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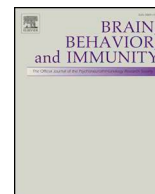
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Psychoneuroimmunology goes East: Development of the PNIRS_{China} affiliate and its expansion into PNIRS_{Asia-Pacific}



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ABSTRACT

The Psychoneuroimmunology Research Society (PNIRS) created an official Chinese regional affiliate in 2012, designated PNIRS_{China}. Now, just eight years later, the program has been so successful in advancing the science of psychoneuroimmunology that it has expanded to the whole of Asia-Oceania. In 2017, PNIRS_{China} became PNIRS_{Asia-Pacific}. Between 2012 and 2019, this outreach affiliate of PNIRS organized seven symposia at major scientific meetings in China as well as nine others in Taiwan, Japan, South Korea, Australia and New Zealand. This paper summarizes the remarkable growth of PNIRS_{Asia-Pacific}. Here, regional experts who have been instrumental in organizing these PNIRS_{Asia-Pacific} symposia briefly review and share their views about the past, present and future state of psychoneuroimmunology research in China, Taiwan, Australia and Japan. The newest initiative of PNIRS_{Asia-Pacific} is connecting Asia-Pacific laboratories with those in Western countries through a simple web-based registration system. These efforts not only contribute to the efforts of PNIRS to serve a truly global scientific society but also to answer the imperative call of increasing diversity in our science.

1. Growth of health expenditure research in Asia-Oceania

Expenditures in biomedical research and development (R&D) are a reliable indicator of not only a country's wealth but of the importance it places on the health of its citizens. It is challenging to estimate global research and development expenditures and compare those results across countries. The two major issues are obtaining health care data from each country and using a common currency conversion over time (Young et al, 2015). Despite these important challenges, Chakma et al (2014) made a legitimate effort to do just that, sourcing data from global biomedical agencies, governments and statistical bureaus and rendering those data into US dollars for legitimate comparisons. According to this analysis, in 2012 the USA spent the most on health care research, amounting to US \$48.9 billion by public institutions and US \$70.4 billion by private industry. The whole of Europe spent US \$81.8 billion. All of the countries in Asia-Oceania spent half the amount of the

USA, amounting to US \$62 billion with 70% of that provided by private industry. Of all the Asia-Oceania countries, the largest investment in health care R&D between 2007 and 2012 was made by Japan, amounting to US \$202.2 billion. Australia, China and South Korea each spent between US \$26 to US \$32 billion. But the story line was not how much biomedical R&D was invested by Asia-Oceania countries. Instead, the take-home point was the trend in their expenditures over time.

During the six-year time span from 2007 to 2012, R&D expenditures declined in all the developed Western countries, which included Canada (−2.6%), USA (−1.9%) and Europe (−0.4%). In contrast, Japan increased its spending by US \$9 billion, amounting to a 5.7% increase. Health care spending by all of the other countries in Asia-Oceania increased as well, including Taiwan (5.2%), India (6.7%), Australia (6.9%), Singapore (10%), South Korea (11.4%) and China (32.8%). These estimates have been revised somewhat (Young et al, 2015), but the broad conclusion remains the same: investment in

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biomedical research increased at a faster pace in Asia-Oceania than in the United States as well as Canada and Europe. In accord with this rising biomedical investment, psychoneuroimmunology research is now growing in the entire Asia-Pacific region.

The increase in biomedical R&D research expenditures in all the countries of Asia-Oceania did not go unnoticed by academia and private industry. There was an increase in competition among countries for recruiting and retaining the best biomedical research talent. This increase in health spending meant more opportunities for Asian-Oceanian scientists to return home to their native country to work and prosper. And, after they returned, many developed productive collaborative research programs with Western scientists where they received their advanced training. It also meant that graduate students, post-docs and professors from countries outside of Asian-Oceania had more employment opportunities in foreign countries. Stated simply, increased funding for biomedical R&D in Asia increased opportunities not only for Asian-Pacific investigators but for scientists around the entire world. The end product has been simply the result of supply and demand. The beneficiaries of this greater investment in biomedical R&D in the entire Asia-Pacific region were not only the investigators but all of us because of the biomedical discoveries that they produced.

Highlighting a potential challenge with global collaboration, the recruitment efforts of one Asia-Oceania country, China, have recently come under scrutiny in the USA based upon economic and national security concerns (Anonymous, 2019a). This development challenges two key features of biomedical research: openness in sharing data and global collaboration. And, this umbrage might spread to all countries in Asia-Oceania. As highlighted by the current pandemic with SARS-CoV-2, this is a time when biomedical scientists and pharmaceutical companies around the world are working together to find both treatments and a vaccine for this very contagious coronavirus (Apuzzo and Kirkpatrick, 2020). Indeed, the former director of the National Institutes of Health, Elias Zerhouni, pointed to the substantial contributions of foreign-national scientists. He noted that foreign nationals have contributed greatly to both patents and scientific discoveries in the USA. He wrote, “No members of any community should be targeted because of their origins....The United States should not risk losing critical intellectual assets such as productive foreign-born scientists and engineers to global competitors...” (Zerhouni, 2019). This cautionary message was more recently reiterated by the editorial staff of the leading journal, *Biological Psychiatry*: “The mission of *Biological Psychiatry* is to publish impactful scientific communications. To further

that mission, we promote diversity in all aspects of the publication process, including authorship, reviewing, and editing. Our diversity efforts aim to increase participation among individuals of under-represented racial, ethnic, and gender identities; from underrepresented countries or disadvantaged backgrounds; and those with disabilities.” (Leibenluft, 2020).

2. Creation of PNIRS_{China}

Biomedical research in China and that in Western countries has proceeded relatively independently. However, as noted above, that focus changed dramatically early in the 21st century. The Psychoneuroimmunology Research Society (PNIRS) is a global non-profit society that was formed in 1993. Its primary goal is to promote the study of interactions between the nervous and immune systems and the relationship between behavior and health. PNIRS has a rich history of promoting basic research that can be translated to the clinic (Kelley and McCusker, 2014; Kelley, 2020), and this extends to Asia. As early as 2002, Christopher Coe, Ph.D., organized a symposium at the annual PNIRS meeting that was held in Madison, Wisconsin. The speakers discussed both traditional Chinese medicine (TCM) and Tai chi (Anonymous, 2002). Ten years later, the society “got ahead of the curve” by recognizing the growing importance of biomedical research in China by forming the Chinese branch of PNIRS, designated PNIRS_{China}, as its official regional affiliate in that country. This PNIRS_{China} affiliate began by serendipity.

Yu-Ping Peng, M.D., Ph.D., invited Professor Virginia Sanders at The Ohio State University to present lectures at Nantong Medical University in 2012. Professor Sanders, who was an Associate Editor of *Brain, Behavior, and Immunity* at the time, was unavailable. As such, she recommended that Professor Peng invite the then Editor-in-Chief of *Brain, Behavior, and Immunity*. Professor Kelley readily accepted the ensuing invitation from Professor Peng to lecture in Nantong. He went on to lecture in Dalian and Beijing. During that trip, lots of brainstorming occurred about the idea of forming liaisons between China, *Brain, Behavior, and Immunity* and PNIRS (Fig. 1). The possibility of creating an Eastern affiliate like PNIRS_{China}, as had previously been done in the West with Germany (German-Endocrine-Brain-Immune-Network (GEBIN; Anonymous, 1997), was considered.

Mind-body relationships have been studied for centuries by Indian, Greek and Egyptian physicians. The practice of TCM has been, and continues to be, used by billions of people in the Sinosphere. The

The Power of an Idea Psychoneuroimmunology Research Society (1993) PNIRS China (2013)



Yu-Ping Peng, M.D., Ph.D.
Nantong University



Qiang Liu, M.D., Ph.D.
Dalian Medical University



Bo Bai, M.D., Ph.D.
Jining Medical University

Fig. 1. Three mainland Chinese academic physicians who were instrumental in the establishment and growth of PNIRS_{China}.



Fig. 2. Traditional Chinese medicine psycho-behavioral interventions improve quality of life for cancer patients. The psycho-behavioral interventions were acupuncture, Chinese massage, traditional Chinese medicine five elements musical intervention, traditional Chinese medicine dietary supplement, qigong and Tai chi. (Tao et al, 2015). Julie McMahon at the University of Illinois Urbana-Champaign is credited for preparing this figure.

essence of TCM is the balance of body and mind (Fig. 2), which is considered to be linked by communication between the brain, neuroendocrine and immune systems. Professor Cobol Su, M.D., Ph.D., at the China Medical University in Taiwan recently eloquently summarized this concept with a simple sentence: “Psychoneuroimmunology has been long stemmed in ancient medicine (Su, 2019).” As such, it seemed logical to develop a plan that would establish more formal relationships with Chinese scientists. This would not only promote a better understanding of psychoneuroimmunology but also serve to contribute to improvement of world-wide health care. Furthermore, sharing Western science with Chinese investigators made sense in order to articulate and better understand if and how TCM aligns with Western scientific principles (Anonymous, 2007). Perhaps the PNIRS affiliate of China would promote development of knowledge about mind-body techniques practiced in other Eastern countries like Taiwan, Japan and South Korea.

A summary of these discussions was shared with the President of the PNIRS at that time, Professor Manfred Schedlowski in Essen, Germany. Following discussions of these and other ideas with the PNIRS Executive officers, Professor Schedlowski formally recognized this affiliation on November 26, 2012, in a letter to Quentin Liu, M.D., Ph.D., stating: “Please accept this letter as an official formal acceptance and recognition of the regional network of Chinese scientists/physicians engaged in research of direct interest to the PNIRS and its official scientific journal, *Brain, Behavior, and Immunity*. Your China Branch of PNIRS (PNIRS_{China}) will be recognized as an official regional affiliate of PNIRS.” (Fig. 3). Professor Schedlowski hoped that creation of the regional affiliate of PNIRS_{China} would someday permit PNIRS to enjoy its first annual meeting in China.

3. Formal opening ceremony of PNIRS_{China} on April 23, 2013

In 2013, Professor Quentin Liu was (and remains) Vice-president of Dalian Medical University and Director of their Institute of Cancer Stem Cells. Dalian Medical University was one of the first universities in China to focus on Clinical Integrative Medicine. This is a curriculum that combines teaching, practice and research in both traditional and western medicine. Following creation of PNIRS_{China}, Professor Liu moved quickly to establish and organize the first official meeting of this new PNIRS affiliate (Anonymous, 2016). The participating organizations were Dalian Medical University, Nantong University, Jining

Medical University and Sun Yat-sen University. Importantly, Professor Liu enlisted the input of Bo Bai, M.D., Ph.D., the president of Jining Medical University. This academic forum was held in conjunction with the Dalian Psychoneuroimmunology Medical Society. A broad goal was developed that aimed to embrace, learn and share knowledge about psychoneuroimmunology with Chinese colleagues. At the opening ceremony of the first PNIRS_{China} meeting on April 23, 2013, Professor Liu outlined three specific goals for the new PNIRS affiliate: (1) Conduct basic research that can be translated into clinically relevant health applications; (2) Promote the growth of interrelationships among scientists of different scientific and medical disciplines; and (3) Build a platform of academic communication for researchers engaged in psychoneuroimmunology research and teaching. The PNIRS_{China} affiliate would help scientists in China develop an international perspective, to identify and cultivate emerging outstanding young investigators and organize academic forums and experience exchanges among laboratories. Professor Kelley, other scientists and university leaders made presentations during the ceremony. This 2013 meeting was well-attended with 250 registrants. Professor Liu formally presented Professor Kelley with a plaque recognizing the formal creation of PNIRS_{China} (Fig. 4). Professor Liu extended the opening of PNIRS_{China} by organizing meetings at Jining Medical University and Sun Yat-sen University in Guangzhou. The integrative aspects of psychoneuroimmunology research were emphasized at all these meetings. Indeed, the call for expanding the knowledge of integrative medicine in continuing medical education programs, as assessed by the Accreditation Council for Continuing Medical Education, has recently been highlighted (Ring et al., 2020).

Following formal creation of PNIRS_{China}, PNIRS established a new committee, designated PNIRS_{China}. This committee aimed to organize symposia and other outreach approaches that would embrace, learn and share knowledge about psychoneuroimmunology with Chinese colleagues. The approach used was simple and cost-effective. Leading psychoneuroimmunology scholars from around the world were invited to participate in symposia submissions to major scientific meetings held in mainland China. Even though no travel funds were available to support expenses, nearly all of the invited experts willingly agreed to pay their own travel. Since the formal opening ceremony in Dalian, there have been six more PNIRS_{Asia-Pacific}-sponsored symposia in Shanghai, Wuzhen, Beijing, Zhanjiang, Tianjin and Nanchang (Fig. 5). A summary of the scientific content, as well as the names and photos of all the

speakers, is available online at the PNIRS home page (<https://pnirs.org/pnirschina/index.cfm>). Each of these meetings attracted around 120 scientists or more. The audience was actively engaged, as assessed by both the number and quality of questions. It was clear to the organizers and speakers that Chinese scientists were interested in learning more about psychoneuroimmunology, PNIRS and *Brain, Behavior, and Immunity*.

4. Association of *Brain, Behavior, and Immunity* with establishment of PNIRS_{China}

In 2000, *Brain, Behavior, and Immunity* became the official journal of PNIRS (Kelley, 2020). Its impact factor has been around 6 since 2013.

And for the past 15 years, the journal has been ranked in the top 15% of all world-wide journals published in the category of neuroscience as well as immunology. It was recently ranked in the top 10% of all psychiatry journals. This has led to the designation of *Brain, Behavior, and Immunity* as, “the best immunology journal in the neurosciences” (Kelley, 2017). As such, it is an appropriate surrogate for describing the progress of psychoneuroimmunology research throughout Asia.

Prior to 2005, only 8 manuscripts with corresponding Chinese authors were submitted for publication to *Brain, Behavior, and Immunity*. Scientists from the United States were the major contributors to the journal. Only eleven years later, 17% of all submissions to *Brain, Behavior, and Immunity* originated in China, making China the second leading country to submit papers to the journal (Kelley, 2017). Since



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Dalian, P. R. China

November 26, 2012

Dear Professor Liu:

I am writing to you in my capacity of President of the Psychoneuroimmunology Research Society (PNIRS; www.pnirs.org). The PNIRS is composed of an international group of scientists/physicians who are defining interactions between the nervous and immune systems and their relationships to behavior and health. My good friend and colleague, Professor Keith W. Kelley at the University of Illinois, has informed me that you would like to create a network of Chinese scientists/physicians who are conducting cutting-edge research in immune-brain-disease communication systems. As you are aware, Dr. Kelley is the Editor-in-Chief of our official PNIRS society scientific journal, *Brain, Behavior, and Immunity*. It is my understanding that your specific goal is to establish an active, vibrant network of Chinese scientists/physicians who are conducting research in this area. One of the clinical thrusts would be the combined use of Traditional Chinese Medicine and Western Medicine for cancer treatments and chronic inflammatory diseases. PNIRS scientists are conducting research that will lead to a better understanding of the crosstalk that occurs between the immune system and brain. Their discoveries will eventually lead to more effective and comprehensive treatments for patients who suffer from a multitude of diseases. We welcome a regional Chinese scientific network that will promote these goals.

When Dr. Kelley informed me of your objective, I immediately supported your idea and goals. That is because the PNIRS has already recognized other successful regional groups in countries like Germany. For example, the German-Endocrine-Brain-Immune-Network (GEBIN) was founded 15 years ago as a similar national brain, behavior, and immunity group with regular meetings and scientific activities. In the United States, Dr. Kelley and colleagues initiated and continue to support the “Brain, Behavior, and Immunity Meetings of Illinois.” This initiative, held in Chicago around the first weekend of December, continues to be very successful. Their 5th Annual Meeting will be held next week in a regional meeting that typically attracts more than a 100 scientists engaged in PNIRS research. This initiative is now a role model for future regional PNIRS/BBI groups because I recently learned that our colleagues in California and Colorado are currently considering a similar activity. I would hope that your network of Chinese PNIRS scientists/physicians would also sponsor and organize a PNIRS regional meeting in China. Perhaps someday this would allow us the opportunity to enjoy our first international PNIRS annual meeting in China.

Please accept this letter as an official formal acceptance and recognition of the regional network of Chinese scientists/physicians engaged in research of direct interest

www.pnirs.org

Fig. 3. Professor Schedlowski’s letter that established creation of the PNIRS_{Asia-Pacific} affiliate in 2012 (Kelley, 2016).



Essen, Germany

Nominating
Monika Fleshner,
PhD
Boulder, Colorado

Communications
Annemieke
Kavelaars, PhD
Houston, Texas

Constitution and By-Laws
Monika Fleshner,
PhD
Boulder, Colorado

Finance
Gayle Page, DNSc,
RN, FAAN
Baltimore, Maryland

Training
Jan Moynihan, PhD
Rochester, New
York

to the PNIRS and its official scientific journal, *Brain, Behavior, and Immunity*. Your China Branch of PNIRS (PNIRS China) will be recognized as an official regional affiliate of PNIRS, similar to the manner in which GEBIN has operated in Germany. I sincerely hope that this formal recognition of a regional PNIRS China community by the President of our international PNIRS community will help attract outstanding Chinese scientists/physicians to this network.

I would personally like to invite you and your PNIRS China colleagues to become formal members of the PNIRS. There are many advantages to membership, as described at our website (www.pnirs.org). Annual dues for full members amount to \$225, which includes an electronic subscription to *Brain, Behavior, and Immunity*. Registration fees at our annual meeting are greatly reduced for PNIRS members. In 2013, our annual meeting will be held in Stockholm, Sweden, and two Nobel Laureates will present invited lectures. It would be wonderful if you and your Chinese associates could find the time to participate in these meetings and learn more about the cutting-edge research that is being conducted by our members.

To recapitulate, I am honored and delighted to officially recognize and welcome the regional network of Chinese scientists/physicians at the regional group, PNIRS China, to our international PNIRS organization.

Sincerely yours,

Manfred Schedlowski, Ph.D.
President, Psychoneuroimmunology Research Society
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www.pnirs.org

Fig. 3. (continued)

the first issue of the journal appeared in 1987, there have been 609 cumulative papers from the Asia-Pacific region published in the journal (Fig. 6). The rise in annual publications from China since 2015 is particularly impressive, with Australia publishing the second largest number of papers. More importantly, the quality of published papers is high, as shown by the skyrocketing increase in citations of papers originating in both China and Australia. Of note, these citation data have not been adjusted for factors like the number of submissions or the population of each country. However, of the top ten most highly 2014 papers that were cited between 2015 and 2016, three of them were from laboratories in China. It is especially noteworthy that the most highly cited paper in the journal in 2015/2016 was published by Bing

Ruan, M.D., Ph.D., whose laboratory is at the First Affiliated Hospital, School of Medicine at Zhejiang University in Hangzhou, Zhejiang (Jiang et al., 2015). This PNIRS award-winning paper was highlighted in *Brain, Behavior, and Immunity* by Dinan and Cryan (2019).

5. 2017: PNIRS_{China} rebranded as PNIRS_{Asia-Pacific}

Beginning in 2000, it seemed that research and high-quality publications in psychoneuroimmunology were increasing throughout Australia, Japan and South Korea. Following the successful organization of seven symposia in mainland China, it was therefore natural to expand these activities to the whole of Asia-Oceania. In addition to East



Fig. 4. Formal initiation of PNIRS_{China} at Dalian Medical University on April 23, 2013. The opening ceremony featured Professors Kelley and Liu and included leadership executives of the university (Kelley, 2016).

History of Development of PNIRS_{China}

- 2012 Prof. Kelley initiates concept of PNIRS_{China} with Prof Peng, Liu and Bai following lectures in Nantong, Dalian and Beijing
- 2012 PNIRS President Manfred Schedlowski officially establishes PNIRS_{China}
- 2013 Prof Kelley to discuss PNIRS_{China} with Prof Lutgendorf at the U. Iowa
- 2013 1st official PNIRS_{China} established and organized by Prof Liu in Dalian
- 2014 Unofficial PNIRS_{China} meeting organized by Prof Hutchinson Sydney
- 2014 2nd official PNIRS_{China} symposium organized by Prof Peng in Shanghai
- 2015 3rd official PNIRS_{China} symposium organized by Prof Peng in Wuzhen
- 2016 4th official PNIRS_{China} symposium organized by Prof Kelley in Beijing
- 2016 5th official PNIRS_{China} symposium organized by Prof Coe in Zhanjiang
- 2017 6th official PNIRS_{China} symposium organized by Prof Peng in Tianjin
- 2017 Prof. Kelley introduces PNIRS at Mind-Body symp. in Taichung, Taiwan
- 2017 Prof. Pariante introduced as incoming EIC of BBI in Nantong and Nanjing
- 2017 7th official PNIRS_{Asia-Pacific} symp. organized by Prof Kelley in Sydney

History of Development of PNIRS_{China} (cont)

- 2017 Unofficial PNIRS_{Asia-Pac} meeting organized by Prof Hutchinson Sydney
- 2017 Unofficial PNIRS_{Asia-Pac} meeting organized by Prof Sloan in Melbourne
- 2018 8th official PNIRS_{Asia-Pac} symposium organized by Kelley/Coe in Taichung
- 2018 9th official PNIRS_{Asia-Pac} symposium organized by Prof Peng Nanchang
- 2019 10th official PNIRS_{Asia-Pac} symposium by Prof Shimada/Kelley Niigata, Japan;
Published in *Clinical & Exper. Neuroimmunology*. doi: 10.1111/cen3.12558
- 2019 11th official PNIRS_{Asia-Pac} symp. Prof Spencer Queenstown, New Zealand
- 2019 12th official PNIRS_{Asia-Pac} symposium Prof. Kelley in Daegu, South Korea;
Published in BBI. doi:doi.org/10.1016/j.bbi.2020.01.022
- 2019 13th official PNIRS_{Asia-Pac} symposium organized by Prof Kelley, Taichung
- 2020 14th official PNIRS_{Asia-Pac} symposium organized by Prof Kelley, Taichung

Fig. 5. Short summary of the history of the development of PNIRS_{China} and PNIRS_{Asia-Pacific}. The first formal meeting was held in 2013 in Dalian, China and celebrated the formation of PNIRS_{China}. Since that time, six more symposia have been held on the mainland. Nine more PNIRS_{Asia-Pacific} symposia have been held in Asia-Oceania. The next one will be held in late October 2020 in Taichung, Taiwan.

Asian countries (e.g., China, Hong Kong, Macau, Japan, the Koreans), these include North (e.g., Siberia), South (e.g., India, Pakistan, Afghanistan, Bangladesh, Bhutan) and Southeast (e.g., Malaysia, Indonesia, Cambodia, Vietnam, Thailand, Singapore, Philippines, Myanmar, Laos) Asia. Oceania countries are plentiful, including Australia and its territories, New Zealand, and all the islands of Melanesia, Polynesia and Micronesia.

The idea of expanding the presence of PNIRAS_{Asia} was presented to the PNIRS Board of Directors. In 2017, they agreed to this proposal and

changed the official name of PNIRS_{China} to PNIRS_{Asia-Pacific} (Anonymous, 2017). The charge was to expand the successful activities of PNIRS_{China} to other countries in Asia-Oceania. Since then, the PNIRS_{Asia-Pacific} affiliate has sponsored nine successful symposia at meetings of scientific societies outside mainland China. These included Taiwan, Australia, Japan, South Korea and New Zealand (Fig. 5). At the end of 2019, 69 expert scientists had participated in the 13 official meetings of the PNIRS_{Asia-Pacific} affiliate. Gender of the speakers was equivalent, and all of these scholars generally paid their entire travel expenses. As a result of these meetings, the official journal of the Japanese Society for Neuroimmunology published a special issue on a PNIRS_{Asia-Pacific} symposium that was accepted for presentation at the 2019 meeting of the Japan Neuroscience Society in Niigata, Japan (Kelley and Shimada, 2020). A second publication was accepted by *Brain, Behavior, and Immunity* as a Special Issue (Kelley and Reaux-Le Goazigo, 2020). This PNIRS_{Asia-Pacific} symposium was selected for presentation at the 2019 meeting of the Federation of the Asian-Oceanian Neuroscience Societies in Daegu, South Korea. The names and photographs of these speakers, as well as a short summary of the scientific content of all these symposia, are also available online (<https://pnirs.org/pnirschina/index.cfm>).

6. Creation of PNIRS_{Asia-Pacific} Global Research Connections

Since its founding in 1993, PNIRS has focused its science on research in the USA and Western Europe. Every three years since that time, the PNIRS has held its annual meeting in Western Europe. But clearly, scientists all over the world are trying to understand interactions between the nervous and immune systems and their effects on behavior and health. Unfortunately, even now very few Western scientists spend time working in Asia, as assessed by post-doc training, collaborative studies and scientific meetings.

This issue was addressed at the 2019 meeting of the PNIRS that was held in Berlin. Members of the PNIRS_{Asia-Pacific} committee recommended that an approach be developed that would facilitate connecting psychoneuroimmunology laboratories in the Asia-Pacific rim with others throughout the world. Based on the outreach success of the PNIRS_{Asia-Pacific} in organizing symposia, an entirely new program was launched in the fall of 2019. This initiative was entitled PNIRS_{Asia-Pacific} Global Research Connections. It was implemented by creating a website

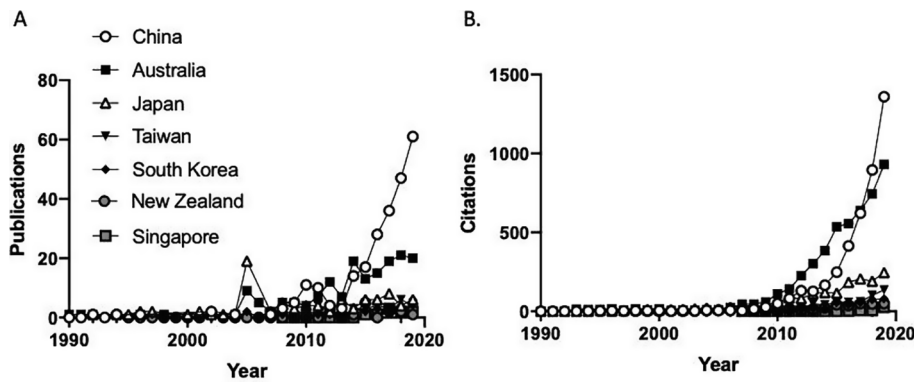


Fig. 6. A. Publication history of Asia-Pacific psychoneuroimmunology research in *Brain, Behavior, and Immunity*. The data show the number of papers published each year between the first issue that appeared in March 1987 through the end of December 2019. Results are based on the address of the corresponding author. Cumulative publications over this same time period were: China (254); Australia (172); Japan (92); Taiwan (33); South Korea (26); New Zealand (15) and Singapore (10). In addition to these data, 4 papers were published from Hong Kong and one each from Vietnam, the Philippines and Malaysia. B. Number of citations of papers published in *Brain, Behavior, and Immunity*, using the same time frame as part A.

that allows interested scientists to join this initiative by simply providing their name, country of origin, a link to their laboratory website, email address and specialty interest (<https://pnirs.ansc.illinois.edu/#>). The goal of this program is to bring together Asia-Pacific psychoneuroimmunology investigators with other laboratories around the world. It will also promote collaborations of scientists within countries in the Asia-Pacific region. As a result, biomedical scientists from both China and Australia have already traveled to other countries to conduct collaborative research.

The following sections contain four “Perspectives” from productive scientists engaged in psychoneuroimmunology research in China, Taiwan, Australia and Japan. At least one PNIRS_{Asia-Pacific} symposium has been organized in each of these countries. These “Perspectives” provide an overview regarding how psychoneuroimmunology research in East Asia has developed over the years.

7. China perspective

There have been several Chinese scientists who have been awarded Nobel Prizes in categories that include peace, literature, chemistry and physics. But it was not until 2015 that a Chinese academic was honored with the Nobel Prize in Physiology or Medicine. Professor Tu Youyou was selected for her research that ultimately culminated in a novel therapy against malaria, thereby preventing millions of deaths throughout the tropics of the world. Her interest and training in Chinese herbal medicine led to discovery of a compound extracted from a plant known as artemisinin. She found that artemisinin is an effective treatment against the protozoan *Plasmodium falciparum* that is responsible for the majority of malaria cases. Professor Youyou was also the first female Chinese Nobel Laureate.

Increased spending in medical R&D research by China has now vaulted it to the second leading country that publishes in top-ranked scientific journals and third in life sciences publications, as assessed by the Nature Index (Anonymous, 2020). This well-respected indicator summarizes institutions and countries that publish papers in 82 leading academic journals. It is noteworthy that the Chinese Academy of Sciences was the fifth most prestigious institution in the world (Anonymous, 2020). As quoted from the Nature Index, “The Chinese Academy of Sciences and Harvard University have maintained the highest positions in the Nature Index for four consecutive years, but the University of Chinese Academy of Sciences made the most impressive gains.” (Anonymous, 2019b).

When it comes to the neuroimmunology research in China, most of the credit goes to Professor Shao-Guang Fan, late Dean of the Medical School at Beijing University. Professor Fan initiated neuroimmunology research in China in the early 1980s. He organized and chaired the International Neuroimmunology Conference in 1997 and 1999, respectively, in China. Professor Fan dedicated his entire academic research career to understanding the relationships between stress and immune system. He discovered a serum factor, a protein with a large molecular weight induced by restraint stress in mice and rats, and demonstrated this serum factor suppresses lymphocyte function (Zha et al., 1992). The groundbreaking research and leadership of Professor Fan contributed greatly to the initiation and development of neuroimmunology research during the last century in China.

China has one of the world’s oldest medical systems. TCM aims to maintain harmony in the body and employs a variety of mind and body approaches. Some of these practices are exercise (Tai chi), dietary therapy (herbal medicine), acupuncture, meditation, cupping therapy, massage and gua sha (literally to “scrape sand” for skin treatment).

China

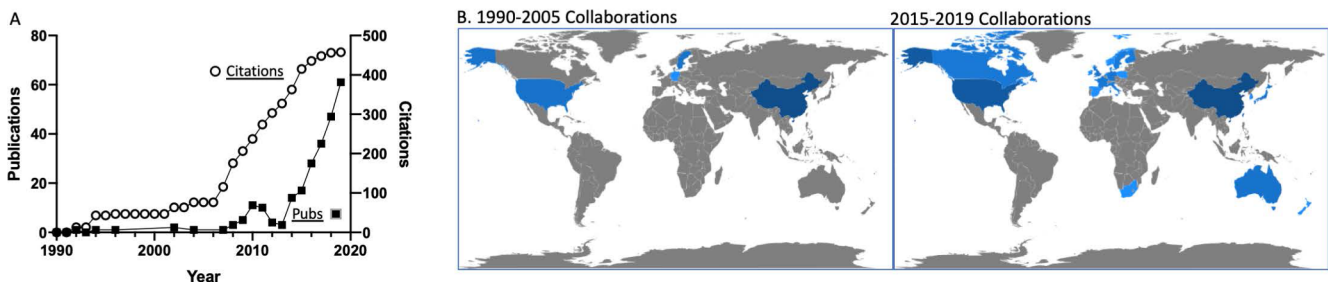


Fig. 7. A. Publication and citation history of Chinese psychoneuroimmunology research published in *Brain, Behavior, and Immunity* beginning in March 1987 through the end of 2019. Since approximately 2012, the number of publications from China has skyrocketed and citations to these articles have also steadily increased in recent years. B. The changing geographic spread of Chinese collaborations published in the journal between 1990–2005 and 2015–2019. Darker blue represents countries of highest collaborative density. Collaborations are defined as affiliations cited in the author information for each article. In the 1990–2005 period, authors from China chiefly collaborated with Chinese and, to a lesser degree, with those from the USA, Sweden and Germany. Since 2015, Chinese are collaborating globally, including with all of Europe and into Africa. Maps created from Bibliometrix version 2.3.0 in R version 3.6.0.

Although not universally accepted by many Chinese physicians, TCM is by its very nature an integrative approach to medicine that has long recognized the connections between mind and body. Yet, despite the rich history of TCM that dates back for centuries, the concept of “neuroimmunology” and “psychoneuroimmunology” has not been familiar to Chinese scientists. As such, prior to the turn of the 21 century, this research field was not very large in China. That is at least partially caused by the very same trend towards increased scientific specialization that occurred in the 20th century (Kelley, 2020). Immunologists collaborated with immunologists and neuroscientists did the same with other neuroscientists. Cross-talk and collaborative efforts between these two disciplines were not well accepted. Training graduate students and post-docs in integrative approaches to biomedical research took a back seat to formal training in specialized disciplines.

All this has changed during the first two decades of this century, during which time there has been a consistent deepening and expansion of psychoneuroimmunology research in China. Increasing evidence has established that immune disorders are involved in many nervous system diseases and that neuroregulatory abnormalities can result in immune dysfunction. Today, more and more Chinese scientists recognize the significance of neuroimmunology and psychoneuroimmunology research in human health and disease therapy and are being attracted to this research field. The establishment of PNIRS_{China} in 2013 was a hallmark development that is already rapidly promoting psychoneuroimmunology research in China. By using data from the official scientific journal of PNIRS, this fact is made clear (Fig. 7A). Prior to 2016, there were fewer than 100 papers per year submitted to *Brain, Behavior, and Immunity*. Now, research papers submitted by mainland scientists to this journal amount to nearly 400 per year. More importantly, the quality of these papers has increased substantially, as assessed by the rapid rise in scientific citations. It is also clear that during the past five years, Chinese scientists have greatly increased their collaborative research efforts with laboratories outside of the mainland, which now includes the United States, all of Europe and Australia (Fig. 7B).

During this decade, most studies on psychoneuroimmunology in China have focused on interactions between immune disorders mediated by microglia and nervous system diseases. Excessive microglial activation is involved in the pathogenesis of many mental health and central nervous system (CNS) disorders, including stress, depression, ischemic or traumatic brain injury and neurodegenerative diseases. In turn, psychological and CNS disorders often cause microglial activation. Inhibition of microglial excessive activation or promotion of microglial polarization from an M1-like towards an M2-like phenotype may help to alleviate some of these disorders. Several relevant studies from China on these topics have been published in *Brain, Behavior, and Immunity*.

1. Microglia and stress, depression and psychological disorders. Microglial activation is involved in stress-induced depressive behavior (Lian et al., 2017; Wang et al., 2018). Importantly, anti-depressive treatment can be implemented by modulation of microglial phenotypes (Zhang et al., 2017).
2. Microglia and ischemic or traumatic brain injury. Nitidine, a benzophenanthridine alkaloid, restricts reactive microgliosis and promotes CNS repair following traumatic injury (Yuan et al., 2015). Suppression of microglial activation by let-7c-5p overexpression is neuroprotective and ameliorates ischemic damage (Ni et al., 2015). Specific deletion of the protein kinase MST1 in microglia mitigates stroke-induced brain injury (Zhao et al., 2016).
3. Microglia and neurodegenerative diseases. TREM2 promotes microglial polarization from an M1-like towards an M2-like phenotype and thereby reduces neuroinflammation in Alzheimer's disease and ameliorates its development (Xu et al., 2019). Trans-cinnamaldehyde, a primary bioactive component derived from the stem bark of *Cinnamomum cassia*, suppresses neuroinflammatory responses by diminishing microglial activation and levels of pro-inflammatory mediators. This reduces memory deficits in mice with Alzheimer's

disease (Zhao et al., 2019). Gut microbial dysbiosis is involved in Parkinson's disease pathogenesis, and fecal microbiota transplantation can protect affected mice by suppressing neuroinflammation and reducing TLR4/TNF- α signaling in microglia (Sun et al., 2018). Galectin-1 reduces neurodegeneration in a Parkinson's disease model by modulating the microglial MAPK/I κ B/NF κ B axis (Li et al., 2020). It is important to note that the triptolide (T10), a Chinese herb, protects against neurotoxicity in Parkinson's disease by inhibiting microglial activation with metabotropic glutamate receptor 5 mediating its effect (Huang et al., 2018). Thus, as was highlighted by Nobel Laureate Professor Tu Youyou, exploring more Chinese herbs and their mechanisms underlying suppression of microglial activation provide an opportunity for Chinese scientists to develop novel therapeutic strategies for targeted psychological and CNS diseases.

In addition to microglial involvement in nervous system disorders, recent evidence has established that the adaptive immune system, particularly T lymphocytes, participates in the processes of neuronal injury and repair. Helper T (Th)17 cells, a subset of CD4+ T lymphocytes, have strong pro-inflammatory properties and are essential in pathogenesis of many inflammatory diseases. Regulatory T (Treg) cells, the Foxp3-expressing CD4+ CD25+ T lymphocyte population, were originally termed “suppressor cells” and are pivotal in suppressing autoimmunity and maintaining immune tolerance. Some findings from China on this important topic have also been published in *Brain, Behavior, and Immunity*.

4. T cells and neurodegenerative diseases. Th17 cells infiltrate the brain parenchyma in Parkinson's disease through a lesioned brain-blood barrier and cause neurotoxicity by both promoting glial activation and directly injuring neurons. The inflammatory cytokine interleukin (IL)-17A released from Th17 cells accelerates this neurodegeneration in models of Parkinson's disease, depending on microglial activation. Supporting this conclusion is the fact that IL-17A deficiency or anti-IL-17A-neutralizing antibody treatment alleviates microglial activation, blood-brain-barrier disruption and Parkinson's disease-like manifestations (Liu et al., 2019). On the other hand, Treg cells protect dopaminergic neurons against 1-methyl-4-phenylpyridinium (MPP) neurotoxicity by a cell-to-cell contact mechanism. TGF- β 1 secreted by Treg cells exerts an indirect protective effect by inhibiting excessive microglial activation (Liu et al., 2016).
5. T cells are involved in brain injury of cerebral ischemia and stroke. Cerebral ischemia increases the number of Treg cells in the bone marrow of mice, which contributes to stroke-induced immunosuppression (Wang et al., 2015). The FasL mutation inhibits both recruitment of peripheral inflammatory cells (neutrophils) and activation of resident glial cells (microglia and astrocytes), and drives the Th1/Th2 balance towards Th2 in the brain and peripheral blood following cerebral ischemia (Niu et al., 2012).
6. T cells also infiltrate the spinal cord with an imbalance of Th17/Treg towards Th17 during the development of bone cancer pain. In turn, this promotes microglial activation and further increases pain, while neutralizing IL-17/IL-17A in the spinal cord ameliorates bone cancer pain (Huo et al., 2019). In addition to the Th17/Treg imbalance, a Th1/Th2 imbalance also occurs in the brain and peripheral blood following cerebral ischemia (Niu et al., 2012). The anti-inflammatory cytokine IL-4 derived from Th2 cells may alleviate neuropathic pain and contribute to other neuropsychiatric disorders (Nie et al., 2018). Thus, blocking proinflammatory immune responses or applying anti-inflammatory cytokines may offer a potential and novel therapeutic strategy for some psychological and nervous system diseases.

8. Taiwan perspective

Asia and the Pacific region are home to 60% of the world's population. Unfortunately, biomedical research, particularly psychoneuroimmunology medicine, is underdeveloped in this region. This could be due to barriers of communication, differences in medical theories and diagnostic systems, lack of a common ground for clinical research design or cultural differences. Indeed, psychopathology manifestations are sensitive to cultural influences (Guinart et al, 2019). Furthermore, immunological status is arguably different regarding significant backgrounds of genomic constitution, dietary patterns and life styles. It is therefore strongly urged that more exploratory, rather than replicated, translational brain research from the East be valued and promoted. This approach is needed to turn empirical practices into precision medicine that is based on innovative and integrative science (Su, 2019).

Psychoneuroimmunology is an emerging field in neuroscience and immunology. Research on this crosstalk between East and West is now happening in Taiwan. According to data available for *Brain, Behavior, and Immunity*, there have been 33 published papers by authors from Taiwan during the past 33 years (Fig. 6). Remarkably, 13 were published in the past two years, supporting the conclusion that translational brain-immune research is rising. In 2017, Professor Keith W. Kelley from the PNIRS was invited as the plenary keynote speaker at the Mind-Body Interface (MBI) International Symposium held in Taiwan. With a mutual interest and a common and achievable goal, this led to an affiliate of PNIRS, PNIRS_{Asia-Pacific}, to propose co-organizing future MBI Symposium. The MBI and PNIRS_{Asia-Pacific} teams have been working together since then. In 2018, Professors Keith Kelley, Chris Coe and Carmine Pariante called for a dozen PNIRS scholars to propose a thematic session for the forthcoming MBI symposium. It was here that the entire organization of PNIRS and *Brain, Behavior, and Immunity* was officially introduced and promoted to scientists in Taiwan. The following year, Professor Deborah Hodgson and another 10 PNIRS scholars presented a PNIRS_{Asia-Pacific} symposium at the 2019 MBI meeting. The next MBI meeting is scheduled to be held in October 2020, and the theme is “The Mind Maze – Early Life Experiences That Shape Adult Health of Mind and Body.” With the support from President Julie Bower and the PNIRS_{Asia-Pacific} affiliate, Michael Irwin, M.D. has been chosen to be the plenary keynote speaker at this 2020 MBI Symposium. His lecture will be complimented by another formal PNIRS_{Asia-Pacific} symposium in Taiwan, which will be four consecutive years in a row.

Influential scientists gather in Taiwan every year to share cutting-edge research discoveries in translational neuroscience. Organized annually by Taiwanese Society for Nutritional Psychiatry Research (TSNPR), the MBI International Symposium has been held annually since 2010. This society vigorously promotes a global agenda of translational medicine by encouraging interdisciplinary research and integrating biomedical discoveries focused on patients. The meeting features a broad range of topics, including immunology, metabolic processes and molecular science, psychopharmacology, psychology and biological processes that underlie links between diet, nutrition and mental health. Furthermore, there is a strong focus on the use of novel technology, artificial intelligence, big data, neuroimaging, personalized medicine, lifestyle intervention and population studies in brain disorders.

Due to the heterogeneity of clinical manifestations and etiological complexity of mental disorders, as well as a paucity of brain research with East Asian subjects, translational approaches bridging bench and bedside are gaining substantial interest. However, the current psychiatric classification system, DSM-V, is not sufficient for clinical studies on mental disorders despite its feasibility for health care practitioners (Chang et al., 2014). Furthermore, there is a fundamental difference in theory between Western and Eastern medicine. Eastern medicine views mind-and-body as inseparable as a meridian system rather than an anatomical structure. Practices include dietary intervention, herbal medicine, acupuncture, massage, meditation or Tai chi.

These treatments aim to bring harmony and alignment back to the mind-and-body as a whole. The benefits of this holistic approach is gaining attention nowadays with robust findings from biomedical research. However, the therapeutic effect of one single life-style intervention is expected to be much smaller and difficult to detect than that with an expensive randomized controlled trial. This is the gold standard for examining the effects of treatments such as anti-depressants on subjects with confirmed diagnoses like major depressive disorders (Su, 2019). It is therefore crucial to advocate for translational brain research in the East with good practices in clinical trials using advanced science. As but one example, new technologies of wearable devices for continuous data collection of brain activities can now be used and summarized with algorithms for these types of big data.

There is no doubt that the MBI Symposium and PNIRS_{Asia-Pacific} affiliate have now provided a platform for scientists in this region to network with one another, to be inspired and to establish research and teaching collaborations. Each year, meeting registrants exceed 150 people from countries worldwide, including Australia, Canada, China, Estonia, France, Germany, Hong Kong, Italy, India, Japan, Macau, Netherlands, South Korea, Russia, United Kingdom, United States and Taiwan. Friendship and partnerships between international societies that share common goals are built to promote good science side by side.

9. Australia perspective

Australia has had a strong niche role in psychoneuroimmunology research from the beginning of the field. The very first edition of *Brain, Behavior, and Immunity*, published in 1987 carried an article by Professor Kusnecov and colleagues, which has since been cited 64 times. In this work, the authors revealed a role for β -endorphin in enhancing lymphocyte reactivity to concanavalin A (Kusnecov et al, 1987). At that time, publications in the journal were dominated by laboratories from the United States (5 articles of the 10 in the first issue). Since then, psychoneuroimmunology research in Australia has gone from strength to strength (Fig. 8A), with a particular boost in 2017 when the PNIRS_{China} initiative was broadened to encompass the rest of Asia and the Pacific. Australians now have the 6th most submissions to *Brain, Behavior, and Immunity* annually, after the United States, China, Brazil, Germany and the United Kingdom (data for 2017 courtesy of Elsevier). These publications are at least as high quality and impactful as those from other countries. The most recent data published in Nature Index noted that between 2017 and 2018, contributions of Australian scientists to the highest quality journals in the life sciences increased by 8.2% (Anonymous, 2020). Australia now contributes approximately the fourth most published articles in *Brain, Behavior, and Immunity* (after the United States, China, United Kingdom and equal to Canada). In 2019, 16 papers were published in *Brain, Behavior, and Immunity* with Australian first or senior authors. An additional four had Australian collaborators and at least ten employed diverse internationally collaborative research teams. Importantly, many of those articles are examples of the truly global nature of current psychoneuroimmunology research. Several featured upwards of five nations in the author list, integrating technologies, ideas, personnel and student experiences towards research outcomes that could not be achieved by one group alone (Fig. 8B). These papers covered such diverse research topics as chlamydia and Alzheimer's disease (Woods et al, 2020) to microglial morphology in post-traumatic stress disorder (Smith et al., 2019) to aging and traumatic brain injury (Sun et al, 2019).

In addition to publication outputs, Australians are now an embedded part of the global psychoneuroimmunology community. As of 2019, there are two Australian Associate Editors at *Brain, Behavior, and Immunity* (as well as one from Taiwan). In 2019, PNIRS elected its first Australian president, Professor Deborah Hodgson. Around 10% of the PNIRS membership is Australian. The few years since the 2017 incorporation of Australia along with the rest of Asia and the Pacific region into the PNIRS_{Asia-Pacific} affiliation have also witnessed an

Australia

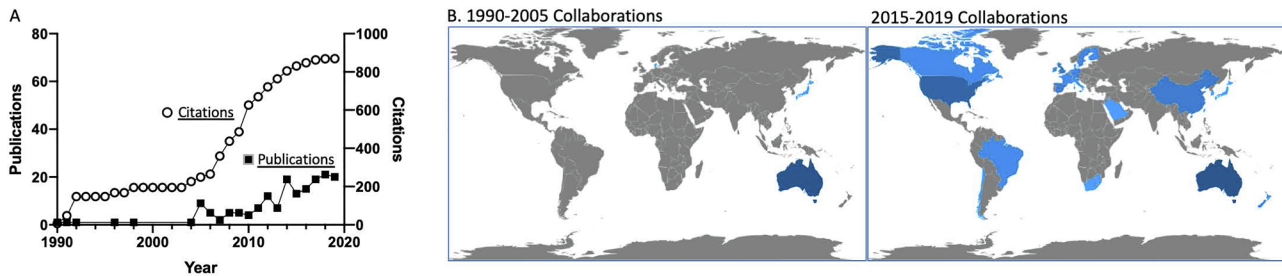


Fig. 8. A. Publication and citation history of Australian psychoneuroimmunology research published in *Brain, Behavior, and Immunity* from the first issue that was published in March 1987 through December 31, 2019. The Australian contribution has been growing across the past 10 years, with these papers showing increasingly high mean citation rates. B. The changing geographic spread of Australian collaborations published in the journal between 1990–2005 and 2015–2019. Darker blue represents countries of highest collaborative density. Collaborations are defined as affiliations cited in the author information for each article. In the 1990–2005, Australians chiefly collaborated with other Australians and, to a lesser extent, with Japan and Denmark. Since 2015 Australians are collaborating globally, across six continents. Maps created from Bibliometrix version 2.3.0 in R version 3.6.0.

explosion of internationally collaborative meetings and symposia showcasing Australian psychoneuroimmunology research. Professor Mark Hutchinson organized a symposium in Sydney in 2014. Three years later, Professor Hutchinson teamed with Dr. Luba Sominsky to organize a psychoneuroimmunology satellite workshop to Australia's premiere neuroscience meeting, the Australasian Neuroscience Conference. The 2019 International Brain Research Organization showcased key Australian elements of the PNIRSA_{Asia-Pacific} initiative, along with Professor Suzi Hong from the Pacific side of the United States at their meeting in Daegu, South Korea. In 2019, there was also a PNIRSA_{Asia-Pacific} symposium integrated into the Queenstown Winter Conference on Brain Research week in Queenstown, New Zealand. This symposium highlighted research from investigators with experience from Australia, Canada, Japan, New Zealand, South Korea and the United States and amply illustrates how far the PNIRS has now come as a global scientific community.

Going forward into 2020 and beyond, we expect to witness even more globalization, integration and transdisciplinary psychoneuroimmunology research incorporating Australia and the rest of the Asia-Pacific region. However, we also expect to see psychoneuroimmunology research becoming more specialized to embrace the specific psychoneuroimmunology needs of different international communities. For instance, the psychoneuroimmunology consequences of endemic diseases like malaria or dengue might be of key relevance for South-East Asia. China may benefit from an individualized response to novel coronaviruses. Australia and the United States are now investing heavily in space exploration, making psychoneuroimmunology research important in this context for these countries. Air pollution may have important psychoneuroimmunology implications all over the world, but the types of pollution may differ. On the other hand, historically different approaches to our understanding of psychoneuroimmunology among different communities worldwide may bring important advances to all of us. The holistic integration of body and mind that is the cornerstone of traditional medicine in China is revolutionizing Western medicine and popular approaches. Likewise, the strong social support networks of indigenous communities have key implications for stress and mental health management for everyone. Thus, globalizing psychoneuroimmunology research does not just mean more of the same in new countries, but a true advance in our approach to understanding how the world we live in affects our brains and bodies.

10. Japan perspective

For the period between 1987 and the end of 2019, there were 92 papers published in *Brain, Behavior, and Immunity* with a primary

corresponding author from Japan (Fig. 6). This placed Japan as the 13th country in the world with the highest number of publications in the journal. In addition, there were 231 Japanese authors that contributed to papers. The number of Japanese members in PNIRS is only four at the present time. Although these data might make it appear as though Japanese investigators do not have a strong interest in psychoneuroimmunology, a growing number of Japanese scientists are performing research related to this field. The Japanese Society for Neuroimmunology was established in 1988 by physicians who specialize in intractable neurological diseases, such as multiple sclerosis, Guillain-Barré syndrome and the paraneoplastic syndrome. These physicians are interested not only in clinical treatments, but also in the basic mechanisms underlying the interactions between the nervous and immune systems. When PNIRSA_{Asia-Pacific} organized a symposium for the first time in Japan at the 2019 annual meeting of the Japan Neuroscience Society, the Japanese Society for Neuroimmunology published a record of this symposium in its official journal (Shimada, 2020; Pal et al., 2020; Kelley and Shimada, 2020). Collaborations between the executive board members of the society and PNIRSA_{Asia-Pacific} are currently in the works, and the Japanese Society for Neuroimmunology and PNIRSA_{Asia-Pacific} hope to hold joint symposia in the near future. In addition, the National Institute of Neuroscience at the National Center of Neurology and Psychiatry has one of the most active laboratories that perform research related to neuroimmunology and neuroinflammation (Yamamura et al., 2019).

A group of Japanese psychologists was inspired by the groundbreaking book “Psychoneuroimmunology” (Ader, 1981), and in 2004, they launched the Psychoneuroendocrinology (PNEI) Research Group, which was sponsored by the Japanese Psychological Association. These psychologists are interested in the interrelationships among stress, changes in the autonomic nervous system and endocrine system, and alterations in immune responses. They have been holding meetings once or twice every year since 2004.

In the history of modern immunology, Japanese immunologists have made outstanding achievements using molecular biological techniques to elucidate the fundamental principles of immunology. The most recent example is from the famous laboratory of Tadimitsu Kishimoto, M.D., from Osaka University. His life work led to development of a humanized monoclonal antibody against the interleukin-6 receptor (Kishimoto, 2005). This antibody, known as tocilizumab, is used for treatment of rheumatoid arthritis. Because of its immunosuppressive properties that inhibit the cytokine storm, it has recently been approved for late stage clinical trials in both China and the USA as treatment for SARS-CoV-2. Professor Susumu Tonegawa was awarded the Nobel Prize in 1987 for his work showing that genetic material rearranges itself to form millions of different antibodies

(Tonegawa, 1983). His discovery revealed the mechanism of the adaptive immune system, which had been the central question of immunology for over 100 years. Professor Tasuku Honjo established the basic conceptual framework of class switch recombination through his discovery of DNA deletion (Honjo and Kataoka, 1978) and activation-induced cytidine deaminase (AID) (Muramatsu et al, 2000). Other leading Japanese immunologists have also contributed to the identification of cytokines, their receptors and signaling pathways, including interferon α , interferon β , interleukin (IL)-4, IL-5, IL-6, IL-18, IL-8/CXCL8, CXCL12, CXCR4, Fas receptor and Fas ligand (Kumanogoh and Ogata, 2000 for a review). The contributions of Japanese research to the field of innate immunity include identification of ligands for most of the Toll-like receptors (Akira and Takeda, 2004). Professor Honjo was awarded the Nobel Prize in 2018 for his discovery of program cell death 1 (PD-1), a negative co-receptor of the effector phase of the immune response. Anti-PD-1 immunotherapy is now approved in the United States, European Union and Japan, and it has revolutionized the treatments for cancer (Chowdhury et al, 2018). PD-1 could also be a novel key molecule in psychoneuroimmunology. Augmented T cell responses in *Pdcd1* $-/-$ mice, which lack the inhibitory receptor PD-1, induce a systemic decrease in tryptophan and tyrosine levels. This leads to a substantial deficiency in brain serotonin and dopamine, resulting in anxiety-like behavior and exacerbated fear responses (Miyajima et al, 2017).

The contributions of Japanese biochemists in uncovering the molecular mechanisms of inflammation can be illustrated by the purification of cyclooxygenase (Miyamoto et al, 1976), the key enzyme in the biosynthesis of prostanooids, and by the cloning of the receptors for platelet-activating factor (Honda et al, 1991), leukotriene B₄ (Yokomizo et al, 1997) and thromboxane A₂ (Hirata et al, 1991), among others. At the forefront of early molecular neuroscience, Japanese biochemists determined the protein-coding sequence of the adrenocorticotrophic hormone (ACTH) precursor gene (Nakanishi et al, 1980). Researchers from the same group cloned the primary structures of different families of receptors and channels, including nicotinic and muscarinic acetylcholine receptors, sodium and calcium channels (Hayaishi, 1992) and N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors (Masu et al, 1991; Moriyoshi et al, 1991).

Achievements from Japanese laboratories of experimental pathology include the discovery of regulatory T cells (Treg cells) as a homeostatic regulator of immune responses (Sakaguchi et al, 2008] as well as development of senescence-accelerated mouse (SAM) strains as a model for aging research (Takeda, 1999). The SAMP10 mouse strain exhibits microglial dystrophy from a young age and lacks the ability to construct a neuroprotective cytokine-mediated glia-neuronal network. This causes the mice to be vulnerable to age-related cognitive impairments (Hasegawa-Ishii et al, 2011). Japanese pathologists also invented a novel bone marrow transplantation method called intra-bone marrow-bone marrow transplantation (IBM-BMT) (Kushida et al, 2001), which led to the determination of the intracranial histological architecture supporting brain-immune cell-cell interactions (Hasegawa-Ishii et al, 2013).

In addition to those mentioned above, there are many other well-trained biomedical scientists and top laboratories in Japan that pioneered research in molecular immunology, neurobiology and pathology. A growing number of scientists, especially those of the younger generation, have become interested in psychoneuroimmunology, and they have started numerous collaborative studies (Furuyashiki et al, 2019). It is therefore an opportune time for the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan to launch a new grant program starting in fiscal year 2020 under the name of “Grant-in-Aid for Transformative Research Areas.” This new grant program aims to promote the creation of novel research areas by young investigators through co-creative and interdisciplinary efforts between researchers in diverse fields that will lead to radical transformation and changes in the existing framework of academic disciplines. Through these efforts, Japanese

scientists of new generations will make significant contributions to the emerging field of psychoneuroimmunology.

11. Coda

PNIRS_{Asia-Pacific} answers the important and pressing call of increasing diversity in science (Leibenluft, 2020). By all accounts, in less than 10 years, this PNIRS affiliate has been very successful in bridging the gap between Eastern and Western scientists interested in psychoneuroimmunology research. This advance is evidenced by the rapid growth in both the number and citations to high-quality manuscripts published in *Brain, Behavior, and Immunity* by countries throughout the Asia-Pacific region. Beginning in 2019, the PNIRS_{Asia-Pacific} committee furthered global collaboration in this field with the creation of a program that promotes scientific exchanges of faculty, post-docs and graduate students between laboratories in the East and West: PNIRS_{Asia-Pacific} Global Research Connections. Biomedical research today is a global enterprise that is becoming more and more integrative in nature. Age-old practices from the East, including meditation/mindfulness, exercise and dietary interventions, are now becoming accepted in the West. It is the continuing goal of the PNIRS_{Asia-Pacific} affiliate to promote crosstalk between biomedical scientists in the East and West.

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