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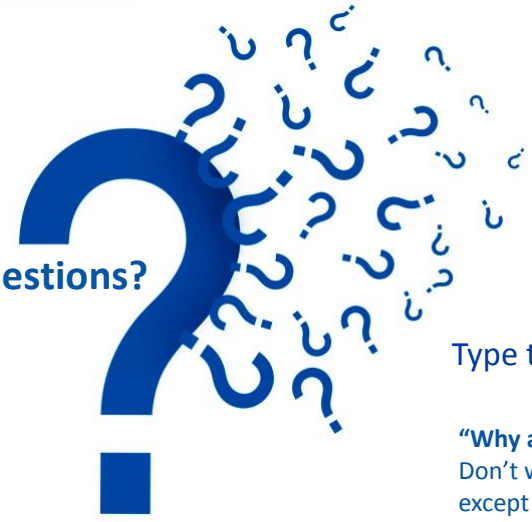

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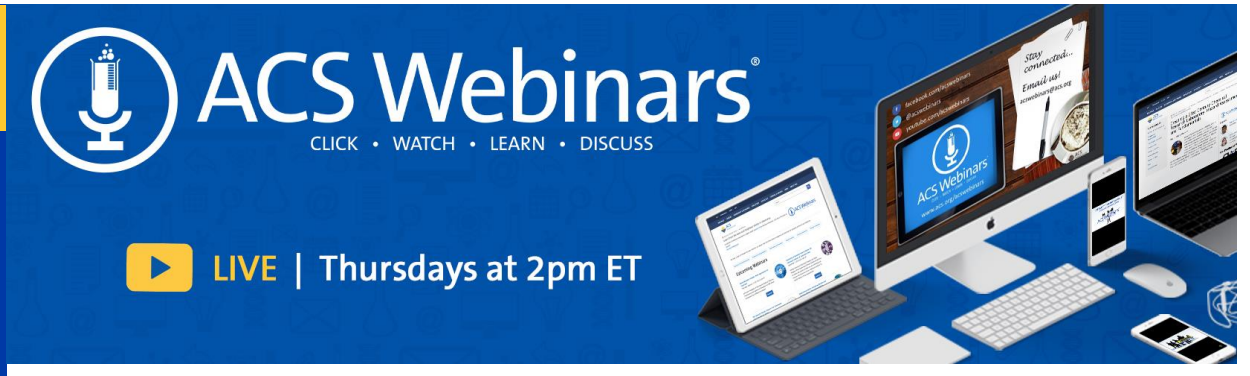

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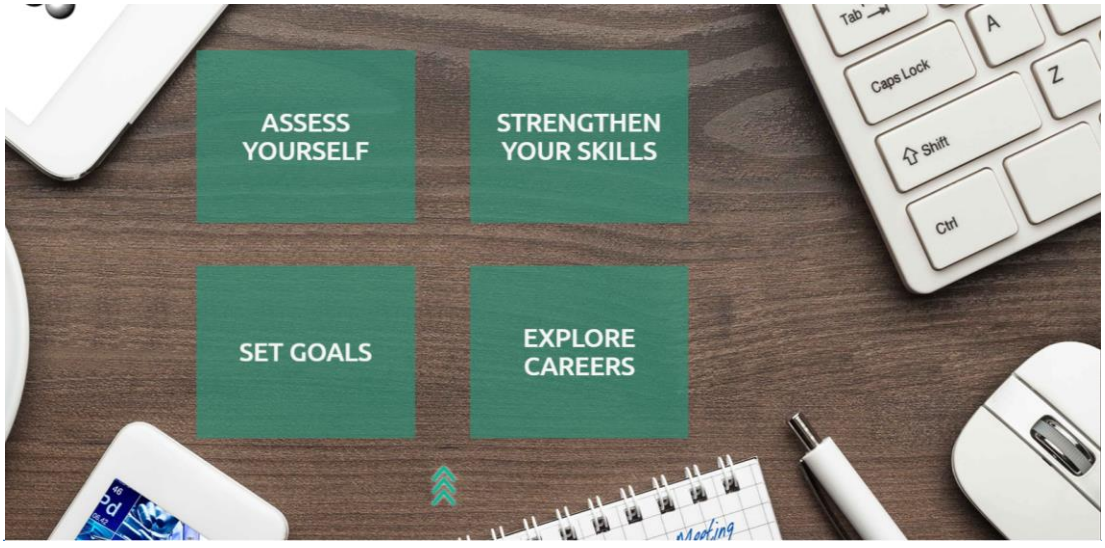

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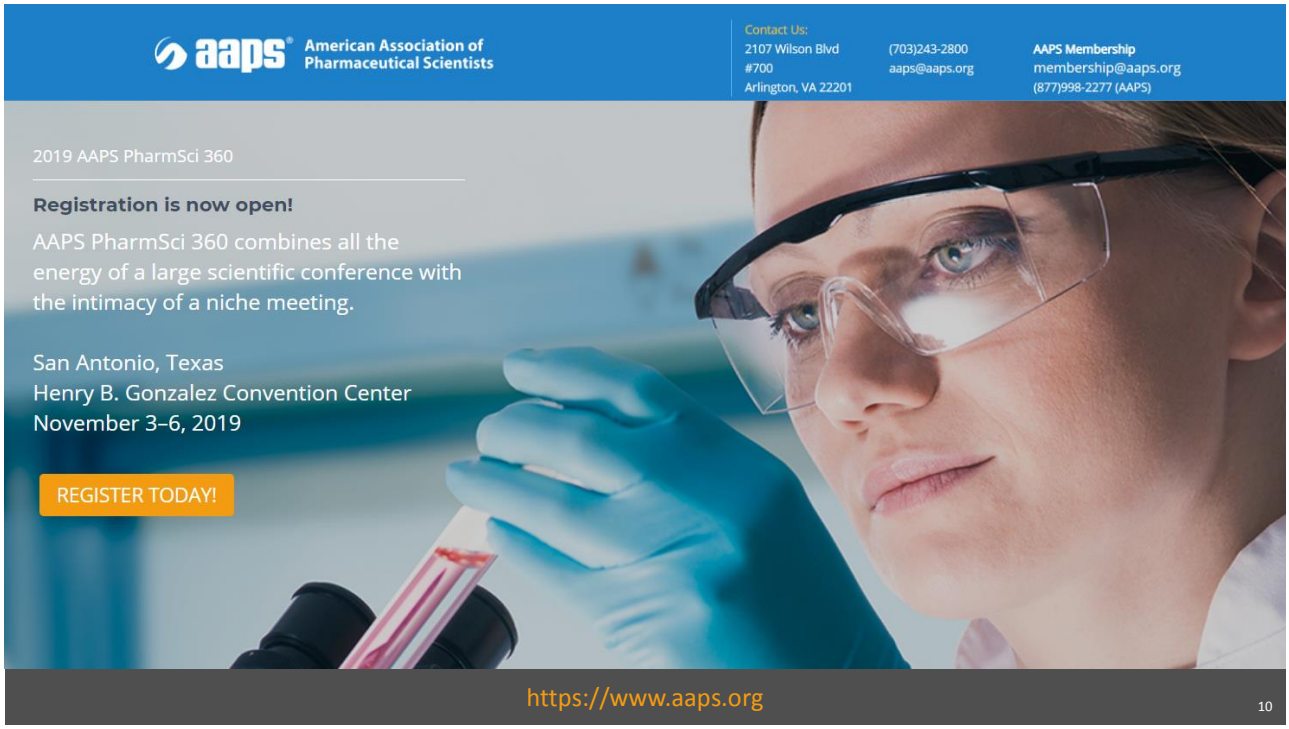

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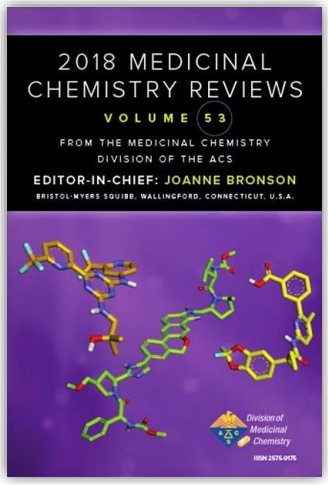

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2019 Drug Design and Delivery Symposium

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Jan 31	**How to Succeed in Drug Discovery: Insight from Medicinal Chemists** (1.5 hrs.)	John Lowe III - JL3 Pharm Mark Murcko - Relay Therapeutics Ann Weber - Kallyope William Greenlee - MedChem Discovery Consulting
Feb 28	**Cosolvent Molecular Dynamics: Mapping Protein Surfaces to Discover Allosteric Sites**	Heather Carlson - University of Michigan Rommie Amaro - UC San Diego
Mar 28	**Women at the Interface of Computational Chemistry and Drug Discovery** (1.5 hrs)	Zoe Cournia - Biomedical Research Foundation and *JCIM* Kate Holloway - Gfree Bio Yvonne C. Martin - Previously of Abbott Laboratories Shana Posy - Bristol-Myers Squibb
Apr 18	**Effective Exploration of Chemical Space in Hit-Finding**	Hanneke Jansen - Novartis Institutes for BioMedical Research Zoe Cournia - Biomedical Research Foundation and *JCIM*
May 30	**Widening the Therapeutic Window: Kinetic Selectivity and Target Vulnerability**	Peter Tonge - Stony Brook University and *ACS Infectious Diseases* Stewart Fisher - C4 Therapeutics
Jun 27	**Precision Control of CRISPR-Cas9**	Amit Choudhary - Broad Institute of Harvard and MIT Venkat Krishnamurthy - AstraZeneca
Aug 8	**Transformation of Recombinant Cells to FDA Approved Products: Clinical Development to Marketplace** (New Date)	Rodney Ho - University of Washington Venkat Krishnamurthy - AstraZeneca
Aug 22	**The Evolving Landscape of the Pharmaceutical CROs**	Bart DeCorte - Mercachem
Sep 19	**Compound Design in the Agricultural Areas**	Fides Benfatti - Syngenta
Oct 17	**To Be Announced**	
Nov 28	**Prodrugs**	Jarkko Rautio - University of Eastern Finland

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Meet the Organizers


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Celebrating 6 years & Over 55 Drug Discovery Webinars!

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2014

- Drug Discovery Series #1 - Current Drug Discovery and Development Process (DDS #1) Watch this overview of the drug discovery and development process to learn the stages and challenges in every step.
- Primer in Drug Target Classes (DDS #2) Listen in on a discussion on the big four druggable families and the difference between small molecule and biotherapeutic targets.
- Key Concepts in Identifying Drug Leads (DDS #3) Discover how drug-likeness is a decaying concept, explore the Rule of Five, and show how lessons from the past may guide the present.
- Lead Optimization – Building Efficacy & Safety (DDS #4) Learn strategies on how to effectively optimize small molecule hits and rapidly assess your findings.
- Tips for Filing IND and Starting your Clinical Trials (DDS #5) What do you need to know when filing for Investigational New Drug submissions to the United States Food and Drug Administration?
- The Role of Chemistry in Clinical Trials: The Big Expense & Lessons Learned (DDS #6) Learn how the properties of the candidate impact decisions in the discovery process.
- Pharmacoeconomics and IP Strategies in Drug Development (DDS #7) Review the basic principles of Pharmacoeconomics in drug development strategies as well as its role in determining health insurance coverage of drug products.
- Future of Drug Discovery - Challenges, Risks and Rewards (DDS #8) Explore how how risks and challenges will be dealt with in the future and the key skill sets required of future medicinal chemists.

2015

- Designing Better Drug Candidates (January) Learn various factors that can be used to improve candidate quality from Dr. Paul Leeson.
- Strategies to Improve Solubility of Drug Candidates (February) Learn a number of different strategies for improving drug solubility through structural modification.
- Fragment-Based Drug Design Strategies (March) Finding the right drug targets is becoming increasingly difficult. Learn how focusing on the smaller picture can have big results.
- Screening Strategies (April) Learn the pros and cons of different screening strategies.
- Avoiding PAINS (pan-assay interference compounds) (May) Jonathan Baell shared some tips on how to avoid the dead ends of drug discovery.
- Accelerating CNS Positron Emission Tomography (PET) Ligand Discovery (June) Join Lai Wang as he lays out a set of preferred parameters for which has yielded successful PET ligands and reduced resources and timelines.
- X-ray Crystallography in Drug Discovery (July) Jon Mason and Mike Congreve describe what protein-ligand X-ray data can do for you.
- Choices and Trends in Solid Dosage Form Selection (August) Discover the pros and cons of the different solid state forms and what to consider when selecting.
- Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies (September) Gain an understanding of acceptable drug delivery approaches to support preclinical dose escalation.
- Pharmacokinetic Considerations in Drug Design and Development Learn about key pharmacokinetic concepts including clearance, volume of distribution, half life and protein binding.
- Prodrugs in Drug Discovery (November) John Wiggins shares the utility of prodrugs, their general properties and prerequisites for optimal performance.

2016

- I - Time: The Fourth Dimension in Drug Discovery
  - The Importance of Drug-Target Kinetics in Drug Design — Robert Copeland - Epizyme, Inc; Dan Eriksson - Carmot Therapeutics
  - Long-Acting Injectable Medications: Strategies and Mechanistic Considerations — Jukes Ramenar - Alkermes; Annette Bak - Merck
  - Modified Release Formulations for Solubility Starved Compounds — Mangkuo Hu - Merck; John Morrison - BMS
  - *The Medicinal Chemist of Tomorrow (Special Topic)* — Joel Barrish - AchilliumRavi Nargund - Merck; Maliy Schmid - Tech Coast Angels
- II - Beyond Traditional Small Molecules
  - Design of Deliverable Macrocycles — Scott Lokey - UC Santa Cruz; Nicholas Meanwell - BMS
  - Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates — L. Nathan Tumey - Pfizer; Peter Senter - Seattle Genetics
  - Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides — Punit Seth - Ionis; Richard Dipon - BMS
  - Crystallography as a Drug Design and Delivery Tool (Special Topic) — Robert Wanslow - Crystal Pharmatech; Vincent Stoll - Abbvie; Andrew Brunskill - Merck
- III - Pharmacology Revisited
  - Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites? — Deepak Dalvie - Pfizer; Frederick Peter Guengerich - Vanderbilt University
  - Rational Design of Small Molecules Targeting RNA — Matt Disney - Scripps Rl Florida; Amanda Garner - University of Michigan
  - Cell Penetrating Peptides to Improve Cellular Drug Uptake — Dehua Pei - The Ohio State University; Scott Hart - Bristol-Myers Squibb

2017

- I - Fighting Cancer
  - Fighting Cancer: Targeting CNS Malignancy with Kinase Inhibitors — Timothy P. Heffron - Genentech; Mark Wittman - Bristol-Myers Squibb
  - Fighting Cancer: Epigenetic targets for Oncology — Stuart Conway - Oxford; Sharan Bagal - AstraZeneca
  - Fighting Cancer: Allostery and Targeting Cancer Cell Metabolism — Stefan Gross - Agios; Scott Edmundson - AstraZeneca
- Special Broadcast
  - Cystic Fibrosis: Discovery of CFTR Modulators — Peter Grootenhuis - Vertex; Nick Meanwell - Bristol-Myers Squibb
- II - Anti-Infectives
  - Anti-Infectives: Rational Approaches to the Design and Optimization — Jason Sello - Brown University; Courtney Aldrich - University of Minnesota
  - Tuberculosis: An Introduction for Medicinal Chemists — Carl Nathan - Weill Cornell Medicine; Christopher Boyce - Merck
  - Viral Hepatitis: The Search for a Cure — Mike Sofia - Arbutus Biopharma; Stephen Mason - CaroGen Corporation
- Special Broadcast
  - Spinal Muscular Atrophy — Kevin Hodgetts - Harvard Medical School; Alyson Weidmann - ACS Publications
- III - Immunology
  - Psoriasis: Treatment and Novel Approaches — Frank Narjes - AstraZeneca; John Morrison - Bristol-Myers Squibb
  - Lupus: Treatment and Novel Approaches — Laurence Menard - Bristol-Myers Squibb; Mary Struthers - Bristol-Myers Squibb

2018

- Jan 25 — A New Strategy in Drug Discovery: Protac-Induced Protein Degradation — Ian Churcher - BenevolentBio; Aaron Balog - Bristol-Myers Squibb
- Feb 22 — Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry — Annette Bak - AstraZeneca; Donna Huryn - University of Pittsburgh; Erika Araujo - Bristol-Myers Squibb; Nurulain Zaveri - Astraea Therapeutics
- Mar 29 — A Nanomedicine Overview for mRNA Delivery: Innovative Methods Using Lipid Nanoparticles — Marianna Yanez Arteta - AstraZeneca; Dennis Lueng - Genentech
- Apr 26 — Nanomaterials for Fighting Antibiotic-Resistant Bacteria — Vincent Rotello - University of Massachusetts at Amherst; Christopher England - American Chemical Society
- May 31 — Advanced Nano-Delivery Systems: Facilitating Tumor Delivery and Mitigating Resistance — Mansoor Amiji - Northeastern University; Venkat Krishnamurthy - AstraZeneca
- Jun 28 — Pitfalls and Promise of Central Nervous System Drug Discovery — Valentin Gribkoff - Yale University; Nicholas Meanwell - Bristol-Myers Squibb
- Jul 26 — How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows — Craig Lindsley - Vanderbilt Center for Neuroscience Drug Discovery; Amy Newman - Intramural Research Program, NIH
- Sept 20 — A Novel Strategy for the Treatment of Chronic Pain: Antagonising PAR2 with a Monoclonal Antibody — Pete Thornton - AstraZeneca; Nurulain Zaveri - Astraea Therapeutics
- Oct 18 — How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling — Elizabeth de Lange - Leiden Academic Center for Drug Research; Alexander Tropsha - University of North Carolina
- Nov 29 — Human Exosomes: An Ideal Vehicle for Delivery of Therapeutic RNAs to Cells and Organs — Hadi Valadi - University of Gothenburg; Alexander Kapuvitin - AstraZeneca

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What You Will Learn

- The most common questions that have been asked by graduate students about legal aspects of their safety responsibilities in the lab
- Guidelines and resources for identifying and understanding researchers' regulatory responsibilities
- Lessons learned about practical aspects of managing regulations in the research lab setting

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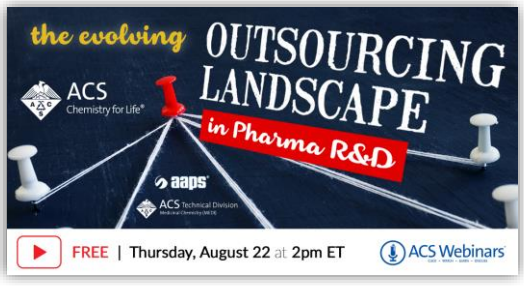

What You Will Learn

- An overview of the evolving role of CROs in drug discovery in the past 20 years
- A profile of different outsourcing models that can be considered
- What to look for as you select a CRO to partner with

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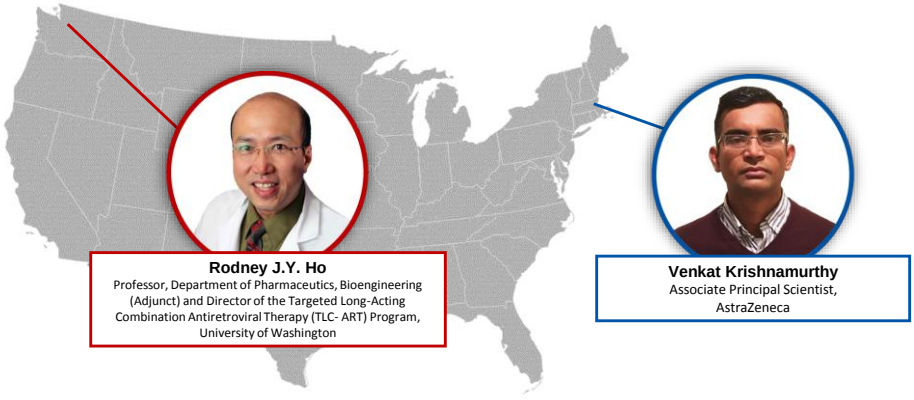
Transformation of Recombinant Cells to FDA Approved Products:
Clinical Development to Marketplace



Rodney J.Y. Ho
Professor, Department of Pharmaceutics, Bioengineering (Adjunct) and Director of the Targeted Long-Acting Combination Antiretroviral Therapy (TLC- ART) Program, University of Washington

Venkat Krishnamurthy
Associate Principal Scientist, AstraZeneca

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SCHOOL OF PHARMACY
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Transformation of Recombinant Cells into FDA Approved Products: Clinical Development to Marketplace *

Rodney J Y Ho, PhD, FAAAS, FAAPS
Professor and Presidential Entrepreneurial Fellow
Director, Targeted and Long-acting Combination Anti-Retroviral Therapeutic (TLC-ART) Program

*Bak et al. J Pharm Sci. 2019 May 29. pii: S0022-3549(19)30360-0. doi: 10.1016/j.xphs.2019.05.027.

Disclosure

- 30+ Years as an HIV/HSV, Cancer and Pain Researcher
- Director of UM1 Targeted and Long-acting Combination Anti-Retroviral Therapeutic-TLC-ART Program
- Professor at U Washington, and FHCRC member, Seattle
- Presidential Entrepreneurial Fellow
- Built Integrated HIV/AIDS and Cancer Programs
- Elected Fellow of
  - American Assoc. for the Advancement of Science (*Science*)
  - American Assoc. of Pharmaceutical Scientists
- Advisor to NIH on Grant and Center Reviews
- Editor, J. Pharmaceutical Sciences
- Dawson Biotechnology Award—Life Time Teaching & Research
- Biotechnology Achievement Award-One of the highest honors endowed by the AAPS
- Volwiler Research Achievement Award- a high honor of the AACP
- Luminary Award—Chinese Institute of Engineers USA
- Founding Member of Several Biotech Companies—Impel, NTN..
- Consultant to Major and Large Pharmaceutical Companies

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Outline

I. Chemical and Biologic versus Recombinant Cell Therapy

II. Why Autologous Recombinant and Live Cells?

III. Transformation of Autologous T cell from the same Patient as a Therapeutic Product

IV. Health Outcomes and System Impact

V. Summary

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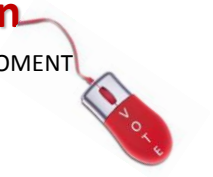
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



Recombinant cells are: (Select all that apply)

- Used to produce proteins; some are marketed as FDA approved prescription pharmaceuticals
- (Fixed or killed) are available as therapeutic products
- Not yet approved by the FDA as live and functional cell therapeutic products
- Approved by the FDA as a part of a regenerative (stem-cell) medicine for spinal cord injury
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

I. Chemical and Biologic vs Recombinant Cell Therapy

- **Chemical based therapeutics or small molecule drugs can be synthesized and the product homogeneity** (purity) **verified**
- **Biologics or large proteins** (MW> 5-10kD) **are often manufactured by recombinant cells and verification of product quality is more challenging** (often not homogenous)
- **The use of recombinant cells** (not the protein produced by these cell) **are even more complex as a therapeutic product**

I. Chemical and Biologic vs Recombinant Cell Therapy

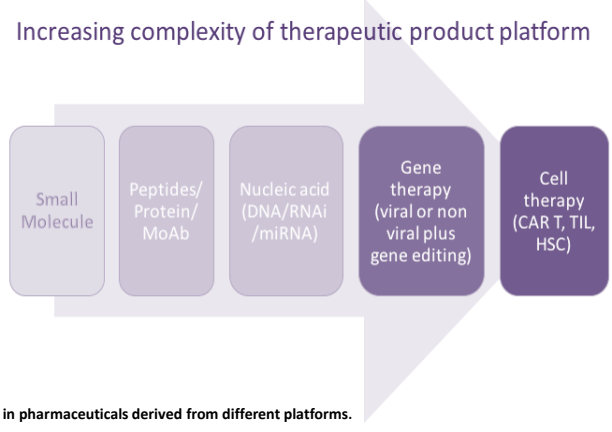


Figure 1. Schematic representation of complexity in pharmaceuticals derived from different platforms.

The scale up and manufacturing of small molecules is well known to the industry and hence generally of lower complexity than biotechnology products. Small molecule drug substances can be made homogenously at nearly 100% purity, a target that larger peptides, proteins, nucleic acid therapeutics, and vectors are unable to achieve. In addition, cell products intended for reintroduction into patients such as viral delivery systems or cell therapy (e.g., chimeric-antigen receptor expressing recombinant autologous T or **CAR** T cell) include logistical and stability complexity. Thus, cell therapy is a considerably more complex therapeutic product platform than small molecules. MoAb, monoclonal antibody; **TIL**, tumor infiltrating lymphocytes; **HSC**, hematopoietic stem cells. (Bak et al., JPS 2019)

Ho, Biotechnology and Biopharmaceuticals, ed2, 2013; doi/book/10.1002/9781118660485

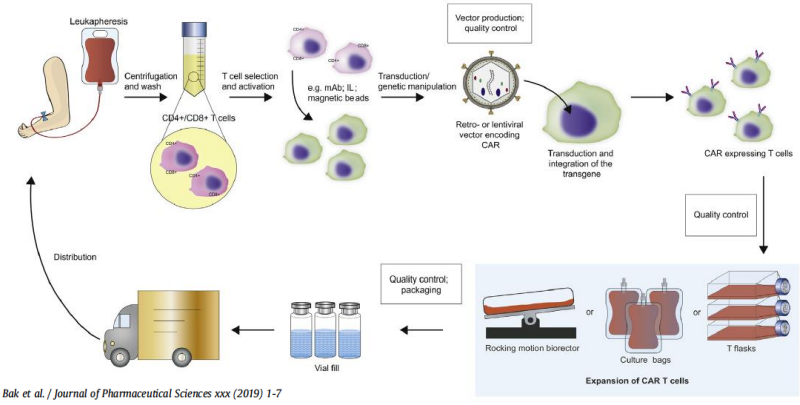
I. Chemical and Biologic vs Recombinant Cell Therapy

Rationale for recombinant vs stem (self-renewal) cell therapy

Intent	Stem Cell	Recombinant Cell
Application	Self-renewal and regenerative medicine	Specific purpose, i.e., immunotherapeutic action
Examples	• Hematopoietic stem cell transplantation (HSCT) for VOD (hepatic veno-occlusive disease) • Bone marrow stem cell for leukemia	• Modified autologous cell for cancer vaccine • Car T cell products as immuno-therapy
FDA approval for use as cells that are modified and expanded in vivo for reinfusion as cell therapeutic product		• Provenge (Sipuleucel-T) autologous T cell vaccine (2010) • Yescarta-CAR T autologous recombinant T cell for B-cell cancer (2017) • Kymriah-CAR T autologous recombinant T cell for leukemia (2017)

I. Chemical and Biologic vs Recombinant Cell Therapy

Overall end-to-end (complex) process of a CAR T cell product



A. Bak et al. / Journal of Pharmaceutical Sciences xxx (2019) 1-7

Figure 3. Schematic overview of the needle-to-needle approach as described for the CTL019 CAR T cell production for early clinical trials. The process involves removing blood from the patient through the process of leukapheresis, separating the leucocytes, and clearing the sample for impurities such as anticoagulants and platelets, enriching for T-cells with separation at the level of CD4+/CD8+ T-cells. Following this the T-cells are activated, often by monoclonal antibodies and interleukins (IL2 or IL7 and IL15) and more specific for CTL019 the activation was carried out with anti-CD3/CD28 magnetic beads. The activated T-cells are hereafter genetically modified with the lentiviral vector encoding for the CAR and the transduced cells are allowed to expand in cell number (various methods have been described for this process including T-flasks, culture bags and bioreactors as reviewed in ref.[7]) before concentrating the CAR T cells (e.g., 5L cell culture is concentrated [up to 100×]) before reinfusion—typically 10 to 250 million cells in 10 to 50 mL volume per dose per patient.

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

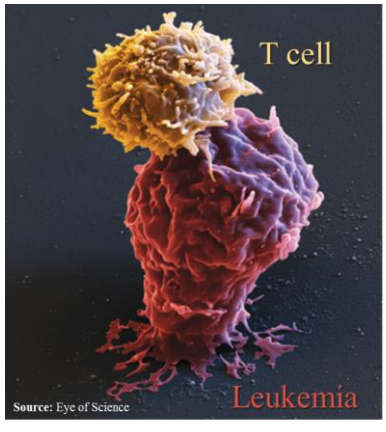
Current Chimeric Antigen Receptor or CAR T cell therapeutic products are personalized and individualized medicine because: (Select all that apply)

- Leukocyte or white blood cells collected from the subject are used as a starting point
- Patient's own cells are transduced to express chimeric antigen receptors to clear cancer
- Transduced cells from cell-lines or other donors may induce a graft-vs-host response or rejection that aborts the function
- The recombinant leukocytes (T cell) verified to express chimeric antigen receptor or CAR (on T cells) are re-introduced into the same patient donor
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

II. Why Autologous Recombinant and Live Cells?

Why these cells be better than platform than that of fixed cell vaccines such as PROVENGE® (sipuleucel-T) autologous T cell product?



II. Why Autologous Recombinant and Live Cells?

Isn't protein therapeutics made by recombinant cells are already complex and challenging enough?

- **Chemical or small molecule** (MW ~500-1kD) **drugs are synthesized and their purity homogeneity readily verified**
- **Biologic or protein** (MW> 5-10kD) **drugs, manufactured with recombinant cells need tighter process controls as verification of final product quality is more challenging** (often not homogenous)
- **The use of recombinant cells** (not the protein produced by these cell) **are even more complex to produce therapeutic products such as Epoetin, Somatotropin, Herceptin** (antibody)

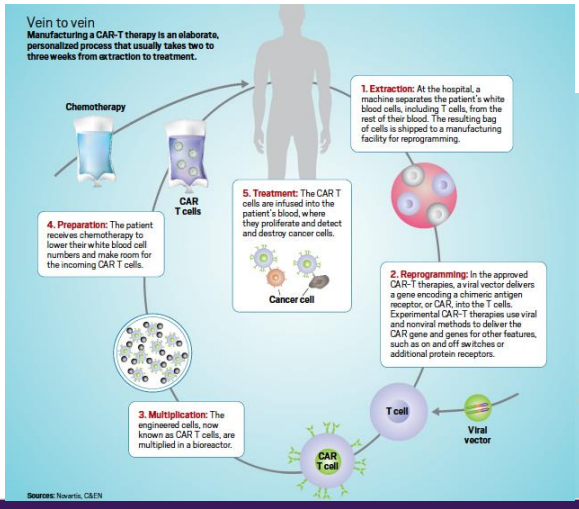
II. Why Autologous Recombinant and Live Cells?

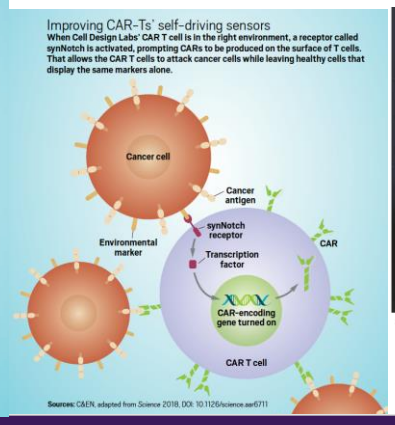
Three essential elements for CAR T cell function

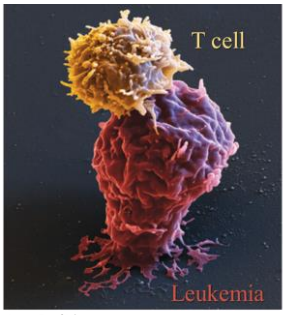
- **Autologous** — T cells from the same patient to prevent rejection (due to inter-individual variations in transplant antigen MHC)
- **Recombinant** — A process used to transform the autologous T cell to recognize target marker (i.e., Chimeric Antigen Receptor or CAR)
- **Live** (functional) **cell** — To produce cell-mediated processes (in the case of CAR-T, to seek out cancer cells and dock them via the chimeric antigen receptor and allow contact-mediated cancer cell killing function of T cells to proceed)

II. Why Autologous Recombinant and Live Cells?

CAR T cell therapeutic integrate all these three aspects







Source: Eye of Science

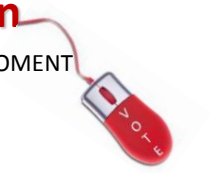
II. Why Autologous Recombinant and Live Cells?

CAR T (functional) cell therapy provides hope and cure for cancer

- Impressive outcomes of the two FDA approved CAR T cell therapies for B-cell cancers
- Works on a majority of previously non-responsive to current drug or biologic therapies
- Over 50% of subjects on the two tested and approved CAR T cell therapy (single infusion dose) experienced event-free survival

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



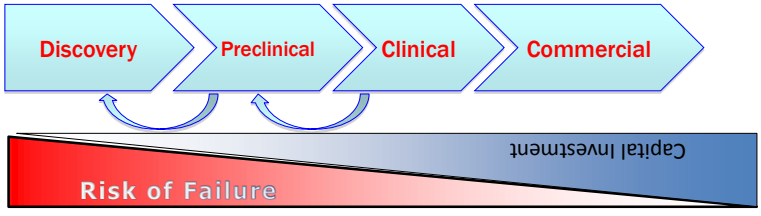
CAR T cell therapeutic product can be manufactured: (Select all that apply)

- With a process similar to making chemical drugs (e.g., Tylenol tablets)
- Only on site at the local blood and cancer research center
- Large-scale in batches intended for hundreds/thousands of people onsite
- At an off-site facility with clearly traceable quality, sterility and chain of custody
- But FDA regulations cover only the manufacturing plants and product released from the respective facility

** If your answer differs greatly from the choices above tell us in the chat!*

III. **Transformation CAR T cell into Therapeutic Product**

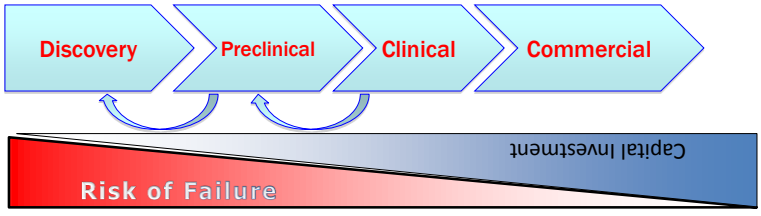
Pharmaceutical Drug Development-Roadmap



III. Transformation CAR T cell into Therapeutic Product

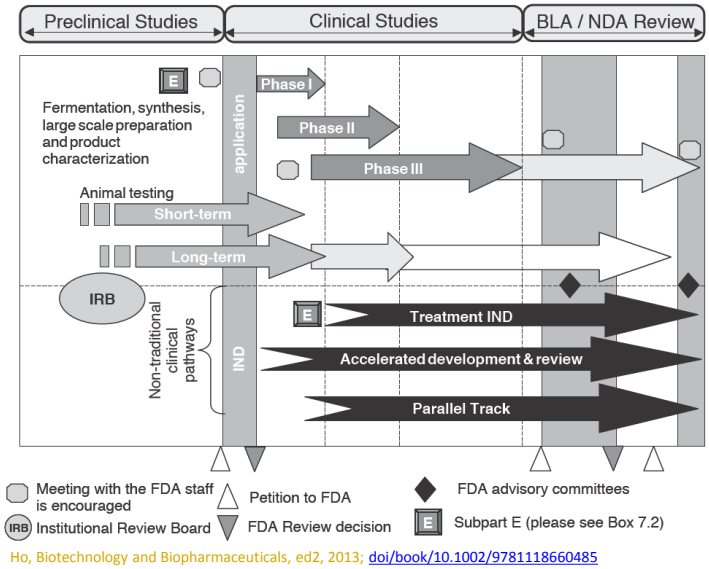
- **Market Drivers for R&D and Clinical Development**
  - Financial ~$2.3 billion annual gene and cell therapeutic market with 50% annual growth (BBC market analysis, 2018); $17.4 billions by 2023.
  - Promised to find a cure for incurable diseases (e.g., Cancer and HIV/AIDS)
- **Manufacture, Logistics and Regulatory Assurance and Approval**

Pharmaceutical Drug Development-Roadmap



Phases of Development
- Discovery
- Preclinical → IND
- Clinical 1,2,3 → NDA / BLA
- Commercial → Phase 4, safety monitoring

III. Transformation CAR T cell into Therapeutic Product



Ho, Biotechnology and Biopharmaceuticals, ed2, 2013; doi/book/10.1002/9781118660485

III. Transformation CAR T cell into Therapeutic Product

In 2017 two CAR T cell products were approved-impressive primary end point—overall remission (response) rate in 3 month or longer

KYMRIAH® (tisagenlecleucel) vs. YESCARTA® (axicabtagene ciloleucel)

- **Kymarih** (Tisagenlecleucel) — **indicated for Acute Lymphoblastic Leukemia** (AML)
  - ELIANA Clinical Trial (multi-center pivotal trial)
  - A single 0.2-5.4 million CAR T cell/kg dose
  - Maude et al., N Engl J Med 2018;378:439-48. DOI: 10.1056/NEJMoa1709866

- **Yescarta** (Axicabtagene ciloleucel) — **indicated for Lymphoma**
  - **ZUMA-1** Clinical Trial (multi-center trial)
  - A single autologous CAR T cell dose of 2 million cells/kg
  - Locke and Neelapu et al., Lancet Oncol 2019; 20: 31–42. DOI: 10.1016/ S1470-2045(18)30864-7

III. Transformation CAR T cell into Therapeutic Product

KYMRIAH® (tisagenlecleucel)

indicated for B-cell Lymphoblastic Leukemia (AML)
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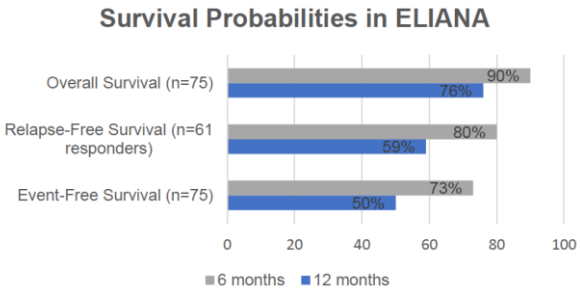
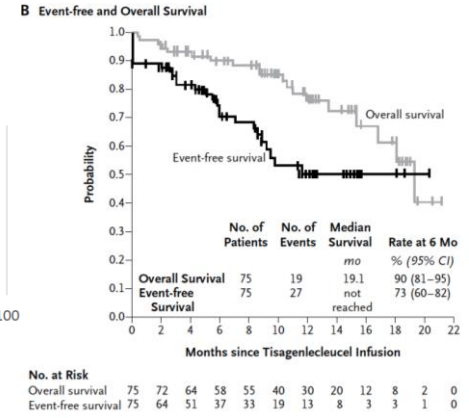




III. Transformation CAR T cell into Therapeutic Product

YESCARTA® (axicabtagene ciloleucel)

indicated for B-cell Lymphoma

- **ZUMA-1** Clinical Trial (multi-center trial)
- Locke and Neelapu et al., Lancet Oncol 2019; 20: 31–42. DOI: 10.1016/ S1470-2045(18)30864-7

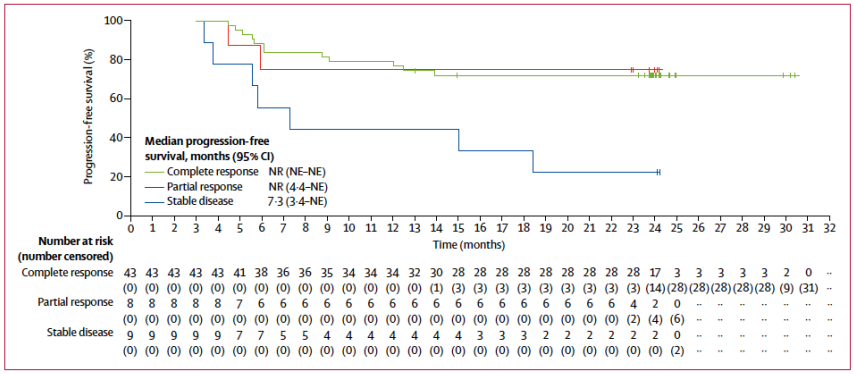


Figure 2: **Post-hoc analysis of investigator-assessed progression-free survival by response status at 3 months after axicabtagene ciloleucel**
60 patients with ongoing complete response, partial response, or stable disease month 3 in phase 2 are shown. The x-axis shows time since infusion of chimeric antigen receptor T cells. Four of eight patients with partial responses and four of nine patients with stable disease at 3 months subsequently converted to complete responses. NR=not reached. NE=not estimable.

III. Transformation CAR T cell into Therapeutic Product

With these impressive immunotherapeutic outcomes, many more cell-therapeutics are in the pipe-line

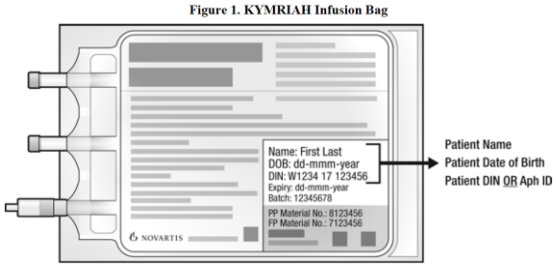
Generic [Trade] name	Conditions	Vector and intervention	Gene editing	Clinical Status	Sponsor
NY-ESO-1	Multiple myeloma, synovial sarcoma, myxoid/round cell liposarcoma, melanoma	Intravenous infusion with NY-ESO-1 redirected autologous T cells (CRISPR edited endogenous TCR and PD-1)	Ex vivo	Phase 1 (NCT03399448)	University of Pennsylvania
CTX001	β-thalassemia and sickle cell disease	Intravenous infusion with autologous CRISPR-Cas9 modified CD34+ Human Hematopoietic Stem and Progenitor Cells	Ex vivo	Phase 1/2 (NCT03655678)	CRISPR Therapeutics/ Vertex Pharmaceuticals
UCART019	B-cell leukemia and B-cell lymphoma	Intravenous infusion with CAR T cells	Ex vivo	Phase 1/2 trial (NCT03166878)	Chinese PLA General Hospital
	Esophageal cancer	Intravenous infusion with PD-1 knockout T-cells	Ex vivo	Phase 2 (NCT03081715)	Hangzhou Cancer Hospital/Anhui Kedgene Biotechnology Co.,Ltd
Voretigene neparvo-vec-rzyl [Luxturna]	Retinal dystrophy: Leber's congenital amaurosis	AAV2; single subretinal injection	In vivo	Approved 2017 (FDA)	Spark Therapeutics
GSK2696273 [Strimvelis]	Adenosine deaminase deficiency-severe combined immunodeficiency	Autologous CD34+ cells modified through lentiviral vector transduction	Ex vivo	Approved 2016 (EMA)	Ochard Therapeutics/ GlaxoSmithKline
Axicabtagene cilo-leucel [Yescarta]	Diffuse large B-cell lymphoma	Intravenous infusion with CAR T cells	Ex vivo	Approved 2017 (FDA), 2018 (EMA)	Gilead
Tisagenlecleucel [Kymriah]	B-cell acute lymphoblastic leukemia	Intravenous infusion with CAR T cells	Ex vivo	Approved 2017 (FDA), 2018 (EMA)	Novartis

Adapted from Bak (and Ho) et al., J Pharm Sci 2019,
Table 3. A representative sample of selected gene therapies in clinical trials as well as current FDA/EMA approvals (as of February 2019)

III. Transformation CAR T cell into Therapeutic Product

Regulatory, Manufacturing, Quality and Logistics and more [Commercial Scale]

- Intended use, product specification, quality assurance, sterility, functional verification, stability (production to infusion site)*
- Who, where and how to ensure the right patient receive within the target schedule time-line.
- Logistics of planning from collecting autologous cells to infusion of recombinant CAR T cell to the same patient.



* FDA regulatory guidance on cell therapeutics preclinical and clinical evaluation including chemistry manufacturing and controls, product specification, quality assurance to ensure the final product meet the defined product specifications based on validated and appropriate assays.

IV. Health Outcomes and System Impact

Who are appropriate candidates and how to gain access?

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Measuring what matters

Institute for Health Metrics and Evaluation

IV. Health Outcomes and System Impact

- **Which patient would benefit?**
  - Not for primary B-cell lymphoma or AML (only refractory or in second or later relapse—there are significant side-effects)
- **Cost of CART T personalized cell medicine**
  - $475k **Kymarih** and $373K **Yescarta** (for a single dose)
- **Cost-effectiveness** (ELIANA cost-effectiveness data; 600-750k)
- **Impact on the overall health system** (overall budget in billions?)
- **Payers perspective**

IV. Health Outcomes and System Impact

*One Large (the Center for Medicare and Medicaid CMS) Payer's perspective**

Price and Cost	Kymarih (Tisagenlecleucel)	Yescarta (Axicabtagene Ciloleucel)
Product Price	US $ 475k	US $ 373K
CMS reimburse (hospital)	$ 500k	$ 400k
Patient (20%)	$ ~100k	$ 79k
But US SS Maximum out of pocket annual co-payment		$1,340

*Weighing the Cost and Value of CAR T-Cell Therapy - The ASCO Post based on panel discussion—accessed 3/26/2019

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Summary

- Recombinant Cell is a Complex Live, Functionally Active Product
- Autologous Recombinant and Live Cells provide therapeutic effects not achievable by other drug platforms
- Transformation of Autologous T cell from the same Patient as a Therapeutic Product have made break-through impact on cancers
- Health Outcomes and System Impact data also point to overall benefit
- This new therapeutic modality may redefine the role of pharmacist and pharmaceutical scientists

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Thank You!

धन्यवाद (Hindi)
ਤੁਹਾਡਾ ਧੰਨਵਾਦ (Pujabi)
આભાર (Gujarati)
ধন্যবাদ (Bangli)
ကျေးဇူးတင်ပါတယ (Burmese)
謝謝 (Chinese)
Merci (French)
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Mahadsanid (Somali)
Gracias

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2014

Drug Discovery Series #1 - Current Drug Discovery and Development Process
(DDS #1) Watch this overview of the drug discovery and development process to learn the stages and challenges in every step.

Primer in Drug Target Classes
(DDS #2) Listen in on a discussion on the big four druggable families and the difference between small molecule and biotherapeutic targets.

Key Concepts in Identifying Drug Leads
(DDS #3) Discover how drug-likeness is a decaying concept, explore the Rule of Five, and show how lessons from the past may guide the present.

Lead Optimization – Building Efficacy & Safety
(DDS #4) Learn strategies on how to effectively optimize small molecule hits and rapidly assess your findings.

Tips for Filing IND and Starting your Clinical Trials
(DDS #5) What do you need to know when filing for Investigational New Drug submissions to the United States Food and Drug Administration?

The Role of Chemistry in Clinical Trials: The Big Expense & Lessons Learned
(DDS #6) Learn how the properties of the candidate impact decisions in the discovery process.

Pharmacoeconomics and IP Strategies in Drug Development
(DDS #7) Review the basic principles of Pharmacoeconomics in drug development strategies as well as its role in determining health insurance coverage of drug products.

Future of Drug Discovery - Challenges, Risks and Rewards
(DDS #8) Explore how how risks and challenges will be dealt with in the future and the key skill sets required of future medicinal chemists.

2015

Designing Better Drug Candidates
(January) Learn various factors that can be used to improve candidate quality from Dr. Paul Leeson.

Strategies to Improve Solubility of Drug Candidates
(February) Learn a number of different strategies for improving drug solubility through structural modification.

Fragment-Based Drug Design Strategies
(March) Finding the right drug targets is becoming increasingly difficult. Learn how focusing on the smaller picture can have big results.

Screening Strategies
(April) Learn the pros and cons of different screening strategies.

Avoiding PAINS (pan-assay interference compounds)
(May) Jonathan Baell shared some tips on how to avoid the dead ends of drug discovery.

Accelerating CNS Positron Emission Tomography (PET) Ligand Discovery
(June) Join Lai Zhang as he lays out a set of preferred parameters for which has yielded successful PET ligands and reduced resources and timelines.

X-ray Crystallography in Drug Discovery
(July) Jon Mason and Miles Congreve describe what protein-ligand X-ray data can do for you.

Choices and Trends in Solid Dosage Form Selection
(August) Discover the pros and cons of the different solid state forms and what to consider when selecting.

Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies
(September) Gain an understanding of acceptable drug delivery approaches to support preclinical dose escalation.

Pharmacokinetic Considerations in Drug Design and Development
Learn about key pharmacokinetic concepts including clearance, volume of distribution, half life and protein binding.

Prodrugs in Drug Discovery
(November) John Wiggins shares the utility of prodrugs, their general properties and prerequisites for optimal performance.

2016

I - Time: The Fourth Dimension in Drug Discovery
1. The Importance of Drug-Target Kinetics in Drug Design — Robert Copeland - Epizyme, Inc; Dan Eriksson - Carmot Therapeutics
2. Long-Acting Injectable Medications: Strategies and Mechanistic Considerations — Jukes Ramenar - Alkermes; Annette Bak - Merck
3. Modified Release Formulations for Solubility Starved Compounds — Mangkuo Hu - Merck; John Morrison - BMS
4. The Medicinal Chemist of Tomorrow (Special Topic) — Joel Barrish - AchilliumRavi Nargund - Merck; Maly Schmid - Tech Coast Angels

II - Beyond Traditional Small Molecules
5. Design of Deliverable Macrocycles — Scott Lokey - UC Santa Cruz; Nicholas Meanwell - BMS
6. Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates — L. Nathan Tumey - Pfizer; Peter Senter - Seattle Genetics
7. Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides — Punit Seth - Ionis; Richard Dipon - BMS
8. Crystallography as a Drug Design and Delivery Tool (Special Topic) — Robert Wanslow - Crystal Pharmatech; Vincent Stoll - Abbvie; Andrew Brunskill - Merck

III - Pharmacology Revisited
9. Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites? — Deepak Dalvie - Pfizer; Frederick Peter Guengerich - Vanderbilt University
10. Rational Design of Small Molecules Targeting RNA — Matt Disney - Scripps Rl Florida; Amanda Garner - University of Michigan
11. Cell Penetrating Peptides to Improve Cellular Drug Uptake — Dehua Pei - The Ohio State University; Scott Hart - Bristol-Myers Squibb

2017

I - Fighting Cancer
1. Fighting Cancer: Targeting CNS Malignancy with Kinase Inhibitors — Timothy P. Heffron - Genentech; Mark Wittman - Bristol-Myers Squibb
2. Fighting Cancer: Epigenetic targets for Oncology — Stuart Conway - Oxford; Sharan Bagal - AstraZeneca
3. Fighting Cancer: Allostery and Targeting Cancer Cell Metabolism — Stefan Gross - Agios; Scott Edmundson - AstraZeneca

Special Broadcast
4. Cystic Fibrosis: Discovery of CFTR Modulators — Peter Grootenhuis - Vertex; Nick Meanwell - Bristol-Myers Squibb

II - Anti-Infectives
5. Anti-Infectives: Rational Approaches to the Design and Optimization — Jason Sello - Brown University; Courtney Aldrich - University of Minnesota
6. Tuberculosis: An Introduction for Medicinal Chemists — Carl Nathan - Weill Cornell Medicine; Christopher Boyce - Merck
7. Viral Hepatitis: The Search for a Cure — Mike Sofia - Arbutus Biopharma; Stephen Mason - CaroGen Corporation

Special Broadcast
8. Spinal Muscular Atrophy — Kevin Hodgetts - Harvard Medical School; Alyson Weidmann - ACS Publications

III - Immunology
9. Psoriasis: Treatment and Novel Approaches — Frank Narjes - AstraZeneca; John Morrison - Bristol-Myers Squibb
10. Lupus: Treatment and Novel Approaches — Laurence Menard - Bristol-Myers Squibb; Mary Struthers - Bristol-Myers Squibb

2018

1. Jan 25 — A New Strategy in Drug Discovery: Protac-Induced Protein Degradation — Ian Churcher - BenevolentBio; Aaron Balog - Bristol-Myers Squibb
2. Feb 22 — Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry — Annette Bak - AstraZeneca; Donna Huryn - University of Pittsburgh; Erika Araujo - Bristol-Myers Squibb; Nurulain Zaveri - Astraea Therapeutics
3. Mar 29 — A Nanomedicine Overview for mRNA Delivery: Innovative Methods Using Lipid Nanoparticles — Marianna Yanez Arteta - AstraZeneca; Dennis Lueng - Genentech
4. Apr 26 — Nanomaterials for Fighting Antibiotic-Resistant Bacteria — Vincent Rotello - University of Massachusetts at Amherst; Christopher England - American Chemical Society
5. May 31 — Advanced Nano-Delivery Systems: Facilitating Tumor Delivery and Mitigating Resistance — Mansoor Amiji - Northeastern University; Venkat Krishnamurthy - AstraZeneca
6. Jun 28 — Pitfalls and Promise of Central Nervous System Drug Discovery — Valentin Gribkoff - Yale University; Nicholas Meanwell - Bristol-Myers Squibb
7. Jul 26 — How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows — Craig Lindsley - Vanderbilt Center for Neuroscience Drug Discovery; Amy Newman - Intramural Research Program, NIH
8. Sept 20 — A Novel Strategy for the Treatment of Chronic Pain: Antagonising PAR2 with a Monoclonal Antibody — Pete Thornton - AstraZeneca; Nurulain Zaveri - Astraea Therapeutics
9. Oct 18 — How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling — Elizabeth de Lange - Leiden Academic Center for Drug Research; Alexander Tropsha - University of North Carolina
10. Nov 29 — Human Exosomes: An Ideal Vehicle for Delivery of Therapeutic RNAs to Cells and Organs — Hadi Valadi - University of Gothenburg; Alexander Kapuuttin - AstraZeneca

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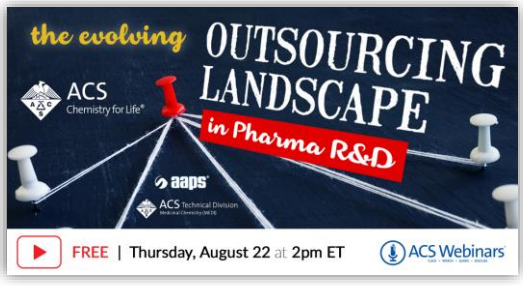

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- A profile of different outsourcing models that can be considered
- What to look for as you select a CRO to partner with

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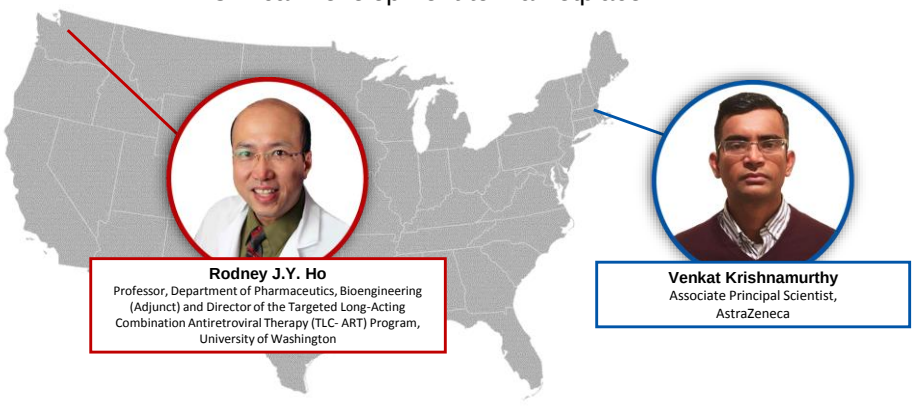

Rodney J.Y. Ho
Professor, Department of Pharmaceutics, Bioengineering (Adjunct) and Director of the Targeted Long-Acting Combination Antiretroviral Therapy (TLC- ART) Program, University of Washington

Venkat Krishnamurthy
Associate Principal Scientist, AstraZeneca

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Fan of the Week

Rafael Álvarez González, PhD
Centennial (1890-1990) Doctoral Alumnus of Biochemistry & Molecular Biology of Cancer, From the Department of Chemistry/Division of Biochemistry (80's), University of North Texas at Denton

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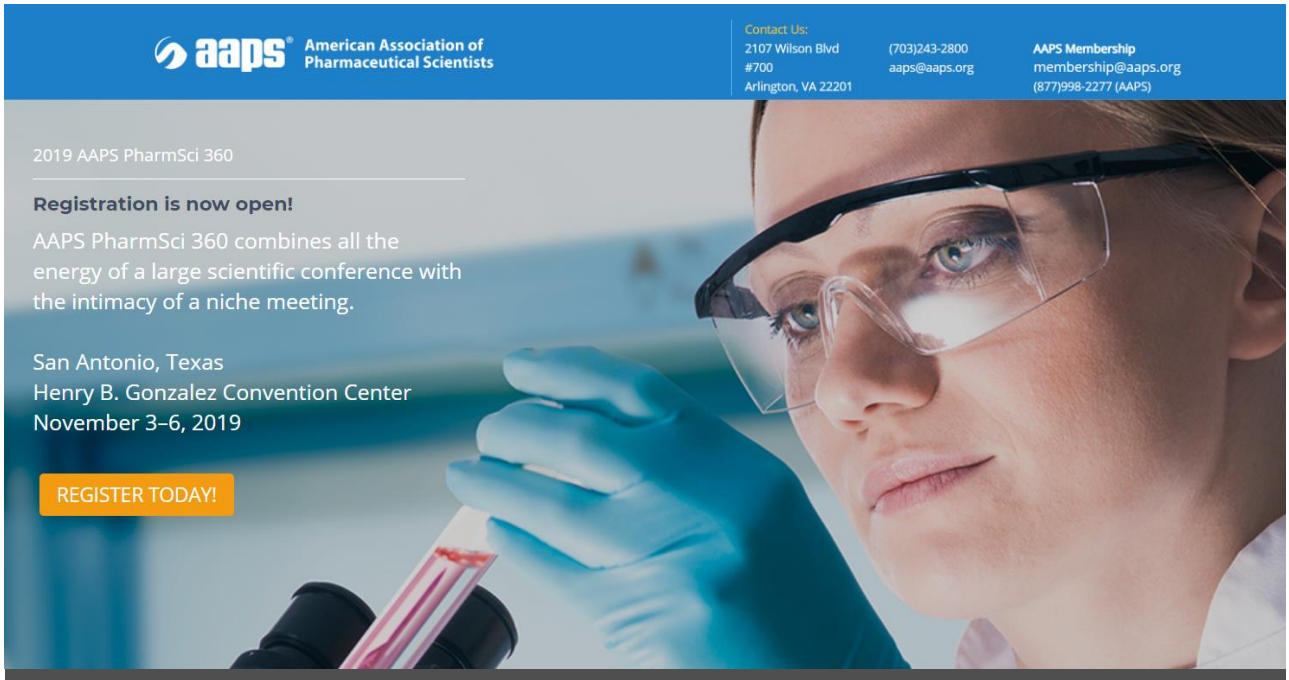

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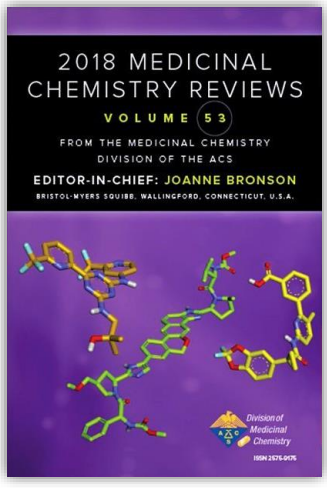

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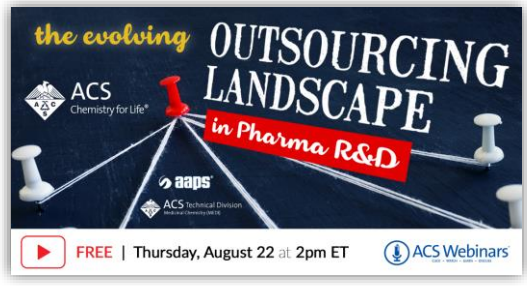

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