Targeting the Elusive RAS Pathway: A Comprehensive Mechanistic Approach

The RAS pathway has long been a formidable challenge in cancer therapy, as mutations in RAS genes are implicated in driving the development and progression of numerous cancers, including lung, colorectal, pancreatic, and melanoma. Despite its significance, directly targeting mutant RAS proteins has proven to be a daunting task, often referred to as the "undruggable" target.

However, recent advancements in our understanding of the RAS signaling cascade have paved the way for innovative strategies to inhibit this critical pathway through various mechanisms of action (MoAs). OniX AI's comprehensive report on RAS pathway inhibitors provides an in-depth analysis of these diverse approaches, offering a powerful tool for researchers, drug developers, and industry professionals alike.

OniX AI's Unparalleled Access to the Research Landscape

What sets OniX AI apart is its unparalleled access to the research landscape that includes preclinical and clinical data. OniX has one of the most extensive preclinical data in the industry, including proprietary information not readily available in the public domain. By harnessing this wealth of fully standardized global data, OniX AI provides an unmatched window into the current and ongoing research landscape. This real-time intelligence can significantly impact strategic decision-making, R&D prioritization, partnership opportunities, go/no-go evaluations, and investment decisions – empowering each company to stay ahead of the curve in an ever-evolving industry.

Mechanism-Based RAS Inhibitor Report

OniX's report on RAS pathway inhibitors showcases the power of OniX AI, presenting a seamless integration of cutting-edge preclinical insights and clinical data, competitive landscapes, and future directions – all structured around distinct MoAs such as:

- **Direct RAS inhibitors**: Compounds that directly bind and inhibit mutant RAS proteins, preventing downstream signaling.
- **RAS-membrane interaction inhibitors**: Molecules that disrupt the interaction between RAS and the cell membrane, preventing proper localization and activation.

- **RAS-GEF inhibitors**: Inhibitors targeting guanine nucleotide exchange factors (GEFs), which activate RAS by facilitating GDP-to-GTP exchange.
- **RAS-GAP inhibitors**: Compounds inhibiting GTPase-activating proteins (GAPs), which inactivate RAS by promoting GTP hydrolysis.
- **Downstream pathway inhibitors**: Agents targeting components downstream of RAS, such as RAF, MEK, or ERK inhibitors, blocking proliferative and survival signals.
- **Synthetic lethal approaches**: Strategies exploiting synthetic lethal interactions, where inhibition of a specific target is lethal to RAS-mutant cancer cells but not normal cells.

This complete report offers a comprehensive view, complete with insightful visuals and industry trends.

Actionable Intelligence for Strategic Advantage

Elevate your decision-making process with OniX AI's unparalleled ability to deliver actionable insights derived from the latest "live" preclinical and clinical data. Whether you are a biotech entrepreneur, pharma executive, or academic researcher, OniX's AI-powered analysis empowers you with authoritative insights and a competitive edge in the quest to de-risk ongoing R&D, make informed go/no-go decisions, identify potential partnership opportunities, and uncover investment opportunities in the RAS pathway inhibitor landscape.

RAS Pathways

RAS pathways

Introduction to the RAS pathway and its role in cancer development

- Overview of the RAS signaling cascade and its dysregulation in various cancers

Number of Projects/Assets/Companies

Mode of Action	Preclinical	Clinical	Biotech/Pharma
1. **Direct RAS inhibitors**	400+	2	15+
2. **RAS-membrane interaction inhibitors**	200+	1	5+
3. **RAS-GEF inhibitors**	~200+	-	1
4. **RAS-GAP inhibitors**	250+	~4	25+
5. **Downstream pathway inhibitors**	500+	~3	10+
6. **Synthetic lethal approaches**	40+	-	1+
7. **Combination therapies and future directions**	1K+	100+	30+

Direct RAS inhibitors

Preclinical studies: Compounds, mechanisms of action, in vitro and in vivo data

Examples

Project: Project 2: Targeting Glutamine Metabolism to Enhance EGFR Blockade in Wild-Type RAS CRC

Organization: Vanderbilt University Medical Center
Project Leader: Jordan Berlin

Research question: To evaluate the efficacy of combined CB-839 (a glutamine metabolism inhibitor) and panitumumab (an EGFR-targeting monoclonal antibody) in patients with wild-type RAS colorectal cancer who have progressed on prior anti-EGFR monoclonal antibody therapy.
Stage: In silico, in vitro, and in vivo (with animals).
Methods: The study will involve a phase II clinical trial (Aim 1) to evaluate the efficacy of the combined therapy. Additionally, the researchers will use quantitative glutamine PET imaging (Aim 2) to predict response to therapy in EGFR monoclonal antibody-naive and EGFR

monoclonal antibody-refractory patients. Finally, they will develop a PET imaging-derived gene signature of glutamine avidity to predict responsiveness to inhibitors of glutamine metabolism (Aim 3).
Drug development: The study aims to develop a new therapeutic combination (CB-839 and panitumumab) to improve response and overcome resistance to anti-EGFR monoclonal antibody therapy in wild-type RAS colorectal cancer. The researchers also aim to establish a new way to identify patients likely to benefit from inhibitors of glutamine metabolism.

Project: Molecular Glues to Target RAS-MAPK Driven Cancers

Organization: Sloan-Kettering Institute, Cancer Center
Project Leader: Arvin Dar

Research question: To develop a new class of drugs for RAS-MAPK driven cancers by targeting the interfacial binding sites of key regulatory complexes within the MAPK/ERK kinase (MEK) cascade.
Stage: In silico, in vitro, and in vivo (with animals).
Methods: The study involves structure-based design and synthesis of advanced trametiglue analogs, including paralog-selective molecular glues to target individual MAPK signaling complexes (Aim 1). It also includes in vivo target engagement and optimization of drug-like properties with this expanded set of analogs (Aim 2), as well as testing in preclinical cancer models, including patient-derived organoids and xenografts (Aim 3).
Drug development: The study aims to develop a new class of drugs that target the interfacial binding sites of key regulatory complexes within the MAPK/ERK kinase (MEK) cascade, moving away from conventional active site-based drugs. This approach has the potential to provide a unique class of compounds with advantages in terms of selectivity, target engagement, therapeutic index, and combinatorial activity to mitigate the emergence of drug resistance.

Project: Identification of resistance mechanisms to direct KRAS inhibition in pancreatic cancer

Organization: University Of Cincinnati
Project Leader: Andrew M Waters

Research question: To develop effective therapies for pancreatic ductal adenocarcinoma (PDAC) by targeting the two lesser-studied, atypical KRAS mutations (KRASG12R and KRASQ61H) and identifying therapeutic resistance mechanisms to KRAS inhibition.
Stage: In silico, in vitro, and in vivo (with animals).
Methods: The study will utilize direct pharmacologic inhibitors of KRASG12R and KRASQ61H in PDAC, and employ system-wide unbiased genetic loss-of-function CRISPR/Cas9 oncogenic signaling pathway libraries to identify therapeutic resistance mechanisms to KRAS inhibition. The researchers will also develop KrasG12R and KrasQ61H syngeneic, orthotopic pancreatic cancer mouse models to define mutation-specific cancer functions and assess the influence of the tumor microenvironment on the consequences of KRAS inhibition alone and in combination.
Drug development: The study aims to develop effective KRAS-targeted therapies for PDAC, which is the 3rd leading cause of cancer death in the USA. The researchers will focus on two lesser-studied, atypical KRAS mutations (KRASG12R and KRASQ61H) and identify mutation-specific resistance mechanisms to KRAS inhibition, with the goal of informing the development of effective combination therapies that can prolong patient response to KRAS-targeted therapies.

Examples

Project: Optimal Anti-EGFR Treatment of mCRC Patients With Low-Frequency RAS Mutation

ID: CT04034173
Phase: 2
Intervention
This trial (NCT04034173) investigates the effectiveness of anti-EGFR treatment in metastatic colorectal cancer (mCRC) patients with low-frequency RAS mutations. The specific drugs being tested are:

- **5-FU (fluorouracil)**
- **Folinic acid**
- **Panitumumab**
- **Irinotecan**

Route of Administration
It is not explicitly stated in the provided summary, but chemotherapy drugs like those used in this trial are typically administered intravenously (IV).
Mode of Action

- **Anti-EGFR agents (panitumumab):** Block EGFR (epidermal growth factor receptor), a protein that promotes cancer cell growth and survival.
- **5-FU:** Disrupts DNA synthesis in cancer cells.
- **Folinic acid:** Enhances the effect of 5-FU.
- **Irinotecan:** Damages DNA in cancer cells.

Target
This trial targets adult patients (18 years or older) of any sex with:

- Histologically confirmed metastatic adenocarcinoma of the colon or rectum (stage IV).
- Primarily non-resectable metastases or surgery refusal.
- RAS mutation detected at a low frequency.

Conditions
The specific condition being studied is mCRC with a low-frequency RAS mutation. RAS mutations are common in mCRC and can indicate resistance to anti-EGFR therapy. This trial aims to see if the treatment is still effective when the mutation rate is low.
Sponsors
The study is sponsored by Ludwig-Maximilians - University of Munich and Amgen.

Project: Study of Binimetinib + Nivolumab Plus or Minus Ipilimumab in Patients With Previously Treated Microsatellite-stable (MSS) Metastatic Colorectal Cancer With RAS Mutation

ID: NCT04034173
Phase: 2
Intervention
This was a phase 1b/2, multicenter, open-label clinical trial evaluating the safety and efficacy of combining binimetinib with nivolumab, and nivolumab with ipilimumab. Binimetinib is a MEK inhibitor, nivolumab is an immune checkpoint inhibitor targeting PD-1, and ipilimumab is another immune checkpoint inhibitor targeting CTLA-4.

Route of Administration
All drugs were administered orally.
Mode of Action
- Binimetinib inhibits a protein involved in cell growth and survival.
- Nivolumab and ipilimumab are designed to help the immune system recognize and attack cancer cells.

Target
This trial targeted adult patients with advanced metastatic colorectal cancer (mCRC) that was microsatellite stable (MSS) and had a RAS mutation. Patients had to have received at least one but no more than two prior lines of therapy.
Conditions
The specific condition being studied was RAS mutation-positive, microsatellite-stable metastatic colorectal cancer that had progressed after prior treatment.
Sponsors
This study was sponsored by Pfizer with collaboration from Bristol-Myers Squibb.

Project: BAY 43-9006 (Sorafenib) to Treat Relapsed Non-Small Cell Lung Cancer

ID: NCT00098254
Phase: 2
Intervention
This clinical trial (NCT00098254) investigated the use of **BAY 43-9006 (Sorafenib)**, a bi-aryl urea class of anti-cancer agent, to treat patients with advanced, recurrent, or refractory non-small cell lung cancer (NSCLC).
Route of Administration
Sorafenib was administered orally in this trial. Patients received the medication twice a day, morning and evening.
Mode of Action
The exact mechanism of action for Sorafenib in treating NSCLC is not fully understood, but it is believed to work through multiple pathways:
- **Inhibition of tumor cell proliferation:** Sorafenib may block signaling pathways that promote cancer cell growth and division.
- **Anti-angiogenesis:** It may hinder the formation of new blood vessels that tumors need for growth and survival.

Target
This trial focused on adult patients (18 years or older) with NSCLC that had:
- Progressed or come back (recurred) after receiving at least one prior chemotherapy regimen.

Conditions
The specific condition being studied was **relapsed non-small cell lung cancer**.
Sponsors
The sponsor is National Cancer Institute (NCI).

Publications:

Project: Tumor-selective activity of RAS-GTP inhibition in pancreatic cancer
Leader: Kenneth P. Olive
Organization: Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY, USA

DOI: 10.1038/s41586-024-07379-z

Research Question:
Can broad-spectrum RAS inhibition be an effective treatment for pancreatic ductal adenocarcinoma (PDAC)?

Stage:
In vivo with animals and in vitro with human cells and tissues.

Methods:

- The study used a highly selective drug called RMC-7977 that targets the active form of RAS proteins (KRAS, HRAS, and NRAS).
- Researchers tested the drug on a variety of PDAC models, including human and mouse cell lines, patient-derived organoids and explants, xenografts, syngeneic allografts, and genetically engineered mice.
- They analyzed the effects of the drug on both tumor and normal tissues.

Drug Development:
The findings suggest that broad-spectrum RAS inhibition with RMC-7977 has promising potential for PDAC treatment. The drug showed significant anti-tumor activity with good tolerability. Interestingly, normal tissues displayed only temporary effects on proliferation without cell death, suggesting a tumor-specific response.

However, the study also identified a potential resistance mechanism involving Myc amplification in relapsed tumors. The researchers propose that combining RMC-7977 with TEAD inhibitors might be a strategy to overcome this resistance.

Overall, this study provides strong preclinical evidence for the development of broad-spectrum RAS inhibitors as a therapeutic approach for PDAC, potentially along with additional drugs to address resistance mechanisms.

RAS-membrane interaction inhibitors

Preclinical research: Strategies for disrupting RAS-membrane interactions

Project:

Organization:
Project Leader:

Clinical trials: Current pipeline, trial designs, and early results

RAS-GEF inhibitors

Preclinical data: Compounds targeting RAS-GEFs, mechanisms, and efficacy

Clinical development: Ongoing trials, target patient populations, companies involved

RAS-GAP inhibitors

Preclinical studies: Rationale for inhibiting RAS-GAPs, compounds under investigation

Clinical trials: Current pipeline, trial designs, and early results

Downstream pathway inhibitors

Preclinical research: Targeting components downstream of RAS (e.g., RAF, MEK, ERK)

Clinical development: Approved and investigational agents, combination strategies

Synthetic lethal approaches

Preclinical studies: Identifying synthetic lethal interactions with RAS mutations

Clinical trials: Current pipeline, trial designs, and early results

Combination therapies and future directions

Rationale for combining different RAS pathway inhibition strategies

Preclinical and clinical evidence for combination approaches

Competitive landscape and market potential

Key players in the RAS pathway inhibitor space (biotech, pharma, and academic institutions)

Biotech

- Mirati Therapeutics (acquired by Bristol Myers Squibb): Developed adagrasib (Krazati), the first approved KRAS G12C inhibitor.
- Amgen: Developing sotorasib, another KRAS G12C inhibitor, currently in clinical trials.
- Revolution Medicines: Working on various RAS inhibitors, including their KRAS G12C inhibitor RMC-6236.
- Arqule (acquired by Merck): Developed the KRAS G12C inhibitor AMG 510 (sotorasib), now under Merck's pipeline.
- Ideaya Biosciences: Developing synthetic lethal approaches for RAS-driven cancers.
- Verastem Oncology: Developing RAF/MEK inhibitors for RAS-mutant cancers.

Pharmaceutical Companies

- Boehringer Ingelheim: Developing BI 1701963, a KRAS G12C inhibitor, in clinical trials.
- Eli Lilly: LY3962673, an oral, highly potent, mutant-selective, and non-covalent KRAS G12D inhibitor demonstrates robust anti-tumor activity in KRAS G12D models.

- Merck: Acquired Arqule, gaining access to the KRAS G12C inhibitor sotorasib.
- Novartis: Developing various RAS pathway inhibitors, including the SHP2 inhibitor TNO155.
- Roche: Developing the KRAS G12C inhibitor GDC-6036 in collaboration with Regeneron.
- AstraZeneca: The deal gives AstraZeneca a global license to UA022, a small molecule inhibitor of the once-undruggable oncogene that was in preclinical development at Usynova..

Academic Institutions

- MD Anderson Cancer Center: Conducting research on RAS pathway inhibitors and synthetic lethality approaches.
- Memorial Sloan Kettering Cancer Center: Investigating combination therapies targeting RAS-driven cancers.
- Dana-Farber Cancer Institute: Studying mechanisms of resistance to RAS inhibitors and developing novel strategies.
- University of California, San Francisco (UCSF): Pioneering research on RAS biology and therapeutic targeting.
- Harvard Medical School: Exploring new approaches for targeting the RAS pathway.
- Massachusetts Institute of Technology (MIT): Developing novel RAS inhibitors and drug delivery systems.

Partnerships, collaborations, and licensing agreements

Market size and growth projections for RAS pathway inhibitors