

Bone Sarcomas

Treatment and biomarkers



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Disclosures

BSc (Hons) Upper second class Pharmacology (CNNA)(1982)
PhD (Medicine) - University of Newcastle Upon Tyne (1986)

Founder member of the Children's Cancer Research Group,
Institute of Medical Research, University of Leeds, UK (1992)

Ewing sarcoma

Other biomarkers and targeted
therapeutics are available



In the next 45 minutes...

Soft tissue and bone sarcoma

Ewing sarcoma

Targeted Treatment

Biomarkers

To improve outcomes for patients



Soft tissue and bone sarcoma

More than 100 subtypes

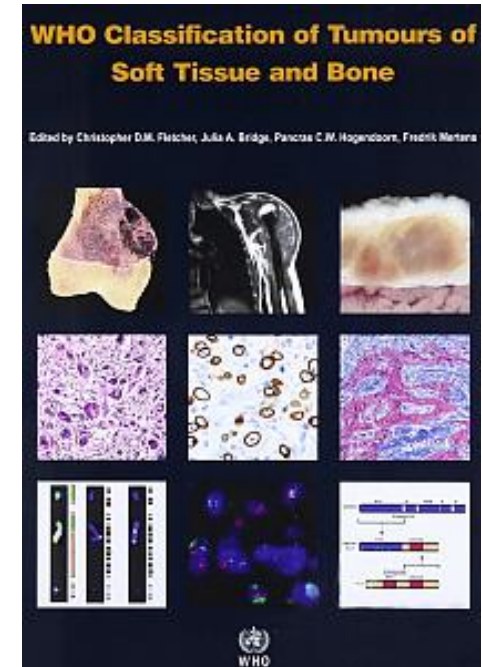


Soft tissue sarcoma



Primary bone sarcoma

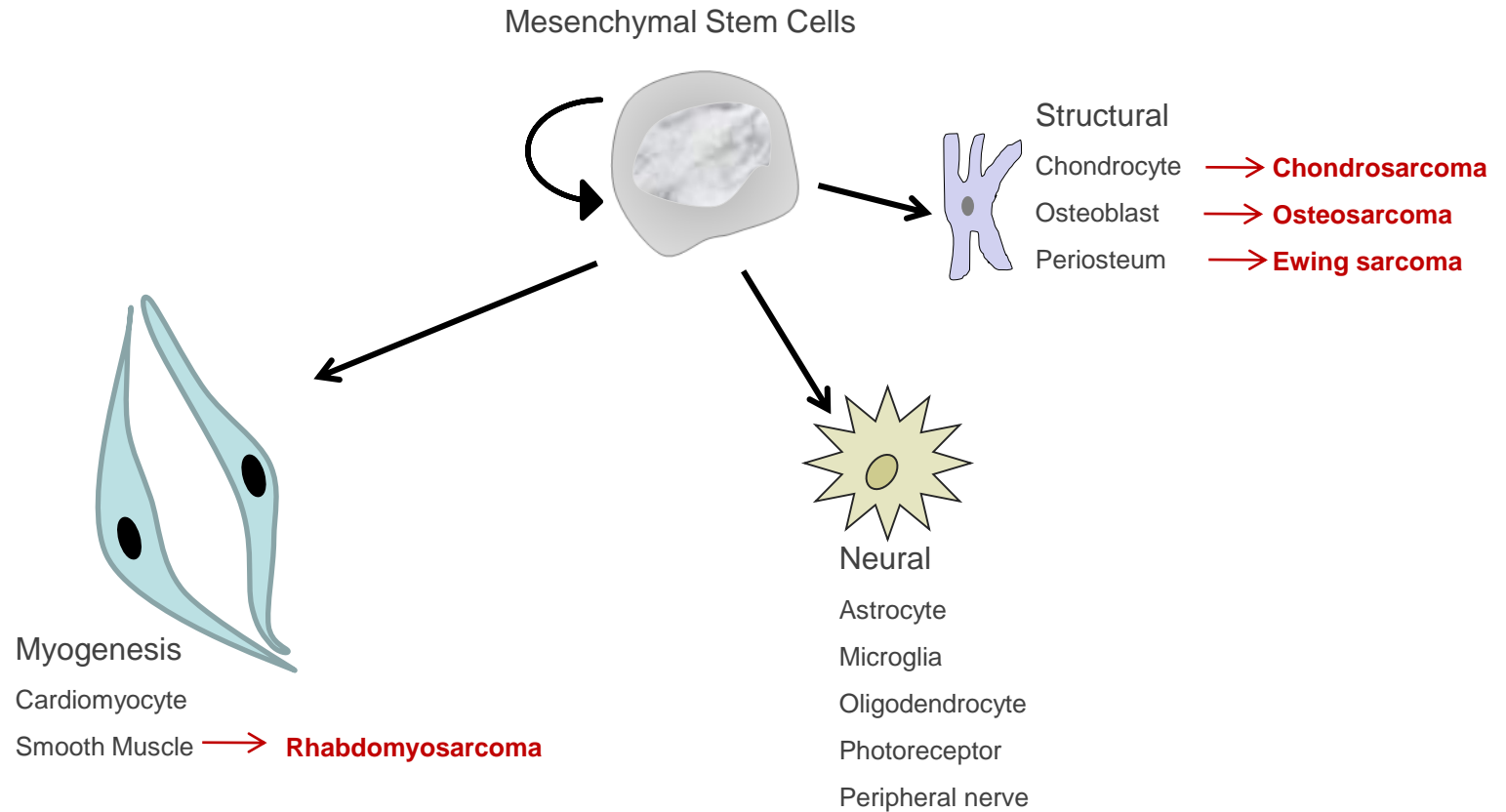
~20% malignancies in children
<1% adults



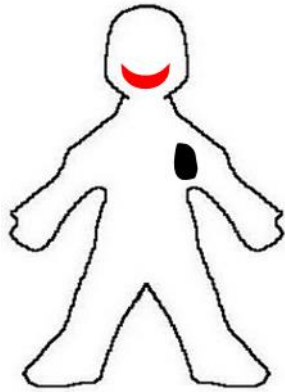
4th edition WHO Classification of
Tumours of Soft Tissue and Bone
February 2013.



Sarcoma



Clinical outcomes

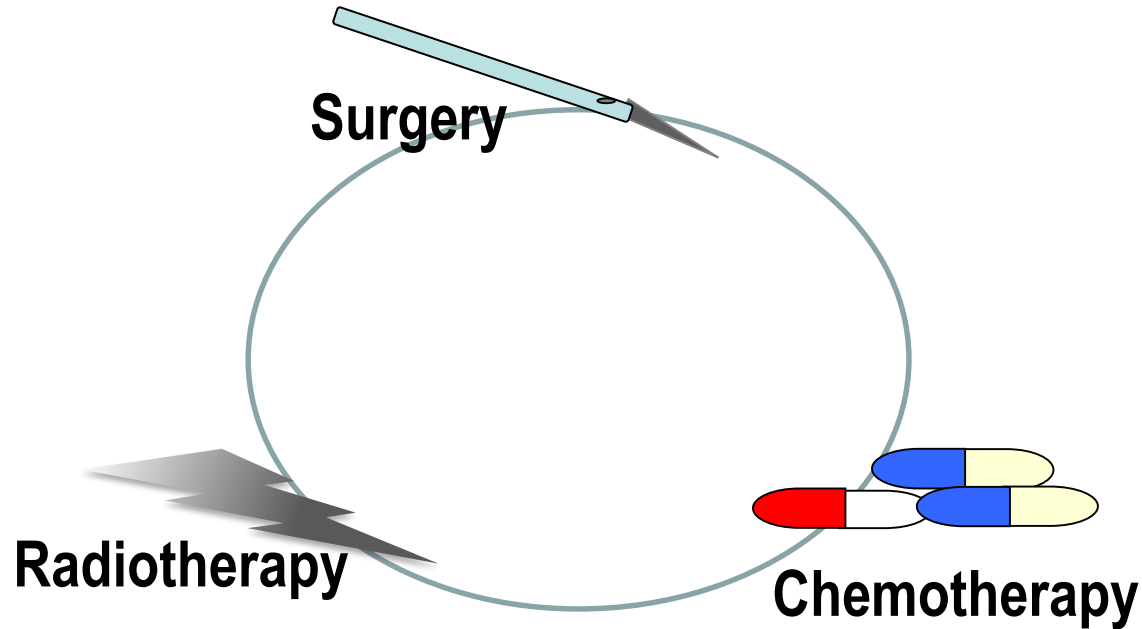


Localised disease
Better outcome



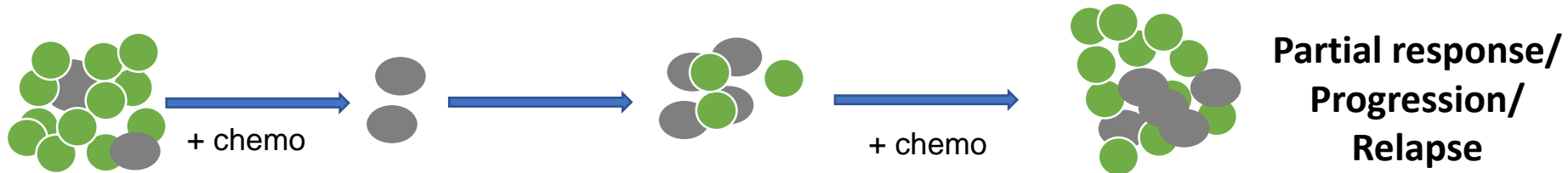
Metastatic disease
Poor outcome

Current treatment

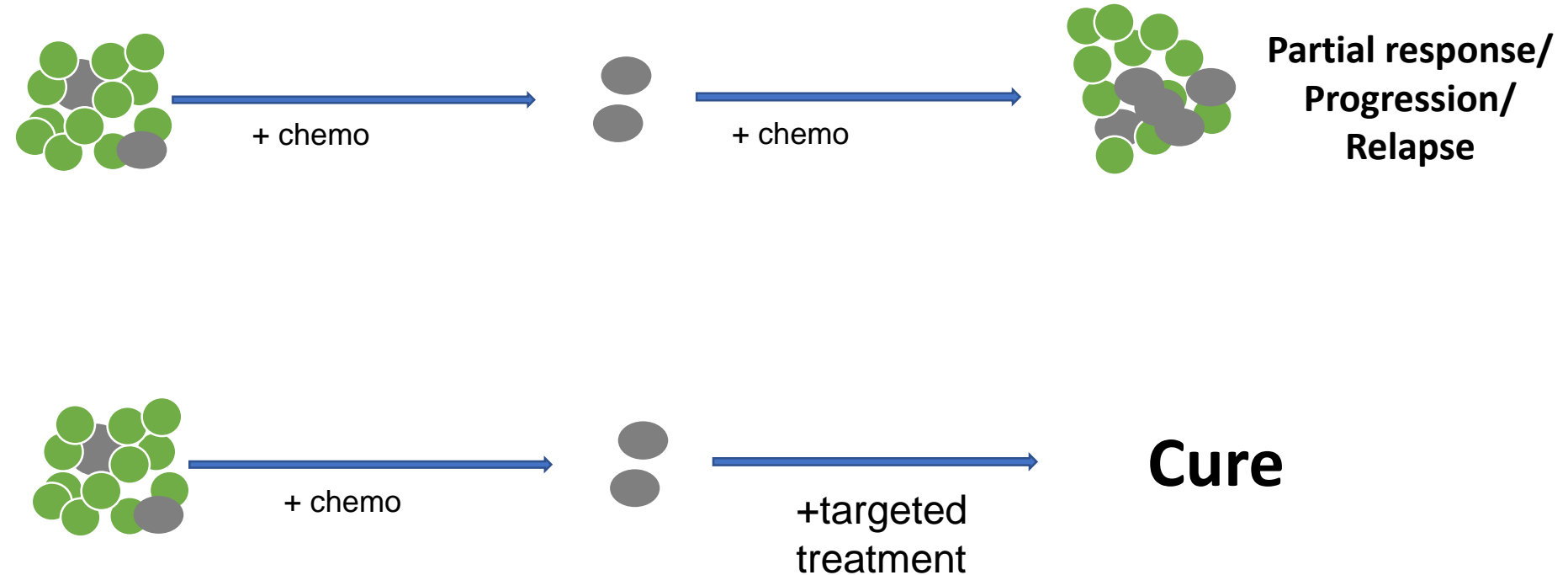


Multi-agent chemotherapies that were developed in the 60's and 70's to target rapidly dividing cells

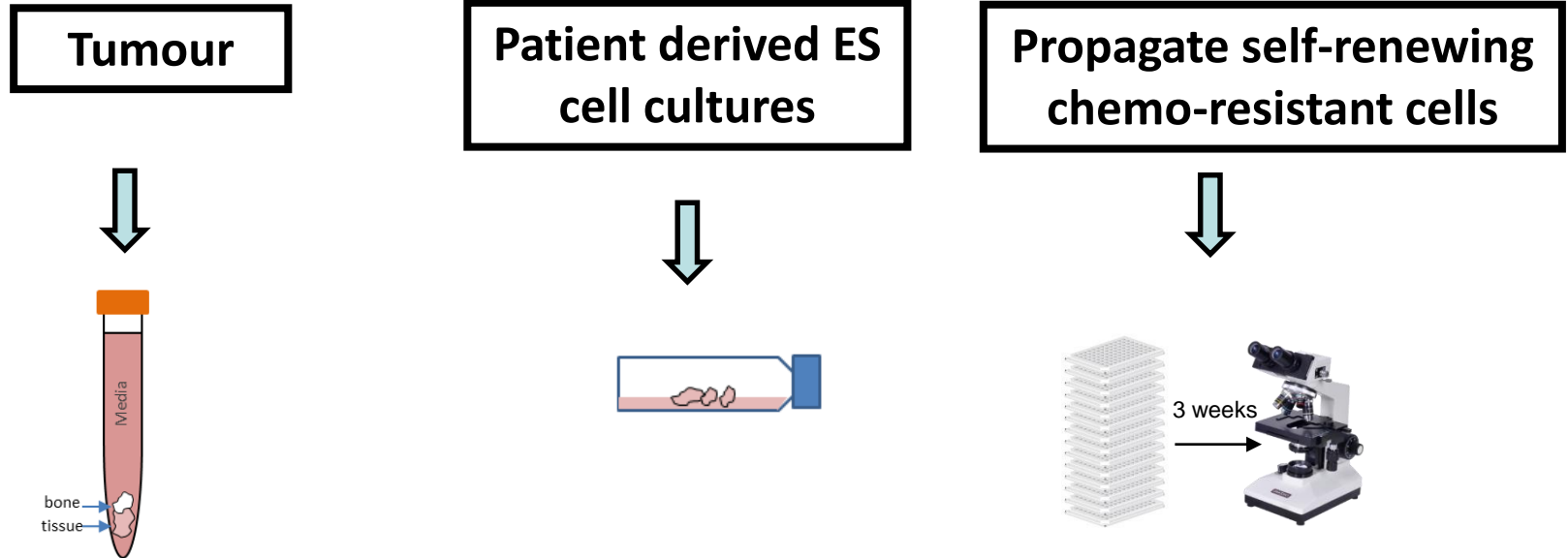
Different responses to chemotherapy



Combination treatment



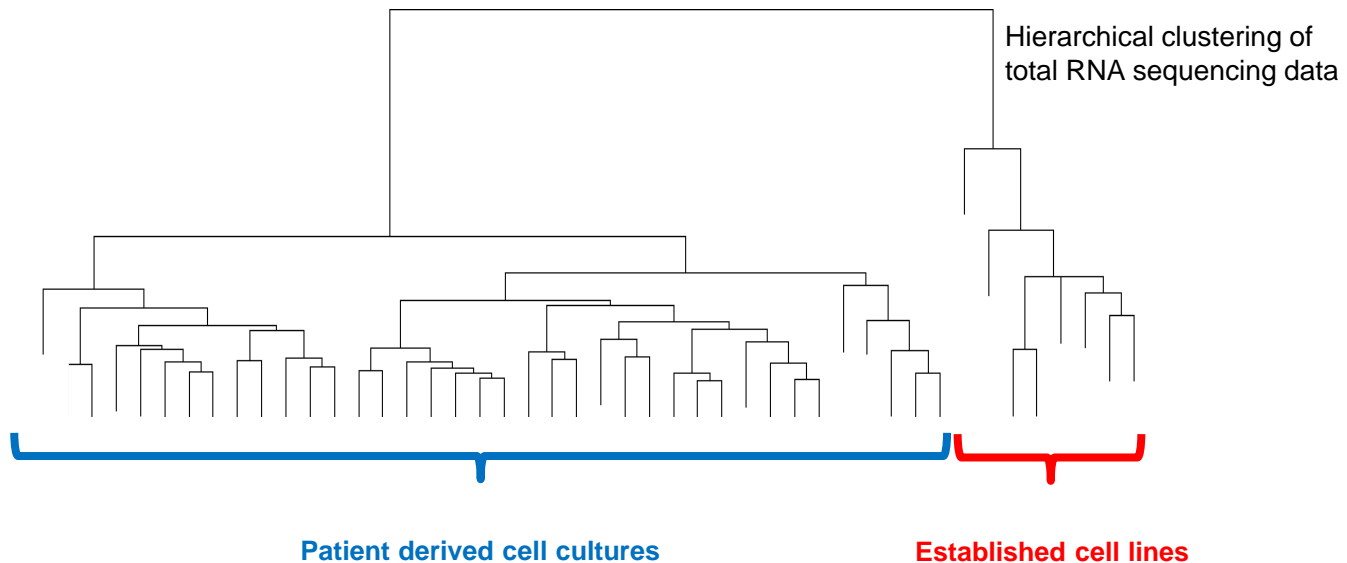
Isolate the self-renewing chemo-resistant cells



Surgical Centre

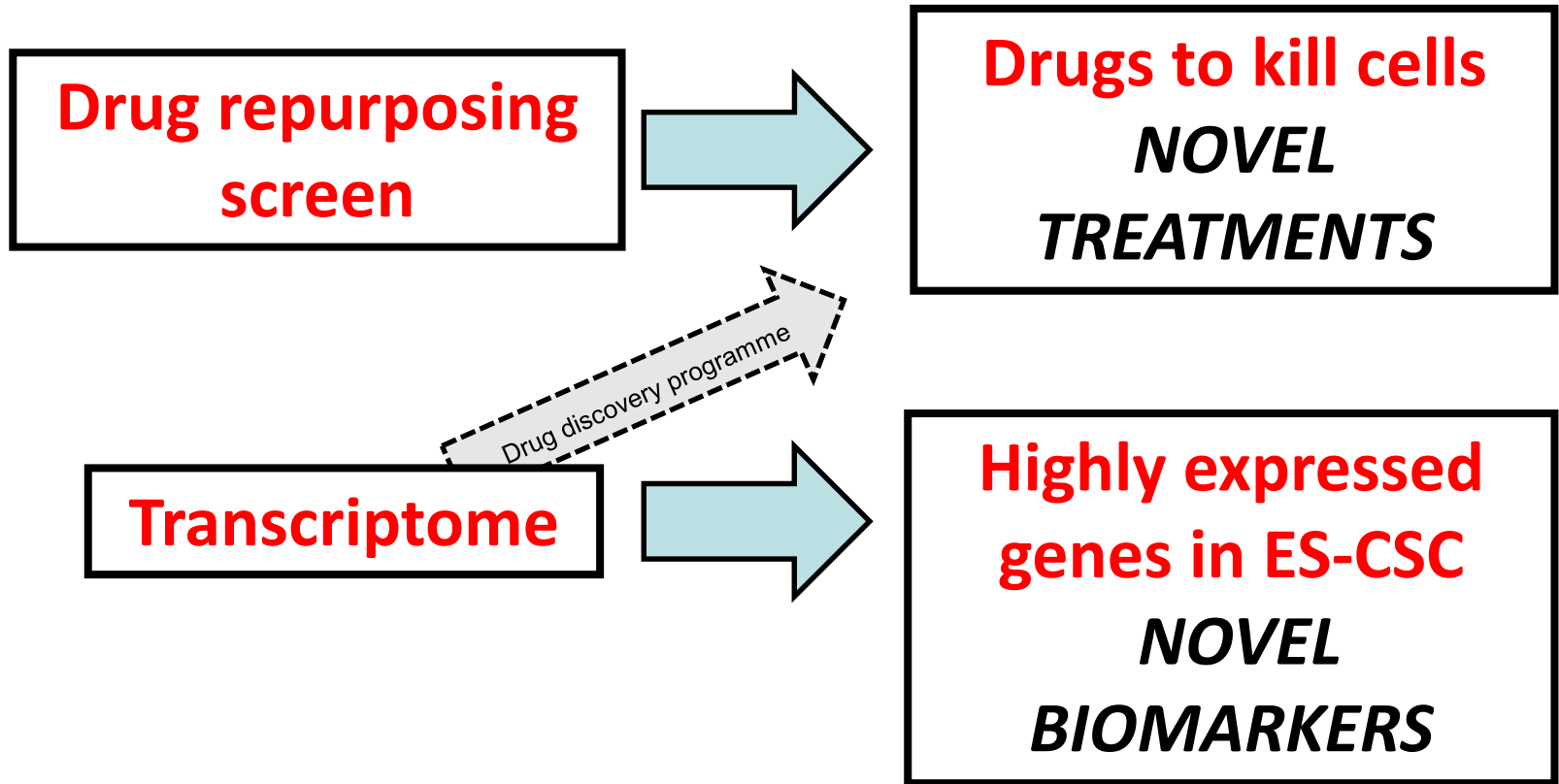
Laboratory in Leeds

Patient-derived cells are different to established cell lines



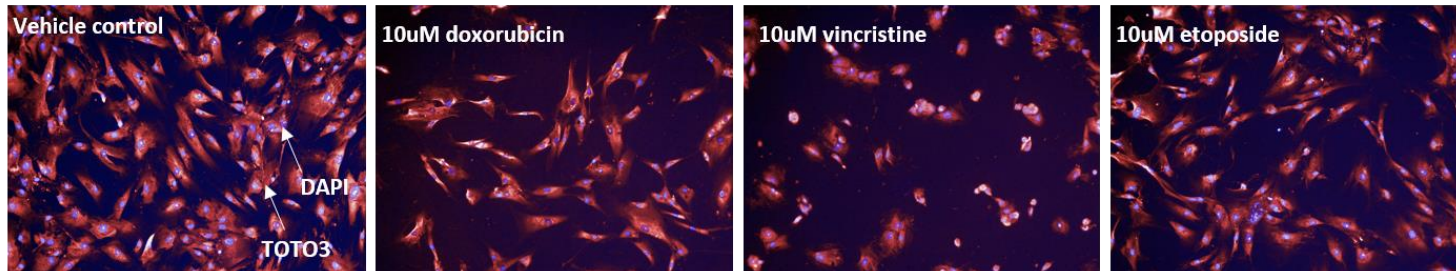
Patient-derived cells should be used in the preclinical pathway

Application of patient-derived cells



Drug repurposing screen

Operetta
Multicellular interactions and high
throughput screen (*in vitro*)



DAPI=nucleus TOTO3=cytoplasm



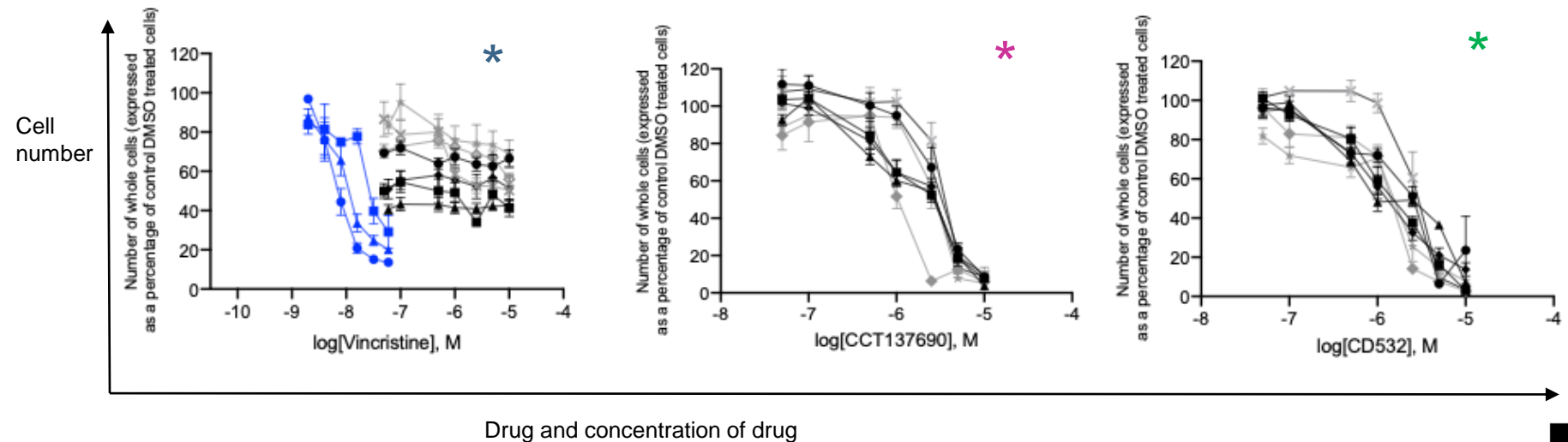
Find existing drugs that might work

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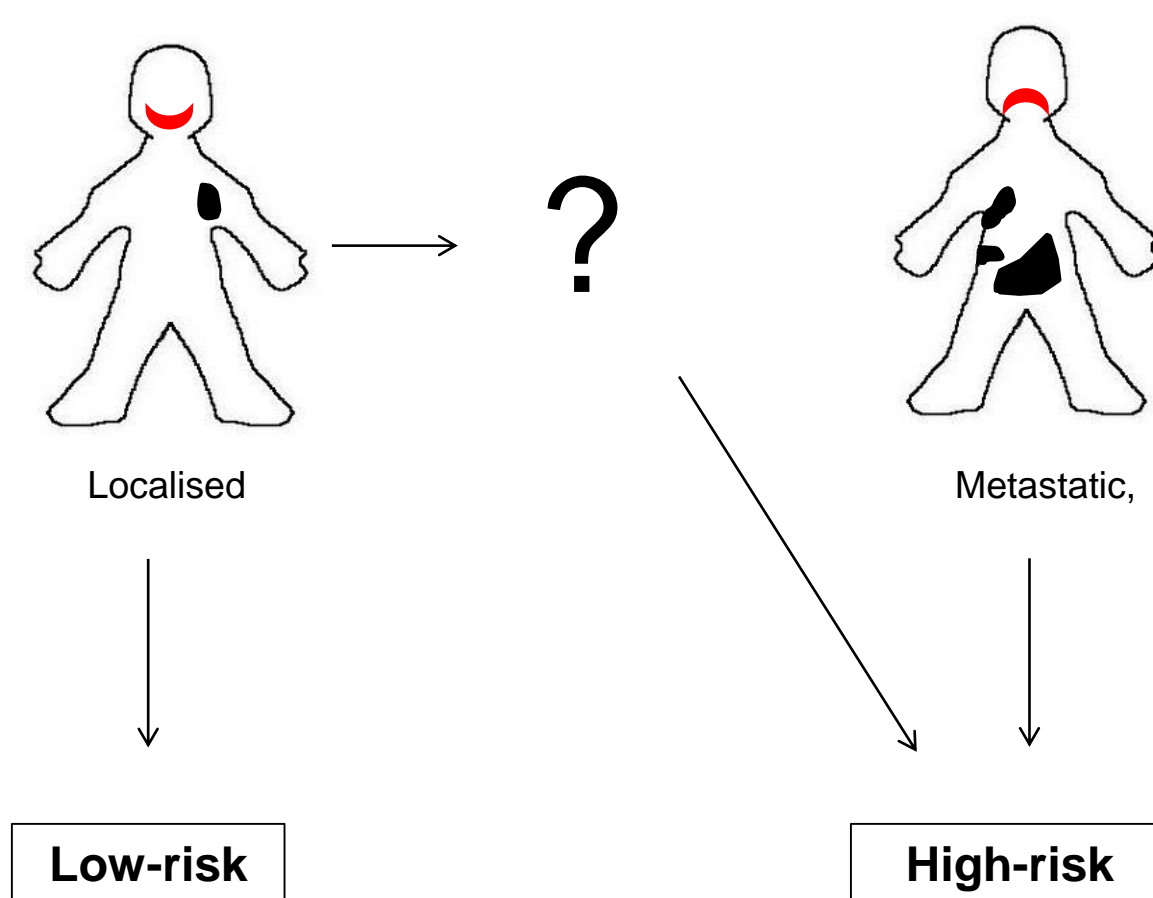
ES-CSC culture number	Doxorubicin	Vincristine	Etoposide	Actinomycin D	YK-4-279	Fenretinide	All-trans retinoic acid	MLN8237	CCT137690	CD532	VX680	VX689
	Chemotherapeutics				EWSR1 RNA helicase targeting SMI	Retinamides		Aurora kinase inhibitor				
ES1-CSC1									****	****		
ES2-CSC1									****	****		
ES2-CSC2	**								****			
ES2-CSC3	****	****	**	**					****	****		
ES3-CSC1	****			****	**			**	****	****	****	**
ES3-CSC2	****	****		****				****	****	****	**	
ES3-CSC3									****	****		
ES4-CSC1			*	**	****				****	****	**	
ES4-CSC2									****	****		



Black lines= ES patient derived cells Grey lines= ES-CSCs Blue lines=cell lines

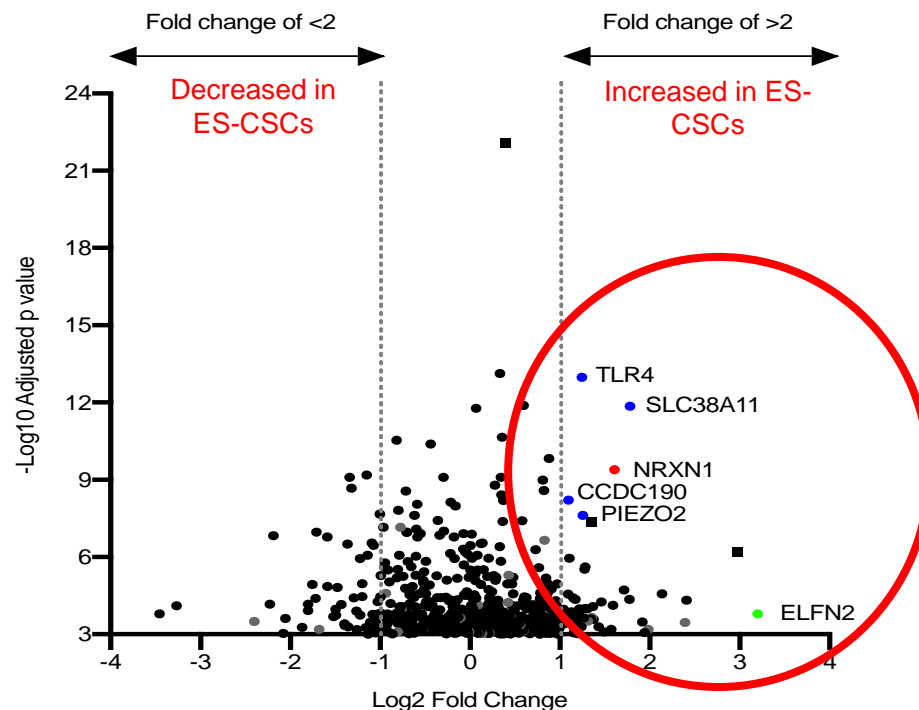


Biology adapted treatment



Interrogate the transcriptome to identify differentially expressed genes

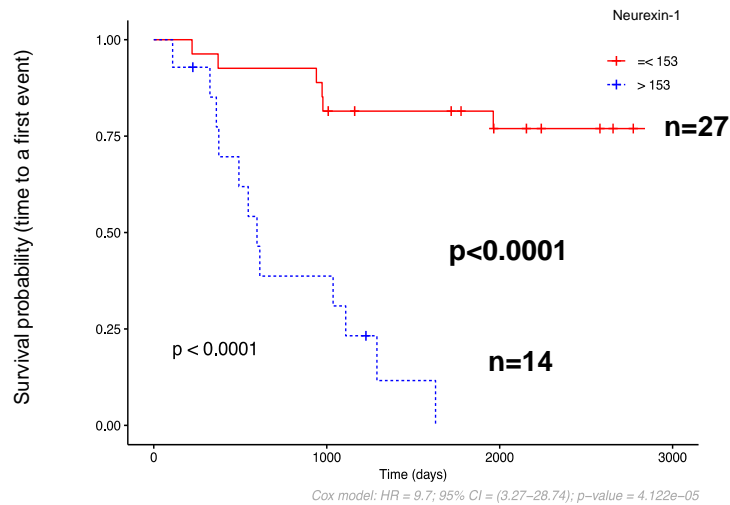
Differential expression of 561 genes in primary ES compared to paired ES-CSCs (adjusted $p < 0.001$).



Significance and fold change in expression <2 or >2

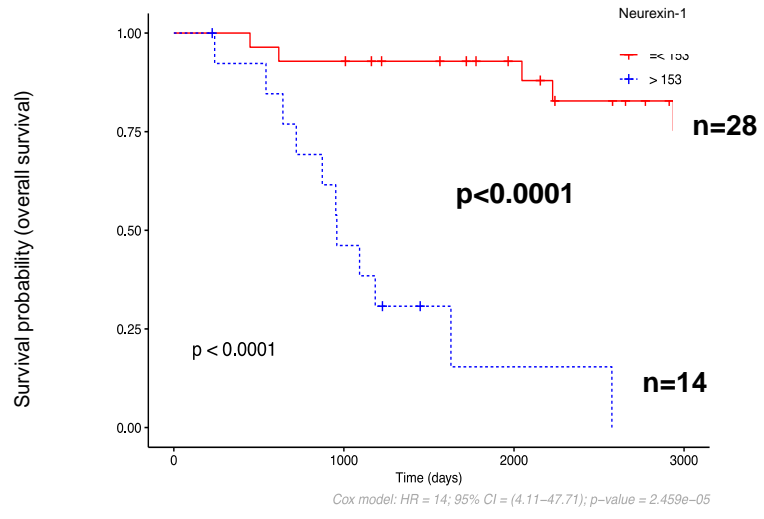
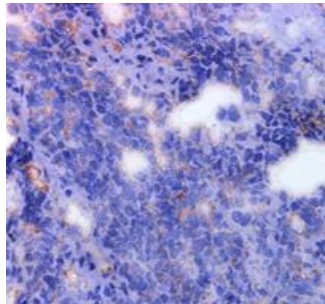


Neurexin-1 predicts outcome (localised disease)



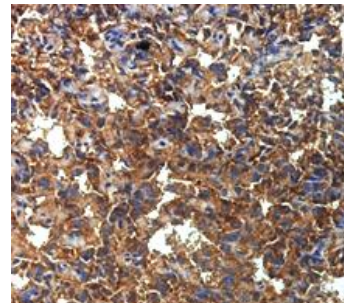
Number at risk (number of events)				
Neurexin-1	0	1000	2000	3000
≤ 153	27 (0)	22 (5)	16 (6)	10 (6)
> 153	14 (0)	5 (8)	0 (12)	0 (12)

Low expression



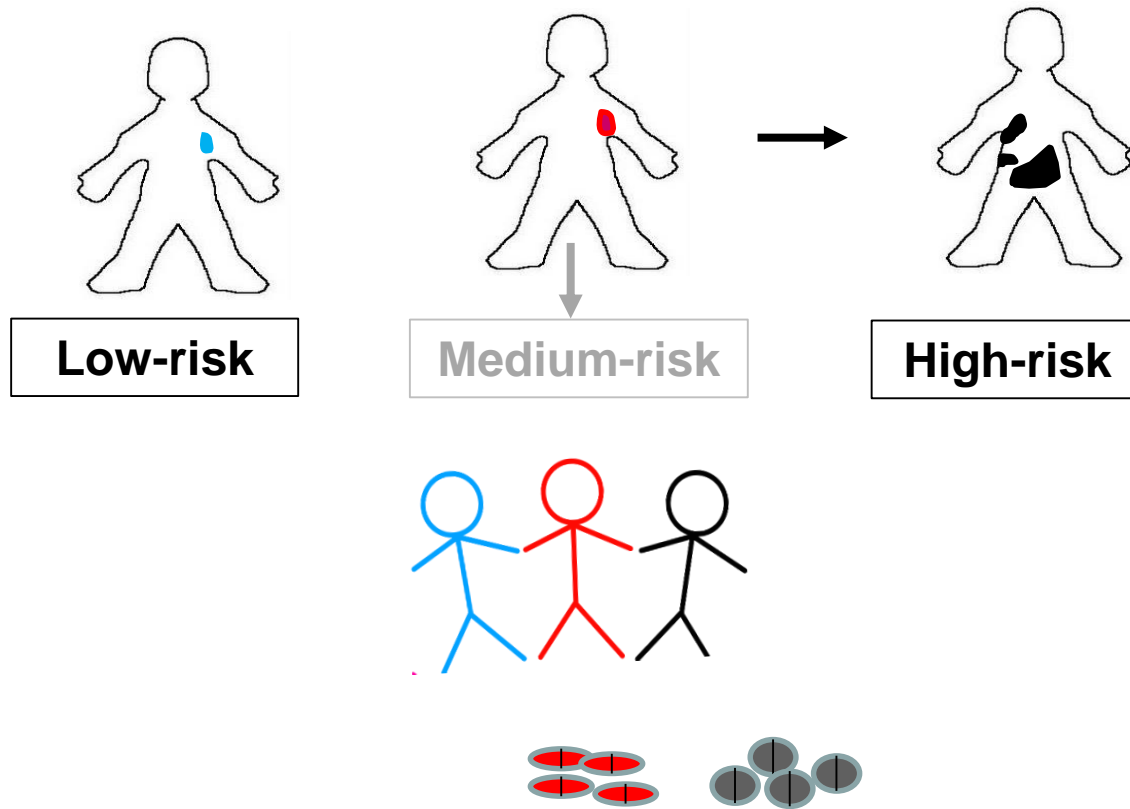
Number at risk (number of events)				
Neurexin-1	0	1000	2000	3000
≤ 153	28 (0)	26 (2)	19 (2)	10 (5)
> 153	14 (0)	6 (7)	1 (10)	0 (11)

High expression



Personalised medicine

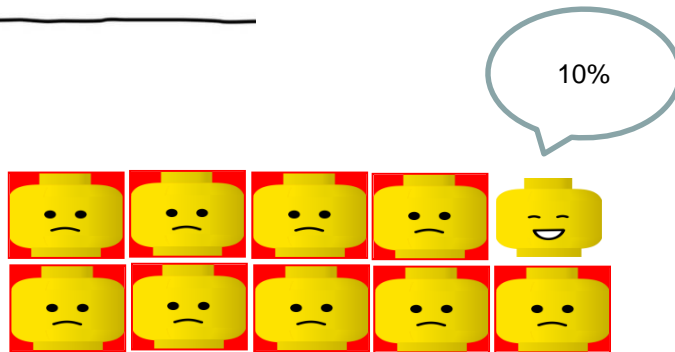
(rather than one-treatment-fits-all)



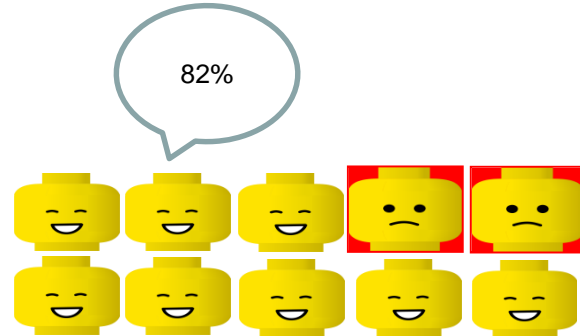
Molecular profiles to 'stratify' patients so they receive the most effective treatment (whilst minimising side-effects) based on biology and the needs of the patient

Research works

More children survive cancer than ever before



1975



2018



THANK YOU

Patients that have gifted samples for the purpose of research



Professor Lee Jeys
Mr Michael Parry



Dr Dan Stark



Dr Dan Yeomanson



Mr Kenneth Rankin



Ms Molly McNae
Dr Elizabeth Roundhill

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