Structure, heterogeneity & developability assessment of therapeutic antibodies, fusion proteins & ADCs

Alain BECK – Festival of Biologics/EAC (Virtual) - Nov 3, 2020

Pierre Fabre

Structure, heterogeneity & developability assessment of therapeutic Abs, fusion proteins & ADCs

Overview of 2020 papers Mass Spec-network (+20):

- LC and 2D-LC-MS (CEX, HIC, HILIC)
- CE-MS (online)/ nrCE-SDS + MS (offline)
- Collision Induced Unfolding (CIU), SEC-CIU
- Host Cell Proteins MS workflow optimization
- Collaborative papers (Top Dow Sequenc., GlycoNIST)
- Fc-fusion proteins & peptides analytics
- ADCs landscape & analytics

Non-denaturing (2D-)LC-MS: IEX, SEC, HIC-MS (JPBA 2020)

Journal of Pharmaceutical and Biomedical Analysis 185 (2020) 113207

Contents lists available at ScienceDirect

Journal of Pharmaceutical a

journal homepage: www.els

ELSEVIER

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Review

Coupling non-denaturing chromatography
the characterization of monoclonal antibod

Evelin Farsang[a], Davy Guillarme[b], Jean-Luc Veuthey[b], A
Andrew Schmudlach[d], Szabolcs Fekete[b,*]

[a] Department of Analytical Chemistry, University of Pannonia, Egyetem u. 10., H-8200 Veszprém
[b] Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, CMU-Rue M
[c] Center of Immunology Pierre Fabre, 5 Avenue Napoléon III, BP 60497, 74160, Saint-Julien-en-G
[d] Waters Corporation, 34 Maple Street, Milford, MA, 01757-3696, United States

- **S. Fekete, D. Guillarme et al**

CEX optimization: column + eluant (JCA 2020)

Journal of Chromatography A 1626 (2020) 461350

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

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Impact of the column on
chromatography, a practi

Evelin Farsang[a], Krisztián Horvá
Davy Guillarme[e], Szabolcs Feket

[a] Department of Analytical Chemistry, University of Pan
[b] Center of Immunology Pierre Fabre, 5 Avenue Napoléo
[c] Waters Corporation, 34 Maple Street, Milford, MA 017
[d] Current Address: Bristol Myers Squibb, 38 Jackson Rd,
[e] Institute of Pharmaceutical Sciences of Western Switze

- **S. Fekete,**
- **D. Guillarme**

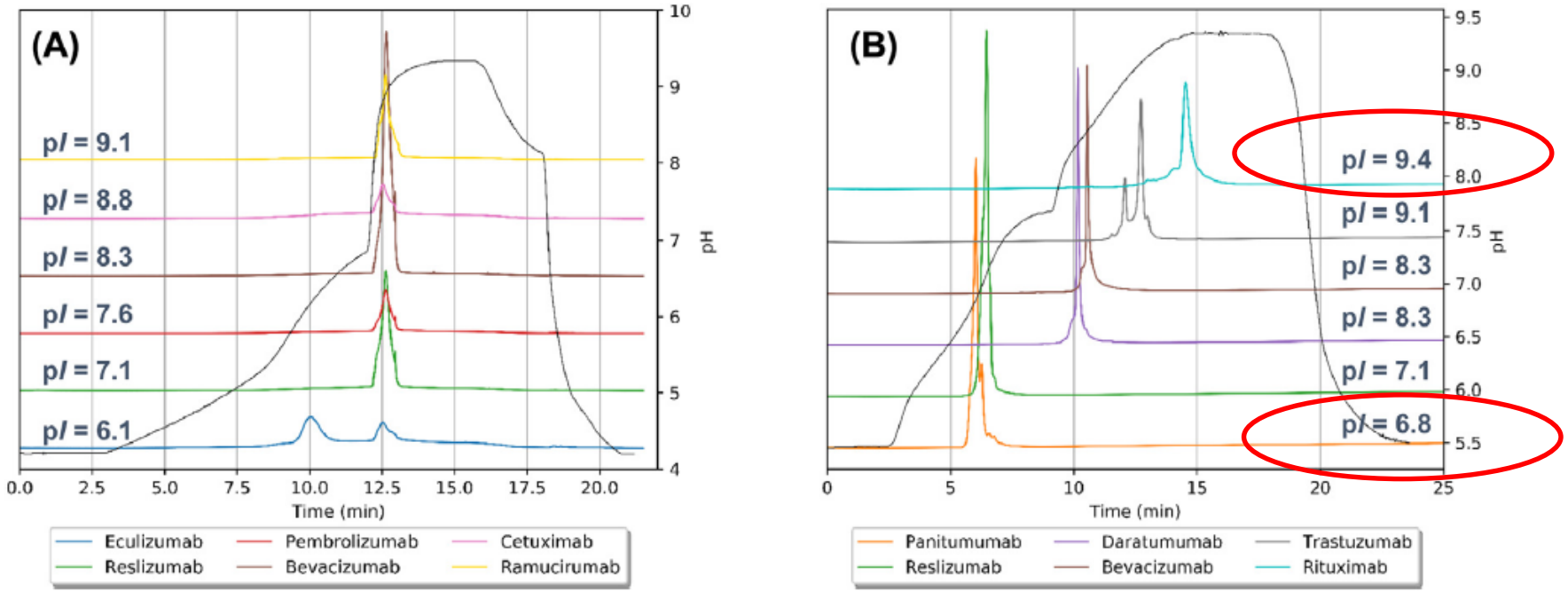


Fig. 5. Chromatograms of intact mAbs eluted from a Thermo ProPac column withCA/CHES/NaOH pH gradient buffer (A) and with MES/DAP pH gradient buffer (B).

Capillary Electrophoreris + MS (CE-MS) (JPBA 2020)

Journal of Pharmaceutical and Biomedical Analysis 182 (2020) 113107

Contents lists available at ScienceDirect

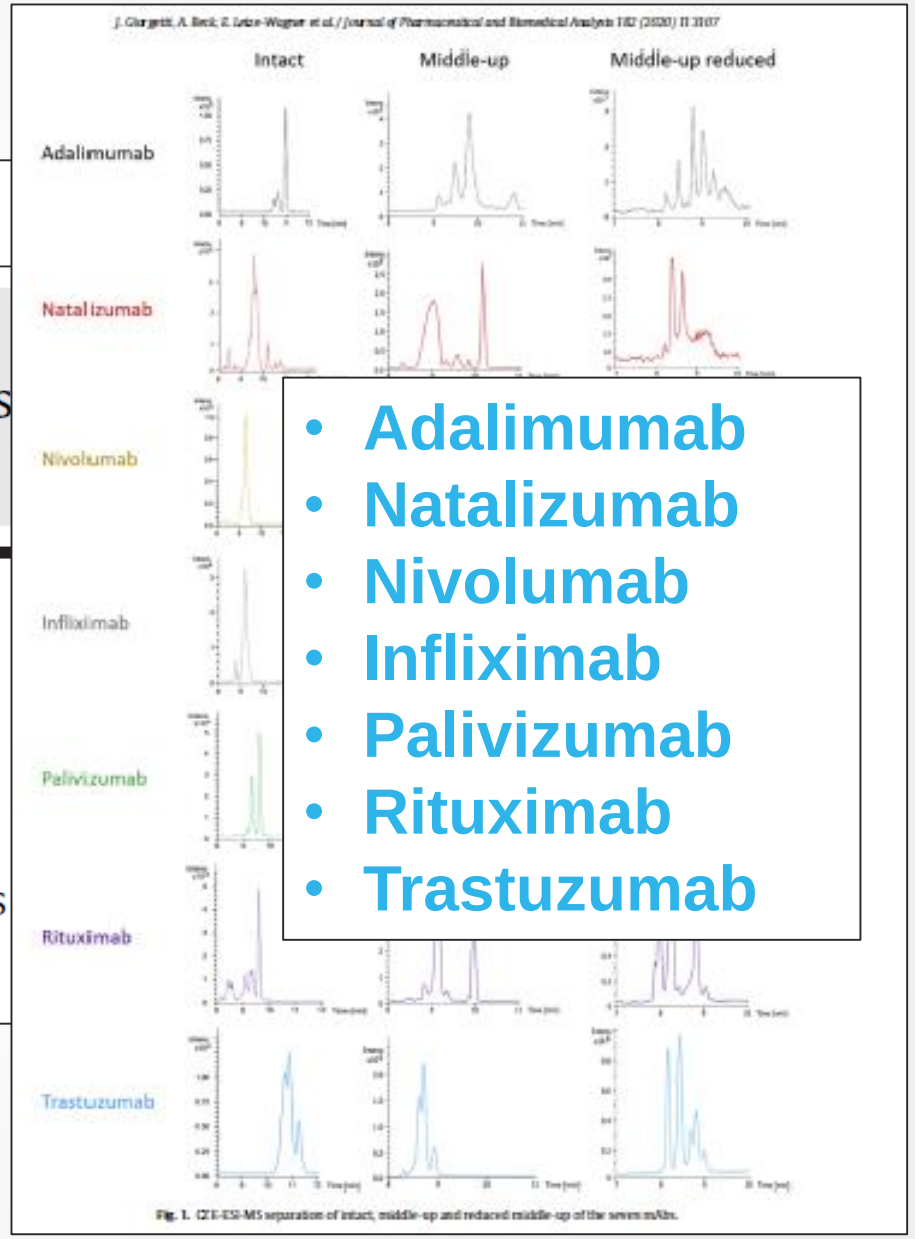
Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Combination of intact, middle-up and bottom-up levels to characterize 7 therapeutic monoclonal antibodies by capillary electrophoresis – Mass spectrometry

Jérémie Giorgetti[a], Alain Beck[b], Emmanuelle Leize-Wagner[a], Yannis-Nicolas François

[a] *Laboratoire de Spectrométrie de Masse des Interactions et des Systèmes (LSMIS) UMR 7140 (Unistra-CNRS), Université de Strasbourg, France*
[b] *Centre d'Immunologie Pierre Fabre, Saint-Julien-en-Genevois, France*



- Adalimumab
- Natalizumab
- Nivolumab
- Infliximab
- Palivizumab
- Rituximab
- Trastuzumab

- Y. François et al

nrCE-SDS: 26 mAbs + 2 ADCs FDA appr. (JPBA 2020)

Journal of Pharmaceutical and Biomedical Analysis 184 (2020) 113166

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Determination of size variants by CE-SDS for approved therapeutic antibodies: Key implications of subclasses and light chain specificiti

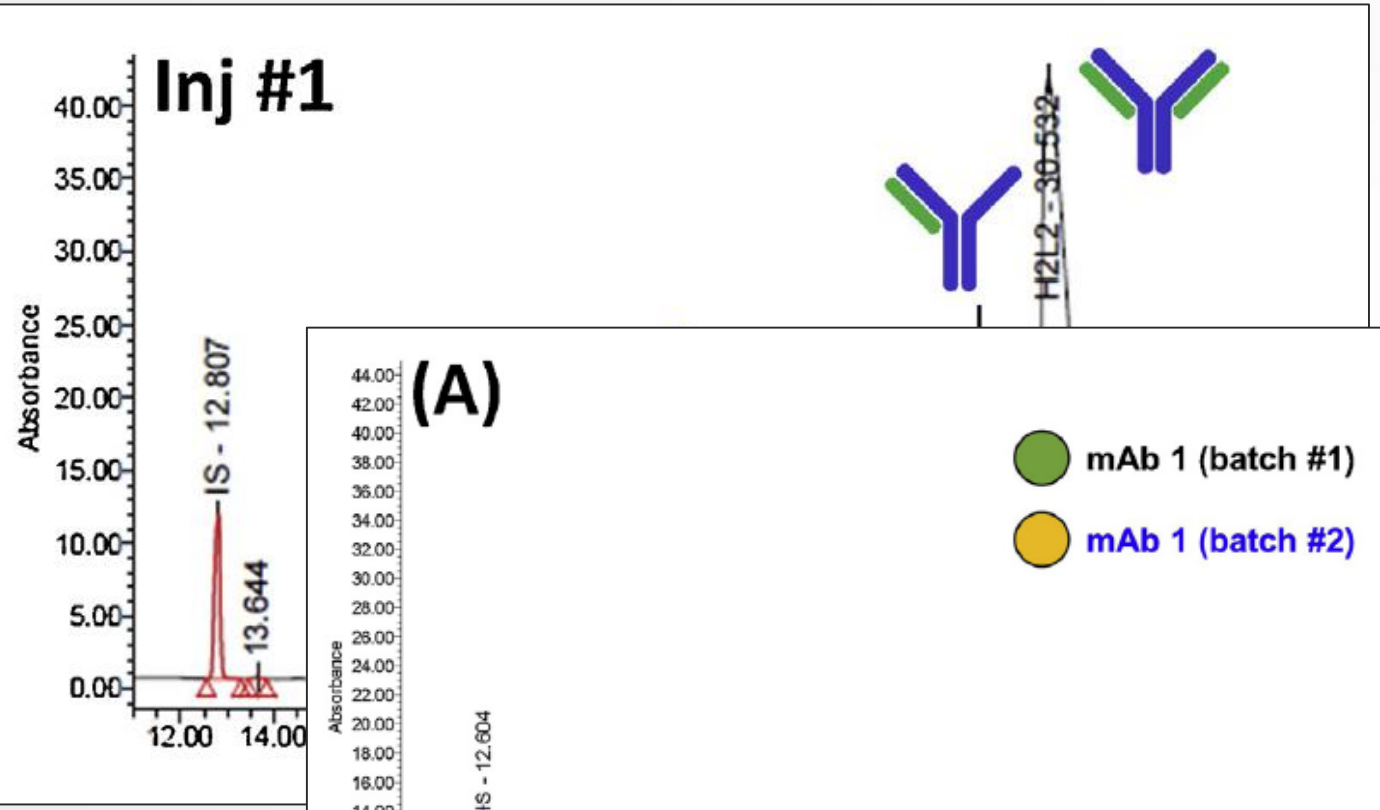
Elsa Wagner[a], Olivier Colas[a], Stéphane Chenu[a], Alexandre Goyon[b], Amarande Murisie, Sarah Cianferani[c], Yannis François[d], Szabolcs Fekete[b], Davy Guillarme[b], Valentina D'Atri[b,*], Alain Beck[a,*]

[a] Biologics CMC and Developability, IRPF - Centre d'Immunologie Pierre-Fabre (CIPF), Saint-Julien-en-Genevois, France
[b] Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, CMU-Rue Michel Servet 1, 1211 Geneva 4, Switzerland
[c] Laboratoire de Spectrométrie de Masse BioOrganique, IPHC UMR 7178, Université de Strasbourg, CNRS, Strasbourg, France
[d] Laboratoire de Spectrométrie de Masse des Interactions et des Systèmes (LSMIS), UMR 7140, Université de Strasbourg, CNRS, Strasbourg, France

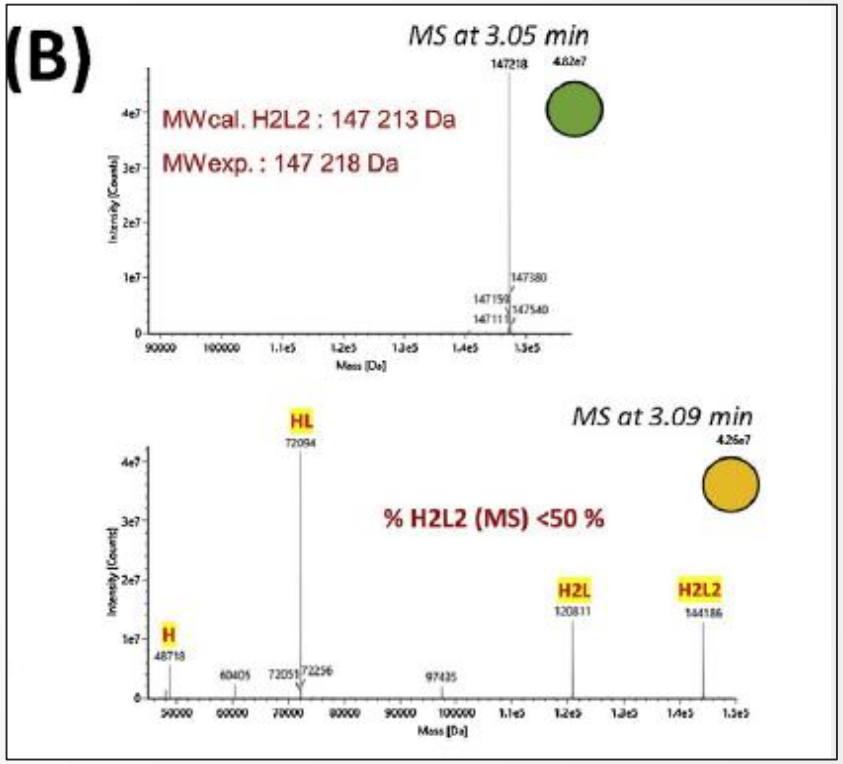
- Ch, Hz, Hu IgGs
- CHO, NS0, SP2/0
- IgG1, 2, 2/4, 4wt, 4stab
- Glyco-engineered
- A-glycosylated
- Kappa & lambda LC
- Partially reduced IgGs
- Biosimilars
- Hinge Cys & Lys ADCs
- NISTmab

- **Standard nrCE-SDS conditions**
- **Specification for H2L2 species ?**

nrCE-SDS IgG profiles: partially reduced profiles

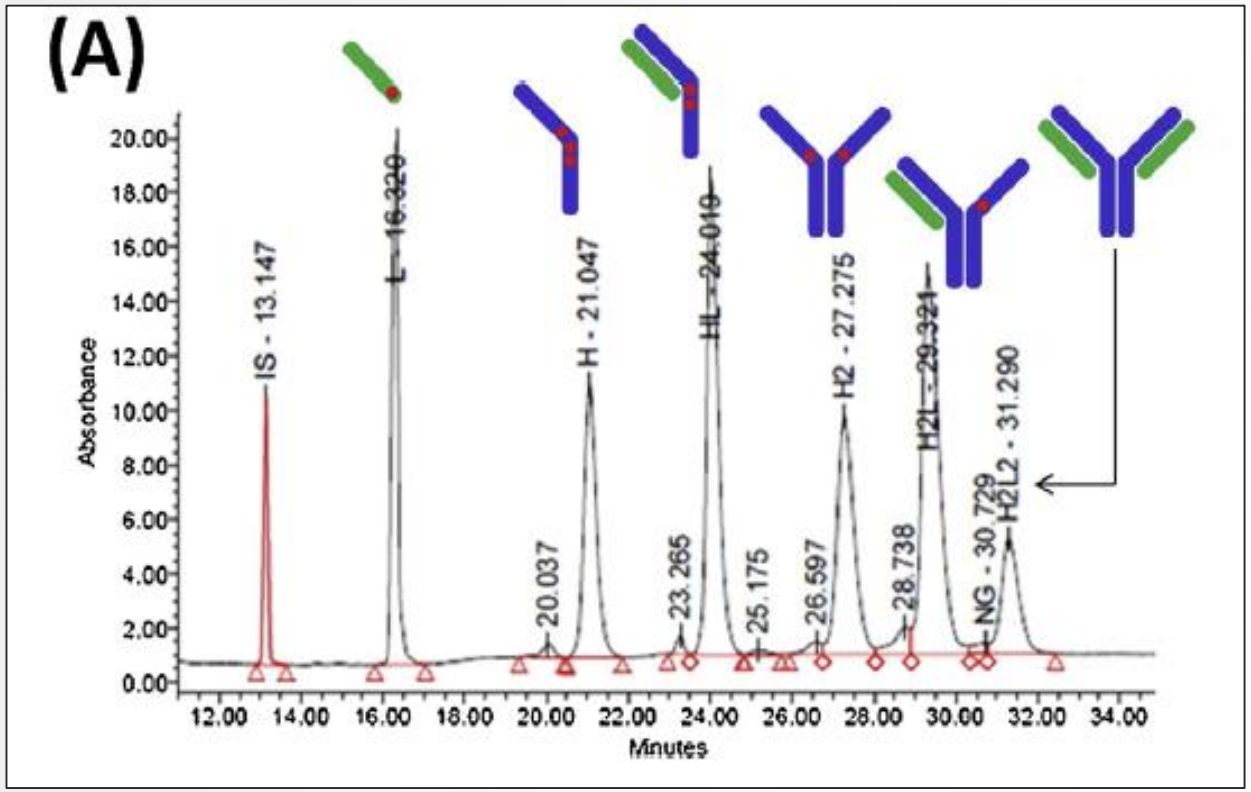


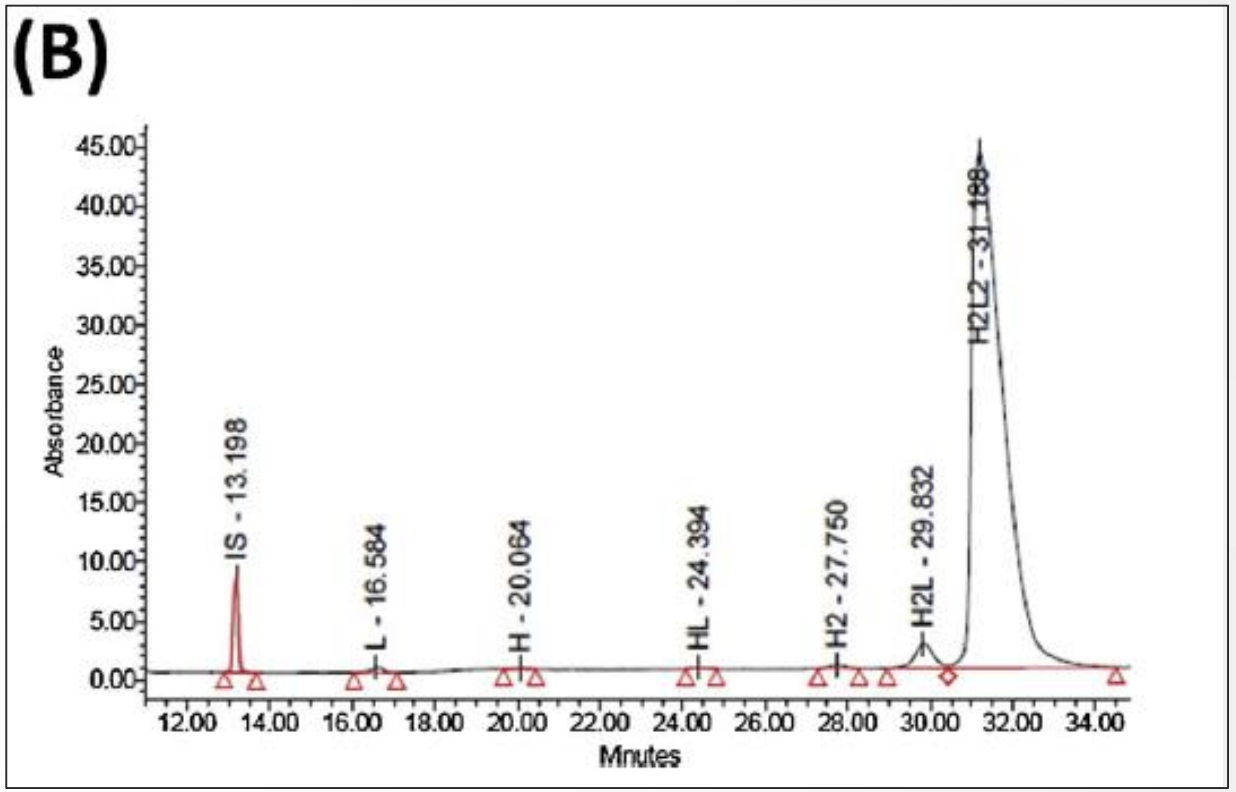
- nrCE-SDS partially reduced IgG profile (denaturing conditions)
- "H2L2" in native conditions (SEC, CEX…)
- Functionally active (ELISA, FcgR, FcRn…)



- Wagner E, Beck A et al, JPBA 2020

nrCE-SDS profiles: Adcetris vs Kadcyla



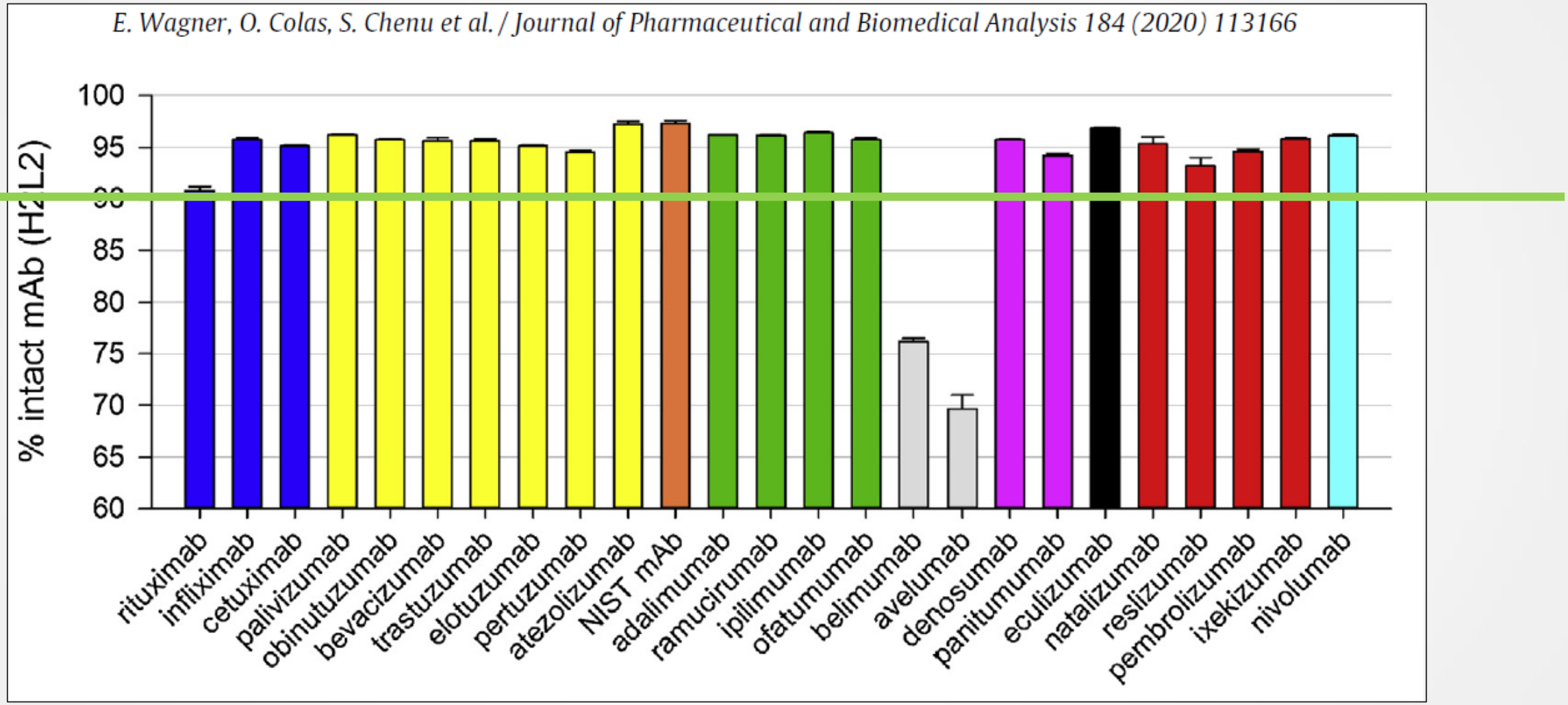


- Adcetris: Hinge LCys-conjugated ADC,
- nr CE-SDS “partially reduced profile”
- “H2L2” in native conditions (SEC, native MS)
- “ Functional” test OK (ELISA, FcgR, FcRn…)

- Kadcyla: Lys-conjugated ADC
- nrCE-SDS comparable to trastuzumab

- Wagner E, Beck A et al, JPBA 2020

nrCE-SDS profiles (H2L2): FDA approved IgGs



- **Standard nrCE-SDS conditions: H2L2 > 90/95% excepted for belimumab and avelumab**

- Wagner E, Beck A et al, JPBA 2020

nrCE-SDS : hIg1Gkappa vs lambda

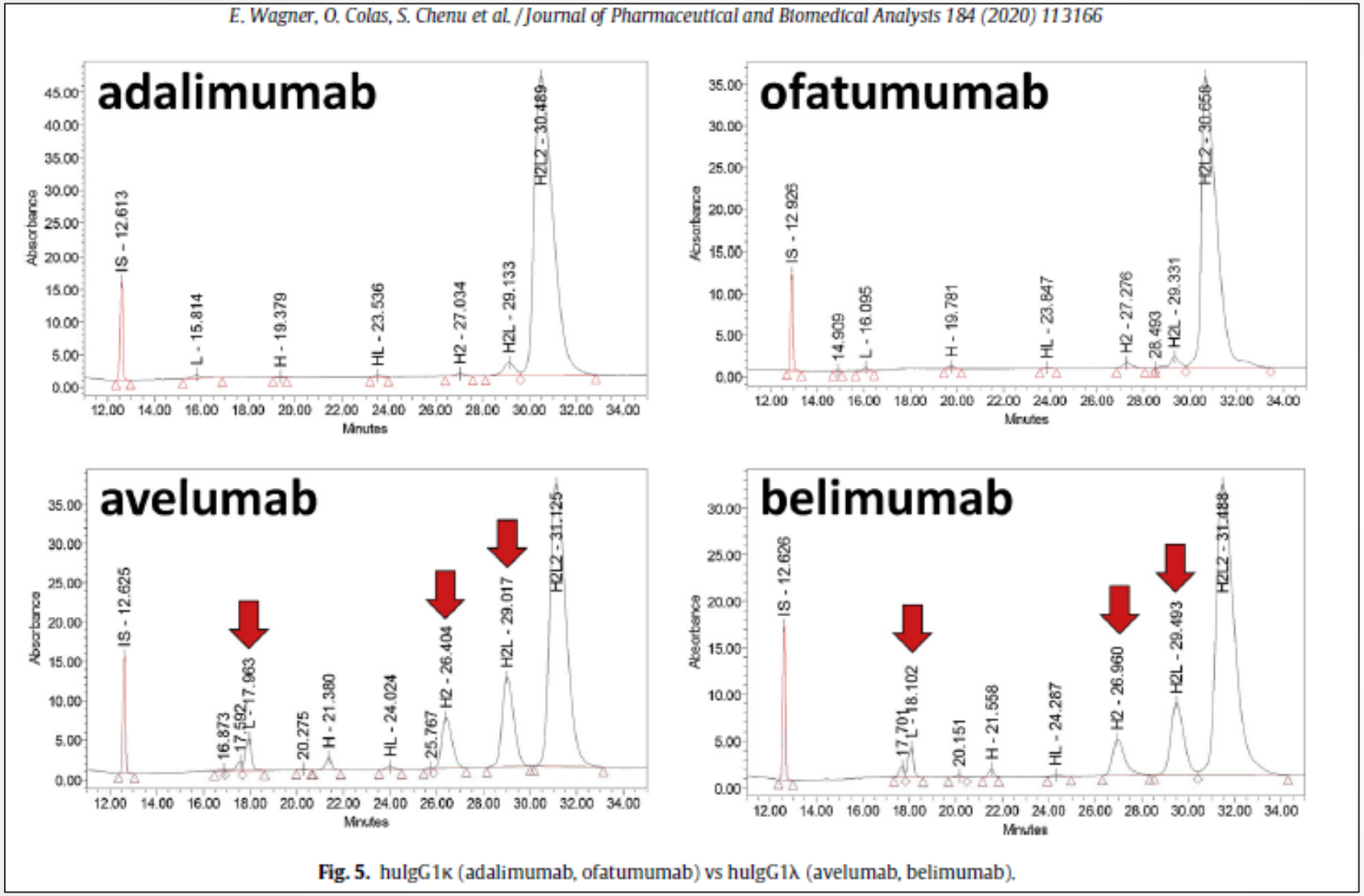


Fig. 5. hulgG1κ (adalimumab, ofatumumab) vs hulgG1λ (avelumab, belimumab).

- **Terminal Ser in lamda light chains have a significant impact on the stability of the interchain L-H binding**
- **This bond weaker than the disulfide bond of the interchain H-H binding**
- **Application of generic nrCE-SDS method for the analysis of huIgG1 lambda may be biased by the sample preparation step (denaturation step at 70◦C for 10 min)**
- **Require further optimization to be successfully applied to this peculiar subclass**

Member of EDQM MAB working group (2017-22)*

MABS
2017, VOL. 0, NO. 0, 1–14
https://doi.org/10.1080/19420862.2017.1386824

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Taylor & Francis Group

REPORT

Check for updates

International standards for monoclonal antibodies to support pre- and post-marketing product consistency: Evaluation of a candidate international standard for the bioactivities of rituximab

Sandra Prior[a], Simon E. Hufton[a], Bernard Fox[a], Thomas Dougall[b], Peter Rigsby[b], Adrian Bristow[b], and participants of the study

[a]Molecular Immunology Section, Biotherapeutics Division, National Institute for Biological Standards and Control, South Mimms, Potters Bar, Hertfordshire, United Kingdom; [b]Technology Development and Infrastructure Division, National Institute for Biological Standards and Control, South Mimms, Potters Bar, Hertfordshire, United Kingdom

- αTNF
- Functional tests (Fab/Fc)
- SEC
- cIEF
- CE-SDS
- CZE

***EDQM (PhEur) +**

- **European National Competent Authorities (eg ANSM, PEI…)**
- **Australia, Canada, South Korea, Taiwan…**
- **AstraZeneca, Lilly, Lonza, Merck, Novartis, Pierre Fabre, Sanofi, UCB**

https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human

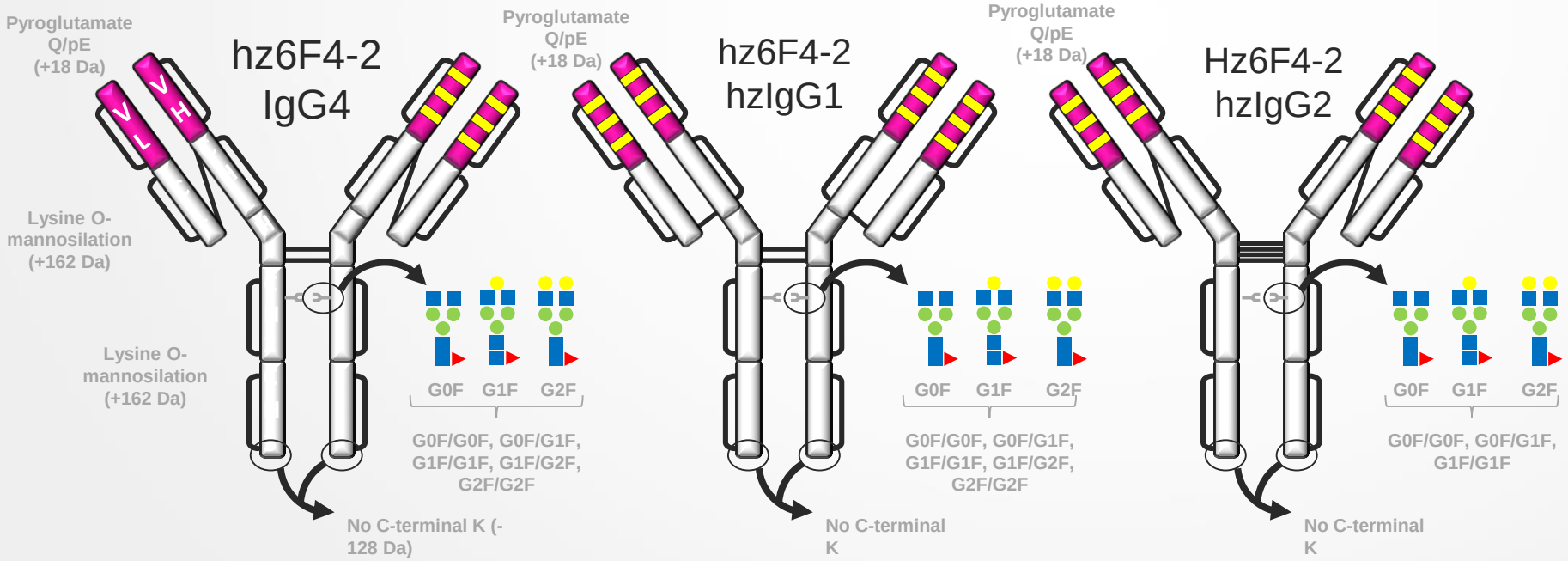
HzIgG1, 2 & 4 subtypes (Structural Bio 2020)

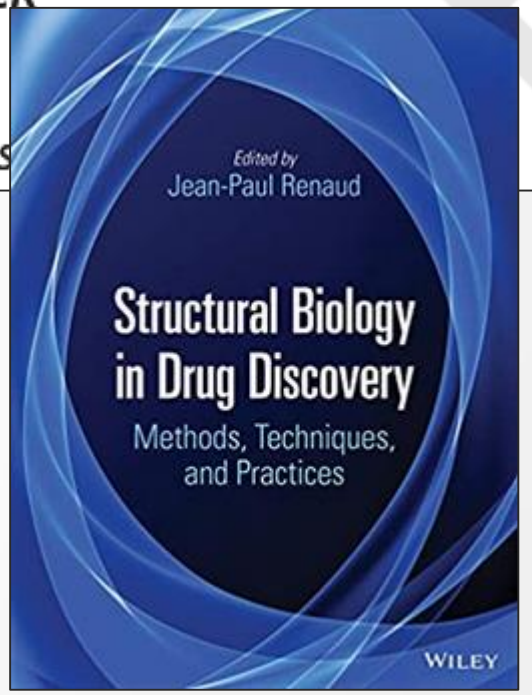
Mass Spectrometry-Based Strategies for Therapeutic Antibodies Extensive Characterization and Optimization (OptimAbs)

Amandine Boeuf[1], François Debaene[2], Daniel Ayoub[1], Hélène Diemer[2], Anthony Ehkirch[2], Elsa Wagner-Rousset[1], Alain Van Dorsselaer[2], Sarah Cianférani[2], and Alain Beck[1]

[1] *Centre d'Immunologie Pierre-Fabre, Saint-Julien en Genevois, France*

[2] *Laboratoire de Spectrométrie de Masse BioOrganique, Institut Pluridisciplinaire Hubert Curien, Université de Strasbourg, CNRS*





Middle-level-IM-MS & CIU (Anal Chem 2020)

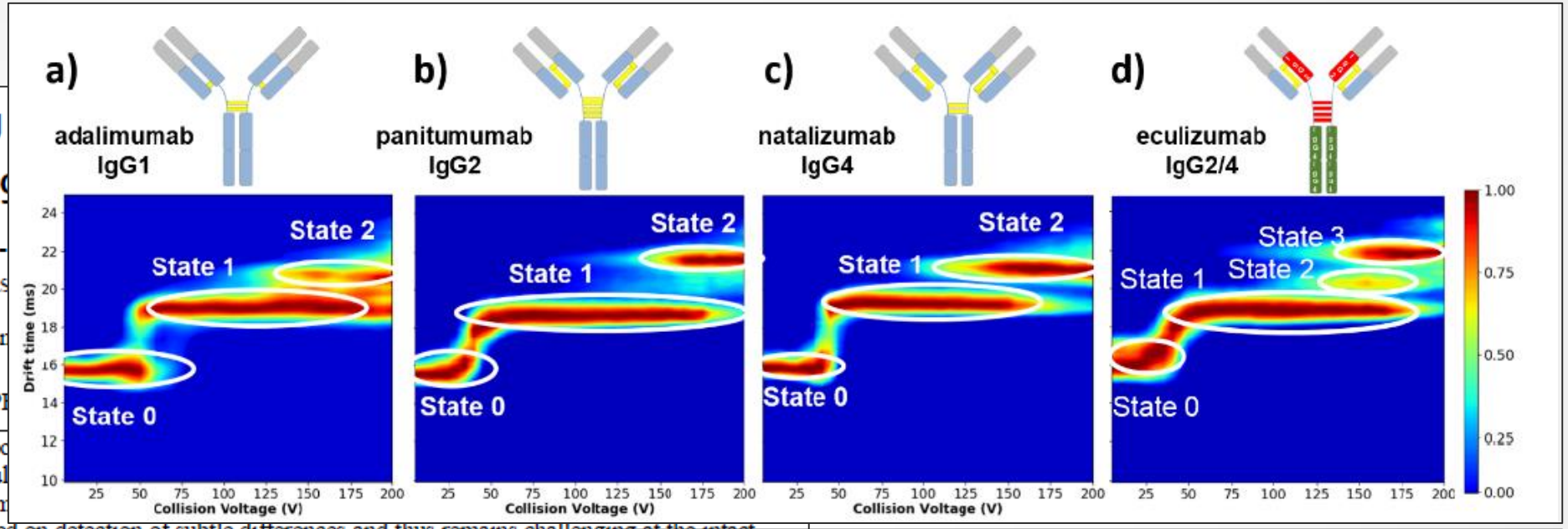
Middle-level IM-MS and CIU immunoglobulin isotype fing

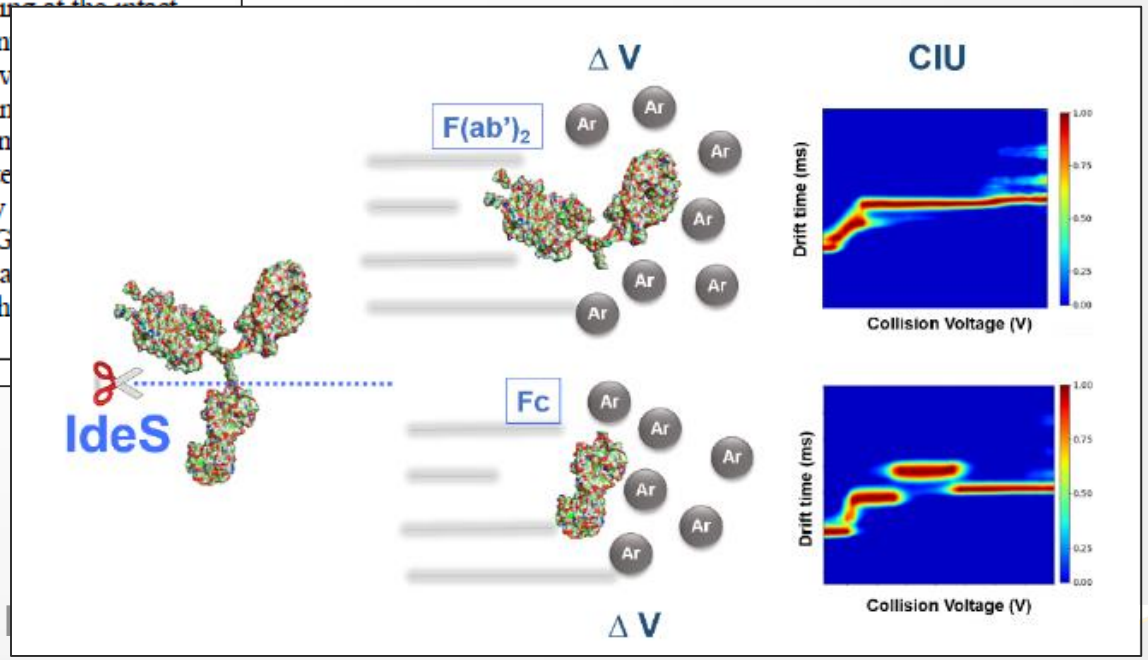
Thomas Botzanowski[1¶], Oscar Hernandez-Desligni[illegible]ère[1], Olivier Colas[2], Jean-François

1 Laboratoire de Spectrométrie de Masse BioOrgan[illegible] bourg, France.

2 IRPF - Centre d'Immunologie Pierre-Fabre (CIP[illegible]

ABSTRACT: Currently approved therapeutic monoc[illegible] types, which differ in their specific inter-chains disul[illegible] for mAb isotyping, among which native ion mobility m[illegible] However, mAb isotyping by these approaches is based on detection of subtle differences and thus remains challengi[illegible] level. We report here on middle-level (after IdeS digestion) IM-MS and CIU approaches to afford better differen[illegible] isotypes. Our method provides simultaneously CIU patterns of F(ab')$_2$ and Fc domains within a single run. Middle-lev[illegible] of F(ab')2 domains enable more reliable classification of mAb isotypes compared to intact level CIU, while CIU fin[illegible] domains are overall less informative for mAb isotyping. F(ab')$_2$ regions can thus be considered as diagnostic don[illegible] specific CIU signatures for mAb isotyping. Benefits of middle-level IM-MS and CIU approaches are further illustrate[illegible] IgG2/IgG4 eculizumab. While classical analytical techniques led to controversial results, middle-level CIU uniquely [illegible] the challenge of eculizumab « hybridicity », highlighting that its F(ab')$_2$ and Fc CIU patterns corresponds to an IgG[illegible] respectively. Altogether, the middle-level CIU approach is more clear-cut, accurate and straightforward for canonica[illegible] complex, engineered next generation mAb formats isotyping. Middle-level CIU thus constitutes a real breakthrough[illegible] protein analysis, paving the way for its implementation in R&D laboratories.





- **O. Hernandez-Alba,**
- **S. Cianférani et al**

Laboratoire de Spectrométrie de LSMBO Masse Bio-Organique

Pierre Fabre

SEC-CIU: workflow automation (Anal Chem 2020)

Analytical Chemistry

Towards automation of Collision Induced Unfo through online Size Exclusion Chromatography Mass Spectrometry.

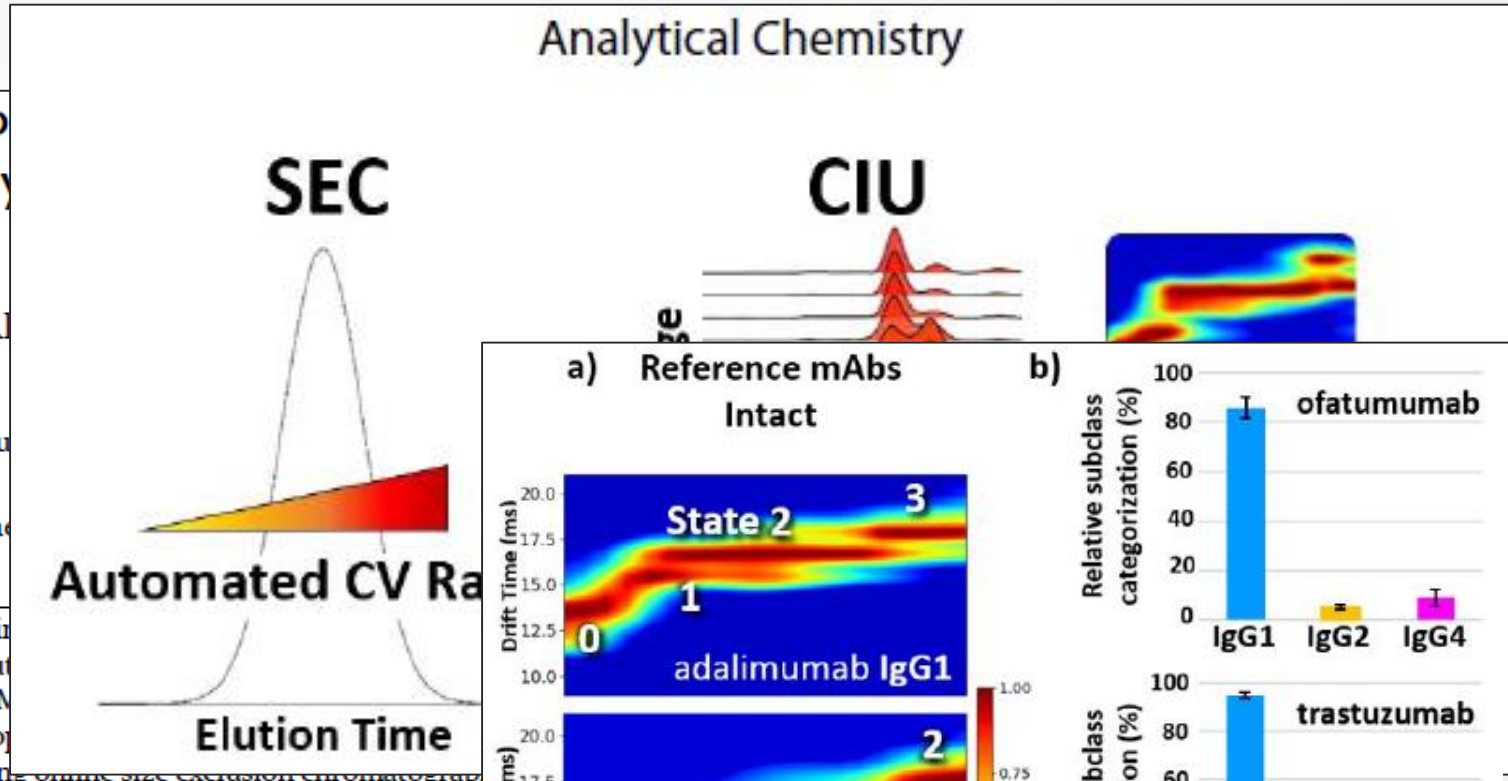
Evolène Deslignière[1], Anthony Ehkirch[1], Thomas Botzanowski[1], Al Alba[1], Sarah Cianférani[1*]

[1] Laboratoire de Spectrométrie de Masse BioOrganique, Université de Strasbou Strasbourg, France.

[2] IRPF - Centre d'Immunologie Pierre-Fabre (CIPF), 74160 Saint-Julien-en-Gen

*Corresponding author: Sarah Cianférani. Email: sarah.cianferani@unistra.fr

ABSTRACT: Ion mobility-based collision induced unfolding (CIU) has gained i unfolding of proteins and their noncovalent complexes, notably for biotherapeu changes of proteins and emerges as an attractive alternative to circumvent poor IM automation for buffer exchange and data acquisition, precluding its wide ado workflow for CIU experiments, from sample preparation to data interpretation usin coupled to native ion mobility mass spectometry (SEC-CIU). Online automated SEC-CIU experiments offer several benef over nanoESI-CIU, among which i) improved and fast desalting compared to manual buffer exchange used for classical C experiments; ii) drastic reduction of the overall data collection time process along with iii) maintaining the number unfolding transitions. We then evaluate the potential of SEC-CIU to distinguish monoclonal antibodies (mAbs) subclass illustrating the efficiency of our method for rapid mAb subclass identification at both intact and middle levels. Finally, demonstrate that CIU data acquisition time can be further reduced either by setting up a scheduled CIU method relying diagnostic trap collision voltages or by implementing mAbs-multiplexed SEC-CIU analyses to maximize informati content in a single experiment. Altogether, our results confirm the suitability of SEC-CIU to automate CIU experimen particularly for the fast characterization of next generation mAb-based products.



- **E. Desligniere, S. Cianférani**

Optimized workflow for MS quantification of Host Cell Proteins (HCPs) (JPR 2020)

Journal of proteome research

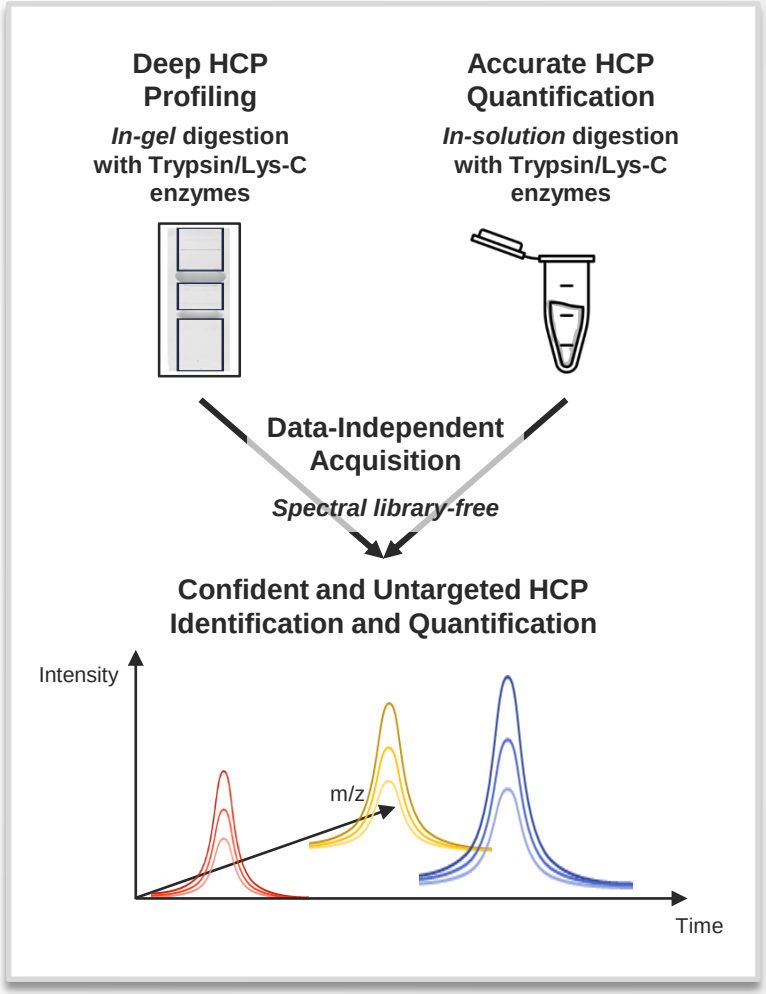
pubs.acs.org/jpr

Article

Optimized Sample Preparation and Data Processing of Data-Independent Acquisition Methods for the Robust Quantification of Trace-Level Host Cell Protein Impurities in Antibody Drug Products

Nicolas Pythoud,[§] Joanna Bons,[§] Geoffroy Mijola, Alain Beck, Sarah Cianférani, and Christine Carapito*

Cite This: https://dx.doi.org/10.1021/acs.jproteome.0c00664 Read Online



- C. Carapito

Laboratoire de Spectrométrie de LSMBO Masse Bio-Organique

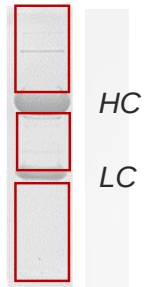
- Adalimumab
- Bevacizumab
- Nivolumab
- Trastuzumab
- NISTmAb

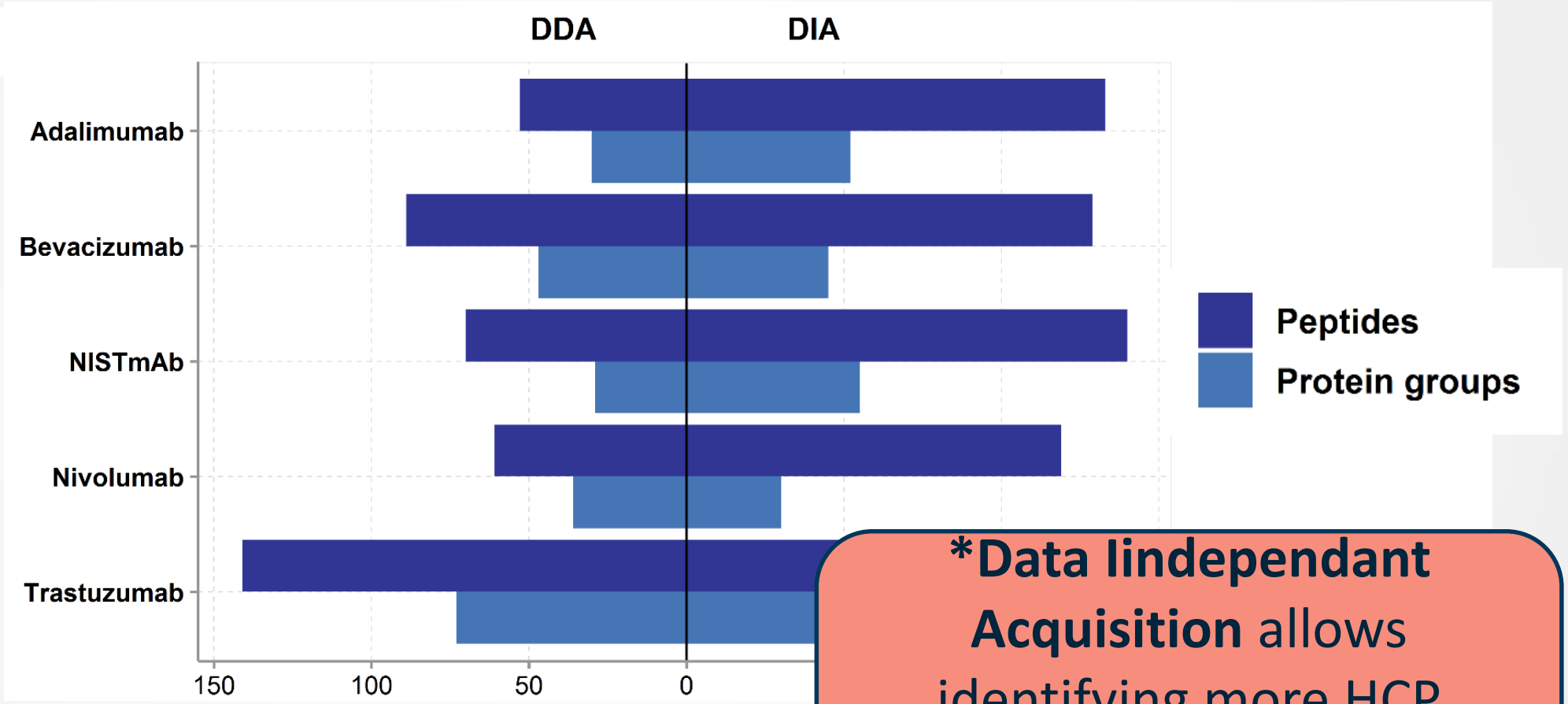
HCP identification in antibody Drug Products

(Data Dependent vs Independant Acquisition)

Identification only

Semi-fractionation





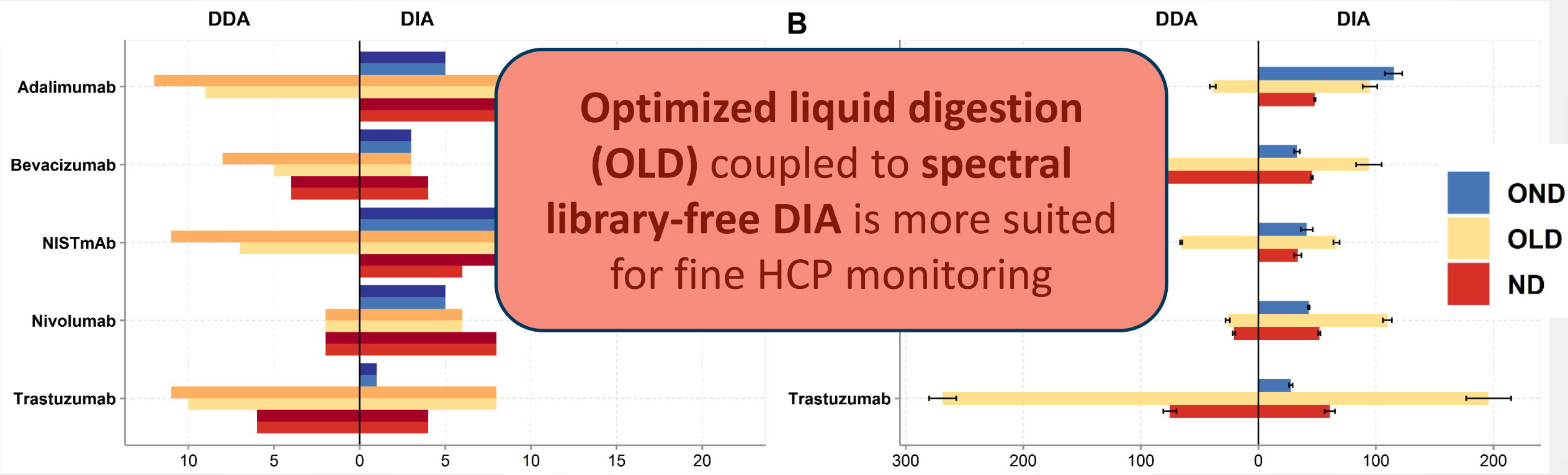
Few 10s of identified HCP

***Data Iindependant Acquisition** allows identifying more HCP
≈ **75%** more **peptides**
≈ **20%** more **protein groups**

- Pythoud N, Bons J, Mijola G, Beck A, Cianferani S, Carapito C, JPR 2020

HCP quantification in antibody Drug Products

Quantification numbers | **Global HCP amount (ppm)**



Optimized liquid digestion (OLD) coupled to **spectral library-free DIA** is more suited for fine HCP monitoring

≈10 quantified HCP

HCP global amount ≈ 100 ppm

- Pythoud N, Bons J, Mijola G, Beck A, Cianferani S, Carapito C. JPR 2020

Interlaboratory Study for Characterizing mAbs by Top-Down and Middle-Down Mass Spec (JASMS 2020)

- Y. Tsybin et al

Journal of the American Society for Mass Spectrometry

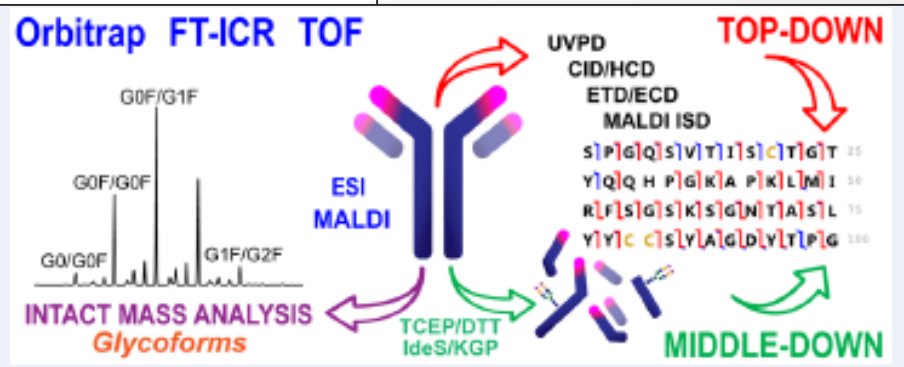
pubs.acs.org/jasms

Interlaboratory Study
Top-Down and Middle

Kristina Srzentić,† Luca Fornelli,†
Lissa C. Anderson, Dina L. Bai, A
Julia Chamot-Rooke, Sneha Chatt
Robert A. D'Ippolito, Mathieu Du
Sylvester Greer, Kim F. Haselman
Matthew V. Holt, Sam Hughes, D
Christian Malosse, Alan G. Marsh
Simone Nicolardi, Ljiljana Paša-T
Wendy Sandoval, Richa Sarin, Ni
Michael R. Shortreed, Lloyd M. Sr
Norelle C. Wildburger, John R. Yates, III, Sung Hwan Yoon, Nicolas L. Young, and Mowei Zhou

ABSTRACT: The Consortium for Top-Down Proteomics (www.topdownproteomics.org) launched the present study to assess the current state of top-down mass spectrometry (TD MS) and middle-down mass spectrometry (MD MS) for characterizing monoclonal antibody (mAb) primary structures, including their modifications. To meet the needs of the rapidly growing therapeutic antibody market, it is important to develop analytical strategies to characterize the heterogeneity of a therapeutic product's primary structure accurately and reproducibly. The major objective of the present study is to determine whether current TD/MD MS technologies and protocols can add value to the more commonly employed bottom-up (BU) approaches with regard to confirming protein integrity, sequencing variable domains, avoiding artifacts, and revealing modifications and their locations. We also aim to gather information on the common TD/MD MS methods and practices in the field. A panel of three mAbs was selected and centrally provided to 20 laboratories worldwide for the analysis: Sigma mAb standard (SiLuLite), NIST mAb standard, and the therapeutic mAb Herceptin (trastuzumab). Various MS instrument platforms and ion dissociation techniques were employed. The present study confirms that TD/MD MS tools are available in laboratories worldwide and provide complementary information to the BU approach that can be crucial for comprehensive mAb characterization. The current limitations, as well as possible solutions to overcome them, are also outlined. A primary limitation revealed by the results of the present study is that the expert knowledge in both experiment and data analysis is indispensable to practice TD/MD MS.

KEYWORDS: *monoclonal antibody, top-down, middle-down, intact mass measurement, mass spectrometry, glycoform*



NISTmAb – Glyco-NIST collab. Study (MCP 2020)

NIST Interlaboratory Study on Glycosyl
Comparison of Results fron

NIST Interlaboratory Study

76 Participants, 103 Datasets

[NIST Interlaboratory Study on Glycosylation Analysis of Monoclonal Antibodies: Comparison of Results from Diverse Analytical Methods.]

De Leoz MLA, Duewer DL, Fung A, Liu L, Yau HK, Potter O, Staples GO, Furuki K, Frenkel R, Hu Y, Sosic Z, Zhang P, Altmann F, Gruber C, Shao C, Zaia J, Evers W, Pangelley S, Suckau D, Wiechmann A, Resemann A, Jabs W, **Beck A**, Froehlich JW, Huang C, Li Y, Liu Y, Sun S, Wang Y, Seo Y, An HJ, Reichardt NC, Ruiz JE, Archer-Hartmann S, Azadi P, Bell L, Lakos Z, An Y, Cipollo JF, Pučić-Baković M, Štambuk J, Lauc G, Li X, Wang PG, Bock A, Hennig R, Rapp E, Creskey M, Cyr T, Nakano M, Sugiyama T, Leung PA, Link-Lenczowski P, Jaworek J, Yang SJ,

Highlights

- A broad-based interlaboratory study of the glycosylation of a reference antibody: NISTmAb.
- 103 reports were received from 76 diverse laboratories worldwide.
- Analysis involved two samples, the NISTmAb and an enzymatically modified sample, enabling within-lab separation of random and systematic errors using the "Youden two-sample" method.
- Consensus values were derived and similar performance across all experimental methods was noted.

Leize-Wagner E, Maier S, Zeck A, Heck AJR, Yang Y, Haselberg R, Yu YQ, Alley W, Leone JW, Yuan H, Stein SE.

Mol Cell Proteomics. 2019 Oct 7. pii: mcp.RA119.001677. doi: 10.1074/mcp.RA119.001677. [Epub ahead of print]
PMID: 31591262 **Free Article**

- **Leoz L, Duewer D, Beck A & 100+ scientists. Mol Cell Proteomics 2020**

Therapeutic Fc-fusion proteins

Received: 3 July 2020 | Revised: 27 August 2020 | Accepted: 7 September 2020

DOI: 10.1002/jssc.202000765

JOURNAL OF SEPARATION SCIENCE

REVIEW ARTICLE

Therapeutic Fc-fusion proteins: Current analytical strategies

Bastiaan L. Duivelshof[1,2] | **Amarande Murisier**[1,2] | **Julien Camperi**[1,2] | **Szabolcs Fekete**[1,2] | **Alain Beck**[3] | **Davy Guillarme**[1,2] | **Valentina D'Atri**[1,2]

[1] School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland

[2] Institute of Pharmaceutical Sciences of Western Switzerland (ISPSO), University of Geneva, Geneva, Switzerland

[3] IRPF - Centre d'Immunologie Pierre-Fabre (CIPF), Saint-Julien-en-Genevois, France

Correspondence
Valentina D'Atri, School of Pharmaceutical Sciences, Institute of Pharmaceutical Sciences of Western Switzerland, University

Fc-Fusion proteins represent a successful class of biopharmaceutical products, with already 13 drugs approved in the European Union and United States as well as three biosimilar versions of etanercept. Fc-Fusion products combine tailored pharmacological properties of biological ligands, together with multiple functions of the fragment crystallizable domain of immunoglobulins. There is a great diversity in terms of possible biological ligands, including the extracellular domains of natural receptors, functionally active peptides, recombinant enzymes, and genetically engineered binding constructs acting as cytokine traps. Due to their highly diverse structures, the analytical characterization of Fc-Fusion proteins is far more complex than that of monoclonal antibodies and requires the use and development of additional product-specific methods over conventional generic/platform methods. This can be explained, for example, by the presence of numerous sialic acids, leading to high diversity in terms of iso-

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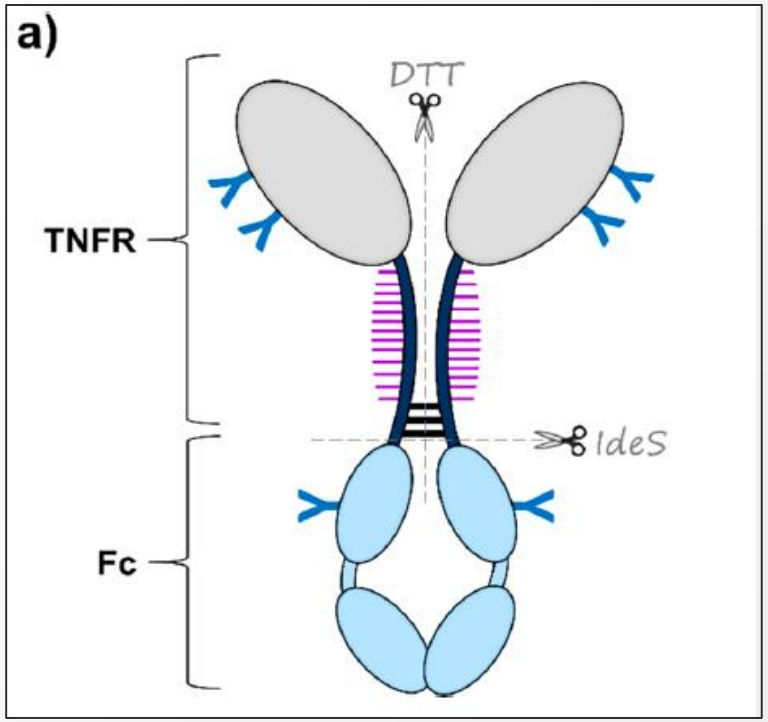
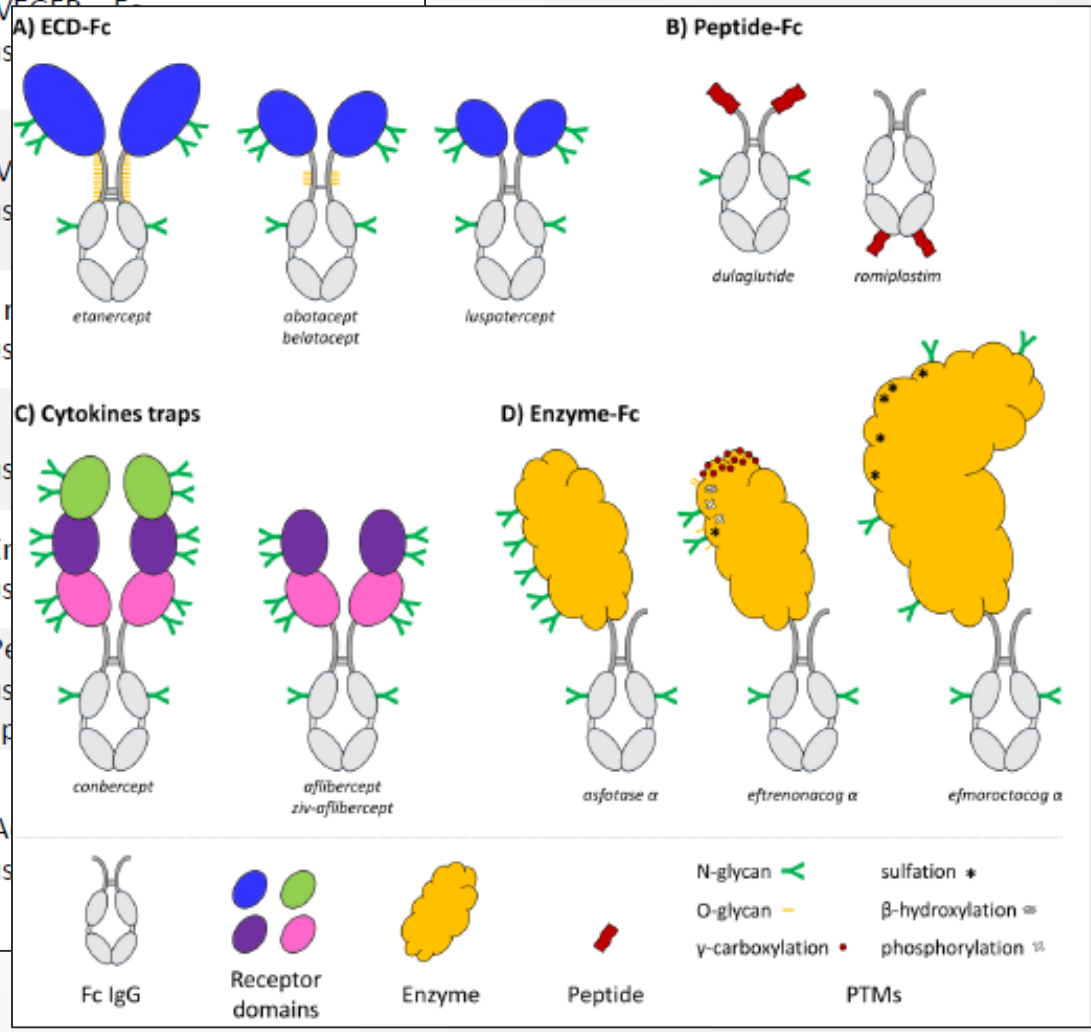


Therapeutic Fc-fusion proteins: current analytical strategies (JSS 2020)

1998	etanercept (Enbrel®)	ECD of the human 75 kDa (p75) tumor necrosis factor receptor (TNFR) fused to human IgG1 Fc	TNFR – Fc fusion protein	TNF-α
2003; withdrawn in 2011	alefacept (Amevive®)			
2005	abatacept (Orencia®)			
2008	rilonacept (Arcalyst®)			
2008	romiplostim (Nplate®)			
2011	belatacept (Nulojix®)			
2011	aflibercept (Eylea®)			
2012	ziv-aflibercept (Zaltrap®)	ECDs of human vascular endothelial growth factor (VEGF) receptor 1 (domain 2) and receptor 2 (domain 3) fused to human IgG1 Fc	V fus	
2013 (by CFDA)	conbercept (Lumitin®)	ECDs of human vascular endothelial growth factor (VEGF) receptor 1 (domain 2) and receptor 2 (domains 3 and 4) fused to human IgG1 Fc	V fus	
2014	efmoroctocog α (Elocta®)	Single molecule of recombinant Factor VIII (rFVIII) fused to human IgG1 Fc	fus	
2014	eftrenonacog α (Alprolix®)	Single molecule of recombinant Factor IX (rFIX) fused to human IgG1 Fc	fus	
2015	asfotase α (Strensiq®)	Catalytic domain of tissue-nonspecific alkaline phosphatase (TNSALP) fused to the human IgG1 Fc	Er fus	
2015	dulaglutide (Trulicity®)	Dipeptidyl peptidase-IV-protected glucagon-like peptide (GLP-1) fused to human IgG4 Fc	Pe fus (p	
2019	luspatercept (Reblozyl®)	Modified ECD of activin receptor type IIB (actRIIb) fused to human IgG1 Fc	A fus	



- **V. D'Atri et al**
- **Duivelshof B, Beck A, Guillarme D, D'Atri V et al, 2020**

ADC Landscape (Pharmaceuticals 2020)

pharmaceuticals

MDPI

Review

Antibody–Drug Conjugates: The Last Decade

Nicolas Joubert [1,*], Alain Beck [2], Charles Dumontet [3,4] and Caroline Denevault-Sab

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Abstract: An armed antibody (antibody–drug conjugate or ADC) is a vectorized
which results from the grafting of a cytotoxic agent onto a monoclonal antibody v
constructed spacer arm. ADCs have made considerable progress in 10 years. Wh
gemtuzumab ozogamicin (Mylotarg®) was used clinically, in 2020, 9 Food and Drug
(FDA)-approved ADCs are available, and more than 80 others are in active clini
review will focus on FDA-approved and late-stage ADCs, their limitations includi
and associated resistance mechanisms, as well as new emerging strategies to addr
and attempt to widen their therapeutic window. Finally, we will discuss their co

- 9 ADC vs 2 BsAbs FDA approv.
- Mature class of oncology drugs

Table 1. Antibody–drug conjugates (ADCs) approved by the Food and Drug Administration (FDA), in advanced clinical trials (Phase III or pivotal phase II) or recently stopped.

Company	ADC (Cytotoxic)	Isotype and Target	Indication/Approval Date (Trade Name)/Clinical Status
Pfizer	gemtuzumab ozogamicin (CAL)	IgG4 CD33	2000–2010/2017 AML (Mylotarg®)
Seattle Genetics	brentuximab vedotin (AUR)	IgG1 CD30	2011 ALCL and Hodgkin lymphoma (Adcetris®)
Roche	trastuzumab emtansine (MAY)	IgG1 HER2+	2013 metastatic HER2+++ breast cancer (Kadcyla®) **
Pfizer	inotuzumab ozogamicin (CAL)	IgG4 CD22	2017 ALL and CLL (Besponsa®)
Roche	polatuzumab vedotin (AUR)	IgG1 CD79b	2019 DLBCL (Polivy®)
Seattle Genetics	enfortumab vedotin (AUR)	IgG1 Nectin 4	2019 urothelial cancer (Padcev®) **
Daiichi Sankyo	trastuzumab deruxtecan (EXA)	IgG1 HER2+	2019 metastatic HER2+++ breast cancer (Enhertu®) **
Immunomedics	sacituzumab govitecan (IRI)	IgG1 TROP-2	2020, metastatic TNBC (Trodelvy®) **
GSK	belantamab mafodotin (AUR, MMAF)	IgG1afuc BCMA	2020, multiple myeloma (Blenrep®)

Open access: https://www.mdpi.com/1424-8247/13/9/245/pdf

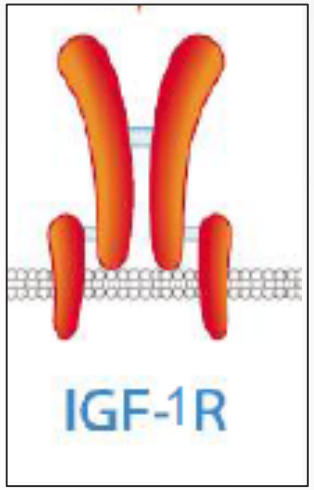
IGFR-1 ADC: W0101 (MCT 2020)

Pierre Fabre

MOLECULAR CANCER THERAPEUTICS | LARGE MOLECULE THERAPEUTICS

Efficacy of the Antibody–Drug Conjugate W0101 in Preclinical Models of IGF-1 Receptor Overexpressing Solid Tumors

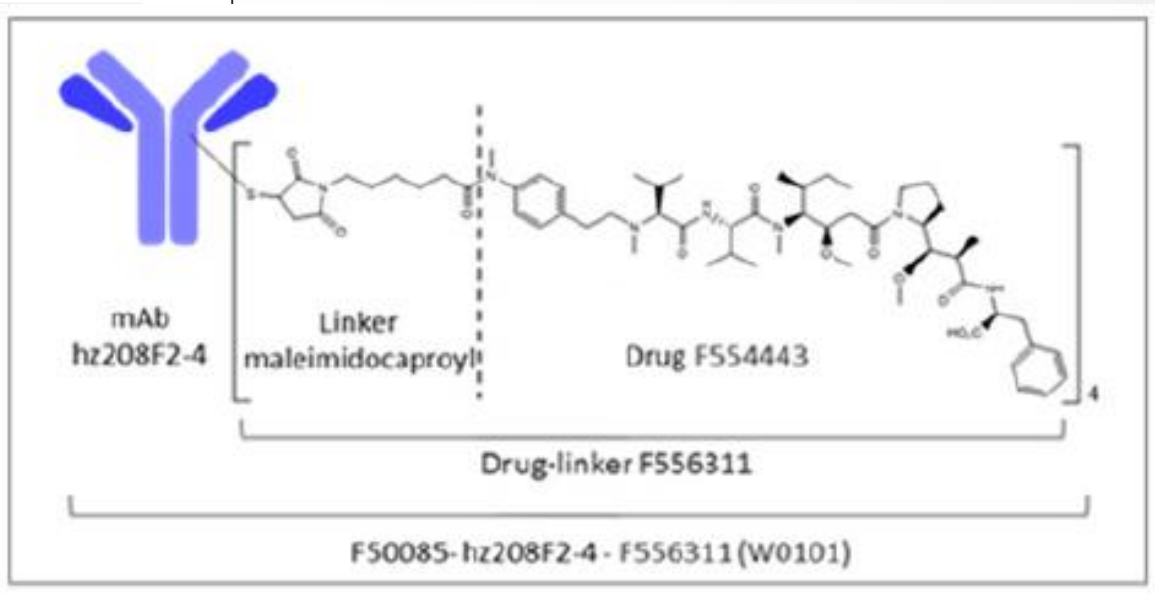
Barbara Akla[1], Matthieu Broussas[1], Noureddine Loukili[1], Alain Robert[1], Charlotte Beau-Larvor[1], Martine Malissard[1], Nicolas Boute[1], Thierry Champion[1], Jean-Francois Haeuw[1], Alain Beck[1], Michel Perez[2], Cyrille Dreyfus[1], Mariya Pavlyuk[2], Eric Chetaille[2], and Nathalie Corvaia[1]



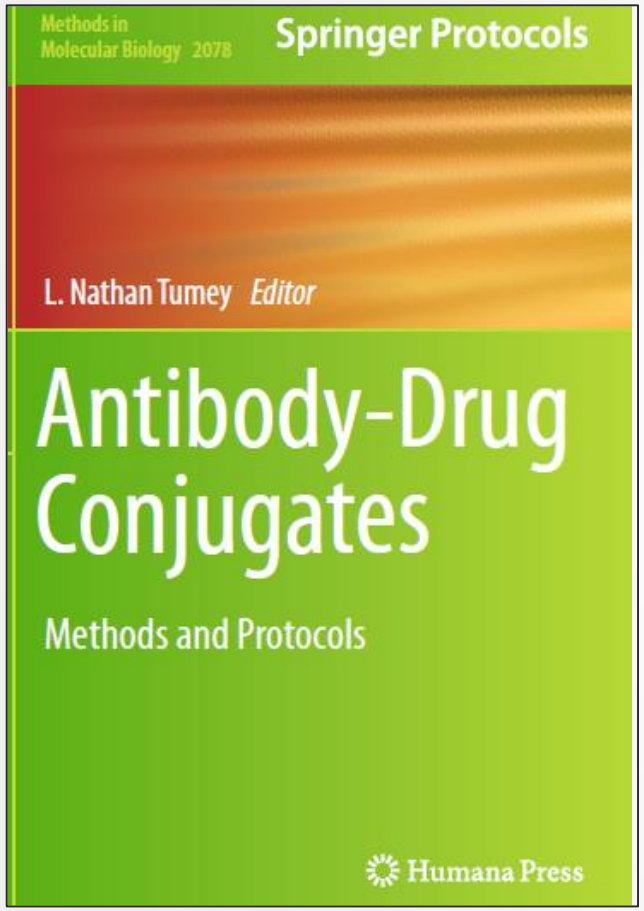
PhI/II trial
NCT03316638
Solid tumors

ABSTRACT

The insulin-like growth factor type 1 receptor (IGF-1R) is important in tumorigenesis, and its overexpression occurs in numerous tumor tissues. To date, therapeutic approaches based on mAbs and tyrosine kinase inhibitors targeting IGF-1R have only shown clinical benefit in specific patient populations. We report a unique IGF-1R–targeted antibody–drug conjugate (ADC), W0101, designed to deliver a highly potent cytotoxic auristatin derivative selectively to IGF-1R overexpressing tumor cells. The mAb (hz208F2-4) used to prepare the ADC was selected for its specific binding properties to IGF-1R compared with the insulin receptor, and for its internalization properties. Conjugation of a novel auristatin derivative drug linker to hz208F2-4 did not alter its binding and internalization properties. W0101 induced receptor-dependent cell cytotox when applied to various cell lines overexpressing IG did not affect normal cells. Efficacy studies were c several mouse models expressing different levels o determine the sensitivity of the tumors to W0 induced potent tumor regression in certain mo Interestingly, the potency of W0101 correlated with sion level of IGF-1R evaluated by IHC. In an M cancer model with high-level IGF-1R expression, a tion of W0101 3 mg/kg led to strong inhibition of tu W0101 provides a potential new therapeutic option overexpressing IGF-1R. A first-in-human trial o currently ongoing to address clinical safety.



ADCs: Methods & Protocols (N. Thumey, MiMB 2020)



Check for updates

Chapter 12

Drug Lo
or IdeS

Elsa Wag
Sabine H

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Chapter 13

Analysis o

Oscar Herna
and Sarah C

Check for updates

Chapter 18

Characterization of the Primary Structure of Cysteine-Linked Antibody-Drug Conjugates Using Capillary Electrophoresis with Mass Spectrometry

Josiane Saadé, Rabah Gahoual, Alain Beck, Emmanuelle Leize-Wagner, and Yannis-Nicolas François

GlyGLICK ADCs (Genovis): HILIC-MS (Anal Chem 2020)

Glycan-mediated technology for obtaining homogeneous site-specific conjugated antibody-drug conjugates: synthesis and analytical characterization by using complementary middle-up LC/HRMS analysis

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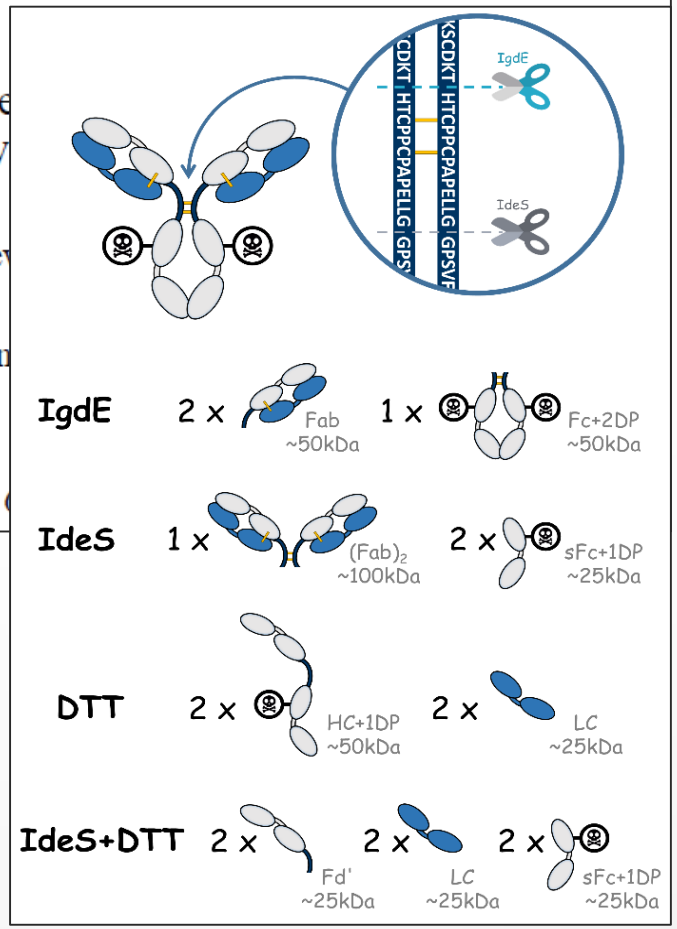

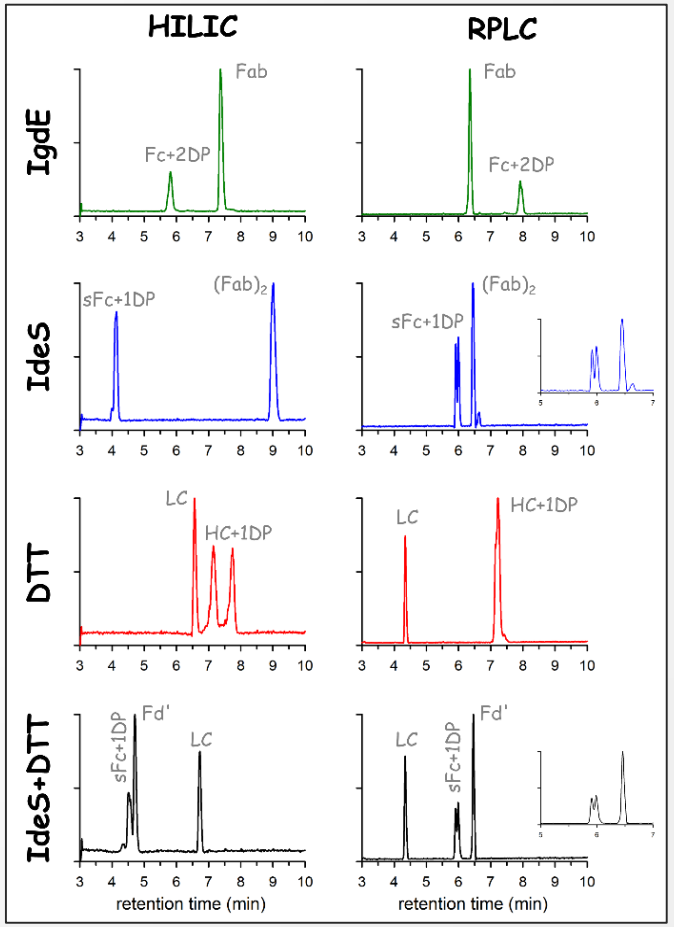

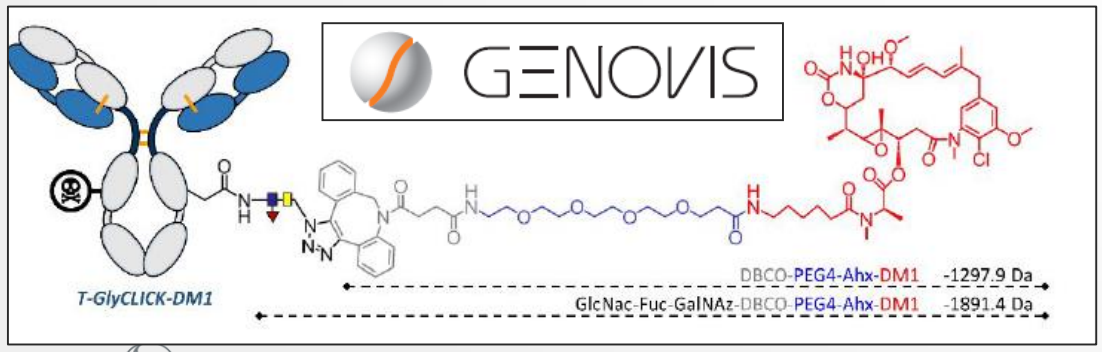

Cutting-edge analytical & structural network: antibody-based drugs (2005-20: +220 papers*, +180 talks)**

OptimAbs

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AB Sciex

Agilent Technologies

Beckman Coulter

usp

PEAKS AB Antibody Characterization Service http://www.bioinfor.com/antibodyservice/

affilogic

World Health Organization

MAB Working Party

edqm European Directorate for the Quality of Medicines & HealthCare

ansm Agence nationale de sécurité du médicament et des produits de santé

NIST National Institute of Standards and Technology U.S. Department of Commerce

Chairman COSSF

MAB DESIGN

Associate Editor

mAbs

* IF51, +11,000 citations

** Open research & innovation

Thank you for your attention





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- E. Wagner, O. Colas, MC. Janin, M. Excoffier
- N. Boute, T. Champion, M. Malissard
- B. Akla, C. Beau-Larvor, N. Loukili et al
- N. Corvaïa, JF Haeuw, P. Lowe et al

CRDPF, Toulouse, FR

- C. Lasserre, N. Regent, MF. Laliberté
- M. Nicolas, L. Liorzou
- M. Pavlyuk, P. Ferre, E. Chetaille et al
- J. Desrivot, F. Lafforgue et al

CEPC, Castres, FR

- S. Couffin, A. Grondin, MO. Roy et al

PF CDMO Biologics, St-Julien-en-Genevois, FR

- M. Culie, S. Chenu, A. Cousinet et al
- S. Demare, C. Truchy, G. Mijola et al
- S. Lauthier, J. Lhermite et al
- C. Borgne, C. Maupas

+ many more (see publications)

Pharma School, University of Geneva, CH (47 papers)

- D. Guillarme, S. Fekete, V. D'Atri, JL. Veuthey et al

LSMBO, University of Strasbourg, FR (30 papers)

- S. Cianferani, O. Hernandez, A. Ehkirch, S. Erb et al

LSMIS, University of Strasbourg, FR (18 papers)

- Y. François, R. Gahoual et al

EPFL/SpectroSwiss, CH/ Thermo, CH (7 papers)

- Y. Tsybin, K. Srzentić, L. Fornelli, D. Ayoub et al

Gustavus Adolphus College, MN/ Agilent (7 papers)

- D. Stoll et al

University of Lyon, CH (4 papers)

- S. Heinisch et al

Waters, FR, UK, US (LC-MS prototypes) (2 papers)

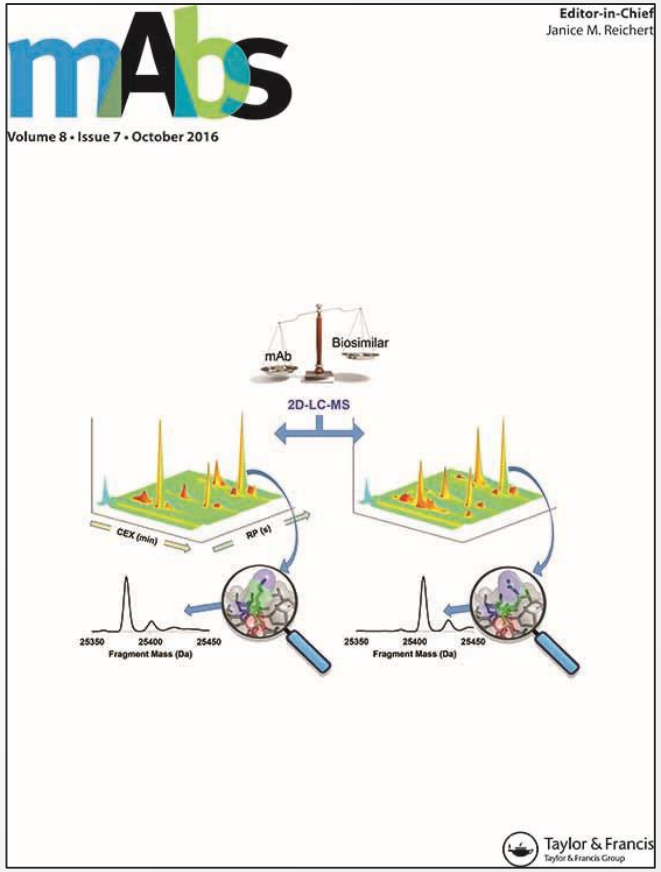
- W. Chen, D. Lascoux, L. Denbigh, J. Gebler et al

Bruker, GER (LC-MS prototypes) (2 papers)

- D. Suckau, A. Resemann, W. Jabs et al

mAbs: 2009-2020 (Open access)

2019 Impact Factor: 4.634



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