UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

CrisDi
Interdepartmental Centre for Crystallography

Giornate del CrisDi

The Role of Crystallography in Drug Science and Biology

5 March, 2018 h 8:50

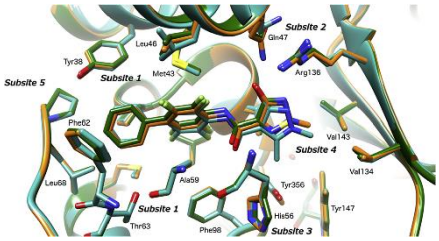
Department of Drug Science and Technology, University of Torino, Via Giuria 9

Room: Aula Magna Guido Tappi

Abstract

Within the activities of the Interdepartmental Centre for Crystallography (CrisDi) of the University of Turin, promotion and dissemination of the crystallography remain a top priority objective.

To this end, CrisDi has planned several workshop which are intended to be an informal discussion meeting, where the crystallography is the common ground, in order to encourage the collaboration between partners of different scientific area.



The first meeting/date is addressed to the Drug Science and Life Science staff. The contributions would display how some crystallographic methodologies, such as X-Ray diffraction, computational modelling or charge density analysis, can be helpful to develop drugs and to understand biological processes.

Finally, case studies will be presented.

Organizers: G. Fiore, M. Lolli, G. Di Nardo, M. Manzoli, D. Marabello

Registration is free, but requested

Please send an e-mail to: gianluca.fiore@unito.it within 15/02/2018

Programme

9:00 - 9:15	*Welcome* R. Arletti – President of the CRISDI Interdepartmental Centre, Dipartimento di Scienze della Terra (UniTO)
9:15 - 9:45	Methodologies – *X-ray diffraction facilities in Turin: single crystal vs powder diffraction for pharmacological questions* D. Marabello – Director of the CRISDI Interdepartmental Centre, Dipartimento di Chimica (UniTO)
9:45 - 10:15	Methodologies – *Protein crystallography for drug synthesis and biocatalysis* G. Di Nardo, G. Gilardi - Dipartimento di Scienze della Vita e Biologia dei Sistemi (UniTO)
10:15 - 10:45	Methodologies – *Structure-based drug design: sometimes x-ray crystallography is not enough* F. Spyrakis - Dipartimento di Scienza e Tecnologia del Farmaco (UniTO)
10:45 - 10:55	Methodologies - *The CCDC suite of software's for small molecules and macromolecules 3D structure investigation* M. Milanesio - Dipartimento di Scienze ed Innovazione Tecnologica (UniPO Amedeo Avogadro)
10:55 - 11:25	Coffee Break
11:25 - 11:55	Methologies – *Gaining insights on chemistry from the analysis of the charge density* L. Lo Presti - Dipartimento di Chimica (UniMI)
11:55 - 12:15	Case Study – *Functional characterization of the US21 protein of Human Cytomegalovirus* G. Gribaudo, A. Luganini - Dipartimento di Scienze della Vita e Biologia dei Sistemi (UniTO)
12:15 - 12:35	Case Study – *Targeting acute myeloid leukemia differentiation: the role of crystallography in the design of potent human dihydroorotate dehydrogenase (hDHODH) inhibitors* M. L. Lolli - Dipartimento di Scienza e Tecnologia del Farmaco (UniTO)
12:35 - 12:45	*Concluding Remarks*

Methodologies

X-ray diffraction facilities in Turin: single crystal vs powder diffraction for pharmacological questions.

D. Marabello - Director of the CRISDI Interdepartmental Centre, Dipartimento di Chimica (Università degli Studi di Torino)

Single crystal (XRD) and powder (XRPD) X-ray diffraction techniques are powerful tools to inspect small molecule and protein structures. XRD technique allows to determine three-dimensional structures and their absolute configuration, to localize hydrogens and to analyze intra- and inter-molecular interactions. XRPD is able to quickly perform a qualitative analysis of the samples and to recognize polymorphs.
The Turin X-ray diffraction facilities for XRD and XRPD, suitable for pharmacological questions, are going to be described.

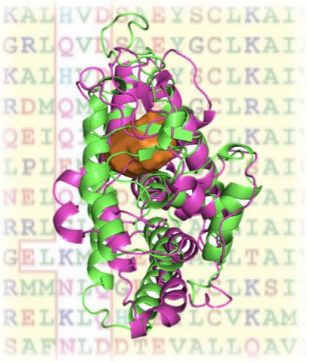
Protein crystallography for drug synthesis and biocatalysis

G. Di Nardo, G. Gilardi - Dipartimento di Scienze della Vita e Biologia dei Sistemi (Università degli Studi di Torino)

X-ray crystallography applied to proteins offers the basis to understand at molecular level the structure-function relationship in these biomolecules that have different applications in the pharmaceutical field.
The crystal structure of drug targets can offer the basis for the development of selective and potent inhibitors. Moreover, the selectivity of enzymes can be exploited for the biosynthesis of compounds of pharmaceuticals interest such as drug metabolites.
An overview of the experimental design to obtain protein crystals and solve the structure will be provided and examples of applications in the pharmaceutical field discussed.

Structure-based drug design: sometimes x-ray crystallography is not enough

Francesca Spyrakis - Dipartimento di Scienza e Tecnologia del Farmaco (Università degli Studi di Torino)

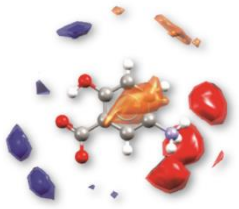


Structure-based drug design strongly relies on the availability of protein crystallographic structures for the design, development and optimization of drugs. Unfortunately X-ray crystallography cannot always provide the right answer. On a total amount of 20000 protein coding genes about 9000 protein structures, and sometimes only part of them, are present in the Protein Data Bank. The remaining part has to be modelled by means of computational methodologies. Homology Modelling currently represents the best method to model unknown structures when a template homolog ancestor is available. The basics and the limits of HM will be described, and real applications reported.

The CCDC suite of software's for small molecules and macromolecules 3D structure investigation

M. Milanesio - Dipartimento di Scienze ed Innovazione Tecnologica (Università Piemonte Orientale - Amedeo Avogadro)

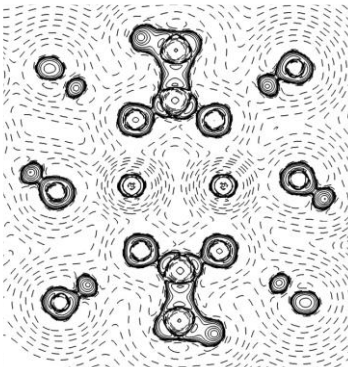
The Cambridge structural database (CCDC or CSD) provides much more than small molecule 3D structural data as in the past. It is now organized in submodules: CSD-System - The essential CSD database and analysis tools for all scientists who need comprehensive and validated structural chemistry data • CSD-Discovery - The set of solutions for users in discovery chemistry operations • CSD-Materials - Our specialist set of solutions for users studying the structure and properties of crystalline materials. For protein scientists, the CSD-System provides a protein-ligand docking application, GOLD widely used in the academic and industrial research. The CCDC suite is licenced full site to all researchers of the University of Turin.



Full interaction map for the anti-inflammatory mesalazine (refcode: SAQJAV01, DOI:10.5517/ccy7cxf)

Gaining insights on chemistry from the analysis of the charge density

L. Lo Presti - Dipartimento di Chimica (Università degli Studi di Milano)



The increasing attention to supramolecular chemistry mirrors a growing interest in chemical bonding. The understanding of factors that influence self-organization of matter lies at the core of the development of functional materials, bioactive compounds and drugs. In this context, the charge density scalar field, $\rho(\mathbf{r})$, plays a central role, as it conveys all the observable physics determined by the equilibrium distribution of electrons and nuclei. Relevant chemistry can be extracted from $\rho(\mathbf{r})$ by studying its topology. Modern experimental and theoretical tools for the topological analysis of the charge density will be here discussed, with focus on molecular recognition and polymorphism.

Case Studies

Functional Characterization of the US21 Protein of Human Cytomegalovirus

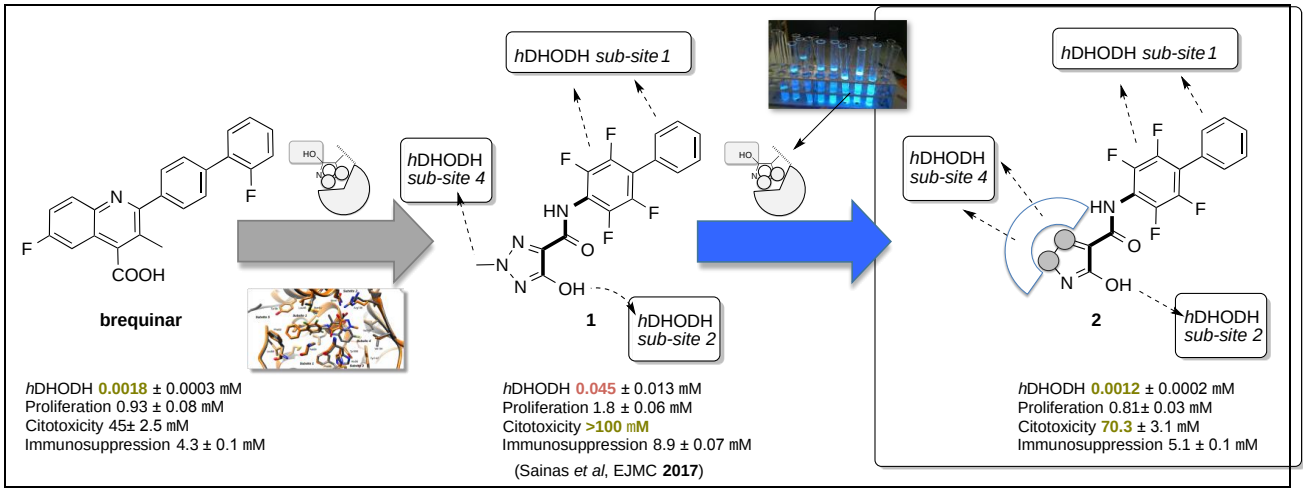
A. Luganini, G. Gribaudo - Dipartimento di Scienze della Vita e Biologia dei Sistemi (Università degli Studi di Torino)

The Human Cytomegalovirus (HCMV) US12 family is a set of 10 contiguous genes (US12 to US21) that constitutes about 5% of HCMV's genetic content. The US12 genes are highly conserved among HCMV strains and with homologs in CMVs of non-human primates. However, in spite of the likely evolutionary importance of the family to HCMV biology, specific functions of US12 proteins have yet to be ascertained. By combining bioinformatics with molecular genetics, biochemistry, and cell biology approaches, we have investigated the pattern of expression of the US21 protein and the mechanisms by which it influences cellular Ca^{2+} homeostasis and control of apoptosis, thus contributing to HCMV pathogenesis.

Targeting acute myeloid leukemia differentiation: the role of crystallography in the design of potent human dihydroorotate dehydrogenase (hDHODH) inhibitors

Marco L. Lolli - Dipartimento di Scienza e Tecnologia del Farmaco (Università degli Studi di Torino)

In 2016 human *dihydroorotate dehydrogenase* (*h*DHODH) was associated to *acute myelogenous leukemia* (AML), a disease that has not seen new therapies in four decades. In this occasion is described the rational process that, starting from known *h*DHODH inhibitors and by applying innovative *scaffold-hopping* replacement, lead to a novel generation of potent and selective *h*DHODH inhibitors.[3] Compound **2** was found able to restore the myeloid differentiation in leukemia cell lines in a range one digit superior then *brequinar*, one the most potent known inhibitors so far discovered. Crystallography supported the entire process by offering single-crystal structure validation and ligand-protein coordinates.



(Sainas *et al*, EJMC **2017**)