

# Large Uterine Leiomyomata: Spatial distribution of the tumorigenic factors

X Zhang, K Mittal, L Chiriboga,  
H Yee, J Wei\*

Department of Pathology, New York University School of  
Medicine, New York



# HYPOTHESIS

Q: Why do large fibroids continue to grow or regrow in the presence of an extensive hyalinized degeneration or necrosis

- Untreated tumors
- Treated by GnRHAs or UAE

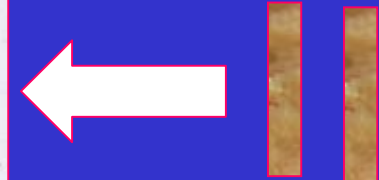
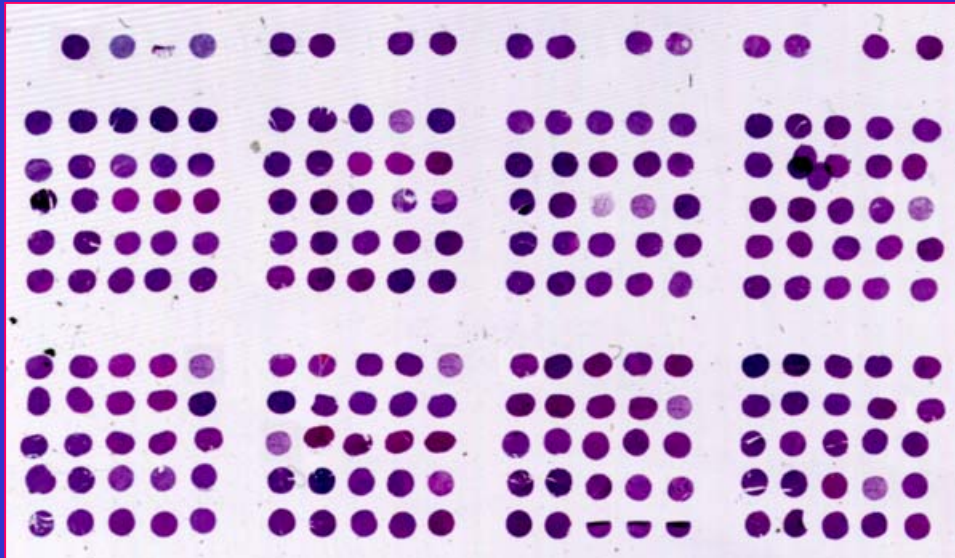
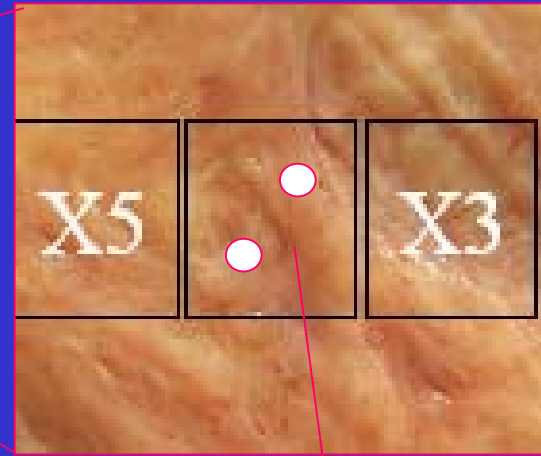
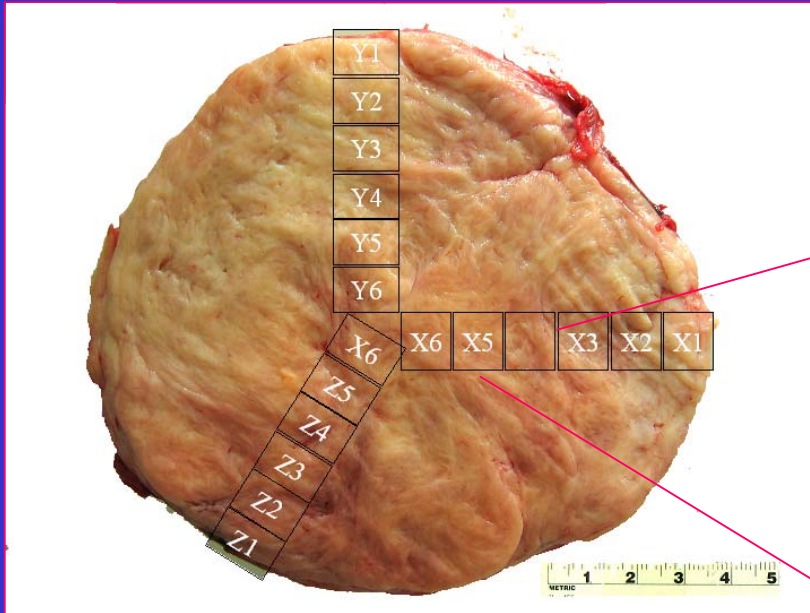
H: There are spatial differences in tumor activity in large fibroids

- Gene expression
- Vasculature
- Degeneration



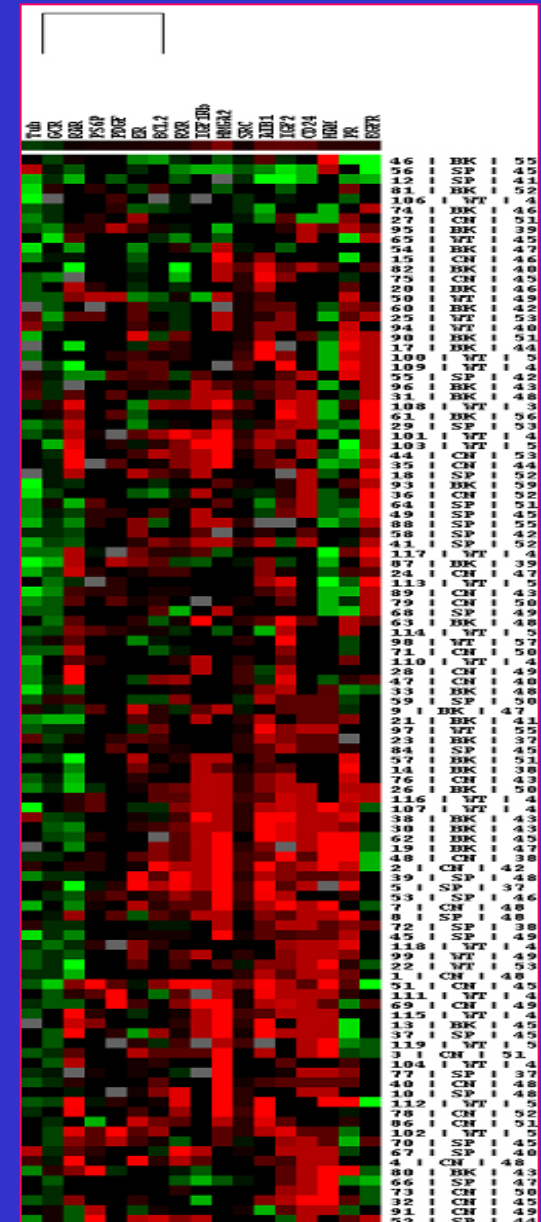
# DESIGNS

	age	Races	size	weight	phase	No.	MM	Large ULM/LMS			Small	cytogenetics	fixed time
	(yrs)		(cm)	(gms)		ULM		X	Y	Z	ULM		(hrs)
ULM1	34	B	10	1550	S	5	2	5	5	5	2	no	24
ULM2	38	B	10	610	S	3	2	6	6	6	2	NM	24
ULM3	47	B	12	1950	P	12	2	6	6	6	2	NM	24
ULM4	45	W	11	1350	P	7	2	6	6	6	2	NM	24
ULM5	52	W	13	1850	I	4	2	6	6	6	2	del (7q22-q32)	24
ULM6	44	A	13	1300	P	8	2	6	6	6	2	NM	24
ULM7	46	W	10	1050	P	10	2	6	6	6	2	add(1p10)	24
LMS1	55	W	14	1350	I	1	2	6	6	6	0	complex	24
LMS2	53		12	1400	I	3	2	6	6	6	2	complex	24
LMS3	63	O	17	946	I	2	2	6	6	6	2	complex	24



# Markers selected based on gene chip and our TMA data

- |            |                         |
|------------|-------------------------|
| 1. ER/PR   | • Sex hormone signaling |
| 2. IGF2    | • IGF signaling         |
| 3. RAR/RXR | • RA signaling          |
| 4. EGFR    | • TGF signaling         |
| 5. GCR     | • Anti-fibrosis         |
| 6. BCL2    | • Anti-apoptosis        |
| 7. F-IIIV  | • Vessel density        |
| 8. MIB1    | • Proliferation index   |
| 9. HMGA2   | • Fibroid associated    |
| 10. CD24   | • Fibroid associated    |



# Immunostains & data analyses

- One and two score systems

1. Immunointensity:  
0 (neg.), 1 (+), 2 (++),  
3 (+++), 4 (++++).
2. Immunopositivity:  
0, 1 (10%), 2 (10-50%),  
3 (51-80%), 4 (>80%).

- Two pathologists

- Score normalization
  - Tumor-myometrium

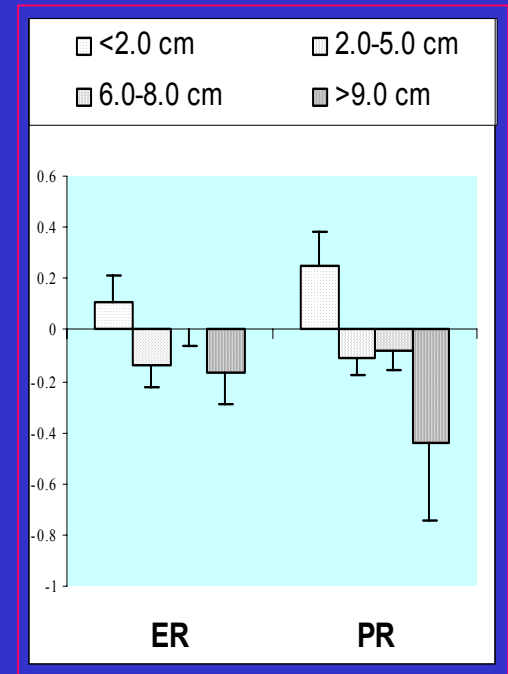
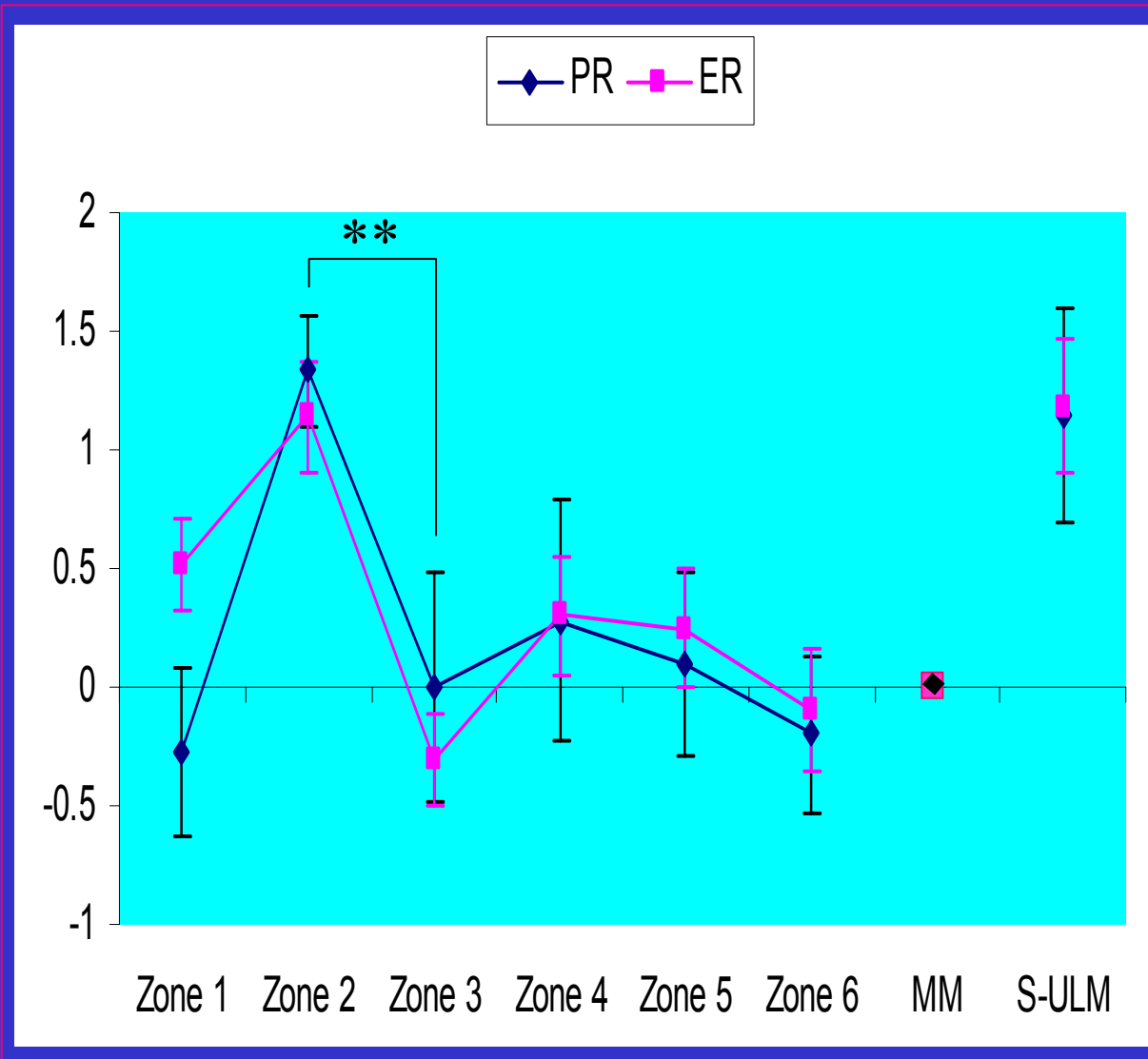
- Statistics

- Mean
- standard error
- p* value

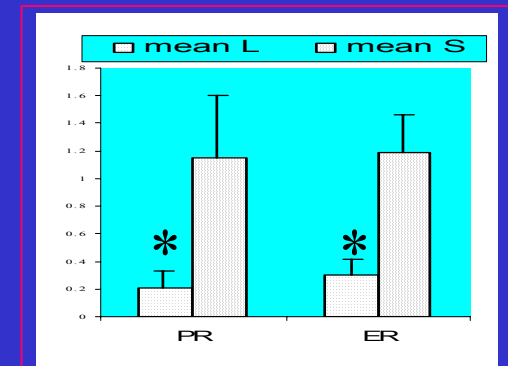
# Semiquantitation of PR from each tumor zone against matched myometrium

Zones	Axis	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	MEAN	SE
1	X	-1.667	-2.667	1.333	1.333	-1.667	-1.667	1.333		
1	Y	-4.667	1.333	1.333	-1.667	3.333	1.333	1.333		
1	Z	-3.667	-1.667	1.333	-1.667	1.333	3.333	1.333	-0.2781	0.3512
2	X	-2.667	-1.667	1.333	7.333	3.333	-2.667	3.333		
2	Y	-2.667	-0.667	3.333	1.333	3.333	1.333	1.333		
2	Z	-3.667	3.333	3.333	3.333	3.333	3.333	3.333	1.333	0.2364
3	X	-2.667	1.333	1.333	-1.667	1.333	-1.667	1.333		
3	Y	-2.667	-1.667	1.333	1.333	1.333	-2.667	1.333		
3	Z	-3.667	1.333	1.333	1.333	1.333	1.333	3.333	0	0.4851
4	X	-1.667	-2.667	1.333	1.333	1.333	-1.667	1.333		
4	Y	-2.667	-2.667	1.333	1.333	1.333	3.333	1.333		
4	Z	-3.667	1.333	1.333	3.333	1.333	1.333	1.333	0.2774	0.5079
5	X		1.333	1.333	-0.667	1.333	-1.667	1.333		
5	Y	-2.667	1.333	-1.667	1.333	1.333	-1.667	-1.667		
5	Z	-2.667	-0.667	-1.667	1.333	1.333	1.333	1.333	0.0977	0.3885
6	X	-4.667	-1.667	1.333	3.333	1.333	1.333	-1.667		
6	Y		-0.667	1.333	-1.667	1.333	1.333	1.333		
6	Z		-1.667	-1.667		-1.667	-0.667	1.333	-0.2003	0.324
Small	ULM	4.667	-0.667	1.333	3.333	-0.667	1.333	-0.667		
Small	ULM	7.333	-0.667	3.333		3.333	1.333	3.333	1.1512	0.4524

# Spatial difference of ER/RP in large myomas

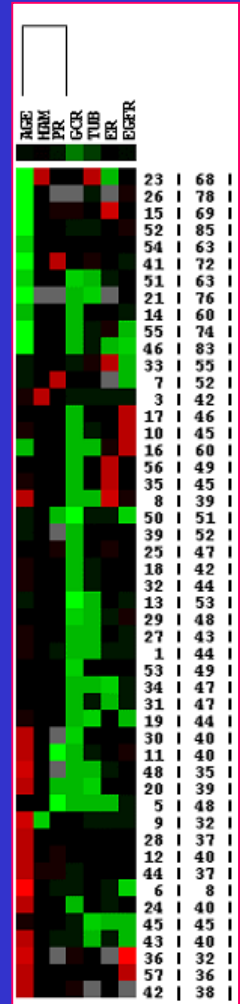
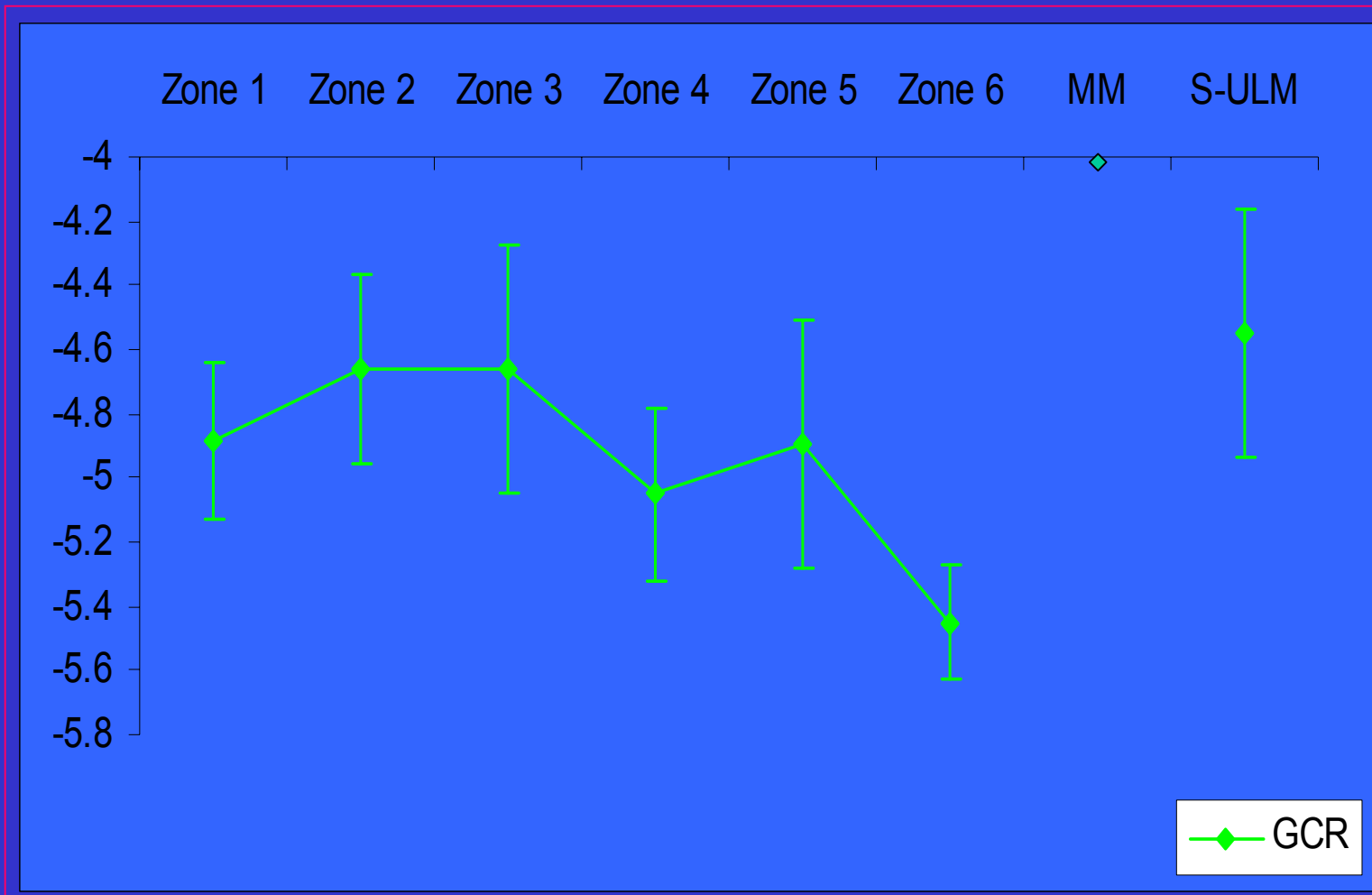


*Wei et al. Fertility & Sterility 2005 in press.*

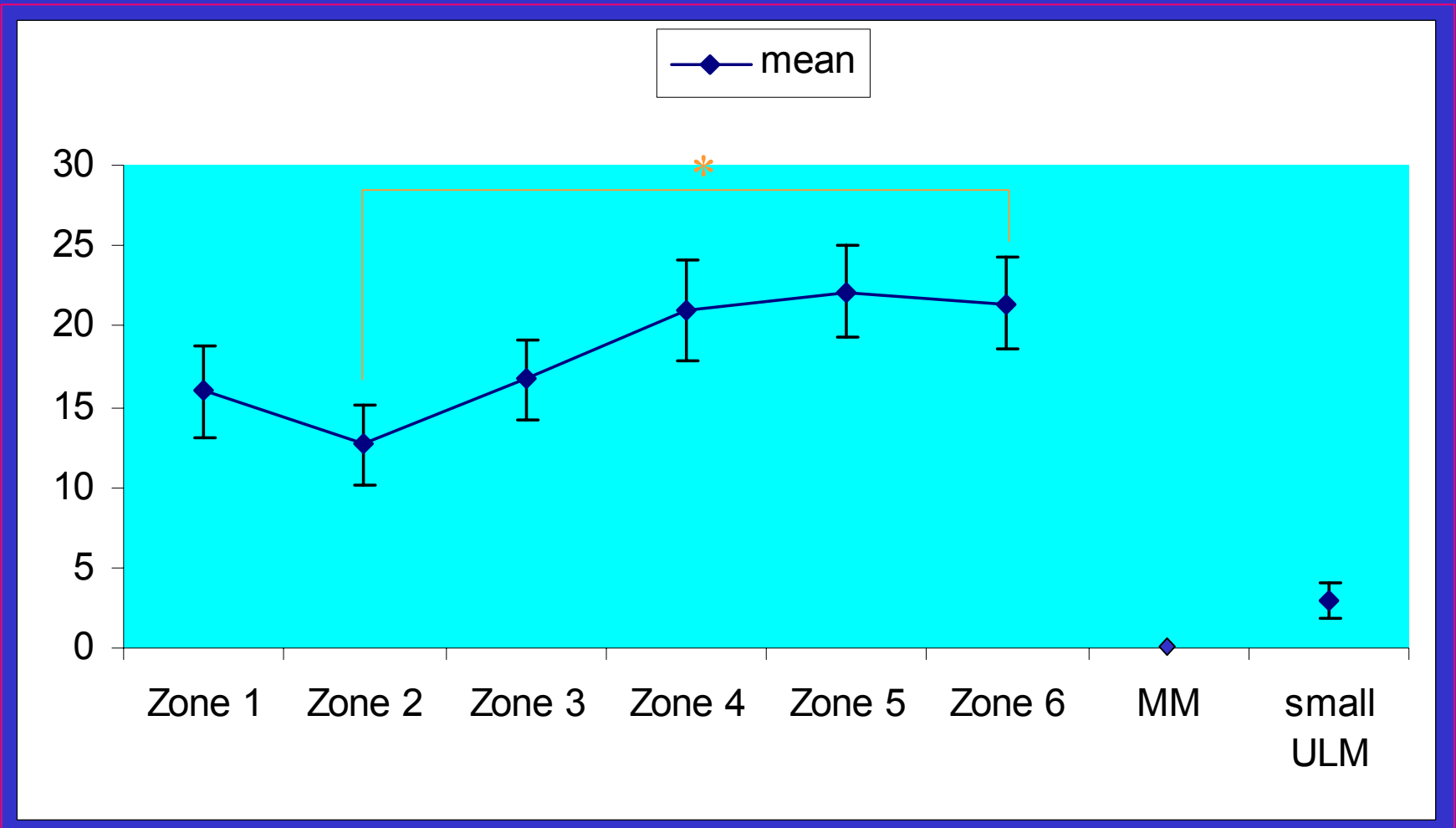




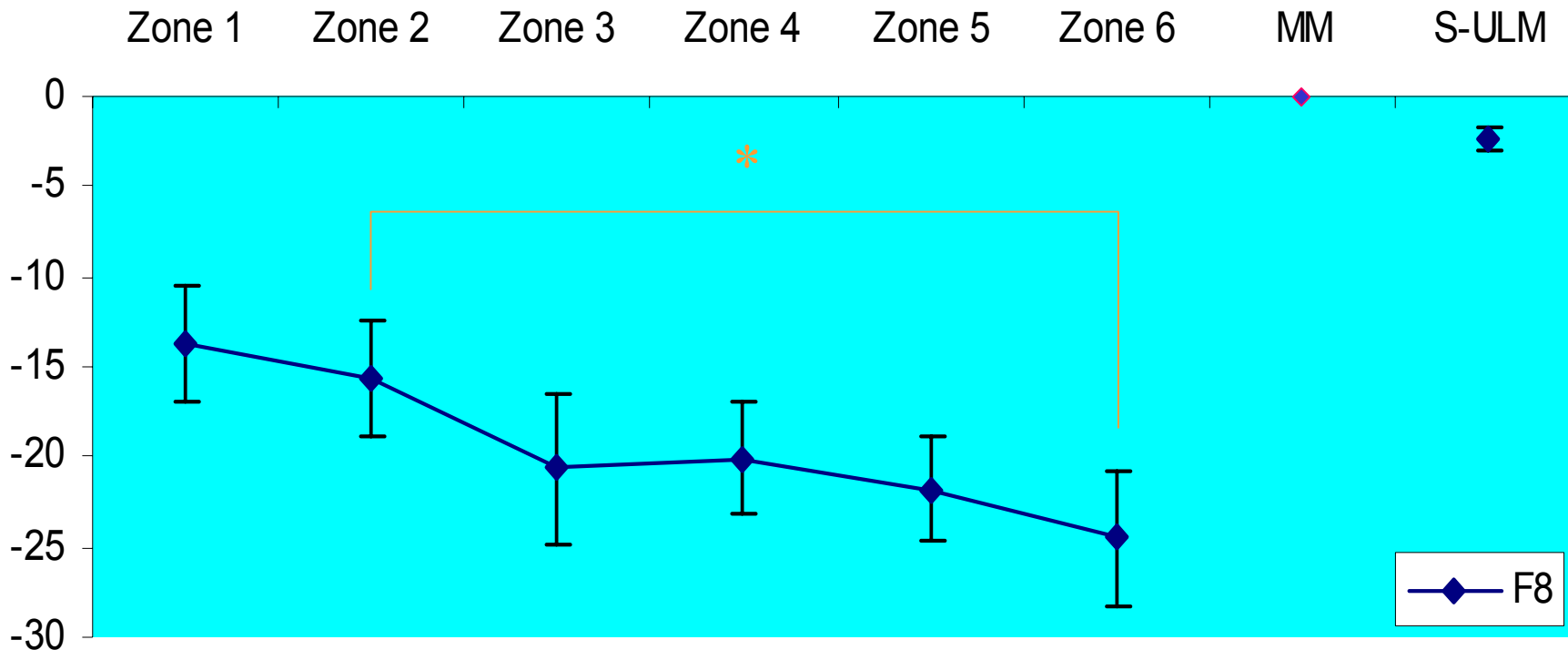
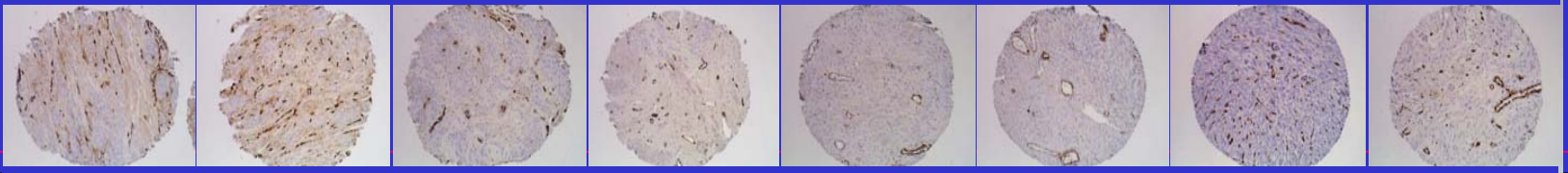
# Down regulation of glucocorticoid receptor in large myomas



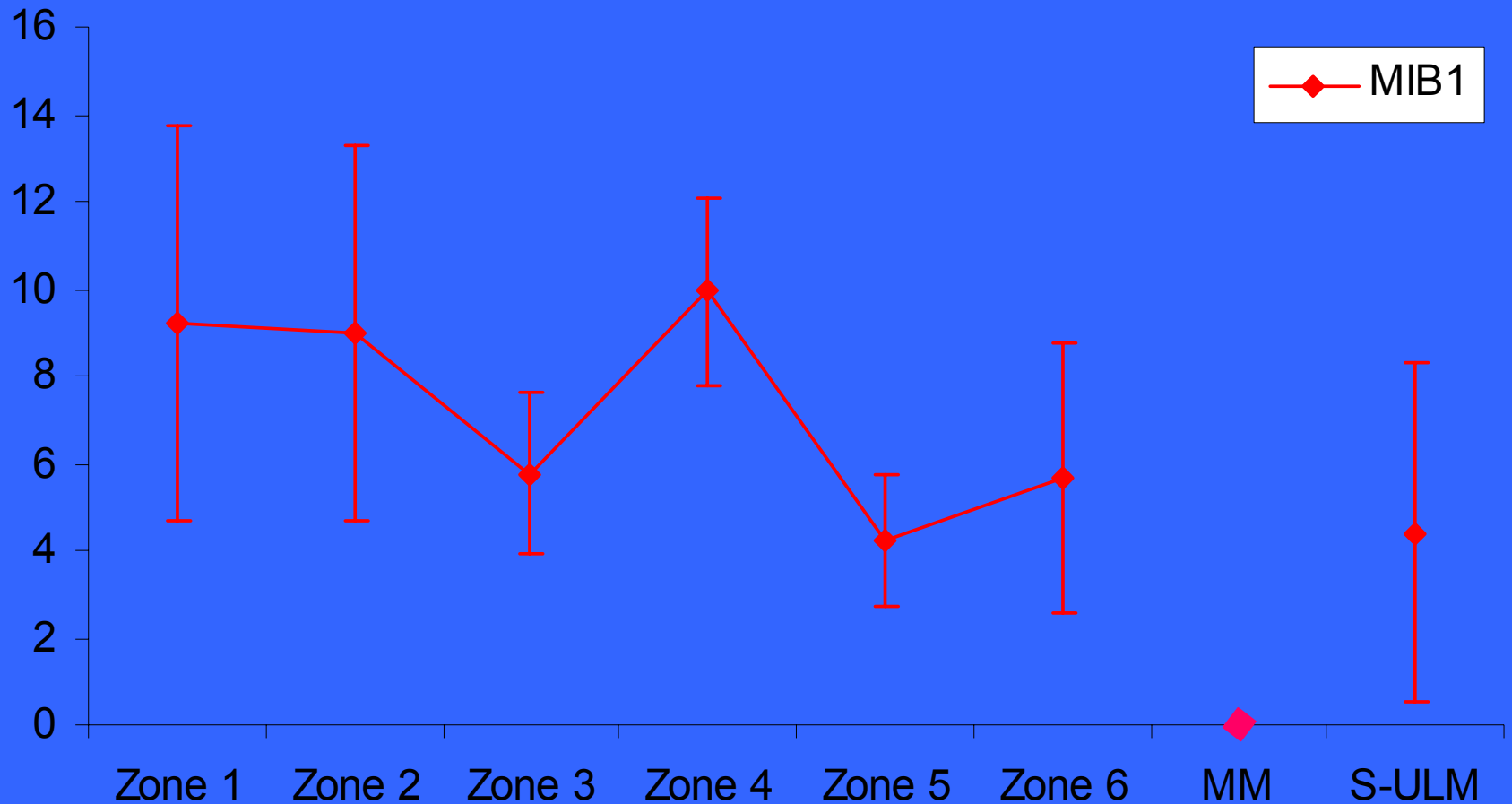
# Spatial distribution of hyalinization/necrosis (%)



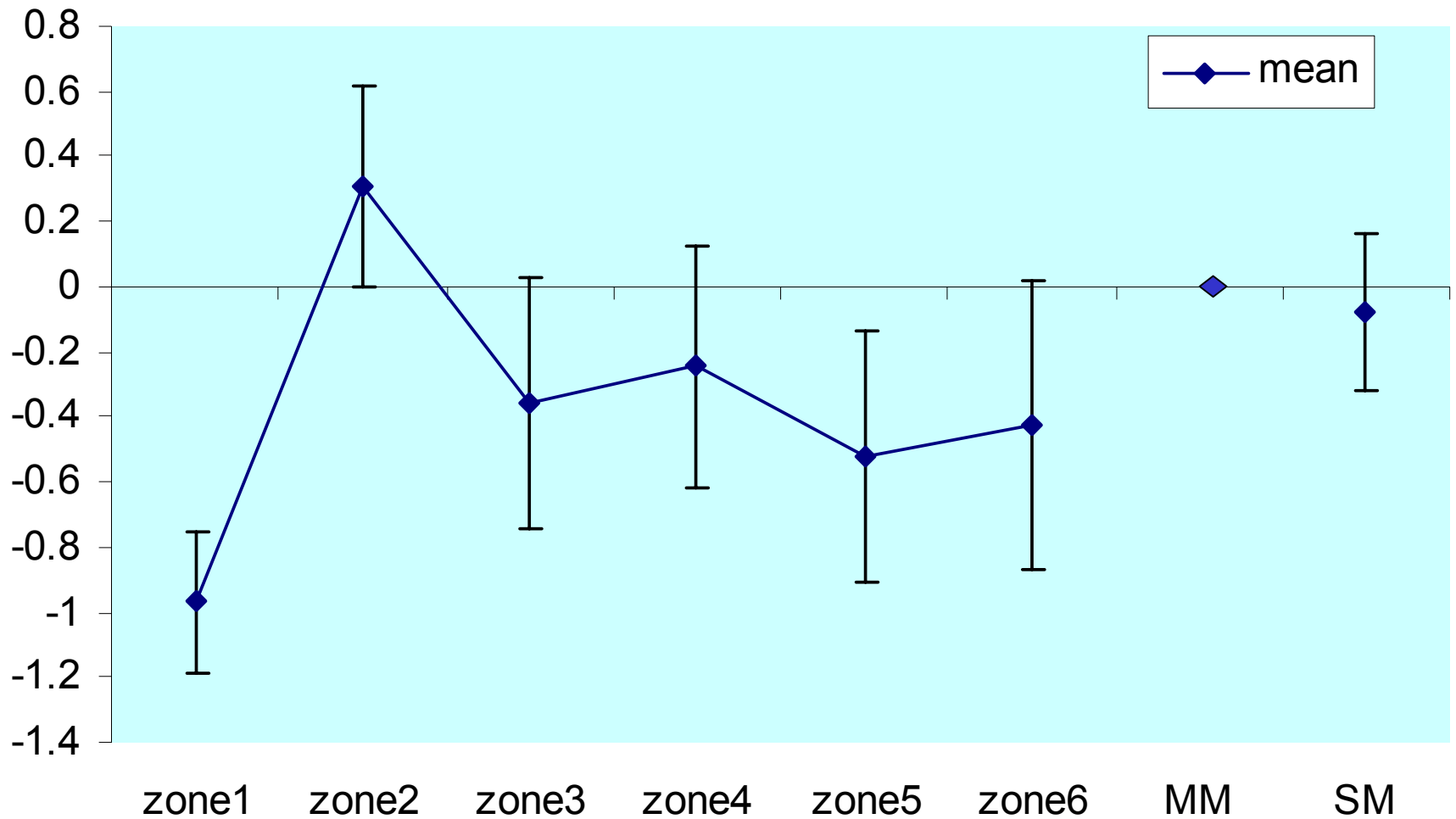
# Level of vascular reductions in different zones in large myomas



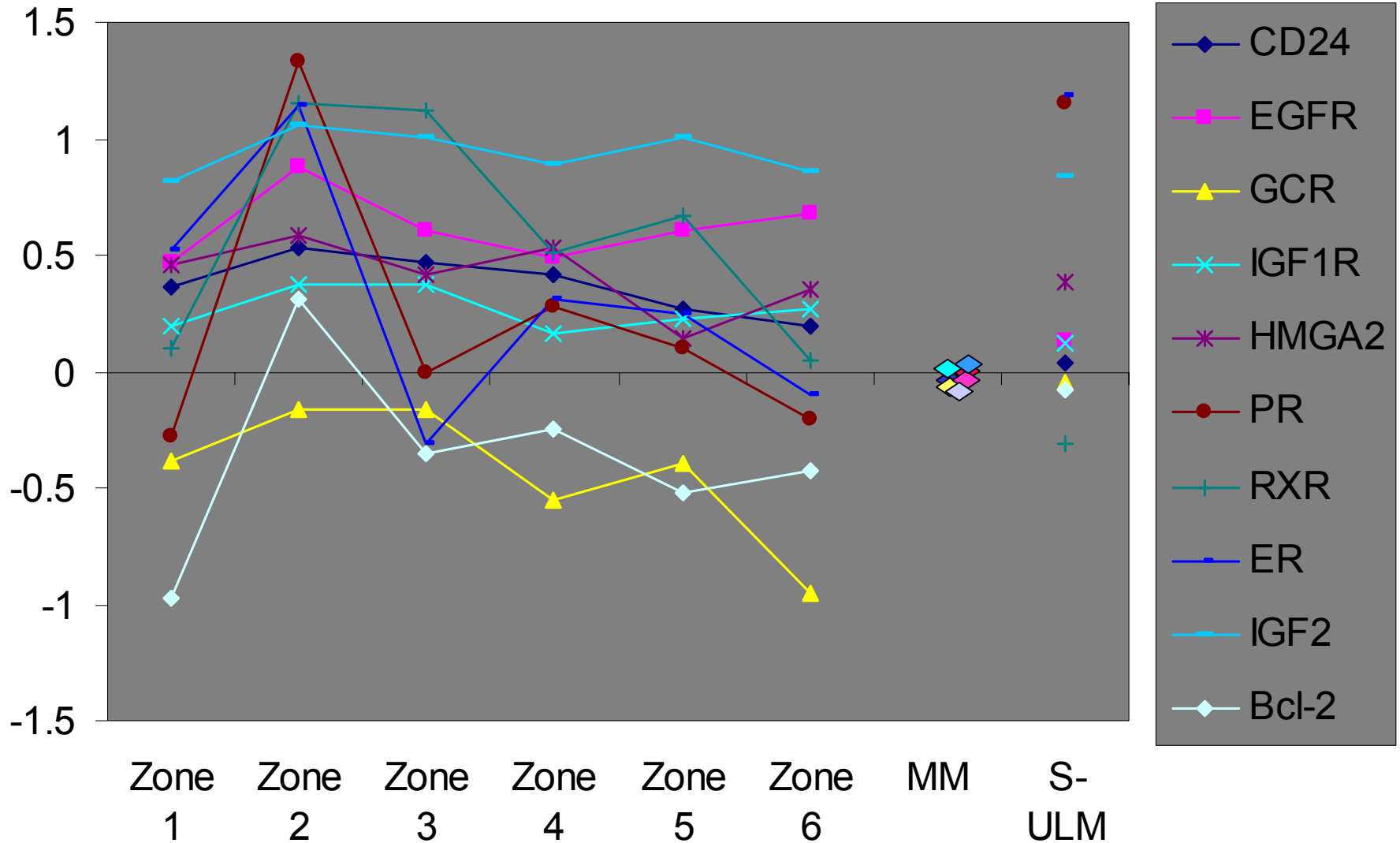
# Proliferative activity in different zones in large myomas



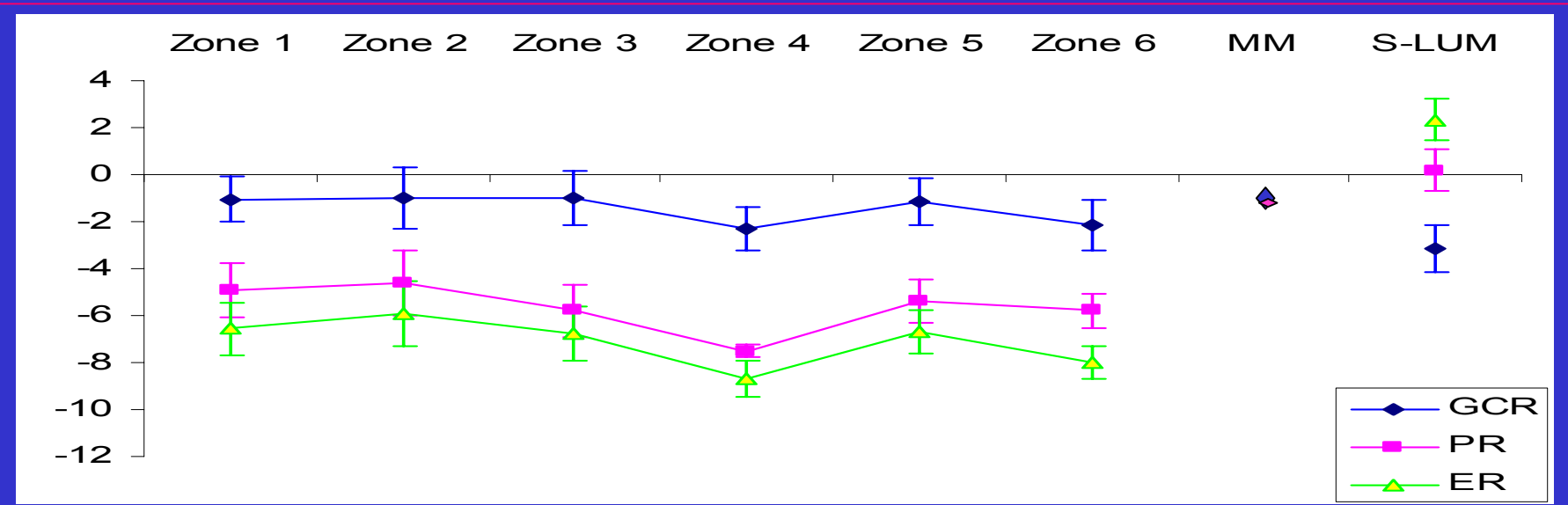
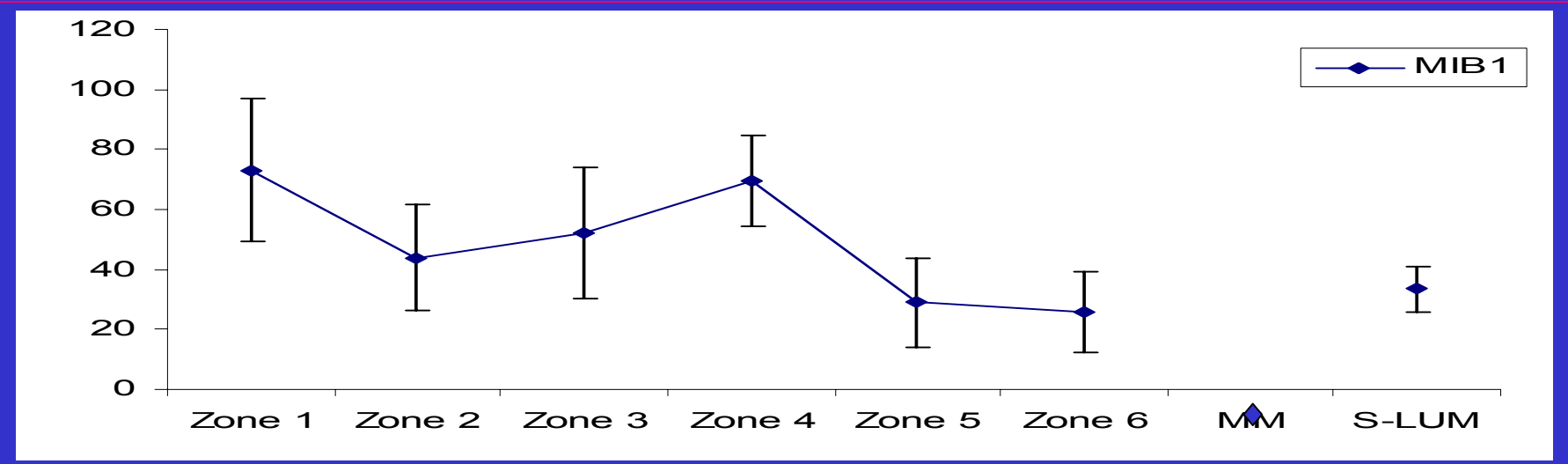
# Spatial distribution of Bcl-2 in large myomas



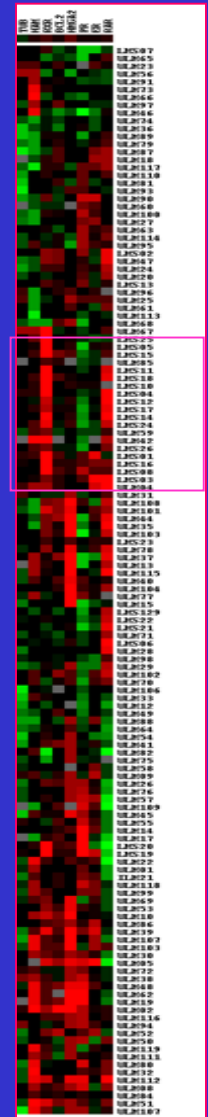
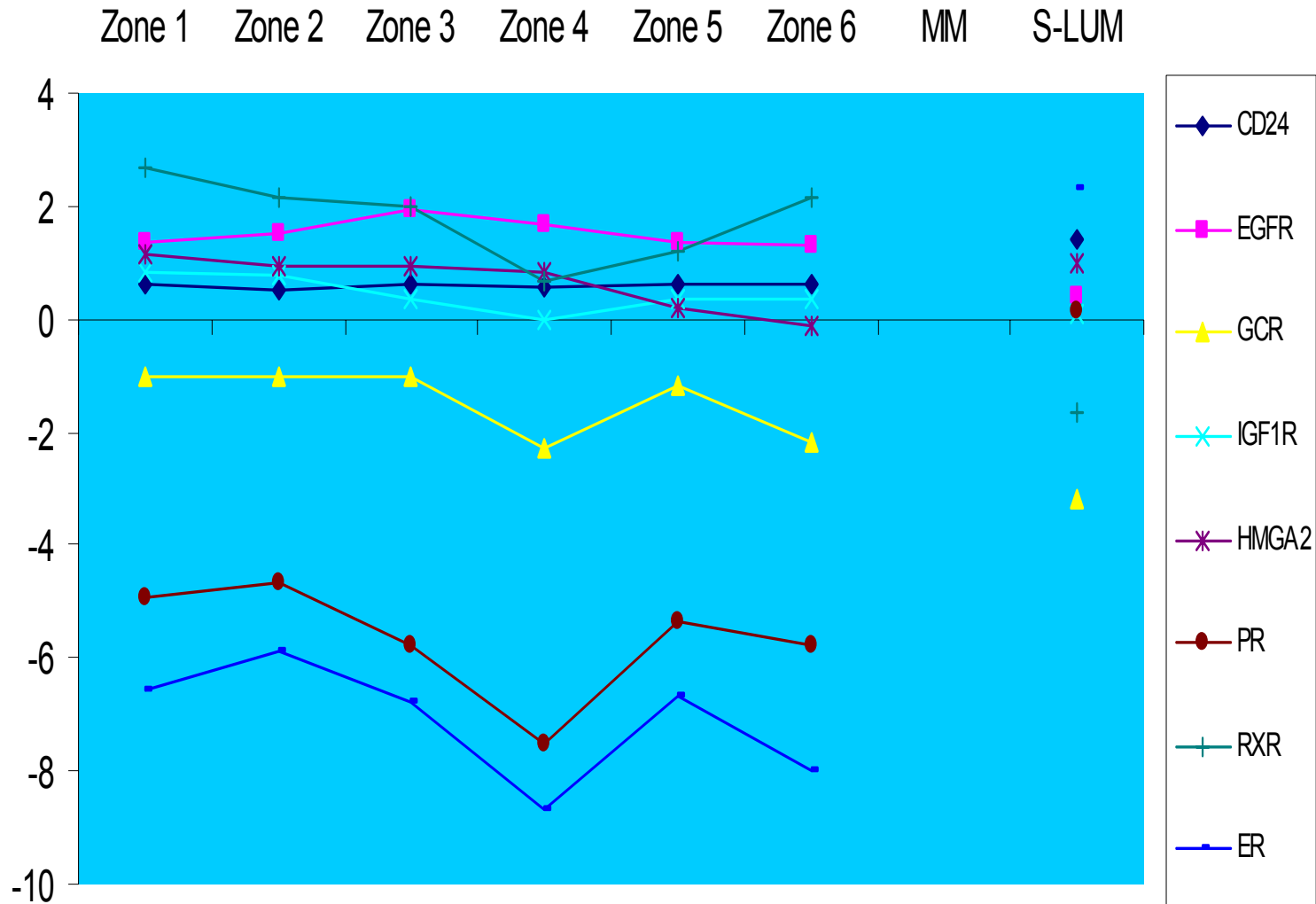
# Spatial expression of the selective dysregulated genes in large myomas



# Spatial distribution of ER/PR & MIB1 in LMS



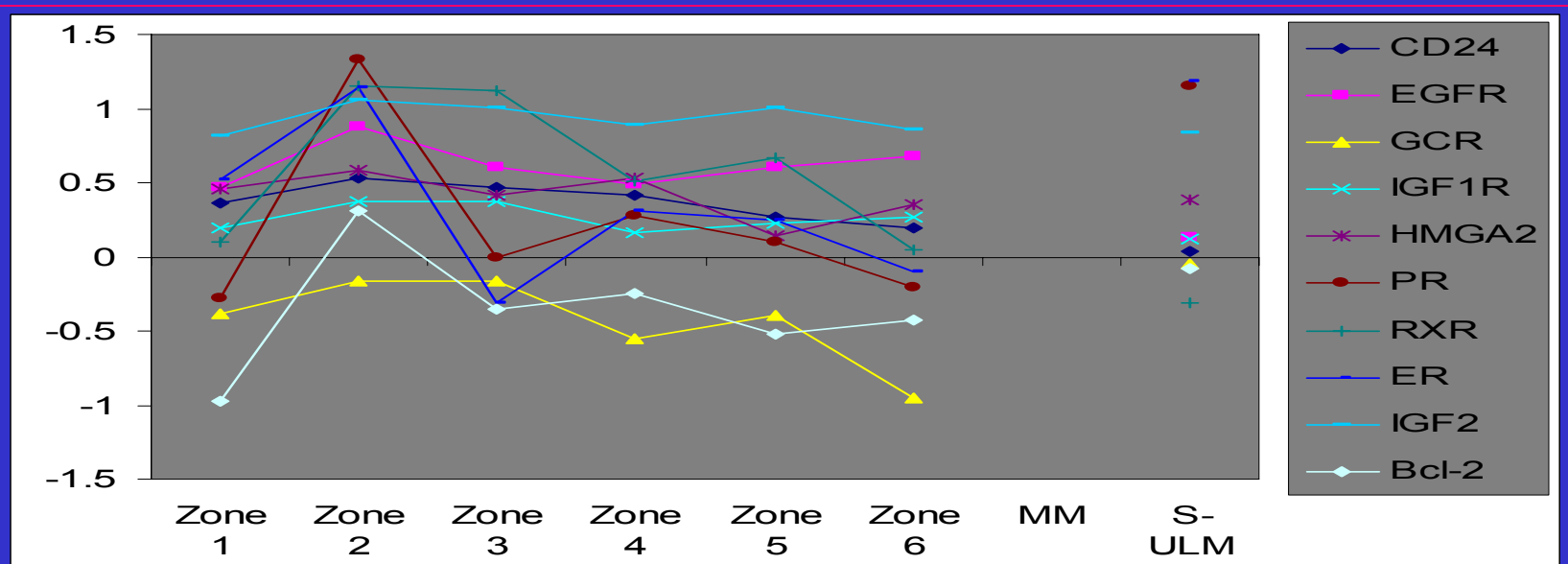
# Spatial distribution of the selected genes in LMS





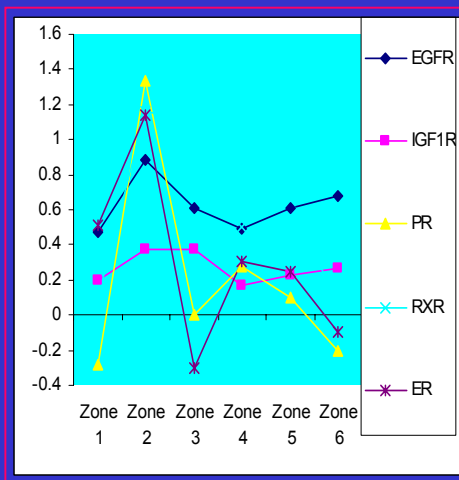
# CONCLUSIONS

1. This is the first attempt in examining the dysregulated gene products in the spatial regions in the large ULM. The regional differences in the gene expressions are found in most, but not all, selected genes in large ULM.

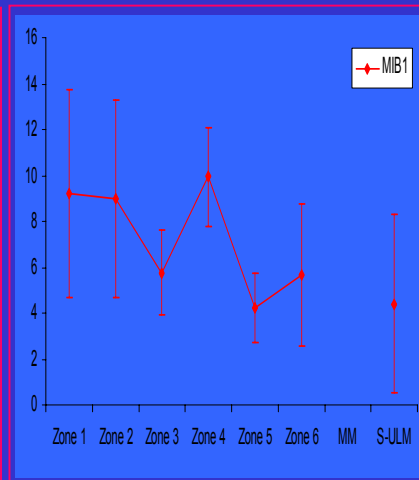


2. Gene dysregulation is the highest in zone 2 (next to peripheral region) in large ULM. The higher level of gene dysregulation is associated with a higher rate of cell proliferation, a higher density of vessels and a lower level of hyalinization.

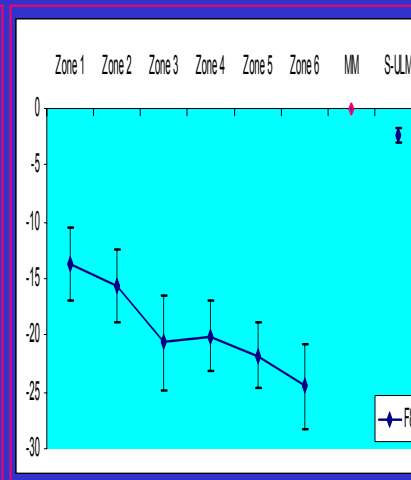
Zone 2



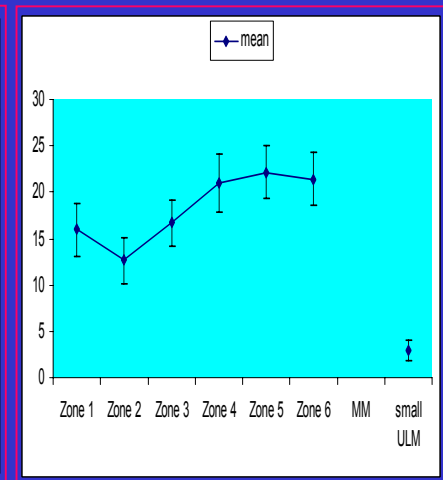
MIB-1



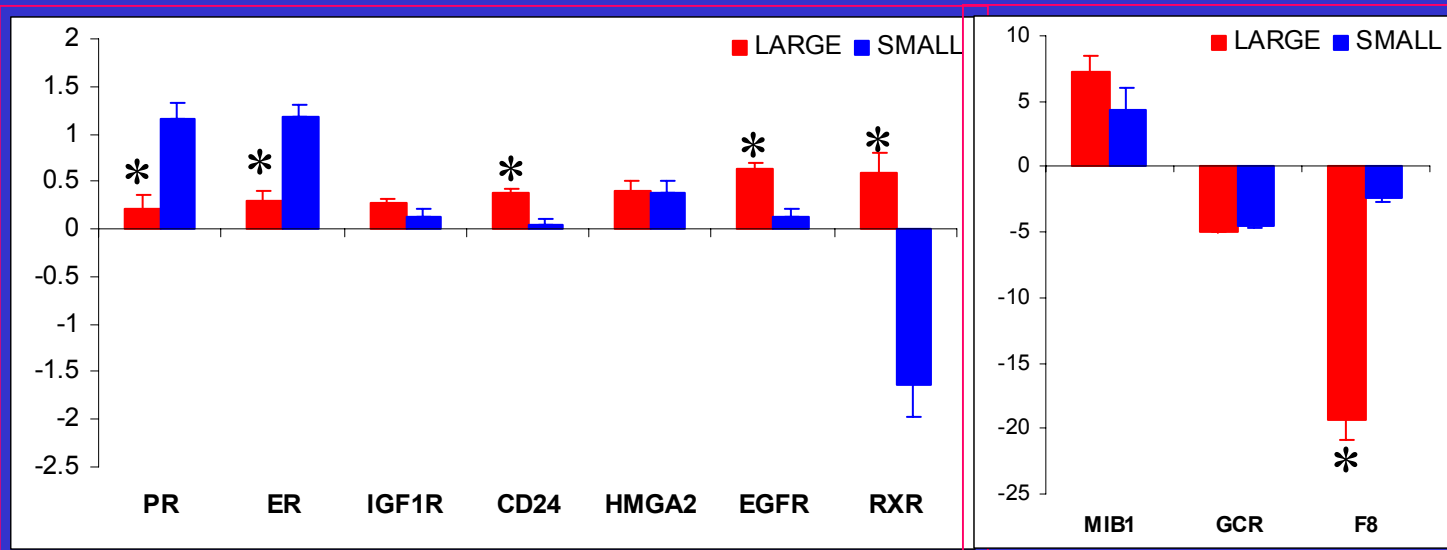
Vessels



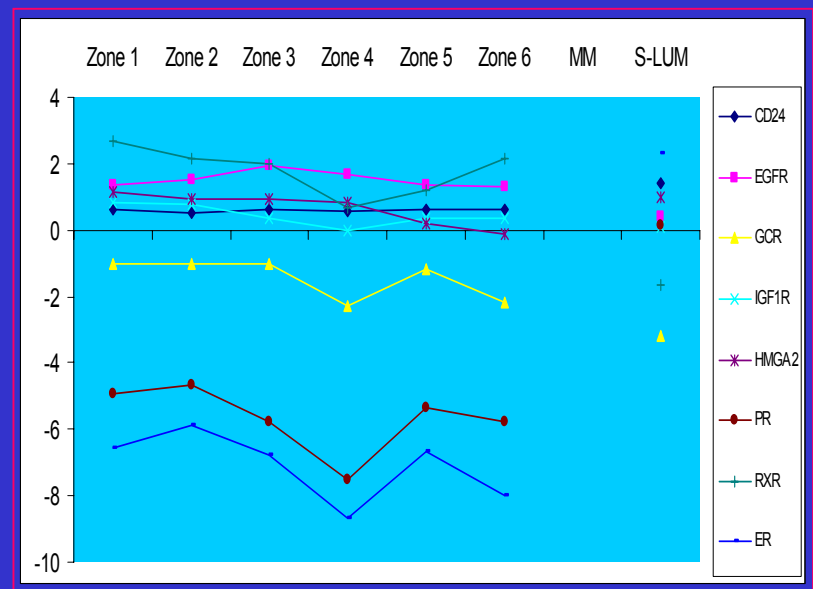
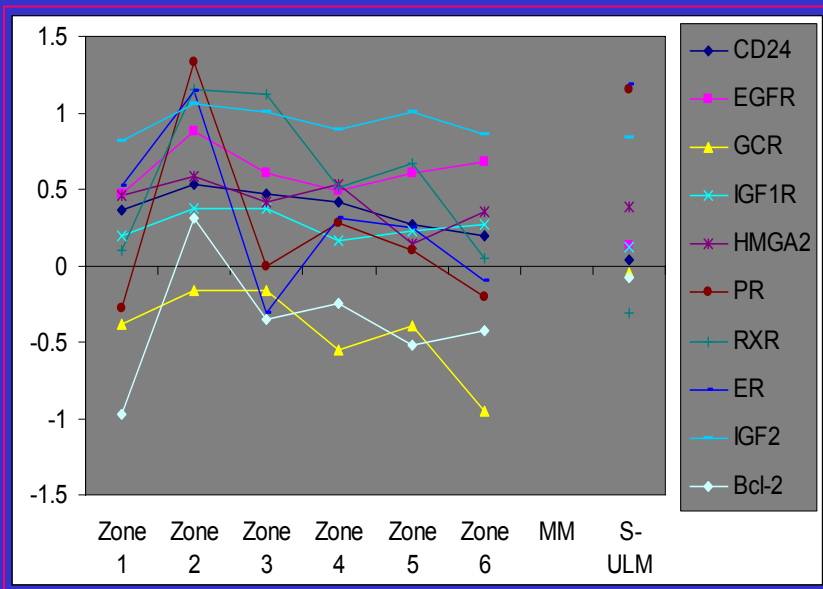
Hyalinization



3. There is a substantial difference of the gene expressions between the large and small ULM. This difference may be caused by a varied regional activity in the large ULM or by a biological difference between the large and small ULM.



# 4. Spatial pattern of the gene dysregulation between the uterine leiomyoma and the uterine leiomyosarcoma suggests a unique growth behavior in large ULM.

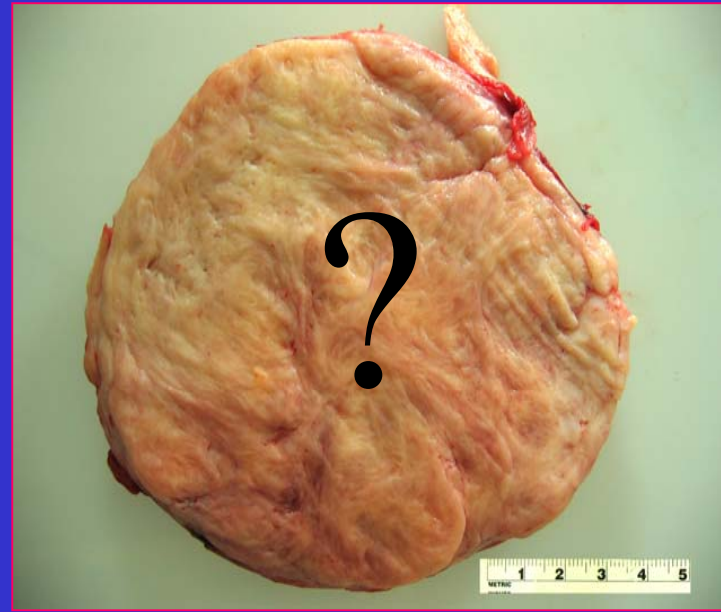


# QUESTIONS & FUTURE DIRECTIONS

1. Does vessel density play a critical role in the spatial biological differences in large ULM?

2. Are the spatial differences dependent on nutrition (transient) or genetics (permanent)?

3. Do the current treatments target the biologically active zone?



*Mapping more large ULM in a well designed protocol!*