Unfolded Protein Response (UPR) is a risk factor for Alveolar Rhabdomyosarcoma (RMS)?

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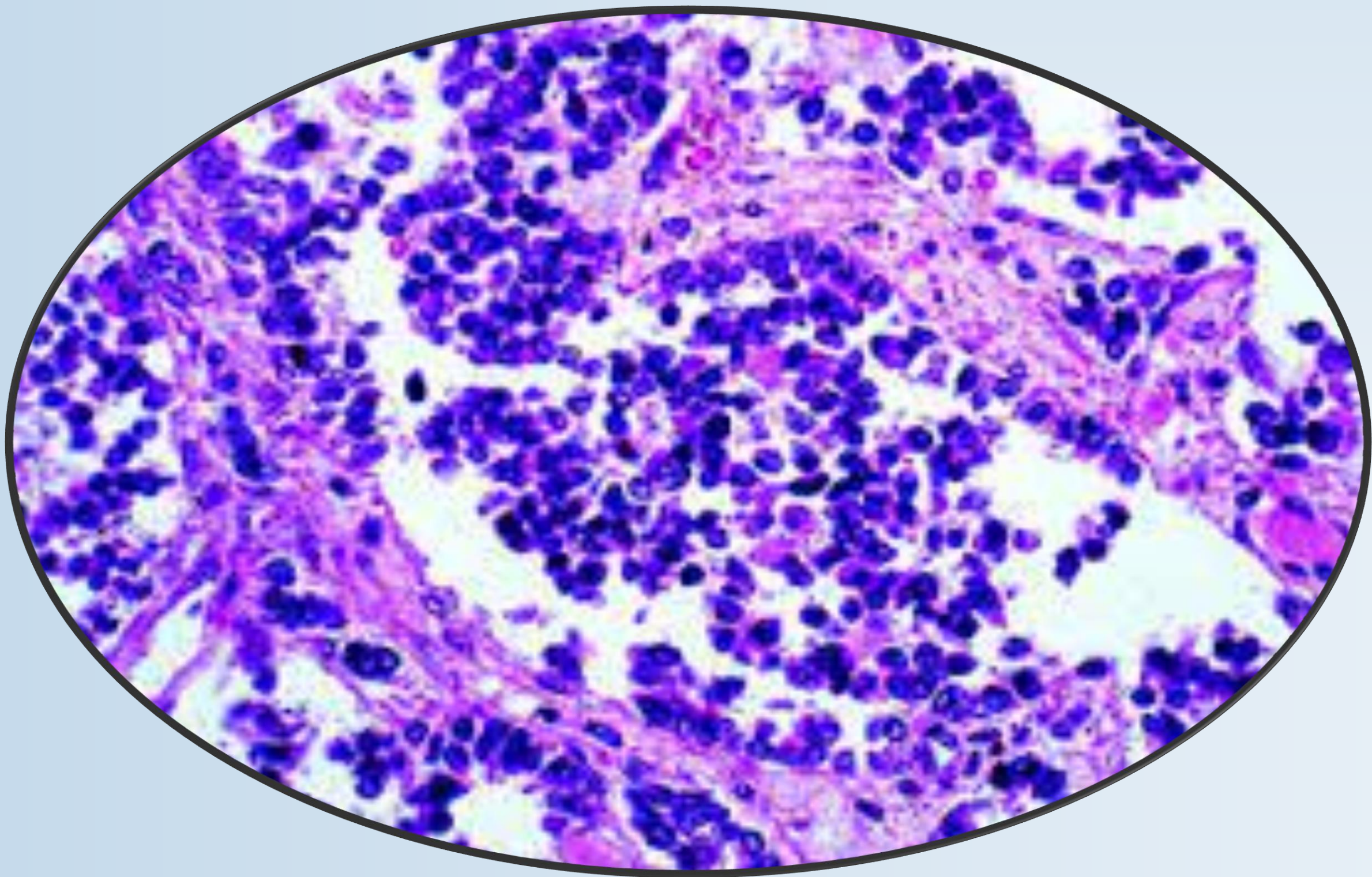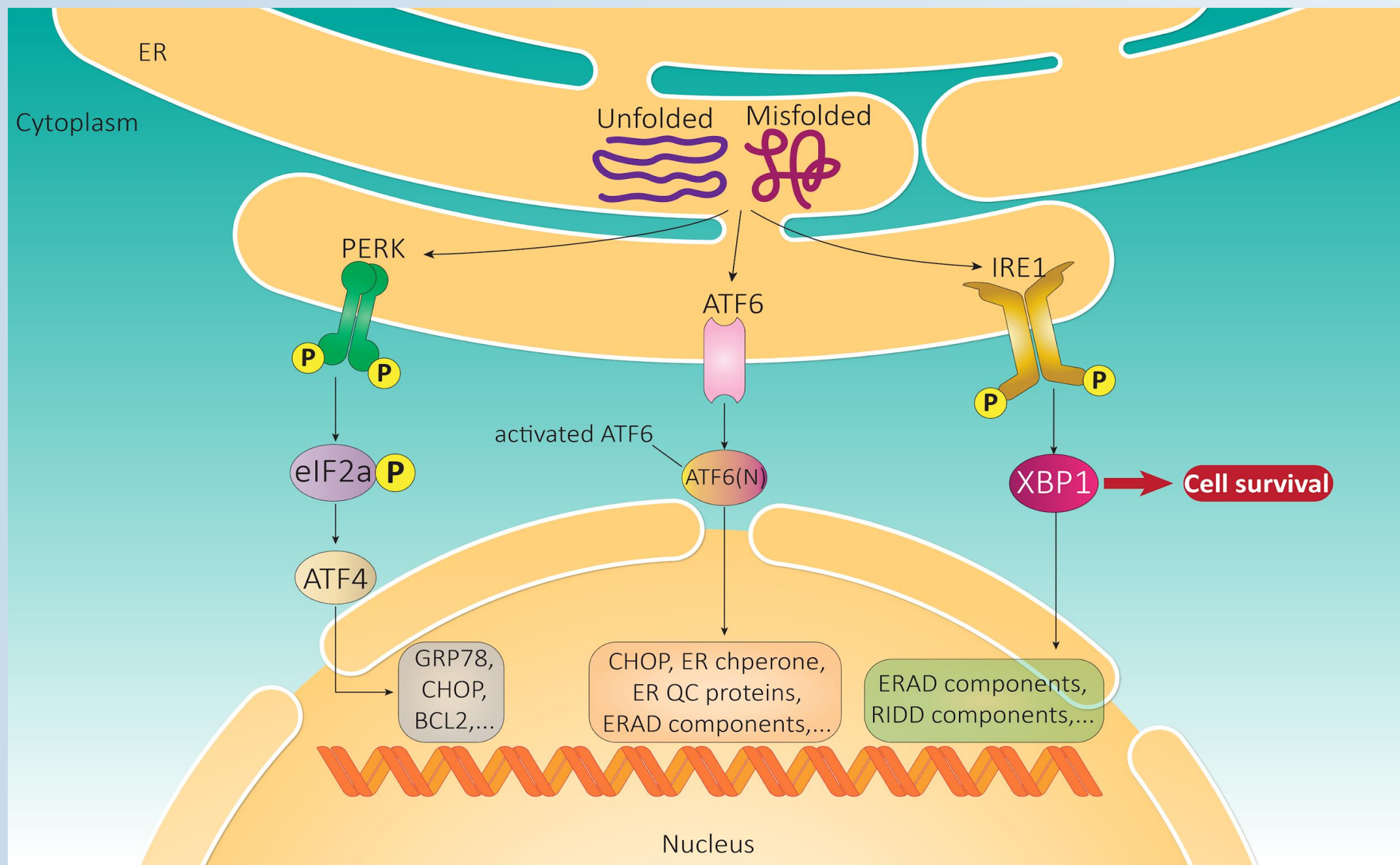
Rationale

Alveolar Rhabdomyosarcoma (ARMS)

- ARMS is a the most malignant childhood and young adult muscle cancer.
- Chemotherapy after surgery is the only available treatment for ARMS (usually ineffective)
- Our recent investigations showed that unfolded Protein Response (UPR) is upregulated in ARMS cells therefore we tested the hypothesis if UPR is correlated with ARMS in human patients.
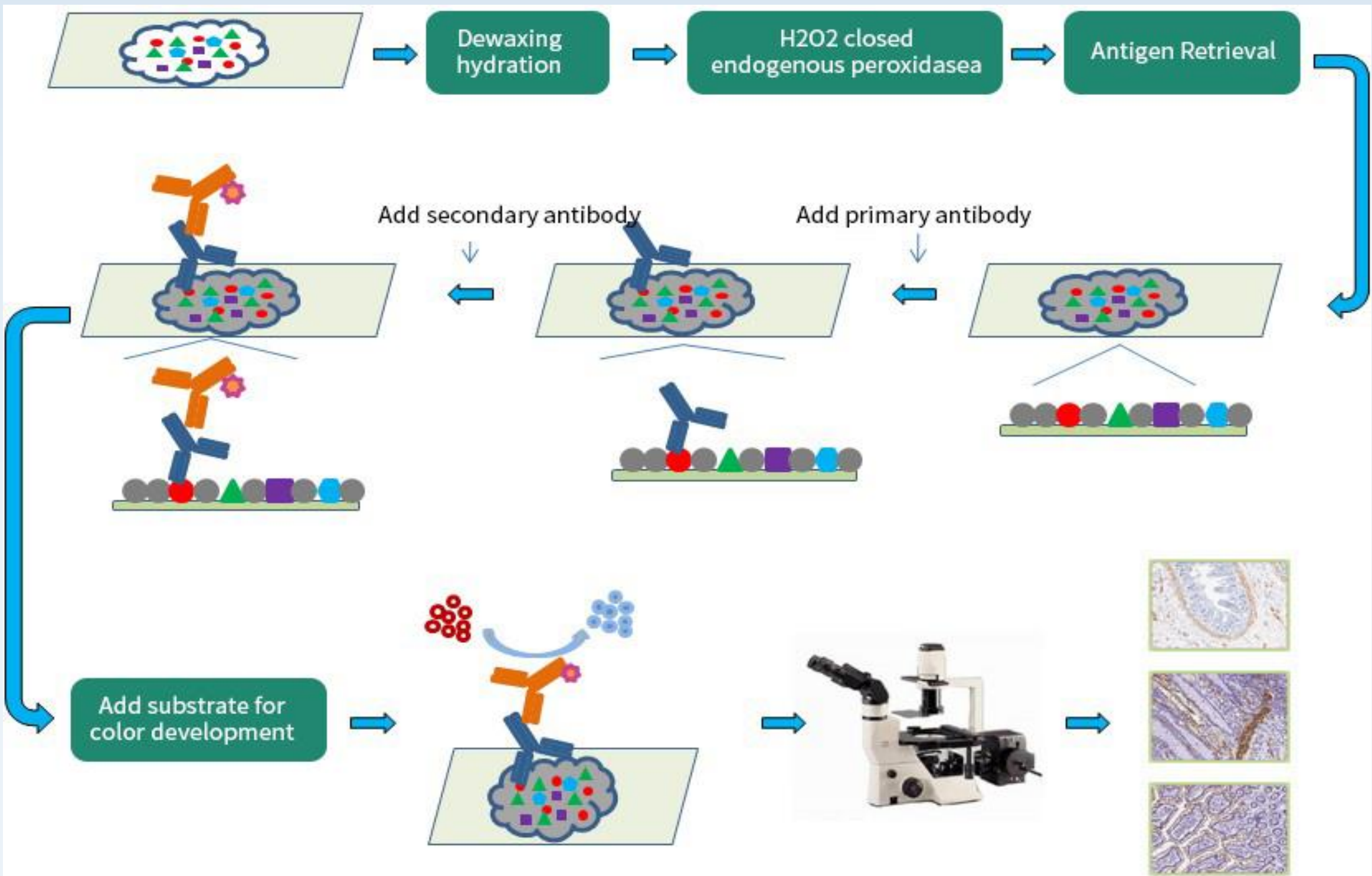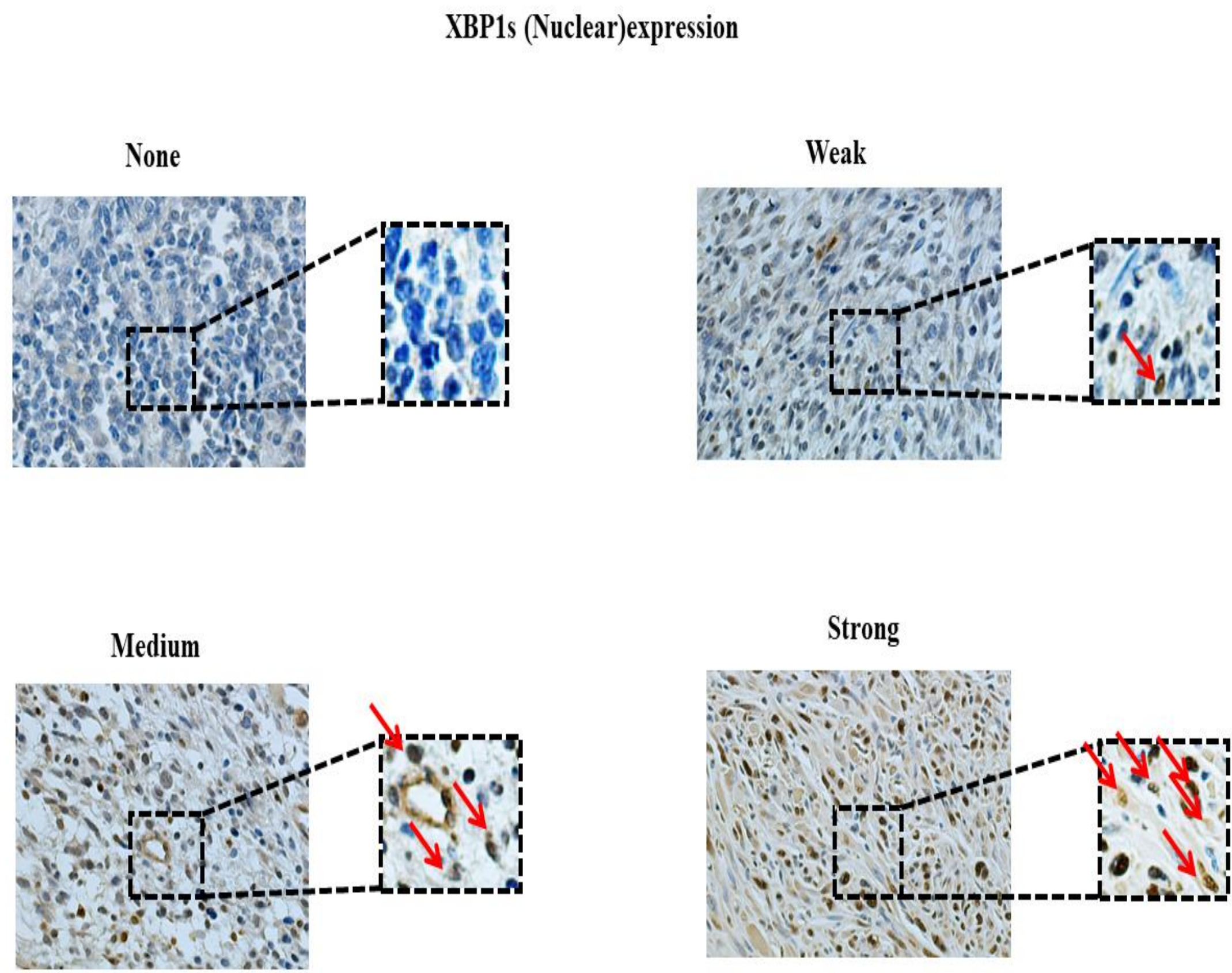
UPR

- The endoplasmic reticulum is responsible for protein folding.
- Incase of stressful stimuli the ER initiates a series of mechanisms called UPR.
- UPR has three arms including IRE1-XBP1 axis
- IRE1-XBP1 axis is involved in tumor proliferation and potential metastasis.

Methods

1- Immunohistochemistry


2- Scoring by Pathologist

XBP1s (Nuclear) expression

3- Statistical Analysis

All data are expressed as n (%) and compared using a χ2 test or Fisher's exact test with SPSS software (version 16.0; SPSS, Inc., Chicago, IL, USA). All p-values are presented as two-tailed; P<0.05 was considered to indicate a difference of statistical significance.
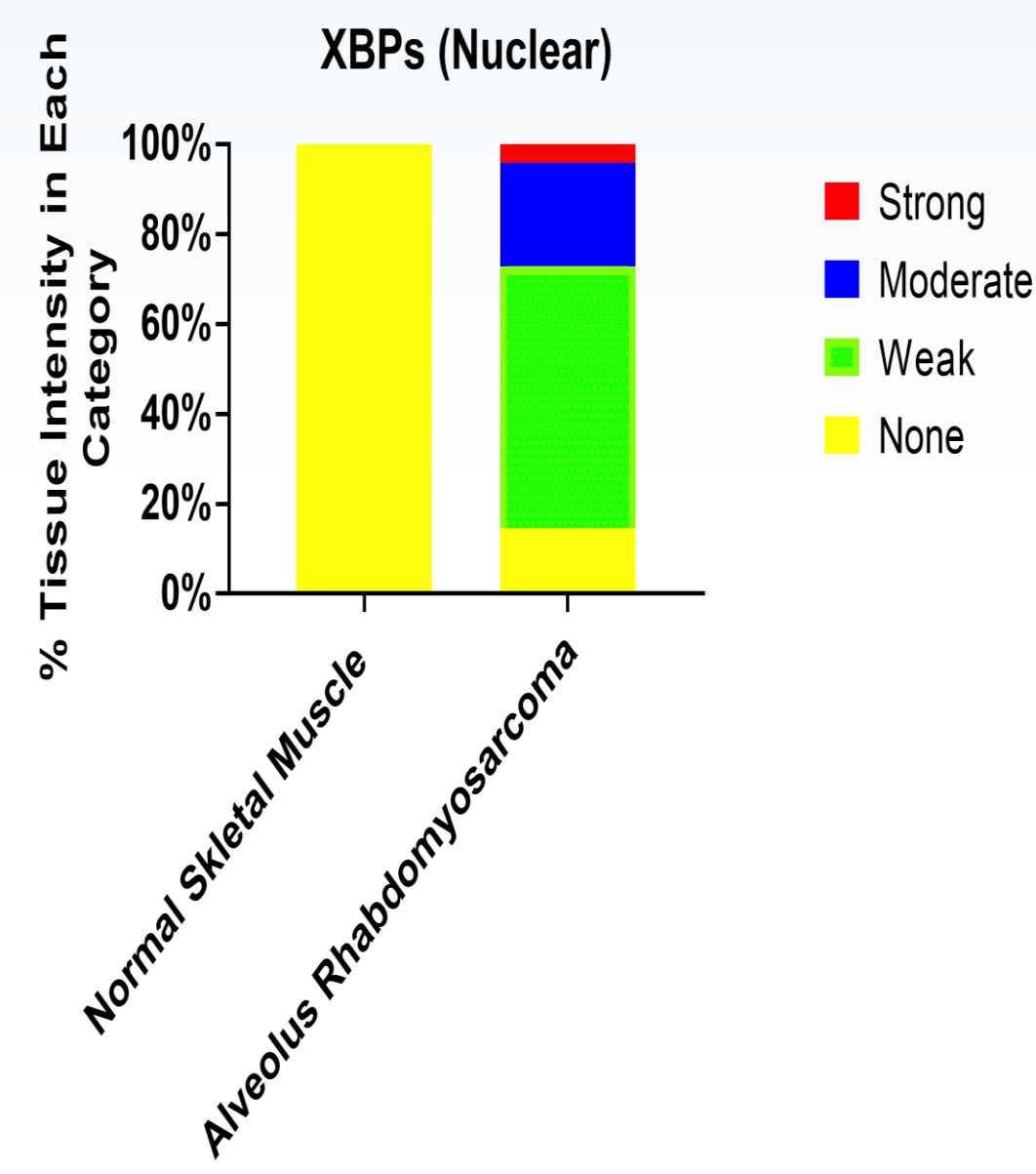
Results

IRE1 expression Correlates with ARMS
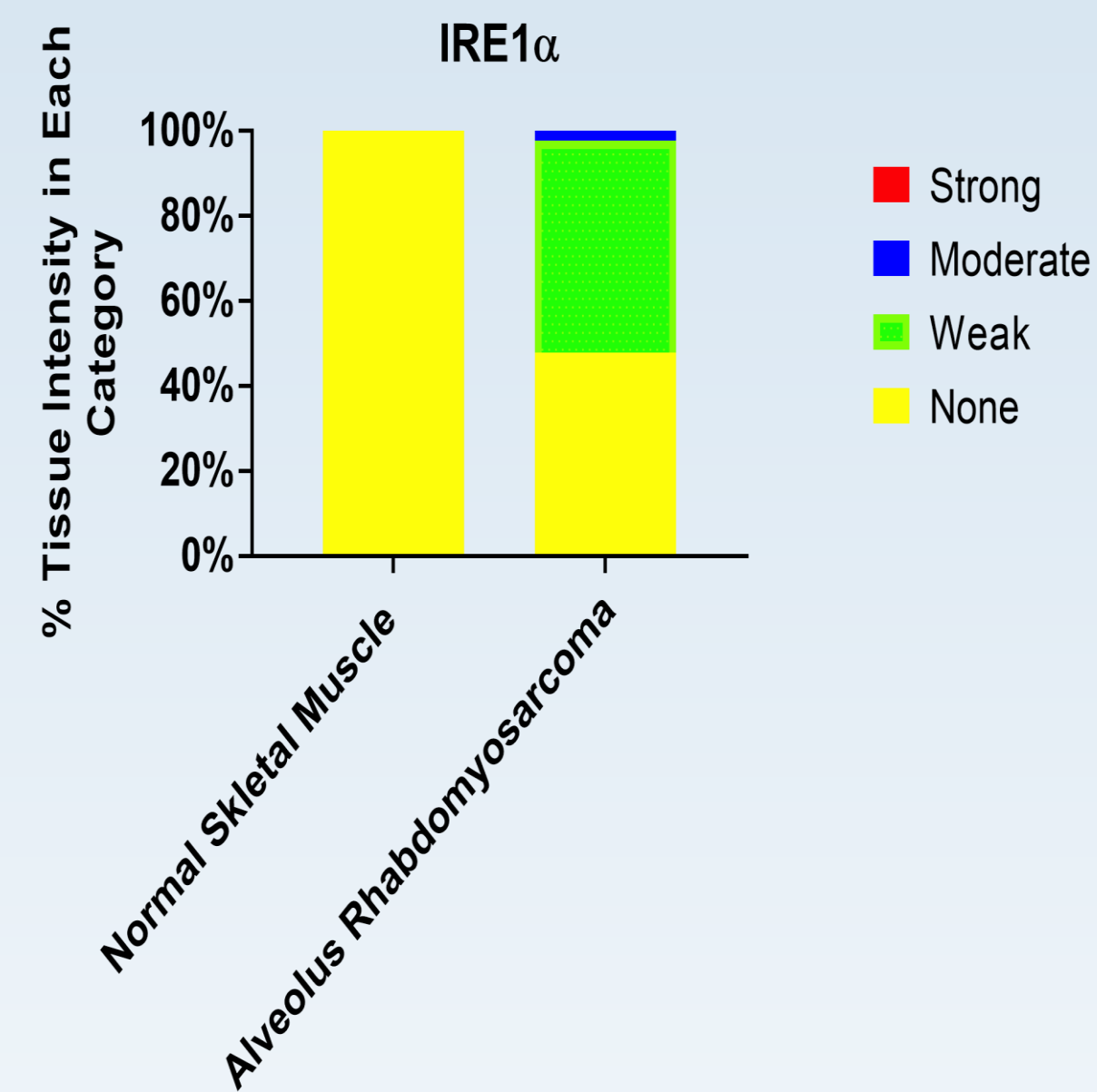
Parameter	RMS subtype	Normal Muscle
	ARMS	Normal
N	48	16
% None	45.8	100
% W	52.1	0
% M	2.1	0
% S	0	0
p-value	0.0001	

XBP1s expression Correlates with ARMS

Parameter	RMS subtype	Normal Muscle	Distant metastasis score	
	ARMS	Normal	M0	M1
N	48	16	44	4
% None	14.6	100	11.4	50
% W	58.3	0	59.1	50
% M	22.9	0	25	0
% S	4.2	0	4.5	0
p-value	0.0001		0.04	

Conclusion and Future Directions

► The results revealed high levels of BIP and IRE1 , XBP1s in the ARMS samples compared to the normal skeletal muscles samples.

► These high expressions show that these proteins are upregulated in ARMS cells, whereas in normal skeletal muscle tissue samples, they are expressed at much lower levels.
► Therefore, these proteins are potential target for future cancer therapy development for ARMS.

► With the knowing that IRE1 is very active in ARMS cells and facilitates their growth the inhibition of IRE1 and the activation of PERK would lead to new and more effective treatments.

► Activating the PERK would signal the cell to stop growing and undergo cell death.

Acknowledgment