L’innovazione tecnologica nella discovery di nuovi farmaci

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Istituto Italiano di Tecnologia
Genoa, Italy

Bergamo - 2019

IIT – Mission and Network

Italian Institute of Technology

Istituto Italiano di Tecnologia
promotes excellence in fundamental and applied research,
develops higher education in the area of science and technology and fosters the evolution
of industry towards the forefront areas of technological innovation.

Genova Central Research Lab

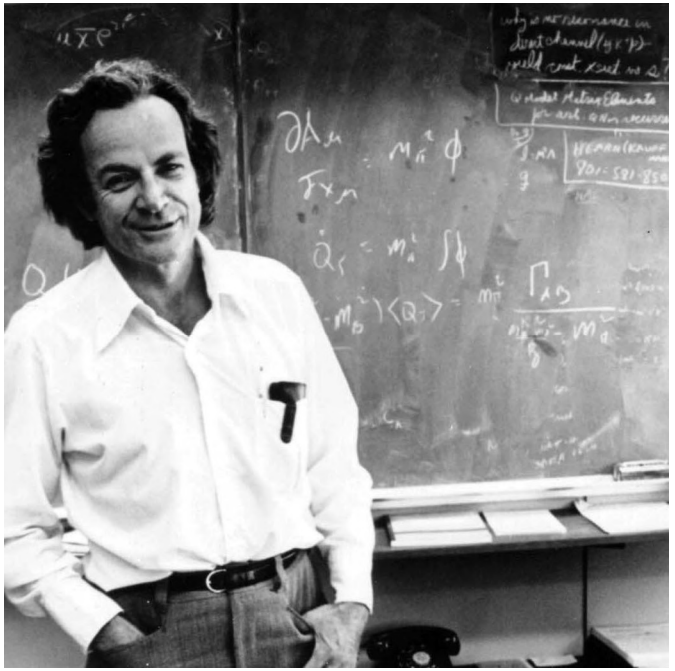
32.000 sqm, fully equipped, one of the largest single-site labs in Europe

Atomi e molecole… per la vita

"Everything that living things do can be understood in terms of the jiggling and wiggling of atoms"

"Tutto cio' che gli esseri viventi fanno puo essere compreso dal dondolare e agitarsi degli atomi"

Richard Feynman (Premio Nobel, '65), dalle sue famose lezioni di fisica nel 1963



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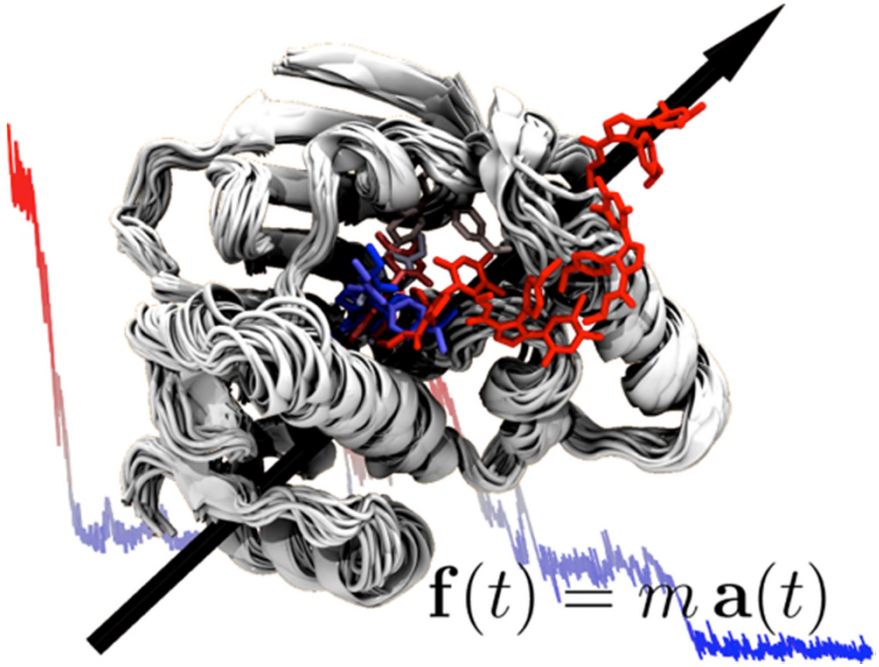
Molecular Simulations



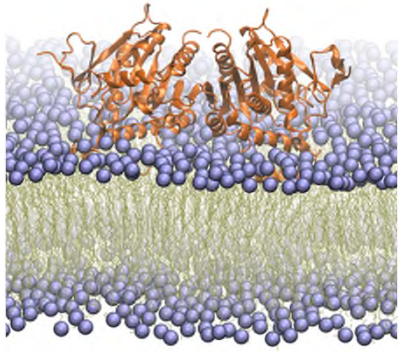
From protein function to drug discovery

www.devivolab.org

Catalysis & Drug Discovery

Computations

Membrane-bound proteins

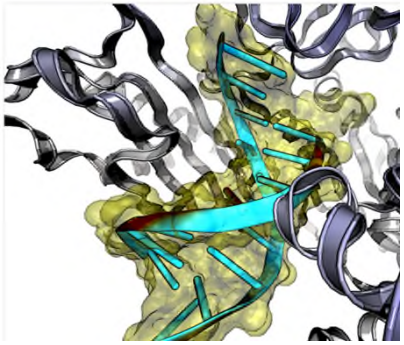


BBA Mol Cell Biol **2017**

Signaling in proteins

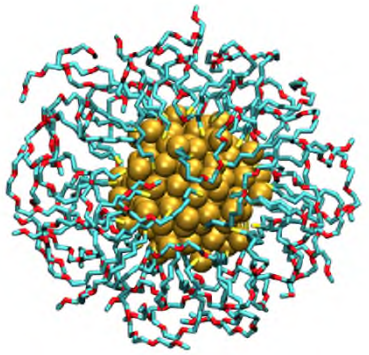
ACS Cent Sci **2017**

DNA/RNA and metalloenzymes



JACS **2016, 2018**

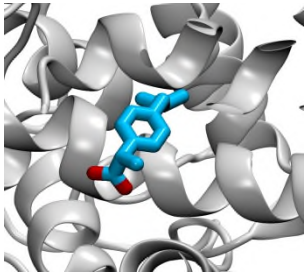
Functionalized nanoparticles

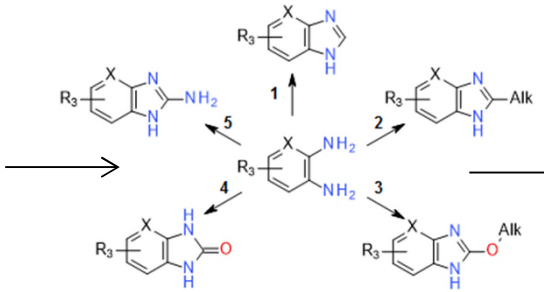


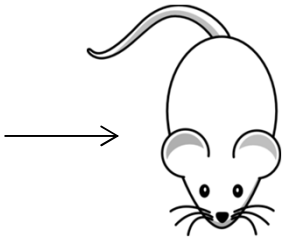
Chem (Cell Press) **2018**

Experiments

Computer-aided drug discovery for cancer and neuroscience







"Role of Molecular Dynamics and Related Methods in Drug Discovery"

De Vivo M., et al. J.Med Chem. **2016**

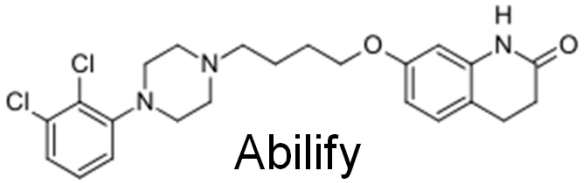
"Recent Advances in Dynamic Docking for Drug Discovery"

De Vivo M. & Cavalli A.

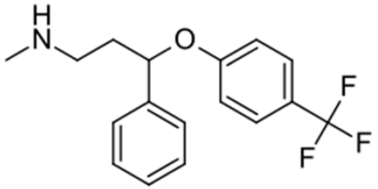
WIREs Comput Mol Sci **2017**, (Cover)

Il Farmaco: Chiave e lucchetto

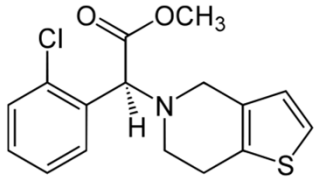
Small molecule drugs



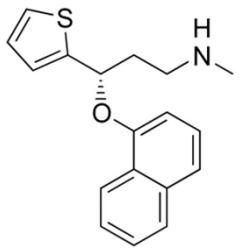
Abilify
(antipsychotic)



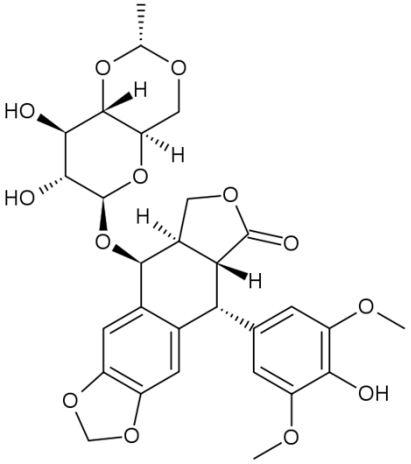
Prozac
(antidepressant)



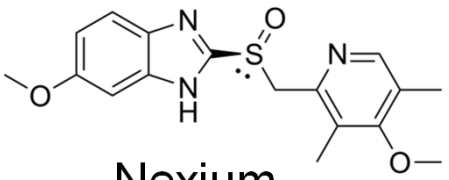
Plavix
(antiplatelet agent)



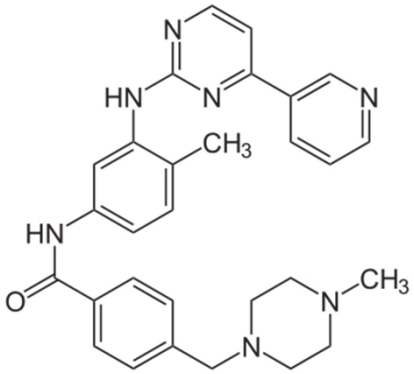
Cymbalta
(pain and anxiety)



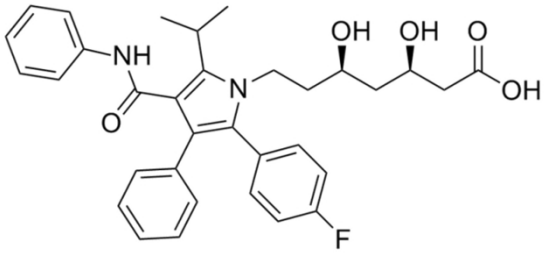
Etoposide
(cancer)



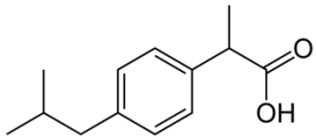
Nexium
(gastric acid)



Gleevec
(cancer)



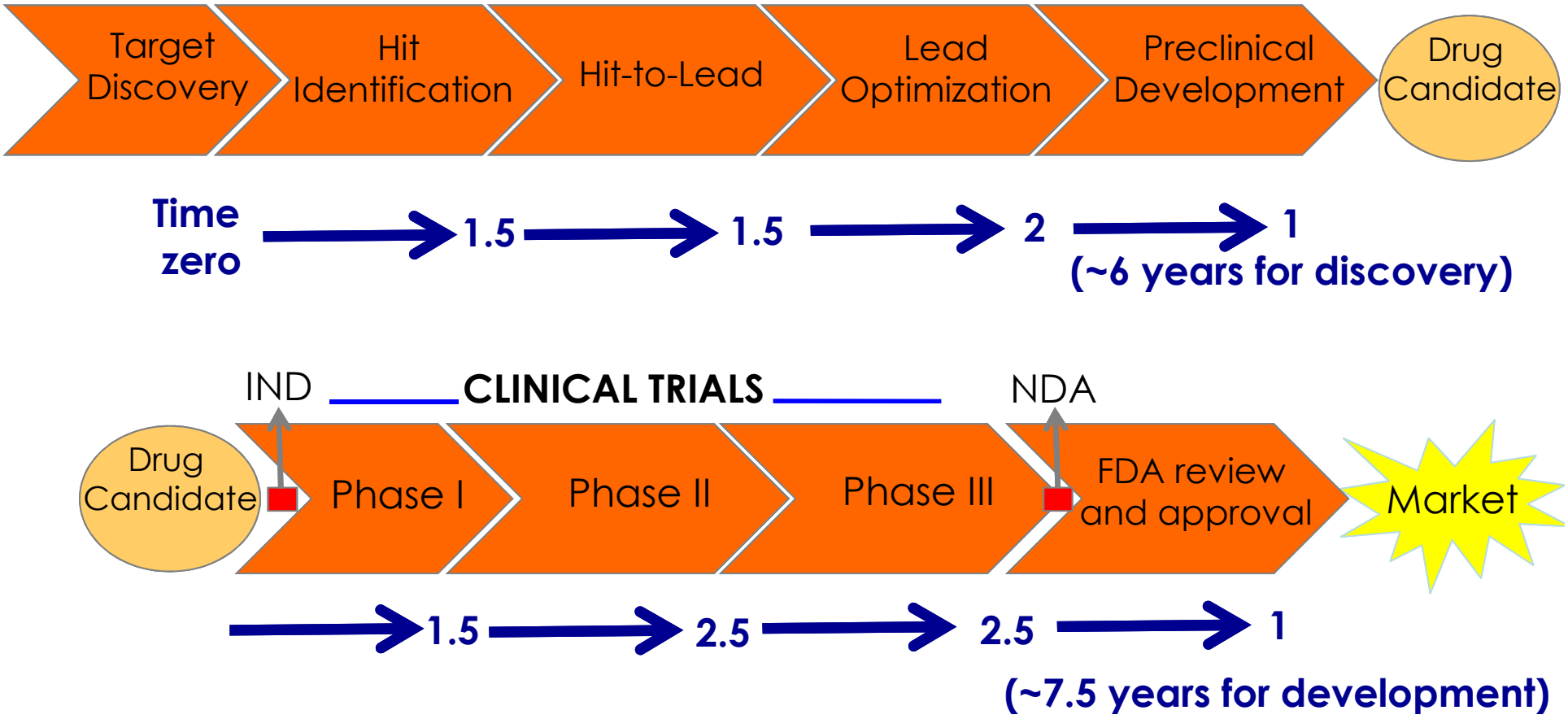
Lipitor
(Cholesterol)



Ibuprofen
(inflammation)

Drug Discovery & Development

Average time requested for it

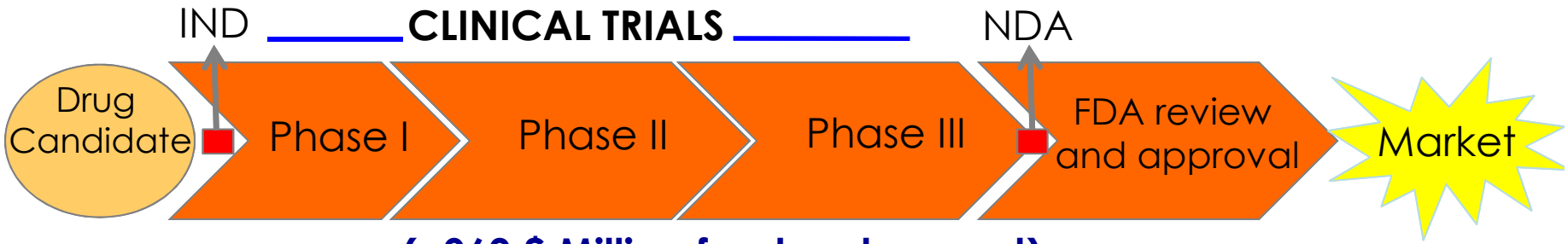


Total time (on average) = ~13.5 years

Drug Discovery & Development

Average cost requested for it

(~820 $ Million for discovery)



(~960 $ Million for development)

Total cost on average = ~1.78 $ Billion for one NME

Source: How to improve R&D productivity: the pharmaceutical industry's grand challenge Steven M. Paul, *Nat. Review Drug Discovery* March Vol. 9 **2010**

Sistemi realistici e dinamici

Simulazioni con il Supercomputer
Alcuni dei centri di supercalcolo in europa:

CINECA

Italia

JÜLICH FORSCHUNGSZENTRUM

Germania

Petascale computing (10^{15}), …. verso Exascale computing (10^{18})

Simulazioni con il Supercomputer

Alcuni dei centri di supercalcolo in europa:

CINECA

Italia

JÜLICH FORSCHUNGSZENTRUM

Germania

La chimica al computer è una lente di ingrandimento per vedere gli atomi in processi chimici !

Petascale computing (10^{15}), …. verso Exascale computing (10^{18})

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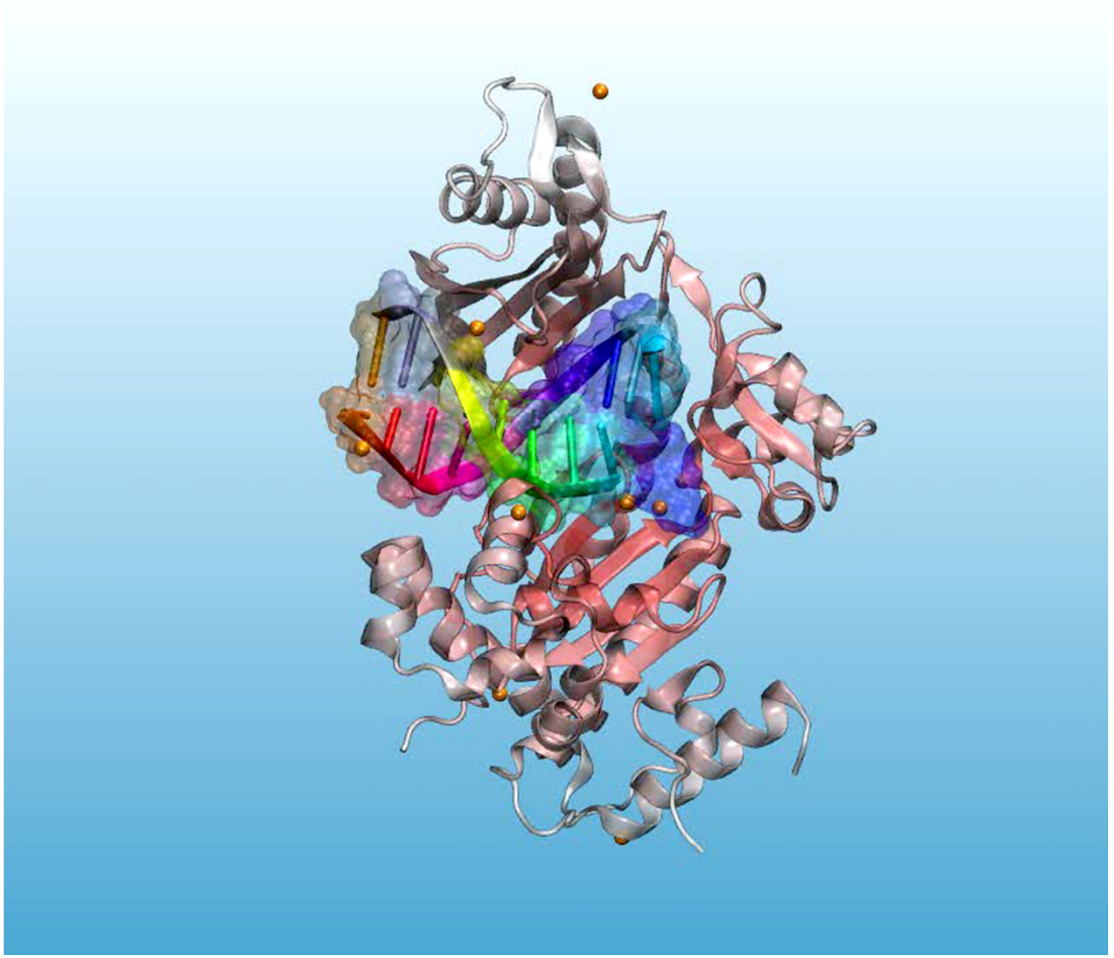
Simulazioni con il Supercomputer



~200 nanosecondi di dinamica della polimerasi e DNA

Comprendere la funzione del target

Computational Enzymology
Function and inhibition

ACS Catalysis
Perspective
Cite This: ACS Catal. 2018, 8, 11103–11118
pubs.acs.org/acscatalysis
2018

The Catalytic Mechanism of DNA and RNA Polymerases

Vito Genna, Elisa Donati, and Marco De Vivo*

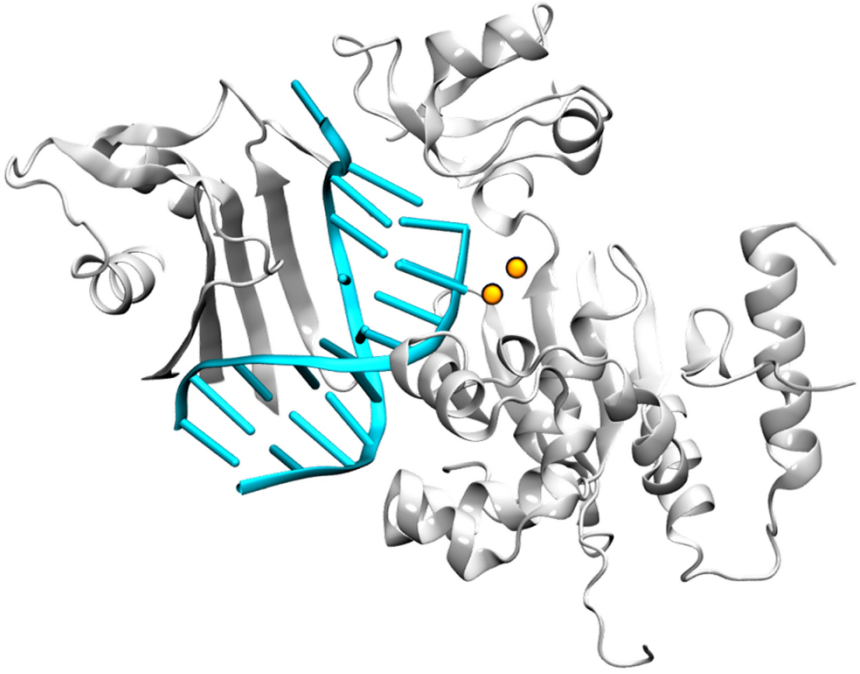
Laboratory of Molecular Modeling and Drug Discovery, Istituto Italiano di Tecnologia, Via Morego 30, 16163, Genoa, Italy

NATURE REVIEWS | CHEMISTRY

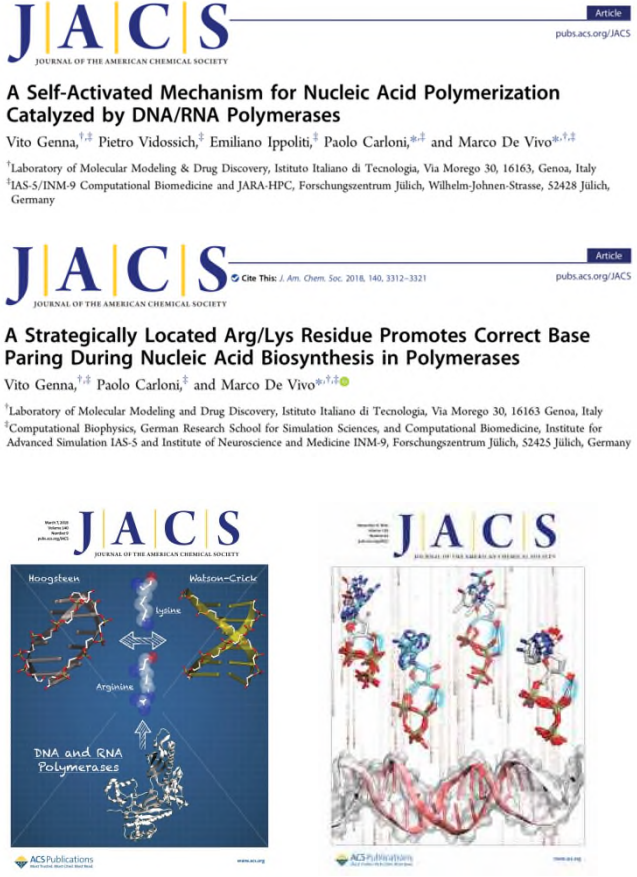
Metal–ligand interactions in drug design

Laura Riccardi, Vito Genna and Marco De Vivo

Nat Rev Chem **2018**



Comprendere la funzione del target



J A C S — JOURNAL OF THE AMERICAN CHEMICAL SOCIETY — Article — pubs.acs.org/JACS

A Self-Activated Mechanism for Nucleic Acid Polymerization Catalyzed by DNA/RNA Polymerases

Vito Genna,[†,‡] Pietro Vidossich,[‡] Emiliano Ippoliti,[‡] Paolo Carloni,[*,‡] and Marco De Vivo[*,†,‡]

[†]Laboratory of Molecular Modeling & Drug Discovery, Istituto Italiano di Tecnologia, Via Morego 30, 16163, Genoa, Italy
[‡]IAS-5/INM-9 Computational Biomedicine and JARA-HPC, Forschungszentrum Jülich, Wilhelm-Johnen-Strasse, 52428 Jülich, Germany

J A C S — JOURNAL OF THE AMERICAN CHEMICAL SOCIETY — Article — Cite This: J. Am. Chem. Soc. 2018, 140, 3312−3321 — pubs.acs.org/JACS

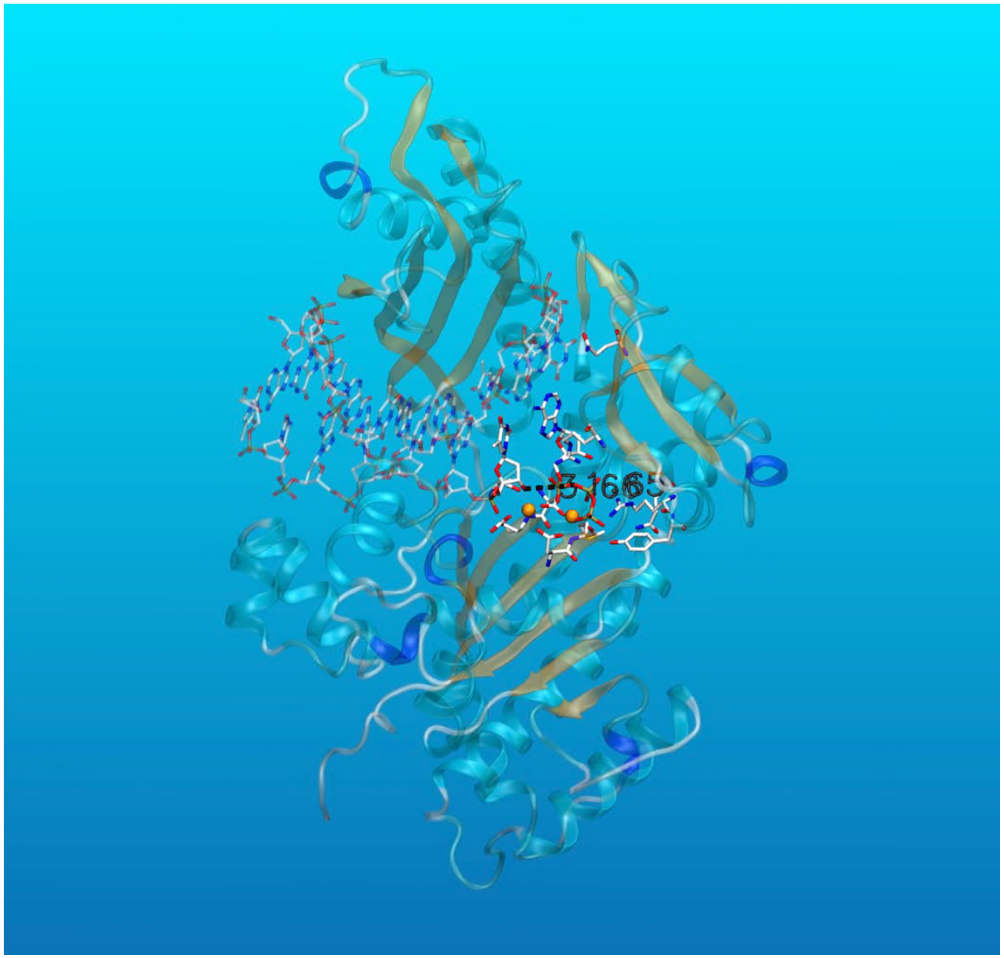
A Strategically Located Arg/Lys Residue Promotes Correct Base Paring During Nucleic Acid Biosynthesis in Polymerases

Vito Genna,[†,‡] Paolo Carloni,[‡] and Marco De Vivo[*,†,‡]

[†]Laboratory of Molecular Modeling and Drug Discovery, Istituto Italiano di Tecnologia, Via Morego 30, 16163 Genoa, Italy
[‡]Computational Biophysics, German Research School for Simulation Sciences, and Computational Biomedicine, Institute for Advanced Simulation IAS-5 and Institute of Neuroscience and Medicine INM-9, Forschungszentrum Jülich, 52425 Jülich, Germany

2016

2018



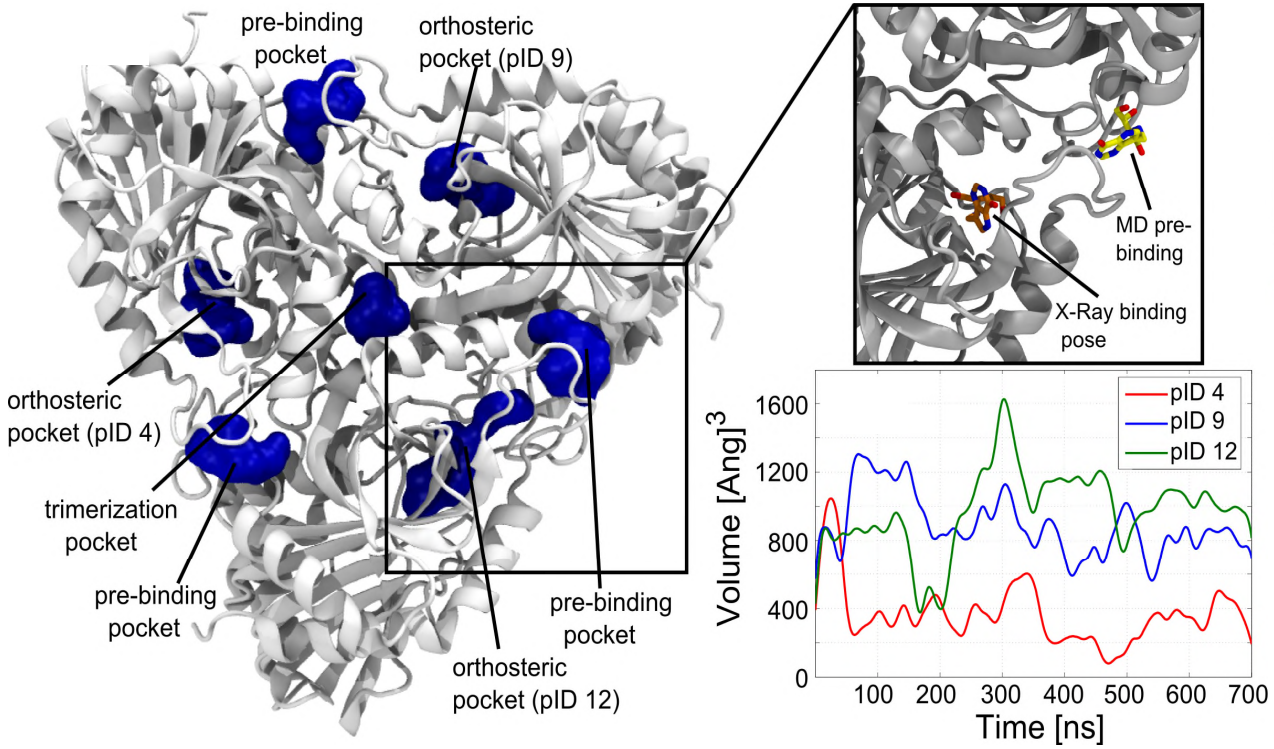
Come il filamento di DNA si duplica….

Una reazione cosi avviene in pochi picosecondi (un millesimo di miliardesimo di secondo)

Identificare nuove pockets per farmaci

Pocket crosstalk analysis: allosteric communication networks in proteins

In collaboration with Rocchia's Lab @IIT



Pocketron available in:

BiKi TECHNOLOGIES designing better medicines

Award: Emerging Technology in Computational Chemistry (ACS Fall mtg in Boston 2018)

Project in collaboration with:

AstraZeneca

La Sala G et al *ACS Central Science.* **2017** (cover)

La Sala G et al *J. Chem. Theory Comput.* **2016** (cover)

Donepezil entra nel suo target

Grazie a Dr. Walter Rocchia

https://www.youtube.com/user/bikitech

Nanoparticelle funzionalizzate per sensing di analiti

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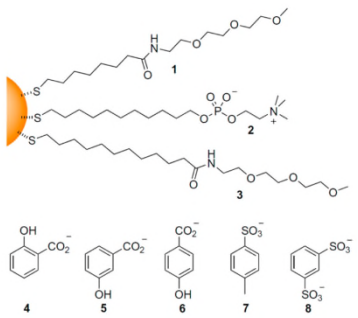
In collaboration with F. Mancin
University of Padova

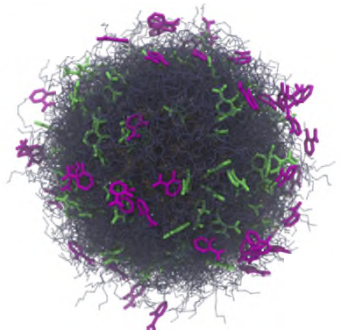
Chem
CellPress
2017

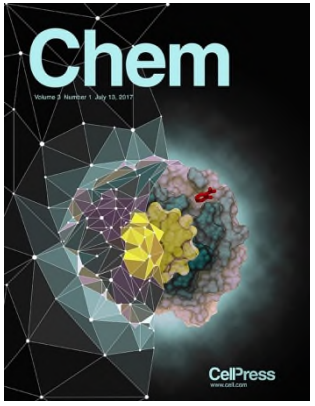
Article

Nanoparticle-Based Receptors Mimic Protein-Ligand Recognition

Laura Riccardi,[1] Luca Gabrielli,[2] Xiaohuan Sun,[2] Federico De Biasi,[2] Federico Rastrelli,[2] Fabrizio Mancin,[2,*] and Marco De Vivo[1,3,4,*]

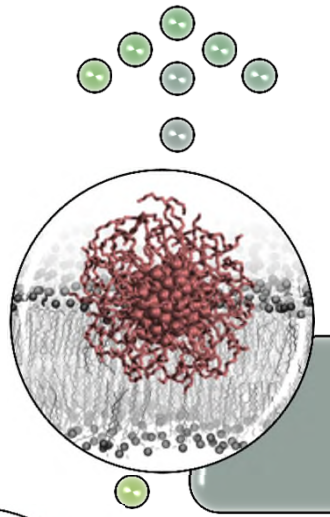




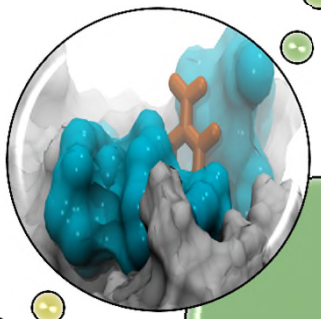


Rational Design

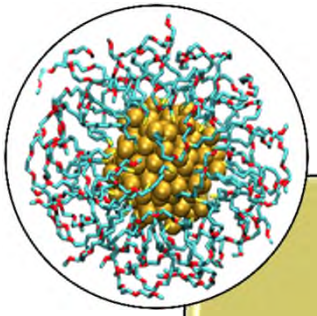
Molecular simulations in explicit solvent



Cellular Uptake – Reactions



Rationale on Sensing Mechanism



Computational Model

NanoModeler Web Server
https://NanoModeler.it

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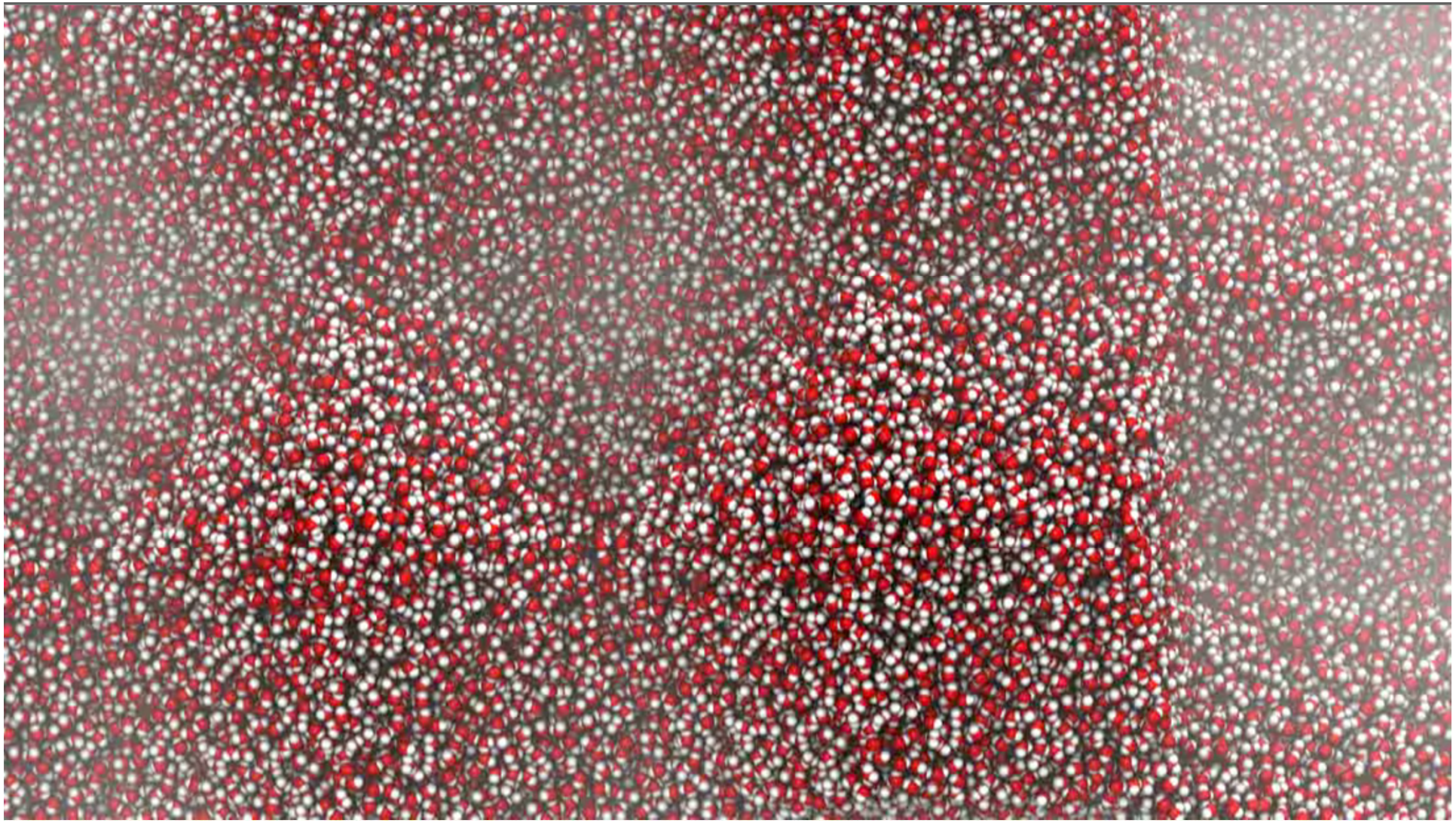
Dinamica e progettazione razionale di nanoparticelle per 'chemosensing'



Binding of AuNP/salicylate

MD simulations

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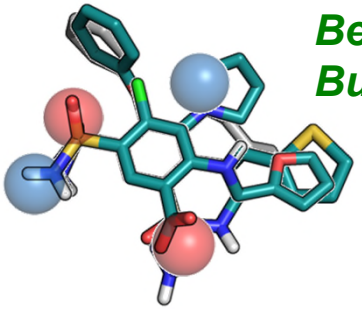
Toward innovative medicines

Computer-aided drug discovery pipeline in IIT

Toward innovative medicines

Computer-aided drug discovery pipeline in IIT

Targeting NKCC1



Beyond Bumetanide!

In collaboration with Dr. L. Cancedda, IIT

Neurodevelopment

My Research Group

Our international Group

Molecular Modeling & Drug Discovery

Active external collaborators:

Dr. Paolo Carloni @ FZJ, Julich, **DE**

Dr. Gian Pietro Miscione @ UDLA Bogotà, **COL**

Dr. Anand Ganesan, MD @ Cancer Research Institute UCI, **USA**

Dr. Neil Osheroff @ Vanderbilt University, **USA**

Dr. Fabrizio Mancin @ Uni Padova, **IT**

Dr. Feferico Rastrelli @ Uni Padova, **IT**

Dr. Marco Marcia @ EMBL Grenoble, **FR**

Dr. Ming Zhou @ Baylor College of Medicine, **USA**

Collaborators @ IIT

Dr. Laura Cancedda, Lab Director

Dr. Walter Rocchia, Lab Director

Dr. Pier Paolo Pompa, Lab Director

External Funds:

Fondazione AIRC Ricerca Cancro

High Performing Computing