



Pharmaceutical Discovery and Development

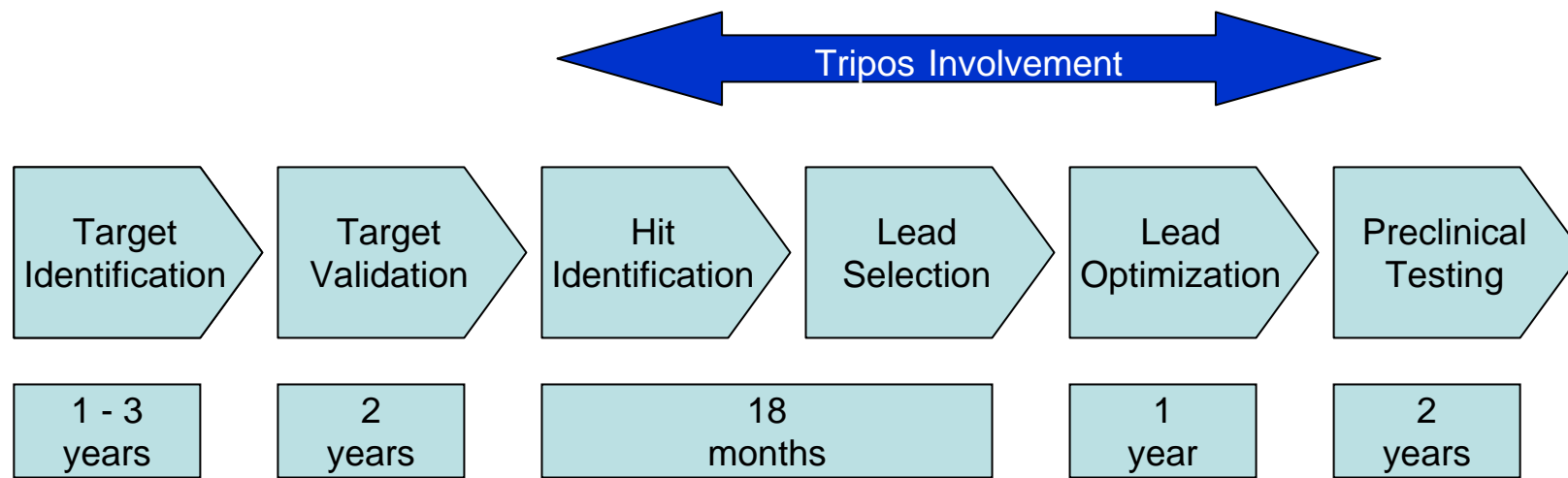
Medical Biotechnology for Non-Scientists

20 January 2006

Presentation Outline

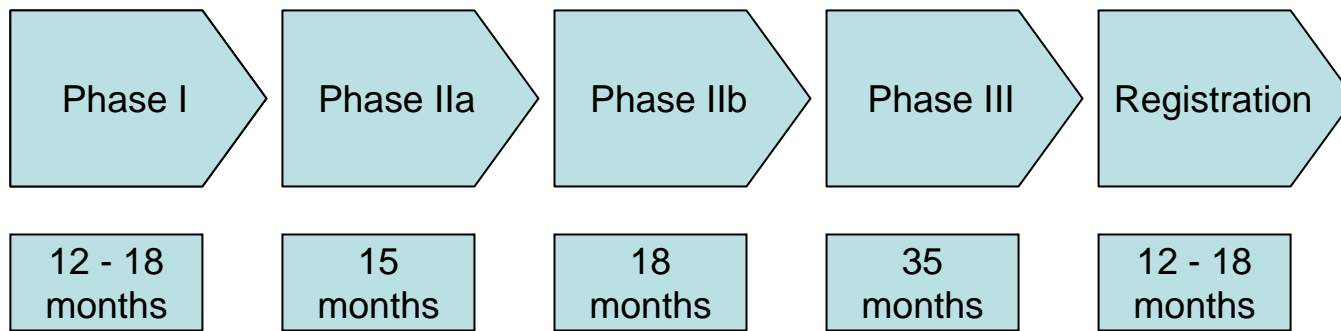
- Traditional Drug Discovery and Development Model
 - Components of Discovery and Development Programs
- Pharmaceutical Industry - On the Cusp of Change
 - Factors of Change
 - Economic Drivers
- Developing a New Paradigm for Drug Discovery and Development
 - Evolution of new technologies into industrial applications

Traditional Drug Discovery Time Lines



- This traditional process works and has been highly optimized
- It is the early research phase of drug discovery
- It does not involve humans and is not highly regulated by the FDA
- Total cost (averaged over industry) per drug: \$335 M

Traditional Drug Development Time Lines



- The development process involves humans and is highly FDA Regulated
- Total cost (averaged over industry) per drug: \$467 M
- Total cost of discovery and development: \$800 M
 - Note that this amortizes all the costs including the pipeline attrition during the process - discussed on the following slides

Characteristics of Discovery

- Target Identification and Validation
 - Traditionally the province of academic scientists
 - Has suffered from traditional funding models
 - Has produced too many “me too” targets
 - It is difficult to closely link new targets to the disease process by traditional methods
- Hit Identification and Lead Selection
 - Traditionally hits were found in natural products (extracts from plants, fungi, ...)
 - Difficult to work with complex natural products to produce drugs, establish Intellectual property
 - This area has been the focus of much technology development during the 1990's
 - Combinatorial and high throughput chemistry
 - High throughput screening

Characteristics of Discovery

- Lead Optimization

- Traditional medicinal chemistry was used to optimize efficacy against the target - typically in an “in vitro” assay
 - Assays in this environment are highly controlled and efficient

- Preclinical Testing

- The purpose of preclinical testing is to establish the “in vivo” characteristics of the newly discovered putative drug
 - Testing in cells and in animals
 - Establish Pharmacokinetics, Toxicity (ADME/Tox)
 - Is the compound toxic?
 - Is the compound absorbed? Does it cross the blood/brain barrier?
 - Is it immediately cleared (excreted)?
 - Is the compound metabolized too quickly? Too slowly? Are the metabolites harmful? Useful?

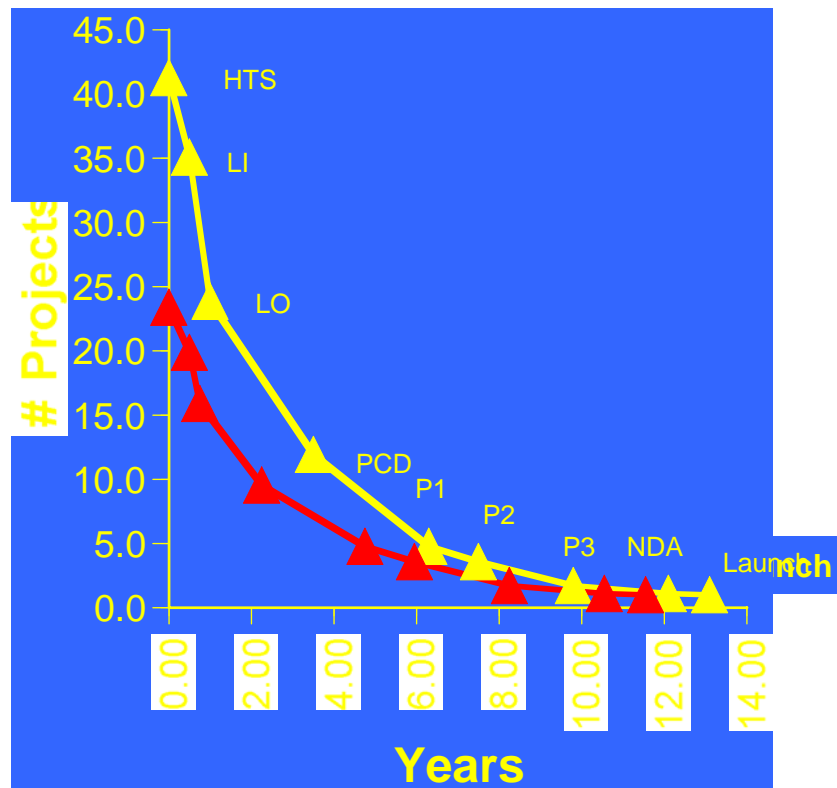
Characteristics of Development

- Phase I
 - Establish gross safety in healthy humans
 - Establish tolerated dosages in healthy humans
- Phase II
 - Establish effectiveness and side effect profiles in small groups of symptomatic humans over a period of time
 - Blind test versus placebo
- Phase III
 - Large population trials for tolerability, efficacy, side effects
- Registration
 - FDA Review and approval
- Phase IV
 - Market surveillance

Pharmaceutical Drug Discovery and Development Cycles

- Typical large pharmaceutical company has many (10's) of therapeutic programs in progress
- Within a therapeutic program, there may be several different therapeutic targets
- For each therapeutic target, the hit identification and lead identification process may require screening 100,000's to 1,000,000's of compounds
- Lead optimization targets production of up to 4 optimized compounds to enter preclinical testing
- Typically one compound and a backup will come out of preclinical and enter the clinical development process

Attrition Rates During Pharmaceutical Development



- Tremendous cost for new drug development is in the attrition from each program
- Looked at another way, 45 programs must be initiated for every drug launch

Improvements in Attrition Rates are Possible

	Industry Standard		With KnowledgeBase	
	Time (yrs)	% Success	Time (yrs)	% Success
LI	0.5	68%	0.25	80%
LO	2.5	50%	1.5	60%
PCD	2.8	40%	2.5	50%

- Further improvements possible if biology is not rate-limiting
- Assume no change in cost change for each phase
- Based on Pfizer File Enrichment project, and experience in multiple LI/LO collaborations

Value Creation by Improving Attrition Rates

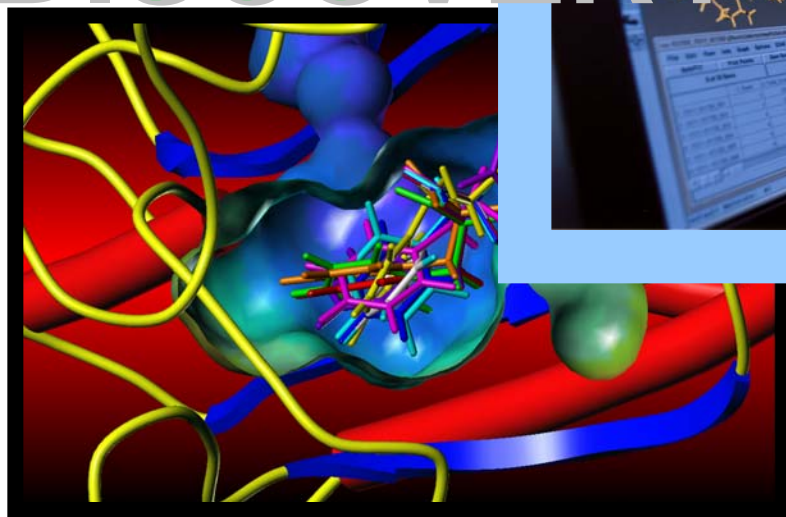
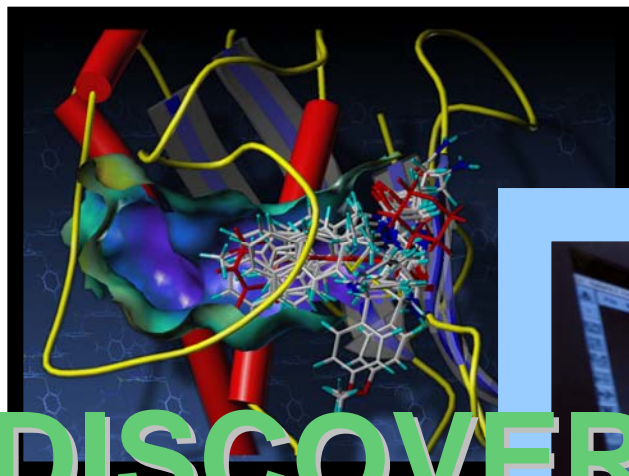
Drugs to market	1	1	2	2	3	3
Total drug revenue	\$2B	\$500M	\$4B	\$1B	\$6B	\$1.5B
# HTS	41	41	83	83	124	124
# HTS w/KB	23	23	47	47	70	70
NPV of portfolio	\$1.2B	\$14M	\$2.3B	\$35M	\$3.8B	\$57M
NPV w/KB	\$1.5B	\$162M	\$3.1B	\$334M	\$5.0B	\$506M
Δ NPV (value added by KB/year)	\$368M	\$148M	\$738M	\$299M	\$1.2B	\$449M

Biotechnology Company Development Profile

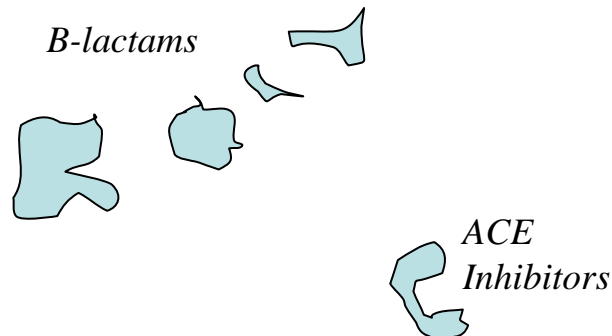
- Unlike pharmaceutical companies, biotechnology companies typically have a single therapeutic program
- Typically there is a single target
- A biotechnology company may screen 1,000's to 10,000's of compounds
- The profile of compounds coming out of the preclinical programs are generally held to the same criteria (4)
- The profile of compounds going into clinical typically is the same: a compound plus a backup

- Consequently, the risk profile of a biotechnology company is substantially greater than that of a pharmaceutical company

DISCOVERY INFORMATICS

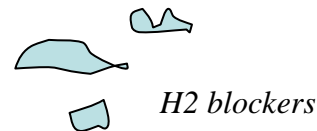
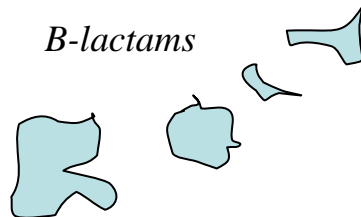


Seeking “Islands of Activity” in Chemistry Space

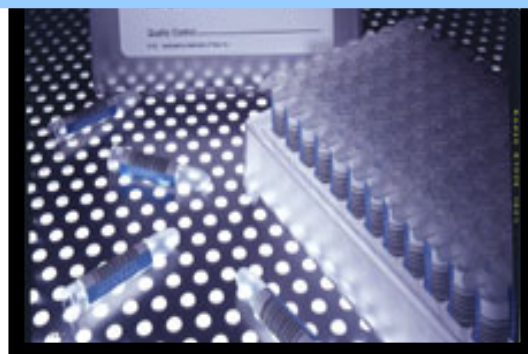


- “**Hit Identification**” = find land
- “**Lead Set Selection**” (“Lead Explosion”) = define / claim island
- “**Lead Hopping**” = find another island
- “**Lead Optimization**” = find high enough peak

Why is “Chemistry Space” Exploration so Hard?



- Instead of the two latitude / longitude dimensions of geographical exploration, with deterministic and continuous effects on altitude
 - Exponentially enormous number of ways to describe “chemistry space”.
 - Discontinuous dependence of biology on most chemistry descriptors
 - Structure / Activity relationships are probabilistic, not deterministic
- Molecular shape provides the best continuity (“neighborhood behavior”) for drug discovery



Pharmaceutical Industry at the Cusp

- The pharmaceutical industry is facing dramatic changes
 - Increasing competitive pressure for small number of well-validated targets
 - Increasing pressure from governments on pricing
 - Patent expirations
 - Dramatic increases in research expenditures have not resulted in increase in new drugs - in fact just the opposite
 - In 1996, \$18B in R&D by industry produced more than 50 new drug approvals
 - In 2003, \$34B in R&D by industry produced only 20 new drug approvals
 - In the intervening years, spending was exponentially increasing and new drug approvals were steadily declining
 - Image of pharmaceutical companies is severely damaged making the public unsympathetic to pricing / value arguments

Pharmaceutical Industry (my opinion)

- Pharmaceutical industry has created tremendous problems for itself with aggressive marketing
- By and large, the recalls, the side effects have been a result of the broad-based use of very powerful medicines where all side-effects cannot possibly be seen in a small sample
- The general health and wellbeing of the developed world has been made tremendously better by pharmaceutical and medical advances
- It is our obligation to in this industry to translate these benefits to the rest of the world
- We must find better ways to identify problems early in the development of medicines

Transitions That Must Occur

- To enable a more efficient and effective pharmaceutical industry
 - The FDA has to be reformed and focused on the approval of effective medicines
 - The regulatory environment throughout the world must be standardized
 - A new development paradigm must be implemented that more closely links disease and therapeutic target
 - Pharmacogenomic (translational medicine) approaches are essential
 - This transition has started (Herceptin, Gleevec)

A New Discovery and Development Paradigm is Required

- Focus on “Translational Medicine”
 - Use methods of genomics, proteomics, “tissomics” to understand the disease model, select target, develop biomarkers
 - Develop disease models in xenograft animals
 - Use traditional hit, lead identification in assays monitored by biomarkers
 - Use biomarkers to select patient populations for clinical trials
 - Use biomarkers to monitor progress of therapy in patients
 - Ultimately use biomarkers to select patients who will respond to particular treatments
 - This package will be known as a “Targeted Treatment Solution”

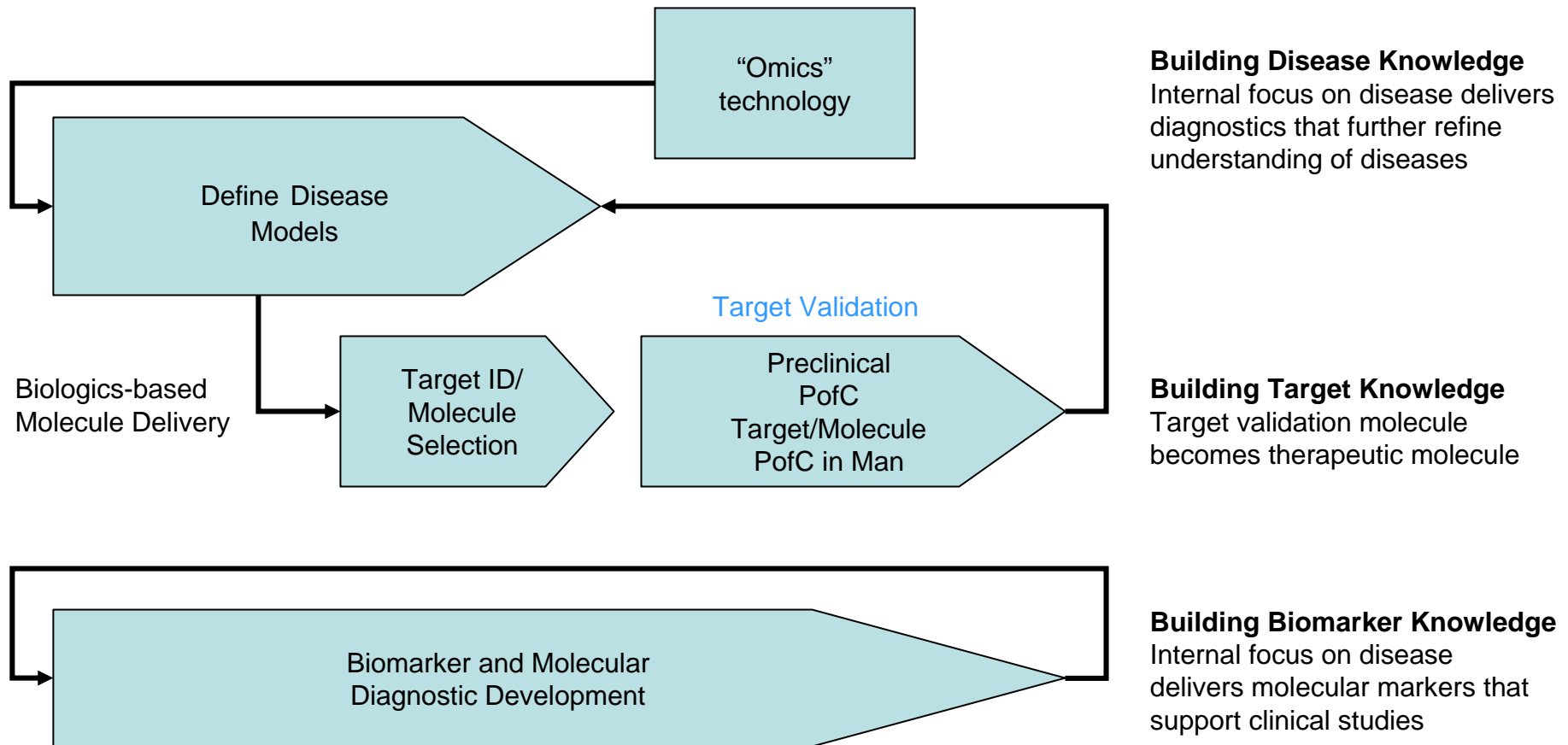
Our Focus in this Area

- Collaboration with a company spun out of a pathology department of a medical university in Graz, Austria
- Assets of the company include a well-documented tissue library or more than 2 million samples
 - Well documented due to medical systems in Austria
 - Multiple samples during lifetime of patients
 - Multiple patients
 - Multiple diseases
- Examine multiple samples to determine up/down-regulation of proteome in disease state
- Raise antibodies to specific proteins of interest to examine causative relationship
- Use this and medical expertise to establish disease model
- Constitute disease model in xenograft animal

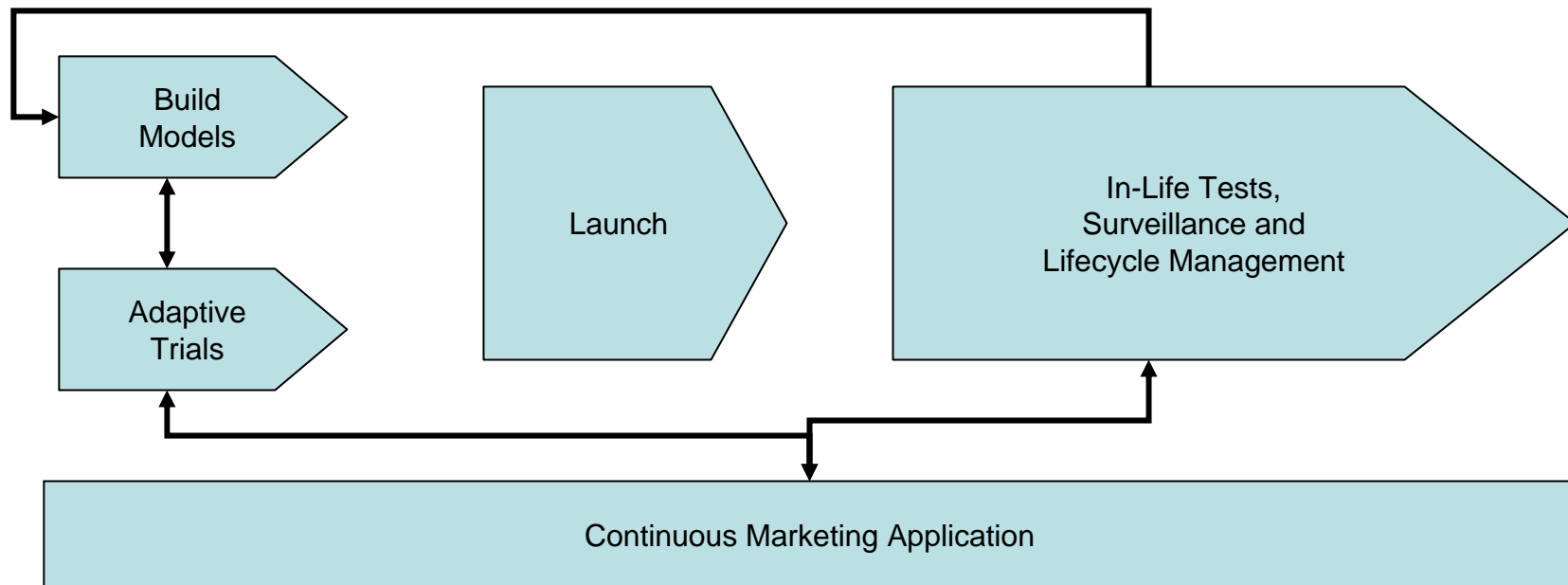
Mechanisms are Extensible

- Using this approach, generally it is possible to understand a family of diseases
- Rapid development of compounds “in vivo”
- Appropriate selection of patients who exhibit specific disease symptoms
- Can progress drugs much more rapidly

Discovery Process in the Future (Systems Biology)



Development Process in the Future



- Disease understanding underpins the entire process
- Develops a whole package: diagnostics, services, therapeutic
- Real outcomes data are collected in in-life tests
- Dynamic product profile as new data emerge
- Ongoing regulatory consultation and review throughout product life

Conclusions

- Pharmaceutical research is an exciting, highly rewarding activity with tremendous societal benefits
- Financing this activity is highly challenging
- The industry is undergoing broad, sweeping change now
- At this cusp there is opportunity for entrepreneurs and entrepreneurial scientists
- The future in this area will continue to evolve rapidly and provide unforeseen developments to apply to human health and wellness