

Figure 1

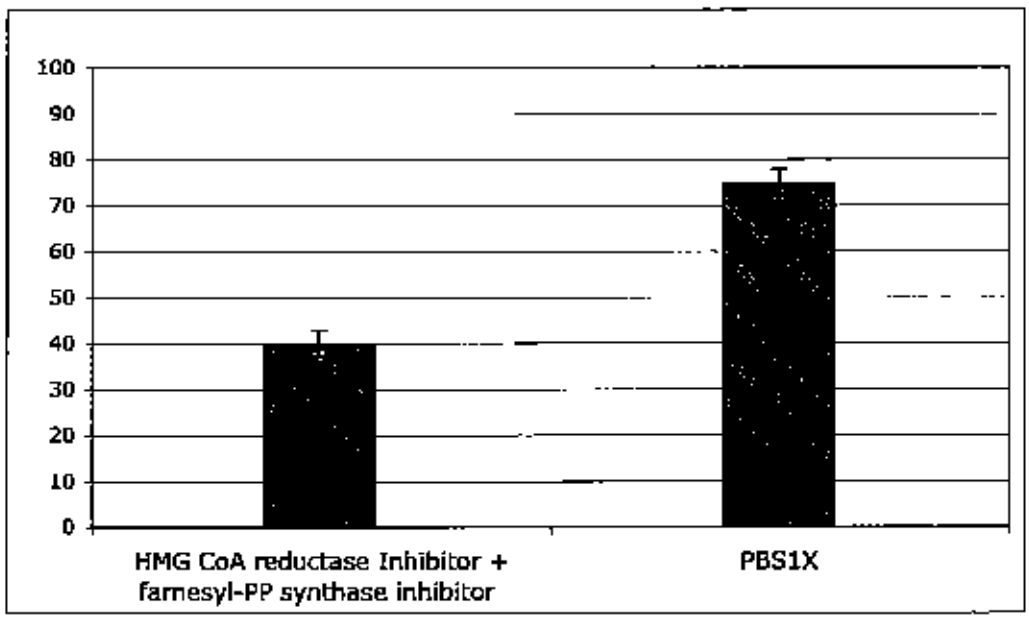


Figure 2

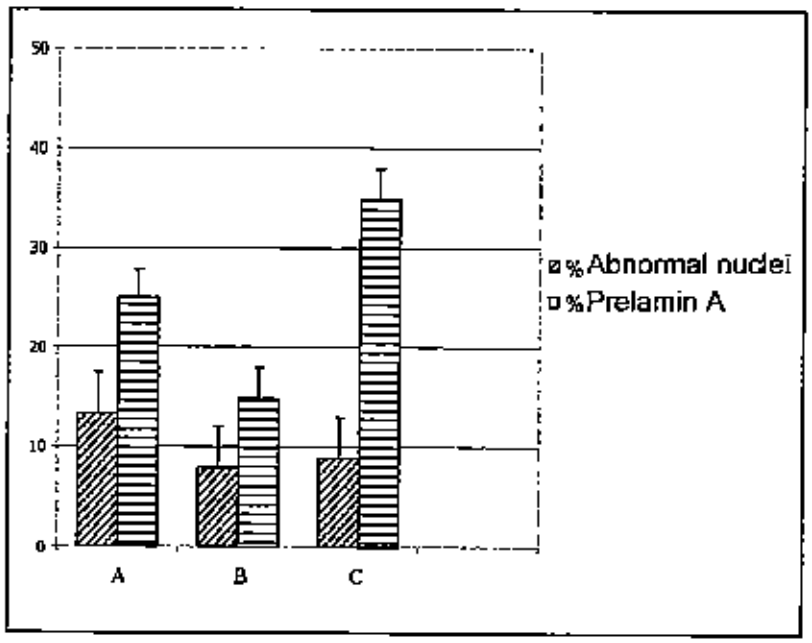


Figure 3

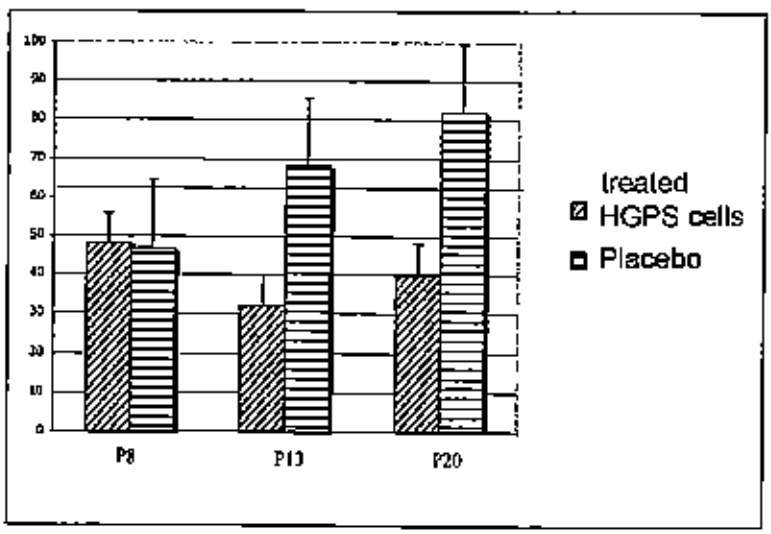


Figure 4

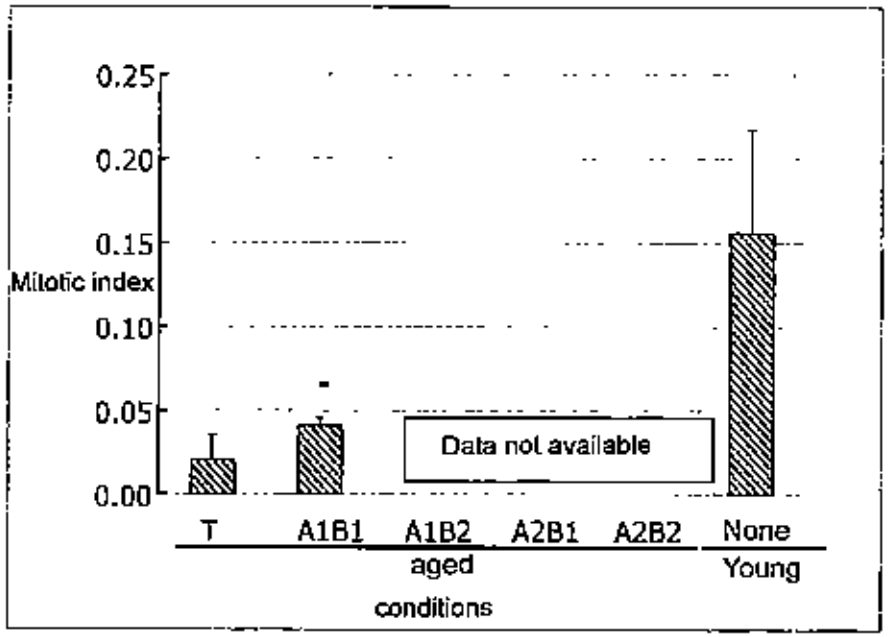


Figure 5

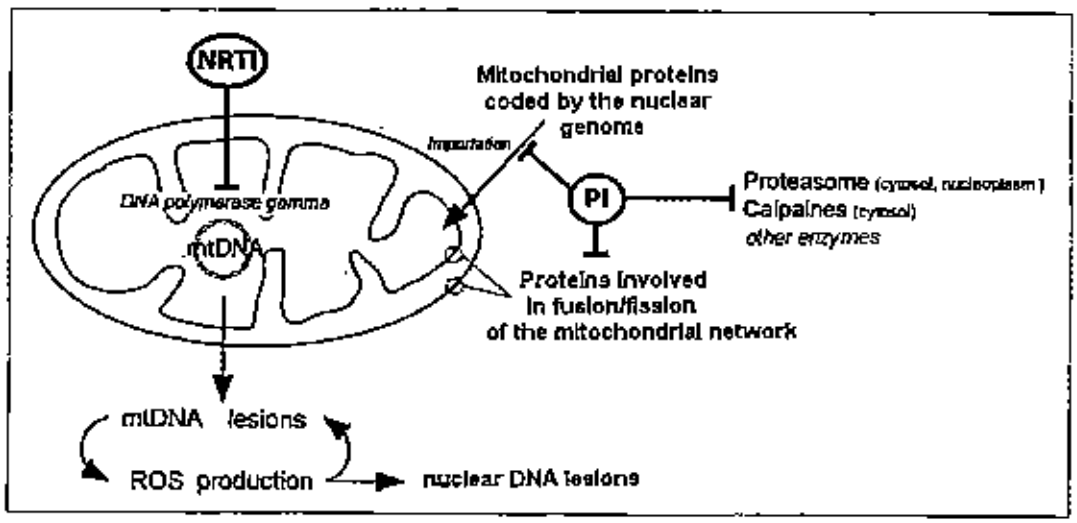


Figure 6

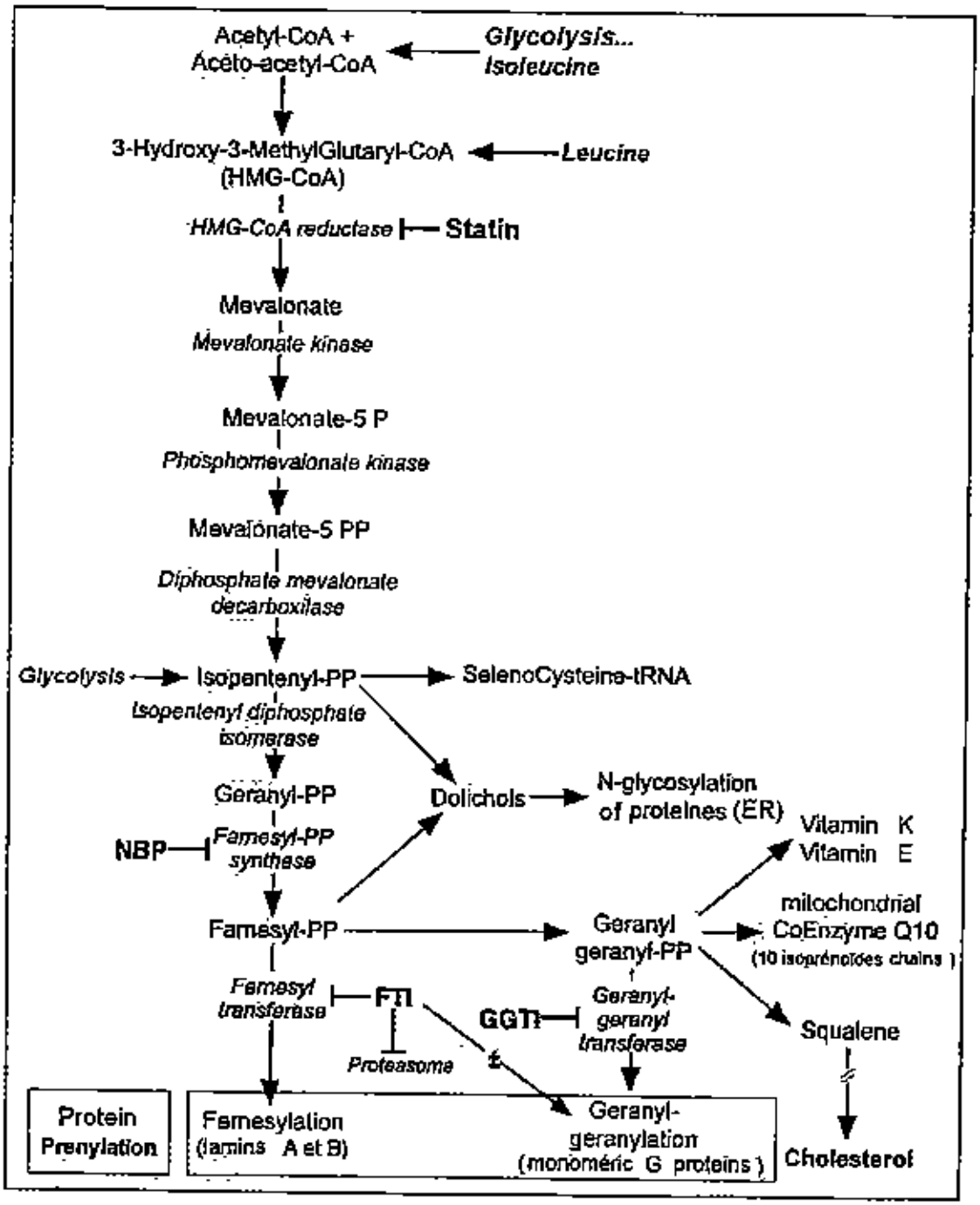

Acetyl-CoA +
Acéto-acetyl-CoA
Glycolysis...
Isoleucine
3-Hydroxy-3-MethylGlutaryl-CoA
(HMG-CoA)
Leucine
HMG-CoA reductase
Statin
Mevalonate
Mevalonate kinase
Mevalonate-5 P
Phosphomevalonate kinase
Mevalonate-5 PP
Diphosphate mevalonate decarboxilase
Glycolysis
Isopentenyl-PP
SelenoCysteine-tRNA
Isopentenyl diphosphate isomerase
Geranyl-PP
Dolichols
N-glycosylation of proteines (ER)
NBP
Farnesyl-PP synthese
Vitamin K
Vitamin E
Farnesyl-PP
Geranyl geranyl-PP
mitochondrial CoEnzyme Q10
(10 isoprénoïdes chains)
Farnesyl transferase
FTI
Proteasome
GGTI
Geranyl-geranyl transferase
Squalene
Protein Prenylation
Farnesylation
(lamins A et B)
Geranyl-geranylation
(monomeric G proteins)
Cholesterol

Figure 7

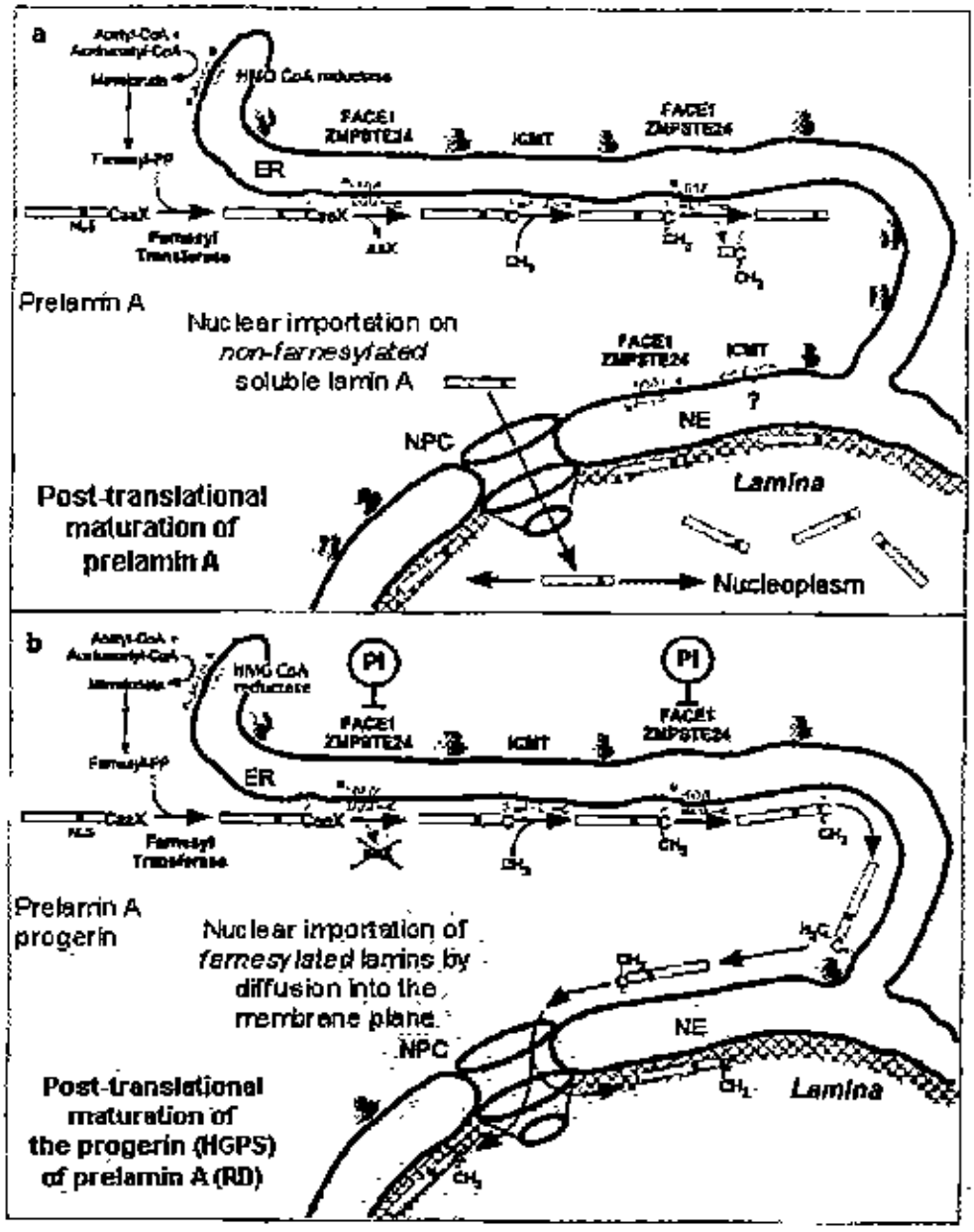

a
HMG CoA reductase
FACE1
ZMPSTE24
ICMT
FACE1
ZMPSTE24
ER
CaaX
Farnesyl
Transferase
AAX
Prelamin A
Nuclear importation of
non-farnesylated
soluble lamin A
FACE1
ZMPSTE24
ICMT
?
NE
NPC
Lamina
Post-translational
maturation of
prelamin A
Nucleoplasm
b
HMG CoA
reductase
PI
PI
FACE1
ZMPSTE24
ICMT
FACE1
ZMPSTE24
ER
CaaX
Farnesyl
Transferase
Prelamin A
progerin
Nuclear importation of
farnesylated lamins by
diffusion into the
membrane plane.
NE
NPC
Lamina
Post-translational
maturation of
the progerin (HGPS)
of prelamin A (RD)

Figure 8

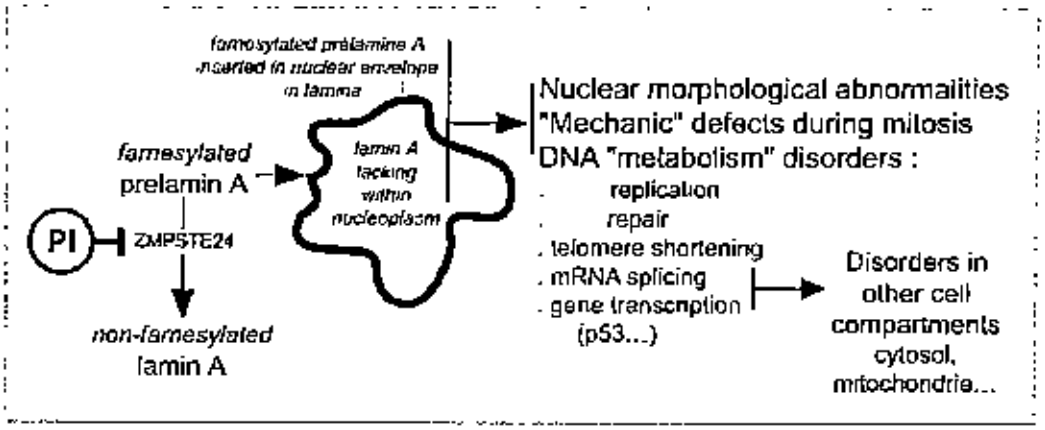


Figure 9

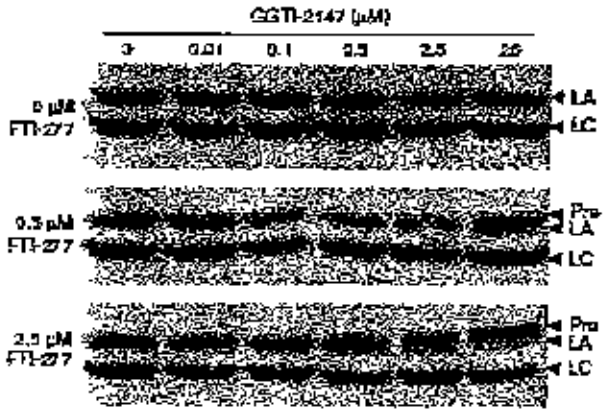


Figure 10

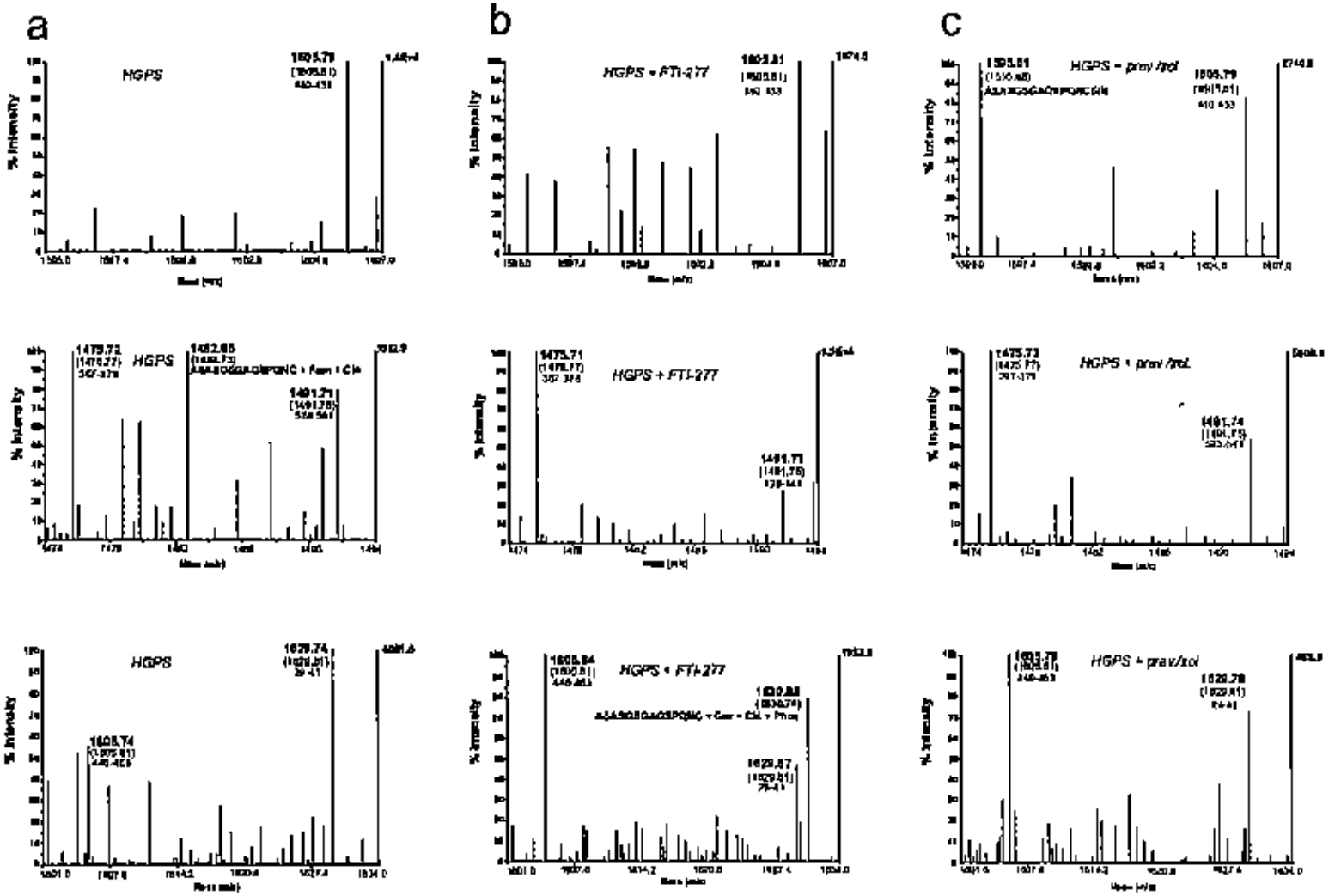


FIGURE 11

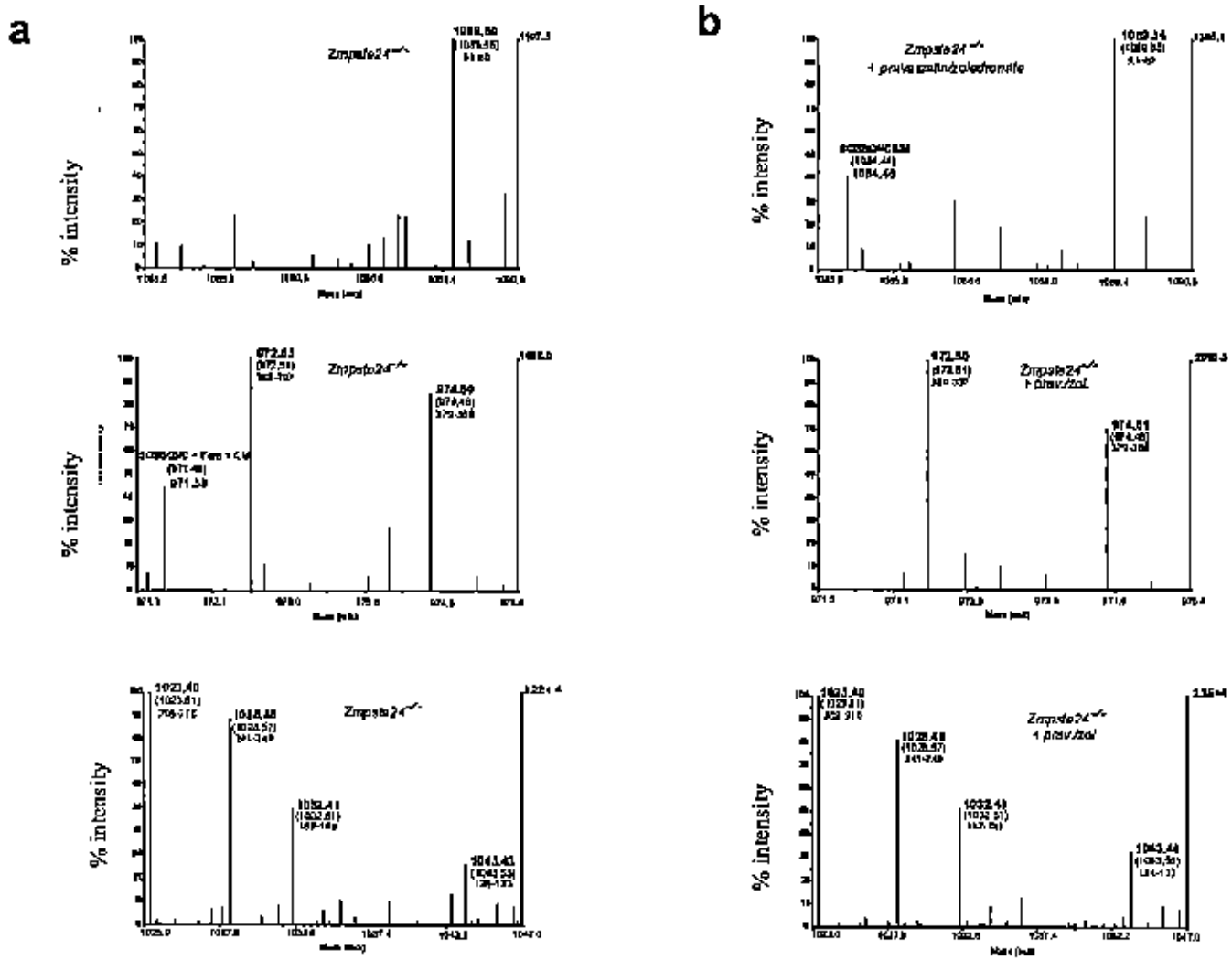

a
b
% intensity
% intensity
% intensity
% intensity
% intensity
% intensity

FIGURE 12

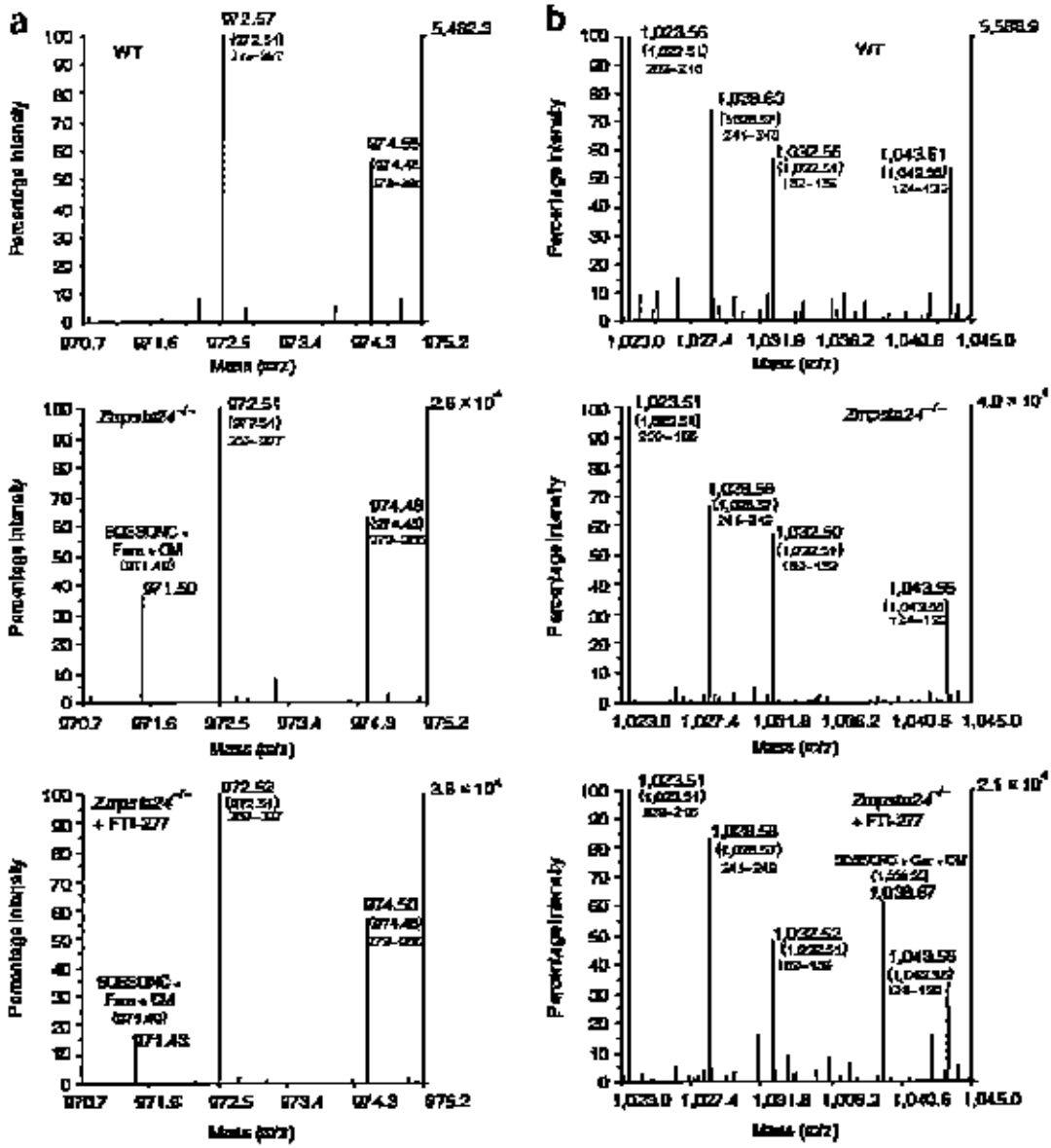

a
WT
Percentage Intensity
Mass (m/z)
b
WT
Percentage Intensity
Mass (m/z)
Zmpste24−/−
Zmpste24−/− + FTI-277

FIGURE 13

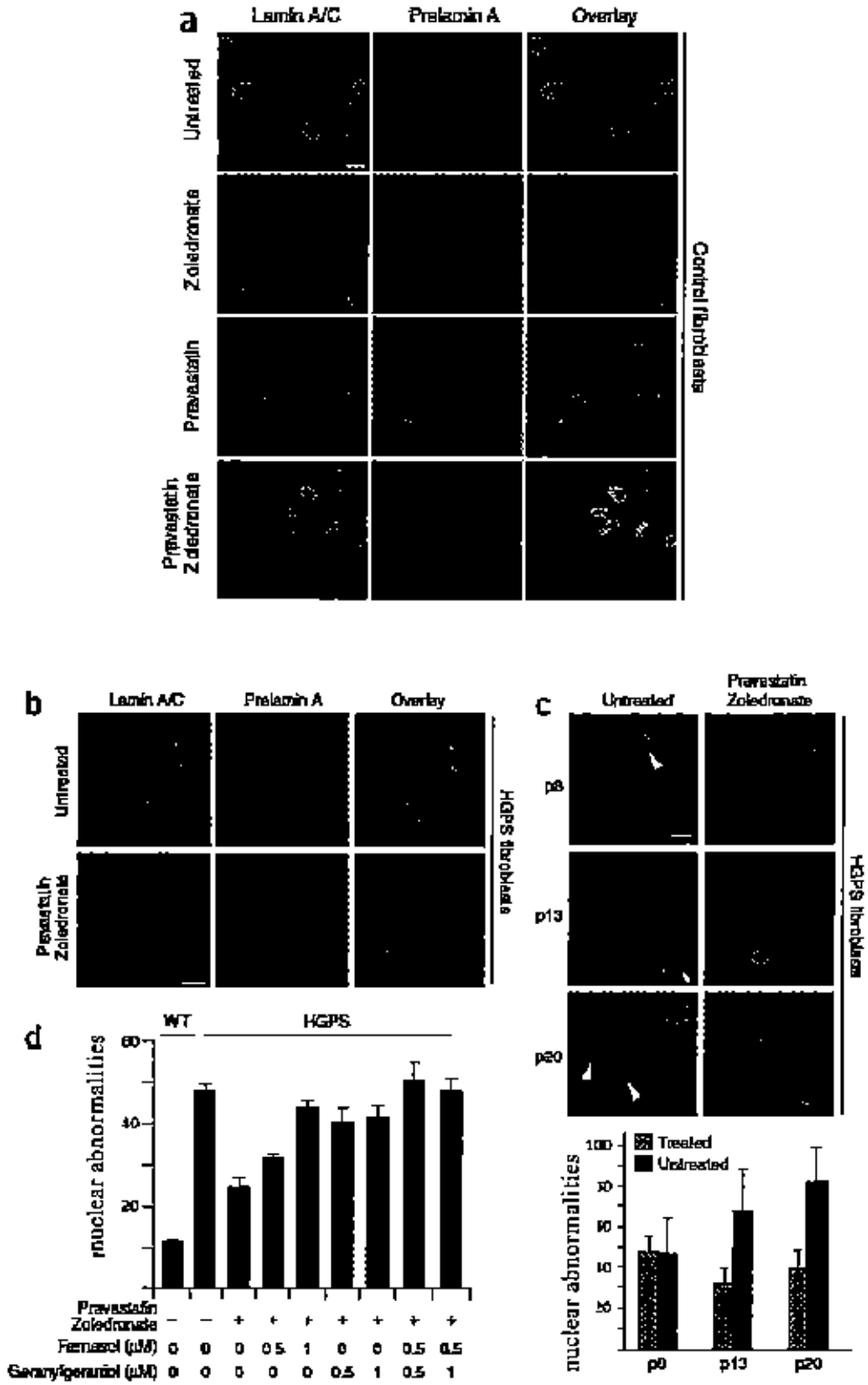

a
Lamin A/C
Prelamin A
Overlay
Untreated
Zoledronate
Pravastatin
Pravastatin Zoledronate
Control fibroblasts
b
Lamin A/C
Prelamin A
Overlay
Untreated
Pravastatin Zoledronate
HGPS fibroblasts
c
Untreated
Pravastatin Zoledronate
p8
p13
p20
HGPS fibroblasts
Treated
Untreated
nuclear abnormalities
p0
p13
p20
d
WT
HGPS
nuclear abnormalities
Pravastatin
Zoledronate
Farnesol (μM)
Geranylgeraniol (μM)

FIGURE 14

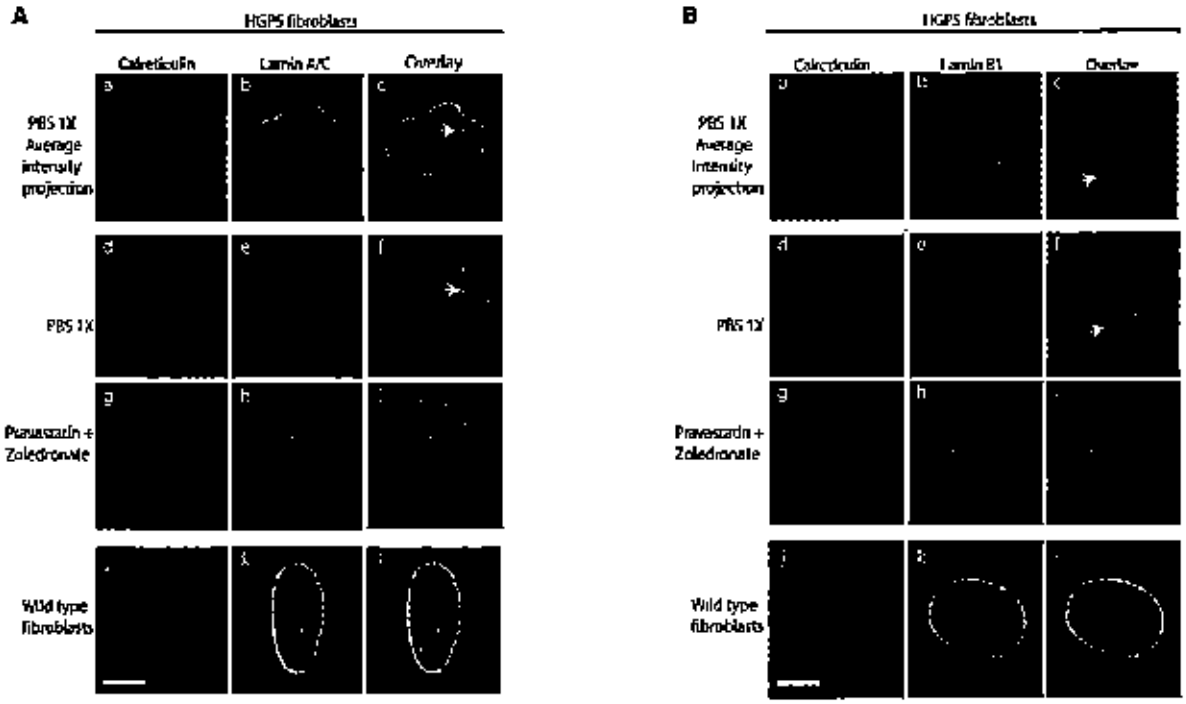
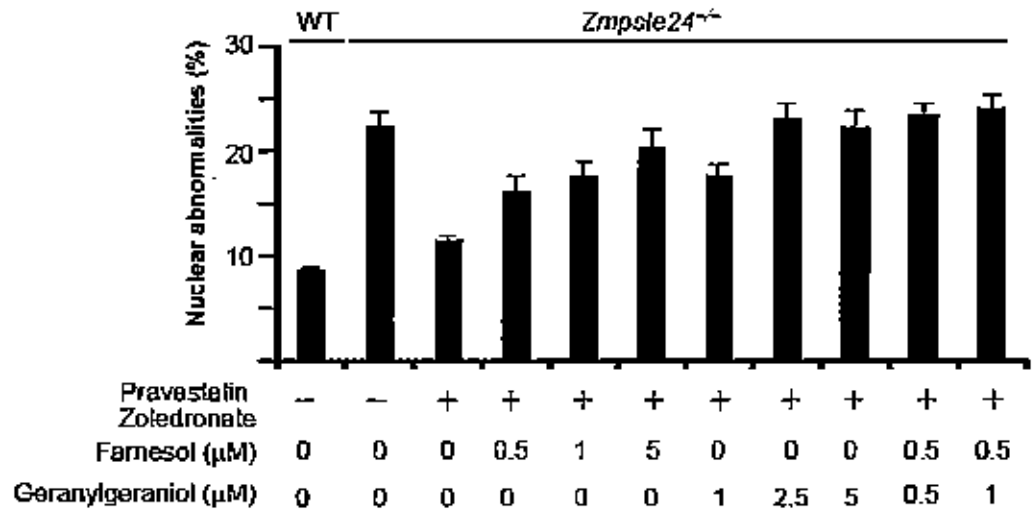
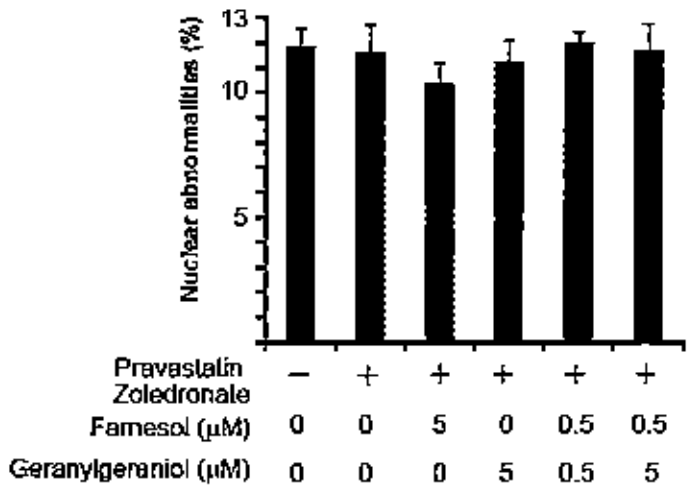

A
HGPS fibroblasts
Calreticulin
Lamin A/C
Overlay
PBS 1X Average intensity projection
PBS 1X
Pravastatin + Zoledronate
Wild type fibroblasts
B
HGPS fibroblasts
Calreticulin
Lamin B1
Overlay
PBS 1X Average intensity projection
PBS 1X
Pravastatin + Zoledronate
Wild type fibroblasts

Figure 15

a



b



Figures 16

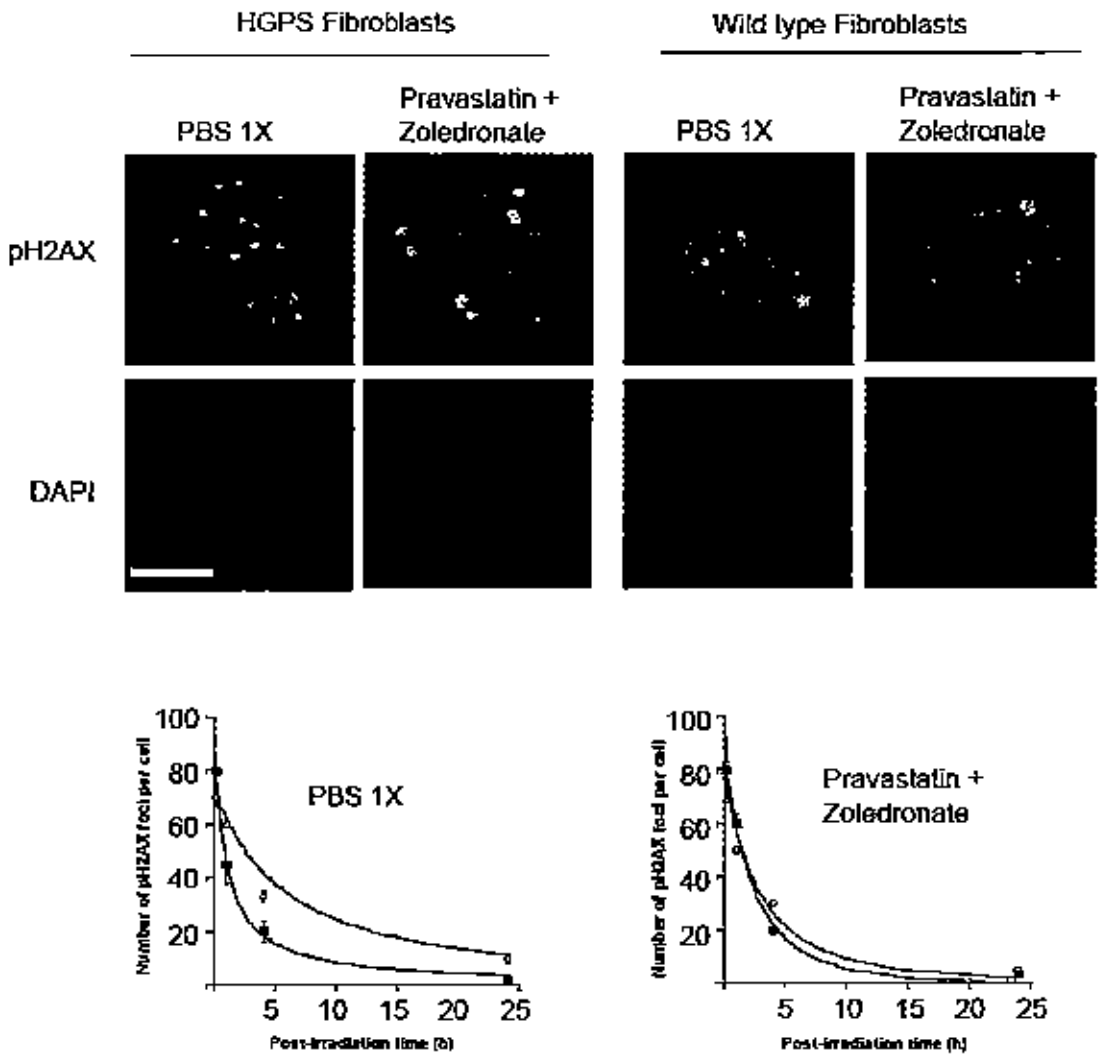

HGPS Fibroblasts
Wild type Fibroblasts
PBS 1X
Pravastatin + Zoledronate
PBS 1X
Pravastatin + Zoledronate
pH2AX
DAPI
PBS 1X
Pravastatin + Zoledronate
Number of pH2AX foci per cell
Post-irradiation time (h)
100
80
60
40
20
5
10
15
20
25

Figure 17

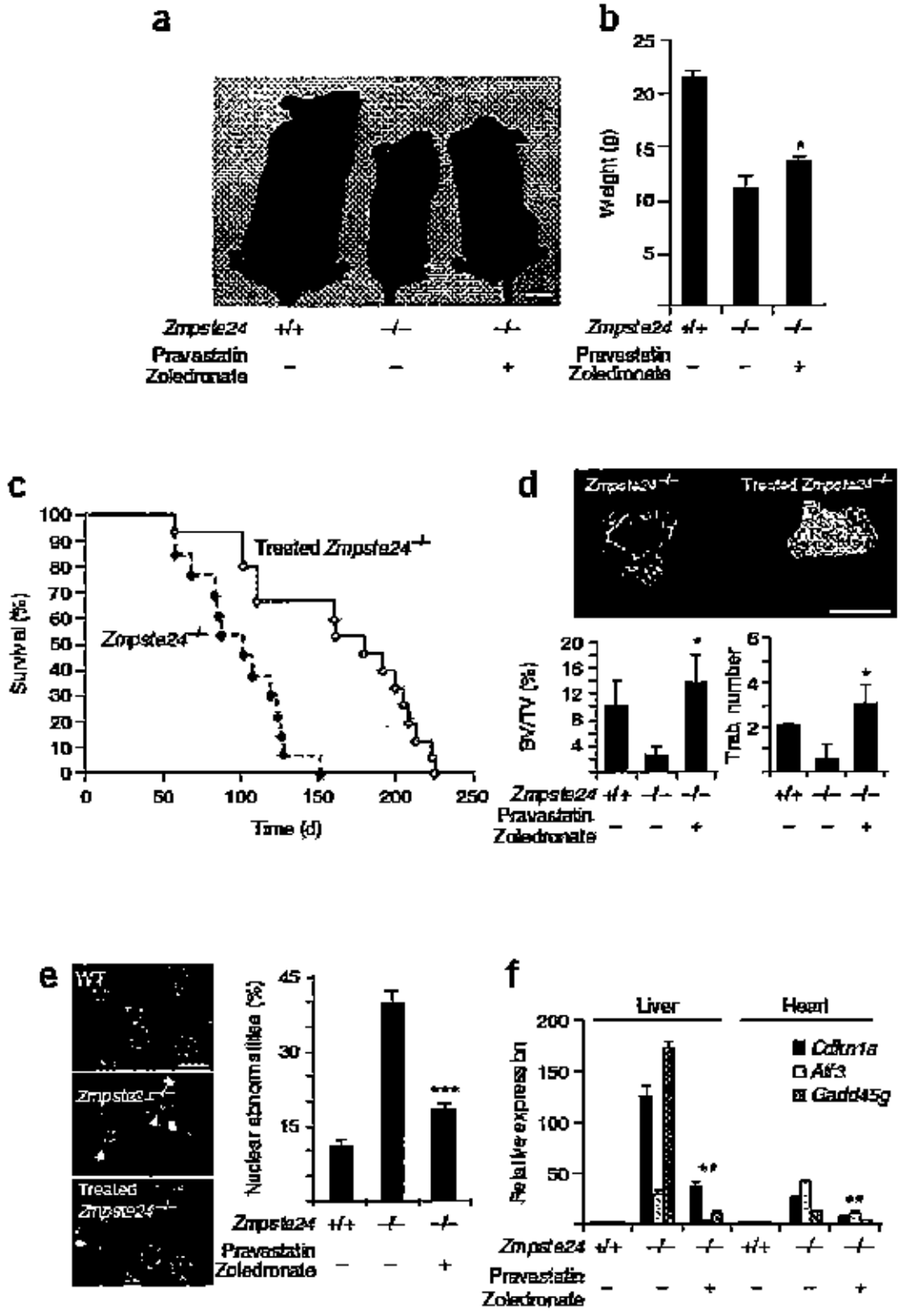
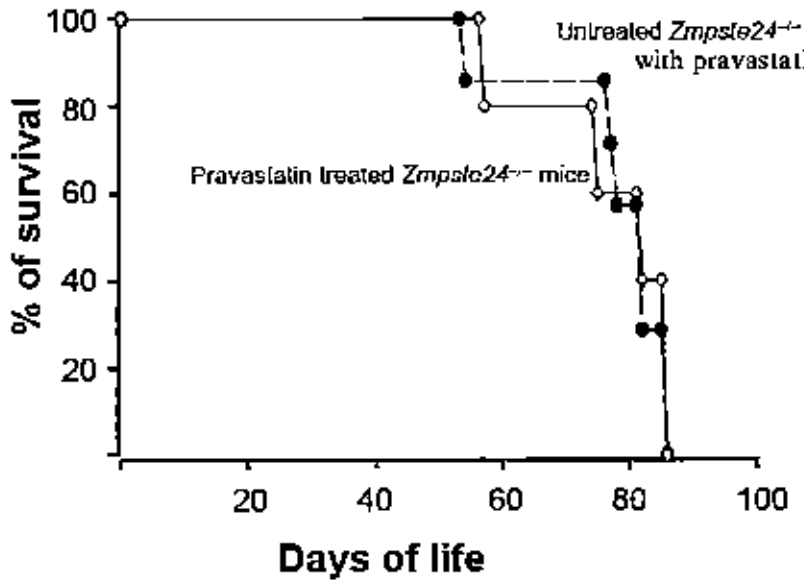

a
b
Zmpste24 +/+ −/− −/−
Pravastatin − − +
Zoledronate
Weight (g)
c
Survival (%)
Time (d)
Treated Zmpste24−/−
Zmpste24−/−
d
BV/TV (%)
Trab. number
e
WT
Zmpste24−/−
Treated Zmpste24−/−
Nuclear abnormalities (%)
***
f
Liver
Heart
Cdkn1a
Atf3
Gadd45g
Relative expression
**

FIGURE 18

a


100
80
60
40
20
% of survival
20
40
60
80
100
Days of life
Untreated Zmpste24-/- mice with pravastatine
Pravastatin treated Zmpste24-/- mice

b

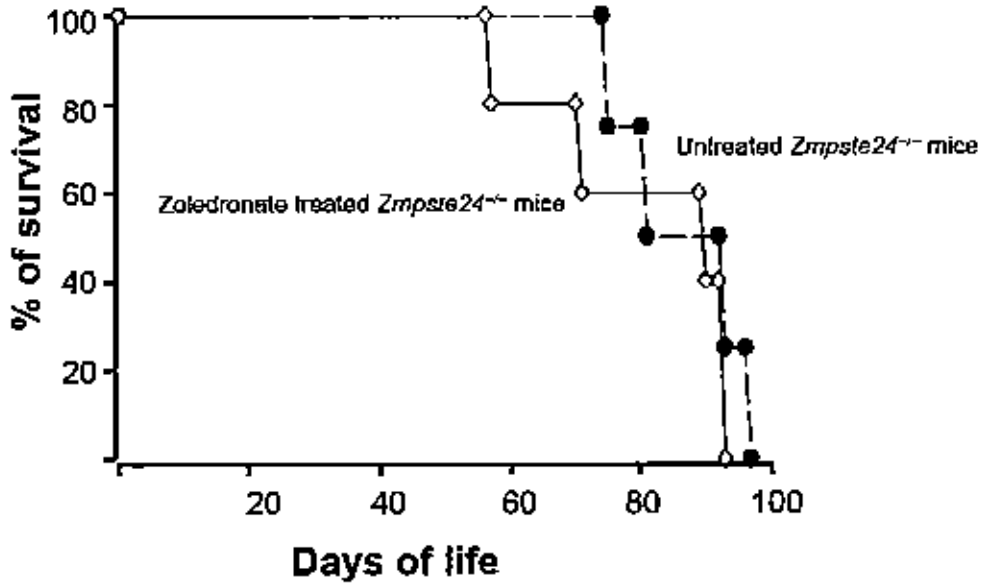

100
80
60
40
20
% of survival
20
40
60
80
100
Days of life
Untreated Zmpste24-/- mice
Zoledronate treated Zmpste24-/- mice

Figure 19

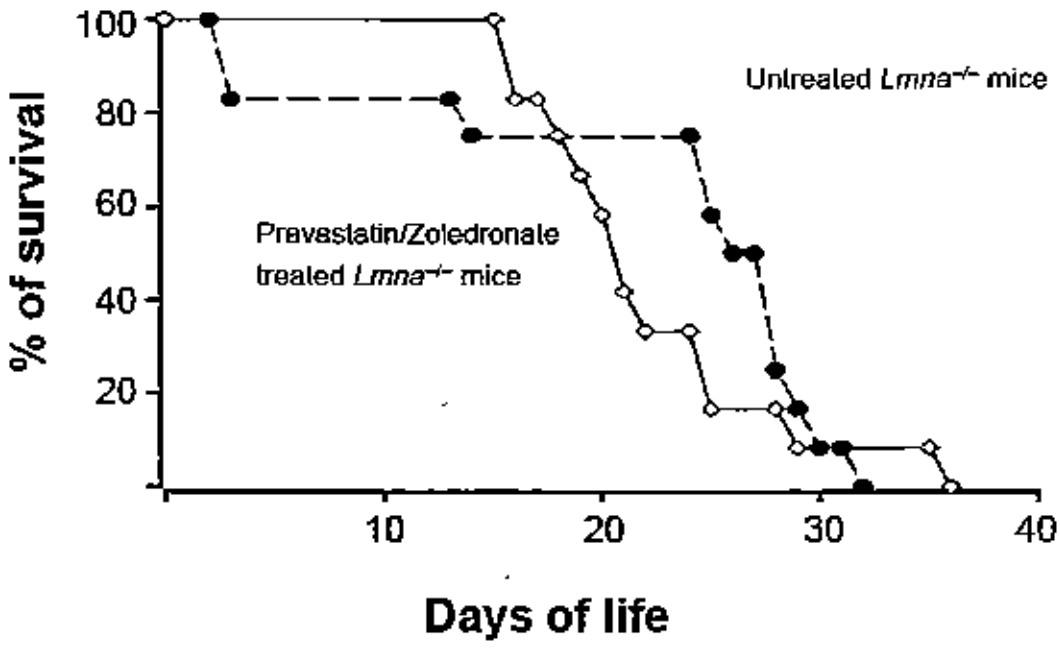

100
80
60
40
20
% of survival
Untreated Lmna-/- mice
Pravastatin/Zoledronate
treated Lmna-/- mice
10
20
30
40
Days of life

Figure 20