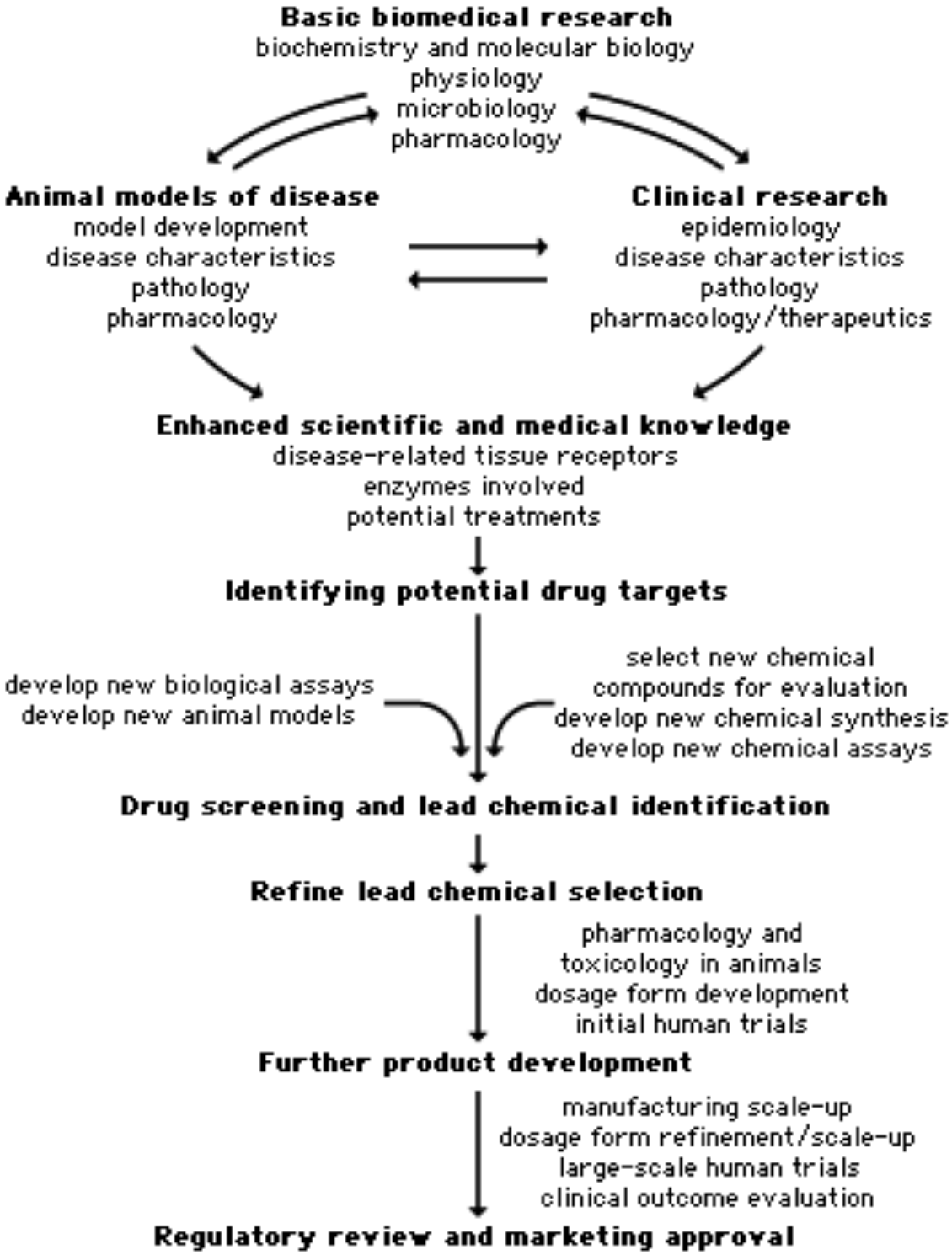
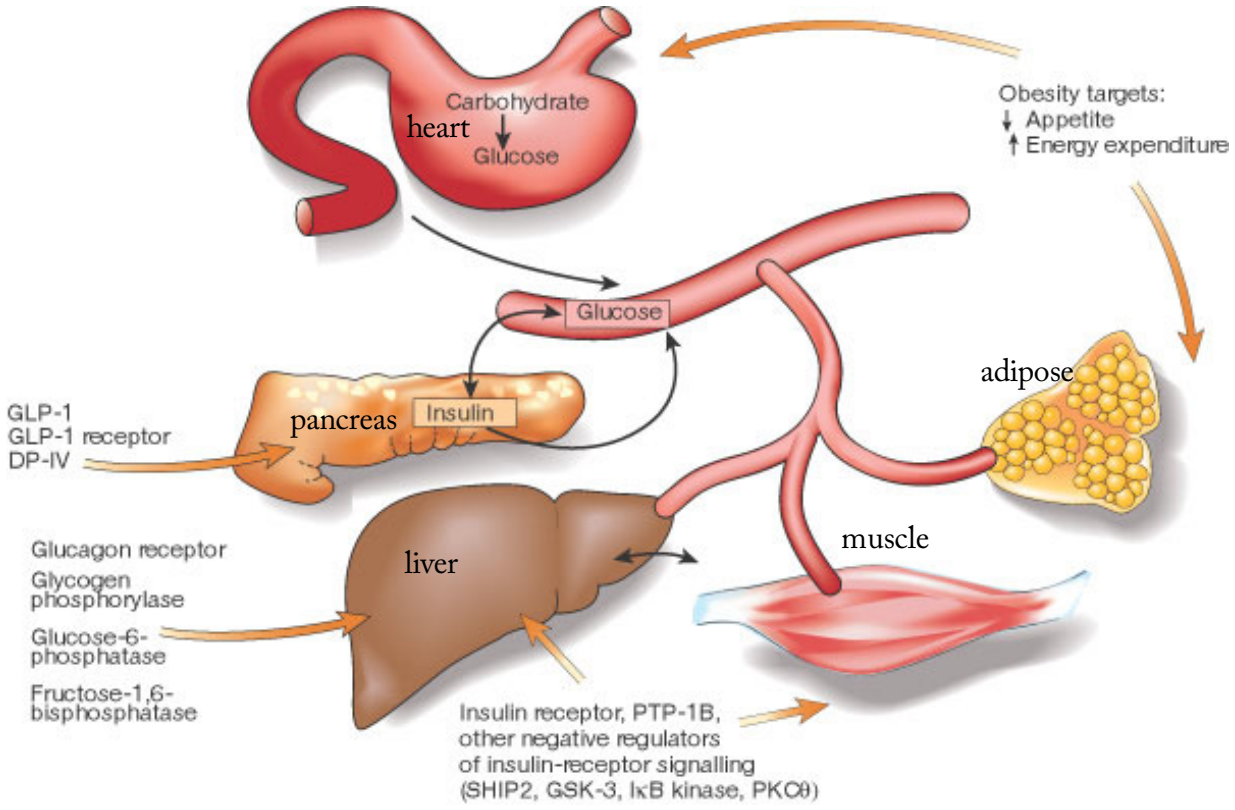


Notes for Systems Biomed- drug discovery



- Goals for basic research and translational research are different
    - Q for students: which approach is likely to be more successful for drug discovery?

- Drug companies are having trouble finding new drugs
    - 1996- 53 new drugs, 2007: 13 new drugs

- Symptoms:
    - hypoglycemia, diabetic ketoacidosis, cardiovascular disease, chronic renal failure, retinal damage (blindness), several types of nerve damage,
    - microvascular damage
        - poor wound healing (gangrene, amputation)
    - Major source (in the developed world:
        - adult blindness in the non-elderly
        - non-traumatic amputation in adults
        - diabetic nephropathy is the main source of renal dialysis

- Diabetes presents special challenges:
    - a truly whole animal, systems problem
    - 'hit' one point, the system either (i) re-calibrates or (ii) shows unexpected side effects
    - some advantage to this vs. cancer: looking for whole body therapy
    - big disadvantage: clinical trials are long and expensive

- Systems approach to diabetes
    - identifying gene in GWAS studies: our collaboration with Francis Collins
    - top ~20 linage loci < 10% of total risk
    - population is truly heterogeneous, with incidence rising rapidly
        - => large environmental component
        - note: not all obese people get T2DM

- Systems approach to cancer
    - in some ways a tougher problem- each tumor *may* be unique
    - example: breast cancer
    - four hit model: Ras-PTEN-P53-LKB1/LRP1 occurs 4 times in 138 samples
        - 3-hit model: 8 times in 138 samples
        - how do you address this

Steps in drug discovery:

- **Target discovery**

  Disease Mechanism

  Disease Genes

  Functional Genomics/Systems Biology

- Target Type and 'Drugability'
    - "drugability":
        - how well a drug/ab can access the target, or by the efficacy a therapeutic can actually achieve.
        - affected by: cellular location, development of resistance, transport mechanisms such as export pumps, side effects, toxicity, and others.
        - Lipinski 'Rule of 5': molecular weight less than 500, a partition coefficient log P less than 5 (similar to solubility), no more than 5 H-bond donors / 10 H-bond acceptors
        - Recent proposed criteria:

            (a) the protein is from a family that is related to a current known target

            (b) sequence variation between the drug-binding domain and that of other related family members of human proteins should exist

            (c) the protein has less than 6 similar proteins in the human family, minimizing off-target effects

            (d) the target protein is involved in only one or two cellular signaling pathways

            (e) the protein is preferentially expressed in tissues specific to the disease state.

        - example: GPCRs are common targets

- **Target validation:**
    - knockout the gene- what does it do?

- **Assay development- key for eventual success**
    - Relevance: Does the readout unequivocally relate to the target?
    - Reliability/Robustness: Are results reproducible and statistically significant?
    - Practicality: Do time, reagents, and effort correlate with quality and quantity of results?
    - Feasibility: Can assay be run with resources at hand?
    - Automation: In order to screen large numbers of compounds, can assay be automated and run in highly parallel format?
    - Cost: Does cost of the assay permit scale-up for high-throughput screening?

- **Screening, Hits-to-Leads: Compound libraries**
  - Total number of compounds that sit in definable 'chemical spaces: <500 MW= ~10^{60}
  - An important practical measure for the value of a random library is chemical diversity, which analyzes how similar one compound in the library is to one other.
  - Types of libraries
    - Natural products- more popular in academia
    - Random libraries that sample broad 'chemical space'.
    - Random libraries exploring a particular "chemical space."
    - Libraries of "privileged" compounds that emphasize 'druggability' and high probability of biological activity
    - Combinatorial libraries
  - Important to determine MOA (Mechanism of Action)
    - difficult, but getting easier

- **Lead optimization**
  - Medicinal Chemistry
    - blends synthetic chemistry, molecular modeling, computational biology, structural genomics, and pharmacology to discover and improve hits
    - Example, medicinal chemists improve drug efficacy, particularly with respect to stability and bioavailability, by developing mechanism-based pro-drugs. Pro-drugs are engineered in such a way that they undergo chemical transformation either in the bloodstream or specific tissues such as the liver. Upon transformation, biologically active metabolites are released, which are the actual drugs.
  - Animal PK/PD/ADME- important, expensive, time-consuming
    - Animal pharmacokinetics (PK), pharmacodynamics (PD), and absorption, distribution, metabolism, and excretion (ADME) assess the general pharmacology and mechanisms of action of drugs.
    - Partial list: bioavailability, target binding; stability and half-life; maximum serum concentration; total exposure; clearance (Cl); drug-drug interactions; onset of drug action; multicompartmental analysis of blood, liver, and other tissues.
    - The main objective is to understand the effects on the whole organism of exposure to a novel chemical entity, and to predict the new drug's behavior in humans.
    - this step is often forgotten by academics
    - Main models used are rodents (dogs, pigs, and, more rarely, monkeys), are also used under certain circumstances.
  - Toxicity and MTD (maximum tolerated dose)
  - Formulation and Delivery

- **Development**
    - investigational new drug (IND) application. 3 parts to application:
        - pharmacology: is it likely safe?
        - manufacturing info: can lots of high quality drug be made?
        - clinical protocols: is a reasonable dosing protocol established?

- **Clinical Trials**
    - Phase I:
        - small trial, closely monitored
        - determine optimal dose, drug metabolism/PK, is it hitting the target?
        - Phase Ib- "Safety and Dosage"
    - Phase II
        - typically 100-300 patients, Random Controlled Trial (RCT)
        - initial efficacy, toxicity studies
        - Phase IIb- broader look at efficacy and toxicity
    - Phase III
        - Much larger study, will determine whether drug is approved
            - Better than placebo or a standard therapy.
            - Double-blinded design
            - Randomized, adequate size

- **After hitting market**
    - Phase IV- more information as drug is more widely used
        - many drugs get pulled based on Phase IV: Vioxx, Fenfluramine (weight loss)