Cystic Fibrosis modulator drugs inhibit migration of colorectal cancer cells

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Summary:

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality, driven by complex genetic, epigenetic, and microenvironmental factors. Recent findings implicate the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel in CRC progression, as CFTR levels are notably reduced in sporadic CRCs, particularly in advanced and metastatic tumors, correlating with poorer patient outcomes. Additionally, cystic fibrosis (CF) patients, who carry CFTR mutations, have a 6-fold increased risk of early-onset CRC, consistent with a proposed role for CFTR in sustaining cell differentiation. Given recent advances in small-molecule modulators that restore CFTR function in CF patients, this study explored the potential of repositioning these modulators to address CFTR downregulation in sporadic CRC.

Using a panel of CRC cell lines, we investigated whether CFTR modulators can increase CFTR functional expression in cells with various genetic backgrounds and whether such improvements could reduce their oncogenic properties. Our data show that treatment with the CFTR folding correctors Tezacaftor (VX661) and Elexacaftor (VX445) led to a significant, approximately three-fold increase in CFTR abundance in CRC cells expressing reduced but detectable levels of the channel. Additionally, these treatments significantly reduced the migratory behavior of Caco2 and DLD1 cells, particularly when combined with the CFTR potentiator Ivacaftor (VX770).

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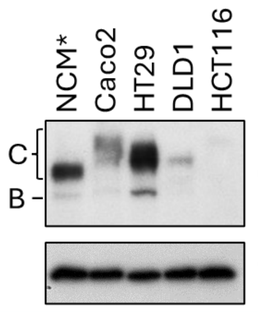
A panel of four CRC cell lines were chosen, with different genetic and epigenetic backgrounds and different CFTR expression levels

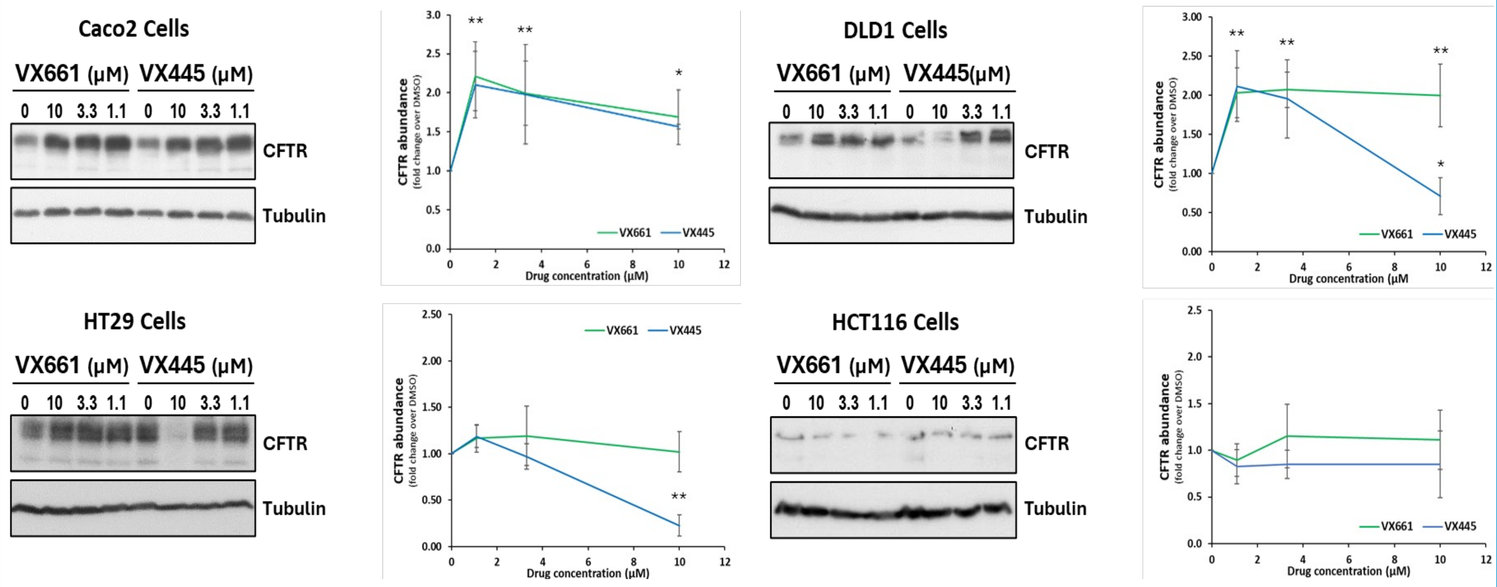
Cell line	Caco2	HT29	DLD1	HCT116
Origin	Primary tumor	Primary tumor	Primary tumor	Primary tumor
Gender	Male	Female	Male	Male
Age	72	44	Adult	48
Stage	Unknown	Dukes' C	Dukes' C	Dukes' D
Phenotype	polarize	colon-like	undiff	undiff
CFTR	wt	wt	wt	p.L863L
APC	p.Q1367X	p.E835X/ p.E1536fs	R2148X/ p.G1398fs	wt
CTNNB1	p.G245A	wt	wt	p.S45del
KRAS	wt	wt	p.G13D	p.G13D
BRAF	wt	V600E	wt	p.I666I
PI3KCA	wt	p.P449T	p.E545K/ p.D549N	p.H1047R
PTEN	wt	wt	wt	wt
TP53	p.E204X	p.R273H	p.S241F	wt
SMAD4	p.D351H	p.Q311X	wt	wt
MSI	-	-	+	+
CIN	+	+	-	-
CIMP	-	+	+	+



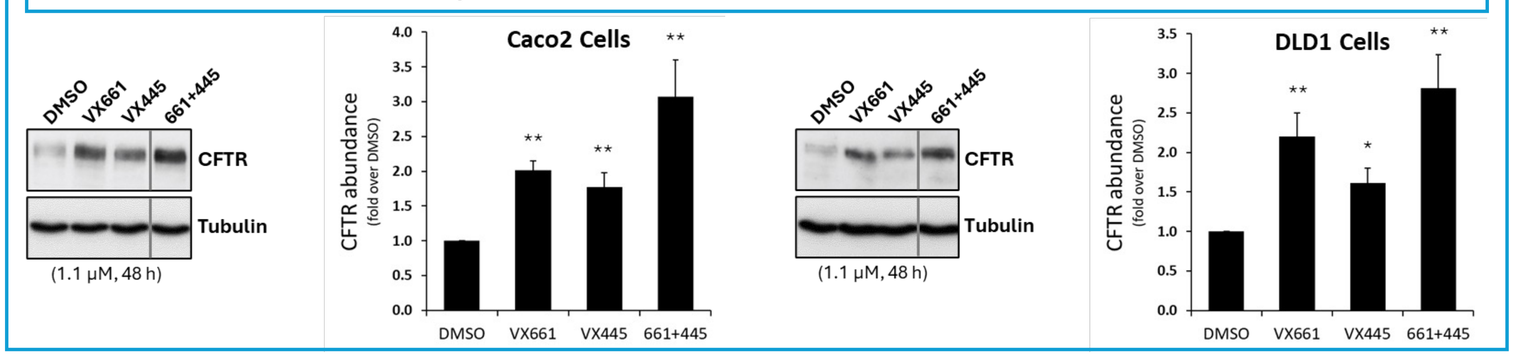
*NCM460, a cell line of non-transformed human colonocytes, representative of a normal colonic mucosa.

Band B= imature, ER-associated CFTR protein;
Band C= mature, fully glycosylated CFTR protein

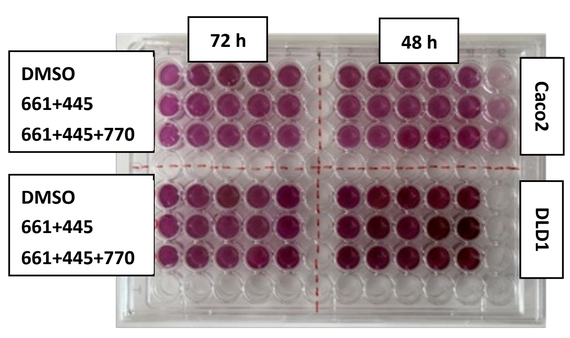
Treatment with CFTR folding correctors VX661 and VX445 significantly increased abundance of mature CFTR protein in Caco2 and DLD1 CRC cells

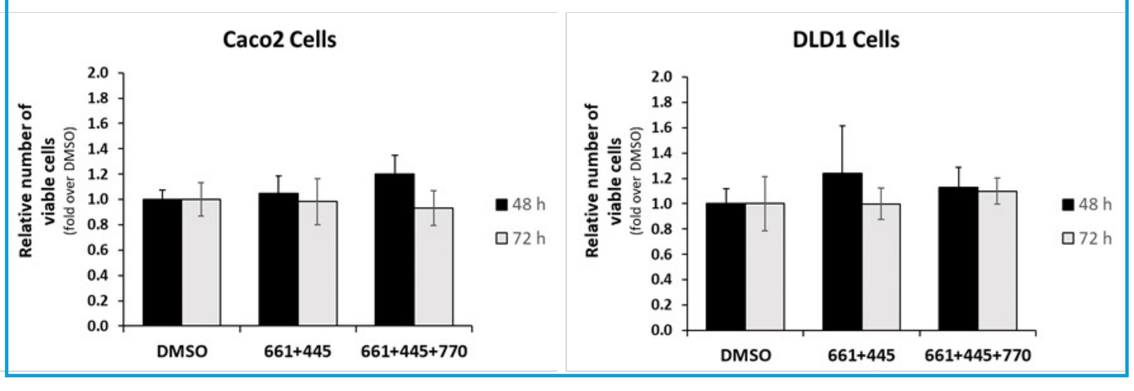


Combination of the two drugs (661+445) was additive, producing an even more pronounced increase in CFTR abundance

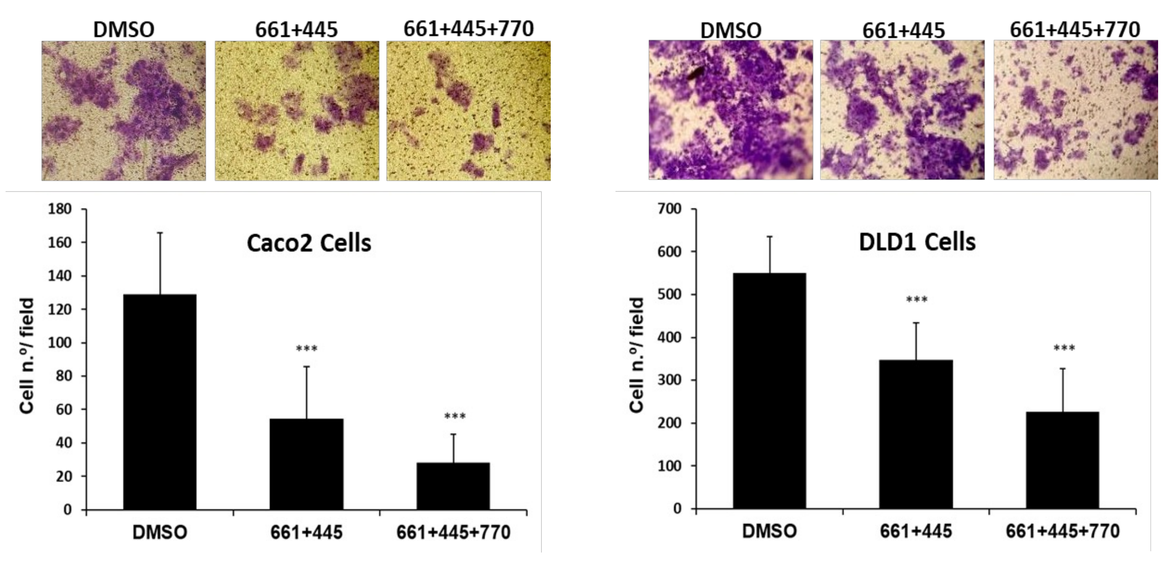


CFTR modulator drugs did not affect CRC cell viability (MTT assay)





CFTR modulator drugs significantly hindered CRC cell migration (Boyden chamber assay)



Conclusions:

- Our findings suggest that CFTR modulators can improve CFTR functional expression in CRC cell lines of reduced but detectable CFTR levels.
- Modulator drug-induced CFTR functional rescue hinders the migratory properties of responsive CRC cells.
- Further *in vivo* studies are necessary to fully assess the potential benefits for repositioning CFTR modulator drugs in CRC treatment.