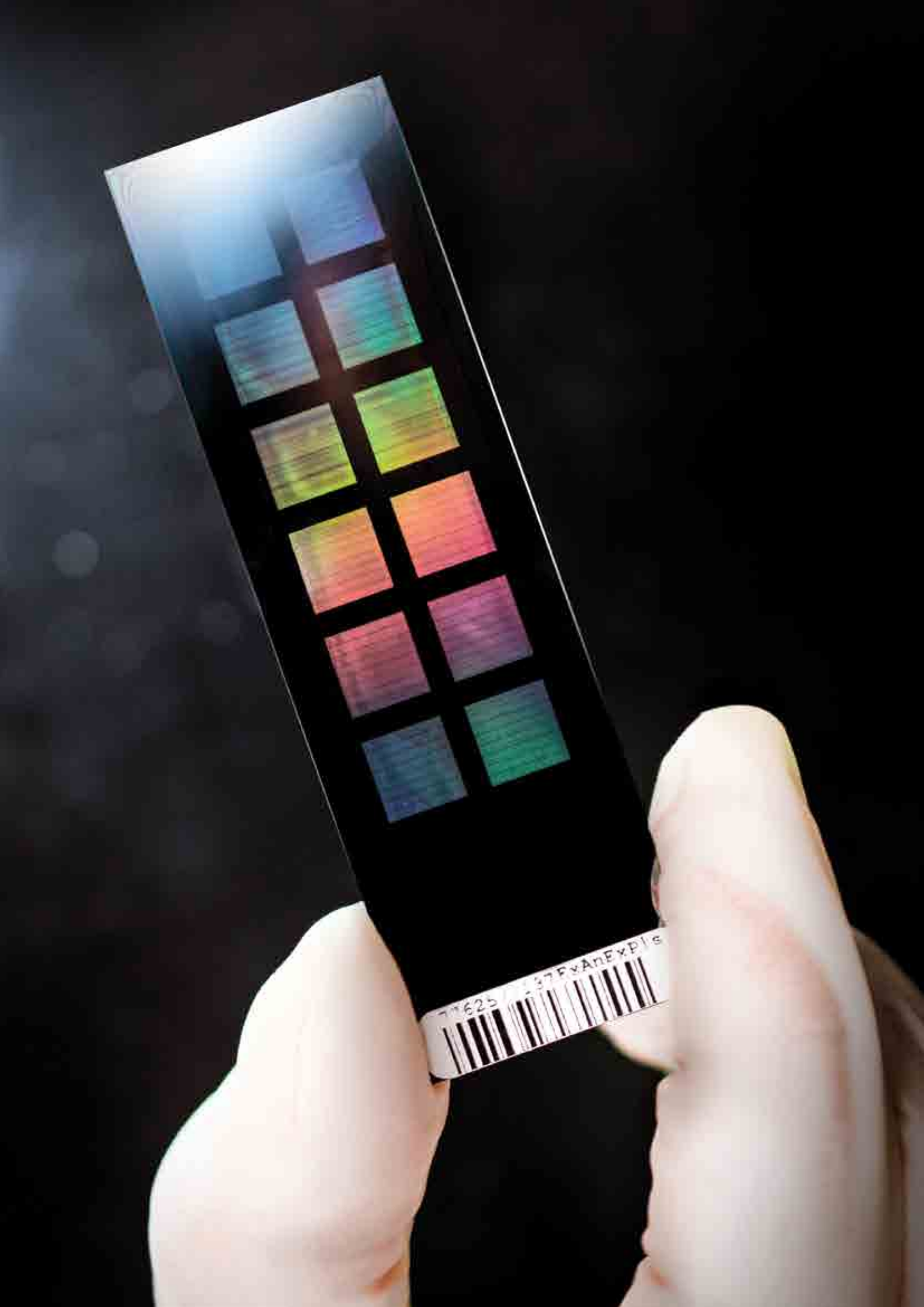
2030 STRATEGIC ROADMAP

GENOME INSTITUTE OF SINGAPORE

AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH (A*STAR)



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ABOUT A*STAR

OUR MISSION

We advance science and develop innovative technology to further economic growth and improve lives.

The Agency for Science, Technology and Research (A*STAR) drives mission-oriented research that advances scientific discovery and technological innovation. We play a key role in nurturing and developing talent and leaders for our Research Institutes, the wider research community, and industry.

Our research creates economic growth and jobs for Singapore. As a Science and Technology Organisation, we bridge the gap between academia and industry in terms of research and development. In these endeavours, we seek to integrate the relevant capabilities of our research institutes and collaborate with the wider research community as well as other public sector agencies towards meaningful and impactful outcomes. Together with the other public sector entities, we develop industry sectors by:

- integrating our capabilities to create impact with Multi-National Corporations and Globally Competitive Companies;
- partnering Local Enterprises for productivity and gearing them for growth; and
- nurturing R&D-driven Start-ups by seeding for surprises and shaping for success.

Our research, in addition, also contributes to societal benefits such as improving outcomes in healthcare, urban living, and sustainability. These serve to enhance lives in Singapore and beyond.

OUR VISION

A global leader in science, technology and open innovation

The Agency for Science, Technology and Research (A*STAR) is a catalyst, enabler and convenor of significant research initiatives among the research community in Singapore and beyond. Through open innovation, we collaborate with our partners in both the public and private sectors, and bring science and technology to benefit the economy and society.

A*STAR BIOMEDICAL RESEARCH INSTITUTES

- Bioinformatics Institute (BII)
- Bioprocessing Technology Institute (BTI)
- Genome Institute of Singapore (GIS)
- Institute of Bioengineering & Nanotechnology (IBN)
- Institute of Medical Biology (IMB)
- Institute of Molecular & Cell Biology (IMCB)
- Singapore Bioimaging Consortium (SBIC)
- Singapore Immunology Network (SIgN)
- Singapore Institute for Clinical Sciences (SICS)
- Skin Research Institute of Singapore (SRIS)
- Singapore Institute of Food and Biotechnology Innovation (SIFBI)

A*STAR SCIENCE AND ENGINEERING RESEARCH INSTITUTES

- Advanced Remanufacturing and Technology Centre (ARTC)
- Institute for Chemical & Engineering Sciences (ICES)
- Institute of High Performance Computing (IHPC)
- Institute for Infocomm Research (I^2R)
- Institute of Materials Research & Engineering (IMRE)
- Institute of Microelectronics (IME)
- National Metrology Centre (NMC)
- Singapore Institute of Manufacturing Technology (SIMTech)

FOREWORD BY THE GIS EXECUTIVE DIRECTOR

Our success lies in focusing on our three core strengths – asking the right biological questions, applying and developing cutting-edge technology platforms, and embracing multi-disciplinary team science where multiple GIS groups and collaborators are brought together to carry out high-impact, mission-oriented research.

For the past 20 years, GIS has played a key role in Singapore's biomedical and life sciences initiatives, branding the country as a leading biomedical research hub in the Asia Pacific and globally. GIS research is regularly published in renowned, high-impact scientific journals, and our scientists work closely with national hospitals and public agencies in many areas of public health and healthcare impact. Beyond academic research, the institute also pursues a vibrant industry-friendly suite of programmes, where GIS faculty are actively encouraged to pursue collaborations with companies, through joint research programmes and laboratories. Early career scientists at GIS are also encouraged to kick-start novel ideas, which may lead to spin-offs and new capabilities for the institute.

Through our efforts in building a well-established infrastructure and quality system, we have been able to promote a smooth transition from basic research towards clinical utility and commercial applications. Our success lies in focusing on our three core strengths – asking the right biological questions, applying and developing cutting-edge technology platforms, and embracing multi-disciplinary team science where multiple GIS groups and collaborators are brought together to carry out high-impact, mission-oriented research.

As a national institute, GIS aims to develop novel solutions to challenging problems that make a difference to society. The Strategy Review presented in this document will ensure GIS stays relevant and on top of technological advancements, positioning GIS as the leading expert in genomic research to discover new frontiers, bridging insights and innovations with state-of-the-art clinical medicine.

I am pleased to welcome you to the Genome Institute of Singapore!

Patrick Tan, MD PhD
Executive Director

Vision of GIS

We read, reveal and (ω)rite DNA for a better Singapore and world.

The Genome Institute of Singapore (GIS) is a national initiative with a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity.

We are the trusted **producer, custodian, and curator of Singapore's genomic data**.

We leverage **core capabilities** in **high quality sequencing** and **large-scale genome informatics**, applied through four **nucleic acid domains**, to achieve impact for A*STAR, Singapore and the world.

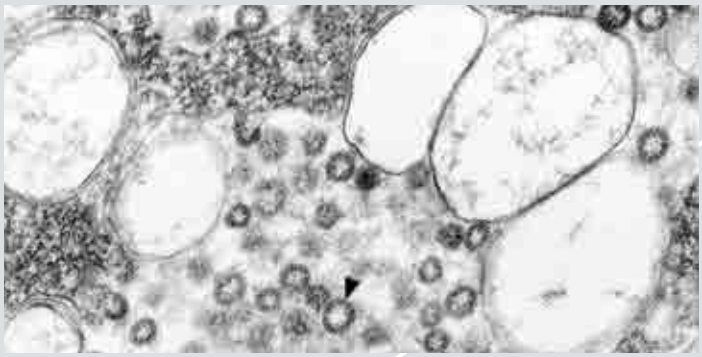
EXECUTIVE SUMMARY

A Strategic Roadmap for the Genome Institute of Singapore

The Genome Institute of Singapore (GIS) is Singapore's leading institution in the fields of genetics and genomics. As part of the Agency for Science Technology and Research (A*STAR), GIS focuses on the intersection of genomics, technology, and biomedical science. Over the past decade, we have uncovered fundamental scientific principles in cancer, stem cells, drug responses, and host-pathogen interactions with a specific concentration on Asian populations to advance medicine and healthcare. As the national flagship programme for genomics, GIS has established a first-class genomic infrastructure for Singapore, recruited outstanding

An Illustrious History

GIS was officially launched as the Singapore Genomics Program in June 2000, the same year the first draft of the human genome was completed. Since its founding, GIS has consistently provided Singapore with genomic solutions in times of need.



Severe Acute Respiratory Syndrome (SARS)

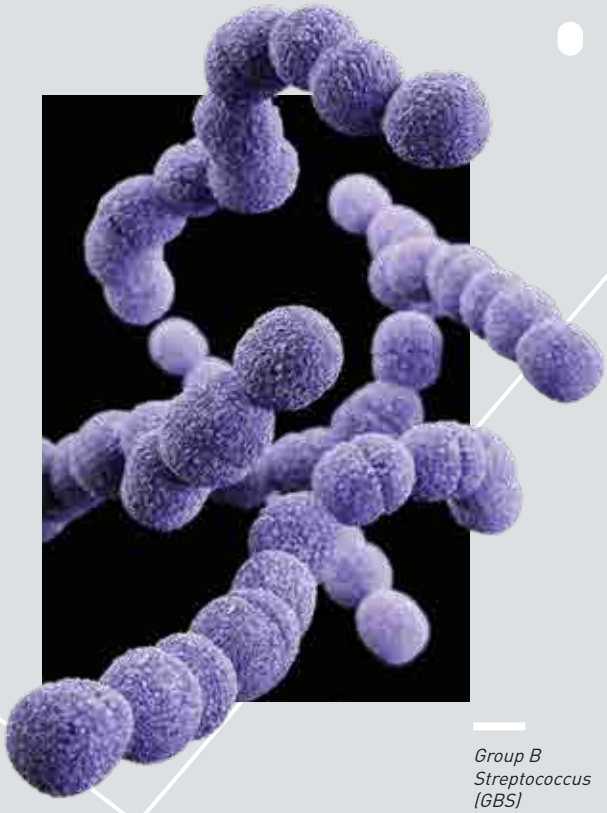
2003 During the severe acute respiratory syndrome (SARS) outbreak, more than 50 GIS scientists from international backgrounds volunteered to sequence the SARS virus genome in just two and a half weeks. This rapidly acquired information enabled characterisation of the genetic diversity of the SARS virus, leading to the development of commercial diagnostic kits. For its contributions, the institute received the Presidential Certificate of Commendation, and then-Executive Director Prof Edison Liu was awarded the Commendation Medal. GIS was also publicly cited by then Prime Minister Goh Chok Tong at his National Day Rally speech in August 2003.

2009 GIS technologies again helped Singapore face the threat of pandemic influenza caused by the H1N1 Influenza A virus. The GIS team established a new rapid whole genome sequencing strategy to detect and characterise the virus, providing important information for predicting vaccine effectiveness and immune evasion. GIS also collaborated with national agencies including the Singapore Armed Forces, Ministry of Health, National University of Singapore, DSO National Laboratories, and Tan Tock Seng Hospital to contain the spread of H1N1. This work, published in the *New England Journal of Medicine*, guided strategies to decrease virus infection rates in army camps from 6.4 percent to just 0.6 percent, and identified whether outbreak clusters were isolated or linked.

Avian Influenza virus H5N1 detection kit

faculty, and groomed a new generation of genomic scientists. We function as a central node for many large-scale collaborative studies, uniting scientists from both academia and industry.

To ensure the continued responsiveness and relevance of GIS to Singapore and the world, a comprehensive strategic review was initiated in 2019 to identify critical target sectors, anticipate emerging disruptive technologies, and refine pathways to strengthen the institute's core competencies. We aligned target sectors with key national priorities and industry needs while also considering new "blue ocean" disciplines in biodiversity and climate change. The review also considered new initiatives to improve our processes for talent management, on-the-job training, and promoting gender diversity. Progress milestones for each activity were defined to facilitate regular reviews, promote stewardship and accountability on the use of public resources, and enable corresponding decision-making to keep the institute aligned to its internal roadmap and the A*STAR mission objectives. Guided by this institutional roadmap, GIS will be well-positioned to contribute to the nation in the next decade.



Group B Streptococcus (GBS)

2015

GIS partnered public agencies and local hospitals to investigate an outbreak of infections associated with eating raw freshwater fish in Singapore. This investigation established a previously unknown causal link between group B streptococcus (GBS) and the outbreak, resulting in improvements in methods for food handling and preventive measures to combat future similar outbreaks that are being evaluated by the United Nations (UN).

2020

GIS responded to the COVID-19 global pandemic as part of Singapore's national strategy. Combining skillsets from the GIS sequencing platform and POLARIS clinical sequencing team, GIS established a clinical-grade diagnostic lab for COVID-19 testing in three weeks and played a leadership role in Operation Stronghold, an all-of-A*STAR effort to establish a massive-throughput COVID-19 testing facility enabling >10,000 tests per day.

Briefing session for researchers at the Stronghold Diagnostics Lab at GIS.

Strong Teams, Great Science for Extraordinary Impact

In addition to tackling acute public health needs, GIS has also applied genomics to other important clinical scenarios.

In 2013, GIS established Singapore's first CAP-accredited next-generation sequencing (NGS) facility (POLARIS). Through partnerships such as the Singapore Undiagnosed Disease Research for Kids (SureKIDS) programme (2015), GIS accelerated the diagnosis of patients with rare paediatric genetic diseases, saving patients and their families from costly diagnostic odysseys. In addition, GIS has made a long-standing effort into charting the genetics of ophthalmology disorders through a global network of universities and hospitals.

In 2019, GIS' work on Singapore's population genomics was featured on the cover of the leading scientific journal *Cell*. This work revealed the genetic diversity in the major Southeast Asian ethnic groups, laying the groundwork for future precision medicine studies. GIS has also acquired industry-standard ISO-certified platforms for the translation of genomic technologies.

The scientific and health impacts achieved by GIS in the past decade were made possible only through deep institutional strengths in genomic medicine, human disease modelling, precision oncology, and data science leveraging state-of-the-art genome technologies. Building on these institutional memories of excellence, this strategic review aims to ensure that GIS remains scientifically competitive and will continue to contribute to national and A*STAR's objectives over the next decade and beyond.

An Inclusive Strategy-Planning Journey

The GIS strategy review adopted a broad and inclusive approach, taking into consideration past accomplishments; existing talents and capabilities; and changes in both the local and the global scientific, biotech, and social environment. Embracing the role of genetic diversity as a major contributor to population fitness, we sought to harness the power of diversity in the strategy review process, tapping into the rich scientific and technological expertise of a broad representation of GIS staff, collaborators, advisory committees, and the wider scientific community to discuss and formulate strategic ideas. Over one third of GIS personnel were actively involved in this review, with representative committees mirroring the professional expertise, gender distribution, and seniority demographics of the institute. Consultation with A*STAR's upper management was also performed to ensure focus on research, industry, and innovation initiatives relevant to the overall A*STAR mission and national needs.

Participants in the review assessed
4 broad categories

1 **Genomic Demand Drivers**

2 **Emerging Genomic Technologies**

3 **Capabilities and Applications of Genomics**

4 **Areas of Disease and Biology**

"Ahead of the curve retreat", October 2019.

These categories were further subdivided into 14 thematic areas. Under the first category, growth and market drivers of genomics and innovation/enterprise/industry engagement approaches were analysed. To investigate how GIS might address challenges in these driver areas, improvements in sequencing platforms, IT platforms, population genomics/precision medicine, and *de novo* sequencing were discussed. The third category challenged the GIS community to go "beyond the genome", tackling epigenetics, epitranscriptomics, single-cell technologies, and spatial transcriptomics. Last but not least, in the fourth category, strategies related to nucleic acid therapeutics, cancer/oncology, ophthalmology, and talent management for early career scientists were laid out. Milestones specific for each of the 14 thematic areas were also suggested to track progress towards attainment.

At the midway point of the strategy planning process, an "Ahead of the Curve" retreat was organised in October 2019 to allow for progress check-in. The retreat served to assess synergies between the 14 committees, gathering over 70 GIS members to identify common themes and to propose Director's projects. The retreat also proposed new initiatives to address human resources, staff training, and talent management concerns. There was also discussion that in the coming decade, the demographics of the GIS community will evolve with an emphasis on workplace diversity and inclusiveness. There was recognition that GIS needs to develop greater awareness for diversity in the workplace and to put in place frameworks to reduce societal and gender imbalances, and improve parenthood support.

After the completion of a draft version of the strategy review, external key opinion leaders were consulted to bolster the strategy planning process, providing an additional layer of unbiased review. These local and international experts spanned several disciplines, ranging from academia, healthcare, government, biotech companies, and start-ups. Over the course of two months, advice and insights were solicited and incorporated into the GIS strategy framework. Through these consultations, the value of GIS to Singapore was re-affirmed, and avenues to strengthen and create partnerships were established. The external advisors also challenged GIS to strive towards greater heights in the next decade.

GIS is on a journey. We have had an illustrious past; however, the real challenges for GIS lie ahead. This review provides a roadmap for GIS to leverage upon existing strengths, fine-tune scientific programmes, and allocate resources to address important critical emerging areas. The strategic roadmap also ensures GIS alignment with A*STAR's mission objectives and staying true to its core mission to ***read, reveal, and (ω)rite DNA for a better Singapore and world***.

A NEW GIS STRATEGIC FRAMEWORK

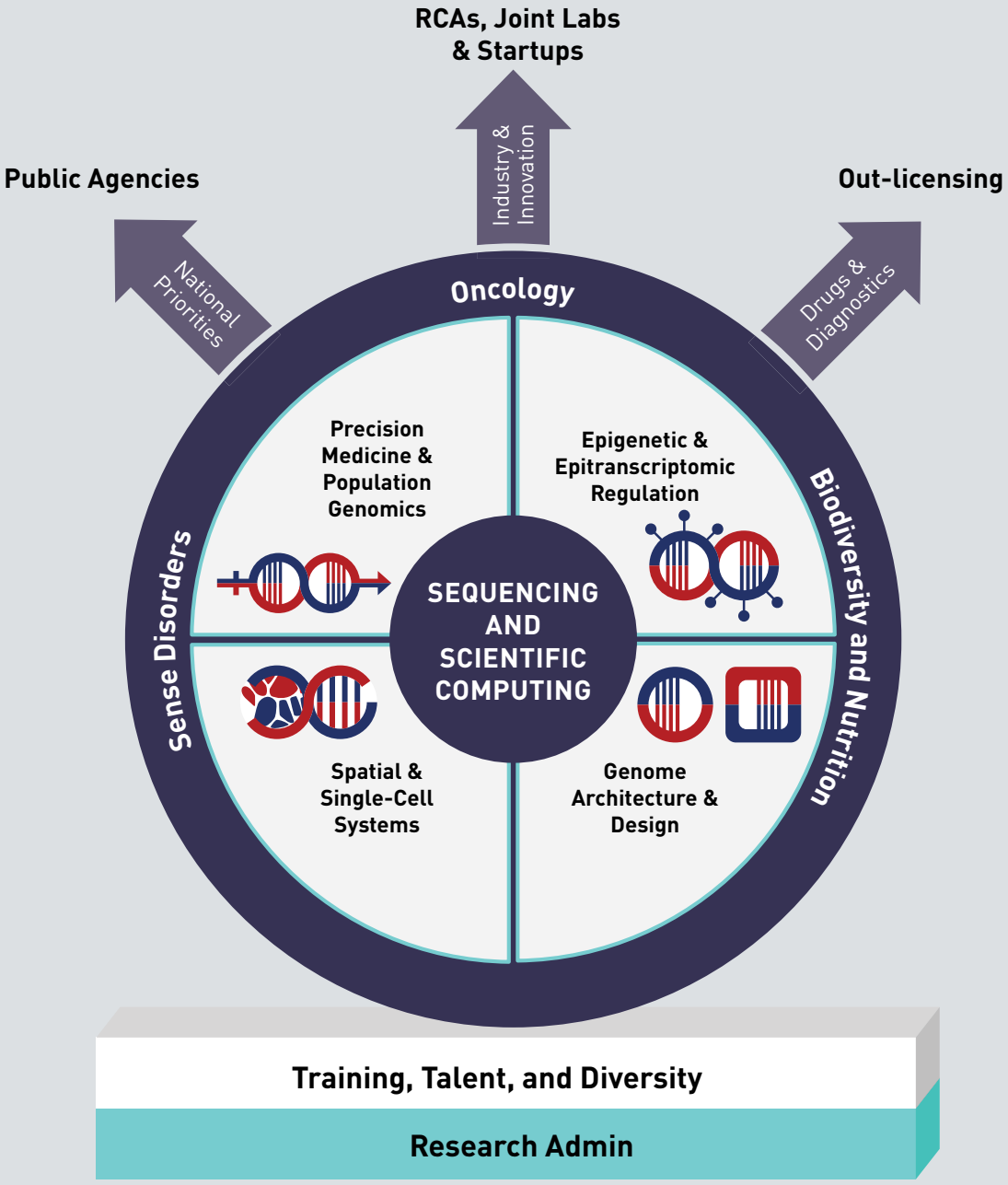


Figure 1. *The GIS Strategic Roadmap 2030.*

GIS will adopt a strategic framework of five elements (figure 1).

1 **At its centre, GIS will continue investing core funding in its "genomic engine", improving its next-generation sequencing and scientific computing capabilities.** GIS will constantly upgrade and acquire the latest genomic technologies to enable GIS investigators and partner agencies to achieve scientific breakthroughs. With increasingly powerful capabilities and economics of computing, GIS will tackle large data challenges in genomics and disease biology, as it plays an increasingly important role as a national-scale data custodian.

2 **The second element of the roadmap consists of four "nucleic acid domains": Precision Medicine and Population Genomics, Epigenetics and Epitranscriptomic Regulation, Spatial and Single-cell Systems, and Genome Architecture and Design.** Through these domains, GIS will lay the groundwork for Asian precision medicine, aiming to treat patients with the optimal medicine using personalised genetic information. Beyond the genetic code, GIS will explore chemical modifications to the genetic code and RNA, three-dimensional arrangements of the genome, and information at the single-cell level within complex organs, which may reveal mechanisms of disease initiation and progression. Additionally, GIS will explore emerging technologies for editing and writing the genetic code to establish novel applications and healthcare solutions.

3 **The third element describes disease and biological areas that GIS will investigate in partnership with key stakeholder institutions.** GIS will build on existing strengths in oncology and neuro-sensory disorders (e.g., ophthalmology) and will also develop competencies in emerging "blue-ocean" challenges in biodiversity and nutrition, tackling climate change, and meeting Singapore's food security needs by 2030 (figure 1, left, The GIS Strategic Roadmap 2030).

4 **The fourth element defines how GIS will continue to leverage on institutional strengths to fulfil national priorities.** This will be achieved through partnerships with public agencies, industry engagements, and innovation initiatives via research collaboration agreements (RCAs), joint labs, and start-ups. As GIS engages in cutting-edge scientific explorations, novel technologies that emerge may be licensed out, contributing to the development of therapeutics and diagnostics for novel solutions to healthcare needs.

5 **The fifth element, the foundation supporting the roadmap, is our people.** GIS looks to empower human capital, talent development, and diversity. Our research administration supports the essential day-to-day functions of the institute. GIS will strive to remain attractive to the next generation of scientists and innovators. By addressing challenges in human resources, GIS aims to provide a strong talent base for the continued success of Singapore's future in the genomic sciences.

NATIONAL AND INTERNATIONAL DEMAND DRIVERS OF GENOMICS

Demand drivers for genomics were analysed in the Strategy Review by examining trends and changes from two different angles – scientific needs and industry interests.

Scientific Drivers and Knowledge Gaps

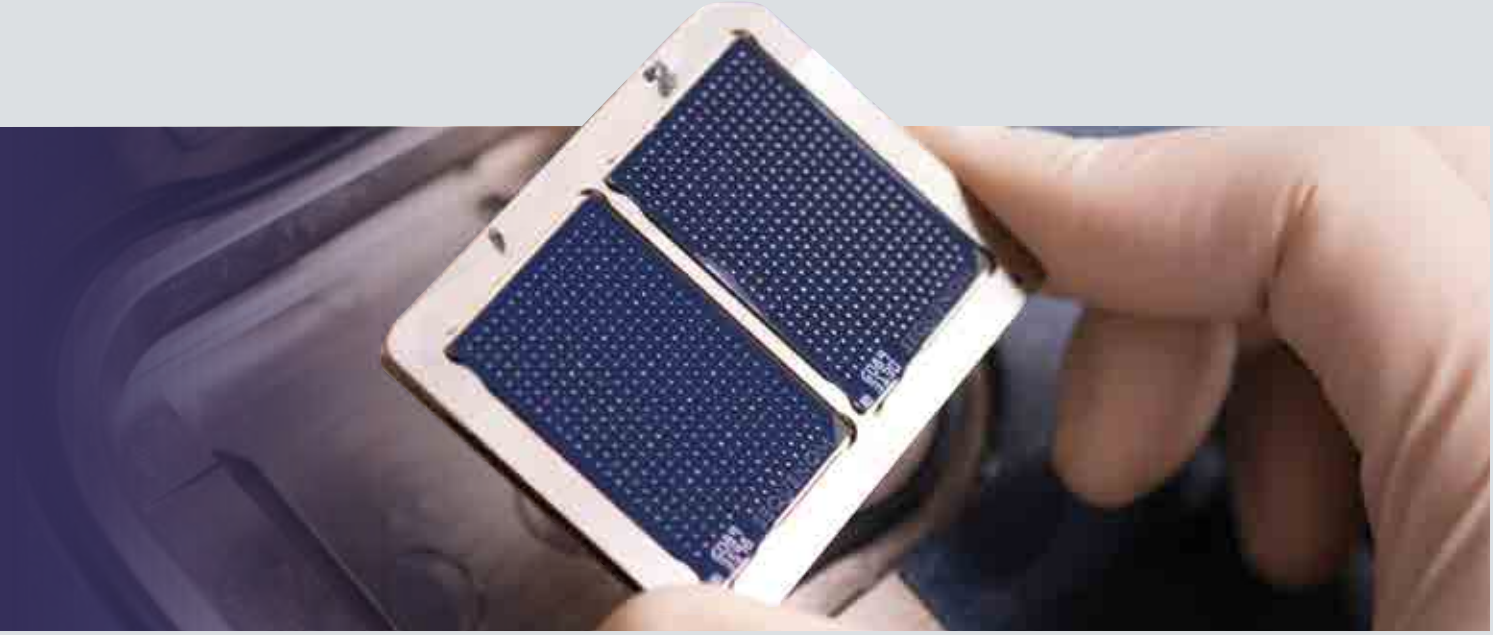
Using SciVal (Elsevier), trends in peer-reviewed publications related to genomics were reviewed to better understand worldwide research trends. A focus on the past decade's literature (2009-2019) revealed a large increase in genomics-related research, in particular relating to nucleotide sequencing, computational biology, and cancer. There was also a clear reduction in the use of microarrays in genomics-related research. This move away from microarrays likely reflects a trend towards the increasing use of next-generation sequencing in larger scale, genome-wide analyses to fulfil needs in translational research as sequencing prices decrease.

EMULSION-Novo Nordisk Asian NAFLD Biomarker Laboratory (ENABL)

The EMULSION-Novo Nordisk Asian NAFLD biomarker laboratory (ENABL) is a joint centre with a focus on the discovery of novel biomarkers for fatty liver disease. This research collaboration will contribute to the understanding of Singaporean- and Asian-centric NAFLD as part of a national research platform named Ensemble of MULti-disciplinary Systems and Integrated Omics for NAFLD (EMULSION) diagnostic and therapeutic discovery. In partnership with Novo Nordisk, a leading global health care company in innovation and diabetes care, this joint investigation aims to accelerate the discovery of novel strategies and solutions for NAFLD therapeutics and diagnostics.

*From left: Prof Ng Huck Hui (Co-Principal Investigator of this research programme and Assistant Chief Executive of A*STAR's Biomedical Research Council), Prof Patrick Tan (Executive Director of GIS), Dr Karin Conde-Knape (Corporate Vice President at Novo Nordisk), Dr Ivan Formentini (Vice President at Novo Nordisk), and Assoc Prof Dan Yock Young (Co-Principal Investigator of this research and Head of the Department of Medicine at NUS Medicine). Photo taken at the EMULSION-Novo Nordisk Asian Biomarker Laboratory (ENABL) at GIS.*

Global grant funding trends were also analysed to provide indicators of upcoming demands for research in various fields of biology. The top disease areas that received the most funding allocations for FY2020 included clinical research, genetics, disease prevention, neurosciences, biotechnology, cancer, and infectious diseases. Interestingly, these seven categories have retained their rank order since 2016, indicating a sustained interest in these research areas. Consistent with publication trends, World RePORT records, by the National Institutes of Health (NIH), also confirmed an increase in the use of genomics-related technologies and identified the addressing of translational research needs as a key focus.



Industry and Commercial Drivers (Start-ups, biotechnologies, and MNCs)

The market sizes and growth rates of several of the most prominent market sectors related to modern genomics were also analysed.

Nalagenetics

Nalagenetics is an example of a GIS-originated medtech company focused on personalised prescriptions. Their mission is to provide actionable and cost-effective pharmacogenomics (PGx) testing for Asian populations. Adverse drug reactions (ADRs) cause eight percent of hospital admissions and are the fourth leading cause of death in the US. Although 30-70 percent of ADRs have genetic associations, genetic testing for drug response (PGx testing) in developing countries is not widely implemented because it is too expensive and unproven in local populations. Thus, Nalagenetics is developing PGx testing that is five times cheaper than current alternatives with clinical decision support to combine genetics with real-world evidence for better prescriptions.

Nalagenetics Team Singapore. *1st row, from left: JJ Liu (Co-Founder, Super Advisor), Levana Sani (Co-Founder, CEO), Anar Kothary (Senior Product Development Officer), Astrid Irwanto (Co-Founder, COO), Jocelyn Tan (Senior Product Development Officer), Minghen Tan (Senior Bioinformatics Specialist), Zhihao Tan (Genetics & QARA Lead). 2nd row, from left: Fadhli Adesta (Product & Patient Care Manager), Sashiraj Chandrasekaran (Senior Software Engineer), Alexander Lezhava (Co-Founder, Super Advisor).*

The largest market segment is precision medicine, valued at US$80-90 billion with a compound annual growth rate (CAGR) of 15-20 percent. Genome reading (e.g., sequencing) and writing (e.g., synthetic biology, oligo synthesis, etc.) are also significant market segments valued at US$30 billion and US$50 billion with CAGRs of 15 percent and 30-45 percent, respectively, with most of this expenditure currently in the research market.

The most prominent upcoming market segments are single-cell and genome-editing technologies. Single-cell technologies and structural biology form a US$18 billion market with a CAGR of 15-20 percent. The genome editing market (e.g., CRISPR technologies) is worth US$10 billion with a CAGR of 15-20 percent. Both of these areas are forecasted to quickly exceed other slower-growing market segments.

Agriculture is a massive industry (US$3,400 billion) that to date has been largely underexplored by GIS. Coupled with increasing national interests in food security (see page 69: Biodiversity and Nutrition), this is a potential new area of research that the institute will be venturing into, working with partners to study plants and species relevant to Singapore and Asia.

Epigenetics and microbiome are niche market segments with high growth rates. Although both are comparably small in market share (US$1.3 billion and US$0.5 billion, respectively), they demonstrate high CAGRs of 13 percent and 22 percent, respectively, and have the potential to become substantial genomics market segments.

Skin Microbiome

Skin health is intricately linked to the different types and the status of microbes that live on the skin. However, what defines a healthy skin microbiome is not currently clear. Driven by the Genome Institute of Singapore and the Skin Research Institute of Singapore, the Asian Skin Microbiome Project (ASMP) brings together researchers and clinicians in Singapore that are at the forefront of skin biology and microbiome research. Focusing on Asian skin types, the project aims to develop and apply a suite of technologies that will unravel the complex relationship between the skin microbiome and skin health. These efforts will catalyse industrial research and the development of novel clinical interventions that can improve skin health.

Start-up listings and venture capital funding trends were also analysed to assess up-and-coming demand drivers of genomics. Biotechnology start-ups founded in the later part of the past decade heavily featured "data" as a keyword, reflecting the importance of big data and machine learning. Of 814 start-ups founded from 2017-2019, 13 percent were using genetics, genomics, transcriptomics, or other omics in their work, frequently as input to power various artificial intelligence (AI) platforms. The increasing importance of big data and AI in healthcare can also be seen in Apple, Amazon, Google, and Microsoft's efforts to move into healthcare as part of their AI and deep learning initiatives. Omics data is expected to be of increasing importance to these companies to improve healthcare deep learning models.

Therapeutics (38 percent) and diagnostics companies (17 percent) accounted for more than half of all genomics start-ups, and 56 percent of the therapeutic start-ups are gene therapy companies. This proportion is similar to that of all biotech start-ups, suggesting that investors are still actively looking to invest in therapeutics and diagnostics.

The Strategy Review also noted an increasing number of microbiome start-ups, in areas as diverse as therapeutics, diagnostics, analytics software, agriculture, and direct-to-consumer offerings. Given that the microbiome field is in its infancy, microbiome research is expected to continue to provide new insights and create additional microbiome-based spin-offs.

Policy and Regulatory Drivers

The developed world, including Singapore, faces a rapidly ageing population. This evolution in global population demographics poses societal and economic challenges that will require responsive and predictive changes to public policies and regulatory frameworks to facilitate the development of novel solutions. A*STAR has likewise enhanced its health and economic objectives to meet Singapore's needs. As the key genomics institution of Singapore and A*STAR, GIS will continue to meet policy and regulatory needs by leveraging genomic technologies to continue making contributions to national and A*STAR objectives in GIS 2030.

National Precision Medicine (NPM)

The SG10K_Health WGS project under Singapore's National Precision Medicine Programme aimed to sequence the genomes of 10,000 Singaporeans. We met this goal ahead of schedule and under budget by delivering >10,000 sequences from several cohorts across Singapore (NTU, NUS, SingHealth, SERI, TTSH, and SICS). Our teams have since expanded on the original scope and will deliver approximately 10,000 methylation profiles matched to participants from the WGS portion of the programme. The success of this effort is attributable to an island-wide collaboration between all pillars of Singapore's health and biomedical research communities.

The SG10K team won the GIS Super Team Award 2018.

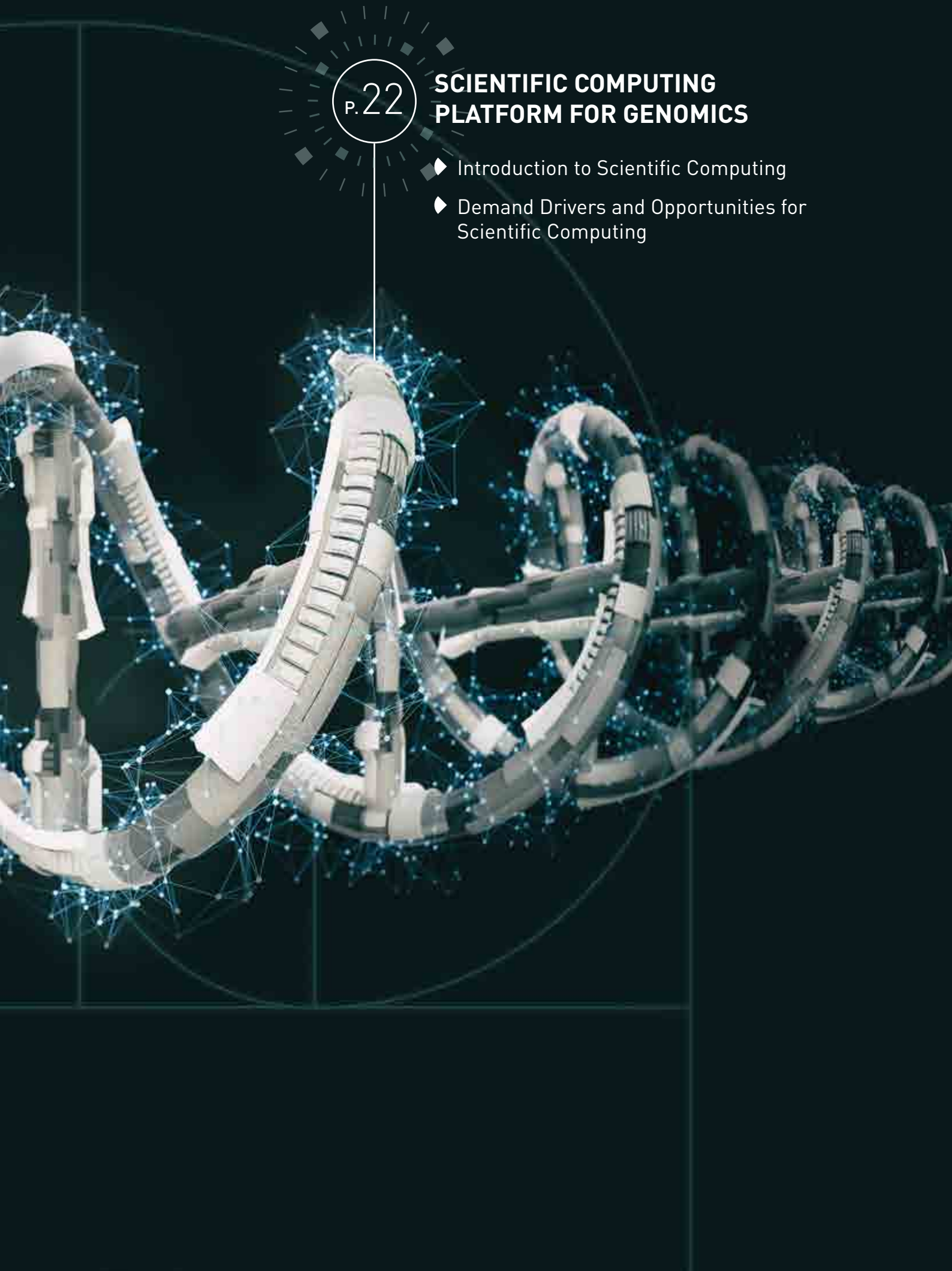
Navigating to GIS 2030

Genomics and omics technologies show continued importance and are increasingly used for translational research needs. Precision medicine, single-cell technologies, and genome editing are important genomics market segments. Agriculture is a large market that is worth exploring. Although epigenetics and the microbiome are smaller market segments, their high growth rates indicate that these areas should not be ignored. This conclusion is corroborated by our analysis of the genomics start-up landscape showing that therapeutics and diagnostics comprise the majority of start-ups with an increase in the number of microbiome start-ups. AI, machine learning, and data analytics are also increasingly important for utilising the growing mountains of genomics and omics data. GIS has domain knowledge in many of these areas and will continue to maintain our core expertise, building upon our existing strengths in these areas.

CORE GENOMIC ENGINES

P. 18 **SEQUENCING PLATFORMS**

- Introduction to Sequencing Platforms
- Demand Drivers in Sequencing Platforms
- Existing Strengths and Opportunities



P. 22

SCIENTIFIC COMPUTING PLATFORM FOR GENOMICS

- Introduction to Scientific Computing
- Demand Drivers and Opportunities for Scientific Computing

SEQUENCING PLATFORMS

High-throughput sequencing of nucleic acids (DNA or RNA) using next-generation technologies provides an enormous volume of sequences with many possible applications for research and diagnostic development. At GIS, our sequencing platform provides access to the most contemporary instrumentation, charged at the correct price point and in a cost-efficient manner. We have a clear policy of being openly available for all users.

Sequencing technologies form a core element of many researchers' needs to measure DNA and RNA variation in research specimens. Broadly, current applications for sequencing platforms include:

- Research in human genetics (including human samples)
- Research in non-human genetics (biodiversity projects involving plants and animals)
- Single-cell genomics
- Cancer genomics
- Validation of gene-editing (CRISPR) screens
- Pathogen outbreak monitoring/environmental quorum sensing
- Sequencing technologies for toxicology and characterisation of foodborne pathogens, food authenticity, and the discovery of allergens in novel food sources
- Development of emerging sequencing technologies (e.g., long-read sequencing) to meet future technological needs

Demand Drivers in Sequencing Platforms

Throughout the world, the demand for high-throughput next generation sequencing is increasing exponentially. This is contributed to increased whole-genome sequencing efforts by national biobanks, RNA sequencing efforts, and whole-genome bisulphite sequencing. There are diverse demand drivers for sequencing technologies, encompassing public, academic, industry, and healthcare institutions with sequencing needs for biospecimens. We observe that the user base for the GIS sequencing platform is rapidly changing, as indicated in the following figures that chart our user demographics from 2012 to 2018.

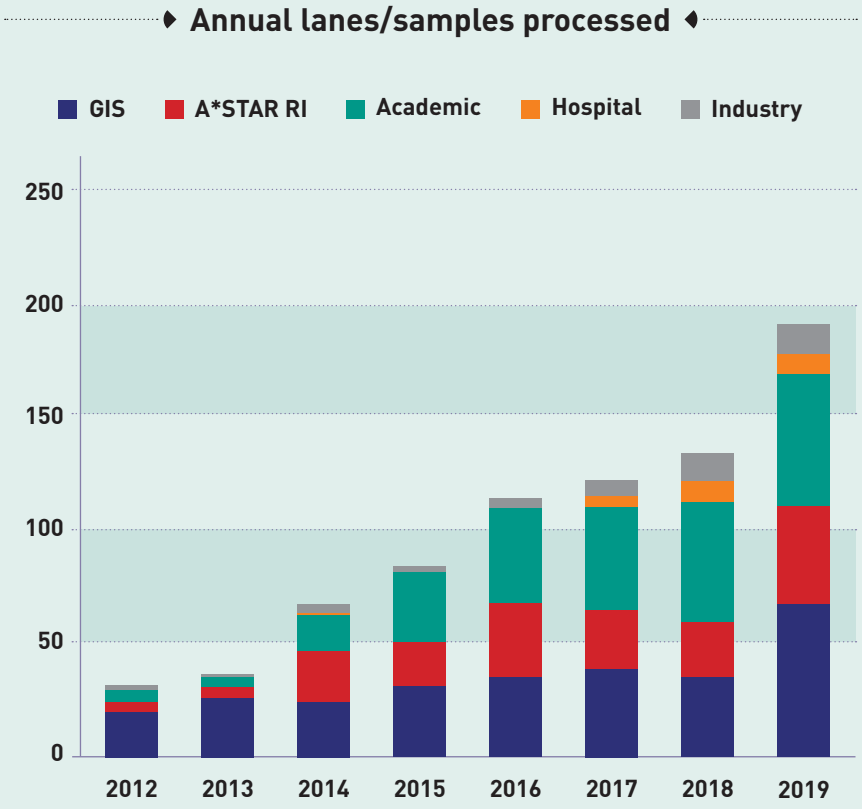


Figure 1, above. *Number of sequencing lanes grouped by users from 2012 – 2018*

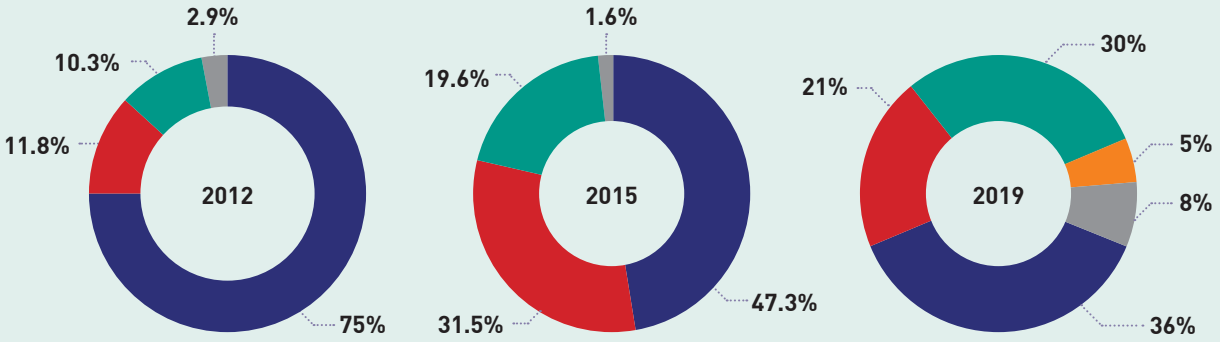


Figure 2, above. *Change in composition of platform user base from 2012 – 2018*

While the GIS sequencing platform has attracted an increasingly number of unique user groups over this period, the number of internal (GIS) users has remained relatively constant. This suggests that the sequencing platform has constantly expanded its services to the wider ecosystem of users—comprising A*STAR Research Institutes, universities, industry, and hospitals.

Existing Strengths and Opportunities

As one of the earliest adopters of high-throughput genotyping and next generation sequencing platforms in Singapore, GIS had the opportunity to test and optimise various sequencing library preparation methods together with a suite of increasingly sophisticated sequencers. This has allowed GIS to pioneer innovative methods that increase efficiency and reduce cost.

MGI's ultra-high-throughput sequencing system DNBSEQ-T7.

The GIS sequencing core has remained an internationally competitive platform that provides the following:

- Cutting-edge instrumentation and techniques available to all users

- Strong trust from users

- Cost-effectiveness and highest cost savings

- Successful delivery of project results to users and collaborators. Over the past five years, genome-wide genotyping has been completed by the platform on more than 100,000 unique samples throughput the world.

We have identified several opportunities for the sequencing platform, including:

- Contribution to the National Precision Medicine (NPM) Programme Phase II, for which the genome-wide profiling of >100,000 Singaporeans is planned. This as an opportunity for GIS to contribute >15 years' experience in genomic research to a new, large-scale national effort. GIS' overall experience in large data (knowledge of parameters, constraints, and requirements), sample handling to minimise errors, and other areas can be harnessed to establish protocols for smooth implementation for whole genome sequencing in the NPM.

- Our lead in adopting Oxford Nanopore long-read technology in Asia opens an opportunity for performing long-read sequencing on NPM projects to provide another dimension—whole genome structural variation—to this national resource. We also foresee a strong opportunity for the platform to be the regional service provider for Oxford Nanopore long-read technology.

- Closer collaboration with public and research institutions with potential needs for sequencing on a moderate to large scale (e.g., in disease research fields such as cancer and cardiovascular, neurological, and ophthalmological diseases, environmental pathogen sensing, and food security). These "demonstration projects" would be helpful in developing further trust between the parties and sharing the utility of genome sequencing in our daily lives.

- Strengths in partnership with commercial sequencing providers Macrogen Singapore and NovogeneAIT to provide cost-effective, commoditised high-throughput sequencing (e.g., 2x151-bp paired-end reads on HiSeq4000 and NovaSeq6000). This has resulted in a 60 percent reduction in sequencing cost over 2019.

SCIENTIFIC COMPUTING PLATFORM FOR GENOMICS

Scientific computing is the heartbeat of genomics. In order to integrate and analyse large and complex data sets and achieve a more complete systems-level understanding of biological processes and diseases, a robust scientific computing platform is necessary.

Demand Drivers and Opportunities for Scientific Computing

Scientific computing is an essential pillar for nearly all research programmes at GIS. These programmes rely on services provided by the scientific computing collective, ranging from petabytes of long-term data archiving to enabling population-scale joint variant calling. Reliable and robust scientific computing is critical for GIS to lead and participate in large research programmes and collaborations.

To become the custodian for Singapore's genomic data, GIS will acquire new capabilities (e.g., secure, standards-compliant data sharing at scale) to drive GIS scientific computing towards a best-in-class platform in Singapore and beyond.

Additionally, the GIS scientific computing platform has acquired experience and skills that are unique in Singapore. The platform is arguably the only local entity capable of supporting genomics research and analysis on a petabyte scale.

The GIS scientific platform has the potential to partner with industry, specifically hyper-scalers and solution providers. We foresee synergistic outcomes for both GIS and potential industry partners through joint-development initiatives.

The GIS scientific computing platform is composed of three teams. The first team manages high performance computing and functions as the system administrator for the GIS computing cluster and the petabyte-scale storage of data. The second team is responsible for applications. This DevOps team is responsible for in-house systems such as NGS LIMS (ELM) and our scientific data archive. Currently, the applications team is building cloud compatibility and capabilities for GIS. The third team builds and maintains various bioinformatics pipelines. In addition, the team assists in research projects requiring common secondary analysis (e.g., variant calling).

The scientific computing platform started as independent teams with distinct functions. As GIS' demand for storage and computing grew, the platform evolved into an integrated entity covering these three areas of operations to meet GIS' scientific computing needs. We are constantly developing ways to provide more integrated approaches for meeting these needs.

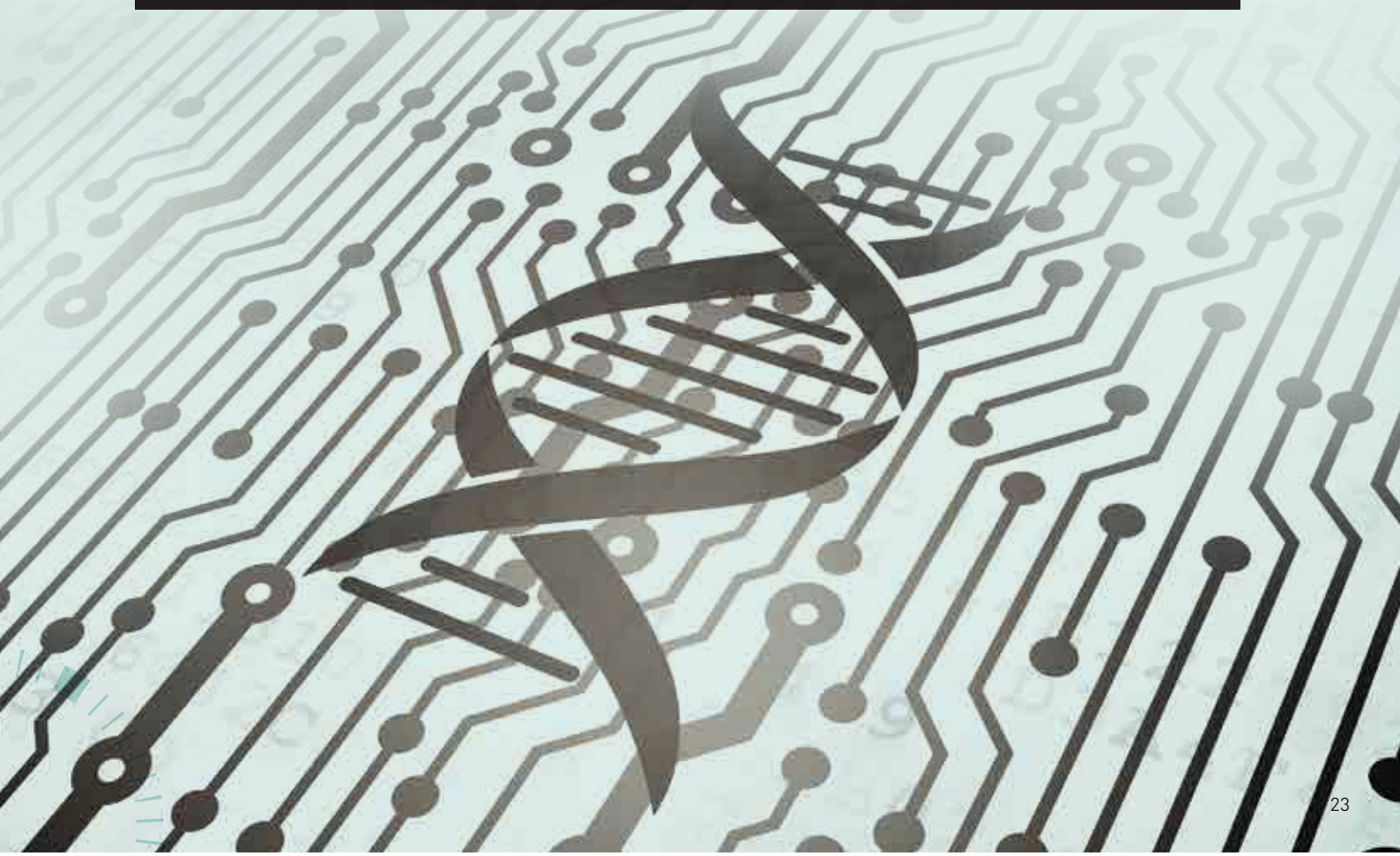
In order to deal with large-scale data generated by research programmes and collaborations at GIS, we also utilise infrastructure at A*STAR Computational Resource Centre (A*CRC) as well as the National Supercomputing Centre and cloud computing. Through the infrastructure built by the scientific computing platform, groups at GIS have contributed to national and international consortia, generating new insights into the role of the genome in human diseases.

Amazon Web Services (AWS) and nf-core

Keeping pace with advances in sequencing technology and analysis algorithms, GIS has also been an early adopter of computational technology. In the past five years, GIS has led the adoption and implementation of cloud-based computing for genomics, in partnership with AWS. As early adoption of sequencing technologies by GIS has led to the spread of genomics throughout the entire Singaporean biomedical ecosystem, GIS is now similarly spreading its early expertise with cloud computing to the rest of the research and scientific community. Examples of these efforts include a genomics-focused cloud training course, co-developed with AWS, to help existing genomics researchers transition to the lower cost, higher scale, and strengthened security offered by cloud computing. As genomics and data analytics grow in the research community, GIS will continue to share its computational expertise through similar outreach and training efforts such as these.

GIS is also using its cloud expertise to drive innovation and improvements in genomics pipelines. Cloud-native serverless computing was first introduced by Amazon web services (AWS) in 2017. GIS co-developed a variant calling pipeline with AWS to demonstrate how this technology can be applied to genomics. This development allows genomics scientists to store data, reduce human error, and enable more efficient applications. The collaboration led to a feature on the AWS website and keynote presentations at the AWS summit in 2018.

In a parallel effort to streamline genomic data analysis, GIS collaborated with SciLifeLab to develop nf-core, a repository of community-curated pipelines to eliminate the need to re-implement well-known genomic data analysis pipelines. This collaboration was featured in *Nature Biotechnology*.



FEATURE

INFECTIOUS DISEASE RESEARCH AT GIS

Susceptibility to infectious diseases may involve genetic variations that are discernible through genomic interrogation. However, there is a second dimension of complexity—a "second genome" originating from the pathogen. Again, the fundamental theme that genetic differences are reflected in phenotypic variability applies. Studying pathogens in infectious diseases presents additional challenges, because the medically important pathogenic species are far more diverse than the human hosts they infect. Furthermore, the differences between the pathogens may span the entirety of the diversity of life. This makes infectious disease a natural fit in the Genome Architecture and Design domain at GIS, where the theme of "Any Genome, Any Analysis, Any Scale" is of paramount importance for studying pathogen behaviour.

Functional genomic approaches also have great utility in infectious disease research. Many of the high-throughput technologies currently in use (even in human systems) today were originally pioneered in or originated from microbial systems, due to inherent advantages in these systems for genetic manipulation and technology. These technologies include the use of large-scale mutagenesis and screening (including with transposons), comparative genomics and comparative functional genomics, and CRISPR-based technologies. More recently, single-cell genomics provides a new horizon for simultaneously exploring host and pathogen gene expression, overlaying a dynamic interaction layer onto the genetic susceptibility mentioned above.

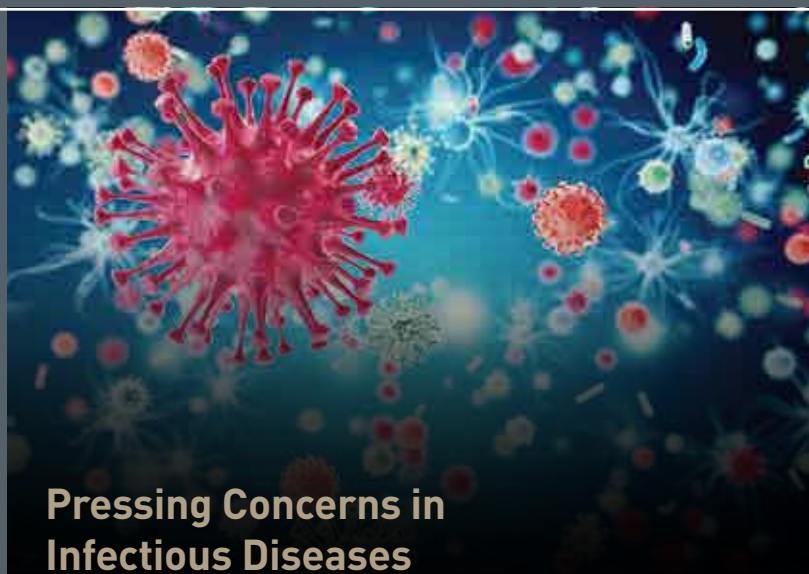
Importance of Infectious Disease Research at GIS

Singapore has experienced several significant infectious disease outbreaks since the founding of GIS, including SARS, H1N1, Group B Streptococcus, Zika, and, most recently, COVID-19. Infectious disease research is therefore a pillar of Singapore's health and biomedical sciences strategy. GIS has played a key role in providing genomic expertise in combating all of these outbreaks. Importantly, genomics is now the gold standard technique for outbreak detection and tracking. Further research into infectious disease genomics is important for preparing Singapore, and the world, for the next inevitable outbreak. The universal applicability across all organisms and disciplines means that genomics also expands beyond human health into food safety and environmental monitoring, especially water.

Highlights of Infectious Disease Research at GIS

At GIS, we have active research programmes in outbreak detection and analysis. The programmes focus on diseases of national and regional importance, but they also provide a general platform that is applicable to the study of nearly any pathogen. This research traces its lineage to the early role of GIS in the SARS pandemic in 2003, which was followed by many years of collaborative work to combat the Dengue virus. Recent highlights of GIS' infectious disease research include collaborative studies to investigate local hospital outbreaks, the Zika virus outbreak, and the yusheng-associated Group B Streptococcus outbreak.

GIS houses some of the few molecular pathogenesis labs in Singapore that use modern functional genomic approaches for bacterial research, integrating genomics with *in vitro* and *in vivo* infection models. One unique aspect of GIS' work on infectious diseases is the ability to co-ordinately develop matched experimental and computational methods to enable the simultaneous analysis of host and pathogen gene expression during *in vivo* infections. This research portfolio covers not only molecular mechanisms of host-pathogen interactions but also antibiotic resistance, the other existential threat (besides pandemics) to modern healthcare systems and society.



Pressing Concerns in Infectious Diseases

Two pressing concerns related to infectious diseases are pandemic risk and antibiotic resistance. The former has been acutely demonstrated by the COVID-19 pandemic, which has rocked the entire world within a matter of months. Earlier, faster, and more widespread genomics capabilities are among the clear key upgrades that the global community requires to mitigate the threat of current and future pandemics and outbreaks. The current outbreak detection and analysis research efforts at GIS are well positioned to dovetail with continued decreases in genome sequencing costs. A key effort will be increased automation and scale that would allow other government agencies within Singapore (such as MOH, SFA, and NParks) to leverage these capabilities.

The threat of antibiotic resistance is a broad cross-industry and all-of-society issue. Key economic, social, and policy tools will be required to reach a solution. Genomics in infectious disease research may contribute to the traditional path of new drug discovery or provide alternative new strategies to turn the tide against antibiotic resistance. This broad problem requires both approaches, and no single institution will be able to pursue all of the efforts required. GIS' infectious disease research portfolio maintains capabilities that contribute to the overall national and global effort, addressing both needs for new anti-infective therapeutics and alternative strategies to reduce antibiotic resistance rates using evolutionary and synthetic biology technologies.

FEATURE

OPERATION STRONGHOLD – GIS' RESPONSE TO THE COVID-19 PANDEMIC

On April 7th 2020, A*STAR was approached by the Ministry of Health for assistance in setting up a large-scale COVID-19 testing facility, as an integral component of an overall national strategy to boost the nation's testing capacity for COVID.

Increasing the nation's testing capacity was deemed, at the very highest levels of the Singapore government, as an essential step in returning the country to economic and social normalcy, as this would enable hospital diagnostic facilities to return to regular clinical testing (for other conditions), facilitate repeated rostered testing, allow screening of high-risk populations, and open up international travel.

In response to this urgent request, A*STAR tasked the GIS to lead Operation Stronghold, an all-of-A*STAR effort to build the Stronghold Diagnostics Labs (SDLs). Leveraging on its prior expertise in clinical grade diagnostic assays through efforts such as POLARIS, high-throughput genomics, and data informatics, >150 staff from GIS worked with >100 counterparts from other A*STAR research institutes (DxDHub, ARTC/Simtech) and strategic partners NUHS and Temasek Holdings to set up the SDL labs. Accomplishing in three

months what would have normally taken nine, the GIS team rapidly established a pilot scale clinical-grade laboratory (SDL@GIS) to develop clinical workflows for the main facility, testing and optimising new equipment, and developing training programmes for SDL staffers to work under a rigorous personal protective equipment (PPE) environment and standard operating protocols to ensure testing operations in a safe and accurate manner.

The GIS team also spearheaded the construction and outfitting of the main 2000 m^2 SDL facility (SDL@Nanos, assisted by teams from the BTI), developed the backend informatics to track samples through the sample workflow and reporting of results directly to national electronic medical records, and worked with colleagues from SERC (ARTC/Simtch) to develop novel robotic and automation solution to process thousands of samples. Through this effort, SDL@GIS and SDL@Nanos were able to 'go-live' to receive clinical samples from May and July 2020 respectively. After a further three months and having successfully achieved its primary mission, management of the SDL labs were handed over from GIS to a separate A*STAR team in Oct 2020.

GENOMIC DOMAINS

GIS is the trusted producer, custodian, and curator of Singapore's genomic data. We leverage core capabilities in high quality sequencing and large-scale genome informatics, applied through four nucleic acid domains, to achieve impact for A*STAR, Singapore, and the world.

RESEARCH FOCUSED ON FOUR KEY NUCLEIC ACID DOMAINS

- Precision Medicine and Population Genomics
- Epigenetic and Epitranscriptomic Regulation
- Spatial and Single-cell Systems
- Genome Architecture and Design

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PRECISION MEDICINE AND POPULATION GENOMICS

- Introduction to Precision Medicine and Population Genomics
- Demand Drivers in Precision Medicine and Population Genomics
- Existing Strengths and Opportunities

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EPIGENETIC AND EPITRANSCRIPTOMIC REGULATION

- Introduction to Epigenetics and Epitranscriptomics
- Demand Drivers in Epigenetics and Epitranscriptomics
- Exciting Strengths and Opportunities

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SPATIAL AND SINGLE-CELL SYSTEMS

- Introduction to Spatial and Single-Cell Omics
- Demand Drivers in Single-Cell Systems
- Demand Drivers in Spatial Omics
- Existing Strengths and Opportunities

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GENOME ARCHITECTURE AND DESIGN

- Introduction to Genome Architecture and Design
- Demand Drivers in Genome Architecture and Design
- Existing Strengths and Opportunities

PRECISION MEDICINE AND POPULATION GENOMICS

Reflecting the global interest in precision medicine, many countries have embarked on national-scale precision medicine (PM) initiatives, and several of these are in various stages of development and implementation. With four billion inhabitants, Asia is home to the largest population in aggregate in the world. However, in contrast to European efforts, there is a current lack of Asian genotypic data in public databases. The current lack of large-scale control databases of Asia-specific genetic variation linked to clinical phenotypes is a major barrier to precision medicine in Asia, because these databases are essential to avoid misdiagnosis and overtreatment due to the mistaken identification of pathogenic variants. With the significant presence of three major Asian ethnic groups (Chinese, Indians, and Malays), there is thus a unique opportunity for Singapore, despite its small size, to contribute to global efforts in PM and complement other large-scale efforts. Insights gained from Singapore may also result in products and services that can be applied to health systems in larger Asian countries.

Singapore's three major ethnic groups – Indian, Chinese, and Malay. The above artwork was featured on the cover of Cell, volume 179, issue 3, 17 October 2019.

(Illustration by Gloria Fuentes - The Visual Thinker LLP)

Singapore also has additional strengths that make the nation competitive in PM. These include strong institutional capabilities in genomics, engineering, and analytics, which can be readily leveraged to implement PM; the nation's reputation as a trusted location for data security and standards; and the use of a unique national identifier (NRIC) that facilitates the integration of healthcare and research datasets across different public healthcare systems. Singapore has an advanced healthcare system with highly trained, globally experienced clinicians, which will allow the adoption of innovations, and Singapore has a rich 20-year ecosystem of biomedical research and national platforms for extending initial discoveries made by PM into therapeutics and diagnostic assays.

Demand Drivers in Precision Medicine and Population Genomics

Singapore's healthcare expenditure is growing, driven by increasing healthcare pressures of an ageing population, longer life expectancies, an increasing chronic disease burden, and the increasing costs of novel therapies. Public healthcare expenditure in 2030 is projected to increase 3.7x from 2015—an unsustainable rise that will require Singapore healthcare to embrace innovative approaches with the potential to transform delivery while containing costs. Initial health economic analysis, both locally and globally, suggests that PM has the potential to transform healthcare at different points of patient care.These include:

- Reducing the burden of late-stage chronic disease through targeted prevention and health promotion at a time when the disease process is reversible.

- Avoiding complications in individuals at risk of serious adverse drug reactions.

- Mitigating the rising costs of expensive new therapies and treatments by identifying patient groups that would benefit most from such treatments.

- Accelerating the definitive diagnosis of patients with serious genetic disease, thereby reducing diagnostic testing and treatment costs.

From the industry perspective, many companies are also actively investing in PM programmes, because these data are invaluable for

- Identifying and validating new targets.
- Accelerating drug development ("quick win, fast fail")
- Identifying patient populations that may best respond to their drugs.

It has been established that drugs for which target validation is supported by human genetics are two times more likely to be successful. The existence of a large-scale PM effort could also catalyse a local public-private hybrid model for population-level genomic sequencing, allowing local companies to tap into base-load demand to build enabling infrastructure and train people to compete for new business. In the informatics sector, the global bioinformatics market is projected to reach US$13 billion by the end of 2025, and it is now recognised by major industry players that data analytics will transform healthcare and wellness. Big data initiatives are also driving new applications of AI in healthcare. Importantly, standards have yet to be set in this space, and different companies can generate different clinical results from the same genomic data, thus creating first-mover opportunities for Singapore to establish "best-of-class" platforms for Asia due to its access to Asian data.

*The team of researchers and clinician-scientists from A*STAR's Genome Institute of Singapore (GIS), Singapore Immunology Network (SIgN), National Cancer Centre Singapore (NCCS), and KK Women's and Children's Hospital (KKH), that identified a pivotal "fetal-like" reprogramming of the tumour ecosystem in human hepatocellular carcinoma (HCC). The research findings were published in the scientific journal Cell, under the title, "Onco-fetal reprogramming of endothelial cells drives immunosuppressive macrophages in Hepatocellular Carcinoma". From left: Dr Florent Ginhoux (SIgN), Prof Jerry Chan (KKH), Prof Pierce Chow (NCCS), Dr Ramanuj DasGupta (GIS), and Dr Ankur Sharma (GIS).*

Existing Strengths and Opportunities

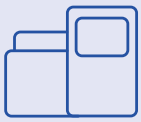
Since its founding in 2000, precision medicine and population genomics have formed a core disease focus of GIS, as exemplified by several genetics labs within GIS and associated external labs.

The key strengths identified are as follows:

- **Human genetics**
  GIS has a strong track record of publications describing the genetic architecture of various disease traits, with a particular focus on conditions of Asian prevalence. These include the identification of genetic variants associated with severe drug reactions, genes related to eye and other neurological conditions, and immunological diseases. GIS is also involved in several large-scale international human genetics consortia, such as global partnerships investigating type 2 diabetes, chronic kidney disease, and breast cancer. GIS is also the home base for the Asian consortia for Parkinson's disease, schizophrenia, and glaucoma.

- **Rare genetic disease and clinical diagnostics**
  Working closely with clinical partners, GIS has participated in the use of genomic sequencing to accelerate the diagnosis of children with rare undiagnosed genetic diseases. To date, >100 children have been successfully diagnosed through these efforts. GIS, through its POLARIS programme, has also contributed efforts towards the translation of these genomic sequencing assays into clinical-grade diagnostic applications for mainstream healthcare implementation.

- **Precision Oncology**
  Oncology has been a major focus area of PM. GIS has many strengths in the oncology space, including the identification of genetic variants linked to cancer susceptibility; expertise in the biological understanding of several Asian-endemic cancers, including lung, liver, and gastric cancers; and leadership in national consortia for clinically annotated longitudinal profiling of cancer patients (liquid biopsies). GIS also has experience in "n-of-1" studies in which cancer patient responses are modelled using organoid platforms.



- **Genomic platforms**
  GIS has developed and maintained core platforms for performing genotyping and sequencing studies at scale, having been heavily involved in almost all large-scale academic biomedical studies to date. GIS, working in public-private partnership with local sequencing providers, has also opened its sequencing platform to other members of the Singapore biomedical community to democratise access to these foundational technologies.

- **Asian population genomics**
  GIS has spearheaded the creation of the largest collection of Asian whole-genome sequencing data, comprising the three major Singapore ethnic groups. Including nearly 10,000 individuals, comparison of this Singapore database to Western population databases revealed the presence of millions of novel genetic variants. The availability of these reference databases forms a foundation for Asian PM.

In the GIS 2030 roadmap, the Precision Medicine and Population Genomics domain will strive to build on these historical strengths and to extend its efforts in novel directions that could more directly impact patient care. Domain activities will include strengthening our leadership role in specific disease areas where GIS has advantages due to its close proximity to leading clinicians and disease centres, and GIS will continue to participate in and provide leadership for international consortia.

Core bioinformatics platforms will also be strengthened to enable the storage, maintenance, and reuse of large-scale databases to fulfil the institute's aspiration to function as a trusted custodian of Singapore's genomic data. Specifically, the domain aims to develop new competencies in the analysis of population genomic data, such as:

- Testing and validation of polygenic risk scores,
- Integration of genetic variation data with other digital phenotypes such as electronic health records and wearables,
- Use of AI and machine learning to improve gene-discovery efforts,
- Exploration of new types of genetic variation such as copy number variation and structural variants, and
- Integrated interrogation of germline and somatic mutations through high-throughput functional assays (e.g., allelic series and saturation mutagenesis) to discern pathogenic from benign variants and to identify within-spectrum variants resulting in altered function.

EPIGENETIC AND EPITRANSCRIPTOMIC REGULATION

Organisms, including humans, have the ability to genetically "remember" events that have occurred in the past, such as famine, and this memory can shape organismal behaviour many generations down the road. This memory is predominately encoded not in our DNA sequence but rather in the histone modifications that coat our DNA. Collectively, DNA and histone modifications make up our epigenome, information encoded beyond the DNA sequence. In addition to DNA and proteins, RNA molecules can also be modified after they are transcribed to regulate gene expression. This collection of RNA modifications forms our epitranscriptome.

Both epigenetic and epitranscriptomic modifications play broad roles in human health. Epigenetic modifications can be altered by nutrition, maternal health, carcinogens, and other exposures to establish cellular memory. Because of their dysregulation in diseases, epigenetic readers, writers, and erasers are potential drug targets in personalised medicine. The National Institutes of Health in the United States has funded two large programmes, ENCODE and the Epigenetics roadmap project, to map epigenetic markers in different cell lines and tissues in the human body. While this deepens our understanding of the distribution and dynamics of epigenetics markers in different cells, how epigenetic marks are regulated in large human cohorts, especially in Asian populations, remains to be studied.

In contrast to epigenetics, in which many histone marks and their associated enzymes have already been identified, the field of epitranscriptomics is fairly nascent. To date, more than 150 RNA modifications have been found. However, the diversity, distribution, prevalence, and functions of these modifications in mRNA remain far from clear. RNA modifications have been associated with different types of cancer, neurological diseases, metabolic diseases, cardiomyopathies, and immunological diseases. Foundational technologies are also continuously being built to study their distribution in human cells and to understand the interplay of genetics, epigenetics, and epitranscriptomics in human health.

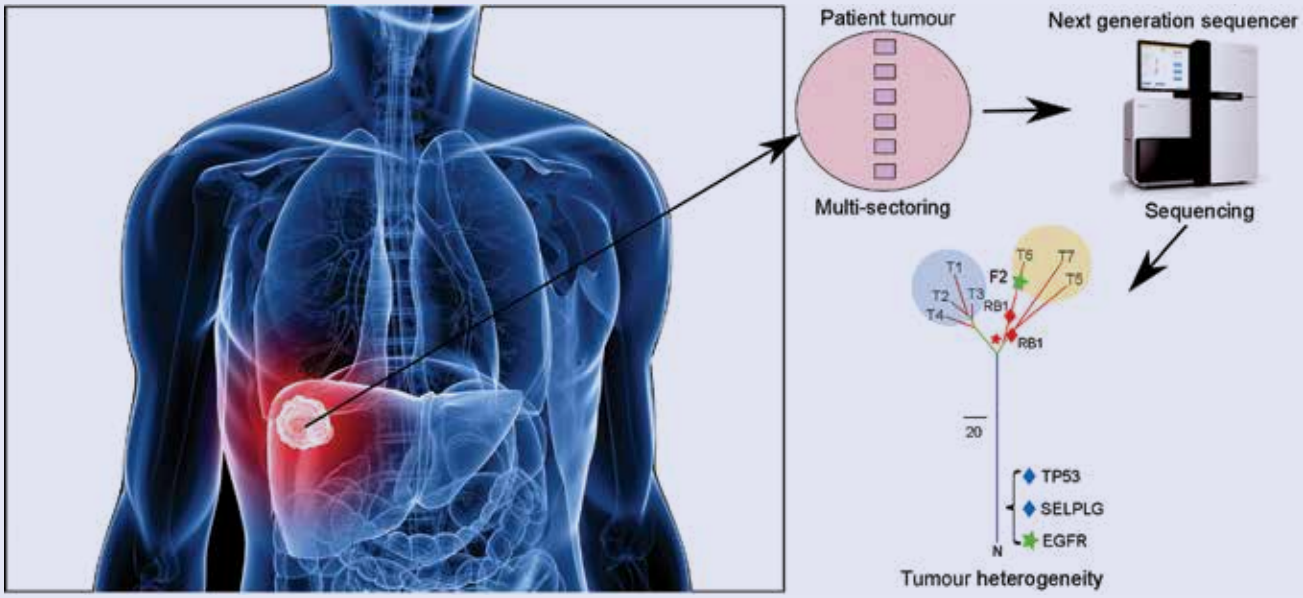
Colourful structural landscapes of transcriptomes in human cells – designed by Dr WAN Yue.

Demand Drivers in Epigenetics and Epitranscriptomics

Singapore, like many other developed countries, has an increasingly ageing population. Because epigenetic and transcriptomic dysregulation frequently underpin diseases such as cancer that increase in incidence with age, epigenetic and epitranscriptomic diseases are likely to become even more important to the Singaporean society in the years ahead. Unlike the DNA sequence, which is much less amenable to changes, epigenetic and epitranscriptomic markers are reversible. The dynamic nature of these markers, together with interpersonal variation and dysregulation in disease, raises the possibility that they might be good drug targets. Unlike genetics, which requires gene editing procedures and may cause consequent germline changes that could affect subsequent generations, epigenetic elements can be modified using conventional chemical or molecular entities. Only somatic cells of interest in the single individual are targeted, which makes epigenetic therapies an overarching, wide-ranging option for exciting and promising alternatives for disease treatment. This promise is reflected by the amount of growth in the Epigenetics Drugs and Diagnostic Technologies Market, which is estimated to exceed US$16.5 billion by 2024 at a CAGR of 19.4 percent. An increase in an ageing world population coupled with the reduced cost of DNA sequencing is boosting the demand for epigenetic technologies. GIS (and Singapore as a whole) is well positioned to tap into the huge Asia-pacific region to integrate genomic, epigenomic, and epitranscriptomic information for precision medicine.

Although epitranscriptomics is a comparatively new field, the dysregulation of RNA epigenetic markers has been identified in diseases, making these markers good drug targets. US$1 billion has been raised for targeting RNA using small molecules since 2017 with a high CAGR of 28.4 percent, indicating its

From left: Prof Liu Jianjun (Deputy Executive Director of GIS), Prof Patrick Tan (Executive Director of GIS), and Prof Cheng Ching-Yu (Principal Clinician Scientist and Head, Ocular Epidemiology Research Group and Data Science Unit, Singapore Eye Research Institute). The photo was taken during the media briefing on the Cell's "Large-scale whole genome sequencing of three diverse Asian populations in Singapore" research paper. GIS' Cell research paper.



By sequencing cancer cells from different parts of the tumour, researchers can profile and understand the level of tumour heterogeneity across liver cancer patients.

large potential and promise for growth. Because the field is nascent, many opportunities exist to discover fundamental principles of RNA and their roles in diseases. These opportunities include the development of new detection methods to determine the distribution and prevalence of RNA modifications in cell lines and primary tissues; the discovery of readers, writers, and erasers using genetic screens; and the identification of epitranscriptomic markers in human populations and diseases to reveal disease-associated markers. Research in these areas will lead to the identification of biomarkers and the development of drug candidates, enabling epitranscriptomics to become an integral part of personalised medicine in Singapore and across the world. Epigenetic and epitranscriptomic marks can influence gene regulation uniquely in diverse human populations, and thus the racial diversity of Singapore enables a deeper understanding of how combinations of epigenetic/transcriptomic markers may create different propensities toward disease, strengthening the value of personalised medicine in Singapore.

In addition to therapeutics, the research industry is also a large demand driver for epigenetics and epitranscriptomics; the development of new methods and reagents will serve a large global market to study epigenetics and epitranscriptomics across diverse organisms and cellular systems.

Existing Strengths and Opportunities

GIS is a powerhouse of bioinformatics and big data with well-established genomics technology platforms and accompanying expertise. The institute was also one of the first to perform genome-wide CHIP experiments to study epigenetics in mouse and human stem cells. In addition, GIS is also one of the first institutes in the world to develop a methodology to map higher-order chromatin conformation (ChIA-PET), transforming our understanding of how chromatin architecture regulates gene expression. GIS researchers have also developed numerous new computational algorithms, including Graphmap and LoFreq, to enable the analysis of large-scale data. Beyond data generation, GIS is also proficient in our ability to study the functional consequences of epigenetics in disease models such as cancer and cardiac diseases, further broadening our understanding of the cellular functions of these modifications. This combination of new methodologies, analytical capabilities, and the ability to interrogate biology in GIS enables us to generate novel and deep insights into the role of epigenetics and epitranscriptomics in human health. Because GIS also has strong collaborations with hospitals and clinicians, we are in a prime position to transfer our understanding of epigenetics and epitranscriptomics into the clinic.

One of the major technological advancements in recent years is the development of the third-generation Oxford nanopore sequencing. Nanopore sequencing allows the direct sequencing of natural DNA and RNA sequences without the need for amplification or cDNA conversion, which enables the direct identification of RNA and DNA modifications. GIS is an early adopter of nanopore sequencing in Asia, giving us a technological advantage for making significant

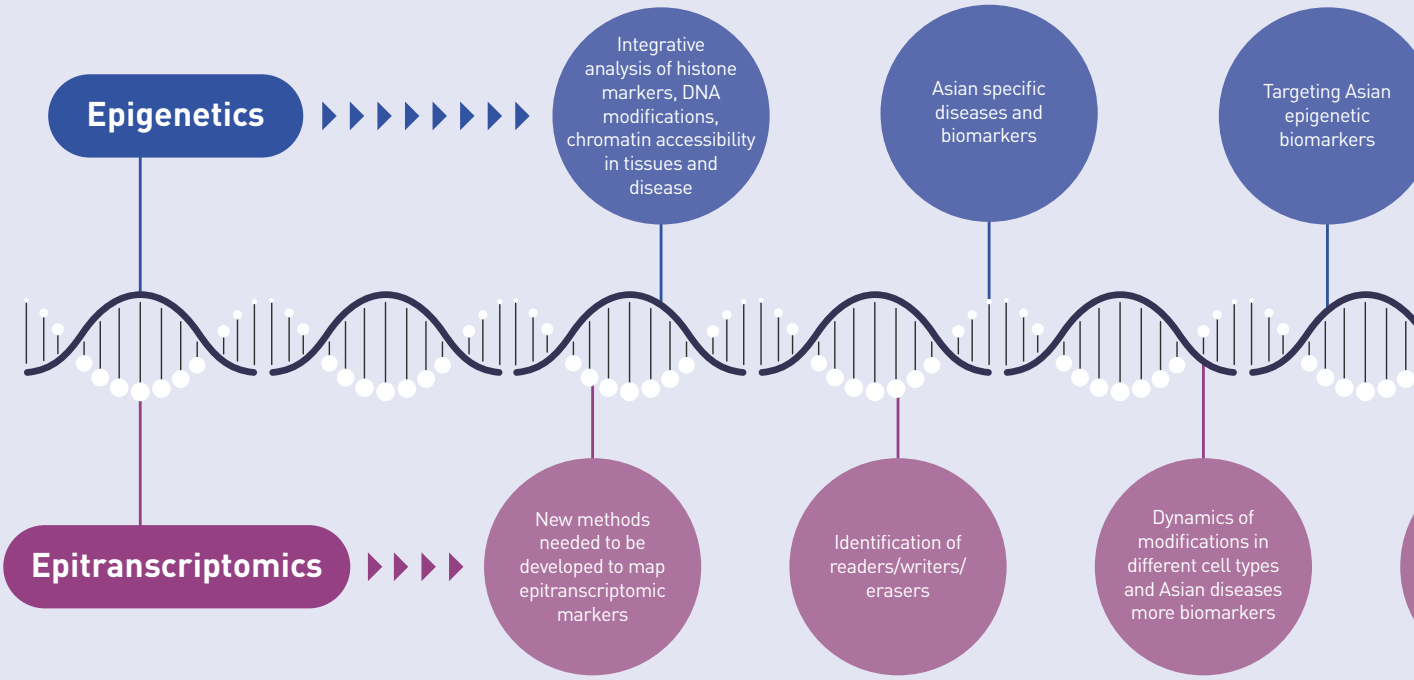
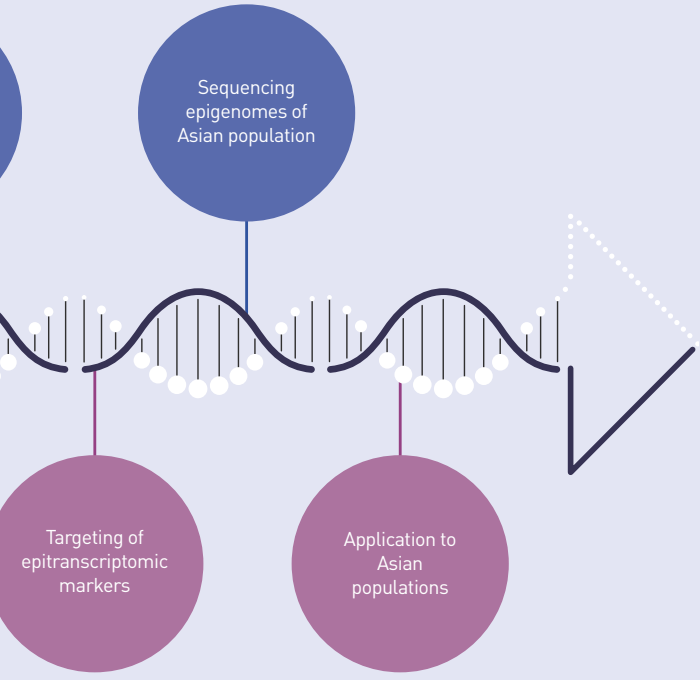


Figure 1 top. Opportunities for epigenetics and epitranscriptomics research at GIS in the next 10 years.

developments and scientific discoveries. Several groups in GIS are developing experimental and analytical strategies to improve our ability to map, assemble, and identify DNA and RNA modifications through signal perturbations across the pore. Furthermore, the ability of nanopore sequencing to perform long-read sequencing enables the phasing of different modifications along an RNA/DNA molecule, allowing us to decipher an epigenetic/epitranscriptomic code that could impact gene regulation at a single-molecule level.

In the GIS 2030 roadmap, the Epigenetics and Epitranscriptomic Regulation domain will focus our efforts on

- Developing new high-throughput methodologies to study various aspects of DNA and RNA modifications and engaging industry to spin off the new technologies.
- Applying new and existing technologies to map epitranscriptomic marks in various Asian-specific cell lines.
- Finding readers, writers, and erasers for new epitranscriptomic marks
- Applying new and existing technologies to map epigenetic marks in the larger population and patient cohorts to generate personalised epigenomes and epitranscriptomes.
- Developing computational strategies to integrate various epigenetic and epitranscriptomic markers to decipher epigenetic codes and their phenotypes in Asian populations.
- Identifying new epigenetic and epitranscriptomic biomarkers in Asian diseases.
- Working with the Experimental Drug Development Centre to identify compounds to target disease-associated RNA markers as new therapeutics.



These are portable DNA sequencing devices created by Oxford Nanopore Technologies, called MinION.

SPATIAL AND SINGLE-CELL SYSTEMS

Single-cell omics technologies have revolutionised biology and recently become the default choice for characterising the states of biological samples in depth and inferring their behaviour. This trend is aided by the availability of plug-and-play equipment and well-validated protocols for diverse single-cell assays, including DNA sequencing (whole genome, exome, targeted), RNA sequencing (scRNA-seq), simultaneous profiling of RNA and cell surface epitopes (CITE-seq), chromatin accessibility (scATAC-seq), simultaneous scRNA-seq and scATACseq on the same cells, ChIP-seq (sc-CUT&Run, scCUT&Tag), methylome sequencing, chromatin conformation (scHi-C), simultaneous CRISPR-based DNA and RNA modification and transcriptome profiling (Perturb-seq), and more. The field of single-cell omics also includes a diverse array of specialised algorithms and data analysis pipelines, many of which are now in a mature state. However, data analysis expertise remains in short supply, and another ongoing challenge is the massive and exponentially growing data volume.

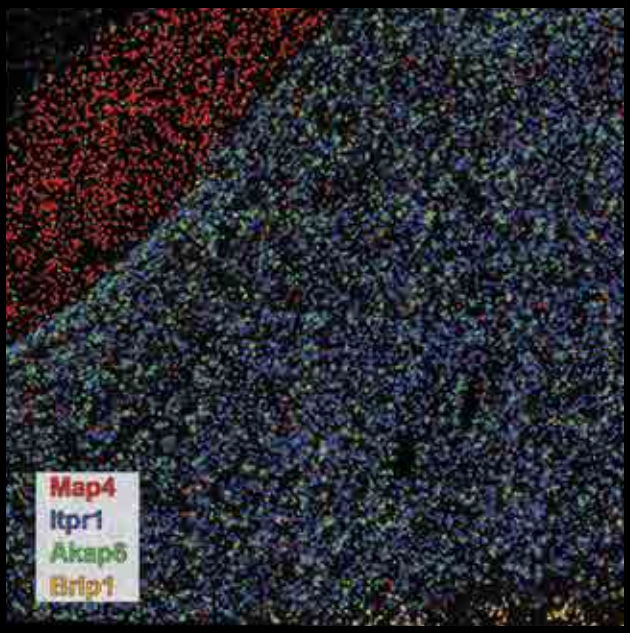
One major limitation of these single-cell technologies is that they are based on cells that have been disaggregated and

then lysed. Spatial information inherent in the tissue architecture or in subcellular organisation is thus lost. To better understand the behaviour, interactions, and functions of cells and tissues, we need to characterise nucleic acids without destroying their native physical structure. In addition to the loss of spatial information, single-cell omics techniques are limited by the fact that tissue dissociation and downstream processing steps tend to alter cellular states. Similarly, cell doublets and debris can generate artefacts that are hard to compensate for. Lastly, genes expressed at low levels are difficult to detect due to the low sensitivity of current single-cell omics approaches.

Spatial omics (SO) promises to overcome these limitations of "traditional" single-cell omics assays, transforming studies in cell and tissue biology with the potential to directly disrupt the pathology market. SO technologies such as array-based spatial RNA-seq, in situ sequencing, spatial sampling, and multiplexed FISH are able to characterise cells (DNA, RNA, morphology) in their native tissue context. These methods define cell types and states in relation to the functional architecture of tissues, identify cell-cell signalling interactions, reveal differentiation trajectories, and correlate genotype and chromosomal architecture to phenotype. SO can also explore subcellular spatial patterns of organisation, molecular correlates of cell morphology, and single-cell responses to external perturbations, and will ultimately help in developing new diagnostics and discovering new disease mechanisms and druggable pathways.

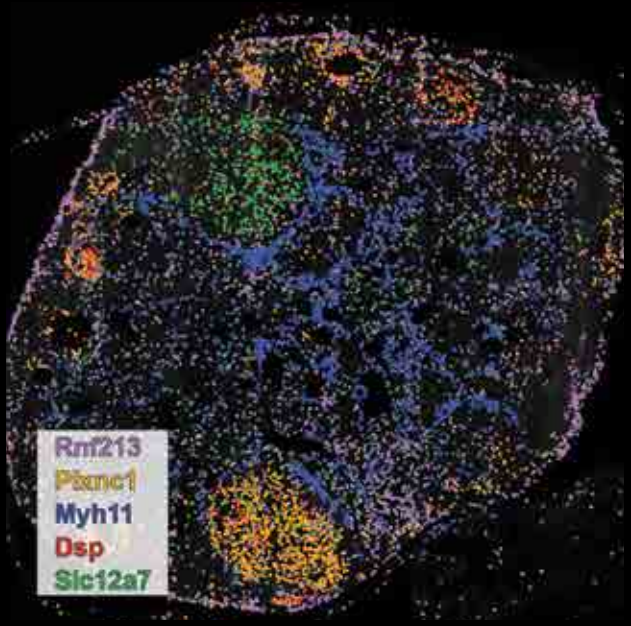
Gene expression maps of various mouse tissues. Individual RNA molecules of selected genes are depicted as coloured dots. Split-FISH analysis on multiple mouse organs revealed diverse and previously unknown localisation patterns for spatial regulation in mammalian tissues.

Brain

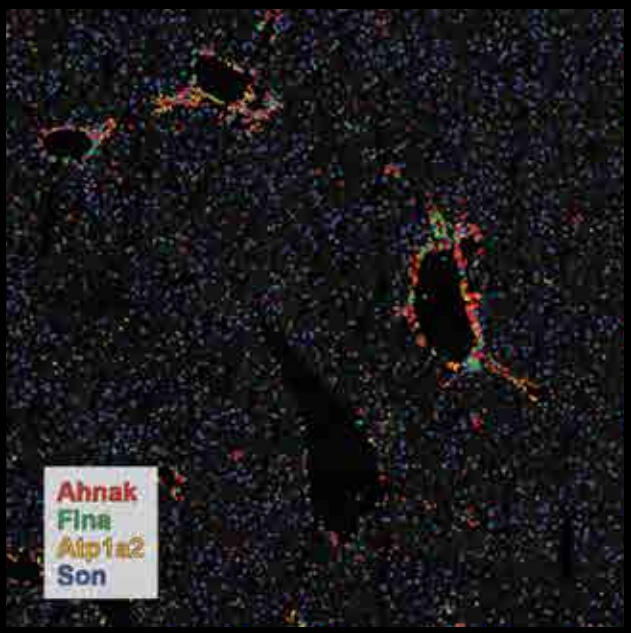


Kidney

Ovary



Liver



Demand Drivers in Single-Cell Systems

Uniform Manifold Approximation and Projection (UMAP plot showing transcriptome landscape of single immune cells.

Academic and Clinical Researchers

The prominence and success of a large number of studies based on single-cell omics has driven an exponential increase in interest among academic and clinical researchers. The international Human Cell Atlas (HCA) has added to this trend by organising the global single-cell community around foundational questions and data resources, thereby raising the profile of the field. Other driver consortia include the US NIH HuBMAP and Human Tumor Atlas programmes and various model organism atlases. We expect at least some of these atlasing programmes to have a long lifespan because they follow the model ENCODE has successfully used for nearly two decades. Simultaneously, programmes and bottom-up projects focused on specific disease areas are also expanding as the field becomes increasingly democratised. Lastly, *in vitro* cell differentiation, reprogramming, and organoid profiling are emerging as major application areas for cell engineering and disease modelling applications.

Industry R&D

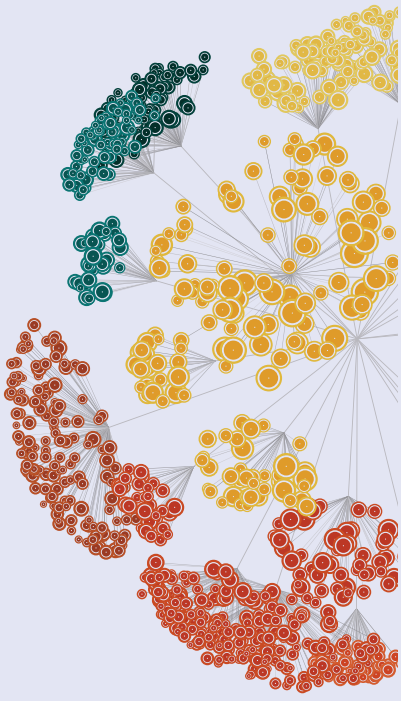
Big pharma has recently increased investments in single-cell omics and done so at scale with a major focus on cancer in addition to other disease areas. The objectives of these investments include biomarker discovery and companion diagnostics, drug response mechanisms, and the discovery of novel druggable pathways. In addition to analysis of *in vivo* samples, pharma may also drive demand for *in vitro* small- and large-molecule screens and mechanism-of-action studies powered by single-cell omics. The R&D divisions of other industry sectors such as food and nutrition, personal care, and toxicology are also likely to join the fray.

Biotech and IT Offerings

Biotech companies have from the outset been interested in the growth potential of products (equipment, reagents) and services in the single-cell omics space. This interest increases the ease of use and exerts downward pressure on prices, thereby increasing demand. Down the line, we anticipate commercial solutions for perturbation-based single-cell analysis, which will democratise lineage tracing and functional screens. We also expect sharp reductions in cost once commercial solutions are developed for microwell-based split-pool single-cell sequencing, which will further broaden the user base and attract researchers from developing countries. IT companies will drive further expansion with convenient, user-friendly solutions for single-cell data management and analysis.

Demand Drivers in Spatial Omics

Demand for SO today resembles that for single-cell omics in 2013, when Fluidigm launched the C1 instrument. As was the case for scRNA-seq in 2013, SO in 2020 is a niche area for a small number of specialists in genome technology and data analytics. Existing technologies have limited reliability with no clear winner, costs are high, algorithmic pipelines barely exist, the number of publications is low, and the value propositions are not widely appreciated. However, over the coming decade, SO will likely go through the same stages of technological improvement, cost reduction, algorithm development, application development, and democratisation as single-cell omics, perhaps at a faster pace because the latter has paved the way for the former.



- **Academic and Clinical Researchers**
  The neuroscience research community drove the initial surge of interest in SO, and now oncology, developmental biology, and other domains are following suit. Reiterating, the HCA, HuBMAP, and others are playing a key role in spurring demand by forming and funding consortia to develop and benchmark SO technologies. We expect cancer to be the largest application area going forward with a particular focus on immunotherapy mechanisms and markers. However, SO will eventually expand to every application area that currently uses single-cell omics.

- **Industry R&D**
  Big pharma is also keen to explore SO for studying the tumour microenvironment, identifying signalling interactions and druggable pathways, performing imaging-based drug screens that sensitively detect markers and cell morphology simultaneously, and establishing companion diagnostics and mechanism-of-action studies (including, but not limited to, immunotherapy).

- **Biotech and IT Offerings**
  There are multiple biotech firms with SO technology offerings, which is essential for driving demand for SO, because the vast majority of researchers do not have the means to implement published methods independently. Commercial solutions are available for both sequencing-based (including in situ sequencing) and hybridisation-based SO. Some of these technologies target specific gene panels, whereas others are unbiased. There is great demand for SO platforms that can process clinical samples, which tend to be formalin fixed and paraffin embedded, and some existing technologies already provide this feature. A significant challenge is that existing commercial *in situ* sequencing solutions have a very low detection sensitivity of 0.5 percent. Hybridisation-based SO methods are currently optimal in terms of detection sensitivity, the number of genes profiled, and spatial resolution. Commercialisation and the refinement of emerging technologies will greatly boost demand for SO.

Existing Strengths and Opportunities

Our major strength has been the ability to form multidisciplinary teams comprising clinician researchers, technologists, biologists, and data analysts. The GIS single-cell omics centre (SCOC) is a core facility that provides training and is another unique asset. Similarly, the GIS bioinformatics core and IT infrastructure have helped us cope with the large datasets generated by single-cell studies, although this is an area that needs further investment to continue to match demand. Finally, GIS is at the cutting edge of single-cell data analytics, having developed multiple innovative algorithms in this space.

Our prominence in international single-cell consortia is another source of strength; we have actively participated in and led HCA committees (Equity Panel, Genetic Diversity Network), obtained CZI HCA funding, and co-founded the HCA-Asia consortium, which is adding new members and expanding links with the Oz Single Cell consortium. GIS is the host institution for HCA-Asia's flagship Asian Immune Diversity Atlas (AIDA) programme. We have also formed a multinational single-cell cancer alliance with Samsung Genome Institute (Korea) and KU Leuven (Belgium), and the first resulting paper has been published (Lee H.O. et al., *Nature Genetics* 2020). Lastly, GIS hosted two major international single cell conferences in 2019: the first *Cell Press* single cell meeting and the third annual meeting of HCA-Asia.

In addition, GIS has a complete ecosystem for the development and application of SO, including clinical collaborations, proprietary multiplexed FISH technology, data analytics expertise, and cutting-edge model systems. GIS is at the forefront of revolutionary new SO technologies.

Official opening ceremony of GIS-Fluidigm Single-Cell Omics Centre on 12 April 2013.

In both single-cell omics and SO, GIS has led multiple RCAs with substantial investments from pharma and biotech industry partners. These partners have provided access to unique clinical cohorts and early-stage pre-commercial technologies to propel our science and value creation programmes.

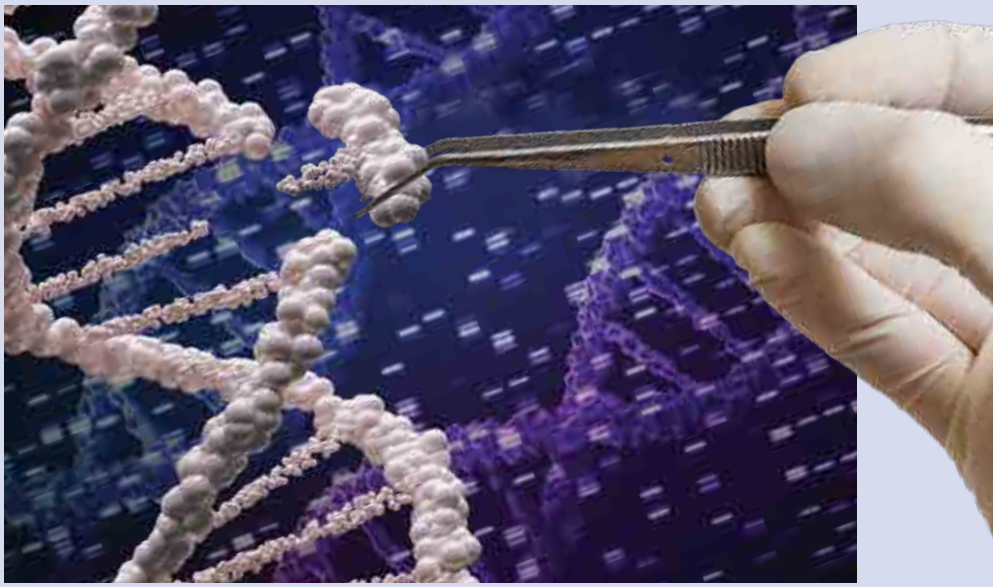
Moving forward, single-cell analysis of infectious diseases is a major opportunity, particularly in light of the COVID-19 pandemic. Single-cell omics represents the most comprehensive approach for characterising immune responses to an infection and thus opens new vistas for biomarker discovery, diagnostics development, and the identification of novel druggable pathways. In collaboration with clinical and immunology partners, we have already initiated single-cell analysis of a sizeable COVID-19 cohort. The capabilities and research facilities developed in the course of this project will also be applicable to other infectious diseases and thus support Singapore's national preparedness for future epidemics and pandemics.

Applications of single-cell omics to precision medicine represent another major opportunity, now that the technology has gained acceptance as a tool for cohort studies. In this space, we will focus on at least two major R&D programmes, one on metabolic disease in partnership with the National Precision Medicine Programme and another aimed at Precision Oncology in partnership with the National Cancer Centre, Singapore, and the Cancer Science Institute at NUS.

In the SO space, we intend to extend our advantage by developing and commercialising novel hybridisation based SO technologies, both independently and in collaboration with Biotech industry partners. We will also work with Pharma to apply these SO technologies to identify new markers, disease and drug response mechanisms, and targetable pathways for various cancers. Our ability to generate unique spatial datasets also creates the opportunity to lead in the field of SO algorithm development. The latter will be a major focus area as we expand and diversify our SO platform.

GENOME ARCHITECTURE AND DESIGN

The Genome Architecture and Design (GAD) domain encompasses two distinct yet complementary activities: reading DNA (Architecture) and writing DNA (Design). Both of these activities have grown exponentially in the past several decades with continuing advances in technology. This domain is unique in that it steps outside of the traditional realm of using genomics to understand life and health; GAD also captures our ability to create in genomics. Therefore, GAD projects onto a broad array of intellectual endeavours and areas of interest, such as infection outbreaks, synthetic biology, genome engineering, DNA storage, agrobiotechnology, and biodiversity studies.



From the architecture point of view, large plant/animal genomes and complex metagenomic communities have recently become routinely amenable to *de novo* whole-genome sequencing, which circumvents the biases and limitations of traditional reference-based analyses. As the vast majority of organisms lack high-quality references, this has led to a revolution in molecular biology studies in these organisms. Leveraging *de novo* analysis requires the agile combination of advances in long-read sequencing, assembly, and structural technologies (such as Hi-C) with sophisticated algorithms and high-performance computing platforms. GIS has significant capabilities and expertise in this area as well as collaborations with groups that actively leverage them in wide-ranging applications from biomedicine to food security and consumer care. As we develop the technologies to read genome architectures faster and more accurately, these technologies illuminate not only the biological implications behind vastly diverse genomes but also the paths towards engineering new genomes and correcting erroneous ones.

Turning to design, *de novo* DNA synthesis has been on a parallel track of exponential progress over the past several decades. More recently, targeted genome editing technologies have gained prominence, marked particularly by the ground-breaking development of CRISPR-Cas systems that enable efficient and sophisticated manipulation of DNA and RNA. The combination of CRISPR-Cas with various viral and non-viral delivery systems enables a resurgence in nucleic acid therapeutics (NATs), in which genome editing is conducted in cells and within the body. NATs hold enormous promise because they enable the direct insertion, deletion, or modification of DNA and RNA, bypassing the mechanisms of traditional small-molecule drugs that primarily interact with proteins and allowing the treatment of previously un-targetable diseases at their root causes. To realise the full potential of NATs and bring these innovations to bear on diseases relevant to Singapore, critical challenges include genome editing efficiency, specificity, delivery, and safety.

Demand Drivers in Genome Architecture and Design

The demand drivers for GAD span the full gamut of genome reading applications and writing technologies. The demand for *de novo* sequencing worldwide is rooted in the study and application of genome science, whereby we seek to have a complete understanding of the genome and the transcriptome, including both structure and regulation in relationship with development, ageing, health, and evolution.

A number of research areas fundamentally require *de novo* sequencing, including:

- **Microbial/Pathogen Science**
  Where there are global and regional needs with respect to antibiotic resistance, food- and vector-borne infections, outbreak and pandemic preparedness, and food/water safety, security, and monitoring.

- **Precision Medicine**
  In which epigenetics and genome structure have not been fully explored, particularly in the Asian context.

- **Plant Biology**
  Where there is a pressing need for harnessing genomic approaches to improve food security, protect biodiversity, and ensure the safety of plant-based products and derivatives.

Mapping antimicrobial resistance in environmental reservoirs

Antimicrobial resistance is a growing global healthcare problem. It is projected to contribute to millions of deaths worldwide, with an estimated economic burden of over 100 trillion dollars by 2050. In an effort to combat this impending threat, GIS conducted a landmark genomic mapping of microbiomes and antibiotic resistance genes in a tertiary hospital in Singapore. This ground-breaking work was published in *Nature Medicine* under the title "Cartography of opportunistic pathogens and antibiotic resistance genes in a tertiary hospital environment". It enlisted the emerging technology of metagenomics to enable a detailed mapping of the diversity of bacteria and antibiotic resistant genes found in hospitals. Gene sequencing technologies were coupled with metagenomic analyses in the study to systematically characterise the distribution of bacteria, with their corresponding antibiotic resistance genes in the hospital. The data achieved enough resolution to enable the identification of microbial reservoirs in hospital environments that pose potential risks for human infections, including organisms that form biofilms. This study was facilitated through a collaboration between GIS, Tan Tock Seng Hospital (TTSH), National Centre for Infectious Diseases (NCID), National University Hospital (NUH), Singapore General Hospital (SGH), Weill Cornell Medicine, and the MetaSUB Consortium.

From a technology standpoint, there are two main additional drivers for *de novo* sequencing and analysis.

Emerging sequencing technologies (long-read sequencing, direct sequencing, accurate single-molecule sequencing, structured sequencing) require novel algorithms and analysis methods to fulfil their potential for new genomic insights.

Improvements in computational hardware have led traditionally non-biological companies to explore genomics applications (e.g., NVIDIA for GPUs), particularly for challenging use cases presented by *de novo* analyses. These application and technology drivers are long-term, structural trends that we anticipate will continue to grow for the foreseeable future.

Our increasing ability to read the (epi)genomes of both individuals and patient biopsies drives the corresponding demand for interventions through genome-writing. With precision medicine forecasted to grow at a CAGR of 10.6 percent to a size of US$3.18 trillion in 2025 (www.researchandmarkets.com), there is increased demand for therapeutics that exploit this understanding. Of particular economic potential is (epi)genome editing using CRISPR-Cas, as evident by the more than 3,000 related patents that have been filed worldwide in the past seven years. The ability to add, ablate, or correct any DNA/RNA sequence can be brought to bear on a range of national disease priorities e.g., cancers, cardiovascular diseases, metabolic conditions, infectious diseases, and neurological disorders. The global genome editing market is estimated to grow to >US$10 billion in 2025 (www.marketstudyreport.com), and CRISPR-Cas registers a tremendous CAGR of >30 percent (www.inkwoodresearch.com). The global gene therapy market is also estimated to reach US$4.4 billion by 2023, registering a CAGR of 33.4 percent (www.alliedmarketresearch.com).

Beyond knowledge-based targeted genome editing applications, infrastructure technology such as delivery vectors present additional opportunities for novel products and services to be developed. These include innovations in the production of vectors for therapeutic delivery, new tropism in organ or cell type-specific targeting, new viral and non-viral compositions, safer modalities, and more efficacious treatment. In the coming five years, the viral vector manufacturing market is expected to grow at a CAGR of 20 percent with adeno-associated viral (AAV) manufacturing accounting for US$8.3 billion in 2022 (BCC Research LLC 2018).

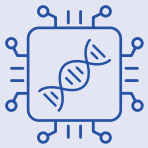
As architecture and design technologies mature, they will push further into non-traditional, non-biological application spaces. Early examples of emerging applications that are enabled by mature genome-read and -write technologies are synthetic biology and DNA storage. It is thus advantageous that the existing close proximity of BMRC and SERC within A*STAR has laid out the broad infrastructure and ecosystem needed to capitalise on these new frontiers and to bring about new opportunities in engineered biomedicine and advanced manufacturing.

Existing Strengths and Opportunities

GIS has many strengths that are unified by the GAD domain. These include multi-disciplinary expertise (genetics, computer science, biology, and medicine), best-in-class infrastructure for molecular bacteriology research and infectious disease monitoring in Southeast Asia, and expertise in genome engineering and gene therapy, which can address specific priorities for Singapore and the region (e.g., biodiversity hotspot, population-diversity, smart nation push, and importance of food security).

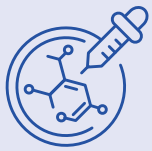
- GIS is nationally and internationally recognised for its contributions to research in infectious diseases (e.g., SARS, Dengue, Zika, and GBS), which can naturally be built upon as we envisage national monitoring, port-to-plate food safety, and high-density food production. As an institute with access to the largest genomic datasets in Singapore and with sophisticated analytical capabilities, GIS is ideally situated to integrate data from diverse surveillance sources (healthcare, water monitoring, food safety, biodefense) into a unified interface for anonymised querying and research applications.

- **Asian Diversity**
  While human genetics research has primarily focused on reference-based analysis, the SG10K project and GIS' strengths in studying Asian genetic diversity serve as an ideal launching pad to establish Asian reference genomes and develop *de novo* human genome assembly capabilities. GIS has a core of expertise in genome assembly that can enable national and international impacts in this field. GIS' strengths in *de novo* assembly will be valuable in a range of applications, particularly in plant genomics and food/biodiversity research as these areas are poised to explode in Singapore and beyond.



- **DNA Sensors**
  As DNA sequencing transitions to an era of miniaturised, real-time, and ubiquitous systems, we envisage that its importance as a "biological sensor" will be integral to Singapore's Smart Nation vision. Our efforts with early systems (MinION from ONT) and their applications to hospital monitoring, food safety, and authenticity are being expanded through engagement with public sector agencies and collaborations with technology providers. This partnership helps cement GIS' relevance to broader national goals beyond healthcare and enables interactions with leaders in the growing data analytics space.

*A*STAR's GIS and BII hosted Second Minister for Trade and Industry and Manpower, Dr Tan See Leng, for a visit on 9 March 2021. We briefed him on GIS' and BII's expertise in genomics and big data analytics that enhance precision medicine for more personalised, accurate and targeted diagnoses and treatments.*



Nucleic Acid Therapeutics

GIS has established resources and foundational capabilities in the past three years in the form of an IAF-PP funded Molecular Therapeutics Programme (MTP) and an AME-funded Automating Macromolecular Manipulation for Manufacturing (AMMM) Programme. Within two years, the MTP has progressed from identification of lead indications to therapeutic evaluation in non-human primates (NHPs). The AAV gene therapy vector core (VectorCore@GIS), spun off from excess capacity at the MTP, has gained significant traction with >20 service and collaborative requests in its 1st year. The AMMM has also recently begun to establish foundational IP in Singapore for nucleic acid engineering. As the coordinated effort of MTP, VectorCore@GIS, AMMM, and new strategic efforts in GIS expand its resourcing and reach, GIS is well-poised to develop the national NAT platform (see figure 2 on the right). The GIS NAT strategy will extend capacity in select disease targets (particularly cancers, infectious diseases, and rare severe diseases) through partnering clinicians associated with hospitals and medical schools, Rare Disorder Society Singapore, A*STAR institutes, and cancer institutions in Singapore.

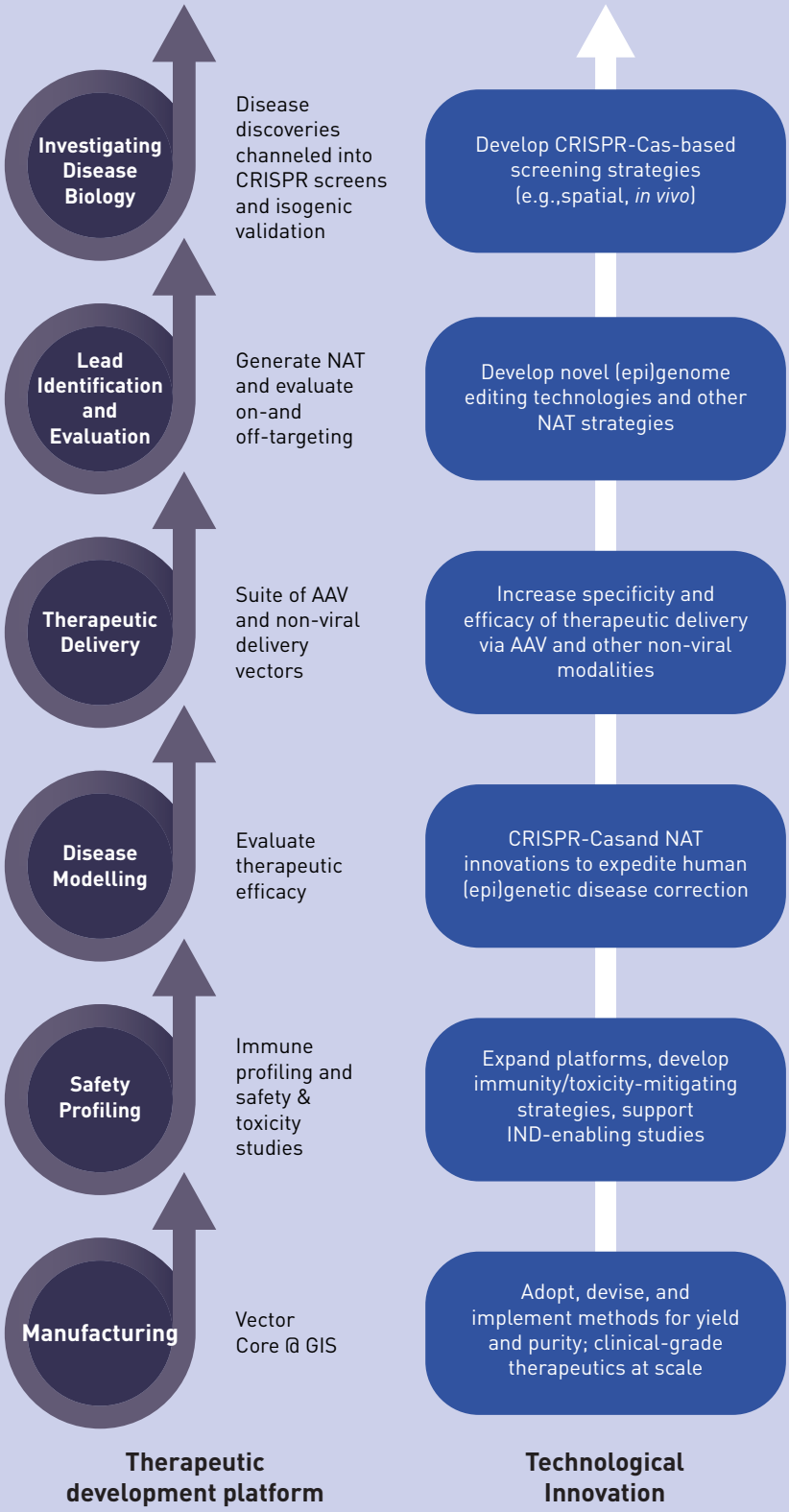


Figure 2, above. *The Development and Technological Innovation Strategy. Thematic sub-areas are indicated in the left bubbles. The strategic strengthening of existing technological expertise and infrastructure (left) seeks to enable therapeutic development and R&D bandwidth. The new technological innovations (right) seek to enhance pipelines and enable new therapeutic possibilities.*

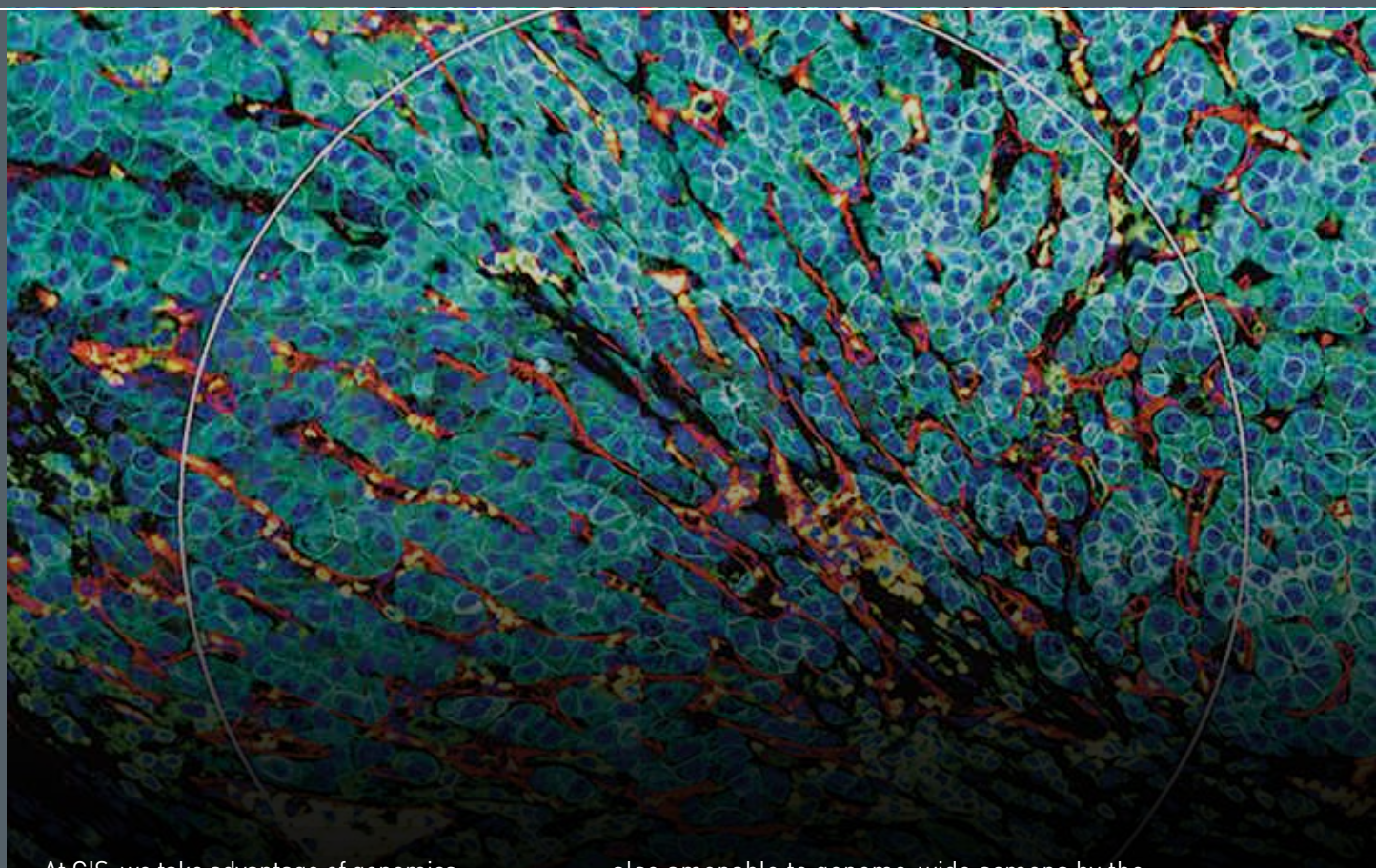
FEATURE

LABORATORY OF *IN VIVO* GENETICS AND GENE THERAPY

Acute and chronic liver failure are major global health concerns. Asia has an especially high burden of hepatitis virus infections (WHO) and an increasing incidence of non-alcoholic fatty liver disease (NAFLD), two major drivers of end-stage liver disease.

Obesity is reaching epidemic proportions. According to the World Gastroenterology Organisation, there are at least 1.46 billion obese adults worldwide. Closely linked to this, NAFLD has emerged as the most common liver disease worldwide. NAFLD is regarded as the hepatic manifestation of metabolic syndrome, which is tightly linked to obesity and type 2 diabetes. NAFLD is also projected to soon be the number one reason for liver transplantation. This situation also contributes to the continuous increase in the number of people with end-stage liver disease and cirrhosis. Currently, the only curative treatment for end-stage liver disease is liver transplantation. In addition to the high costs accompanying liver transplantation, donor organs are limited. End-stage liver disease patients may also experience complications that render them unfit for major surgery such as transplantation. Furthermore, most liver cancer arises in the background of a cirrhotic liver. Therefore, we urgently need to develop new treatment approaches and identify new drug targets.

Mini midbrain organoids developed in GIS



At GIS, we take advantage of genomics, advanced mouse models, and sophisticated human liver organoids to address this unmet need. This is a collaborative effort of several groups in combination with our clinical partners at NUHS. In the Laboratory of In Vivo Genetics and Gene Therapy, we focus on mouse models recapitulating different liver diseases. We use these models to unravel disease mechanisms and pinpoint therapeutic targets to intercept disease progression and allow recovery to a healthier liver. Through the combination of different complementary disease models and reference to human patient samples, identified bona fide therapeutic targets are then advanced for translation to the clinic in close interaction with industry.

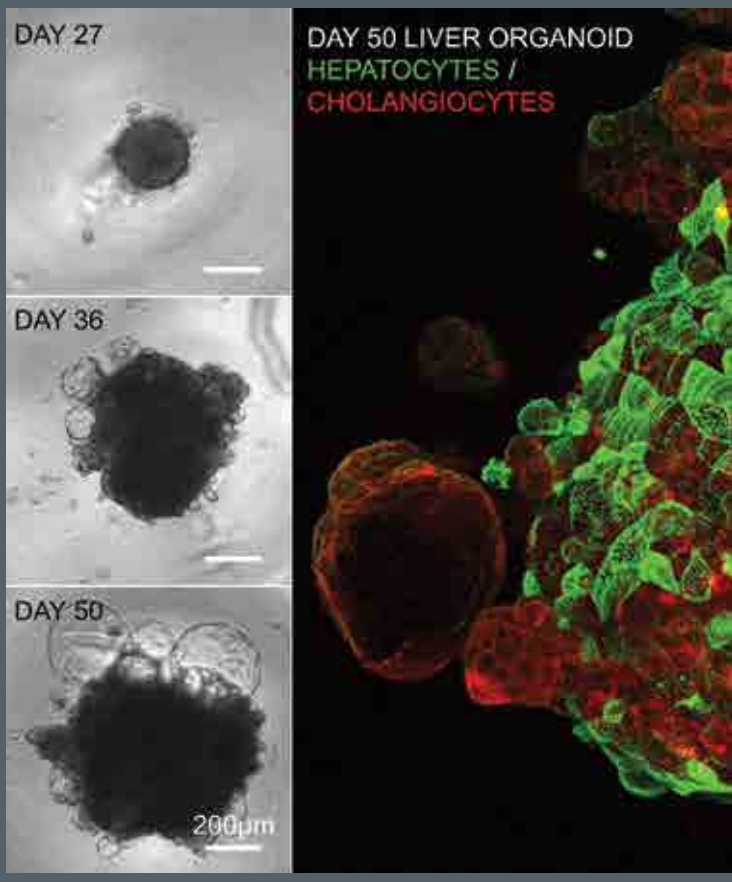
To perform high-throughput target discovery, we developed a sophisticated *in vivo* RNAi screening platform. We are currently conducting screens in two diet-induced NAFLD models, chemically induced (e.g., thioacetamide (TAA)) chronic liver disease models, and different defined genetic models. This approach is highly flexible and allows the screening of focused pools of up to 5,000 individual shRNAs but is also amenable to genome-wide screens by the use of sub-pools. For example, we are currently conducting a genome-wide screen of more than 70,000 shRNAs, sub-divided into 32 pools, in the "Western diet" mouse model of NAFLD. To identify precision medicine targets to suppress disease progression from simple steatosis to non-alcoholic steatohepatitis (NASH), we modified our system for inducible shRNA expression. Our unbiased screens have already identified several completely new therapeutic targets, which we are currently in the process of bringing to the clinic. As a member of the collaborative approach EMULSION (Ensemble of Multi-disciplinary Systems and Integrated Omics for NAFLD), we have access to a cohort of local NAFLD patients, and we can leverage this valuable resource for exploratory and validation purposes. These resources are also used in partnership with the Danish pharmaceutical company Novo Nordisk to identify disease stage-specific biomarkers. For this purpose, a joint-lab ENABL (EMULSION-Novo Nordisk Asian NAFLD Biomarker Laboratory) was established at GIS. There is an unmet need for NAFLD diagnostics, because current methods require invasive liver biopsy.

FEATURE

In another collaboration, we are working closely with Janssen Pharmaceutica, a daughter of Johnson & Johnson, to establish a liquid biopsy-based disease signature for NAFLD. Our approach is to combine mouse models of NAFLD, humanised mice, and human patient serum. Through cross-referencing between these systems, a conserved signature can be established, thus allowing cheap and efficient screening for NAFLD patients.

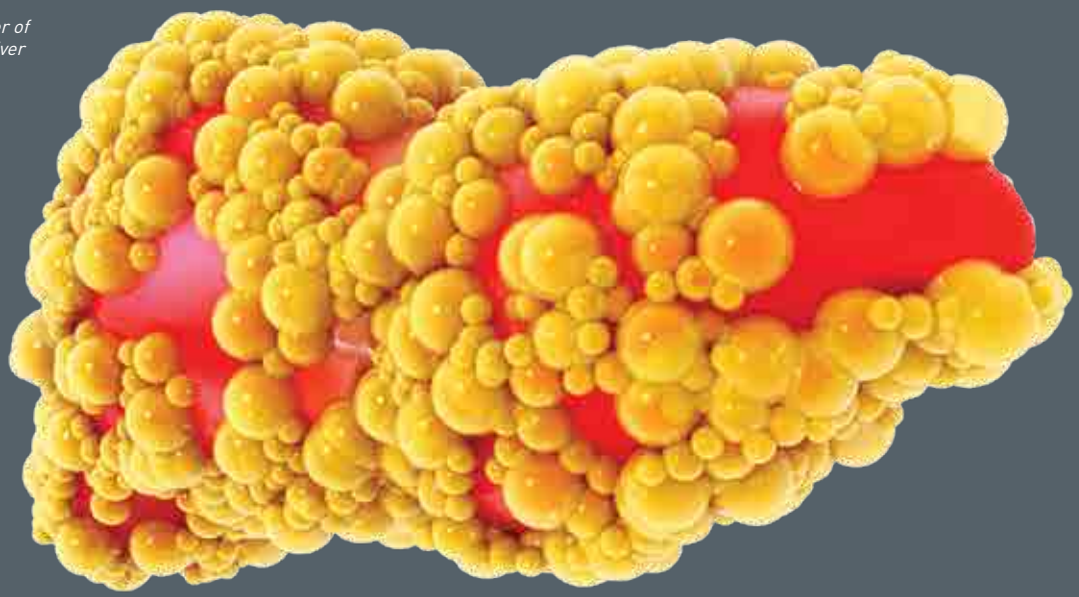
In addition, we are conducting *in vivo* functional genetic screens to identify modulators of liver regeneration and ageing. Our ultimate goal is to establish targets for regenerative medicine by enhancing the regenerative capacity of hepatocytes. Interestingly, we are seeing overlaps with targets counteracting chronic liver disease and enhancing regeneration. Importantly, by tuning the intrinsic regenerative potential, our approach will not introduce foreign antigens and will therefore be immune response "neutral".

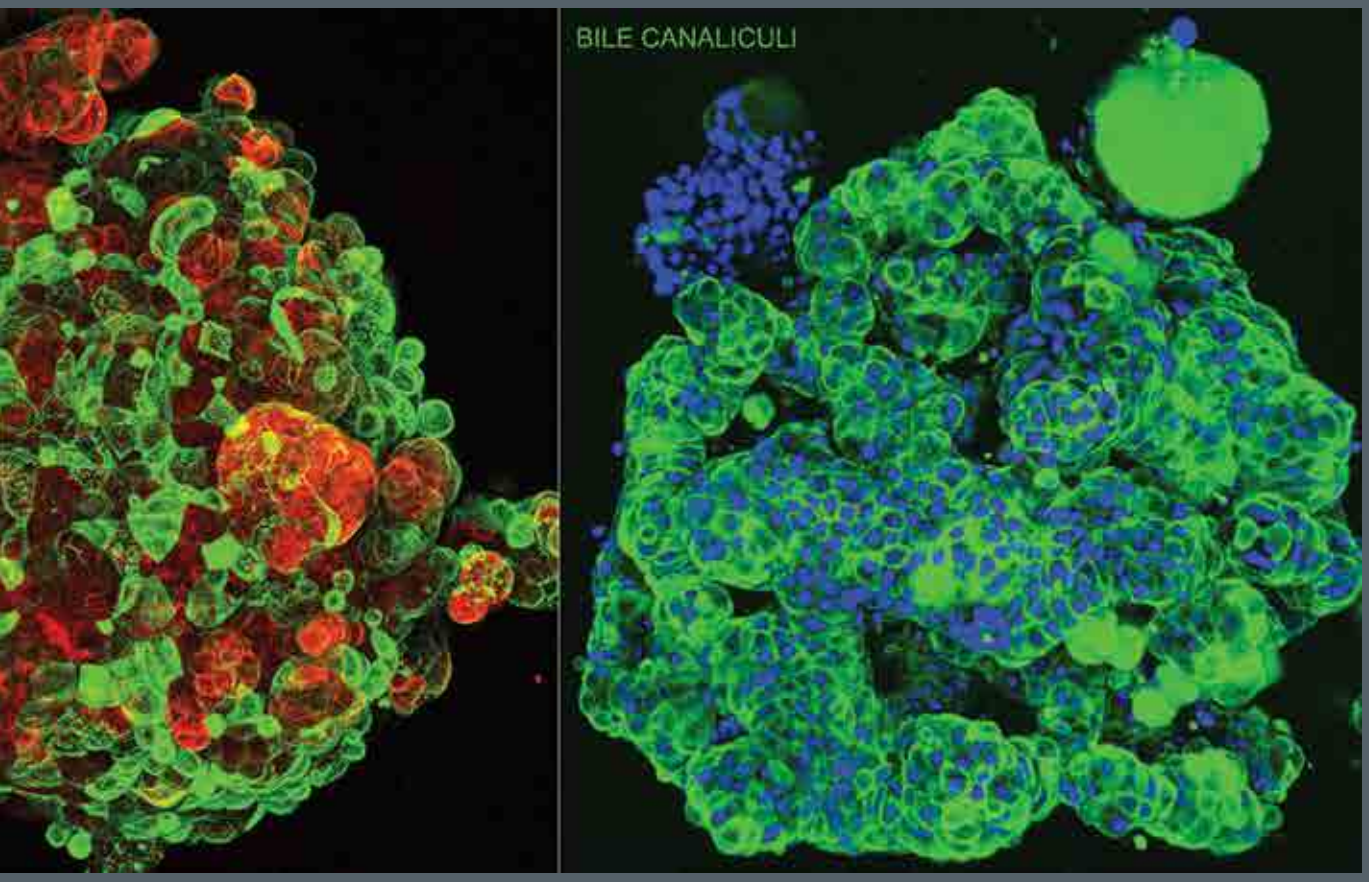
In the context of liver regeneration and ageing, our group in close collaboration with a group at NTU is investigating the implications of hepatocyte ploidy changes. We are combining liver perfusion, ploidy-based FACS, and genomic, epigenomic, transcriptomic, and chromatin-organisation analysis to gain an in-depth understanding. In the liver, the ploidy profile changes during ageing, and liver disease can also be a driver of these shifts. Therefore, we hope to identify new treatment and intervention paradigms through this approach.



Singapore scientists grow liver organoids in a dish that mimics the complex structural features of a human liver organ (Left brightfield images: Liver organoids developing over time in the dish. Right fluorescence images: Visualisation of different cell types and liver organ structures in the organoids)

3D render of human liver cirrhosis

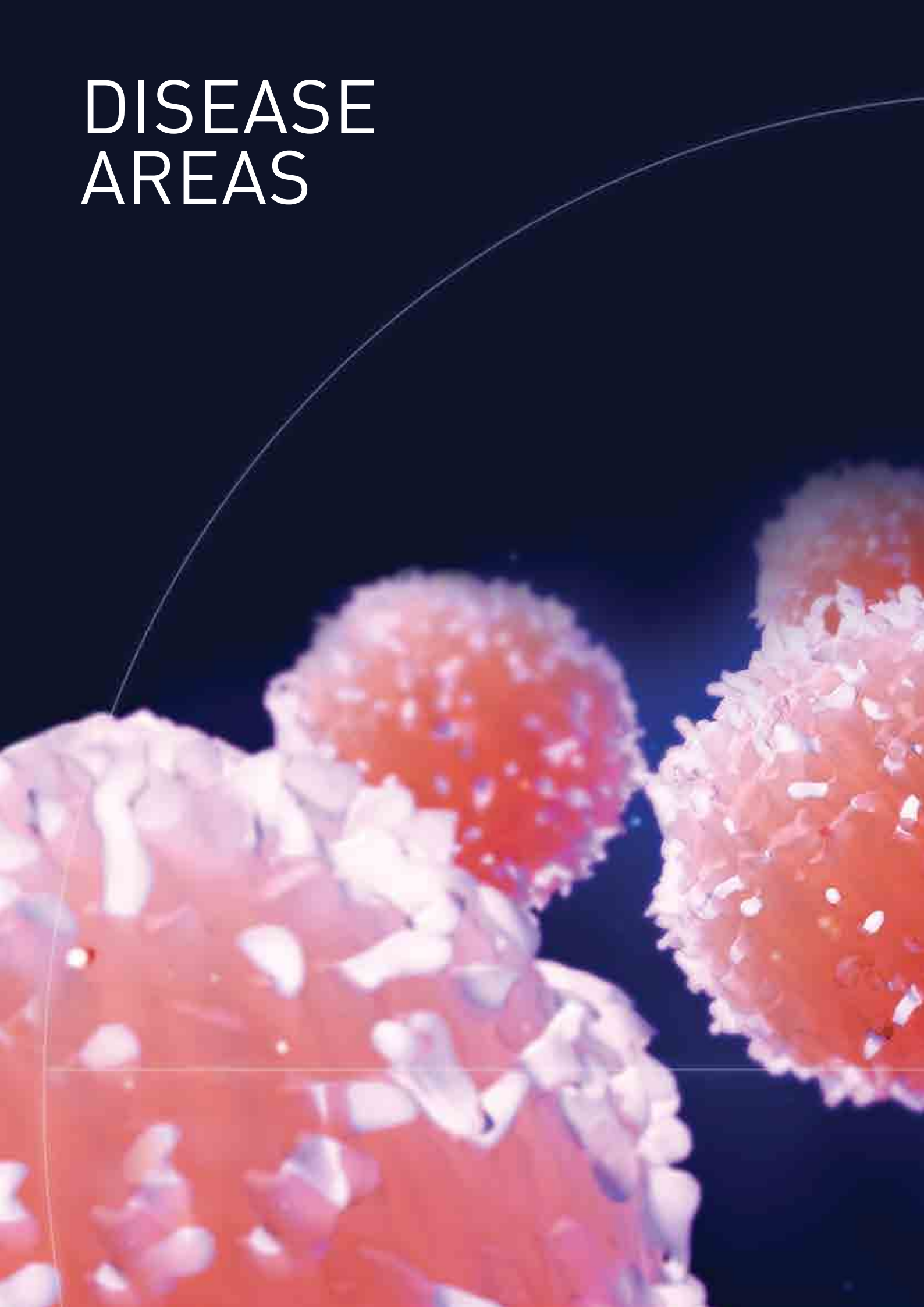


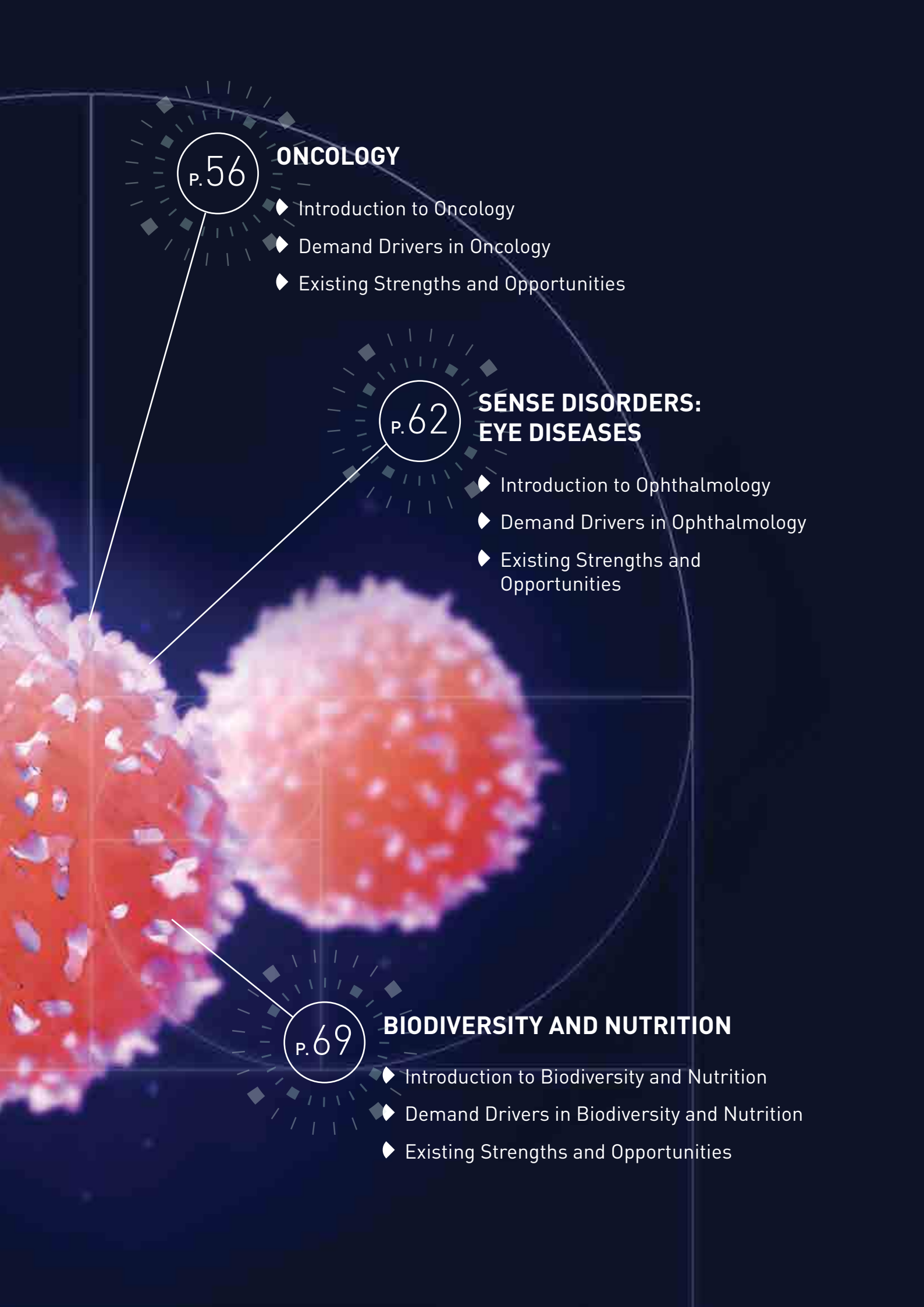


Another focus of our research is to understand the early steps of pre-malignant to malignant transition. We established a chimeric mouse model using immune-competent mice in which pre-malignant cells are surrounded by wild-type cells. These cells are normally eliminated by immune surveillance, and no transformation or tumour development is observed. However, introducing liver damage leads to pre-malignant to malignant transformation, immune escape, cell expansion, and ultimate liver tumour formation. Through an in-depth analysis of this process, we identified a target that allows the separation of immune escape from transformation. In this case, we suppress tumour development, but immune surveillance is interrupted. As a result, cells are not eliminated. In addition to identifying cancer vulnerabilities, this system is used to better understand immune evasion for optimising immunotherapy.

In summary, we established platform technologies and mouse model resources for identifying new therapeutic and diagnostic approaches for chronic liver disease and liver cancer. Both are diseases with very limited therapeutic options and a huge impact on society and the health system. Subsequently, we collaborate closely with industry and start-up companies to bring these gene therapies to the clinic.

DISEASE AREAS





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ONCOLOGY

- Introduction to Oncology
- Demand Drivers in Oncology
- Existing Strengths and Opportunities

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SENSE DISORDERS: EYE DISEASES

- Introduction to Ophthalmology
- Demand Drivers in Ophthalmology
- Existing Strengths and Opportunities

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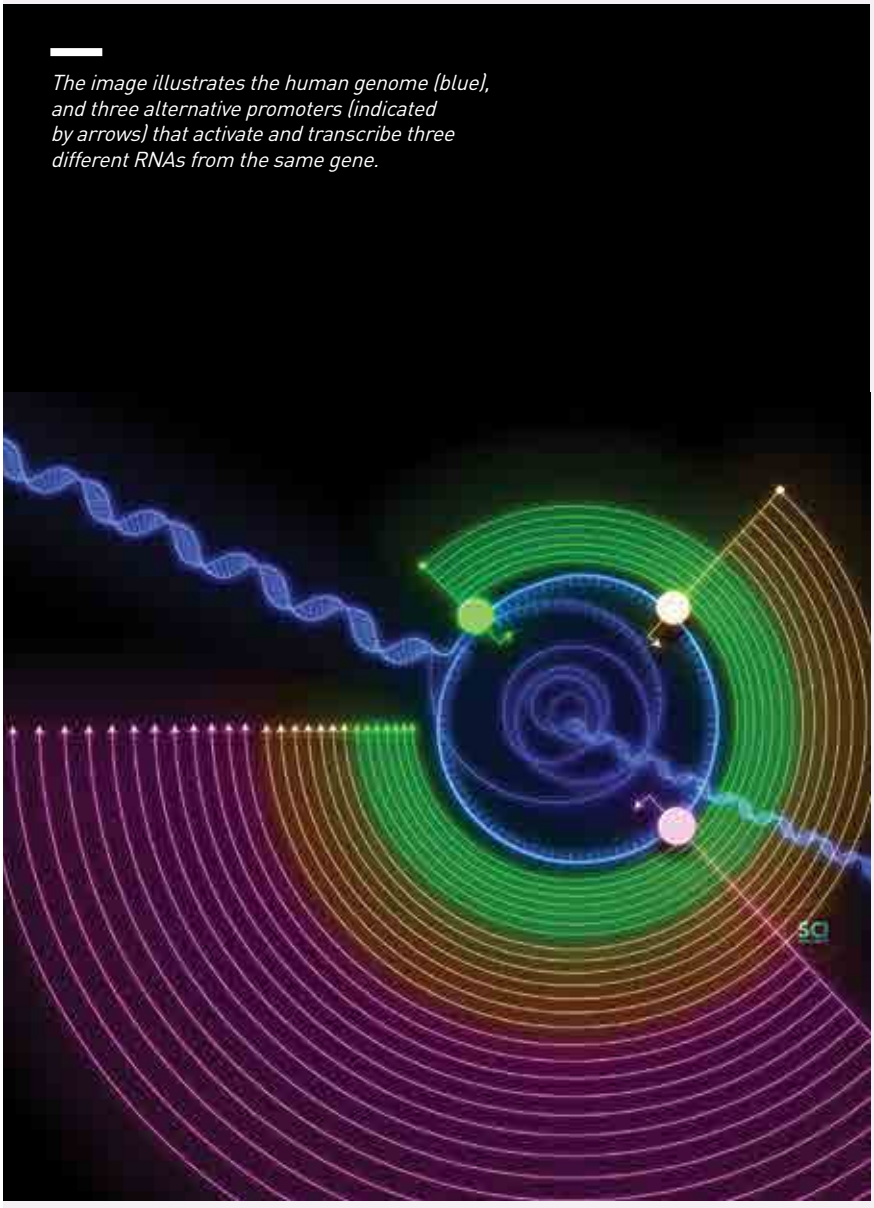
BIODIVERSITY AND NUTRITION

- Introduction to Biodiversity and Nutrition
- Demand Drivers in Biodiversity and Nutrition
- Existing Strengths and Opportunities

ONCOLOGY

Cancer is the leading cause of death in developed countries, and the global cancer burden is expected to increase. In Singapore, one in four to five people are expected to develop cancer in their lifetime. While significant progress has been made in the development and clinical application of therapeutics for specific types of cancers, long-term remission for most cancers is rare. Additionally, because early detection remains elusive, cancer treatments are often used late in disease progression and are therefore expensive, imprecise, and ineffective.



The image illustrates the human genome (blue), and three alternative promoters (indicated by arrows) that activate and transcribe three different RNAs from the same gene.

There are three key roadblocks in oncology.

The molecular trajectory of cancer progression is poorly mapped out for many types of cancer

The molecular routes (and vulnerabilities) of cancer progression are poorly modelled in human-relevant physiological systems

Clinical trials of biologically informed interventions therapeutics designed to intercept key molecular bottlenecks are scarce

These factors lead to the imprecise deployment of treatment modalities and therapeutics that result in ineffective responses.

The costs of new drug development and drug administration are expensive, but they do not ensure optimal treatment responses, in part due to variations in the molecular and genetic features across patient tumours and even within individual tumours. Personalised cancer genomics may provide clinical solutions by mapping the evolutionary and clinical trajectories of tumours for better prognosis, intervention, and the deployment of appropriate treatments—essentially informing the right treatment (or non-treatment) for the right patient at the right time. Personalised cancer genomics may also enable discoveries for new diagnostic blomarkers and therapeutic targets. We believe that developments in genomic technologies will advance diagnostic and monitoring capabilities, thus facilitating shifts in cancer treatment paradigms. Combined with the understanding that cancer is a chronic disease, we see paradigms for oncology shifting towards "maintenance" as an intermediate step in the push towards real cures. Treatments of the future will likely be anchored upon a comprehensive understanding of the molecular, evolutionary, and adaptive nature of individual tumours to deploy suitable therapeutics in the "right patient" context (right drug, right patient, right time). Treatment may involve complex cocktails of drugs that are dynamically modified as tumour characteristics change to ensure maximal efficacy and durability. Thus, the future of oncology is likely to be driven by "patient-centricity" and healthcare provision from the patient perspective.

Demand Drivers in Oncology

The need for effective therapeutics and diagnostics is the primary driver of oncology research. The costs associated with oncology are generally higher than those for other diseases, leading to a demand for robust evidence-based measures for treatment success, and this is an emerging new driver. Genomic stratification of current broad cancer-typing for diagnosis may alleviate these rising cost pressures.

Oncology care is pivoting away from the "one-size-fits-all" concept to the search for each therapy or combination regimen. Cancer management approaches are also being extended to cover not only treatment but also the prevention of cancer. These approaches necessitate data gathering and predictive analytics that will become increasingly essential in defining treatment value. Live tracking will reveal aspects of the patient journey and identify barriers to effective treatment delivery. Precision medicine is now an accepted paradigm and operational domain that encompasses the integration of complex, multimodal information for better patient treatment and management at the various stage of an individual's journey. Beyond treatment, precision medicine may include the "pre-disease" or "prevention" phase, whereas healthy or at-risk individuals are being "profiled" and monitored.

Other demand drivers in oncology include the following:

- **Physicians** seeking better tools for detecting early malignancies, more precise and less invasive methods for molecular diagnostics, better therapeutics for lasting response, and medical or technological breakthroughs in cancer research and management at every stage of the patient's journey.

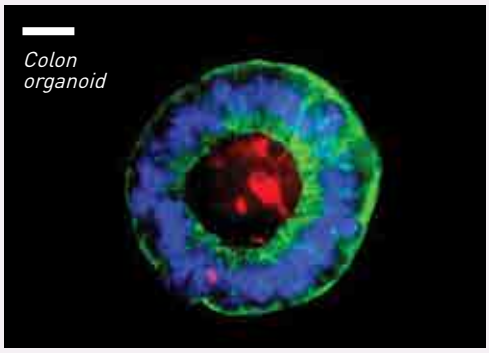
- **Biotechnology** companies and start-ups seeking the development of research and clinical tools, the discovery of new drug targets, the creation of disruptive therapeutic modalities, and the harnessing of data science for value addition to their R&D pipelines.

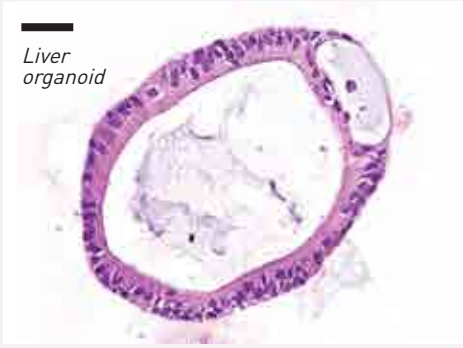
- **Pharmaceutical** companies investing in the development of oncology drugs.

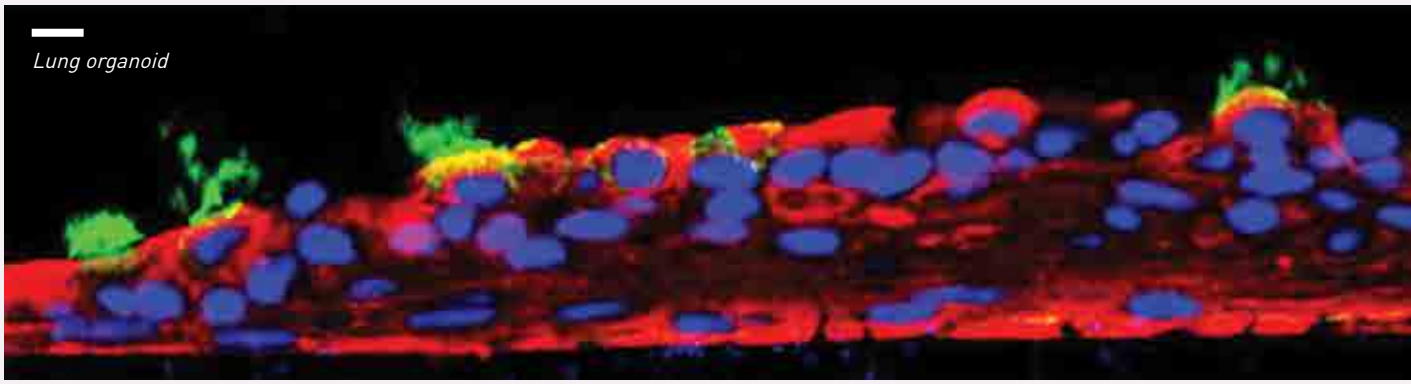
Existing Strengths and Opportunities

Maintaining a Legacy of Excellence in Cancer Genomics

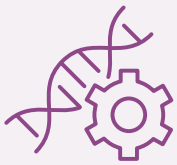
Since its founding in 2000, GIS has retained cancer research as a core disease focus.There is a substantial number of cancer research labs within GIS and associated external labs. Our key strengths are:


Colon organoid


Liver organoid

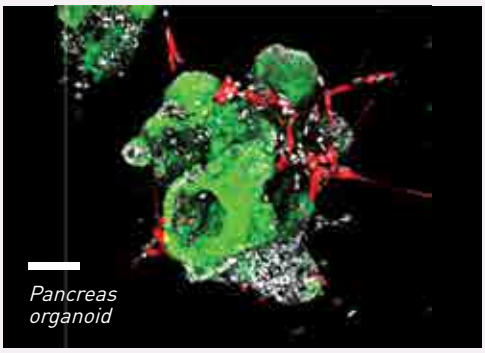

Lung organoid

- **Computational Biology and Big Data Analytics**
  With the capacity to produce, host, and analyse large cancer datasets, GIS also has world-leading expertise in regulatory genomics, systems biology, algorithm and tool development, single-cell genomics and biology, tumour heterogeneity and tumour evolution (see also Sequencing and Scientific Computing Review sections).

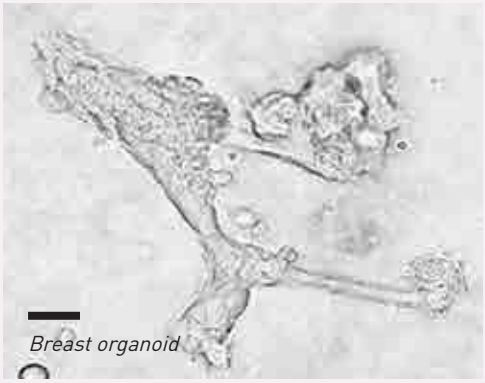


- **Functional Genomics**
  This area is a lynchpin of cancer research; in-house capabilities include the functionalisation of genes (epigenetic factors, metabolic enzymes, transcription regulators, kinases) involved in resistance and metastasis and the regulation of the tumour-microenvironment. Applications include target discovery, early therapeutic development, biomarker discovery, and liquid biopsies.

- **Clinical Genomics**
  Aided by close collaboration with clinical partners, GIS has sequenced and analysed tumours from local (and overseas) healthcare institutions through various programmes. Indications studied include lung cancer, gastric cancer, liver cancer, viral-driven cancers, lymphoma, and others. We also have expertise in cancer genetics and epidemiology. GIS is the custodian of cancer genomic datasets from different cancer types/programmes.



Pancreas organoid



Breast organoid

Precision-driven Approach

Our starting hypothesis is that every patient's tumour is potentially unique. We seek to learn from a cancer patient's genetics, disease history, treatment responses, and progression to illuminate and understand disease trajectory. The endpoint is a precision-based, biomarker-based approach to treatment/intervention in the form of better drug selection, drug combination, patient stratification, and prediction of responses.

A two-pronged strategy is recommended to identify molecular dependencies informing next-generation clinical trials that intervene at key cancer progression bottlenecks (figure 1).

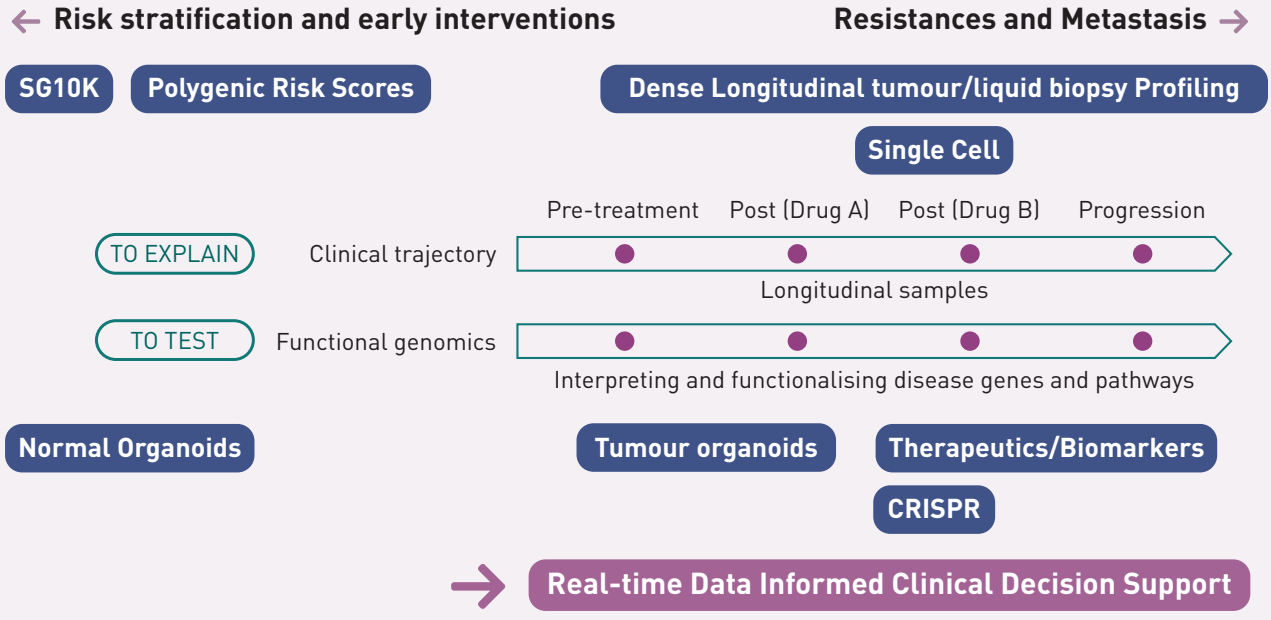
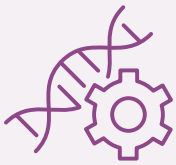


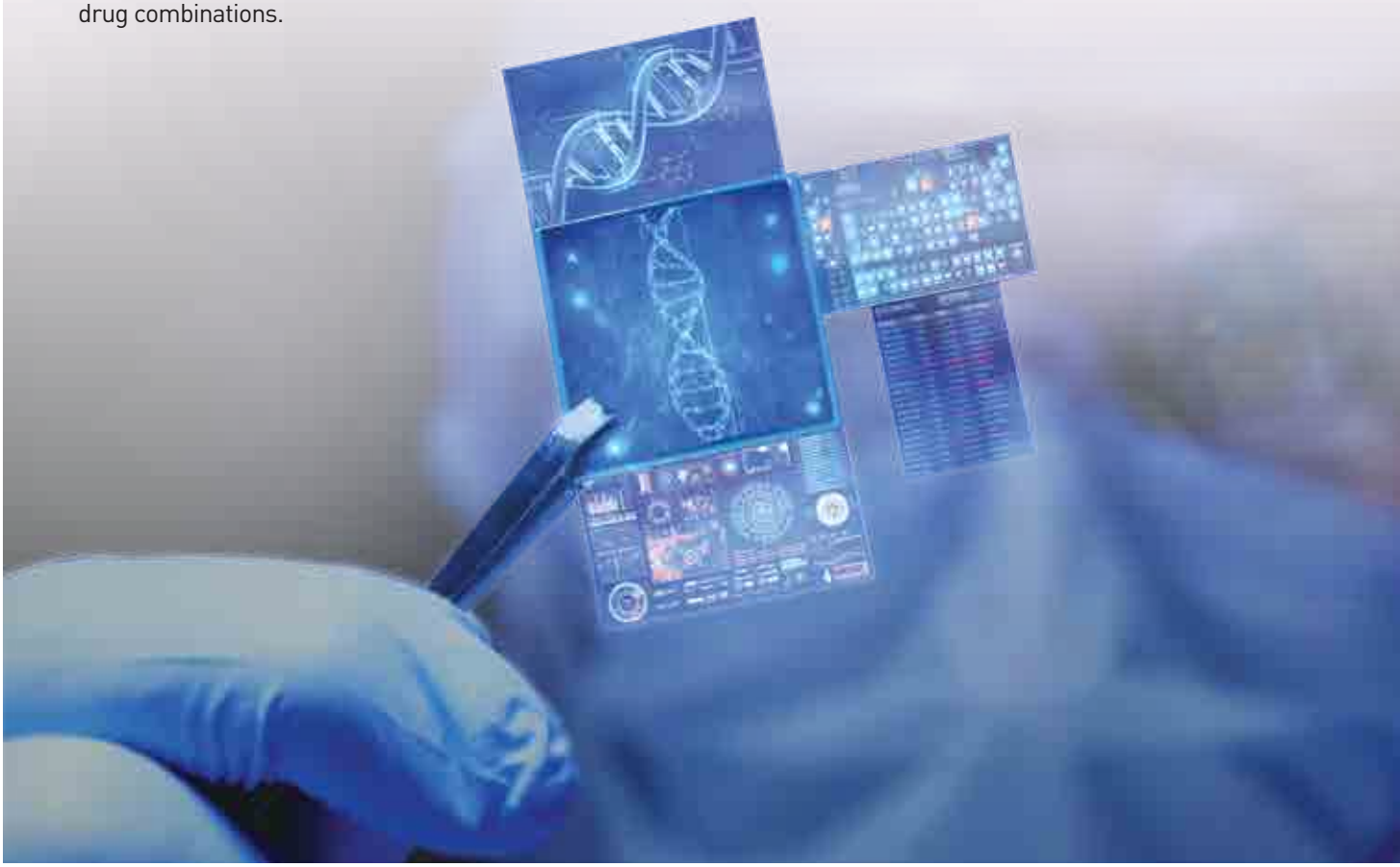
Figure 1, above. *A two-pronged strategy to explain the clinical trajectory of patients and to test intervention measures.*

- **Clinical Trajectory**
  GIS has produced and analysed substantial cancer sequencing data. One objective is the convergence of cancer databases. These include data from tumours collected from retrospective/static studies and from prospective longitudinal treatment studies. The sequencing of (static) tumours alone (in the absence of treatment context) may no longer be sufficient to gain new insights. The adaptive behaviours of tumours and their clinical trajectory upon therapeutic pressure will provide essential information for guiding the application of specific treatment methods, including drug combinations.



- **Functional Genomics**
  GIS has generated a collection of patient-derived cell lines and organoids, which are valuable tools for testing the genomic and genetic underpinnings of disease. While valuable as target/pathway discovery and validation resources on their own, the value of these cell lines and organoids can be maximised by using them to recapitulate human cancer phenotypes and their responses upon treatment perturbations to inform next-gen clinical trials and to test potential intervention measures.

Clinical genomics information, on its own, does not enable experimental validation or the discovery of optimal intervention methods. These data describe the adaptive behaviours of tumours. Static experimental models alone do not uncover the molecular pathways for tumour progression. Through the synergistic integration of clinical sequencing data with experimental systems, we will be able to recapitulate disease progression and treatment responses, thereby providing powerful approaches for more meaningful interventions. These efforts may include the appropriate application of existing drugs, new pathways to be considered, better biomarker analysis for patient stratification, better biomarker analysis for predicting responses, and new candidate targets to be discovered for drug development.



Emerging Opportunities

Three areas of opportunity have been identified (figure 2):

GIS should capitalise on expanding from "classic" genomics to "new" genomics, which encompasses epigenomics, epitranscriptomics, single-cell omics, spatial omics, EWAS, non-coding and structural genomics, and germline genetics; these fields represent reasonably niche areas with the potential for building a distinguishing identity.

GIS should embark on realising long-term opportunities in the arena of early detection (e.g., early somatic events, polygenic risk scores) and early disease control and/or maintenance (e.g., precision-based therapeutic interventions) earlier in the disease trajectory.

GIS should continue to maintain leadership in key strategic programmes, particularly in clinically-driven large collaborative/ programmatic grants and platform-driven initiatives.

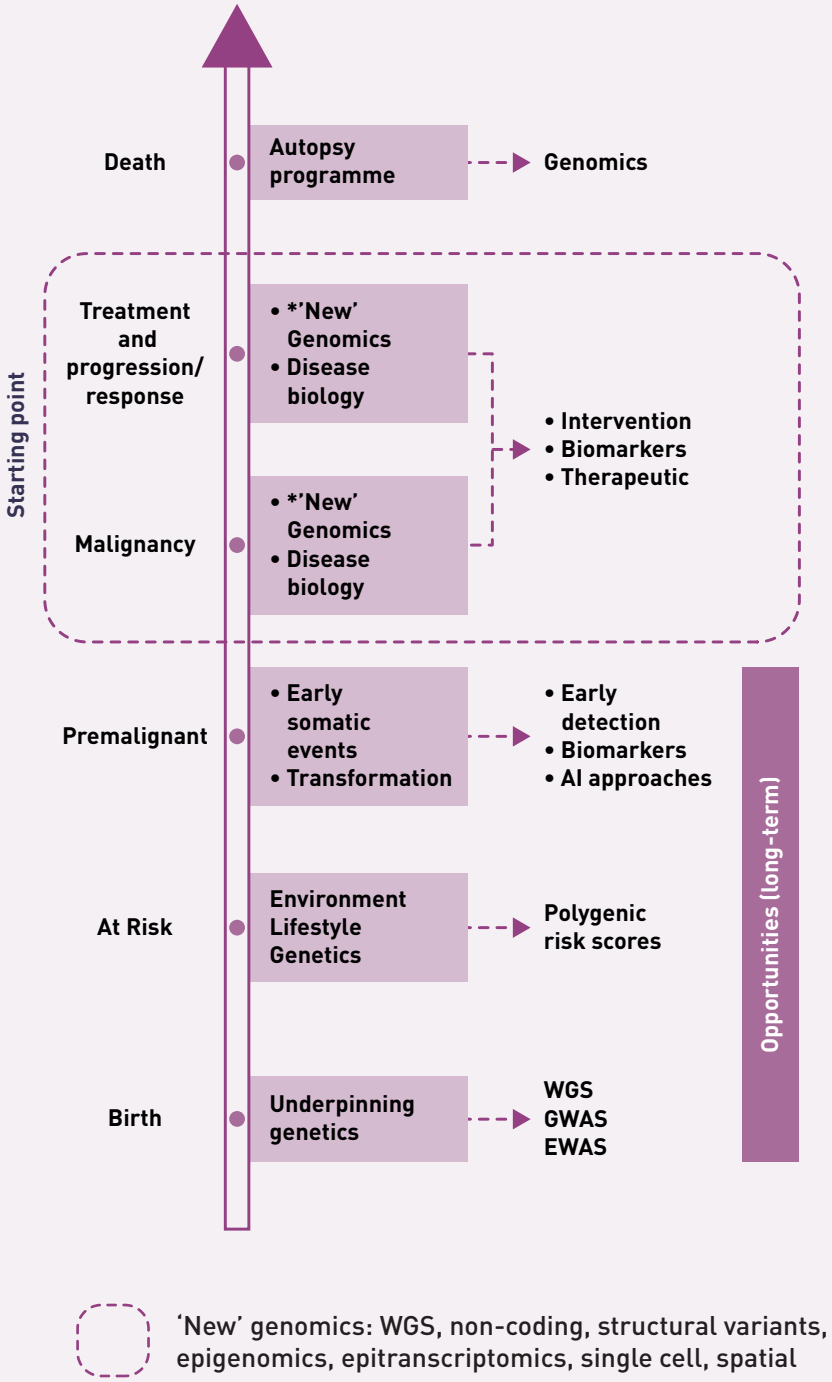
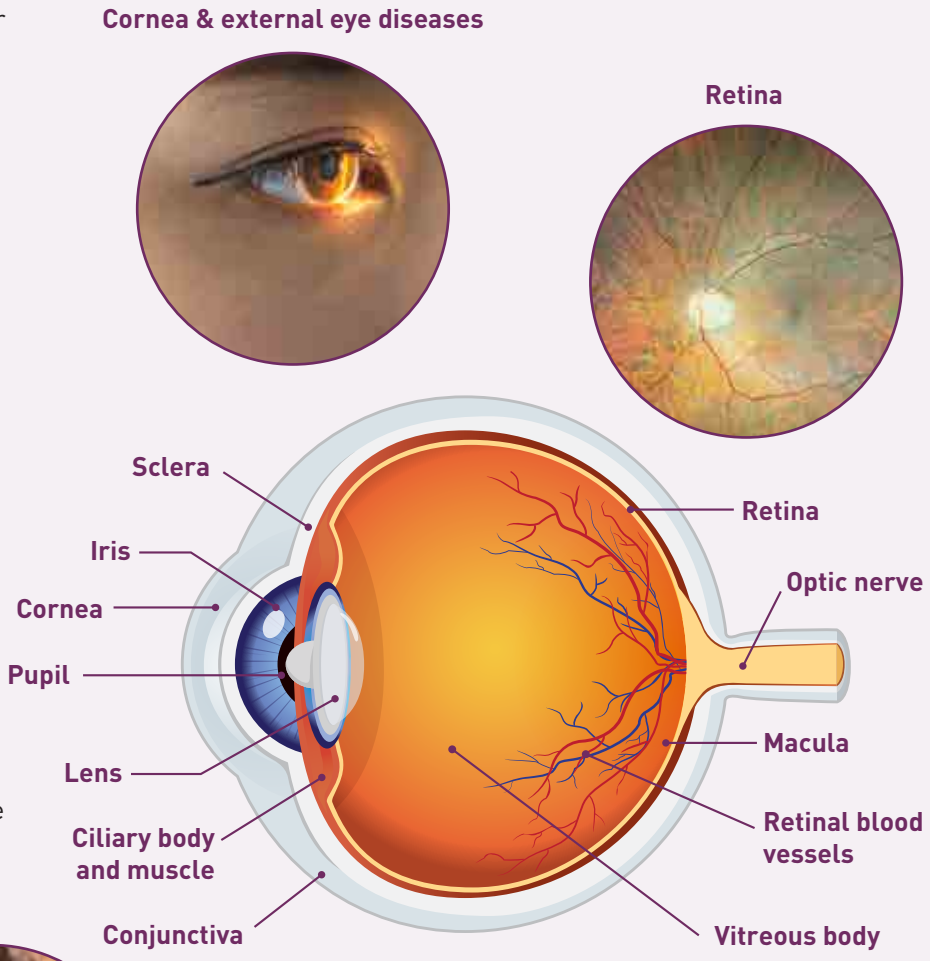


Figure 2, above. *A longer-term strategy of capturing new opportunities in the domains of underlying germline genetics, early detection, early somatic events, and early intervention, in addition to "newer" layers of genomics to be adopted for cancer research at GIS.*

SENSE DISORDERS: EYE DISEASES

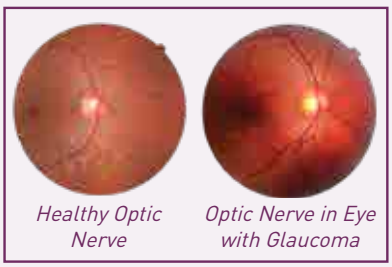
Sight is one of our five major senses through which we perceive our surroundings. Disruptions to sight result in a drastically decreased quality of life. Much of the blindness caused by eye diseases is potentially preventable by earlier detection and intervention.

The most common causes of irreversible blindness in Singapore and worldwide are age-related macular degeneration and glaucoma. The current hypothesis of this thematic area is that blindness results from eye diseases that ultimately converge onto a limited number of final common pathways. Thus, the search for biological insights providing an improved understanding of eye disease mechanisms is a priority.



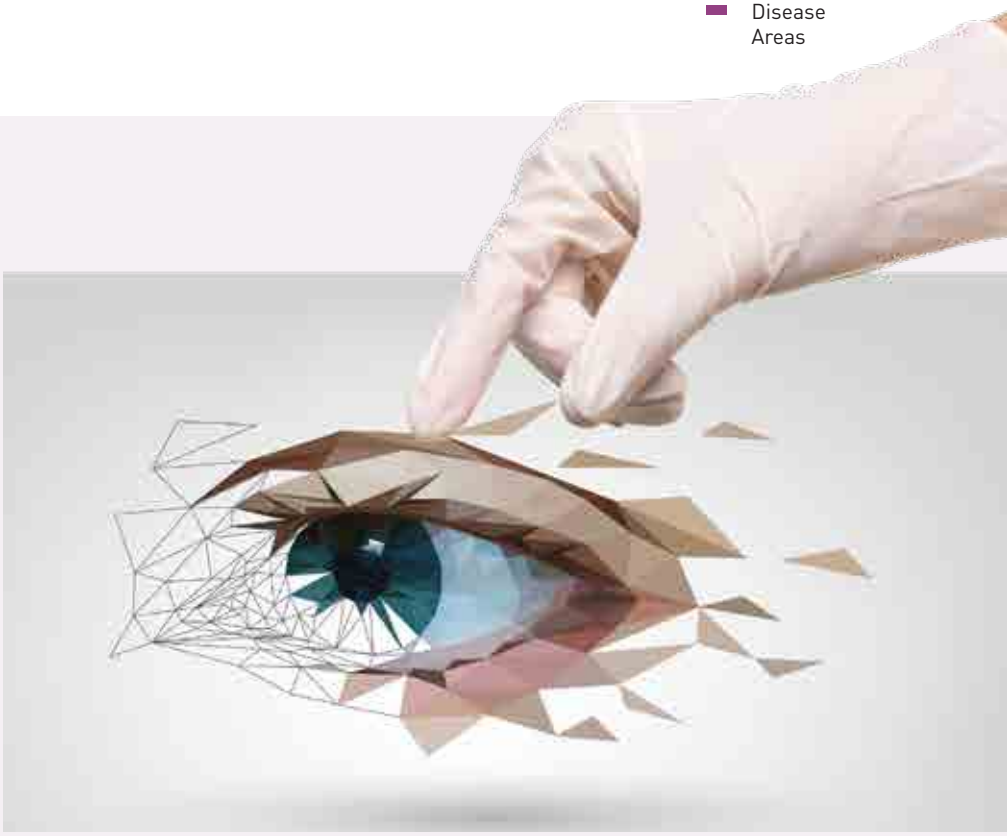
Glaucoma & anterior segment

Exfoliative glaucoma



Optic nerve head

Figure 3, right. *The different domains of eye diseases. In Singapore, the strongest domain in terms of overall research interest, capability, and funding is in the field of glaucoma.*



Genes are instructions that tell the cells of the body how to make all the proteins it needs to survive and grow. By identifying each of these proteins, scientists hope to better understand how our body works and what is happening when it does not work properly. It is hoped that this knowledge will eventually lead to more effective medicines and treatments.

An ideal medicine should target only the part of your body that is ill. Unfortunately, many medicines have side effects, some serious. If scientists can identify the proteins involved in an illness, they may then be able to design new medicines that affect only these proteins, causing fewer and less serious side effects.

At GIS, we are using genetic studies as a starting tool to discover molecular mechanisms underlying eye diseases. Promising "hits" emerging from the discovery programme will be assessed using bioinformatics and biological experiments for application as a precision medicine tool in the clinic and/or as a therapeutic target for disease interception. We also foresee tremendous benefits in linking eye genetic data, clinical information, and imaging modalities using AI learning methods to construct personalised risk models for disease prediction.

Demand Drivers in Ophthalmology

Demand drivers in ophthalmology encompass academic, industry, and healthcare institutions.

- **Academic demand drivers**

  Research institutions derive use because the biological insights from the data will illuminate new research directions as well as opportunities for collaboration.

- **Industry demand drivers**

  Pharmaceutical companies are particularly interested due to the illumination of drug targets through genetic studies applied on a large scale for eye diseases. This is particularly true, because for irreversible blinding disorders, very few treatment options exist (one to two drugs, which only work in <50 percent of patients). The scale of the genetic studies provides a measure of credibility to the candidate genes arising from them.

- **Healthcare demand drivers**

  Interest from the healthcare sector arises from the potential opportunities for early detection of asymptomatic disease and for the stratification of patients at higher risk (due to their genetic profile) for earlier intervention.

An emerging area in this thematic area is the use of AI in imaging diagnostics of eye diseases. This new technology raises the question whether the incorporation of patient-level genomic information could further improve the diagnostic yield.

FEATURE

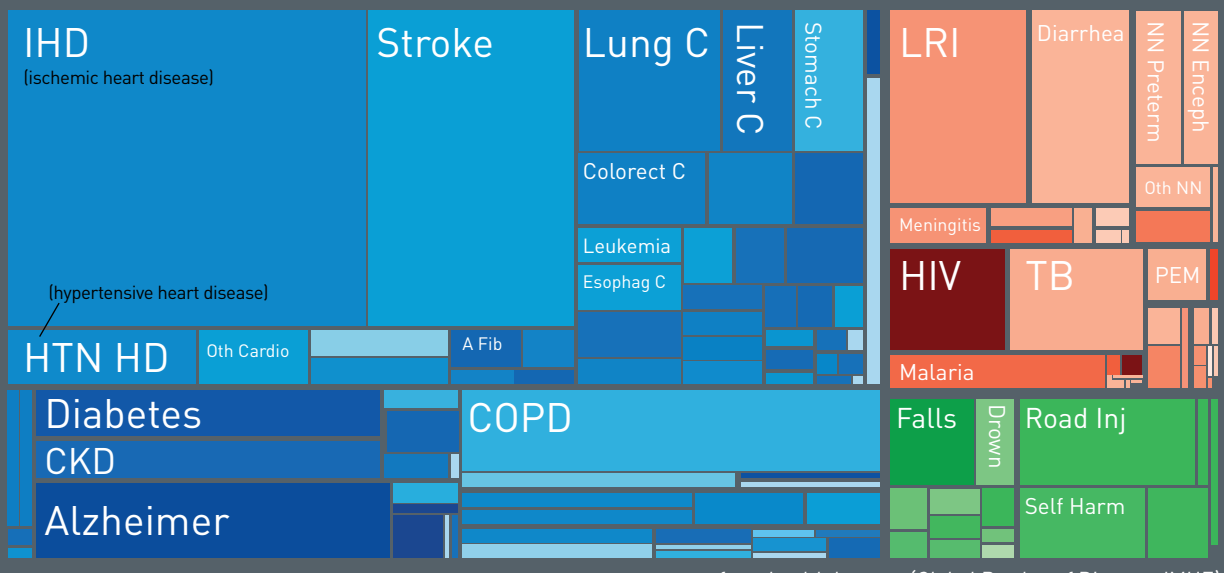
CARDIOVASCULAR DISEASE RESEARCH AT GIS

Cardiovascular disease (CVD) refers collectively to the broad spectrum of different conditions affecting the heart, coronary arteries, and systemic vasculature; these conditions include hypertension, metabolic heart disease, ischaemic heart disease, heart muscle disease, valve disease, arrhythmia, and atherosclerosis.

Despite myriad combinations of initial causes and risk factors, including lifestyle, exercise, diet, family history (genetics), smoking, and others, all CVD converge on the final common pathway of heart failure (HF). Much of this convergence is also underpinned by unifying genomic and gene programme changes, emphasising the cornerstone participation of our programme in the Genome Institute of Singapore. As a collection, HF and CVD afflict millions of patients globally (figure 1), and the incidence is increasing because of ageing populations in many different countries. In Singapore, CVD accounted for approximately 30 percent of all deaths in 2015, equating to 16 deaths per day. CVD is a top disease and healthcare burden in our country (figure 2). Moreover, especially in Singapore (and Asia), CVD appears to affect Singaporeans approximately ten years younger than western contemporaries. Most crucially, the five-year mortality for HF is about 50 percent, which is even worse than that for some well-known cancers (figure 3).

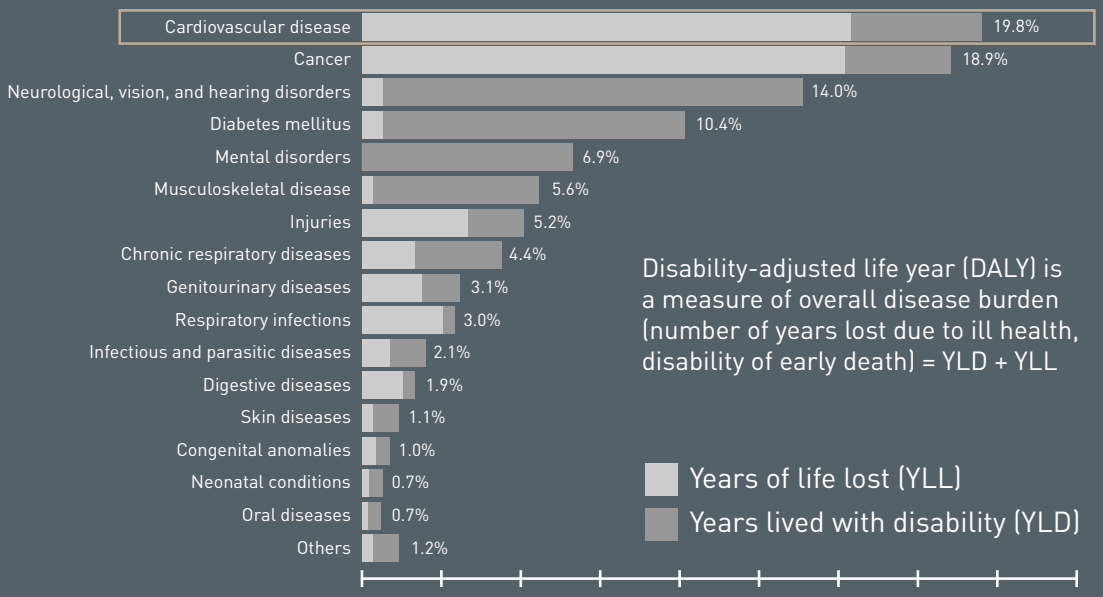
However, CVD research is a Cinderella story, because global CVD research funding lags significantly behind other areas such as cancer research (figure 4). For example, despite the scale of the global health problem, there was only one drug approved by the FDA for CVD in 2018 (figure 5).

Global cause of death worldwide, all ages (2016)



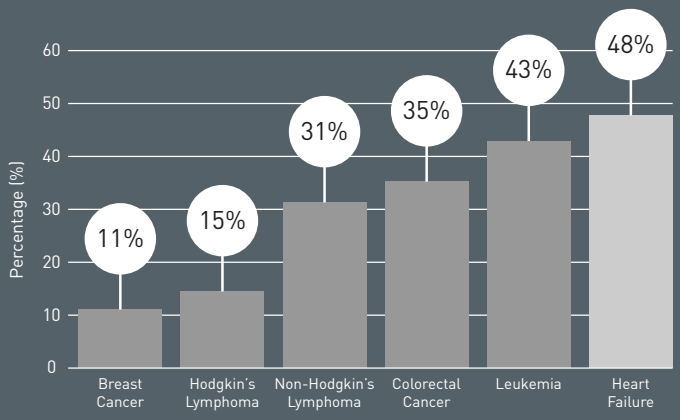
from healthdata.org (Global Burden of Disease, IMHE)

Global cause of death worldwide, all ages (2016)



Singapore MOH CVD Taskforce, 2018

Five-year Death Rates



Data from Novartis.com

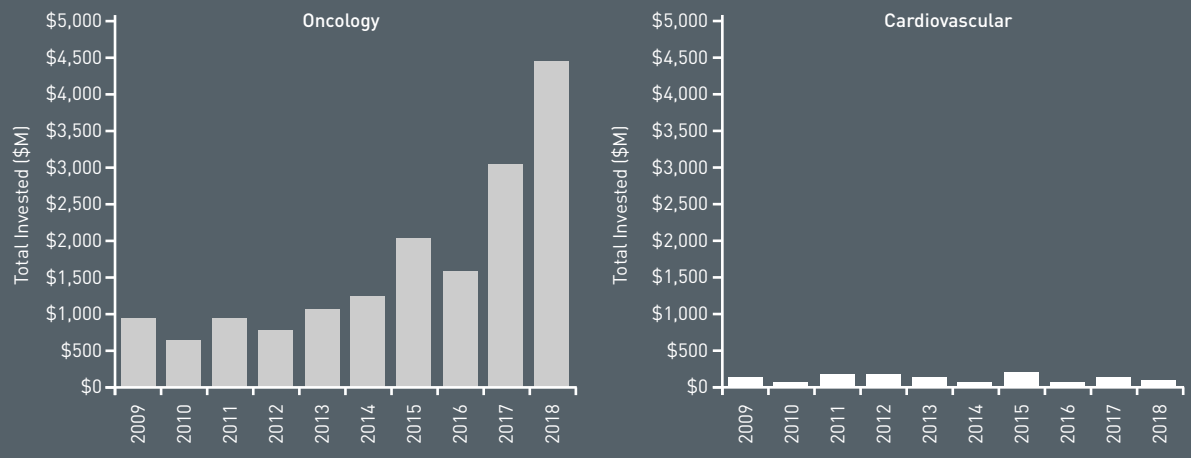
Figure 1, page 50. *The global burden of CVD is very high, even when compared to other well-known disease pathologies.*

Figure 2, Above. *CVD burden in Singapore (and Asia, not shown) is very high.*

Figure 3, Left. *The 5-year mortality for Heart Failure from onset of diagnosis is ~50%.*

Figure 4(a), below. *CVD drug discovery merits more investment.*

2009-2018 Venture Investment into U.S. Companies with Lead Novel Drug Programmes in Oncology VS. Cardiovascular AR Disease



From healthdata.org (Global Burden of Disease, IMHE)

FEATURE

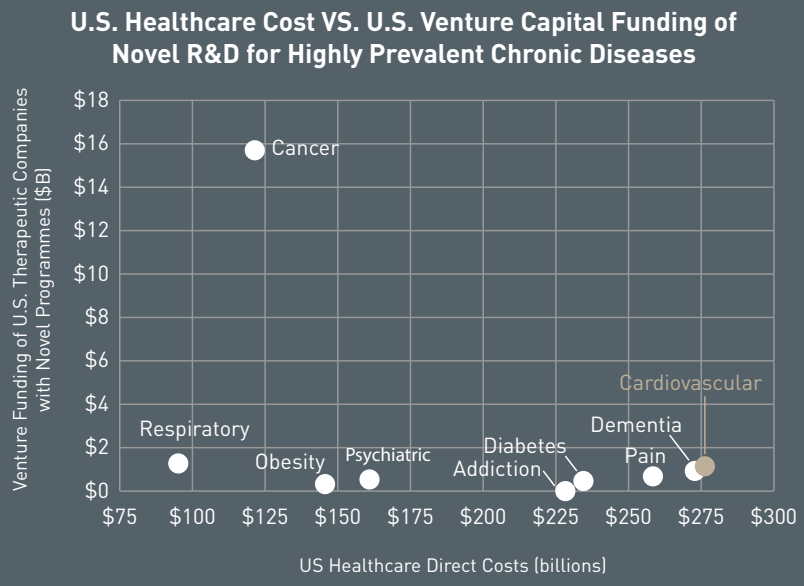
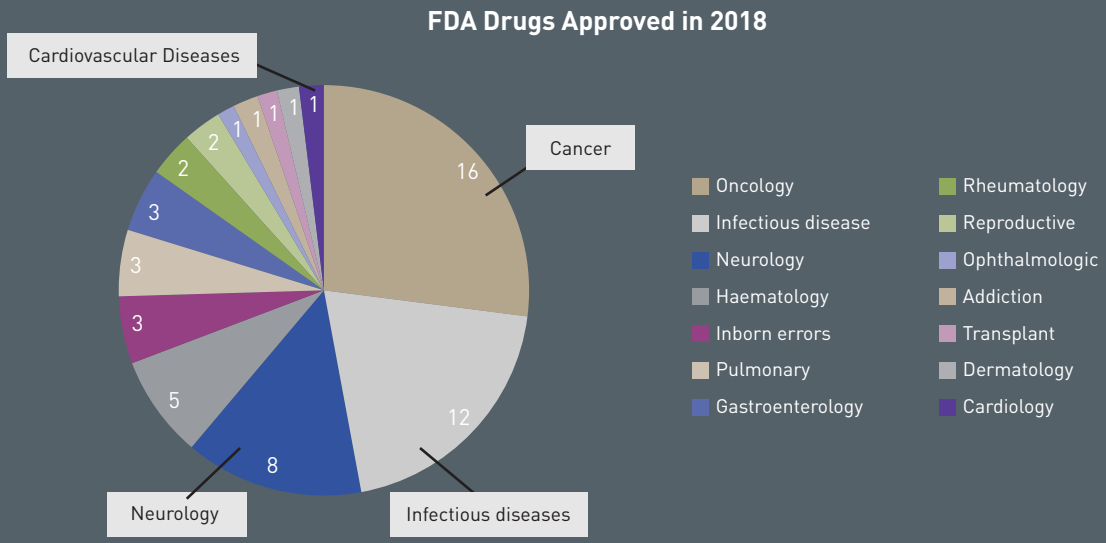


Figure 4(b), Left. *CVD drug discovery merits more investments, and is currently not propotional to its significant healthcare direct costs*

Figure 5, Bottom. *Only one FDA-approved drug for CVD in 2018, compared to many others for cancer and other diseases.*



New approaches and a deep understanding of CVD and HF in the Asian population are urgently needed, and these efforts will ideally be driven by our own part of the world. The treatment steps and drug classes being used to treat CVD and HF today are the same as those used for the past two to three decades. New medicines and new drug classes are desperately needed to address the expanding worldwide problem of CVD. Although current treatments are beneficial, they are no longer sufficient. New medicines and new drug classes are desperately needed to address the tremendous worldwide problem of CVD.

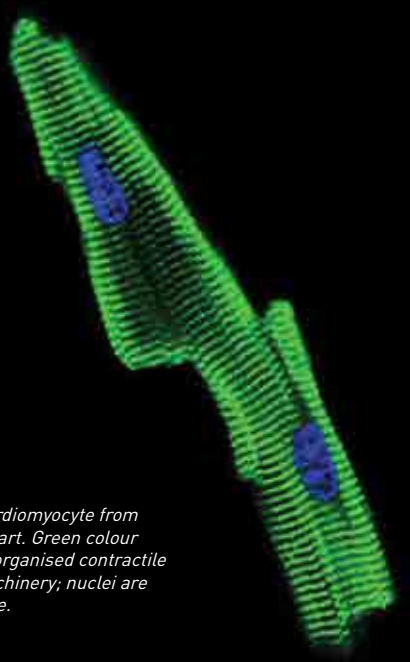
This theme sets out to leverage advanced technologies of single-cell RNA-seq, high content high-throughput phenotypic screens, and CRISPR-based *in vitro* and *in vivo* screening to identify and prioritise candidate genes (and epigenetic loci) for therapeutic targeting. We make use of at least two platforms of disease models. In the first, human pluripotent stem cell-derived cardiomyocytes are cultured *in vitro* or fashioned into three-dimensional engineered heart tissue organoids, and their electrophysiological and contractile properties are studied using time-lapse video microscopy. The other platform involves a small rodent model of surgery-induced HF or genetic knockout models of HF. Mice are phenotyped for HF using echocardiography, LV catheterisation, and histological analysis. AAV viruses are generated at scale in our labs to perform proof of-concept tests for gene targets. Although current treatments are beneficial, they are no longer sufficient.

CVD RESEARCH THEMES AT GIS

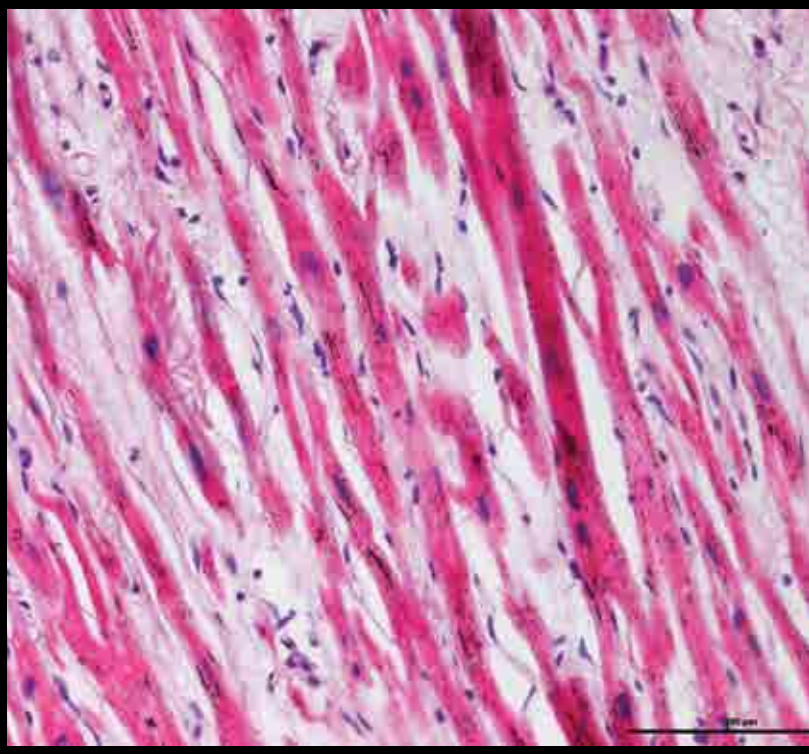
Asian-centric CVD genomics, genetics, and regulatory epigenomics

Collaborations involved: Foo, Liu, Khor, and Prabhakar labs

Thus far, CVD research at GIS has built upon the BMRC-funded ATTRaCT Heart Failure (HF) research programme. ATTRaCT is Asia's single largest HF cohort with over 2,500 patients and matched controls, two-year longitudinal follow-up, and deep and wide phenotyping, including whole genome sequencing, ~ten circulating biomarkers, and echo, MRI, and CT-based cardiac imaging. The overarching aim of this theme is to map the genomic architecture of HF disease among Asians and to identify Asian-centric genetic markers of disease and prognosis associated with the multiple phenotypic datasets in the same cohort. The regulatory epigenomic study of HF, using precious and limited heart muscle biopsies, focuses on identifying the role of genetic variants across the vast non-coding genome, such as by employing ChIP-seq and chromatin conformation analysis, to map out enhancer and regulatory elements in the cardiac genome.



A single cardiomyocyte from an adult heart. Green colour highlights organised contractile protein machinery; nuclei are stained blue.



Histological section of human left ventricle myocardium, exhibiting dilated cardiomyopathy and fibrosis.

Therapeutic target discovery, screens, and gene/epigenetic therapies for HF

Collaborations involved: Foo and Chew labs, AstraZeneca, and NovoNordisk

This theme sets out to leverage advanced technologies of single-cell RNA-seq, high-content high-throughput phenotypic screens, and CRISPR-based *in vitro* and *in vivo* screening to identify and prioritise candidate genes (and epigenetic loci) for therapeutic targeting. We make use of at least two platforms of disease models. In the first, human pluripotent stem cell-derived cardiomyocytes are cultured *in vitro* or fashioned into three-dimensional engineered heart tissue organoids, and their electrophysiological and contractile properties are studied using time-lapse videomicroscopy. The other platform involves a small rodent model of surgery-induced HF or genetic knockout models of HF. Mice are phenotyped for HF using echocardiography, LV catheterisation, and histological analysis. AAV viruses are generated at scale in our labs to perform proof-of-concept tests for gene targets.

Khor Chiea Chuen (Associate Director of Precision Medicine and Population Genomics, GIS), Michael Hauser (Professor, Duke University Medical Center), Janey Wiggs (Co-director, Glaucoma Center of Excellence), Aung Tin (Clinician Scientist, Singapore National Eye Center), Louis Pasquale (Professor, Mount Sinai), Mineo Ozaki (Director, Ozaki Eye Hospital), the late R Rand Allingham (Professor, Duke University Medical Center).

Existing Strengths and Opportunities

The GIS glaucoma programme partners with an excellent clinical team at the Singapore Eye Research Institute. The strong research culture of the team allows a large number of well-characterised samples to be available locally and internationally from a multicentre international consortium. In addition, the glaucoma team at SNEC is also a world leader in clinical trial participation and a leader in genetic studies based on Singapore and Asian samples.

Genomic tools (exome and genome sequencing) for both glaucoma and other eye disorders can be applied for discovery science, precision medicine, and therapeutic target identification.

Within Singapore's Health and Biomedical Science (HBMS) framework, glaucoma and ophthalmology are within the neuroscience and sense disorders domain. There is strong synergy with the movement disorders research team (centred on Parkinson's disease) jointly led by the National Neuroscience Institute and the Lee Kong Chian School of Medicine. This Parkinson's disease research team has also assembled a multi-centre consortium partnership of Asian investigators to study the genetic basis of Parkinson's disease.

There is substantial cross-fertilisation of ideas and research methodologies and sharing of genetic resources such as control populations (N > 30,000 participants) for genome-wide association studies and whole exome sequencing, and moving forward, there will be sharing of whole genome sequencing of the Singaporean population.

BIODIVERSITY AND NUTRITION

Biodiversity and Nutrition are two areas that contribute critically to human health and well-being; genetic studies of diverse living organisms from different biosystems remain highly underexplored, and these scientific opportunities and national priorities in Singapore intersect (figure 4).

Singapore is located at the centre of a key biodiversity hotspot (Sundaland, consisting of Borneo, Sumatra, Java, and Peninsular Malaysia), where major agricultural and industrialisation activities have imposed tremendous pressure on the environment and biodiversity. Conserving Singapore's biodiversity is at the heart of a national strategy that recognises the value of ecosystem services in an era of global warming, and it is in line with the vision of a "city in a garden" that needs to be preserved for future generations.

A related priority is meeting the nutritional needs of a rapidly ageing society for which a significant fraction of food is imported. Ensuring the safety and authenticity of the food that we consume, optimising scarce agricultural resources, identifying alternative foods, and understanding their impact on human health are all challenges where genomics can help meet Singapore's goals of sourcing 30 percent of its food locally by 2030.

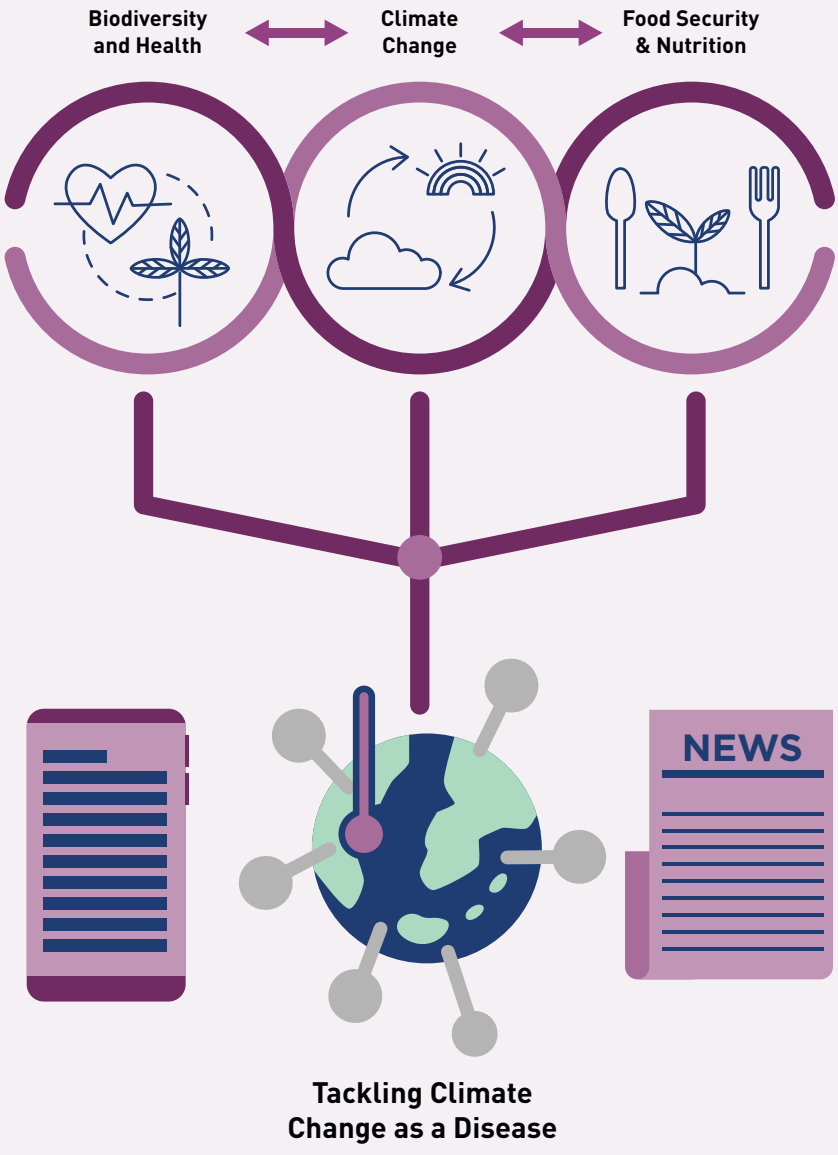


Figure 4, above. *Climate change-associated national priorities in Singapore.*

Demand Drivers in Biodiversity and Nutrition

- **Biodiversity and Human Health**
  Biodiversity underpins many terrestrial and aquatic complexes that contribute critically to human health and well-being, as publicly endorsed by leading organisations such as the World Health Organization, which has stated:

> *People depend on biodiversity in their daily lives, in ways that are not always apparent or appreciated. Human health ultimately depends upon ecosystem products and services (such as availability of fresh water, food and fuel sources) which are requisite for good human health and productive livelihoods... Additionally, biophysical diversity of microorganisms, flora and fauna provides extensive knowledge which carry important benefits for biological, health, and pharmacological sciences. Significant medical and pharmacological discoveries are made through greater understanding of the earth's biodiversity.* ***Loss in biodiversity may limit discovery of potential treatments for many diseases and health problems."***

In medicine, biodiversity studies have contributed directly to human health through the identification of drugs originating from plants, including paclitaxel (Pacific Yew), etoposide (May Apple), and vincristine (Madagascar Periwinkle). In Asia, there is widespread traditional use of local medicinal plants for promoting health and treating diseases, despite the fact that their modes of action and side-effects remain relatively unknown.

Nutrition/Urban Farming

At the dietary level, comprehensive characterisation of vegetables, fruits, and their sub-species may provide insights into their different nutritional benefits, which could potentially be further customised according to the genetics and health status of individuals and groups. Agricultural biodiversity is becoming increasingly prominent in the context of meeting global food supply needs in a period of climate change. More recently, increasing emphasis on urban biodiversity (e.g., neighbourhood gardening) has also highlighted an essential role for plants and animals (e.g., pets) in improving our living environment, which can have a positive impact on mental health.

Horticulture Industry

Explorations of biodiversity also have significant economic and commercial potential. For example, the orchid family (Orchidaceae) is the second largest family of flowering plants, with approximately 25,000-30,000 different species distributed nearly worldwide. The Phalaenopsis orchid is a key species in international floriculture, an industry valued at approximately US$300 million, and orchid growers constantly search for valuable floriculture traits from exotic genetics derived from species such as Dendobiums and Cymbidiums. In the case of durian, an increasingly popular fruit among Chinese, exports to China will grow from US$600 million currently to an estimated US$2 billion in the next few years, and this caters to only one to two percent of the Chinese population. The global herbal medicine market is expected to reach US$117 billion by 2024, due to the increasing popularity of herbal therapeutics compared to conventional drugs. This huge market also signals tremendous related commercial opportunities, including novel phytochemical discovery, new product development, and biosafety.

Metagenome

Antibiotic-resistant microorganisms have become a major threat to healthcare systems worldwide. The human gut harbours trillions of bacteria that benefit the host in various ways—breaking down undigested food, producing essential vitamins and nutrients, and training the immune system—but the gut also serves as a reservoir for antibiotic-resistant bacteria. We developed a novel genome assembler, OPERA-MS, that leverages portable DNA sequencing technology and sophisticated clustering algorithms to analyse complex bacterial communities in the gut by pulling together their entire genetic code to track the spread of antibiotic resistance and study microbial contributions to human health.

Existing Strengths and Opportunities

- **Singapore as a Centre for Southeast Asian Biodiversity**
  A well-known biodiversity project in Singapore is the National Orchid Garden, which houses over 1,000 Orchid species and 2,000 hybrids. However, to date, there has not been a coordinated, collective, and systematic initiative in Singapore or Southeast Asia to accelerate biodiversity research and its translation to impact health and medicine. As a leading nation in biotechnology and a hub of medicine in the region, it is of economic, medical, and cultural value for Singapore to fully appreciate the importance of Southeast Asian biodiversity and to harness its therapeutic, nutritional, and health potential, which can be uncovered through the use of cutting-edge technologies. In addition, the ecosystem services provided by Singapore's biodiversity are essential to the prosperity of this island nation, and it is critical that we use modern genetic techniques to understand the potential impact of climate change on the biological landscape.

- **Orchid Genetics**
  Orchids are Singapore's national flower and a national icon, attracting international and public attention through horticulture efforts and public displays at venues such as the National Orchid Garden (NOG). NOG's "orchid diplomacy" programme has been very successful in generating novel hybrids named after celebrities, political leaders, and notable individuals. The generation of genomics resources for orchids can integrate with NOG's expertise to contribute to international orchid conservation programmes, create value to the orchid industry, and further facilitate orchid diplomacy. For example, through genomics, one could select and cross genetic material associated with desired traits to create hybrids or species that can grow in otherwise incompatible conditions, possibly enriching the spectrum of species that can be suitably planted in urban environments including high-rise, land-scarce settings with varied requirements (e.g., sun, exposure, water, and fertiliser). This effort could further promote the NOG as a global resource and conservation centre in orchid species.

Advances in Sequencing Technologies and Algorithms

Recent developments in next-generation sequencing (NGS) technologies now make genomic studies of biodiversity feasible at scale and at affordable cost. Some advances include the development of new library preparation protocols that can produce high-quality reads with minimal biological material and simpler preparations, thereby reducing the costs and duration of analysis. The availability of long-read NGS platforms has allowed researchers to unravel the diverse genomes of plants with unprecedented speed and accuracy; examples of these technologies include Oxford Nanopore, which can generate read sequences longer than two Mbp, and Pacific Bioscience's (PacBio) Single Molecule Real-Time (SMRT) sequencing, which has the potential to sequence DNA with an average 30-kbp read length with accuracy >99 percent. Examples of plant genome scaffolds assembled by PacBio SMRT sequencing include the draft genome of *Durio Ziebethinus* (Teh et al., 2017), sugarcane (*Saccharum* spp.) (Olivier Garsmeur et al., 2018), raspberry (Vanburen, Robert et al., 2018), Tibetan hulless barley (Niyma Tashi et al., 2018), and others. Other important technologies for generating chromosome-level scaffolds are Hi-C (e.g., from Dovetail Genomics) and optical mapping (e.g., from Bionano Genomics). The successful exploitation of different datatypes for *de novo* analysis is also closely coupled with the ability to develop novel algorithms and to exploit advances in computational hardware.

Herbal Medicine

Global herbal medicine is a multi-billion-dollar industry that is not restricted to Chinese herbal medicine; medicines associated with other ethnicities, cultures, and geography are also influential in this market. Numerous phytochemicals with potential or established biological activities have been identified. For most of these preparations, little is known about the molecular basis of their purported benefits, while some are known to have adverse effects. One example is *Aristolochia*, a herbal plant genus with approximately 500 species widely distributed in tropical and subtropical areas, of which 23 species are used in Chinese herbal medicine. Several species of *Aristolochia* are known to produce the carcinogen aristolochic acid. However, the genetic basis of carcinogen production and of the active products with medicinal potential remain unknown.

Food Safety and Security

Food safety and security are crucial to Singapore, a country that relies heavily on imported food. Approximately 90 percent of the nation's food supply comes from over 160 countries, which exposes Singapore to the volatility of the global food market.

A study by the United Nations reports how "humanity's increasing demand for land and sea resources, coupled with climate change and sea-level rise, pollution and invasive species, demonstrated that food security is a worldwide threat". Singapore's high reliance on imports makes it more susceptible to associated risks.

To overcome our resource constraints, Singapore has set a 30 percent goal for domestically grown food by 2030. By embracing indoor agri-tech solutions and looking at new sources and novel foods of high nutritional value, Singapore can strengthen the resilience of its food supply through the improved cultivation of vegetables and fruit. Biotechnology solutions can be used to boost protein production and maximise land productivity and energy and water resources.

FEATURE

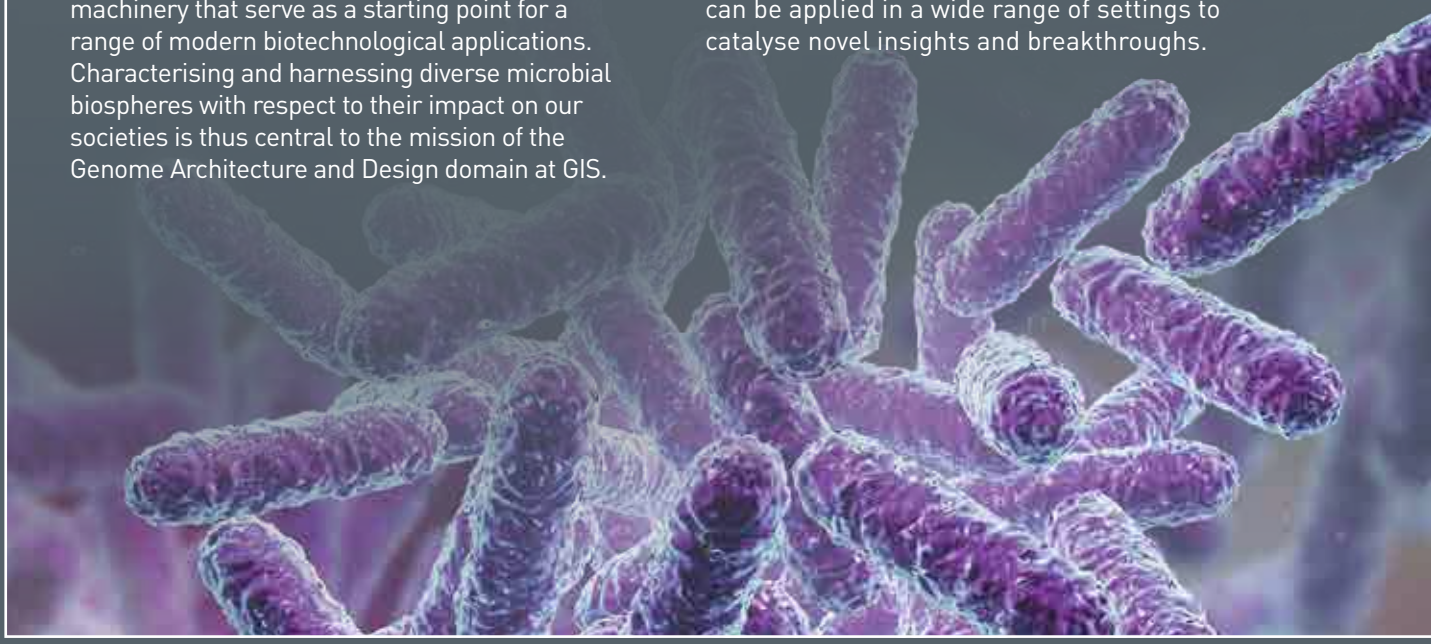
MICROBIOME RESEARCH AT GIS

Microbes are a ubiquitous, unseen presence on earth with an influence that is pervasive. While our perceptions of them are largely framed by the pathogens that we encounter, an accumulating body of evidence highlights the critical biochemical functions they perform in the environment and as commensal organisms in our bodies

The ability to isolate and culture specific microbes has allowed us to study them individually, in aggregate, and in interaction with different environments (e.g., with host cells). Recent advances in metagenomic techniques have further accelerated the high-throughput investigation of complex microbial communities in their natural habitats, expanding our understanding of the vast majority of microbes that we are unable to culture at present. The diverse forms and adaptations of life that microbes represent also capture most of the naturally evolved biological functions and machinery that serve as a starting point for a range of modern biotechnological applications. Characterising and harnessing diverse microbial biospheres with respect to their impact on our societies is thus central to the mission of the Genome Architecture and Design domain at GIS.

Technological Advances for Breakthrough Discovery

Microbial communities are often composed of hundreds of distinct species that co-operate, compete, or kill each other to produce complex dynamics. Many species have also co-evolved to benefit from exchange of metabolites, setting up chains of cross-feeding interactions that construct microbial food-webs. In the context of the human body, the trillions of bacteria that cohabit in the gut have several host-beneficial functions and are often seen as a dynamic microbial organ that responds to our varying dietary patterns. Understanding these "microbiomes" thus requires not only new modalities to capture information about their genetic composition, cellular activity, and metabolite exchange but also a systems biology approach to model, manipulate, and engineer in the presence of such complexity. Microbiome research at GIS thus has a strong focus on technologies to observe (e.g., long-read metagenomics), model (predator-prey or metabolic interactions), and engineer (*in vitro* models, RNA sensors) microbial consortia that can be applied in a wide range of settings to catalyse novel insights and breakthroughs.



Key Focus

Microbiome as a Mediator

Interactions between a host or environment and a potential pathogen are frequently influenced or mediated by a commensal microbiome. A systems understanding of these interactions can thus directly lead to the design of rational interventions that prevent pathogen colonisation or promote decolonisation. This emerging frontier of microbiome research and systems biology is a key focus at GIS, impacting studies in a variety of domains such as:

- Antibiotic-induced dysbiosis in the gut and subsequent pathogen colonisation
- Decolonisation of multi-drug-resistant pathogens from the gut microbiome
- Skin microbiome configurations and functions that prevent *S. aureus* overgrowth in atopic dermatitis
- Distribution of pathogens and antibiotic resistance in hospital environments
- Impact of environmental microbiomes on food safety

Collaborative microbiome research at GIS thus aims to span the gamut from discovery science to impactful applications, leveraging in-house technological advances together with our academic, clinical, and industrial partners.

INDUSTRY ENGAGEMENT AND INNOVATION

The aim of innovation at GIS is to leverage the strengths of genomic sciences for value creation through industry engagement and start-up initiatives.

GIS has invested public research funds as a base for intellectual property generation, leading to industry collaborations and spin-offs. These activities have been successful in attracting more private funding, generating value through jobs creation and impacts on public health. Industry partnerships and start-up development are key drivers for GIS to leverage our scientific strengths to create economic value and impact public health.

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INDUSTRY ENGAGEMENT AT GIS

- Industry-ready capabilities at GIS
- Mechanisms for partnering with industry
- Refining mechanisms for partnerships

P. 82

INNOVATION AND ENTREPRENEURSHIP AT GIS

- Understanding and navigating the innovation landscape
- Engaging investors in therapeutics and diagnostics spaces
- Leveraging on synergistic collaborations
- Filling the gaps in IP assets
- Value Creation for GIS 2030

INDUSTRY ENGAGEMENT AT GIS

The review committee recommended three strategic areas that are crucial for GIS in engagements with industry (multi-national companies (MNCs) and large local enterprises (LLEs)).

Industry-ready capabilities at GIS

To translate leading academic strengths into economic impact, GIS has in-house ISO-certified facilities and CAP-accredited facilities as part of the Centre for Genome Diagnostics to support translational initiatives. Leveraging the cutting-edge technologies in precision medicine, single-cell genomics, and computational biology, GIS has attained a level of infrastructure and "know-how" that make us attractive to partners in diverse industries.

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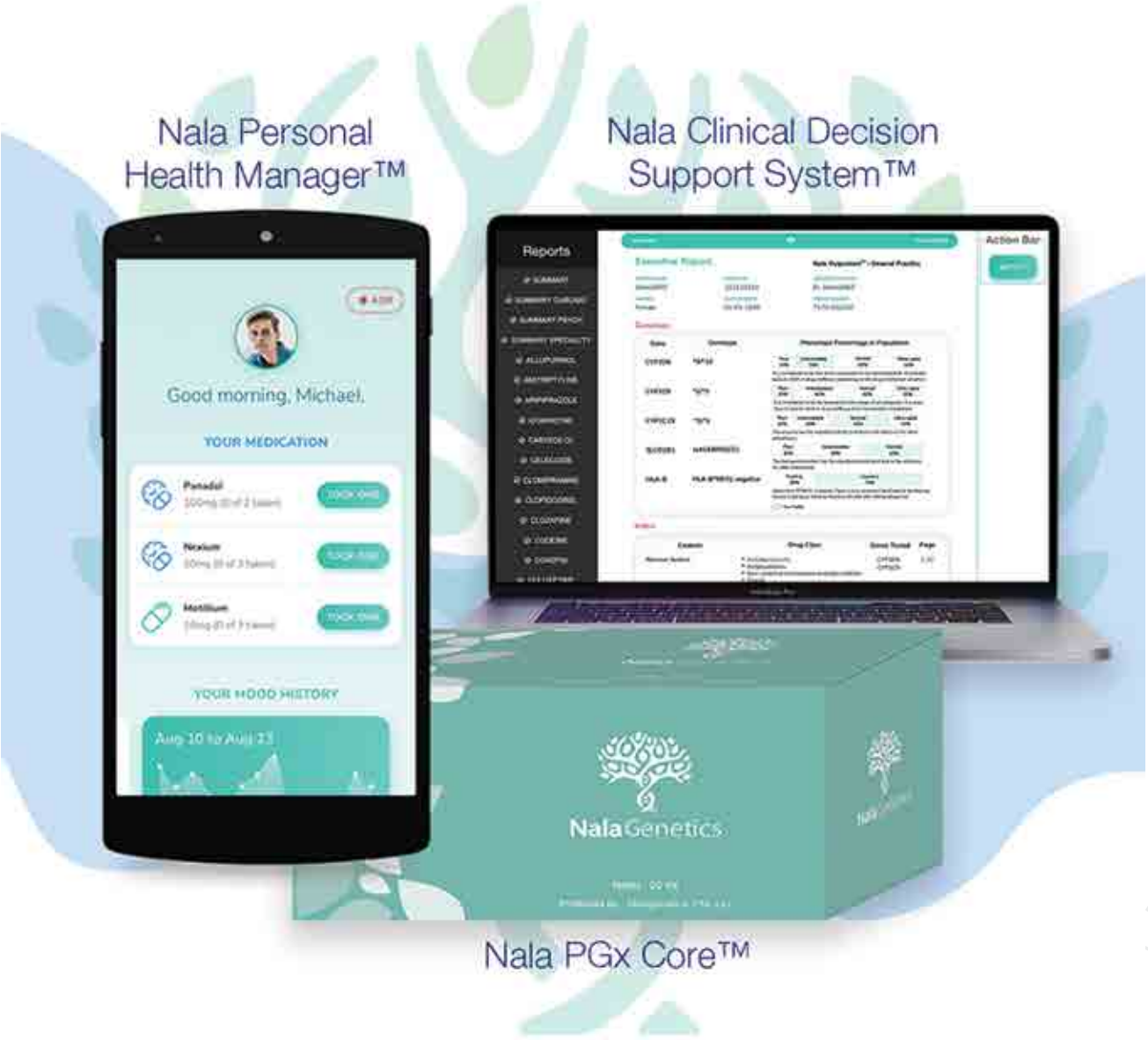
1. One BioMed-GIS Centre for Integrated Molecular Diagnostics
2. Centre for Precision Oncology: PuRPOSE Programme
3. GIS-NovogeneAIT Next Generation Sequencing (NGS) Platform



PGx Suite TM is an end-to-end Pharmacogenomics (PGx) testing tool for healthcare providers. Nalagenetics (a GIS-originated medtech company) created an algorithm to select the most important PGx biomarkers in Asia, developed their own clinical-grade genetic test kit, leveraged real-world evidence with a clinical decision support tool for the physicians, and created a patient engagement platform to facilitate follow up and data collection from patients.

GIS needs to continue to be flexible and adaptive in changing global and volatile business landscapes with evolving public/private research funding environments to remain competitive and attractive to MNCs and LLEs. One example of an emerging trend is the increased application of adaptive/artificial intelligence for understanding genomic sciences and aiding drug discovery. GIS will retain its relevance to industry through various measures, such as acquiring emerging technologies that are in line with GIS' overall mission and continually upgrading relevant talent and infrastructure.

Mechanisms for partnering with industry

GIS has an excellent track record of engaging MNCs and LLEs. GIS has developed capabilities for proof-of-principle studies and validation experiments to determine the feasibility, potential, and scalability of project ideas—important capabilities attractive to industry partners. These companies in turn offer complementary capability building for GIS, resulting in a "win-win" for both parties.

GIS has adopted a flexible policy for industry partnerships via the following four mechanisms to design efficient and effective project plans and craft agreements that fully meet the needs of all parties. In most cases, these projects are joint efforts that lead to shared intellectual property. Our partners would then have an opportunity to license any mutually developed IP.

Service Agreement

This allows the delivery of results to a partner when a project is straightforward and does not include significant novel research. This may include a sequencing project, data or genome analytics project, or consultancy.

Research Collaboration Agreement

GIS performs research and development with our partners to generate new intellectual property (IP) and know-how that addresses our partners' needs. This will enhance the partners' technological edge and could result in a downstream licensing agreement. Once a partnership is established, the GIS Office of Strategic Alliances department maintains the working relationship throughout the partnership, establishing lines of communication and project-specific governance structures.

The past decade has seen a substantial increase in the number and scale of industry collaborations with GIS and our partners. GIS has signed over 80 industry research collaboration agreements in the past seven years and is envisioning further partnerships with companies. Working with commercial partners is essential for translating excellent science to the implementation of new technologies and the delivery of novel services and products.

The broad range of scientific and technical expertise enables GIS to work with a wide variety of partners from large multinational companies to local start-ups across diverse sectors such as consumer, precision engineering, biotech, and pharmaceuticals.

Joint Lab

GIS engages with partners on a long-term strategic basis. In this case, the company sets up an R&D lab in the Genome building, and company personnel work closely with GIS scientists on research projects. Dedicated GIS resources are accessible to our partners, and vice versa, to advance research, technology transfer, and capability building for our partners.

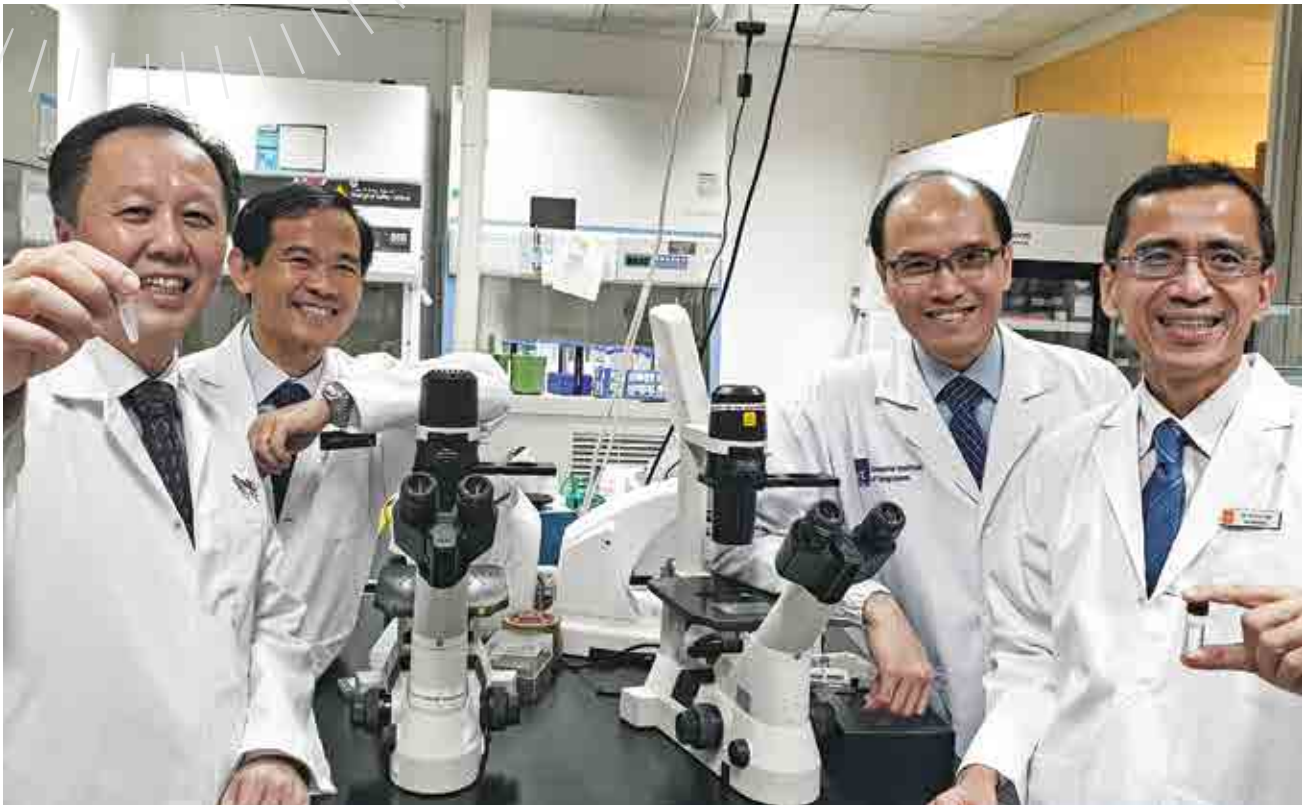
Co-operation

Recently, GIS pioneered a new model for industry collaboration—the co-operation agreement. This model enables a public-private partnership that harnesses industry resources and investment to accelerate our research. In this model, companies may locate their staff and equipment within GIS' dedicated facilities, where they can provide services required for our research efforts. Any extra capacity can then be directed to the provision of commercial services. This collaborative model benefits both parties.

Refining mechanisms for partnerships

There are existing standard operating protocols at GIS for principal investigators (PIs) to formalise partnerships with industry as described above. These standard procedures for establishing partnerships with industry should be continuously refined and improved, with the goal of facilitating administrative procedures without sacrificing the protection of GIS interests and the rigor of the industry partnership formation process.

INNOVATION AND ENTREPRENEURSHIP AT GIS



*Winners of the President's Science Award (team) 2018. From left: Associate Prof Lim Kah Leong (Head of Department of Physiology, Yong Loo Lin School of Medicine, NUS), Associate Prof Louis Tan (Senior Consultant, Neurology, National Neuroscience Institute), Prof Ng Huck Hui (then Executive Director of Genome Institute of Singapore, A*STAR), and Prof Tan Eng King (Deputy Medical Director of Academic Affairs, National Neuroscience Institute)*

GIS has a nascent **second arm of innovation—start-ups**, or spin-offs of GIS technologies, as a driver complementary to industry collaborations for translating technologies for "Bench-to-Bedside" initiatives and value creation.

Over the past decade, hundreds of acquisition and licensing deals between pharmaceutical companies and biotech companies were made annually. The first quarter of 2018 alone saw nearly 900 new deals (excluding mergers and acquisitions) with an estimated value of US$35 billion (Cortellis Competitive Intelligence). These biotech companies originated as spin-offs from academic research programmes (Vantage Pharma, Biotech and Medtech in Review 2019). These start-up initiatives are synergistic with industry engagement, enable intellectual property generation, and may result in future industry engagement.

The review committee recommended four strategic areas for the formulation of a robust start-up framework that will enable and incentivise GIS PIs to protect IP, enable the formation of more GIS spin-offs, and facilitate "Bench-to-Bedside" translation of GIS discoveries.

Understanding and navigating the innovation landscape

Trends in the biotechnology and start-up space are highly dynamic, and it can be challenging for scientists to keep up with these developments. Similar to cutting-edge research, the best ideas in biotechnology often remain dormant (or in stealth mode), incubated to certain stages of maturity before strategic announcements are made to the public. As such, scientists need to make informed choices about the best funding mechanisms to bring their ideas to market.

Engaging investors in therapeutics and diagnostics spaces

Therapeutics and diagnostics account for more than half of all biotech start-ups. By leveraging intellectual assets and know-how from mining human omics and metagenomics data to elucidate disease mechanisms, GIS is in a favourable position for spinning off drug discovery and diagnostics start-ups. GIS has been and will continue to engage stakeholders and investors who have working insights into the therapeutics and diagnostics start-up space.

Leveraging synergistic collaborations

Scientific discoveries that generate protectable intellectual assets are the foundation for spin-offs, and GIS is consistently focused on IP generation for value creation. Through industry collaborations, GIS has accelerated scientific research to develop biological insight and IP assets. This strategy has resulted in GIS partnering diverse companies and engagement with drug companies during later-stage GIS discoveries, generating more value for the institution.

In addition, GIS will be exploring the possibility of partnering and synergising strengths with fellow institutes within A*STAR for spin-offs.

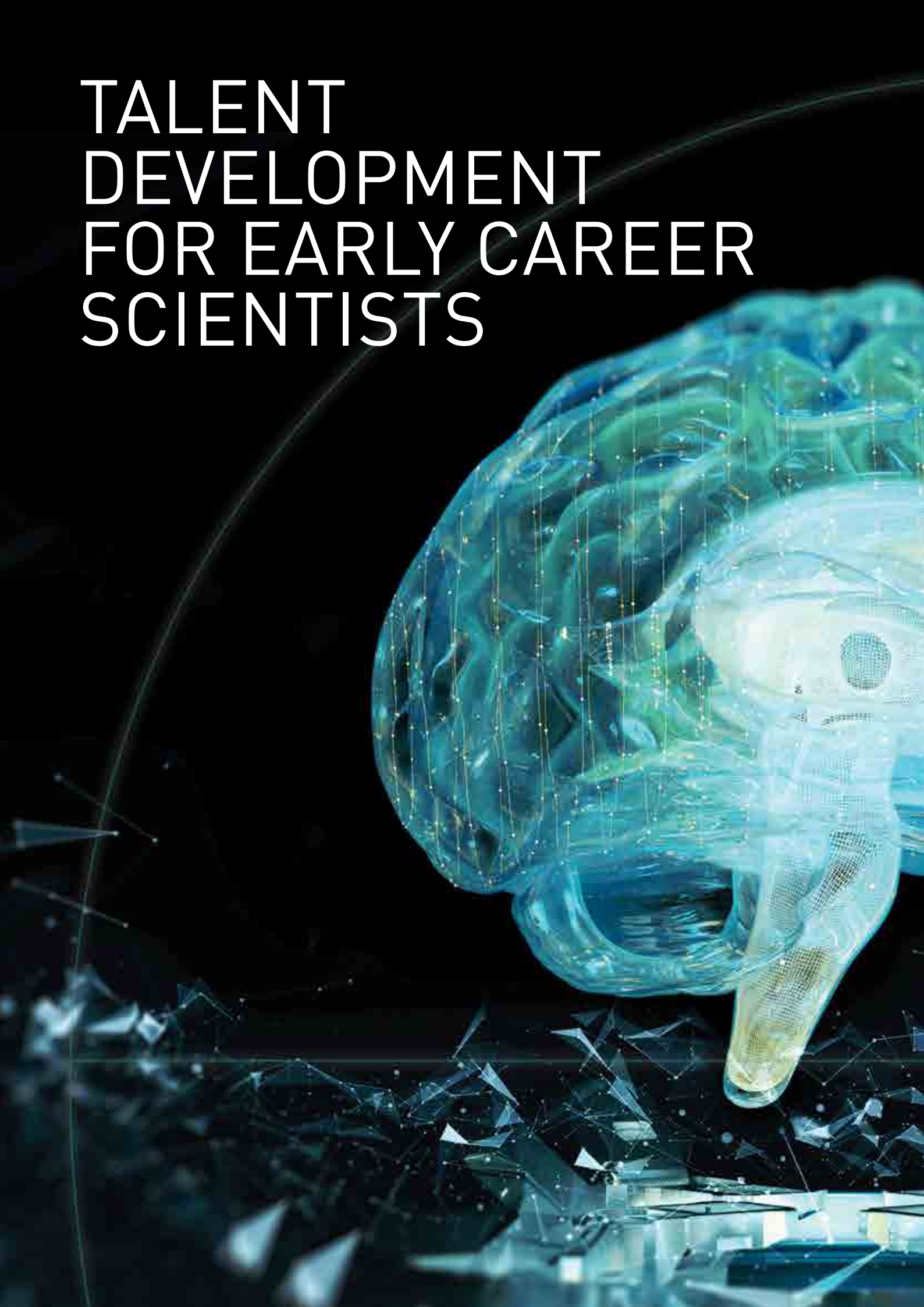
Filling the gaps in IP assets

Translating discoveries into therapeutics involves clinical trials of potential drug candidates. Both industry and investors have expressed interest in tangible assets against putative targets ("hit" or "lead" compounds). Emerging technologies such as CRISPR and RNA-based therapeutics enable the diversification of potential assets that GIS can develop, in addition to small molecules and compounds.

Value Creation for GIS 2030

Creating value through innovation initiatives requires dual-pronged strategies for industry engagement and the nurturing of GIS spin-offs. Despite the relatively short span of time since her entry into biomedical research, Singapore has made great strides in scientific advances and establishing a depth of biological insights. For GIS to achieve the desired outcomes in economic and public health impacts, concerted efforts need to be made in line with national mandates. Above all, GIS needs to be nimble and adaptive to remain competitive and cutting-edge.

TALENT DEVELOPMENT FOR EARLY CAREER SCIENTISTS



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JOINING THE GIS FAMILY

- Development of Genomics-Relevant Skillsets
- Factors Important to Career Progression
- Aspirations of Research Officers
- Potential Career Paths
- Talent Development Initiatives at GIS
- Summary

JOINING THE GIS FAMILY

Talent management continues to be one of the top concerns for human resources departments globally. Talent management is a commitment from an organisation to recruit, engage, motivate, develop, and retain employees. There are approximately 300 staff working in GIS, comprising principal investigators (PIs), platform leaders (PLs), administrative staff, postdocs, research officers (ROs), and graduate students. The GIS ECS talent pool as of end 2019 includes 96 postdocs, 42 graduate students, and 90 ROs. This group represents a significant proportion of the workforce at GIS.

To understand the needs of our early career scientist (ECS) talent at GIS, a survey was conducted to gather data on employment length at GIS, the kinds of skillsets desired and necessary for development, and factors perceived as important for career progression or transition. The objective of this survey was to determine optimal ways for GIS to support and empower these ROs, graduate students, and postdoctoral fellows towards maximum growth within the institute.

Development of Genomics-Relevant Skillsets

The ECSs highlighted communications, networking, interpersonal, leadership, and mentoring skills as the most important skillsets preferred for deeper development. Interview skills and presentation skills were also highly desired. Bioinformatics and data analytics capabilities were indicated as important expertise for development that could potentially provide alternative career options.

Factors Important to Career Progression

Awareness of available career options and access to career guidance were of paramount importance to the ECSs. Opportunities to network with local and international speakers in a less-formal setting to maximise interactions are deemed important for building the professional network of our ECS talents.

As a starting ground for building and developing communication and networking skills, both postdocs and graduate students were in favour of organising peer-reviewed research symposia in the absence of senior staff. In addition, the ECSs were highly receptive to the idea of an internal grant competition. Such competitions are considered capability-building opportunities contributing towards desired career progression.

Aspirations of Research Officers

82 percent of ROs surveyed wished for better career progression pathways, including opportunities to attend training courses and conferences. Job stability and clearer communication from supervisors regarding promotion criteria were highly important factors. Work-life balance and mentorship towards career progression were also highlighted.

Potential Career Paths

More than 65 percent of the ROs surveyed are open to the possibility of joining parallel industries (e.g., hospitals and commercial entities), whereas 40 percent are interested in administration careers (e.g., lab managers or secretarial roles in research offices). Approximately one third expressed interest in receiving re-training for switching from wet laboratory to dry laboratory research. The committee highly recommended empowering ROs suitable for this switch, given the increasing need for computational expertise within genomics research. Approximately 20 percent of the ROs also considered careers in A*STAR corporate departments (e.g., auditing, IPFM, and legal).

Talent Development Initiatives at GIS

The Talent Development Committee recommended the following training courses to develop and empower our GIS ECS talents.

Training Courses	GD	PD	RO	Conducted by
Effective Communication & Relationship Building	●	●	●	External Trainers
Teamwork Skills	●	●	●	External Trainers
Data Analytics	●	●	●	Internal
Project Management Skills	●	●	●	External Trainers
Adobe Illustrator	●	●	●	External Trainers
Leadership Skills		●	●	External Trainers
Interview Skills/CV Crafting	●	●		GIS HR Admin
Presentation Skills	●	●		External Trainers

GD Graduate Students PD Postdocs RO Research Officers

The committee also suggested the following initiatives in response to ECS needs.

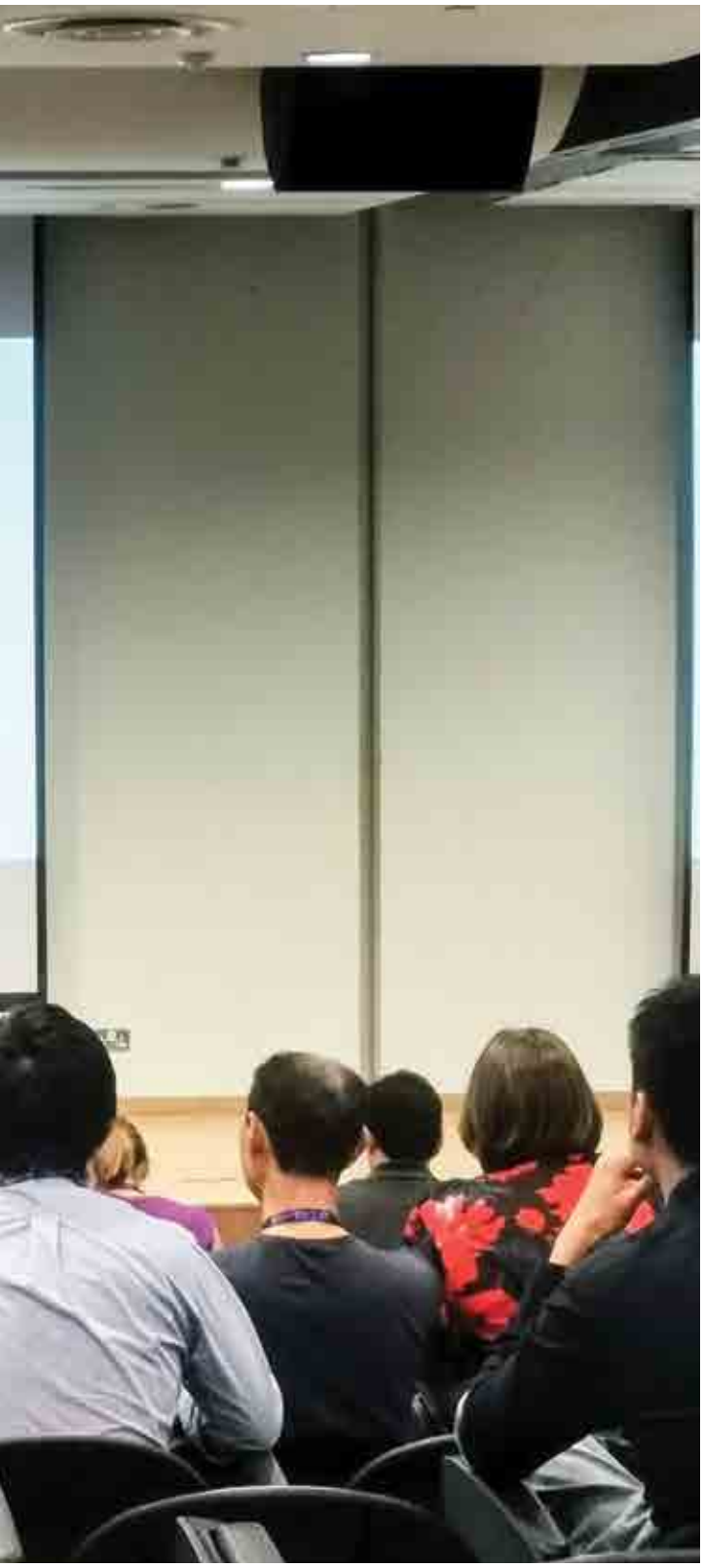
Proposed Initiative	Purpose
GIS Career Series	To create awareness among graduate students and postdocs about potential career paths beyond academic research.
Network Luncheon with Invited Speakers	Networking opportunities with both local and international invited speakers.
Structured Career Paths for Postdocs	Proposed to develop four career paths: Academic, Scientific, Platforms, and Innovation Fellows.
Chat/Support Groups	To strengthen personal bonds and provide an avenue for ECS talents to obtain help and support for professional and personal matters
Career Switches from Wet to Dry Bench	This provides a tangible way GIS can fulfil the personal aspirations of our talents while meeting the needs for computational talents in the institute.
Improving Opportunities for GIS Early Career Scientists	Feedback system for addressing concerns and improving processes. This system will allow everyone in the GIS community to voice their concerns and contribute to the ground-up development of the institute.

Summary

GIS aims to continue being a people-oriented organisation that recruits, develops, empowers, and retains talent. In line with the wider vision of A*STAR for talent attraction and development, GIS seeks to stay relevant to the evolving aspirations and career needs of GIS staff and students.

ENGAGEMENT EVENTS

GIS has a track record of partnering with respected organisations in genomics and big data analysis.




GoldenHelix
PHARMACOGENOMICS DAY
Singapore
Agilent

15th Asian Epigenomics Meeting (AEM)

2021

The 15th AEM 2021 was GIS' first virtual conference held on Zoom from 24 to 25 February 2021. It garnered over 650 participants from 18 countries, and featured a stellar line-up of keynote speakers comprising – Howard Chang (Stanford University, USA), Anne C Ferguson-Smith (University of Cambridge, UK), Eileen Furlong (European Molecular Biology Laboratory, Germany), Ana Pombo (Berlin Institute for Medical Systems Biology, Germany) and Bing Ren (University of California San Diego, USA). It also featured 18 invited speakers, six speakers from contributed abstracts, and 16 poster presentations. The meeting series was created in 2006 as a showcase for cutting-edge Asian science, and to seed collaborations and exchange of ideas between world-leading epigenetics researchers in Asia and beyond. These meetings cover a range of topics from basic biochemistry and biophysics of chromatin to gene regulation in development and disease. The series is hosted on a rotating basis by the six member countries: China, India, Japan, Singapore, South Korea, and Taiwan.

c-BIG Symposium

2019

Two-day symposium that provided a platform for discussions around big data and its role in precision medicine. c-BIG (the Centre for Big data and Integrative Genomics) is a multi-institute R&D consortium in Singapore composed of four A*STAR research institutes—GIS, Bioinformatics Institute, Institute for Infocomm Research, and Institute for High Performance Computing. c-BIG is tasked with building the genomics data management and analytics infrastructure for Singapore's National Precision Medicine Programme (NPMP).

Cell Symposium — Single cells: Technology to Biology

2019

Emerging technologies for single-cell omics for the study of genomes, epigenomics, transcriptomes, and proteomes are becoming increasingly widespread. This prompted GIS and Cell to co-organise a three-day conference, which provided a forum for sharing and disseminating cutting-edge technologies, biological insights, and biomedical applications in the field of single-cell analysis. Topics covered included atlasing cell types, perturbing and recording single cells, spatial profiling, epigenetics and multimodal profiling, data analytics, and precision medicine.

21st Golden Helix Pharmacogenomics Day

2018

This international event was co-organised by SAPhIRE (Surveillance and Pharmacogenomics of Adverse Drug Reactions, an A*STAR-funded programme). It featured presentations from local and international speakers on the impact of pharmacogenomics in various medical specialities, focusing in particular on bioinformatics solutions in pharmacogenomics.

Singapore-EMBL Symposium on Precision Medicine

2017

The symposium consisted of a public scientific conference focused on the emerging and cross-disciplinary field of precision medicine. The programme covered a wide range of topics spanning from computation genomics and bioinformatics to genetic and genomic databases with the aim of sharing the most up-to-date research trends, results, information, and databases.

Singapore Nanopore Camp

2018

The first edition in Asia since its inauguration in 2015, this five-day training bootcamp was based around Oxford Nanopore Technology (ONT)'s MinION sequencing system, which had been used to monitor the Ebola outbreak in 2015 and the Zika outbreak in 2016 and was the first sequencer in space. The workshop was a unique opportunity for hands-on experience generating and analysing MinION data. A field trip to the Singapore Botanic Gardens was held on the final day, when participants engaged in the sequencing and analysing of *Trametes sanguinea* (more commonly known as the lingzhi mushroom).

c-BIG Symposium

2016

An inaugural c-BIG symposium was held to bring together thought leaders across the entire spectrum of big data analytics, from infrastructure to algorithms, from omics to medical records, and from bench to bedside to cover the entire health system. The purpose of this engagement was to spur a larger national conversation on big data, foster interactions across institutional borders, and nucleate new initiatives. It also aimed to increase awareness of the importance of this area for precision medicine and the challenges and opportunities that lie ahead.

Cell Symposium – Human Genomics

2015

The first Cell Symposium held in Singapore. The aim of this meeting was to bring together leading researchers investigating a variety of aspects of human disease through genomic approaches, to share their findings, and to offer insights into future avenues for research and treatment. Some of the technological breakthroughs that were pushing this field forward were also highlighted.

International Conference on Systems Biology

2015

The ICSM has become one of the most important forums for the global systems biology community. The annual gathering attracted top systems biologists and interdisciplinary researchers from all over the world to display and discuss the most recent achievements and discoveries.

Forum on Genomic Medicine

2015

This forum was organised to discuss the impact of large-scale whole genome sequencing and analysis on biomedical research and healthcare service. The rapid development of NGS technologies, especially those related to large-scale whole genome sequencing, was transforming the landscape of biomedical research and potentially transforming clinical practice. Renowned speakers from Genomics England, The Children's Hospital of Philadelphia, deCODE, and Stanford University were invited to discuss how large-scale whole genome sequencing technologies were being employed to enhance national infrastructure for healthcare service and economic development, advance the clinical management of diseases, optimise the pipeline for drug development, and pursue personalised genomic medicine. By organising an event such as this, GIS and its partners aimed to create a national platform in Singapore for discussing the impact of large-scale whole genome sequencing analysis on biomedical research and healthcare service and for exploring a national strategy for advancing genomic medicine through the adoption of these technologies.

BaseSpace Worldwide Developers Conference

2014

Illumina and GIS jointly organised the first Singapore Worldwide Application Developers meeting for BaseSpace. At the training workshop, participants learned how to build and launch their own bioinformatics apps on BaseSpace.

RESEARCH STEWARDSHIP

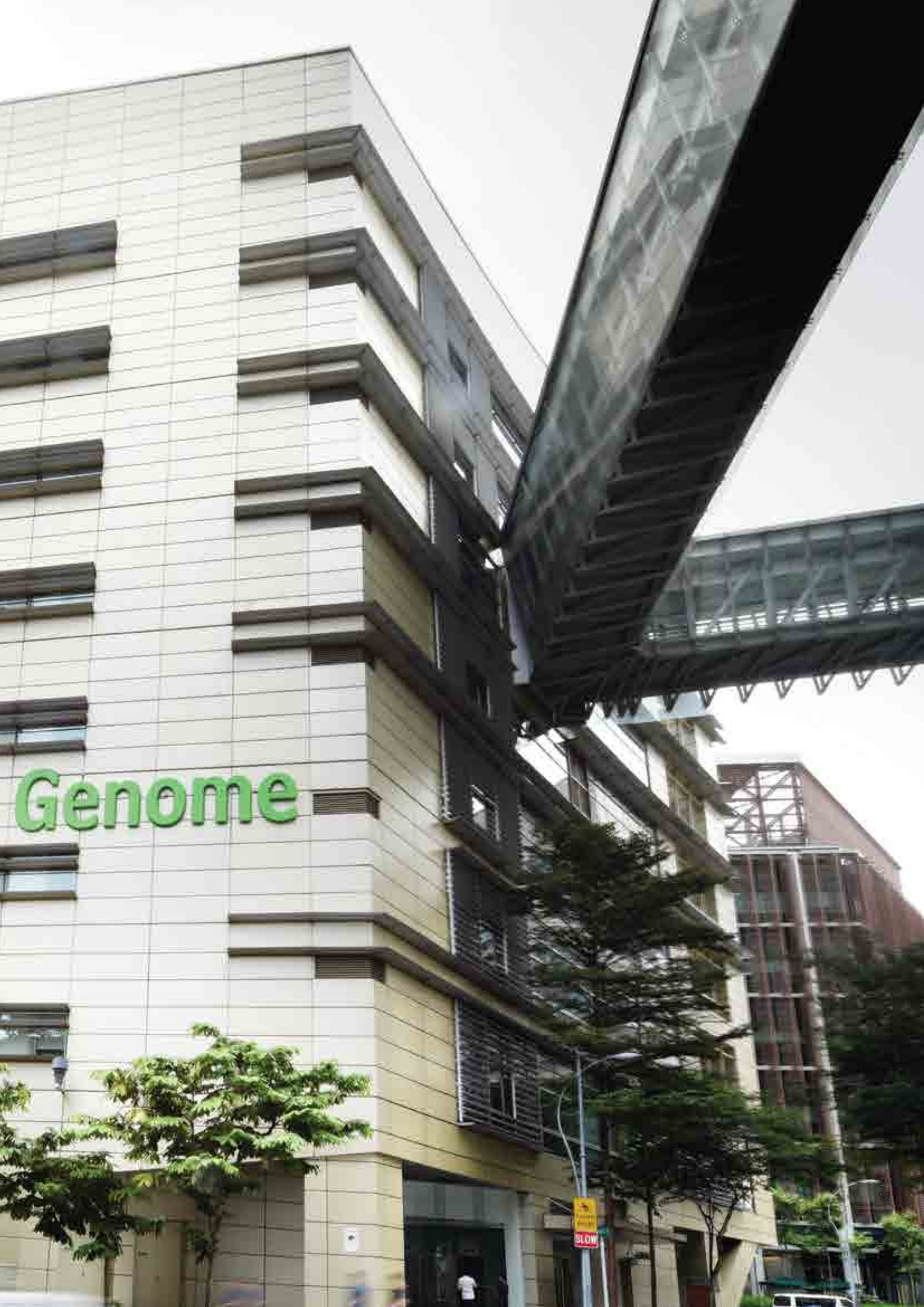
The GIS Research Administration division supports multiple areas necessary to operate the institute. Working closely with the GIS scientific units and external collaborators, this division strives to promote corporate innovation, uphold a safe and conducive working environment for all staff, and provide the infrastructure, network, and hardware that are required for GIS to operate as a world-class research institute.

As a leader in genomic science, GIS recognises that people are the essential building blocks for innovation and breakthroughs. We place great emphasis on attracting and nurturing talent as we strongly believe in people-centric leadership. The Research Administration works closely with the scientific domains to establish a framework that is anchored on recruiting and training the next generation of scientific leaders, nurturing human capital, and cultivating a positive environment for success. To this end, the various offices within Research Administration work intimately with internal colleagues, external publics, as well as other units and departments at A*STAR to ensure the smooth-running of the scientific research activities of the institute. Together, they form an integral network of functions that serve to promote, enhance, and engineer a healthier lifestyle.

The Research Administration division comprises the following cornerstones of GIS' genomic science:

- Office of Academic Affairs
- Office of Corporate Communications
- Office of Entrepreneurship & Innovation
- Office of Facility Planning & Laboratory Safety
- Office of Grant Management
- Office of Human Resources
- Office of Procurement
- Office of Research IT
- Office of Research Operations
- Office of Research Planning & Management
- Office of Strategic Alliances
- Office of Training & Diversity


Biopolis Dr


Genome
SLOW

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Biodiversity and Nutrition
Chew Wei Leong, Hazel Khoo (SIFBI), Khor Chiea Chuen, Li Jingmei, Rachel Low (BII), Niranjan Nagarajan, Patrick Tan

Cancer
Tam Wai Leong and Iain Tan (Chairs), Guo Yu Amanda, Loo Jia Min, Anders Jacobsen Skanderup, Raghav Sundar, Daniel Tan, Patrick Tan, Yeo Zhen Zhen Joanna, Yu Qiang

Cardiovascular Disease
Roger Foo

***De Novo* Sequencing**
Swaine Chen and Niranjan Nagarajan (Chairs), Matt Ackers-Johnson, Chen Ying, Li Zheng, Sarah Ng, Mile Sikic, Wendy Soon

EMULSION
Winston Chan

Epigenetics
George Anene, Roger Foo, and the Epigenetics strategy team (GIS)

Epitranscriptomics
Wan Yue (Chair), Ashley Aw, Sho Goh, Jonathan Göke, Pornchai Kaewsapsak, Pratanwanich Naruemon

Growth/Market Drivers of Genomics
Wendy Soon and Tan Yann Chong (Chairs), Sarah Geiger, Egor Revkov, Anders Jacobsen Skanderup

Infectious Disease
Swaine Chen

Innovation/Industry Engagement
Alexander Lezhava and Tan Yann Chong (Chairs), Nirmala Arul Rayan, Do Dang Vinh, Sarah Ng, Daniel Tan, Torsten Wustefeld, Daniel Yim

Liver Disease
Torsten Wustefeld

Metagenome
Denis Bertrand

Microbiome
Niranjan Nagarajan

Nalagenetics
Astrid Irwanto, Margaret Margaret

National Precision Medicine
Claire Bellis, Liu Jianjun, Patrick Tan

Nucleic Acid Therapeutics
Chew Wei Leong (Chair), Lavenniah Annadoray, Eddie Keng Choong Tat, Hannah Nicholas, Lavina Tay

Scientific Computing
Nicolas Bertin and Shih Chih Chuan (Chairs), Ang Chew Boon, Sarah Ng, Anders Jacobsen Skanderup, Jeffery Tay

Sequencing Platforms
Khor Chiea Chuen and Liu Jianjun (Chairs), Chau Man Ling, Sarah Ng, Anders Jacobsen Skanderup, Wang Jiaxu

Single Cell Genomics
Ramanuj DasGupta and Shyam Prabhakar (Chairs), Chew Wei Leong, Roger Foo, Florent Ginhoux, William Huang, Ankur Sharma, Wan Yue

Talent Development
Wan Yue (Chair), Jane Lee, Loo Jia Min, Bobby Tan

Secretariat
Wendy Soon, Daniel Yim, Winnie Lim, Lyn Lai

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