

THE EMT-ACTIVATOR ZEB1 IS UNRELATED TO PLATINUM DRUG RESISTANCE IN OVARIAN CANCER BUT PREDICTIVE OF SURVIVAL

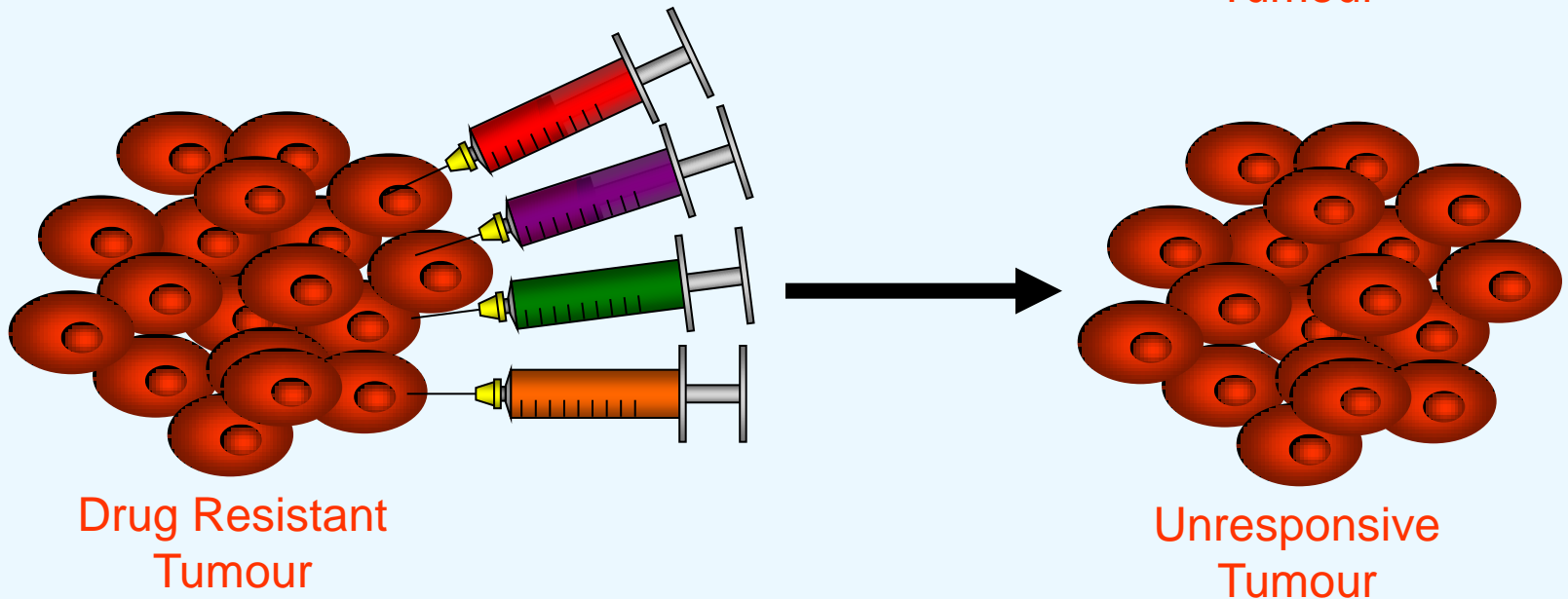
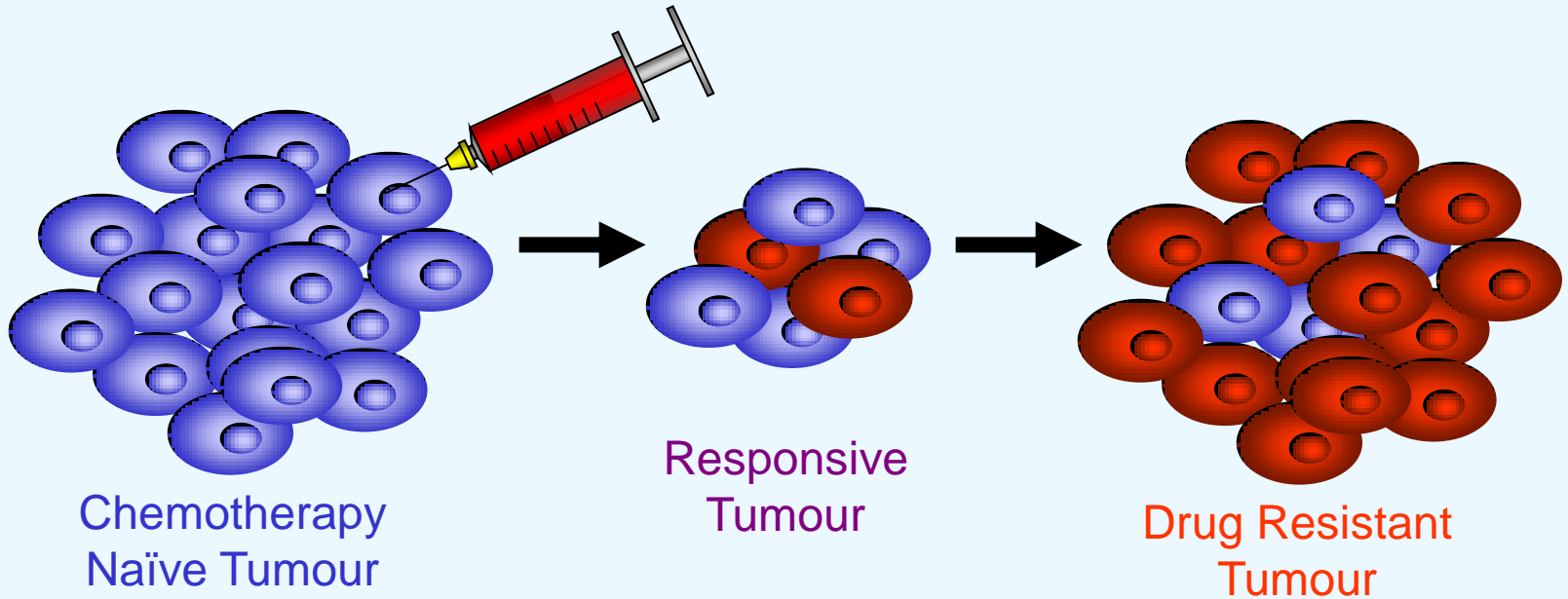
Britta Stordal^{1,2}, Joanne Keenan², Cathy Spillane¹, Gordon Blackshields¹, Marion Hamon² Stephen F. Madden² and John J. O'Leary¹.

1) Department of Histopathology, St James' Hospital and Trinity College Dublin, Dublin 8, IRELAND.

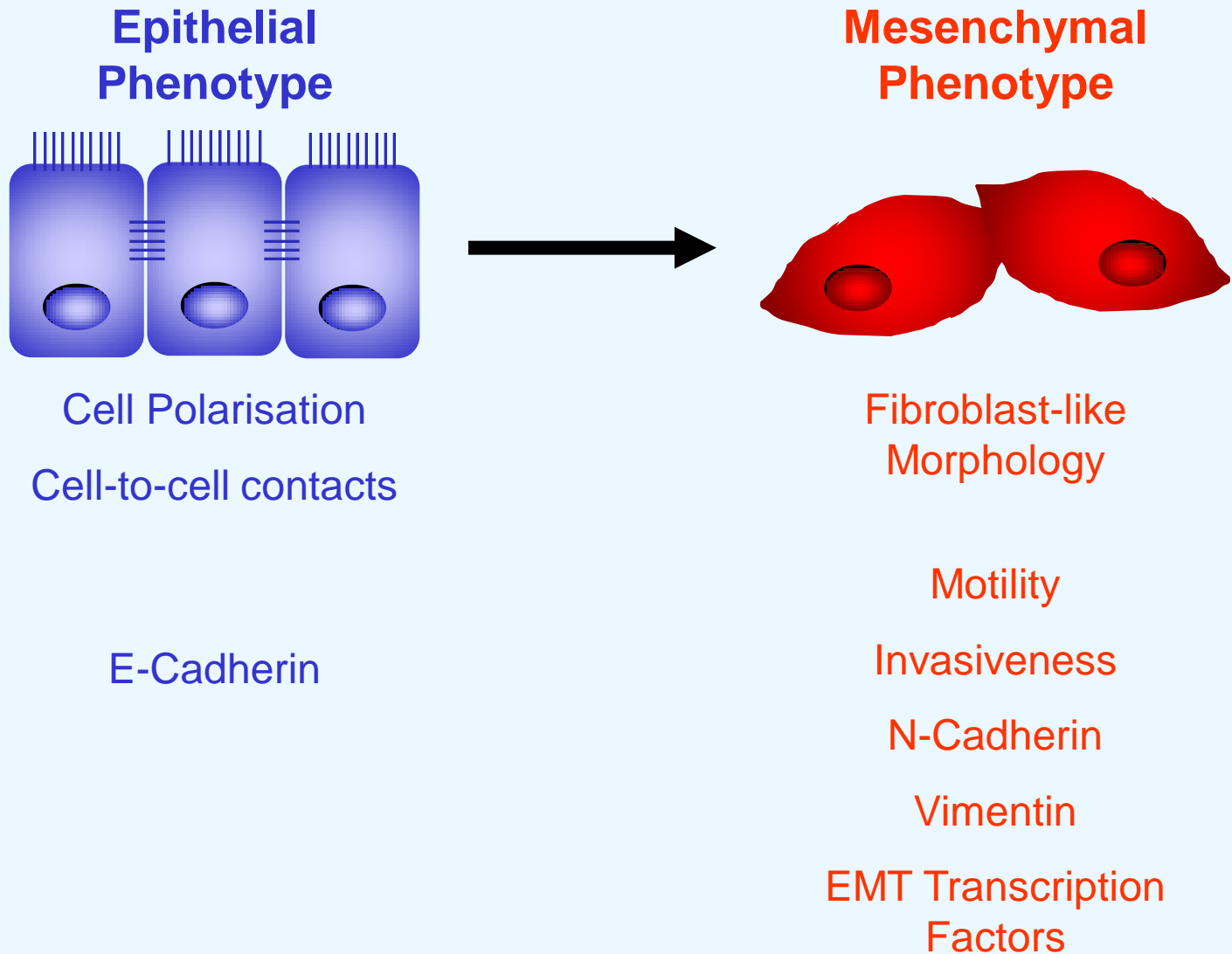
2) National Institute for Cellular Biotechnology, Dublin City University, Glasnevin, Dublin 9, IRELAND.



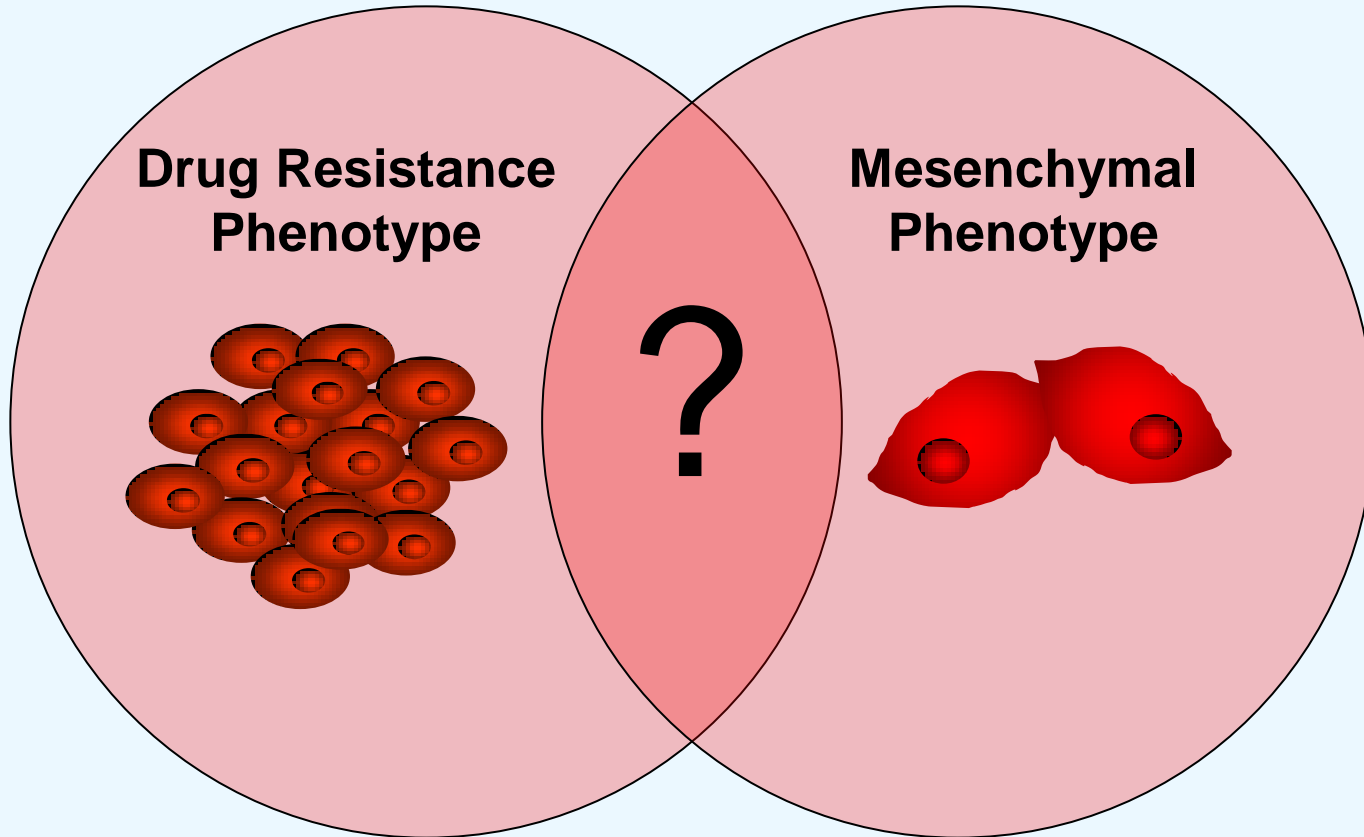
What is Drug Resistance?



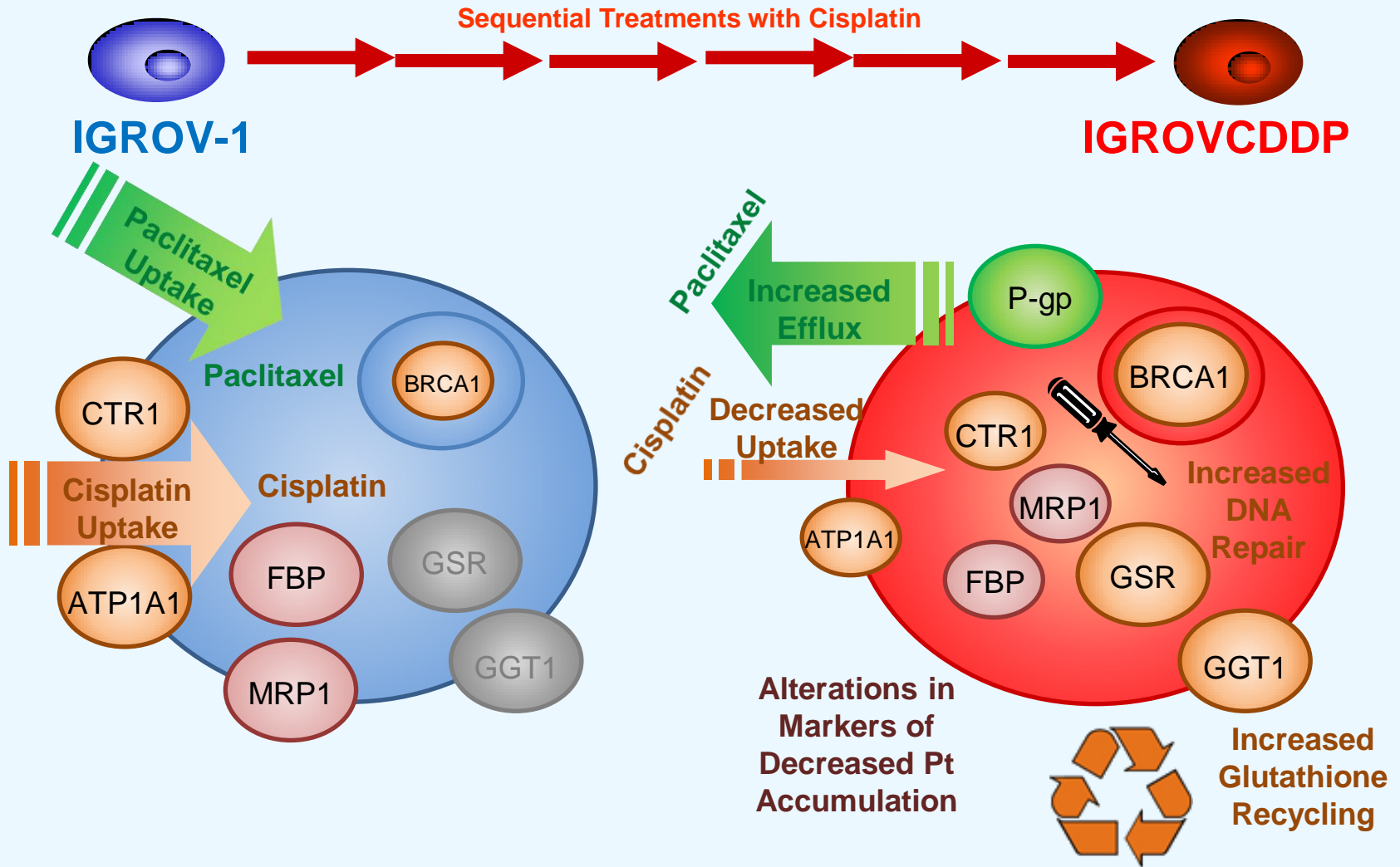
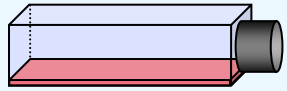
What is Epithelial to Mesenchymal Transition?



Overlapping Phenotypes

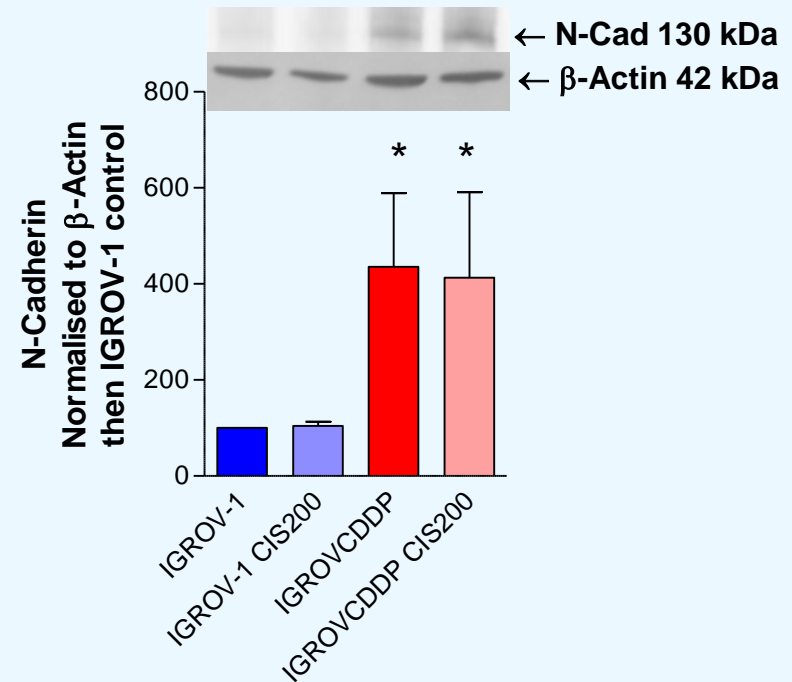
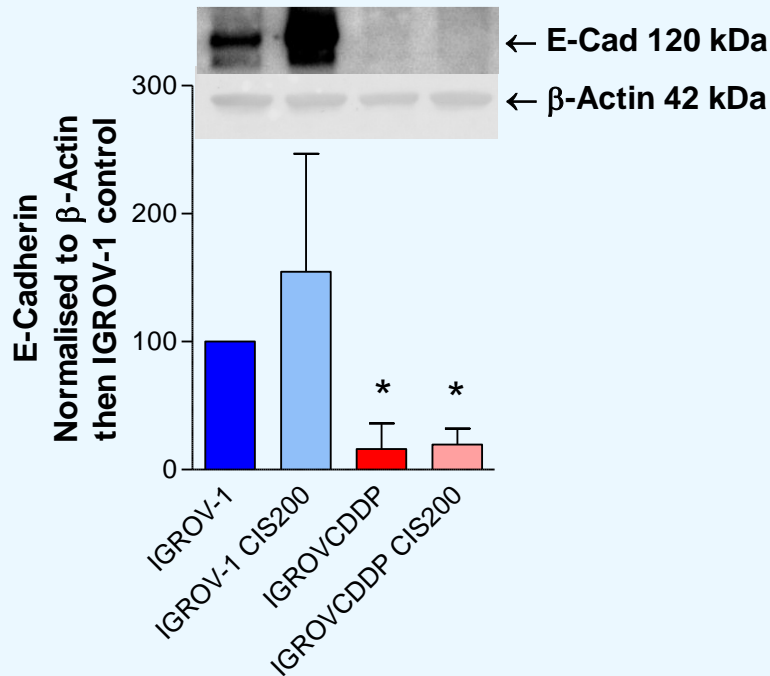
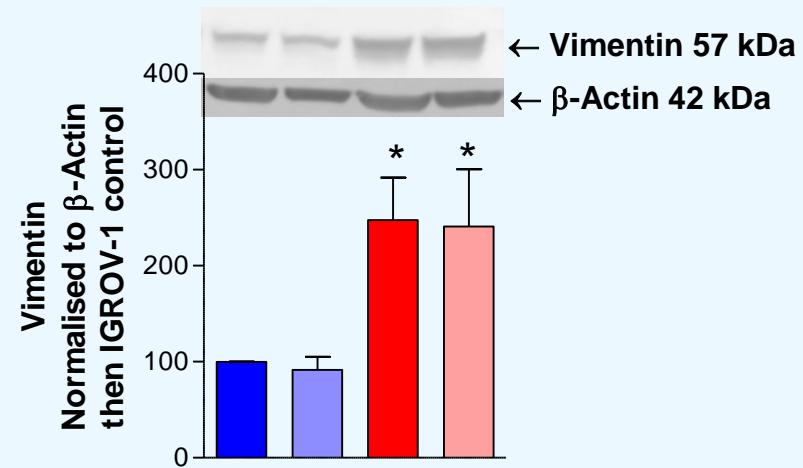


IGROVCDDP Resistant Ovarian Cancer

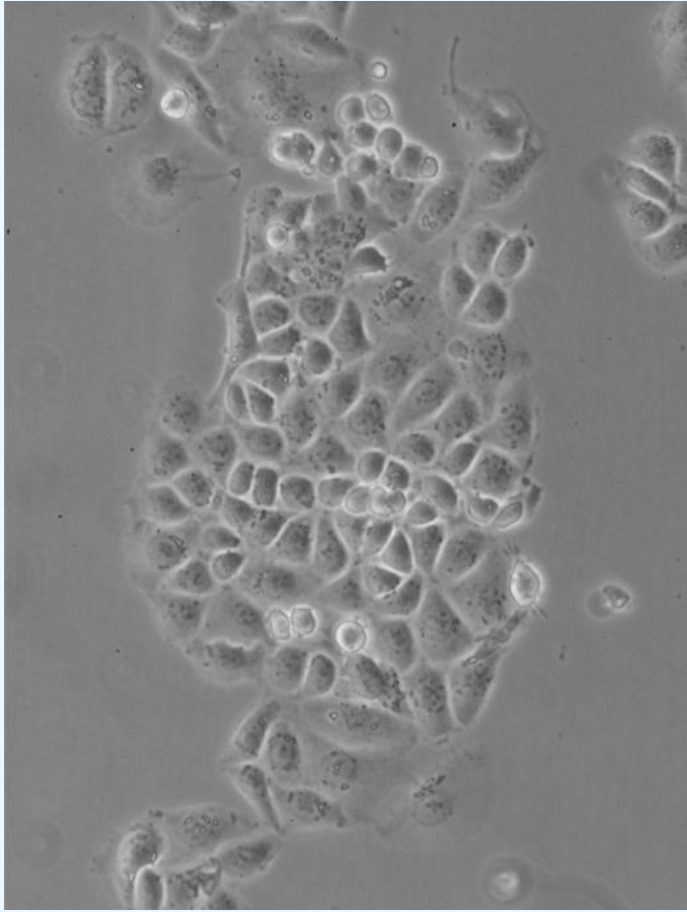


EMT Markers

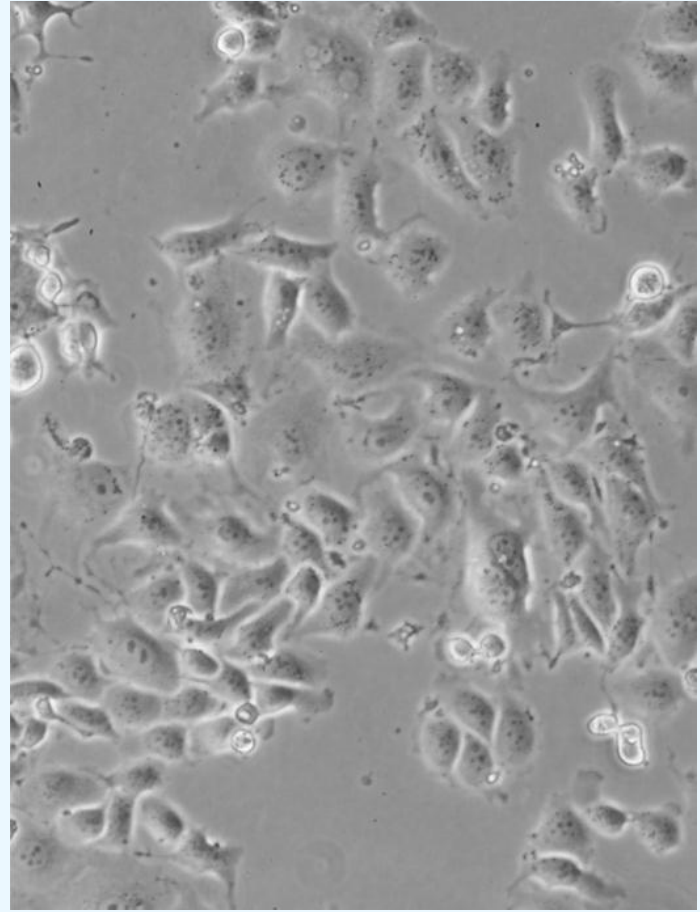
Gene	Full Name		Fold Change	FDR
<i>CDH1</i>	E-Cadherin	↓	-7.33	1.53E-05
<i>CDH2</i>	N-Cadherin	↑	2.14	9.80E-08
<i>VIM</i>	Vimentin	-	-1.29	4.53E-02



Morphology

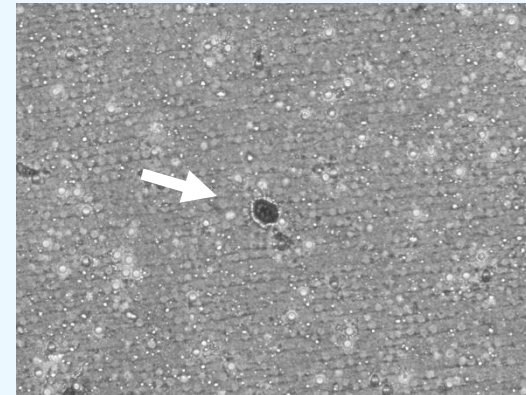
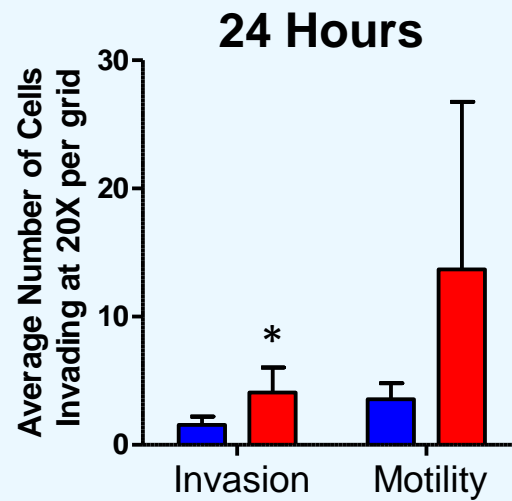


IGROV-1

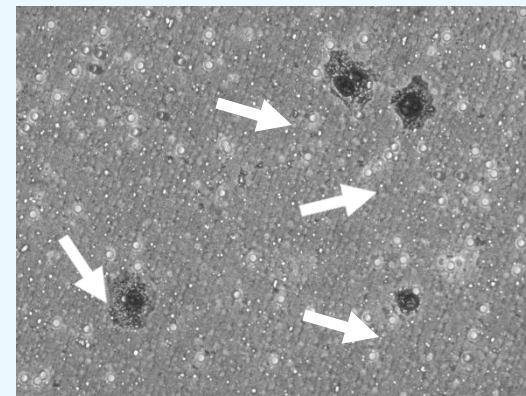


IGROVCDDP

Invasion and Motility



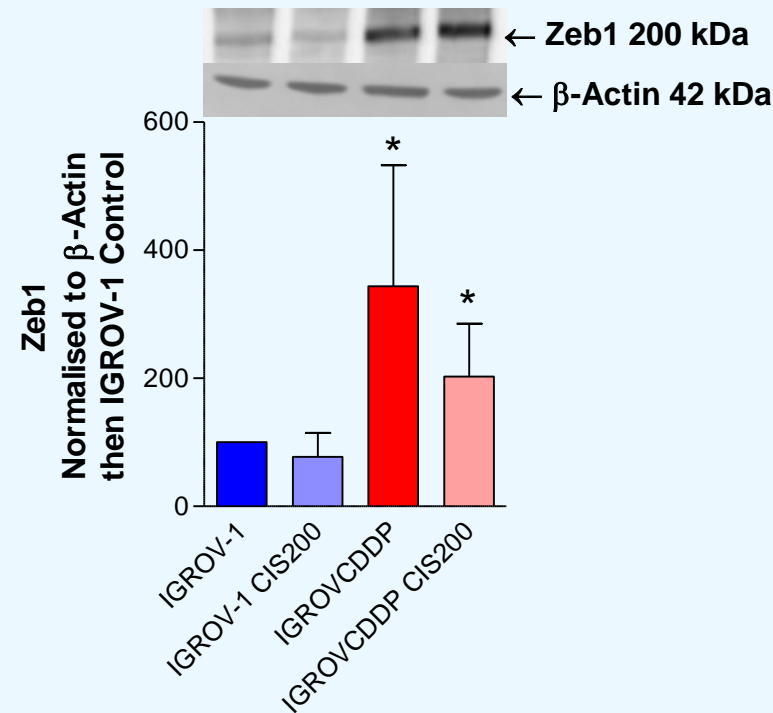
IGROV-1



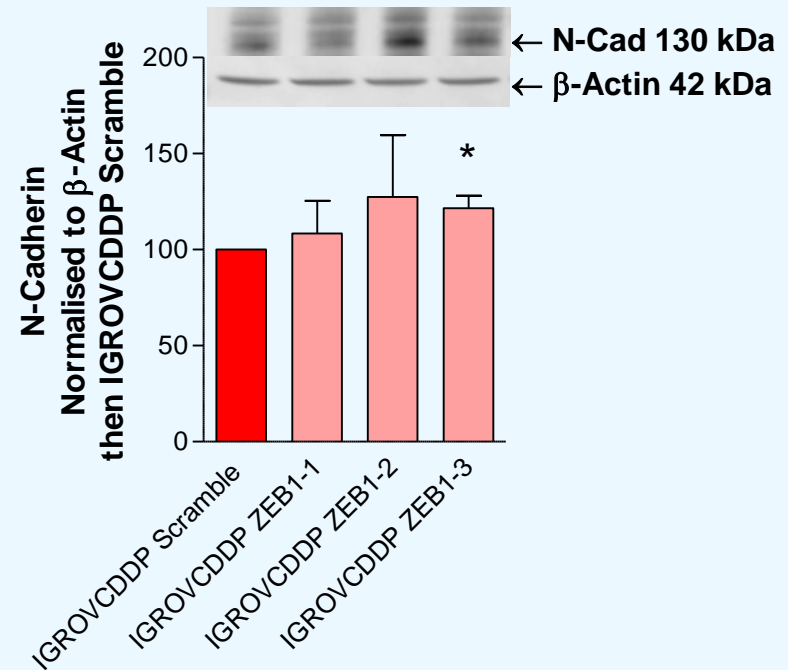
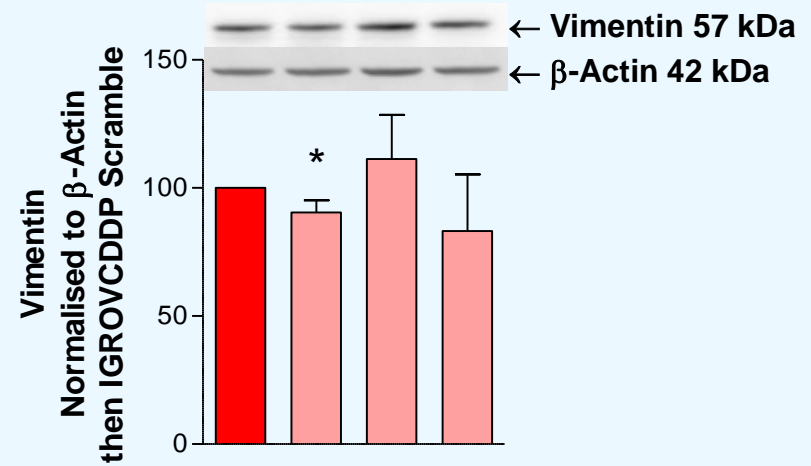
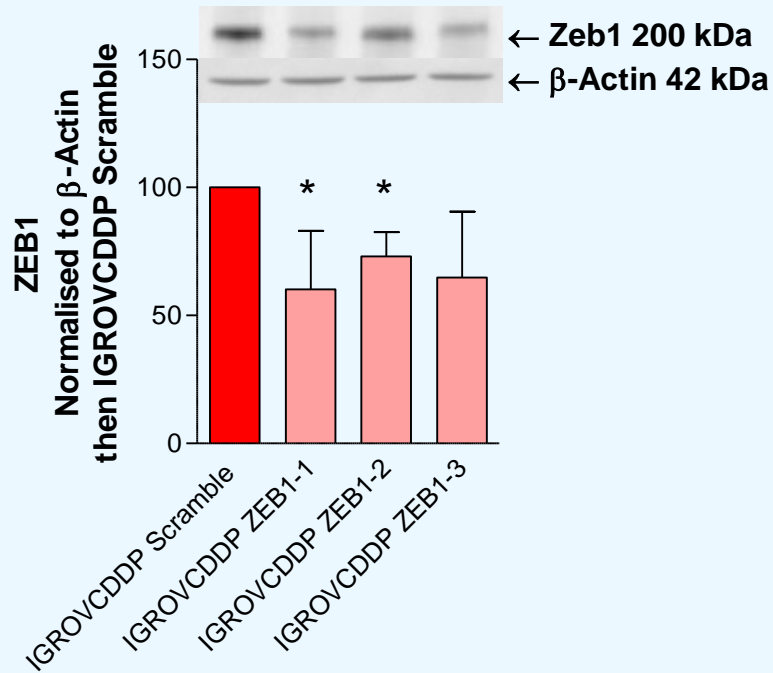
IGROVCDDP

EMT Transcription Factors

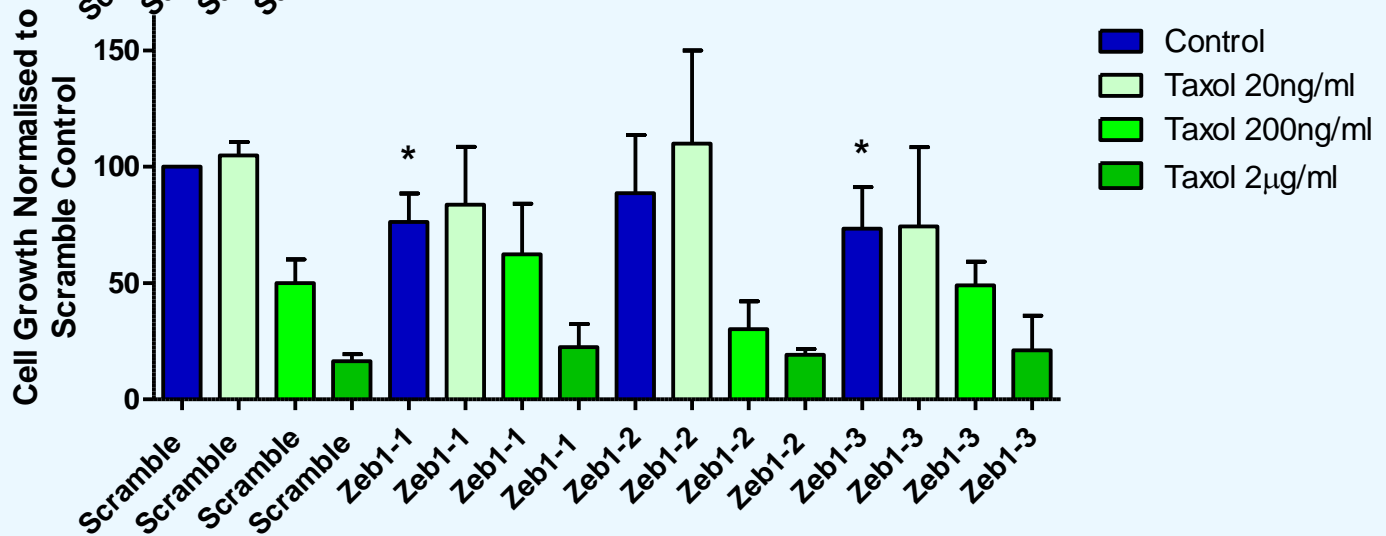
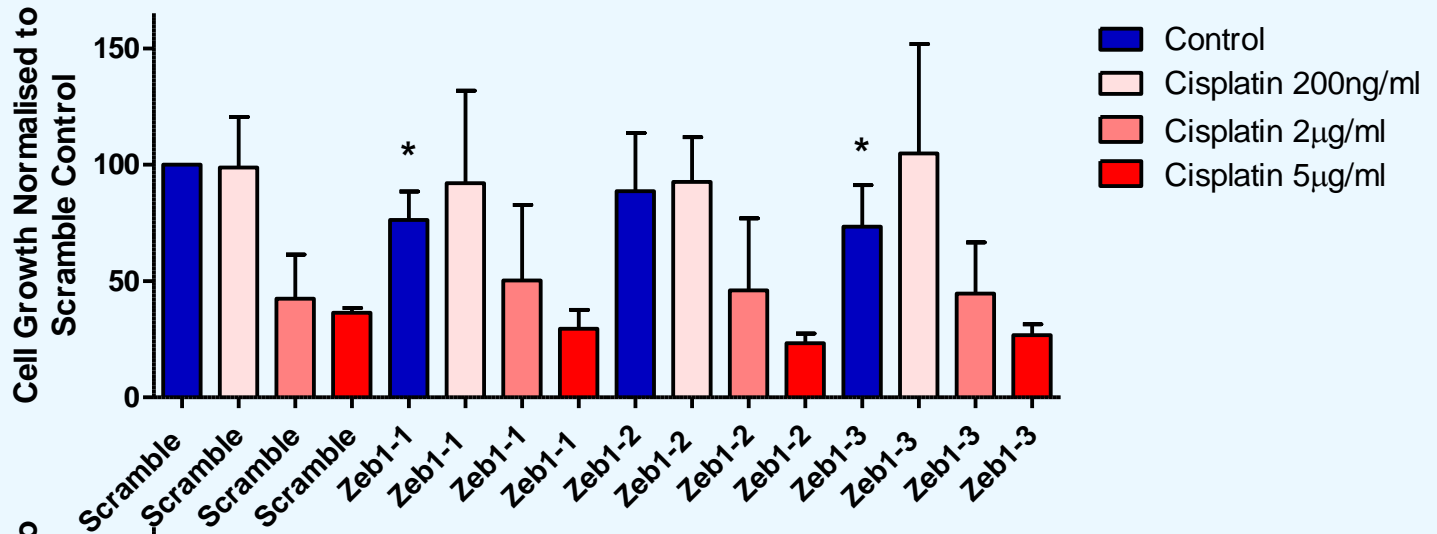
Gene	Full Name		Fold Change	FDR
<i>SNAI1</i>	Snail family zinc finger 1	-	N/A	N/A
<i>SNAI2</i>	Snail family zinc finger 2	-	N/A	N/A
<i>TWIST</i>	Twist family bHLH transcription factor 1	↓	- 4.20	2.07E-03
<i>ZEB1</i>	Zinc finger E-box binding homeobox 1	↑	1.37	9.25E-03



ZEB1 Knockdown



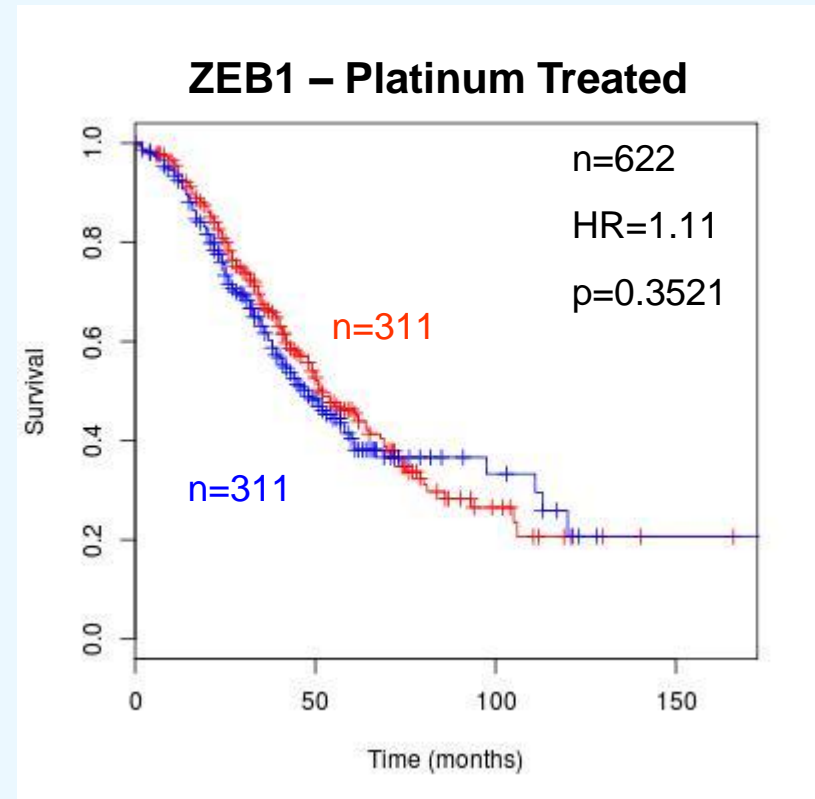
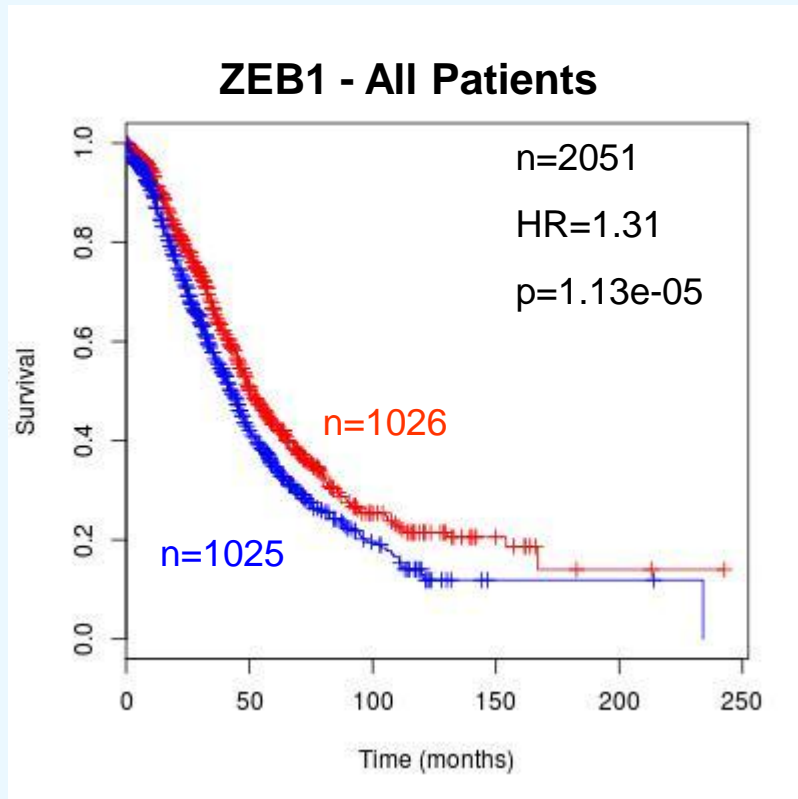
ZEB1 Knockdown



Publically Available Ovarian Cancer Data

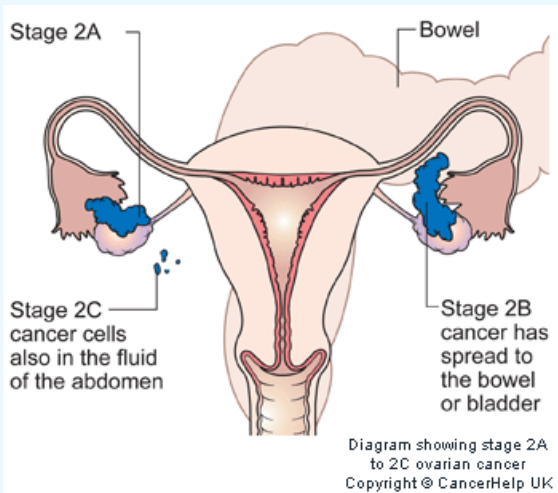
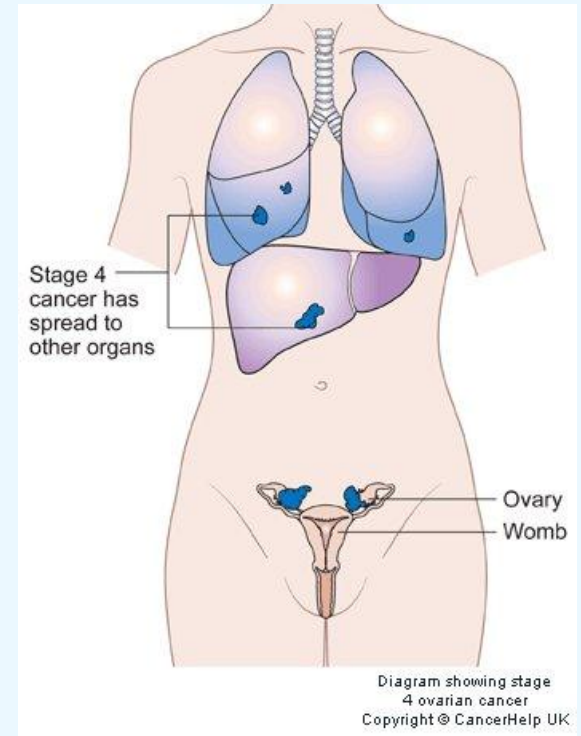
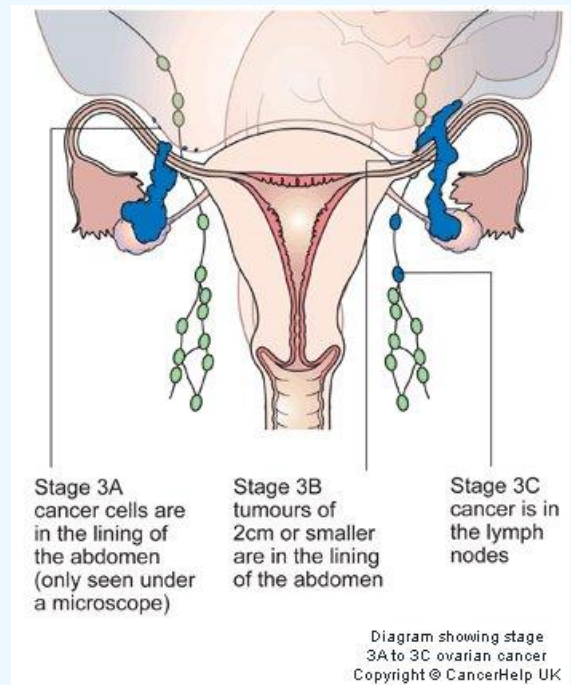
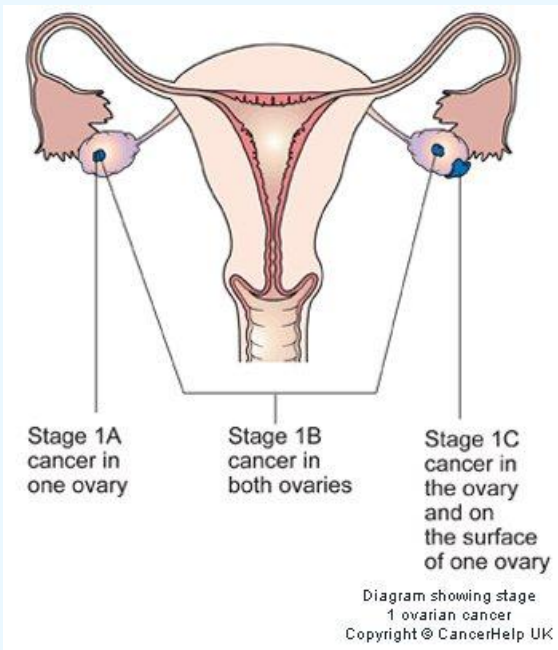
Dataset	GEO Accession	Survival Information	Sample Number
Crijns <i>et al.</i> (2009)	GSE13876	OS	157
Denkert <i>et al.</i> (2009)	GSE14764	OS	80
Yoshihara <i>et al.</i> (2010)	GSE17260	PFS/OS	110
Mok <i>et al.</i> (2009)	GSE18520	OS	53
Tothill <i>et al.</i> (2008)	GSE9899	PFS/OS	285
Kostantinopoulos <i>et al.</i> (2011)	GSE19161	OS	61
Kostantinopoulos <i>et al.</i> (2010)	GSE19829	OS	70
Bonome <i>et al.</i> (2008)	GSE26712	OS	185
Ferriss <i>et al.</i> (2012)	GSE30161	PFS/OS	58
Spentzos <i>et al.</i> (2005)	GSE31245	OS	57
Yoshinara <i>et al.</i> (2012)	GSE32062	PFS/OS	260
N/A	TCGA	OS	562
Total			1932

Survival Analysis



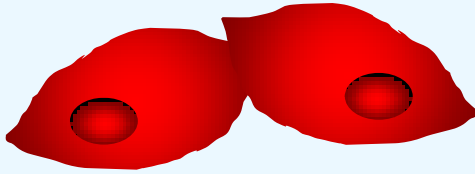
- A multivariate analysis was performed and high ZEB1 is associated with a poor prognosis adjusted for both patient age and grade, increasing the HR to 2.21 $p = 0.0069$

Clinical Ovarian Cancer

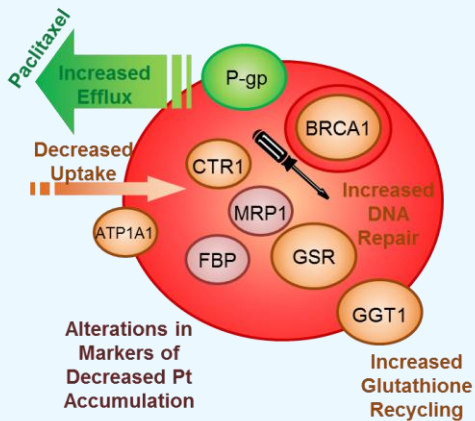


- Unfortunately, the survival analysis cannot be adjusted for stage as we have so few Stage I/II patients, and only 2 studies reported this information.

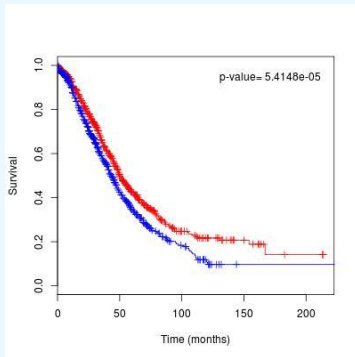
Conclusions



- IGROVCDDP has undergone EMT.



- ZEB1 does not appear to be mediating drug resistance in IGROVCDDP. ZEB1 is a potential mediator of the EMT phenotype.



- ZEB1 is predictive of survival in ovarian cancer, but does not appear to be suitable as a marker of platinum resistance

Acknowledgements

Funding

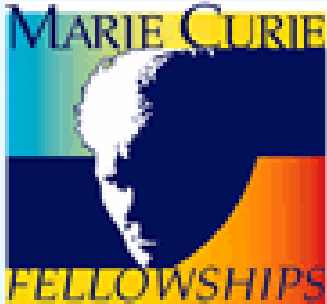


Stordal Research Group (Past and Present)

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Collaborators from Dublin City University

Dr. Joanne Keenan, Dr. Stephen Madden



Colleagues at Trinity College Dublin:

Dr. Cathy Spillane, Dr. Gordon Blackshields, Prof. John O'Leary.

