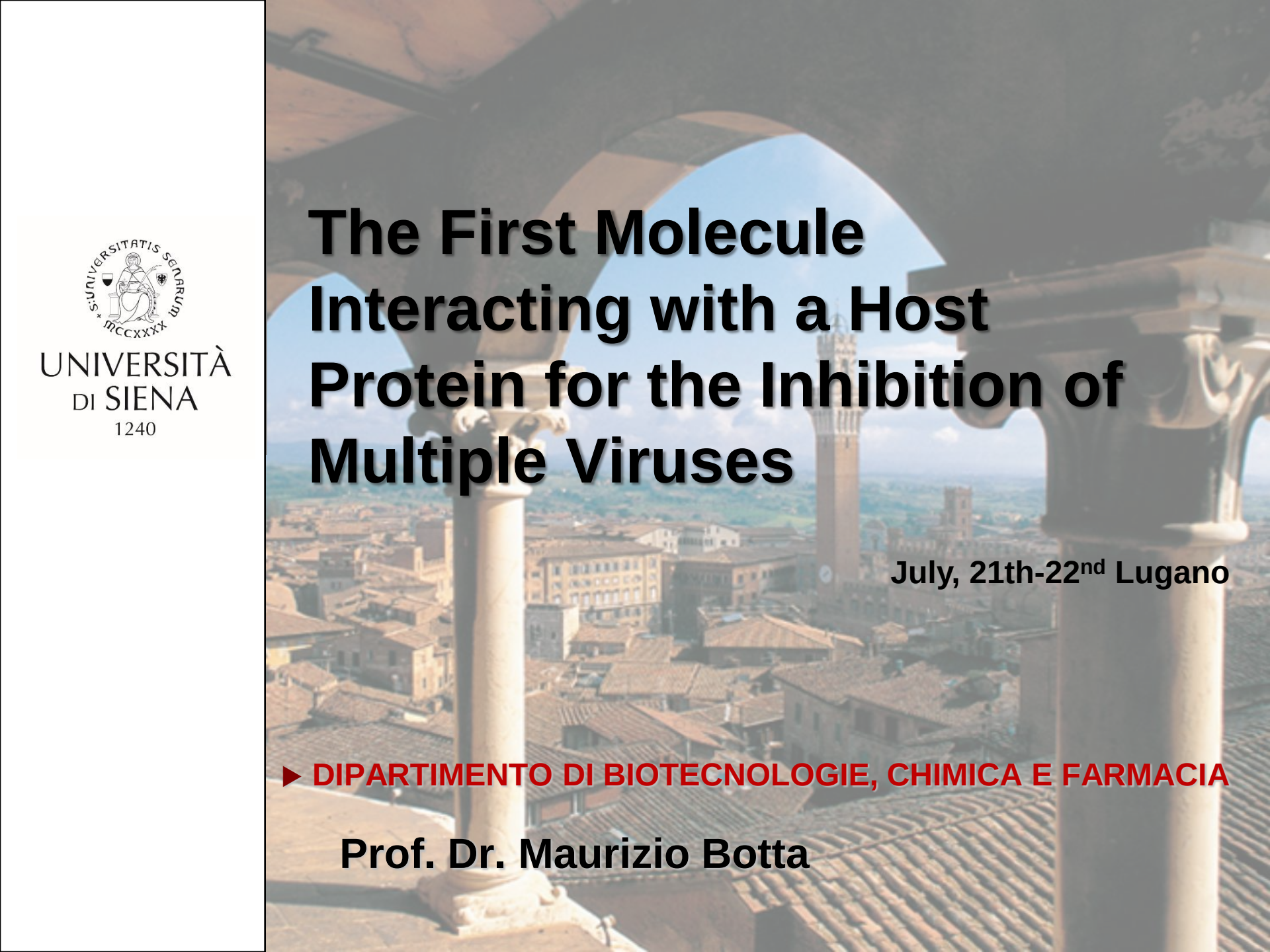

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The First Molecule Interacting with a Host Protein for the Inhibition of Multiple Viruses

July, 21th-22nd Lugano

▶ DIPARTIMENTO DI BIOTECNOLOGIE, CHIMICA E FARMACIA

Prof. Dr. Maurizio Botta

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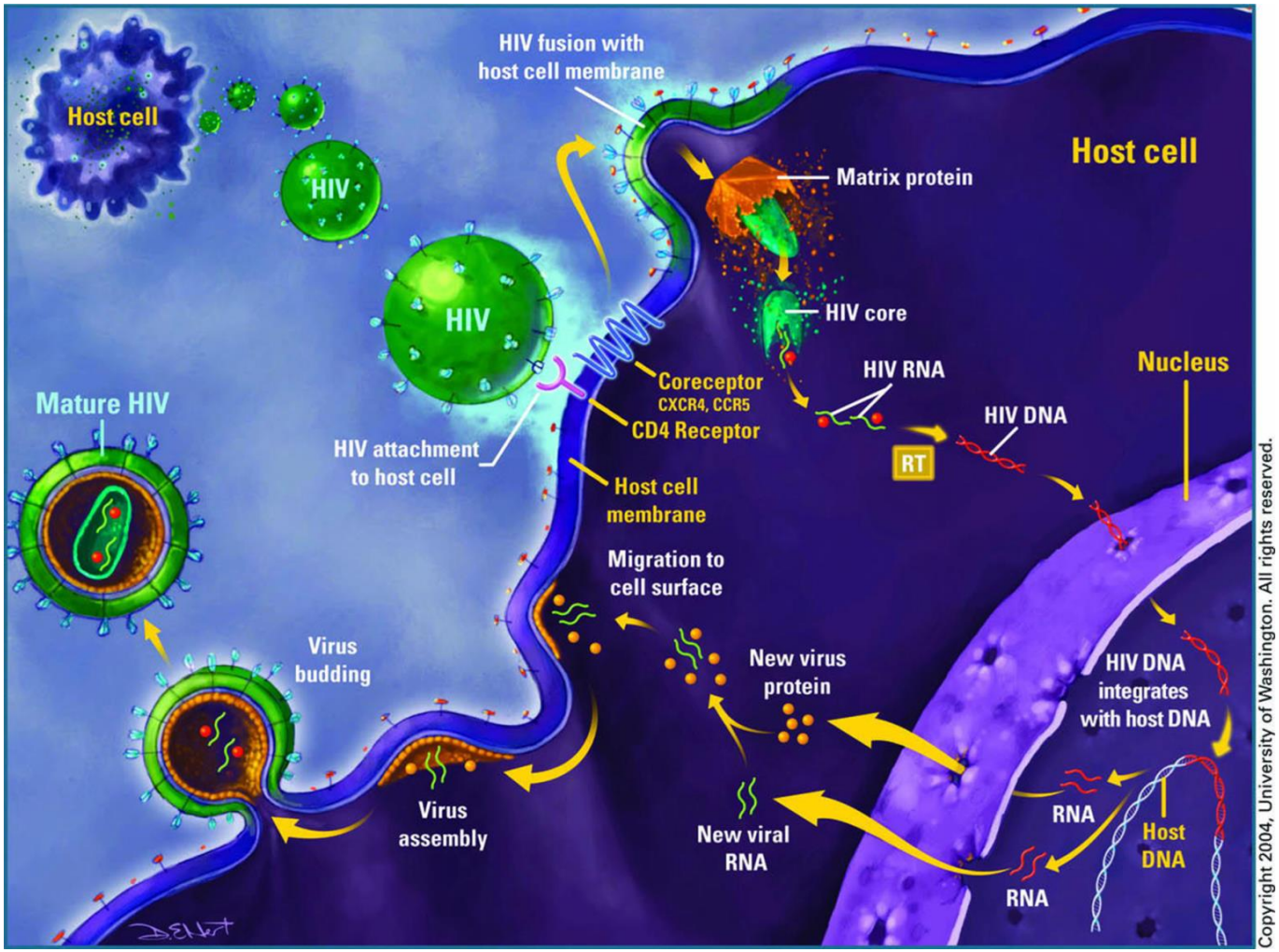
HIV LIFE CYCLE



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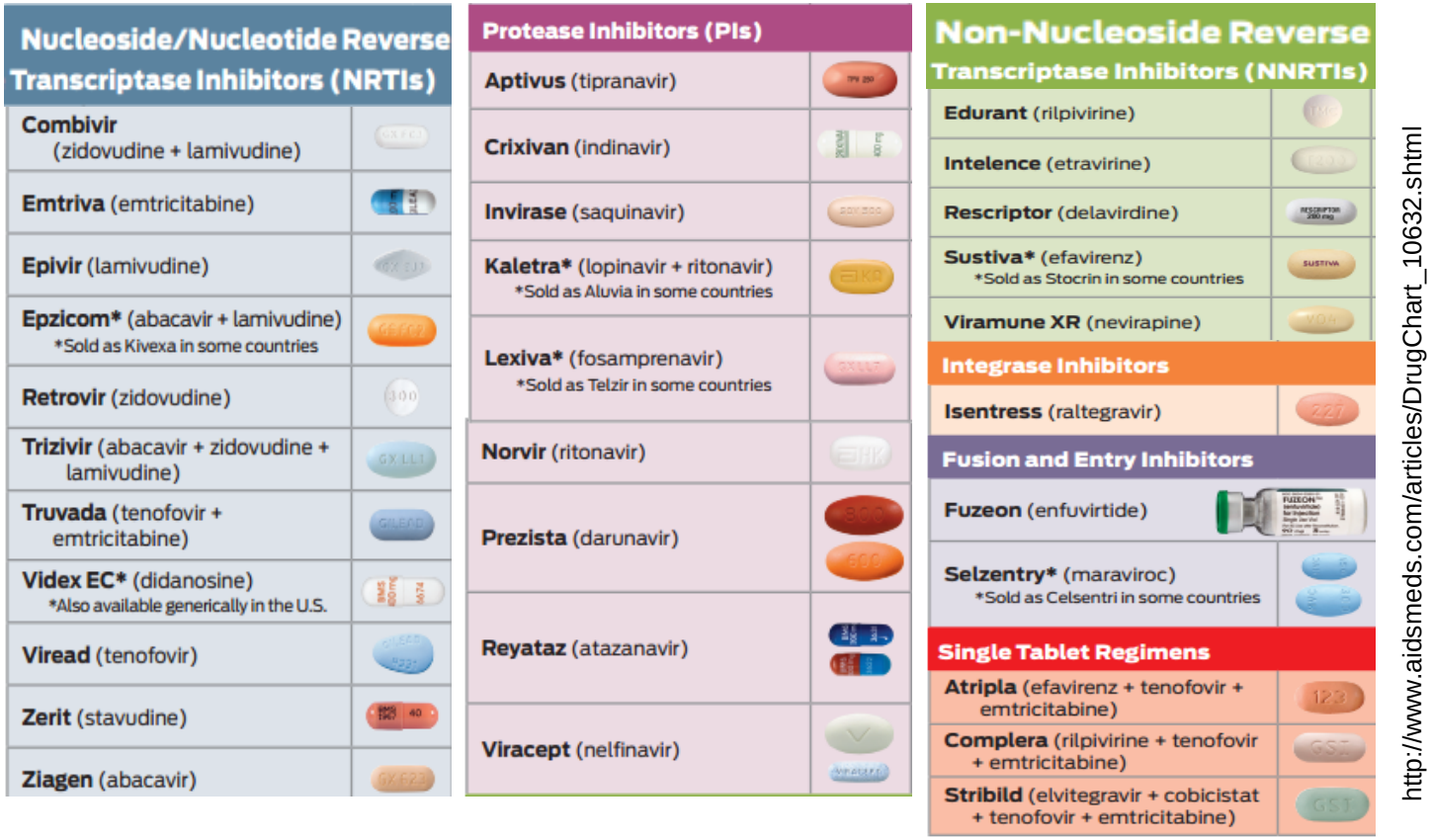
BRIEF HISTORY OF AIDS THERAPY

1981: First reported case of AIDS

- It has been estimated that more than 25 million people were killed since the HIV virus was first recognized.
- Estimated number of people living with the HIV virus is now over 40 million worldwide.



http://www.aidsmeds.com/articles/DrugChart_10632.shtml

2013: FDA has approved 37 drugs belonging to six different classes of anti-HIV inhibitors

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DRUG RESISTANCE AND NEW TARGETS

As a result of the high HIV-1 mutation rate or insufficient efficacy of chosen compounds combinations, drug resistant strains emerge, **resulting in therapeutic failure**.

New anti-HIV drugs are needed, which should represent novel chemical entities **targeting new steps of HIV** replication cycle.

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DRUG RESISTANCE AND NEW TARGETS

- **Inhibition of the Integrase Dimerization**
- **Inhibition of the Reverse Transcriptase Dimerization**
- **Inhibitors of HIV-1 RT competing with the nucleotide substrate.**
- **NCp7 Inhibitors**
- **Inhibition of a cellular cofactor (DDX3)**

By targeting cellular co-factors **essential for HIV** replication and whose inhibition is **not harming the uninfected cells**, drug resistance is less likely to occur.

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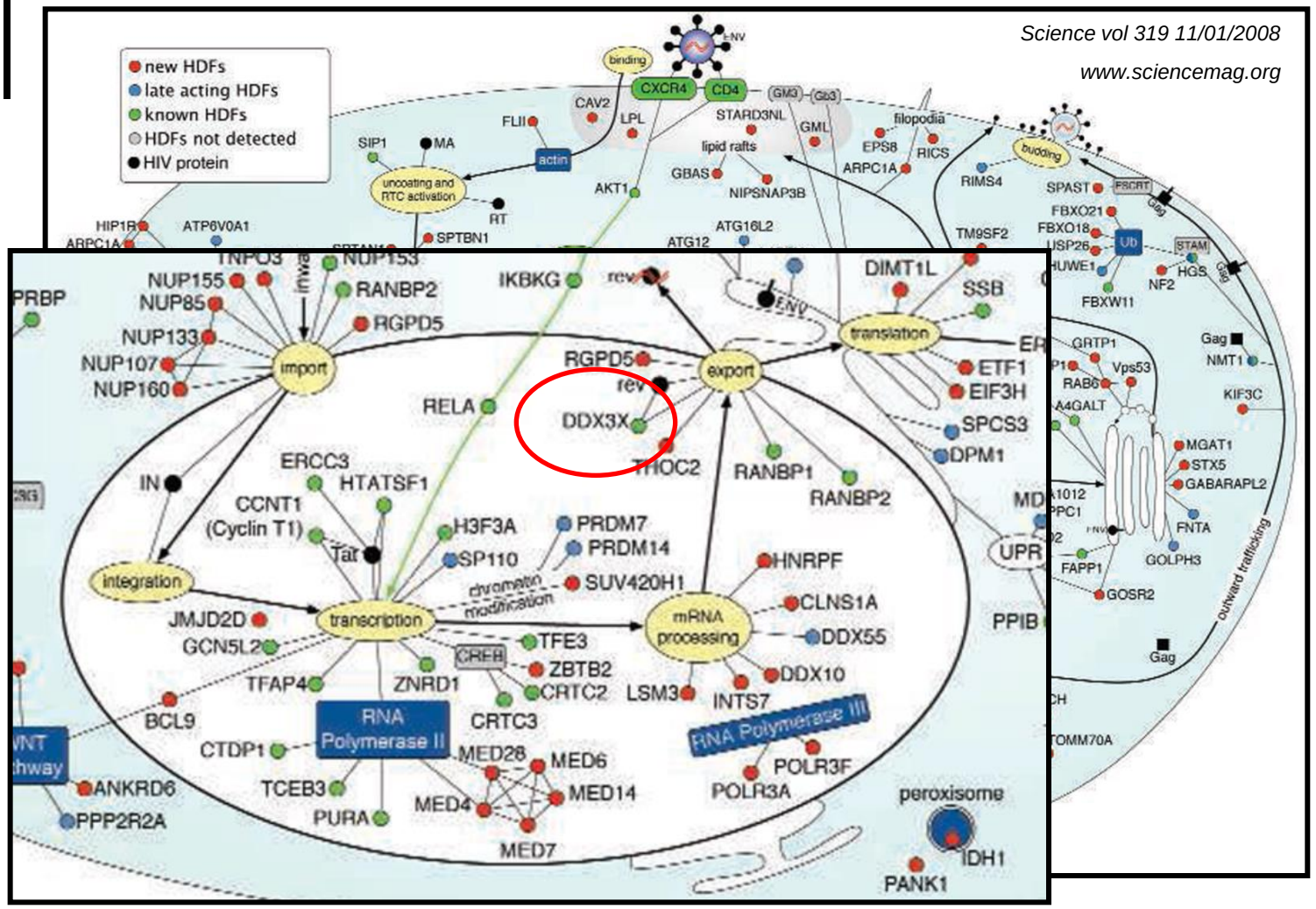
COMPLEX RELATIONSHIP

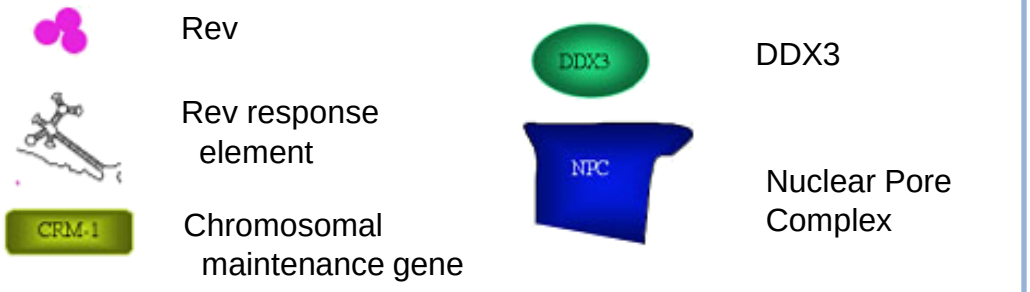


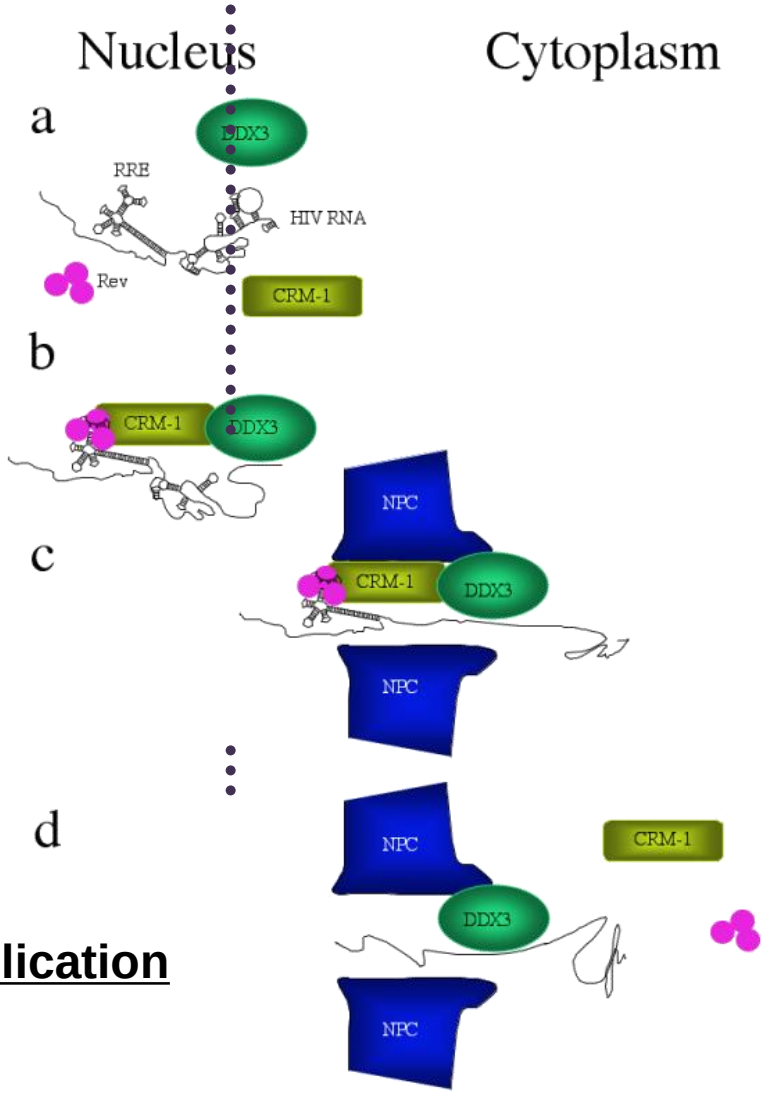
HIV relies on **more than 200 human proteins** to infect immune cells, enter the nucleus, integrate itself into the chromosomes, and then make copies of itself.

HDDX3 IN HIV-1

REV-RRE/CRM1 PATHWAY RNA EXPORT

a, Viral RNA develops a secondary structure before binding critical protein components of the export pathway. **b**, Rev protein binds the RRE, forming a complex of REV, viral RNA, CRM-I and DDX3, which begins to unwind the secondary structure. **c**, The export complex enters the nucleopore, where both CRM-I and DDX3 interact with nucleoporins. **d**, Even after CRM-I and Rev are released from the export complex, DDX3 may still pull RNA through the complex through its action.





knock-down of DDX3 are able to inhibit HIV replication without affecting cell viability

A. Dayton (2004): Within you, without you: HIV-1 Rev and RNA export. Retrovirology 2004, 1:35 doi:10.1186/1742-4690-1-35

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HUMAN DDX3 DEAD-BOX PROTEIN

The human DEAD-box RNA helicase DDX3 has been implicated to play a role in a whole repertoire of processes:

- RNA METABOLISM
- VIRAL REPLICATION
- INNATE IMMUNE SIGNALLING PATHWAYS
- CELL CYCLE CONTROL
- TUMORIGENESIS

DDX3 represents an attractive target for the treatment of cancer, viral diseases and autoimmune disorders

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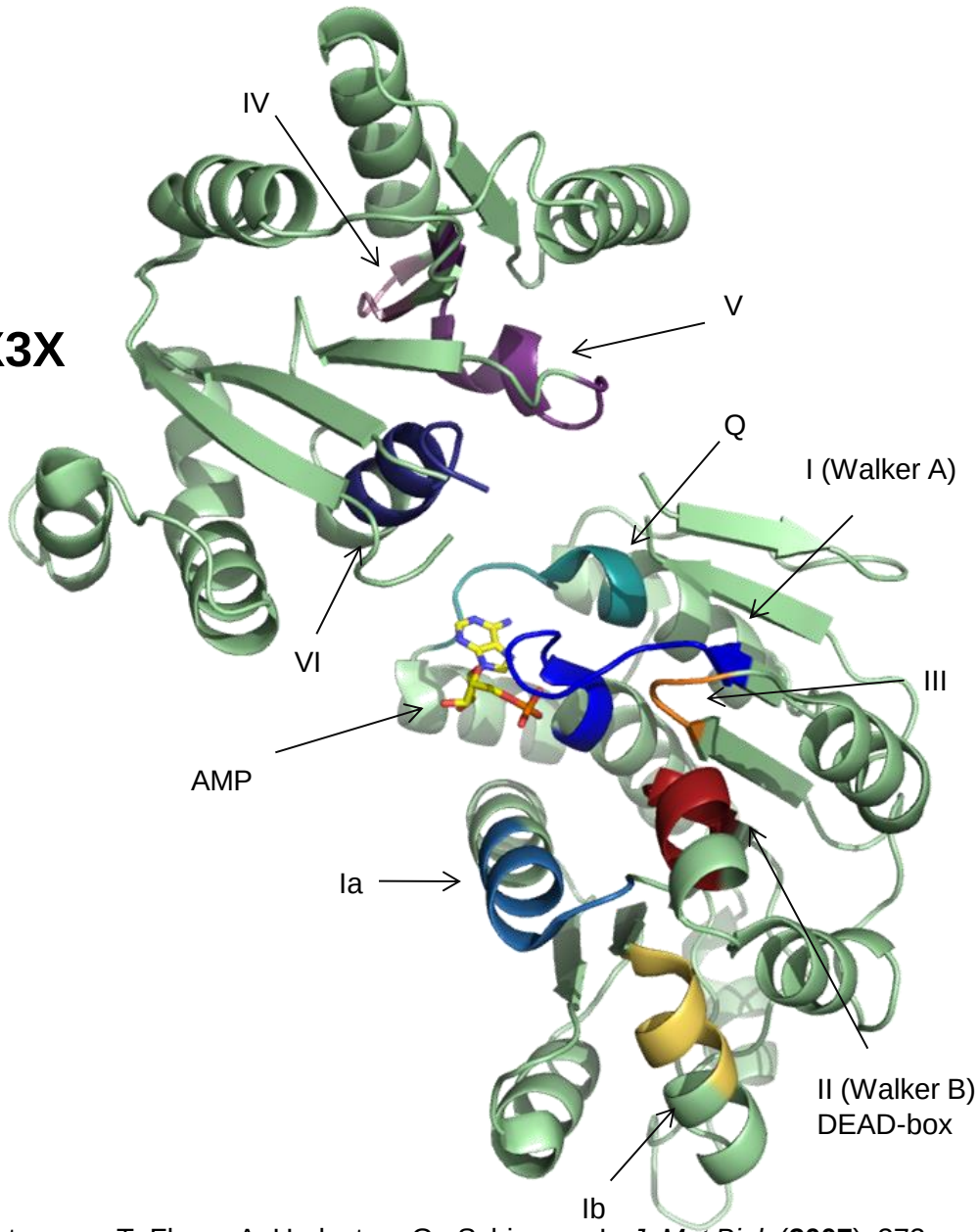
HUMAN DDX3
OVERVIEW

Human DEAD-box Helicase DDX3X
Crystal structure (PDB 2I4I)

- All nine conserved motifs characterizing SF2 RNA helicase family
- Two subdomains connected via a short flexible linker



Hogbom M, Collins R, van de BergS, Jenvert RM, Karlberg T, Kotenyova T, Flores A, Hedestam G, Schiavone L, *J. Mol.Biol* (**2007**), 372 150-159

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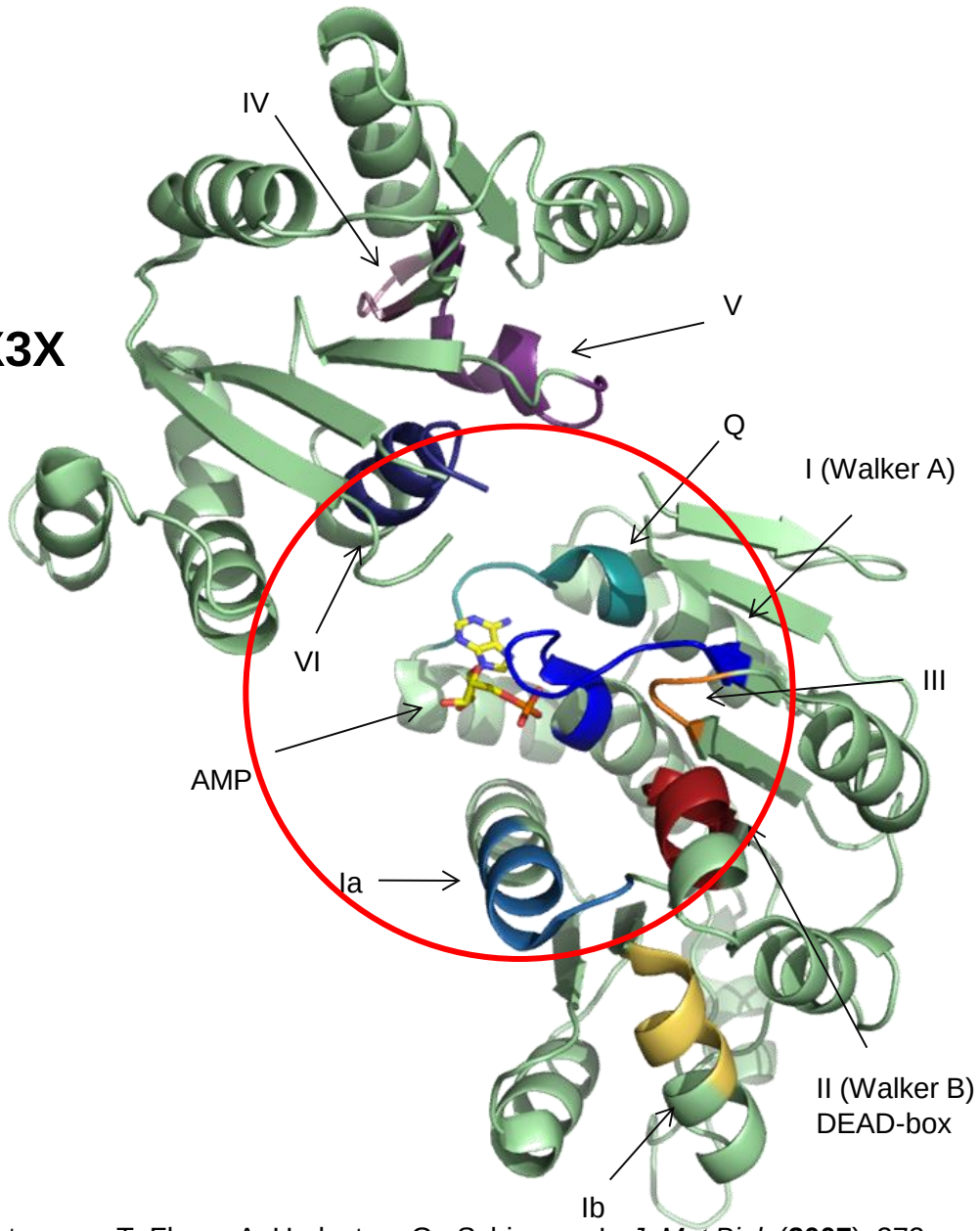
HUMAN DDX3
OVERVIEW

Human DEAD-box Helicase DDX3X
Crystal structure (PDB 2I4I)

- All nine conserved motifs characterizing SF2 RNA helicase family
- Two subdomains connected via a short flexible linker
- **ATPase binding site**



Hogbom M, Collins R, van de BergS, Jenvert RM, Karlberg T, Kotenyova T, Flores A, Hedestam G, Schiavone L, *J. Mol.Biol* (**2007**), 372 150-159

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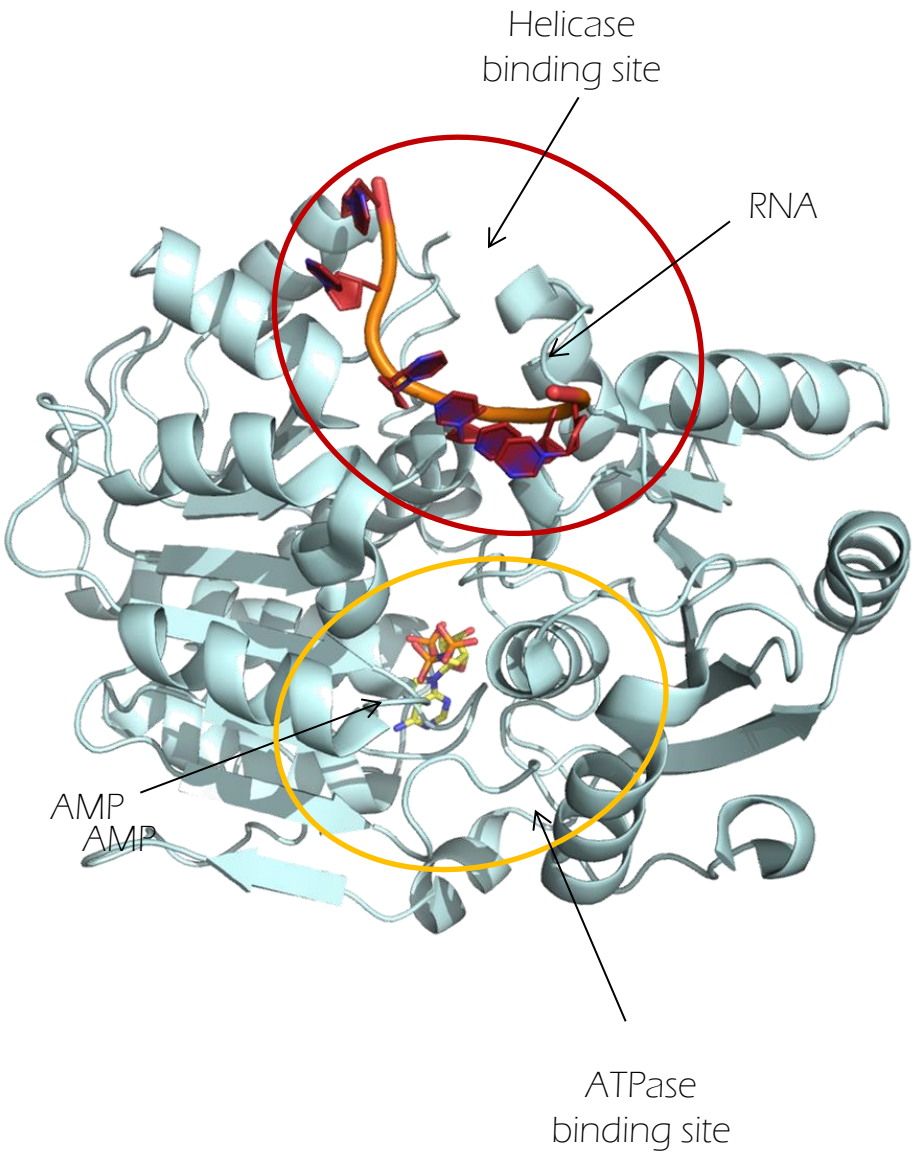
HUMAN DDX3

Drosophila Vasa DEAD-box protein
Crystal structure (PDB 2DB3)

- No hDDX3 crystal structure available for the closed conformation
- Two different active sites:
  - ATPase binding site
  - Helicase binding site



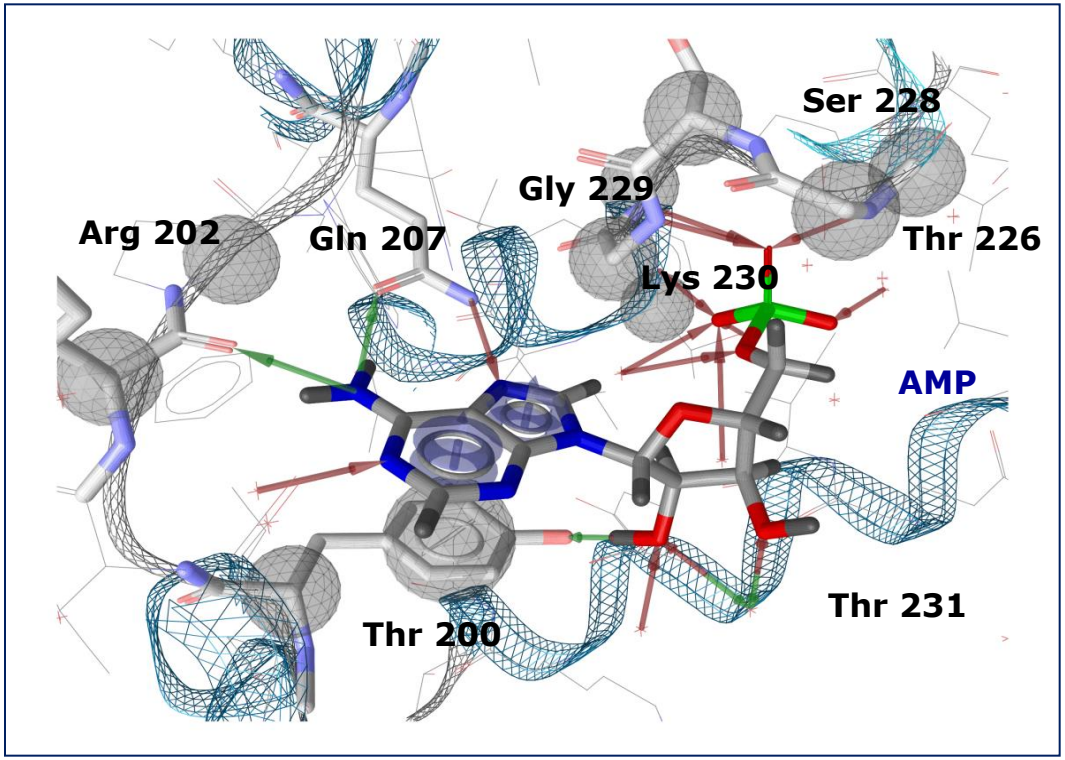
Sengoku T, Nureki O, Nakamura A, Kobayashi S, Yokoyama S, *Cell* ,125(**2006**) 287-300

STRUCTURE-BASED PHARMACOPHORE MODELING

The software **LigandScout** was used for the detection and interpretation of the **crucial interaction** pattern between **AMP** and the human protein helicase **DDX3** (PDB code *2I4I*).

In our study, **protein-ligand interactions** (the pharmacophore) identified by *LigandScout* were exported and translated into the *Catalyst* software.

The model obtained was then optimized by *Catalyst*.



Aromatic Ring violet

H-bond Donor green arrows

Volume Excluded grey spheres

H-bond Acceptor red arrows

\+ **Water**

Maga, G.; Falchi, F.; Garbelli, A.; Belfiore, A.; Witvrouw, M.; Manetti, F.; Botta, M. *J. Med. Chem.*; (Letter); **2008**; *51*, 6635–6638

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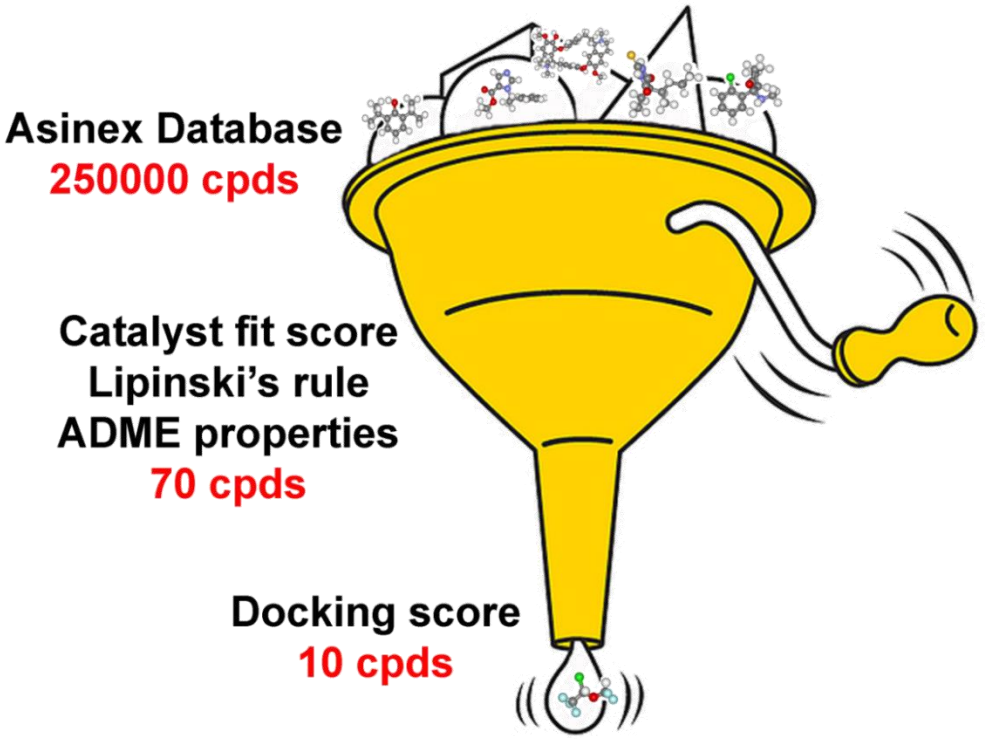
IN *SILICO* SCREENING

The **pharmacophoric model** was used as a 3D query to screen the **Asinex molecular database** with the software *Catalyst*.

Docking calculations were performed using the *software GOLD*, in order to rank compounds on the basis of their ability to form favorable **interactions with the ATP binding site.**



Lipinski's rules and **ADME properties** were also used as additional filters.

10 commercial compounds were selected.

Maga, G.; Falchi, F.; Garbelli, A.; Belfiore, A.; Witvrouw, M.; Manetti, F.; Botta, M. *J. Med. Chem.*; (Letter); **2008**; *51*, 6635–6638

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RESULTS

Compound ID	*Activity IC_{50} μM*
FE 1	**> 1000**
FE 2	**200**
FE 3	**> 1000**
FE 4	**> 1000**
FE 5	**> 1000**
FE 6	**300**
FE 7	**> 1000**
FE 8	**> 1000**
FE 9	**> 1000**
FE 10	**90**

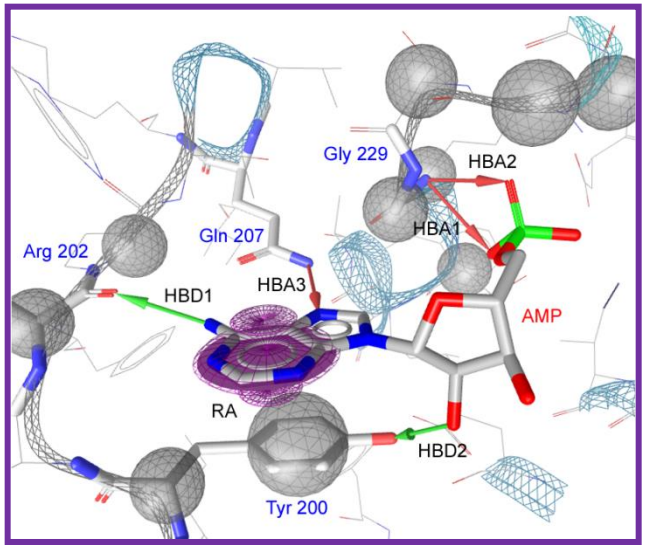
The **10 compounds** have been purchased from *Asinex* and submitted for **ATPase activity** assays on the hDDX3 protein.

The results on **enzymatic assays** are reported in the table.

FE10 has been selected as hit compounds for further optimization.

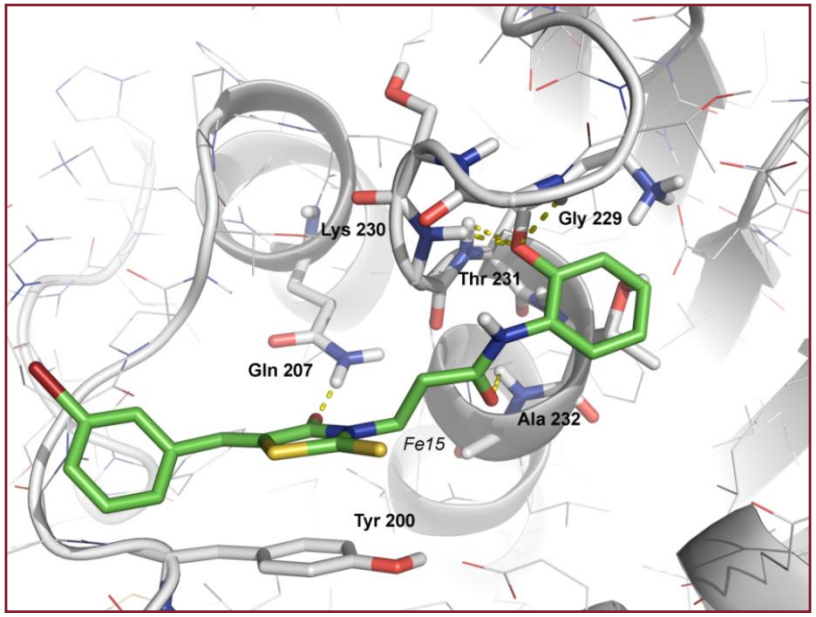
Maga, G.; Falchi, F.; Garbelli, A.; Belfiore, A.; Witvrouw, M.; Manetti, F.; Botta, M. *J. Med. Chem.*; (Letter); **2008**; *51*, 6635–6638

BINDING MODE



Excellent agreement with the Pharmacophore:

- **OH group** is in the position normally occupied by the **phosphate of ATP**
- **H-bond between** OH and Gly229
- **π - π Interaction**



Considerations:

- Replacement of the **2-OH group** with bioisosteric groups
- **Nitrogen alkylation** to give additional interactions in the "unoccupied space" of the site (Large improvement of the in silico score)

Maga, G.; Falchi, F.; Garbelli, A.; Belfiore, A.; Witvrouw, M.; Manetti, F.; Botta, M. *J. Med. Chem.*; (Letter); **2008**; *51*, 6635–6638

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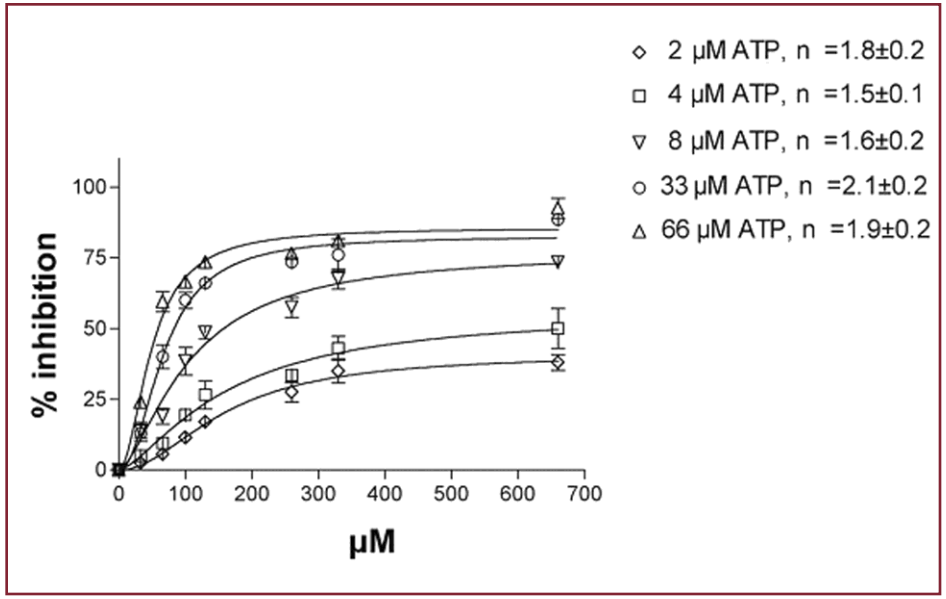
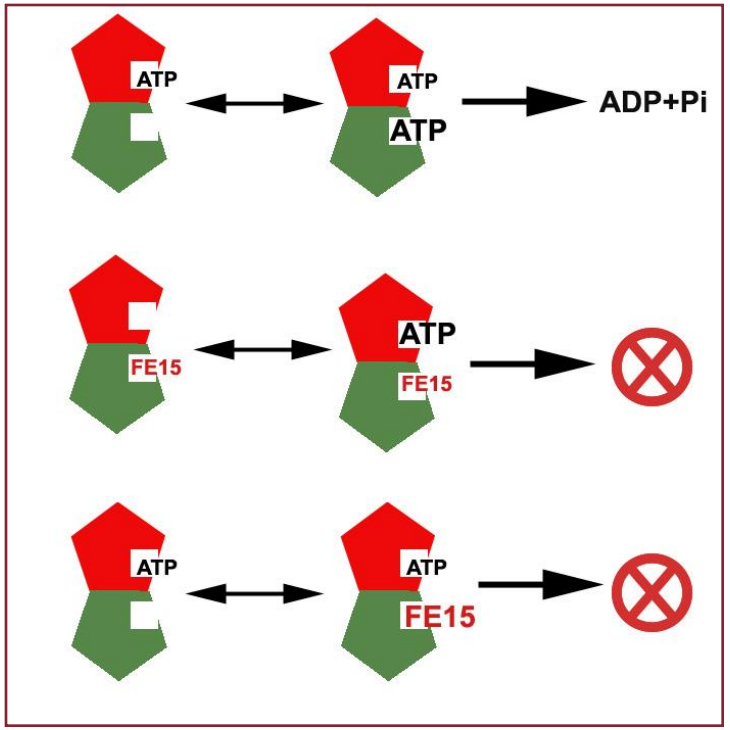
FE15 BIOLOGICAL DATA



Dose-dependent inhibition of the ATPase activity of human DDX3 by ***FE15*** at different ATP concentrations



Cooperative mechanism

Enzymatic inhibitory potency:

IC50 of 5.4 (μM). Inhibition of the ATPase activity changes as a function of the ATP concentration. These results suggested that ***FE15*** is a noncompetitive inhibitor. Probably DDX3 acts as a multimeric enzyme and the binding of the first ATP molecule causes cooperative binding of the second one.

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FE15 BIOLOGICAL DATA

Selectivity:
When tested up to 100 μM against **other ATP-dependent enzymes** (HCV/NS3 ATPase/helicase, T4 polynucleotide kinase, c-Src protein kinase), ***FE15*** did **not show inhibitory activity**.

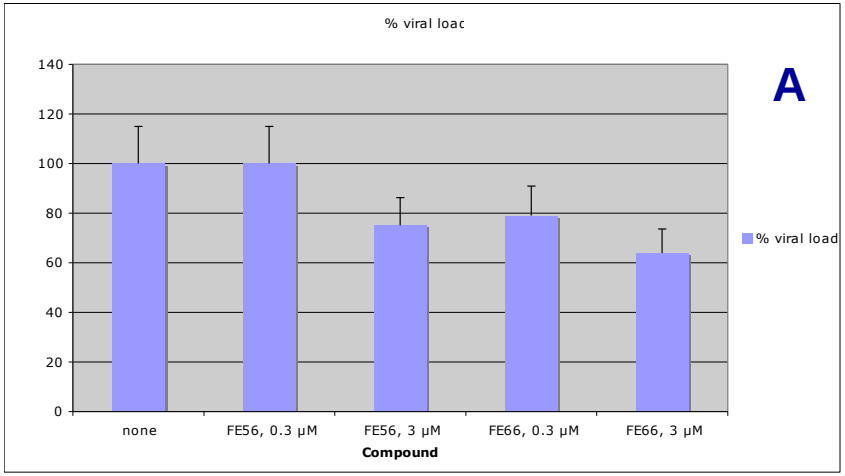
Cellular inhibitory potency:
FE15 inhibited the replication of **HIV-1(IIIB) in MT-4** cells with an **EC50 of 86.7 μM**, without showing cytotoxicity at 125 μM.
No toxicity up to 200 μM was found in **MOLT-4 T-lymphocytic cells** either.
The antiviral activity of ***FE15*** found in MT-4 cells was lower than the ATPase inhibitory effect observed in recombinant DDX3. This might be explained by its unfavorable pharmacokinetic properties.

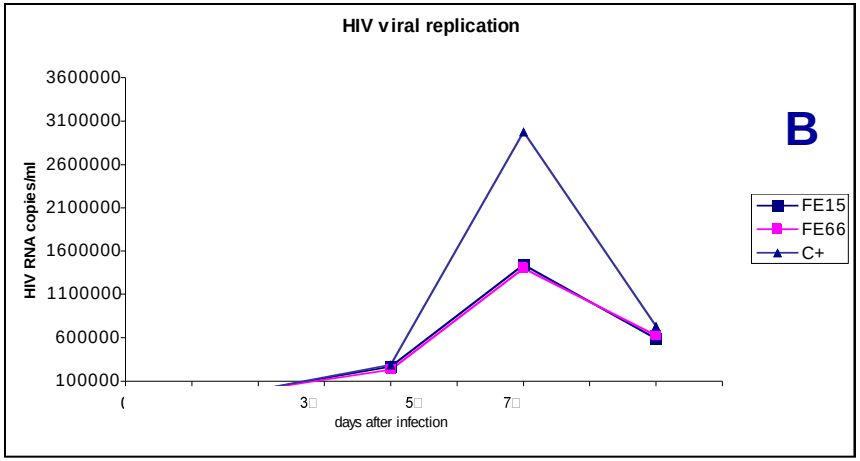
TARGET VALIDATION

FE15, ***FE56*** and ***FE66*** were tested against **HIV-1 replication** in two different model systems.

Figure A shows the effects of compounds ***FE56*** and ***FE66*** against HIV-1 single-round replication in *HeLaCD4+ cells* infected with a wild type HIV-1 strain. Data clearly showed a **dose-dependent reduction** of viral load (quantified as viral RNA copies), indicative of an inhibition of viral replication.

Figure B shows the effects of compounds ***FE15*** and ***FE66*** against multiple rounds of replication of wt HIV-1 in natural target cells (*Peripheral Blood Mononuclear Cell*). Data clearly showed a significative reduction of viral RNA at 7 days post infection.





Maga, G., Falchi, F., Radi, M., Botta, L., Casaluce, G., Bernardini, M., Irannejad, H., Manetti, F., Garbelli, A., Samuele, A., Zanoli, S., Esté, J. A., Gonzalez, E., Zucca, E., Paolucci, S., Baldanti, F., De Rijck, J., Debyser, Z. and Botta, M. (**2011**), *ChemMedChem*, 6: 1371–1389

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TODAY'S TALK

DDX3: a cellular target for next generation of broad spectrum antivirals

- Structure and functions
- ATPase Binding site
  - Virtual screening using structure-based pharmacophore models
- **Helicase Binding site**
  - **High-throughput docking**
- Antiviral activity data
- About Selectivity

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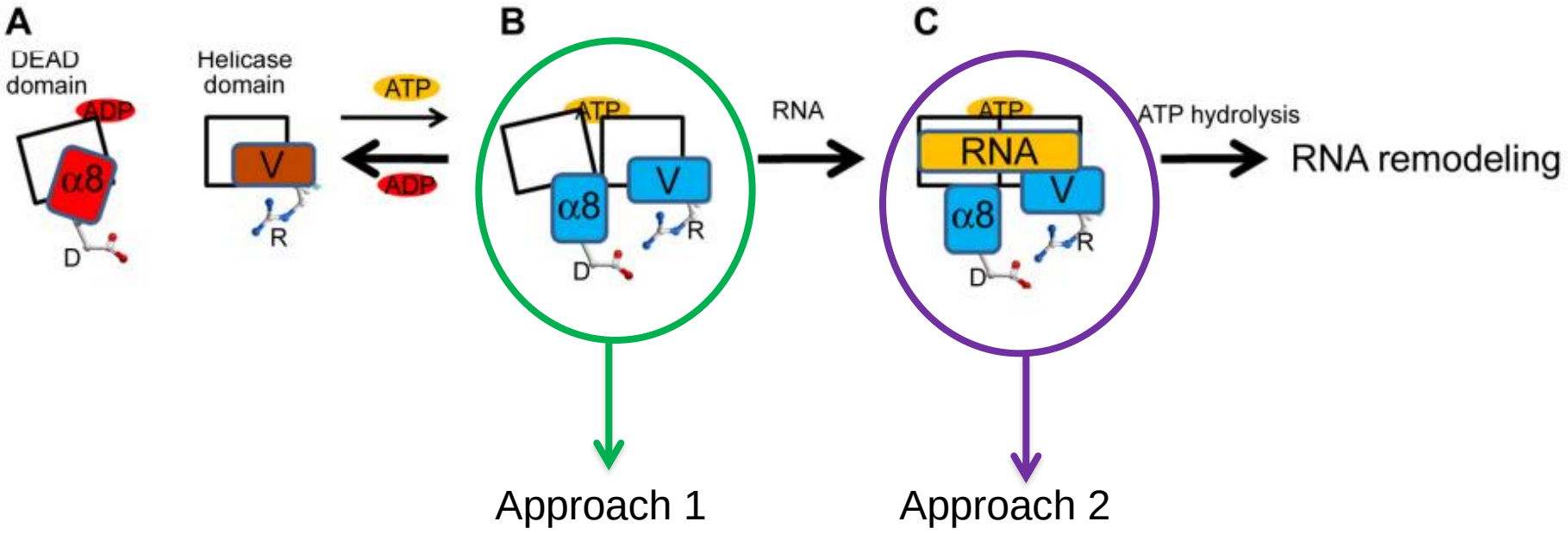
HUMAN DDX3

OPEN/CLOSED CONFORMATION THEORY

NO HUMAN DDX3 CRYSTAL STRUCTURE AVAILABLE FOR THE CLOSED CONFORMATION



Schütz P, Karlberg T, van de Berg S, Collins R, Lehtiö L, et al. *PLOS ONE* 5(9) (**2010**) e12791

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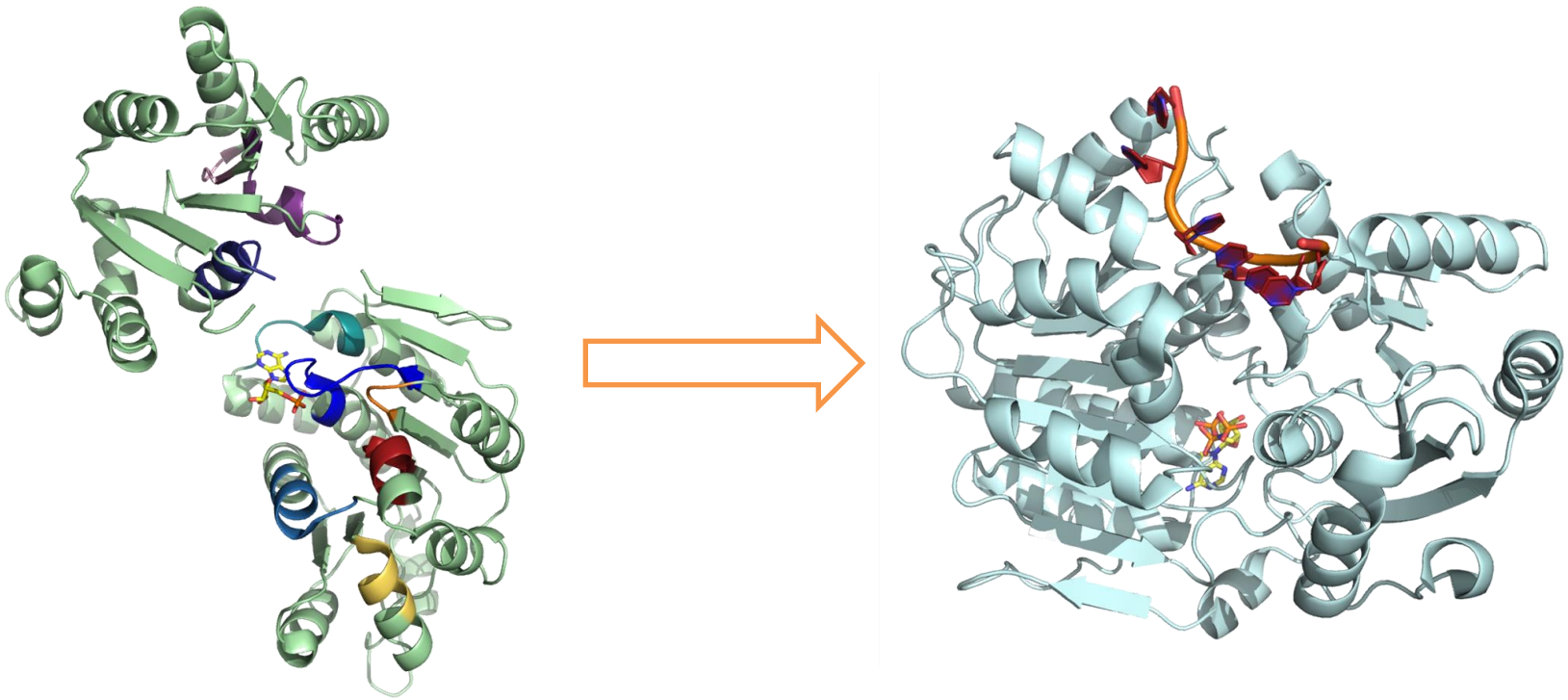
OPEN TO CLOSED CONFORMATION

DIFFERENT APPROACHES



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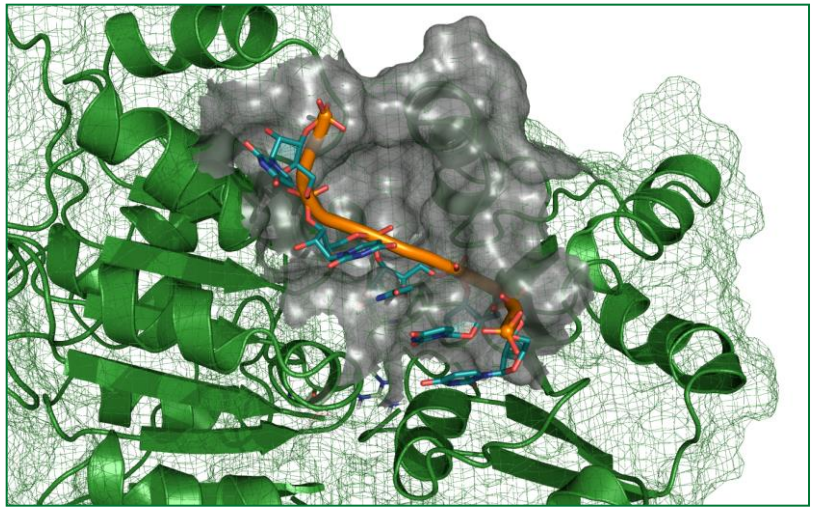
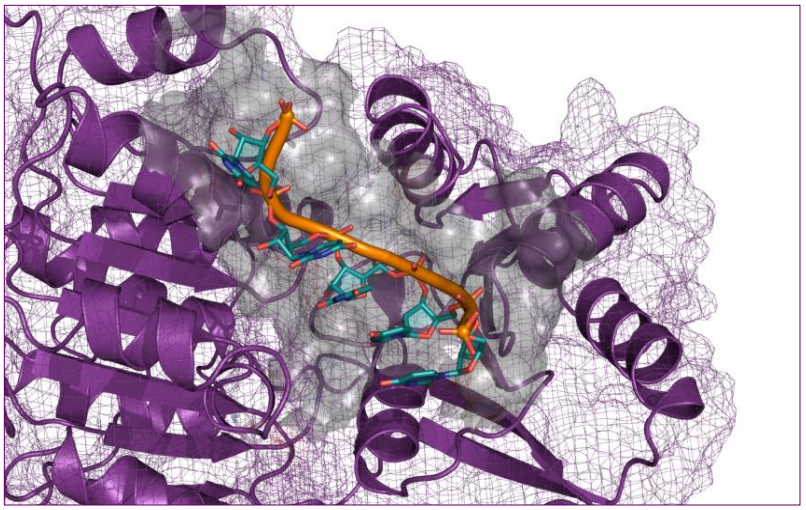
MODELS COMPARISON

HELICASE BINDING SITE





APPROACH 1:

- Not enough space for RNA strand

-- **Pre-RNA pocket**

APPROACH 2:

- RNA strand is perfectly placed in the pocket

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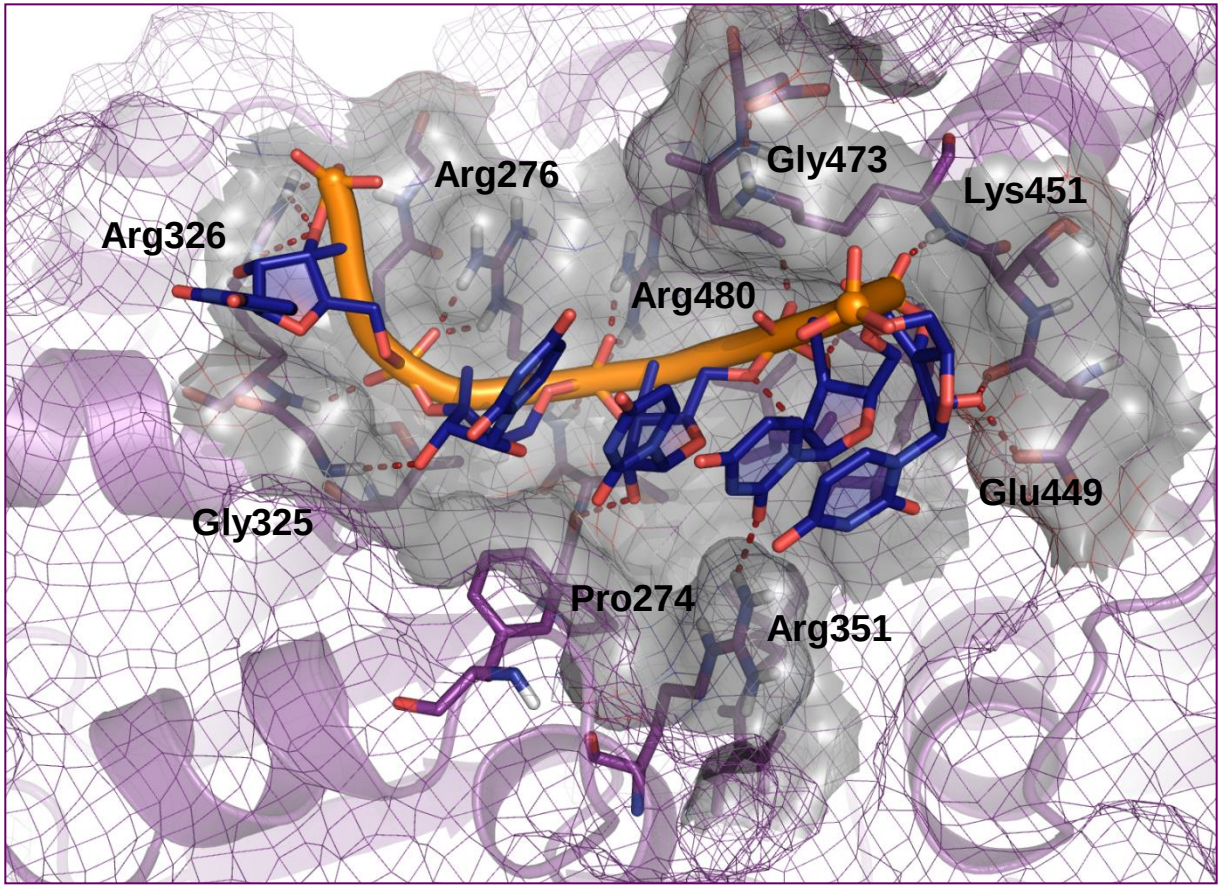
HELICASE BINDING SITE

RNA MAIN INTERACTIONS



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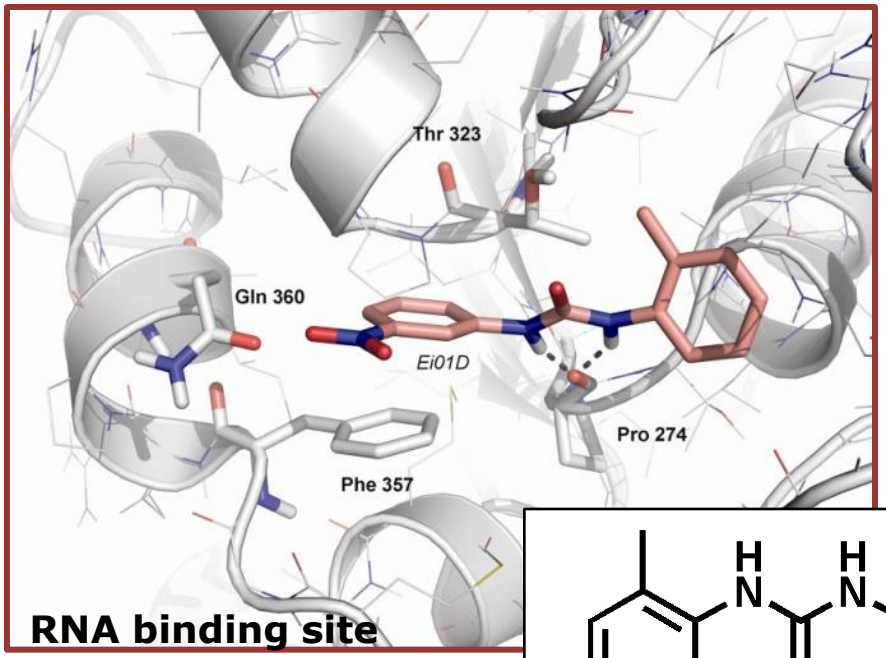
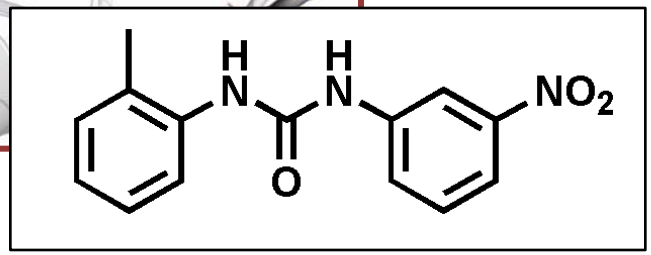
APPROACH 1

RESULTS





CMPD	ID_{50} (μM)
EI 01 A	131
EI 01 B	> 1000
EI 01 C	*
EI 01 D	**1**
EI 01 E	5.7
EI 01 F	52
EI 01 G	24
EI 01 H	> 1000
EI 01 I	> 1000

* NOT SOLUBLE

One of the tested compounds (***EI01D***) showed a good inhibition of helicase activity (**1 μm**) and showed an ATPase activity of **11 μm**.

Radi M, Falchi F, Garbelli A, Samuele A, Bernardo V, Paolucci S, Baldandi F, Schenone S, Manetti F, Maga G, Botta M, *Bioorg. Med. Chem. Lett*. 22 (**2012**) 2094-2098

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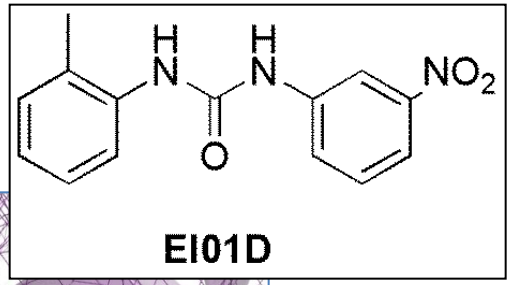
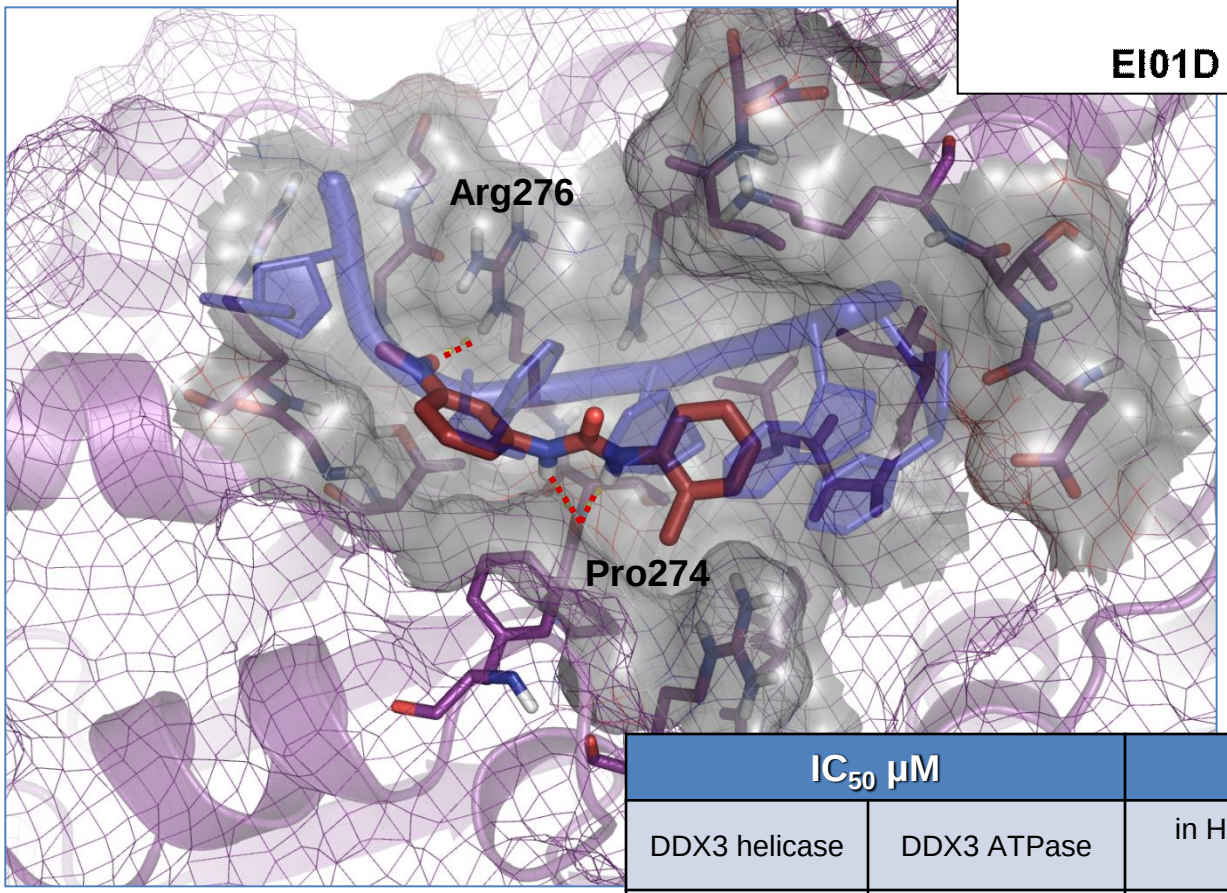
HELICASE BINDING SITE

EI01D MAIN INTERACTIONS



EI01D



IC_{50} µM		EC_{50} µM
DDX3 helicase	DDX3 ATPase	in HIV-1 infected PBMC cells
1 ± 0.2	20 ± 3	10 ± 1

Radi M, Falchi F, Garbelli A, Samuele A, Bernardo V, Paolucci S, Baldandi F, Schenone S, Manetti F, Maga G, Botta M, *Bioorg. Med. Chem. Lett*. 22 (**2012**) 2094-2098

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WORKFLOW
HIT TO LEAD OPTIMIZATION

EI01D-based Virtual library

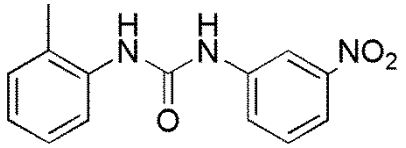
Docking

Biological Assay

Synthesis

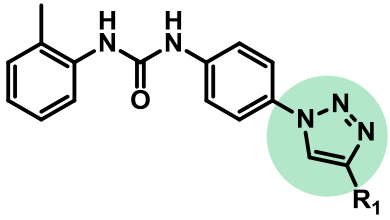
Table 1			
ID Cmpd	IC_{50} (μM)	ID Cmpd	IC_{50} (μM)
BA06	0.3	BA02	3.36
BA107	0.98	BA117	2.9
BA345	11	BA333	4.9
BA329	0.94	BA353	1.47
BA103	0.3	MG162	1

SYNTHESIS OF NEW POTENTIAL INHIBITORS



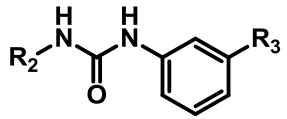
EI01D

HIT COMPOUND



Introduction of a **triazole ring**

Substitutions on the two phenyl scaffolds



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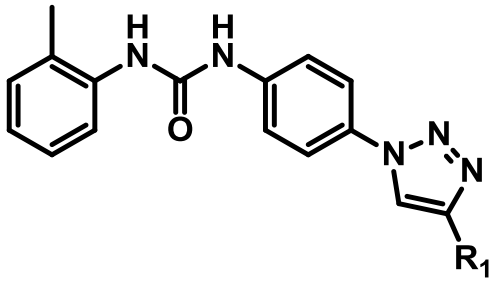
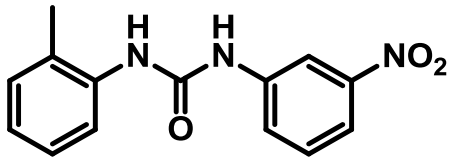
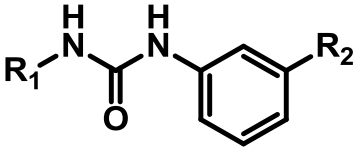
DDX3 ACTIVITY





EI01D



DDX3 activity		
Cmpd.	R_1	IC_{50} [a,b] (μM)
BA 1	-phenyl	n.d
BA 2	-*t*butyl	3.36
BA 3	-CH_2OH	17.5
BA 6	**-butyl**	**0.3**
BA 7	-$CH_2N(CH_3)$benzyl	22.8

[a]Data represent mean two values of the least two experiments; [b] IC_{50}: inhibiting concentration 50 or needed concentration to inhibit 50% of the enzyme.

DDX3 activity			
Cmpd.	R_1	R_2	IC_{50} [a,b] (μM)
BA 4	naphtyl	NO_2	145
BA 5	cycloexyl	NO_2	>200
BA 9	tolyl	COOH	>200
BA 10	tolyl	COOEt	71.6
EI01D	tolyl	NO_2	1 ± 0.2

[a]Data represent mean two values of the least two experiments; [b] IC_{50}: inhibiting concentration 50 or needed concentration to inhibit 50% of the enzyme.

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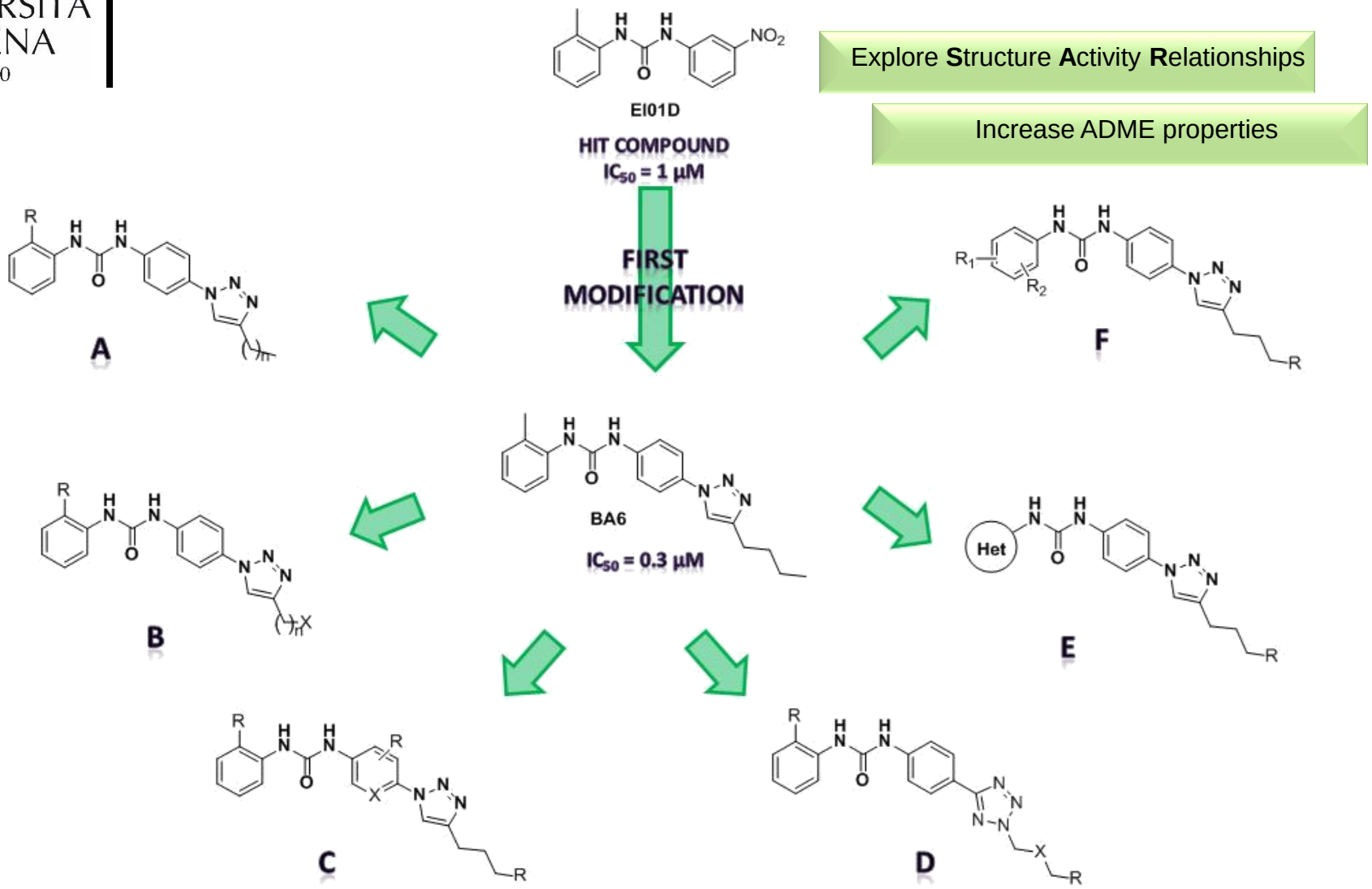
HIT TO LEAD OPTIMIZATION

Explore **S**tructure **A**ctivity **R**elationships

Increase ADME properties



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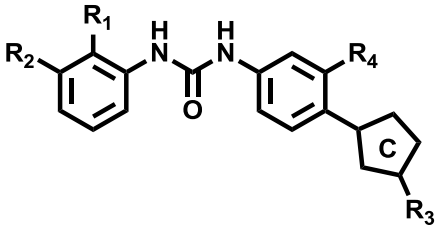
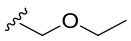
In vitro ADME Studies



✓**GOOD METABOLIC STABILITY** has been obtained (about 98% in human microsomes)

Cmpd ID	Structure					Papp *10-6 (cm/s)	Aq. Solub. (µg/mL)		QP Pred.
	R1	R2	R3	R4	C	GI (RM%)	Kin.	LogS	LogS
BA 6	**CH_3**	**H**	**butyl**	**H**	**triazole**	**2.86 (19.1)**	**0.135**	**-7.05**	**-6.4**
BA 345	CH_3	H	isopentyl	H	triazole	1.93 (26.7)	<0.001	<-8.6	<-6.7
BA 544	CH_3	Cl	isopentyl	H	triazole	2.51 (59.1)	<0.001	<-8.6	-7.3
BA 119	CF_3	H	butyl	F	triazole	7.22 (30.4)	80.11	-6.4	-7.3
BA 103	CF_3	H	butyl	H	triazole	7.47 (23.9)	0.107	-7.43	-7.1
BA 526	CF_3	H	isopentyl	H	triazole	7.41 (24.8)	0.002	<-8.6	-7.5
BA 333	CH_3	H	butyl	H	tetrazole	7.57 (24.8)	<0.001	<-8.5	-5.74
BA 329	**CH_3**	**H**		**H**	**triazole**	**0.69 (7.4)**	**26.27**	**-4.3**	**-5.12**

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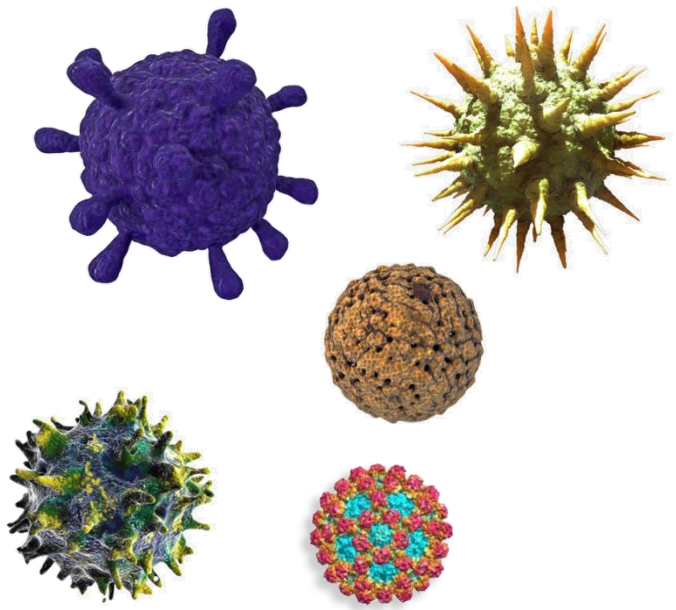
DDX3 IN VIRAL INFECTIONS

DDX3 is not only involved in HIV replication. During these three years, publications have increased substantially (30/46) and showed that DDX3 is **involved in several viral infections.**



HCV: interacts with HCV core protein which is used by virus to build its nucleocapsid.

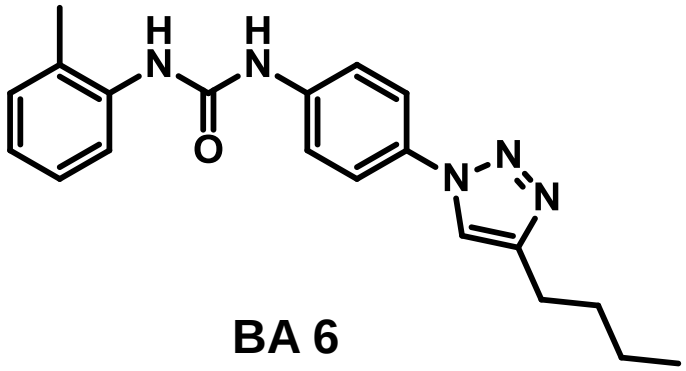
Japanese Encephalitis V: binds the viral RNA during viral replication.

Poxvirus: binds K7 protein, essential to overcome the IFN-mediated cellular response.

West Nile V, Dengue V: unknown mechanism

Yedavalli et al. **2004** *Cell* 119(3):381-92; Owsianka AM, Patel AH, **1999** *Virology*. 257(2):330-40;Ward et al. **2011** *RNA Biol*. 8(6):1173-86; Chahar et al. **2013** *Virology* 436(1):1-7; Mao et al. **2014** *Virology* 449:70-81; Goodfellow et al. **2012** *J Virol*. 86(22):11977-9; Oda et al. **2009** *Structure* 17(11):1528-37; Ishaq et al. *Mol Biotechnol*. **2008**; 39:231-8.

BA6 ACTIVITY PROFILE

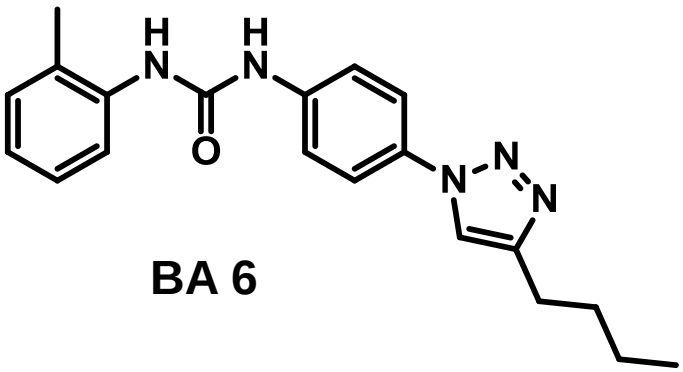


BA 6

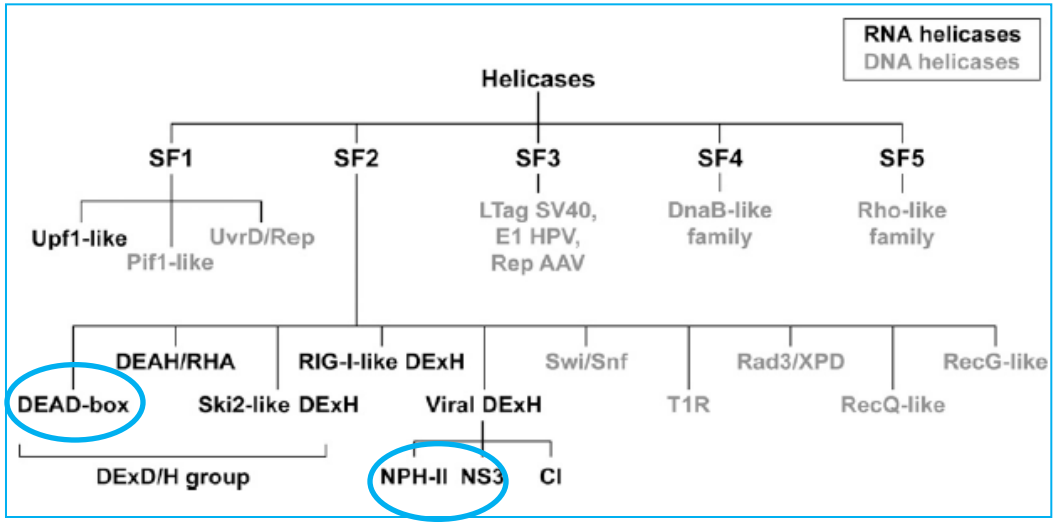
Cmpd ID	DDX3 (μM)	HIV [a] (μM)	HCV [b] (μM)	JEV [c] (μM)	WNV [b] (μM)	Dengue [b] (μM)
BA6	0.3	1.1	0.97	20	16.05	2.55

a. PBMC: Peripheral Blood Mononuclear Cells; **b. Huh7**: Hepato cellular carcinoma cells; **c. BHK-21 cells:** Baby hamster kidney cells

BA6 SELECTIVITY PROFILE



BA 6



DDX3 is a member of SF2 RNA helicases family (the same of NS3 viral helicases), however compound BA6 **showed a good selectivity profile**.

ATPase DDX3 IC_{50}, µM	**DDX1 IC_{50}, µM**	**NS3 (DENV) IC_{50}, µM**	**NS3 (HCV) IC_{50}, µM**
>200[a]	>200	>200	16.8

[a] The value >200 indicates that less than 20% of inhibition was observed at 200 µM, the highest concentration tested.

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DDX3 VS VIRUSES

Human Immunodeficiency Virus-1 Resistant Strains

The antiviral activity of BA6 was investigated against HIV-1 strains carrying the most common patterns of resistance mutations selected by drugs currently used to treat HIV-1 infection.

HIV-1 STRAIN[a]	DRUG RESISTANCE CLASS[b]	IC_{50} [95% CI] (μM)	Fold change[c]
114[d]	**wild type**	1.11 [0.31-3.90]	/
11808	**PIs**	0.23 [0.08-0.65]	0.2
7406	**NRTIs**	0.33 [0.13-0.87]	0.3
7404	**NRTIs**	0.22 [0.11-0.47]	0.2
12227	**NNRTIs**	0.94 [0.21-1.34]	0.8
12235	**NNRTIs**	0.36 [0.15-0.87]	0.3
11845	**INIs**	0.37 [0.26-0.52]	0.3

[a] NIH AIDS Reagent Program catalogue number (www.aidsreagent.org). [b] PIs: protease inhibitors; NRTIs: nucleos(t)ide reverse transcriptase inhibitors; NNRTIs: non nucleos(t)ide reverse transcriptase inhibitors; INIs: integrase inhibitors. [c] Resistant strain IC50 to wild type strain IC50 ratio. [d] NL4-3 HIV-1 wild type reference strain.

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Compound BA6 **retained full activity** against all the resistant viruses tested, confirming its **novel mechanism of action** and the potential to **overcome HIV resistance**		0.23 [0.08-0.65]	0.2
		0.33 [0.13-0.87]	0.3
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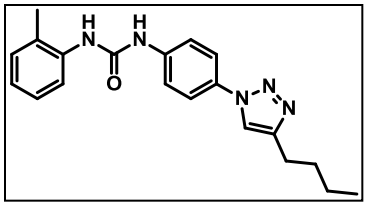
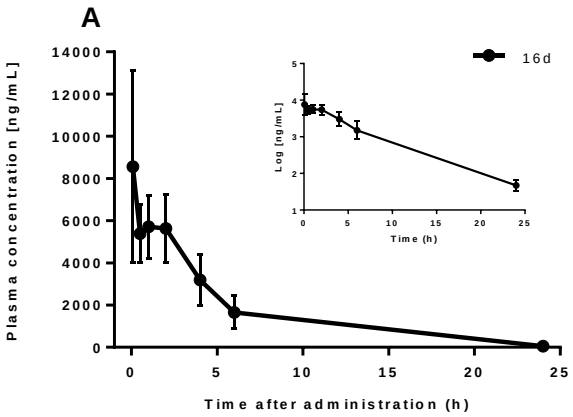
IN VIVO PRELIMINARY STUDIES
PK studies

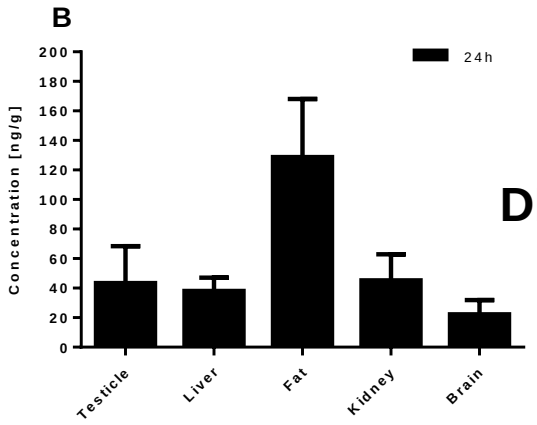
PHARMACOKINETIC PARAMETERS	BA6[A]
Dose (mg/kg)	10.00
MRT (h)	3.98 ± 0.38
AUC $_{0-\infty}$ (µg*h/mL)	39.95 ± 13.50
AUC $_{0-24}$ (µg*h/mL)	39.77 ± 13.51
CL (mL/min)	1.29 ± 0.54
$T_{1/2\,\beta}$ (h)	3.19 ± 0.24

[a] All data are expressed as mean ± SD (n=3); MRT mean residence time, AUC $_{0-\infty}$ and AUC $_{0-24}$ area under the plasma concentration - time curve, CL plasma clearance, $T_{1/2\,\beta}$ plasma half-life.

Pharmacokinetic parameters of **BA6** after intravenous administration at a dose of **10mg/Kg**.



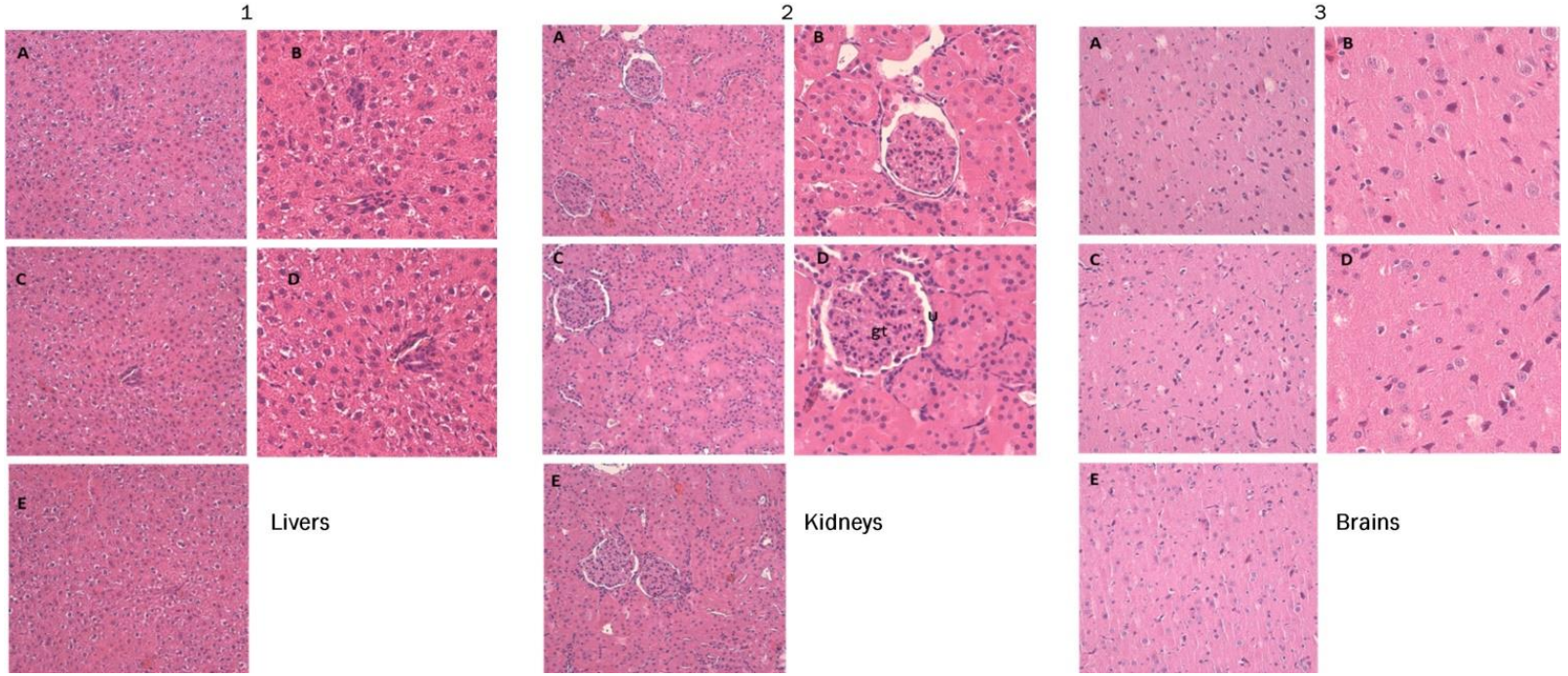




TISSUE DISTRIBUTION

IN VIVO PRELIMINARY STUDIES
Toxicity assays

BA6 was administered to Wistar rats via tail vein in a single systemic dose of **20 mg/kg**



Representative images of the histological examination of HE-stained sections of livers (1), kidneys (2), and brains (3) from three groups of rats. **A-B**: Vehicle group, **C-D**: Treated group, **E**: Wilde Type group. Treated rats does not exhibit abnormal histopathological changes compared with control group. The microphotographs were taken using digital camera (Nikon SLR-D3000) at original magnification of 100X & 200X.

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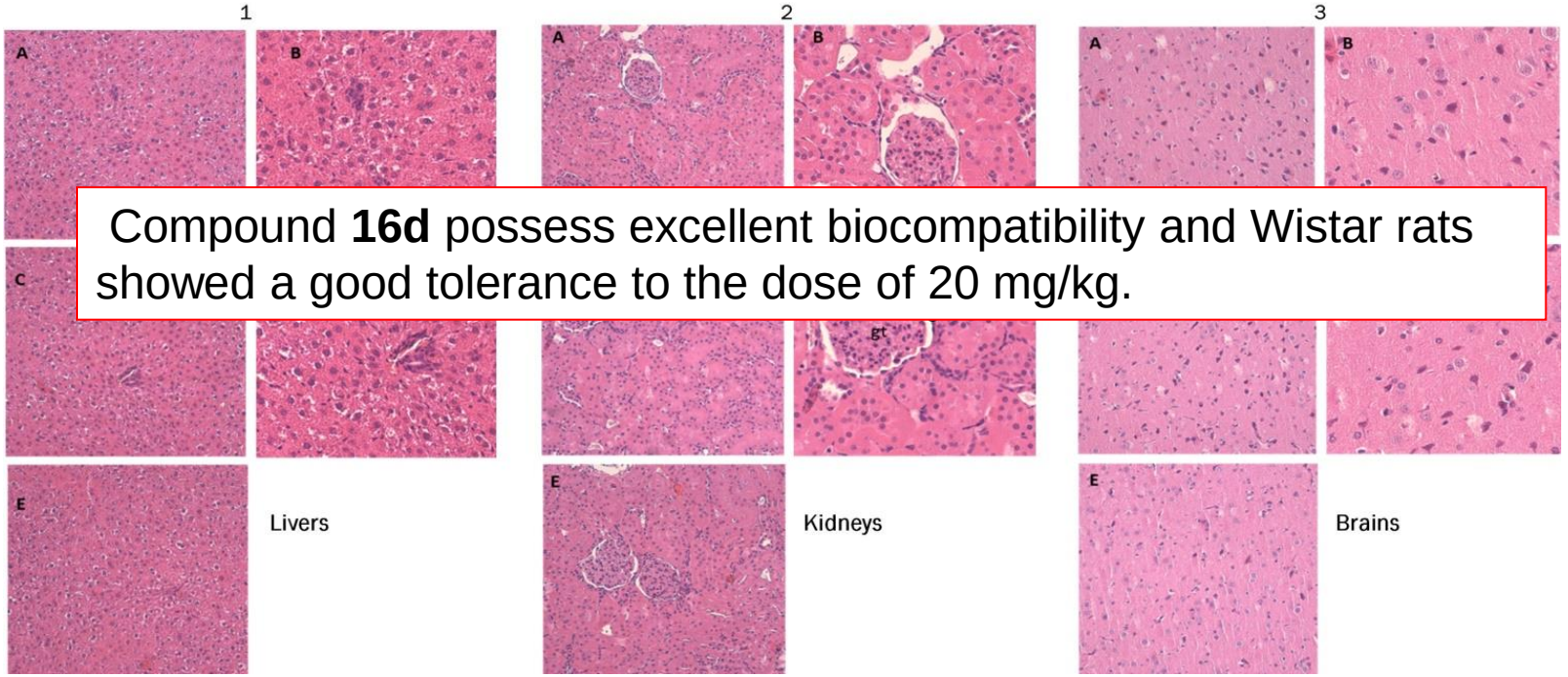

Compound **16d** possess excellent biocompatibility and Wistar rats showed a good tolerance to the dose of 20 mg/kg.

Representative images of the histological examination of HE-stained sections of livers (1), kidneys (2), and brains (3) from three groups of rats. **A-B**: Vehicle group, **C-D**: Treated group, **E**: Wilde Type group. Treated rats does not exhibit abnormal histopathological changes compared with control group. The microphotographs were taken using digital camera (Nikon SLR-D3000) at original magnification of 100X & 200X.

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CONCLUSIONS

✓ Discovery of **first small molecules** able to target **either one of the active sites** and inhibit DDX3 activity

✓ For the first time, DDX3 inhibitors proved to be active against **different type of viruses**

Cmpd ID	DDX3	DDX1	HIV	HCV	JEV	DENV	WNV
BA06	0.3	n.a*	1.1	0.97	20	2.55	16.05
BA103	0.3	n.a*	-	0.3	-	0.74	1.12
BA335	0.4	n.a*	26	-	6.09		
BA333	4.9	n.a*	5.2	7.16	7.12		

*n.a: not active

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Anticancer activity

Since DDX3 is overexpressed in several aggressive cancers (lung cancer, prostate cancer, breast cancer) our DDX3 inhibitors have been sent for biological evaluation.

We have just received very interesting data that will be reported in due course.

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Finding a drug is a complex combination of many disciplines such as structural biology, molecular biology, synthetic chemistry, computational chemistry, physical chemistry, pharmacology and medicine.

Only a good collaboration can drive the work to the final goal.

Maurizio Botta

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Prof. Miguel A. Martinez

Nanjing Agricoltural University:
Prof. Xiang Mao

Universitat Pompeu Fabra
Prof. A. Meyerhans
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Dr. Cristina Tintori
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Dr. Annalaura Brai
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Dott. Simona D'Amato
Dott. Deborah Sementa
Dr. Claudio Zamperini

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CHAARM project

Regione Toscana

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Thank you for your kind attention!!!

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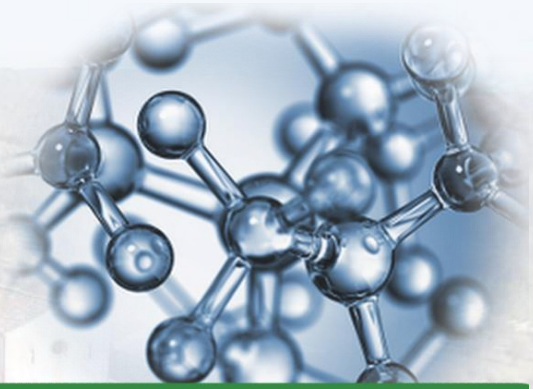
VI EWDSy

European workshop in drug synthesis



Società Chimica Italiana
Divisione di
Chimica Farmaceutica

THINPAD

VERTEX
THE SCIENCE of POSSIBILITY

Certosa di Pontignano, Siena, May 15th-19th 2016

- Dedicated to researchers from Universities and Pharmaceutical Industries
- Participation to EWDSy is limited to 65 attendants
- Fee for participation will include all meals and hotel accomodation for 4 nights/5 days

FELLOWSHIPS ARE AVAILABLE!

This year, the workshop will be focused on:

- Novel Synthetic Procedures in Medicinal Chemistry
- ADMET
- HIV Research
- Neglected Diseases

For info and registration: **www.ewdsy.it** **ewdsy.siena@gmail.com**

VI EWDSy VI European workshop in drug synthesis

The following eminent scientists already accepted to lecture:

Alan Kozikowski - University of Illinois, Chicago (USA)

Christian Ottmann - Eindhoven University of Technology (Netherlands)

Dennis Liotta - Emory University (USA)

Dieter Schinzer - University of Magdeburg (Germany)

Fernando Albericio - IRB, Barcelona (Spain)

Gabriele Cruciani - Università di Perugia (Italy)

Helena Danielson - Uppsala University (Sweden)

Hugo Kubinyi - BASF SE and University of Heidelberg (retired) (Germany)

Karl-Heinz Altmann - ETH (Switzerland)

Katherine L. Seley-Radkte - University of Maryland, Baltimore Co. (USA)

Kevin Burgess - Texas A & M University (USA)

Maria José Camarasa - Consejo Superior de Investigaciones Científicas (Spain)

Markus Kalesse - Leibniz Universität Hannover (Germany)

Matteo Zanda - University of Aberdeen (UK)

Paolo Melchiorre - ICIQ (Spain)

Stephen Hanessian - University of Montreal (Canada) and University of California (USA)

Stephen Neidle - University College, London (UK)

Thierry Langer - University of Vienna (Austria)

Ulrike Holzgrabe - University of Würzburg (Germany)

William Jorgensen - Yale University (USA)

Youssef Bennani - Vertex Pharmaceuticals (Canada)

Yves Mely - University of Strasbourg (France)

For info and registration: **www.ewdsy.it** **ewdsy.siena@gmail.com**