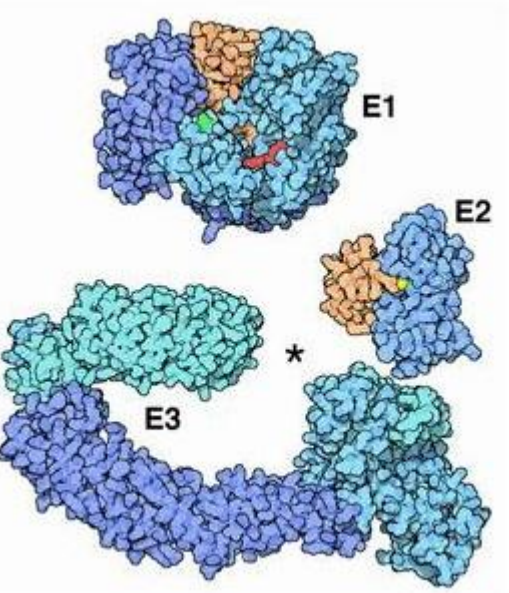
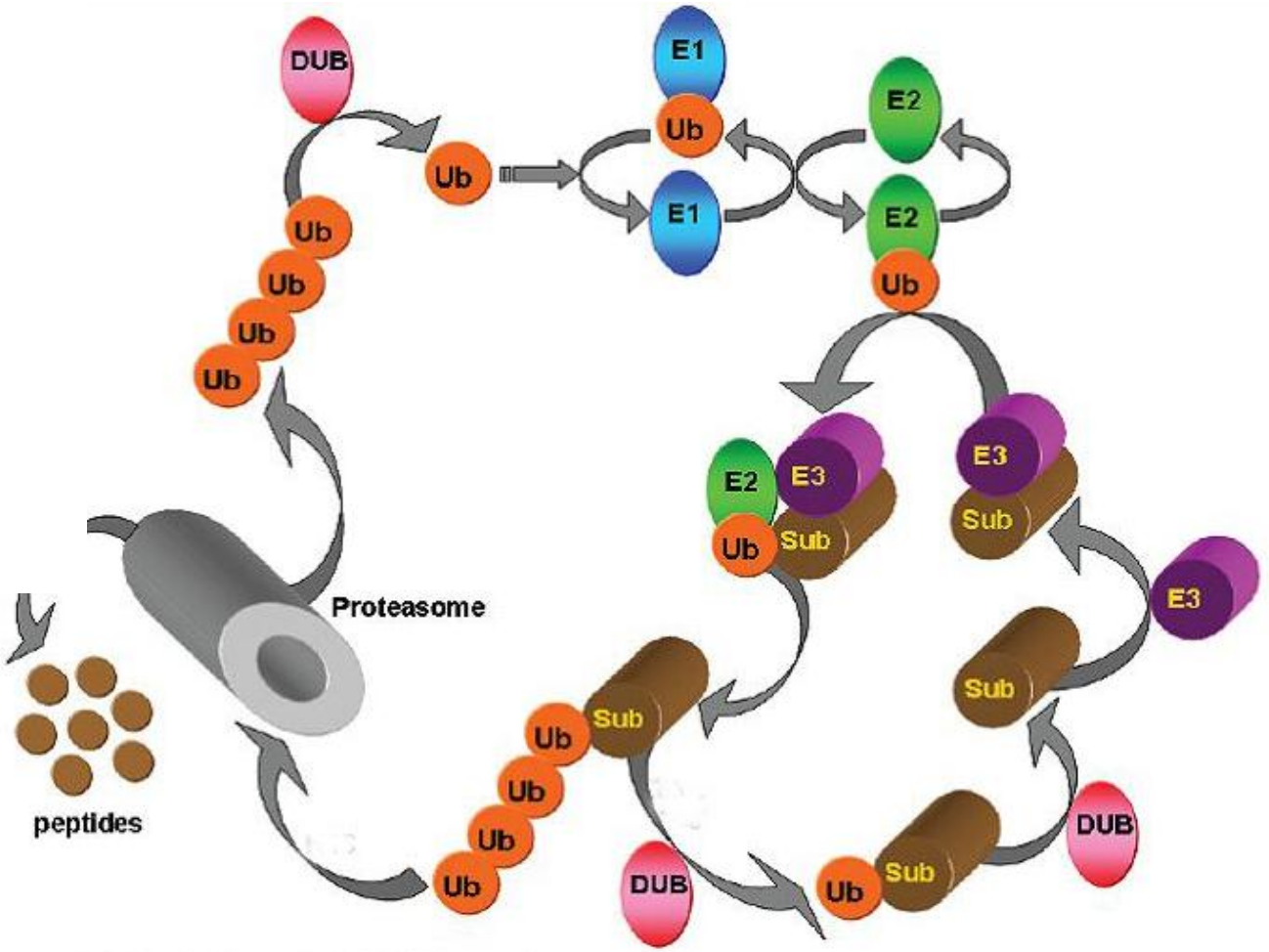
Exploring the molecular mechanism of FBXW7 promoting GATA3 destablization and its biological significance in breast cancer

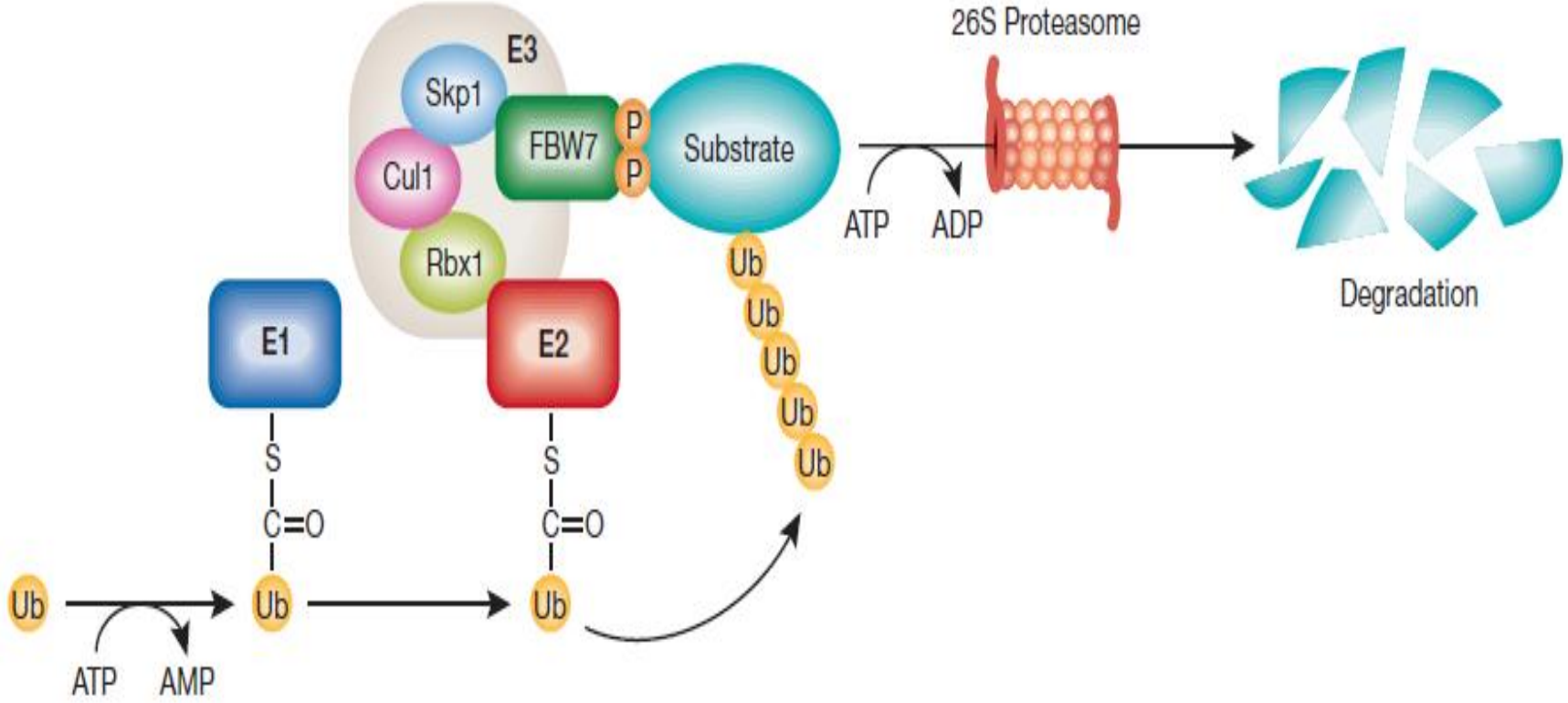
Background



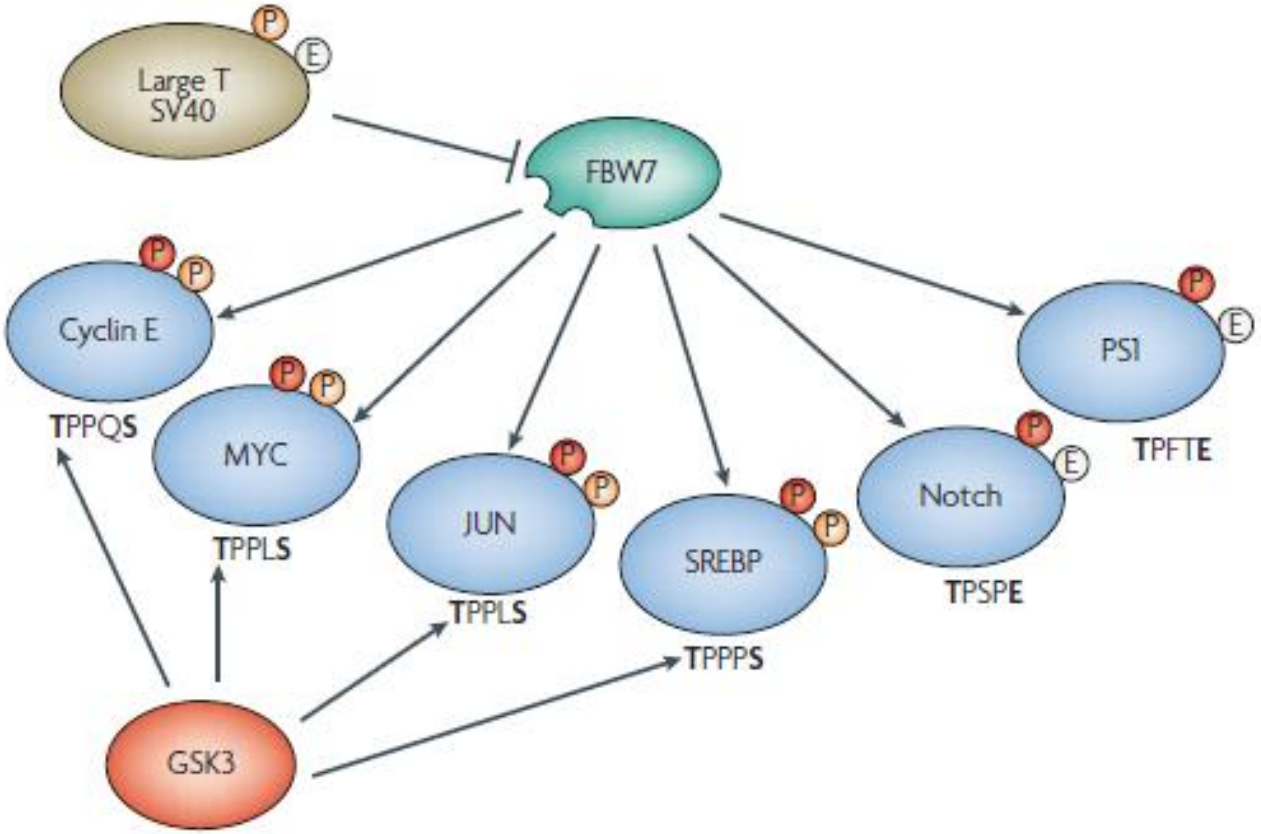


Ref: *Marblestone et al,* 2010 (in press)

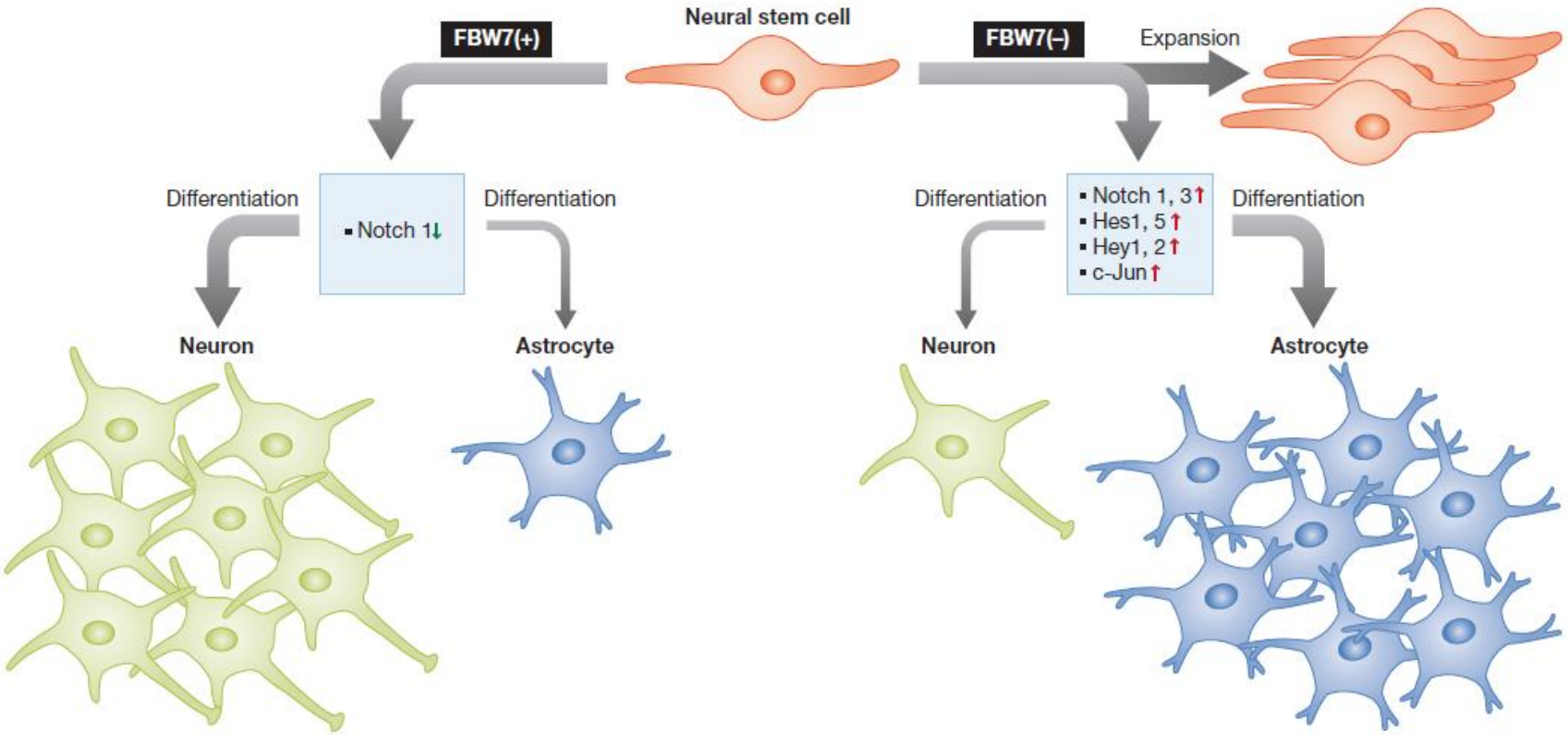
Background


E3
Skp1
Cul1
FBW7
P
P
Substrate
Rbx1
E1
E2
Ub
Ub
Ub
Ub
Ub
S
C=O
S
C=O
Ub
Ub
Ub
ATP
AMP
ATP
ADP
26S Proteasome
Degradation

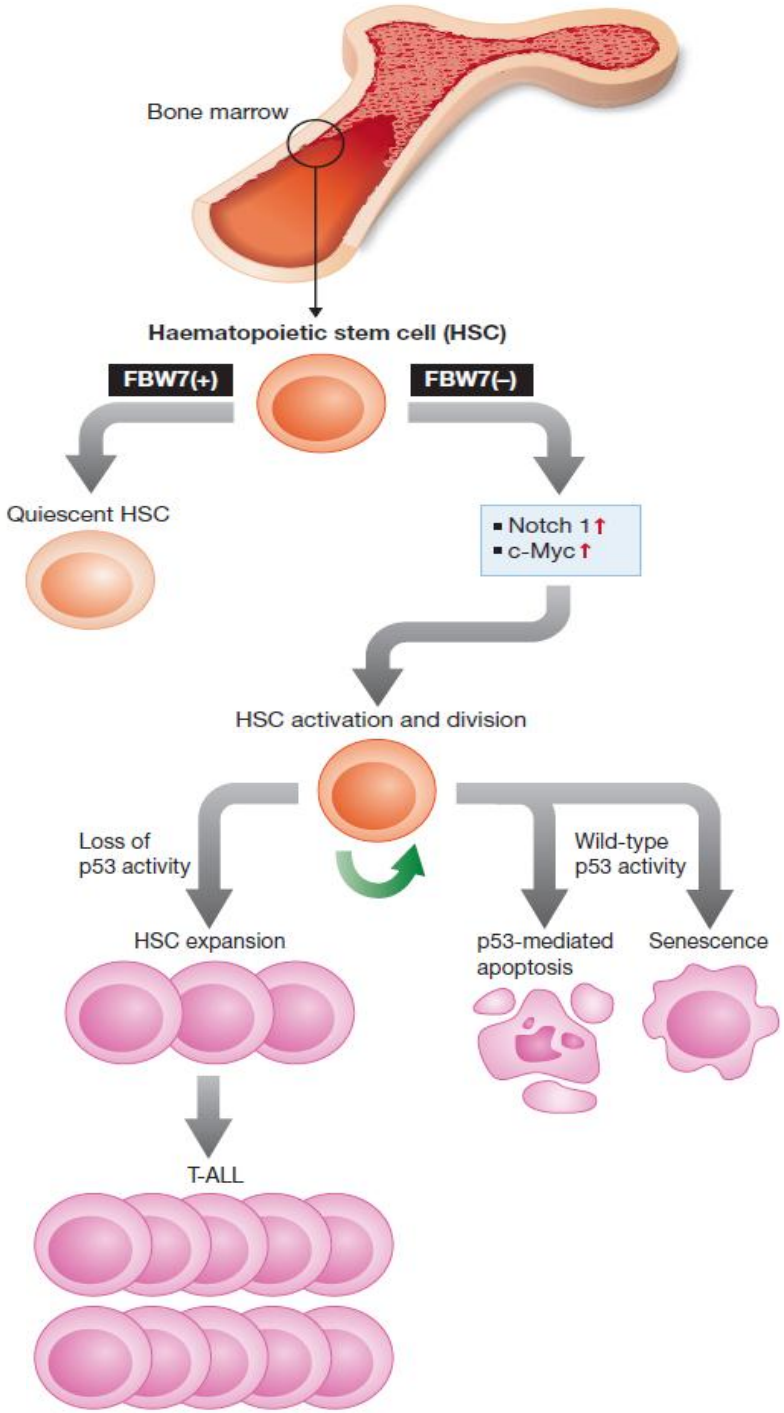
Background


Large T
SV40
FBW7
Cyclin E
TPPQS
MYC
TPPLS
JUN
TPPLS
SREBP
TPPPS
Notch
TPSPE
PS1
TPFTE
GSK3

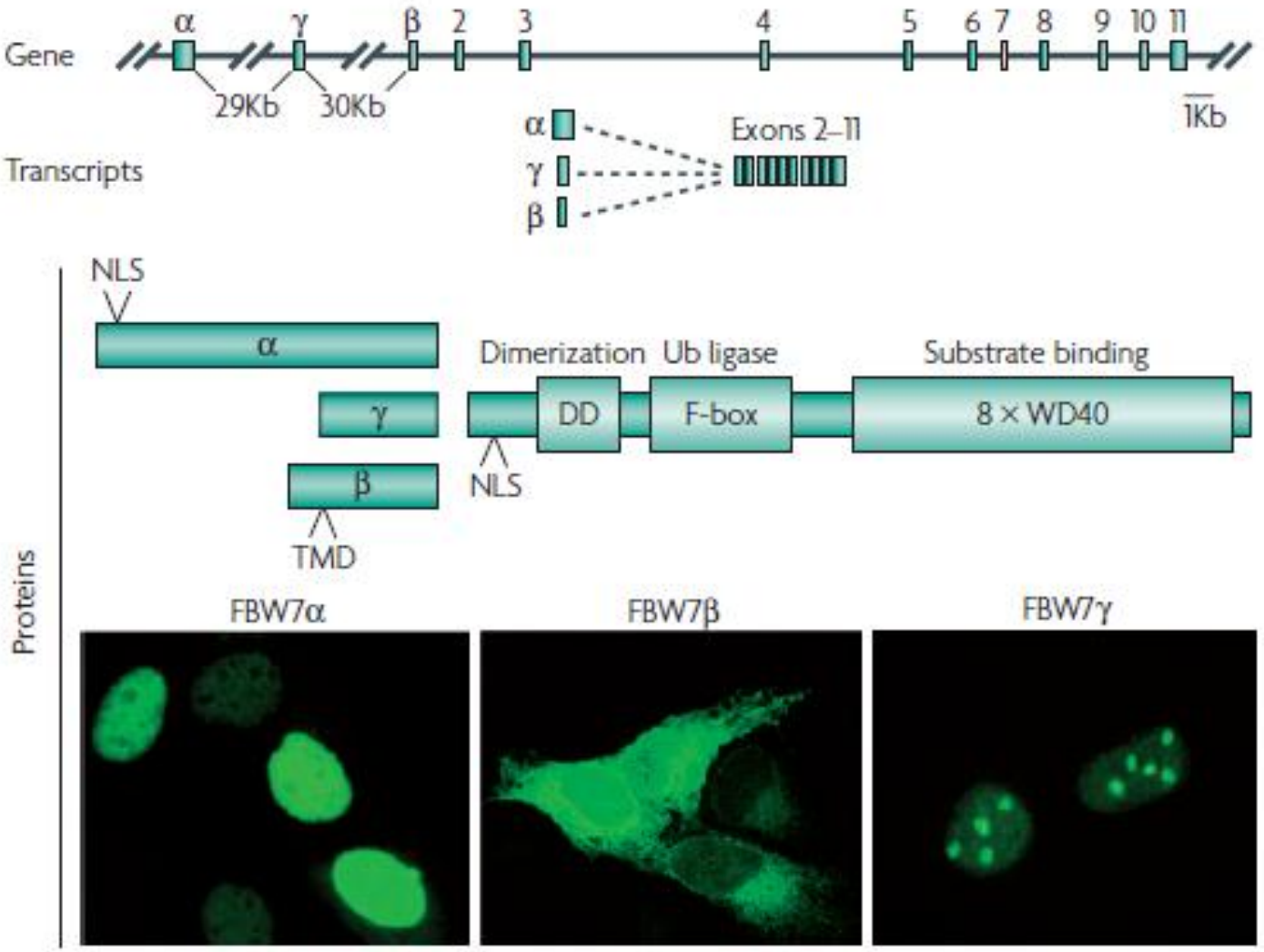
Background


Neural stem cell
FBW7(+)
FBW7(–)
Expansion
Differentiation
▪ Notch 1↓
Differentiation
Neuron
Astrocyte
Differentiation
▪ Notch 1, 3↑
▪ Hes1, 5↑
▪ Hey1, 2↑
▪ c-Jun↑
Differentiation
Neuron
Astrocyte

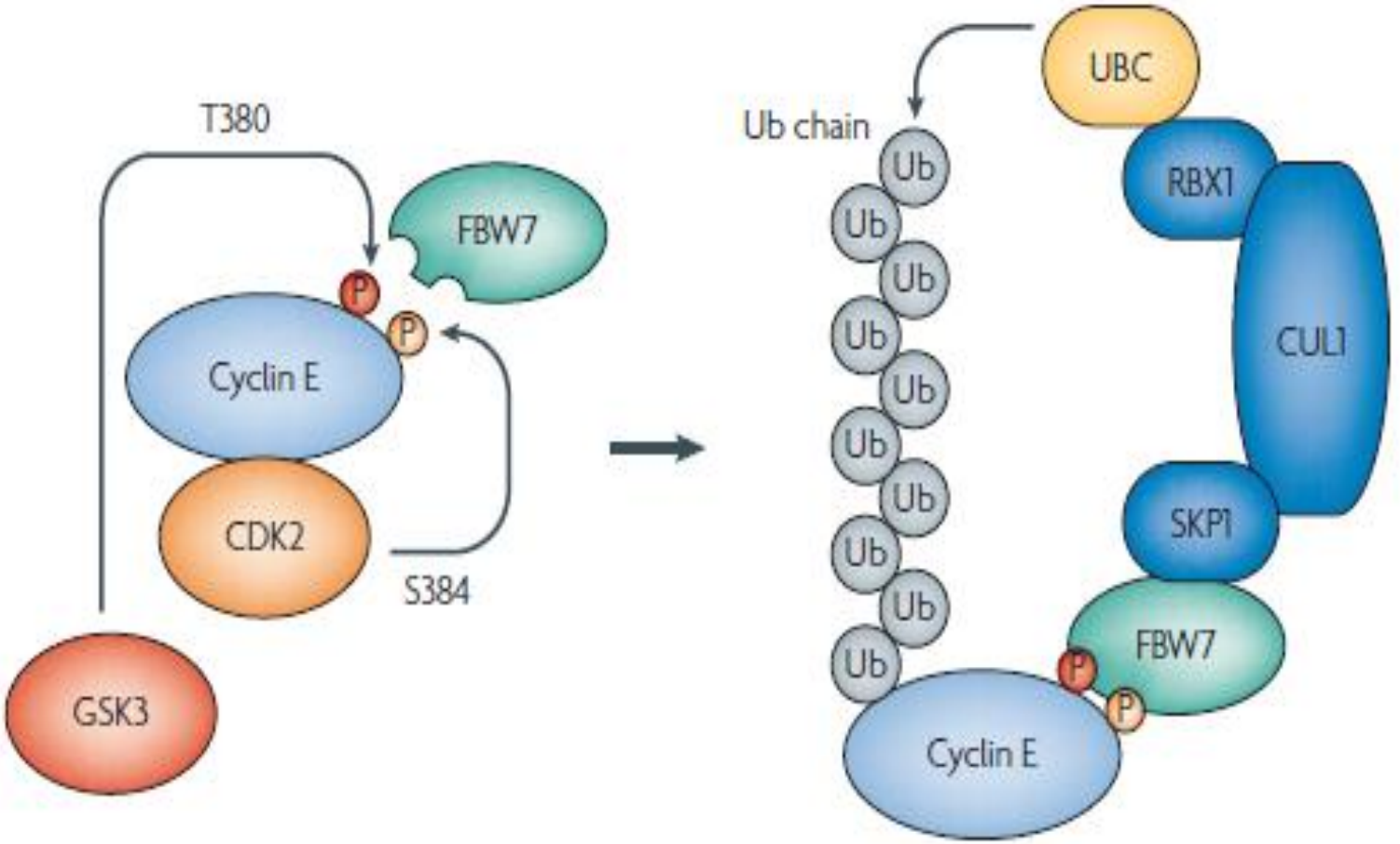
Background


Bone marrow
Haematopoietic stem cell (HSC)
FBW7(+)
FBW7(–)
Quiescent HSC
▪ Notch 1↑
▪ c-Myc↑
HSC activation and division
Loss of p53 activity
Wild-type p53 activity
HSC expansion
p53-mediated apoptosis
Senescence
T-ALL

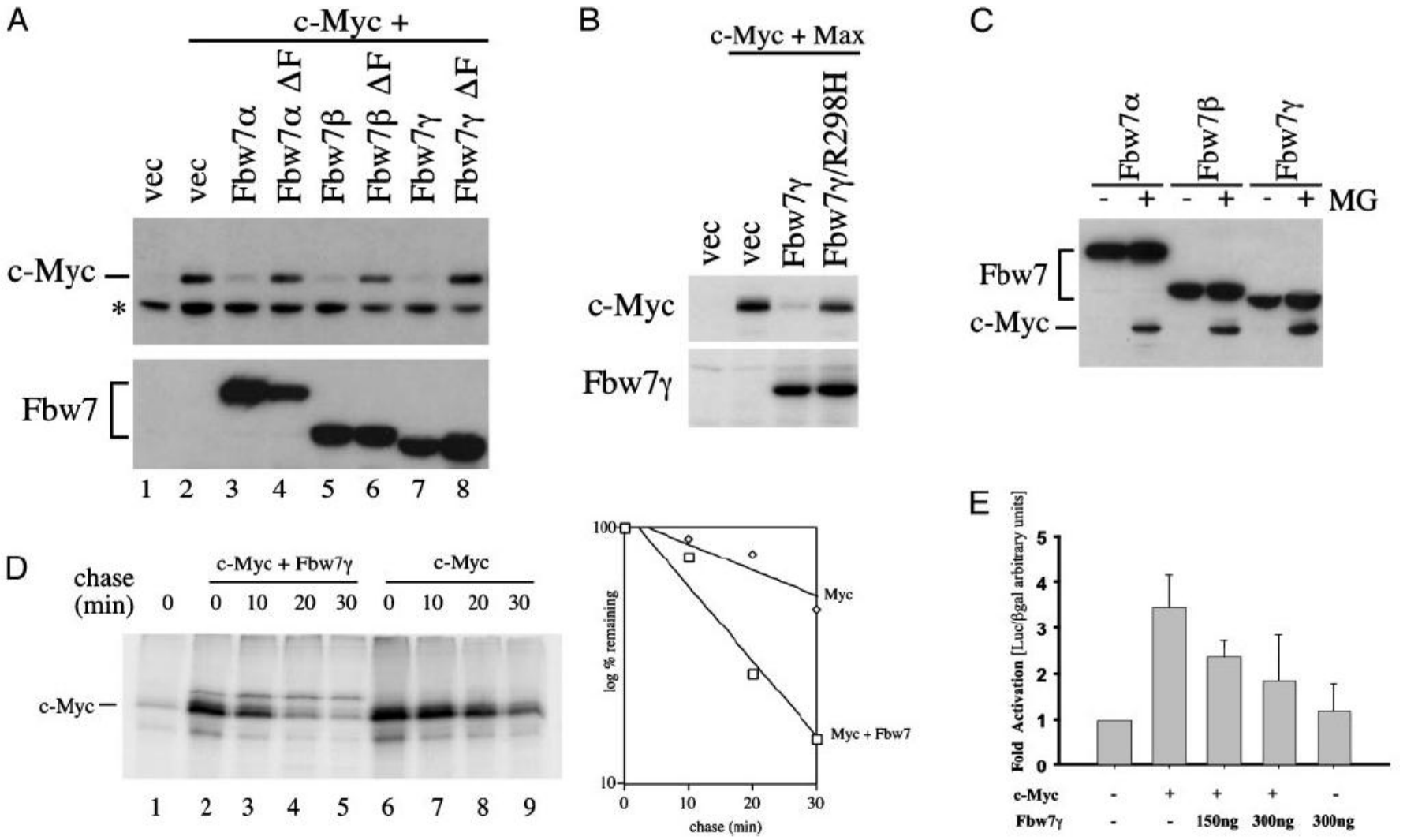
Background


Gene
α
γ
β
2
3
4
5
6
7
8
9
10
11
29Kb
30Kb
1Kb
Transcripts
Exons 2–11
NLS
α
γ
β
TMD
Dimerization
Ub ligase
Substrate binding
DD
F-box
8 × WD40
NLS
Proteins
FBW7α
FBW7β
FBW7γ

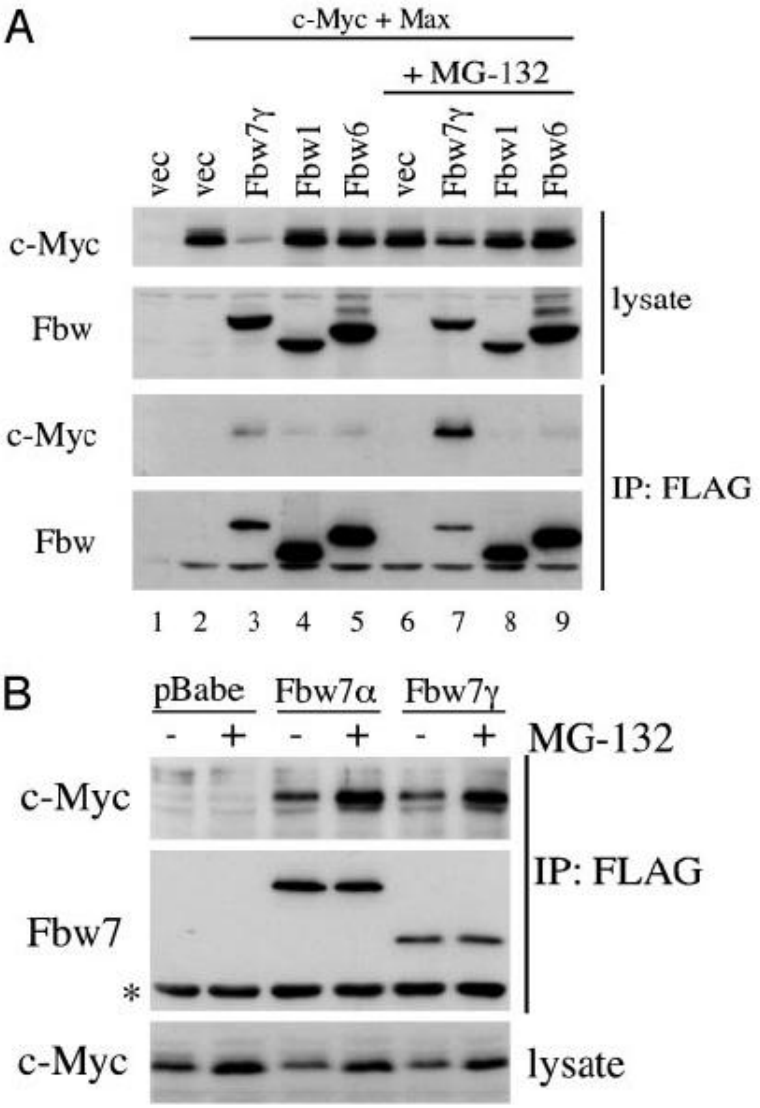
Background


T380
FBW7
P
P
Cyclin E
CDK2
S384
GSK3
UBC
Ub chain
Ub
Ub
Ub
Ub
Ub
Ub
Ub
Ub
Ub
RBX1
CUL1
SKP1
FBW7
P
P
Cyclin E

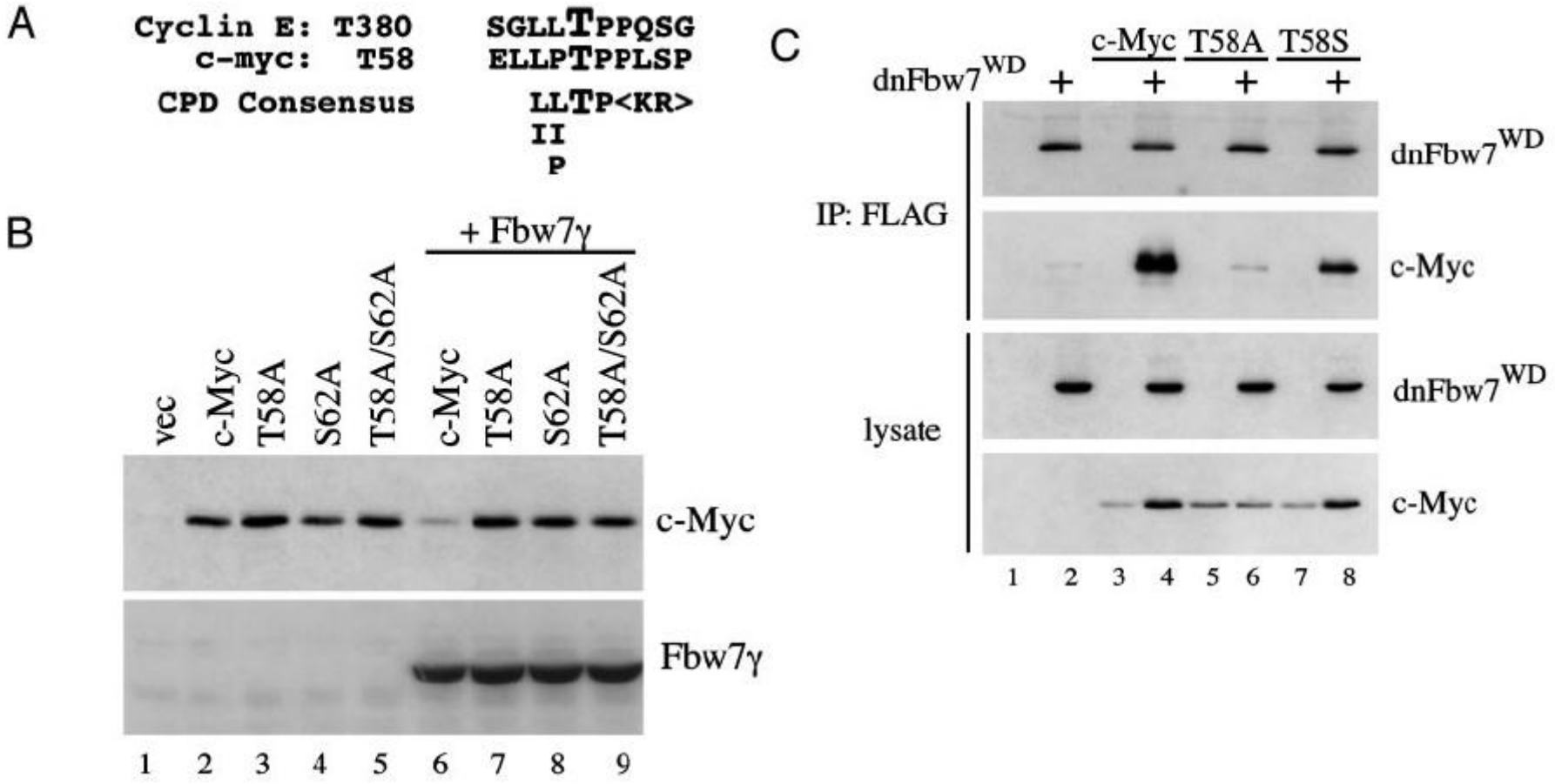
Fbw7 Negatively Regulates c-Myc Turnover and Function



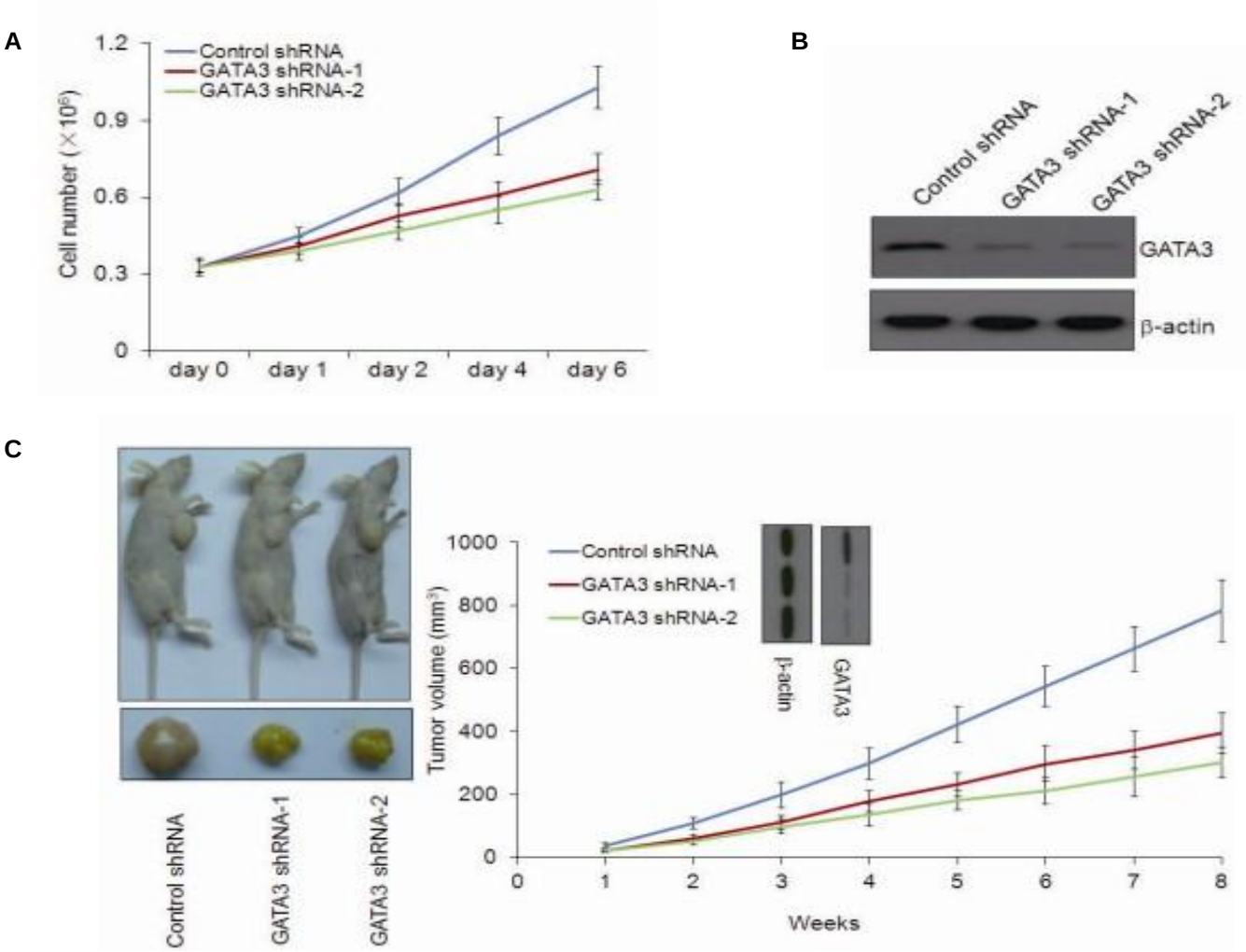
The physical interaction of Fbw7 and c-Myc is sensitive to proteasomal function



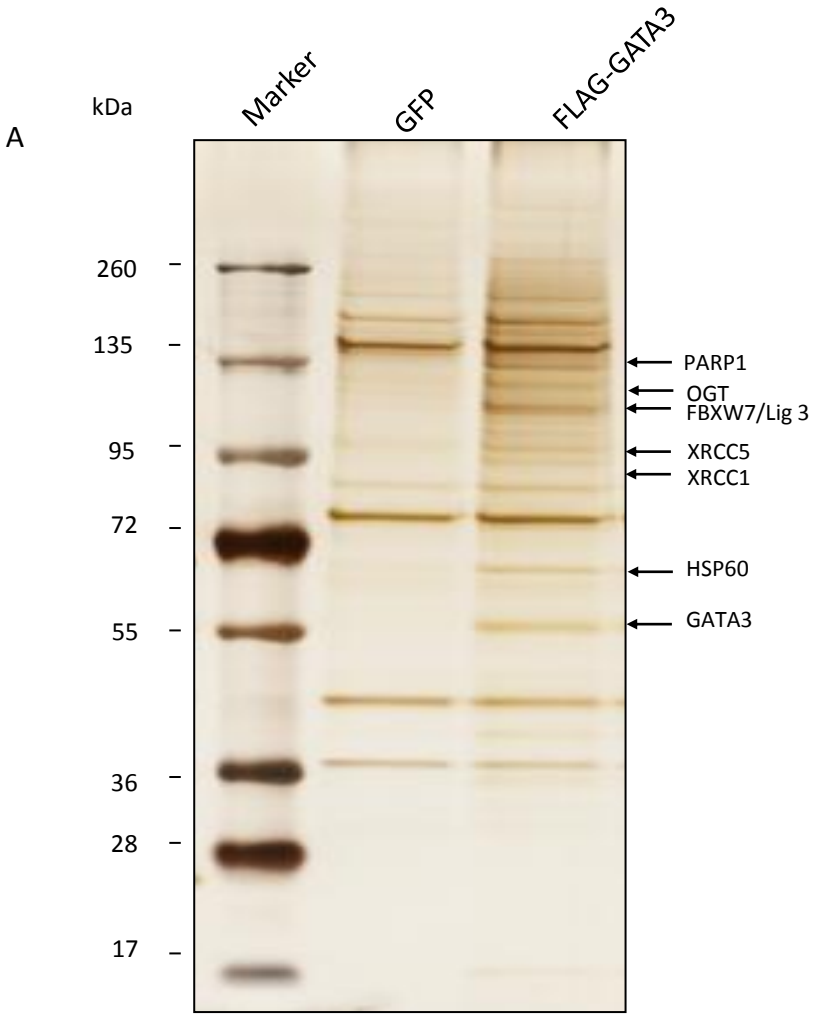
The regulation of c-Myc by Fbw7 requires both GSK-3 activity and c-Myc T58

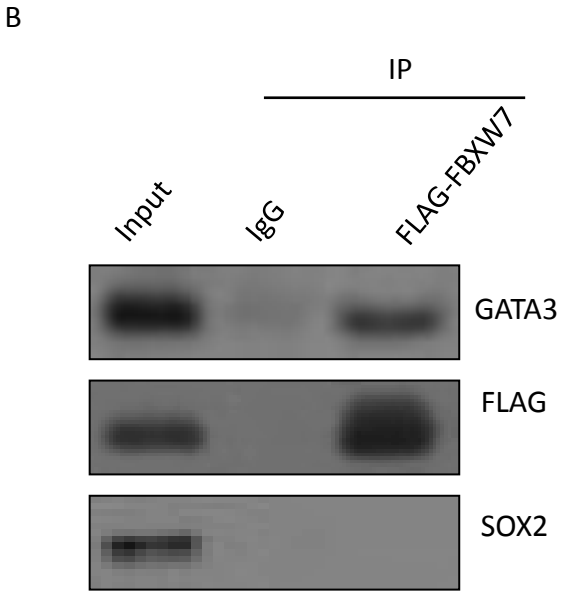


Background

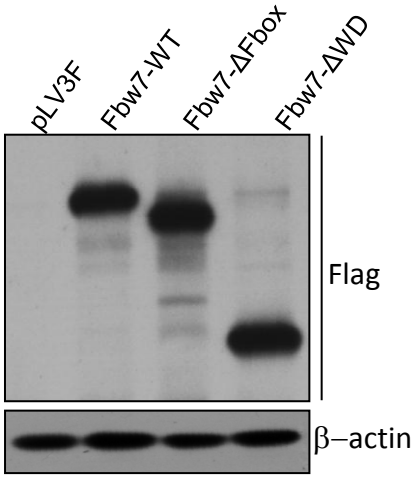

A
Control shRNA
GATA3 shRNA-1
GATA3 shRNA-2
Cell number (×10⁵)
1.2
0.9
0.6
0.3
0
day 0
day 1
day 2
day 4
day 6
B
Control shRNA
GATA3 shRNA-1
GATA3 shRNA-2
GATA3
β-actin
C
Control shRNA
GATA3 shRNA-1
GATA3 shRNA-2
β-actin
GATA3
Tumor volume (mm³)
1000
800
600
400
200
0
0
1
2
3
4
5
6
7
8
Weeks

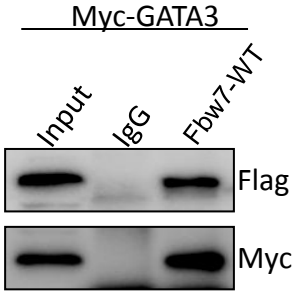
GATA3 interactome

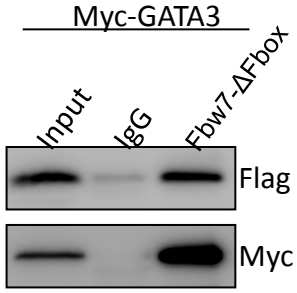


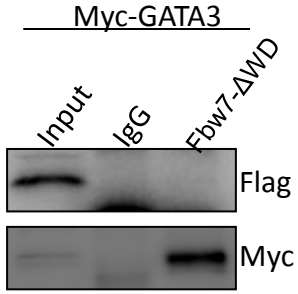


FBXW7 physically associates with GATA3

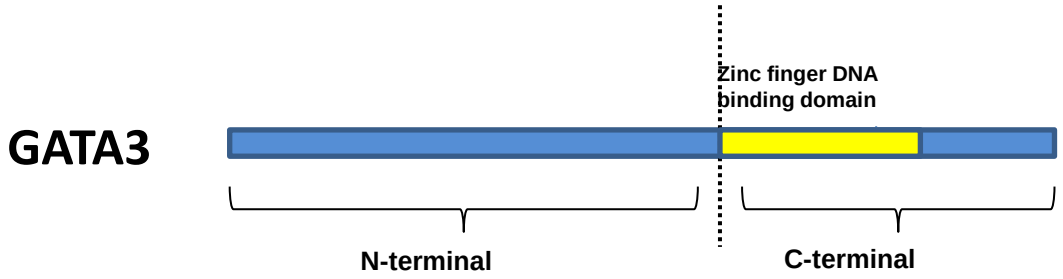


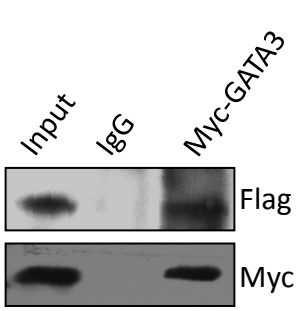


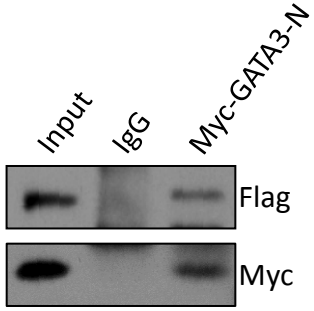


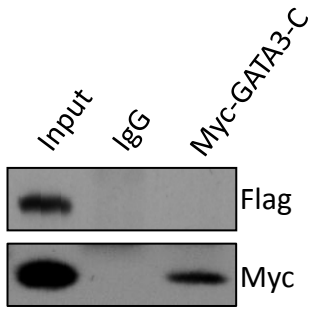


FBXW7 physically associates with GATA3

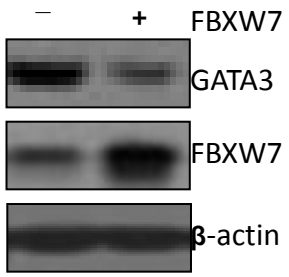


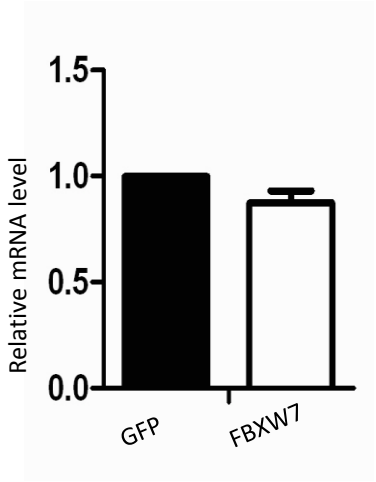


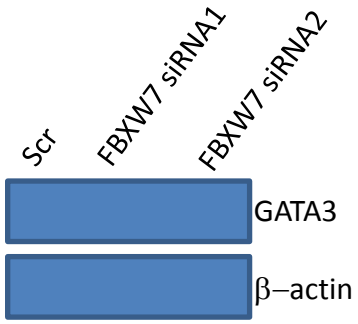




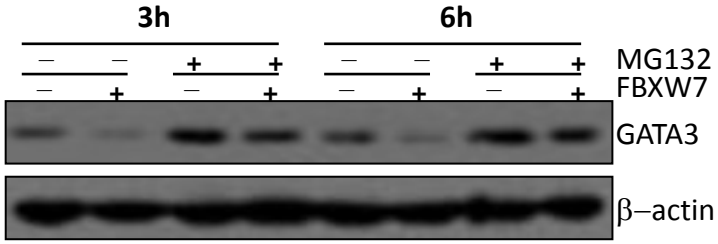
FBXW7 regulates GATA3 stability

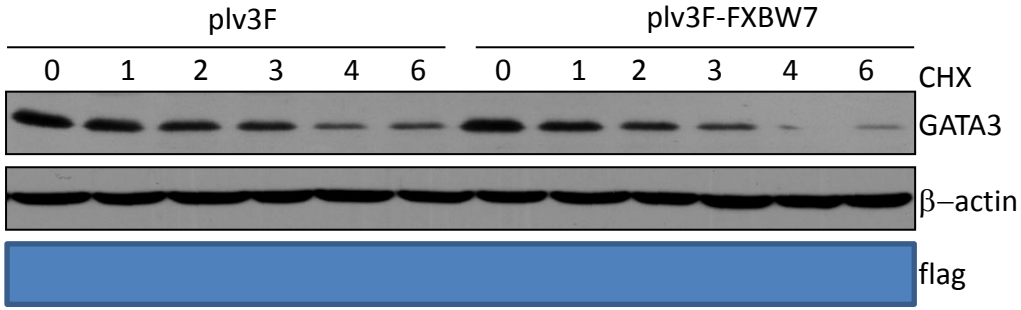




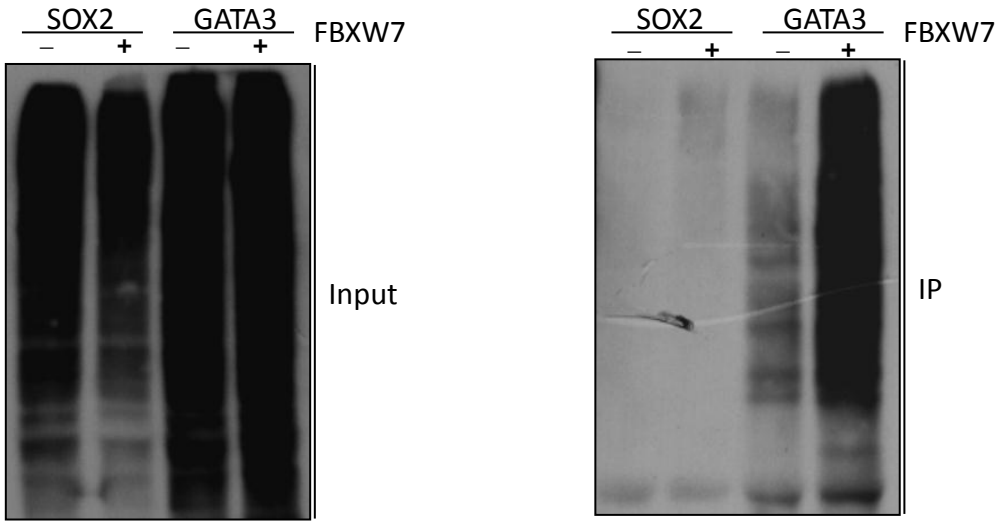


FBXW7 regulates GATA3 stability

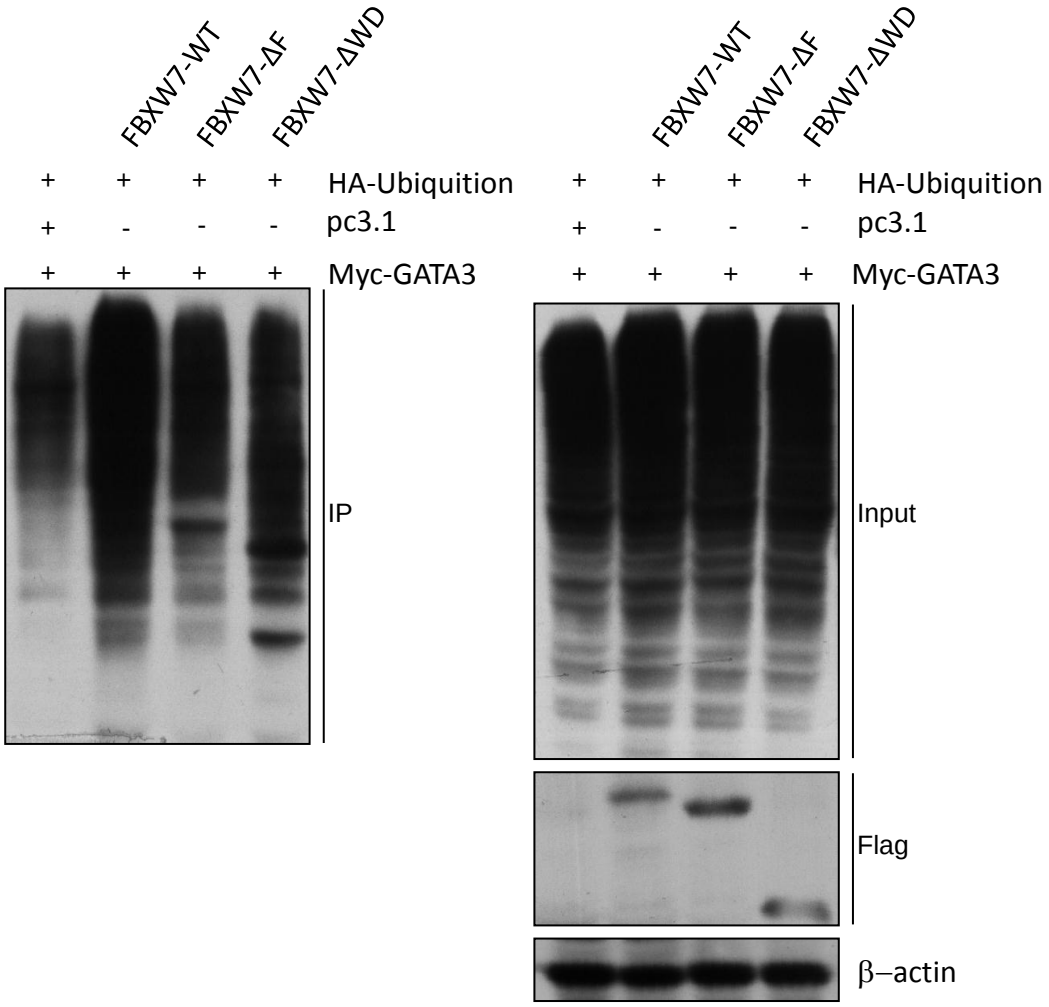




FBXW7 promotes GATA3 ubiquitination



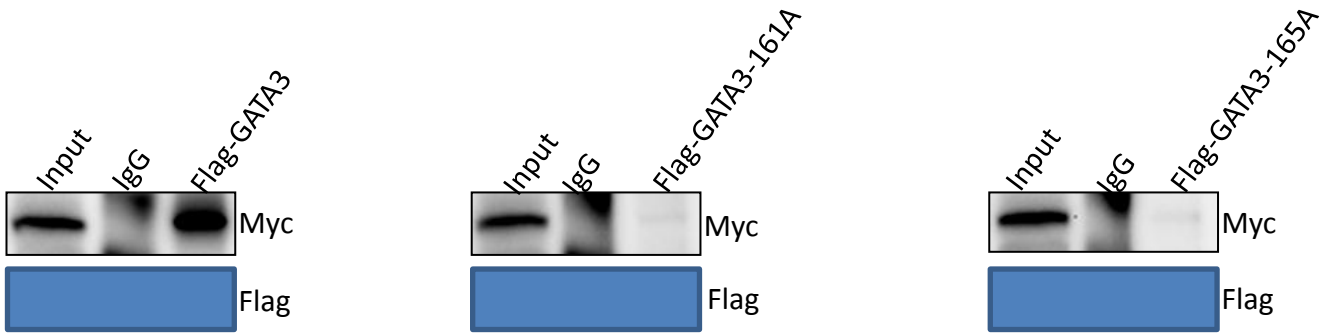
FBXW7 promotes GATA3 ubiquitination



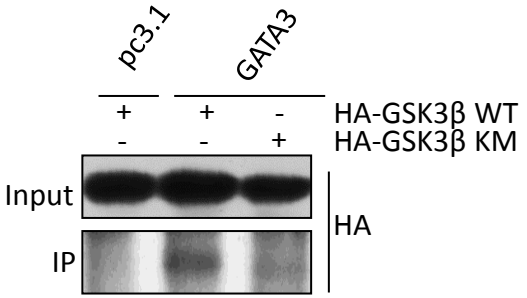
FBXW7-catalyzed GATA3 turnover requires GATA3 serine-161/165 and GSK3β

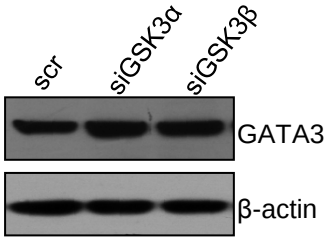
Cyclin E	378	LL	T	PPQ	S	G	385
c-Myc	56	LP	T	PPL	S	P	63
GATA3	159	DV	S	PDP	S	L	166

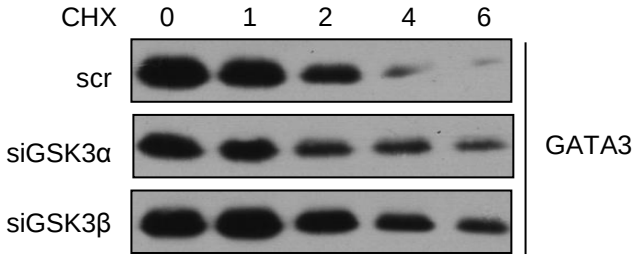
FBXW7 phosphodegron

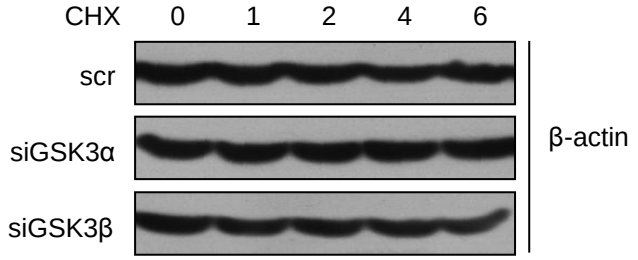


FBXW7-catalyzed GATA3 turnover requires GATA3 serine-161/165 and GSK3β

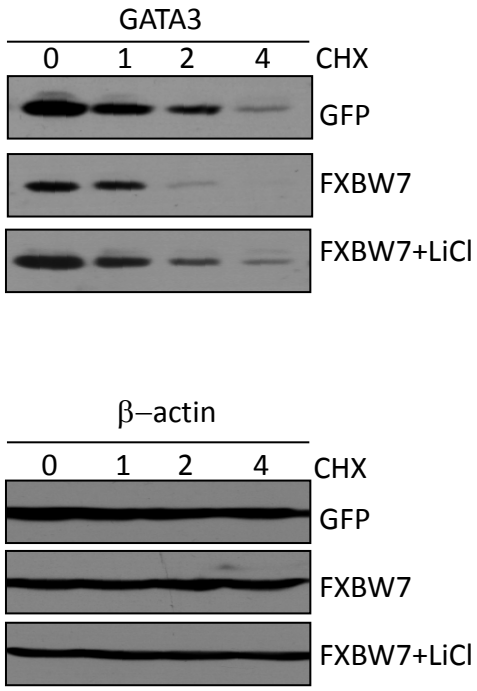


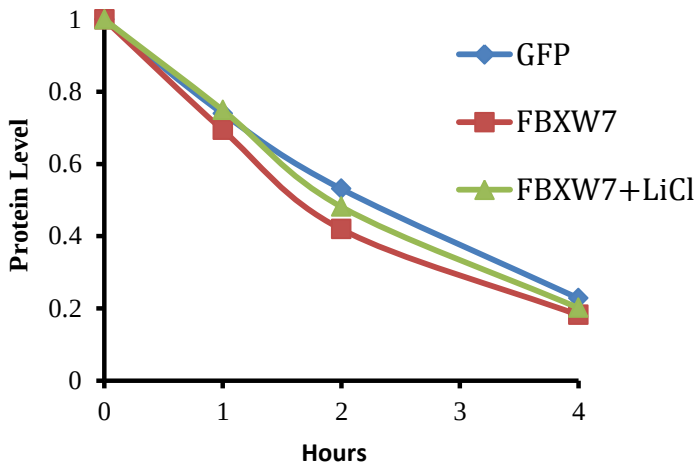




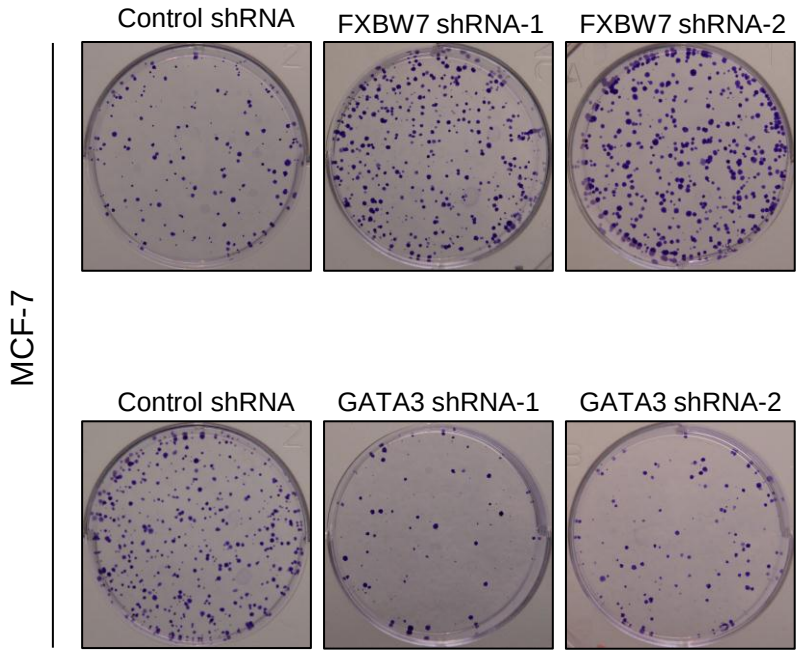


FBXW7-catalyzed GATA3 turnover requires GATA3 serine-161/165 and GSK3β





phenotype


Control shRNA
FXBW7 shRNA-1
FXBW7 shRNA-2
MCF-7
Control shRNA
GATA3 shRNA-1
GATA3 shRNA-2

Thanks for your attention!