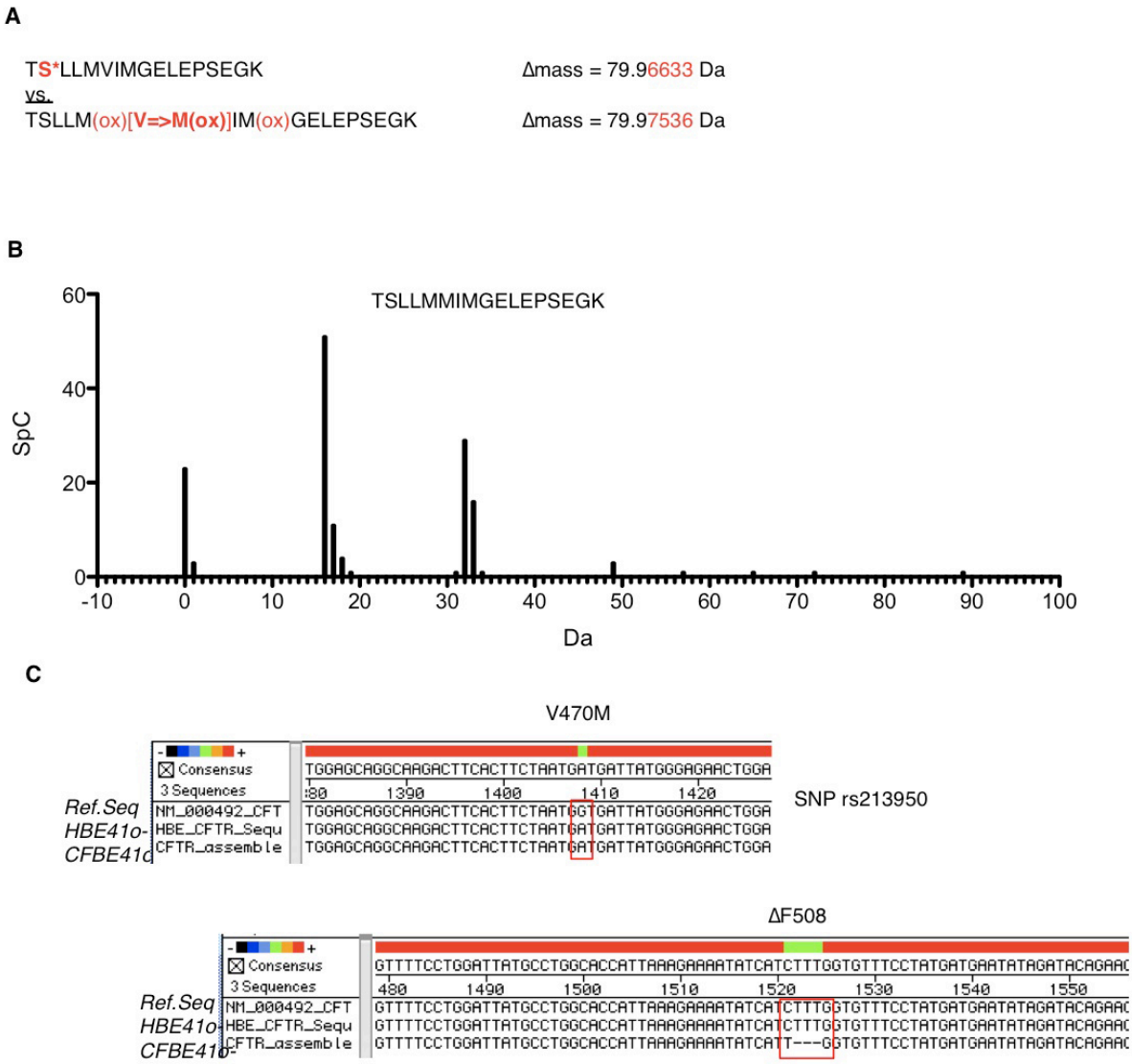

Figure S1. Identification of CFTR SNPs in CFBE41o- and HBE41o- cell lines. (A and B) Blind-PTM identifies SNP rs213950 in CFBE41o- cells, whereas forward search against current Uniprot releases (04-2012 to 06-2016) would indicate a mass similar to phosphorylation of the adjacent residue, Ser^{466}. **(C)** RT-PCR and sequencing of the PCR product confirms presence of SNP rs213950 in CFBE41o- and HBE41o- cells.

[*Figure and legend continues, next page*].

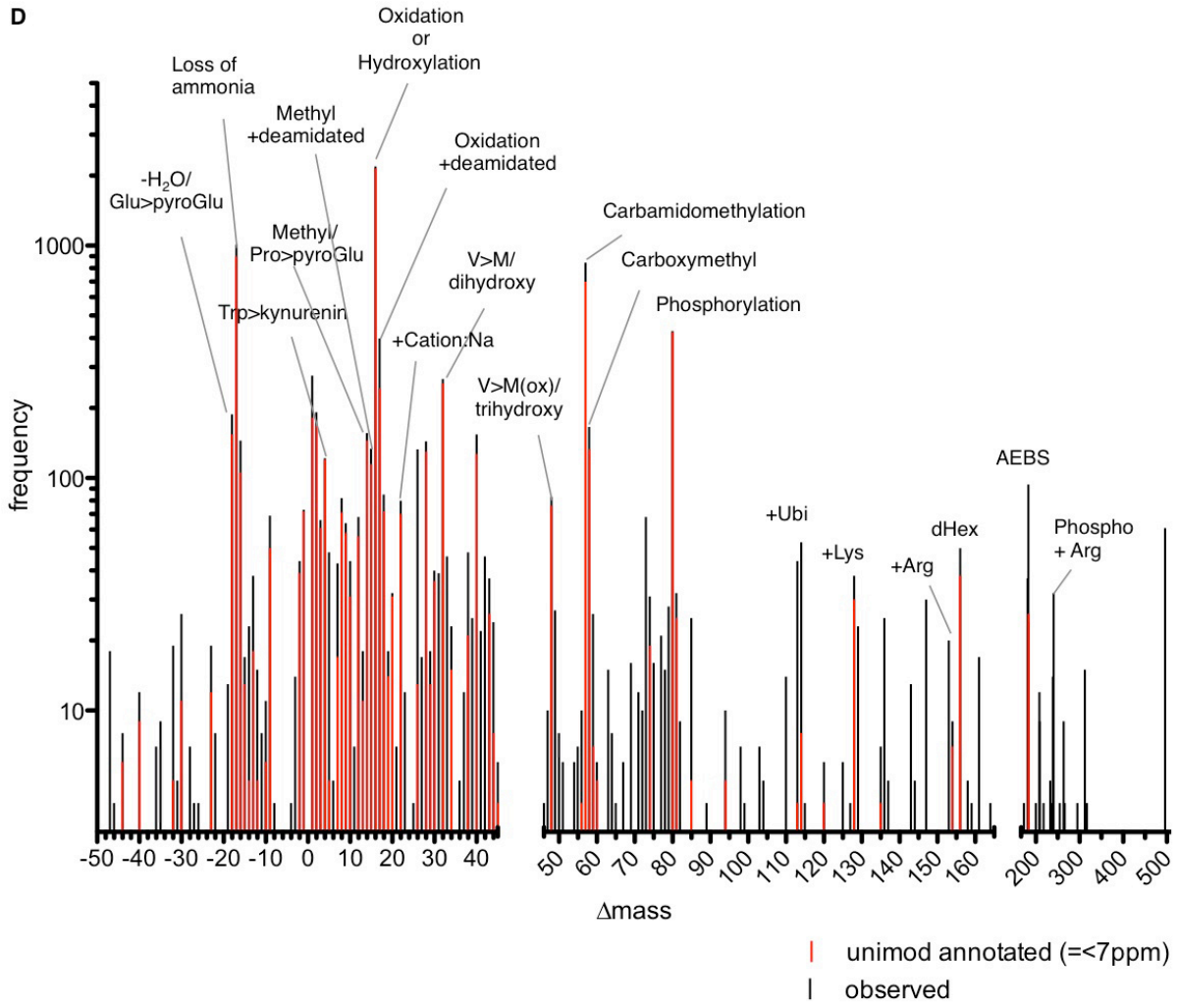

Figure S1, *continued*: (D) Modified CFTR spectra identified with Blind-PTM and binned by mass shift. Possible interpretation of several mass shifts is indicated. Data represent independent biological replicates (ΔF508, n=17; wt, n= 14).

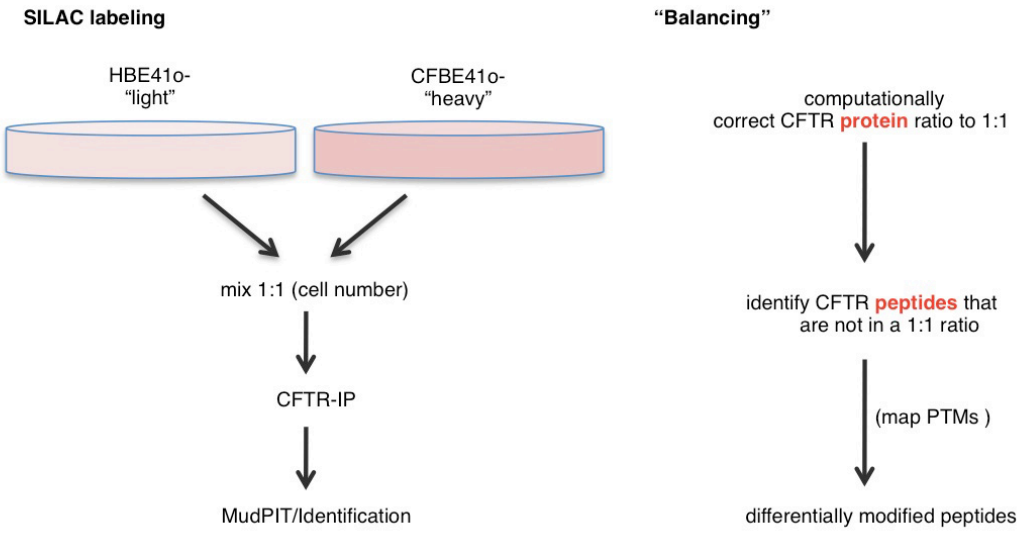

Figure S2. Balanced SILAC approach. Outline of experimental and computational approach.

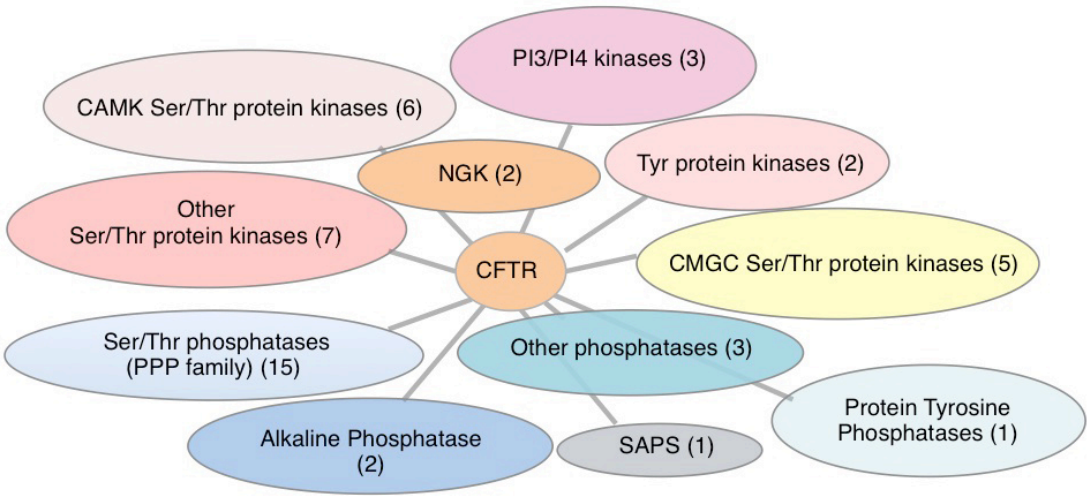

Figure S3. **Kinase families in the CFTR interactome.** The graph shows the kinase families and number of identified individual members (in parentheses) in the CFTR interactome (30). .

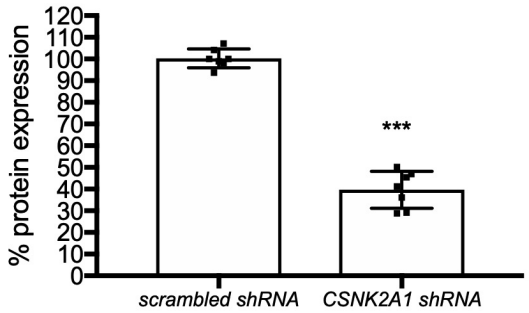

Figure S4. **CK2α knockdown**. Relative CK2α protein abundance in CFBE41o-cells upon control or shRNA-mediated knockdown with a *CSNK2A1*-specific shRNA. Data are mean ± S.D. of three independent biological replicates per treatment. Unpaired t-test: ****$P <$ 0.0001.

Phosphopeptide sequence	Site	A-score (-10xlog(P))	Mutation in CF patients	Clinical significance	Xcorr	DeltaCN
LELSDIYQIPSVDS*ADNLSEK	S45	42.44			4.0429	0.3716
LVITS*EMIENIQSVK	S263	0			4.1106	0.3345
T*SNGDDSLFFSNFSLLGTPVLK	T421	19.21	T421A	CBAVD	4.1574	0.401
TS*NGDDSLFFSNFSLLGTPVLK	S422	14.12			3.4131	0.3547
TSNGDDS*LFFSNFSLLGTPVLK	S427	30.66			5.1744	0.4506
TSNGDDSLFFSNFSLLGT*PVLK	T438	40.34	T438A	CBAVD (5T mutation on the other allele)	4.9924	0.4065
IS*FCSQFSWIMPGTIK	S489	24.76	S489X	CF	2.9974	0.3319
DNIVLGEGGITLS*GGQR	S549	64.79	S549N, S549I, S549F, S549R	CF, severe clinical phenotype	4.4221	0.3623
LMGCDS*FDQFSAER	S649	84.83			3.1118	0.2678
NS*ILTETLHR	S660	56.02	S660T	asymptomatic	4.3942	0.3164
FS*LEGDAPVSWTETK	S670	109.73			4.023	0.3694
FSLEGDAPVS*WTETK	S678 ?	11.36			3.7289	0.3749
NS*ILNPINSIR	S700	117.01			2.9966	0.3042
T*PLQMNGIEEDSDEPLER	T717	70.1			3.6552	0.4598
TPLQMNGIEEDS*DEPLER	S728	121.23			5.7429	0.4231
LS*LVPDSEQGEAILPR	S737	94.12	S737F	elevated sweat chloride	3.1023	0.3604
VS*LAPQANLTELDIYSR	S795	89.21			5.6752	0.4943
LS*QETGLEISEEINEEDLK	S813	69.89	S813P	very mild CF	4.9931	0.3953
LSQET*GLEISEEINEEDLK	T816	20.9			6.9409	0.3009
LSQETGLEIS*EEINEEDLK	S821	93.13			5.2613	0.3691
ECFFDDMES*IPAVTTWNTYLR	S839	69.99			4.1339	0.1801

Table S1. **Identified phosphopeptides**. Given are sequences with PTM site position, A-score value for phosphorylation site, Xcorr and ΔCn values as well as mutations occurring in CF patients and their clinical significance (if any). Table summarizes n= 90 independent biological experiments.

A

ubiquitinated peptide sequence	position	Mutation in CF patients	clinical significance
SPLEK(114.0429)ASVVSK	K8		
LELSDIYQIPSVDSADNLSEK(114.0429)LER	K52		
AVYK(114.0429)DADLYLLDSPFGYLDVLTEK	K564	K564E	CBAVD
DADLYLLDSPFGYLDVLTEK(114.0429)EIFESCVCK	K584		
FIDMPTEGK(114.0429)PTK	K1174		
SVIK(114.0429)ACQLEEDISK	K522		
K(114.0429)TSNGDDSLFFSNFSLLGTPVLK	K420		
TSNGDDSLFFSNFSLLGTPVLK(114.0429)DINFK	K442		
TGSGK(114.0429)STLLSAFLR	K1250		K1250A mutation dramatically prolonged burst duration (abolishes ATP hydrolysis)

B

methylated peptide sequence	position	Mutation in CF patients	clinical significance
TSNGDDSLFFSNFSLLGTPVLK(14.0157)DI	K442		
GQLLAVAGSTGAGK(14.0157)T	K464	K464N	Severe phenotype at early age with pancreatic insufficiency, chronic cough and bronchial infection. 3659delC mutation on the other chromosome (expected to lead to pancreatic insufficiency)
RNSILTETHR(14.0157)R	R668	R668C	does not cause CF
K(14.0157)NSILNPINSIR	K698		
LSLVPDSEQGEAILPR(14.0157)I	R751	R751P, R751C, R751L	lung disease, carrier testing for R751C
ISVISTGPTLQAR(14.0157)R	R764		
VSLAPQANLTELDIYSR(14.0157)R	R810	R810G	CBAVD (ΔF508 on other allele)

Table S2. **CFTR ubiquitination and methylation sites identified in the forward search**. Given are identified peptide sequences, PTM site, mutations occurring in CF patients and their clinical significance. Table summarizes n= 90 independent biological experiments.