

# Prediction of sensitivity to genotoxic drug by modeling cancer cell lines and patient omics data in the context of comprehensive DNA repair signaling network

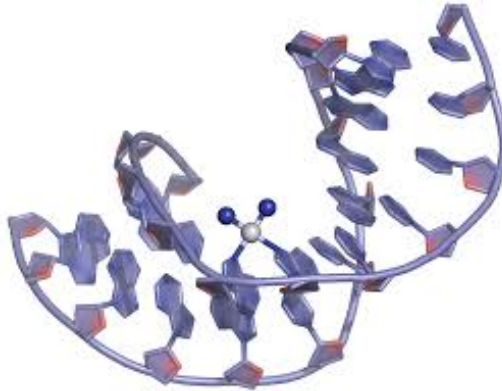
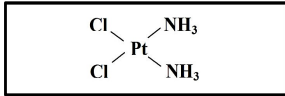
Inna Kuperstein

“Computational Systems Biology of Cancer”  
U900 Institut Curie/INSERM/Ecole des Mines ParisTech, Paris, France

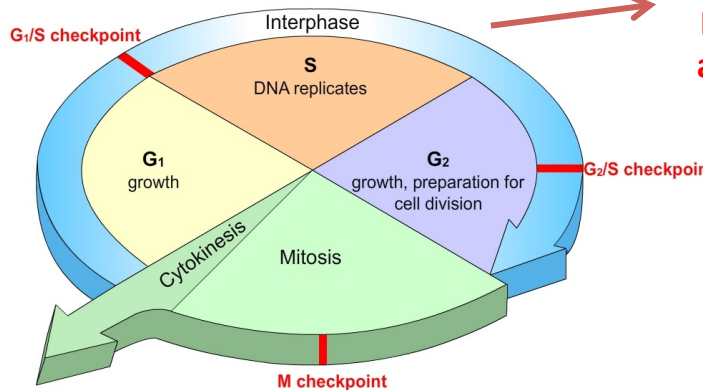
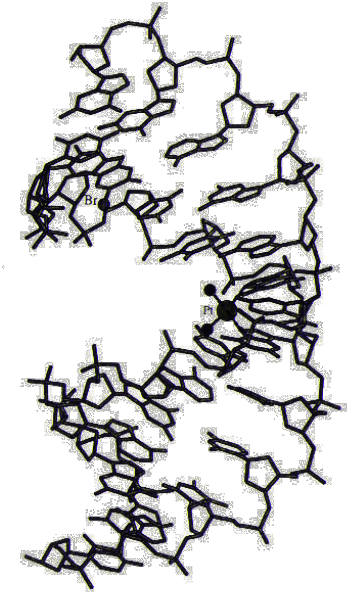
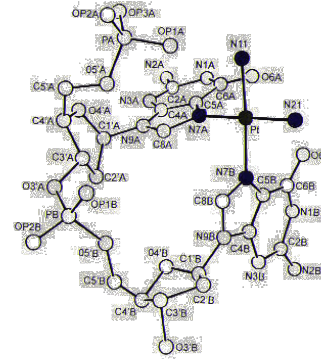
# Treatment approaches in cancer

## Genotoxic drugs

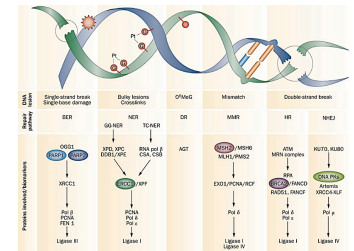
Cisplatin



DNA cross-links

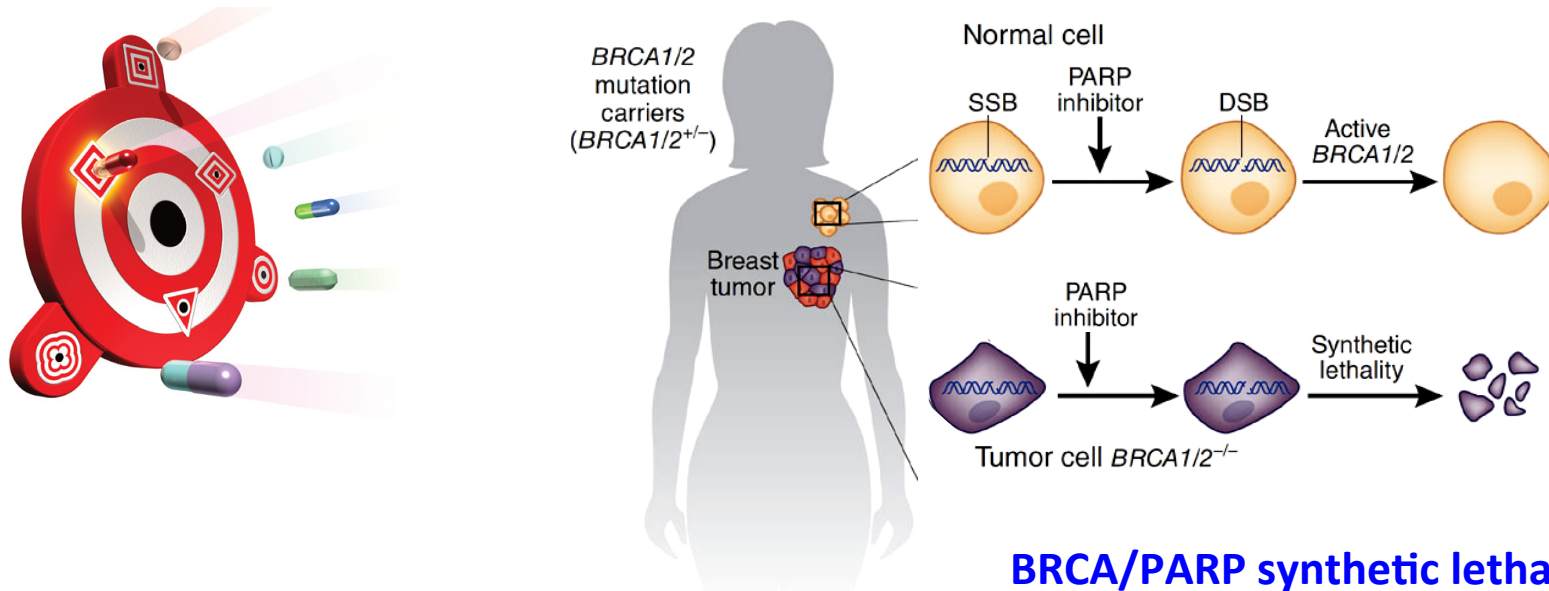


DNA repair machinery



# Treatment approaches in cancer

## Targeted drugs: synthetic lethality paradigm



### BRCA/PARP synthetic lethal pair

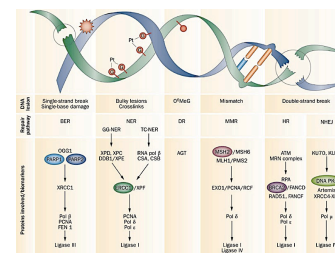
#### Approach

Exploit specificities of the synthetic lethal pair. Targeting the



Suppression or function of one gene from synthetic lethal pair leads to the killing of tumor cells.

#### DNA repair machinery



Hartwell et al. Science (1997)

# Synthetic genetic interactions

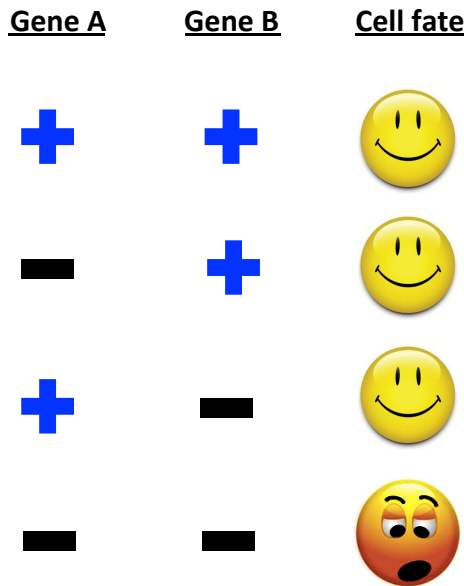
Mutations in number of genes producing a phenotype that is significantly different from each mutation's individual effects

Negative genetic interaction: **aggravating** effect

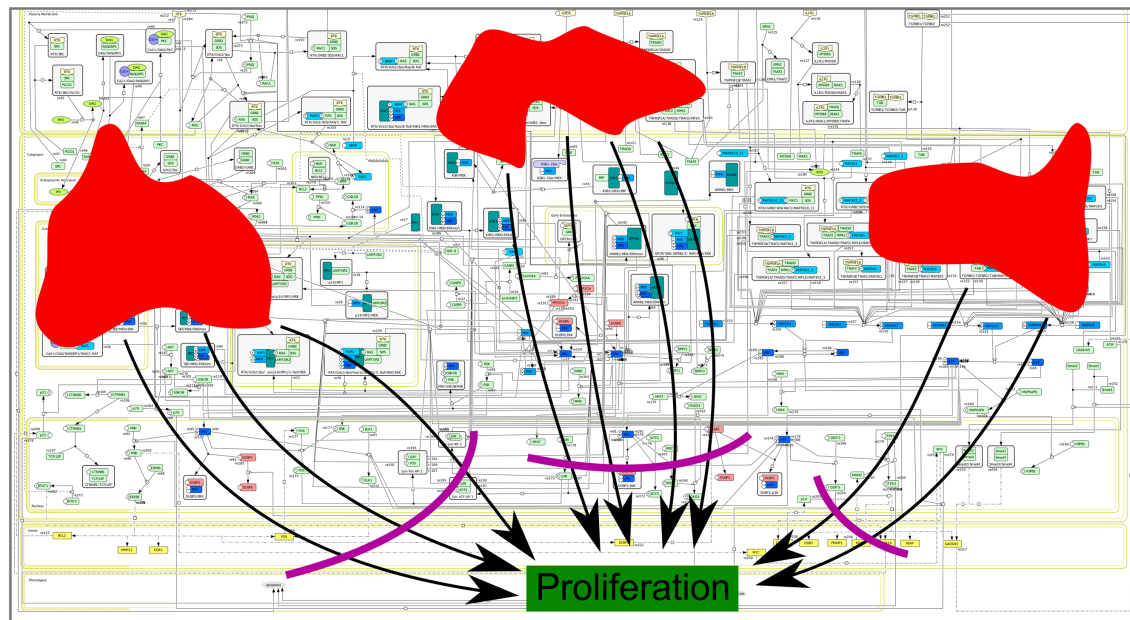
Positive genetic interaction: **ameliorating** effect

## Synthetic lethality between two genes

Extreme case of negative genetic interactions

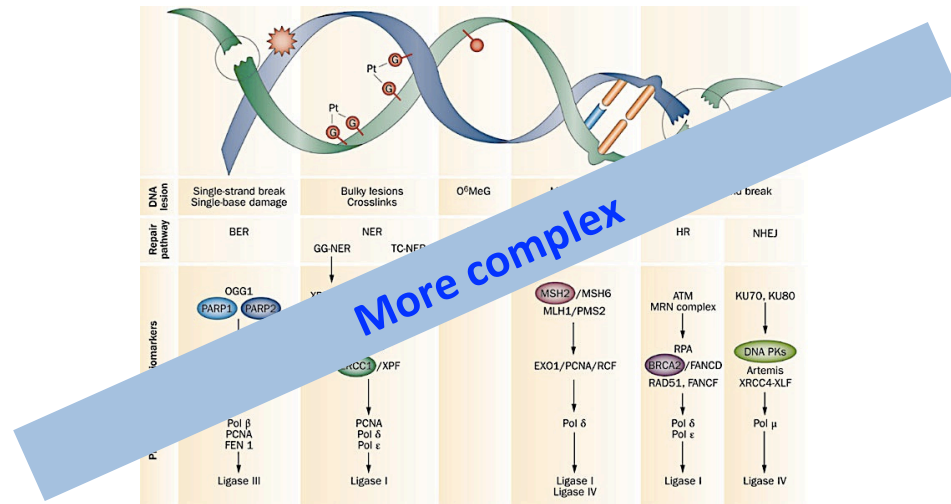


## Synthetic lethal gene set = intervention gene set



# Aim

Assemble, represent and analyze molecular processes depicting complexity of DNA repair mechanisms

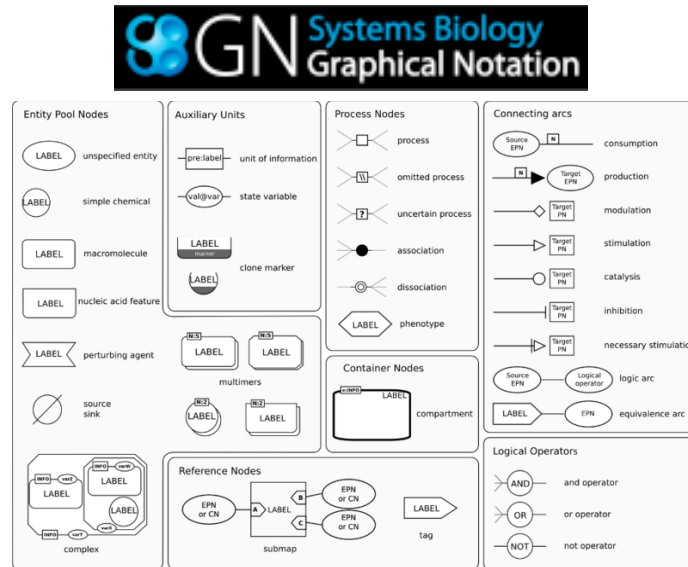


# Standards and tools for signaling networks construction

## Visual syntax

### Systems Biology Graphical Notation (SBGN)

Biological molecules and interactions representation



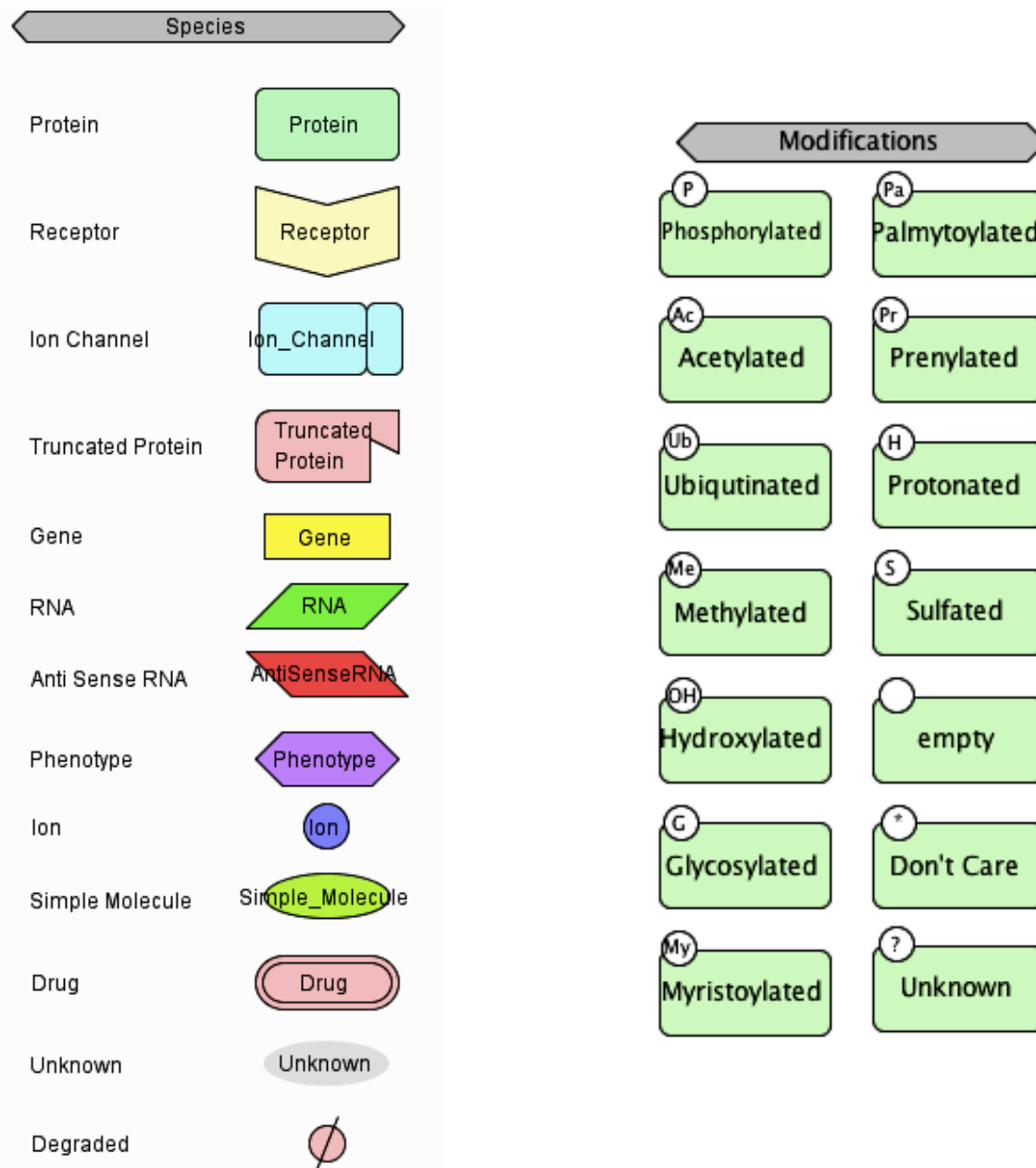
## Tool: CellDesigner

Diagram editor for signalling networks representation



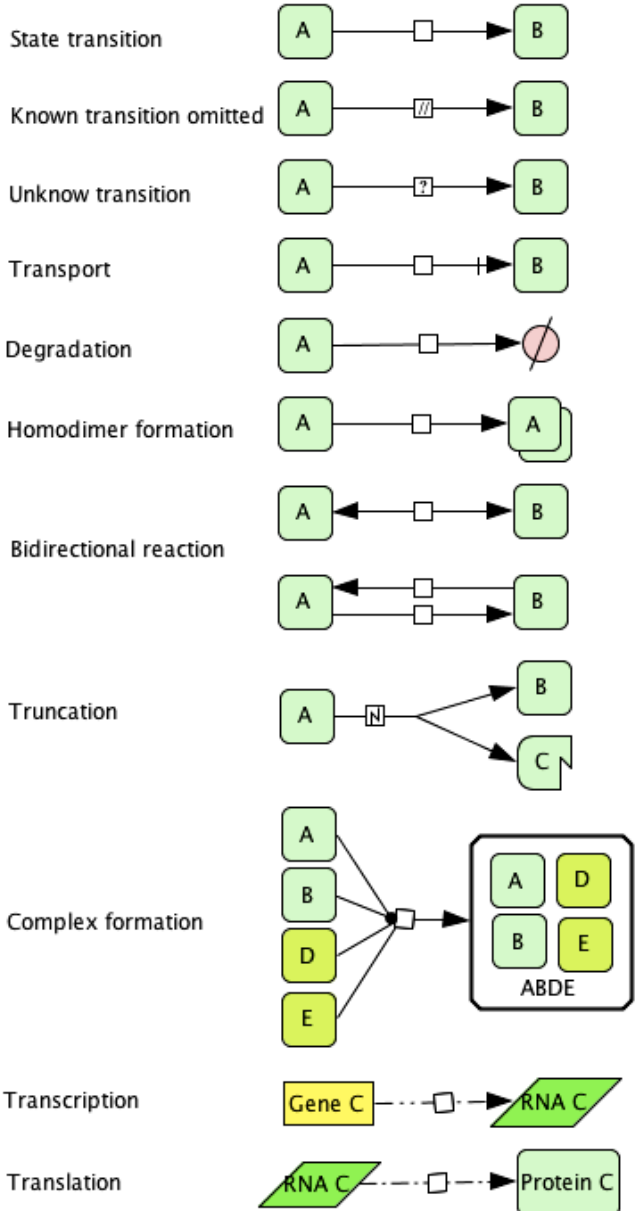
# Systems Biology Graphical Notation (SBGN)

## Biological molecules and post translational modifications

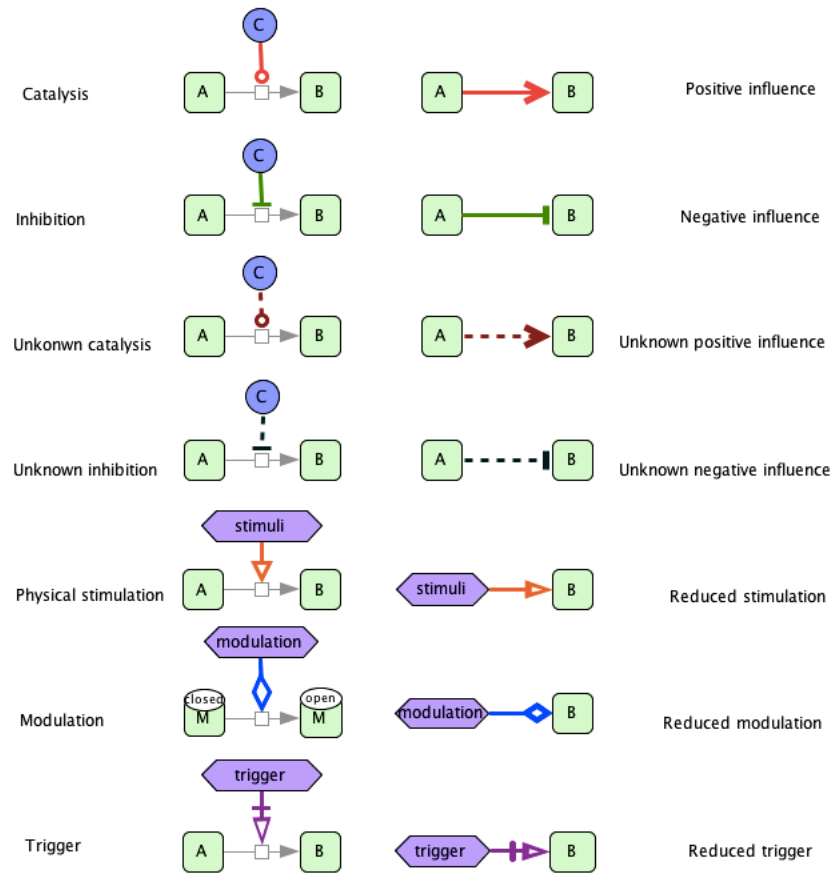


## Reaction types and regulation

### Reaction types



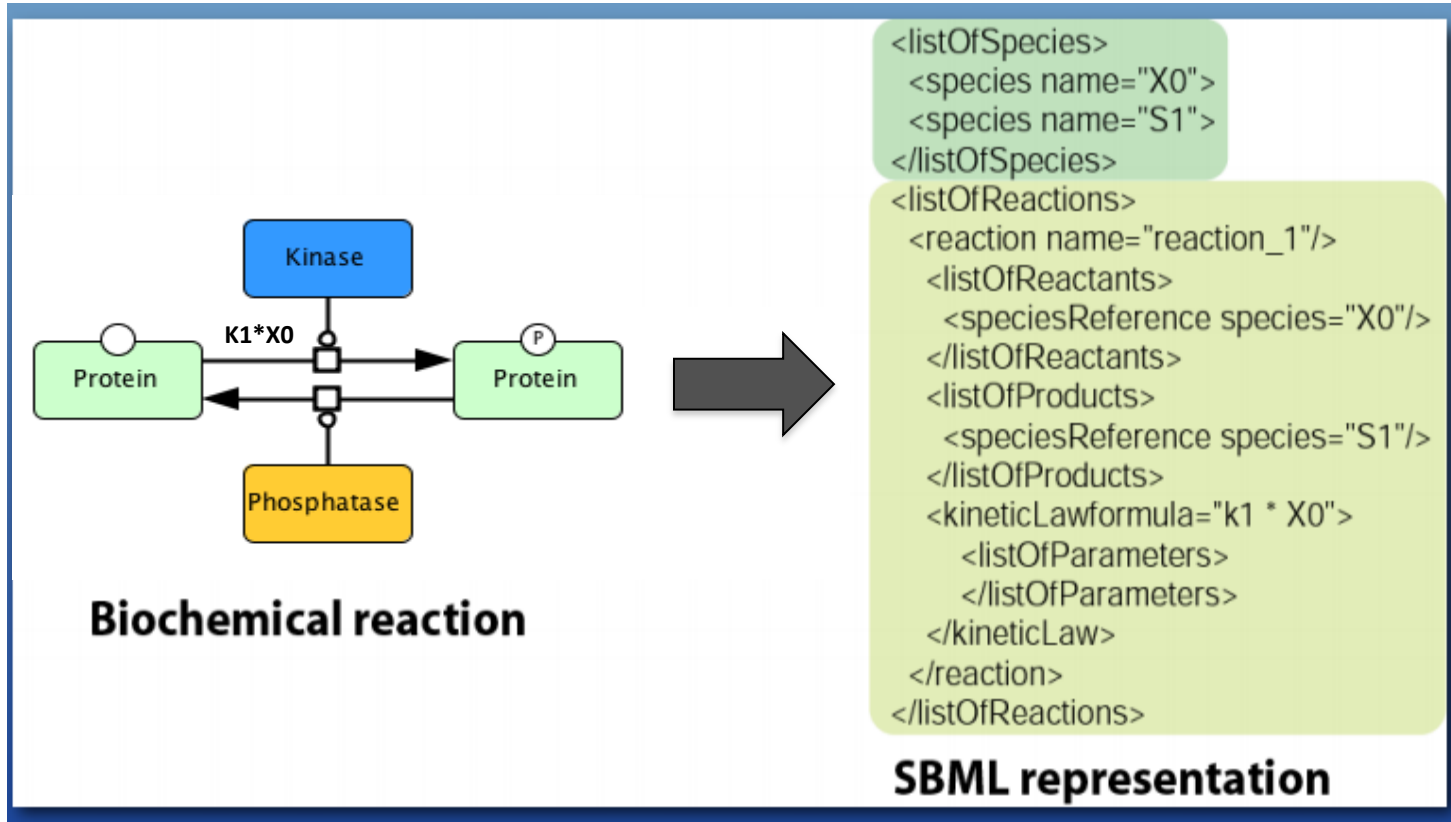
### Reaction regulation types





# Standards and tools for signaling networks construction

Systems Biology Markup Language (SBML)  
Computational representation of biochemical processes



# DNA repair and Cell Cycle map

4 cell cycle phases

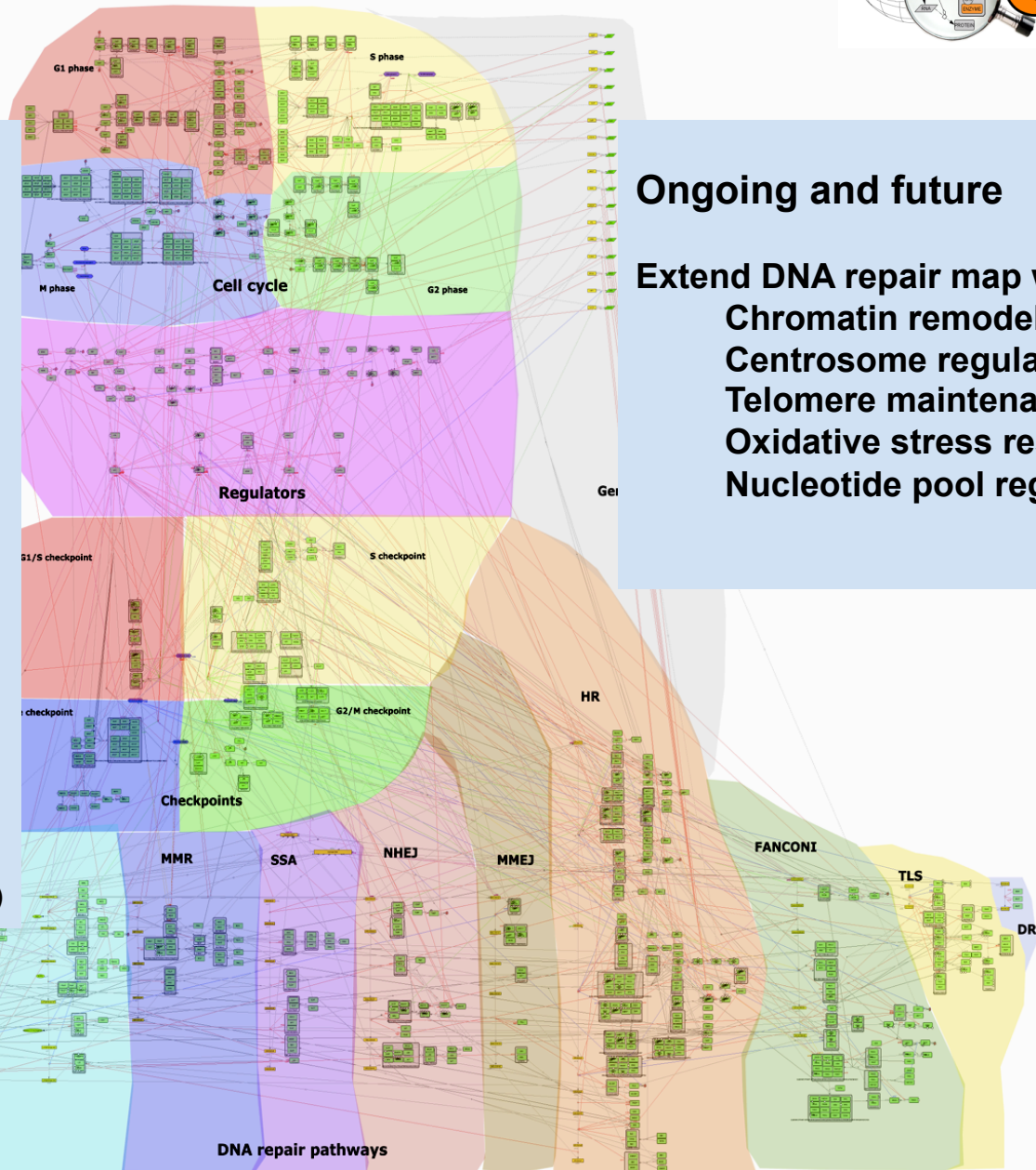
4 checkpoints

10 DNA repair pathways

- NER
- BER
- MMR
- SSA
- NHEJ
- MMEJ
- HR
- Fanconi
- TLS
- DR

Drugs and DNA damaging agents classes

(UV, IR, alkylators, cross-linkers, Ros, Dbait)



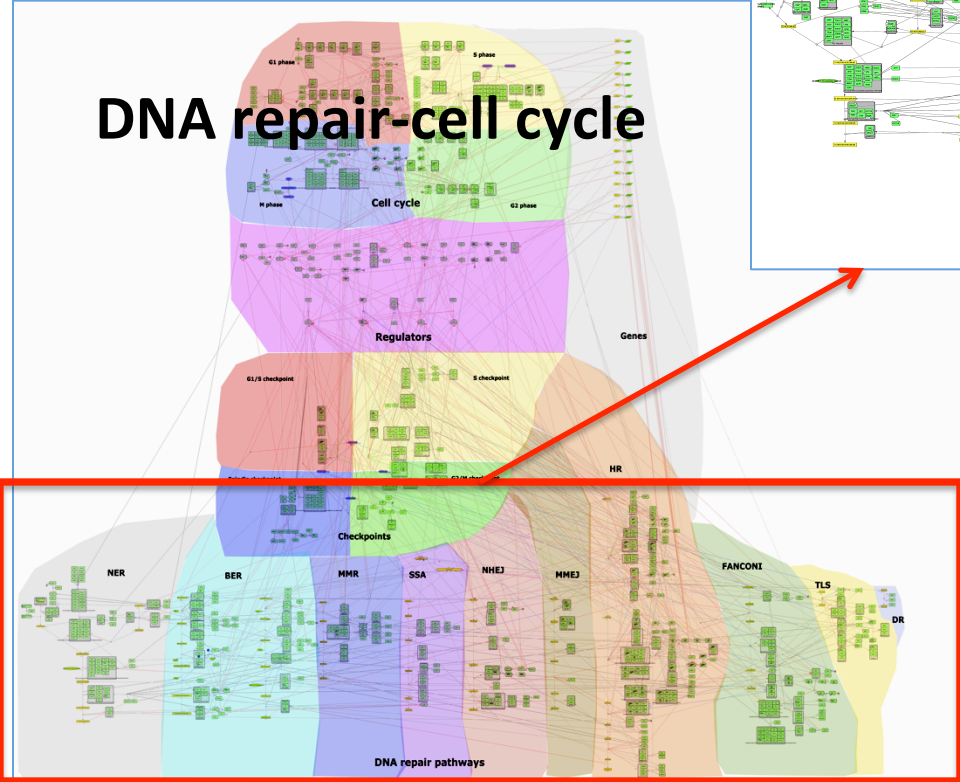
Ongoing and future

- Extend DNA repair map with
- Chromatin remodeling
- Centrosome regulation
- Telomere maintenance
- Oxidative stress response
- Nucleotide pool regulation

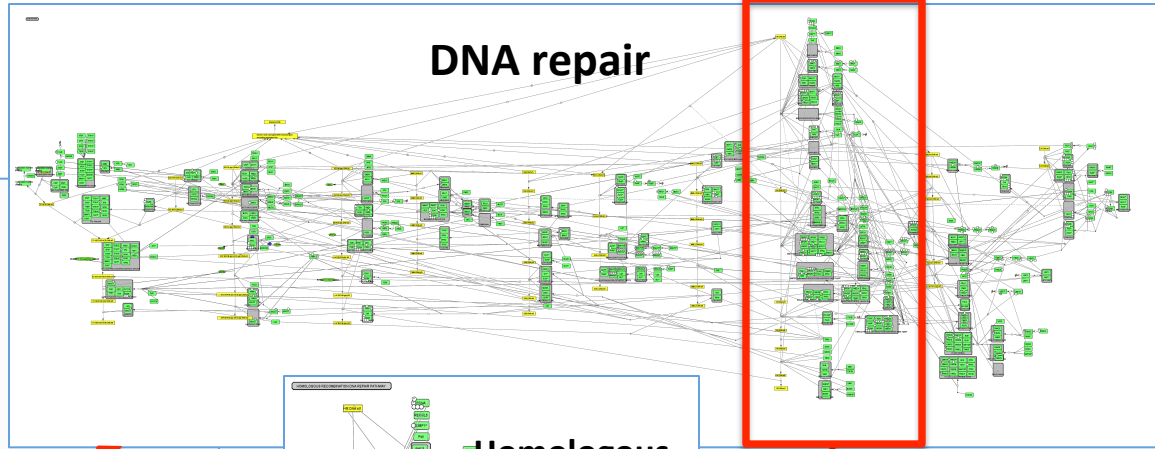
DNA repair pathways

# Modular interconnected and exhaustive map

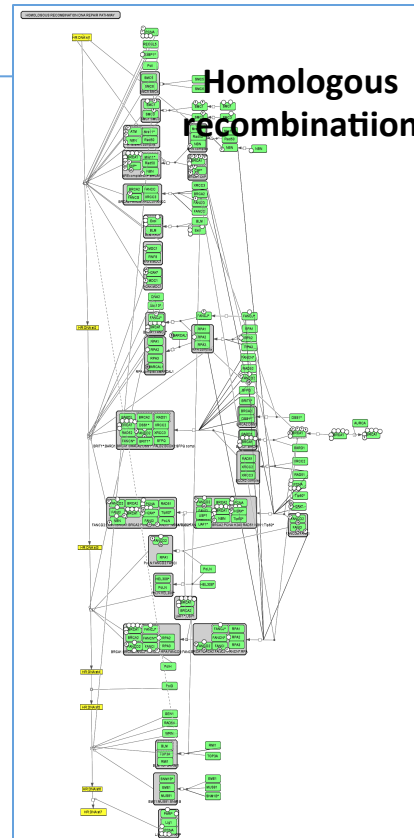
## DNA repair-cell cycle



## DNA repair



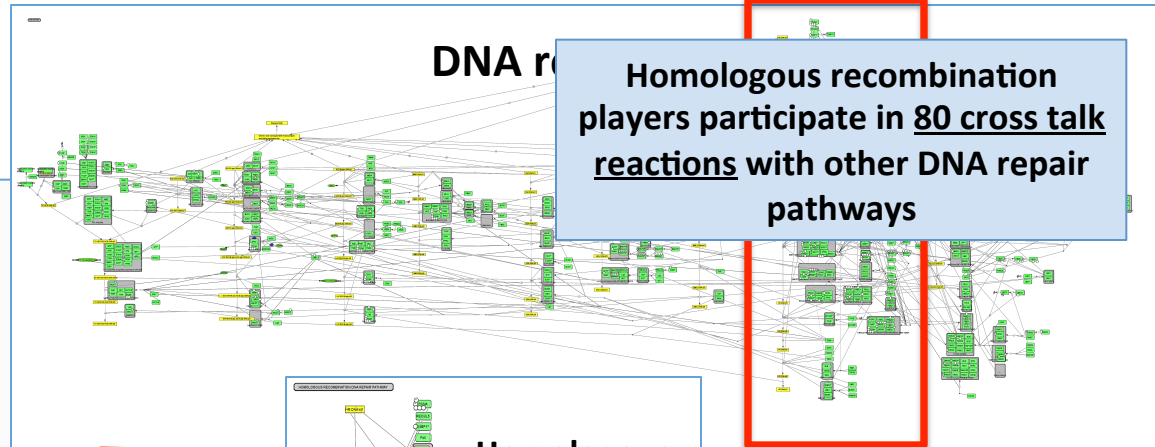
## Homologous recombination



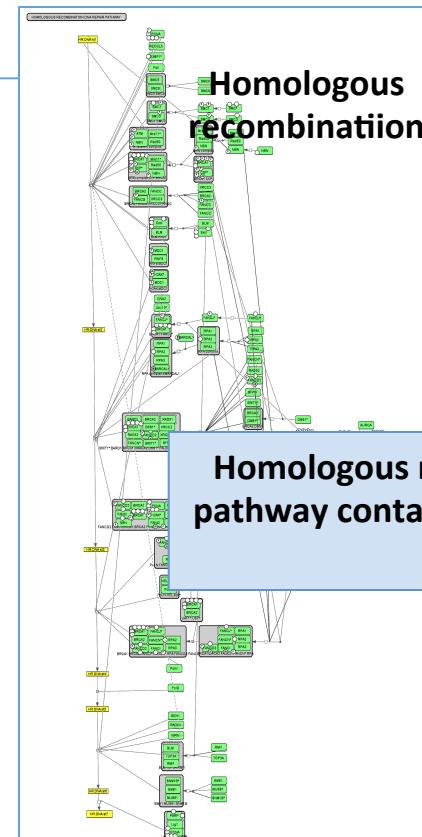
# Modular interconnected and exhaustive maps

## DNA repair-cell cycle

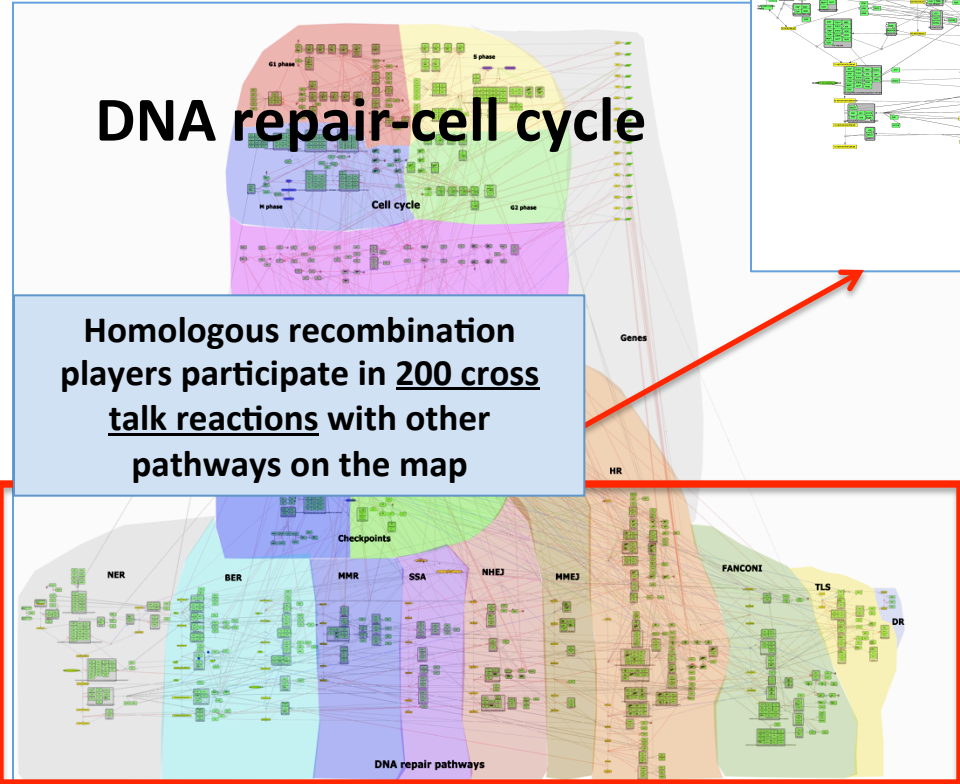
Homologous recombination players participate in 200 cross talk reactions with other pathways on the map



Homologous recombination players participate in 80 cross talk reactions with other DNA repair pathways



Homologous recombination pathway contains 33 reactions

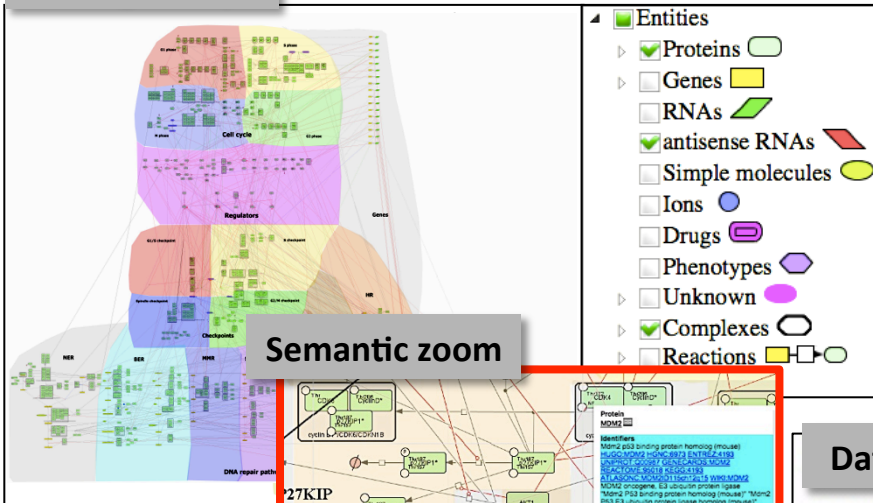




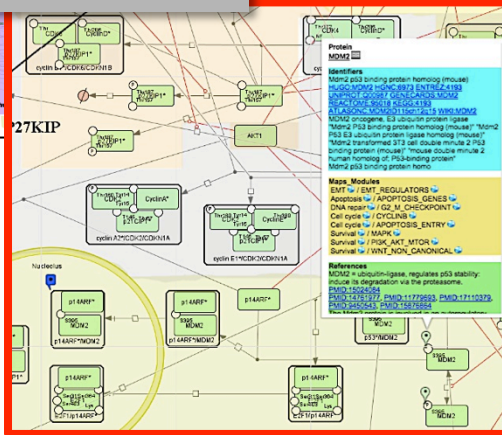
# A web tool for navigation, curation and data analysis in the context of signaling networks

NaviCell = Map (Google Maps engine) + Blog (WordPress) + ToolBox

## Google map



## Semantic zoom



## Data integration

Load Data

My Data

Sample Annotations

Drawing Configuration

Functional Analysis

## Blog

AKT\*

[Leave a reply](#)

Protein AKT\*

### Identifiers

v-akt murine thymoma viral oncogene homolog 1  
[HUGO-AKT1](#) [HGNC:381](#) [ENTREZ-207](#) [UNIPROT:P31749](#) [GENECARDS:AKT1](#) [REACTOME-58253](#)  
[KEGG-207](#) [ATLASONC-AKT1D3656h14q32](#) [WIKI-AKT1](#)

v-akt murine thymoma viral oncogene homolog 2  
[HUGO-AKT2](#) [HGNC:392](#) [ENTREZ-208](#) [UNIPROT:P31751](#) [GENECARDS:AKT2](#) [REACTOME-49860](#)  
[KEGG-208](#) [ATLASONC-AKT2ID517ch19e13](#) [WIKI-AKT2](#)

v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)  
[HUGO-AKT3](#) [HGNC:393](#) [ENTREZ-10000](#) [UNIPROT:Q9Y243](#) [GENECARDS:AKT3](#) [REACTOME-415917](#)  
[KEGG-10000](#) [ATLASONC-AKT3ID615ch1e44](#) [WIKI-AKT3](#)

[HUGO-AKT3](#) [HGNC:393](#) [ENTREZ-10000](#) [UNIPROT:Q9Y243](#) [GENECARDS:AKT3](#) [REACTOME-415917](#)  
[KEGG-10000](#) [ATLASONC-AKT3ID615ch1e44](#) [WIKI-AKT3](#) [HUGO-CDH2](#) [HGNC:1758](#) [ENTREZ-1000](#)  
[UNIPROT:P18022](#) [GENECARDS:CDH2](#) [REACTOME-51212](#) [KEGG-1000](#) [ATLASONC:GG\\_CDH2](#)  
[WIKI-CDH2](#)

### Maps\_Modules

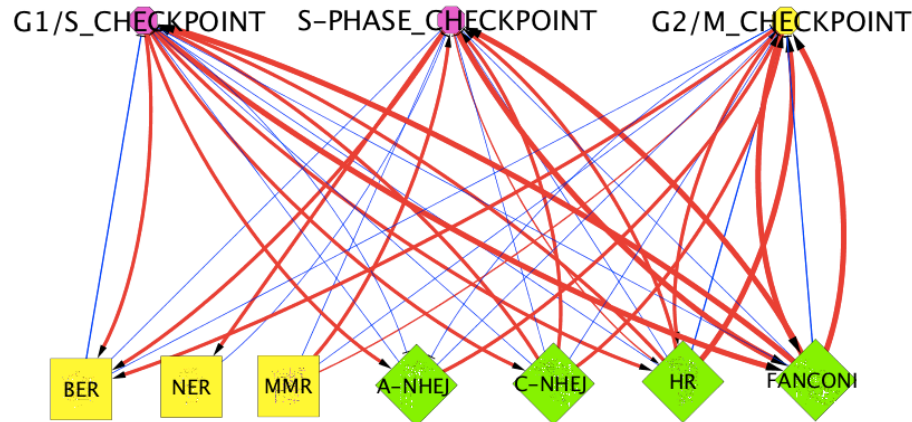
Apoptosis [/](#) AKT\_MTOR [/](#) CASPASES [/](#) MITOCH\_METABOLISM [/](#) MOMP\_REGULATION [/](#) DNA\_repair [/](#) G1\_S\_CHECKPOINT [/](#) Survival [/](#) HEDGEHOG [/](#) MAPK [/](#) PI3K\_AKT\_MTOR [/](#) WNT\_NON\_CANONICAL

### References

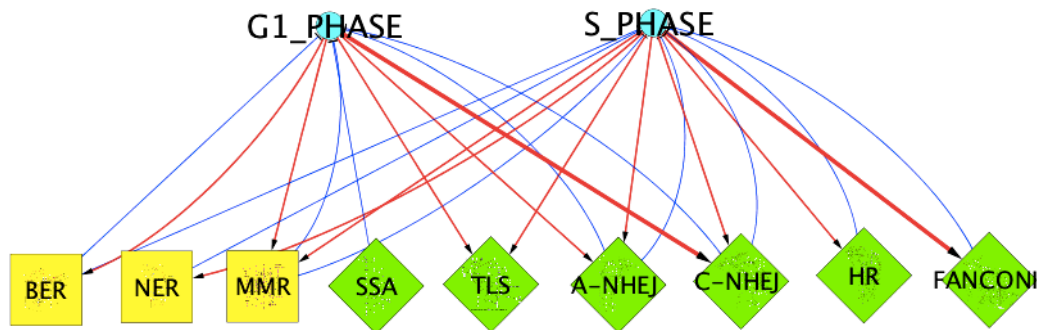
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[PMID:17680028](#)  
[PMID:26398329](#)

# DNA repair map: network of modules

## Checkpoints and DNA repair



## Cell cycle phases and DNA repair



Network of modules derived from the comprehensive map using Cytoscape plugin BiNoM. Following structural analysis and network reduction. The thickness of edges reflects number of regulatory reactions.

# Aim

**Suggest intervention gene sets for ovarian cancer patients resistant to genotoxic treatment**



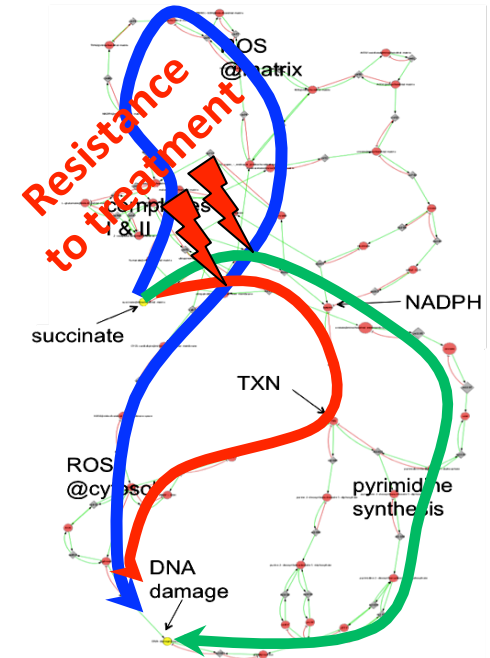
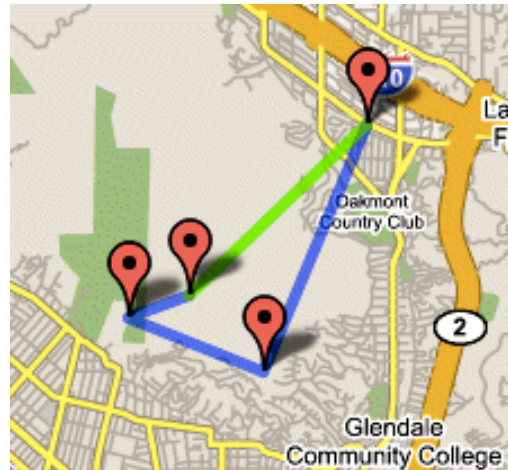
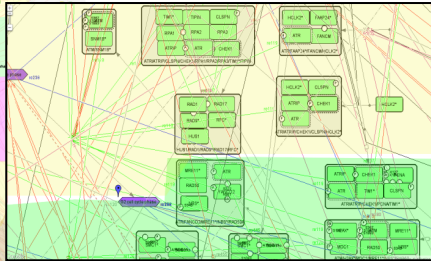
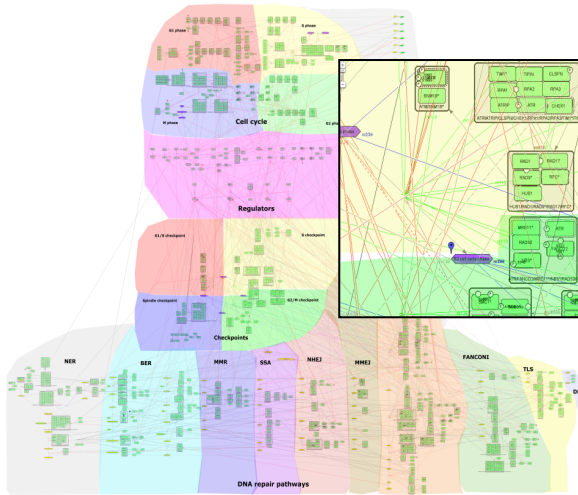
# Approach

To overcome Cisplatin resistance in ovarian cancer, we searched for synthetically interacting combinations of genes to interfere with DNA repair machinery and to restore drug sensitivity:

- Construction of comprehensive DNA repair and cell signaling map
- Deriving a state transition graph from the map and retrieving all paths from a damaged DNA to the repaired DNA state
- Using OCSANA algorithm to search the Minimal Cut Sets (MCS) to interfere with DNA repair
- Prioritizing MCSs based on genomic, expression and mutation data from ovarian cancer patients

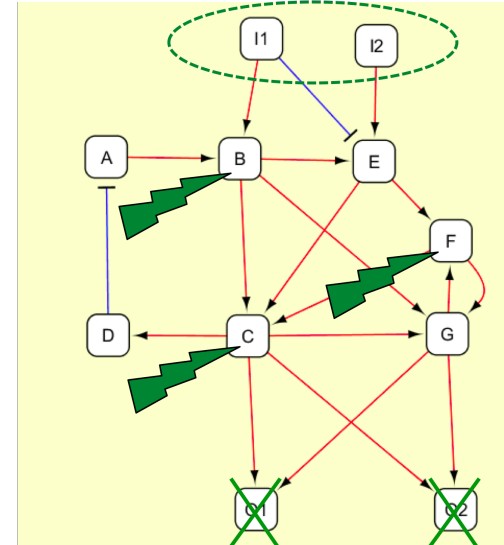
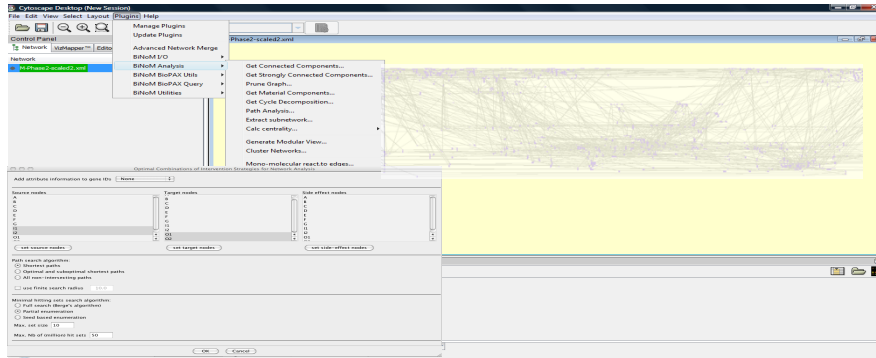
# Signaling networks for intervention strategy design

Complex intervention gene sets derived from data-driven network analysis





# OCSANA: an integrative pathway analysis to reveal synthetic lethal sets



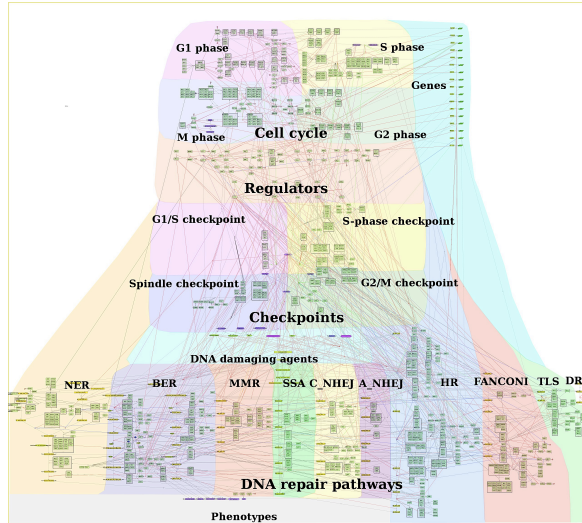
- {I1, I2}
- {C,G}
- {B,E}
- {C,F,I1}
- {B,C,F}

Identifying points of fragility in the network  
 Identifying synthetic lethal combinations

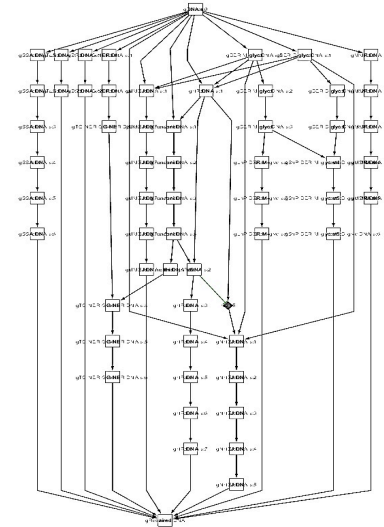
Conf. information	Elementary Pathways	Elementary Nodes	Computation Time	Total Number of MinHitSets	MinHitSets Size 1	MinHitSets Size 2	MinHitSets Size 3	MinHitSets Size 4	MinHitSets Size 5	Comments
	2300	198	5.51	252	0	0	108	42	102	
	2214	131	7.43	74	9	5	12	7	42	
	15	71	7.40	38336	6	0	160	4848	33322	
	198	126	2.04	74	8	5	12	7	42	
	529	171	2.40	112	0	6	30	32	44	Antiapoptotic
1476	121	1.21	74	1	5	12	7	42	Downregulated by BRCA1 and p53. Upregulated by USF-1 (which is upregulated by BRCA2)	
246	119	0.24	86	21	0	12	7	42	Study of Combinations	

# Retrieve minimal cut sets (MCSs) to interfere with signal propagation

Comprehensive DNA repair map

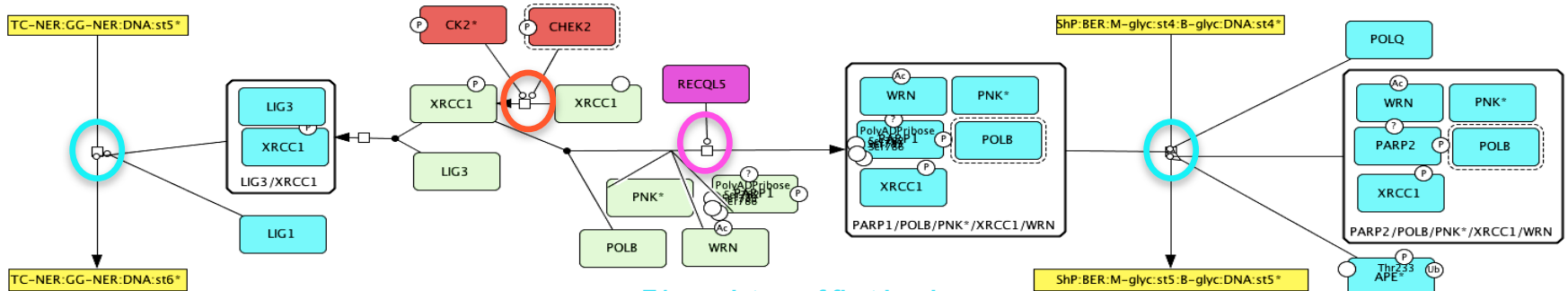


State transition graph and all regulations on DNA repair map



State transition graph retrieval  
 →

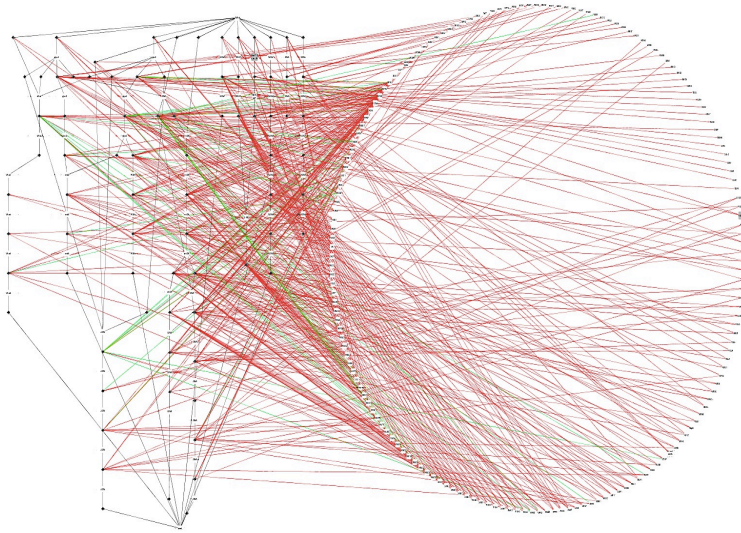
Regulators of each state transition on DNA repair map



E1-regulators of first level  
 E2-regulators of second level  
 E3-regulators of third level

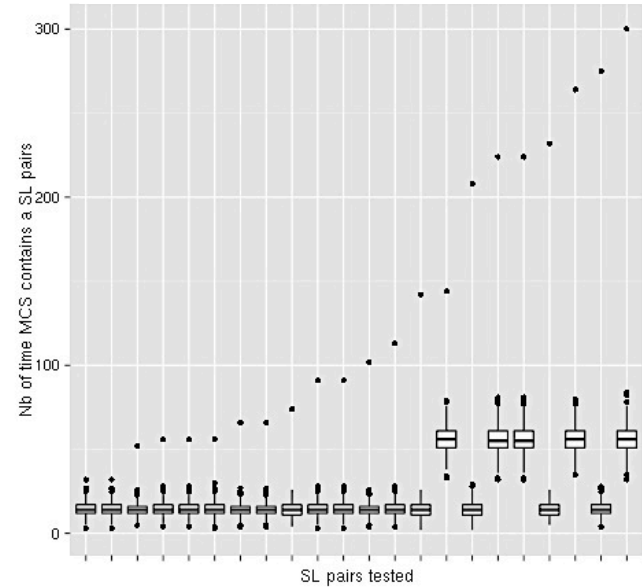
# Retrieve minimal cut sets (MCSs) to interfere with signal propagation

State transition graph and all regulators of DNA repair steps



State transition graph, including all paths leading to repaired DNA and genes regulating each step has been derived (regulators of first level)

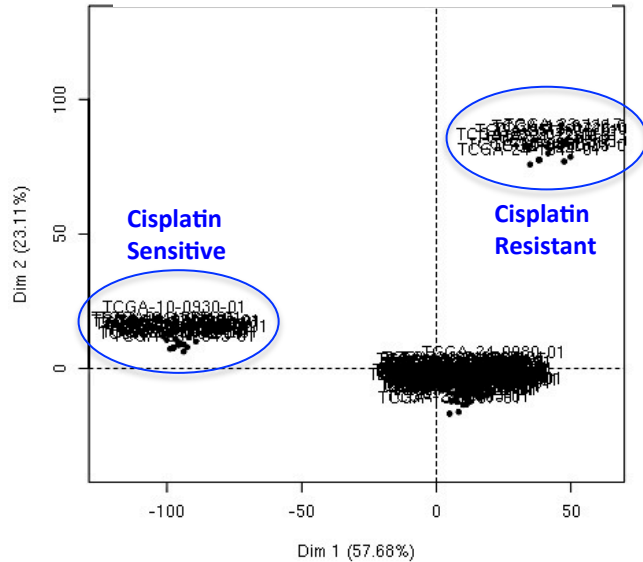
Enrichment of SL pairs in 'real' vs. pseudo-MCSs



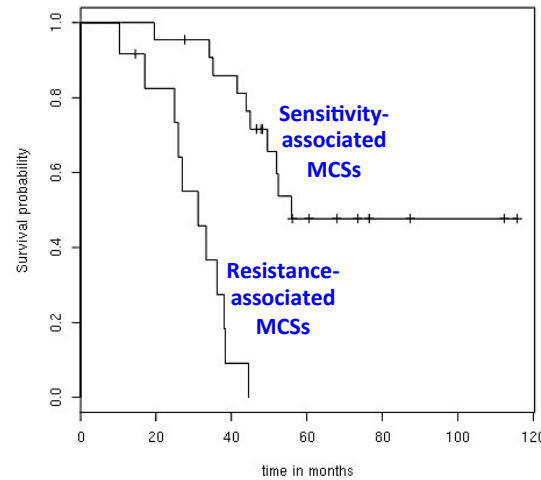
The coherence of the method has been validated using experimentally-proven SL pairs from shRNA screen, verifying the enrichment of the SL pair in real vs. randomly-generated (pseudo)-MCSs (DECIPHER project) in 'real' vs. pseudo-MCSs pairs from shRNA screen.

# Complex intervention gene sets derived from data-driven network analysis for patients resistant to Cisplatin

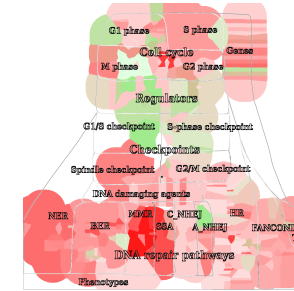
Three top groups of patients associated with unique MCS lists



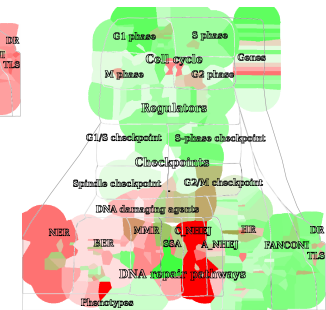
Survival curves comparing Cisplatin resistant and sensitive patients



Molecular portrait of treatment resistant sample



Molecular portrait of treatment sensitive sample



For selection of top-ranked MCS to be suggested as intervention sets, we identified altered components in MCSs for each patient using mRNA, copy number and mutation information.

Exploiting the patient's background, it is possible to target the remaining 'active' components in the set to achieve synthetic lethality.

## Intervention sets ranking

- Gene status
- Expression
- Copy number
- Mutations
- Number of path hits (NPH)
- Druggability

## Top ranked intervention sets for Cisplatin-resistant ovary cancer patients (example)

Resistant			
XRCC5	MUS81	PARP2	POLD4
XRCC5	PARP2	POLD4	SLX1A
EXO1	XRCC5	PARP2	POLD4
XRCC5	PARP2	POLD4	RPA3
PRKDC	MSH2	PARP2	POLD4

green-inhibited gene, red-activated gene

# Conclusions

- DNA repair creates an interconnected network with multiple redundant paths
- Comprehensive map of DNA repair is a resource for data integration and analysis
- Using MCS search method we suggest a complementary intervention scheme for genotoxic treatment by targeting specifically certain targets in DNA repair machinery

# Acknowledgements

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