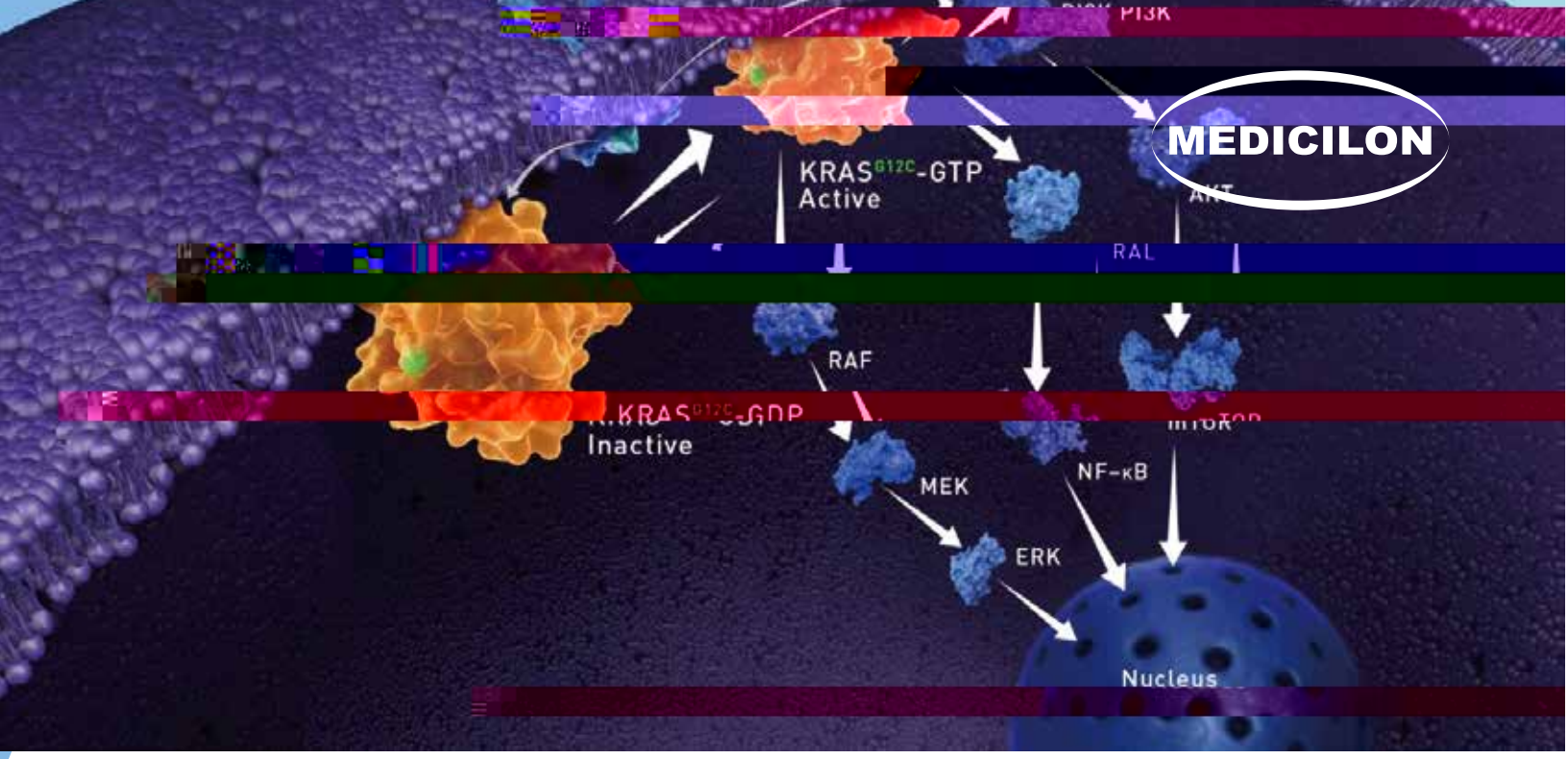
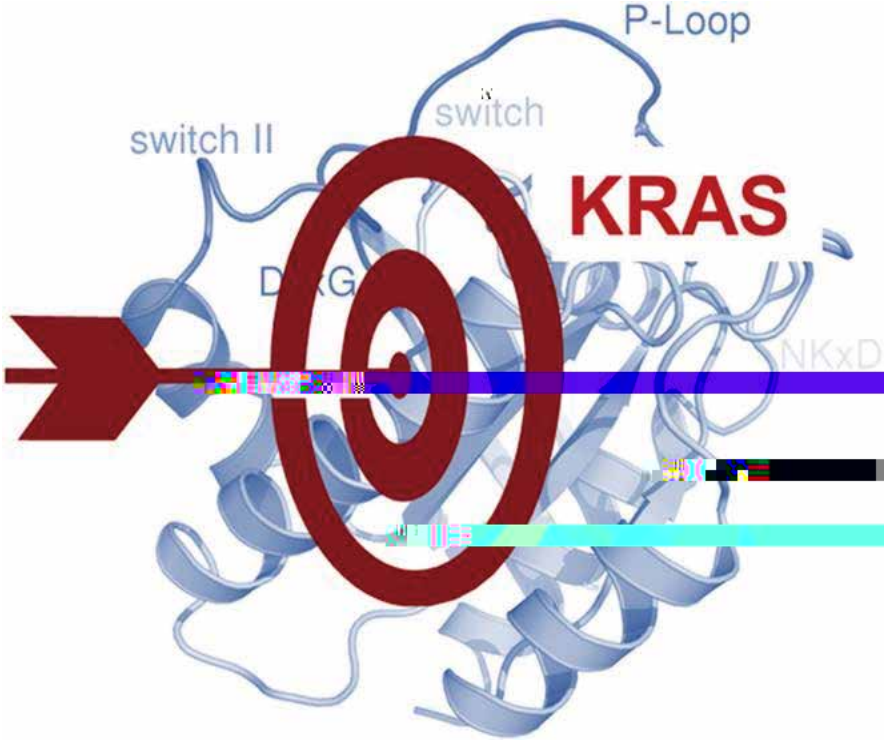



RAS KRAS RAS 85% KRAS
RAS

KRAS

KRAS CMC (API+ )

PK




KRAS[1]

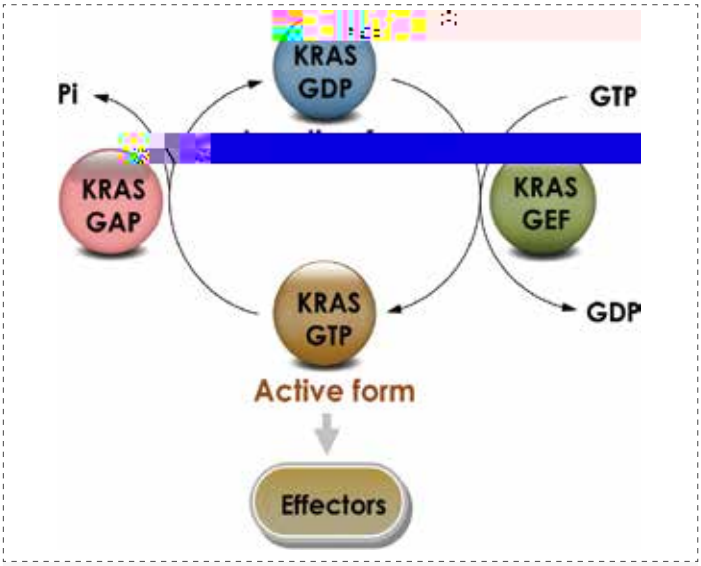
RAS GTPase
RAS HRAS KRAS NRAS RAS
KRAS NRAS HRAS KRAS

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

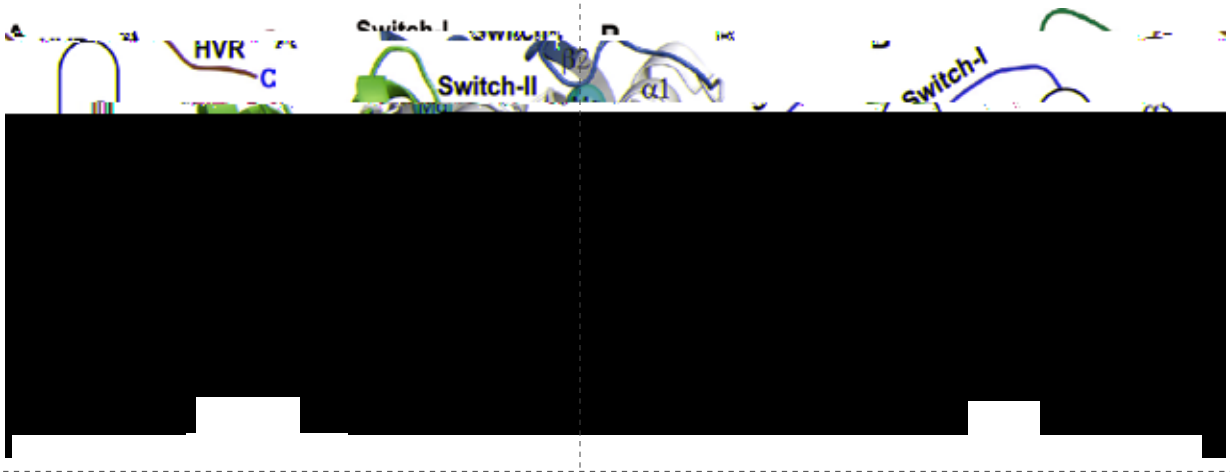
KRAS GTP
(GEFs)
GTP SOS(son of sevenless) Ras
GTP p120GAP (NF1)




KRAS GTPase [1]

GTPase (GAPs)

KRAS RAS N
KRAS G- KRAS 21 kDa 6 β- (
) 5 α 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

GTP/GDP KRAS

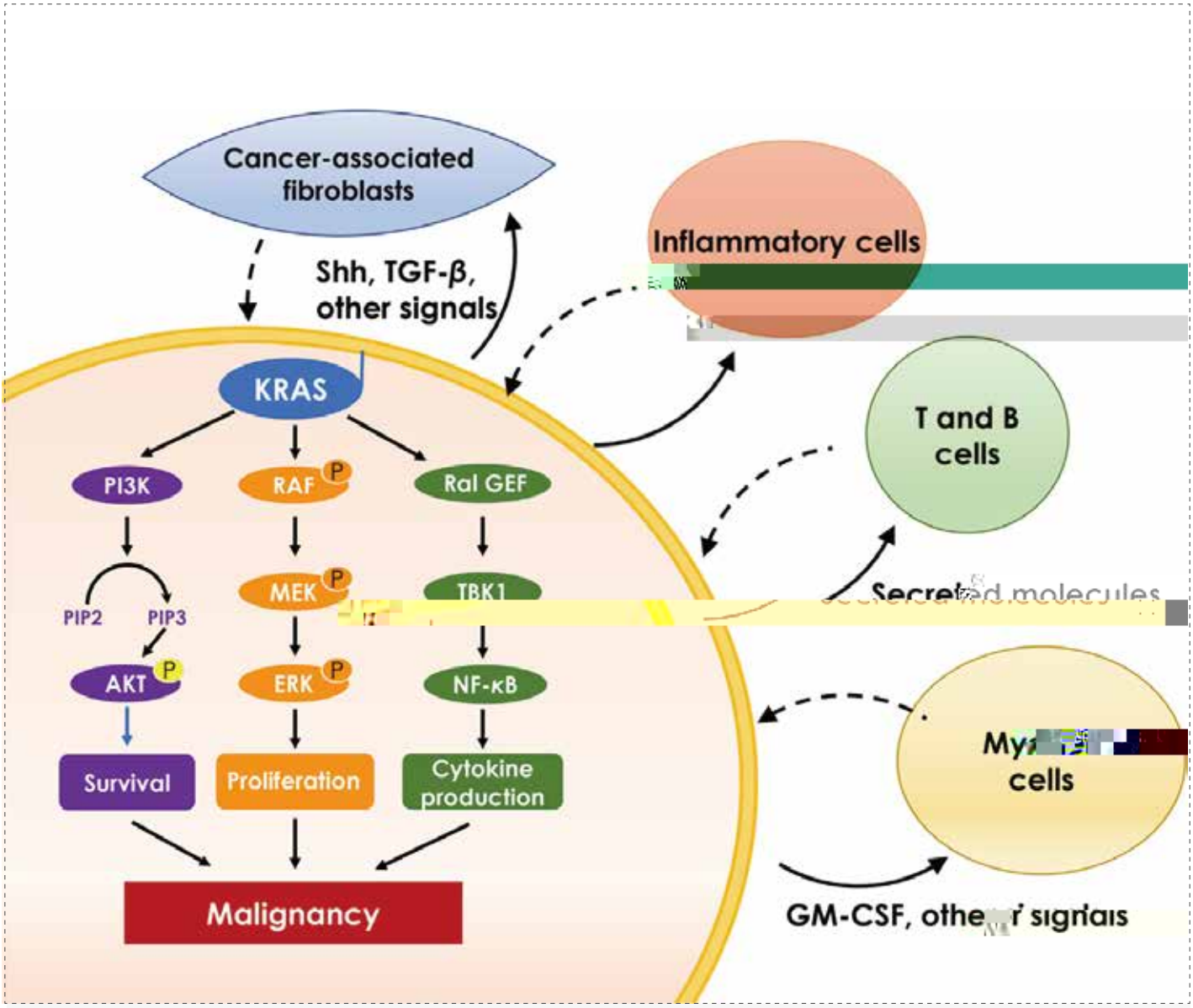
KRAS

KRAS KRAS ( )

RAS-GDP RAS-GTP MAPK

PI3K Ral-GEFs MAPK RAS-GTP RAF RAF

RAF MEK ERK

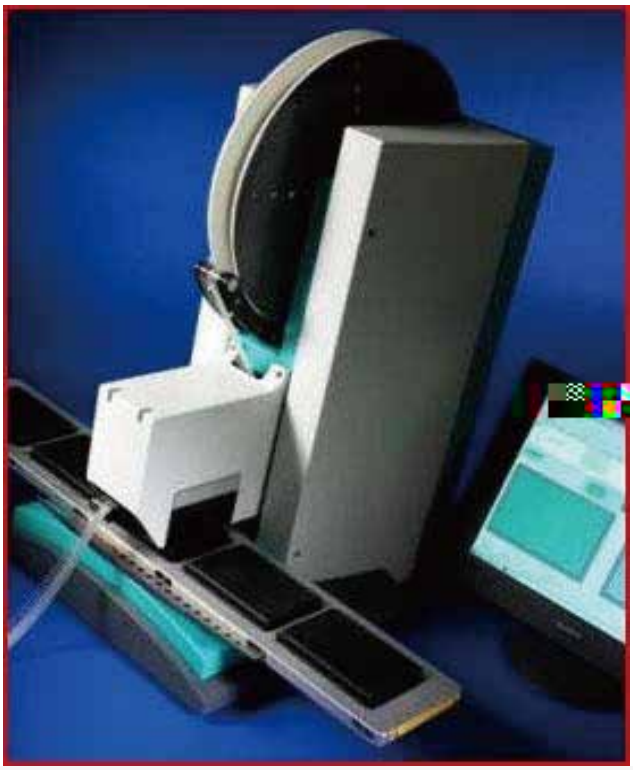



KRAS [1]

1000+

Hampton research HT Kits

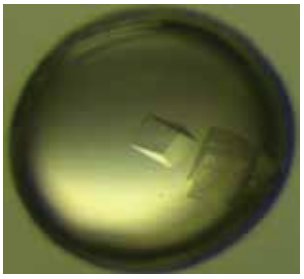
QIAGEN HT Classics Suite



Mosquito

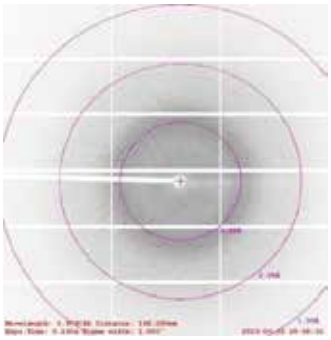
2009 7

- 
- 
- 3.5 GeV
- 
-



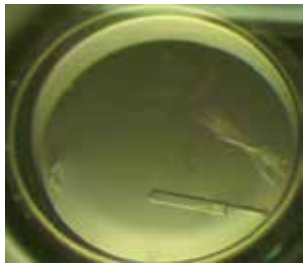
0.17 M
0.085 M pH 4.6
15% (v/v)
25.5% (w/v) PEG 4000

0.2 M
0.1 M Tris·HCl pH 8.5
30% (w/v) PEG 4000



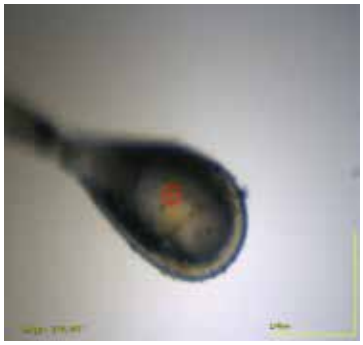
$KRAS^{G12D}$

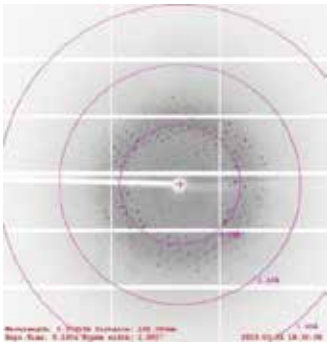
$KRAS^{G12D}$ X



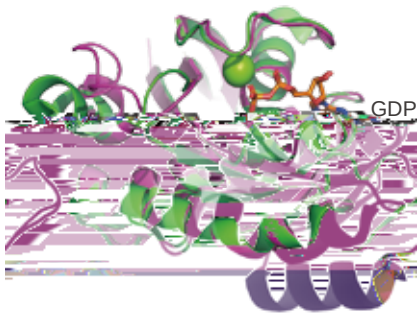
0.17 M
15% (v/v)
25.5% (w/v) PEG 4000

0.2 M
0.1 M pH 4.6
25 % (w/v) PEG 4000

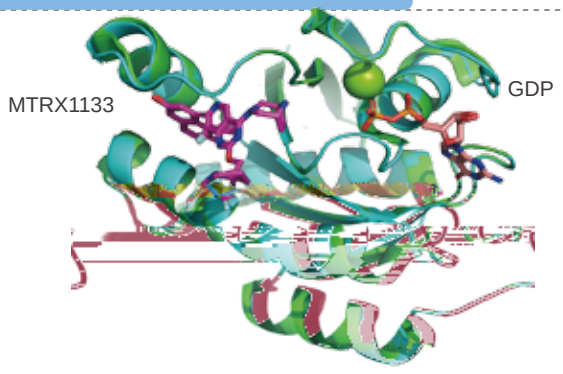




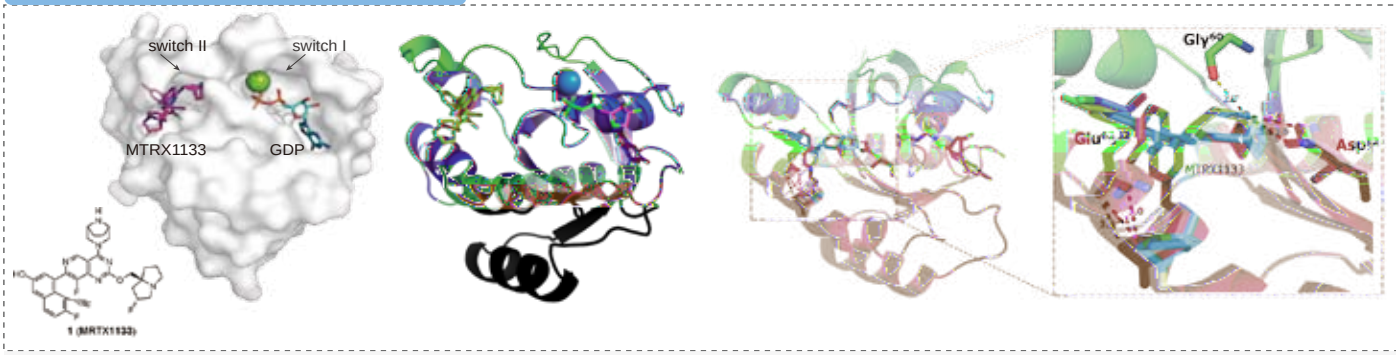
X




$KRAS^{G12D}$ 7RPZ PDB ID 7RPZ




$KRAS^{G12D}$ MRTX1133 (7RPZ, PDB)
PDB ID 7RPZ

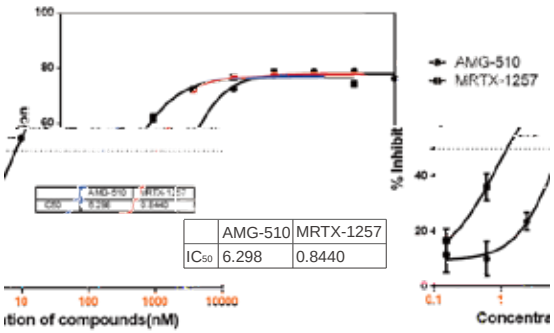



GDP KRAS$^{G12D}$ MRTX1133

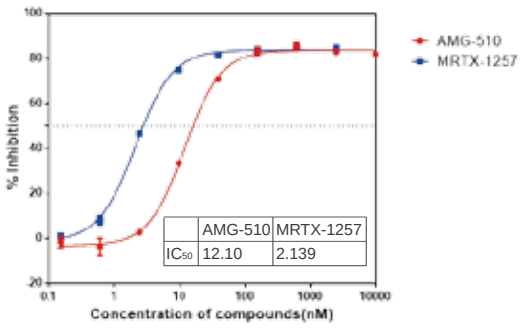
KRAS KRAS

KRAS

KRAS 2D 3D KRAS




| | AMG-510 | MRTX-1257 |
|---|---|---|
| $IC_{50}$ | 6.298 | 0.8440 |



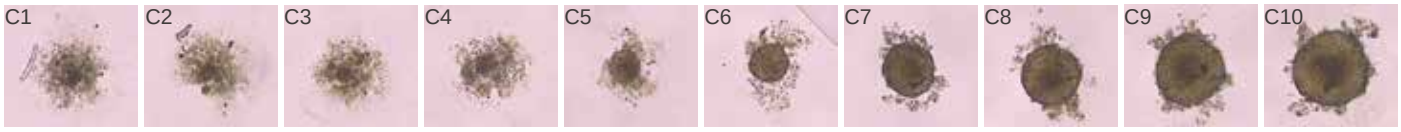

| | AMG-510 | MRTX-1257 |
|---|---|---|
| $IC_{50}$ | 12.10 | 2.139 |

| | | |
|---|---|---|
| AsPC-1 | pancreas | G12D |
| Capan-1 | pancreas | G12V |
| Capan-2 | pancreas | G12V |
| CFPAC-1 | pancreas | G12V |
| HPAF-II | pancreas | G12D |
| MIAPaCa-2 | pancreas | G12C |
| Panc 10.05 | pancreas | G12D |
| SU.86.86 | pancreas | G12D |
| HCT116 | large_intestine | G13D |
| HCT15 | large_intestine | G13D |
| LoVo | large_intestine | G13D |
| T84 | large_intestine | G13D |
| Calu-1 | lung | G12C |
| NCI-H2122 | lung | G12C |
| NCI-H23 | lung | G12C |
| NCI-H358 | lung | G12C |
| NCI-H441 | lung | G12V |
| SW1463 | large_intestine | G12C |
| SW480 | large_intestine | G12V |
| SW620 | large_intestine | G12V |
| SW837 | large_intestine | G12C |

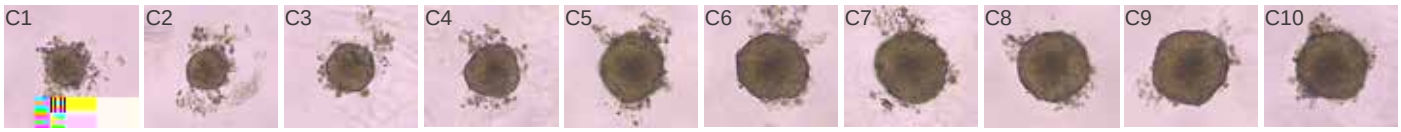
CellTiter-Glo 2D

| | C1 | C2 | C3 | C4 | C5 | C6 | C7 | C8 | C9 | C10 |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1000 | 333.3 | 111.1 | 37.04 | 12.35 | 4.115 | 1.372 | 0.457 | 0.152 | 0 |

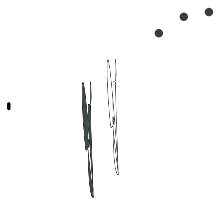
| Compound | Cell line | Incubation time (Day) | Start conc | Dilution fold |
|---|---|---|---|---|
| AMG510 | NCI-H358 | 12 | 1 μM | 3-fold diluted |




| Compound | Cell line | Incubation time (Day) | Start conc | Dilution fold |
|---|---|---|---|---|
| BI3406 | NCI-H358 | 12 | 1 μM | 3-fold diluted |

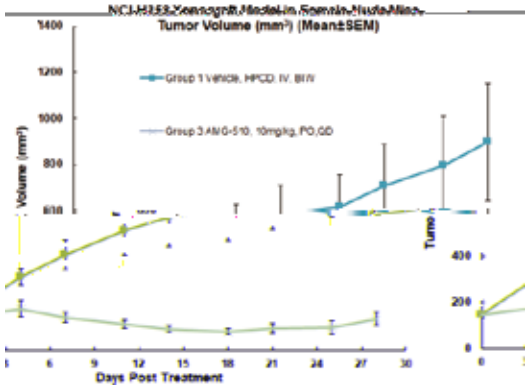



| Compound | CTG-$IC_{50}$s on NCI-H358 cells (nM) | Top Inhibition(%) | Start conc | Dilution fold |
|---|---|---|---|---|
| AMG510 | 1.386 | 99.52 | 1 μM | 3-fold diluted |
| BI3406 | 48.23 | 71.53 | 1 μM | 3-fold diluted |



1 μM 1:3 NCI-H358 288 h

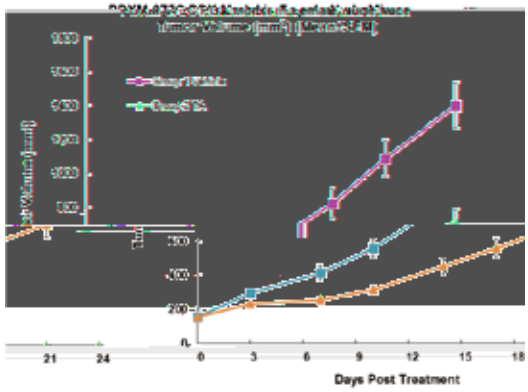
| | | | |
|---|---|---|---|
| KRAS G12C | MIA PaCa-2, NCI-H358, UM-UC-3, Calu-1 | KRAS G12V | SW480, CAPAN-1, NCI-H727 |
| KRAS G12D | GP2D, SW1990, AsPC-1 | KRAS G13D | LoVo, HCT-116, HT15 |




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

| | | | |
|---|---|---|---|
| KRAS Mutation | PDXM-060C (p.G12V), PDXM-069C (p.G12V), PDXM-075C (p.G12D), PDXM-076C (p.G13D), PDXM-212Li (p.G12D) | BCR-ABL Fusion | PDXM-242Le |
| | | ERBB2 Overexpression | PDXM-069C, PDXM-016C, PDXM-060C, PDXM-087C, PDXM-104C… |
| TP53 Mutation | PDXM-060C (p.R273H), PDXM-072C(p.Y234H) | … | … |
| PIK3CA Mutation | PDXM-075C (p.H1047L), PDXM-092Ga (p.E545G) | | |

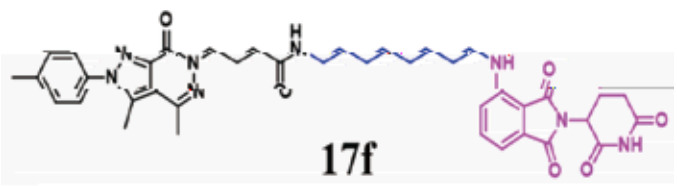
| | | | |
|---|---|---|---|
| Docetaxel + Cisplatin | PDXM-271O (Ovarian cancer) | Radiation | PDXM-311(H&N) |
| VDLP + MA + CVAD | PDXM-293Le (Leukemia) | … | … |




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

KRAS PK

KRAS-PDEδ - PROTAC PDEδ
Compound 17f KRAS PROTAC PDEδ Compound 17f KRAS-PDEδ
Compound 17f SW480
KRAS-PDEδ KRAS




PROTAC KRAS-PDEδ Compound 17f[3]