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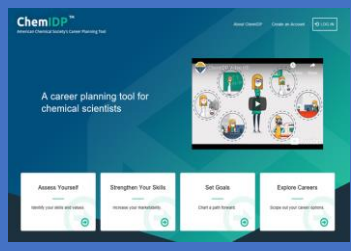

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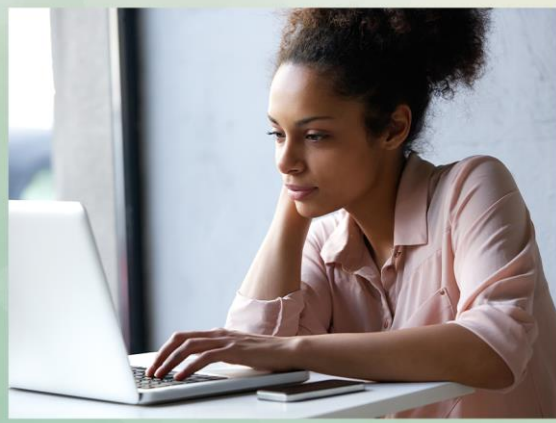

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Date: Wednesday, March 3, 2021 @ 2-3pm ET
Speaker: Robert Migliorini, Exxon Mobil Corporation
Moderator: Bryan Tweedy, American Chemical Society

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What You Will Learn:

- Learn about the major sections of a contract and common types of IP related agreements, including confidentiality/non-disclosure, material transfer, and more
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- Know the appropriate type of IP agreement to put in place prior to working with an outside party

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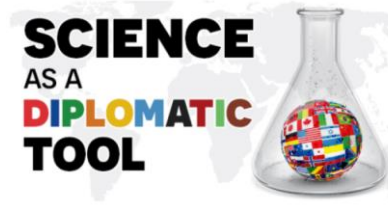

Date: Wednesday, March 10, 2021 @ 11am-12pm ET
Speakers: Zafra Lerman, Malta Conferences Foundation / Peter Hotchkiss, Organisation for the Prohibition of Chemical Weapons / Vaughan Turekian, National Academies' Policy and Global Affairs Division
Moderator: Lori Brown, American Chemical Society

Register for Free!

What You Will Learn:

- How the OPCW works with the governments of 193 countries to prevent the use of chemical weapons
- How the US National Academies' Policy and Global Affairs office mobilizes experts and networks around the world to increase the use of evidence to advance local, national and global policy and capacity
- How the Malta Conferences uses science diplomacy to overcome cultural, religious, and political barriers in the Middle East

Co-produced with: ACS External Affairs & Communcations

Date: Thursday, March 11, 2021 @ 1-2pm ET
Speakers: Julie Mann, PURIS Holdings, LLC / Joshua March, Artemys Foods / Andrew Ive, Big Idea Venture
Moderator: Christopher Gregson, Greenstalk Food Consulting LLC

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What You Will Learn:

- A better understanding of the most significant transformation of the food industry in decades
- The challenges of formulating plant-based products or using cell cultures to "grow" meat
- How it will affect peoples' dietary choices in the future

Co-produced with: The Science History Institute and Chemical & Engineering News

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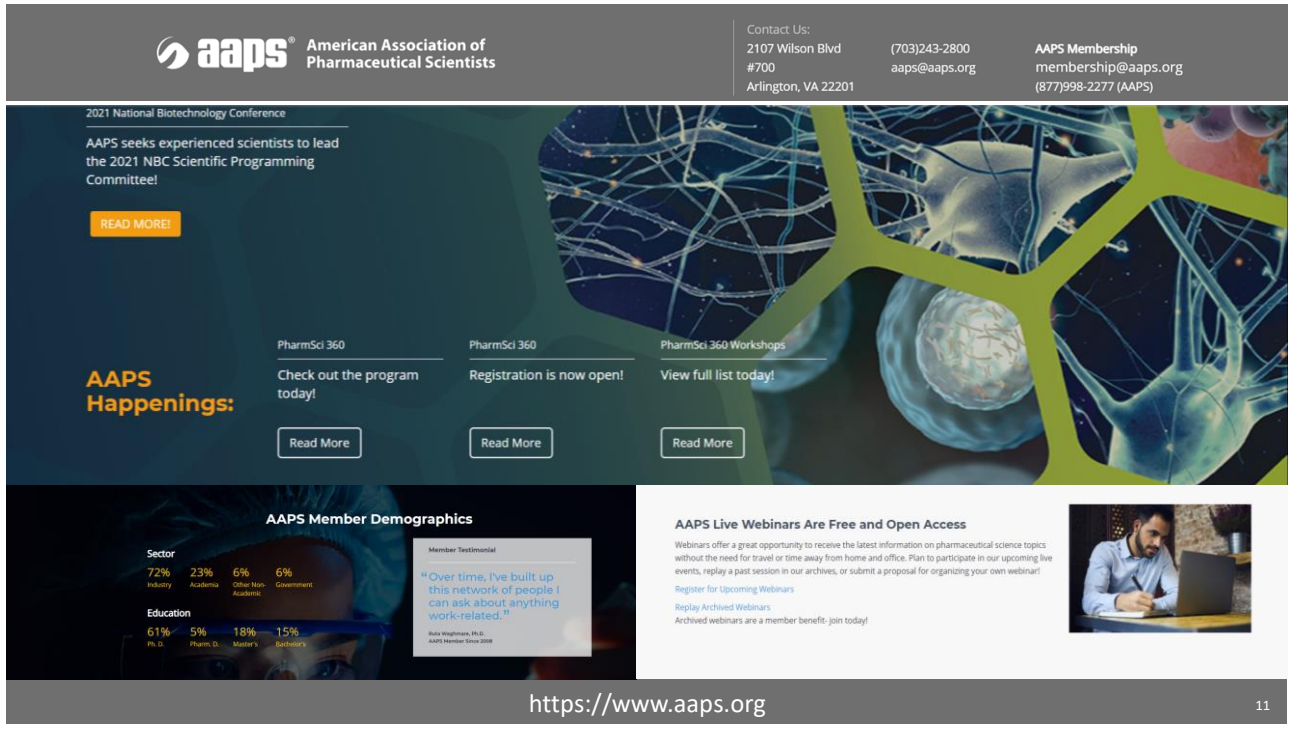

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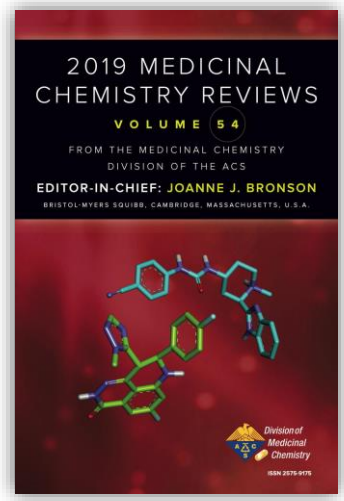

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2021 Drug Design and Delivery Series

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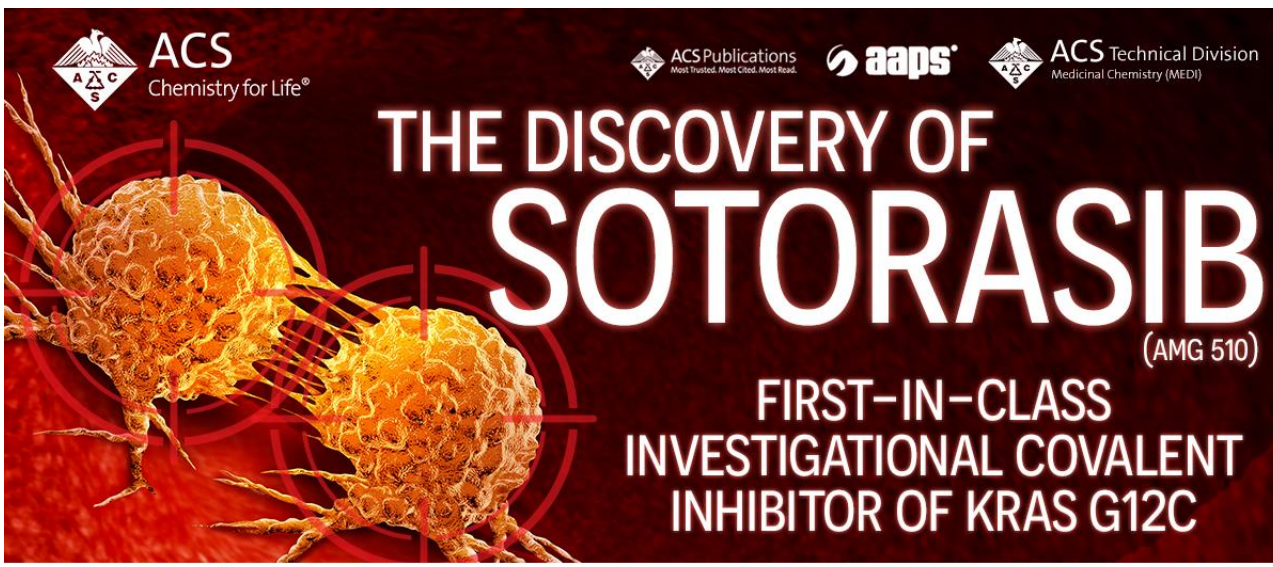

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The Discovery of Sotorasib (AMG 510): First-in-Class Investigational Covalent Inhibitor of KRAS G12C

Brian Lanman
Director Research,
Medicinal Chemistry, Amgen, Inc.

Ariamala Gopalsamy
Director, Interim Head of Boston Oncology
Chemistry, AstraZeneca

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RAS, A MOLECULAR SWITCH REGULATING CELLULAR PROLIFERATION

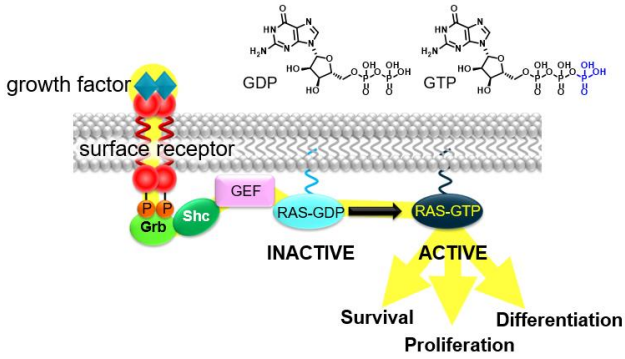


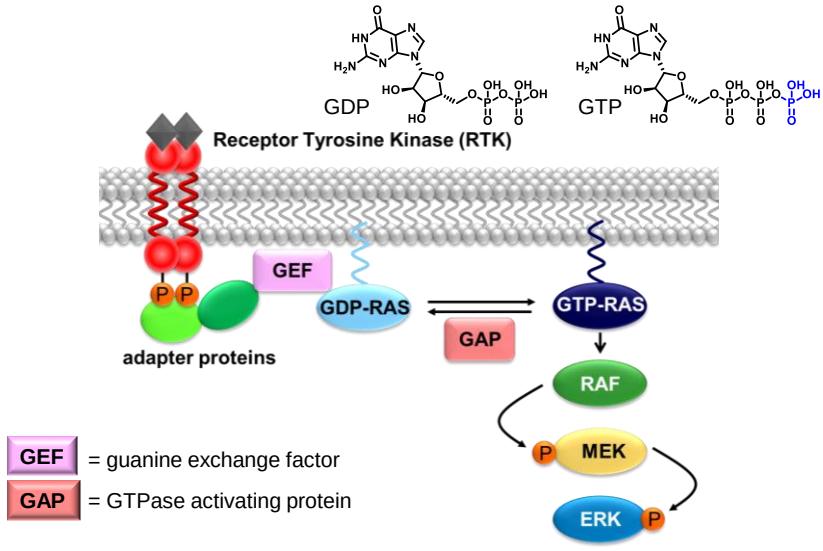
Table 1 | **Activation of RAS signalling pathways in different tumours**

Defect or mutation	Tumour type	Frequency (%)
RAS mutation	Pancreas	90 (K)
	Lung adenocarcinoma (non-small-cell)	35 (K)
	Colorectal	45 (K)
	Thyroid (Follicular)	55 (H, K, N)
	Thyroid (Undifferentiated papillary)	60 (H, K, N)
	Seminoma	45 (K, N)
	Melanoma	15 (N)
	Bladder	10 (H)
	Liver	30 (N)
	Kidney	10 (H)
	Myelodysplastic syndrome	40 (N, K)
	Acute myelogenous leukaemia	30 (N)

Downward, J. *Nat. Rev. Cancer* **2003**, *3*, 11–22

Nearly 50% of all cancers demonstrate oncogenic mutations of the Ras signaling pathway

WORK IN THE 1980s DEFINED THE RAS SIGNALING PATHWAY



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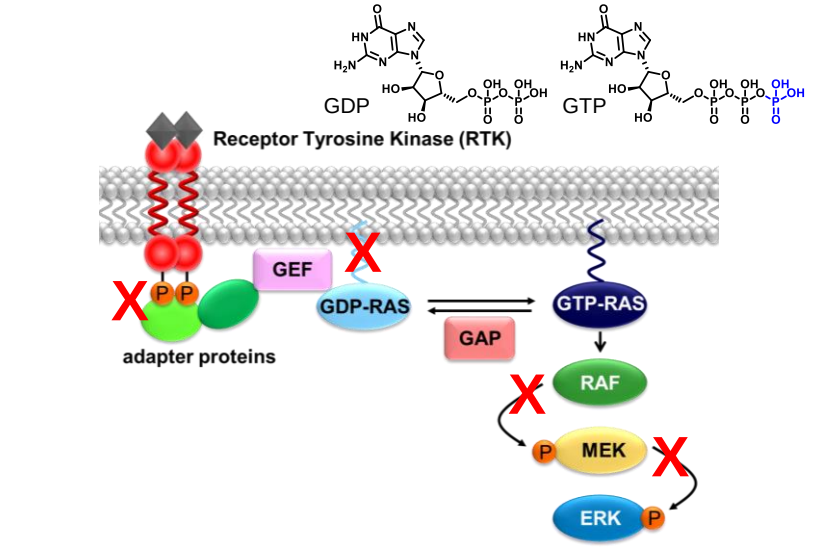
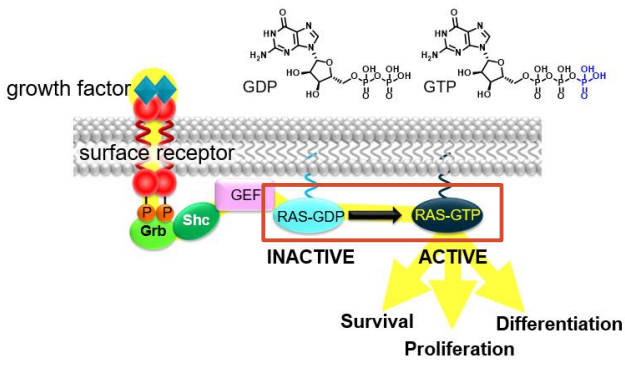
PROGRESS IN INHIBITING THIS PATHWAY BEGAN IN THE EARLY 2000s



Therapeutically useful inhibitors of Ras have remained elusive for over 30 years

"UNDRUGGABLE": DIRECT INHIBITORS OF RAS REMAINED ELUSIVE



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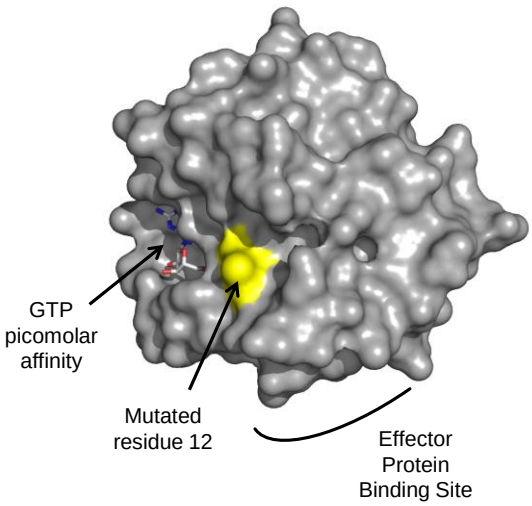
Downward, J. *Nat. Rev. Cancer* **2003**, *3*, 11–22

Nearly 50% of all cancers demonstrate oncogenic mutations of the Ras signaling pathway

WHY HAS KRAS SIGNALING REMAINED RESISTANT TO INHIBITION?

Active GTP-KRAS



- **GTP-KRAS is a good approximation of the definition of "undruggable"**
  - GTP pocket: **K_d ~ 10 pM**
    Intracellular GTP concentration: **0.5 mM**
  - Other surface clefts too small (<100 Å^3) to enable high-affinity binding

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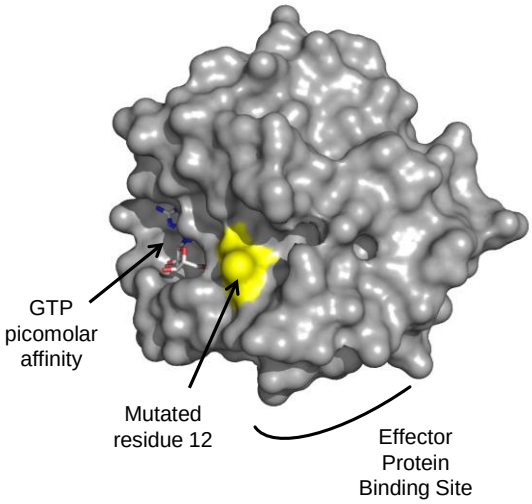
WHY HAS KRAS SIGNALING REMAINED RESISTANT TO INHIBITION?

Active GTP-KRAS



https://disney.fandom.com/wiki/Death_Star

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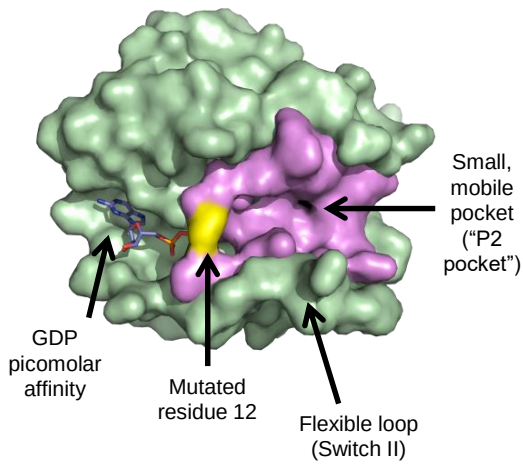
A NEW STRATEGY: COULD INHIBITING GDP-KRAS SUPPRESS SIGNALING?

Inactive GDP-KRAS



- **GDP binding induces a small, flexible pocket adjacent to the GDP binding side**
- **Small size (139–213 Å^3) & limited enclosure precluded the identification of high-affinity binders**
- **Proximity to a frequently mutated residue, Gly12, suggested a potential strategy…**

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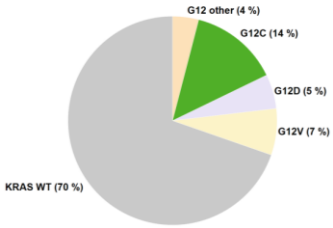
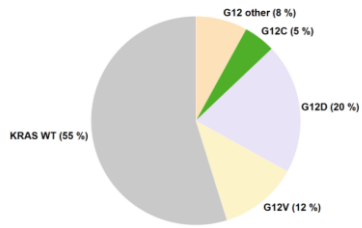
THE G12C MUTANT OFFERS A UNIQUE OPPORTUNITY IN TARGETING GDP-KRAS BECAUSE IT POSITIONS A REACTIVE CYS RESIDUE NEXT TO THE P2 POCKET

Codon 12 mutation frequency in select solid tumors

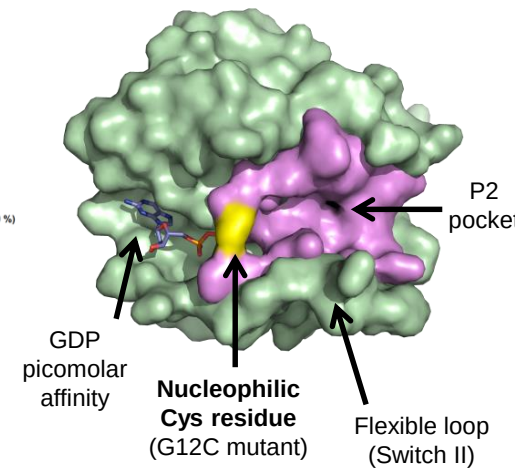
Lung Adenocarcinoma (LAC)



Colorectal Carcinoma (CRC)

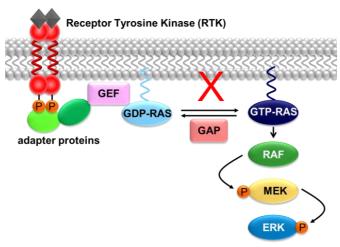


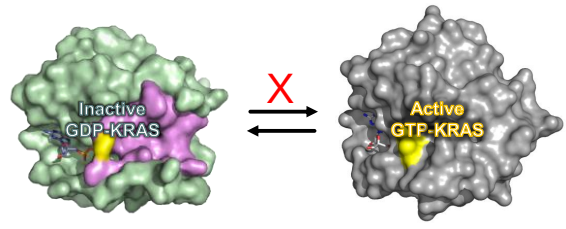
Inactive GDP-KRAS



Survey of COSMIC, cBioPortal, TumorPortal, and ICGC data portal. *Nat. Rev. Drug Disc*. **2014**, *13*, 828−851

PROJECT GOAL: LOCK GDP-KRAS^{G12C} IN ITS INACTIVE STATE...





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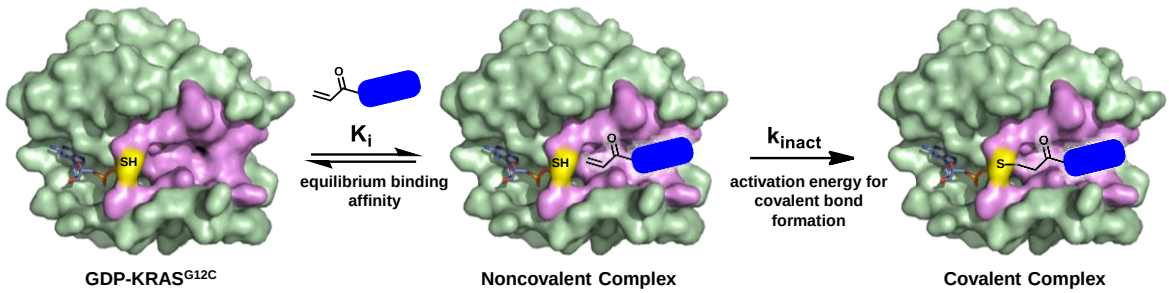
…WITH A COVALENT INHIBITOR OF KRAS^{G12C}



Motivations & potential benefits:

- Moderately druggable pocket ⇒ only low-affinity ligands (K_i) likely to be identified; Covalent binding (k_{inact}) should afford **enhanced potency**
- Targeting G12C allows for selectivity toward non-mutant KRAS, **mitigating off-target toxicity**
- Irreversible inhibition should allow for **persistent pharmacological effects** (i.e., persisting until unmodified protein is resynthesized and lasting even after elimination of circulating drug)

Review of covalent inhibitors as a therapeutic class: J. Singh, *et al.*, *Nat. Rev. Drug Disc.* **2011**, *10*, 307−317

POLL QUESTION: FIRST COVALENT INHIBITOR?

Which of the following was the first marketed covalent inhibitor drug?

- benzylpenicillin (Penicillin G)
- acetylsalicylic acid (Aspirin)
- omeprazole (Prilosec)
- clopidogrel (Plavix)

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POLL QUESTION: FIRST COVALENT INHIBITOR?

Answer: acetylsalicylic acid (Aspirin)

- benzylpenicillin (Penicillin G) – 1942
- **acetylsalicylic acid (Aspirin) – 1899**
- omeprazole (Prilosec) – 1988
- clopidogrel (Plavix) – 1997

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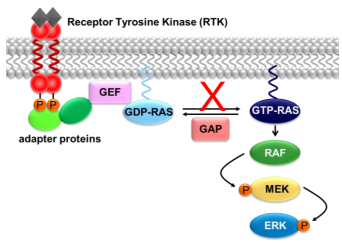
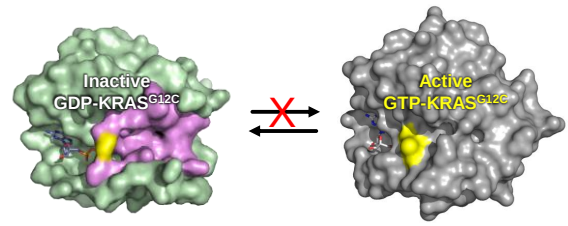
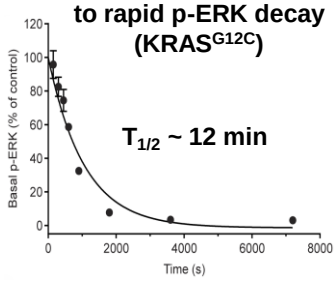
ASSESSING FEASIBILITY: LOCKING GDP-KRAS^{G12C} IN ITS INACTIVE STATE

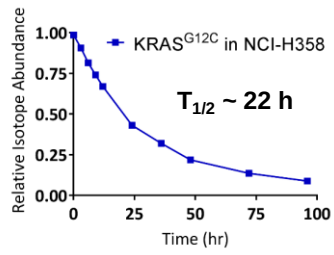




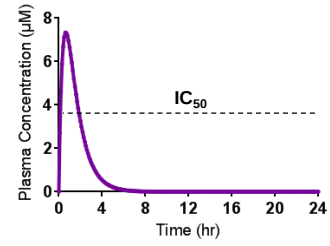
Pathway blockade leads to rapid p-ERK decay (KRAS^{G12C})



Long KRAS Protein Half-Life



Hypothetical Minimum PK Profile



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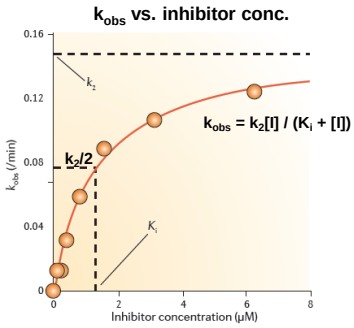
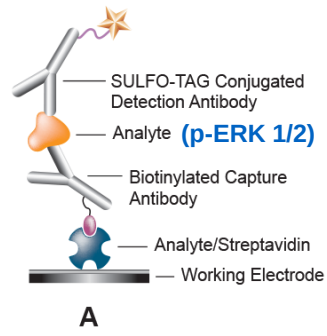
ASSESSING LEADS: AN OVERVIEW OF KRAS ASSAYS

Inactivation kinetics
(mass spectrometry)

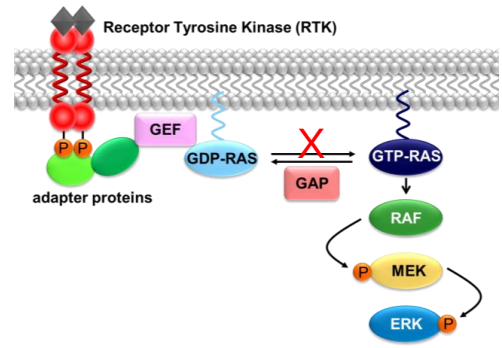


J. Singh, *et al.*, *Nat. Rev. Drug Disc.* **2011**, *10*, 307−317

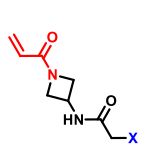
Signaling disruption
(fluorescence assay)



https://www.mesoscale.com/en/products_and_services/assay_development_tools/msd_gold_product_and_services/msd_gold_plates

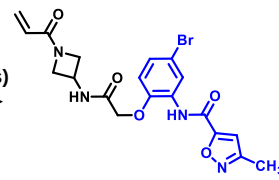


THE SEARCH FOR A STARTING POINT: SCREENING LIBRARIES OF CYS-REACTIVE COMPOUNDS IDENTIFIED A NOVEL INHIBITOR SCAFFOLD



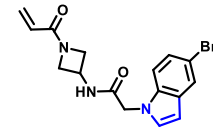
Cys-reactive template
Fragments installed at **X**

Library Synthesis & Screening (w/ Carmot Therapeutics)



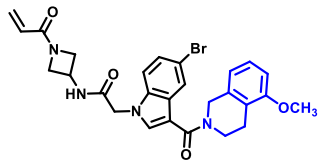
Library Hit
G12C MS $k_{obs}/[I]$ = 2 $M^{-1}s^{-1}$

Medicinal Chemistry



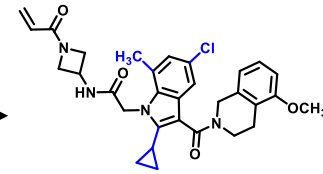
Truncated Hit
G12C $k_{obs}/[I]$ = 2 $M^{-1}s^{-1}$

2nd Iteration Library Synthesis & Screening



Early Lead
G12C $k_{obs}/[I]$ = 230 $M^{-1}s^{-1}$
Cell* p-ERK 2 h IC_{50} = 11.4 μM

Medicinal Chemistry



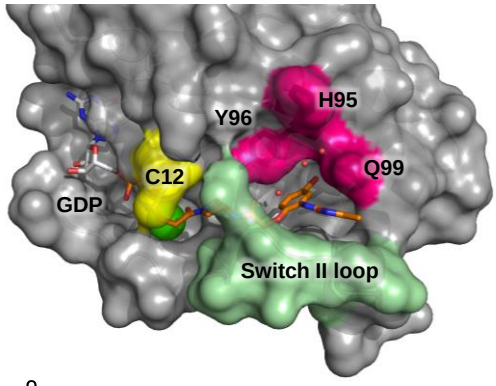
Advanced Lead
G12C $k_{obs}/[I]$ = 2,640 $M^{-1}s^{-1}$
Cell p-ERK 2 h IC_{50} = 0.22 μM
Cell* Viability 72 h IC_{50} = 0.07 μM

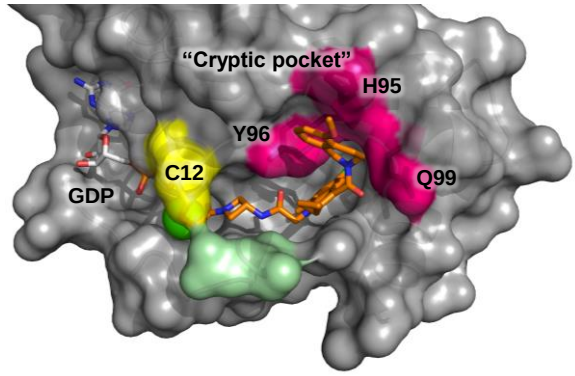
Y. Shin, *et al.*, *ACS Med. Chem. Lett.* **2019**, *10*, 1302–1308

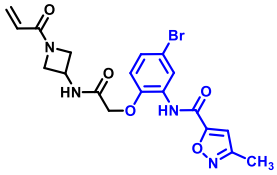
* MIA PaCa-2 human pancreatic tumor (homozygous *KRAS p.G12C*-mutant)

AMGEN

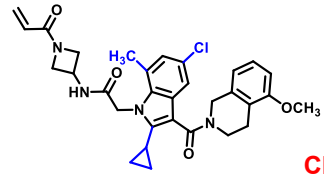
NEW SCAFFOLDS ENGAGED A PROXIMAL CRYPTIC POCKET







Library Hit
G12C $k_{obs}/[I]$ = 2 $M^{-1}s^{-1}$



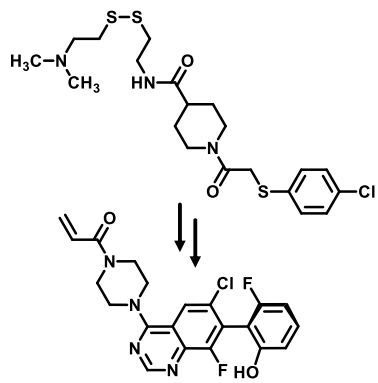
Advanced Lead
G12C $k_{obs}/[I]$ = 2,640 $M^{-1}s^{-1}$
Cell p-ERK 2 h IC_{50} = 0.22 μM
Cell Viability 72 h IC_{50} = 0.07 μM

CL ≈ Q_h (mouse, rat); v. low %F

Y. Shin, *et al*., *ACS Med. Chem. Lett.* **2019**, *10*, 1302–1308

AMGEN

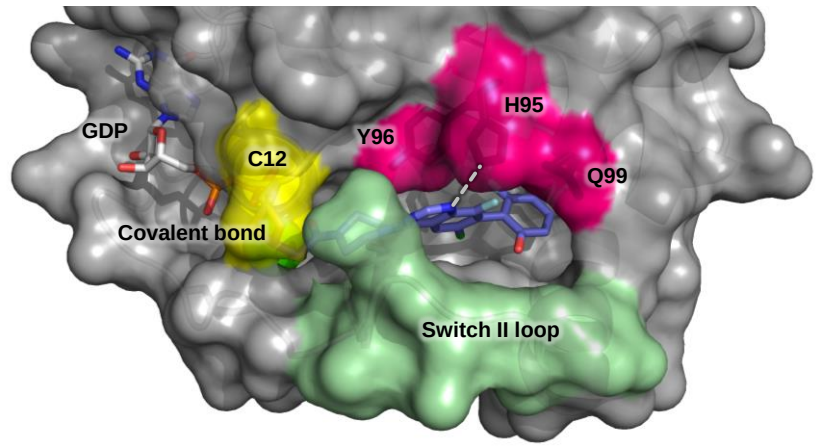
STRUCTURAL BIOLOGY OF A PUBLISHED KRAS^{G12C} INHIBITOR



ARS-1620

G12C $k_{obs}/[I]$ = 272 $M^{-1}s^{-1}$
Cell p-ERK 2 h IC_{50} = 0.83 μM
Cell Viability 72 h IC_{50} = 0.24 μM

M. R. Janes, *et al. Cell* **2018**, *172*, 578–589



X-ray structure of
GDP-KRAS^{G12C} + **ARS-1620**

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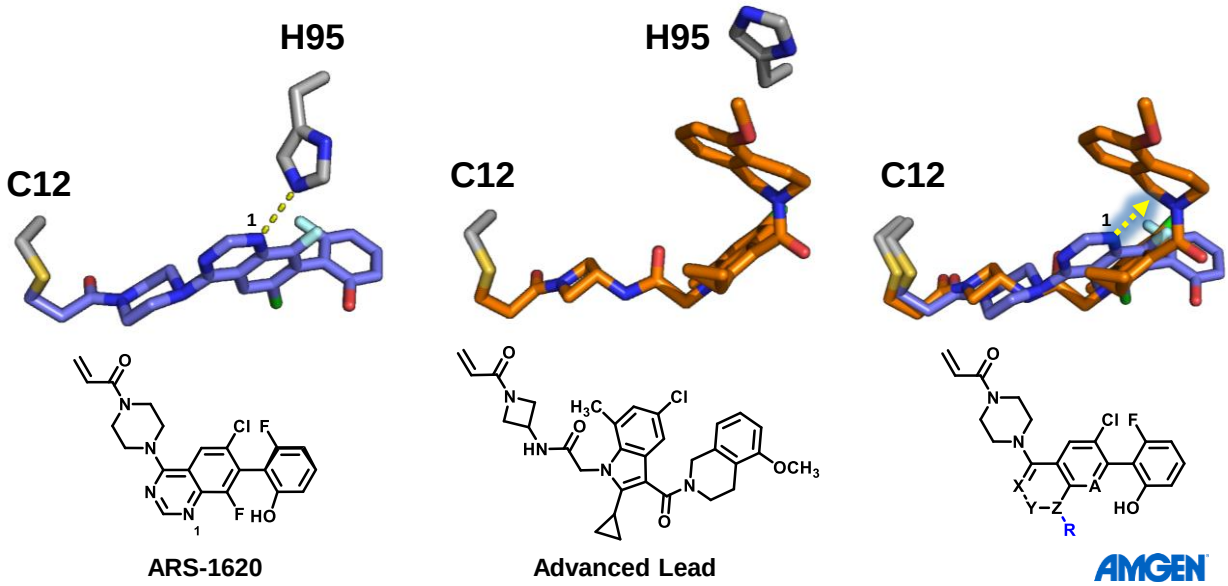
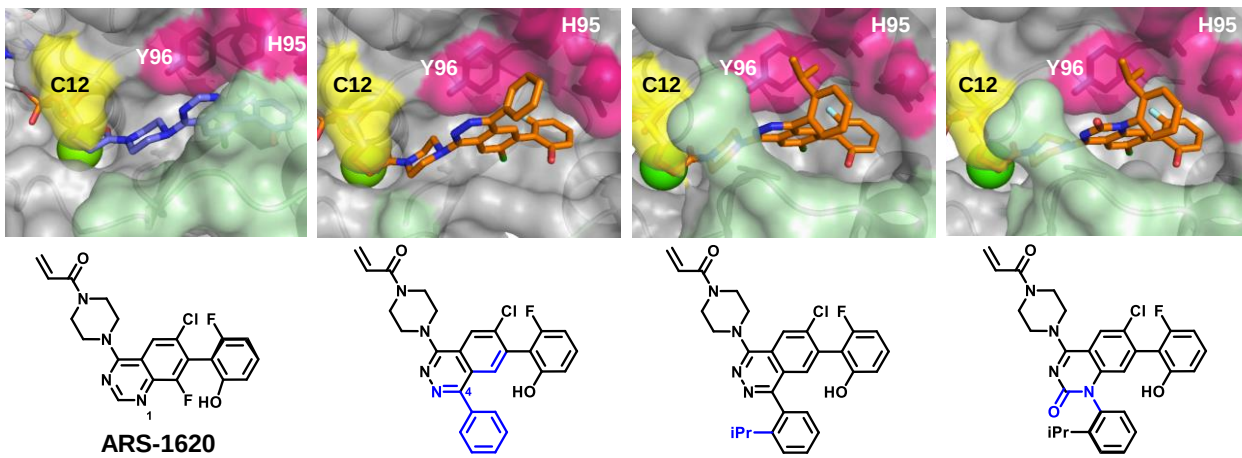
HYBRIDIZING SCAFFOLDS TO IDENTIFY NEW CHEMICAL MATTER WITH IMPROVED PHARMACEUTICAL PROPERTIES



HYBRID SCAFFOLDS EXPLOIT THE CRYPTIC POCKET & GAIN POTENCY

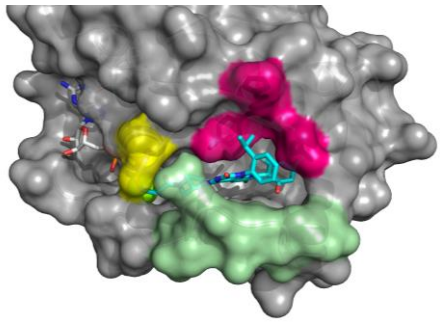


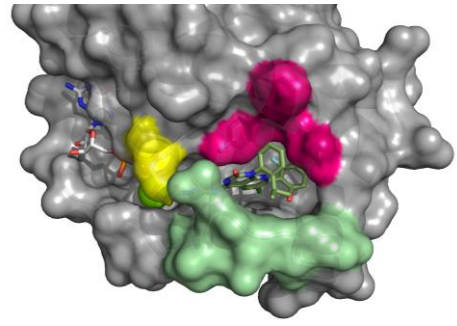
Cell p-ERK 2 h IC_{50} (μM)			
2.89 (0.831*)	**58.0**	**3.47**	**0.211** (0.130*)
Cell Viability 72 h IC_{50} (μM)			
0.492 (0.246*)	n.d.	**1.10**	**0.113** (0.093*)

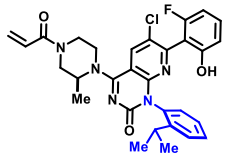
* Single atropisomer

Lanman, *et al.*, *J. Med. Chem.* **2020**, *1*, 52–65

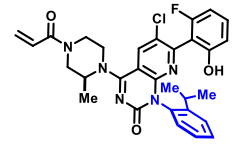
…BUT WITH A STEREOCHEMICAL COMPLICATION







$\Delta G^{\ddagger}$ = 26 kcal/mol
$t_{1/2}$ = 8 days



N-Aryl Quinazolinone (*R*)-Atropisomer
Cell p-ERK 2 h IC_{50} = 0.043 μM
Cell Viability 72 h IC_{50} = 0.005 μM

N-Aryl Quinazolinone (*S*)-Atropisomer
Cell p-ERK 2 h IC_{50} = 0.500 μM
Cell Viability 72 h IC_{50} = 0.045 μM

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POLL QUESTION: ATROPISOMERISM

When was phenomena of atropisomerism first reported in the literature?

- 1815
- 1848
- 1893
- 1922

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POLL QUESTION: ATROPISOMERISM

When was phenomena of atropisomerism first reported in the literature?

- 1815 – Jean-Baptiste Biot; rotation of plane-polarized light
- 1848 – Louis Pasteur; discovery of enantiomers
- 1893 – Lord Kelvin coined the term “chirality”
- **1922 – James Kenner & George Hallatt Christie (Univ. of Sheffield); atropisomer separation by crystallization**

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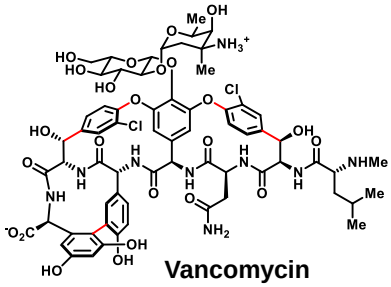
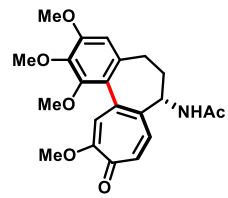
FAST FACTS: ATROPISOMERISM

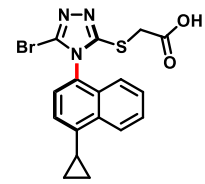
- The term *atropisomer* was first proposed in 1933 by Richard Kuhn (Univ. of Heidelberg; 1938 Nobel Laureate in Chemistry)
- *Atropisomer* is derived from the Greek *atropos*, meaning “without turn”
- Examples of FDA-approved atropisomerically stable drugs:



Vancomycin (1988)



Colchicine (2009)



Lesinurad (2015; discontinued)

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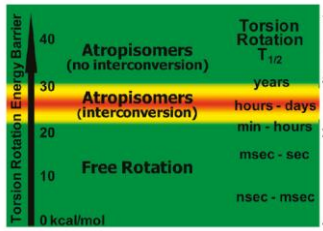
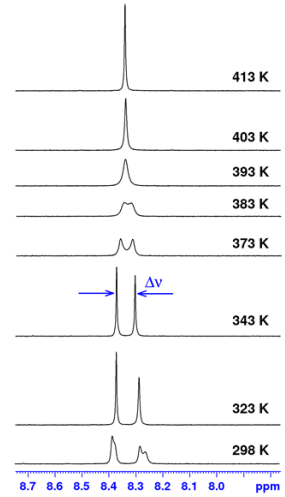
HOW TO DEAL WITH META-STABLE ATROPISOMERS?



LaPlante, S. R., et al. *J. Med. Chem.,* **2011**, *54*, 7005–7022

$$\Delta G^{\ddagger} = 0.0191 \cdot T_c \left(9.97 + \ln\left(\frac{T_c}{\Delta\nu}\right)\right)$$



Strategies: (1) Lock biaryl bond rotation
(2) Completely free rotation of biaryl bond
(3) Remove axial chirality

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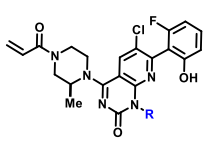
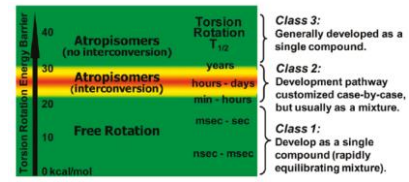
OPTIMIZATION OF ATROPISOMER STABILITY & KRAS ACTIVITY



Cmpd	R	Coupled Exchange IC_{50} (μM)	p-ERK IC_{50} (μM)	Interconversion barrier ($\Delta G^{\ddagger}$, kcal/mol) [a]
(*R*)-**18**	*i*-Pr	0.051	0.044	26.0[1]
(*R*)-**23**	*t*-Bu	0.117	0.051	>30[2]
(*R*)-**24**	Me, *i*-Pr	0.025	0.028	**>30[2]**
26	N, *i*-Pr	0.083	0.053	23.5[2]
28	S, N, *i*-Pr	0.081	0.063	**17.5[2]**
31	Et, Et, *i*-Pr	0.068	0.036	**NA**
33	N, N, *i*-Pr	0.021	0.025	**NA**

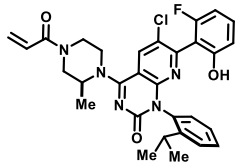
[a] Interconversion barriers measured by [1]time-course or [2]VT NMR

Cmpd	CL (L/h/kg)	PPB (f_u)	$t_{1/2}$ (h)	%F	10 mg/kg $C_{max,u}$ / p-ERK IC_{50}
(*R*)-**24**	2.7	0.03	0.5	21	4.5
28	2.2	0.02	1.1	22	1.5
31	3.3	0.03	0.5	8	0.8
33	2.3	0.03	0.8	13	0.8



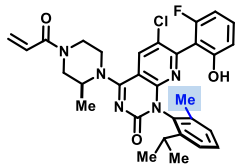
Lanman, *et al*., *J. Med. Chem.* **2020**, *1*, 52–65

BIS-ORTHO SUBSTITUTION AFFORDS A CONFIGURATIONALLY STABLE LEAD



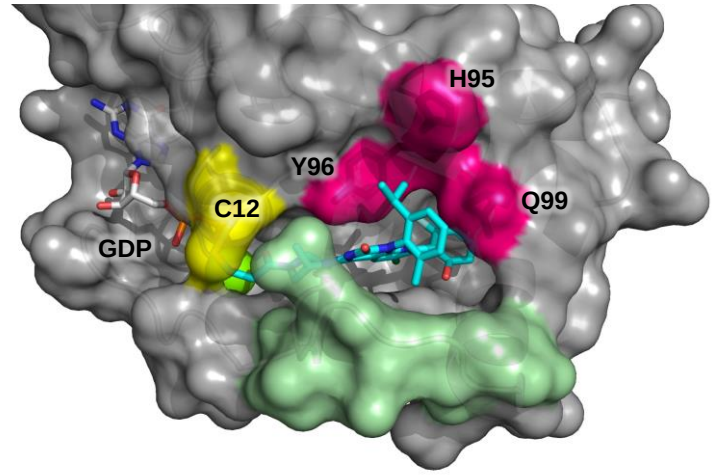
$k_{obs}/[I]$ = 5,800 $M^{-1}s^{-1}$
Cell p-ERK 2 h IC_{50} = 0.043 μM
Cell Viability 72 h IC_{50} = 0.005 μM

$\Delta G^{‡}$ = 26 kcal/mol (DMSO); $t_{1/2}$ = 8 days



$k_{obs}/[I]$ = 23,500 $M^{-1}s^{-1}$
Cell p-ERK 2 h IC_{50} = 0.033 μM
Cell Viability 72 h IC_{50} = 0.002 μM

$\Delta G^{‡}$ = 35 kcal/mol (DMSO); $t_{1/2}$ = >2,000 years



Bis-ortho substitution restricts C–N bond rotation, affording separable & highly stable atropisomers

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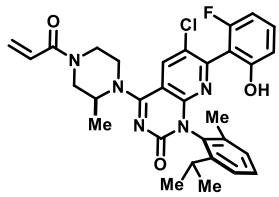
FROM LEAD TO DRUG: OPTIMIZATION OF PHARMACEUTICAL PROPERTIES

Configurationally-Stable Lead



Cell p-ERK 2 h IC_{50} = 0.033 μM
Cell Viability 72 h IC_{50} = 0.002 μM

	Solubility (mg/mL)	
	Amorphous	Crystalline
FaSSGF (pH 1.6)	0.108	0.001
PBS (pH 7.4)	0.115	<0.001
FaSSIF (pH 6.8)	0.118	0.004

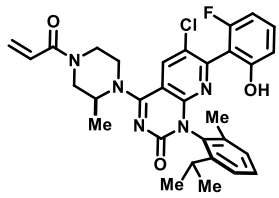
Oral bioavailability (%F) markedly impacted by crystalline form

Lanman, *et al.*, *J. Med. Chem.* **2020**, *1*, 52–65

AMGEN

FROM LEAD TO DRUG: OPTIMIZATION OF PHARMACEUTICAL PROPERTIES

Configurationally-Stable Lead



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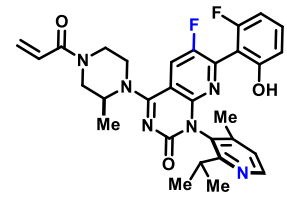
Oral bioavailability (%F) markedly impacted by crystalline form

Sotorasib (AMG 510)



Cell p-ERK 2 h IC_{50} = 0.070 μM
Cell Viability 72 h IC_{50} = 0.005 μM

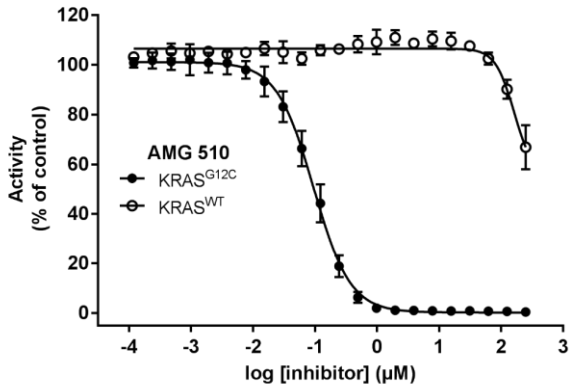
	Solubility (mg/mL)	
	Amorphous	Crystalline
FaSSGF (pH 1.6)	4.2	2.4
PBS (pH 7.4)	0.10	0.052
FaSSIF (pH 6.8)	0.17	0.070

Oral bioavailability (%F) similar across different physical forms

Lanman, *et al.*, *J. Med. Chem.* **2020**, *1*, 52–65

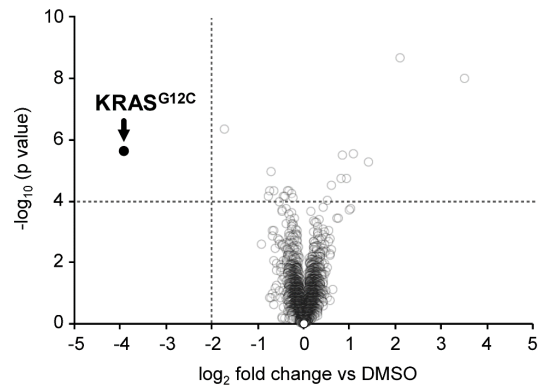
SOTORASIB (AMG 510) IS HIGHLY SELECTIVE FOR $KRAS^{G12C}$

Coupled Nucleotide Exchange



40 min SOS-1-catalyzed GDP/GTP exchange coupled to binding of c-RAF RAS-binding domain (RBD)

NCI-H358 Cysteine Proteome (Sotorasib vs DMSO)

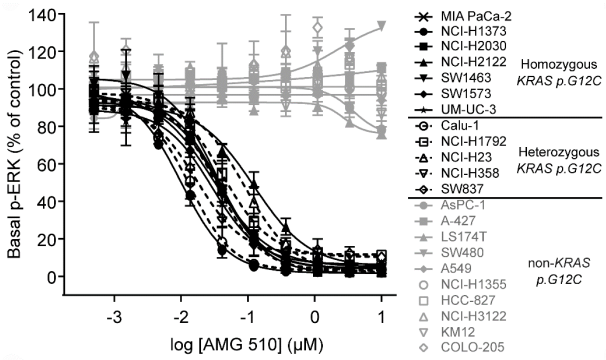


6451 unique cysteine-containing peptides identified

Canon, *et al.*, *Nature* **2019**, *575*, 217–223

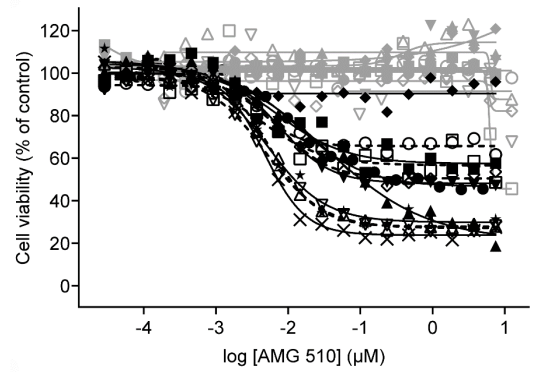
SOTORASIB INHIBITS SIGNALING AND IMPAIRS VIABILITY ONLY IN *KRAS p.G12C* MUTANT CELL LINES

ERK phosphorylation



2 h incubation

Cell Viability



72 h incubation

adherent '2D' cell culture conditions

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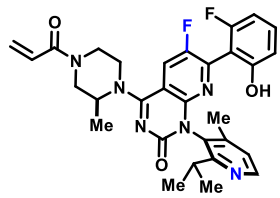
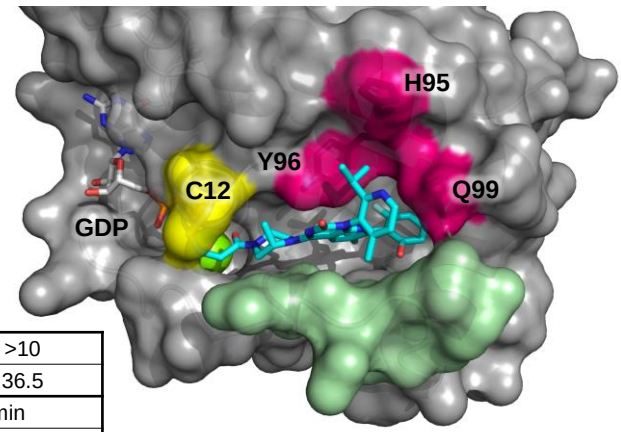
IN VITRO & PHARMACOKINETIC PROFILE OF SOTORASIB



G12C k_{inact}/K_I = 9,900 $M^{-1}s^{-1}$



X-ray structure of KRAS^{G12C}-GDP + sotorasib

Cell	p-ERK 2 h IC_{50} MIA PaCa-2 | A549 (μM)	0.070 | >10
	Viability 72 h IC_{50} MIA PaCa-2 | A549 (μM)	0.005 | 36.5
in vitro ADME	5 mM GSH $t_{1/2}$ (min)	200 min
	MuLM | RLM | DLM | HLM (μL/min/mg)	21 | 18 | 16 | 17
	Mu | R | D | H hep CL_{int} (μL/min/10^6 cells)	36 | 25 | 11 | 9
	PPB Mu | R | D | Hu (0.25 μM, UC, f_u)	0.06 | 0.05 | 0.17 | 0.09
	Solubility (mg/mL, PBS | FaSSIF | FaSSGF)	0.05 | 0.07 | 2.4
in vivo (10 mpk)	Mouse CL (L/h/kg) | V_{ss}(L/kg) | $t_{1/2}$ (h) | %F	1.6 | 0.74 | 0.3 | 31
	Rat CL (L/h/kg) | V_{ss} (L/kg) | $t_{1/2}$ (h) | %F	3.4 | 2.0 | 0.5 | 30
	Dog CL (L/h/kg) | V_{ss} (L/kg) | $t_{1/2}$ (h) | %F	2.2 | 0.73 | 0.4 | 34

KRAS^{G12C} protein $t_{1/2}$ ~ **22 h** (stable-isotope labeling)

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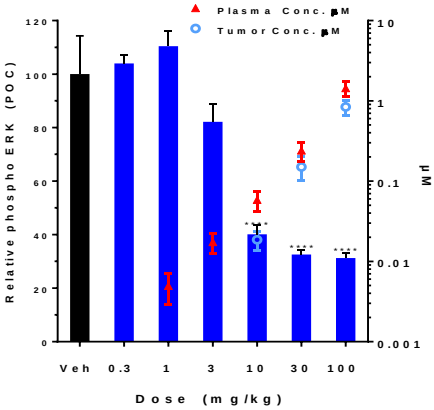
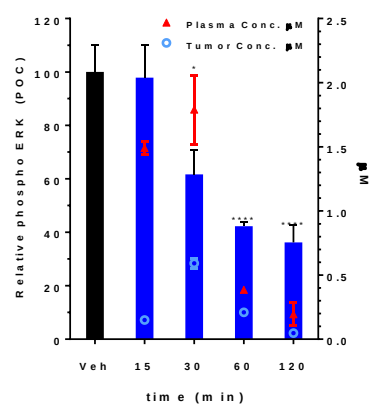
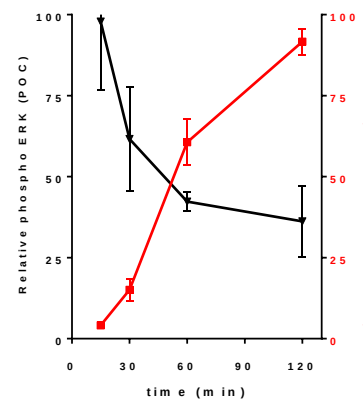
SOTORASIB INHIBITS ERK1/2 PHOSPHORYLATION IN *KRAS p.G12C* TUMORS (MIA PACA-2 T2); INHIBITION CORRELATES W/ OCCUPANCY

Single dose (2 h time-point)



Single dose (10 mg/kg; time-course)





* p<0.05, ****p<0.0001 by One-Way Anova followed by Dunnett's post hoc

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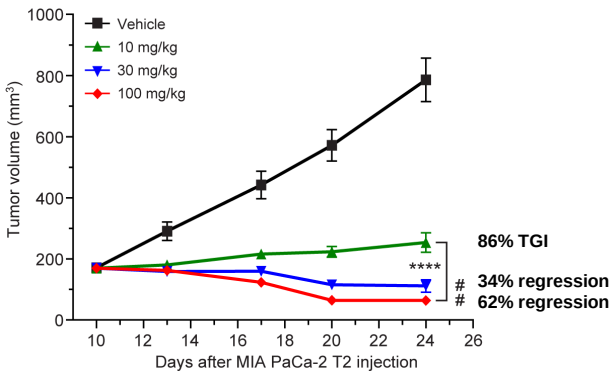
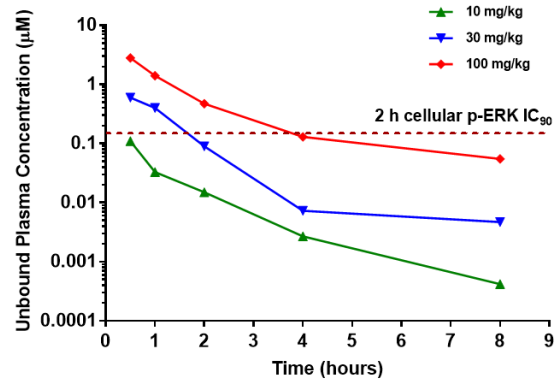
SOTORASIB DOSED ORALLY ONCE DAILY RESULTS IN REGRESSION OF *KRAS p.G12C* TUMOR XENOGRAFTS





Sotorasib exposure >IC_{90} for 2+ hours results in tumor regression

**** p < 0.0001 comparisons of vehicle to treatment group by Dunnett's
# p<0.05 regression by paired t-test

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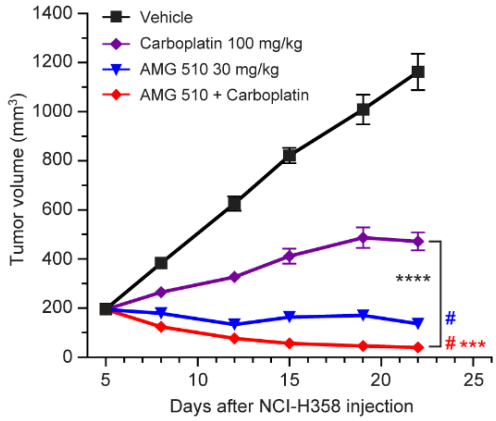
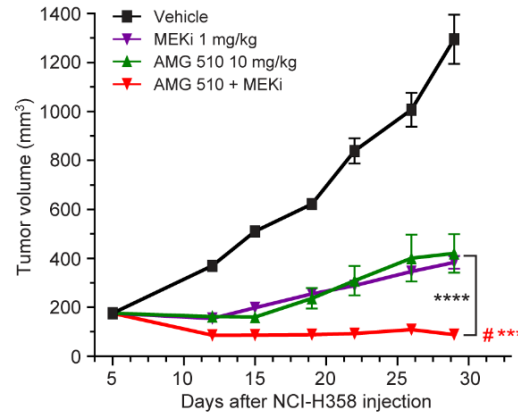
ASSESSING THE POTENTIAL OF SOTORASIB IN COMBINATION WITH CYTOTOXIC & TARGETED AGENTS

Sotorasib (AMG 510) + carboplatin

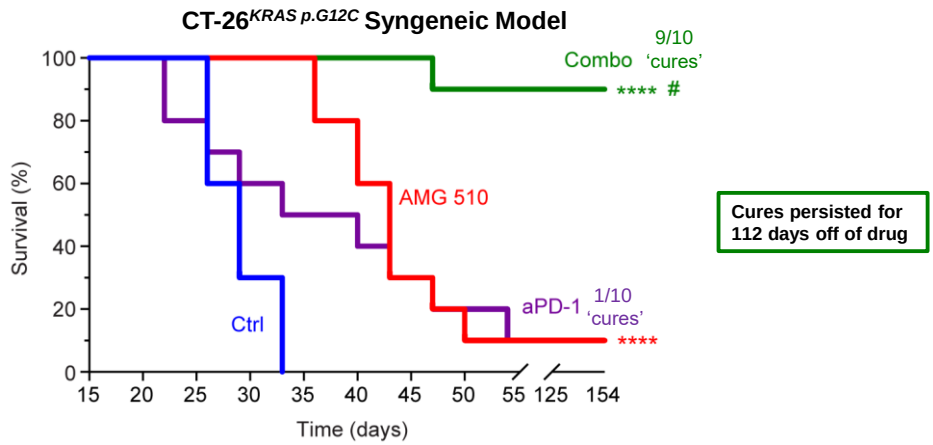


Sotorasib + MEK inhibitor



*** P < 0.001 combination treatment compared to each single agent by Dunnett's
# P < 0.001 regression by paired t-test
Results from all treatment groups were significant compared with vehicle (**** P < 0.0001 by Dunnett's)

SOTORASIB + IMMUNE CHECKPOINT INHIBITION RESULTS IN DURABLE CURES IN A CT-26$^{KRAS\ p.G12C}$ SYNGENEIC MODEL

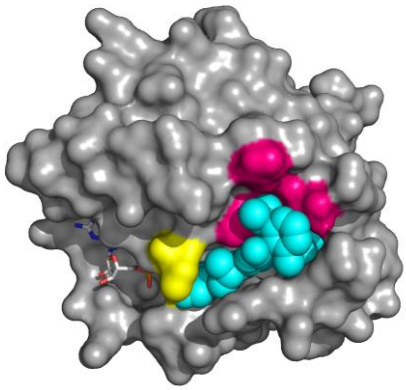


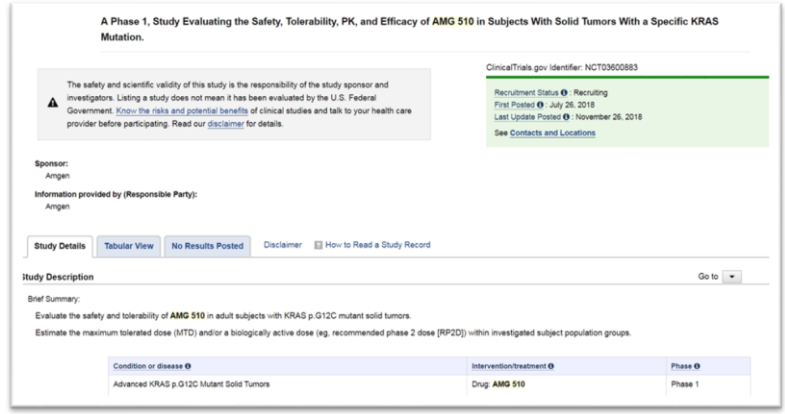
AMG 510 was dosed orally once daily at 100 mg/kg; anti-PD-1 29F.1A12 was administered once every 3 days for a total of 3 injections by IP

Canon, *et al.*, *Nature* **2019**, *575*, 217–223

**** p < 0.0001 comparisons of vehicle to treatment groups by Mantel-Cox. # p<0.005 combination vs AMG 510 or anti-PD-1

DISCOVERY OF THE FIRST CLINICAL KRAS^{G12C} INHIBITOR





In June 2018, Sotorasib (AMG 510) became the first KRAS^{G12C} inhibitor to enter human clinical testing. For more information, visit clinicaltrials.gov

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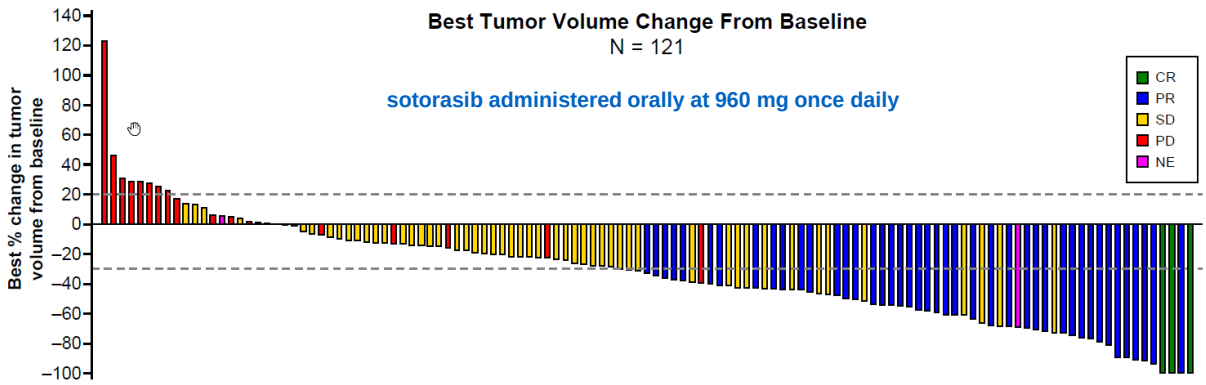
clinicaltrials.gov identifier: NCT03500883

Depth of Tumor Response

Tumor shrinkage of any magnitude was observed in 81% of patients (101/124)
Median percentage of best tumor shrinkage among all responders was 60%

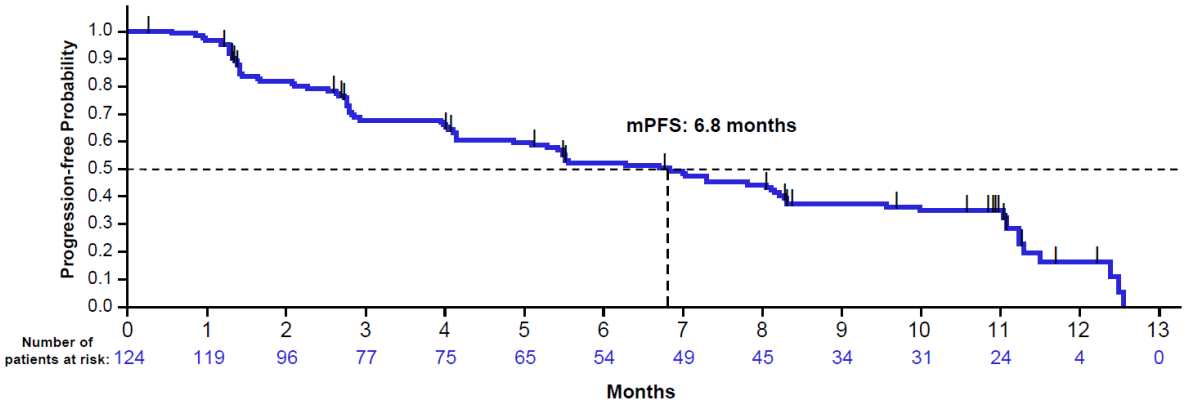


Graph excluded 3 patients without post-baseline measurement in target lesions.
CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable.

IASLC 2020 World Conference on Lung Cancer Singapore
JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

Progression-Free Survival

Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2)



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FOCUSED EFFORT ON A KEY ONCOGENE HAS YIELDED A NEW APPROACH

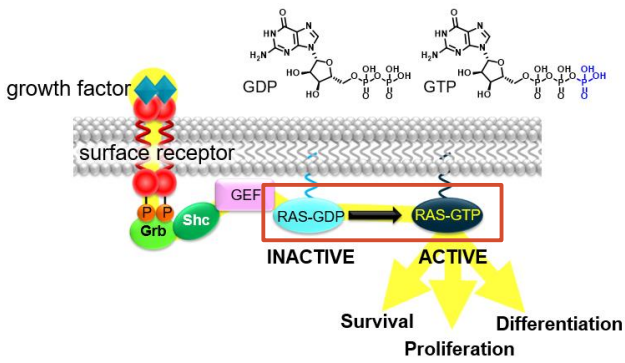


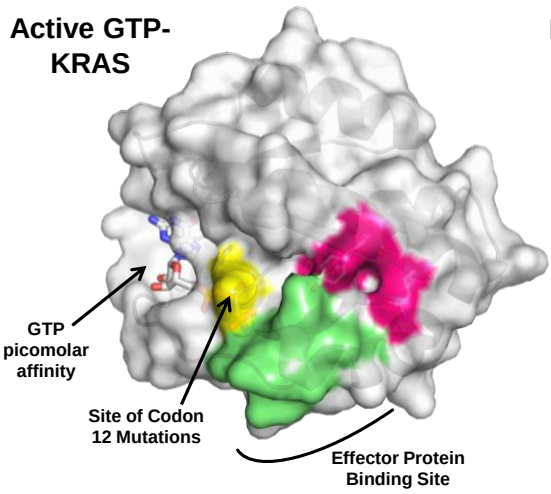
Table 1 | **Activation of RAS signalling pathways in different tumours**

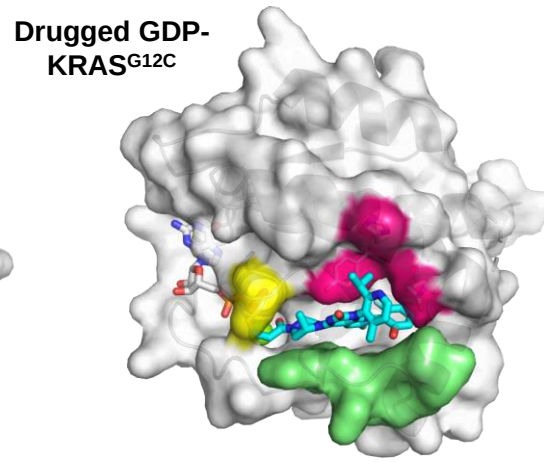
Defect or mutation	Tumour type	Frequency (%)
RAS mutation	Pancreas	90 (K)
	Lung adenocarcinoma (non-small-cell)	35 (K)
	Colorectal	45 (K)
	Thyroid (Follicular)	55 (H, K, N)
	Thyroid (Undifferentiated papillary)	60 (H, K, N)
	Seminoma	45 (K, N)
	Melanoma	15 (N)
	Bladder	10 (H)
	Liver	30 (N)
	Kidney	10 (H)
	Myelodysplastic syndrome	40 (N, K)
	Acute myelogenous leukaemia	30 (N)

Downward, J. *Nat. Rev. Cancer* **2003**, *3*, 11–22

Nearly 50% of all cancers demonstrate oncogenic mutations of the Ras signaling pathway

A STRUCTURAL VIEW OF "DRUGGING THE UNDRUGGABLE"





Sotorasib (AMG 510) is the first direct KRAS^{G12C} inhibitor to enter human clinical testing (NCT03600883)

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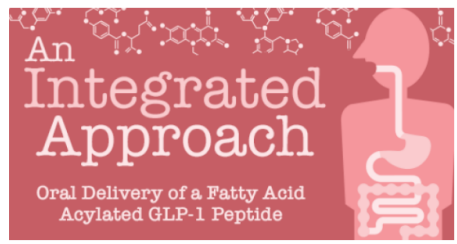

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The Discovery of Sotorasib (AMG 510): First-in-Class Investigational Covalent Inhibitor of KRAS G12C

Brian Lanman
Director Research,
Medicinal Chemistry, Amgen, Inc.

Ariamala Gopalsamy
Director, Interim Head of Boston Oncology
Chemistry, AstraZeneca

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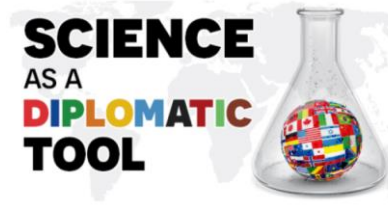

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Moderator: Christopher Gregson, Greenstalk Food Consulting LLC

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