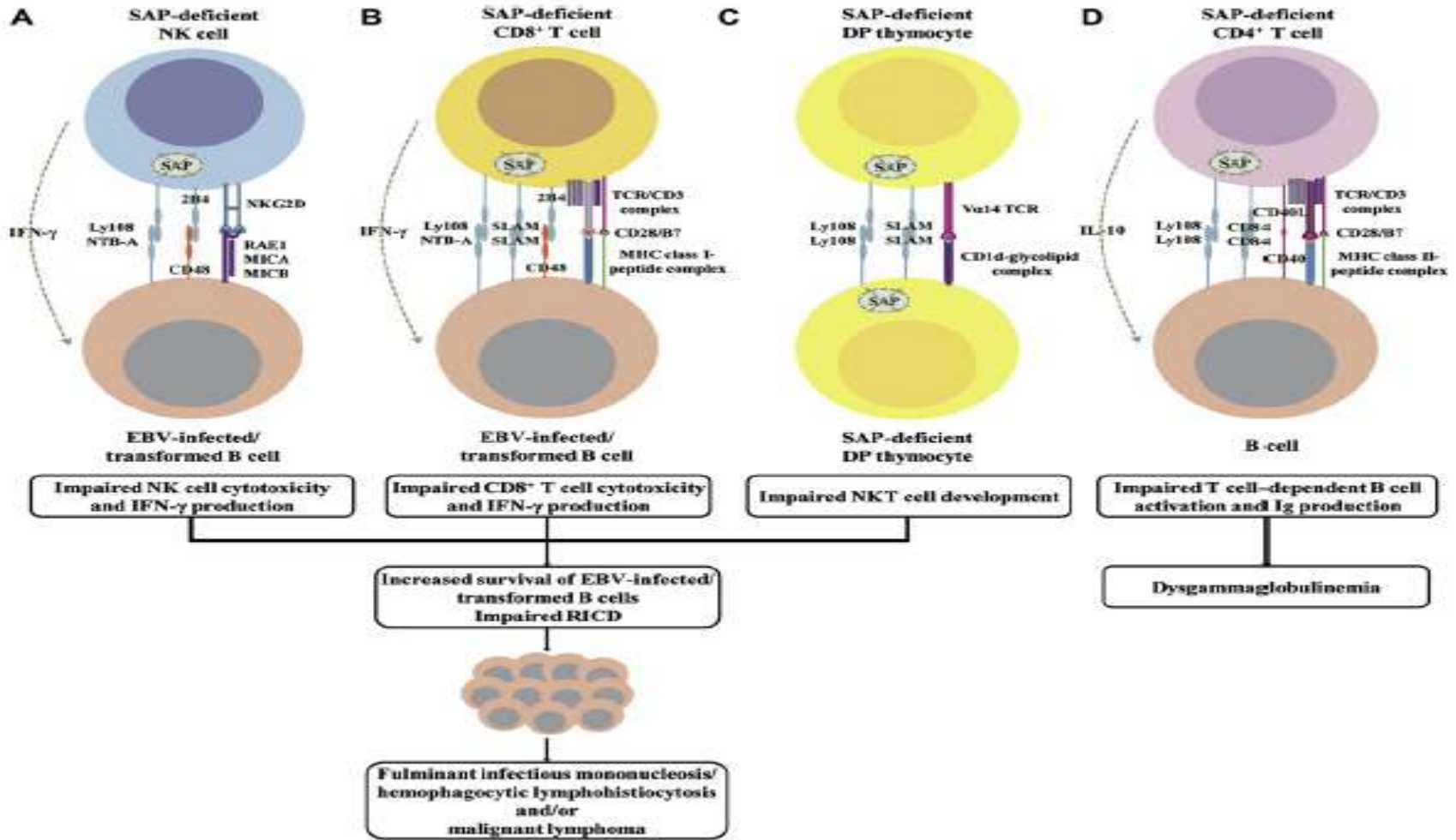
rescue autoreactive B cells from deletion
activation low affinity self reactive B cells



Interaction of factors contributing to cancer in PID



XLP & SLAM Associated Protein deficiency (*SH2D1A*, *XIAP*)





**Aveva ragione Burnet sulla
immunosorveglianza!**



Autoimmunità e tumori possono essere considerate immunodeficienze per se

Autoimmunity

Subclinical infections and
autoimmunity

Immunodeficiency

Severe **infections** and
autoimmunity

Low

Severity of immune defect

High

L'importanza del moderno lavorare in rete

La conoscenza della tipologia dei tumori nelle diverse
PID ci consente una migliore sorveglianza clinica