ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

We will begin momentarily at 2pm ET

Slides available now! Recordings will be available to ACS members after one week.

www.acs.org/acswebinars

Have Questions?

ACS Chemistry for Life®

"Why am I muted?"
Don't worry. Everyone is muted except the presenter and host. Thank you and enjoy the show.

Type them into questions box!

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Have you discovered the missing element?

http://bit.ly/ACSjoin

Find the many benefits of ACS membership!

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Benefits of ACS Membership

C&EN
CHEMICAL & ENGINEERING NEWS

Chemical & Engineering News (C&EN)
The preeminent weekly news source.

ACS Presentations on Demand™
YOUR SOURCE FOR RECORDED MEETING CONTENT

NEW! Free Access to ACS Presentations on Demand®
ACS Member only access to over 1,000 presentation recordings from recent ACS meetings and select events.

NEW! ACS Career Navigator
Your source for leadership development, professional education, career services, and much more.

http://bit.ly/ACSjoin

Let's get Social…post, tweet, and link to ACS Webinars during today's broadcast!

facebook.com/acswebinars

@acswebinars

Search for "acswebinars" and connect!

5

How has ACS Webinars® benefited you?

"ACS Webinars keep me up to date on new developments in sub-disciplines of chemistry, other than my own. As a Biochemist, I enjoyed today's presentation on medicinal chemistry's novel approaches for drug design and delivery."

Fan of the Week

Rafael Álvarez-González, Ph.D.
CEO, AGORA Scientific Services, LLC

Be a featured fan on an upcoming webinar! Write to us @ acswebinars@acs.org

6

ACS Webinars®
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

7

ACS Webinars®
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Learn from the best and brightest minds in chemistry! Hundreds of webinars presented by subject matter experts in the chemical enterprise.

Recordings are available to current ACS members one week after the Live broadcast date. **www.acs.org/acswebinars**

Broadcasts of ACS Webinars® continue to be available to the general public LIVE every Thursday at 2pm ET!

www.acs.org/acswebinars

8

2016 Drug Design and Delivery Symposium

	I - Time: The Fourth Dimension in Drug Discovery
January 28	The Importance of Drug-Target Kinetics in Drug Design Robert Copeland - Epizyme, Inc
February 25	Long-Acting Injectable Medications: Strategies and Mechanistic Considerations Jules Remenar - Alkermes
March 31	Modified Release Formulations for Solubility Starved Compounds Mengwei Hu - Merck
April 28	*The Medicinal Chemist of Tomorrow (Special Topic)*
	II - Beyond Traditional Small Molecules
May 19	Design of Deliverable Macrocycles
June 23	Culture Clash - Antibody Drug Conjugates
July 28	Nucleic Acids Therapeutics - Making Sense of Antisense Oligonucleotides
August 18	*Special Topic (To Be Announced)*
	III - Pharmacology Revisited
September 29	Designing Around Toxicophores
October 27	RNA by design and phenotypic screening
November 10	Cell Penetrating Peptides to Improve Cellular Drug Uptake

Meet the Organizers

Nicholas Meanwell
BMS

John Morrison
BMS

Co-Produced By

Division of Medicinal Chemistry

aaps American Association of Pharmaceutical Scientists

Content Advisors

Richard Connell
Pfizer

Annette Bak
Merck Research Laboratories

Dan Erlanson
Carmot Therapeutics

Mark Tichenor
Janssen Research and Development

http://bit.ly/2016ddds

Upcoming ACS Webinars®

www.acs.org/acswebinars

Thursday, February 4, 2016

"Chemistry of Hello: The Next Generation of Circuitry"

Tobin Marks, Professor of Catalytic Chemistry and Professor of Material Science and Engineering, Department of Chemistry, Northwestern University

Mark Jones, Executive External Strategy and Communications Fellow, Dow Chemical

Thursday, February 18, 2016

Is Your Etiquette Holding Back Your Career?

Patricia Simpson, Owner/Consultant, Game Changing Etiquette
Director of Academic Advising and Career Services, University of Illinois

David Harwell, Assistant Director of Industry Member Programs, American Chemical Society

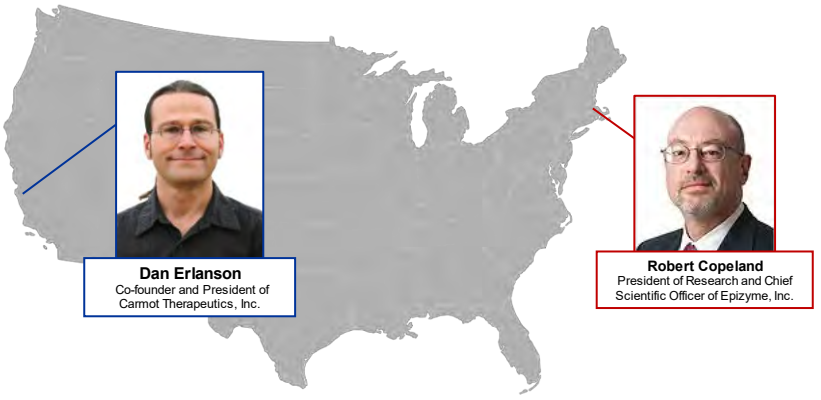
Contact ACS Webinars ® at acswebinars@acs.org

ACS Webinars
CLICK · WATCH · LEARN · DISCUSS

ACS Chemistry for Life®

2016 Drug Design and Delivery Symposium

"Drug-Target Kinetics in Drug Design"



Dan Erlanson
Co-founder and President of Carmot Therapeutics, Inc.

Robert Copeland
President of Research and Chief Scientific Officer of Epizyme, Inc.

Slides available now! Recordings will be available to ACS members after one week

www.acs.org/acswebinars

The 2016 DDDS is co-produced with ACS Division of Medicinal Chemistry and the AAPS

11

Epizyme

Drug-Target Residence Time

An Alternative Approach to Drug Optimization

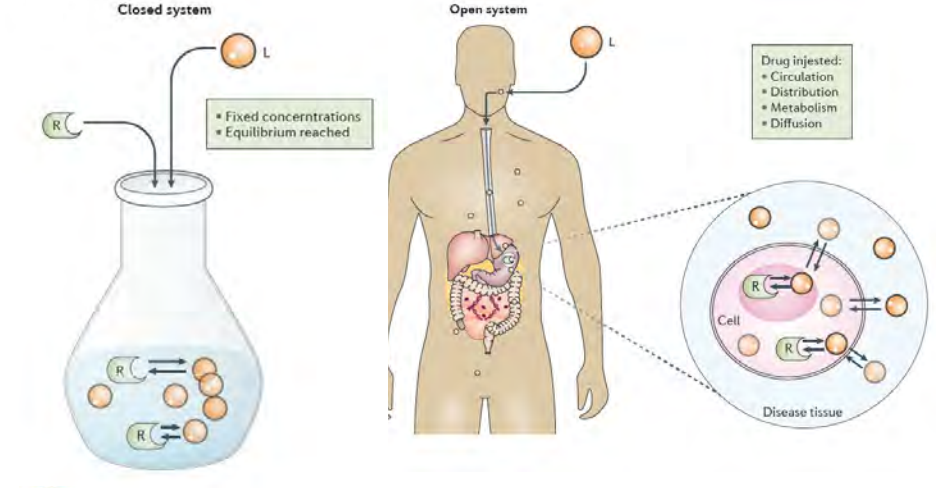
Robert A. Copeland, Ph.D.

Session 1 of the 2016 Drug Design and Delivery Symposium

Key Tenet of the Drug-Target Residence Time Model

- The key tenet of this model is that the lifetime, or residence time, of the binary drug-target complex and not the binding affinity *per se*, dictates much of *in vivo* pharmacological activity.

Open & Closed Systems



Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Who first proposed that drugs work by binding to specific receptors in the body?

- Archimedes
- Ehrlich
- Pasteur
- Curie

Poll Question #1

Question: Who first proposed that drugs work by binding to specific receptors in the body?

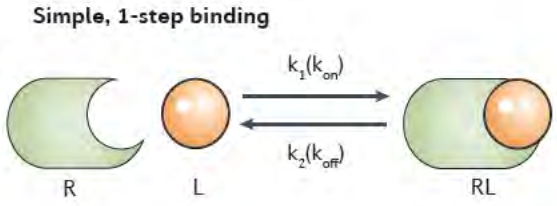
Answer: Paul Ehrlich (1854 –1915)

- 1908 Nobel prize in Physiology or Medicine
- Proposed the receptor theory of drug action in 1913 [1]
- Coined the phrase *Corpora non agunt nisi fixate (a substance will not work unless it is bound).*

[1] Ehrlich, P. Chemotherapeutics: Scientific Principles, Methods and Results. *Lancet* **182**, 445-451 (1913).

Epizyme

Some Basic Definitions of Drug-Target Equilibrium



$$K_d = \frac{k_{off}}{k_{on}}$$

Residence Time = τ

$$\tau = \frac{1}{k_{off}} \qquad t_{1/2} = \frac{0.693}{k_{off}}$$

17

Epizyme

A Baseball Analogy

The runner is inhibited from stealing second base while the ball is in residence with the first basemen. As soon as the ball dissociates back to the pitcher, the inhibition of the runner is relieved.

18

Epizyme

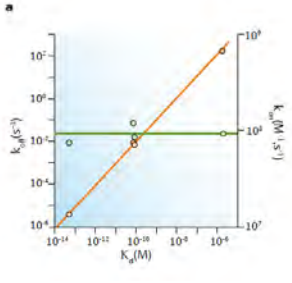
Drug-Target Dissociation is Affected by Physico-chemical Forces that are Familiar to Medicinal Chemists

- Common Elements of Molecular Recognition
  - Hydrogen bonding patterns.
  - Apolar surface interactions.
  - Well oriented, polarizable groups.
  - van der Waals forces.
  - Conformational distortions of the binding pocket.

Often SAR efforts aimed at potency optimization are actually optimizing residence time, but this often goes unrecognized by medicinal chemists.

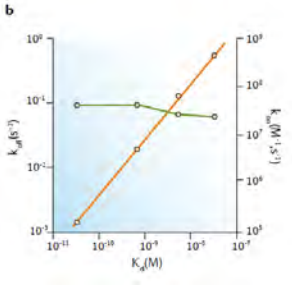
Residence Time Often Drives Binding Affinity

Biotin-Streptavidin Mutants



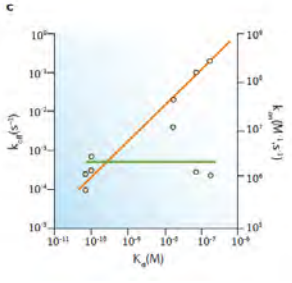
Hyre et al. (2006) *Protein Sci.* **15**: 459-474

Saquinavir-HIV Protease Mutants



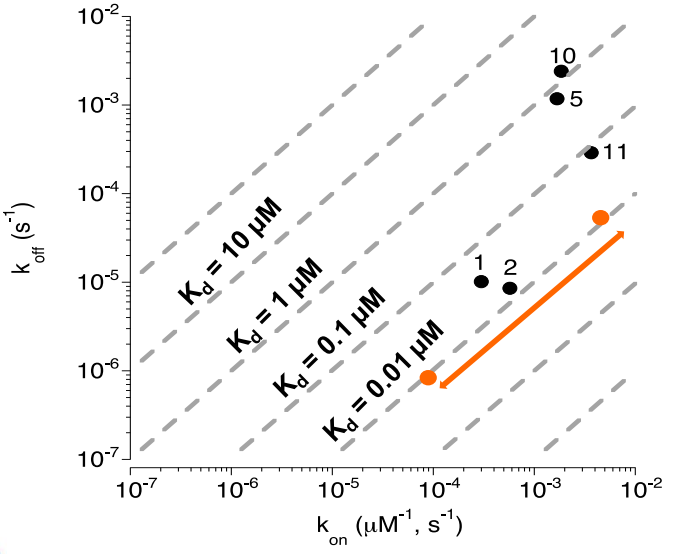
Maschera et al. (1996) *J. Biol. Chem.* **271**: 33231-35

Aminonucleoside Inhibitors of DOT1L



Basavapathruni et al. (2012) *Chem. Biol. Drug. Des.* **80**: 971-980

Residence Time Often Drives Binding Affinity, but Not Always: Need for Simultaneous Measurement of Kd and Residence Time



Epizyme

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

When was the first study of drug-receptor association and dissociation kinetics published?

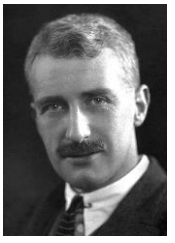
- 2006
- 1965
- 1938
- 1909

Poll Question # 2

Question: When was the first study of drug-receptor association and dissociation kinetics published?

Answer: 1909 by Archibald Vivian Hill (1866 – 1977)

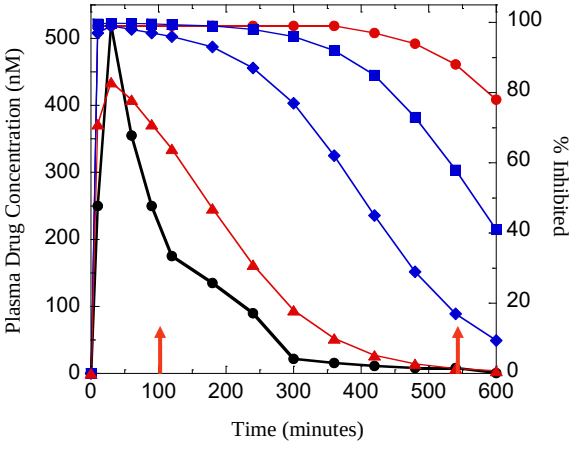
- 1922 Nobel prize in physiology or medicine
- Measured rate of onset of nicotine-induced contractions and rate of relaxation after wash-out in frog abdominal muscle [1]
- Also developed Hill Equation for equilibrium binding
- Father of the field of biophysics.



[1] Hill, A. V. The mode of action of nicotine and curari, determined by the form of the contraction curve and the method of temperature coefficients. *J. Physiol.* **39**, 361-373 (1909).

Epizyme

Compound Selectivity is a Time-Dependent Parameter

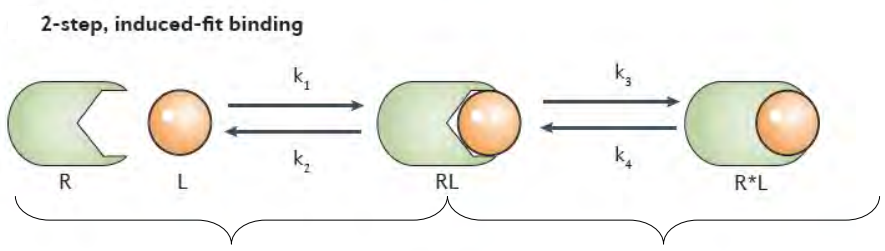


Selectivity for the primary target vs. other targets Depends on when one measures relative inhibition.

Sustained target inhibition at times when plasma levels of drug approach zero can help to minimize toxicity due to off-target effects.

Epizyme

Some Basic Definitions of Drug-Target Equilibrium



$$K_d = \frac{k_2}{k_1}$$

$$K_d^* = \frac{K_d}{1 + \left(\frac{k_3}{k_4}\right)}$$

$$k_{off} = \frac{k_2 k_4}{k_2 + k_3 + k_4}$$

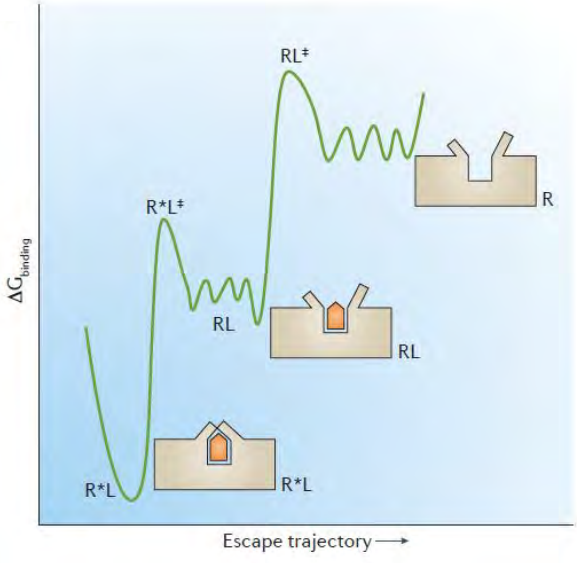
$$\tau = \frac{1}{k_{off}}$$

$$t_{1/2} = \frac{0.693}{k_{off}}$$

25

Epizyme

Retrograde Induced-Fit Mechanism of Compound



26

Epizyme

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Who first proposed that transition state complementarity was key to biological binding interactions such as enzyme activity?

- Hill
- Langmuir
- Pauling
- Heisenberg

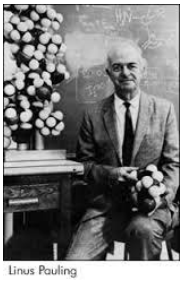
Poll Question # 3

Question: Who first proposed that transition state complementarity was key to biological binding interactions such as enzyme activity?
(A) Hill, (B) Langmuir, (C) Pauling

Answer: Linus C. Pauling (1901 – 1994)

- 1954 Nobel prize in chemistry, 1962 Nobel peace prize
- Proposed critical nature of transition state binding in 1946 [1]

[1] Pauling, L. Molecular architecture and biological reactions. *Chem. Eng. News* **24**, 1375-1377 (1946).


Linus Pauling

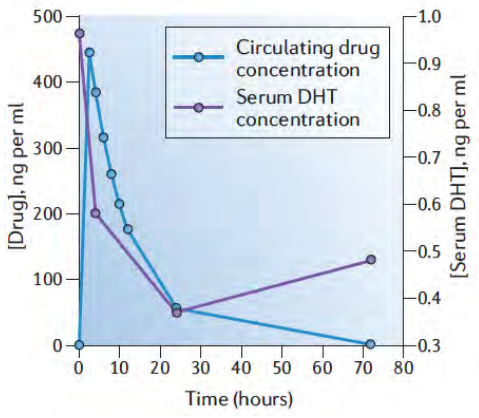
Epizyme

A Few Examples from the Recent Literature

Steroid 5α-reductase Inhibitors

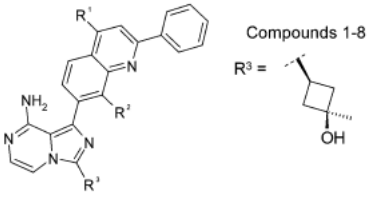
Tian, G. (1996) *J. Pharma. Sci.* **85**: 106-111.

- Finasteride is a mechanism-based, reversible inhibitor of the enzyme. K_i* = 0.3 pM.
- PK half-life = 4-7 hours.
- $t_{½}^{dissoc.}$ = > 30 days.
- PD effect = decrease in serum DHT levels
- PD half-life > 72 hours.
- After 1 or 10 mg dosing of finasteride for 7 day (qd), serum DHT levels remain suppressed for 7 days (after last dose).
- Suggested that recovery of DHT levels due to new enzyme synthesis = "*ultimate physiological inhibition*".

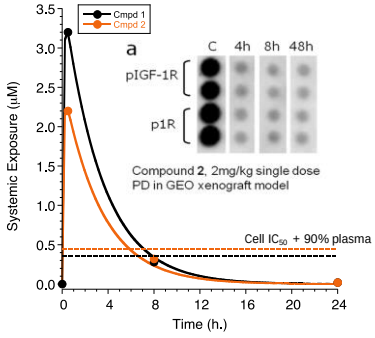


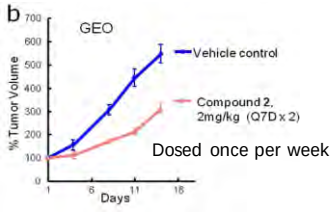
Copeland et al (2006) *Nature Rev. Drug Discov.* **5**: 730-739

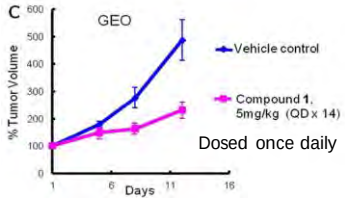
Example of Long Residence Time Translating into Extended PD: Inhibitors of IGF-1 Receptor



Compound	R¹	R²	Residence Time (h.)	Cell IC_{50} + 90% plasma (μM)
1	OMe	H	3.9	0.32
2	OEt	H	192	0.44



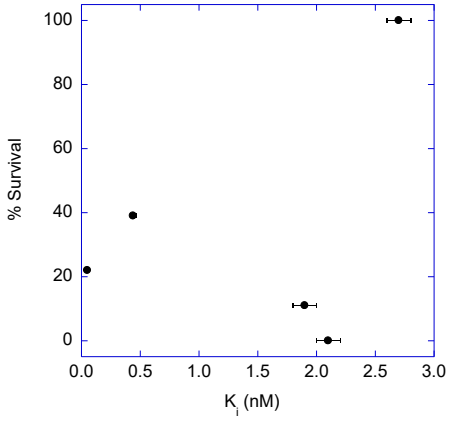


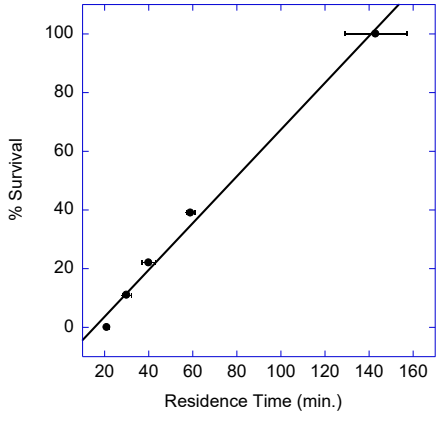


Jin et al. (2013) *ACS Med. Chem. Lett.* 4: 627-631

Epizyme

Residence Time, not K_i, Defines In Vivo Efficacy of FabI Enoyl Reductase Inhibitors as Antimicrobials Against *Francisella tularensis* Infection



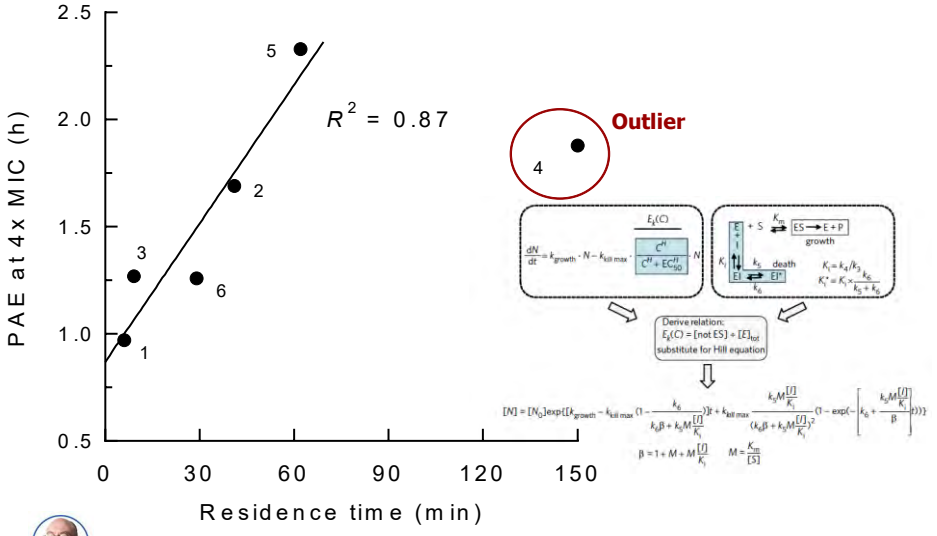


Source: Lu et al (2009) Slow-onset inhibition of the FabI enoyl reductase from *Francisella tularensis*: Residence time and in vivo activity. *ACS Chem. Biol.* 4: 221-231.

Epizyme

Predicting PD with Residence Time:

Walkup et al. (2015) *Nature Chem. Biol.* **11**: 416-423.



33

Epizyme

Examples for Which Long Residence Time is Contraindicated

Clincial Indication	Target	Example Drug	Clinical Toxicity
Thrombosis	$P2Y_{12}$ receptor	Clopidogrel	Exended bleeding
Thrombosis	IIb/IIIa receptor	Roxifiban	Thrombocytopenia
Antipsychosis	D_2 receptor	Chlorpromazine	Extrapyramidal (Parkinson-like) symptoms

Source: R. A. Copeland (2010) *Expert Opinions Drug Discov.*, 5: 305-310.

34

Epizyme

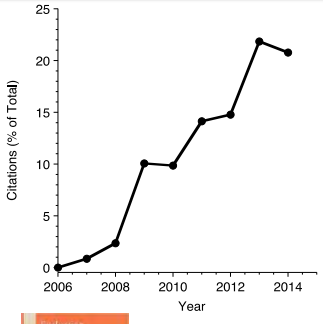
Lessons Learned

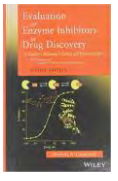
- Drug-target residence time can have a direct effect on PD, efficacy and duration.
- Drug-target residence time allows for sustained target effects far beyond the PK half-life of drugs.
- Off-target toxicity may be ameliorated by compounds with long target residence time but short residence time for off-target binders.
- Residence time is best quantified in vitro by measuring the values of k_{off} and from this, calculating $t_{½}^{dissociation}$.
- Modern biochemistry laboratories are well equipped for routine measurement of drug-target off rates, hence residence time.

Epizyme

Key References & Additional Resources

- Copeland et al (2006) Drug-Target Residence Time and its Implications for Lead Optimization. *Nature Rev. Drug Discov.*, **5**: 730-739.
  - Cited > 550 times.
- Tummino and Copeland (2008) Residence Time of Receptor-Ligand Complexes and its Effect on Biological Function. *Biochemistry* **47**: 5481-5492.
  - Cited > 240 times.
- Copeland (2011) Conformational Adaptation in Drug-Target Interactions and Residence Time. *Future Med. Chem.* **3**: 1491-1501.
  - Cited 75 times.
- Copeland (2013) Evaluation of Enzyme Inhibitors in Drug Discovery: A Guide for Medicinal Chemists and Pharmacologists, 2nd Edition, Wiley, New York.
  - Cited > 570 times.
- Copeland (2016) The Drug-Target Residence Time Model: A 10-Year Retrospective. *Nature Rev. Drug Discov.* Published online 18-Dec 2015. DOI: 10.1038/nrd.2015.18.





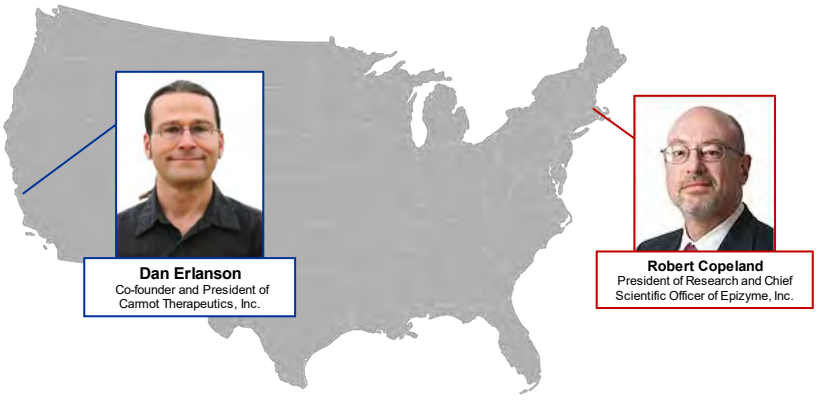
Epizyme

ACS Webinars
CLICK · WATCH · LEARN · DISCUSS

ACS Chemistry for Life®

2016 Drug Design and Delivery Symposium

"Drug-Target Kinetics in Drug Design"



Dan Erlanson
Co-founder and President of Carmot Therapeutics, Inc.

Robert Copeland
President of Research and Chief Scientific Officer of Epizyme, Inc.

Slides available now! Recordings will be available to ACS members after one week

www.acs.org/acswebinars

The 2016 DDDS is co-produced with ACS Division of Medicinal Chemistry and the AAPS

37

2016 Drug Design and Delivery Symposium

ACS Chemistry for Life®

	I - Time: The Fourth Dimension in Drug Discovery
January 28	The Importance of Drug-Target Kinetics in Drug Design Robert Copeland - Epizyme, Inc
February 25	Long-Acting Injectable Medications: Strategies and Mechanistic Considerations Jules Remenar - Alkermes
March 31	Modified Release Formulations for Solubility Starved Compounds Mengwei Hu - Merck
April 28	*The Medicinal Chemist of Tomorrow (Special Topic)*
	II - Beyond Traditional Small Molecules
May 19	Design of Deliverable Macrocycles
June 23	Culture Clash - Antibody Drug Conjugates
July 28	Nucleic Acids Therapeutics - Making Sense of Antisense Oligonucleotides
August 18	*Special Topic (To Be Announced)*
	III - Pharmacology Revisited
September 29	Designing Around Toxicophores
October 27	RNA by design and phenotypic screening
November 10	Cell Penetrating Peptides to Improve Cellular Drug Uptake

Meet the Organizers

Nicholas Meanwell
BMS

John Morrison
BMS

Co-Produced By

Division of Medicinal Chemistry

aaps American Association of Pharmaceutical Scientists

Content Advisors

Richard Connell
Pfizer

Arinette Bak
Merck Research Laboratories

Dan Erlanson
Carmot Therapeutics

Mark Tichenor
Janssen Research and Development

http://bit.ly/2016ddds

38

Upcoming ACS Webinars®

www.acs.org/acswebinars

Thursday, February 4, 2016

"Chemistry of Hello: The Next Generation of Circuitry"

Tobin Marks, Professor of Catalytic Chemistry and Professor of Material Science and Engineering, Department of Chemistry, Northwestern University

Mark Jones, Executive External Strategy and Communications Fellow, Dow Chemical

Thursday, February 18, 2016

Is Your Etiquette Holding Back Your Career?

Patricia Simpson, Owner/Consultant, Game Changing Etiquette
Director of Academic Advising and Career Services, University of Illinois

David Harwell, Assistant Director of Industry Member Programs, American Chemical Society

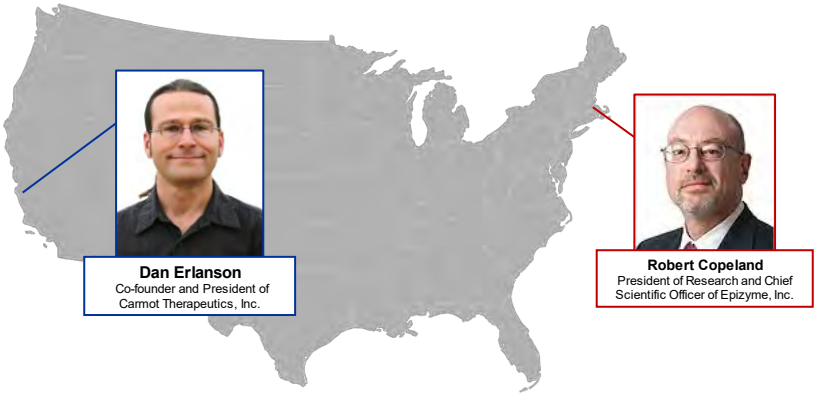
Contact ACS Webinars ® at acswebinars@acs.org

39

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

2016 Drug Design and Delivery Symposium

"Drug-Target Kinetics in Drug Design"



Dan Erlanson
Co-founder and President of Carmot Therapeutics, Inc.

Robert Copeland
President of Research and Chief Scientific Officer of Epizyme, Inc.

Slides available now! Recordings will be available to ACS members after one week

www.acs.org/acswebinars

The 2016 DDDS is co-produced with ACS Division of Medicinal Chemistry and the AAPS

40

How has ACS Webinars® benefited you?

ACS Chemistry for Life®

"ACS Webinars keep me up to date on new developments in sub-disciplines of chemistry, other than my own. As a Biochemist, I enjoyed today's presentation on medicinal chemistry's novel approaches for drug design and delivery."

Fan of the Week

Rafael Álvarez-González, Ph.D.
CEO, AGORA Scientific Services, LLC

Be a featured fan on an upcoming webinar! Write to us @ acswebinars@acs.org

41

Join the ACS Division of Medicinal Chemistry Today!

ACS Chemistry for Life®

Division of Medicinal Chemistry

For $25 ($10 for students)**, You Will Receive:**

- A free copy of our annual medicinal chemistry review volume (over 600 pages, $160 retail price)
- Abstracts of MEDI programming at national meetings
- Access to student travel grants and fellowships

Find out more about the ACS MEDI Division! www.acsmedchem.org

ACS Publications
Most Trusted. Most Cited. Most Read.

ACS Chemistry for Life®

ACS offers a number of publications that feature the hottest research in drug design.

Make sure to check out the February Special Issue of ACS Medicinal Chemistry Letters on Epigenetics, featuring a viewpoint from Bob Copeland.

This Issue will be published on February 11th!

pubs.acs.org/acsmedchemlett

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

45

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Benefits of ACS Membership

C&EN CHEMICAL & ENGINEERING NEWS

Chemical & Engineering News (C&EN)
The preeminent weekly news source.

ACS Presentations on Demand™
YOUR SOURCE FOR RECORDED MEETING CONTENT

NEW! Free Access to ACS Presentations on Demand®
ACS Member only access to over 1,000 presentation recordings from recent ACS meetings and select events.

NEW! ACS Career Navigator
Your source for leadership development, professional education, career services, and much more.

http://bit.ly/ACSjoin

46

ACS Webinars® does not endorse any products or services. The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the American Chemical Society.

Upcoming ACS Webinars®

www.acs.org/acswebinars

Thursday, February 4, 2016

"Chemistry of Hello: The Next Generation of Circuitry"

Tobin Marks, Professor of Catalytic Chemistry and Professor of Material Science and Engineering, Department of Chemistry, Northwestern University

Mark Jones, Executive External Strategy and Communications Fellow, Dow Chemical

Thursday, February 18, 2016

Is Your Etiquette Holding Back Your Career?

Patricia Simpson, Owner/Consultant, Game Changing Etiquette
Director of Academic Advising and Career Services, University of Illinois

David Harwell, Assistant Director of Industry Member Programs, American Chemical Society