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Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

Razionale per il *targeting* non convenzionale dell'attività di IDO1 nel cancro: disegno e validazione di IDO1 *degraders*

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Urbino, 17 Dicembre 2024

Spoke 8
WP1 – Accelerare la scoperta preclinica di farmaci

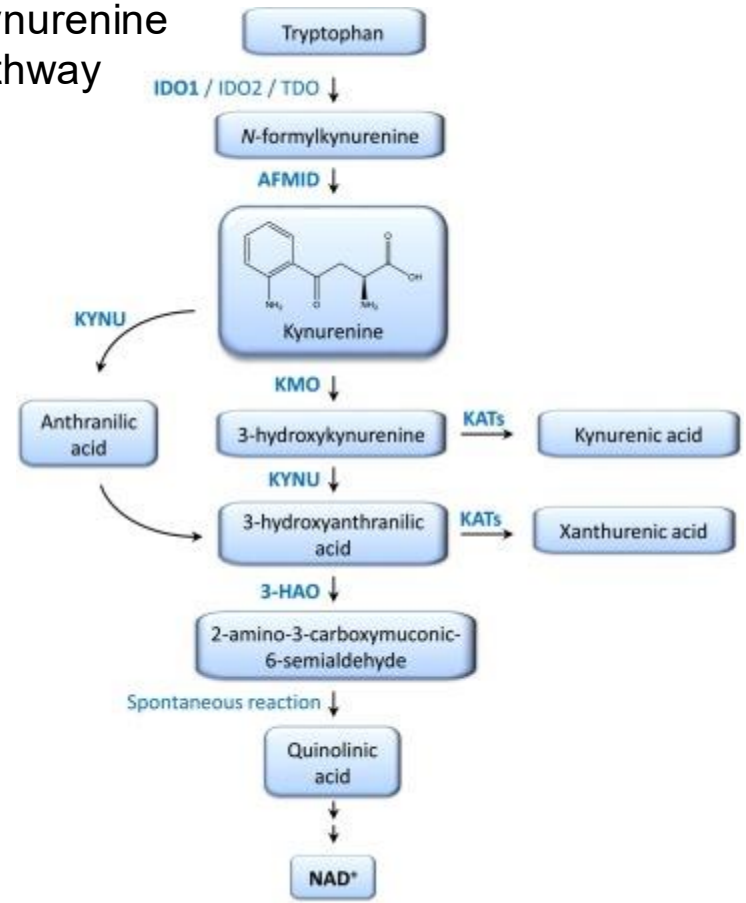
Academic participants

UniUrb	UniPg	U'dA
Giovanni Bottegoni*	**Antimo Gioiello***	**Nazzareno Re***
Andrea Duranti	Francesco Galli	Barbara Ghinassi
Gianfranco Favi	Laura Goracci	Marcello Locatelli
Emanuela Frangipani	Antonio Macchiarulo	Giovanna Murmura
Michele Mari	Ciriana Orabona	Azzurra Stefanucci
Sara Montagna	Luigi Vaccaro	Fabio Verginelli
Giovanni Piersanti	Teresa Zelante	Ester Vitacolonna
Gilberto Spadoni		

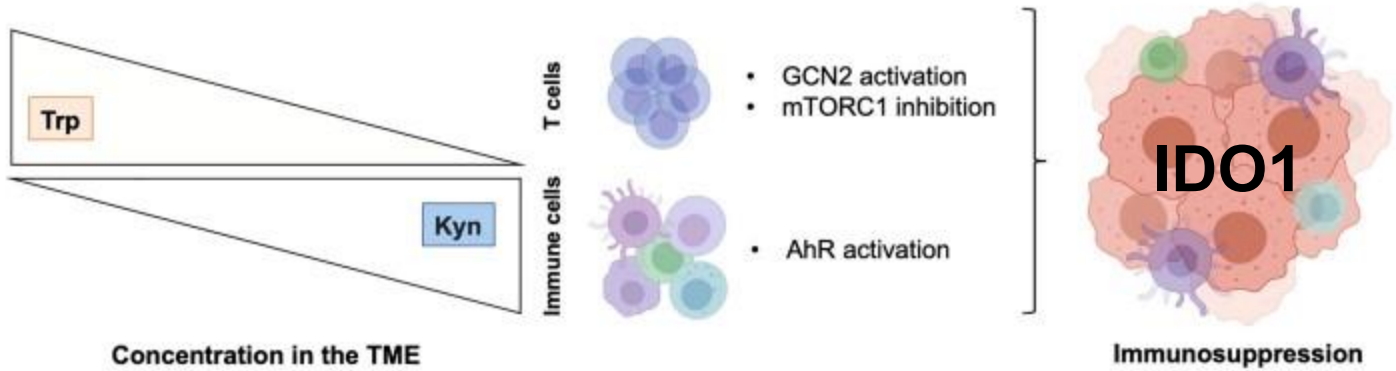
Title: **Design and development of IDO1 protein degraders**
PI: **Ciriana Orabona**

Indoleamine 2,3-dioxygenase 1 (IDO1) is a crucial tumor-escape mechanism

The kynurenine pathway



IDO1 enzyme-dependent immunosuppression in cancer



IDO1 targeting in cancer

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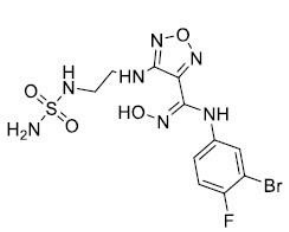
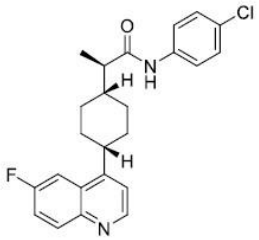
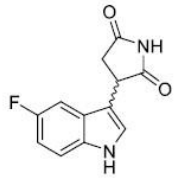
IDO1 catalytic inhibitors failed as anti-cancer drugs



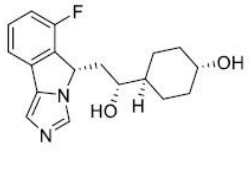
Epacadostat (Phase 3)
IDO1 IC_{50} = 73 nM
HeLa IDO1 IC_{50} = 7.4 nM



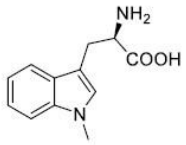
BMS-986205 (Phase 3)
IDO1 IC_{50} = 0.5 nM



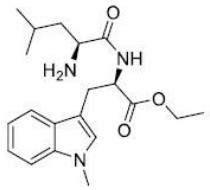
PF-06840003 (Phase 1)
IDO1 IC_{50} = 0.41 μM
HeLa IDO1 IC_{50} = 1.8 μM



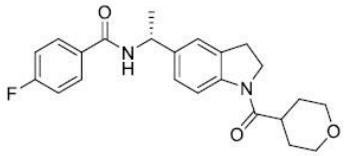
Navoximod (Phase 1)
IDO1 IC_{50} = 28 nM



Indoximod (Phase 3)
IDO1 K_i = 34 μM



NLG802 (Phase 1)



LY3381916 (Phase 1)
IDO1 IC_{50} = 7 nM

IDO1 catalytic inhibition in cancer

2018
Epacadostat failed in the phase III clinical trial ECHO-301/KEYNOTE-252

Why?

Annual Review of Cancer Biology

Is There a Clinical Future for IDO1 Inhibitors After the Failure of Epacadostat in Melanoma?

Benoit J. Van den Eynde,[1,2,3] Nicolas van Baren,[2] and Jean-François Baurain[4,5]

- Partial inhibition of IDO1 catalytic activity?
- Compensatory expression of TDO and IDO2?
- Activation of AhR by epacadostat?
- Selection of patients for tumoral IDO1 expression?
- Anti-PD1 therapy as a wrong combination?
- **Non-catalytic effects of IDO1?**

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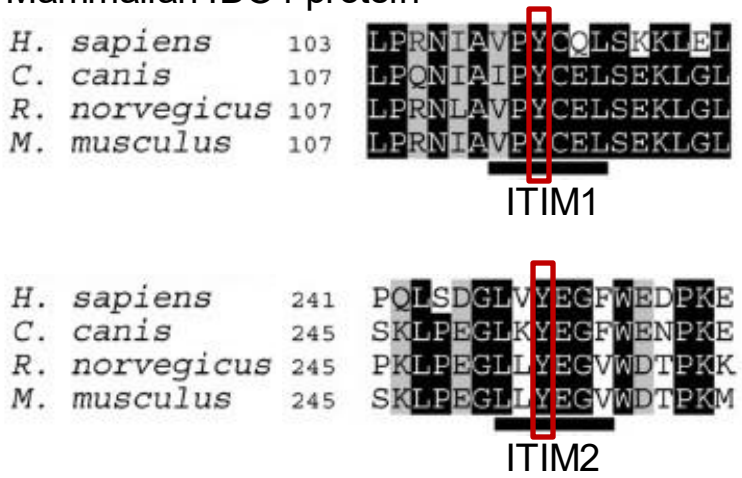
Italiadomani VITALITY

Non-enzymatic effects of IDO1

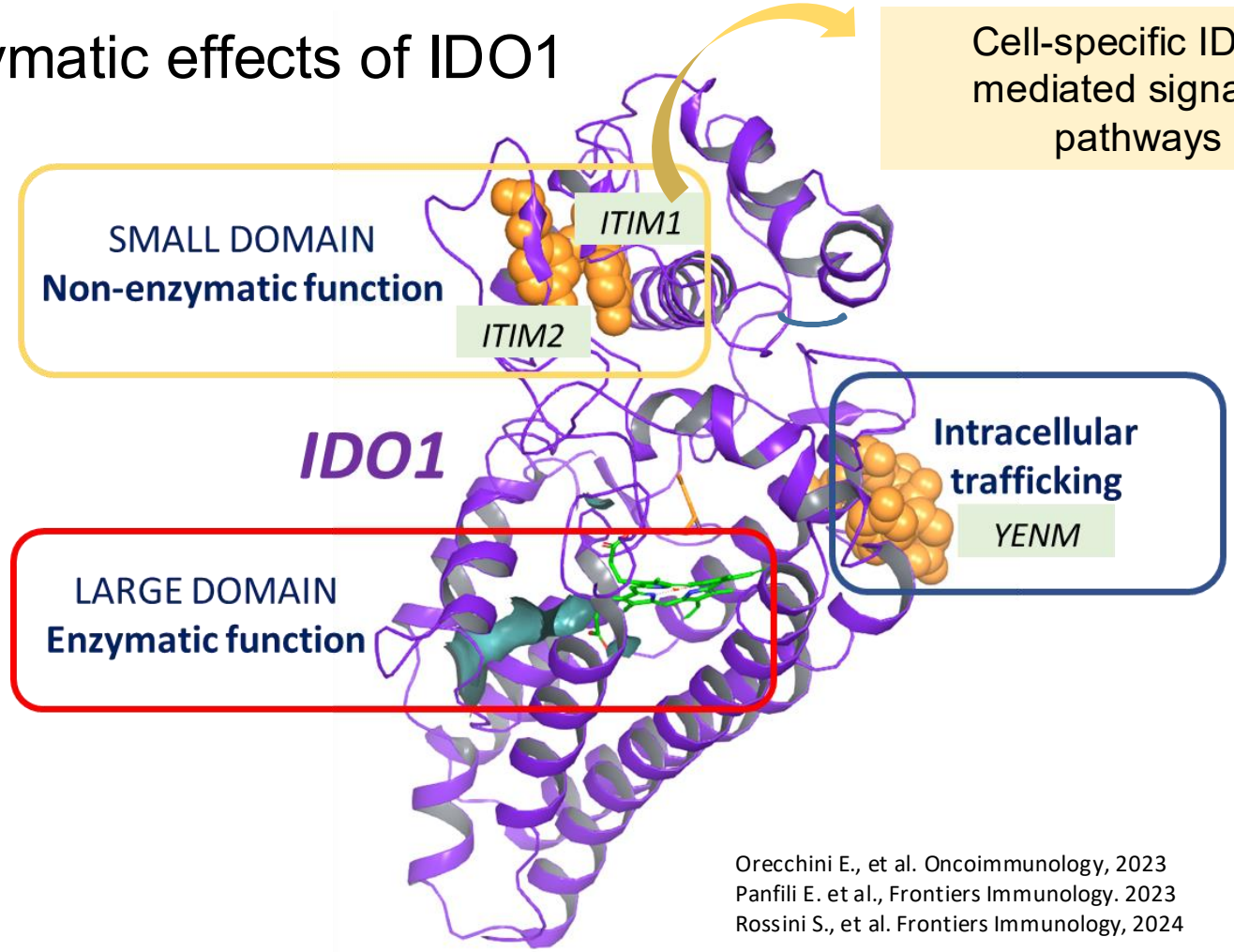
Immunoreceptor Tyrosine-based Inhibitory Motif (ITIM) consensus sequence

I/V/L/SxYxxL/V/F

Mammalian IDO1 protein



Orabona C. et al., Proc Natl Acad Sci U S A. 2008
Orabona C. et al., Mol Med. 2012 Jul 18;18(1):834-42.



Orecchini E., et al. Oncoimmunology, 2023
Panfili E. et al., Frontiers Immunology. 2023
Rossini S., et al. Frontiers Immunology, 2024

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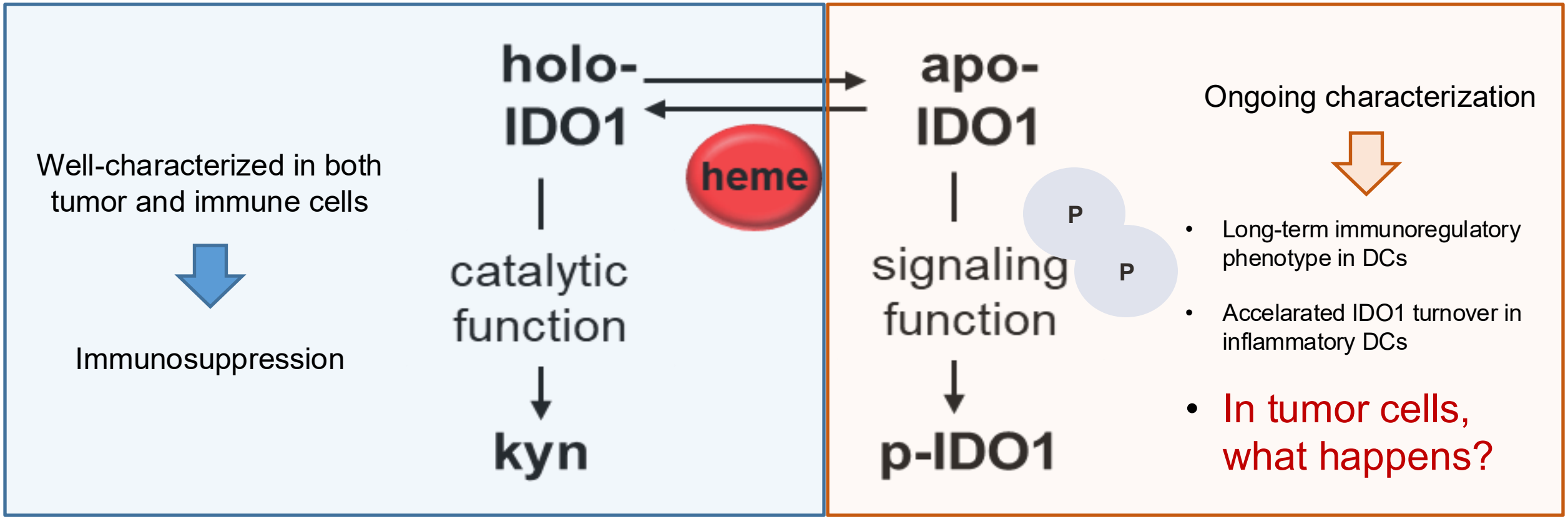
DISTINCT IDO1 CONFORMATIONS MEDIATE DISTINCT IDO1 FUNCTIONS



Dynamical balance between holo-/apo-conformations of IDO1

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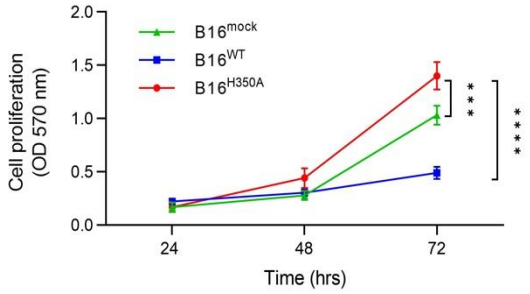
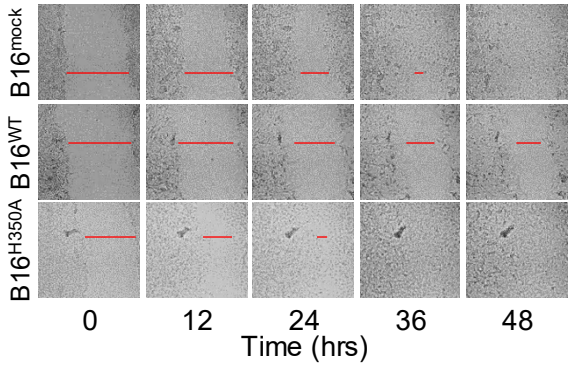
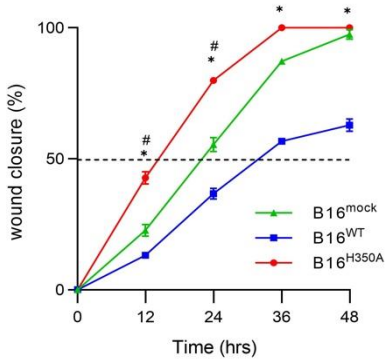
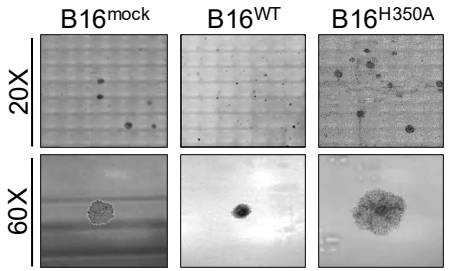
The non-enzymatic IDO1 confers a pro-tumorigenic phenotype to B16 melanoma cells

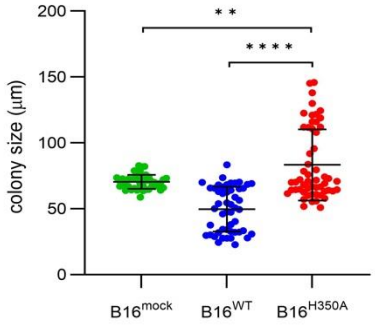
In vitro tumor growth and migration

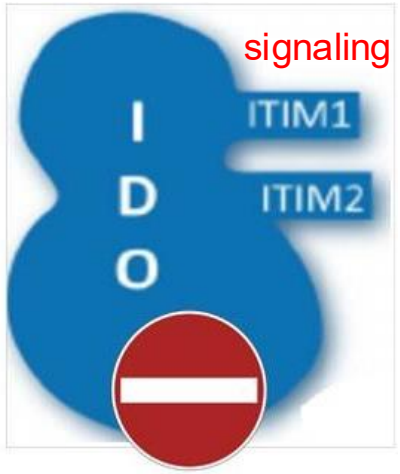








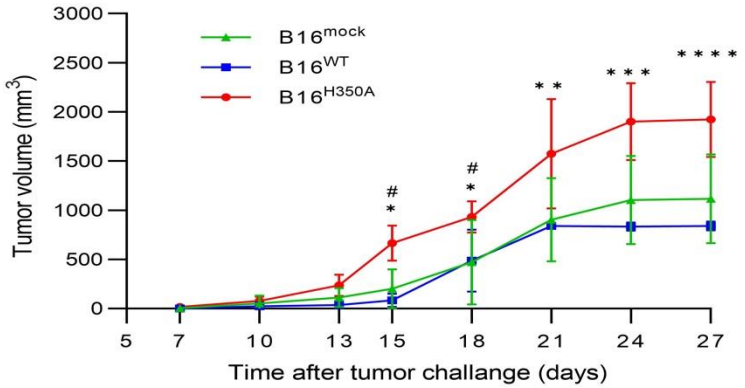


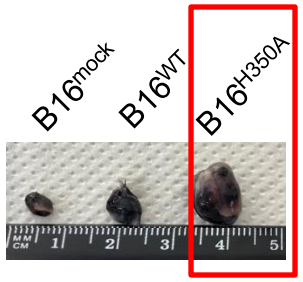


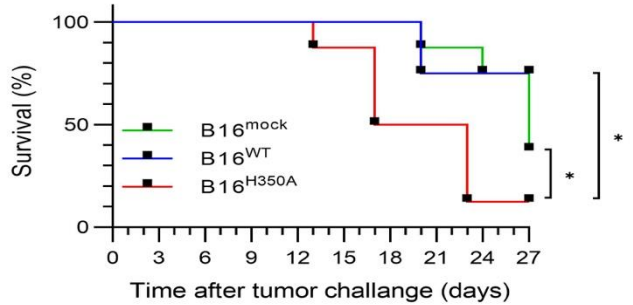
signaling function

catalytic function

In vivo tumor growth and survival







Orecchini E., et al., Oncoimmunology, 2023

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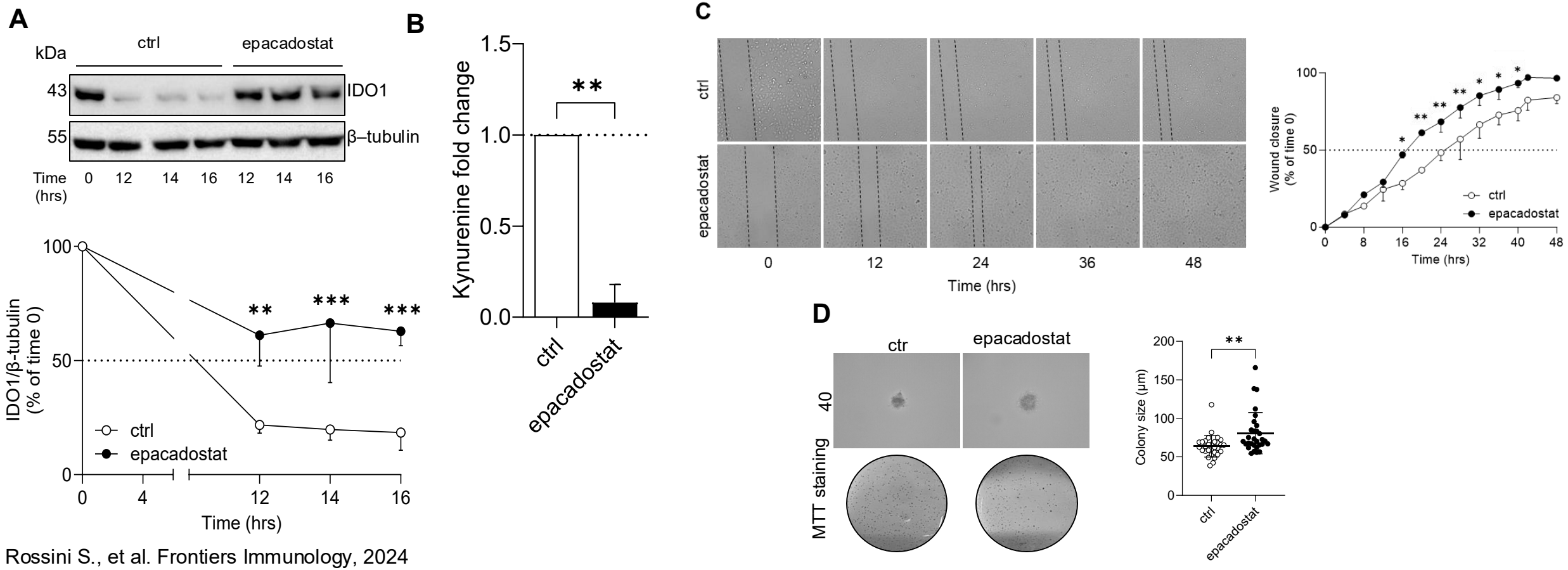
Epacadostat signals a protumorigenic pathway in human ovarian cancer cells (SKOV-3) via IDO1 protein stabilization



Rossini S., et al. Frontiers Immunology, 2024

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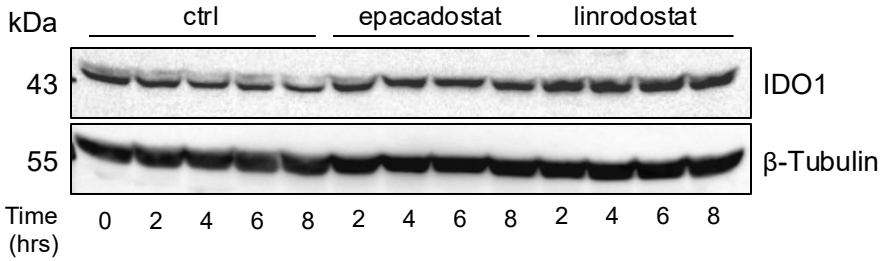
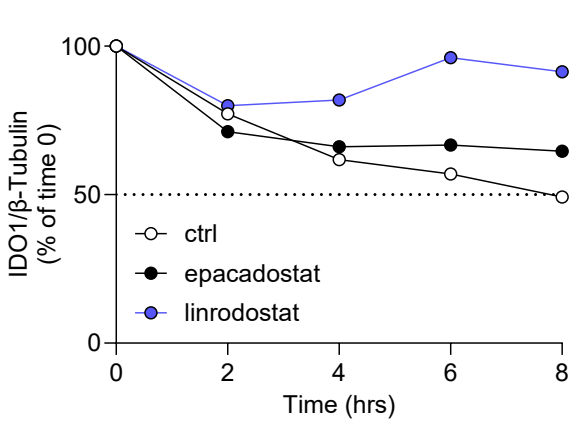
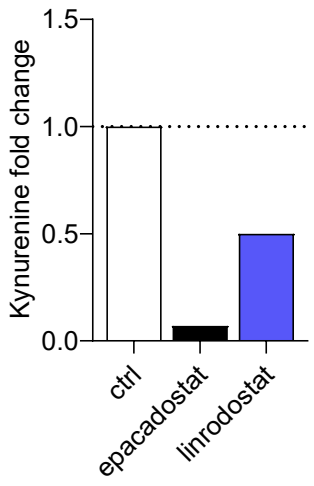
IDO1 catalytic inhibitors stabilize IDO1 in different human tumor cell lines

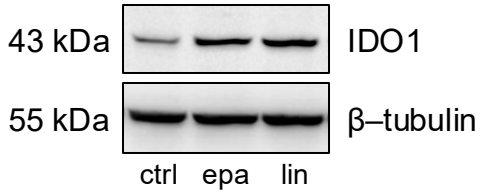
Follicular thyroid carcinoma cell line (FTC-133)

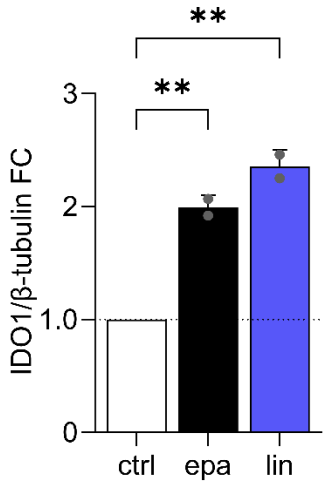


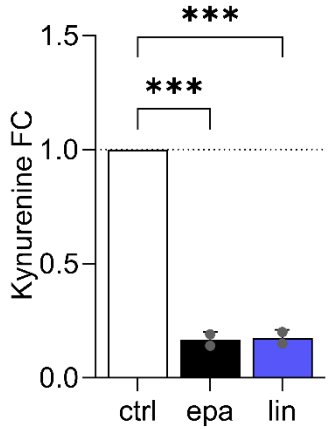




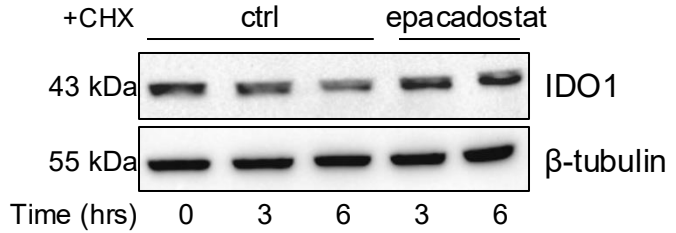
Papillary thyroid cancer cell line (B-CPAP)

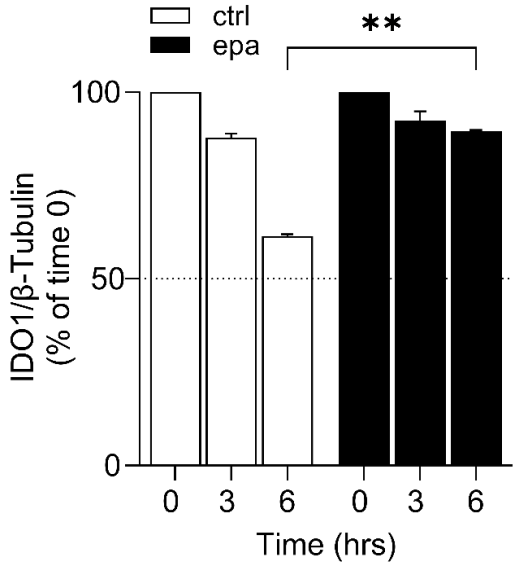






B cell lymphoma (RC-K8)





Unpublished data

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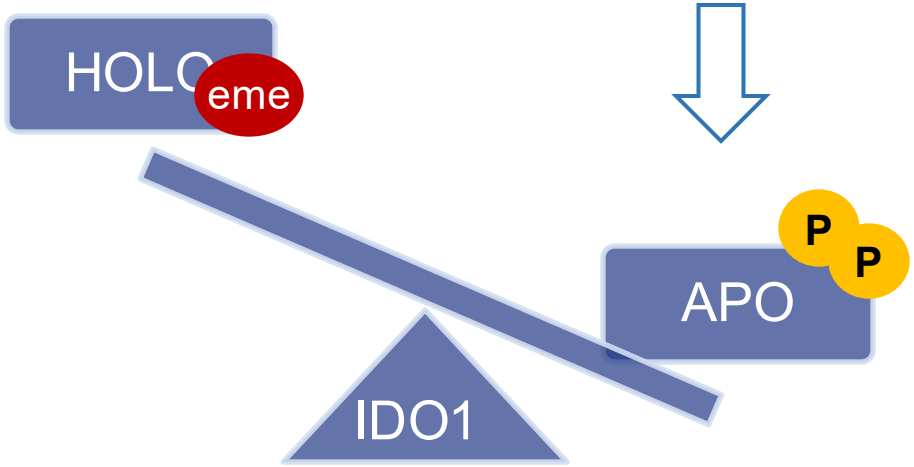
TAKE HOME MESSAGES

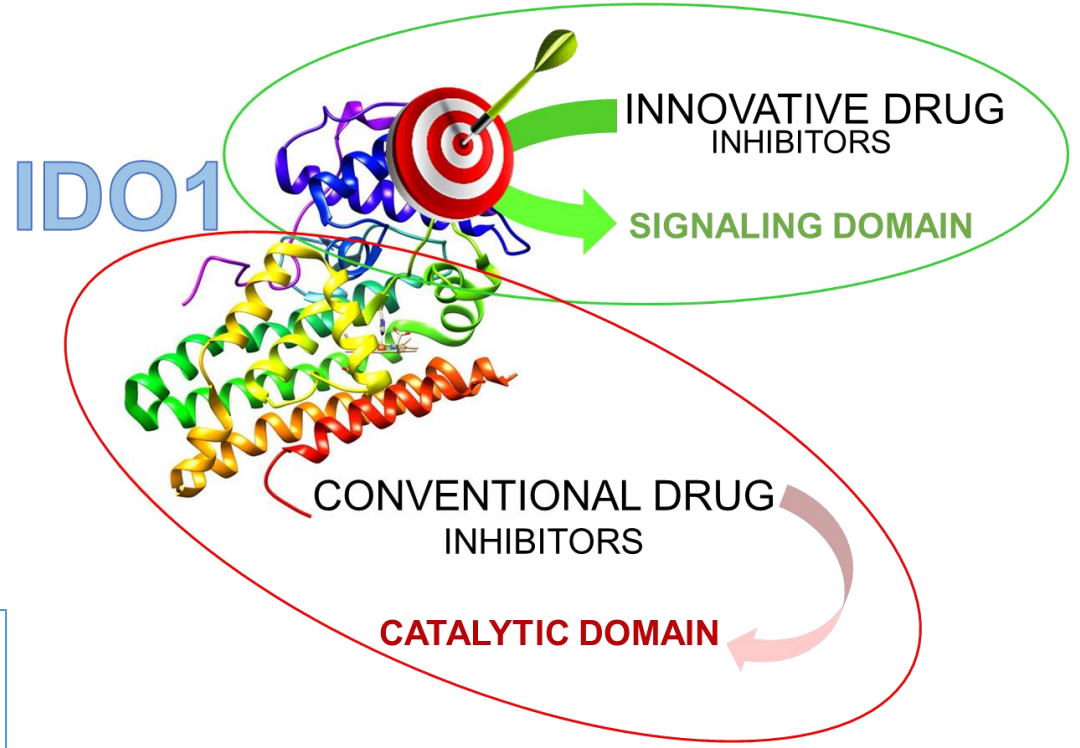
IDO1 catalytic inhibitors stabilize the apo-IDO1 in human tumor cell lines



Protumorigenic signaling pathways

Failure of IDO1 catalytic inhibitors as anti-cancer drug

INNOVATIVE IDO1 INHIBITORS



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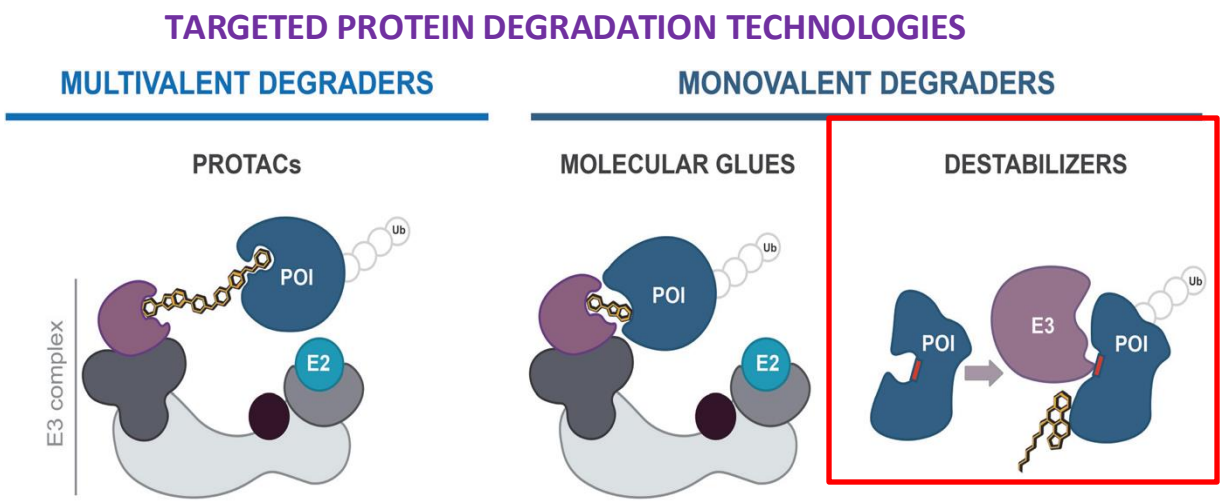
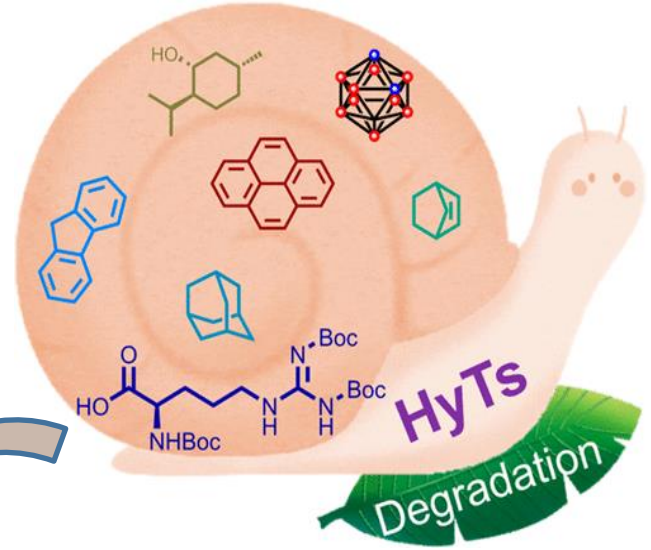
Design and development of innovative drugs for IDO1 degradation



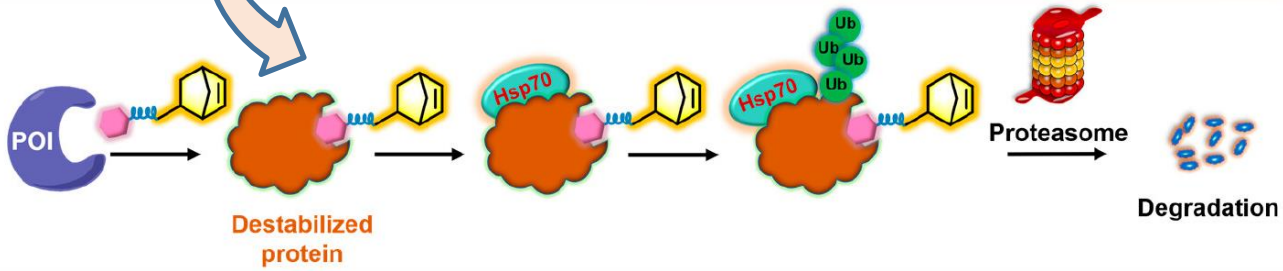
Hydrophobic Tagging



Xie et al., *J. Med. Chem.* 2023, 66, 10917−10933

HyTs vs PROTAC

- lower molecular weight
- reduced numbers of hydrogen bond donors/acceptors
- enhanced druglike properties



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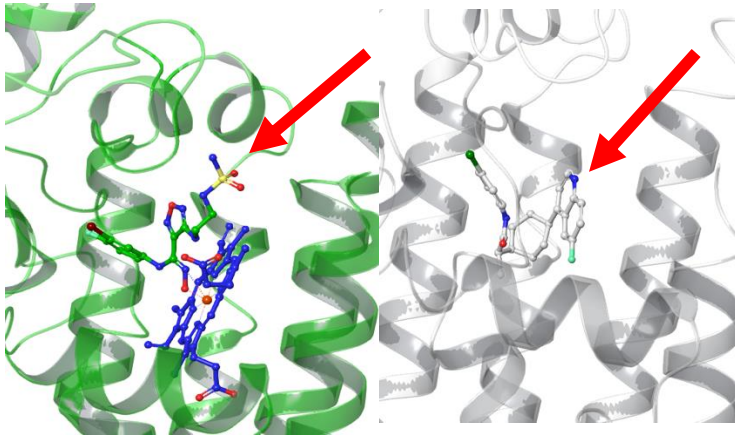
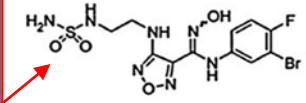
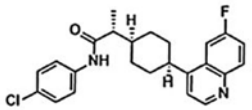
IDO1 hydrophobic tagging: rational drug design

(A. Carotti – DSF UNIPG)

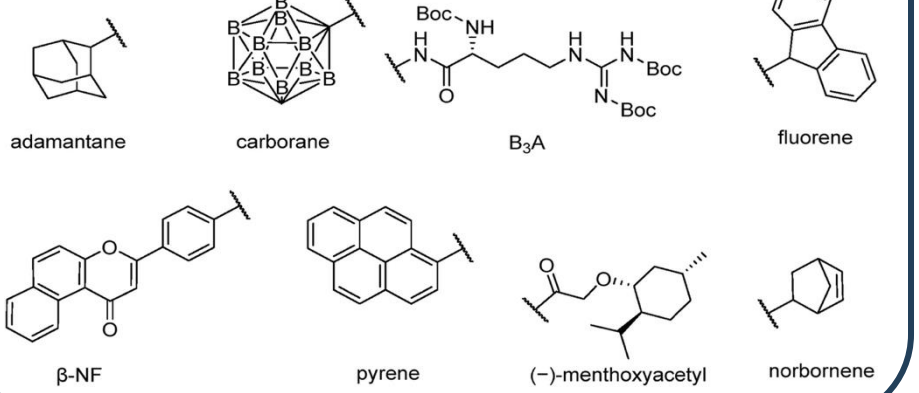
IDO1 ligands



Features	Epacadostat	Linrodostat
PDB Code	6E40	6DPQ
Heme	Interaction	Displacement

Incyte	BMS *Flexus*
Epacadostat *INCB024360*	BMS-986205 *F001287*
	
Catalytic inhibitor	Suicide inhibitor
Tryptophan c ompetitive	Irreversible
12 nmol/L	2 nmol/L
>100-fold	>100-fold
2012	2015
Phase III	Phase II
Epacadostat	Linrodostat

Hydrophobic Tags



Priority selection criteria

- ✓ Synthetic accessibility/feasibility
- ✓ Molecular modeling results (Docking/Molecular dynamics)
- ✓ PK/PD predicted profiles
- ✓ Intellectual Property

Putative regions to modify with hydrophobic tags in order to reach the protein surface and activate the proteasome degradation.

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Turning Discovery Into Health

VITALITY

Italian Minister of University and Research

Grazie per l'attenzione

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