Cheminformatics-Driven Identification of Inhibitors of Protein-Protein Interactions

VANCOUVER PROSTATE CENTRE
A UBC & VGH Centre of Excellence

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June 28, 2012

1. Targeting Protein Indels

2. Why PPI-s are good targets?

3. Example: MRSA Pyruvate Kinase

ANTIBIOTIC RESISTANCE!

Gonorrhea Becoming 'Incurable'

STD MUTATING SO FAST THAT ANTIBIOTICS CAN'T KEEP

(NEWSER) - The clap is mutating so quickly that there is a real danger that it will become incurable unless new treatments are developed, British doctors warn. The bacterium that causes gonorrhea—the second most common STD in the US—is rema adaptable and has proven resistant to the primary drug used... More »

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Deadly TB Coursing Through Europe

THOUSANDS WILL DIE UNLESS AUTHORITIES STEP IN: V

(NEWSER) - Ominous news from WHO: Incredibly drug-resista forms of tuberculosis are coursing through Europe, and will kill thousands unless health officials intervene. WHO's regional dir blamed the resurgence on complacency, noted that the diseas evolving with a vengeance," and announced the creation of a p More »

First Drug-Resistant Strain of Gonorrhea Discovered

'SUPERBUG' COULD SPREAD GLOBALLY WITHIN DECADI

(NEWSER) - A "superbug" strain of gonorrhea, the first ever to r all currently recommended treatments, has been discovered in Japan. The strain, called H041, could quickly spread around the globe, scientists warn. While gonorrhea was once an easily trea STD, it has shown a "remarkable capacity" to develop drug... M

Tamiflu Useless Against Dominant Flu Strain

SUBSTITUTE ISN'T SAFE FOR EVERYONE

(NEWSER) - The dominant flu strain circulating in much of the U nearly 100% resistant to Tamiflu, the most commonly used antiv the *Los Angeles Times* reports. Despite a milder than usual flu season, the resistance is still causing concern, and the CDC is advising doctors to substitute Tamiflu with Relenza,... More »

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Super-TB Cases Hit Record High

WHO CALLS FOR URGENT ACTION

(NEWSER) - Drug-resistant strains of tuberculosis are at the highest levels disease experts have ever seen, warns the World Health Organization. A survey of 81 countries found that levels of multi-drug resistant TB and even hardier, almost untreatable TB were much higher than expected, reports the BBC. Urgent action is needed to... More »

This Year's Flu Vaccine Missing the Mark

ONLY 40% EFFECTIVE AS UNEXPECTED VIRUS STRAINS HIT THE PUBLIC

(NEWSER) - Flu season peaks in early February and experts say this could be a very bad year. Health officials say that is partly because this year's flu vaccines aren't effective enough, the AP reports. "Every area of the country is experiencing lots of flu right now," said a doctor... More »

Common Flu Exhibits Drug Resistance

UP TO 10% OF CASES IN WEST DON'T RESPOND TO TAMIFLU TREATMENT

Staph Strain Explodes Immune Cells

PART OF PUZZLE EXPLAINS INFECTION'S DEADLY PUNCH

(NEWSER) - A key reason why a powerful strain of drug-resistant staph infections known as MRSA has proven so deadly is because it produces a compound that causes immune cells to explode, a new study in *Nature* concludes. The finding helps explain why MRSA, usually found in hospitals in patients with weakened... More »

Hospitals Ramp Up Screening for Superbug

FOUR CHICAGO FACILITIES WILL TEST ALL NEW PATIENTS FOR THE STAPH INFECTION

(NEWSER) - Four hospitals in the Chicago area will start screening all patients for drug-resistant "superbug" bacteria, the *Chicago Tribune* reports. The intensive screening is known as "search and destroy" in Europe, but it is uncommon in the US. The moves comes as hospitals around the nation evaluate safety procedures... More »

Drug-Proof Superbug Turns Deadly

ANTIBIOTIC-RESISTANT STAPH KILLS MORE AMERICANS THAN AIDS

(NEWSER) - An antibiotic-resistant strain of staph kills more Americans each year than HIV, accounting for almost 19,000 deaths annually, the first national stats on the superbug reveal. The super-staph is treatable but can quickly lead to dangerous "flesh-eating" infections. "We really need to be on guard against these... More »

ANTIBIOT

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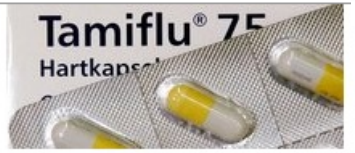
First Drug-Resistant Strain of Gonorrhea Discovered

Jul 11, 2011 7:49 AM CDT



Tamiflu Useless Against Dominant Flu Strain

Feb 7, 2009 2:26 PM CST

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SUBSTITUTE ISN'T SAFE FOR EVERYONE

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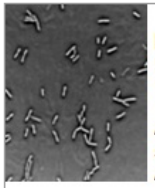

Drug-Proof Superbug Turns Deadly

Antibiotic-resistant staph kills more Americans than AIDS

Oct 16, 2007 11:26 PM CDT

Drug-Proof Superbug Turns Deadly

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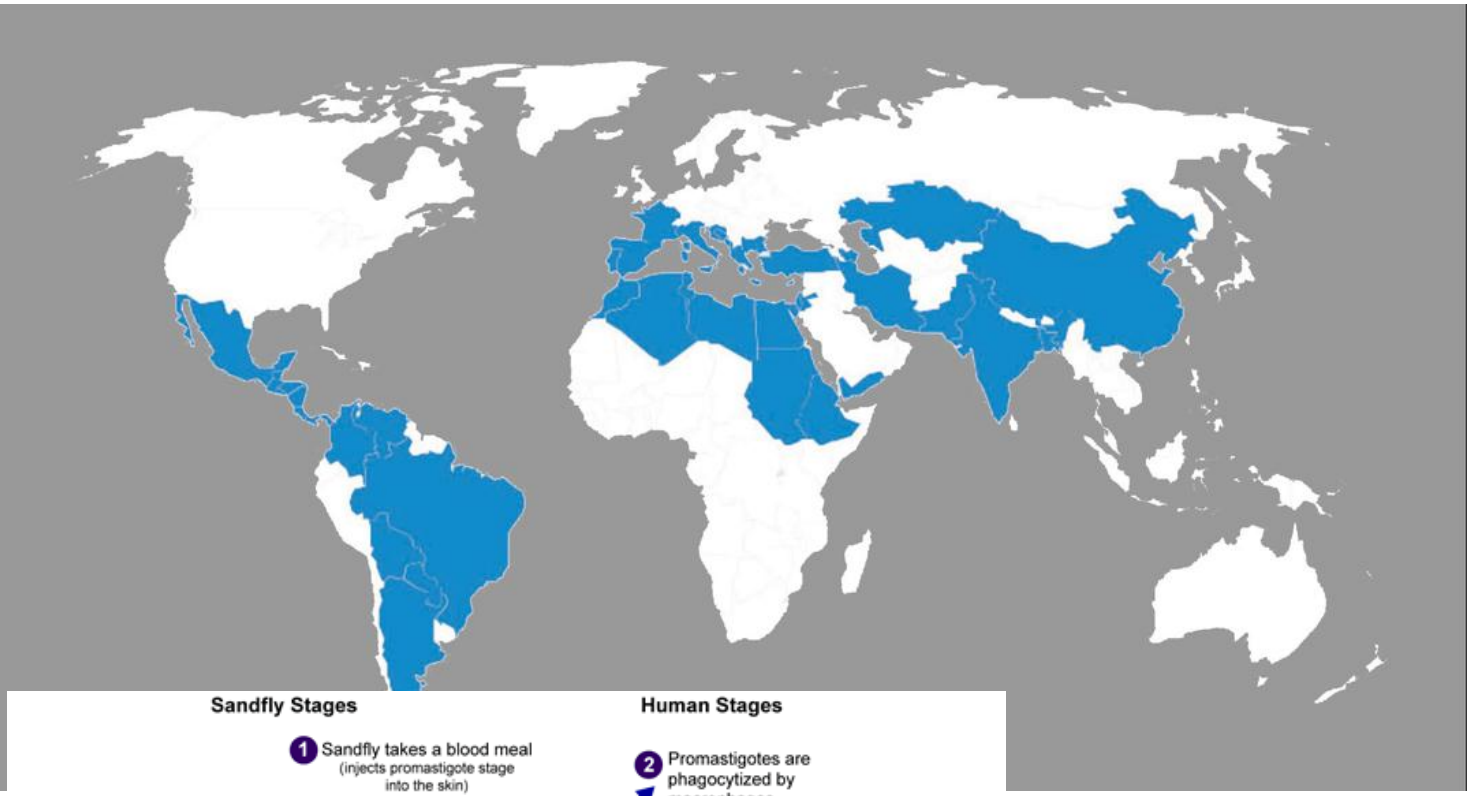
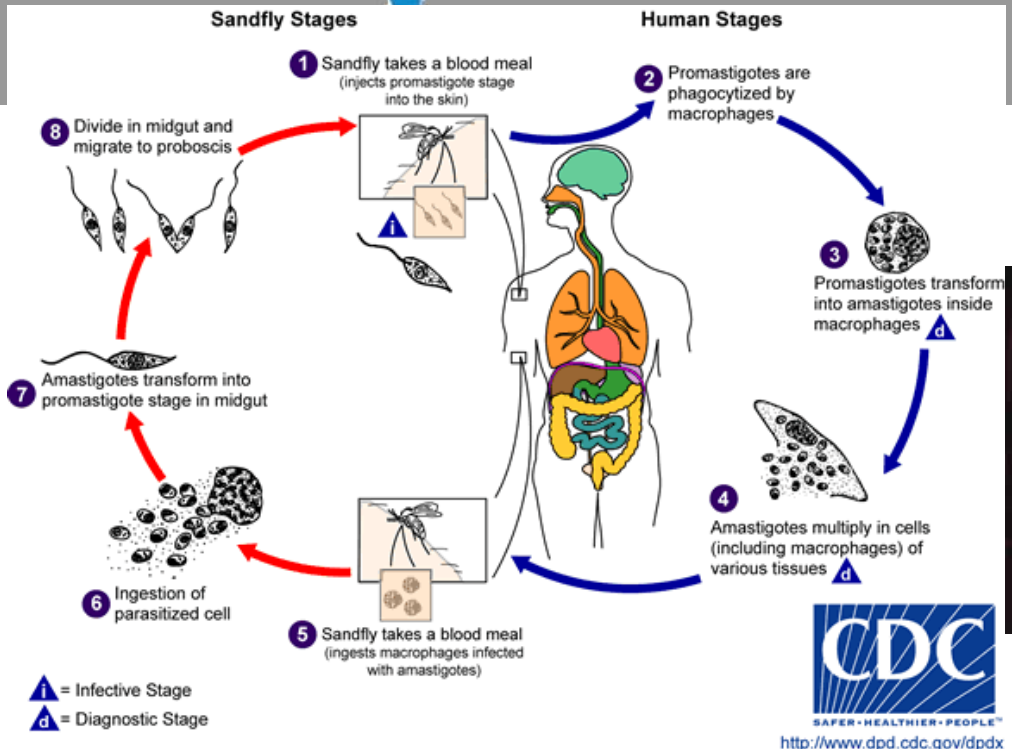
1. Targeting Protein Indels





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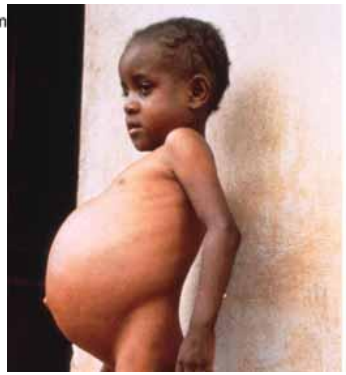
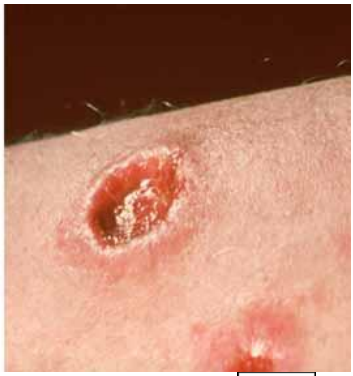
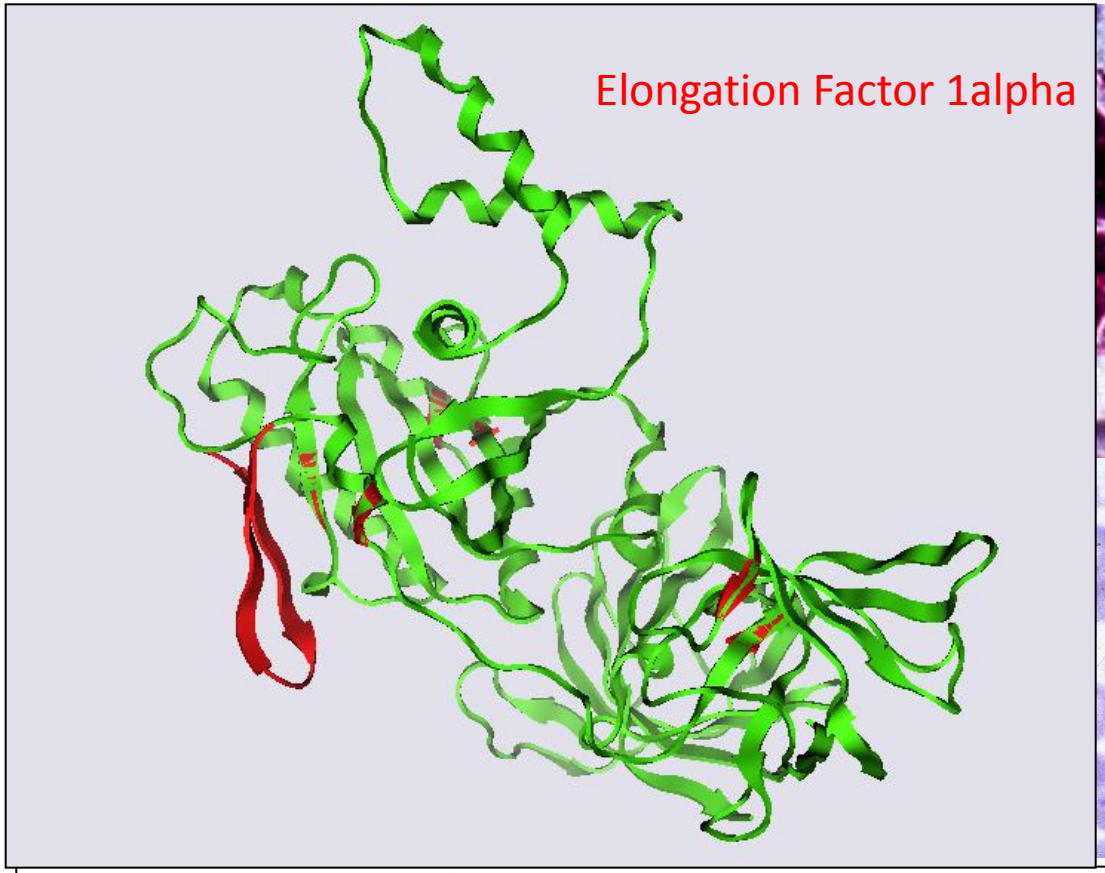
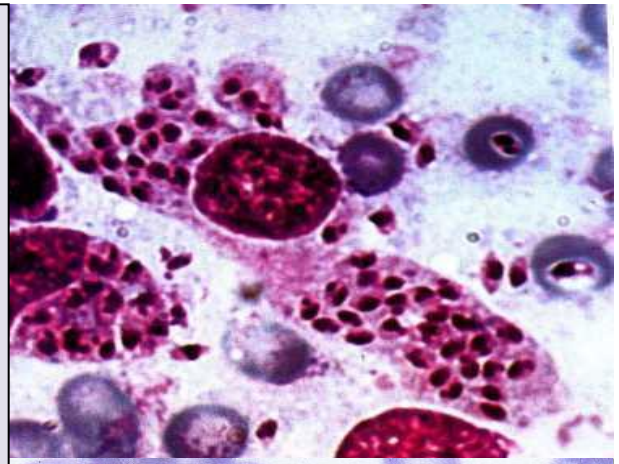
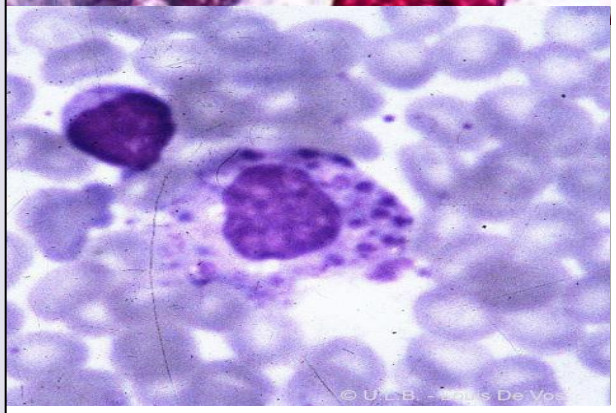






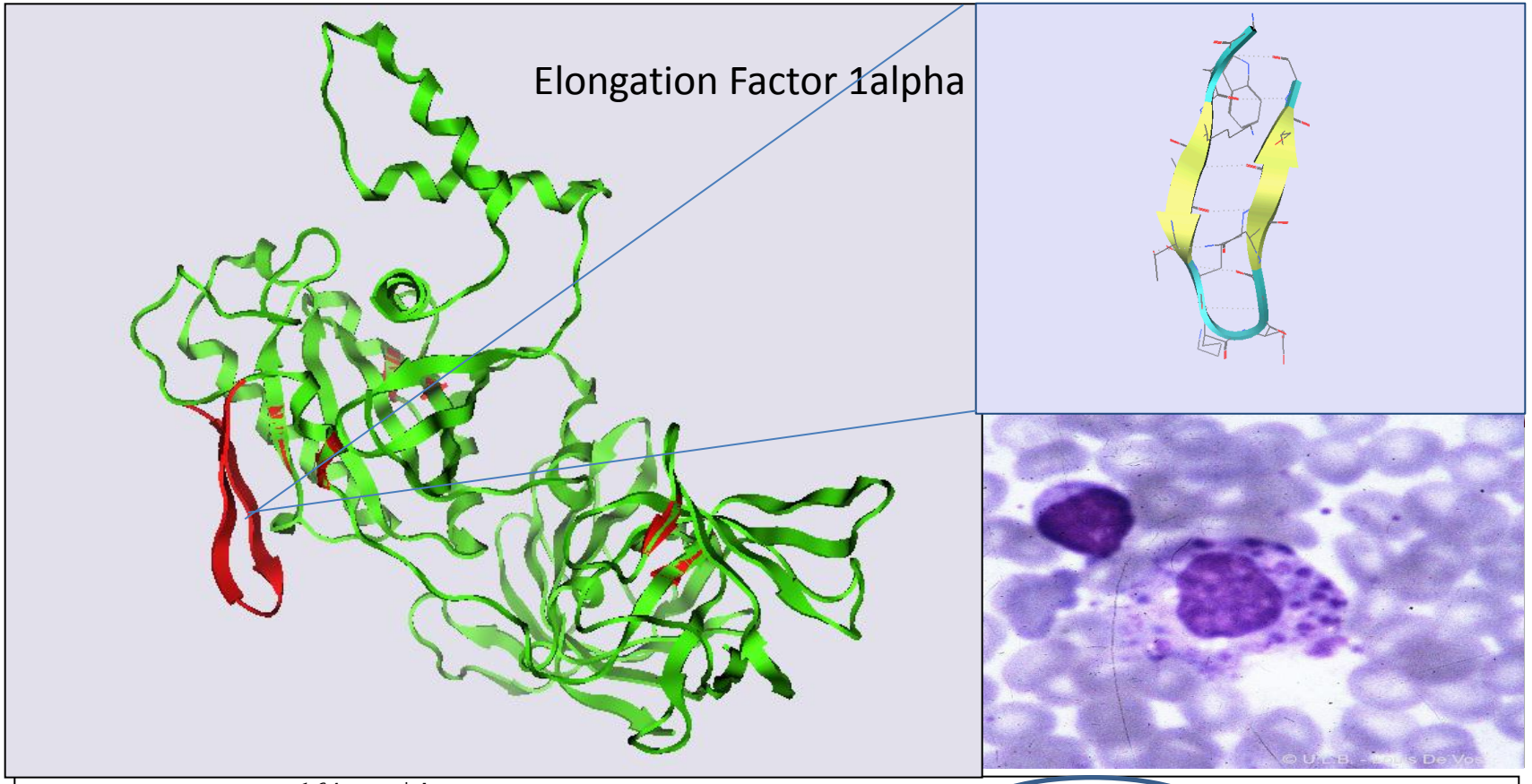




n ~ 164 residues

Giardia	QERYEEIKKEISAFLKKTGYNPDKIPFVPISGFQGDNMIEPSTNMPWYK	GPTLIGALDSVTPPERP
Entamoeba	QERYEEIKKEISAFLKKTGYNPDKIPFVPISGFQGDNMIEPSTNMPWYK	GPTLIGALDSVTPPERP
Trypanosoma	QSRFDEIFNEVDGYLKKVGYNTEKIPFVAISGFVGDNMVERSDKMPWYK	GKTLVEALDTMEPPKRP
Crypto.	QSRFDEIFNEVDGYLKKVGYNTEKIPFVAISGFVGDNMVERSDKMPWYK	GKTLVEALDTMEPPKRP
Plasmodium	EDRYEEIKKEVKDYLKKVGYQADKVDFIPISGFEGDNLIEKSDKTPWYK	GRTLIEALDTMEPPKRP
Leishmania	QSRYDEISKEVGAYLKRVGYNPEKVRFIPISGWQGDNMIERSDNMPWYK	GPTLLDALDMLEPPVRP
Homo sapiens	QKRYEEIVKEVSTYIKKIGYNPDTVAFVPISGWNGDNMLEPSANMPWFKG**WKVTRKDGNAS**	GTTLLEALDCILPPTRP
Canis familiaris	QKRYEEIVKEVSTYIKKIGYNPDTVAFVPISGWNGDNMLEPSANMPWFKG**WKVTRKDGNAS**	GTTLLEALDCILPPTRP
Mus musculus	QKRYEEIVKEVSTYIKKIGYNPDTVAFVPISGWNGDNMLEPSANMPWFKG**WKVTRKDGSAS**	GTTLLEALDCILPPTRP
Drosophila	EARYEEIKKEVSSYIKKIGYNPAAVAFVPISGWHGDNMLEPSTNMPWFKG**WKVERKEGNAD**	GKTLIDALDAILPPARP

A. Cherkasov et al, *Proteins* 2005, 2006



n ~ 164 residues

INDEL

```
Giardia             QERYEEIKKEISAFLKKTGYNPDKIPFVPISGFQGDNMIEPSTNMPWYK          GPTLIGALDSVTPPERP
Entamoeba           QERYEEIKKEISAFLKKTGYNPDKIPFVPISGFQGDNMIEPSTNMPWYK          GPTLIGALDSVTPPERP
Trypanosoma         QSRFDEIFNEVDGYLKKVGYNTEKIPFVAISGFVGDNMVERSDKMPWYK          GKTLVEALDTMEPPKRP
Crypto.             QSRFDEIFNEVDGYLKKVGYNTEKIPFVAISGFVGDNMVERSDKMPWYK          GKTLVEALDTMEPPKRP
Plasmodium          EDRYEEIKKEVKDYLKKVGYQADKVDFIPISGFEGDNLIEKSDKTPWYK          GRTLIEALDTMEPPKRP
Leishmania          QSRYDEISKEVGAYLKRVGYNPEKVRFIPISGWQGDNMIERSDNMPWYK          GPTLLDALDMLEPPVRP
Homo sapiens        QKRYEEIVKEVSTYIKKIGYNPDTVAFVPISGWNGDNMLEPSANMPWFKGWKVTRKDGNASGTTLLEALDCILPPTRP
Canis familiaris    QKRYEEIVKEVSTYIKKIGYNPDTVAFVPISGWNGDNMLEPSANMPWFKGWKVTRKDGNASGTTLLEALDCILPPTRP
Mus musculus        QKRYEEIVKEVSTYIKKIGYNPDTVAFVPISGWNGDNMLEPSANMPWFKGWKVTRKDGSASGTTLLEALDCILPPTRP
Drosophila          EARYEEIKKEVSSYIKKIGYNPAAVAFVPISGWHGDNMLEPSTNMPWFKGWKVERKEGNADGKTLIDALDAILPPARP
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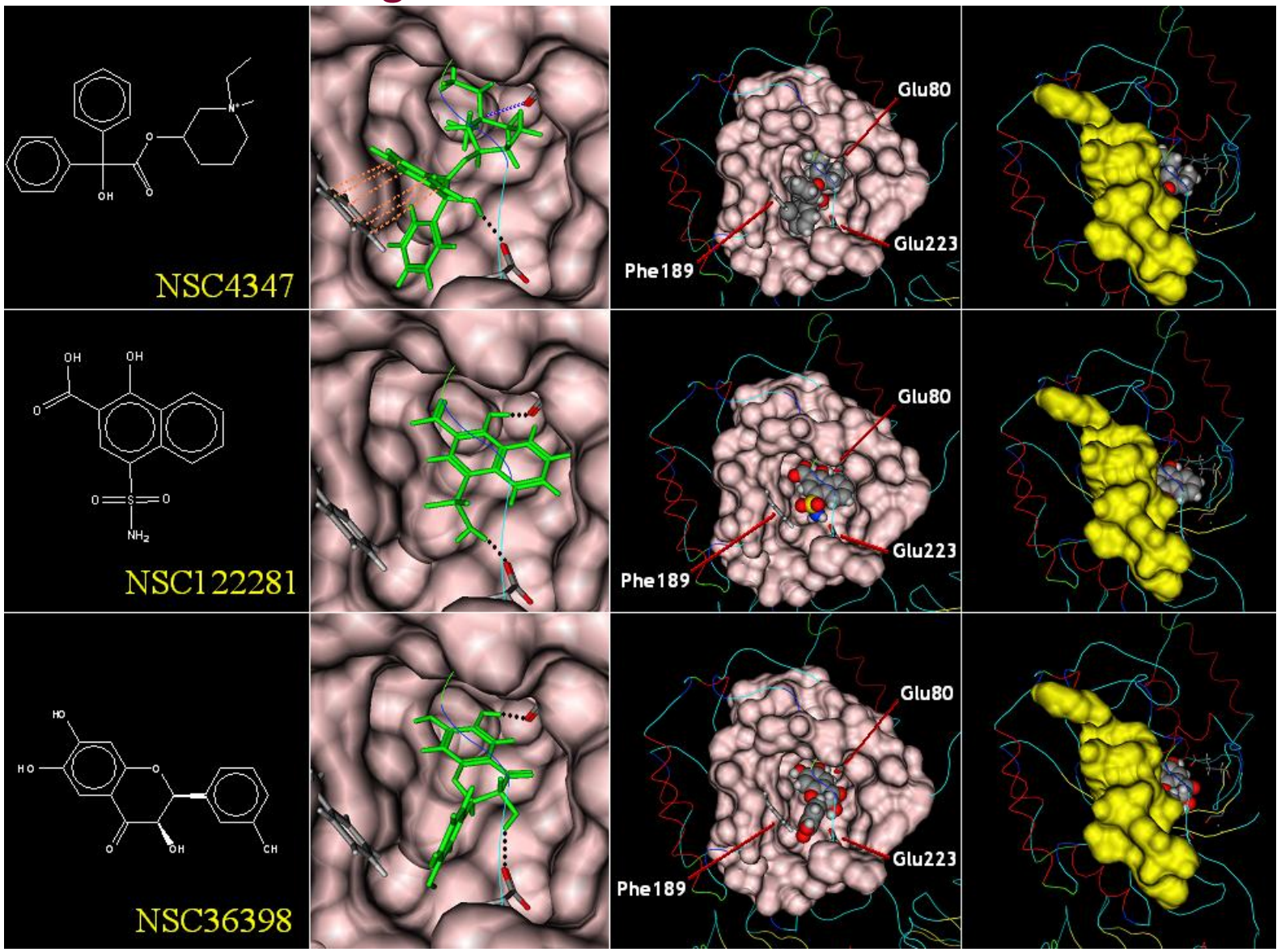
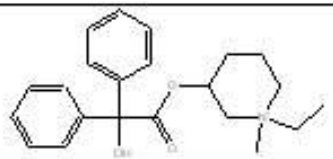
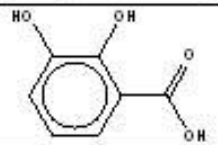
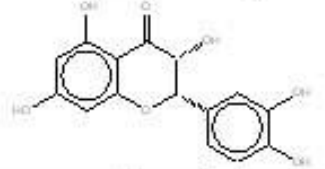
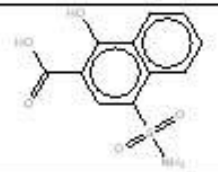
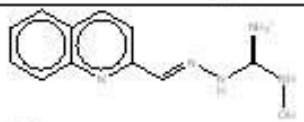
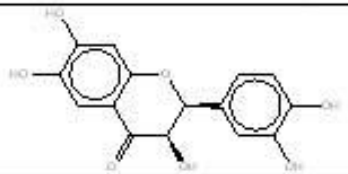
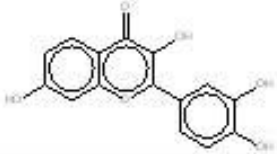
A. Cherkasov et al, *Proteins* 2005, 2006

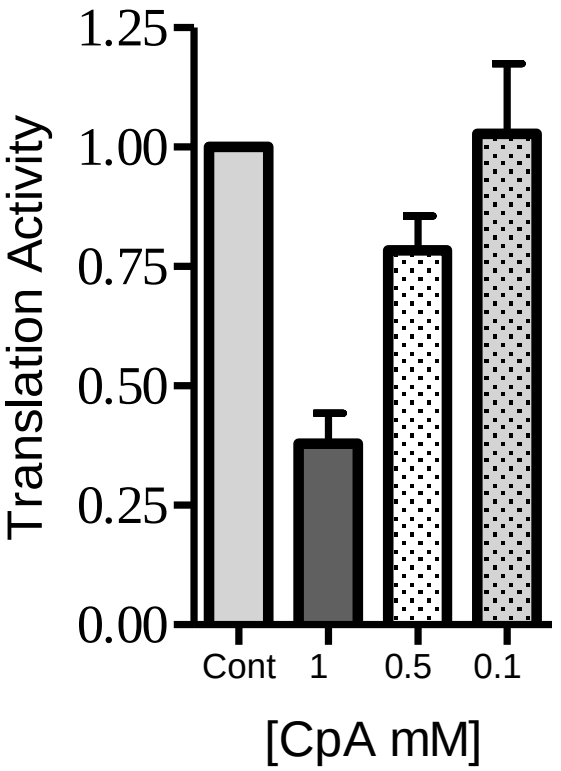
EF-1α: Attacking the Deletion



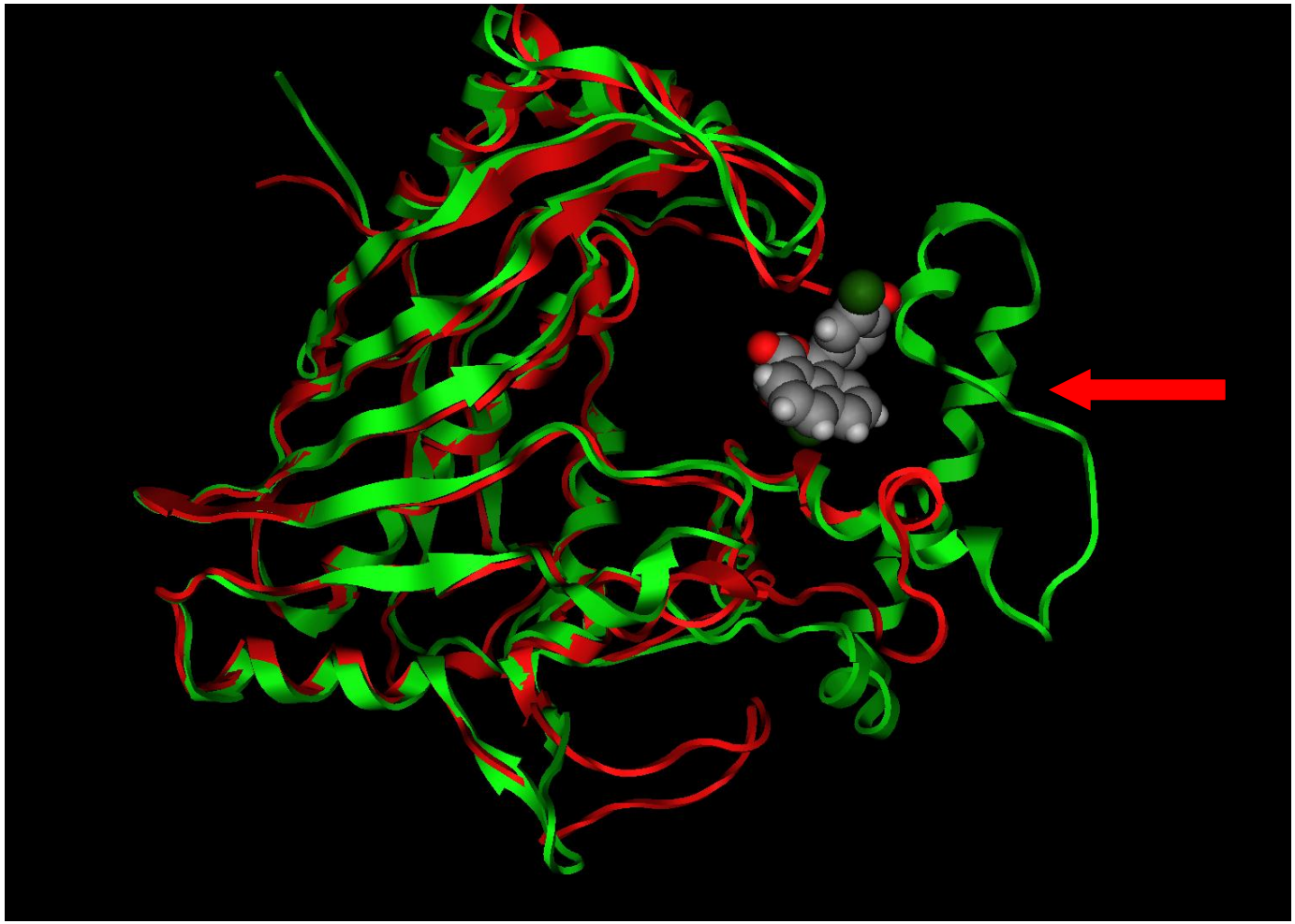
A. Cherkasov et al, *Proteins* 2005, 2006

EF-1α: Attacking the Deletion

Compound	Structure	Dock score Leishmania EF-1α	% Inhibition of Leishmania translation
NSC4347		-7.46	**75**
NSC27435		-7.28	
NSC2801		-7.22	
NSC122281		-7.07	**49**
NSC376464		-7.07	
NSC36398		-6.89	**55**
NSC407010		-6.55	



Attacking the Insertion: *Superimposed models of thymidine synthase proteins from S. areus (in green) and human (in red). The insertion in the sequence of bacterial protein is indicated by red arrow.*



```
Staph.    AFENYIKSDEYKGPDMTDFGHRALSDPEFNEQYKEQMKQFKQRILEDDTFAKQFGDLGNVYGKQWRDWVDK
Human     GSRDFLDSLGFS----------------------------------------TREEGDLGPVYGFQWRHFGAE
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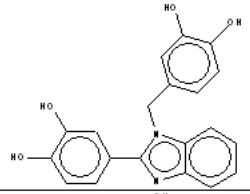
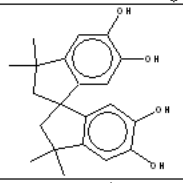
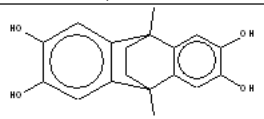
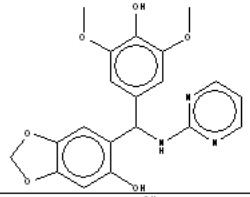
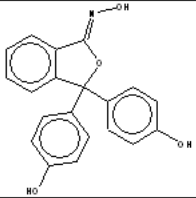
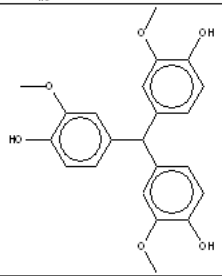
Initial set of Drug leads identified for S aureus TS-ase protein. The docking scores reflect how well the compounds can bind to insertion site.

Compound	Structure	Dock score MRSA	Dock score Human
01663069		-8.56	N/A
00045127		-7.98	N/A
01617880		-7.81	N/A
01586979		-7.76	N/A
04683248		-7.5	N/A
04692031		-7.46	N/A

	Organism	Proteins studied	Proteins w. human hmlgs	INSERTIONS					DELETIONS				
				Insertions	*Insertions expected*	α	β	r^2	*Deletions*	*Deletions expected*	α	β	r^2
1	*Rhodopseudomonas palustris*	9663	1565	568	547	0.25	0.37	0.95	701	731	0.26	0.35	0.94
2	*Streptomyces avermitilis*	7705	1013	383	436	0.21	0.37	0.94	508	583	0.21	0.35	0.92
3	*Streptomyces coelicolor*	8183	996	372	463	0.16	0.35	0.95	508	619	0.17	0.33	0.92
36	*Plasmodium falciparum (isolate 3D7)*	5308	2284	1310	300	1.82	0.44	0.94	1209	402	1.64	0.44	0.95
37	*Giardia lamblia ATCC 50803*	6395	1296	630	362	0.23	0.30	0.95	604	484	0.43	0.40	0.94
38	*Pseudomonas aeruginosa*	7225	888	310	409	0.08	0.30	0.97	454	547	0.15	0.32	0.92
39	*Leishmania donovani*	1542	103	294	87	1.02	0.37	0.95	259	117	0.96	0.41	0.95
40	*Bordetella parapertussis*	4045	665	284	229	0.25	0.36	0.95	327	306	0.28	0.35	0.93
41	*Mycobacterium tuberculosis*	4881	694	284	276	0.20	0.35	0.93	341	369	0.23	0.35	0.93
42	*Bacillus anthracis (strain Ames)*	5315	721	280	301	0.18	0.35	0.94	401	402	0.17	0.31	0.91
43	*Yersinia pestis*	5511	706	266	312	0.14	0.33	0.95	368	417	0.17	0.32	0.93
44	*Shigella flexneri*	5453	656	263	309	0.11	0.31	0.94	328	413	0.13	0.31	0.93
45	*Streptococcus pneumoniae*	3730	550	249	211	0.26	0.38	0.90	291	282	0.22	0.33	0.90
46	*Escherichia coli O157:H7*	5730	626	233	324	0.10	0.31	0.94	314	433	0.08	0.28	0.92

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Indel Therapeutics

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Indel Therapeutics Inc. is a biopharmaceutical company dedicated to developing new drugs to address the global health crisis caused by antibiotic resistance. The Company has a growing pipeline of novel antibiotic drug discovery programs that focus on curing difficult-to-treat and hospital-acquired infections. These programs are based on Indel's paradigm-changing antimicrobial drug discovery platform, a patented technology that has opened a rich, new area of drug targets for the treatment of bacterial and parasitic infections and, potentially, fungal and viral infections.

Canada's Top 10 Life Science Companies Competitor Winner

Red Herring Winner 50 Canada

LATEST NEWS

April 28, 2011
Indel Raises second financing and Allan Collings joining board of directors

September 24, 2009
Finalist for the New Ventures BC Competition - One of top ten companies selected as a finalist

August 11, 2009
Allowance/issuance of key platform patent entitled Diagnosis and Treatment of Infectious Disease through INDEL-Differentiated Proteins by the U.S. Trademark and Patent Office

604.551.8464 info@indelrx.com

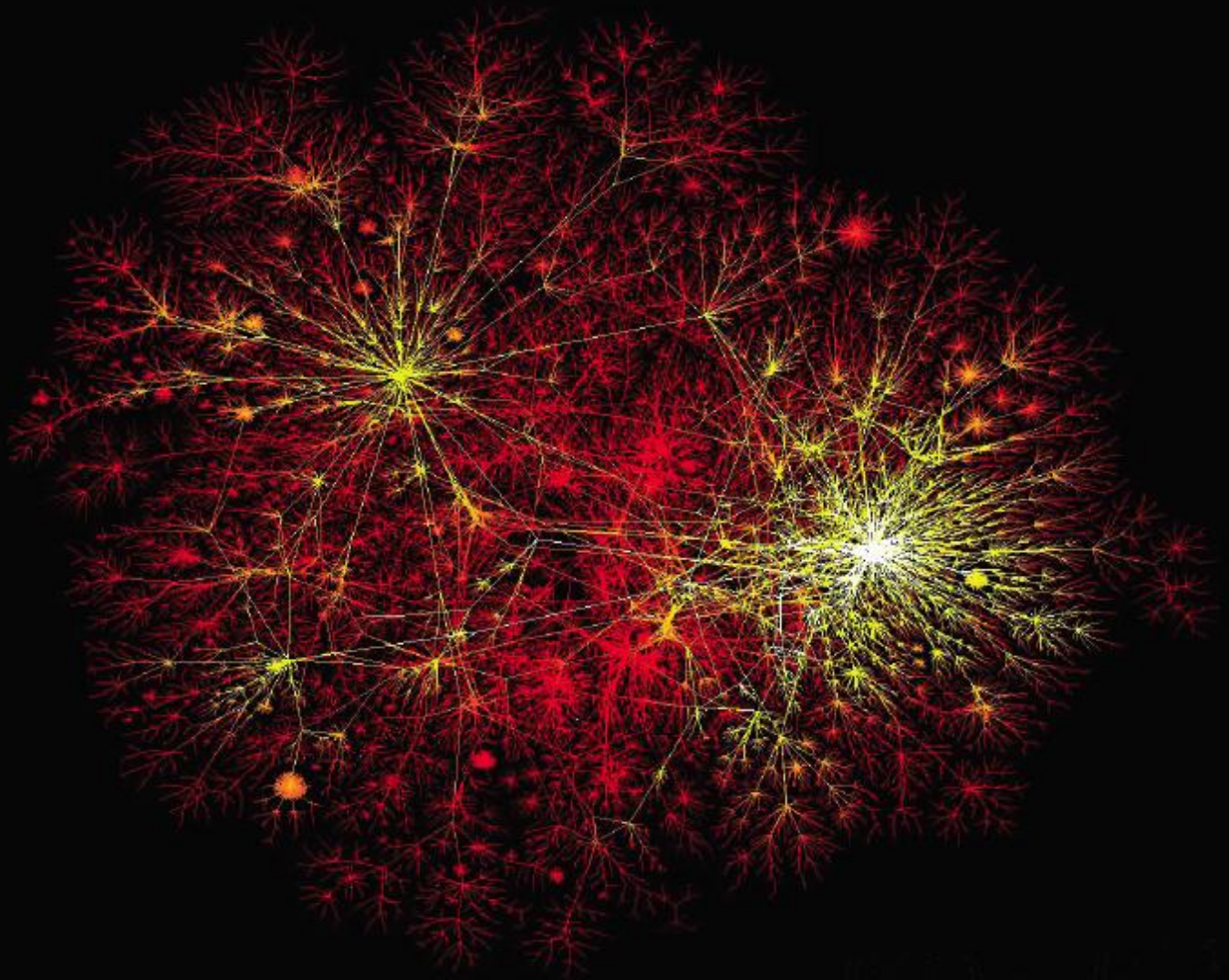
EN 8:04 PM 07/06/2011

2. Why PPI-s are good targets?

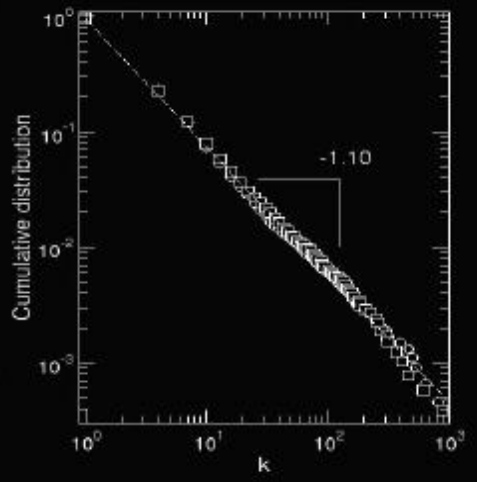
MRSA

- Multidrug-resistant bacteria such as MRSA are a serious threat to human health and MRSA is the most common cause of hospital-acquired infections worldwide.
  - Approximately 20,000 deaths in 2005 in US.
- While antibiotics resistance is on the rise, antimicrobial discovery research is on the decline.
  - There is an urgent need for the discovery and development of new classes of antibiotics to combat these bacterial pathogens.
- One strategy would be to use large-scale, genome-wide protein interaction networks in bacteria to identify highly connected essential hubs as potential novel antibacterial drug targets.
  - They are expected to be less prone to genetic mutations and subsequent resistance emergence due to the network centrality-lethality rule.

Complex networks are scale-free



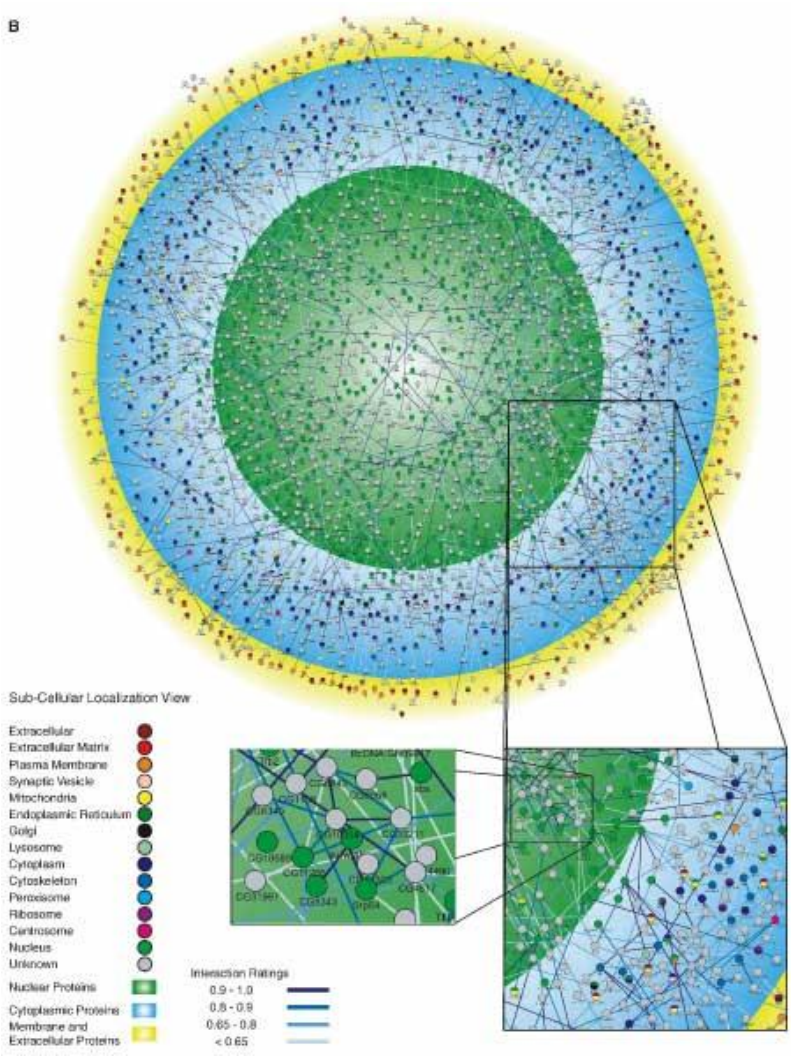
$$P(k) \sim k^{-\gamma}\phi(k/\xi)$$



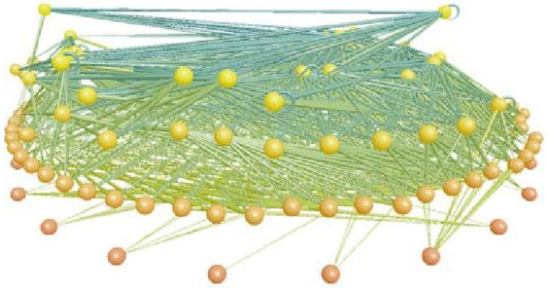
Barabási, Albert-László (2004). *Linked How Everything is Connected to Everything Else*

Protein interaction networks

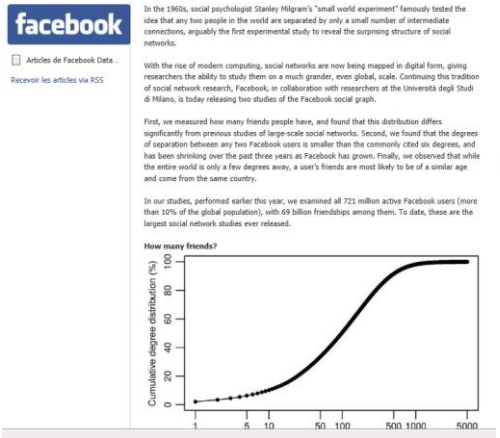
are scale-free networks

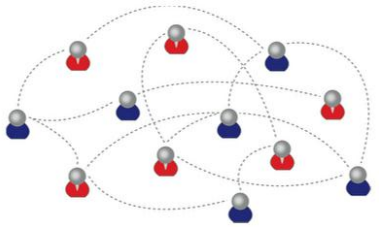


The web of human sexual contacts (Liljeros et al., Nature, 411 (2001) 907.

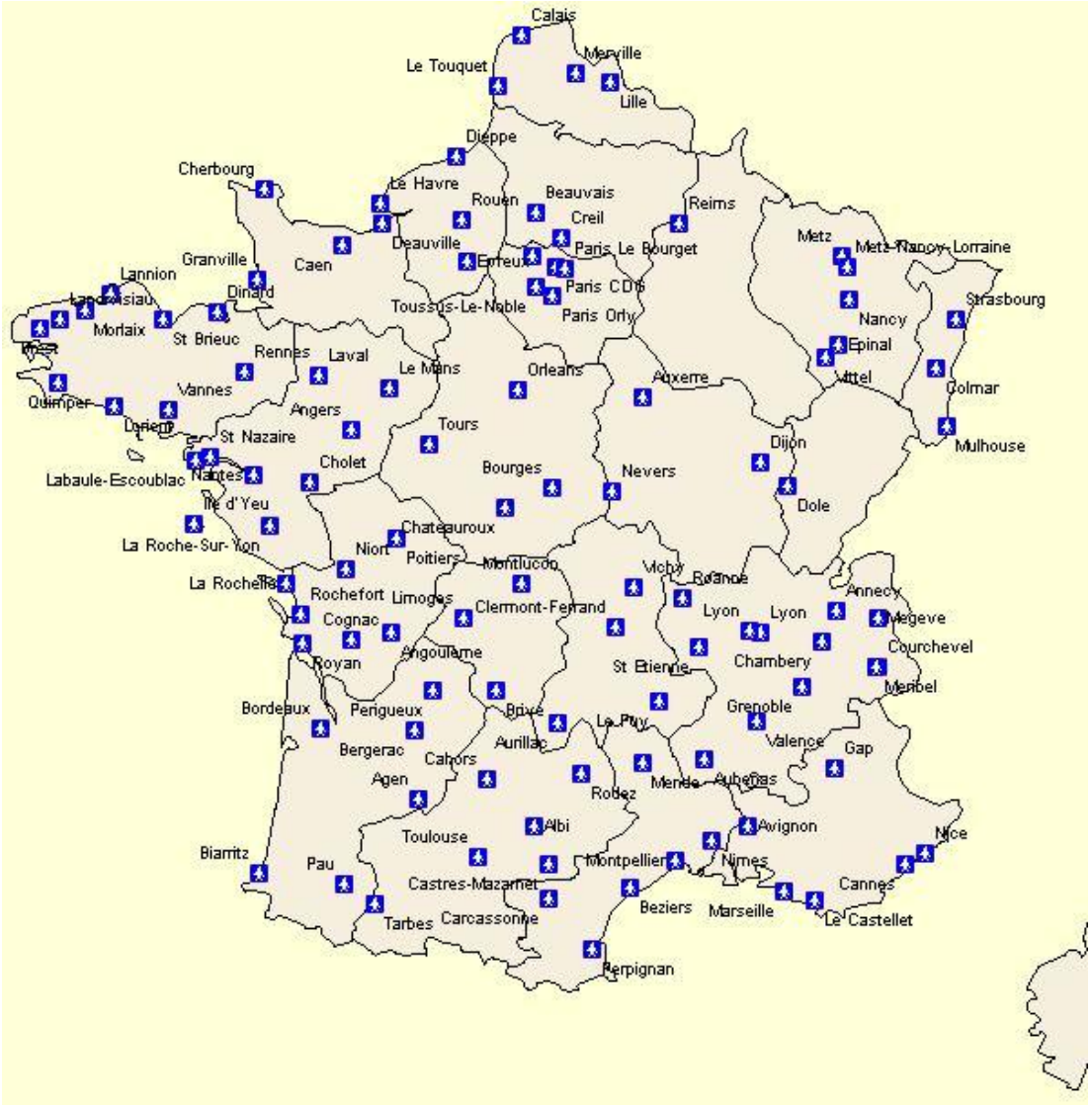


The food network

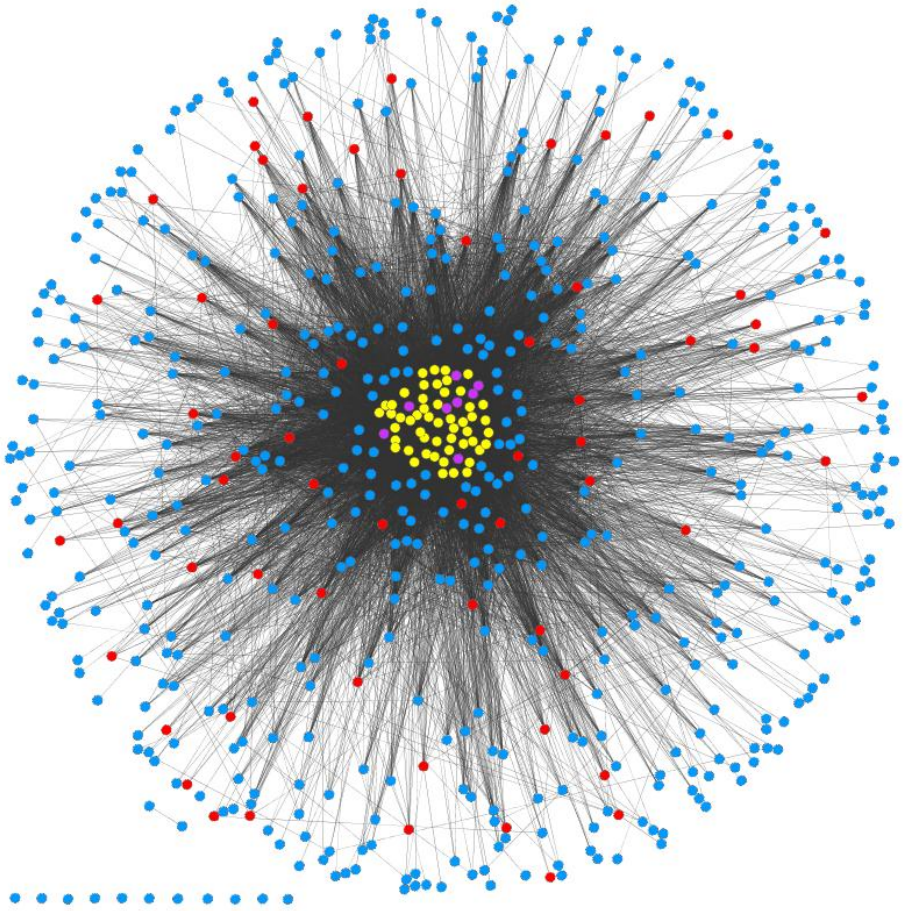




475 airports in France



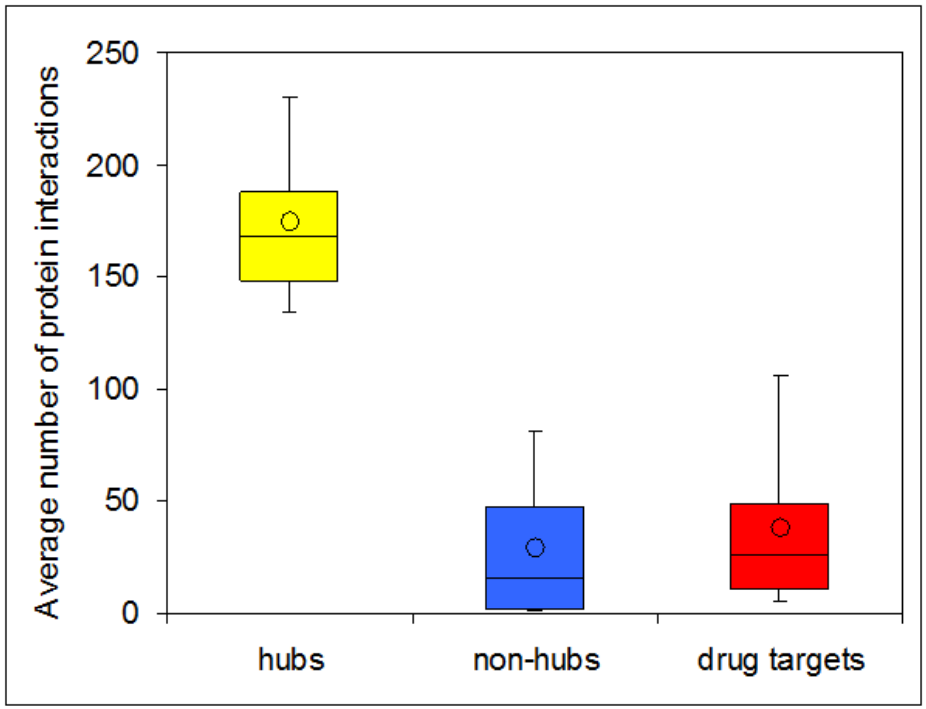
MRSA Proteins Interactions Network, 13k interactions, >600 proteins

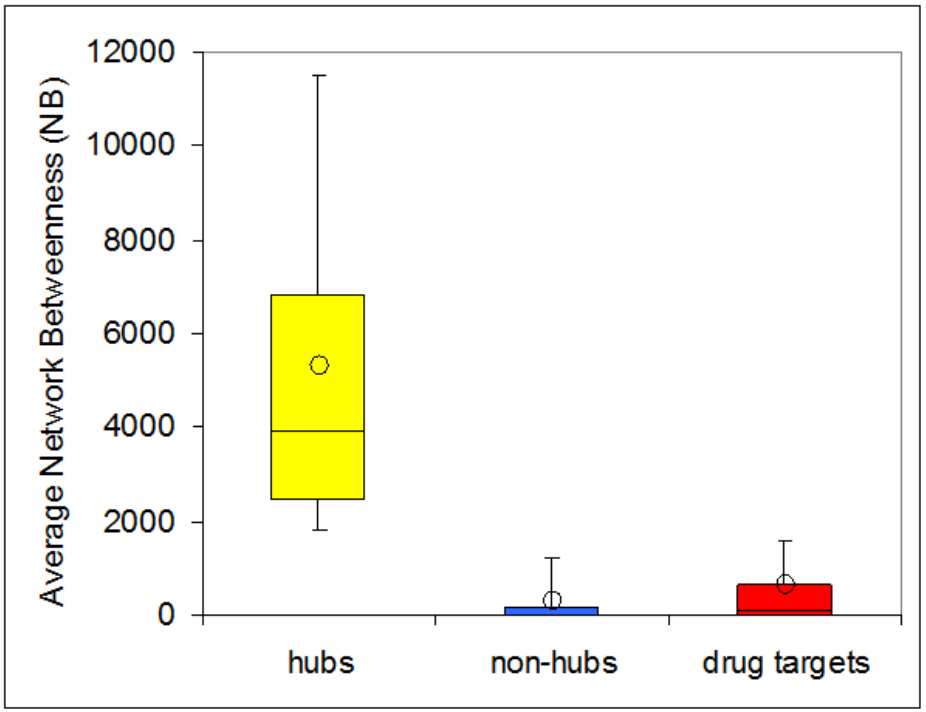


2D representation of the MS-MS derived MRSA PIN. Hub proteins are marked in yellow and non-hubs are in blue. The conventional antimicrobial targets are marked in red if they are also non-hubs. The conventional antimicrobial targets are marked in pink if they are also hubs.

A. Cherkasov et al, *Prot Research* 2011

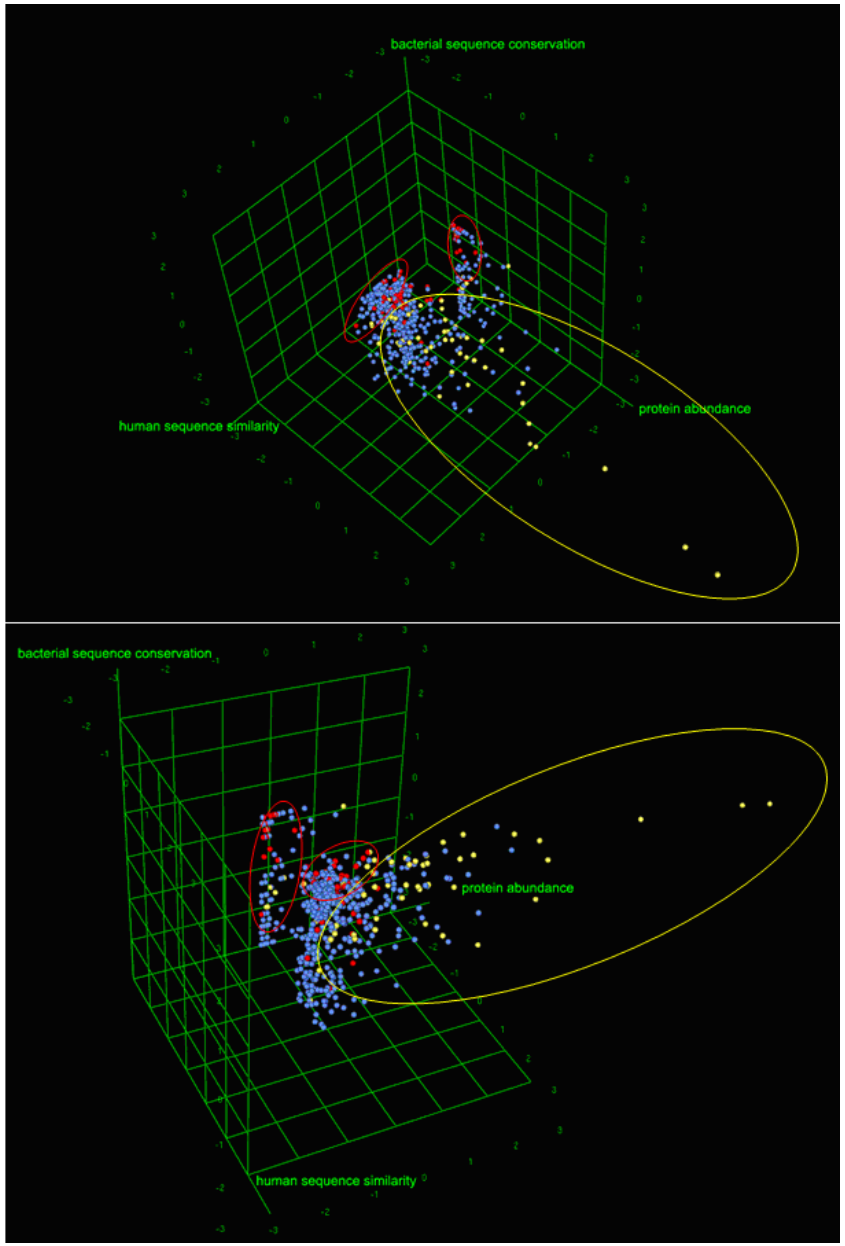
Results: MRSA PIN analysis





Average number of protein interactions among drug targets, hubs and non-hubs (left panel). Network Betweenness (NB) values for drug targets, hubs and non-hubs (right panel).

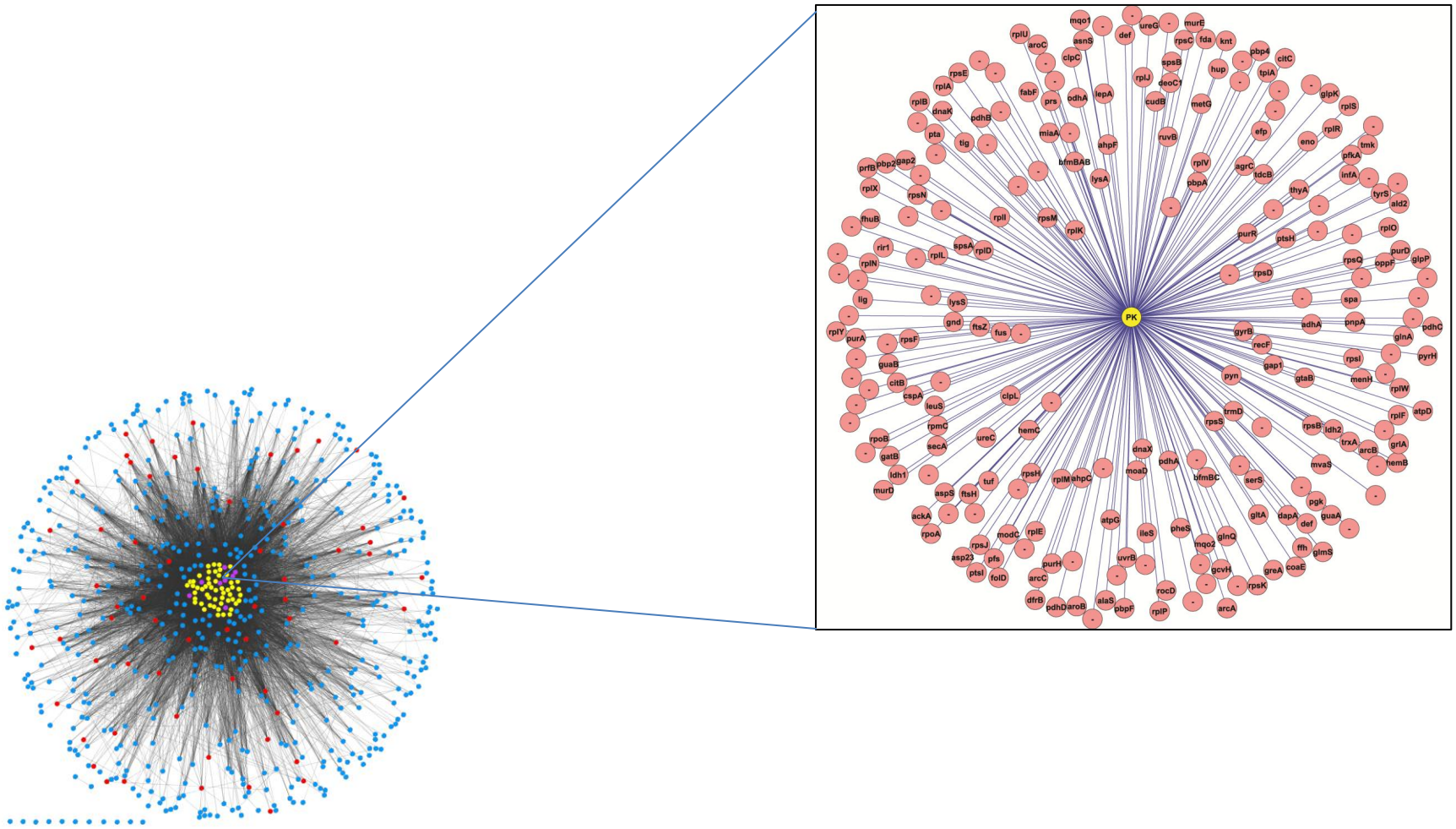
Results: MRSA PIN analysis



Separation of hubs non-hubs and antimicrobial targets in the three-dimensional space of protein **abundance, protein conservation and similarity** to human proteins.
A) Top view of the space, B) side view. The areas of the 3D space where targets are grouped marked with red ovals and the MRSA hubs are highlighted within the yellow ovals.

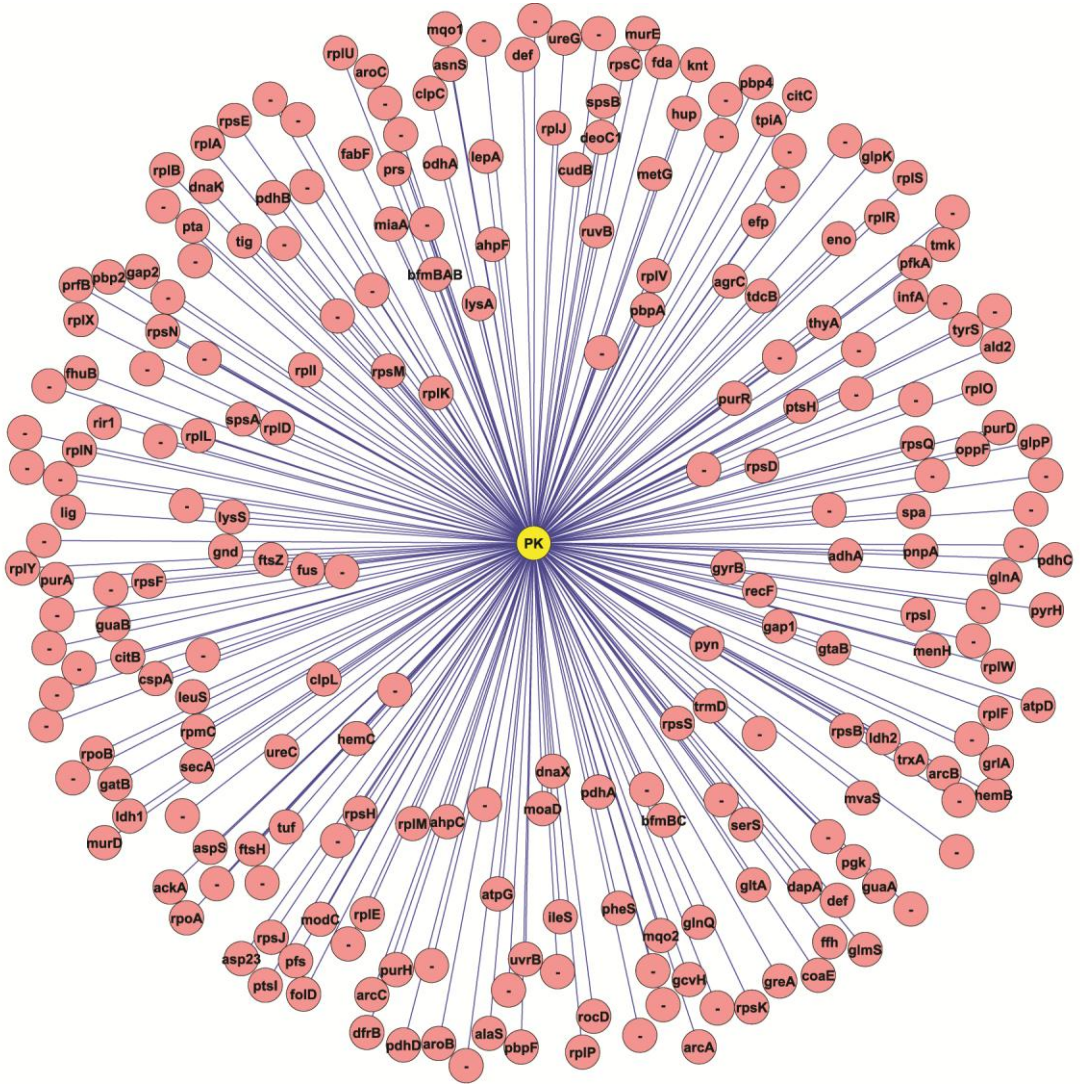
3. Example: MRSA Pyruvate Kinase

MRSA Proteins Interactions Network



2D representation of Pyurvate Kinase in the context of its protein-protein interactions.

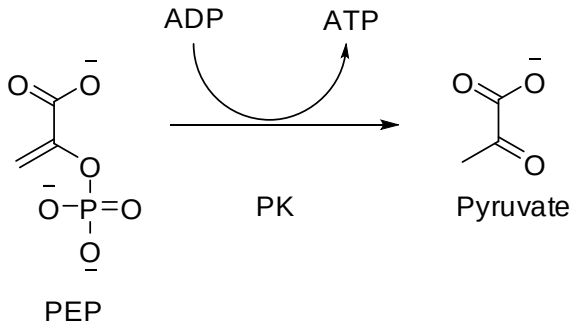
MRSA Proteins Interactions Network



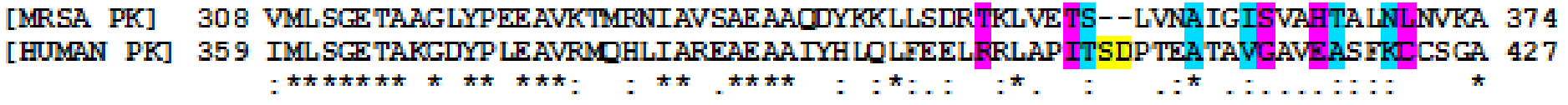
2D representation of Pyurvate Kinase in the context of its protein-protein interactions.

Pyruvate Kinase

- Pyruvate kinase (PK) was identified as a highly connected hub protein in MRSA.
  - Essential for S. aureus viability.
  - Pyruvate is used in a number of biosynthetic pathways, placing PK at a pivotal metabolic intersection.



MRSA PK might be a good HUB target, BUT - highly similar to human PKs

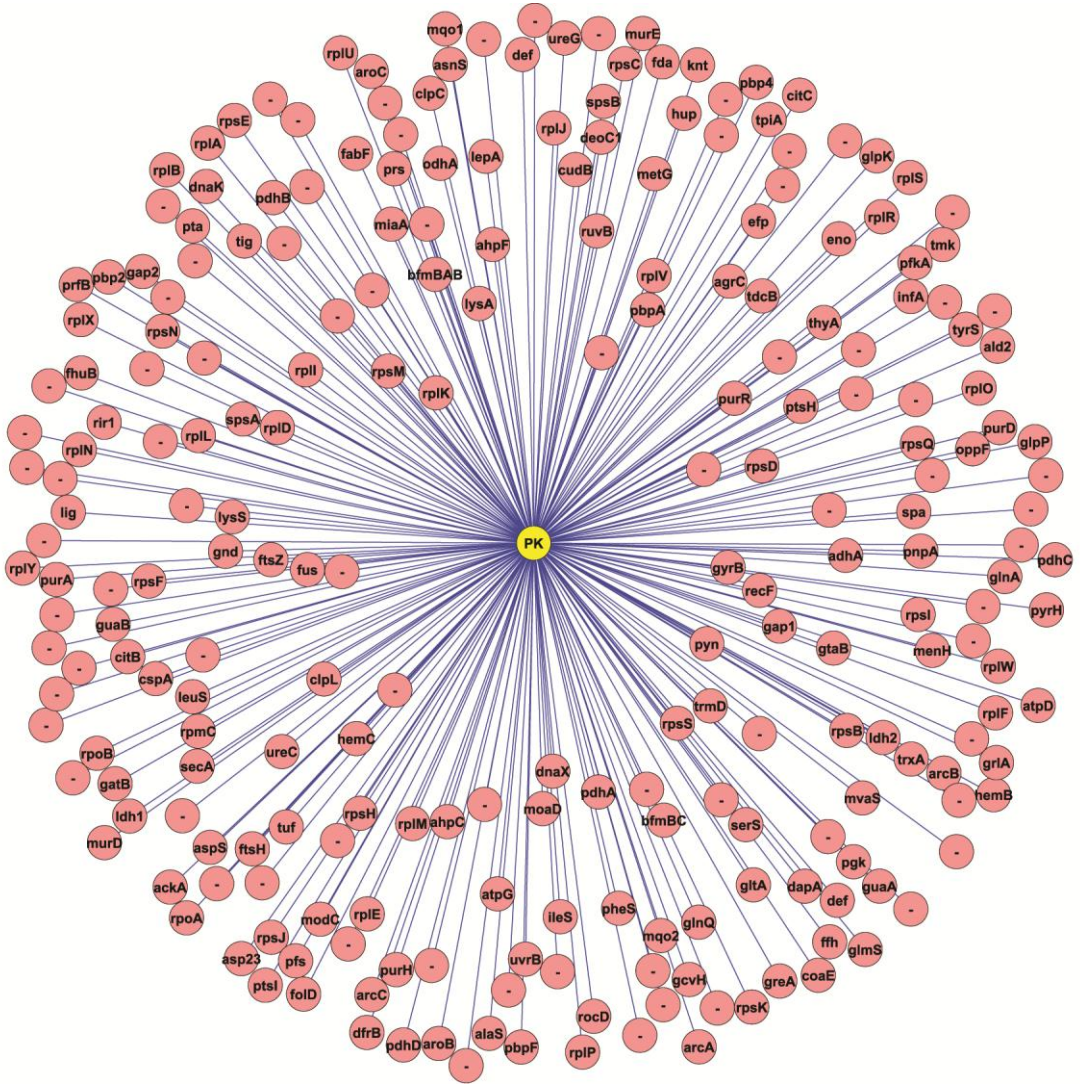


MRSA Pyruvate Kinase (PK) might be a good HUB target,
BUT
- highly similar to human PKs

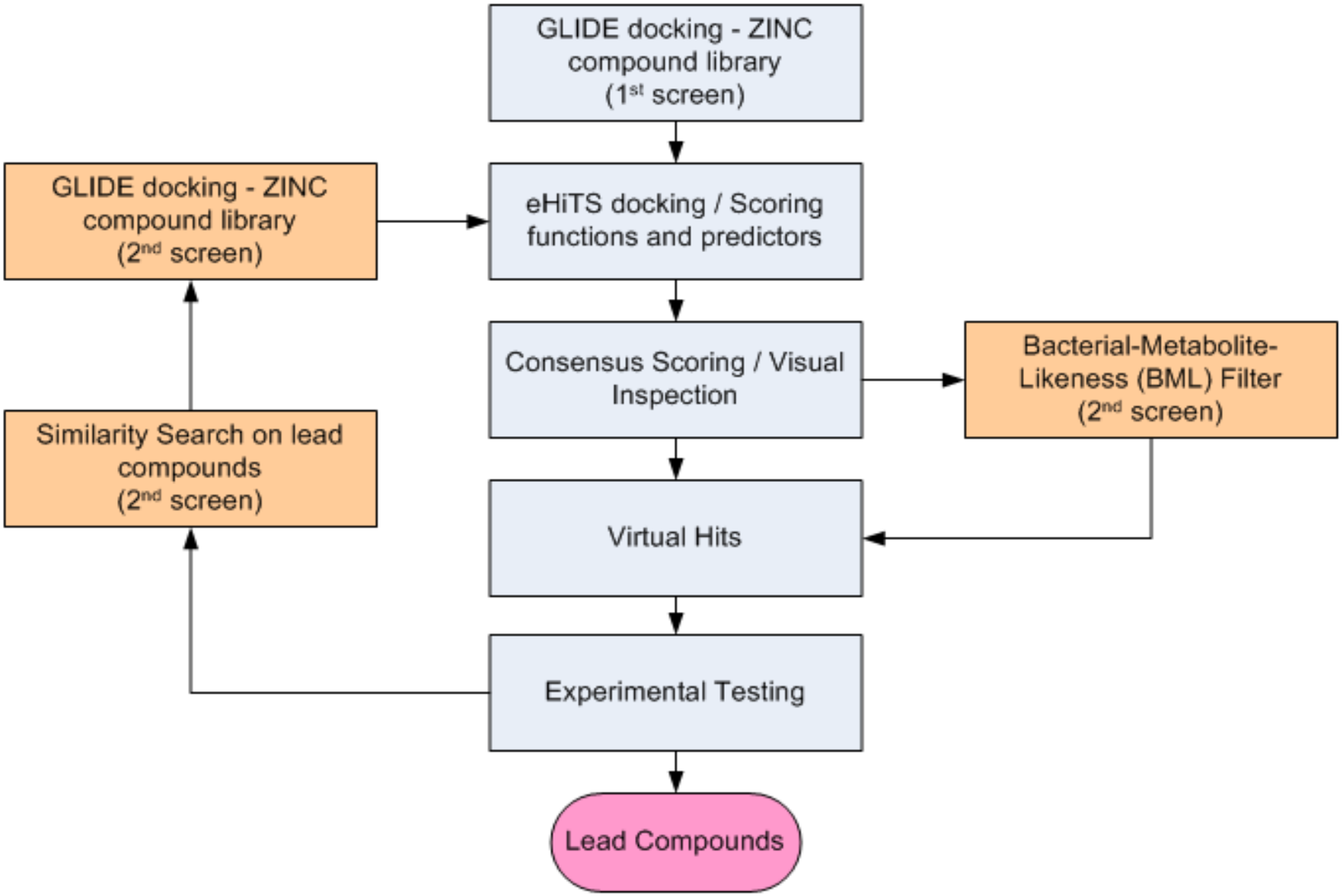
```
[MRSA PK]   308 VMLSGETAAGLYPEEAVKTMRNIAVSAEAAQDYKKLLSDRIKLVETS--LVNAIGISVAHTALNLNVKA 374
[HUMAN PK]  359 IMLSGETAKGDYPLEAVRMQHLIAREAEAAIYHLQLFEELRRLAPITSDPTEATAVGAVEASFKCCSGA 427
                :******* * ** ***:   : ** .****   : :*:.:   :*.  :    .:* .:.....::     *
```

IN(sertions) DEL(etions) = INDELs

MRSA Proteins Interactions Network



2D representation of **Pyruvate Kinase** in the context of its protein-protein interactions.


GLIDE docking - ZINC compound library (1st screen)
GLIDE docking - ZINC compound library (2nd screen)
eHiTS docking / Scoring functions and predictors
Consensus Scoring / Visual Inspection
Bacterial-Metabolite-Likeness (BML) Filter (2nd screen)
Similarity Search on lead compounds (2nd screen)
Virtual Hits
Experimental Testing
Lead Compounds

```
[MRSA PK]   308 VMLSGETAAGLYPEEAVKTMRNIAVSAEAAQDYKKLLSDRTKLVETS--LVNAIGISVAHTALNLNVKA 374
[HUMAN PK]  359 IMLSGETAKGDYPLEAVRMQHLIAREAEAAIYHLQLFEELRRLAPITSDPTEATAVGAVEASFKCCSGA 427
                :******* * ** ***:   : ** .****  : :*:.:  :*.  :   .:* .:.....:::     *
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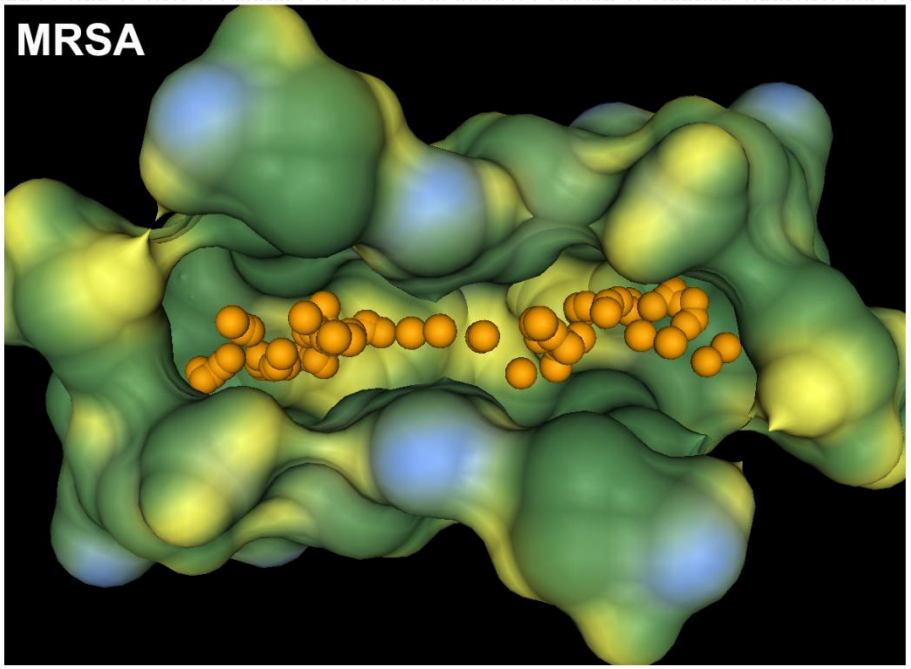
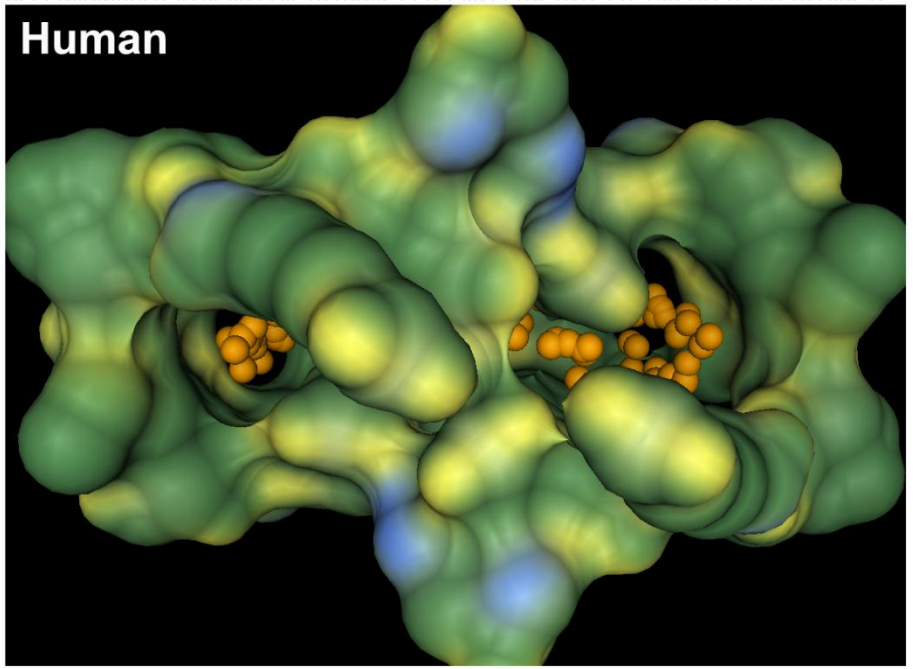




Structural model of the interface-binding site for MRSA and human PK. Orange spheres show the interface cavity in MRSA and human.

The MRSA PK model shows an assessable binding pocket located at the interface of two PK monomers. Whereas, the pocket in human PK is partially closed by five amino acid residues (Glu418-B, Arg399-A, B and Arg400-A, B).

Can 'Bacterial-Metabolite-Likeness' Model Improve Odds of 'in Silico' Antibiotic Discovery?

Artem Cherkasov*

Division of Infectious Diseases, Faculty of Medicine, University of British Columbia, 2733 Heather Street, Vancouver, British Columbia V5Z 3J5, Canada

Received November 1, 2005

'Inductive' QSAR descriptors have been used to develop the series of QSAR models enabling 'in silico' distinguishing between antimicrobial compounds, conventional drugs, and druglike substances. The constructed neural network-based models operating by 30 'inductive' parameters have been validated on an extensive set of 2686 chemical structures and resulted in up to 97% accurate separation of the three types of molecular activities. The demonstrated ability of 'inductive' parameters to adequately capture molecular features determining 'antibiotic-like' and 'druglike' potentials have been further utilized to construct a model of 'Bacterial-Metabolite-Likeness' (BML). The same 'inductive' descriptors have been used to train a neural network that could very accurately recognize substances involved into bacterial metabolism (that have been experimentally identified). When the developed model has been applied to the mixed set of antimicrobials, drugs, and druglike chemicals (not used for training the BML model), it exhibited a 2−5-fold recognition preference toward antimicrobial compounds compared to general drugs and an 18- to 45-fold preference when compared to a druglike substance (depending on the model stringency). These results illustrate immanent similarity between conventional antimicrobials and native bacterial metabolites and suggest that the developed BML model can be an effective classification tool for 'in silico' antibiotic studies.

INTRODUCTION

In the series of our previous works we reported the development of 3D-sensitive QSAR descriptors called 'inductive' and demonstrated their successful application in a number of molecular modeling studies including quantification of antibacterial activity of organic compounds[1] and cationic peptides,[1,2] computation of partial charges in small molecules[3] and proteins,[4] and in comparative docking analysis[4,5] as well as in 'in silico' lead discovery.[4,5] The detailed description of 'inductive' QSAR descriptors and their rationale can be found in the recent review.[1]

In summary, all 'inductive' QSAR parameters are related to atomic electronegativity (χ), covalent radii (R), and

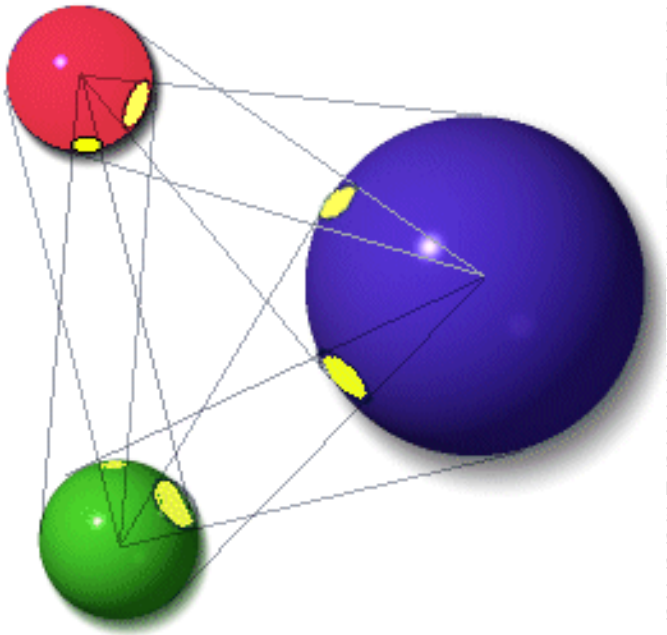
$$\sigma^*_{j\to N-1} = \beta \sum_{i\neq j}^{N-1} \frac{(\chi_j^0 - \chi_i^0)R_j^2}{r_{j-i}^2}$$

$$\sigma^*_{G\to j} = \beta \sum_{i\subset G, i\neq j}^{n} \frac{(\chi_i^0 - \chi_j^0)R_i^2}{r_{i-j}^2} \quad (2)$$

$$\chi_{N-1\to j}^0 = \frac{\sum_{i\neq j}^{N-1} \frac{\chi_i^0(R_i^2 + R_j^2)}{r_{i-j}^2}}{\sum_{i\neq j}^{N-1} \frac{R_i^2 + R_j^2}{r_{i-j}^2}} \quad \chi_{N-1\to j}^0 = \frac{\sum_{i\neq j}^{N-1} \frac{\chi_i^0(R_i^2 + R_j^2)}{r_{i-j}^2}}{\sum_{i\neq j}^{N-1} \frac{R_i^2 + R_j^2}{r_{i-j}^2}} \quad (3)$$

Descriptors: "Inductive" *etc*

$$\Delta N_j = Q_j + \gamma \sum_{i \neq j}^{N-1} \frac{(\chi_j - \chi_i)(R_j^2 + R_i^2)}{r_{j-i}^2}$$



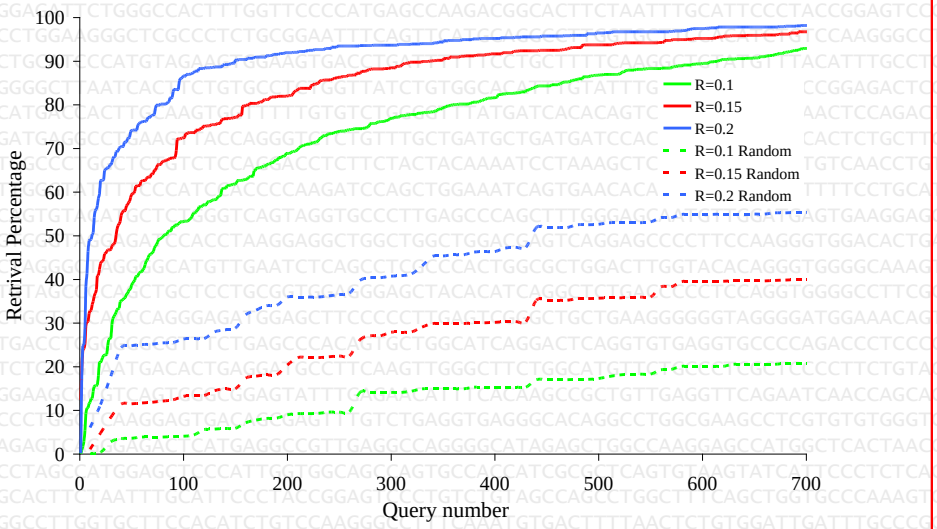
$$s_{MOL} = \sum_{j \neq i}^{N} \sum_{j \neq i}^{N} \frac{R_j^2 + R_i^2}{r_{j-i}^2}$$

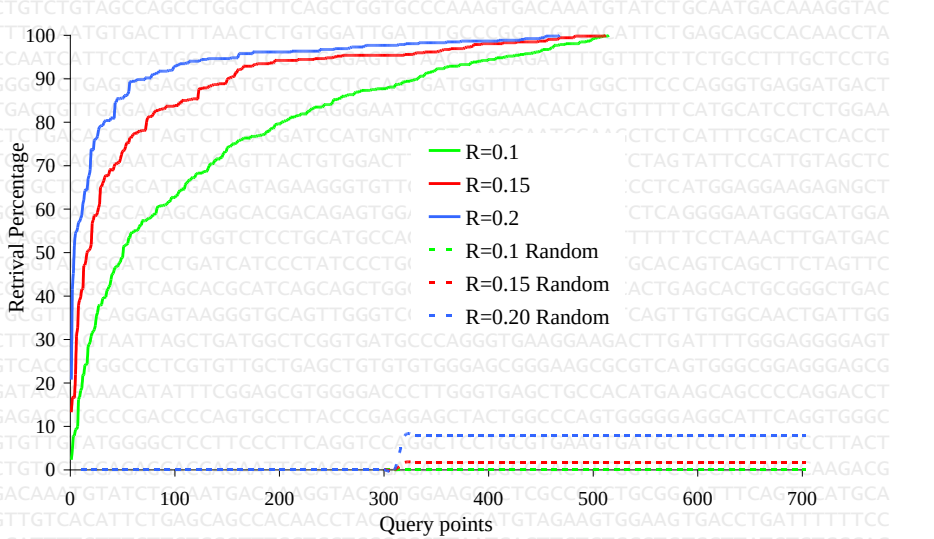
$$\eta_{MOL} = \frac{1}{s_{MOL}} = \frac{1}{2\sum_{j \neq i}^{N-1} \frac{R_j^2 + R_i^2}{r_{j-i}^2}}$$

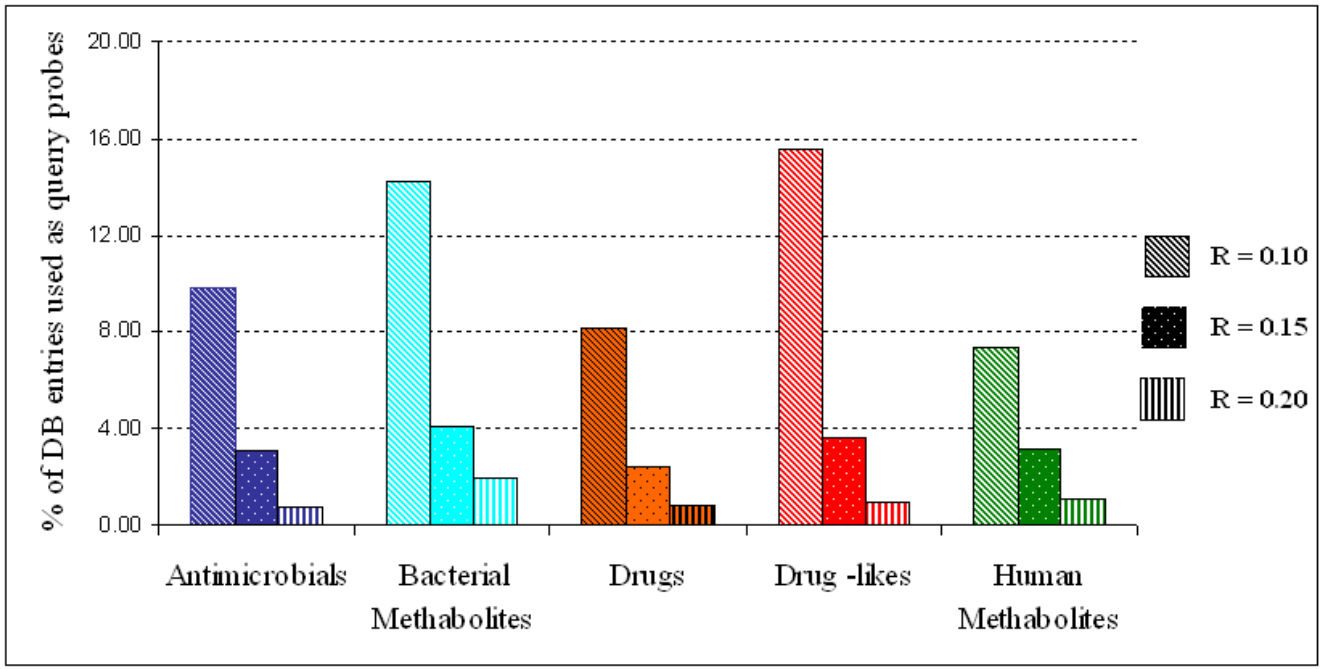
A number of QSAR models have been elaborated to separate individual clusters within the dataset of 958 human therapeutics, 519 antimicrobials, 1202 drug-like chemicals, as well as 1102 human-, 551 bacterial-, 2351 plant- and 825 fungal metabolites.

	Antimicrobials from Drugs		*Antimicrobials from Drug-likes*		*Distinguishing Antimicrobials from all others*		*Distinguishing Antimicrobials versus Drugs versus Drug-likes*		*QSAR model for Bacterial Metabolites*	
	Train	***Test***	***Train***	***Test***	***Train***	***Test***	***Train***	***Test***	***Train***	***Test***
T_P	327	130	332	140	294	124	270	89	360	139
T_N	631	248	841	342	1490	621	1486	644	792	347
F_P	49	33	7	14	32	20	17	14	39	26
F_N	33	35	30	23	66	41	108	58	48	19
SPEC	0.93	0.88	0.99	0.96	0.98	0.97	0.99	0.98	0.95	0.93
SENS	0.91	0.79	0.92	0.86	0.82	0.75	0.71	0.61	0.88	0.88
ACCUR	**0.92**	**0.85**	**0.97**	**0.93**	**0.95**	**0.92**	**0.93**	**0.91**	**0.93**	**0.92**
PPV	0.87	0.80	0.98	0.91	0.90	0.86	0.94	0.86	0.90	0.84
NPV	0.95	0.88	0.97	0.94	0.96	0.94	0.93	0.92	0.94	0.95

Method	Validation	True Posit.	TrueNegat	FalsePosit.	FalseNegat	Spec.	Sens.	Accur	PPV	NPV
Antibacterials *versus* (Drugs + Drug-likes + Bacteria Metabolites + Human Metabolites)										
***k*NN**	*Training 70%*	269	2610	9	95	0.97	0.74	**0.95**	0.80	0.96
	Testing 30%	117	1119	8	39	0.98	0.75	**0.95**	0.81	0.97
	LOO	400	3727	9	120	0.97	0.77	**0.95**	0.80	0.97
LDA	*Training 70%*	364	0	2679	0	0.00	1.00	**0.12**	0.12	0.00
	Testing 30%	156	0	1147	0	0.00	1.00	**0.12**	0.12	0.00
	LOO	261	3751	75	259	0.98	0.50	**0.92**	0.78	0.94
MLR	*Training 70%*	194	564	2115	170	0.21	0.53	**0.25**	0.08	0.77
	Testing 30%	61	1129	18	95	0.98	0.39	**0.91**	0.77	0.92
	LOO	279	3726	100	241	0.97	0.54	**0.92**	0.74	0.94
ANN	*Training 70%*	294	2651	27	70	0.99	0.81	**0.97**	0.92	0.97
	Testing 30%	129	1132	16	27	0.99	0.83	**0.97**	0.89	0.98
	LOO	449	3821	5	71	0.99	0.86	**0.98**	0.99	0.98
Bacteria Metabolites *versus* (Drugs + Drug-likes + Antibacterials + Human Metabolites)										
***k*NN**	*Training 70%*	311	2537	112	83	0.96	0.79	**0.94**	074	0.97
	Testing 30%	135	1091	44	33	0.96	0.80	**0.94**	0.75	0.97
	LOO	455	3637	147	107	0.96	0.81	**0.94**	0.76	0.97
LDA	*Training 70%*	240	2587	62	154	0.98	0.61	**0.93**	0.79	0.94
	Testing 30%	90	1088	47	78	0.96	0.54	**0.90**	0.66	0.93
	LOO	336	3665	119	226	0.97	0.60	**0.92**	0.74	0.94
MLR	*Training 70%*	301	2525	124	93	0.95	0.76	**0.93**	0.71	0.96
	Testing 30%	119	1073	62	49	0.95	0.71	**0.91**	0.66	0.96
	LOO	406	3603	181	156	0.95	0.72	**0.92**	0.69	0.96
ANN	*Training 70%*	338	2597	52	55	0.98	0.86	**0.96**	0.87	0.98
	Testing 30%	159	1076	59	10	0.95	0.94	**0.95**	0.73	0.99
	LOO	534	3780	4	28	0.99	0.95	**0.99**	0.99	0.9

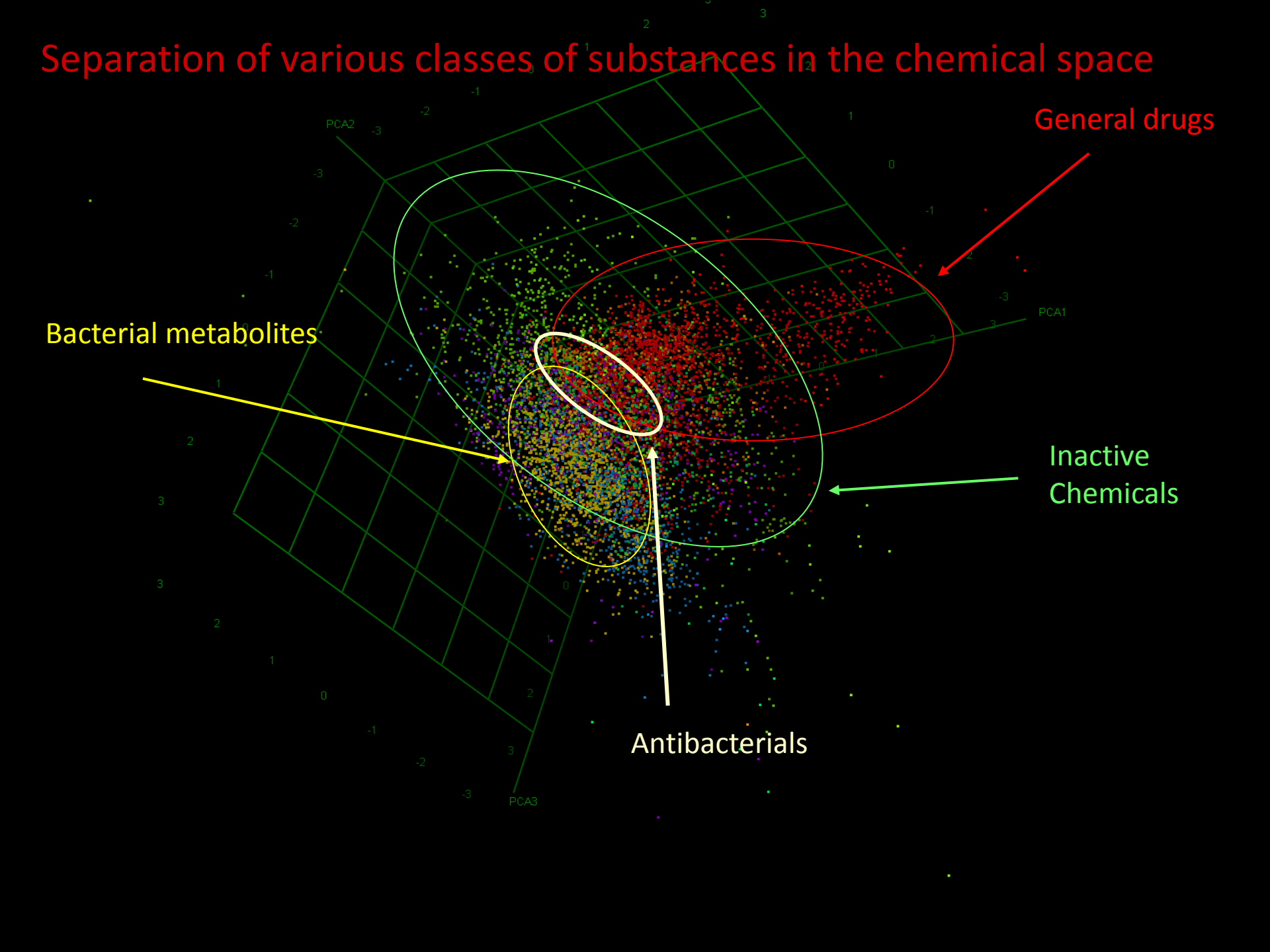


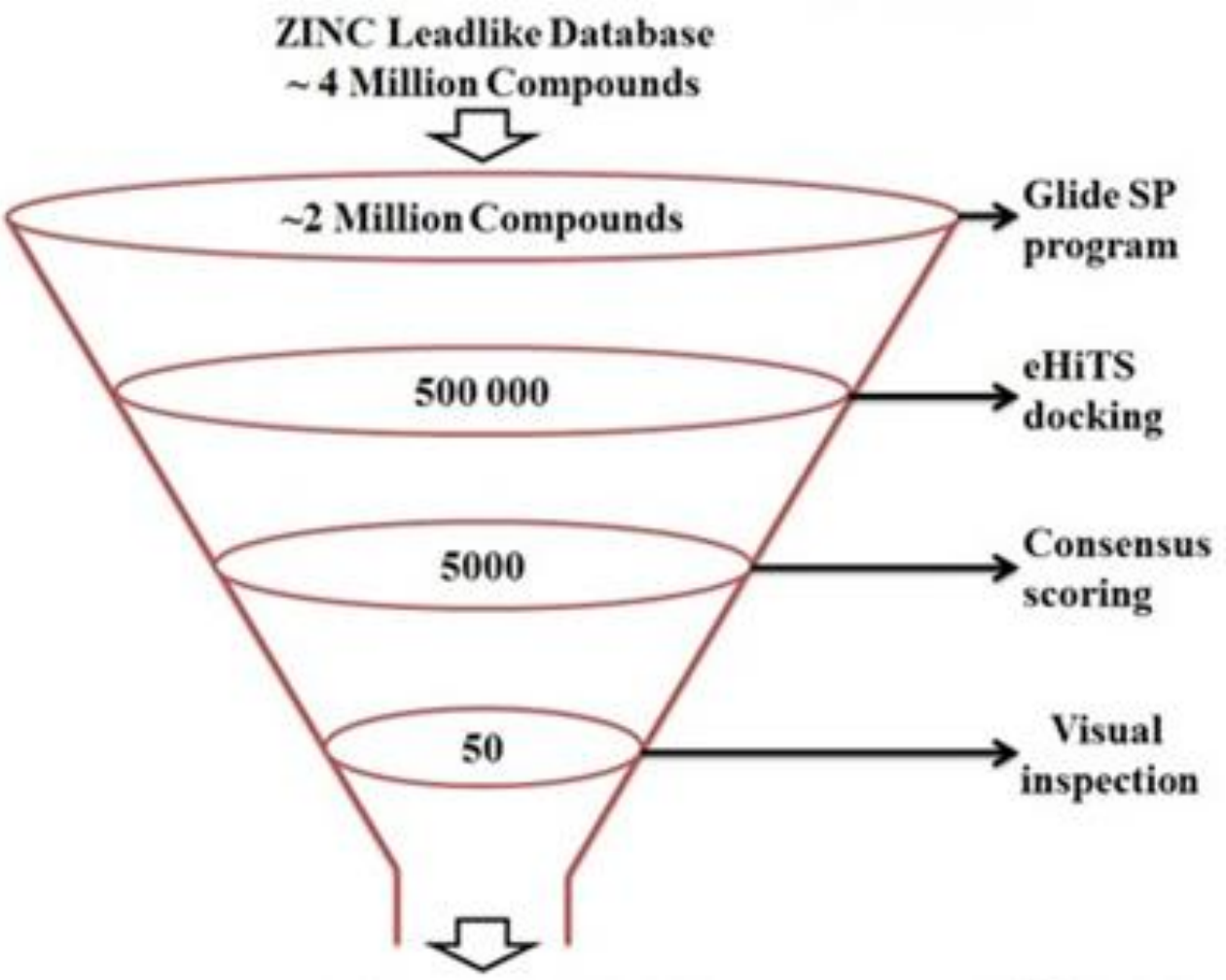




THE UNIVERSITY OF BRITISH COLUMBIA
MEDICINE INFECTIOUS DISEASES

Separation of various classes of substances in the chemical space

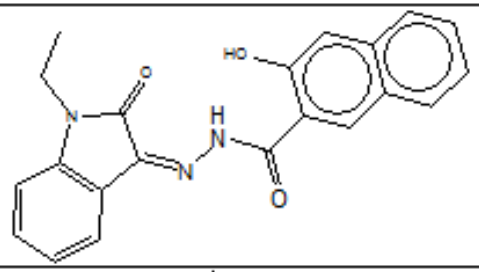
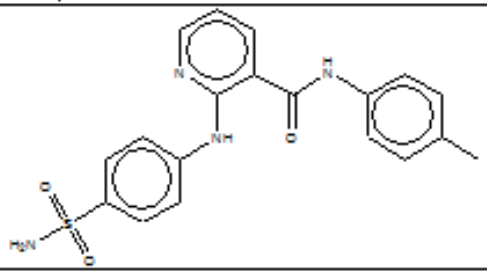
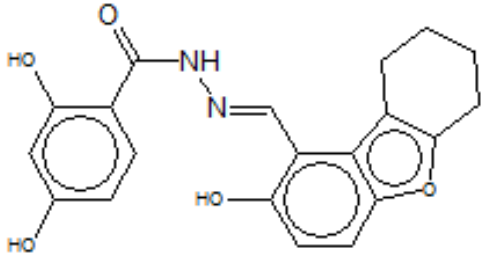
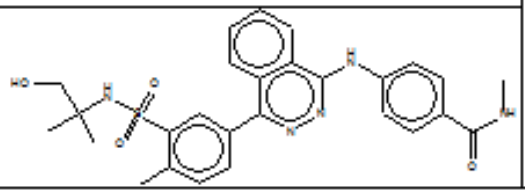


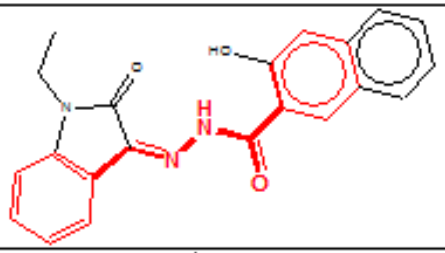
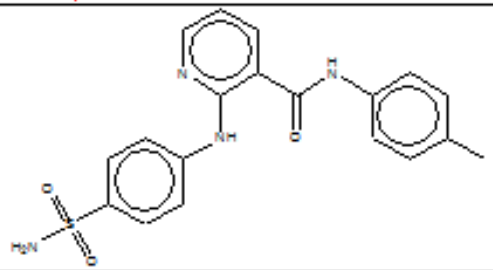
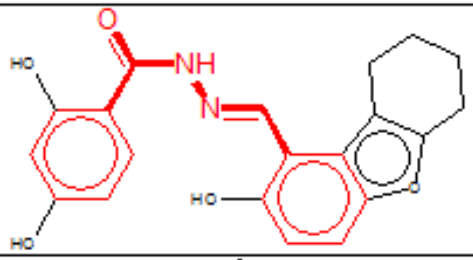
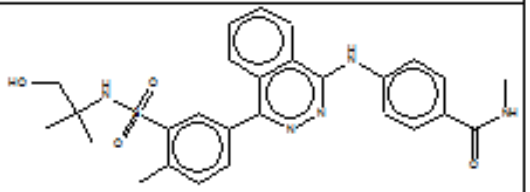

ZINC Leadlike Database
~ 4 Million Compounds
~2 Million Compounds
Glide SP program
500 000
eHiTS docking
5000
Consensus scoring
50
Visual inspection

structure—based pipeline

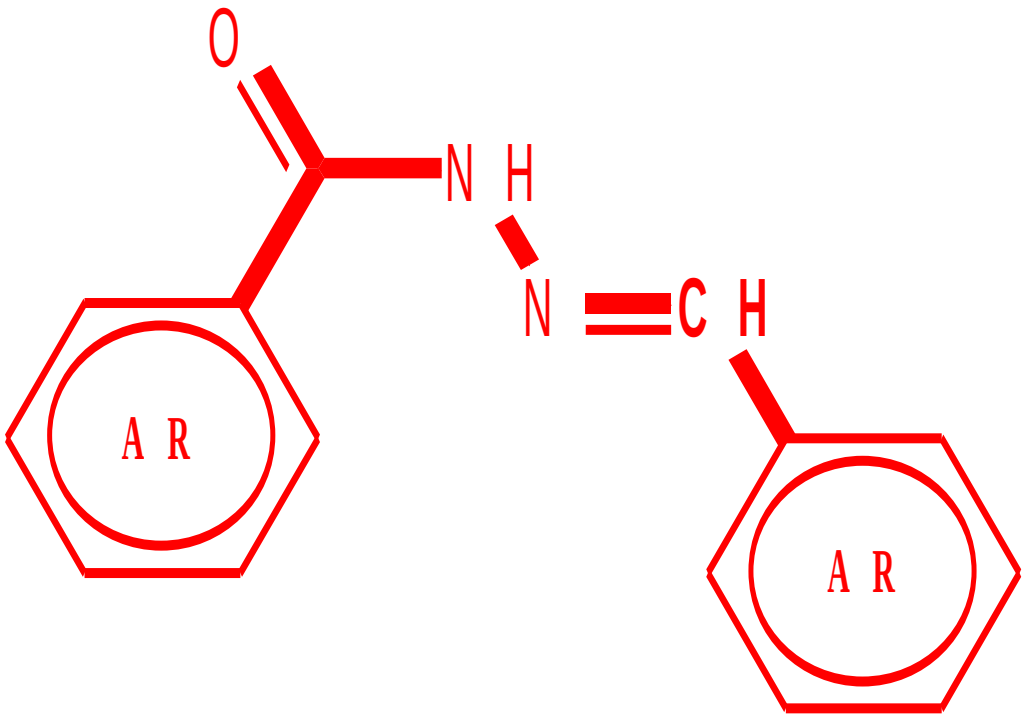
~80 cmps

4 hits

ID	structure	IC50 MRSA PK, μM	MIC MRSA μM	I	II	III	IV	V
IS-63		0.911	>500	83.9	15	1.3	13.5	22.2
IS-168				79.5	17.6	12.6	30.6	24.7
IS-53				77.8	39.3	57.5	78.1	87.8
IS-165				54.6	25.8	8.3	15.3	9.4

ID	structure	IC 50 MRSA PK, µM	MIC MRSA µM	I	II	III	IV	V
IS-63		0.911	>500	83.9	15	1.3	13.5	22.2
IS-168				79.5	17.6	12.6	30.6	24.7
IS-53				77.8	39.3	57.5	78.1	87.8
IS-165				54.6	25.8	8.3	15.3	9.4

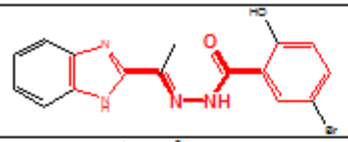
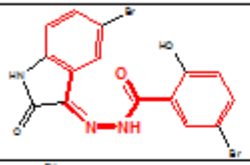
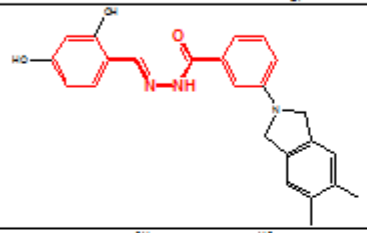
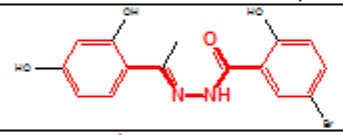
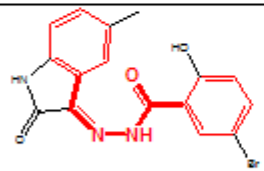
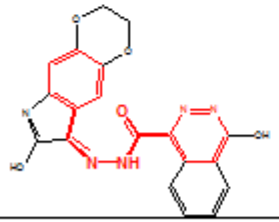
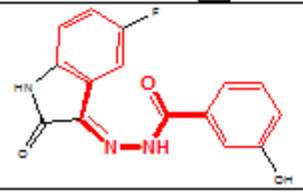
TOPOLOGICAL QUERRY



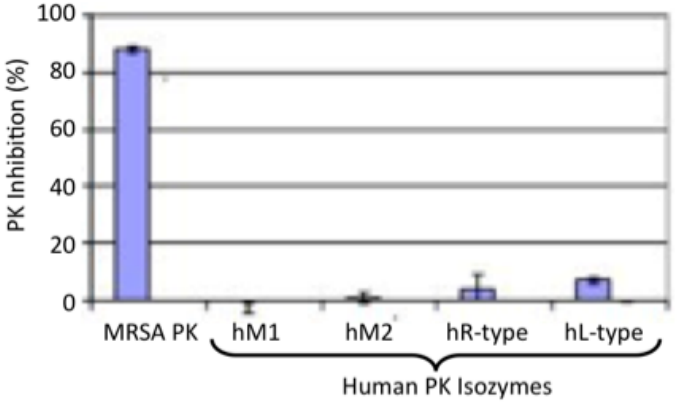
LIGAND-BASED SEARCH

~80 cmps

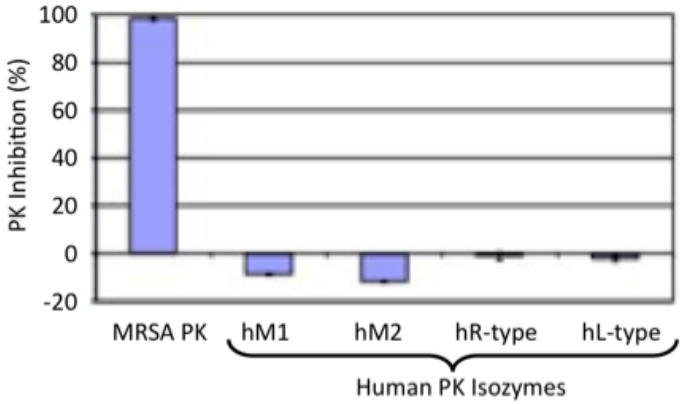
6 hits

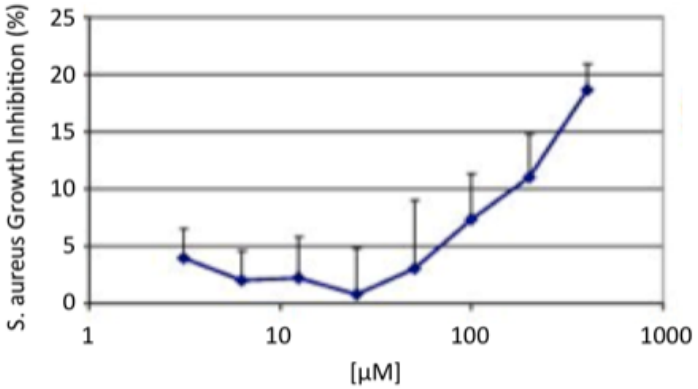
structure	IC50 MRSA PK, µM	MIC MRSA µM	I	II	III	IV	V	Tanimoto to IS-63
IS-130 	0.091	>500	98.5	-8.7	-11.9	-1.2	-2.1	0.63
			78.8	10.9	10.2	7.3	-4.7	0.72
			78.3	22.8	26.7	15.7	20.8	0.76
			71.1	-1.7	2.2	9.8	0.9	0.60
			66.4	13.0	11.8	7.1	-1.0	0.76
			60.6	3.6	25.3	5.6	12.3	0.64
			50.0	10.4	10.2	0.4	0.8	0.70

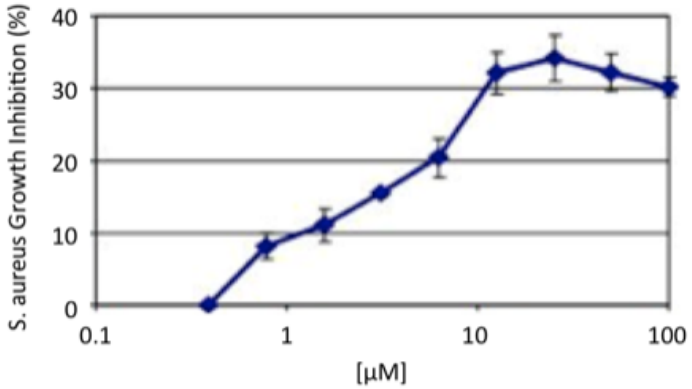
Compound NSK-460

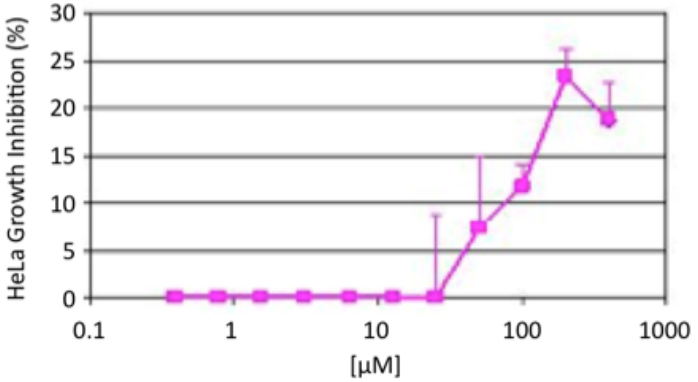


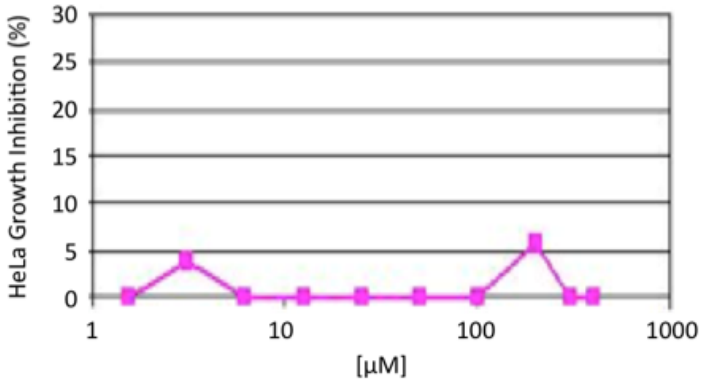
Compound NSK-465











```
[MRSA PK]   308 VMLSGETAAGLYPEEAVKTMRNIAVSAEAAQDYKKLLSDRTKLVETS--LVNAIGISVAHTALNLNVKA 374
[HUMAN PK]  359 IMLSGETAKGDYPLEAVRMQHLIAREAEAAIYHLQLFEELRRLAPITSDPTEATAVGAVEASFKCCSGA 427
                :******* * ** ***:   : ** .****   : :*:.:   :*.   :    .:*  .:.....::::     *
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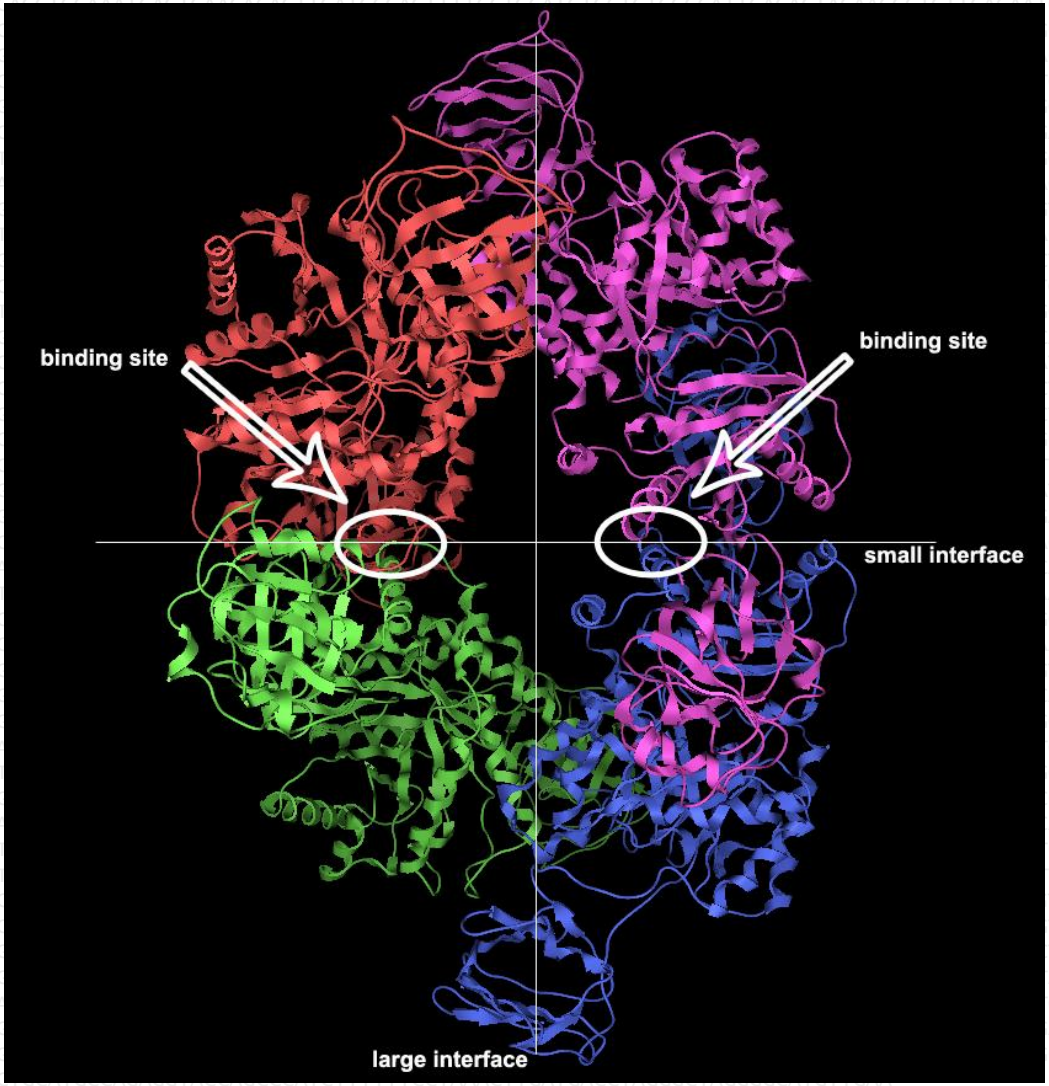
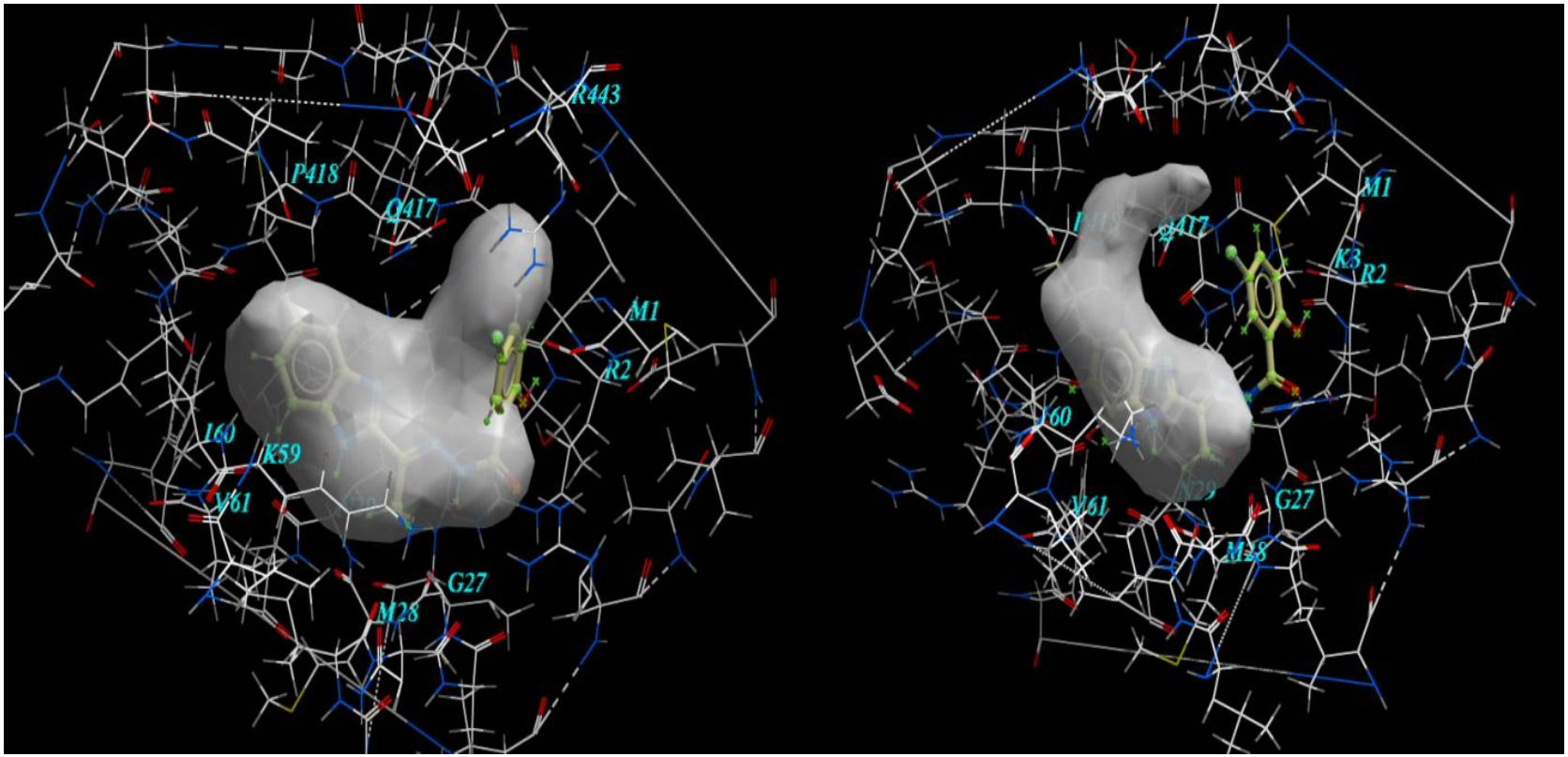
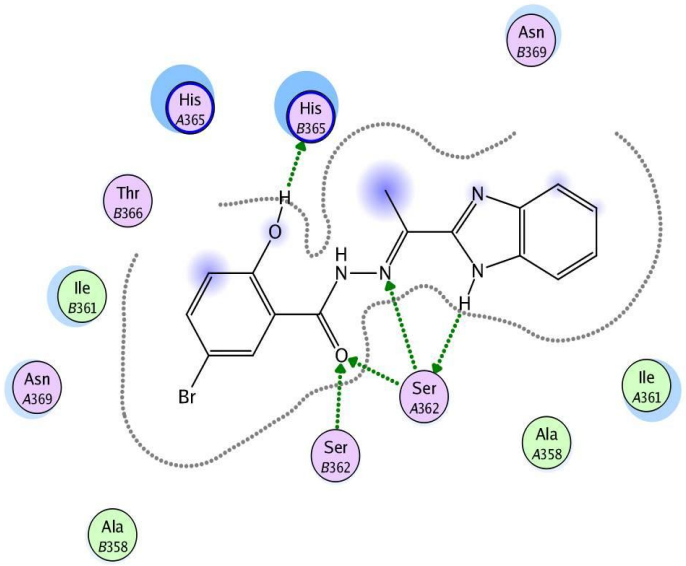
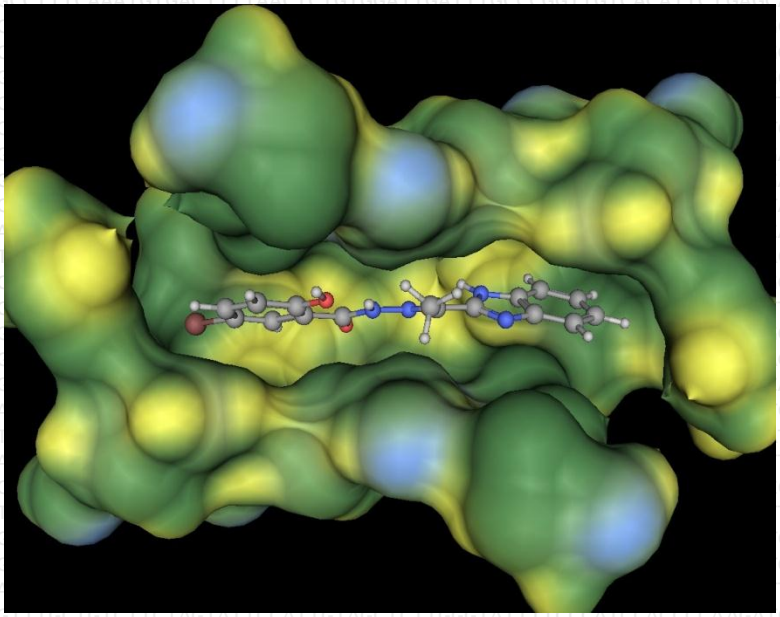




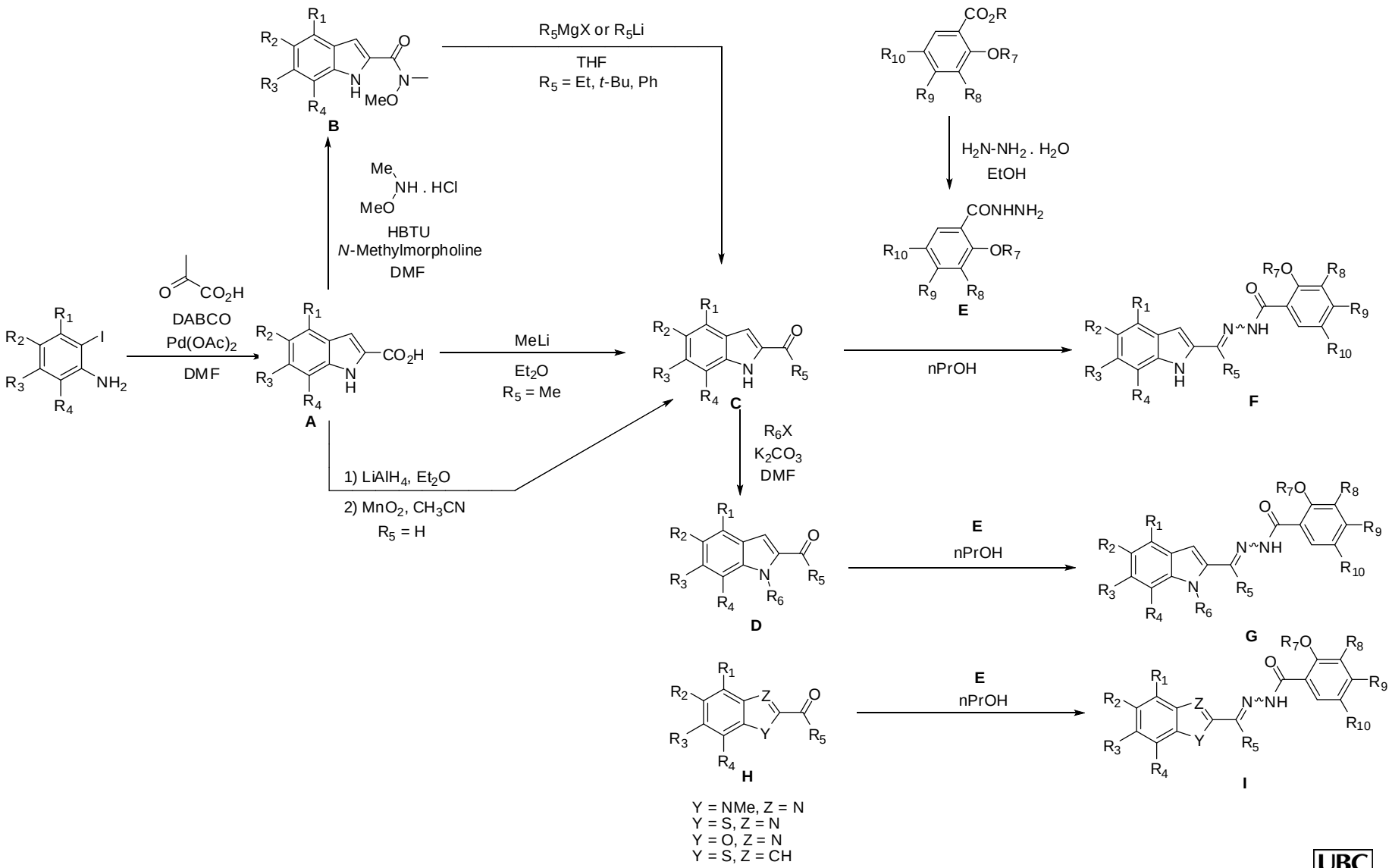
Structural model illustrating the differences in the spatial orientation of the 6 amino-acid binding site from the homology model (left) and the MRSA252 pyruvate kinase crystal structure (right).





Binding mode of IS-130 at the interface binding site a) A two-dimensional map of the binding interactions between IS-130 and the interface site based on its co-crystallization with MRSA PK. Green arrows depict hydrogen-accepting interactions between IS-130 and MRSA PK residues from the interface. b) Binding orientation of IS-130 within the interface-binding pocket based on the protein-ligand crystallized structure. The protein surface is rendered where green protein surface depicts the hydrophobic interface and yellow depicts the hydrophilic surface.

Synthesis of IS-130 Analogues



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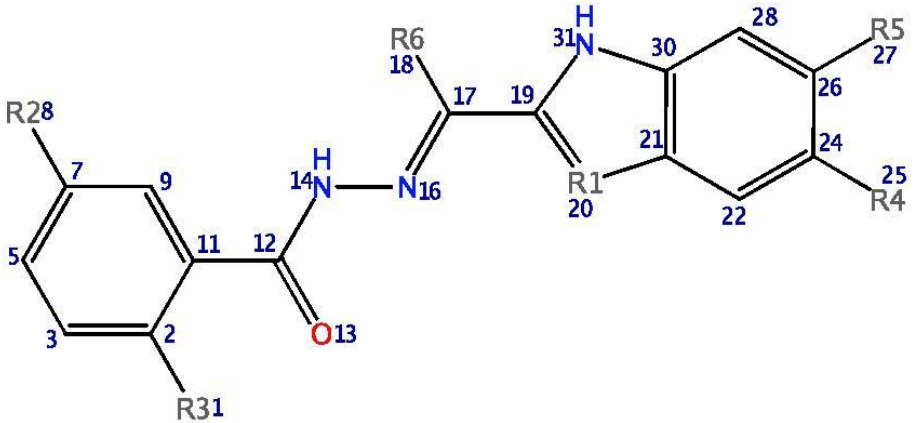
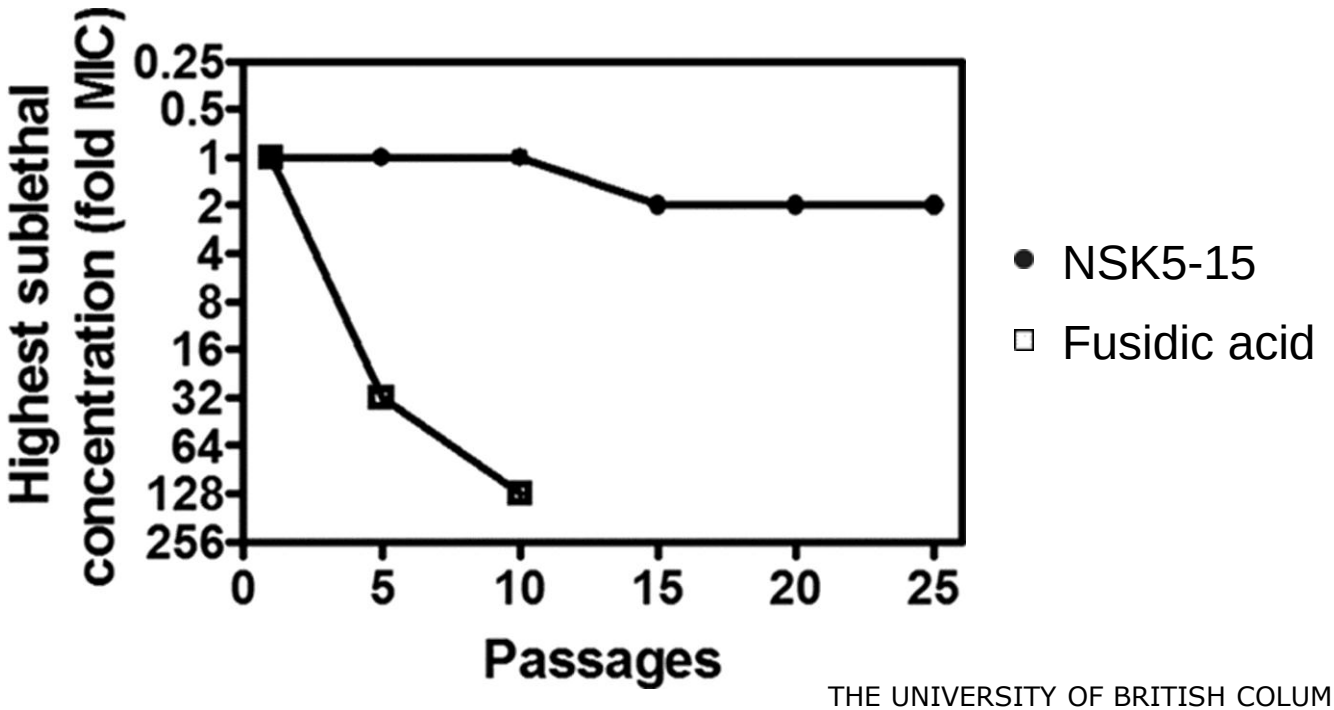


Analogues	IC_{50} (nM)	MIC (µM)	MIC (µg/mL)	R1	R2	R3	R4	R5	R6
IS-130	91	>500	>186.6	N	Br	OH	H	H	CH_3
NSK-466	84	>500	>186.11	C	Br	OH	H	H	CH_3
NSK-479	8150	-	-	C	Br	H	H	H	CH_3
NSK-482	8615	>200	>58.66	C	H	OH	H	H	CH_3
NSK-477	381	12	4.8	C	Br	OH	H	CH3	CH3
NSK-515	185	3.1	1.5	C	Br	OH	Br	CH3	CH3
AM-165	165	6.2	2.5	C	Br	OH	F	CH3	CH3
AM-160	45	>500	>195.1	C	Br	OH	F	H	CH_3
AM-213	16	>200	>81.6	C	Br	OH	F	F	CH_3
AM-168	114	25	9.66	C	Br	OH	H	H	C_2H_5

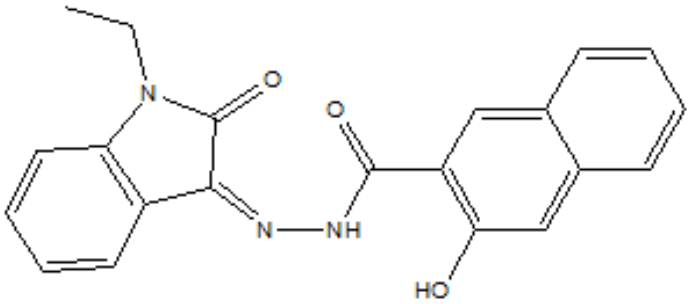
Resistance Studies

- To assess the potential for cells to become resistance to NSK5-15, we tried to generate resistant mutants by using S. *aureus* RN4220.
- Cells were passaged for up to 25 consecutive generations in the presence of sublethal concentration of NSK5-15 or for 10 generation with fusidic acid.

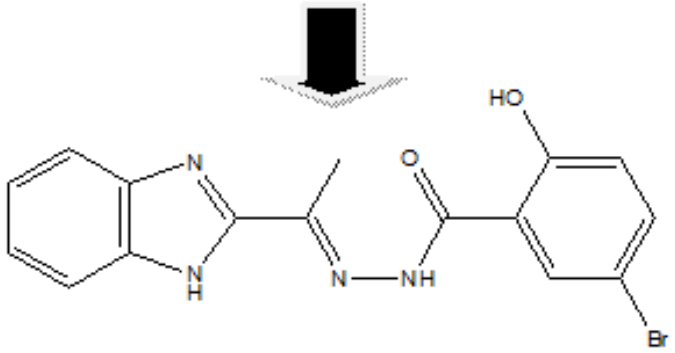


Antibacterial activities of three potent PK inhibitors against selected staphylococci, non-staphylococcal Gram-positive pathogens, and Gram-negative pathogens compared to standard antibiotics.

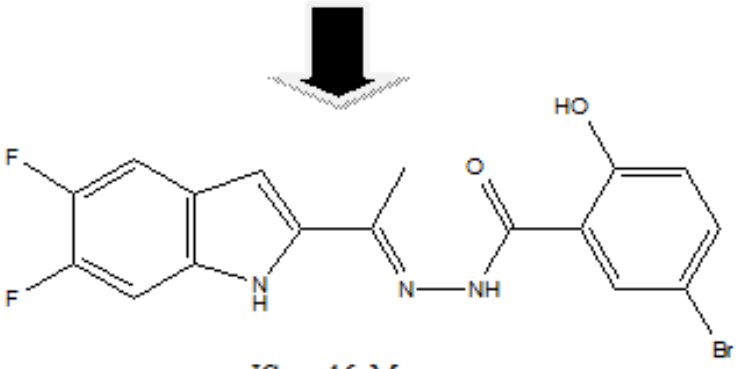
	MIC (μg/ml)			
Strain	NSK-477	NSK-515	AM-165	**Control**
Gram positive bacteria				
Staphylococcus aureus RN4220	4.8	1.4	2.5	[a]0.5, [b]1, [c]0.5
Staphylococcus aureus ATCC 25923	9.6	2.9	5.0	[a]0.5, [b]1
Staphylococcus aureus CA-MRSA (USA400)	9.6	2.9	5.0	[a]0.75, [b]1
Staphylococcus aureus HA-MRSA (COL)	9.6	5.8	ND	[a]0.30
Staphylococcus aureus HA-MRSA252	9.6	2.9	5.0	[a]>10, [b]0.5
Staphylococcus aureus MDRSA*	9.6	1.4	2.5	[a]>16
Staphylococcus epidermidis	9.6	1.4	2.5	[c]>4, [b]1
Staphylococcus. haemolyticus	19.2	2.9	5.0	[c]0.1
Staphylococcus saprophyticus	9.6	2.9	5.0	[b]1, [c]0.5
Enterococcus faecalis ATCC29212$^{\nabla}$	>64	2	>64	[b]2-4, [c]<0.03
Enterococcus faecium ATCC35667$^{\nabla}$	>64	1	>64	[b]2, [c]0.125
Enterococcus faecium ATCC700221 (VRE)$^{\nabla}$	8	0.25	ND	[b]>64, [c]64
Listeria monocytogenes ATCC19115	>77	>93	ND	[c]25
Streptococcus pneumoniae ATCC49619$^{\Delta}$	0.5	1	0.5	[a]<0.03, [b]0.25
Streptococcus pyogenes ATCC700294$^{\Delta}$	8	8	8	[a]<0.125, [b]2
Gram negative bacteria				
Acinetobacter baumannii X270295	>77	>186	>162	[c]0.8
Escherichia coli DY330	>77	>93	ND	[c]0.2
ESBL-producing Klebsiella pneumoniae	NA	>93	>81	[c]>50
Pseudomonas aeruginosa PA0-1	>193	>233	>162	[c]0.25
Samonella typhimurium SL1344	>193	>233	ND	[c]<0.1



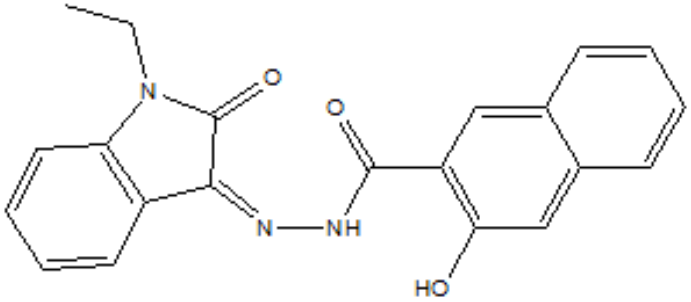
IC_{50} (MRSA Pyruvate kinase) = 911nM



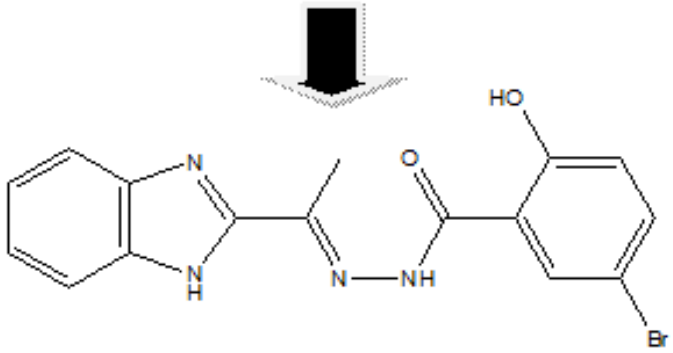
IC_{50} = 91nM



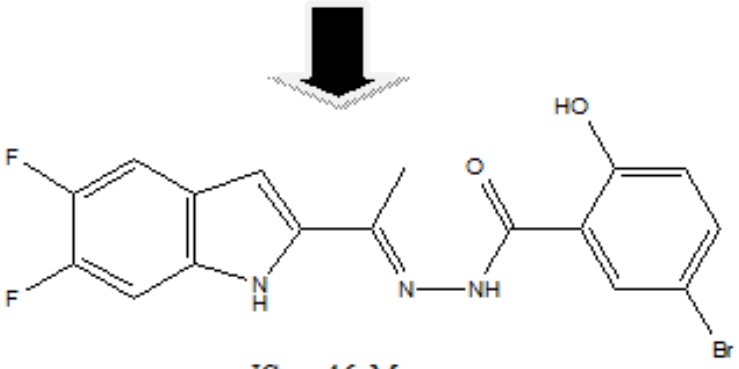
IC_{50} = 16nM



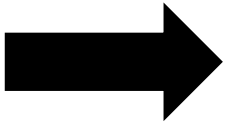
IC_{50} (MRSA Pyruvate kinase) = 911nM

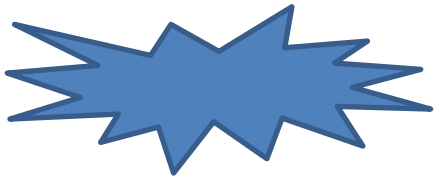


IC_{50} = 91nM



IC_{50} = 16nM





IC50 < 1 nM

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Nag S. Kumar,
Robert N. Young,

B. Brett Finlay and Neil E Reiner.

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