Hematology Department

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HDACi in Multiple Myeloma

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HDACi in Myeloma

- Mechanism of action of HDACi
- Anti-MM activity of HDACi in monotherapy
- Combinations of HDACi in MM

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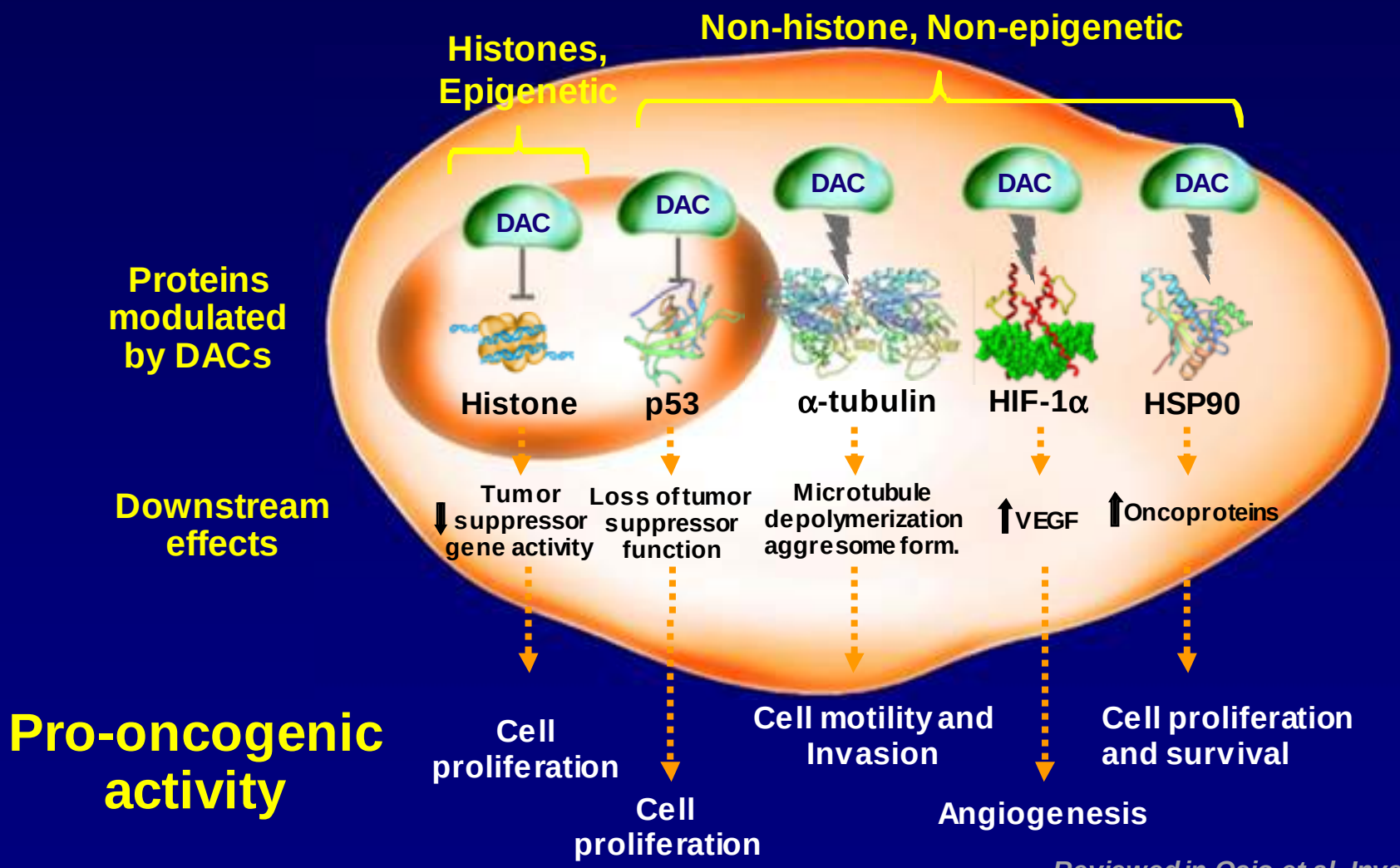
What are Deacetylases?

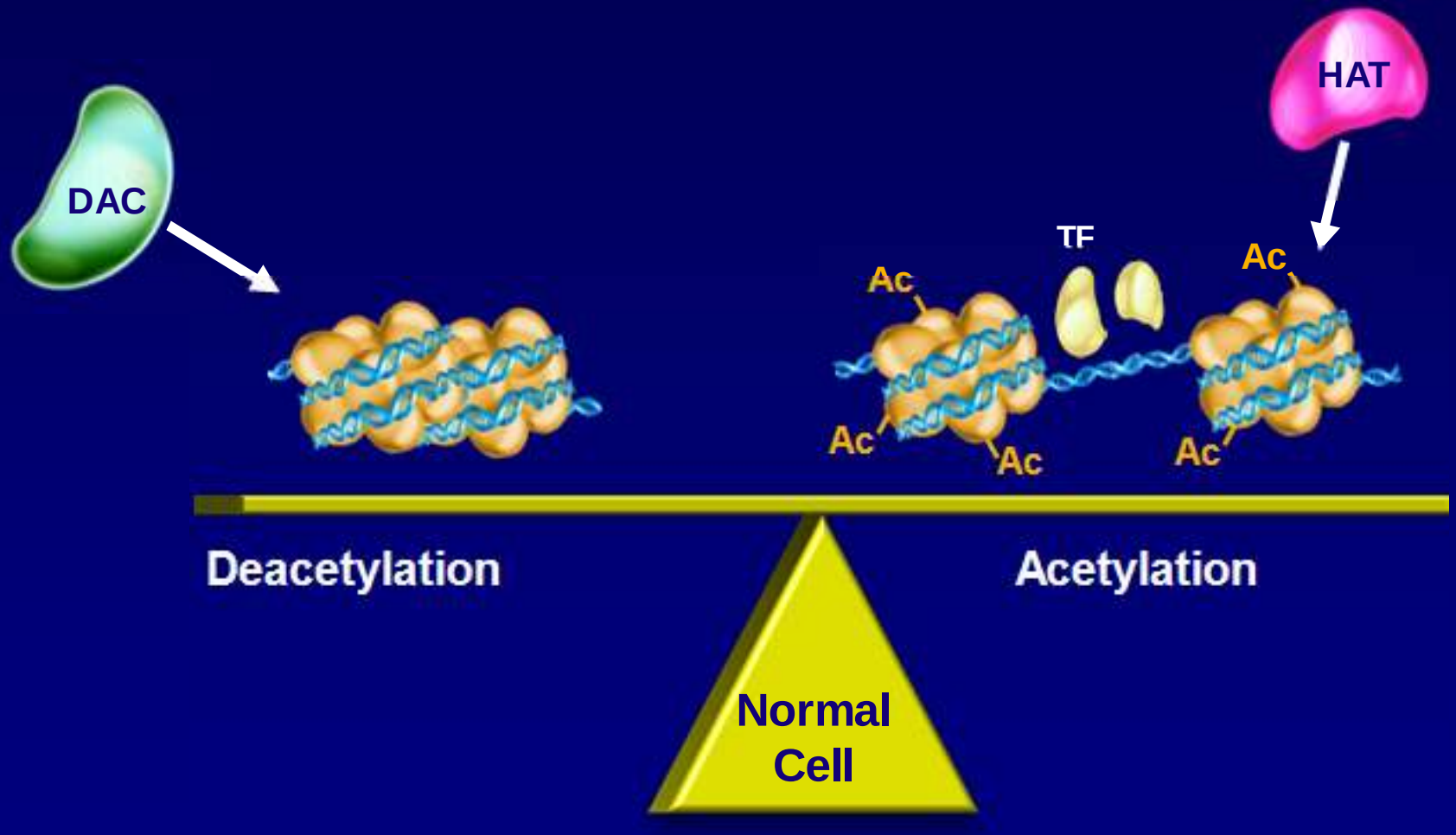
DACs are enzymes that remove acetyl groups from their client proteins and modulate their activity



Reviewed in Ocio et al. Invest New Drugs. 2010

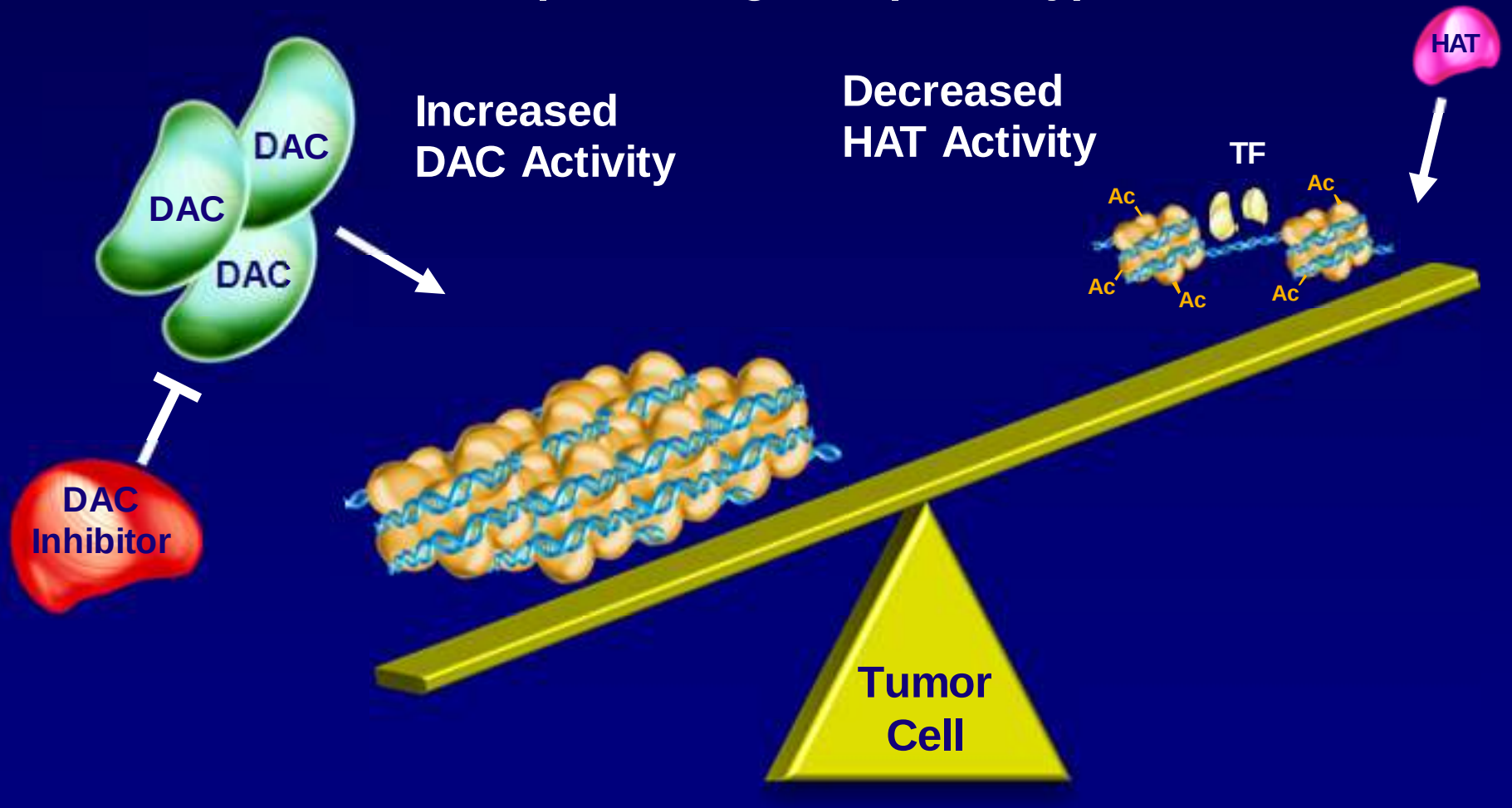
Increased DAC activity in tumor cells

There is a balance between acetyl transferase and deacetylase activity in normal cells



Increased DAC activity in tumor cells

In tumor cells there is an increase in deacetylase activity that results in a pro-oncogenic phenotype



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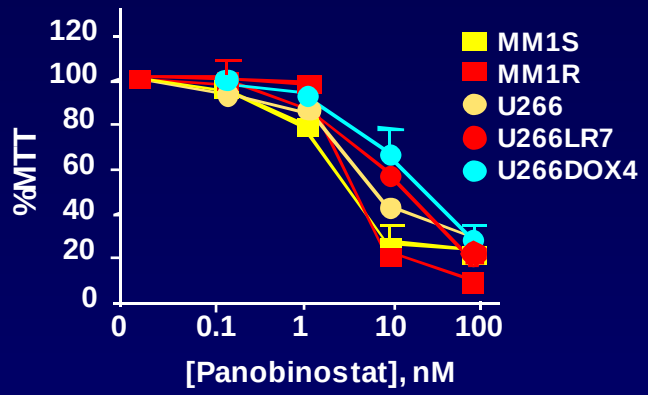
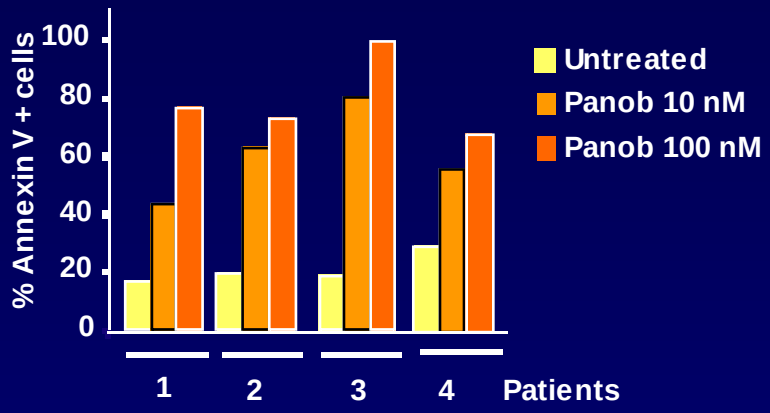
Preclinical anti-MM activity of Panobinostat

Cell lines



Patients' cells

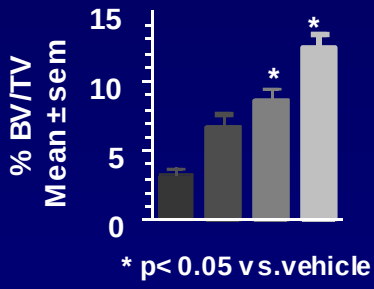


Bone Density

Trabecular Bone

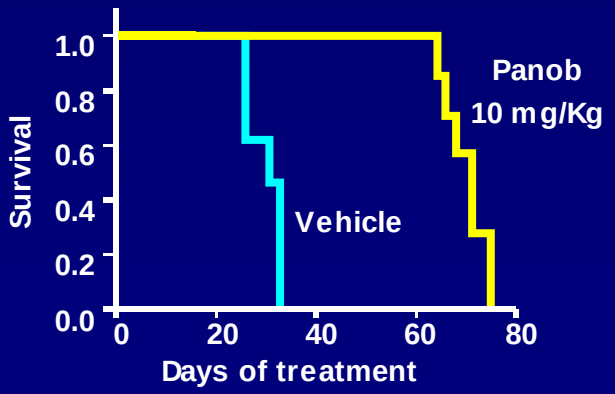
Vehicle

Panobinostat

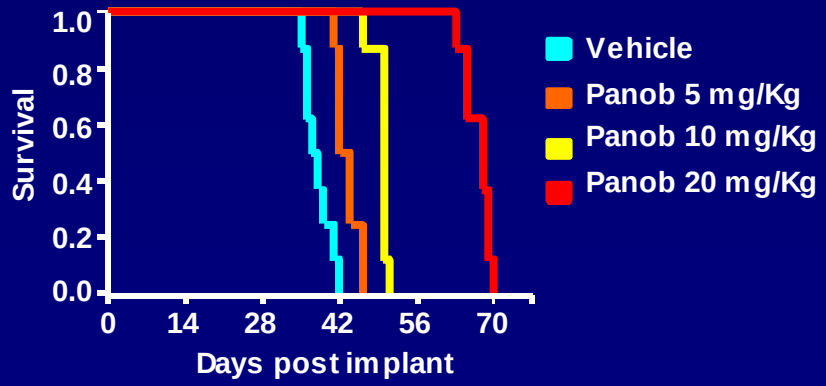


Survival *in vivo*

sc plasmacytoma



Disseminated MM



Maiso P. Cancer Res. 2006; Ocio EM, Haematologica 2010

Khan SB, Br J Haem. 2004 Romidepsin
Mitsiades CS, PNAS 2004 Vorinostat
Golay J, Leukemia 2007 Givinostat

Activity of HDACi in monotherapy in MM

	n	ORR	Responses
Vorinostat[1] (*SAHA*)	10	0%	1 MR, 9 SD
Panobinostat[2] (*LBH589*)	38	3%	1PR, 1 MR, 1 SD
Givinostat[3] (*ITF2357*)	19	0%	5 SD
Romidepsin[4] (*FK228*)	12	0%	4 SD

1. Richardson PG, Leuk Lymphoma 2008

2. Wolf, ASH 2008. Abstract 2774

3. Galli M, Ann Hematol 2010

4. Niesvizky R, Cancer 2011

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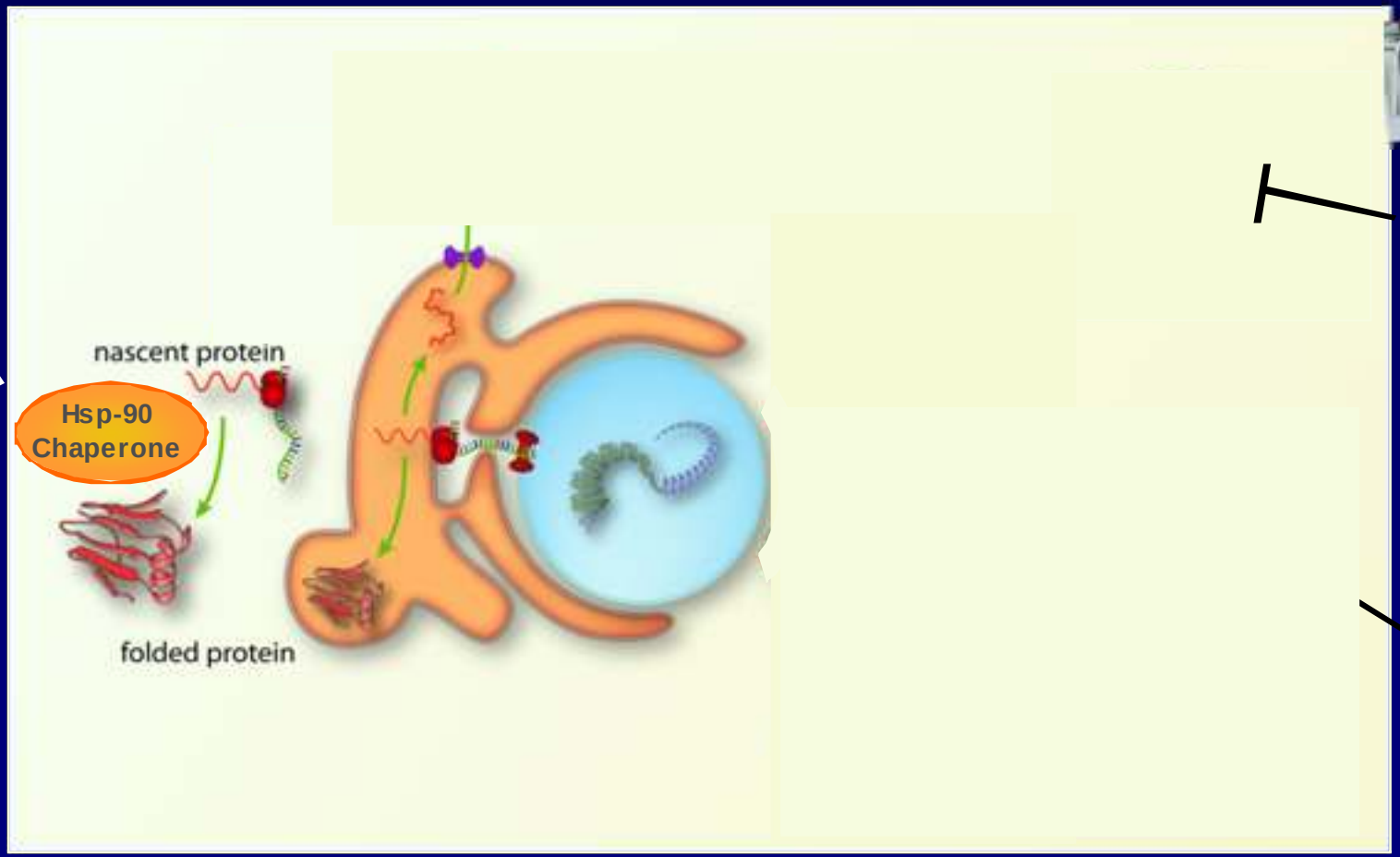
Rationale for combining DACi + Bortezomib

Unfolded Protein Response

Tanespymicin
HDACi

Hsp90 inhibitors



Proteasome inhibitors

Bortezomib
Carfilzomib

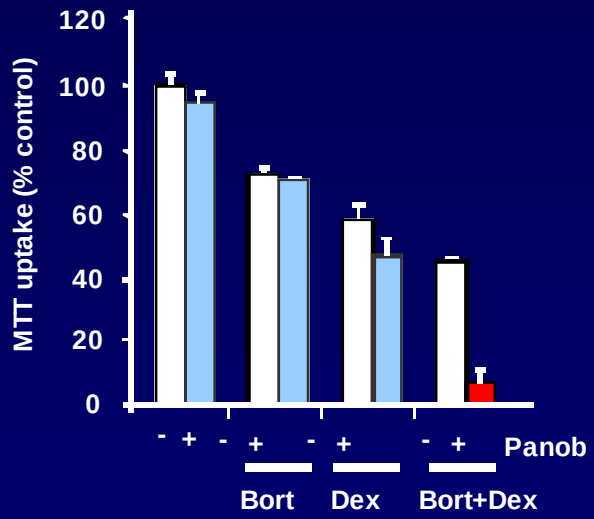
HDAC6 inhibitors

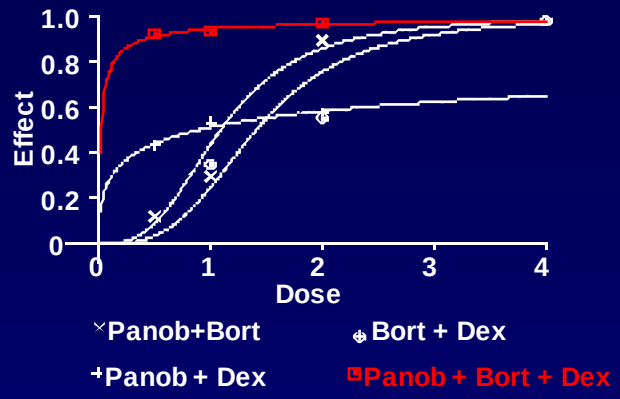
Tubacin
HDACi

Kindly provided by Dr. James Bradner and adapted

Preclinical activity of HDACi + Bort + Dex in MM

Activity in vitro

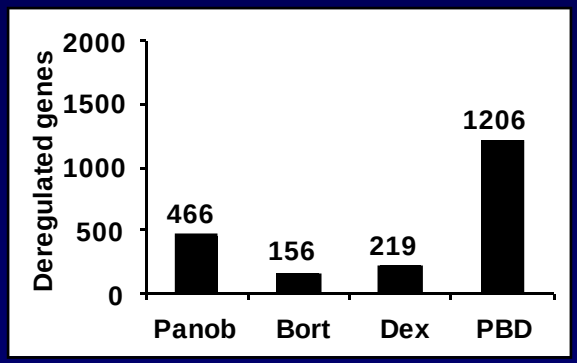




CI in the highly synergistic range (0.1-0.2)

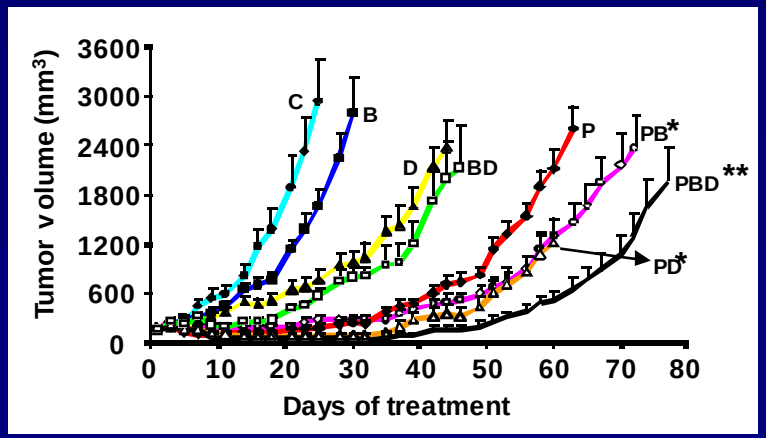
Changes in GEP

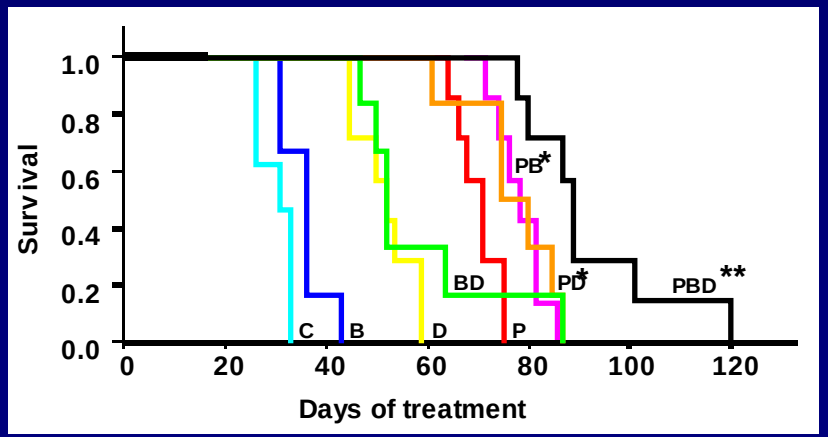
Apoptosis 15-25%



895 genes exclusive of PBD

Activity in vivo





* p<0.05 related to singles ** p<0.05 related to doubles

Ocio EM, Haematologica 2010

Efficacy of HDACi + Bortezomib +/- Dex

	Vorinostat[1]	Vorinostat[2]	Panobinostat[3]	Romidepsin[4]
Dose	Vor 400 mg po 4-11 Bort 1.3 mg/m^2 1,4,8,11 Dex* 20 mg po 4-8	Vor 400 mg po 1-14 Bort 0.7-1.3 mg/m^2 1,4,8,11 Dex* 20 mg po 1-4, 9-12	Pan 20 mg po L,X,V x 2w/3w Bort 1.3 mg/m^2 1,4,8,11 Dex* 20 mg 1-2, 4-5, 8-9, 11-12	Rom 10 mg/m^2 iv 1, 8, 15 Bort 1.3 mg/m^2 1,4,8,11 Dex 20 mg 1-2, 4-5, 8-9, 11-12
n	23	34	62	25
≥PR	43%	47%	55%	60%
≥MR	NR	NR	65%	72%
% prior Btz	83%	38%	63%	24%
% Btz Refr.	39%	NR	31%	NR

* Dex added in cycle 2 if suboptimal response

** 100% prior Thal & 74% prior Len

Bortezomib (APEX)[5] ≥ *PR 43%* Bortezomib + Dex[6,7] ≥ *PR 51%*-59%*

1. Badros A. Clin Cancer Res 2009
2. Weber, IMW 2009 Abs 246, 248
3. San Miguel JF, IMW 2011 Abs P-238
4. Harrison S, IMW 2011. Abs P-233
5. Richardson PG, NEJM 2005 & Blood 2007
6. Mikhael JR, Br J Haematol 2009
7. Corso A, Eur J Haematol 2009

Efficacy of HDACi + Bortezomib +/- Dex in Bortezomib-refractory pts

- **Vorinostat[1,2]**
  - n=8 → *37% PR, 50% SD*
  - n=7 → *29% PR, 29% MR*
- **Panobinostat[3]**
  - n=19 → *37% PR, 26% MR*
  - *14 patients previously progressing under Btz → 57% ≥MR*

1. Badros A. Clin Cancer Res 2009 *2. Weber D, ASH 2008 Abs 3711* *3. San Miguel JF, IMW 2011 Abs P-238*

Efficacy of HDACi + Bortezomib +/- Dex

Two ongoing randomized trials will answer this question

VANTAGE 088
Multiple Myeloma

A Phase 3, International, Multicenter, Randomized, Double-Blind Study of the HDAC Inhibitor Vorinostat or Placebo in Combination With Bortezomib in Patients With MM

PANORAMA 1
PANobinostat ORAl in Multiple myelomA

Global randomized Phase III trial evaluating oral Panobinostat in combination with Bortezomib and Dexamethasone in relapsed or relapsed & refractory MM

Safety of HDACi + Bortezomib +/- Dex

	Vorinostat[1]		Panobinostat[2]		Romidepsin[3]	
	All (%)	G3/4 (%)	All (%)	G3/4 (%)	All (%)	G3/4 (%)
Haematological						
Thrombocytopenia	74	57	87	79	-	64
Neutropenia	30	13	71	55	-	36
Anemia	70	22	52	18	-	36
Non Haematological						
Diarrhea	48	9	73	14	-	4
Nausea	52	0	61	3	-	-
Fatigue	48	22	52	10	-	20
Pyrexia	17	0	47	6	-	-
Asthenia	-	-	44	26	-	-
Anorexia	-	-	42	2	-	-
P. Neuropathy	61	4	37	3	-	8

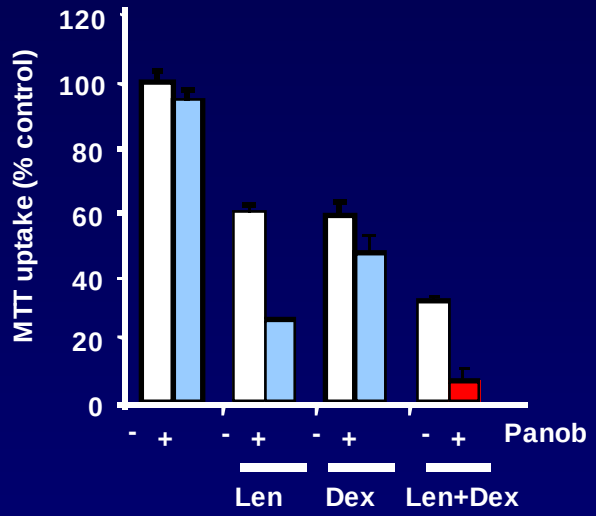
1. Badros A. Clin Cancer Res 2009

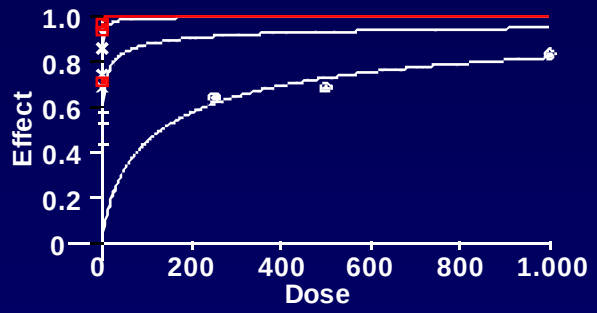
2. San Miguel JF, IMW 2011 Abs P-238

3. Harrison S, IMW 2011. Abs P-233

Preclinical activity of HDACi + Len + Dex in MM

Activity in vitro



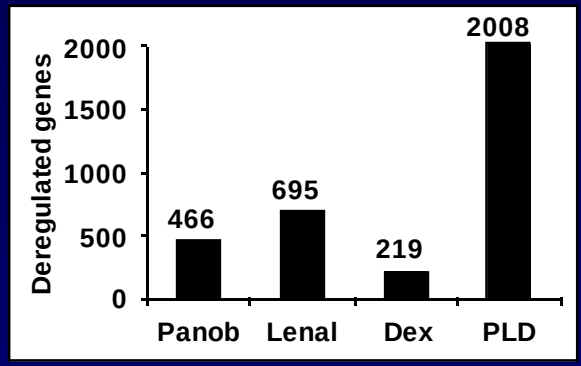


×Panob + Lenal
◆Lenal + Dex
+Panob + Dex
⊞Panob + Len + Dex

CI in the highly synergistic range (<0.1)

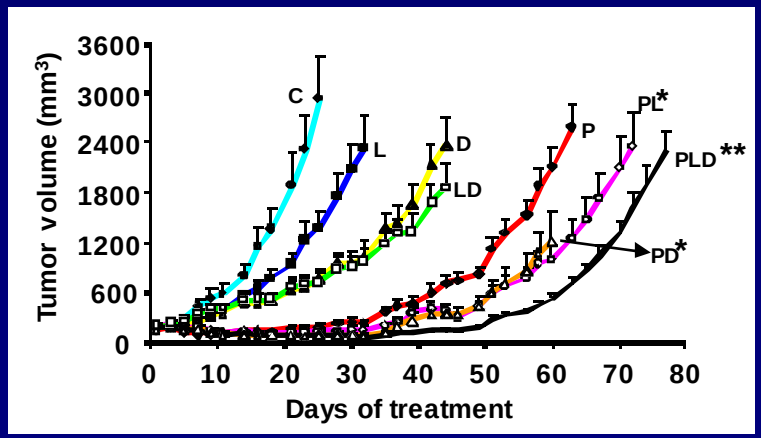
Changes in GEP

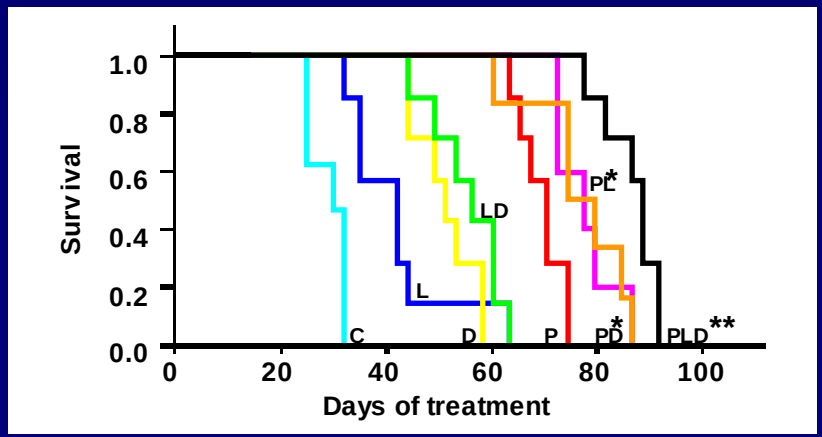
Apoptosis 15-25%



1323 genes exclusive of PLD

Activity in vivo





* p<0.05 related to singles ** p<0.05 related to doubles

Ocio EM, Haematologica 2010

Efficacy of HDACi + Lenalidomide + Dex

		Vorinostat[1]	Panobinostat[2]	Vorinostat[3]
Dose		Vor 400 mg po 1-7, 15-21 Lenalidomide 25 mg po 1-21 Dex 40 mg po 1, 8, 15, 22	Panob 20 mg L, X, V Lenalidomide 25 mg po 1-21 Dex 40 mg po 1-4, 9-12, 17-20*	Vor 300-400 mg po 1-7, 15-21 Lenalidomide 10-25 mg po 1-21 Dex 20-40 mg po 1, 8, 15, 22
n		31	46	25
≥PR		53%	59%	28%
≥MR		70%	65%	48%
% Prior	Thal	68%	63%	-
	Len	45%	17%	100%**
	Bort	68%	61%	-

* 1-4 after cycle 5

** all of them previously refractory to Len-Dex

Lenalidomide + Dex[4] ≥ PR: 60% (15% CR)

1. Richardson PG, ASH 2010 Abstr 1951

2. Mateos MV, ASCO 2010. Abs 8030

3. Bilotti E, IMW 2011. Abs P-215

4. Dimopoulos M, Leukemia 2009

Safety of HDACi + Lenalidomide + Dex

	Vorinostat[1]		Panobinostat[2*]	
	All	G 3/4	All	G 3/4
Haematological				
Thrombocytopenia	48	16	54	50
Neutropenia	39	26	50	48
Anemia	32	10	46	26
Non Haematological				
Diarrhea	48	13	48	6
Nausea	26	3	48	2
Fatigue	52	10	37	13
Pyrexia	-	-	43	4
Asthenia	13	0	37	9
Anorexia	23	0	28	9

**In the Panobinostat study a high incidence of DLTs and SAEs were observed (mostly infectious), probably related to the high doses of Dexamethasone and the continuous treatment with Panobinostat.*

1. Richardson PG, ASH 2010 Abs 1951

2. Mateos MV, ASCO 2010. Abs 8030

Other combinations with DACi in MM

- Panobinostat + Melphalan[1] → ≥PR 16% — 64% previous Melph. Haem toxicity
- Panobinostat + MPT[2] → ≥PR 50% — Haem tox (70% neutropenia G ¾)
- Vorinostat + PLD + Bort[3] → ≥PR 72% — *In Bz refr* → ≥PR 44%. General & GI AEs
- Vor + Len + Bort + Dex
  - *Refr. to RVD*[4] → ≥PR 44% — General & Haem tox (89% Thromb G3/4)
  - *Newly diagnosed*[5] → 41% nCR/CR, 24% VGPR, 29% PR — 47% PN (6% G3)

1. Berenson J, IMW 2011 Abstr P-206
2. Offidani. IMW 2011 Abstr P-191
3. Voorhes. ASH 2010 Abstr 1955
4. Siegel D, IMW 2011 Abstr P-216
5. Kaufmann J, IMW 2011 Abstr P-235

Summary

- There is a clear preclinical rationale for the use of HDACi in MM based on epigenetic and non-epigenetic mechanisms
- The clinical activity of HDACi in monotherapy in MM has been quite modest, nevertheless,…
- , … several combinations such as those with Bortezomib or Lenalidomide and Dex have demonstrated activity even in previously refractory patients.
- The most significant AEs associated with these drugs are Haematological side effects, constitutional symptoms and GI symptoms

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