

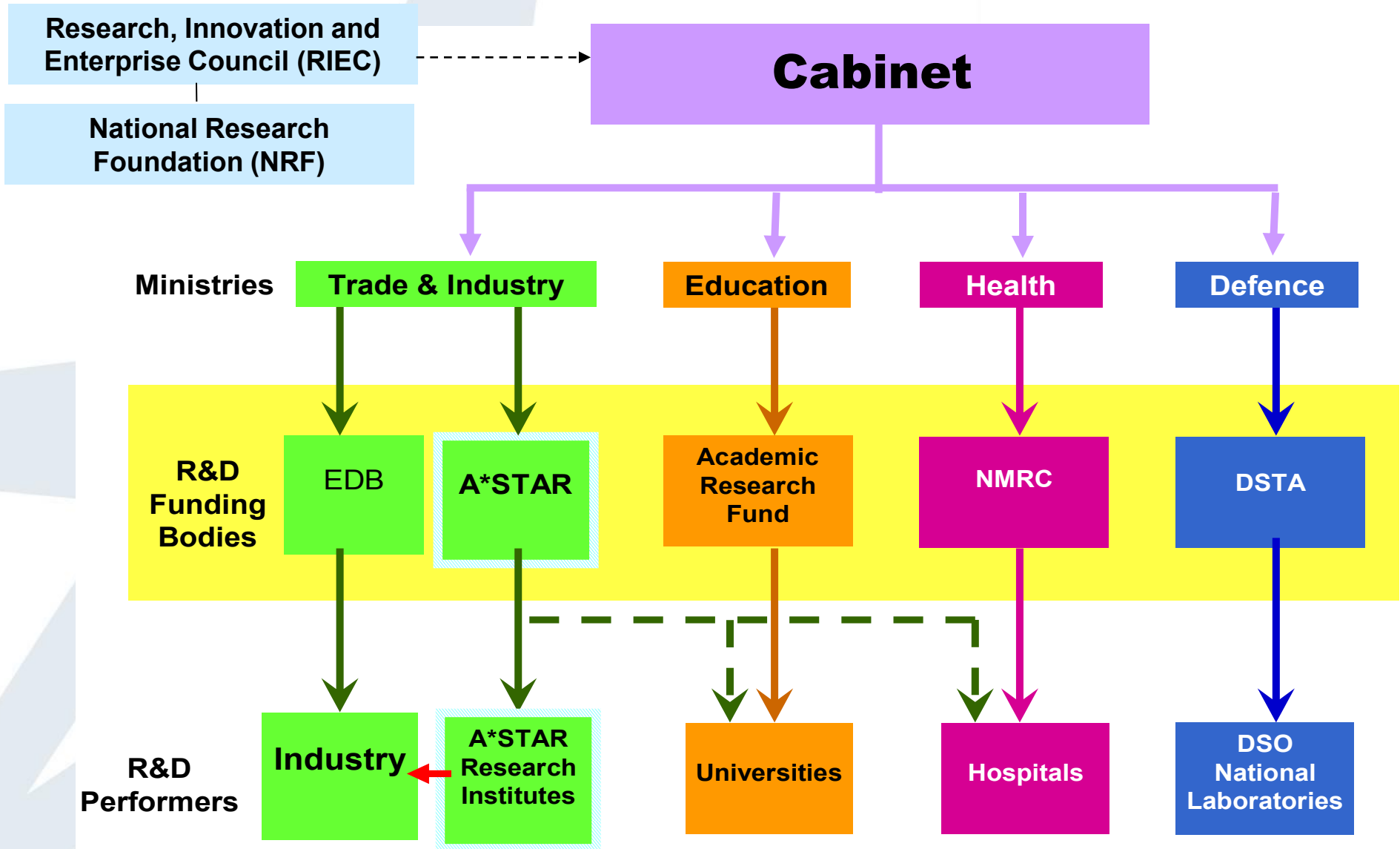
2nd SRC Bioelectronics Roundtable (BERT2)



Outline

- **Singapore R&D Framework**
- **IME R&D Structure**
- **Bioelectronics (BE) Program @ IME**
 - **Point-of-care diagnostics**
 - **Drug discovery tools**
 - **Miniaturized medical devices**
- **BE overall collaboration strategy**
- **Summary**

Singapore National R&D Framework

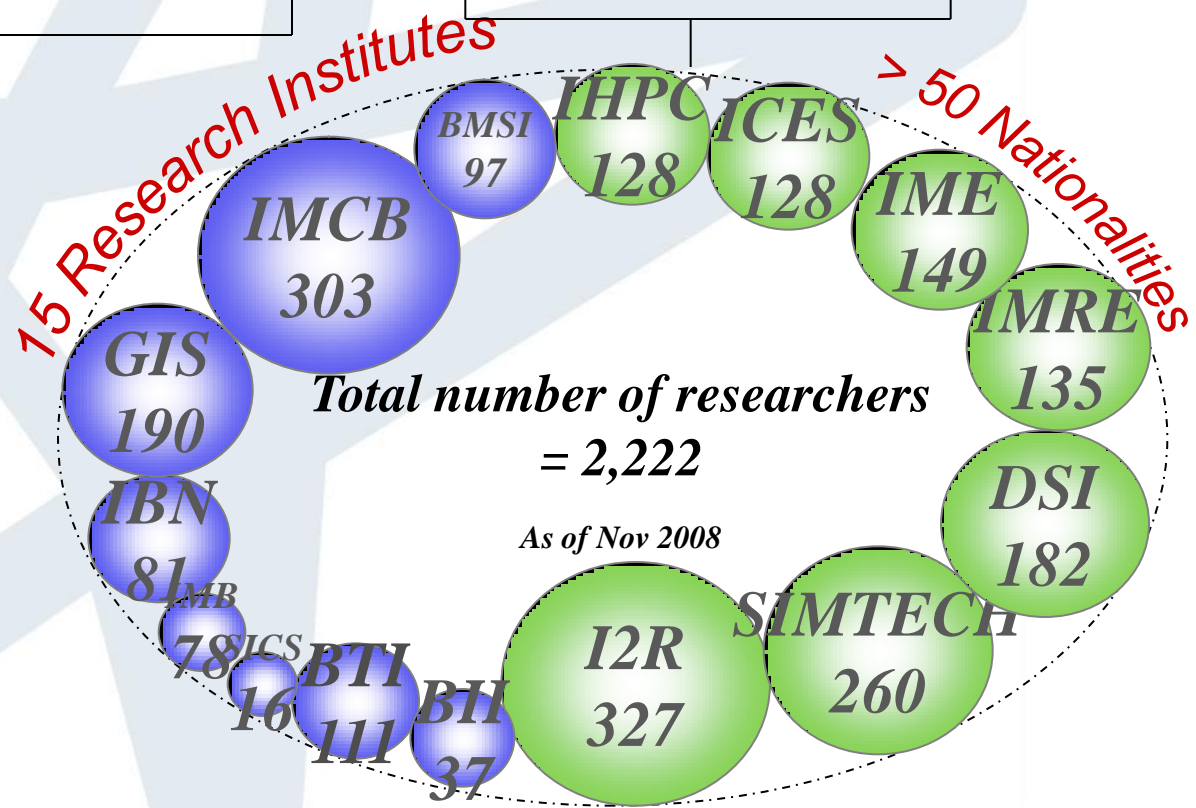
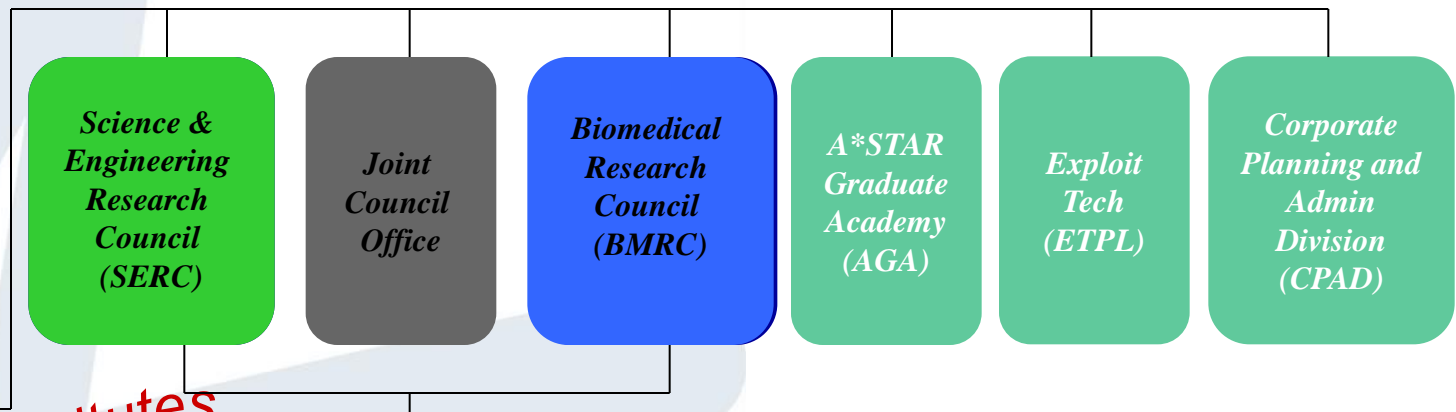


A*STAR

Mr Lim Chuan Poh
Chairman

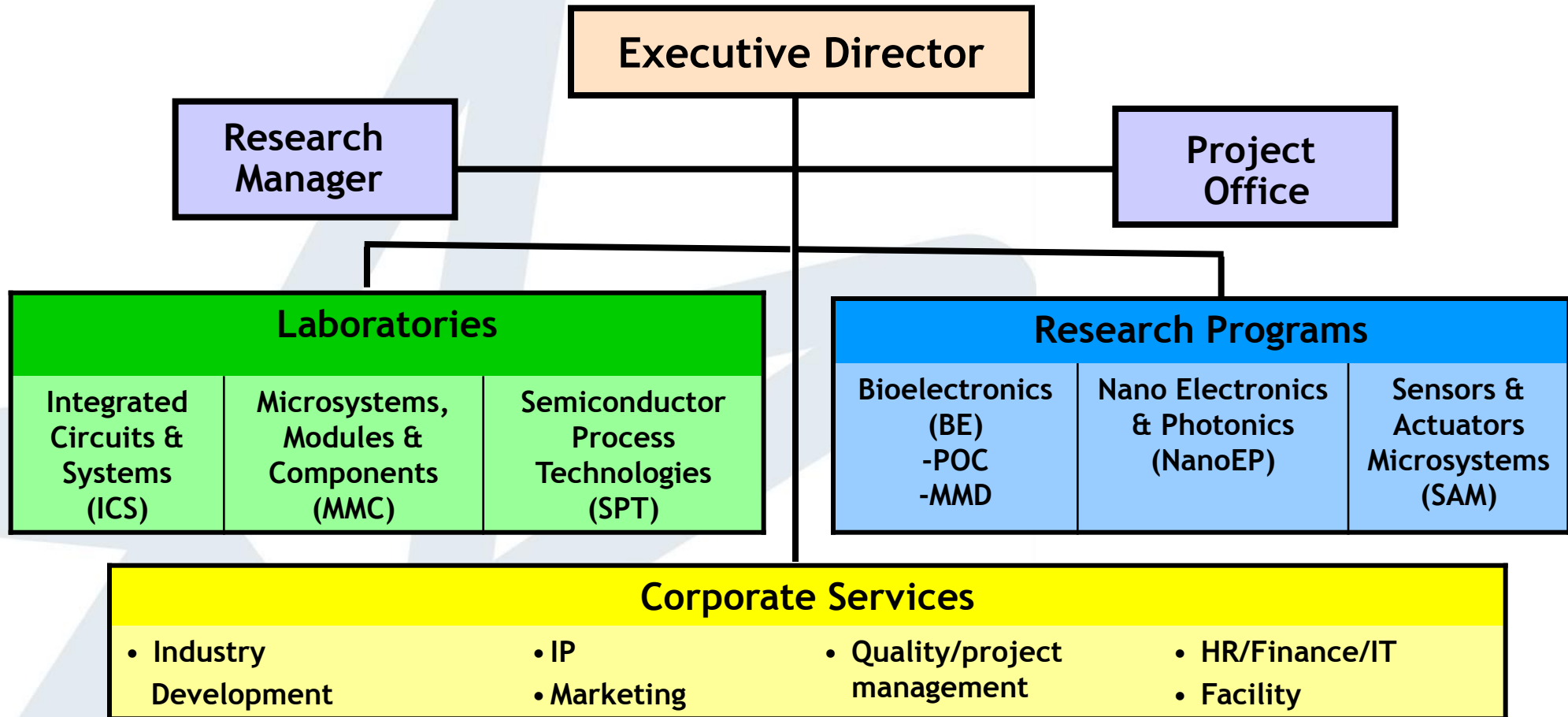
Prof Tan Chorh Chuan
Dy Chairman

Ms Yena Lim
Managing Director



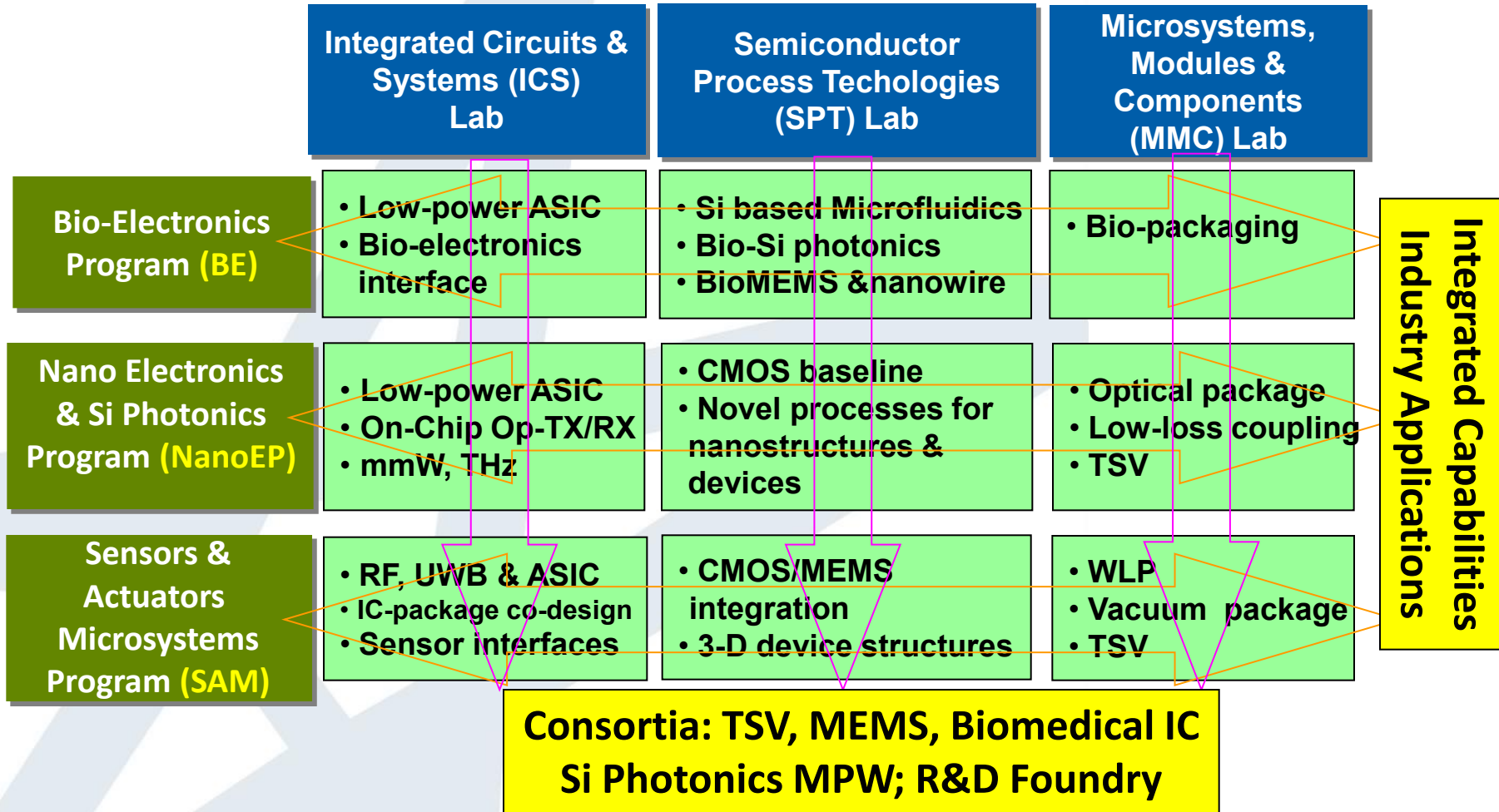
IME Confidential & Proprietary

IME Organization



- Staff: 270 (Researcher: 145)
 - Researcher: 145 from 13 nationalities; 60% with Ph.D. degree
- Ph. D. students from local universities: 65

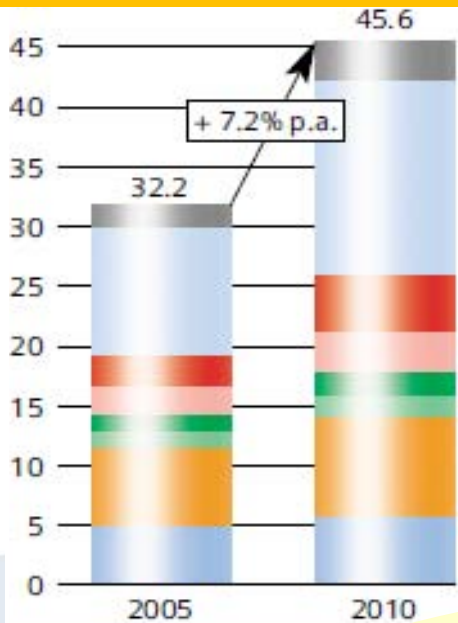
IME R&D Structure



- Key capabilities to conduct vertically integrated, multi-disciplinary projects
- Design/Modeling, Fabrication, Characterization, Packaging, Circuits and Interfaces
- All programs involve strategic partners from industry, medical centers, hospitals, universities

BioElectronics (BE) Program

Motivation, Mission and Focus



Program's mission:
Integrate novel miniaturized components into complete reliable systems

Point-of-Care Diagnostics

- **Early detection of diseases**
Sensitivity & Specificity
Rapidly & Repeatability
- **Personalized therapy**
Cheap & Automated

Drug Discovery Tools

- **Increased throughput**
Sensitivity & Specificity
Rapidly & Repeatability
- **High information value**
Multiplexed data & Complex systems

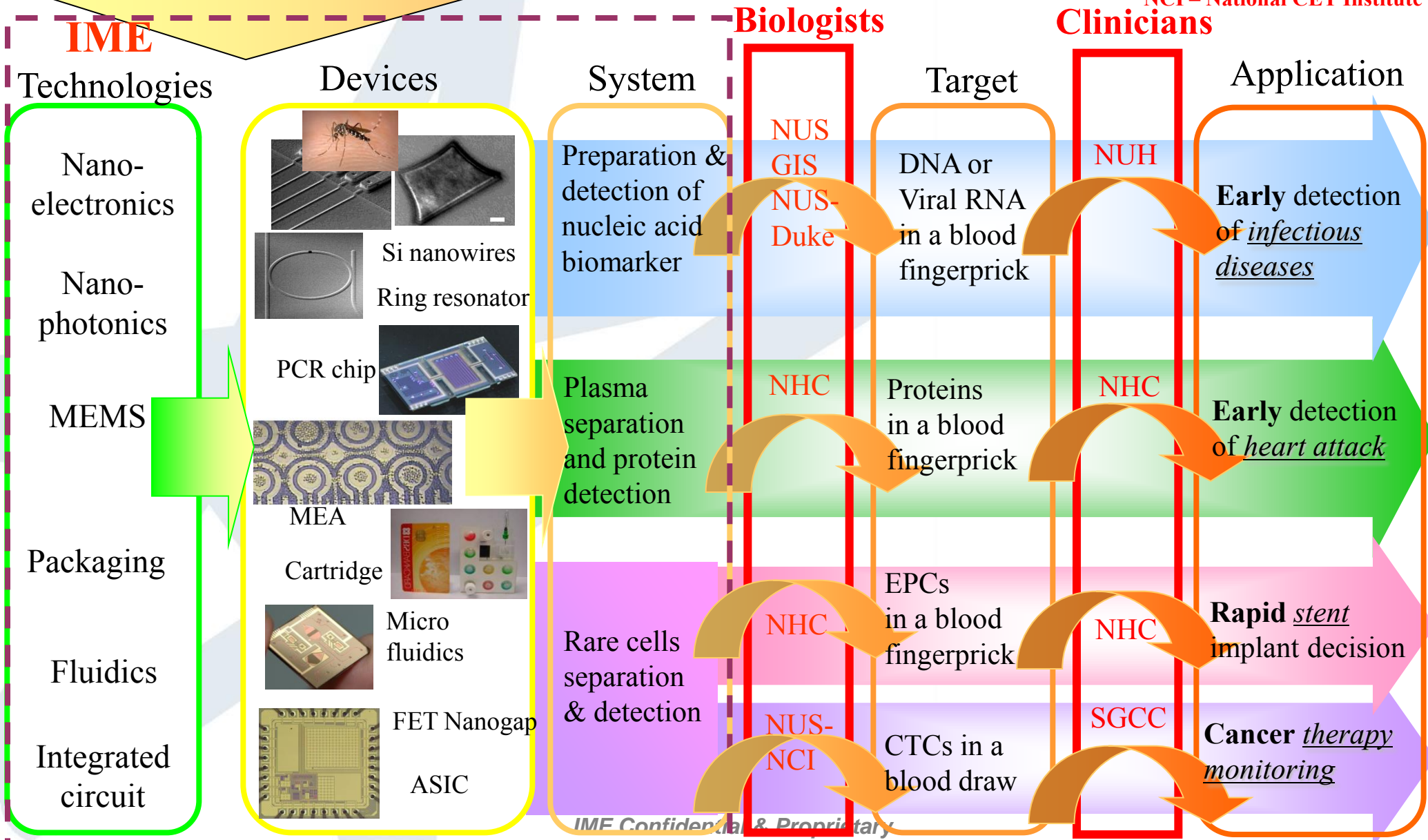
Miniaturized Medical Devices

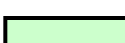
- **Measure physiological parameters**
Sensitive & Miniaturized MEMS
Design, Fabricate & Package
- **ASIC platform**
Wireless interface circuits
Ultra low power consumption

Point of Care Diagnostics


POC Research model

NUH – National University Hospital
 SGCC – Singapore Gastric Cancer Consortium
 NHC – National Heart Center
 NUS – National University of Singapore
 GIS – Genome Institute of Singapore
 NCI – National CET Institute



 Existing Capabilities

POC and drug discovery core capabilities

 Capabilities under development

MEMS Devices (microfluidics)

- DNA extraction
- RNA extraction
- Micro PCR
- Plasma separation
- Micro filtration
- Micro mixer
- Dielectrophoresis
- Droplet microfluidics
- Protein/nucleic acid enrichment
- Single cell manipulation and analysis
- Micropump and valve

Detection/ Biopackaging

- Silicon nanowire
- Silicon nanogap
- Microelectrode array (MEA)
 - Impedance sensors
 - Electrochemical sensors
- Surface-Enhanced Raman Spectroscopy Substrate (SERS)
- Silicon Biophotonics
- Biopackaging (enclosed cartridge)

ICs

- Simultaneous detection of multiple biomarkers
- High sensitivity detection (<10pA)
- Biosensor data calibration (robustness to sensor variability)
- Differential sensing (robustness to environmental fluctuation)

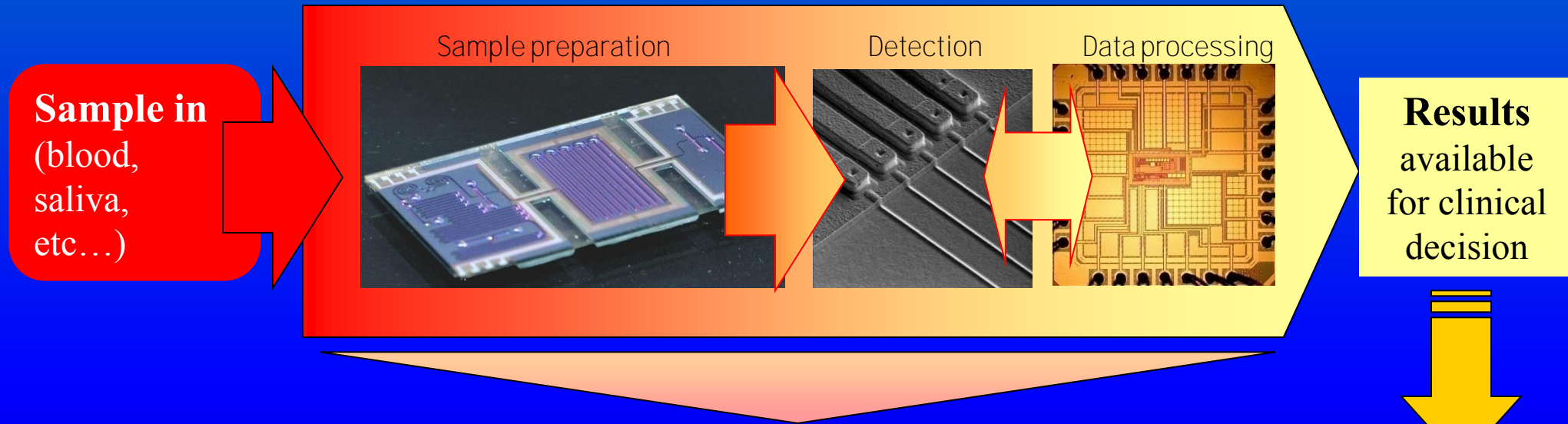
System Integration

- Nucleic acid based detection (infectious disease biomarkers)
- Protein based detection (cardiac biomarkers)
- Rare cell detection
 - Endothelial Progenitor Cells (EPCs)
 - Circulating Tumor Cells (CTCs)
- Si photonics sensing system (for low affinity interaction for drug screening)
- High throughput patch clamp

Testing and Characterization

- Biosensors
 - FET
 - Electrochemical
 - Resistance/Conductance based
 - Si Photonics
 - Fluorescence optical
- Cell based testing
 - Single cell
 - Conventional patch clamp
 - Chip based patch clamp
 - 2D cells
 - Real time in situ monitoring cell growth and drug effects
 - Real time in situ cytokine from cells and drug effects
 - 3D cells
 - Real time monitoring cell growth and drug effects

POC focus: Sample-to-answer integrated microsystem



Bioelectronics POC Program

1. Molecular diagnostics

Early diagnosis of diseases

Nucleic acid and protein

Biomarker detection

2. Cell-based diagnostics

Therapy monitoring

Rare circulating cells detection



Molecular diagnostics

Decentralized labs/solutions are needed to quickly detect infectious diseases

Nucleic acid based infectious disease diagnostics

Extraction + RT-PCR + Cooling set-up

extraction + RT-PCR cooling module fluidic inlet/outlet

Extractor PCR

Microelectrofluidic packaging

real-time monitoring of temperature profile

temperature controller

electrical control signal communication

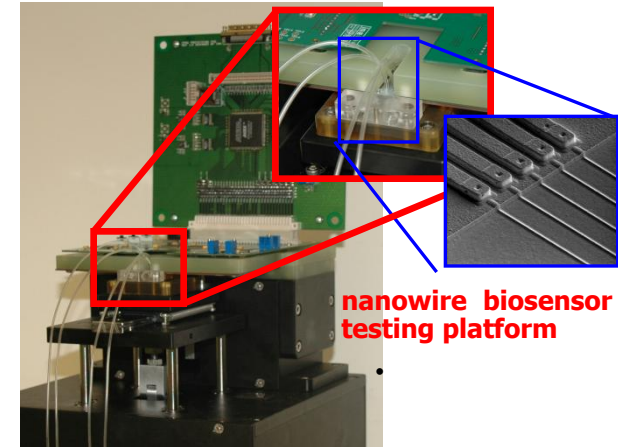
Protein based cardiac biomarkers diagnostics

Integrated sample preparation and detection chip

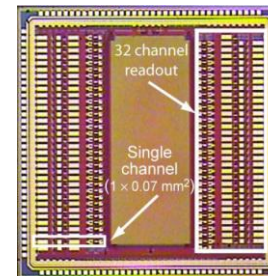
back-to-back integrated microchip

Microelectrofluidic packaging

Nanowire measurement platform



3.3mW, 4.3x4.3mm²

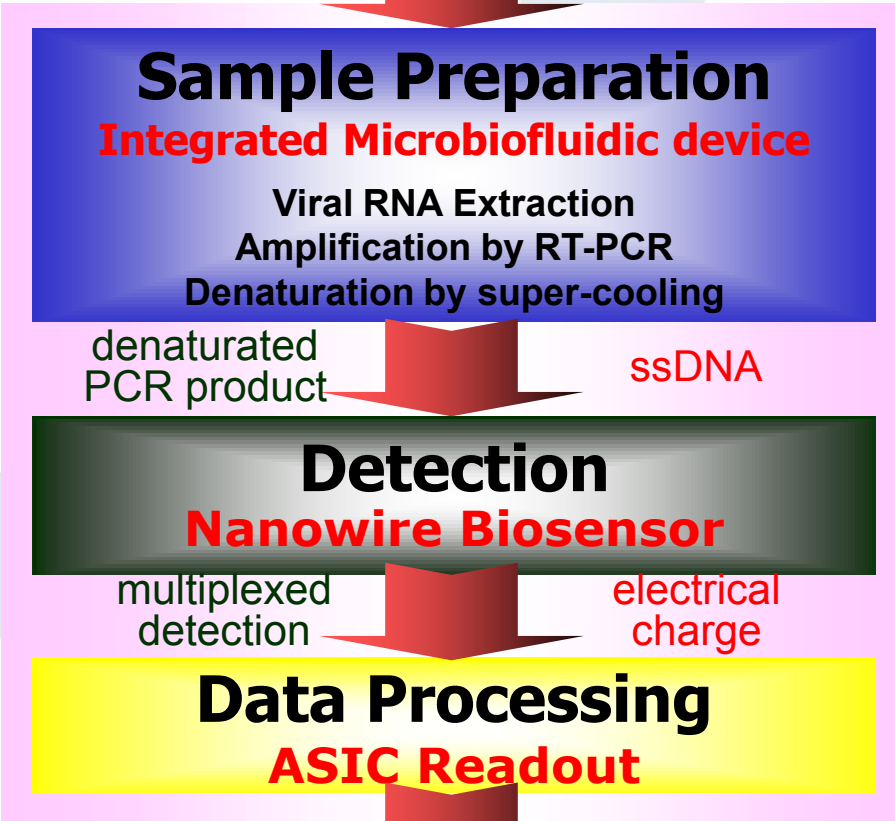


| | Probe Station + 4156A | Test Jig + ASIC |
|---------|-----------------------|-----------------|
| Average | 19.6MΩ | 21.0MΩ |
| STD | 2.96MΩ | 3.12MΩ |

- 255 Nanowire measurement in less than 1 min
- The resistance value from ASIC and probe station correlated

An Integrated system for multiplexing molecular diagnostics

blood

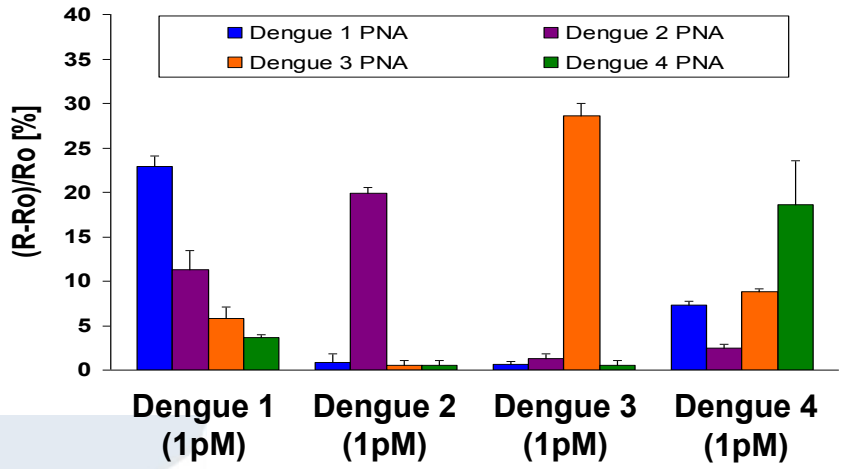


Probe station:
>1hr /255 wires

ASIC read out speed:
<1min/ 255 NW wires

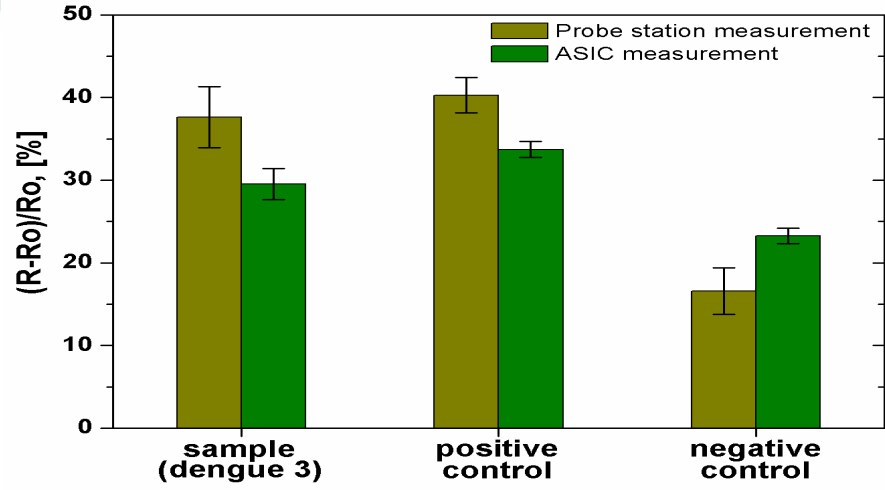
results

Multiplexing Specificity



Integrated System Testing

(Probe station vs ASIC)



Demonstrated 4 serotypes dengue virus in blood. The virus concentration is equivalent to symptoms occurring

Ongoing industry collaboration

drops of fever



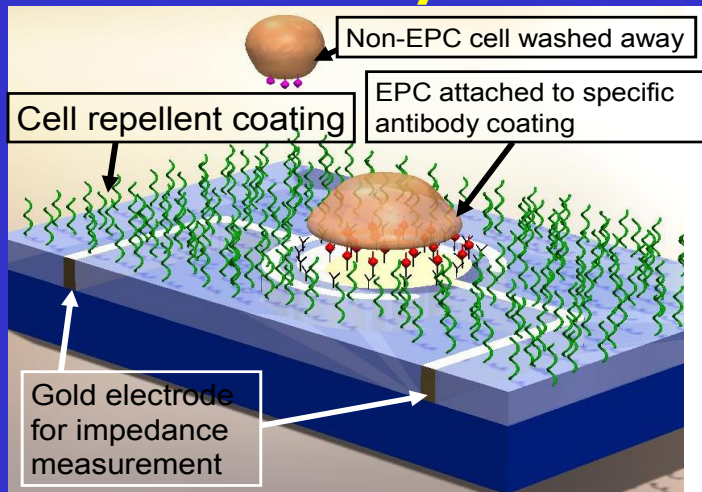
Cell-based diagnostics

Cardiologists request an EPC bedside detection system to aid decision on the kind of stents to be deployed in a patient

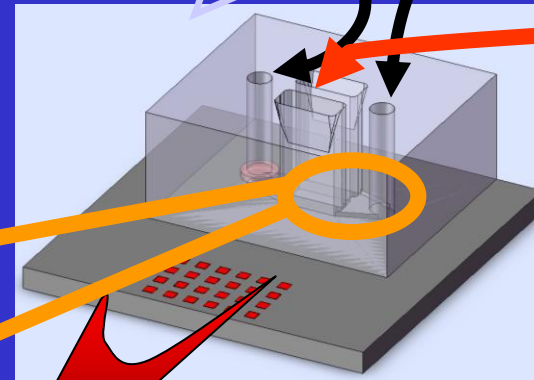
Highly sensitive detection of EPCs (**0.1% in PBMCs**)

Integrated sample preparation for point-of-care processing of small volumes (**<100ul**) of blood

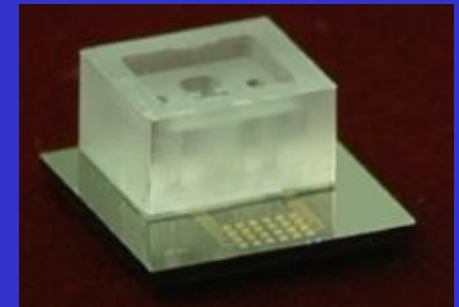
Detection Electrode Array



Buffer fluidics



Blood Input



Dielectrophoresis + antibody-assisted impedance detection

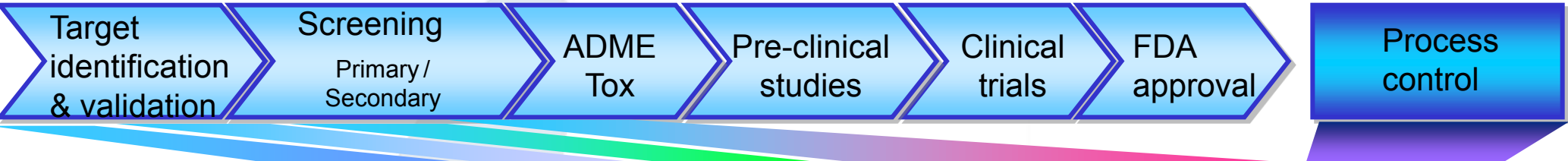
Drug discovery tools

Research model: Drug discovery tools

Drug Discovery Tools

Source: Alcimed 2003

Pharma Manufacturing



Application

Genetic target identification



Low affinity binding



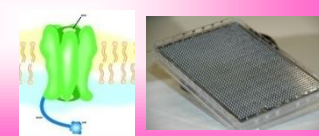
HT high affinity analysis



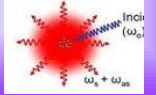
Metabolic diseases



High-throughput patch-clamping



Product detection, quality control



Biologists & Chemists *GIS, IMRE ETC* *SBIC Industry ICES*

Detection Target

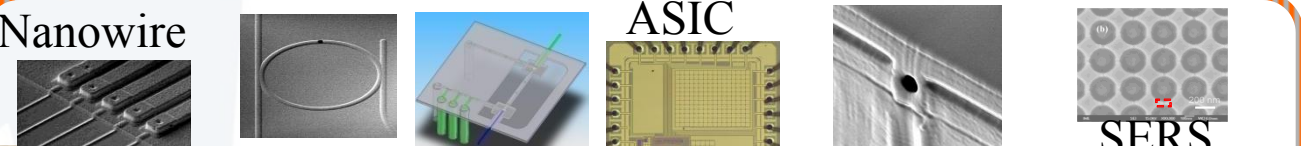


IME

System



Device



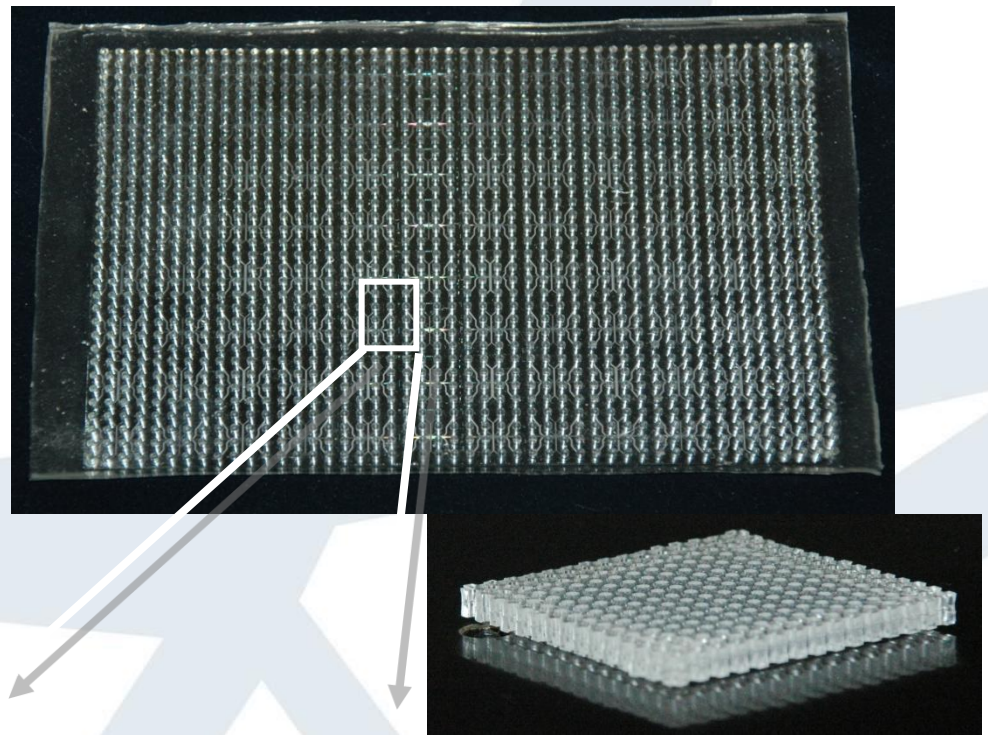
Technology



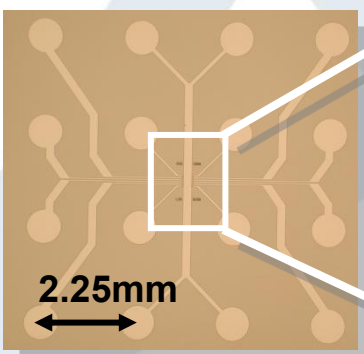
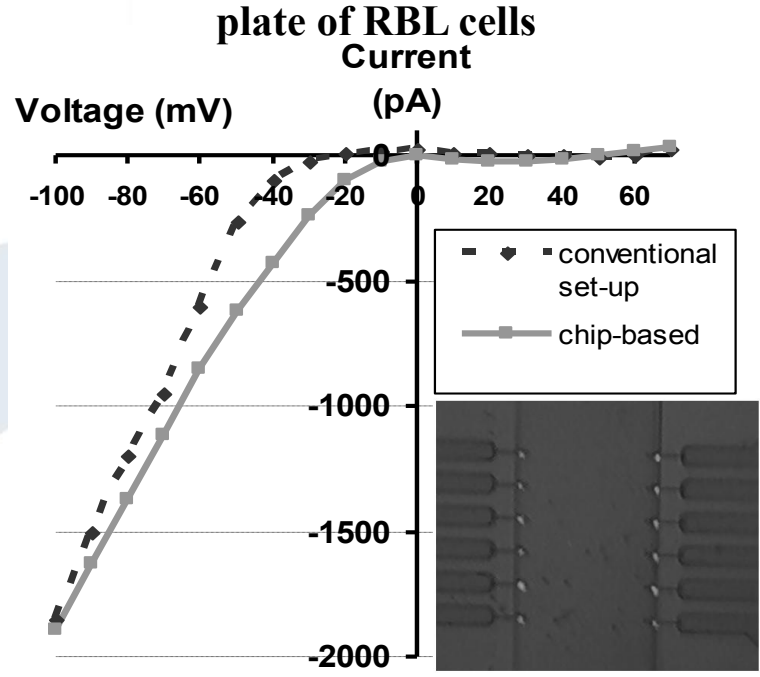
Silicon based High-Throughput patch-clamp chip

Ion channel activity response is important to observe for potential drug candidates

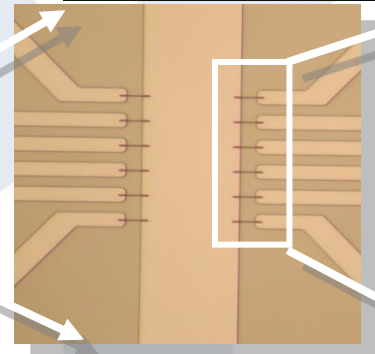
1536 well-plate containing 1152 patch sites



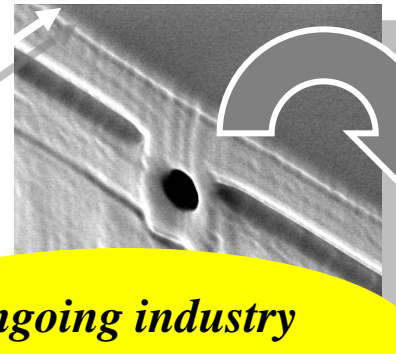
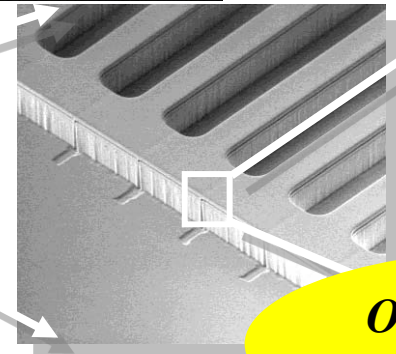
Multiple captures and recordings on a patch-clamp plate of RBL cells



Single unit

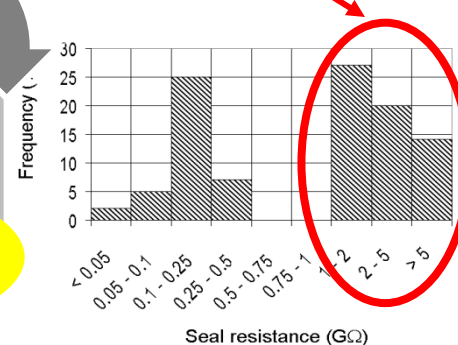


12 laterally embedded patch pipettes



Ongoing industry collaboration

High gigaseal rate >60% (100 experiments)

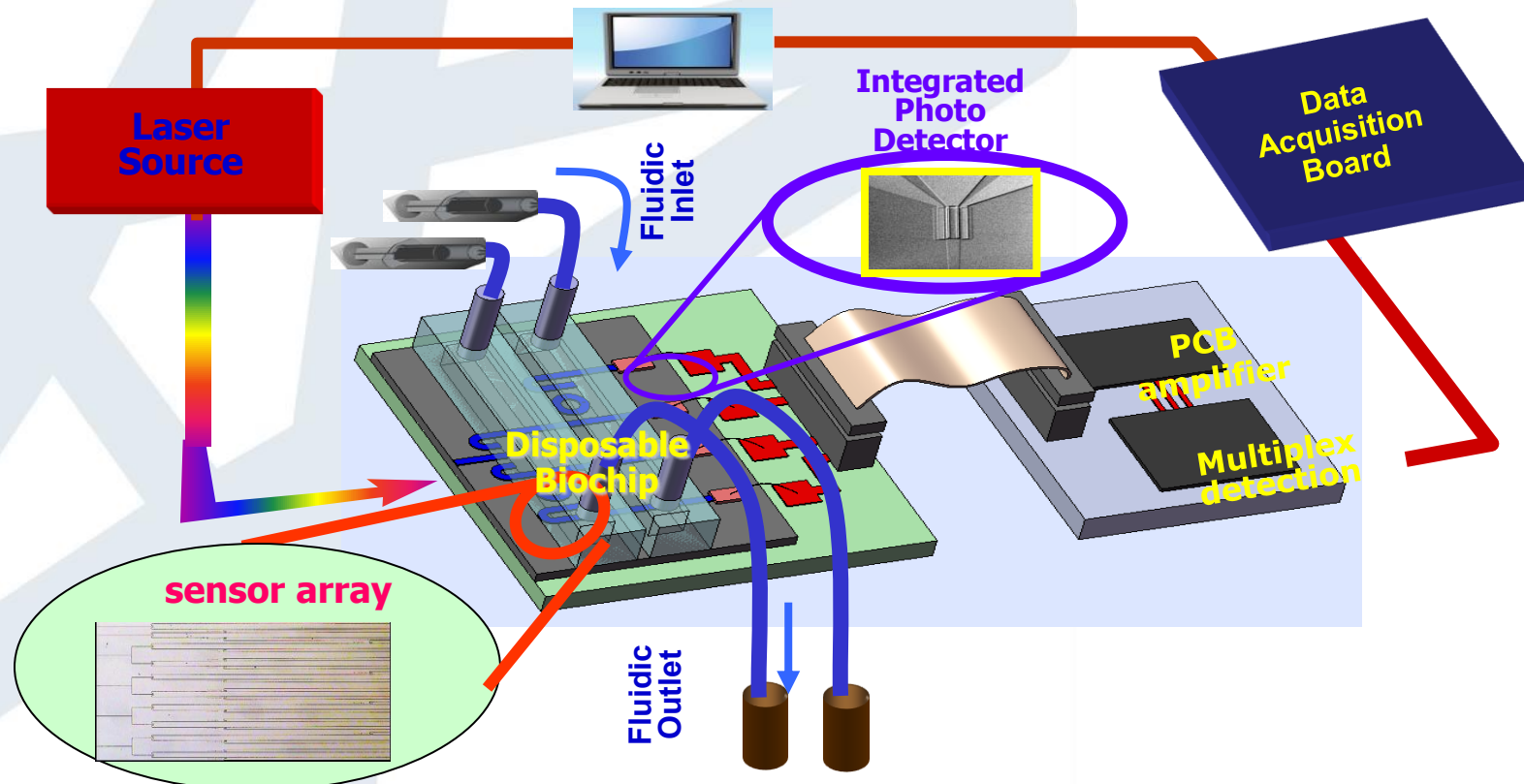


Photonic Sensor to detect molecular interactions for drug screening

Motivation: Low affinity protein-to-protein, protein-to-ligand interaction detection for drug discovery and screening is a challenge.

Current technologies can achieve $K_d = 10^{-6}M \sim 10^{-4}M$

Targeted Specifications: $K_d = 10^{-3}M$ real time detection



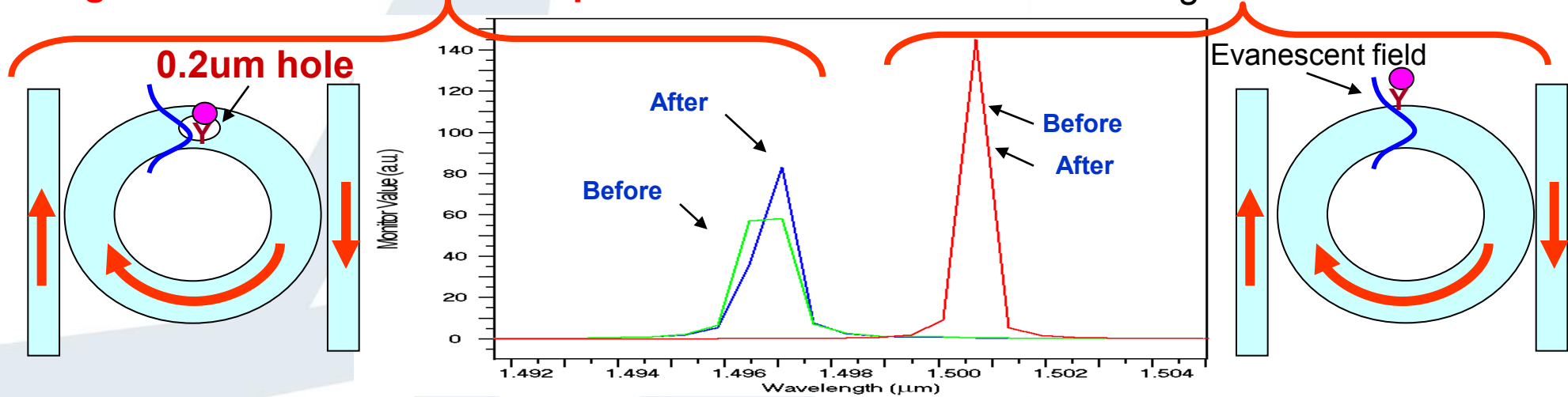
Photonic Sensing for low-affinity molecular interaction for drug screening page 19

drug screening

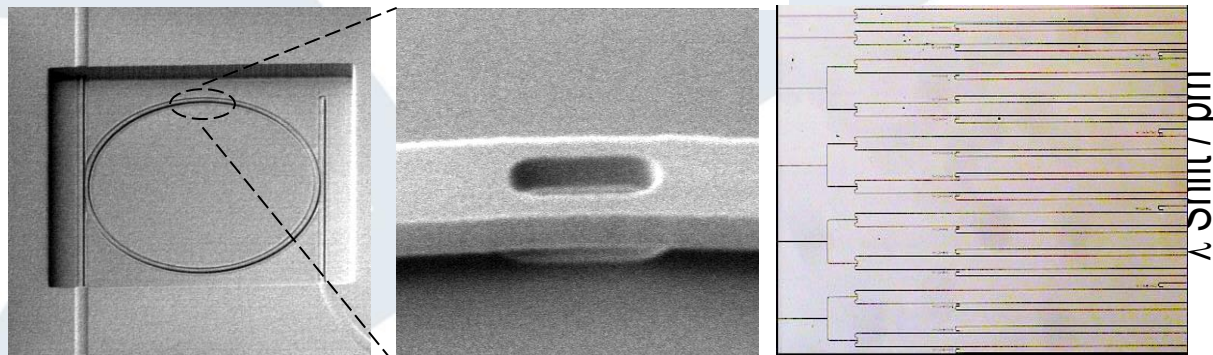
Ring-hole resonator: Hole increases light-matter interaction

Ring/hole device detects a 200pm λ -shift

Conventional ring device: No shift

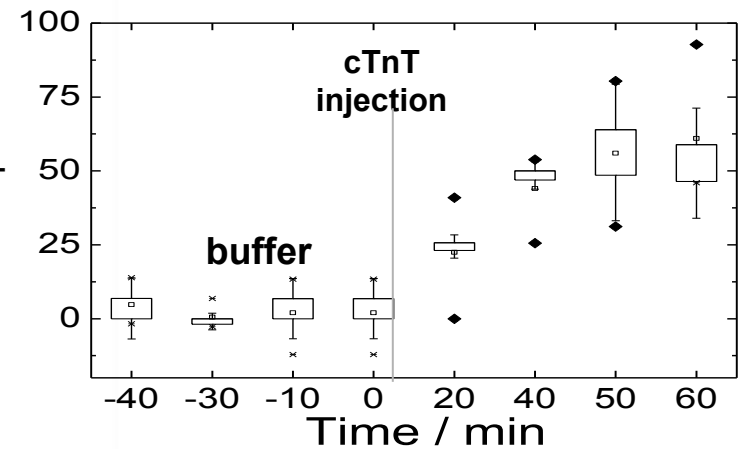


IME's Device



ring/hole resonator

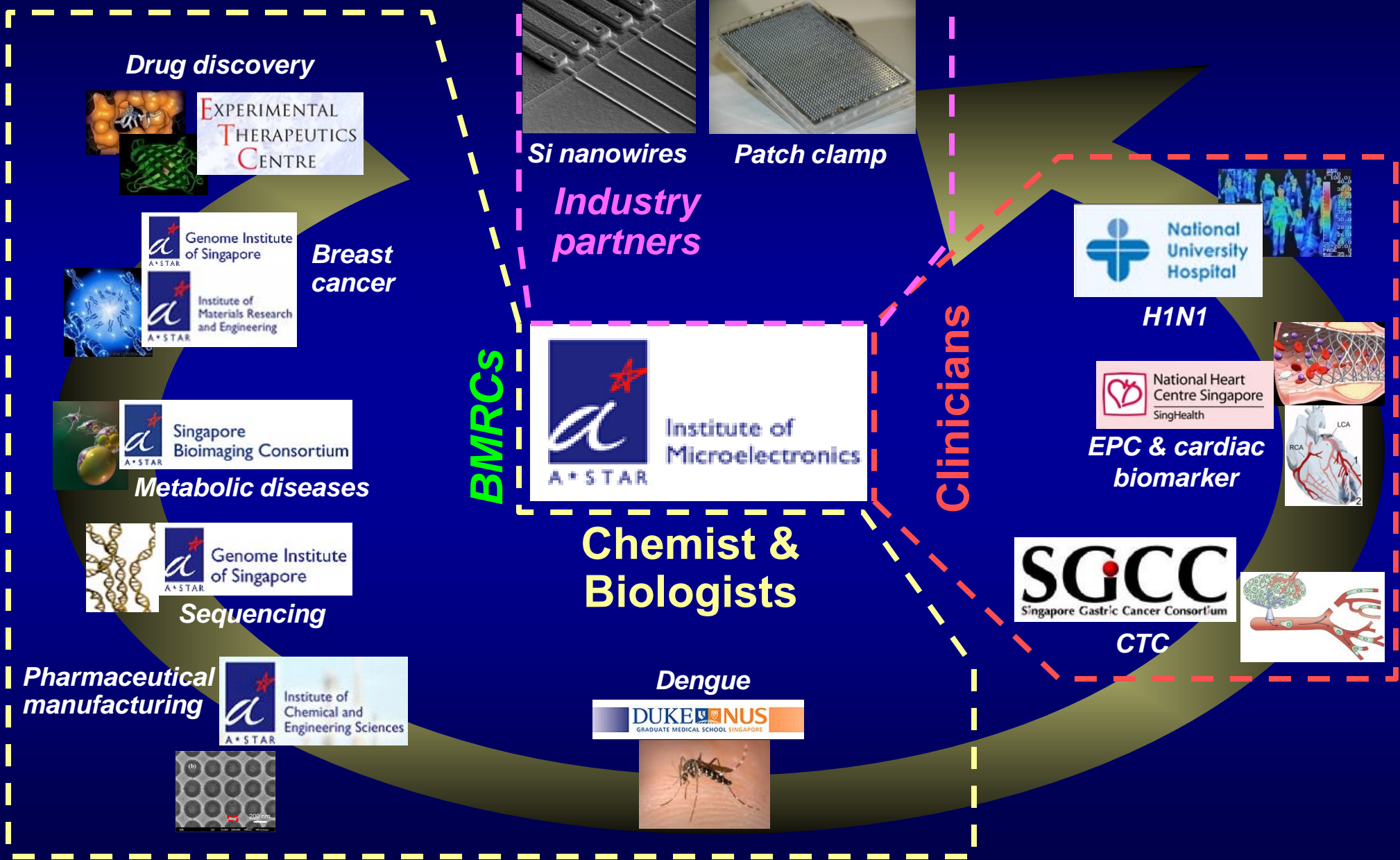
multiplexing waveguide



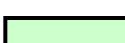
Demonstrated detection of 100fg/ml of Troponin T

IME Confidential & Proprietary


BE Collaboration strategy



Miniaturized medical devices

 Existing Capabilities

MMD Core Capabilities

 Capabilities under development

MEMS/NEMS Devices

- Pressure/flow/tactile sensors
- Micromirrors
- Ultrasound transducers
- Neural probes for recording
- Ultracapacitors for energy storage
- Strain Gauge sensors
- Thermal sensors
- Neural probes for stimulation
- Energy scavengers

Device interface & signal processing

- Pressure/ flow/tactile sensor interface IC
- Micromirror interface IC
- Neural recording amplifiers
- ULP data converters
- ULP digital signal processor
- Ultrasound transducer interface IC
- ULP voltage converter & power management
- Neural stimulation interface IC

Wireless power transfer & data communication

- High efficiency inductive power link
- Implantable passive TRx
- MedRadio/MICS
- MIMO wideband TRx for PillCam
- High-data-rate wide-band TRx for neural recording

Packaging/ Integration

- TSV technology
- Miniaturized 3D packaging
- Passive device integration
- Hermetic encapsulation
- Biocompatible encapsulation
- Biocompatible flexible interconnection cables

Testing and Characterization

- MEMS device mechanical testing
- MEMS device electrical testing
- Analog & mixed signal IC testing
- Wireless IC testing
- Hermeticity testing
- Reliability testing
- Biocompatibility testing

Summary

- *Recognized world class R&D capabilities*
- *Dedicated commercialization teams and framework*
- *BE @ IME leverages across entire microelectronics value chain and strategic collaborations to develop biomedical solutions*
- *Semiconductor industry's expertise in making high quality complex devices at low prices is definitely needed !!*

*Come visit us in Singapore!!
(www.ime.a-star.edu.sg)*

"Fusionopolis and Biopolis are the anchors of the one-north development, which is designed as an entire integrated innovation ecosystem."

*- Mr. Lee Hsien Loong
Prime Minister, Singapore*



S'pore team develops faster dengue test kit

RESEARCHERS from the Institute of Microelectronics (IME) under the Agency for Science, Technology and Research have come up with a diagnostic kit which can test for dengue in a much shorter time. With current dengue diagnostic tests in hospitals, it can take up to a day before results are known.

The new kit, which requires just a finger-prick amount of blood, takes just four hours and still maintains the level of accuracy. It can differentiate between four dengue serotypes.

The new test kit can significantly reduce the reliance on labour-intensive and time-consuming laboratory tests which require highly skilled personnel to carry out.

The shorter waiting time also means it can be deployed at areas such as clinics, hospitals and airport gantries.

Associate Professor Ooi Eng Eong from the Duke-NUS Graduate Medical School, who worked closely with the IME team on this project and has more than 10 years of research experience in infectious diseases, believes the dengue diagnostic kit was only a starting point.

He said the technology has the potential to be expanded to include testing for other pathogens such as chikungunya, influenza A and B viruses including those responsible for the avian and H1N1 flu, as well as coronaviruses including that which causes Sars.

IME's senior research engineer, Dr Kang Tae Goo, who was involved in the development of the dengue diagnostic test, said they were looking for industry partners to jointly develop the prototype.

They are also looking to work with clinicians to carry out more studies on blood samples from dengue-infected patients.

About 50 million people worldwide are infected with the dengue virus each year.

In Singapore, there have been about 11,000 dengue cases in the last two years.

BEN NADARAJAN

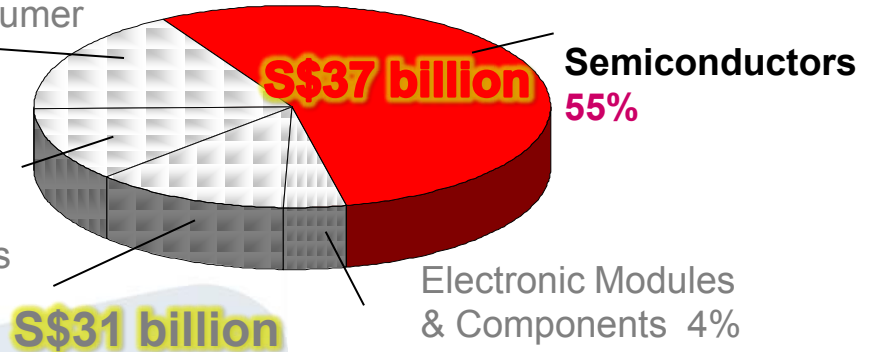
Singapore Semiconductor Industry

2008 Projected Electronics Mfg Output
S\$68 billion

Infocomms and Consumer Electronics 17%

Data Storage 12%

Computer Peripherals & EMS 12%



Source: EDB

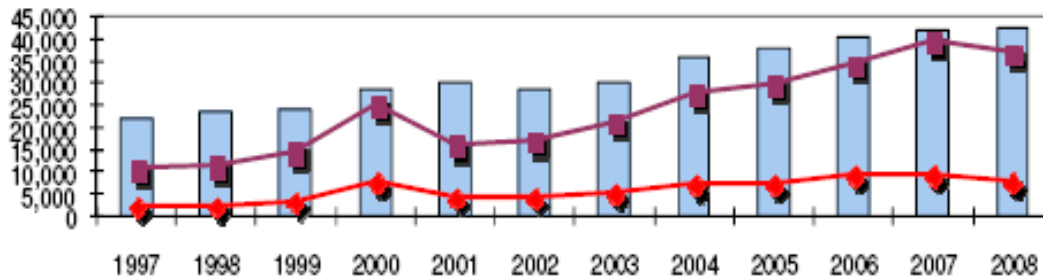
18

Semiconductors
15% of Total Mfg Output 2008(p)



A Major Area of Focus for Singapore

| | |
|----------------------|------------------------------|
| Manufacturing Output | : S\$37.3 bil (US\$26.3 bil) |
| Value Added (VA) | : S\$7.8 bil (US\$5.5 bil) |
| Employment | : ~40,000 |



Employment Output (S\$million) VA (S\$million)

- Semiconductor Industry
 - 40 IC design companies
 - 14 wafer fabs (3 12")
 - 20 assembly and test comp

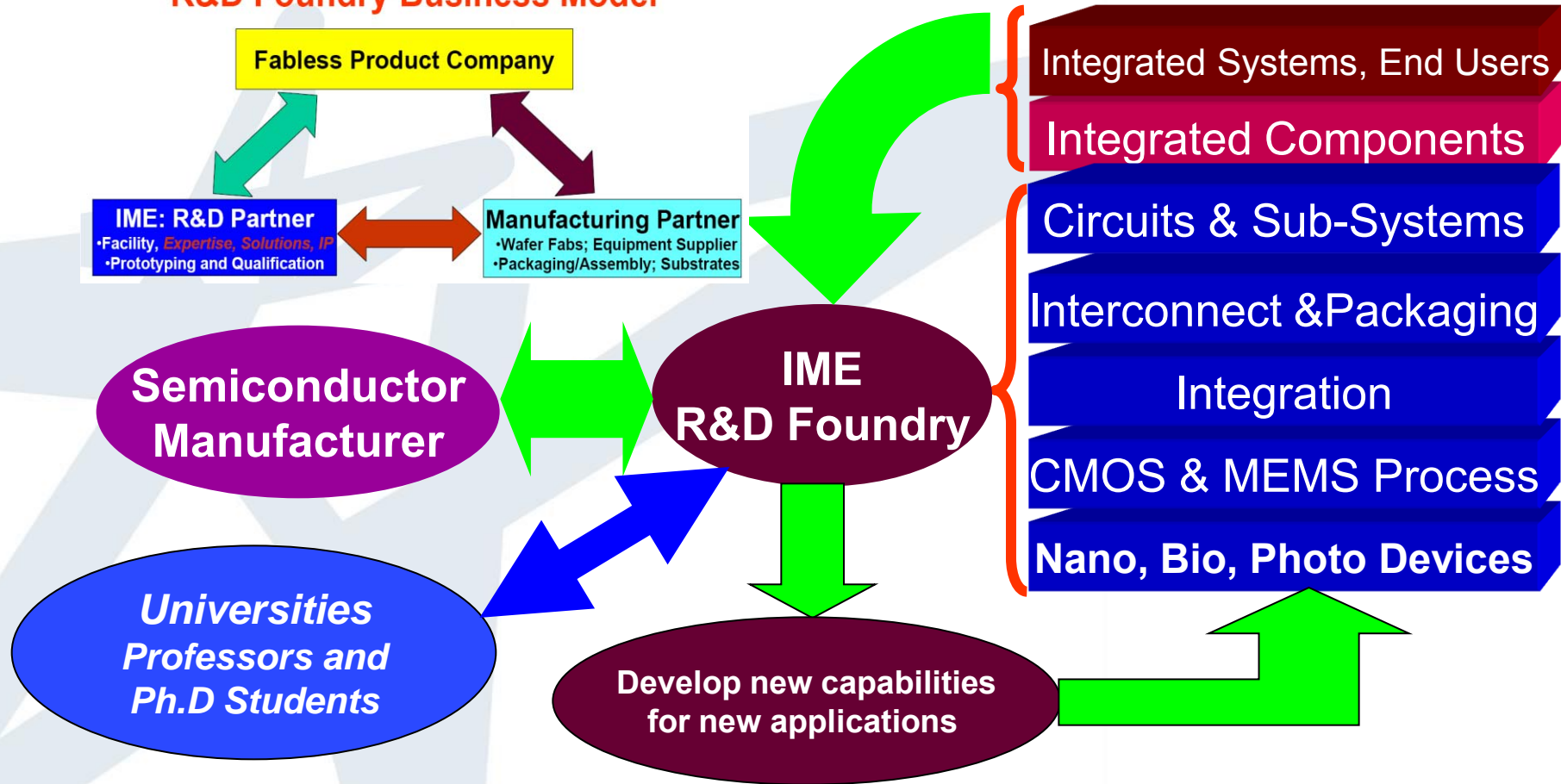
- World-wide market share
 - 6% (1998) → 12% (2008)
 - 20% (2020)

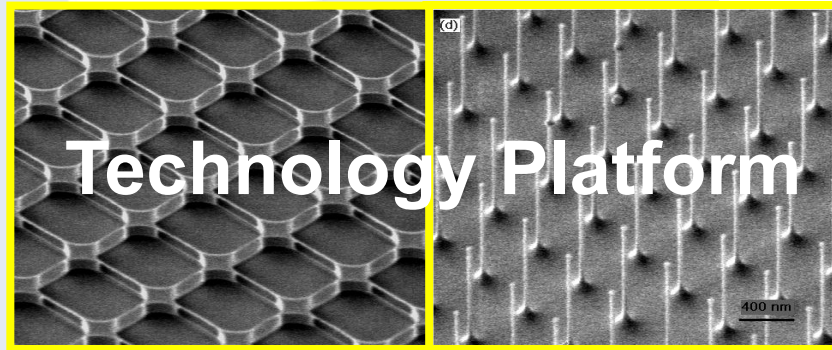
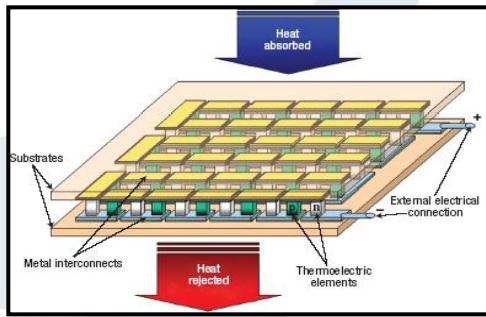
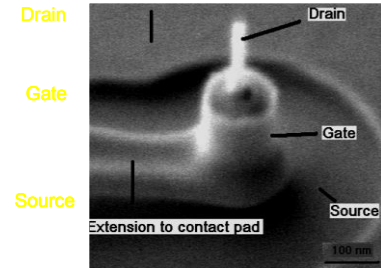
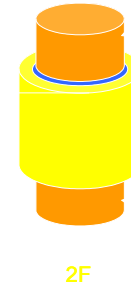
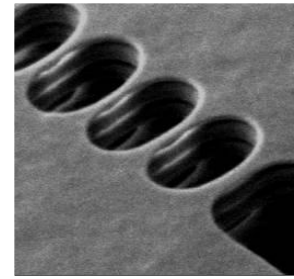
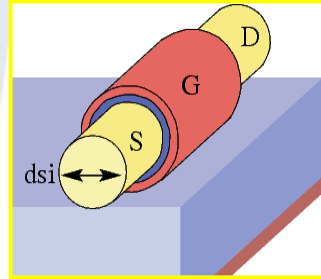
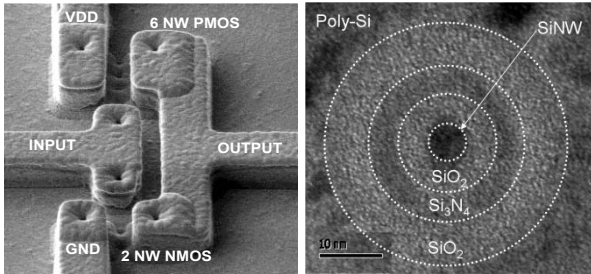
R&D Strategy: Top-Down Approach

- Research driven substantially by commercial applications as the end goal
- Joint development of new capabilities with strategic partners (industry, hospitals, biomedical institutes, universities) by sharing of talents, costs, risks

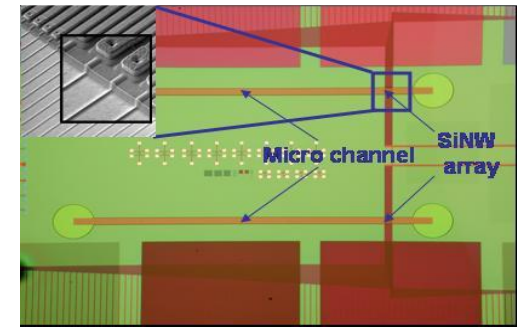
R&D Foundry Business Model

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Technology Platform



Chip-NW-TE

