Collaboration for a Cure: DTRF
Duke Orthopaedic Surgery
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Compounds library screen data: 55 selected for rescreen

TOCRIS:
Lobeline hydrochloride
Nocodazole
Actinomycin D
D-64131
SB 225002

SCS
Methyl 2,5-dihydroxyclinnamate
Iressa
1-Acetyl-4-methylpiperazine hydrochloride
N-Acetyl-N-acetoxy-4-chlorobenzenesulfonamide
Procaterol hydrochloride
WAY 170523
KF 38789
D-64131
Cirazoline hydrochloride
N-ArachidonylGABA
Tacrine hydrochloride
Y 29794 oxalate

PF03084014-Notch inhibitor

Kl:

Staurosporine
GSK-1059615, GSK-615 Pl-103
Dasatanib
WYE-125132, WYE-132 FAK Inhibitor 14
TCS 2312 dihydrochloride
TAE-684
TCSJNK 5a
Ryuvidine (AV412, IKK16)

NIH:

CPDOOO469211 ALOSETRON HCl
CPDOOOO58555 LY 171883
CPD00058959 ITRACO NAZO LE
CPDO00469222 TELITH ROMYCIN
CPDOOOO59010 DOCETAXEL

PRESTWICK:

Paclitaxel
Evoxine
Digoxigenin
Papaverine hydrochloride
Skimmianine
Eserine sulfate, physostigmine sulfate
Lymecycline
Letrozole
Cycloheximide
Ciclopirox ethanolamine
Harmine hydrochloride
Lanatoside C

NIH:

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CPDO00469222 TELITH ROMYCIN
CPDOOOO59010 DOCETAXEL

TOOLKIT:

6-Anilinoquinoline-5,8-quinone, LY-83,583
KRIBB3
NIH, 311
SC-1, Pluripotin
Bortezomib, Velcade, MG-341, PS-341
Daunorubicin hydrochloride, Rubidomycin hydrochloride
1. Dasatinib- oral multi- BCR/Abll and Src family tyrosine kinase inhibitor. Used in patients with CML and ALL.

2. Letrozole- FDA approved for treatment of local or metastatic breast cancer that is hormone receptor positive.

3. FAK inhibitor 14- direct inhibitor of FAK1 auto phosphorylation; promotes cell detachment and inhibits cell adhesion.

4. PF-3084014- a selective gamma-secretase inhibitor. It binds to gamma secretase, blocking proteolytic activation of Notch receptors leading to apoptosis in cells that overexpress Notch.
5. PI-103- inhibits both rapamycin sensitive (mTORC1) and rapamycin- insensitive (mTORC2) complexes of protein kinase mTOR. Also inhibits constitutive and growth factor induced PI3K/Akt and mTORC1 activation.

6. Dexamethasone-used to treat many inflammatory and autoimmune conditions.

7. AV412- is a dual EGFR/ErbB2 kinase inhibitors. It shows antitumor effects against various tumor models expressing EGFR, ErbB2 or both receptors, such as breast cancer KPL-4, prostate cancer DU145 and lung cancer.

8. TCS-JNK 5α - Selective inhibitor of JNK2 and JNK3.
9. Y26763- K+ channel blocker (ATP sensitive)

10. KBR7943- Selective inhibitor of the reverse mode of Na+/Ca2+ exchanger

11. IKK16- Potent and selective inhibitor of IκB kinase (IKK)

12. Pazopanib- a multi-targeted receptor tyrosine kinase inhibitor that blocks tumour growth and inhibits angiogenesis. (VEGFR1, VEGFR2, VEGFR3, PDGFR, FGFR, c-Kit and c-Fms) Approved to use on advanced renal cell carcinoma and advanced soft tissue sarcomas
Dasatinib is a PI3K inhibitor and a FAK inhibitor.
Pathways involved in scar
µM DEX

Vehicle

Dexamethasone

Control

Treatment

BrdU Incorporation (Relative OD Value)

0.0 0.2 0.4 0.6 0.8 1.0 1.2

0 0.001 0.01 0.1 1.0 10.0 µM DEX

Vehicle  Dexamethasone
Data by Interaction Potency Model

AV412 + PF-3084014– showed synergistic effect
Data by Interaction Potency Model

AV412 + IKK16 – showed no synergistic effect
Tumor volume mm$^3$

- Control: 100
- Dex: 60
- Fak-I: 40
- Dex & Fak-I: 20
Investigating tumor-stroma interactions in desmoid tumors
Clonal expansion of desmoid tumor cells identify mutant and non-mutant populations from the same sample.
Surface marker screen based on single cell-derived clones identifies CD142, CD252, and Podoplanin as potential markers.
Cell sorting based on identified surface markers can distinguish mutant and non-mutant populations.
Antibody array analysis of conditioned media of mutant and non-mutant populations identifies differentially secreted cytokines (e.g. Thrombospondin-1).
Beta-catenin may regulate the expression of some secreted factors (e.g. Thrombospondin-1 and IGFBP3).

A

**Mutant vs Non-Mutant**

B

**Wnt3a vs Control**

Log$_2$ Relative Expression

**Mut v Non-Mut**

- DKK1
- THBS1
- ANGPT1
- IGFBP3
- PTX3
- CXCL12
- CCL2
- CHI3L1

* P < 0.05. n=4

* P < 0.05. n=3
Inhibition of Thrombospondin-TGFβ interaction by LSKL peptide can reduce desmoid tumor cell proliferation.