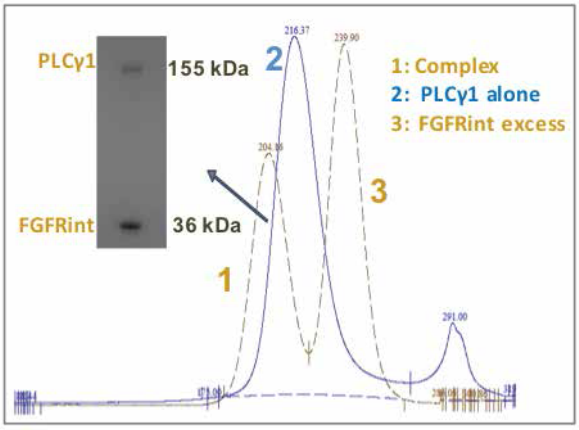
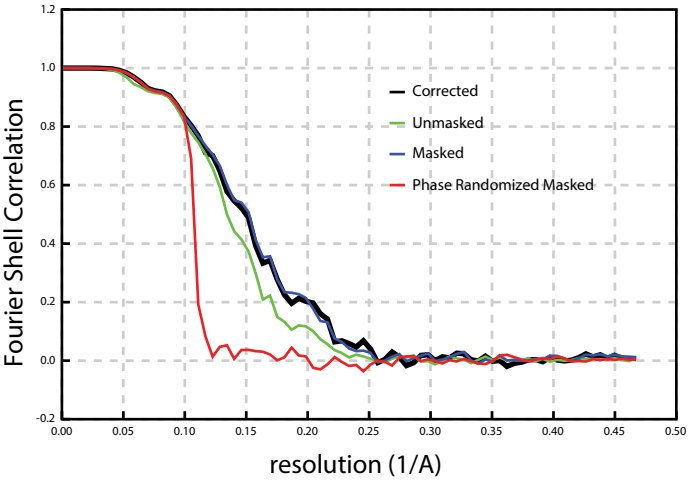
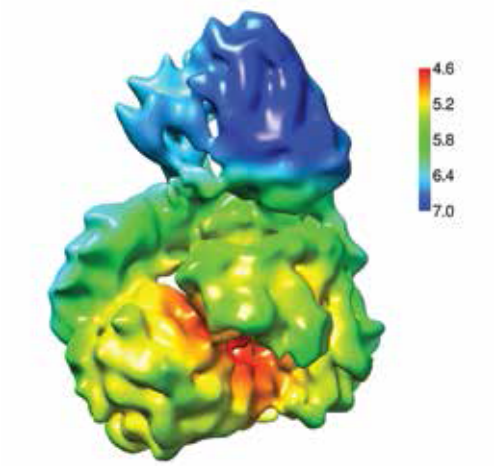
a



b



c



d

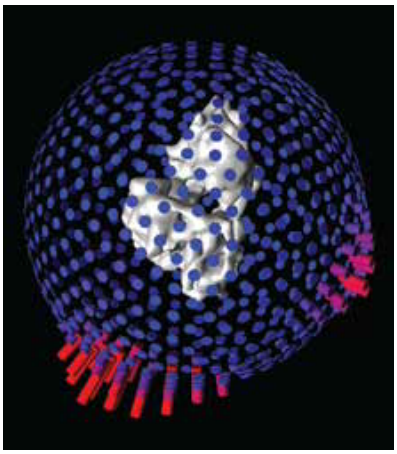
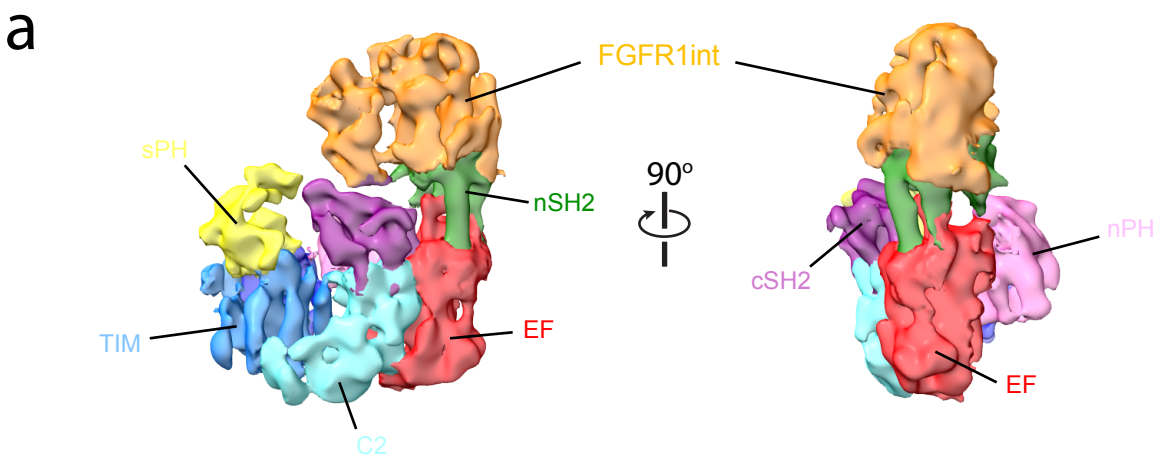
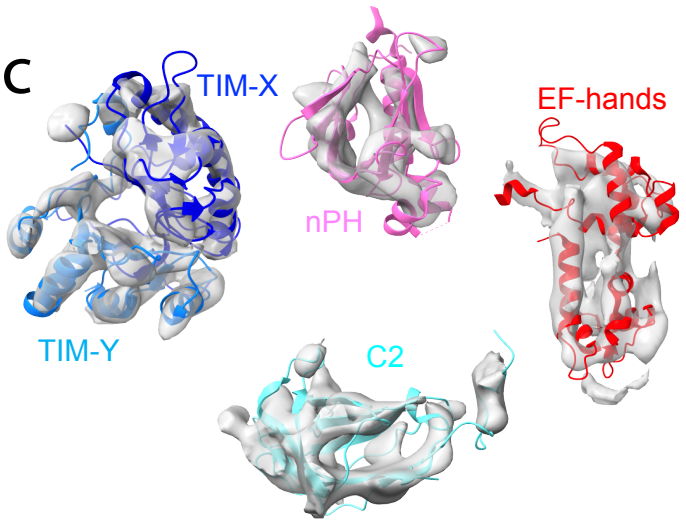


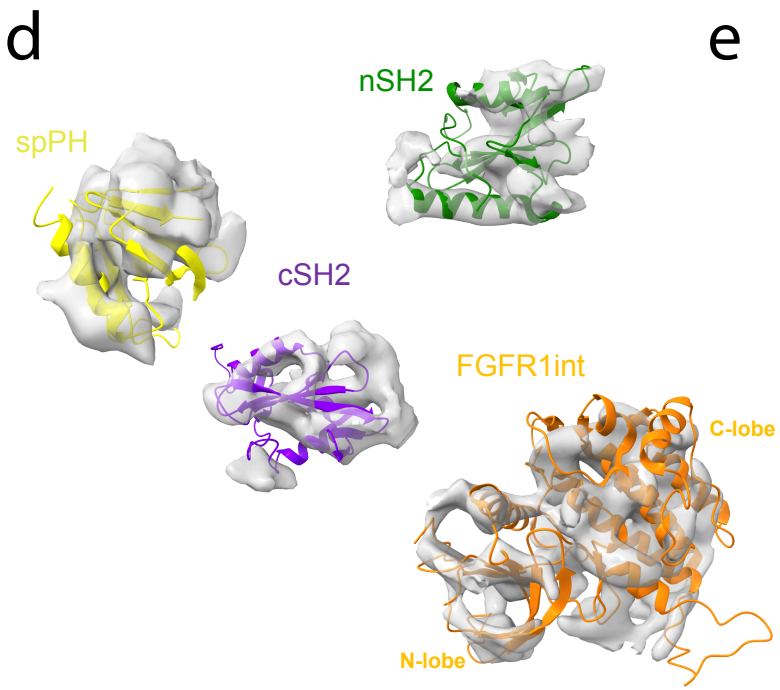
Figure S1



b

Domain	σ level	CC value
nPH	0.025	0.8066
EF	0.025	0.7768
TIM-X	0.03	0.8329
sPH	0.02	0.8230
nSH2	0.025	0.8647
cSH2	0.02	0.8173
TIM-Y	0.03	0.8476
C2	0.025	0.8472
FGFR1int	0.02	0.8092





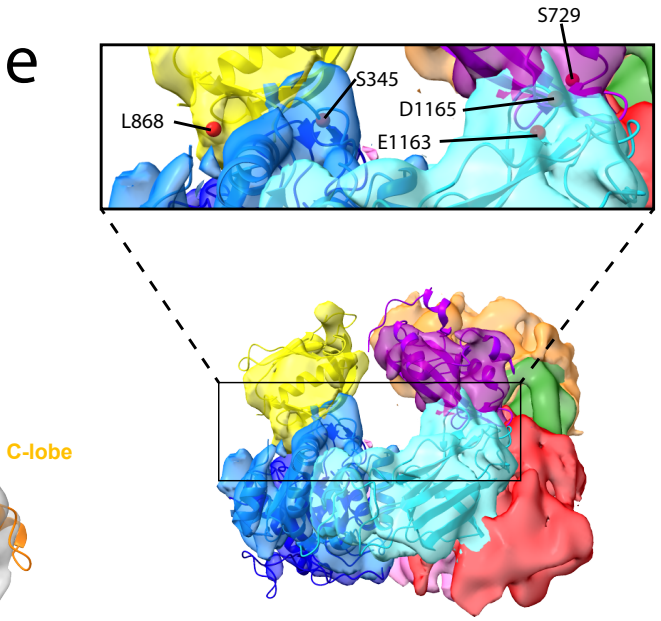
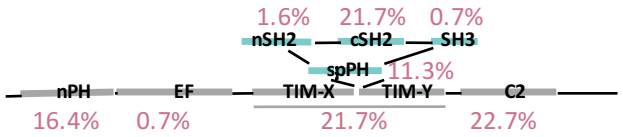


Figure S2

a



Total number of observations = 432

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PLCG2 -------MSTTVNVDSLAEYEKSQIKRALELGTVMTVFSFR-KSTPERRTVQVIMETRQV  52

PLCG1 TWSRGADKIEGAIDIREIKEIRPGKTSRDFDRYQEDPAFRPDQSHCFVILYGMEFRLKTL 120
PLCG2 AWSKTADKIEGFLDIMEIKEIRPGKNSKDFERA---KAVRQKEDCCFTILYGTQFVLSTL 109
                                      EF
PLCG1 SLQATSEDEVNMWIKGLTWLMEDTLQAPTPLQIERWLRKQFYSVDRNREDRISAKDLKNM 180
PLCG2 SLAADSKEDAVNWLSGLKILHQEAMNASTPTIIESWLRKQIYSVDQTRRNSISLRELKTI 169

PLCG1 LSQVNYRVPNMRFLRERLTDLEQRSGDITYGQFAQLYRSLMYSAQKTMDLPFLEASRRRT 237
PLCG2 LPLINFKVSSAKFLKDKFVEIGAHKDELSFEQFHLFYKKLMFEQQKSILDEFKKDSSVFI 229

PLCG1 LRAGERPELCRVSLPEFQQFLLDYQGELWAVDRLQVQEFMLSFLRDPLREIEEPYFFLDE 297
PLCG2 LGNTDRPDASAVYLHDFQRFLIHEQQEHWAQDLNKVRERMTKFIDDTMRETAEPFLFVDE 289
                                      TIM-X
PLCG1 FVTFLFSKENSVWNSQLDAVCPDTMNNPLSHYWISSSHNTYLTGDQFSSESSLEAYARCL 357
PLCG2 FLTYLFSRENSIWDEKYDAVDMQDMNNPLSHYWISSSHNTYLTGDQLRSESSPEAYIRCL 349

PLCG1 RMGCRCIELDCWDGPDGMPVIYHGHTLTTKIKFSDVLHTIKEHAFVASEYPVILSIEDHC 417
PLCG2 RMGCRCIELDCWDGPDGKPVIYHGWTRTTKIKFDDVVQAIKDHAFVTSSFPVILSIEEHC 409
                                                        ------
PLCG1 SIAQQRNMAQYFKKVLGDTLLTKPVEISADGLPSPNQLKRKILIKHKKLAEGSAYEEVPT 477
PLCG2 SVEQQRHMAKAFKEVFGDLLLTKPTEASADQLPSPSQLREKIIIKHKKLGPRGDVDV--- 466
      -------    spPH-p1
PLCG1 SMMYSENDISNSIKNGILYLEDPVNHEWYPHYFVLTSSKIYYSEETSSDQGNEDEEEPKE 537
PLCG2 ---NMEDKKDEHKQQGELYMWDSIDQKWTRHYCAIADAKLSFSDDIEQTM----EEEVPQ 519
                 nSH2
PLCG1 VSSSTELHSNEKWFHGKLGAGRDGRHIAERLLTEYCIETGAPDGSFLVRESETFVGDYTL 597
PLCG2 DIPPTELHFGEKWFHKKVEK----RTSAEKLLQEYCMETGGKDGTFLVRESETFPNDYTL 575

PLCG1 SFWRNGKVQHCRIHSRQDAGTPKFFLTDNLVFDSLYDLITHYQQVPLRCNEFEMRLSEPV 657
PLCG2 SFWRSGRVQHCRIRSTMEGGTLKYYLTDNLTFSSIYALIQHYRETHLRCAEFELRLTDPV 635
               cSH2
PLCG1 PQTNAHESKEWYHASLTRAQAEHMLMRVPRDGAFLVRKRNEPNSYAISFRAEGKIKHCRV 717
PLCG2 PNPNPHESKPWYYDSLSRGEAEDMLMRIPRDGAFLIRKREGSDSYAITFRARGKVKHCRI 695
                  --
PLCG1 QQEGQTVMLGNSE-FDSLVDLISYYEKHPLYRKMKLRYPINEEALEKIGTAEPDYGALYE 776
PLCG2 NRDGRHFVLGTSA-YFESLVELVSYYEKHSLYRKMRLRYPVTPELLERYNME-RDINSLYD 754
                     SH3
PLCG1 GRNPGFYVEANP--MPTFKCAVKALFDYKAQREDELTFIKSAIIQNVEKQEGGWWRGDYG 834
PLCG2 VS--RMYVDPSEINPSMPQRTVKALYDYKAKRSDELSFCRGALIHNVSKEPGGWWKGDYG 812
                                  spPH-p2
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PLCG2 TRIQQYFPSNYVEDISTAD-FEELEKQIIEDNPLGSLCRGILDLNTYNVVKAPQGKNQKS 871
                                                        TIM-Y
PLCG1 FVFSISMASVAHWSLDVAADSQEELQDWVKKIREVAQTADARLTEGKIMERRKKIALELS 954
PLCG2 FVFILEPKQQGDPPVEFATDRVEELFEWFQSIREITWKIDTKENNMKYWEKNQSIAIELS 931

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                 C2
PLCG1 DPFDKSSLRGLEFCAISIEVLGARHLPKNGRGIVCPFVEIEVAGAEYDSTKQKTEFVVDN 1134
PLCG2 DPMPPESQRKIL-MTLTVKVLGARHLPKLGRSIACPFVEVEICGAEYDNNKFKTTVVNDN 1107
                                      ------  -----
PLCG1 GLNPVWPAK--PFHFQISNPEFAFLRFVVYEEDMFSDQMFLAQATFPVKGLKTGYRAVPL 1192
PLCG2 GLSPIWAPTQEKVTFEIYDPNLAFLRFVVYEEDMFSDPNFLAHATYPIKAVKSGFRSVPL 1167

PLCG1 KNNYSEDLELASLLIKIDIFPAKENGDLSPFSGTSLRERGSDASGQLFHGRAREGSFESR 1252
PLCG2 KNGYSEDIELASLLVFCEMRPVLESEEELYSSCRQLRRRQEELNNQLFLYDTHQNLRNAN 1227

PLCG1 YQQPFEDFRISQEHLADHFDSRERRAPRRTRVNGDNRL- 1290
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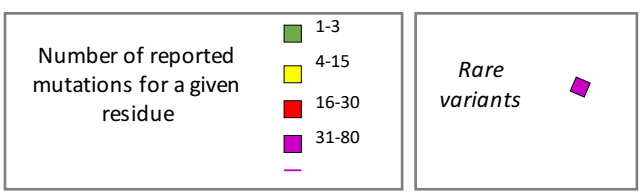
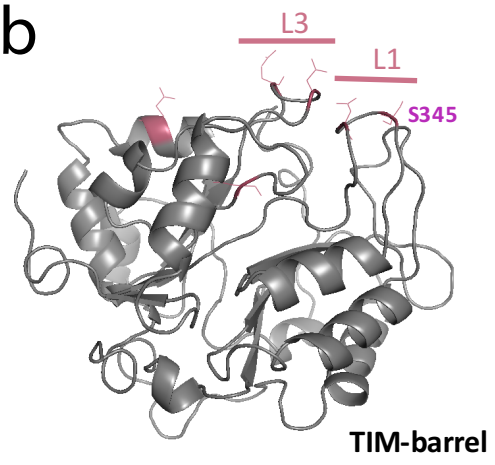
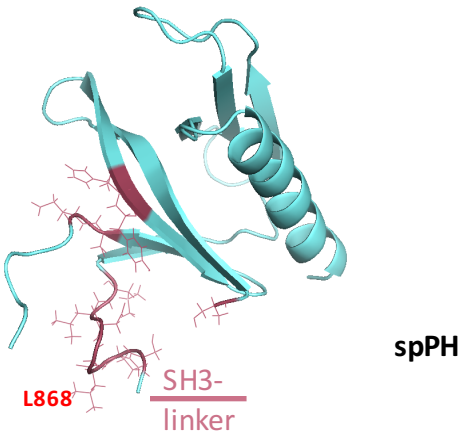
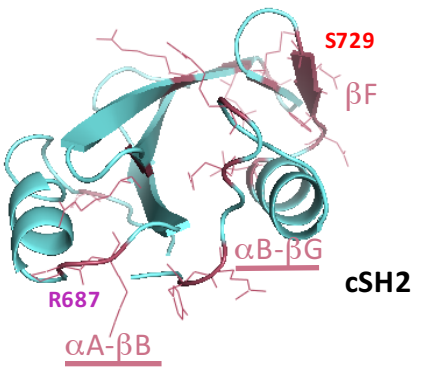


b







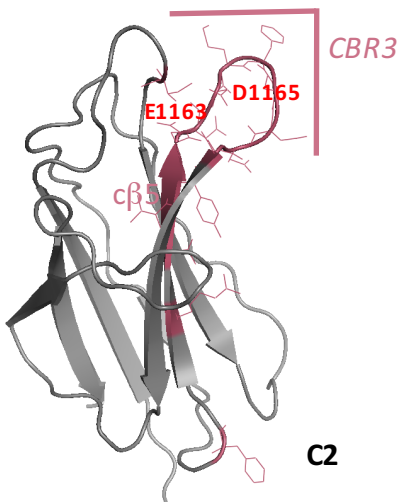
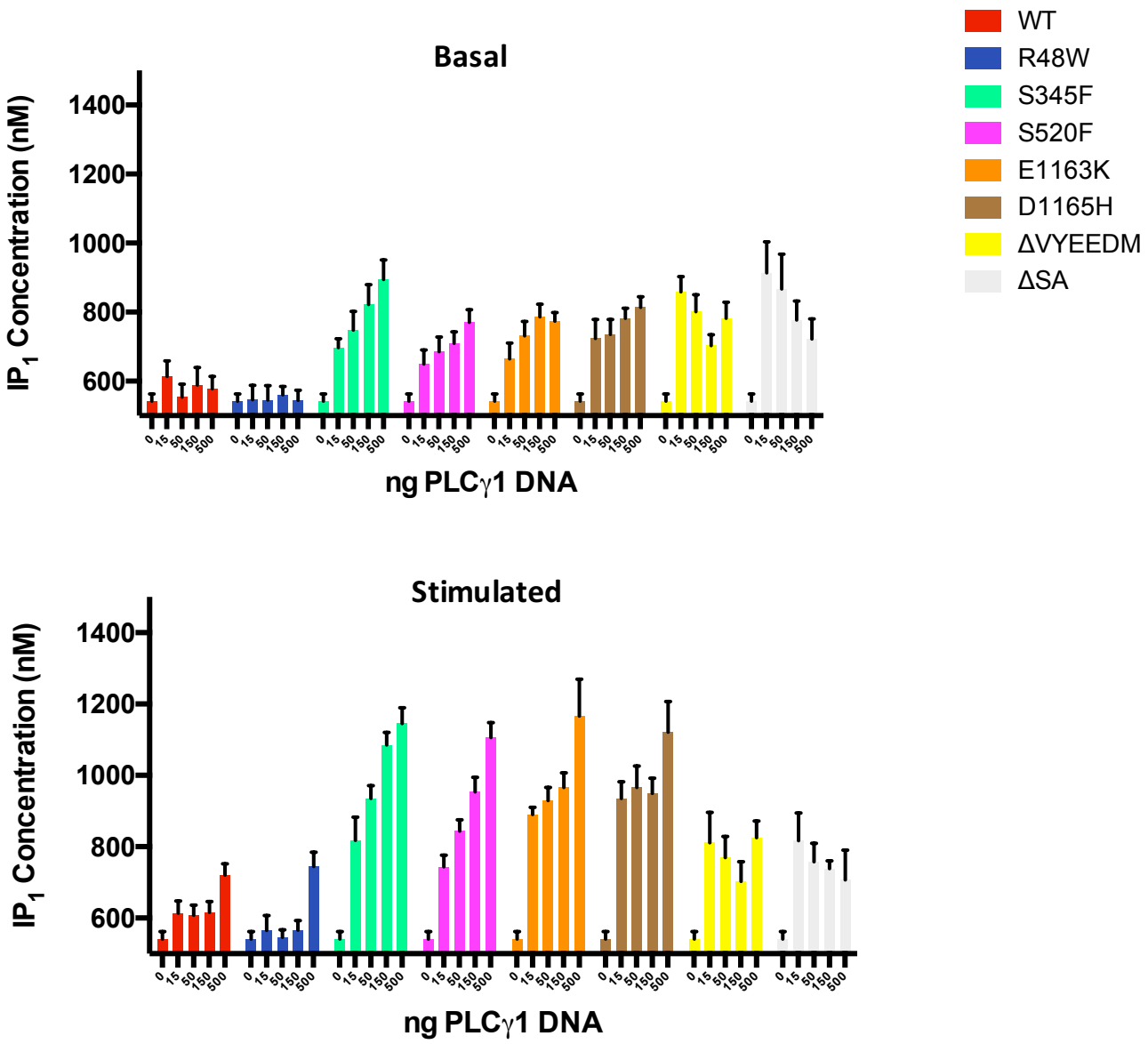


Figure S3

a


Basal
IP1 Concentration (nM)
1400
1200
1000
800
600
0 15 50 150 500
ng PLCγ1 DNA
WT
R48W
S345F
S520F
E1163K
D1165H
ΔVYEEDM
ΔSA
Stimulated
IP1 Concentration (nM)
1400
1200
1000
800
600
0 15 50 150 500
ng PLCγ1 DNA

b

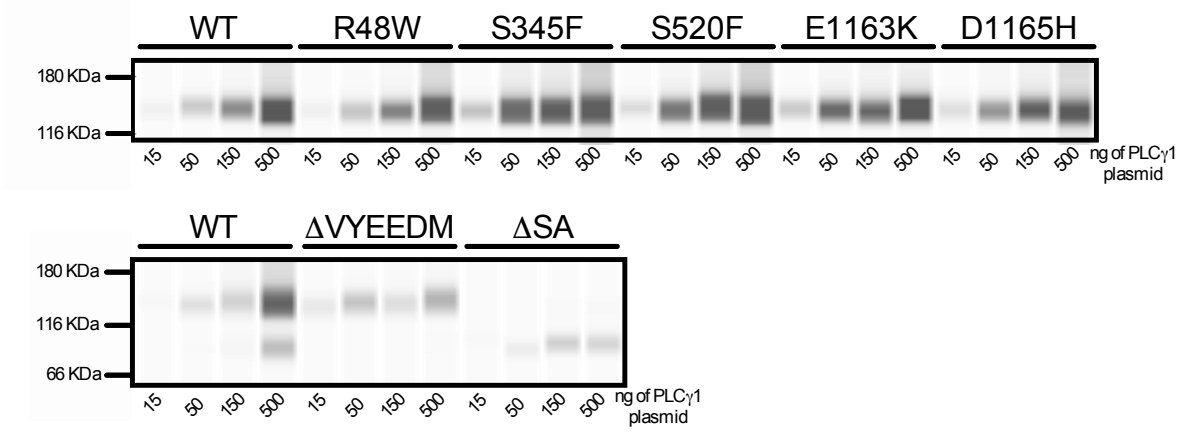

WT
R48W
S345F
S520F
E1163K
D1165H
180 KDa
116 KDa
15 50 150 500
ng of PLCγ1 plasmid
WT
ΔVYEEDM
ΔSA
180 KDa
116 KDa
66 KDa
15 50 150 500
ng of PLCγ1 plasmid

Figure S4

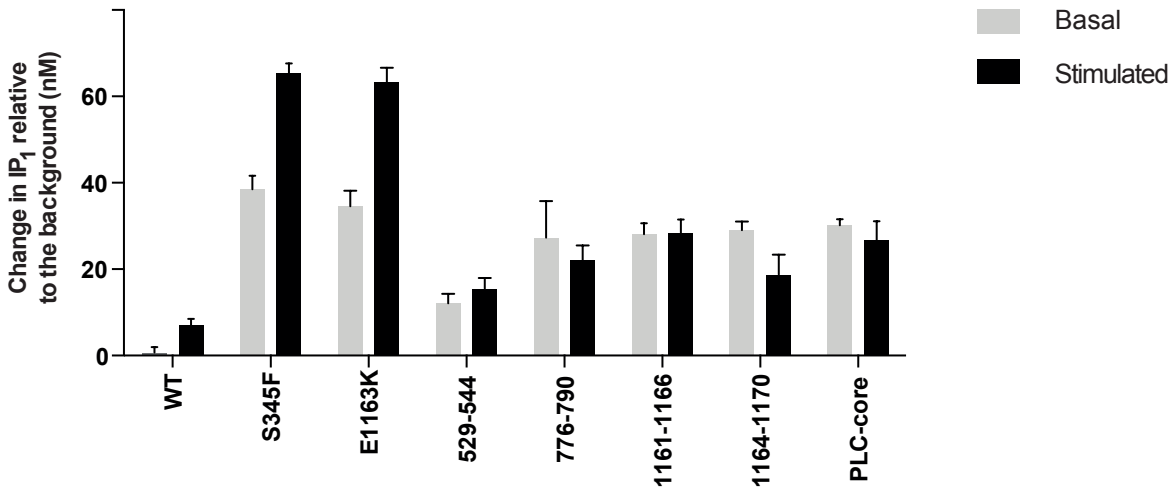
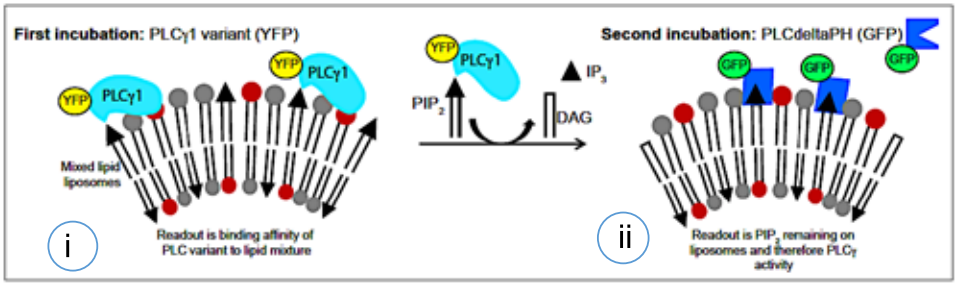

Basal
Stimulated
Change in IP1 relative to the background (nM)
0
20
40
60
WT
S345F
E1163K
529-544
776-790
1161-1166
1164-1170
PLC-core

Figure S5

a



b

ii

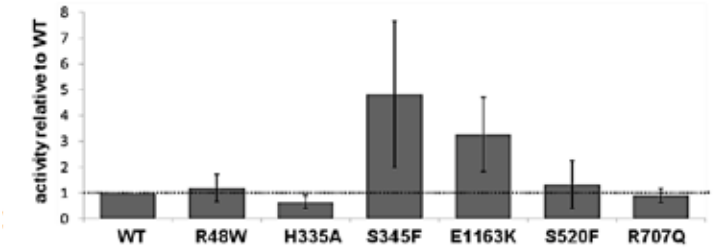
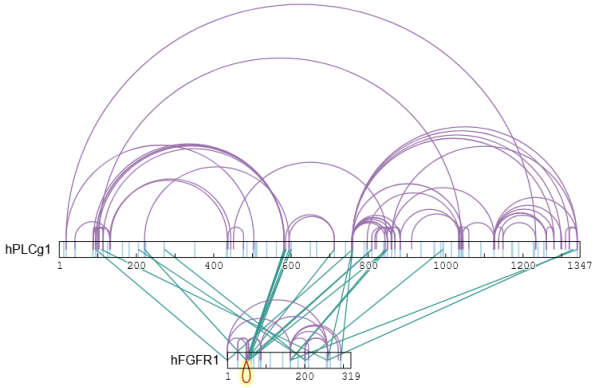


Figure S6

a


hPLCg1
1
200
400
600
800
1000
1200
1347
hFGFR1
1
200
319

b

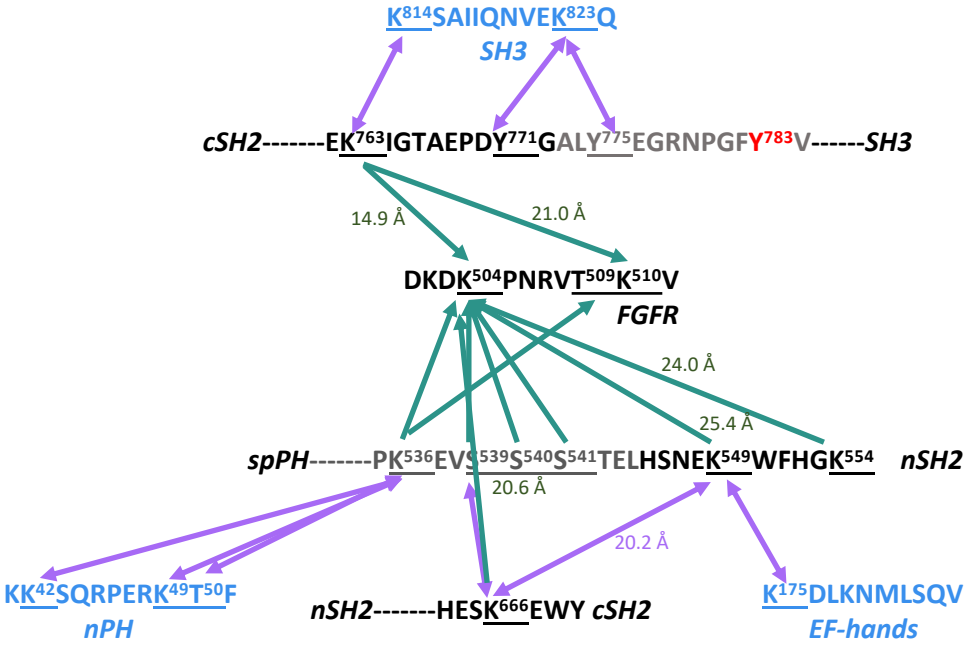

K814SAIIQNVEK823Q
SH3
cSH2-------EK763IGTAEPDY771GALY775EGRNPGFY783V------SH3
14.9 Å
21.0 Å
DKDK504PNRVT509K510V
FGFR
24.0 Å
25.4 Å
spPH-------PK536EVS539S540S541TELHSNEK549WFHGK554 nSH2
20.6 Å
20.2 Å
KK42SQRPERK49T50F
nPH
nSH2-------HESK666EWY cSH2
K175DLKNMLSQV
EF-hands

Figure S7

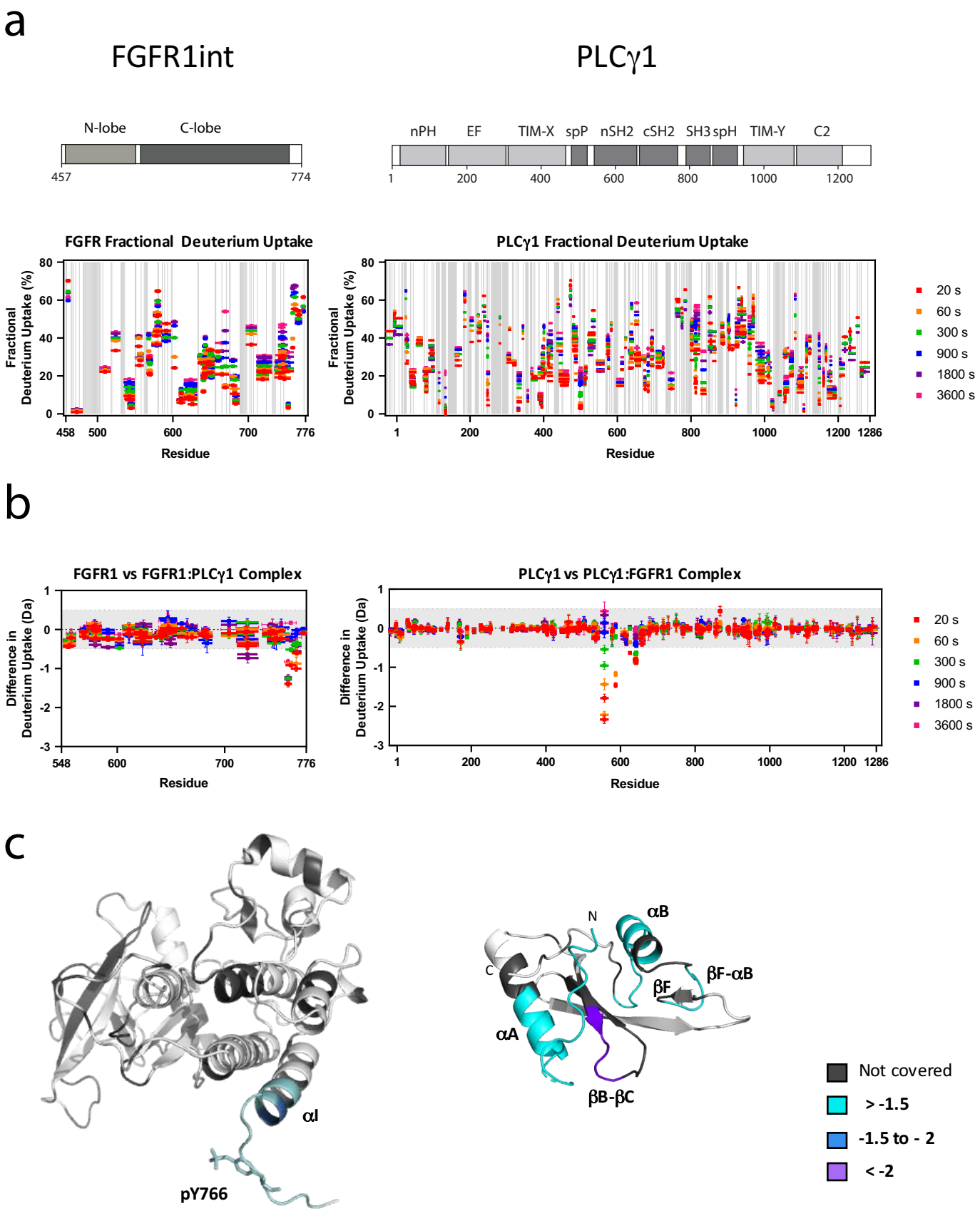

a
FGFR1int
PLCγ1
N-lobe
C-lobe
457
774
nPH
EF
TIM-X
spP
nSH2
cSH2
SH3
spH
TIM-Y
C2
1
200
400
600
800
1000
1200
FGFR Fractional Deuterium Uptake
PLCγ1 Fractional Deuterium Uptake
Fractional Deuterium Uptake (%)
Residue
20 s
60 s
300 s
900 s
1800 s
3600 s
b
FGFR1 vs FGFR1:PLCγ1 Complex
PLCγ1 vs PLCγ1:FGFR1 Complex
Difference in Deuterium Uptake (Da)
Residue
c
αI
pY766
N
C
αB
βF-αB
βF
αA
βB-βC
Not covered
> -1.5
-1.5 to - 2
< -2

Figure S8