Overview

• What is NLARF?
• Infrastructure and Services provided by NLARF
• Progress and Future of NLARF
• Challenges at Current Site
• Process of Relocating NLARF
What is NLARF?

NLARF is Singapore’s “National Large Animal Research Facility”

NLARF “Large Animals”  
(Biomedical Research and Training)

- Pigs
- NHPs
- Rabbits
- Bats
- Chickens
- Goats
- Sheep
- Ferrets
- Others
Earlier History of NLARF

• 4.7 hectare (11.6 acre) site in Northern Singapore ("Farm")
• Originally developed in the 1960s by the Agri-food and Veterinary Authority for research and quarantine of animals, Animal Hospital and Holding (AH&H)

Taken over by Singapore Health Services in 2001

SingHealth

• Managing organization of NLARF is Singapore Health Services Pte Ltd. (SingHealth)

• SingHealth is the Nation’s Largest Health Care Cluster and it is partnered with Duke-NUS Medical School as an Academic Medical Centre

• With a network of four hospitals, five national specialty centres, and eight polyclinics offering over 40 clinical specialties, the SingHealth Duke-NUS Academic Medical Centre draws on the collective strengths of SingHealth and Duke-NUS Medical School to drive the transformation of healthcare and provide affordable, accessible and quality healthcare.
SingHealth Experimental Medicine Centre (SEMC)

- The SingHealth Animal Care and Use Program is operated through the SingHealth Experimental Medical Centre (SEMC)

- SEMC directly manages three animals facilities
  - SEMC Academia Animal Facility (Main SGH Campus)
  - Duke-NUS Rodent Vivarium (Main SGH Campus)
  - National Large Animal Research Facility (NLARF at Sembawang)

- Plus, SEMC oversees the National Cancer Centre Mouse Facility
  (Main Campus)

National Large Animal Research Facility (NLARF)

- Formerly Sembawang Animal Husbandry and Hospital

- Land area 47,200m²

- Build up area (GFA): ~2,800m²

- ~20 km north of Main (SingHealth/SGH) Campus
In 2012, a $10 million grant from the National Medical Research Council (NMRC) was awarded to SingHealth and the National University Hospital Singapore (NUHS) 

$5 million each to collaborate to setup a National Large Animal Research Facility (NLARF) in SEMC Sembawang AH&H 

NLARF’s initial grant period was 5 years, commencing 1 Dec 2012 

Entire Sembawang AH&H and its activities were included in the NLARF project.
Daily operations managed by the SingHealth Experimental Medicine (SEMC)

A Governing Board (GB) oversees NLARF (SingHealth, NUHS, NMRC)

NLARF Governing Board:
  - Chairperson (2 year rotation)
  - Members:
    - Two from SingHealth / Duke-NUS
    - Two from NUHS
    - One from NMRC, MOH

In 2017 NMRC approved $7 mil to extended the NLARF grant another five years, from 1 Dec 2017 to 31 Mar 2021

Using the established support network in SingHealth
  - SingHealth Office of Research (OoR)
  - IACUC
  - IBC
  - Research Safety Office
  - Facilities Development (FD)
  - Legal Dpt.
  - Finance
  - Procurement
  - others
Vision:
To be a state-of-the-art Biomedical Research and Training Centre, adhering to the highest International Standards

Mission:
We deliver quality services to researchers / investigators and quality humane care to animals used in research and teaching

Animal Care and Use Program

- Licensed by Singapore Animal and Veterinary Service (AVS/NPARKS)
- Accredited by AAALAC International
  - First accreditation in 2006
  - Continued full accreditation (includes NLARF)
- AAALAC International accredits animal research facilities that meet or exceed applicable National and International standards
- Demonstrates SEMC’s commitment to responsible animal research
Infrastructure and Services Provided by NLARF

NLARF Entrance
• Eight sheltered outdoor housing (SOH) buildings
  • Seven are repurposed and renovated 40+ year old structures
  • Two have indoor surgery, procedure and lab space
  • One SOH building less than 10 years old
• One ABSL2 indoor housing Building
• Duke-NUS ABSL3/BSL3 building (less than 5 years old)
• One office and meeting building
• General support building
• One cage storage building, formerly used for SOH for animal housing
  • Dedicated Electrical substation building (less than six years old)
Sheltered Outdoor Housing Buildings

Animal Housing and Support

OT, Procedure, X-Ray
ABSL2, International Quarantine, Necropsy and Lab Buildings

General Support Building

Feed and bedding storage, diet kitchen, chicken egg incubators, staff locker rooms and laundry
NLARF Animal Holding and Support

- Domestic Swine breeding, holding and research
- Cave nectar bat breeding, holding and research
- NHP holding and research
- Rabbit holding and research
- ABSL2 (four holding rooms)
- ABSL3 (two holding rooms)
- Four international quarantine rooms
- Surgery suite
- Procedure rooms (including radiology and ultrasound)
- Minor diagnostic lab

NLARF Equipment

- Cages and pens
  - Fixed pens
  - Modular pens
  - Mobile cage units
  - Social housing/Enrichment
- Power washers (hand held, no automatic cage washer)
- Large animal handling and restraint trolleys/boxes, scales, etc
- Air Conditioned Lorry (transport truck)
- Digital flat-film radiograph
- Isoflurane anesthetic machines, plus monitors
- etc.
Pig Pens in SOH

Pig Pens in SOH
Modular Pens in SOH

Mobile and Fixed Cages for NHPs
Marmoset Cages

Bat Cages in SOH
OT and X-Ray Rooms

Duke-NUS ABSL3 (NLARF Sub-Tenant)

• Completed - late 2014

• BSL3 Lab – Infectious Disease Research

• Two ABSL3 housing and procedure rooms
  • Rodent
  • Monkeys
  • Bats
  • Ferret

• Staffed by Duke-NUS (SEMC /NLARF provides support services)
• Modules from Germfree in Florida, USA
• Assembled within an outer shell

Duke-NUS ABSL3 Facility

Important Roles of NLARF in Singapore

Unique capabilities, not available in other local facilities:

• Supply of local animals for scientific purpose:
  • In-house High Health Status (HHS) pig breeding colony
  • Conditioned AVA wild-caught NHPs

• AVS-approved international quarantine facilities for large animals:
  • Import of HHS pigs and SPF NHPs from overseas sources

• Large animal housing facility:
  • Long term housing / supply of aged animals
  • Large pigs, animals with special health status
    • Large Animal Biosafety Level 3 (ABSL3)
NLARF Services

- Research project support (PI advice and training)
- Provision of technical services
- Surgical support services
- Supply of animal samples
- Sale of supplies
- Use of shared facilities
- Transport of animals to other facilities

Progress and Future of NLARF
Pig Import, Quarantine & Breeding

- NLARF started the first batch of importation of high health status (HHS) pigs from Netherlands in November 2013
- Imported pigs are quarantined for 30 days in mosquito and bird proof outdoor shed
- NLARF started breeding and developing its local colony in January 2015 and have produced and sold high health status pigs to different research institutions.

Pig Breeding Performance

2018

<table>
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<tr>
<th>Parameters</th>
<th>2018</th>
<th>2017</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Boars</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No. of Sows</td>
<td>13</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Average Age of Sow (Yrs.)</td>
<td>4.2</td>
<td>3.93</td>
<td>2.92</td>
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<tr>
<td>Ave. Conception Rate</td>
<td>95%</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Weaning age (days)</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Total Piglet Production (hds.)</td>
<td>387</td>
<td>333</td>
<td>331</td>
</tr>
<tr>
<td>LSBA (Litter Size at Birth Born Alive)</td>
<td>12.9</td>
<td>13.0</td>
<td>13.2</td>
</tr>
<tr>
<td>Piglet Survival Rate</td>
<td>98%</td>
<td>97%</td>
<td>98%</td>
</tr>
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</table>
Distribution of NLARF Pigs

- 31% of pigs produced by NLARF are used for training workshops in the SEMC Academia, NUHS and NLARF, benefiting Clinical and Research Skills Training

**Figure:** Distribution of NLARF Pigs Used for Training Courses

Research Uses of NLARF Pigs

- Cardiovascular
- Orthopedic surgery
- Device testing
- Organ transplant
- Wound healing
NHP Quarantine and Conditioning

- Macaca fascicularis (cynomolgous macaque, cynos)
  - Several shipments through NLARF quarantine per year
    - (50-200 cynos/year)
  - Also, local wild caught conditioning
  - Use at NLARF, SEMC Academia,
  - Supplied to other facilities in Singapore
- Callithrix jacchus (common marmoset)
  - Two shipments through NLARF quarantine
  - Supplied to two facilities in Singapore
  - One facility now breeding
- Macaca mulatta (rhesus macaque)
  - One shipment through NLARF quarantine

Research Uses of NHPs

- Intrauterine gene therapy
- Ophthalmology
- Dental
- Neuroscience
- Infectious diseases
- Alopecia
- Organ transplant
Animals used by Singapore biomedical research and training community: 70% pigs, 29% NHPs, 1% others (goats, rabbits, etc). Rabbits housing only started in end FY16
• NLARF has supported more than 200 IACUC protocols, including research projects and training workshops

• Research and training activities mainly use Pigs and NHPs

• Other species
  • Goats (local dairy)
  • Dogs (conditioned impounded feral animals)
  • Rabbits (imported)
  • Bats (local caught, in-house breeding)
  • Chickens (eggs hatched in NLARF incubators)

Bat Breeding Colony at NLARF

• Setup the first breeding colony of captive bats in Singapore for use in Research
• Established in Q4 2015 and produced its first batch of pups in 2016
• Used in immunology and infectious disease research
Cave Nectar Bat (*Eonycteris spelaea*)

- Breeding:
  - Gestation – ~120 days
  - Newborn Crown:Rump length - 44 mm
  - Lactation - ~60 days
  - Adult weight - ~59 grams
- Research Uses: Immunology; Emerging Infectious Diseases
- Useful Facts:
  - Nectarivore - flower nectar and pollen, fruits
  - May commute over 10 metres to find food
  - Important pollinator of fruit trees, such as durian
  - Size: head and body – 8.5-11 cm; tail – 1/5-1.8 cm; forearm – 6-7 cm
  - Life span: 20-30+ years
  - Nocturnal; Roost (huddled) during the day

Myocardial Infarction (MI) Studies in Piglets

- MI in 14 day old piglets
- Followed by intravenous cord blood transplantation
- Donor from same litter
Notable Research Outcomes at NLARF

• Dental reconstructive surgery

• Development of 3D tooth implants using NHP and Rabbits as experimental models

• ZIKA and Dengue Virus research using local wild caught NHPs

Future of NLARF

• Opportunities
  • Mini and Micro-pig
    • Import and breeding for research (adult, embryos, semen)
    • Genetically modified (diabetes, atherosclerosis, etc.)
  • Other species
    • Sheep for cardiovascular studies
    • Ferrets
  • Sustainability
    • Will need continuing support from NMRC
    • Continue to demonstrate value
Challenges at Current Site

Infrastructure Challenges

- Aging buildings
  - Structural reinforcement
  - Pest control (rodent, birds, insects)
- Change in power source
  - Previously shared electrical substation
  - Forced to build our own 22 Kv electrical substation
- Upgrade of Water Supply System
- Upgrade of Water Hydrant System
- Security
  - Perimeter fence
  - Security guard
Other Challenges

- Rodent exclusion
  - Rat assault
  - Bioexclusion
- Maintaining the grounds
  - Regular grass trimming
  - Grass fire prevention
- Distance from main campus
- Supply of NHPs
  - Commercial airlines not shipping NHPs for research
  - Expensive charter flights
- Regulatory approval process for animal suppliers
- NHPs from AAALAC accredited facilities

Biggest Challenge

For NLARF

Relocation!!!
Process of Relocating NLARF

• Original deadline to vacate current NLARF site January 2019
• Government limiting size of land plot to 0.7 hectares
  • Reduction from 4.7 hectares
  • Must build vertically (multistory)
• Very Challenging to find new site
• Delays
  • Finding suitable site
  • Slow responses from government agencies
• Surprises
• Several extensions to the deadline granted by government (reluctantly)
First Proposed Site (Sungei Tengah)

- 0.7 hectare site
- Preliminary feasibility study beginning January 2017
- Included meeting with Government Agencies (no major issues)
- Preliminary design
- Three story building

Sungei Tengah Site

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<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>Roof</td>
<td>ACMV equipment, etc, with capability to expand</td>
</tr>
<tr>
<td>Level 3</td>
<td>ABSL3 lab, utility plants, etc</td>
</tr>
<tr>
<td>Level 2</td>
<td>Laboratories, Operating Theatres, Procedure Rooms, in-door animal holding, staff &amp; visitor areas, etc</td>
</tr>
<tr>
<td>Level 1</td>
<td>Sheltered outdoor housing of animals, substation, waste management, water tank, bin centre, other utility plants, etc</td>
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Preliminary Design (front façade)

Preliminary Design (back façade)
Feasibility Study completed Q3 2017
- Consulted URA, LTA, PUB, NEA and AVA
- Approved by NLARF Governing Board

Main Consultancy: Jan 2018–Present
- Nearly completed Concept Design
- April 2018 Meeting with URA, LTA, PUB, NEA and AVA

PUB informed us that the proposed NLARF Site is in the Water Catchment Area

PUB Bomb!!

- Public Utility Board (PUB) Requirement to Discharge Storm Water to Sea (6 km pipeline)
- Because they fear NLARF’s Storm Water will contaminate Singapore’s Water Supply
Straining at a gnat while swallowing a camel

• Quietly accepting a situation of significant proportions while baulking at something comparatively trivial
• Accepting all other more likely sources of contamination of storm water
• Baulking at potential for pig or monkey feces to make its way to the parking lot and end up in storm drain

Delays

• Months of negotiations failed
• No amount of reasoning with them changed PUB’s position
• Sungei Tengah site was no longer feasible
• URA offered an alternative site
Latest Site Offered for NLARF

(Lear Strait of Johor)
Issues With Latest Site Offered

• No Municipal sewer line until 2023
• Require our own sewage treatment plant
• Sewage (effluent) treatment requirements ??
  • Processed effluent to drain into sea
  • Concerns about fish farms and nature reserve
• Government agencies ruled that animal sewage cannot be dumped into the municipal sewer line
• Quantitative risk assessment
• Environmental impact study

More Delays

• Up to a year delay possible while studies performed
• No guarantee Government Agencies will accept
• New site requested by NLARF
• To be out of water catchment area
• Away from fish farms and nature reserves
Update and Conclusions

- NLARF is important to the Biomedical Research Community in Singapore (funded by National Research Foundation and Ministry of Health)
- Other Ministries and Government Agencies are not as supportive
- A new site may be offered, with fewer challenges????
- The block of funding for construction and move is being consumed with delays
- May end up with smaller NLARF
- Further extensions of deadline to vacate Sembawang
  - Dec. 2022?
- Hopefully will avoid period of downtime
- NLARF will continue with business as usual, if possible

Questions?