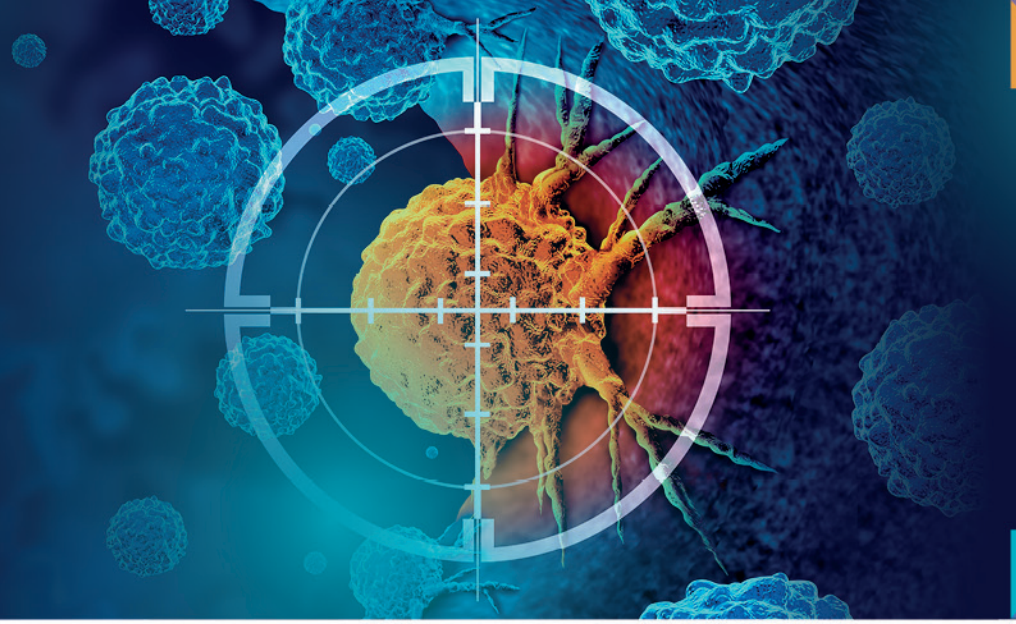
XVIII SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER



Bases biológicas para vencer la resistencia en cáncer de cabeza y cuello

Mónica Álvarez Fernández, Centro de Investigación del Cáncer, Salamanca

CIC Centro de Investigación del Cáncer

Resistencia a terapia: un fenómeno en evolución

> Proc Soc Exp Biol Med. 1945 Oct:60:55-8. doi: 10.3181/00379727-60-15089.

Penicillin resistant staphylococci

A BONDI Jr, C C DIETZ

PMID: 21004029 DOI: 10.3181/00379727-60-15089

1945 1958 1959 1998

> Ann N Y Acad Sci. 1958 Sep 30;71(6):976-93. doi: 10.1111/j.1749-6632.1958.tb46817.x.

Some aspects of drug resistance in neoplasms

L W LAW

PMID: 13583865 DOI: 10.1111/j.1749-6632.1958.tb46817.x

> Cancer Res. 1959 May;19(4):359-71.

The problem of drug resistance in cancer chemotherapy

A D WELCH

PMID: 13652119

Case Reports > J Clin Oncol. 1998 Dec;16(12):3916.

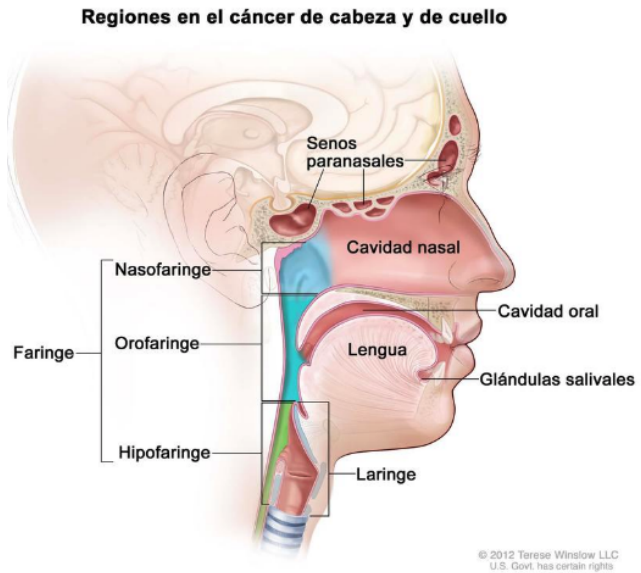
CD20-negative relapse in B-cell lymphoma after treatment with Rituximab

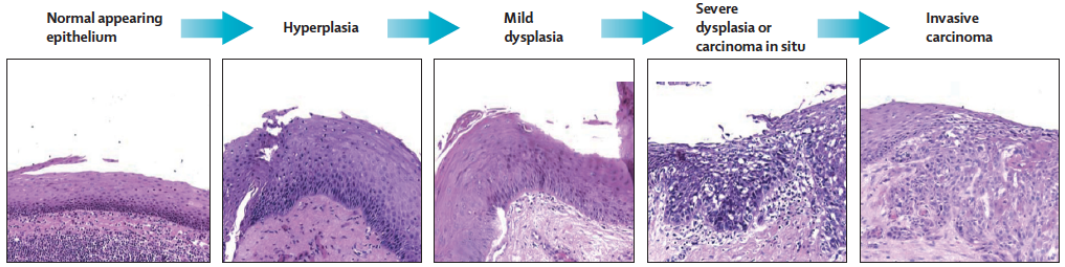
T Kinoshita, H Nagai, T Murate, H Saito

PMID: 9850038

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Carcinomas Escamosos de Cabeza y Cuello (CECC)





Argiris, A. *et al*. *The Lancet*, 2008

- Origen epitelial- 90% de todos los tumores de cabeza y cuello
- > 50% tasa de mortalidad
- Factores etiológicos
  - Tabaco/alcohol
  - Infección VPH: VPH-16, 18, 31, 33 (tumores orofaríngeos)
- SOC
  - Cirugía (+ *RT en pacientes de alto riesgo*)
  - QRT (RT + platino)

  TR: 60-70% VPH- vs 85% VPH+
- Terapias dirigidas
  - Cetuximab (anti-EGFR)
  - Nivolumab/ Pembrolizumab (anti-PD-1)

  TR: 10%-35%

Recidivas: 40-60%

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¿Por qué unos tumores responden y otros no a un mismo tratamiento?

? PREDECIR LA RESPUESTA

¿Qué pacientes se beneficiarán de cada tratamiento?

BIOMARCADORES DE RESPUESTA

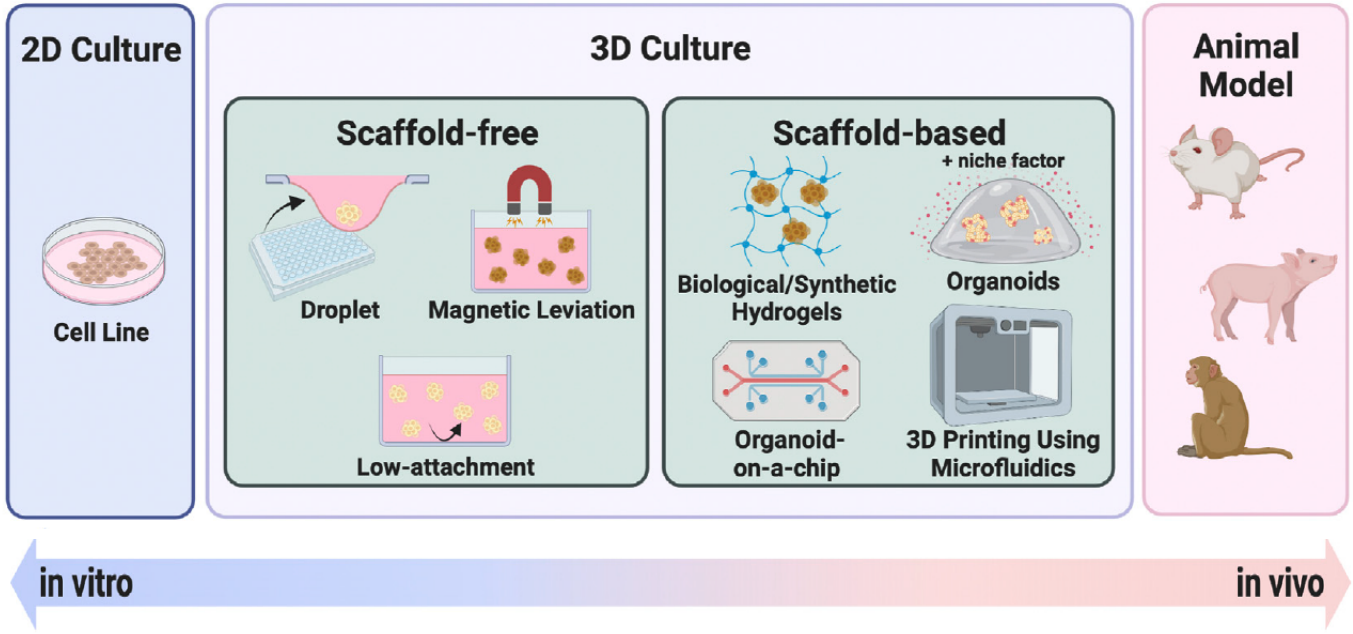
+ MEJORAR LA EFICACIA

¿Cómo podemos sensibilizar los tumores resistentes?

NUEVAS ESTRATEGIAS TERAPÉUTICAS

Componentes clave para el estudio de la resistencia a terapia en el laboratorio

1 Modelo preclínico



Adaptado de Harada K and Sakamoto, N. Frontiers in Molecular Biosciences (2022)

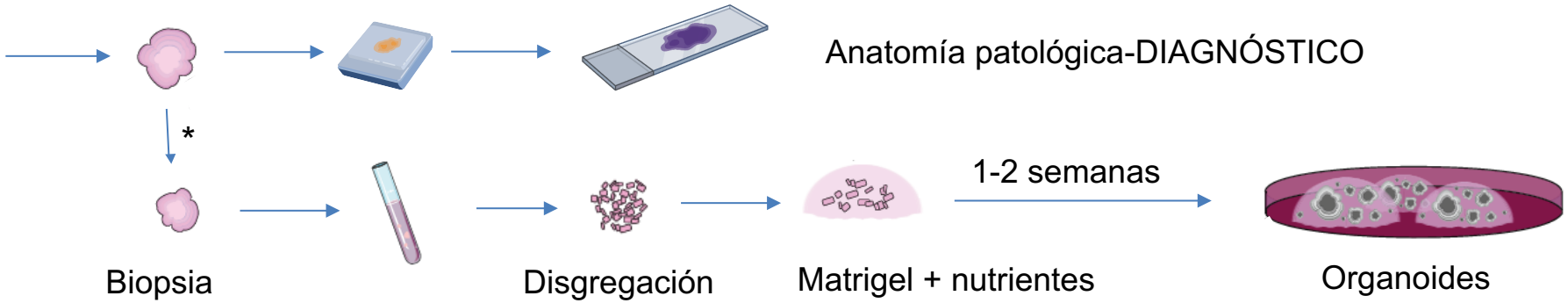
- Heterogeneidad intratumoral
- Microambiente tumoral
- Contexto sistémico
- Coste temporal y económico
- Fenotipo resistente

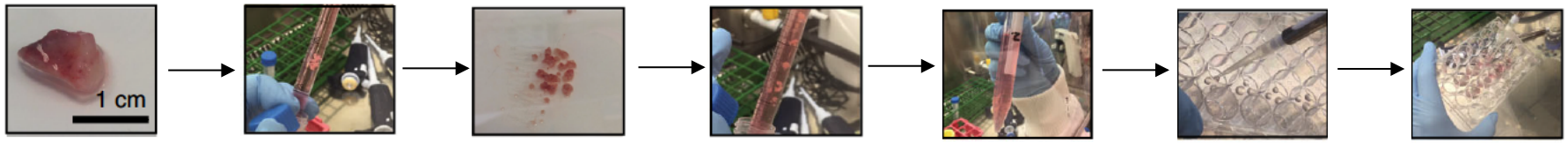
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Organoides tumorales derivados de pacientes con CECC



* tejido fresco obtenido con CI





Mantenimiento en incubadores de CO_2 (37ºC)

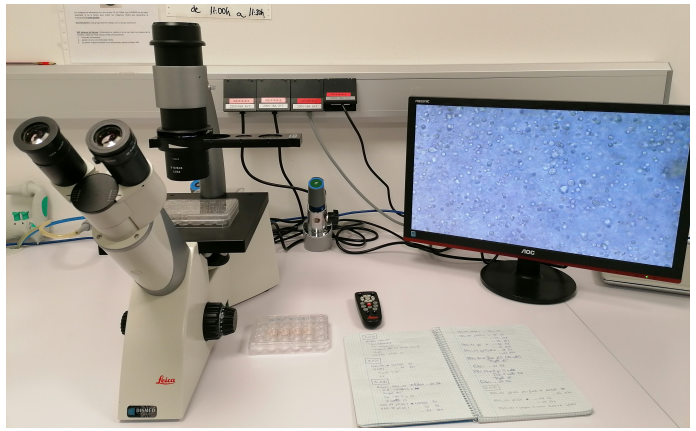




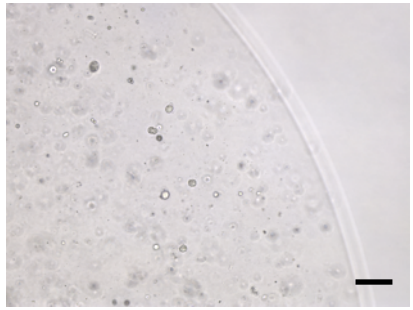
Criopreservación en N2 (-182 ºC)

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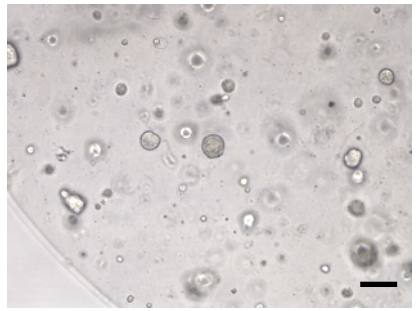
Organoides tumorales derivados de pacientes con CECC



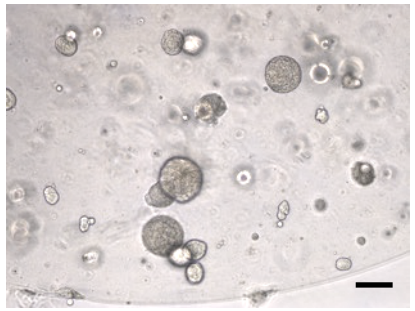
Día 1



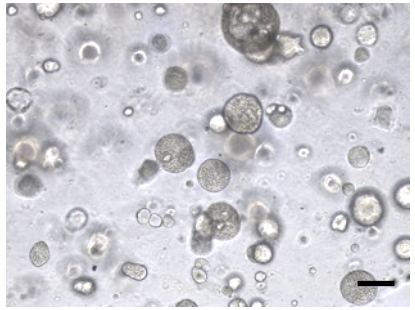
Día 4



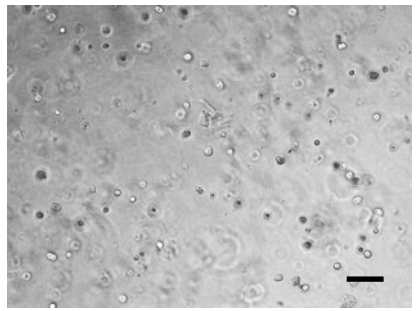
Día 6



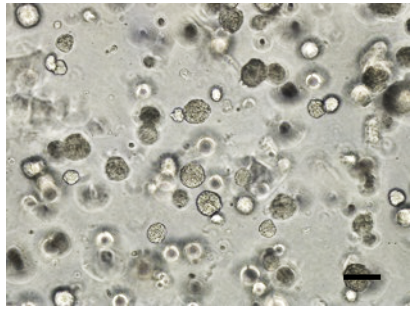
Día 8



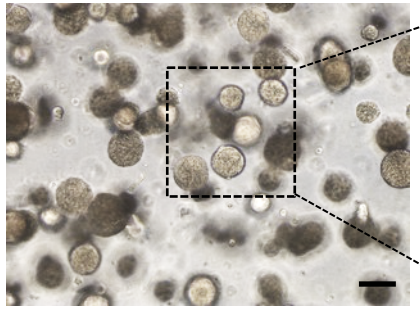
Pase 1 Día 2

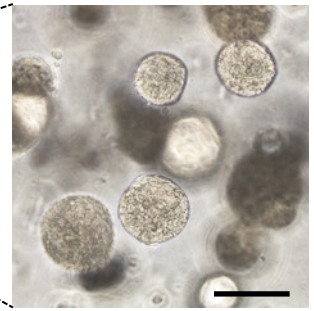


Pase 1 Día 5



Pase 1 Día 7

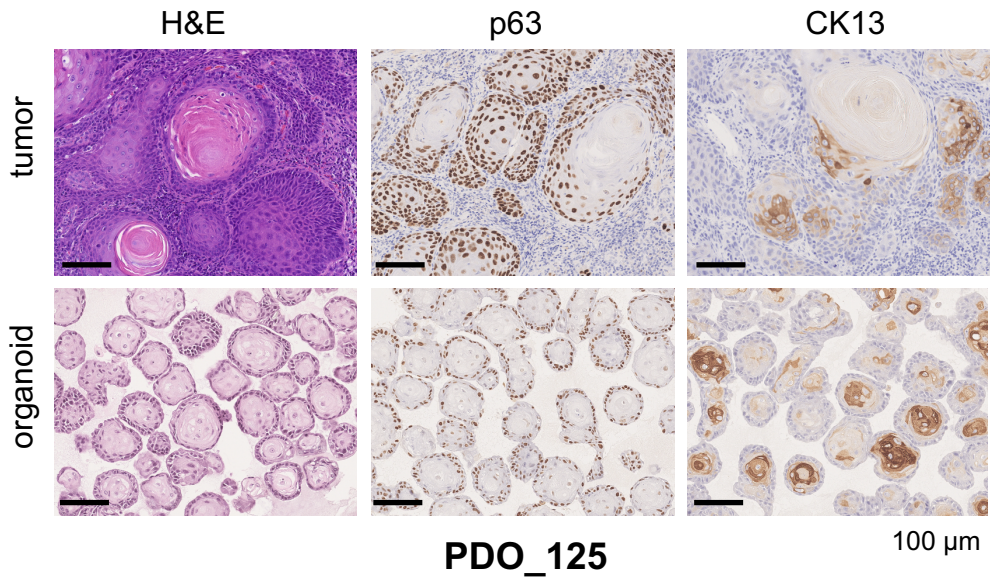




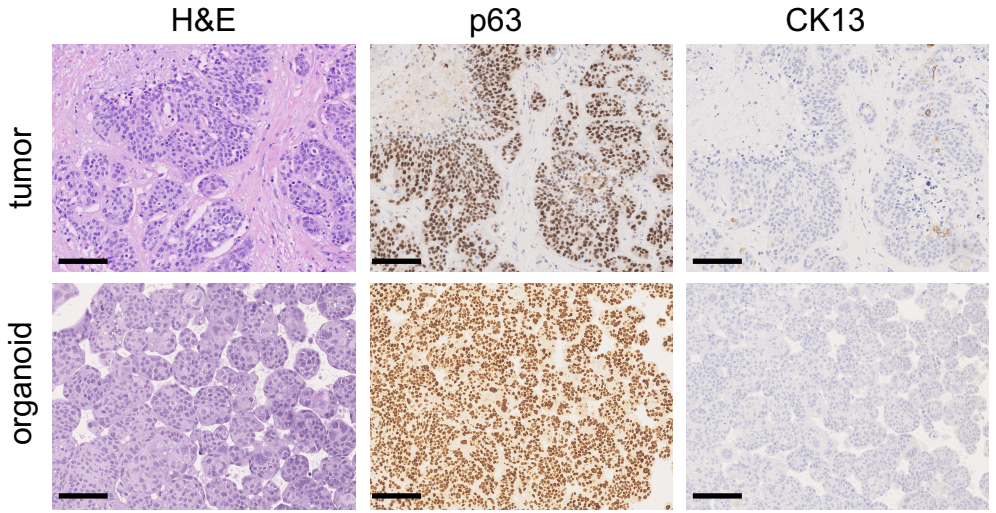
Escala, 200 µm

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Organoides tumorales derivados de pacientes con CECC



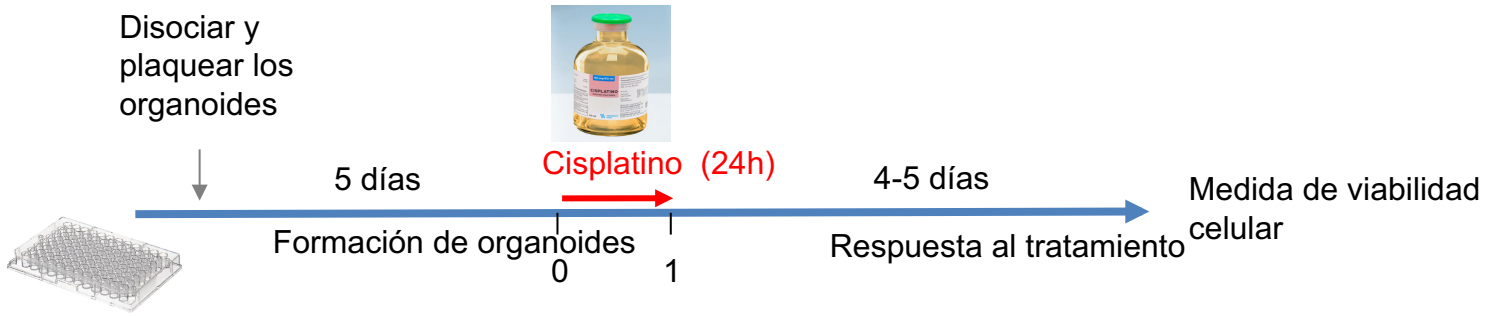
PDO_125



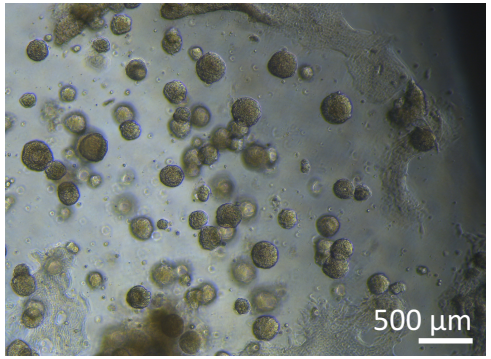
PDO_28

Recapitulan las características histológicas del tumor de origen

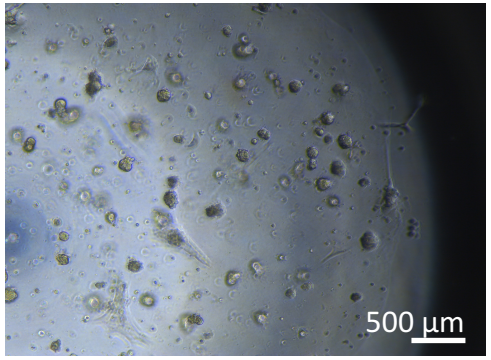
Organoides tumorales derivados de pacientes con CECC

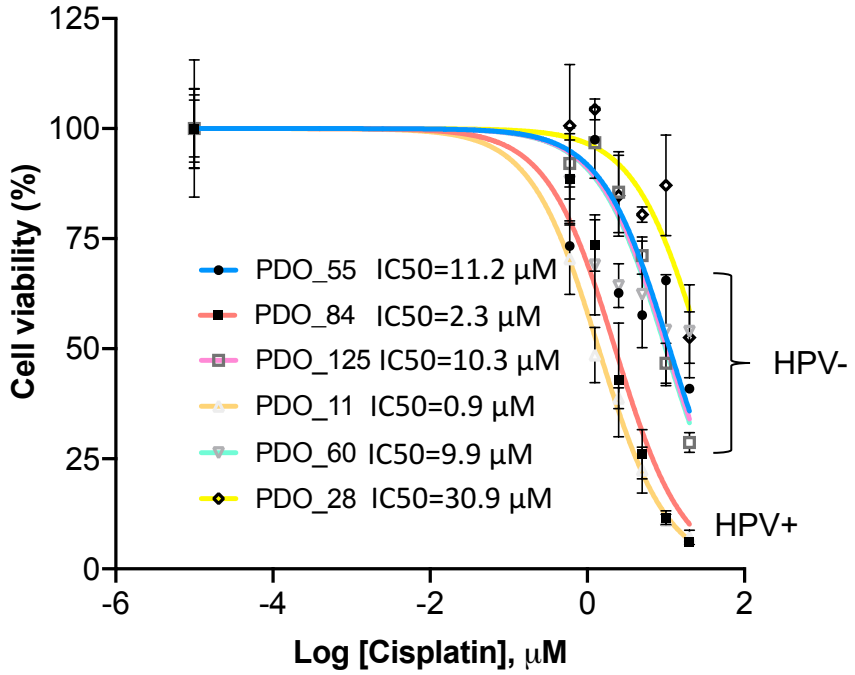


No tratado



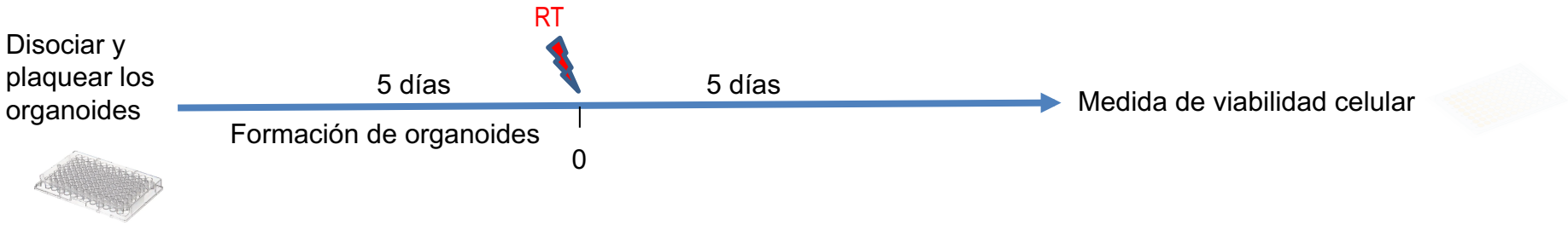
Cisplatino (10 µM)





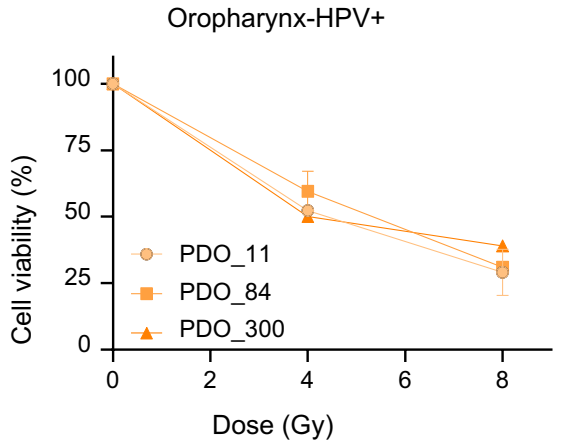
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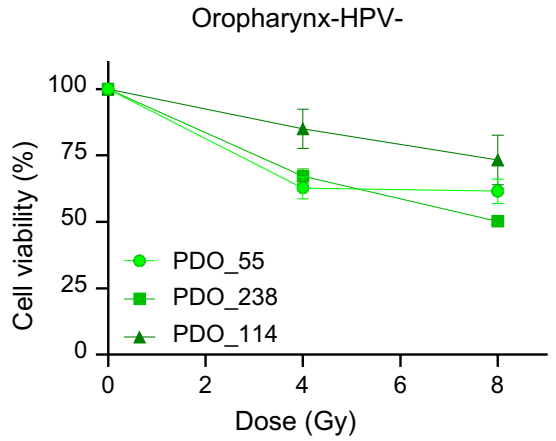
Organoides tumorales derivados de pacientes con CECC











Muestran una respuesta diferencial a los tratamientos

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nature medicine

Review article

https://doi.org/10.1038/s41591-024-03489-3

Clinical applications of human organoids

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Published online: 3 February 2025

Monique M. A. Verstegen[1], Rob P. Coppes[2], Anne Beghin[3,4,5], Paolo De Coppi[6], Mattia F. M. Gerli[7], Nienke de Graeff[8,9], Qiuwei Pan[10], Yoshimasa Saito[11], Shaojun Shi[12], Amir A. Zadpoor[13] & Luc J. W. van der Laan[1,13]

Table 1 | Ongoing clinical trials using organoids for personalized medicine

NCT number	Study title	Status	Condition	Phase	Enrolled	Type (int/obs)	Location	Posted
NCT06315868	Breast cancer subtype characterization through patient's derived organoids	Recruiting	Breast cancer		306	Obs	Italy	March 2024
NCT06102824	Organoid-based functional precision therapy for advanced breast cancer	Recruiting	Breast cancer (HER2⁻/advanced)	2	252	Int	China	October 2023
NCT04450706	Functional precision oncology for metastatic breast cancer	Recruiting	Breast cancer (HER2⁻)	N/A	15	Int	United States	June 2020
NCT06268652	Patient derived organoid-guided personalized treatment versus treatment of physician's choice in breast cancer	Recruiting	Breast cancer/ refractory breast carcinoma	3	302	Int	China	February 2024
NCT05304741	The culture of advanced/recurrent/ metastatic colorectal cancer organoids and drug screening	Recruiting	Colorectal cancer		30	Obs	China	March 2022
NCT05725200	Study to investigate outcome of individualized treatment in patients with metastatic colorectal cancer	Recruiting	Colorectal cancer (metastatic)	2	40	Int	Norway	February 2023
NCT05401318	Tailoring treatment in colorectal cancer	Recruiting	Colorectal neoplasms		40	Obs	Norway	June 2022
NCT02732860	Personalized patient derived xenograft (pPDX) modeling to test drug response in matching host	Recruiting	Colorectal/ breast/ovarian (neoplasms/cancer)		120	Obs	Canada	April 2016
NCT06332716	Research on the correlation between organoid drug sensitivity testing and precise treatment of gastrointestinal tumors	Recruiting	Gastrointestinal tumors	3	68	Int	China	March 2024
NCT03890614	Novel 3D hematological malignancy organoid to study disease biology and chemosensitivity	Recruiting	Hematologic malignancy		70	Obs	United States	March 2019
NCT05913141	PDO/PDO-TIL/PDOTS for drug screen	Recruiting	Liver cancer/ metastatic liver cancer		30	Obs	China	June 2023
NCT05669586	Organoids predict therapeutic response in patients with multi-line drug-resistant lung cancer	Recruiting	Lung cancer	2	50	Int	China	January 2023
NCT06406608	Patient-derived organoid drug sensitivity guided treatment for drug-resistant recurrent non-small cell lung cancer	Recruiting	Lung cancer (nSCLC)	N/A	20	Int	China	May 2024
NCT06406660	Patient-derived organoid drug sensitivity guided treatment for recurrent small cell lung cancer	Recruiting	Lung cancer (SCLC)	N/A	20	Int	China	May 2024
NCT04768270	The culture of ovarian cancer organoids and drug screening	Recruiting	Ovarian cancer		30	Obs	China	February 2021
NCT06482086	Efficacy of organoid-based drug screening to guide treatment for locally advanced thyroid cancer	Recruiting	Thyroid gland carcinoma (locally advanced)	2	75	Int	China	July 2024
NCT05267912	Prospective multicenter study evaluating feasibility and efficacy of tumor organoid-based precision medicine in patients with advanced refractory cancers	Not recruiting/ active	Advanced, pretreated solid tumors	N/A	61	Int	France	March 2022
NCT04561453	Feasibility study of multi-platform profiling of resected biliary tract cancer	Not recruiting/ active	Biliary tract cancer		14	Obs	United States	September 2020
NCT05196334	Pharmacotyping of pancreatic patient-derived organoids	Not recruiting/ active	Pancreatic cancer		88	Obs	Denmark	January 2022
NCT04342286	To establish a reproducible organoid culture model with human kidney cancer	Completed	Kidney cancer		20	Obs	Hong Kong	April 2020

Componentes clave para el estudio de la resistencia a terapia en el laboratorio

2 Abordaje experimental

¿Qué diferencia a un tumor resistente?

Comparar modelos resistentes y sensibles

ANÁLISIS MOLECULAR
- Genómico
- Epigenómico
- Transcriptómico
- Proteómico
- Metabolómico

HETEROGENEIDAD
- Celular
- Espacial
- Temporal

¿Qué podemos modificar para revertir la resistencia?

Cribados genómicos funcionales

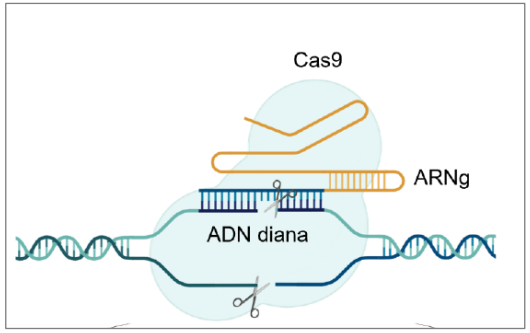
Genes y vías que modulan la respuesta

Cribados farmacológicos

Fármacos y combinaciones terapéuticas

BIOMARCADORES DE RESPUESTA | **VULNERABILIDADES / DIANAS**

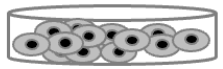
Genómica funcional: cribados basados en la tecnología CRISPR/Cas9

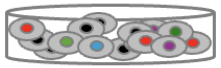


SISTEMA CRISPR/CAS9 DE PÉRDIDA DE FUNCIÓN (KNOCK-OUT)

HCA-LSC-1 _Cas9

FaDu_Cas9





Cobertura: 200X

MOI:0.3



Lentivirus

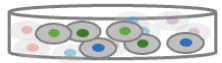


Librería YUSA
(90.709 ARNg, 18.010 genes)

SIN TRATAMIENTO

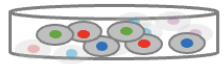


CISPLATINO



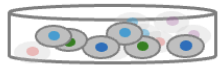
0,25 µM, 1 µM

IRRADIACIÓN (IR)



2 Gy, 8 Gy

IR + CISPLATINO

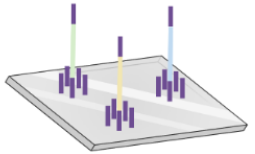


2 Gy, 0,25 µM

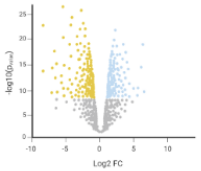
x2



Aislamiento ADN genómico y amplificación de ARNguías

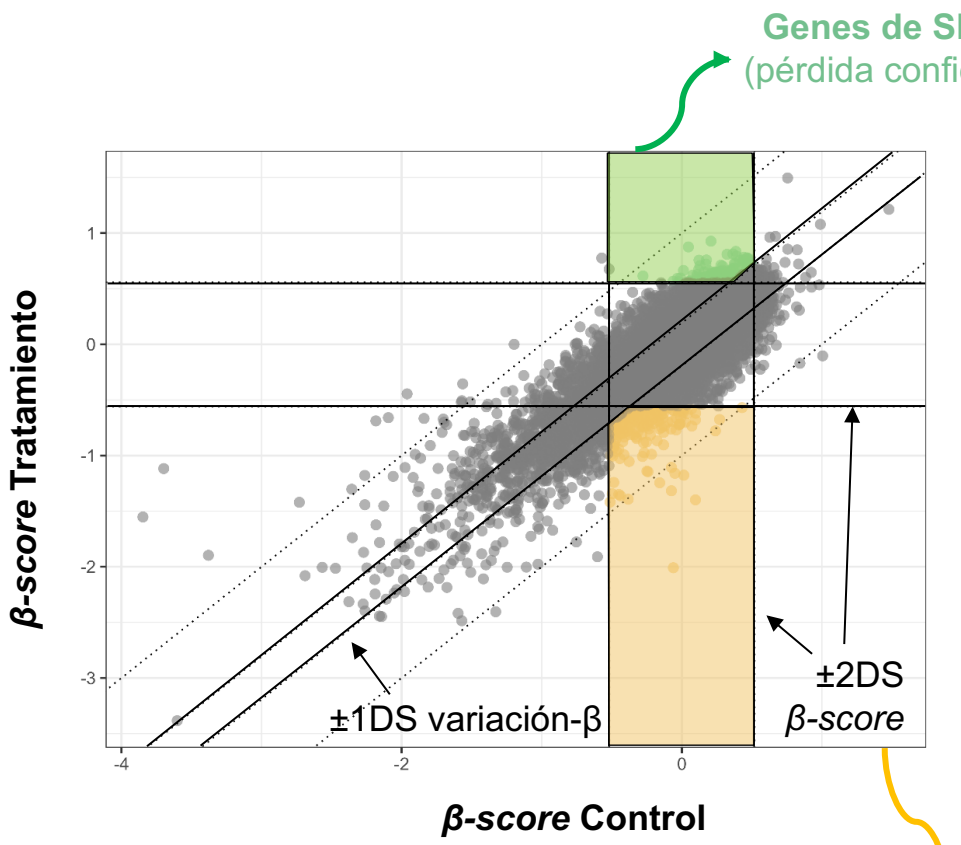


Secuenciación
(Illumina)



Análisis de enriquecimiento de ARNg en tratamiento vs control
(MAGeCK)

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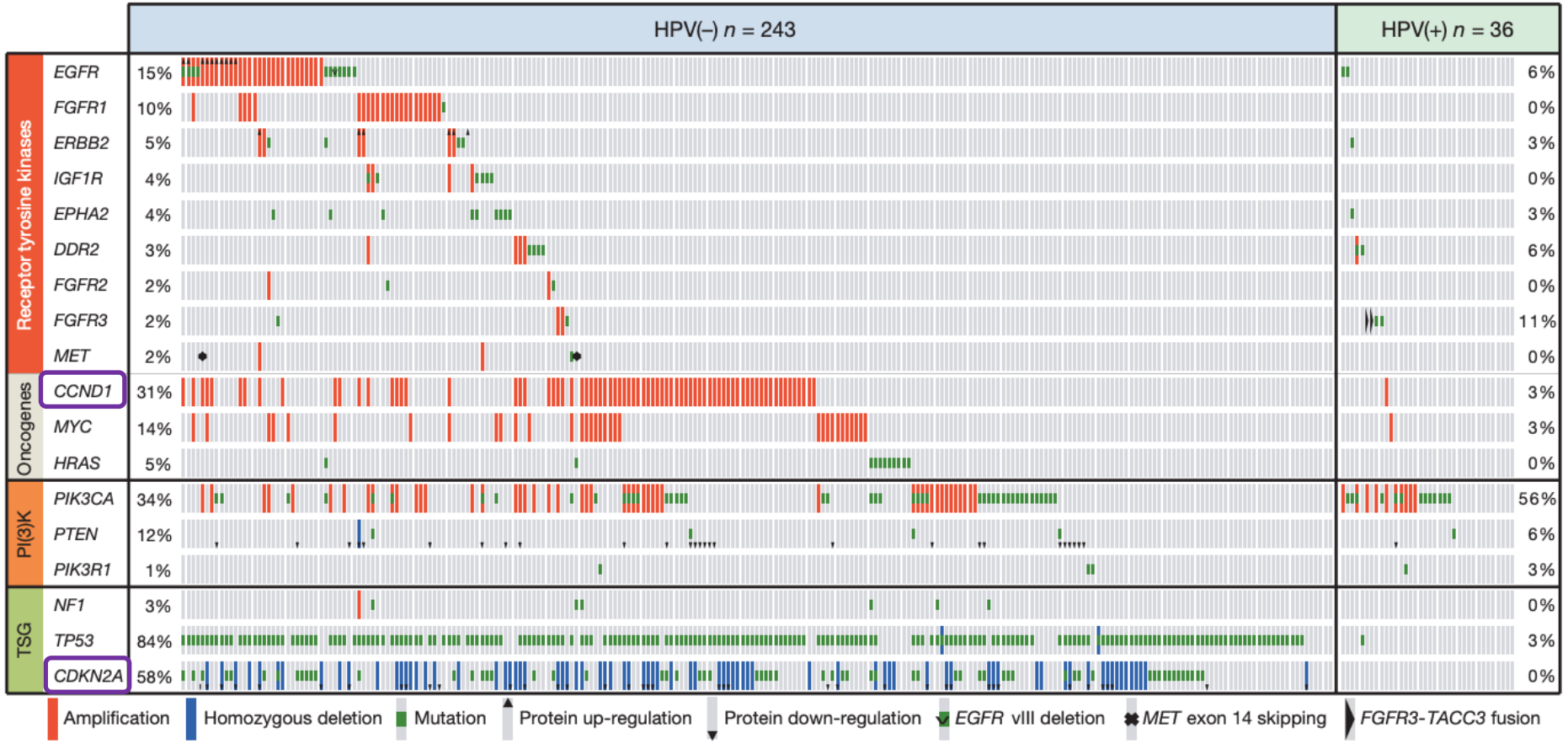
CISPLATIN		RADIO	COMBO	
SLC1A1*	GEMIN2	ALG3	**TMSB4X †**	ARMC1
CSH2*	KLF10	**TMSB4X †**	C5orf58	ZIM3
SRP72*	UBA3	SKAP2	ARL4A	B3GAT3
HUWE1*	ZNF567	LPAR6	PAWR	ARL5B
NEK2	LRRC49	**BTC †**	ACBD7	STON1
PDZRN4	TAS2R7	ZNF443	GKAP1	LMX1A
PRKACA	LPGAT1	POC1B-GALNT4	CLEC6A	**C2orf76 †**
OTC	DCAF6	NBPF6	POTEF	MRPS9
DEFB110	DNAJC19	MRPL18	GLIPR1	TMA7
GNB1	RPIA	INTS4	MAPK10	LYRM7
PDCD6IP	CNGB3	**AMD1 †**	AMY2B	SRFBP1
KCTD9	VDAC1	SNX16	**BTC †**	ACTR3
POTEE	BIRC8	**C2orf76 †**	RAB28	CSTF2
MTERFD3	WDR41		ALKBH3	**AMD1 †**
FCRL3	HEMGN		FAM9B	HMGB1
DEFB123	METTL1		NAA16	PABPN1
CELF1	MRPS10		KRTAP4-12	WAPAL
ANGPTL5	C18orf21		GTF2A1L	RTN4IP1

CISPLATIN		RADIO	COMBO	
HELQ*	PRAMEF2	ATAD5*	PPIA	C5orf51
BRIP1*•	C4orf21	DEFB110*	**FANCL•**	PNMA6C
GTF2H5*•	SCFD1	ERGIC2*	**ALG10B †**	ZCCHC6
FAM21B*	FAM133B	VCX	TMEM258	C17orf53
ARHGEF5	TXNDC17	**KERA≈**	ZNF486	HMGN1
BRCA2	SPIN2A	DEPDC1	MRPS7	NAP1L1
ZNF69	DAXX	GYPE	**TADA2B•**	IFNGR1
DCUN1D5	CENPH	ELMOD2	CEP57	ATG3
AKAP13	CCT5	GPR107	AKNAD1	SLC9C1
C8orf44	**FANCL•**	DPY19L4	RBM48	TMSB4Y
STYX	**KERA≈**	KRTAP22-2	PTP4A1	POLE4
SMG6	HPR	RFPL4A	SEL1L	ADAMDEC1
RNMT	SPINK7	KRTAP10-6	ZNF285	USP48
DEFB106B	TMEM133	PHGR1	DCP2	CDCA3
TYW5	GAGE12H	EIF4A2	TCEAL2	CAPRIN1
FANCA•	ZNF404	**ZNF69**	HSP90AB1	EHMT1
MORF4L1	FAM200A	**CKS2≈**	CHCHD5	MYO6
MCM9	CCZ1	OCIAD1	FOXP2	SPESP1
ATG10	**TADA2B•**	CTAGE9	**GTF2H5•**	GSTA2
CKS2≈	C5orf58	S100A12	MCM8	**BRIP1•**
GLRA2	TAS2R8	CCDC67	ERGIC2	**ZNF69**
PRR23B	FAM133A	BCL2L1	C1orf112	FANCI
RGPD4	HIST2H2BE	**ALG10B †**	FANCF	**FANCA•**
			SLC37A1	REV1

MAGeCK software (MLE algorithm)

Inhibición de CDK4/6 como posible estrategia de sensibilización en CECC

Una combinación con base biológica pero inesperada

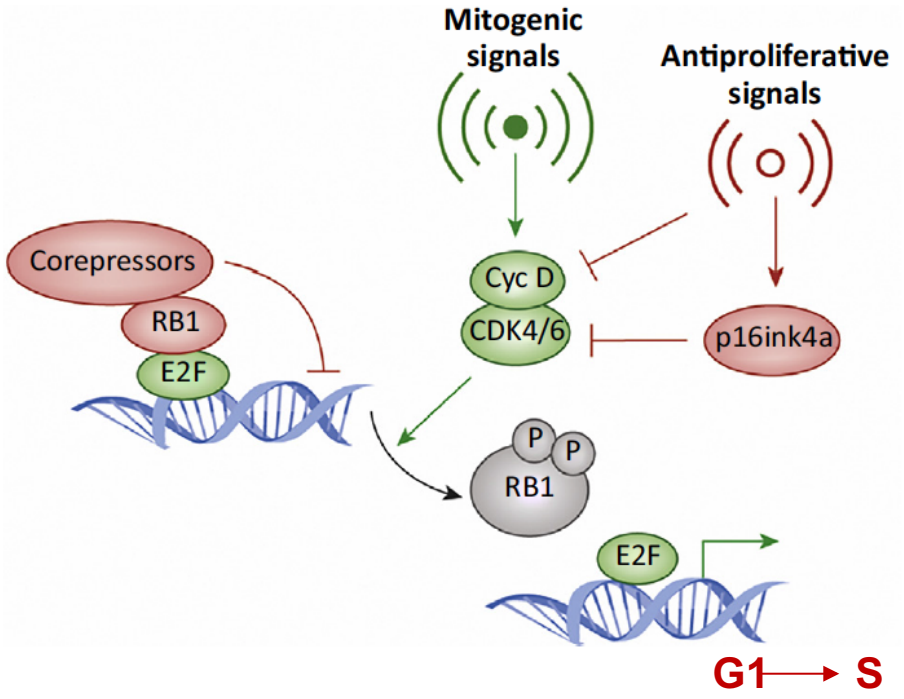


TCGA, *Nature*, 2015

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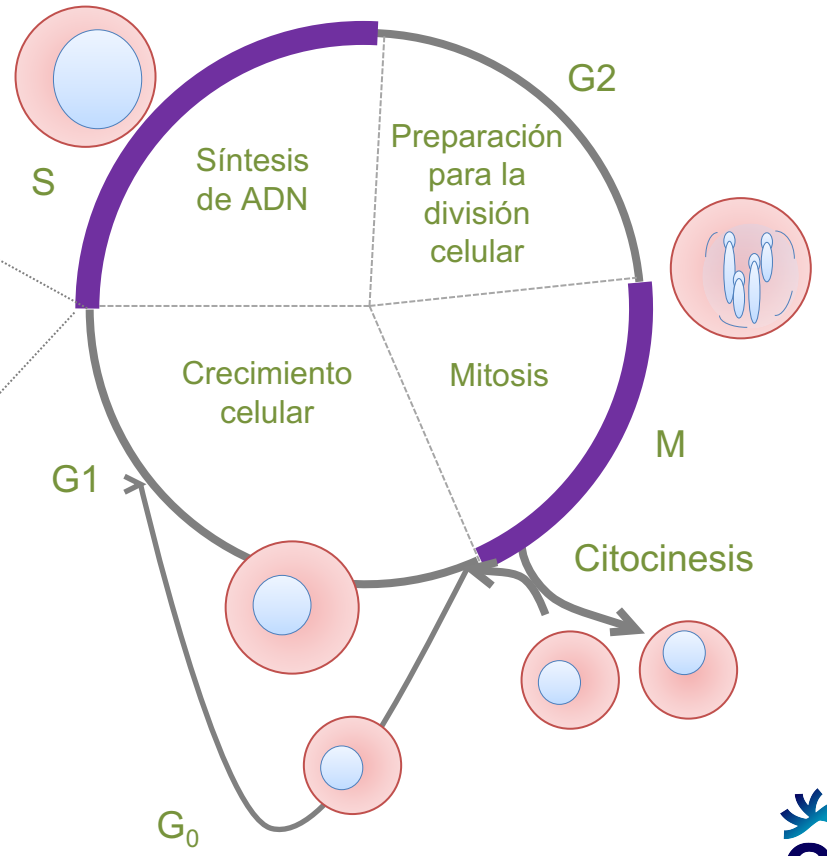
Inhibidores CDK4/6

Palbociclib (Pfizer)
Abemaciclib (Lilly)
Ribociclib (Novartis)
Dalpiciclib (Herngri)



Adapted from Knudsen E. *Trends in Cancer* 2019

Agentes genotóxicos

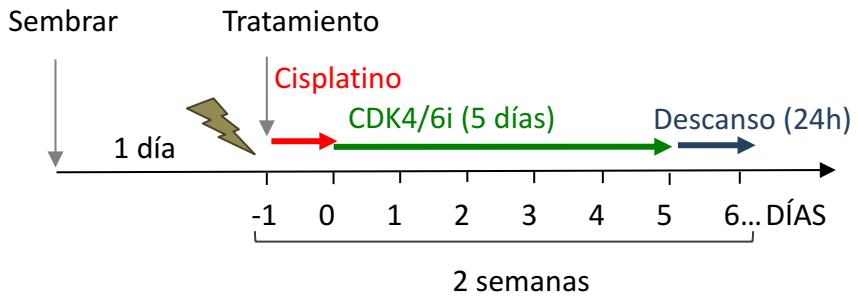


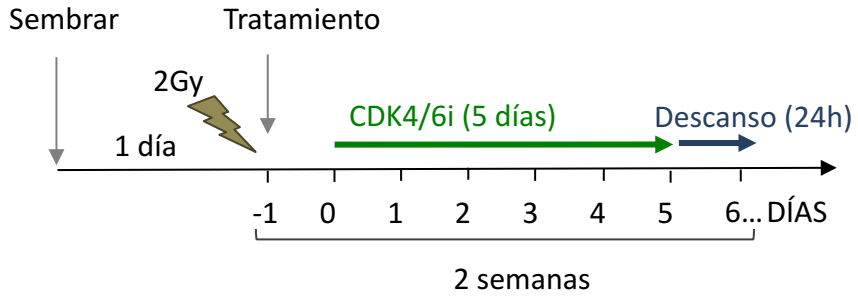
Agentes antimitóticos

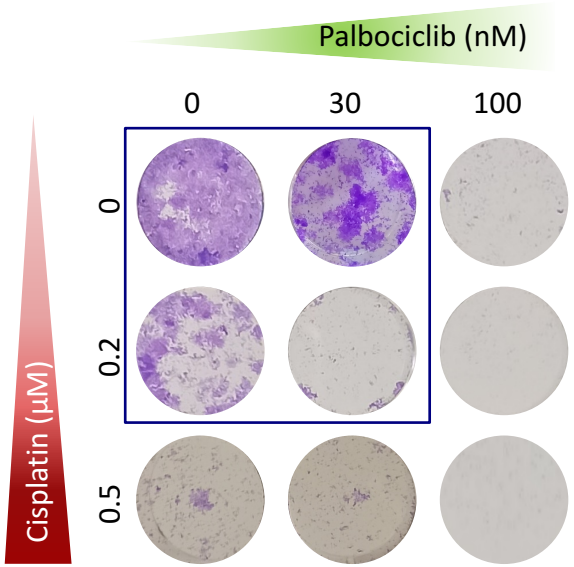
Parada reversible del ciclo celular

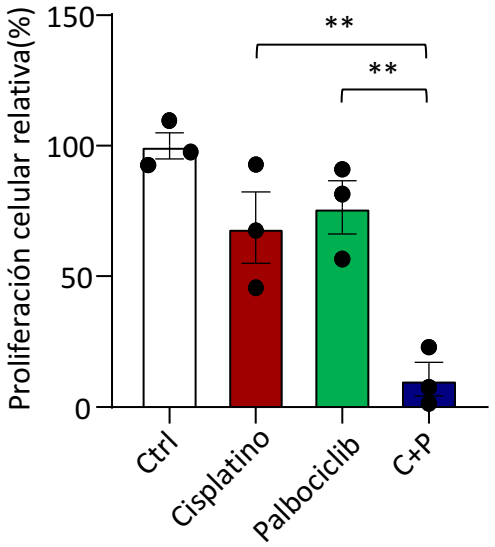
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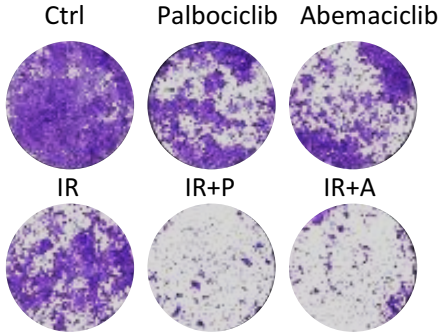
Tratamiento secuencial combinado de QT/RT con CDK4/6i

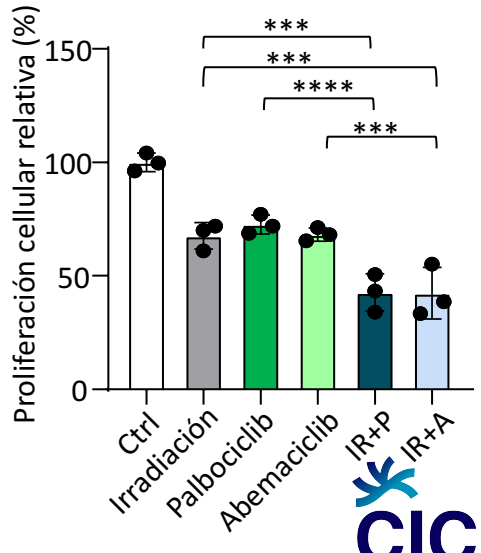






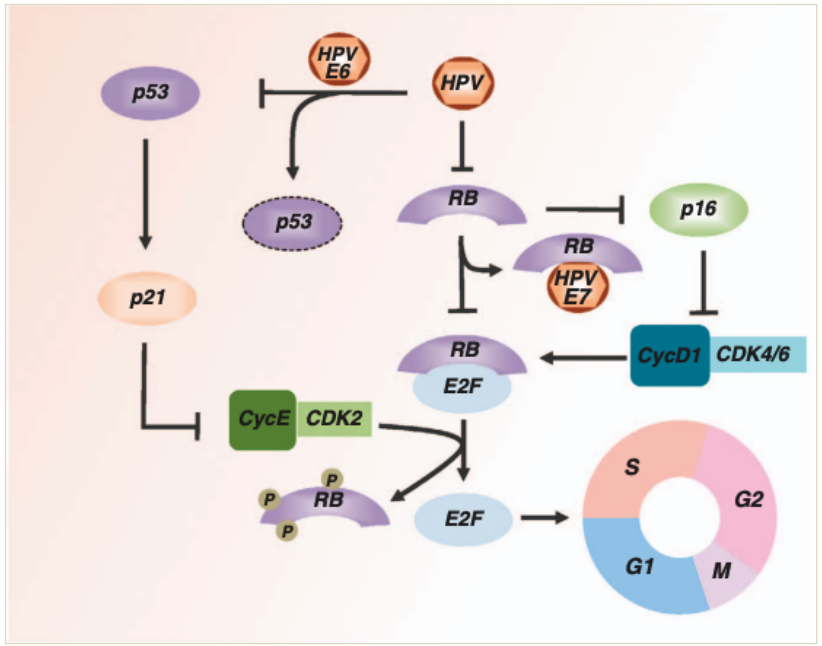




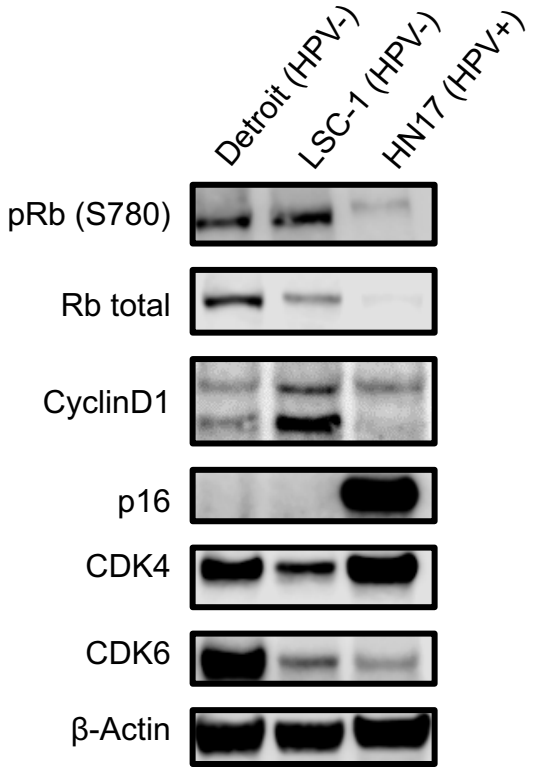


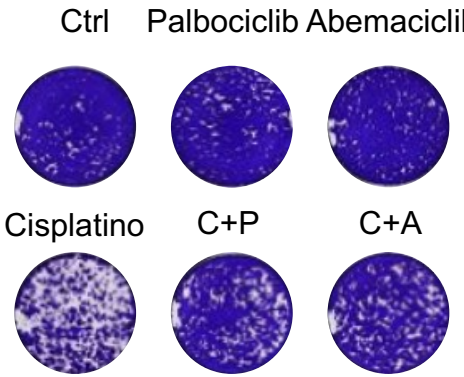
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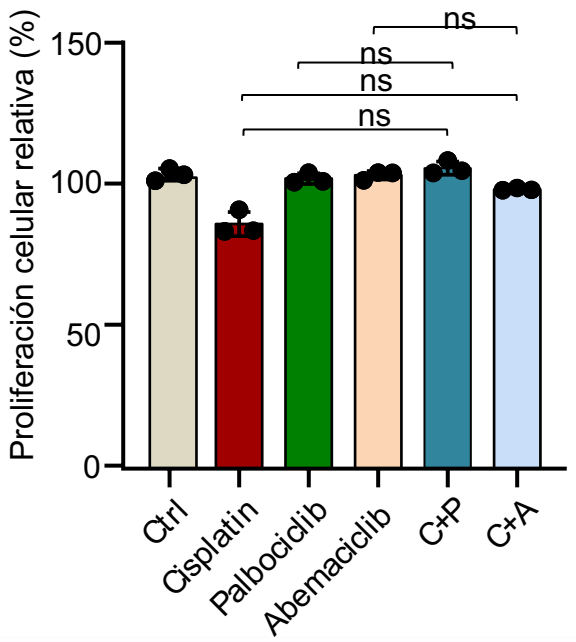
Tratamiento secuencial combinado de QT/RT con CDK4/6i



Su H, and Tavassoli, M. *Cell Death Dis.*, 2014

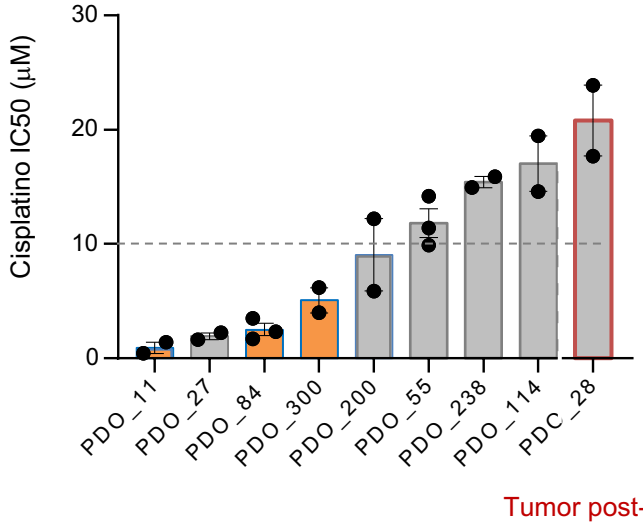




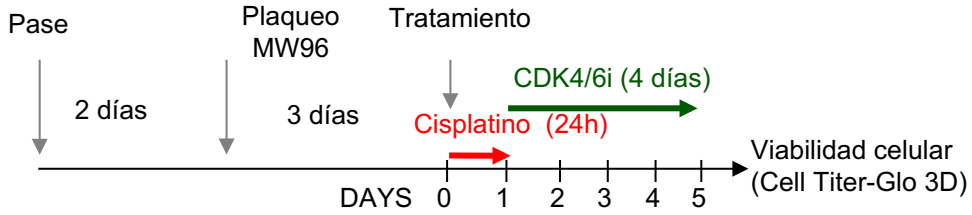


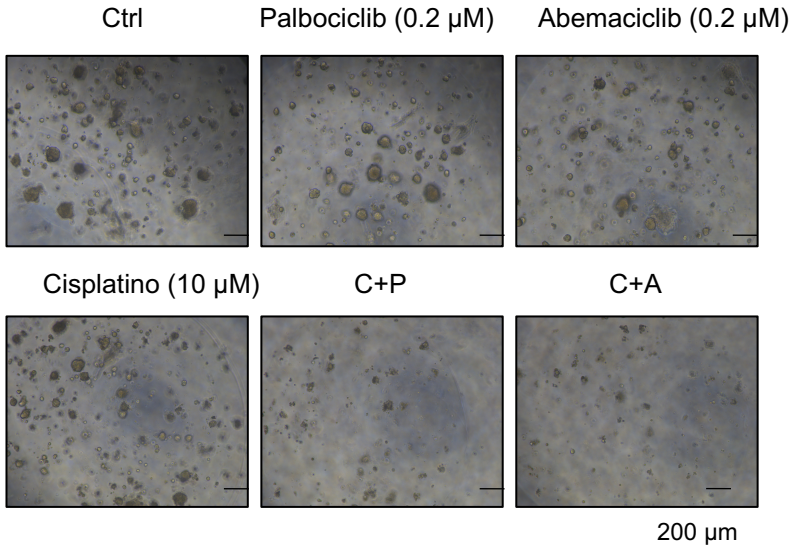
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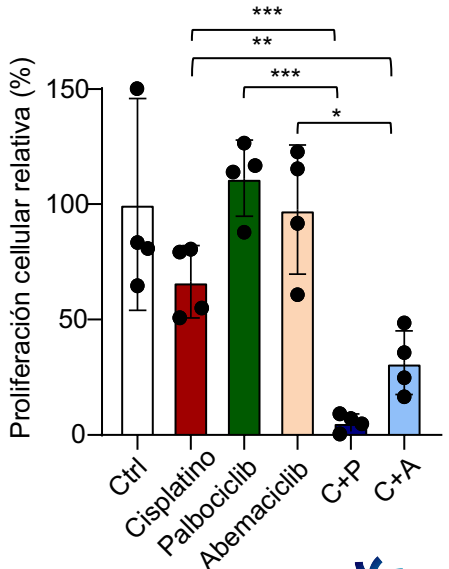
Validación en organoides derivados de pacientes



Tumor post-QRT





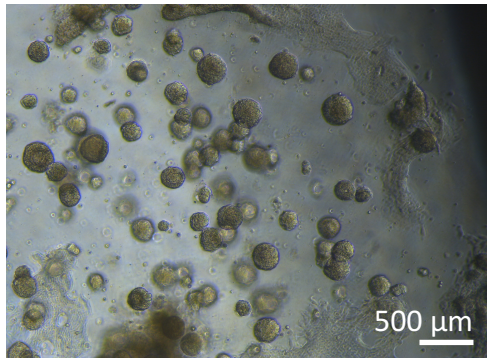


La inhibición de CDK4/6 aumenta la sensibilidad a tratamientos de QT/RT en modelos preclínicos de CECC VPH-

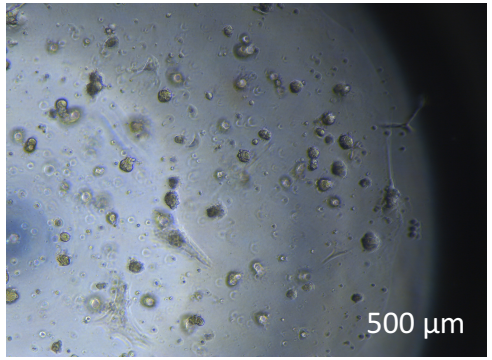
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El reto de las células persistentes/tolerantes al tratamiento

No tratado



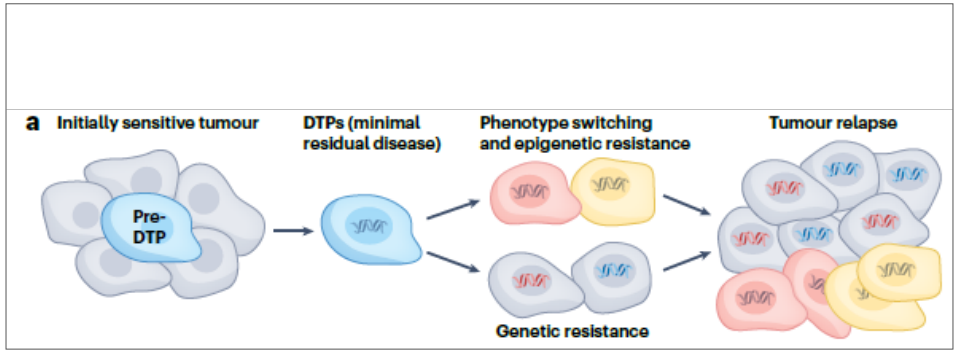
Cisplatino (10 µM)



Cell. 2010 Apr 2;141(1):69-80. doi: 10.1016/j.cell.2010.02.027.

A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations

Sreenath V Sharma [1], Diana Y Lee, Bihua Li, Margaret P Quinlan, Fumiyuki Takahashi, Shyamala Maheswaran, Ultan McDermott, Nancy Azizian, Lee Zou, Michael A Fischbach, Kwok-Kin Wong, Kathleyn Brandstetter, Ben Wittner, Sridhar Ramaswamy, Marie Classon, Jeff Settleman



Russo M, Nat Rev Can 2024

¿Podremos prevenir/reducir las recidivas?

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¿Qué necesitamos para superar la resistencia terapéutica?

1 Modelos relevantes

Reproducir la heterogeneidad tumoral y estudiar la respuesta a tratamientos

→

2 Conocimiento mecanístico

Identificar los mecanismos biológicos de resistencia y posibles vulnerabilidades

→

3 Validación traslacional

Evaluar biomarcadores y estrategias terapéuticas con relevancia clínica

Clínica ⟷ Laboratorio

Grupo de cáncer de cabeza y cuello/ ORL HUCA



Maxilofacial HUCA

O. Radioterápica HUCA
Radiofísica HUCA



Juana María García Pedrero
Juan Pablo Rodrigo

Grupo de resistencia a terapia- CIC



Andrea Blázquez Isabel Quiñones Lucía Cuenca
Helena Codina Lydia Cilla Patricia Rodríguez

Grupo de Inmunooncología-CIC
J.A. López Domínguez

Oncología Molecular (CAUSA)
Edel del Barco/ Alejandro Olivares

Otorrinolaringología (CAUSA)
Pedro Blanco/ Pablo Santos

Oncología Radioterápica/Radiofísica
L. A. P. Romasanta/ C.M. Rincón/ Cristina Arroyo

Gracias a los pacientes!!!