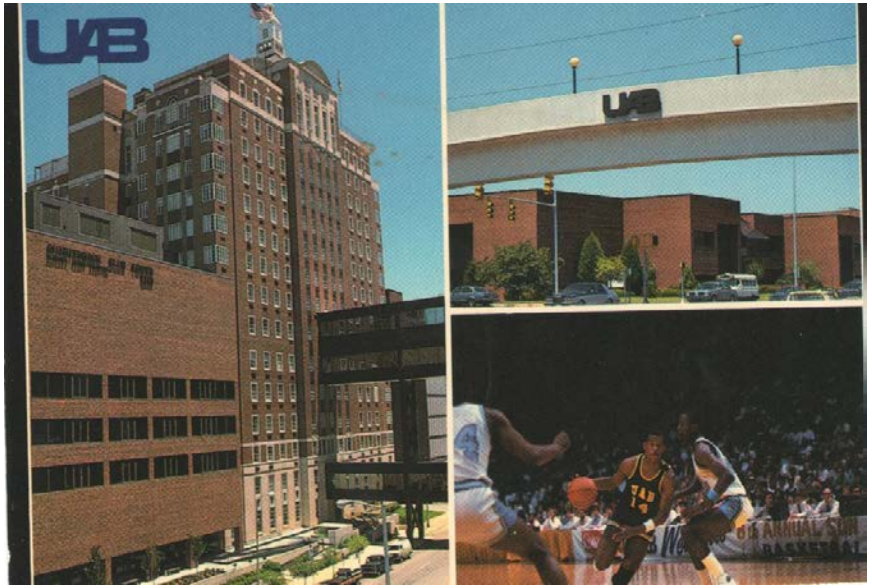
Personal Experience of Russian Researcher's Collaboration with U.S. Investigators

Vladimir Poroikov, Prof. Dr.

Institute of Biomedical Chemistry

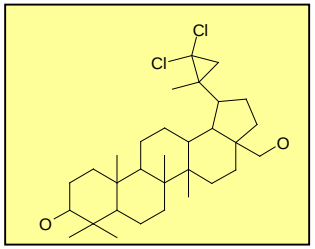
Moscow, Russia

My first visit to the United States
(University of Alabama at Birmingham, October, 1989)



PASS: Prediction of Activity Spectra for Substances

Structure of new compound



Estimating the probability that it has a particular biological activity

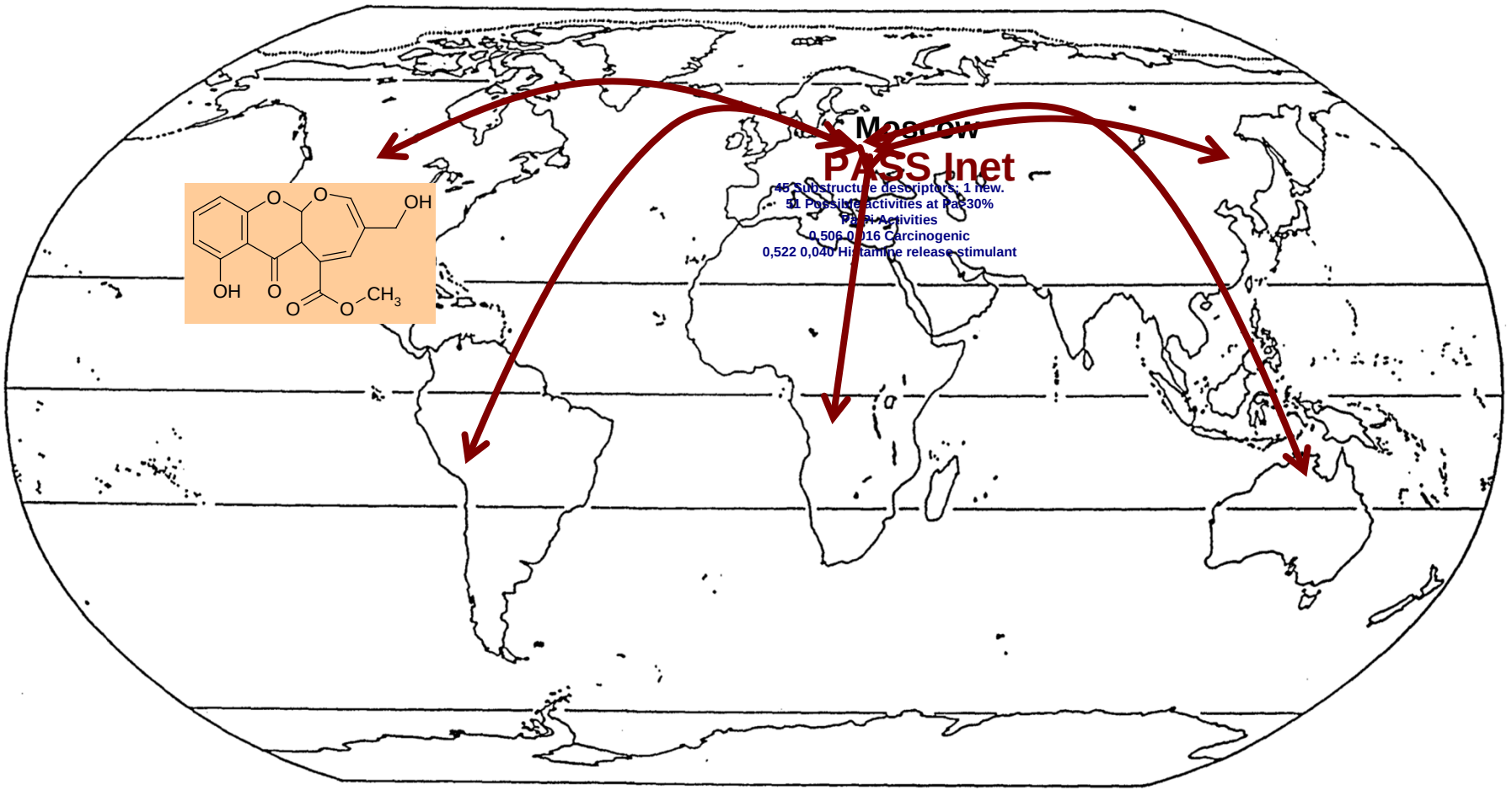
Anxiolytic
Sedative
5HT1A Inhibitor
Carcinogen
. . .

Predicted biological activity spectrum

Pa	Pi	for Activity:
0.853	0.020	Anxiolytic
0.694	0.035	Sedative
	. . .	

Totally, predicts about 700 biological activities.

~1998-1999



To provide the possibility of bioactivity prediction worldwide, PASS INet system has been developed (http://ibmc.msk.ru/PASS).

Currently: http://way2drug.com/passonline

FREDIRICK – MOSCOW COLLABORATION

Lab. Med. Chem., NCI, NIH

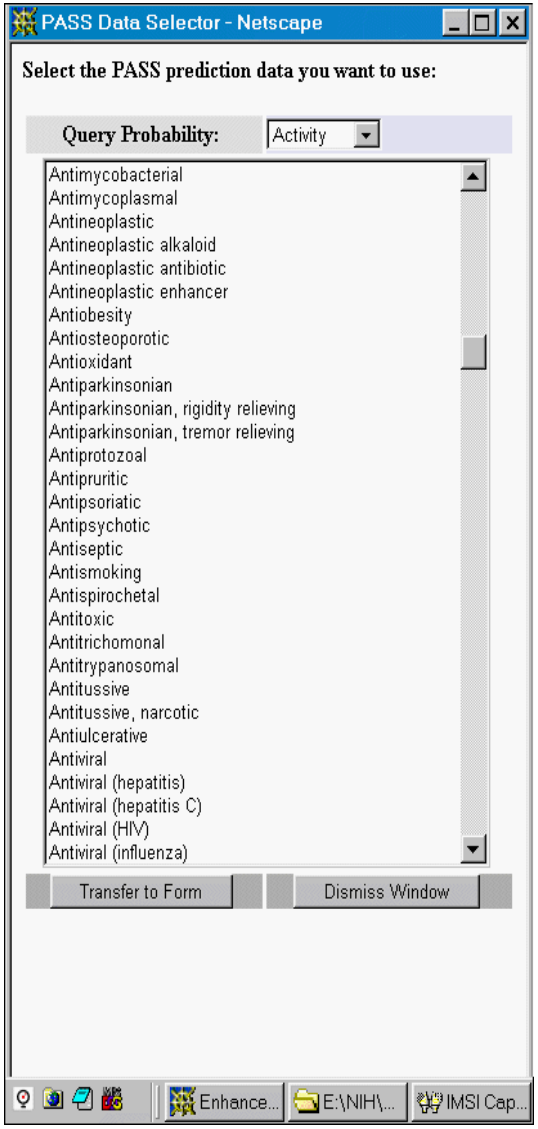
Lab. Str.-Funct. Based Drug Des., IBMC, RAMS

Computer-assisted mechanism-of-action analysis of large databases including 250,000 chemical compounds registered by NCI

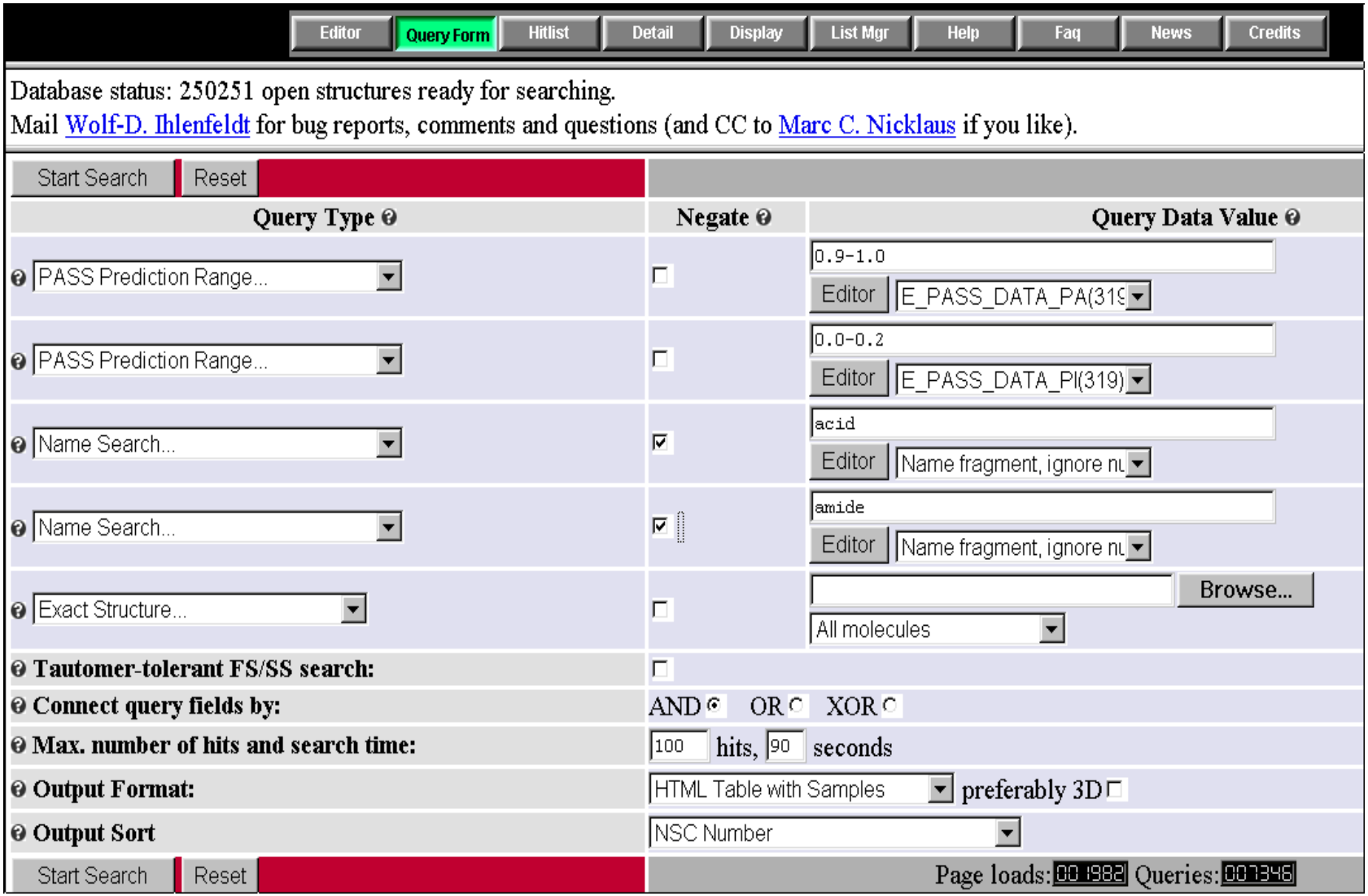
Supported by the CRDF Grant # RC1-2064 (2000-2001).

PASS Predictions Searchable in NCI DB Browser (http://cactus.nci.nih.gov)

- More than 64 million PASS predictions included.
- More than 700 activities available.
- Predictions separately searchable by probabilities of activity and inactivity.
- Both types combinable by logical AND.
- Predictions searchable by probability ranges (in subintervals of 0.0 – 1.0).
- PASS searches combinable with any other search criteria.



Combined Search: PASS Antiangiogenesis Prediction & Name (Fragment) Exclusion



Search Results: Hitlist

Editor | Query Form | Hitlist | Detail | Display | List Mgr | Help | Faq | News | Credits

Database status: 250251 open structures ready for searching.
Mail Wolf-D. Ihlenfeldt for bug reports, comments and questions (and CC to Marc C. Nicklaus if you like).

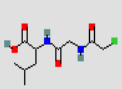
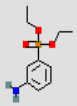
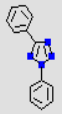
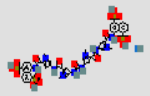
Operations with this Dataset of 83 Structures:

Data Retrieval: Format: SDFile 3D ☐ Fields: NSC Number, Molecular Weight, Name (ACD) — Retrieve

Visualization: GIF Image Gallery — Display

Miscellaneous: Restart Query (at first record) — Execute

Sample Structures

89667	96667	141177	141869	645795
				

	NSC Number	Formula	CAS	#Names	Sample Name
☑	7965	$C_3H_4ClN_5$	3397-62-4	8	6-chloro-1,3,5-triazine-2,4-diamine
☑	9665	$C_{16}H_{26}O_4$	*(None)*	7	5-methoxy-4-(2-methyl-3-(3-methyl-2-butenyl)-2-oxiranyl)-1-oxaspiro[2.5]octan-6-ol
☑	10374	$C_5H_8ClNO_3$	691-80-5	1	N-(chloroacetyl)alanine
☑	13914	$C_5H_8ClN_5$	32998-04-2	1	6-chloro-N^2,N^2-dimethyl-1,3,5-triazine-2,4-diamine
☑	32859	$C_5H_8ClNO_3$	6092-47-3	1	ethyl chloroacetylcarbamate
☑	32864	$C_6H_{11}ClN_2O_2$	7248-86-4	1	N-(chloroacetyl)-N'-isopropylurea
☑	33713	$C_{10}H_{18}O_3$	*(None)*	1	2,2,5,5-tetramethyltetrahydro-3-furanyl acetate
☑	51808	$C_{12}H_8F_3N$	401-17-2	2	2,5-difluoro-N-(4-fluorophenyl)aniline

PASS Evaluation Vs. NCI DTP Anti-HIV Screening Results

Open NCI Database (250,251 compounds):

Tested in anti-HIV asay: 42,689 compounds

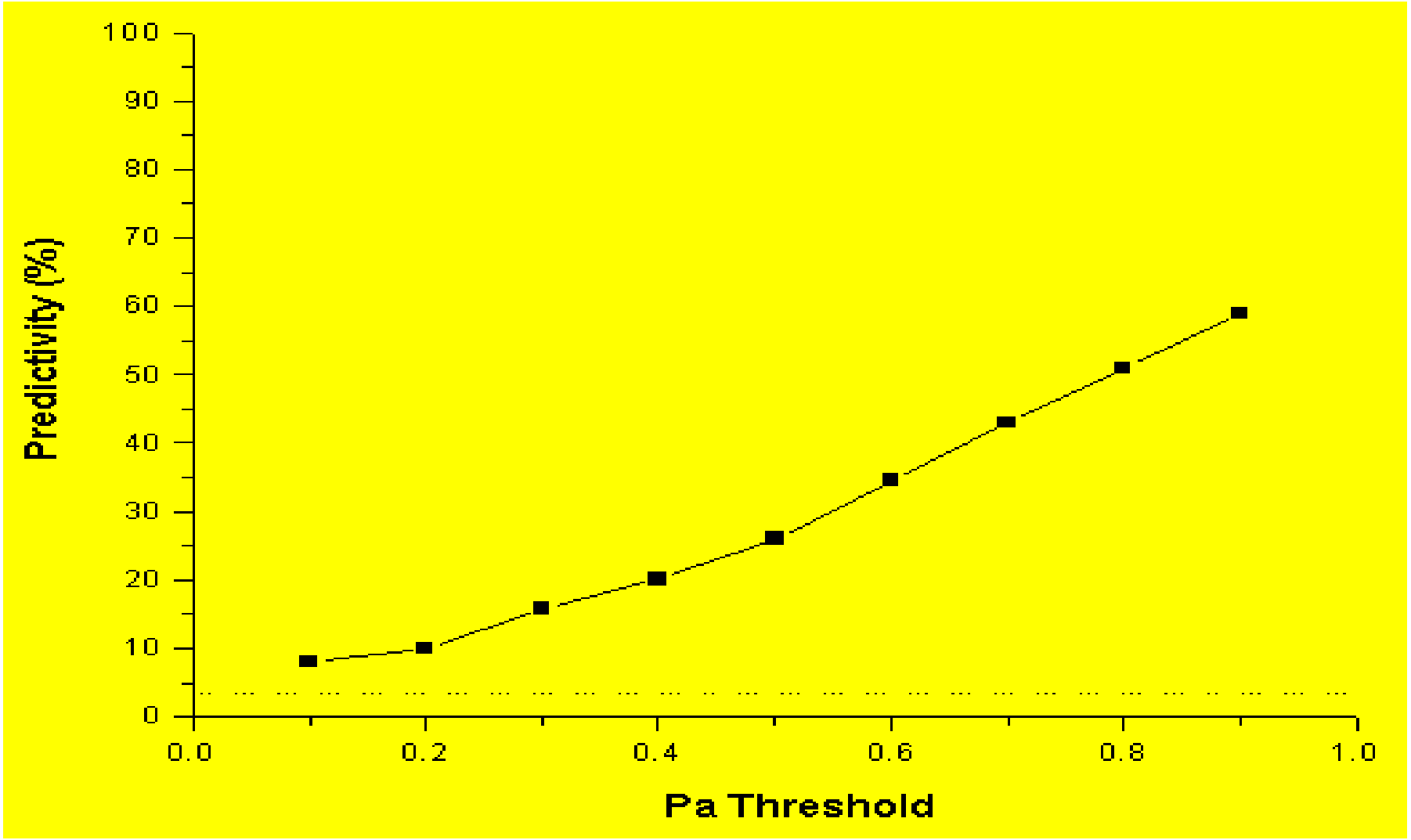
"Actives" (A & MA): 1,505 compounds

"Inactives": 41,185 compounds

Percentage of actives: 1,540/42,689 = 3,52%.

A random selection would therefore preserve this ratio.

PASS application increases the number of “actives” in the selected sub-set from 2.2 to 16.8 times

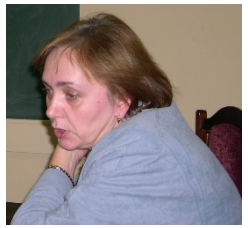


Poroikov V. et al. *J. Chem. Inform. Comput. Sci.*, **2003**, *43*: 228-236.

Predictions of Broad Activity Spectra for Large Chemical Databases: 64 Million PASS Results made Searchable on the Enhanced NCI Database Browser

Marc C. Nicklaus, Computer-Aided Drug Design (CADD) MiniCore Facility, Lab. of Medicinal Chemistry, CCR, NCI, NIH, Frederick, and Vladimir V. Poroikov, Dmitrii A. Filimonov and Alexey A. Lagunin, Laboratory of Structure-Function Based Drug Design, Institute of Biomedical Chemistry, Russian Academy of Medical Sciences, Moscow

Computer-Aided Discovery of New HIV-1 Integrase Inhibitors (ISTC/BTEP project # 3197/111) *2005-2008*



Institute of Biomedical Chemistry of RAMS, Moscow (Vladimir Poroikov team - computer-aided drug discovery).

Institute of Organic Chemistry of RAS, Moscow (Svyatoslav Shevelev team - chemical synthesis of potential ant-HIV agents).

Institute of Physical-Chemical Biology of MSU, Moscow (Marina Gottikh team - testing of potential anti-HIV agents *in vitro*).

National Cancer Institute, NIH, Frederick, MD (Marc Nicklaus - molecular modelling, Vinay Pathak - testing in cell culture).

BTEP Biotechnology Engagement Program

INTERNATIONAL SCIENCE & TECHNOLOGY CENTER
ISTC МНТЦ
Nonproliferation Through Science Cooperation

Computer-aided discovery of new HIV-1 integrase inhibitors: some obtained results

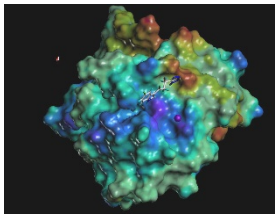
217 compounds were selected as hits, synthesized (or purchased from vendors of commercially available samples)

187 compounds were tested *in vitro* on inhibition for strand transfer and 51 compounds were tested on inhibition for 3' processing.

18 compounds were identified as HIV-1 integrase inhibiting agents with IC_{50} values in the micromolar and sub-micromolar range.

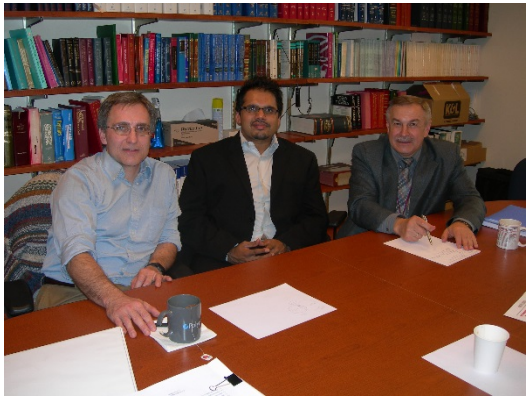
For 3 most active compounds results were further confirmed by *in vitro* testing at NCI.

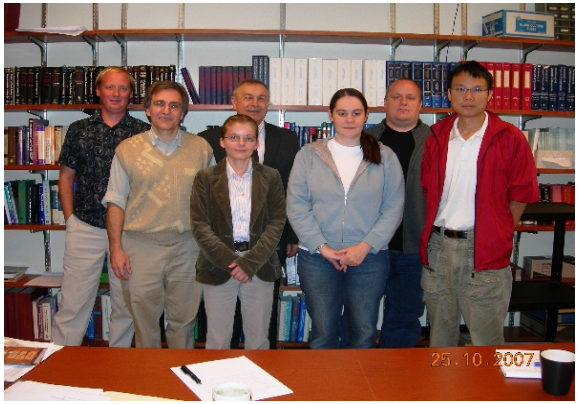
The discovered compounds belong to the chemical series where this activity was unknown (NCEs).



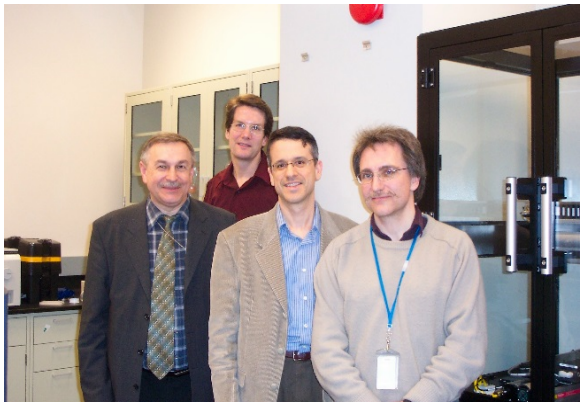
Королев С.П. и др. *Acta Naturae*, **2013**, *5*: 75-85.

Druzhilovsky D.S. et al. *Biochemistry (Moscow) Suppl. B. Biomedical Chemistry*, **2010**, *4*: 59-67.




25.10.2007


Licensing Exercise
Examining the licensee-licensor perspectives
Small group discussions
Define the two or three most important considerations for a licensing professional contemplating a prospective license in the area of IP assigned.




EXIT


WHAT'S YOUR RESEARCH ABOUT?
GETTING GRANTS!
10'000 f.

Roadmap Data: New Possibilities for Computer-Aided Drug Discovery

Vladimir Poroikov, Dmitry Filimonov,

Marc Nicklaus

Institute of Biomedical Chemistry of Rus. Acad. Med. Sci., Moscow, Russia; Laboratory of Medicinal Chemistry, NCI/NIH, Frederick, MD, USA

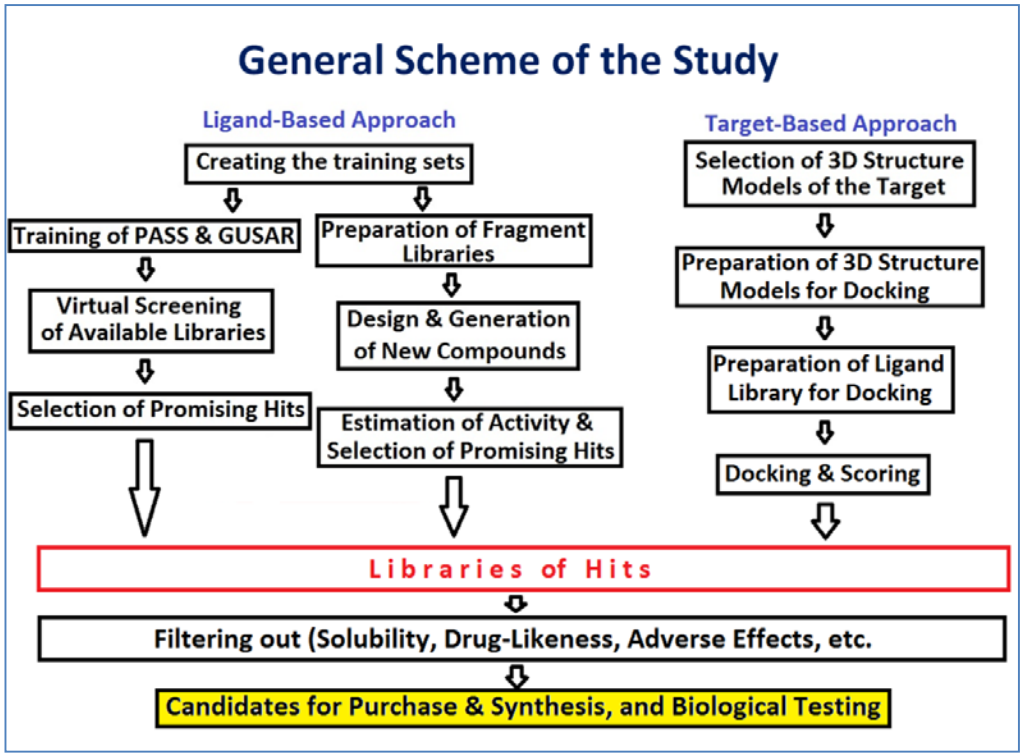
235th ACS Meeting, April 6-10, 2008,

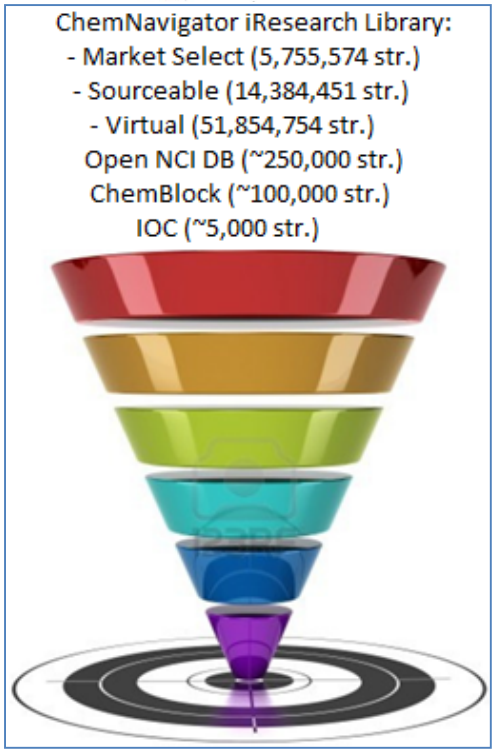
New Orleans, LA, CINF-58

COMPUTER-AIDED DESIGN AND BIOLOGICAL TESTING OF NOVEL COMPOUNDS TOWARDS PREVENTION AND CURE OF HIV/AIDS

RFBR/NIH Project # 13-04-91455

Co-PIs: Marc C. Nicklaus, Ph.D. (NCI/NIH)
Vladimir Poroikov, Dr. Sci. (IBMC)





The first round: **45 compounds purchased; 16 active at IC_{50}<50 μM; 4 active at IC_{50}~1 μM.**

The second round: **15 compounds designed and obtained from IOC, all – inactive at IC_{50}<10 μM.**

The third round: **148 compounds obtained from ChemNav, the syntheses of (up to) 20 compounds are underway, 10 known reference drug compounds ordered. All compounds will be tested in one cell-based and three enzymatic assays (IN, RT, PR) at ImQuest (contract of NCI with ImQuest is under preparation) .**

Publications and presentations: **4 journal articles, 1 book chapter, 6 abstracts published; 5 oral presentations (3 at the American Chemical Society Meetings), 2 posters.**

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

QSAR Modeling Using Large-Scale Databases: Case Study for HIV-1 Reverse Transcriptase Inhibitors

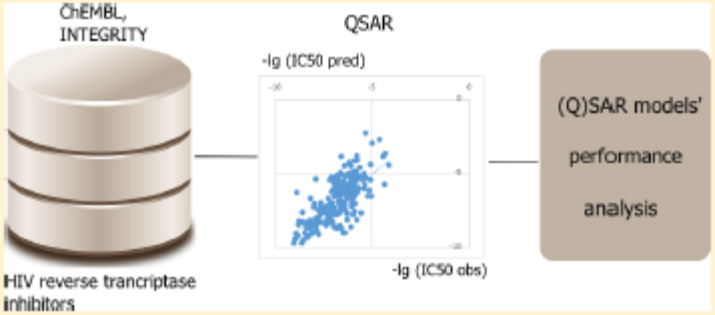
Olga A. Tarasova,*[,†] Aleksandra F. Urusova,[†] Dmitry A. Filimonov,[†] Marc C. Nicklaus,[‡] Alexey V. Zakharov,[‡] and Vladimir V. Poroikov[†]

[†]Institute of Biochemical Chemistry, 10-8, Pogodinskaya St., 119121, Moscow, Russia

[‡]CADD Group, Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, DHHS, NCI-Frederick, 376 Boyles St., Frederick, Maryland 21702, United States

Supporting Information

ABSTRACT: Large-scale databases are important sources of training sets for various QSAR modeling approaches. Generally, these databases contain information extracted from different sources. This variety of sources can produce inconsistency in the data, defined as sometimes widely diverging activity results for the same compound against the same target. Because such inconsistency can reduce the accuracy of predictive models built from these data, we are addressing the question of how best to use data from publicly and commercially accessible databases to create accurate and predictive QSAR models. We investigate the suitability of commercially and publicly available databases to QSAR modeling of antiviral activity (HIV-1 reverse transcriptase (RT) inhibition). We present several methods for the creation of modeling (i.e., training and test) sets from two, either commercially or freely available, databases: Thomson Reuters Integrity and ChEMBL. We found that the typical predictivities of QSAR models obtained using these different modeling set compilation methods differ significantly from each other. The best results were obtained using training sets compiled for compounds tested using only one method and material (i.e., a specific type of biological assay). Compound sets aggregated by target only typically yielded poorly predictive models. We discuss the possibility of "mix-and-matching" assay data across aggregating databases such as ChEMBL and Integrity and their current severe limitations for this purpose. One of them is the general lack of complete and semantic/computer-parsable descriptions of assay methodology carried by these databases that would allow one to determine mix-and-matchability of result sets at the assay level.



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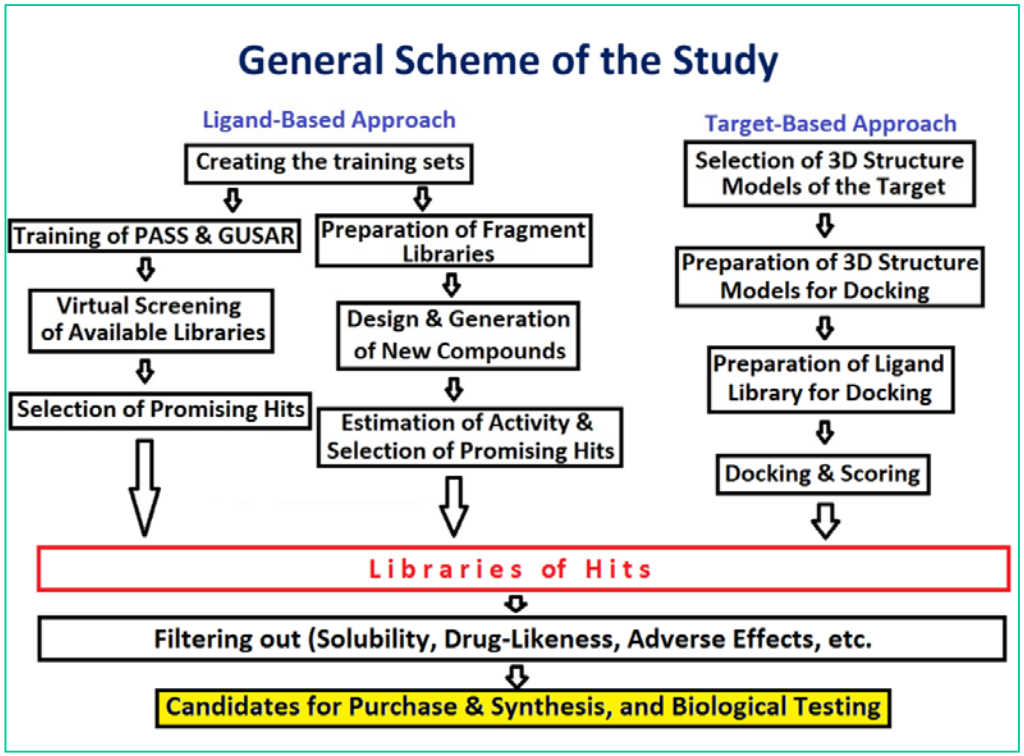

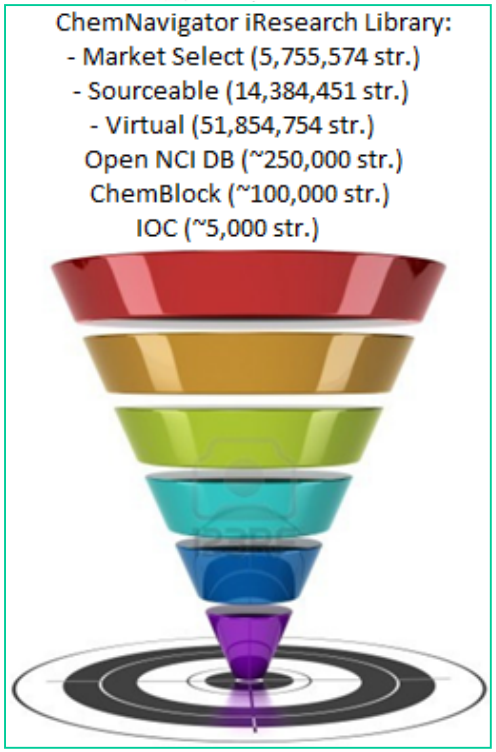

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Exchange by people (mobility)

Yulia Borodina

Our graduate student and PhD student.

Currently works at FDA.

Vladimir Potapov

Our graduate student.

Currently works at MIT.

Alexey Zakharov

Our graduate student and PhD student.

After post-doc position in NCI, currently works at NCATS.

Which pre-requisites are crucial for successful scientific collaboration?

I would add "a long-term"...

Complementary:

- **Background**
- **Experience**
- **Facilities**

Mutual:

- **Efforts, efforts, efforts...**

Acting in this way, you will obtain non-additive value results, which no one team could achieve working separately.

Good luck!