GLOBAL LEADERS IN GENOMIC MEDICINE MEETING

Indian Perspective

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Ministry of Science and Technology
STRUCTURE OF THE PRESENTATION

- Strategy: Benefits and targets in Indian Context
- Implementation of Genomic Medicine in India: DBT initiatives
- Hurdles in Implementation
- Collaborations
Strategy: Benefits and targets in Indian Context

- Implementation of Genomic Medicine in India: DBT initiatives
- Hurdles in Implementation
- Collaborations
AREAS LIKELY TO BE BENEFITTED

Diseases
- Adult onset
- Rare diseases

Prediction
- Adverse drug effects
- Pregnancy

Diagnostics
- Point of care
- Affordable
- Novel

Increased Knowledge
- Integrated body functioning
- Organismal adaptability to genetic changes
- Translational research boost
Strategy: Benefits and targets in Indian Context

Implementation of Genomic Medicine in India: DBT initiatives

Hurdles in Implementation

Collaborations
INFRASTRUCTURE DEVELOPMENT AT INSTITUTES FOR ADVANCED GENOMIC RESEARCH AND PHARMACOGENOMICS IMPLEMENTATION
GENETIC CATALOGUING OF ETHNIC GROUPS

Data coordination

1. Clinicians
2. Molecular Geneticists
3. Anthropologists

Creation of baseline data on various ethnic groups for disease susceptibility
PROMOTING TRANSLATIONAL RESEARCH

- Diagnostic kits
- Vaccines using reverse genetics
- Molecular tool for surveillance
- Control of Newcastle disease by siRNA mediated inhibition of virus
- Disease based sequence analysis
PRE-NATAL CARE

✓ Maternal risk and pregnancy risk prediction
✓ Fetal Risk Prediction and anomaly diagnosis
✓ initiating programs involving Developmental biology, Pregnancy Risks and Pre-term Birth
✓ Setting up of Genetic Clinics
Genomics and Epigenomics of Cancer

Transcriptomics of Cancer

NIBMG is a part of the International Cancer Genome Consortium (Oral Cancer)
OTHER AREAS

✓ Strengthening of bioinformatics network by creating Genome Mirror sites

✓ Regulatory guidelines for Genomic Medicine techniques, research activities and harmonisation with international ethical guidelines (National Bioethics Commitee- DBT nodal agency).

✓ Manpower training in various aspects of Genomic Medicine

✓ Establishment of transformed cell line for rare and genetic diseases and their genetic analysis

✓ Funding of research in areas like genotype-phenotype correlation in oxidative stress related gene polymorphisms, DNA repair proteins, mutation screening in Congenital Adrenal Hyperplasia, finding drug targets in P.falciparum, diagnosis using pharmacogenetic tools, biomarkers, cancer genomics
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Collaborations
COMMON BARRIERS IN IMPLEMENTATION

✓ Handling large dataset
✓ Evidence for health treatments are based on research goals
✓ Research waste due to lack of expertise
✓ Lack of regulatory guidelines
✓ Incidental findings majorly
✓ Lack of knowledge in primary healthcare providers
✓ Need for better technologies
✓ Large dataset for patients and lack of translation/interpretation
✓ Funding and political will
Strategy: Benefits and targets in Indian Context

Implementation of Genomic Medicine in India: DBT initiatives

Hurdles in Implementation

Collaborations
POSSIBLE AVENUES FOR COLLABORATION

✓ Streamlining of guidelines for implementation and preclinical/clinical trials
✓ Use of traditional knowledge and integration into modern genetics
✓ Cloudsourcing for translation of genetic data
✓ Development of new methods of disease classification based on recently discovered genetic principles
✓ Building community interest and participation
✓ Building data sharing capabilities
✓ Unify strategies ongoing at various places
✓ Set up biobanking facilities
✓ Training of Manpower
✓ Building study cohorts
THANK YOU
Over to

PARTHA MAJUMDER
National Institute of Biomedical Genomics
Kalyani, India

Genetic Epidemiology of Cancer in India
CANCER ATLAS OF INDIA

Indian Council of Medical Research
(in collaboration with WHO)

1980-2000
Districtwise Minimum Age Adjusted Incidence Rate Per 100,000
tongue
(ICD10,C01-C02) - Males
Districtwise Minimum Age Adjusted Incidence Rate Per 100,000
TONSIL
(ICD10, C09) - Males
Districtwise Minimum Age Adjusted Incidence Rate Per 100,000

**OROPHARYNX**

(ICD10, C10) - Males
Institutions involved in Cancer Research

Clinical cum Basic
1. All India Institute of Medical Sciences (AIIMS), New Delhi
2. Kidwai Memorial Institute of Oncology (KMIO), Bengaluru
3. Tata Memorial Hospital (TMH), Mumbai
4. Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai
5. Cancer Institute (WIA), Chennai
6. Rajiv Gandhi Center For Biotechnology (RGCB), Thiruvananthapuram
7. Institute of Cytology & Preventive Oncology (ICPO), Noida

Basic Biology of Cancers
1. National Centre for Cell Sciences (NCCS), Pune
2. National Brain Research Centre (NBRC), Manesar
3. National Centre for Biological Sciences (NCBS), Bengaluru
4. National Institute of Immunology (NII), New Delhi
5. Mazumdar Shaw Cancer Center (MSCC), Bengaluru
6. Indian Institute of Science (IISc), Bengaluru
7. Institute of Life Sciences, Bhubaneshwar

Adjunct Facilities
1. C-CAMP, Bengaluru
2. Institute of Bioinformatics, Bengaluru
3. C-DAC, Pune

Slide Courtesy:
Dr. Bindu Dey, Adviser, DBT
Focus of Research

Based on Disease-burden
- Oral/Head & Neck cancer
- Cervical cancer
- Breast cancer sp. triple-negative, pre-menopausal cancer

Uniqueness to India
- Nasopharyngeal cancer- NER
- Gall Bladder cancer- Along Ganges belt; mostly in women
- Gastric cancer from Nagaland (Naga cancer)/Kashmir

Competence availability
- Gliomas (funding primarily by CSIR)
- Leukemias

Work initiated
- Lung cancer
- Pancreatic cancer

Slide Courtesy:
Dr. Bindu Dey, Adviser, DBT
<table>
<thead>
<tr>
<th>Lead Jurisdiction</th>
<th>Funding Organization</th>
<th>Tumor Type</th>
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<tbody>
<tr>
<td>Australia</td>
<td>National Health and Medical Research Council</td>
<td>Pancreatic Cancer&lt;br&gt;Ductal adenocarcinoma&lt;br&gt;Ovarian Cancer&lt;br&gt;Serous adenocarcinoma</td>
</tr>
<tr>
<td>Canada</td>
<td>Ontario Institute for Cancer Research&lt;br&gt;Ontario Ministry of Research and Innovation</td>
<td>Pancreatic Cancer&lt;br&gt;Ductal adenocarcinoma</td>
</tr>
<tr>
<td>China</td>
<td>Chinese Cancer Genome Consortium</td>
<td>Gastric Cancer&lt;br&gt;Intestinal- and Diffuse-type</td>
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<tr>
<td>European Union/France</td>
<td>European Commission FP7</td>
<td>Renal Cancer&lt;br&gt;Renal cell carcinoma&lt;br&gt;Focus on but not limited to clear cell subtype</td>
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<tr>
<td>European Union/United Kingdom</td>
<td>European Commission FP7</td>
<td>Breast Cancer&lt;br&gt;Subtypes defined by an amplification of ER+ HER2: ductal-type</td>
</tr>
<tr>
<td>France</td>
<td>Institut National du Cancer</td>
<td>Breast Cancer&lt;br&gt;HER2 positive&lt;br&gt;Liver Cancer&lt;br&gt;Hepatocellular carcinoma&lt;br&gt;Secondary to alcohol and adiposity</td>
</tr>
<tr>
<td>Germany</td>
<td>Federal Ministry of Education and Research&lt;br&gt;German Cancer Aid</td>
<td>Pediatric Brain Tumors&lt;br&gt;Medulloblastoma</td>
</tr>
<tr>
<td>India</td>
<td>Department of Biotechnology, Ministry of Science &amp; Technology</td>
<td>Oral Cancer&lt;br&gt;Gingivobuccal&lt;br&gt;Enteroctodermal carcinomas and rare enterochromaffin-like tumors</td>
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<tr>
<td>Japan</td>
<td>RIKEN&lt;br&gt;National Institute of Biomedical Innovation</td>
<td>Liver Cancer&lt;br&gt;Hepatocellular carcinoma&lt;br&gt;Virus associated</td>
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<tr>
<td>Spain</td>
<td>Spanish Ministry of Science and Innovation</td>
<td>Chronic Lymphocytic Leukemia&lt;br&gt;CLL with mutated and unmuted IgVH</td>
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<tr>
<td>United Kingdom</td>
<td>Wellcome Trust&lt;br&gt;Breaththrough Breast Cancer</td>
<td>Breast Cancer&lt;br&gt;Triple Negative/Lobular/Other</td>
</tr>
<tr>
<td>United States</td>
<td>National Institutes of Health</td>
<td>Brain Cancer&lt;br&gt;Glioblastoma multiforme&lt;br&gt;Ovarian Cancer&lt;br&gt;Serous cystadenocarcinoma&lt;br&gt;Lung Cancer&lt;br&gt;Squamous cell carcinoma&lt;br&gt;Adenocarcinoma&lt;br&gt;Leukemia&lt;br&gt;Acute myeloid leukemia&lt;br&gt;Colon Cancer&lt;br&gt;Adenocarcinoma</td>
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Squamous Cell Carcinoma of the Oral Cavity: Epidemiological Features

• 8th most common cancer
• ~260,000 new cases annually
• 2/3rd in developing countries
• 128,000 deaths annually

• Accounts for ~1/3rd of all tobacco-related cancers in India.
Site Distribution of Oral Cancer

INDIA

- 73.4% Gingivobuccal Complex
- 26.6% Tongue & Floor of Mouth

WEST

- 68% Gingivobuccal Complex
- 22% Tongue & Floor of Mouth

Gingivobuccal Complex
Buccal Mucosa, Lower Gum, Retromolar Trigone (RMT)

Slide courtesy: Dr. Anil D’Cruz, Tata Memorial Hospital, Mumbai
<table>
<thead>
<tr>
<th>Gene</th>
<th>p-value</th>
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<tbody>
<tr>
<td>CASP8</td>
<td>&lt;10^{-13}</td>
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<tr>
<td>TP53</td>
<td>&lt;10^{-13}</td>
</tr>
<tr>
<td>FAT1</td>
<td>4.10 x 10^{-13}</td>
</tr>
<tr>
<td>HRAS</td>
<td>3.42 x 10^{-05}</td>
</tr>
<tr>
<td>ARID2</td>
<td>1.85 x 10^{-04}</td>
</tr>
<tr>
<td>TRPM3</td>
<td>1.84 x 10^{-03}</td>
</tr>
<tr>
<td>UNC13C</td>
<td>1.90 x 10^{-03}</td>
</tr>
<tr>
<td>USP9X</td>
<td>2.56 x 10^{-03}</td>
</tr>
<tr>
<td>MLL4</td>
<td>1.22 x 10^{-02}</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>1.43 x 10^{-02}</td>
</tr>
</tbody>
</table>

Discovery Sample Size = 50 patients
Validation Sample Size = 60 patients
## Pathways Most Significantly Altered

<table>
<thead>
<tr>
<th>Description of pathway</th>
<th>No. of patients affected</th>
<th>p-value</th>
<th>% of genes altered in pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 signaling pathway</td>
<td>36</td>
<td>4.87E-09</td>
<td>41.2</td>
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<tr>
<td>Apoptosis</td>
<td>37</td>
<td>5.21E-09</td>
<td>42.0</td>
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<tr>
<td>Viral carcinogenesis</td>
<td>39</td>
<td>2.12E-06</td>
<td>36.7</td>
</tr>
<tr>
<td>Neurotrophin signaling pathway</td>
<td>40</td>
<td>7.12E-06</td>
<td>41.7</td>
</tr>
<tr>
<td>Wnt signaling pathway</td>
<td>39</td>
<td>0.00095</td>
<td>37.7</td>
</tr>
</tbody>
</table>
Profile of ‘Significant’ Genomic Alterations

Risk exposure
- Tobacco
- Areca nut
- Alcohol
- HPV

Significantly altered genes
- TP53
- FAT1
- CASP8
- USP9X
- MLL4
- NOTCH1
- HRAS
- UNC13C
- ARID2
- TRPM3
- PCLO
- FAT3
- SMG1
- MLL2
- SYNE2
- EP300

Genes with copy number alteration
- 11q13.3 - CCND1
- 5p13.3 - CDH1, DROSHA
- 3q26.2 - MECOM
- 9p22.3 - NFIB
- 11q22.2 - MMP, YAP1
- 22q11.23 - GSTT1
- 9p21.3 - CDKN2A
- Xp11.4 - DDX3X
- 16q22.1 - CDH19

No. of mutations, Mb
- Silent Mutations
- Non-Silent Mutations

Frequencies of various types of SNVs and indels
- Indel
- A→mutation (T→mutation)
- CpG C→A/G (G→T/C)
- CpG C→G (G→A)
- Non-CpG C→G/T (G→C/A)
- Non-CpG C→A (G→T)

Legend:
- Nonsense / Frame-shift / Splice-site
- Missense / In-frame Insertion-Deletion
- Deletion
- Amplification
We obtained evidence of whole genome duplication in at least 7 tumor samples (Ploidy > 4n).
Patients Form 3 Groups by the Spectra of Mutations
Patients with Mutations in *MLL4* Have Longer Disease Free Survival

With mutation (GREEN line): 20.4±3.1 months
Without mutation (BLUE line): 13.5±0.9 months

*p*=0.047
Mutational landscape of gingivo-buccal oral squamous cell carcinoma reveals new recurrently-mutated genes and molecular subgroups

India Project Team of the International Cancer Genome Consortium