ALK/Ack1 Dual Inhibitors for Cancer Treatment

Technology Overview

- Preclinical candidates for anti-cancer drug development
- Excellent activities for a well-known drug target, ALK
- Excellent activities for a 1st in class drug target, Ack1
- No serious off-target binding & little possibility of harmful side effects

Core Technologies

- KRCA-0008, KRICT leading compounds, show;
- More potent *in vitro* activities toward ALK cell lines than commercial ALK inhibitors, even toward Crizotinib-resistant cell lines;
- Better *in vivo* activities than Crizotinib in mouse xenograft model

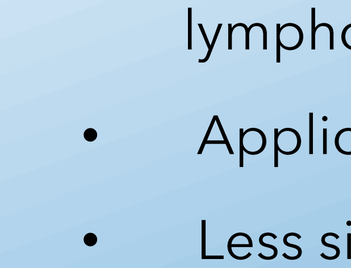
Application Area and Advantages

- Anti-cancer drug for non-small cell lung cancer(NSCLC) or anaplastic large cell lymphoma
- Applicable for NSCLC patients with Crizotinib resistant ALK mutants
- Less side-effects from off-target binding is expected

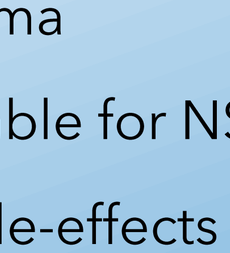
Accomplishments

- Strong IP Portfolios
- Looking for licensing & collaborative research opportunities

KRCA-0008 Cell Phosphorylation Assay (Immunoblot)



Cells are incubated with 200 nM concentration of each chemical for 6 hours, and cell lysates are prepared for western blot analysis with indicated antibodies to see the level of the phosphorylated ALK, Akt, and Erk.



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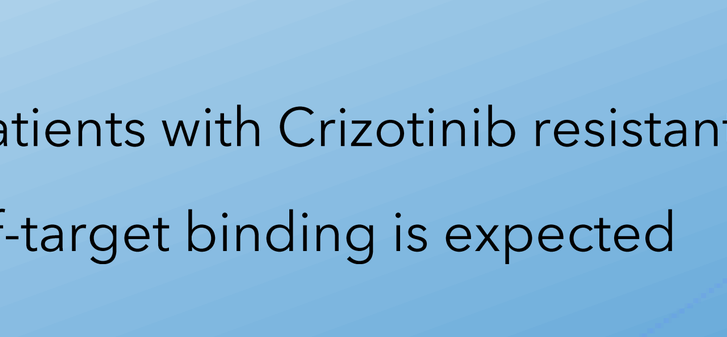
Potent & specific to ALK.

KRCA-0008 Tumor Growth Inhibition



- ✓ Effects of compounds on growth of H3122 human lung cancer in nude mice. H3122 cells were implanted S.C. into the right flanks of female nude mice. Drug treatment was initiated after tumor volumes reached about 200 mm^3. KRCA-0008 and Crizotinib were administered by p.o.. The data are expressed as the mean tumor size ± S.E.
- ✓ 8 mice/group, Formulation : 20% PEG400, 3% Tween80 in DDW, Route: PO, Schedule: BID x 14 (5 days on, 2 days off) [Crizotinib: p.o. 25 mpk, QD]
- ✓ No significant body weight change observed.

Kinase Activity Profile of KRCA-0002

>60% kinase activity @ 1uM

Abl(h), ALK4(h), ARK5(h), ASK1(h), Aurora-B(h), Axl(h), Blk(h), BrSK1(h), BTK(h), CaMKI(h), CDK1/cyclinB(h), CDK2/cyclinA(h), CDK2/cyclinE(h), CHK1(h), CHK2(h), CK2(h), cKit(h), CSK(h), c-RAF(h), cSRC(h), DDR2(h), EGFR(h), EphA1(h), EphA2(h), EphB1(h), FGFR1(h), Flt3(h), Fyn(h), GSK3β(h), Hck(h), IGF-1R(h), IKKα(h), IKKβ(h), IR(h, IC_{50} = >10000 nM), JAK2(h), JAK3(h), KDR(h), Lck(h), LOK(h), Lyn(h), MAPK1(h), MAPK2(h), MAPKAP-K2(h), MEK1(h), Mer(h), Met(h), MSK1(h), MST1(h), mTOR(h), MuSK(h), NLK(h), PAK2(h), PDGFRα(h), PDGFRβ(h), PDK1(h), PHKγ2(h), PI3 Kinase (p110b/p85a)(h), PI3 Kinase (p110D/p85a)(h), PI3 Kinase (p110a(E542K)/p85a)(h), PI3 Kinase (p110a/p65a)(h), Pim-1(h), Pim-2(h), PKA(h), PKBα(h), PKBβ(h), PKCα(h), Plk1(h), Plk3(h), PRAK(h), PRK2(h), Ret(h), ROCK-Ⅰ(h), ROCK-Ⅱ(h), Ron(h), Rse(h), Rsk1(h), SAPK2a(h), Syk(h), TAK1(h), TAO1(h), TBK1(h), Tie2(h), TLK2(h), TrkA(h), TrkB(h), WNK2(h), Yes(h), ZAP-70(h)

≤60% kinase activity @ 1uM

ACK1(h, IC_{50} =18 nM), ALK(h, IC_{50} = 20 nM), Aurora-A(h), EGFR(T790M, L858R)(h), FAK(h), Fms(h, IC_{50} =103 nM), JNK1α1(h, IC_{50} =1920 nM), JNK3(h, IC_{50} =55 nM), Pyk2(h), Ros(h), TSSK1(h, IC_{50} =1630 nM)

KRCA-0002 is a structurally close analog to KRCA-0008 and selective to ALK & ACK1.