19 May 2015
Hospital Authority Convention 2015
Corporate Scholarship Presentation II
Paediatric Services

Inborn Errors of Metabolism
From Neonatal Screening
to Metabolic Pathways

Dr Grace Poon
Associate Consultant
Department of Paediatrics and Adolescent Medicine
Queen Mary Hospital
July – September 2014

Department of Molecular & Human Genetics
Baylor College of Medicine
Texas Children Hospital
Houston, Texas, USA

Funded by
The Centre of Excellence in Paediatrics (CEP)
2014/2015 Overseas Training Programme for Doctors
and supported by the Hospital Authority of Hong Kong
Professor Brendan Lee, MD, PhD

Robert and Janice McNair
Endowed Chair in Molecular
and Human Genetics

Professor and Chairman,
Department of Molecular
and Human Genetics,
Baylor College of Medicine
Professor Fernando Scaglia, MD
Houston, Texas
Texas Medical Center

World’s largest medical complex:
- 21 renowned hospitals
- 13 supporting organizations
- 8 academic and research institutions
- 6 nursing programmes
- 3 public health organizations
- 3 medical schools
- 2 universities
- 2 pharmacy schools
- 1 dental school
Texas Medical Center
Texas Medical Center
Texas Medical Center
Baylor College of Medicine
Department of Molecular & Human Genetics
Baylor College of Medicine

• Embodies 5 decades of organized genetics activity
• Starting in 1970’s with the arrival of Dr C Thomas Caskey and Dr Arthur Beaudet
• Now one of the leading genetics programme in the world
• Integrating basic research in genetic and genomic mechanisms, translational research in disease models, observational and therapeutic clinical trials in genetic diseases
• Providing prenatal, paediatric and adult medical genetics care and cutting edge genetic diagnostic services
Department of Molecular & Human Genetics
Baylor College of Medicine

Rank # 1 in grants and funding from the National Institutes of Health (NIH) amongst genetics departments in USA

- More than 80 faculty members – in research, graduate training, clinical, diagnostic laboratory and genetic counselling
- More than 20 clinical faculty members
- 6 metabolic physicians:
  - Lindsay Burrage, MD, PhD
  - William Craigen, MD, PhD
  - Brett Graham, MD, PhD
  - Brendan Lee, MD, PhD
  - Fernando Scaglia, MD
  - V Reid Sutton, MD
Texas Children Hospital
Texas Children Hospital (TCH)

- Paediatric hospital in Texas Medical Center
- The largest children’s hospital in USA
- Affiliated with Baylor College of Medicine
- 1561 doctors
- 595 beds with 25,966 admissions in the most recent year reported
- Rank 4th amongst paediatric hospitals in the nation (US News Best Children Hospitals 2014-2015 ranking)
- Rank 2nd nationally in cardiology & heart surgery and in neonatology
- Features the largest level-3 NICU in the nation with more than 170 NICU beds
Texas Children Hospital (TCH)

- WEST TOWER – paediatric wards, PNICU, Emergency Center
- Clinical CARE CENTER – outpatient clinics
- FEIGIN CENTER – pediatric research
- ABERCROMBIE BUILDING – pathology, auxiliary and volunteer services, international services, medical staff and security services
- Pavilion for Women – Ob/Gyn
- St Luke’s Episcopal Hospital – adult hospital
Texas Children Hospital (TCH)

- WEST TOWER – paediatric wards, PNICU, Emergency Center
- Clinical CARE CENTER – outpatient clinics
- FEIGIN CENTER – pediatric research
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- Pavilion for Women – Ob/Gyn
- St Luke’s Episcopal Hospital – adult hospital
Standard paediatric room
Texas Children Hospital (TCH)

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- Clinical CARE CENTER – outpatient clinics
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- Pavilion for Women – Ob/Gyn
- St Luke’s Episcopal Hospital – adult hospital
Clinical Care Center
Texas Children Hospital (TCH)

- WEST TOWER – paediatric wards, PNICU, Emergency Center
- Clinical CARE CENTER – outpatient clinics
  - FEIGIN CENTER – pediatric research
- ABERCROMBIE BUILDING – pathology, auxiliary and volunteer services, international services, medical staff and security services
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Texas Children Hospital
Feigin Center
Texas Children Hospital (TCH)

- **WEST TOWER** – paediatric wards, PNICU, Emergency Center
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Professor Carlos Bacino, M.D.

- Chief of Genetics Service, Texas Children’s Hospital
- Director of Pediatric Genetics Clinic
- Medical Director of Cytogenetics Laboratory, Baylor Miraca Genetics Laboratories
The Metabolic Team
Clinical Faculty

• Dr Linsay Burrage
• Prof William Craigen
• Dr Brett Graham
• Prof Brendan Lee
• Prof Fernando Scaglia
• Prof V. Reid Sutton
Other metabolic team members

1. Kerri Lamance
   Metabolic Clinic Coordinator

2. Kristian “Kiki” Ugarte
   Metabolic nurse

3. Catherine Loffredo
   Research nurse

4. Suzanne Boyer
   Metabolic dietitian and clinical programme coordinator
Professor Vernon Reid Sutton

- Medical Director of Biochemical Genetics Laboratory, Baylor Miraca Genetics Laboratories
- Director of ABMG Diagnostic Laboratory Training Programs
- Director of Medical Genetics Residency & Fellowship Programs
<table>
<thead>
<tr>
<th>Time</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
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<tbody>
<tr>
<td>8:00</td>
<td>TCH Faculty Genetics Clinic</td>
<td>Smith Clinic (Harris Health System) Adult Clinic</td>
<td>VA Adult Genetics Clinic</td>
<td>TCH Pediatric Genetics Clinic</td>
<td>Baylor Clinic Adult Genetics Clinic</td>
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<tr>
<td>11:00</td>
<td>ABMG trainee lecture</td>
<td>Biochemical Genetics Case Review</td>
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<td>12:00</td>
<td>Clinical Genetics Seminar</td>
<td>Research Seminar</td>
<td>TCH Metabolic Clinic</td>
<td>TCH Pediatric Cancer Genetics Clinic</td>
<td>Genetics Grand Rounds</td>
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<td>Post-Clinic Conference</td>
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**Genetics Elective**

*Block Diagram of Outpatient Clinics & Conferences for Pediatric Residents*

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<thead>
<tr>
<th>TCH Clinics</th>
<th>VA Clinic</th>
<th>Baylor Clinic</th>
<th>Harris Health Clinics</th>
<th>Conferences</th>
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</thead>
</table>
BCM Genetics /Metabolic training programme (I)

- **Inpatient metabolic ward round** (general wards, NICU, PICU) & **consultation service** (O&G in Pavilion for Women, adult wards in St Luke’s)
- **Infusion center** – enzyme replacement therapy for lysosomal storage disorders; biphosphonate infusion for osteogenesis imperfecta and juvenile osteoporosis
- **Outpatient clinics and Genetic Counselling**
  - **Genetics Clinic** – every Monday and Thursday
  - **Metabolic Clinic** – every Wednesday
  - **Gender Medicine Clinic** – fortnightly on Monday afternoon
  - **Skeletal Dysplasia Clinic** – monthly on Friday
BCM Genetics /Metabolic training programme (II)

- **Meetings and seminars**
  - Monday ABMG trainee lecture & clinical genetics seminar
  - Tuesday biochemical signout meeting & research seminar
  - Wednesday mitochondrial signout meeting
  - Thursday post-clinic conference
  - Friday grand rounds / monthly whole exome sequencing (WES) signout meeting

- **The Baylor Miraca Genetics Laboratories**

- **Evenings with Genetics**
The Baylor Miraca Genetics Laboratories located in the McGovern Campus
The Baylor Miraca Genetics Laboratories

Dedicated to provide high quality comprehensive diagnostic services for the medical genetics community:

- Biochemical Genetics Laboratory
- Cytogenetics and Microarray Laboratories
- DNA Diagnostic Laboratory
- Mitochondrial Laboratory
- Whole Genome Laboratory
Professor Lee-Jun Wong, PhD
Vice President, Senior Laboratory Director
Baylor Miraca Genetics Laboratory
Biochemical Genetics Laboratory

Dr Sarah Elsea, PhD
Laboratory Director

Dr Qin Sun, PhD
Assistant Laboratory Director
Evenings with Genetics
A seminar series open to the public
Offering the most current information on care and research for many genetic conditions

Susan Fernbach
Director of Genetic Outreach
Children's Museum of Houston
Texas Department of State Health Services
Austin, Texas
Policy Address

IX. Healthcare

186. The ageing population brings challenges to our healthcare services. We will continue to enhance healthcare service provision, plan for healthcare manpower and improve regulation.

Public Healthcare Services

187. The Steering Committee on Review of Hospital Authority has reviewed the organisation structure, cluster arrangement, resources, performance and personnel management system of the HA to explore directions for enhancement and improvement. The Steering Committee will put forward recommendations within this year.

188. In 2015-16, the HA plans to spend about $1 billion out of the $13 billion provision granted for minor works projects to improve the facilities of public hospitals and clinics, such as adding hospital beds and other treatment and diagnostic facilities.

189. The Government will pursue the construction of an acute general hospital in the Kai Tak Development Area. Upon completion of Phase 1, there will be an oncology centre, as well as inpatient and ambulatory services. In addition, the HA plans to provide approximately 250 additional hospital beds, and increase operating theatre sessions and quota for endoscopy examination to cope with escalating demand.

190. The HA also plans to increase the general out-patient clinic episodic quota in the Kowloon Central, Kowloon East, Kowloon West, New Territories East and New Territories West Clusters in 2015-16. It will also enhance the effectiveness of medical treatment by expanding the coverage of the Drug Formulary.

191. The DH and the HA have set up a working group to study the feasibility of trying out in the public healthcare system a screening programme for newborn babies for inborn errors of metabolism. The working group will study the types of disease to be screened, scientific evidence on the effectiveness of screening, actual arrangements and related recommendations.
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Newborn screening (NBS)

- Preventative medicine
- Public health programme aiming for early identification of serious but treatable congenital and hereditary conditions
- These disorders may cause severe intellectual disability, illness, or death if not treated early in life
- If treated early, affected individuals may live relatively normal lives
- Early identification and timely treatment decrease emotional and financial burden on families
- Results in savings in medical costs over time and decreases burden on healthcare service of the society
Newborn screening criteria

Based on the classic Wilson and Jungner screening criteria and the revisited emerging screening criteria (WHO, 2008), **4 criteria** (from clinical perspective) need to be considered before determining whether an IEM disorder should be included in a NBS programme:

1. **Screening capability** - availability of inexpensive, practical and reliable screening tests, and accurate diagnostic tests in our local laboratory

2. **Clinical significance** – life threatening and/or catastrophic condition; number of cases encountered in our locality

3. **Available treatment** – effective treatment which prevents complications

4. **Early treatment outcome** - adequacy of the understanding of the natural history of the condition and its long-term outcome with early treatment
History of newborn screening

- Began in the early 1960’s
- In 1961, Dr Robert Guthrie developed a bacteria inhibitor assay that could detect elevated phenylalanine from a single drop of an infant’s blood
- By 1965, over half of US states had mandated screening for phenylketonuria (PKU)
- 1970’s other screening tests became available on filter paper
Robert Guthrie and PKU test
Expansion of newborn screening for inborn errors of metabolism

- 1990 David Millington introduced tandem mass spectrometry (MS/MS) in newborn screening
- Traditional screening – one test for one disease, one marker, one cut-off
- New screening with MS/MS – one test for multiple biochemical markers, many cut-off values and screening for many diseases using the same drop of blood
- Compounds analyzed are amino acids and acylcarnitines
  - Amino acids = building blocks for proteins
  - Acylcarnitines = carnitine + fatty acids
Acylcarnitines
Amino acids
> 40 metabolites in 2 mins
Newborn screening is more than just a test

- Newborn screening represents a complex system
- Far more than just taking the blood from newborns, shipping the filter paper to the screening lab, testing in the laboratory, and reporting the results of the screening test
- The emphasis is on the importance of pre-symptomatic diagnosis, timely initiation of treatment and long-term follow-up
- Unusual events in a complex environment provide the opportunity for errors at the many steps in the system
- Collaboration is the key to success
Texas Department of State Health Service
Newborn Screening Programme

- Texas babies are mandated to have 2 newborn screens: first screen at 24-48 hours, and second screen at 1-2 weeks of age, unless parents object for religious reasons.
- Even for NICU babies, first screen must be taken at 24-48 hours of life, regardless of feeding status or birth weight.
- With an annual birth rate of around 380,000 live births in Texas and operating six days per week, the Texas DSHS is screening more than 2,400 specimens per work day.
- The largest test volume NBS programme in the world.
Disorders included in the Texas Newborn Screening Panel Tested at DSHS Laboratory (29)

- 6 Amino acid metabolism disorders
- 6 Fatty acid oxidation disorders
- 8 Organic acid metabolism disorders
- 3 Haemoglobinopathies
- 2 Endocrine disorders
- 4 Other disorders
The Lord of the Rings
Amino acid metabolism disorders (6)

- ASA – Argininosuccinic acidaemia
- CIT – Citrullinaemia
- HCY – Homocystinuria
- MSUD – Maple syrup urine disease
- PKU – Phenylketonuria
- TYR 1 – Tyrosinaemia type 1
Fatty acid oxidation disorders (6)

- MCAD – Medium-chain acyl-CoA dehydrogenase deficiency
- VLCAD – Very long-chain acyl-CoA dehydrogenase deficiency
- LCHAD – Long-chain 3-OH acyl-CoA dehydrogenase deficiency
- TFP – Trifunctional protein deficiency
- CUD – Carnitine uptake defect
- CPT 1 – Carnitine palmitoyl transferase 1 deficiency
Organic acid metabolism disorders (8)

- GA-1 – Glutaric aciduria type 1
- HMG – 3-OH-3-Methyl glutaric aciduria
- IVA – Isovaleric acidaemia
- MCD – Multiple carboxylase deficiency
- 3-MCC – 3-Methylcrotonyl-CoA carboxylase deficiency
- MMA – Methylmalonic acidaemia
- PROP – Propionic acidaemia
- BKT – Beta-ketothiolase deficiency
Haemoglobinopathies (3)

- Hb S/S – Sickle cell anaemia
- Hb S/Th – Hb S/Beta-thalassaemia
- Hb S/C – Hb S/C disease
Endocrine disorders (2)

• CH – Congenital hypothyroidism
• CAH – Congenital adrenal hyperplasia
Others (4)

- BIOT – Biotinidase deficiency
- CF – Cystic fibrosis
- GALT – Classic galactosaemia
- SCID – Severe combined immunodeficiency
Texas Department of State Health Service
Newborn Screening Programme

In addition to the 29 conditions that may be detected through blood screens, Texas DSHS has also implemented point-of-care screenings for:

• Newborn hearing

• Critical congenital heart disease

Texas DSHS also has plans to increase the number of disorders detectable through the Newborn Screening laboratory testing from 29 to 53 conditions later this year.
The future

• Current screening relies on detecting biochemical markers using MS/MS

• This methodology enables expansion of newborn screening in an inexpensive, rapid and easy manner

• The future lies in DNA-based screening

• This will undoubtedly raise the spectrum of diseases to be screened and will require a lot more paediatricians

• DNA testing has implications for individuals, families and society at a social, moral and ethical level and these issues will need to be addressed
Hermann Park

Thank You