Draft Minutes

IUPAC DIVISION VII CHEMISTRY AND HUMAN HEALTH

SUBCOMMITTEE ON DRUG DISCOVERY AND DEVELOPMENT

(SC D3)

San Diego (USA) (Omni Hotel, 675 L Street)

Saturday, 12 March 2016, 9 AM - 5 PM

Attendees: Janos Fischer (Chair), Balu Balasubramanian, Wayne E. Childers, Mukund Chorghade, Paul W Erhardt, Toshi Kobayashi, Michael Liebman, Yvonne C Martin, Tom Perun, John Proudfoot and Patrick M. Woster**:**

Introduction:

The subcommittee meeting started with a welcome remark from Janos Fischer. The SC members remembered Camille Georges Wermuth, who died in September 2015 at the age of 82. His outstanding IUPAC activity in the Medicinal Chemistry Section (1987), then as president of the Chemistry and Human Health (1998-99) and afterwards as Chair of this subcommittee represented a great contribution to the role of medicinal chemistry at IUPAC. Wayne E. Childers (Temple University) was introduced as a new member, followed by individual reports from those present updating their current professional activities at their institution and IUPAC.

Some highlights of the last meetings in Rio de Janeiro and Antwerp were overviewed and the minutes of Antwerp were approved.

Membership:

Tom Perun suggested three individuals to be invited to the SC : Jonathan Blackburn (South Africa), Bengt Haug (Norway) and Nestor Carballeira (Puerto Rico).

IUPAC-Richter Prize:

A new agreement has been signed by Erik Bogsch (CEO, Richter Plc) and Mark Cesa (IUPAC president) in November 2015 for the continuation of the IUPAC-Richter Prize between 2016-2024 :

IUPAC-Richter Prize in Medicinal Chemistry

(2015-2024)

1. The IUPAC Richter Prize in Medicinal Chemistry has been established by a generous gift from the Hungarian Pharmaceutical Company Gedeon Richter, Plc. (Budapest, Hungary) to acknowledge the key role that medicinal chemistry plays toward improving human health.

2. The prize of $ 10,000 will be awarded to an internationally-recognized scientist (medicinal chemist) whose activities or published accounts have made an outstanding contribution to the practice of medicinal chemistry or, more importantly, to an outstanding example of new drug discovery.

3. Richter Plc. will provide the cost of the prize five times in the period of ten years following the execution of this agreement between Richter Plc. and IUPAC. The prize should be awarded biennially. Richter Plc. will transfer USD 10 000 (ten thousand) to IUPAC 30 days before the award ceremony. IUPAC will prepare the plaque and check for the awardee and send them to the organisers of the prize giving ceremony.

4. A selection committee should be appointed at least six months prior to each award by a consensus of the Division VII. Subcommittee on Drug Discovery and Development. The selection committee should consist of:

   (i) Non-voting Chair;

   (ii) Four additional Subcommittee members drawn to represent as many continents as possible;

   (iii) An outside IUPAC established scientist, who is affiliated with the ACS Nat. MC Symposium;

   (iv) An outside IUPAC established scientist who is affiliated with the European MC Symposium;

   (v) An outside IUPAC established scientist who is affiliated with the Asian AIMECS Meeting;

   (vi) Non-voting representative of Richter Plc.

5. Although coordinated through the IUPAC Secretariat, advertising should be done through all of the professional organizations and their associated journals that are relevant to MC. Applicants should be received electronically by NOMINATION only with just one person needing to serve in that capacity, although a total of five (5) individuals should be listed as references overall. The package should contain a complete resume, a professional autobiography of not more than two pages, and a one page summary of what the individual considers to be his/her activities, accomplishments and/or publications that have had the most significant impact upon the field of MC. Renominations may be accepted, depending on the circumstances.

6. The site of the award ceremony will be determined by IUPAC. Preferably this should be an international conference where medicinal chemistry plays an important role. The ceremony should include a lecture of the awardee whose reasonable travelling cost will be covered by Richter Plc. Representative of Richter Plc. has the right to participate in the award ceremony. Preferably, the awardee will also give the lecture at a second conference location determined by IUPAC, provided that the conference organisers help to defray the travel expenses of the awardee.

(Mark Cesa, President, IUPAC) (Erik Bogsch, CEO, Richter Plc.)

JF as Chair of the SC D3 served as non-voting chair of the Selection Committee of the 2016 IUPAC-Richter Prize.

The Selection Committee had the following members :

Fischer, Janos (Chair)

Augustyns, Koen (EFMC)

Buschmann, Helmut (awardee of the 2014 IUPAC-Richter Prize)

Differding, Edmond (IUPAC, Div. VII, SC D3 secretary)

Hwu, Reuben (AFMC)

Kobayashi, Toshi-Hiko (research advisor)

Kondo, Kazumi (Otsuka, Japan)

Perun, Tom (IUPAC Div. VII president)

Rotella, David (Montclair University)

Woster, Patrick M. (ACS, Medicinal Chemistry Division)

Nomination of the 2016 IUPAC-Richter Prize has been announced by IUPAC, EFMC, AFMC, ACS among others and the nomination deadline was January 31, 2016. The Selection Committee received 15 nominations and IUPAC has been informed in March that Michael J. Sofia received the 2016 IUPAC Richter prize for his outstanding contributions to the discovery and development of the antiviral drug sofosbuvir. The prize winner will give two lectures : in Chicago at the Medicinal Chemistry Symposium in June, where he will be introduced by Patrick M Woster and the award lecture will be given in Manchester at the EFMC Symposium.

The nomination process was discussed among the attendees and some suggestions were made to update the qualification for the selection of this prize.

Projects

In general the subcommittee wants to complete projects according to the deadline and it is promising that the number of long-standing projects is decreasing.

1. Nomenclature and terminology

Glossary terms are mostly easily accessible, nevertheless, it has a great scientific value if glossaries are validated by a group a scientists at IUPAC and glossary projects represent a useful part of IUPAC acitivities.

1.1. Drug Metabolism Terms (Paul Erhardt) **Project 2000-009-1-700**

It was presented by Paul Erhard. Status: Little advancement of project and initial working party has 'wound-down.' From feedback at invited international lectures and consulting by PWE a tutorial emphasis would be of much more value than just a list of terms with definitions; Advances in access to high quality didactic technical information *via* the Internet continue to underscore this revelation. **Action item**: Bring the project to a closure. Website to be opened up at the IUPAC site to update the static/dynamic aspects of the terms and periodically to be edited as needed basis. Complete Term/Tutorial by early Fall including review by newly recruited working party. Submit to *PAC* prior to the end of 2016.

1.2 Glossary of Combinatorial Chemistry Terms (Ganesan) **Project 2003-044-1-700** was not presented at this meeting and will be discussed at the next meeting.

1.3 Glossary of Terms used in Computational Drug Design Project (Yvonne Martin) **2010-057-1-700** was presented by the project leader. Publication in PAC is in progress.

2. New Technologies and Special Topics

2.1 Human Drug Metabolism Database (hDMdb) Paul Erhardt updated the **Project 2011-018-1-700**: History and Status: 2005- (also had been funded initially by a $50K grant from the ICSU) Established 'founding' working party of 5 experts including initial participation by IUPHAR (subsequently withdrew along with remaining ICSU funds); Skeleton for assembly of clinical-derived information input and retrieval was established according to JAVA programming for an Academic Oracle database; Initiated programming with small dataset to establish an early prototype (later shown to be flawed).

2015- Lack of funding and departures of student participants prevented advancement of the project and remainder of initial working party 'wound-down.' Revived as a potential project by Division VII; Advances in computer technology now allow for much simpler databases and software to be deployed, even on desk-top computer (or hand-held device) hardware systems such that platform and software costs are no longer an issue (labor still lingers), nor are previous proprietary aspects associated with placement on the Internet and allowing for open access.

2016- Need to re-evaluate the merit of establishing an hDMdb based upon what's now become available and potential users' present level of interest. Given the advancements in computer and software technologies, can it now include animal and *in vitro* data to so as to provide even more value (this transition still looms as a hurdle during drug development)?

Action Items : Complete a review of present resources in this arena and a survey of users from the public (NIH etc.), academic and private (small and big pharma) sectors while including representation from several countries besides the U.S.; and generate an article based upon these findings for *PAC*

that can also be used to guide subsequent decisions about potentially proceeding with such a project with or without direct IUPAC involvement.

Timetable : It is anticipated that this plan can nearly overlap or trail just behind the DM Terms project thus having a target completion date of end-2016 to early 2017.

2.2 Successful Drug Discovery Volume II (Janos Fischer) **Project 2015-026-1-700**

The second volume of the book series has been edited by János Fischer and Wayne E. Childers.The layout phase is underway at Wiley-VCH with the following finalized contents and publication is expected in October 2016.

I. HDAC Inhibitor Anticancer Drug Discovery.

Section Editor: A. Ganesan (University of East Anglia, Norwich, UK)

1. *Vorinostat*

Ronald Breslow (Columbia University, USA) described the discovery of vorinostat which is a pioneer HDAC inibitor which started from dimethylsulfoxide as a lead molecule.

2. *Romidepsin*

Ganesan gives an overview on the discovery of romidepsin, a depsipeptide natural product. High throughput screening led to an anticancer drug which proved to be a potent inhibitor of class I HDACs.

3. *Belinostat*

Paul W. Finn and coworkers (University of Buckingham, UK) report on belinostat which is a potent, pan-inhibitor of class I and II HDACs. It was approved in 2014 for the treatment of peripheral T-cell lymphoma.

4. *Panobinostat*

Peter Atadja and coworker (Novartis Institute for Biomedical Research, US & China) present the story of how a functional high throughput screen looking for inducers of CDK inhibitor p21 provided hits that were identified as HDAC inhibitors, ultimately resulting in the discovery of panobinostat.

5. *Chidamide*

Xian-Ping Lu and coworkers (Shenzen Chipscreen Biosciences, China) described the discovery and development of chidamide which is a novel benzamide type inhibitor of class I HDACs and class IIb HDAC10.

II. Steroidal CYP17 Inhibitor Anticancer Drug Discovery.

Section Editor : Juan-Miguel Jimenez (Vertex Pharmaceuticals , UK)

Abiraterone acetate

Gabriel Martinez Botella and coworkers (SAGE Therapeutics, USA) have written a chapter on the discovery of abiraterone acetate which is a key therapeutic in the treatment of metastatic castrate resistant prostate cancer.

III. Anti-infective Drug Discoveries

Section Editor : John Proudfoot (Boehringer-Ingelheim, Ridgefield, USA)

1. Delamanid

Hidetsugu Tsubouchi and coworkers (Otsuka, Japan) summarized the discovery of delamanid which is a new drug for the treatment of multidrug-resistant pulmonary tuberculosis.

2. Sofosbuvir

Michael J. Sofia (Arbutus Biopharma, USA) described the discovery of sofosbuvir which has become the backbone agent of combination curative therapy for hepatitis C virus infection.

IV. CNS Drug Discovery

Section Editor : Helmut Buschmann (Aachen, Germany)

Vortioxetine

Benny Bang-Andersen and coworkers (Lundbeck, Denmark and USA) give an overview on the discovery of vortioxetine, a new *multimodal* antidepressant drug with serotonin modulator and stimulator activity.

V. Antiulcer Drug Discovery

Section Editor : Jörg Senn-Bilfinger (Konstanz, Germany)

Vonoprazan fumarate

Haruyuki Nishida (Takeda, Japan) described the discovery of vonoprazan fumarate which is a novel, potent and long-lasting potassium-competitive acid blocker showing several advantages over proton pump inhibitors.

VI. Cross Therapeutic Drug Discovery (Respiratory Diseases/Anticancer)

Section Editor : Stefan Laufer (University of Tübingen, Germany)

Nintedanib

Gerald J. Roth and coworkers (Boehringer Ingelheim, Biberach, Germany) summarize the discovery and development of nintedanib, which represents a pioneer discovery of a cross therapeutic research for the treatment of solid tumors and idiopathic pulmonary fibrosis.

2.3 Emerging Problem of Novel Psychoactive Substances (Vincenzo Abbate)

Project 2014-019-1-700 was presented as a slide. **Action Item**: Last draft to be circulated for peer review by 12/2016 and the submission to PAC is expected in 2Q 2017.

3. Training and Development

3.1 A Survey of Research into New Drugs for Neglected Diseases in Latin America (Robin Ganellin)

Project 2009-033-1-700 update was presented on behalf of Robin. Lack of relevant contact in LATAM appears to be the stumbling block. Some suggestions for possible avenues to reach a broader audience: a) Creation of a New Website to seek the survey and to disseminate the gathered information (example of a related website at U of Texas Austin: https://texasend7.com/); b) organizing a workshop to bring people together for an interdepartmental discussion (zika virus fund raising is proposed as a possibility). **Action item**: Review the path forward at the next subcommittee meeting in Manchester.

4. New Project proposals

4.1 Successful Drug Discovery - Volume III (János Fischer)

It is already in progress to continue the book series. The third volume will be edited by János Fischer (Richter Plc), Wayne E. Childers (Temple University) and Christian Klein (Roche).

Draft contents of the book :

I. General Aspects

Two chapters are planned: an introductory chapter compares the discovery and development of small molecule drugs and biologics (Schnorrenberg et al) and another chapter focuses on patenting questions of these two types of medicines (Ulrich Storz)

II. Drug Class

This part of the book is planned with two chapters. A chapter describes the drug class of androgen receptor antagonists and optimization of therapy with help of analogues (Arwed Cleve, Bayer). Another chapter will give an overview on DPP-IV inhibitors for the treatment of type 2 diabetes (Tesfaye Biftu, Merck, USA).

III. Case Studies

1. Blinatumomab is the first bispecific antibody targeting CD19 and CD3 antigens. Amgen received approval in 2014 for the treatment of special case of acute lymphoblastic leukemia (ALL). (Patrick A. Baeuerle).

2. Cariprazine is a new antipsychotic drug of Richter Plc. It is a dopamine D3 preferring D3/D2 partial agonist, which has been approved by FDA in 2015 for the treatment of acute mania associated with bipolar I disorder and for the treatment of schizophrenia. This chapter has already been planned in the previous volume, but it has not been approved by the involved companies in time. (Bela Kiss and Gyorgy Domany (Richter Plc).

3. Ceritinib is an ALK inhibitor. It has been approved in 2014 for the treatment of ALK-positive metastatic non-small cell lung cancer. (Pierre-Yves Michellys (Novartis)

4. Daratumumab is a fully human antibody approved by FDA for the treatment of multiple myeloma in 2015. (Paul Parren, Genmab, DK)

5. Obeticholic acid is a pioneer and potent farnesoid X receptor agonist. It has been approved by FDA in 2016 for the treatment of primary biliary cirrhosis. (Roberto Pellicciari, TES Pharma, Perugia, Italy).

6. Obinutuzumab is a new humanized anti-CD20 monoclonal antibody approved by FDA in 2013 for the treatment of chronic lymphocytic leukemia. (Christian Klein, Roche)

7. Opicapone is a new drug for treatment of Parkinson's disease which has a COMT inhibitor mechanism of action. It has been approved by EMA in 2016. (Laszlo Kiss, BIAL, Portugal).

8. Osimertinib mesylate is a new EGFR inhibitor drug for the treatment of NSCLC. It has been approved by FDA in 2015.

9 Palbociclib is a selective inhibitor of cyclin-dependent kinases CDK4 and CDK6. The drug has been approved by FDA in 2015 for the treatment of advanced breast cancer. (Peter L. Toogood, Lycear Corporation, USA).

10. Pitolisant hydrochloride is a new drug for the treatment of narcolepsy with H3 receptor inverse agonist mechanism of action. It has been approved by EMA in 2016. (Robin Ganellin)

11. Safinamide is an new Parkinson's drug with multiple mechanism of action. It has been approved in 2015 by EMA. (Mario Varasi, IFOM, Milan, Italy)

Synopsis deadline is June 30 and the authors are requested to deliver their manuscriupts by December 15.

The Publisher Wiley-VCH commented on the new book project on June 16 as follows :

Publisher's commentary on the outline for Vol. 3 of "Successful Drug Discovery"

As the publisher of this series, we are delighted to see it continued with another substantial and broadly applicable volume. It is good to see that this volume closely follows the philosophy of the first SDD volume, with two chapters on general issues, one chapter on an important drug class, and 11 case studies, all of which describe new drugs that have very recently entered the market. We also note with satisfaction that the editor team now includes Dr. Christian Klein, thereby adding important expertise in the area of biopharmaceuticals, which account for an ever-increasing percentage of new drugs.

We will be glad to publish this new volume and wish the editors success in bringing it to completion in a timely manner. We also gratefully acknowledge the support and expertise of IUPAC's division of chemistry and human health in making this new volume possible. (Frank Weinreich, Wiley-VCH)

4.2 Medicinal Chemistry Drug Discovery and Development India, III (MCADDI 2017) (Balu Balasubramanian)

Based on the previous two residential courses feedback, the venue for the 2017 program will be changed to Bangalore instead of Chennai. This would allow access to larger industrial and academic participants. We have also expanded the course to fit the current trend in Drug Discovery and Development that is covering the Biologics area.

The course content now will span from the fundamentals of Medicinal Chemistry in Drug design and how Medicinal Chemistry is impacting in the Translational Medicine loop in terms optimizing the clinically relevance qualities of the drug to improve the safety and efficacy. Thus the course also includes an hour long introduction and impact of Proof of Concept (PoC) early clinical development studies as well as regulatory framework. The course also emphasizes the importance of ethics in conducting and publication of research as well as intellectual property protection. This project proposal was submitted for approval after the meeting.

A suggestion to invite participation from South East Asia and South Africa will be considered at the 2017 program. The program is also funded by ACS and ACS MEDI division.

4.3 Dealing with the Reality of Co-morbidities (Michael Liebman)

The abstract is the same as in last meeting minutes. Lot of discussion surfaced regarding the area of relevance to the areas of Chemistry /drug discovery sciences. The group recommended highlighting the direct relevance to Chemistry prior to submitting the proposal.

4.4 Systematic Analysis pf Pharmaceutical Impurities and Degradation Products (Helmut Buschmann)

An impurity database and library proposal will be discussed at the next meeting in Manchester.

5. Other Business

European Conferences:

a. European Federation for Medicinal Chemistry:

EFMC - ISMC: Manchester, UK - August 28 - September 1, 2016

b. EuCheMS (European Association for Chemical and Molecular Sciences)

6th EuCheMS Chemistry Conference Seville, Spain - 11-15 September 2016

Asian Federation for Medicinal Chemistry

Toshi Kobayashi encouraged increased interaction of other regional IUPAC countries with this group.

Upcoming meetings:

a. The upcoming SC-D3 meeting is scheduled for August 27, 2016 (Manchester) prior to the EFMC Medicinal Chemistry Symposium

b. 6th EuCheMS Chemistry Conference (European Association of Chemical and Molecular Sciences) Seville, Spain - 11-15 September 2016
2016 IUPAC-Richter Prize

c. 11th AFMC International Medicinal Chemistry Symposium, 3 days in July 2017 (between 23rd and 28th) in Melbourne, Australia ; Chemistry in Drug Discovery, Design & Development