The Role of National Core Facilities in the NRPGM and in Research

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The National Research Program for Genomic Medicine (NRPGM) was launched in 2002 as one of nine national priority programs in Taiwan. Three government agencies — the National Science Council, the Department of Health, and the Ministry of Economic Affairs — have joined and funded this national program. The goal in the first phase of the NRPGM (2002–2005) was to establish the basic infrastructure for genomic medicine research and to explore studies related to ethical, legal, and social implications (so called "ELSI" subjects). The second phase of the NRPGM (2006–2010) focuses on disease-oriented research subjects; lung cancers, liver cancers, infectious diseases, and highly inheritable diseases are the major research targets.

National core facilities is one of four major components of the NRPGM (the other components are research program, industrial/academia collaboration, and international collaboration). The comprehensive national core facilities were purposely designed to facilitate research development needs within the genomic medicine program, with sophisticated instrumentation and cutting edge technology staffed by highly trained technical personnel. An advisory/oversight committee was set up to oversee the National Core Facility Program and a core facility administration office was formed to monitor the general core facility operation, collect service fees, audit the service process, and other administration work. For individual core facilities, a technical advisory board could provide scientific advice and a user committee could give user feedback and service advice (see operation chart in Fig. 1).

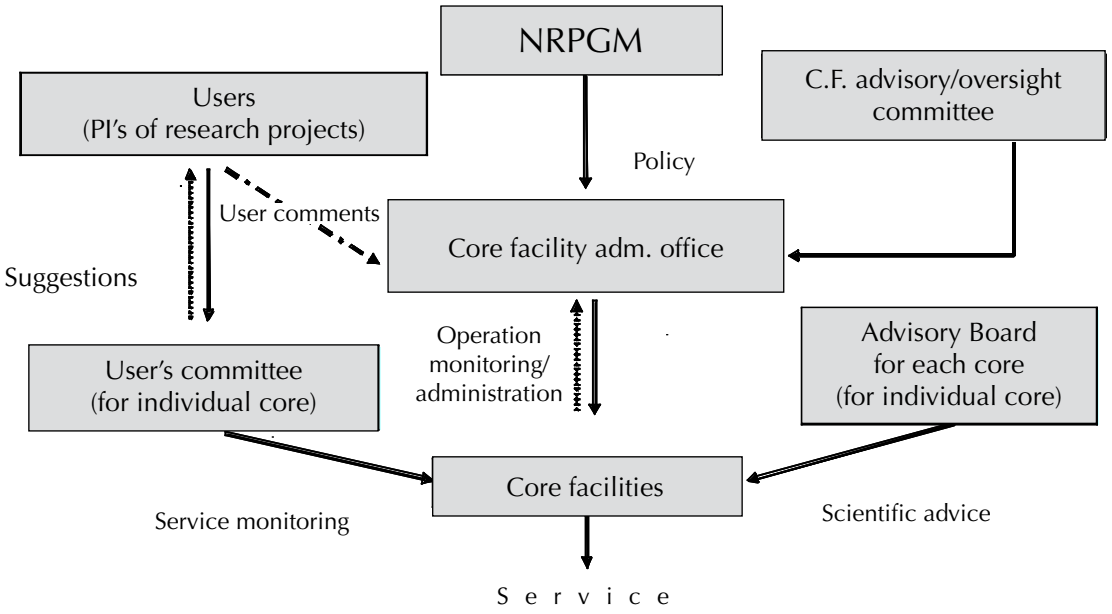

Fig. 1. Operation of the national core facility program.

The establishment of the core facility infrastructure was one of the major accomplishments in the first phase; altogether, 19 core facilities were constructed and fully open for service by the end of 2006 in the second phase. The national core facilities include five major fields: animal models for human diseases and phenotyping facilities, clinical sample banks, facilities for basic genomics, facilities for proteomics and structural genomics, and facilities for bioinformatics. A general introduction to these national core facilities is provided below.

Animal Models for Human Diseases and Phenotyping Facilities

There are five facilities in this field. The Mouse Mutagenesis Program Core Facility has already successfully produced a number of ENU phenodeviant mice with identified mutant genes for further collaborative study or distribution. The Functional and Micro-Magnetic Resonance Imaging Core Facility provides state-of-the-art MR equipment and comprehensive magnetic resonance technical support including experimental design, targeted technology development, imaging data analysis, and education for research in magnetic resonance imaging and spectroscopy as well as their biomedical applications. The Molecular-Genetic Imaging Core Facility is composed of specialists in chemistry, molecular and cell biology, molecular imaging, gene expression imaging, and imaging data analysis; and is well equipped with micro-PET, PET, autoradiography, and optical imaging systems. The service of the

Micro-Magnetic Resonance Imaging System

Transgenic Mouse Model Core Facility includes embryonic stem cell gene targeting and microinjection of the targeted embryo stem cell into blastocysts to produce chimera; in addition, the targeting vector for constructing gene knockout is also in service. The Optical and Scanning Probe Microscopy Core Facility aims at developing biological molecular imaging technologies using optical and scanning probe microscopy methods, and at identifying significant applications in medicine and the life sciences. Core services include scanning multiphoton microscopy image acquisition, confocal reflection/ fluorescence microscopic imaging, and postimaging processing support.

Clinical Sample Banks

Two facilities are established in this field. The National Clinical Core for Genomic Medicine was established with the mission to train genetic counseling professionals and to aid in the development of the nation's genetic medicine research. This core facility has also helped many gene studies, such as single gene disorder and pharmacogenetic researches, and has already finished the set up of the Chinese cell line of Taiwan. The Tumor Tissue Bank located in Southern Taiwan keeps fresh tumor tissues and patients' blood (obtained in real time from the operation room with the relevant medical data), and systematically carries out the collection of tumor cells from a specific population by utilizing a laser microdissection system for helping in the study of cancer. A tissue microarray system has also been set up.

Facilities for Basic Genomics

Five facilities were set up for basic genomic study needs. The National Core Facility for High-Throughput Physical Mapping and DNA Sequencing is located at the National Yang Ming University Genome Center. It has participated in the Human Genome Project and contributed 12-Mbp human genome sequences *(Nature, 2001)*, and is also a member of the International Consortium for Chimpanzee Genome Sequencing (human-chimpanzee clone mapping in *Science, 2002*, and chimpanzee chromosome 22 sequencing in *Nature, 2004*). Currently, this core facility has a daily sequencing capacity of 5,000 samples with Phred Q20 > 500 bp. This sequencing capacity enables a 50-Mbp genome (e.g. a fungus genome) to be sequenced with 10-fold genome coverage in one year; while for a bacterial genome with 5 Mbp, this could be accomplished in four months.

The National Genotyping Core Facility located at Academia Sinica is established to help identify disease-causing and drug-susceptible genes from the vast human genome by providing high-throughput SNP (single nucleotide polymorphism) and STRP (short tandem repeat polymorphism) genotyping services. The Microarray and Gene Expression Analysis Core Facility at Yang Ming University has established professional technology platforms for cDNA microarray, oligo microarray, real-time quantitative PCR, array CGH, and high-throughput cloning to provide the core competence for the NRPGM, academics, and bioindustry of Taiwan. The Microarray and SNP Core Facility for Genomic Medicine at National Taiwan University Hospital offers high-quality microarray services, including Affymetrix microarray, in house spotting oligo microarray both in membrane and glass formats, cell-based array, and SNP analysis by the Beckman system. The RNAi Core Facility was established under the support of The RNAi Consortium (TRC; the Taiwan National Science Council is one of its sponsoring members) to receive, distribute, and maintain RNAi resources (lentiviral-based RNAi libraries targeting 15,000 human and 15,000 mouse transcripts), in addition to its platform for RNAi screening, assay, and analysis.

High Throughput Genotyping Facility

High Throughput Liquid Handling System

Facilities for Proteomics and Structural Genomics

Five facilities have been built to serve all proteomics and structural genomics studies. The Recombinant Protein Production Core Facility uses sticky-end PCR technology *(Protein Science, 2002)* to insert any gene into different expression vectors simultaneously (parallel cloning). Researchers here mainly use *E. coli* as the expression system and different conditions to increase the solubility of proteins with a quality control protocol in order to enhance the stability of the technology platform. As of December 2005, around 230 soluble proteins were expressed with an 80% success rate. The Core Facility for Proteomics specializes in applying state-of-the-art mass spectrometry techniques to rapidly and accurately identify proteins, and to define their physiological expression levels and post-translational modifications. The High-Throughput Protein X-ray Crystallography Core Facility is equipped with all necessary software and hardware required for protein X-ray crystallography analysis. This core facility will soon complete the pipeline of an MAD experiment and participate in the establishment of the U.S.A. Advanced Light Source (ALS) high-resolution synchrotron radiation beamline (sponsored by Academia Sinica), assisting researchers to use synchrotron radiation light source in the experiment.

State-of-art Mass Spectrometers

Funded principally by the NRPGM office, the National Synchrotron Radiation Research Center (NSRRC) of Taiwan has constructed two dedicated high-throughput Synchrotron Radiation Protein Crystallography Facility (SPXF) beamlines for structural genomics research. This core facility includes one superconducting multipole wiggler (SMPW), one beamline front end, two SPXF beamlines, and two SPX end stations. The SPXF facility was open for users on September 20, 2005, after 3½ years of construction. The High-Field Nuclear Magnetic Resonance Core Facility maintains many state-of-the-art nuclear magnetic resonance (NMR) spectrometers, and provides high level technology to support high level relevant research on NMR structural genomics in NRPGM research projects.

Facilities for Bioinformatics

Two facilities are in operation for the purpose of bioinformatics. The Bioinformatics Core for Genomic Medicine and Biotechnology Development is composed of component units in specific areas in bioinformatics. Integration of manpower and expertise has been emphasized to provide comprehensive and in-depth services to investigators in genomics research. The technical domains of this core facility include statistical genetics, computational proteomics, comparative genomics, interactomics, structural bioinformatics, and applied medical genomics. Several dozen kinds of analysis tools and network service database are offered on its website. The Advanced Bioinformatics

Core Facility has experts in the fields of biology, physical sciences, and information sciences to help researchers. The "functional" and "comparative" bioinformatics teams are the brokers between researchers and experts in "genomic statistics" and "information technology" teams. Therefore, they can (1) help researchers to take advantage of the available bioinformation and to use bioinformatics tools; (2) become the information center of the NRPGM in order to integrate and share the information generated by this national program; and (3) develop next-generation bioinformatics tools to increase our competitiveness.

From the above detailed description and function, national core facilities can very well meet the NRPGM projects' needs in all research planning. Basic genomics core facilities provide high-throughput screening tools — such as whole-genome sequencing and microarray platforms for expression and SNP profiling — to quickly identify or locate disease gene targets. Proteomics core facilities help to express the identified genes, characterize their proteins, and prepare for future drug screening. Imaging and animal core facilities provide the platform for researchers to use MRI, micro-PET, and microscopic imaging equipment in order to understand the genes and the associated diseases in animal models constructed or produced by transgenic mice and ENU mutagenesis core facilities. Tissue sample banks keep the tissue samples obtained from hospitals to help in clinical studies of the diseases. Bioinformatics core facilities provide analysis tools and an integrated network to help researchers analyze the data generated from genomic, proteomic, and imaging services. The National Clinical Core Facility helps to train genetic counselors and design future gene studies.

Advanced NMR Facilities

Five major activities — service, collaboration, R&D, dissemination, and training — are the goals for each national core facility. Since 2002, they have served more than 1358 PIs/laboratories (see Fig. 2 for details) and recovered more than US$11.7 million from service-consumable charges (see Fig. 3 for details). Users were not only from the NRPGM, but also from all life science communities in Taiwan, including universities, research institutes, and industries. There are more than 192 reported collaborative projects and the core facilities contribute to more than hundreds of research publications each year, as well as many patents and technology transfer cases. More than 275 conference and training courses have been hosted by the core facilities and have attracted more than 13,216 scientists.

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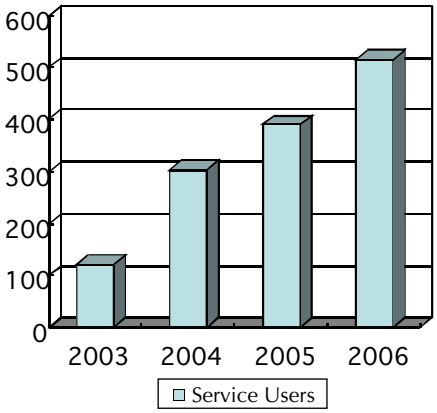

Fig. 2. Core facilities' serviced users.

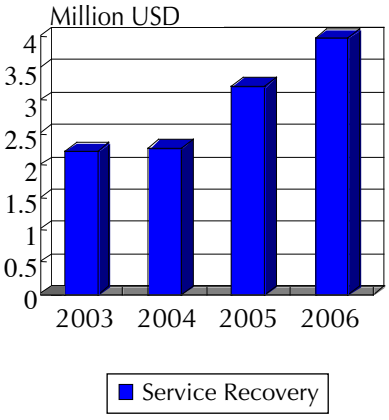

Fig. 3. Core facilities service-consumable charge.

In nearly six years of operation, the national core facilities have successfully supported NRPGM research projects and have also built up their service reputation to the life science communities internationally. Many visitors from foreign institutions have praised the success of the program in a short time. The impact of the cores goes beyond what can be measured by papers, patents, or service charges. It has become an essential component of life sciences R&D in Taiwan, and it even leads the course in some cases. The core program has also trained a large number of highly technical personnel who can help the long-term development of the biotech industry in Taiwan. In addition, the National Research Program of Genomic Medicine is willing to share its experience in core facility technologies with any international research institute and leading biotech industry, and is open for chances in international service and research collaboration. For program information, please visit our website at http://nrpgm.sinica.edu.tw

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