

IS5400 Medical Literacy: Introduction

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Goals of Presentation

- **Present a Systems Engineering Overview of the Human Organism:**
 - Biology
 - Physiology
 - Pathology
 - At the Individual and Population Levels
- **Review the Course Curriculum in Light of This Systems Engineering Paradigm**
- **Provide My Rationale as to the Importance of this Course and this Track More Generally**



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Google earth

The Human Organism in Health and Disease

- **Generally Organized into Organ Systems**
- **Subdivided into Organs or Equivalents**
- **Further Subdivided into Functional Units**
- **Functional Units Composed of Cells and Supporting Infrastructure**
- **Cells Include Subdivisions Such as Membranes, Intracellular Support Structures, and Organelles**
- **Organelles May Also Contain Functional Units**
- **Within and Surrounding the Cellular Components Are Molecules, Elements, and Ions**

Organ Systems Include

- **Neurological**
- **Cardiovascular (sometimes coupled with Pulmonary as Cardiopulmonary)**
- **Pulmonary or Respiratory**
- **Lymphatic (sometimes included within Cardiovascular)**
- **Gastrointestinal**
- **Genitourinary (sometimes separated into Urinary and Reproductive)**
- **Musculoskeletal**
- **Hematologic (often including the cellular component of Immunological)**
- **Endocrine**
- **Integumentary**
- **Etc. (Breast, Exocrine, Immunologic, Other)**

Examples of Organs Within Organ Systems

- **Neurological**
 - Brain
 - Spinal Cord
 - Ganglia
 - Peripheral Nerves (Sensory, Motor)
 - Autonomic Nervous System (Sympathetic, Parasympathetic)
 - “Connections” with Other Organ Systems (e.g., Muscles, Skin)
 - Etc.
- **Cardiovascular**
 - Heart
 - Systemic Arteries and Veins
 - Pulmonary Arteries and Veins
 - Splanchnic / Portal Circulation
 - Capillaries and Micro-circulation
 - Etc.

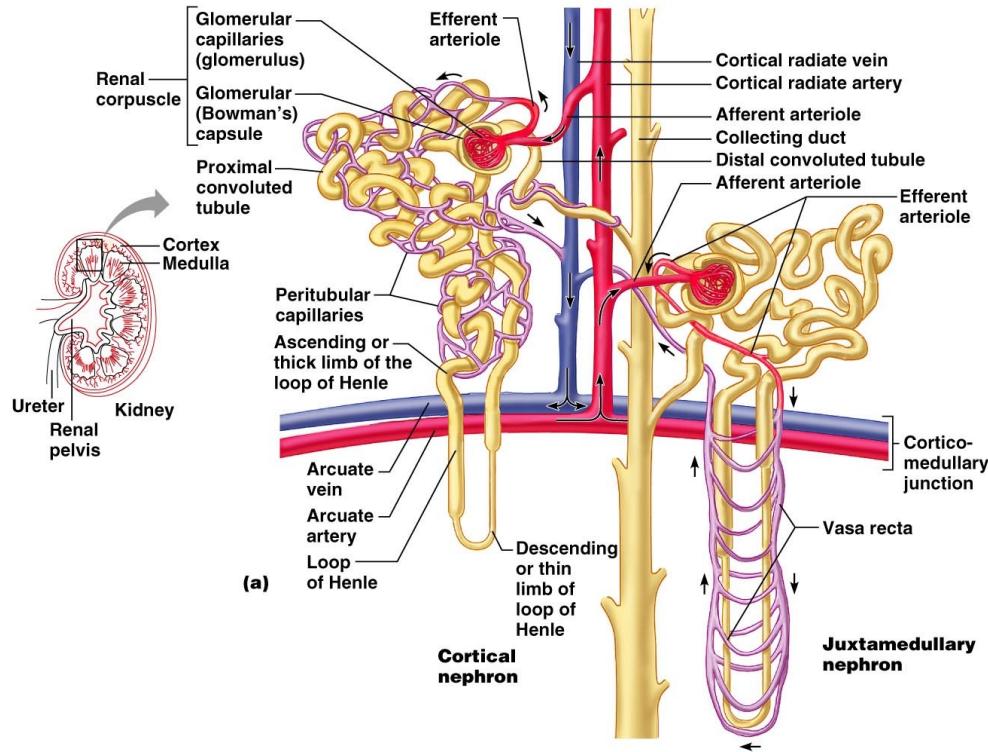
Examples of Organs Within Organ Systems

- **Gastrointestinal**
 - Oropharynx
 - Esophagus
 - Stomach
 - Small Intestines (Duodenum, Jejunum, Ilium)
 - Appendix
 - Large Intestine
 - Rectum and Anus
 - Liver, Gall Bladder, Pancreas
 - Mesentery
 - Etc.
- **There is Overlap Among Various Organ Systems**
 - Vessels Part of the CV System but also Within Individual Organ Systems
 - Pancreas has both GI and Endocrine Functions

Examples of Functional Units within Organs

- **Kidney (Renal) Functional Unit is the Nephron**

- Glomerulus
- Afferent and Efferent Arteriole
- Bowman's Capsule
- Proximal Convolved Tubule
- Cortical Collecting Duct
- Distal Convolved Tubule
- Loop of Henle
- Papillary Duct
- Peritubular Capillaries
- Arcuate Artery and Vein
- Juxtaglomerular Apparatus

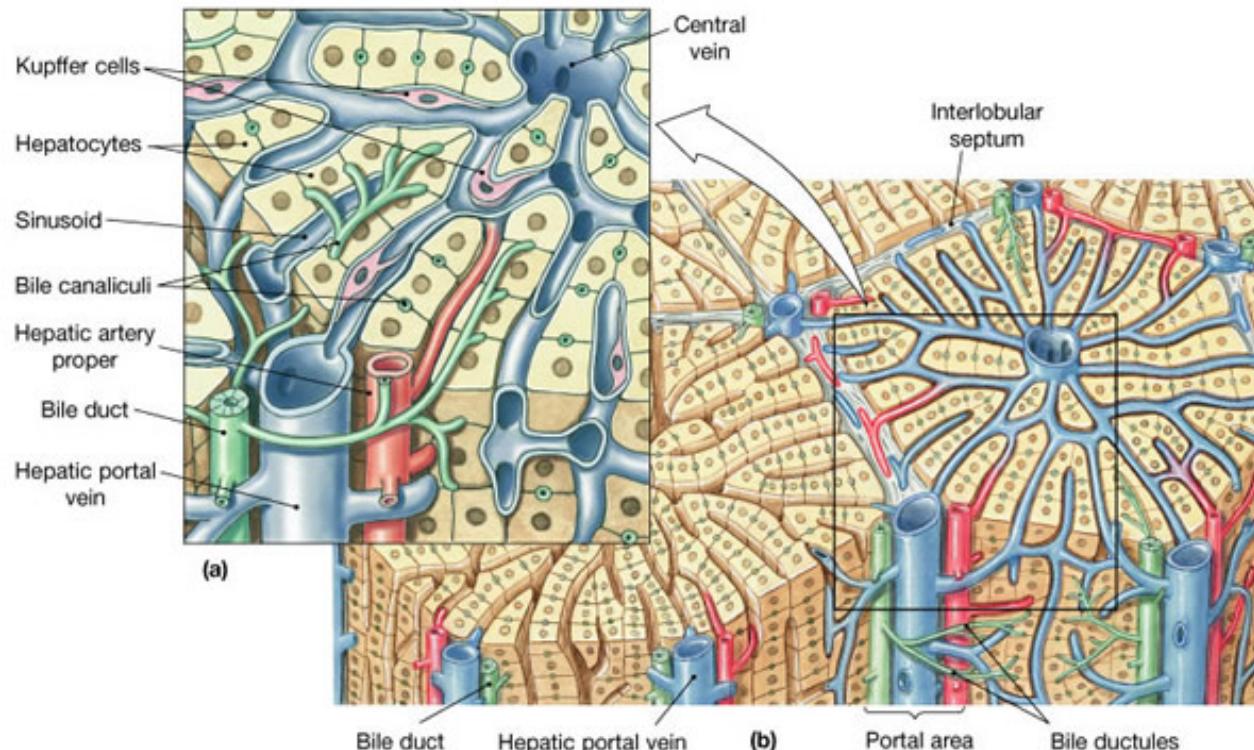


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Examples of Functional Units within Organs

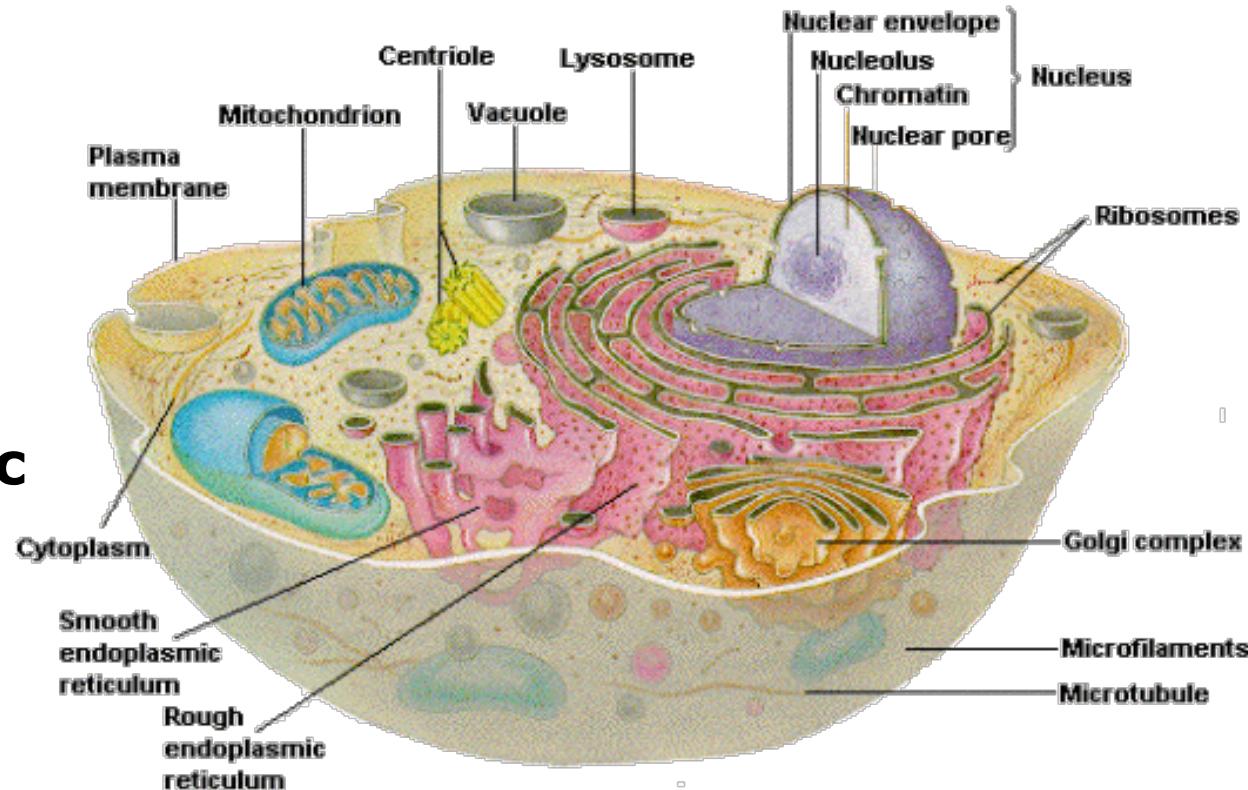
- **Liver (GI) Functional Unit is the Hepatic Lobule**
 - Central Vein (From the Interlobular Vein)
 - Plates of Hepatocytes
 - Kupffer Cells
 - Sinusoids
 - Portal Arterioles and Venules*
 - Bile Ducts
 - Surrounding Connective Tissue

*Arterioles from HA; Venules from PV



Eukaryotic Cells Within the Human Organism

- **About 100×10^{14} Cells in a Human**
- **Cells within Specialized Context Differentiate**
 - Muscle Cells of Various Types
 - Endothelial Cells Lining the Gut
 - Specialized Cells within the Nephron
 - RBC Lacks Most Organelles
 - Etc.
- **Cells Have Specific Lifespans and Lifecycles**



Archetypical Eukaryotic Cell

- **Cytoplasm (within a Membrane) Containing Biomolecules and Organelles**
- **Cell Membrane (Active, Semi-permeable, and with Integrated Receptors)**
- **Nucleus and Nucleolus (except RBC)**
- **Genetic Material (Nuclear and Mitochondrial DNA and RNA (mRA, tRNA, rRNA))**
- **Cytoskeleton (Microfilaments, Intermediate Filaments, Microtubules)**
- **Mitochondria**
- **Endoplasmic Reticulum (Smooth and Rough) and Ribosomes (Bound and Free)**

Archetypical Eukaryotic Cell

- **Golgi Apparatus**
- **Lysosomes and Peroxisomes**
- **Centrosome**
- **Vacuoles**
- **Molecular Pathways Involving Cells and Cell Components Have a Major Role in Health and Disease States**
- **These Molecular Pathways May be Targeted by Various Therapies**

EGFR

Membrane

Bound

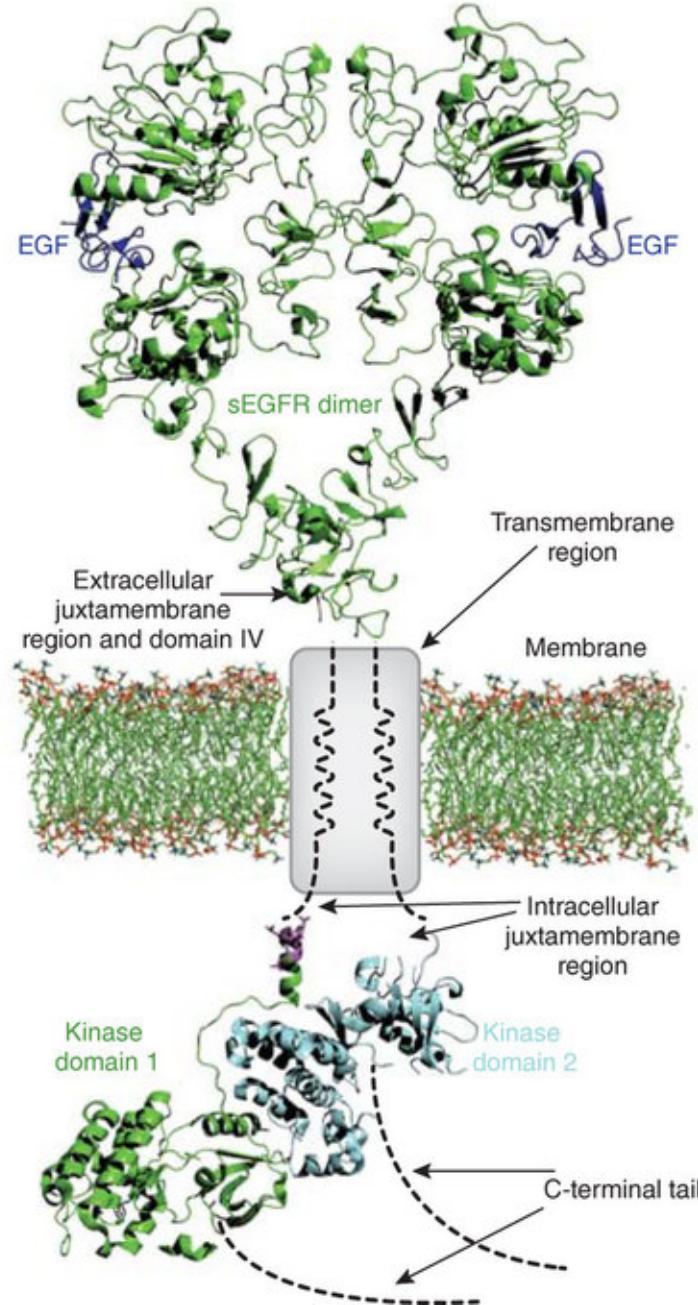
Receptor:

Epidermal

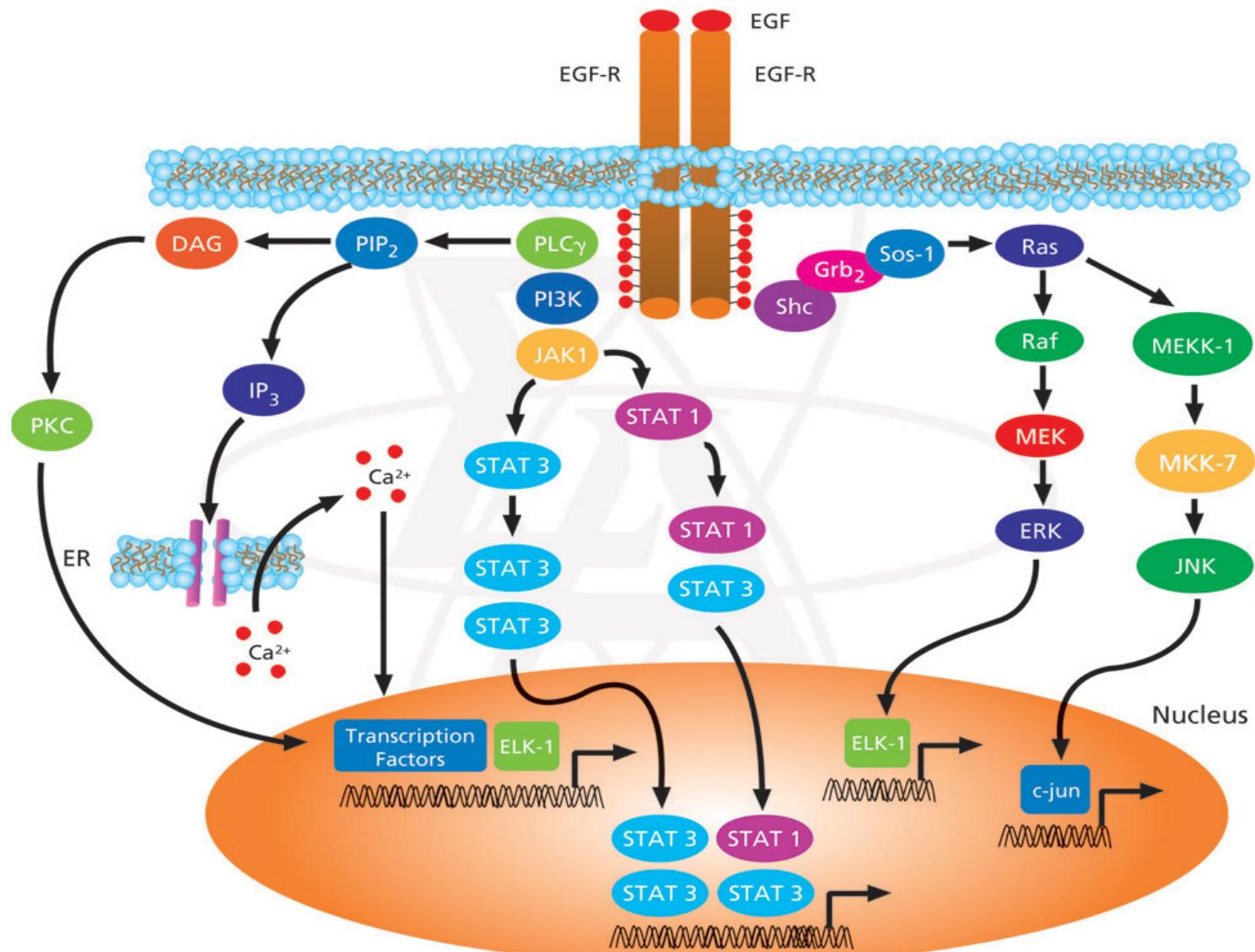
Growth

Factor

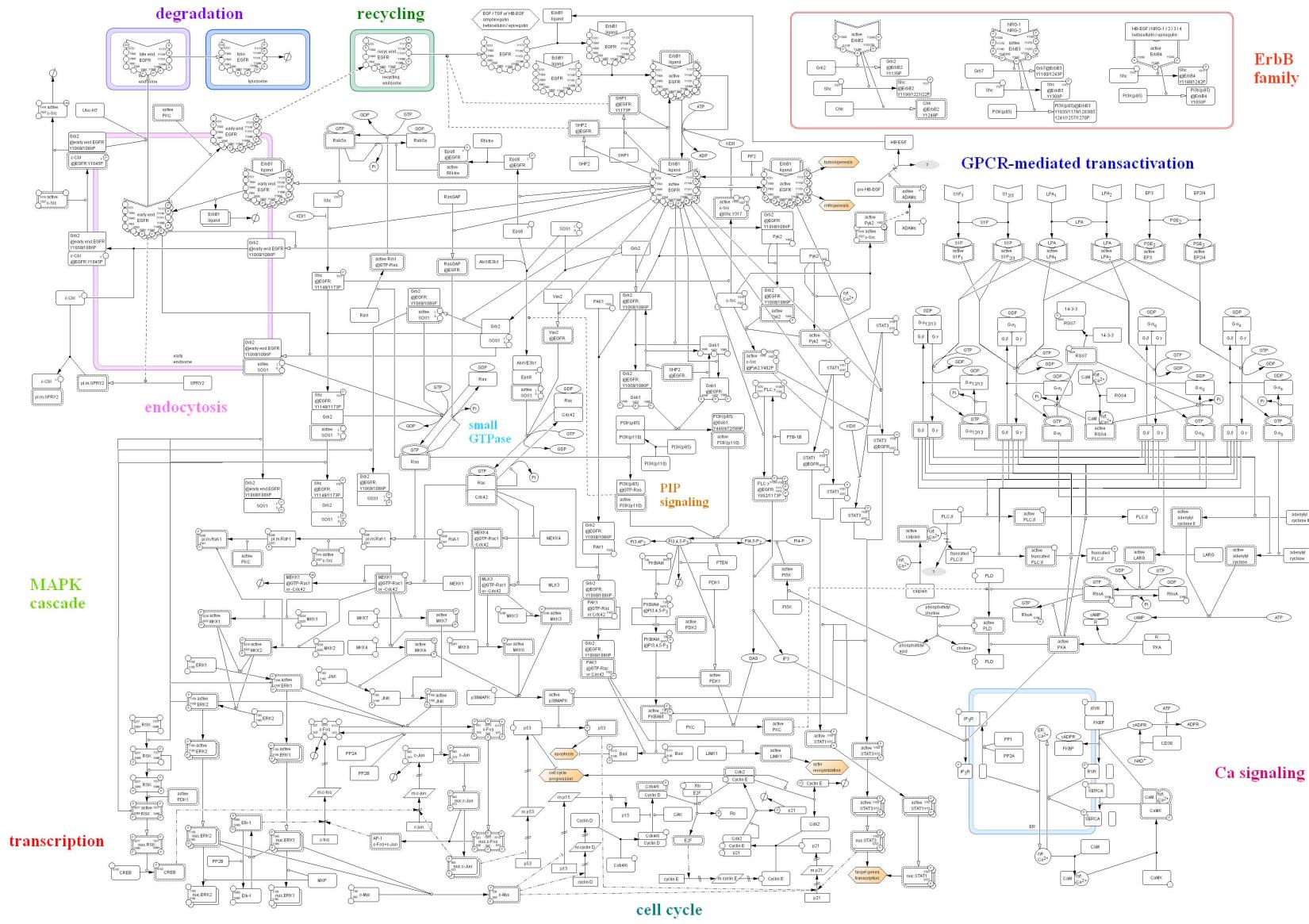
Receptor



EGFR Signal Transduction Pathway



EGFR Signal Transduction Pathway



EGFR-TKI Therapy in NSCLC:

By Way of Example

- **Iressa (Gefitinib) initially failed approval for NSCLC 2° lack of response in Phase III trial**
- **Approved 5/03 for NSCLC on the basis of “response” in sub-group analysis**
 - Response in only 10% of patients (AdenoCA, non-smokers, East Asian, female)
 - “Favorable” EGFR mutations present in 90% of responders, 0% of non-responders
 - Added K-RAS mutation imparts 1° drug resistance
- **Had this been known prior to Phase III trial, design (including but not limited to cohort selection) would have been changed thereby altering trial costs (and likely proposed clinical indications)**
- **But there is more to this story.....**

The Organ Systems, Organs, Functional Units, Cells, Organelles, and Molecules

- **Do Not Function Independently of One Another in Health and Diseases**
- **Have Common Themes that Are Often Repeated Across Organizational Units**
- **Therefore, Fall Prey to Common Insults in Similar Ways**
 - **Clinical Presentations May Differ**
 - **Mitochondrial Dysfunction in the Brain Is Different than in Muscle**
- **Conversely, Disparate Causations May have Similar Clinical Presentations Secondary to Limited Variations in Response by the Human**
 - **The Symptom of Pain May Have Various Causations**
 - **Skin, Soft Tissue, Deep Organs, Neurologic, Etc.**

Physiologic Processes, Biologic Functions

- **Processes Occur at Organ System, Organ, Functional Unit, Cell, Organelle, and Molecular Levels**
- **Some are Unique to a Particular Anatomy, Some Are Ubiquitous**
 - **Systemic Respiration (Gas Exchange) – Pulmonary Compared with**
 - **Cellular Respiration (Oxygen Dependent Energy Production) – Mitochondria**
 - **Blood Flow (Nutrients to Cells / Removal of Waste Material – Cardiovascular Compared with**
 - **Cellular Intake and Egress – Vacuoles Coupled with Organelle and Cell Membranes**

Physiologic Processes, Biologic Functions

- **Most Processes Take Place Across Several Organ Systems and/or Organs**
 - **Waste Removal – GI, Urinary, Respiratory**
 - **Signaling – Neurologic, Endocrine**
 - **Movement – Musculoskeletal, Neurologic with Supporting Roles from Cardiovascular and Respiratory**
Compared with
 - **Cellular Level Motility – Cytoskeleton, Cell and Organelle Membranes with Supporting Role from Mitochondria**
- **Many Organs Participate in Multiple Organ Systems and/or Classes of Physiologic Processes**
 - **Pancreas – GI, Endocrine**
 - **Kidney – Urinary, BP / Electrolyte Homeostasis**

Physiologic Processes, Biologic Functions

- **Google Earth Analogy Continued**
 - **Organ Systems Are More Like States or Cities;**
 - **While Organs Are More Like Local Neighborhoods or City Blocks**
 - **These Neighborhoods or Blocks Have Multi-Use Buildings (Functional Units Represent the Multiple Uses)**
 - **Include the Relevant Avenues, Streets, and Alleyways**
 - **The Latter Are the Arteries and Veins that Support the Functional Units, Organs, and Organ Systems, But**
 - **These Thoroughfares Are Also Included within the Cardiovascular System and Could Be Mapped Out Separately (Google Map, for example)**
 - **Each of the Specific Businesses and Homes also Have Organizational Structures within (akin to Cells with Organelles)**

Concept of Homeostasis

- **Physiologic Processes Vary about a Set Point Using Positive and Negative Feedback Loops**
 - BP, Heart Rate, Cardiac Output (Stroke Volume x Heart Rate) Is Kept within a Narrow Range Based on Circulating Blood Volume, Electrolyte Levels, Activity and Anxiety Level, Etc.
 - Flight or Fight Response Alters the Set Point – But with Return to Normalcy Once the Threat is Gone
- **Pathologic Changes in BP, HR, CO May Be Secondary to Injuries to the Participating Organs, Organ Systems, and Constituent Cells**
 - Neurologic, Cardiovascular, Pulmonary, Renal, Endocrine, Hematologic, Etc.
 - Reversible or Not; and By What Means (Time, Rx, Etc.)
- **This Concept Is Ubiquitous Throughout the Organism and Its Subdivisions at all Levels**

Normal and Abnormal Outcomes of Biologic and Physiologic Processes

- **Immune Response**
 - **Valuable in Recognizing “Self” from “Non-Self”**
 - **Eradication of Unhealthy Bacteria, Viruses, Cancer Cells**
 - **Problems – Pancreas, DM; Gut, Crohn Disease; Skin / MSK, Psoriasis; Brain – MS**
- **Scarring – Fibrosis**
 - **Valuable to Heal Underlying Injury**
 - **Post-operative Healing, Closing Puncture Wounds, Etc.**
 - **Problems – Liver, Cirrhosis; Heart, Dysrhythmia; Brain, Epileptic Focus**
- **REM Sleep**
 - **What about Aquatic Mammals; Sleep Would Lead to Drowning; Solution is “Half-Brain REM Sleep”**
 - **Half-Brain REM Sleep in Humans Uses the Same Evolutionary Circuits, but Contributors to Sleep Walking**
- **Inflammation, Angiogenesis, Etc.**

Review Course Curriculum

- **Series of Clinical Vignettes During which Faculty Will Review**
 - **Various Disease States and Clinical Presentations**
 - **Anatomy, Physiology, and Pathology of Relevant Organ System, Constituent Organs, Functional Units, and Specialized Cells**
- **While Doing So, the Class Will Be Exposed to Language and Descriptions of Normal and Abnormal Anatomy, Biology, and Physiology**
- **The Class Will Also Learn a Bit about Various Tests, Treatments, and Data Associated with those Diseases, Tests, and Treatments**
- **However, there Are Some Important Contexts that Will Not Be Covered within this Course, but Will Be Covered Elsewhere in Your Curriculum**



Cygnus

Cygnus

Lynx

Leo Minor

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Google earth

Why Is This Movie Relevant?

- **Possibly to Highlight that there Are More than 100 Billion Neurons in the Human Brain – More than Stars in the Milky Way!**
- **But No – Instead the Point Is that Just as We May Zoom In from the Human Organism to Organ Systems, Organs, Functional Units, Cells, and Molecules; So Too May We Zoom Out**
- **Better Understand the Place of Each Human Organism within Several Greater Contexts**
- **Within Each of these Contexts, there Are Interesting and Important Relationships Between**
 - **Health and Disease**
 - **CS/IS and Health-related Data**

Brain Networks, REM Sleep, and Ducks

- **Half-Brain REM Sleep – Important to Aquatic Mammals as Individuals**
- **Half-Brain REM Sleep – Also Important to Mallard Ducks as a Societal Unit**
- **Humans Also Have Adaptations that Are Societal**
 - **Healthy Adaptations Related to Sleep Patterns**
 - **Also Health Risks that are Influenced by Societal Organization Such as Infections, Psychosocial Disabilities, Nutritional Risks**
- **There Are Also Critical Keys to Understanding Disease and Treatments Largely Accessible by Analyzing Population Data**
 - **Need to Understand “Big Data” Derived from Populations**
 - **But Also Need to Understand the Underlying Biology**

EGFR-TKI Therapy in NSCLC:

The Story Continues

- **Iressa acquired (2°) resistance similar to other TKI therapies in other diseases (e.g., Gleevec in GIST)**
 - However, 2° resistance secondary to different mutations than 1° resistance (e.g., IGF-1)
 - Initial biomarker assessment would not be sufficient
- **However, even in Iressa responders – no improvement in overall survival!**
- **Tarceva (Erlotinib) another EGFR-TKI has similar cohort selection factors and resistance pathways, but DOES impart a survival benefit**
- **Targeted therapies often not so “targeted”**
 - Erbitux (Cetuximab) is an EGFR-Ab but also decreases circulating VEGF secondary to downstream HIF-1 α inhibition

Health-Related Data: Utilities, Caveats, Pitfalls

- **Electronic Medical Record (EMR) – Vagaries Secondary to Mode of Entry, Purposes of Data, But Closest to Point of Care**
- **Insurance Data – Purpose of Data (To Get Paid) May Not Reflect What Actually Occurred, But Has Other Virtues**
- **Clinical Trial Data – Vagaries Related to Type fo Research, Conduct of the Study, Etc.**
- **Etc.**
- **Etc.**
- **Etc.**
- **However, You Should and Will Have a Better Understanding of Health-Related Data and How It Is Derived Based on Your Curriculum**

One Person's Rationale as to the Importance of This Course and Your Curriculum

- Many (Most?) Physicians and Medical Scientists Do Not Understand How to Communicate with IS/CS Health Scientists**
 - These Individuals Do Not Understand the Potentials and Limitations of IS/CS Health Sciences**
- Many (Most?) IS/CS Health Scientists Do Not Understand How to Communicate with Physicians and Medical Scientists**
 - These Individuals Do Not Understand the Opportunities and Impediments Facing Care Providers, Medical Scientists, and the Health Care System More Generally**
- Worse Yet, When Attempting to Communicate Each Group Often Presents Solutions to the Other; Prior to Fully Understanding the Opportunities**
 - Thusly Limiting Novel Application of Potential Solutions Leading to Incremental rather than Transformative Gains**