HELM for the masses

A notation standard for representing Biologics

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Domain Lead – Sergio Rotstein, Pfizer

Pistoia Alliance

The Pistoia Mission…

Lower the barriers to innovation

by improving inter-operability of R&D business processes

through pre competitive collaboration

Pistoia Alliance

Q2 2013

Pistoia Alliance Membership

Unmet need

„At present most pharma companies have **no way of storing complete structural machine-readable information** about the macromolecules they prepare or use in their research projects.”

HELM project charter / Dec. 2012

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HELM

Value Proposition

- HELM has been developed, tested and used by Pfizer
- HELM is being published and its supporting software tools will be put into the open-source public domain
- Pistoia Alliance to "sign-post" this standard and foster its adoption throughout the Pistoia Alliance community
- Pistoia Alliance to provide *ad interim* governance for the controlled evolution of the standard.

Business Case

- ***Projected Shared Project Costs ~$125,000 [Project Coordinator, Governance, Promotion, Meeting]***
- ***Estimated value for the industry of implementing this project is ~$437m***
  - Driven by productivity savings (e.g. fewer notation queries/resolutions from non-standard language)
  - Standard reference notation for macromolecules in pharma compound registration systems
  - The PA is the best-positioned, formally-established, x-company organization equipped to coordinate this kind of pre-competitive collaboration

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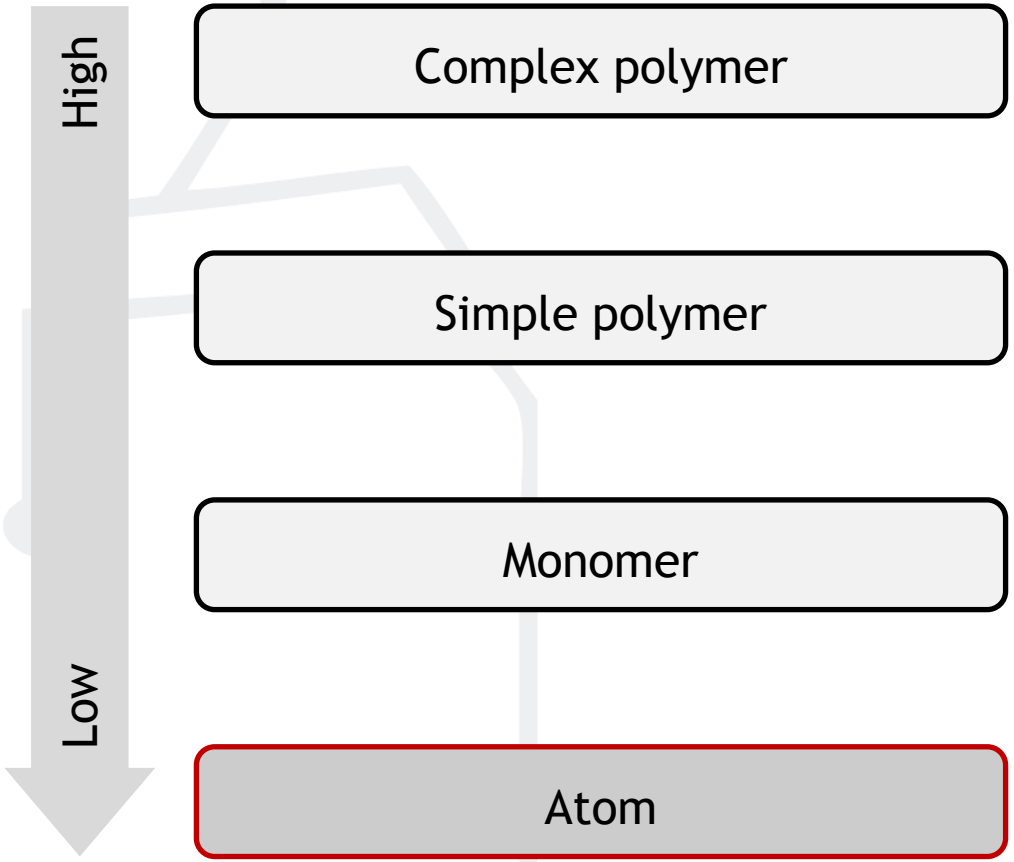
Hierarchical Editing Language for Macromolecules

- Macromolecules
  - Non-small molecules, Biologics
- Editing Language
  - Notation system
  - Grammar and vocabulary
- Hierarchy
  - Atom
  - Monomer
  - Simple Polymer
  - Complex Polymer

Structure hierarchy

- Higher level components are a combination of lower level components



- Molecules described by a HELM notation consist of atoms and bonds

Structure hierarchy

- Higher level components are a combination of lower level components

High

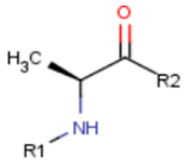
Low

Complex polymer

Simple polymer

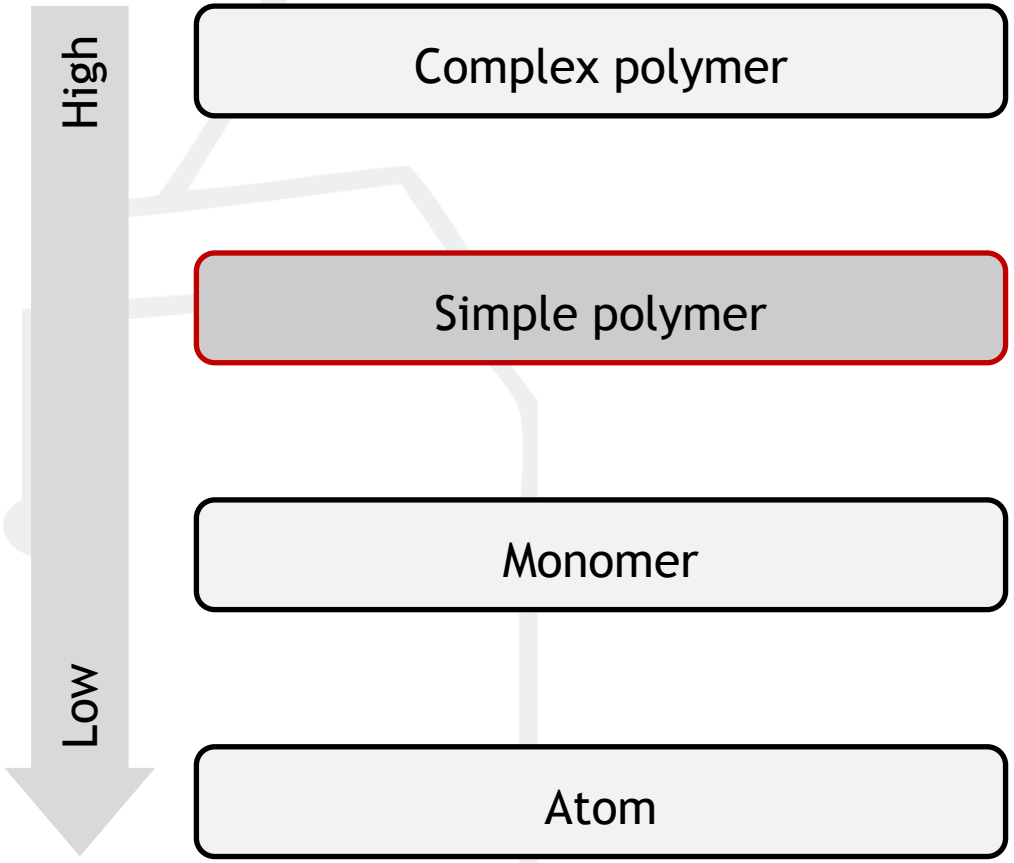
Monomer

Atom

Structure	
SMILES	C[C@H](N[*])C([*])=O |r,$;;;_R1;;_R2;$|
ID	A
Attachment Points	R1-H R2-OH
Natural Analog	A
Polymer Type	PEPTIDE
Monomer Type	Backbone
Name	L-Alanine

Structure hierarchy

- Higher level components are a combination of lower level components

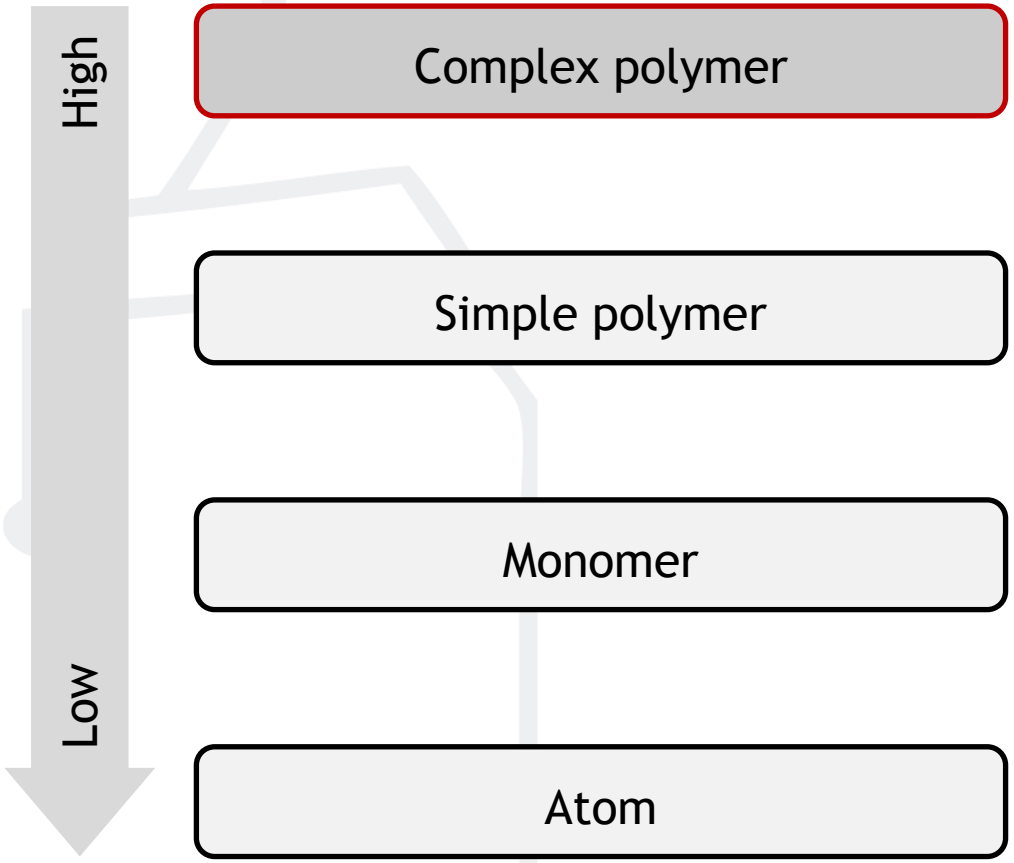


- Linear chains of Monomers or monomer units of a single biological molecule type (e.g. peptide chain, singular nucleic acid strand

Type	Monomer (unit)
Peptide	A - Alanine
Nucleic acid	R(A)P R – Ribose A – Adenine P – Phosphate
Chem	[PEG3] – Pegylation

Structure hierarchy

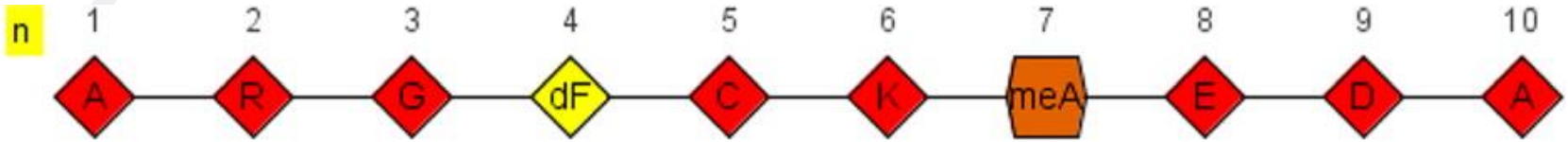
- Higher level components are a combination of lower level components



- Entire chemical structure information of the macromolecule
- May include annotations per Simple polymer

Example: Linear Peptide

A



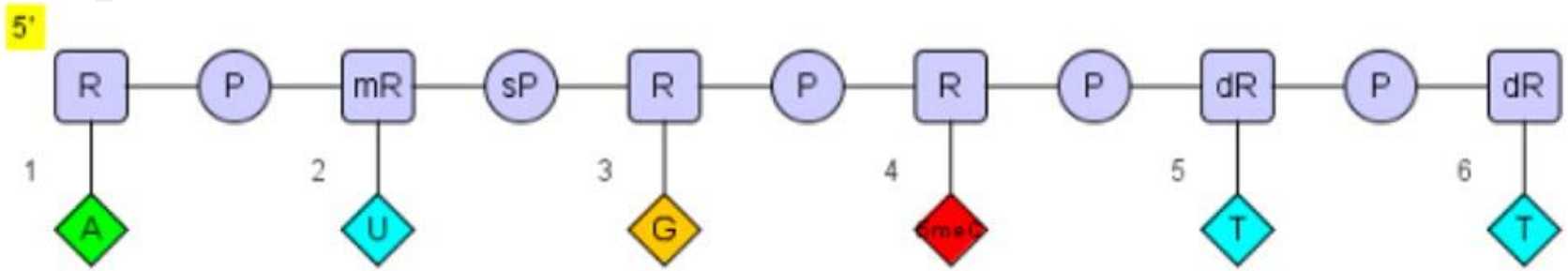
B PEPTIDE1{A.R.G.[dF].C.K.[meA].E.D.A}$$$$

A. Monomer Graph View

B. HELM Notation

Example: Linear Oligonucleotide

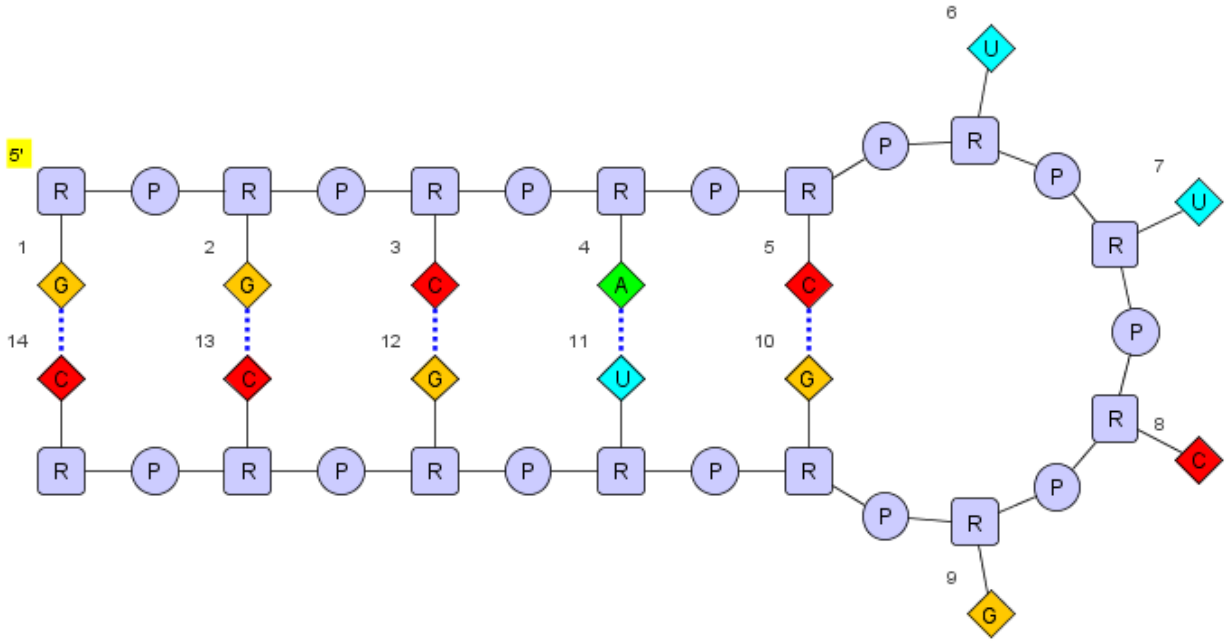
A



B RNA1{R(A)P.[mR](U)[sP].R(G)P.R([5meC])P.[dR](T)P.[dR](T)}$$$$

A. Monomer Graph View B. HELM Notation

Example: Stem-loops (e.g. Tetraloops)

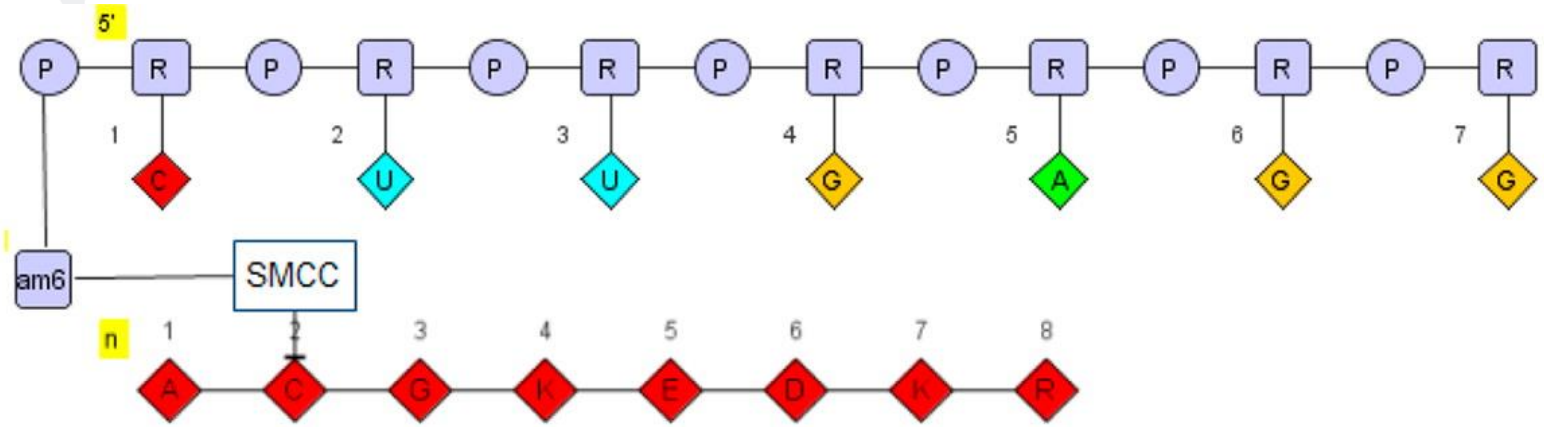


HELM notation:

RNA1{R(G)P.R(G)P.R(C)P.R(A)P.R(C)P.R(U)P.R(U)P.R(C)P.R(G)P.R(G)P.R(U)P.R(G)P.R(C)P.R(C)}$$$RNA1,RNA1,11:pair-32:pair|RNA1,RNA1,5:pair-38:pair|RNA1,RNA1,14:pair-29:pair|RNA1,RNA1,8:pair-35:pair|RNA1,RNA1,2:pair-41:pair$$

Example: Oligonucleotide Peptide Conjugate

A

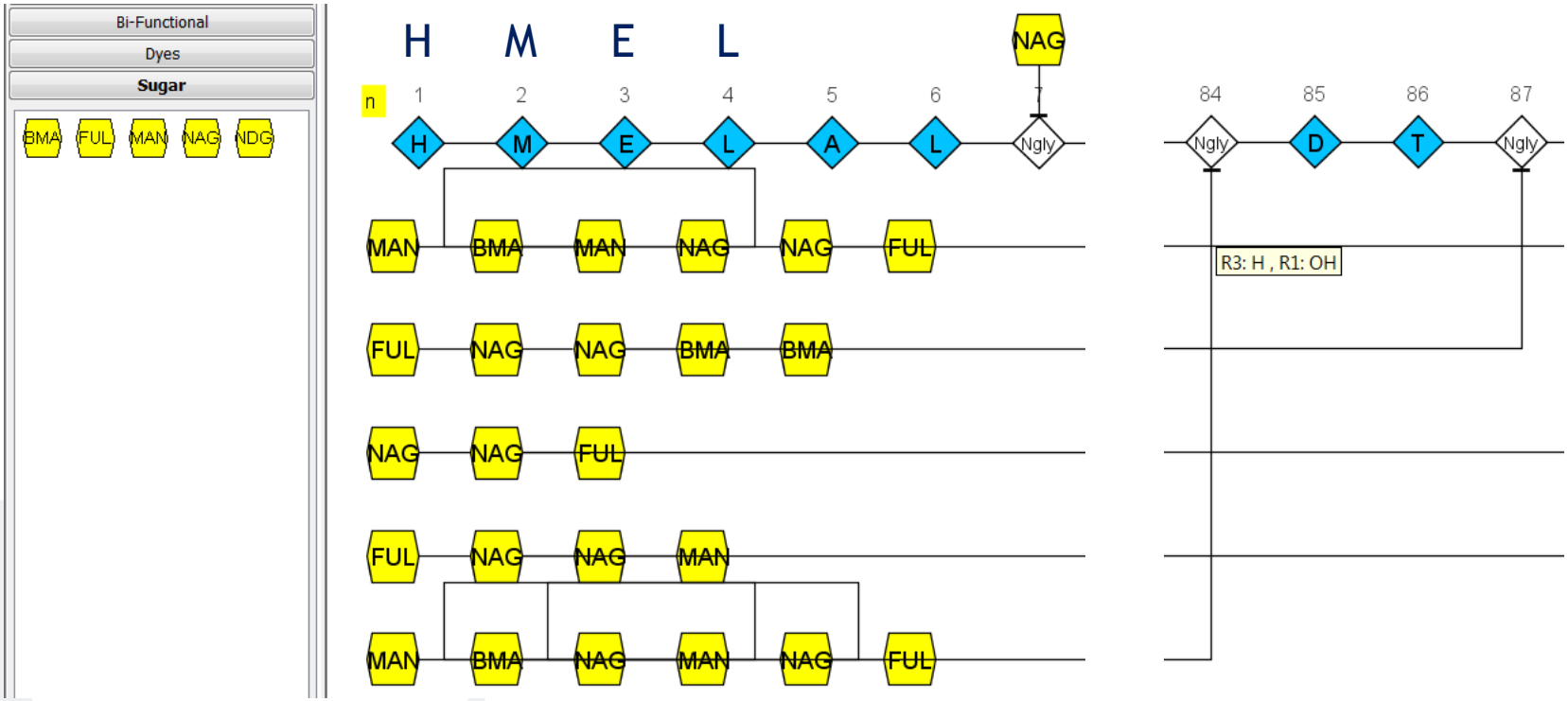


B

RNA1{[am6]P.R(C)P.R(U)P.R(U)P.R(G)P.R(A)P.R(G)P.R(G)}|PEPTIDE1{A.C.G.K.E.D.K.R}|CHEM1{SMCC}$PEPTIDE1,CHEM1,2:R3-1:R2|RNA1,CHEM1,1:R1-1:R1$$$

A. Monomer Graph View B. HELM Notation

Example: Glycoprotein (PDB:3FUS)



HELM notation:

CHEM1{BMA}|CHEM2{MAN}|CHEM3{MAN}|CHEM4{NAG}|CHEM5{FUL}|CHEM6{NAG}|CHEM7{NAG}|CHEM8{NAG}|CHEM9{FUL}|CHEM10{BMA}|CHEM11{BMA}|CHEM12{NAG}|CHEM13{NAG}|CHEM14{FUL}|CHEM15{NAG}|CHEM16{FUL}|CHEM17{NAG}|CHEM18{MAN}|CHEM19{BMA}|CHEM20{MAN}|CHEM21{MAN}|CHEM22{NAG}|CHEM23{NAG}|CHEM24{FUL}|CHEM25{MAN}|CHEM26{BMA}|CHEM27{NAG}|CHEM28{NAG}|PEPTIDE1{H.M.E.L.A.L.[Ngly].V.T.E.S.F.D.A.W.E.N.T.V.T.E.Q.A.I.E.D.V.W.Q.L.F.E.T.S.I.K.P.C.V.K.L.S.P.L.C.I.G.A.G.H.C.[Ngly].T.S.I.I.Q.E.S.C.D.K.H.Y.W.D.T.I.R.F.R.Y.C.A.P.P.G.Y.A.L.L.R.C.[Ngly].D.T.[Ngly].Y.S.G.F.M.P.K.C.S.K.V.V.V.S.S.C.T.R.M.M.E.T.Q.T.S.T.W.F.G.F.[Ngly].G.T.R.A.E.[Ngly].R.T.Y.I.Y.W.H.G.R.D.[Ngly].R.T.I.I.S.L.N.K.Y.Y.[Ngly].L.T.M.K.C.R.G.A.G.W.C.W.F.G.G.N.W.K.D.A.I.K.E.M.K.Q.T.I.V.K.H.P.R.Y.T.G.T.[Ngly].N.T.D.K.I.[Ngly].L.T.A.P.R.G.G.D.P.E.V.T.F.M.W.T.N.C.R.G.E.F.L.Y.C.K.M.N.W.F.L.N.W.V.E.D.R.D.V.T.N.Q.R.P.K.E.R.H.R.R.N.Y.V.P.C.H.I.R.Q.I.I.N.T.W.H.K.V.G.K.N.V.Y.L.P.P.R.E.G.D.L.T.C.[Ngly].S.T.V.T.S.L.I.A.N.I.D.W.T.D.G.[Ngly].Q.T.[Ngly].I.T.M.S.A.E.V.A.E.L.Y.R.L.E.L.G.D.Y.K.L.V.E.I.T}|CHEM29{NAG}|CHEM30{NAG}|CHEM31{BMA}|CHEM32{MAN}|CHEM33{MAN}|CHEM34{MAN}|CHEM35{NAG}|CHEM36{NAG}|CHEM37{BMA}|CHEM38{MAN}|CHEM39{BMA}|CHEM40{BMA}|CHEM41{MAN}|CHEM42{NAG}|CHEM43{NAG}|CHEM44{BMA}|CHEM45{NAG}|CHEM46{NAG}|CHEM47{FUL}|CHEM48{NDG}|CHEM49{NAG}|CHEM50{MAN}|CHEM51{BMA}|CHEM52{BMA}|CHEM53{NAG}|CHEM54{NDG}|CHEM55{FUL}$CHEM1,CHEM2,1:R2-1:R1|CHEM5,CHEM6,1:R1-1:R3|CHEM16,CHEM15,1:R1-1:R3|PEPTIDE1,CHEM30,52:R3-1:R1|PEPTIDE1,CHEM8,87:R3-1:R3|CHEM19,CHEM21,1:R3-1:R1|CHEM8,CHEM7,1:R1-1:R2|CHEM22,CHEM23,1:R1-1:R2|PEPTIDE1,CHEM28,292:R3-1:R1|PEPTIDE1,CHEM43,273:R3-1:R1|PEPTIDE1,CHEM46,146:R3-1:R1|PEPTIDE1,CHEM15,135:R3-1:R1|CHEM10,CHEM8,1:R1-1:R2|PEPTIDE1,CHEM36,289:R3-1:R1|CHEM51,CHEM50,1:R2-1:R1|CHEM39,CHEM41,1:R3-1:R1|PEPTIDE1,CHEM12,124:R3-1:R1|PEPTIDE1,CHEM29,7:R3-1:R1|CHEM39,CHEM38,1:R1-1:R2|CHEM20,CHEM19,1:R1-1:R2|CHEM17,CHEM15,1:R1-1:R2|CHEM12,CHEM13,1:R2-1:R1|CHEM46,CHEM47,1:R3-1:R1|CHEM32,CHEM31,1:R1-1:R3|CHEM52,CHEM51,1:R3-1:R1|PEPTIDE1,CHEM23,84:R3-1:R1|CHEM28,CHEM27,1:R2-1:R1|CHEM4,CHEM1,1:R2-1:R1|CHEM31,CHEM33,1:R2-1:R1|PEPTIDE1,CHEM54,190:R3-1:R1|CHEM34,CHEM33,1:R1-1:R2|CHEM18,CHEM17,1:R1-1:R2|CHEM31,CHEM35,1:R1-1:R2|CHEM9,CHEM7,1:R1-1:R3|CHEM26,CHEM27,1:R1-1:R2|CHEM54,CHEM53,1:R2-1:R1|CHEM6,CHEM4,1:R2-1:R1|CHEM1,CHEM3,1:R3-1:R1|CHEM25,CHEM26,1:R1-1:R2|CHEM54,CHEM55,1:R3-1:R1|CHEM43,CHEM42,1:R2-1:R1|CHEM40,CHEM37,1:R2-1:R1|CHEM46,CHEM45,1:R2-1:R1|CHEM12,CHEM14,1:R3-1:R1|CHEM42,CHEM40,1:R2-1:R1|PEPTIDE1,CHEM6,118:R3-1:R1|CHEM24,CHEM23,1:R1-1:R3|CHEM22,CHEM19,1:R2-1:R1|CHEM53,CHEM52,1:R2-1:R1|CHEM48,CHEM49,1:R2-1:R1|PEPTIDE1,CHEM48,184:R3-1:R1|CHEM45,CHEM44,1:R2-1:R1|CHEM37,CHEM38,1:R2-1:R1|CHEM11,CHEM10,1:R1-1:R2|CHEM36,CHEM35,1:R2-1:R1$$$

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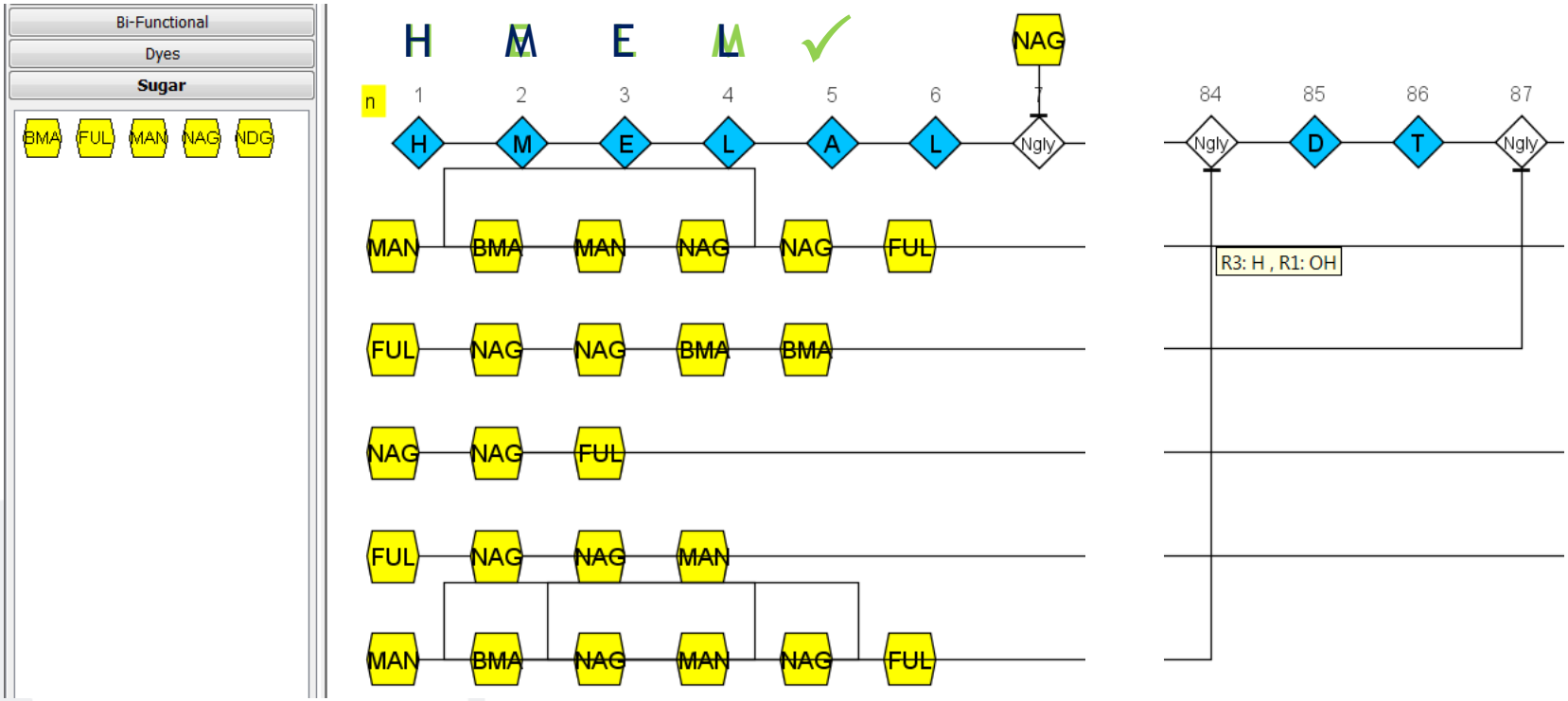
Example: Glycoprotein (PDB:3FUS)



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Does HELM meet requirements?

"Standard reference notation for macromolecules in pharma compound registration systems"

Requirements:

- ❑ Use case coverage
- ❑ Specification and Documentation
- ❑ Interoperability
- ❑ Registrability
- ❑ Long-term stability
- ❑ Adoption

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Use case coverage

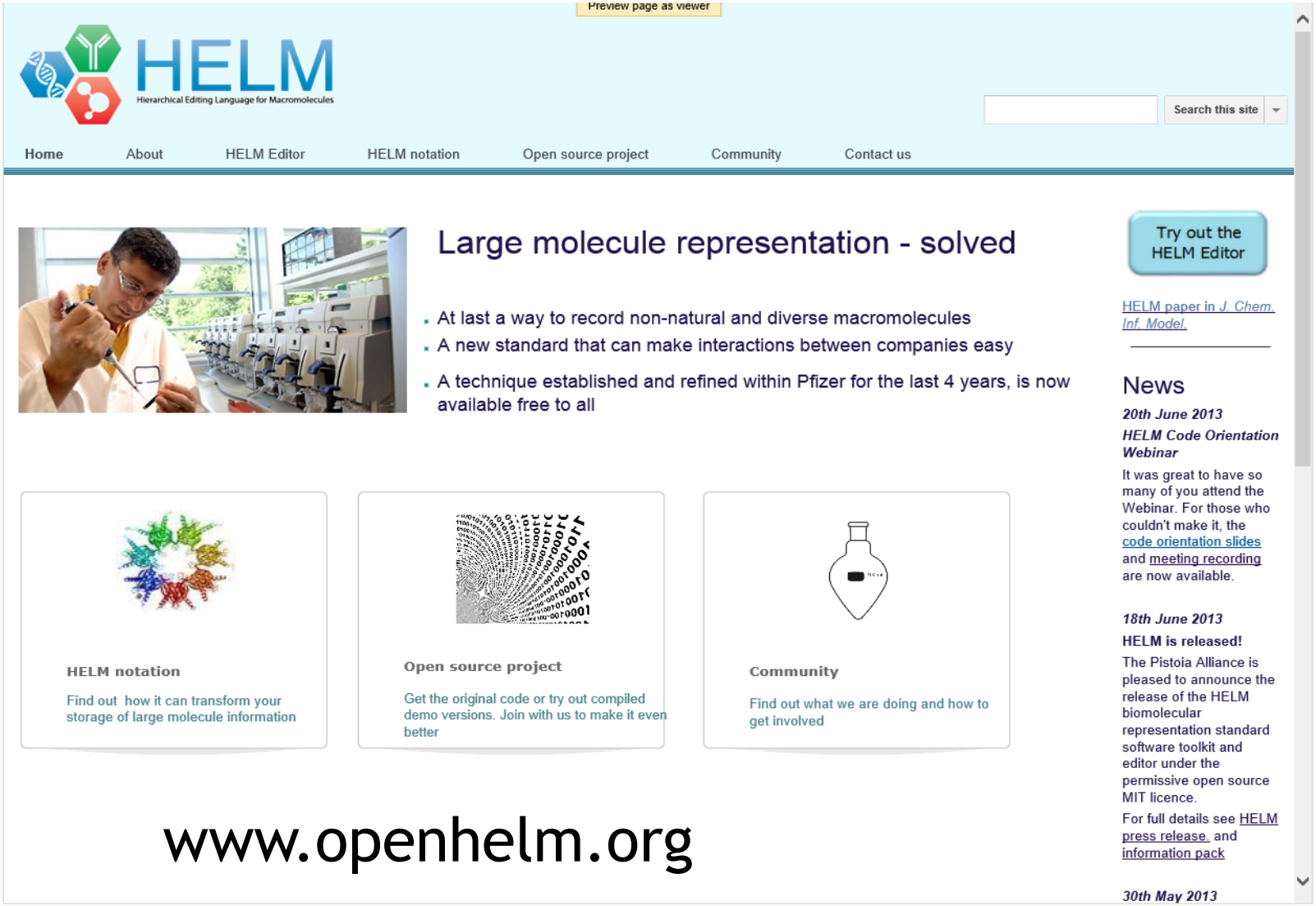
Unmodified and modified biological molecules

- ✓ Nucleic acids – dsDNA, siRNA, locked DNA/RNA...
- ✓ Proteins – Antibodies, proteins with PTMs
- ○ Glycoproteins

Conjugated molecules

- ✓ Covalently linked peptide-RNA hybrid molecules
- ○ Chemically crosslinked molecules – ADCs

Specification and Documentation



www.openhelm.org

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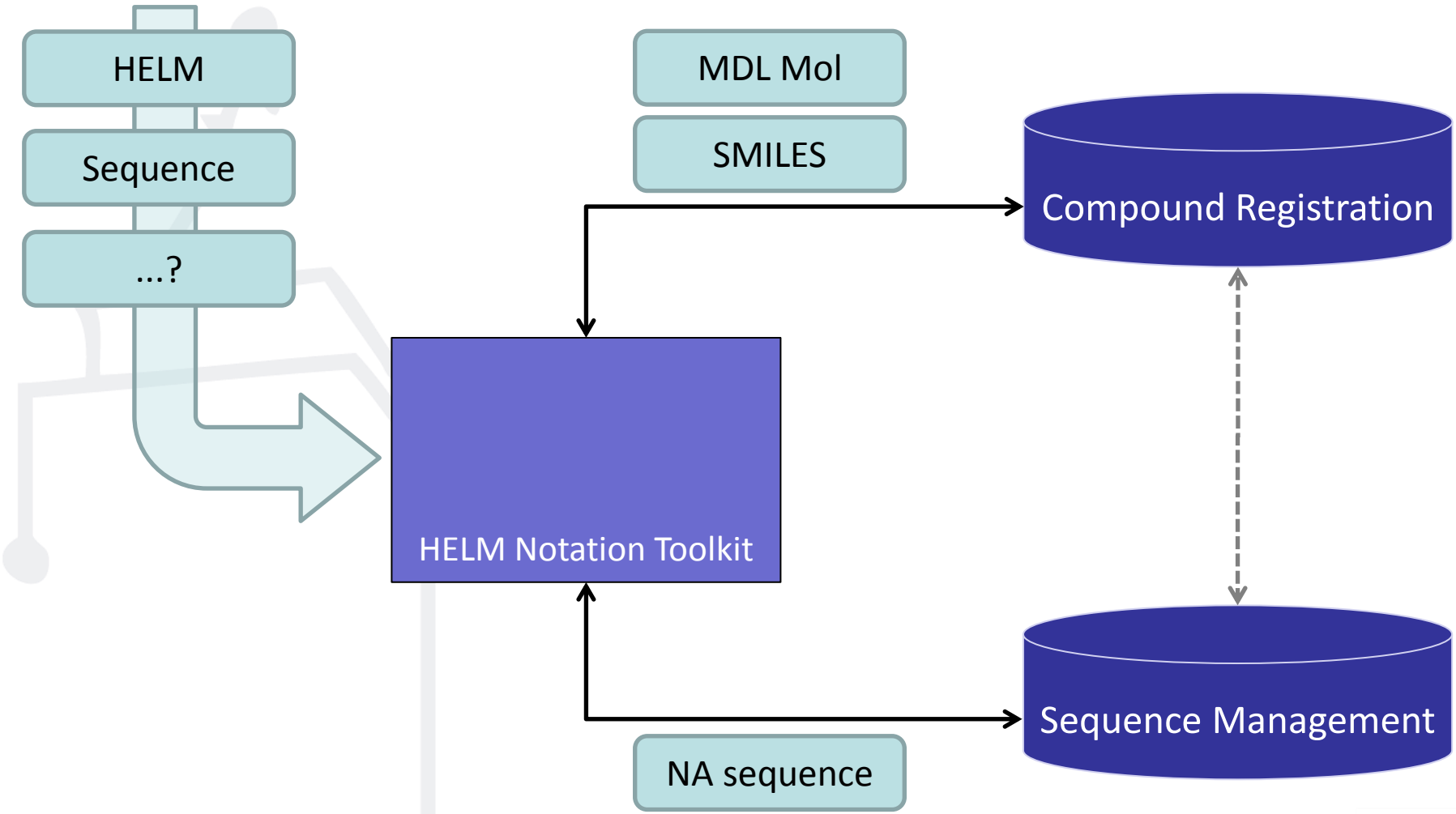
Interoperability



Central HELM monomer administration

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Interoperability

- Available tools currently export a HELM notation only
  - To regenerate the entire atomic structure the monomer information has to be passed on additionally (current PA project activity)
- Harmonization of differing monomer dictionaries between partnering organizations
  - To avoid ambiguity of macromolecule representation for registration

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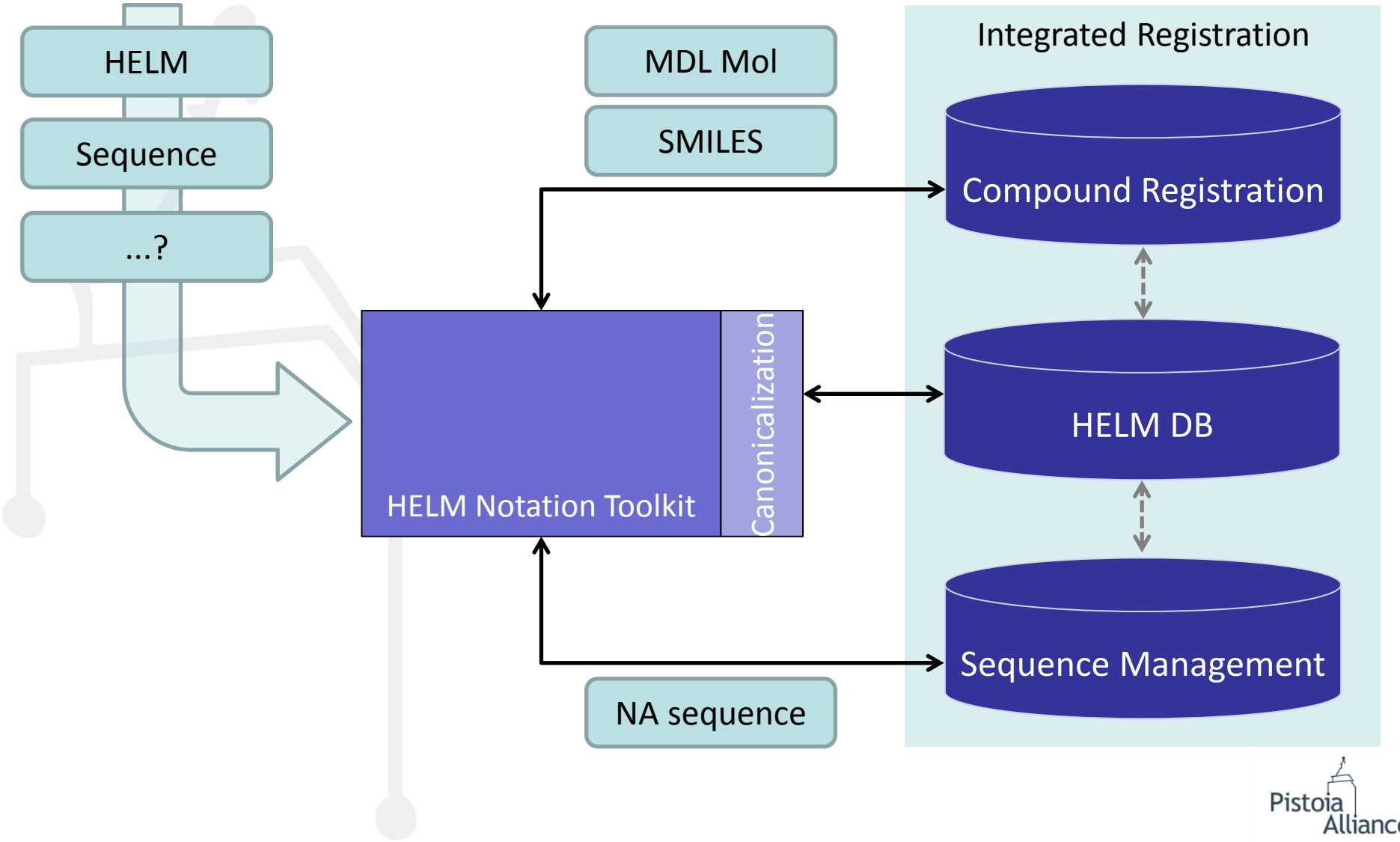
Registrability



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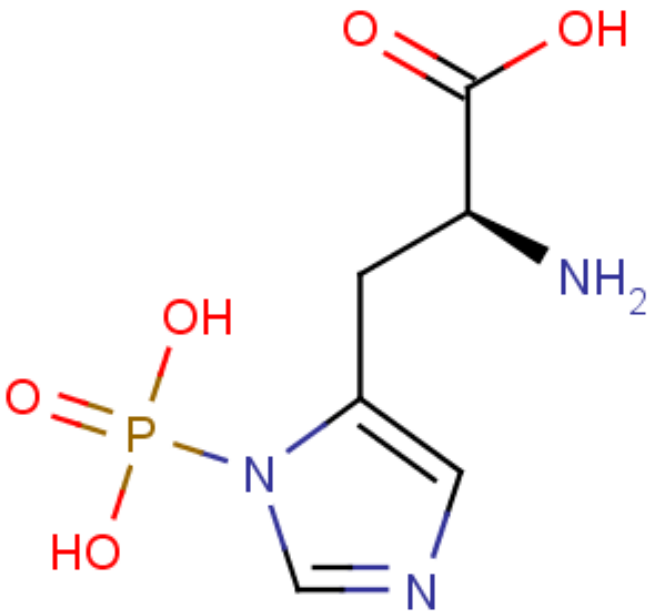
Registrability

- Consistent automated registration of new HELM monomers is challenging



1-Phospho-histidine

Histidine + Phosphate

or

1-Phospho-histidine

?

Long-term stability

- ✓ PA to „sign-post“ the HELM standard and foster adoption throughout PA community
- ✓ PA to provide *ad interim* governance for controlled evolution of the standard
- ✓ Release of HELM tools to the Open Source public domain facilitates public discourse
- ○ Widespread adoption

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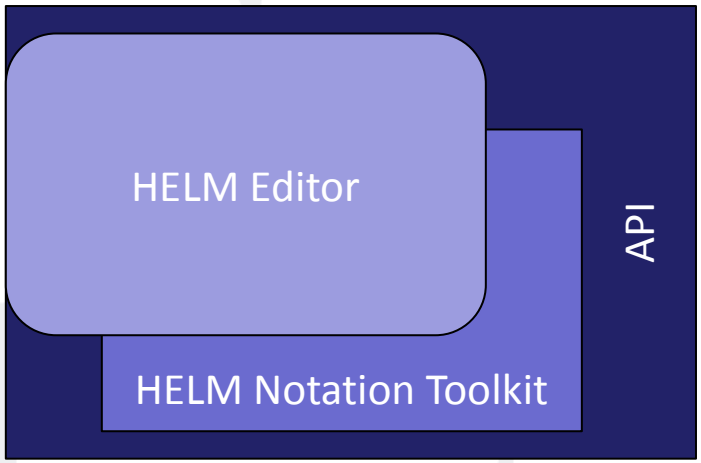
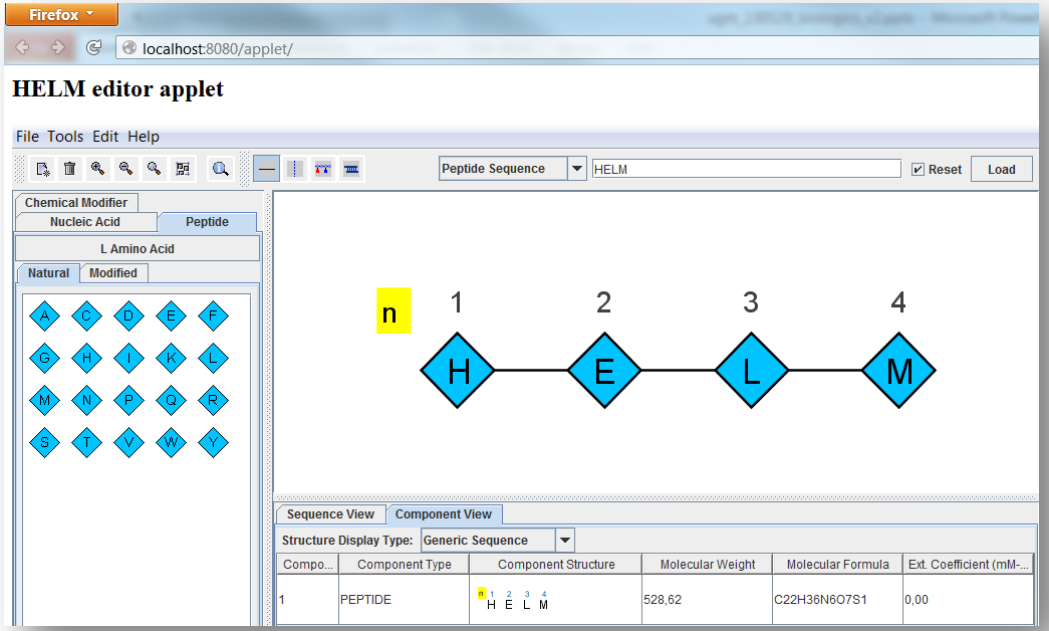
Which tools are available?





https://github.com/PistoiaHELM

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Adoption

- ✓ Vendors
- ✓ Pharma-/Polymer chemistry companies
- ○ Content providers
- ○ Academia
- ○ State agencies

Open HELM Standard is young, requires thorough assessment

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HELM is already meeting most of the requirements for broad adoption

With your help we can make HELM the “language of the macromolecules”

Requirements:

- ☑ Use case coverage
- ☑ Specification and Documentation
- ☑ Interoperability
- ☑ Registrability
- ☑ Long-term stability
- ☐ Adoption – over to you!

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HELM

For more information please visit
http://openhelm.org

or contact us at info@openhelm.org

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