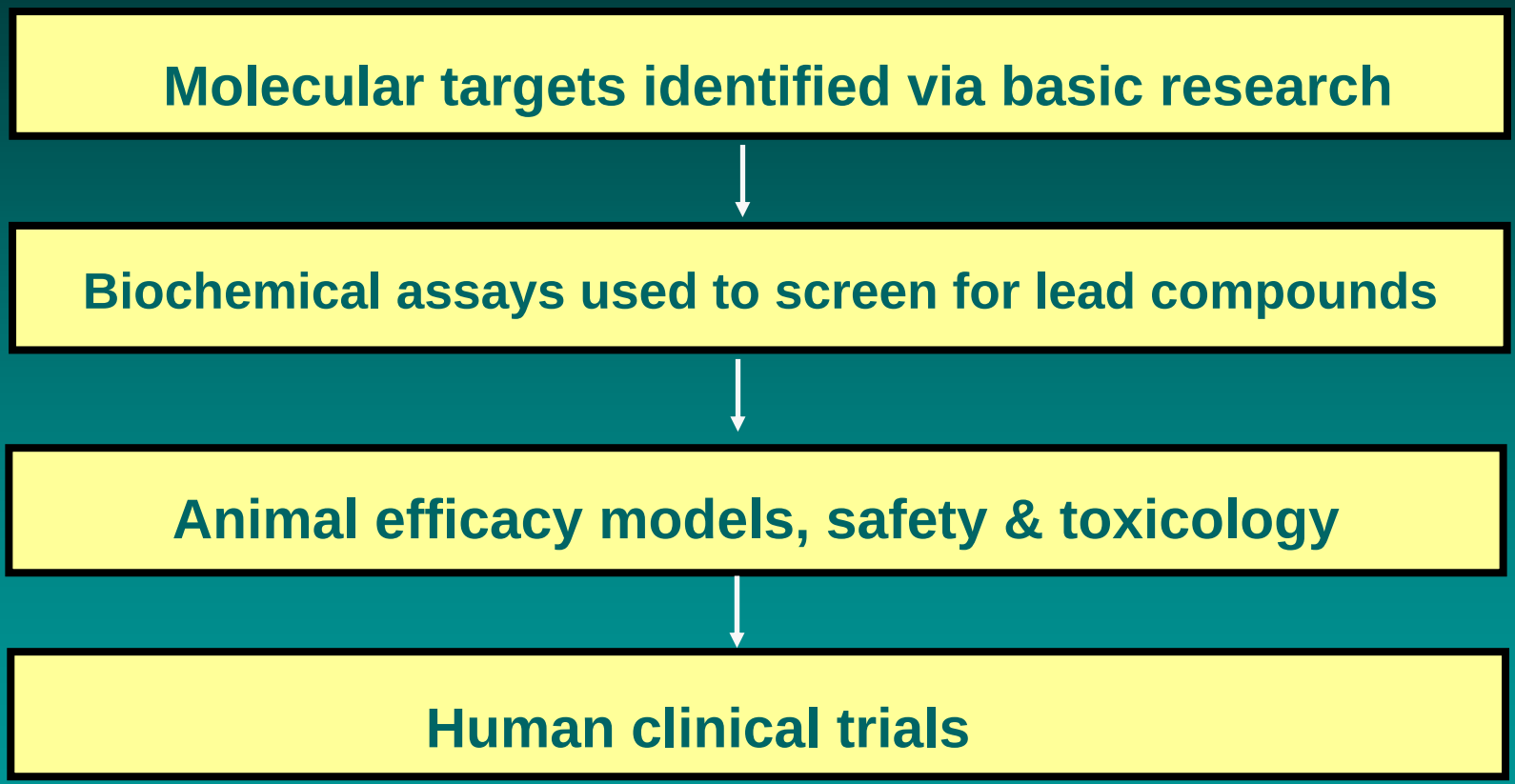
Pathways To Facilitate Basic Science To New Medicines

Edward M. Scolnick, M.D.

March 2006

Modern Paradigm of Drug Discovery



Example of Paradigm for Atherosclerosis
The Development of Statins

- ***1948*** - In Framingham, MA, a large study shows an association between cholesterol and coronary risk
- ***1958*** - HMG-CoA reductase shown to be the rate-limiting enzyme in cholesterol biosynthesis
- ***1973-1974*** – Discovery of role of LDL receptors in regulatory HMG CoA reductase activity and LDL levels in blood
- ***1978*** - An inhibitor of HMG-CoA reductase discovered
- ***1979 - 1980*** - Clinical trials begun
- ***1987*** - Cholesterol lowering demonstrated, 1st medicine approved
- ***1994*** - Long-term effectiveness studies show decreases in heart attacks and mortality

Fosamax for Osteoporosis

- Fosamax: Mode of Action
  and Pharmacokinetics
- Animal bone biology
- How to choose a dose
  - Clinical trial
    vs
  - Some biochemical assay

Gideon Rodan

Crixivan for HIV Infection

- What defines efficacy in:
  - Initial trials
  - Later trials

- Assays used
  - CD4 cell counts
  - Viral antigen
  - Viral RNA

Singulair for Asthma: An Example

- Singulair is a leukotriene receptor antagonist
- Initial clinical trial
  - Dose ranging debate
- Possible assays
  - Blood levels of drug
  - Leukotriene receptor blockade
  - Antigen challenge
  - Clinical asthma study

Importance of Knowing Mechanism of Action

- Guiding medicinal chemistry
- Potency, specificity, drug metabolism, toxicology, oral bioavailability

Importance of Pharmacodynamic Assay

- Role of preclinical animal assay
  - Biochemical
  - Biological
- Carry over to initial clinical trials
  - Biochemical assay
  - Clinical assay

Leukotriene Biosynthesis Inhibitor

- Animal Models of asthma
- Biochemistry of leukotrienes

Impact of Genetics on Biomedicine: Discovery of Drug Targets

- Statins and HMG Coa reductase
- Proscar and benign prostatic hyperplasia (5alpha reductase)
- Gleevec and CML (aberrant kinase)
- New approaches to Alzheimer's (secretases)
- Herceptin antibody to Her2 for breast cancer
- New target for age-related macular degeneration (complement pathway)
- Gain of function dominant enzyme
  - Parkinson's disease
  - Autoimmune disease

Recent Discoveries in Human Genetics and Implications for Treatment

- Age-related macular degeneration
  - Complement factor H
- TCF 7L2 transcription factor (type II diabetes)
- IRF-4 binding protein (autoimmunity)
- PCSK-9 serine kinase regulation LDL receptor levels
- LRRK-2 serine kinase in Parkinson's disease