Role of Academic Research in Innovative Drug Discovery and Development:

Opportunities for Taiwan-based Research Institutions

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KT Wang Lecture, Academia Sinica

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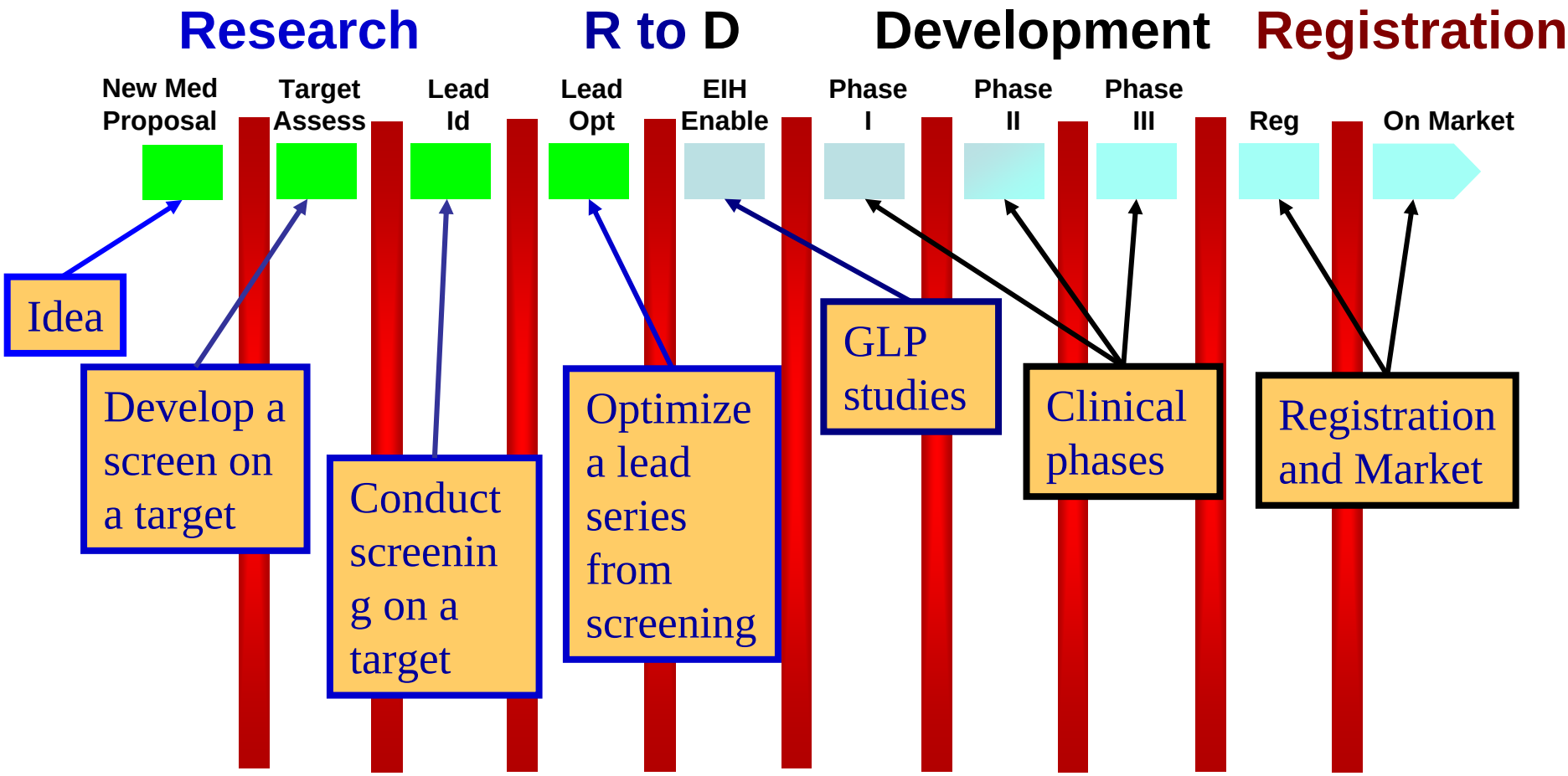
Changing Economics of the Pharmaceutical Business

- Since 1945 through the 90's, pharmaceuticals was, on average, the most profitable sector of the US economy
- Pillars of profitability
  - long product life cycles (IP)
  - pricing flexibility
  - "blockbuster" products
  - R&D productivity

Value Chain for New Drug Discovery, Development, and Registration: A Well-Defined Process



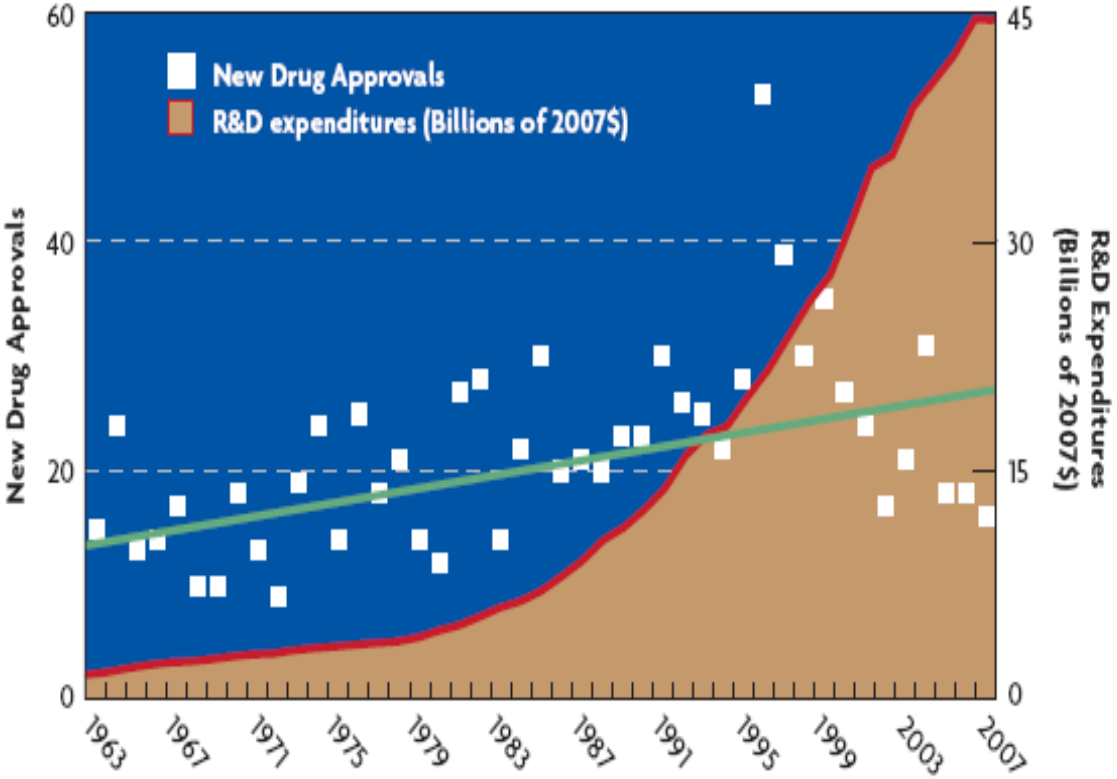
Excellent R & D Productivity in Pharmaceutical Business

- It was a numbers game
- We were able to build all necessary tools and maintain full capability in research platforms and tool boxes
- High rate of return on investment

  (Roche bench mark was 14%)

NEW DRUG OUTPUT CONTINUES TO STAGNATE, WHILE R&D COSTS REMAIN HIGH

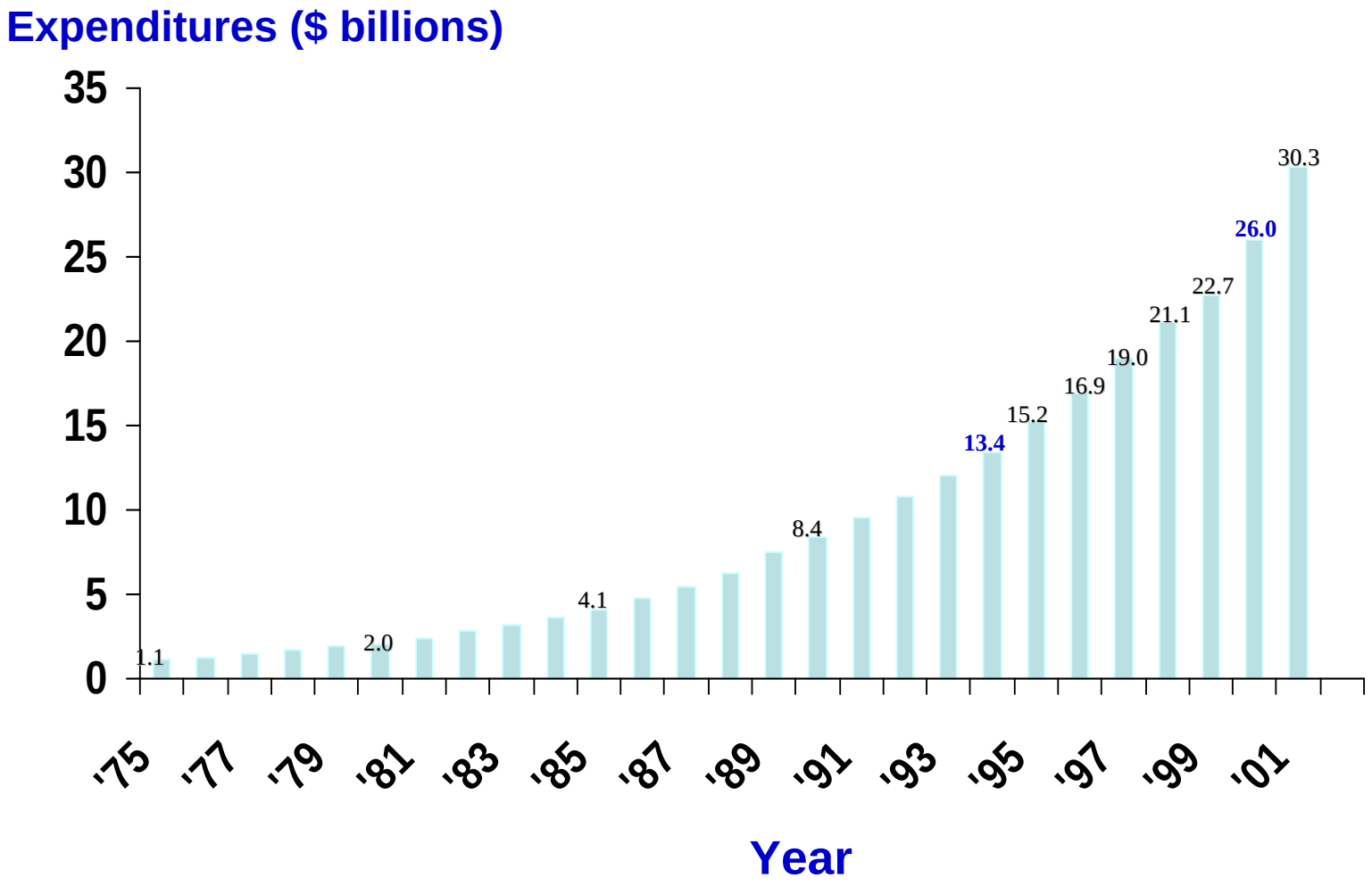
New Drug Approvals and R&D Spending



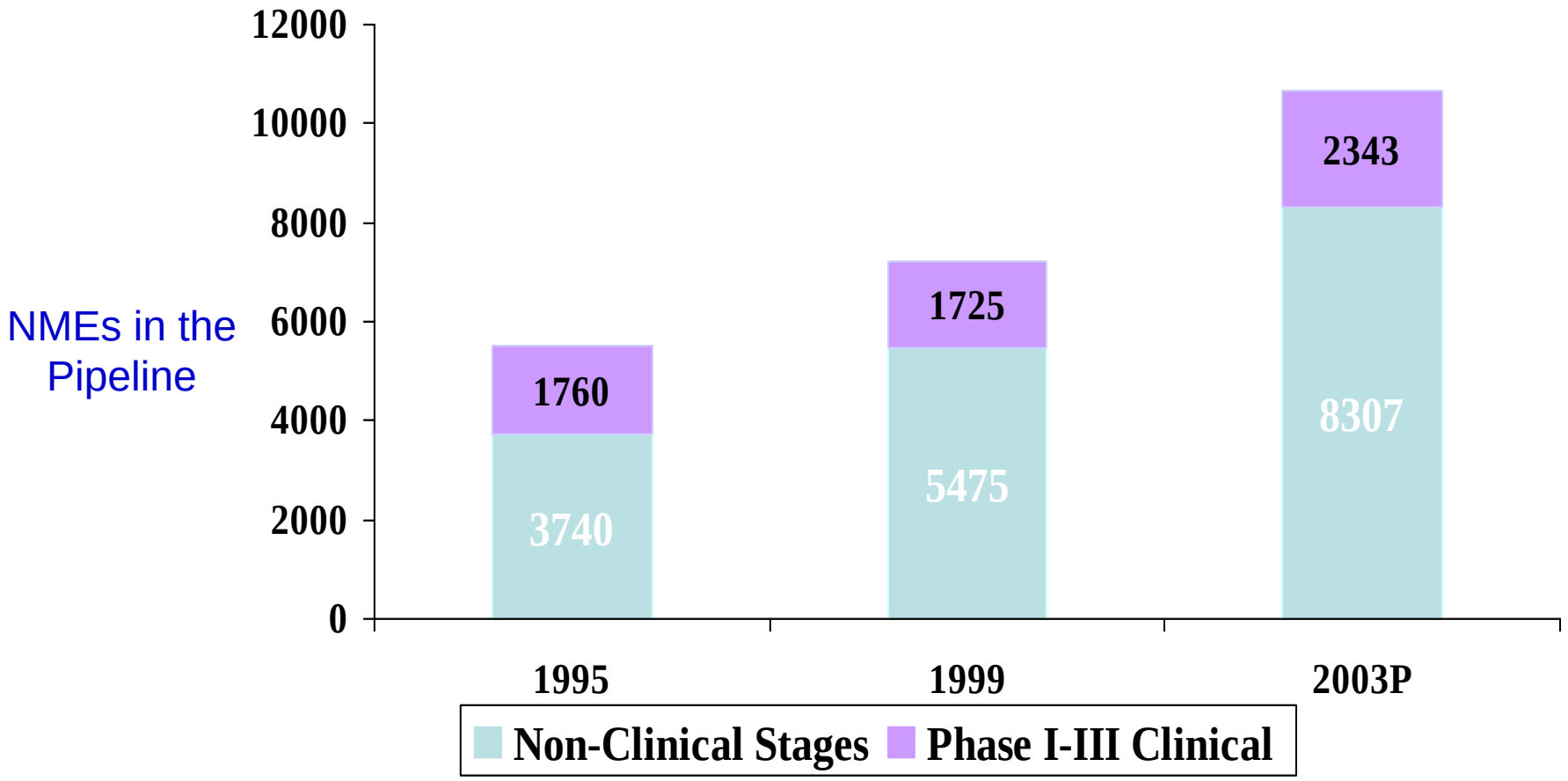
Source: Tufts Center for the Study of Drug Development, PhRMA

Despite use of adaptive trials, improved project management, and increased reliance on global partners, the cost of drug development remains stubbornly high. Among the reasons behind this is growing protocol design complexity, which leads to longer clinical time. For example, while average approval time in the U.S. has declined in recent years, total development time (clinical plus approval) has remained relatively flat, averaging 8.6 years since 2002.

R&D Investment by Pharmaceutical Companies



Productivity Problem is not due to Lack of Numbers of Projects



Evolving Pharmaceutical R and D Benchmarks

- Cost more

  >1 billion dollars to develop a new drug
- Longer research and development cycle

  10 to 14 years to bring a drug to the market
- Lower Success Rate

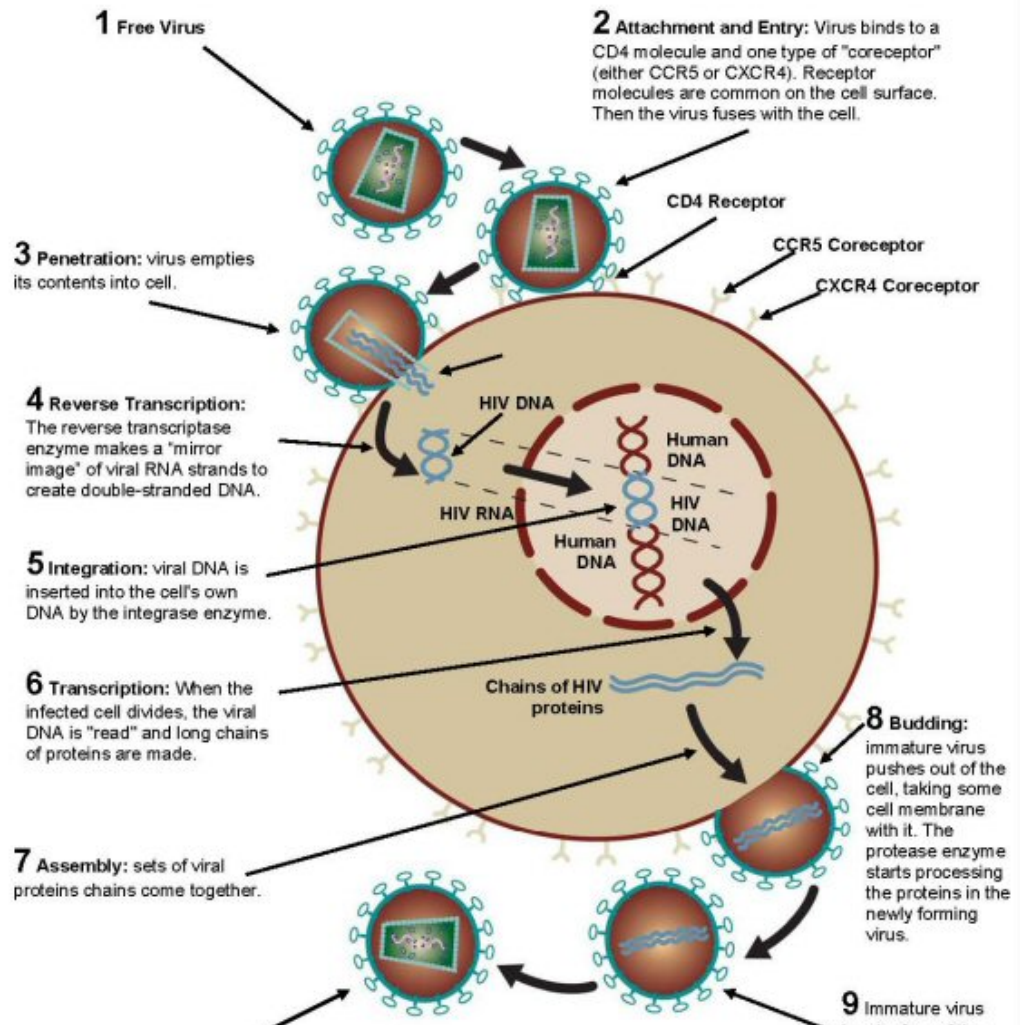
  <1 in 10 candidate molecules succeed after initiation of clinical trials

Deteriorating R & D Productivity in Pharmaceutical Business

- It is no longer a numbers game
- All four pillars are eroding
  - Shorter product life cycles
  - Less pricing flexibility
  - Potentially fragmented markets
  - High costs/R&D productivity
- Low (or negative) rate of return on investment

AIDS InfoNet www.aidsinfonet.org Fact Sheet Number 106

HIV LIFE CYCLE



Revised April 21 2010

A project of the New Mexico AIDS Education and Training Center. Partially funded by the National Library of Medicine
Fact Sheets can be downloaded from the Internet at http://www.aidsinfonet.org

“Low-hanging Fruits” for New Drug Discovery and Development Targets

- Histamine H2 receptor
- Proton pump
- HMG-CoA reductase
- Leukotriene receptor
- Growth factors and enzyme replacement therapies
- Dopamine and serotonin receptors

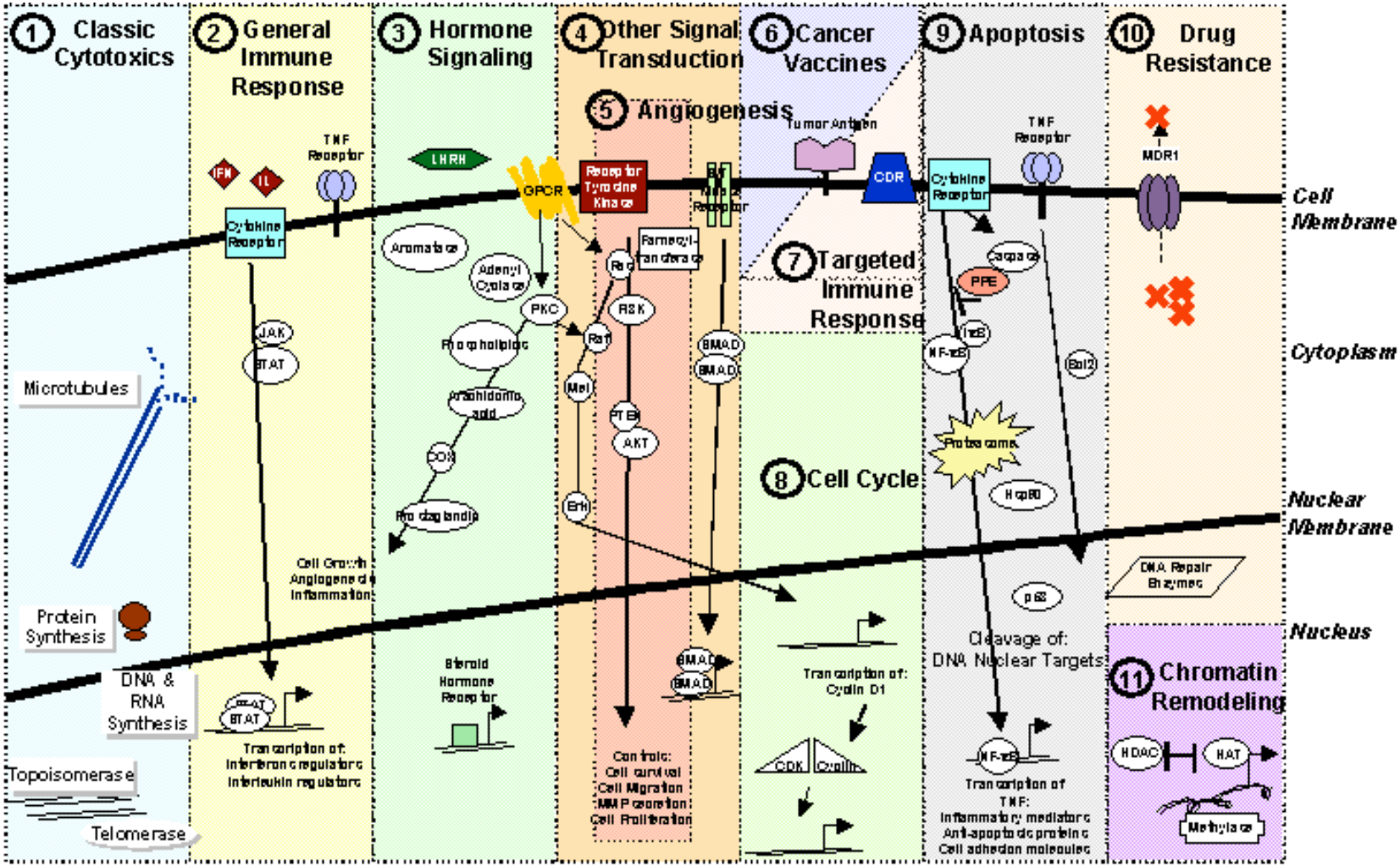
Historical Perspective

- The early leaders in our sector were “Tool Builders:”
  - Medicinal chemistry, computer-aid design, cell-line and protein engineering, purification, enhancing yield, pilot and large-scale supply, assay development, etc.
- Tools applied to “low-hanging fruits:”
  - Interferons, vaccines, antivirals, antibiotics, growth factors, small molecule inhibitors of receptors in straight-forward disease pathology, etc.
- We became “inward looking” to protect our tools, know-how, skill sets, and capacity

Current Challenges

- There are no “low-hanging fruit” left
- Target identification and validation have become the critical early steps to successful R&D
- Our classic tool box is very full – we spend more on infrastructure than on project-specific work
- But our tools are not fully developed for new endeavors: genomics, proteomics, systems biology, molecular imaging, etc.
- Competitiveness today requires “collaborative inquiry” with biomedical community at-large.

Multiple Pathways Are Being Targeted...



Source : L.E.K. analysis

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Solutions

Value creation lies at the boundary between biology and medicine

- We need more bias toward human biology to lessen reliance on animal disease models
- We cannot disengage scientific support once programs enter development
- We need to break down the barriers between discovery and medical research

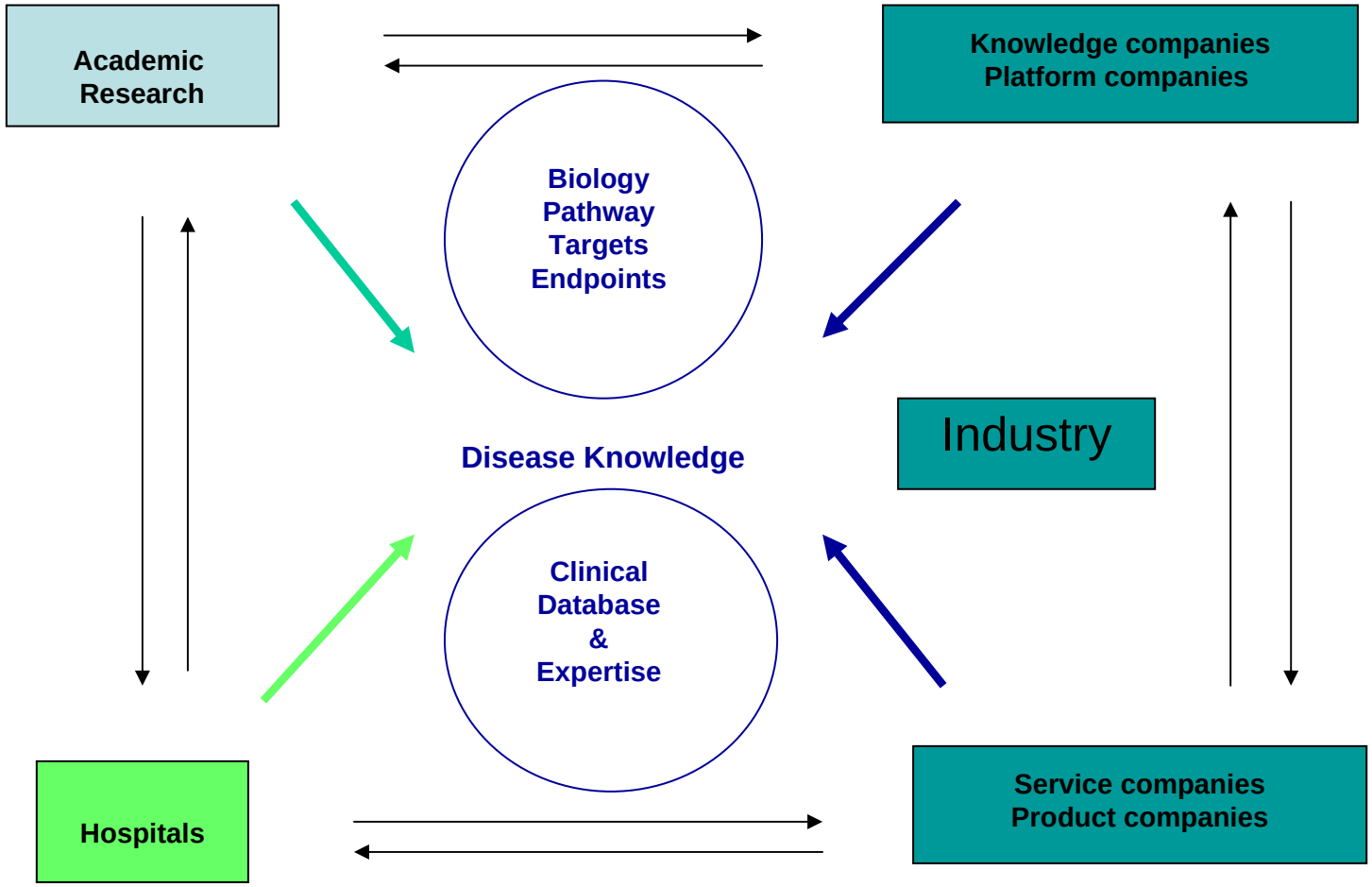
Solutions

- Research and early-development will be driven by therapeutic areas with distinct disease strategies with Intense focus on early identification of the therapeutic molecular entity and Proof of Concept (“POC”) in humans
- Full participation from clinicians at all stage of research activities, from target selection through POC clinical studies; full participation of researchers in development support
- Significant inflow of target opportunities and toolbox capability building through heavily interdisciplinary “collaborative inquiry” with academia (*Most value will be found on the outside)*

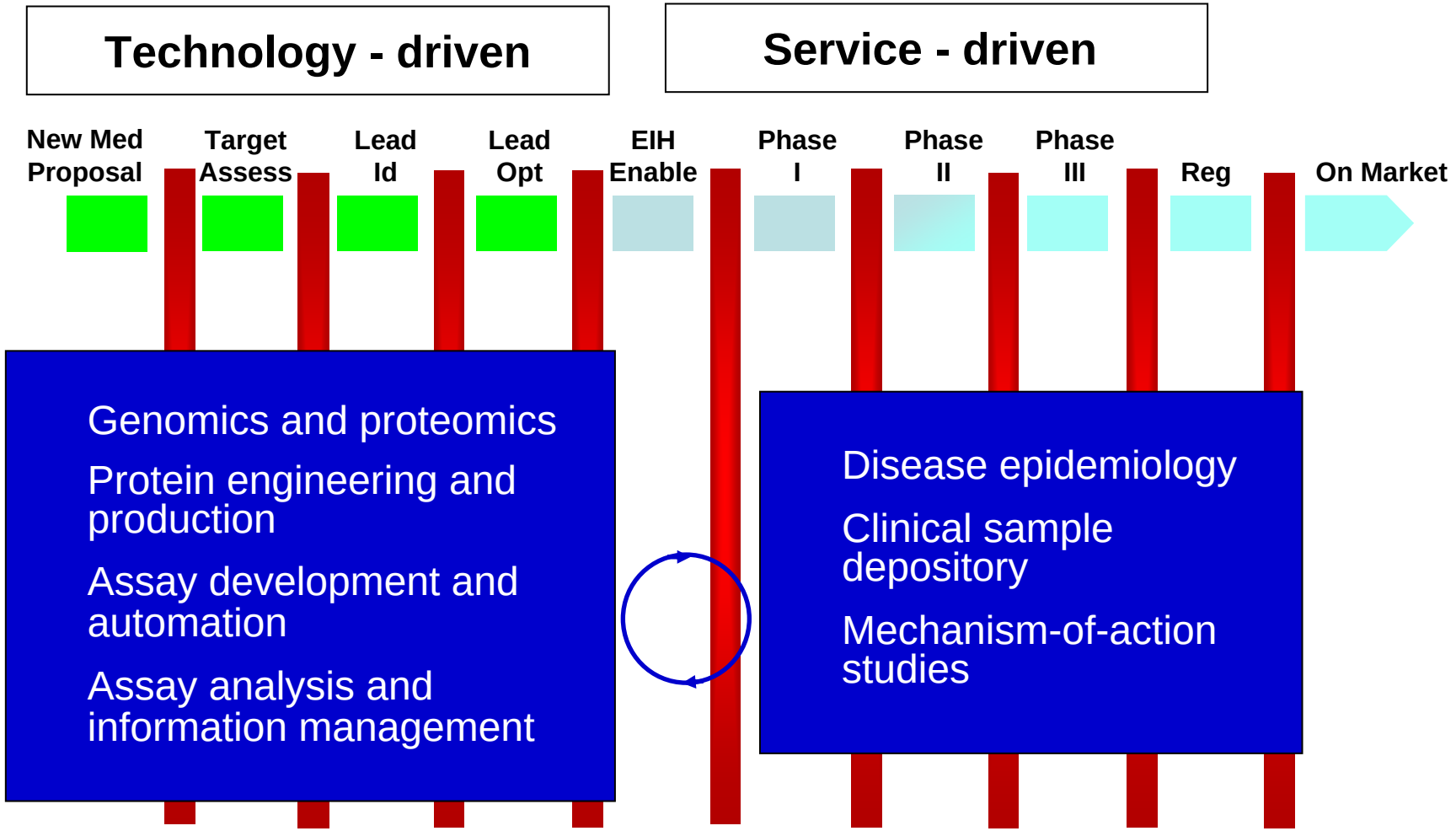
How Academia can Help Drug Discovery and Development

- Focus on the interface between biology and medicine
  - Recognize and forge links between biology and medicine
  - Knowledge-generating activities on human disease
  - Work on projects we have explicit path to clinical proof-of-concept
- While building tools, keep an eye on effective application to human disease biology and drug discovery
- Hodgedog concept

Future Drug R & D Value Chain and Stakeholders



Translational Medicine in Drug Discovery and Development



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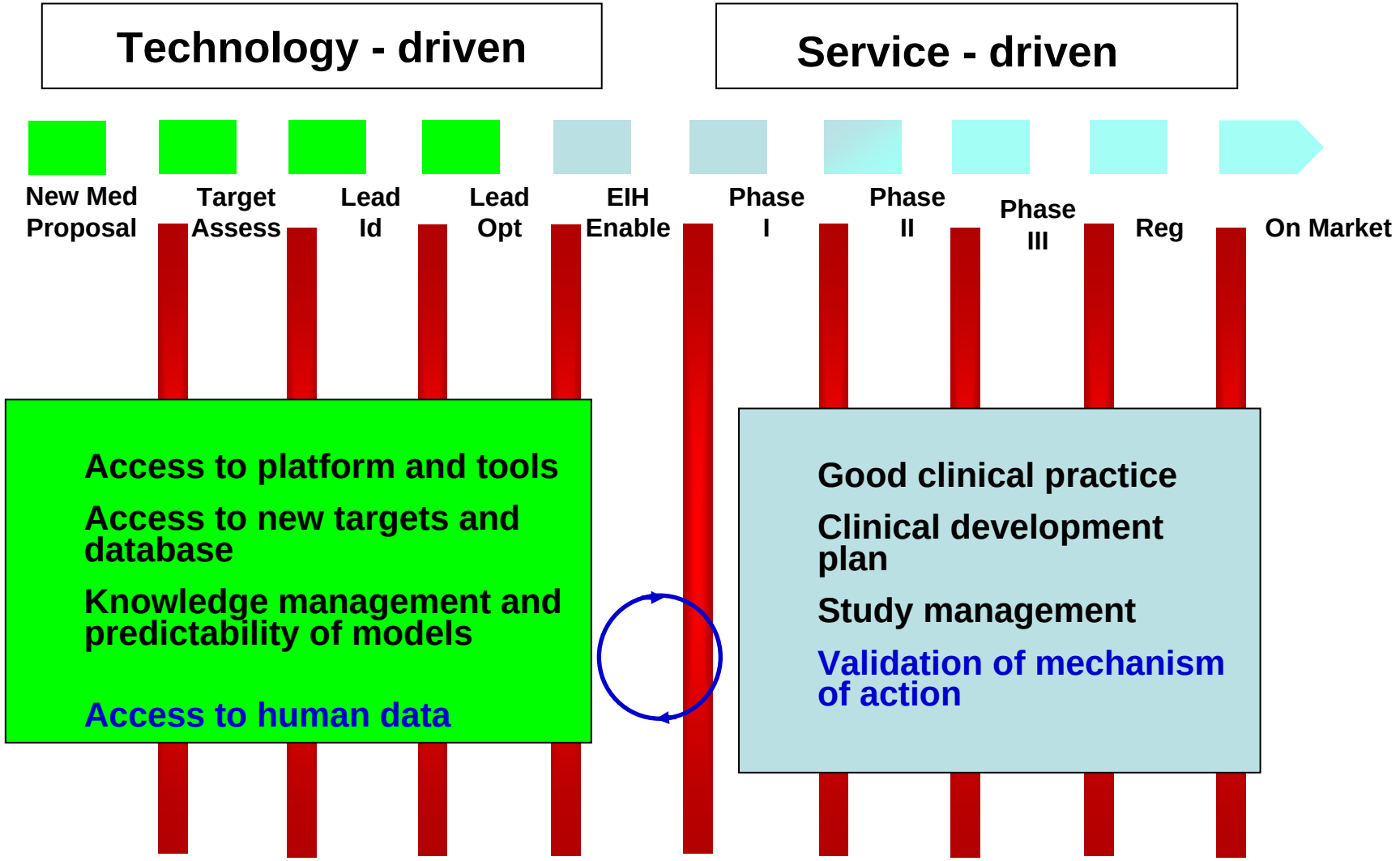

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Disciplined Thought: “Hedgehog Concept”

“The fox knows many things,
but the hedgehog knows one big thing,”
Isaiah Berlin, *The Hedgehog and the Fox,* 1993

Disciplined Thought:
"Hedgehog Concept"

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but the hedgehog knows one big thing,"
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"Foxes pursue many ends at the same time and see the world in all its complexity. They are 'scattered or diffused, moving on many levels.' Hedgehogs . . . simplify a complex world into a single organizing idea, a basic principle or concept that unifies and guides everything,"
Jim Collins, *Good to Great, 2001*

Academic Research in Drug Discovery Focus on One Big Thing: Value Chain

- Know the biology/pathology
- Understand the disease target, not just the mouse model
- Choose the best molecules, not the first
- Know the mechanism of action and pharmacology early on
- Anticipate toxicity issues

Biotech for Medicines in Taiwan:
A Model for Winning for the Future

- Value chain integration and disease knowledge/ capability-building to establish A/P leadership role in certain disease areas
- Efficient domestic technology transfer from academia and incubation
- Oversea technology sourcing and strategic partnership
- Formation of start-up company and business support
- “One-Stop” biotech park

Focus on New Drug Discovery and Development Disease Targets in Taiwan

- Epidemiology and unmet medical needs
- Available and buildable value chain research platforms, core facilities, disease knowledge, and scientific expertise
- Clinical and regulatory feasibility
- Asia Pacific business opportunity
- Oversea technology sourcing and strategic partnership

Focus on New Drug Discovery and Development Disease Targets in Taiwan

- Cancer – lung, gastric, liver, head and Neck, prostate, lymphoma
- Infectious diseases
- Metabolic diseases - diabetes
- Cardiovascular diseases
- CNS diseases

Value Chain Integration and One-stop Shop

- Most capabilities are either one-off or oligomeric in Taiwan
- High priority is to drive domestic R to D technology flow
- Can be basis for global strategic partnership
- Should benefit from central coordination and Integration

Role of Taiwan Academia in Drug Discovery and Development

- Knowledge generation (working with clinicians)
- New research platform and technology
- Tool box application
- Value chain and work flow contribution
- Drug discovery research and technology transfer
  - Spin off and start-up companies

What Questions Academic Research in Cancer Drug Research Need to Ask

- Pathobiologic relevance
- Tumor spectrum and heterogeneity
- Relevant biomarkers
- Convincing models predictive of clinical outcome

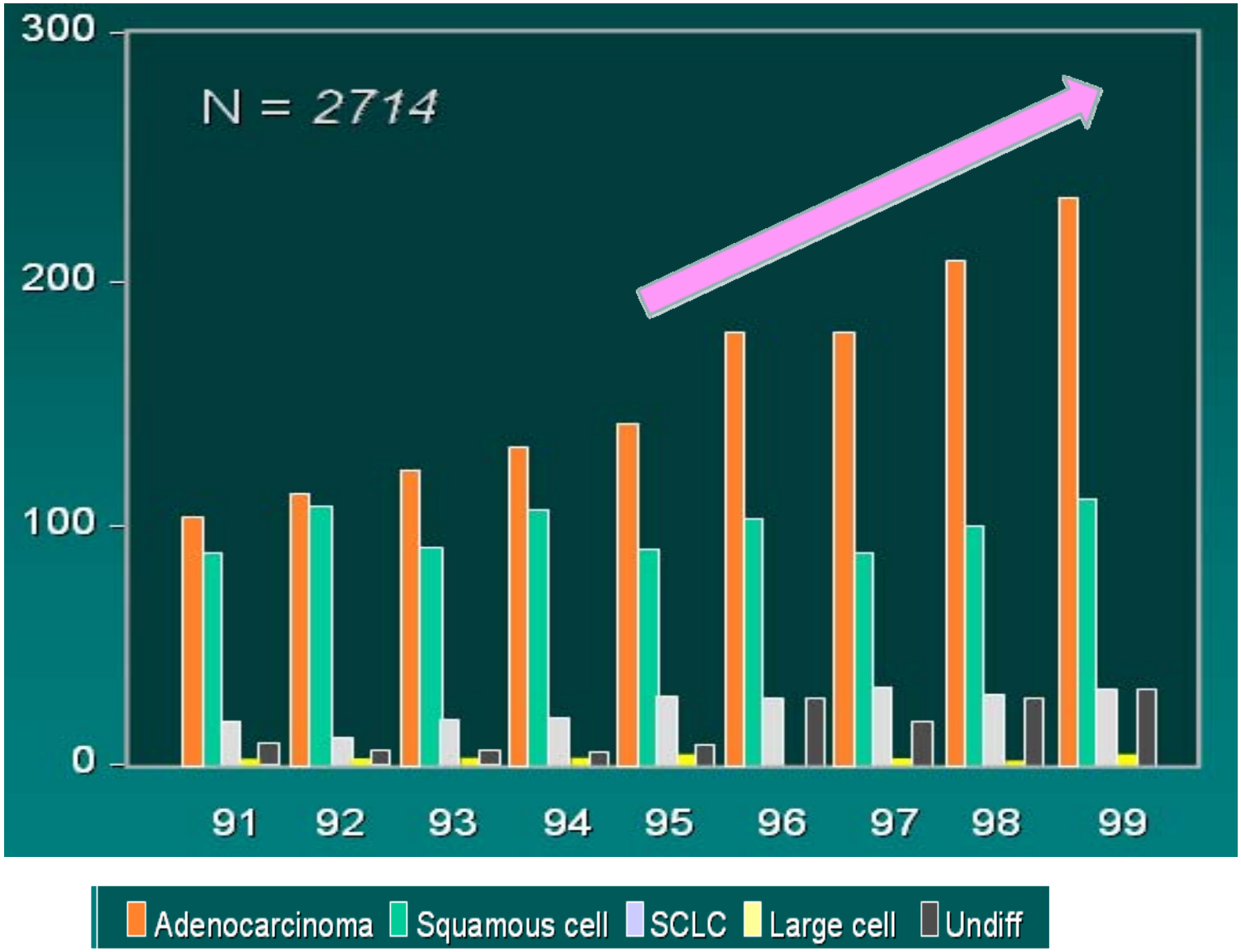
Oncology R&D Is Going Through a Paradigm Shift

Kill Proliferating Cells	Biological Mechanism of Disease
Toxic	Nontoxic
Nonspecific	Targeted
Short-term therapy	Chronic long-term therapy
Single	Combinations/sequences
Survival/recurrence endpoints	Surrogate markers as endpoints
One mechanism	Complex mechanisms and pathways interplays

Lung Cancer in East Asia

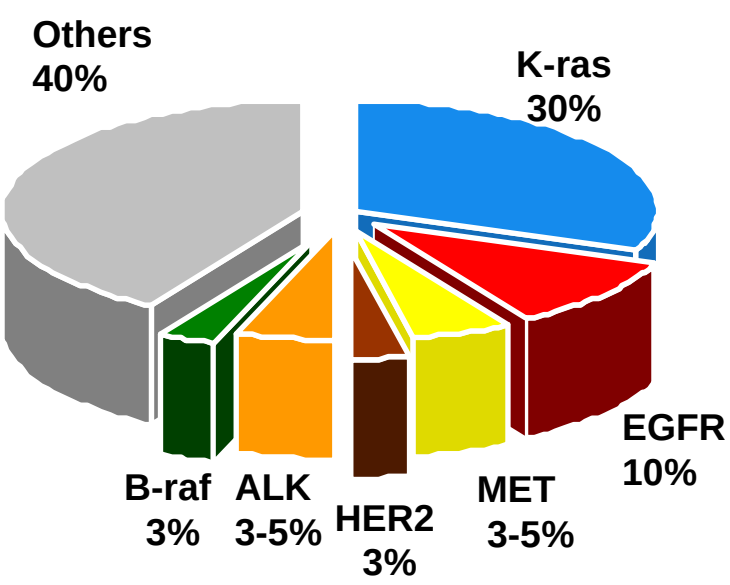
- Serious health threat and number one cancer mortality
- Persistent increase of non-smoker adenocarcinoma
- Asymptomatic, early metastasis
- Ethnic differences in pharmacogenomics
- High EGFR mutations and good response to TKI
- Mechanism for development of resistance to TKI therapy not known
- Unmet medical need for TKI resistant patients

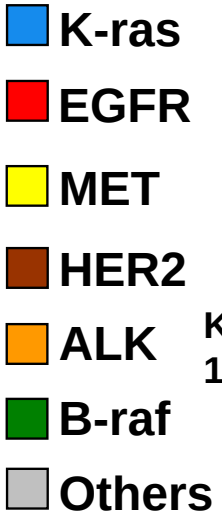
Cell Type Distribution of Lung Cancer in Taiwan



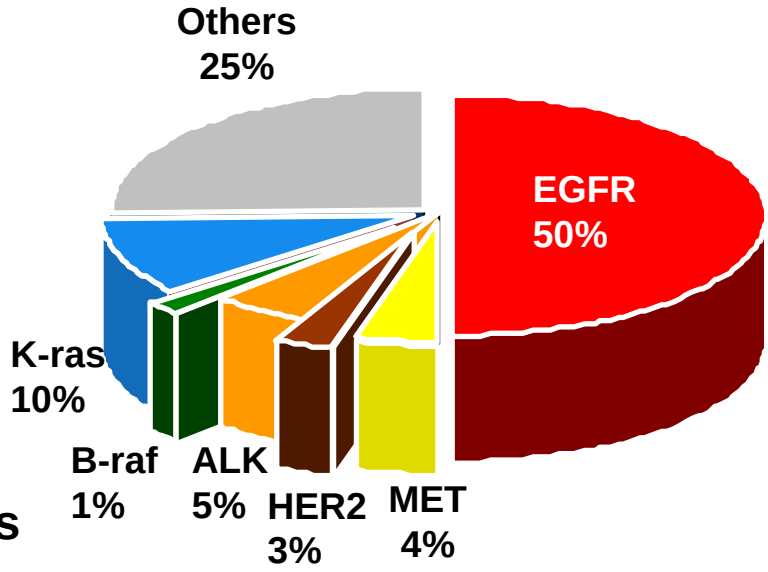
Driver Genes of Lung Adenocarcinoma-2011

Caucasians





East Asia



Taiwan Lung Cancer Group

- National Program Projects (NRPGM & NRPB)
  - Genetic Epidemiology of Lung Adenoca (GELAC)
  - Molecular carcinogenesis, new driver identification
  - Biomarker and personalized therapy
  - Cancer stem/initiating cells and microenvironment
  - Novel therapy targeting driver pathway
  - Solution for drug resistance
- Taiwan Clinical Trial Consortium

Taiwan Lung Cancer Drug Discovery and Development Value Chain Capability

- Availability of tissues and primary lung adenocarcinoma cell lines from patients with various EGFR activating mutations and wild type, as well as TKI resistance cell lines
- Availability of the orthotopic lung xenograft model and transgenic mouse lung adenocarcinoma mouse model.
- High-throughput gene sequencing capability
- Molecular imaging for phase I clinical trials

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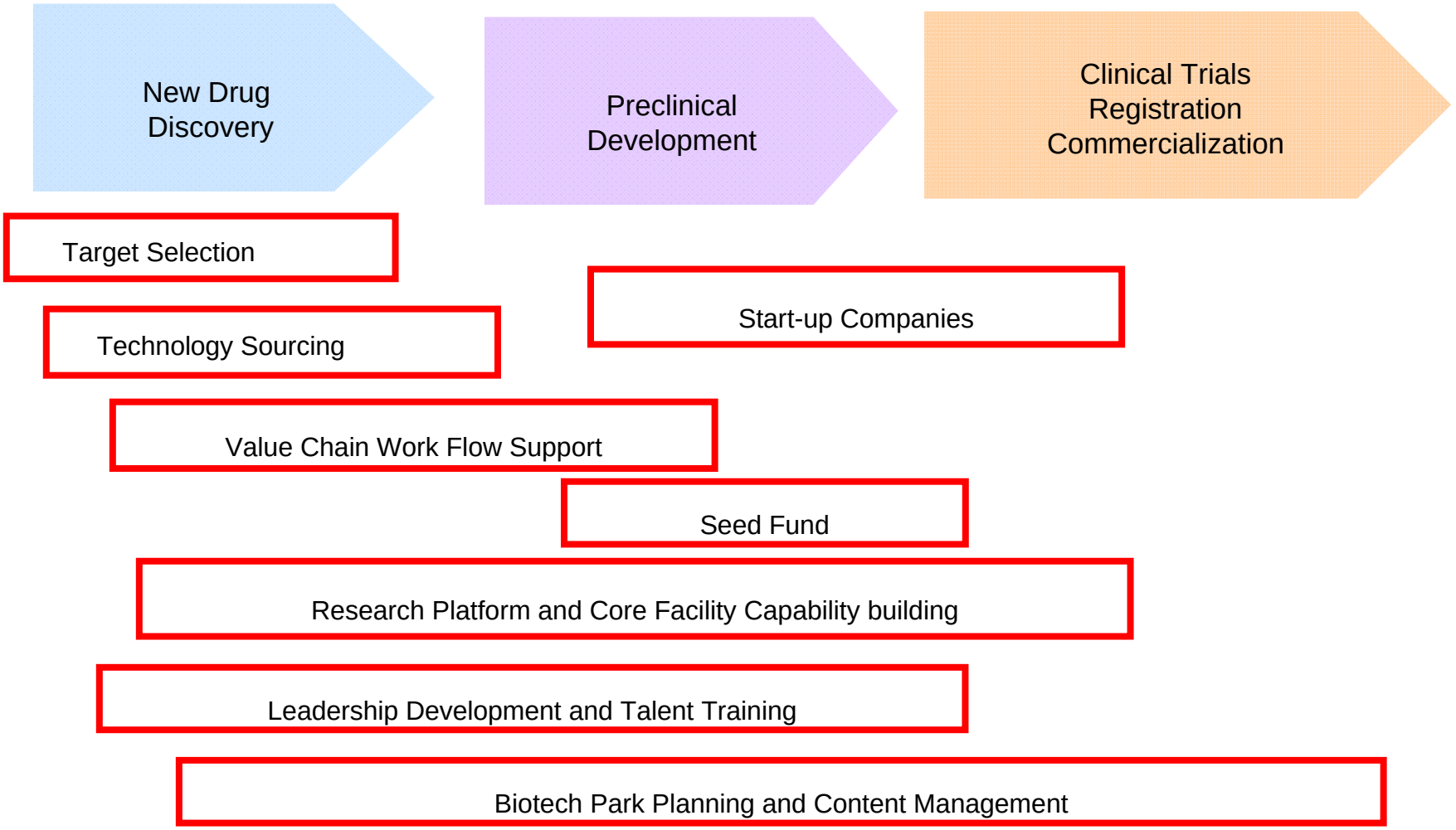
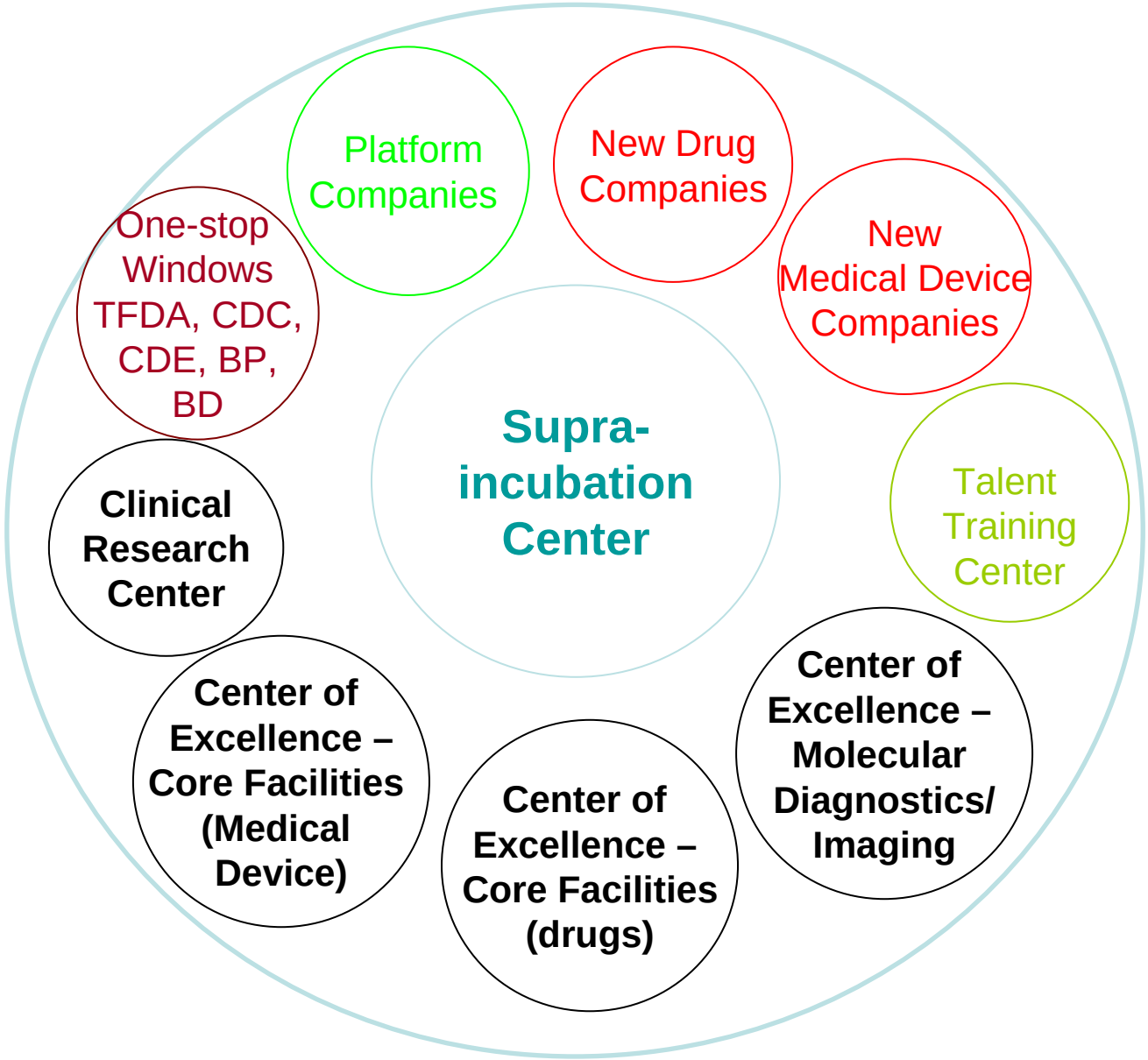
Taiwan Supra Incubation and Integration Center

- Value chain integration and capability-building to establish A/P leadership role for Taiwan in
  - new drug discovery and development (selected diseases)
  - medical device (selected product categories)
- Planning and content management of “one-stop shop” biotech parks
- Domestic technology transfer from academia and incubation
- Oversea technology sourcing
- New co formation
- Strategic partnership

Taiwan Supra Integration and Incubation Center Operation Framework



Supra Integration and Incubation Center and Biotech Park



Role of Academic Research in Innovative Drug Discovery and Development:

Joining Hands with Taiwan-based Research Institutions in Winning for the Future