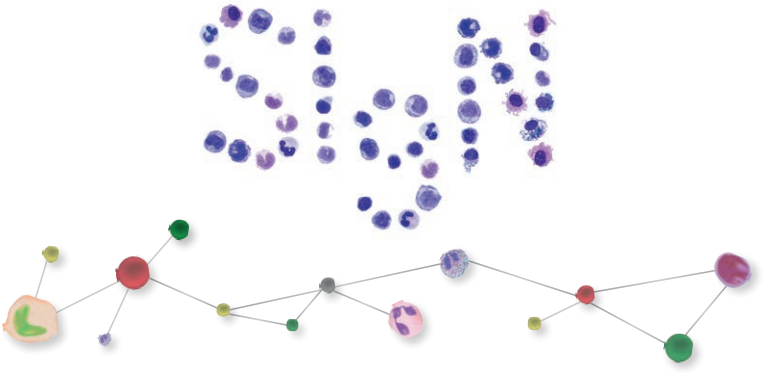
SIgN

SINGAPORE
IMMUNOLOGY
NETWORK



Towards Research Excellence in Human Immunology

Celebrating 10 years

2006 – 2016

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Foreword from Prof Laurent Rénia

Executive Director
Singapore Immunology Network

As the Executive Director of SIgN, I am extremely honoured to present this report covering our first 10 years of activities. Since its conceptualization in 2005 and establishment in 2006 by Prof Philippe Kourilsky and Prof Lam Kong Peng, SIgN has been dedicated to Human Immunology with a mission to improve health and create value for the society.

Moving with the times

SIgN has established itself as an international centre for Immunology focusing on Infection and Immunity, Inflammation and Immunoregulation. Significant developments have been achieved through our team of dedicated researchers and external collaborators from Singapore and abroad. As a dynamic institute, SIgN has undergone changes in its scientific leadership: pioneer researcher leaders, who have played significant roles in establishing SIgN, have moved to new endeavours. Young talented research leaders have joined and will now lead SIgN to new heights.

Translating research

At SIgN, we have gained recognition over the years for our ability to translate research into innovations. Through close partnerships between SIgN researchers and commercial and public entities, we have developed many projects that have generated new knowledge and innovations to further economic growth and improve lives.

Developing for the future

SIgN firmly believes the importance of nurturing young scientists and is supporting multiple activities to simulate analytical thinking, interdisciplinary collaboration and entrepreneurial spirit. Equipped with these skill sets, we are confident that our young researchers will be ready to face and solve challenges of the future.

As SIgN matures, its importance as an International Centre of Excellence grows. We are proud to lead the way in bringing integrated cross-disciplinary approaches to problems of both local and international significance. SIgN is committed to maintain scientific excellence and originality, which are alongside A*STAR's philosophy and mission. I look forward to seeing more contributions from SIgN in the next decade.

Message by
Mr Lim Chuan Poh

Chairman
Agency for Science, Technology and Research

The establishment of SIgN was a critical part of the Biomedical Sciences (BMS) initiative launched in 2000 to develop BMS as one of the key industry sector. Phase 1 of the BMS initiative, from 2001 to 2005, was focused on developing a critical mass of basic research capabilities. Phase 2 built on the efforts of Phase 1 to develop Translational and Clinical Research (TCR) capabilities to close the gap between bench and bedside. SIgN was therefore born in 2006 as part of this TCR efforts in Singapore, and pertinently, chose to focus on human immunology.

In just one decade, SIgN has built a strong core of research capabilities in human immunology and elevated Singapore's position within the international research community in this area. SIgN has published close to 650 scientific papers since 2007, with more than half in scientific journals with impact factor above 5. These include several papers in top tier journals such as Nature and Science. With a strong emphasis on TCR, the institute successfully established a network of scientists and clinicians with a shared objective to resolve the complexity of the immune system and translate this knowledge into useful clinical applications. In RIE 2015, SIgN fostered collaborations with over 30 clinicians and clinician-scientists covering important medical and healthcare areas such as infectious diseases, cancer, immunotherapy, aging and allergy. The joint project between SIgN and the National University Health System (NUHS) to study allergy in Singapore is a good example. The study, which identified that house dust mites is the major cause for common airway allergies in Singapore, has deepened our understanding of the local environment, and encouraged further research to improve allergy management in Singapore.

With SIgN's expertise in immunology and the collaborations with the clinical community, SIgN has also attracted interest in partnerships from multiple companies on translational and clinical research. In the last five years, SIgN has formed research collaborations with 21 biopharmaceutical, consumer care, and food and nutrition companies including industry giants such as Sanofi, Merck, Janssen and Nestle, as well as local SMEs such as Veredus, Curiox Biosystems and Apta Biosciences on research areas ranging from infectious diseases to aging. More specifically, SIgN is working with Sanofi Pasteur to jointly conduct a three-year clinical trial to understand age-related loss of immunity.

Despite being a young research institute, SIgN has already nurtured several promising young scientific talent for both A*STAR and the wider BMS community. Dr Florent Ginhoux, Senior Principal Investigator at SIgN, for example, has received various accolades for his outstanding research in the area of dendritic cells. He was one of the few scientists outside of Europe to be named an EMBO Young Investigator in 2013, and was also awarded the European Macrophage and Dendritic Cell Society Junior Prize. Another outstanding scientist is Dr Lisa Ng, who is widely recognized for her major contributions in the prevention and treatment of epidemic viral infections such as SARS and influenza. Lisa's work has also added immensely to SIgN's advance in the area of infectious diseases particularly in the chikungunya virus.

As we prepare to enter RIE 2020, I am confident that SIgN will continue to do well and contribute to A*STAR's mission of advancing science and developing innovative technology to further economic growth and improve lives.

On this very meaningful occasion, I would like to congratulate Prof Laurent Renia and his team at SIgN for the success thus far and I look forward to greater contributions from the institute in the next decade.

Message by
Dr Benjamin Seet

Executive Director
Biomedical Research Council

Our understanding of the immune system and our ability to better regulate and harness it for therapeutic purposes will have profound impact on the practice of medicine. The boundaries of immunology as a scientific discipline will overlap and merge with those of other biomedical sciences; whilst the clinical relevance of immunology will become increasingly important in the diagnosis, prognosis, treatment and prevention of acute and chronic diseases, including major health challenges like cancer, diabetes and cardiovascular disease.

The Singapore Immunology Network or SIgN, has in the short decade since its founding, established a strong foundation and expertise in scientific discovery and clinical application in the field of immunology. For example, it has developed a comprehensive immunomonitoring platform that utilises a systems approach for biomarker discovery, identifying novel therapeutic targets and clinical trials monitoring. It also has notable capabilities in the functional studies of immune cell behaviour; in human monoclonal antibody development; in understanding the role of the microbiome in health and disease; as well as in senescence of the immune system as we age.

Together with its strong network of clinical partners in Singapore and internationally, SIgN has translated its research to addressing emerging infectious disease threats like Chikungunya, Zika and Ebola; towards understanding allergy and atopy in Singapore children; and in the contribution of the immune system to the development of cancer, diabetes and heart failure. This has allowed it to establish its place and relevance in the Singapore biomedical research landscape.

I would like to congratulate SIgN for its outstanding work and many collaborative efforts over the decade, and I look forward for more impactful contributions to come.

Beginnings
Pioneers, Alumni

VIPs at the official inauguration of SIgN on 15 January 2008.

(**From left to right**: **Prof Paola Castagnoli**, then-Scientific Director of SIgN; **Mr Philip Yeo**, former Chairman of A*STAR; **Prof Philippe Kourilsky**, then-Chairman of SIgN; **Mr S Iswaran,** then-Minister of State, Ministry of Trade and Industry (MTI); **Mr Lim Chuan Poh**, Chairman of A*STAR; **Prof Lam Kong Peng**, then-Executive Director of SIgN)

The SIgN of Times

The Singapore Immunology Network was conceptualized during the formulation of the nation's Science & Technology (S&T) 2010 plan. I proposed to set up a collaborative program in immunology research that would involve laboratories in Biopolis, universities and hospitals working together. The idea was endorsed by then A*STAR Chairman, Mr Philip Yeo, A*STAR Deputy Chairman and NUS Provost, Prof Tan Chorh Chuan, and BMRC Chairman, Dr Sydney Brenner. Thus, in 2006, the Singapore Immunology Network was born.

SIgN has come a long way and has done very well in recruiting eminent scientists to Singapore, training a new generation of immunologists and publishing high impact research in top-tier journals. The current Executive Director, Professor Laurent Renia, was one of the earliest scientists to join SIgN and has contributed immensely to the institute's achievements, especially in the area of infectious diseases. Other early recruits that had contributed to SIgN's success included Drs Phillipe Kourilsky, Paola Castagnoli, Jean-Pierre Abastado, Ren Ee Chee and many others.

I have no doubt that SIgN is as relevant today as it was 10 years ago. The recent spectacular success of antibody-based checkpoint inhibitor drugs against cancers and the future potential applications of chimeric antigen-receptor (CAR) T cells in immunotherapy illustrated the tremendous translational potential of immunology to human healthcare. And not to forget the ever-increasing needs for new vaccines and therapies to combat infectious diseases such as Dengue, MERS and SARS. The future for SIgN is very bright indeed.

PROF LAM KONG PENG,
Founding Executive Director, 2006-2008

WHAT IS YOUR SWEETEST MEMORY OF SIGN IN THE GOOD OLD DAYS ?

"The day we moved into Immunos building. A new home where the SIgN family can embark on our journey together as one entity."

WONG SIEW CHENG, Principal Investigator
Joined in January 2006

"One of the oldest memories I have is the exciting time we had when some of us were sharing the "temporary" SIgN Lab at IMCB level 6 before moving to Immunos."

SUBHRA KUMAR BISWAS, Principal Investigator
Joined in May 2006

"My sweetest memory at SIgN was the first retreat initiated and organized by Jo Eyles-Keeble at Bintan."

JEAN-PIERRE ABASTADO, Principal Investigator
Joined in May 2006 and left in September 2013

"When I arrived in 2006 we only had some lab space in Proteos…and a PCR machine! There was no cutting-edge technology, only the idea of a project, and little SIgN identity…the people joining one by one all contributed to create the infrastructure and the research from that nothing – it was very challenging but also very exciting."

ALESSANDRA NARDIN, Head, Translational Immunology Group
Joined in August 2006

"I remember getting to know new cultures (more European focus) and build up the infrastructure and science."

LISA NG, Principal Investigator
Joined in March 2007

"I was fascinated by the idea of a special place right here in Singapore where immunology and immunologists can flourish. You can count the number of similar entities in the world on one hand."

REN EE CHEE, Principal Investigator
Joined in April 2008

Milestones

2006

- **Conceptualization of SIgN**
- Founding Chairman: Prof Philippe Kourilsky
- Founding Executive Director: Prof Lam Kong Peng

2007

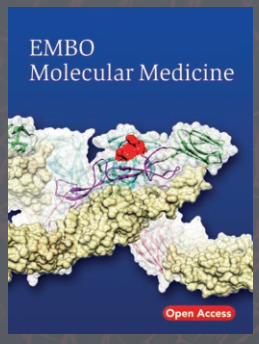
- Immunology labs across Biopolis were grouped under SIgN at the new Immunos building of Biopolis Phase 2
- Prof Paola Castagnoli appointed as Scientific Director

2008

- Official inauguration of SIgN
- Launch of Singaporean Society for Immunology (SgSI)
  Founding President: Prof Mike Kemeny
- First International Singapore Symposium of Immunology by SIgN & SgSI
- Dr Lisa Ng received the 8th Asean Young Scientist and Technologist Award

2012

- Discovered early immune responses in Chikungunya fever relevant for rational design of Chikungunya virus vaccines and diagnostics development. (Lisa Ng's Lab. Kam YW *et al. EMBO Mol Med.* 2012)



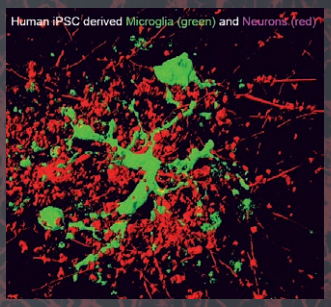
- Collaboration with L'Oreal to study immune responses in the skin
- Inaugural NIF School on Advanced Immunology by iFReC (Japan) and SIgN (Singapore)

2013

- Prof Laurent Renia appointed as Acting Executive Director
- Launch of first Lab-on-Chip for detection of multiple tropical infectious diseases developed in collaboration with Veredus Laboratories
- Hosted Singapore's inaugural European Molecular Biology Organisation (EMBO) Workshop on Complex Systems in Immunology
- Dr Florent Ginhoux received the EMBO Young Investigator Award
- Collaboration with Sanofi Pasteur, NUS and NUH to study loss of immunity and reduced responsiveness to vaccination in elderly

2009

- Set up of Human Monoclonal Antibodies platform
- Set up of 2-Photon imaging facility
- Development of a novel immunisation method to induce fast and effective protection in humans against the life-threatening malaria parasite (Laurent Renia's Lab. Roestenberg M *et al. N Engl J Med*. 2009)



2010

- Discovery of brain immune cells origin that can lead to new strategies to manipulate microglia for treatment of brain disorders (Florent Ginhoux's Lab. Ginhoux F *et al. Science*. 2010)
- Launch of SIgN-NTU PhD Program in Immunology with 7 students selected for the first intake
- Dr Norman Pavelka awarded A*STAR Investigatorship

2011

- Set up of CyTOF facility
- First of several collaborations with Servier to develop immunity-modulating drugs to combat cancer and autoimmune diseases
- Launch of SIgN Association of Post-Docs (SIgNAPs)

2014

- Elucidation of human skin antigen-presenting cells that may facilitate systemic spread of Dengue virus infection (Katja Fink's Lab. Cerny D *et al. PLoS Pathog*. 2014)
- Discovery of exposure to house dust mites as the primary case of respiratory allergies in Singapore (Olaf Rotzschke's Lab. Andiappan AK *et al. Allergy* 2014)
- Consolidation of Clinical Immunomonitoring platform (Flow Cytometry, CyTOF, Genomics, Bioinformatics, Translational Immunology)
- Prof Laurent Renia appointed as Executive Director

2015

- Development of sophisticated mass cytometry panel for high-dimensional unambiguous and unbiased characterization of the myeloid cell system (Evan Newell's Lab. Becher B *et al. Nat Immunol*. 2015)
- Collaboration with Chugai for the development of an anti-Dengue therapeutic antibody
- Collaboration with Janssen on immunomonitoring of HBV-specific T cell responses
- Co-organized with SgSI the 6th Congress of the FIMSA (Federation of Immunological Societies of Asia-Oceania) held for first time in Singapore

FIMSA2015
"Frontiers in Immune Modulation"

Our Scientists

INFECTION **INFLAMMATION** **IMMUNOREGULATION**

LAURENT RÉNIA
2007
Knowing your enemies:
infectious ideas against pathogens

LISA NG
2007
Immune responses of arthrogenic arboviruses in patients and experimental animal models to develop rationally-guided immune-based therapies

KATJA FINK
2009
Dengue vaccine and
immunotherapeutics development

GENNARO DE LIBERO
2010-2016
Tuberculosis Lipid Immunity

NORMAN PAVELKA
2011
Host-fungal interactions and microbiota

EVAN NEWELL
2012
High dimensional analysis of
antigen-specific T cells

INFECTION INFLAMMATION IMMUNOREGULATION

SUBHRA BISWAS
2006
A dysregulated monocyte/macrophage response underlies the pathogenesis of several human diseases

WONG SIEW CHENG
2006
Characterisation of myeloid cells and their subsets in health and disease

ALESSANDRA MORTELLARO
2008
Inflammasome-mediated innate immune responses to pathogens and danger signals

FLORENT GINHOUX
2009
Dendritic cell and macrophage ontogeny and differentiation

MARIA LAFAILLE
2009-2015
Allergy and inflammation

LUCIA MORI
2010-2016
T cell immunity to lipids and metabolites

INFECTION INFLAMMATION IMMUNOREGULATION

OLAF RÖTZSCHKE
2008
Genetic and functional analysis of allergy and immune-regulatory pathways

REN EE CHEE
2008
Redefining existing paradigms with new perspectives

NG LAI GUAN
2009
Studying how cells move *in vivo* to allow a better understanding of the immune system

ANIS LARBI
2010
Biology of aging and immunophenotyping: the place of immunity in the biology of aging

ANNA-MARIE FAIRHURST
2010
Examination of immune regulators in autoimmune mouse models and clinical samples

TECHNOLOGY PLATFORMS

Immunomonitoring Platform:
Biomarker discovery, identifying novel points of therapeutic intervention, clinical trials monitoring

Translational Immunology Group:
Planning and management of translational immunology projects originated from SIgN discovery research

Flow Cytometry:
State-of-the-art cell sorting and flow cytometry facility

Deep Immunophenotyping:
High-dimensional cell analysis by CyTOF

Functional Genomics:
Transcriptomics and sequencing technologies for immunogenomics research

Bioinformatics:
State-of-the-art analytical methods to derive knowledge from generated data

Human Monoclonal Ab Technologies:
Generation of novel therapeutic human monoclonal antibodies against various targets

Functional Imaging:
Multi-photon imaging technologies for examining dynamics of immune cell behavior

Mouse Models Of Human Diseases:
Modeling human pathologies and developing novel therapeutics

ALESSANDRA NARDIN
2006
Translational Immunology Group

FRANCESCA ZOLEZZI
2011-2016
Functional Genomics
Genomics technologies to support all aspects of immunogenomics research

WANG CHENG-I
2009
Human Monoclonal Ab Technologies

ZHONG PINGYU
2012
Human Monoclonal Ab Technologies

MICHAEL POIDINGER
2011
Bioinformatics

Nurturing Talent
Students, Scholars

To date, SIgN has nurtured and trained:

- 29 returning A*STAR scholars
- 60 post graduate PhD students
- 303 internship students
  (from universities, polytechnics, junior colleges and secondary schools)

Partners and Programs

- National University of Singapore (NUS)
- Nanyang Technological University (NTU)
- A*STAR Graduate Academy (A*GA)
- SIgN-NTU Immunology PhD Program
- A*STAR Graduate Scholarship (AGS)
- A*STAR Research Attachment Program (ARAP)
- Singapore International Graduate Award (SINGA)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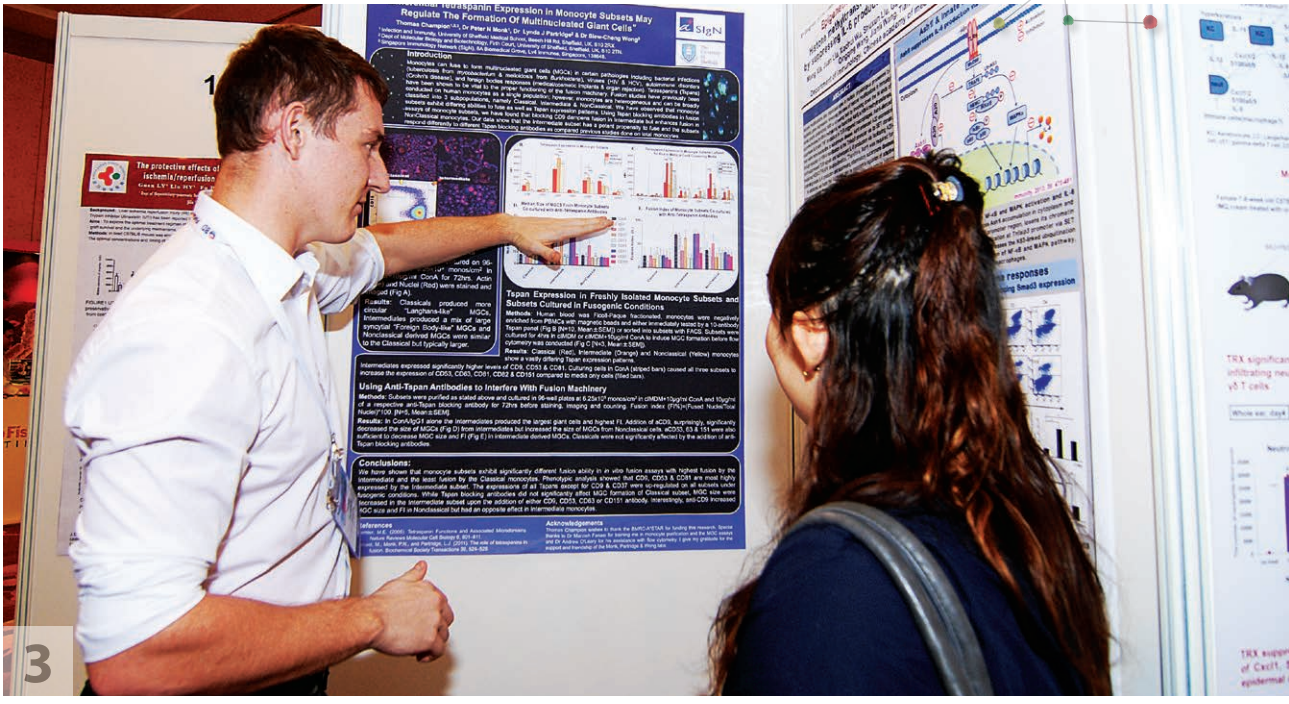

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1. 2012: Pioneer batch of SIgN Immunotechnologies Training Course (ITTC) students.

2. Sharrada Subramaniam, PhD student from NTU attached to Dr Maria Lafaille's Lab won Best Poster at SgSI's 6th Symposium in 2013.

3. PhD student Thomas Champion from University of Manchester attached to Dr Wong Siew Cheng's lab presenting his poster during FIMSA2015.

4. Choo Zheng Chen from Raffles Institution, attached to Dr Alessandra Mortellaro's lab in 2014 presented his project and shared his time and experience at SIgN during the A*STAR Student Research Attachment Program 2014 Closing Ceremony.

5. Teo Teck Hui and Lum Fok Moon, NUS PhD Students attached to Prof Laurent Renia and Dr Lisa Ng, at their graduation party after obtaining their PhDs in 2015.

SIgN Culture & Philosophy

SIgN Spirit

SIgN organizes off-site annual Scientific Training Retreats since 2009 for all staff to promote skills development in our workforce, strengthen staff interactions and foster team-building.

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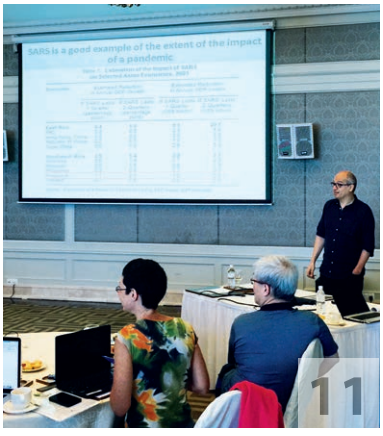


3. 2009: SIgN's 1st Scientific Retreat - Bintan Lagoon Resort

1. 2011: Turi Beach Batam

2.4.8. 2012: Nirwana Gardens

5.6.7.10.12. 2015: Bintan Lagoon Resort

9.11. 2016: SIgN's 1st PI Leadership Retreat – Penang Eastern & Oriental Hotel

Outreach

1. **2013 Biopolis Carnivale**

   For Biopolis' 10th anniversary celebration, SIgN showcased our research activities and facilitated lab tours to students and members of the public.

2. **2014 inaugural A*STAR Corporate Social Responsibility Day**

   SIgN participated in the fund-raising bazaar for charity. Donations collected through the sales of home-made baked goods and pre-loved items were donated to Singapore Children Society and the Community Chest.

3. **2015 Sg50 Science Jubilee! A*STAR Open House**

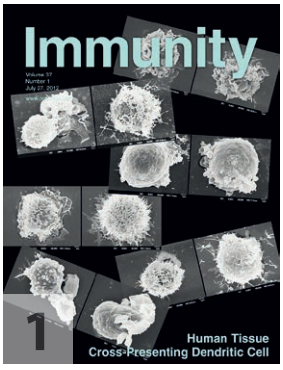
   SIgN showcased our research to members of the public during A*STAR Open House for Science@50 celebration. Our exhibit focused on arboviruses and allergies and lab tours were conducted for visitors.

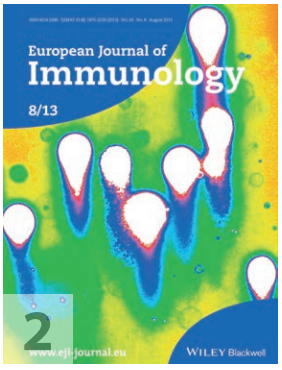
4. **Singapore Science Festival - X-periment!**

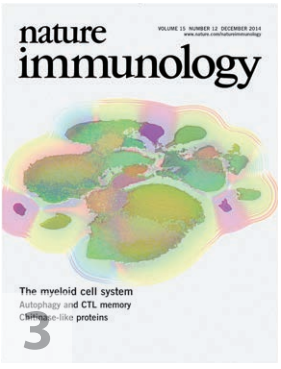
   Since 2011, SIgNAPs (SIgN Association of Post-Docs) actively participates to X-periment! organized annually by Science Centre Singapore. Themes such as "Allergies and Asthma" and "Immunology in Everyday Life & Health" were showcased with hands-on activities organized for the public.

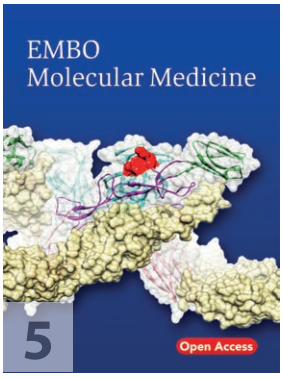
Scientific Breakthroughs

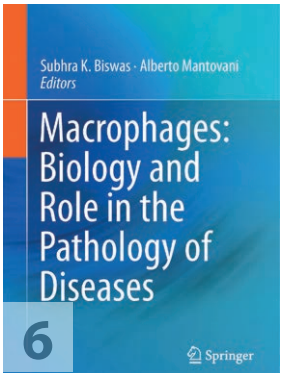
SIgN Papers Featured on Journal Covers

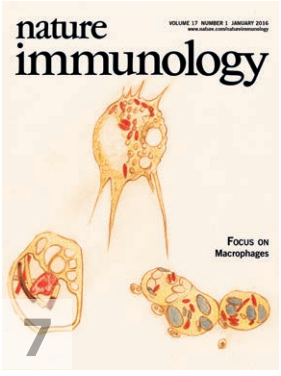












1. Haniffa M, Shin A, Bigley V, McGovern N, Teo P, See P, Wasan PS, Wang XN, Malinarich F, Malleret B, Larbi A, Tan P, Zhao H, Poidinger M, Pagan S, Cookson S, Dickinson R, Dimmick I, Jarrett RF, Renia L, Tam J, Song C, Connolly J, Chan JK, Gehring A, Bertoletti A, Collin M, Ginhoux F. Human Tissues Contain CD141(hi) Cross-Presenting Dendritic Cells with Functional Homology to Mouse CD103(+) Nonlymphoid Dendritic Cells. ***Immunity.*** 2012 Jul 27;37(1):60-73.

2. Licandro G, Khor HL, Beretta O, Lai J, Derks H, Laudisi F, Conforti-Andreoni C, Qian HL, Teng GG, Ricciardi-Castagnoli P, Mortellaro A. The NLRP3 inflammasome affects DNA damage responses after oxidative and genotoxic stress in dendritic cells. ***Eur J Immunol.*** 2013 Aug;43(8):2126-37.

3. Becher B, Schlitzer A, Chen J, Mair F, Sumatoh HR, Teng KW, Low D, Ruedl C, Riccardi-Castagnoli P, Poidinger M, Greter M, Ginhoux F, Newell EW. High-dimensional analysis of the murine myeloid cell system. ***Nat Immunol***. 2014 Dec;15(12):1181-9.

4. Evrard M, Chong SZ, Devi S, Chew WK, Lee B, Poidinger M, Ginhoux F, Tan SM, Ng LG. Visualization of bone marrow monocyte mobilization using Cx3cr1gfp/+Flt3L-/- reporter mouse by multiphoton intravital microscopy. ***J Leukoc Biol.*** 2015 Mar;97(3):611-9.

5. Kam YW, Lum FM, Teo TH, Lee WW, Simarmata D, Harjanto S, Chua CL, Chan YF, Wee JK, Chow A, Lin RT, Leo YS, Le Grand R, Sam IC, Tong JC, Roques P, Wiesmüller KH, Rénia L, Rotzschke O, Ng LF. Early neutralizing IgG response to Chikungunya virus in infected patients targets a dominant linear epitope on the E2 glycoprotein. ***EMBO Mol Med.*** 2012 Apr;4(4):330-43.

6. Biswas SK, Mantovani A. Orchestration of metabolism by macrophages. ***Cell Metab.*** Apr 4 2012; 15(4):432-437.

7. Ginhoux F, Schultze JL, Murray PJ, Ochando J, Biswas SK. New insights into the multidimensional concept of macrophage ontogeny, activation and function. ***Nat Immunol.*** 2015 Dec 17;17(1):34-40.

8. Newell EW, Davis MM. Beyond model antigens: high-dimensional methods for the analysis of antigen-specific T cells. ***Nat Biotechnol***. 2014 Feb;32(2):149-57.

Special Editorial Mentions of SIgN Papers

Immunity
Previews

Cell PRESS

Professional Cross-Presenting CD8α-Type CD141^{hi} Dendritic Cells: We Have Got You in Our Skin!

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*Correspondence: dalod@ciml.univ-mrs.fr
http://dx.doi.org/10.1016/j.immuni.2012.07.008

In this issue of *Immunity*, **Haniffa et al. (2012)** identify the presence of professional cross-presenting human dendritic cells in the skin, the liver, and the lung and also presented comparative genomics to align human and mouse dendritic cell types across tissues.

NEWS AND VIEWS

DCs are ready to commit

Deborah R Winter & Ido Amit

Dendritic cell progenitors commit to a specific conventional dendritic cell fate earlier than previously thought, by initiating transcription-factor regulatory circuits unique to their subtype.

Dendritic cells (DCs) are a critical compartment of innate immunity and perform several specialized immunological functions[1]. In this issue of *Nature Immunology*, two studies critically contribute to the understanding of DC origins by demonstrating how progenitor cells commit to the various DC subtypes in mice through distinct intermediate stages. Schlitzer *et al.* use single-cell mRNA sequencing to analyze the heterogeneity of progenitor DC populations and find, among individual cells, varying levels of commitment to develop into specific conventional DCs (cDCs)[2]. Grajales-Reyes *et al.* use mice with expression of green fluorescent protein (GFP) from the locus encoding the transcription factor Zbtb46, selectively expressed by cDCs (*Zbtb46*^{GFP}), and a defined sorting scheme to identify progenitors of cDC subtypes. Through the use of chromatin profiling, they identify the transcription factor IRF8 as a critical factor in the early regulatory circuits that lock cDC fate[3].

DCs were first observed in 1973 (ref. 4), but their location among the myeloid and lymphoid branches of the hematopoietic tree has yet to be agreed upon[5]. Although understanding of how the DC lineage develops

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NEWS AND VIEWS

Beyond the age of cellular discovery

Jonathan Michael Irish

The combination of machine-learning tools and mass-cytometry measurements of more than 30 protein markers per cell comprehensively maps cell identity in the heterogeneous myeloid cell system and reveals the global effect of deletion of the gene encoding the receptor for the growth factor GM-CSF.

High-content single-cell biology and machine-learning tools are powering a new era of 'systems immunology'. Routine mass-cytometry experiments now measure more than 30 features of each of millions of cells, and comprehensive maps of cell identity can be derived from a single cytometry tube[1,2]. The application of computational tools has substantially augmented the ability to visualize high-dimensional mass-cytometry data and model results[3–6]. These modern tools have revealed that traditional analyses can overlook killer cells, nonlymphoid dendritic cells (DCs), alveolar macrophages and eosinophils[7].

The study by Becher *et al.* increases the understanding of known cells and resolves previously obscure populations[7]. For example, three previously unknown cell populations identified by unsupervised analysis are Siglec-F^{hi}SSC^{hi} eosinophils, Ly6C^{hi}CD43^{+} monocytes and a CD11b^{hi} stage of Nkp46^{+}NK1.1^{+} innate lymphocytes. The authors confirm these cellular identities by traditional fluorescence-activated cell sorting followed by Giemsa staining. Another striking aspect of the study is the use of eight different mouse tissues: lungs, spleen, bone marrow, thymus, brain, liver, mesenteric lymph nodes, and kidneys. The speed with which the healthy landscape can be defined in detail is impressive. As research moves forward to study disease populations or animal models, the question will regularly be "Is this abnormal?" This study provides an outstanding reference point for mapping disease states.

Previous observation have shown that mice lacking *Csf2rb* have deficits in various myeloid

NEWS AND VIEWS

Cracking the code of human T-cell immunity

Christopher J Harvey & Kai W Wucherpfennig

Combinatorial tetramer staining coupled with mass cytometry allows simultaneous detection of T cells specific for a wide array of peptide epitopes.

The ability to identify and track cytotoxic T cells capable of recognizing particular epitopes is essential for studying human immune responses in the context of infectious diseases, cancer and autoimmunity. Yet despite the centrality of T cell–epitope interactions to the immune response, our ability to determine which epitopes are important in a given individual is extremely limited. In this issue, Newell *et al.*[1] present an elegant approach for simultaneous detection of T cells specific for a large number of candidate epitopes. The authors apply their novel technique to define they suffer from an inherent technical limitation imposed by spectral overlap. The recent development of quantum dots with narrow spectral windows has expanded the number of parameters that researchers can detect simultaneously using flow cytometry, but 'compensating' for spectral bleed-through becomes increasingly complex as the number of fluorescent parameters is increased[3].

Mass cytometry represents an elegant, highly innovative solution to this problem. This breakthrough technology—first described in 2009 by Scott Tanner and colleagues* at the

Newell *et al.*[1] have exploited the advantages of mass cytometry to simultaneously analyze the specificities of many T cells. Because the cytotoxic function of CD8 T cells is triggered by T-cell receptor (TCR) recognition of epitopes presented by major histocompatibility complex (MHC) class I molecules on target cells, they stained T cells with panels of peptide-MHC tetramers. As shown by Altman and Davis in 1996, virus-specific T cells can be visualized and isolated with fluorescently labeled tetramers of peptide-MHC complexes[2]. Since then, tetramers have become an essen-

Immunity
Previews

CellPress

HIF1α Allows Monocytes to Take a Breather during Sepsis

Derek W. Gilroy[1,*] and Simon Yona[1,*]
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*Correspondence: d.gilroy@ucl.ac.uk (D.W.G.), s.yona@ucl.ac.uk (S.Y.)
http://dx.doi.org/10.1016/j.immuni.2015.02.016

How the immune system is negatively affected by sepsis is not fully understood. In this issue of *Immunity*, **Shalova et al. (2015)** show that during human sepsis monocytes upregulate hypoxia-inducible factor-α (HIF1-α) activity and acquire an immunosuppressive phenotype while retaining anti-bacterial and wound-healing properties.

RESEARCH HIGHLIGHTS

Nature Reviews Genetics | Published online 14 December 2015; doi:10.1038/nrg.2015.23

EVOLUTION

Redefining gene essentiality

ORIGINAL ARTICLE Liu, G. et al. Gene essentiality is a quantitative property linked to cellular evolvability. Cell http://dx.doi.org/10.1016/j.cell.2015.10.009 (2015)

JVI Journals.ASM.org

SPOTLIGHT

Articles of Significant Interest Selected from This Issue by the Editors

Chikungunya Virus-Specific Epitopes for Diagnostics and Vaccine Development

Chikungunya virus (CHIKV) is an alphavirus that causes chronic and incapacitating arthralgia in humans. Although anti-CHIKV antibodies have been reported, the fine specificity of the antibody response against CHIKV is not known. Kam et al. (p. 13005–13015) show that the E2 and E3 glycoproteins, capsid, and nsP3 proteins are targets of anti-CHIKV antibody responses in patient cohorts. These findings identify CHIKV-specific epitopes for use in future seroepidemiological studies that will enhance an understanding of the CHIKV-specific immune response and foster development of CHIKV vaccines.

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SPOTLIGHT

Articles of Significant Interest Selected from This Issue by the Editors

Regulatory T Cells Limit Chikungunya Virus-Induced Joint Pathology

Persons infected with chikungunya virus (CHIKV) develop incapacitating joint pain that compromises daily activities. CD4^{+} T cells contribute to joint inflammation during the course of CHIKV infection in mice. The JES6-1 anti-IL-2 antibody selectively expands mouse regulatory T cells (Tregs) by forming a complex with interleukin-2 (IL-2). Lee et al. (p. 7893–7904) show that IL-2 JES6-1-mediated expansion of Tregs ameliorates CHIKV-induced joint pathology by inhibiting the infiltration of CD4^{+} T cells. These findings suggest that activation of Tregs could serve to control CHIKV-mediated disease.

Expansion of Tregs abrogates CHIKV-induced joint pathology.

EDITORS' CHOICE | SEPSIS

HIF-1α at the center of the sepsis Yin and Yang

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Immunity
Previews

CellPress

tEMPting Fate MaYBe the Solution

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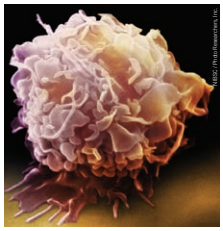
http://dx.doi.org/10.1016/j.immuni.2015.04.001

In the present issue of *Immunity*, **Hoeffel et al. (2015)** reconcile a controversy by demonstrating that a distinct wave of yolk-sac-derived erythro-myeloid progenitors (EMPs) differentiate to fetal monocytes in the liver and further to adult macrophages in the majority of tissues.

COMMUNITY CORNER

Microglial pilgrimage to the brain

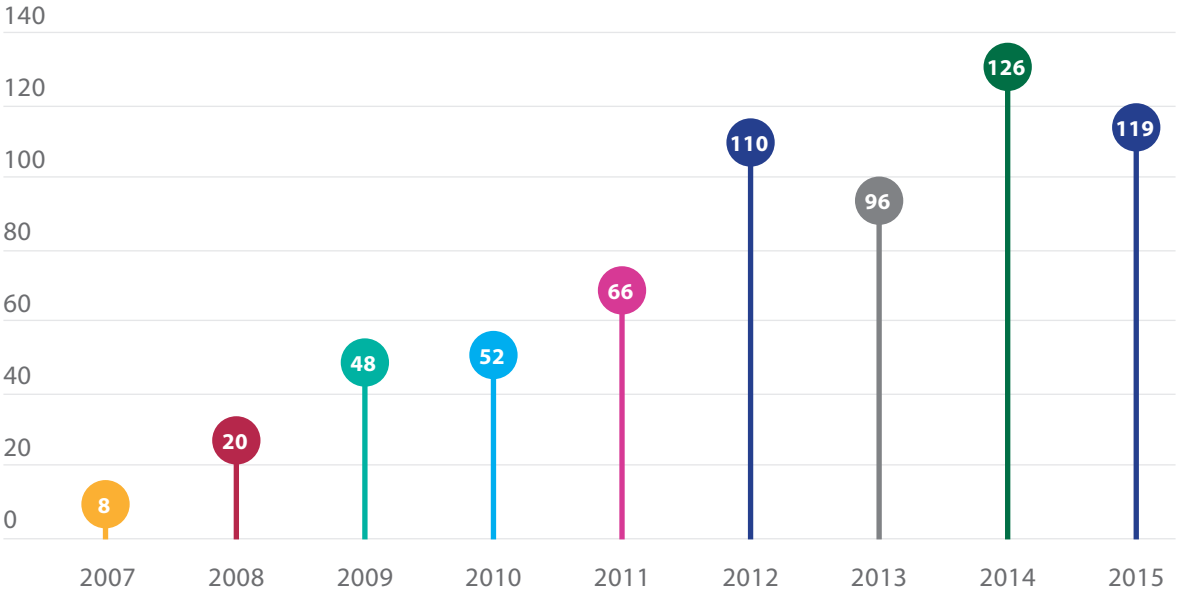
The origin of microglia and how their homeostasis is maintained in the brain have been controversial since their discovery as resident macrophages. Since the 1990's, embryonic and postnatal myeloid progenitors were assumed to contribute to adult microglia in the brain, but how microglia originate was still under debate. A recent study by Florent Ginhoux *et al.*[1] in mice discovered that embryonic macrophages from the yolk sac, formed before embryonic day 8, gave rise to almost the entire population of microglia found in the adult brain. Furthermore, peripheral myeloid cells from fetal and adult hematopoiesis contributed minimally, if at all. Microglia and their yolk sac progenitors also depended on different receptors and ligands compared to other monocytes and tissue macrophages. These findings may bring to an end the long-running dispute about the origin of these multifaceted brain cells.



Microglia in the adult brain come from primitive macrophages in the yolk sac.

Publications

645 scientific publications from 2007-2015



Impact Factor

>20: 42

10-20: 86

5-10: 195

N.A. or < 5: 322

Publication Hightlights

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Translational Programs

Human Immunology has great potential for translation into clinical applications. Translational research with cohorts of patients and healthy volunteers is facilitated in SIgN by cutting-edge translational platforms (Clinical Immunomonitoring and Human Therapeutic Antibodies) and clinical project management. Below are some of the areas in which SIgN investigators have engaged the Singapore clinical community.

Area	Program and clinical collaborators
INFECTIONS	Immune responses in dengue patients, biomarkers of dengue severity, functions of skin immune cells after dengue infection (TTSH)
	Immunity studies of Chikungunya virus, influenza virus and other respiratory pathogens in Singapore (TTSH)
	New biomarkers and drugs in tuberculosis (TTSH)
	Immunoclinical investigations in malaria (TTSH)
	Immune responses in Hepatitis B Virus infection (NUHS)
	Gut microbiome and nosocomial infection (NUHS)
CANCER AND IMMUNITY	Metabolomics and microenvironment modelling platform for HCC therapeutics and biomarker development (NCC)
	Novel human antibodies against breast cancer cells (NCC)
	Novel therapeutic antibodies against acute myeloid leukemia and gastric cancer stem cells (NUH)
	Immune microenvironment of hepatocellular carcinoma, gastric and pancreatic cancer (NCC, SGH, NUH)
	IBD and colorectal cancer biomarkers (NUH)
	Tumor-associated immune cells in human cancers (NUH)

INFLAMMATION AND AUTOIMMUNITY

- HLA associations with hypersensitivity and adverse drug reactions (SGH, CGH, HSA)
- Immune pathogenesis of rheumatoid arthritis, gout, systemic lupus erythematosus, idiopathic uveitis (NUH, SERI)
- Anti-inflammatory and anti-infectious therapeutic targets (Duke-NUS)

SKIN IMMUNITY

- Pathophysiology of itch in Atopic Dermatitis and Psoriasis (NSC)
- Skin-specific immunity in aging (NSC)
- Immune cell subsets in the skin (SGH)

ALLERGY

- Studies of atopy and allergic diseases in Chinese Singaporeans (NUS)
- Progenitor cells in respiratory diseases (NUH, NUS)

IMMUNOTHERAPY

- Adoptive transfer of human regulatory T cell to treat graft-versus-host disease

AGING AND IMMUNITY

- Immunoaging, immune biomarkers in frailty and response to vaccination in elderly (NUHS)

MATERNAL AND PEDIATRIC IMMUNITY

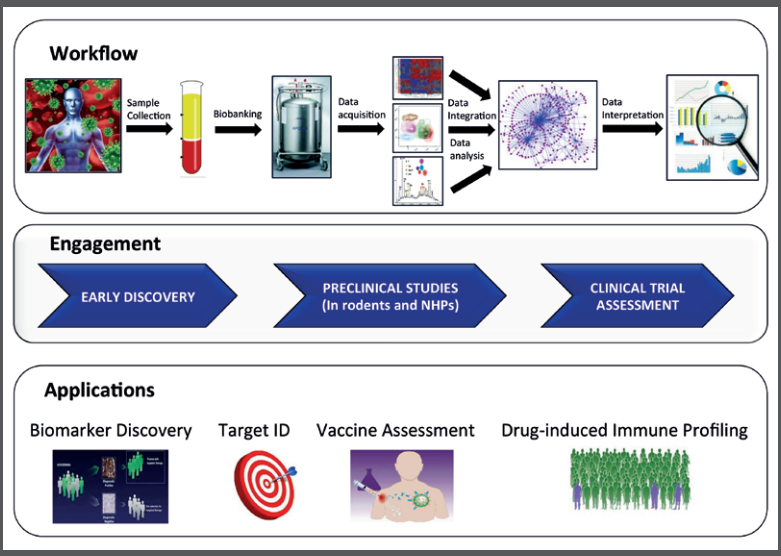
- Immune cells during fetal development (KKH)

CARDIOVASCULAR

- Asian Network for Translational Research and Cardiovascular trials (ATTRaCT) - Biomarkers and Immunology

CLINICAL IMMUNOMONITORING PLATFORM

SIgN's Clinical Immunomonitoring platform is dedicated to the definition of immunomarkers and immunological endpoints with clinically relevant impact via:



The platform comprises 4 cores, namely (i) Flow Cytometry Core, (ii) CyTOF Core, (iii) Functional Genomics Core and (iv) Bioinformatics Core. The integrated workflow of the platform incorporates upstream study design, SOP-driven sample collection and biobanking, as well as high-throughput analysis of samples using the most sophisticated technologies available and bioinformatics analysis downstream.

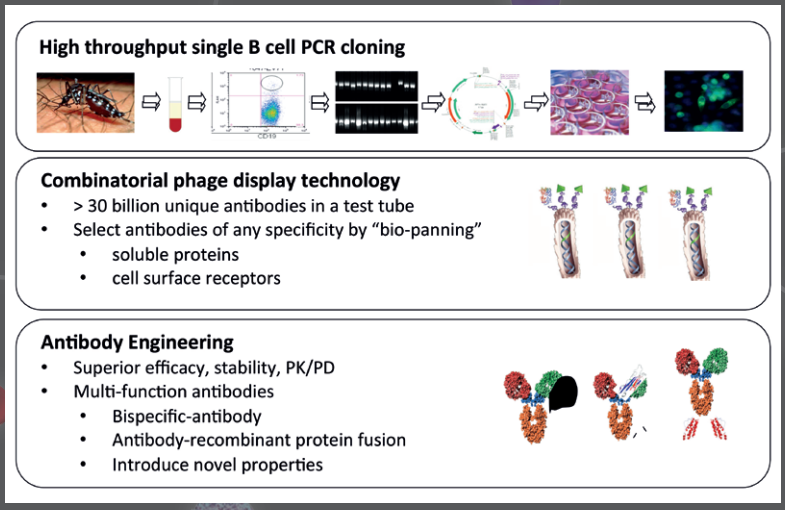
The platform is engaged in several collaborations with Industry and clinical partners. Some of these studies address diseased populations with unmet clinical needs that may benefit from a better understanding of disease biology, ultimately leading to predictive or diagnostic biomarkers improving patient care or new targets for clinical interventions. Studies in healthy individuals such as vaccine clinical trials potentially contribute to rational vaccine design for long-term protective immunity against infectious diseases. Examples of such studies include a Phase IV clinical trial study with Sanofi Pasteur and NUHS aimed at understanding the loss of immunity and reduced responsiveness to vaccination in the elderly, and the ATTRaCT Study (a collaborative effort between A*STAR, SingHealth and NUHS institutions), which aims to gain deeper insight into the role of inflammation in heart failure, the leading cause of mortality worldwide.

HUMAN THERAPEUTIC ANTIBODIES PLATFORM

The Human Therapeutic Antibodies platform at SIgN utilizes state-of-the-art antibody technologies to discover, engineer and characterize novel fully human antibodies and develop them into therapeutic candidates to treat a wide range of medical conditions, including infection, cancer, inflammation, and autoimmune diseases.

The platform has developed streamlined, high-throughput single B cell PCR cloning technology to isolate natural disease-fighting antibodies directly from virus-infected patients. A large panel of neutralizing antibodies against dengue virus has also been discovered. In addition, the combinatorial phage display technology is employed to discover antibodies against human disease antigens, including cytokines and tumor markers on cancer stem cells, from a proprietary library of more than 30 billion unique clones.

The platform's advanced antibody discovery/engineering technologies have attracted the interest of various biotech and pharmaceutical companies to co-develop and/or license therapeutic antibody candidates. Much interest has also been generated within Singapore clinical community which sees in our antibody technologies a way to address unmet medical needs in the future.



Industry Partnerships

2009

Vivalis
Therapeutic antibodies against Chikungunya virus

2010

Cytos Biotechnology
VLP-based influenza vaccine

Siena Biotech
Development of anti-DKK-1 therapeutic antibodies

Veredus Laboratories
Lab-on-chip diagnostic kit for tropical diseases

2013

Servier
Mechanism of action of a candidate therapeutic antibody

Servier
Identification of HLA alleles associated with drug-related adverse events

BD
Dissecting phenotype and function of myeloid immune cell subsets

Sanofi Pasteur
Frailty, immunosenescence and vaccination in the elderly

2014

Menarini Biomarkers Singapore
Novel procedure for selection of rare fetal cells from maternal blood

Curiox Biosystems Pte Ltd
Miniaturization of Luminex assay using DropArray technology

Bioo Scientific
Development of a new technology for the sequencing of rare transcripts

2011

Galderma R&D
Immunopathogenesis of acne

Servier
Antibodies to breast cancer

2012

L'Oréal Singapore Advanced Research
Immune responses in the skin

Servier
Natural compounds for dendritic cell immunomodulation

Novartis
In vitro and ex vivo evaluation of antimalarial drugs

2015

Sengenics International Pte Ltd
Aging, Biology and Computing: the ABC of Health-Span

Janssen Sciences Ireland UC
Immunomonitoring of HBV-specific T cells

Mead Johnson & Company, LLC
Effect of nutritional components on modulation of allergic asthma

MSD
Development of imaging probes using fibronectin protein scaffolds

MSD
Deep immunophenotyping of tumor-specific T cells in a mouse model

Nestec and Sanofi Pasteur
Aging, nutrition and immunity in Singapore

Servier
Novel targets and antibodies in autoimmune diseases

Chugai Pharmaceutical Co Ltd
Optimization of a potential therapeutic antibody candidate

Apta Biosciences
Functional characterization of Seligo targeted at chemokine receptor

MSD
Study on mechanisms of neurodegeneration using in vitro differentiated microglia

Science through Art

Winner of the 2011 Competition

1. **A Fusion to Great Perfection**
   Weng Keong Chew, Yilin Wang, Jackson Li, Samantha Chew, Chi Ching Goh, Vanessa Manoharan, Nadja Bakocevic and Jo Keeble

   Add together different experiences and expertise, blend with teamwork, and let the magic begin! Images from our laboratory swirl together to show the beauty of using different scientific techniques and tools to understand the immune system.

2. **Perspective**
   Deming Lee, Benjamin Toh, Chrissie Lim, Muly Tham, Michelle Hong and Lu-En Wai

3. **Poly-maze Chaotic Reaction**
   Fabien Decaillot

4. **Divided**
   Victor de Vries

5. **The Angiogenic Tree**
   Irina Shalova, Manesh Chittezhath and Subhra Biswas

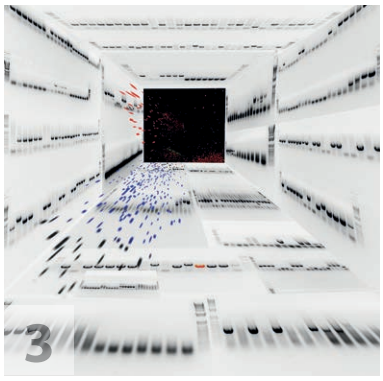
6. **Look At Me**
   Jia Shee Hee

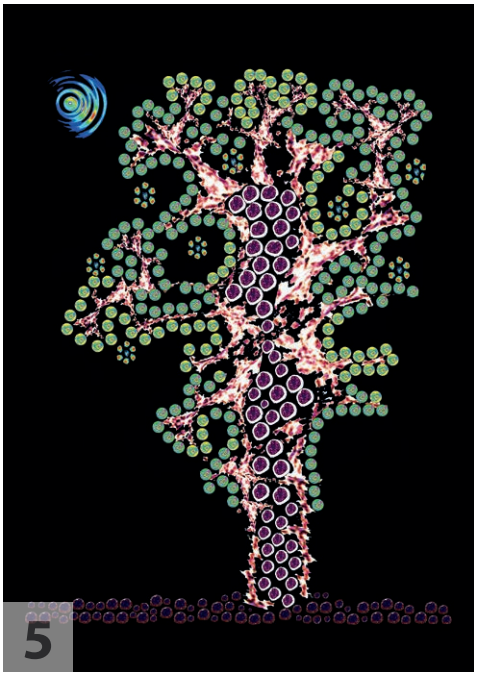
7. **The Stuff Dreams Are Made Of**
   Joe Yeong

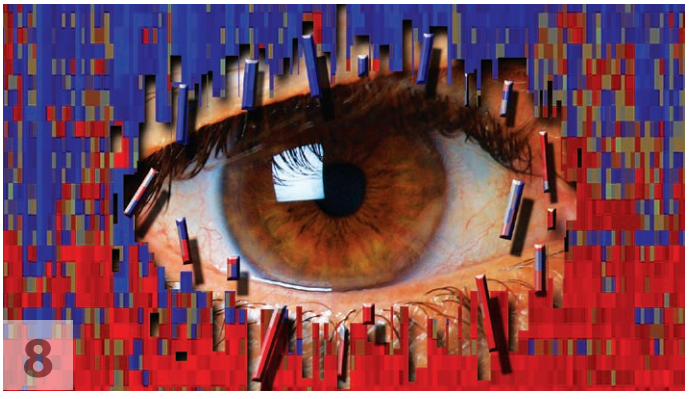
8. **Breakthrough**
   Benjamin Toh, Deming Lee, Xilei Dai and Jean-Pierre Abastado

9. **The Immune Odyssey**
   Preston Teng, Christelle Gabriel and Jason Kam

Finalists of the 2011 Competition







Acknowledgements

This commemorative book would not have been possible without the contributions of many people. We would like to take this opportunity to thank all SIgN staff, alumni and partners who have shared their valuable inputs for the realization of this book.

COMMEMORATIVE BOOK COMMITTEE

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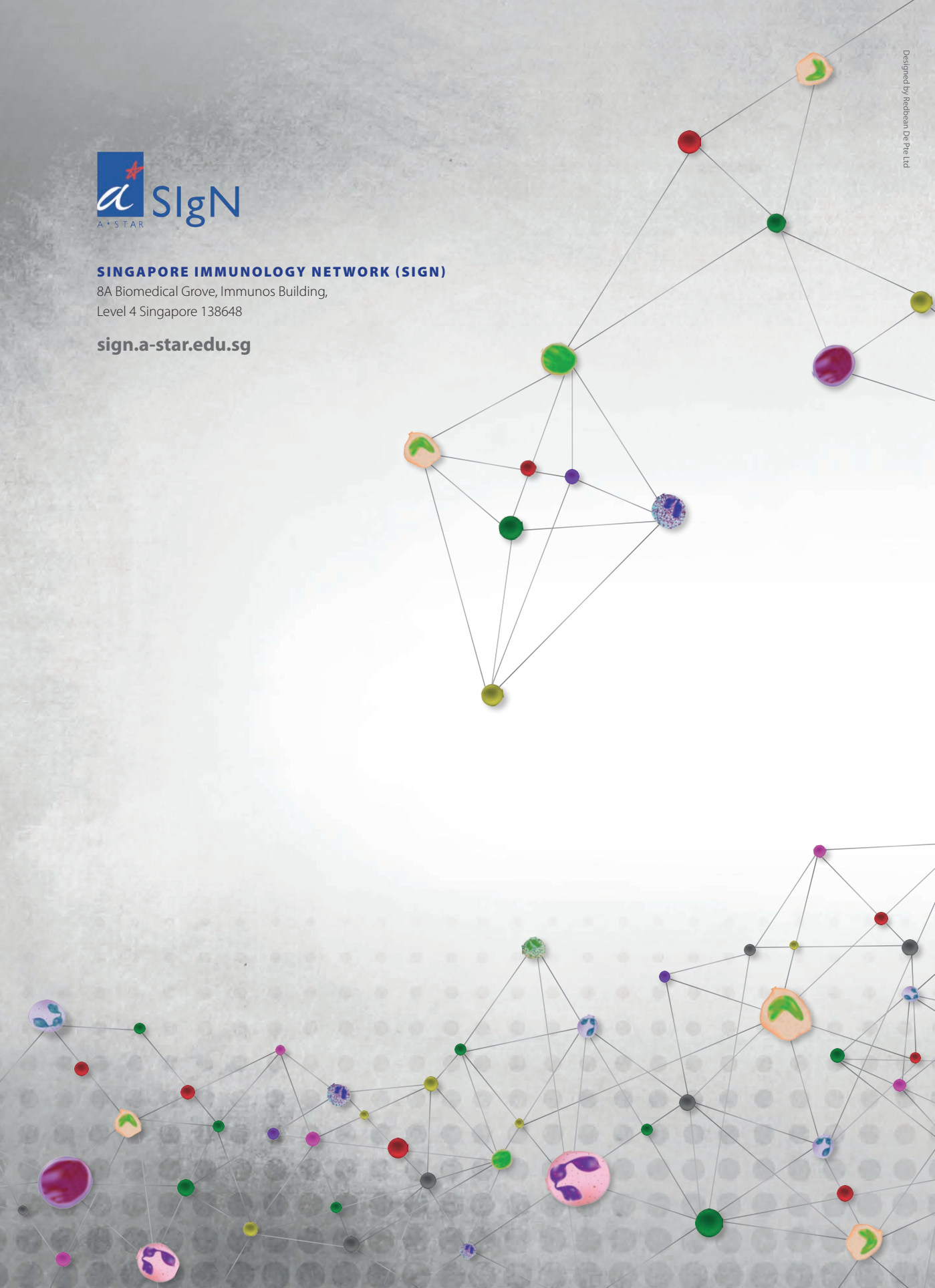

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