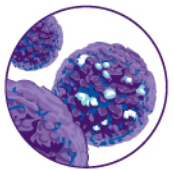
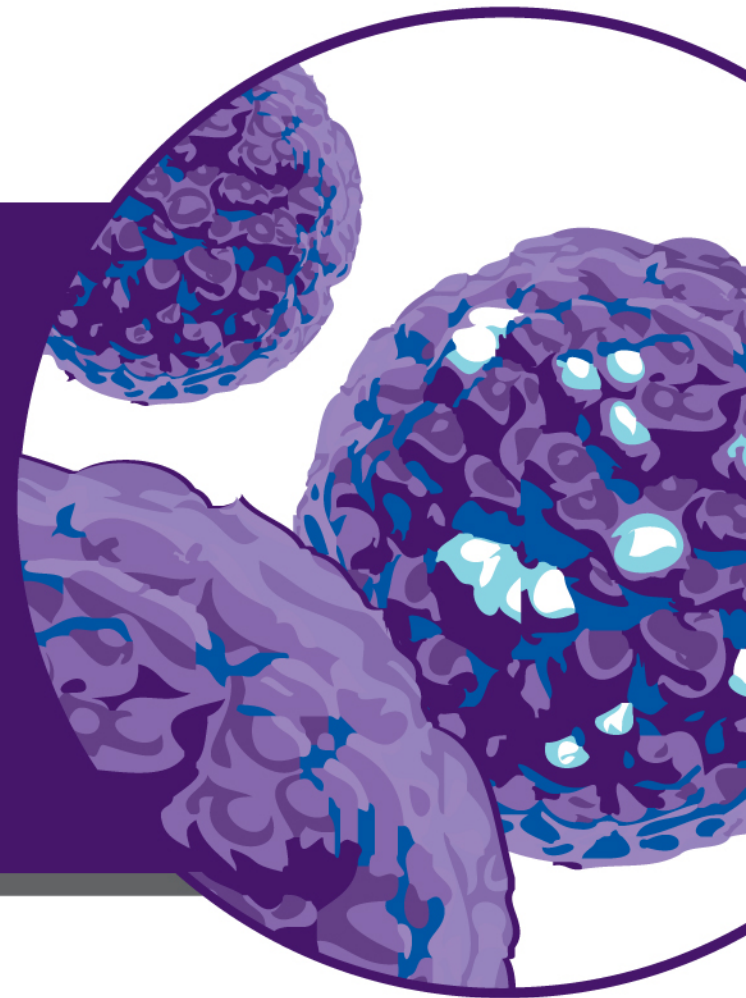


Integrated analysis of TCGA identifies targets and patient populations for Antibody-Drug Conjugates

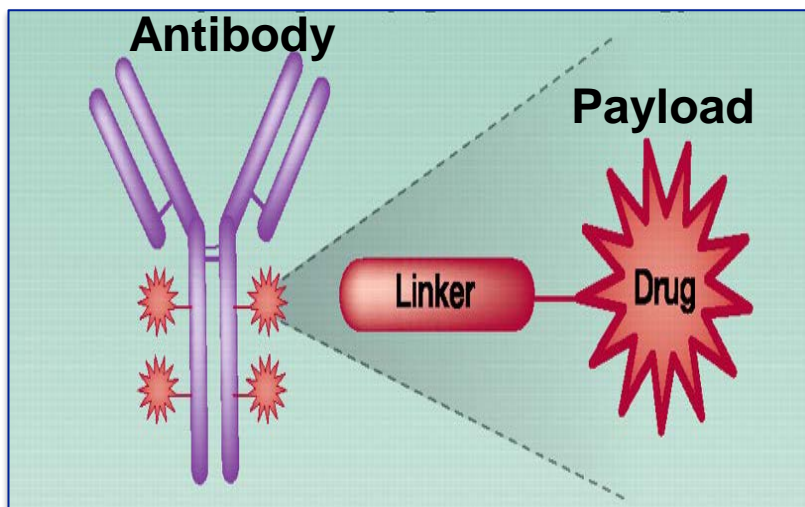
Wenyan Zhong, Pfizer Inc.
TCGA Symposium
05/11/2015



Oncology
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Antibody-drug conjugate (ADC)

Antibody-Drug Conjugate



What makes an optimal ADC?

Antibody

- Target recognition unaltered compared with naked Ab
- **Abundant target expression** and rapid internalization

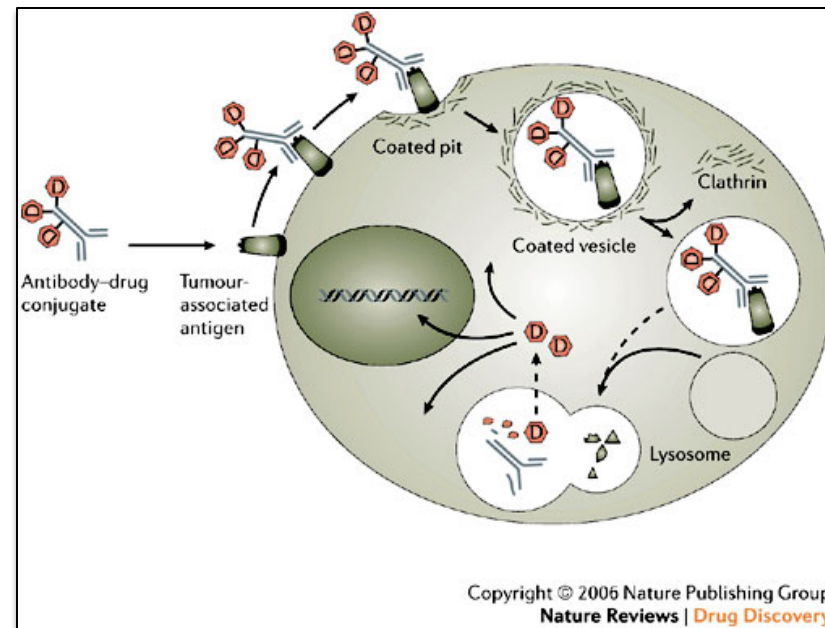
Drug

- Highly potent cytotoxic agent (\leq nM IC90 as free drug)
- Validated mechanism of action (microtubule inhibition, DNA damage)

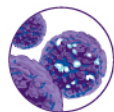
Linker

- Stable in plasma to avoid premature release of the drug
- Labile once internalized to release the drug in its active form

Mechanism of Action



Nature Reviews Drug Discovery 5, 147-159 (2006)



Clin Cancer Res 17, 6389-6397 (2011);
Curr. Cancer Drug Targets 9, 982-1004 (2009)

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Antibody-drug conjugate pipeline hits 30

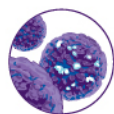
ADC on Market

ADC	Target	Indication
Brentuximab vedotin	CD30	relapsed or refractory Hodgkin's lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma
T-DM1	HER2	HER2-positive metastatic breast cancer

ADC in clinical trial

ADC	Lead	Lead indications	Target	Payload	Phase
Inotuzumab ozogamicin (CMC-544)	Pfizer	Aggressive non-Hodgkin's lymphoma; acute lymphoblastic leukaemia	CD22	Calicheamicin	III
RG-7596	Genentech	DLBCL and follicular non-Hodgkin's lymphoma	CD79b	MMAE	II
Pinatuzumab vedotin (RG-7593)	Genentech	DLBCL and follicular non-Hodgkin's lymphoma	CD22	MMAE	II
Glembatumab vedotin	Celldex	Breast cancer	GPNCB	MMAE	II
SAR-3419	Sanofi	DLBCL; acute lymphoblastic leukaemia	CD19	DM4	II
Lorvotuzumab mertansine (IMGN-901)	ImmunoGen	Small-cell lung cancer	CD56	DM1	II
BT-062	BioTest	Multiple myeloma	CD138	DM4	II
PSMA-ADC	Progenics	Prostate cancer	PSMA	MMAE	II
ABT-414	AbbVie	Glioblastoma; non-small-cell lung cancer; solid tumour	EGFR	Not disclosed	I/II
Milatuzumab doxorubicin	Immunomedics	Chronic lymphocytic leukaemia; multiple myeloma; non-Hodgkin's lymphoma	CD74	Doxorubicin	I/II
IMMU-132	Immunomedics	Solid tumour	TACSTD2 (also known as TROP2 or EGP1)	Irinotecan metabolite	I
Labetuzumab-SN-38	Immunomedics	Cancer; colorectal cancer	CEA (also known as CD66e)	Irinotecan metabolite	I
IMGN-853	ImmunoGen	Ovarian tumour; solid tumour	Folate receptor 1	DM4	I
IMGN-529	ImmunoGen	B cell lymphoma; chronic lymphocytic leukaemia; non-Hodgkin's lymphoma	CD37	DM1	I
RG-7458	Genentech	Ovarian tumour	Mucin 16	MMAE	I
RG-7636	Genentech	Melanoma	Endothelin receptor ETB	MMAE	I
RG-7450	Genentech	Prostate cancer	STEAP1	MMAE	I
RG-7600	Genentech	Ovarian tumour; pancreatic tumour	Not disclosed	Not disclosed	I
RG-7598	Genentech	Multiple myeloma	Not disclosed	Not disclosed	I
RG-7599	Genentech	Non-small-cell lung cancer; ovarian tumour	Not disclosed	Not disclosed	I
SGN-CD19A	Seattle Genetics	Acute lymphoblastic leukaemia, aggressive non-Hodgkin's lymphoma	CD19	MMAE	I
Vorsetuzumab mafodotin	Seattle Genetics	Non-Hodgkin's lymphoma; renal cell carcinoma	CD70	MMAF	I
ASG-5ME	Agensys	Cancer; pancreatic tumour; stomach tumour	SLC44A4 (AGS-5)	MMAE	I
ASG-22ME	Agensys	Solid tumour	Nectin 4	MMAE	I
AGS-16M8F	Agensys	Cancer; renal cell carcinoma	AGS-16	MMAF	I
MLN-0264	Millennium	Gastrointestinal tumour; solid tumour	Guanylyl cyclase C	MMAE	I
SAR-566658	Sanofi	Solid tumour	Mucin 1	DM4	I
AMG-172	Amgen	Cancer; renal cell carcinoma	CD70	Not disclosed	I
AMG-595	Amgen	Glioma	EGFRvIII	DM1	I
BAY-94-9343	Bayer	Cancer; mesothelioma	Mesothelin	DM4	I

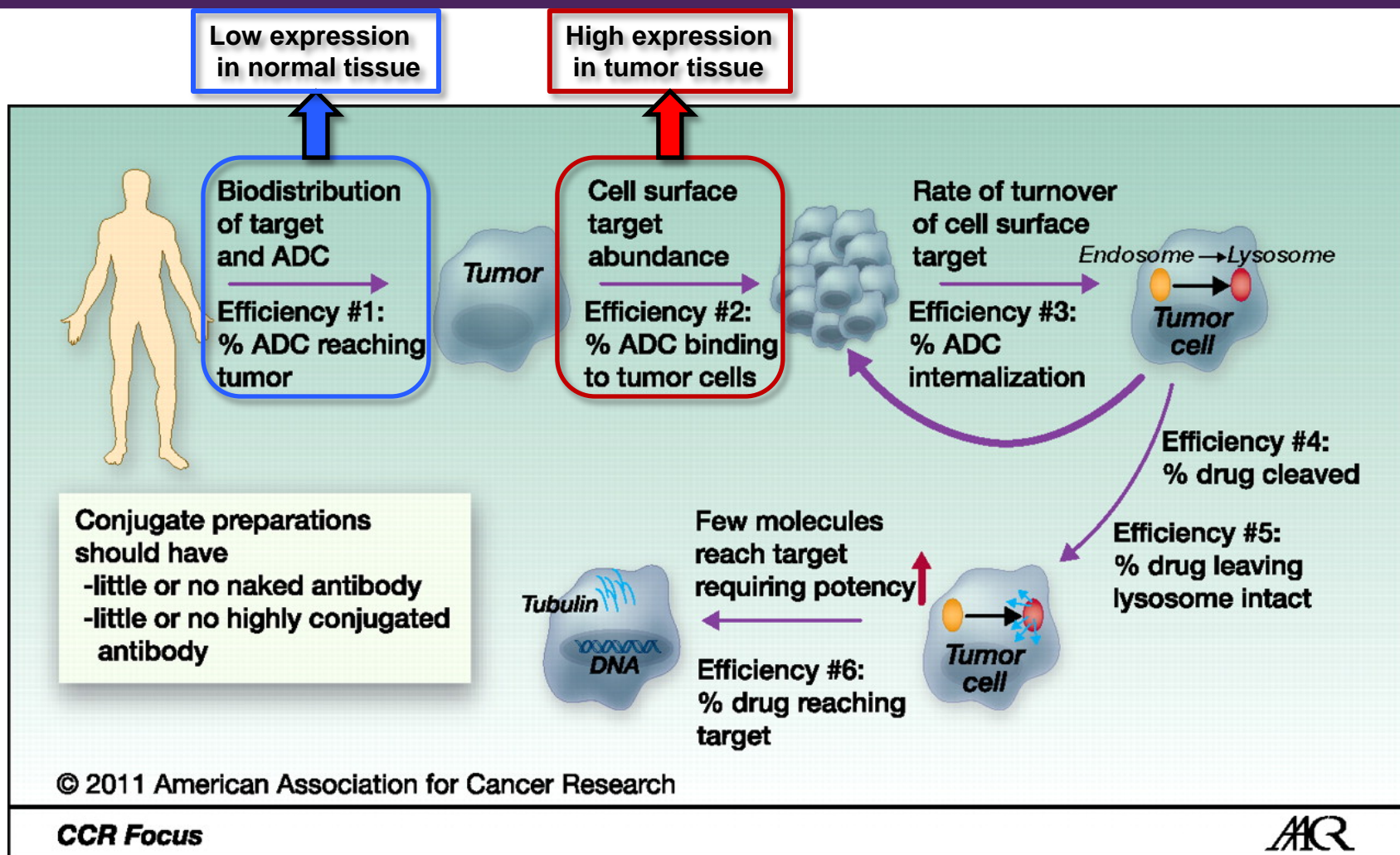
ADC, antibody-drug conjugate; CEA, carcinoembryonic antigen; DLBCL, diffuse large B cell lymphoma; EGFR, epidermal growth factor receptor; GPNCB, glycoprotein NMB; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; PSMA, prostate-specific membrane antigen; STEAP1, six-transmembrane epithelial antigen of prostate 1; TACSTD2, tumour-associated calcium signal transducer 2.



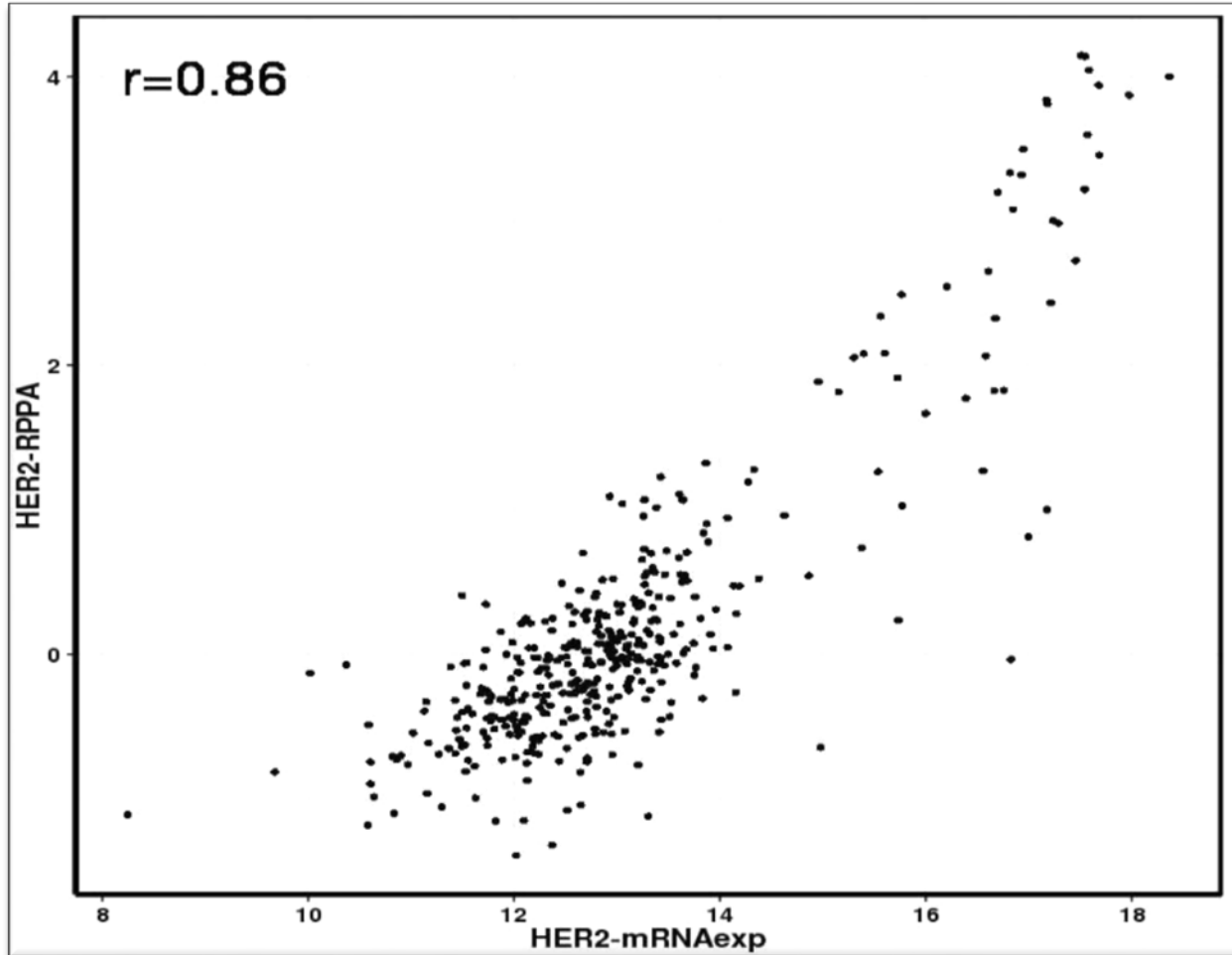
Oncology

A **Pfizer** Research Unit *Nature reviews drug discovery* 12, 329 (2013)

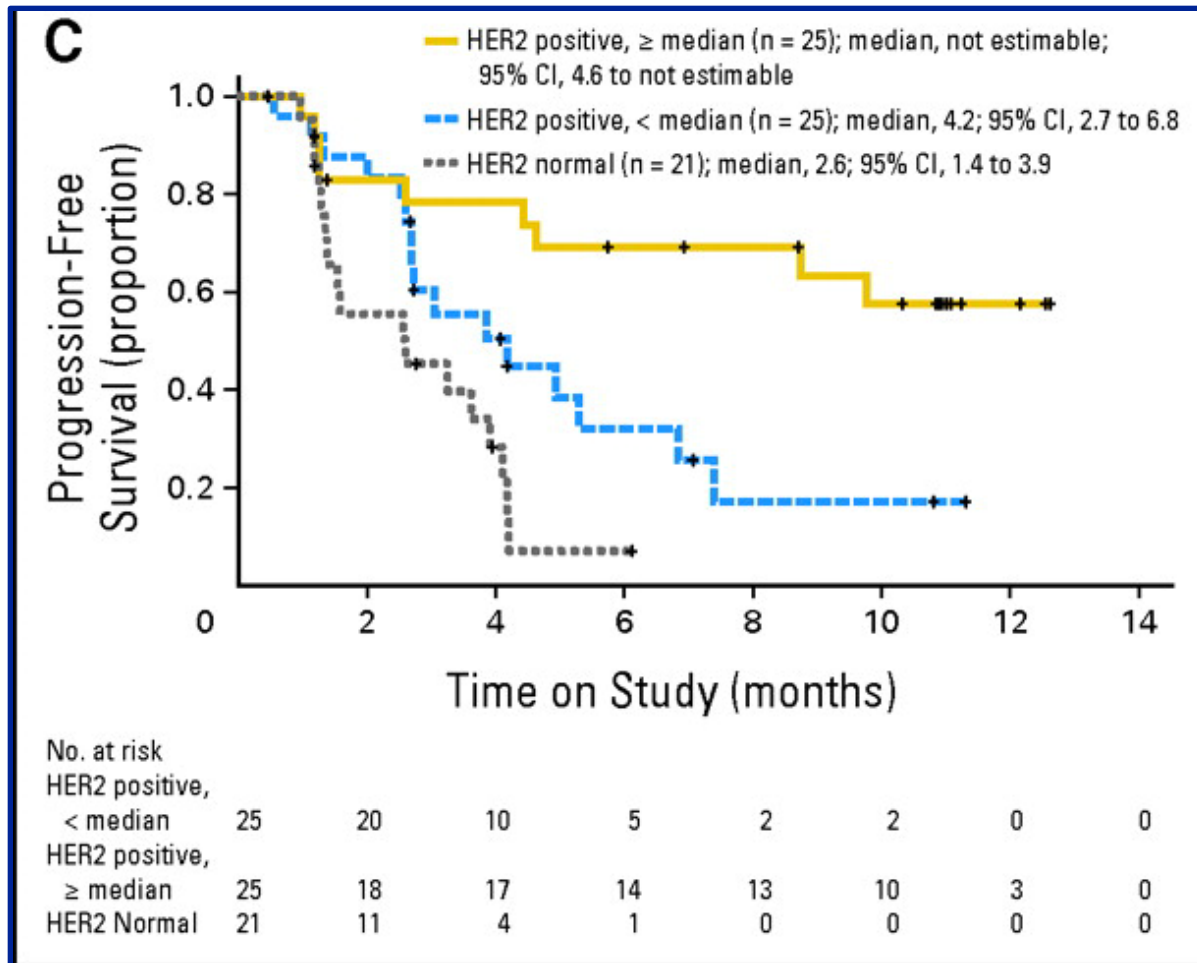
Steps from administration of ADC to the release of toxic agent



HER2 mRNA level correlates well with protein expression (RPPA)



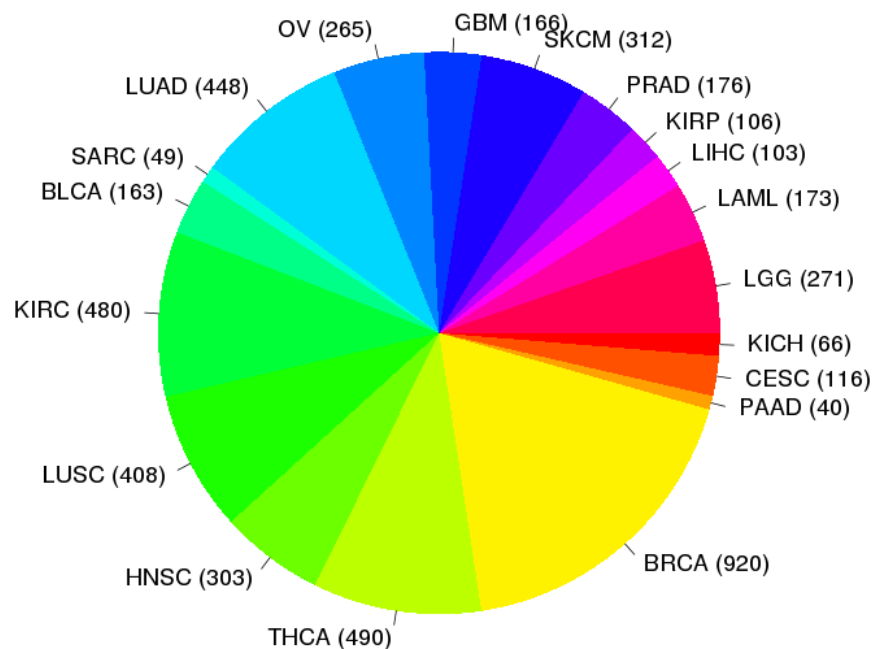
Higher response rate (T-DM1) observed for patient with higher HER2 mRNA expression (qRT-PCR)



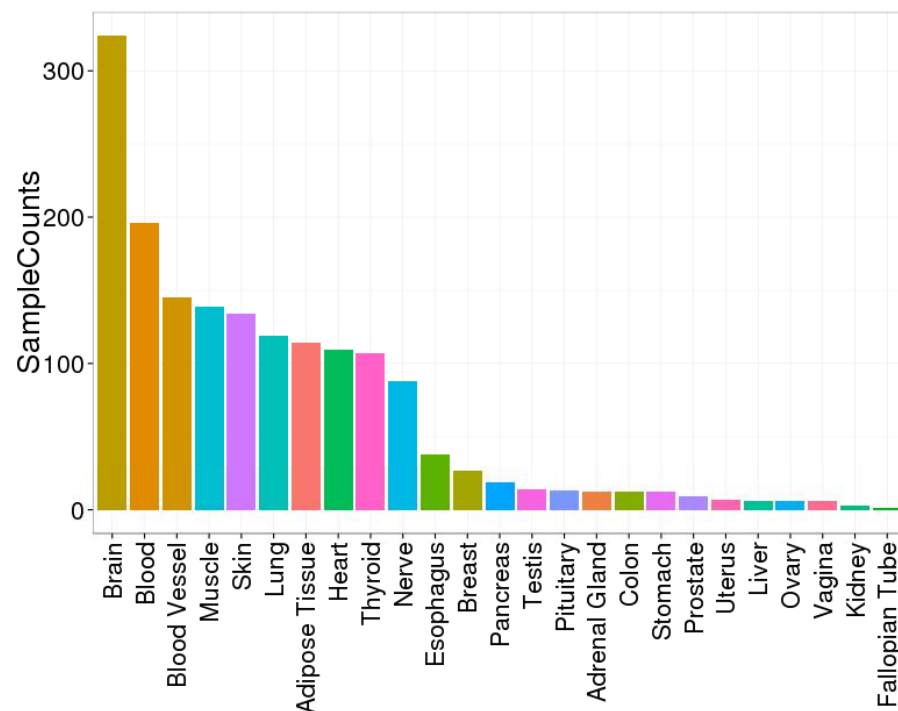
HER2 positive (IHC 3+ or FISH positive)

Genomic Data Resources

TCGA



GTEx



Matching ADC payload class to target selection

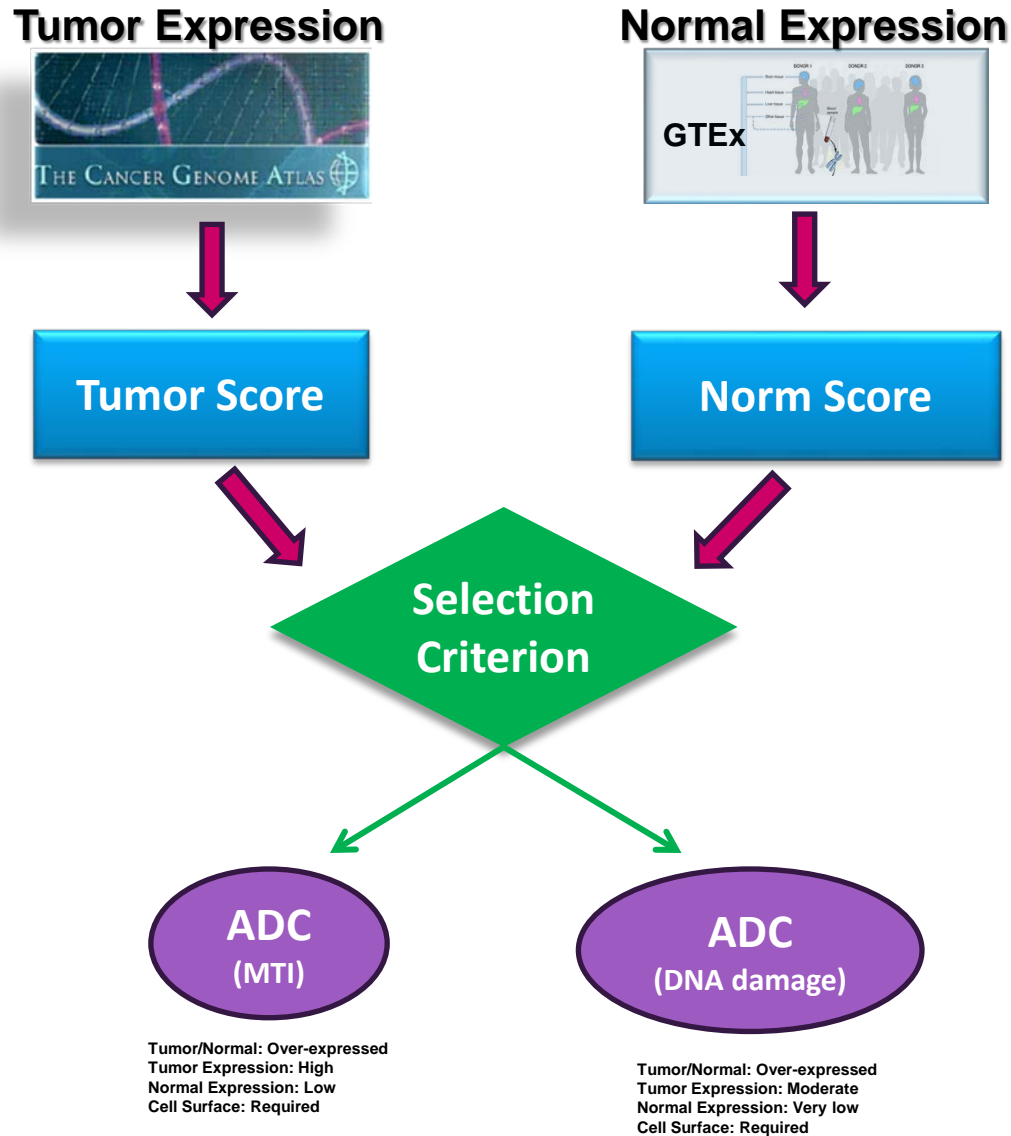
ADC Payload	MOA	Targeting cell type
DM1, DM4	Tubulin (MTI)	Proliferating
MMAE MMAF	Tubulin (MTI)	Proliferating
Calicheamicin PBD	DNA Damage	Proliferating & Non-proliferating
MGBA	DNA Alkylation	

Target Characteristics

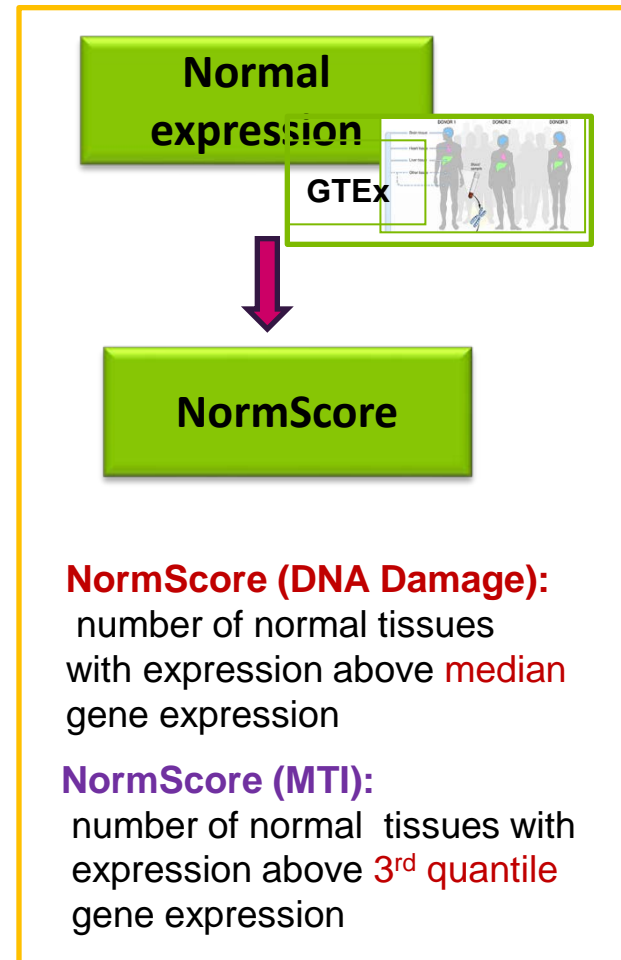
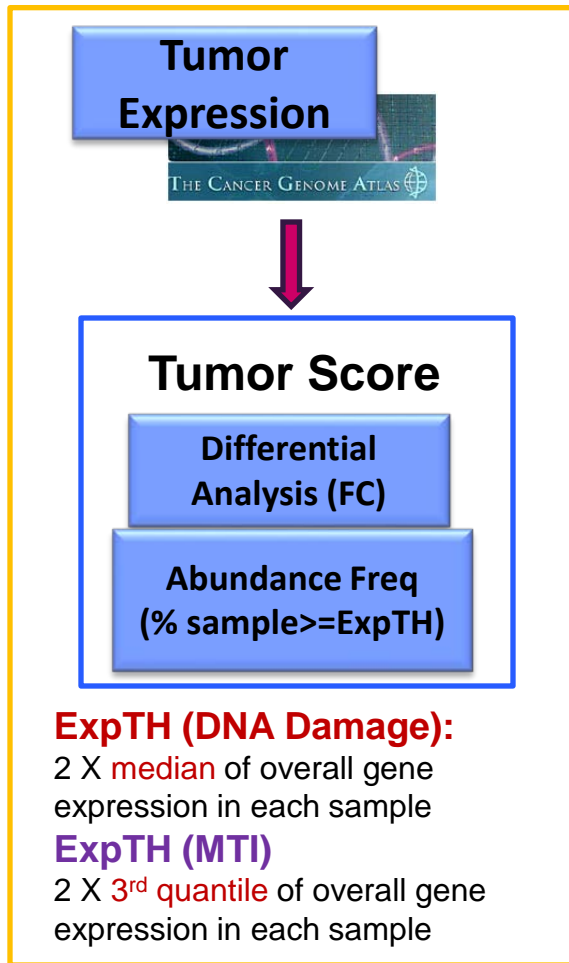
Tumor expression: High Level
Normal expression: low-medium expression tolerated (HER2)

Tumor expression: Lower level expression
Normal expression: Very low level (CD33)

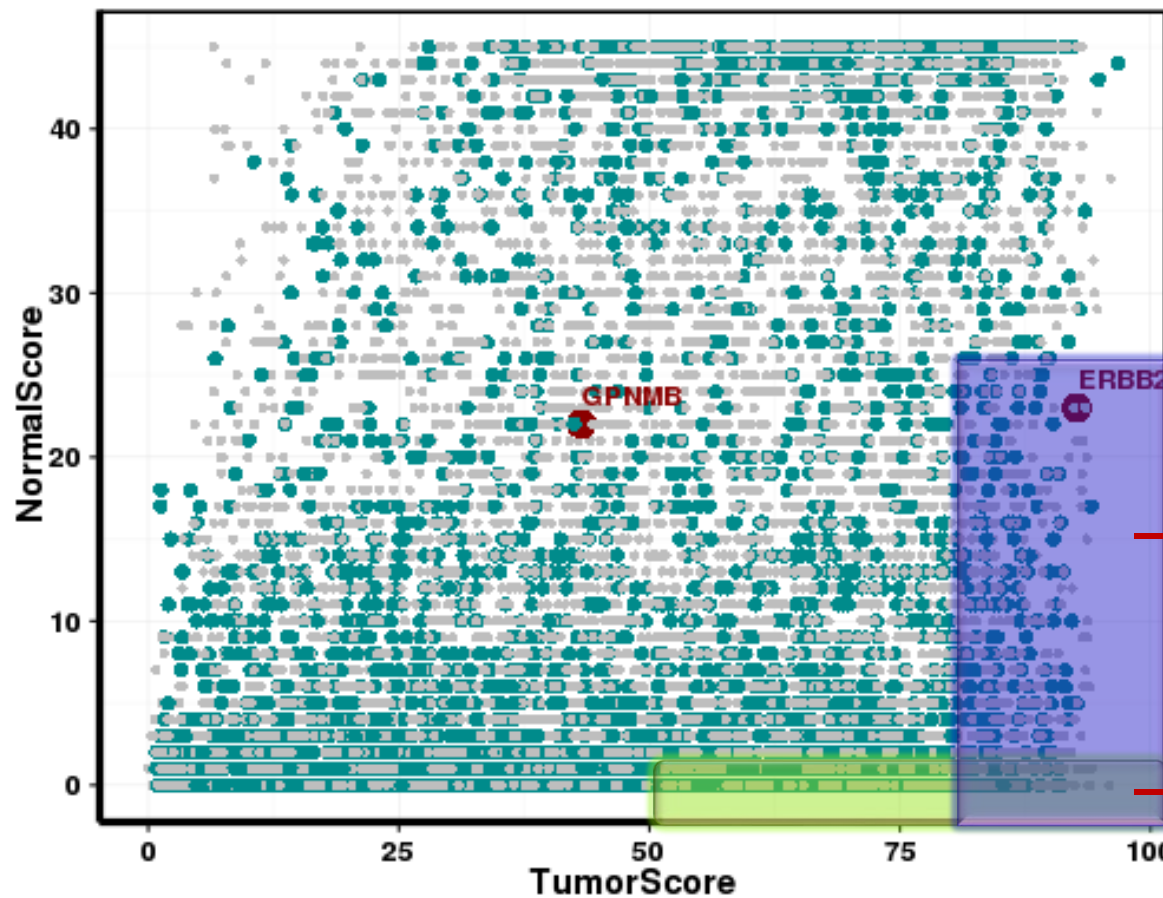
Target Identification - Strategy



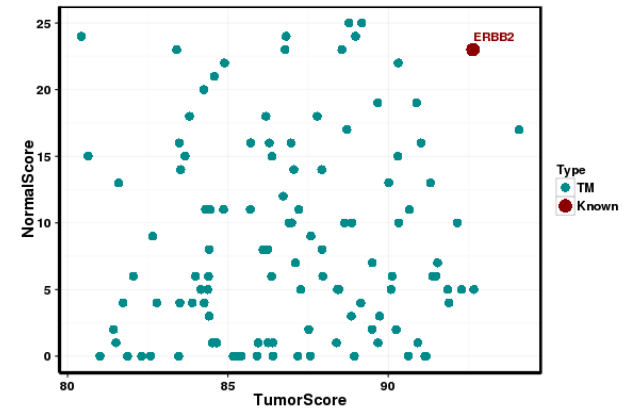
RNASeq based target selection: Score calculation



Target selection example – Breast Cancer



115 candidate targets

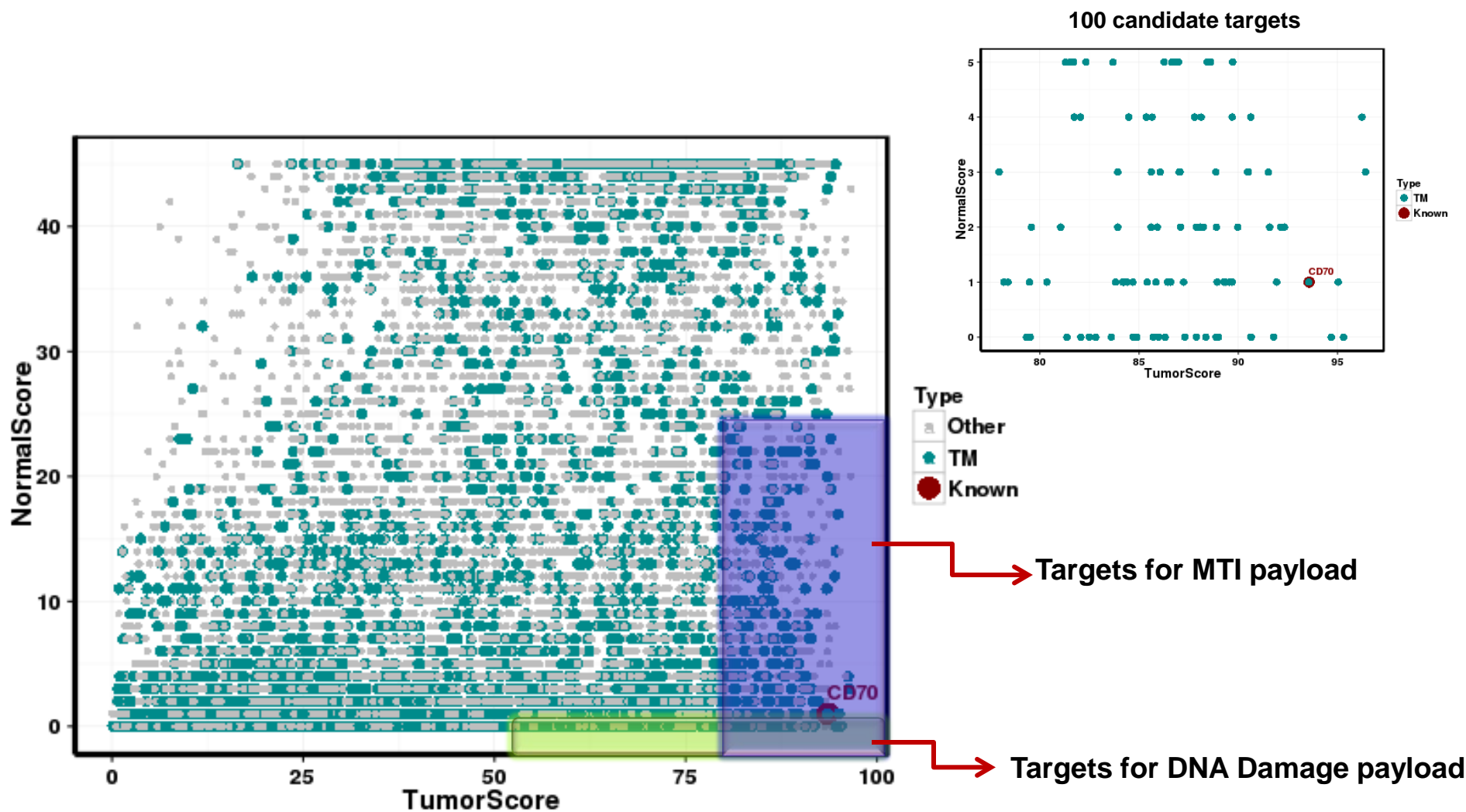


Type
Other
TM
Known

Targets for MTI payload

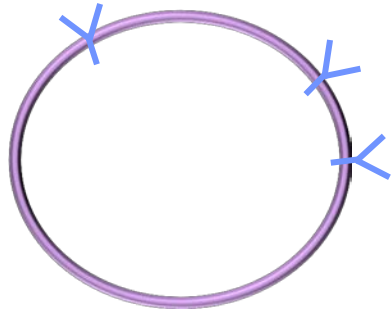
Targets for DNA Damage payload

Target selection example – Kidney renal clear cell carcinoma

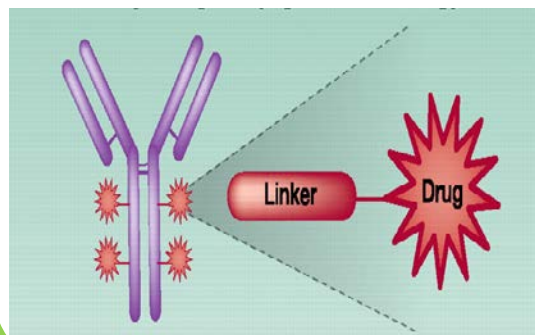


Patient selection strategy for ADC therapeutics

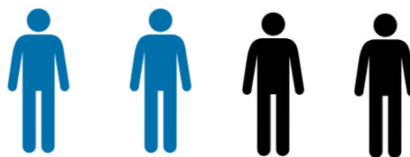
Target antigen



ADC



Patient selection



Companion Diagnostic
(Target expression(IHC, ISH))

Traditional

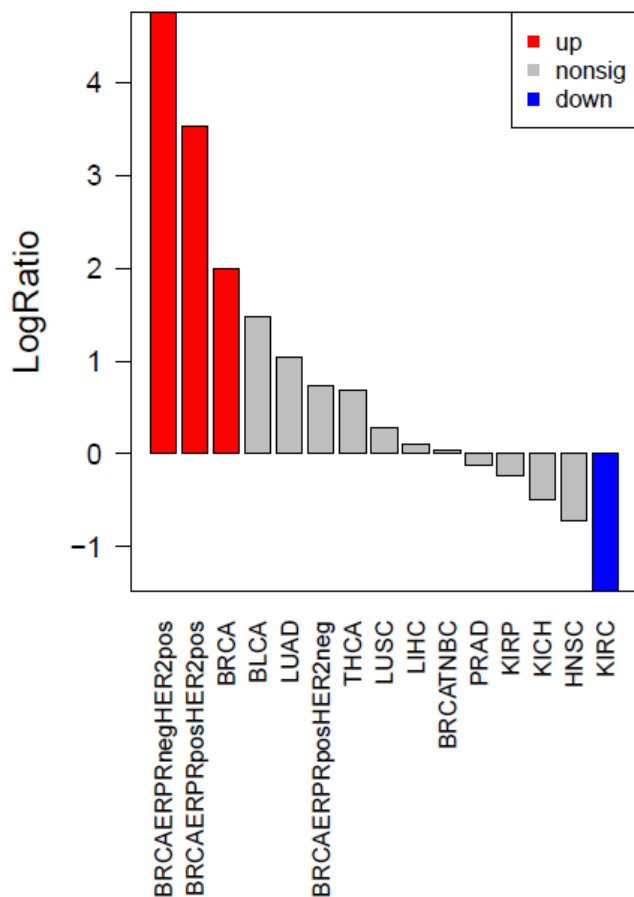
**Target expression
based Biomarker**

Exploratory

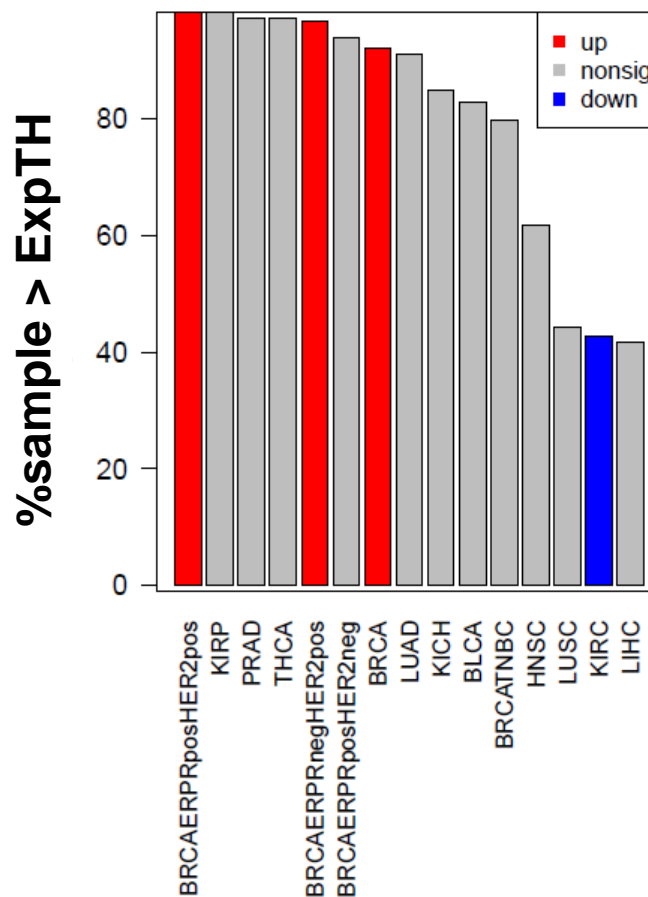
**Genetic based
Biomarker**

HER2+ subtype represents the major indication for HER2 ADC based on target expression

Differential Expression of-ERBB2

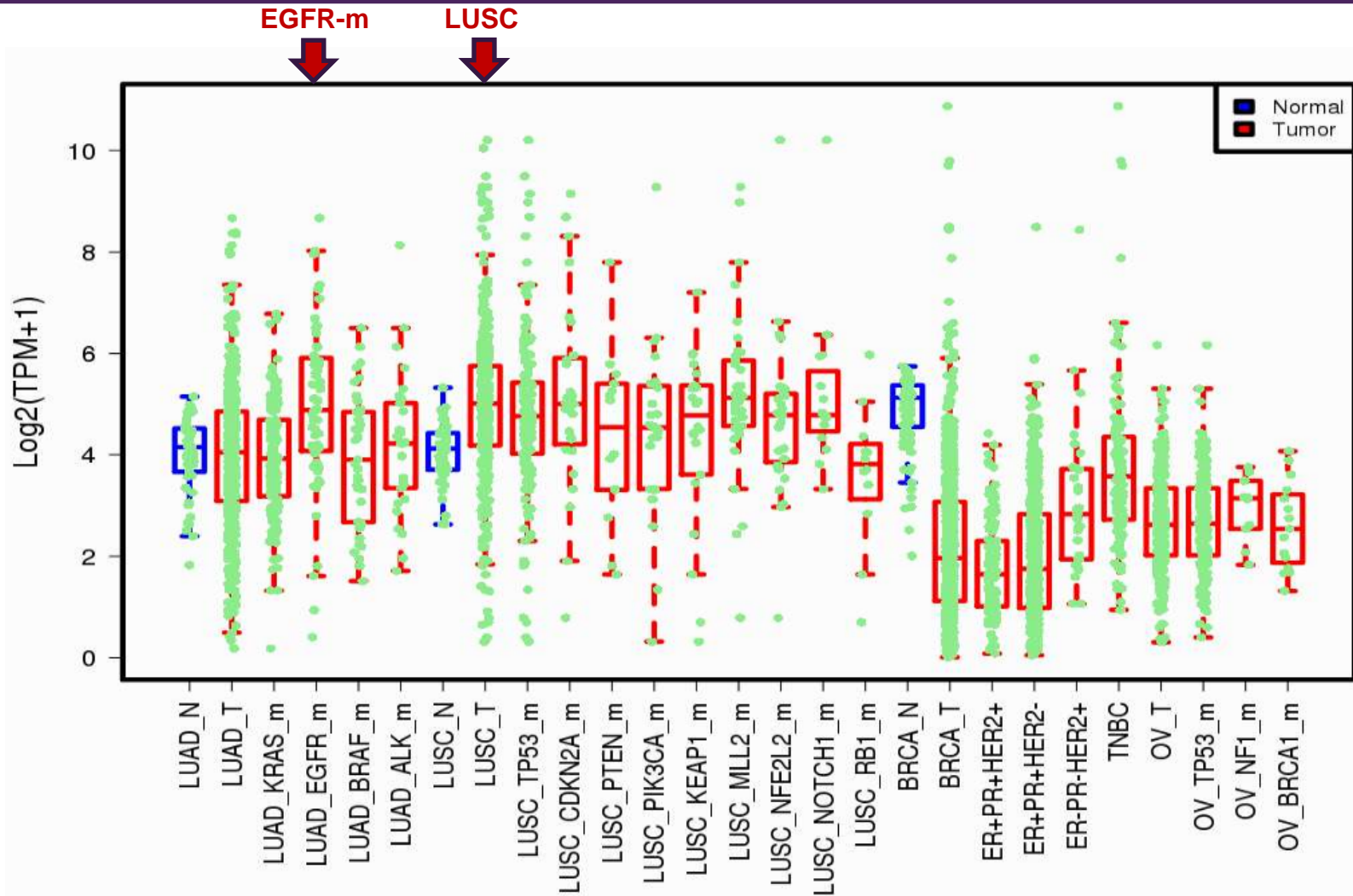


Relative gene abundance of-ERBB2

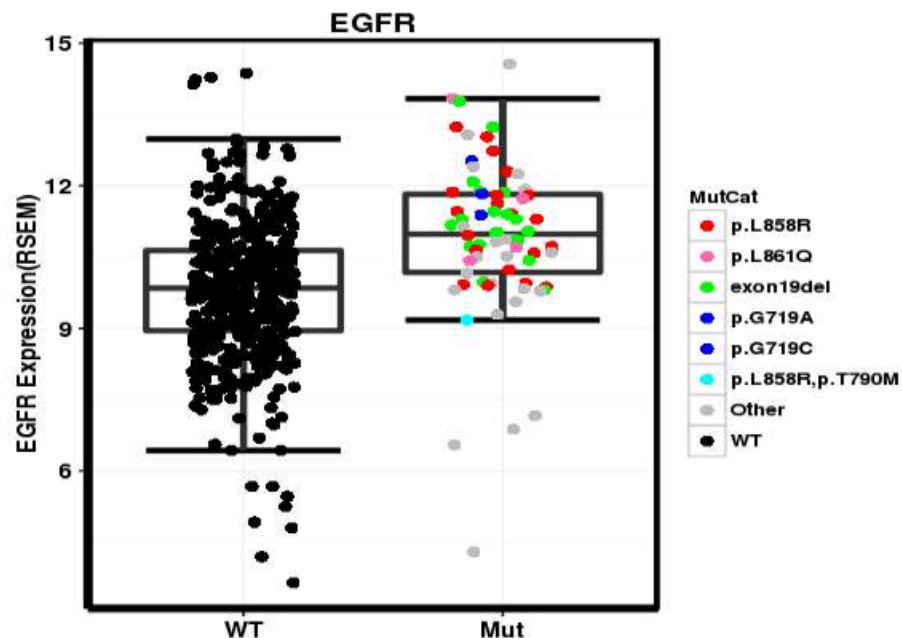


ExpTH: 2 X of 3rd quantile

EGFR expression in various mutation segments and cancer subtypes



EGFR mutation subpopulation correlates with high EGFR expression



Mutation	Freq	Percentage(Mut)	Percentage(All)
Other	22	31	4
p.L858R	20	29	4
exon19del	20	29	4
p.G719A	2	3	0
p.L861Q	4	6	1
p.G719C	1	1	0
p.L858R,p.T790M	1	1	0
WT	459	NA	87

Summary

- Computational strategy was developed employing TCGA RNASeq data for identifying novel ADC targets.
- RNASeq from large panel of TCGA is an excellent data resource for estimating the prevalence of ADC target expression
 - Providing guidance for companion diagnostic development and clinical trial design
- Genetic based biomarker as potential alternative biomarkers was explored using TCGA mutation data
 - High EGFR expressing tumors are enriched in EGFR mutation containing patients

Acknowledgement

CompBio/PM

Paul Rejto

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Kai Wang

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Zhou Zhu

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IBB

Kim Arndt

Jeremy Myers

Bingwen Lu

Eugene Melamud

Max Follettie

Donald Apanovitch

Statistics

Shibing Deng

Fred Immermann

BDD

Puja Sapra

Marc Damelin

Ken Geles

Boris Shor

Dangshe Ma

Chad May

Hans-Peter Geber

TCGA