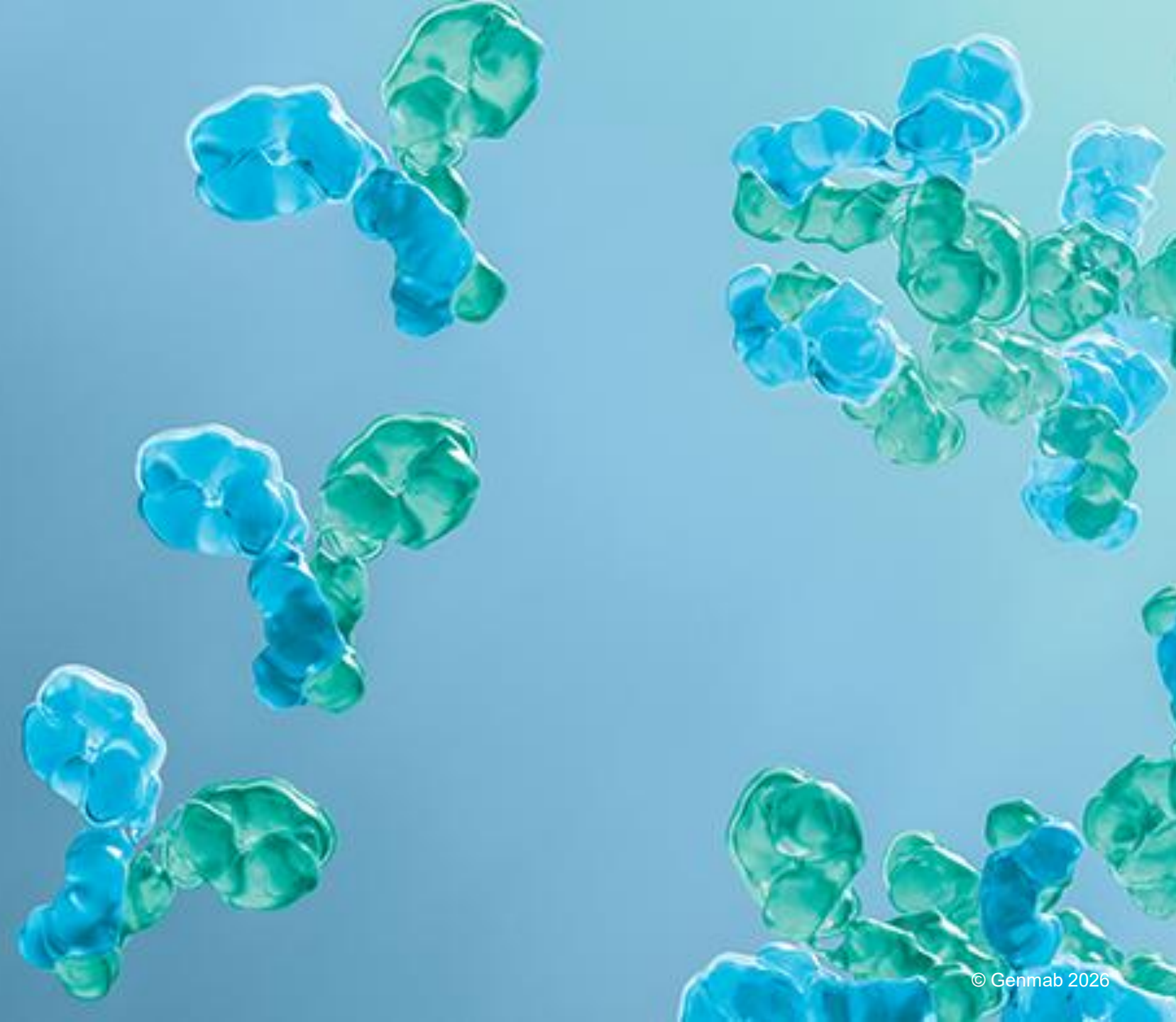
Genmab

From Bench to Bedside: How CMC Brings Biologics to Patients



BCF 2026
Leonardo Rosado

Agenda

1. Genmab
2. Personal journey
3. Drug Discovery and Chemistry Manufacturing and Controls
4. Personal remarks

Genmab

Genmab At-A-Glance

A Leading International Biotechnology Company

Who We Are:

Genmab is focused on the creation, development and commercialization of differentiated antibody therapeutics for the treatment of cancer and other serious diseases

- Founded in 1999

- Dual-listed
- NASDAQ Copenhagen & Nasdaq Global Select Market

- **HQ and Technical Operations**: Denmark
- **Global R&D Center:** Netherlands
- **R&D, Commercial, Field-based:** USA, Japan, Germany, UK & France
- **R&D:** China

- 8 approved medicines incorporating Genmab's innovation
- Over 45 INDs
- ~7 products in clinical development

- More than 3,000+ team members

Genmab

Genmab's Future Growing Organization & Growing Presence

Cambridge MA, US
- Late-Stage Clinical Development
- Corporate Functions

Princeton, NJ, US
- Translational and Quantitative Sciences
- Clinical Development
- Development Operations
- U.S. Market Operations
- Corporate Functions

Utrecht, The Netherlands
- Discovery and Antibody Research
- Translational and Quantitative Sciences
- Development Operations
- Corporate Functions

Copenhagen, Denmark
- Headquarters
- Chemistry, Manufacturing and Controls (CMC)
- Development Operations
- Quality Control Laboratory
- Corporate Functions

Tokyo, Japan
- Development Operations
- Japan Market Operations
- Corporate Functions

Suzhou, China
Shanghai, China
- Early-stage R&D
- Chemistry, Manufacturing and Controls (CMC)
- Corporate Functions

Regional Field Offices
- Munich, Germany
- London, United Kingdom
- Paris, France

Genmab

Our Solid Foundation is Built on ....

Royalty Medicines Portfolio

- TIVDAK®[1]
- EPKINLY®[2]/TEPKINLY®[2]
- DARZALEX®/ DARZALEX *FASPRO*®[3]
- Kesimpta®[4]
- TEPEZZA®[5]
- RYBREVANT®[3]
- TECVAYLI®[3]
- TALVEY®[3]
- BIZENGRI®[6]

Our Own Clinical Pipeline

- Epcoritamab[2]
- Tisotumab vedotin[1]
- Rina-S®
- Petosemtamab
- GEN1059 (BNT314)
- GEN1057
- GEN3018
- GEN1079

Technologies & Pre-Clinical

- DuoBody®
- ADC technology
- Biclonics®
- HexaBody ®
- DuoHexaBody®
- HexElect®
- Rich Pre-Clinical Pipeline

Solid Financial Base Significant Potential

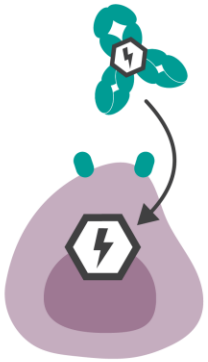
Fueling Innovative Clinical Pipeline

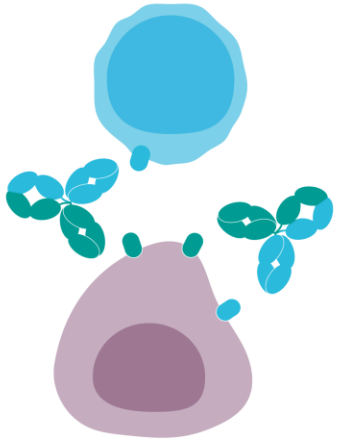
R&D Engine

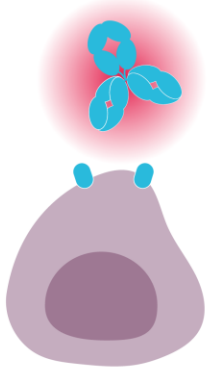
[1]Co-development Genmab & Pfizer; [2]Co-development Genmab & AbbVie; [3]J&J Biotech, Inc.; [4]Novartis; [5]Amgen; [6]Partner Therapeutics

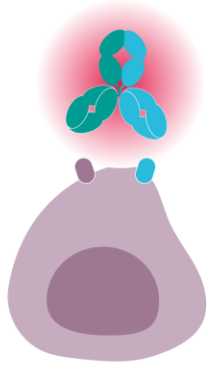
Genmab's Proprietary & Licensed Antibody Technology Innovation Creates Differentiated Antibody Products

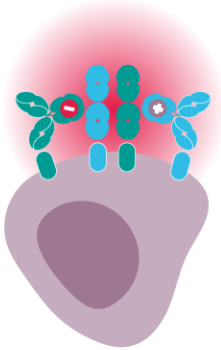
Naked IgG	ADC	Bispecific IgG	Enhanced IgG	Enhanced Bispecific IgG	Selective Enhanced IgG
HuMAb-Mouse® (Inlicensing, Medarex)	Drug/linker	DuoBody®	HexaBody®	DuoHexaBody®	HexElect®





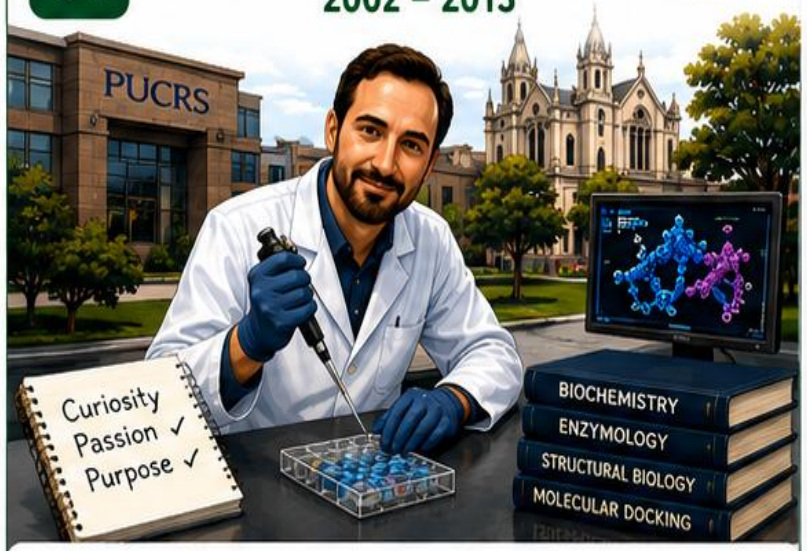






Personal Journey

01 PORTO ALEGRE, BRAZIL
2002 – 2013



STUDENT • BSc • MSc • PhD

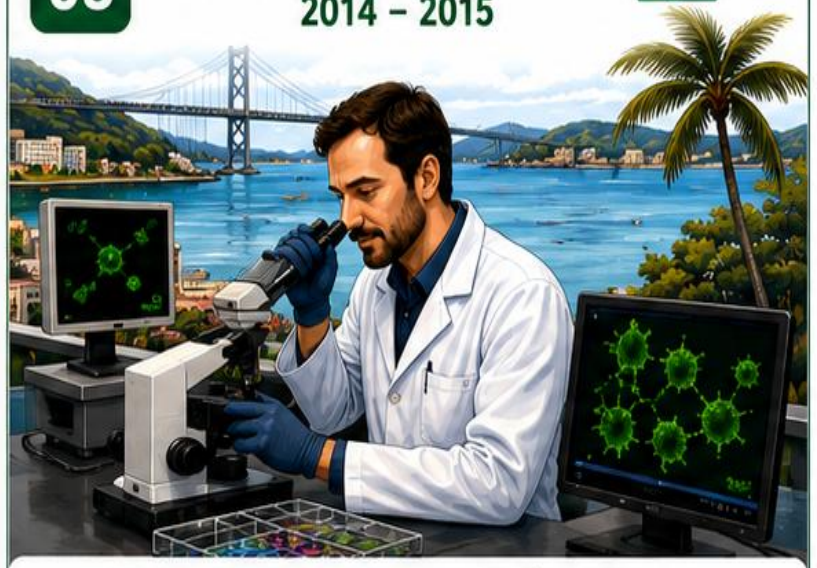
- BSc in Biological Sciences – PUCRS
- CIENTEC – Research Assistant
- MSc & PhD in Molecular Pharmacology
- Tuberculosis drug target discovery
- Enzymology, protein purification, biochemical assays, molecular docking

02 MIT, USA
2013 – 2014

POSTDOCTORAL RESEARCH ASSOCIATE

- Chemical Biology & Structural Studies
- Ribonucleotide Reductase (RNR)
- Protein structure, kinetics and thermodynamics
- International collaboration

03 FLORIANÓPOLIS, BRAZIL
2014 – 2015



RESEARCH MEMBER – UFSC / INCT

- Structural Biology & Bioimaging
- Protein characterization
- Post-translational modifications
- Assay development & small-molecule screening

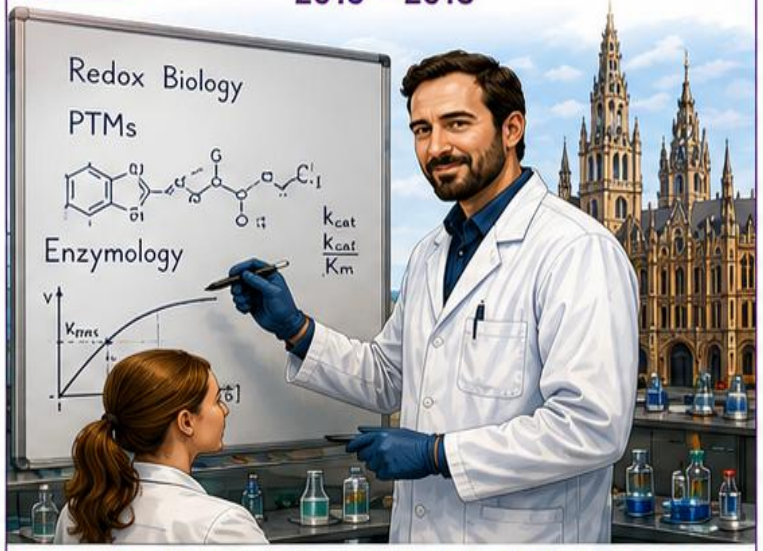
MY JOURNEY

PORTO ALEGRE
BRAZIL

CAMBRIDGE, MA
USA

FLORIANÓPOLIS
BRAZIL

04 BRUSSELS, BELGIUM
2015 – 2018



POSTDOCTORAL RESEARCH ASSOCIATE
VIB & VRIJE UNIVERSITEIT BRUSSEL (VUB)

- Redox biology & protein modifications
- Biochemical, biophysical and microbiological approaches
- Mentoring students and scientific leadership
- International collaborations

05 LEUVEN, BELGIUM
2018 – 2020

SCIENTIST // PROJECT MANAGER
KBI BIOPHARMA

- Analytical & formulation development
- GMP stability testing (DS & DP)
- SOPs, validations, CAPA, deviations
- Built the laboratory & obtained GMP license in 9 months
- Led small teams & client projects

06 NETHERLANDS
2020 – PRESENT

DIRECTOR & HEAD OF
DRUG PRODUCT DEVELOPMENT
GENMAB

- Leading Drug Product Development
- CMC strategy & team leadership
- Bispecific antibodies & ADCs
- Managing global teams (35+ FTE)
- Building laboratories & capabilities
- Driving innovation & delivering better medicines

MY JOURNEY CONTINUES

Drug Discovery and Chemistry Manufacturing and Controls

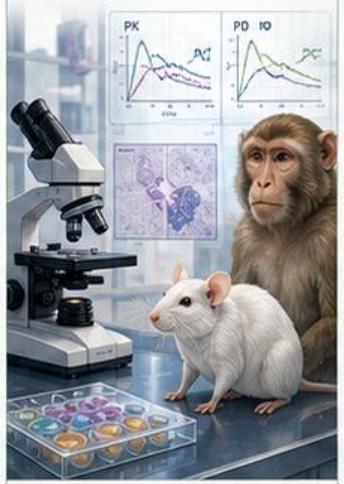
1 DISCOVERY

Identify targets and discover & engineer antibody candidates.

- Target identification & validation
- Antibody discovery (phage display, single B cell, transgenic mice)
- Screening & lead selection
- Engineering & optimization

2 PRECLINICAL

Evaluate safety, efficacy and developability in the lab and in animal models.



- *In vitro* characterization
- Efficacy in animal models
- Toxicology & safety
- PK/PD & immunogenicity
- CMC & GMP manufacturing for clinical supply

3 FIRST-IN-HUMAN (PHASE I)

First administration in humans to evaluate safety and dosing.

- Safety & tolerability
- Dose escalation
- PK/PD
- Biomarker activity

4 PHASE II

Evaluate efficacy and further assess safety in patients.

- Proof of concept
- Dose optimization
- Efficacy signals
- Expanded safety

5 PHASE III

Confirm efficacy and safety in large patient populations across multiple sites.

- Large, randomized studies
- Compare to standard of care
- Confirm efficacy & safety
- Support for registration

6 REGULATORY APPROVAL

Submit data to regulatory agencies for review and approval.

- Regulatory submission (BLA/MAA)
- Agency review
- Inspection & assessment
- Marketing authorization

7 COMMERCIAL LAUNCH

Manufacture at scale and deliver the medicine to patients.

- Commercial manufacturing
- Fill & finish
- Quality control
- Global supply chain
- Market launch

8 LIFECYCLE MANAGEMENT

Maximize value and impact throughout the product lifecycle.

- Pharmacovigilance
- Real-world data
- New indications
- Formulation improvements
- Lifecycle optimization


1. DEVELOPABILITY
Stability
Aggregation
Viscosity
Binding
2. CELL LINE DEVELOPMENT
CHO Cells
Plasmid
Transfection
Single Cell
Cloning
Screening
Selected Clone
Cryogenic Cell Banking
3. UPSTREAM PROCESSING (USP)
Shake Flasks
Nutrients
pH
Dissolved Oxygen
Temperature
4. DOWNSTREAM PROCESSING (DSP)
Harvest Clarification
Protein A Chromatography
Viral Filtration
Ultrafiltration/ Diafiltration
Antibody
Impurities
5. DRUG SUBSTANCE STORAGE
2-8°C
6. ANALYTICAL DEVELOPMENT
LC-MS
HPLC
Capillary Electrophoresis
Potency Assay
7. FORMULATION DEVELOPMENT
Stability Studies
Viscosity Testing
Syringeability
8. FILL & FINISH
Vial Filling
Stoppering & Capping
Prefilled Syringes
Inspection
Packaging
9. IN-USE & COMPATIBILITY
Compatibility Testing
Stable in Solution
Safe Administration
10. QUALITY & CONTROL
Purity
Identity
Potency
Safety
Stability
Consistency
11. COLD CHAIN & DISTRIBUTION
2-8°C
12. FINAL PRODUCT

Personal remarks

Translatable skills

Think in a broader way about how your skills can support the company’s goals

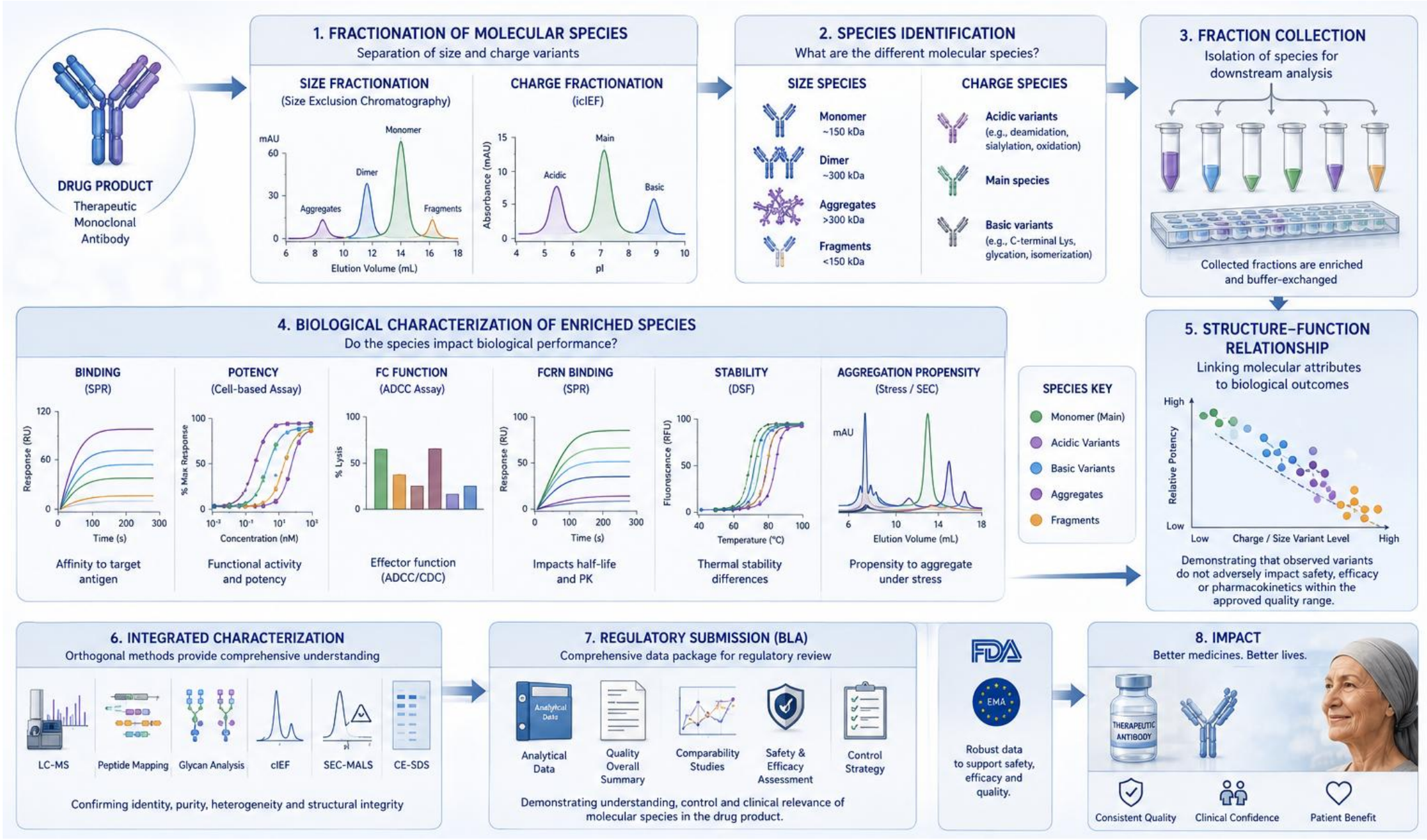
Scientific skills vs Corporate skills

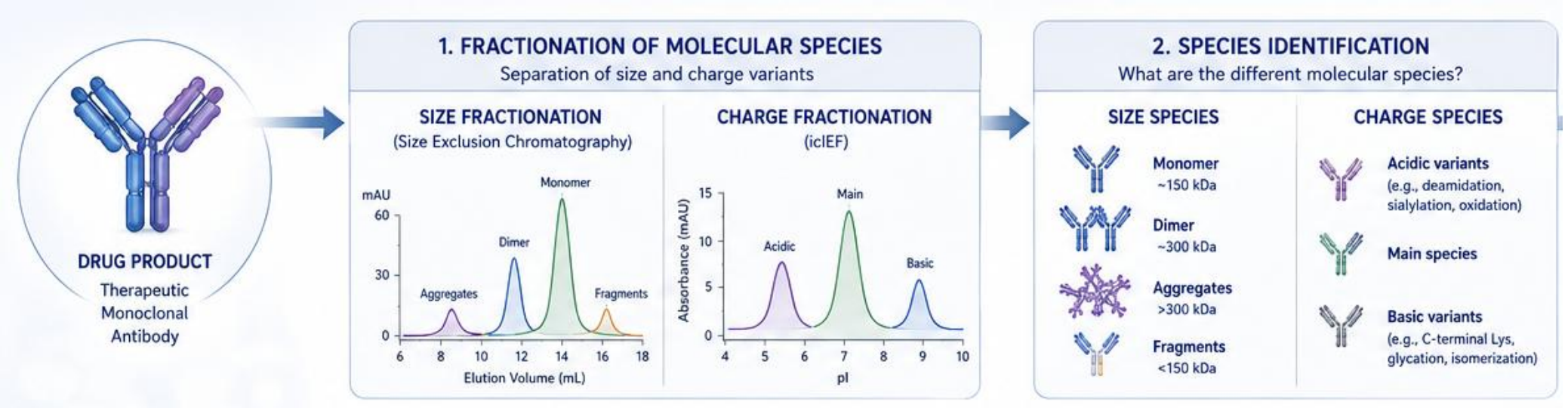
Think about what is missing in your corporate skills to maximize the impact of your scientific skills

Connections

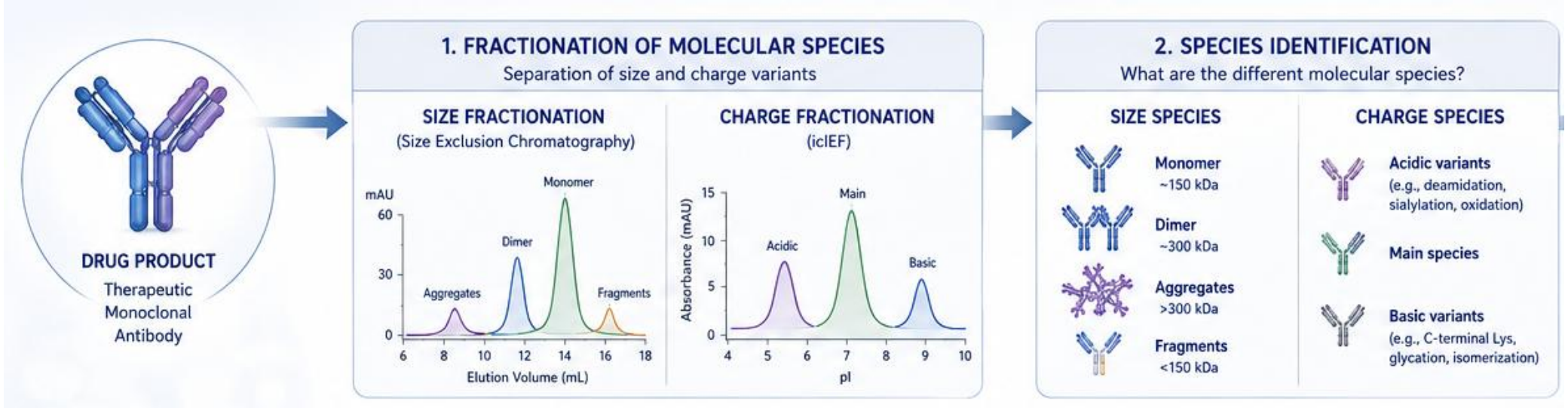
Make real connections along the way. You will have more fun ☺

Academic → Industry


DRUG PRODUCT
Therapeutic Monoclonal Antibody
1. FRACTIONATION OF MOLECULAR SPECIES
Separation of size and charge variants
SIZE FRACTIONATION
(Size Exclusion Chromatography)
mAU
Monomer
Dimer
Aggregates
Fragments
Elution Volume (mL)
CHARGE FRACTIONATION
(icIEF)
Absorbance (mAU)
Main
Acidic
Basic
pI
2. SPECIES IDENTIFICATION
What are the different molecular species?
SIZE SPECIES
Monomer ~150 kDa
Dimer ~300 kDa
Aggregates >300 kDa
Fragments <150 kDa
CHARGE SPECIES
Acidic variants (e.g., deamidation, sialylation, oxidation)
Main species
Basic variants (e.g., C-terminal Lys, glycation, isomerization)
3. FRACTION COLLECTION
Isolation of species for downstream analysis
Collected fractions are enriched and buffer-exchanged
4. BIOLOGICAL CHARACTERIZATION OF ENRICHED SPECIES
Do the species impact biological performance?
BINDING
(SPR)
Response (RU)
Time (s)
Affinity to target antigen
POTENCY
(Cell-based Assay)
% Max Response
Concentration (nM)
Functional activity and potency
FC FUNCTION
(ADCC Assay)
% Lysis
Effector function (ADCC/CDC)
FCRN BINDING
(SPR)
Response (RU)
Time (s)
Impacts half-life and PK
STABILITY
(DSF)
Fluorescence (RFU)
Temperature (°C)
Thermal stability differences
AGGREGATION PROPENSITY
(Stress / SEC)
mAU
Elution Volume (mL)
Propensity to aggregate under stress
SPECIES KEY
Monomer (Main)
Acidic Variants
Basic Variants
Aggregates
Fragments
5. STRUCTURE–FUNCTION RELATIONSHIP
Linking molecular attributes to biological outcomes
High
Relative Potency
Low
Low
Charge / Size Variant Level
High
Demonstrating that observed variants do not adversely impact safety, efficacy or pharmacokinetics within the approved quality range.
6. INTEGRATED CHARACTERIZATION
Orthogonal methods provide comprehensive understanding
LC-MS
Peptide Mapping
Glycan Analysis
cIEF
SEC-MALS
CE-SDS
Confirming identity, purity, heterogeneity and structural integrity
7. REGULATORY SUBMISSION (BLA)
Comprehensive data package for regulatory review
Analytical Data
Quality Overall Summary
Comparability Studies
Safety & Efficacy Assessment
Control Strategy
Demonstrating understanding, control and clinical relevance of molecular species in the drug product.
FDA
EMA
Robust data to support safety, efficacy and quality.
8. IMPACT
Better medicines. Better lives.
THERAPEUTIC ANTIBODY
Consistent Quality
Clinical Confidence
Patient Benefit



Histidine modification linked to aggregate formation.



PNAS PNAS

CrossMark click for updates

The class III ribonucleotide reductase from *Neisseria bacilliformis* can utilize thioredoxin as a reductant

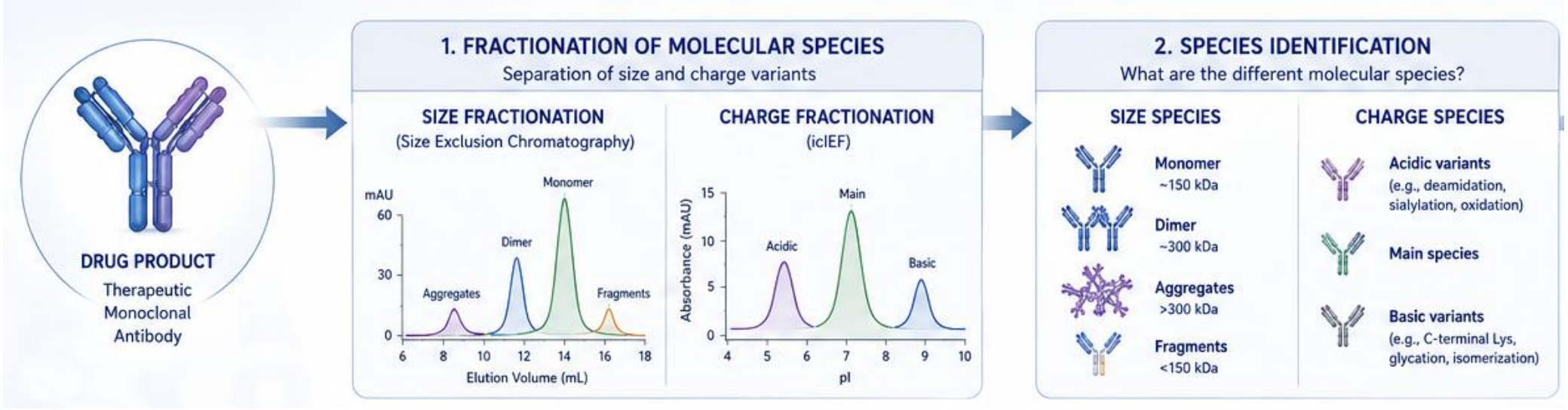
Yifeng Wei[a,1], Michael A. Funk[a], Leonardo A. Rosado[a], Jiyeon Baek[a], Catherine L. Drennan[a,b,c,1], and JoAnne Stubbe[a,b,1]

Departments of [a]Chemistry and [b]Biology, and [c]Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA 02139

Contributed by JoAnne Stubbe, July 29, 2014 (sent for review July 13, 2014)

The class III anaerobic ribonucleotide reductases (RNRs) studied to date couple the reduction of ribonucleotides to deoxynucleotides with the oxidation of formate to CO_2. Here we report the cloning and heterologous expression of the *Neisseria bacilliformis* class III RNR and show that it can catalyze nucleotide reduction using the ubiquitous thioredoxin/thioredoxin reductase/NADPH system. We present a structural model based on a crystal structure of the homologous *Thermotoga maritima* class III RNR, showing its architecture and the position of conserved residues in the active site. Phylogenetic studies suggest that this form of class III RNR is present in bacteria and archaea that carry out diverse types of anaerobic metabolism.

the formate-hydrogenlyase pathway in which it is converted to the waste products H_2 and CO_2 by formate dehydrogenase (FDH) and hydrogenase (16). However, there are many proteins annotated as class III RNRs present in diverse bacteria and archaea (17, 18) which do not possess PFL or generate formate as an intermediate or end product in their primary metabolism (19), suggesting that an alternative reducing system for class III RNRs might be involved. This variability in the presence of formate-producing pathways is in contrast to the ubiquitous distribution of thioredoxin-like proteins used by the class I and II RNRs. This observation prompted us to carry out a bioinformatics search for candidate class III RNRs that use disulfide chemistry similar to



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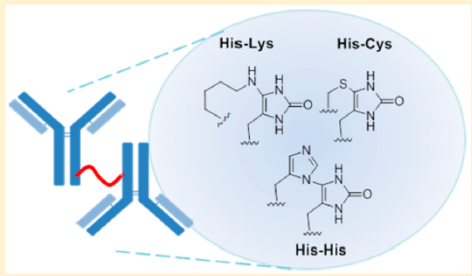
Discovery and Characterization of Histidine Oxidation Initiated Cross-links in an IgG1 Monoclonal Antibody

Chong-Feng Xu,[†,∥] Yunqiu Chen,[†,∥] Linda Yi,[†] Tim Brantley,[‡] Brad Stanley,[§] Zoran Sosic,[†] and Li Zang*[,†]

[†]Analytical Development, [‡]Cell Culture Development, and [§]Process Biochemistry, Biogen, Cambridge, Massachusetts 02142, United States

Supporting Information

ABSTRACT: Novel cross-links between an oxidized histidine and intact histidine, lysine, or cysteine residues were discovered and characterized from high-molecular weight (HMW) fractions of an IgG1 monoclonal antibody (mAb). The mAb HMW fractions were collected using preparative size-exclusion chromatography (SEC) and extensively characterized to understand the mechanism of formation of the nonreducible and covalently linked portion of the HMWs. The HMW fractions were IdeS digested, reduced, and analyzed by size-exclusion chromatography coupled with mass spectrometry (SEC-MS). The nonreducible cross-links were found to be enriched in the fragment crystallizable (Fc) region of the heavy chain, with a net mass increase of 14 Da. Detailed peptide mapping revealed as many as seven covalent cross-links in the HMW fractions, where oxidized histidines react with intact histidine, lysine, and free cysteine to form cross-links. It is the first time that histidine−cysteine (His−Cys) and histidine−lysine (His−Lys) in addition to histidine−histidine (His−His) cross-links were discovered in monoclonal antibody HMW species. The histidine oxidation hot spots were identified, which include conserved histidine residues His292 and His440 in the Fc region and His231 in the hinge region of the IgG1 mAb heavy chain. Their cross-linking partners include His231, His292, His440, and Cys233 in the hinge region and Lys297 in the Fc region. A cross-linking mechanism has been proposed that involves nucleophilic addition by histidine, cysteine, or lysine residues to the carbonyl-containing histidine oxidation intermediates to form the cross-links.



Genmab

Translating basic research into applied knowledge

PNAS

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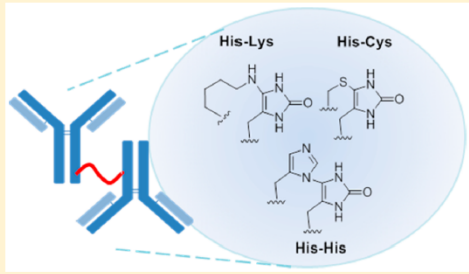

Genmab