IUPHAR
INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY

IUPHAR-CNPHARS Webinar

Clinical Research on Anti-COVID-19 Drugs

Program

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April 7th, 2020

IUPHAR-CNPHARS Webinar: Clinical Research on Anti-COVID-19 Drugs

抗新冠肺炎药物临床研究网络研讨会

5:00-6:30pm (GMT+8), April 7th, 2020
2020 年 4 月 7 日 17:00-18:30

Organization 会议组织

➢ Organizing Institutions 组织机构

International Union of Basic and Clinical Pharmacology (IUPHAR)
国际药理学联合会

Chinese Pharmacological Society (CNPHARS)
中国药理学会

➢ Co-chairs 会议共同主席

Ingolf Cascorbi

Professor, Director of the Institute of Experimental and Clinical Pharmacology, University of Kiel, Germany; President of IUPHAR

德国基尔大学实验与临床药理学系主任，IUPHAR 主席

Yongxiang Zhang 张永祥

Professor in Beijing Institute of Pharmacology and Toxicology; President of CNPHARS

北京药理毒理研究所研究员，中国药理学会理事长

Program 会议日程

Webinar Co-Chairs 主持人: Michael Spedding, Guanhua Du（杜冠华）

Time (GMT+8) 时 间	Program 日 程
Opening Ceremony 开幕式	
17:00—17:10	1. Opening speech by CNPHARS President, **Yongxiang Zhang** 中国药理学会理事长**张永祥**发言 2. Opening speech by IUPHAR President, **Ingolf Cascorbi** IUPHAR 主席 **Ingolf Cascorbi** 发言
CNPHARS Reports 专题报告	
17:10—17:25	**Dongyang Liu** Drug Clinical Trial Center of Peking University Third Hospital **刘东阳** 北京大学第三医院药物临床试验机构 Title: Current status and thinking of clinical development for small molecule anti-COVID-19 drugs（小分子抗新冠病毒药物临床开发现状与思考）
17:25—17:40	**Junhua Zhang** Evidence-based Medicine Center at Tianjin University of Traditional Chinese Medicine **张俊华** 天津中医药大学循证医学中心 Title: Clinical studies of Chinese medicine for COVID-19, a brief introduction（中医药防治新冠肺炎临床研究概述）
Comments of IUPHAR Experts IUPHAR 专家发言	
17:40—18:00	**Ingolf Cascorbi** (Germany) **Michael Spedding** (France) **Francesca Levi-Schaffer** (Israel) **James Barrett** (USA) **David Webb** (UK) **Caroline Samer** (Switzerland) **Maria Isabel Lucena** (Spain) **Nilima Kshirsagar** (India) **Stephen Alexander** (UK) **Jamie Davies** (UK)
Comprehensive Discussion 综合讨论	
18:00—18:20	Q&A, Discussion 提问与回答，自由发言，参会代表与专家互动讨论。
Closing Remarks 闭幕总结	
18:20—18:30	1. Closing remarks by CNPHARS Vice-President, **Guanhua Du** 中国药理学会副理事长**杜冠华**发言 2. Closing remarks by IUPHAR Secretary-General, **Michael Spedding** IUPHAR 秘书长 **Michael Spedding** 发言

Invited Experts 参会专家

➢ Webinar co-chairs 会议主持人

Michael Spedding

Professor, President of Spedding Research Solutions, France; Secretary-General of IUPHAR

研究员，法国 Spedding 研究所所长，IUPHAR 秘书长

Guanhua Du 杜冠华

Professor, Director of National Centre for Pharmaceutical Screening; Vice-President of CNPHARS; IUPHAR Councilor

研究员，国家药物筛选中心主任，中国药理学会副理事长，IUPHAR 执委

➢ CNPHARS Reporters 中国药理学会报告人

Dongyang Liu 刘东阳

Associate Professor, Deputy Director of Drug Clinical Trial Center of Peking University Third Hospital; Vice-Chair of Division of Pharmacometrics, CNPHARS

副研究员，北京大学第三医院药物临床试验机构副主任，中国药理学会定量药理专业委员会副主任委员

Junhua Zhang 张俊华

Professor, Director of Evidence-based medicine center at Tianjin University of traditional Chinese medicine; Secretary-General of the clinical pharmacology at Chinese Society of Traditional Chinese Medicine

教授，天津中医药大学循证医学中心主任，中华中医药学会中药临床药理分会秘书长

➢ IUPHAR Experts　IUPHAR 专家

Francesca Levi-Schaffer

Professor in the Hebrew University of Jerusalem, Israel; First Vice-President of IUPHAR
以色列耶路撒冷希伯来大学教授，IUPHAR 第一副主席

James Barrett

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美国德雷塞尔大学教授，IUPHAR 司库

David J Webb

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Maria Isabel Lucena

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Nilima Kshirsagar

Professor, National Chair Clinical Pharmacology of ICMR, India; Secretary-General of Clinical Division, IUPHAR
研究员，印度国家医学研究理事会临床药理部主任，IUPHAR 临床药理学分会秘书长

Jamie Davies

Professor at the University of Edinburgh, UK; PI of the IUPHAR/ BPS GtoPdb database
英国爱丁堡大学教授，IUPHAR/英国药理学会 GtoP 数据库首席科学家

Stephen Alexander

Associate Professor of Molecular Pharmacology at the University of Nottingham, UK; Chair of NC-IUPHAR
英国诺丁汉大学副教授，IUPHAR 命名与标准委员会（NC-IUPHAR）主席

➢ Special-invited Experts 特邀专家

Mei Wang 王梅

Professor, Chairperson of LU-European Center for Chinese Medicine and Natural compounds in Leiden University, Netherland; member of TCM working party at European pharmacopeia
教授，荷兰莱顿大学“欧洲中医药与天然产物研究中心”主任，欧洲药典中药委员会专家委员

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➢ CNPHARS Experts 中国药理学会专家

Zhibin Lin 林志彬

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教授，华中科技大学副校长，中国药理学会副理事长

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Dayue Duan　段大跃

Special Appointed Professor in Southwest Medical University; Former Chair of North American Chapter, CNPHARS
西南医科大学特聘教授，中国药理学会北美分会前任主任委员

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教授，北京同仁医院国家药物临床试验机构副主任，中国药理学会药物临床试验专业委员会主任委员

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Brief report on the joint meeting of CNPHARS – IUPHAR, 2020-04-07

Cochairs: Ingolf Cascorbi (President IUPHAR). Yongxiang Zhang (President CN-PHARS).

Attendance:

Chinese Attendees Included:

Guan-Hua Du
Dongyang Liu
Junhua Zhang
Mei Wang
Tao Wang
Zhibin Lin
Jianguo Chen
Wei Wei
Jingshan Shi
Yonghe Zhang
Xuejun Li
Wenxia Zhou
Yimin Cui
Dayue Duan
Xiuli Zhao
Lan Zhang
Xiumei Gao
Ying Zhao

IUPHAR Attendees Included :

Michael Spedding
Francesca Levi-Schaffer
James Barrett
David Webb
Caroline Samer
Maria Isabel Lucena
Nilima Kshirsagar
Jamie Davis
Steve Alexander
René Ciarametaro
Olayinka Ogunleye
Francisco Ruiz Cabello

Introductory section:

The meeting began with a summary of the history and challenges of COVID-19 pharmacology, from the meeting co-chairs.

CNPHARS reports:

Dongyang Liu, of the Drug Clinical Trial Centre of Peking University, 3rd Hospital, gave an account of clinical trials conducted on small-molecule drugs against COVID-19. He began by stressing that an early priority for the trials was to find any agent that could slow the spread of the outbreak (as it then was). One useful starting point was the observation that SARS-CoV2 has a homology with SARS-COV of 79% at the amino acid level (51.8 at the RNA level), suggesting that knowledge gained in the SARS outbreak could be useful for the COVID-19 outbreak. Conducting clinical trials is made complicated by the range of symptoms of different COVID-19 patients, and also different trajectories through the disease, This means that it is not 'one disease' from the point of view of treatment, and patient stratification is a critical issue. We should not therefore expect to have one drug useful for everyone. Three classes of drug emerged as leaders based on rational discussions (before trials); inhibitors of the endosomal/ lysosomal entry path (eg chroloquine - CQ, hydroxychloroquin- HCQ), proteolysis inhibitors (eg lopinavir), and inhibitors of nucleic acid replication (eg favipiravir, remdesivir). The main challenges for clinical development were summarized as; choice of drug, dose regimen, patient stratification, choice of outcome measure, drug-drug interactions and availability in the clinical context (important for developing world medicine). There are also serious challenged of holding trials in an emergency situation with frightened doctors and

patients and a constantly changing background of best care practice (extending beyond drugs) as more is learned.

In vitro studies showed promise for remdesivir at EC50s reasonable for human plasma concentration (.77uM) and for HCQ, with an interaction between EC50 and time (6uM for 24h., 0.7uM for 48h).

Clinical trials have been complicated by the changing background of care, the issue of distinguishing efficacy when so many patients whose self-limiting disease anyway (a problem of stratification/ prediction) and also now by the happy 'problem' of there being too few patients for a large scale trial to take place.

For HCQ, the Shanghai trial, small and low dose, showed no useful effect. The French trial has raised expectations but its design has been controversial and nobody in the conference felt that useful meaning could be extracted from it. The Peking 3rd hospital trials, which separated severe and mild patients, have undergone several stages and several comparisons (eg CQ vs HCQ, CQ vs lopinavir); the trial sizes have meant that there are significantly conclusive data on the drugs so far but there is valuable information to be passed on to subsequent trials. There is also some promising data from survival curves for Favipiravir.

In summary, HCQ and Favipiravir continue to be promising to some extent, but falling numbers of patients mean that the baton now needs to be handed on to other countries still suffering high rates of infection. An international cooperation wisely utilizing Chinese available experiences is warranted in case the 3rd or fourth waves of virus coming in the future in the world.

Junhua Zhang, from the Evidence-based medicine Center at Tianjin University of Chinese Traditional Medicine, explained that there are 49 trials registered for Traditional Chinese Medicine (TCM) approaches before Feb 16, and outlined the principles of their trial registration and design, the number raised to about 100 till April 5. In a systematic review, which included 11 studies, 4 of them were randomized control studies, the other no-randomised clinical control studies. Often the study was asking whether addition of TCM to a conventional pharmacological intervention improved outcome (so the question was about joint use of approaches, not TCM versus conventional pharmacology). There were three main medicines tested; Lianhua-Qingwen reduces SARS-CoV-2 replication in vitro and reduces pro-inflammatory signals, and has been studied in a multi-centre trial; there are modest positive effects on a variety of outcomes, supported by strong p values; Jin Hua Qing Gan was tested on a 5-day treatment of mild patients, with a small positive effect and good p value; Xuan Fei Bai Du was studied on 280 patients and also showed a modest positive effect.

The talk closed with some important comments to take forward to future trials (of any kind of medicine); too many clinical trials use various and irrational outcomes and there is a very urgent need to adopt standardized set of outcomes.

IUPHAR's role

Michael Spedding summarized the role of IUPHAR.org in centralising, with its limited resources, the responses of the world's pharmacology societies, and also governmental guidelines.
Steve Alexander told the conference about a paper, in final stages of preparation, from NC-IUPHAR and collaborations, on a rational roadmap for COVID-19 drug design.
Jamie Davies told the conference about the COVID-19 pharmacology database set up by IUPHAR, fully open and able to surface pre-publication data, subject to IUPHAR-organized rapid peer review. There as discussion about its also hosting a document on trial design, drawn from the comments made in this meeting. The database is at https://www.guidetopharmacology.org/coronavirus.jsp

Summary of Discussion

There was a wide-ranging discussion of points arising from the two reports and also from other aspects of COVID-19. This summary is arranged around points made rather than speakers, to cut down on repetition.

As China is emerging from lock-down, cautiously, it is passing on its experience with early trials to the rest fo the world to run future trials, learning from China's experience. Much current focus is now on the emergence from lock-down and gaining experience that will again help the rest of the world as different countries enter this phase at different times.

There are about 500 clinical trials now registered world-wide. Caroline Samer, in considering them, made the following six key points (many of which were repeated by other speakers);

1. Be careful about translating between *in vitro* data to *in vivo* use. Examples are provided by chloroquine, ivermectine (where concentrations used in *in vitro* studies are not compatible with human dosing), and by cases where metabolism/ excretion are not adequately considered when making the transition,). In vitro data may speak for an antiviral efficacy but do not always reflect clinical efficacy as suggested by the hydroxychloroquine data with another RNA virus chikungunya.

2. Do not cut corners with study designs - whatever the emergency, we still need <u>good clinical study design in humans</u>: randomized control trials, sample size calculation, intention to treat analysis if patient withdrawal-> avoid bias and importance of control group to rule out the normal course of the disease

3. <u>Drug testing needs rational use</u> especially knowledge of PK/PD, drug regimen (eg hydroxychloroquine has a long half-life and requires a loading dose), knowledge of drug-drug interactions, contra-indications and clear pharmacovigilance (eg long QT for hydroxychloroquine, azithromycine and lopinavir/ritonavir)

4. Have clear and ideally standardized Inclusion/exclusion criteria, for patients, with a decision protocol, eg PCT/Clinical, CT scans, severity, that is accessible to most relevant

centers. Avoid decision protocols based on exotic technologies. eg define method for COVID-19 confirmation (PCR? radiology? clinical?), severity of illness at entry pneumonia? clinical? radiological? saturation <94% on room air, classification: supplemental O2 requirement, ventilation requirement) & underlying conditions/co-medications. Need a core protocol (eg Dean et al attached)

5. Critically, defined and standardize appropriate clinically relevant output criteria to assess efficacy. Clinically Relevant Outcomes such as mortality, duration of intensive care unit/ventilation, hospital stay/7-point scoring of the European Discovery trial (vs viral clearance/shedding that may not be clinically relevant) as well as safety outcomes

6. Ensure proper regulatory and peer review, including ethical review and pre-registration of the trial, with proper power calculations, patients' consent, registered trial, data management tools, data monitoring, peer-reviews journals, access to raw data, results also available in English

Because two of the drugs in which there is strong interest, CQ and HCQ, are hazardous (long QT), it is critical that we be sure of the benefits before using them widely. Approaches to assessing this need to be scalable to large studies (including the SOLIDARITY mega-trials under WHO).

David Webb made the strong point that we need to avoid repeating the errors made in the Ebola outbreak, in which there were many studies but few followed the principles of good design (randomization, placebo-control, blindness) which meant that little useful came out of them. We need randomised, blinded, placebo-controlled RCTs with reliable trial design and sufficient size to be powered for clear and hard outcomes - mortality critical, but other clinically relevant endpoints may be useful (such as ITU time). A very valuable guide is the recent Framework paper (Dean et al. NEJM 2020; 382:1366 [US/UK])

Because of the rapidly changing state of knowledge, not just about drugs but also about other things, even the way a patient lies down or breathes, we will need adaptive trial designs that can accommodate changes part-way through, including removal of drugs from trials once it is clear they cause harm, or no benefit, and replacement with more promising agents. A core protocol is critical (Dean et al., 2020) as are the outcome measures. Michael Spedding recommended the approach of the ALS-FRS-R, which had a very useful rating scale in motor neurone disease which may be a useful model to design a universally accepted COVID-19 rating scale.

Nilima Kshirsagar described the situation in India, but also made the comment that for natural products it was essential to know the active principles, with quality assurance of the active ingredients. The use of metabolomics may yield important progress.

The importance of the immune response, especially in driving interstitial lung disease, was stressed by several including Francesca Levi-Shaffer. Important unanswered questions were highlighted, such as whether the reduction in blood white cells reflects their disappearance from the body or their accumulation in the lungs. For some patients, intervention to prevent a cytokine storm is critical. It is important to assess the role of an early innate immune system response and a later adaptive one. Clarification of the input of each response in a mild-moderate or severe patient is needed to guide which drug intervention to adopt. It seems

right now that in young patients we have to downregulate the cytokine storm, caused mainly by over reaction of the innate immune system, with anti-inflammatory drugs, IL1β or IL6 receptor antagonists or some TCM compounds. Later on we have to strengthen the adaptive immune response with immunostimulants. The role of INF-γ is still to be evaluated.
It was felt that we need a follow-up meeting on the immunopharmacology of the disease.

Our clinical approaches against COVID-19 are not based on high quality empirical evidence and therefore, it is an ethical responsibility to gain knowledge about the efficacy and safety of suggested therapies while treating by collecting real world data.

Therefore, we need well conducted and powered clinical trials in which standard of care should be considered as an alternative arm of treatment.

There is a need to design studies to approach preventive strategies pre and post exposition to COVID-19 especially in populations with higher vulnerability

The design of a collaborative common database (registry) to encourage healthcare professionals to collect data on COVID-19 patients that it is intended to provide answers to hypothesis driven studies, epidemiological studies, while being efficient and not duplicate efforts. All contributors are to be given credit in publications derived from this work

These collaborative efforts may provide basis to identify differences between presentations between countries and geographies that may underly genetic and other host-dependent factors which influence the different phenotypic presentations of this COVID-19 infection.

To gain mechanistic insights on the different types of presentation of the disease exploring the immunological response is paramount. It is relevant to consider two additional aspects that may explain the higher mortality rate observed in older patients (as compared with the benign disease in children) and also the remarkable presentation of the disease with lymphopenia which predicts disease severity of COVID-19 infection.

Closing remarks

IUPHAR stressed that success of the Chinese containment is highly commendable, in that are virtually no new cases, and the rapid construction of very early clinical trials in the crisis was also extremely useful. Now we may need different drugs, testing and therapeutic approaches at the different stages, both of the disease and also for attacking the pandemic, or stopping the re-emergence after lockdown is eased.

Action points

Organization of a follow-up meeting with a strong focus on immunopharmacology

Discussion about hosting information on trial experiences and lessons on the database

CRITICAL: dissemination of lessons as the trial baton is handed on. Especially to WHO.

Snapshots of the meeting: