

# G-749, a novel selective inhibitor of FLT3 kinase as a therapeutics for AML

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## Abstract

Acute myeloid leukemia (AML) is an aggressive cancer, representing 90% of all adult acute leukemias, with an estimated incidence of 200,000 cases each year worldwide. Noticeably, malignant cells in the majority of AML patients possess aberrantly expressed FLT3. The corresponding tumor-cell genotyping indicates that 25 - 30% of the AML blasts carry FLT3 mutations. In recent years, there has been an enormous development of potential inhibitors such as AC-220, CEP-701, MLN-518, PKC-412, Sunitinib, and Sorafenib, against FLT3 mutations.

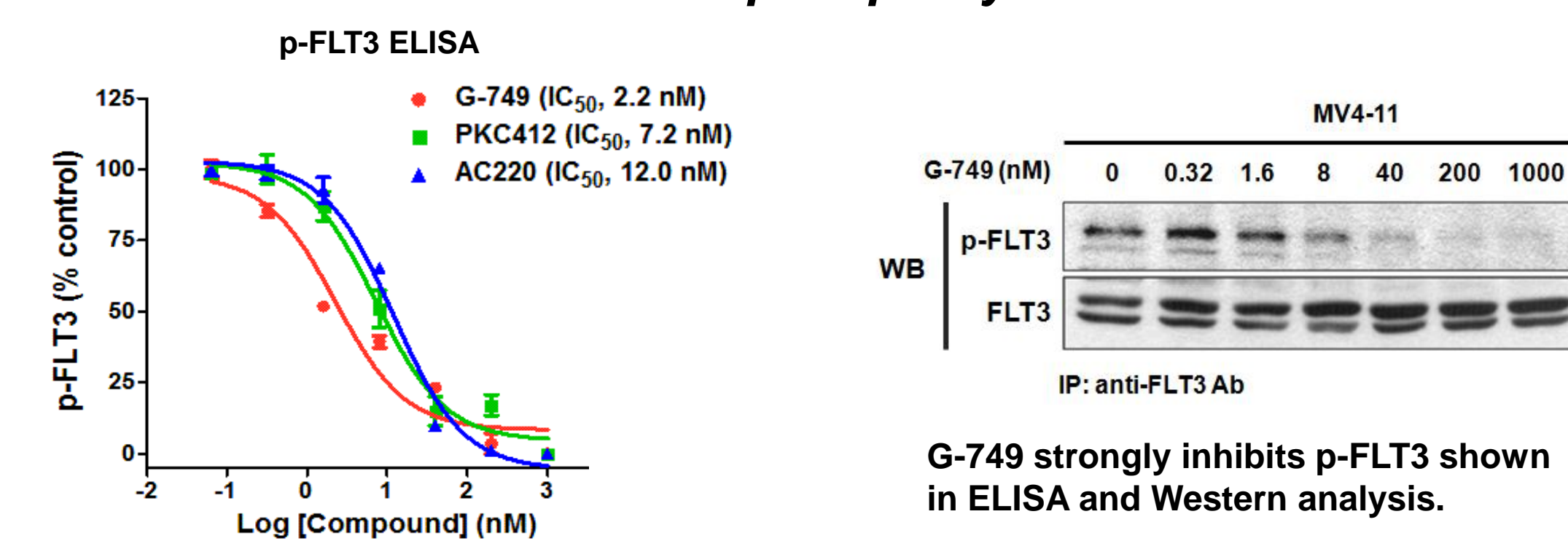
However, their clinical responses have been below expectation likely due to the influence of plasma inhibitory activity, the lack of strong inhibition of downstream effectors involved in aberrant activation of growth pathway, and/or the lack of substantially sustained inhibition of FLT3 activity, consequently resulting in drug resistance.

To overcome the major challenges toward new drugs, we have developed a series of highly selective FLT3 inhibitors possessing extreme potency against clinically known FLT3-mutants. Moreover, one of our lead candidates, G-749, showed strong synergistic effect combined with AraC, which was greater compared to that of the known FLT3 inhibitors. It also showed strong induction of apoptosis. The tight binding property and high potency of G-749 led to a sustained strong inhibitory activity in the presence of human plasma and high FLT3L milieu. As predicted, oral administration resulted in complete tumor regression without any relapse in a mouse xenograft model after dosing stopped. These results were confirmed with strong cell death of primary patient cells of AML.

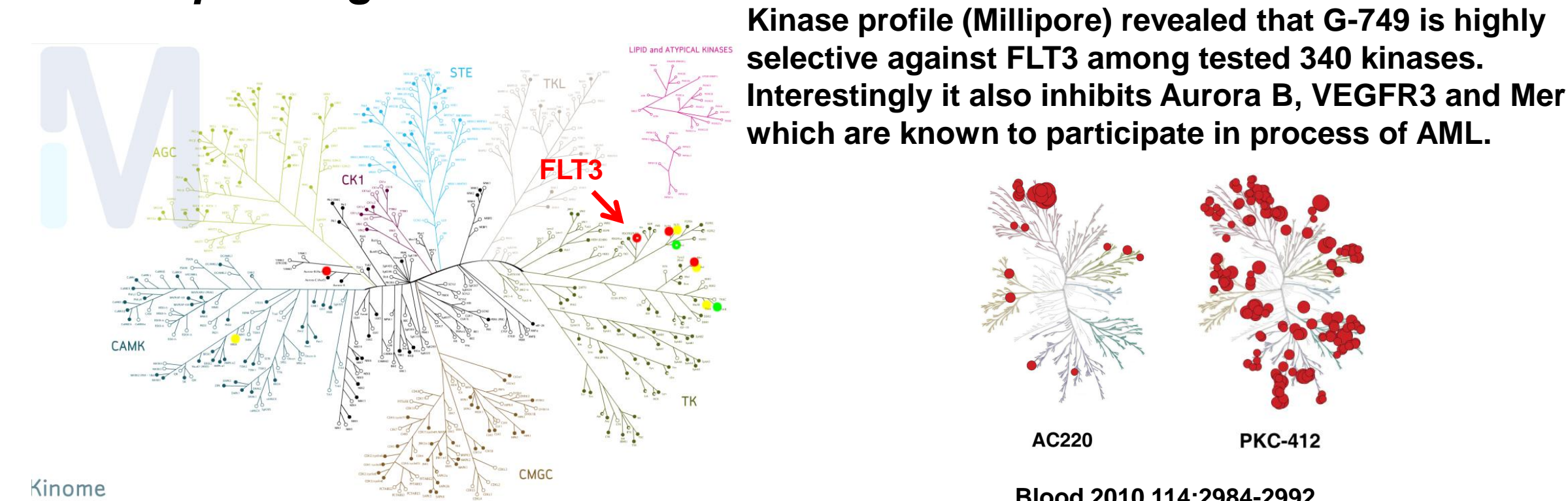
These desirable characteristics of G-749 would ostensibly overcome the documented drug-resistance confronted by previous FLT3 targeted inhibitors such as AC220, PKC-412, and CEP701. Therefore, we are confident that our lead candidate will be a promising acute myeloid leukemia drug.

One of lead candidates will be planed to enter to preclinical study in Q1, 2012.

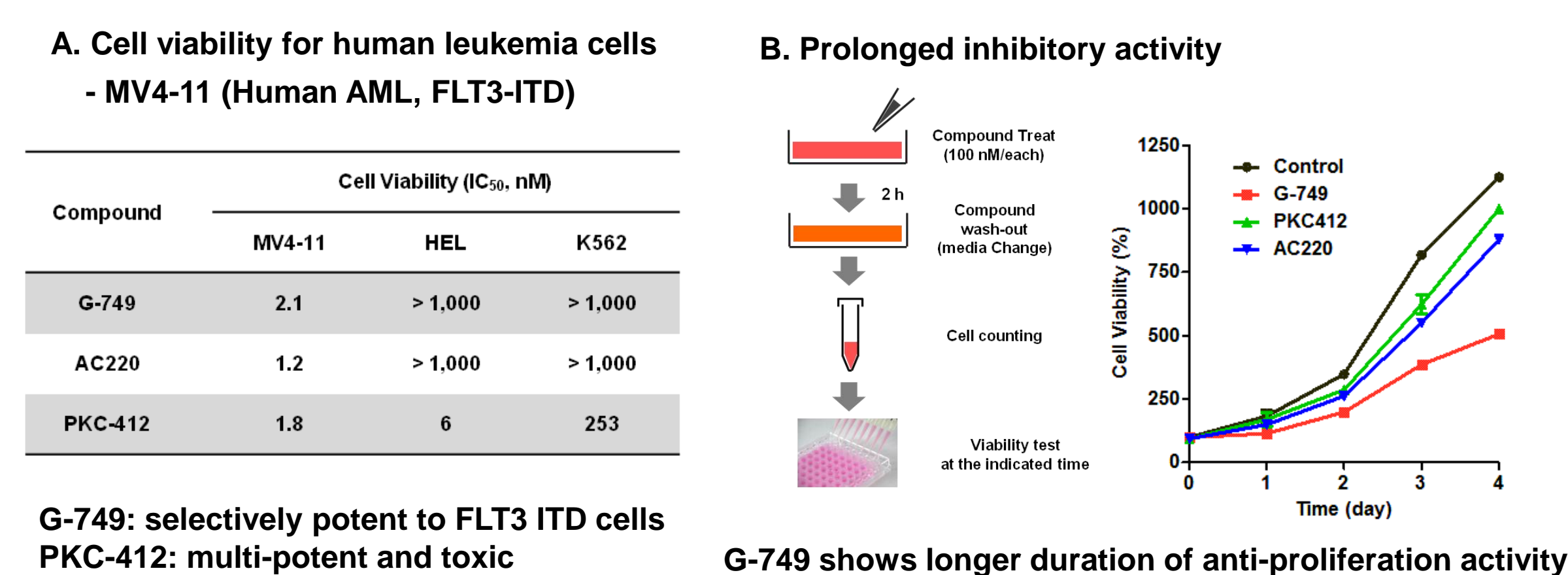
## Potent inhibition of FLT3 autophosphorylation



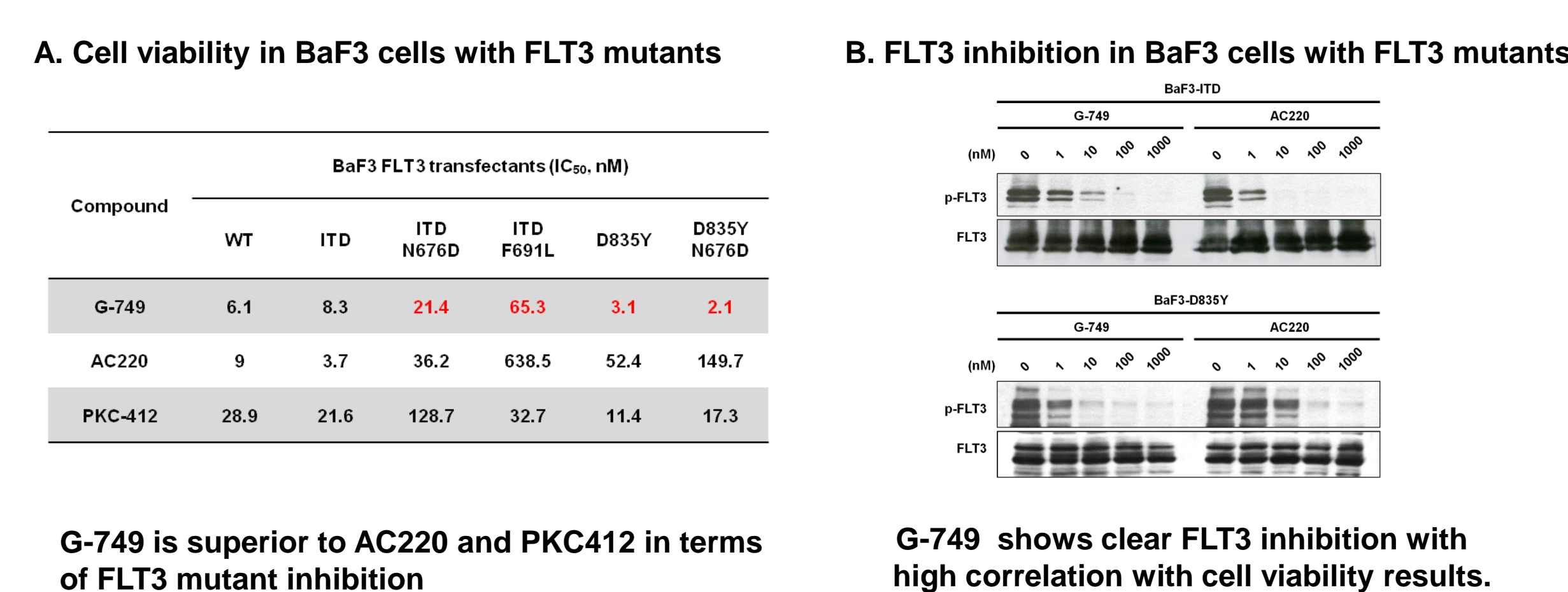
## Kinase profiling of G-749



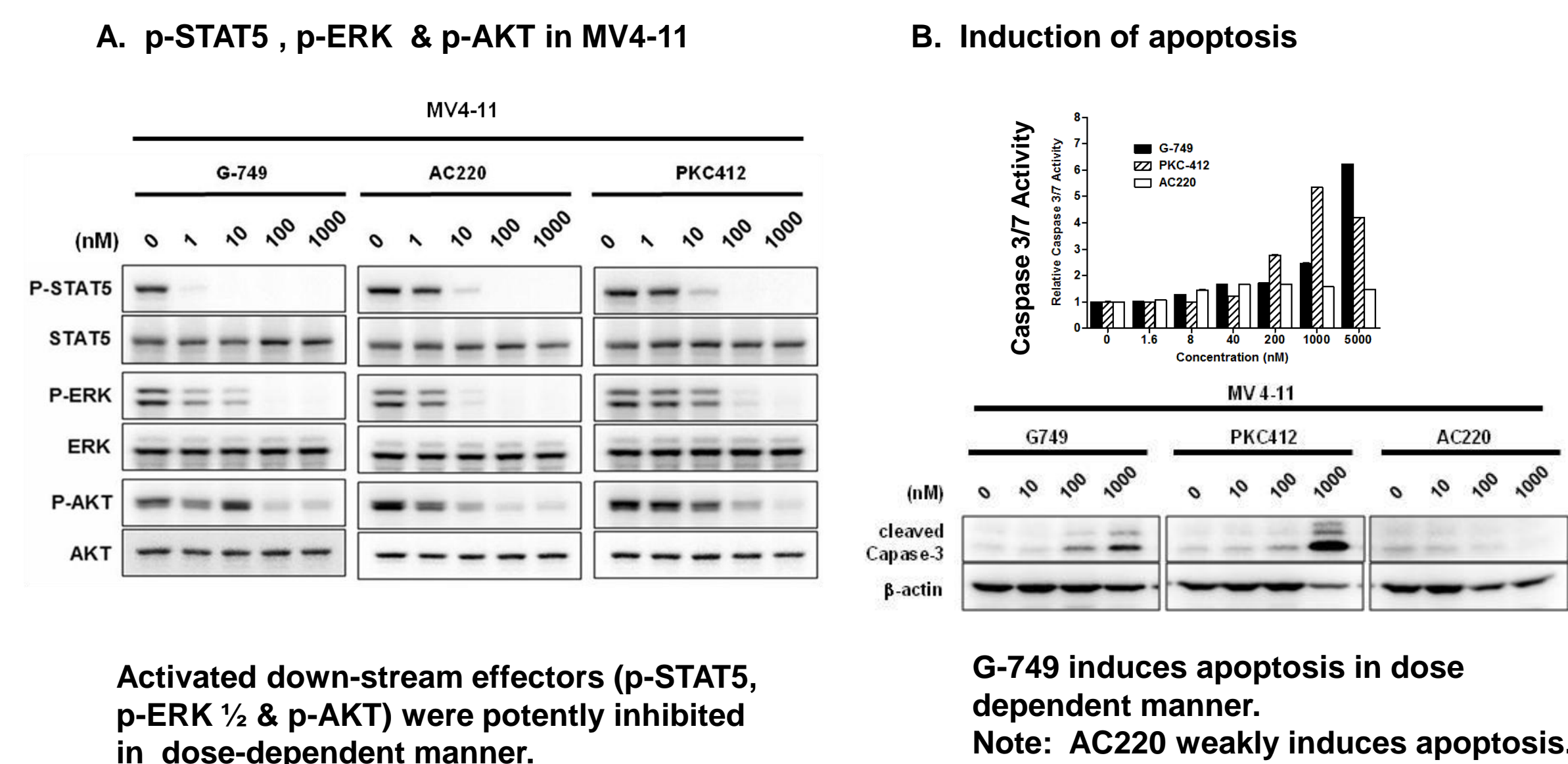
## Highly potent and selective to AML leukemia cell



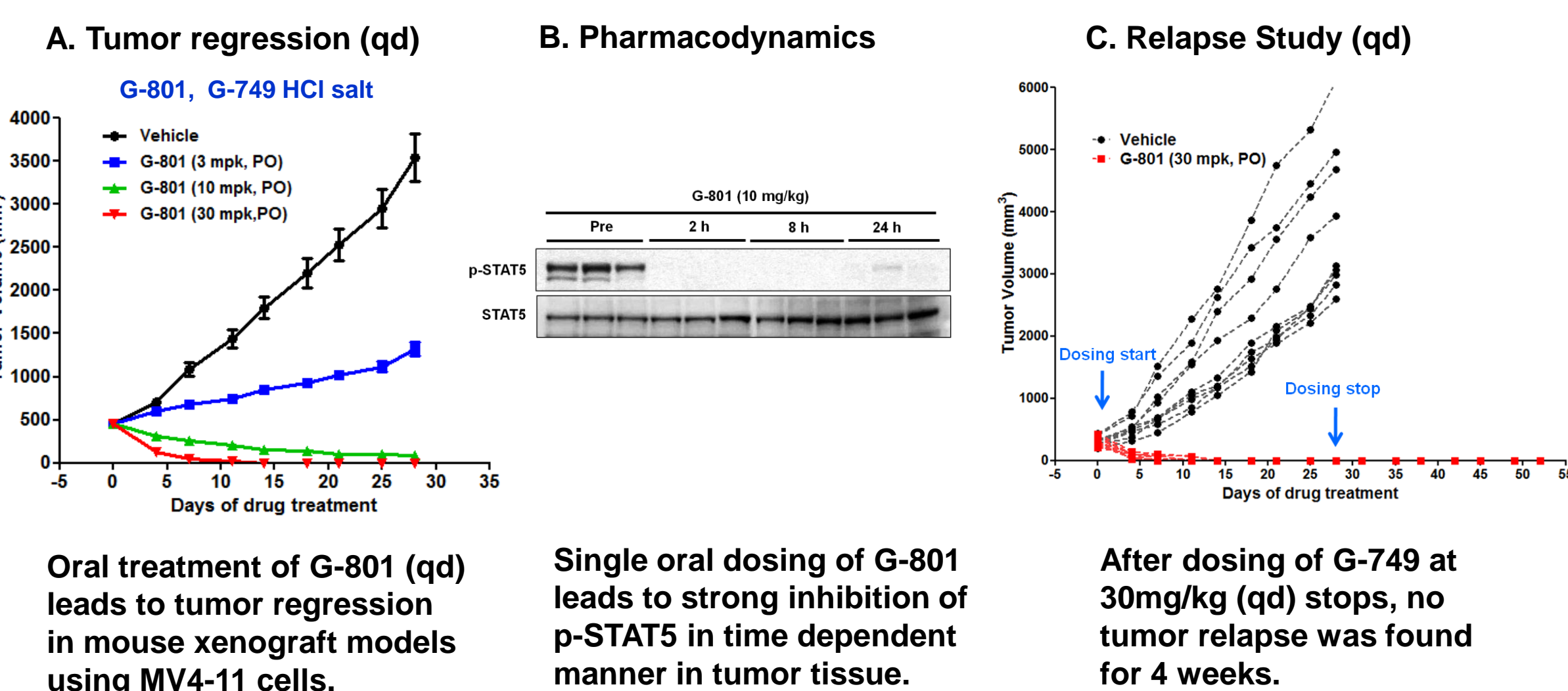
## Highly potent to clinically known FLT3 mutants



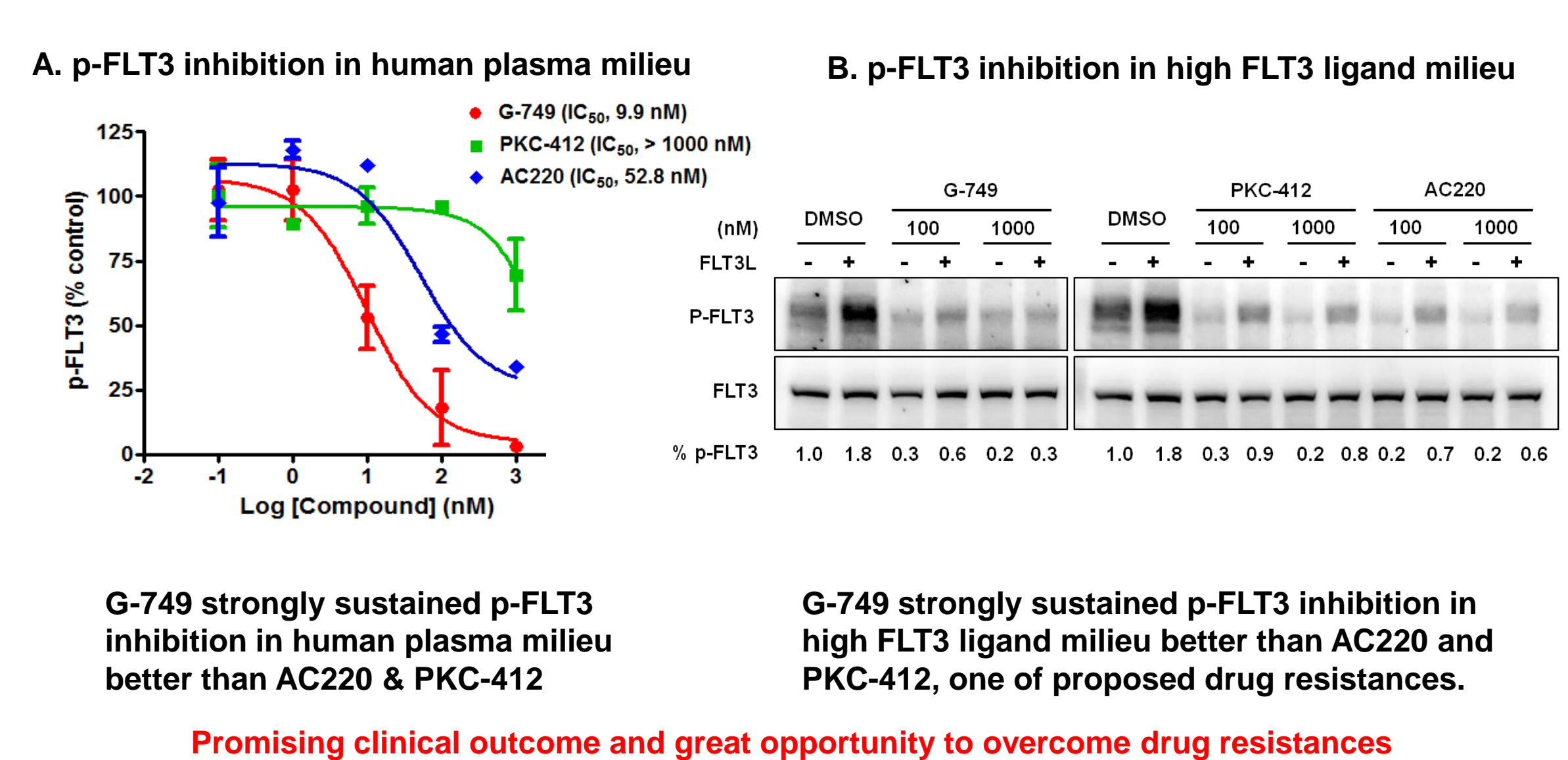
## Potent inhibition of down-stream effectors



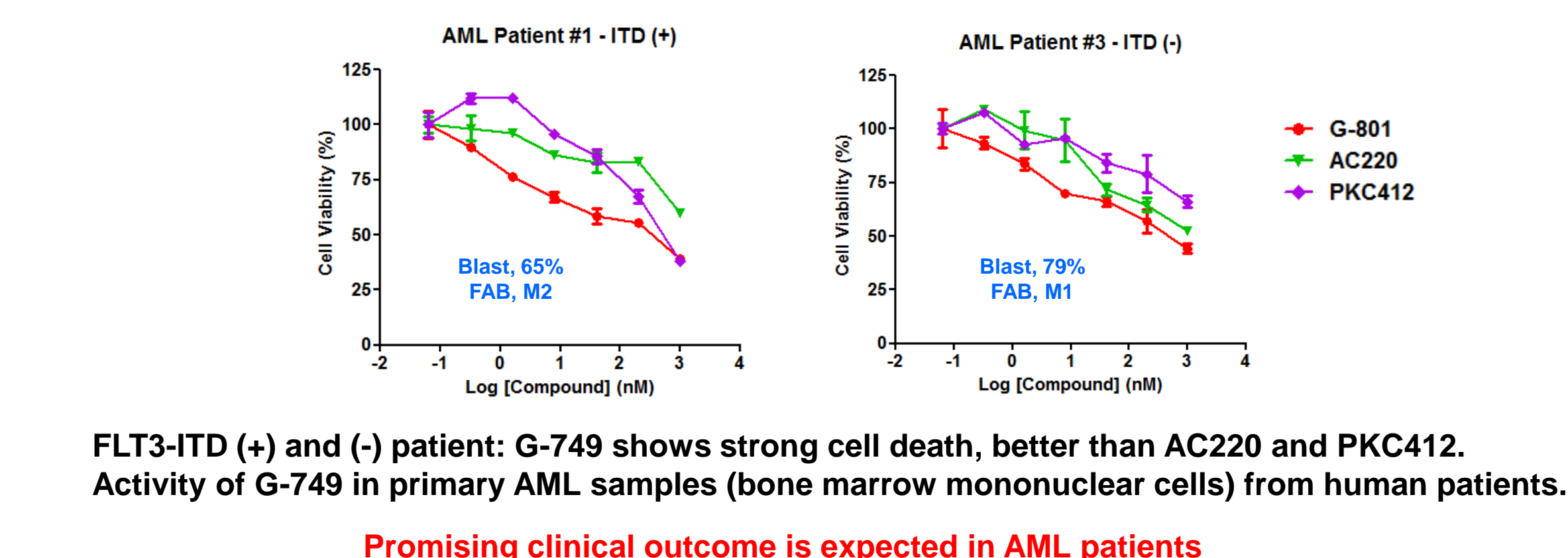
## Complete tumor regression in xenograft model using MV4-11 cells



## Strongly sustained FLT3 inhibition



## Activity of G-749 in primary AML cells from human patients



## ADME/Tox, PK

Physicochemical Property		ADME/Toxicology	
Chiral center	No	Plasma protein binding	99.0% (mouse, rat, human)
Synthesis	4 step straightforward	Metabolic stability	> 60 min (rat, human)
Molecular weight	521.41	Bioavailability	~41% (rat)
cLogP	4.87 (<5)	5 CYPs, IC <sub>50</sub>	~ 10uM (human)
PSA (Polar Surface Area)	90 (<140)	hERG, IC <sub>50</sub>	> 3,000 fold than cellular ED <sub>50</sub>
Mouse PK parameter (10 mg/kg, PO)		5 day MTD	250 mg/kg, mouse PO
Cmax	241 ng/mL		
Tmax	2 h		
T <sub>1/2</sub>	4.1 h		
AUC <sub>0-24h</sub>	2,408 ng·h/mL		

## Conclusion

- High potency and selectivity against FLT3 kinase
- Strong suppression of aberrant activation of down-stream signaling via FLT3 mutant receptor
- Strong induction of apoptosis
- Complete tumor regression at an xenograft model with no relapse
- High inhibition activity against various FLT3 mutants induced leukemia
- Strongly sustained inhibitory activity in human plasma and high FLT3 ligand milieu
- Cell death of AML primary cells
  - Best-in-class, which ostensibly overcomes drug resistances faced by other kinase inhibitors
  - Promising clinical outcome expected

## Background

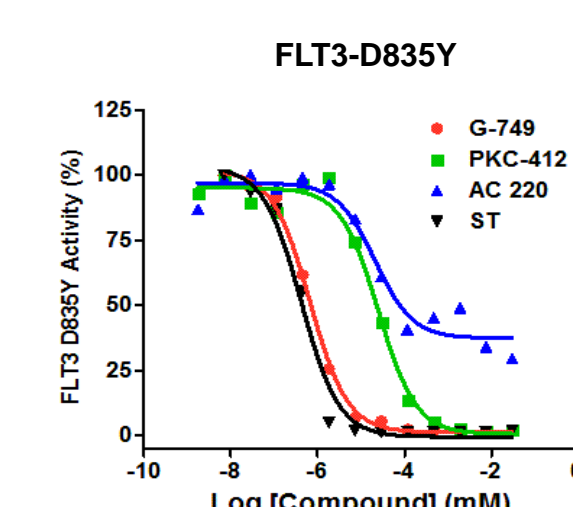
### FLT3, a promising therapeutic target for AML

- Member of Class III receptor tyrosine kinases (RTK) that includes FMS, c-kit & PDGFR
- Overexpressed in > 50% of AML's
- Mutations leading to constitutive activation occur in ~35% of patients
  - FLT3-ITD: 25-30% have a 3-33 amino acid repeat in JM domain
  - FLT3-TKD: 5-10% have point mutations in the activation loop
  - Stimulate proliferation and inhibit apoptosis of AML cells
- Adverse prognosis
  - Increased leukocytosis and blast counts
  - Higher risk of relapse
  - Reduced overall survival

## Results

### G-749 is a potent FLT3 inhibitor.

Compound	Kinase assay (IC <sub>50</sub> , nM)	
	WTFLT3	FLT3 D835Y
G-749	0.2	0.3
AC220	8.8	28.2
PKC-412	15.4	24.2



Our candidate G-749 is superior to AC220 and PKC412 in terms of biochemical potency.