CERTAINTY DISCOVERY

CERTARA | Chemaxon

Recent use of D360 at AstraZeneca and expanding beyond small molecules

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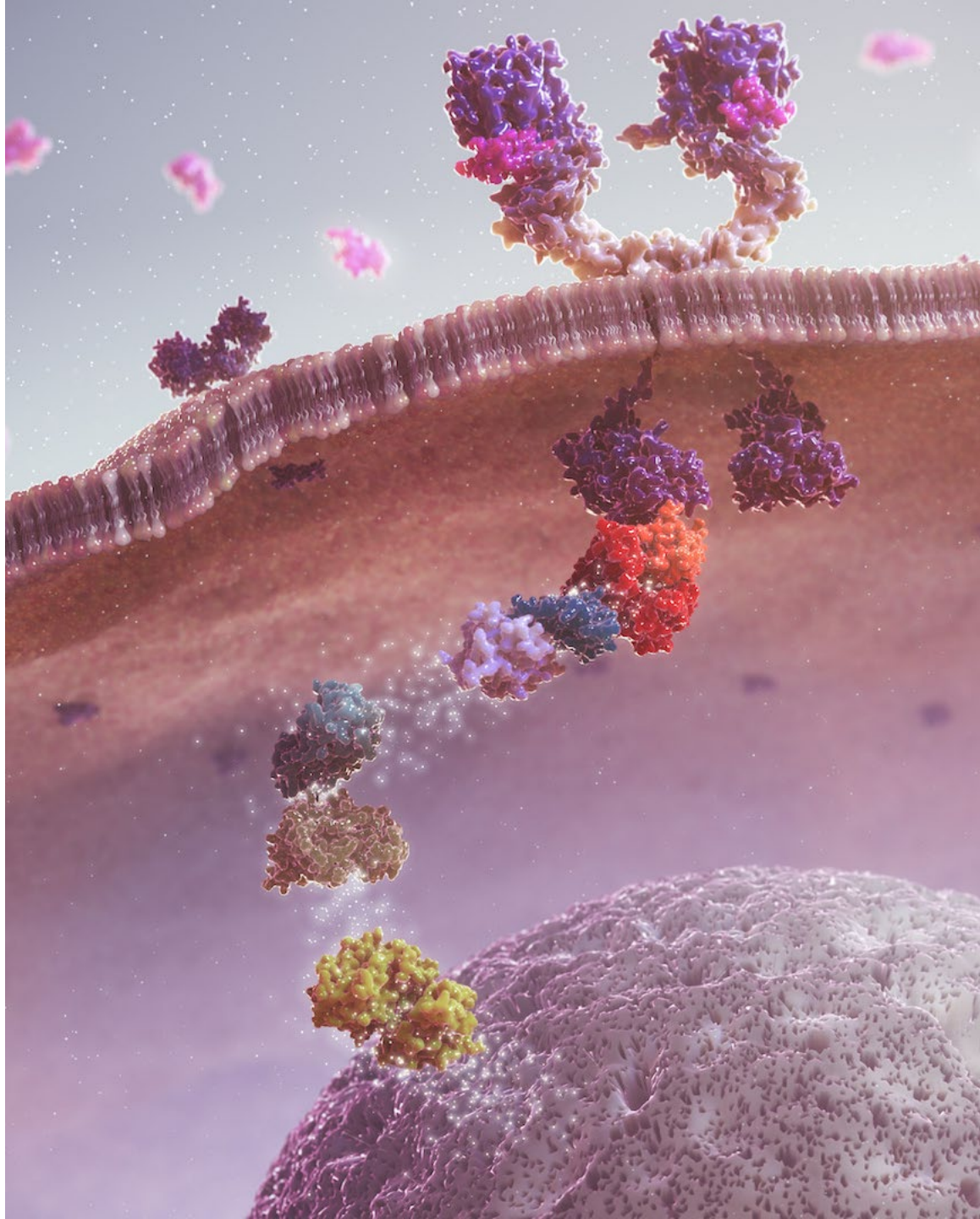
Design Offices Frankfurt Wiesenhüttenplatz, Frankfurt, Germany



About me

Bill McCoull

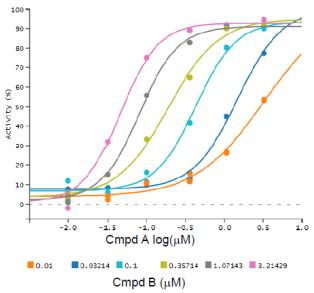
- AstraZeneca D360 business lead
- Do data analysis every day in projects
- 20+ year involvement with AZ analysis tools
- Everyday user - “I care what the tool does and how to use it”
- Disclaimer - ask Giammy if you want to know about the technical details!

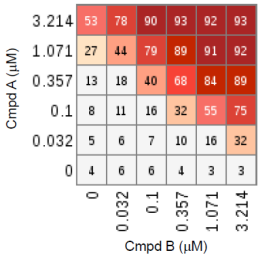
Outline

- Introduction: D360 at AstraZeneca
- Popular recent features
    - Curve viewing
    - Project progress tracking
- Moving beyond small molecule use of D360
    - Categorisation of modalities
    - Peptide DMTA & SAR
    - Antibody Drug Conjugates (ADCs)
- Conclusion

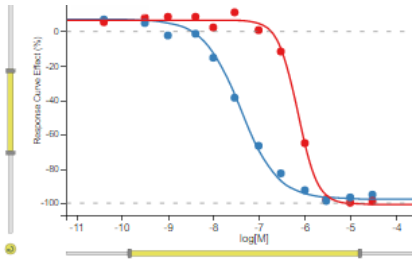
D360 used as a query, analysis & visualisation tool to help projects at AZ

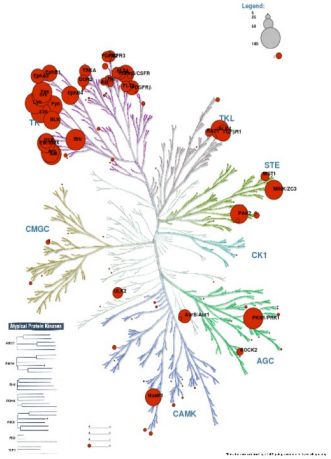
Spreadsheet view plus dynamic visualisations





Extendable plug-ins to support new data analysis





Export to key tools for advanced analysis

Predictive Insight Platform

Predictive models

ISAC

AZ compound & sample data

IBIS Datamart

AZ test results data

PredICT

PK-PD, in vivo data

Chemistry Connect

Patent db

Internal & external SAR data

chemTraX

Design set data

DemCap

Cascade data

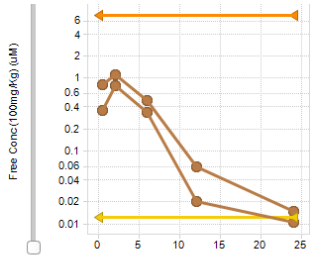
HTS db datamart etc.

Bespoke data e.g. csv, sdf

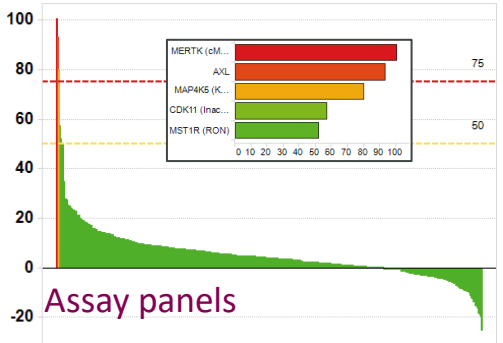
Multiple data sources brought together

jmp

Spotfire® TIBCO Software



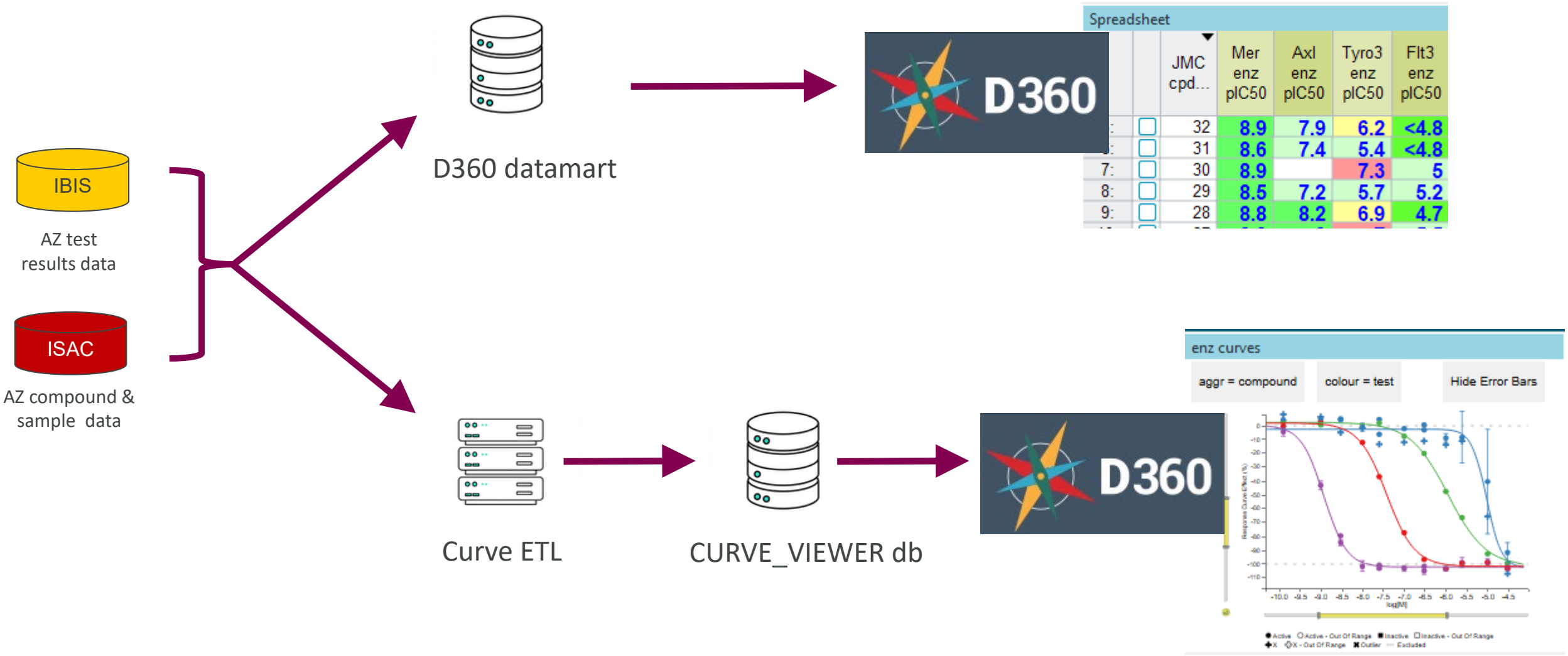
PK tools



Assay panels

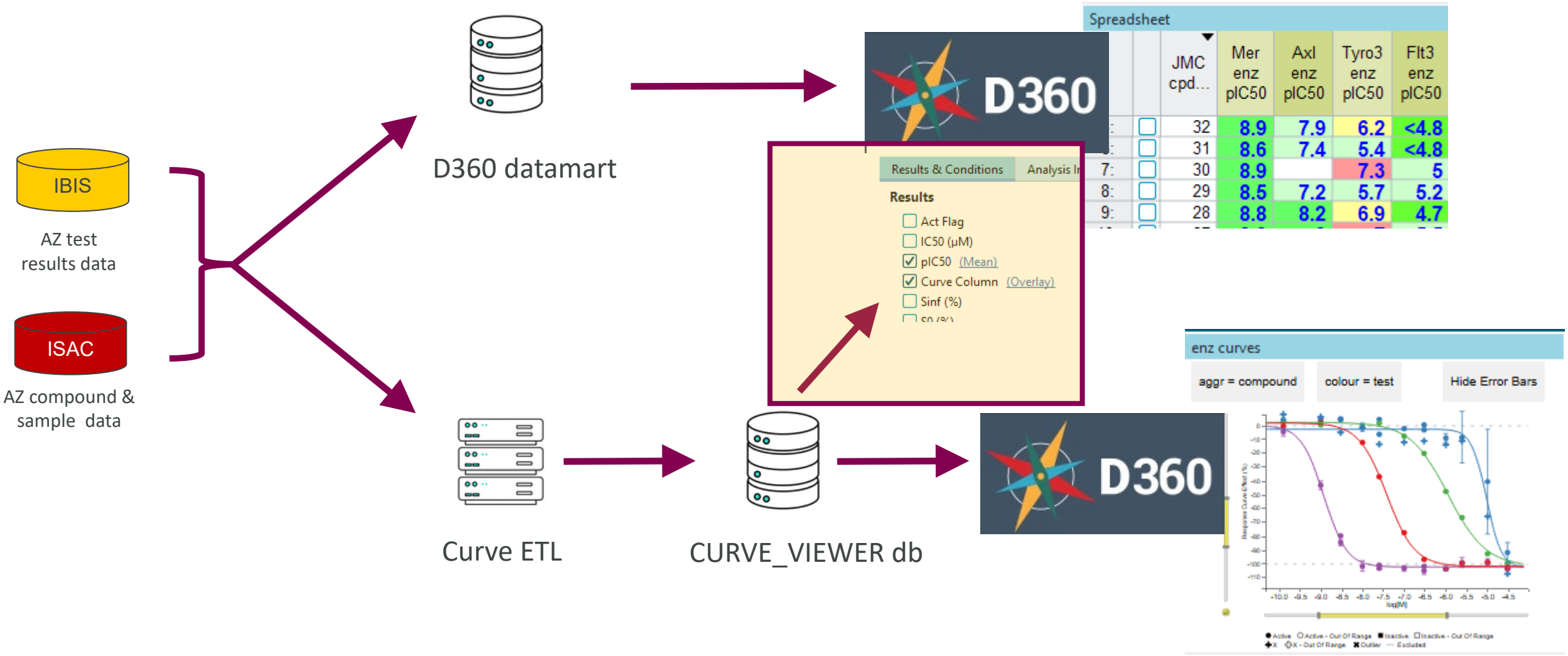
Curve viewing

Curve viewing



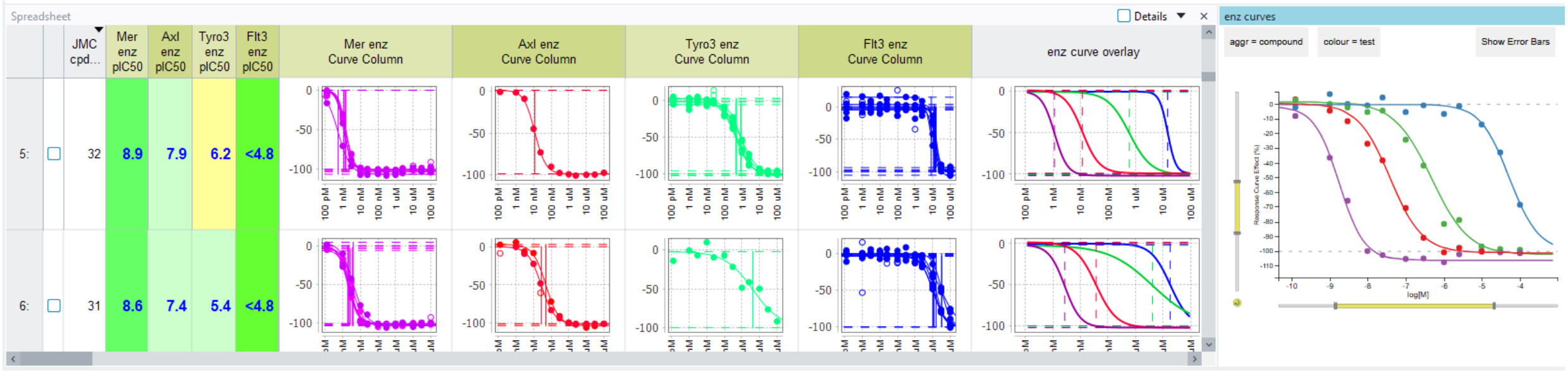
- All curve related information is pulled into a curve viewer db with some data cleansing
- AZ curve viewer utlises curve viewer db

Curve viewing

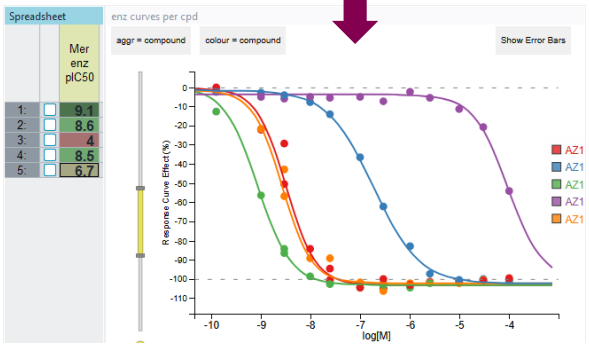


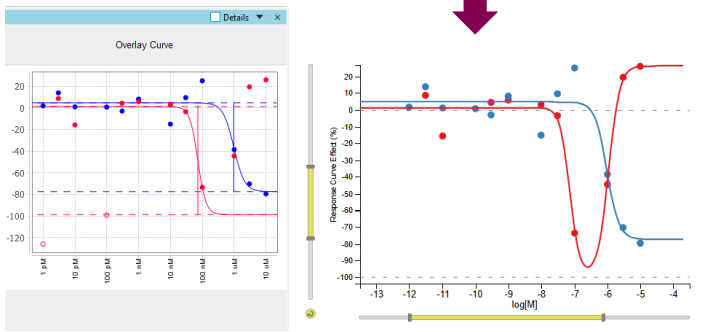
- AZ legacy curve column lapsed thus introduction of D360 curve column very welcome
- Pull data from curve viewer db into D360 curve column

Curve viewing



- Curve columns allows for a different type of browsing & cpd comparison than viewer
- As curve fitting in GeneData Screener evolves, quicker to implement in viewer e.g. Hook curves
- Curve viewer good for multiple cpd viewing





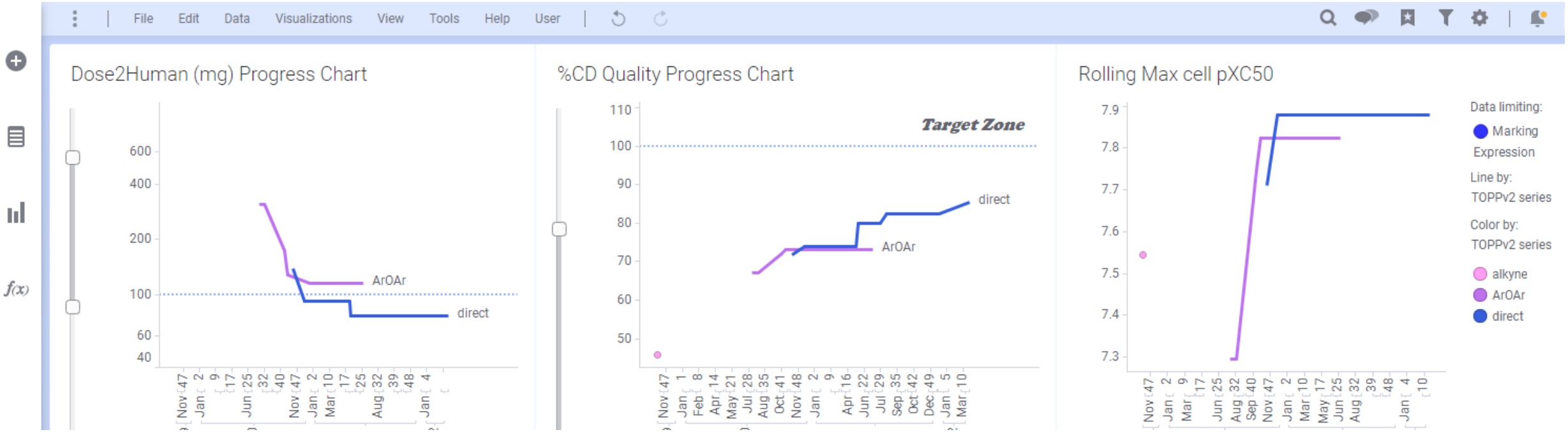
Project progress tracking

Project progress tracking

NB publn subset of cpds shown for a project

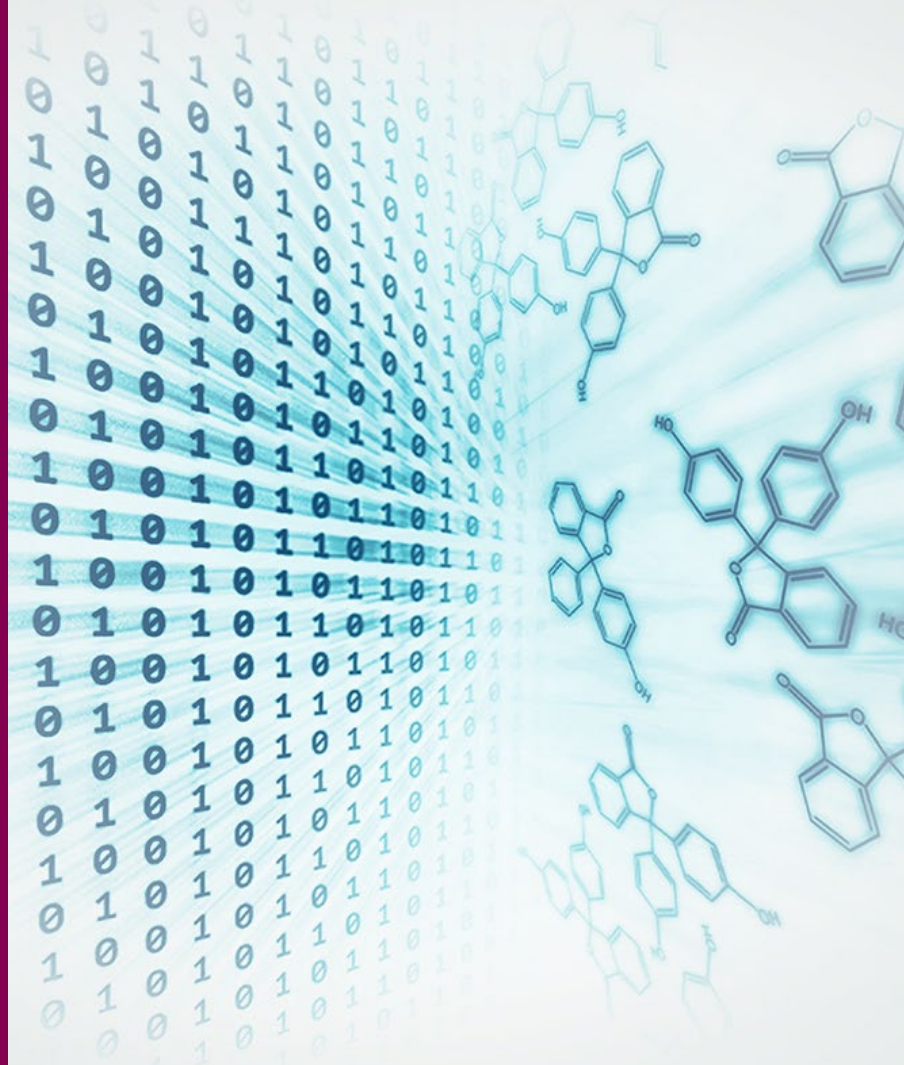
- Tracking Of Project Progress (TOPP) query is generic D360 query used across projects
- Autofill of annotations allows each project to fill into the same generic query – some issues with column type

Project progress tracking

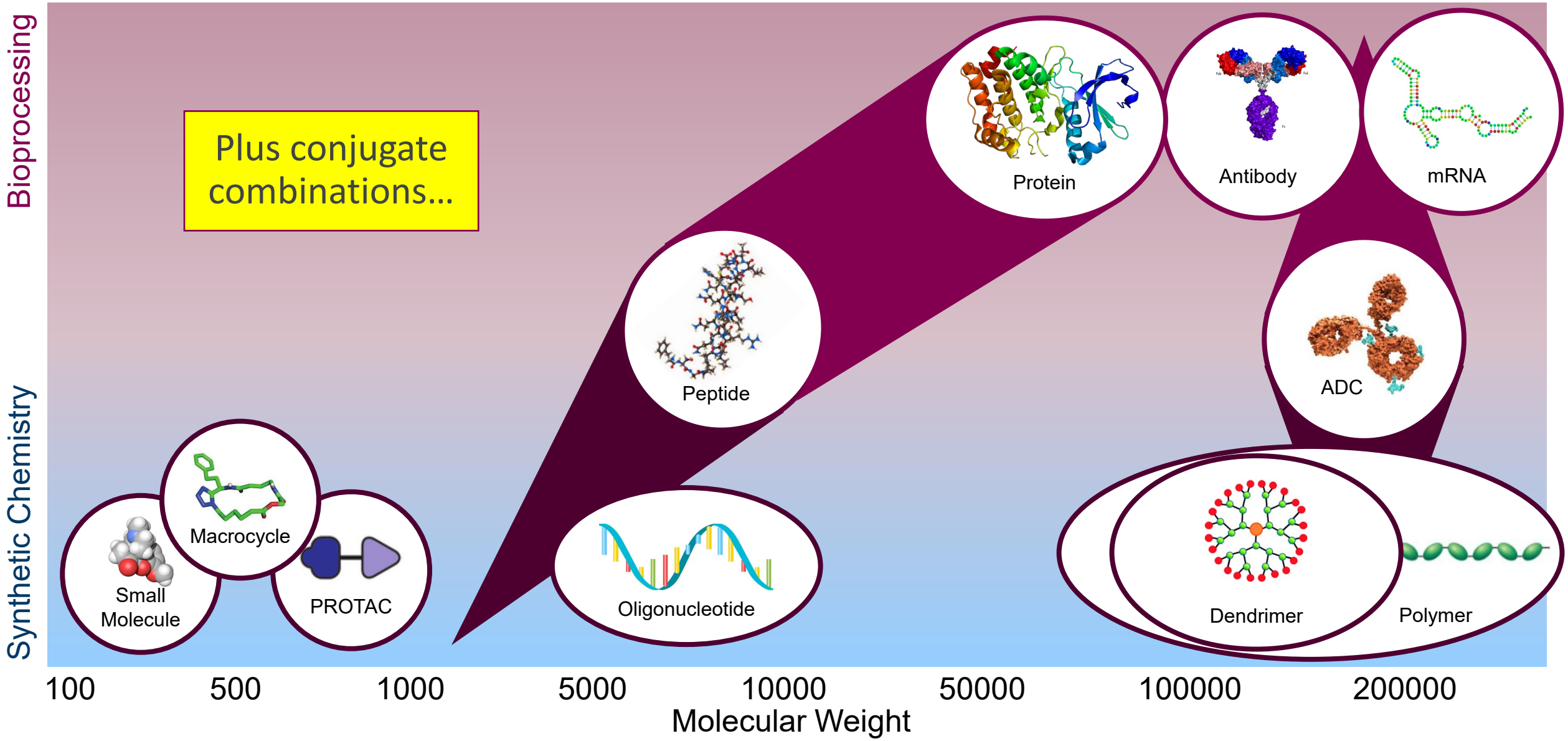


- Spotfire viewer allows for additional analysis & visualisation, tracking progress over time
- Rolling average data & multiple data columns on y-axis particularly useful

Modalities beyond small molecules…



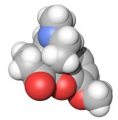
Modalities beyond small molecules...



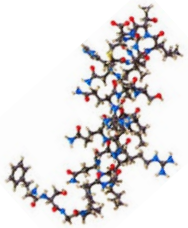
Substance type…. structural class…. modality

- **Substance type** is set for regulatory purposes
  - Not concise enough or aligned to how a scientist thinks to be helpful for everyday project use

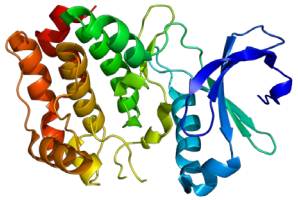
- **Structure class** is based on substructure matches & sets of rules defined with diverse scientist input
  - Decision tree approach
  - Run as a calculation that can evolve over time
  - Registration system input meta data can be used
  - Used to apply appropriate business rules and property calculations
  - Examples below + functionalisation, + combinations



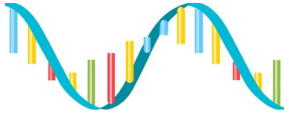
Small Molecule



Peptide

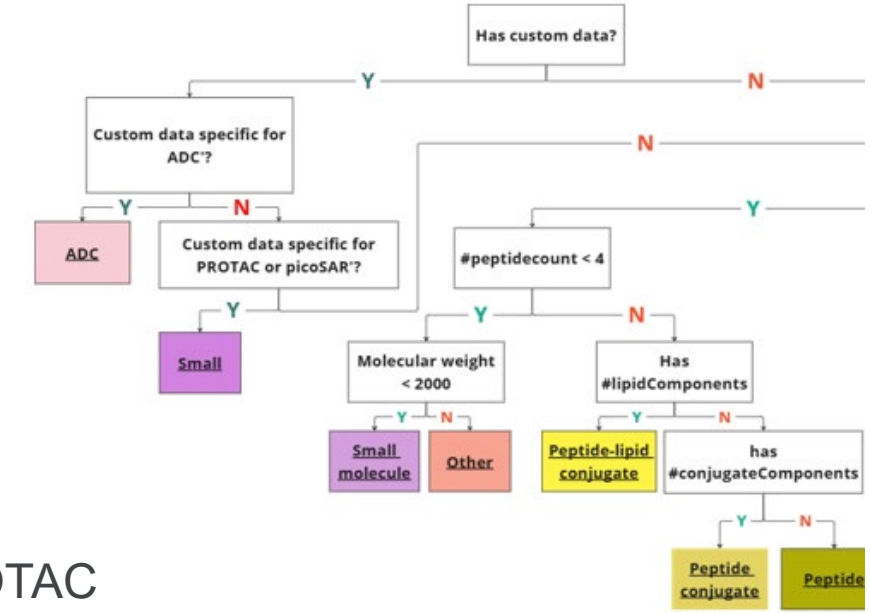


Protein

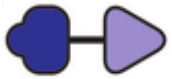


Oligonucleotide

ADC



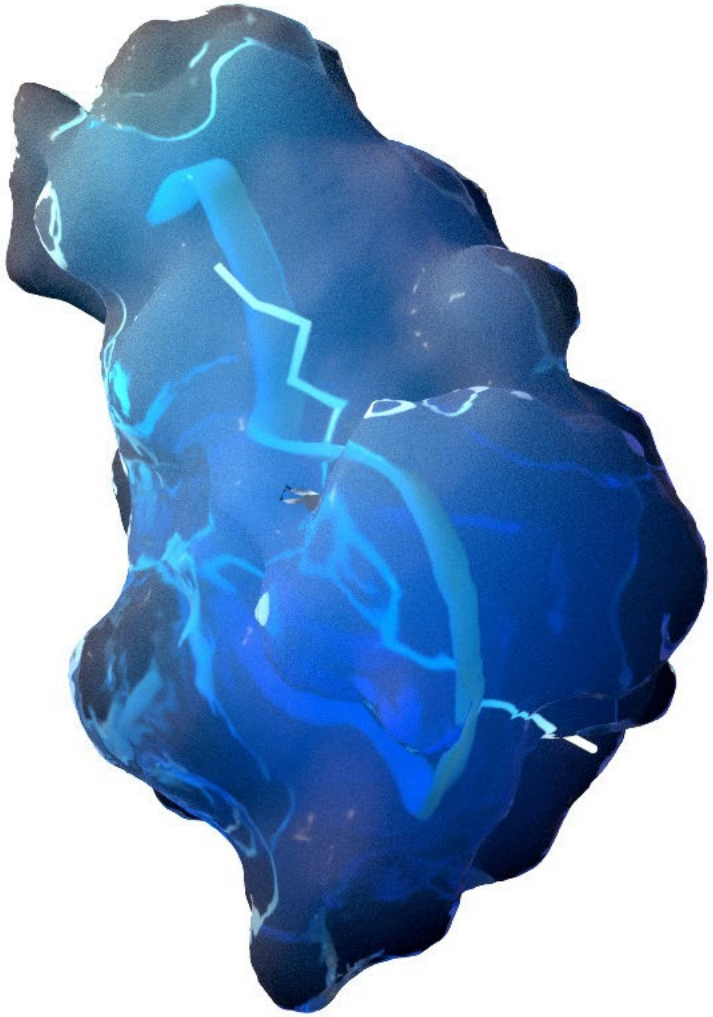
- **Modality** is a user-assigned, function-based classification e.g. PROTAC
  - No good way currently of doing this…….



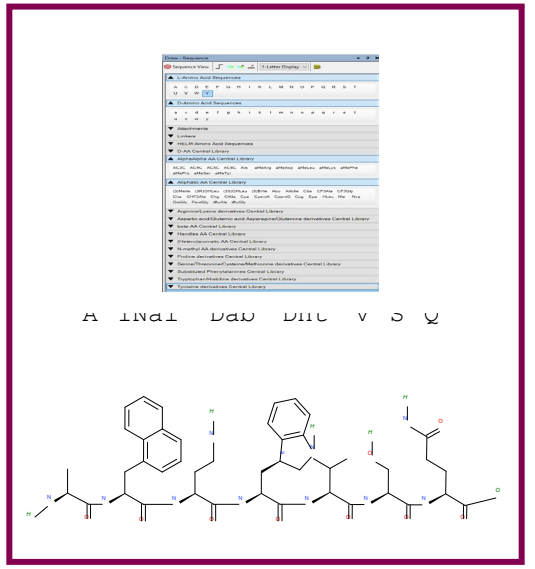
PROTAC

- Scientists just want to run a D360 query that “gives me all the small molecules/peptides/ADCs/PROTACs etc”

Peptides



Peptides: DMTA enabled by curated building-block collection deployed to key tools



Centralised storage

Amino acid naming rules

AstraZeneca established standards

Standardised names

Hub

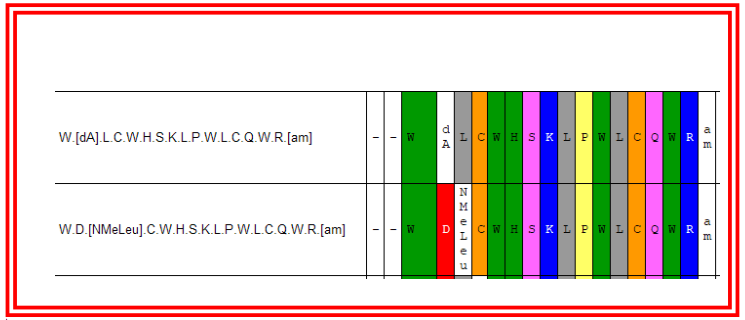
Synthesizers

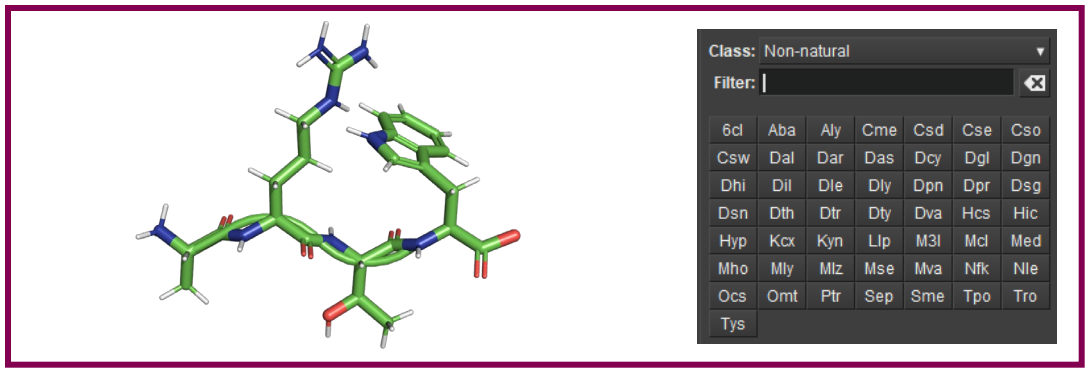
Drawing Tools

SAR

Registration

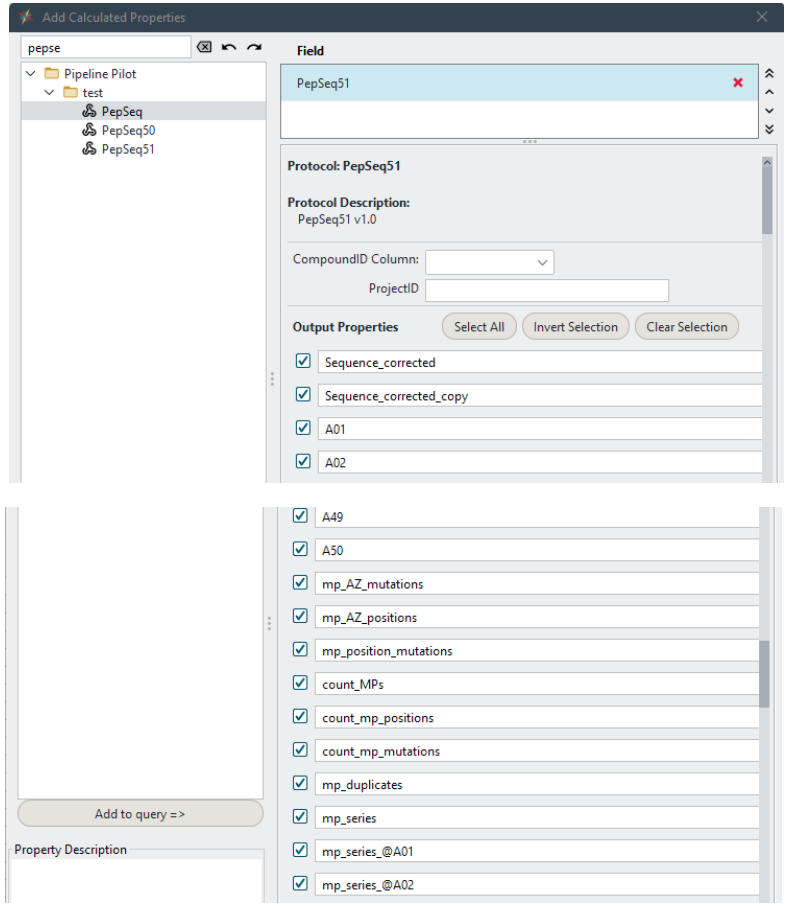
Modelling Tools

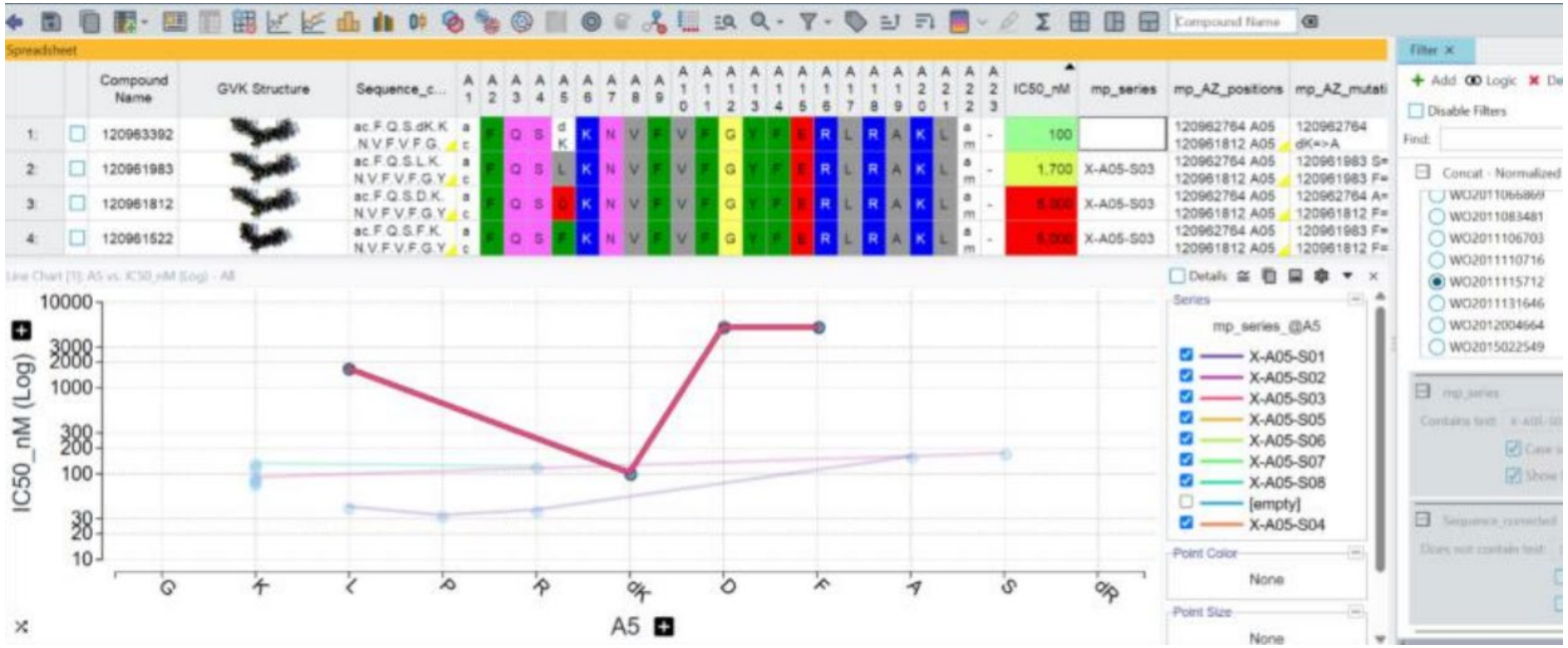




Sequence-based registration for New Modalities

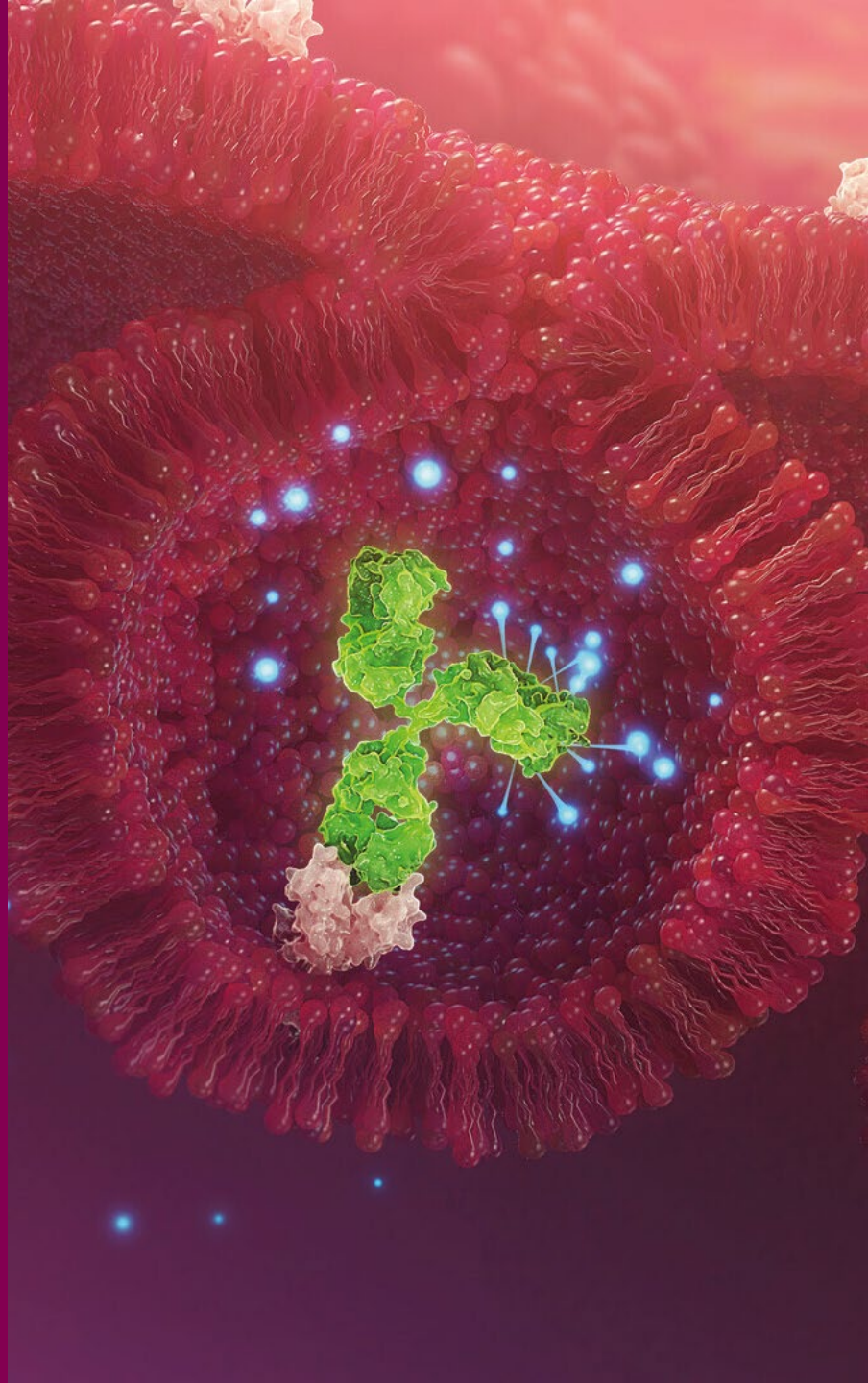
Peptide SAR in D360





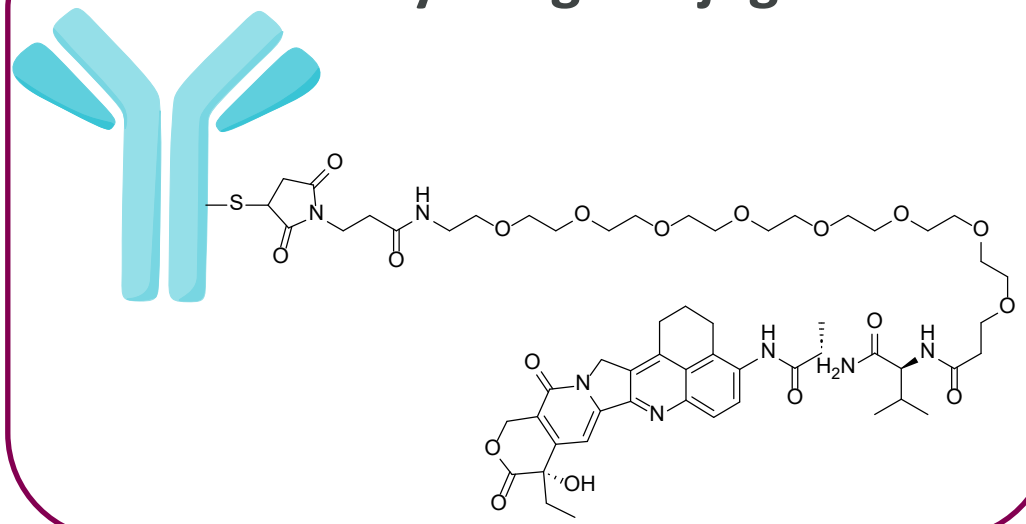
- PepSeq51 plug-in created to enable analysis of HELM 2D peptide sequences
- Sequences (up to 50AA) are aligned and matched pair analysis across sequences conducted
- Visualisation in datatable, new customised columns and filters to explore mutation SAR
- AZ keen to contribute to Certara x-pharma peptide working group to improve peptide analytics in D360

Antibody Drug Conjugates (ADCs)



Antibody Drug Conjugates (ADCs)

Antibody Drug Conjugate

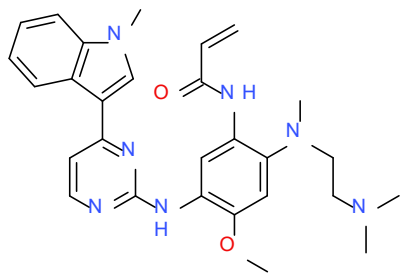


ITcode → IBIS → AZ test results data

AZnumber SNumber → ISAC → AZ compound & sample data

→ D360

Small Molecule

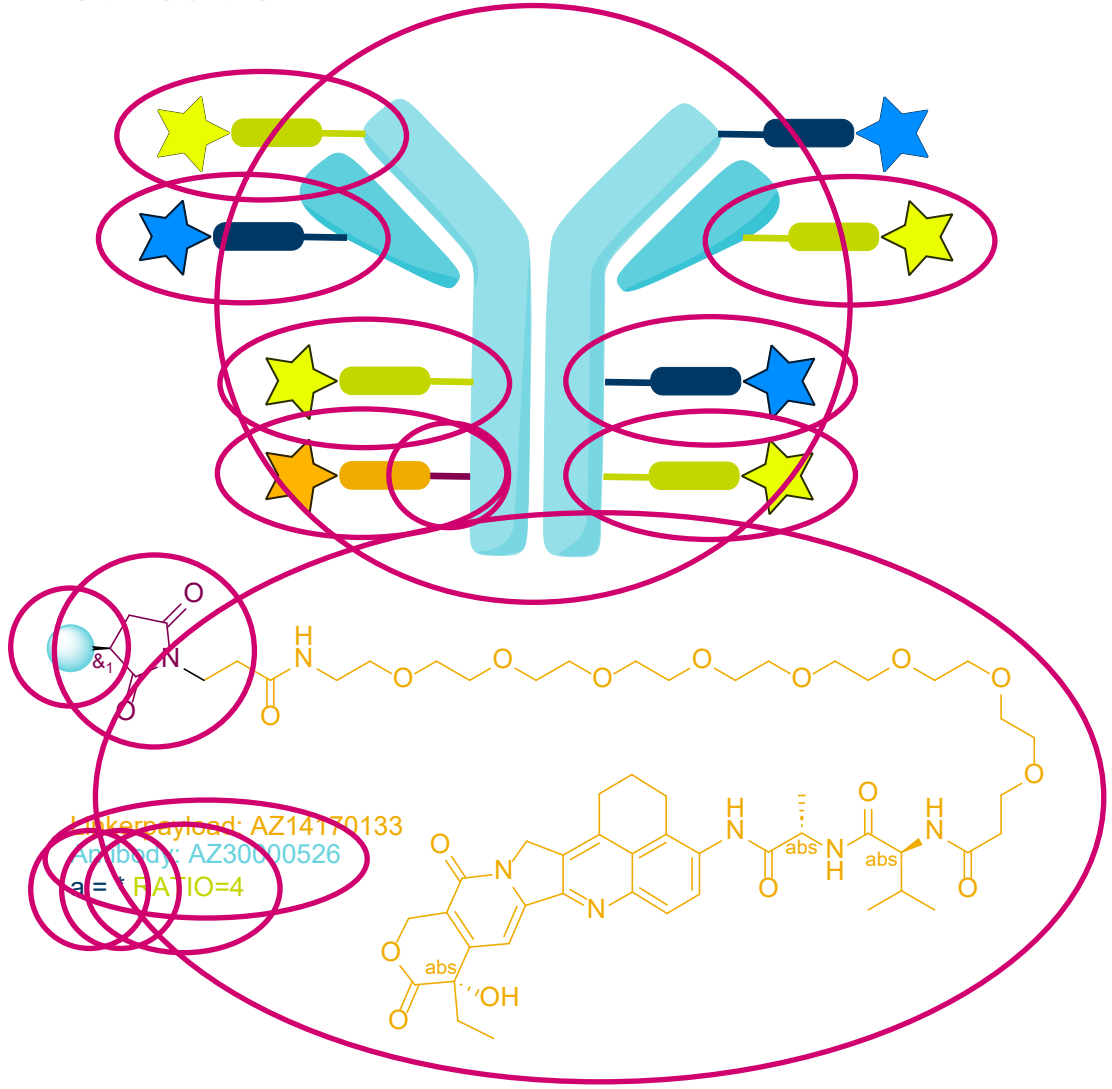


Tagrisso®

- ADCs are an increasingly common modality in drug discovery
- Registration & analysis of ADCs provided new challenges for AZ workflows
- In principle, as long as we can register (AZnumber) and test (ITcode) then can use existing workflows in D360

ADCs provide a challenge for molecular registration

- Uniqueness checking criteria for ADC parametrisation:
  - Linker-payload Compound Name
  - Antibody Compound Name
  - Conjugation Type
  - Conjugation Distribution
  - Drug-Antibody Ratio
  - Conjugation Site



ADC workflow involves many scientists

Chemistry

Linker-payload registration

Biovia Draw

ISAC

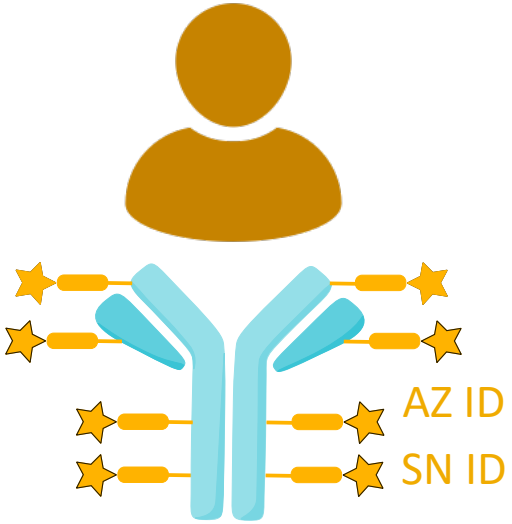
Biologics Expression

Antibody registration

GeneData Biologics

ISAC

Bioconjugation

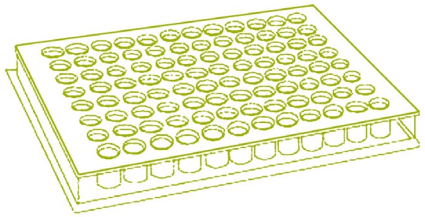


ADC registration

GeneData Biologics

ISAC

Bioscience



ITcode & IC_{50}

GeneData Screener

IBIS

- Individual components are registered then ADCs is registered

Every registered ADC now has data in D360 (Phase 1)

Data office definition

PIP calculaton

3 ADC components

Linker Payload (LP) info

Spreadsheet

		cpd	Substance Type	Structure Class	Carrier Compound Name	Linker Payload Compound Name	Payload Compound Name	Linker Payload Conjugation Site	Linker Payload Conjugation Type	Linker Payload DAR	Linker Payload Distribution Type	Linker Payload Conjugation Order	Expression Host Type
1:	☐	AZ	chemical substance	Small molecule									
2:	☐	AZ	recombinant protein conjugate	ADC	AZ	AZ	AZ1	HC:C178	Thiol-Maleimid	2.0	Site-Specific	1	Mammalia
3:	☐	AZ	recombinant protein conjugate	ADC	AZ	AZ1	AZ1		Thiol-Maleimid	4.0	Stochastic	1	Mammalia
4:	☐	AZ	recombinant protein conjugate	ADC	AZ	AZ1	AZ	LC:C215|H	Thiol-Maleimid	8.0	Site-Specific	1	Mammalia
5:	☐	AZ	recombinant protein conjugate	ADC	AZ	AZ1	AZ		Thiol-Maleimid	4.0	Stochastic	1	Mammalia
	☐	AZ	recombinant peptide/protein										Mammalia

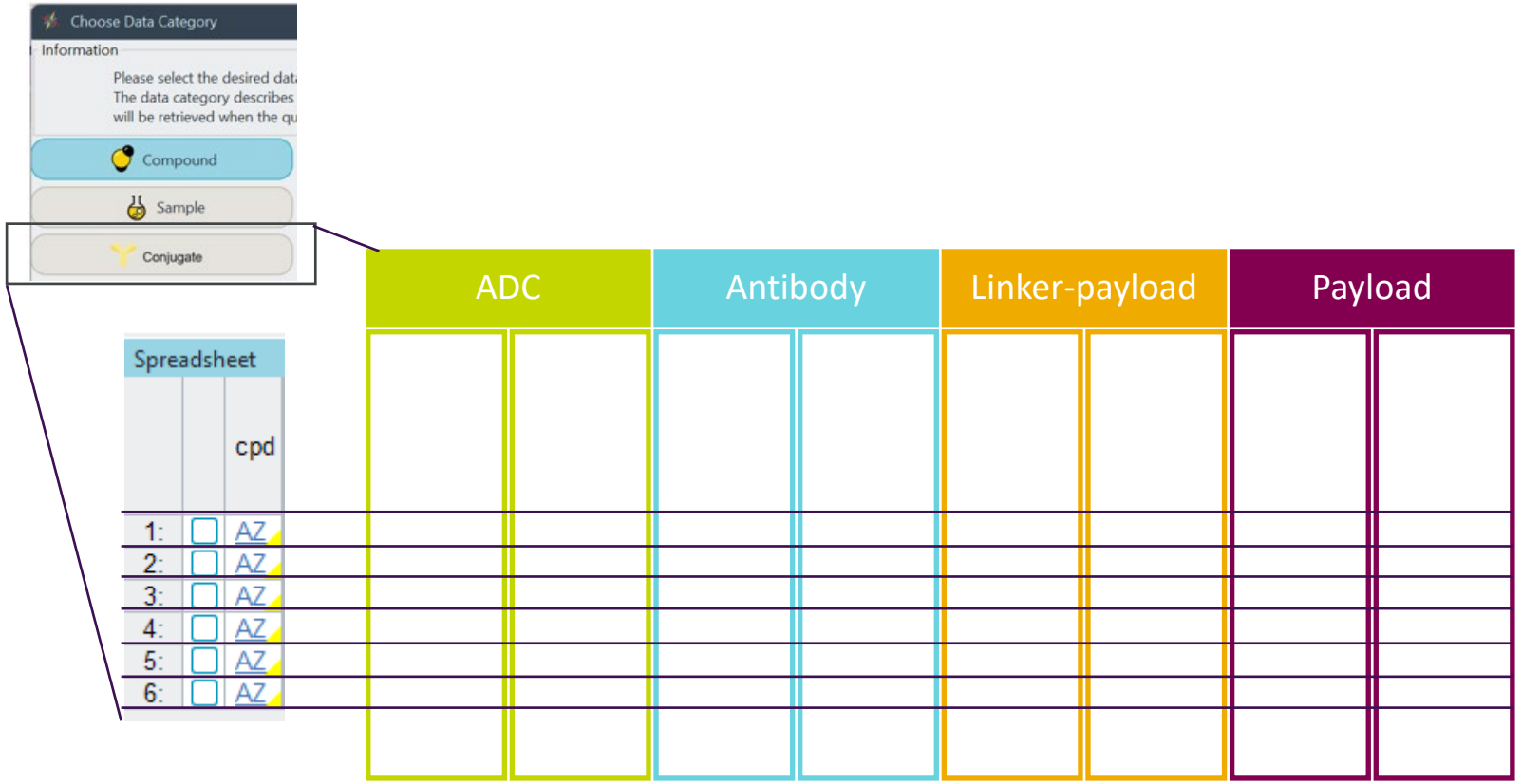
Antibody (no structural class yet)

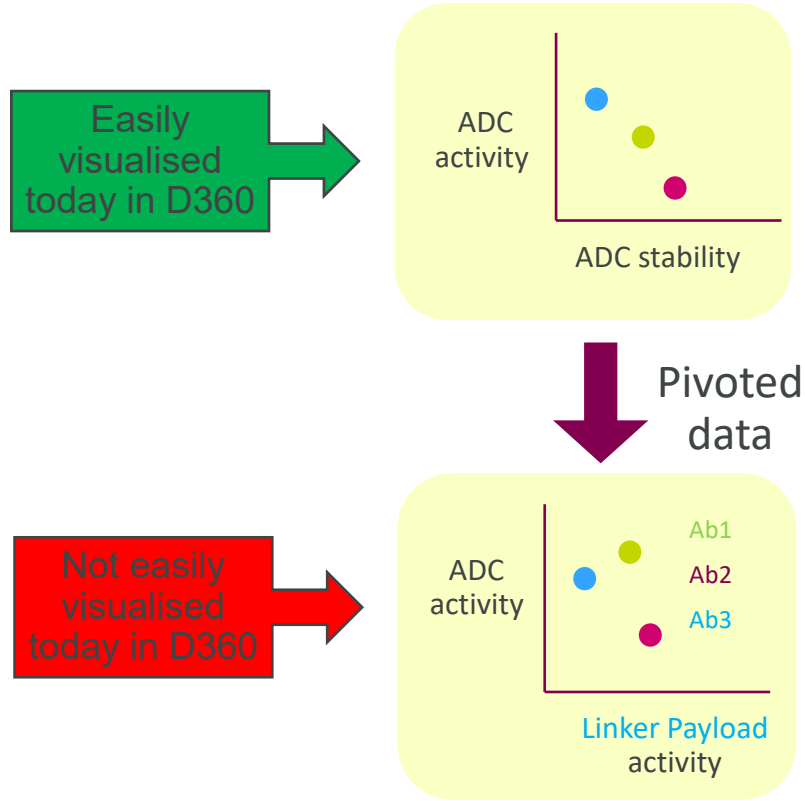
Antibody info (for Ab or ADC)

Expression Host Type	Antibody Target	Sequence Origin	Macro Molecular Format	Macro Molecular Glyph SVG Image	MacroMolecular Fmt Glyph Url	MacroMolecular Format type	Amino Acid Sequence	Sub Unit Type	Modification Type
Mammalia			Fab (2-1)		https://gdbi	Antibody	QA	Light Chain	C-terminal Lysine
Mammalia			Fab (2-1)		https://gdbi	Antibody	DIQ	Light Chain	C-terminal Lysine
Mammalia			Fab (2-1)		https://gdbi	Antibody	EIV	Light Chain	C-terminal Lysine
Mammalia			Fab (2-1)		https://gdbi	Antibody	AIR	Light Chain	C-terminal Lysine
Mammalia	4-hydrox	Human	Fab (2-1)		https://gdbi	Antibody	AIR	Light Chain	C-terminal Lysine

- One line per compound & can filter out to just ADCs or other structural classes
- All data present to compare Payload, Linker Payload, Ab and ADC in the same assay
- Aim is to genericise this initial application for ADCs to types of conjugates

Future ADC Phase 2: separate conjugate data category





- One line per conjugate (ADC) with pivoted test data on each of component parts
- Today data is merged in TIBCO spotfire for ADC projects to do full analysis – more efficient if do in D360
- Any better ways to do this? …… relational datasets?

Summary

- D360 firmly established in AZ small molecule workflows but new features can still make significant improvements for projects
- Moving beyond small molecule use of D360 has challenges that will take time to achieve maximum value
- Opportunistic use of D360 HELM capabilities to enable peptide SAR
- Conjugates (including ADCs) are a work-in-progress for optimal D360 exploitation

Acknowledgements

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