Use of Computational Tools in Medicinal Chemistry Projects

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Research Topic Seminar

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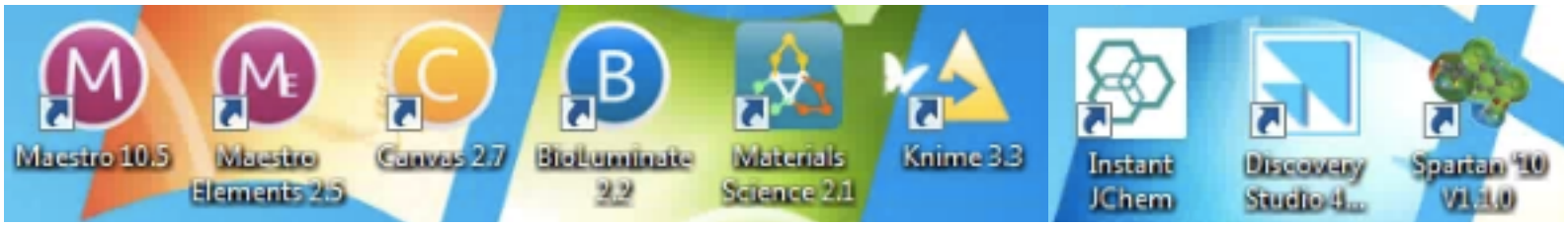
Wipf Group

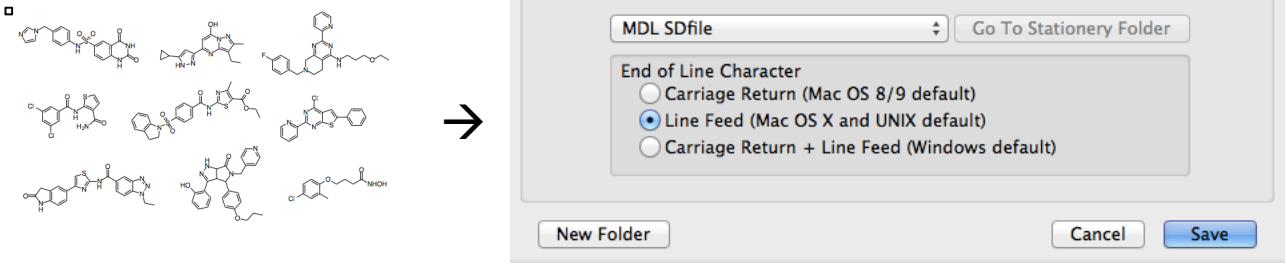
Computational Tools in Wipf Group

- **Instant JChem (Group License) / Instant JChem for Excel**
  - Create, explore and share chemical and non-chemical data
  - Physical-chemical property and molecular descriptor calculations
  - Structure search, substructure filter, property filter (Lead-like filter)
  - List and query management
- **Schrödinger software** - Small Molecule Drug Discovery Suite (7th floor computer)
  - Maestro: All purpose molecular modeling environment. Protein target preparation, ligand preparation, general modeling tools, etc…
  - Canvas: A comprehensive cheminformatics computing environment. Fingerprint-based similarity searching and substructure matching, clustering and diversity selection, chemistry filters, etc…
- **Spartan (University License)**
  - A general purpose modeling tool: provide information about molecular structure, energy, reactivity, selectivity and a wide range of molecular properties
  - Molecular mechanics calculations and quantum chemical calculations



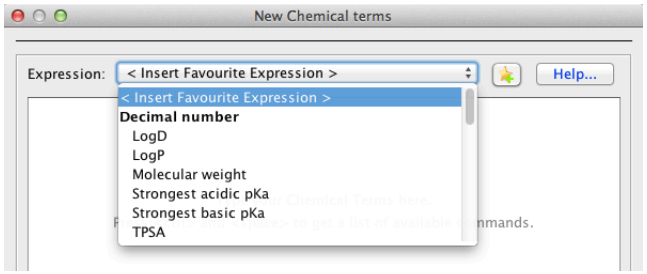
Quick Guide for Instant JChem

i) Generate SD file: ChemDraw/InstantJChem/DiscoveryStudioViewer, etc…

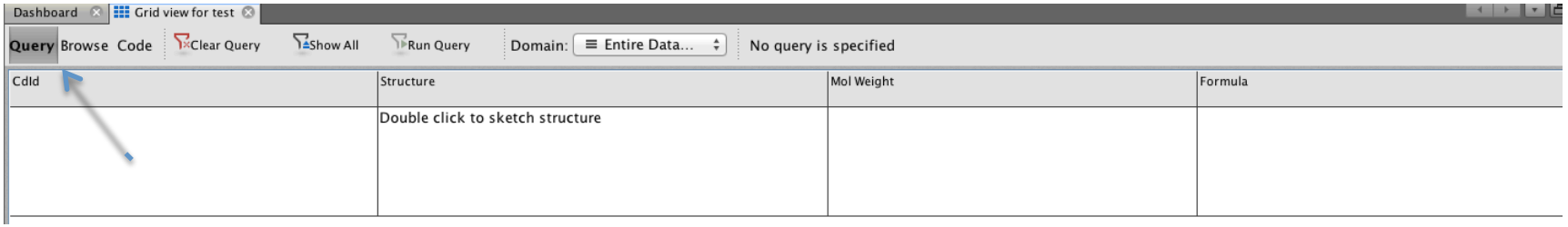


ii) Import File: File – Import file or click the icon

iii) Properties calculation: Click “New Chemical Terms Field”



iv) Filter, substructure search: Click Query



Schrodinger Maestro & Canvas

- **Schrödinger software** - Small Molecule Drug Discovery Suite (7th floor computer)

  - **Maestro**: All purpose molecular modeling environment. Protein target preparation, ligand preparation, general modeling tools, etc…
  - Quick guide for docking

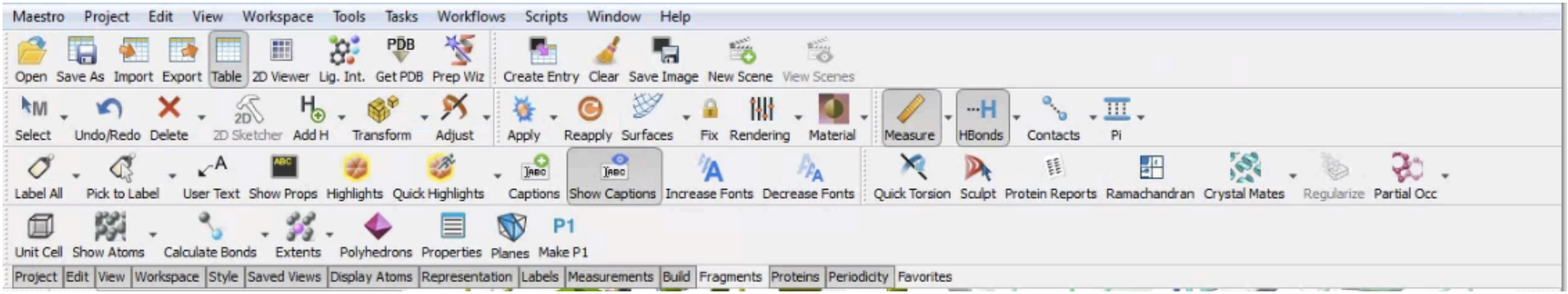
  i) Importing and Editing Molecules with Maestro: Get PDB (from RCSB or import directly from Maestro)

  ii) Prepare Protein: Protein Preparation Wizard

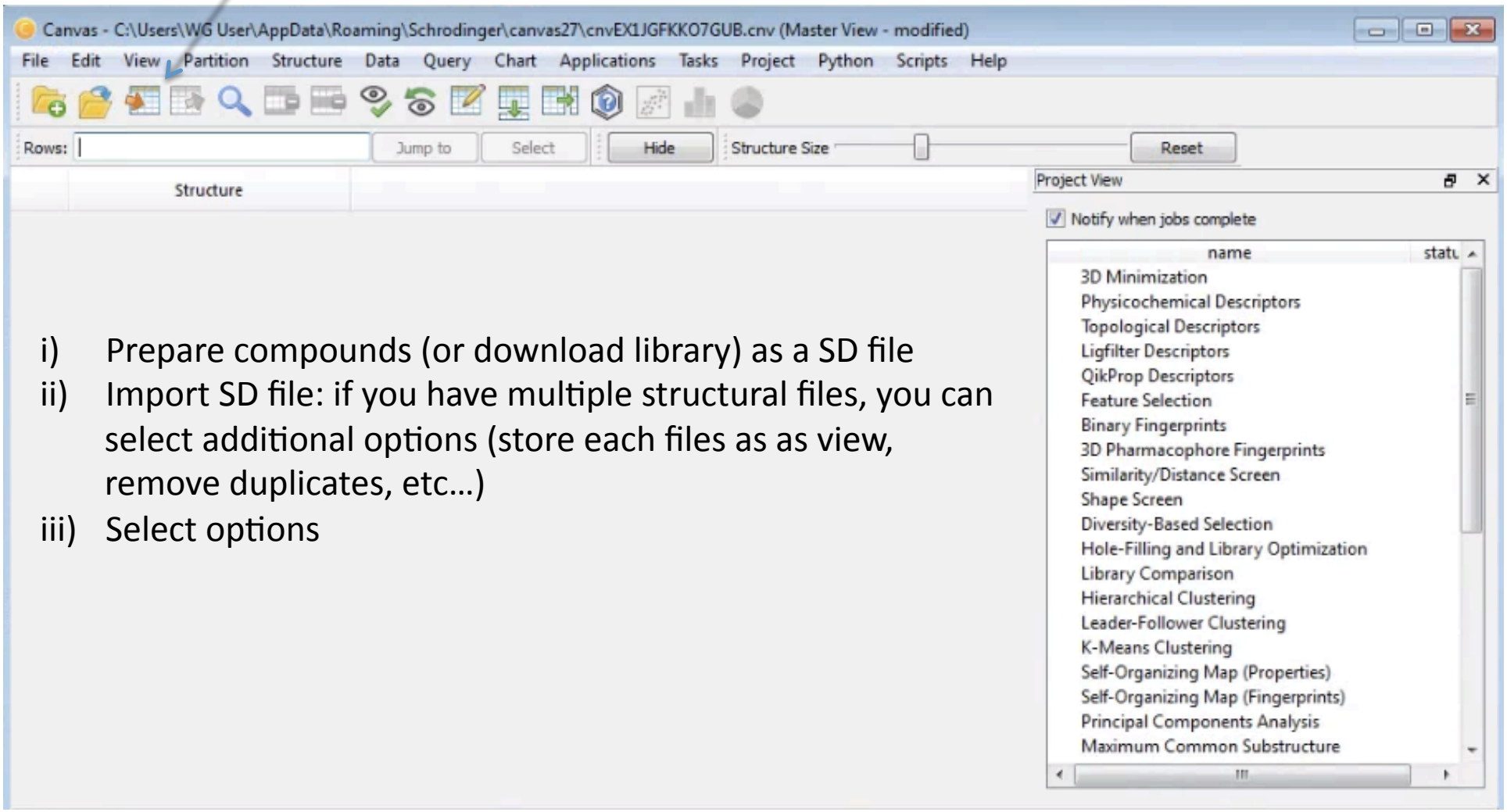
  iii) Prepare Ligand: Import compounds as a SD/mol file format (or Draw) then 'Applications – LigPrep'

  iv) Generate the Grid

  v) Glide Dock (Rigid docking)



Schrodinger Maestro & Canvas

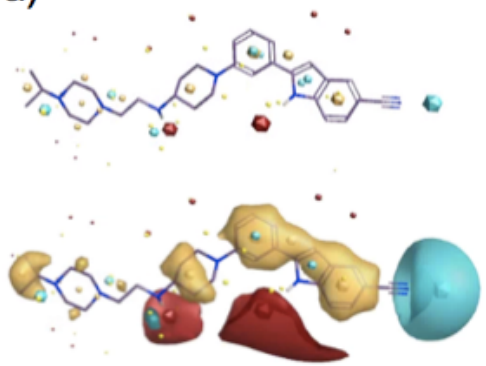


i) Prepare compounds (or download library) as a SD file
ii) Import SD file: if you have multiple structural files, you can select additional options (store each files as as view, remove duplicates, etc…)
iii) Select options

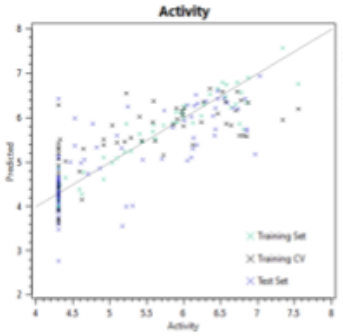
Target 1 – p97 AAA ATPase

- p97 modulates protein processes related to protein homeostasis in cancer
- Developed a **3D-QSAR model** for a series of 2-phenyl indole analogs based on ca. 150 synthetic compounds with biochemical assay information
- The predicted pIC_{50} from the model correlate well with the observed pIC_{50} (R^2 = 0.914, q^2 = 0.589) and the phenyl indole orientation of the reference structure was matched by the protein bound conformation from a cryo-EM structure that was subsequently obtained
- **Further optimization of the binding mode** of phenyl indole analogs using docking simulations and a refined protein model.

a)



b) R^2 = 0.914 (q^2 = 0.589)
Reference: **5-CN** (UPCDC30283)
(pIC_{50}, Median value)



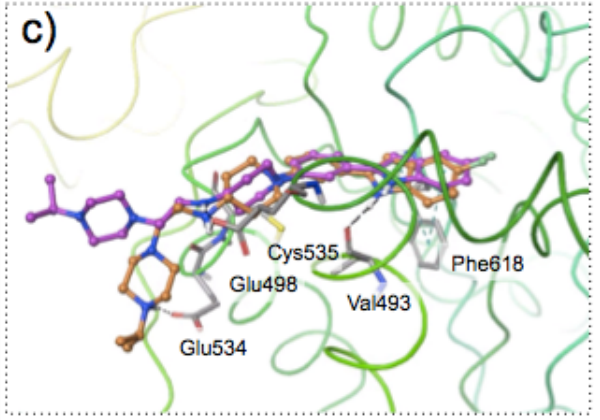
Training set (73)

Activity (pIC_{50})	Active (≥ 5.0)	Inactive (< 5.0)
Predicted	38	35
Observed	36/38	35/35
Predictability (%)	95%	100%

Test set (74)

Activity (pIC_{50})	Active (≥ 5.0)	Inactive (< 5.0)
Predicted	44	30
Observed	34/44	28/30
Predictability (%)	77%	93%

c)



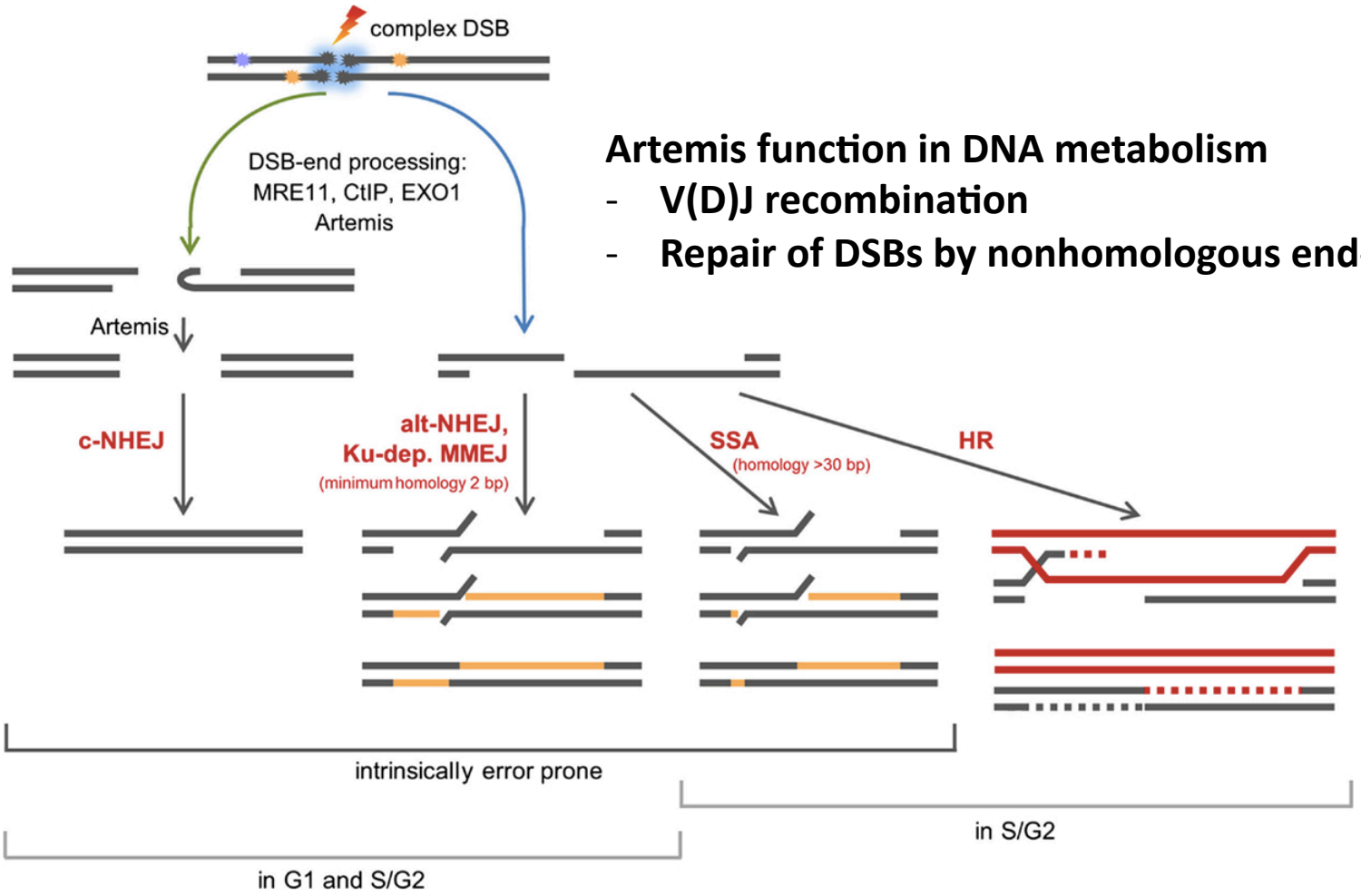
Artemis Endonuclease

- A member of the metallo-β-lactamase protein family
- **Critical for the major pathway of double-strand break repair**
- **Endonuclease activity** at DNA hairpins and at 5'- and 3'-DNA overhangs of duplex DNA, and this endonucleolytic activity is dependent upon DNA-PKcs
- Essential for the successful V(D)J recombination in lymphocytes

→ Valuable therapeutic target for human acute lymphoblastic lymphoma and leukemia

DNA Double Strand Break (DSB) Repair

Major pathways of DNA double-strand break repair



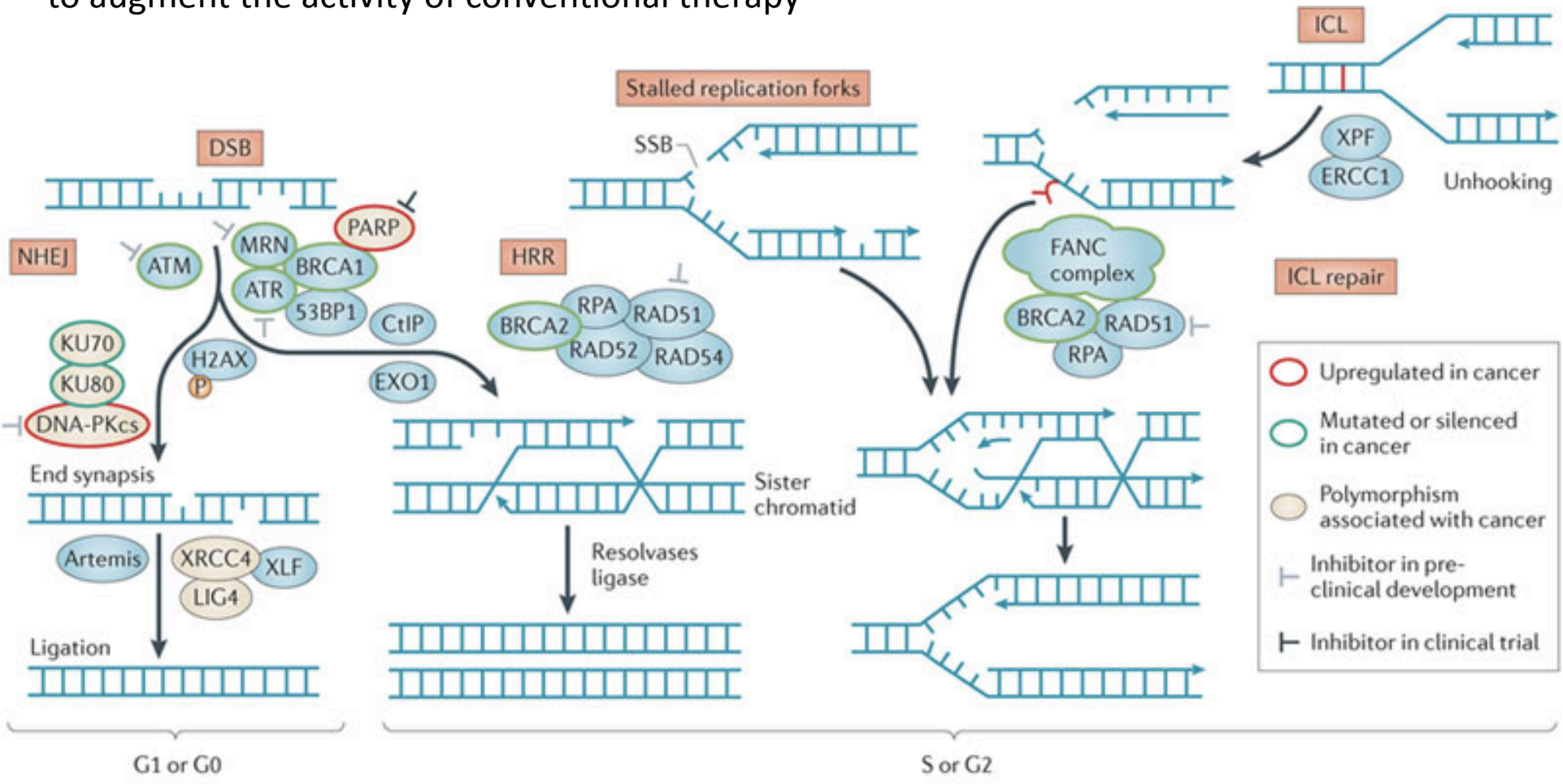
Artemis function in DNA metabolism

- **V(D)J recombination**
- **Repair of DSBs by nonhomologous end-joining (NHEJ)**

Front. Oncol. 6:28. doi: 10.3389/fonc.2016.00028

Therapeutic Targeting of DNA Damage Repair

*Inhibitors of the DDR have been developed to overcome resistance and to augment the activity of conventional therapy



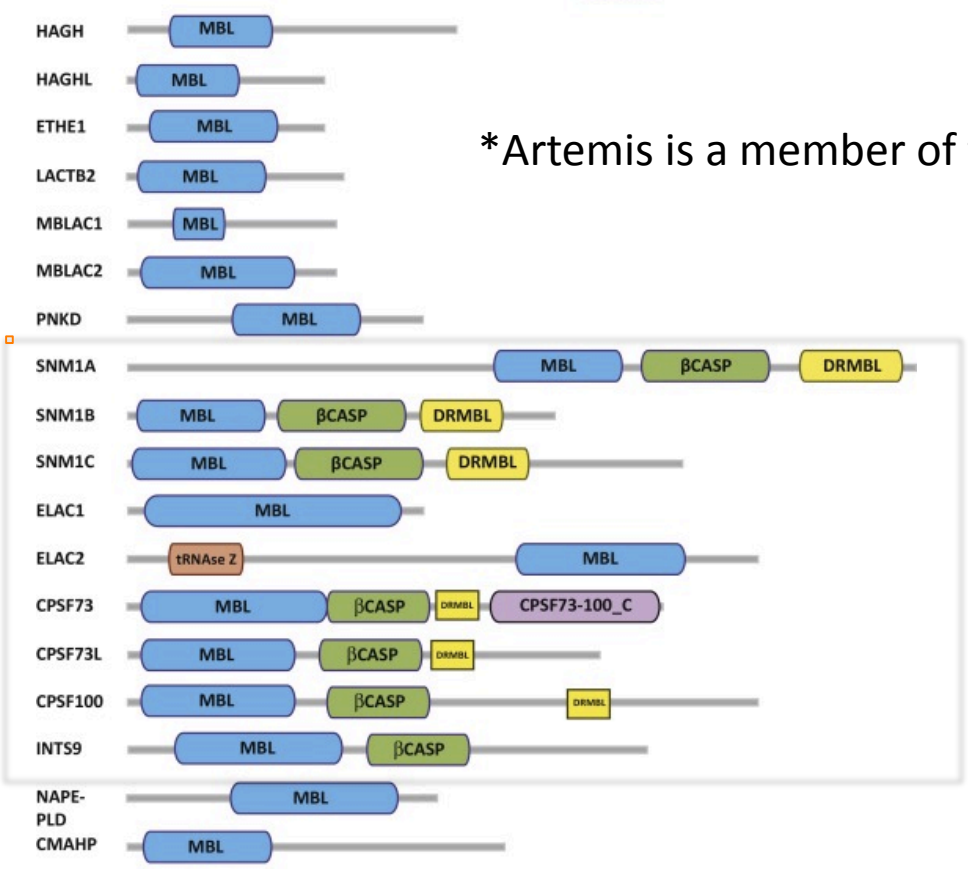
<DNA double-strand break and interstrand crosslink repair>

Nature Reviews | Cancer

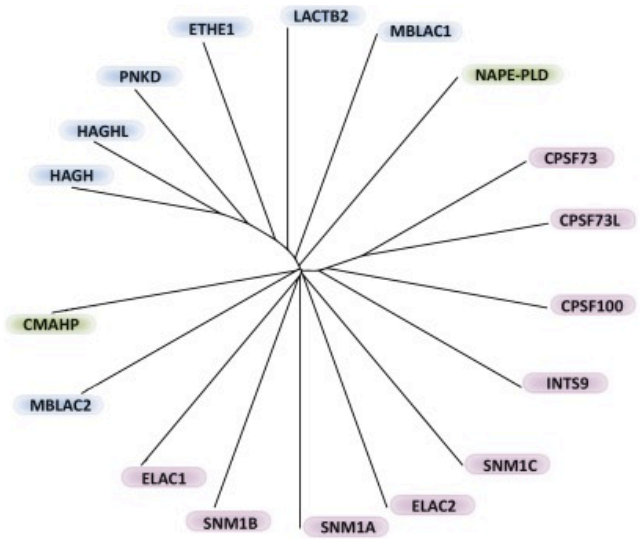
Nature Reviews Cancer **2012**, *12*, 801-817 | doi:10.1038/nrc3399

Humann Metallo-β-Lactamase Protein Family

- A small family of approximately 18 zinc- and iron-dependent proteins with roles in metabolism and/or detoxification and nucleic acid modification.
- Group 1, The Glyoxalase II Subfamily
- Group 2, **The DNA/RNA Interacting hMBLf Subfamily**
- Group 3, NAPE-PLD and CMAH



*Artemis is a member of the metallo-β-lactamase protein family



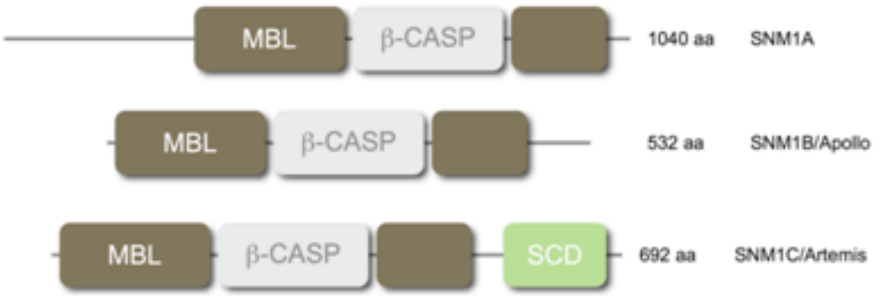
In-class Selectivity within β-CASP family

- SNM1 enzymes (SNM1A, SNM1B, and SNM1C (Artemis)) involved in DNA repair pathways

DNA lesion	DNA Repair Pathway	Nucleases	Fold
DSB	Non-homologous end joining (NHEJ)	Mre11	PP2B
		Artemis	MBL
DSB	Homologous recombination (HR)	Mre11	PP2B
DSB	Microhomology-mediated end joining	Mre11	PP2B
ICL	Repair of interstrand crosslinks (ICL)	SNM1A/B	MBL

		Metallo-β-lactamase			
		I	II	III	IV
Human	SNM1A	FTVDAF	LTHFHSDHYA	ANHCP	ILHTGDFR
Yeast	SNM1/Pso2	IVVDGF	LSHFHSDHYI	ANHCP	ILHTGDFR
Human	SNM1B/Apollo	IAVDFW	LSHFHSDHYT	ANHCP	ILYTGDFR
Human	SNM1C/Artemis	ISIDRF	LSHCHKDHMK	AGHCP	VLYTGDFR
Human	CPSF-73	IMLDCG	ISHFHLDHCG	AGHVL	LLYTGDFR
E. coli	UlaG	VCVDFW	ATHDHNDHID	AFDRT	LYHSGDSH
B. cereus	BLM	VLVDSS	ITHAHADRIG	KGHTE	ILVCGCLV

		β-CASP domain		
		A	B	C
Human	SNM1A	LYLDTT	EHSSY	IPTVN
Yeast	SNM1/Pso2	LYLDTT	EHSSF	IPTVN
Human	SNM1B/Apollo	LYLDNT	DHSSY	VPIVS
Human	SNM1C/Artemis	VYLDTT	FHSSY	YPNVI
Human	CPSF-73	LIIEST	AHTDY	ILVHG



Characteristic sequence motifs of DNA nucleases of the MBL/β-CASP family

Available from: http://www.intechopen.com/books/dna-repair-on-the-pathways-to-fixing-dna-damage-and-errors/nucleases-ofmetallo-beta-lactamase-and-protein-phosphatase-families-in-dna-repair

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National Cancer Institute

NIH National Institutes of Health

leidos Leidos Biomedical Research, Inc.

NExT NCI Experimental Therapeutics Program