ONIRIA THERAPEUTICS

Modulating new targets to overcome cancer persistence

Carles Galdeano

Co-funder and drug discovery advisor

VHIO Vall d'Hebron Institute of Oncology

Universitat de Barcelona Spin-off

ICREA

Mind the Gap | Fundación Botín

Sabadell BStartup

asociación española contra el cáncer

INTRODUCTION

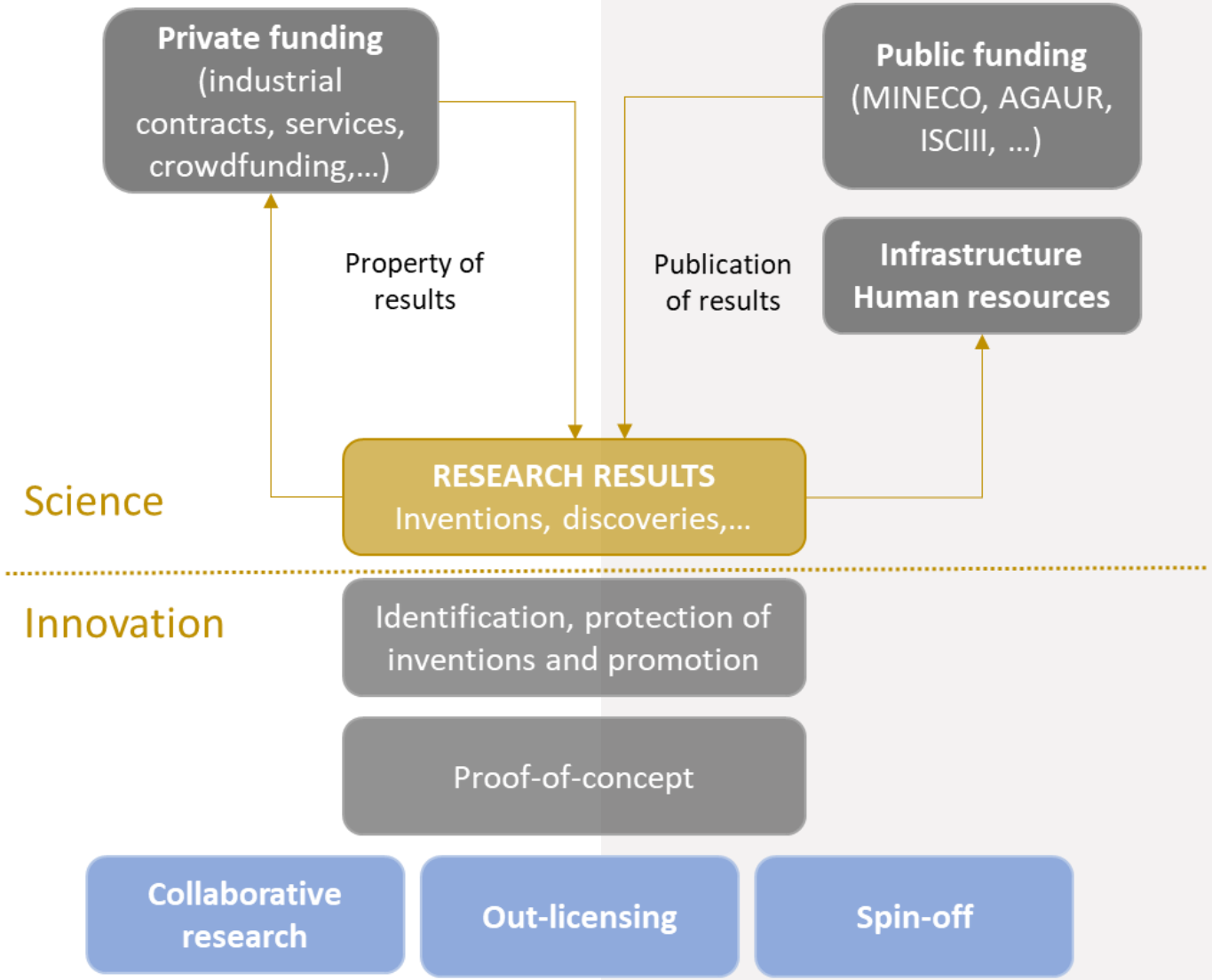
Oniria Therapeutics, S.L.

Oniria Therapeutics, S.L. is a biopharmaceutical company in the field of **PRECISION ONCOLOGY** and focused on **CANCER PERSISTENCE** and recurrence.

Oniria Therapeutics aims to develop innovative therapies to improve **LONG-TERM OUTCOMES** for cancer patients by targeting new mechanisms to overcome cancer persistence. Their goal is to achieve a **CANCER-FREE LIFE** by focusing on eliminating the tumor cells responsible for acquiring drug resistance that promote disease progression or recurrence.

Oniria Therapeutics is in Barcelona, Spain, and it is a spin-off of the Vall d'Hebrón Institute of Oncology (VHIO), the University of Barcelona (UB), and the Catalan Institution for Research and Advanced Studies (ICREA).

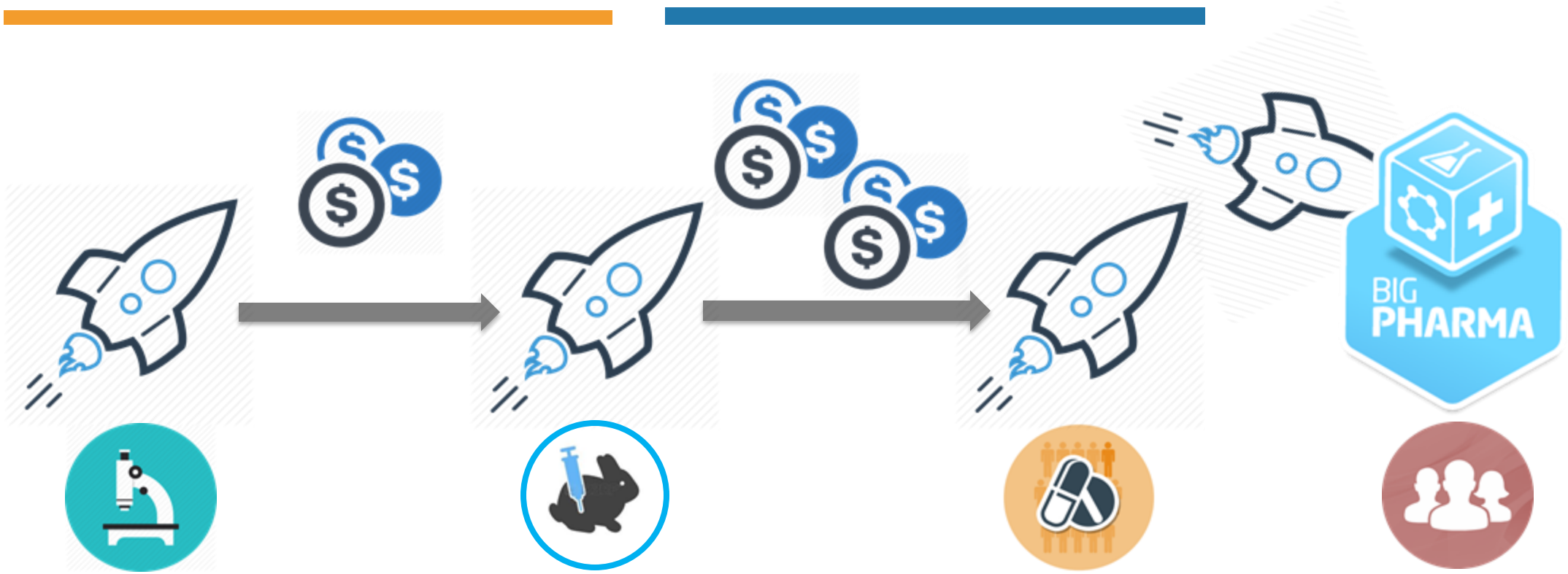
Current investors include the Fundación Botín, Banco Sabadell and several Business Angels and Family offices. Oniria has recently signed a convertible loan with the Spanish Association Against Cancer (AECC).

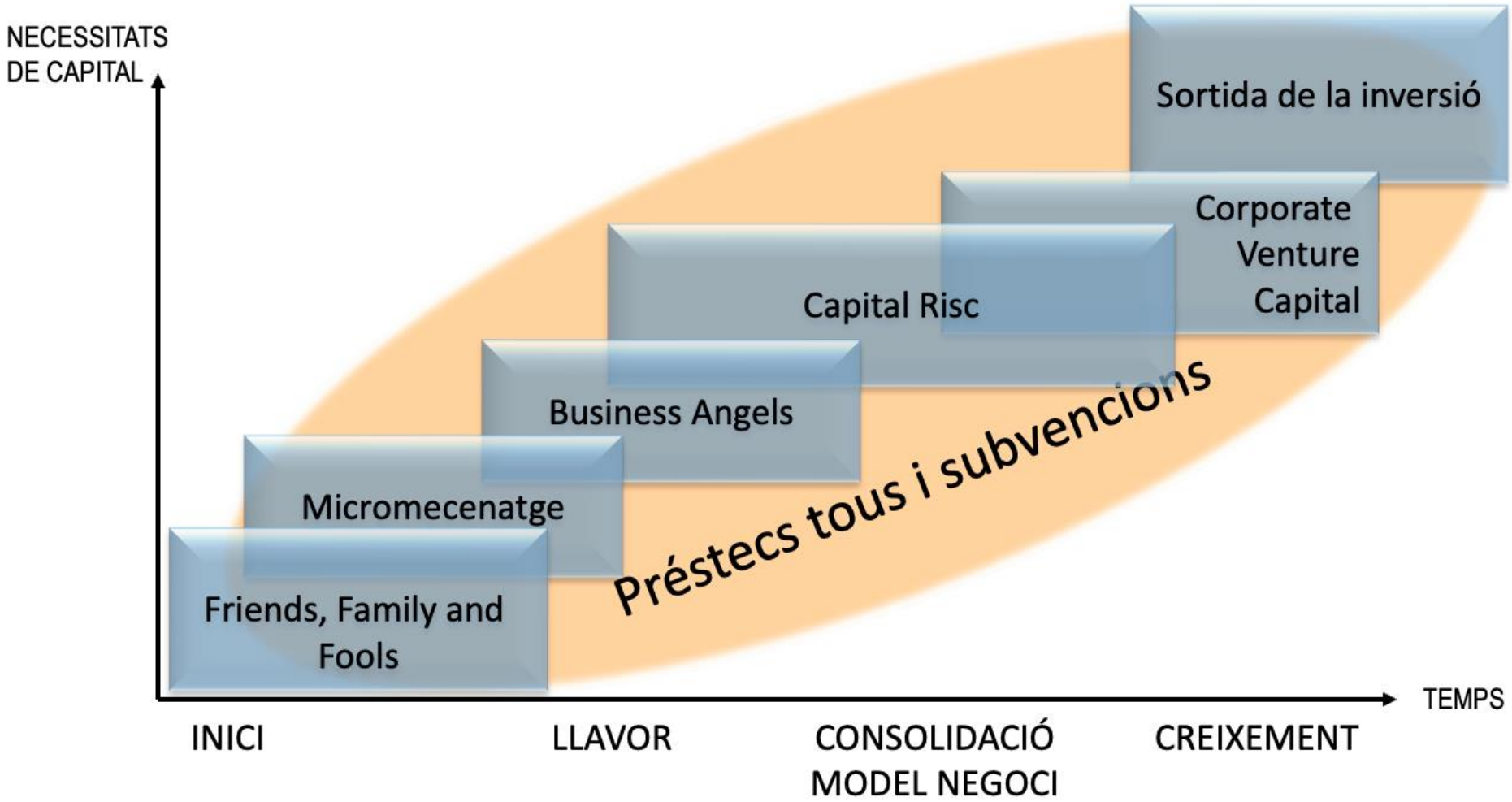

Private funding
(industrial contracts, services, crowdfunding,…)
Public funding
(MINECO, AGAUR, ISCIII, …)
Property of results
Publication of results
Infrastructure
Human resources
Science
RESEARCH RESULTS
Inventions, discoveries,…
Innovation
Identification, protection of inventions and promotion
Proof-of-concept
Collaborative research
Out-licensing
Spin-off

ONIRIA THERAPEUTICS

ACADEMIA

SPIN-OFFS




NECESSITATS
DE CAPITAL
Sortida de la inversió
Corporate
Venture
Capital
Capital Risc
Business Angels
Micromecenatge
Friends, Family and
Fools
Préstecs tous i subvencions
TEMPS
INICI
LLAVOR
CONSOLIDACIÓ
MODEL NEGOCI
CREIXEMENT

WHO ARE WE?

CORE FOUNDERS TEAM

A solid team combining expertise in drug discovery, clinical oncology and business management

Esther Riambau, MBA

Chief Executive Officer & Co-President of the Board

- >20 years in **Technology Transfer**
- Co-founder & Board Member at Gate2Brain company
- Member of the Steering Committee of i4Kids (Pediatric Hospital Accelerator)

upf. Ventures · Universitat de Barcelona · Gate2Brain

Héctor G. Palmer, PhD

Chief Scientific Officer & President of the Board

- Head of the Stem Cells and Cancer Group at VHIO
- 25 years in cancer biology research & **Drug Resistance**
- >16 years developing drugs with pharmaceutical industry
- Generation of patient-derived cancer models

VHIO · Cancer Research UK

Isabel Puig, PhD

Life Science Research Director

- >20 years studying mechanisms of tumorigenesis
- **TET2 specialist**

VHIO · institut Curie

Josep Tabernero, MD, PhD

Chief Medical Advisor

- VHIO & Caixa Research Institute Director
- Head of **Medical Oncology** Department at Vall d´Hebrón Hospital
- Former ESMO president
- World reference in clinical development of new drugs in oncology

VHIO · Vall d'Hebron

Xavier Barril, PhD

Computational Chemistry & Drug Discovery

- Currently: Associate Director at Boehringer Ingelheim
- ICREA Research Professor at University of Barcelona
- Scientist in **Computational Chemistry** and **Drug Discovery**
- Vernalis R&D
- Serial Entrepreneur: Minoryx Therapeutics & Gain Therapeutics

Boehringer Ingelheim · Universitat de Barcelona · minoryx therapeutics · GAIN THERAPEUTICS

Carles Galdeano, PhD

Targeted Protein Degradation & Drug Discovery Advisor

- Head of **Protein Degradation** (PROTAC) Lab at University of Barcelona
- Expert in Medical Chemistry

Universitat de Barcelona · University of Dundee · University of Cambridge

ONIRIA TEAM

BUSINESS MANAGEMENT

Jordi Petit, MBA
Chief Financial Officer

Marc Ramis, PhD, MBA
MtG/F.Botín Advisor

Natalia Ricco, PhD
Innovation Manager

Colin Moore, PhD
Regulatory & Preclinical Manager

Queralt Farreras
Junior Innovation Manager

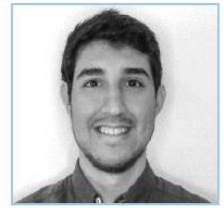
Gemma Dorrego
Junior Preclinical Manager

SCIENTIFIC RESEARCH

Elsa Martínez, PhD
Head of Chemistry

Tuo Chen
Chemistry PhD Student

David Aguilar, PhD
Head of Biology



Iris Marcote
Life Science PhD Student

Laia Cabellos
Laboratory Manager

Clara Diaz
Life Science Technician

Sònia Farran, PhD
Life Science Research Scientist

ADVISORY BOARD

Mark Graham, PhD
Safety

Joan Albertí, PhD
DMPK

Cristina Balagué, PhD
Pharmacology

Xavier Luria, PhD
Regulatory Affairs

Diego Muñoz, PhD
Medicinal Chemistry

Tony Senso, PhD
CMC

CLINICAL ADVISORS at VHIO:

Francesc Bosch, MD, PhD
Hematoncology

Eva Muñoz, MD, PhD
Melanoma

Elena Élez, MD, PhD
Colorectal Cancer

Elena Garralda, MD, PhD
Early Phase Clinical Drug Development

Irene Braña, MD, PhD
Early Phase Clinical Epigenetic Drug Development

ONIRIA THERAPEUTICS

THE PROBLEM

Cancer Persistence & Recurrence

One of the major challenges in modern cancer treatment is addressing **CANCER PERSISTENCE** and **RECURRENCE**. Despite initial successful treatments, some cancer cells survive and can lead to disease progression or relapse.

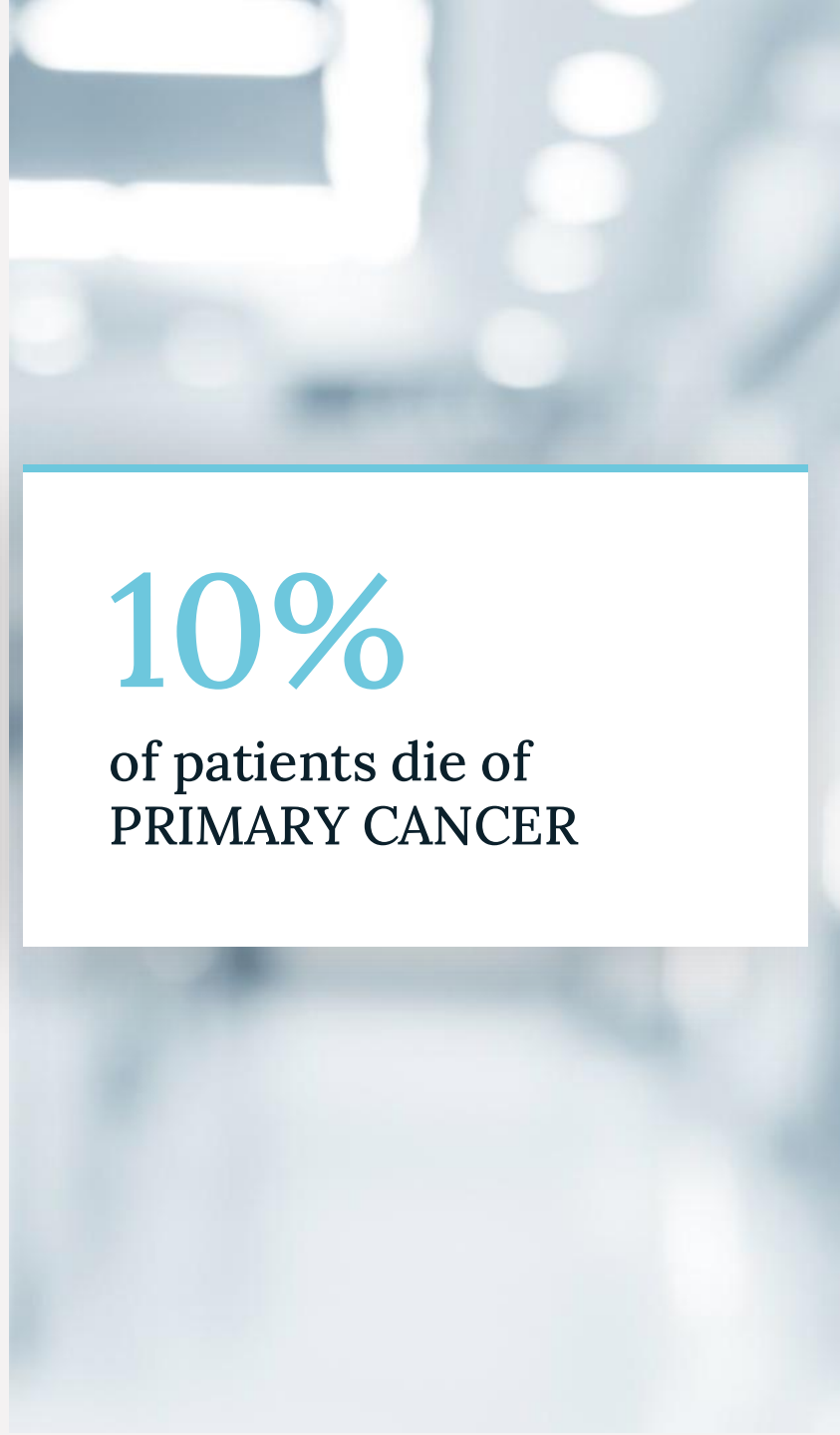
This persistence and recurrence requires the development of new therapies specifically designed to target these **PERSISTENT CANCER CELLS**, with the aim of improving long-term patient outcomes and achieving sustained remission.

90%

of patients die of CANCER RECURRENCE

10%

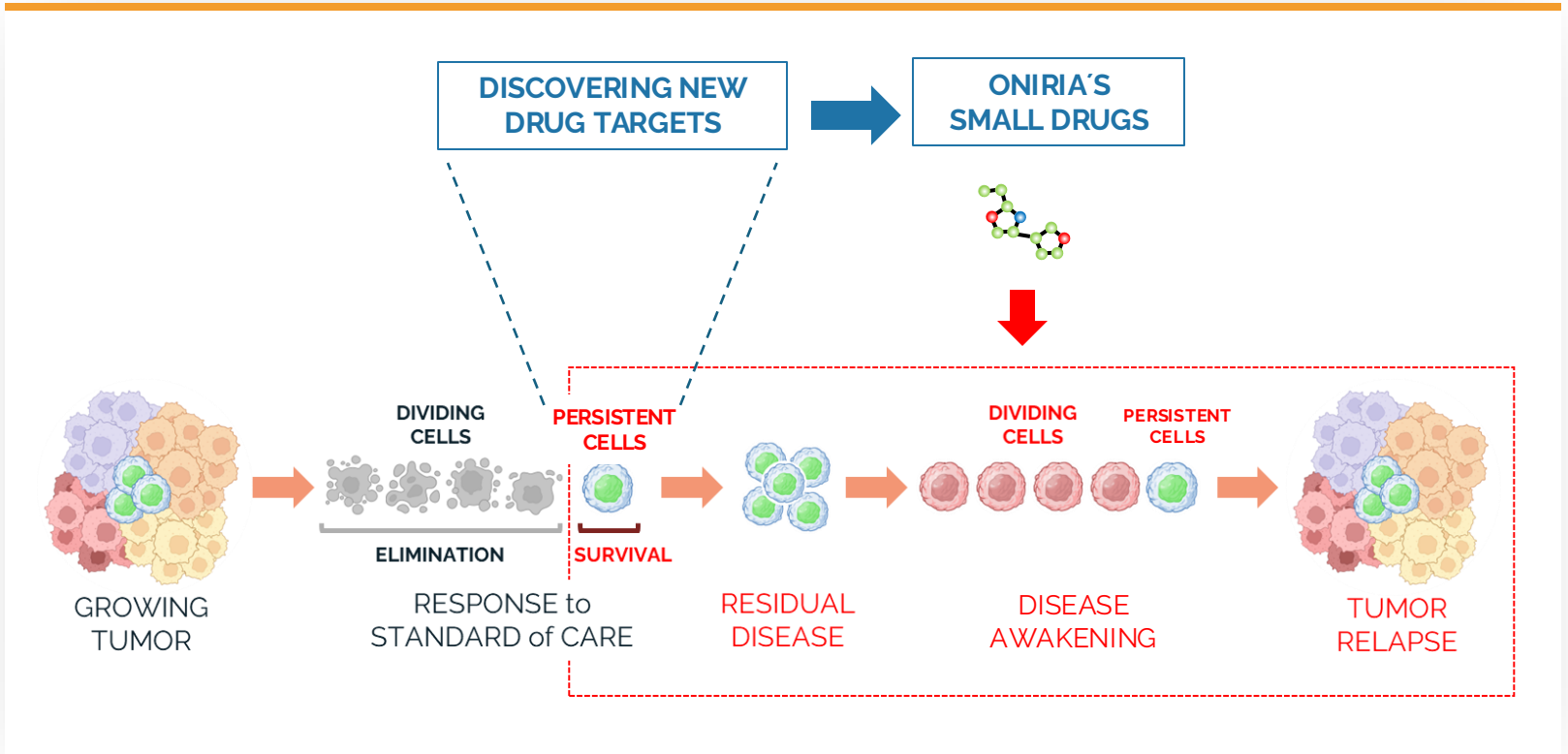
of patients die of PRIMARY CANCER



THE STRATEGY

Modulating new targets discovered in persistent tumor cells to treat cancer

We are targeting **VULNERABILITIES** in **PERSISTENT CANCER CELLS** backed by 16 years of research into the weaknesses of resilient cancer cells.



Puig I. et al., *J Clin Invest*, 2018; DOI: https://doi.org/10.1172/JCI96393
Puig i. et al. Methods Mol Bio, 2022; DOI: 10.1007/978-1-0716-2513-2_7
Cuesta E. et al., *Cell Reports*, 2023; DOI: 10.1016/j.celrep.2023.112927
Mur A. et al, *In preparation*

ONIRIA THERAPEUTICS

PIPELINE

PRODUCT	INDICATION	TARGET DISCOVERY	HIT-TO-LEAD	LEAD OPTIMIZATION	CANDIDATE SELECTION	PRE-CLINICAL REGULATORY	PHASE I/IIA	PHASE II	PHASE III	REGULATORY SUBMISSION	STATUS
ONR-001 TET2 ACTIVATOR	MELANOMA, AML, MDS, CRC										CANDIDATE SELECTION & PRE-CLINICAL NON-REGULATORY STUDIES
ONR-002 TET2 INHIBITOR	ONCOLOGY										HIT-TO-LEAD
ONR-003 TET2 PROTAC	ONCOLOGY										HIT-TO-LEAD
NEW TARGETS	ONCOLOGY										DISCOVERY
ONR-004 TET2 ACTIVATOR	AGING			*ACTIVELY LOOKING FOR A CO-DEVELOPMENT PROGRAM*							CANDIDATE SELECTION & PRE-CLINICAL NON-REGULATORY STUDIES

PRODUCT	INDICATION	DISCOVERY	DEVELOPMENT	PRE-CLINICAL VALIDATION	CLINICAL VALIDATION & PRODUCT APPROVAL	PHASE III CLINICAL USE	MARKET USE	STATUS
BIOMARKER 5hmC	TET2 ACTIVATOR & INHIBITOR							DEVELOPMENT

ONIRIA THERAPEUTICS

OUR MOST ADVANCED DRUG

First-in-class Small Drug TET2 Activator

ONR-001 is a first-in-class small molecule that allosterically and specifically activates TET2, a master epigenetic enzyme, causing tumor cells to enter a dormant state and even die.

This unique method can be successfully used at all stages of the disease, from naïve primary tumors to recurrent resistant metastatic cancer – thus "making a world of difference".

Oral Efficacy

Small molecule (MW400, LOGP 3,5)
Good potency (sub-µM)
Efficacy in animal models of cancer

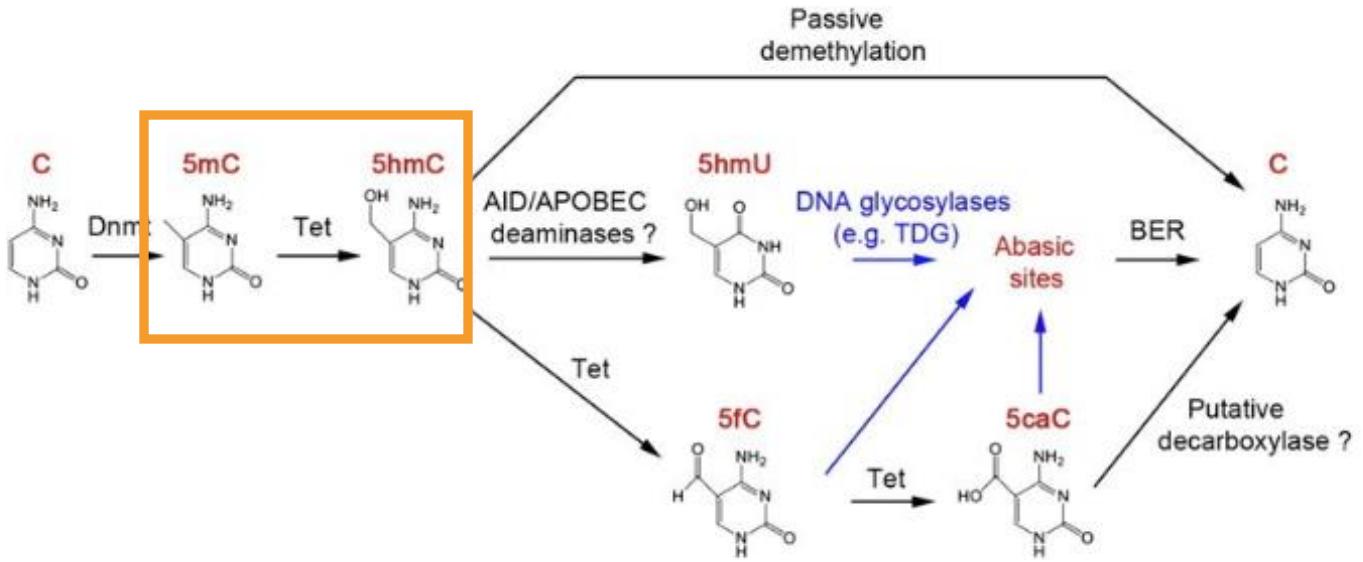
Reaches the target

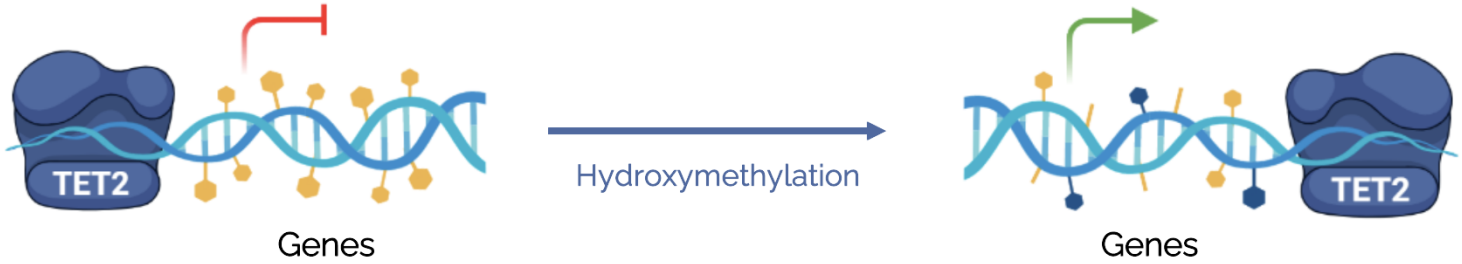
Crosses the cell and nuclear membranes
Activates TET2 in vivo and in the tumor tissue

Safe

Target Selectivity
High Acute & Chronic Tolerability in rodents
Clear PK/PD relationship

TET2 has a fundamental role in the survival of tumor dormant cells

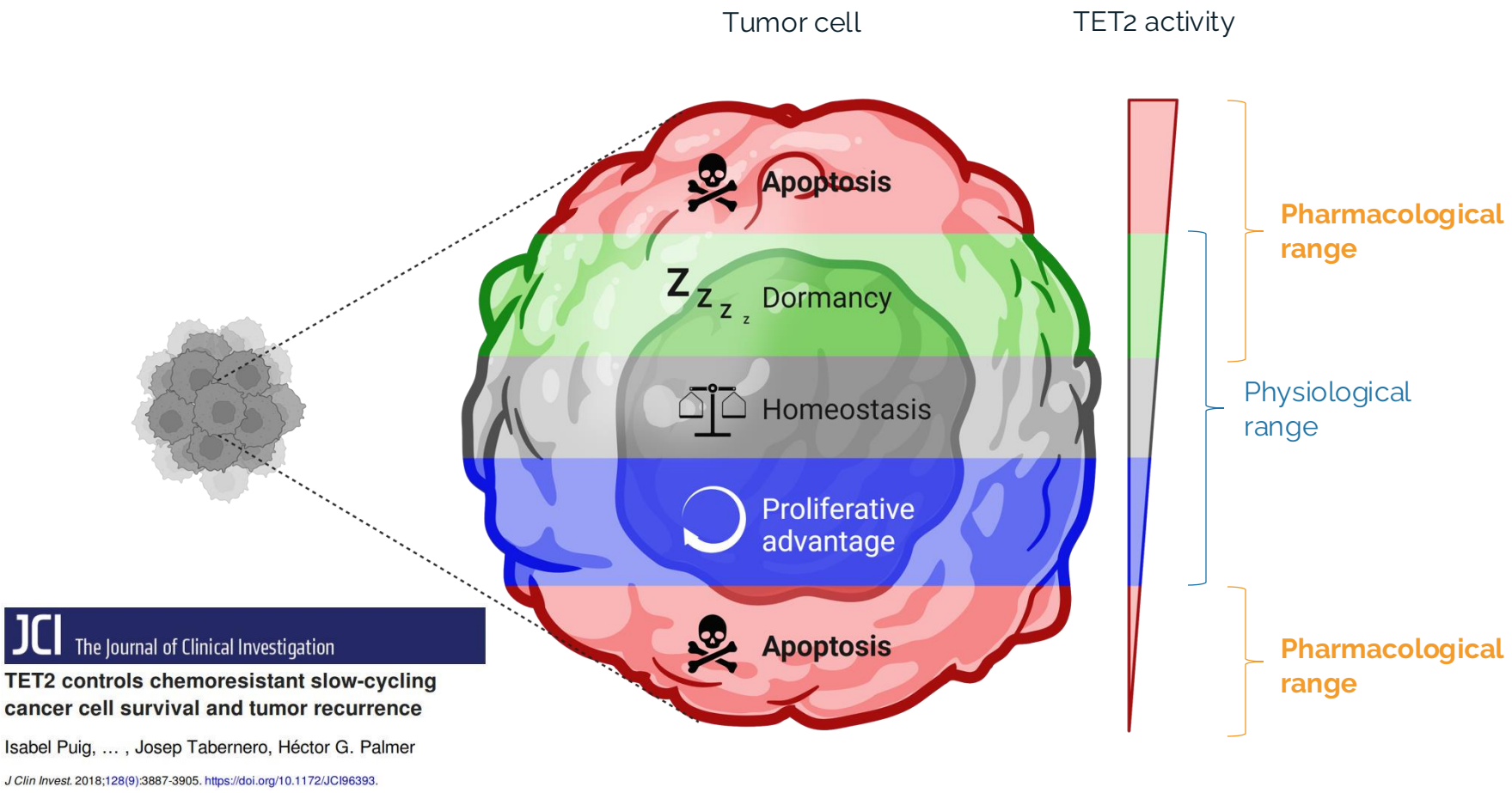




THE TARGET

TET2 activity is essential in controlling cancer cell fate

Modulation of TET2 activity determines cell fate.
The flagship product of Oniria Therapeutics is **ONR-001,** a small-molecule that allosterically **OVER-ACTIVATES TET2** beyond a therapeutic threshold, triggering cell cycle arrest and apoptosis in cancer cells.



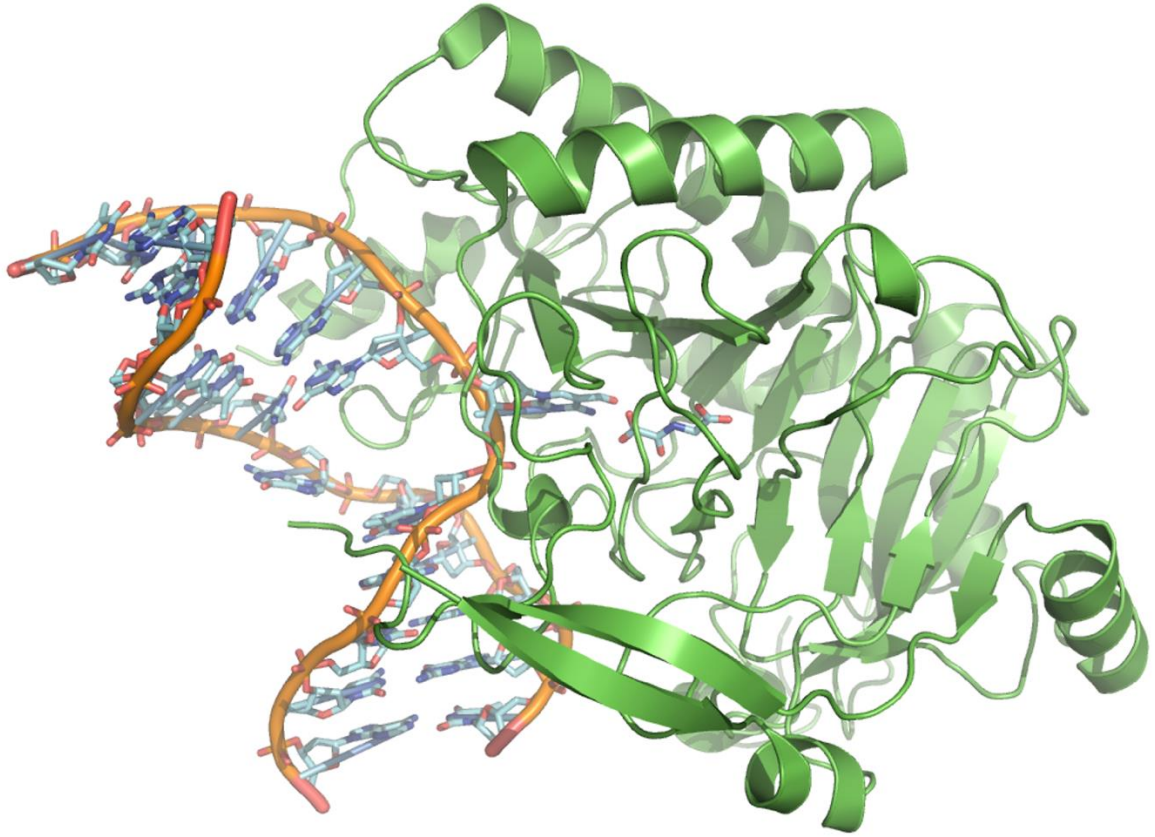
JCI The Journal of Clinical Investigation

TET2 controls chemoresistant slow-cycling cancer cell survival and tumor recurrence

Isabel Puig, … , Josep Tabernero, Héctor G. Palmer

J Clin Invest. 2018;128(9):3887-3905. https://doi.org/10.1172/JCI96393.

Structure-based approach

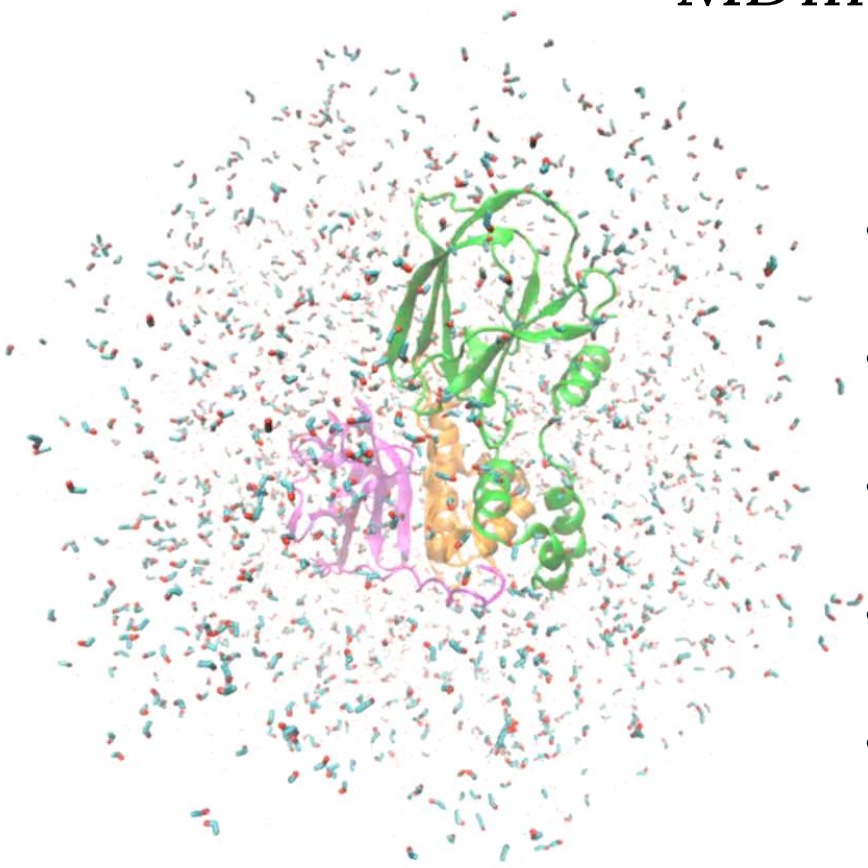


(2015) Nature **527**: 118-122

(2013) Cell **155**: 1545-1555

How we discovery ligandable pockets?

MDmix – One-stop shop for:



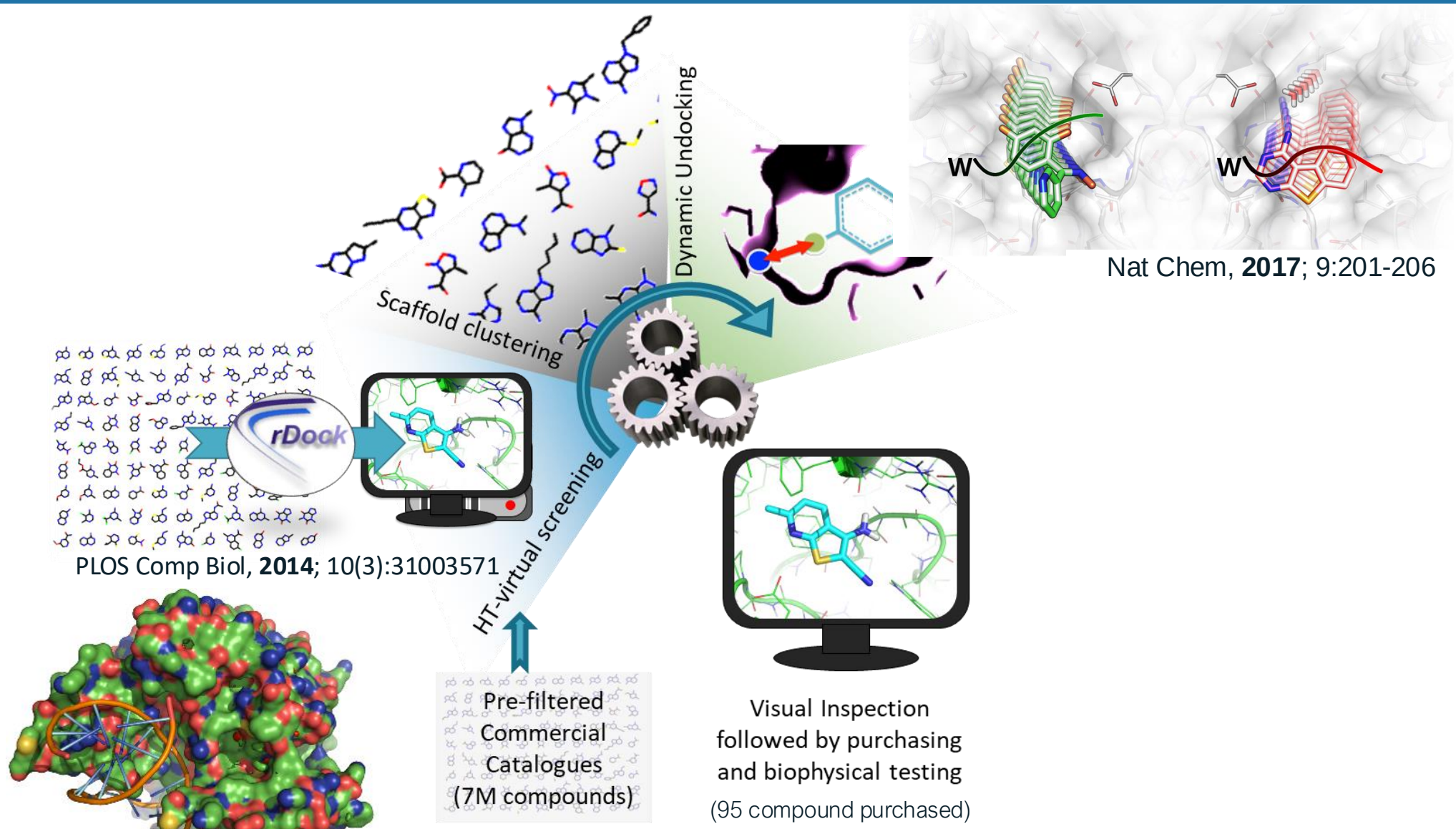
- **Identification and quantification of ligandable binding sites**

  J. Med. Chem. 2009, 52, 2363 *J. Med. Chem*. 2014, 57, 8530
- **Prediction of pharmacophoric points**
- Binding site characterization: hydration sites, flexibility
- Guiding ligand optimisation

  J. Chem. Inf. Model. 2017, 57, 846
- Binding mode prediction

  J. Chem. Inf. Model. 2019, 59, 3572

High-throughput virtual screening TET2



Nat Chem, **2017**; 9:201-206

PLOS Comp Biol, **2014**; 10(3):31003571

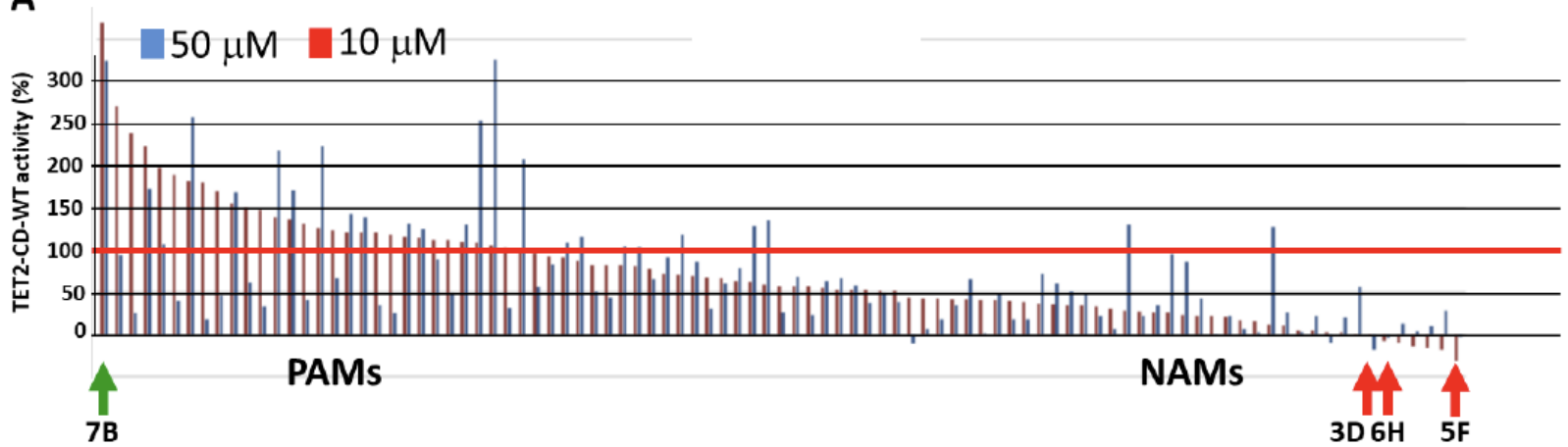
HIT DISCOVERY

TET2 enzymatic assay

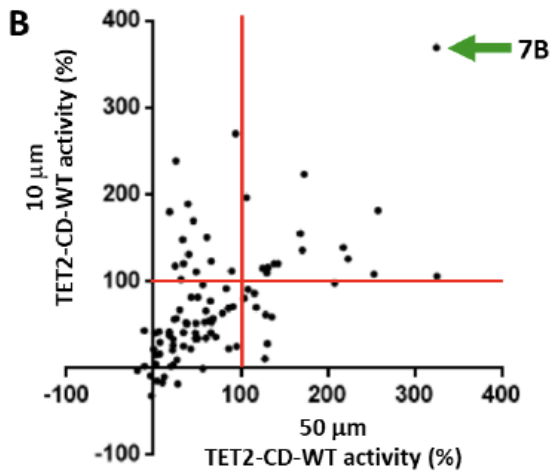
From the initial **95 Hit list**, we identified some Negative Allosteric Modulators (NAMs) and some Positive Allosteric Modulators (PAMs) of TET2 enzymatic activity.

*7B=ONR-001

A



B

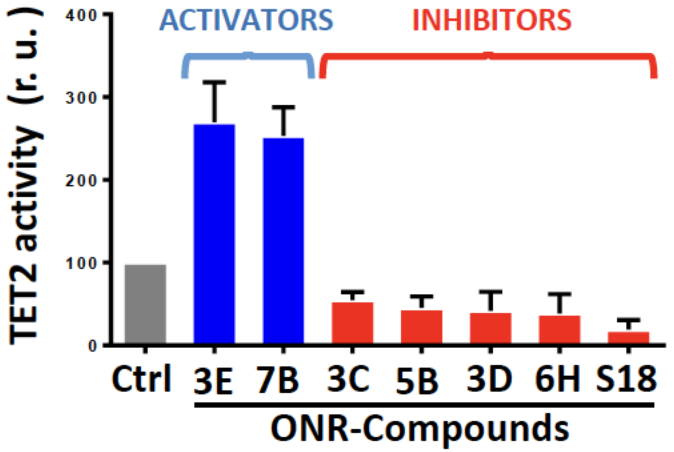


C

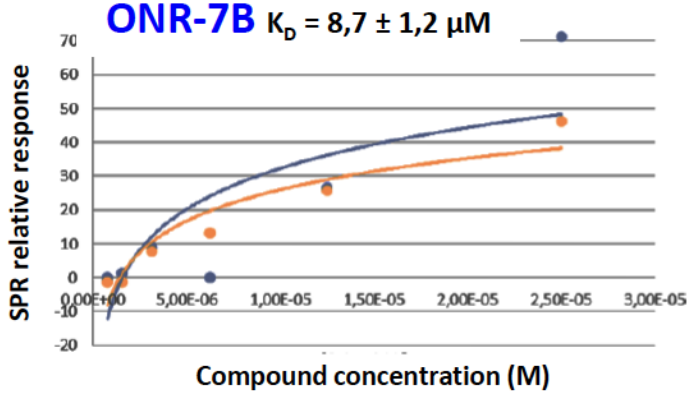
TET2 ACTIVITY (% CONTROL)		
Well	50uM	10uM
05_F	-2,66	-31,67
05_E	9,82	-16,27
05_D	3,54	-14,46
06_H	12,14	-9,82
03_D	-3,86	-8,38
09_D	-18,74222859	-2,358286713
03_C	-10,54	2,30
S18	1,985931858	4,716589609
03_E	2,06	15,75
05_B	6,62	16,47
09_C	21,96939185	26,56186548
01_G	6,82	29,95
07_B	324,94827	369,5076359

TET2 hits validation

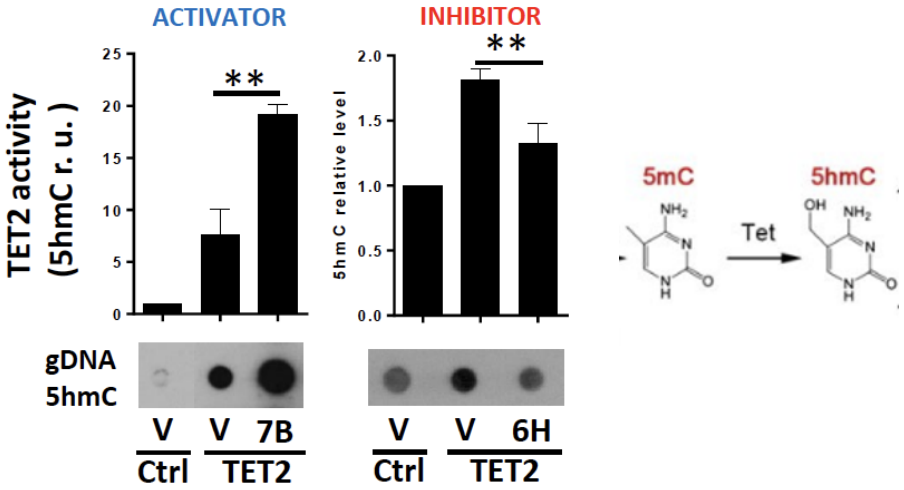
Screening of Enzymatic Activity



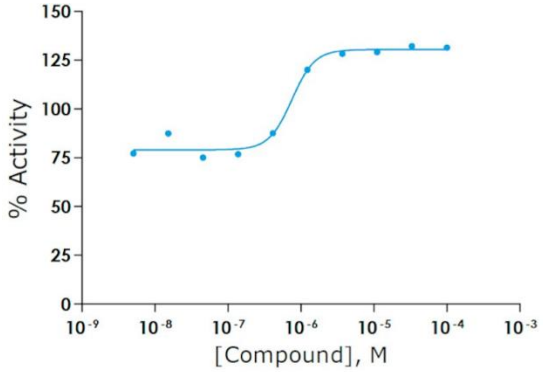
Direct Drug-Target Binding (SPR)



TET Activity in Cancer Cells

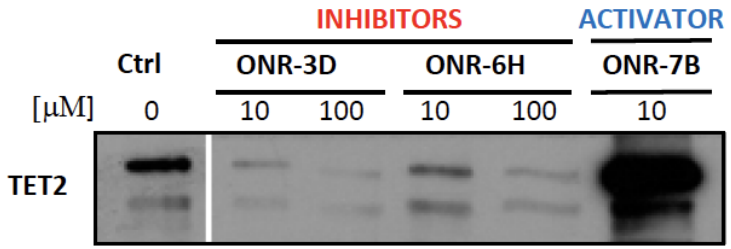


Increase TET2 Enzymatic Activity



	Bottom	Top	HillSlope	EC50
7B	79.06	130.46	2.77	7.51e-007

MMoA Stabilization of TET2



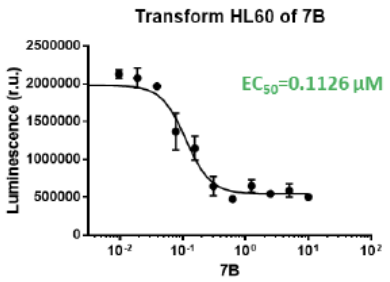
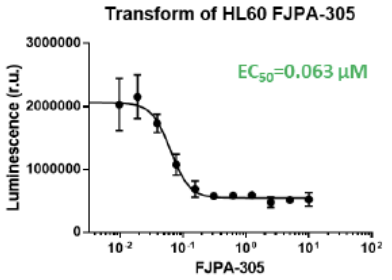
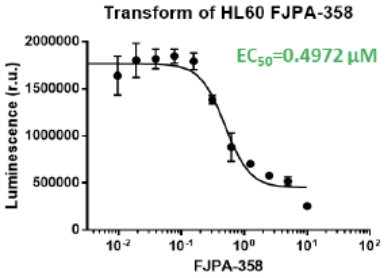
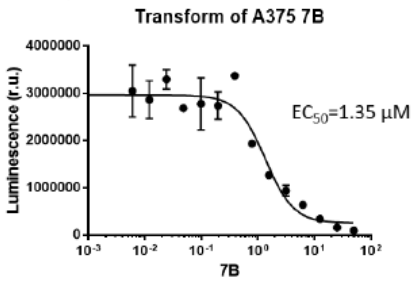
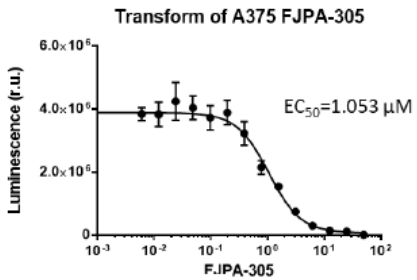
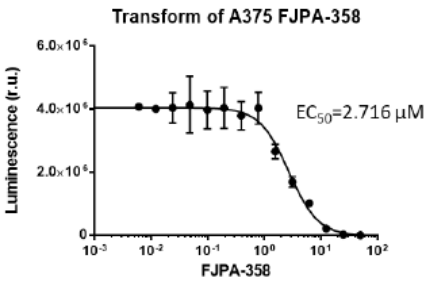
TET2 hits validation

HIT VALIDATION

TET2 activators impact on cancer cell viability

Anti-tumoral efficacy potency of the Hits was assessed by calculating their EC_{50} values in cell lines of different cancer types.

We define the response as sensitive when the EC50 concentration is in the nM range.

	ONR-001	FJPA-305	FJPA-358
LEUKEMIA			
MELANOMA			

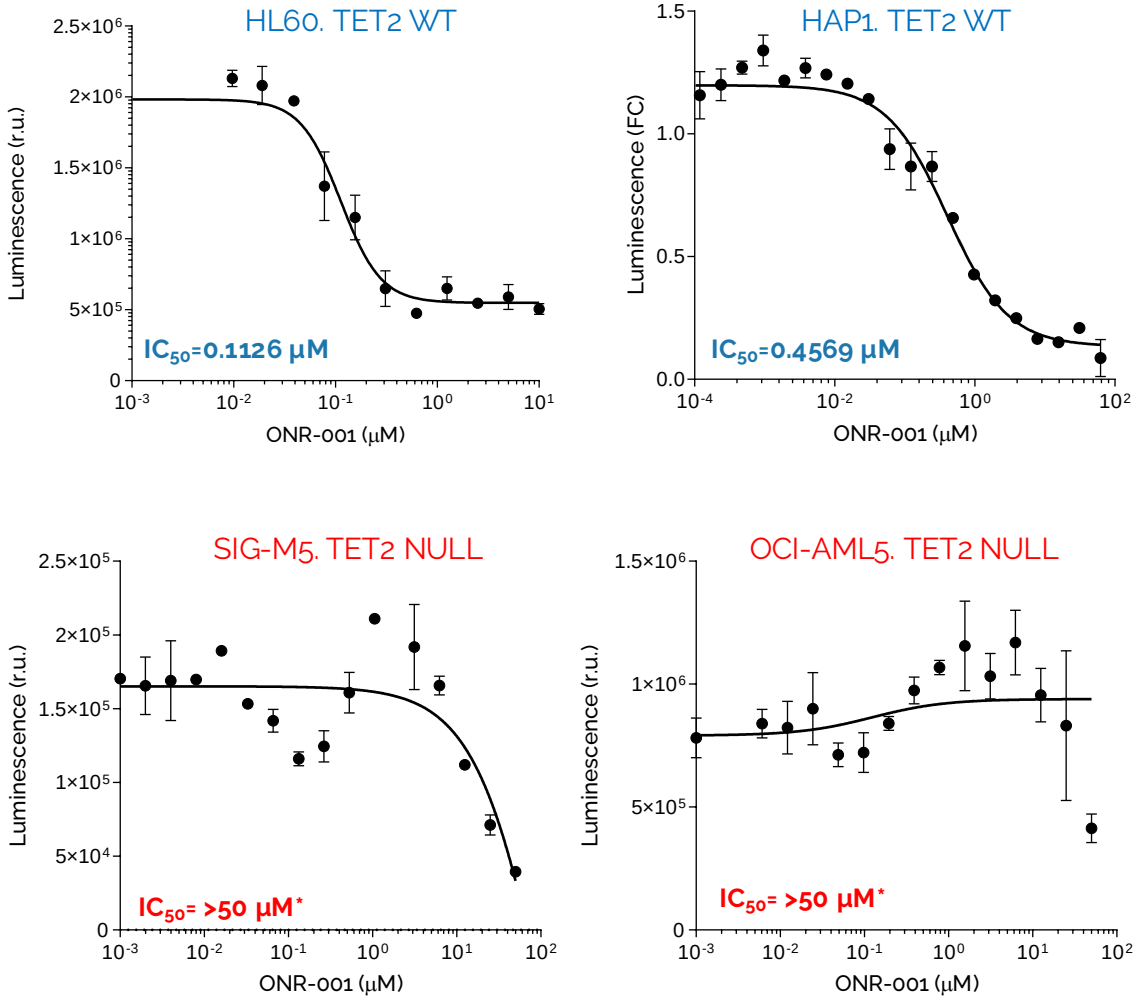
*7B=ONR-001

Only a few examples are shown

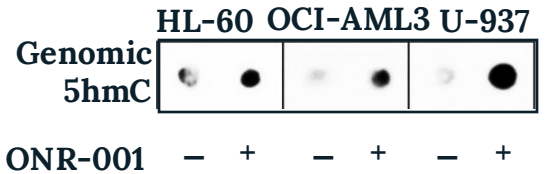
EFFICACY

ONR-001 activity and specificity

ONR-001 Efficacy on Cell Viability



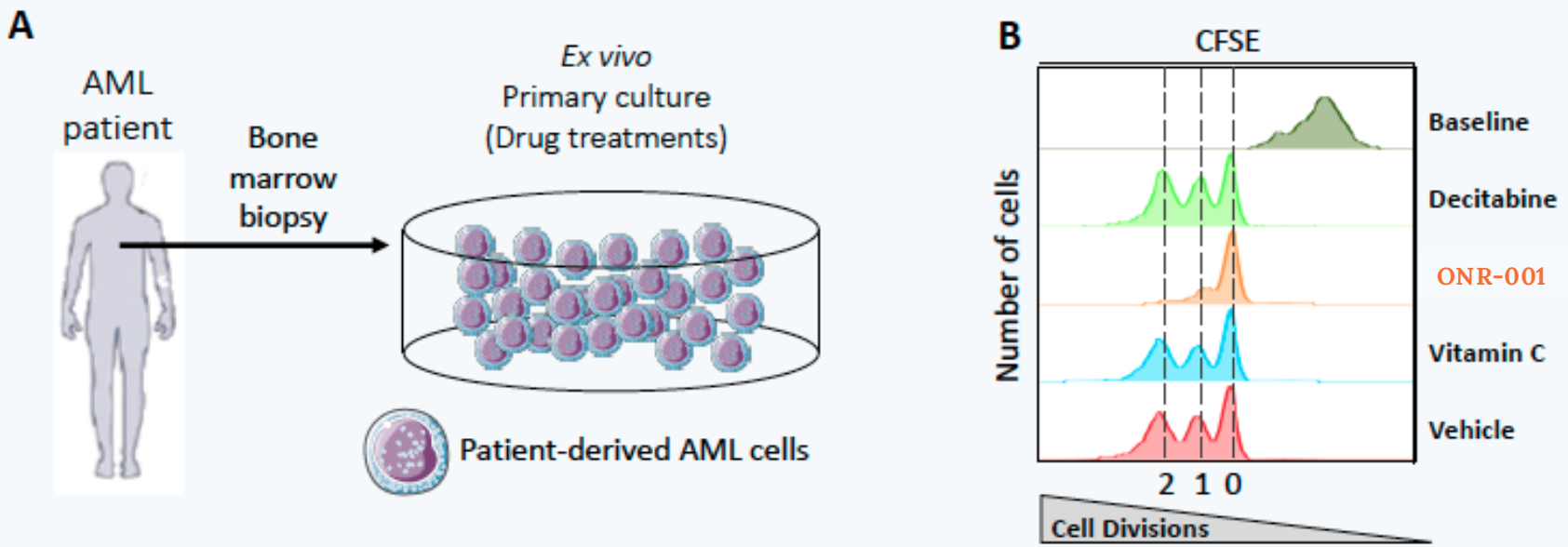
ONR-001 Increases TET2 Activity



Leukaemia cancer cells

	TET1	*TET2*	*TET3*
OCI-AML5	WT	S825*	WT
		Y1148C	
SIG-M5	WT	F1041Ifs*2	WT
		Y1182Ifs*44	
		S1203R	
HL60	WT	WT	WT
HAP1	WT	WT	WT
OCI-AML3	WT	WT	WT
U-937	WT	WT	WT

ONR-001 blocks the proliferation of patient-derived AML cells



Cells directly derived from the bone marrow of AML patients were cultured *ex vivo* (A). ONR-7B blocks the proliferation of patient-derived AML cells whereas the unspecific TET2 activator Vitamin C or the general hypomethyltating agent decitabine do not (B).

TET2 loss promotes melanoma progression, which is reversed by TET2 rescue

Loss of 5-Hydroxymethylcytosine Is an Epigenetic Hallmark of Melanoma

Cell

Cell *150*, 1135–1146, September 14, 2012

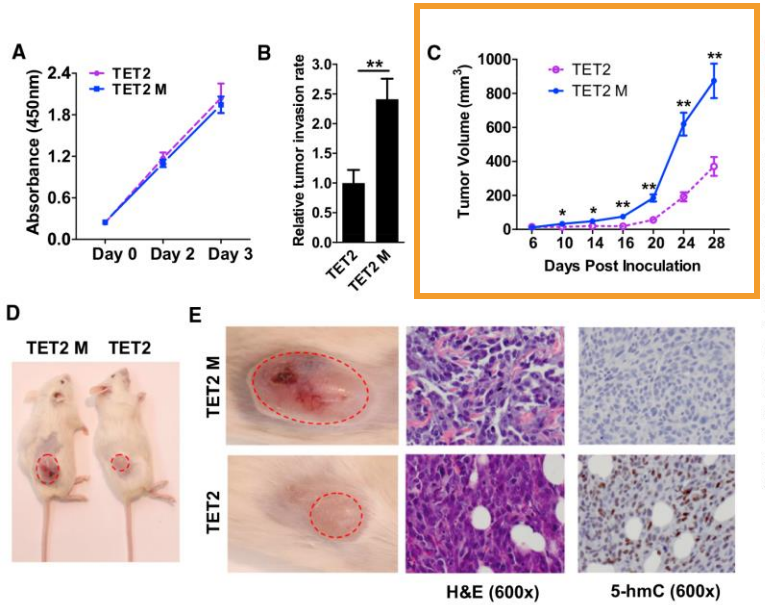


Figure 6. Overexpression of TET2 in Human Melanoma Cells Suppresses Tumor Growth in NSG Xenograft Mice

(A) The proliferation curves of A2058 TET2 and A2058 TET2 M stable cell lines. Data are shown as mean ± SD (n = 4).

(B) A2058 TET2 melanoma cells show less in vitro invasion than A2058 TET2 M melanoma cells by Matrigel tumor invasion assay. Data are shown as mean ± SD (n = 3). **p < 0.01 by Student's t test.

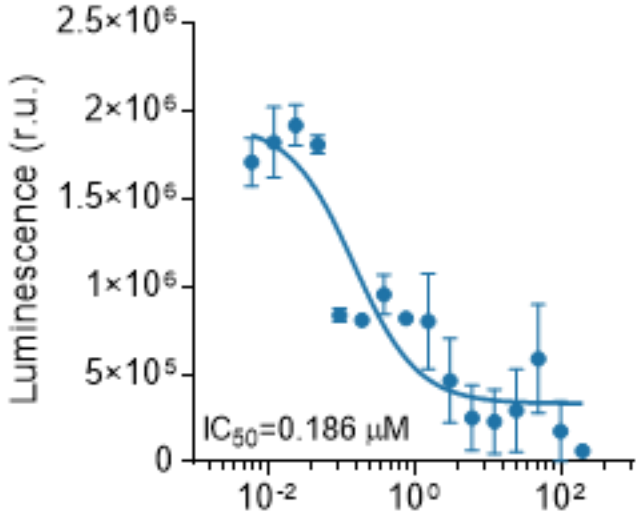
(C) Tumor growth curves of A2058 TET2 and A2058 TET2 M cells xenografted to NSG mice. Data are shown as mean ± SEM (n = 10). *p < 0.05, **p < 0.01 by Student's t test.

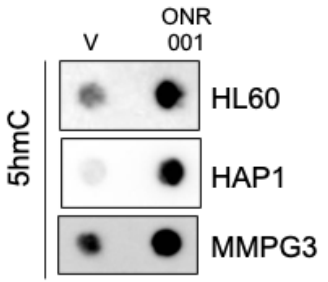
(D) Representative images of tumor-bearing NSG mice xenografted with A2058 TET2 M (left) or A2058 TET2 cells (right) at 4 weeks post-inoculation.

(E) H&E and 5-hmC IHC staining of TET2 M (top) and TET2 (bottom) xenografts. The regions shown in left panels are noted by red dash circles in (D).

Genetic rescue of TET2 blocks melanoma growth

Melanoma (BRAF wt, NRAS wt)
MMPG3





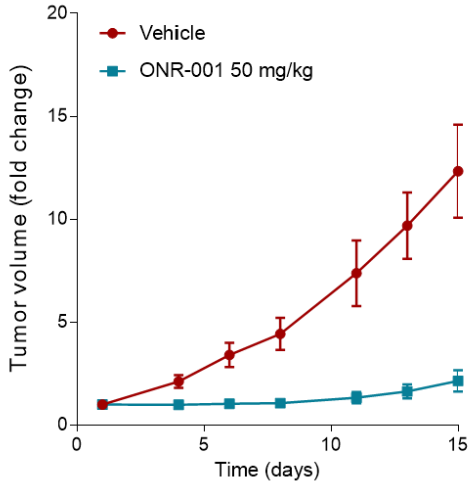
IN VIVO

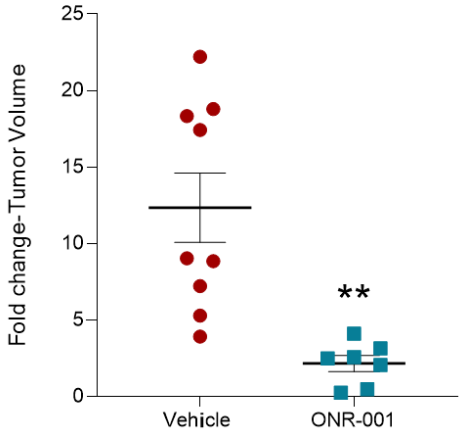
PROOF-OF-CONCEPT

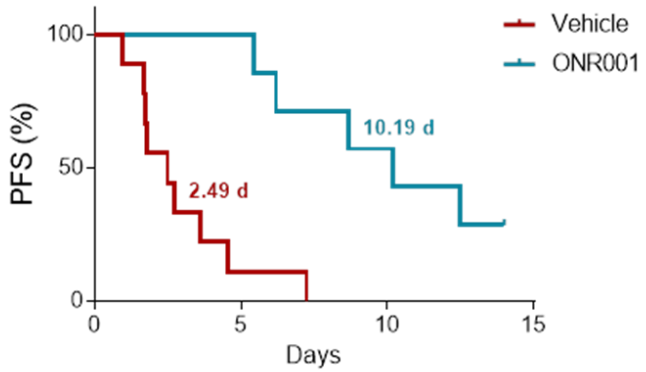
STANDALONE

ONR-001 is an effective small molecule in vivo in Melanoma

Melanoma BRAFwt, NRASwt PDX-MMPG3 subcutaneous injection, oral ONR-001 (50mg/kg)





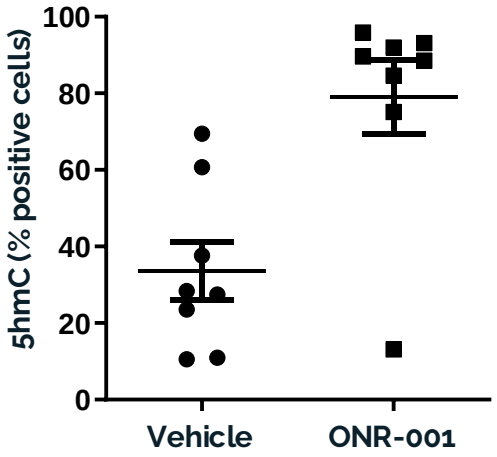


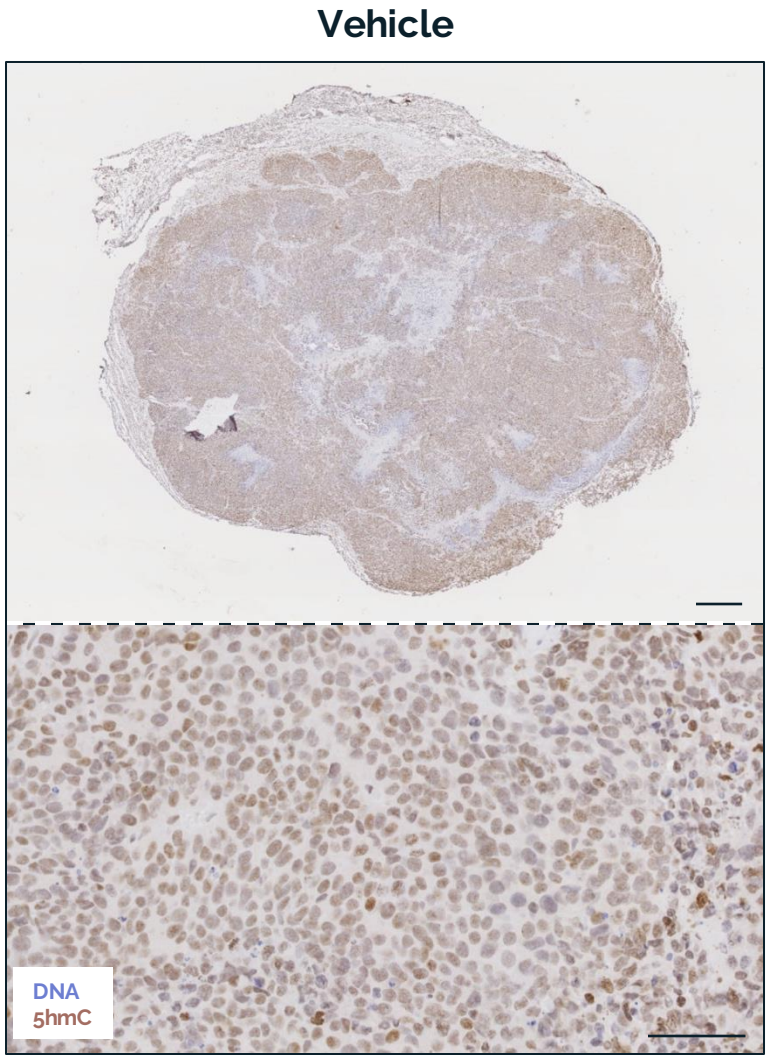
ONR-001 Cuadruplicates the time to progression free survival (Standalone treatment)

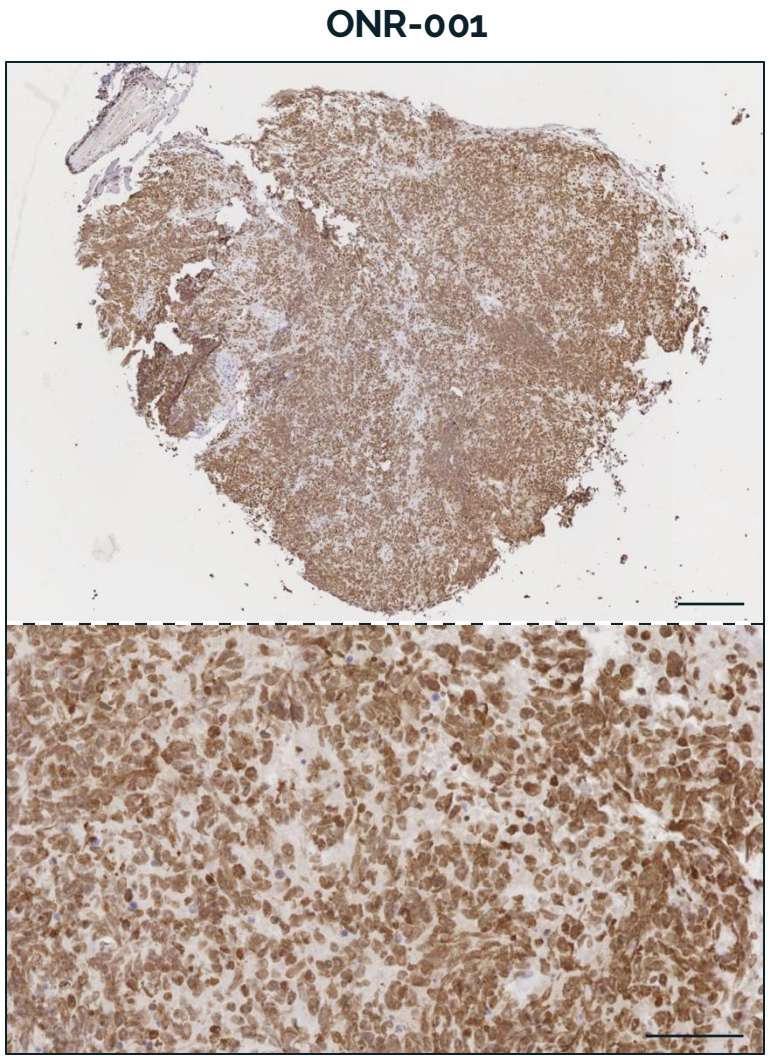
Treatment with ONR-001 in combination or at progression to immunotherapy have been evaluated (confidential)

ONR-001 increases 5hmc in melanoma xenograft tumors

PDX-MMPG3 *BRAFwt, NRASwt*, subcutaneous injection, oral 50 mg/kg



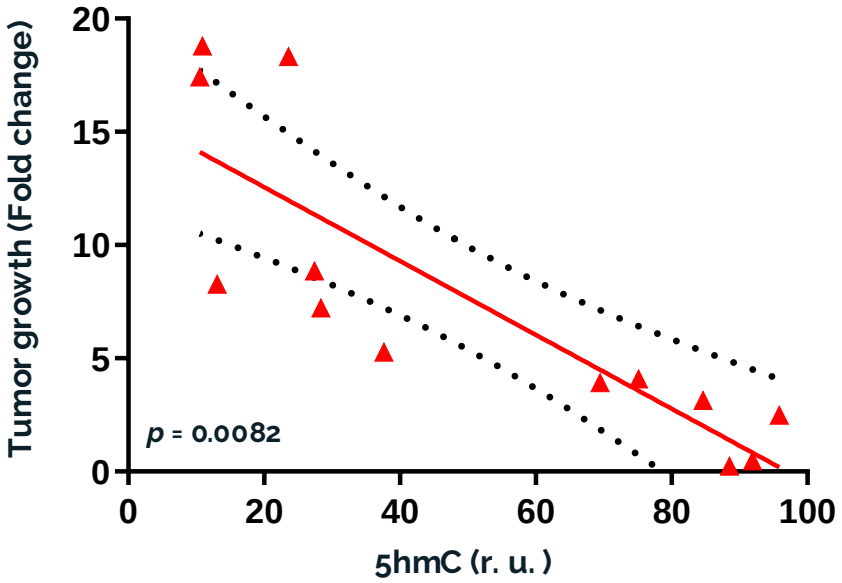




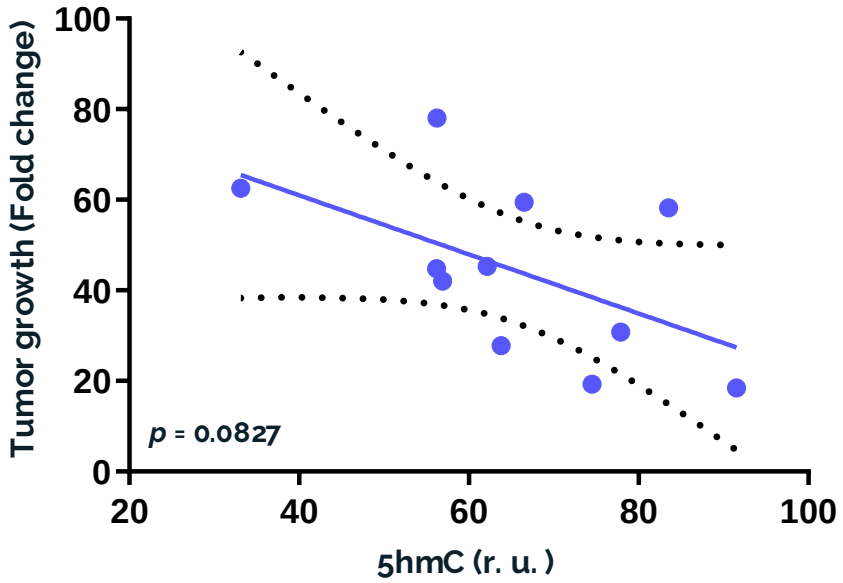
5hmC as PHARMACODYNAMIC MARKER

The increase of 5hmC by ONR-001 correlates with tumor growth blockade

PDX-MMPG3. MELANOMA



HL60. LEUKEMIA

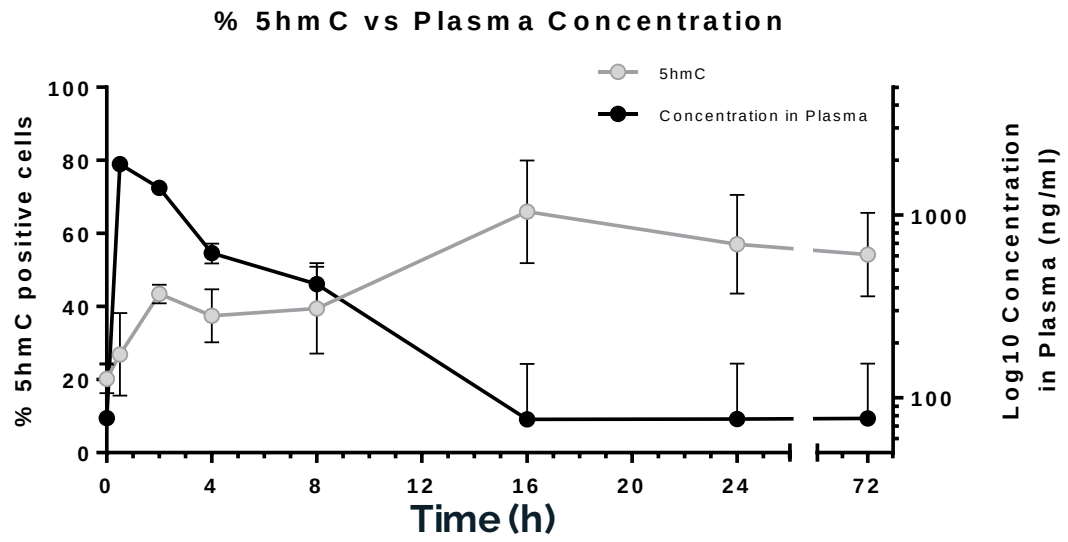


5hmC will be measured in Phase Ia/b clinical trials from liquid biopsies as pharmacodynamic marker for correlating with potential responses to ONR-001

In vivo: Oral ONR-001 shows a clear PK/PD relationship

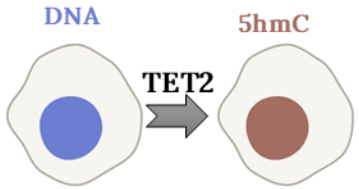
EFFICACY

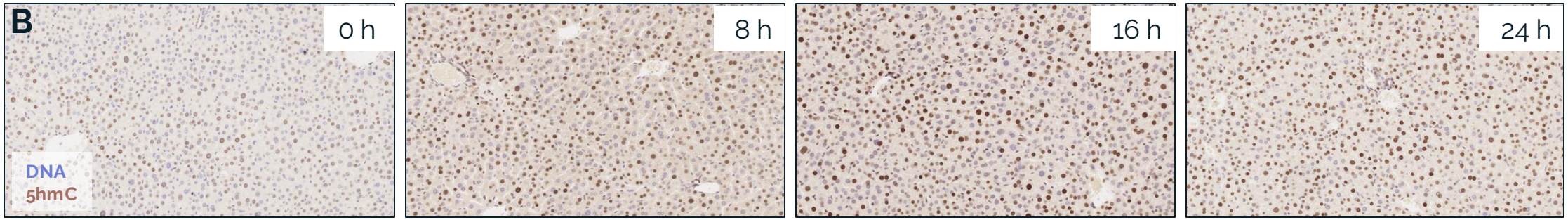
A



A single oral dose of 10 mpk in mice shows a pharmacokinetics in plasma with a rapid Cmax of 2 mM and 3 hours $T_{1/2}$ (A). This profile is equivalent to that observed in other blockbuster drugs in oncology.

Pharmacodynamics: Target activation is observed in livers by an increase in TET2 enzymatic product 5hmC (A and B).



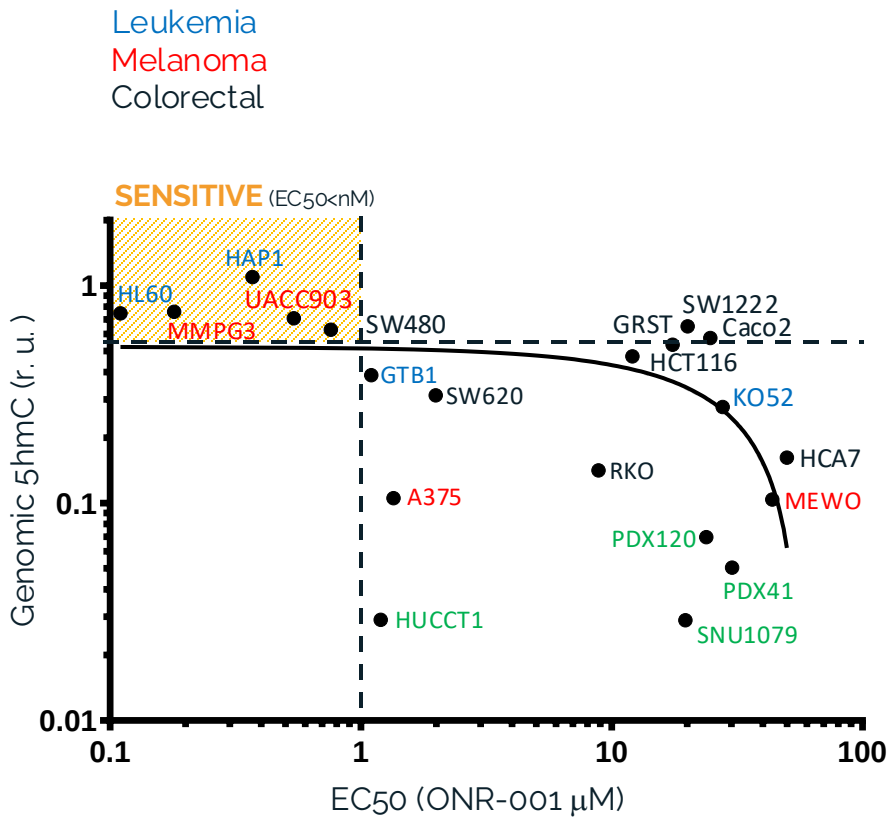


PRECISION ONCOLOGY: 5hmC as future biomarker for patient selection and PD

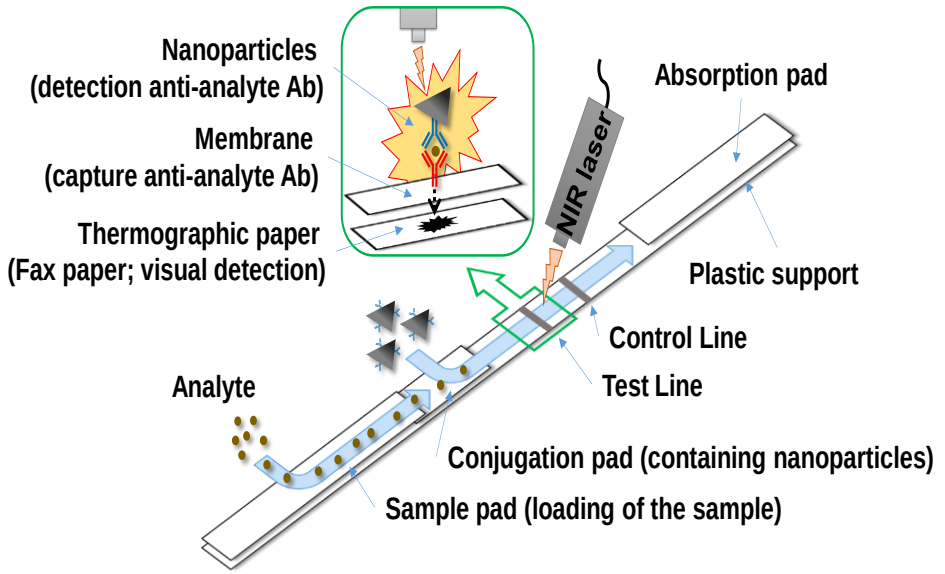
ONR-001 requires a minimum basal levels of 5hmC for being anti-tumoral

ONIRIA THERAPEUTICS

A Correlating genomic 5hmC levels and response to ONR-001



B Lateral Flow Chromatography Assay (LFIA) & Plasmonic-driven termal sensing



COMPANION DIAGNOSTIC TEST
Analysis of 5hmC in ctDNA from liquid biopsies

icma Instituto de Ciencia de Materiales de Aragón

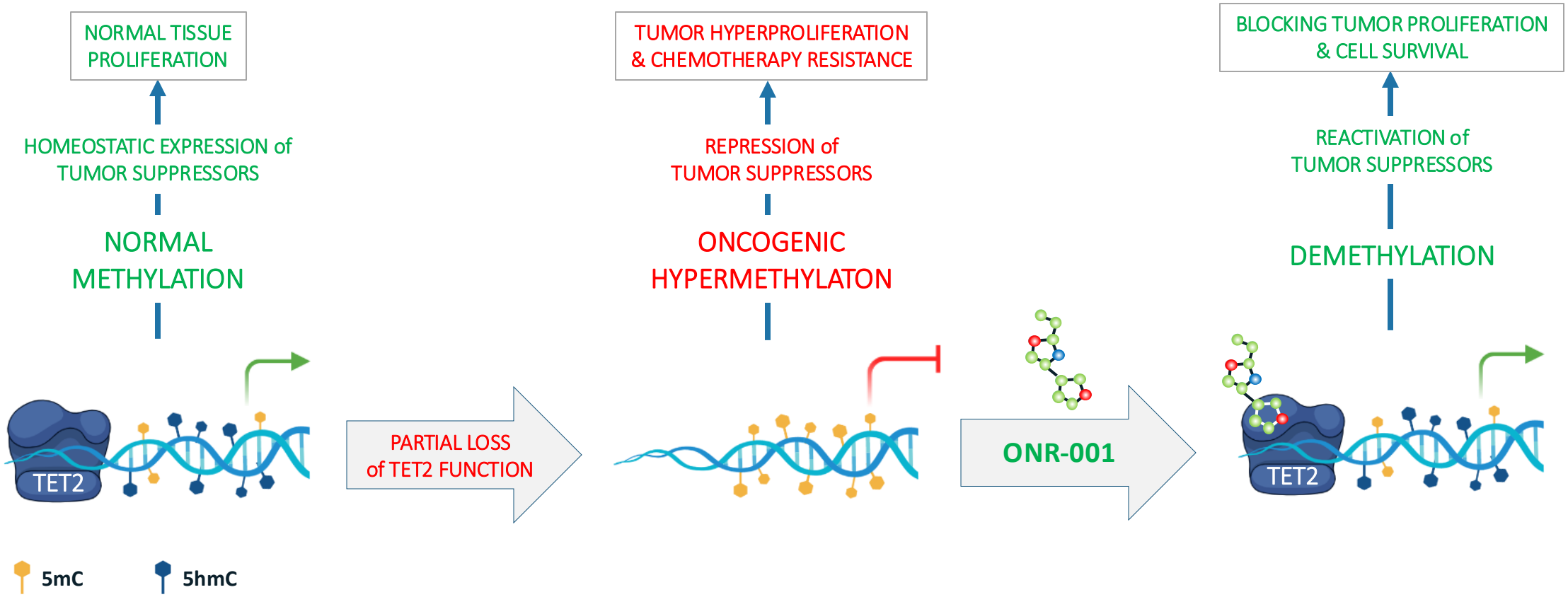
Jesús Martínez de la Fuente, PhD.
CSIC.

ACCIÓ Catalonia Trade & Investment

Generalitat de Catalunya

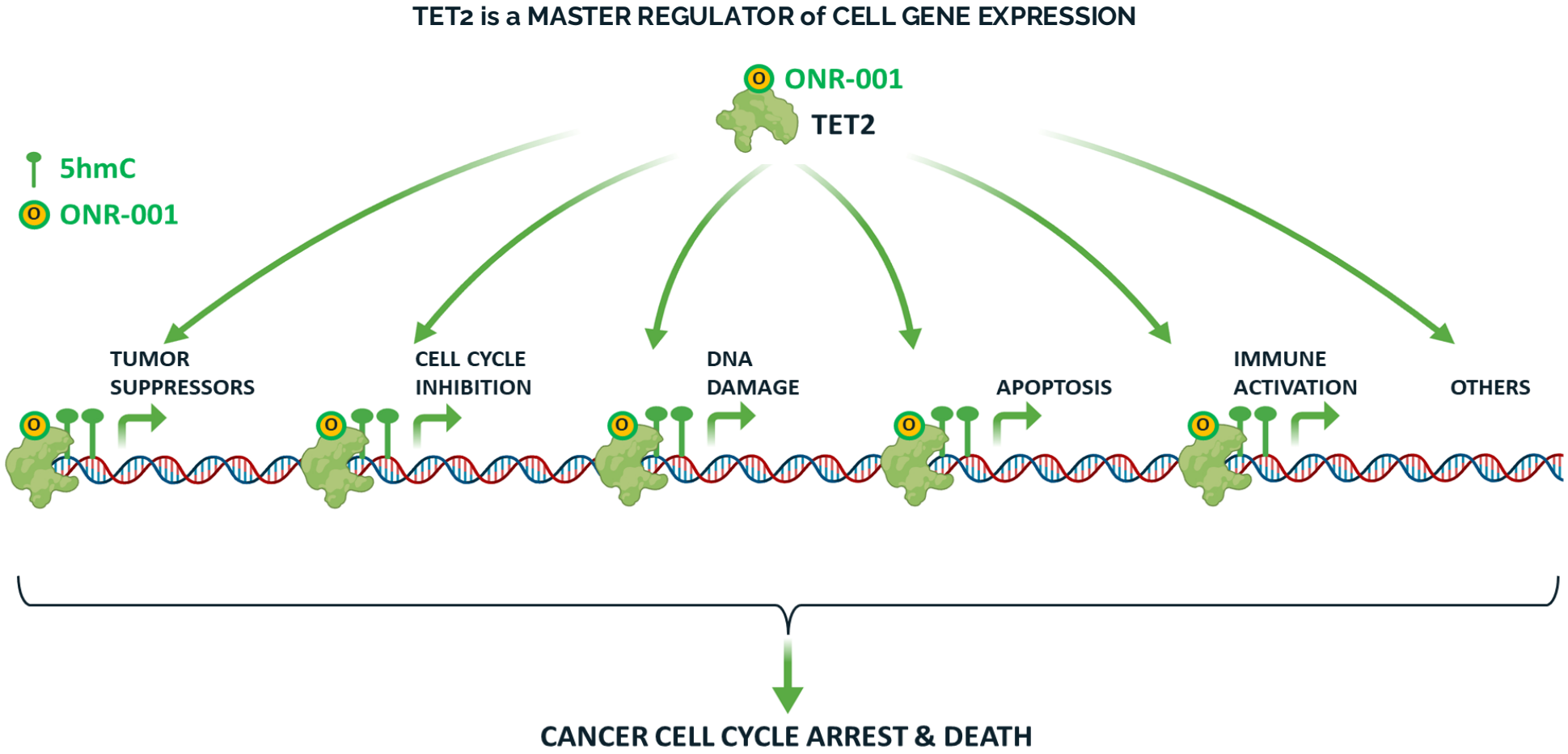
DRUG MECHANISM of ACTION

ONR-001 is a first-in-class small molecule activator of TET2



ONR-001 is a specific demethylating agent through overactivation of TET2

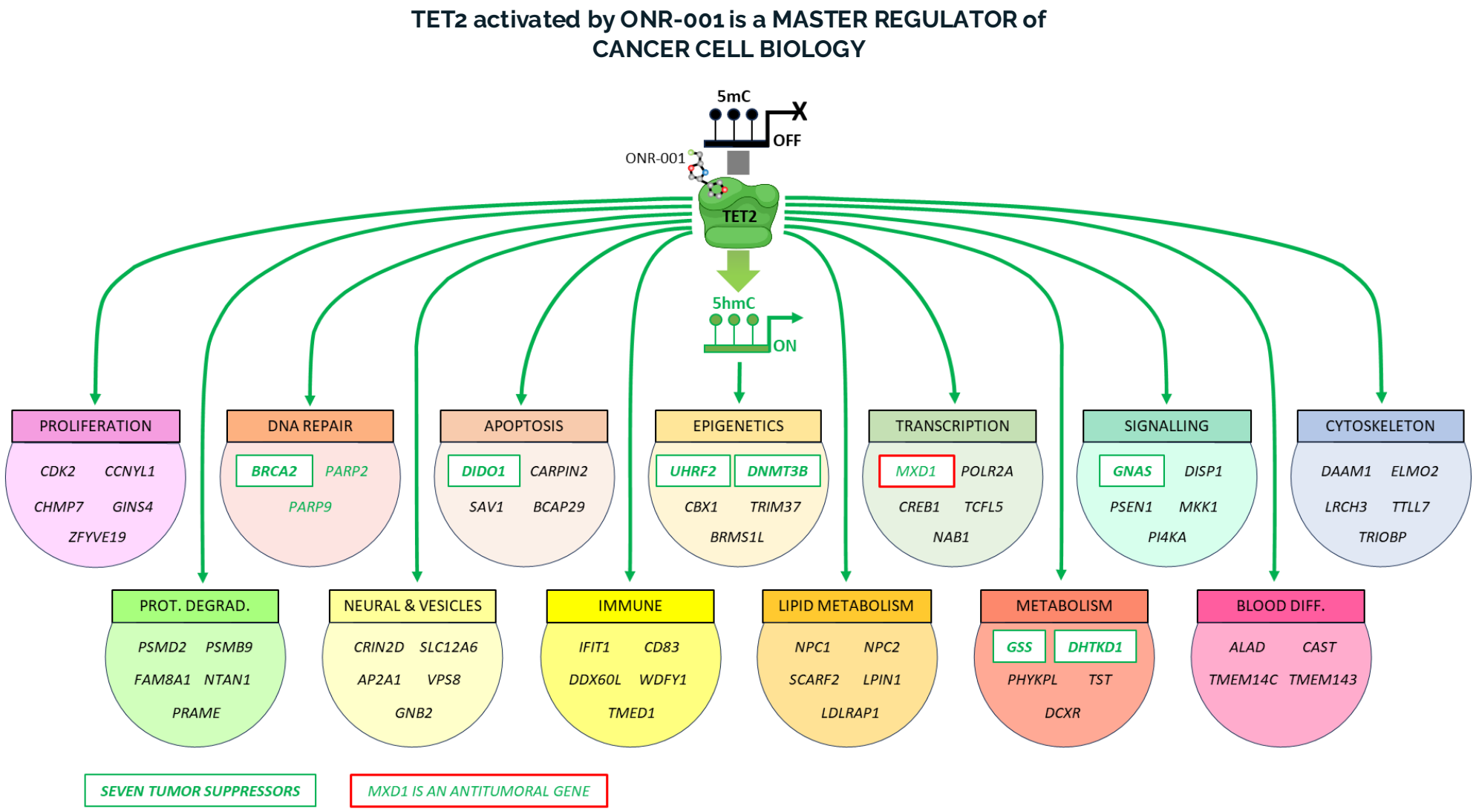
TET2 oxidizes methylated DNA for a coordinated gene expression reactivation



ONR-001 over-activates TET2, and it reactivates several **TUMOR SUPPRESSORS**, **ANTITUMORAL GENES**, and genes related with cell cycle inhibition, DNA repair, apoptosis, immune activation, metabolism of the tumoral cells, etc…

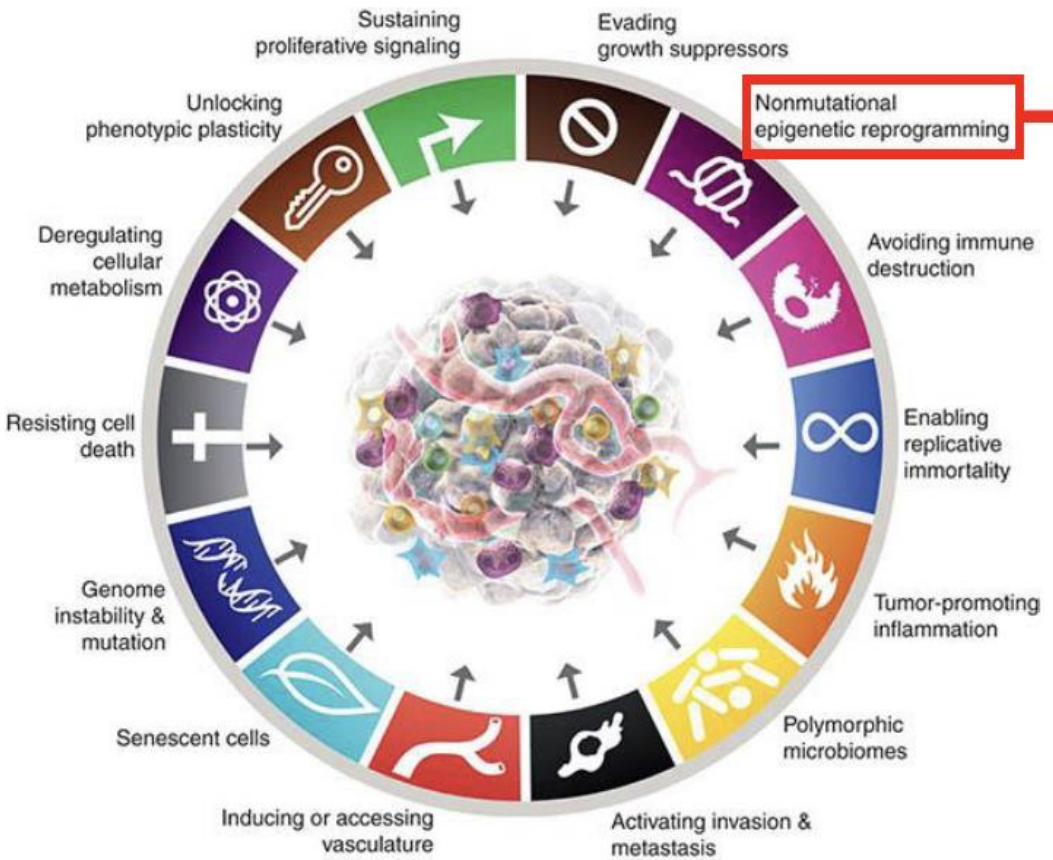
NO ONCOGENE IS REACTIVATED

TET2 demethylates DNA for a coordinated gene expression reactivation



Epigenetic DNA hypermethylation is an essential hallmark of cancer

CANCER HALLMARKS



ONCOGENIC HYPERMETHYLATON

e.g. Tumor suppressor genes

Many tumors affected by hypermethylation: **BIBLIOGRAPHIC RATIONALE:**

- **HEMATOLOGICAL** cancer,
- **COLORECTAL** cancer,
- **MELANOMA**,
- **PROSTATE** cancer,
- **GASTRIC** cancer,
- **GLIOBLASTOMA**, etc.

We have already demonstrated *in-vivo* efficacy in these three indications

EMPIRICAL RATIONALE: We are currently collaborating with the Broad Institute by using their PRISM platform to identify which other types of cancer or molecular alterations show a positive correlation with ONR001 efficacy. They are screening ONR-001 across more than 900 human cancer cell lines using a high-throughput multiplexed approach. Results will be available in September 2024.

BROAD INSTITUTE

ONIRIA THERAPEUTICS

GRACIAS!

THANKS!

GRÀCIES!

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THERAPEUTICS