CERTAINTY DISCOVERY

CERTARA | Chemaxon

Empowering Research: D360 Integration in NBE and ADC Discovery at Merck

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Certainty Discovery
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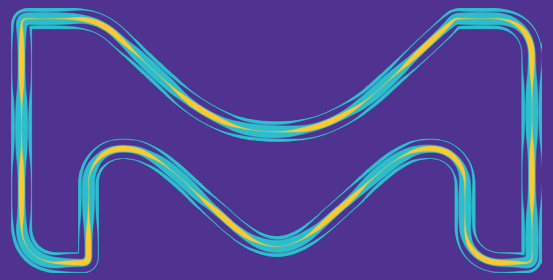


Merck

Agenda

01 Merck - Who we are and what we do

02 Biologics Discovery Footprint at Merck

03 NBE/ADC Discovery in the Research Data Landscape

04 D360 Overview

05 Challenges for integrating ADC Data in D360

06 NBE/ADC Data Portal in D360

07 Outlook and Acknowledgements

Merck KGaA, Darmstadt, Germany holds the rights to the name and trademark “MERCK” internationally, except for the United States and Canada

we are Merck

Every day, our more than **62,000 employees** work in **65 countries** to make a positive difference to millions of people’s lives by creating more joyful and sustainable ways to live.

EMD Serono MilliporeSigma EMD Electronics

In the U.S. and Canada we operate as EMD Serono in the Healthcare business, MilliporeSigma in the Life Science business, and EMD Electronics in the high-tech materials business.

We are on a mission

to help patients.

In Healthcare, we are united by our purpose: To help create, improve and prolong lives – as one for patients.

This purpose reflects the way we think, act, care and succeed as a global team.

our expertise

Areas of focus

Our portfolio addresses therapeutic areas such as:

- Oncology

- Neurology & Immunology

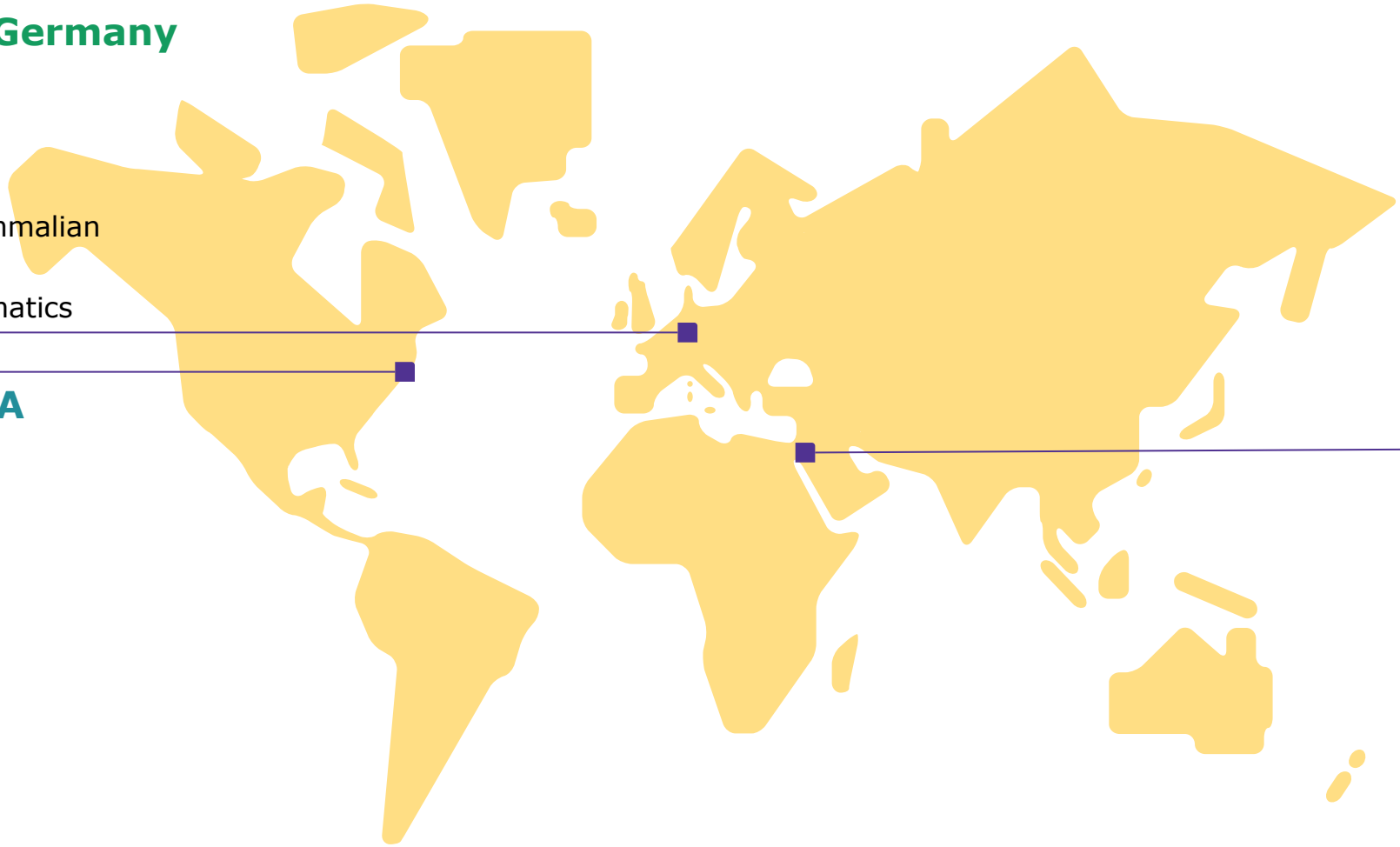
- Cardiovascular Metabolism and Endocrinology

- Fertility

Overview of Biologics Discovery
Three Sites for Biologics Discovery

Darmstadt, Germany
- Phage Display
- Yeast Display
- ADC
- Microbial & Mammalian Expression
- Research Informatics

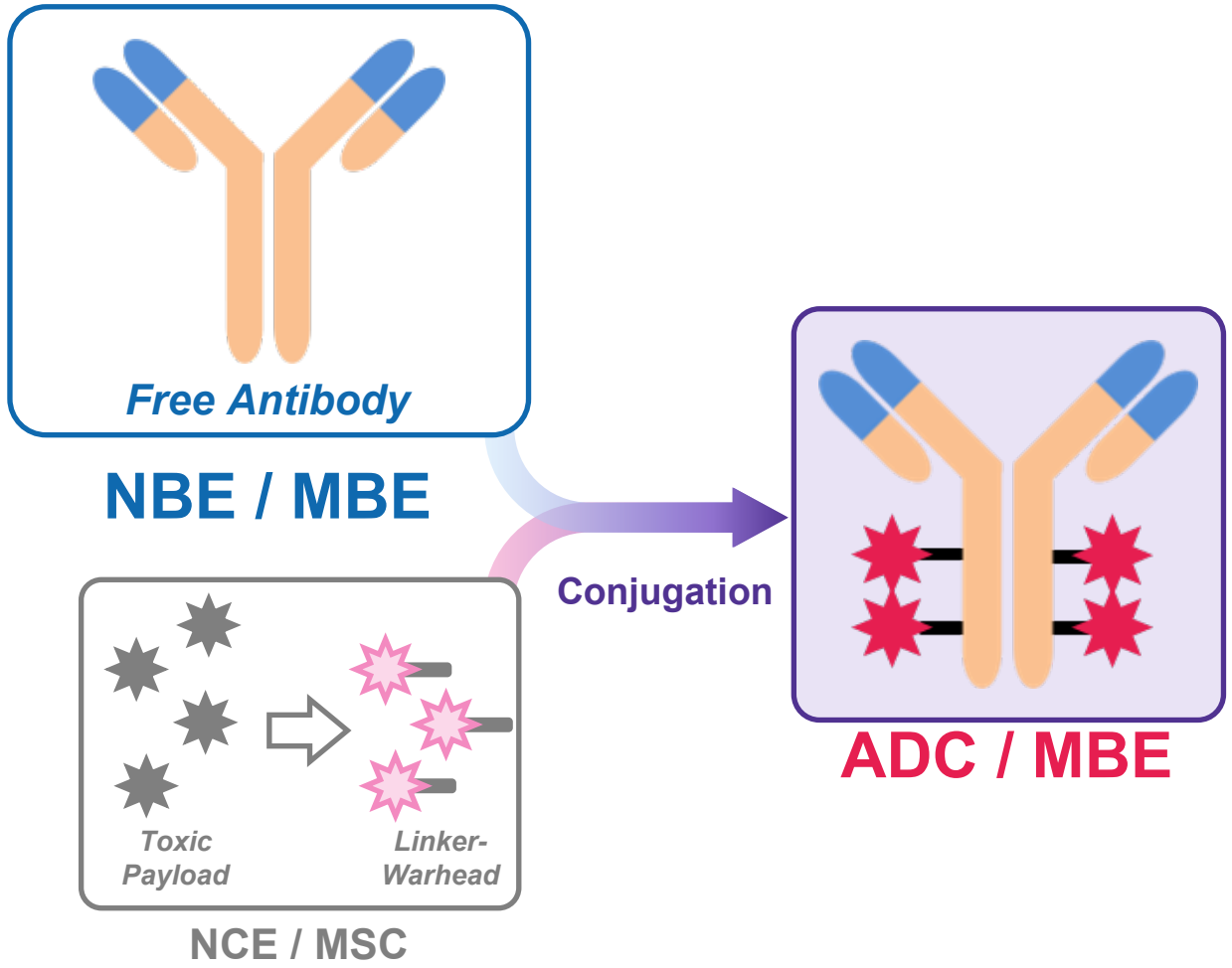
Billerica, USA
- B-cell Cloning
- Yeast Display
- NGS
- Mammalian Expression
- Research Informatics



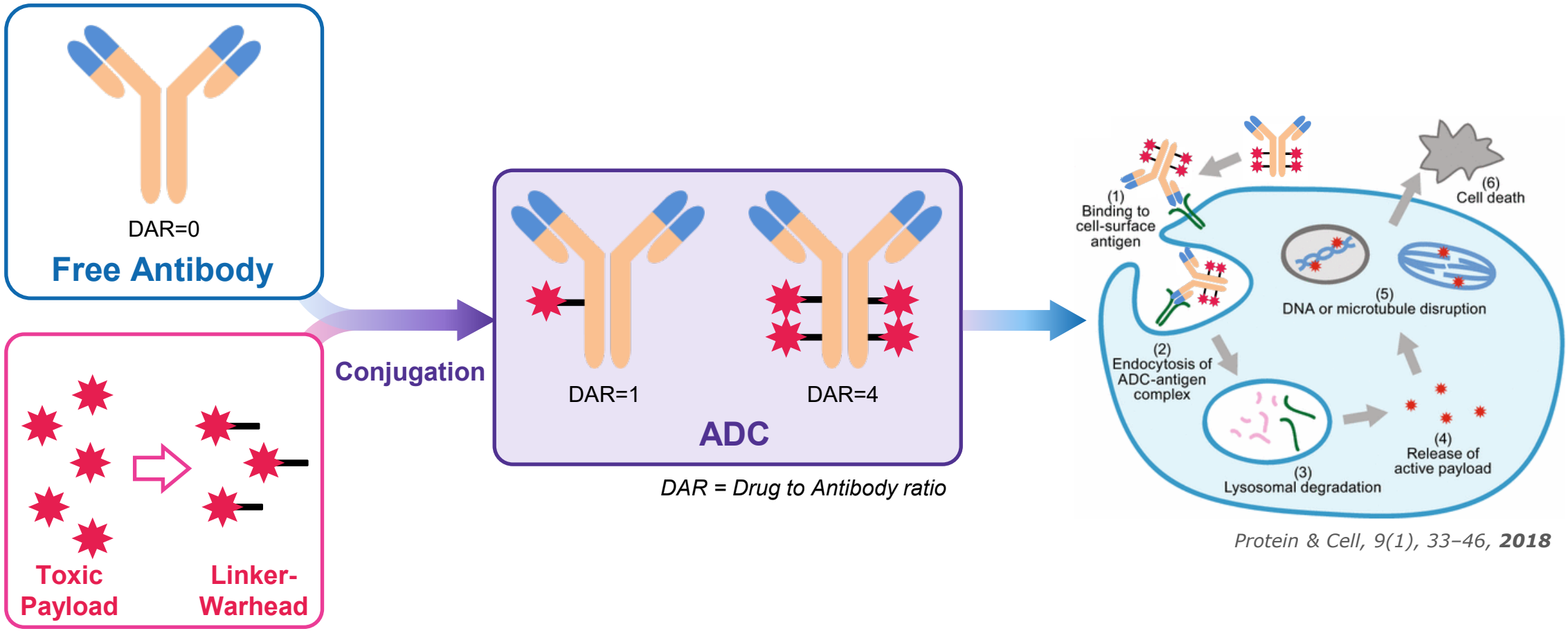
Yavne, Israel
- Yeast Display
- ADC

From small-molecules to biologics and ADCs
Quick overview of identifiers and abbreviations

NCE	**New Chemical Entity** (small-molecule)
MSC	**Merck Chemical Entity**
NBE	**New Biological Entity**
ADC	**Antibody-Drug Conjugate**
PPB	**Protein Purification Batch**
MBE	**Merck Biological Entity** (Unique Substance Identifier) *aka.* **APP** = Actual Product Protein
ROP	**Research Operating Procedure**
BRAIN	**Biologics Research All-In-One** Genedata Biologics @ Merck/EMD



Antibody-Drug Conjugates
Structure and mechanism of action of ADC



Protein & Cell, 9(1), 33–46, ***2018***

Research Data Landscape
Orchestration of Data from different streams

Genedata SCREENER

Biorails

automated calculation of *in silico* properties

NBE, NCE, ADC definitions and **Biological Results** *in vitro, in vivo, in silico, ..*

Bio-Assay Result Posting

Research Database

ELN

ROP*

Characterization
—
QC Analytics
—
Mass Spec

Result Posting

BRAIN

MBE and PPB registration

Genedata BIOLOGICS

Entity Definition and Results

Retrieval of Entity Definitions and Biological Results

- **F** Findable
- **A** Accessible
- **I** Interoperable
- **R** Reusable

Arena360

D360

ADC Portal
NBE Data Portal

BRAIN, Genedata Biologics @ Merck/EMD

ROP, Research **O**perating **P**rocedure: describes method and obtained results

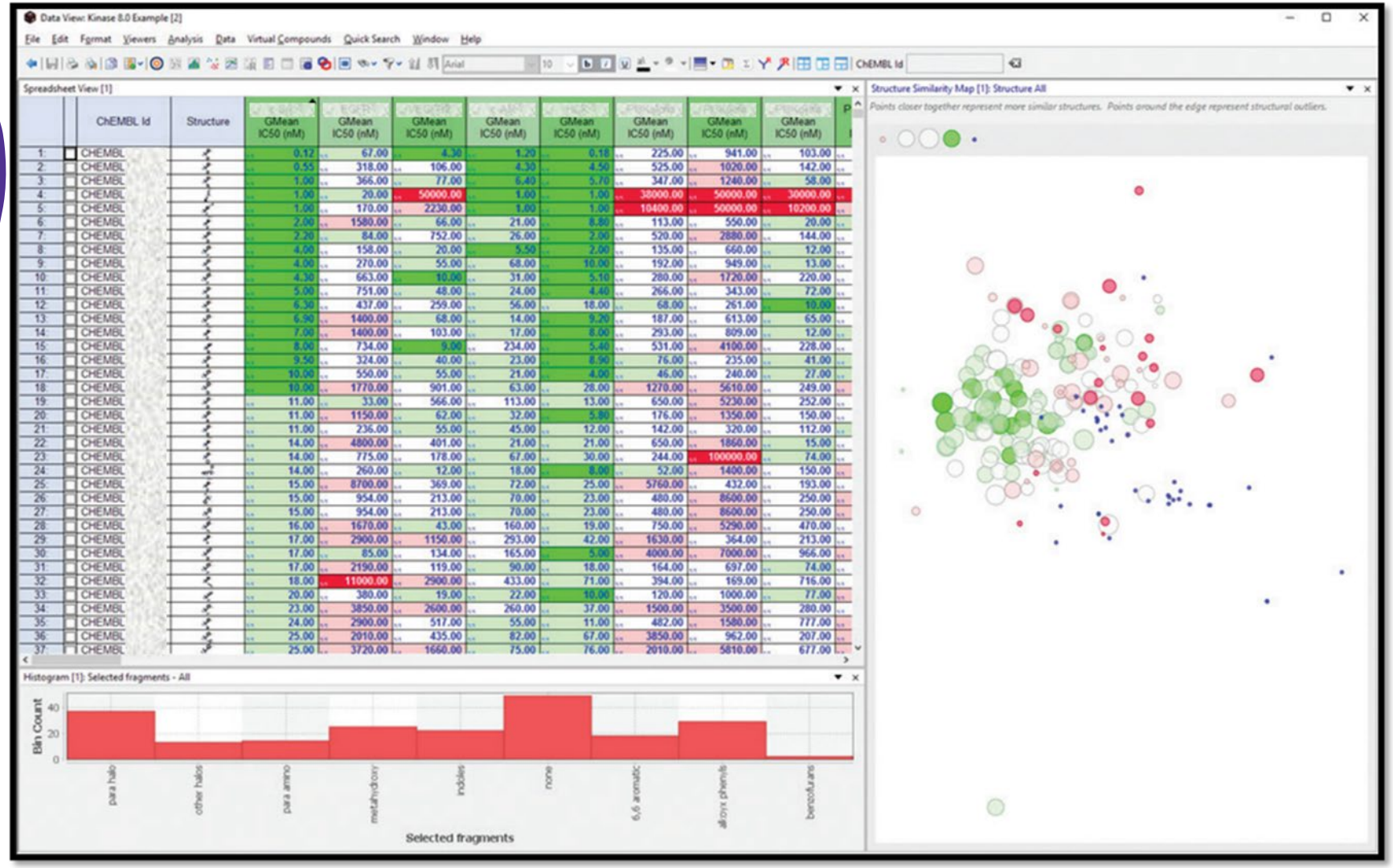
MBE, NBE substance = APP

Arena360 Web-portal to the Research Database @EMD

D360, Spotfire Data Visualization & analytics platforms

Data Retrieval for Informed Decision Making
D360 – Quick Overview

- D360 by Certara, Scientific data Informatics tool.
- **Tailored For Discovery Research Scientists**
- Self-service real time data access, analysis and visualization.
- Informed decision making in Drug Development Project Teams

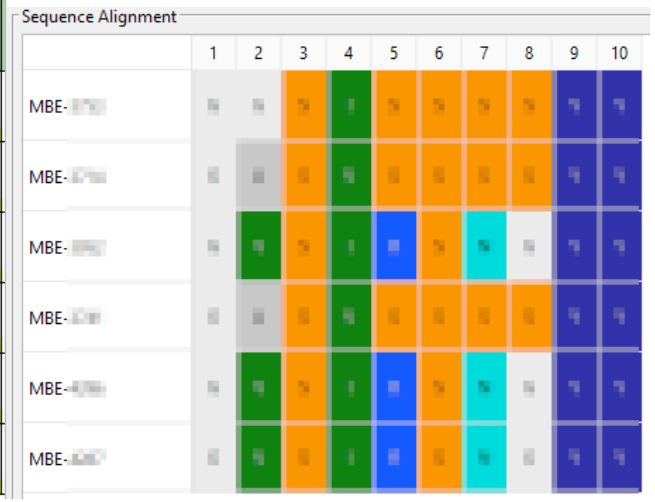


NBE Data Portal in D360

Putting complex molecule assay data in context

Batch & Substance Data					Func. Assays	QC Assays		*In silico* Preds.	Chain & Feature Sequences		Sequence Alignment (for SAR)
		MBE Code	Concat PPB Code	MBE Format	MBE Alias	KD (uM) [redacted]	ROP64003 Analytical SEC Mean % Purity-SEC (%) Result Grouping Code: null	ROP64003 Analytical SEC Mean % Aggregation (%) Result Grouping Code: null	ROP63006 In Silico Predictions - Protein-Sol Properties Mean % Solubility (%)	MBE Chain Features Concat Feature AA Sequence Feature Name: HCDR1 Feature Name Number: 1	MBE Chain Features Concat Feature AA Sequence Feature Name: HFW2 Feature Name Number: 1
1:		MBE [redacted]	PPB [redacted]	[redacted]	[redacted]	0.209 1/1	93.400 1/1	6.600 1/1	41.790 1/1	[redacted]	[redacted]
2:		MBE [redacted]	PPB [redacted]	[redacted]	[redacted]	0.013 1/1	92.600 1/1	7.400 1/1	42.600 1/1	[redacted]	[redacted]
3:		MBE [redacted]	PPB [redacted]	[redacted]	[redacted]	0.006 1/1	94.700 1/1	5.300 1/1	42.060 1/1	[redacted]	[redacted]
4:		MBE [redacted]	PPB [redacted]	[redacted]	[redacted]	0.003 1/1	90.900 1/1	9.100 1/1	42.470 1/1	[redacted]	[redacted]
5:		MBE [redacted]	PPB [redacted]	[redacted]	[redacted]	0.001 1/1	98.600 1/1	1.400 1/1	42.200 1/1	[redacted]	[redacted]
6:		MBE [redacted]	PPB [redacted]	[redacted]	[redacted]	0.001 1/1	98.200 1/1	1.800 1/1	42.610 1/1	[redacted]	[redacted]

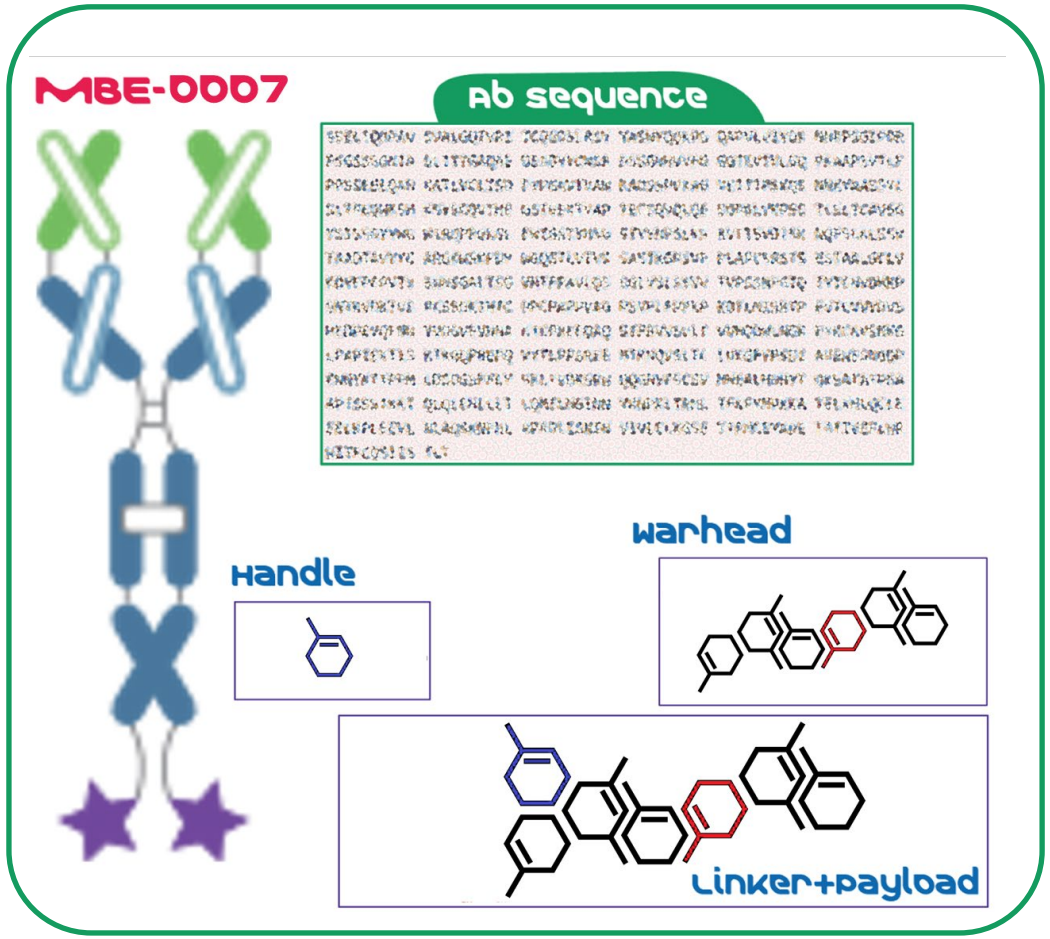
HCDR1

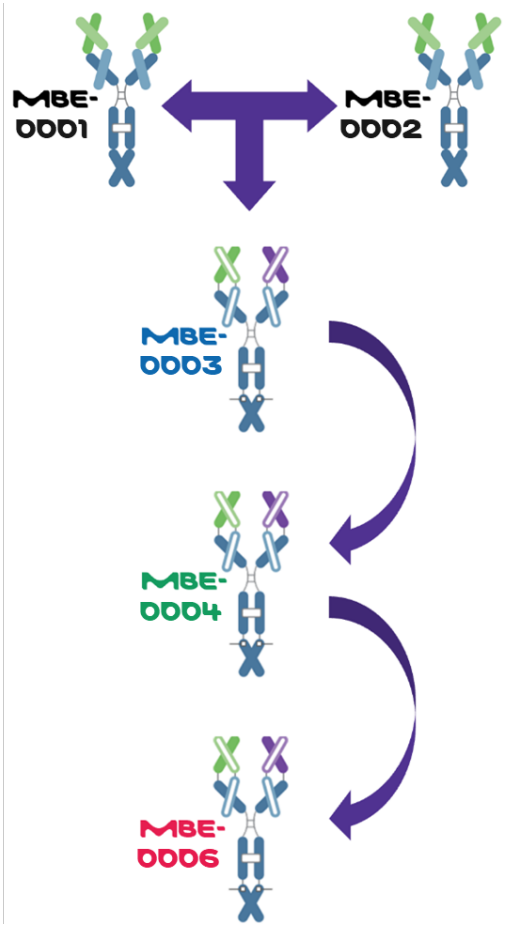


Data originate from BRAIN

Data from the RDB

D360 ADC Portal
ADC – Why Dedicated Portal?



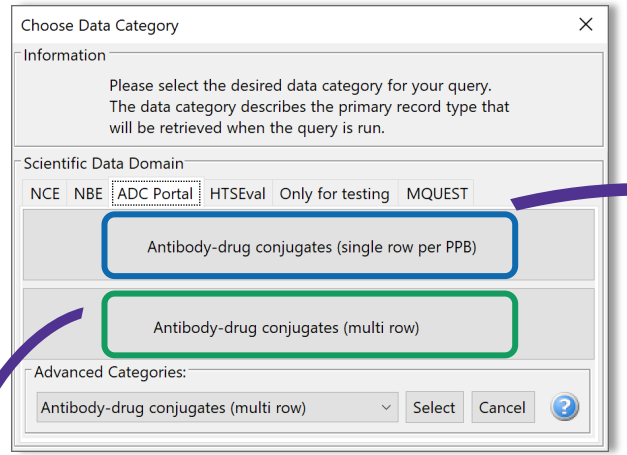


ADC Group has unique needs due to..

- **Complexity of Molecules**
  Profile over both:
  - **Whole Molecule**
  - **Constituent parts**
- **Ancestry Requirements**
  - **Incorporate results from pre-cursor molecules**
  - **Both direct & Indirect ancestors**
- **Experimental Results Across Modalities**
  - **Small molecule assays for conjugated molecules**
  - **MBE assays for whole molecule and antibody**

D360 ADC Portal – Data Presentation Layer

Two Views over ADCs – Single Row vs Multi Row



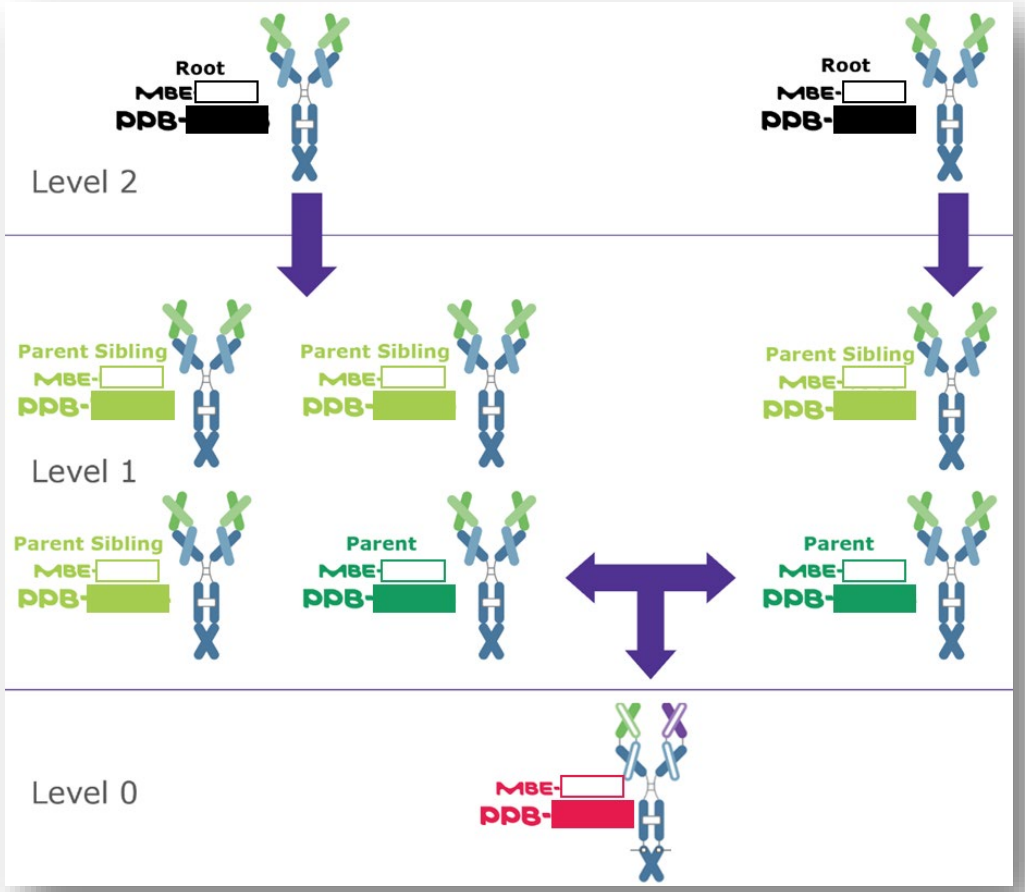
PPB Code	PPB Alias	MBE Format	Conjugation Site	Conjugation Component Type No	Conjugation Component Type	Conjugated MS Entity	Conjugated MS Entity Structure
PPB-				1	Handle		
PPB-					Linker+Payload		
PPB-		IgG	cysteines	1	Linker+Payload		
PPB-		IgG	interchain cysteines	1	Warhead		
PPB-		IgG	interchain cysteines	2	Linker+Payload		
PPB-		IgG	interchain cysteines	2	Warhead		

- ADC described over multiple rows.
- One row per conjugated component

PPB Code	PPB Alias	MBE Format	Conjugation Site(s)	Linker+Payload MS Code	Linker+Payload Structure	Warhead MS Entity	Warhead Structure	Linker MS Entity	Linker Structure	Handle 1 MS Entity	Handle 1 Structure
PPB-		IgG	interchain cysteines			MSC					
PPB-		IgG	HC_Q295			MSC				MSC	
PPB-		IgG	HC_Q295			MSC				MSC	
PPB-		IgG	interchain cysteines			MSC					
PPB-		IgG	interchain cysteines			MSC					
PPB-		IgG	HC_Q295							MSC	
										MSC	
						MSC					
						MSC					

- One row per ADC
- Conjugated components returned in columns

D360 ADC Portal – Data Presentation Layer
Molecule Hierarchy Information



Ancestor information covers…

- **Pre-cursor Molecules**
  - **All hierarchy levels from parent(s) through to root(s).**
  - **Direct and indirect ancestors**
- **Ancestry Results**
  - **I.e., assay results of all ancestor molecules**

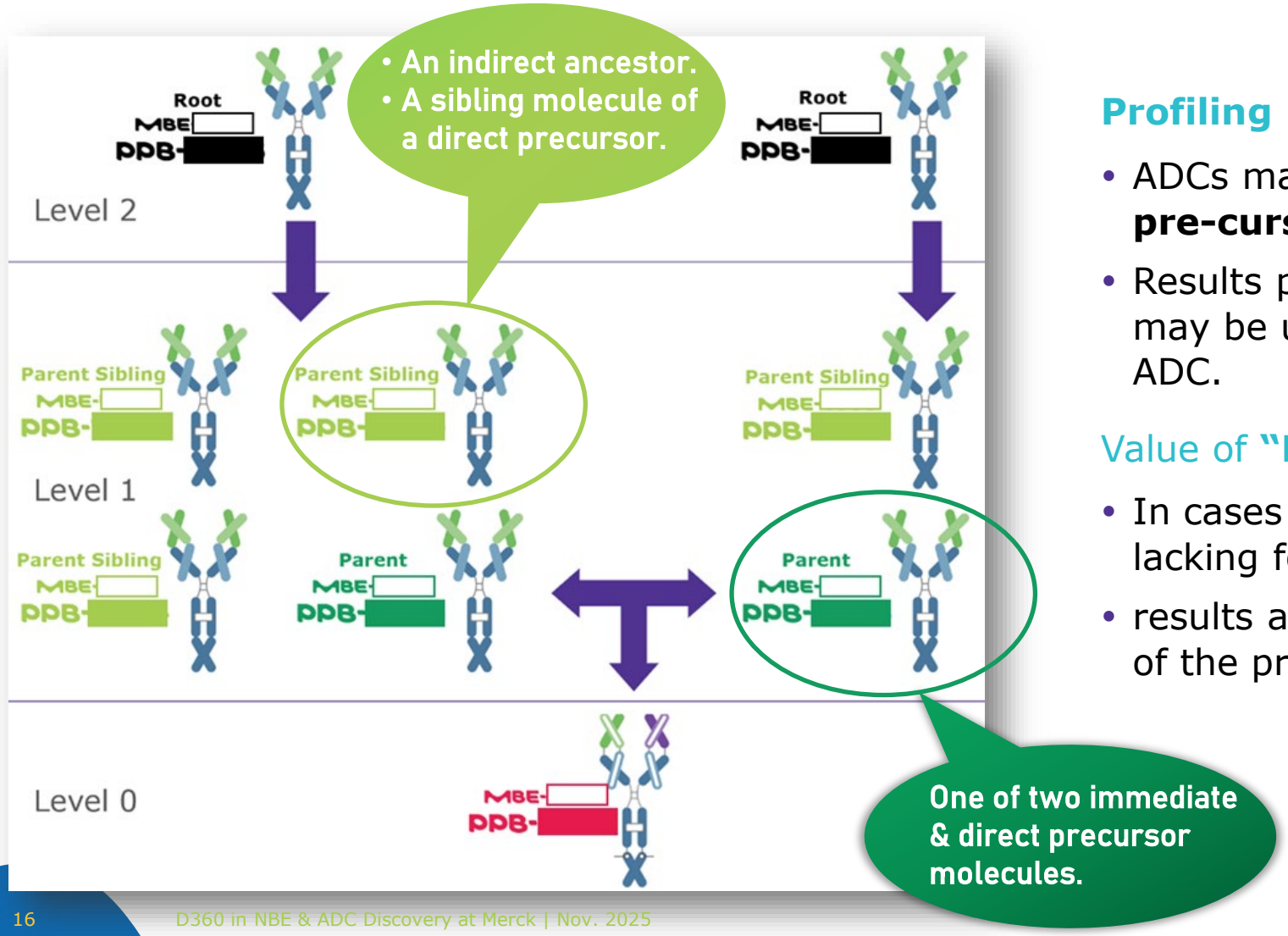
Results of Siblings of Parents

MBE Code	PPB Code	Ancestor MBE	Ancestor PPB	Ancestor Level	Ancestor is Parent?	Ancestor is Parent Sibling?	Ancestor is Root?	Directly or Indirectly Related?	ROP60111 ADC Direct Ancestors	ROP60111 ADC Indirect Ancestors
MBE-	PPB-	MBE-	PPB-	1.0	Y	N	N	Direct	0	
		MBE-	PPB-	1.0	Y	N	N	Direct		
		MBE-	PPB-	1.0	N	Y	N	Indirect		
		MBE-	PPB-	1.0	N	Y	N	Indirect	0.002	0.016
		MBE-	PPB-	1.0	N	Y	N	Indirect		
		MBE-	PPB-	1.0	N	Y	N	Indirect		
		MBE-	PPB-	2.0	N	N	Y	Direct		
		MBE-	PPB-	2.0	N	N	Y	Direct	2/2	1/1

Results of Parent Molecules

ADC Data Portal in D360 – Unique Challenges for ADCs

Molecular Heritage



Profiling based upon Ancestor Molecules

- ADCs may be built-up from multiple **pre-cursor molecules**
- Results pertaining to pre-cursor molecules may be used in assessing / profiling the final ADC.

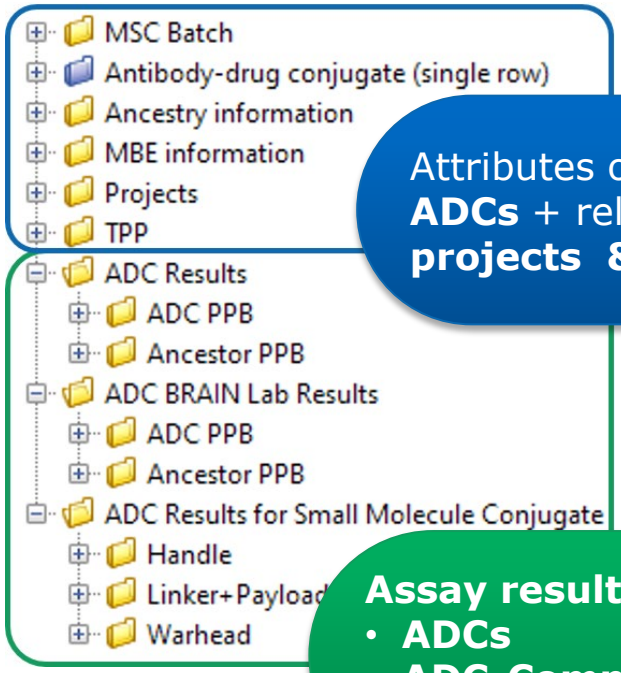
Value of **"Direct" and "Indirect" Ancestors**

- In cases where experimental results are lacking for immediate pre-cursor molecules
- results associated with the sibling molecules of the pre-cursors may be used.

ADC Data Portal in D360 – The solution

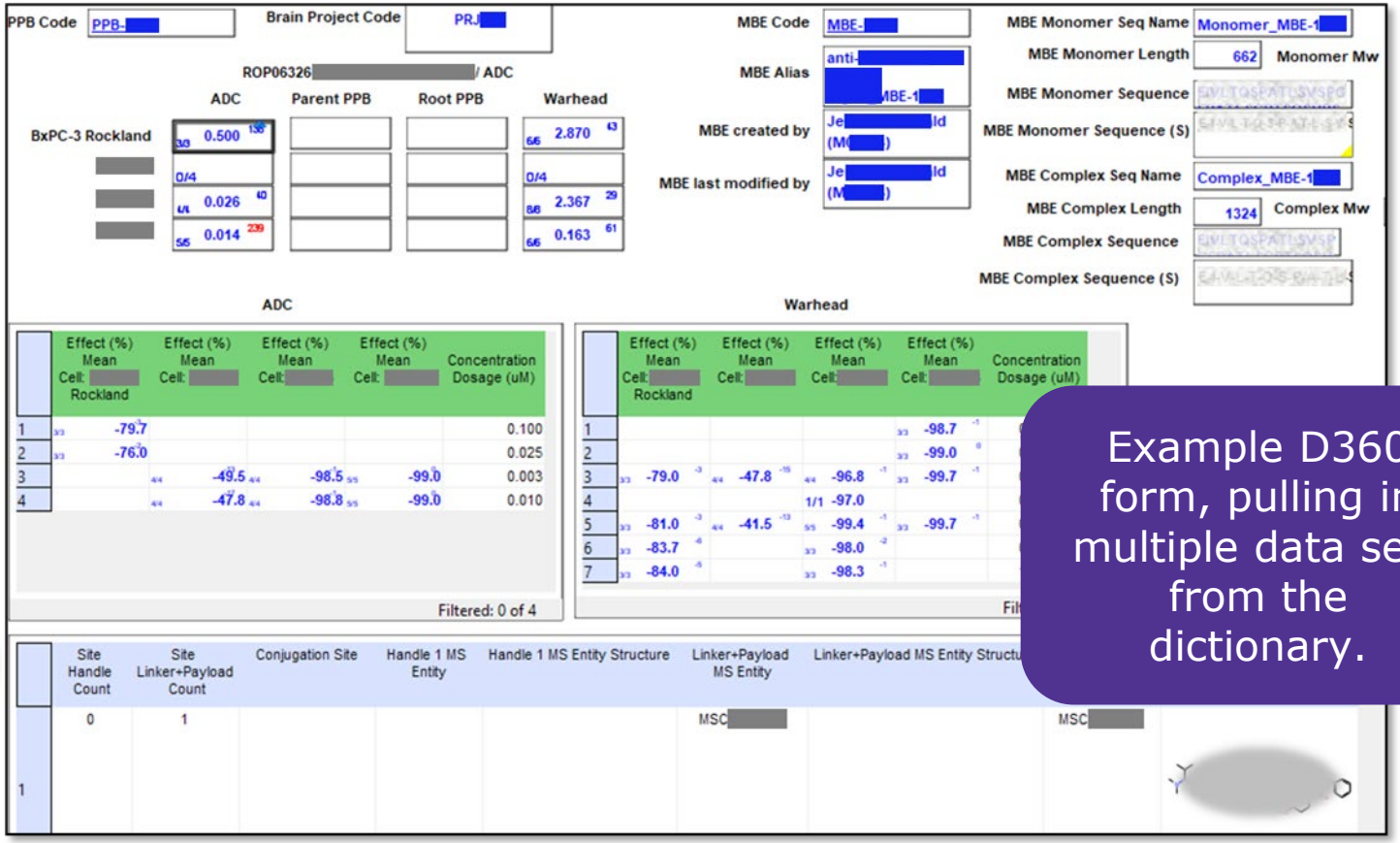
ADC-specific data catalog

- The ADC portal contains a comprehensive, ADC-specific data dictionary.
- This allows users to easily find all data associated with ADCs, their components and related entities.



Attributes of the **ADCs** + related **projects & TPPS**

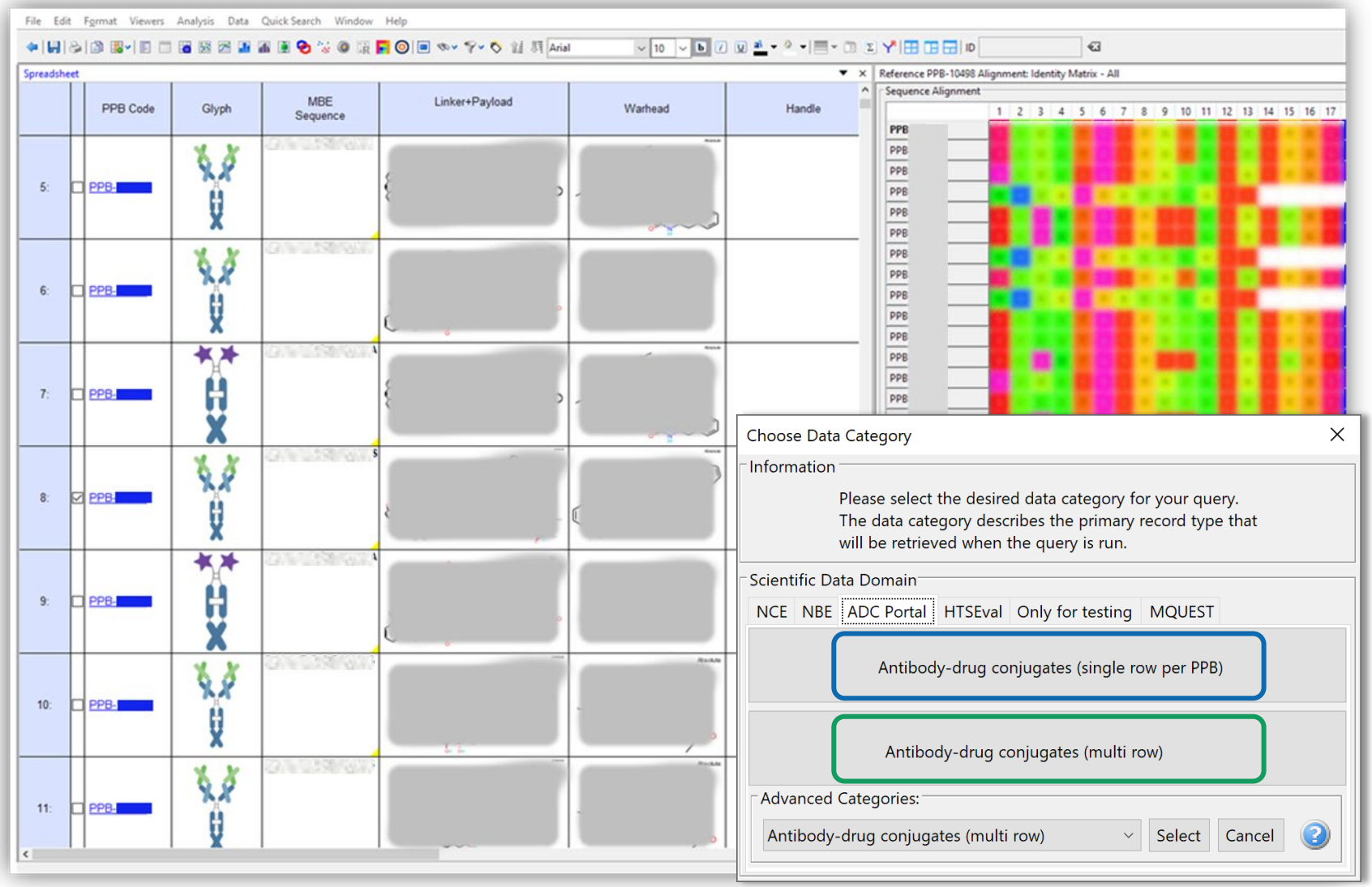
Assay results for all
- **ADCs**
- **ADC-Components**
- **Ancestor molecules**



Example D360 form, pulling in multiple data sets from the dictionary.

ADC Portal in D360
Insights to drive ADC discovery

- The "D360 ADC Portal" is a dedicated portal with two flavors:
  One Batch per row
  and
  One Conjugate per row
- Designed to meet the specific needs and challenges in support of our Antibody-Drug Conjugate (ADC) molecule activities.



D360 for NBE/ADC Discovery
Challenges and Opportunities

- Wide **Diversity and Complexity** of ADC Constructs
- Support for **sequence-based filters** in queries
- **Sequence Viewer: annotations** and custom **numbering schemes**
- More **functions** for sequence columns

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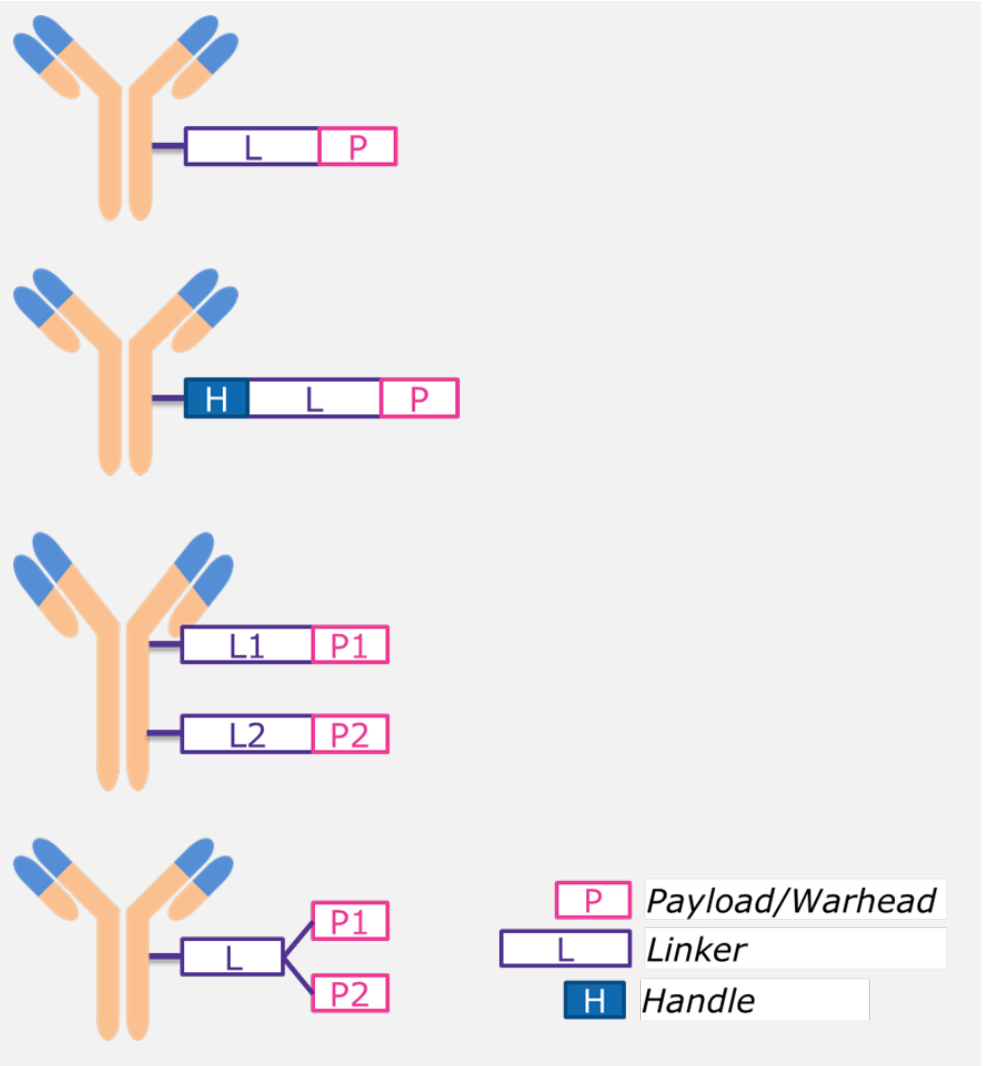

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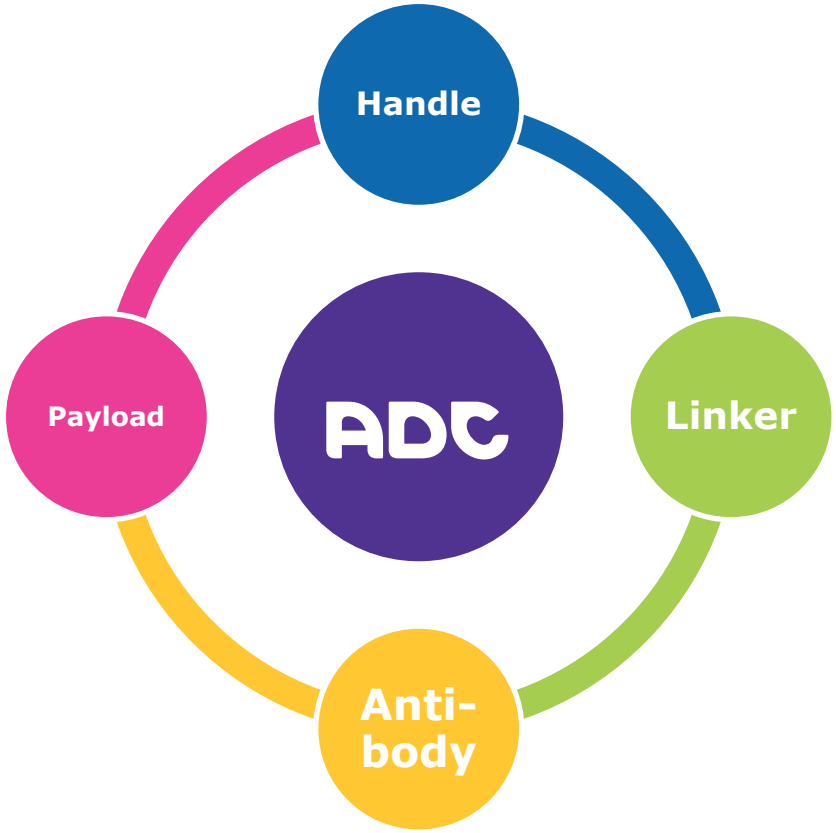

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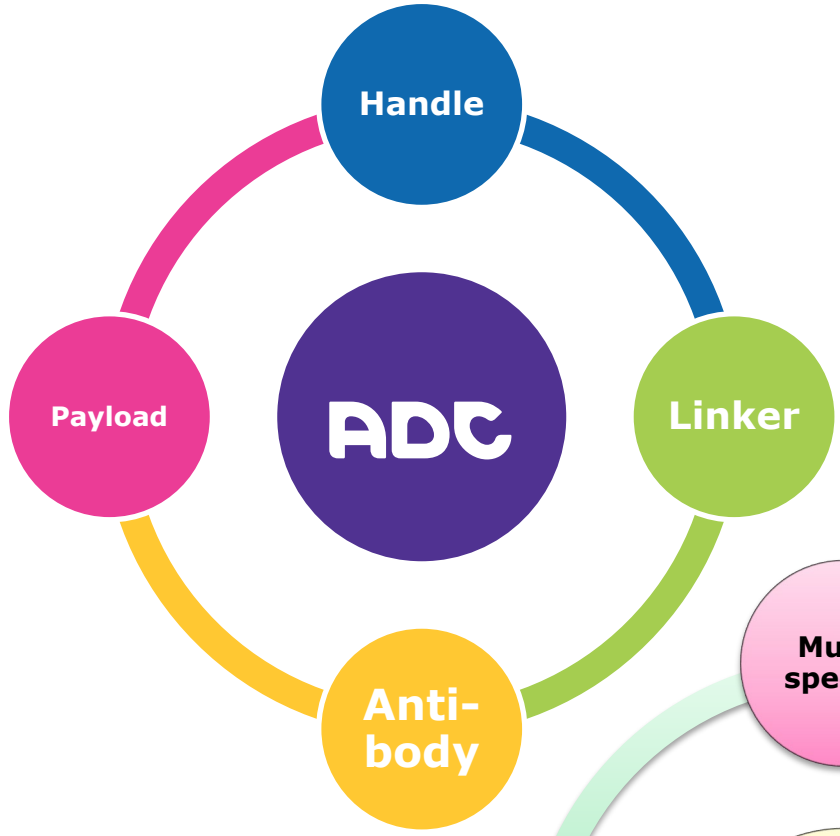

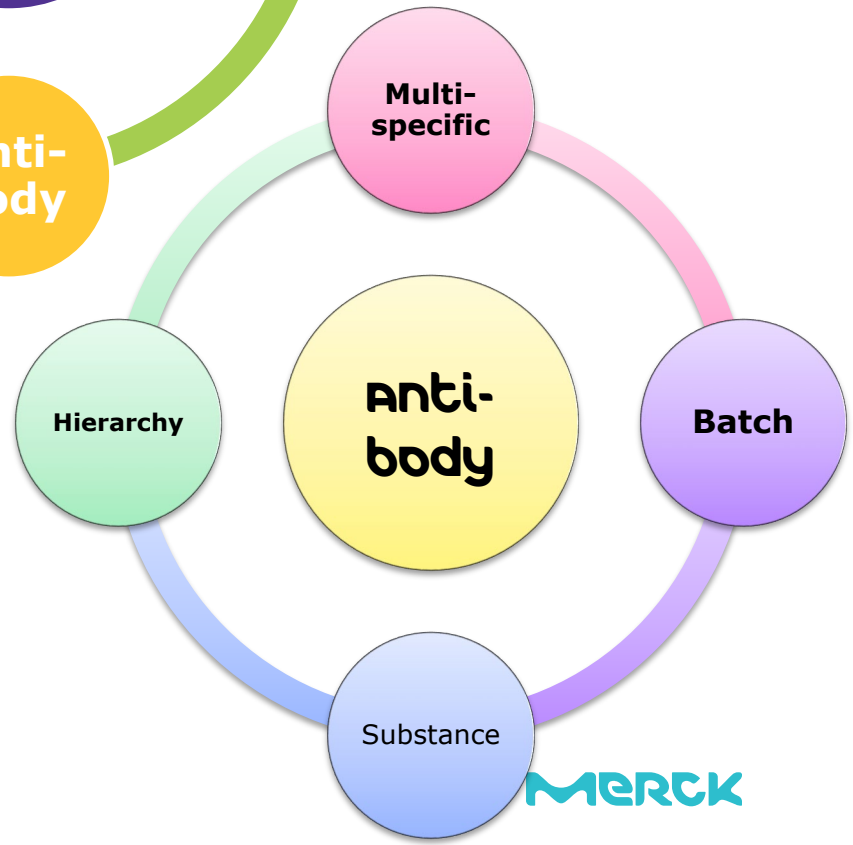

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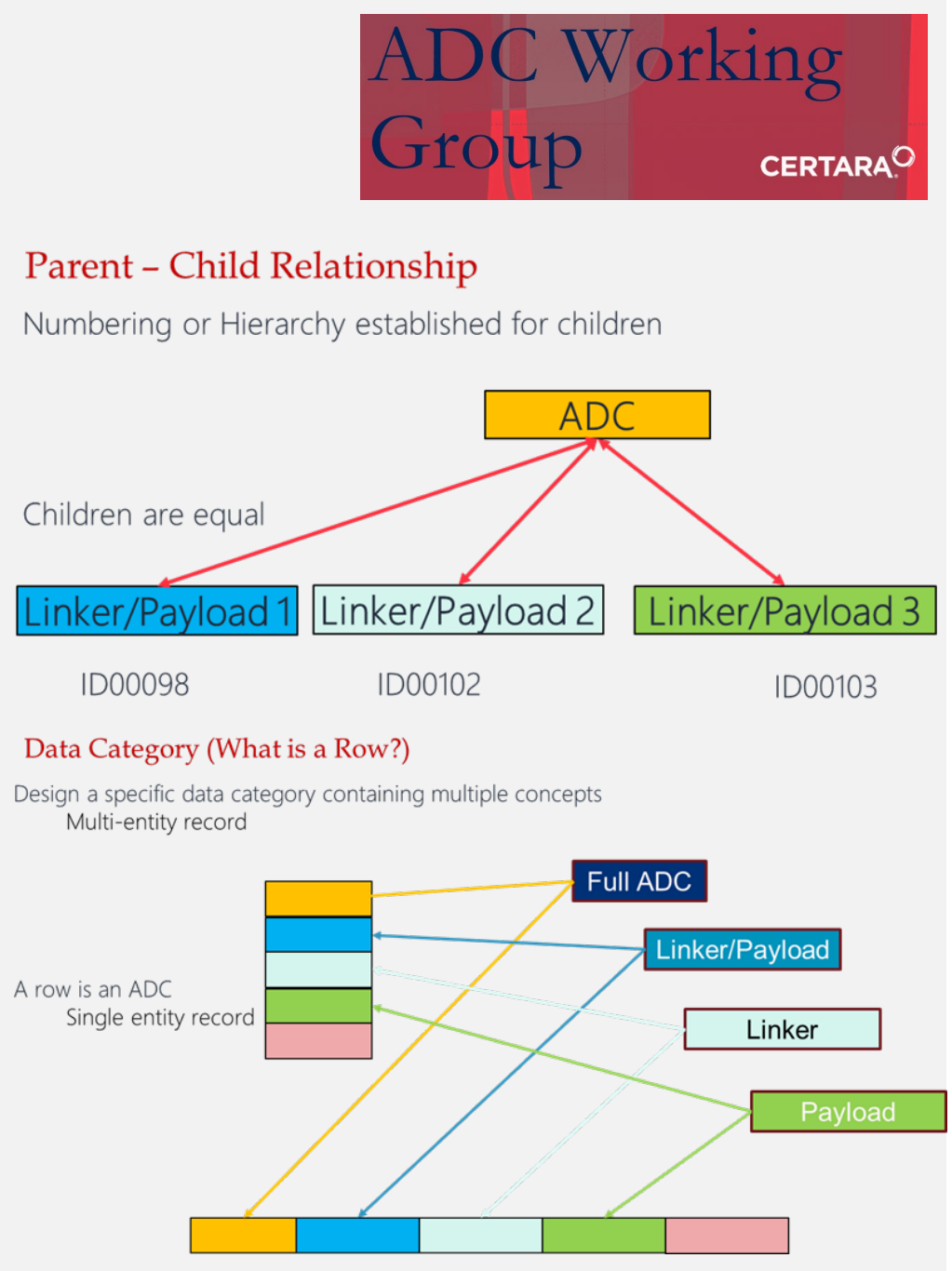

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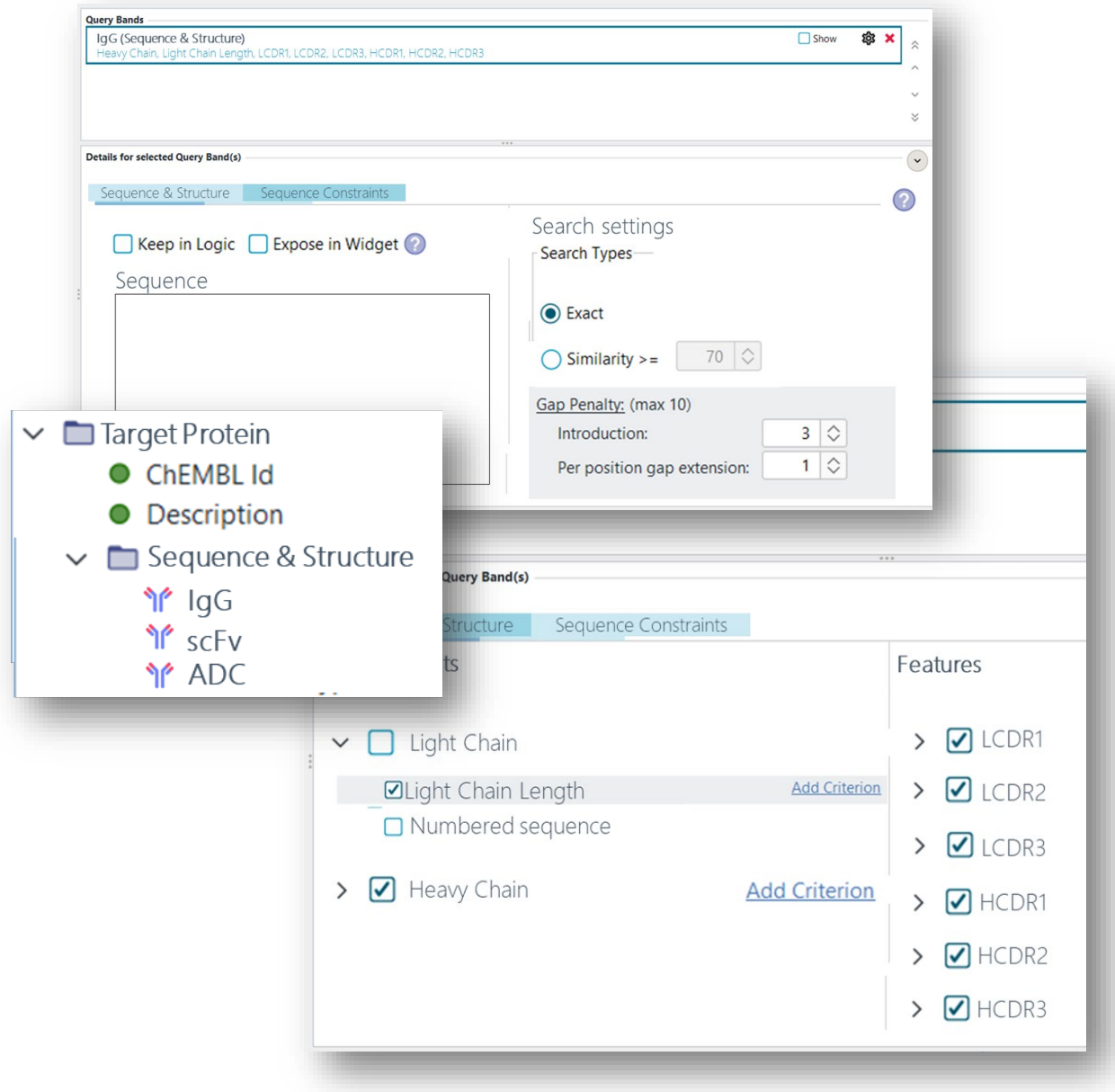

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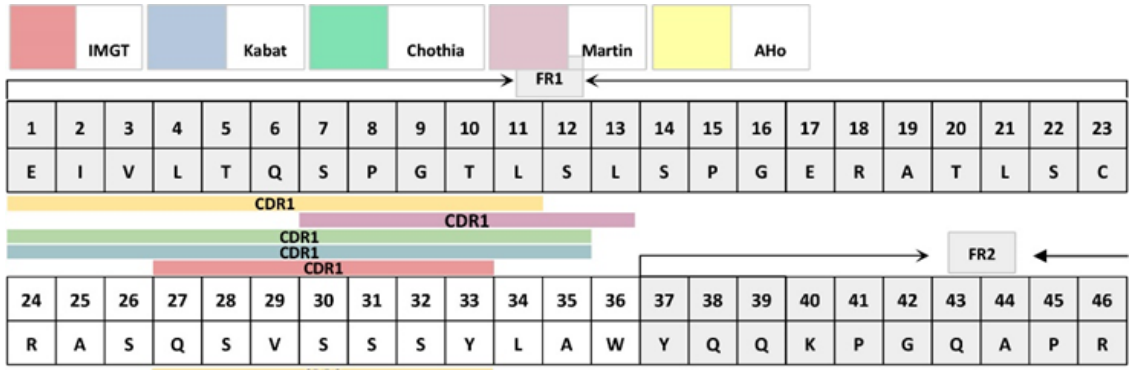

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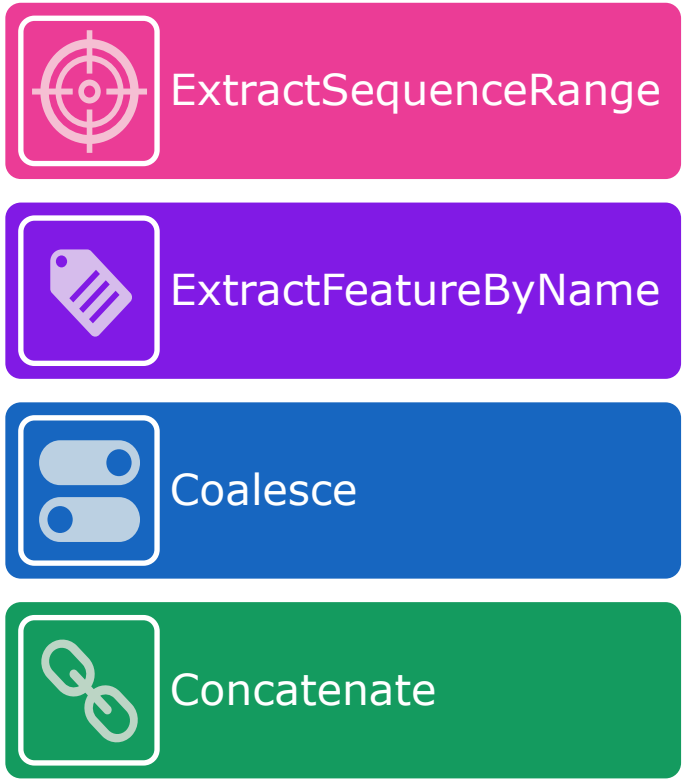

Acknowledgements
a team effort