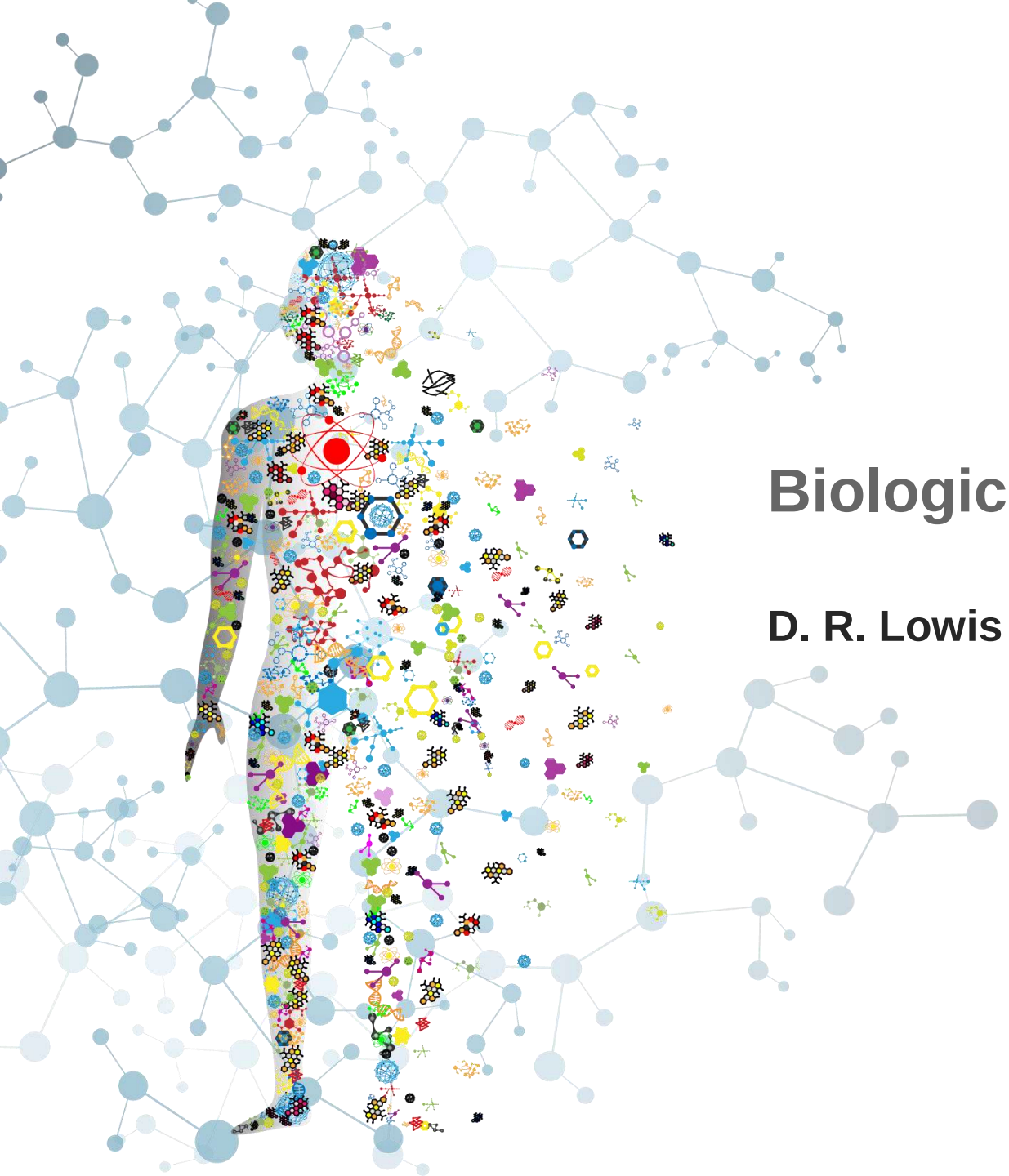
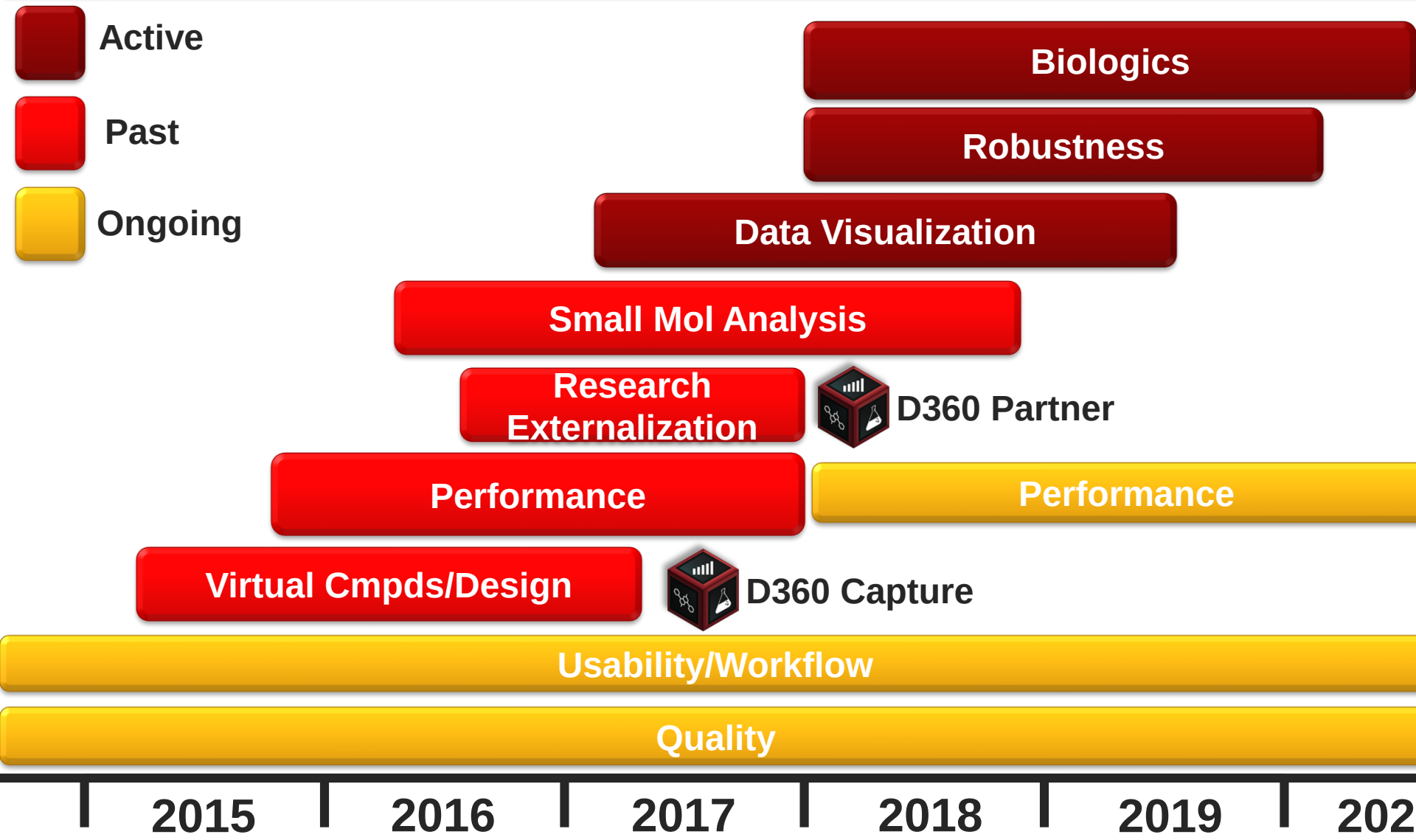


Biologics and D360

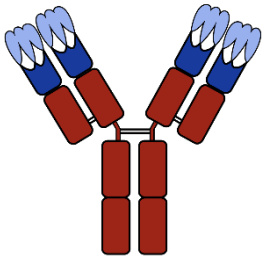
D. R. Lowis D. Phil.

D360 Product Development Themes

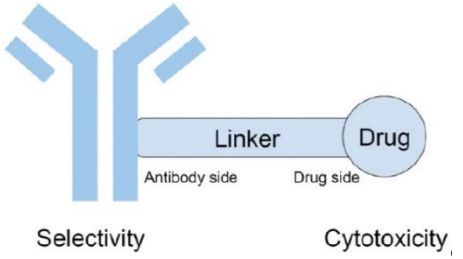


Multiple Types of Biologic/Research Process

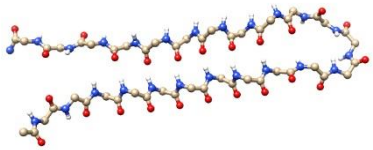
- Antibodies
  - Very different workflow from small molecules
  - Large number of entities, focus jointly on bioprofile and producability



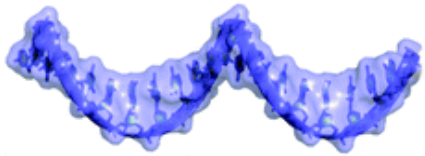
- ADCs
  - Small number of antibodies, different liners/warheads
  - Reduces to a small-molecule-esque workflow



- Peptides
  - Similar to small molecule workflow – Sequence-Activity relationsips



- Oligonucleotides
  - Somewhat similar to small molecule workflow depending on mechanism of action



- Other
  - Vaccines, mixtures of the above concepts, …

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A Simple Question

Given that D360 already provides the infrastructure for the data…

What additional tools can be provided that assist data-driven decision making for each new therapeutic modality?

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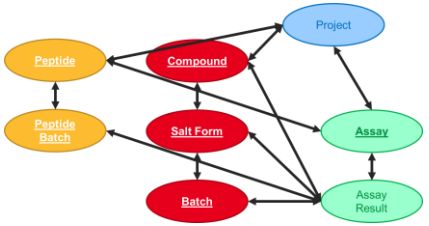
D360 Support for Biologics - Strategy

- Implement General Concepts
  - Multiple new entities – a potential data catalog explosion and data configuration
  - General representation of entities



HELM
Hierarchical Editing Language for Macromolecules

- Implement Modality-specific Concepts
  1. Specific entity representation
     - Sequence (including non-natural monomers)
     - Search, formatting, find, filtering, …
  2. Basic analysis
     - Determining measures of similarity
     - Comparison methods
       - Alignment
       - Clustering
  3. Advanced Analysis
     - Extraction of therapeutic-relevant knowledge
     - “Structure”-Activity relationships

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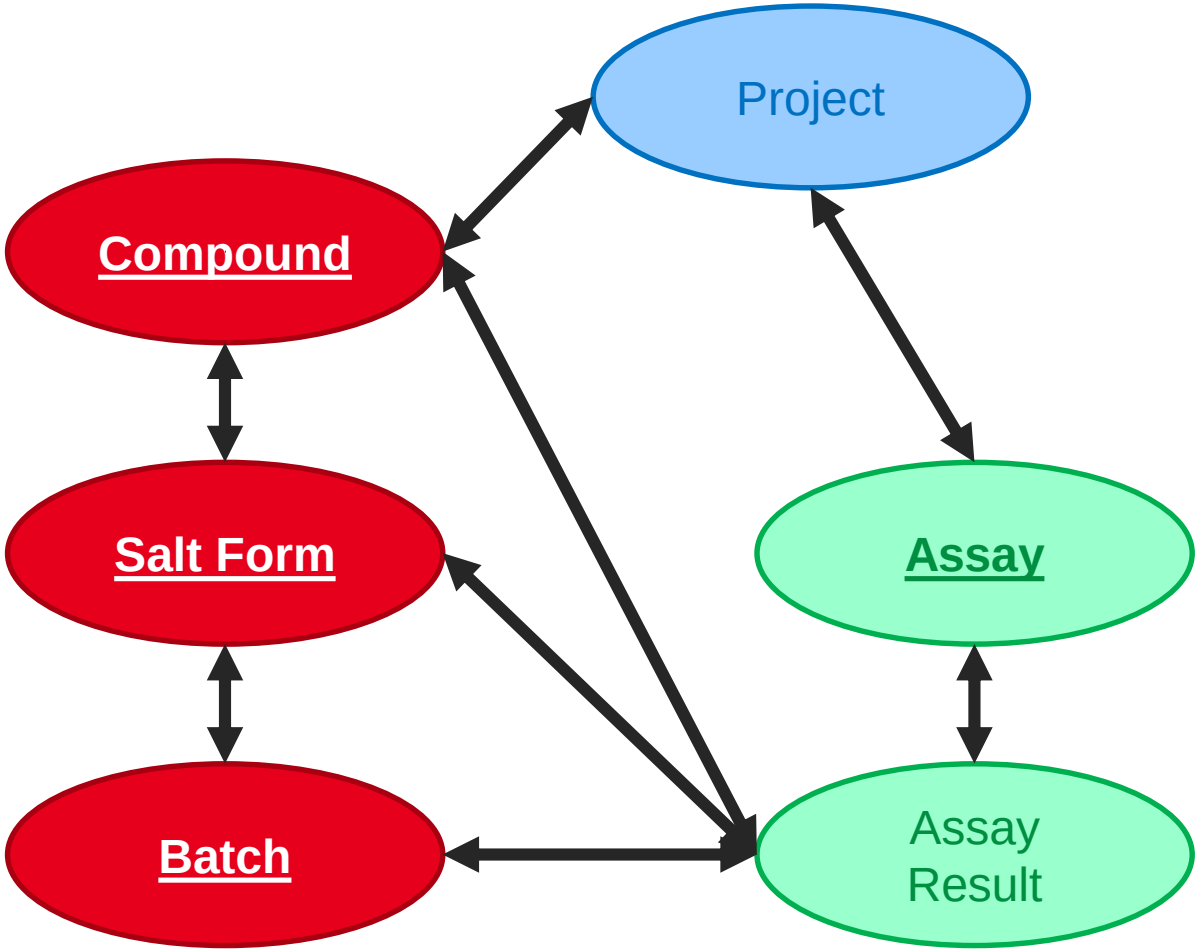
Multiple Entities/Data Configuration



Example Small Molecule Data Catalog

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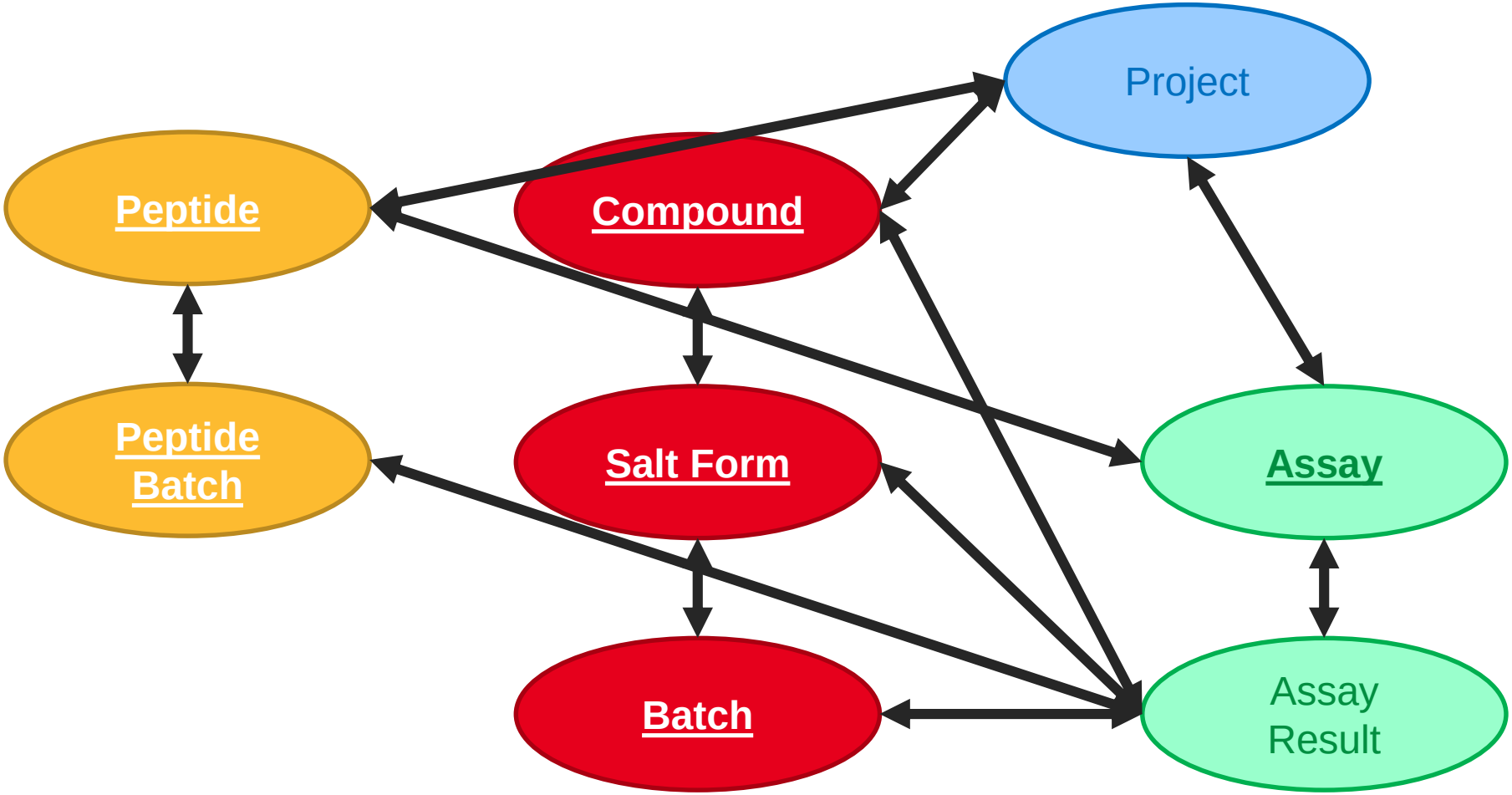
Multiple Entities/Data Configuration



…adding Peptides

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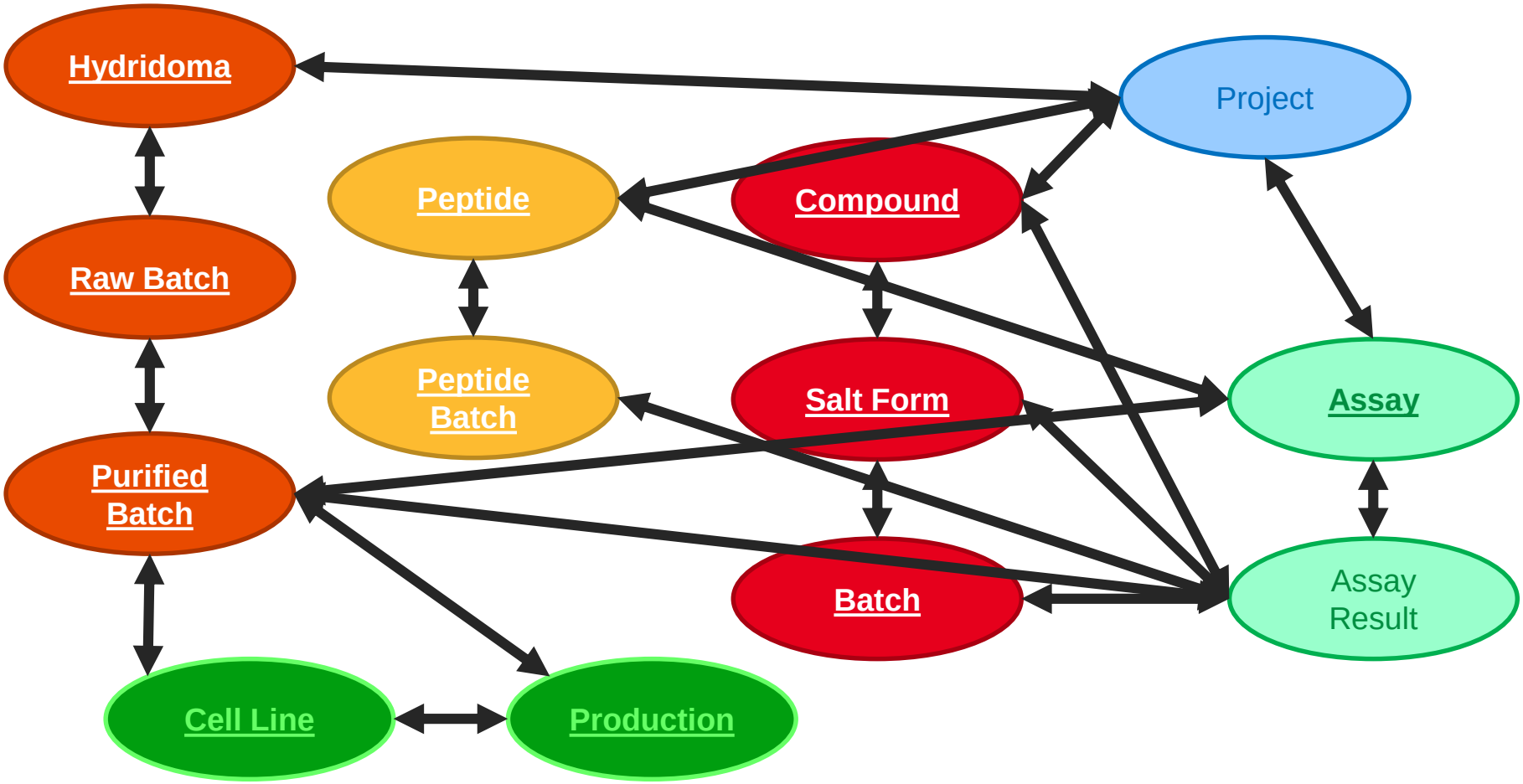
Multiple Entities/Data Configuration



…adding Antibodies

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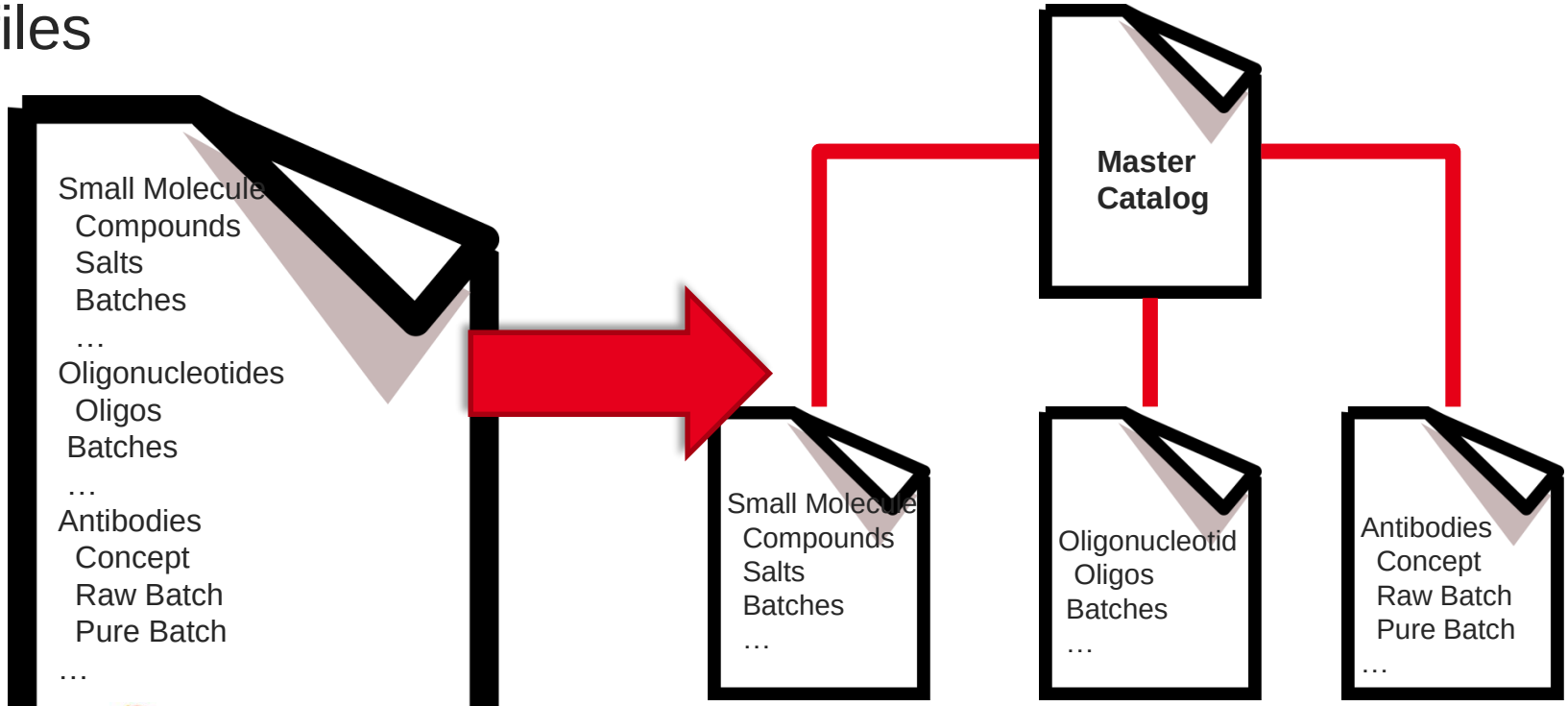
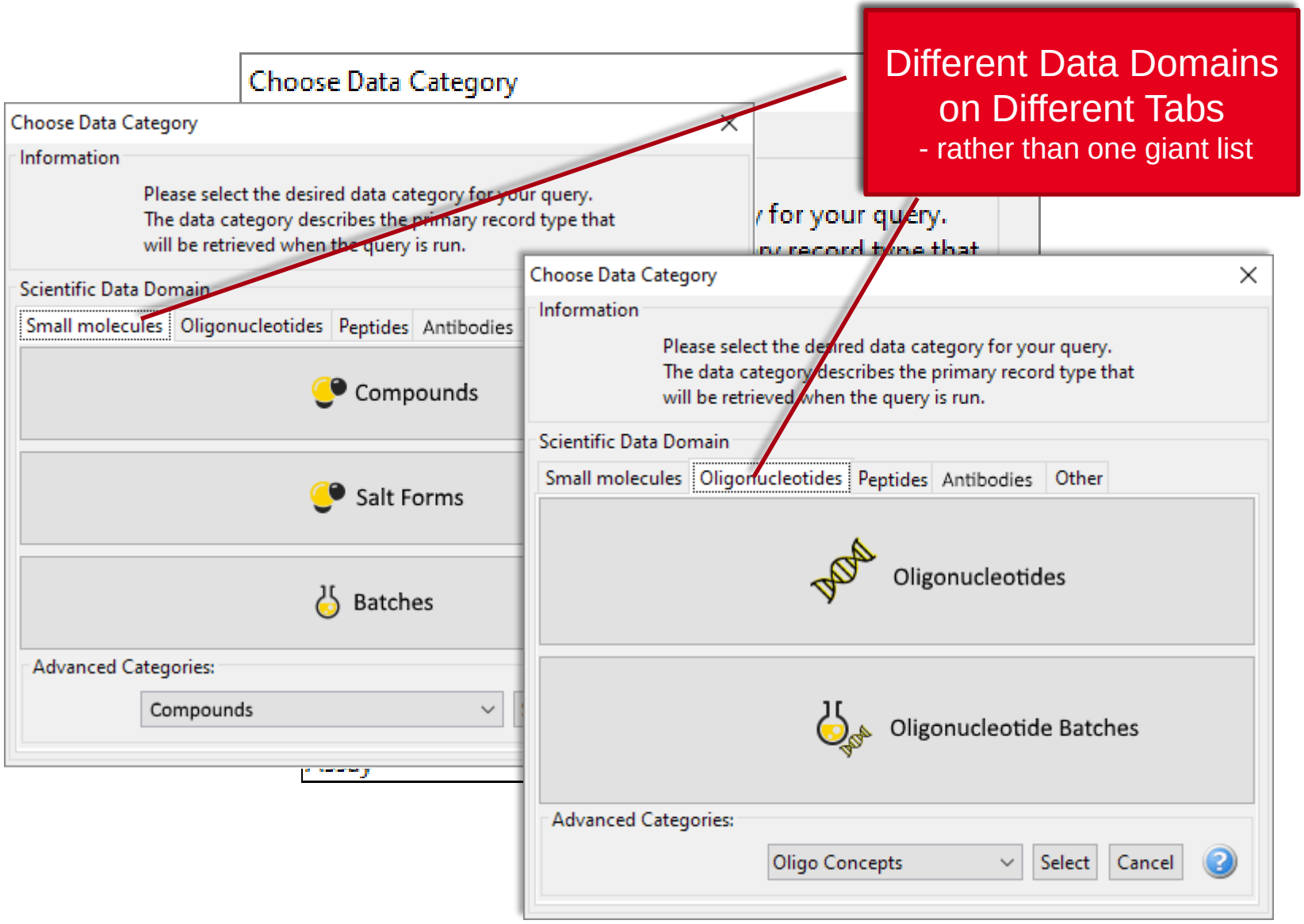
Assisting the Configuration

- General Configuration
  - Not an issue for D360 – at its core it is data agnostic
  - But…. More entities, more data fields, more relationships can make configuration management more complex

- D360 Updated to allow data catalog to be split over multiple files



Assisting the End User: Data Category Selection



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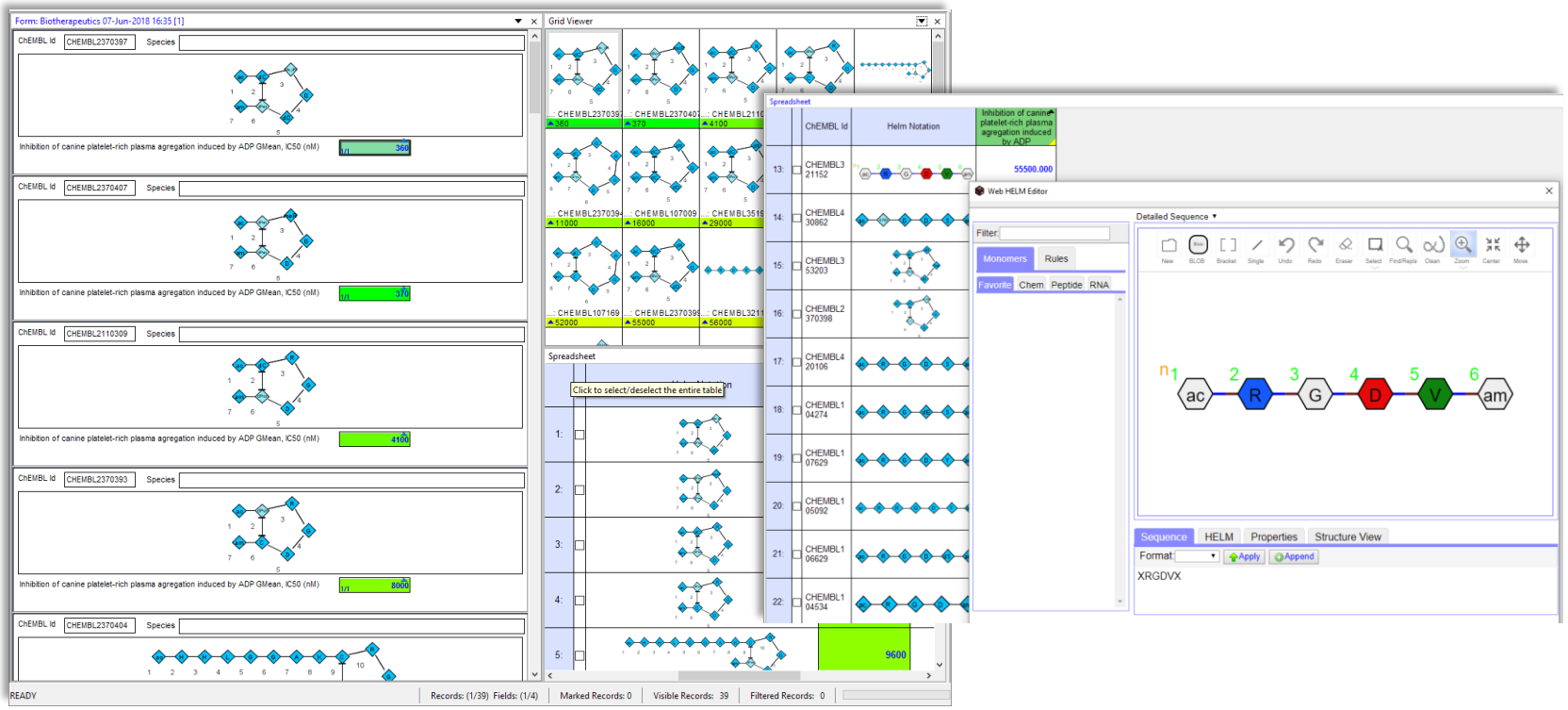
Moving to Representation - General and Specific

General Representation

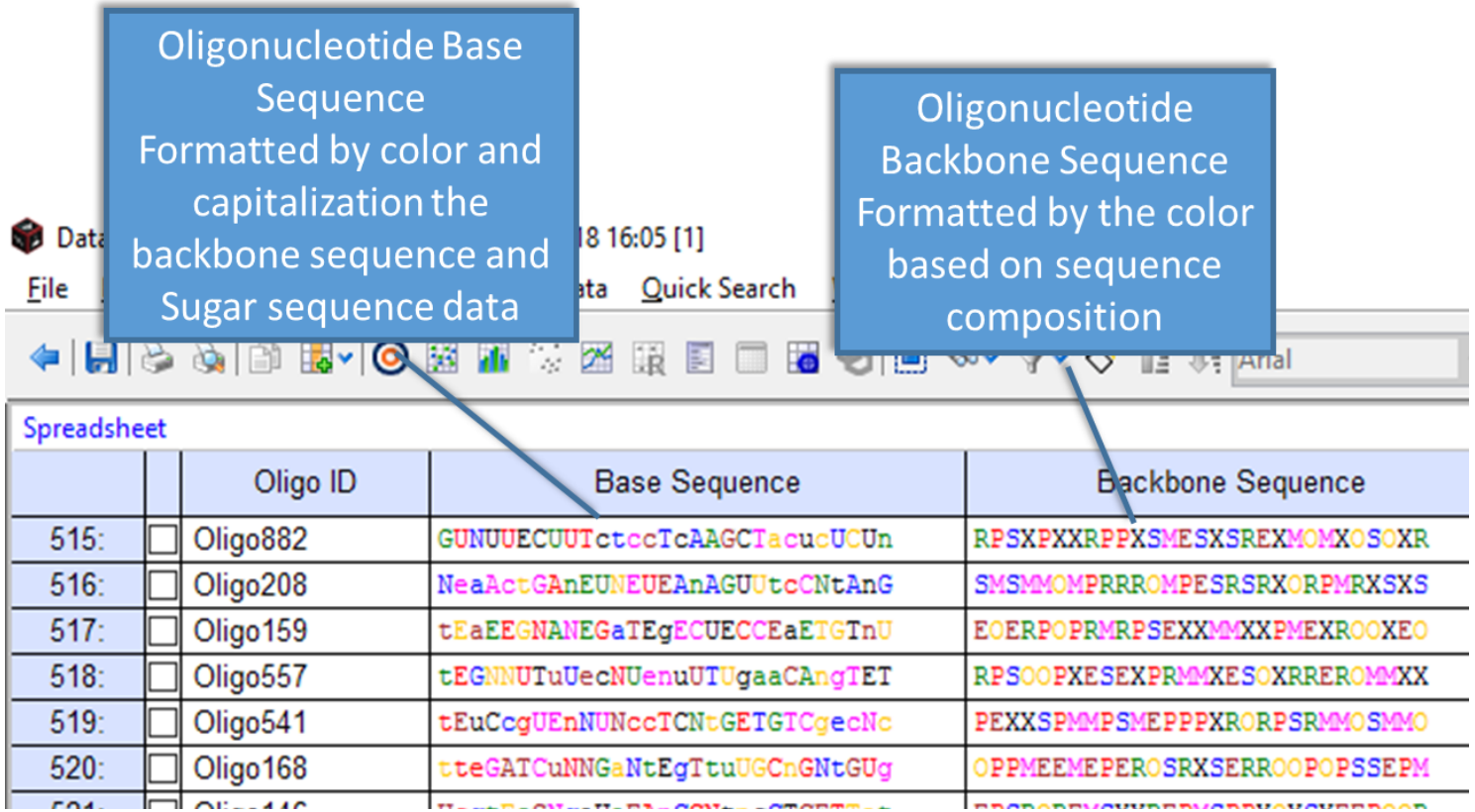
- Support for HELM Notification
  - Allows HELM to be presented
  - Integration with HELM viewer/editor



- Product support for BioVia Renderer
  - Allows Biovia notation presented

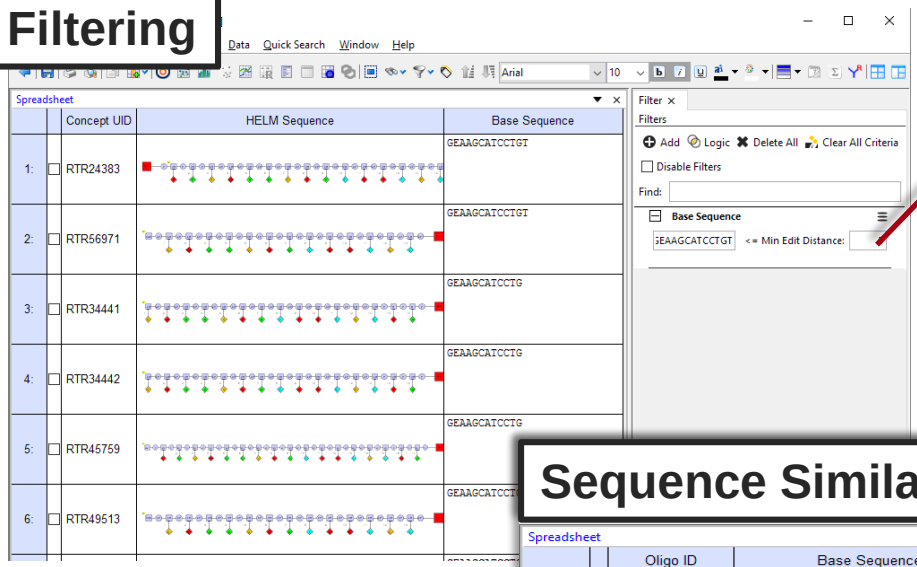
Oligonucleotide Representations

- Multiple, sequence-based, oligonucleotide representations
  - HELM, Biovia, single sequence custom format, multi-sequence custom format



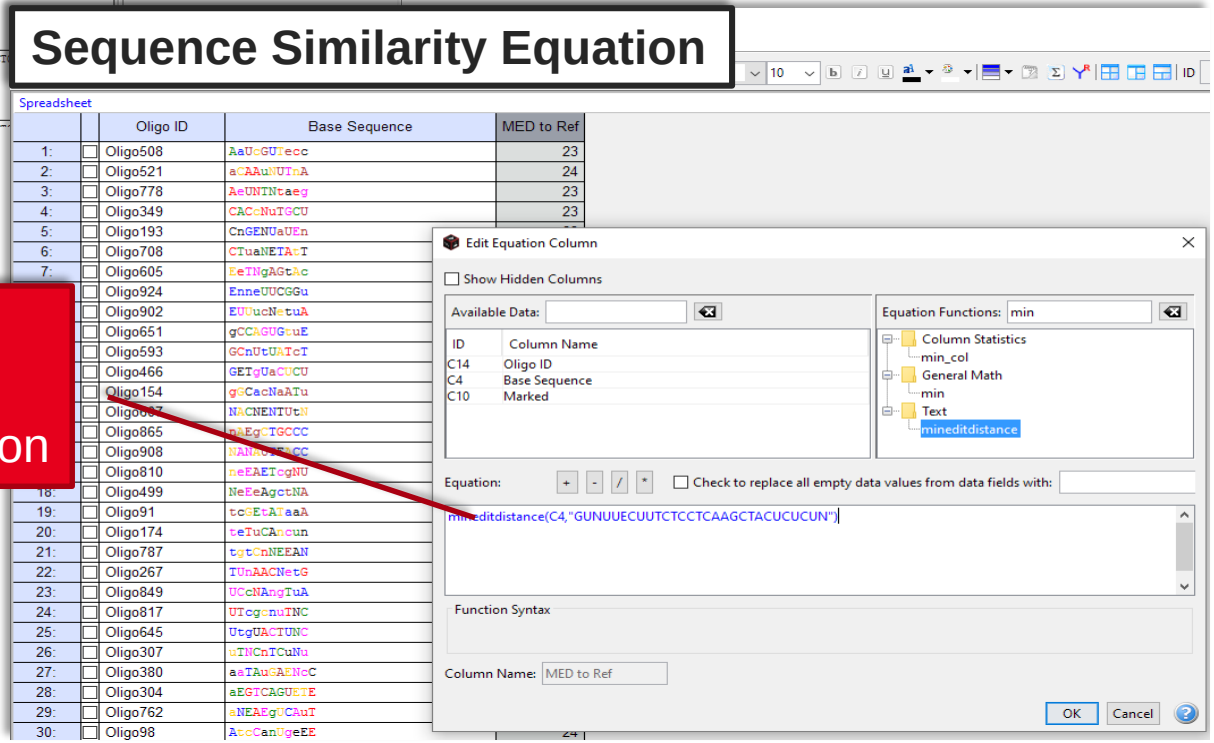
Oligonucleotide Support: Filtering and Equations

Filtering



Filter by text or Similarity

Sequence Similarity Equation



Sequence Similarity Equation Function

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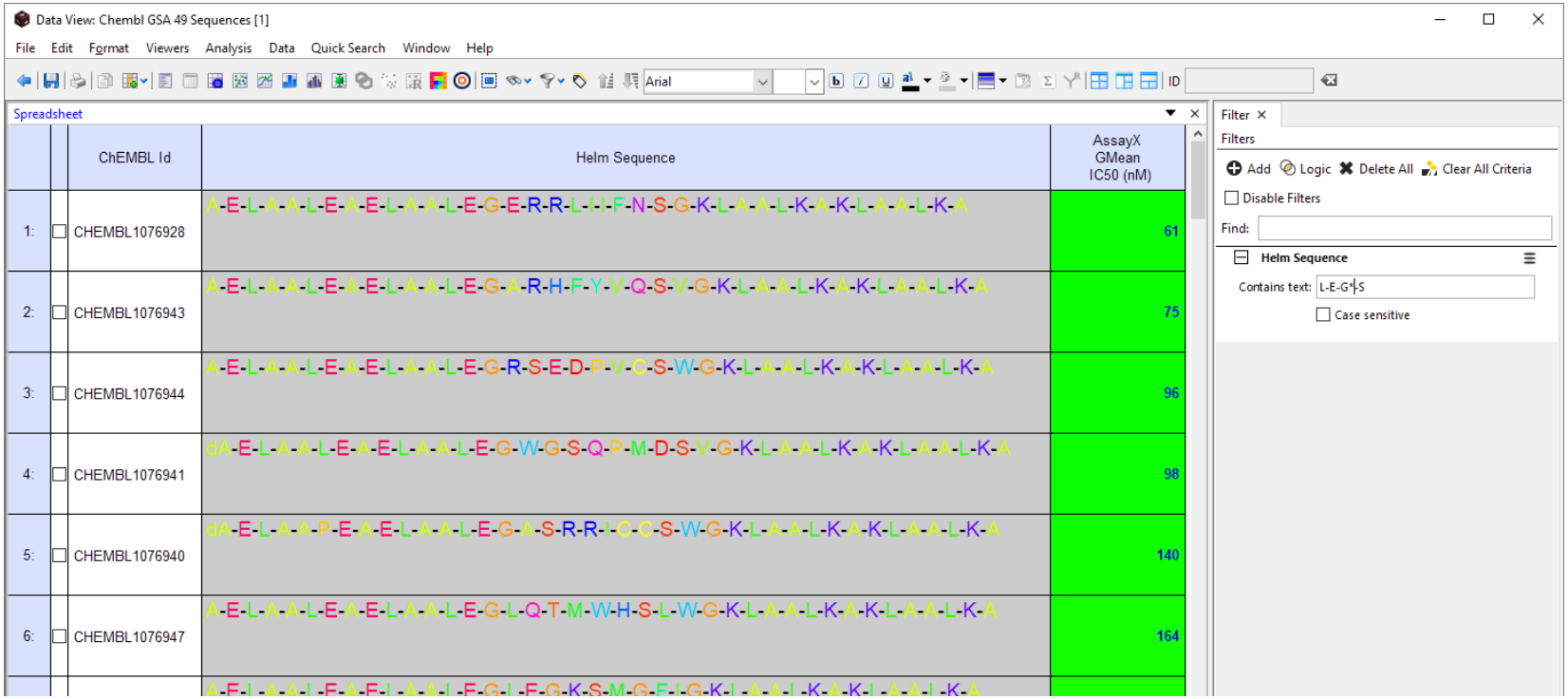
Peptide/Protein Representations

- Multiple, sequence-based, oligonucleotide representations
  - Peptides: HELM, Biovia, single sequence custom format
  - Proteins: Standard sequence representations
  - Added complication of non-natural monomers
    - Splits concepts of proteins *vs.* peptides



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Moving to Basic Analysis - Sequence Alignment

Medicinally Relevant Peptide Sequence Alignment

- Bioinformatics studies protein (and DNA/RNA) sequences via sequence alignment

- BUT:
  - Bioinformatics looks for evolutionary relationships between sequences
  - Bioinformatics deals only with naturally occurring monomers
- What we want:
  - Must deal with unnatural monomers
  - We care about structural and chemical similarity NOT evolutionary distance
- So:
  - We utilize standard bioinformatics alignment algorithms but apply chemical similarity matrices to score alignments
  - Bioinformatics: X matched Y scores 0.7 since there is a 70% chance of an evolutionary mutation
  - D360: X matched Y scores 0.6 since X and Y are 60% chemically similar
  - **This makes D360 sequence alignments medicinally relevant**

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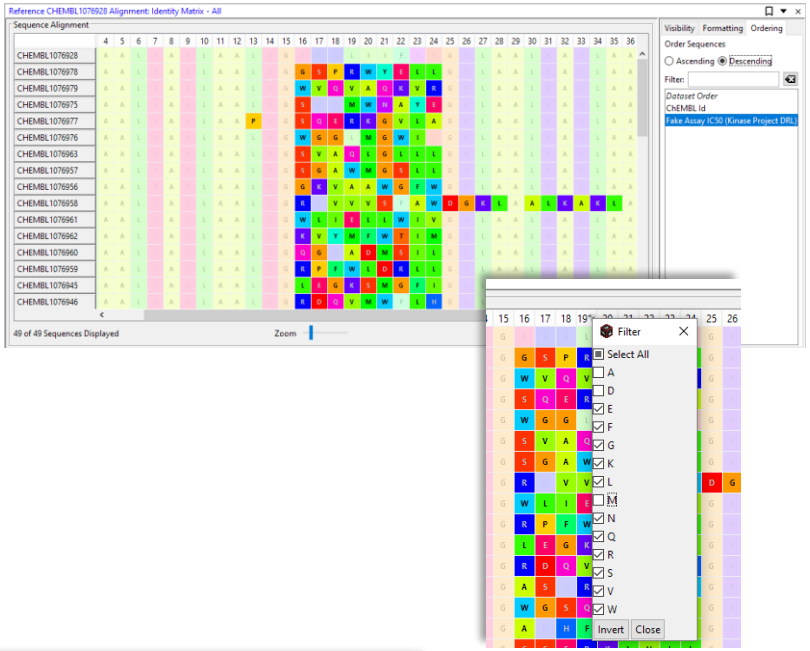
What can we do with the Sequence Alignment?

- Alignment options
  - Align to reference sequence
    - Comparison of sequences with a reference
  - Multiple alignment
    - View overall similarity/differences across a set of sequences
  - For both natural and unnatural monomers

- Format and Highlight
  - Color by monomer properties
  - Highlight differences at aligned positions
  - Order sequences by assay data



- Filter sequences
  - By monomer X at position Y

To allow users to understand what sequence changes give improved bio-properties

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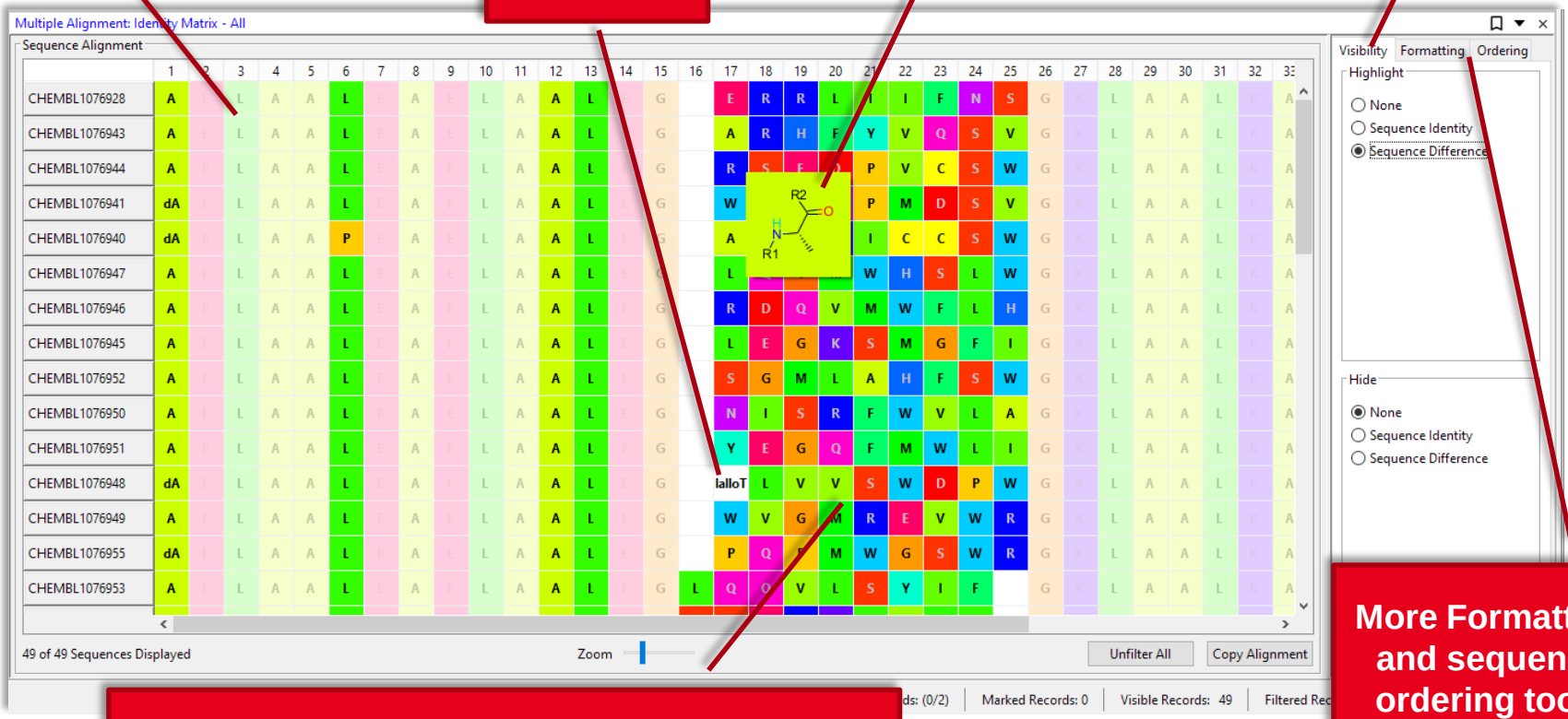
Basic Analysis: Peptide Sequence Alignment Viewer

Aligned Peptide Sequences
- color coded by monomer chemical properties

An example of an unnatural monomer

Chemical structures are displayed with tooltip or my zooming in

Tools to Highlight/Show/Hide differences and similarities

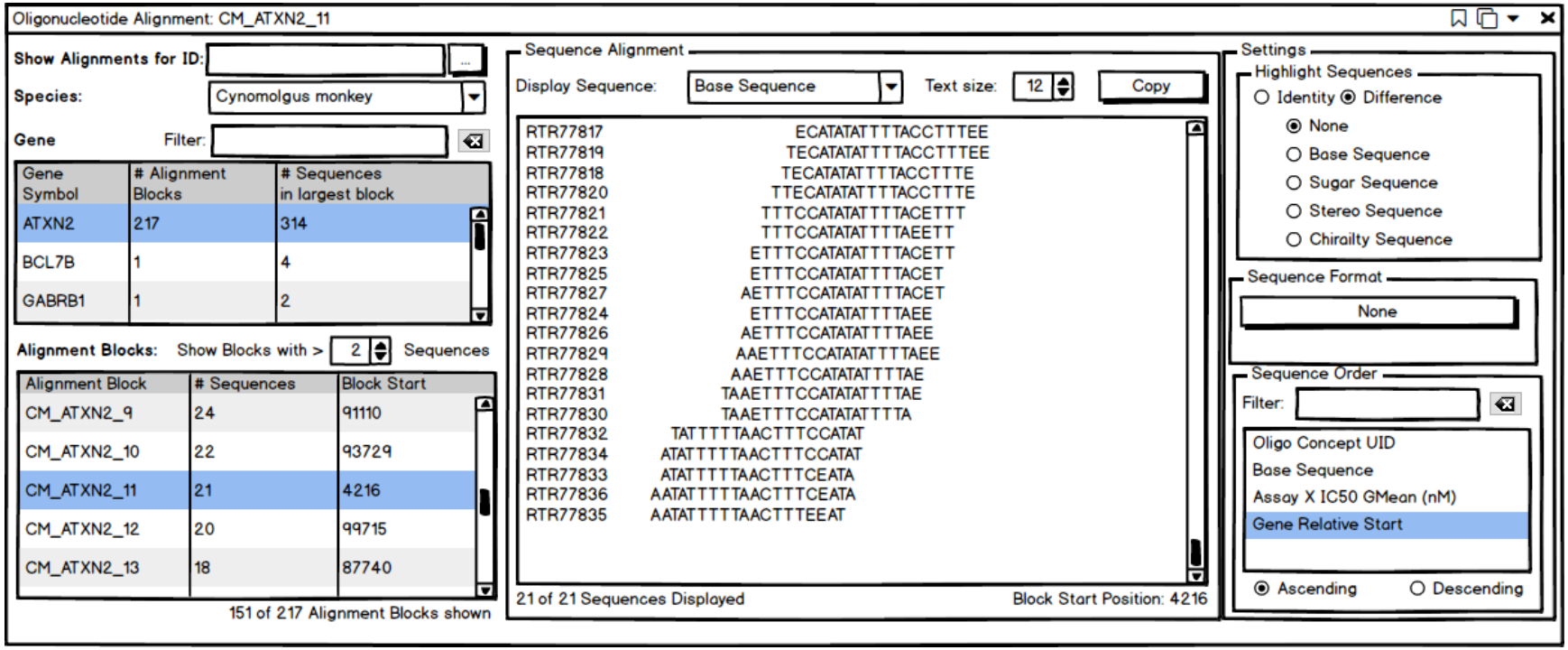


More Formatting and sequence ordering tools

Sequence Alignment shows similarities and differences between sequences which can be compared with changes in biological activity

What about olgio and protein sequence alignment?

- Protein sequences
  - Just need to add in standard similarity matrices
- Oligo sequence alignment
  - Need to consider the alignment against the gene



Where Next…

	Oligos	Peptides	Antibodies
General Representation	Complete for presentation. Sequence parsers created ad-hoc.	Complete for presentation. Sequence parsers created ad-hoc.	Complete for presentation. Sequence parsers from standard formats.
Basic Analysis	Alignment In Design	Alignment complete.	Alignment to be based on Peptide
Advanced Analysis		In Progress: Extraction of sub-sequence/chemical structure	

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Questions?