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

Manchester Convention Centre, Manchester, UK
Saturday, August 27, 2016 – 9am-6pm

Attendees: Eli Breuer (EB), H. Buschmann (HB), E. Differding (ED) (Secretary), J. Fischer (JF)(Chair), R. Ganellin (RG), M. Liebman (ML), T. Perun (TP), G. Schnorrenberg (GS), J. Senn-Bilfinger (JSB), C. Suckling (CS)

Excused: Vincenzo Abbate, David Alker, Sergey Bachurin, Jonathan Baell, Balu Balasubramanian, Benny Bang-Andersen, Nestor M. Carballeira, Wayne E. Childers, Paul W. Erhardt, Flavio da Silva Emery, Ray Finlay, A. Ganesan, Reuben Hwu, Toshi Kobayashi, Barry Potter, Patrick M. Woster and Zhu-Ju, Yao

1. Introductions, Opening Remarks, and Minutes of the Previous Meeting in San Diego

JF opens the meeting with a short overview of the structure of IUPAC and activities of its Subcommittee on Drug Discovery and Development, such as books, glossaries, articles, the IUPAC Richter Prize and training activities in Brazil and India.

The minutes of the San Diego meeting are accepted.

Matters arising from the minutes:

The need for IUPAC glossaries under the current paper and online format is discussed. 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. Membership

Wayne E. Childers (Temple University, USA) is a new SC member.

3. IUPAC–Richter Prize

JF summarizes the process, including the worldwide publication of the call for nominations, and the selection process by the jury, chaired by himself (as non-voting member), that led to this year's prize winner Michael Sofia, for his contribution to the discovery and development of Sofosbuvir. JF will chair the Prize session during EFMC-ISMC 2016 in Manchester, UK, and present the IUPAC plaque to Michael who will give his lecture.

Post-meeting information: the 2016 IUPAC-Richter Prize was given in Manchester on August 31. JF, as chair of the Selection committee gave the following speech:

"As a representative of IUPAC, the International Union of Pure and Applied Chemistry, and the Hungarian Pharmaceutical Company Gedeon Richter Plc in Budapest, I am honored to announce the 2016 IUPAC-Richter Prize. This year the 10-member International Selection Committee has awarded the prize to Dr. Michael Sofia from the United States of America. The

Selection Committee provided the following justification for this decision. Hepatitis C infection is a serious disease and a hidden epidemic causing more than 300.000 deaths worldwide annually. Before 2013, standard therapy had achieved a cure rate of about 75 %. This situation changed dramatically with the introduction of sofosbuvir. Sofosbuvir inhibits the HCV RNA polymerase, which the hepatitis C virus uses to replicate its RNA. Compared to previous treatments, sofosbuvir-based regimens achieved a higher cure rate with fewer side effects and a significantly reduced duration of therapy. Sofosbuvir was discovered by Michael Sofia and developed by Gilead Sciences. Sofosbuvir and its combinations have significantly improved the treatment of all genotypes of hepatitis C. It is estimated that approximately 1 million HCV infected patients have been cured by sofosbuvir-based therapies. I would like to congratulate Michael Sofia for his excellent work and his contribution to humanity by presenting to him this plaque as a symbol of the 2016 IUPAC-Richter Prize".

4. Projects

4.1. Successful Drug Discovery, Volume 2 - Project 2015-026-1-700 (JF)

Volume 2 of this series will be published in November 2016

JF discusses the concept of this book series, focussing on case studies with existing drugs, which is different from the ACS series 'Medicinal Chemistry Reviews' (previously Annual Reports in Medicinal Chemistry), which rather targets a broad variety of emerging treatments, including only 2or 3 case studies of recently approved new chemical entities.

The final content of the book is the following:

Editors: Janos Fischer and Wayne E. Childers

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 whose discovery 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.

4.2. Emerging problem of Novel Psychoactive Substances - Project 2014-019-1-700 (Vincenzo Abbate (VA))

As the project leader was unable to attend the subcommittee meeting, it is proposed to discuss this project in detail at the upcoming Division VII meeting in Copenhagen, for which VA has confirmed his attendance. There is agreement that the title needs to be more specific, and will have to include the notion of ‘drugs of abuse’ and to mention the report’s focus on cannabinoids and cathinones.

5. Project proposals

5.1. Successful Drug Discovery, Volume 3 – Project proposal 2016-027-1 (JF)

Volume 3 of this series will be co-edited by JF and Christian Klein (Head Oncology Programs, Hoffmann - La Roche). Time scale: synopses by June 2016, draft manuscripts by December 2016, print-ready manuscripts by June 2017, book to be published: October 2017

The following chapters are planned:

I. General Aspects
1. New Trends in Drug Discovery (Gerd Schnorrenberg, Boehringer Ingelheim, Germany)
2. Patenting Drugs and Biologics (Ulrich Storz, Michalski Huettermann & Partner, Düsseldorf, Germany)
II. Drug Class Study
1. Evolution of Non-Steroidal Androgen Receptor Antagonists (Arwed Cleve, Bayer Pharma Berlin, Germany)
2. T-Cell-engaging Bispecific Antibody Construct Blinatumomab for the Treatment of Patients with Relapsed and Refractory Acute B-Lymhoblastic Leukemia (Patrick A. Baeuerle, MPM Capital, Cambridge, USA)
3. Successful Drug Discovery: Ceritinib (Pierre-Yves Michellys, Novartis, Switzerland))
4. Discovery and Mechanisms of Action of the CD38-Targeting Antibody Daratumomab (Paul Parren, Genmab BV, Utrecht,The Netherlands)
5. The Discovery of Obeticholic Acid (OCALIVA), First in Class FXR Agonist (Roberto Pellicciari, TES Pharma S.r.l., Perugia, Italy)
6. Discovery and Development of Obinutuzumab, a Glycoengineered Type II CD20 Antibody (GAZYVA, GAZYVARO) (Christian Klein, Roche Pharmaceutical Research, Schlieren, Switzerland)
7. Omarigliptin (MARIZEV): A Once-weekly Oral Antidiabetic Agent (Tesfaye Biftu, Merck & Co., Kenilworth, USA)
8. Opicapone,a Novel Catechol-O-Methyltransferase Inhibitor (COMT) to Manage the Symptoms of Parkinson's Disease (Laszlo Kiss, BIAL-PORTELA S.A., Mamede do Coronado, Portugal)
9. Discovery and Development of Safinamide, a New Drug for the Treatment of Parkinson's Disease (Mario Varasi, IFOM Institute, Milan, Italy)

GS gives an outline on his views on 'Current Trends in Drug Discovery' with the boom in recent years of NBEs due to their reduced attrition rate and shorter timelines, their higher specificity, new formats such as bispecific antibodies, a better understanding of immunogenicity and aggregation, but also their limitations such as their restriction to extracellular targets. The chapter also includes a discussion on vaccines, the need for a better understanding of diseases, the use of biomarkers, and new emerging treatments using cell and gene-based therapies.

HB suggests to include aspects on registration, or patent protection, including exclusivity timelines.

Both the editors and the publisher aim at making 'Successful Drug Discovery' an annual publication. This comes with a few scientific and organizational challenges, such as the identification of Editorial Committees per therapeutic area, the fast identification of key inventors, and the understanding of company policies for publications and approval processes.

ML proposes to include in the 'General Aspects' section of upcoming volumes the analysis of previously published work on e.g. the evolution of screening technologies, the fate of first-in class compounds, the success of repositioning existing drugs, the analysis of the geography of approvals (US, EU, other), etc…

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

ML presents his views on how the reductionist approaches of the drug discovery and development process fail to identify the risks associated with co-morbidities and the resulting polypharmacology. The project intends to develop a web-accessible database that would provide critical information into the early stages of drug development, focused on identifying what are likely co-morbidities and/or drugs in target patient populations so that these can be considered in terms of potential risk for drug interactions, side-effects and impact on efficacy.

5.3 Systematic Analysis of pharmaceutical impurities and degradation products as basis for an impurity database and library (HB)

HB presents his proposal on impurities and degradation products. The aims are to generate a better understanding of the instability of drugs, including in the solid state, and to create a database with degradation products identified during forced degradation studies in the solid state using immobilized catalyst under mechano-activation. The project for which IUPAC funding will be requested would lead to a pilot database including the creation of specific fields to capture relevant information, and focussing on a selection of major target classes."

5.4. Medicinal Chemistry in India, 3rd edition 2017 – Balu Balasubramanian)

The two first editions have been a success, and the third is scheduled for February 14-18, 2017. It will be held at Biocon Academy in Bangalore on, with plans for 21 lectures, 3 case histories, banquet, roundtable discussion, as well as a keynote lecture. The organizers expect 100 - 120 participants from industry and academia. Funding and co-sponsorship have been requested from IUPAC ($6.000), and from ACS IAC, ACS Publications and MEDI. The website will be live by the end of August www.mcaddi.com

The program is as follows:

1. Basic Principals of Medicinal Chemistry - 1 (Prof. Thomas Prisinzano, Univ. of Kansas)
2. Basic Principals of Medicinal Chemistry - 2 (Prof. Thomas Prisinzano, Univ. of Kansas)
3. Target Identification and validation (Dr. Manjunath Ramarao, BMS-Biocon Research Center)
4. Receptors, Enzymes and Ion Channels, (Dr. Manjunath Ramarao, BMS-Biocon Research Center)
5. Hit Identification – HTS, FBDD, Phenotypic and Virtual screening (TBD)
6. Hit-to-Lead Process (Prof. Craig Lindsley, Vanderbilt University)
7. Lead Optimization (Prof. Craig Lindsley, Vanderbilt University)
8. Drug-Like Properties in Drug Discovery (Dr. Swamy Yeleswaram, Incyte)
9. Bioisosteres (Dr. Nick Meanwell, Bristol-Myers Squibb)
10. Physicochemical Properties in Drug Design (Dr. Nick Meanwell, Bristol-Myers Squibb)
11. G-Protein Coupled Receptors (Prof. Craig Lindsley, Vanderbilt University)
12. Structure-Based Drug Design (TBD)
13. Molecular Modeling (TBD)
14. Protein Binding (Dr. Swamy Yeleswaram, Incyte)
15. Drug Metabolism and Pharmacokinetics (Dr. Swamy Yeleswaram, Incyte)
16. Toxic Pharmacophores (Dr. Nick Meanwell, Bristol-Myers Squibb)
17. Pharmaceutics and Developability Characteristics of Drug Candidates (Dr. Nancy Barbour, Bristol-Myers Squibb, USA)
18. Preclinical Toxicity Evaluation - 1 (Dr. Bruce Car, BMS-Biocon Research Center)
19. Preclinical Toxicity Evaluation - 2 (Dr. Bruce Car, BMS-Biocon Research Center)
20. Clinical Development (TBD)
21. Introduction to Biologics – I (Dr. Nitin Dample, Sun Pharma)
22. Introduction to Biologics – 2 (Dr. Nitin Dample, Sun Pharma)
23. Case History Presentation 1 (Pfizer)
24. Case History Presentation 2, (Amgen)
25. Case History Presentation 3 (BMS/Merck)
26. Keynote Lecture (Wednesday evening banquet) – Dr. Carl Decicc, Bristol-Myers Squibb

TP proposes that future editions should not be limited to India, but reach out to other Asian countries, such as e.g. Singapore or China.

5.5. Training on Entrepreneurship – Mukund Chorghade (MC) (via Skype)

MC, who is a member of the ACS Entrepreneurship Task Force, presents his plans to organise a training on Entrepreneurship, to be held at the occasion of the IUPAC World Congress in Sao Paulo, Brazil in 2017. Planned speakers would include Nobel laureates, scientists who have launched successfully their own businesses, and venture groups that would present on investors' views.

CS shares his experience with "Scottish Crucible", a leadership and development program held in Scotland since 2009, which helps researchers to see the bigger picture, and to get an understanding of how science can impact society. This includes training on entrepreneurship during intensive two-day workshops, and goes beyond just raising awareness, as presentations in a one-day symposium might only be able to do.

TP follows up with Mukund Chorghade, as this potential project is also under discussion with ACS.

5.6. Flavio Emery

Flavio Emery (pharmaceutical faculty of Ribeirao Preto, Brazil) proposes the following potential projects:

1. Summer School in Medicinal Chemistry/Drug Discovery (during the XI. Brazilian Congress of Pharmaceutical Sciences, 2017)
2. Heterocyclic Fragments in Drug Discovery
3. Contacts with researchers in Latin America on neglected diseases

Post-meeting remark: JF tried to contact Flavio to discuss his plans in a more detailed form, but until now without results, because the emails remained unanswered.

6. Other Business

6.1. European Federation for Medicinal Chemistry (EFMC)

EFMC-ISMC 2016, with over 1.000 participants, is the biennial flagship conference of EFMC and is held in Manchester on Aug 28-Sep 8, 2016. JF will update EFMC on the activities of IUPAC's Subcommittee on Drug Discovery and Development during the EFMC Council meeting on Aug 28.

XXV EFMC International Symposium on Medicinal Chemistry (EFMC-ISMC 2018), is scheduled for September 2-6, 2018 Ljubljana, Slovenia.

6.2. Asian Federation for Medicinal Chemistry

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 in San Francisco on April 1st 2017 prior to the ACS National Meeting and will be made accessible via Skype to allow a broader participation.

The following 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.