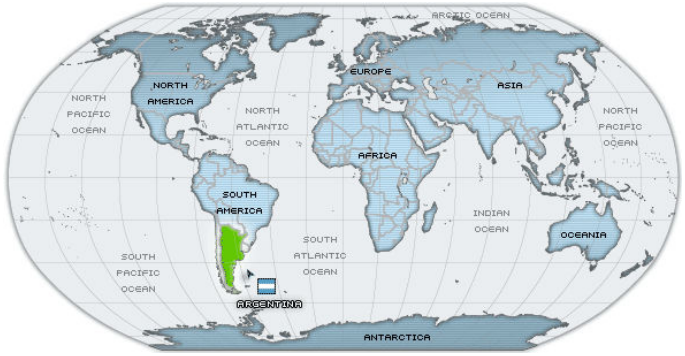
DEVELOPMENT OF NOVEL AGENTS FOR THE TREATMENT OF AGGRESSIVE CANCERS:

Targeting tumor-promoting Rho GTPases as a therapeutic strategy.

Annual Congress Inspire2Live
30th November 2023

Georgina Cardama
MSc, PhD

Argentina and Cancer



Numbers at a glance

Total population

45 195 777

Number of new cases

130 878

Number of deaths

70 074

Number of prevalent cases (5-year)

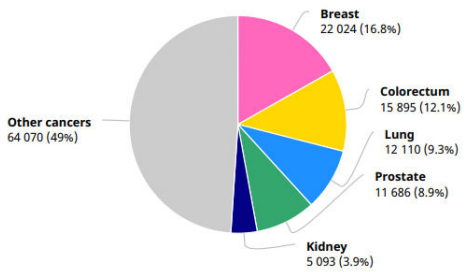
358 627

Summary statistic 2020

	Males	Females	Both sexes
Population	22 049 146	23 146 631	45 195 777
Number of new cancer cases	62 327	68 551	130 878
Age-standardized incidence rate (World)	230.7	213.3	218.2
Risk of developing cancer before the age of 75 years (%)	23.9	21.4	22.4
Number of cancer deaths	35 742	34 332	70 074
Age-standardized mortality rate (World)	126.1	92.9	106.1
Risk of dying from cancer before the age of 75 years (%)	13.1	9.8	11.3
5-year prevalent cases	159 188	199 439	358 627
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Prostate Colorectum Lung Kidney Bladder	Breast Colorectum Cervix uteri Lung Thyroid	Breast Colorectum Lung Prostate Kidney

medium to high incidence of cancer

Number of new cases in 2020, both sexes, all ages



Source: Globocan, 2020

Center of Molecular and Translational Oncology (COMTRa)

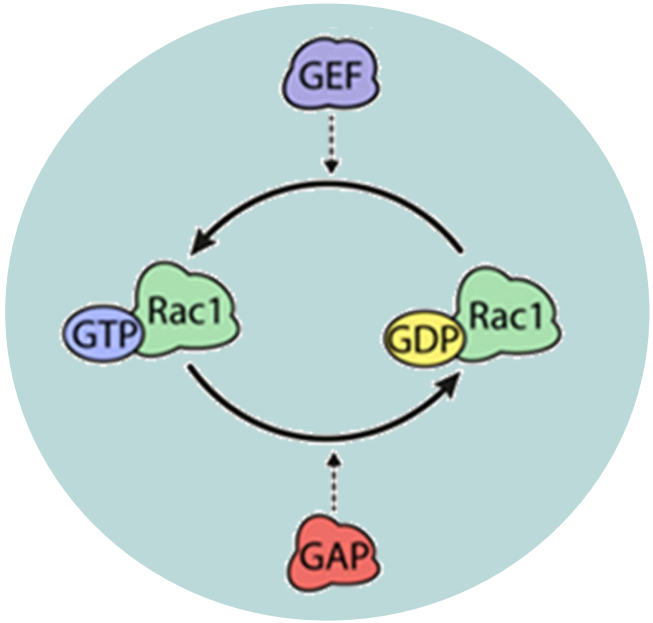
Department of Science and Technology
Quilmes National University
Bernal, Buenos Aires, Argentina.

- **Minimal Residual Disease** and cancer
- **Neuroendocrine Tumors** - Repurposing
- **Aberrant Glycosylation** in cancer – Novel Target validation
- **Phytotherapy** – Natural extracts
- **Telomerase** as therapeutic target in cancer – Repurposing and Drug discovery
- **Rho GTPases** as therapeutic targets in cancer – Drug Discovery
- **Vasopressin related genes** as therapeutic targets in cancer - Repurposing
- **NeuGC** as therapeutic target in cancer – Vaccine development
- **Beta-blockers** as therapeutic agents in oncopediatrics – Repurposing

Disclosure
Served as consultant for Chemo-romikin S.A (2018-2021) and Mabxience S.A.U (2021- 2023).

Rho GTPases

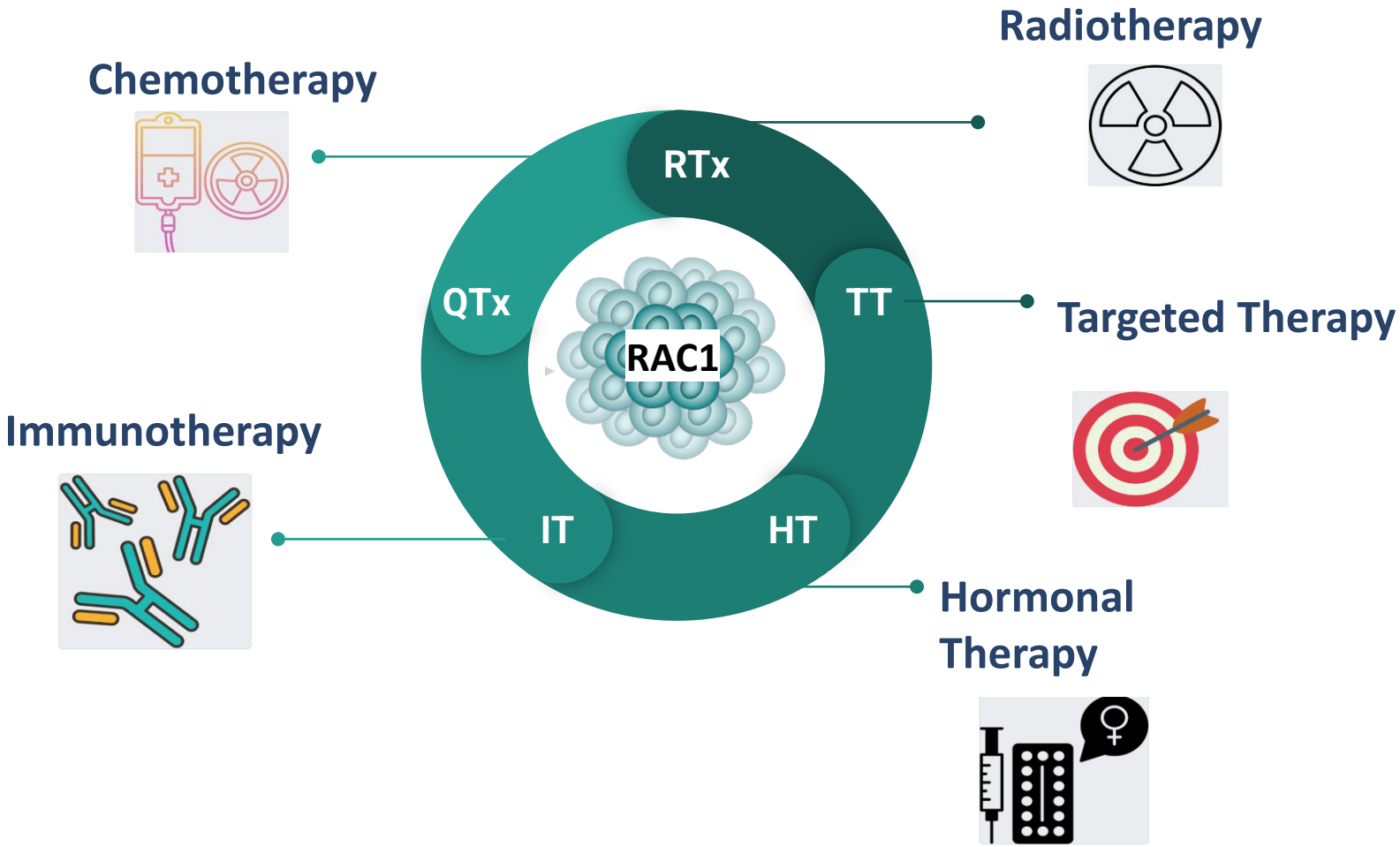
- Molecular **Switches**: on/off
- **Rac1,** Cdc42 and Rho: most studied members
- **Signaling pathways** involved in:
  - Apoptosis
  - Cell Growth
  - Cell migration and invasion
  - Angiogenesis



Rac1 in cancer

- **Overexpression** and/or overactivation in various types of cancer
- Involved in **cancer progression**
- **Prognostic factor** in various cancer types.
- Involved in **treatment resistance**

Rac1 and therapy resistance



Cardama et al, *Crit Rev Oncol Hematol*., 2018

Rac1 as a drug target

Target Validation

- Key molecule in cancer progression and metastasis:

Breast cancer, glioblastoma, colon cancer.

Drug Development

<u>Repurposing:</u>

- **Azathioprine**
- **R-ketorolac / R-naproxen**

.

<u>De novo Drug Discovery</u>

- 1A-116

Preclinical development

In vitro and *in vivo* settings with translational relevance

De novo drug discovery

Rac1

Rac1 inhibitor

Docking-based VLS

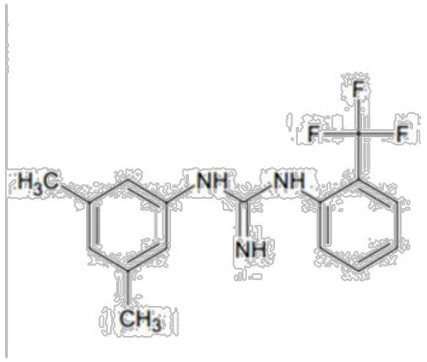
Public data base

ZINC

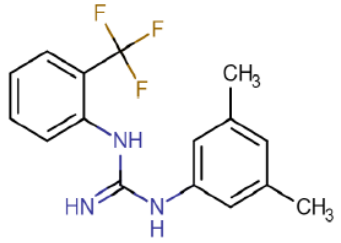
Over 200.000 drug-like compounds

Candidates

Rational optimization



1A116



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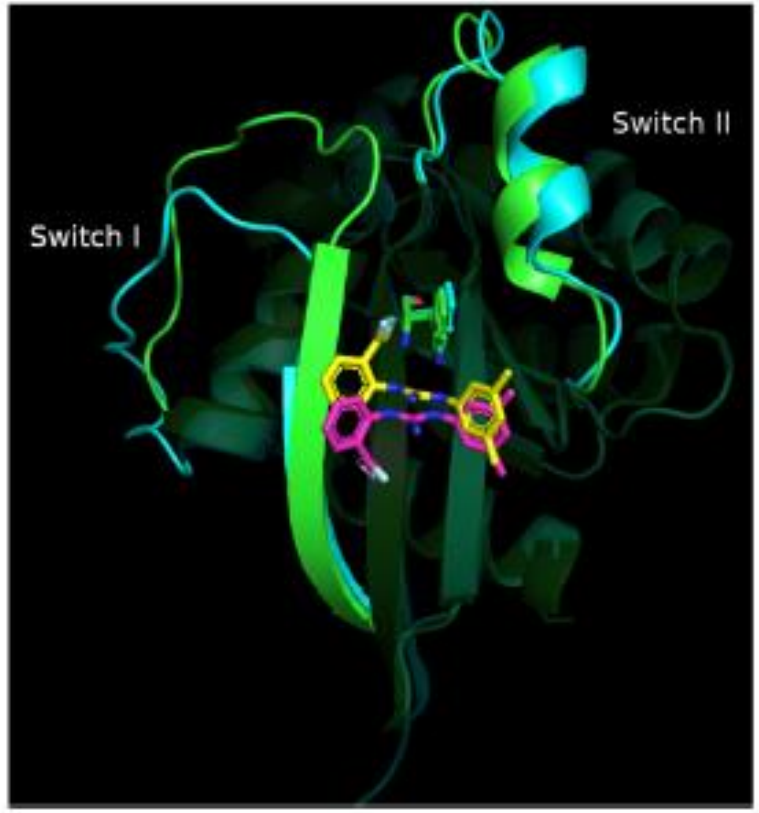


Public-private partnership

Universidad Nacional de Quilmes

CHEMO ROMIKIN

mAbxience
From lab to life

1A-116 physicochemical properties

Property	Value
MW ($g.mol^{-1}$)	307.32
logP	4.67
Rotatable bonds	3
Rings	2
H-bond donors	2
H-bond acceptors	3
Polar surface area ($Å^2$)	50.41

- GMP compound
- Scalable synthesis route
- Possible oral formulation

Cardama *et al,* Anticancer Agents Med Chem., 2014
Gonzalez et al, *Front Cell Dev Biol*., 2020

1A-116 toxicology

Acute Toxicity

Administration route	MTD (Maximum Tolerable Dose)	Preliminary LD_{50}
Oral	200-400 mg/kg	>800 mg/kg
I.V	4-8 mg/kg	Not defined
I.P	40-80 mg/kg	98 mg/kg

Sub-acute Toxicity

Route	Schedule	Doses	Observations
Oral	Daily for 28 days	2.5 mg/kg	- Normal increase of body weight - No deterioration of body condition - No significant changes in hematological determinations - Normal organ weight
		10 mg/kg	
		50 mg/kg	
I.V	3 times/weeks for 4 weeks	0.1 mg/kg	
		0.2 mg/kg	- Increased blood sugar - Accumulation of glycogen in the liver
		1 mg/kg	

1A-116 PK

In silico predictions

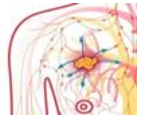
- 1A-116 is predicted to:
  - Penetrate the Blood–Brain Barrier
  - Exert high gastrointestinal absorption
  - Not to be a P-gp substrate

P-gp in cancer cells is a major cause of resistance to chemotherapy

Cardama et al, Cancers (Basel), 2022

Rac1 and 1A-116 in different cancer types

Breast Cancer



Combination with **endocrine therapies**
Gonzalez et al, Cell Signal. 2017

Combination with **anti HER-2** therapies
(Dr. Fiszman, Instituto Roffo)

Glioblastoma

Combination with chemotherapy (TMZ)

Combination with anti-EGFR agents

Chronopharmacology 1A-116
Trebucq et al, Pharmaceutics. 2021

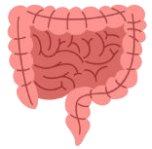
Leukemia

1A-116 in AML
Cabrera et al, Oncotarget., 2017

Kaposi Sarcoma

Rac1 in KS malignant transformation.

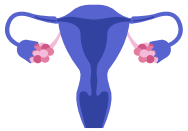
Colorectal cancer



Combination with chemotherapy: 5-FU, OXA

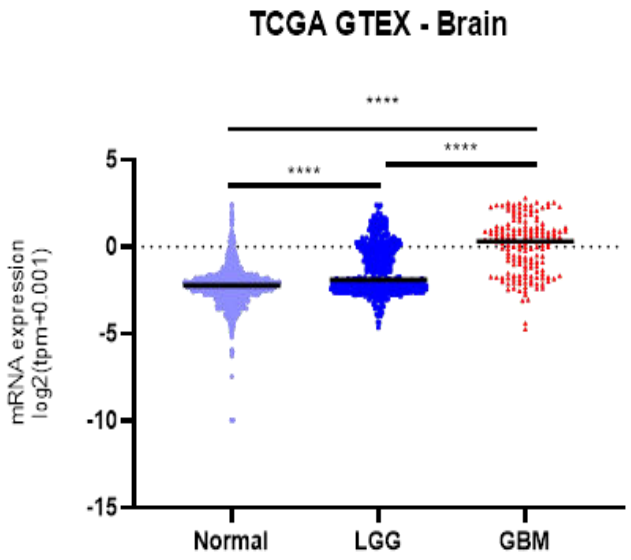
Combination with immunotherapy (ICIs) in pMMR cancer

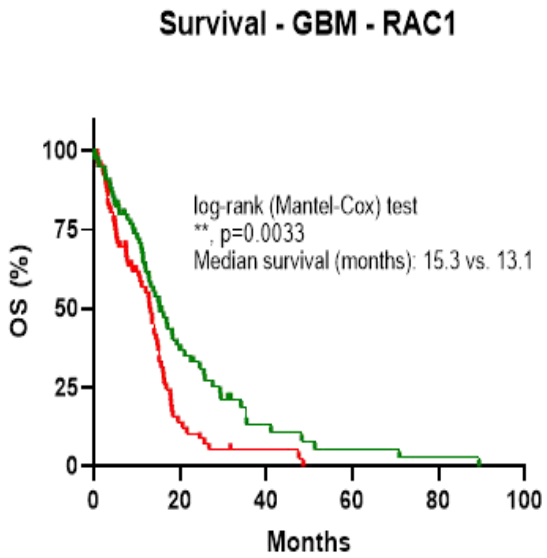
HPV-positive cervical cancer

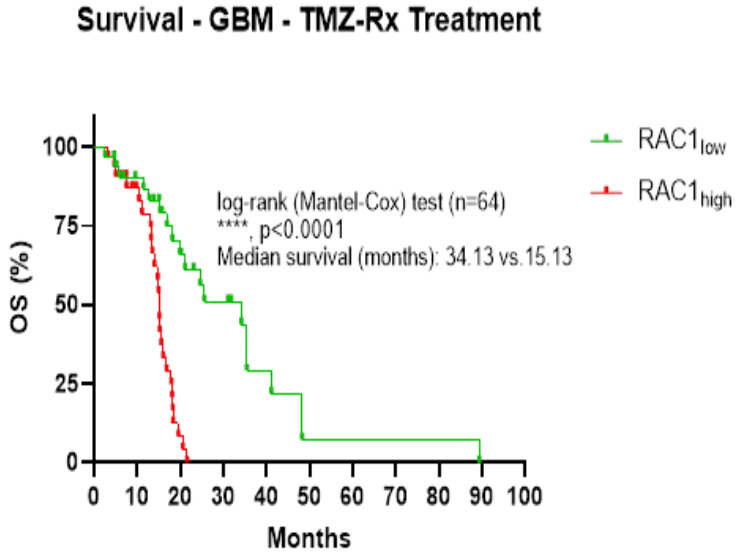


1A-116 as potential therapeutic agent in HPV-positive cervical cancer

Rac1 expression in glioblastoma (GBM) patients







RNA-Seq expression data of Rac1 (Illumina HiSeq 2000 RNA sequencing platform) from 420 low-grade gliomas (LGG, IDH1 mutated (mIDH1) samples and 154 GBM samples were obtained from The Cancer Genome Atlas (TCGA) and analyzed using the UCSC Xena browser

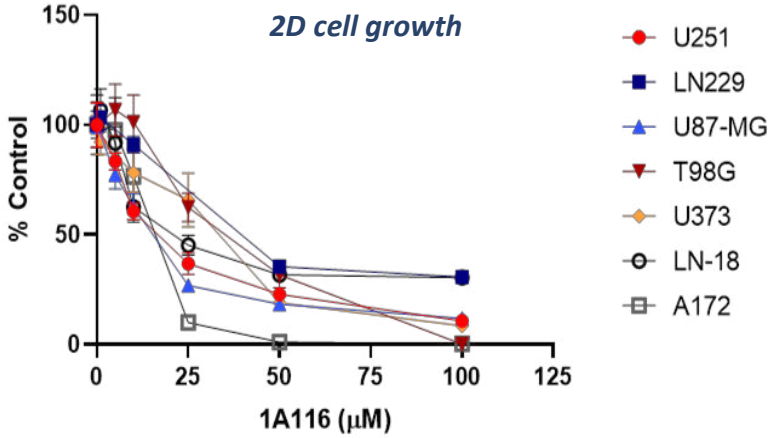
Cardama et al, Cancers (Basel), 2022

Preclinical evaluation of 1A-116 in GBM

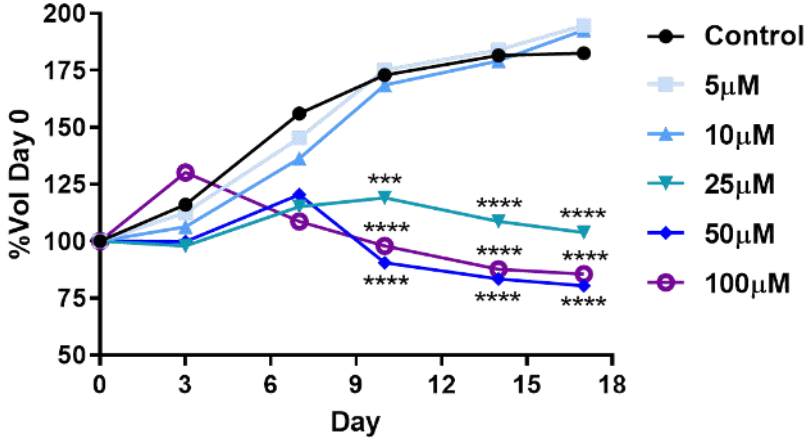
In vitro

GBM Cell lines

2D cell growth

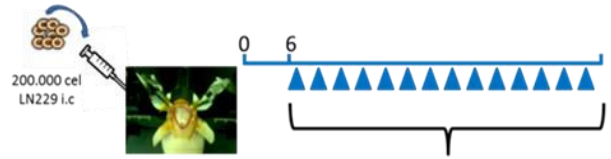


3D cell growth

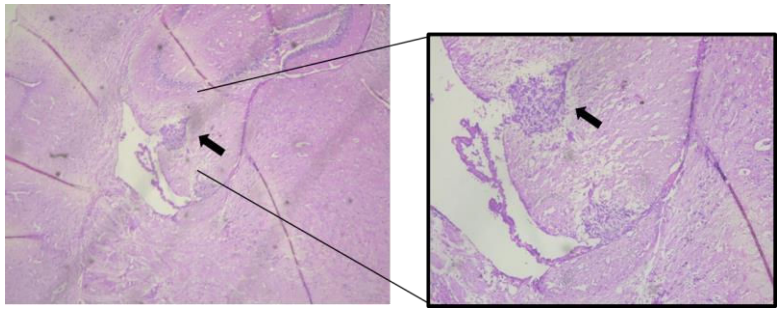


In vivo

Orthotopic intracraneal model



1A-116

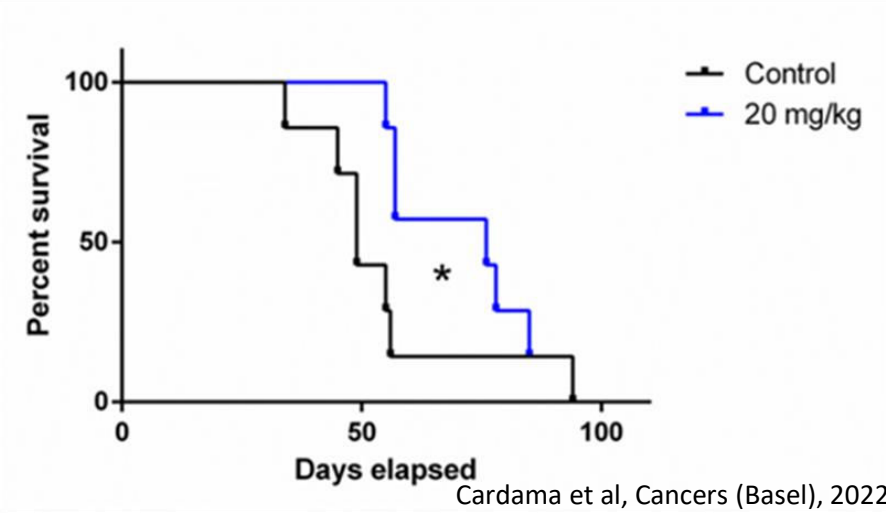


LN229 cells were orthotopically implanted in mice striatum

genotyping using MLPA.

Gene name		Status
IDH1	variant R132H	N/D
	variant R132C	N/D
IDH2	variant R172K	N/D
	variant R172M	N/D
PDGFRA		Normal
EGFR	wt	Amp (r=1.5)
	vIII	N/D
CDKN2A		Del
PTEN		Normal
CDK4		Amp (r=1.47)
MIR26A2		Amp (r=1.38)
MDM2		Normal
NFKBIA		Normal
TP53		normal

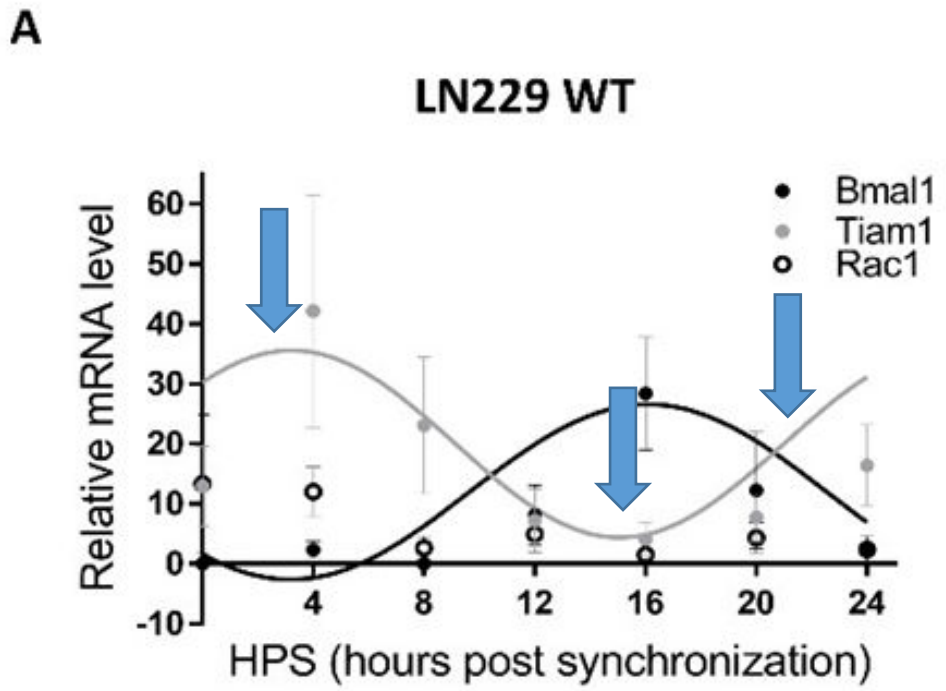
Median Survival (Days)		% increase vs. control
Control	49	0%
5 mg/kg/day	49	
Control	50	10%
10 mg/kg/day	55	
Control	49	55%
20 mg/kg/day	76	

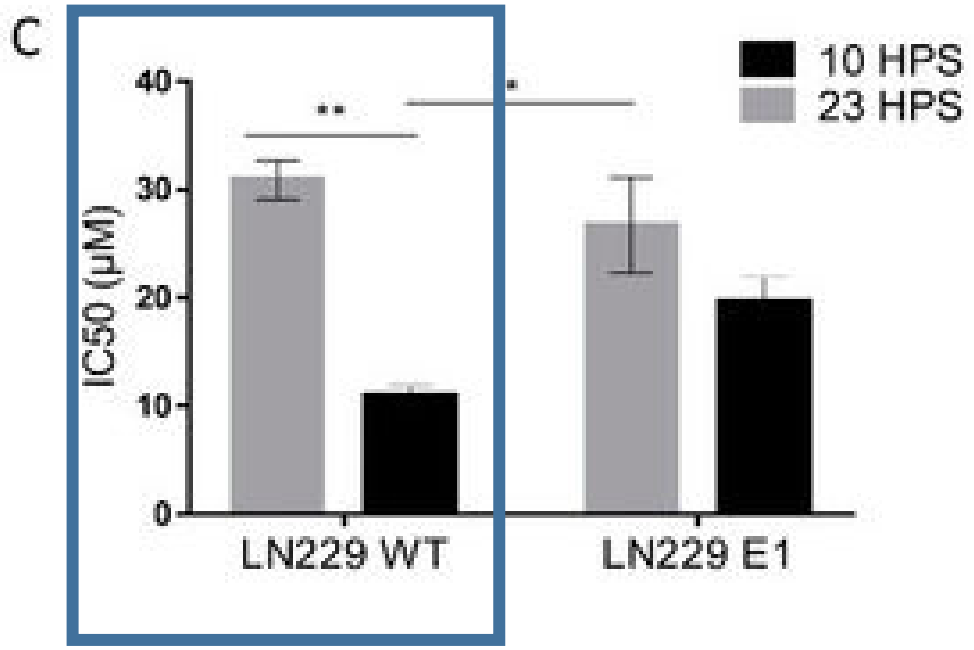


Cardama et al, Cancers (Basel), 2022

Chronopharmacology of 1A-116 in GBM

Effectiveness of 1A-116 could be further improved by finding the **best time** for delivery





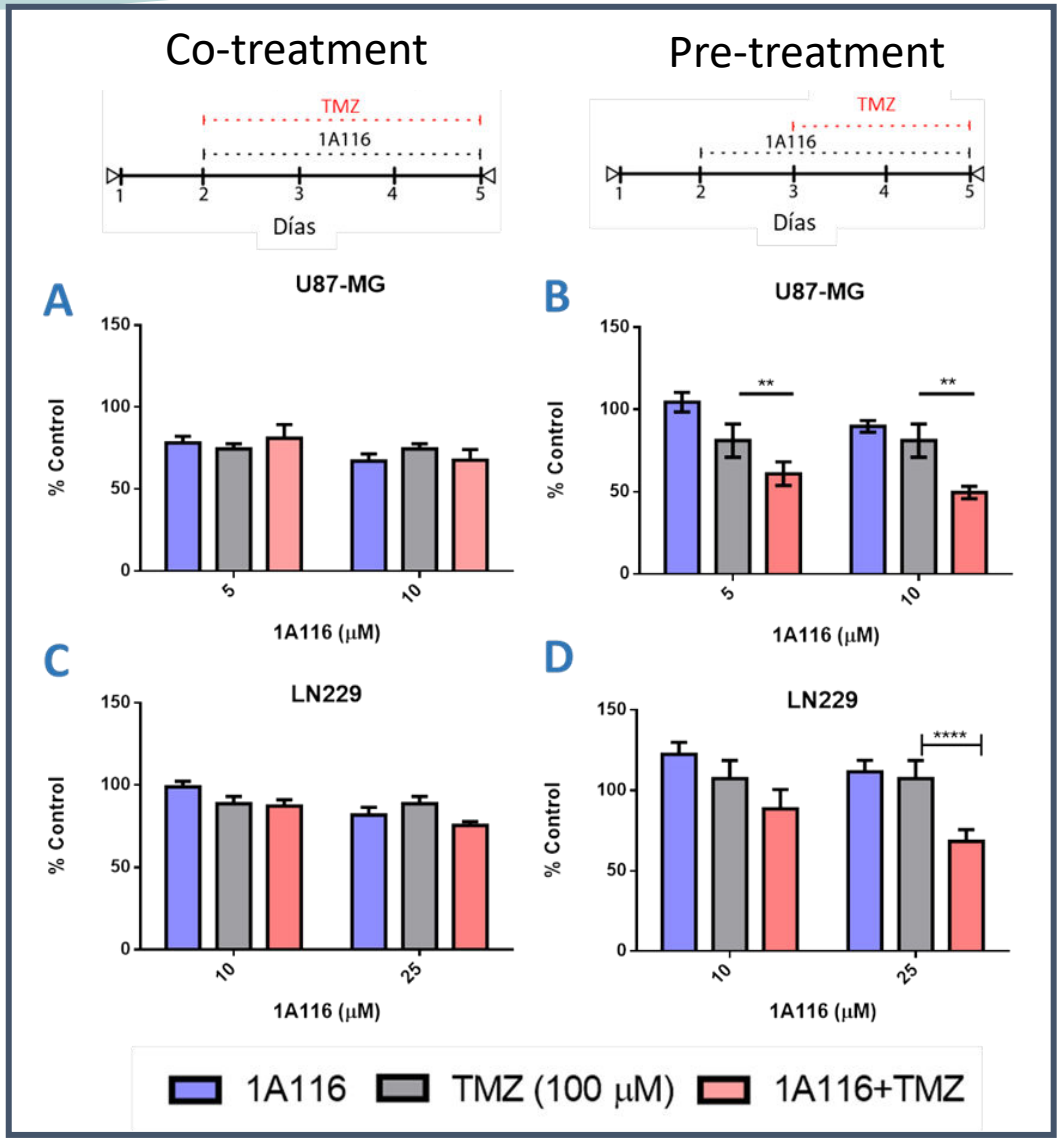
controlling administration time leads to lower toxicity and higher efficacy

Collab with Chronobiology Lab - UNQ

Trebucq et al, Pharmaceutics, 2021

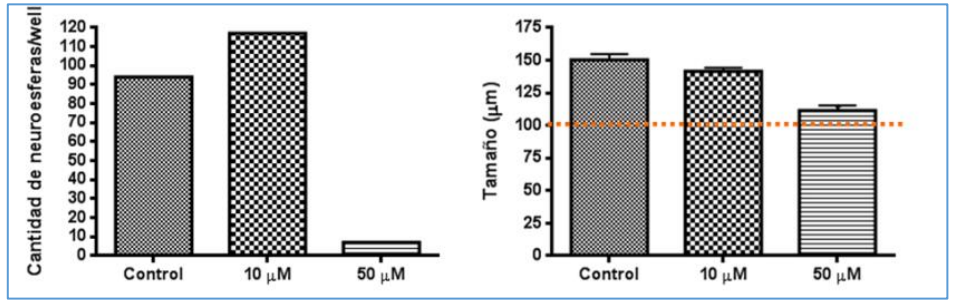
1A-116 and chemoresistance in GBM

1A-116 and TMZ combination



1A-116 inhibits GS-like Cells

Neurospheres



- **1A-116 as a biomodulator for TMZ activity**

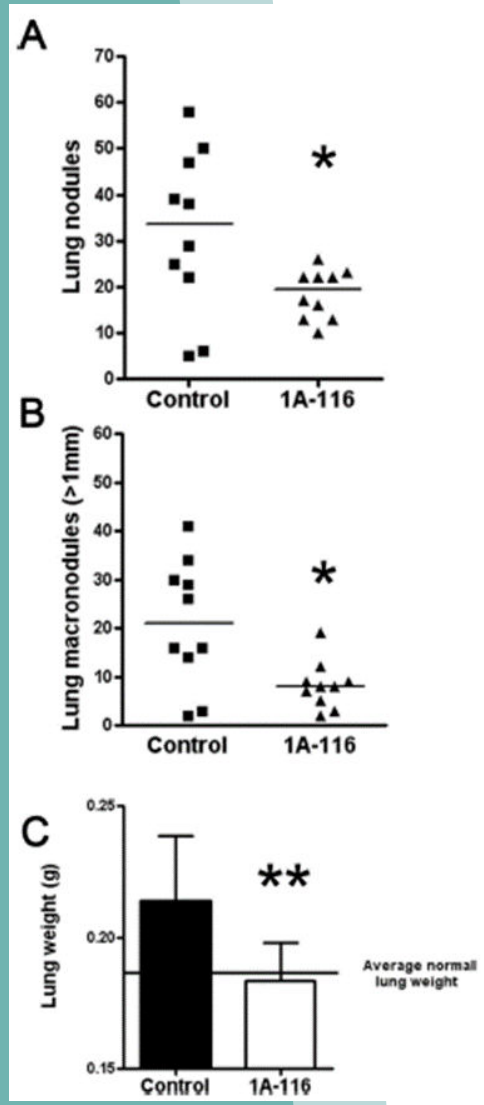
Potentiate efficacy, lower therapeutic doses, affecting resistant cells

- **Looking for the maximum therapeutic index**

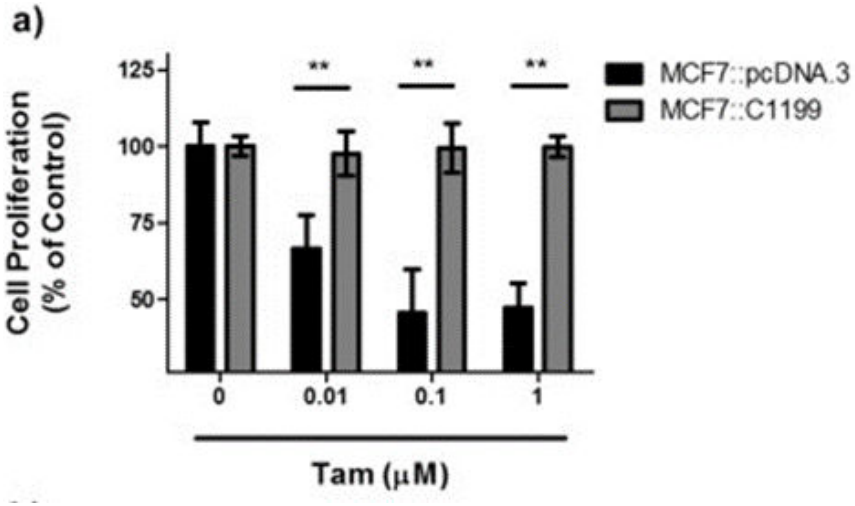
(the largest ratio between desired and side effects)

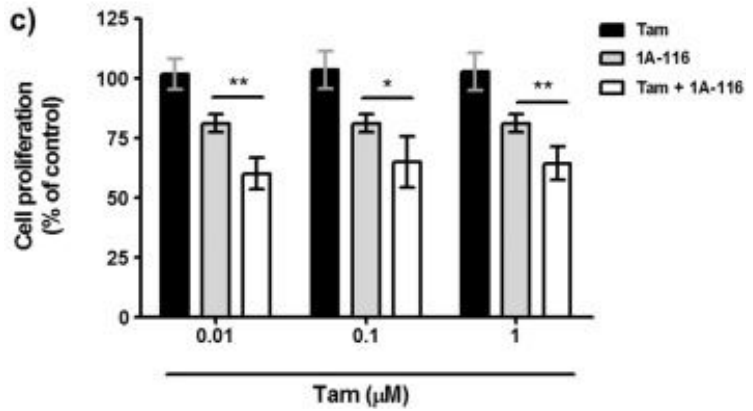
1A-116 restores tamoxifen sensitivity in human resistant breast cancer cells

Mammary carcinoma Metastasis
(Experimental Metastasis Model)



Rac1 overactivation involved in Tam Resistance

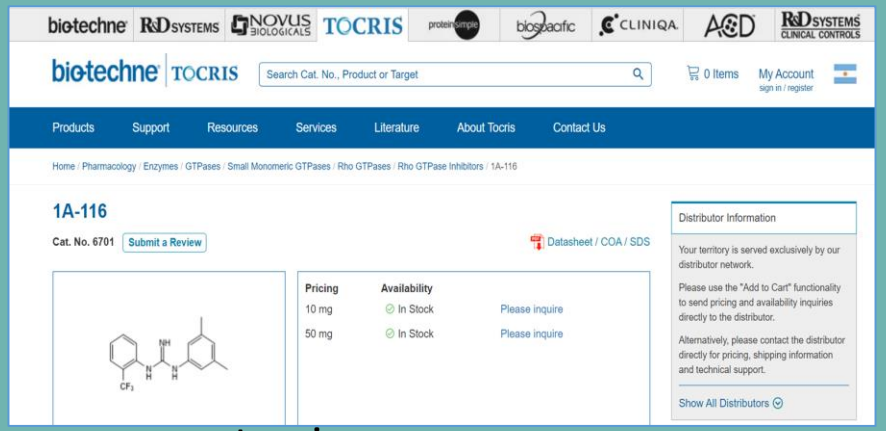




*1A-116 could serve as a **resensibilization agent for acquired resistance to Tamoxifen** treatment in breast cancer*

Gonzalez et al, Cell Signal. 2017
Cardama *et al,* Anticancer Agents Med Chem., 2014

License: 1A-116 commercially available for non clinical investigation



www.tocris.com

www.nature.com/onc

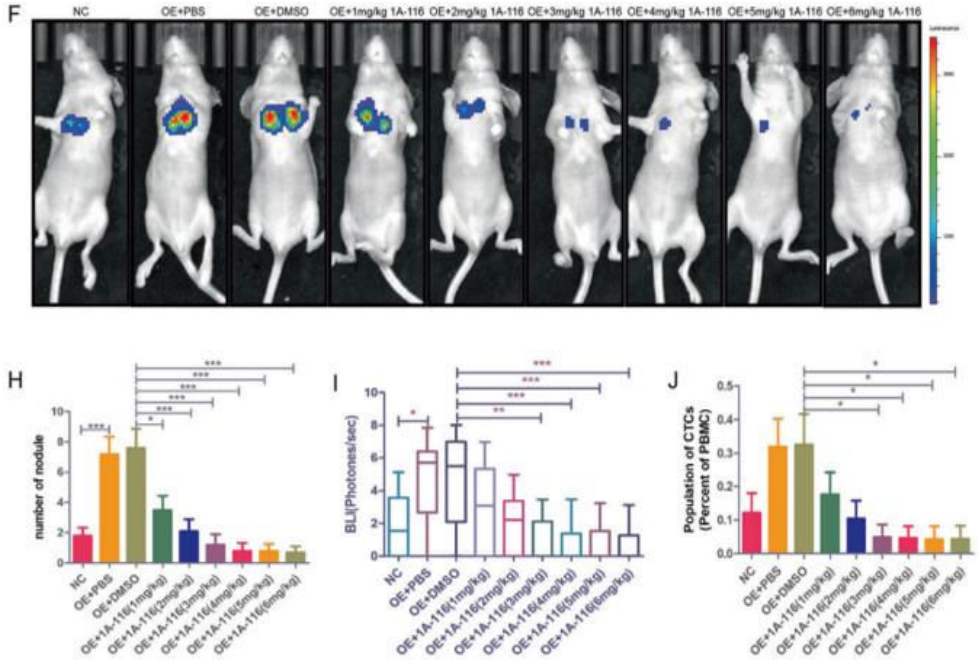
Oncogene

ARTICLE OPEN

Check for updates

Fermitin family member 2 promotes melanoma progression by enhancing the binding of p-α-Pix to Rac1 to activate the MAPK pathway

Shaobin Huang[1,2,3,5], Wuguo Deng[2,5], Peng Wang[1,5], Yue Yan[2], Chuanbo Xie[2], Xiaoling Cao[1], Miao Chen[2], Changlin Zhang[2], Dingbo Shi[2], Yunxian Dong[1], Pu Cheng[1], Hailin Xu[1], Wenkai Zhu[4], Zhicheng Hu[1✉], Bing Tang[1✉] and Jiayuan Zhu[1✉]



Open Access Article

NPM1-Mutated Patient-Derived AML Cells Are More Vulnerable to Rac1 Inhibition

by Anette Lodvir Hemsing [1,2], Kristin Paulsen Rye [2], Kimberley Joanne Hatfield [2,3] and Håkon Reikvam [1,2,*]

[1] Department of Medicine, Haukeland University Hospital, 5021 Bergen, Norway

Cardiovascular Drugs and Therapy
https://doi.org/10.1007/s10557-023-07442-3

ORIGINAL ARTICLE

Check for updates

Pharmacological Inhibition of P-Rex1/Rac1 Axis Blocked Angiotensin II-Induced Cardiac Fibrosis

Jianyuan Pan[1] · Ming Liu[1] · Huimin Su[1] · Hao Hu[1] · Hongwu Chen[1] · Likun Ma[1]

Accepted: 15 February 2023

Conclusions

- Rac1 is an interesting drug target
- **1A-116 is a promising therapeutic agent** in combinational therapeutic schemes
- Finding the best time for delivery can contribute to improve effectiveness

Take home messages…

- Drug discovery is feasible in LMIC
- Public-private partnerships to leverage R&D may be a good idea
- From the beginning: which group of patients would benefit from this type of therapy?
- Clinically relevant models are key component

Thank you!

Center of Molecular and Translational Oncology (COMTRa)

Centro de Oncología Molecular y Traslacional

Contact
georgina.cardama@unq.edu.ar
gcardama@gmail.com

Web
www.lomunq.com
www.psbunq.com

Argentina