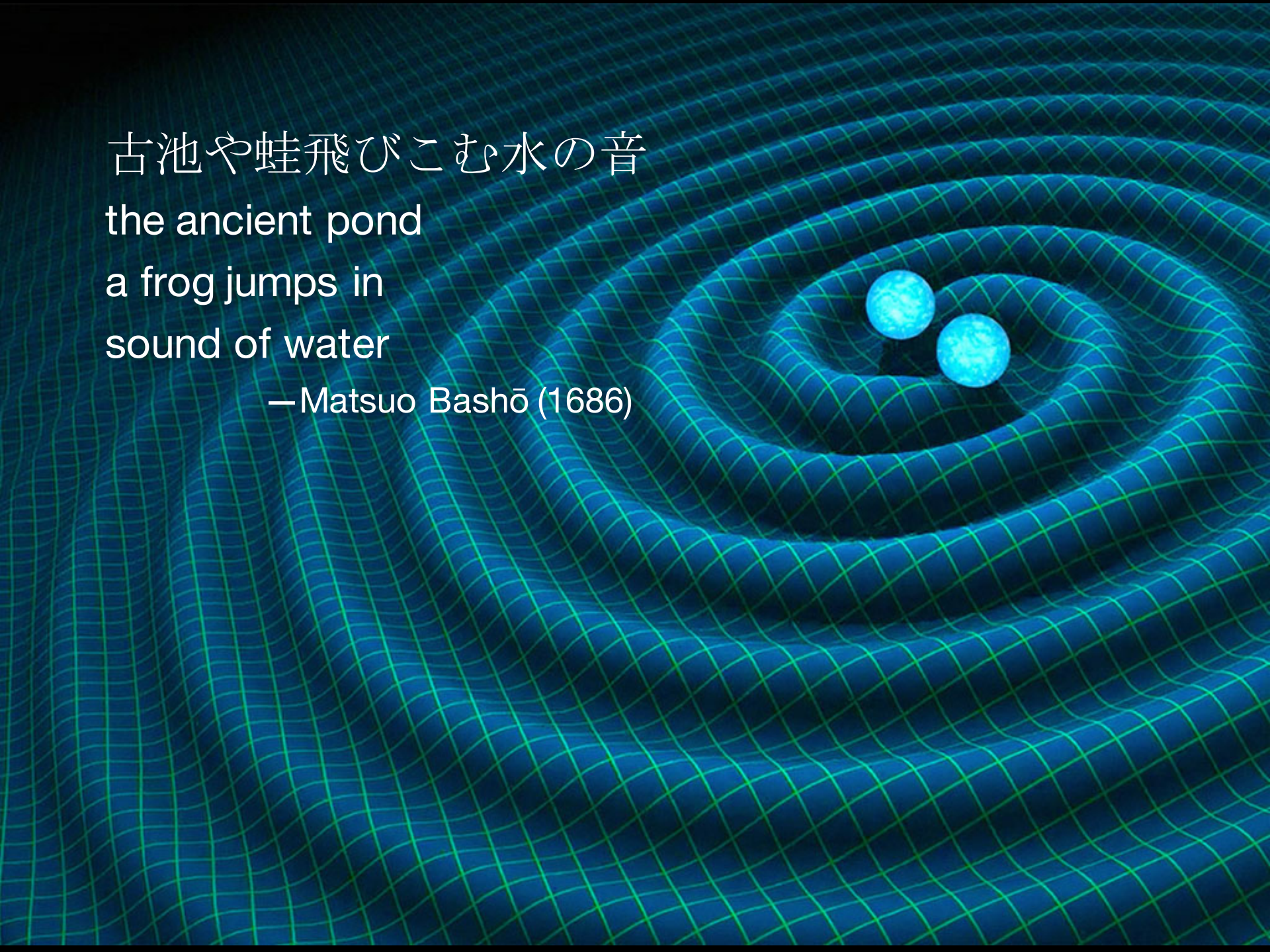

古池や蛙飛びこむ水の音
the ancient pond
a frog jumps in
sound of water
—Matsuo Bashō (1686)

Bioanalysis of Antibody-Drug Conjugates (ADCs): an overview of current approaches and case studies illustrating the challenges presented by hybrid biotherapeutic molecules

Rand Jenkins

7th JBF Symposium
Tokyo Japan, 09 March 2016

HELPING DELIVER LIFE CHANGING THERAPIES

PPD®

Overview

1. Introduction to ADCs
2. BA complexity & current approaches
3. LC-MS/MS assay options
4. Need for characterization—LC-HRAMS
5. BA practicality challenges
6. Final thoughts

Biotherapeutics innovation

peptides

mAbs

bispecifics (bsAbs, DART®s, BiTE®s)

ADCs

prodrug/carrier conjugates (albumin, PEG)

fusion proteins

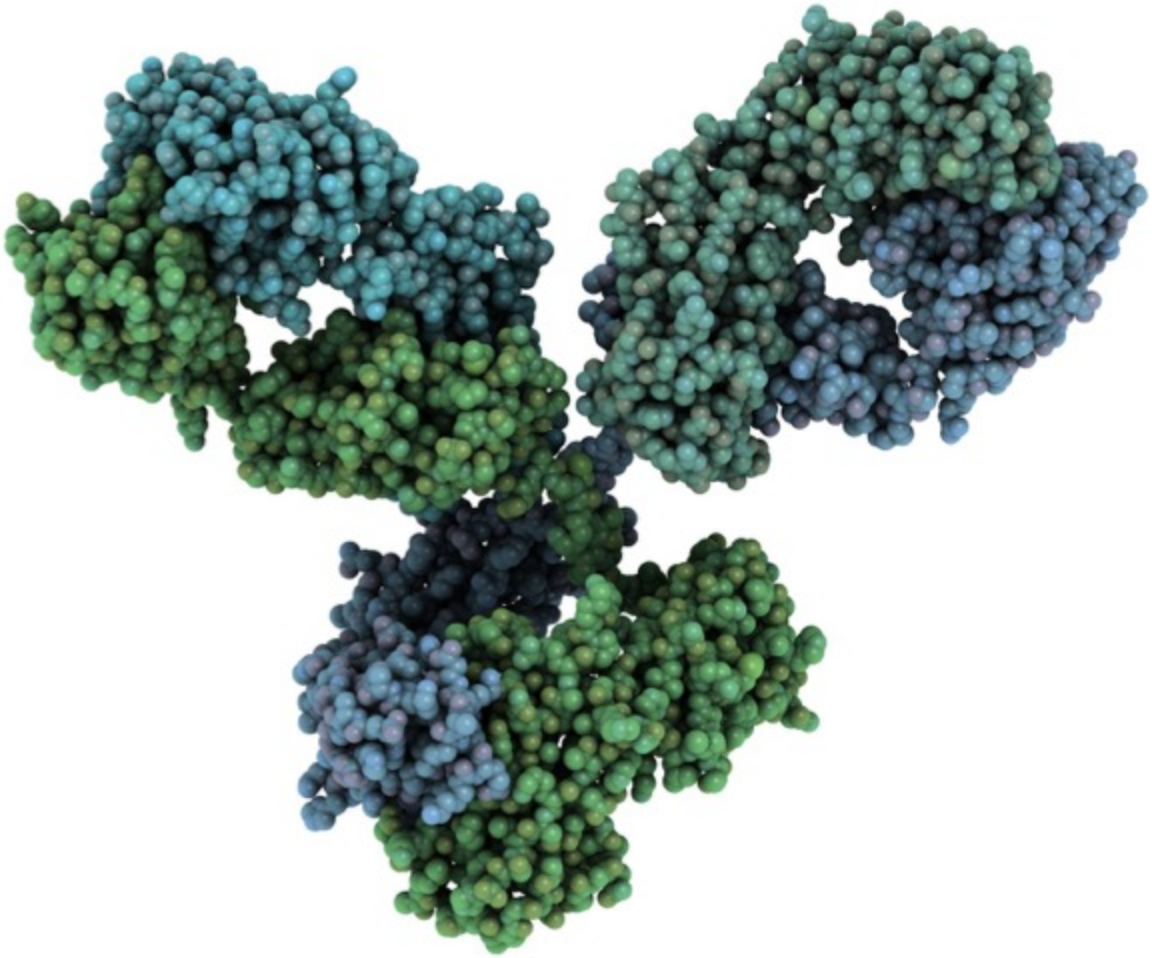
messenger RNA therapeutics™

oligonucleotides (ssDNA, siRNA, mRNA)

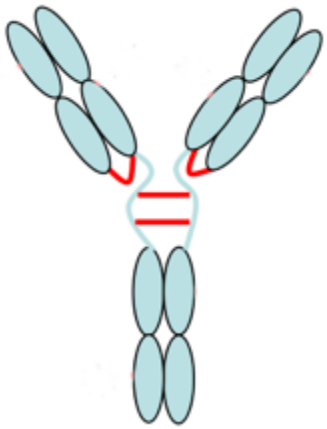
CAR-Ts

ADCs

Monoclonal antibody drugs



Monoclonal antibody drugs in cancer therapy

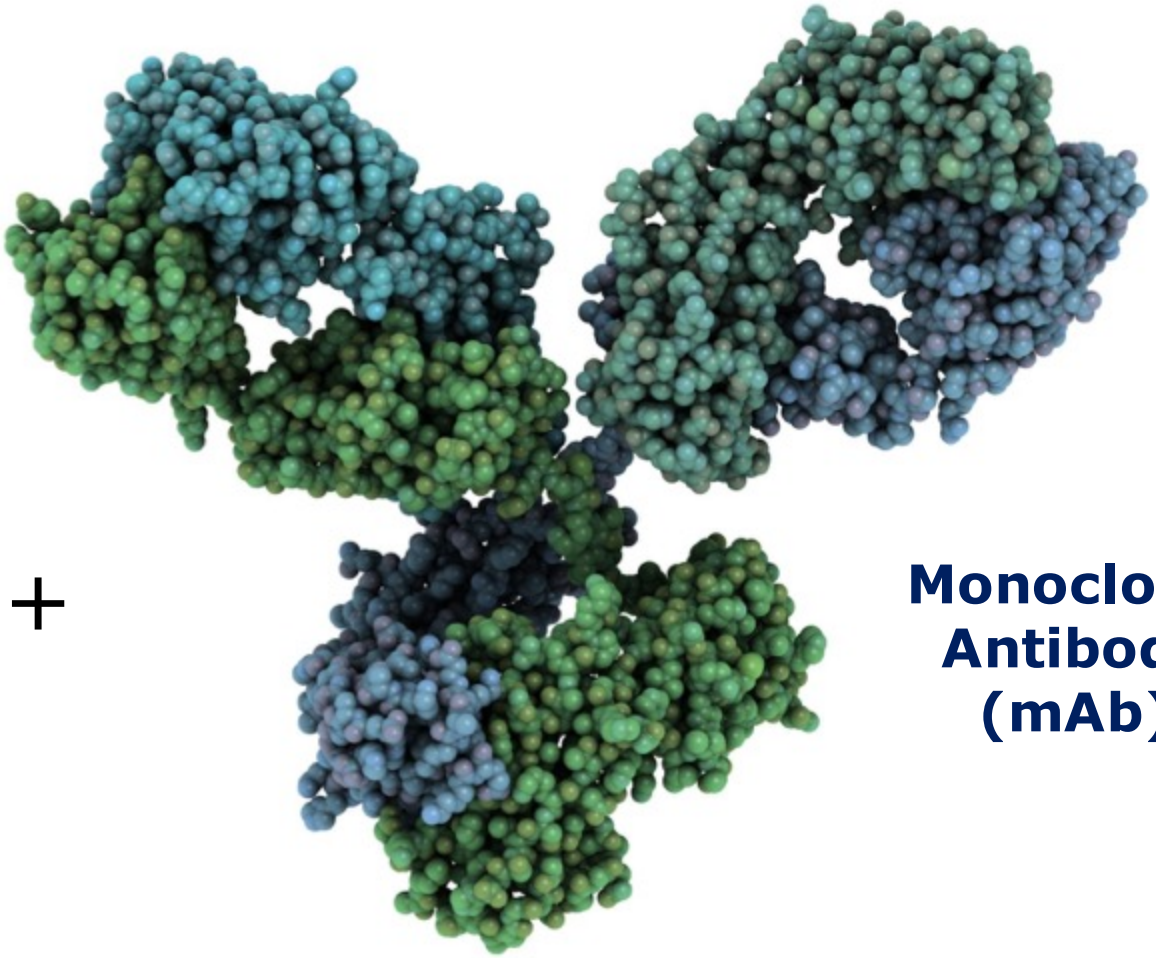


- Effective for blood cancers
  - e.g. **Rituximab** for B-cell non-Hodgkin lymphoma
- *Limited* effectiveness for solid tumors
  - e.g. **Herceptin** for HER2+ breast cancers (20-25%)
  - *Usually require co-therapy with standard cytotoxic "chemo" drugs such as paclitaxel or doxorubicin*

Creating a "*magic bullet*"

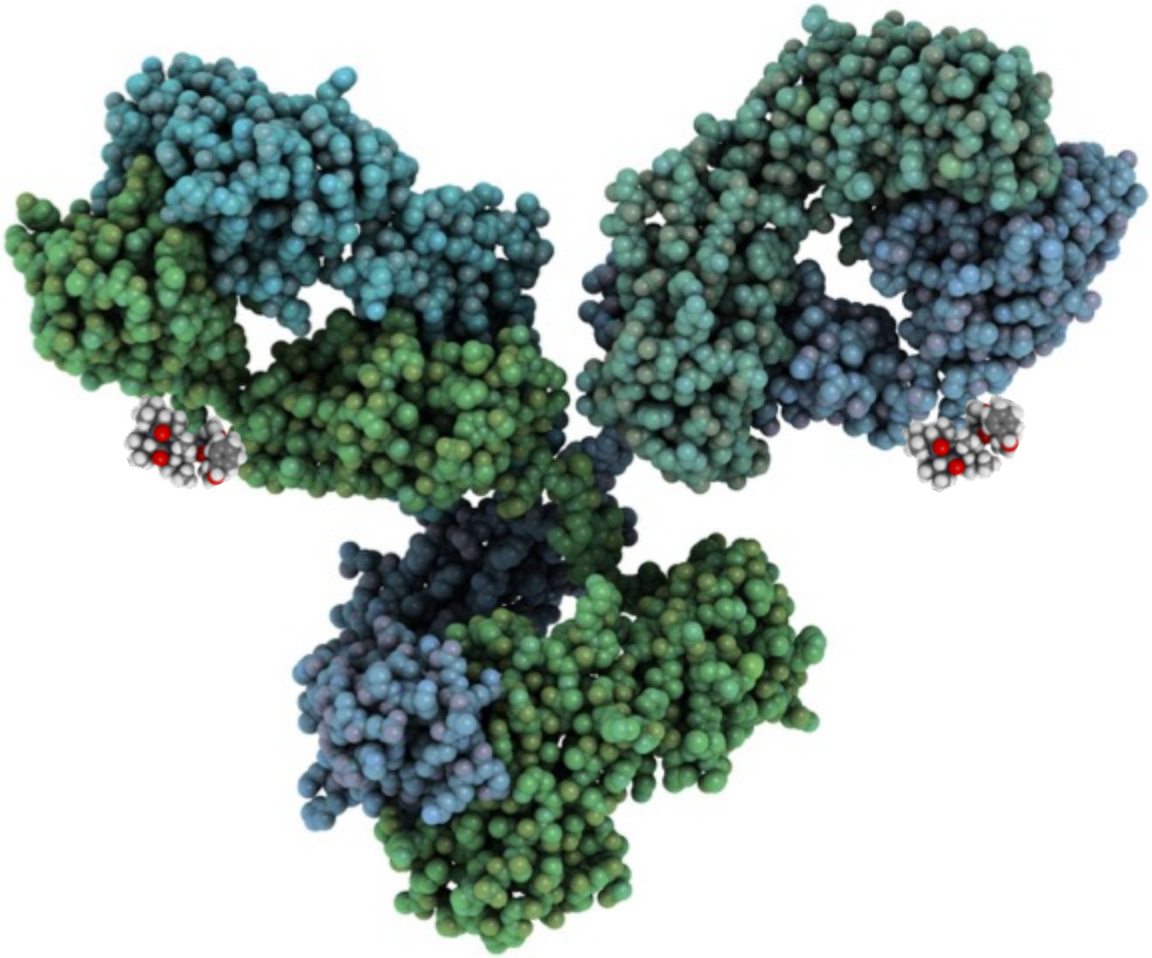
Small Cytotoxic "Drug"

+



Monoclonal Antibody (mAb)

Antibody-Drug Conjugate



Antibody-Drug Conjugate

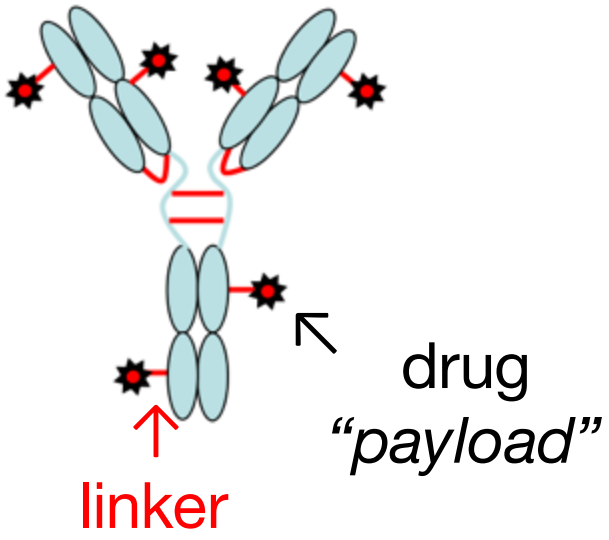
Like a mAb drug

- Seeks out & binds to specific tumor cells
- Long half life

ADC advantages

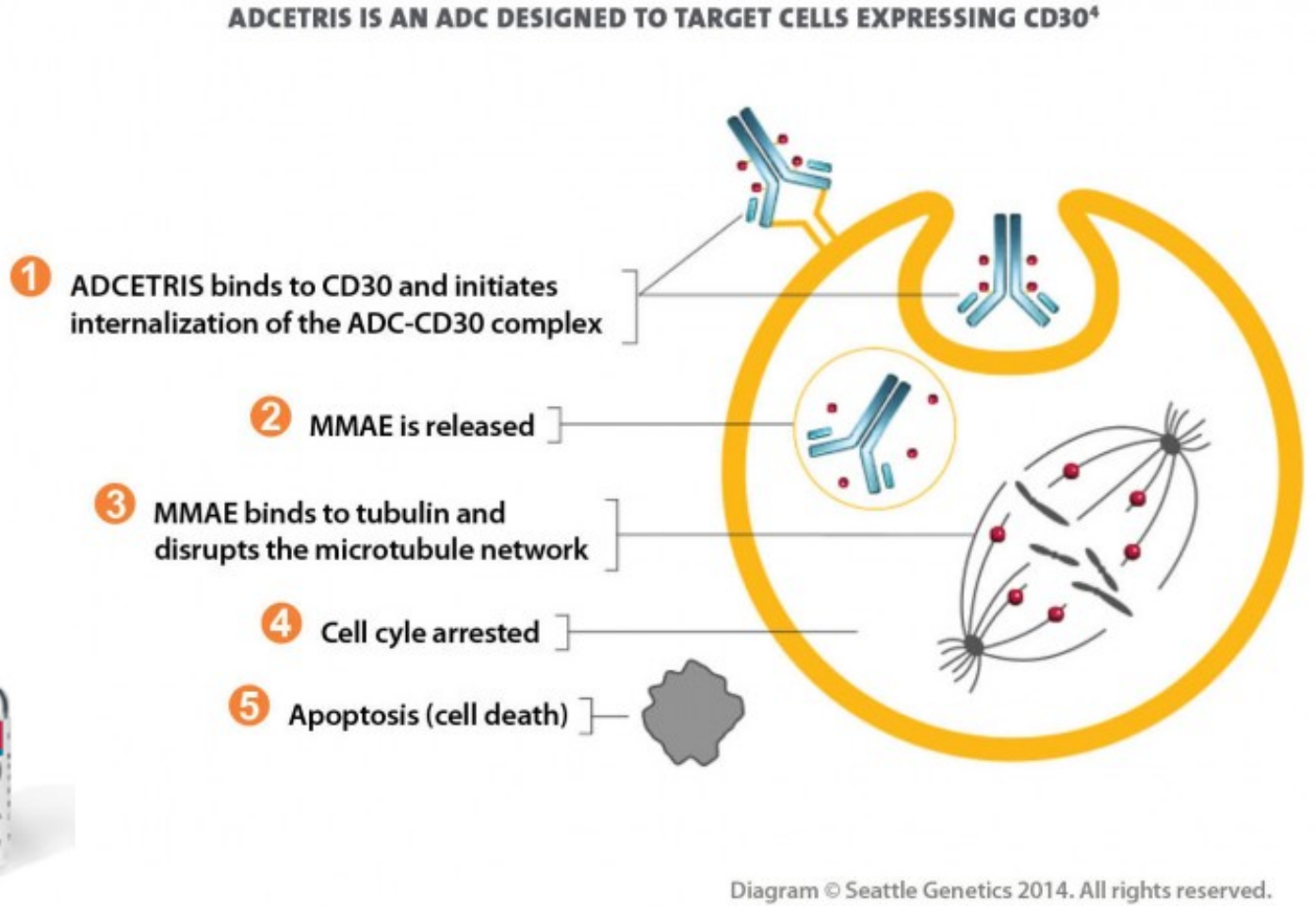
- Non-toxic in circulation
- Delivers highly toxic payload to tumor cells
- Toxin released inside to "safely" kill cells

ADC



drug-antibody ratio (DAR) = 6

ADC technology – how they function



FDA approved ADC products

NEWS RELEASE: Aug. 19, 2011 (Seattle Genetics)

FDA approves ADC to treat two types of lymphoma

"The U.S. Food and Drug Administration today approved ***ADCETRIS*** *(brentuximab vedotin) to treat Hodgkin lymphoma (HL) and a rare lymphoma known as systemic anaplastic large cell lymphoma (ALCL)"*

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncementsucm268781.htm

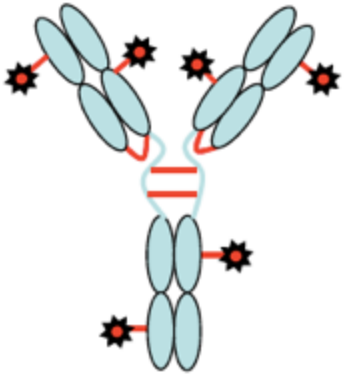
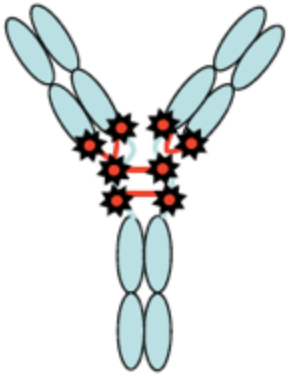
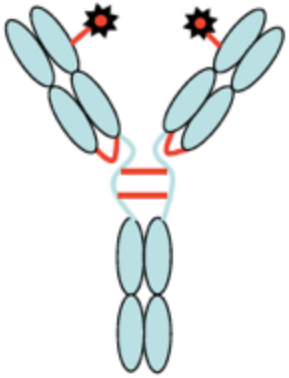
NEWS RELEASE: Feb. 22, 2013 (Genentech/Roche)

FDA approves new treatment for late-stage breast cancer

"The U.S. Food and Drug Administration today approved ***Kadcyla*** *(ado-trastuzumab emtansine), a new therapy for patients with HER2-positive, late-stage (metastatic) breast cancer"*

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncementsucm340704.htm

ADC Conjugation Sites & Heterogeneity

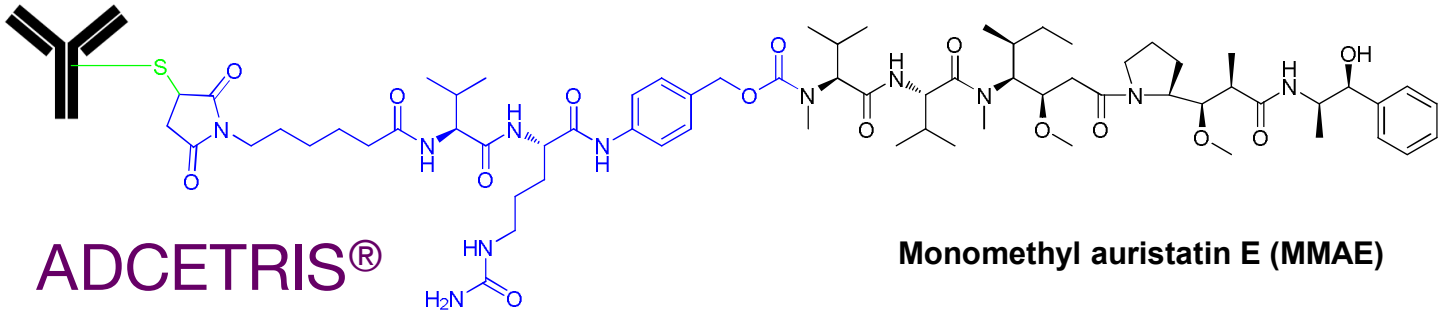
Conjugation through lysines	Conjugation through reduced internal disulfide bonds	Conjugation through engineered cysteines
		
Kadcyla®	ADCETRIS®	*newer engineered designs*

S. Kaur, Land O'Lakes, ADC Bioanalysis, 07.18.13

ADC diversity

linkers & payloads

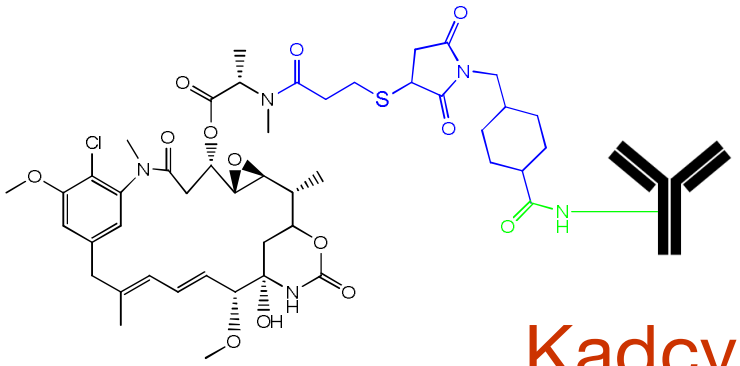
Examples of ADC's and Linkers and Payloads



ADCETRIS®

Monomethyl auristatin E (MMAE)

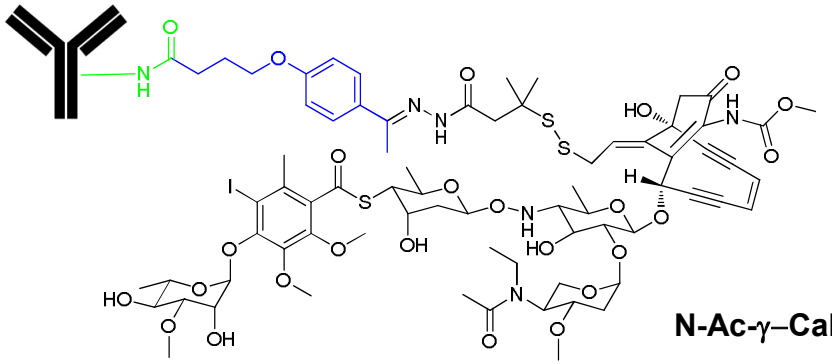
Adcetris
Brentuximab vedotin
(SGN-35)
Seattle Genetics
Payload - Monomethyl auristatin E (MMAE)
Cleavable payload



Maytansinoid (DM)

Kadcyla®

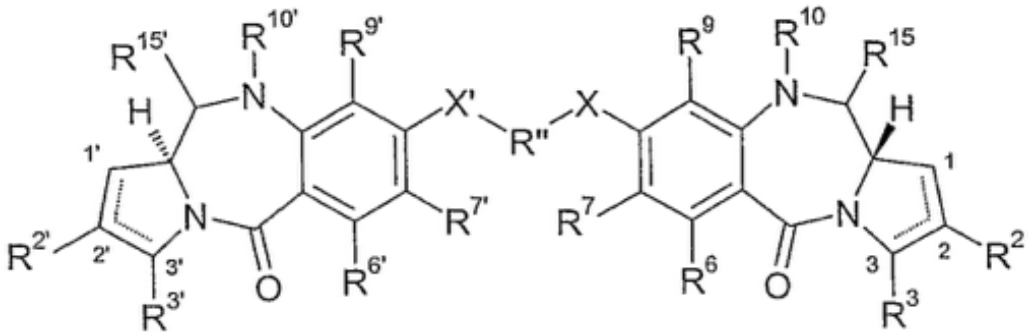
Kadcyla
Trastuzumab emtansine, ado-trastuzumab emtansine
(T-DM1)
Genentech
Payload – Maytansinoid (DM)
Non-cleavable payload



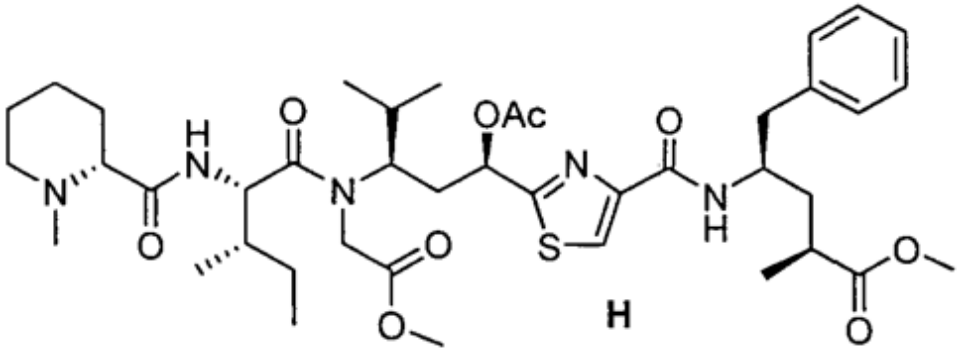
N-Ac-γ–Calicheamicin DMH

Inotuzumab ozogamicin
(INO, CMC-544)
and Mylotarg
Pfizer
Payload - N-Ac-γ–Calicheamicin DMH
Cleavable payload

Other payloads…

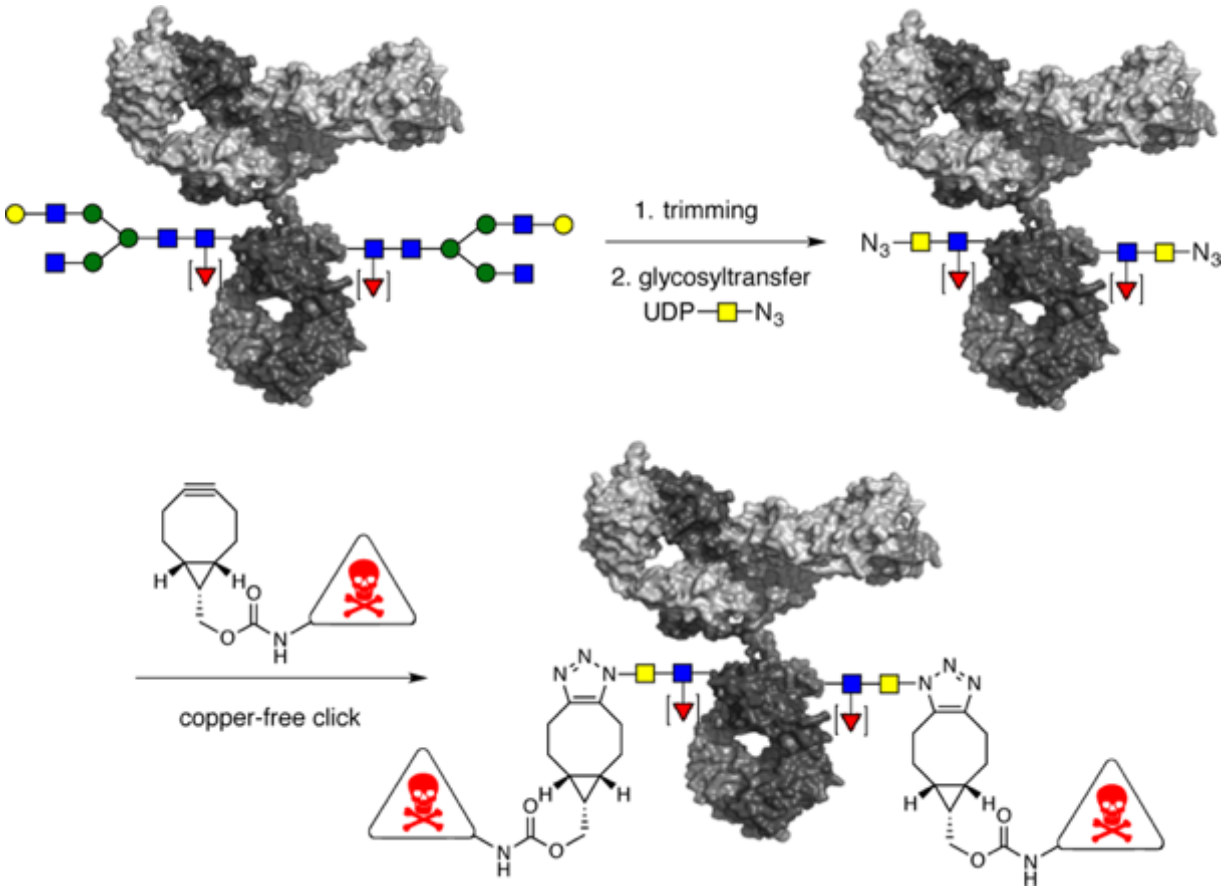


Pyrrolobenzodiazapine (PBD) dimers



Tubulysin analogues

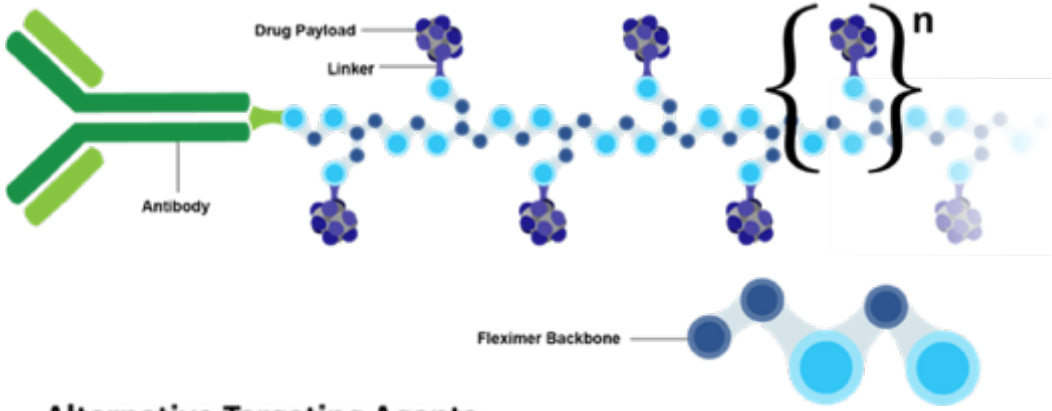
New ADC conjugation idea: GlycoConnect™

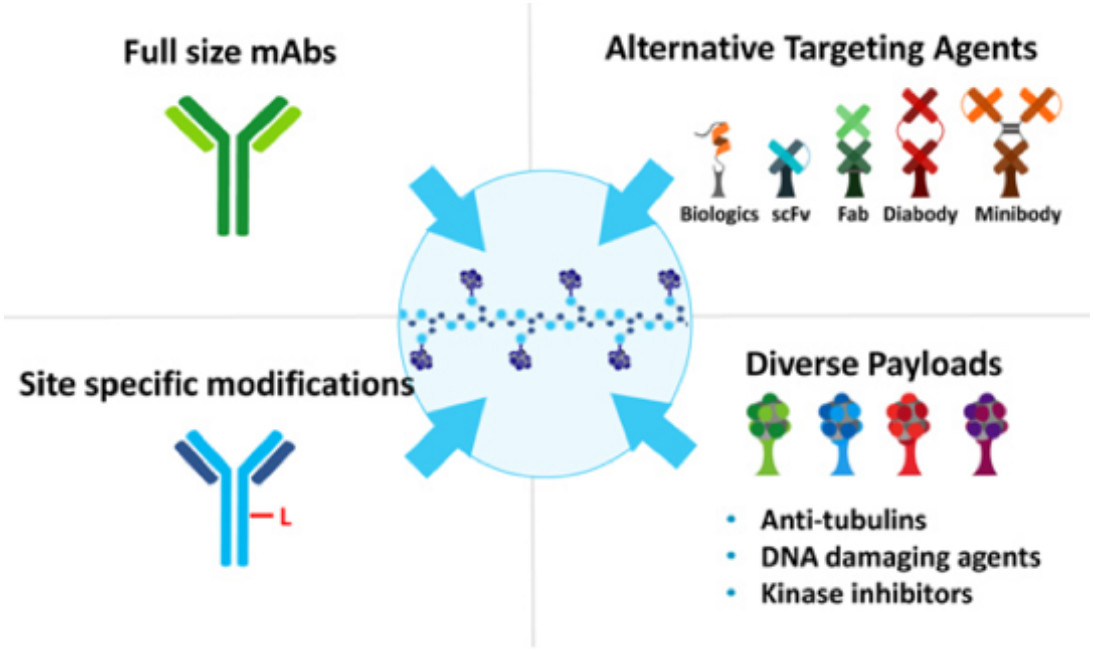


Remon van Geel *et al*, Chemoenzymatic Conjugation of Toxic Payloads to the Globally Conserved N-Glycan of Native mAbs Provides Homogeneous and Highly Efficacious Antibody−Drug Conjugates, *Bioconjugate Chem*. 2015, in press

New ADC conjugation idea: Fleximer polymers

Mersana THERAPEUTICS



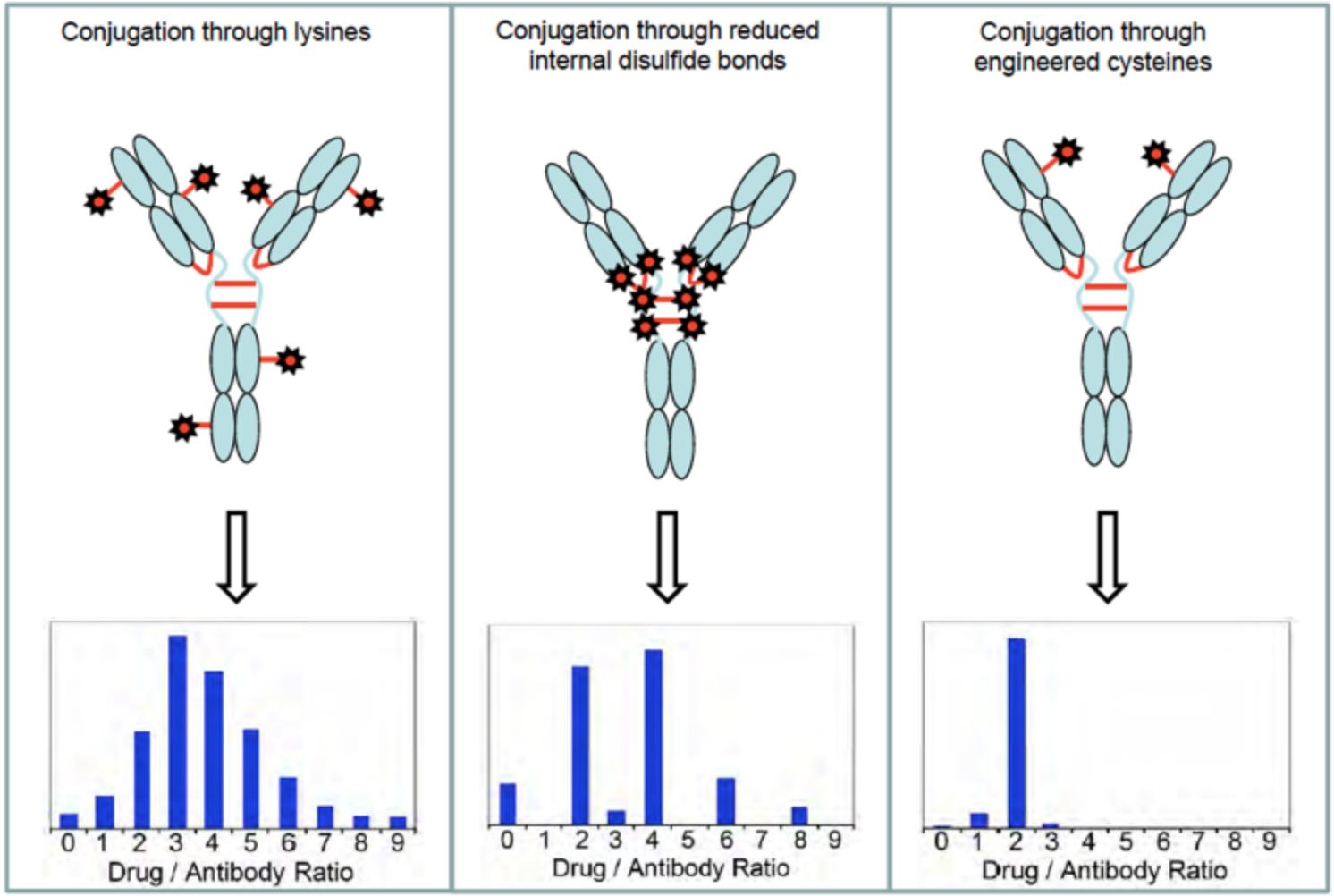


PPD

ADC complexity

What should be measured?

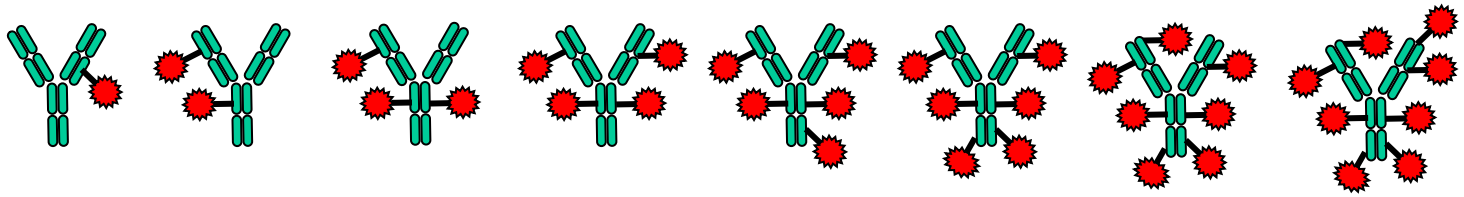
ADC Conjugation Sites & Heterogeneity



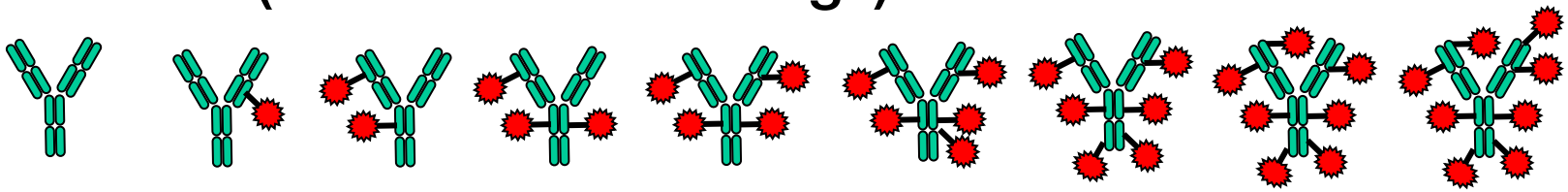
S. Kaur, Land O'Lakes, ADC Bioanalysis, 07.18.13

Heterogeneity challenge for bioanalysis
(Kadcyla® example)

Conjugated “active” ADCs



Total mAb (with or without drugs)



“Free” drug (and other forms)

DM1 dimer

DM1

Other
DM1-S-S-X

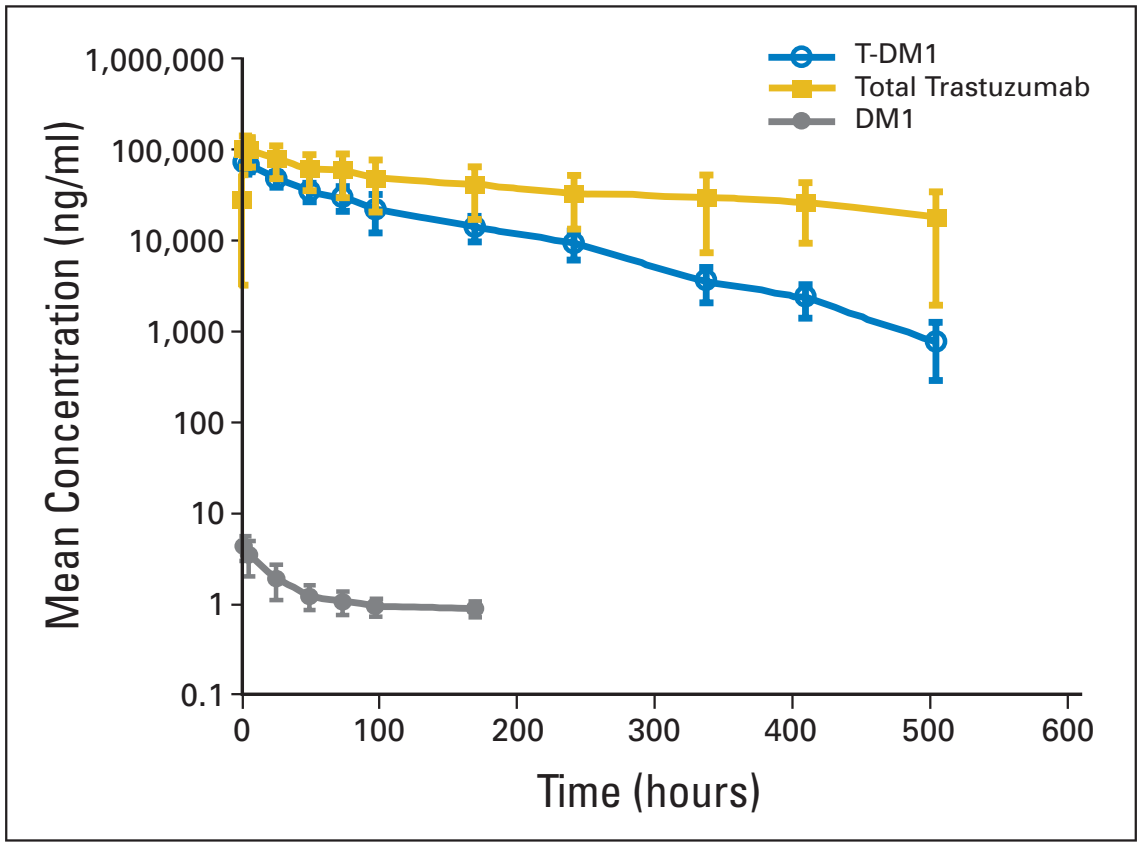
DM1-albumin

DM1 disulfide bound
to antibody

Standard ADC bioanalytical assays

Assay	Technology
Total Antibody, DAR ≥0 Assess general mAb PK behavior—*efficacy*	LBA (ELISA)
Conjugated Antibody, DAR ≥1 Measure total ADC molecules—*efficacy*	LBA (ELISA)
Anti-Therapeutic Antibody (ATA) Detect immune response—*efficacy & safety*	LBA (ELISA) and Cell-based NAb
Unconjugated Drug Detect "free" drug—*safety*	LC-MS/MS

Pharmacokinetic data
(Kadcyla® example)



← Total mAb

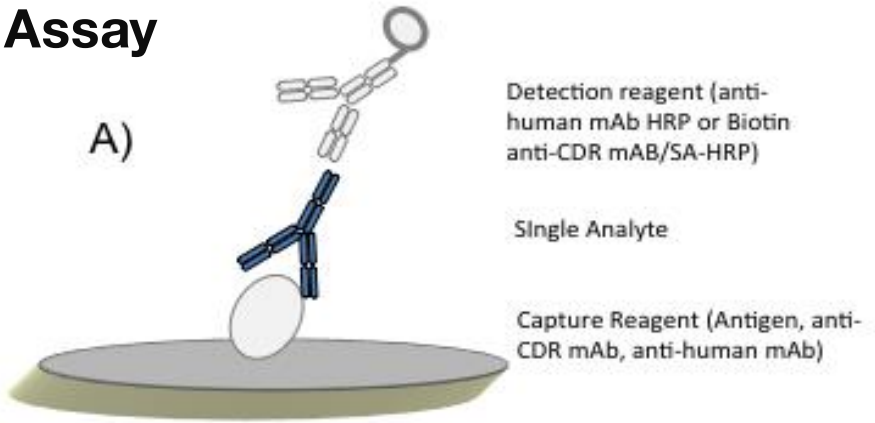
← Conjugated "active" ADC

← "Free" drug

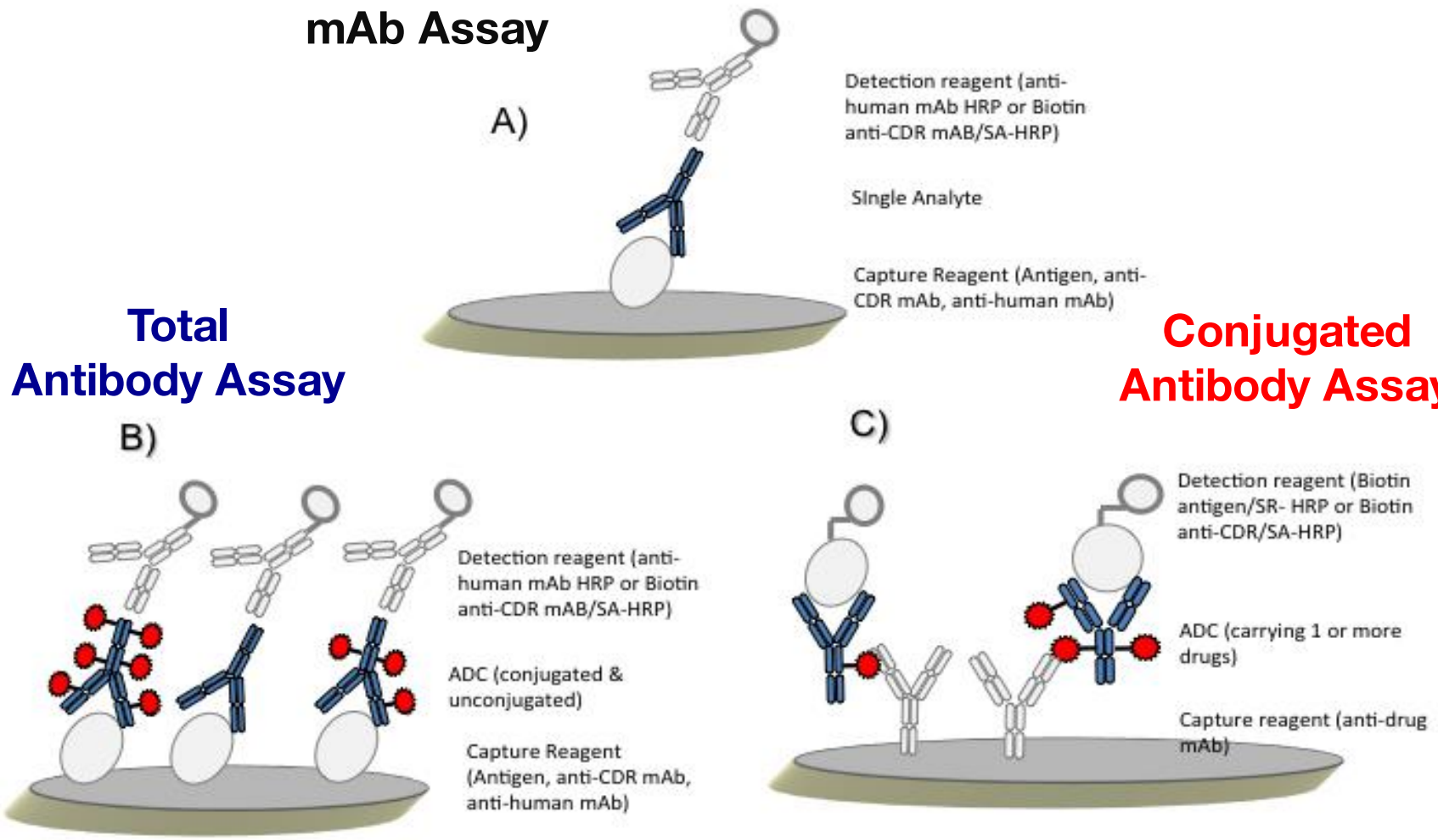
Fig 3. Mean levels of trastuzumab-DM1 (T-DM1), total trastuzumab, and DM1 over time are shown for patients after the first dose of T-DM1 administered at the maximum-tolerated does of 3.6 mg/kg. Standard deviation is shown in error bars.

LBA Assays for ADCs are More Complex than LBA for mAb Therapeutics

mAb Assay



LBA Assays for ADCs are More Complex than LBA for mAb Therapeutics

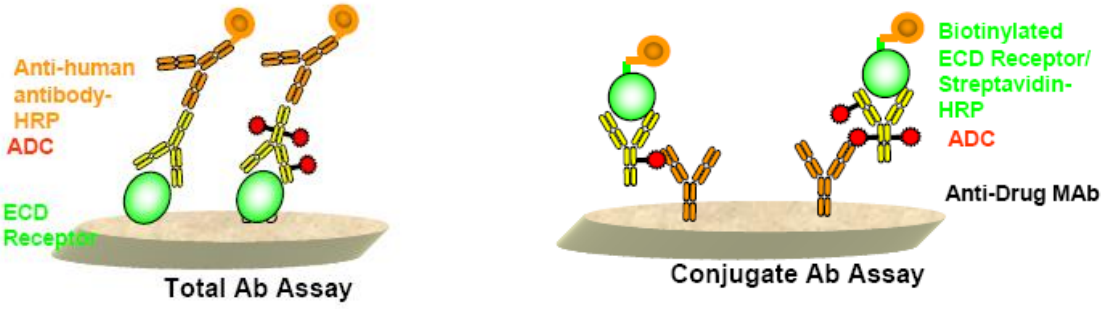


Characterize Ligand Binding Assays with Individual DARs Identified in Plasma to Evaluate Assay performance

	Anti-STEAP1 ADC Purified DAR				
Assay	**0**	**1**	**2**	**4**	**6**
Total Antibody ELISA (% recovery)[1]	88	78	86	92	92
Conjugated-Antibody ELISA (% recovery) [1]	NA	11	102	99	64

specificity issue

[1] Based on expected nominal concentration of individual DARs spiked into serum



- Used individual DAR controls from plasma to test with ELISA ligand binding reagents
- No single anti-Drug mAb reagent in conjugate Ab assay appropriate for all DARs

ADC bioanalysis using LBAs

Advantages

- Traditional approach – *the gold standard*
- High throughput and low cost per sample

Challenges

- MD expensive and time-consuming
- Potential interference from soluble target
- Reagents may show variable response to DARs

ADC bioanalysis

LC-MS/MS alternatives

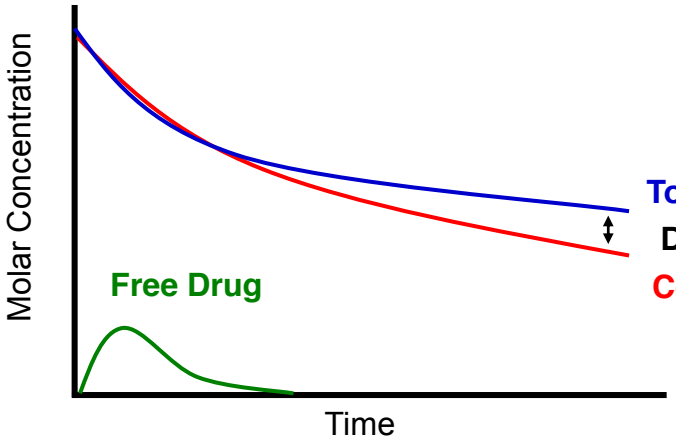
Alternative ADC bioanalytical assays

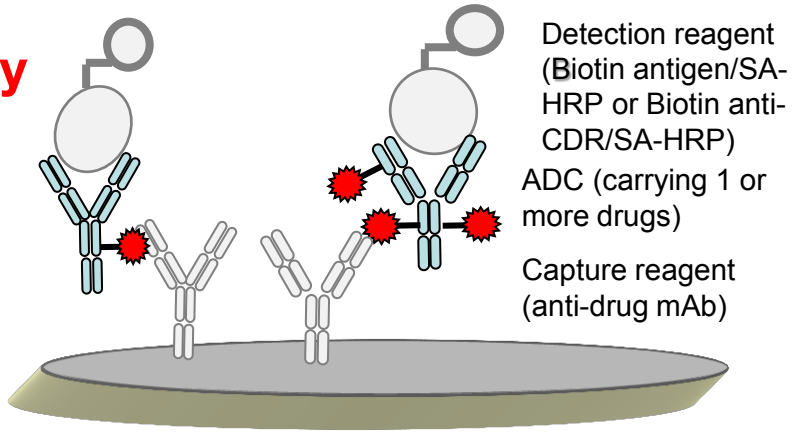
	Assay	Technology
**	**Total Antibody**, DAR ≥0	LBA (ELISA)
*	**Conjugated Antibody**, DAR ≥1 *Measure of conjugated antibodies only*	LBA (ELISA)
*	**Antibody-conjugated Drug**, DAR ≥1 *Measure of conjugated "active" drug load*	Affinity capture LC-MS/MS *(requires cleavable linkers)*
**	**Total Antibody**, DAR ≥0 *Most convenient for non-clinical*	Affinity capture LC-MS/MS

Develop Appropriate PK Assays:

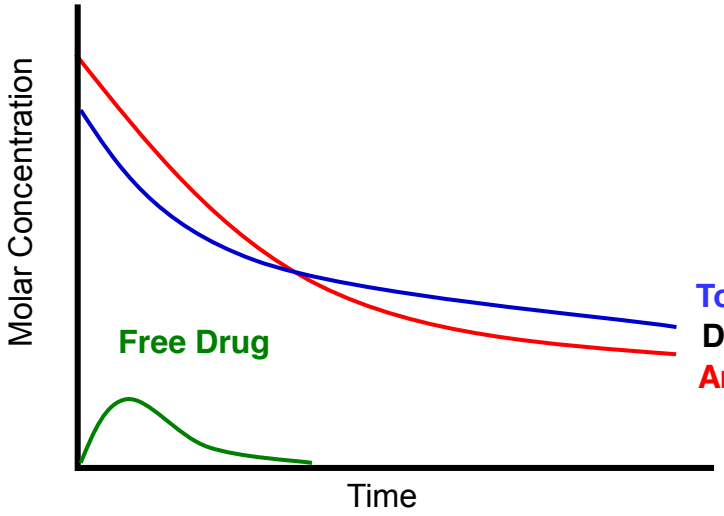
Hybrid Binding LC-MS/MS & LBA Conjugate Assay Formats

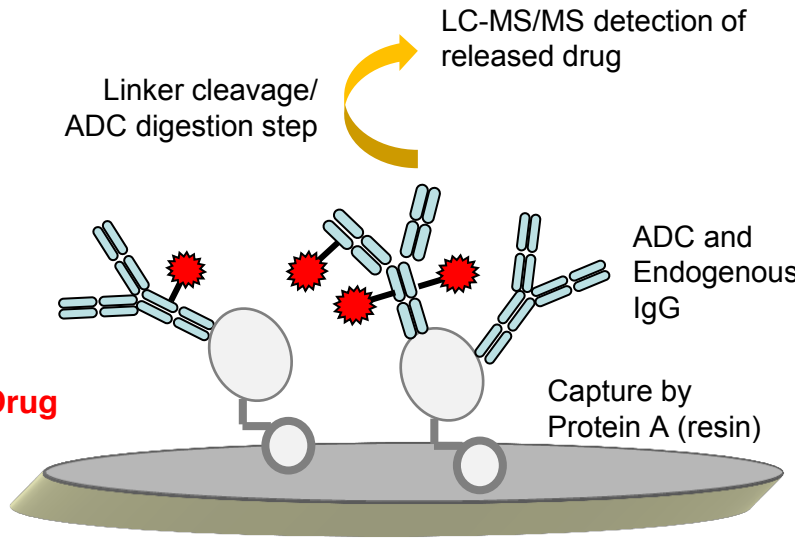
Conjugated Antibody Assay





Antibody-Conjugated Drug Assay





Ab-conjugated drug AC-LC-MS/MS assay

Inter-assay accuracy & precision

Run ID	QC 1 (nM)	QC 2 (nM)	QC 3 (nM)	QC 4 (nM)	QC 5 (nM)
1YIY2-A	1.11	2.10	5.20	12.8	37.7
	0.931	2.08	5.26	12.5	39.3
2YIY2-B	0.990	2.05	5.18	11.9	39.9
	0.993	2.08	5.34	12.5	38.7
3YIY2-A	1.10	2.03	5.24	12.7	41.4
	1.01	2.05	5.23	12.3	40.6
4YIY2-A	0.965	2.16	4.80	12.1	37.3
	1.06	2.16	4.92	11.9	39.3
5YIY2-A	1.09	2.21	5.48	12.7	39.3
	1.03	2.04	5.40	12.5	39.4
N	10	10	10	10	10
Theo. Conc.	1.00	2.00	5.00	12.0	39.0
Mean	**1.03**	**2.10**	**5.20**	**12.4**	**39.3**
S.D.	0.0606	0.0605	0.208	0.318	1.21
%C.V.	5.90	2.88	3.99	2.56	3.08
%Bias	2.81	4.77	4.09	3.24	0.731
Calc'd ADC	(ng/mL)	(ng/mL)	(ng/mL)	(ng/mL)	(ng/mL)
	41.7	**83.3**	**208**	**500**	**1630**

Total mAb *universal* AC-LC-MS/MS assay
(*non-clinical applications*)

1. Generic affinity capture

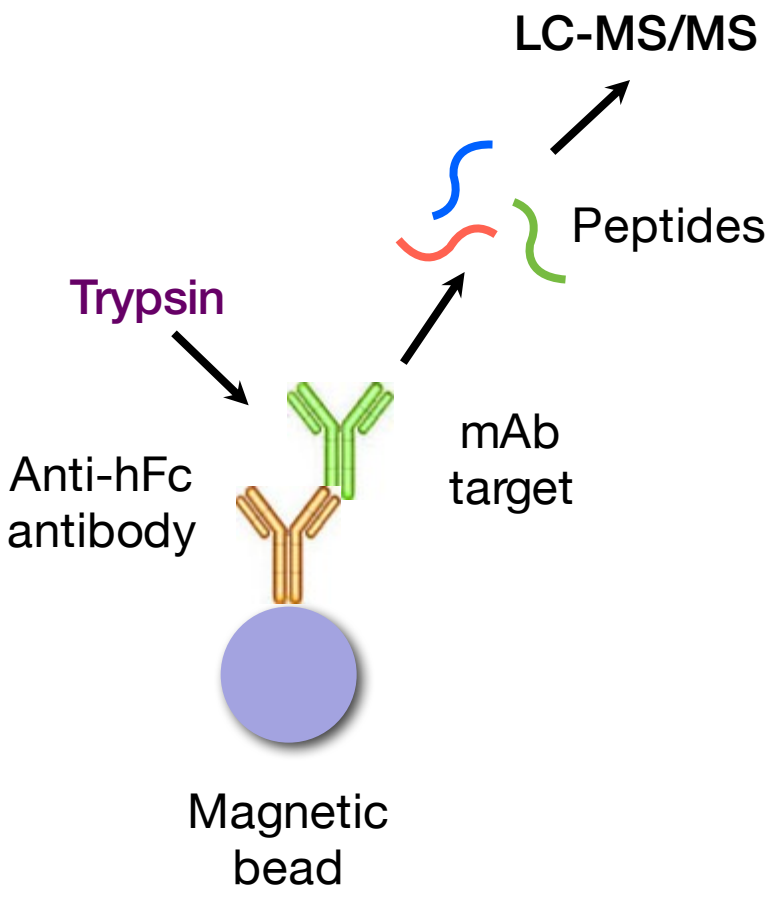
- Anti-human Fc
- Protein A or G

2. "On-bead" processing

- Typical chemistry steps:
  - Denaturation
  - Reduction
  - Alkylation
  - Trypsin digestion

3. LC-MS/MS Detection

- Human IgG peptides



Unique human mAb peptide choices
(*non-clinical applications*)

Table 1. Amino acid sequences of universal peptide candidates.

Peptide		Sequence	Human heavy chain subclass
Light chain candidates[†]			
LC-1	TVAA→	TVAAPSVFIFPPSDEQLK	NA
LC-2	SGTA→	SGTASVVCLLNNFYPR[‡]	NA
LC-3		VDNALQSGNSQESVTEQDSK	NA
LC-4		DSTYSLSSTLTLSK	NA
Heavy chain candidates			
HC-1		TPEVTCVVVDVSHEDPEVK[‡]	IgG1
HC-2		FNWYVDGVEVHNAK	IgG1
HC-3	VVSV→	VVSVLTVLHQDWLNGK[§]	IgG1, IgG4
HC-4		GFYPSDIAVEWESNGQPENNYK	IgG1, IgG2, IgG4
HC-5	TTPP→	TTPPVLDSDGSFFLYSK	IgG1

[†]*All light chain peptide candidates are in the constant region of the κ-class.*
[‡]*Peptide quantified as the S-carboxymethylcysteine derivative.*
[§]*Peptide HC-3 was previously identified as a universal peptide* [7].

Michael T Furlong, Song Zhao, William Mylott, Rand Jenkins, Mian Gao, Vendana Hegde, James Tamura, Adrienne Tymiak & Mohammed Jemal, *Bioanalysis* **2013**, 5(11), 1363−1376.

Total mAb Method Performance Evaluation (MPE): calibration standards and batch acceptance QCs

Run ID	CAL 1	CAL 2	CAL 3	CAL 4	CAL 5	CAL 6	CAL 7	CAL 8		QC 1	QC 2	QC 3
	(µg/mL)	(µg/mL)	(µg/mL)	(µg/mL)	(µg/mL)	(µg/mL)	(µg/mL)	(µg/mL)		(µg/mL)	(µg/mL)	(µg/mL)
1RBFE2-A	0.0492	0.0946	0.191	0.859	3.05	11.4	41.7	48.7		0.148	1.46	35.2
	0.0509	0.105	0.203	0.835	2.98	11.4	39.0	50.7		0.144	1.39	34.6
2RBFE2-A	0.0538	0.096	0.217	0.802	3.02	12.5	42.7	49.8		0.151	1.49	35.9
	0.0473	0.0971	0.194	0.805	3.01	11.6	37.5	48.5		0.140	1.51	36.8
Theoretical Concentration	0.0500	0.100	0.200	0.800	3.00	12.0	40.0	50.0		0.150	1.50	37.5
Mean	0.0503	0.0982	0.201	0.825	3.01	11.7	40.2	49.4		0.146	1.46	35.6
%C.V.	5.51	4.78	5.87	3.25	0.892	4.28	5.99	2.06		3.33	3.48	2.62
% Bias	0.579	-1.82	0.545	3.13	0.437	-2.27	0.548	-1.15		-2.98	-2.40	-5.04

Acceptance criteria: ±25% for the LLOQ and ±20% for all other levels

references

"Dual universal peptide approach to bioanalysis of human monoclonal antibody protein drug candidates in animal studies"

Michael T Furlong, Song Zhao, William Mylott, Rand Jenkins, Mian Gao, Vendana Hegde, James Tamura, Adrienne Tymiak & Mohammed Jemal, *Bioanalysis* **2013**, 5(11), 1363−1376.

"A general LC-MS/MS method approach using a common whole molecule SIL-IS and a common immuno-capture for sample clean up and enrichment that is applicable to various mAbs in different matrixes"

Li, H.; Ortiz, R; Tran, L; Hall, M; Spahr,C; Walker, K; Laudemann, J; Miller, S; Salimi-Moosavi, H; and Lee, J.W., *Anal. Chem.* **2012**, 84, 1267−1273.

PPD®

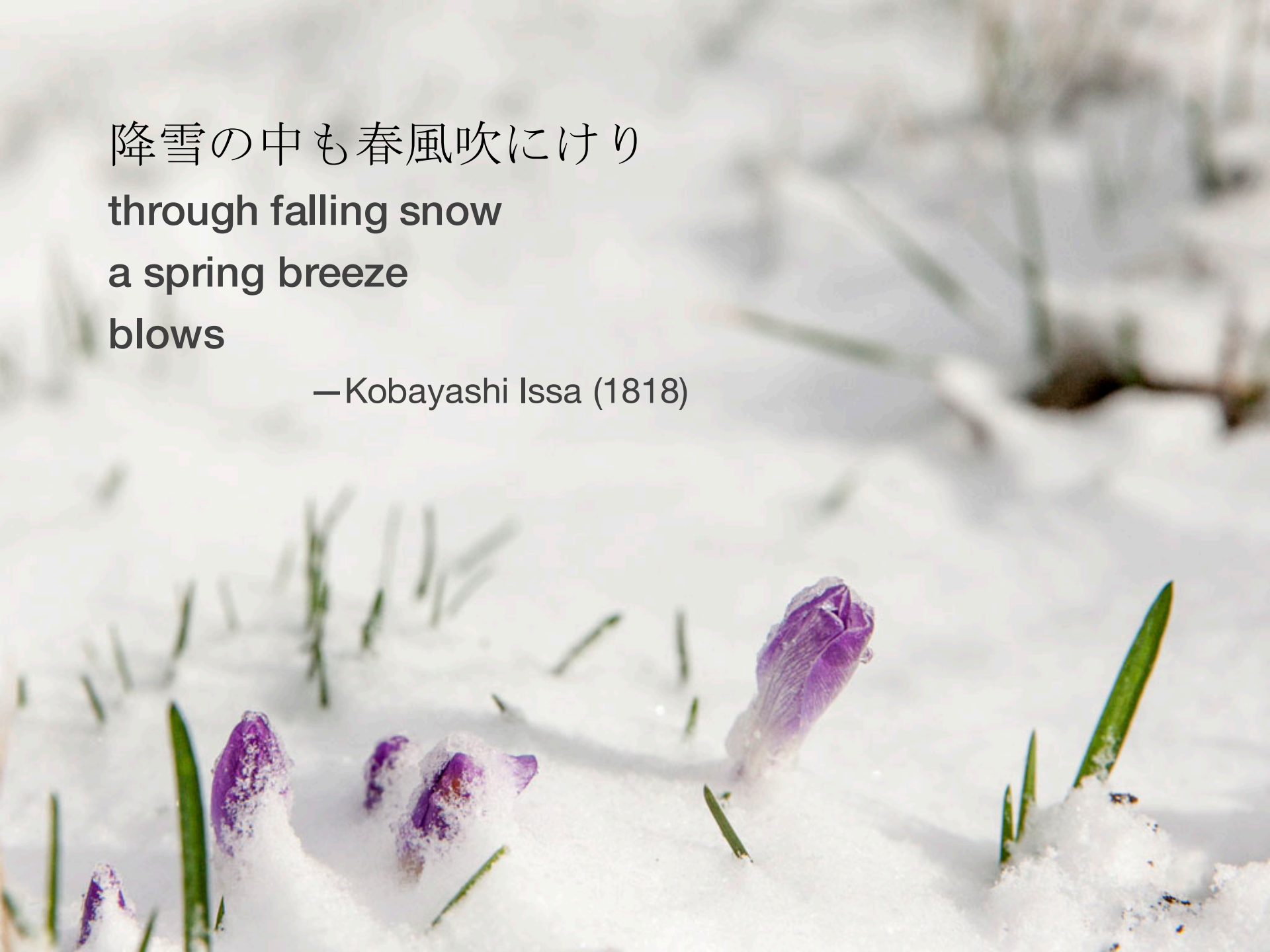
ADC bioanalysis using LC-MS/MS

Advantages

- Standard approach for small molecules
- “Direct” detection of molecules or fragments
- High sensitivity and selectivity/specificity
- MD relatively rapid; universal methods possible
- Data complimentary to LBAs

Challenges

- Complex and expensive instrumentation
- Lower throughput and higher costs per sample


降雪の中も春風吹にけり
through falling snow
a spring breeze
blows
—Kobayashi Issa (1818)

ADC biotransformation

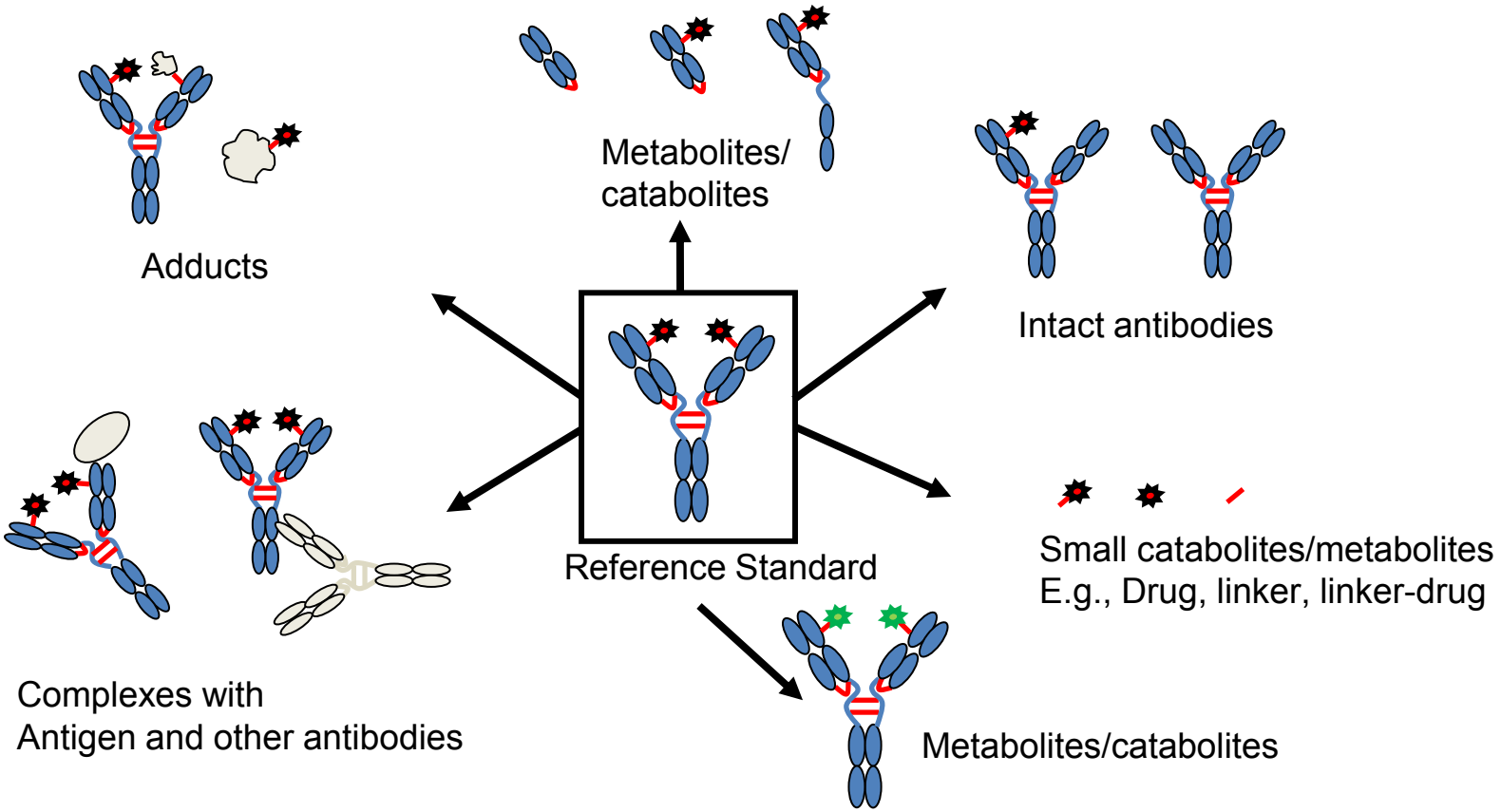
characterization needed

ADCs Can Undergo Biotransformations *In Vivo*: Analytes & Assay Standard Curve May Differ

Analysis of small molecule drug transformations in vivo is well established

- Absorption, Distribution, Metabolism and Excretion (ADME) by LC-MS/MS. (E.g., cytochrome P450 induction/inhibition, metabolic profiling, plasma protein binding and P-gp transporters)

Analysis of protein or ADC transformations in vivo is challenging



ADC characterization needed

Because:

- Drug-antibody (DAR) distribution *in vivo* is dynamic
- Drug payload can prematurely deconjugate
- Higher drug-loaded species undergo faster clearance
- Standard bioanalytical assays don't detect post-dose changes in DAR distribution
- PK-PD modeling may be incorrect
- Catabolism/metabolism-related changes may impact efficacy and/or safety

LC-MS ADC characterization

Assay	Technology
Drug or drug-linker metabolites *Which species exist and are important?*	LC-MS/MS
Catabolites (ADC or mAb) *Which species exist and are important?*	Affinity capture LC-HRAMS
DAR Distribution Assess ADC stability (*in vitro* / *in vivo*)	Affinity capture LC-HRAMS or HIC
Critical reagent DAR specificity Assess LBA reagents	Affinity capture LC-HRAMS or HIC

Major focus on DAR distribution

To:

- Evaluate ADC reference and dosing material
- Assess stability-related changes *in vitro*
- Assess biotransformation-related changes *in vivo*
- Evaluate critical reagent specificity (for LBAs)

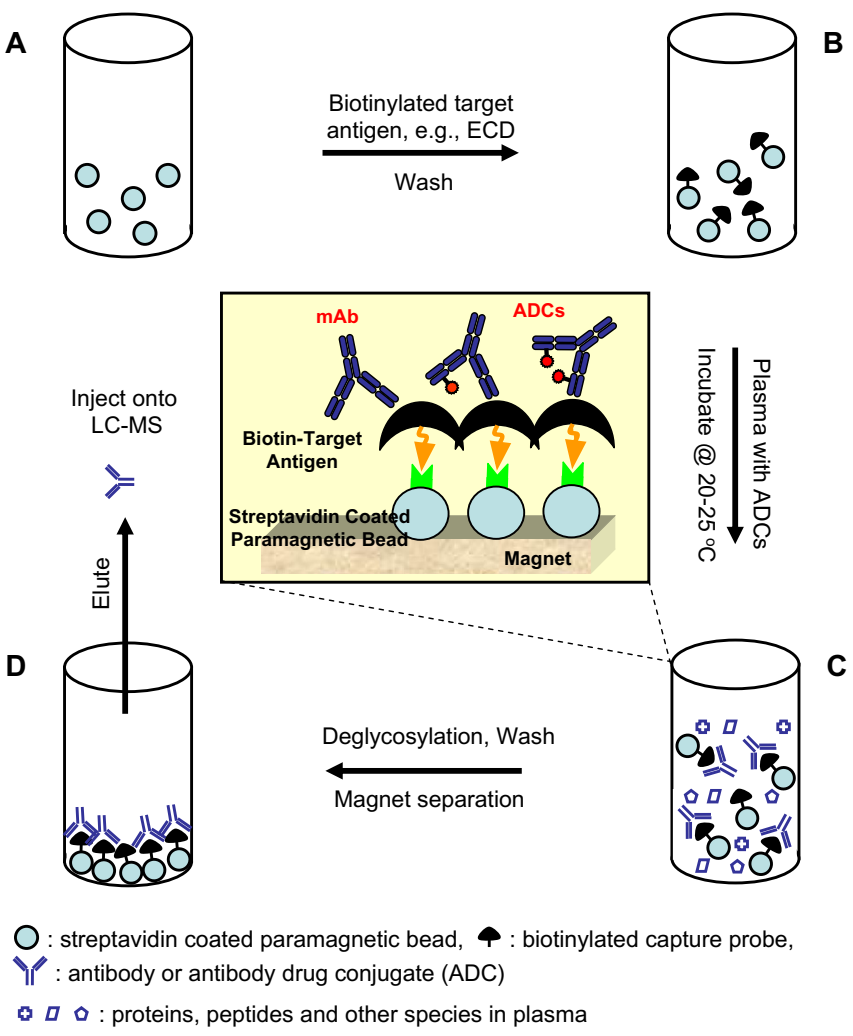
Results are generally qualitative or semi-quantitative

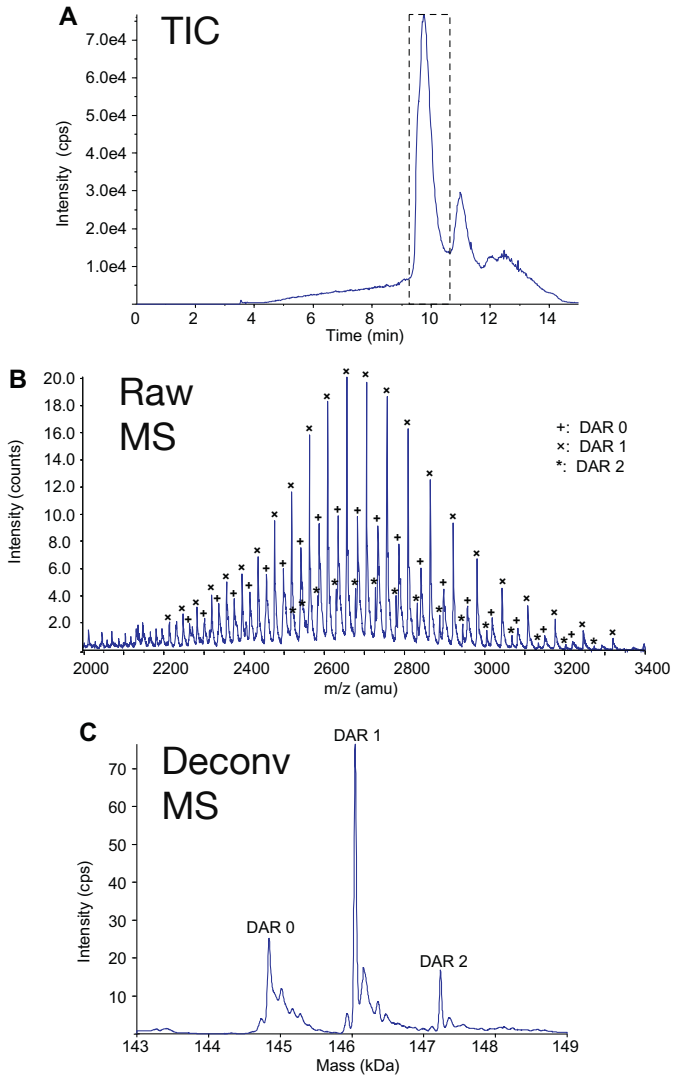
ADC characterization

Drug-Antibody Ratio (DAR)

Affinity Capture-LC-HRAMS
workflow courtesy of
Keyang Xu, Genentech

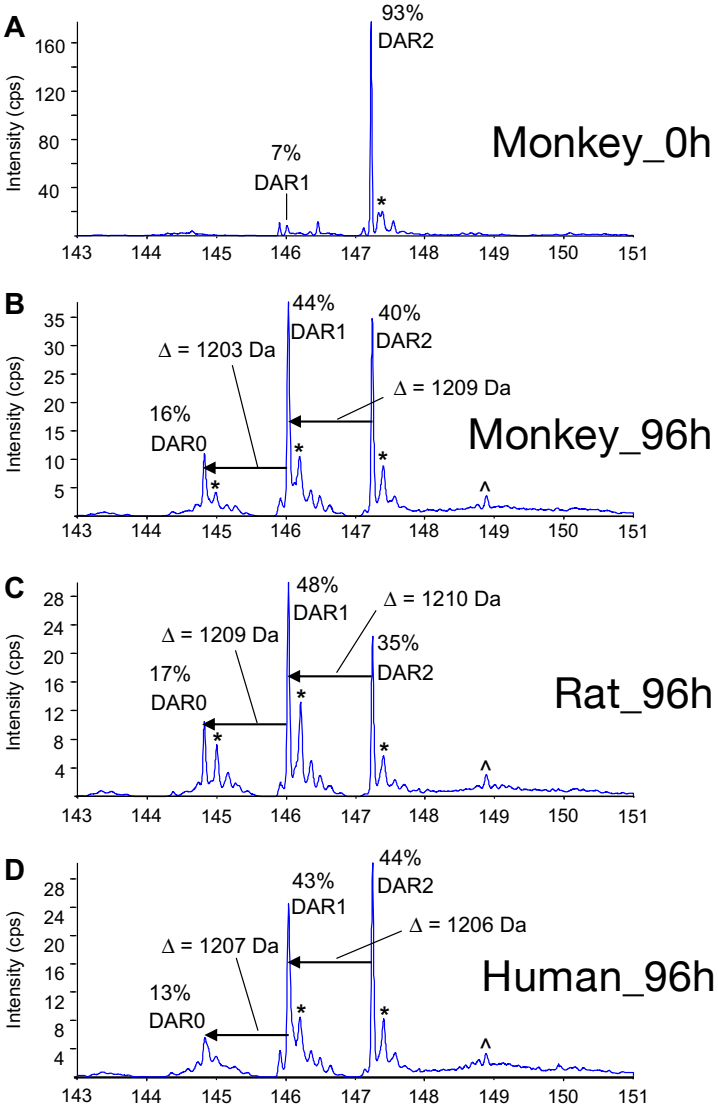
Affinity Capture LC-HRAMS allows direct measurement of *intact* ADC changes

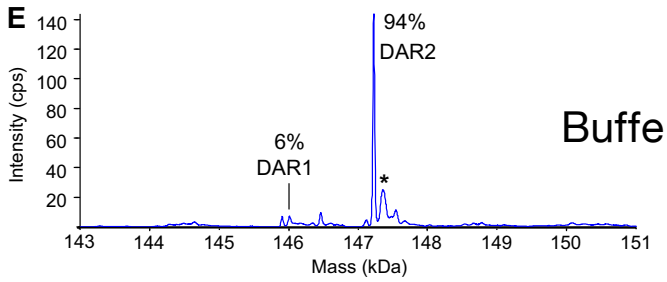




Xu K, Liu L, Saad O, et al, Anal Biochem, 412, 56–66 (2011).

in vitro ADC plasma stability





Drug release in a plasma stability study of anti-MUC16 TDC in vitro. An aliquot of 100 µg/ml anti-MUC16 TDC (DAR 2) was incubated in plasma from different species and buffer control (PBS with 0.5% BSA) at 37° C for up to 96 h.

Xu K *et al*, *Anal. Biochem*, 412, 56–66 (2011)

in vivo ADC characterization

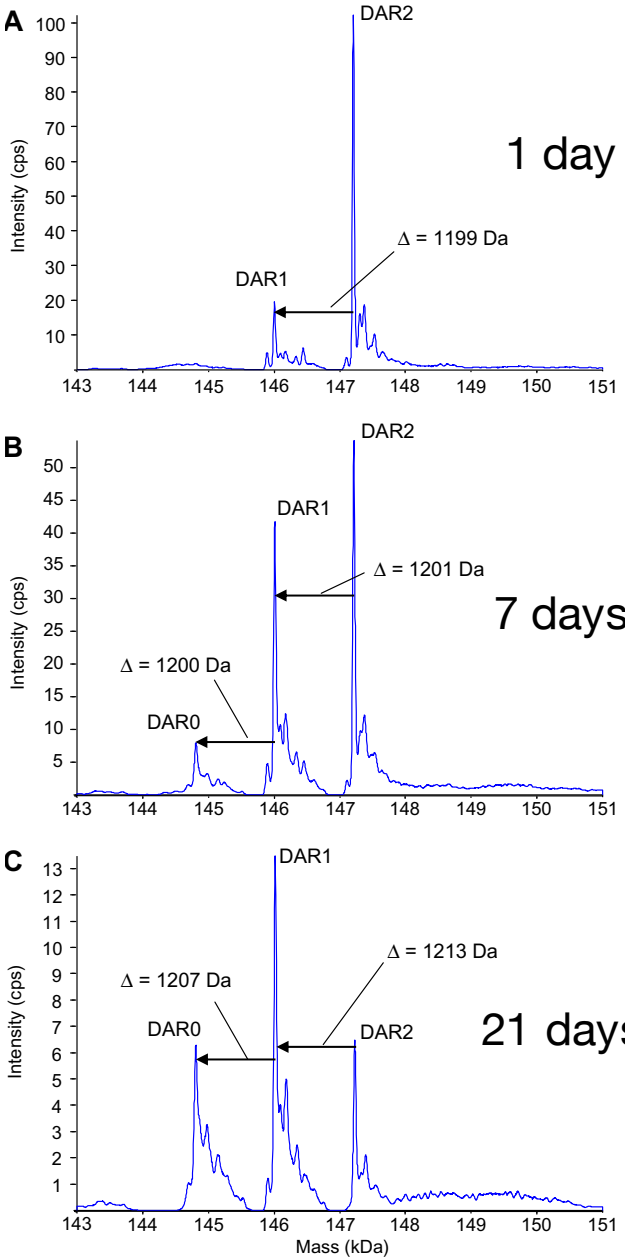
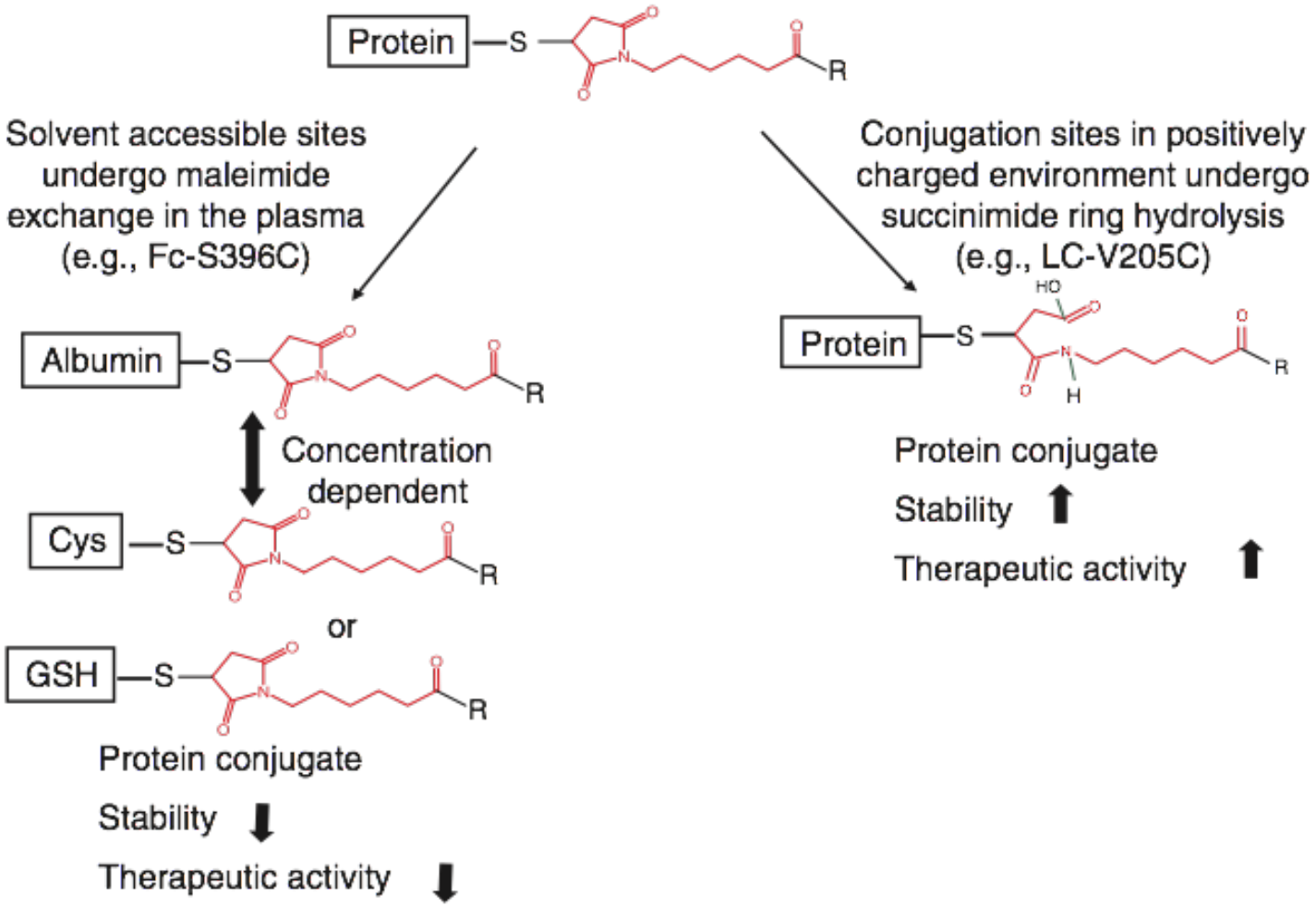


Fig.6. Drug release observed in a multiple-dose toxicokinetic study of anti-MUC16 TDC *in vivo*. Anti-MUC16 TDC (DAR 2) was administered to cynomolgus monkeys intravenously once every 3 weeks for a total of four doses. Three dose groups at 6, 10, and 20 mg/kg were evaluated. Deconvoluted mass spectra of the TDC species of a representative animal receiving the first dose of 6 mg/kg anti-MUC16 TDC show the drug release from DAR 2 to form DAR 1 and DAR 0 with time: (A) 1 day postdose; (B) 7 days postdose; (C) 21 days postdose.

Xu K *et al*, *Anal. Biochem*, 412, 56–66 (2011)

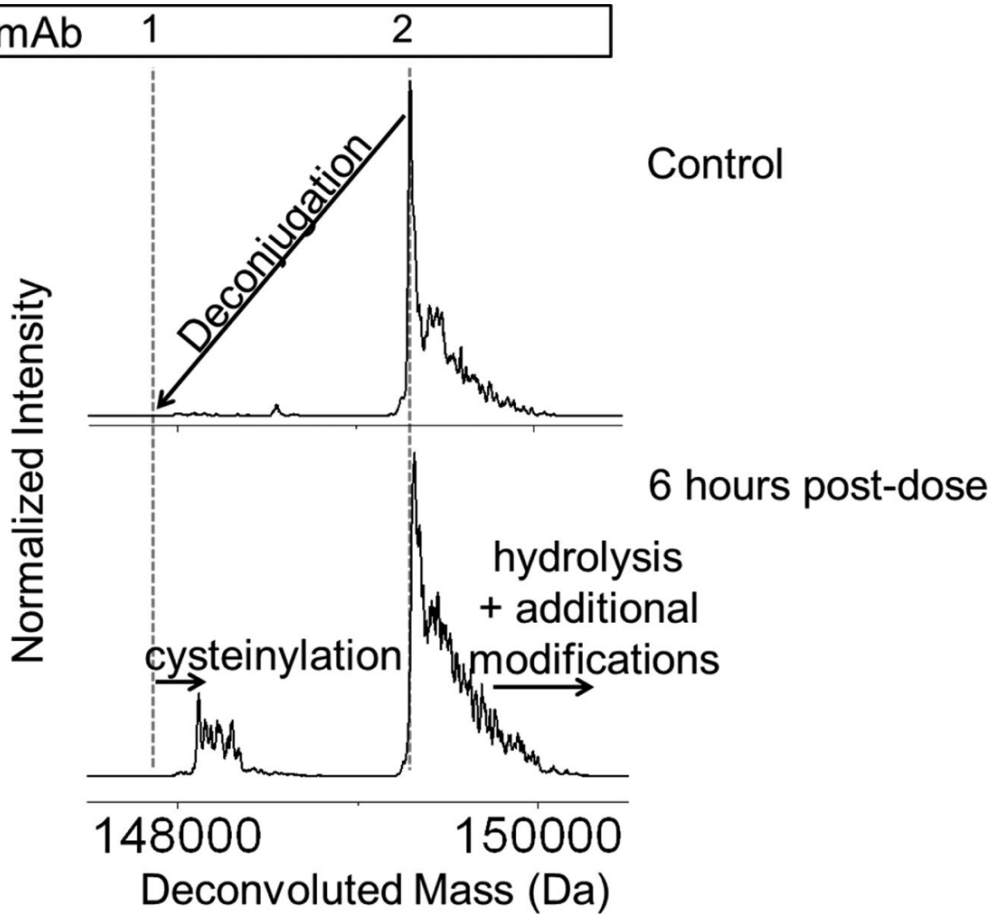
Conjugation site influences linker stability and therapeutic activity of ADCs



Shen B-Q *et al*. *Nature Biotechnology,* 30(2), 184–191 (2012)

in vivo ADC (reduced interchain S-S) characterization

Figure 7. Summary of mass shifts and peak asymmetry observed in cysteine-linked ADCs *in vivo*. Detection of odd loaded species at masses higher than expected was attributed to modification at the deconjugated drug-linker sites, specifically cysteinylation, and observed asymmetry in the deconvoluted data over time is hypothesized to be a consequence of increased sample heterogeneity due to *in vivo* modifications, including hydrolysis.



Hengel SM *et al. Anal. Chem*. 2014, 86, 3420–3425.

Non-cleavable ADC with site-specific catabolism

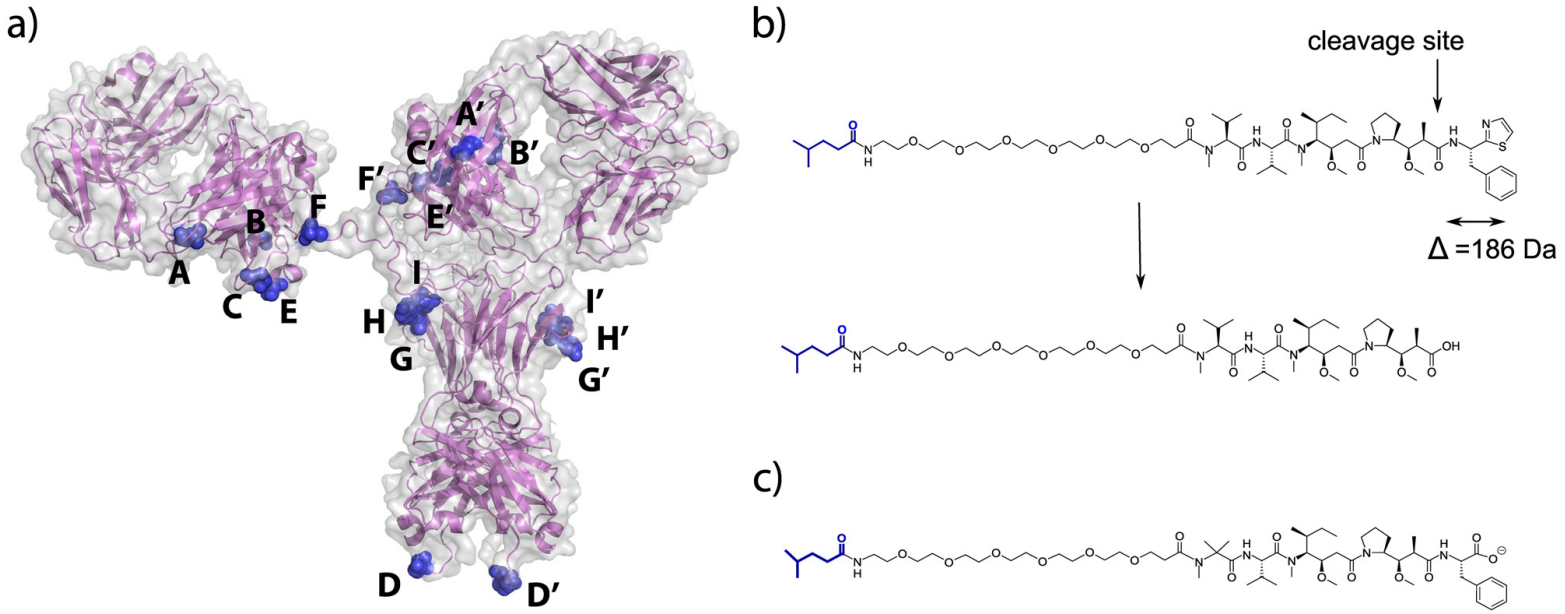


Fig 1. Stability studies of site-specific non-cleavable ADCs. a) Positions of conjugation sites on an antibody. b) Structure of the PEG6-C2-MMAD non-cleavable payload conjugated to the glutamine tag on the antibody, and its cleavage product. The glutamine residue is shown in blue. c) Structure of the PEG6-C2-Aur3377 non-cleavable payload conjugated to the glutamine tag shown in blue.

doi:10.1371/journal.pone.0132282.g001

Magdalena Dorywalska *et al*, Site-Dependent Degradation of a Non-Cleavable Auristatin-Based Linker-Payload in Rodent Plasma and Its Effect on ADC Efficacy, PLOS ONE | DOI:10.1371/journal.pone.0132282 July 10, 2015

Non-cleavable ADC with site-specific catabolism

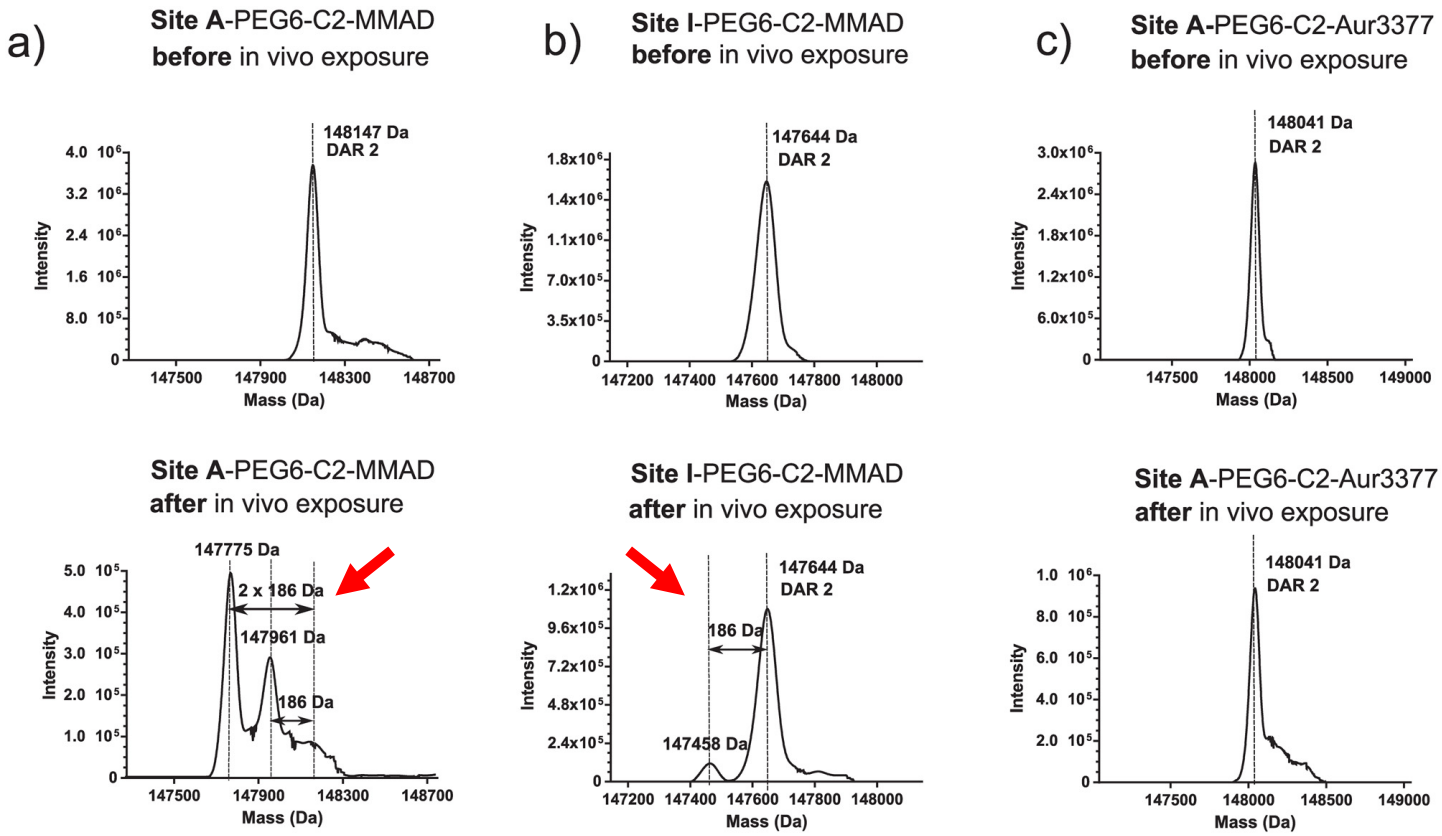
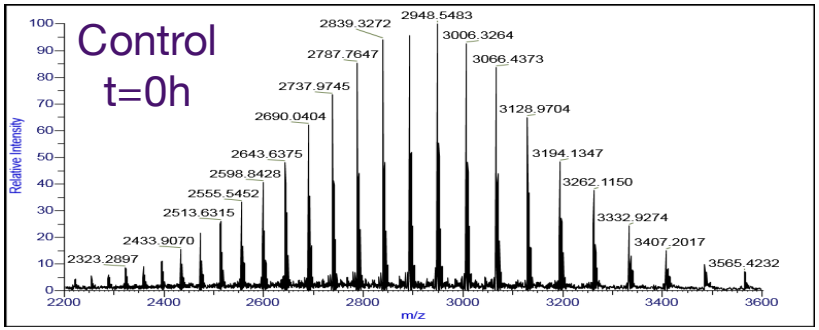
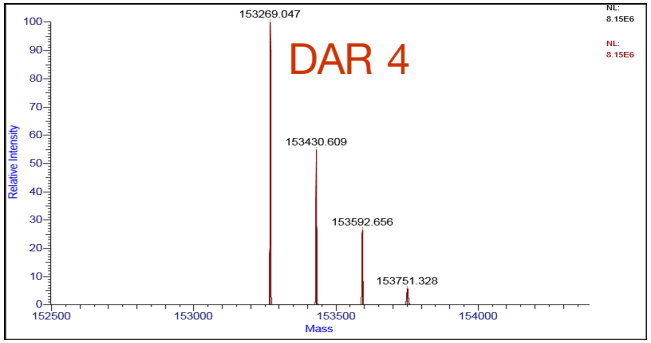


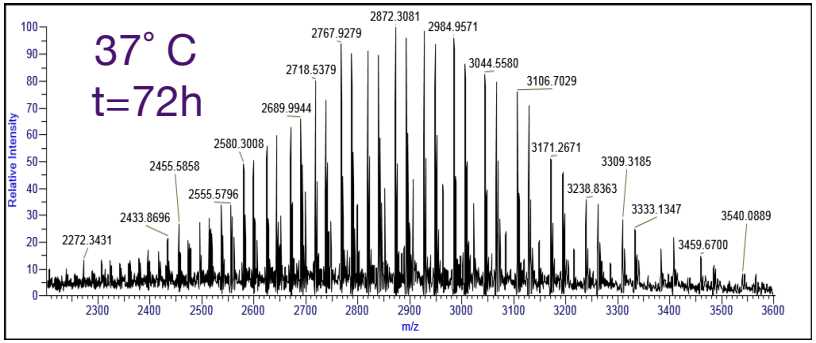
Fig 2. Mass spectrometric analysis of non-cleavable conjugates

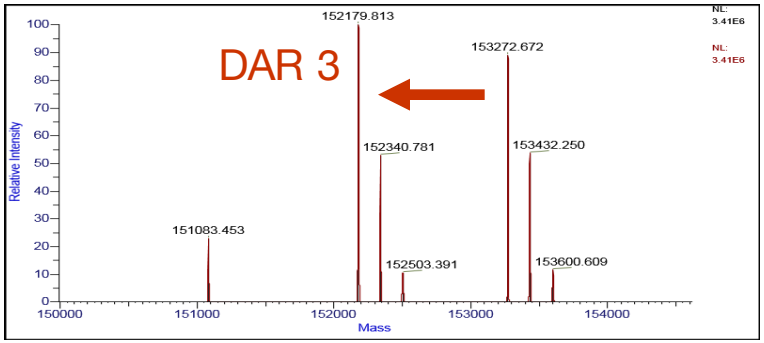
Magdalena Dorywalska *et al*, Site-Dependent Degradation of a Non-Cleavable Auristatin-Based Linker-Payload in Rodent Plasma and Its Effect on ADC Efficacy, PLOS ONE | DOI:10.1371/journal.pone.0132282 July 10, 2015

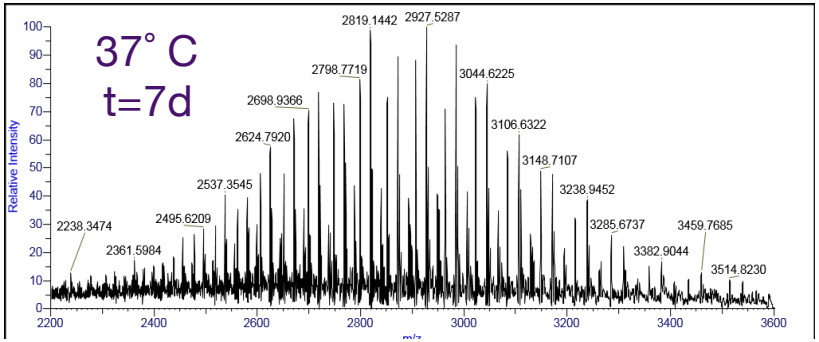
Engineered ADC (DAR4) *in vitro* plasma stability

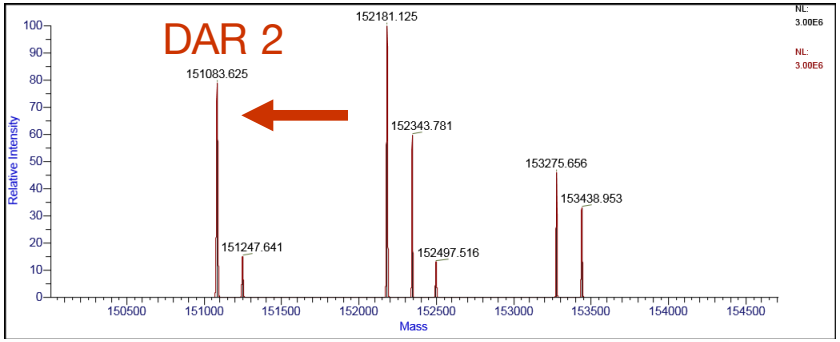












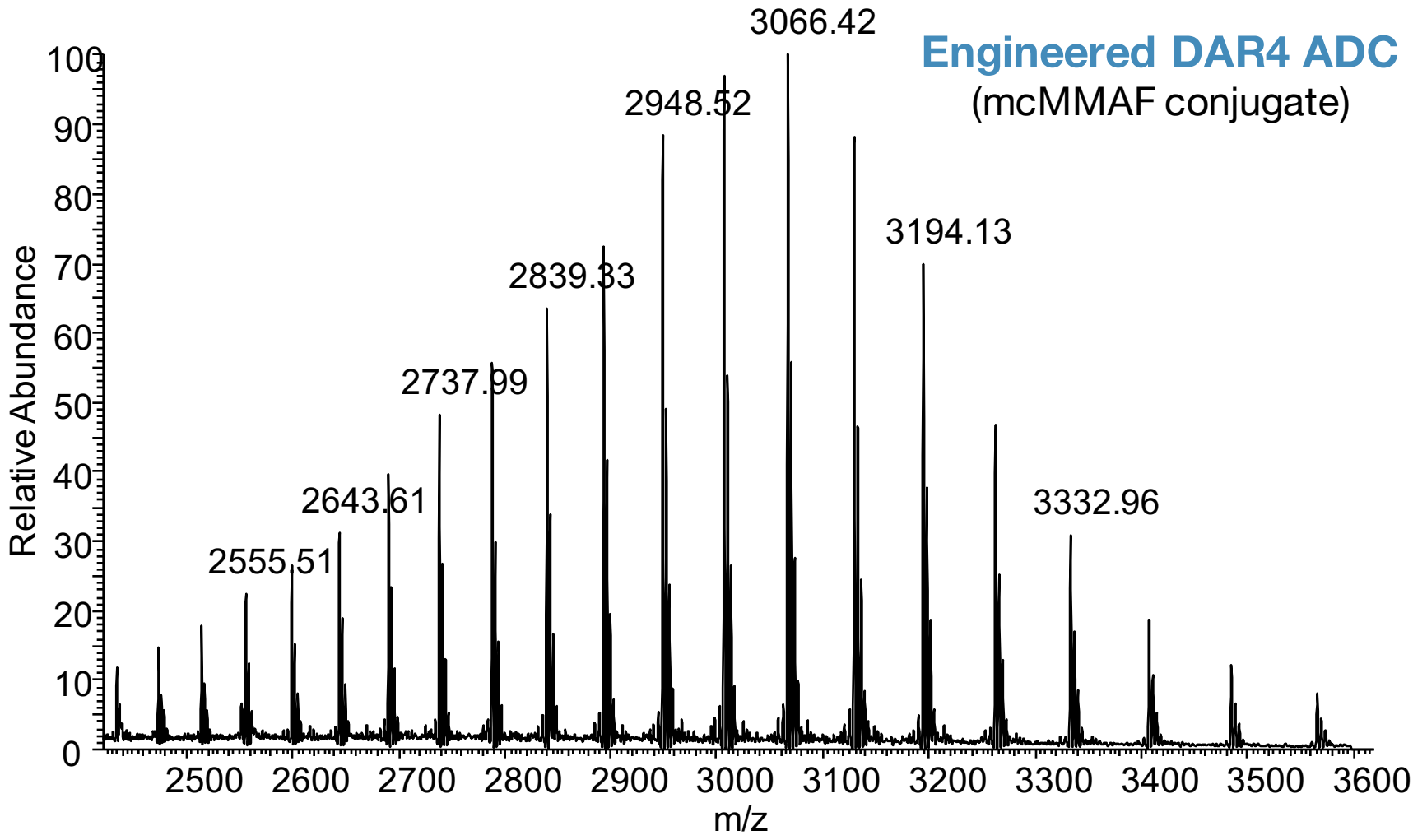
LC-MS ADC characterization *and beyond*

Assay	Technology
Drug or drug-linker metabolites *Which species exist and are important?*	LC-MS/MS
Catabolites (ADC or mAb) *Which species exist and are important?*	Affinity capture LC-HRAMS
DAR Distribution Assess ADC stability (in vitro / in vivo)	Affinity capture LC-HRAMS or HIC
Critical reagent DAR specificity Assess LBA reagents	Affinity capture LC-HRAMS or HIC
Intact ADC quantification *Useful to measure individual DARs or catabolites?*	**Affinity capture LC-HRAMS**

Intact ADC quantification

PPD-ThermoFisher Scientific collaboration

Raw HR mass spectrum



LC-HRAMS quantitation data processing

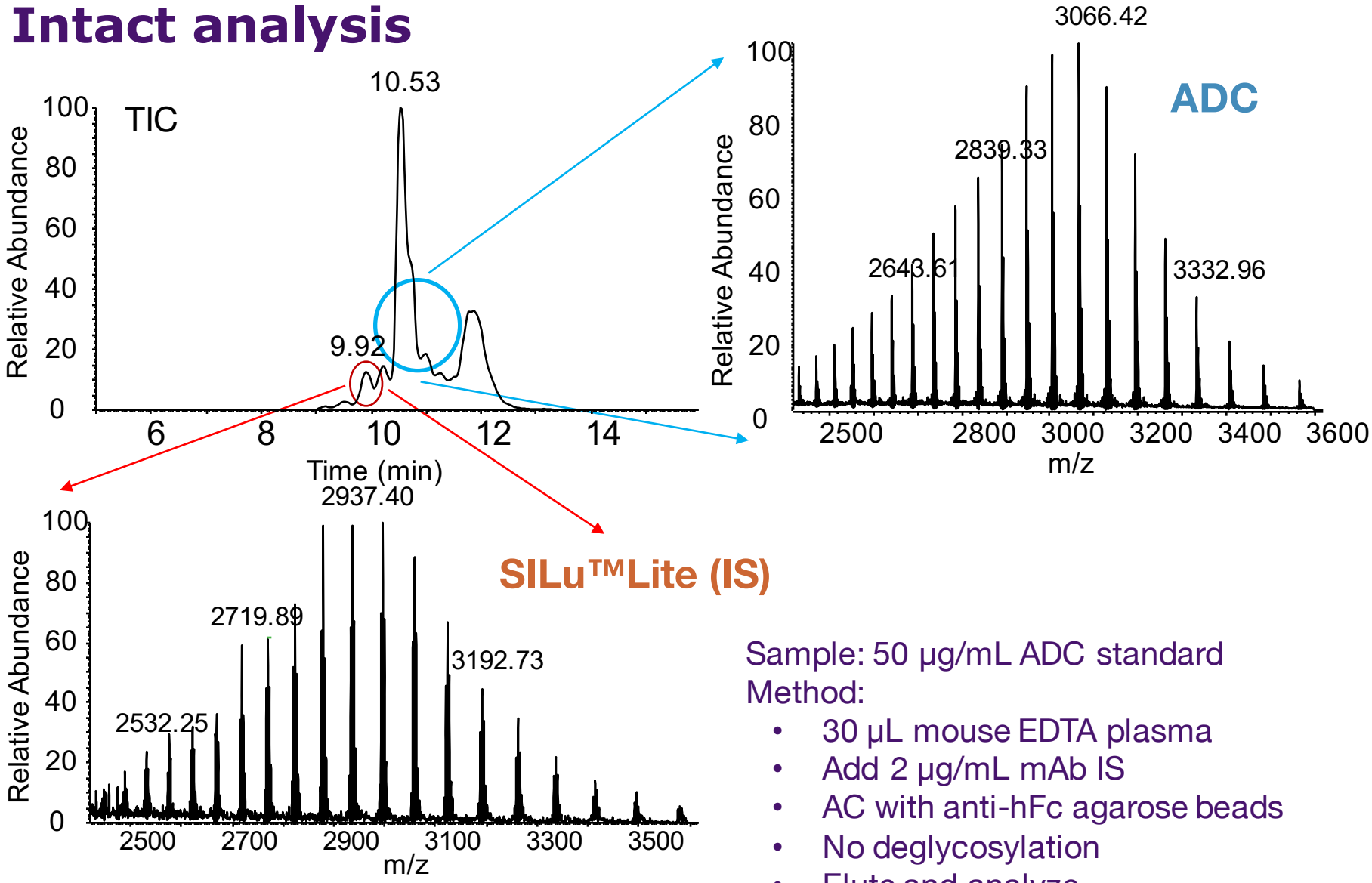
Potential options using full spectrum (FS) data acquisition

+ **XICs and traditional peak integration**
  - select m/z charge state(s), individual or summed
  - use narrow data extraction window (e.g. 5 mDa)
  - integrate XIC peak area

+ **Deconvoluted composite spectrum**
  - average/sum FS across entire chromatographic peak
  - peak area = total "zero-charge" state response

+ **Deconvoluted individual FS**
  - generate "zero-charge" state XIC
  - integrate XIC peak area

Intact analysis

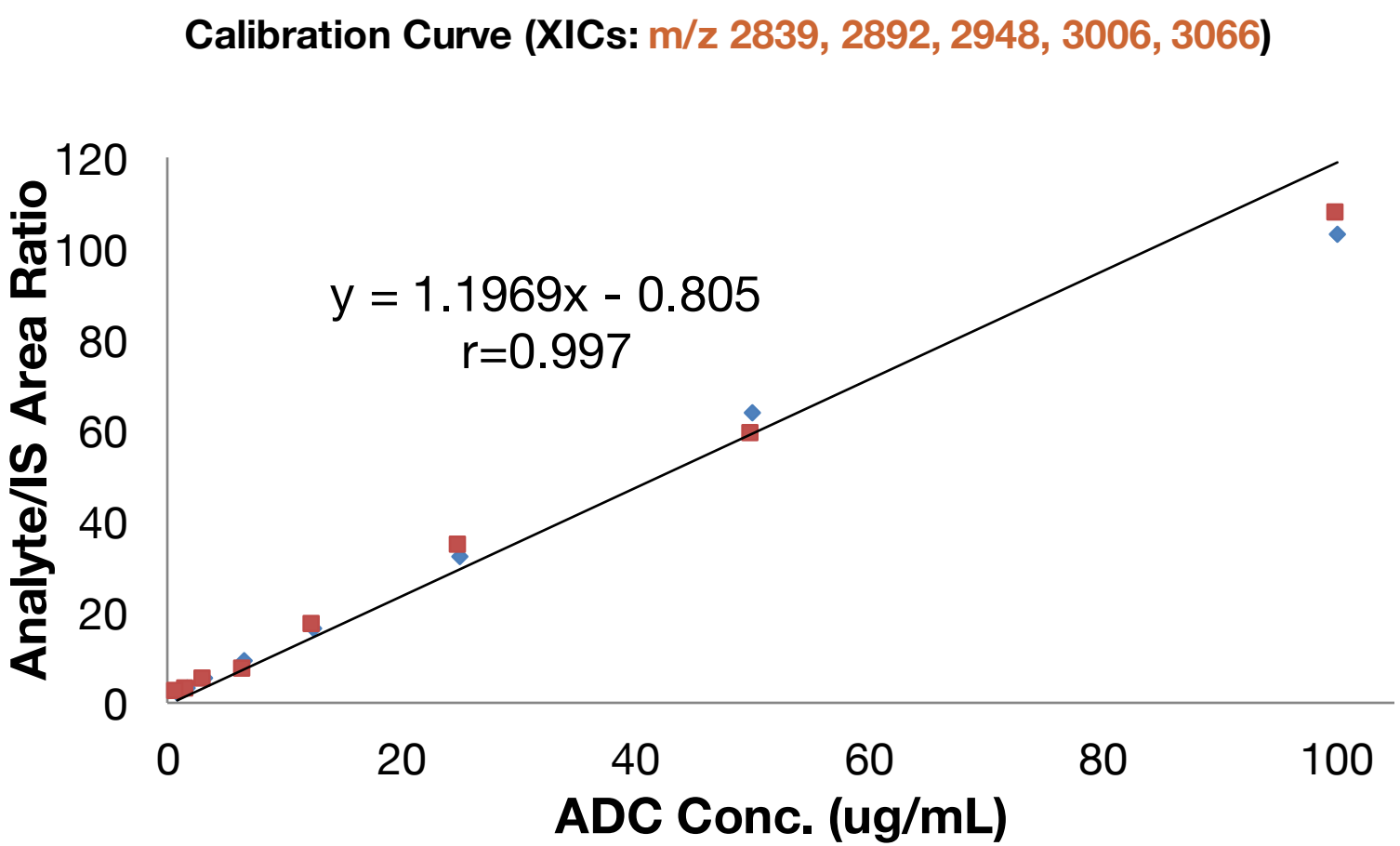


Sample: 50 µg/mL ADC standard

Method:

- 30 µL mouse EDTA plasma
- Add 2 µg/mL mAb IS
- AC with anti-hFc agarose beads
- No deglycosylation
- Elute and analyze

Summed XICs approach (with mAb IS)

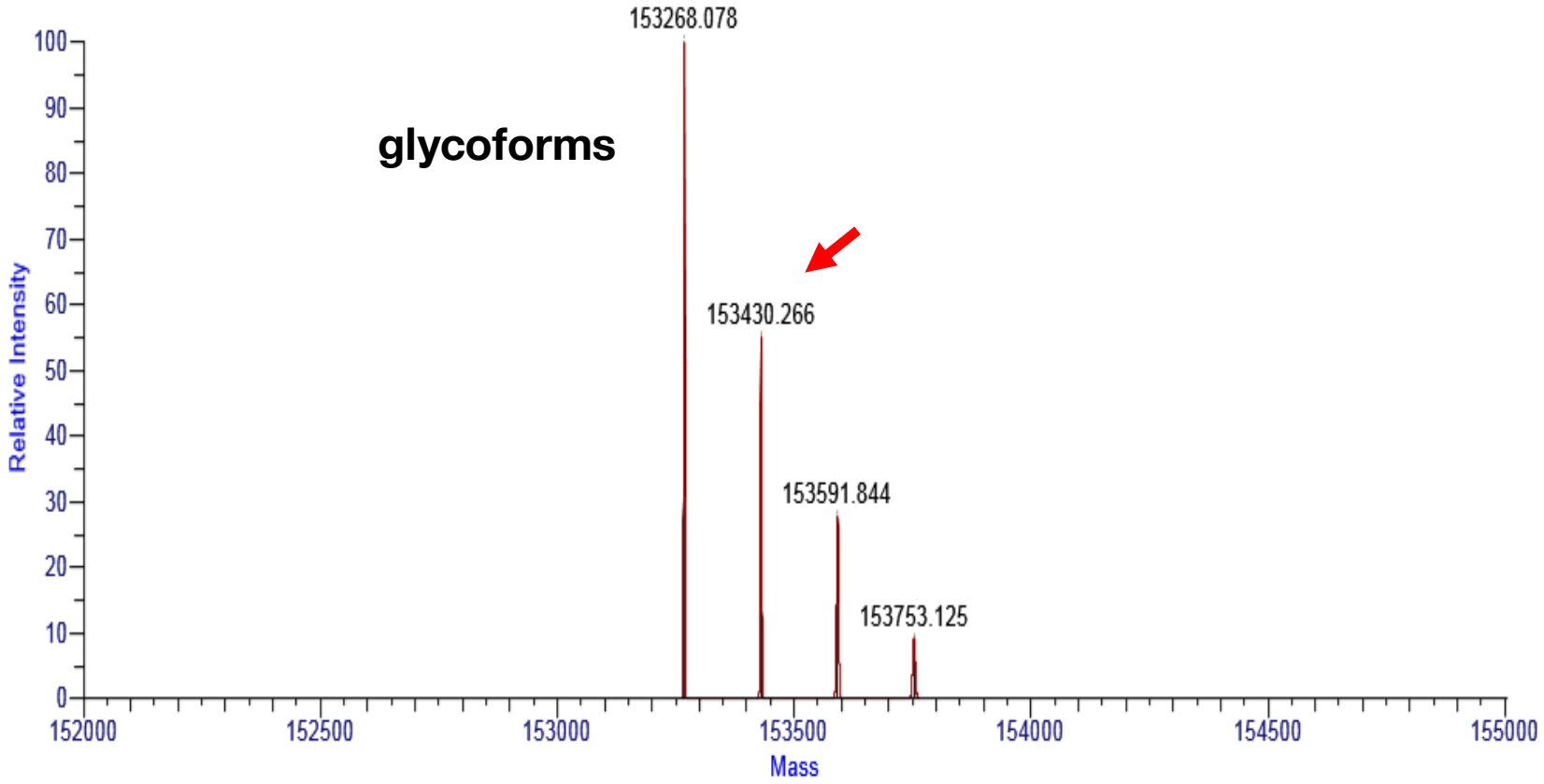


A&P - Summed XICs approach (with mAb IS)

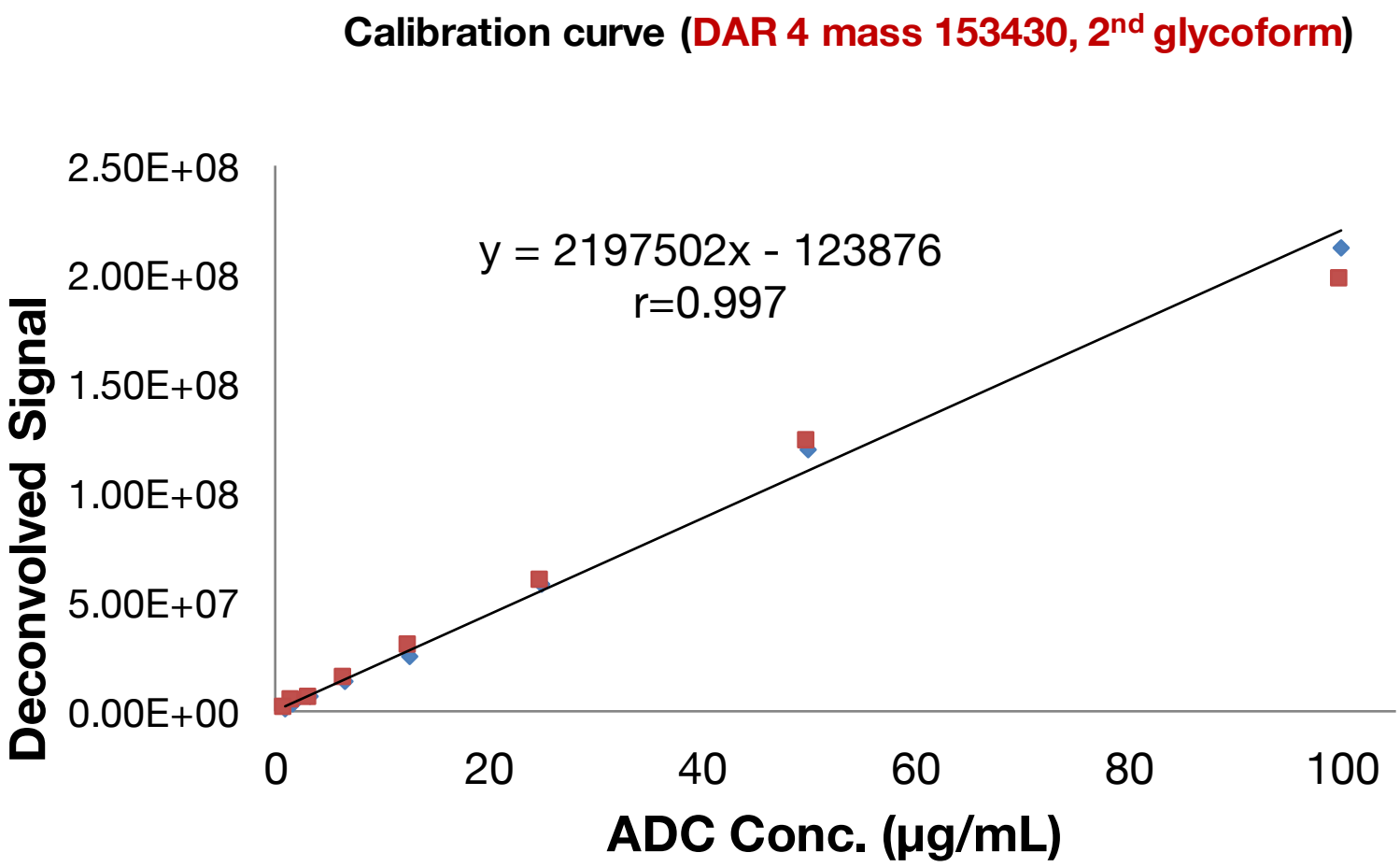
QCs	Analyte/IS	Cal. Conc. (ug/mL)	Nominal Conc. (ug/mL)	Accuracy	CV%
QC 1-1	3.00	1.83	1.6	115	11.7
QC 1-2	2.79	1.66	1.6	104	
QC 1-3	2.49	1.41	1.6	88.1	
QC 1-4	2.51	1.42	1.6	89.0	
QC 1-5	2.56	1.47	1.6	91.9	
QC 2-1	17.3	13.8	12.5	110	8.35
QC 2-2	15.2	12.0	12.5	96.3	
QC 2-3	14.9	11.8	12.5	94.1	
QC 2-4	17.8	14.2	12.5	114	
QC 2-5	16.0	12.7	12.5	101	
QC 3-1	108	89.3	100	89.3	3.01
QC 3-2	106	88.2	100	88.2	
QC 3-3	108	89.9	100	89.9	
QC 3-4	102	84.3	100	84.3	
QC 3-5	102	84.6	100	84.6	

Deconvoluted mass spectrum

Engineered DAR4 ADC
(mcMMAF conjugate)



Deconvoluted MS approach (no IS)



A&P - Deconvoluted MS approach (no IS)

QCs	Intensity	Cal. Conc. (ug/mL)	Nominal Conc. (ug/mL)	Accuracy	CV%
QC 1-1	3040465	1.44	1.60	90.0	12.1
QC 1-2	3171365	1.50	1.60	93.7	
QC 1-3	3384557	1.60	1.60	99.8	
QC 1-4	2532637	1.21	1.60	75.6	
QC 1-5	3566412	1.68	1.60	105.0	
QC 2-1	28494807	13.0	12.5	104.2	3.99
QC 2-2	26480701	12.1	12.5	96.9	
QC 2-3	25990923	11.9	12.5	95.1	
QC 2-4	28256266	12.9	12.5	103.3	
QC 2-5	27660784	12.6	12.5	101.1	
QC 3-1	201954923	92.0	100	92.0	2.03
QC 3-2	202279068	92.1	100	92.1	
QC 3-3	200604530	91.3	100	91.3	
QC 3-4	210591547	95.9	100	95.9	
QC 3-5	206835150	94.2	100	94.2	

ADC bioanalysis

other challenges

Practicality issues for ADC bioanalysis

Resource and time intensive

- Several different assays needed for each study
- Parallel sample analyses desirable, requiring multiple technologies, staff and instruments

Preclinical/early development

- Several species to evaluate
- Multiple ADC constructs to compare
- Restricted sample volumes

A work in progress...

Final thoughts

- Keeping up with biotherapeutics innovation is a challenge for analytics (CMC) and bioanalysis
- Answering critical drug development questions requires both LBA and LC-MS assay technologies
- Inherent ADC heterogeneity and dynamic changes *in vivo* require in-depth characterization
- MS-based methods, including AC-LC-HRAMS, are emerging as increasingly versatile tools
- Regulators are aware and likely to increase their expectations

Acknowledgements

Acknowledgements

PPD® Laboratories
- Dongliang Zhan
- Diego Cortes
- William Mylott
- Pat Bennett

ThermoFisher SCIENTIFIC
- Kwasi Antwi
- Jonathan Josephs
- Urban A. Kiernan
- Keeley Murphy
- Eric E. Niederkofler

Genentech
- Keyang Xu
- Surinder Kaur

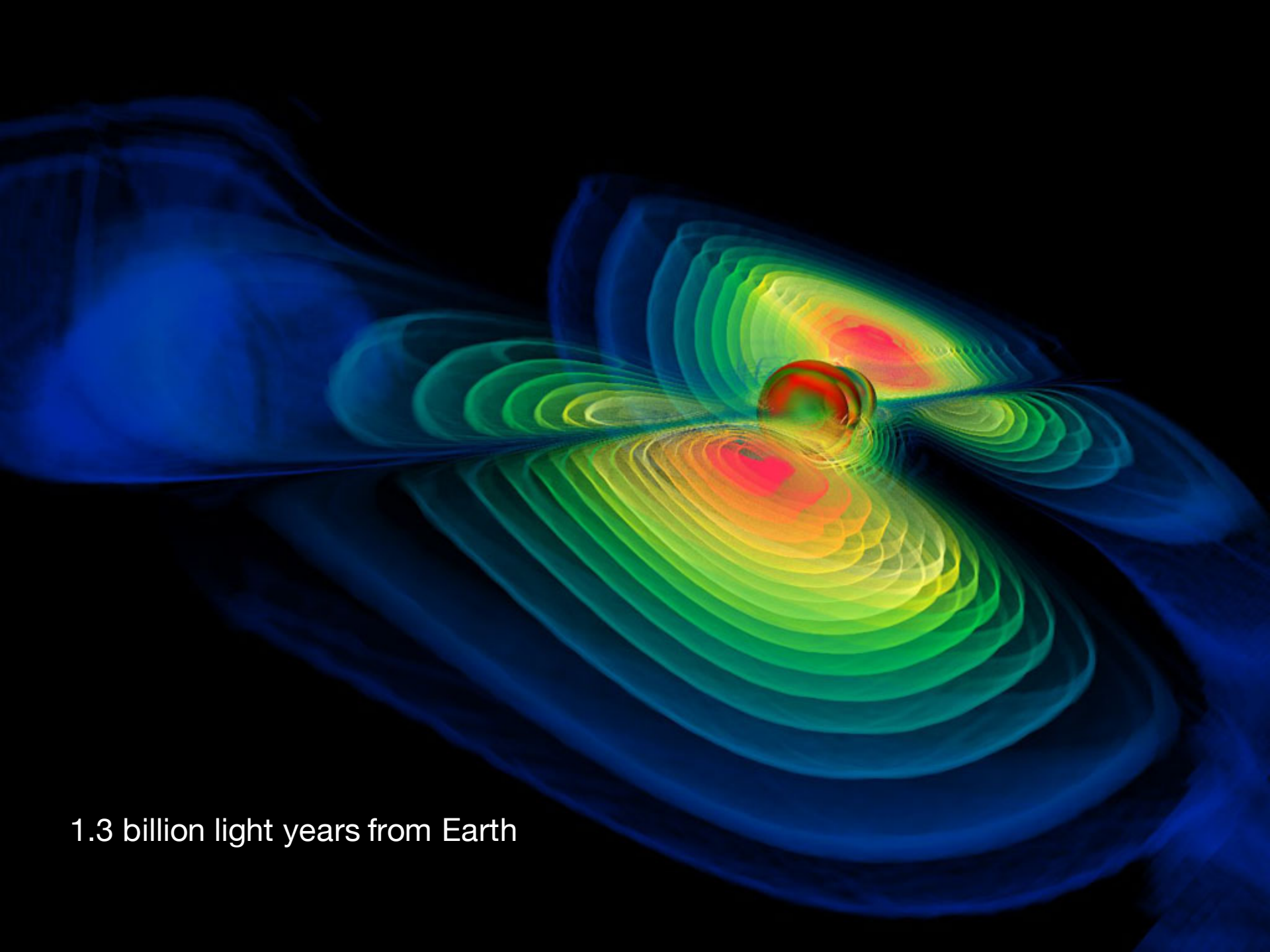
Seattle Genetics
- Shawna Hengel
- Steve Alley

Pfizer
- Leo Kirkovsky

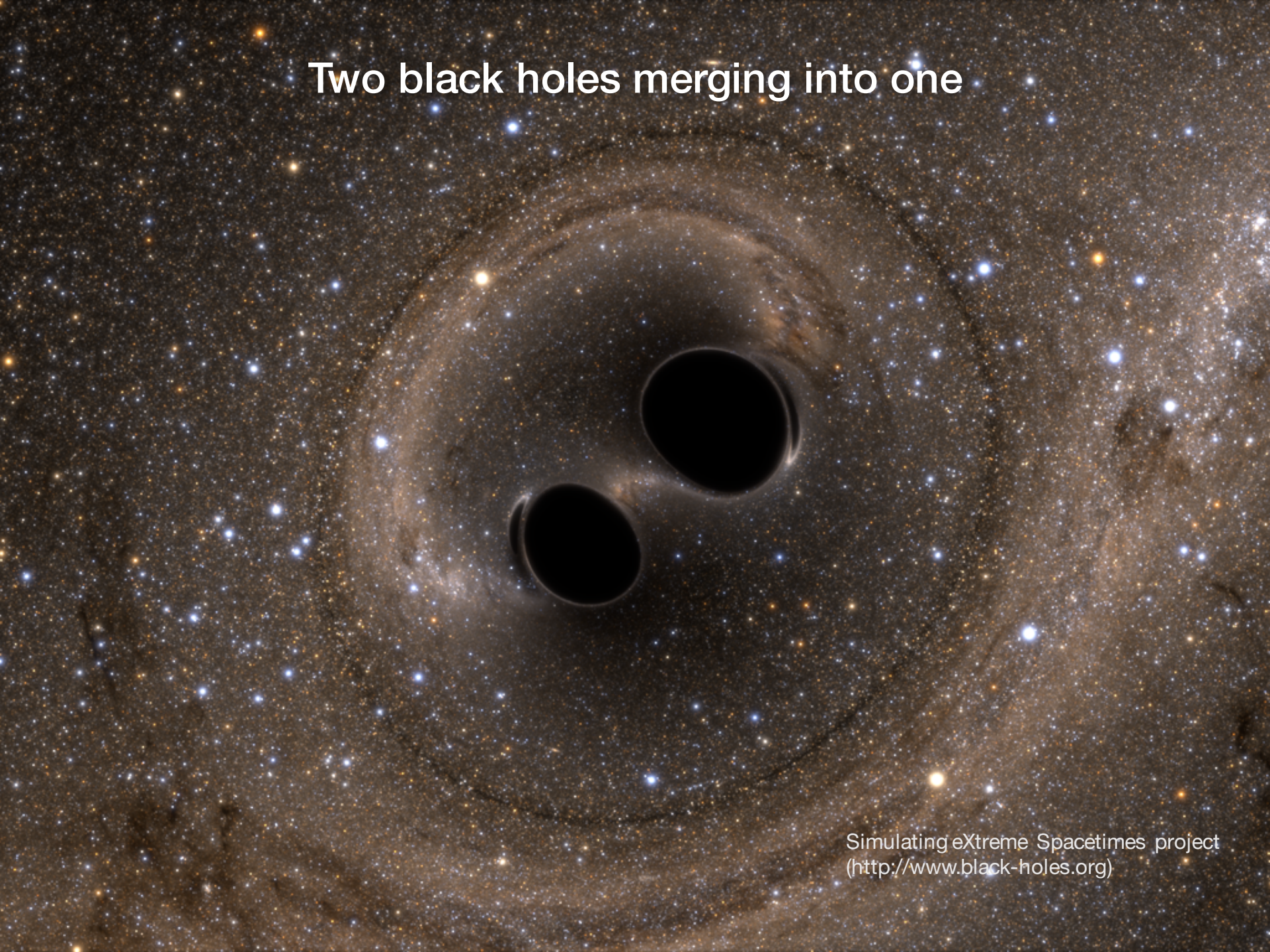
Also
- Jun Hosogi (JBF)
- Shinobu Kudoh (JBF)

...and many others

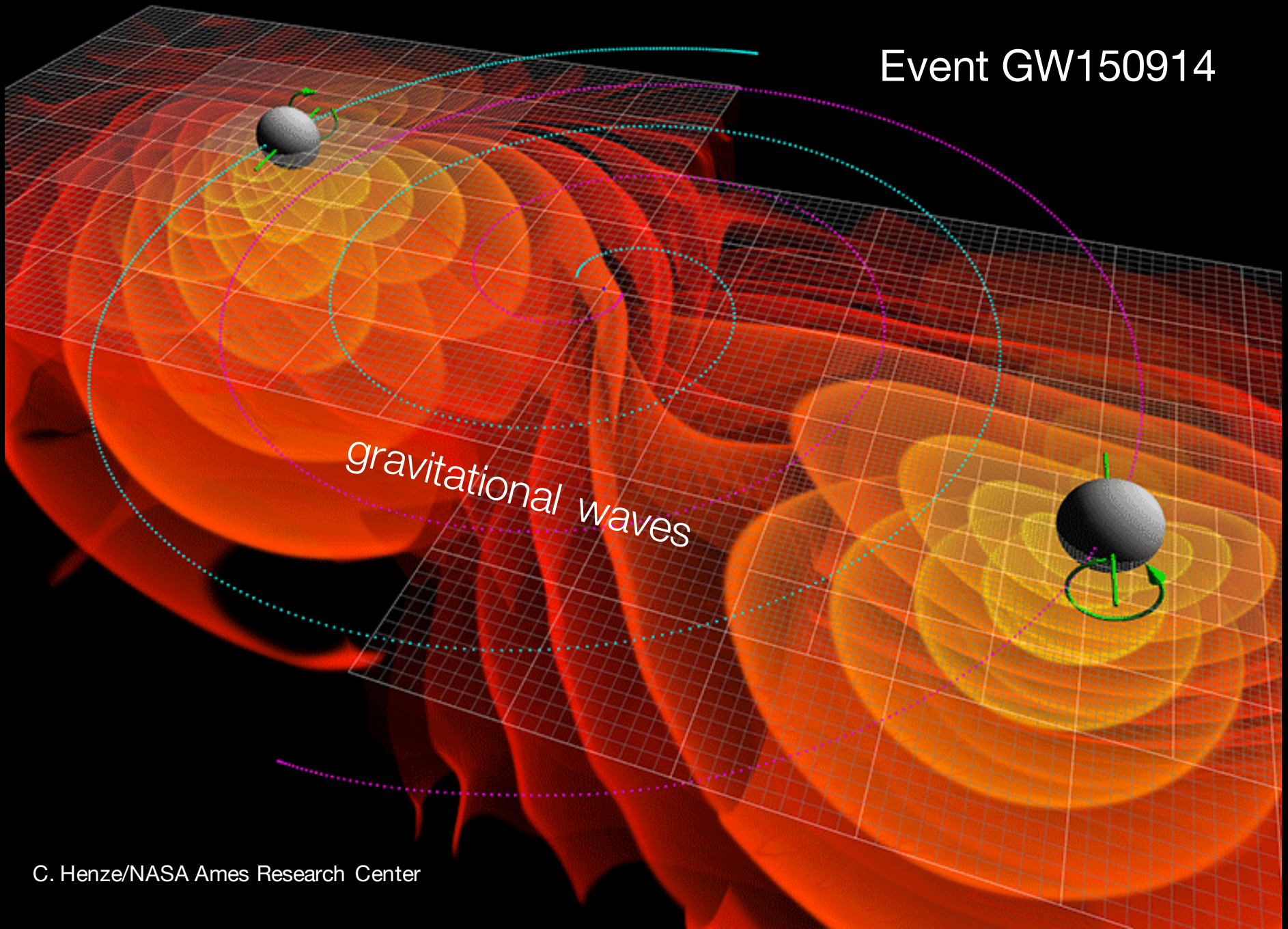
A story…


1.3 billion light years from Earth

Two black holes merging into one

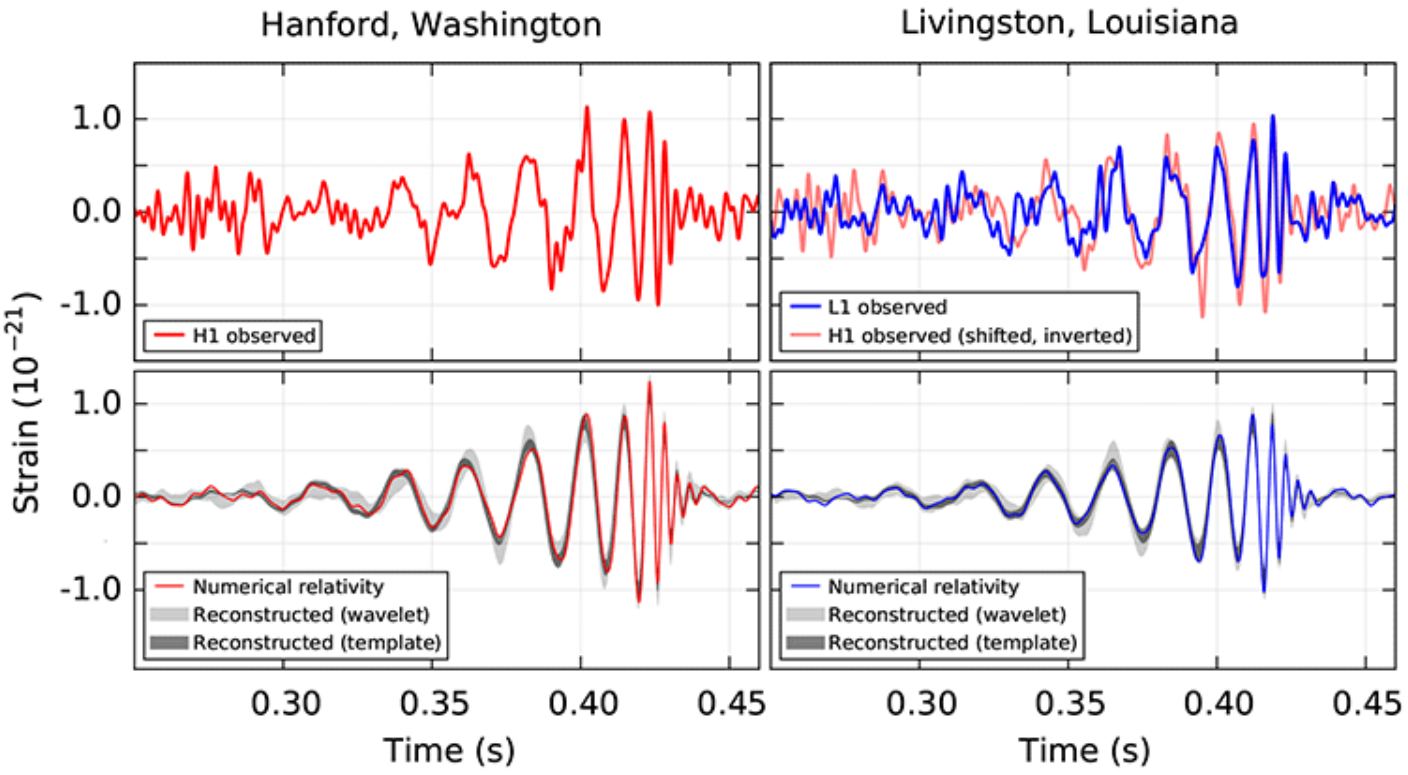


Simulating eXtreme Spacetimes project
(http://www.black-holes.org)


Event GW150914
gravitational waves
C. Henze/NASA Ames Research Center

The “sound” of two black holes merging

14 September 2015 at 09:50:45 UTC

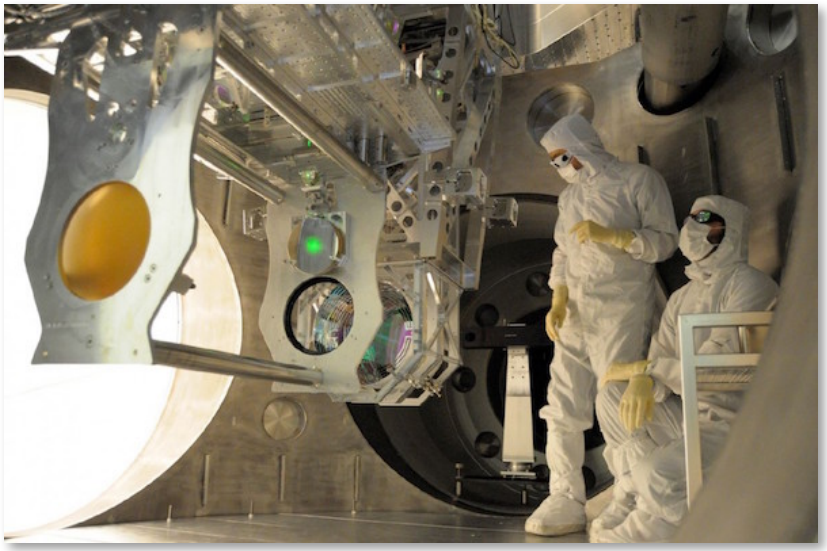


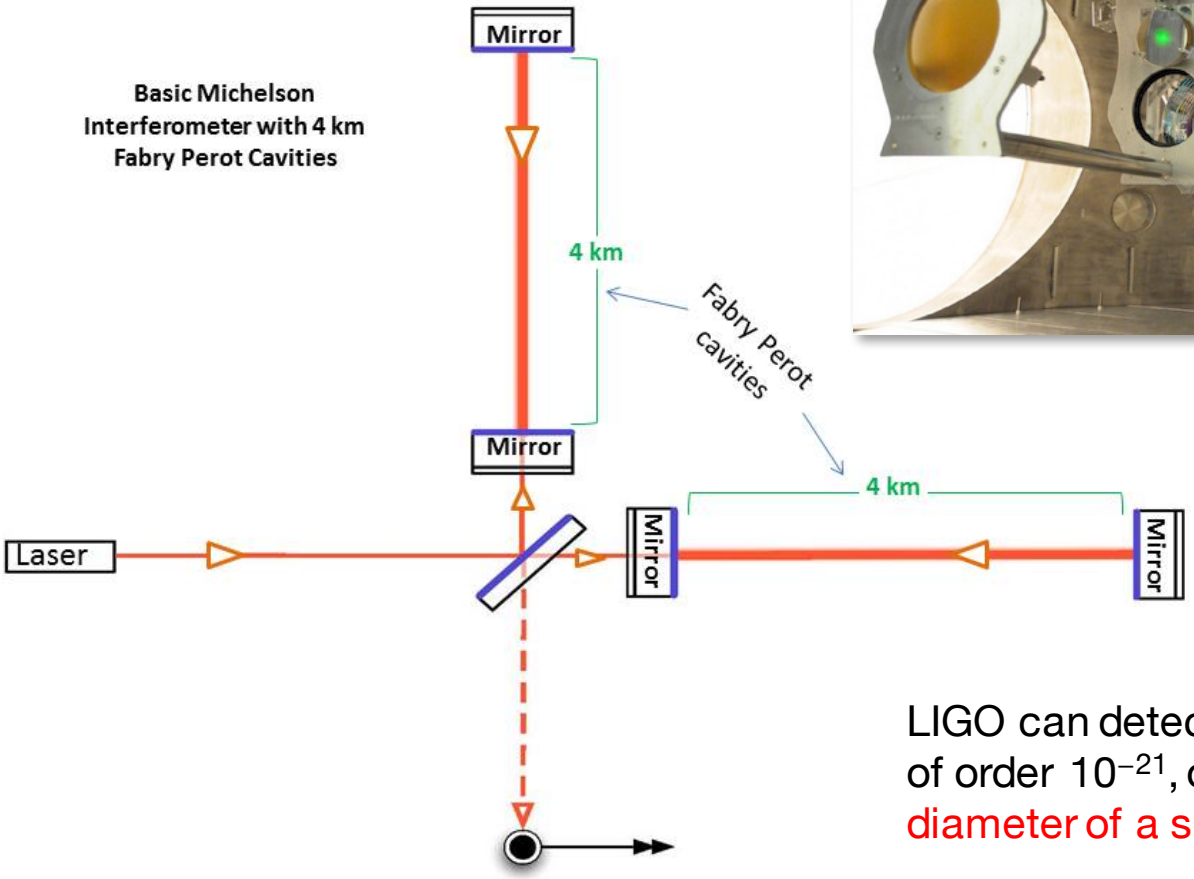
Top panels show the measured signals in the LIGO detectors.
Bottom panels show the expected signal based on numerical simulations.

B. P. Abbott *et al.* (LIGO Scientific Collaboration and Virgo Collaboration), “Observation of Gravitational Waves from a Binary Black Hole Merger,” *Phys. Rev. Lett.* **116**, 061102 (2016)


Advanced LIGO
Hanford, Washington, USA

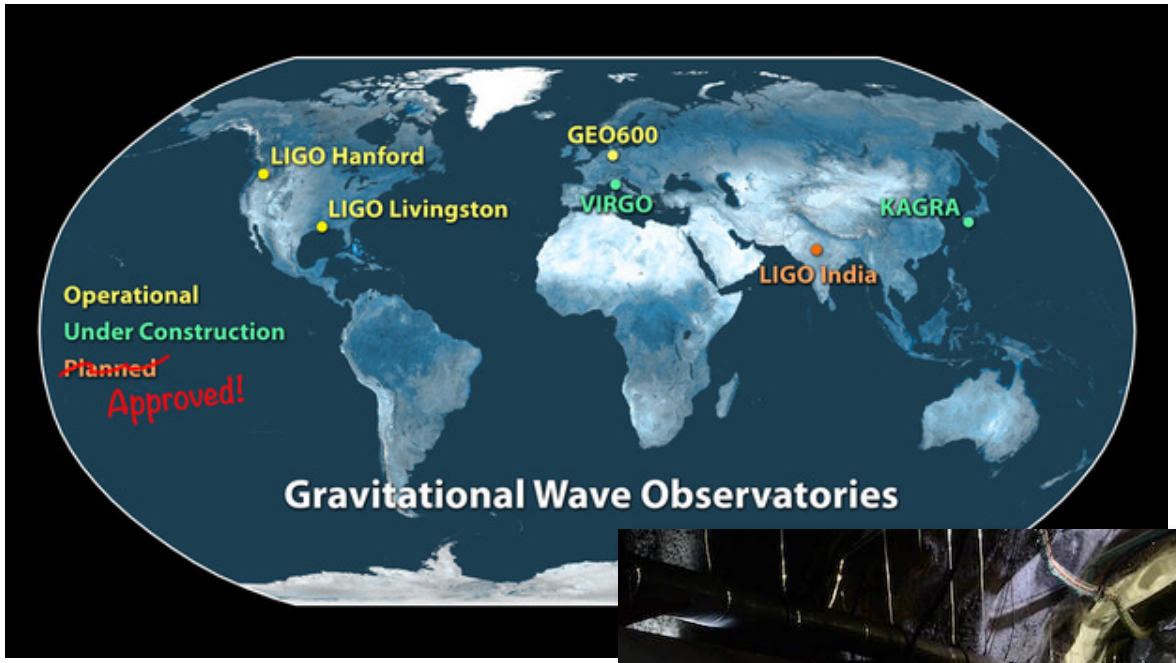
Laser Interferometer Gravitational-wave Observatory (LIGO)





LIGO can detect relative length variations of order 10^{-21}, or one ten-thousandth the diameter of a single proton

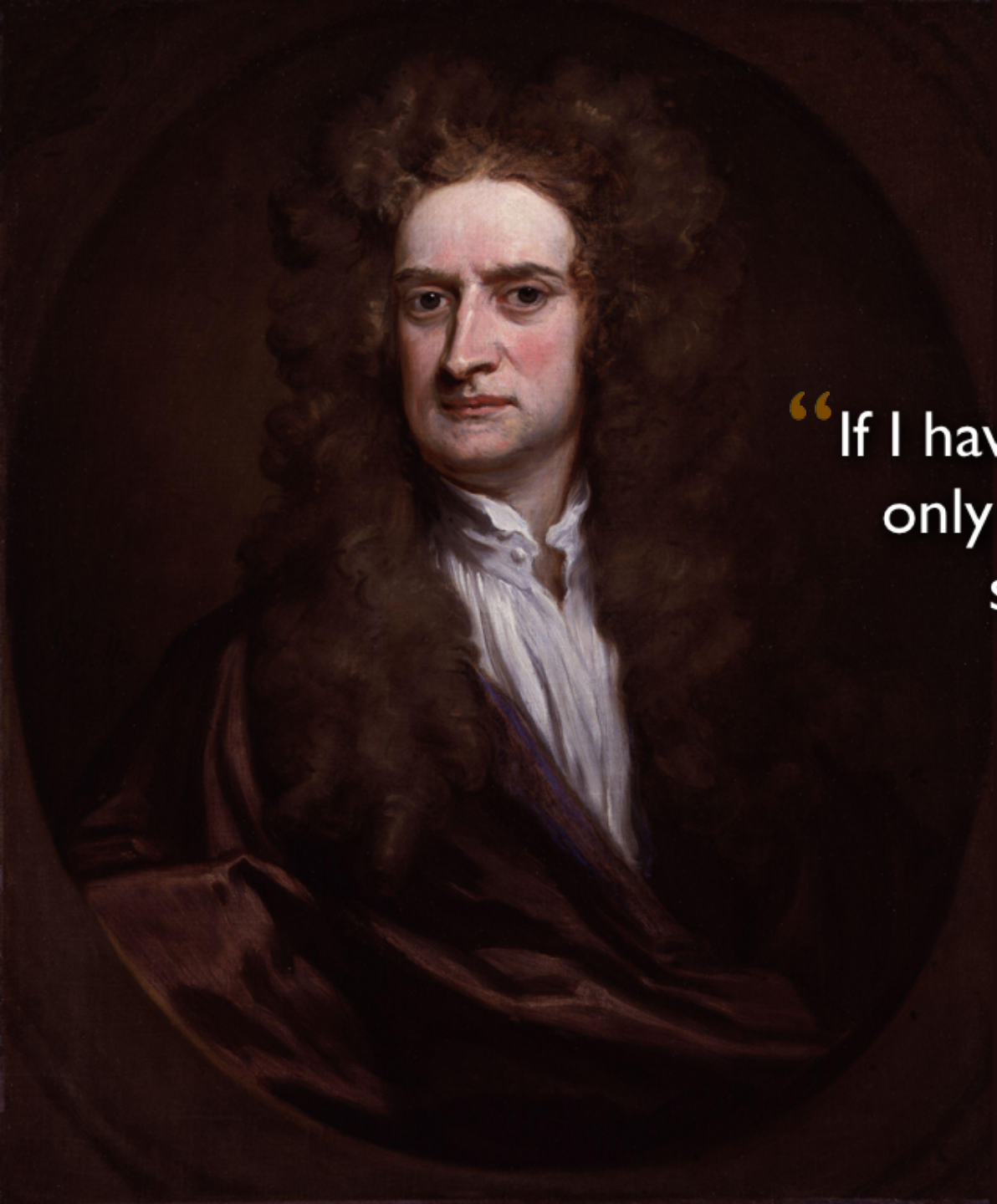
Observatories and LIGO Scientific Collaboration (LSC)



Kamioka Gravitational Wave Detector (KAGRA), Japan

Important players in the LIGO project, from left to right: Kip Thorne of the California Institute of Technology, France A. Córdova of the National Science Foundation, Rainer Weiss of the Massachusetts Institute of Technology, David Reitze of Caltech and Gabriela González of Louisiana State University.

Credit: Lexey Swall for The New York Times



“If I have seen further it is only by standing on the shoulders of giants.”

— Sir Isaac Newton


ありがとうございます
Thank you