UNLOCKING THE PREVIOUSLY 'UNDRUGGABLE'

2nd Annual
SEPTEMBER 15-16th, 2021 | EST TIMEZONE

In recent years, there has been a huge explosion in drug R&D seeking to unlock previously "undruggable" targets, and after a phenomenal year for the industry, there has never been more interest and focus on these emerging modalities. However, crucial questions must be answered to ensure that these ground-breaking approaches reach their potential.

Fresh off the back of the hugely successful 2020 event, the next installment in Undruggable Leaders is set to showcase the best approaches against historically intractable targets from global leaders and pioneers. Utilising the very best of virtual, the Undruggable Leaders Forum brings together thought-leaders and pioneers from all aspects of 'undruggable' to discuss the scientific, technical and commercial challenges facing the industry.

Wednesday, September 15th, 2021
9:00am EST **Chair's Opening Remarks & Setting the Scene** **Shawn Davis,** Head of Drug Delivery, **AstraZeneca**
9:05am EST Keynote Presentation - **Towards Universal Druggability** **Greg Verdine,** Erving Professor of Chemistry, Emeritus | President, CEO, and CSO, **Harvard University & Harvard Medical School | FogPharma & LifeMine Therapeutics**
9:30am EST Wellness Break

9:35am - 10:30am EST Keynote Panel Discussion with Open Q&A: **Are We Any Closer to Unlocking the 'Undruggable'?**

- What does 'undruggable' really mean, and how can we define everyone working in this space?
- What major industry-shaping developments have we seen over the last 12 months?
- Will the lessons learned from 2020 enable us to accelerate innovation and success?
- What gaps in our scientific understanding should we all focus on to see the greatest progress?
- What are the commonalities and challenges linking everyone working against 'undruggable' targets, and are collaborations the key to unlocking future success in the industry?
- What are the key obstacles we need to overcome in order to drug 'undruggable' targets?

Greg Verdine, Erving Professor of Chemistry, Emeritus | President, CEO, and CSO, **Harvard University & Harvard Medical School | FogPharma & LifeMine Therapeutics**
Matt Disney, Scientific Founder | Professor, **Expansion Therapeutics | Scripps Research Institute**
Darryl McConnell, SVP, Research Site Head Austria, **Boehringer Ingelheim**
Moderated by: Danette Daniels, R&D Group Leader, **Promega**

10:30am EST Extended Wellness Break

Undruggable Leaders Showcase

11:00am EST Presentation - **Protein Degradation of Key Nodes in Clinically Validated Pathways**

- Discuss Kymera's approach to targeted protein degradation, and their drug discovery platform Pegasus enabling rational design of protein degrader therapies
- A closer look at Kymera's current pipeline targeting IRAK4, IRAKIMiD and STAT3, designed to treat serious immune inflammatory diseases and cancers with limited or no treatment options

Chris De Savi, VP, Head of Drug Discovery, **Kymera Therapeutics**

11:25 am EST Wellness Break

11:30 am EST Presentation: **Reinventing Therapeutic Antibodies for the Treatment of Cancer**

Amy Peterson, EVP, Chief Development Officer, **CytomX Therapeutics**

11:55 am EST Wellness Break

12:00pm EST Fireside Chat with Open Q&A - **Pharma/Biotech Collaborations for Neurological Diseases**

Anima Biotech, a leader in mRNA translation modulators, and Takeda, a leading global biopharmaceutical company with deep scientific expertise in neuroscience, announced one of the latest industry collaborations underlining the growing interest of big pharma in 'undruggable' and the significant value of such collaborations. This session will explore this collaboration on the mRNA translation modulator treatments for genetically defined neurological diseases, initially including Anima's early Huntington's Disease programme against huntingtin (HTT) alongside two additional targets set by Takeda. We will particularly explore how the collaboration aims to further the progress of this innovative treatment modality, as well as how each company is leveraging the collaboration as an opportunity to further learn and contribute in treating patients in an unprecedented way.

- What is unique in Anima's approach in the mRNA space?
- Why was this partnership, and this partner specifically, attractive to you?
- What is your vision for this collaboration?
- How does the partnership enable each company to better address patient needs and delve deeper into the undruggable aspect of neurological diseases?
- How do you hope this partnership will shape the undruggable landscape?

Yochi Slonim, CEO, **Anima Biotech**
Beth Shafer, Head of Neuroscience, Drug Discovery Sciences & Externalization Business Development, **Takeda**

12:40pm EST Wellness Break

12:45pm - 1:30pm EST Panel Discussion with Open Q&A: **The Pharma Perspective: Mitigating Risk, Choosing Targets and Expanding Portfolios**

- How are pharma approaching historically intractable targets?
- Pros and cons of in-house development vs strategic collaborations?
- What lessons are being learned from partnerships in this space?
- What key considerations are used to mitigate risk when developing an 'undruggable' pipeline, and have pharma become more or less adverse to 'undruggable' projects and targets?
- What is the main factor holding back increased pharma engagement across the 'undruggable' industry?

Stephen Fawell, Vice President, Head Oncology Discovery, **AstraZeneca**
Louis Lombardo, VP, Global Head of Discovery Chemistry, **The Janssen Pharmaceutical Companies of Johnson & Johnson**
Carla Gauss, Senior Application Scientist (Medicinal Chemistry), **Nanome**

Nanome

1:30pm - 2:00pm EST Lunch

2:00pm EST Presentation - **Designed Degraders of PCSK9 in Nanome**

- Scientists at Merck attempted to identify ligands that interfere with the protein-protein interaction (PPI) between the serine protease PCSK9, and the low-density lipoprotein, or LDL, receptor [Petrilli, W. L. et al. From Screening to Targeted Degradation: Strategies for the Discovery and Optimization of Small Molecule Ligands for PCSK9. Cell Chemical Biology 27, 32-40.e3 (2020).]
- Nanome's scientists explored and analyzed three X-Ray structures (PDB ID's: 3P5B, 6U3X, and 6U26) described in the Merck publication with particular attention to the drug design challenges posed by the structural nature of the PPI interface
- We showcase the ultimate solution pursued by Merck: optimization of ligands that bind an allosteric site of PCSK9 and were modified to induce its degradation by the proteasome

Jonathon Gast, Application Scientist, **Nanome**

2:25pm EST Wellness Break

2:30pm EST Case Study - **Targeting the Once "Undruggable" KRAS Mutation with PLK1 Inhibition in Metastatic Colorectal Cancer (mCRC)**

Approximately 50% of CRC patients have a KRAS mutation, which is believed to drive aggressive tumor growth and resistance to current treatments. Treatment of mCRC in the KRAS-mutated population has been hampered by failure of direct targeting of KRAS with the exception of KRAS inhibitors developed to target the KRAS G12C mutation. However, KRAS G12C represents only 8% of KRAS variants in CRC, and so far, KRAS G12C inhibitors have shown limited activity in mCRC patients. Inhibiting PLK1 function may be selectively efficacious in treating mutant KRAS-driven tumors, with limited side-effects on wild-type KRAS normal cells. These data make PLK1 an appealing target in KRAS mutated colorectal cancer where treatment options in the second-line setting are limited.

This presentation will discuss:

- The vulnerability of CRC tumor cells harboring a KRAS mutation to cell death with PLK1 inhibition
- The development and use of a highly selective, oral PLK1 inhibitor onvansertib, which works synergistically in combination with standard of care (SOC), as a second-line treatment to target these previously undruggable mutations
- The to-date results from a Phase 1b /2 study of onvansertib in combination with FOLFIRI/bevacizumab

Mark Erlander, CEO, **Cardiff Oncology**

2:55pm EST Wellness Break

3:00pm EST Presentation - **Harnessing The Chromatin Regulatory System for Gene Expression**

- A look at how the chromatin regulatory system directs which genes our cells express, and how this system can be manipulated
- Discuss how this novel approach compares to the more common gene-editing approach
- Explore how Foghorn have developed their Gene Traffic Control Product Platform to advance over preclinical 10 programs targeting diseases with genetically determined dependencies in the chromatin regulatory system

Cigall Kadoch, Associate Professor | Scientific Founder, **Dana-Farber Cancer Institute | Foghorn Therapeutics**

3:25pm EST Wellness Break

3:30pm EST Presentation - **Translating Frontier Oncology Targets to Outsmart Cancer**
Drugging the RAS(ON) Form of Diverse Oncogenic RAS Mutations

- Revolution Medicines is developing novel RAS(ON) Inhibitors based on our proprietary tri-complex technology platform, enabling a highly differentiated approach to inhibiting the active, GTP-bound form of RAS (RAS(ON)). These RAS proteins, which cycle between the inactive RAS(OFF) form and the active RAS(ON) form, engage and activate downstream molecules that play crucial roles in cell regulation. Mutant forms of RAS that bias the proteins to the RAS(ON) state, and thereby make them significantly more active than normal, can cause cancers such as lung and colon cancer.
- In this presentation we will discuss a portfolio of compounds that we believe are the first and only RAS(ON) inhibitors to use this mechanism of action. RMC-6291, our inhibitor targeting KRASG12C/NRASG12C(ON), and RMC-6236, our inhibitor of multiple RAS variants (RASMULTI(ON)), are in IND-enabling preclinical development.

John Knox, Senior Director, Head of Structural Chemistry, **Revolution Medicines**

3:55pm EST Extended Wellness Break

4:20pm - 5:15pm EST Panel Discussion with Open Q&A - **How Do We Address the Key Challenges in Undruggable?**

- What is the single biggest challenge when tackling previously undrugged targets?
- How can we accelerate proof of concept for undruggable targets?
- What potential do synthetic lethality and synergy provide as rationale for the development of new therapeutic options?
- What opportunities and challenges exist with monotherapies and combination therapies for undruggable mutations?
- How are innovations for undrugged targets accelerating medicine for oncology patients?
- How can we define when a target has been drugged, and how else can we define success in this industry?

Nello Mainolfi, Founder, President & CEO, **Kymera Therapeutics**
Shuling Guo, Vice President, Antisense Drug Discovery, **Ionis Pharma**

Cigall Kadoch, Associate Professor | Scientific Founder, **Dana-Farber Cancer Institute | Foghorn Therapeutics**
Mark Erlander, CEO, **Cardiff Oncology**
Angela Zhou, Head of Scientific Insights, **CAS**

Close of Day 1

Thursday, September 16th, 2021

9:00am EST **Chair's Opening Remarks**

Shawn Davis, Head of Drug Delivery, **AstraZeneca**

9:05am EST Keynote Presentation - **Leveraging Biodegraders as Tools to Probe the Degradability of KRAS**

- Introduction to biodegraders with different RAS isoforms and nucleotide-state specificities
- Engineering cell lines with doxycycline-induced expression of NanoLuc-tagged RAS proteins to understand degradation specificities and prevalence of nucleotide-loaded states
- Measuring degradation kinetics in a panel of CRISPR-edited HiBiT-tagged KRAS cell lines and correlating degradation efficiency with impact on cell viability

Shuhui Lim, Associate Principal Scientist, **Merck**
Sponsored by **Promega**

9:30am EST Wellness Break

Pioneers in Discovery

9:35am EST Presentation - **Rational Design of Specific, Potent Small Molecule Binders of RNA**

- A look at how Expansion have assembled key platform enabling technologies and tools to allow for the identification of specific, potent, novel small molecule binds of RNA, which can be applied to any RNA that folds
- Learn how this platform has led to the identification of numerous small molecules interacting with RNA (SMiRNA), such as mRNA and ncRNA, across therapeutic areas such as oncology, infectious disease and expansion repeat diseases
- Explore the founding work that gave rise to Expansion, their current pipeline and aims for the coming years

Matt Disney, Scientific Founder | Professor, **Expansion Therapeutics | Scripps Research Institute**

10:00am EST Wellness Break

10:05am EST Fireside Chat with Open Q&A: **Unlocking the Secrets of Protein Motion**

- How are Relay Therapeutics creating new possibilities in drug discovery?
- What is the vision for Relay Therapeutics?
- How can we work together to see progress across the industry?

Don Bergstrom, Executive Vice President, Head of Research & Development, **Relay Therapeutics**

Moderated by: Pete Rahmer, SVP, Head of Corporate Affairs and Investor Relations**, Relay Therapeutics**

10:50am EST Extended Wellness Break

11:20am EST Presentation - **Using Chemoproteomics To Identify Hotspots on 'Undruggable' Proteins**

- Learn how Frontier Medicines are leveraging chemoproteomics to identify temporary binding pockets on 'undruggable' proteins to make them accessible for therapeutic intervention, and to develop an ever-growing database of these hotspots
- A look at how Frontier have used this database in conjunction with an expanding library of chemically diverse compounds and machine learning to find high quality matches for each hotspot
- Explore how this proprietary chemoproteomics platform has potential for small molecule identification across oncology, immunology and a whole host of other difficult-to-drug protein targets

Kevin Webster, CSO, **Frontier Medicines**

11:45 am EST Wellness Break

11:50am EST Presentation - **Gain an Information Advantage to Unlock Undruggable Targets**

CAS
A division of the American Chemical Society

- Explore how to improve your ability to identify targets within the increasingly complex and interconnected chemical and biological spaces
- Learn how to accelerate innovation by uncovering novel insights from vast amounts of data in areas such as RNA, protein therapeutics, and biologics
- A look at a case study exploring innovative approaches to data retrieval and management that improve R&D efficiency

Matthew McBride, Director of IP Services, **CAS**

12:15pm EST Wellness Break

The Next Undruggable Leaders

12:20pm EST Lightning Talk - **Modulators of 14-3-3 Protein–Protein Interactions**

Nancy Pryer, CSO, **Ambagon Therapeutics**

12:40pm EST Lightning Talk - **Selective Targeting of Misfolded Pathogenic Proteins in Neurodegenerative Diseases**

- Learn how ProMIS Neurosciences are using a computational modeling platform to generate monoclonal antibodies selectively targeting conformational epitopes on toxic oligomers of proteins implicated in the pathogenesis of neurodegenerative diseases including Alzheimer's disease, ALS and Parkinson's disease.

Johanne Kaplan, Chief Development Officer, **ProMIS Neuroscience**

1:00pm EST Lightning Talk - **Discovering and Developing Next Generation GPCR-Targeted Therapeutics**

Oliver Hartley, VP, Drug Discovery, **Orion Biotechnology**

1:20pm EST Lightning Talk - **Identifying Druggable Active sites in Misfolded Protein Targets.**

- Discuss how Treventis Corporation are utilizing a proprietary, patent-pending discovery engine to identify druggable active sites in misfolded protein targets to treat and prevent protein misfolding diseases

Mark Reed, CSO, **Treventis Corporation**

1:40pm EST Wellness Break

1:45pm - 2:30pm EST Panel Discussion with Open Q&A: **Injecting Capital into 'Undruggable'**

- Are investors actively looking at the 'undruggable' industry, and if so, what is stopping them from pulling the trigger on investment?
- How is the risk profile of the 'undruggable' industry viewed by investors? Are some approaches deemed riskier than others?
- Has the pandemic increased or decreased the attractiveness of 'undruggable' targets to investors?
- What do investors need to see from companies in this space in terms of data and validation to prompt investment, and how can companies demonstrate value to investors?
- Do investors believe that we will see success in the near future against 'undruggable' targets?

Luke Evnin, Co-Founder & Managing Director, **MPM Capital**
Laura Tadvalkar, Principal, **RA Capital Management**
Chris O'Donnell, Executive Director & Principal, **Pfizer Ventures**
Laura Brass, Managing Director, **Novartis Venture Fund**

Close of the Undruggable Leaders Forum 2021