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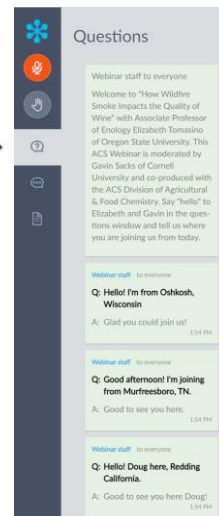
Questions or Comments?

Type them into the questions box!



"Why am I muted?"

Don't worry. Everyone is muted except the Presenter and the Host. Thank you and enjoy the show.



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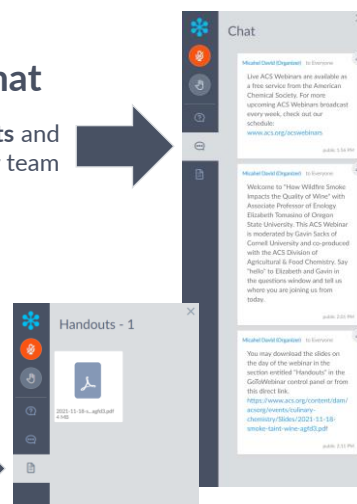
Chat

Announcements and hyperlinks from our team



Handouts

Download the PDF of today's slide deck



2

2

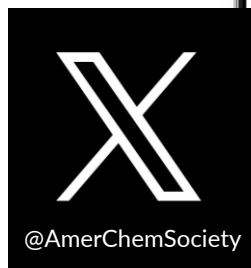


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All Registrants

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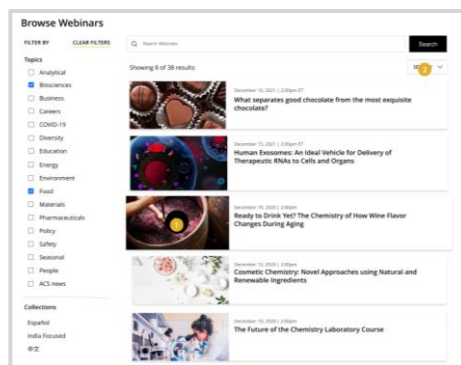
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Being a part of the ACS Bridge program has benefited me in several ways. I was able to pursue fully independent, fascinating research at a top institution, but even more importantly, I was exposed to a number of opportunities (such as conferences, career events, etc.) I never would have known about otherwise. The best thing about Bridge in my opinion, are the people at ACS who have worked to make it happen. Their dedication to helping me develop professionally and supporting me in good or bad times I will forever be grateful for.

Hanin Sarhan, Bridge Fellow at Indiana University

”



Group picture from 2022 CKS at ACS HQ in Washington, DC

American Chemical Society

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ACS Scholar Adunoluwa Obisesan

BS, Massachusetts Institute of Technology, June 2021
(Chemical-biological Engineering, Computer Science & Molecular Biology)



“The ACS Scholars Program provided me with monetary support as well as a valuable network of peers and mentors who have transformed my life and will help me in my future endeavors. The program enabled me to achieve more than I could have ever dreamed. Thank you so much!”

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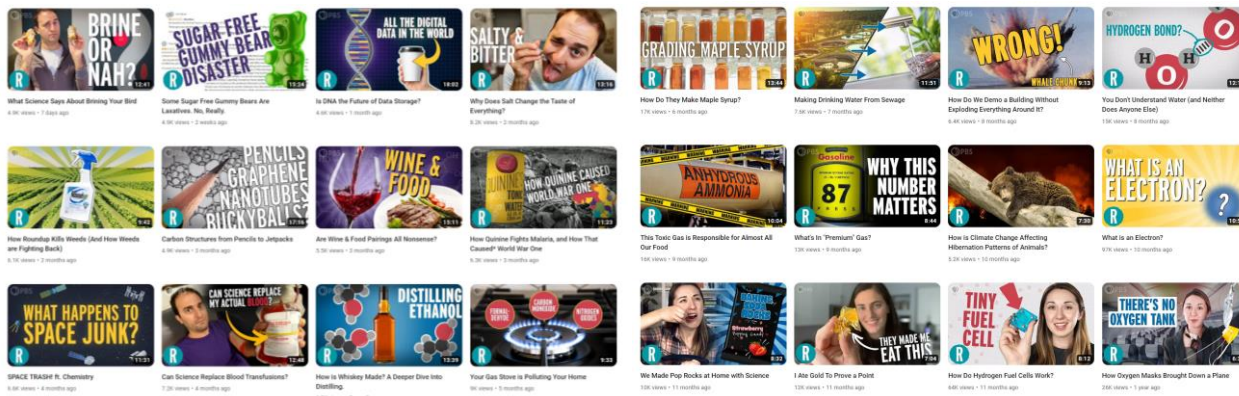



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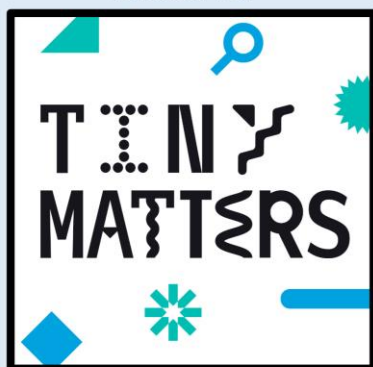
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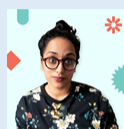
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Sam Jones, PhD
 Science Writer & Exec Producer



Deboki Chakravarti, PhD
 Science Writer & Co-Host

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acsoncampus.acs.org

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ACS Career Resources



Virtual Office Hours



<https://www.acs.org/careerconsulting.html>

Personal Career Consultations

Jim Tung
Marketing
Lucamas Laboratories
B.S., Biochemistry, University of Oregon
Ph.D., Organic Chemistry, University of Notre Dame

Jim Tung works at Lucamas Laboratories in Portland, OR, currently as a business development manager. He has been with Lucamas for 10 years, working on developing new chemical manufacturing projects. Before that, he was a senior research chemist at Oblet Research in Champaign, IL, performing kilo-scale organic chemistry.

An Oregon native, Jim got his B.S. in biochemistry from the University of Oregon, his Ph.D. in organic chemistry from the University of Notre Dame, with postdoctoral experience at Pfizer's laboratories in La Jolla, CA. He is past chair of the Portland Section of the American Chemical Society and was 2019 general co-chair of NORM 2019. He has interests in process chemistry, labor economics, social media outreach and encouraging career exploration and development for younger chemists.

Ask me about:
Working in industry
Applying for academic jobs
Getting your first job

Contact with Jim

<https://www.acs.org/careerconsulting.html>

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<https://www.acs.org/linkedinlearning>

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ACS Advocacy
See your influence in action!



The impact and results of **ACS member advocacy** outreach and efforts by the numbers!



Get Involved



Enroll in a workshop



Become a Fellow



Take Action

American Chemical Society

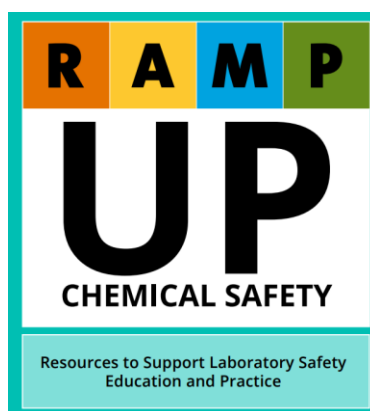
<https://www.acs.org/policy>

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A complete listing of ACS Safety Programs and Resources



Download it for free in the "Projects & Announcements" Section! www.acs.org/ccs



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ACS OFFICE OF DEIR

Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect



Resources

Inclusivity Style Guide Designed to help staff and members use language and images that respect diversity in all its forms. →	ACS Webinars on Diversity Covering diversity and inclusion at the workplace →
ACS Publications DEIR Hub See what ACS Publications is doing for fostering inclusivity in scholarly publishing →	ACS Volunteer and ACS Meetings Code of Conduct Fostering a positive and welcoming environment for attendees, volunteers and staff. →
C&EN Trailblazers C&EN highlights scientists from different backgrounds who are making an impact in chemistry. →	NEW! Download DEIR Educational Resources Download this educational guide for additional recommendations on videos, articles, books, podcasts, and more on diversity, inclusion, and related topics. →
Quick Guide: Inclusion Moments Learn more about what Inclusion Moments are and see ideas to host them during your meetings. →	Quick Guide: How to host inclusive in-person events Recommendations and best practices to ensure that your events can accommodate everyone. →

Diversity, Equity, Inclusion, and Respect

**Adapted from definitions from the Ford Foundation Center for Social Justice:

Equity**

Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

Diversity**

The representation of varied identities and differences (race, ethnicity, gender, disability, sexual orientation, gender identity, national origin, tribe, caste, socioeconomic status, thinking and communication styles, etc.), collectively and as individuals. ACS seeks to proactively engage, understand, and draw on a variety of perspectives.

Inclusion**

Builds a culture of belonging by actively inviting the contribution and participation of all people. Every person's voice adds value, and ACS strives to create balance in the face of power differences. In addition, no one person can or should be called upon to represent an entire community.

Respect

Ensures that each person is treated with professionalism, integrity, and ethics underpinning all interpersonal interactions.

<https://www.acs.org/diversity>

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NEXT WEEK!



Wednesday, June 12, 2024 | 2pm-3pm ET

Talking Science: Communicating Your Research to Diverse Audiences

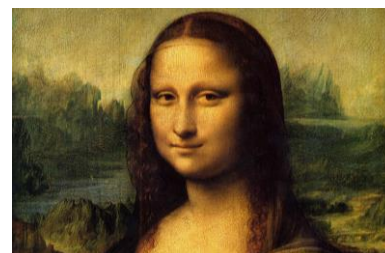
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Thursday, June 13, 2024 | 2pm-3pm ET

Chemistry and the Economy: One Door Closes as Another Opens

Co-produced with ACS Industry Member Programs and ACS Division of Business Development and Management



Thursday, June 20, 2024 | 11am-12pm ET

Revealing Mona Lisa's Secrets Through Advanced Analytical Chemistry

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**THIS ACS WEBINAR®
WILL BEGIN SHORTLY...**

👋 Say hello in the questions window!

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Pharmacology for Chemists



Terry Kenakin, PhD

Professor of Pharmacology,
UNC School of Medicine



BRYAN TWEEDY, PhD

Assistant Director, ACS Education,
Office of Career and Professional
Education, American Chemical Society

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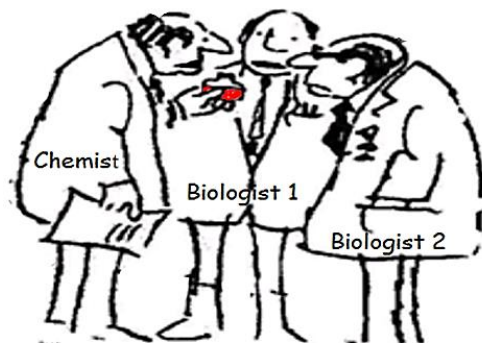
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Pharmacology for Chemists

Terry Kenakin PhD

Dept Pharmacology, University of North Carolina, School of Medicine. Chapel Hill, NC

Course Outline



6 weeks / 1 hr/wk

Recorded / slide pdf provided



Terry Kenakin Ph.D.

BS Chemistry, PhD Pharmacology
University of Alberta, Edmonton, Canada

7 Yr. Burroughs-Wellcome Co.
25 yr GlaxoSmithKline

13 yr University of North Carolina
School of Medicine

Development Reports (Pharmacokinetics, Safety, Pharmacology)

- Early Safety Studies / Translation of Drug Activity In Vivo
- Clinical Testing

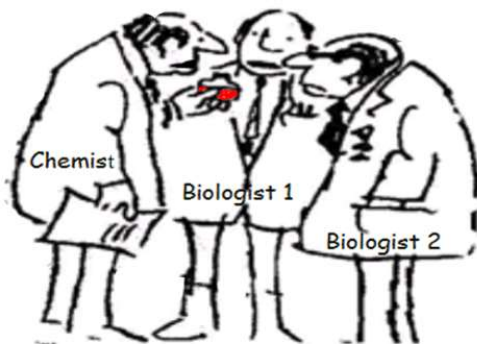
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Pharmacology for Chemists

Terry Kenakin PhD

Dept Pharmacology, University of North Carolina, School of Medicine. Chapel Hill, NC



6 weeks / 1 hr/wk
Recorded / slide pdf provided

Course Outline

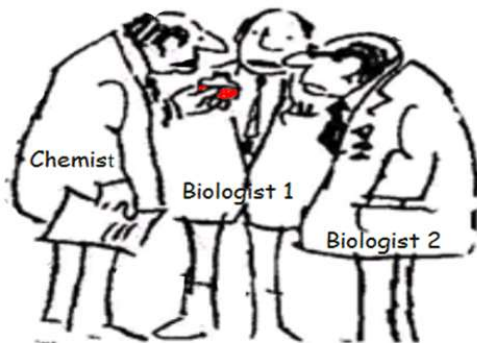
- What is Pharmacology? (Historical Perspective)
- Pharmacology for Drug Discovery (Biologist / Med Chemist Interface)
- Drug Discovery: Target-based vs System-based Projects
- Drug Targets and Drug Target Validation
- What Molecules make Good Drugs? (Small molecules / Biologicals)
- Screening for New Drugs
- Agonists, Antagonists and Allosteric Modulators
- The Lead Optimization Process (Binding / Function)
- Demonstrating Target Engagement In Vitro
- Development Properties (Pharmacokinetics, Safety Pharmacology)
- Early Safety Studies / Translation of Drug Activity In Vivo
- Clinical Testing

1

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7 Yr. Burroughs-Wellcome Co.
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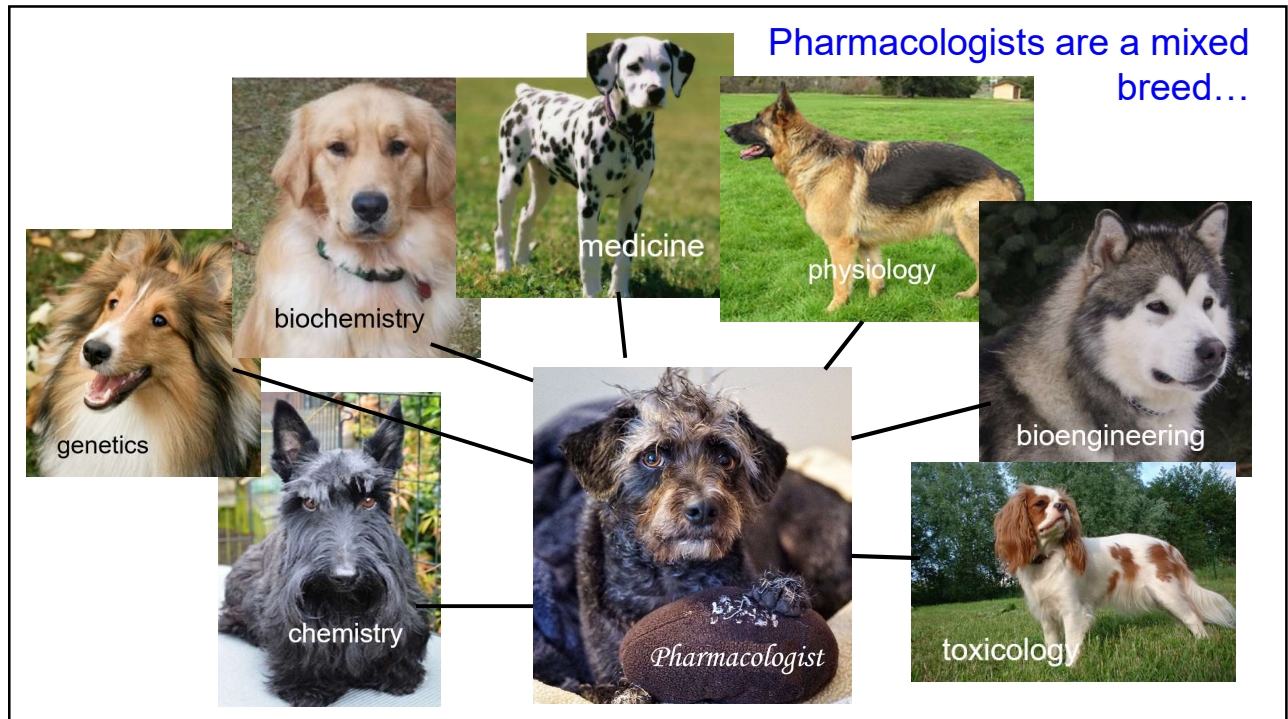
13 yr University of North Carolina
School of Medicine

- Early Safety Studies / Translation of Drug Activity In Vivo
- Clinical Testing

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What is Pharmacology?

3



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- **Pharmacology is Unique and Essential to Drug Discovery**
- The Pharmacology / Med Chem Interface
- Drug Discovery: State of the Art
- Tools of the Trade: Pharmacologic Assays
- Tools of the Trade: Biological Drug Targets
- 'Drugging' Targets :The Art of Finding Molecules
- Applying the Tools: How do Drugs Work?
- What is Drug Efficacy?
- How Do Drugs Interact with Targets?
- In Vivo Testing and Drug Development


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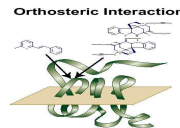
There are basically four properties of a molecule that can be used to predict activity in all physiological systems:

- 1. Affinity:** what concentrations of drug are needed to engage the drug target?

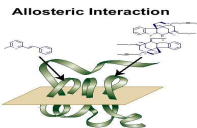

- 2. Efficacy:** What pharmacological effect will be observed upon target engagement and to what extent are they biased toward some pathways over others?

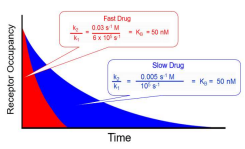

- 3. Does the ligand bind in an orthosteric or allosteric manner with the target in terms of the natural agonist(s).**

Orthosteric Interaction



Allosteric Interaction


- 4. What are the kinetics of interaction of the molecule with the target, i.e. rate of offset. This defines target coverage in vivo.**



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What a drug does...and what a drug is...

New synthetic agonist prenalterol

Thyrox. GP Right Axis
Full Agonist

GP Left Axis
Partial Agonist

No direct effect/blocks isoproterenol
Antagonist

GP Extremity D.L.

On Tuesday you said it was a full agonist... on Thursday you said partial agonist...this Monday its now an antagonist...how can you be so wrong so often?

Biologist

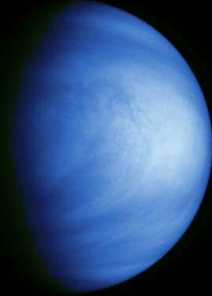
Chemist

* Agonist: Drug that produces a cellular Response

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Chemists are from ~~Venus~~ Mars and
Biologists are from ~~Mars~~ Venus

Physical Sciences have
absolute scales



Biological Sciences have
moving scales

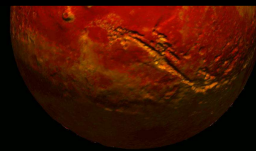


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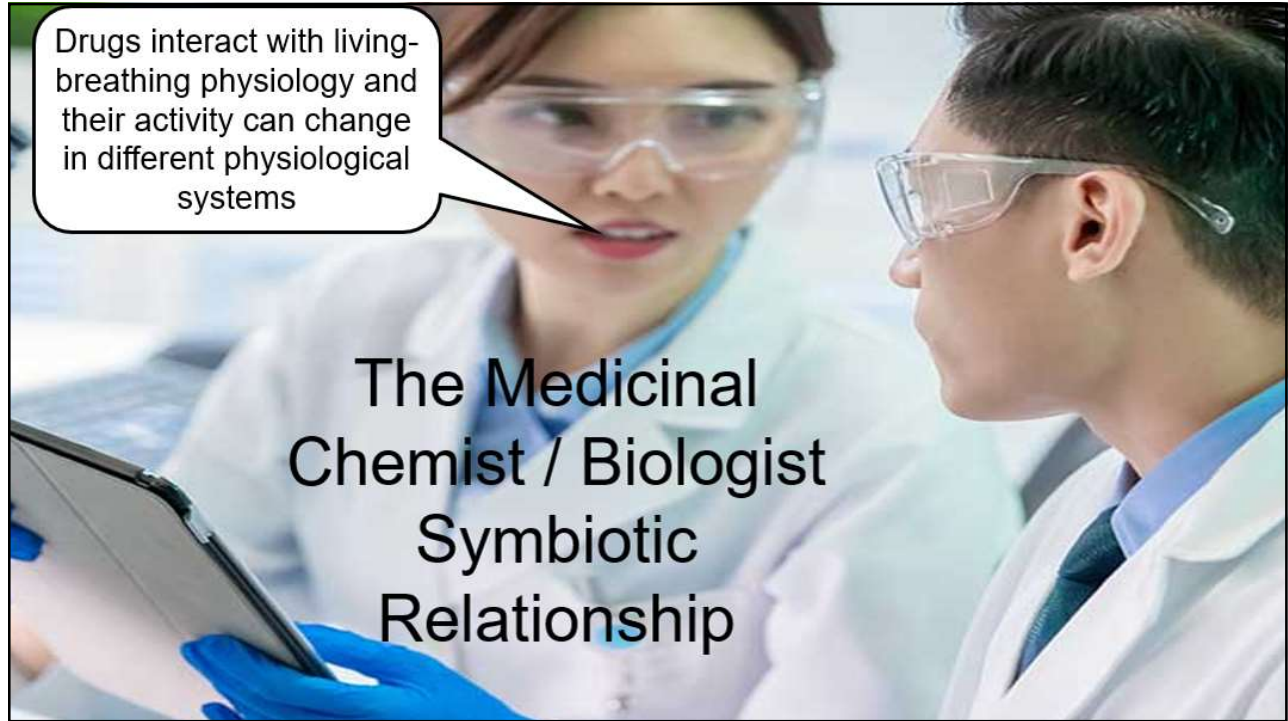


The Protean Nature of
Drug Activity....

(Drugs change their activity profile
in different physiological systems)



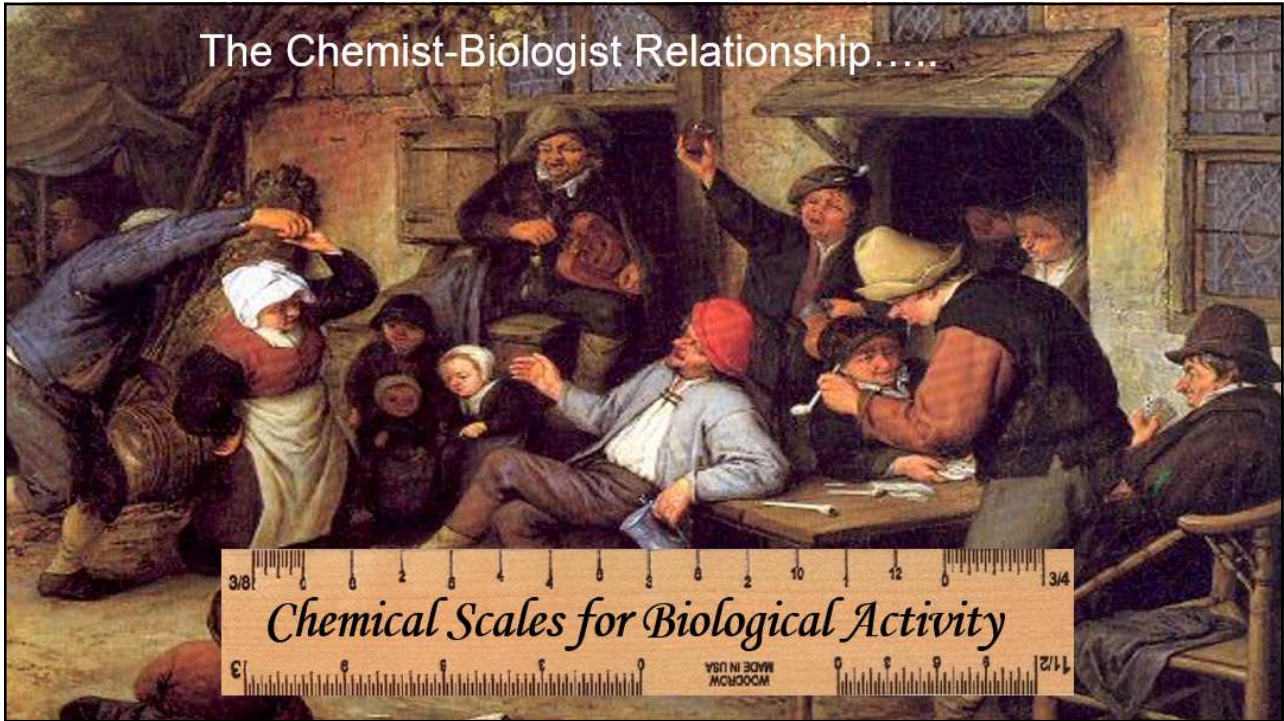
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Fundamentals of Pharmacology

Characterizing Drug Action

Pharmacologically Answerable Questions....

Answer: NO...these are behaviors, not molecular properties

Should I care?

Your compound is a full agonist

Your compound is a partial agonist

Chemist

Biologist 1

Biologist 2

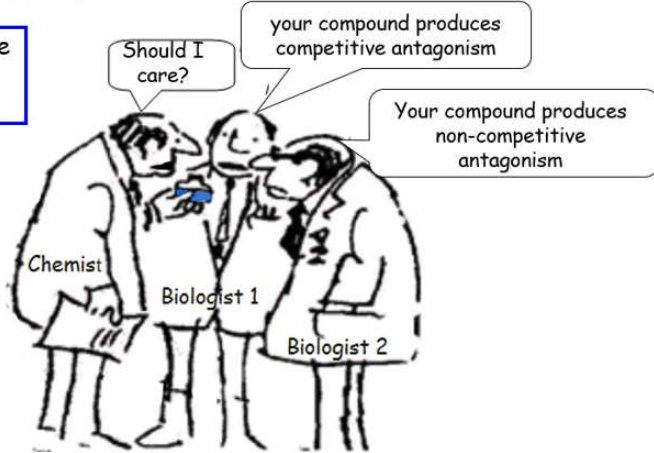
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Fundamentals of Pharmacology

Characterizing Drug Action

Pharmacologically Answerable Questions....

Answer: NO...these are kinetic behaviors, not molecular properties



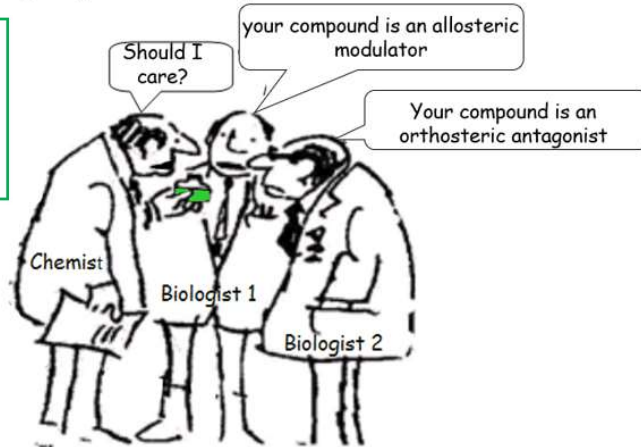
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Fundamentals of Pharmacology

Characterizing Drug Action

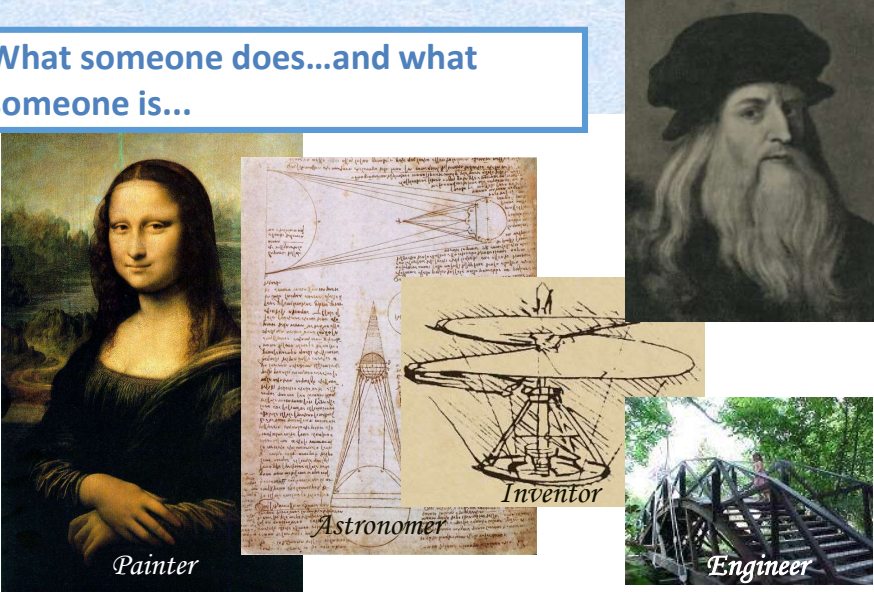
Pharmacologically Answerable Questions....

Answer: YES...these are two separate molecular mechanisms of action and both can't be correct. Each comes with a separate and different set of therapeutic behaviors



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What someone does...and what someone is...



Painter

Inventor

Astronomer

Engineer

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Aim of Receptor Pharmacology

What something does....
Snapshot of behavior in time..

What something is...
Predictor of Spectrum of Behaviors...

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Aim of Receptor Pharmacology

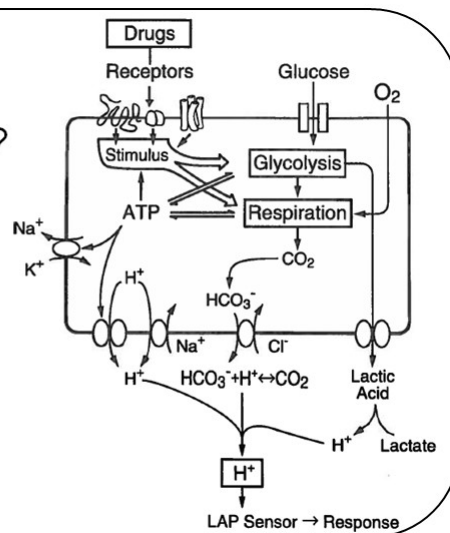
Pharmacologists should be telling medicinal chemists what their compounds **are**

not just what they do...

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Aim of Pharmacology in Drug Discovery

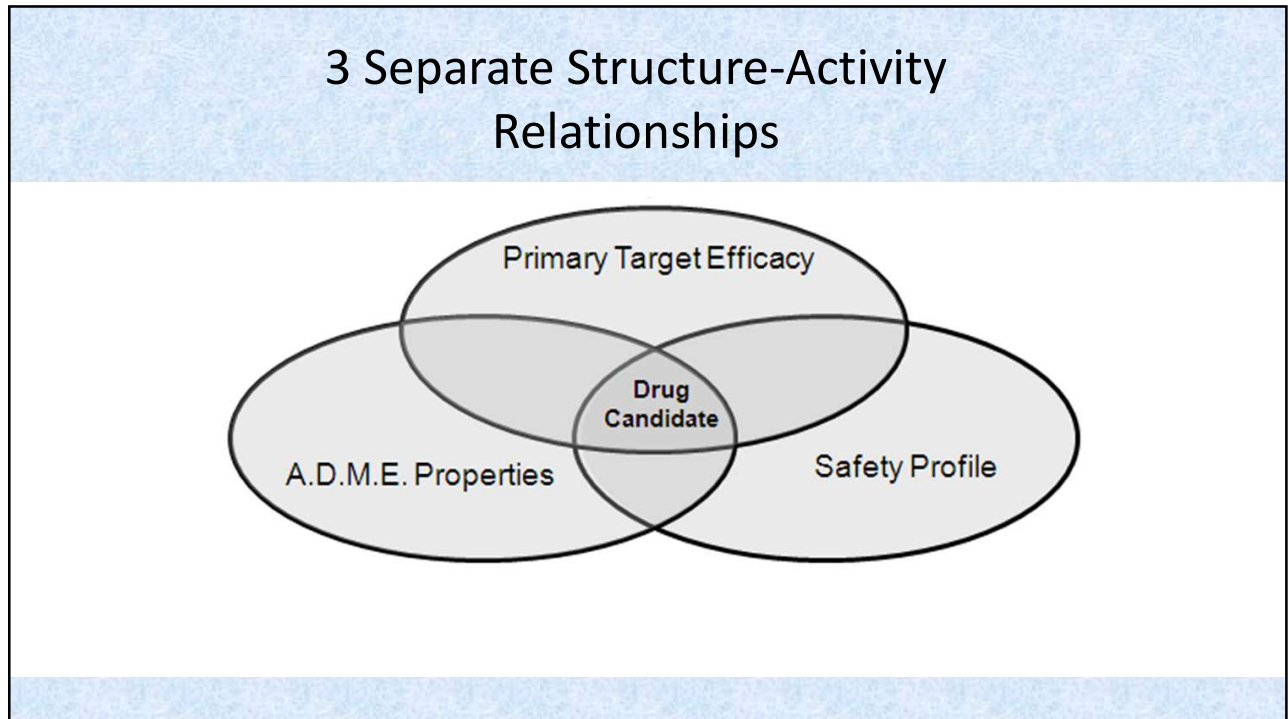
Recreate Physiology?



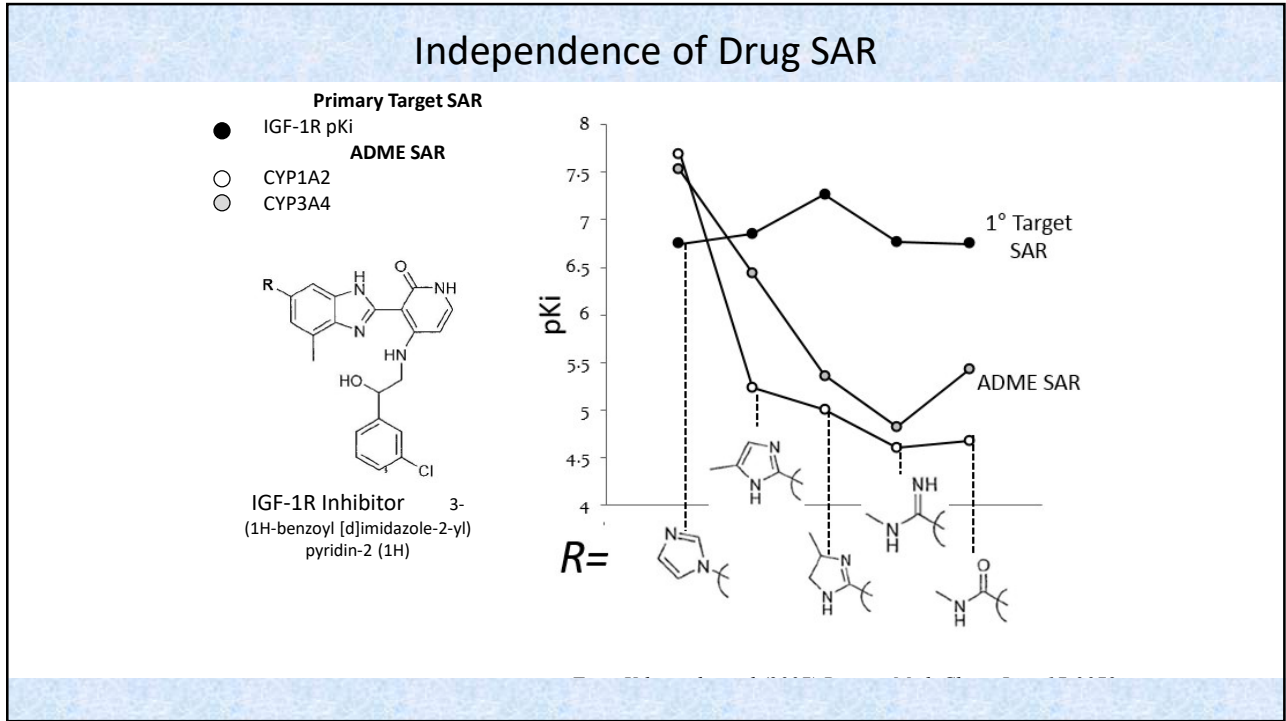
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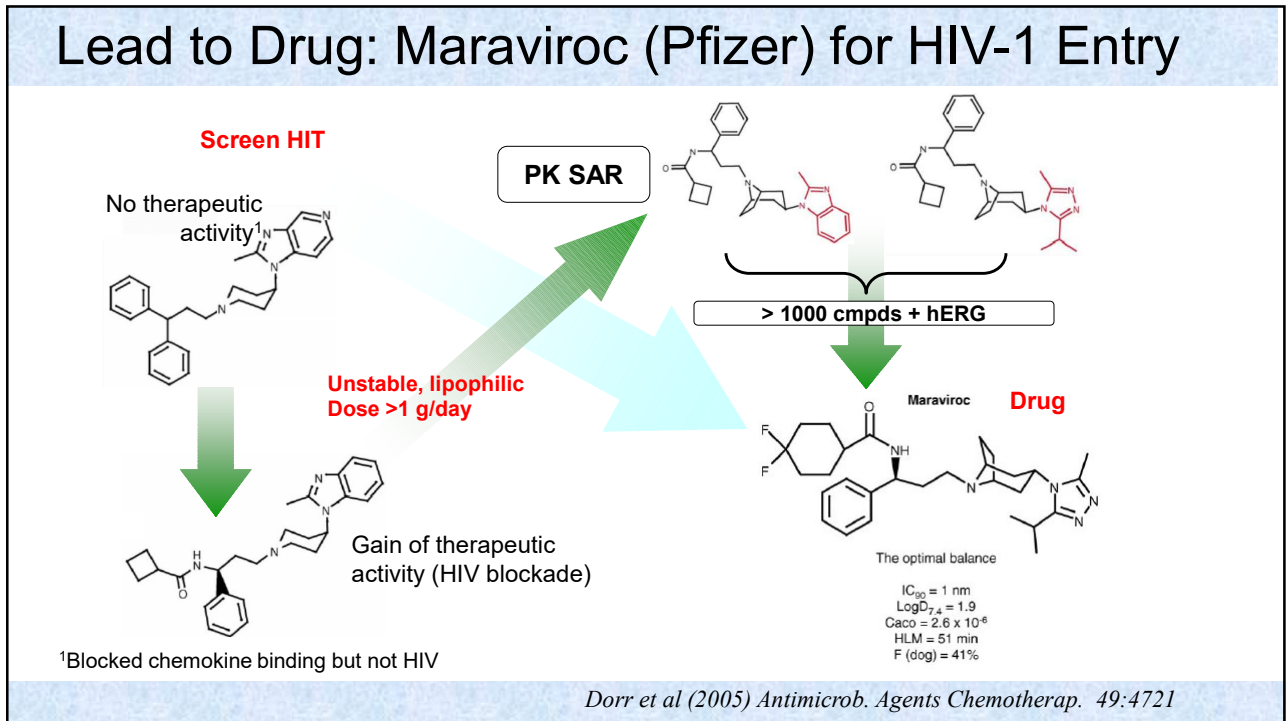
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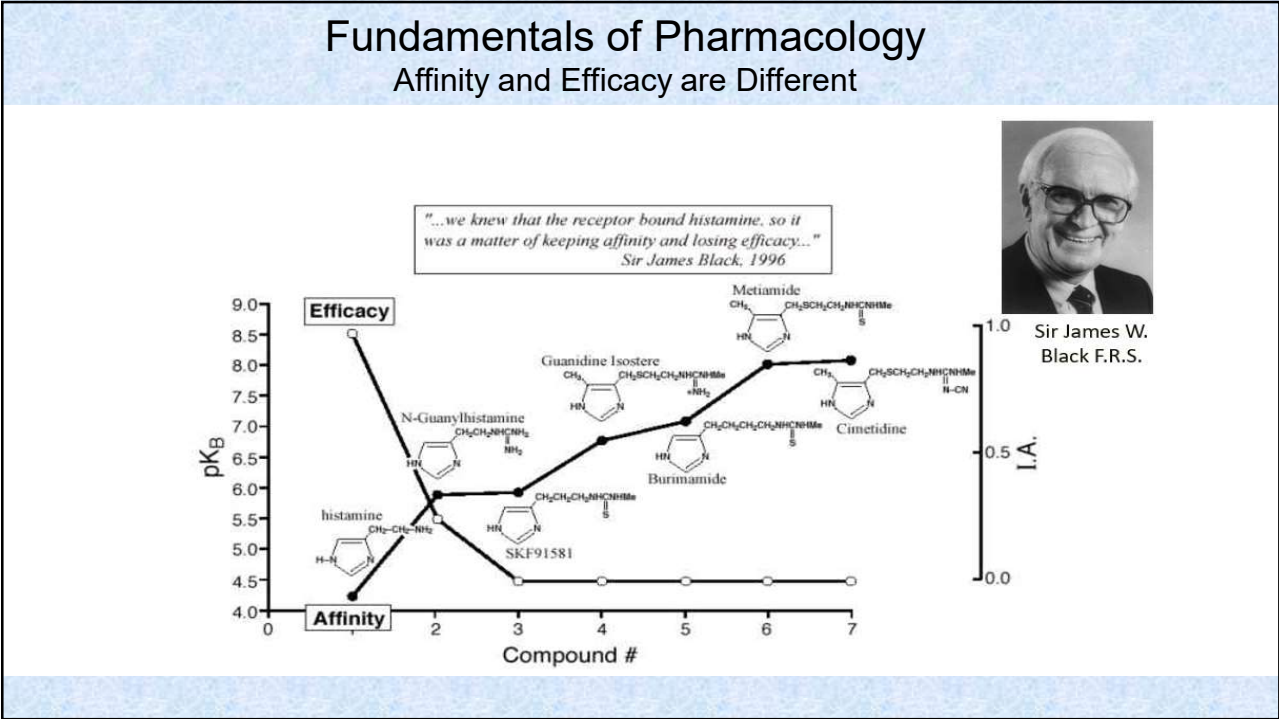
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Drug Discovery is Hard..... It's Really Hard.....

Success is the ability to go from one failure to another with no loss of enthusiasm.....

Winston Churchill
(1874-1965)

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50% Attrition Rate

- Pharmacology is Unique and Essential to Drug Discovery
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* Drug does what it is supposed to do in the disease indicated

29

50% Attrition Rate for New* Drug Candidates due to lack of Efficacy*

* Drug does what it is supposed to do in the disease indicated

30



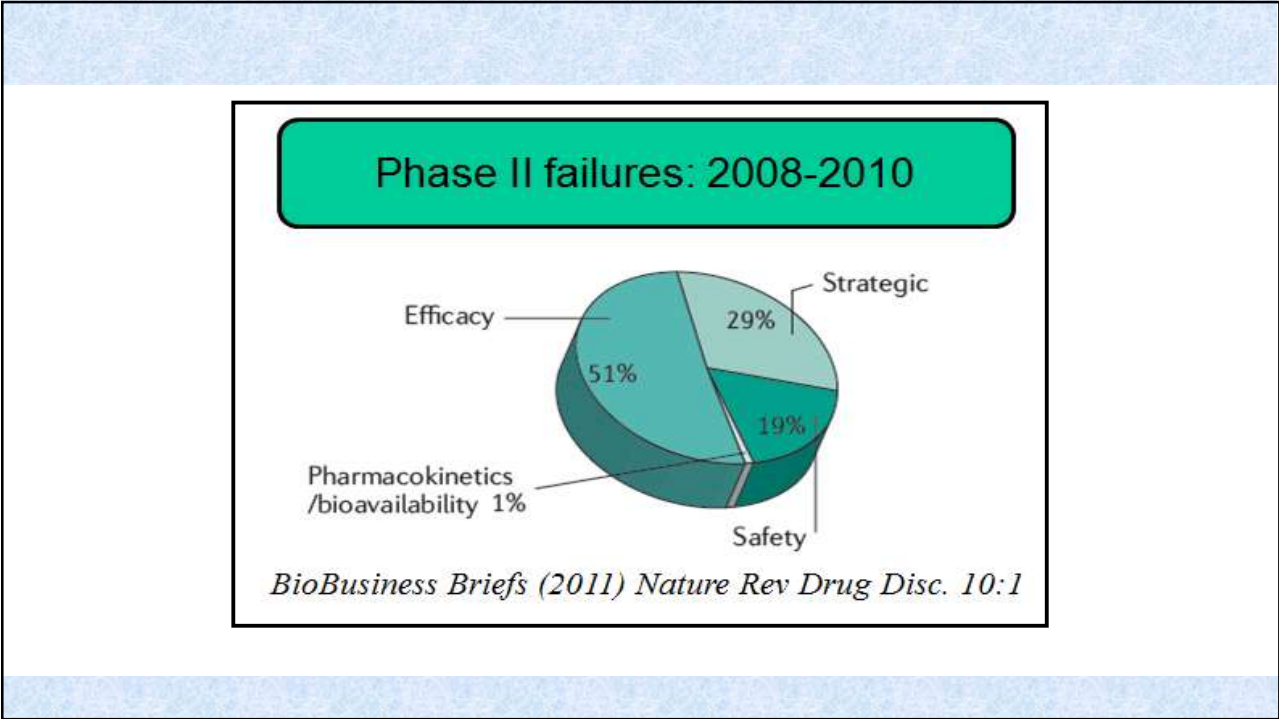
31

A man in a dark jacket and light-colored pants is walking away from the camera on a dirt path. The path is marked with a sign that reads "RIP Clinical Candidate". The background shows a hilly landscape with some buildings in the distance. A large white text box with a blue border is overlaid on the image, containing the following text:

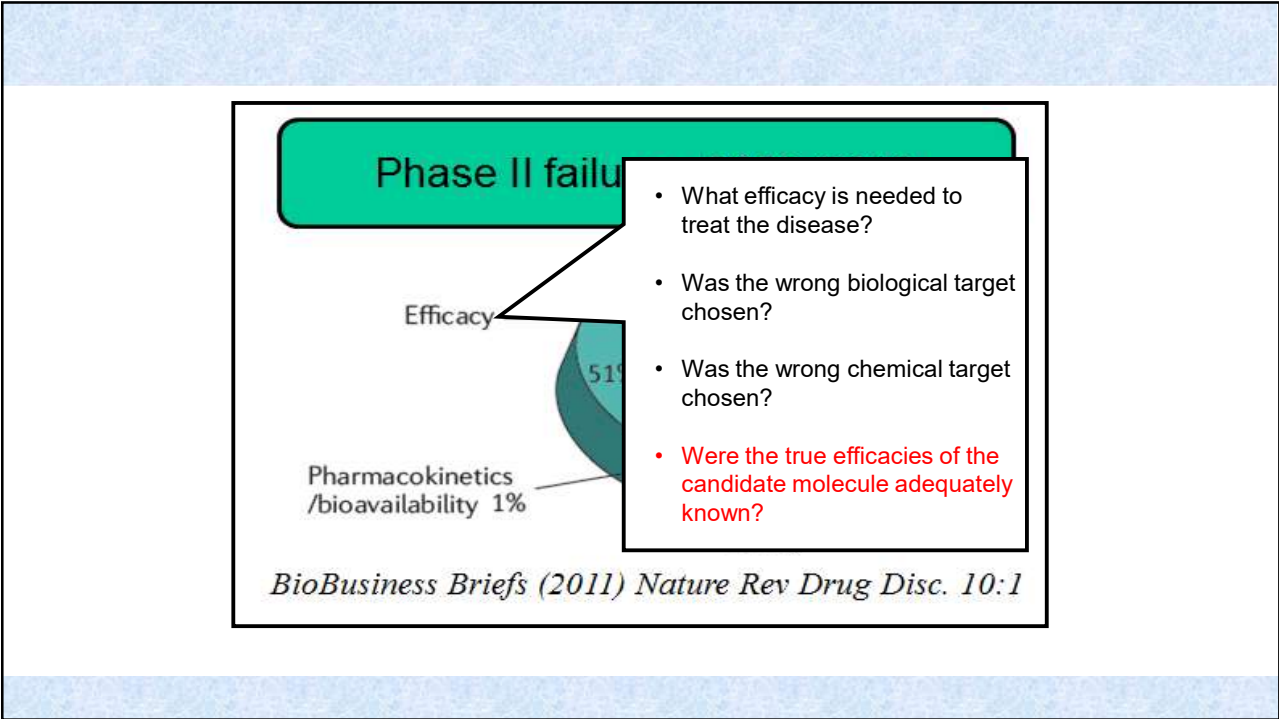
Why do we need to Know our Molecule?
(Pharmacological Examination of the properties of Molecules Advanced to Drug Candidate Status)

- Gain insight into disease state and what is required (of next molecule)
- Avoid pitfalls and not follow failed candidates with another copy of the same thing

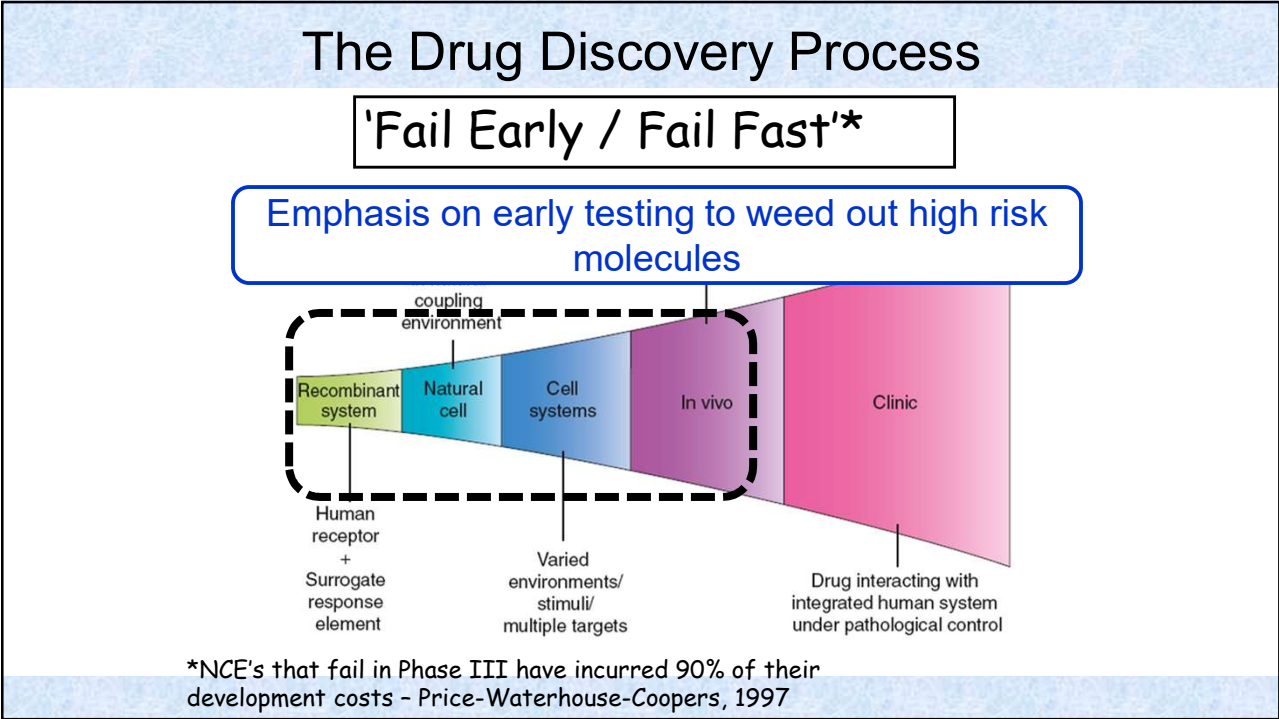
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- Pharmacology is Unique and Essential to Drug Discovery
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Two Fundamental Properties of All Assays

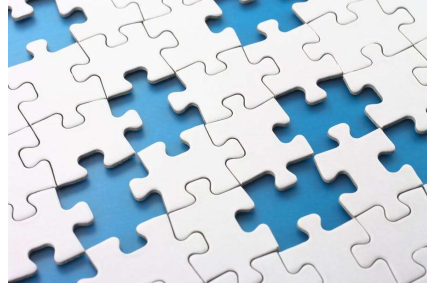
Sensitivity

What is the lowest level of signal that the assay can detect?



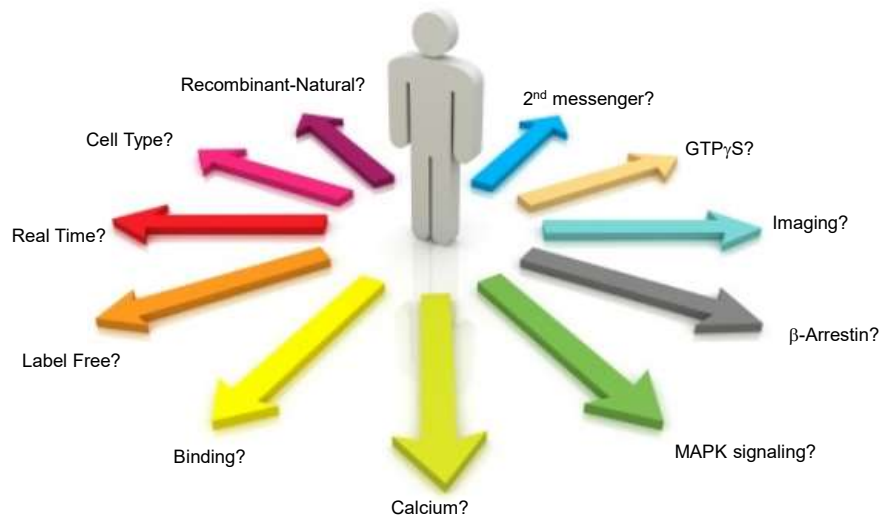
Comprehensiveness

Are all the components present in the assay to correctly reflect drug activity?



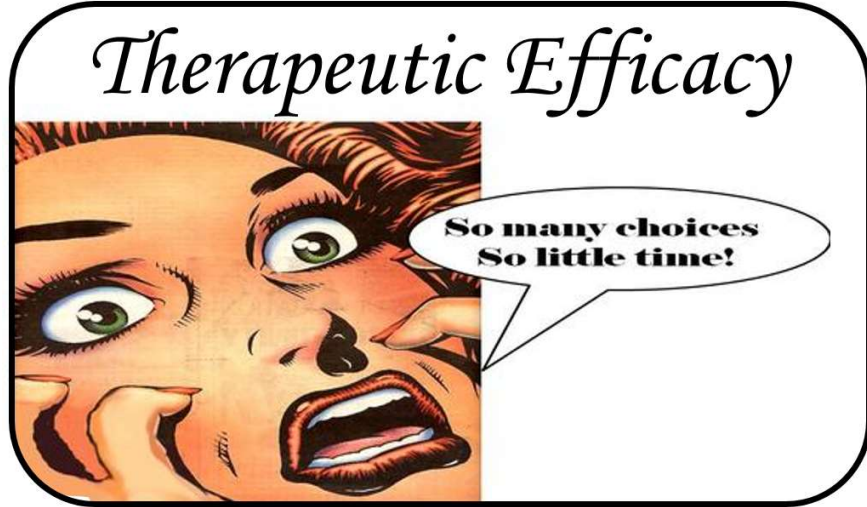
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Assay Technologies Explode.....



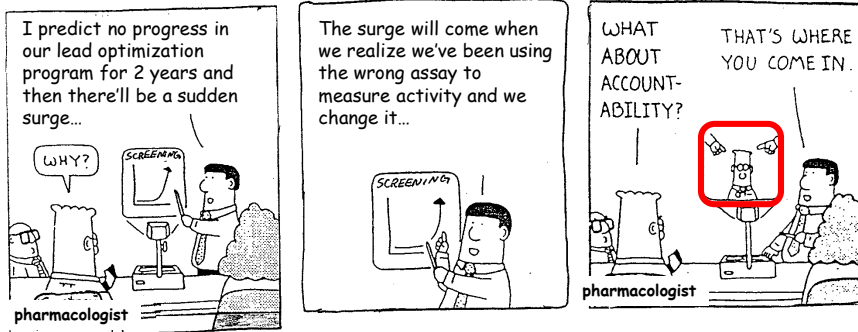
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Assay Technologies Explode.....



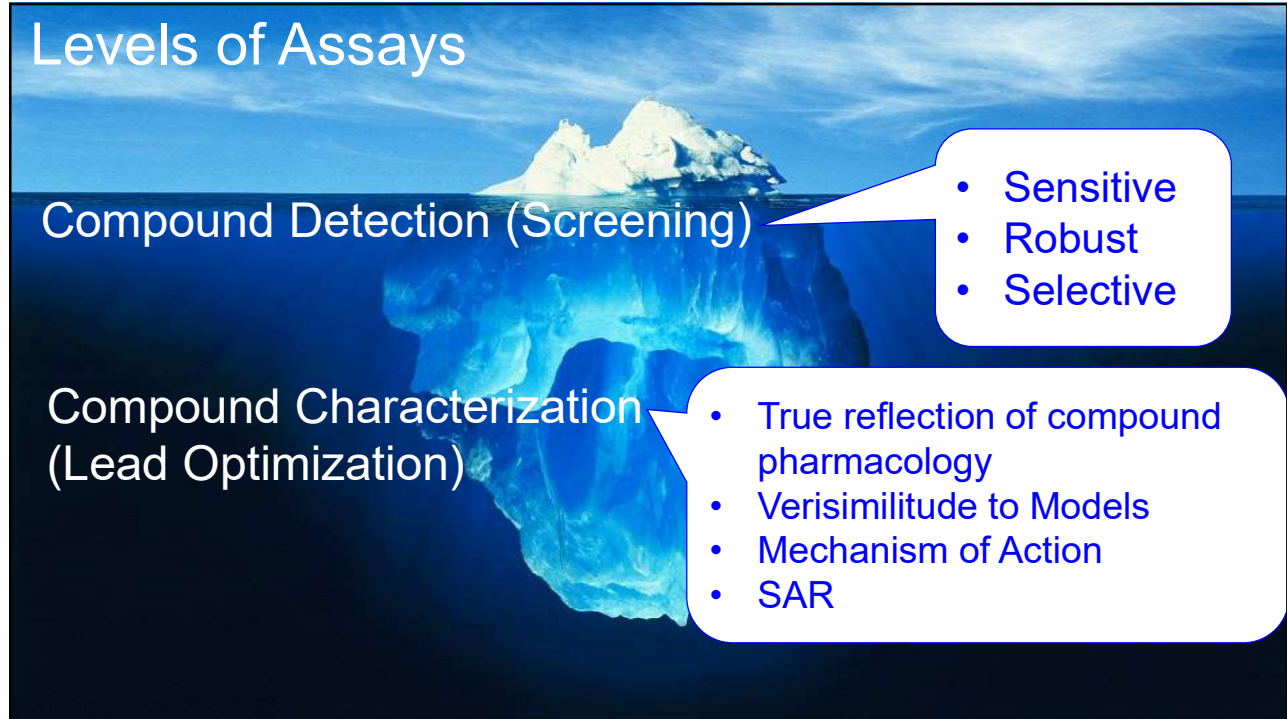
39

Pharmacology's Responsibility to use the 'Right' Assay



40

Levels of Assays



Compound Detection (Screening)

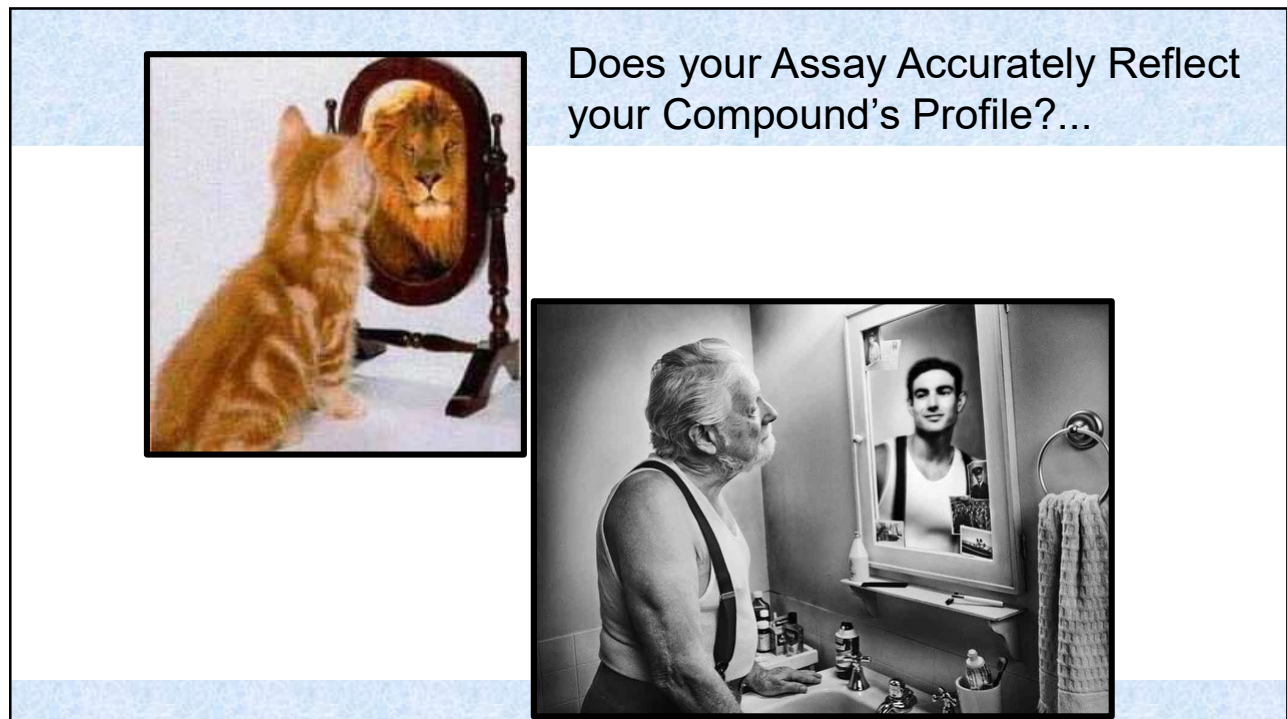
- Sensitive
- Robust
- Selective

Compound Characterization (Lead Optimization)

- True reflection of compound pharmacology
- Verisimilitude to Models
- Mechanism of Action
- SAR

41

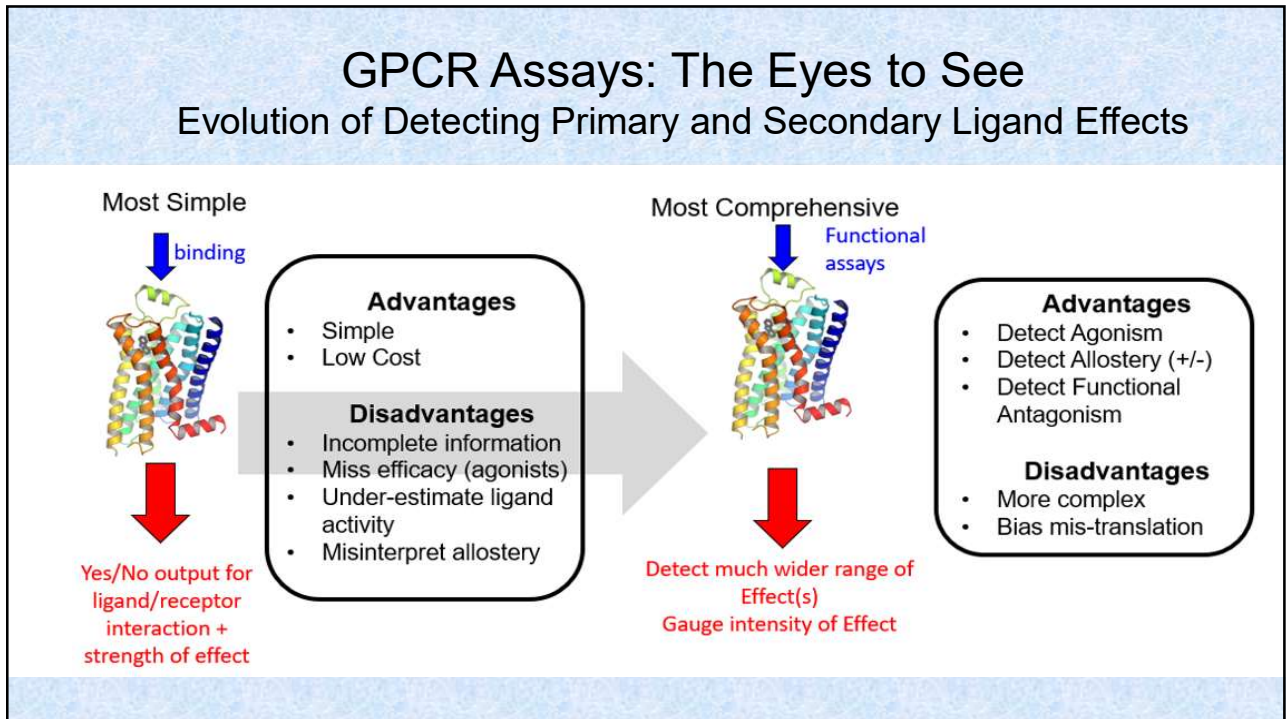
Does your Assay Accurately Reflect your Compound's Profile?...



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- Pharmacology is Unique and Essential to Drug Discovery
- The Pharmacology / Med Chem Interface
- Drug Discovery: State of the Art
- Tools of the Trade: Pharmacologic Assays
- **Tools of the Trade: Biological Drug Targets**
- ‘Drugging’ Targets :The Art of Finding Molecules
- Applying the Tools: How do Drugs Work?
- What is Drug Efficacy?
- How Do Drugs Interact with Targets?
- In Vivo Testing and Drug Development

* Currently Industry and Academia pursue \approx 240-280 gene targets *from Hopkins and Groom (2002) Nature Rev. Drug Disc.1:727*

45

Target Selection for Drug Discovery

Human Genome \approx 30,000 genes

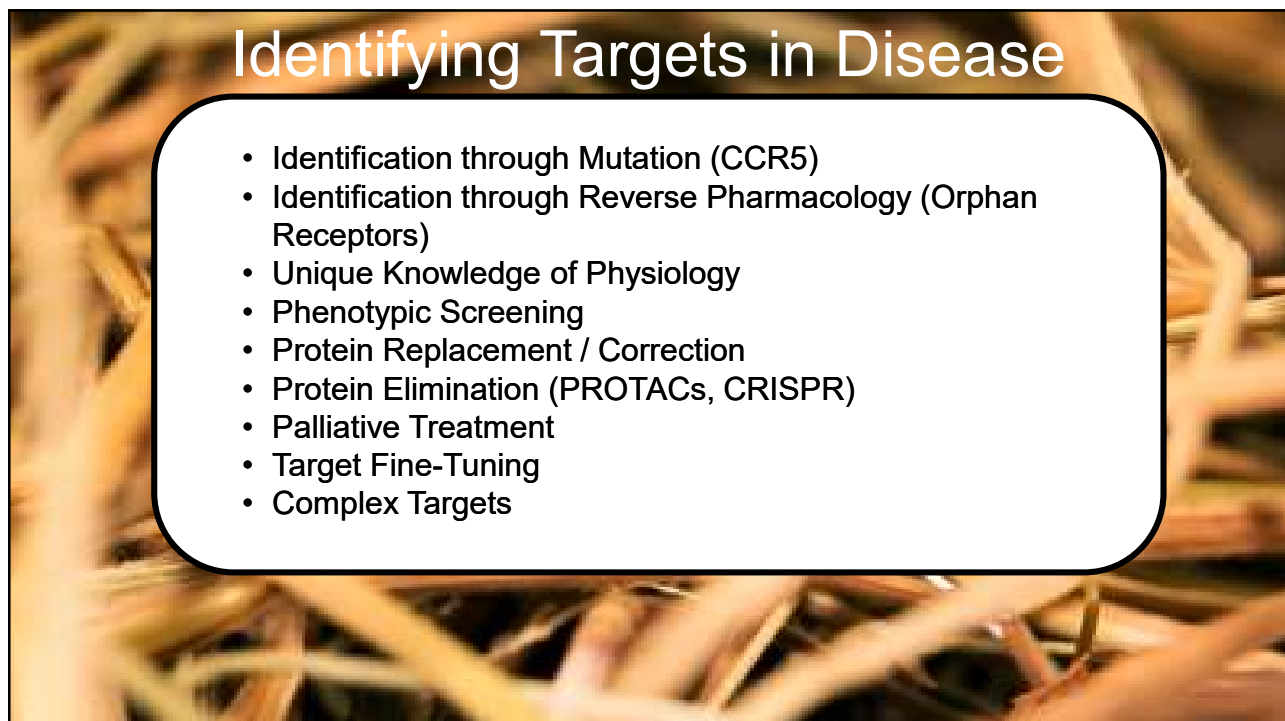
Druggable Genome \approx 3,000 genes **Drug Targets \approx 600-1500 genes*** **Disease-modifying genes \approx 3,000 genes**

* Currently Industry and Academia pursue \approx 240-280 gene targets *from Hopkins and Groom (2002) Nature Rev. Drug Disc.1:727*

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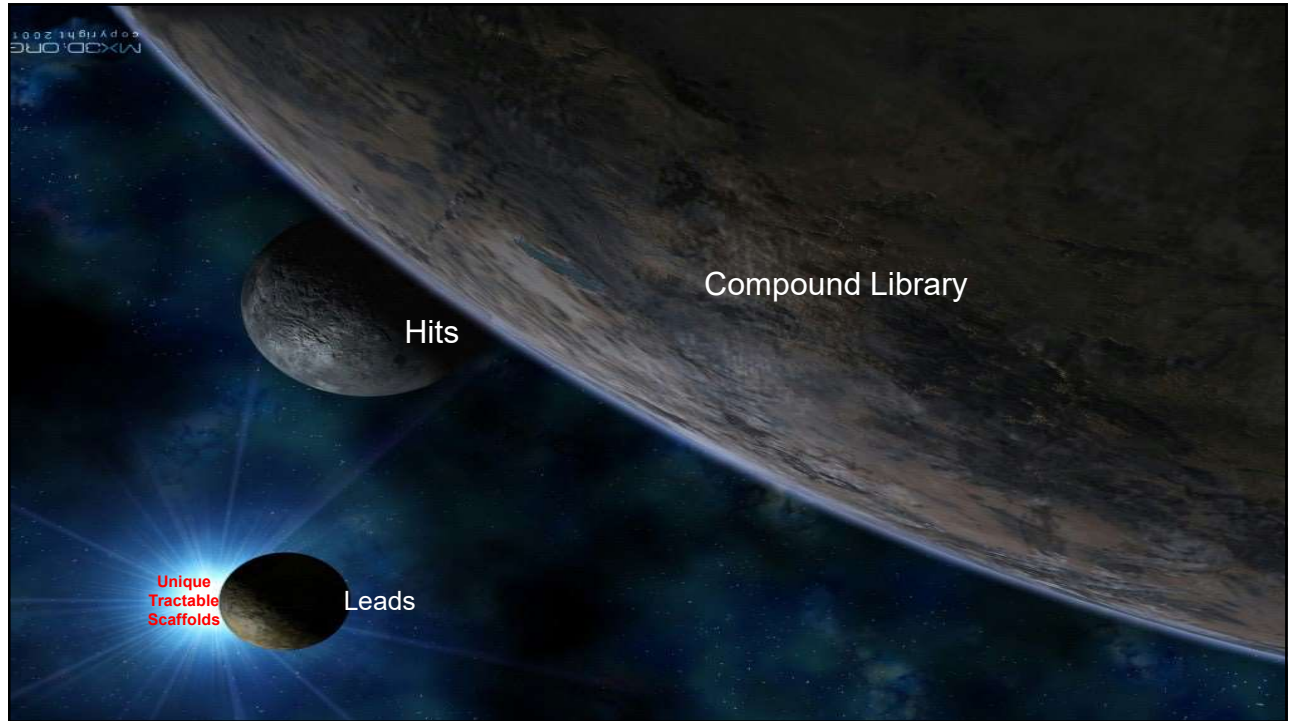
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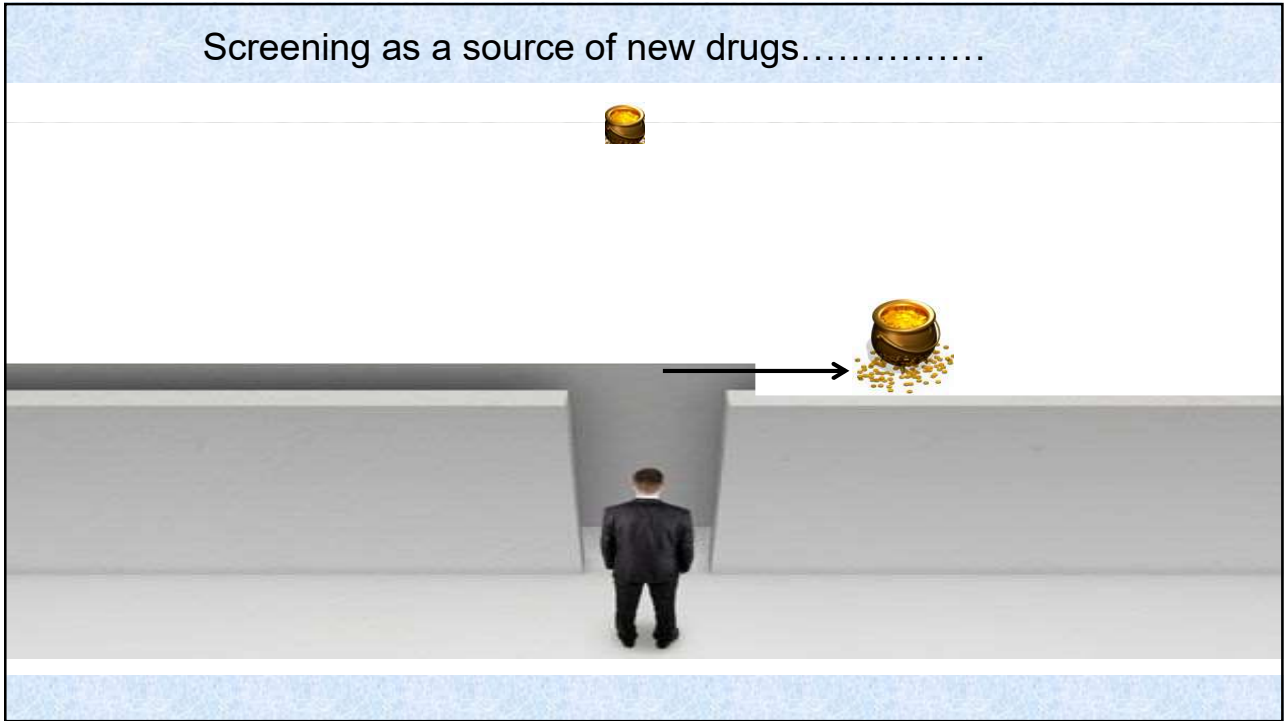
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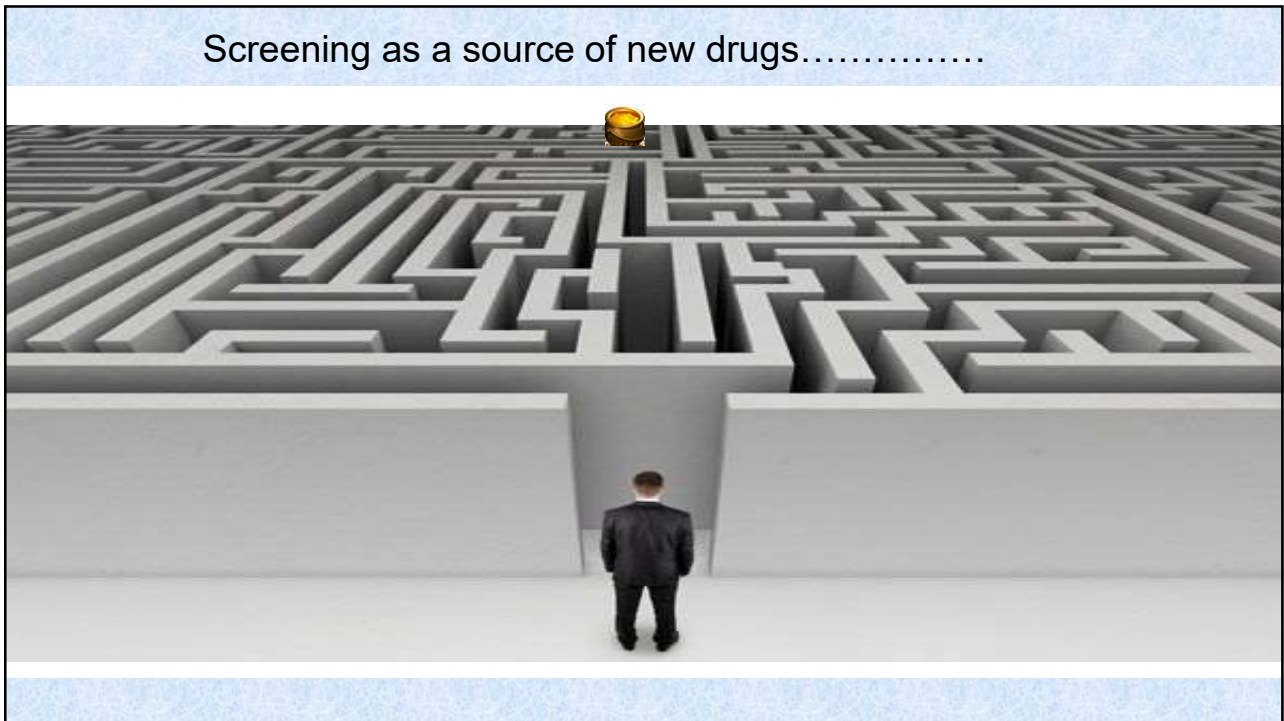
51



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Target 'Drugability'

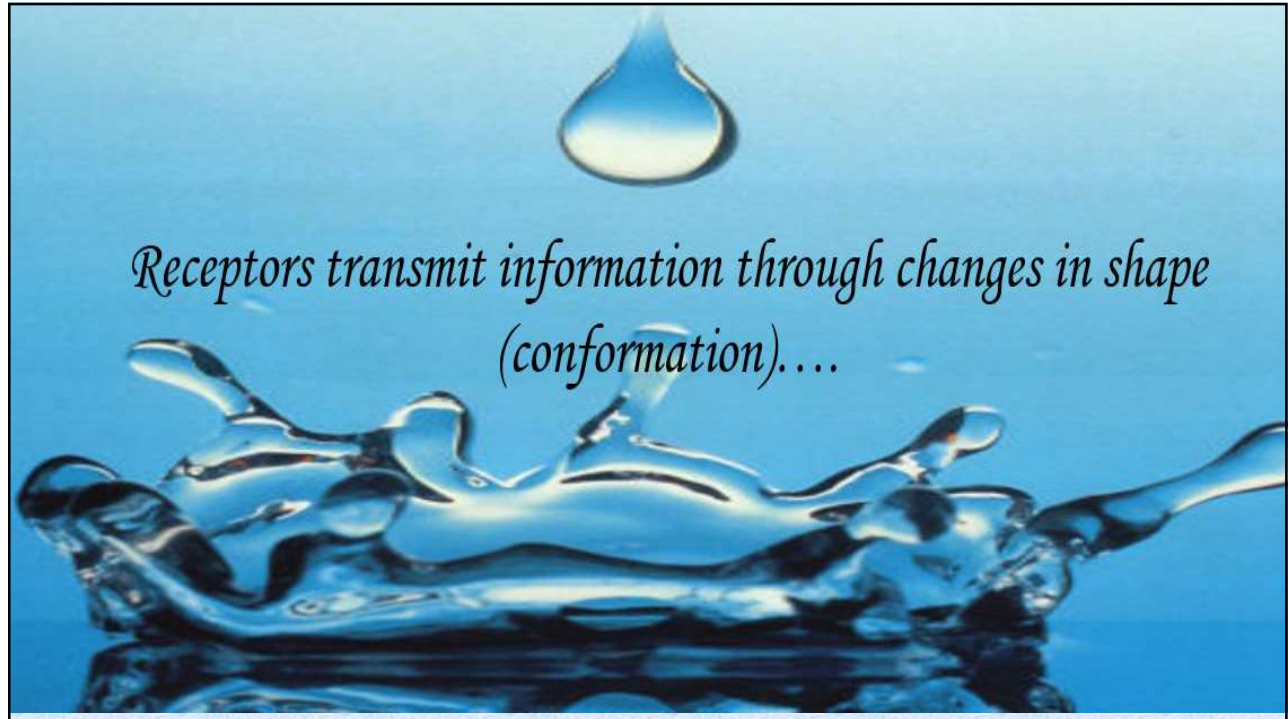
(Finding Ligands for Drug Targets)

- 'Conventional' Highthroughput Screening
- Fragment-based Screening
- Phenotypic Screening
- Utilization of Target Crystal Structures
- Docking and Virtual Screening
- Orphan (Constitutive) Screening)

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Characterizing Agonists Molecular Mechanism of Efficacy

Conformational Selection : Drugs enter the
Conformational Cafeteria

Native Ensemble

Add ligand

Liganded Ensemble



Henri Louis
Le Chatelier
(1815-1873)

Le Chatelier's Principle
'If a dynamic equilibrium is disturbed by changing the conditions, the position of the equilibrium moves to counteract the change'


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Fundamentals of Pharmacology

Value of Predictive Data


What We See
(in any given experiment)

Descriptive Data
(What we Observe)



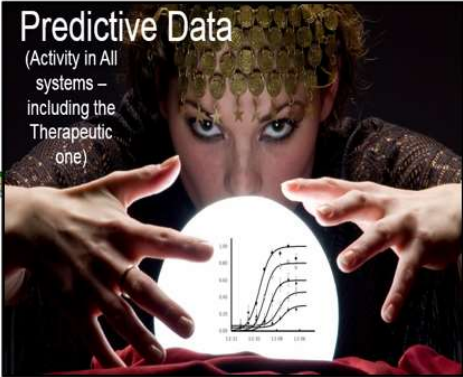
System Independent
Pharmacological Parameters
(τ , K_d , α , β , K_i)

Derived from Mathematical
Models



What We Predict
(will happen in all experiments)

Predictive Data
(Activity in All systems – including the Therapeutic one)




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Fundamentals of Pharmacology
Determining Mechanism of Action

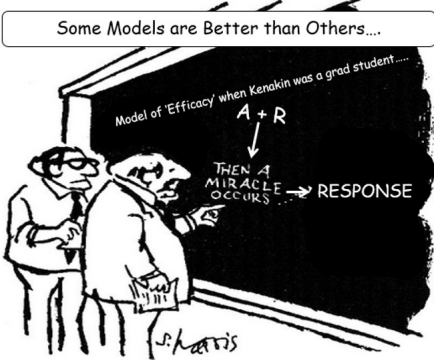
We Link What We See as Mechanism Through Models



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Fundamentals of Pharmacology
Comparing Data to Models

Some Models are Better than Others....



"I think you should be more explicit here in step two."

The best models have rules ...
(mathematical models)



'What is it that breathes fire into the equations and makes a universe for them to describe?...'

Stephen W. Hawking (1991)

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ABOUT TO BEGIN!**

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in the questions window!



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Research to Diverse Audiences**

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Closes as Another Opens**

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**Revealing Mona Lisa's Secrets Through
Advanced Analytical Chemistry**

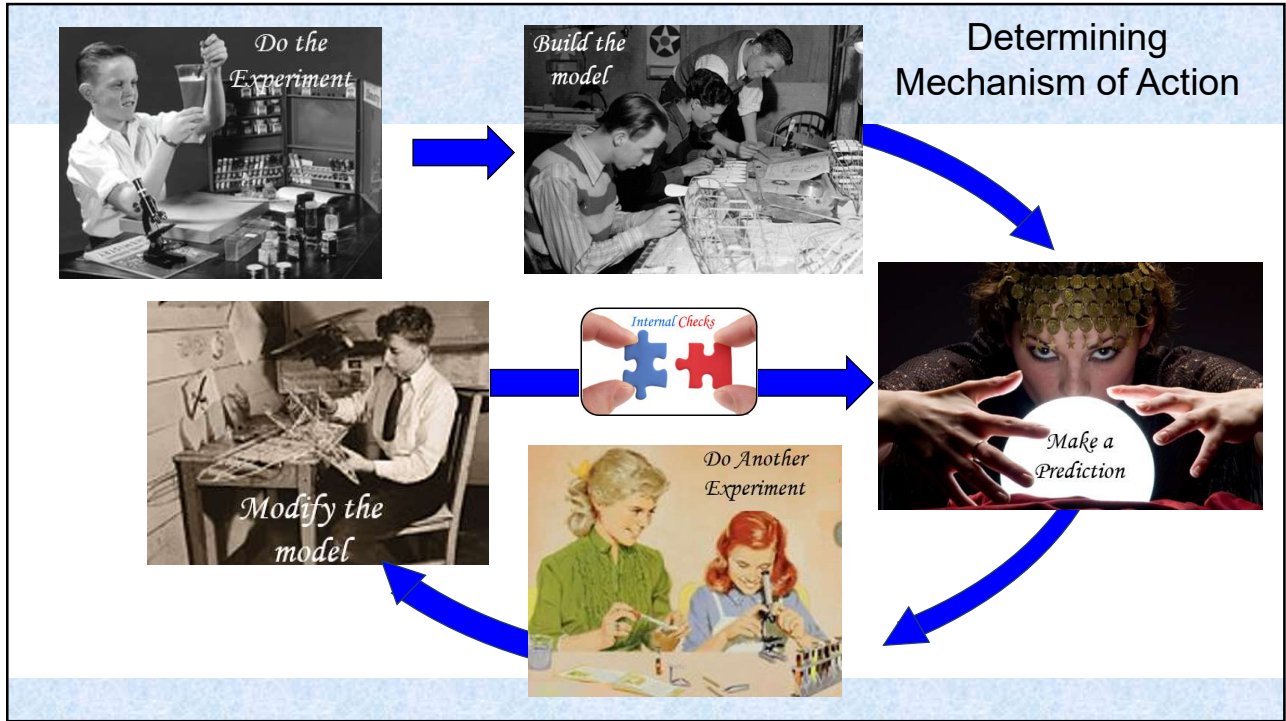
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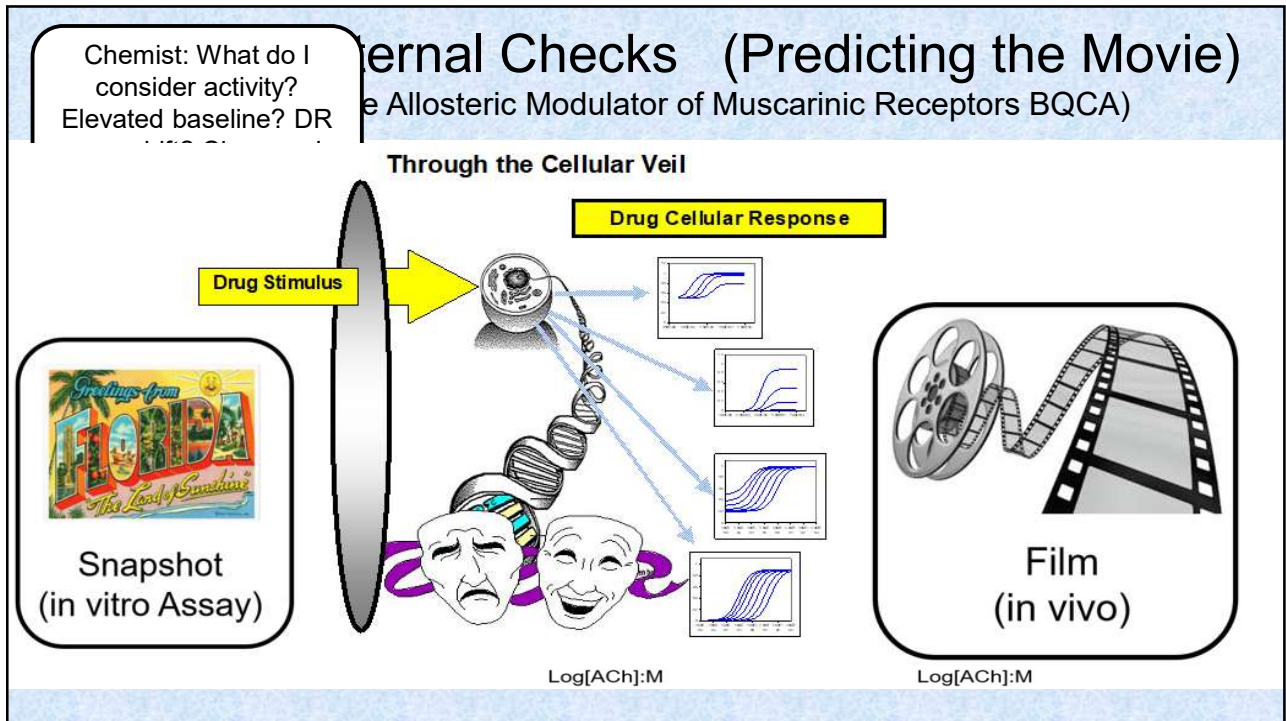
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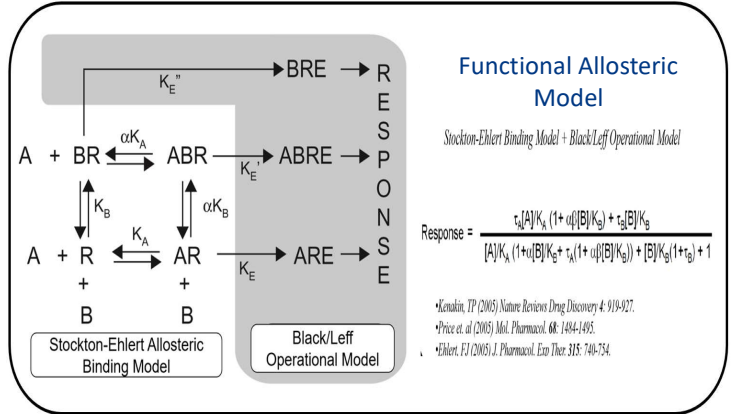
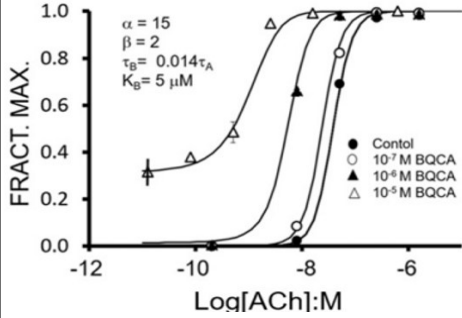
63



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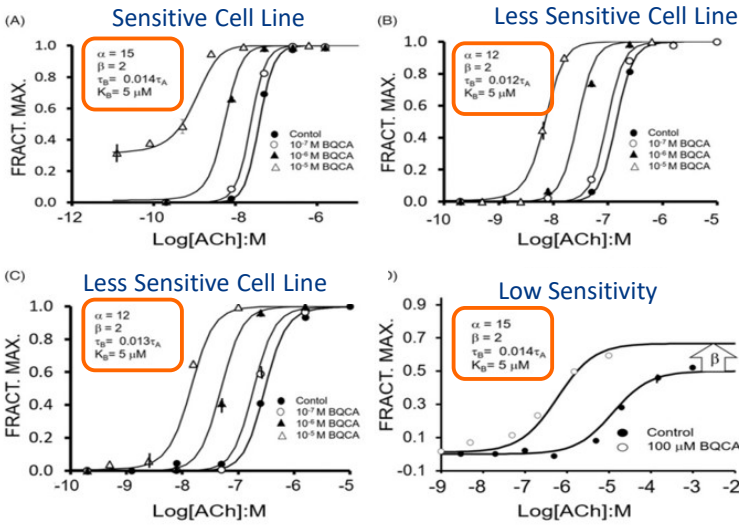
Know Your Molecule (BQCA Allosteric potentiation)

Effects of a PAM-Agonist on Acetylcholine Response

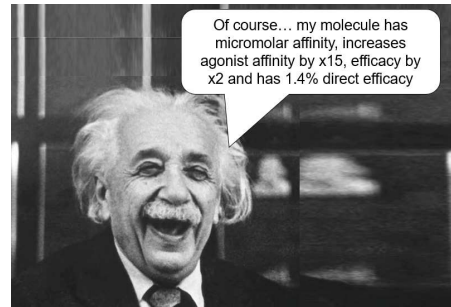


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Know Your Molecule (BQCA Allosteric potentiation)



Bdioui et al (2019) J Recept Signal Transd. 39: 106-113

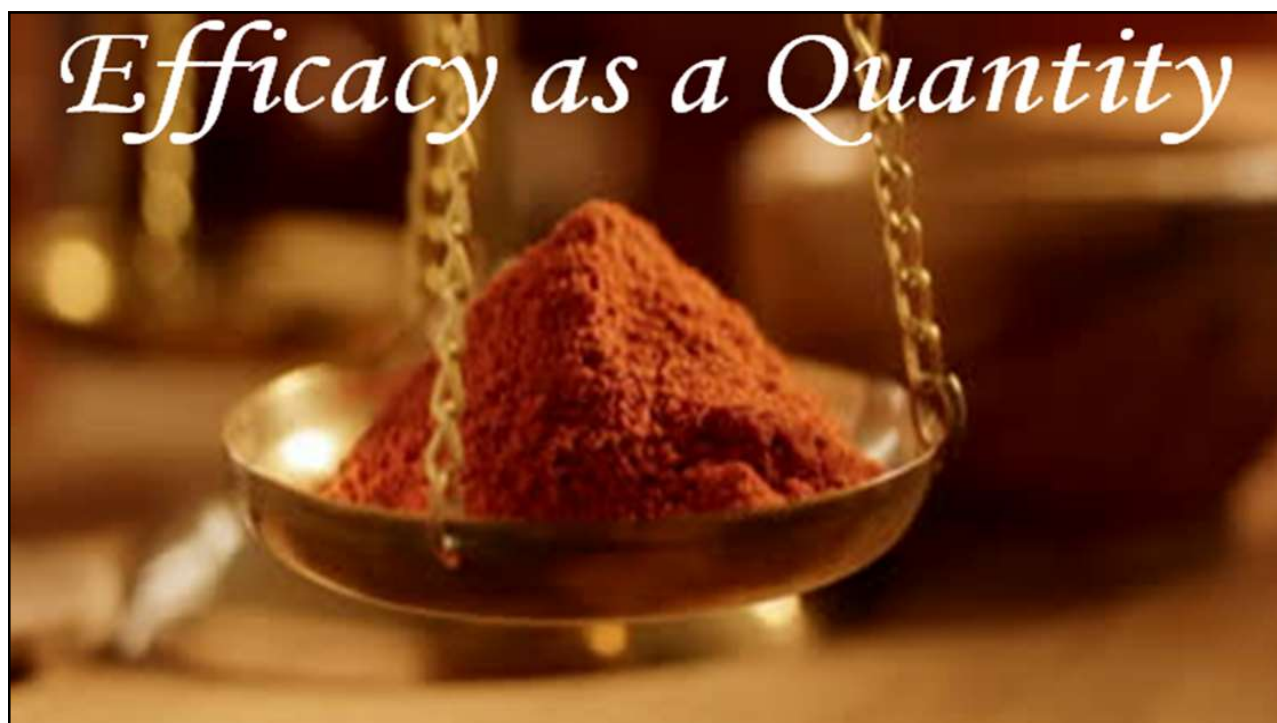


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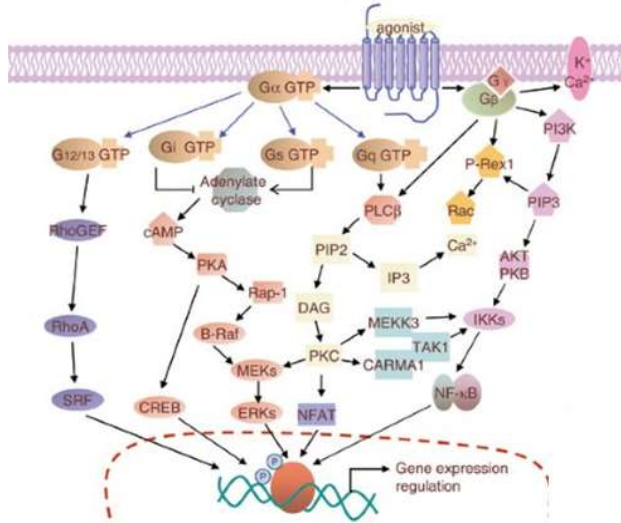
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The Multiplicity of Efficacy



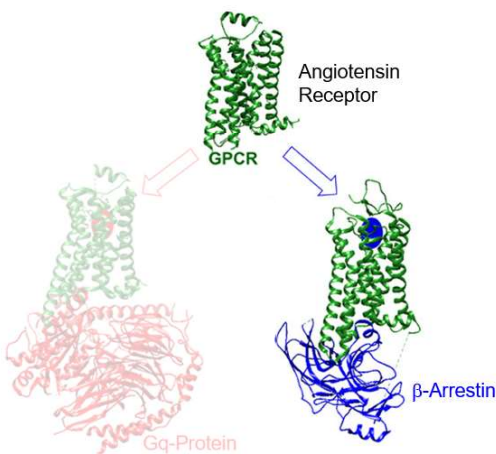
GPCRs are Pleiotropically Coupled to many Signaling Pathways in Cells

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Fundamentals of Pharmacology

Efficacy: Do All Drugs Activate Pathways Uniformly?

Not All Agonists Activate All Pathways Equally



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TRENDS in Pharmacological Sciences
INCLUDING TOXICOLOGICAL SCIENCES

7 Transmembrane Receptor Signaling

Terry Kenakin, Robert Lefkowitz, Michel Bouvier, Jonathan Violin, Genevieve Oligny-Longpre

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7TM Receptor activation of cyclic AMP-dependent PKA

Rules of β -arrestin-dependent Recruitment of Src Kinases in GPCR Signaling

7TM Receptor activation of PLC

Collateral Efficacy Imposed on Agonists by Allosteric Modulators

Natural Signaling

Angiotensin II

Fraction Maximum vs Log [Angiotensin II]

G-protein and β -Arrestin

from Violin et al (2003) Proc. Natl. Acad. Sci. 100: 10782

Attenuation of GPCR signaling

β -Arrestin Signatures

7TM Receptor Signaling

7TM Receptor as Allosteric Protein

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Collateral Efficacy Imposed on Agonists by Allosteric Modulators

Biased Signaling

TRV120027

Fraction Maximum vs Log [TRV120027]

β -Arrestin and G-protein

from Violin et al (2003) Proc. Natl. Acad. Sci. 100: 10782

Attenuation of GPCR signaling

β -Arrestin Signatures

7TM Receptor Signaling

7TM Receptor as Allosteric Protein

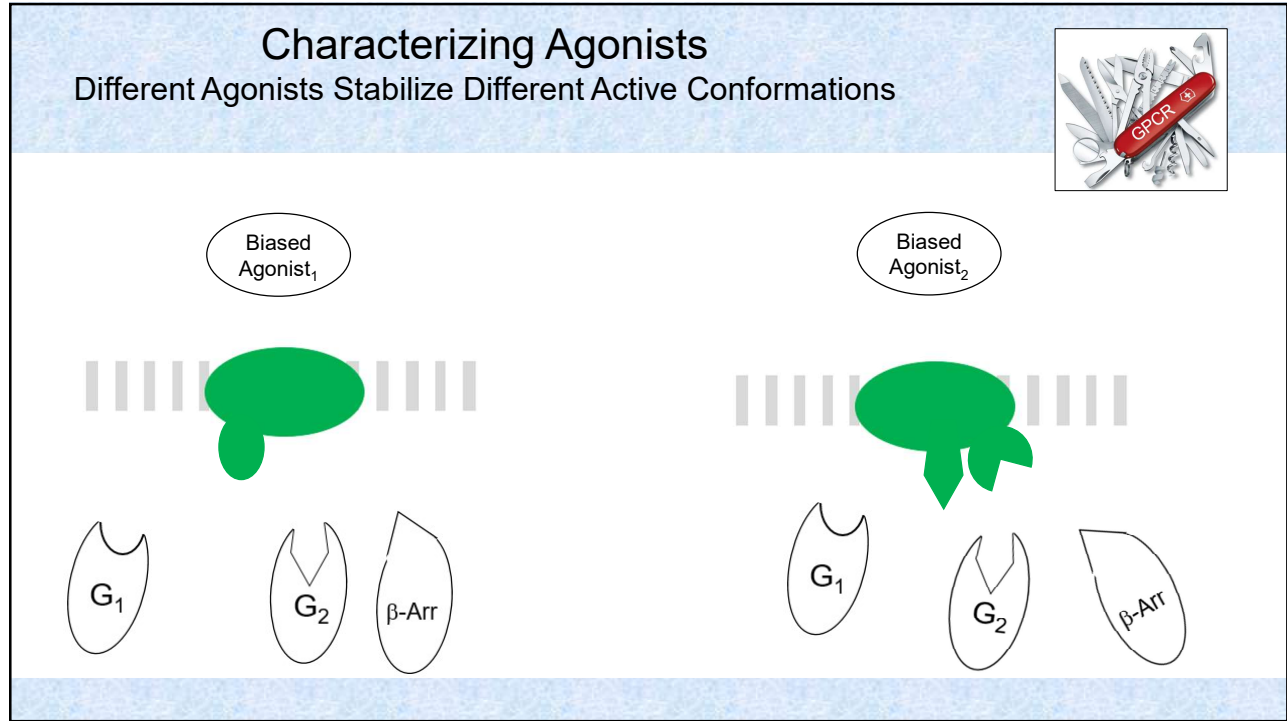
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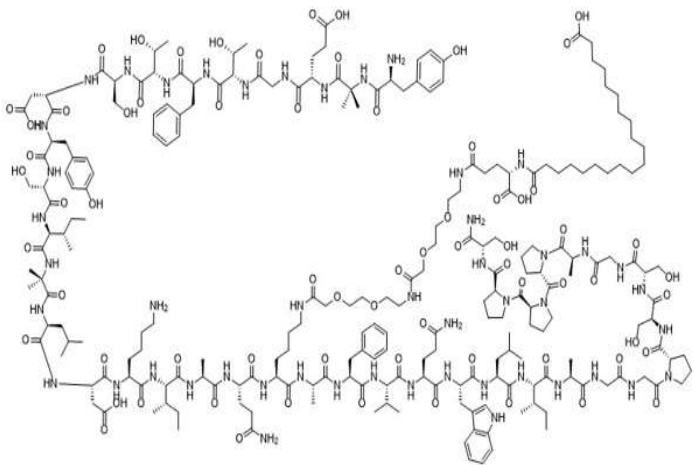
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Signaling Bias

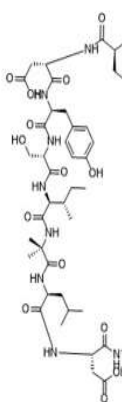
Tirzepatide: GLP-1 Agonist Biased away from β -arrestin



- Willard et al (2020) Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight*, 5, e140532. <https://doi.org/10.1172/jci>
- Yuliantie et al (2020) Pharmacological characterization of mono-, dual- and tri-peptidic agonists at GIP and GLP-1 receptors *Biochem. Pharmacol.* 177:114001

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Signaling Bias



Should an agonist program seek bias?

No need....

Bias will seek the agonist program'

GLP-1
532.
/
i-
4001

76



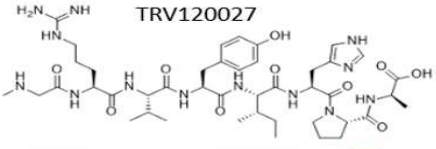
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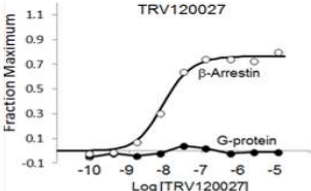
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Drugs Can Have Many Faces

Drug Nomenclature Becomes a Problem in Onomastics



TRV120027

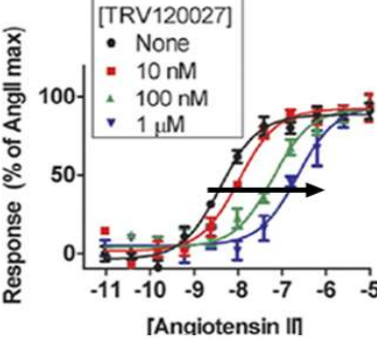


TRV120027

β-Arrestin

G-protein

β-Arrestin
TRV120027
is an
AGONIST



[TRV120027]

- None
- 10 nM
- ▲ 100 nM
- ▼ 1 μM

Response (% of AngII max)

[Angiotensin II]

Gq-Protein:
TRV120027 is an
ANTAGONIST

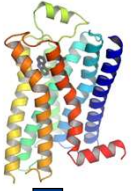
Violin et al (2003) Proc Natl Acad Sci USA 100:10782

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The Evolution of Pharmacologic Agonism

First Historical Model

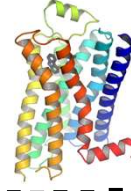
agonism



Monotonic Cellular Signal varying only in Strength

1970's


agonism



Pleiotropic Signal (Efficacy has 'Quality')

1990's

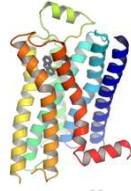
agonism



Agonists can 'Bias' Cell Signals

Present Day

agonism



Different Cell Types

Cells can Modify Bias (Problems in Translation)

80

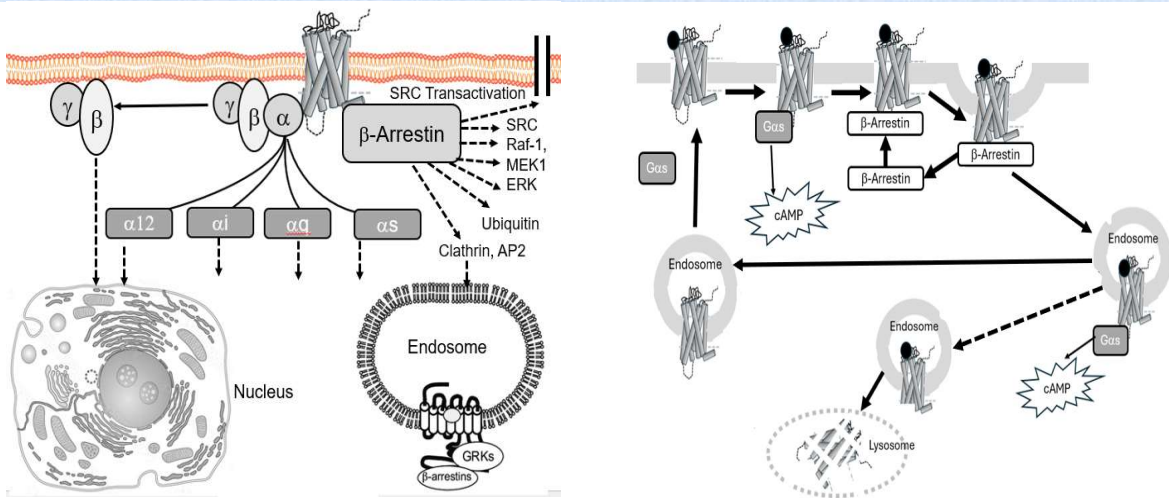
What is Drug Efficacy? (Beyond Second Messengers)



GPCRs:
Physiology's 'Swiss Army Knife' for the control of Cellular Function

81


What is Drug Efficacy? (Beyond Second Messengers)



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What is Drug Efficacy?

Efficacy...
just because
you don't see
it does not
mean it's not
there...



miss
the
lar

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Efficacy defined as the ability of molecule to make the target (receptor) change its' behavior towards it's host (cell)



*Screening
Hits*

EFFICACIES

ASSAYS

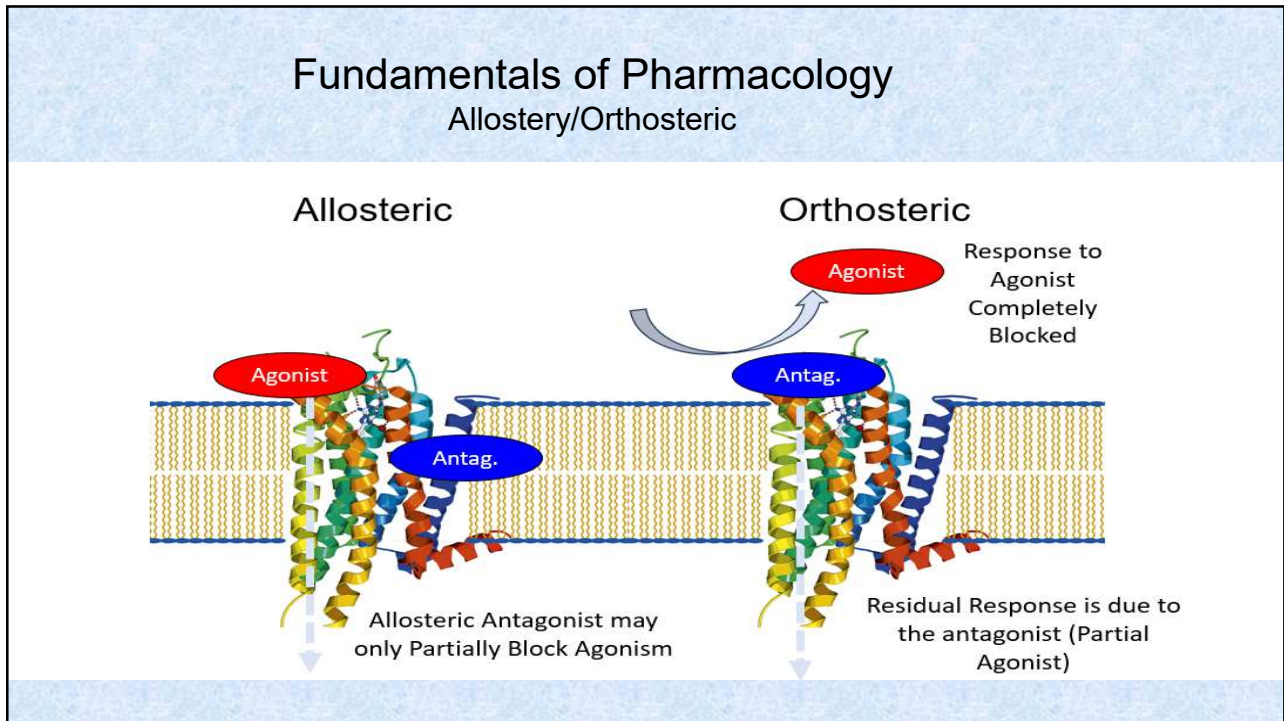
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Allosteric Antagonist may only Partially Block Agonism

to the antagonist (Partial Agonist)

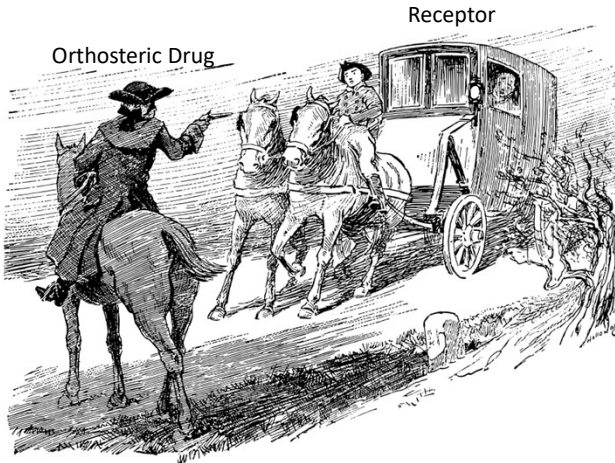
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Fundamentals of Pharmacology

Allo vs Ortho: Why is it important?



In vivo Orthosteric Drugs 'Hijack' the Receptor stopping Natural Signaling and Imparting their own Efficacy

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Fundamentals of Pharmacology

Allo vs Ortho: Why is it important?



In vivo Allosteric Drugs Partner with the Receptor: Resulting Efficacy is a mix of Natural and Allosteric

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Fundamentals of Pharmacology

Orthosteric and Allosteric Drugs are Apples and Oranges



Orthosteric Drugs

- Impart their Efficacy on the System
- Limitless effect (i.e. no saturation of effect)
- Duration of Action linked with Intensity of Action
- Effect identical for all physiologic agonists

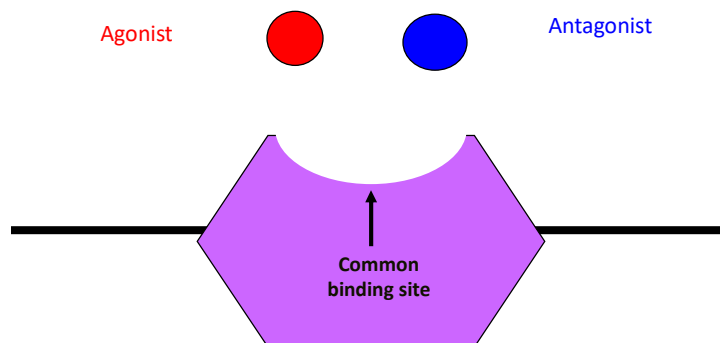


Allosteric Drugs

- Partner with natural system; result an amalgam of effects
- Effects could be 'probe dependent': not constant for all natural agonists
- Duration of Action not necessarily linked with Intensity of Action
- Limited effect: no possible overdose

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Orthosteric Interaction



The Drug with the highest Affinity and/or highest Concentration Wins!

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Receptor Allostery.....

Agonist



Batman

Bruce Wayne

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Methods to Demonstrate Target Engagement

Physical Interaction

- Binding
- Isothermal Titration Calorimetry
- Free Solution Analysis
- CETSA
- X-Ray Crystal Structures
- NMR

Functional Response

- Collateral Presence: Recombinant host cell Systems
- Multiple Pathway Analysis
- Biosensors
- Label Free
- Knockouts

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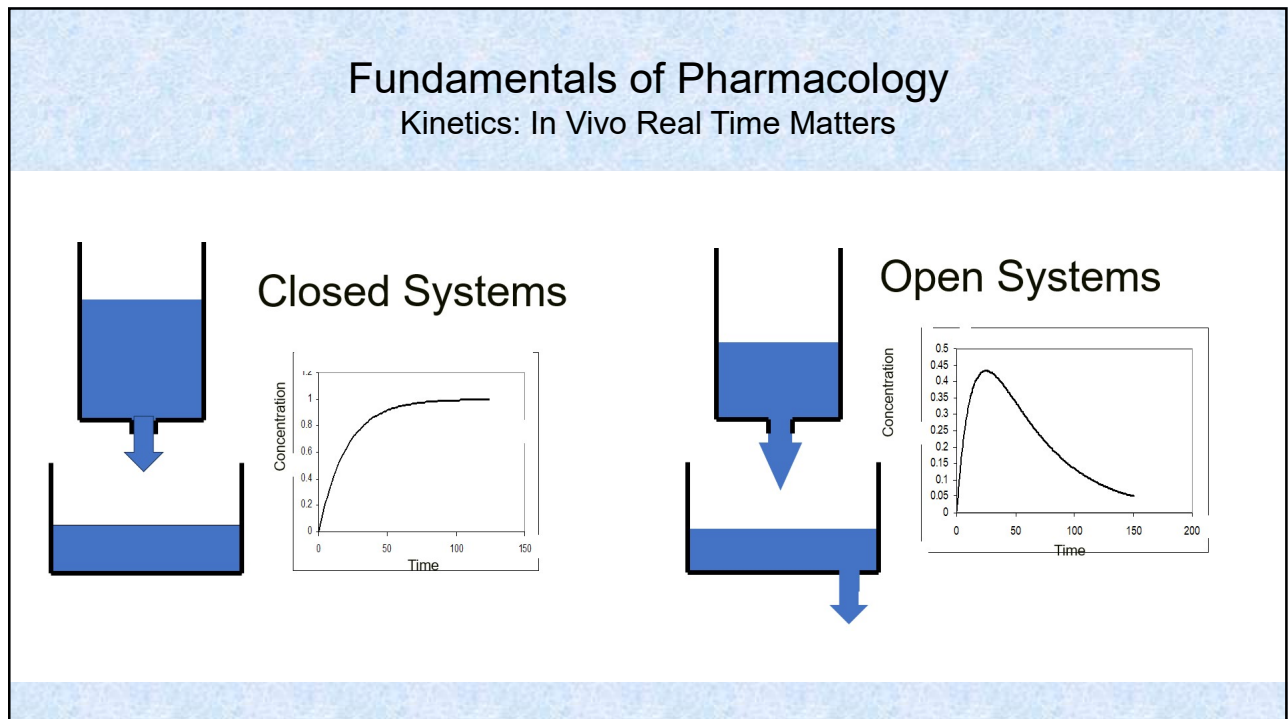
A Test Compound Goes In Vivo

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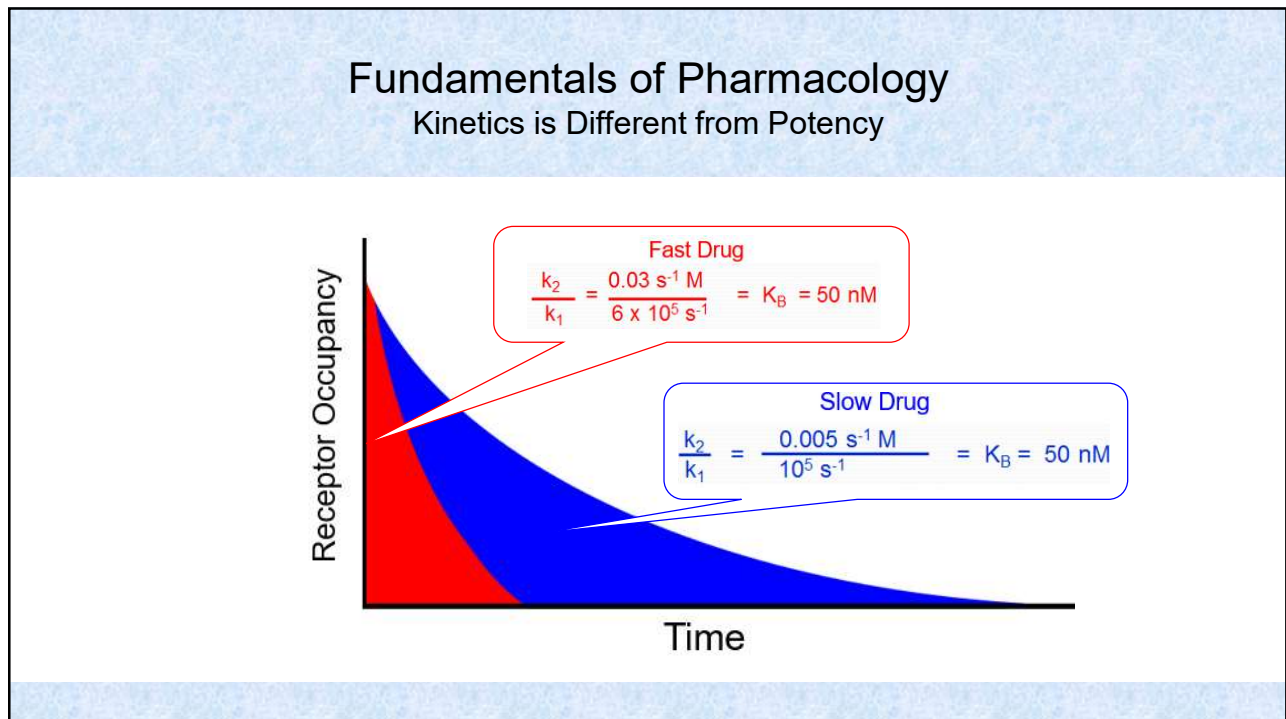
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Drug-like Properties for Therapeutic Influence.....



Every biological Drug Target

- Receptors, Enzymes, ion Channels, Transporters, Nuclear Receptors

For every Therapeutic Indication

- Cardiovascular, CNS, GI, Immunology, Oncology, Endocrinology

MUST be able to :

- Enter the Body
- Distribute to the Therapeutic target organ
- Remain there long enough to cause response
- Cause NO HARM

Every biological Drug Target

- Receptors, Enzymes, ion Channels, Transporters, Nuclear Receptors

For every Therapeutic Indication

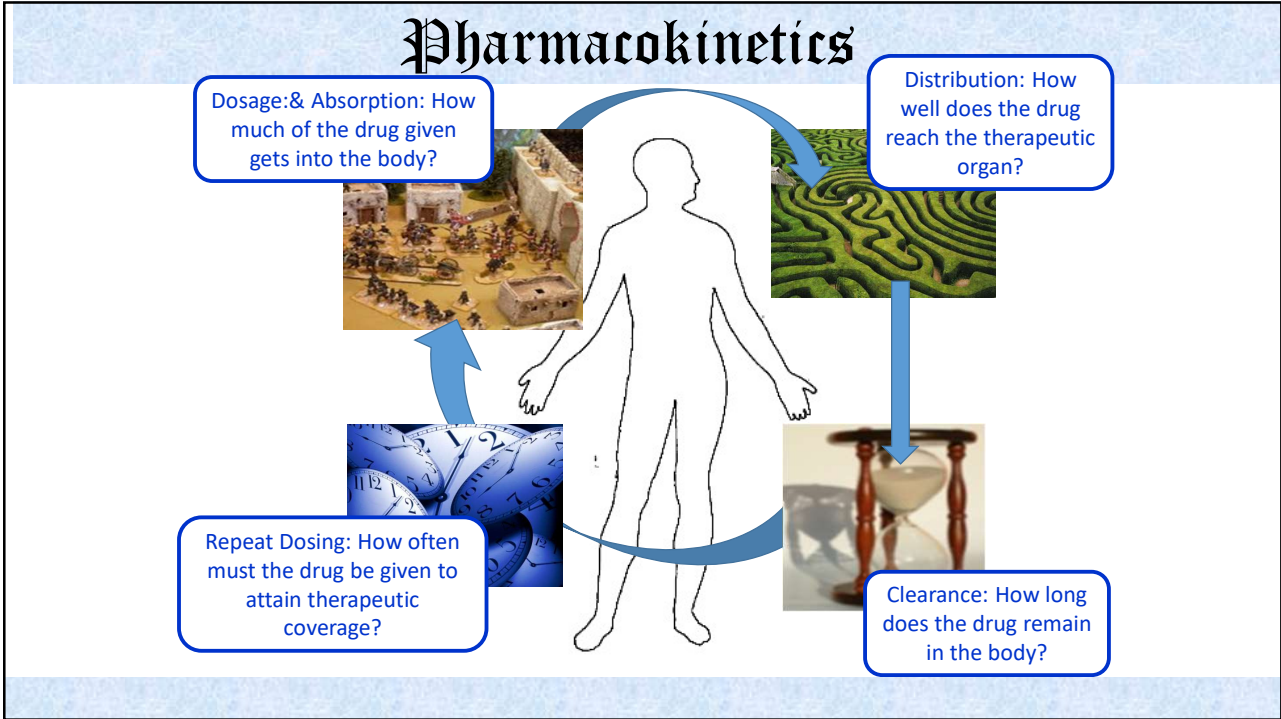
- Cardiovascular, CNS, GI, Immunology, Oncology, Endocrinology

MUST be able to :

- Enter the Body
- Distribute to the Therapeutic target organ
- Remain there long enough to cause response
- Cause NO HARM

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Pharmacokinetics



Dosage: & Absorption: How much of the drug given gets into the body?

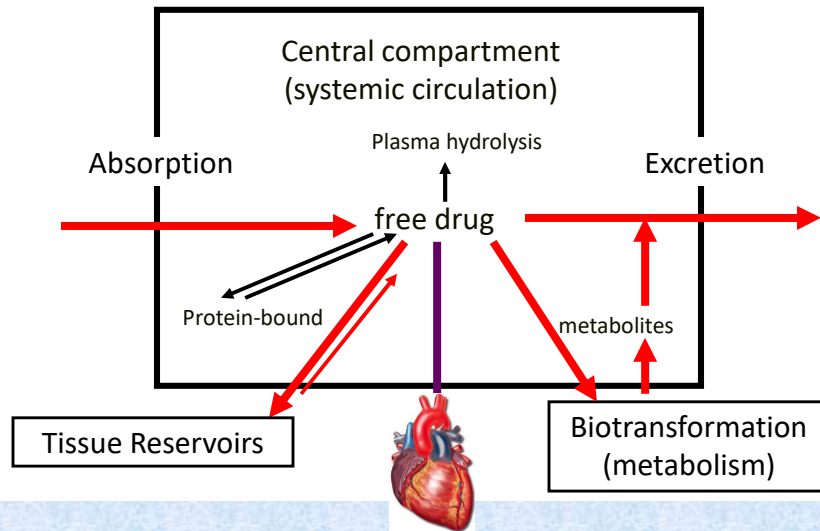
Distribution: How well does the drug reach the therapeutic organ?

Repeat Dosing: How often must the drug be given to attain therapeutic coverage?

Clearance: How long does the drug remain in the body?

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Pharmacokinetics



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Early Safety Testing

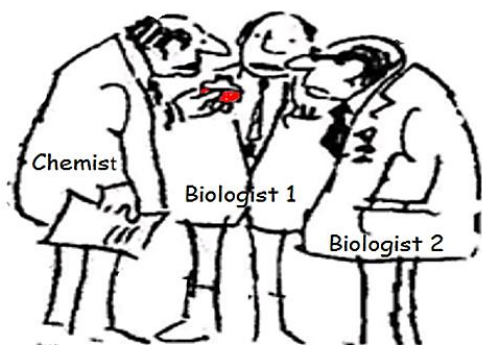
- hERG Channels
- Off-target Effects
- Cytotoxicity
- Ames Test
- Drug-Drug Interactions
- Hepatotoxicity

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Pharmacology for Chemists

Terry Kenakin PhD

Dept Pharmacology, University of North Carolina, School of Medicine. Chapel Hill, NC



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