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Meeting Report:

Japan – Singapore International Skin Conference, Singapore April 10-12, 2019

The Japan – Singapore International Skin Conference took place from April 10-12th 2019 at the Clinical Sciences Building in Novena, Singapore. The conference was jointly organized by the Skin Research Society (Singapore), the Japan Skin Research Club, the Japanese Society for Investigative Dermatology (JSID), and supported by the Skin Research Institute of Singapore (SRIS). The organization of this cross-border meeting was led by Oliver Dreesen (Chair, Singapore), Daisuke Nanba (Co-Chair, Tokyo, Japan), Birgit Lane (Singapore), Hironobu Fujiwara (Kobe, Japan), Paola Florez de Sessions (Singapore) and Kenji Kabashima (Kyoto, Japan) (Figure 1).

Figure 1: The scientific organizing committee consisted of (from left to right): Hironobu Fujiwara, Birgit Lane, Oliver Dreesen (Chair), Daisuke Nanba (Co-chair) and Kenji Kabashima.

Skin research in Singapore is flourishing and the South-East Asian city state is rapidly gaining recognition as a hub for great academic, clinical and industry-focused research. In contrast, Japan has a longstanding tradition of conducting excellent academic and clinical research and is a leader in skin and hair research, stem cells and regenerative medicine. Furthermore, Japan is home to a large community of outstanding academic scientists, clinicians and many skin care companies.

Our goal was to bring researchers and clinicians from different research institutes and universities across Singapore and Japan together and create a platform for them to discuss science, enjoy good food and embark on new cross-country collaborations. We hope that we accomplished this mission. The 3-day meeting saw 375 registered participants from Japan, Singapore, Korea, Malaysia, Thailand, Myanmar, Australia, New Zealand, United Kingdom, Germany, Israel, France and USA. In addition, the excitement for this conference was reflected in the generous support that we received from numerous companies, academic institutions and societies based in Singapore, Japan and around the world.

We also had a lot of fun organizing this conference. We first started advertising the conference in late summer 2018 with a flyer that combined Japan's Mount Fuji with the iconic Marina Bay Sands building of Singapore (Figure 2). In December, we came up with the idea to send out a Happy Holiday-style Christmas flyer. We enjoyed this so much that we followed up with Chinese New Year and Valentine's Day flyers in February, and a special Sakura flyer (not shown) to celebrate the seasonal cherry blossoms in March and April (Figure 2).

Figure 2: Advertisement flyers for the Japan – Singapore Skin Conference: Upper panel: Original Flyer combining Mount Fuji with the iconic Marina Bay Sands building in Singapore. Bottom left: Happy Holiday Season Flyer (December 2018), Bottom right: Lunar New Year advertisement (February 2019). The flyer design was created by Sebastien Teissier.

The meeting finally started on Wednesday April 10th with a rather informal opening speech by Oliver Dreesen and Daisuke Nanba. Dreesen spoke about the culinary and cultural benefits of attending

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the JSID annual meeting, while Nanba tried to drum up support for an "alternative" meeting program that featured swimming, casino visits, recreational excursions, shopping and lavish dinners.

The scientific program was kicked off with the *Skin Ageing & Homeostasis session* and a talk by **Emi Nishimura** (Tokyo Medical and Dental University, Japan). Nishimura presented brand new data (published one week earlier in Nature) on how stem cell competition within the basal layer orchestrates skin homeostasis and ageing. Her results demonstrate that COL17A1 is not only an excellent marker to identify epidermal stem cells, but its levels also predict the regenerative capacity of these cells. Similar to her previously published results, stabilizing COL17A1, either by ectopic expression or by small molecules, promotes tissue integrity and regeneration. **Pritinder Kaur** (Curtin University, Australia) presented data on how pericytes modulate the extracellular matrix to promote human skin regeneration. **Oliver Dreesen's** (Skin Research Institute of Singapore) presentation dissected the molecular mechanism how a mutant form of the lamin A protein, responsible for causing the accelerated ageing syndrome Hutchinson-Gilford Progeria, triggers heterochromatin loss, DNA damage and premature cellular senescence. He also discussed how these results may be relevant to normal chronological human ageing. His talk was followed by a presentation by **Kentaro Kajiya** (Shiseido Global Innovation Center, Yokohama, Japan) who introduced novel techniques to visualize blood vessels during ageing and in age-related skin pathologies, such as solar lentigo.

The Stem Cell and Regeneration session started with **Sophie Bellanger** (Skin Research Institute of Singapore) who showed recently published data on how nicotinamide metabolism modulates the delicate balance between keratinocytes differentiation and proliferation. **Hirotaka Takeuchi** (POLA Chemical Industries, Yokohama, Japan) presented interesting data on how neutrophils accumulate at wrinkles and secrete neutrophil elastase, a serine protease that degrades collagen and elastin. In addition, he showed how retinacula cutis, fibular components in the hypodermis, contribute to skin sagging. **Ken Natsuga's** (Hokkaido University, Japan) talk focused on subepidermal blistering diseases such as epidermolysis bullosa and pemphigoid. To model and study the healing process, he developed a suction blistering technique to generate subepidermal blisters on mouse skin, and investigated how the progeny of upper hair follicle stem cells contribute to the epidermal healing process. **Toru Hiratsuka** (King's College, London, UK) presented *in vitro* and *in vivo* imaging data on extracellular-regulated kinase (ERK) pulse kinetics during mouse epidermal stem cell proliferation and differentiation. He observed that cells with pulsing ERK signaling have an advantage in cell proliferation whereas ERK pulse downregulation correlated with stem cell differentiation.

The next two presenters study stem cells in the hematopoietic system and intestine / stomach, respectively. Both were invited with the aim to expose our more skin-centric audience to inspiring results from other organ systems. First, **Toshio Suda** (Cancer Science Institute, Singapore) presented exciting results on how hematopoietic stem cells (HSC) regulate their metabolism during proliferation and quiescence. Maintaining HSC quiescence is essential to prevent excessive proliferation that would ultimately result in stem cell exhaustion or ageing. The Suda lab found that this important decision is regulated by intracellular Ca^{2+} levels: Upon stress, an influx of mitochondrial Ca^{2+} results in mitochondrial activation and cell division; a process that can be prevented by Nifedipine, a drug that selectively blocks Ca^{2+} channels. In 2007, **Nick Barker** (Institute of Medical Biology, Singapore and Kanazawa University, Japan) originally described Lgr5 as a marker for stem cells in the colon and small intestine. He has now extended this work to identify cycling stem cells in the pyloric stomach, hair follicles, ovary and embryonic kidney. In a series of elegant experiments (ablating Lgr5 and lineage tracing), he demonstrated that Lgr5+ cells are essential in maintaining homeostasis in all these different epithelia. Furthermore, by studying the transcriptome of Lgr5+ cells, he identified novel gastric stem cell markers that can be used to either selectively isolate these cells for regenerative purposes, or to selectively target them during gastric cancer initiation or progression. In line with the "stem cell" theme of this session, **Ryuichiro Kurata** (Mandom Corporation and Osaka University, Japan) introduced novel markers to identify and isolate human sweat gland stem cells. These cells exhibited the ability to differentiate into sweat gland luminal cells and formed the exocrine gland-like hollow structures. Further experiments will investigate the functionality of these cells.

A major challenge in the field of skin regeneration is the non-invasive identification of stem cells that exhibit extensive proliferative capacity. Towards this goal, **Daisuke Nanba** (Tokyo Medical and Dental University, Japan) developed an automated cell tracking system by using deep learning, and proved that cell motility is correlated with proliferative capacity in human keratinocytes. **Jun-ichi Sakabe** (Institute of Medical Biology, Singapore) discussed the similarities between human epidermis and human thymic epithelial cells, using clonal analysis, live cell imaging and single cell genetics. **Aiko Sada** (University of Tsukuba, Japan) previously reported that the interfollicular epidermis contains two distinct stem cell populations. In her presentation, she further characterized these populations and found that Fibulin-7 is expressed preferentially in fast-dividing stem cells and involved in controlling their proliferation rate and stem cell potential. Sada suggested that Fibulin-7 may accomplish this by its interaction with growth factors, glycans and basement membrane components.

The first conference day ended with the viewing of 51 posters over wine and cheese – and the invited speakers took a bus to the National Gallery where they enjoyed local Peranakan cuisine at the Violet Oon Restaurant.

The scientific program of the second day commenced with a *Skin Cancer* session and a beautiful presentation by **Sir David Lane** (p53 laboratory, A*STAR, Singapore), the co-discoverer of the p53 protein. By using RNAscope, he demonstrated that p53 transcription is elevated in proliferating and stem cell compartments, whilst protein expression levels remain low (due to rapid turn over). Mutations in p53 are frequently associated with higher levels of p53 expression, a finding that has been recapitulated in UV-induced skin cancer models. Lane's lecture highlighted the importance of various p53 mutations in skin cancer and discussed the possibility of turning off p53 expression as a novel approach to treat skin cancers.

Senescent, irreversibly growth-arrested cells accumulate in aged tissues and in pre-neoplastic lesions. However, markers that unambiguously detect senescent cells are rare. **Audrey Wang** (Skin Research Institute of Singapore) presented compelling evidence that lamin B1 and HMGB1 loss serve as novel markers to detect and quantify senescent cells during chronological skin ageing, as well as during accelerated skin ageing due to exposure to environmental conditions, such as UV irradiation. To identify the origin of skin metastatic cancers which primary site remains unclear, **Daisuke Utsumi** (Graduate School of Medicine, University of the Ryukyus, Japan) and colleagues developed a bioinformatics algorithm through machine learning, based on RNA sequencing data of the tumor. The mutation profile of the secondary tumor (KRAS, STK11 and KEAP1) provided information that the primary tumor is a lung adenocarcinoma. This approach may provide clinicians with new possibilities to predict the site of primary tumors. **Kiarash Khosrotehrani** (University of Queensland, Diamantina Institute, Australia) used single cell RNA sequencing to identify

endothelial progenitors among the heterogeneous endothelial cell populations. He then elucidated the molecular pathways that enable these cells to either generate myofibroblasts or to form the endothelium. These findings have important implications for the treatment of pathological conditions, such as wound healing, fibrosis and cancer vascularization.

Before heading for coffee and tea, we decided to spontaneously pose for a conference group picture with thumbs up for skin research! (Figure 3).

Figure 3: Group picture of happy Japan – Singapore Skin Conference participants.

The session on *Skin Diseases* started with a lecture by **Birgit Lane** (Skin Research Institute of Singapore). Mutations in keratins result in a number of rare genetic skin fragility disorders, including epidermolysis bullosa simplex (EBS). In severe cases of EBS, mutated keratins tend to form aggregates. Lane showed that keratins have an extremely high number of phosphorylation sites, some of which appear to be critical for filament assembly dynamics and cell division. The theme of EB continued with the next presentation by **Osamu Ansai** (Niigata University, Japan). Ansai found that mitochondria connect to keratin 14 fibers via a protein called Mfn2. In EB mutations, mitochondria cluster in keratin aggregates similar to what Birgit Lane mentioned in her talk. Moreover, mitochondria movement was severely impaired in cells with keratin mutations, suggesting a potential role of mitochondrial movement and function in EB. **Hideyuki Ujiie** (Hokkaido University, Japan) provided insight into the mechanism of autoantibody production in the autoimmune blistering disease bullous pemphigoid (BP). BP is caused by autoantibodies against COL17 and BP230. However, the trigger of these autoantibodies remains unclear. Ujiie reported that dysfunctional regulatory T cells (Tregs), as well as follicular helper T cells are involved in inducing autoantibodies against COL17 and BP230 in mouse and human. He speculated that Tregs dysfunction may trigger the production of autoantibodies against COL17 and BP230 and subsequent epitope spreading may finally lead to BP. **Riichiro Abe** (Niigata University, Japan) presented the mechanism of keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Abe's results suggest that the interaction of annexin A1 and formyl peptide receptor 1 induces necroptosis, a programmed form of necrosis, in keratinocytes during adverse drug reaction. **Maurice van Steensel** (Skin Research Institute of Singapore) provided the audience with a crash course in "Singlish" (Singapore-style English) and made the case for Zebrafish as a useful model system to study human genetic skin disorders.

Masayuki Amagai (Keio University, Japan) was the first speaker of the *Skin Immunology Session 1*. He described the development of a dual fluorescent protein reporter mouse (pH sensitive and pH insensitive fluorescent markers) to visualize the pH within the epidermis in normal mouse skin as well as inflamed skin. The goal is to understand how changes in the structure and pH of the stratum corneum may favor homing of certain microbes, and lead to changes in the microbiome and skin disease. **Satoshi Nakamizo** (Skin Research Institute of Singapore) presented mechanistic insights on how a western diet results in increased susceptibility to inflammatory skin diseases. **Sayuri Yamazaki** (Nagoya City University, Japan) demonstrated that ultraviolet B-induced Treg cell expansion is mediated by a specialized subset of dendritic cells in the skin, which are not Langerhans cells. By using a Staphylococcus aureus-induced chronic skin inflammation model, **Chisa Nakashima** (Kyoto University, Japan) provided evidence that both basophils and peripheral nerves are involved in the exacerbation of atopic dermatitis. **Niranjan Nagarajan** (Genome Institute of Singapore) analyzed the skin microbiome of patients with atopic dermatitis and identified microbial signatures that correlated with clinical conditions.

The second day concluded with a keynote lecture to celebrate the outstanding achievements of a Japanese woman in science. Our speaker, **Yoshiko Takahashi** (Kyoto University, Japan) was introduced by Sir David Lane, who also generously supported this l ecture. Takahashi described her scientific journey from being the only female graduate student in her department at Kyoto University, to her postdoctoral training in the laboratory of the developmental biologist Nicole Le Douarin in Nogent-sur-Marne near Paris, who is a pioneer in the research of the neural crest, stints in laboratories in the USA and then her return to Japan. Skin melanocytes, the peripheral nervous system and craniofacial bones are all derived from the neural crest. To study the fundamental question how skin melanocytes transfer pigment to neighboring keratinocytes, Takahashi combined developmental biology tricks with live cell imaging: melanocytes are notoriously difficult to transduce – to circumvent this problem, she introduced a membrane-bound GFP into neural crest cells and then derived GFP-tagged melanocytes from these. This allowed her to visualize how melanosome-containing membrane vesicles bud off from melanocytes (in a RhoA-dependent manner) and are taken up by keratinocytes. Lastly, she shared inspiring personal insights on what it takes to succeed in science: Originality, Creativity, Curiosity and Passion. She also encouraged young scientists to challenge unexplored fields, to share the excitement for scientific research, and to develop their ability to convince others that their work is interesting. Her advice certainly applies to both women and men in science! To commemorate the occasion, Yoshiko Takahashi was presented with a glass crystal displaying the conference logo.

Day 3 started with the *Skin Immunology Session 2* and a presentation by **Kenji Kabashima** (Kyoto University, Japan). Kabashima used multiphoton imaging in conjunction with transgenic reporter mice and fluorescent dyes to visualize both skin structures and various components of the immune system. This allowed him to visualize how the immune system responds to external stimuli and how this process is impaired in diseased skin. Lastly, he shared his passion for ultra-trail running and admitted that such excessive exertion may actually be rather harmful for the body. This claim was backed up by exciting new data from his marathon mouse model. **James Wells** (University of Queensland, Australia) purified bona fide $CD^{4+}CD^{8+}$ T cells using a novel isolation and enrichment strategy, and demonstrated that these cells remain detectable for 3 months after injection and suppress skin CD^{8+} T cells in 2 different mouse models. **Mika Takaichi** (Osaka City University, Japan) shared fascinating results on the mechanism how psychological stress can exacerbate

skin inflammatory diseases such as atopic dermatitis. **Baptiste Janela** (Singapore Immunology Network, Singapore) focused on skin bacterial infections that can cause acne or trigger autoimmune-diseases such as psoriasis or atopic dermatitis. Janela found that upon exposure to Propionibacterium acnes, a subtype of conventional dendritic cells (cDC), named cDC1, control the recruitment and activation of neutrophils via the VEGFa/VEGFR1 pathway. Thus, cDC1 can control the intensity of the ensuing immune response and represent a new cellular target to modulate skin immunity.

The first speaker of our *Technologies to Study Skin Health* session was **Takehiko Yokomizo** (Juntendo University, Japan) who discussed how dysregulated fatty acids metabolism impairs skin barrier function and can result in skin diseases such as psoriasis and ichthyosis. In addition, treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin impairs wound healing and skin barrier function. However, the precise mechanism remains elusive. Yokomizo provided evidence that this effect is caused by inhibiting the biosynthesis of 12-HHT (hydroxyheptadeca-trienoic acid), a fatty acid ligand for BLT2, a G-protein coupled receptor that he originally discovered. BLT2 knockout mice exhibit impaired skin barrier function with antigen invasion, trans-epidermal water loss and delayed wound healing, without affecting inflammation. These results suggest that the adverse effects of NSAIDs could be counteracted by altering BLT2 signalling. **Sierin Lim** (Nanyang Technological University, Singapore) described self-assembling protein cages that can be used as potential carriers to deliver pharmaceutical or cosmetic ingredients into the skin. **Yingrou Tan** (Singapore Immunology Network and National Skin Centre, Singapore) used whole mount immunostaining, optical clearing and three-dimensional volumetric imaging to visualize and quantify intra-epidermal nerve fibers in atopic dermatitis and psoriasis lesions. This provides a platform to systematically analyze nerve density and structure in various different skin conditions. This session concluded with a talk by **Markus Wenk** (National University of Singapore) who described methodologies developed by the Singapore Lipodomics Incubator (SLING) to study the lipid composition in various tissues including skin and hair.

The meeting concluded with two sessions that focused on hair biology. **Colin Jahoda** (Durham University, UK) provided the audience with a comprehensive overview of the hair biology field. He started his talk by describing his groundbreaking hair follicle transplantation experiments from 1999. The ability of dermal papilla (DP) cells to generate a full hair led researchers onto a quest to grow and expand these cells *in vitro*. However, no one has been able to culture these cells and retain their hair-inductive capacity. Jahoda described how the transition to *in vitro* culture rapidly affects transcriptional and epigenetic regulation in these cells, ultimately resulting in loss of their hair-induction capacity. **Mikiro Takaishi** (Kochi University, Japan) characterized the functions of *Ahed*, which codes for an uncharacterized nuclear protein. By knocking down Ahed in mouse skin, he demonstrated that Ahed plays a key role in epidermal development and homeostasis. **Nikolaos Pantelireis** (Imperial College, London, UK and Skin Research Institute of Singapore) combined RNA sequencing and ATAC sequencing to evaluate epigenetic changes that underlie gene expression in an *in vitro* model of hair follicle induction. His work has led to the identification of several transcription factors which he plans to interrogate in order to understand how changes in cell type and cell culture conditions affect dermal cells' ability to induce hair follicle morphogenesis. **Chin Yan Lim** (Skin Research Institute of Singapore) reported on epigenetic changes that occur in epidermal cells during embryonic development. **Joy Ng** (Skin Research Institute of Singapore) presented some interesting findings on using a novel genetic tool to target the DP. Ng found a consistent co-localization between the Leptin Receptor (LepR) and DP cells throughout hair follicle morphogenesis and the hair cycle. In addition, she used LepR-Cre to ablate Sox2 in the DP and observed a phenotypic switch in coat colour that correlated with a temporal upregulation of agouti and downregulation of MC1R gene transcripts.

The second *Hair Biology* session started with a presentation by **Mayumi Ito** (New York University, USA). Mammalian wounds heal by fibrotic repair without hair follicle regeneration. Ito's goal was to determine whether scarred tissue could be modulated towards healing and hair follicle regeneration. Her results demonstrate that activation of Sonic hedgehog signalling induces DP and hair follicle neogenesis after wounding, thus providing new insight into the mechanisms of scarring and regeneration in mammalian skin. **Etienne Wang** (Columbia University, USA and National Skin Center, Singapore) demonstrated that Oncostatin M, secreted from a distinct subset of dermal macrophages, maintains hair follicle stem cell quiescence via JAK-STAT5 signalling. **Kenneth Lay** (The Rockefeller University, USA and Institute of Medical Biology, Singapore) discussed how hair follicle stem cells are able to deviate from their normal task of regenerating tissues and respond to insults in their niche by orchestrating a communication relay with immune cells. When cell-cell junctions are perturbed in the hair follicle bulge, bacteria infiltrate the hair follicles. Yet, regardless of the presence of bacteria, stem cells respond to the disrupted cellular junctions in their niche, upregulate a repertoire of immune response genes and become capable of recruiting dendritic cells and regulatory T cells to the bulge. In turn, these immune cells induce stem cells to proliferate. Lay then showed that instead of migrating out of the bulge to make new hair, the proliferating stem cells and their progeny remain within the bulge to amplify the immune response and patch the breached epithelial barrier. The last speaker of this conference, **Hironobu Fujiwara** (RIKEN Center for Biosystems Dynamics Research, Japan) investigated the developmental origin and induction processes of hair follicle stem cells using a combination of single-cell resolution 3-dimensional live cell imaging and single-cell transcriptomics. Live cell imaging of hair follicle development in cultured vibrissae explants identified the origin and lineage of hair follicle epidermal cells. Subsequent transcriptome analysis revealed their unique transcriptional signature, novel markers, and the dynamic changes that occur during stem cell induction. By integrating these results, Fujiwara proposed a new model for hair follicle development and epidermal stem cell induction.

The meeting concluded with an award ceremony for Best Poster and Travel Grant Awards. 6 presenters won Poster Awards (300 S$ each) and 3 oral presentations were selected for Travel Awards (2500 S$ each).

Benjamin Walters won the **L'Oréal** Poster Award
Hiroyuki Matsumura won the **JSID** Poster Award
Muly Tham won the **Arysta Health & Nutritional Sciences** Poster Award
Zoe Lim won the **Biomedical Research Council (BMRC) A*STAR** Poster Award
Ritsuko Morita received the **Procter & Gamble** Poster Award
Jamien Lim received the **Bioderma** Poster Award
2 Travel Awards were generously sponsored by L'Oréal and 1 Travel Award by JSID. The winners were: **Kenneth Lay, Toru Hiratsuka** and **Chisa Nakashima**.

The award ceremony was followed by concluding remarks from Birgit Lane, Kenji Kabashima and Hironobu Fujiwara. We celebrated the conference with a big bang: dinner, champagne and wines at Privé, Asian Civilization Museum located by the beautiful Singapore River.

Conclusions:
Based on the feedback from participants and sponsors, the meeting was a great success both scientifically and socially. We think it would be outstanding to have another Japan – Singapore Skin Conference – maybe in a couple of years in Japan – to further strengthen the academic, clinical and industrial ties between Singapore, Japan and the rest of the scientific world!

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In addition, the administrative planning of the conference was led by Gerald Udolph, Oliver Dreesen and a team of enthusiastic, hard-working volunteers, including Julin Wong, Rajinder Kaur, Vivien Chua, Sebastien Teissier, Audrey Wang, Hujija Chen, Jun-ichi Sakabe, Hideki Itoh and Licheng Ng.

Lastly and most importantly, we thank the conference participants who made this both an excellent conference and a memorable experience – THANK YOU & ありがとうございました!

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