2021 Annual Report

INSTITUT PASTEUR KOREA

Asia-Pacific Regional Hub of Infectious Disease Research
Contributing to Global Public Health

Institut Pasteur Korea

Contents

Message from the CEO 03

Vision, Mission & Core Values 04

2021 Summary 05

01. Responding to COVID-19
02. Global & Domestic Activities towards Public Health
03. New strategies implemented under new leadership
04. Promoting Scientific Exchange and Communications
05. Advancement of R&D Infrastructure
06. Acknowledgment by the Government of Excellent LMO Safety Management

2021 Key Milestones 12

2021 Major Achievement 14

IPK's R&D at a glance 16

2021 Research Highlight 18

- Discovery Biology
- Translational Research
- Biobank, Startup Incubation, PIU

2021 Publications 52

R&D Infrastructure 55

Research & Technology Services 58

2021 Collaborations 59

Pasteur Network 62

IPK Leadership 65

Message from the CEO

Since the beginning of the COVID-19 pandemic, the Institut Pasteur Korea (IPK) has engaged in various research activities in contribution to COVID-19 responses at both the national and global levels. The year of 2021 will be remembered as one of the most productive years since the IPK's establishment in 2004. A 5-year R&D strategic plan with 5 pillars has been developed to guide the IPK's research directions for 2022-2026.This plan will combine with the Institut's mid- to long-term plan scheduled to be developed by early 2023 for positioning the IPK for the next 10 years in infectious disease research.

Newly appointed to the Board of the Asia-Pacific Region of the Pasteur Network, I, together with my colleagues, have exerted efforts to contribute to the coordination of R&D activities between the 10 institutes in this region as well as cooperation with the Institut Pasteur Paris and other members of the Pasteur Network. Since July 2021, the Asia-Pacific members have shared knowledge and experience regarding antimicrobial resistance and COVID-19 among others through their bi-monthly meetings. The PIU [1], the Pasteur Joint International Research Unit between IPK and IP Paris has been established for Artificial Intelligence for image-based drug discovery and development (Ai3D) in 2021 and researchers from IPK and IP Paris are regularly exchanging scientific data to develop next-generation tools for therapeutics discovery.

The IPK has also joined the GVN [2] as a Centre for Excellence, and has been given the status of an antiviral drug evaluation flagship laboratory new reference centre by the KDCA [3]. It has also been designated as one of the national preclinical evaluation centres and virus research cooperation councils by the Ministry of Science and ICT. Besides, it joined the consortium of infectious disease research institutes in 2021.

With a view to promoting scientific exchanges between researchers, the IPK has organized scientific sessions during major academic society symposiums, such as the KSBMB [4] and the KSMCB [5], and has hosted the KSM [6]'s annual symposiums and mini-symposiums on various topics including bioinformatics and biobank.

To further strengthen its role as a leading infectious disease research institute in Korea and beyond, the IPK has established a Research Strategy Advisory Committee in addition to the existing Scientific Advisory Committee. The Research Strategy Advisory Committee was convened twice in 2021 to discuss how to expand research cooperation with external partners.

With the support of the Ministry of Science and ICT, the IPK began a project to establish a new virus research resource centre in 2021, along with the incubation of 5 start-up companies within the Institut. The virus research resource centre, which will operate BSL-3 and ABSL-3 spaces open to external partners and biobank by 2023, is expected to be a significant asset for Korea's preparedness and responses to infectious diseases.

The IPK will continue to pursue scientific excellence and strengthened engagement with public health initiatives as the Asia-Pacific regional hub for the Pasteur Network.

Youngmee Jee, MD, PhD

CEO, Institut Pasteur Korea

1) Pasteur International Unit, 2) Global Virus Network, 3) Korea Disease Control Agency, 4) Korean Society for Biochemistry and Molecular Biology, 5) Korean Society for Molecular and Cellular Biology, 6) Korean Society for Microbiology

Vision, Mission & Core Values

VISION

Institut Pasteur Korea pursues scientific excellence and performs the role as the Asia-Pacific regional hub for the Pasteur Network by strengthening its engagement with public health initiatives.

MISSION

Reseach

Reinforce the connection between basic/translational infectious disease research and commercialization.

Public Health & International Collaboration

Strengthen partnerships with the Pasteur Network, especially in the Asia-Pacific region, and expand collaboration with domestic/international research institutes, health organizations, industry and academia.

Education

Activate scientific exchange through training courses utilizing the Pasteur Network, and advance the education, including the Master's and Doctoral programs of the University of Science and Technology-IPK Campus, in collaboration with domestic/international universities and related institutes.

Core Values

Communication | **C**ollaboration | **C**ompetency

Professionalism | **P**articipation | **P**artnership

3Cs & 3Ps

2021 Summary

01 Responding to COVID-19
02 Global & Domestic Activities towards Public Health
03 New Steps Forward with New Leadership
04 Promoting Scientific Exchange and Communications
05 Advancement of R&D Infrastructure
06 Acknowledgment by the Government of Excellent LMO Safety Management

01 | Responding to COVID-19

In response to the COVID-19, the public health emergency of international concern (PHEIC) declared by WHO on 30 January 2020, IPK deployed a rapid drug repositioning screening strategy based on its previous research on SARS-CoV and MERS-CoV and identified potent therapeutic candidates for SARS-CoV-2. Further development of the drug candidate were fast-tracked through international clinical trials leveraged by IPK's R&D network.

The collaborative efforts steered by internal experts of viral infectious diseases, drug screening and medicinal chemistry brought IPK to be vanguard in early identification of SARS-CoV-2 anti-viral properties among FDA-approved drugs and bio-active libraries.

With four candidate drugs identified, nafamostat, camostat, ciclesonide and niclosamide, IPK proceeded to work with Korean domestic pharmaceutical companies, clinical partners and the Ministry of Science & ICT to establish agreements opening the way to the sponsorship of clinical trials. In efforts to accelerate the process, we worked with the Pasteur Network (PN) to successfully build in parallel clinical-trial collaborations with international partners in Senegal, Mexico, and Australia.

Our study also revealed that selected anti-SARS- CoV-2 drug candidates are equally effective against the alpha- and beta-variants compared to the original SARS-CoV-2, which indicated that COVID-19 therapeutics may provide important clinical therapy recourse to emerging variants.

The COVID-19 pandemic provided an opportunity for IPK to demonstrate its value to all stakeholders including the Korean government, scientific community, and industry, attracting public and media interest globally.

Importantly, IPK leveraged expertise in infectious disease and drug screening to support the government's response to the pandemic as a member of Korea's pan-governmental COVID-19 treatment and vaccine R&D supporting group, the COVID-19 Response R&D Support Council, etc.

IPK also engaged in collaborations with >100 domestic and international institutions and partners in COVID-19 research on therapeutics and vaccines during 2020-2021. In addition, IPK expanded collaborations with major hospitals to analyze immunological profiles of individuals vaccinated with Pfizer, AstraZeneca, and Moderna COVID-19 vaccines aiming to characterize the vaccine-induced immunological response profile.

The COVID-19 IHR Emergency Committee

World Health Organization

IPK CEO Dr. Youngmee Jee, who has actively engaged in the World Health Organization (WHO) as a member of the WHO Scientific Advisory Group for Blueprint on Research and Development Preparedness, WHO Strategic Advisory Group of Experts on Immunization, etc., joined the WHO COVID-19 IHR Emergency Committee and discussed and coordinated the strategies for global joint response. She also contributed to the development of vaccines, including Korea's the first COVID-19 vaccine (SKYCovione™ of SK bio-science), by sharing her expertise in immunology and vaccines as a member of the CEPI Safety Platform for Emergency vACcines Data and Safety Monitoring Board.

02 | Global & Domestic Activities towards Public Health

Among the lessons highlighted by the COVID-19 pandemic was the importance of cooperation. Since its foundation in 2004, IPK has been a frontier for infectious disease R&D driving open innovation and promoting collaboration within domestic and global research communities. In 2021 we greatly expanded research collaboration and exchange with new and existing partners in Korea and abroad.

Taking the lead in R&D for AI-based drug discovery, IPK in collaboration with Institut Pasteur Paris established the Pasteur Joint International Research Unit "Artificial intelligence for image-based drug discovery and development" (PIU-Ai3D). This unit brings together a coalition of the willing from IP-Paris and IPK talent with technology savvy to develop next-generation tools for infectious disease therapeutics discovery using advanced capabilities in image-based drug screening and computational biology.

Following reorganization of the PN governance, IPK stepped up to a greater role and responsibility with the Asia-Pacific Hub. In June 2021, the IPK CEO Dr. Youngmee Jee was appointed as co-representative of the Asia-Pacific region consisting of 10 institutes of the total 33 members globally. With a focus on COVID-19 and AMR various strategies are promoting PN scientific exchange including the initiation of bi-monthly meetings, and scientific symposia such as the 1st Pasteur Network Asia Hub AMR Workshop (Feb 22~26, 2021). Notably, IPK joined the Global Virus Network (GVN) as a Center of Excellence embedding to a milieu of eminent human and animal virologists worldwide. Affiliated with the GVN we aim to leverage technology transfer and interdisciplinary research by establishing exchange programs, bilateral-training, and transversal international collaboration.

Aiming to address the urgent global health issues derived by AMR, IPK held a joint webinar co-organized by International Vaccine Institute (IVI), Asian Development Bank (ADB), the Embassy of Denmark in Korea, and the International Centre for Antimicrobial Resistance Solutions (ICARS) on Dec. 7. Gathering the leading scientists, public health professionals, and policymakers, the webinar focused on addressing effective strategies for strengthening global and local capacities and capabilities, including national AMR surveillance. IPK also played a pivotal role in accelerating infectious diseases drug discovery in the domestic scientific community. Here are representative examples in 2021: Operation of one of the Korea Disease Control and Prevention Agency (KDCA)'s reference centers for drug efficacy tests against viruses, Initiation of the Ministry of Science and ICT's project to establish a virus research resource center in IPK (see 'Advancement of R&D Infrastructure' on P.10), and Taking part in various national consortiums and councils, as listed below, that support domestic research in academia, institute, and industry.

MOU Signing Ceremony for the Consortium of Infectious Disease Research Institute (Nov. 2021)

IPK's participation in the efforts for national preparation and response to infectious disease

- National Institute of Infectious Disease's Antiviral Drug Evaluation Flagship Laboratory
- Consortium of Infectious Disease Research Institute
- Virus Research Cooperation Council
- National Preclinical Evaluation Center

03 | Steps Forward with New Leadership

Drawing the Outline of IPK's Five-Year R&D Strategic Plan

The IPK Executive Team and the Heads of the research and administrative teams outlined the IPK's five-year R&D Strategic Plan that will guide the operation from 2022 to 2026. Consisted of five pillars, it proposes a rejuvenation of IPK's scientific mission, including the development of new infrastructure and technology and new scientific thematic:

Pillar 1
Expand research areas to broaden responsiveness to emerging diseases

Pillar 2
Empower AI-based research to establish IPK as a world-class center for excellence in infectious disease high-throughput screening serving Korea and the Pasteur Network

Pillar 3
Reinforce preclinical research to accelerate the translation of screening results to public health

Pillar 4
Establish a Research Resource Center as a ONE-STOP research support system for responding to infectious disease threats

Pillar 5
Activate international networks and lead the Asia-Pacific region as a research hub

Establishment of Research Strategy Advisory Committee

In the new era of the COVID-19 pandemic and afterward, IPK will need to strengthen its role as a research institute focusing on drug discovery for infectious diseases, especially by utilizing its image-based high-throughput/content screening platforms and strong domestic and international network. Continuously advancing its core technology platform, introducing the latest imaging informatics and data management, and effectively disseminating it to collaborators and partners are the requirements to cope with the changing environment. For this matter, IPK established a new Research Strategy Advisory Committee (RSAC) consisting of leading Korean infectious disease experts in 2021. The committee met twice in Mar and Oct and provided various opinions on how to expand domestic research cooperation and utilize its core drug discovery capabilities in order to strengthen the research base for infectious diseases in Korea.

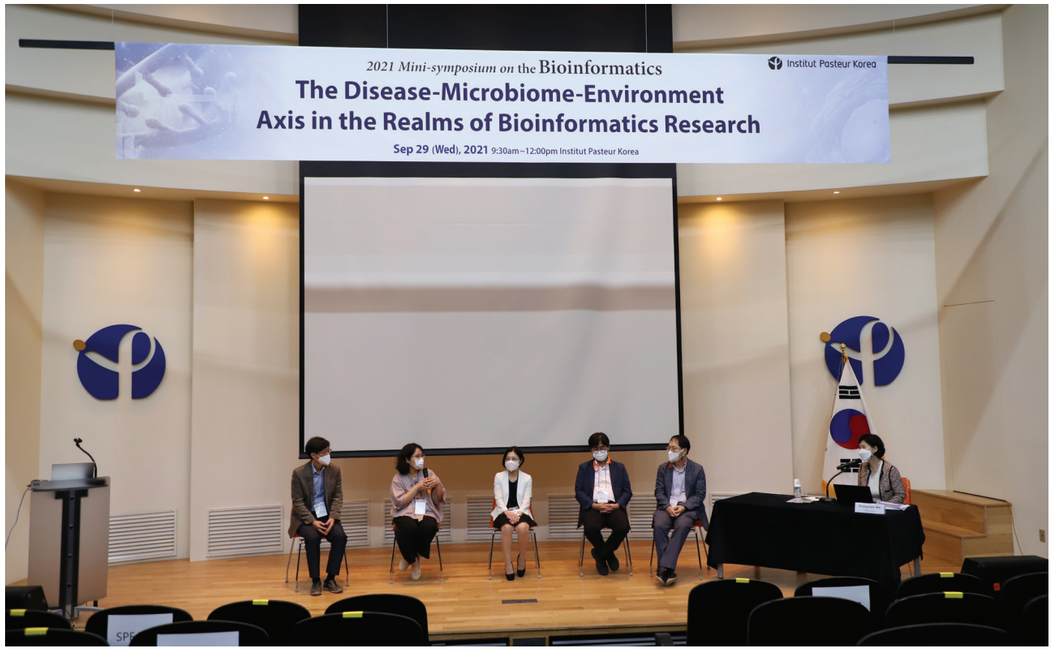
The 1st Research Strategy Advisory Committee Meeting (Mar. 2021)

Expansion and Reinforcement of Research Areas

IPK's research areas were expanded to vaccines, immunology, and antibody therapeutics. In particular, IPK initiated collaboration with major hospitals in Korea, such as Asan Medical Center and Seoul National University Bundang Hospital, and the Green Cross Laboratories (GC labs), to conduct immunological studies on COVID-19 and other studies involving human samples. Also, the Institutional Review Board, reorganized with a new chairperson and members, was held to review new projects using clinical samples. In addition, new research teams, Antibody Therapeutics Lab and Biobank, are established to expand IPK's research capabilities and resources.

04 | Promoting Scientific Exchange and Communications

Putting emphasis on scientific exchanges and communications, the IPK CEO Dr. Youngmee Jee shared her expertise in infectious diseases at various domestic and international seminars and symposia mainly on the theme of COVID-19 organized by Columbia University, the World Bank, the Paris Peace Forum, the Korean Ministry of Foreign Affairs, etc. The members of IPK actively engaged in international conferences held by major Korean scientific societies throughout the year, including the Korean Society for Biochemistry and Molecular Biology (KSBMB), the Korean Society for Molecular and Cellular Biology (KSMCB), the Pharmaceutical Society of Korea (PSK), and the Korean Society for Microbiology (KSM), where they presented the latest research activities and facilitated networking through operating satellite sessions, etc. IPK encouraged domestic and international scientific communities to interact through a mini-symposium on bioinformatics and a seminar on biobank, and provided weekly seminars involving internal researchers and top external scientists in Korea and abroad to regularly accelerate the exchange of knowledge, inter-team collaboration, and cooperation with external experts.



2021 Mini-symposium on the Bioinformatics, titled "The Disease-Microbiome-Environment Axis in the Realms of Bioinformatics Research" (Sep. 2021)

05 | Advancement of R&D Infrastructure

New Virus Research Resource Center under Construction

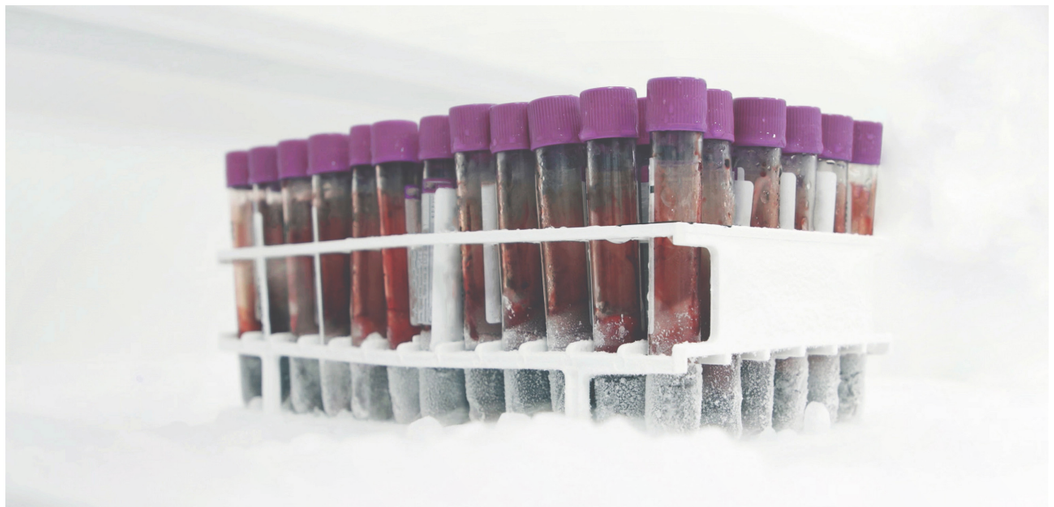
With support from the Ministry of Science and ICT, IPK is constructing a Virus Research Resource Center on the 6th floor of its R&D building, in which a new biosafety level 3 (BSL-3), animal BSL-3 laboratories, and a biobank will be facilitated. These new facilities will be an operational pillar to the new Korea Virus Research Institute (KVRI) and strategic asset to Korea's infectious disease preparedness and response. For this matter, IPK will provide an access to the special infrastructure and disseminate its operational expertise and know-how, further facilitating IPK's collaboration with research partners in Korea. We aim to launch the center open to external research partners by 2023.

Advancing Screening Platforms with Newest Equipment and Enlarged Chemical Space

Complementing the two High-Content Screening (HCS) machines and state-of-art equipment for medicinal chemistry that started to operate at IPK during the last two years, a state-of-art advanced confocal HCS image-reader was purchased in 2021. In addition, the chemical space of the IPK in-house library was expanded by adding 7,000 diverse compounds and 2,300 drug repurposing compounds. This new hardware, in combination with the human expertise of the newly launched Bioinformatics & Data Analysis team, and PIU-Ai3D supporting the analysis of cell image data using AI technology, makes IPK's image-based screening capabilities again cutting-edge at world-class level.

Biobank

The Biobank Team was newly established and an experienced biobanking expert joined to lead the setup and operation of IPK's biobank. The IPK Biobank will function as a systematic reservoir and provider of biological resources for infectious diseases, including pathogens, as one of the key compartments of the Virus Research Resource Center currently under construction. IPK utilized the international partnerships with Centre National de Transfusion Sanguine (CNTS, Cote d'Ivoire), Pasteur International Biobank Network, and the European Virus Archive Global (EVAg) to secure bioresources.



06 | Acknowledgment by the Government of Excellent LMO Safety Management

IPK was selected as "2021 Excellent Institution for LMO Safety Management" by the Ministry of Science and ICT, which makes the 4th Minister's Awards, following the commendations by the Ministry of Trade, Industry and Energy in 2019, the Ministry of Health and Welfare in 2013, and the Ministry of Education, Science and Technology in 2009, that recognized IPK's good practices for biosafety management. In particular, IPK's regular safety education, routine monitoring of BSL-2 and BSL-3 laboratories, implementation of in-house developed safety measures, and establishment of biosafety through the active operation of the Biosafety Committee were listed as key differentiating features in terms of excellent performance in 2021. IPK was the first to obtain national certification for its BSL-3 research facility in 2008. For nearly 15 years it has been pioneering safety compliancy culture in Korea through exemplary operation and management of IPK's specialized infectious disease research facilities.

Mr. Euiseong Kang, Head of Safety Management (left), and Dr. Youngmee Jee, the IPK CEO

Awards Recognizing IPK's Excellent Biosafety Facility Operation

- **(2019)** Institution of Merit for Biosafety Management (Awarded by Minister of Trade, Industry and Energy)
- **(2013)** Institution of Merit for Biosafety Management (Awarded by Minister of Health and Welfare)
- **(2009)** Excellent Lab Safety Management Award (By Minister of Education and Science Technology)

2021 Key Milestones

Jan 1

Dr. Youngmee Jee was inaugurated as the 4th CEO of IPK.

Feb 2

Dr. Youngmee Jee met H.E. Philippe Lefort, the French Ambassador to Korea, discussing opportunities for French-Korean collaboration in the biomedical field.

Feb 22 ~ 26

The 1st IPIN-Asia-Hub "Innovative Technologies for AMR" Workshop was held co-hosted by Institut Pasteur Korea and Institut Pasteur du Cambodge with participants from 10 institutes in the Institut Pasteur International Network (IPIN). During the 5 days event, researchers had in-depth scientific discussions around the AMR thematic exchanging research interests for open innovation technologies and identifying avenues for collaborative research.

Mar 3

IPK established the Korean Research Strategy Advisory Committee (RSAC) and held the first meeting

Mar 23

IPK joined the Global Virus Network (GVN) as a Center of Excellence.

Apr 14

IPK confirmed that IPK's selected drug candidates* and the COVID-19 therapeutics under development exhibit equal antiviral efficacy against the SARS-CoV-2 Alpha and Beta variants.

* Nafamostat, Camostat, Niclosamide, and Ciclesonide

May 21

IPK and Institut Pasteur (Paris) announced the creation of a Pasteur International Joint Research Unit (PIU) named "Artificial intelligence for image-based drug discovery & development" (Ai3D).

May 25

IPK held a Satellite Session at the Korean Society for Biochemistry and Molecular Biology (KSBMB) International Conference 2021.

Jun 10

IPK held a Satellite Session at BIO KOREA 2021 International Convention, introducing drug development strategies using deep learning.

Jun 11

IPK was selected to operate a drug evaluation flagship laboratory supported by the Korea National Institute of Infectious Diseases to accelerate Korea's antiviral drug discovery.

Jun 18

H.E. Philippe Lefort, the French Ambassador to Korea, awarded Dr. Wangshick Ryu (IPK CEO 2017-2020) and Dr Spencer Shorte (IPK CSO 2018- Jul 2022) "Médaille d'honneur des affaires étrangères," a French government service medal recognizing contributions to the international interest of France and its allies, specifically for their leadership and work during COVID-19 pandemic.

Jul 9

KDB Bank and IPK sought cooperation in nurturing five bio startup companies participating in the Bio Core Facility Project at IPK.

Jul 13

The 1st Joint Symposium of IPK and Peter Doherty Institute for Infection and Immunity was held, where the COVID-19 response strategies covering drug discovery, vaccine development, and genomics studies were exchanged.

Sep 29

IPK held a mini symposium themed "The Disease-Microbiome-Environment Axis in the Realms of Bioinformatics Research

Oct 28

Mr. Philippe Lacoste, Director of Sustainable Development at French Ministry of Europe and Foreign Affairs, visited IPK to discuss innovative solutions for sustainable public health.

Nov 5

IPK held a symposium session titled "R&D Preparedness for Infectious Disease and International and National Cooperation" at the 2021 Korean Society for Molecular and Cellular Biology (KSMCB) International Conference.

Dec 1

IPK hosted a joint effort seminar with startup companies participating in the Bio Core Facility Establishment Project.

Dec 28

IPK received "2021 Excellent Institution for LMO Safety Management" Award from the Ministry of Science and ICT.

2021 Major Achievement

Sharing Knowledge

50
publications at SCI-level

24
first or corresponding authors

127%
increase from the No. of peer-reviewed papers published in the previous year

R&D Project*

16
newly awarded projects (including 5 international)

16
continued projects (including 2 international)

8.2
billion KRW secured from the R&D projects

49%
increase from the funding amount received in the previous year

* R&D project secured by each team and not including an institutional project

Research Collaborations

13
memorandum of understanding agreements

8
joint research agreements

14
material transfer agreements

97
sponsored research

70
COVID-19 related research collaborations

Technology Transfer

14
patents filed, including 5 international

10
patents issued, including 7 international

1
out-licensing agreement (Compounds against multidrug resistant Gram positive bacterial pathogens)

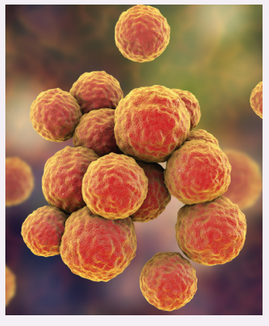
Patent Issued

No	Title	Country	Date of Grant	Issued Patent No.
1	Antibodies which bind to SFTSV * Developed in collaboration with Seoul National University	Korea	2021.1.05	10-2201391
2	Anti-infective compounds (for tuberculosis)	Europe	2021.7.21	3027615
3		Korea	2021.8.17	10-2292293
4		Vietnam	2021.10.18	30168
5	Compounds for Treating Viral Infections (for hepatitis C)	India	2021.1.26	356693
6		Korea	2021.12.29	10-2346605
7	Anti-infective compounds (for tuberculosis)	Russia	2021.8.16	2753403
8	Compounds for treatment of inflammatory diseases, cancer, stroke, and Alzheimer's disease	Hong Kong	2021.2.05	1236196
9		China	2021.8.03	ZL201580053161.X
10	Novel heteroaryl compounds, its enantiomers, its diastereomers or its pharmaceutically acceptable salt and antiviral composition containing the same as an active ingredient (Influenza THO) * Developed in collaboration with ST Pharm	USA	2021.10.19	11,149,033

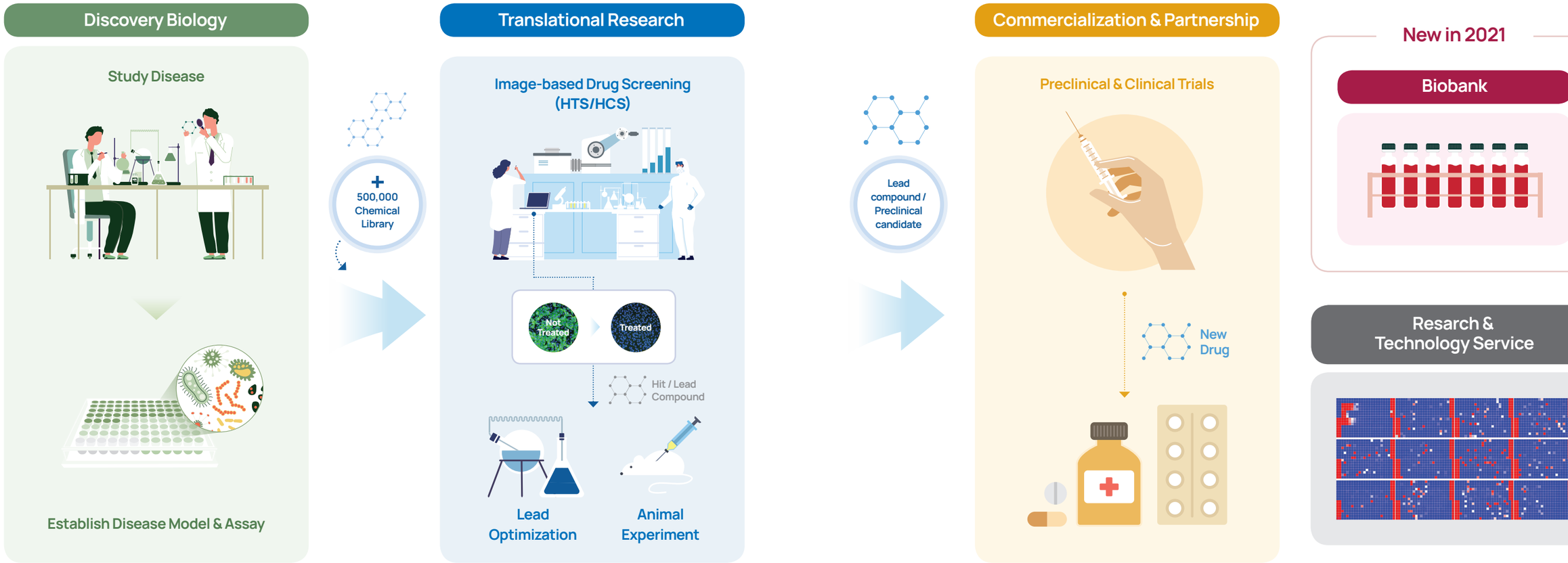
Out-licensing agreement

IPK's Antibacterial Resistance Lab. developed new antibacterial molecules in collaboration with the Korean Research Institute of Chemical Technology (KRICT); and J2HBiotech, a Korean pharmaceutical venture company. As a result of image-based screening of over 100 thousands of compounds, IPK researchers successfully identified potent candidates that are effective against multidrug-resistant gram-positive bacterial pathogens as well as have novel antibacterial mechanisms. In March 2021, the compounds* were licensed out to J2HBiotech and further development will be conducted jointly by IPK.

Institut Pasteur Korea J2H BIOTECH KRICT



IPK's R&D at a glance



DISCOVERY BIOLOGY

Discovery Biology Division studies diseases and pathogens, from which researchers establish disease models and assays for drug screening. Additionally, target identification and studies for the mechanism of action (MoA) are conducted for the candidates identified from screening.

- Zoonotic Virus Lab
- Viral Immunology Lab
- Applied Molecular Virology Lab
- Tuberculosis Research Laboratory
- Antibacterial Resistance Lab
- Host-Parasite Research Lab
- Advanced Biomedical Research Lab

TRANSLATIONAL RESEARCH

Translational Research Division evaluates the drug efficacy of thousands of compounds through the cell- and image-based screening operated in the BSL-2 and BSL-3 laboratories and identifies novel candidates. The identified candidates are further developed to have more drug-like properties by SAR, toxicity and lead optimization studies and their in-vivo efficacy is evaluated in animal experiments.

- Screening Discovery Platform
- Medicinal Chemistry
- Animal Facility & Lab Support
- Technology Development Platform

COMMERCIALIZATION & INDUSTRIAL PARTNERSHIP

The drug candidates are transferred for subsequent development including (pre-) clinical trials. Institut Pasteur Korea works closely in collaboration with the pharmaceutical industry, bio venture companies, academia and hospitals to enable its research technology and output to be utilized in helping the patients in need.

BIOBANK
‹NEW in 2021›

The IPK Biobank secures, standardizes, and supplies high-risk and emerging infectious disease pathogens and human samples for the research community and contributes to the preparation and timely response to public health crises.

Research & Technology Service

IPK renders access to our innovative drug screening expertise and technologies in biosafety level-2/-3 laboratories providing domestic and international partners the opportunity to advance their own drug development programs. The highly experienced professionals of IPK provide various services through all stages of the screening process including bio-chemical, cell-based, or custom assay design and adaptation, combinatorial screening, proof-of-concept screening, small to large scale screenings, dose-response studies, as well as chemical analysis and molecular modeling. (See 'Research & Technology Services' on P. 58)

2021
Research Highlight

01 Discovery Biology

02 Translational Research

03 Biobank, Startup Incubation, PIU

01
Discovery Biology

Zoonotic Virus Laboratory 20

Viral Immunology Laboratory 22

Tuberculosis Research Laboratory 24

Antibacterial Resistance Laboratory 26

Applied Molecular Virology Laboratory 28

Host-Parasite Research Laboratory 30

Advanced Biomedical Research Laboratory 32

Zoonotic Virus Laboratory

Collaboration makes difference!

We are investigating emerging and re-emerging viruses. Due to the current global burden of COVID-19, most of our research activities in 2021 were focused on investigation of coronaviruses including SARS-CoV-2 and MERS-CoV. But, we are also interested in others, specifically severe fever with thrombocytopenia syndrome virus (SFTSV) and dengue virus. Ultimately, we aim to better understand viruses and develop therein therapeutics against viral infectious diseases.

Multidisciplinary approaches are essential for innovative research.

We can do something by ourselves but we can do this much better by collaboration!

Dr. Seungtaek Kim, Head of Zoonotic Virus Lab.

In 2021, our lab's expertise in virology and drug discovery has brought about numerous opportunities for research collaborations with outstanding domestic and foreign investigators since the beginning of COVID-19 pandemic. Most of our collaboration partners have different academic backgrounds and combining strengths from different disciplines in these collaborations has made novel approaches in antiviral drug discovery possible with synergistic effects.

2021 RESEARCH HIGHLIGHT

Drugs repurposed for COVID-19 by virtual screening of 6,218 drugs and cell-based assay

Recent spread of SARS-CoV-2 has sparked significant health concerns of emerging infectious viruses. Drug repurposing is a rational strategy for developing antiviral agents within a short period. In general, drug repurposing starts with virtual screening of approved drugs employing docking simulations.

However, the actual hit rate is low, and most of the predicted compounds are false positives. To tackle the challenges, we report advanced virtual screening with pre- and post-docking pharmacophore filtering of 6,218 drugs for COVID-19. Notably, 7 out of 38 compounds showed efficacies in inhibiting SARS-CoV-2 in Vero cells. Three of these were also found to inhibit SARS-CoV-2 in human Calu-3 cells. Furthermore, three drug combinations showed strong synergistic effects in SARS-CoV-2 inhibition at clinically achievable concentrations.

Proc Natl Acad Sci USA. 2021 Jul 27;118(30):e2024302118. doi: 10.1073/pnas.2024302118.

Platycodin D, a natural component of Platycodon grandiflorum, prevents both lysosome- and TMPRSS2-driven SARS-CoV-2 infection by hindering membrane fusion

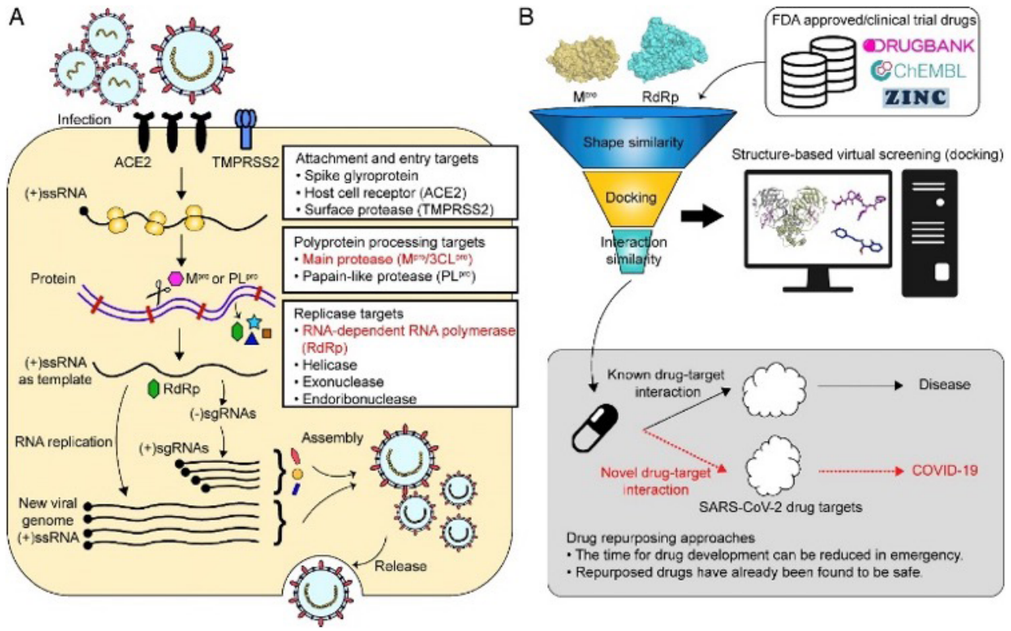
Herbal medicines and their derived natural products have drawn much attention in the treatment of COVID-19, but the detailed mechanisms by which natural products inhibit SARS-CoV-2 have not been elucidated. Here, we show that platycodin D (PD), a triterpenoid saponin abundant in Platycodon grandiflorum (PG), a dietary and medicinal herb commonly used in East Asia, effectively blocks the two main SARS-CoV-2 infection routes via lysosome- and transmembrane protease serine 2 (TMPRSS2)-driven entry. Mechanistically, PD prevents host entry of SARS-CoV-2 by redistributing membrane cholesterol to prevent membrane fusion, which can be reinstated by treatment with a PD-encapsulating agent. Furthermore, the inhibitory effects of PD are recapitulated by the pharmacological inhibition or gene silencing of NPC1, which is mutated in patients with Niemann–Pick type C (NPC) displaying disrupted membrane cholesterol distribution. Finally, readily available local foods or herbal medicines containing PG root show similar inhibitory effects against SARS-CoV-2 infection. Our study proposes that PD is a potent natural product for preventing or treating COVID-19 and that briefly disrupting the distribution of membrane cholesterol is a potential novel therapeutic strategy for SARS-CoV-2 infection.

Exp Mol Med. 2021 May;53(5):956-972. doi: 10.1038/s12276-021-00624-9.

TMPRSS2 and RNA-Dependent RNA Polymerase Are Effective Targets of Therapeutic Intervention for Treatment of COVID-19 Caused by SARS-CoV-2 Variants (B.1.1.7 and B.1.351)

While some vaccines and monoclonal antibodies have proven protective and/or therapeutic efficacy, this may be challenged by emerging variants of the causative SARS-CoV-2. We assessed antiviral efficacy of small-molecule inhibitors against emerging SARS-CoV-2 variants and found them to be effective. We propose these results may be understood because all of the small-molecule inhibitors tested target viral or host factors other than the mutated sequence of the viral spike protein. Accordingly we concluded that the tested molecules can be expected to be remain potent as tools to control against COVID-19.

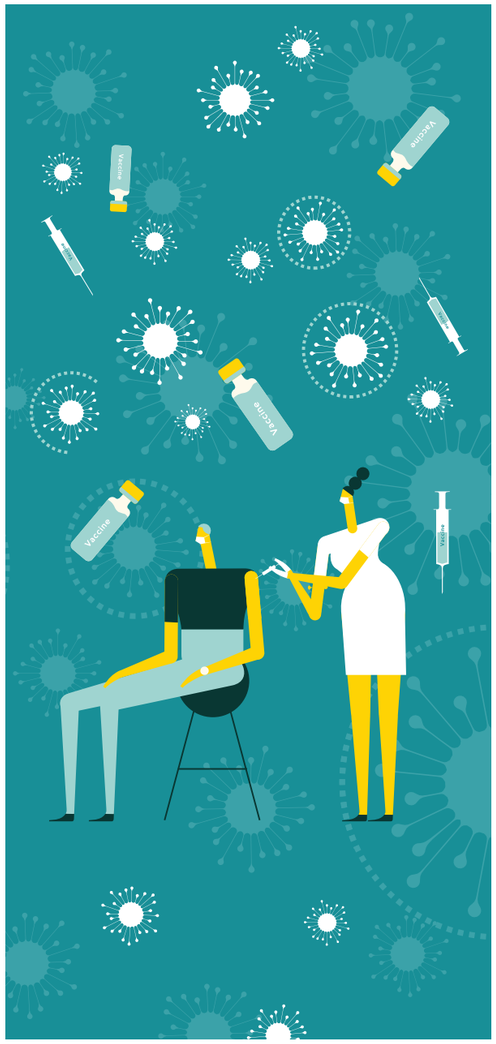
Microbiol Spectr. 2021 Sep 3;9(1):e0047221. doi: 10.1128/Spectrum.00472-21.



Drug targets against SARS-CoV-2 and computational drug repurposing strategy. (Proc Natl Acad Sci USA. 2021 Jul 27;118(30):e2024302118)

Viral Immunology Laboratory

You never fail until you stop trying. (Albert Einstein)



The Viral Immunology Laboratory (VIL) aims to deeply understand immunological principles underlying responses to viral infections and vaccinations and ultimately develop preventive and therapeutic measures for immune-associated diseases including infectious diseases and cancers. In addition, studying molecular and cellular mechanisms of immuno-pathogenesis during respiratory viral infections such as influenza virus and SARS-CoV-2 (COVID-19 virus) are one of current research topics. Especially, we are investigating how the innate immune system bolsters antibody and T cell responses, seeking to establish the bases for modulating the magnitude and longevity of immune protection. In translational research axis, we are contributing to the development of advanced vaccine platforms including mRNA and microneedle vaccines.

Preventive vaccines against SARS-CoV-2 were developed with unprecedented speed and contributed crucially to controlling the pandemic. Therapeutics including monoclonal antibodies and immune-suppressive drugs have saved many lives. By supporting preclinical efficacy studies VIL will continue to serve in the development of COVID-19 mRNA vaccines, and our team remains motivated by the hope that our immunology research will help address global infectious disease threats.

Dr. Euiho Kim, Head of Viral Immunology Lab.

In 2021, one of VIL's goals in 2021 was to be prepared for a deep dive into the immunological research. Because IPK is a research institute focusing on infectious diseases, the training process for a new researcher to perform safe research is quite intense. During 2021, as a new research team, we faced the challenge to set up cell and animal models for studying viral infections and vaccinations. Also, we aimed to establish research projects studying immunological mechanisms of vaccine and COVID-19 vaccine-induced immunity in humans. Finally, we also aimed to establish screening of antiviral & anti-inflammatory agents from natural substance libraries.

2021 RESEARCH HIGHLIGHT

Understanding COVID-19 vaccine-induced immune response in human

New platforms (mRNA & viral vector) of vaccines for SARS-CoV-2 have been developed at a record-breaking pace an unprecedented pace, and deployed under an emergency use authorization, meaning their use was subject to continuous review for possible side effects. In collaboration with Asan Medical Center, VIL participated in a human vaccine trial assessing COVID-19 mRNA vaccine induced immunity. We observed a faster, higher vaccine-induced immune response among COVID-19 convalescents (individuals previously infected & recovered). VIL continues this work tracking long-term immune response by mRNA & viral vector vaccines in collaboration with KIRAMS.

J Infect. 2022 Jan;84(1):94-118. doi: 10.1016/j.jinf.2021.07.032.

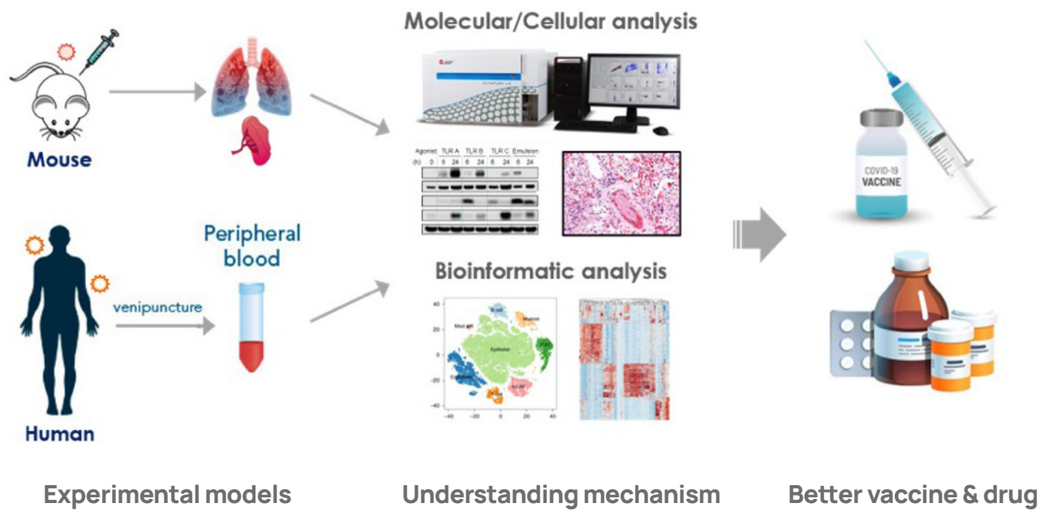
Role of cell death and damage-associated molecular pattern pathways in immunity

The role of cell death & danger signal release are appreciated for inflammation and immunity in the context of infectious disease, cancer and inflammatory disease. Investigating the role of these important pathways in the context of vaccination and viral infection, VIL published a paper highlighting how cell death and danger signals control vaccine-, or adjuvant-induced immune response.

Viruses 2021 Nov 23;13(12):2340. doi: 10.3390/v13122340.

Cooperative effort to develop more effective and convenient vaccines

VIL received government research grants from MFDS (Ministry of Food and Drug Safety) and MOHW (Ministry of Health and Welfare) for collaboration with university and biotech companies, engaging a research program aimed at improving mRNA vaccine efficacy & safety, specifically developing a (pain-free) microneedle-based vaccine.



This figure describes how to investigate complicated immune responses triggered by viral infection or vaccination. Findings from these studies can be re-applied for the development of better vaccines and treatments.

Tuberculosis Research Laboratory

Providing the tools and knowledge to aid the discovery of new drugs against tuberculosis

Since its discovery tuberculosis (TB) has continued to be a problem for human health, with an estimated 1.4 million deaths annually. Delays in diagnosis, lengthy treatment programs, and inefficient vaccination protection have all contributed to the emergence of drug resistant strains of TB. If the TB pandemic is to be ended by 2030, then new therapeutic targets, drugs, and vaccines must be identified and developed. The Tuberculosis Research Lab (TRL) is engaged in research focused on studying the pathogen/host interactions and developing the assays and methods for the identification of new active molecules, which can be used therapeutically.

The progress to TB eradication is slowed due to continued emergence of drug-resistant strains.
Only by furthering our fundamental basic science understanding of the infection and disease progress can we find new targets for therapeutic manipulation.

Dr. Connor Wood, Acting Head of Tuberculosis Research Lab.

In 2021, we had three target areas.

Drug discovery: we focused primarily on the bacterial folate pathway, specifically on the multi-functionally protein FolB, which is essential for bacterial growth. Using purified protein and a fluorescent based assay to measure the aldolase activity, we can screen compounds that targeted this pathway.

Host-pathogen Interactions: we focused on the interaction of the macrophage and the surrounding lung epithelium, in order to understand how the regulation of the immune response is controlled.

Assay/Tool Development: in 2021, our primary focus was the incorporation of new tools into our existing systems. Mtb-Crimson strains into our microscopy and FACs assays for infection, Krammnik-MPI and IFN-a/b- MPI lineages for infection studies, and use of web-based data analysis software for data processing.

2021 RESEARCH HIGHLIGHT

The development of a web-based application to aid data analysis of multi-well plates

PlateEditor is powered by JavaScript and runs fully client side (no data uploaded to sever). It allows for the definition of plate layouts and the visualization/aggregation of results, including screening data (big files, multiples plates). The application is open-source (source-code available on GitHub) and freely available on-line (https://plateeditor.sourceforge.io/).

PLOS ONE. 2021 May 28; doi.org/10.1371/journal.pone.0252488

Identification and characterization of new structural scaffolds modulating the activity of FolB

Using purified protein and fluorescence monitoring of the aldolase activity we screened over 9000 compounds to identify hit clusters for activity against FolB. These hits underwent additional screening and docking/enzymatic studies to understand the mechanisms for this inhibition.

Publication manuscript in preparation

Enhancement of the macrophage immune response by direct contact with epithelial cells

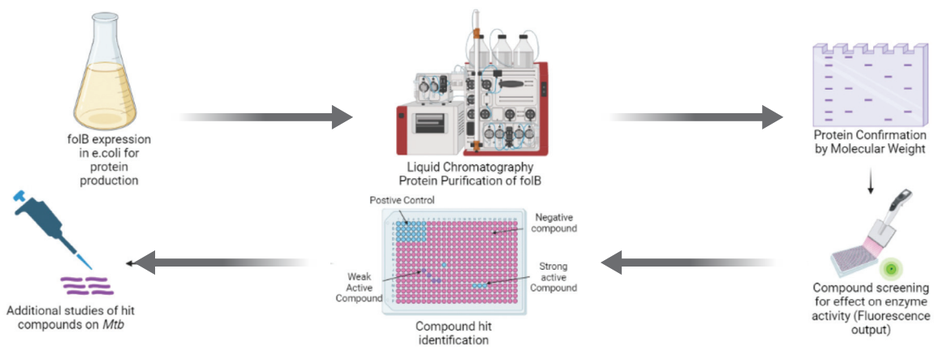
Using MPI cells as an alveolar macrophage model to study regulation with the alveolar epithelial cell line MLE-12. We identified the need for direct contact of cells to cause an enhanced inflammatory response. Additionally, adhesion molecules such as ICAM1 were upregulated on both cell types during this contact. In MLE-12 ICAM1 expression was induced by MPI inflammatory secretions, and appears to act as a positive feedback for these secretions in the inflammatory environment.

Publication manuscript in preparation

Additional compound screening with IPK Screening Development Platform, and Medicinal Chemistry teams

Para-aminosalicylic acid (PAS) is an antibiotic that was largely used for the multi-therapy of tuberculosis in the twentieth century. To try to overcome the inconvenience of its low efficacy and poor tolerance, we searched for novel chemical entities able to synergize with PAS using a combination screening against growing axenic Mycobacterium tuberculosis. The screening was performed at a sub-inhibitory concentration of PAS on a library of about 100,000 small molecules. Selected hit compounds were analyzed by dose-response and further probed with an intracellular macrophage assay. Scaffolds with potential additive effect with PAS are reported, opening interesting prospects for mechanism of action studies. We also report here evidence of an as yet unknown bio-activation mechanism, involving activation of pyrido[1,2-a] pyrimidin-4-one (PP) derivatives through the Rv3087 protein.

Scientific Reports. 2022 April 4; doi: 10.1038/s41598-022-08209-w



Anti-FolB compound screening methodology

Antibacterial Resistance Laboratory

Tackling Antibiotic Resistance from Environment to Human

Antibiotic resistance is one of the greatest threats to global public health, and increased antibiotic usage during the pandemic treating secondary infections among COVID-19 patients further compounds this global problem. The Antibacterial Resistance Laboratory (ARL) focuses on discovery of new antibiotic therapeutics, studying bacterial physiology and resistance mechanisms to identify novel targets and antibacterial molecules.

No one can do everything. I believe that collaboration and cooperation are the key words for the battle against antibiotic resistance. I feel blessed to work with our team members and my collaborators around the world. Because of their hard work, ARL never stops and moves forward to find solutions to antibiotic resistance.

Dr. Soojin Jang, Head of Antibacterial Resistance Lab.

In 2021, despite disruption to research activities due to the COVID-19 pandemic ARL strategic goals remained as planned. Ergo to strengthen our capacity for studies aiming to understand the fundamental mechanisms of antibiotic resistance we aimed to secure substantial research funds to build our research capacity and broaden domestic and international collaborative.

2021 RESEARCH HIGHLIGHT

Licensing out of new drug candidates for multidrug resistant Gram-positive bacteria

In 2021 we licensed out our new antibacterial molecules identified in collaboration with the Korean Research Institute of Chemical Technology (KRICT); and J2HBiotech, a Korean pharmaceutical venture company. The new molecules have a novel antibacterial mechanism and elicits lower resistance compared with currently available antibiotics, indicating utility for clinical use. Further development of the molecules will conducted jointly by IPK and J2HBiotech.

Technology transfer to J2HBiotech (2021. Mar)
"Compounds acting against multidrug resistant Gram-positive bacterial pathogens focusing on methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant Enterococcus faecium (VRE) and Streptococcus Pneumoniae (Pneumococcus)

Repurposing Eltrombopag for staphylococcal infections

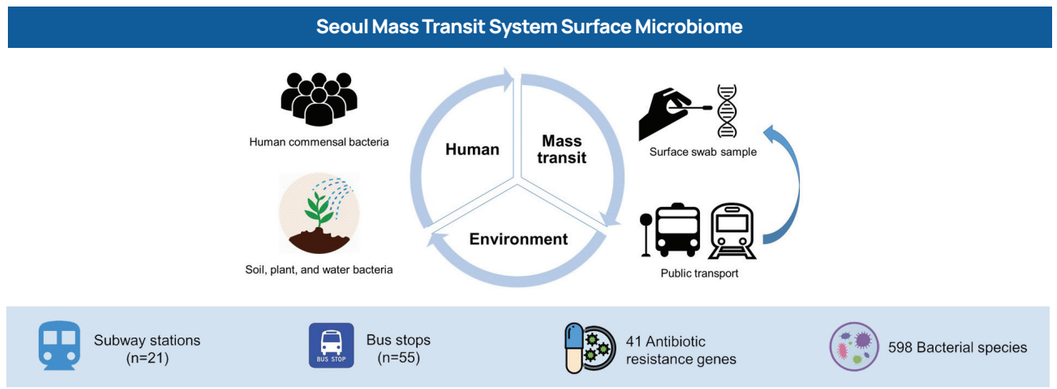
Drug repurposing is an attractive strategy that could significantly shorten the time to deliver new antibiotics for the clinical use. In this path, we screened 182 FDA approved drugs to identify candidates that can be repurposed for staphylococcal infections and found that eltrombopag, a drug approved for thrombocytopenia, effectively inhibits the growth of Staphylococcus aureus analyzed in 55 methicillin-resistant (MRSA) clinical isolates (including 5 multidrug resistant strains). Furthermore, we demonstrated that the antibacterial activity of eltrombopag is preserved in both cell-infection, and in vivo mouse models.

Antibiotics. 021 Nov 9; 10(11): 1372.

Surveillance of community-based antibiotic resistance

Working with the MetaSUB consortium, we have been investigating global community-based antibiotic resistance by analyzing environmental microbiome samples from the Seoul public transport (bus stops and subway stations). In May 2021, the first consortium article was published in Cell, providing the first most comprehensive global microbiome analysis focused on an urban environment. ARL is embarking deeper analyses on antibiotic resistance and pathogens specifically in the Korean samples.

Cell. 2021 Jun 24;184(13):3376-3393.e17.

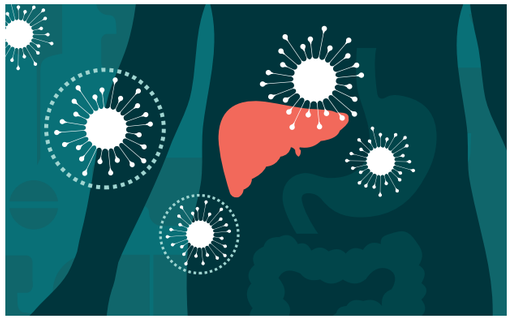


Metagenomic characterization of bacterial community and antibiotic resistance genes found in the mass transit system in Seoul. Major bacterial species and antibiotic resistance genes found in the subway stations and bus stops in Seoul (Ecotoxicol Environ Saf. 2022 Nov;246:114176).

Applied Molecular Virology Laboratory

All the essential steps during the viral life cycle involve a complex interplay between viral and host factors, and are all potential targets for antiviral drugs.

Viral hepatitis is a global challenge caused by hepatitis virus strains (types A, B, C, D and E, mainly). Vaccines and/or specific antiviral treatments are not yet available to fight them all. Worldwide, ~250 million people are chronically infected with HBV, ~20 million are co-infected with HDV, and ~1 million die annually from subsequent liver diseases. The Applied Molecular Virology Laboratory (AMVL) is conducting translational research to develop therapeutics against these diseases. Our work aims at characterizing virus-host interactions to identify viral vulnerabilities for therapeutic intervention.



We are working on solutions that benefit patients directly and indirectly by developing first-in-class drug candidates and state-of-the-art platforms to study all aspects of hepatic viral diseases, respectively.

Dr. Kyuho Paul Park, Acting Head of Applied Molecular Virology Lab.

In 2021, HBV infection is a leading cause of life-threatening liver diseases, including hepatocellular carcinoma (HCC). Currently available drugs for chronic HBV patients allow to control the viral load, but do not cure, and this sets AMVL long-term goal and purpose. Indeed, for decades, new drug development was hampered by the lack of a convenient and clinically/biologically relevant cellular model of infection recapitulating virus susceptibility, permissiveness, and viral spread. In 2021 we aimed to capitalize upon our unique HBV platform supporting the entire HBV life cycle seeking to identify antivirals and cellular factors crucial to the virus. With cellular models, we used drug screening and "OMICS" to characterize spatiotemporal molecular changes during infection with the goal to translate insight on molecular mechanism into discovery of new therapeutic options.

2021 RESEARCH HIGHLIGHT

A new high-content screening assay of the entire hepatitis B virus life cycle identifies novel antivirals.

Our HBV platform supporting the entire HBV life cycle was used to screen ~2100 drugs and bioactives, and identified 3 early and 38 late novel HBV life cycle inhibitors using infectious HBV. The mode of action for two early inhibitors, pranlukast and cytochalasin D, and 2 late inhibitors, fludarabine and dexmedetomidine, could be determined.

Furthermore, their biological activity could be confirmed using patient-derived HBV in our infectious system. Our newly developed high-content assay is suitable to screen large-scale drug libraries, enabling monitoring of the entire HBV life cycle, and discriminates between inhibition of early and late viral life cycle events. We expect this assay will be an important new tool to study the viral life cycle and accelerate the development of novel therapeutic strategies.

JHep Report. April 30, 2021. doi: 10.1016/j.jhepr.2021.100296.

Determination of infectious hepatitis B virus particles by an end-point dilution assay identifies a novel class of inhibitors

The quantification of infectious virus particles is fundamental to perform in vitro virology studies. To determine the number of HBV genome-containing particles, the genome equivalents (GEq) are measured using quantitative PCR (qPCR). However, in addition to infectious virions, HBV DNA-containing but non-infectious particles are also produced in vitro, which can lead to an overestimation by qPCR.

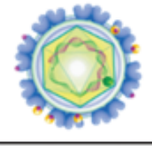
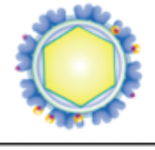
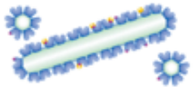
We established an end-point dilution assay to determine the number of infectious HBV particles, using a cell-based HBV infection assay in a 384-well plate format. This assay allowed us to calculate the 50% tissue culture infective dose (TCID50) from HBV infected samples, including patient-derived HBV sera. Combined with qPCR analysis results the specific infectivity can then be assessed, which allows for HBV infection assay standardization and sample comparison.

This end-point dilution assay is one key element to study the mechanism of action of novel HBV inhibitors.

Antiviral Res. December, 2021. doi.org/10.1016/j.antiviral.2021.105195

HBV Transcriptomics workflow

Taking advantage of our HBV platform highly susceptible for HBV and HDV, we successfully conducted whole-genome transcriptome analysis and separated clusters of genes at different status and time-point of infection. By analyzing the transcriptome data, we will have better understanding of cell biology closely related with viral infection. We now are embarking deep bioinformatics based analysis of these valuable cutting-edge data.

HBV particles	Complete virion (HBs + HBc + DNA)	Naked capsid (HBc + DNA)	Empty/incomplete virion (HBs + HBc)	Spheres/Filaments (HBs)
				
Infectious	+	-	-	-
qPCR	+	+	-	-
ELISA	+	-	+	+
$TCID_{50}$	+	-	-	-

Types of particles detected upon in vitro HBV infection. Four representative particles with their structures, infectivity, and selected possible detection methods. Only the complete virion and spherical/filamentous particles are detected in vivo. Legends: HBs, HBV surface proteins; HBc, HBV core protein; DNA, viral genome.

Host-Parasite Research Laboratory

Therapeutic interventions for protozoan infections

The Host-Parasite Research Laboratory focuses on research related to protozoan parasites including Leishmania and Plasmodium (Malaria). Leishmaniasis is a major neglected tropical disease effecting 12 million people in 98 countries for which there are no vaccines, and relatively ineffective treatments and diagnostics. Whereas, Malaria is responsible for 241 million cases worldwide resulting in an estimated 627,000 deaths (annual statistic 2020). The recently developed WHO approved malaria vaccine demands a complicated dose regimen and has modest (30%) efficacy protecting against severe malaria disease (in child). For both leishmaniasis and Malaria therapeutics are becoming ineffective due to drug resistance. Therefore, our laboratory focuses on developing new therapeutic interventions for leishmaniasis and malaria, founded upon basic research on parasite, and host-parasite models.

Despite high negative impact on public health and socio-economics parasitic diseases suffer a death of private sector investment due mainly to the poor returns expected from research investment for therapeutics. As a non-for-profit research organization, IPK is able to facilitate research without these constraints, but seeks industrial, government and NGO partners to translate potential clinical technology. In the meantime, we also use these fascinating pathogens as model organisms to better understand the human body's response to infection.

Dr. Joohwan No, Head of g Host-Parasite Research Lab.

In 2021, the key research areas are: 1) discovery of novel inhibitors and their targets against Plasmodium and Leishmania parasites using cutting-edge high-throughput high-content screening platforms; and 2) understanding the fundamental biology of protozoan infection with a special emphasis on the host macrophage cell. Articulating these two approaches, we ultimately aim to understand the underlying mechanism of parasite pathogenesis as well as to deliver novel therapeutic interventions. With expertise in high throughput screening, molecular parasitology, next-generation sequencing, molecular modelling, biochemistry and biophysics, we approach the target system from molecular, organelle, isolated parasite and infected animal level. In 2021 we also aimed to expand our portfolio of parasitic pathogens by collaborating, for example, investigating Toxoplasma, Clonorchis.

2021 RESEARCH HIGHLIGHT

Pyrrolidine-based 3-deoxysphingosylphosphorylcholine analogs as possible candidates against Leishmania donovani

Using a rational-based approach repurposing pyrrolidine-based 3-deoxysphingosylphosphorylcholine analogs bearing variable acyl chains, we extrapolated the importance of different stereochemical configurations and/or positional relationships. Structural features were highly influential on activity. Among a saturated palmitoyl chain and an opposite stereochemical configuration to natural sphingolipids a potent hit compound against promastigotes was identified. In silico docking studies using a homology model of Leishmania donovani inositol phosphoceramide synthase (IPCS) provided plausible reasoning for the molecular factors underlying the anti-parasitic activity.

J Enzyme Inhib Med Chem. (2021) 36(1):1922-1930.

Discovery of Leishmania donovani topoisomerase IB selective inhibitors by targeting protein-protein interactions between the large and small subunits

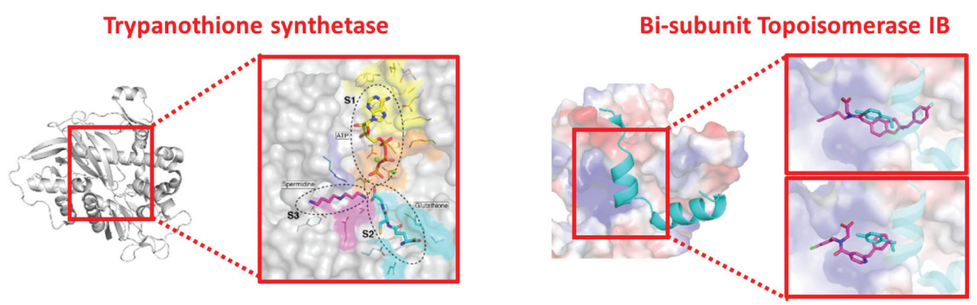
Topoisomerase IB (TopIB) is an essential enzyme for Leishmania survival. The enzyme is organized as a bi-subunit that is distinct from the human monomeric topoisomerase I. Based on this unique feature, we synthesized peptides composed of partial amino acid sequences of small subunit of Leishmania donovani (Ld) TopIB to confirm a decrease in catalytic activity by interfering with the interaction between the two subunits. In addition, by virtual screening we identified small molecules which disrupt the interaction to abrogate the activity of enzyme with anti-leishmanial activity in vitro.

Biochem Biophys Res Commun. (2021) 569:193-198

Drug-like molecules with anti-trypanothione synthetase activity identified by high throughput screening

Trypanothione synthetase (TryS) catalyzes the synthesis of N1,N8-bis(glutathionyl)spermidine (trypanothione), which is the main low molecular mass thiol supporting several redox functions in trypanosomatids. TryS attracts attention as molecular target for drug development against pathogens, but unfortunately also causes severe and fatal diseases in mammals. A drug discovery campaign aimed to identify and characterize new inhibitors of TryS with promising biological activity was conducted. A n=51,624 compound library selected for drug-like properties, was screened against TryS from Trypanosoma brucei (TbTryS). With a true-hit rate of 0.056%, several of the TbTryS hits (IC50 from 1.2 to 36 μM) also targeted the homologue enzyme from Leishmania infantum and Trypanosoma cruzi. Seven hits showed a significantly higher selectivity against T.brucei (selectivity index from 11 to 182). The most potent TbTryS inhibitor exerted a non-covalent, non-competitive inhibition of the enzyme.

J Enzyme Inhib Med Chem. (2022) 37(1):912-929



(Left) The overall and active site structure of Leishmania Trypanothione Synthetase (Right) The structure of Leishmania Topoisomerase large and small subunit interaction site used for virtual inhibitor screenings.

Advanced Biomedical Research Laboratory

Accelerating drug development by expanding our fundamental research know-how in cancer to infectious diseases

Potential risk factors such as viruses, lifestyle factors, environmental exposure, etc. can cause fibrosis and cancers. Since there is currently no standard treatment for hepatic fibrosis, the greatest unmet need for fibrosis is for safe and effective medications. We expect that our 3D hepatics model offers an efficient, high-throughput strategy to identify new drugs and targets to identify anti-fibrotic, and anti-cancer drugs.

Dr. Haengran Seo, Head of Advnaced BioMedical Research Lab.

As the Cancer Biology Research Lab, our work has previously been focused on hepato-cellular carcinoma (HCC) and we sought to identify new HCC therapeutics and diagnostics. HCC is one of the most common malignant cancers worldwide and is notorious for poor prognosis because patients only present symptoms symptoms of liver dysfunction associated with advanced-stage cancer when treatment options are limited. Taking a new step with the inauguration of the Advanced Biomedical Research Laboratory (ABRL) in 2021, we expanded our research areas from cancer and metabolic and inflammatory diseases to infectious diseases. This is a strategic transformation to keep the proper balance between the team's identity, research trends and the needs of IPK as an Asian-Pacific infectious diseases research hub. As the ABRL, we are implementing various strategies to apply our expertise in anti-fibrotic, anti-inflammatory, molecular target approaches, and regulation of metabolic dysregulation in liver disease to infectious diseases. Additionally, small molecules, recombinant proteins, natural compounds, and traditional Chinese medicine are being redeployed to drug discovery paradigms in infection.

In 2021, we aimed to evaluate the combination treatment of anti-cancer and –fibrosis drugs for HCC therapy. To this end, we identified and validated novel anti-fibrotic drugs (GSK3β inhibitor, flavanone derivative, 11βHSD1 inhibitors, etc.). A large percentage of patients with hepatocellular carcinoma (HCC) who undergo surgical resection experience a recurrence of their disease. A lack of prognostic biomarkers will prevent assigning effective therapy to patients, which in turn reduces their OS and PFS, resulting in a shorter duration of treatment. Hence, we aimed to determine if serum sorbitol dehydrogenase (SORD) levels, an enzyme that reflects liver damage, was associated with the length of recurrence-free survival. As a new project, we initiated the establishment of 3D spheroid models for the development of novel infectious disease therapeutic drugs such as leishmanial, bacteria, etc.

2021 RESEARCH HIGHLIGHT

Identification of novel therapeutic targets and hits from multicellular tumor spheroids for HCC therapy

Our work has identified new targets for HCC drug discovery using HCC tumor spheroids and we found that argininosuccinate synthase 1 (ASS1) expression was higher in 3D cells than in 2D cells due to upregulated endoplasmic reticulum (ER) stress responses. ASS1 overexpression effectively inhibited tumor growth and enhanced the efficacy of in vitro and in vivo anti-HCC combination chemotherapy via activation of the PERK/eIF2α/ATF4/CHOP axis, but was not dependent on the status of p53 and arginine metabolism.

J Exp Clin Cancer Res. 2021 Apr 10;40(1):127. doi: 10.1186/s13046-021-01912-y

Development of therapeutics through validation of SORD (Sorbitol dehydrogenase) as novel target of HCC

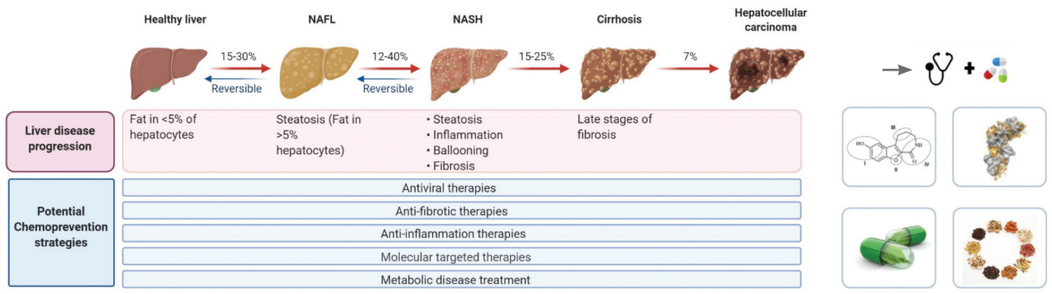
The majority of patients with hepatocellular carcinoma (HCC) undergoing curative resection experience tumor recurrence. To examine the association between preoperative serum sorbitol dehydrogenase (SORD), a liver-derived enzyme that reflects liver damage, and recurrence of HCC after curative resection, 92 patients were randomly selected who underwent curative resection for HCC between 2011 and 2012 from a prospective registry. Recurrence-free survival (RFS) was compared based on serum SORD levels. When patients were stratified by baseline serum SORD and AFP levels, patients with serum AFP levels ≥400 ng/mL and serum SORD levels ≥15 ng/mL had a distinctly poor prognosis with the lowest RFS rates. Hence, baseline serum SORD is an effective prognostic factor for HCC after resection. It may help guide patient selection for surgery, especially when combined with serum AFP levels.

Cancers (Basel). 2021 Dec 6;13(23):6143. doi: 10.3390/cancers13236143.

Identification of hepatic fibrosis inhibitors through morphometry analysis of a hepatic multicellular spheroids models (MCTSs)

We applied MCTSs for high-throughput screening (HTS) to identify compounds that may be able to treat liver fibrosis. To reflect extensive fibrosis in vitro, human HCC cells were grown together with human fibroblasts (WI38), human HSCs (LX2), and human umbilical endothelial cells (HUVEC) in MCTSs. Subsequently, we performed HTS with FDA-approved drugs to identify compounds that specifically reversed the fibrotic properties in MCTSs. We found that anti-fibrotic drugs are not only effective in the treatment of liver fibrosis, but can also enhance the anti-cancer activity of other therapeutics by increasing tissue permeability, allowing drug delivery to cancer cells of interest.

Sci Rep. 2021 May 25;11(1):10931. doi: 10.1038/s41598-021-90263-x.



ABRL challenged various strategies such as anti-fibrotic, anti-inflammatory, molecular target approaches and regulation of metabolic dysregulation in liver disease using a small molecule, recombinant proteins, natural compounds, and traditional Chinese medicine for HCC-preventive interventions of HCC development in progressive fibrotic liver diseases.

2021
Research Highlight

02
Translational Research

Screening Discovery Platform 36

Technology Development Platform 38

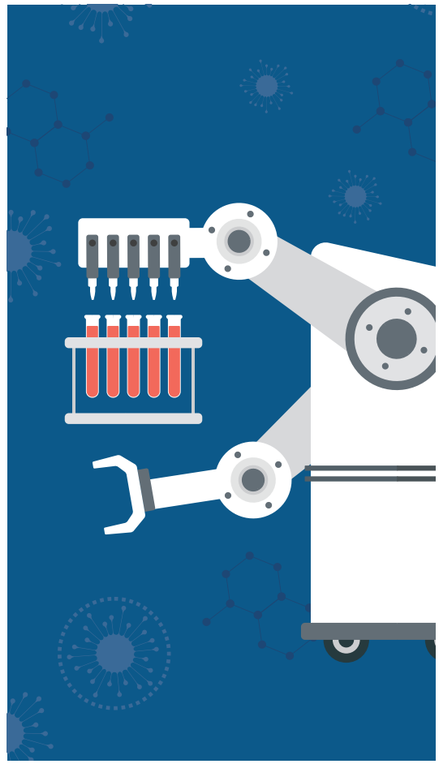
Animal Facility & Lab Support 40

Medicinal Chemistry 42

Screening Discovery Platform

AI-based drug screening platform to prepare and respond to pandemics

New treatments are urgently needed to meet global health and future emerging pandemic threats. Drug discovery programs encompassing high-throughput / high-content screening or HTS/HCS are a hallmark feature of the research and development landscape. HTS/HCS uses automated robotics and miniaturized assay models to rapidly test thousands of compounds or natural products for disease specific activity. These large data sets are analyzed with Ai-based computational engines to extract subtle details and features to understand the disease. This multi-disciplinary approach has the potential to uncover new promising therapeutics through rapid testing and data learning for today's challenges.



SDP is accelerating the pace of drug development through HTS/HCS screening, target deconvolution, omics, and big data. We are committed to providing next-generation solutions to meet current global health challenges as well as preparing for the future.

Mr. David Shum, Head of Screening Discovery Platform

In 2021, traditional drug discovery is a time consuming and expensive process, lasting 10-15 years and costing approximately $1.8 billion. For the thousands of compounds that enter the R&D pipeline, ultimately only one receives approval. At IPK, we focus on HCS approaches for drug discovery. Using advanced imaging and cellular disease models we are able to identify chemicals that reverse disease-specific phenotypes. Screening technologies enable rapid assessment of compound and natural extract libraries for drug discovery. The large data sets are then interrogated with computational engines and informatic databases to identify those acting on the disease models. We anticipate that data will drive the development on new therapeutics as AI-driven approaches evolve to better interpret the mechanism of action. Through a combination of traditional approaches and new technologies, the drug discovery process and failure rates will be greatly reduced leading to overall improvements in pipelines for future global health.

2021 RESEARCH HIGHLIGHT

Implementation of Pasteur International Unit – Artificial Intelligence for Image-Based Drug Discovery & Development (Ai3D)

Pasteur International Unit led by Dr. Spencer Shorte (IP Korea) and Dr. Christophe Zimmer (IP Paris) was embedded into SDP to take advantage of the HTS platform and expertise in imaging. Recruitment of several key members including computational scientists has created a dynamic environment to build an AI-based pipeline that utilizes phenotype to understand cellular function. Cell profiling machine-learning (Cell Painting) methodologies and paradigms are being developed to generate reference data sets for IND & FDA drugs to aid in the development of new therapeutics.

Antiviral Drug Efficacy Evaluation Laboratory Operation Program & Covid-19 Response

Korean National Institute of Health initiative led by Dr. Jiho Kim (IP-Korea) established an HTS-based antiviral evaluation platform in BSL-3 environment to respond to pandemics. COVID-19 including variants were used to test and design assay models for use in future drug discovery pipelines.

Collaboration work between SDP and Asan Medical Center to investigate the neutralizing antibody response of vaccines on COVID-19 in frontline health care workers (HCW). Microneutralization assays were adapted for high-throughput and use to assess the response and immunity of hundreds of samples in various vaccination & infection statuses. Two manuscripts published in 2021 as coauthors (Soonju Park, IP-Korea) and corresponding.

Immune Netw. 2021 Aug 30;21(4):e29. doi: 10.4110/in.2021.21.e29

Immune Netw. 2021 Dec 17;21(6):e41. doi: 10.4110/in.2021.21.e41

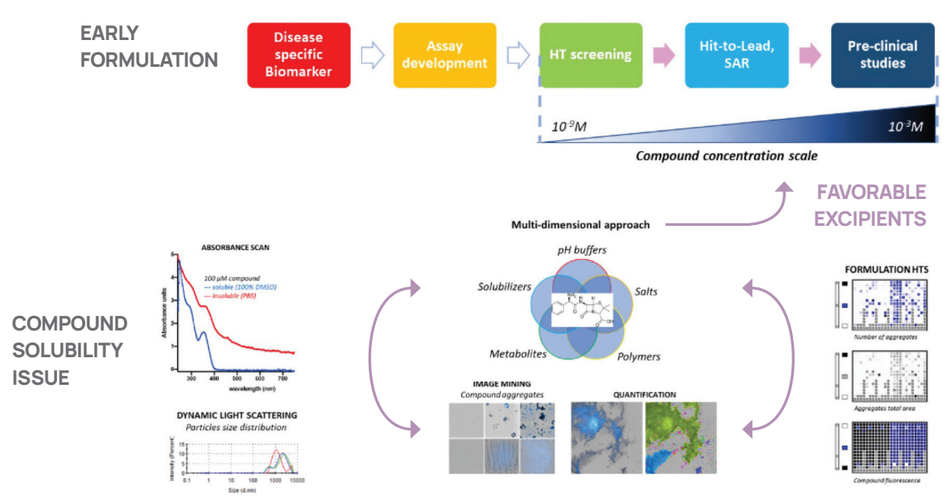
International Grant Funding for Therapeutic Development across Diseases

SDP received grant funding and supported work for therapeutic development outside the traditional programs at IPK. Multi-center screening collaborations included Dengue NS1 oligomerization and secretion inhibitors by Dr. Kyuho Paul Park (IP-Korea) and Dr. Marie Flamand (IP Paris); inhibitory screening of CyaA in Bordetella pertussis or whooping cough with Dr. Alexandre Chenal (IP-Paris); targeting multidrug resistant yeast Candida auris with Dr. Sadri Znaidi (IP-Tunis); identification of natural therapeutic compounds for mitochondrial diseases by Dr. Honggun Lee (IP-Korea) and Dr. Timothy Wai (IP-Paris).

INSTITUT PASTEUR Institut Pasteur de Tunis

Compound solubility and Formulation Platform

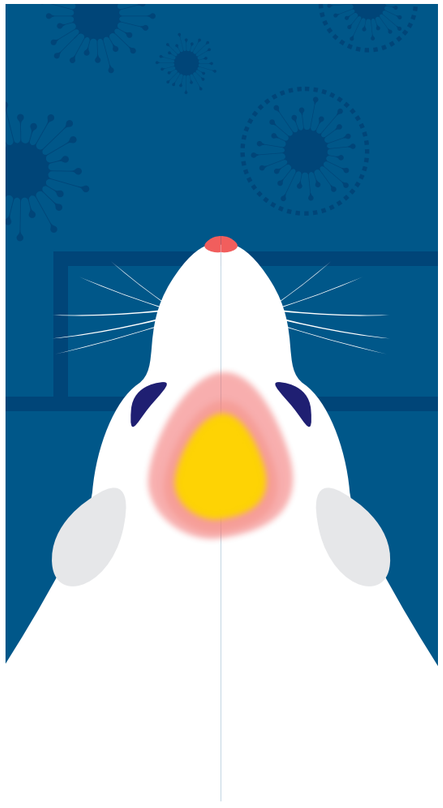
In collaboration with TRL, SDP has obtained support from IP-Paris International Division/Pierre Ledoux Jeunesse Internationale Foundation to further develop its high-throughput compound solubility and early formulation platform for water-insoluble drugs that have interesting biological properties. High-throughput lipid-nanoparticle formulation can be applied to compounds as well as biological polymers.



Formulation Platform: Understanding solubility to improve lead candidates.

Technology Development Platform

Thinking outside the box: Developing research technologies for affordable and accessible augmented image detection and quantification of biological models.



The maintenance of IPK's phenotypic screening facility requires a steady and consistent improvement of advanced cutting-edge screening technologies. The mission we pursue is to develop novel non-invasive quantitative screening technologies to investigate the molecular pathways in any given pathology. Taking advantage of our multidisciplinary team composed of biologists, biophysicists, and microscopy specialists, we are developing optical technologies to study infectious and ageing-related diseases at the nano- to macroscale in cell and animal models.

Expensive equipment is often considered a prerequisite for good science. We believe that the development of technology affordable and accessible to many will promote a greater diversity of scientific thinking. We are committed to affordable and accessible technology innovation that we believe going forwards is an important driving force behind democratization of cutting-edge research technologies to the benefit of all.

Dr. Regis Grailhe, Head of Technology Development Platform

In 2021, our objective is to bridge the gap between molecules, cells, tissues, and animal models using optical imaging. To increase the relevance of our cellular models, we are developing and adapting stem-cell-derived from patients to high content screening (HCS) pipelines. Using selection bioluminescence and fluorescence markers, we study the protein-protein interaction (PPI) network in living cells occurring between the pathogen and the host cell. We capitalize near-infrared (NIR) and Thermal sensors to quantify respectively inflammatory and behavioral responses in animal models using luminescent and fluorescence technologies.

2021 RESEARCH HIGHLIGHT

Rabies transcriptomic regulation using patient-derived neurons

In this study, we characterized the early-regulated host target genes that contribute to the functional defects occurring in human neurons subjected to RABV infection. We examined the innate immune responses against RABV, and found that these pathways contribute to the changes in neuronal function-associated processes. We found regulated genes that could impact neuronal functions, and demonstrated using calcium imaging that indeed the spontaneous activity of neurons is influenced by RABV infection. A detailed analysis of the pathways involved indicates that these virus-induced transcriptional changes promote survival and limit infected neurons' innate immune response.

Front Microbiol. 2021 December 13 I doi.org/10.3389/\ fmicb.2021.730892

HCS drug identification using patient-derived model of Parkinson's disease

Combining high throughput screening approaches with induced pluripotent stem cell (iPSC)-based disease modeling represents a promising unbiased strategy to identify therapies for neurodegenerative disorders. Here we applied high content imaging on iPSC-derived neurons from patients with familial Parkinson's disease bearing the G209A (p.A53T) α-synuclein (αSyn) mutation and launched a screening campaign on a small kinase inhibitor library.

We identified a promising small molecule BX795 with neuroprotective actions as a candidate therapeutic for Parkinson's disease and other protein conformational disorders. BX795 was found to facilitate the autophagy and therefore restore key components of the mTORC1 pathway.

NPJ Parkinsons Dis. 2022 Feb 11;8(1):15. I doi.org/10.1038/ s41531-022-00278-y.

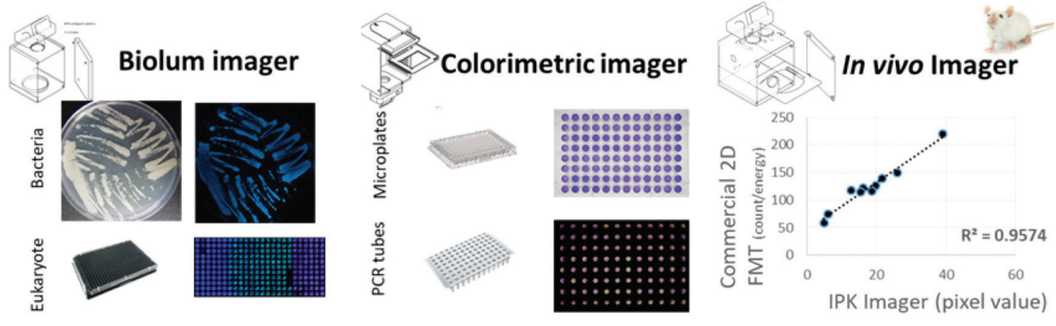
Measles Virus Protein C Interaction With p65-iASPP Protein Complex

Measles virus (MV) encodes two nonstructural proteins MV-V and MV-C known to counteract the host interferon response and to regulate cell death pathways. Direct protein interaction partners of MV-C were determined by applying protein complementation assay and the bioluminescence resonance energy transfer (BRET) approach. As a result, we found that MV-C protein specifically interacts with p65-iASPP protein complex that controls cell death and innate immunity pathways.

Mol Cell Proteomics. 2021;20:100049. doi: 10.1016/j. mcpro.2021.100049.

Multi-purposed optical imaging platforms for all

We designed and manufactured using the latest 3D printing technology and CMOS sensor, three-imager instruments tailored for bioluminescence, colorimetry and rodent in vivo imaging. Such devices support research activity in a whole variety of experimental paradigms and contexts at IP-Korea, and IP-Cameroon.



Multi purposed imager devices for everyone. Left, sensitive bioluminescence imaging multichannel for prokaryote and eukaryotic cells. **Center,** colorimetric imaging applied to HTS microplate format, and PCR/LAMP quantification. **Right,** high dynamic range In vivo imaging tailored to E2-crimson fluorescence probe.

Animal Facility & Lab Support

Rendering research resources supporting pre-clinical testing for drug development.

Our group supports all pre-clinical studies activities performed at the Institut Pasteur Korea. The use of animal models is critical for understanding the complex relationships occurring in infectious diseases involving the body, its immune systems, and the infectious organisms. This work is essential for the validation of the safety and efficacy of new anti-infectious drug candidates. In addition to this activity, our team supports small equipment design and fabrication, large equipment maintenance, quality control, as well as technical and administrative daily research activities.

> *Animal models continue to prove their value in the pre-clinical drug discovery process, as they are essential to predict toxicity and efficacy of drug candidates in patients.*
>
> ***Dr. Regis Grailhe, Head of Animal Facility & Lab Support***

In 2021, the challenge of our animal studies is to adapt our animal model to our facility composed of Specific Pathogen-free laboratory (SPF), animal biosafety level 2 laboratory (ABSL-2), and animal biosafety level 3 (ABSL-3) laboratories. Technically our laboratory spaces are serviced by a functional air-handling unit (AHU) unit with pre- & medium filters, activated carbon filters and HEPA filters allowing fresh air supply and 100% exhaust air. The AHU system allows us to maintain effective experimental animal research into infectious diseases, and automated HTS/HCS activities including the development of new therapies. We provide sperm cryopreservation and in vitro fertilization service in particular for securing transgenic mice. Importantly, we are particularly vigilant to ensure that the highest animal welfare standards are maintained along with every experiment.

2021 RESEARCH HIGHLIGHT

Animal Biosafety support

Our animal Biosafety Level 2 is built upon the practices, procedures, containment equipment, and facility requirements of ABSL-2 and -3. It is suitable for work involving laboratory animals infected with agents associated with human disease, and posing moderate biohazard risk to personnel and the environment. We support the Institutional Animal Care and Use Committee (IACUC) protocols accreditation of every research team on 8 different diseases as well as ensuring researcher training in safety conduct, animal experimentation, and pathogen handling. In 2021, twenty new IACUC protocols were granted.

Histology support

Attempts to understand disease in humans and animal models are both needed and can support and inform each other. In 2021, animal histopathology to study infectious models for acute pneumonia and for preclinical drug efficacy tests were performed.

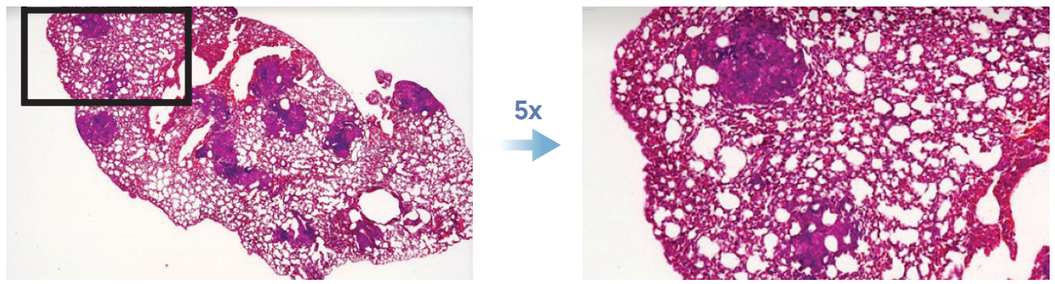
Cryobanking

Cryobanking of sperm, oocytes, and embryos is a useful means to efficiently maintain mouse colonies without breeding live animals. To maintain various types of genetically modified mice in IPK, in vitro fertilization using cryopreserved sperm and fertilized egg transplantation methods technology was implemented.

Pre-clinical in vivo imaging

Optical imaging techniques such as bioluminescence imaging (BLI) and fluorescence imaging (FLI) are approaches that are commonly used in small animals. *In vivo* fluorescence and bioluminescence imaging instrumentation were installed in BSL2 facilities (NEWTON 7.0 - *In Vivo* & *In Vitro* Imaging I VILBER; and *In Vivo* Imaging I Fluorescence I FOBI I CELLGENTEK).

H&E tissue histology of mice lungs



The figure corresponds to colorimetric imaging of the mice's lung sections to visualize the necrotic area in mice lungs chronically infected with mycobacterium tuberculosis.

Medicinal Chemistry

Development of small molecule drug candidates based on infectious disease big data

IPK's Medicinal Chemistry (MC) group develops small molecule drug candidates. We have established the MC platform, which is the "one-stop" place responsible for drug design up to the preclinical stage incorporating an AI/Big data-driven approach, chemical synthesis, quality control of synthesized molecules, and consultation of ADMET properties of the designed drugs. We are conducting research to develop new drugs mainly for infectious diseases as well as anti-cancer and anti-fibrosis.

Entering into the Big-Data/AI-driven era, our team is connecting virtual and real chemical space for innovative drug development.

Dr. Inhee Choi, Head of Medicinal Chemistry

In 2021, we have created the MC ADME/Tox fragment database based on synthesized compounds (9,500 compounds) with annotated ADME/Tox data (2,300 compounds). Small-molecule synthesis for drug discovery is effectively done where SAR (structure-activity relationship) and SPR (structure-physicochemical relationship) were both obtained by designing compounds utilizing this database.

2021 RESEARCH HIGHLIGHT

Compound repurposing of proprietary MC compounds to develop novel antibacterial drug targeting S. aureus

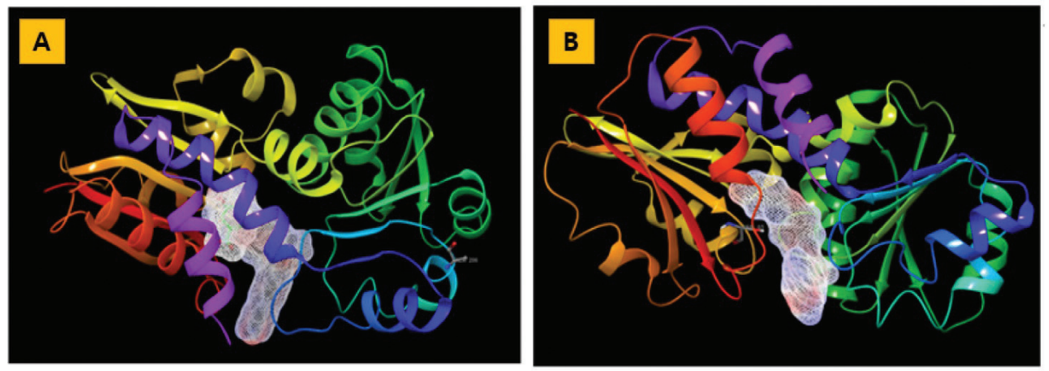
Through the activity confirmation step, we have discovered a novel scaffold: TA, which has better inhibition value than the control, Vancomycin. However, initial hit and derivative had CYP450 inhibition issues. This has been improved by bioisosteric replacement from MC ADME/Tox fragment database. Currently, MoA study is ongoing with one of the lead candidates.

Compound repurposing of proprietary MC compounds to develop novel anti-Chagas drug

Using high-throughput phenotypic screening technique, we have successfully repurposed previously developed HIV antivirals into anti-Chagas, DOQ. Metabolic stability, plasma stability and CYP450 inhibition results show that these compounds have drug-like properties and relatively safe profiles. We have successively discovered and developed the novel compound, DOQ, which shows activities in both amastigote and epimastigote forms of the Trypanosome cruzi which can potentially be developed as novel anti-trypanosomal drug.

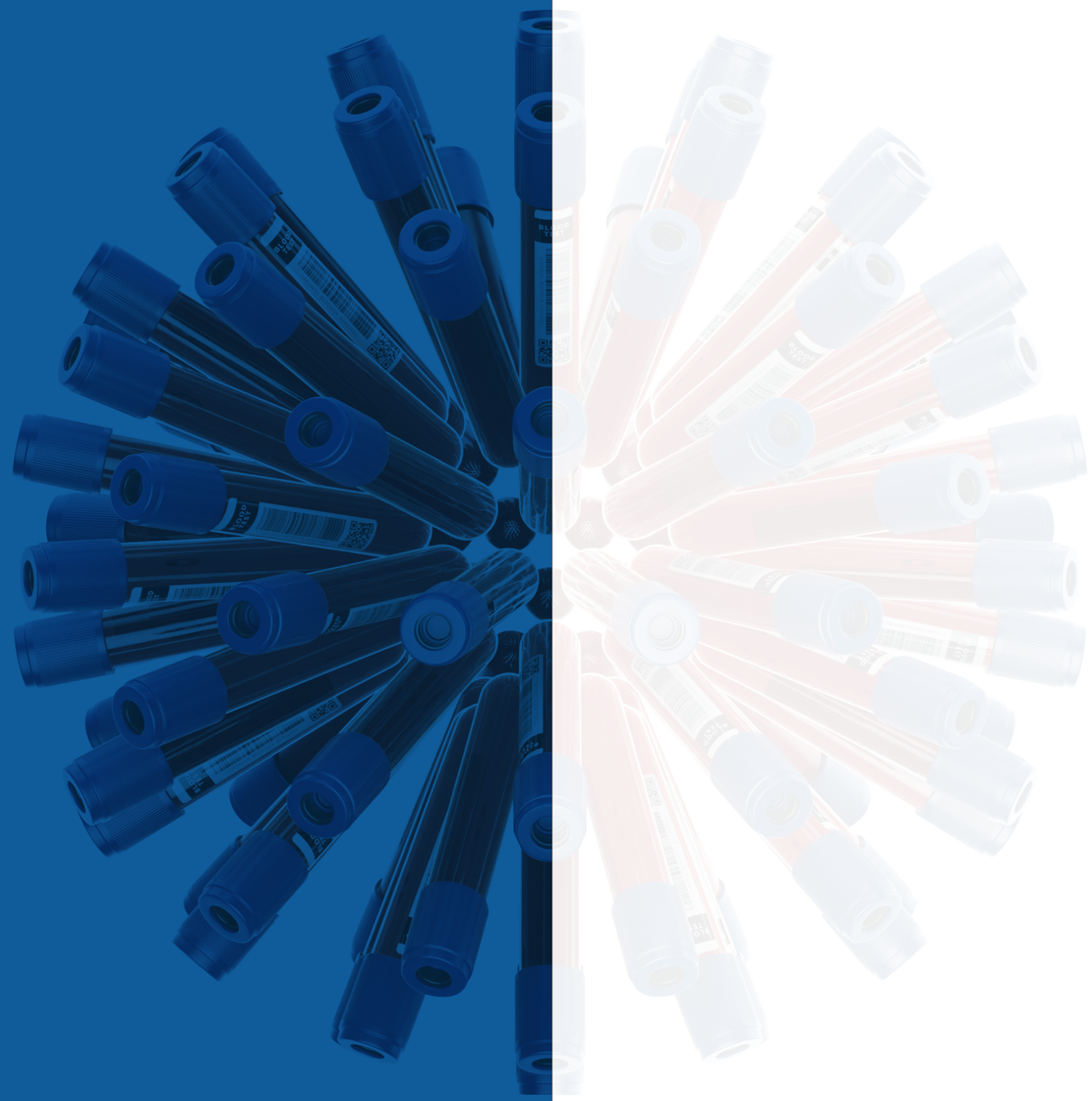
Revolutionary data-based drug discovery to combat drug susceptible TB

Novel targets of TB were selected from next generation sequencing analysis of multi-drug resistant and extremely drug resistant (M/XDR) clinical isolates. Hit compounds - POM scaffold - were identified from virtual screening against these selected TB target proteins. Derivatives were designed from fragment-based approach from previously researched tuberculosis related projects. These compounds are effective against Bedaquiline resistant clinical strains (including drug-sensitive (DS), drug-resistant (DR), M/XDR strains). Good metabolic stability and plasma stability and no CYP inhibition results show that these compounds have drug-like properties and relatively safe profiles.



Binding modes of POM compound docked into 3D structures of selected target proteins (A. Wild type structure; B. mutant structure)

2021
Research Highlight



03

Biobank
Startup Incubation
PIU

Biobank 46

Bio Startup Incubation 48

Pasteur Joint **I**nternational Research **U**nit 50

Biobank

Establishment of BioResource Center (BRC) for emerging and dangerous infectious disease preparedness

When a new infectious disease emerges and causes a significant epidemic, countries around the world engage collaboratively in efforts to collect, manage and share biological resources including pathogens. Bioresources play a crucial role in the emergency response by enabling the characterization of the newly discovered pathogen and developing diagnostics, vaccines, and treatments.

The IPK Biobank team secures high-risk and emerging infectious disease pathogens and human samples, standardizes and supplies them, and supports the preparation and timely response to public health crises. Furthermore, the Biobank team plans to take the lead in spreading expertise and know-how in the effective utilization of infectious materials through education and training programs.

IPK BRC's mission is to provide high-quality, standardized bioresources needed to create novel therapeutics, vaccines, and diagnostic tools.

Prof. Youngjoo Cha, Head of Biobank

In 2021, IPK recruited Young Joo Cha, MD, PhD., as head of Biobank, and promoted the construction of related essential facilities and equipment.

Our activity focuses on:

- Establishment of the Human Bioresource Bank that will collect and provide human specimens containing high-risk viruses/antigens/antibodies/nucleic acids to the biomedical research and industry communities.
- Establishment of the Customized Pathogen Culture Collection that will collect and distribute pathogens based on the needs of researchers studying new and emerging infections.
- Production of Standardized Bioresources for quality assurance of biological medicines and diagnostics.
- Education and Training opportunities for the diverse needs of researchers who are not familiar with the field but want to conduct infectious bioresources-based research.

2021 RESEARCH HIGHLIGHT

The IPK BioBank team promoted the network with the National Blood Transfusion Center of Côte d'Ivoire (CNTS Côte d'Ivoire) to launch a mutual collaboration to strengthen infectious diseases research capabilities based on sharing of bio-resource, thereby securing human resources for infectious diseases. In addition, it took the first step in establishing a network of infectious disease research bioresources by holding online and offline seminars under the theme of "Exploring High Value-Added Pathogens Resources" in December 2021.

Seminar, titled "In Search of High Value-Added Pathogen Resource," held to discuss strategies for responding to infectious diseases through the effective utilization of pathogen resources. (Dec. 2021 @ IPK)

Bio Startup Incubation

A core component of the IPK mission is to assure scientific discovery is delivered as applications in the real world for the benefit of public health. This requires working closely with industry partners and helping biotech startups build themselves.

Since 2017, IPK has supported bio-tech startup companies through the "Bio Core Facility" project financed by the Ministry of Science and ICT. The purpose of this program is to strengthen R&D capabilities, promoting entrepreneurial and business management activities, in a domestic and global network context. Making the opportunity even more attractive to small enterprise IPK offers its advanced research equipment, infrastructure and expertise to the benefit of the selected start-ups.

In 2021, the second phase of the Bio Core Faciity program brought IPK to select five new beneficiary startups. Concurrent candidate companies were selected based on their research innovation area, their potential commercialization opportunities their corporate competitiveness, and their likelihood of establishing synergy with IPK. Accordingly, CTCELLS, CellenGene, CELLAPEUTICSBIO, IPSBIO, and Aevisbio were selected as participating companies. These companies are all now fully engaged actively conducting research innovation activities within IPK's Bio Core Facility startup platform and will remain doing so for three years (2021 to 2024).

Company benefits include training on the use of high-tech research equipment, mentoring, and seminars; research cooperation workshops with IPK, production of corporate promotional materials, and development of technology. Further, IPK's prime location in Pangyo Techno Valley also provides Bio Core Facility tenant companies ample opportunities to collaborate with diverse partners in academia, industry, and hospitals.

Bio Core Facility Project at a Glance

- **Purpose**: To support growth and advancement of the young start-ups utilizing the core facility, global research network and start-up platform of IPK
- **Project Period**: June 2017 ~ June 2024 (7 years)
- **Funding Agency**: Ministry of Science and ICT
- **Funding**: 1.5 billion KRW per year, 10.5 billion KRW in total for the project
- **Supporting Programs**
  - Provide free use of laboratories and office spaces in the IPK's Startup Platform
  - Give access to its research infrastructure (common facility and equipment needed for basic biology and drug discovery research)
  - Mentoring and education for research and operation activities and consultation to advance technology and value up the company
  - Support with commercialization strategy and establishment of networks

* Five companies are selected every three years (in 2017 and 2020), and the supporting program is no longer than 3 years.

Five Companies Currently Participating in IPK's Bio Core Facility Project

CTCELLS | CellenGene Cell and Gene therapy | CELLA PEUTICSBIO | iPSBIO | AevisBio

2021 RESEARCH HIGHLIGHT

- **3** technology transfers
- **55 million KRW** upfront payment received
- **5** patents registered & **44** filed
- **97** new hires
- **40.6 billion KRW** investment secured

IPK - Bio Core Facility Project Participating Companies Joint Seminar (Dec. 1, 2021 @ IPK)

Pasteur Joint International Research Unit

2021 marked the inauguration of a new Pasteur Joint International Research Unit: “Artificial intelligence for image-based drug discovery and development” (PIU-Ai3D).

Evaluated under mandate from the Scientific Direction of Institut Pasteur the Pasteur International Unit led by Dr. Spencer Shorte (IP Korea) and Dr. Christophe Zimmer (IP Paris) was founded based upon a scientific program aiming to develop cutting-edge approaches for image-based drug discovery using machine-learning methods, and in particular deep-learning (a.k.a. “Artificial Intelligence” or AI). The “virtual research unit” framework is based upon an IPK/IP-Paris joint research agreement, providing an agility for integrating new team members, laboratories and expertise according to the evolving needs of the scientific program. In this way the PIU-Ai3D research unit is currently comprised from an amalgam “coalition of the willing” of around 20 multi-disciplined scientists from ten research-technology teams between IPK and IP-Paris.

The PIU-Ai3D is physically embedded within the technologies and expert resources of IPK’s Screening Discovery Platform so that it is fully congruous with the high-throughput image data generation and workflows therein.

Accordingly, we envisage the maximum scientific and technological interplay to benefit of both institutes, and ultimately to render the new technology resource available to the all the members of the Pasteur International Network.

In 2021 the PIU-Ai3D benefitted significant financial resources accorded through the IPK/IP-Paris joint agreement (plus Korean government funding) sufficient to upgrade the high-throughput image data acquisition platform, improving optical performance, robotics automation and computational capacity. Implementing state-of-the-art image scanners and parallel processing computational capacity has enhanced the quality of core IPK data workflows and assured them fully amenable to machine-learning and deep-learning image data processing. This setup is now fully supported by recently recruited scientists in both Korea and France allowing the PIU-Ai3D consortium to progress several key project areas in parallel.

2021 HIGHLIGHTS

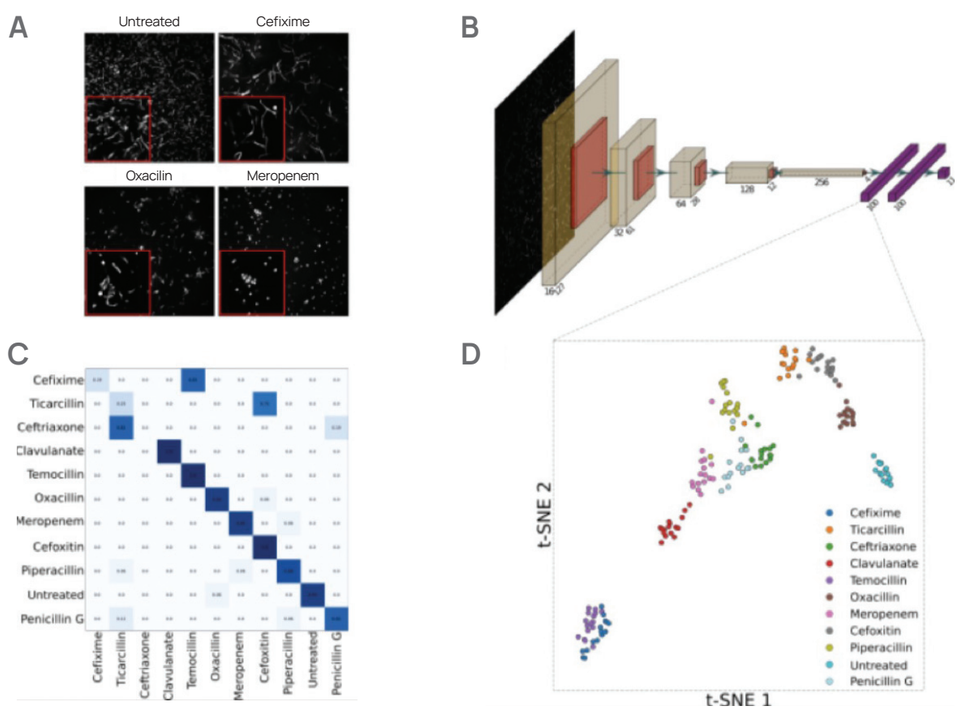
Antibiotic Discovery

The PIU-Ai3D is developing a new deep-learning based approach for anti-bacterial target and drug screening aiming at new antibiotic discovery. As specified in the original proposal this project aims at combining high-throughput imaging and deep-learning to analyze bacterial mutagenic libraries (Pseudomonas aeruginosa) for morphological phenotypes linked to specific genes.

Optimized quality fluorescence and brightfield image data sets generated from entire P. aeruginosa mutant library are being processed by deep-learning, providing morphological insight on genotype-phenotype that will then be used for unsupervised antibiotic drug screening and MoA/target discovery.

Enhanced sensitivity drug screening

The consortium is developing image data acquisition and workflows aimed at enhanced sensitivity detection of weak effects of chemogenomic perturbagens. Specifically, we are adopting methods based on so-called Cell Painting technology that allows for computationally enhanced detection of phenotypic changes in higher-eukaryotic cell morphology from extrapolation among thousands of image data feature parameters in single-cells. These techniques applied to diverse cell/disease models (macrophages, fibroblasts, cancer and stem cells) are expected to allow detection of weakly acting chemical biology effectors thereby providing powerful insight on natural product screening, complex mixtures, and drug lead-optimization.



Deep-Learning based image analysis performed on bacteria clusters specific antibiotic effects based entirely on morphological phenotype.
Unpublished: Schema & figure courtesy Krentzel & Zimmer et al., 2021

2021 Publications

01 Neutralization of Zika virus by E protein domain III-Specific human monoclonal antibody.
Biochem Biophys Res Commun. 2021 Mar 19;545:33-39. doi: 10.1016/j.bbrc.2021.01.075.

02 KIF11 inhibition decreases cytopathogenesis and replication of influenza A virus.
Mol Cell Toxicol. 2021 Feb 26;17:201-212. doi: 10.1007/s13273-021-00126-9.

03 Molecular basis of the interaction of the human tyrosine phosphatase PTPN3 with the hepatitis B virus core protein.
Sci Rep. 2021 Jan 13;11(1):944. doi: 10.1038/s41598-020-79580-9.

04 The amphibian peptide Yodha is virucidal for Zika and dengue viruses.
Sci Rep. 2021 Jan 12;11(1):602. doi: 10.1038/s41598-020-80596-4.

05 Expression of HYOU1 via Reciprocal Crosstalk between NSCLC Cells and HUVECs Control Cancer Progression and Chemoresistance in Tumor Spheroids.
Mol Cells. 2021 Jan 31;44(1):50-62. doi: 10.14348/molcells.2020.0212.

06 Discovery of cyclic sulfonamide derivatives as potent inhibitors of SARS-CoV-2.
Bioorg Med Chem Lett. 2021 Jan 1;31:127667. doi: 10.1016/j.bmcl.2020.127667.

07 Antiviral activity against Middle East Respiratory Syndrome coronavirus by Montelukast, an anti-asthma drug.
Antiviral Res. 2021 Jan;185:104996. doi: 10.1016/j.antiviral.2020.104996.

08 Discovery of 4H-chromeno[2,3-d]pyrimidin-4-one derivatives as senescence inducers and their senescence-associated antiproliferative activities on cancer cells using advanced phenotypic assay.
Eur J Med Chem. 2021 Jan 1;209:112550. doi: 10.1016/j.ejmech.2020.112550.

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Front Immunol. 2021 Jan 11;11:569331. doi: 10.3389/fimmu.2020.569331.

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RSC Med Chem. 2021 Jan 21;12(3):384-393. doi: 10.1039/d0md00353k.

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ACS Med Chem Lett. 2021 Mar 22;12(4):563-571. doi: 10.1021/acsmedchemlett.0c00570.

13 Screening of FDA-Approved Drugs using a MERS-CoV Clinical Isolate from South Korea Identifies Potential Therapeutic Options for COVID-19.
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14 Comparative analysis of antiviral efficacy of FDA-approved drugs against SARS-CoV-2 in human lung cells.
J Med Virol. 2021 Mar;93(3):1403-1408. doi: 10.1002/jmv.26397.

15 Comparison of Digital PCR and Quantitative PCR with Various SARS-CoV-2 Primer-Probe Sets.
Lancet Microbe. 2021 Dec;2(12):e704-e714. doi: 10.1016/S2666-5247(21)00214-7.

16 Noncanonical immune response to the inhibition of DNA methylation by Staufen1 via stabilization of endogenous retrovirus RNAs.
Proc Natl Acad Sci USA. 2021 Mar 30;118(13):e2016289118. doi: 10.1073/pnas.2016289118.

17 Design, synthesis and biological evaluation of 2-aminoquinazolin-4(3H)-one derivatives as potential SARS-CoV-2 and MERS-CoV treatments.
Bioorg Med Chem Lett. 2021 May 1;39:127885. doi: 10.1016/j.bmcl.2021.127885.

18 Proteomic Analysis Uncovers Measles Virus Protein C Interaction With p65-iASPP Protein Complex.
Mol Cell Proteomics. 2021;20:100049. doi: 10.1016/j.mcpro.2021.100049.

19 Lycorine, a non-nucleoside RNA dependent RNA polymerase inhibitor, as potential treatment for emerging coronavirus infections.
Phytomedicine. 2021 Jun;86:153440. doi: 10.1016/j.phymed.2020.153440.

20 Identification of hepatic fibrosis inhibitors through morphometry analysis of a hepatic multicellular spheroids model.
Sci Rep. 2021 May 25;11(1):10931. doi: 10.1038/s41598-021-90263-x.

21 Platycodin D, a natural component of Platycodon grandiflorum, prevents both lysosome- and TMPRSS2-driven SARS-CoV-2 infection by hindering membrane fusion.
Exp Mol Med. 2021 May;53(5):956-972. doi: 10.1038/s12276-021-00624-9.

22 A global metagenomic map of urban microbiomes and antimicrobial resistance.
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PLoS One. 2021 May 28;16(5):e0252488. doi: 10.1371/journal.pone.0252488.

Anti-Cancer Effect of Moroccan Cobra Naja haje Venom and Its Fractions against Hepatocellular Carcinoma in 3D Cell Culture.
Toxins (Basel). 2021 Jun 4;13(6):402. doi: 10.3390/toxins13060402.

24 Bioinformatic Analyses of Canonical Pathways of TSPOAP1 and its Roles in Human Diseases.
Front Mol Biosci. 2021 Jun 15;8:667947. doi: 10.3389/fmolb.2021.667947.

25 A new high-content screening assay of the entire hepatitis B virus life cycle identifies novel antivirals.
JHEP Rep. 2021 Apr 30;3(4):100296. doi: 10.1016/j.jhepr.2021.100296.

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27 Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals.
Brief Bioinform. 2021 Nov 5;22(6):bbab249. doi: 10.1093/bib/bbab249.

28 Discovery of Leishmania donovani topoisomerase IB selective inhibitors by targeting protein-protein interactions between the large and small subunits.
Biochem Biophys Res Commun. 2021 Sep 10;569:193-198. doi: 10.1016/j.bbrc.2021.07.019.

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31 TMPRSS2 and RNA-dependent RNA polymerase are effective targets of therapeutic intervention for treatment of COVID-19 caused by SARS-CoV-2 variants (B.1.1.7 and B.1.351).
Microbiol Spectr. 2021 Sep 3;9(1):e0047221. doi: 10.1128/Spectrum.00472-21.

32 Pyrrolidine-based 3-deoxysphingosylphosphorylcholine analogs as possible candidates against neglected tropical diseases (NTDs): identification of hit compounds towards development of potential treatment of Leishmania donovani.
J Enzyme Inhib Med Chem. 2021 Dec;36(1):1922-1930. doi: 10.1080/14756366.2021.1969385.

33 Comparison of Antibody and T Cell Responses Induced by Single Doses of ChAdOx1 nCoV-19 and BNT162b2 Vaccines.
Immune Netw. 2021 Aug 30;21(4):e29. doi: 10.4110/in.2021.21.e29.

34 Marine dissolved organic matter: a vast and unexplored molecular space.
Appl Microbiol Biotechnol. 2021 Oct;105(19):7225-7239. doi: 10.1007/s00253-021-11489-3.

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R&D Infrastructure

IPK employs dynamic robotic platforms for high-throughput screening of chemical libraries and RNAi collections.

Our fully-automated robotic platforms are located in BSL-2 and BSL-3 laboratories suitable for most pathogens and biological research.

Physical Containment Laboratories

Biosafety Level 3 Laboratory (BSL-3)

- Certified with the approval of Korea Center for Disease Control & Prevention (KCDC, currently KDCA) in March, 2009 (Reconfirmed in 2012, 2015, 2018 and 2021)
- Designed to handle the risk group 3 pathogens such as M. tuberculosis, SARS-CoV, SARS-CoV-2, MERS-CoV, and SFTSV

Biosafety Level 2 Laboratory (BSL-2)

- Registered in Korea's Ministry of Science & ICT according to the Transboundary Movement, etc. of Living Modified Organisms Act
- Designed to handle risk group 2 pathogens such as influenza virus, Zika, Dengue, HBV, Leishmania, T. cruzi and S. aureus

Animal Laboratory

- Composed of specific pathogen-free(SPF) laboratory, animal biosafety level 2 laboratory (ABSL-2) and animal biosafety level 3 laboratory (ABSL-3) with individual ventilation cage system
- Exquisitely controlled environment for care and maintenance of experimental animals

Innovative Screening Platform

Chemical Screening

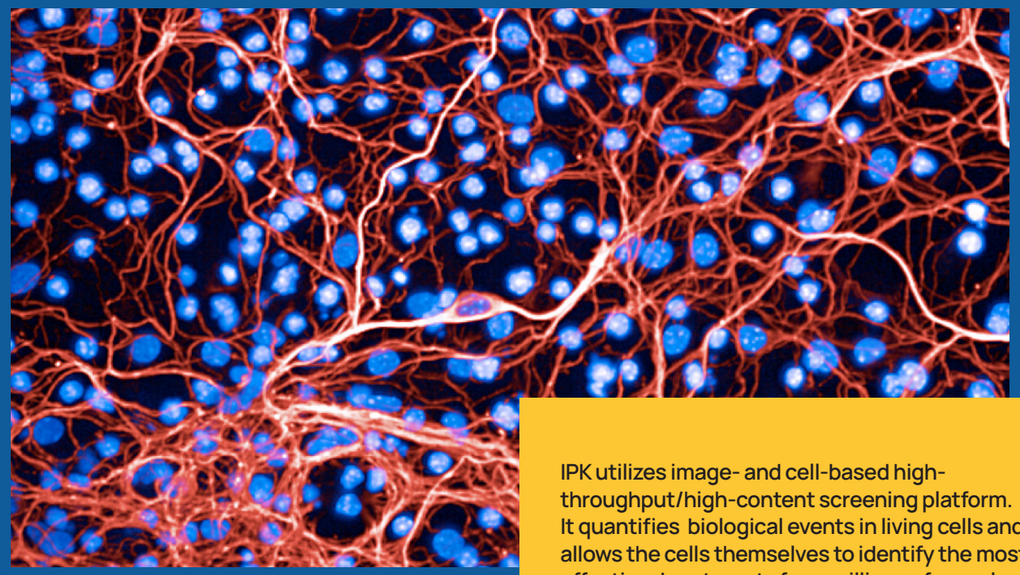
Chemical screening can be used to identify molecules with biological activity from our libraries covering 500,000 compounds including synthetics and natural products. The diverse collection was assembled with the help of the in-house chemistry and cheminformatics experts, as well as established strategic partners.

RNAi Screening

RNAi technology enables sequence specific knockdown of genes to identify new targets and cell signaling pathways for disease understanding. Our RNAi collections cover both siRNA and shRNA technologies for gene by gene systematic interrogation of our biological models.

Automation Management Solutions

Multimodality instrumentation and automated microscopes are integrated into our robotic platforms for fast reliable data acquisition.



IPK utilizes image- and cell-based high-throughput/high-content screening platform. It quantifies biological events in living cells and allows the cells themselves to identify the most effective drug targets from millions of complex molecular interactions. Disease mechanisms addressed by the identified compounds are likely to be physiologically relevant since compounds are tested and studied in cells.

Establishment of Virus Research Resource Center (by 2023)

IPK was the first in Korea to obtain BSL-3 research facility permission in 2008. This particular facility capable of handling high-risk pathogens has proved its value and necessity in tackling infectious diseases in combination with IPK's research expertise and know-how. IPK built a series of track records responding promptly to (re-) emerging infectious diseases during the past 15 years, including especially the recent COVID-19 pandemic, by utilizing the facility. With the support of the Korean Ministry of Science and ICT, IPK embarked on building a 1,688 m^2 Virus Research Resource Center in 2021, one of the strategic pillars of the Korea Virus Research Institut (KVRI). Equipped with new BSL-3 & ABSL-3 facilities and a Biobank, this Center will play a pivotal role in national and international cooperation, in studying infectious diseases and engaging the public and private sectors; as well as in reinforcing our emergency response capabilities.

BSL-3 facility
(Approx. 243 m^2, 4 laboratories)

Facilities for testing and researching risk group 3 pathogens, such as COVID-19, MERS,and Mycobacterium tuberculosis

ABSL-3 facility
(Approx. 322 m^2, 3 laboratories, 2 breeding rooms, 2 autopsy rooms)

Facilities for testing and researching animal infection models, comparable to a general BSL-3 research facility

Biobank facility
(Approx. 140 m^2, 2 storage rooms, 3 laboratories)

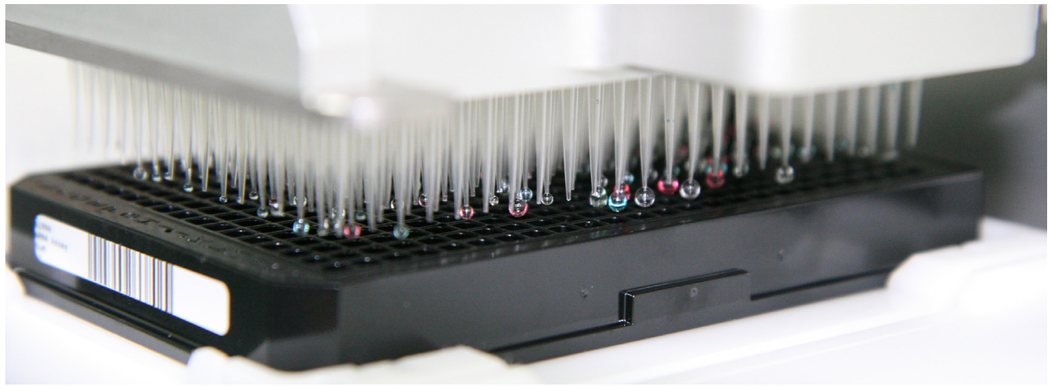
Facilities for rapid acquisition of pathogens, sample production, and storage

BSL-3

The Center will be established on the 6th floor and be open for the use of scientists and researchers in the industry, institutes, and academia in the metropolitan areas as a core infrastructure instrumental for basic virus research and response to the (re)emerging infectious diseases. The Center is under construction with a timeline for completion in 2023.

Research & Technology Services

Innovative IPK Screening Platforms Accelerating Drug Discovery for All



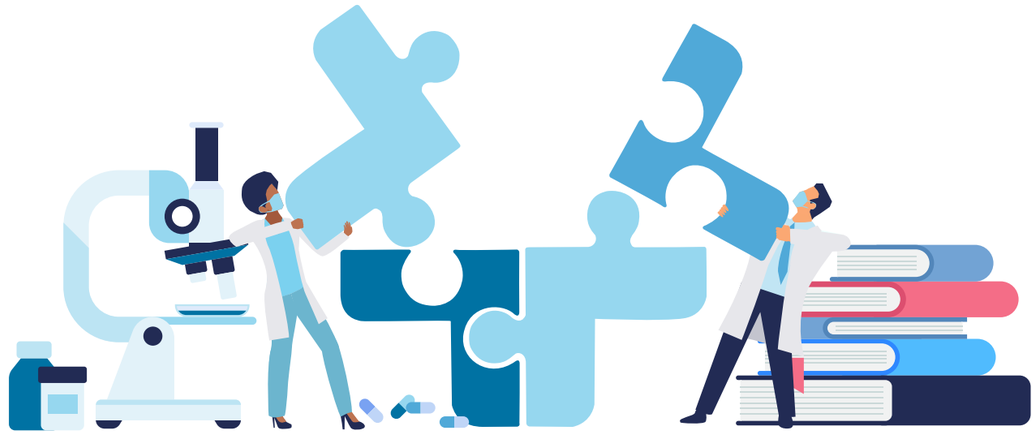
IPK renders access to our innovative drug screening expertise and technologies in biosafety level-2/-3 laboratories enabling domestic and international partners the opportunity to advance their own drug development programs.

The highly experienced professionals of IPK provide various services through all stages of the screening process including biochemical, cell-based, or custom assay design and adaptation, combinatorial screening, proof-of- concept screening, small to large scale screenings, dose-response studies, as well as chemical analysis and molecular modeling.

Over the fifteen years since our founding, IPK has established itself an international reputation as a go-to-partner for pre-clinical screening in infectious disease. In this context we are sought by many partners from academia, public/private-research institutes, NGO's and industry.
This was exemplified in 2020 and 2021 as IPK expedited fee-for-service support for COVID-19 related screening requests for nearly 100 organizations that approached us for support and partnership.

These activities included the evaluation of antiviral efficacy for candidate compounds and antibodies against SARS-CoV-2 using our already developed cell-based assays. Through these partnerships, IPK has screened approx. 10,000 third-party molecules and antibodies in the past two years. Indeed, our own studies revealed potent candidates now undergoing clinical trials. Importantly, as a member of the Korean government's COVID-19 response R&D supporting group, IPK has been helping Korean domestic companies with in vitro drug efficacy evaluation.

2021 Collaborations



MOU Agreement

- Catholic Univ. Bio-health Convergence Material Education and Research Group
- National Medical Center
- International Vaccine Institute
- Genexine
- GC Green Cross Labs
- National Blood Transfusion Center (CNTS) of Cote d' Ivoire
- Consortium of Infectious Disease Research Institute*
  * 15 affiliated institutions: Institut Pasteur Korea, National Institute of Infectious Diseases, Korea Health Industry Development Institute, Korea Virus Research Institute, Korea Research Institute of Bioscience & Biotechnology, Korea Research Institute of Chemical Technology, Korea Institute of Toxicology, Animal and Plant Quarantine Agency, National Wildlife Disease Control Center, Korea Evaluation Institute of Industrial Technology, National Disaster Management Research Institute, National Institute of Food and Drug Safety Evaluation, Jeonbuk National University Korea Zoonosis Research Institute, National Institute of Fisheries Science, International Vaccine Institute
- Noul
- KMEDI hub
- KEY BIO Inc.
- JLK Bio Inc.
- Standigm Inc.
- Virus Research Cooperation Council and Korea Preclinical Evaluation Center*
  * 8 affiliated institutions: Institut Pasteur Korea, Korea Research Institute of Bioscience and Biotechnology, Korea Research Institute of Chemical Technology, Korea Institute of Toxicology, Korea Mouse Phenotyping Center, Korea Virus Research Institute, KBIO Health, KMEDI hub

Joint Research Agreement

- Korea Railroad Research Institute (KRRI), Sundosoft, Eulji University
- Standigm
- HITS
- KaiPharm Co., Ltd.
- Eyegene
- Gwangju Institute of Science and Technology
- AevisBio, National Institute on Aging (NIA)

Recognitions by Key Persons

Prof. Neil Carragher

Chair, IPK Scientific Advisory Committee

The IPK has demonstrated international leadership in the research battle against infectious disease. This is most clearly exemplified over the past 2 years by their participation in multiple academic and industry collaborations to support COVID-19 research on therapeutics and vaccines. Effective cross-disciplinary collaboration between the Zoonotic Virus Laboratory, the Screening Discovery Platform and Medicinal Chemistry Group mobilized IPK research to lead the identification of clinical candidates during the Covid-19 pandemic.

As a result of these activities the IPK is well placed to play a leading role in future pre-pandemic preparedness activity. The IPK has also contributed significantly to a consortium monitoring health surveillance of antimicrobial resistance in the community. Antimicrobial resistance is of increasing heath concern globally and it is encouraging to see the Antimicrobial Resistance Group working together with colleagues at IPK to develop new therapeutic solutions and industry partnerships in this area. The contributions of the Technology Development Group and implementation of an artificial intelligence supported image based drug discovery initiative ensure IPK continues to innovate their technical capabilities and support all of the IPK research programs to be internationally competitive and in doing so maximize the impact of IPK research on society.

Dr. Hani Kim

Executive Director of Research Investment for Global Health Technology Foundation (RIGHT Foundation)

RIGHT foundation deeply values our partnership with IP Korea in discovering a new class of therapeutics to treat tuberculosis, and developing a much needed high-quality, affordable rapid diagnotic test to diagnose visceral leishmaniasis. Both diseases are associated with disproportionate burdens of disease and deaths in resource-constrained countries especially within marginalized communities.

As a result, they represent sources of global health inequity. In addition to IP Korea's R&D efforts, we appreciate their commitment to collaboration with international partners, and global access. We very much look forward to seeing the fruits of their efforts in the coming years.

Scientific Epilogue

Following the peak of the COVID pandemic 2021 brought IPK researchers to reflect on strategies for the future in the context of "pandemic preparedness". Under the mandate of new CEO leadership of Dr Youngmee Jee MD/PhD IPK has sought to reposition basic and translational research activities, with priorities strongly guided by the vision to improve public health.

During 2021 Professor Jee has invigorated scientific and administrative staff of IPK augmenting output in the form of patents, high-level peer-reviewed publications, plus significantly increased levels of competitive funding. Dr. Jee has especially focused on IPK's role as a Korean institute, with international pedigree to assuage the need for articulating and coordinating purposeful collaboration among Korean and International entities. For example, rejuvenating, or adding new instruments for strategic scientific policy implementation such as the Korean Strategic Advisory Committee, the Global Virus Network, and the Pasteur International Network Asia-Hub.

With such vehicles Dr Jee has assured IPK's domestic Korean contribution as an international entity and insisted on the role of Institut Pasteur in the Korean research landscape. These strategic initiatives have been further reinforced by concrete scientific research and resource actions, for example, the implementation of the BioResource Center biobanking facilities, formation of the joint-international unit for AI-driven image-based drug discovery (PIU-Ai3D), and reorganization of IPK scientific teams and facilities to better focus on IPK research priorities.

These changes have introduced a dynamic flux to IPK's research activities making IPK more attractive to industry and startups both as those in the BioCore Facility innovation center, and as a translational research partner (e.g. Standigm, J2H).

In this same spirit of innovation and entrepreneurship, IPK has proven its capacity as a service provider becoming the go-to expertise for pre-clinical chemical screening assay-development, phenotypic high-throughput screening, and chemical drug design and synthesis. In part, driven by the pandemic precipitating a broad public understanding for the need for and importance of life science and infectious disease research, there is a deep appreciation for the value rendered by IPK's agile research resources as quintessential to the national and international pandemic preparedness response capacity.

Accordingly, 2021 brought deeper engagement and coordination with the Korean Ministry of Science (MSIT), and manifest advocacy and support from the French Government (French Ministry of Foreign Affairs). And as Korea takes its place among the global actors looking to optimize the public health strategies for handling future pandemics, IPK and Institut Pasteur International Network are readying our scientific research tools and knowledge to persevere the challenges ahead.

Spencer L. Shorte

Chief Scientific Officer

Pasteur Network

Pasteur Network is a worldwide network of 33 members, united by Pasteurian values, which contribute to the improvement of global health.

Pasteur Network, previously known as the Institut Pasteur International Network, brings together 33 institutes located in 25 countries across the five continents, united by the same missions, culture, and values of Pasteurian. Leveraging its vast human and scientific community, the Network is involved in international research projects, public health, teaching, and training programs. For the past century, it has served as a sentinel for emerging infectious diseases in several endemic regions of the world, leveraging unique multidisciplinary cooperation in the field of human health by fighting against infectious diseases.

The CEO of Institut Pasteur Korea, Dr. Youngmee Jee, was elected as a co-representative of the Asia-Pacific Region of the Network, along with Dr. Leo POON, Co-Director of the Pasteur Institute in Hong Kong, in Jun 2021. Dr. Jee has facilitated scientific exchange and research collaboration between 10 members in the region by initiating and operating bi-monthly meetings and joint seminars.

Institut Pasteur and the Pasteur Network call for annual projects, such as Pasteur International Joint Research Unit (PIU), Inter Concerted Pasteurian Actions (ACIP), and Transversal Research Projects (PTR). These projects are dedicated to the Pasteurians with an ambition to facilitate scientific collaboration within the Network. In 2021 IPK has conducted six projects supported by the Network, in which three are newly initiated in the year:

- **[PTR]** Proof of concept study: targeting DENV NS1 to reduce viremia and alleviate of plasma leakage(2021~2023 / In collaboration with Institut Pasteur)
- **[PTR]** Chemical RNA modifications in RIG-I-like receptors signaling(2021~2023 / In collaboration with Institut Pasteur)
- **[PTR]** OrganoEar - Organoids-on-chip: role of Sonic-Hedgehog signaling on the development of inner ear organoids (2020~2021 / In collaboration with Institut Pasteur)
- **[PIU]** Artificial intelligence for image-based drug discovery & development (Ai3D) (2021~2025 / In collaboration with Institut Pasteur)
- **[COVID-19]** Development of a high-throughput loop-mediated isothermal amplification (LAMP) assay for rapid mass testing of mobile populations to limit the spread of COVID-19 infections (2020~2021 / In collaboration with Institut Pasteur Cameroon)
- **[COVID-19]** Drug Discovery Against the Major Protease of SARS-CoV-2 (2020~2021 / In collaboration with Institut Pasteur Montevideo, Institut Pasteur of Shanghai, FIOCRUZ)

Statements from the Representatives of the Pasteur Network

Prof. Stewart Cole

President of Institut Pasteur, France

Throughout 2021, as the world gradually learned to live with Covid-19, Institut Pasteur Korea (IPK) attentively pursued the significant work on the pandemic that it began in 2020 while also strategically shifting its mid- and long-term priorities back into focus. Under both Dr Youngmee Jee's steady leadership and Dr Spencer Shorte's scientific expertise, IPK's advances in drug discovery for repositioning have come to constitute singular contributions to the fight against the pandemic and further underscore IPK's unique value proposition. Among the collaborations between IPK and the Institut Pasteur that blossomed this year, I am especially pleased to note the creation of the Pasteur Joint International Research Unit on "Artificial Intelligence for Image-Based Drug Discovery & Development" (Ai3D), a landmark initiative in a cutting-edge area of research. These major contributions to France-Korea scientific cooperation would not be possible without the clear and shared scientific vision of the CEO and the CSO, and I hope this partnership continues to grow stronger in the years to come.

Dr. Rebecca Grais

Executive Director of the Pasteur Network

IPK plays a key role within the Pasteur Network. As one of the two regional representatives for Asia-Pacific, Dr Jee has placed IPK at the heart of a new dynamism federating the region's diverse members around common goals, all in the service of Pasteurian missions and values. Furthermore, IPK has continued to expand its participation in numerous Pasteur Network research projects and to share its expertise through various training programmes. I am confident that IPK, as an active member of the worldwide Pasteurian community, will continue to thrive and flourish in the face of new challenges in global public health as it heads into the future.

IPK Leadership (As of Dec 31. 2021)

Board of Directors

Yong-Kyung Choe (Chairman)
(Former) Director of Korean Bioinformation Center (KOBIC), Korea Research Institute of Bioscience and Biotechnology (KRIBB)

Man-Seong Park
Professor, College of Medicine, Korea University

Hyuk Lee
Principal researcher, Research Strategy Division, Korea Research Institute of Chemical Technology (KRICT)

Chang-Yoon Lee
Director-General of R&D Policy Bureau, Ministry of Science and ICT

Kwang-Yeol Ryu
Assistant Governor, Economy Office, Gyeonggi Provincial Government

Stewart Cole
President, Institut Pasteur

Pierre-Marie Girard
Executive Vice-President for International Affairs, Institut Pasteur

Youngmee Jee
Chief Executive Officer, Institut Pasteur Korea

Spencer Shorte
Chief Scientific Officer, Institut Pasteur Korea

Isabelle Buckle
Executive Vice-President for Technology Transfer and Industrial Partnership, Institut Pasteur

Jinsun Park
(Former) Secretary-General, Korea Nuclear International Cooperation Foundation

Scientific Advisory Committee

Alex Matter (Chair)
Adjunct Professor, Duke-NUS Singapore

Seonggu Ro
Chief Executive Officer, PiMedBio Inc.

Seung Bum Park
Professor, Dept. of Chemistry, Seoul National University

Neil Carragher
Professor and Chair of Drug Discovery and Director of Translation, University of Edinburgh

Ivo Gomperts Boneca
Head of Unit, Biology and Genetics of the Bacterial Cell Wall, Institut Pasteur

Jae U. Jung
Professor and Chair in Cancer Biology, Lerner Research Institute, Cleveland Clinic

Koo Lee
Chief Executive Officer, Interpark Bio Convergence Corp

Tae-Wook Chun
Senior Investigator and Chief of HIV Immunovirology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Eui-Cheol Shin
Professor, Graduate School of Medical Science & Engineering, KAIST

Yae-Jean Kim
Professor, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine

Malik Peiris
Professor and Chair of Virology, School of Public Health, University of Hong Kong

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