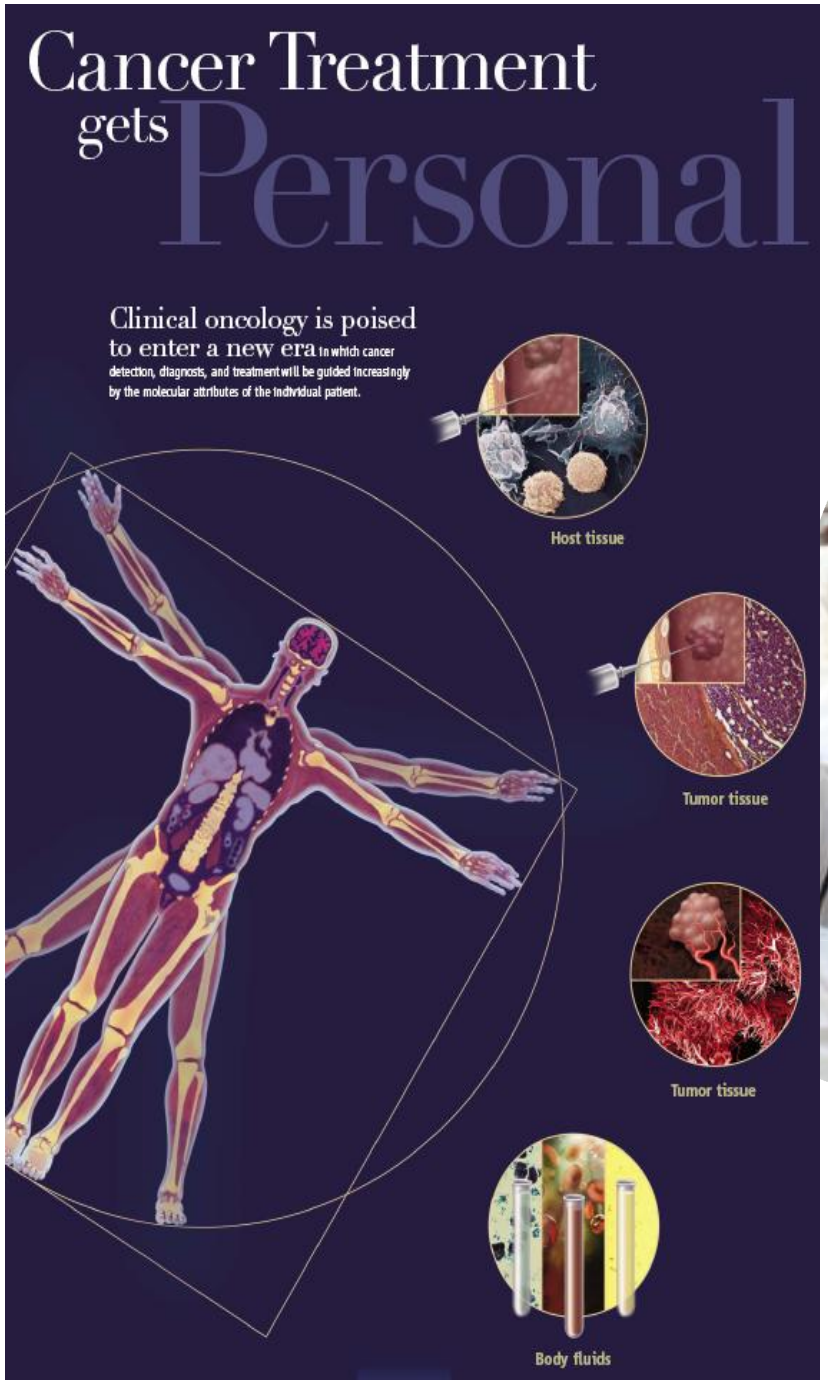
PERSPECTIVE

The New Era in Cancer Research

Harold Varmus

SCIENCE VOL 312 26 MAY 2006


Cancer Treatment
gets Personal
Clinical oncology is poised to enter a new era in which cancer detection, diagnosis, and treatment will be guided increasingly by the molecular attributes of the individual patient.
Host tissue
Tumor tissue
Tumor tissue
Body fluids


Science
Cancer Treatment
gets Personal
AAAS

PERSPECTIVE

Targeting Tyrosine Kinases in Cancer: The Second Wave

Jose Baselga

Where are the pediatric cancers?

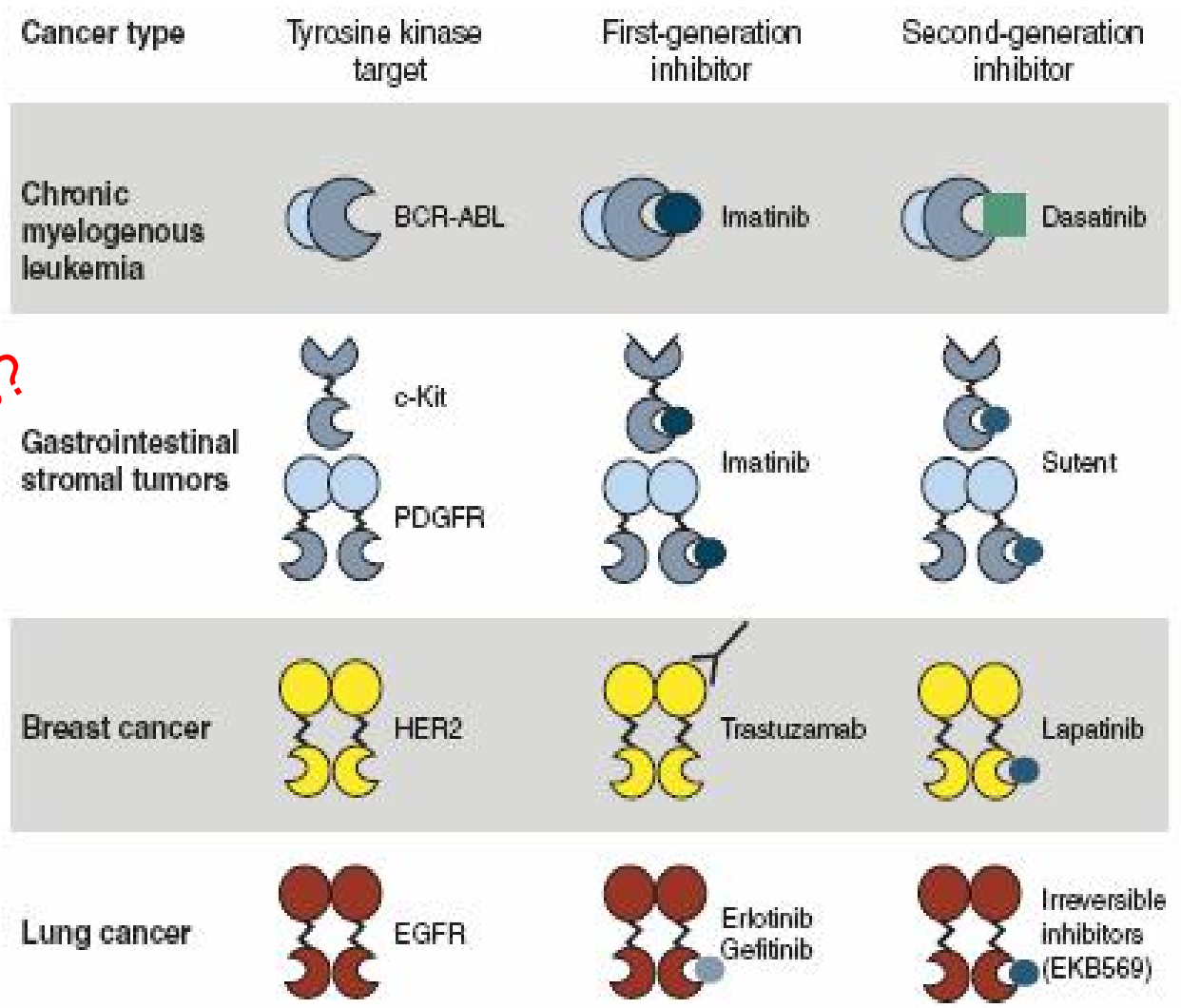


Fig. 1. First- and second-generation tyrosine kinase inhibitors for cancer treatment. Over time,

FRONTIERS IN CANCER RESEARCH

PERSPECTIVE

The New Era in Cancer Research

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Molecularly targeted cancer treatment: *who will make this happen for children*?

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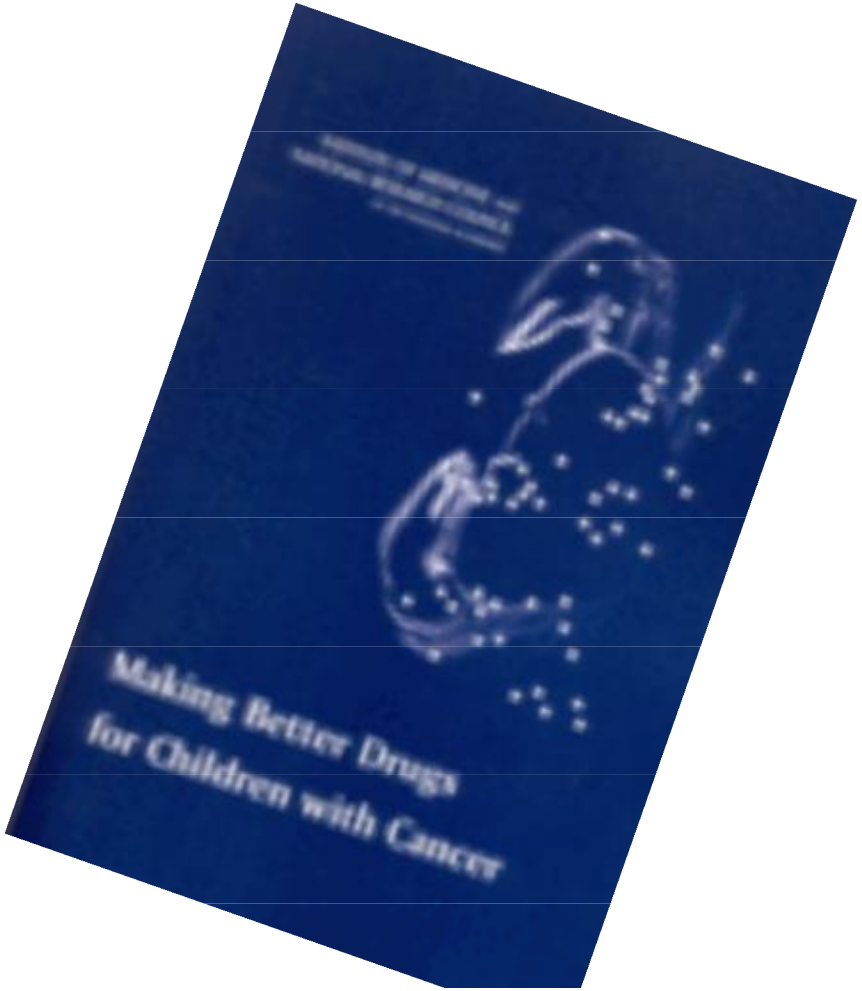
Making Better Drugs for Children with Cancer

April 18, 2005



Pediatric cancers are distinct from adult cancers

- Incidence
- Clinical
- Pathology
- Cytology
- Molecular Abnormalities

Market forces work against childhood cancers

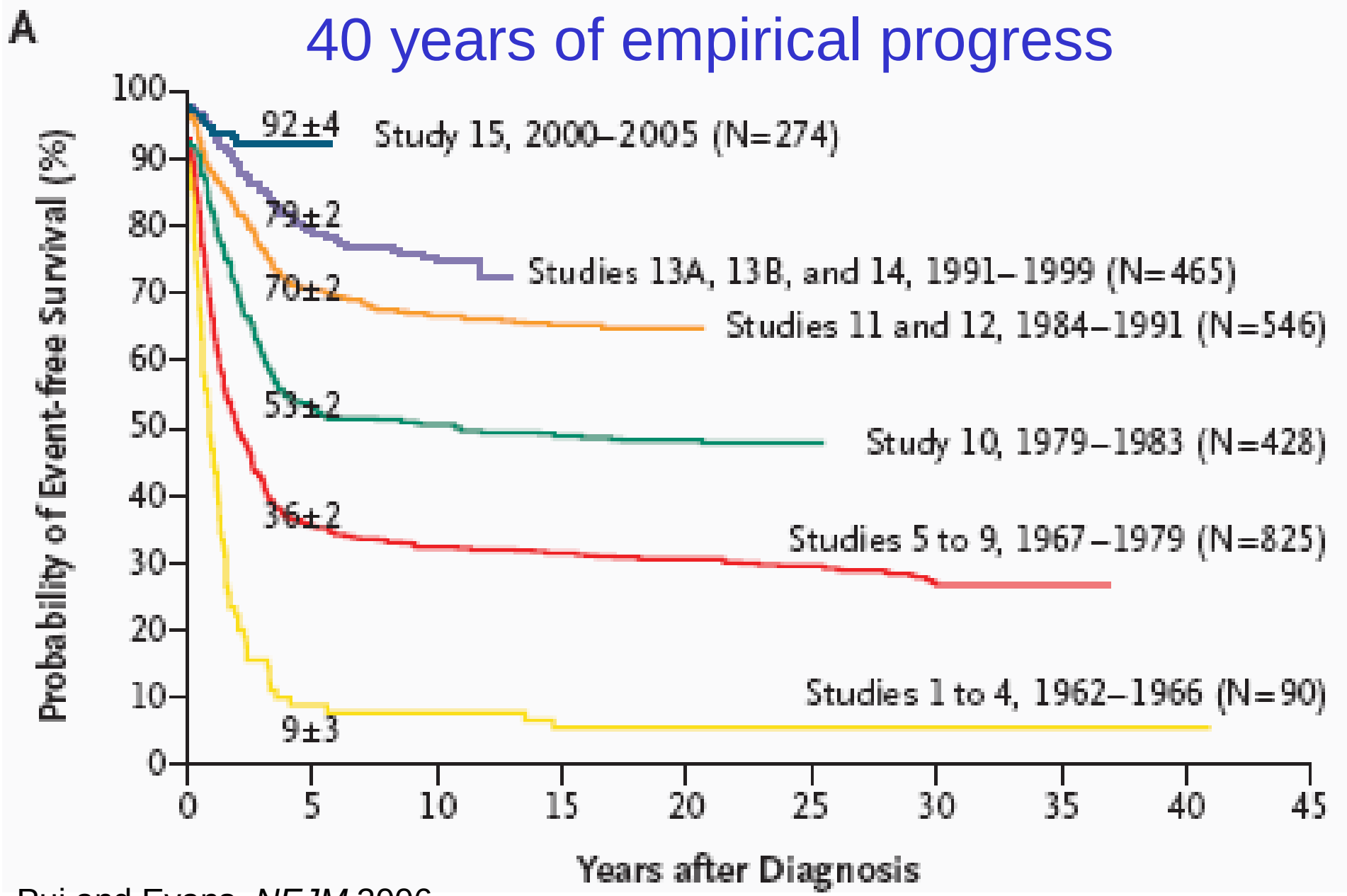
All pediatric cancers in US = ~9000

- ADULT CANCERS:
- Breast Cancer ~200,000
- Prostate Cancer ~190,000
- Lung Cancer ~160,000
- Colorectal Cancer ~150,000
- Leukemia ~ 30,000

Why little interest in pediatric cancers in pharmaceutical industry?

- Too few cases to be profitable?
- Too challenging for clinical trials?
- Too many bad things can happen?
- Not likely to be good Rx for adults?

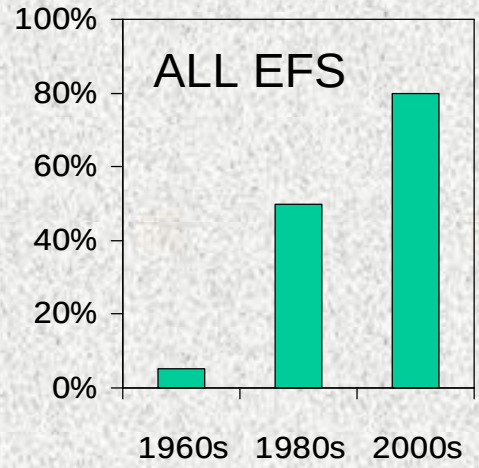
Treatment of childhood ALL
40 years of empirical progress



Pui and Evans, *NEJM* 2006

A.L.L. Chemotherapy

Antileukemic agent	FDA Approval
Mercaptopurine	1953
Methotrexate	1953
Prednisone	1955
Dexamethasone	1958
Cyclophosphamide	1959
Vincristine	1964
Cytarabine	1969
Asparaginase	1978
Daunomycin	1979
Etoposide	1983



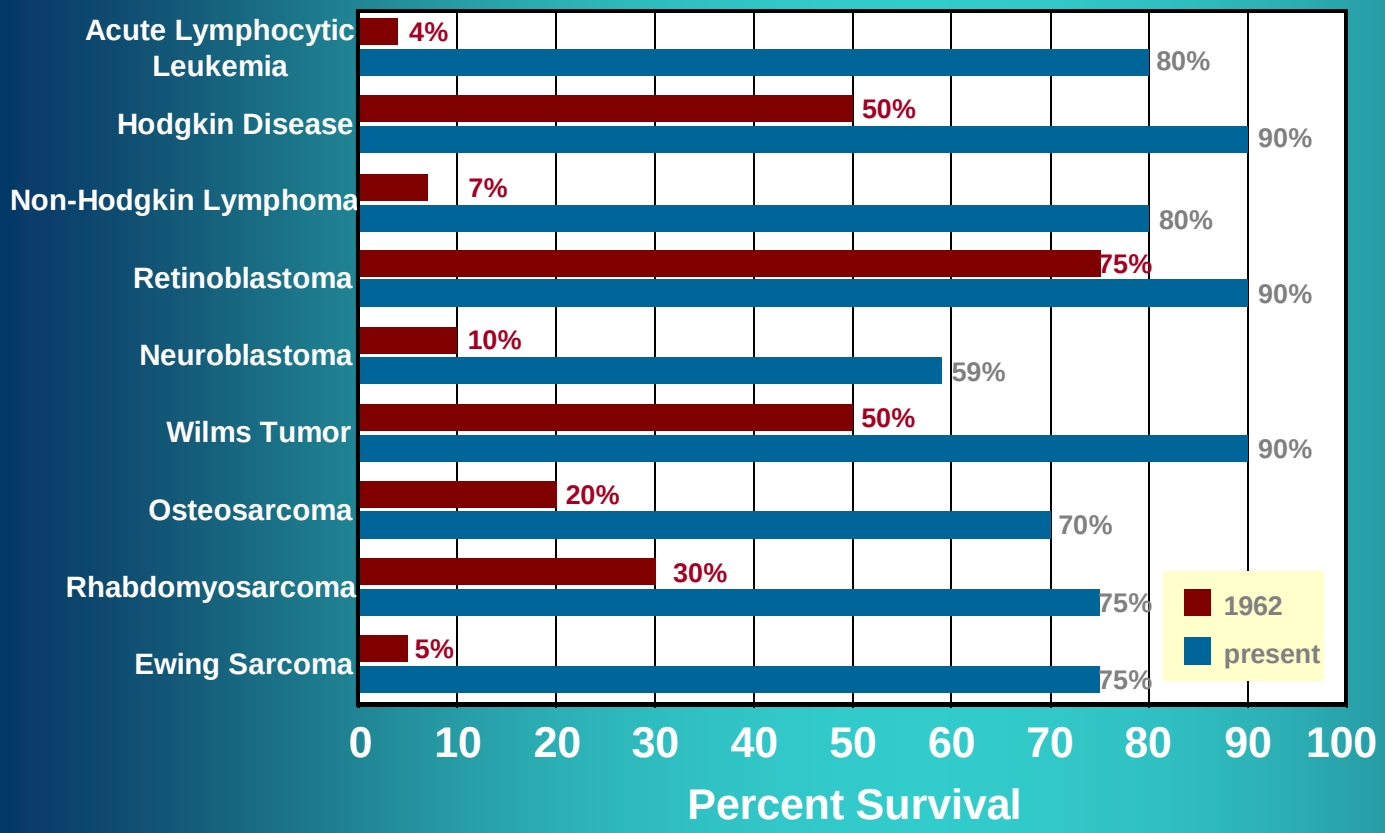
← ~ 20 years ago

During last 20 years, EFS of childhood ALL has improved from ~ 50% to ~ 80% by using old drugs better.....

despite no new anticancer agents developed for children

Childhood Cancer Survival Rates

1962 vs. 2002



The problems

- Cure rates could be better for all pediatric cancers
- Cure rates still very low for some pediatric cancers
- Treatment is toxic (acute & late ADEs)
- Therapy is not capitalizing fully on today's science

What is required to develop new drugs just for kids?

- Basic Science (target I.D. & validation)
- Drug Discovery (screening libraries, lead op)
- Drug Development (formulation, clinical trials)
- Production and Supply

The "Gaps"

" r " marks the problem

- ü Basic Science (target I.D. & validation)
- r Drug Discovery (screening libraries, lead optimization)
- ü Drug Development (clinical trials)
- r Production and supply (not trivial)

WE NEED:

Motivation (systemic), Organization, Resources (>$)

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Making Better Drugs for Children with Cancer

April 18, 2005

Rec #1: *A new public-private partnership involving government, industry, academic and other research institutions….should be formed to lead pediatric cancer drug discovery and development."*

THE NATIONAL ACADEMIES PRESS

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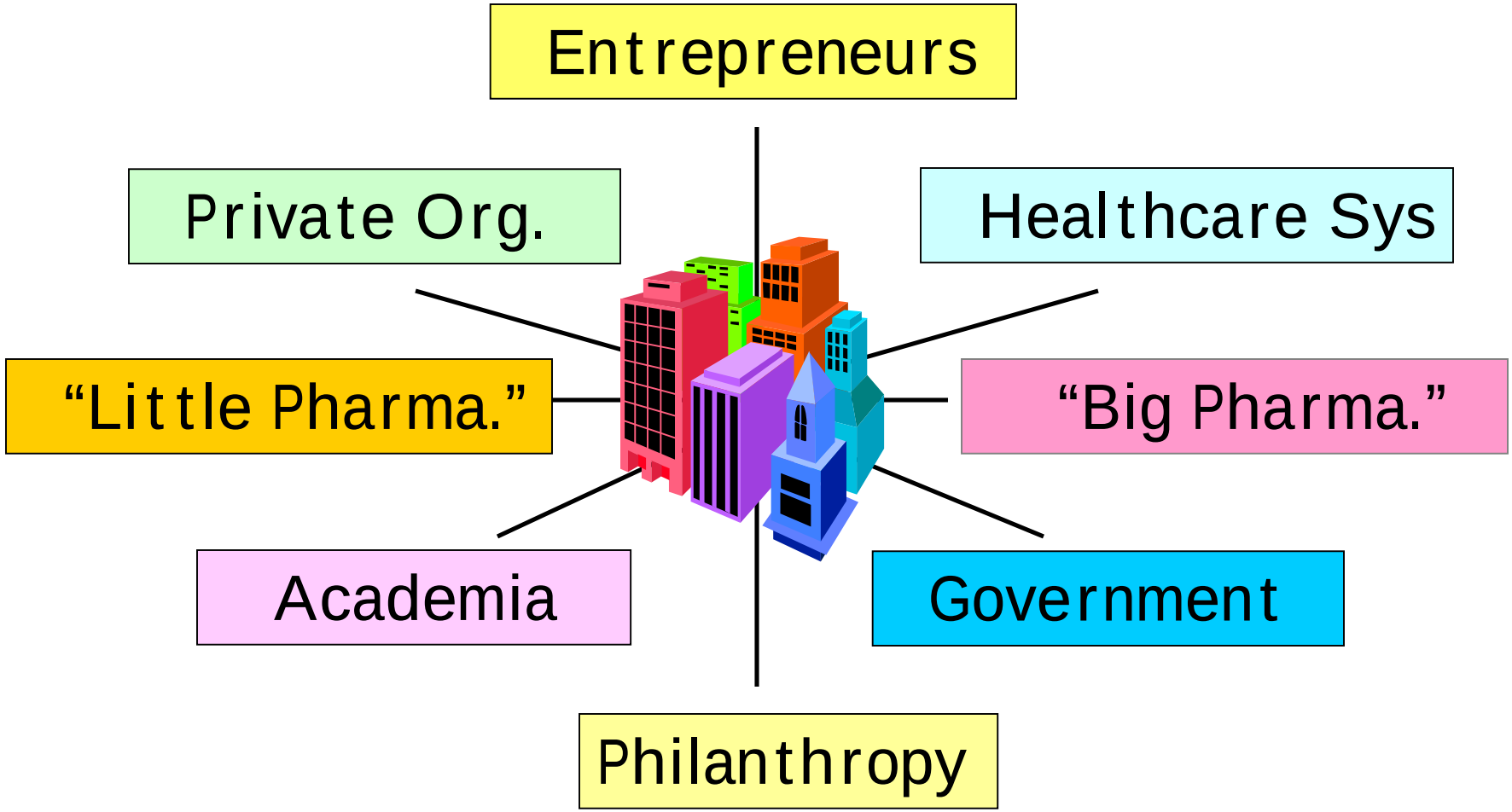
Advisers to the Nation on Science, Engineering, and Medicine

Can we launch a successful public-private effort?




St. Jude Children's Research Hospital
2006
3400 people, 2.2 million gsf, $410MM oper. budget

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SJCRH Initiatives for childhood cancer drug discovery and development

---------- **1962**

- **Basic Science (e.g., cancer biology)**
- **Translational Research (eg, pharmacogenomics)**
- **Clinical Trials (SJ and consortia)**

---------- **2003**

- **GMP Facility (65k sf)**
- **NCI Ped. Cancer Drug Discovery Consortium (P Houghton, PI)**
- **Chemical Biology and Therapeutics (*new*)**

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GMP Facility (2003)

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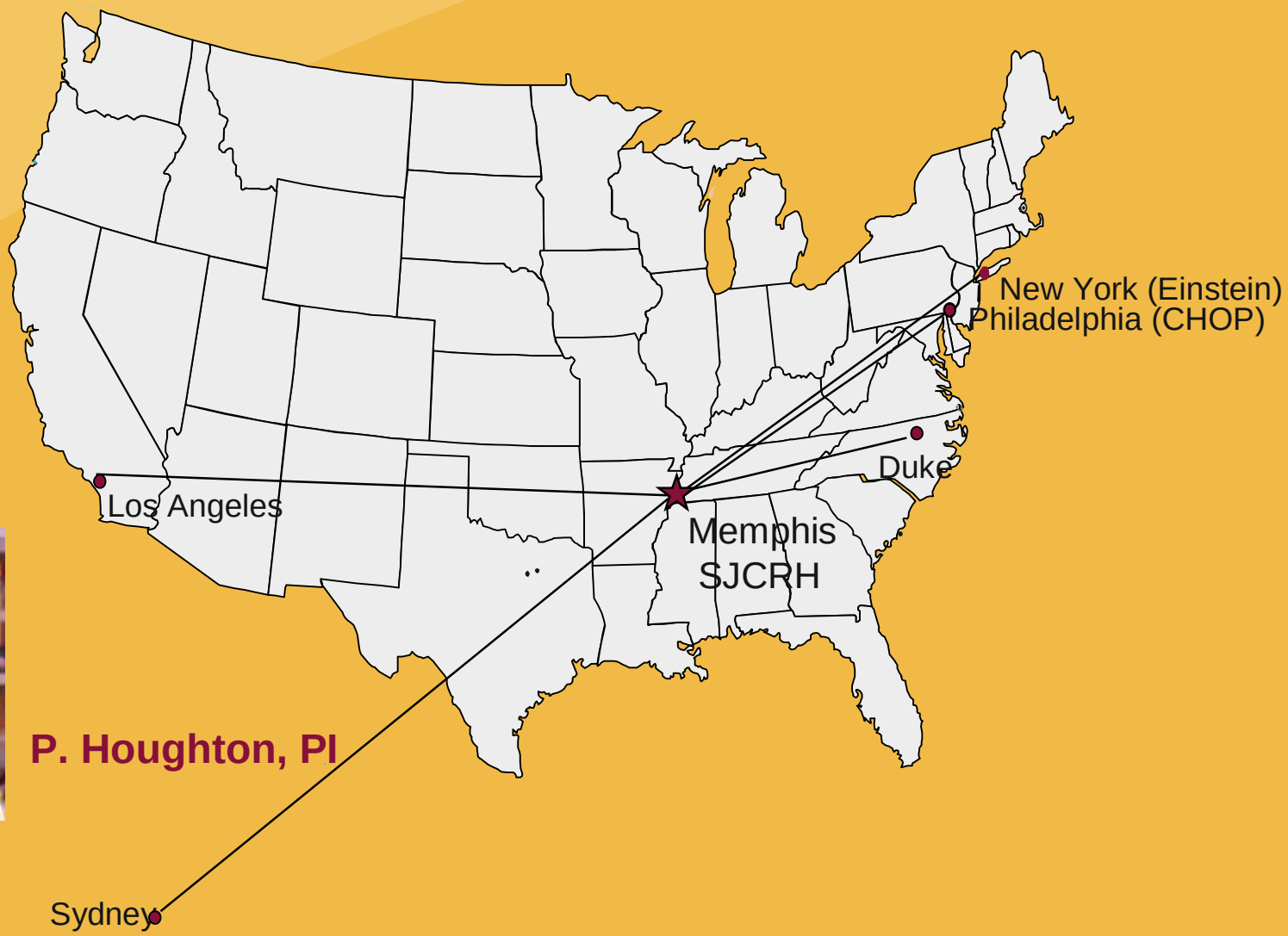
NCI Pediatric Cancer Drug Discovery Consortium

P. Houghton, PI



P. Houghton, PI

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SJCRH Initiatives for cancer drug discovery

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R. Kip Guy, Ph.D.

Chair Chemical Biology and Therapeutics

(Formerly Professor at UCSF)

PhD: Scripps with KC Nicolaou (taxol synthesis)

Post-doc: UT-SW, Brown and Goldstein


Chemical Biology & Therapeutics
9th Floor IRC Building

St. Jude Children's Research Hospital
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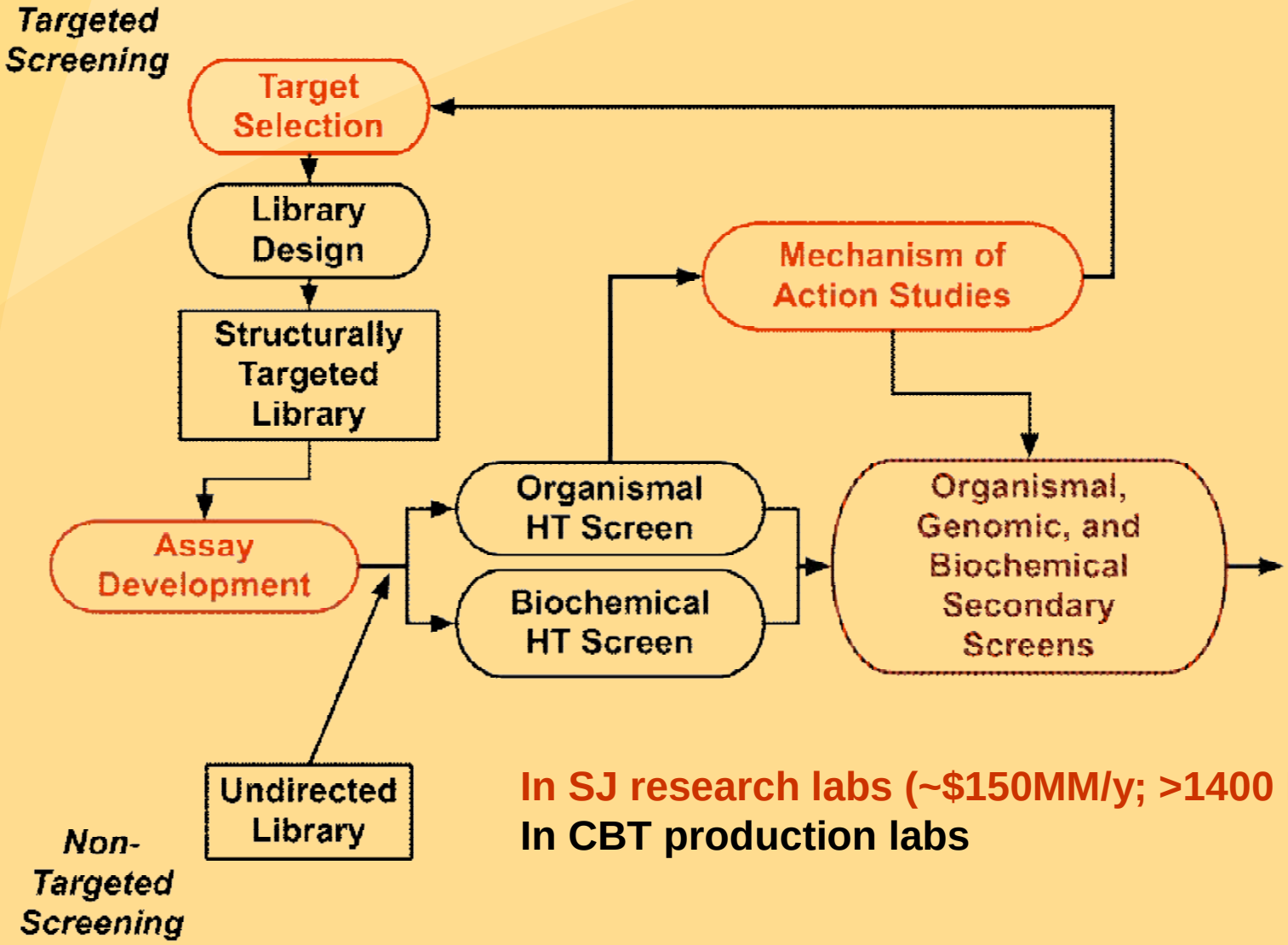
Screening Process at SJCRH



In SJ research labs (~$150MM/y; >1400 FTEs)

In CBT production labs

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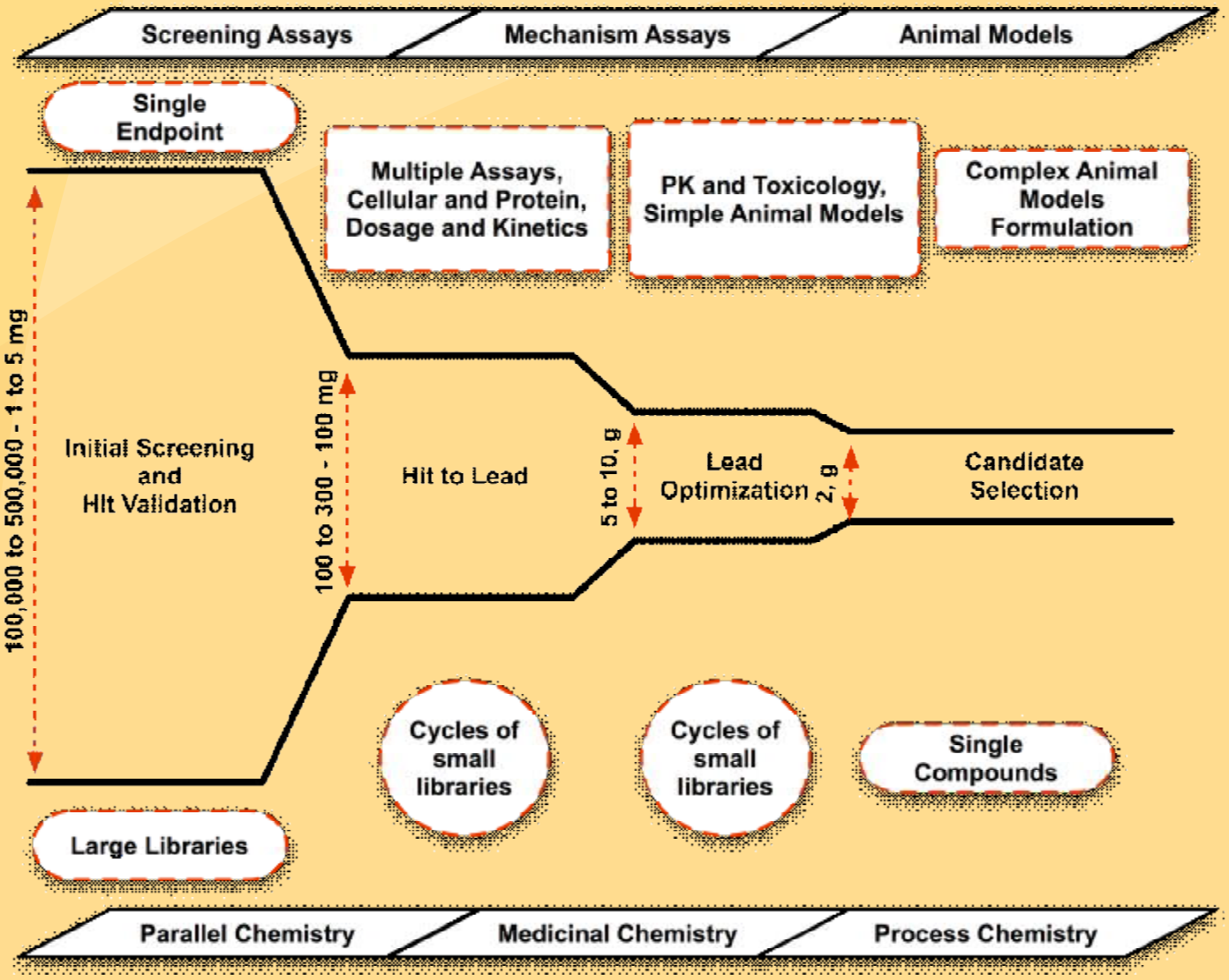
Candidate Progression Operations



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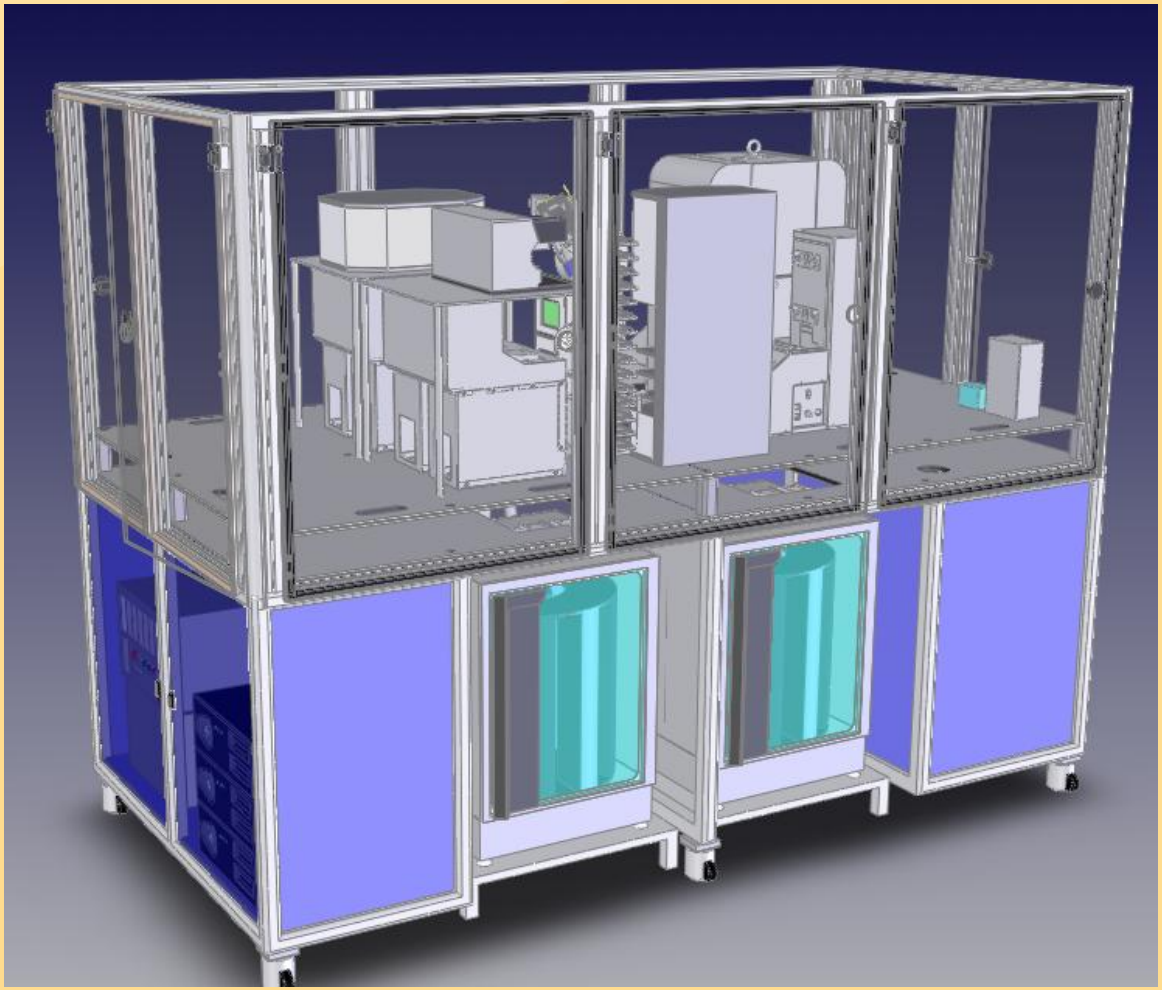
Compound Replating System



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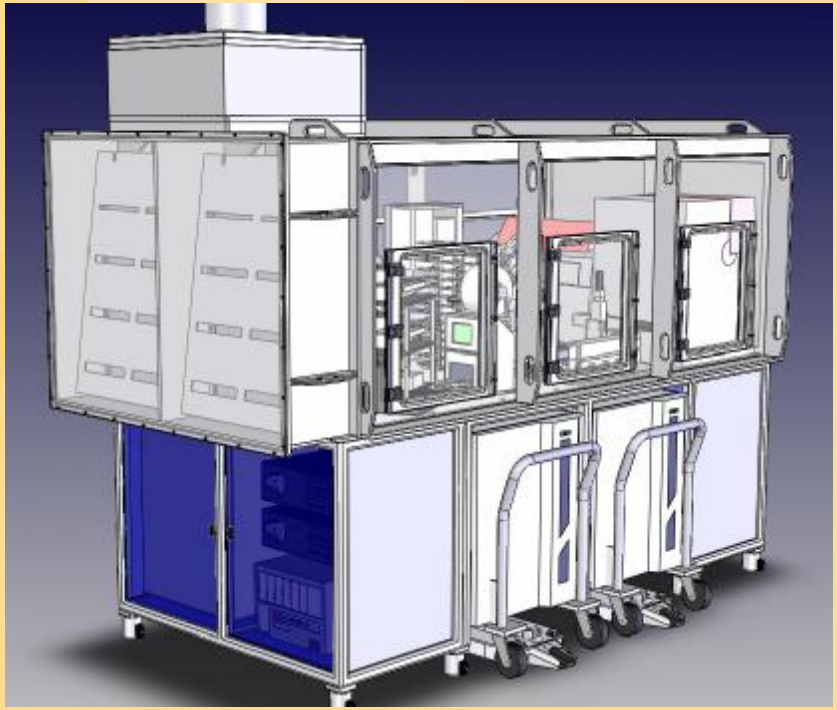
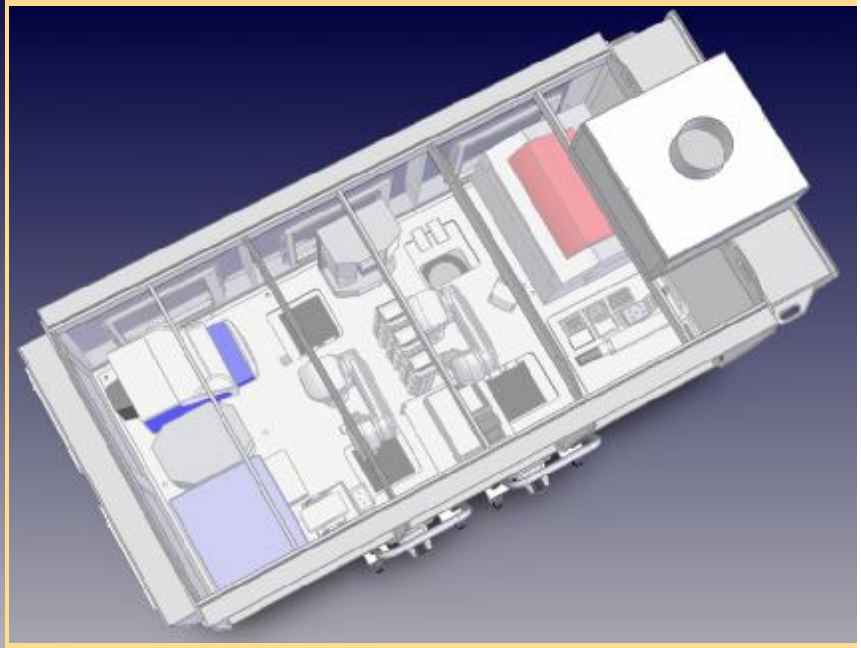
BSL2+ Compliant Cell Based HTS





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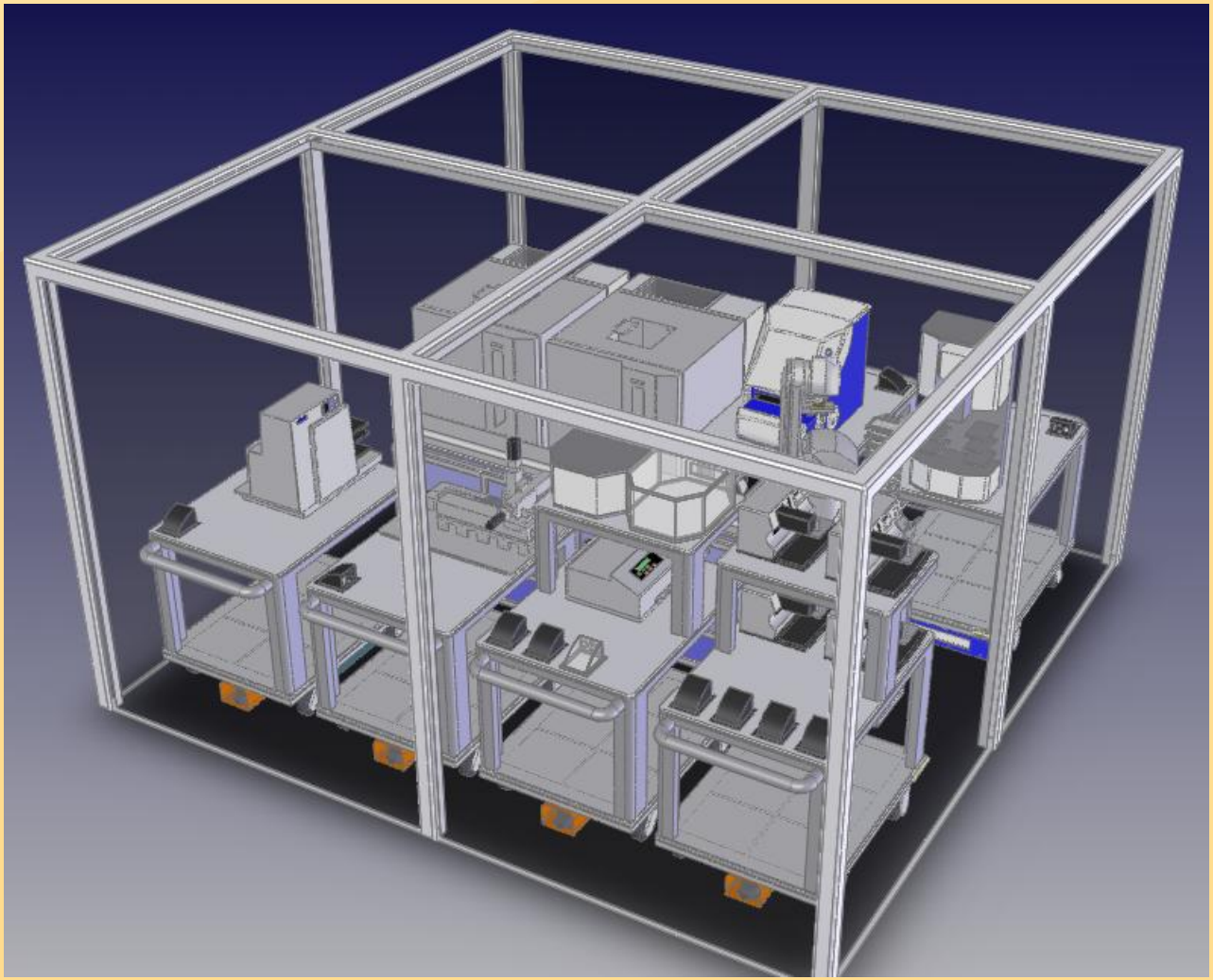
Enzymatic Screening System



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aving children. ST. JUDE CHILDREN'S RESEARCH HOSP

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Curation of Libraries

- **REMP minitube system: working copies in single use aliquots (384 tubes) or high density plates (1536 for pin transfers)**
- **~ 2.0 MM compounds**
- **Store at 10% RH, -20 C**

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SJCRH Chemical Library Storage and Retrieval Facility

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REMP Storage Facility

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Goals for Chemical Biology & Therapeutics @ SJCRH

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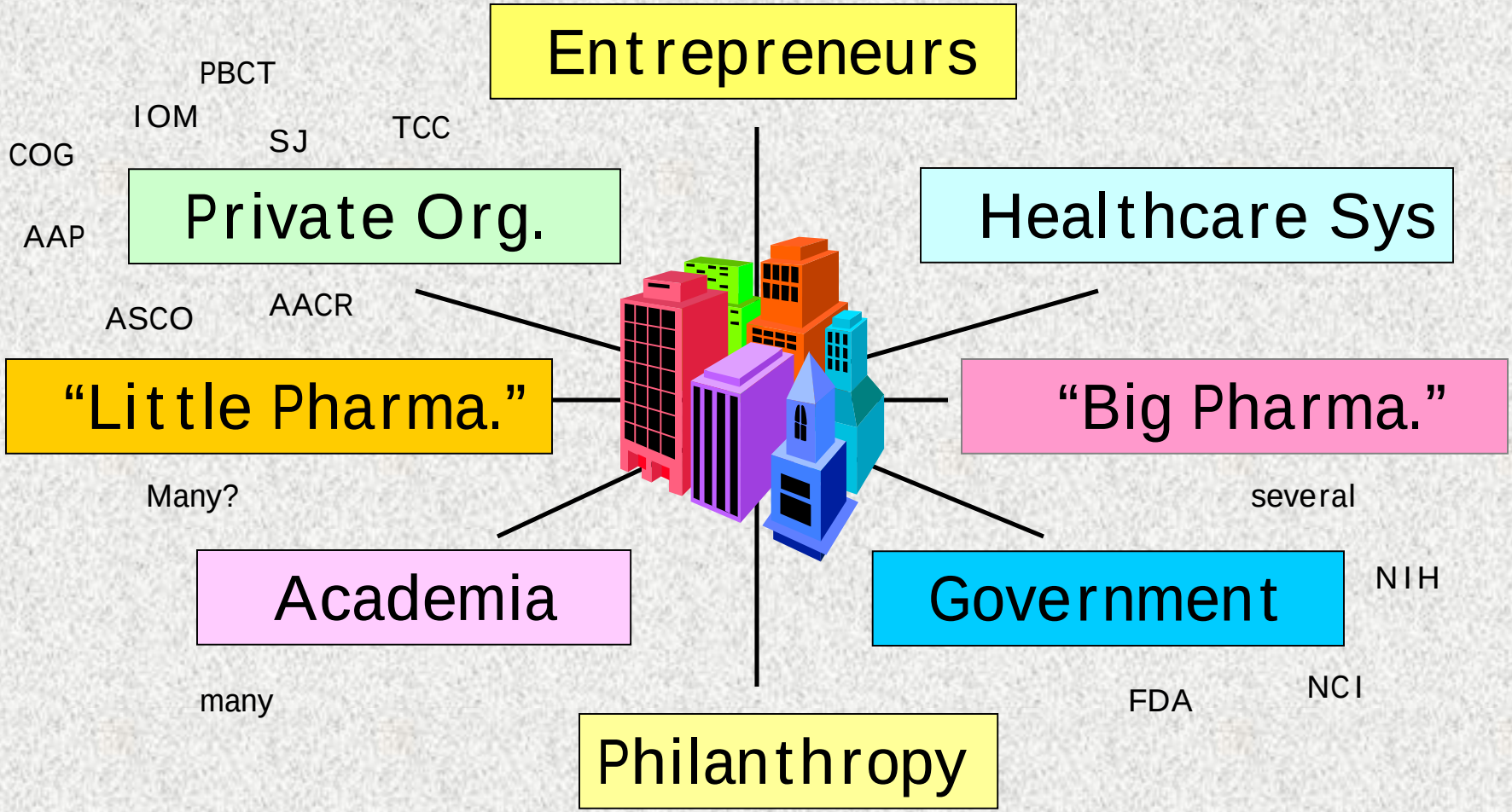
Using molecular targets identified in pediatric cancers (@ SJ or elsewhere):

1. Identify small molecules as tools for laboratory experiments (chemical KOs)

2. Identify candidate small molecules for preclinical testing vs pediatric cancers

3. Network with others to enhance capacity (e.g., VU) and advance to clinic

Who are the players?
Is it feasible?



The Risk!!

"There will be no pediatric 'Gleevecs' unless steps are taken to make them happen."

National Cancer Policy Board
IOM 2002

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Basic science is doing its job for pediatric cancers

- We know the molecular abnormalities for many pediatric cancers
- Many represent valid (putative) targets

Drug development is *lagging*

- Companies are not screening their chemical libraries against pediatric targets (no motive)
- Academic efforts are modest & often naive (not high throughput, small libraries, inexperienced at lead optimization, not able to move forward efficiently...)

Clinical trial machinery for childhood cancer is ready & well-oiled!!

- ü Track record of Phase I-II trials is strong
- ü Clinical trials the norm in pediatric cancer
- ü Translational research is strong
- ü Interest is high
- ü Need is great (improve cures, reduce toxicity)

This is not the problem!

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Examples of molecular abnormalities that are *common* in pediatric cancers but not in adult cancers

Disease	Molecular abnl.	# cases/yr
• Alveolar Rhabdo	*PAX3-FKHR*	<200
• Ewing's Sarcoma	EWS-FLI1 (etc)	<400
• Meduloblastoma	*PTC* abnl	<500
• ALL	TEL/AML1	<500

All pediatric cancers in US = ~9000