

Signal transduction and survival IL-6 and IGF-1

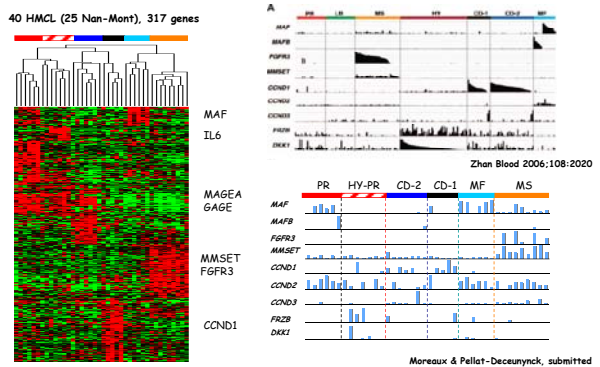
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Heterogeneity of MM is of biological origin

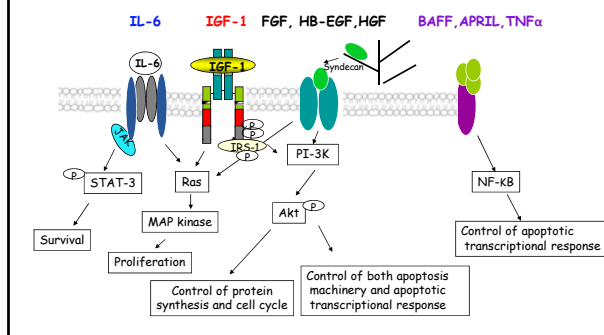
- Genomic heterogeneity: hyperdiploidy and translocations
- Phenotypic heterogeneity: CD19/20, CD28, CD45, CD117
- Functional heterogeneity: growth factor responses, survival molecules



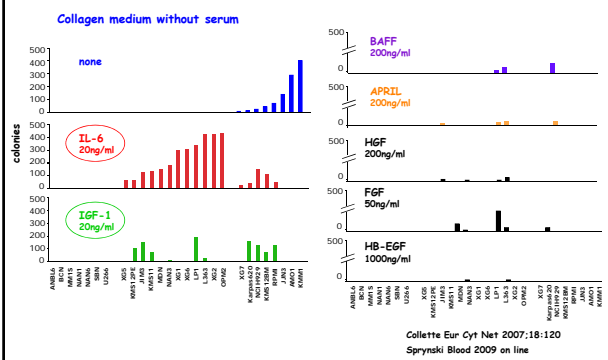
Molecular validation of HMCL heterogeneity



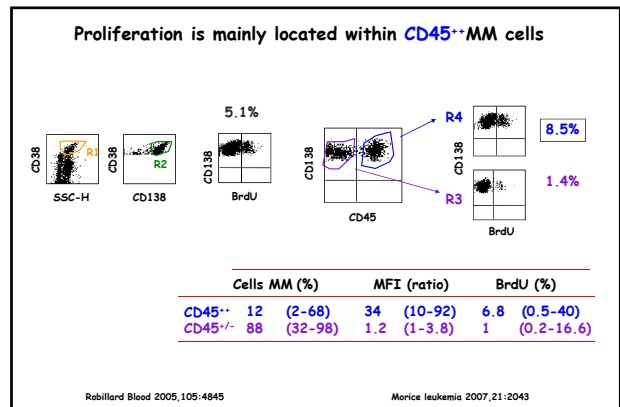
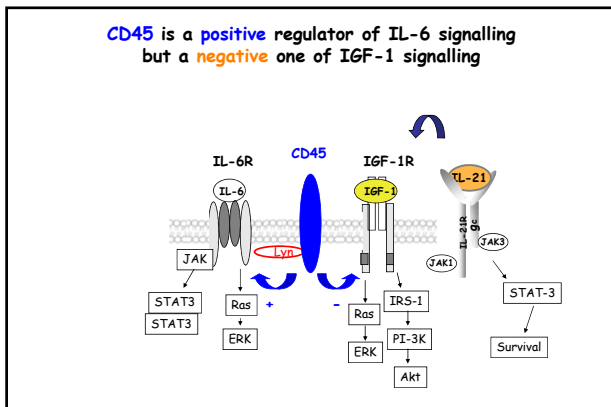
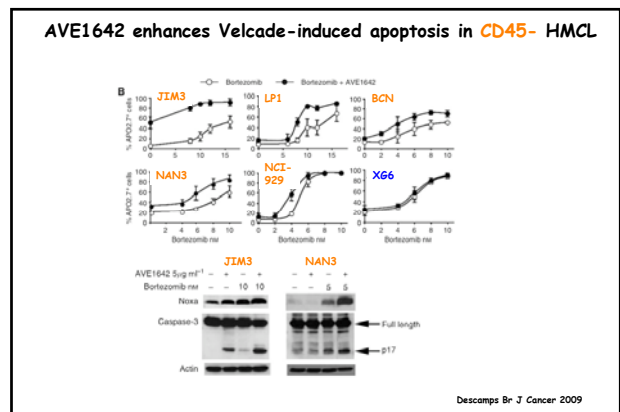
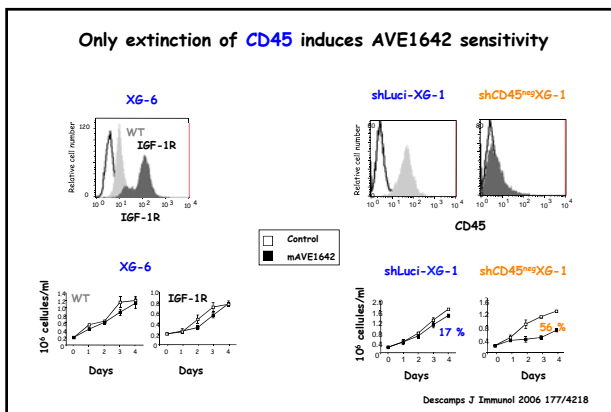
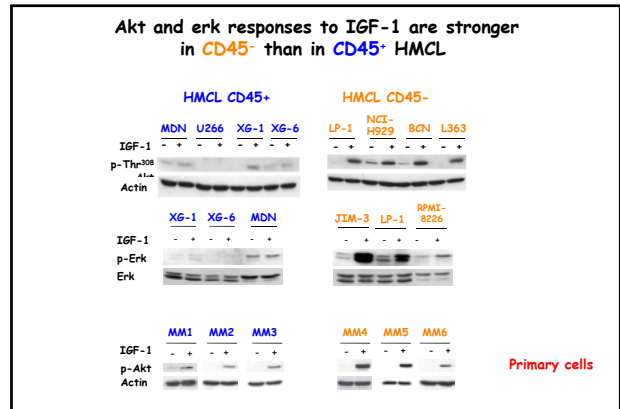
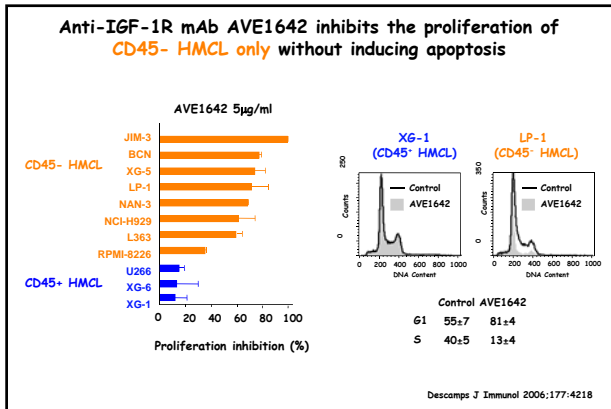
Major growth factors of myeloma cells

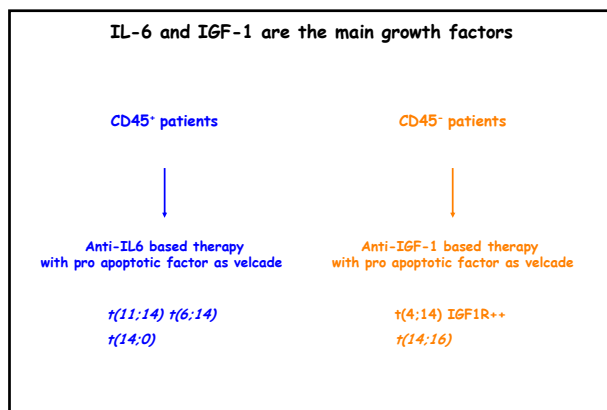
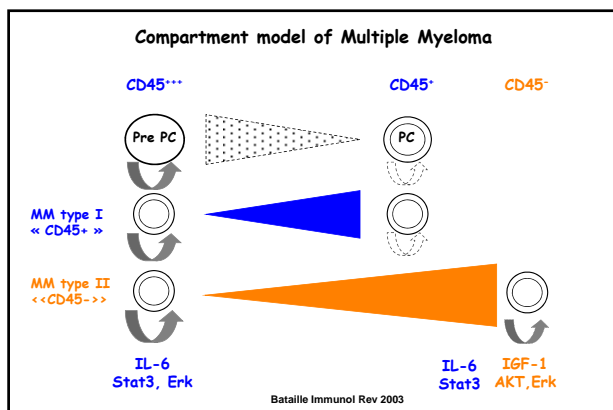


IL-6 and IGF-1 are the main growth factors



IL6





Phase I clinical trials with anti-IGF-1R human mAb

47 patients in relapse or refractory (median: 4 treatments), 11 cohorts

Table 1. Dosing Summary

Dose Cohort (mg/kg)	No. of Patients	No. of Cycles of CP-751,871 Alone	No. of Patients Receiving		No. of Cycles per Cohort	No. of Cycles per Patient
			Dexamethasone	Rapamycin		
0.025	3	4	---	---	5	1.7
0.05	4	5	3	---	12	3.0
0.1	3	17	2	---	21	7.0
0.2	3	21	1	---	28	9.3
0.4	4	12	3	---	28	7.0
0.8	3	18	1	---	18	6.0
1.6	3	8	3	---	24	8.0
3	4	8	3	---	11	2.8
6	3	10	---	---	10	3.3
12*	7	25	5	1	38	5.4
24*	10	14	5	3	32	3.2
Doses ongoing dosing cohort		47	27	4		

Day 1 of 4-week treatment cycles
 CP-751,871 Pfizer

Dexamethasone addition
 At cycle 2 when progressive disease
 At cycle 4 when less than partial response
 (40mg/day), 4 days/week, 3-week cycle, 3 cycles
 Ex 40mg/day days 1 to 4 for subsequent cycles

No objective responses
 28 stabilization (6 months for 6 pts)

13 stable disease
 9 objective responses (2-14 months)

IGF1 might mediate dexamethasone resistance

Lacy JCO 2008;26:3196

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