National Lymphoma Translational Research Program: From Genomics to Therapeutics
A National Concerted Effort Needed: Rising Incidence of NHL

5th most common in Singaporean Males

6th most common in Singaporean Females

Increasing trend observed in Singapore

Singapore Cancer Registry 2008-2012

Singapore Cancer Registry 2003-2007
Peripheral T Cell and NK/T cell Lymphoma (PTCL & NKTL): Geographical Distribution

Non-Hodgkin’s Lymphoma

B cell  T cell

PTCL  NKTL

Novelty of the proposal built around the endemic problem of T cell lymphomas in Asia

Frequencies of PTCL and NKTL in Asia and the Far West
### WHO Classification of Mature T-cell and NK-Cell Neoplasms

<table>
<thead>
<tr>
<th>LEUKEMIC or DISSEMINATED</th>
<th>CUTANEOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>T-cell granular lymphocytic leukemia</td>
<td>Mucocutaneous (\gamma\delta)T-cell lymphoma</td>
</tr>
<tr>
<td>Aggressive NK-cell leukemia</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Adult T-cell lymphoma/leukemia</td>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXTRANODAL</th>
<th>MAINLY NODAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td>Peripheral T-cell lymphoma,nos</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Anaplastic large cell lymphoma</td>
</tr>
</tbody>
</table>
NK/T Cell Lymphoma

Tse E, and Kwong Y Blood 2013;121:4997-5005
EBV PCR Clinical Trial

SMILE Regimen

Clinical Trial
Undetected
Undetected
PTCL and NKTL: An Unmet Need Globally and Asia in particular

Inferior survival of PTCL & NKTL compared to aggressive B cell NHL

Lack of therapeutic targets $P<0.0001$

Lacks molecular prognostic classifiers $P = 0.55$

Poor survival across major subtypes of PTCL and NKTL
Unraveling Mature T Cell Lymphoma: Three-prong approach

**Approach 1:** Integrated genomic profiling
- Mutational landscape
  - JAK3 activating mutation (*Cancer Discovery* 2012)
  - Genetic predisposition
    - BCL6-LPP germline driver in B-cell lymphoma (*Nature Genetics* 2013)
- Host-pathogens

**Approach 2:** Functional studies driven by genomic discoveries
- Inhibition of JAK/STAT pathway
- Inhibition of NFkB, EZH2 (*AJP, 2012; Blood* 2013)
- Inhibition of DNA methylation (manuscript in preparation)
- Inhibition of MATK (*Leukemia* 2012, 2013)

**Approach 3:** Towards rational targeted molecular therapy
- Translate findings from research grade material to clinically implementable assays
- Molecular biological and prognostic subgroups (*Blood, accepted*)

**Unraveling Mature T Cell Lymphoma:**
- Mutational landscape
- Host-pathogens
### Approach 1: Integrated Genomic Profiling

#### Availability of Tissues: A Competitive advantage

<table>
<thead>
<tr>
<th>Clinico-Pathological Database</th>
<th>Total Cases</th>
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</thead>
<tbody>
<tr>
<td>Diffuse Large B Cell Lymphoma</td>
<td>1520</td>
</tr>
<tr>
<td>Follicular Lymphoma</td>
<td>365</td>
</tr>
<tr>
<td>Marginal Zone Lymphoma</td>
<td>264</td>
</tr>
<tr>
<td>Primary CNS Lymphoma</td>
<td>125</td>
</tr>
<tr>
<td>PTCL/NKTL</td>
<td>350</td>
</tr>
<tr>
<td>Others</td>
<td>600</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3224</strong></td>
</tr>
<tr>
<td><strong>Tissue Samples</strong></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>1200</td>
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<tr>
<td>Fresh Frozen</td>
<td>370</td>
</tr>
<tr>
<td><strong>Paired PTCL/NKTL</strong></td>
<td><strong>74</strong></td>
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Janus Kinase 3–Activating Mutations Identified in Natural Killer/T-cell Lymphoma

Cancer Discovery 2012
Nuclear expression of MATK is a novel marker of type II enteropathy-associated T-cell lymphoma

Leukemia (2011) 25, 555–557; doi:10.1038/leu.2010.295; published online 14 January 2011

Classical enteropathy-associated T-cell lymphoma (EATL) is an uncommon neoplasm associated with a history of childhood coeliac disease. This tumour is characterized by ulcerating

Using a commercially available antibody (Santa Cruz SC-53 Santa Cruz, CA, USA) directed against MATK/Lsk (a non-receptor tyrosine kinase) in a number of immunolabelling techniques, we examined the expression of this molecule in 22 cases of type EATL, and in a wide variety of normal lymphoid tissues (tons lymph node, Peyer's patches in the ileum and appendix) at

Tan SY, SGH

ORIGINAL ARTICLE
Type II EATL (epithelialotrophic intestinal T-cell lymphoma): a neoplasm of intra-epithelial T-cells with predominant CD8αα phenotype

S-Y Tan1,2,3,19, S-S Chuang4,5,6, T Tang7, L Tan1, Y-H Ko8, K-L Chuah9, S-B Ng10, W-J Chng11,12, K Gatter13, F Loong14, Y-H Liu15, P Hosking16, P-L Cheah2, B-T Teh17,18, K Tay7, M Koh3 and S-T Lim7
Further pinpointed culprit for high risk of follicular lymphoma
- American Journal of Human Genetics
## Angioimmunoblastic T Cell Lymphoma: mutation spectrum

<table>
<thead>
<tr>
<th>Mutation</th>
<th>TET2</th>
<th>RHOA</th>
<th>DNMT3A</th>
<th>IDH2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>x</td>
<td>0.152</td>
<td>0.081</td>
<td>1</td>
</tr>
<tr>
<td>RHOA</td>
<td></td>
<td>1</td>
<td>0.135</td>
<td></td>
</tr>
<tr>
<td>DNMT3A</td>
<td></td>
<td></td>
<td>0.323</td>
<td>x</td>
</tr>
<tr>
<td>IDH2</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>TET2</th>
<th>RHOA</th>
<th>DNMT3A</th>
<th>IDH2</th>
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</thead>
<tbody>
<tr>
<td>70%</td>
<td>37.5%</td>
<td>17.5%</td>
<td>5%</td>
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</table>

<table>
<thead>
<tr>
<th>Mutation</th>
<th>TET2</th>
<th>RHOA</th>
<th>DNMT3A</th>
<th>IDH2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>RHOA</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IDH2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ASXL3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IDH2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>KDM5B</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>TP53</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>EP400</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>KSR2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ROR2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>RAD23A</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SOX9</td>
<td>2</td>
<td>2</td>
<td>2</td>
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</tr>
<tr>
<td>USP1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Mutation frequency (N)**

- **TET2**: 70% (28)
- **RHOA**: 37.5% (15)
- **DNMT3A**: 17.5% (7)
- **IDH2**: 5% (2)
- **ASXL3**: 5% (2)
- **IDH2**: 5% (2)
- **KDM5B**: 5% (2)
- **TP53**: 5% (2)
- **CDKN2A**: 2.5% (1)
- **EP400**: 2.5% (1)
- **KSR2**: 2.5% (1)
- **ROR2**: 2.5% (1)
- **RAD23A**: 2.5% (1)
- **SOX9**: 2.5% (1)
- **USP1**: 2.5% (1)
**Pathways involved**

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Mutation N</th>
<th>%</th>
<th>Gene Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>28</td>
<td>70</td>
<td>Involved in DNA demethylation</td>
</tr>
<tr>
<td>RHOA†</td>
<td>15</td>
<td>37.5</td>
<td>Small GTPase; regulates cell motility</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>7</td>
<td>17.5</td>
<td>DNA methyltransferase</td>
</tr>
<tr>
<td>ASXL3</td>
<td>2</td>
<td>5</td>
<td>Polycomb group protein; putative histone methyltransferase</td>
</tr>
<tr>
<td>IDH2</td>
<td>2</td>
<td>5</td>
<td>Involved in Krebs cycle; role in DNA methylation</td>
</tr>
<tr>
<td>KDM5B</td>
<td>2</td>
<td>5</td>
<td>Histone demethylase</td>
</tr>
<tr>
<td>TP53</td>
<td>2</td>
<td>5</td>
<td>Tumor suppressor; induces growth arrest or apoptosis</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>1</td>
<td>2.5</td>
<td>Tumor suppressor; stabilises p53; cyclin-dependent kinase inhibitor</td>
</tr>
<tr>
<td>EP400</td>
<td>1</td>
<td>2.5</td>
<td>Component of histone acetyltransferase complex</td>
</tr>
<tr>
<td>KSR2</td>
<td>1</td>
<td>2.5</td>
<td>Kinase suppressor of RAS2; negative regulator of MAP signaling</td>
</tr>
<tr>
<td>ROR2</td>
<td>1</td>
<td>2.5</td>
<td>Receptor tyrosine kinase; involved in the early formation of chondrocytes</td>
</tr>
<tr>
<td>RAD23A</td>
<td>1</td>
<td>2.5</td>
<td>Involved in nucleotide excision repair</td>
</tr>
<tr>
<td>SOX9</td>
<td>1</td>
<td>2.5</td>
<td>Involved in skeletal development</td>
</tr>
<tr>
<td>USP1</td>
<td>1</td>
<td>2.5</td>
<td>Deubiquitinating enzyme</td>
</tr>
</tbody>
</table>

Manuscript in revision
Oncogenic activation of JAK3 in NKTL

Constitutive JAK3 activation in >70% NKTL

Cancer Discovery 2012

Leukemia 2013

Results validated

Janus Kinase 3–Activating Mutations Identified in Natural Killer/T-cell Lymphoma

Janus kinase 3 (JAK3)
### JAK-Related Disorders and JAK Inhibitors.

<table>
<thead>
<tr>
<th>JAK</th>
<th>Activating Cytokines</th>
<th>Disorders Caused by Loss-of-Function Mutations</th>
<th>Disorders Caused by Gain-of-Function (Activating) Mutations</th>
<th>Pharmacologic Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1</td>
<td>Common γ-chain cytokines; interleukin-6 family; interleukins 10, 13, and 22; granulocyte colony-stimulating factor; interferons α, β, and γ</td>
<td>T-cell acute lymphocytic leukemia, B-cell acute lymphocytic leukemia, acute myeloid leukemia, ABC diffuse large-B-cell lymphoma, acute myeloid leukemia with severe congenital neutropenia</td>
<td>Ruxolitinib, baricitinib, tofacitinib, GLPG0634, ASP015K, AZD1480</td>
<td></td>
</tr>
<tr>
<td>JAK2</td>
<td>Erythropoietin and other hormonelike cytokines; interleukin-3 family; interleukin-6 family; interleukins 12 and 23; interleukin-13; granulocyte colony-stimulating factor; interferon-γ</td>
<td>Myeloproliferative neoplasm, polycythemia vera, essential thrombocythemia, primary myelofibrosis, Down’s syndrome-associated B-cell acute lymphoblastic leukemia, B-cell acute lymphocytic leukemia, primary mediastinal B-cell lymphoma, Hodgkin’s lymphoma</td>
<td>Ruxolitinib, baricitinib, tofacitinib, pacritinib, lestaurtinib, AZD1480</td>
<td></td>
</tr>
<tr>
<td>TYK2</td>
<td>Interferons α and β; interleukins 6, 10, and 13; granulocyte colony-stimulating factor; interleukins 12 and 23</td>
<td>Primary immunodeficiency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The hormonelike cytokines include growth hormone, prolactin, thrombopoietin, and leptin. The interleukin-3 family comprises cytokines that use the common β subunit, including interleukins 3 and 5 and granulocyte colony-stimulating factor. The interleukin-6 family comprises cytokines that use glycoprotein 130, including interleukins 6, 11, and 27; oncostatin M; ciliary neurotrophic factor; cardiotrophin-1; and leptin. Cytokines that use the common γ chain include interleukins 2, 4, 7, 9, 15, and 21. ABC denotes activated B-cell-like, JAK Janus kinase, and SCID severe combined immune deficiency.*
LYMPHOID NEOPLASIA

EZH2 overexpression in natural killer/T-cell lymphoma confers growth advantage independently of histone methyltransferase activity

Junli Yan,1 Siok-Bian Ng,1,3 Jim Liang-Seah Tay,3 Baohong Lin,4 Tze Loong Koh,4 Joy Tan,3 Viknesvaran Selvarajan,2,3 Shaw-Cheng Liu,1 Chonglei Bi,1 Shi Wang,2 Shoa-Nian Choo,2,3 Norio Shimizu,5 Gaofeng Huang,1 Qiang Yu,6 and Wee-Joo Chng1,3,4

1Cancer Science Institute of Singapore, National University of Singapore, Singapore; 2Department of Pathology, National University Health System, Singapore; 3Yong Loo Lin School of Medicine, National University of Singapore, Singapore; 4Department of Haematology-Oncology, National University Cancer Institute of Singapore, National University Health System, Singapore; 5Department of Virology, Tokyo Medical and Dental University, Tokyo, Japan; and 6Department of Cancer Biology and Pharmacology, Genome Institute of Singapore, Agency for Science, Technology and Research, Biopolis, Singapore

LYMPHOID NEOPLASIA

Dysregulated microRNAs affect pathways and targets of biologic relevance in nasal-type natural killer/T-cell lymphoma

Siok-Bian Ng,1 *Junli Yan,2 *Gaofeng Huang,3 Viknesvaran Selvarajan,1 Jim Liang-Seah Tay,4 Baohong Lin,3 Chonglei Bi,2 Joy Tan,4 Yok-Lam Kwong,5 Norio Shimizu,5 Katsuyuki Aozasa,7 and Wee-Joo Chng2,4

1Department of Pathology, National University Health System, Singapore; 2Cancer Science Institute of Singapore, National University of Singapore, Singapore; 3Department of Haematology-Oncology, National University Cancer Institute of Singapore, National University Health System, Singapore; 4Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; 5Division of Haematology/Oncology and Bone Marrow Transplantation, Queen Mary Hospital, Hong Kong; 6Department of Virology, Tokyo Medical and Dental University, Tokyo, Japan; and 7Department of Pathology, Osaka University Graduate School of Medicine, Osaka, Japan
Proposed model of NKTL pathogenesis

- EBV infection
  - JAK3 mutations (35%)
  - LMP-1 or other factors
  - MYC activation (45%)
    - ↓ miRNA
    - ↑ EZH2
  - STAT activation
  - NF-KB activation
    - Induce Survivin
      - P53 Deregulation (67%)
  - Anti-apoptotic
  - Proliferation

- P53 mutations (40%)
Translational Relevance

- **JAK3 activating mutations**
  - JAK3 inhibitors
  - STAT3 inhibitors

- **Myc activation**
  - EZH2 overexpression
  - EZH2 inhibitors

- **Stats activation**
  - NFKB activation
  - NFKB inhibitors

- **NKTL Proliferation and survival**
Epitheliotropic Intestinal T Cell Lymphoma

Leukemia 2012
Approach 3: Biological rationale and perspectives that can be translated in clinical practice both diagnostically and therapeutically.
Bortezomib (BTZ) and Panobinostat (PAN) Combination Is Effective in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma (PTCL) or NK/T-Cell Lymphoma (NKL) and Maintenance Treatment May Be Essential for Sustained Response

**Program:** Oral and Poster Abstracts

**Session:** 623. Lymphoma - Chemotherapy, excluding Pre-Clinical Models: Poster III

**Monday, December 10, 2012, 6:00 PM-8:00 PM**

Hall B1-B2, Level 1, Building B (Georgia World Congress Center)

**Authors:**

Daryl Tan, MD1,2, William YK Hwang, MBBS, FRCP, FAMS3,4, Colin Phipps Diong5*, Wee Lee Goh, BSc6*, Lionel K.Y See, BSc3*, Yiong Huak Chan, PhD7*, Soon Thye Lim, MRCP MBBS8*, Soo Chin Ng, MBBS MRCP9*, S Fadilah, MBBS10*, Soo-Yong Tan, MBBS, FRCPath, DPhil11*, Won Seog Kim, MD12* and Yeow Tee Goh, MD* 

1Department of Hematology, Singapore General Hospital, SG, Singapore
2Raffles Cancer Center, Singapore, Singapore
3Department of Hematology, Singapore General Hospital, Singapore, Singapore
4Cancer and Stem Cell Biology, Duke-NUS Graduate Medical School Singapore, Singapore, Singapore
5Department of Hematology, Singapore General Hospital
6Department of Hematology, Singapore General Hospital, Singapore, Singapore
7Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
8Medical Oncology, National Cancer Centre of Singapore, Singapore, Singapore
9Sime Darby Medical Centre, Kuala Lumpur, Malaysia
10Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
11Department of Pathology, Singapore General Hospital
12Samsung Medical Center, Seoul, South Korea

**Background**

BTZ and PAN have demonstrated activity in T- and NK/TLymphomas. BTZ is an active ingredient in the ASH recommendation for NK/T-cell lymphoma. Combination chemotherapy has been shown to improve outcomes in PTCL. However, the role of maintenance therapy remains undefined.
Approach 3: Clinical Applications

Robust molecular classifiers and oncogenic pathways that reflect the pathobiology of tumor cells and their microenvironment were identified for major PTCL-entities.

Substantial number of cases of PTCL-nos were re-classified into recognized PTCL subgroups.

Molecularly defined entities

Singapore Lymphoma Study Group
The Lymphoma Leukemia Molecular Profiling Project
Published in Blood
Clinical Applications

Gene expression signatures delineate prognostic subgroups of PTCL

NEJM, under review
Translational Relevance

- Defined robust molecular diagnostic and prognostic signatures for the more common subtypes of PTCL and segregated them into meaningful biological and prognostic subtypes
- Identified enriched oncogenic pathways associated with the different PTCL entities and the biologic insight gained provides possible novel therapeutic targets for intervention

Next Aim:
To translate this to daily clinical application using readily available Formalin Fixed Paraffin Embedded Tissue (FFPE)
Potential Strategies for PTCL

- **AITL:**
  - NF-κB pathway via bortezomib or carfilzomib
  - Specific inhibitors against IDH2 mutation that are being developed.
  - Reverse the immunosuppressive microenvironment (e.g. lenalidomide)

- **ALK(-) ALCL:**
  - Drugs that target mitotic cells (e.g. aurora kinase inhibitors) in combination with drugs that target PI3-Kinase/AKT pathway.

- **GATA3 subgroup PTCL-NOS:**
  - Drugs that target mTOR (e.g. rapamycin, temsirolimus)
Asian Lymphoma Study Group

Blood 2012

Management of T-cell and natural-killer-cell neoplasms in Asia: consensus statement from the Asian Oncology Summit 2009

Yok-Lam Kwong, Benjamin O’Anderson, Ronjana Advani, Won-Seog Kim, Alexandra M Levine, Soon-Thye Lim

T-cell and natural-killer (NK)-cell lymphomas are neoplasms with geographical variations in frequencies. T-cell lymphomas are more prevalent in Asia than in Europe and North America, and NK-cell lymphomas occur almost exclusively in Asia and South America. These low frequencies mean that the diagnosis and optimum treatment of patients with T-cell and NK-cell lymphomas have not been studied prospectively in randomised controlled trials. Because T-cell and NK-cell lymphomas are more prevalent in Asia, the establishment of management recommendations

Management of B-cell non-Hodgkin lymphoma in Asia: resource-stratified guidelines

Dr Daryl Tan MD a b, Soo Yong Tan MD c d e, Soon Thye Lim MD d f, Seok Jin Kim MD g, Prof Won-Seog Kim MD g, Prof Ronjana Advani MD b, Prof Yok-Lam Kwong MD b

Summary

Treatment of B-cell non-Hodgkin lymphomas has undergone substantial developments in the past 10 years. The introduction of rituximab has greatly improved survival outcomes in patients. Clinical practice guidelines based on current evidence have been developed to provide recommendations for standard treatment approaches. However, guidelines do not take into account resource limitations in resource-poor countries. The huge disparities in economy, health-care infrastructure, and access to novel drugs between Asian countries can hinder the delivery of optimum care to patients with lymphoma in Asia. We outline guidelines appropriate to different levels of health-care resources and expertise, aiming to provide advice on diagnosis and treatment, unify interpretation of results, and allow the design of future studies in Asia. In this resource-adapted consensus, we summarise recommendations for diagnosis, staging, risk stratification, and treatment of common B-cell non-Hodgkin lymphomas in Asia.
Our competitive advantage:
Significant Scientific Recognition

- A focus and niche problem
- Establish track records
- Build on existing structure
- Patient samples, cell lines, xenografts
- Extensive collaborations
- Multi Institutional Team
- Inter-disciplinary research
- Pharmaceutical Interest, clinical impact

Singapore Lymphoma Study Group
Metagenomic and Methylation Profiling of Gastrointestinal Lymphomas
Dr Joanne Ngeow, NCCS

Delineating oncogenic pathways of Natural Killer / T-cell Lymphoma and identification of molecular subsets of prognostic and clinical importance
Dr. Ng Siok Bian, NUHS
National Lymphoma Translational Research Road Map

We are here

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-trial validation</th>
<th>Clinical Trials</th>
<th>Implementation: Routine care</th>
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<tbody>
<tr>
<td>• Characterization of mutational landscape</td>
<td>• Validation of mutational data &amp; outcomes correlation</td>
<td>• Integration of genomics data into clinical trials</td>
<td>• Routine diagnostic tests</td>
</tr>
<tr>
<td>• Highly recurrent mutations</td>
<td>• Functional studies</td>
<td>• Personalized medicine initiatives</td>
<td>• Treatment decisions</td>
</tr>
<tr>
<td>• Definition of molecular subtypes</td>
<td>• Establish clinically useful platforms</td>
<td>• Commercial collaborations</td>
<td>• Implementation of novel agents targeting molecular subtypes</td>
</tr>
<tr>
<td>• Molecular epidemiology</td>
<td>• Commercial collaborations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Commercial collaborations
• Integration of genomics data into clinical trials
• Personalized medicine initiatives
• Commercial collaborations
• Routine diagnostic tests
• Treatment decisions
• Implementation of novel agents targeting molecular subtypes