Editorial
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Special Issue

# 2020 Italian Special Anniversary Collection: Celebrating NMMC 2019 and 40 Years of the DCF-SCI

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## *Overview of the XXVI National Meeting in Medicinal Chemistry*

The **XXVI National Meeting in Medicinal Chemistry** (NMMC 2019) was held from July 16th to 19th 2019 in the beautiful monumental complex of the Ca' Granda (Figure 1), the headquarters of the "Statale" University of Milan, under the patronage of the Società Chimica Italiana (SCI), the European Federation for Medicinal Chemistry (EFMC), and the generous support of pharma-related companies. As in the recent past, NMMC 2019 has been coupled with the **12th Young Medicinal Chemists Symposium** ("Nuove Prospettive in Chimica Farmaceutica", NPCF 12), a parallel event specifically devoted to PhD students and young scientists, operating within academic and nonacademic institutions, which are involved in the various fields of the medicinal chemistry research.

The 2019 edition of NMMC was especially meaningful for the Italian scientific community, since it coincided with the **40th anniversary of the establishment of the Italian Medicinal Chemistry Division** (Divisione di Chimica Farmaceutica, DCF) of the SCI. The DCF (now counting 550 members) was founded in 1979 with the objective to advance the science of medicinal chemistry by encouraging and strengthening cooperation among Italian scientists and promoting links with colleagues belonging to the national organizations adhering to EFMC, which had been founded nine years before. The first National Meeting in Medicinal Chemistry took place on December 1979 in Pisa (Figure 2), and, since then, this annual appointment represents the reference scientific event for the Italian researchers working in the field of medicinal chemistry.

NMMC 2019 aimed at continuing a long-standing tradition of excellent science in the major research areas of medicinal chemistry, bringing together more than 300 delegates from industry, academia, and government institutions across Europe and throughout the world. The meeting created a forum for in-depth, informed discussions, regarding both basic science and applications in medicinal chemistry.

The multidisciplinary scientific program was of interest to medicinal chemists, biologists, and clinicians involved in drug research and development. The main therapeutic areas were covered by XXVI NMMC 2019 and NPCF 12, among them oncology, immune-oncology, infectious diseases, neurodegenerative diseases, rare and neglected diseases. cardiovascular diseases, inflammation, and metabolic diseases. In the frame of these

**Figure 1.** The Central Courtyard (*Cortile d'Onore*) of the Ca' Granda.


**Figure 2.** The first Italian Meeting in Medicinal Chemistry (Pisa, 1979) organized by the DCF-SCI.

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general areas of interest, the scientific sessions included plenary and keynote lectures, oral/flash and poster presentations focusing on the following main topics:

- First disclosures
- New mechanisms, targets and proof of concept studies
- Drug repurposing
- New modalities in drug discovery
- Omics applied to the identification of biomarkers and to target identification and validation
- Nutraceuticals and nutragenomics
- DMPK & ADMET
- Drug design & structural biology
- Biophysics and analytics in drug discovery
- New synthetic strategies in medicinal chemistry
- Cheminformatics
- Biological drugs

The participants were welcomed by **Maria Pia Abbracchio** (Pro-Rector of the University of Milan), **Gabriele Costantino** (Chairman of the Scientific Committee), **Gianluca Sbardella** (President of the Medicinal Chemistry Division), and **Marina Carini** and **Marco De Amici**, (Co-chairs of the Organizing Committee) (Figure 3).

During the inaugural ceremony, **Alberto Massarotti** (University of Piemonte Orientale, Novara) and **Salvatore Di Maro** (University "Luigi Vanvitelli", Caserta) were appointed with the Medicinal Chemistry Division of the Italian Chemical Society award, whereas **Tommaso Felicetti** (University of Perugia) and **Francesco Saccoliti** (IIT, Genoa, and La Sapienza University, Rome) received the Best Doctoral Thesis award.

Then, two distinguished scientists, **Federico Da Settimo** (University of Pisa) and **Daniele Donati** (Nerviano Medical Sciences S.r.l. - Nerviano, Milan), were awarded, respectively, with the Musajo Medal and the Seal of the Medicinal Chemistry Division of the Italian Chemical Society (Figures 4 and 5).


**Figure 3.** The *Aula Magna* of the University of Milan during the inaugural ceremony.

**In the opening lecture**, **"Breakthroughs in GPCR structural biology and their impact on computer-aided drug design", Kenneth A. Jacobson** (National Institutes of Health, Bethesda, MD (USA)) (Figure 6) illustrated some recent results of his research group on the combined application of chemical, pharmacological and structural approaches to the discovery and characterization of new receptor ligands modulating purinergic signaling. In particular, the approach to potent and selective ligands of the $A_3$AR and $P2Y_{14}$R, both inflammation-related GPCRs, with the aid of molecular modeling based on homology to X-ray structures of related receptors was discussed. Moreover, several ribose-containing $A_3$AR agonists have advanced in clinic trials for treatment of inflammatory diseases and cancer, and other second generation, conformationally-locked agonists of even greater selectivity are being considered

Marina Carini (degree in Pharmacy, 1979) has been a full professor of Medicinal Chemistry since 2001 (Faculty of Pharmacy, University of Milan). From 2009 to 2017 she was Director of the Department of Pharmaceutical Sciences, and coordinator of the PhD in Pharmaceutical Chemistry (2005-2008) and Pharmaceutical Sciences (2012-2015). She was Director of the Postgraduate School of Specialization in Cosmetic Science and Technology (2001-2005) and still coordinates the Postgraduate Specialization Courses in Cosmetic Science (since 2005) and in Cosmetic Products: from formulation to consumer (since 2016). Since November 2018, she has been appointed at the University of Milan as the delegated pro-rector of the Third Mission, Territory and Cultural Activities. Her research activity has resulted in the publication of 195 scientific articles (185 of which in international journals with Impact Factor and 10 as volume contributions), 7 patents and in more than 250 conferences/communications/posters at national and international congresses, many of them by invitation. H index (Scopus) = 48.

Marco De Amici graduated in Chemistry in 1978 and is a professor of Medicinal Chemistry at the Department of Pharmaceutical Sciences, University of Milan. He spent one year (1989) as a visiting researcher in the group headed by professor Povl Krogsgaard-Larsen at the Royal Danish School of Pharmacy, Copenhagen. From 1992 to 1995 he was associate professor at the University of Trieste. His more recent scientific interests mainly focus on the design, synthesis and structure/activity relationships of novel cholinergic ligands and their mechanism of activation of nicotinic or muscarinic receptor responses. He is coauthor of 140 original articles and 3 reviews, and coinventor of 4 patents. He was the coordinator of the PhD course in Pharmaceutical Sciences (2015-2017) and, since 2014, has been a member of the Quality Assurance Board, which is responsible for implementing the quality policies of the University of Milan.

**Figure 4.** Federico Da Settimo (University of Pisa), recipient of the Musajo Medal of the DCF-SCI, with Gianluca Sbardella and Gabriele Costantino.

**Figure 5.** Daniele Donati (Nerviano Medical Sciences S.r.l. - Nerviano, Milan), recipient of the Seal of the DCF-SCI, with Gabriele Costantino and Gianluca Sbardella.

**Figure 6.** Kenneth A. Jacobson and Maria Pia Abbracchio.

for chronic neuropathic pain treatment. Thus, purine receptor structures have enabled novel ligand discovery, the elucidation of their biological role and the conceptualization of future therapeutics.

**In the second plenary lecture, titled "Inducing protein degradation with small molecules: how PROTACs work", Alessio Ciulli** (University of Dundee, UK) reviewed the increasing role of targeted protein degradation with small molecules as a new modality of chemical intervention that could lead to new medicines against targets conventionally thought of as undruggable. Proteolysis-targeting chimeras (PROTACs) are "tailored" double-headed ligands that, at variance with conventional protein inhibitors, recruit a target protein to an E3 ubiquitin ligase, thus co-opting the ligase activity leading to the protein being ubiquitylated and degraded by the proteasome. The results from Ciulli's group and other laboratories have collectively contributed to making targeted protein degradation by PROTACs a powerful tool to probe biology and an innovative therapeutic approach.

**The third plenary lecture, "Implementing molecular interaction kinetic analysis for drug discovery", given by Helena Danielson (Uppsala University, Sweden),** dealt with the impact of the use/improvement of biophysical methods on the strategies applied to drug development. The presentation focused on the exploitation of biosensor technology for detailed studies of enzyme-inhibitor interactions and other relevant recognition processes in the life science area. The discussed results concerned the kinetic analysis of interactions at varying conditions, which underlined the importance of defining the mode-of-action via characterization of the complexities of molecular interactions. The discussed results suggest that structure kinetic relationship analyses and identification of dominating interactions for optimization of lead compounds should ideally be based on intrinsic rate constants instead of the more easily accessible observed kinetic constants.

As suggested in the title, **the fourth plenary lecture: "Artificial intelligence. Not just another tool in the toolbox", by David E. Leahy** (The Discovery Bus Ltd, Macclesfield, UK), asked whether all the artificial intelligence (AI) computer-based methods do represent a step-change in medicines R&D or whether they are considered 'just another tool in the toolbox'. The take-home message of the presentation was that AI as autonomous software systems that build on medicinal chemistry know-how, our rich heritage of computer aided drug design systems and the massive chemical and biological information sources have breakthrough potential for our industry. There is a good case to be made that "real AI", if defined differently from 'just another tool', has the potential to deliver true changes in productivity and output of new medicines.

**In the closing plenary lecture, "Integrated structural biology: approaching infectious and degenerative diseases", Martino Bolognesi (University of Milan, Italy)** clarified the importance of discovering the structural details and dynamic properties of proteins as the challenging but necessary step for the rational design of new drugs. The biophysical and biochemical tools currently available allow us to tailor mole-

cules for maximal target specificity and affinity, thus encoding two key properties for an effective drug.

Single particle cryo-EM provides a new approach that allows reaching residue resolution in complex protein aggregates that cannot be crystallized. The potential of this recently introduced branch of structural biology was presented by exposing the study of *ex-vivo* amyloid deposits from a patient affected by systemic amyloidosis with severe heart involvement. The same technique provided the best approach to the study of membrane proteins, well known targets of at least 30% of the active drugs. Specifically, heart voltage-gated ionic channels are a target on reach, for which preliminary results were discussed.

**The scientific program also included three days of keynote lectures (10), oral (44) and flash (14) communications as well as poster presentations (112), which were exhibited throughout the whole meeting's duration.**

During the meeting, a Round Table was organized to celebrate the 40th anniversary of the Divisione di Chimica Farmaceutica della Società Chimica Italiana (DCF-SCI), with the contribution of **Angela Agostiano** (SCI President), **Gianluca Sbardella** (DFC President), **Girolamo Cirrincione** and **Gabriele Costantino** (DFC Past Presidents). During the Round Table, a short celebration was also devoted to the 100th anniversary of the journal "La Chimica e l'Industria", which is the official organ of the SCI. The Gala Dinner (Figure 7) took place at Villa Necchi, surrounded by a peaceful garden in the heart of Milan, housing sensational works of art, a legacy of the glamorous atmosphere of Milan's interwar years.

**Figure 7.** The staff of the Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Milan during the Gala Dinner at Villa Necchi.

## *Special Collection Dedicated to NMMC 2019*

As a reminder of the successful meeting in Milan and in connection with the DCF 40th Anniversary, this *ChemMedChem* Special Collection was conceived, with the aim to offer a representative overview of recent scientific advances achieved by researchers belonging to the Italian medicinal chemistry community. The collection includes 34 contributions, among them five Review articles, one Minireview, one Concept paper, three Communications, and twenty-four Full Papers; their contents maybe broadly grouped as indicated in the following:

- Enzyme or protein inhibitors (12 papers)
- Antiproliferative agents (5 papers)
- Multitarget compounds (4 papers)
- Antiviral agents (3 papers)
- GPCR signaling modulators (2 papers)
- Antibacterial agents (1 paper)
- Antiarrythmic and antioxidant agents (1 paper)
- Antidiabetic and hypolipidemic derivatives (1 paper)
- Antiprotozoal agents (1 paper)
- Endocannabinoid metabolism modulators (1 paper)
- Fluorescent probes (1 paper)
- Glycoconjugated metal complexes (1 paper)
- Inhibitors of β-catenin signaling (1 paper)

A small selection of papers is briefly commented below. The choice has been restricted to those authors presenting plenary or keynote lectures at the meeting, which contributed with a review or a full paper to the Special Issue.

**Antonio Macchiarulo** and co-workers performed a detailed study of several groups of crystal structures of IDO1 (Indoleamine 2,3-dioxygenase 1), a relatively novel immune checkpoint protein, with multiple effects on effector and regulatory pathways of the immune response.[1] The investigated structures have been disclosed in the last decade in the apo/holo form and/or in complex with small-molecule inhibitors. The analysis suggested that unrelated conformations of the enzyme have been solved with different ligand-induced changes of secondary motifs that localize even in regions remote from the catalytic site. In addition, the study evidenced an unexplored region of molecular-recognition space covered by IDO1 binding sites; this region could drive the selection of diverse molecular skeletons for further structure-based drug design aimed at identifying new lead compounds with different chemical scaffolds.

The review article by **Roberta Costi** and **Francesco Saccoliti** focused on trypanothione metabolism as a target in the search for innovative antiprotozoal agents.[2] The unique trypanothione-based redox pathway, which is absent in human hosts, is vital for all trypanosomatids and offers valuable opportunities to the design of broad-spectrum and innovative anti-trypanosomatid agents. Research efforts are addressed to the key metabolic enzymes trypanothione synthetase-amidase and trypanothione reductase, whose inhibition should affect the entire pathway, and thus the parasite survival.

To improve the therapeutic potential of mustard-based DNA alkylating agents, **Barbara Gatto** and co-workers designed, synthesized and tested a group of novel aromatic *bis*- and *tris*-3-chloropiperidines (B-CePs and Tri-CePs, respectively).[3] A structure-activity relationship analysis of B-CePs suggested that the arrangement of the reactive units affects the DNA alkylating activity, with a correlation between the electron density of the aromatic system and the reactivity with biologically relevant nucleophiles. The investigated small molecules exhibited a marked anti-proliferative effect preferentially against BxPC-3 pancreatic adenocarcinoma cells in 2D and 3D cultures,

showing potential as promising candidates for a further development of sustainable chemotherapeutics active against pancreatic tumors.

In their review article, **Kenneth A. Jacobson** and **Veronica Salmaso** further stressed the relevance of the availability GPCR structures, such as adenosine and P2Y receptors, in the design of novel ligands, among them high-affinity fluorescent probes and other high-affinity tools for drug discovery.[4] The authors focused on selective purinergic agonists ($A_1$, $A_3$), antagonists ($A_3$, $P2Y_{14}$), and allosteric modulators ($P2Y_1$, $A_3$). Examples of successful structure-based design, including the rational modification of known ligands, are discussed for antithrombotic $P2Y_1R$ antagonists, and anti-inflammatory $P2Y_{14}R$ antagonists and $A_3AR$ agonists. Moreover, rigidified $A_3AR$ agonists are a potential, nonaddictive treatment for chronic neuropathic pain.

**Cosimo Damiano Altomare**, **Rosa Purgatorio** and co-workers reported on the synthesis of a group of 1,2,3,4-tetrahydrochromeno[3,2-*c*]pyridin-10-one derivatives, which were screened against various targets involved in the onset and progression of Alzheimer's disease, i.e. acetyl- and butyrylcholinesterase (AChE and BuChE), monoamine oxidases A and B (MAO A and MAO B), aggregation of β-amyloid (Aβ) and reactive oxygen species (ROS) production.[5] Some of the compounds showed multifaceted activities with well-balanced multitargeting inhibitory profiles. One of the investigated analogs was characterized as a potent and selective MAO B inhibitor and proved to be a safe neuroprotectant in a human neuroblastoma cell line, by improving viability impaired by $A\beta_{1\text{-}42}$ and pro-oxidant insult. Docking studies were also performed in the study.

## *DCF Activities in 2020 and Upcoming Scientific Events*

As in all over the world, the research activities in Italy have been severely compromised by the COVID-19 pandemic, to a larger extent in Northern Italy in the first half of 2020. The obvious decision of the DCF and of all the Divisions of the SCI was to postpone to 2021 the scientific events planned in 2020.

However, the virtual **Italian Young Medicinal Chemistry Virtual Meeting (I-YMC-VMeet)** was held from July 22$^{nd}$ to 24$^{th}$ 2020, which has been a quite successful event due to the enthusiastic efforts of the group of young researchers belonging to the DCF Communication Team. 364 participants from 38 countries all over the world were registered (with an average of 1200 visualizations through the EFMC YouTube channel for each of the three days), 20 speakers and 66 poster presentations (the virtual poster session made use of the Twitter account of the DCF). The generous contribution from several sponsors allowed to award the best oral communication as well as the best seven posters, that were selected by the Scientific Committee. A special "social poster" prize was assigned to the poster with the highest number of interactions on Twitter.

Moreover, a stimulating round table discussion on the career opportunities for young medicinal chemists was moderated by Gabriele Costantino (DCF Past President), with the contribution of Yves Auberson (EFMC President, Novartis, Basel, CH), Kristina Goncharenko (EFMC-Young Scientists Network, SpiroChem, CH), Rui Moreira (President Elect EFMC, University of Lisbon, PT), and David Peralta (Editor-in-Chief, *ChemMedChem*, Chemistry Europe, DE).

Based on the fruitful experience of I-YMC-VMeet, the **Autumn Meeting for Young Chemists in Biomedical Sciences (AMYC Biomed 2020)** was organized from October 13$^{th}$ to 14$^{th}$ 2020 under the patronage of the SCI, and supported by Wiley and Elsevier. This short online symposium targeted young scientists under the age of 40 from all over the globe and involved in research across biomedical sciences. It aimed to allow participants to share ideas among young researchers, while taking inspiration from leading scientists with diverse expertise and background in the field of biomedical sciences. The event was an initiative from young researchers at the Department of Excellence of Pharmacy, University of Naples Federico II, Italy.

About 150 participants from 10 countries all over the world were registered; the program included 3 plenary lectures, 3 keynote lectures and 33 oral communications, the latter organized in three sessions: analytical chemistry, medicinal chemistry and pharmaceutical technology. 35 poster presentations were shared through the YouTube channel.

In 2021, the DCF-SCI will take part in the **XXVI EFMC International Symposium on Medicinal Chemistry (EFMC-ISMC 2021)**, the main biennal event of the EFMC, which has been postponed by one year, The symposium (www.efmcism-c.org) will take place in Basel from August 29 to September 2, 2021 and will be organized by the Division of Medicinal Chemistry and Chemical Biology of the Swiss Chemical Society (SCS). In the hope that the situation will allow for a physical event to take place, however the format of the symposium will be adapted based on the evolution of the COVID-19 pandemic.


**Figure 8.** Upcoming events in 2021.

From September 12th to 16th 2021, the DCF-SCI will also take part in the **XXVII National Conference of the Italian Chemical Society** (www.sci2020.org), which will be co-organized in Milan by the Universities of Milan and Milan-Bicocca. As in the previous editions, this triennial event, initially scheduled in September 2020, will gather members of the various Divisions of the SCI, with a scientific program including plenary lectures on subjects of general interest and a number of parallel sessions organized by the different Divisions of the SCI.

The inaugural lecture of the conference will be given by **professor M. Stanley Whittingham, Nobel Prize Laureate in Chemistry 2019**. The Executive Board of DCF has already selected the following keynote speakers for the XXVII National Conference of the Italian Chemical Society:

- **Giancarlo Aldini** (University of Milan)
- **Tracey Pirali** (University of Piemonte Orientale)
- **Andrea Stevenazzi** (Italfarmaco, Milan)
- **Tiziano Bandiera** (IIT, Genoa)
- **Giuseppe Campiani** (University of Siena)
- **Marco Radi** (University of Parma)
- **Antimo Gioiello** (University of Perugia)

From April 28th to 29th 2021, the University of Florence (Chairpersons: Novella Romanelli and Claudio Supuran) will host the **13th Young Medicinal Chemists Symposium** ("Nuove Prospettive in Chimica Farmaceutica", NPCF 13) (www.npcf13.unifi.it/).

Marco Macchia, Director of **ESMEC (European School of Medicinal Chemistry)** and Manuela Bartolini, Director of **SSPA (Summer School of Pharmaceutical Analysis)**, confirmed that the two events scheduled in 2020 have been postponed to 2021, June 27 - July 1 in Urbino, and 22–24 September in Rimini, respectively (Figure 8).

Finally, the first **Italian Flow Chemistry Symposium** (**IFCS**), formerly planned on November 2020 in Milan, has been postponed by one year. The meeting, which will focus on the different aspects and applications of flow technologies (www.soc.chim.it/en/printpdf/2335), is organized by **Antimo Gioiello** (University of Perugia) and **Lucia Tamborini** (University of Milan) (Figure 8)

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