Patología digital en linfoma de Hodgkin clásico

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INSTITUTO DE INVESTIGACIÓN E INNOVACIÓN BIOMÉDICA DE CÁDIZ

Hospital Universitario
Puerta del Mar

ÍNDICE

Thomas Hodgkin (1798-1866)

ON SOME

MORBID APPEARANCES

OF

THE ABSORBENT GLANDS

AND

SPLEEN.

BY DR. HODGKIN.

PRESENTED

BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

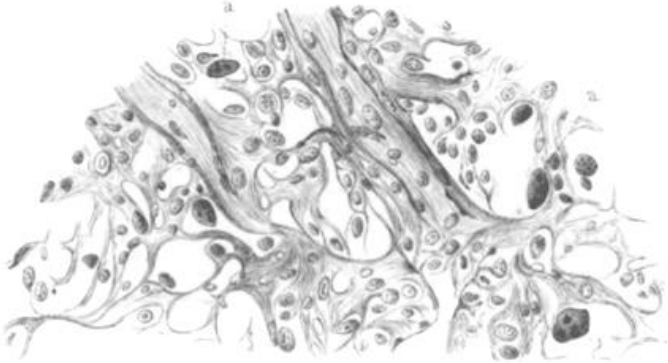
CASES OF

ENLARGEMENT OF THE LYMPHATIC GLANDS AND SPLEEN,

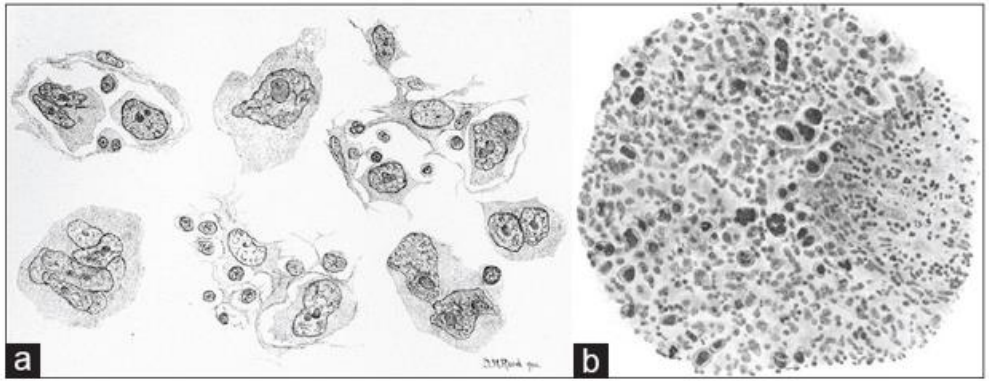
(OR, HODGKIN'S DISEASE,)

WITH REMARKS.

By SAMUEL WILKS, M.D.



Primer dibujo de la histología de la enfermedad de Hodgkin (Greenfield, 1878)



Dibujos originales de **Dorothy Reed** (1874-1964) y **Carl Sternberg** (1872-1935) de las células definitorias de la enfermedad de Hodgkin

Dorothy Reed (1874-1964)

Carl Sternberg (1872-1935)

¡1989!

EDITORIAL FREE PREVIEW ARCHIVE

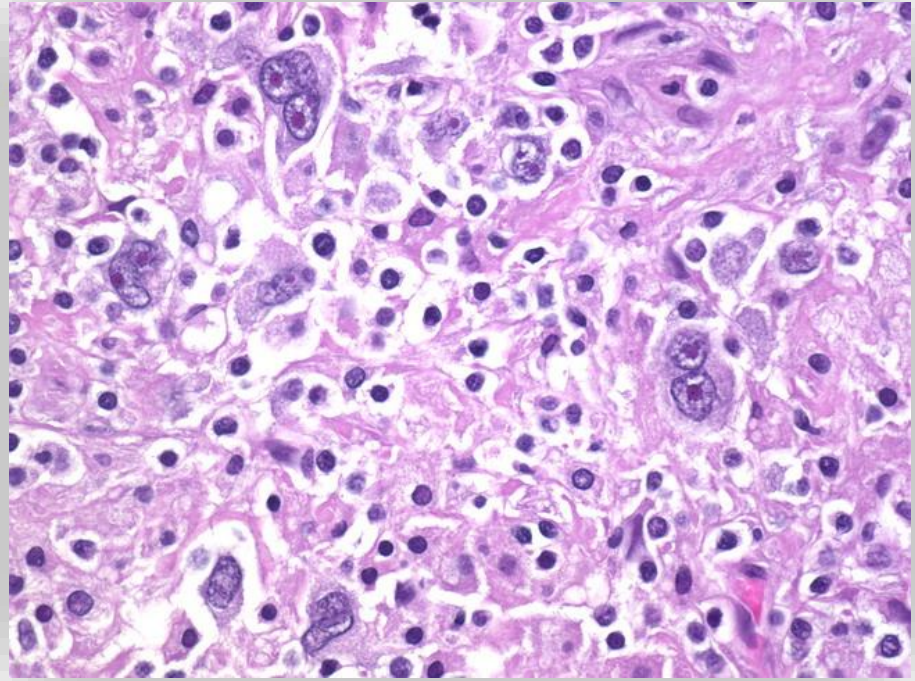
The Elusive Reed–Sternberg Cell

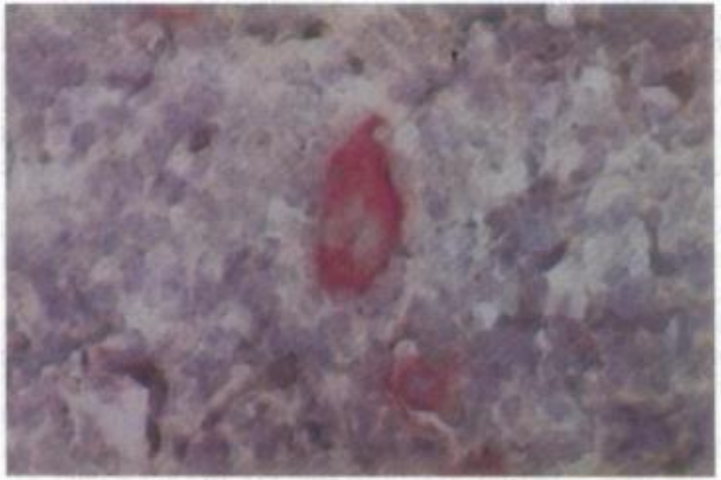
Elaine S. Jaffe, M.D.

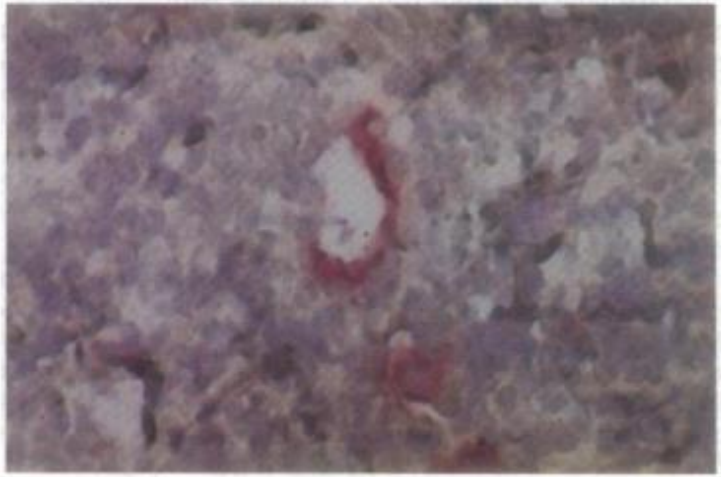
¿ ?

Although Hodgkin's disease was the first of the malignant lymphomas to be described as a specific disease process, this unique cancer has been the source of many persistent questions over the past 150 years. One enigma has been the paucity of the Reed–Sternberg cells and their variants (thought to be the malignant cells in this disease) in comparison to the large numbers of normal inflammatory cells. This apparent imbalance raises questions about the pathogenesis of the disease process. Is it infectious or neoplastic? If neoplastic, is the exuberant host response secondary to neoantigens expressed on the malignant cells, or does . . .

Elaine Jaffe (1943-)







The EMBO Journal vol.12 no.13 pp.4955–4967, 1993

Tracing B cell development in human germinal centres by molecular analysis of single cells picked from histological sections

Ralf Küppers[1], Min Zhao[2], Martin-L.Hansmann[2] and Klaus Rajewsky

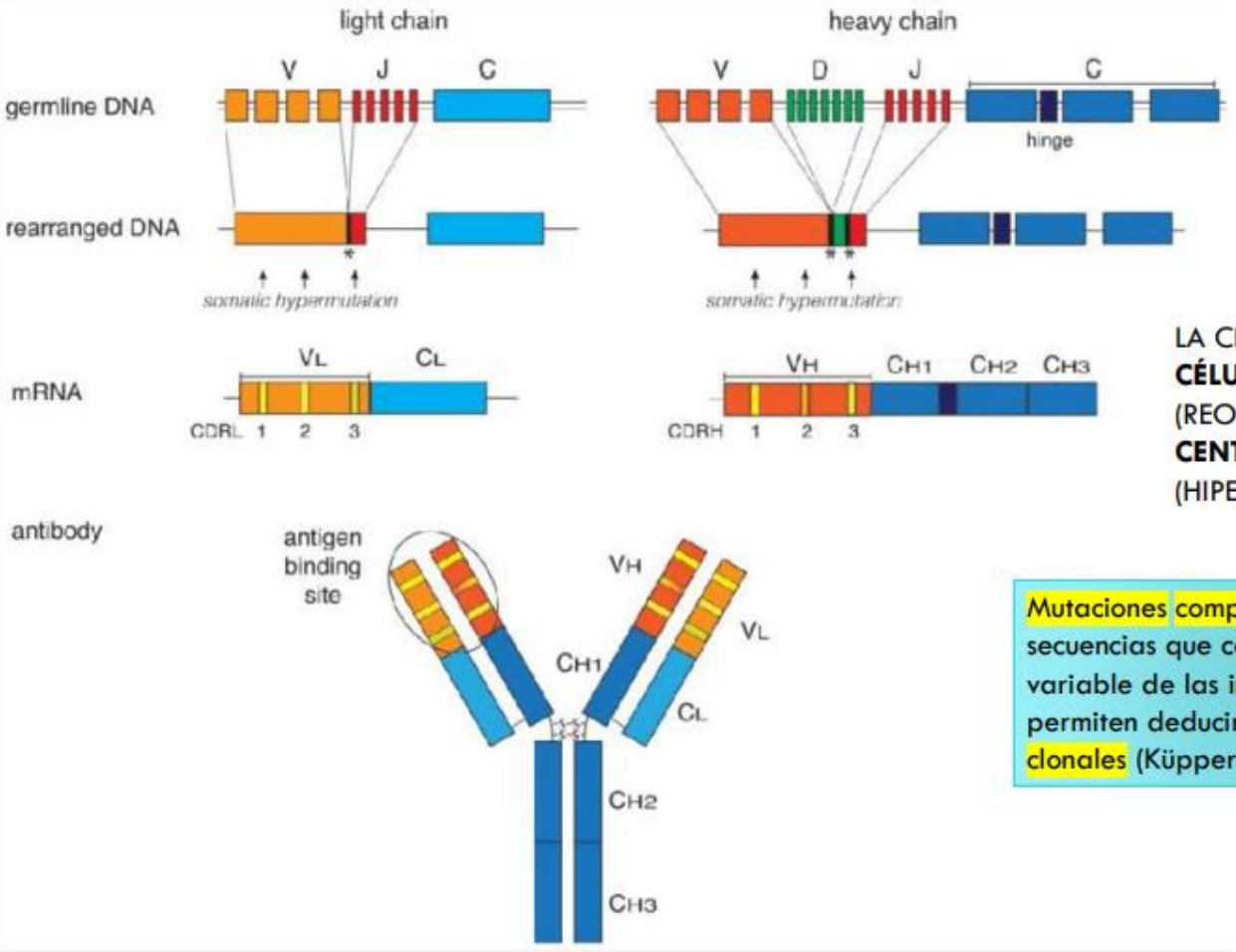
Estudios moleculares en células aisladas por micromanipulación (**PCR de célula individual**)

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 10962–10966, November 1994
Medical Sciences

Hodgkin disease: Hodgkin and Reed–Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development

RALF KÜPPERS*†, KLAUS RAJEWSKY*, MIN ZHAO†, GÜNTHER SIMONS‡, RALF LAUMANN*, ROBERT FISCHER‡, AND MARTIN-LEO HANSMANN‡

*Institute for Genetics, and ‡Department of Pathology, University of Cologne, 50931 Cologne, Germany



LA CÉLULA DE HRS ES UNA **CÉLULA LINFOIDE B** (REORDENAMIENTO IG) Y DE **CENTRO GERMINAL** (HIPERMUTACIÓN SOMÁTICA)

Mutaciones compartidas en las secuencias que codifican la región variable de las inmunoglobulinas permiten deducir genealogías clonales (Küppers et al. 1993)

DISCORDANCIA GENOTIPO-FENOTIPO

(crippling mutations, silenciamiento epigenético)

LA EXPRESIÓN DE IG SUPERFICIE ES UNA PRERROGATIVA PARA EL DESARROLLO LINFOIDE B

ACTIVACIÓN CONSTITUTIVA DE LA RUTA JAK/STAT

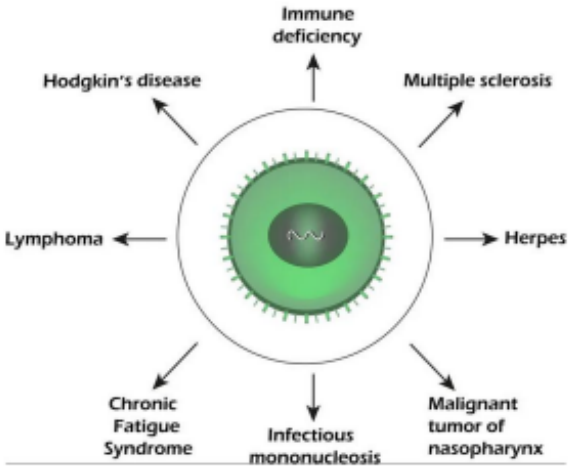
RUTA DEL FACTOR NUCLEAR KAPPA B (NFKB)

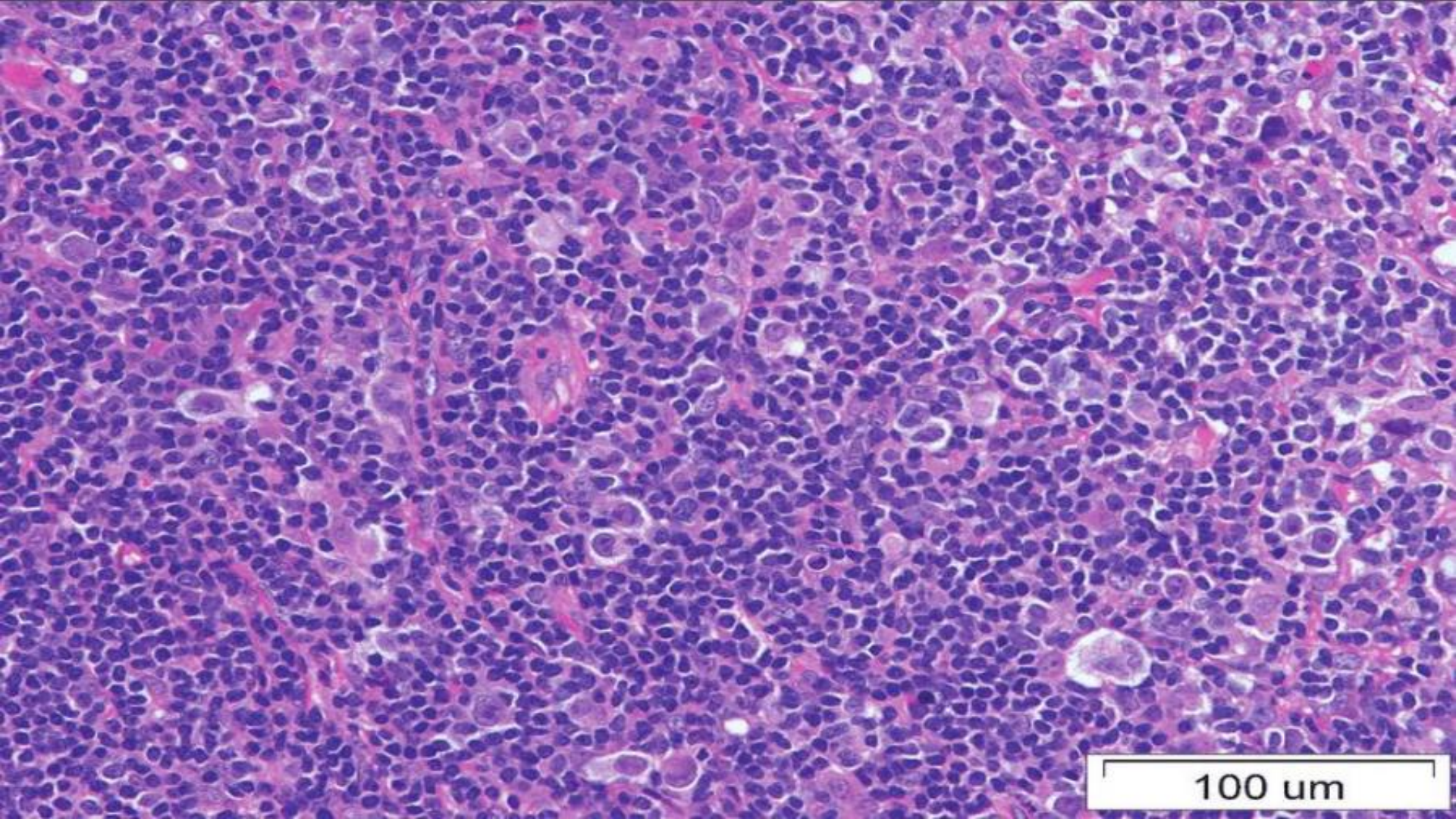
VENTAJA PROLIFERATIVA

EVASIÓN DE LA APOPTOSIS (EXPRESIÓN DE PROTEÍNAS ANTIAPOPTÓTICAS Bcl-2, Bcl-XL, BAX)

AMPLIFICACIÓN DE 9p24.1 (JAK, PDL-1, PDL-2)

Epstein-Barr virus




100 um

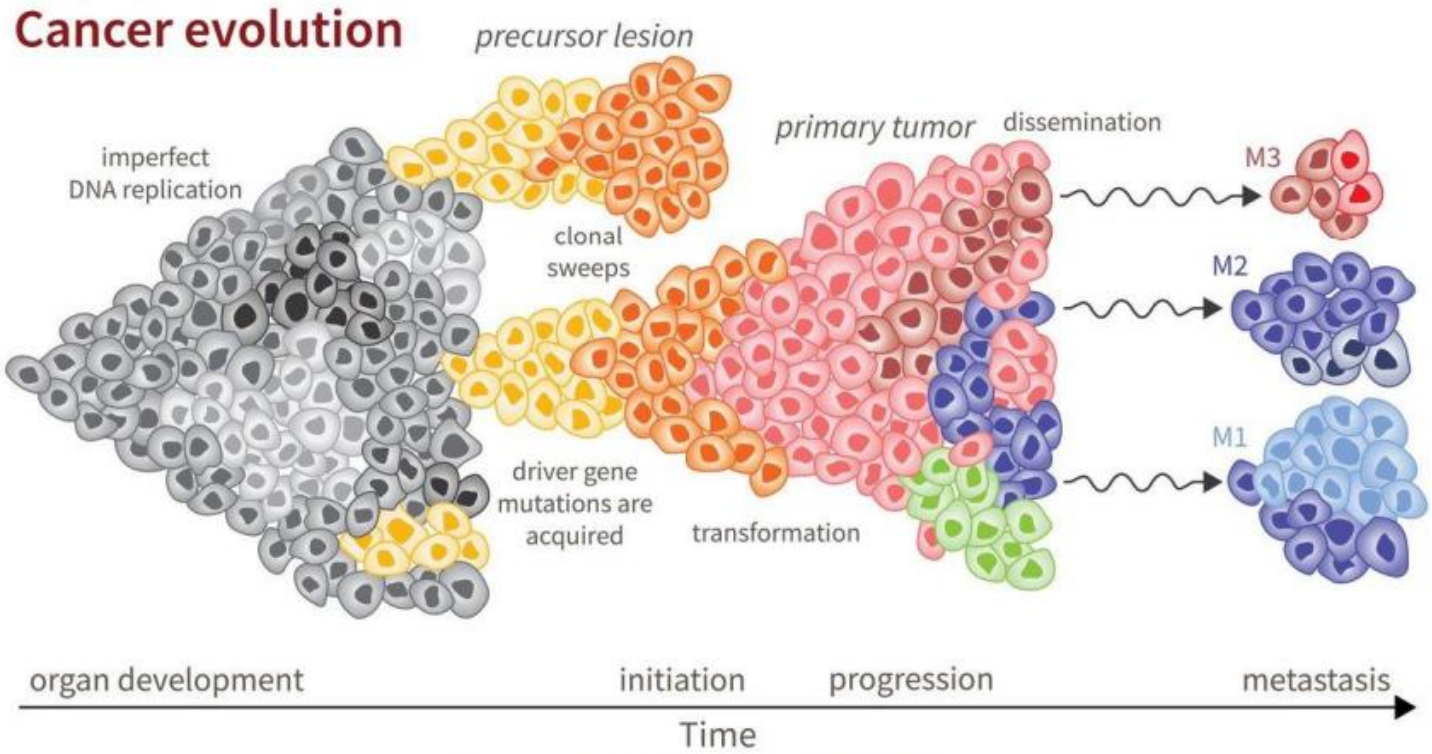
Received: 17 January 2020 | Revised: 15 June 2020 | Accepted: 17 June 2020
DOI: 10.1002/ece3.6590

REVIEW

Ecology and Evolution WILEY

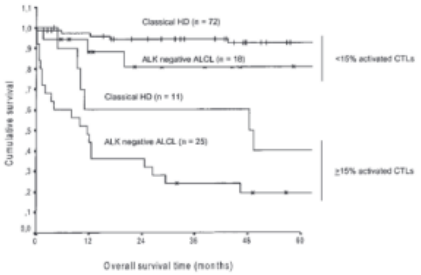
Eco-oncology: Applying ecological principles to understand and manage cancer

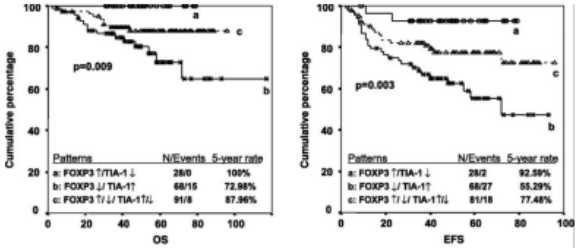
Brent A. Reynolds[1] | Monika W. Oli[2] | Madan K. Oli[3]



El cáncer es un fenómeno **darwiniano (1)**

IMPACTO PRONÓSTICO DE DIFERENTES POBLACIONES CELULARES DEL MICROAMBIENTE PERITUMORAL EN LINFOMA DE HODGKIN CLÁSICO

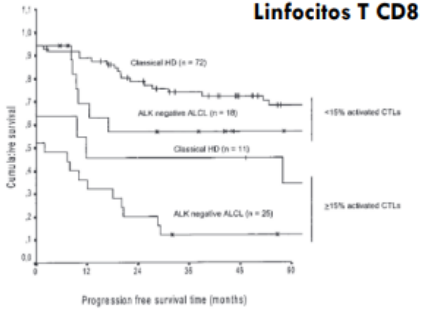




Linfocitos T reguladores y TIA-1

EJE PD1-PDL1

Linfocitos T CD8



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 11, 2010 VOL. 362 NO. 10

Tumor-Associated Macrophages and Survival in Classic Hodgkin's Lymphoma

Macrófagos

cancers MDPI

Review

The Hodgkin Lymphoma Immune Microenvironment: Turning Bad News into Good

Victoria Menéndez [1,†], José L. Solórzano [2,†], Sara Fernández [1], Carlos Montalbán [3] and Juan F. García [2,4,*]

The Nobel Prize in Physiology or Medicine 2018

© Nobel Media AB. Photo: A. Mahmoud

James P. Allison

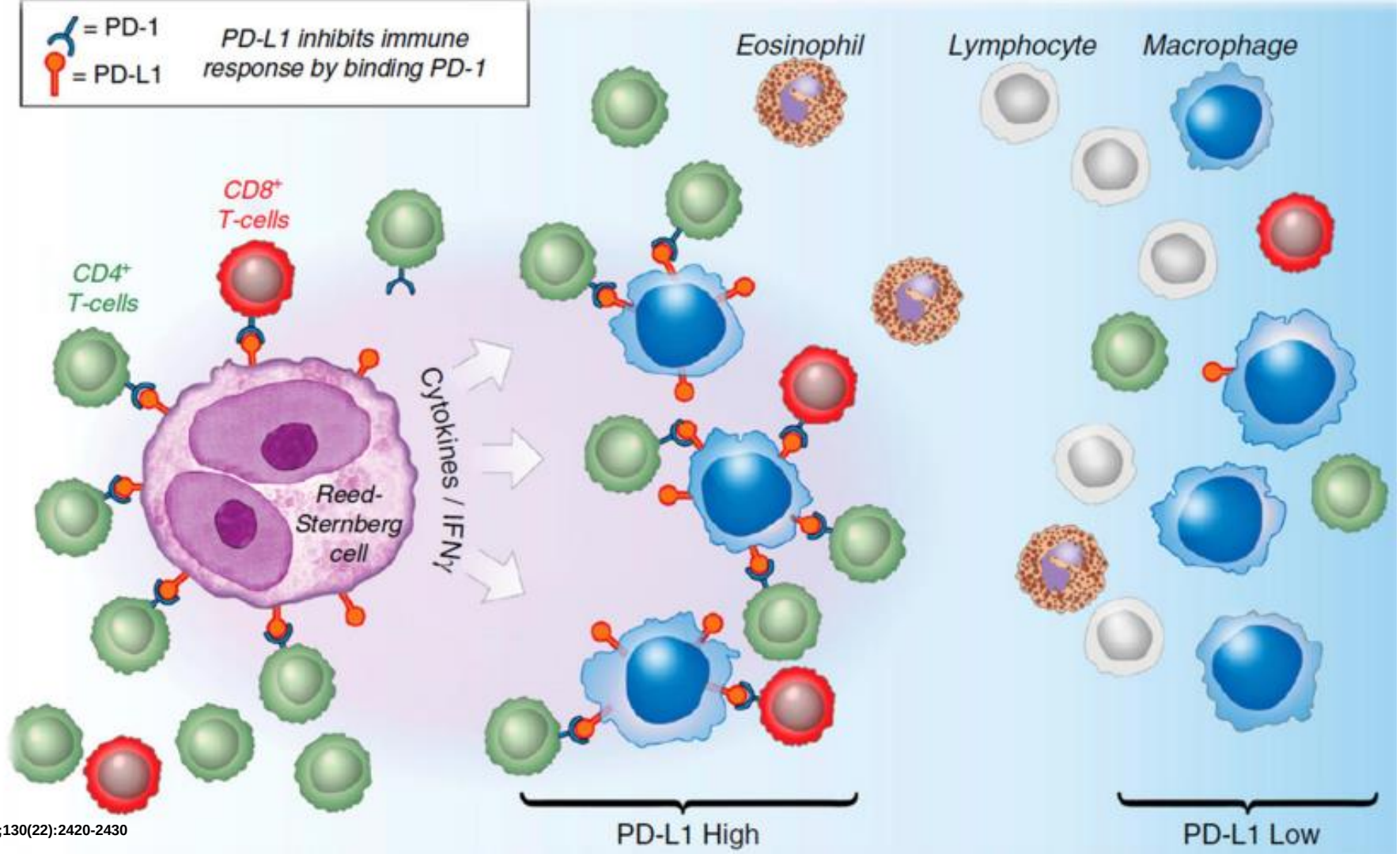
Prize share: 1/2

© Nobel Media AB. Photo: A. Mahmoud

Tasuku Honjo

Prize share: 1/2

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."



Blood. 2017;130(22):2420-2430

2. Cuestiones abiertas.

1. Las cuestiones abiertas en el Hodgin derivan de una **NECESIDAD CLÍNICA.**
   ¿Son suficientes los modelos pronóstico tradicionales (IPS, GHSG, EORTC)?
   Los modelos aplicados en la clínica no contemplan
   Información genómica **(inexistencia de firmas genéticas definitorias).**
   Rol del microambiente peritumoral **(necesidad de enfoques escalables y reproducibles).**
   Es **necesario** el desarrollo de **nuevos modelos** que permitan **intensificaciones y desescaladas** de tratamiento en pacientes con LHc.

JUNTA DE ANDALUCIA

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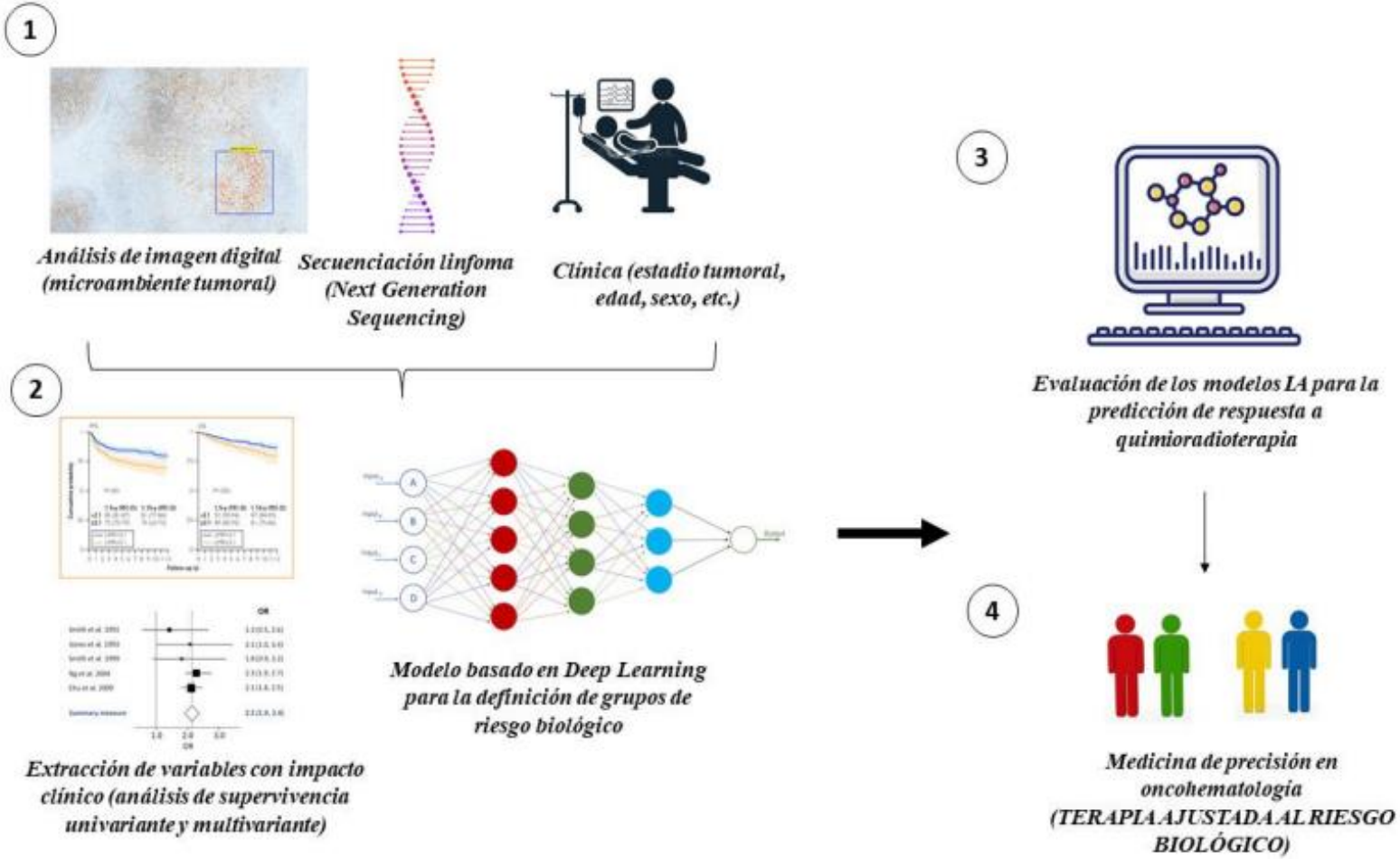
CONSEJERÍA DE SALUD Y FAMILIAS

INTELIGENCIA ARTIFICIAL EN LA INTEGRACIÓN DE DATOS CLÍNICOS, MORFOLÓGICOS Y GENÓMICOS EN ONCOHEMATOLOGÍA (RH-0145-2020)


1
Análisis de imagen digital (microambiente tumoral)
Secuenciación linfoma (Next Generation Sequencing)
Clínica (estadio tumoral, edad, sexo, etc.)
2
Extracción de variables con impacto clínico (análisis de supervivencia univariante y multivariante)
Modelo basado en Deep Learning para la definición de grupos de riesgo biológico
3
Evaluación de los modelos LA para la predicción de respuesta a quimioradioterapia
4
Medicina de precisión en oncohematología (TERAPIA AJUSTADA AL RIESGO BIOLÓGICO)

2. Cuestiones abiertas.

¿Se ha aplicado la PATOLOGÍA DIGITAL al estudio del LINFOMA DE HODGKIN CLÁSICO?

ELSEVIER

Computational Biology and Chemistry

Volume 46, October 2013, Pages 1-7

Image database analysis of Hodgkin lymphoma

Tim Schäfer [a, 1], Hendrik Schäfer [a, 1], Alexander Schmitz [a, 1], Jörg Ackermann [a], Norbert Dichter [a], Claudia Döring [b], Sylvia Hartmann [b], Martin-Leo Hansmann [b], Ina Koch [a]

1. Desarrollo de un flujo de trabajo para analizar preparaciones de **LHc** (subtipos **EN** y **CM**) mediante la asignación de píxeles a seis clases predefinidas y diferenciarlas de casos de **linfadenitis.** Solo se evalúan preparaciones teñidas para CD30 (Schäfer et al. 2013).
2. Aplicación de la **teoría de redes** a la distribución de células CD30+ para generar un **grafo celular CD30** y dar **las propiedades** de red: su *grado* es mayor que el de un modelo aleatorio (existe clustering), no son libres de escala (no hay grandes hubs celulares) (Schäffer et al. 2016).

Bioinformatics. 2016 Jan 1;32(1):122-9. doi: 10.1093/bioinformatics/btv542. Epub 2015 Sep 11.

CD30 cell graphs of Hodgkin lymphoma are not scale-free--an image analysis approach

Hendrik Schäfer [1], Tim Schäfer [1], Jörg Ackermann [1], Norbert Dichter [1], Claudia Döring [2], Sylvia Hartmann [2], Martin-Leo Hansmann [2], Ina Koch [1]

PLOS | COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Bioinformatics analysis of whole slide images reveals significant neighborhood preferences of tumor cells in Hodgkin lymphoma

Jennifer Hannig[1☯], Hendrik Schäfer[2☯], Jörg Ackermann[2], Marie Hebel[3], Tim Schäfer[4], Claudia Döring[5], Sylvia Hartmann[5], Martin-Leo Hansmann[6‡], Ina Koch[2‡*]

Molecular Bioinformatics - Goethe-Universität Frankfurt

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Dr. Senckenberg Institute of Pathology

Project: **Digital pathology: Analysis of the spatial distribution of tumour cells in Hodgkin lymphoma**

Martin-Leo Hansmann

ARTICLE

Hodgkin Lymphoma

Ferrata Storti Foundation

Whole-slide image analysis of the tumor microenvironment identifies low B-cell content as a predictor of adverse outcome in patients with advanced-stage classical Hodgkin lymphoma treated with BEACOPP

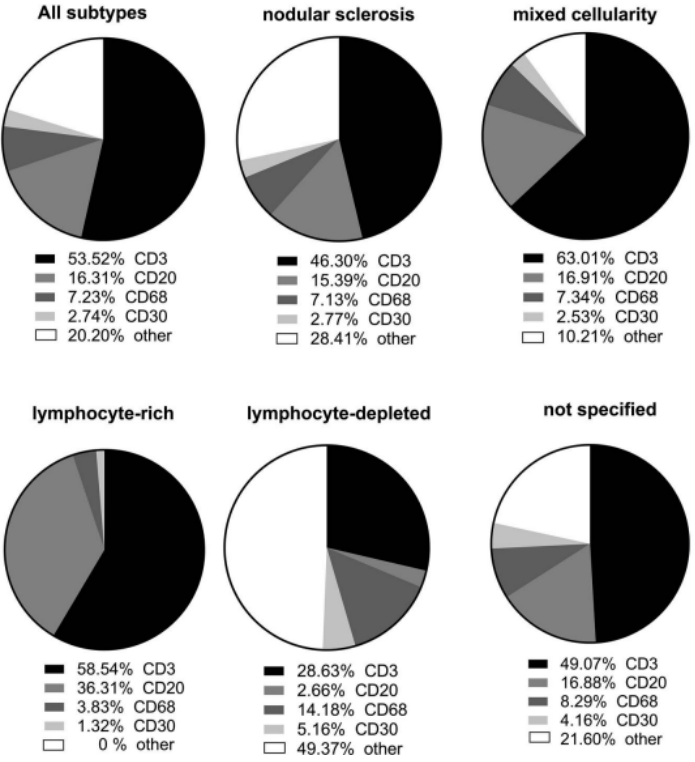
Ron Daniel Jachimowicz,[1,2,3*] Luise Pieper,[4*] Sarah Reinke,[4,*] Artur Gontarewicz,[4,*] Annette Plütschow,[1] Heinz Haverkamp,[1] Leonie Frauenfeld,[5] Falko Fend,[5] Mathis Overkamp,[5] Franziska Jochims,[4] Christoph Thorns,[6] Martin Leo Hansmann,[7] Peter Möller,[8] Andreas Rosenwald,[9] Harald Stein,[10] Hans Christian Reinhardt,[2,3,11,12] Peter Borchmann,[1,3] Bastian von Tresckow,[1,3] Andreas Engert[1,3] and Wolfram Klapper[4]

Haematologica 2021
Volume 106(6):1684-1692

340 patients with **advanced-stage** cHL enrolled in the HD12 and HD15 trials of the German Hodgkin Study Group (GHSG)

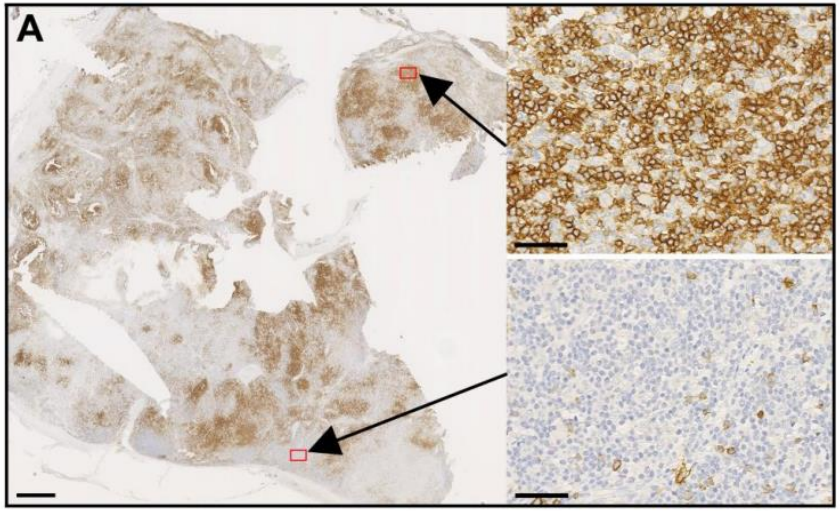
Quantifying **T cells** (CD3), **B cells** (CD20), **Hodgkin and Reed-Sternberg** (CD30) cells and **macrophages** (CD68) with WSI

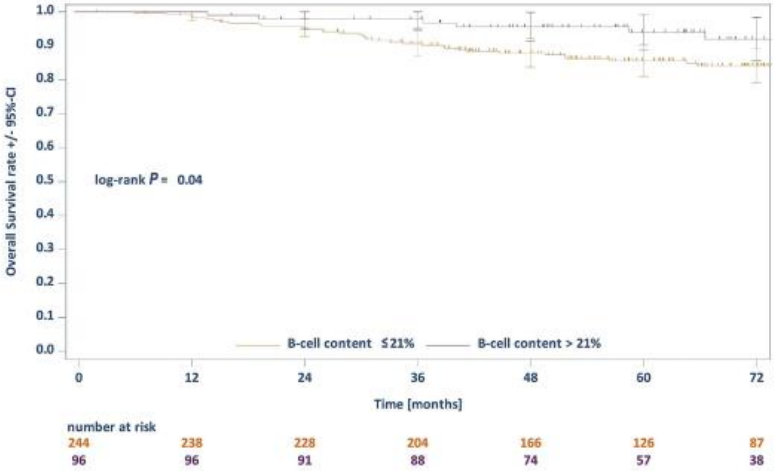
Low B-cell count (<21%) was associated with *significantly reduced progression-free survival and overall survival*



Cellular composition of cHL

Distribution of B cells





Survival impact on PFS and OS

In summary, B-cell content assessed by WSI in advanced-stage cHL allows for a robust discrimination of patients at high risk of experiencing relapse or progressive disease and thus identifies a population of patients who may qualify for novel first-line treatment strategies. Furthermore, we envision that WSI may also be applied to identify patients in whom de-escalation of treatment intensity may be possible. We thus anticipate the use of WSI in all future GHSG studies. Even though additional testing is required to define cut-off values, this approach is close to clinical application since the data required (CD20 staining) are generated in the standard diagnostic workup of any cHL around the world. We cannot imagine any other technology with such a broad potential for application, considering that even in less well-developed countries access may be affordable. Finally, this is a unique opportunity to establish a risk model looking specifically at the microenvironment in prospective clinical trials.

viruses

MDPI

Article

Prognostic Role of the Expression of Latent-Membrane Protein 1 of Epstein–Barr Virus in Classical Hodgkin Lymphoma

Antonio Santisteban-Espejo [1,2,3,*], Jose Perez-Requena [1], Lidia Atienza-Cuevas [1], Julia Moran-Sanchez [3,4], Maria del Carmen Fernandez-Valle [4], Irene Bernal-Florindo [2], Raquel Romero-Garcia [2] and Marcial Garcia-Rojo [1,2]

diagnostics

MDPI

Systematic Review

The Need for Standardization in Next-Generation Sequencing Studies for Classic Hodgkin Lymphoma: A Systematic Review

Antonio Santisteban-Espejo [1,2,3], Irene Bernal-Florindo [2,*], Jose Perez-Requena [1], Lidia Atienza-Cuevas [1], Julia Moran-Sanchez [3,4], María del Carmen Fernandez-Valle [4], Raquel Romero-Garcia [2] and Marcial Garcia-Rojo [1,2]

Supplementary Table S2. Proposal of NGS panel for classic Hodgkin lymphoma.

Gene	Chromosome	Number of Amplicons	Total bases	Covered bases	Missed bases	Coverage
ID3	Chr1	5	400	400	0	1.000
ARID1A	Chr1	87	7258	7187	71	0.969
BCL10	Chr1	10	762	762	0	1.000
NOTCH2	Chr1	102	8149	7958	191	0.731
XPO1	Chr2	51	3696	3674	22	0.916
CXCR4	Chr2	13	1126	1126	0	1.000
SF3B1	Chr2	68	4505	4478	27	0.961
CASP8	Chr2	24	1913	1889	24	0.984
MYD88	Chr3	14	1054	1054	0	1.000
CD38	Chr4	15	1063	1063	0	1.000
CSF2	Chr5	9	515	515	0	1.000
CSF1R	Chr5	51	3339	3339	0	1.000
NFKBIE	Chr6	21	1623	1623	0	1.000
MYB	Chr6	38	2606	2596	10	0.984
TNFAIP3	Chr6	26	2533	2515	18	0.990
CARD11	Chr7	54	3945	3945	0	1.000
BRAF	Chr7	42	2661	2655	6	0.997
EZH2	Chr7	40	2636	2636	0	1.000
MYC	Chr8	15	1425	1425	0	1.000
PTPRD	Chr9	84	6539	6516	23	0.996
CDKN2A	Chr9	11	1012	1008	4	0.996
ABL1	Chr9	45	3769	3759	10	0.991
NOTCH1	Chr9	111	8348	8274	74	0.973
TRAF2	Chr9	21	1706	1706	0	1.000
FAS	Chr10	17	1188	1188	0	1.000
CCND1	Chr11	14	988	988	0	1.000
BIRC3	Chr11	28	1975	1971	4	0.997
STAT6	Chr12	42	2964	2955	9	0.996
FOXO1	Chr13	19	2608	1929	79	0.939
LCP1	Chr13	30	2184	2184	0	1.000
NFKBIA	Chr14	16	1074	1074	0	1.000
B2M	Chr15	7	420	420	0	1.000
IL32	Chr16	9	805	605	200	0.896
CREBBP	Chr16	95	7949	7926	23	0.995
CD19	Chr16	32	1954	1954	0	1.000
CYLD	Chr16	43	3211	3144	67	0.978
PLCG2	Chr16	62	4438	4438	0	1.000
TP53	Chr17	24	1503	1503	0	1.000
CD79B	Chr17	12	813	813	0	1.000
BCL2	Chr18	9	793	793	0	1.000
TCF3	Chr19	35	2572	2567	5	0.997
KLF2	Chr19	12	1128	968	160	0.936
MEF2B	Chr19	16	1267	1267	0	1.000
CD79A	Chr19	12	781	781	0	1.000
CSF2RB	Chr22	38	2954	2954	0	1.000
EP300	Chr22	97	7865	7865	0	1.000
BTK	ChrX	33	2462	2402	0	1.000

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 20 October 2022
DOI 10.3389/fonc.2022.1000762

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Santisteban-Espejo A, Bernal-Florindo I, Perez-Requena J, Atienza-Cuevas L, Maira-Gonzalez N and Garcia-Rojo M (2022) Whole-slide image analysis identifies a high content of Hodgkin Reed-Sternberg cells and a low content of T lymphocytes in tumor microenvironment as

Whole-slide image analysis identifies a high content of Hodgkin Reed-Sternberg cells and a low content of T lymphocytes in tumor microenvironment as predictors of adverse outcome in patients with classic Hodgkin lymphoma treated with ABVD

Antonio Santisteban-Espejo[1,2,3], Irene Bernal-Florindo[2,4*], Jose Perez-Requena[1], Lidia Atienza-Cuevas[1], Nieves Maira-Gonzalez[5] and Marcial Garcia-Rojo[2,4]

[1]Department of Pathology, Puerta del Mar University Hospital, Cadiz, Spain, [2]Institute of Research and Innovation in Biomedical Sciences of the Province of Cadiz (INiBICA), Cadiz, Spain, [3]Department of Medicine, Faculty of Medicine, University of Cadiz, Cadiz, Spain, [4]Department of Pathology, Jerez de la Frontera University Hospital, Cadiz, Spain, [5]Department of Pathology, Puerto Real University Hospital, Cadiz, Spain

85 patients diagnosed with cHL at the Pathology Department of HUPM treated with ABVD

Digitization and quantification of **255 cHL slides**; Hodgkin and Reed-Sternberg cells (**CD30**), B-lymphocytes (**CD20**) and T-lymphocytes (**CD3**) using ***WSI technique***

High CD30 content (>2%) and **low CD3 content (<26.7%)** were associated with *significantly reduced overall survival and progression-free survival*

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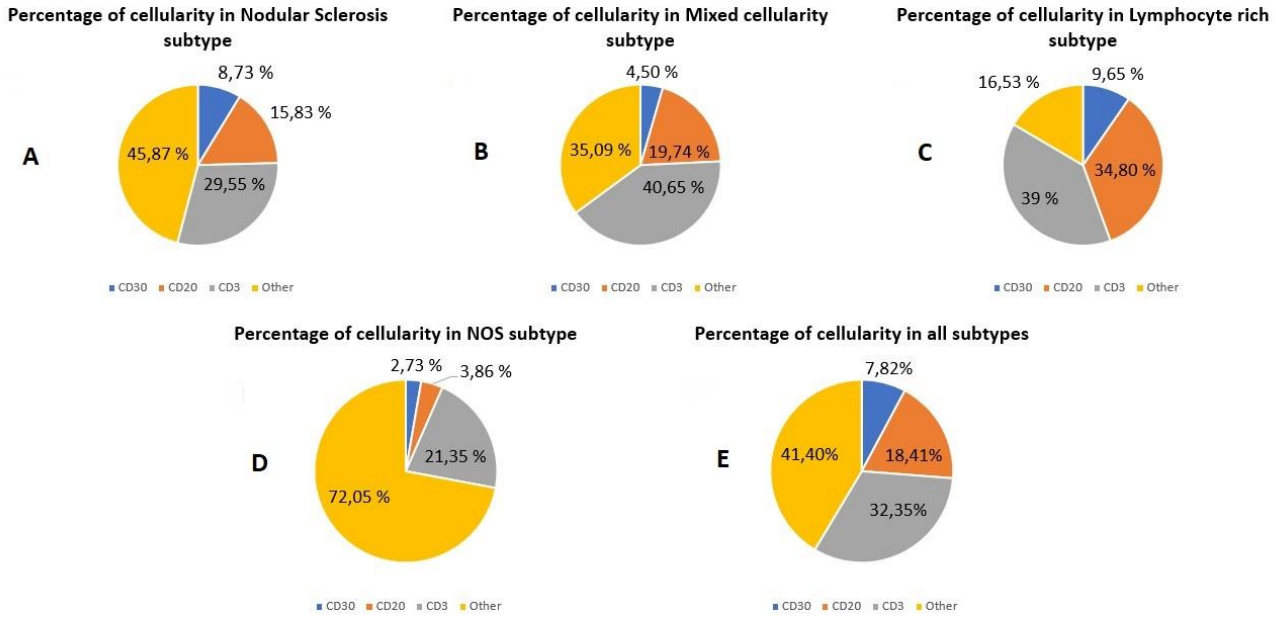

Cellular composition of classic Hodgkin lymphoma (cHL) assessed by whole-slide imaging. Cell percentages for HRS cells (CD30), B cells (CD20) and T cells (CD3)

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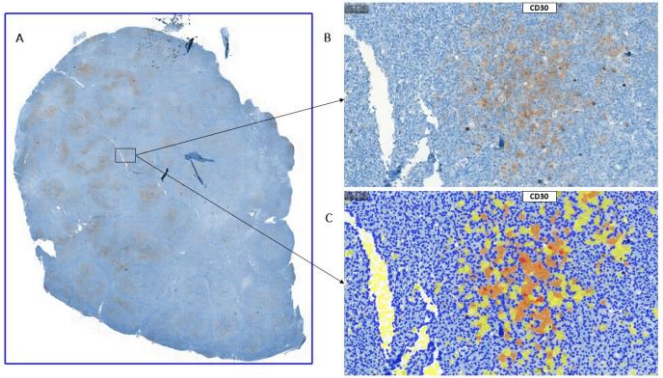
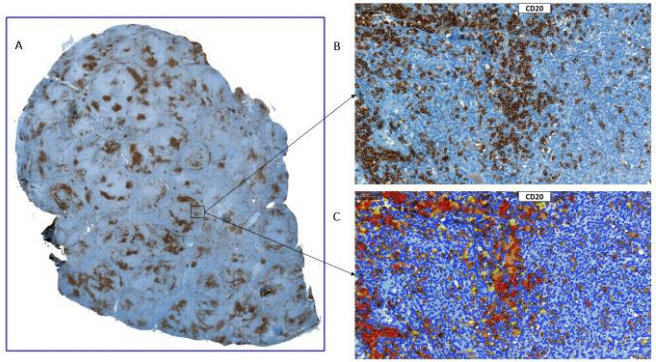
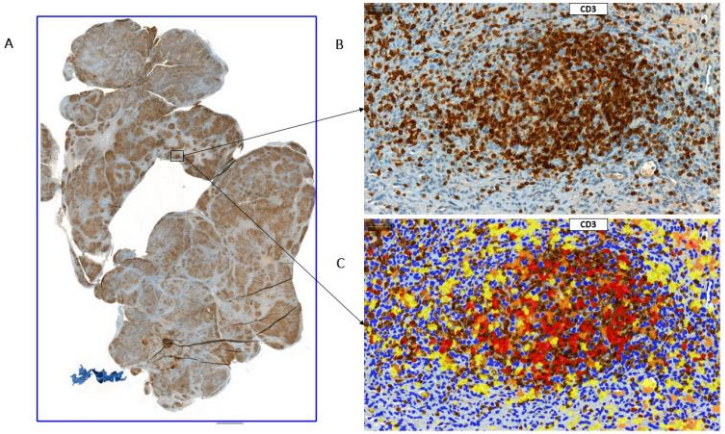
TYPE Original Research
PUBLISHED 20 October 2022
DOI 10.3389/fonc.2022.1000762

Assessment of **CD30, CD20** and **CD3** cellularity in cHL lymph node.







A) Whole lymph nodes stained for different cellularities (0.4X)

A) Magnified areas (10X)

A) Same region ***after cell quantification*** using the MembraneQuant algorithm (3D Histech Ltd., Budapest, Hungary)

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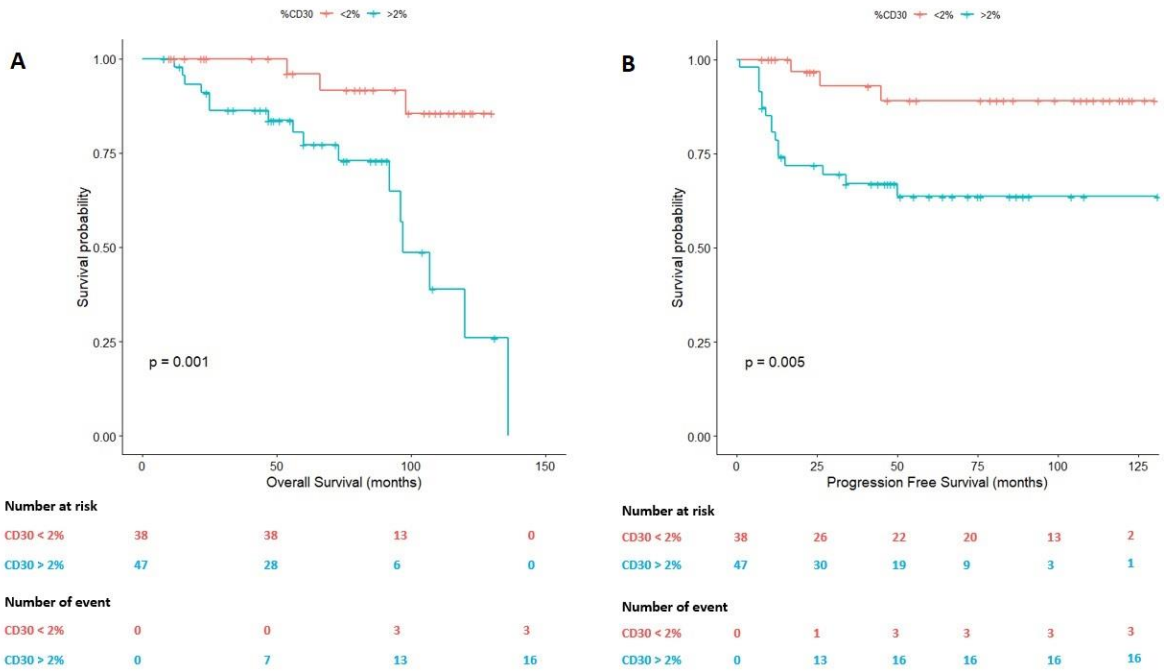
Survival plots (Kaplan-Meier) according to the percentage of HRS cells assessed by WSI



Cut off value calculated using ROC curves; **2%** of HRS cells

CD30 < 2% ➡ Higher survival time

CD30 > 2% ➡ Lower survival time

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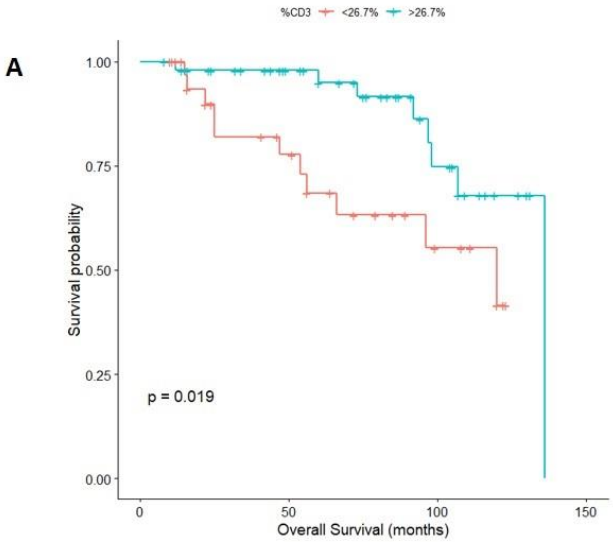
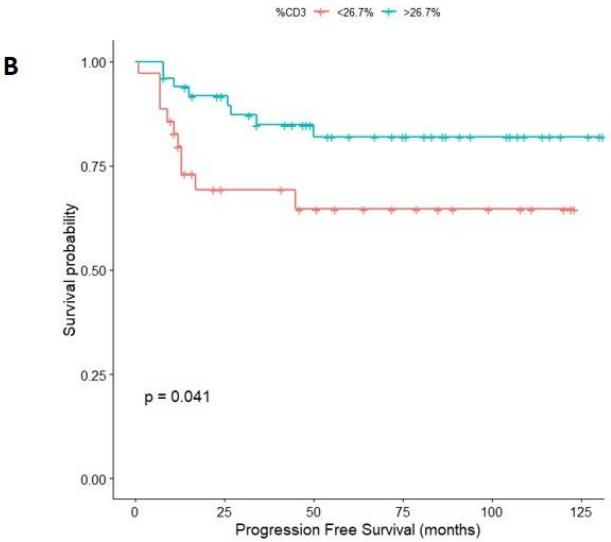
Survival plots (Kaplan-Meier) according to the percentage of T-cells assessed by WSI



Number at risk				
CD3 < 26.7%	35	18	6	0
CD3 > 26.7%	50	35	13	0

Number of event				
CD3 < 26.7%	0	6	10	11
CD3 > 26.7%	0	1	6	8



Number at risk						
CD3 < 26.7%	35	16	13	9	5	0
CD3 > 26.7%	50	40	28	20	11	3

Number of event						
CD3 < 26.7%	0	10	11	11	11	11
CD3 > 26.7%	0	4	8	8	8	8

Cut off value calculated using ROC curves; **26.7%** of T-lymphocytes

CD3 < 26.7% ➡ Lower survival time

CD3 > 26.7% ➡ Higher survival time

Objetivos a futuro

Integración datos de secuenciación con análisis de imagen digital

GRACIAS POR VUESTRA ATENCIÓN

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