Predicting synergism of anti-HIV drug pair combinations

Alexey A. Lagunin^{1,2*}, Sergey M. Ivanov^{1,2}, Roman Yu. Shobik²,
Alexandra S. Khromova², Anton S. Smirnov², Nadezhda Yu. Bizyukova²,
Dmitry A. Filimonov¹, Olga A. Tarasova¹, Vladimir V. Poroikov¹.

alexey.lagunin@ibmc.msk.ru

(1) Department for Bioinformatics, Institute of Biomedical Chemistry, Moscow, Russia

(2) Department for Bioinformatics, Pirogov Russian National Research Medical University, Moscow, Russia

Background

Summary of the global HIV epidemic (2018)

	People living with HIV in 2018	People newly infected with HIV in 2018	HIV-related deaths 2018
Total	37.9 million [32.7 million – 44.0 million]	1.7 million [1.4 million – 2.3 million]	770 000 [570 000 – 1.1 million]
Adults	36.2 million [31.3 million – 42.0 million]	1.6 million [1.2 million – 2.1 million]	670 000 [500 000 – 920 000]
Women	18.8 million [16.4 million – 21.7 million]	–	–
Men	17.4 million [14.8 million – 20.5 million]	–	–
Children (<15 years)	1.7 million [1.3 million – 2.2 million]	160 000 [110 000 – 260 000]	100 000 [64 000 – 160 000]

Source: UNAIDS/WHO estimates

Antiretroviral drug combinations for the treatment of HIV/AIDS

- Antiretroviral therapy (ART) including 2 or 3 antiretroviral drugs simultaneously has been successfully used for over 20 years.
- Simultaneous action on different targets decrease possibility to get drug resistance.
- Some combinations of currently used ART may have side effects, toxicity, especially among people living with HIV within the group of patients over 50 years old.
- The number of pairwise combinations for approved drugs is extremely high, therefore we need a rational approach for predicting the synergism of anti-HIV drug pair combinations.

Experimental data

~ 500,000 from 1000 FDA-approved drugs or clinically tested drugs and identified drugs that synergize to inhibit HIV replication.

To reduce the number of experiments. The study was made on two stages. It was called MuSIC screen.

nature
biotechnology

Systematic identification of synergistic drug pairs targeting HIV

Xu Tan¹, Long Hu^{2,4}, Lovelace J Luquette III^{3,4}, Geng Gao¹, Yifang Liu², Hongjing Qu¹, Ruibin Xi³, Zhi John Lu², Peter J Park³ & Stephen J Elledge¹

The systematic identification of effective drug combinations has been hindered by the unavailability of methods that can explore the large combinatorial search space of drug interactions. Here we present multiplex screening for interacting compounds (MuSIC), which expedites the comprehensive assessment of pairwise compound interactions. We examined ~500,000 drug pairs from 1,000 US Food and Drug Administration (FDA)-approved or clinically tested drugs and identified drugs that synergize to inhibit HIV replication. Our analysis reveals an enrichment of anti-inflammatory drugs in drug combinations that synergize against HIV. As inflammation accompanies HIV infection, these findings indicate that inhibiting inflammation could curb HIV propagation. Multiple drug pairs identified in this study, including various glucocorticoids and nitazoxanide (NTZ), synergize by targeting different steps in the HIV life cycle. MuSIC can be applied to a wide variety of disease-relevant screens to facilitate efficient identification of compound combinations.

HIV has plagued humans for at least 30 years, infecting 60 million people and causing >25 million deaths. AIDS patients can be effectively treated with highly active antiretroviral therapy (HAART), which usually comprises a combination of three anti-HIV drugs¹. However, the cost of current HAART is prohibitive in developing countries. In addition, long-term HAART can have serious side effects such as lipodystrophy, hyperglycemia, pancreatitis and liver toxicity². New therapies are needed to expand the current HAART repertoire, to provide hope for a cure and to reduce the cost of treatment and side effects^{3,4}.

inhibitors⁹ and to look for synergistic anti-inflammatory compound pairs¹⁰, although the latter study did not yield any novel pairs. We have developed MuSIC, a pooled screening method, to screen a large collection of diverse FDA-approved or clinically tested compounds. The MuSIC screening library was designed to contain ten compounds in each well of a 384-well plate and cover all the possible pairwise combinations among these compounds using <3% of the number of wells needed in a standard pairwise screen. For pools that contained potentially strong synergistic interactions, we deconvoluted each of them into 45 drug pairs in a secondary screen to identify eff-

© 2012 Nature America, Inc. All rights reserved.

Xu Tan et al., Nat Biotechnol. 2012, 30(11):1125-30

MuSIC screen

116 drug pairs reduced the HIV infection rate were tested on synergism by HSE and Bliss methods

12,904 unique drug pairs was tested on two scores (Z1 and Z2)

288 active and low toxic pools were selected

Xu Tan et al., Nat Biotechnol. 2012, 30(11):1125-30

Software

Special version of GUSAR [1] and PASS [2] software for prediction drug-drug interactions (DDI) were used for SAR modeling.

GUSAR DDI

Zakharov A.V. et al., *Mol. Pharmaceutics*, 2016, 13(2), 545

PASS DDI

Dmitriev A. et al., *Molecules* 2019, 24(21), 3955

GUSAR DDI

- Self-Consistent Regression
- QNA (Quantitative Neighborhoods of Atoms) descriptors:

$$\mathbf{P}_i = \mathbf{B}_i \sum_k (\text{Exp}(-\frac{1}{2}\mathbf{C}))_{ik} \mathbf{B}_k \quad \mathbf{Q}_i = \mathbf{B}_i \sum_k (\text{Exp}(-\frac{1}{2}\mathbf{C}))_{ik} \mathbf{B}_k \mathbf{A}_k$$

$$\mathbf{A} = \frac{1}{2}(\mathbf{IP} + \mathbf{EA}), \quad \mathbf{B} = (\mathbf{IP} - \mathbf{EA})^{-\frac{1}{2}},$$

IP - ionization potential, **EA** – electron affinity

Filimonov D. et al., SAR and QSAR in Environmental Research, 2009, 20, 679-709

Lagunin A. et al. SAR and QSAR in Environmental Research, 2007, 18, 285-298

QNA (Quantitative Neighborhoods of Atoms) descriptors:

	EA	IP	A	B	P	Q
C	1.263	11.26	6.262	0.316	-0.00218	-0.1820
O	1.461	13.62	7.541	0.287	0.02944	0.3019
O	1.461	13.62	7.541	0.287	0.06199	0.5297
H	0.754	13.60	7.177	0.279	0.05812	0.4706
H	0.754	13.60	7.177	0.279	0.05304	0.3533

d)

Two-dimensional Chebyshev polynomials are used for approximating the functions P and Q over all atoms of the molecule.

Structures		
QNA descriptors	$P^1, Q^1: (P_1^1, Q_1^1), (P_2^1, Q_2^1), \dots (P_n^1, Q_n^1)$	$P^2, Q^2: (P_1^2, Q_1^2), (P_2^2, Q_2^2), \dots (P_m^2, Q_m^2)$
“Mixture” of QNA descriptors	$P^{1,2}, Q^{1,2}: (P_1^1, Q_1^1), (P_2^1, Q_2^1), \dots (P_n^1, Q_n^1), (P_1^2, Q_1^2), (P_2^2, Q_2^2), \dots (P_m^2, Q_m^2)$	

PASS DDI

- Bayesian-like approach
- Pairs of Substances Multilevel Neighbourhoods of Atoms (PoSMNA) descriptors

PoSMNA is based on Multilevel Neighbourhoods of Atoms (MNA) descriptor:

MNA/1: C(CN-H)

MNA/2: C(C(CC-H)N(CC)-H(C))

Filimonov D.A. et al. J. Chem. Inform. Computer Sci., 1999, 39, 666.
Poroikov V.V. et al. J. Chem. Inform. Computer Sci., 2000, 40, 1349.

Pairs of Substances Multilevel Neighbourhoods of Atoms (PoSMNA) descriptors

Dmitriev A. et al., Molecules 2019, 24(21), 3955

Accuracy of SAR models created on 116 drug pairs results of synergistic studies

Can we select candidate synergistic drug pairs based on Z1 and Z2 scores?

116 drug pairs were selected based on the highest values of Z1 and Z2 scores

Number of drug pairs. Experimental data		
Method	Synergy	No synergy
BLISS	66	50
HSA	77	39
Both	41	75

Yes! From 35% (Both) to 66% (HSA) selected drug pairs revealed anti-HIV synergism measured by different methods.

Xu Tan et al., Nat Biotechnol. 2012, 30(11):1125-30

Accuracy of SAR models created based on Z score data

- the structures for ~ 12,000 drug pairs with Z1 or Z2 scores were used as the training set

- the structures for ~ 12,000 drug pairs with Z1 or Z2 scores + all drug pairs (~150,000) from the first pool, which showed no anti-HIV activity.

Drug pairs with Z1 or Z2 scores with less -1 values were considered as actives, others were considered as inactives.

Accuracy of synergism prediction for 116 drug pairs based on the results of SAR models created using Z score data

	PASS DDI			GUSAR DDI		
Methods	Sen	Spec	Acc	Sen	Spec	Acc
<i>Z score 12000 part 1</i>						
BLISS	0.85	0.29	0.61	0.85	0.20	0.57
HSA	0.73	0.10	0.52	0.76	0.05	0.52
Both	0.80	0.23	0.42	0.78	0.15	0.37
<i>Z score 12000 part 2</i>						
BLISS	0.85	0.29	0.61	0.80	0.33	0.60
HSA	0.71	0.05	0.48	0.65	0.08	0.46
Both	0.77	0.20	0.40	0.70	0.23	0.39
<i>Z score 12000 part 1 and Z score 12000 part 2</i>						
BLISS	0.83	0.33	0.61	0.77	0.35	0.59
HSA	0.69	0.10	0.49	0.61	0.08	0.43
Both	0.78	0.24	0.43	0.65	0.24	0.39
<i>Z score part 1 + all inactive</i>						
BLISS	0.89	0.20	0.60			
HSA	0.81	0.08	0.56			
Both	0.88	0.16	0.41			
<i>Z score part 2 + all inactive</i>						
BLISS	0.84	0.29	0.60			
HSA	0.72	0.05	0.49			
Both	0.80	0.20	0.41			
<i>Z score part 1 + all inactive and Z score part 2 + all inactive</i>						
BLISS	0.85	0.33	0.62			
HSA	0.71	0.10	0.50			
Both	0.80	0.24	0.44			

Selection of new possible synergistic anti-HIV drug pair combinations

- 997 FDA approved drugs different from 1000 drugs used in MuSIC screen were selected from DrugBank 4.1.
- They were used for generation of the set of ~ 500,000 new drug pairs.
- The set was used for two step virtual screening based on PASS DDI (the results given on the training sets with Z scores (*Z score part 1 + all inactive and Z score part 2 + all inactive data*) and GUSAR DDI (the training set with 116 drug pairs (*Both data*)) models.

PASS DDI prediction results for ~500,000 drug pairs

	$P_{a>P_i}$	$P_{a>0.3}$	$P_{a>0.5}$	$P_{a>0.7}$
Z1 score	119244	69362	32080	6606
Z2 score	112869	51841	14532	5635

P_a – a probability that a pair of drugs displays anti-HIV activity

P_i – a probability that a pair of drugs does not display anti-HIV activity

Intersection of Z1 and Z2 with $P_{a>0.7}$ = 5430 drug pairs

GUSAR DDI prediction results

- 1974 new drug pairs were predicted by GUSAR DDI to be anti-HIV synergistic from 5430 drug pairs selected based on PASS DDI prediction results for Z1 and Z2 scores.
- 89 new drug pairs were predicted to be anti-HIV synergistic with probability > 60%
- 5 new drug pairs were predicted to be anti-HIV synergistic with probability > 70%:
 - **Auranofin/Fluocinonide**
 - **Auranofin/Difluprednate**
 - **Auranofin/Fluocinolone Acetonide**
 - **Bismuth Subsalicylate/Fluocinonide**
 - **Icosapent/Difluprednate**

Targets of the selected drug pairs (DrugBank data)

Drug	Target	Drug	Target
Auranofin	Peroxisome proliferator-activated receptor gamma	Fluocinonide	Glucocorticoid receptor
	Inhibitor of nuclear factor kappa-B kinase subunit beta		Smoothed homolog
		Difluprednate	Glucocorticoid receptor
		Fluocinolone Acetonide	Glucocorticoid receptor
			Annexin A1
			Annexin A2
			Annexin A3
			Annexin A4
			Annexin A5
Bismuth Subsalicylate	Serotransferrin	Fluocinonide	Glucocorticoid receptor
			Smoothed homolog
Icosapent	Prostaglandin G/H synthase 2	Difluprednate	Glucocorticoid receptor
	Prostaglandin G/H synthase 2		
	AProstaglandin G/H synthase 1		
	APeroxisome proliferator-activated receptor gamma		
	APeroxisome proliferator-activated receptor delta		
	UFatty acid desaturase 1		
	ULong-chain-fatty-acid--CoA ligase 4		
	ULong-chain-fatty-acid--CoA ligase 3		
	AFree fatty acid receptor 1		
	ASodium/calcium exchanger 1		
	UTransient receptor potential cation channel subfamily V member 1		
	UPeroxisome proliferator-activated receptor alpha		

Comparison with the experimental data given by MuSIC screen

Betamethazone + NTZ – the most active drug pair

- Betamethasone - **Glucocorticoid receptor** (target)
- NTZ (Nitazoxanide) - Pyruvate-flavodoxin oxidoreductase (catalyzes the ferredoxin-dependent oxidative decarboxylation of pyruvate). It has been also studied as a broad-spectrum antiviral agent due to its ability to inhibit the replication of several RNA and DNA viruses.

Xu Tan et al., Nat Biotechnol. 2012, 30(11):1125-30

Acknowledgments

This work was supported by Russian Science Foundation grant [number 19-75-10097].