

Minutes

IUPAC DIVISION VII CHEMISTRY AND HUMAN HEALTH SUBCOMMITTEE ON DRUG DISCOVERY AND DEVELOPMENT

San Francisco, USA

Saturday, April 1, 2017 – 9 am - 6 pm

Attendees in-person: Janos Fischer (JF, Hungary), Balu Balasubramanian (BB, USA) Jonathan Baell (JB, Australia), Nestor Carballeira (NC, Puerto Rico), Mukund Chorghade (MC, USA), William Greenlee (BG, USA), Toshi Kobayashi (TK, Japan), Michael Liebman (ML, USA), Tom Perun (TP, USA), Gerd Schnorrenberg (GS, Germany), Patrick A. Woster (PW, USA)

Attendees Go-to- Meeting: Vincenzo Abbate (VA, Italy-UK), Wayne E. Childers (WC, USA), Paul W. Erhardt (PE, USA) and John Proudfoot (JP, USA)



(from left : Gerd Schnorrenberg, Tom Perun, Patrick Woster, Mukund Chorghade, Jonathan Baell, Janos Fischer (Chair), Nestor Carballeira, Toshi Kobayashi, Michael Liebman and Balu Balasubramanian)

1. Introductions, Opening Remarks.

The “go-to Meeting” format was set up for the remote participants by ML. The remote participation from UK to USA with remote slide presentation format was a successful experiment. This feature may be used for the future meetings as well.

JF opened the meeting with a reminder ACS Award for Computers in Chemical and Pharmaceutical Research -Symposium in honor of Yvonne C. Martin to be held at ACS meetings on April 4, 2017. This was followed by an overview of the mission of IUPAC Division VII Chemistry and Human Health activities of its Subcommittees on Drug Discovery and Development, Toxicology and Risk Assessment and Nomenclature for Properties and Unites - Focus on chemical sciences that impact human health; Promote the use of chemical tools for disease prevention or treatment.

JF also highlighted the published Glossaries and books from the division as well as individuals recognized for their meritorious service to the division.

The minutes of the Manchester meeting was accepted and approved.

Matters arising from the minutes:

The need for IUPAC glossaries under the current paper and online format is discussed again. The online version has an advantage, because it can be easier updated. The glossaries also are available on the IUPAC website, however, it is not easy to find them, especially for people who do not know the structure of IUPAC.

2. IUPAC News:

Tom Perun (TP) highlighted the current membership process that next line of office members will be selected by election and the CV of the current members were requested by Rita Cornelis (RC). There are total of 10 Titular Members, 6 Associate Members, and 10 National Representatives. He also brought up the upcoming IUPAC General Assembly and Congress in Sao Paulo. The 100 year anniversary of the founding of IUPAC will be celebrated in Paris in the year 2019. TP also gave a quick update of Emeritus Fellows Program: Former members of the Division VII and its Subcommittees who have made outstanding contributions to IUPAC and, through chemistry, to the health sciences in general can be awarded, one fellowship per subcommittee and biennium. It is not excluded that an Emeritus Fellow later becomes Division VII member again; examples are R. Cornelis and U. Forsum. Proposals for Emeritus Fellow candidates (2017) are now welcome. Each subcommittee can name two candidates. R. Cornelis will write a proposal to nominate J. Duffus; J. Fischer suggests Toshi Kobayashi.

RC will be the next President of the Division as TP becomes the recent Past President.

Vladimir Gubala becomes the New Secretary as the current secretary (Michael Schwenk) finished the 8 year term. Helle Johannessen will be the Vice President starting from 2018.

Post-meeting informations :

Titular Members (TMs) for biennium 2018-2019 : Vincenzo Abbate (Italy) Adriano Andricopulo (Brazil), GeokBee (Sharon) Teh (Malaysia), A. Ganesan (Malaysia-UK), Gerd Schnorrenberg (Germany), Michael Schwenk (Germany)

Associate Members: Balu Balasubramanian (USA) and Janos Fischer (Hungary), Urban Forsum (Sweden), Linda Johnston (Canada) and Brandon Presley (USA)

National Representatives : Nestor Carballeira (Puerto Rico) and 9 further persons (see IUPAC website)

3. Projects

3.1 **Emerging Problem of Novel Psychoactive Substances** (Project 2014-019-1-700)

Vincenzo Abbate (UK, remote participant):

The goal of this project is the review of two main subgroups of novel psychoactive substances : Part I : synthetic cannabinoids and Part II : synthetic cathinones. Vincenzo has given an overview on Part I in a lecture with help of a remote presentation. The synthetic cannabinoids consist of heterogeneous subclasses of compounds composed of four segments: a ring head (naphthalene); a link (e.g. methanone); a core (e.g. indole), and a tail (e.g. alkyl chain). One of their representative is JWH-018, synthesized by John W. Huffman, and abused by drug users in products branded with names such as "Spice" and "K2", containing inert plant materials sprayed with synthetic cannabinoid chemicals. JWH-018 is a full agonist of CB₁ and CB₂ receptors. After the illegal ban dozens of close analogues appeared on the black market. Time Table for this project – Part I is completed and ready for submission as a manuscript. Part II is 30% completed and will be asking for extension for another manuscript by Dec 2017. Funding: The project funding is approved and is there to cover the Part II.

Comments: Control substance registration is being established country wide. CNR with EMCCDA data modelling for medical use vs abuse is ongoing. ACS established Cannabinoid division. Ongoing issues; How to make it impactful? Work with Agencies to identify use vs abuse nature of these compounds.

3.2 **Successful Drug Discovery-Volume-2** (Project 2015-026-1-700)

Janos Fischer

JF presented the importance of continuing this book series project and the overall accomplishments over the past 10 years in this projects. He also highlighted the range of topics covered in these series. The following challenges are discussed : i) Identification of competent authors -publications (patents, articles), personal contacts; ii) Company approval -withdrawal of already existing manuscripts; iii) Publication policy - a book series would help the publicity; iv) Diversity -research fields, companies, countries etc.; v) Biopharmaceuticals (co-editor)

JF received very positive usage analysis of SDD-Vol-1 from the Publisher (Wiley-VCH). F. Weinreich sent the following letter :

“Overall usage is pretty good, and it is remarkable that the difference between the most downloaded and the least downloaded chapter is only 30 %. It is a clear indication that the entire content of the volume is perceived as valuable and nothing is out of place. Summary : the Chapter selection of Volume 1 is perfect.”

SDD-Volume-1 Usage Analysis

Title	Full Text Access	Abstract
Swinney: Molecular Mechanism	208	348
Fischer: Serendipity	141	142
Wasburn: Dapagliflozin	196	349
Eckhardt: Linagliptin	196	302
Ghirish: Trastuzumab emtansine	116	174
Yamada: Avanafil	141	266
Beals: Insulin analogues	90	106
Taylor: Pemetrexed	126	181
Hibi: Perampanel	76	80
Rao: Telaprevir	91	155
Shinkai: Elvitegravir	78	102

Volume-2 of this book series has been published at the end of 2016. The book described 11 case histories from different therapeutic fields of drug research. Section editors helped the book.

Part I consisted of five case histories of HDAA inhibitor anticancer drugs (vorinostat, romidepsin, belinostat, panobinostat and chidamide).

Part II described the discovery and development of abiraterone acetate, which is a steroidal CYP17 inhibitor anticancer drug.

Part III consisted of two case histories of anti-infective drug discoveries (delamanid and sofosbuvir)

Part IV described the discovery and development of vortioxetine.

Part V was a case history of vonoprazan fumarate.

Part VI described a case history of nintedanib.

The project concerning Volume 2 of Successful Drug Discovery could be completed according to the IUPAC project and the plans of the Publisher.

3.3 Successful Drug Discovery - Volume 3 Project 2016-027-1 (JF)

Timeline: Volume 3 of this series is co-edited by János Fischer (Richter Plc), Wayne E. Childers (Temple University) and Christian Klein (Head Oncology Programs, Hoffmann - La Roche). The manuscripts have been sent in March to Wiley-VCH. Proof-reading is expected in July and the book to be published: December 2017.

The following sections are discussed:

Part I. General Aspects

1. Gerd Schnorrenberg (Boehringer Ingelheim)
New Trends in Drug Discovery (NCEs and NBEs)
2. Ulrich Storz (Michalski Hüttermann & Partner)
Patent Protection for Small and Large Pharmaceutical Molecules

Part II. Drug Class Studies

1. Day Nguyen and Arwed Cleve (Bayer)
Evolution of Non-steroidal Androgen Receptor Antagonist
2. Peng Wu and Amit Choudhary (MIT, USA)
Kinase Inhibitor Drugs

Part III. Case Studies

1. Patrick A. Baeuerle (MPM Capital)
T-Cell-engaging Bispecific Antibody Construct Blinatumomab for Treatment of Patients with Relapsed and Refractory Acute B-lymphoblastic Leukemia
2. Pierre-Yves Michellys (Novartis)
Ceritinib. A Potent ALK Inhibitor for the Treatment of Crizotinib-Resistant Non-Small Cell Lung Cancer Tumors
3. Maarten L. Janmaat (Genmab)
Discovery and Mechanisms of Action of the CD38-targeting Antibody Daratumumab (Janmaat)
4. Roberto Pellicciari (TES Pharma)
The Discovery of Obeticholic Acid (OCALIVA), First in Class FXR Agonist
5. Christian Klein (Roche)
Discovery and Development of Obinutuzumab, a Glycoengineered Type II CD20 antibody (Gazyva, Gazyvaro)
6. Tesfaye Biftu (Merck, ASTU-Institute)
Omarigliptin (Marizev TM): A Once-weekly Oral Antidiabetic Agent
7. László E. Kiss (BIAL)
Opicapone, a Novel Catechol-O-Methyltransferase Inhibitor (COMT) to Manage the Symptoms of Parkinson's Disease (PD) (Kiss)
8. Micael J. Waring (Newcastle University, UK)
The Discovery of Osimertinib
9. C. Robin Ganellin (London University)
Discovery of Pitolisant, the First Marketed Histamine H₃-Receptor Inverse Agonist/Antagonist for Treating Narcolepsy
10. Mario Varasi (IFOM, Milan, Italy)
Discovery and Development of Safinamide, a New Drug for the

Treatment of Parkinson's Disease

11. Teiji Takechi (Taiho Pharmaceutical Co.)

Discovery and Development of Trifluridine/Tipiracil (Lonsurf®)

4. Project proposals

4.1. Medicinal Chemistry Training: WC of Temple University discussed the need to address the changing paradigm of training graduating chemists as Medicinal Chemists. There was consensus among the team members that this is an important topic. The major outcome of the discussion was that to do a survey on this topic from the pharma, biotech industry and academic groups. The following factors were discussed as the driving forces for training and the exposure for a medicinal chemistry graduates. : i) changing landscape of modalities (small molecules vs biologics) in drug discovery; ii) the shift in emphasis in big pharma vs small, medium size companies in terms of focus on discovery vs development ; iii) biopharma companies focus on large molecules; iv) the emphasis on R &D in developed and developing countries vs the unmet medical needs;

4.2. Medicinal Chemistry Training India

Held at Biocon Academy in Bangalore on February 14-18, 2017. • Previous courses held in 2013 and 2015 (Chennai). • 20 lectures, 3 case histories, and two keynote lectures (Banquet). • 95 participants from industry and academia. • Funding and co-sponsorship from ACS, ACS MEDI and IUPAC • Co-Organizers - Balu Balasubramanian, Bill Greenlee • MEDI participation – Tom Prisinzano, Nick Meanwell • Two representatives for ACS Publications on site for the entire course • High ratings from the participants for the lectures and organization • Attendees offered complementary 1-year ACS and ACS/MEDI memberships - 61 new members • Exploring interest in an ACS local chapter in Bangalore area. • MCADDI 2019 – likely to be held in Bangalore or Hyderabad

Discussion was centered on how IUPAC can take advantage of such sponsored residential programs and symposia to propagate their missions.

4.3. Training on Entrepreneurship (MC)

Highlighted the importance of conducting programs to train both entry level and experienced chemists, medicinal chemists to become successful entrepreneurs. Planned events at IUPAC and ACS meetings

- i) Lectures by four successful entrepreneurs who transitioned their ideas to commercial success in pharma, biotech / therapeutics, materials science and medical devices
- ii) Teaching workshops on Entrepreneurship, writing of business plans, making a business case / pitch, negotiating a business deal.
- iii) Lectures by four Nobel Laureates on how they contributed to innovation / entrepreneurship; how they established companies and parlayed with VCs and

angel Investors. “Nobel Prize Winning Discoveries that Revolutionized Advanced Materials, Technologies, Systems and Processes”.

Comments: While the importance of the concept of Entrepreneurship was well received by the team, the way to link this to the mission of IUPAC was raised. TP follows up with MC, as this potential project is also under discussion with ACS.

4.4. Drug Discovery: Dealing with the Reality of Co-morbidities (ML)

Essentially every pharma company, today, has a department/division/activity termed “real world evidence”. The focus of these activities is to examine what is frequently termed Phase IV clinical studies, i.e. the examination of what happens after regulatory approval and a drug goes onto market in terms of interaction with real world patient response and side-effects and real world physician prescribing behaviour. It is well understood that these post-approval activities significantly impact the value of a drug in which full development investment, e.g. discovery, clinical development, regulatory submission, has already been invested.

This project proposal is designed to create a database that can move the evaluation of such critical factors to an earlier position in the drug development process, e.g. discovery, to enable more efficient and effective drug design and development to take place and improve the potential for success, not only in the regulatory process but also upon market introduction.

4.5_ Successful Drug Discovery-Vol-4 (JF)

This is a continuation of the book series ; the editors this time consist of : Janos Fischer, Wayne E. Childers and Christian Klein; Manuscript deadline : 15-December-2017

10-12 chapters that covers i) General Aspects ii) Drug Class Studies iii) Case Histories. Publication (Wiley-VCH) at the end of 2018

Wiley-VCH is ready to publish the fourth volume. of this book series.

4.6 Evaluation of toxicological and unintended side-effects on the failure in clinical trials of new drugs (new proposal proposal to be considered jointly between SC-D3 and SC on Toxicology) (ML)

A critical aspect of failure in clinical trials of new drugs is the appearance of toxicological effects and/or side-effects that are not anticipated during the discovery process. This project will jointly involve the subcommittees in Division VII that focus on D3 and on Toxicology to develop a database of such events and analyze (and report) on the occurrences and likely sources of such effects that

cause clinical trial failures in an effort to improve the efficiency and efficacy in early drug development.

5. Other Business

5.1 **ACS Medicinal Chemistry News** (PW) Highlighted the current make up of the MEDI division as well as their upcoming co sponsorship programs Ex: AIMECS-ACS 2017 program in Australia and EFMC-ACS 2017 program in Philadelphia. Emphasized the fact that MEDI web site and the News letter, The Reaction Times, combined cover as the single source of communication for the division. Also discussed the genesis of the e-publication Medicinal Chemistry Reviews (previously known as Annual Report in Medicinal Chemistry). Switching from Elsevier publication to e-version resulted in huge saving for the division.

5.2. European Federation for Medicinal Chemistry (EFMC) (JF)

Upcoming Medicinal Chemistry Conferences:

- a) Toulouse (July 5-7, 2017) Drug Discovery and Selection;
- b) Vienna (August 27-31, 2017) Advances in Synthetic and Medicinal Chemistry;
- c) Ljubljana (September 2-6, 2018) XXV EFMC International Symposium on Medicinal Chemistr.

5.2. Asian Federation for Medicinal Chemistry (JB and TK)

AIMECS 2017 will be held on 23-26 July 2017 in Melbourne, Australia, and will be chaired by Dr. Renate Griffith, professor for Medicinal and Biomolecular Chemistry at UNSW in Sidney.

The program is available at <http://www.racicongress.com/AIMECS2017/>

6.3. Upcoming IUPAC meetings

The next IUPAC General Assembly will be held at the occasion of the 46th IUPAC World Chemistry Congress 'Sustainability & Diversity through Chemistry' on July 9 to 14, 2017 in São Paulo, Brazil (<http://www.iupac2017.org>)

IUPAC will celebrate 100 years holding its 50th General Assembly at 'Palais des Congrès' in Paris France, together with the 47th IUPAC World Chemistry Congress, on July 7 to 12, 2019, with a focus on Chemistry for Life, Chemistry for Energy and Resources, and Chemistry for Environment.

6.4. Next SC D3 meeting

The next SCD3 meeting will be held on August 26, 2017, in Vienna prior to EFMC-ASMC, the EFMC symposium on advances in synthetic and medicinal chemistry.