



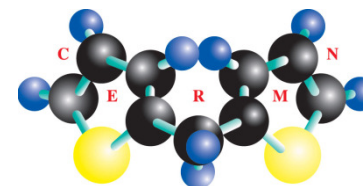
UNIVERSITÉ
CAEN
NORMANDIE



STRUCTURE-GUIDED DESIGN OF PYRIDOCLAX DERIVATIVES WITH NOXA LIKE MCL-1 BINDING PROFILE

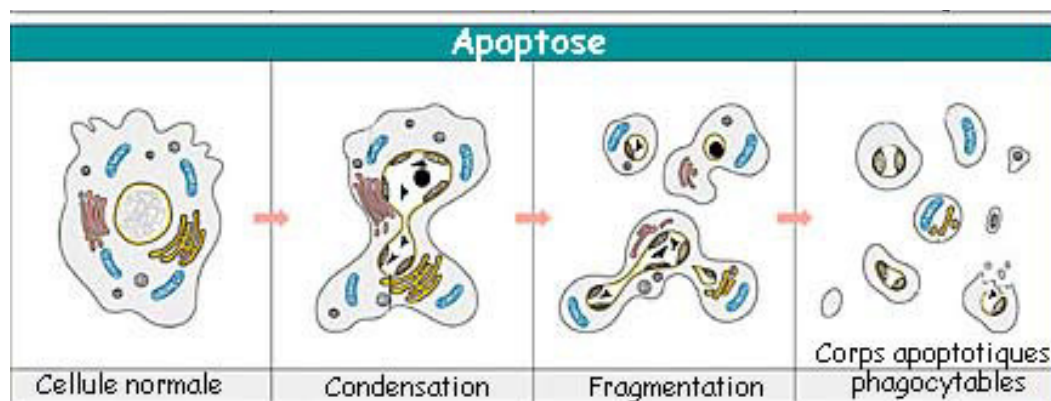
Jana SOPKOVA-DE OLIVEIRA SANTOS

Centre d'Etudes et de Recherche sur le
Médicament de Normandie



Le cancer touche 350.000 personnes par an en France et il est la première cause de mortalité.

La vie d'une cellule dépend d'un équilibre entre des facteurs moléculaires qui favorisent la survie cellulaire et des facteurs moléculaires qui provoquent la mort cellulaire.



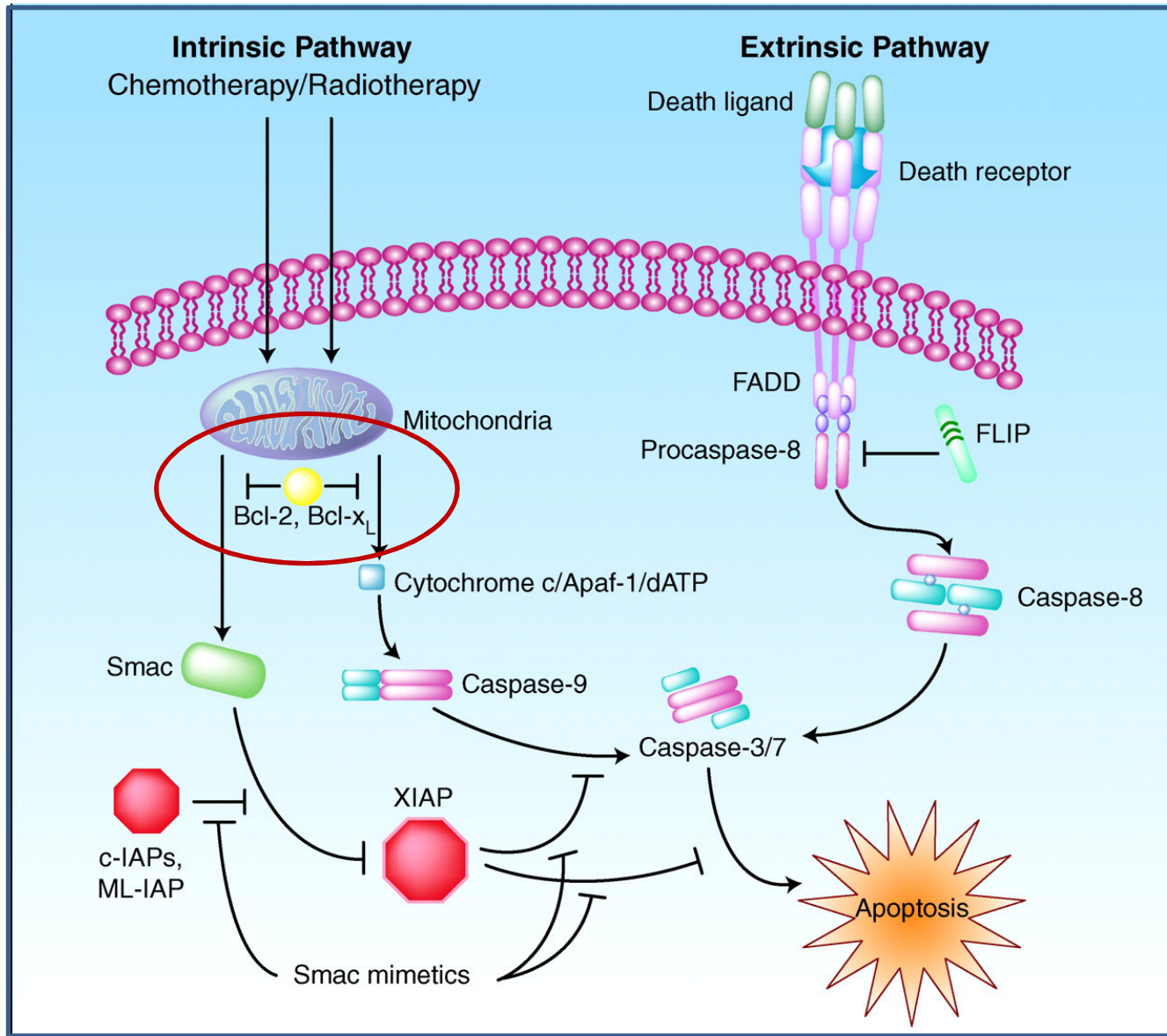
APOPTOSE OU MORT CELLULAIRE PROGRAMMÉE.

C'est un mécanisme cellulaire, normal, intrinsèquement programmé, par lequel des cellules s'autodétruisent en réponse à un signal interne.

Pour se protéger, les cellules cancéreuses inhibent les mécanismes de l'**APOPTOSE**.

- Prolifération des cellules tumorales
- Chimiorésistance

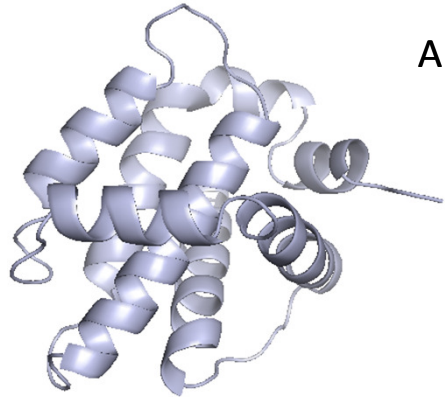
APOPTOSE



LA FAMILLE BCL-2: PORTRAIT DE FAMILLE

PROTEINES ANTI-APOPTOTIQUES

Bcl-2
Bcl-x_L
Mcl-1
A1 ou Bfl-1
Bcl-W



PROTEINES PRO-APOPTOTIQUES

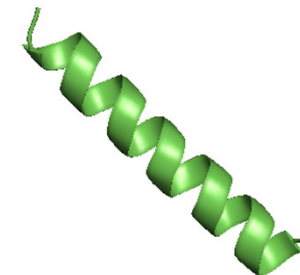
Multidomaines:

Bax
Bak
Bok

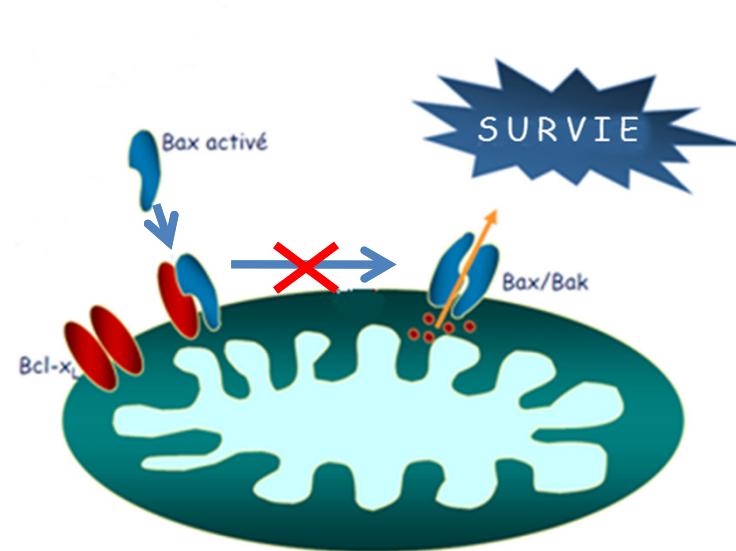
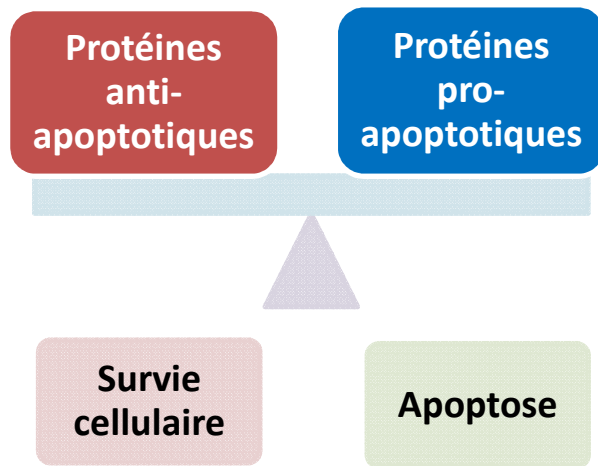


BH3-only:

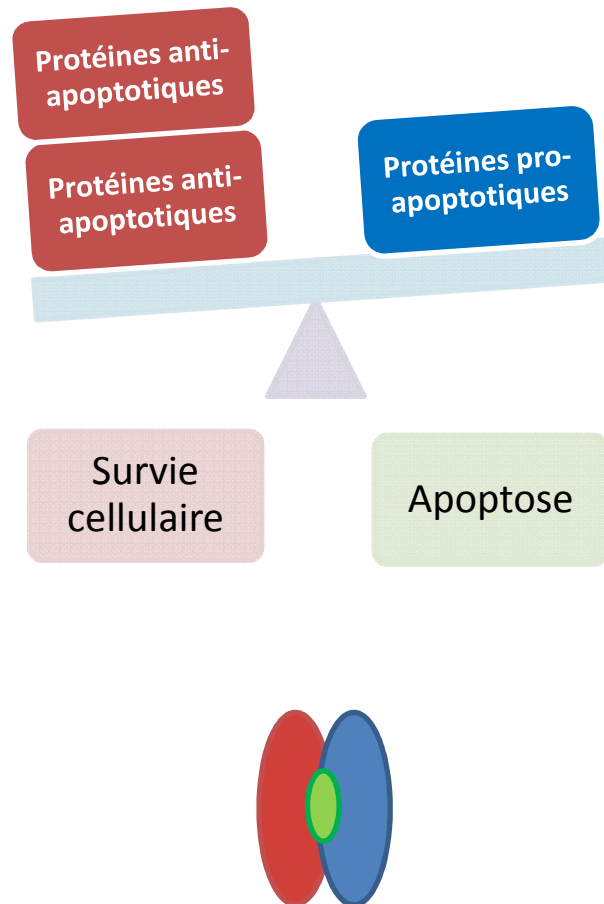
Puma
Bim
Noxa
Bid
Bmf



LA FAMILLE BCL-2: MECANISME D'ACTION



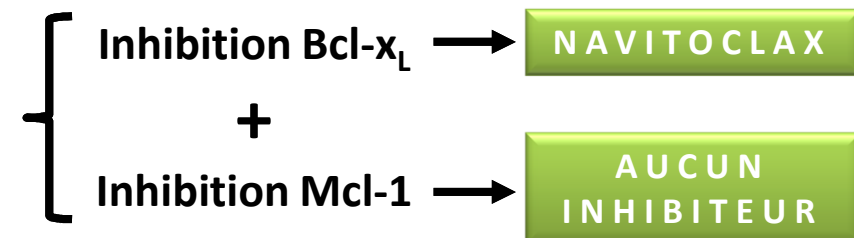
DÉRÉGULATION DE LA VOIE APOPTOTIQUE CANCER DE L'OVAIRE



Coopération de Bcl-x_L et Mcl-1

Brotin *et al.*, *Int J Cancer* 2010, 885-895

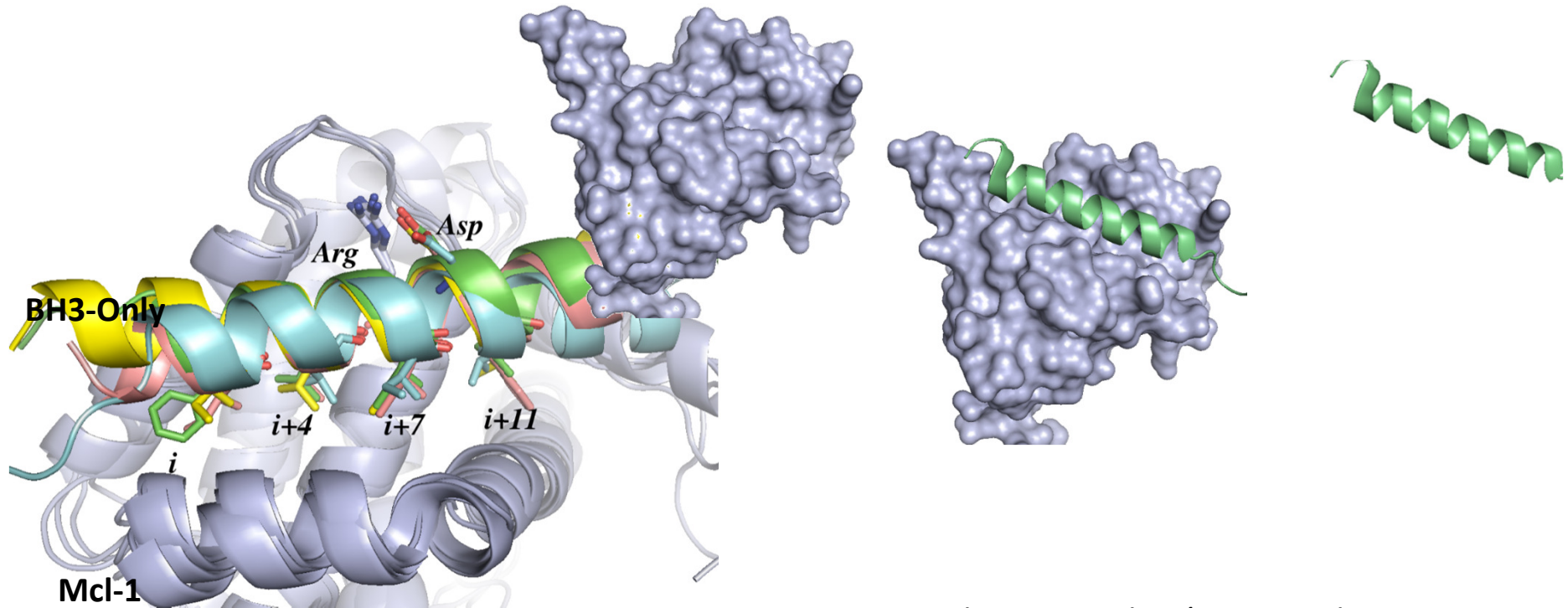
- Destruction des cellules tumorales



Kirkin *et al.* *Biochim. Biophys. Acta* 2004, 229-249
Luo *et al.* *Biochem Cell Biol.* 2000, 119-126
Lebedeva *et al.* *Cancer Res.* 2000, 6052-6060

CRIANN 4 juin 2018

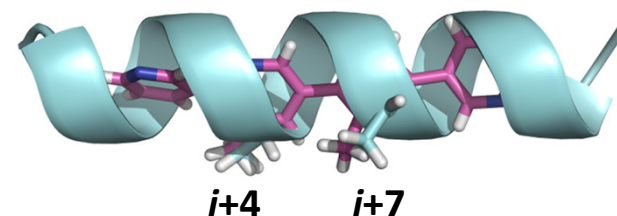
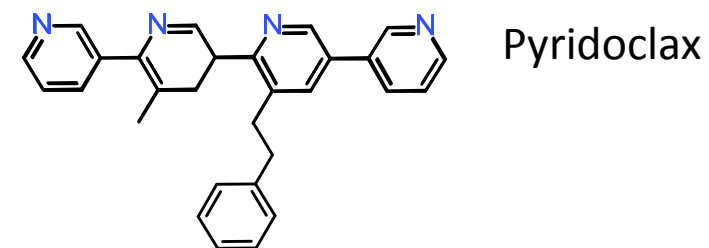
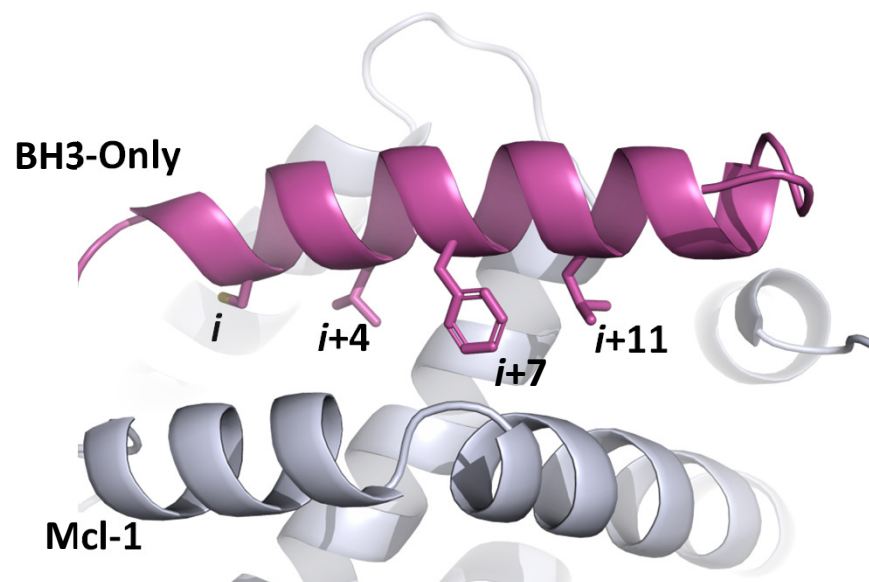
INTERACTION MCL-1 ET BH3-ONLY



Alignement de Structures 3D des complexes Mcl-1 et BH3-only

Alignement de Séquences de protéines BH3-only

	<i>i</i>	<i>i+4</i>	<i>i+7</i>	<i>i+11</i>											
mPuma	E	G	L	I	D	L	N	A	Q	Y	E	R	R	M	-
hBim	-	-	R	I	A	D	F	N	A	Y	Y	A	R	-	-
hNoxa	-	A	E	L	E	V	C	A	T	Q	L	R	R	F	G

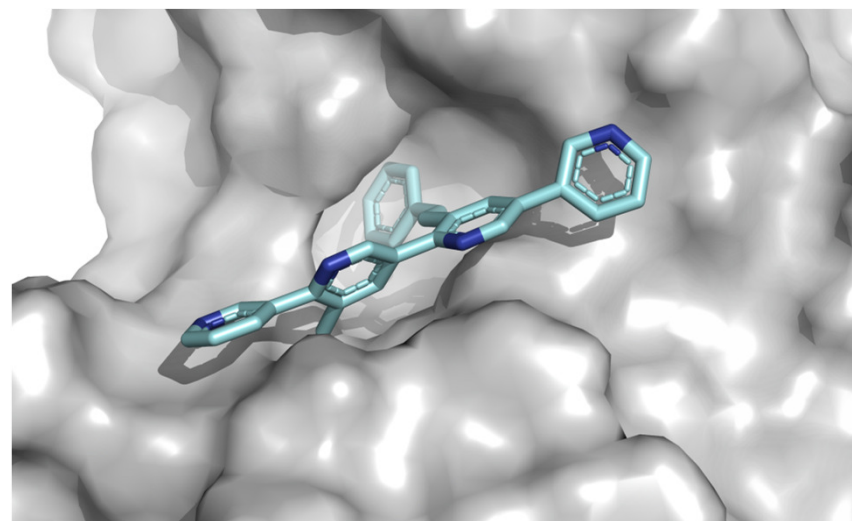


Sopkova et al., *Chem. Inf. Model.* 2012, 429-439.
Perato et al., *J. Chem. Inf. Model.* 2013, 2671-2680

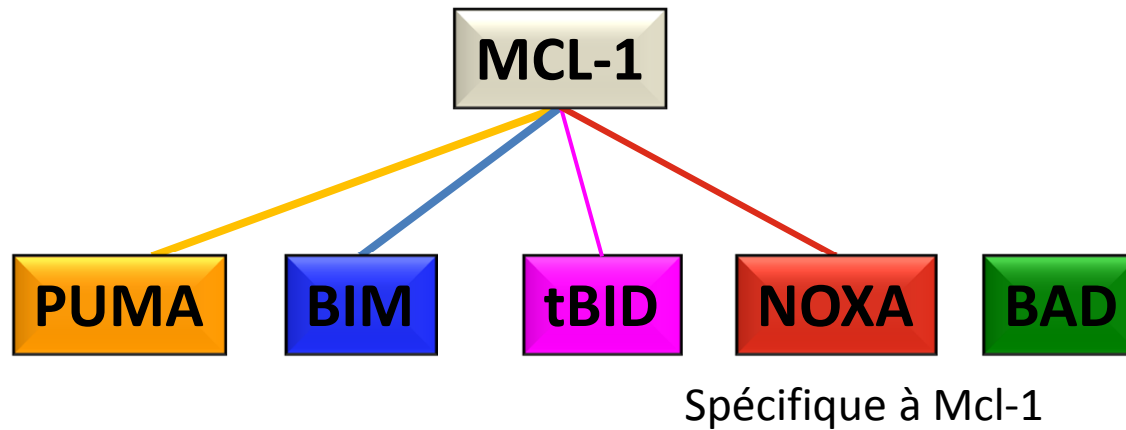
Inhibition de Mcl-1 \Rightarrow

Sensibilisation des cellules cancéreuses
aux stratégies ciblant Bcl-x_L

Patent: Poulain et al., EP14305309, 04/03/2014
Gloaguen et al., *J. Med. Chem.* 2015, 58 (4), 1644-1668



INTERACTION MCL-1 / BH3-ONLY (MM-PBSA)



MM-PBSA

Les contributions de chaque résidu de BH3 à ΔG du complexe (ΔG_{pol} et ΔG_{nonpol}) :

$$\Delta G_{polar} = \Delta G_{PB} + \Delta G_{elec}$$

ΔG_{PB} : l'énergie de solvation électrostatique (éq. Poisson-Boltzmann)

ΔG_{elec} : énergie d'interaction électrostatique

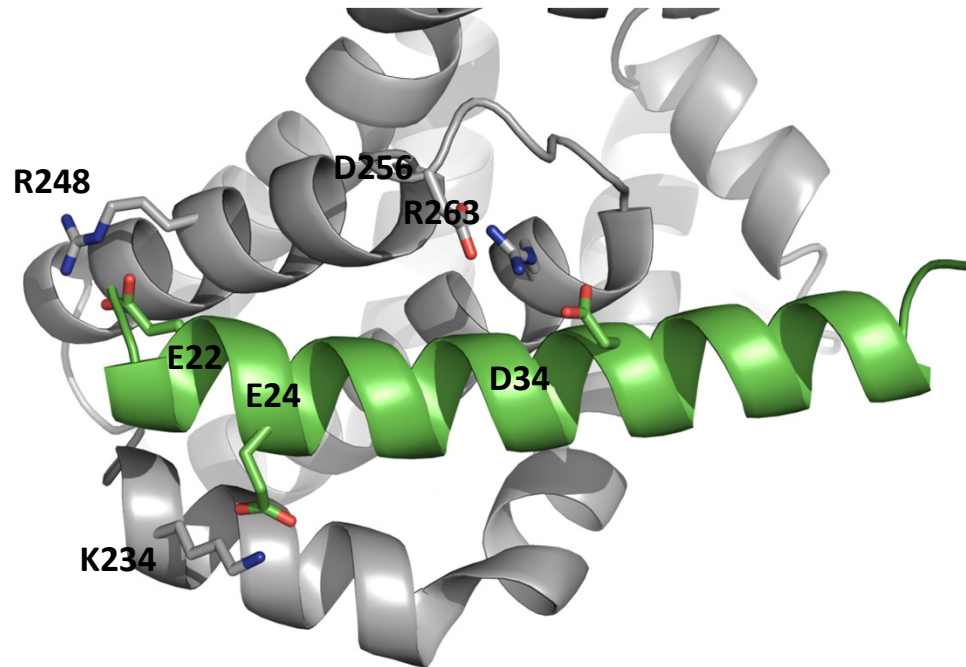
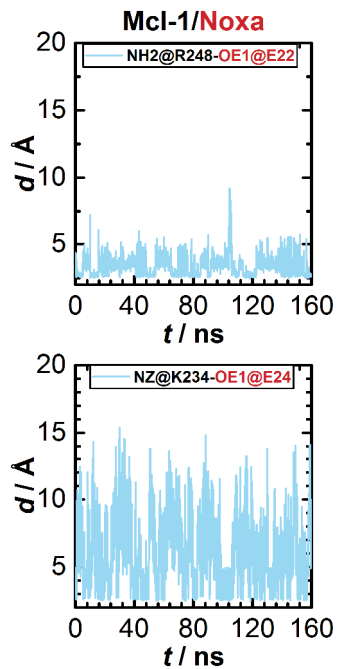
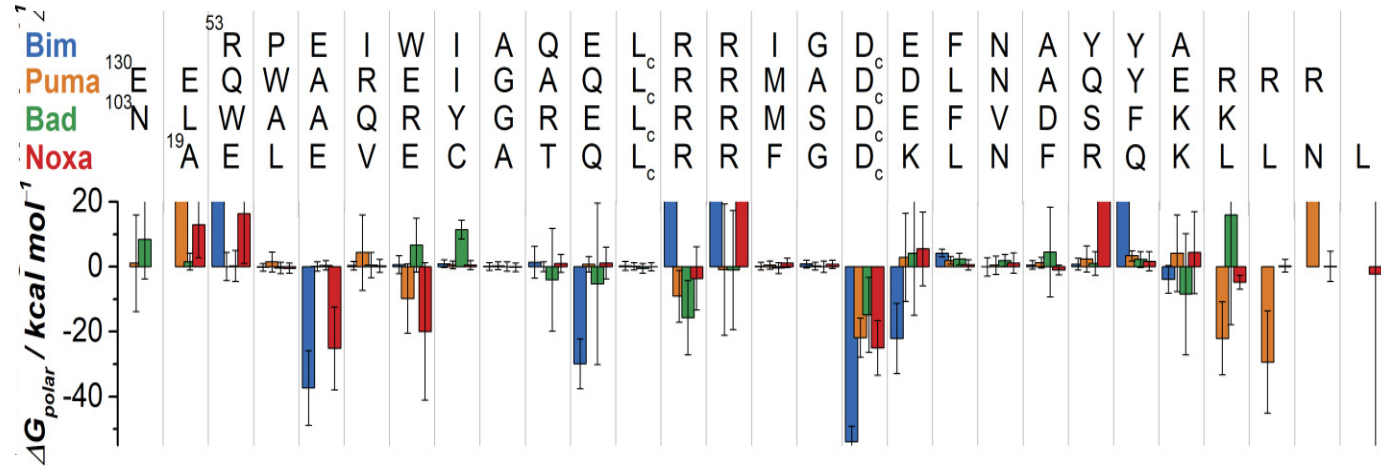
$$\Delta G_{nonpolar} = \Delta G_{nps} + \Delta G_{vdW}$$

ΔG_{nps} : solvation non polaire (γ SASA + β), SASA étant une surface accessible

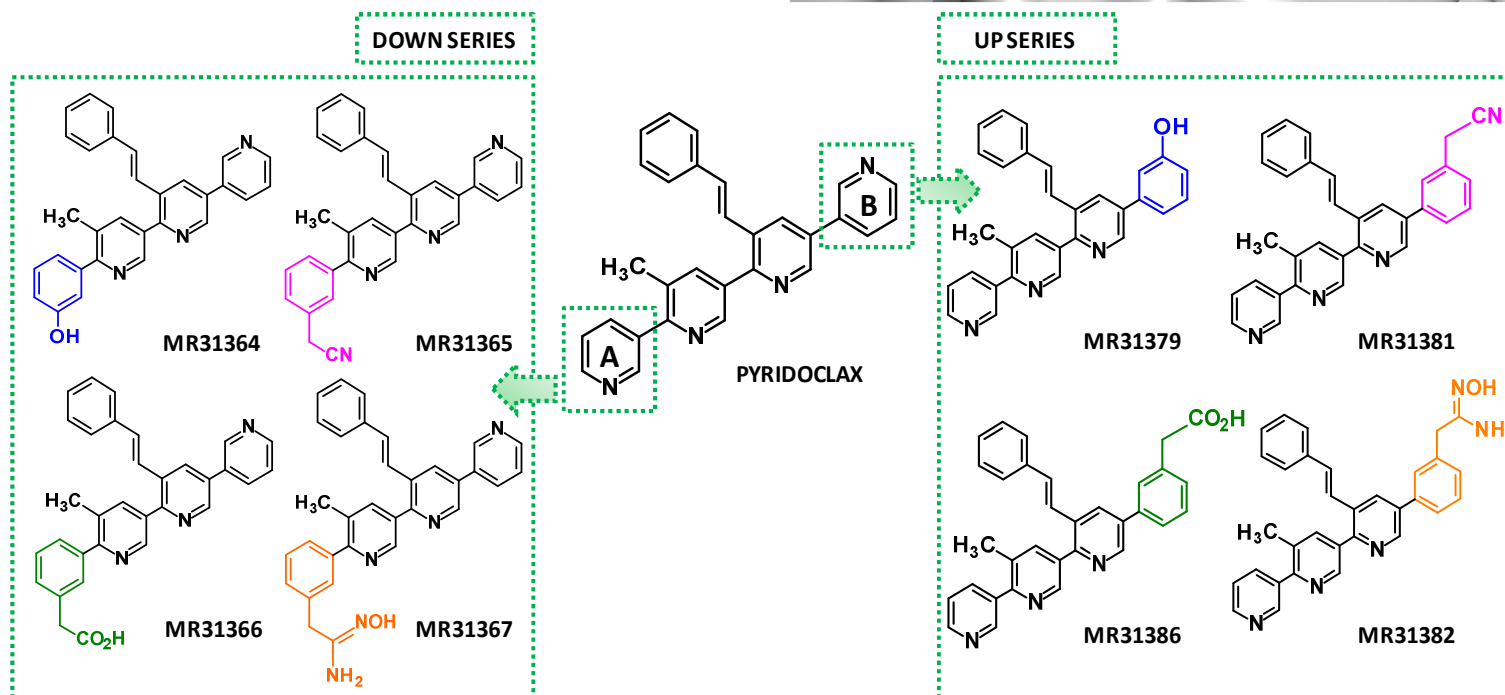
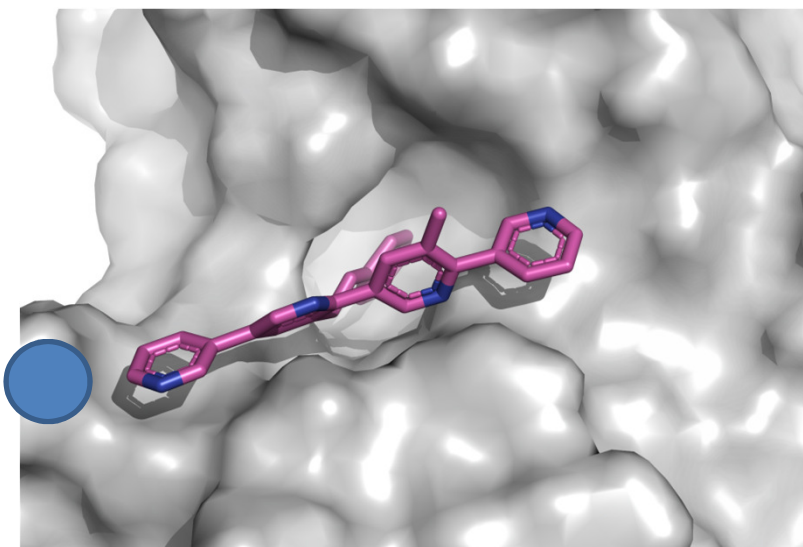
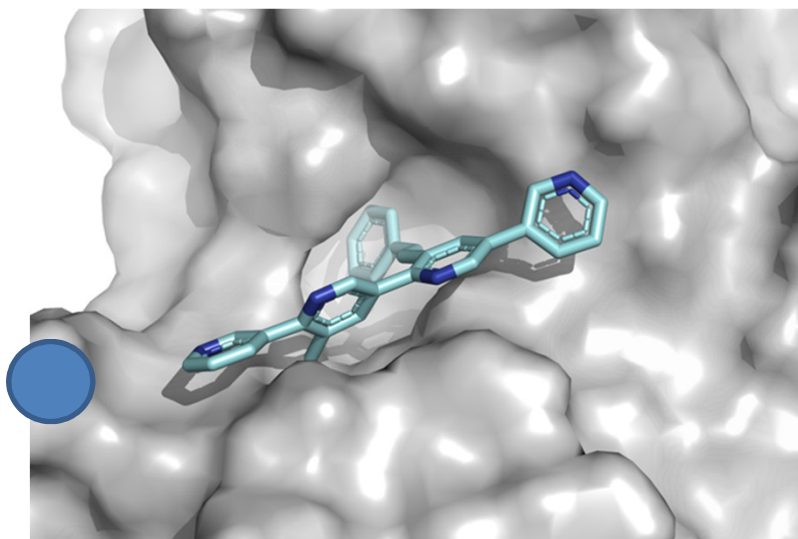
ΔG_{vdw} : interaction énergie vdW

Dynamique
moléculaire NAMD:
160 ns (GPU)

MM-PBSA home
made script
CHARMm



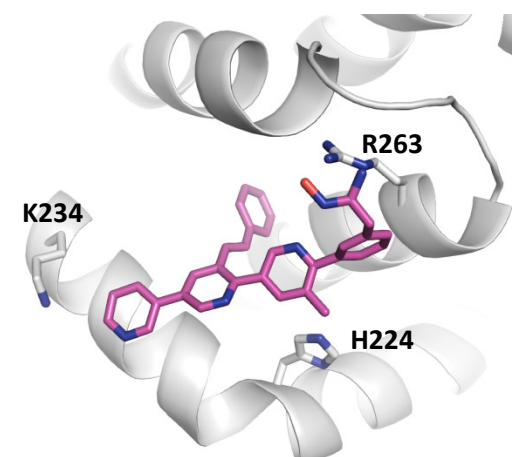
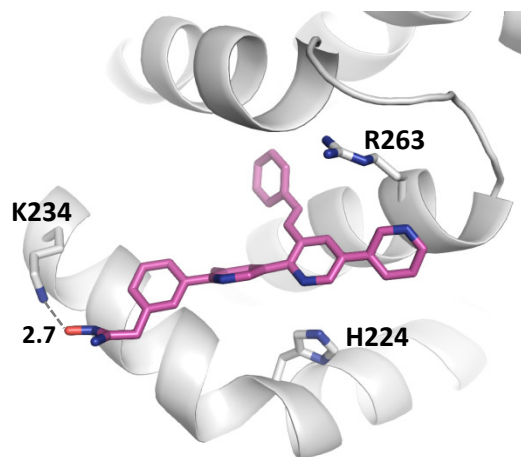
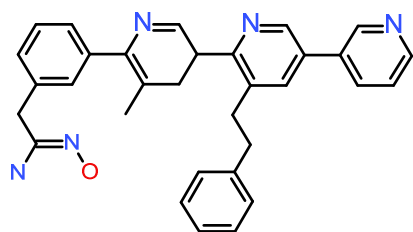
DERIVES NOXA-like



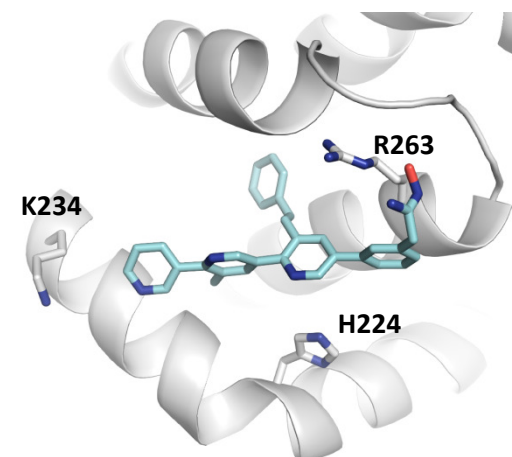
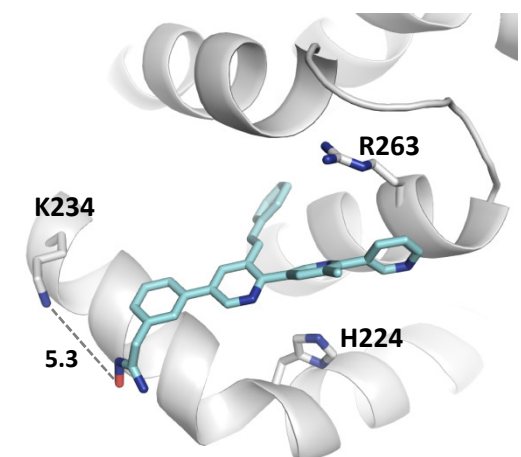
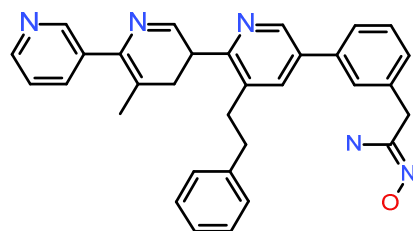
DOCKING DES DERIVES NOXA-like

Logiciel GOLD

Down



Up



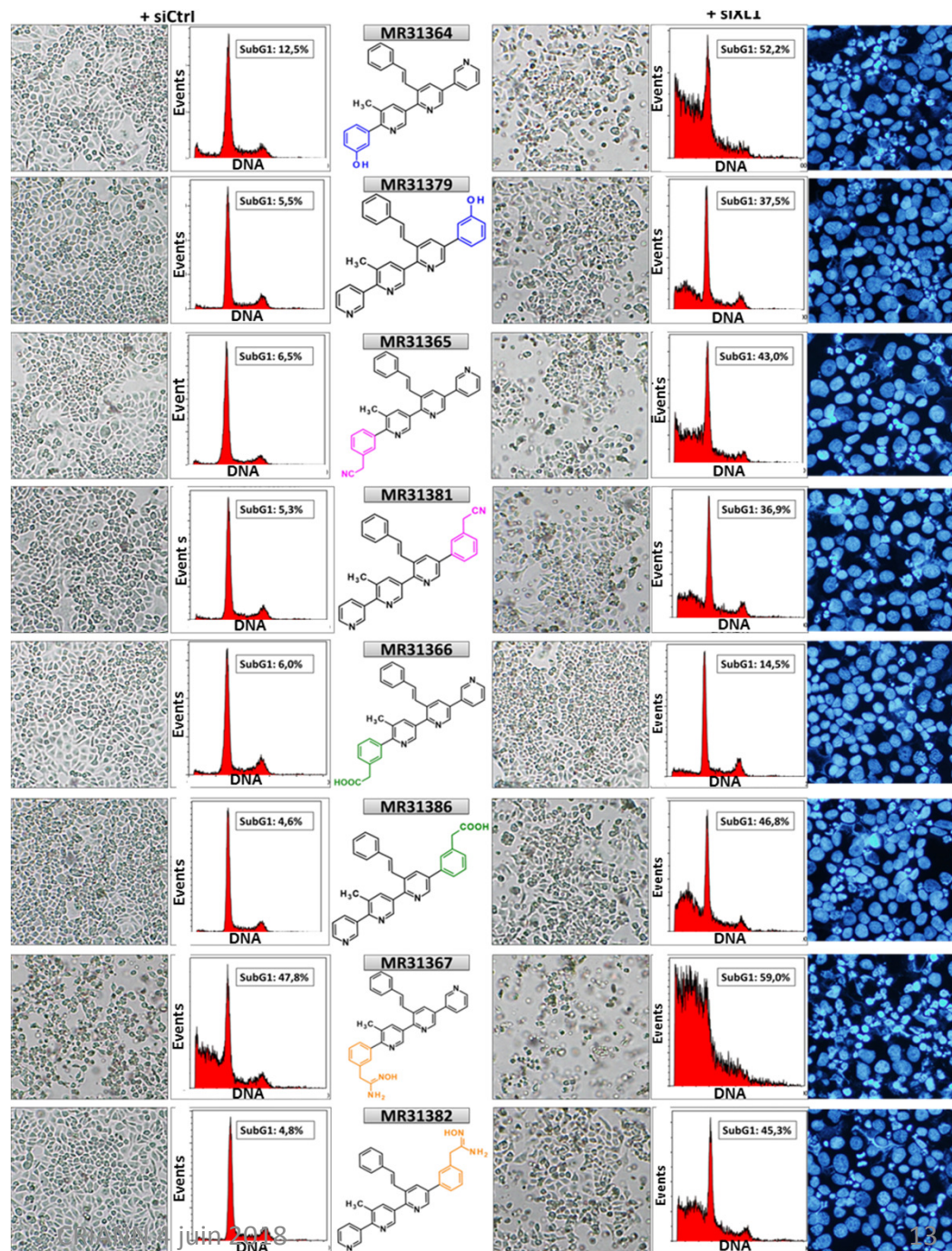
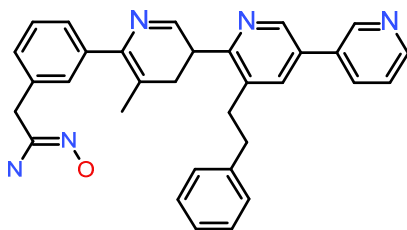
EVALUATION in vitro



L. Poulain

Effets des dérivés de Pyridoclastax sur les cellules cancéreuses de l'ovaire IGROV1-R10 en monothérapie ou associées à un siRNA ciblant Bcl-x₁ (siXL1).

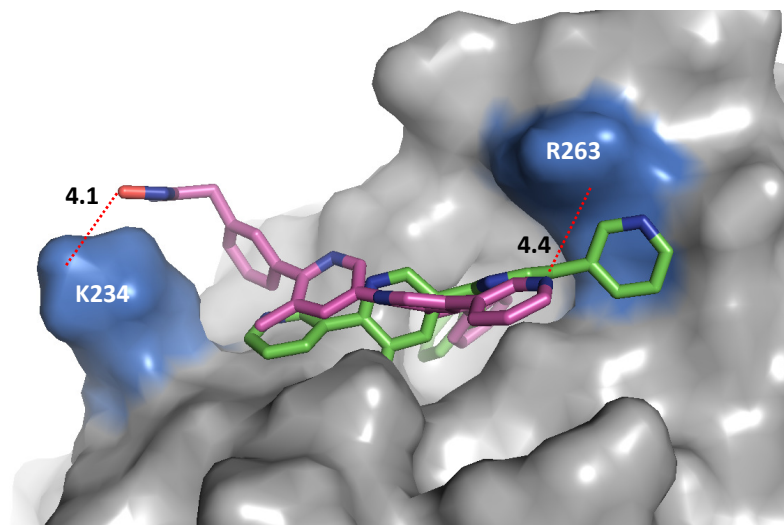
MR31367



juin 2008

Dynamique moléculaire NAMD:
100 ns (GPU CRIANN)

Analyses
script CHARMM



REMERCIEMENTS

Partenaires biologiques



BioTICLA

L Poulain, S Hedir



Ph Juin, F Gautier



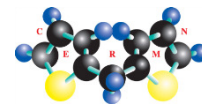
F Lopez, L Ligat

Partenaires analystes



A. Bourafai , H Oulyadi, M Sebban

Partenaires chimistes



C. Denis, M. De Pascale,
M. Jouanne, AS Voisin-Chiret

Partenaires financiers *Programme Emergence*

