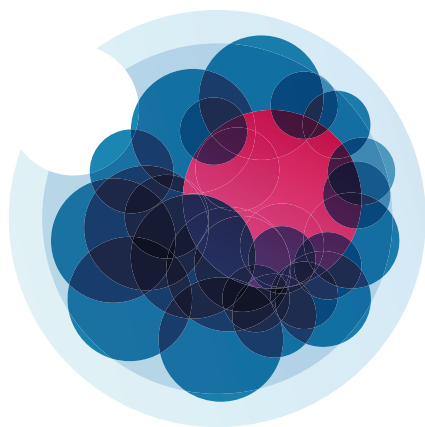


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www.ras-drugdiscovery.com



RAS-Targeted Drug Discovery

Finally Drug the "UnDruggable" RAS

**Enable Novel Target Site Discovery, Improve
the Predictability of Patient-Derived RAS-
Models and Accelerate the Translation of
Potent & Mutation-Specific RAS Targeted
Therapeutics into the Clinic**

Expert Speakers Include:



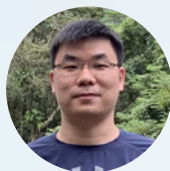
Haby Henary
Medical Director,
Oncology Global
Development
Amgen



Matthew A. Marx
Vice President, Drug
Discovery
Mirati Therapeutics



Laurent Debussche
Vice President, Global
Head Molecular
Oncology Research
Therapeutic Area
Sanofi R&D



Huaixiang Hao
Investigator III
**Novartis Institutes for
BioMedical Research**



Sarah Ross
Team Leader & Lead
Bioscientist
**AstraZeneca, Early
Oncology TDE**



Francis Burrows
Vice President,
Translational Research
Kura Oncology



Jan Smith
Vice President, Biology
Revolution Medicines



Sean Buchanan
Research Fellow
Eli Lilly



Benjamin Bader
Senior Scientist, Small
Molecule Innovation
Bayer AG

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RAS- Targeted Drug Discovery Summit

Finally Drug the “~~Un~~Druggable” RAS

Enable Novel Target Site Discovery, Improve the Predictability of Patient-Derived RAS-Models and Accelerate the Translation of Potent & Mutation-Specific RAS Targeted Therapeutics into the Clinic

Following the exciting clinical progression from Amgen and Mirati Therapeutics, at a time when there is a translational opportunity to finally “drug” RAS proteins with clinically meaningful success, the 1st **RAS- Targeted Drug Discovery Summit** has been established to unite large pharma, biotech and academic KOLs who are striving to capitalize on the therapeutic potential of targeting RAS.

With RAS mutations prevalent in approximately 30% of all cancers diagnosed, the clinical, patient outcome and commercial opportunity are tremendous. As such, the RAS- Targeted Drug Discovery Summit will be dedicated to helping oncology drug discovery and development professionals **understand the cutting edge dynamics and function of RAS biology, identify and validate druggable target sites and improve the preclinical predictability of patient derived and disease-specific RAS models.**

With numerous approaches emerging that demonstrate genuinely viable efficacy in targeting the RAS family of proteins, join the 1st **RAS- Targeted Drug Discovery Summit – the only industry and translational focused conference** dedicated to advancing pioneering RAS biology and drug discovery into successful clinical candidates.

What are our speakers looking forward to at this summit?

It is always extremely valuable to interact with other drug discovery specialists trying to solve the same problems that we ourselves are invested in. The interactions with biopharma industry attendees are particularly important as there are fewer chances for these interactions in regular scientific meetings

Sean Buchanan, Research Fellow, **Eli Lilly**

For the first time it is now possible to directly target some RAS isoforms with potent, selective drugs. RAS biology remains incompletely understood and RAS activity is isoform and tissue context-dependent, but I'm optimistic that focused meetings of this nature can accelerate our progress by revealing common themes and novel mechanisms

Francis Burrows, Vice President, Translational Research, **Kura Oncology**

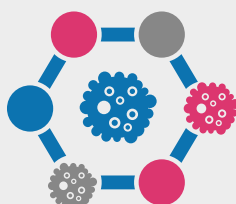
Why Attend the 1st RAS- Targeted Drug Discovery Summit?



Leverage the latest understanding of the dynamics and function of RAS biology to identify mutation-specific vulnerabilities with insights from **Frederick National Laboratory for Cancer Research, UT Southwestern Medical Center & University of Eastern Finland**



Enable your novel target site discovery and early anti-RAS research efforts by harnessing the latest tools and technologies with insights from **Sanofi, Bayer & Texas Health Science Center**



Overcome drug resistance, chemistry & pharmacology hurdles of rational and direct anti-RAS therapies for robust translation into clinical development with insights from **Mirati Therapeutics, Amgen & AstraZeneca**



Optimize predictability of patient-derived RAS-models, patient selection and anti-RAS combination strategies with insights from **Eli Lilly, BiotheryX & Dana-Farber Cancer Institute**



Join the momentum to reverse the undruggable nature of RAS family of proteins and seize the enormous therapeutic potential in anti-RAS strategies with insights from **Wellspring Biosciences, Revolution Medicines & Kura Oncology**

YOUR EXPERT SPEAKERS



Haby Henary
Medical Director,
Oncology Global
Development
Amgen



Matthew A. Marx
Vice President, Drug
Discovery
Mirati Therapeutics



Laurent Debussche
Vice President, Global
Head Molecular
Oncology Research
Therapeutic Area
Sanofi R&D



Dominic Esposito
Director, Protein
Expression Laboratory,
NCI RAS Initiative
**Frederick National
Laboratory for Cancer
Research**



Mariano Barbacid
AXA-CNIO Professor of
Molecular Oncology and
Head of the Experimental
Oncology Group
**Spanish National Cancer
Research Center**



Yi Liu
Chief Scientific Officer
Wellspring Biosciences



Ralph Minter
Senior Director, Fellow,
Antibody Discovery and
Protein Engineering
(ADPE)
AstraZeneca



Huaixiang Hao
Investigator III
**Novartis Institutes for
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Sarah Ross
Team Leader & Lead
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Kura Oncology



Terry Rabbitts
Professor of Molecular
Immunology
**Weatherall Institute
of Molecular Medicine,
University of Oxford**



Jan Smith
Vice President, Biology
Revolution Medicines



Russell Lipford
Director, Oncology
Research
Amgen



Sean Buchanan
Research Fellow
Eli Lilly



Kenneth Westover
Associate Professor
**UT Southwestern
Medical Center**



Benjamin Bader
Senior Scientist, Small
Molecule Innovation
Bayer AG



Chiara Ambrogio
Senior Scientist
**Dana-Farber Cancer
Institute**



Magnus Jaderberg
Head of R&D
Targovax



Antti Poso
Professor of Drug Design
**University of Eastern
Finland & University of
Tübingen**



**Aparajita Hoskote
Chourasia**
Senior Scientist & Team
Leader
BioTherYX



Alemayehu Gorge
Associate Professor
**McGovern Medical
School, University of
Texas Health Science
Center at Houston**



Shohei Koide
Professor of Biologics
Design
**New York University
School of Medicine
and Perlmutter Cancer
Center**



Tatu Päätsä
Marie Skłodowska-Curie
Fellow
University of Tübingen



Behnam Nabet
Research Fellow
**Dana-Farber Cancer
Institute**

WHY ARE OUR EXPERT SPEAKERS GETTING INVOLVED AT THE SUMMIT?

“I am looking forward to participating in this summit focused on one of the most elusive oncology drug targets of the past three decades. The first wave of mutant-targeted therapeutics has entered the clinic, and we will soon understand the single-agent utility and potential for combination treatments with covalent G12C-mutant inhibitors. This discussion will advance our understanding of the translational pharmacology for this target, and set the stage for the 2nd generation KRAS-modulating therapies yet to come”



Matthew A. Marx
 Vice President, Drug
 Discovery
Mirati Therapeutics

“This meeting will bring together many experts in RAS drug discovery both from academia and pharma industry. Fifteen years ago, RAS was deemed undruggable, but now the field has exploded and new ways to tackle the undruggable are being explored”



Benjamin Bader
 Senior Scientist,
 Small Molecule
 Innovation
Bayer AG

“This is a fantastic opportunity to bring the RAS research community together, at a time when there is a real prospect of finally drugging this important target. I hope to learn more about the many different strategies being pursued in the field”



Yi Liu
 Chief Scientific Officer
Wellspring Biosciences

“Taking part at the RAS-Targeted Drug Discovery summit is a unique opportunity to share and debate breakthrough ideas which could eventually lead to novel effective therapies for RAS-driven cancers, which represent a major unmet medical need for over 1 million new KRAS cancers annually worldwide”



Laurent Debussche
 Vice President, Global
 Head Molecular
 Oncology Research
 Therapeutic Area
Sanofi R&D

“This is the first RAS meeting focusing on drug discovery that I am aware of and it covers several therapeutic modalities targeting RAS. I look forward to the learnings and discussions with invited speakers and summit participants”



Huaixiang Hao
 Investigator III
**Novartis Institutes for
 BioMedical Research**

PRE-CONFERENCE WORKSHOP DAY

TUESDAY | SEPTEMBER 17, 2019

Workshop A

10.30am – 13.00pm

Exploring Current Caveats and Future Challenges in Understanding Oncogenic RAS Structure and Function: Influence of the Mutations

Enabled by the latest technological advances, our understanding in RAS biology and its oncogenic properties has taken a giant leap in recent years. Still, our limited knowledge is hindering the ongoing efforts to develop RAS-targeting therapies. In this workshop we discuss to what extent we currently understand the oncoprotein and its behavior. Also, we will cover the important aspects that need to be addressed to enable successful RAS-therapies in future.

Workshop Leader


Tatu Pantsar

 Marie Skłodowska-Curie Fellow
University of Tübingen

Topics to be covered:

- What does the publicly available RAS structural data tell us and what does it not?
- Are oncogenic RAS mutations totally random events or are they context dependent (cell- and tissue-specific)?
- How similar are RAS missense mutants in different positions (e.g. pos. 12 vs. 61) and in the same position (e.g. G12D vs. G12V)?
- What is the influence of a mutation to RAS dynamics?
- What would be the optimal balance between promiscuous (all isoforms, wild-type) and a mutation specific (e.g. G12C) RAS-targeting?

Workshop B

14.00pm – 16.30pm

Empowering Anti-RAS Strategies: From Mouse Models to Clinical Research

KRAS is one of the most frequently mutated oncogenes in cancer and KRAS mutations are commonly associated with resistance to therapy and poor prognosis. Till very recently, KRAS was not directly druggable and modeling therapeutic strategies for KRAS mutant cancers were oriented towards the identification of susceptibilities in downstream signaling pathways. One unresolved aspect of KRAS biology with potential to translate in patient stratification criteria is the difference between distinct KRAS activating mutations in terms of downstream signaling, regulation and drug sensitivity.

KRAS dimerization/clusterization may play a critical role in generating these differences and this aspect is largely unstudied. Understanding the biochemical and biological differences among specific KRAS mutants and the properties of RAS dimerization is essential to discover new actionable vulnerabilities for mutant KRAS.

Workshop Co-Leaders


Chiara Ambrogio

 Senior Scientist
Dana-Farber Cancer Institute

Kenneth Westover

 Associate Professor
UT Southwestern Medical Center

Topics to be covered:

- State of the art of KRAS-driven mouse models
- How can we improve the identification of biomarkers for better treatment options?
- Understanding the biological differences between specific mutant KRAS isoforms. What are meaningful measures of differences?
- How can genetic models help us define RAS mutation-specific differences in signal transduction pathways?
- What are weaknesses in widely used mouse models of KRAS-driven disease that may obscure identification of mutation-specific differences in vivo?
- How can genetic models allow us to differentiate between tumor initiating and tumor maintaining effects of RAS.
- How can genetic models be used to predict the toxicity of new RAS-directed strategies?

CONFERENCE DAY ONE

WEDNESDAY | SEPTEMBER 18, 2019

	8.00 Registration & Networking Coffee
Chiara Ambrogio Senior Scientist Dana-Farber Cancer Institute	8.50 Chair's Opening Remarks
Rising to the Undruggable Challenge: Delivering a New Pass Forward to Target RAS with Novel Strategies	
Dominic Esposito Director, Protein Expression Laboratory, NCI RAS Initiative Frederick National Laboratory for Cancer Research	9.00 Targeting KRAS Directly with Novel Drug Discovery Efforts at the NCI RAS Initiative - The NCI RAS Initiative is developing new approaches for direct targeting of KRAS - New technologies and assays from the RAS Initiative can enable other drug discovery efforts on RAS - Collaborative efforts between industry, academic, and the RAS Initiative have had significant impacts on improving our understanding of the biochemistry and biophysics of RAS at the plasma membrane
Kenneth Westover Associate Professor UT Southwestern Medical Center	9.30 Mutation-Specific Strategies for Targeting RAS Driven Diseases - RAS mutations cause changes in protein dynamics that lead to dramatic changes in protein behavior - Changes in protein behavior lead to changes in regulatory mechanisms and signaling - These changes may present as mutation-specific vulnerabilities for therapy
Antti Poso Professor of Drug Design University of Eastern Finland & University of Tübingen	10.00 Allosteric Modulation of KRAS by G12X Mutations - KRAS long timescale dynamics investigated by extensive atomistic molecular dynamics simulations reveals complex allosteric signaling network within the protein - Dynamics of KRAS is altered by G12X missense mutants via the hydrophobic allosteric network. This is mutation-specific and the effect on KRAS dynamics is especially manifested in the effector protein binding interface - Different KRAS G12X mutations are not equal; therefore, this should be carefully considered in KRAS targeting and therapies
	10.30 Speed Networking & Morning Refreshments
Laurent Debussche Vice President, Global Head Molecular Oncology Research Therapeutic Area Sanofi R&D	11.30 RAS Protein Flexibility and How to Target Cryptic Pockets to Drug the Undruggable Master Oncogene - RAS is a very flexible protein without any apparent druggable pocket which has resisted three decades of efforts to drug it - Cryptic or induced pockets can be identified in addition to so-called SII pocket - DNA-encoded library approach is a powerful approach to drug cryptic pockets such as SII pocket
Benjamin Bader Senior Scientist, Small Molecule Innovation Bayer AG	12.00 Disruption of the RAS-SOS1 Interaction – Enabling Lead Discovery by a Combination of High-Throughput and Fragment Screening - Combination of high-throughput & fragment screening enabled a new approach to target KRAS - Structure-guided optimization of potent and selective SOS1 inhibitors - Cellular data support a possible combination potential of SOS1 inhibitors with covalent inhibitors of KRAS^{G12C}

Alemayehu Gorfe
 Associate Professor
**McGovern Medical
 School, University
 of Texas Health
 Science Center at
 Houston**

12.30 Membrane Binding and Druggability of RAS

- The genesis of RAS allostery, and its impact on current efforts toward direct RAS inhibitors
- Dynamics-guided computational and experimental approaches for lead generation
- The relevance of RAS membrane binding, orientational dynamics, and self-assembly for the development of potentially selective inhibitors

13.00 Networking Lunch

Translating Effective Anti-RAS Strategies into Novel Cancer Therapies

Huaxiang Hao
 Investigator III
**Novartis Institutes
 for BioMedical
 Research**

14.00 Targeting Upstream Activation of Mutant KRAS via Allosteric Inhibition of SHP2 Phosphatase

- The newly appreciated role of RTK and SHP2 for mutant KRAS activation
- The RTK/SHP2 mediated MAPK pathway feedback activation upon ERK inhibition
- Potential mechanisms of resistance to SHP2 inhibitors

Ralph Minter
 Senior Director,
 Fellow, Antibody
 Discovery and Protein
 Engineering (ADPE)
AstraZeneca

14.30 RAS Inhibitory Biologics - A Novel Approach to Cancer Therapy

- Overcoming engineering challenge of identifying selective and potent antibody-like proteins to target RAS
- Mechanism of action and pros and cons against small molecule approaches to target RAS
- Optimization of biologics delivery to enable viable clinical strategies

Magnus Jaderberg
 Head of R&D
Targovax

15.00 TG - A RAS Mutation Specific Vaccine for the Treatment of Solid Tumors

- TG01, a cocktail of 7 peptides mimicking the 7 RAS mutations seen in pancreas cancer
- Ability of TG01 to induce relevant immune activation
- Signal of efficacy from TG01 in pancreas cancer and update of ongoing platform research

15.30 Afternoon Refreshments & Poster Session

Terry Rabbitts
 Professor of Molecular
 Immunology
**Weatherall Institute
 of Molecular
 Medicine, University
 of Oxford**

16.00 Intracellular Antibody Fragments as Starting Points for Drug Discovery and as Macrodrugs for Therapy

- Discovery of novel RAS-binding compounds using intracellular antibody competition in compound library screens for inhibitors on protein-protein interactions
- Using intracellular antibodies screening methods to develop RAS isoform specific macromolecular drugs (macrodrugs)
- Employing intracellular antibody macrodrugs to invoke KRAS-specific proteasome degradation in KRAS-mutant cells

Shohei Koide
 Professor of Biologics
 Design
**New York University
 School of Medicine
 and Perlmutter
 Cancer Center**

16.30 **Discovery of Novel RAS Vulnerability Using Monobodies**

- The current challenge in developing RAS-targeting drugs suggests the need for innovative approaches for discovering methods to control RAS function
- We have established a platform to rapidly develop monobodies, synthetic binding proteins, with high selectivity and potency and to utilize them as genetically encoded “tool” biologics against intracellular targets such as RAS
- Our approach has led to the discovery of novel sites for allosterically inhibiting RAS, which guides drug discovery and gives new insights into the molecular mechanism underlying RAS signaling

17.00 **Interactive Round Table Discussions**

Our breakout roundtables will allow you to have more intimate and open discussions on some of the hottest topics and key areas of debate. Drive your own learning, crowd-source ideas and get inspired. Immerse yourself in the following discussions:

1

**How to enable
 novel anti-RAS drug
 discovery through
 advancements of
 cellular assays,
 phenotypic screening
 and chemical tools?**

2

**How to successfully
 screen for and
 design anti-RAS
 small molecules with
 sufficient potency
 and drug-like
 characteristics?**

3

**How to reimagine
 the future of finally
 drugging RAS
 through combination
 strategies?**

17.30 **Chair's Closing Remarks & End of Day One**

■ This is a fantastic opportunity to bring the RAS research community together, at a time when there is a real prospect of finally drugging this important target. I hope to learn more about the many different strategies being pursued in the field ■

Ralph Minter, Senior Director, Fellow, Antibody Discovery and Protein Engineering (ADPE), **AstraZeneca**

CONFERENCE DAY TWO

THURSDAY | SEPTEMBER 19, 2019

	8.30 Coffee & Networking
Mariano Barbacid AXA-CNIO Professor of Molecular Oncology Spanish National Cancer Research Center	8.55 Chair's Opening Remarks
The "Holy Grail" Oncology Target: Delivering on the Breakthrough Vision of Directly Targeting RAS	
Haby Henary Medical Director, Oncology Global Development Amgen	9.00 Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics (PK) and Efficacy of AMG 510, a Novel, First in Class, Irreversible Inhibitor of KRAS^{G12C} • AMG 510 FIH study • Safety and tolerability of AMG 510 • AMG 510 clinical anti tumor activity
Matthew A. Marx Vice President, Drug Discovery Mirati Therapeutics	9.30 Discovery and Preclinical Characterization of MRTX1257, a Selective, Covalent KRAS G12C Inhibitor with Oral Activity in Animal Models of Cancer • We have identified a series of orally active, covalent inhibitors of oncogenic mutant KRAS G12C • These inhibitors, exemplified by MRTX1257, drive regressions in a series of xenograft and PDX models as single agents • A comprehensive translational pharmacology evaluation has identified combination strategies that enhance single-agent activity in certain models
Yi Liu Chief Scientific Officer Wellspring Biosciences	10.00 Drugging Undruggable with a Covalent Approach • Developed a covalent approach to selectively target KRAS G12C mutant protein • First to demonstrate KRAS G12C mutant proteins cycle between active GTP state and inactive GDP state • Explored KRAS dependency in mouse tumor models
Sarah Ross Team Leader & Lead Bioscientist AstraZeneca, Early Oncology TDE	10.30 Developing Small Molecule Inhibitors of KRAS^{G12C} • Discovery of novel G12C inhibitors • Overview of activity in preclinical disease models • Building an understanding of what mediates sensitivity/resistance to G12C inhibitors
	11.00 Morning Refreshments & Networking
From Discovery to Clinic: Overcoming Translational Challenges & Combination Strategies	
Francis Burrows Vice President, Translational Research Kura Oncology	11.30 Precision Medicine for HRAS-Mutant Cancer Using Tipifarnib • HRAS is unique among RAS proteins because it requires farnesylation for activity • Tipifarnib is a potent, selective farnesyltransferase activity with a manageable safety profile • Tipifarnib is highly active in preclinical models of HRAS-mutant cancer and has recently entered pivotal testing in HRAS-mutant HNSCC patients
Russell Lipford Director, Oncology Research Amgen	12.00 Pre-Clinical Development of AMG 510: The First Inhibitor of KRAS^{G12C} in Clinical Testing • AMG 510 is a covalent inhibitor of KRAS^{G12C} that exploits a unique groove to enhance potency and selectivity • AMG 510 treatment gives rise to robust pre-clinical efficacy in multiple settings as monotherapy and in combination with SOC and targeted therapies • AMG 510 inflames tumor cells and drives anti-tumor immunity in a syngeneic tumor model in immunocompetent mice

Jan Smith Vice President, Biology Revolution Medicines	12.30 Translating Frontier Targets in the RAS Signaling Pathway to Outsmart Cancer • SHP2 is upstream of KRAS but regulates key mutational drivers in the RAS pathway • Targeting KRAS(GTP) may be superior to KRAS(GDP) inhibitors • Effective and rational combinations are required to effectively abrogate emergent resistance mechanisms
Mariano Barbacid AXA-CNIO Professor of Molecular Oncology and Head of the Experimental Oncology Group Spanish National Cancer Research Center	13.00 Targeting KRAS Mutant Lung and Pancreatic Tumors • Genetic studies using genetically engineered KRAS/TP53-driven mouse lung and pancreatic tumor models (including a KRASG12C strain) with which we have validated the therapeutic potential of K-RAS itself as a target as well as of each of the downstream kinases of the MAPK and PI3K pathways • Our results illustrate the toxic consequences of genetically ablating or inactivating these kinases in a systemic fashion, thus predicting some of the negative results already observed in the clinic • Our recent results demonstrate the therapeutic properties of ablating RAF1 in lung adenocarcinomas and the RAF1+EGFR combination in pancreatic tumors
	13.30 Networking Lunch
14.30 Panel Discussion: Advancing Successful Clinical Translation of RAS Targeted Therapies • How to translate the promising science and the clear opportunity into safe and effective anti-RAS therapies? • Routes for translational success from discovery to clinic: What will be the key factors for generating successful clinical results? • What will investors and collaborators look for in the next few years and what are the major challenges to be overcome in order to secure investments?  Matthew A. Marx Vice President, Drug Discovery Mirati Therapeutics  Laurent Debussche Vice President, Global Head Molecular Oncology Research Therapeutic Area Sanofi R&D  Francis Burrows Vice President, Translational Research Kura Oncology  Jan Smith Vice President, Biology Revolution Medicines	
Sean Buchanan Research Fellow Eli Lilly	15.00 Combination Strategies to Target RAS Mutant Cancers • RAS mutant cancers have been largely refractory to monotherapy treatment strategies • Preclinical studies have shown that RAS mutant cancers are partially vulnerable to inhibitors of (1) the MAPK pathway and (2) CDK4 • We have performed CRISPR and drug screens anchored on these inhibitors to identify new combination strategies
Aparajita Hoskote Chourasia Senior Scientist & Team Leader BioTherX	15.30 Targeted Protein Degradation as a Therapeutic Strategy for RAS-Driven Cancers • Targeted protein degradation is the next generation drug discovery platform for successfully attacking previously “undruggable” targets such as RAS • Developing small molecule cereblon-directed Protein Homeostatic Modulators (PHMs™) – molecular glue – to selectively target oncogenic RAS activation • Develop PROTACs that target RAS to explore their potential in oncology
Behnam Nabet Research Fellow Dana-Farber Cancer Institute	16.00 Leveraging Targeted Protein Degradation to Tackle Cancer Dependencies • Advances in targeted protein degradation • Challenges and promise of targeting KRAS for degradation • Case studies highlighting functional evaluation of cancer dependencies including KRAS using the dTAG system
	16.30 Chair’s Closing Remarks & Close of Inaugural RAS- Targeted Drug Discovery Summit 2019

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Position Yourself as an Industry Expert

With the emergence of biotech companies focused on developing mutant-targeted RAS therapies, followed by interest shown from large pharma and investors, this meeting is a dedicated platform to put your independent expertise in front of the key decision makers in the field



Meet and Network with Industry Pioneers

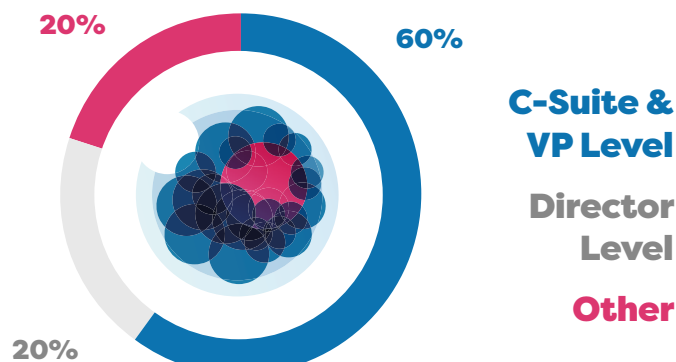
With a room full of drug developers looking to see how they can effectively translate their exciting early discovery efforts into safe and effective therapeutics, meet prospective clients during speed networking breaks, 1-2-1 meetings and more informal networking receptions



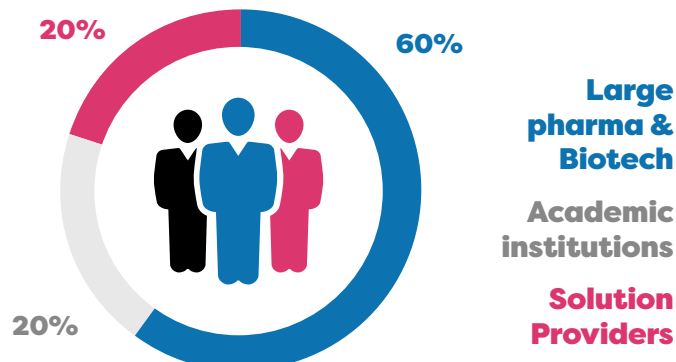
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 Partnerships Director
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SAVE valuable time and resources by learning how the leading companies in the space are advancing their anti-RAS strategies



GAIN first-hand insights on challenges and strategies on how to robustly translate promising direct anti-RAS therapies into clinical development and increase your success rate



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