



We will begin momentarily at 2pm ET



Recordings will be available to ACS members after three weeks

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Upcoming ACS Webinars®

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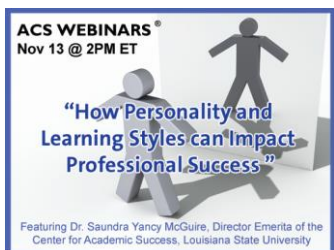


Thursday, November 6, 2014

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Did you miss the past recordings in the Drug Discovery Series?



www.acs.org/content/acs/en/events/acs-webinars/drug-discovery-series-2014.html

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Join us in 2015 for a NEW Drug Discovery Series co-produced with



Dr. Nicholas Meanwell
ACS Division of Medicinal Chemistry



Dr. John Morrison
American Association of
Pharmaceutical Scientists (AAPS)



What You Will Learn:

- Improving Drug Design Efficiency and Efficacy
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“The Future of Drug Discovery: Challenges, Risks, and Rewards”



Dr. Jeff Zablocki
Senior Director,
Gilead Sciences



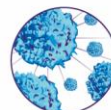
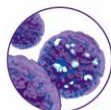
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The Future of Drug Discovery: Challenges, Risks, and Rewards?”

Rick Connell and Jeff Zablocki



WORLDWIDE RESEARCH & DEVELOPMENT
Medicinal Chemistry

Science Challenges to Drug Discovery

- Information (unfiltered) Overload
- Picking a Viable Targets in a disease area
 - The “Easy” targets are picked over ...☹.
- Diseases Disease Complexity
 - ...halting one pathway may not be sufficient for efficacy
- Competition for “validated targets” is high
 - ...which is good for patients...☺
- Disease Knowledge: Sometimes outside of Pharma Walls
- Access to Human or Phenotypic assays and reagents
- Increasing complexity of Drug Discovery Process
 - Larger, more diverse teams of specialized skills needed for success



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Business Challenges to Drug Discovery

- Freedom to operate
 - Groups patenting targets
 - Prior Art and broad Composition of Matter Patents
- Access to Patients
 - The right ones...
 - At the right sites...
 - In a high enough volume to complete studies swiftly
- Research Funding Priorities
 - Advances projects over early ones?
 - Commercially important Diseases (inc. Orphan) get priority?



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Audience Question

How often do you think of “risk” in your work?

- Daily
- Weekly
- Monthly or Quarterly
- Doesn't apply (not my job)

Risks

- Insufficient knowledge of the target
- Unforeseen Toxicity sidelining a lead / program
- Mutations rendering new therapies less effective over time
 - Alk mutants of Xalkori®
 - EGFR mutants of Iressa® and Tarceva®
- Targeted therapies may have a smaller patient market
- Funding:
 - Payers may not agree with cost/benefit of new Therapies
 - Companies may decide to fund late stage over Discovery
- Standard of care can change during clinical trials
 - Impact on Approval Pathway may be extended
- Failure. More things fail than succeed.

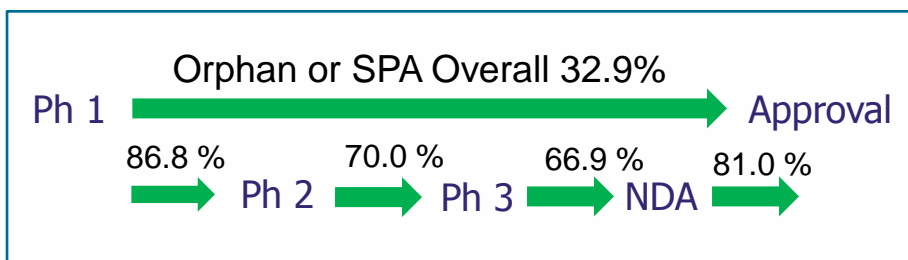
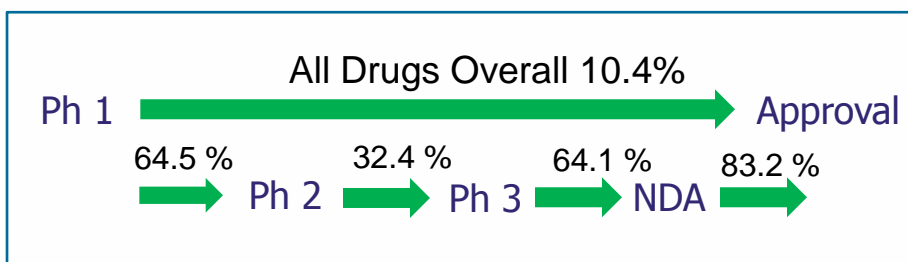


Audience Question

Why do you think research in Orphan Diseases is increasing?

- better science
- more funding
- role of advocacy groups and social media
- commercial potential
- all the above

Risks – All Drugs Vs. Orphan Phase Success (2003-2011)



Rewards

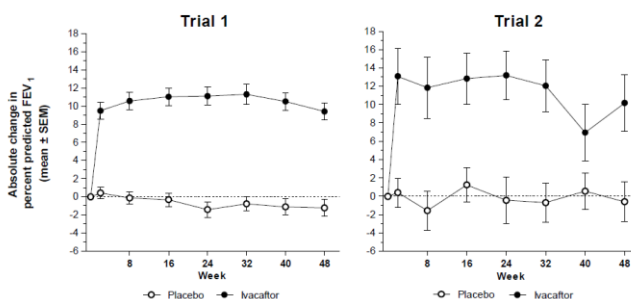
- Making a difference for patients.
- Contributing to medical knowledge in Society.
- Expansion: More adjacent research (diagnostics, personalized medicine, etc.) spurred by deeper knowledge and big data
- Financial...ability to work on more programs



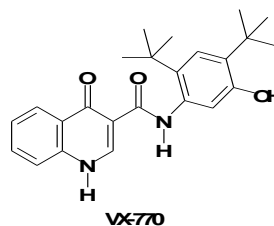
Rewards - Orphan Drug - Making a difference for Cystic Fibrosis patients

- KALYDECO™ (ivacaftor) – Orphan Drug - CF patients with G551D mutation in the CF transmembrane conductance regulator (*CFTR*) gene
- VX-770 (Vertex)
- Improved lung function forced expiratory volume 1

Figure 3: Mean Absolute Change from Baseline in Percent Predicted FEV₁ *



*Primary endpoint was assessed at the 24-week time point.

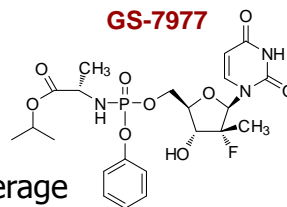


US Package Insert ivacaftor - Vertex

Rewards – Hepatitis C Patients - Sofosbuvir



- Global Prevalence of HCV Estimated to Be 160 Million⁽¹⁾
- GS-7977 (Sofosbuvir) for HCV⁽²⁾



- Once-daily, broad HCV genotype coverage

Sofosbuvir Phase 3 Data⁽²⁾

HCV Genotype	Regimen	Overall SVR
1, 4, 5, 6	SOF + RBV + PegIFN (12 weeks)	90%

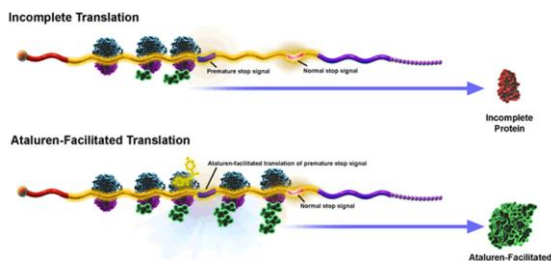
⁽¹⁾Lavanchy, 2011 Clin Microbiol Infect. 2011 Feb;17(2):107-15.

⁽²⁾Sofia, et al J. Med. Chem. 2010, 53, 7202–7218.

Future Areas – Orphan Drug Indications



- Long QT 3 Patients (LQT-3) – GS-6615 Late INa inhibitor (Gilead)⁽¹⁾
 - Sodium channel mutations lead to sudden cardiac death (SCD)
- Hypertrophic cardiomyopathy - GS-6615 Late INa inhibitor (Gilead)
 - Sarcomere mutations lead to Late INa
- Duchenes muscular dystrophy - approximately 1 in 3,500 live male births. (PTC Therapeutics)⁽²⁾
 - mutation of the dystrophin gene - muscle fibers undergo necrosis
 - nonsense mutation 13% of patients - Translarna™ (ataluren PTC Therapeutics)



- ⁽¹⁾ Gilead website
⁽²⁾ PTC Therapeutics

Future Areas of Drug Discovery



- **Epigenetics**
 - Bromodomain-4 (BRD4) – histone acetylated lysine reader
 - Oncoethix, GSK, Constellation, Tensha – Ph ^a
- **Antibody drug conjugates** - Brentuximab Vedotin (Adcetris®)
 - anti-CD30 antibody conjugated to monomethyl auristatin E^b
- **Regenerative medicine**
 - Kartogenin - chondrogenesis for osteoarthritis (Schultz)^c
- **Alternate signaling for GPCRs** – G-Protein vs β -arrestin pathway
 - TRV027 blocks the G-protein signaling of ATR1 (Ang II R) pathway of ATII but activates the β -arrestin pathway^d
- **Targeting RNA** – small molecules bind to hairpin (Disney)
 - Benzimidazole 1 - microRNA-96 precursor led to apoptosis^e

^aThomson Integrity Database; ^bSassoon and Blanc in Antibody Drug Conjugates 2013

^cSchultz *Science* **336**, 717 (2012); ^dCorrell and McKittrick *J. Med. Chem.* 2014, 57, 6887–6896

^eDisney *nature CHEMICAL BIOLOGY* April 2014

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Future Medicinal Chemists – Skill Sets



- Maintain strong synthetic knowledge – focused expertise
- Good communication skills
- Demonstrate problem solving skills
- Work in a matrix interdisciplinary environment
- Broad scientific background
 - chemists in a biologists/clinicians world
- Comfortable with change as opposed to status quo

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Audience Question

How many hours a week do you spend staying current in your scientific field?

- 0-2 hours
- 2-4 hours
- 4-8 hours
- >8 hours a week

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Additional Resources

Staying Current – applications, news feeds, and programs

Applications

- ACS Mobile – abstracts with potential to link to full article
- Feedly – News and Journals – contents - <https://feedly.com/>
- Endnote
- Reference Manager

News Feeds

- Fierce Biotech
- Drug Discovery and Development
- Thomson Daily Drug News



Programs

- Scifinder – standard search queries
- Thomson Reuters Integrity
- World Wide Web of Science
- PubMed



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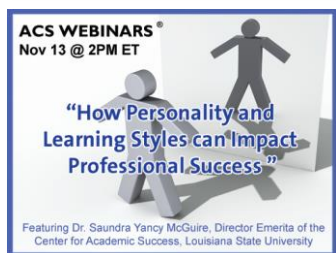


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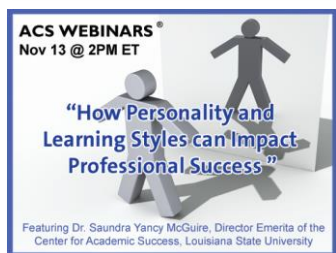


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