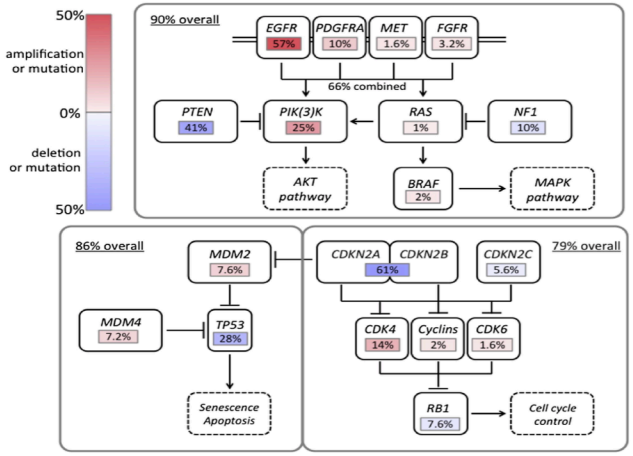
Glioblastoma

- Brain tumour arising from astrocytes, 15 months survival
- The most common primary tumour
- Despite being the 1st tumour profiled by TCGA, glioblastoma patients have yet not benefited from molecularly-targeted therapy

Genomic landscape



Glioblastoma subtypes

Classical: EGFR amp/mut, *Ink4a/ARF* del
Mesenchymal: cMET over-expression, *NF1* mut/del
Pro-neural: PDGFRA abnormalities, *IDH1* and *TP53* mut
Neural: highly differentiated phenotype

Inter-tumour heterogeneity

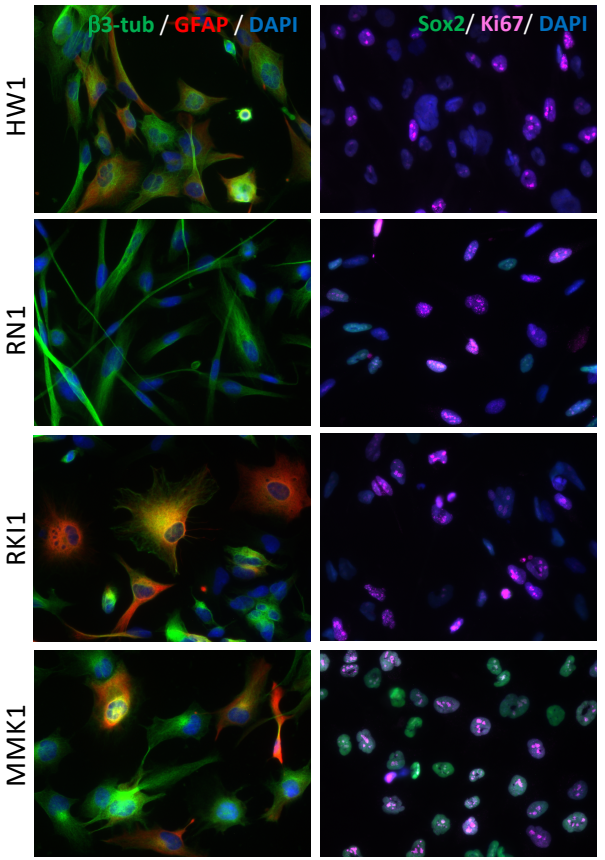
		Classical				Mesenchymal				Proneural			
Pathway	Gene	WK1	PB1	HW1	SB2b	RN1	FPW1	RKI1	MN1	JK2	SJH1	MMK1	BAH1
RTK	*EGFR*			A289V	A289V H304Y								vIII
	MET				C800F	T992I			E168D		H289R		
	EPHA2										V589M R721Q		
PI3K	*PIK3CA*	H1047Y			Y1021H								
	PIK3R1												
	PIK3C2G		X1446S		A2T				P129T				
	PIK3C2A												T1415A
MAPK	*PTEN*		R130*	Spl inct			R130Q					F56V	V133I
	NF1						Spl inct				Spl inct		
P53	*MYC*												
	TP53									R110L	G105C		
RB1	*MDM2*				W329C								
	CDKN2A												
	CDKN2B												
Chromatin modifiers	*IDH1*				V178I							Y183C	
	ATRX							D808G					
	SEDT2	E670K			T451A			R472H					

Homozygous deletion | Heterozygous deletion | Amplification | Gain

Q-Cell Panel (Bryan Day & Brett Stringer, QIMR Berghofer)

Glioblastoma stem-like cells (maintained serum-free)
Full genome profile
Full mRNA sequencing
Subtype assignment

Intra-tumour heterogeneity



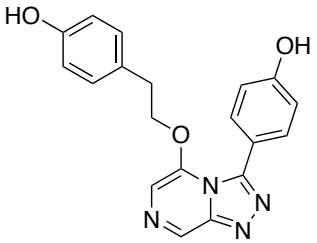
TCGA: Nature 2008, Cell 2010, Cell 2013

Ariadna Recasens

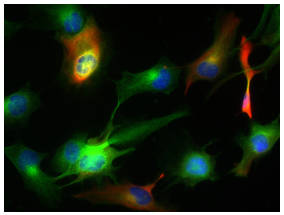
Cell Signalling (Munoz) Lab @ Charles Perkins Centre

Phenotypic screening
Drug-target validation
Mechanism of action

Targets
Kinases
Microtubules
Epigenetic enzymes



Goal: to understand the pathological mechanisms of glioblastoma and use this knowledge to develop effective treatments (*or vice versa*)



***In vitro* inhibition assays**
Structure-activity studies
Metabolic stability

Efficacy in cells
- Relative metrics: EC_{50}, E_{max}, AUC
- GR metrics: GR_{50}, GR_{max}, GR_{AOC}
- Spheroid assays

Functional assays
- apoptosis, senescence, dormancy

Validation of targets
- Genetic inhibition (siRNA, sgRNA)
- Expression in glioblastoma tissues (TMAs)

Delineation of signaling pathways
- Transcription of genes
- Protein stability
- Shuttling of proteins
- Post-translational modifications
- Live cell imaging
- FUCCI platform for cell cycle analysis