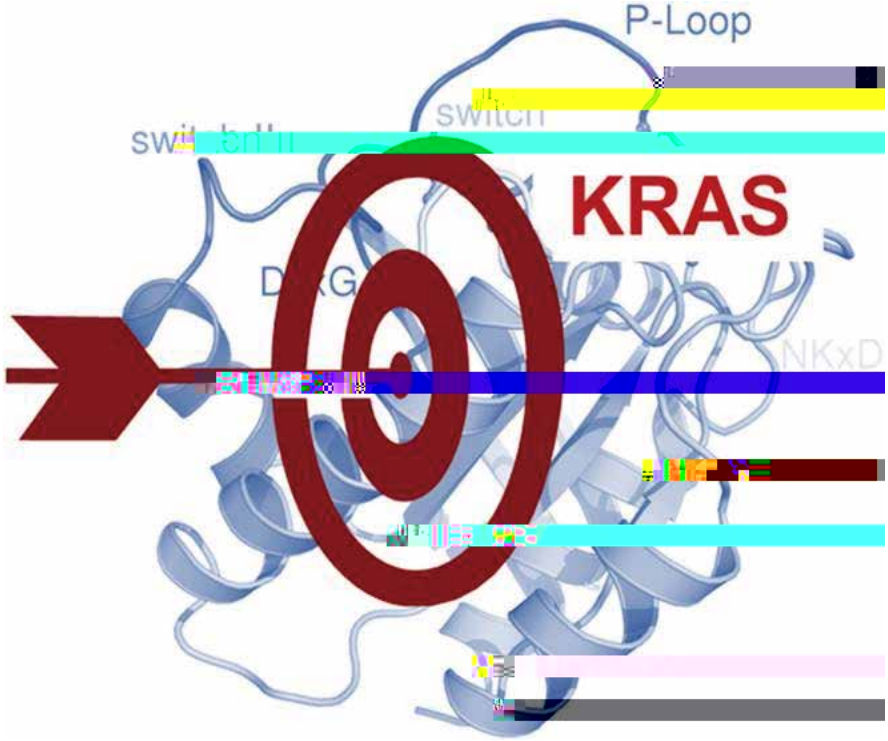
KRAS

RAS KRAS RAS 85% KRAS
RAS

KRAS

KRAS CMC (API+)

PK



KRAS[1]

KRAS

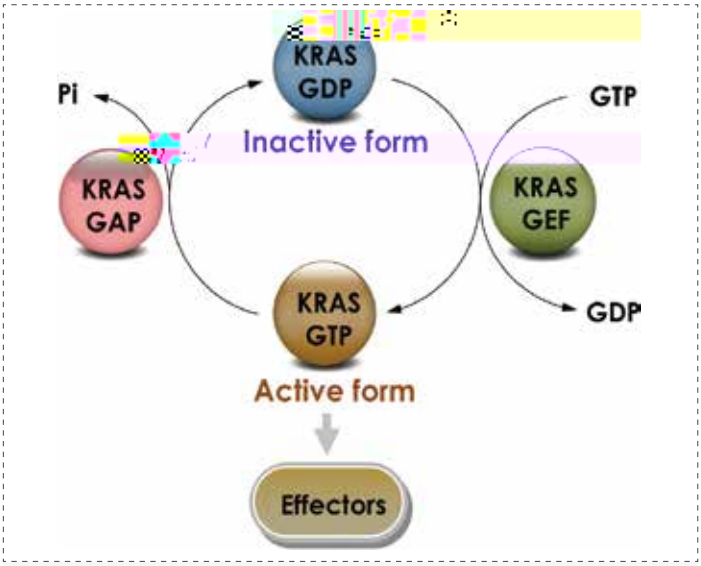
RAS GTPase
RAS HRAS KRAS NRAS RAS
KRAS NRAS HRAS KRAS

G12 G13 Q61 KRAS
KRAS4A KRAS4B KRAS4B

KRAS(Kirsten rat sarcoma 2 viral oncogene homolog Kirsten) GTP/GDP
GTPase RAS

KRAS GDP GTP
KRAS GTP
GDP

KRAS GTP
(GEFs)
GTP SOS(son of sevenless) Ras
GTP p120GAP (NF1)

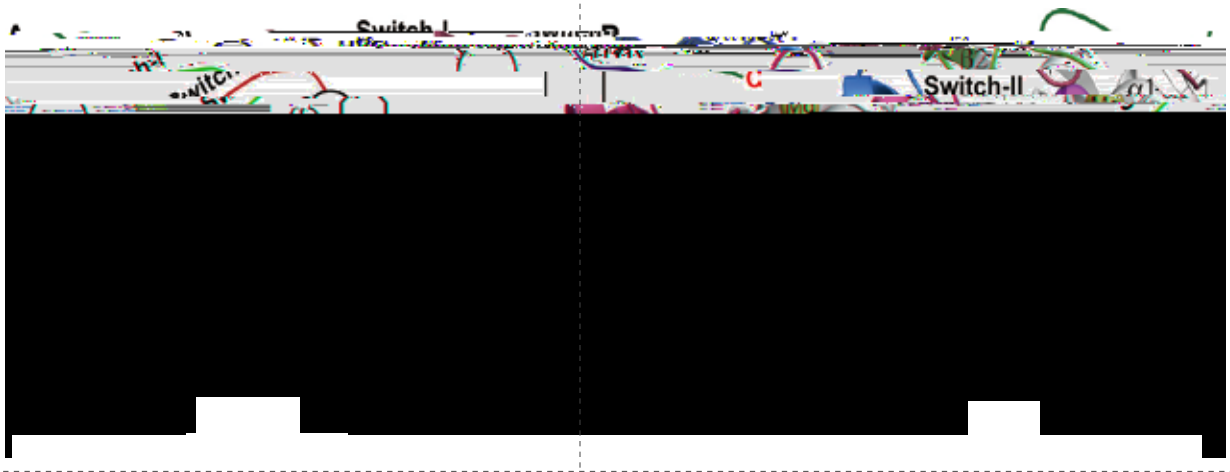


KRAS GTPase [1]

GTPase (GAPs)

KRAS

KRAS RAS N
KRAS G- KRAS 21 kDa 6 (
) 5 G C KRAS G 1-166 GTP
GTPase (GAPs) G
GDP-GTP switch I switch II C CAAX (C= A= X=)
RAS



KRAS [2]

KRAS [2]

KRAS

KRAS

GTP/GDP KRAS

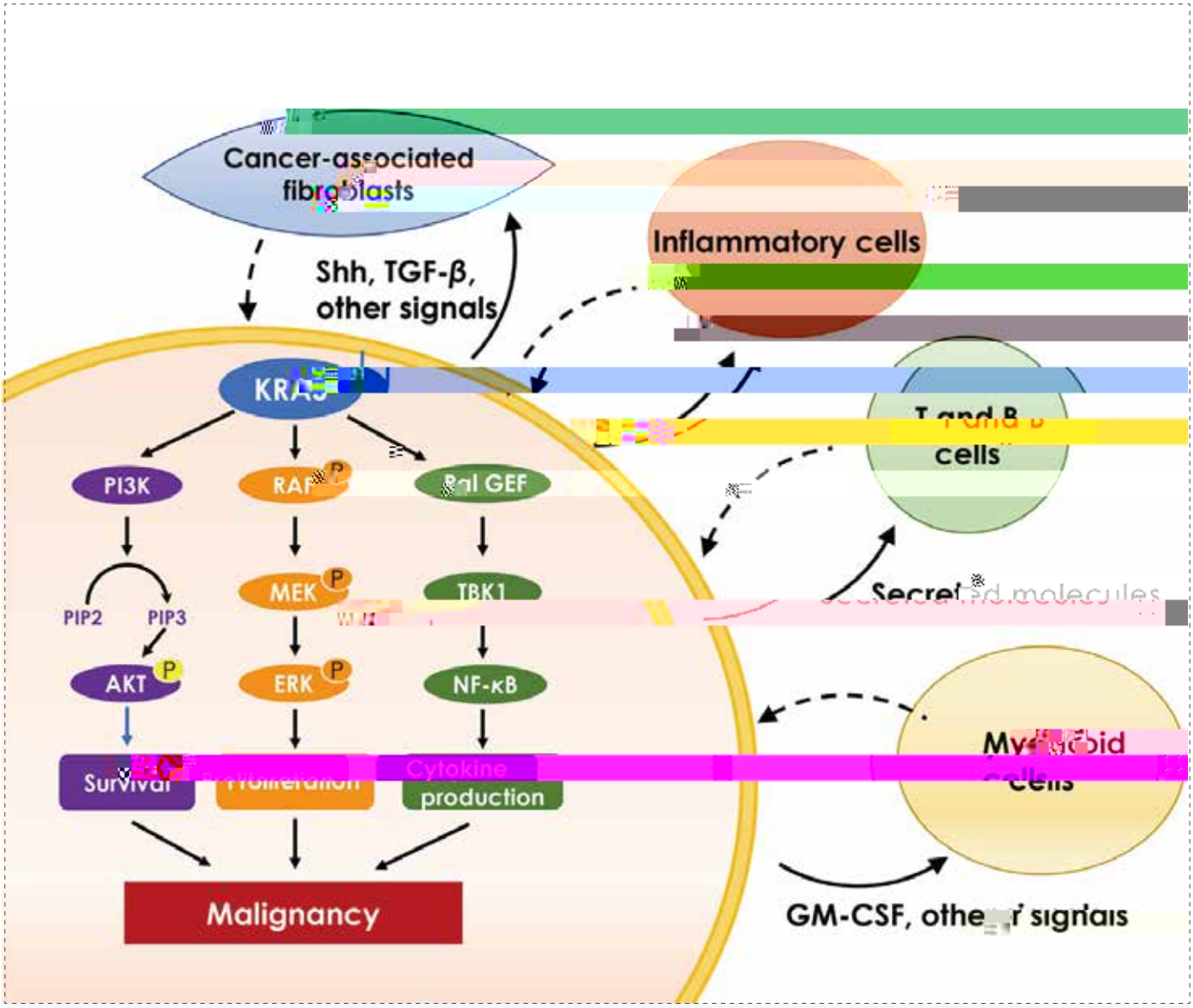
KRAS

KRAS KRAS ( )

RAS-GDP RAS-GTP MAPK

PI3K Ral-GEFs MAPK RAS-GTP RAF RAF

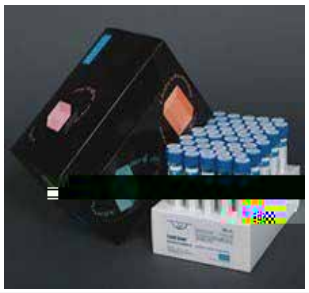
RAF MEK ERK



KRAS [1]

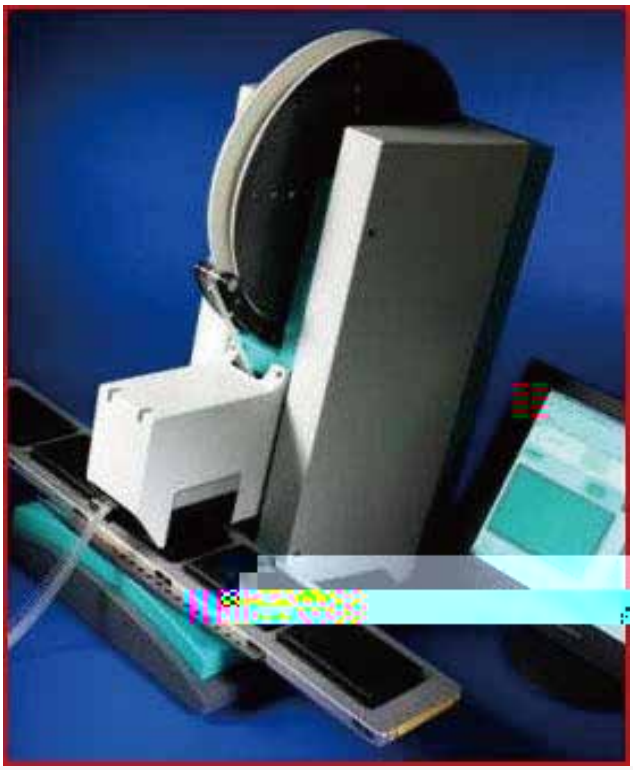
KRAS

1000+



Hampton research HT Kits

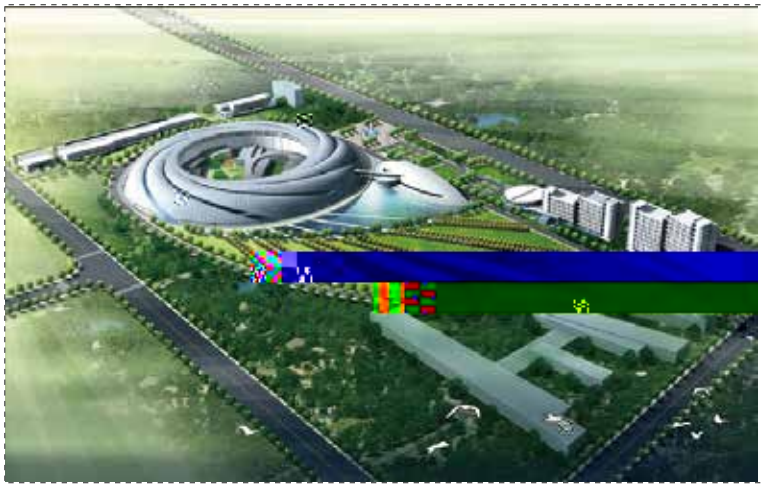
QIAGEN HT Classics Suite



Mosquito

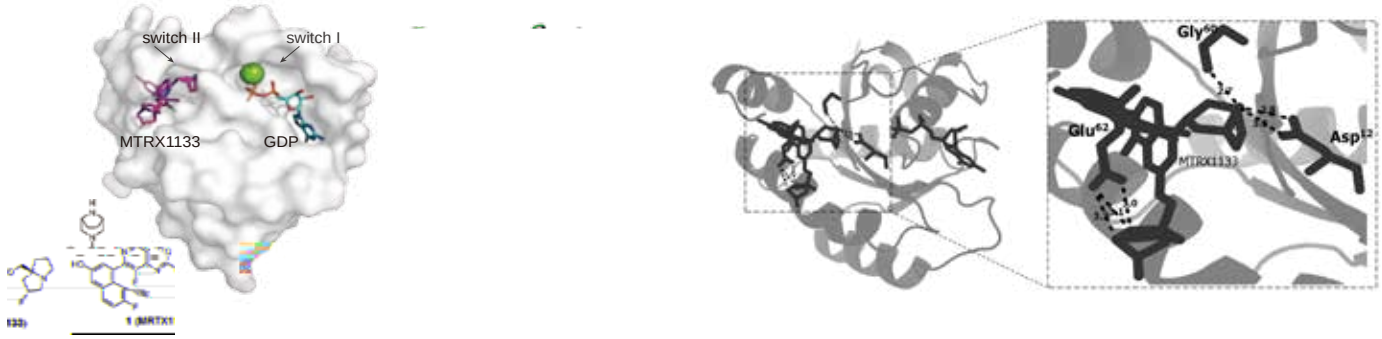
(Shanghai Synchrotron Radiation Facility; SSRF)

2009 7



-
-
- 3.5 GeV
-
-

KRAS-G12D with MRTX1133



GDP KRAS^{G12D} MRTX1133

KRAS

KRAS KRAS

KRAS

KRAS

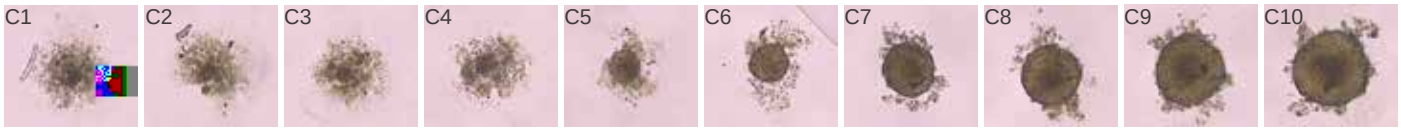
KRAS 2D 3D KRAS

(3D)

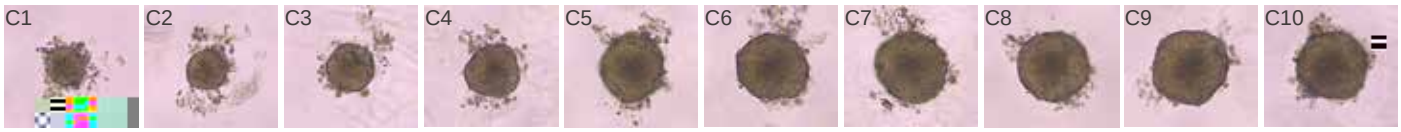
NCI-H358 (Lung, KRAS^{G12C}) Cell Cytotoxity Assay (3D)

Group	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Concentration (nM)	1000	333.3	111.1	37.04	12.35	4.115	1.372	0.457	0.152	0

Compound	Cell line	Incubation time (Day)	Start conc	Dilution fold
AMG510	NCI-H358	12		3-fold diluted



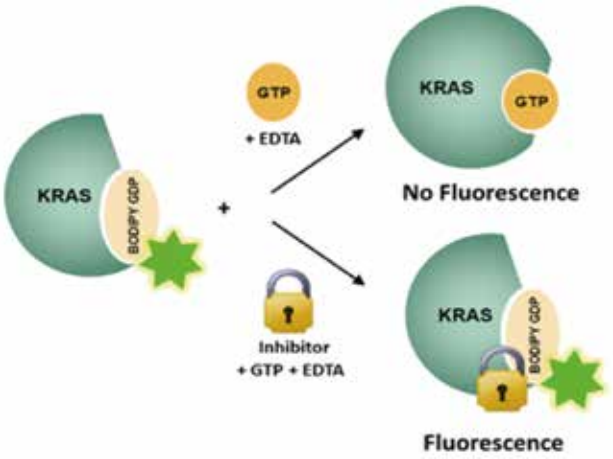
Compound	Cell line	Incubation time (Day)	Start conc	Dilution fold
BI3406	NCI-H358	12		3-fold diluted



NCI-H358 (Lung, KRAS^{G12C}) Cell Cytotoxity CTG Assay (3D;12 days)

Compound	CTG-IC_{50}s on NCI-H358 cells (nM)	Top Inhibition(%)	Start conc	Dilution fold
AMG510	1.386	99.52		3-fold diluted
BI3406	48.23	71.53		3-fold diluted

1:3 NCI-H358 288 h



EC_{50}	61.03

1 10 100 1000 10000

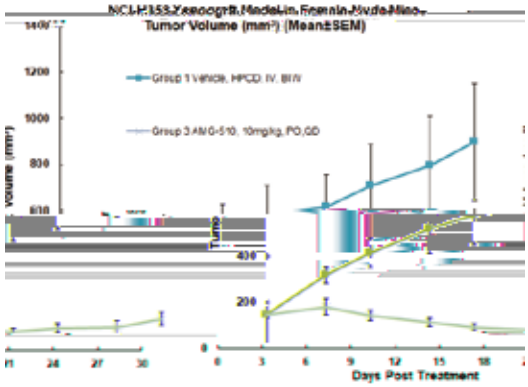
AMG510, Log[nM]

KRAS

KRAS -CDX

Cancer Type	Cell Lines	Cancer Type	Cell Lines
KRAS G12C	MIA PaCa-2, NCI-H358, UM-UC-3, Calu-1	KRAS G12V	SW480, CAPAN-1, NCI-H727
KRAS G12D	GP2D, SW1990, AsPC-1	KRAS G13D	LoVo, HCT-116, HT15

Medicilon Case: CDX - KRAS Mutation (G12C)



- **Animals:**
  Female BALB/c Nude mice
- **Cells:**
  NCI-H358
- **Model Establishment:**
  Right flank, SC

´ PDX / /

Medicilon Case: PDX -- KRAS Mutation (G12D)

- **Animals:**
  Female BALB/c Nude mice
- **Tissue:**
  PDX Colon Cancer
- **Model Establishment:**
  Right flank SC Trocar

KRAS

KRAS PK

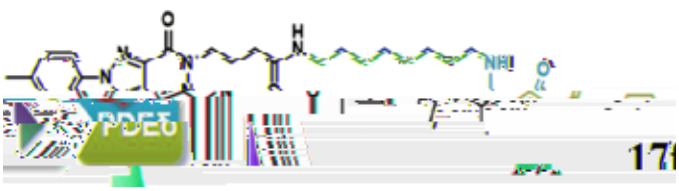
P

-

Compound 17f KRAS Compound 17f

Compound 17f SW480

KRAS



PROTAC Compound 17f[3]