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## January 30 – February 1, 2018 | Boston, MA

www.synthetic-lethality-summit.com

# Synthetic Lethality Summit

- Identify the next Generation of Synthetic Lethal Pairs
- Establish Efficacy across a Range of Contexts
- Exploit Key Targets of Mechanisms of Resistance

## Expert Speakers Including:

**Jeffrey Hanke**
CSO & EVP, R&D
**Tesaro**

**Carl Barrett**
VP Translational Sciences
**AstraZeneca**

**Simone Botti**
CEO
**MetaboMed**

**Daniel Durocher**
Co-founder
**Repare Therapeutics**

**Graeme Smith**
CSO
**Artios Pharma**

**Mark Kowalski**
CMO
**Sierra Oncology**

**René Bernards**
Group Leader and Head of Division
**Netherlands Cancer Institute**

**Alexandra Grassian**
Senior Scientist
**Epizyme**

**Bill Forrester**
Principal Investigator
**Novartis**

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"This meeting gathered all experts in the field to share ideas and data. It was quite an eye opener. I feel I came home with excitement and a brand new mind towards my work in the field"
**Past CVI Summit Attendee, Pfizer**

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# Welcome to the Synthetic Lethality Summit 2018

**The first industry-dedicated meeting focused on identifying the next generation of synthetic lethal pairs, achieving efficacy across a range of contexts, optimizing synthetic lethal screening techniques and exploiting key targets of mechanisms of resistance.**

The synthetic lethality space is experiencing a surge of activity, fueled by the recent successes of PARP inhibitors. The ***Synthetic Lethality Summit*** will gather the leading stakeholders from across drug development to discuss the key breakthroughs.

The ***Synthetic Lethality Summit*** will provide a comprehensive analysis of the fundamental science and clinical development process in this space, leveraging collective expert knowledge to optimize the identification and therapeutic exploitation of robust synthetic lethal pairs.

Take the lessons learned from the success of PARP inhibitors and apply these to understanding the dynamics of the synthetic pairs, establishing efficacy across contexts, targeting mechanisms of resistance and stratifying patient populations.

Join the foremost industry experts from a diverse range of companies to advance the research and development of drugs targeting novel synthetic lethal pairs.

**Hear what previous Hanson Wade CVI Summit attendees have to say:**

"A very rich environment for discussion, problem solving, and networking with all key players and up and coming players in the field. Great meeting."
**Eureka Therapeutics**

"This was an eclectic and dynamic conference, with all the key players and decision-makers assembled, willing to share their science and perspective, in very meaningful ways. Let's see this conference happen again next year!"
**Juno Therapeutics**

## Gain Unique Insights into the Key Issues Facing This Industry

**1.**

**Achieving Efficacy across Contexts:**
Define the key steps required to identify and therapeutically exploit robust synthetic lethal interactions that are conserved across a variety of defined contexts.

**2.**

**Optimize Patient Stratification:**
Streamline clinical trials by improving the recruitment and stratification of patients, increasing efficiency.

**3.**

**Apply Lessons Learned from PARP Inhibitors:**
Analyze key aspects of the development of PARP inhibitors through case studies, and determine how we can use these insights to advance R&D of new synthetic lethal drugs.

**4.**

**Exploit Key Targets of Mechanisms of Resistance:**
Assess the most effective methods for identifying and utilizing mechanisms of resistance to optimize cancer treatment.

**5.**

**Harnessing Bioinformatics and Computational Approaches:**
Exploring the latest advances in identifying clinically relevant synthetic lethal interactions from genome wide screens.

# Expert Speakers

**Graeme Smith**
CSO
**Artios Pharma**

**Carl Barrett**
VP Translational Sciences
**AstraZeneca**

**Aviad Tsherniak**
Associate Director, Cancer Data Science
**Broad Institute of MIT and Harvard**

**Alexandra Grassian**
Senior Scientist
**Epizyme**

**Cyril Benes**
Director, Center for Molecular Therapeutics
**Massachusetts General Center for Cancer Research**

**Simone Botti**
CEO
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**Sierra Oncology**

**Jeffrey Hanke**
CSO & EVP, R&D
**Tesaro**

**Kevin Coleman**
Executive Director, Translational R&D, Experimental Biology
**Tesaro**

**Angelique Whitehurst**
Associate Professor
**UT Southwestern**

**Lars Zender**
Professor, Gastroenterology/ Oncology
**University Hospital Tübingen**

**Eytan Ruppin**
Director, Center of Bioinformatics & Computational Biology
**University of Maryland**

**Stephane Angers**
Professor & Associate Dean Research, Faculty of Pharmacy & Department of Biochemistry
**University of Toronto**

**Daniel Durocher**
Co-founder
**Repare Therapeutics**

> "Extremely useful conference to meet other players in modern OV development, which will make a change in how we are going to treat diseases like cancer."
>
> **Past CVI summit attendee, Boehringer Ingelheim**

# Conference Day One | Wednesday January 31st, 2018

**8.00 Coffee & Registration**

**8.50 Chairman's Opening Remarks**

## Advancing Synthetic Lethal Screening

**Stephane Angers**
Professor & Associate Dean Research, Faculty of Pharmacy & Department of Biochemistry
**University of Toronto**

**9.00 Leveraging Genome-wide CRISPR Screens and Synthetic Lethal Interactions for Novel Cancer Therapeutics**

- Novel genome-wide CRISPR-Cas9 functional screening approaches to probe the genetic wiring of cancer cells
- Identification of "core" fitness genes required for the growth of all cell types and of "context-specific" fitness genes required specifically for a limited number of cancer types
- Case study in pancreatic cancers revealing the Wnt receptor FZD5 as one such "context-specific" fitness gene for which we have developed a monoclonal antibody exhibiting tumor growth inhibition
- Performing CRISPR-Cas9 essentiality and chemogenomic screens to reveal new genetic vulnerabilities of Glioblastoma stem cells and identify mechanisms of drug resistance and hypersensitivity

**Alexandra Grassian**
Senior Scientist
**Epizyme**

**9.30 Identifying Differential Dependencies on Epigenetic Pathways and Synthetic Lethal Relationships with CRISPR Pooled Screening of Hundreds of Cancer Cell Lines**

- Identifying both pan-essential genes as well as genes which display selective sensitivity upon knockout with high quality and reproducible data from CRISPR pooled screening
- Integrating pooled screening data with other genomic information can aid in the identification of novel synthetic lethality interactions
- Gene amplifications can generate false positive data in CRISPR pooled screening
- Determining the domain responsible for the observed proliferation effect with domain-focused CRISPR screening

**Kevin Coleman**
Executive Director, Translational R&D
**Tesaro**

**Stephane Angers**
Associate Dean Research, Department of Biochemistry
**University of Toronto**

**Alexandra Grassian**
Senior Scientist
**Epizyme**

**10.00 *Panel:* Comparison of Approaches and Best Practices for Synthetic Lethal Screening**

- Assessing the benefits and drawbacks of CRISPR full knockout, CRISPR-I/CRISPR-A and RNAi
- Examining overlap among different silencing modalities
- Optimal practices for double-knockout library screening to identify synergistic effects and reliably recognize artefacts
- Capitalizing on screening data – planning chemical pipelines to identify inhibitor compounds for targets nominated by screening efforts

**10.45 Speed Networking & Refreshments**

## Optimizing Bioinformatics & Holistic Approaches to Synthetic Lethality

**Simone Botti**
CEO
**MetaboMed**

**11.45 Exploiting Synthetic Lethality and Induced Essentiality in the Context of Cancer Metabolism with a Combined Computational and Metabolomic Approach**

- Overview of the landscape in cancer metabolism and Metabomed's approach to identifying synthetic lethal and induced essential targets in different cancer types
- Identifying and targeting synthetic lethal vulnerabilities in the context of cancers characterized by impaired or lost function of the SDH complex
- Exploiting specific metabolic stressors of the tumor microenvironment to reveal induced essential targets
- Passenger deletions alter tumor metabolism, revealing synthetic lethal vulnerability
- Computational identification of Synthetic Lethality networks as a tool to generate a stratification strategy for drug therapies based on synthetic lethality

**Aviad Tsherniak**
Associate Director, Cancer Data Science
**Broad Institute of MIT and Harvard**

**12.15 Prioritizing Targets for Therapeutic Development by Defining a Cancer Dependency Map**

- Understanding the relationships between the genetic alterations of cancer and cancer dependencies by building a "cancer dependency map"
- Systematically identifying genetic and small molecule vulnerabilities and determining the molecular markers that are associated with them
- Developing computational methods that correct off-target effects in RNAi screens (DEMETER) and copy number effects in CRISPR screens (CERES)
- Our analysis reveals hundreds of genes that are preferential dependencies in subsets of cell lines

**Eytan Ruppin**
Director, Center of Bioinformatics & Computational Biology
**University of Maryland**

**12.45 Harnessing Synthetic Lethality to Predict Patient Response and Synergistic Combinations in Cancer**

- Exploring ISLE (Identification of clinically relevant Synthetic Lethality), a data-driven approach that mines the TCGA cohort to identify a subset of clinically relevant SL interactions (cSLi) from an initial pool of screened SL interactions
- Testing a select set of predicted cSLi via new experiments, validating their predicted context sensitivity and demonstrating their utility in predicting synergistic drug combinations
- Evidence of successful prediction of patients' treatment response and predicted cSLi providing readily available biological signatures for patient treatment stratification
- Taken together, ISLE complements existing mutation-based methods for precision cancer therapy, extending their scope from few hundreds of cancer driver genes to that of the whole genome

**1.15 Lunch & Networking**

## Overcoming the Lack of Single Agent Activity: Finding Effective Combinations

**Jeffrey Hanke**
CSO & EVP, R&D
**Tesaro**

**2.15 PARP Inhibition Meets Tumor Immune Modulation: Rationale and Patient Positioning Considerations**

- Rationale and opportunity for combination of PARP inhibitors with immune checkpoint modulation
- Leveraging the rapidly emerging key clinical data on PARP inhibitors such as niraparib
- Examining approval pf PD1/L1 immune checkpoint inhibitors across tumor types

**René Bernards**
Group Leader and Head of Division
**Netherlands Cancer Institute**

**2.45 Synthetic Lethality as a Tool to Resuscitate Abandoned Drugs That Experienced Poor Single Agent Activity**

- Exploring relevant synthetic lethality screening strategies
- Identifying effective drug combinations
- Harnessing synthetic lethality to find drug response biomarkers
- Analyzing effective validation strategies

**Jeffrey Hanke**
CSO & EVP, R&D
**Tesaro**

**René Bernards**
Group Leader and Head of Division
**Netherlands Cancer Institute**

**Eytan Ruppin**
Director, Center of Bioinformatics & Computational Biology
**University of Maryland**

**3.15 *Panel:* Mapping the Landscape of Future Combinations for Synthetic Lethal Drugs**

- Examining the industry's current combination trends and identifying the avenues that will be of the highest therapeutic value in the next five years
- Preparing for the implementation of these with the wave of new synthetic lethal drugs set to enter the clinic
- Exploring chemical interactions between targeted therapies and immunotherapies
- Using these insights to balance synthetic lethal drugs with an immunotherapy that can take advantage of the local conditions
- Methods for overcoming potential phasing issues

**4.00 Afternoon Refreshments & Networking**

**4.30 Synthetic Lethality Roundtables**

Discussions led by:  **Graeme Smith**, CSO, **Artios Pharma**

**Mechanisms of Resistance**

- Explore methods for overcoming target-mediated and non-target-mediated resistance
- What methods best determine origins of resistance?
- How can we leverage these to re-sensitize tumors to a synthetic lethal drug?

**Expanding Synthetic Lethality based Therapies Beyond Oncology**

- How can we widen the scope of synthetic lethal drugs to treat a more diverse range of diseases?
- How do we navigate the landscape of possible conditions in which synthetic lethal interactions play a key role and can be targeted?

**Required Steps for Developing Context Independent Synthetic Lethal Drugs**

- How can screening methods best be used to identify synthetic lethal interactions with the potential to be highly stable across contexts?
- What types and combinations of models are required to comprehensively test therapies across contexts?

**5.30 Chairman's Closing Remarks**

# Conference Day Two | Thursday February 1st, 2018

**8.00 Coffee & Registration**

**9.00 Chairman's Opening Remarks & Day 1 Summary**

## Improving Model Systems for Synthetic Lethality

**Cyril Benes**
Director, Center for Molecular Therapeutics
**Massachusetts General Center for Cancer Research**

**9.15 Modeling Cancer Drug Response *in vitro:* Pharmacogenomics and Patient Derived Models**

- Successes and challenges in personalized cancer treatment development
- Approaches for discovery of the optimum context for both old and new drugs
- Analyzing the limit of genomic insight
- Proteomics to the rescue?
- Drug combinations: Discovery process and outcomes of large scale screens
- Patient derived models: From biopsy to screenable models

**Lars Zender**
Professor, Gastroenterology/ Oncology
**University Hospital Tübingen**

**9.45 Non-germline Genetically Engineered Cancer Mouse Models and *in vivo* Functional Genetic Screening**

- Examining with case studies how non-genetically engineered cancer mouse models can be combined with stable in vivo RNAi or Crispr/Cas9 screening technology to identify new therapeutic targets
- The pivotal role of academic drug discovery infrastructures for rapidly translating validated therapeutic target structures into clinical applications
- Exploring an example of a novel and promising drug for the treatment of liver cancer which first went into man less than two years after completion of preclinical testing
- Current research activities on a functional identification of vulnerabilities in senescent cancer cells (therapy induced senescence) as a prerequisite for the development of novel senolytic drugs

**Lars Zender**
Professor, Gastroenterology/ Oncology
**University Hospital Tübingen**

**Cyril Benes**
Director, Center for Molecular Therapeutics
**Massachusetts General Center for Cancer Research**

**10.15 *Panel:* Comparison of Current Modeling Techniques for Synthetic Lethality**

- Identifying the strengths and weaknesses of current model systems
- Strategic modeling approaches to thoroughly test whether interactions are specific to certain cells lines
- Plans for overcoming the lack of appropriate models in the synthetic lethality space

**11.00 Morning Refreshments & Networking**

## Applying Lessons Learned from PARP and DNA Damage Response

**Carl Barrett**
VP Translational Sciences
**AstraZeneca**

**11.30 Synthetic Lethality and DNA Damage and Response Inhibitors in the Clinic**

- Clinical development of olaparib in ovarian cancer, the first PARP inhibitor developed based on the synthetic lethality concept
- Widening the scope of PARP inhibitors beyond ovarian cancer
- Expansion of the synthetic lethality concept beyond BRCA
- Extending the successes of synthetic lethality to other DDR inhibitors

**Daniel Durocher**
Co-founder
**Repare Therapeutics**

**12.00 Charting the Genetic Architecture of the Response to DNA Damage**

- Using CRISPR/Cas9 screen to chart the response to DNA damaging agents
- New types of vulnerability to PARP inhibitors
- Novel mechanisms of resistance to PARP inhibitors in BRCA1-deficient cells
- Translational potential of chemogenomic mapping of drug responses

**Carl Barrett**
VP Translational Sciences
**AstraZeneca**

**Jeffrey Hanke**
CSO & EVP, R&D
**Tesaro**

**Graeme Smith**
CSO
**Artios Pharma**

**Daniel Durocher**
Co-founder
**Repare Therapeutics**

**12.30 *Panel:* Developing A Roadmap for Applying the Lessons Learned From PARP Inhibitors to the Next Generation of Synthetic Lethal Drugs**

- Analyzing the effective practices that contributed to the success of PARP Inhibitors
- Investigating the sources of error and inefficiencies, and plans that can be implemented to avoid these with future synthetic lethal drugs
- Future use of PARP inhibitors in absence of the BRCA mutation – targeting Tumors with homologous replication deficiency
- Examining indications and causes of DNA replication stress, and using it as a marker for sensitivity of new drugs

**1.15 Lunch & Networking**

## Exploiting Mechanisms of Resistance & Optimizing Patient Stratification

**Mark Kowalski**
CMO
**Sierra Oncology**

**2.15 Leveraging Synthetic Lethality to Enhance Clinical Trials with SRA737, a Next-generation Chk1 Inhibitor**

- SRA737 is a potent, highly selective, orally bioavailable small molecule inhibitor of Chk1 with best-in-class potential
- Sierra Oncology is exploiting synthetic lethal relationships between Chk1 inhibition and deficient tumor DNA repair pathways to enhance and optimize the design of two early phase trials of SRA737
- To optimize patient recruitment strategies for patient eligibility, Sierra is enrolling patients with tumors identified to have genetic aberrations hypothesized to confer sensitivity to SRA737 via synthetic lethality, as a monotherapy or in combination
- Replication stress induced by low-dose gemcitabine may further potentiate the effects of SRA737 induced Chk1 inhibition when administered in combination

**Angelique Whitehurst**
Associate Professor
**UT Southwestern**

**2.45 Mechanisms of Tumor-activated Gametogenic Proteins in Tumor Cell Behaviors**

- Chemical and genetic synthetic lethal approaches to identifying novel regulators of tumor cell survival
- Strategies for follow-up of nominated targets using orthogonal approaches
- Vignettes on the mechanisms of gametogenic protein function in tumor cells
- Implications for gametogenic genes as biomarkers for therapies

**3.15 Chairman's Closing Remarks**

**3.30 Close of Synthetic Lethality Summit**

# WORKSHOPS

## Workshop Day | Tuesday January 30th, 2018

## Workshop A

### Optimizing Synthetic Lethal Screens: CRISPR/Cas9 Identification of Interactions for Cancer Drug Discovery

**9:00am – 12:00pm**

The deployment of CRISPR/Cas9 technology as a genome editing and screening tool has the potential to facilitate the identification of novel cancer targets and provide the opportunity for mapping pairwise genetic interactions that can be used to identify synergistic drug combinations.

Join Kevin Coleman, Executive Director of Translational Research & Development Experimental Biology at Tesaro to:

- Design and implement CRISPR/Cas9-based synthetic lethal screens for the identification of pairwise genetic interactions in human cancer cells
- Personalize cancer treatment through the utilization of gene essentiality databases with a case study in tumors harboring a deficiency in the homologous recombination pathway
- Explore emerging CRISPR/Cas9 screening approaches such as CRISPR-based double knockout (CDKO) systems, kinetic analysis of double gene knockouts, and gene essentiality profiling employing a panel of cell lines

**Workshop Leader**
**Kevin Coleman**
Executive Director, Translational R&D, Experimental Biology
**Tesaro**

Kevin Coleman leads an experimental pharmacology group at TESARO that is focused on mechanism-of-action and efficacy studies designed to support the advancement of TESARO's small molecule and biologics cancer pipeline. Prior to TESARO, Kevin held a series of drug discovery and management positions with Arvinas, Merck, Pfizer, and BMS. He earned his BS in Biology at University of Connecticut, his Ph.D. in Cellular and Molecular Biology at the University of Michigan, and conducted his postdoctoral studies in the Department of Biochemistry and Biophysics at the University of California, San Francisco

## Workshop B

### Advancing Bioinformatics in Synthetic Lethality: Identifying and Harnessing Synthetic Lethal and Synthetic Rescue Interactions to Treat Cancer

**1:00pm – 4:00pm**

Novel bioinformatics approaches will allow us to extend the scope of our work from analyzing actionable mutations in a few hundred cancer driver genes to the whole cancer genome, drastically increasing patients' coverage.

Join Eytan Ruppin, whose computational methods laid the foundations for MetaboMed's work on Synthetic Lethality, to:

- Explore computational methods developed for the genome wide identification of synthetic lethal and synthetic rescue
- Examine case studies demonstrating that this approach can accurately predict and target cancer-specific vulnerabilities in individual patients
- Learn how harnessing synthetic rescues will enable us to identify synergistic drug combinations that will substantially decrease the emergence of resistance to a wide variety of extant cancer therapies

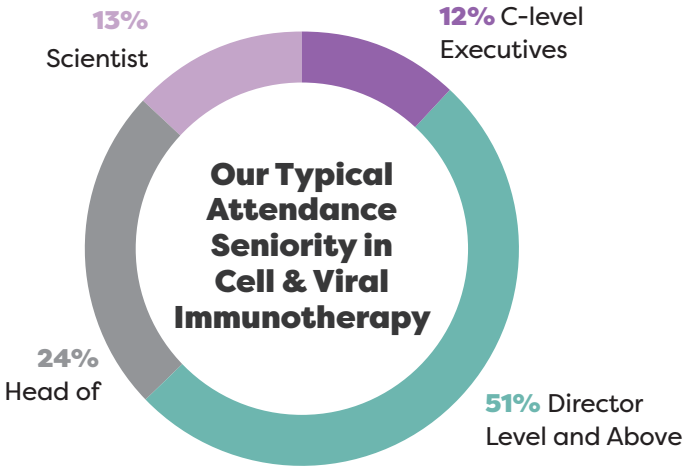
**Workshop Leader**
**Eytan Ruppin** Director, Center of Bioinformatics & Computational Biology
**University of Maryland**

Eytan Ruppin (MD, PhD) is the director of the center for bioinformatics at the University of Maryland. His research is focused on collaborating with numerous experimental cancer labs, developing and utilizing computational approaches to gain a systems view and predict and test novel drug targets and biomarkers to treat cancer more effectively. His lab has identified the first synthetic lethal drug targets in renal cancer and the first genome-wide tumor-derived synthetic lethal networks in cancer. Recently, the lab developed a new data mining pipeline for identifying molecular pathways of resistance to both targeted and immune therapy in cancer.

# SPONSOR

**Sierra Oncology**, Partner

Sierra Oncology is a clinical stage drug development company advancing targeted therapeutics for the treatment of patients with cancer. Our lead product candidate, SRA737, is a potent, highly selective, orally bioavailable small molecule inhibitor of Checkpoint kinase 1 (Chk1). SRA737 is currently in two Phase 1 clinical trials focused on enrolling patients with tumors identified to have genetic aberrations hypothesized to confer sensitivity to Chk1 inhibition via synthetic lethality, as a monotherapy or in combination.
**www.sierraoncology.com**

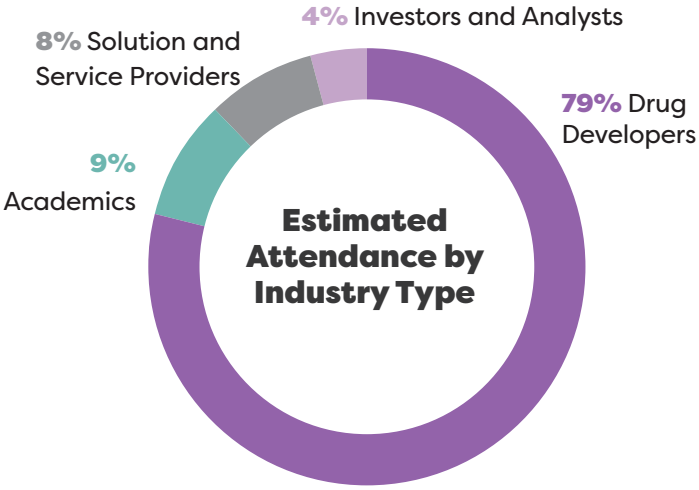



## Are you front of mind when pharma and biotech look to develop commercially viable synthetic lethal drugs?

Key synthetic lethal drug developers have informed us that one of the most pressing problems in this rapidly growing field is that service providers lack knowledge and experience of the industry, forcing developers to use time and resources on work that they would rather outsource.

The ***Synthetic Lethality Summit*** will allow partners to gain a deep understanding of the most pressing concerns that the industry leading developers have with CRISPR & RNA Screening Companies, Model Developers and CROs, and strategies for how these could be overcome. Partnering with us will enable you to meet with high-level representatives from a range of companies, hear exactly what criteria they use to select vendors, and act on these insights to offer highly tailored products and services for synthetic lethal drug developers.

Seize this unparalleled opportunity to demonstrate that you have the desire and capability to meet the increasing demands of this emerging field, and cement your position as the industry leader.




"A very targeted meeting filled with KOLs and industry leaders in this exciting field. The meeting was organized and run better than any other conference I have attended."
**Past CVI summit attendee, IntelliCyt**

"One of the most efficient and valuable opportunities to overview the field and meet the key developers."
**Past CVI summit attendee, AGC Business Development Americas**

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**Jennifer Mackay**
**Commercial Director, Cell & Viral Immunotherapy**
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# PRICING

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- **10% discount** – 3 delegates
- **15% discount** – 4 delegates
- **20% discount** – 5 or more delegates

Please note that discounts are only valid when three or more delegates from one company book and pay at the same time.

## Top 3 Benefits of Attending

1. Determine the key steps required to identify and therapeutically exploit robust synthetic lethal interactions that are conserved across a variety of defined contexts
2. Apply the lessons learned from PARP inhibitors to optimize new synthetic lethal drugs, with insights from top Lynparza and Rubraca developers
3. Streamline clinical trials by improving the recruitment and stratification of patients, increasing efficiency

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