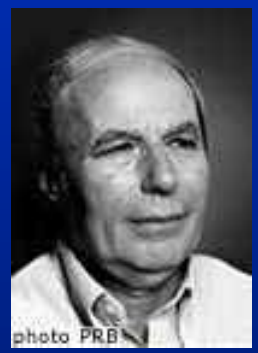
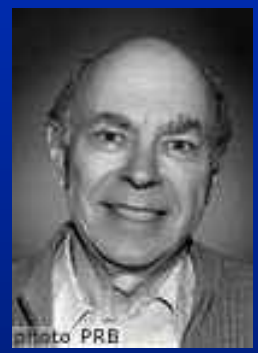
8. 12. 2004 Nobel prize - biochemistry

… for ubiquitin mediated protein degradation.





Aaron Ciechanover a Avram Hershko

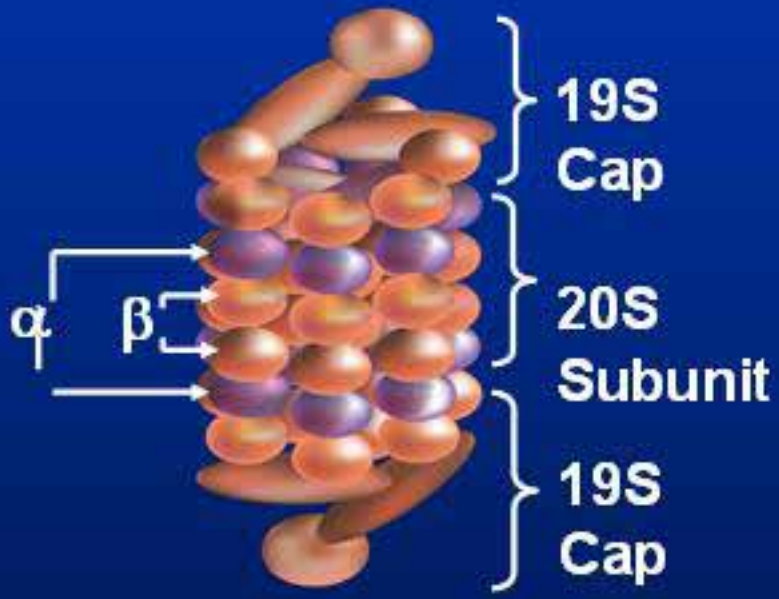
Technion, Israel Institute of Technology, Haifa,

Irwin Rose

University ofCalifornia, Irvine,

Proteasome

26S Proteasome



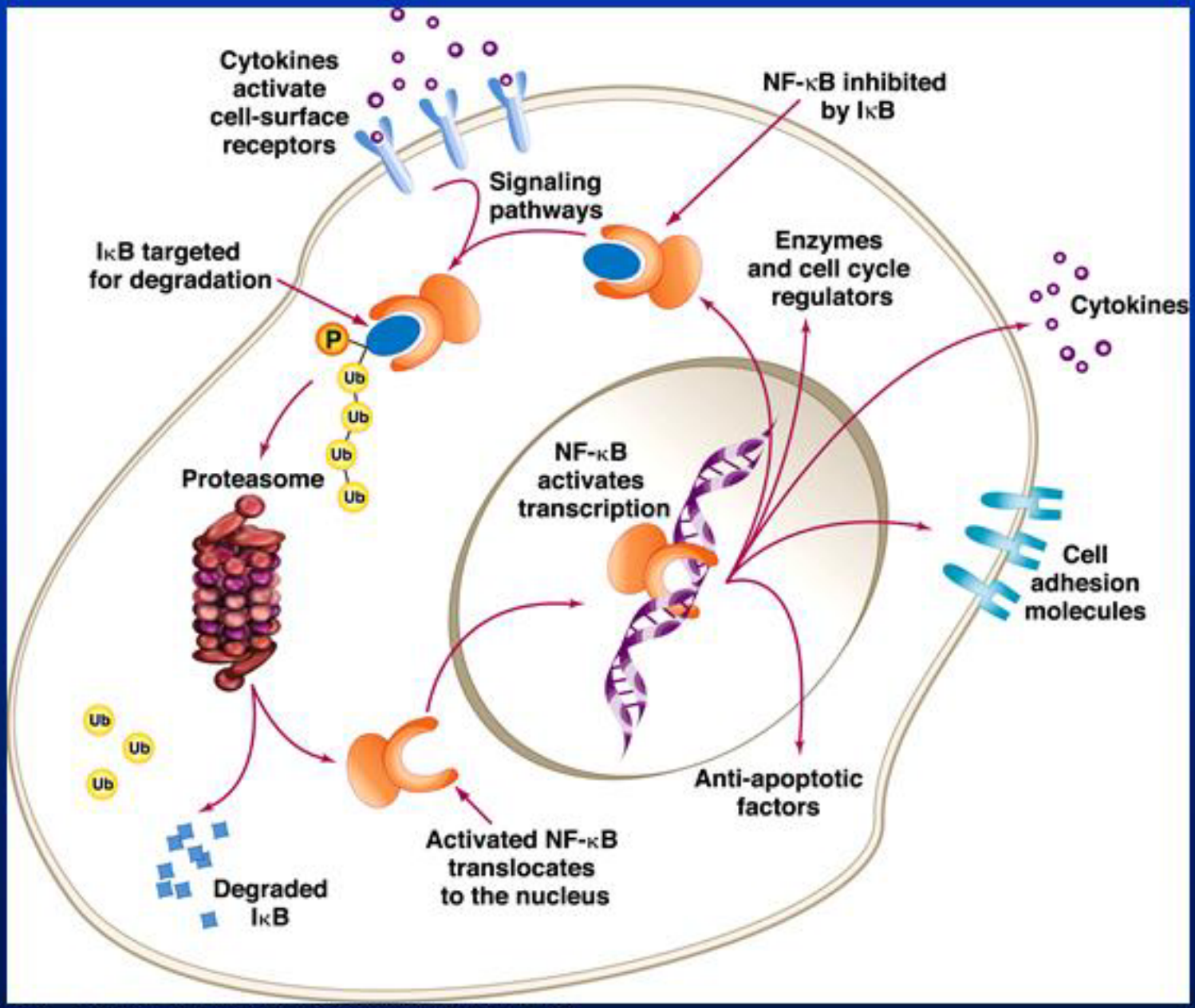
- Degrades ubiquitinated proteins
- Proteolysis is ATP-dependent

Cross section of β ring

- Chymotryptic site is rate-limiting in protein degradation

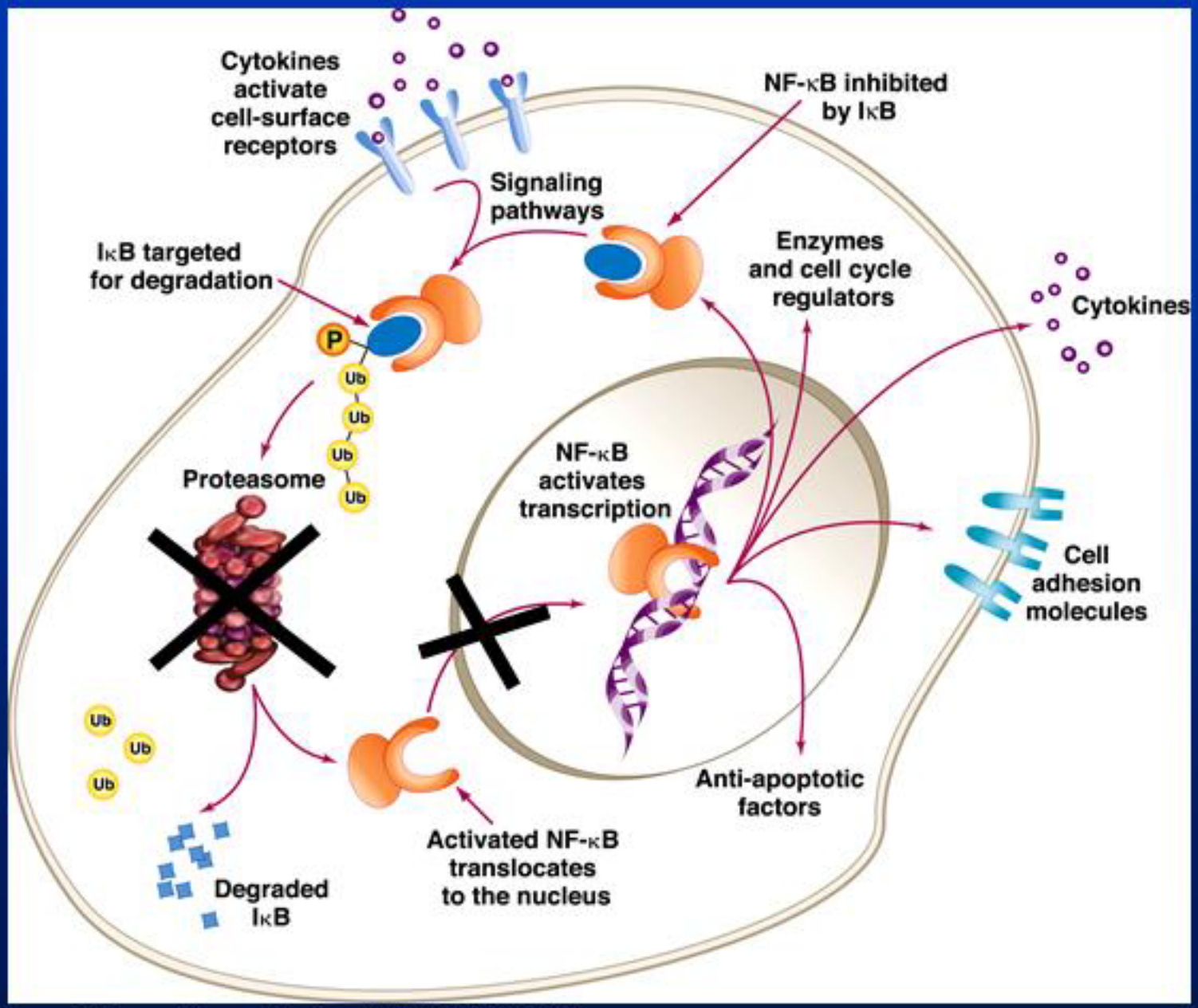
1. DeMartino GN et al. *J Biol Chem.* 1999;274:22123-22126.
2. Seemuller E et al. *Science.* 1995;268:579-582.
3. Adams J et al. *Bioorg Med Chem Lett.* 1998;8:333-338.

Ubiquitin – proteasome cycle



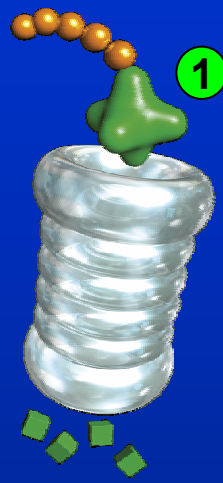
Adams J. *Drug Discov Today*. 2003;8:307-315.

Proteasome inhibition

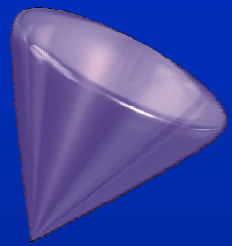


Adams J. *Drug Discov Today*. 2003;8:307-315.

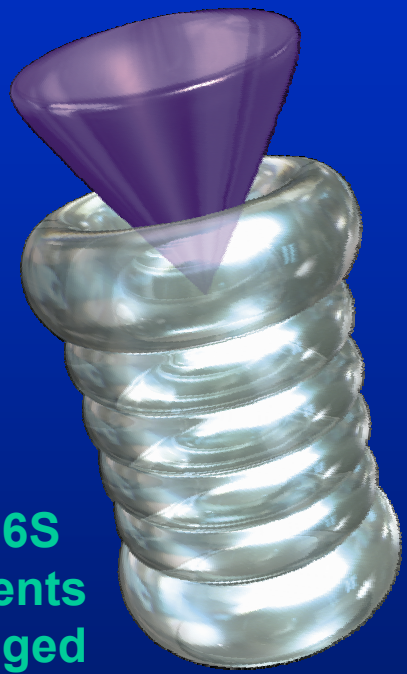
Summary: Mechanism of Action of Bortezomib (VELCADE®)



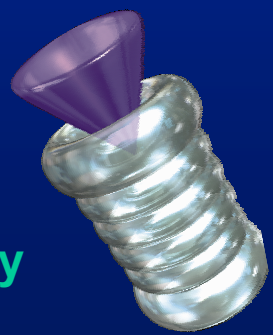
1. The 26S proteasome is a large protein complex that degrades tagged proteins



2. Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome



3. Inhibition of the 26S proteasome prevents proteolysis of tagged proteins which can affect multiple signaling cascades with the cell



4. Nonclinical studies showed bortezomib to be cytotoxic to a variety of cancer cell types

Millennium Pharmaceuticals, Inc., 2003.
Adams J. *Drug Discov Today*. 2003;8:307-315.

Rationale for Phase II Trials in Multiple Myeloma

- Myeloma cells dependent on NF-κB transcription
  - Cell-cycle regulation
  - Production of cytokines, adhesion molecules, and antiapoptotic factors
- Proteasome inhibition prevents activation of NF-κB
- Phase I trial demonstrated encouraging clinical activity of bortezomib (VELCADE®) in multiple myeloma

Czech Velcade experience.
Centers of Czech Myeloma Group (CMG)

1st Dept.Int.Med. General Faculty Hosp.,Charles Univ.Hosp., Prague Ass.Prof. Dr. Ivan Špička, Ph.D. 12 pts.	3rd Dept.of Int.Med. Univ. Hosp. Olomouc Prof. Dr. Vlastimil Ščudla, Ph.D., Dr.Marketa Vytrasova 4 pts.
Dept. of Hemato-oncology Univ. Hosp. Brno Ass.Prof.Dr.Roman Hájek, Ph.D. 5 pts.	Division of clinical hematology Charles Univ. Hosp. Praha 10 Dr. Evžen Gregora 3 pts.
Division of clinical hematology Univ. Hosp. Hradec Králové Dr. Vladimír Maisnar, Ph.D. 3 pts.	Division of clinical hematology Univ. Hosp. Plzeň Dr. Miroslava Schützová 2 pts.

Velcade – Czech reults 1/05. Design of therapy

- Relapsed and refractory multiple myeloma
  - At least 2 prior lines of treatment
  - Progressing on last therapy
  - Platelet count ≥30,000/μL
  - Creatinine clearance ≥30 mL/min

Treatment Plan

- VELCADE® 1.3 mg/m^2 IV push over 3-5 seconds
- 21-day cycle
  - Administered on days 1, 4, 8, and 11
- 6-cycle period
  - CR patients—2 cycles beyond confirmed CR
  - Addition of dexamethasone permitted
    - PD patients after 2 cycles
    - SD patients after at least 4 cycles
  - Extension protocol available for patients continuing to benefit

Velcade study – Czech results 1/05

Patient demographics and baseline characteristics

Age	median	61	(42-80)
Gender	M	18	
	F	11	
Stage (Durie-Salmon)	I. A	1	
	II. A	9	
	III. A	16	
	III. B	3	
M-component	IgG	18	
	IgA	7	
	LC	4	
Linie therapy	2	11	
	3	11	
	4	4	
	5	2	
	6	1	
No of previous lines of therapy			
ASCT single		5	
ASCT double		8	
ASCT triple		3	
Allo ASCT		1	
Thalidomide		11	

Summary results

CR: 4x (13,8%)

PR:10x (34,5%)

CR+PR: 14x (48,3%)

SD or better: 22x (75,9%)

Progression: 6 (20,7%)

Early death (after 1st dose): 1x

Response independent upon: MM type, del.13 (if available), beta2-mg

Mean time to response: 2,7 cycles

Velcade – výsledky v ČR. Odpověď nezávislá na počtu a typu předchozích režimů

Number of previous lines of treatment	Number of patients	Complete remission	Partial response	Minor response	Treatment failure
2	11	2	4	4	1
3	11	2	3	2	4
4	4	0	2	1	1
5	2	0	1	1	0
6	1	0	0	0	+

Addition of H-Dex

Total: 9 pts.

Results:

- better response: 4x
- no response: 2x
- progression (th.failure): 3x

Toxicity – overall (28 pts.)

Thrombocytopenia: 16x (57,1%)

Neuropathy: 8x (28,6%)

Other:

- Anemia: 10x (35,7%)
- GIT: 7x (25%)
- Renal: 4x (14,3%)
- Fatigue: 4x (14,3%)
- Liver: 2x
- Leucopenia: 2x
- Skin: 1x

Toxicity – grade 4 (28 pts.)

Thrombocytopenia: 5x

GIT: 2x

Renal: 2x

Hepatopathy: 1x

Leucopenia: 1x

Anemia: 1x

Total: 44,8%

Neurotoxicity – the most serious problem of Velcade therapy?

- SUMMIT – 31%
  - SUMMIT gr.3/4 – 17%
- Czech experience – 31%
  - Gr.3/4 – 10,7%
- In 1 patient therapy discontinued due to gr.3 neurotoxicity
- PN present in 80% pts. during therapy according to some studies

drug	sensoric	motoric
Thalidomid	12-47%	29%
Vincristin	75%	19%
Platin	13-86%	NA

Thrombocytopenia – minor problem of Velcade therapy?

- SUMMIT incidence: 40%

  Gr.3/4: 31% (gr.3-28, gr.4-3%)
- Czech experience:incidence 55,2%

  Gr.3/4: 32%
- Transitory, day 1-11, mostly improved day 12-21 (dose reduction)

Case report

Female E.C., age 43

Multiple myeloma, LCL, clin.st. III B, dg.1/99

Induction 4xVAD, stem cells not collected (2x mobilisation-CFA+G-CSF, G-CSF)

4xVAD, radiation (S 1)

PR achieved, maint. th.IFN-alfa

1st relaps 9/03, 3x VID, 2nd PR

2nd relaps 4/04

Velcade 1,3 mg/m started 5/04. Creatinine 220 umol/L

Acute renal failure (ARF) after 2nd cycle, 2x HD

Dose reduction from 3rd cycle (1 mg/m), iv. hydration before and after Velcade administration

CR 6/04 up to now

SINGLE vs DOUBLE ASCT RANDOMIZED STUDIES

	No. of pts	Age	Results
IFM 94 (*N Engl J Med* 03)	399	< 61	EFS and OS ↗
MAG 95 (Turin 04)	227	< 56	No difference
Bologna (Turin 04)	220	< 61	EFS ↗
GMMG (Turin 04)	261	< 66	EFS ↗
Hovon (Turin 04)	303	< 66	CR and EFS ↗

SINGLE vs DOUBLE ASCT
CONCLUSION

- The only study with mature data shows a significant benefit (EFS, OS) with double ASCT

- 4/5 randomized trials are currently in favor of double ASCT (↗ EFS)

- However, long-term EFS is only 20% (IFM 94)

- Patients with poor-risk characteristics have a poor outcome even with tandem ASCT (Arkansas)

CONCLUSION

- Autologous SC transplantation is now the standard of care, but the introduction of novel agents is changing the scene

- Rather than again comparing ASCT with standard-dose therapy, including novel agents (MPT, MPV)

- It appears more attractive to evaluate the impact of combining these novel agents with ASCT

- The role of allogeneic SCT in MM still needs further study