INTRODUCTION

KINASES ARE IMPORTANT IN HUMAN BIOLOGY/DISEASE:
- Kinases are a superfamily of proteins (5th largest in humans)
- 518 genes and 106 pseudogenes
- Diverse in size, subunit structure, and cellular location
- ~260 residues make up their conserved catalytic core
- Dysregulation of kinases occurs in many diseases (cancer, inflammatory, degenerative, and autoimmune diseases)
- 244 of the 518 map to disease loci

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GROUP MEETING INCLUDES:
- Introduction to signal transduction
- Introduction to therapeutically relevant kinase targets
- Introduction to kinase structure
- Case studies in targets and their inhibitors
- Introduction to drug resistance to kinase inhibitors
- Introduction to drug discovery in kinase inhibitors
- Introduction to perspectives on the future of kinase inhibitors
- Summary of all FDA approved kinase inhibitors

GROUP MEETING DOES NOT INCLUDE:
- An exhaustive discussion of any of the above topics

SIGNAL TRANSDUCTION

The process describing how a signal (chemical/physical) is transmitted through a cell ultimately resulting in a cellular response

- Signals can originate inside or outside the cell
- Signals generally passed through a series of steps (signal transduction pathway) often consisting of multiple enzymes and messengers
- Pathways open possibility for signal amplification (>1x10^6)
- Extracellular signals transduced by RTKs, GPCR’s, guanlyl cyclases, or ligand-gated ion channels
- Phosphorylation is the most prominent covalent modification/signal in cellular regulation
- “Converter enzymes” (protein kinases and phosphoprotein phosphorlyases) are regulated; conserve ATP/maintain desired target protein state
- Pathway ends by affecting biomolecule function or gene expression

Protein Kinases:
- Generally highly specific often recognizing consensus sequences in their target (contains target residue)
- Can phosphorylate one or many residues on a protein
- Residues phosphorylated bear a free hydroxyl/phenol (serine, threonine, tyrosine)
- Tyrosine kinases only exist in multi-cellular organisms – important for intercellular communication
- Usually locked in their “inactive conformations” – blocked by intrasteric control/pseudosubstrates
- Turned on by interaction with messengers (cyclic nucleotides, Ca^{2+}, etc.) or phosphorylation/dephosphorylation
- Tyrosine kinases broken into two broad categories (RTK’s and NRTK’s)
- 90 tyrosine kinases - 58 RTK’s and 32 NRTK’s
**Kinase Inhibitors: An Introduction**

**KINASE-MEDIATED SIGNAL TRANSDUCTION PATHWAY:**
1. Receptor binding - results in conformational change/dimerization of RTK
2. Phosphorylation on RTK - (trans)autophosphorylation via now active kinase
3. Recognition of phosphoprotein - SH-2 domain binds phospho-RTK
4. Transphosphorylation - newly bound protein is phosphorylated
5. Cascade continues - successive recognitions and phosphorylations
6. Effector reached - cascade ends by modulating final target and its function

**PROTEIN KINASE CLASSES:**
1. Ser/Thr Protein Kinases
   a. Cyclic nucleotide dependent
   b. Ca\(^2+\)-calmodulin dependent (CaM)
   c. Protein kinase C (PKC)
   d. mitogen activated protein kinases (MAP)
   e. G-protein-coupled/Rhodopsin/BARK
2. Ser/Thr/Tyr Protein Kinases
   a. MAP kinase kinase (MAPK)
3. Tyr Protein Kinases
   a. Cytosolic tyrosine kinases
   b. Receptor tyrosine kinases (RTKs)

**THERAPEUTIC TARGETS**

Below is a list of clinically validated kinase targets:

- **BCR-Abl** - fusion kinase in some cancers; NRTK; activates numerous pathways
- **cKit** - RTK; activates numerous MAP-Kinase pathways
- **EGFR** - epidermal growth factor receptor; also ErB1; RTK
- **VEGFR** - vascular endothelial growth factor receptor; RTK
- **PDGFR** - platelet derived growth factor receptor; RTK
- **ErbB** - (also called HER) other RTK’s important in regulating growth
- **ALK** - anaplastic lymphoma kinase; NRTK
- **B-raf** - Ser/Thr kinase; MAP/ERK pathway
- **JAK** - Janus kinase; NRTK; part of JAK-STAT pathway
- **BTK** - Bruton’s tyrosine kinase; RTK; activates numerous pathways
- **CDK** - cyclin-dependent kinase; Ser/Thr kinase; help regulate cell cycle
- **Rho** - also ROCK; Ser/Thr kinase; associated with degenerative diseases
- **TRK** - tropomyosin receptor kinase; RTK; activates MAP and PI3 pathways
- **Syk** - spleen tyrosine kinase; NRTK
- **Flt3** - also CD135; RTK; one of most frequently mutated genes in AML
- **PI3K** - phosphoinositol 3 kinase; lipid kinase; PI3 involved in diverse signaling
- **FKBP/mTor** - mammalian target of rapamycin; Ser/Thr kinase; FKBP association necessary for activity

- **TARGETS MUST BE LINKED TO PHENOTYPE**
  - Most targets are oncogenes discovered by clinical/biochemical investigation
  - Some above targets are markers for certain cancer (or disease) types
  - Not all kinase targets are oncogene products
  - All kinase targets are involved in cell cycle/cell growth regulation
  - Many are in or are upstream of MAP-kinase pathways (stimulate cell division)
  - Certain disease states demonstrate activated kinase forms (abnormally active or constitutively)
  - Some cancer cells rely heavily on the above targets/pathways
  - Makes them particularly sensitive to inhibition - therapeutic index
  - Some inhibitors target a single kinase (selective/mono-specific)
  - Some inhibitors target multiple kinases (poly-specific)

**Oncogene** - a gene that has the potential to cause cancer via mutation/overexpression

**Proto-oncogene** - a gene in its normal state that could become an oncogene

**Phenotype** - physiological/observable characteristics of an organism
Kinase Inhibitors: An Introduction

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Baran Group Meeting
2/2/19

**KINASE STRUCTURE**

**N-lobe** - N-terminal small lobe of mostly β-sheet
- G-rich loop over ATP
- Hinge
- Seryl substrate
- Catalytic loop
- K71-E91 salt bridge
- L116
- T88
- Mg$^{2+}$-binding loop

**C-lobe** - C-terminal large lobe of mostly α-helix
- Protein substrate
- αC
- Activation segment pT197

**Hinge** - short portion connecting the N- and C-lobes; important for inhibitor binding
- αB

**K/E/D/D** - signature motif defining functional kinases (stabilizing/active-site residues)

**Activation Segment** - regulatory loop that changes conformation upon activation
- DFG - three residue motif at beginning of activation segment; large role in catalysis

**C-Spine** - 8 hydrophobic residues that facilitate ATP binding

**R-spine** - 4 hydrophobic residues that position substrate appropriately

**Shell residues** - 3 residues surrounding/stabilizing the R-spine

**SH2 (Gatekeeper)** - shell residue controlling access to an important binding pocket

**αC-helix** - dynamic motif whose conformation dictates binding of some inhibitors

**IMPORTANT STRUCTURAL MOTIFS:**

- **Activation Segment** - regulatory loop that changes conformation upon activation
- **DFG** - three residue motif at beginning of activation segment; large role in catalysis
- **C-Spine** - 8 hydrophobic residues that facilitate ATP binding
- **R-spine** - 4 hydrophobic residues that position substrate appropriately
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- **αC-helix** - dynamic motif whose conformation dictates binding of some inhibitors

**INHIBITOR BINDING MOTIFS:**

- **Activation Segment** - regulatory loop that changes conformation upon activation
- **DFG** - three residue motif at beginning of activation segment; large role in catalysis
- **C-Spine** - 8 hydrophobic residues that facilitate ATP binding
- **R-spine** - 4 hydrophobic residues that position substrate appropriately
- **Shell residues** - 3 residues surrounding/stabilizing the R-spine
- **SH2 (Gatekeeper)** - shell residue controlling access to an important binding pocket
- **αC-helix** - dynamic motif whose conformation dictates binding of some inhibitors

- **Activation usually result of phosphorylation or binding a “signal”**
- **Activation changes DFG orientation (below)**
- **ACTIVE = AS open; αC in; DFG-Asp in**

- **the “spines” are linear arrangements of hydrophobic residues**
- **formation necessary for function**
- **functions validated by mutation**
- **some tolerance**

**INHIBITOR BINDING MOTIFS:**

- **figure at left depicts pockets/regions generally utilized by inhibitors**
- **most inhibitors make 1-3 hydrogen bonds w/ hinge residues**
- **specificity defined largely by alternative pockets**
- **gatekeeper residue size determines access to hydrophobic pocket II**
- **binding active vs. inactive state provides access to different pockets**
**INHIBITOR TYPES**

**TYPE I** - Binds in ATP binding pocket; active form; DFG-Asp IN

**TYPE I 1/2** - Binds in ATP binding pocket; inactive form; DFG-Asp IN

**TYPE II** - Binds in ATP binding pocket; active form; DFG-Asp Out

**TYPE III** - Allosteric inhibitor binding near ATP site

**TYPE IV** - Allosteric inhibitor binding away from ATP site

**TYPE V** - Bivalent inhibitor spanning two regions

**TYPE VI** - Covalent inhibitors; partially fall into types I and II

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**INHIBITOR BINDING, SPECIFICITY, AND IMATINIB**

**Imatinib** (Gleevec, Novartis) 2001; Bcr-ABL

- Increased cellular activity
- Improved solubility/oral bio-availability
- Abolished PKC activity

**Bosutinib** (Bosulif, Wyeth) 2012, CML

- Provided Tyr-kinase activity
- Hydrophobic pocket

**BCR-Abl**

- BCR-Abl is a fusion gene (hybrid of two previously separate genes)
- Two original genes normally exist on different chromosomes
- Expression of fusion results in a constitutively active Abl kinase
- First discovery of a genetic abnormality directly associated with a cancer
- Decreases apoptotic potential and activates MAP kinase pathways at Ras
- Associated with various leukemias (CML and ALL)
- First clinically validated kinase target; target of imatninib

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**Philadelphia Chromosome**

- Normal chromosomes
- Chromosomes break
- Changed chromosomes
- Chromosome 9
- Chromosome 22
- Philadelphia chromosome
- BCR-ABL gene

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**Synthesis**

1. N-Me-piperazine, NaH
2. H2, Pd/C

**Vaidyanathan, OPRD 2013, 500.**
**Kinase Inhibitors: An Introduction**

**GROWTH FACTOR RECEPTORS**  
*(EGFR, VEGFR, PDGFR)*

- All are closely related receptor tyrosine kinases
- All have ability to activate multiple pathways (depends upon phosphorylation pattern) - MAPK, PI3K, STAT
- Each has multiple subtypes and vary by receptor and tissue distribution
- Variously associated with certain types of cancers
- When implicated, overexpression is usually the cause of aberrant activity
- EGFR one of the most commonly drugged kinases
- The target of the antibody kinase inhibitors
- 4-aminoquinazoline is everywhere!!
- In 6 FDA-approved EGFR inhibitors

**MEK1/2**

- MEK is a midstream part of Ras-MAP pathway
- Oncogenes generally upstream
- Activation of ERK signals for cell proliferation
- MAP pathways implicated in many cancer types

**Pazopanib**  
*(Votrient, GSK)*  
*2009; RCC, soft tissue sarcomas*

**Trametinib**  
*(Mekinist, GSK)*  
*2013; melanoma*

**Erlotinib**  
*(Tarceva, Genentech)*  
*2004; NSCLC, pancreatic cancer*


**Kinase Inhibitors: An Introduction**

**PI3K (phosphoinositide 3-kinase)**

- PI3 kinases are a class of lipid kinases
- Type I: PI3K\(\alpha\) and PI3K\(\gamma\) are therapeutically relevant
- Catalyze: PI(4,5)\(P_2\) $\rightarrow$ PI(3,4,5)\(P_3\)
- PI3P is a signaling molecule that has multiple implications in cancer phenotypes
- Control numerous diverse cellular functions (growth, motility, differentiation, and intracellular trafficking)
- Many ongoing clinical trials targeting these enzymes
- PI3K can be activated by numerous receptors

**Idelalisib (Zydelig; Gilead)**

2014; CLL, SLL, follicular lymphoma

**BTK (Bruton’s Tyrosine Kinase)**

- Extremely important kinase in B-cell development
- Targeted for lymphomas (B-cells are a type of lymphocyte)
- Low expression in many types of tissues - good therapeutic index
- Interest is high for treatment of autoimmune disorders (many ongoing clinical trials)
- Many of the inhibitors of interest are covalent

**Idelalisib**

2014; CLL, SLL, follicular lymphoma

Phosphatidylinositol (4,5) diphosphate - PI(4,5)\(P_2\)

**Moturu, RSC Adv. 2018, 15863.**

Hughes, OPRD 2016, 1855.
Kinase Inhibitors: An Introduction

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JAK (Janus kinase)
- The beginning of the JAK-STAT pathway
- STAT = signal transduction activator of transcription
- 4 types (JAK1, JAK2, JAK3, TYK2)
- JAKs are receptor-associated kinases (often cytokine receptors; immune system)
- single point mutations are often associated with proliferative effects/autoimmunity
- associated with leukemias, psoriasis, rheumatic diseases
- kinase target of the first non-cancer approved kinase inhibitor
- continues to be an active area of research for a variety of disease types

Tofacitinib (Xeljanz, Pfizer) 2012; rheumatoid arthritis

CDK4/6
- cyclins are a number of small proteins involved in regulating cell cycle
- different cyclin pair w/ different CDK’s to activate different cell stages
- activated CDK’s trigger changes in transcription to enter next phase
- CDK4/6 phosphorylate a repressor allowing S phase to start
- "R" = checkpoint where cells can trigger apoptosis (programmed cell death)
- other CDKs are of interest as therapeutic targets

Palbociclib (Ibrance, Park Davis) 2015; ER2+ and HER2+ breast cancer

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**DRUG RESISTANCE**
- treatment of cancer with kinase inhibitors applies a selection pressure to the cells it affects
- cancer cells divide unchecked and are prone to further mutation
- resistance to kinase inhibitors generally arises rapidly (a few months to a year)
- type of resistance varies between type of cancer treated and drug used
- biggest drawback to this type of therapy

**TYPES OF RESISTANCE:**
A. Target Dependent Resistance
   1. target protein point mutation
   2. target protein amplification/overexpression
B. Target Independent Resistance
   1. decreased drug uptake
   2. increased drug efflux
   3. upregulation of alternative/ downstream pathways

**CASE STUDY: IMATINIB**
- target point mutation is the prominent resistance mechanism
- >100 different point mutations have been described in resistant patients
- only ponatinib is active against imatinib resistant cancers (gatekeeper)
- four mutations account for 60% of the resistant mutants
  1. Thr-315-Ile (gatekeeper mutation)
  2. Tyr-253-Phe (changes in van der Waals forces)
  3. Glu-255-Lys/Val (inside ATP binding pocket)
  4. Met-351-Thr (αE-helix of C-lobe; mechanism unclear)

**DRUG DISCOVERY**
Solved Problems:
- poster child of rational drug design
- thousands of kinase structures known
- much known about kinase binding
- kinase inhibitors historically found via HTS or fragment-based approaches

Current/Future Challenges:
- finding novel hinge binders
- rapidly evaluating whole-cell kinase selectivity
- creating proper biological models

New Technologies:
- Activity-based protein profiling (ABPP) rapidly generates kinome coverage data
- Thermal proteome profiling (TPP) generates data about other off-targets
- computational techniques (FEP and WaterMap) helps predict & rationalize SAR

**COVALENT INHIBITORS**
- heightened interest in covalent inhibitors
- shown they can be selective and safe
- limited to kinases w/ accessible residues
- benefits include: prolonged pharmacodynamics, high potency, rapid validation
- drawback of straightforward resistance
- much discussion about “kinetic selectivity”
- some solutions: reversible covalent & metabolically limited warheads
- opportunities may lie in targeting other residues (non-Cys)
- list at left are a few examples of explored warheads and targeted residues

**GOING FORWARD**
- still active areas of research - academia and industry
- new cancer targets include: TAM kinases and other CDK’s
- potential synergies with immunotherapy
- PROTACs w/ kinase inhibitors being investigated
- high interest in entering disease areas outside of cancer
- selectivity becomes paramount in treatment of non-terminal diseases
- necessity of role of selectivity debated in kinase inhibitor cancer treatment

**OTHER DISEASE AREAS**
1. Autoimmune disease
   - 20 JAK inhibitors in clinical trials for autoimmune disorders
   - generating biological models is largest challenge
2. Degenerative disease
   - challenging; poor of understanding disease mechanism
   - chronic unfolded protein response mediated by kinases
3. Infectious disease
   - Plasmodium falciparum-selective kinases
4. Angiogenesis
   - systemic VEGFR inhibitors for macular degeneration (intravitreal injection only other option)

**SOLVED PROBLEMS**

**NEW TECHNOLOGIES**

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**Imatinib** (Gleevec, Novartis)
2001; CML, ALL, CEL/HES, GIST, DFSP, mastocytosis
BCR-Abl, Kit, PDGFR

**Bosutinib** (Bosulif, Wyeth)
2012, CML
BCR-Abl, Src, Hck, Lyn

**Ribociclib** (Kisqali, Novartis)
2017, ER2* and HER2* breast cancer
CDK 4/6

**Dasatinib** (Sprycel, BMS)
2006; CML
BCR-Abl, (PD)(E)GFR, Src, Kit, EphA2, Lck

**Vemurafenib** (Zelboraf, Genentech)
2011; melanoma (V600E)
A/B/C-raf

**Dabrafenib** (Tafinlar; GSK)
2013; melanoma
B-raf

**Palbociclib** (Ibrance, Park Davis)
2015; ER2* and HER2* breast cancer
CDK 4/6

**Nilotinib** (Tasigna, Novartis)
2007; CML
BCR-Abl, PDGFR, DDR1

**Dabrafenib** (Tafinlar; GSK)
2013; melanoma
B-raf

**Abemaciclib** (Verzenio, Eli Lilly)
2017; HER2+/− breast cancer
CDK4/6

**Ponatinib** (Iclusiq, Ariad)
2012; CML, ALL
BCR-Abl, (V)(PD)(E)GFR, Src

**Encorafenib** (Braftovi, Array)
2018; melanoma
B-raf

**Netarsudil** (Rhopressa, Aerie Pharm.)
2018; Glaucoma
Rho kinase
Kinase Inhibitors: An Introduction

Gefitinib (Iressa, Astra Zeneca) 2003/2015; NSCLC EGFR

Dacomitinib (Visimpro, Pfizer) 2018; NSCLC EGFR

Erlotinib (Tarceva, Genentech) 2004; NSCLC, pancreatic cancer EGFR

Gefitinib (Iressa, Astra Zeneca) 2003/2015; NSCLC EGFR

Regorafenib (Stivarga, Bayer) 2012; CRC (VE)(PD)(F)GFR, BCR-Abl, B-raf, Kit, RET

Lapatinib (Tykerb, GSK) 2007; HER2+ breast cancer EGFR; ErbB2

Afatinib (Gilotrif, B-I) 2013; NSCLC EGFR; ErbB2/4

Neratinib (Nerlynx, Puma) 2017; HER2+ breast cancer ErbB2

Nintedanib (Ofev/Vargatef, B-I) 2014; idiopathic pulmonary fibrosis VEGFR, PDGFR, FGFR

Osimertinib (Astra Zeneca) 2015; NSCLC EGFR

Nintedanib (Ofev/Vargatef, B-I) 2014; idiopathic pulmonary fibrosis VEGFR, PDGFR, FGFR

Lenvatinib (Lenvima, Eisai) 2015; thyroid cancer (VE)(PD)(V)GFR, Kit, RET

Cabozantinib (Cometriq; Exelixis) 2012; Thyroid cancer, RCC, HCC RET, MET, Kit, VEGFR, Flt3, Azl, TrkB

Lenvatinib (Lenvima, Eisai) 2015; thyroid cancer (VE)(PD)(V)GFR, Kit, RET

Cabozantinib (Cometriq; Exelixis) 2012; Thyroid cancer, RCC, HCC RET, MET, Kit, VEGFR, Flt3, Azl, TrkB

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Vandetanib (Caprelsa, Astra Zeneca) 2011; Thyroid cancer (V)EGFR, RET, Src, Brk, EphR

Regorafenib (Stivarga, Bayer) 2012; CRC (VE)(PD)(F)GFR, BCR-Abl, B-raf, Kit, RET

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Vandetanib (Caprelsa, Astra Zeneca) 2011; Thyroid cancer (V)EGFR, RET, Src, Brk, EphR

Vandetanib (Caprelsa, Astra Zeneca) 2011; Thyroid cancer (V)EGFR, RET, Src, Brk, EphR
**Kinase Inhibitors: An Introduction**

**AXITINIB (Inlyta, Pfizer)**
- 2012: RCC
- VEGFR, PDGFR

**SORAFENIB (Nexavar, Bayer)**
- 2005: thyroid cancer, HCC, RCC
- VEGFR, PDGFR, B/C-raf, Kit, Flt3, RET

**PAZOPANIB (Votrient, GSK)**
- 2009: RCC, soft tissue sarcomas
- VEGFR, PDGFR, FGFR, Kit, Lck, Fms

**SU Ninib (Sutentm, Pfizer)**
- 2006: RCC, GIST, pancreatic NET
- PDGFR, VEGFR, Kit, RET, Axl, Flt3

**SUNITINIB**

**LAROTRECTINIB (Vitrakvi, Bayer)**
- 2018: solid tumors w/ NTRK fusions
- TRK

**IDELALISIB (Zydelig; Gilead)**
- 2014: CLL, SLL, follicular lymphoma
- PI3K

**DUVELISIB (Copiktra; Verastem)**
- 2018: CLL, SLL, follicular lymphoma
- PI3K

**COPANLISIB (Aliqopa; Bayer)**
- 2017: follicular lymphoma
- PI3K

**AXITINIB**

**SUNITINIB**

**COPANLISIB**

**MEANING OF ABBREVIATIONS**

- ALL = acute lymphoid leukemia
- AML = acute myeloid leukemia
- DFSP = dermatofibrosarcoma protuberans
- CEL = chronic eosinophilic leukemia
- CLL = chronic lymphocytic leukemia
- CML = chronic myeloid leukemia
- GIST = gastrointestinal stromal tumor
- HCC = hepatocellular carcinoma
- HES = hypereosinophilic syndrome
- NSCLC = non-small cell lung cancer
- RCC = renal cell carcinoma
- SLL = small lymphocytic lymphoma

**BINDERS OF FKBP12/mTOR**

- R = OH
  - Rapamycin/Sirolimus (Rapamune, Wyeth) 1999
  - Temsirolimus (Torisel, Wyeth) 2007
  - Everolimus (Afinitor, Novartis) 2009
Major References/Resources:

Garrett; Grisham, *Biochemistry*, Boston: Brooks/Cole, **2010**.