RICE ENGINEERING
Bioengineering

**Systems, Synthetic, and Physical Biology**

SSPB RICE

# Functional interactions of nanomaterials with cellular clearance and stress response pathways


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**Cell and Protein Engineering Research**


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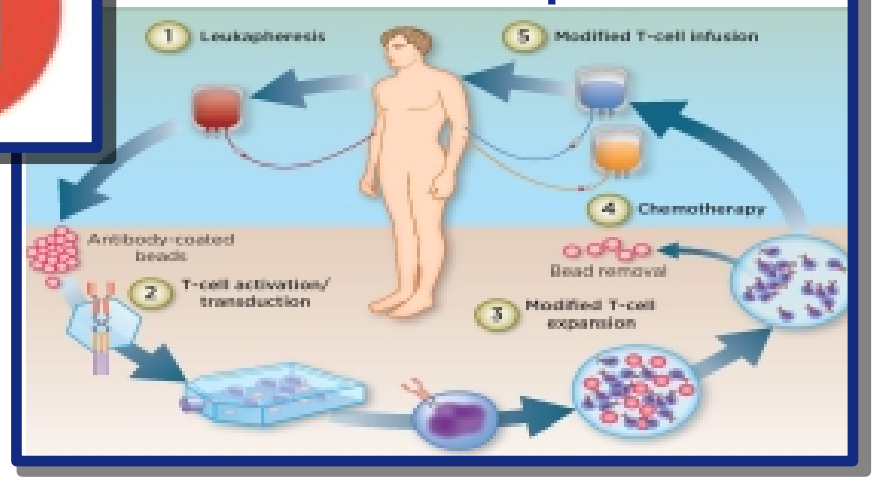
# Designer cells that sense and respond

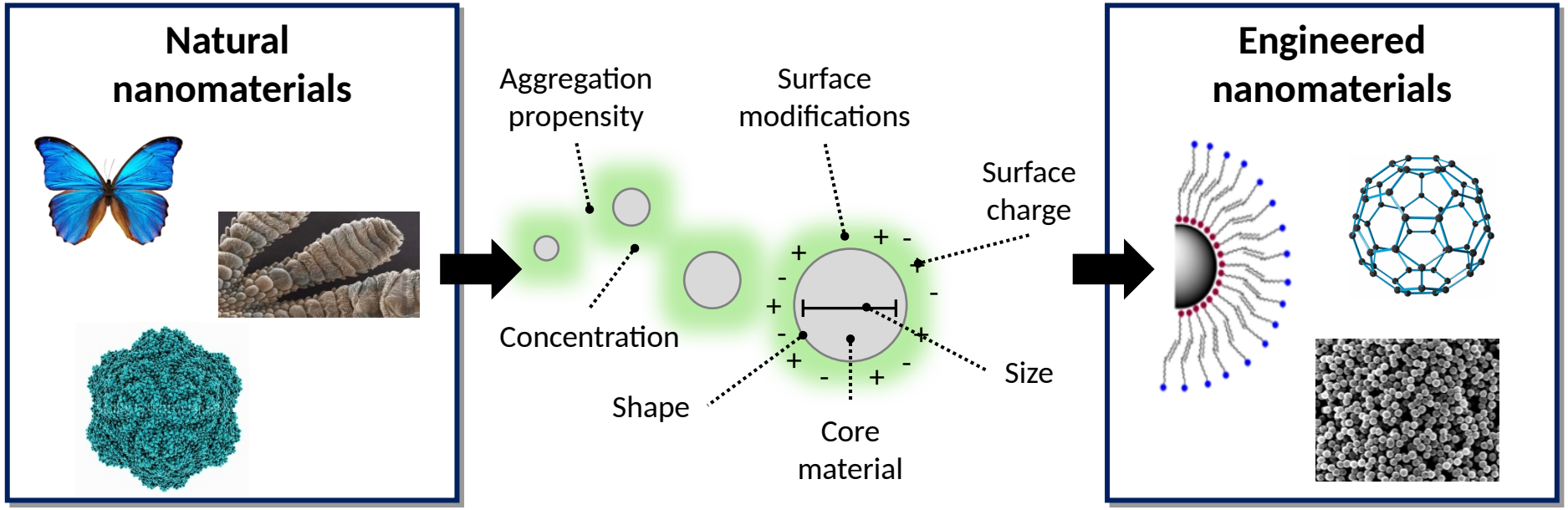
## Biomanufacturing

## Diagnostics

## Cell therapies

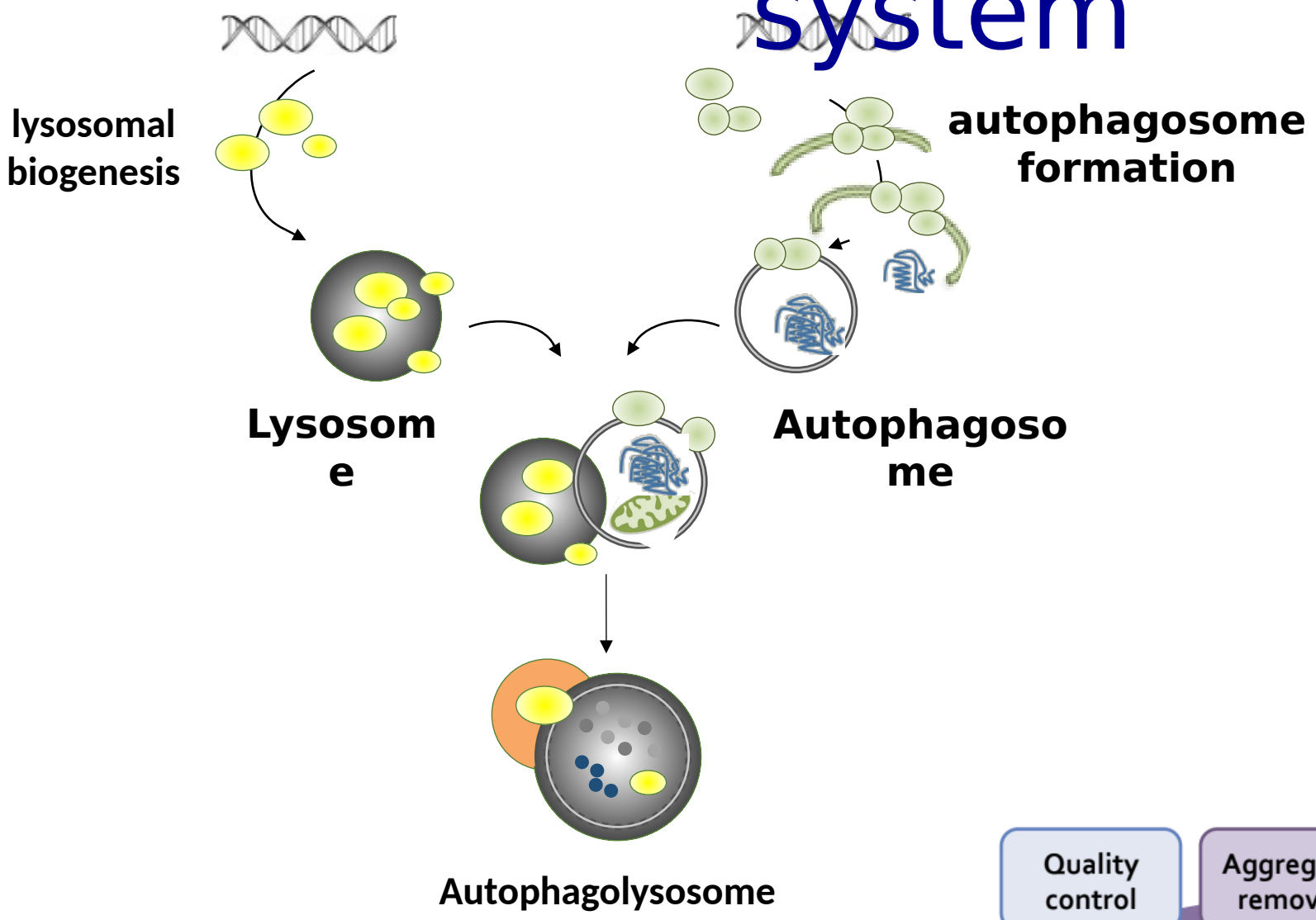


# Understanding nano-bio interfaces

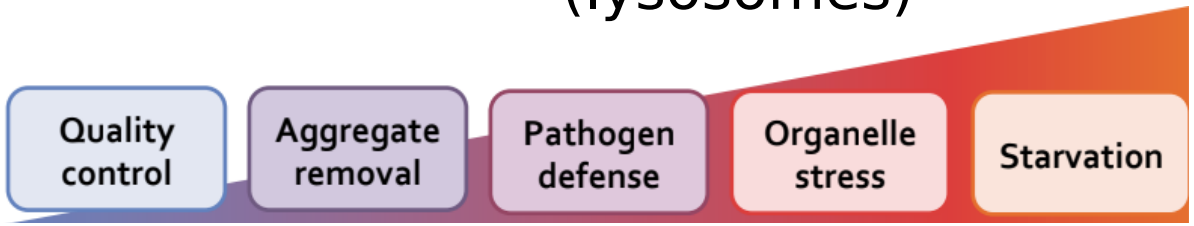



When nano-sized materials are internalized into cells, they are likely to be perceived as foreign or toxic and may stimulate the activation of cellular clearance and stress response pathways

# The lysosome-autophagy system



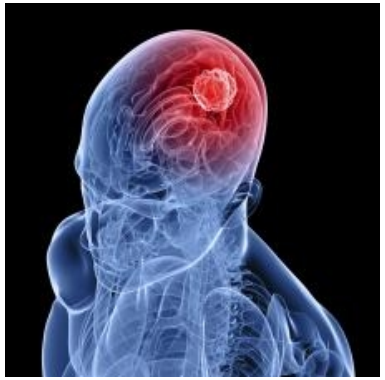

- → Nano size
- → Perceived as foreign or toxic by cells
- → Indirect response to nanoparticle effect on cell physiology (oxidative stress)
- → Specific interaction with cellular components (lysosomes)

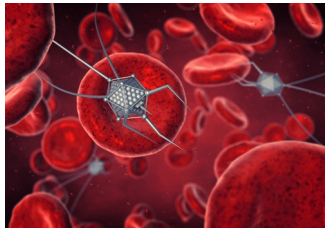


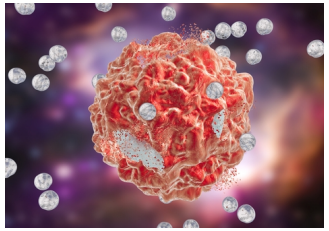
# Significance: environmental health and safety of nanomaterials


**Health & safety**

Consumer products
Industrial production of nanoparticles

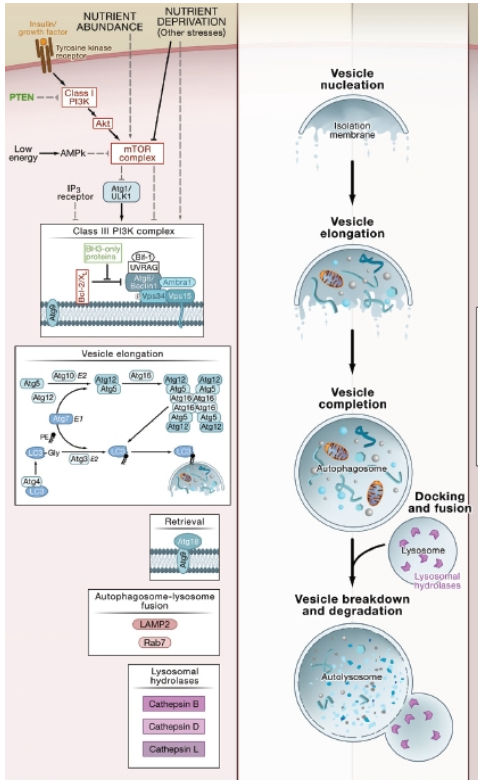






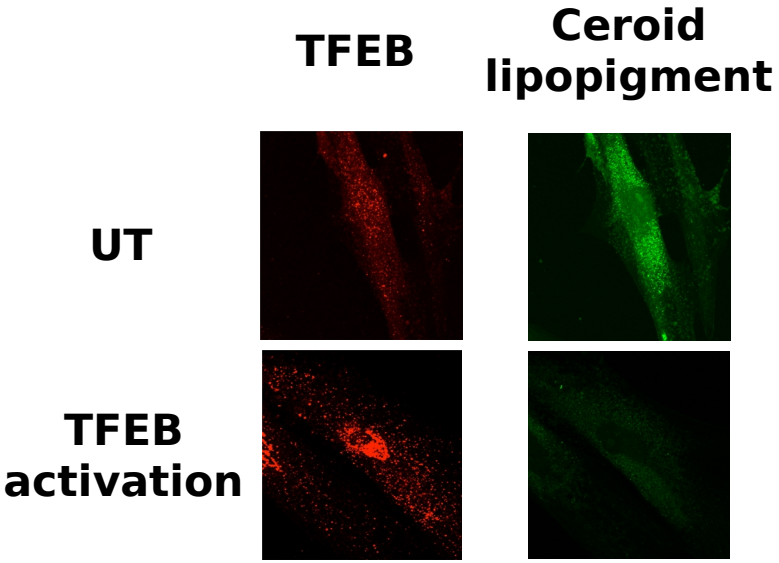
**Imaging, diagnostics, therapeutics**

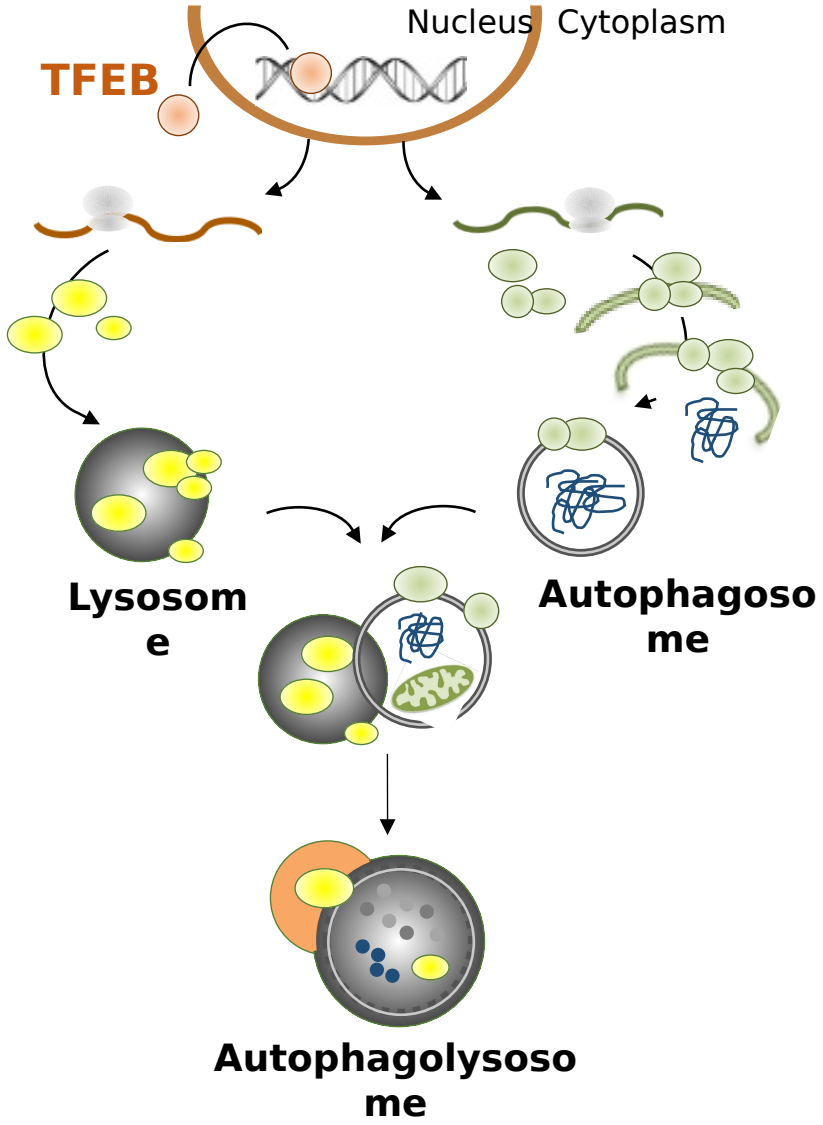
Enhancement of inefficient autophagic clearance vs Impaired cargo delivery



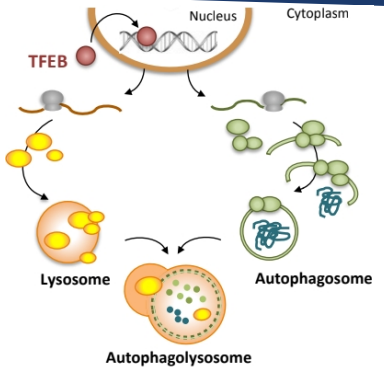

**Fundamental studies**

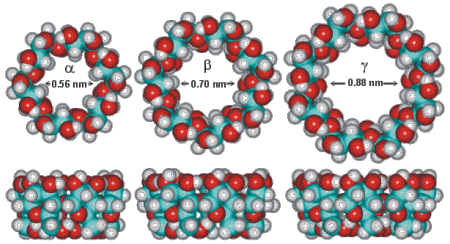
# Autophagic response to nano-sized particles



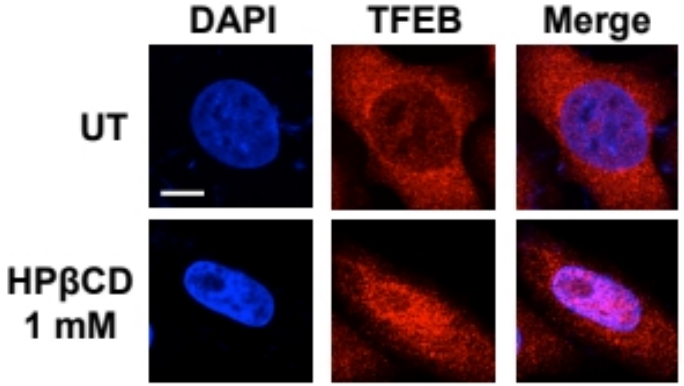



# β-cyclodextrin activates TFEB and enhances clearance

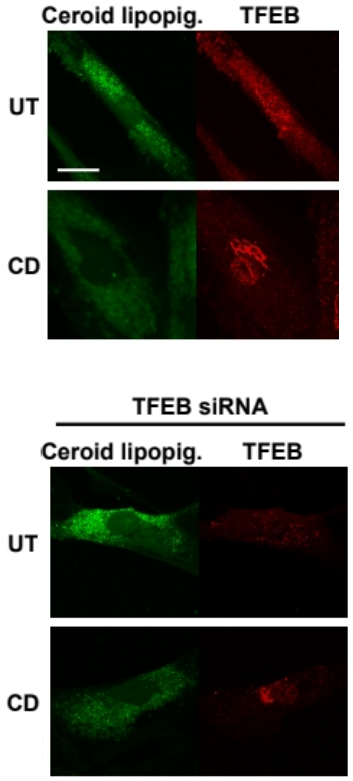


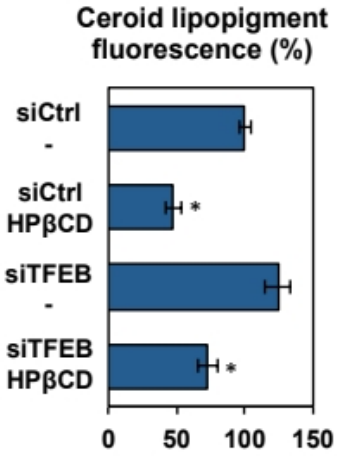




## HeLa/TFEB

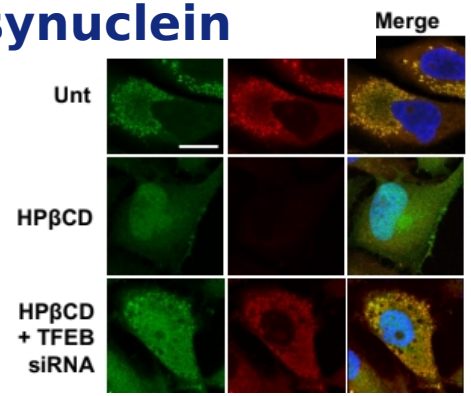


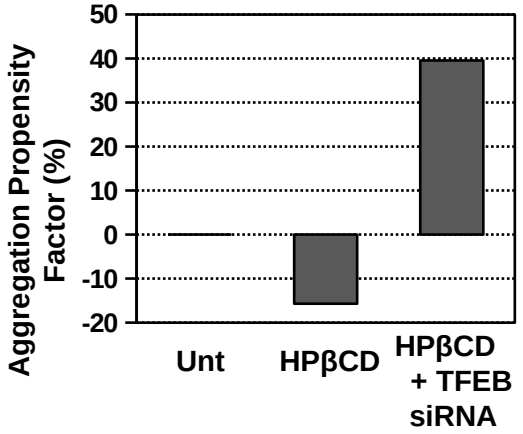

## Ceroid lipofuscinosis patient-derived fibroblasts



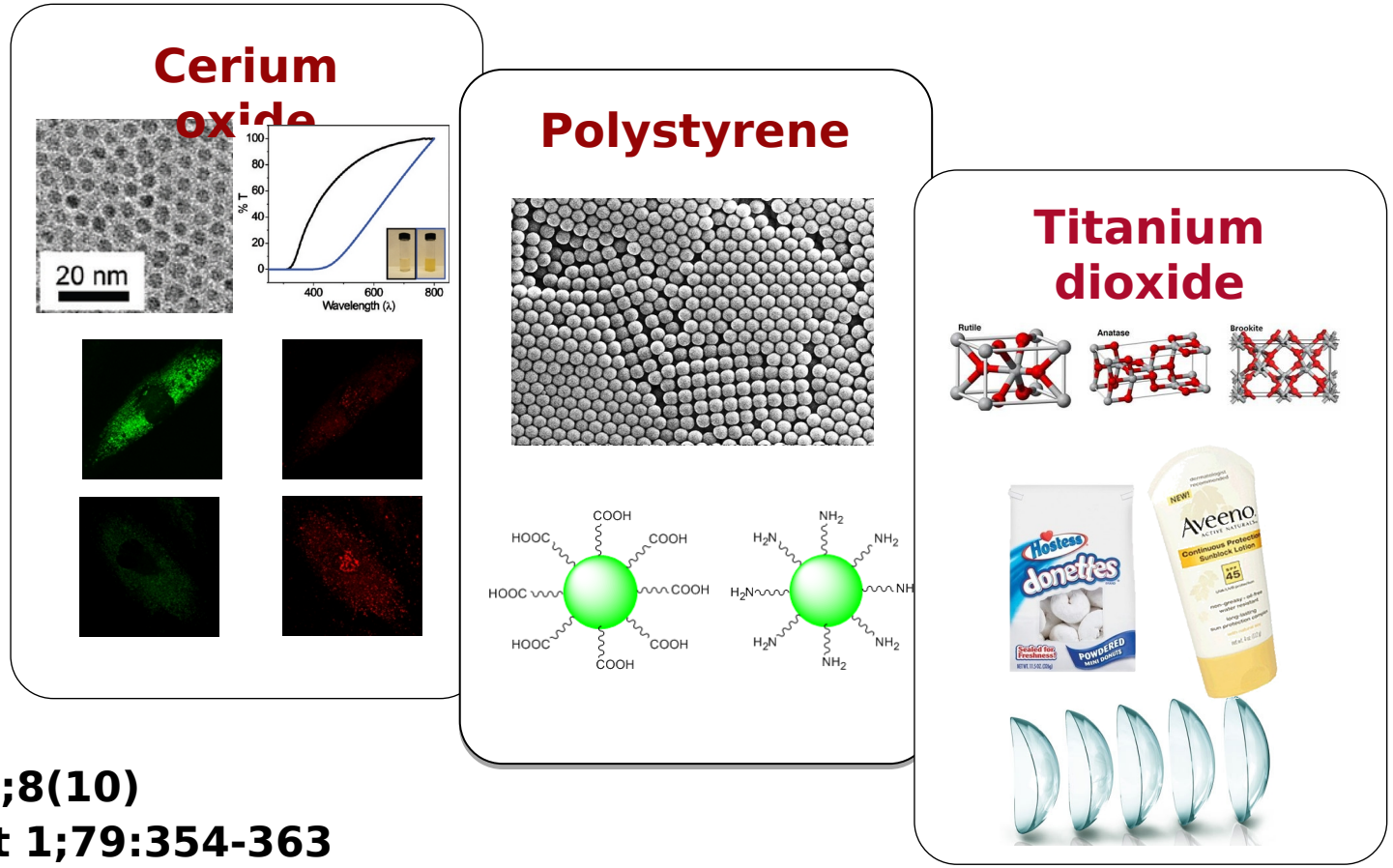

## Neuroblastoma α-synuclein



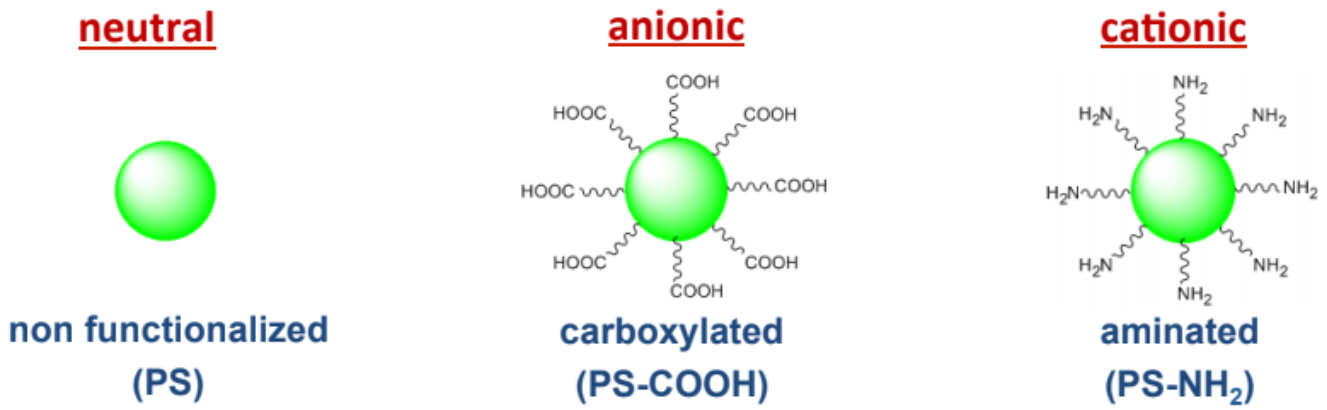

J Biol Chem. 2014 Apr 4;289(14)
PLoS One. 2015 Mar 19;10(3)

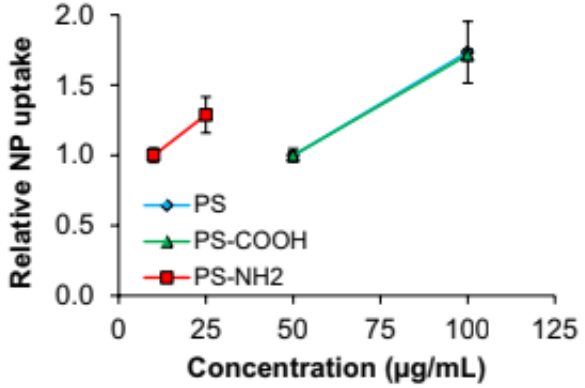
# Design rules of nanomaterials with desired autophagy inducing properties

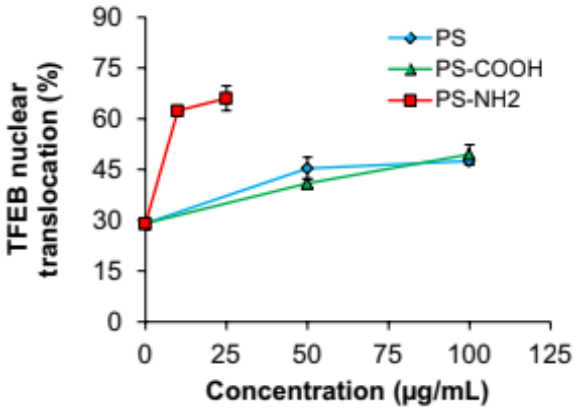


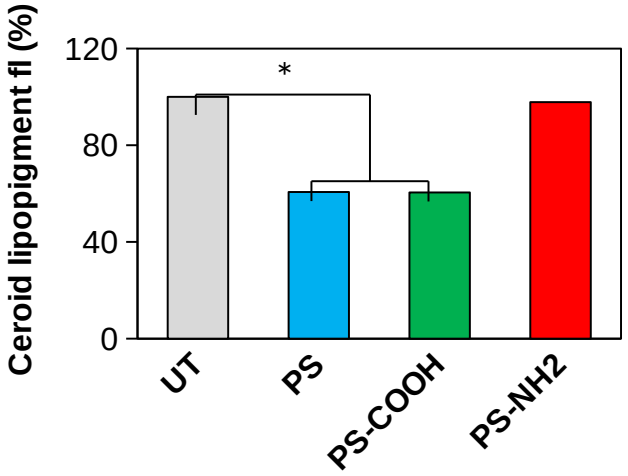

ACS Nano. 2014 Oct 28;8(10)
Acta Biomater. 2018 Oct 1;79:354-363
Virology. 2017 Oct;510:1-8
Nanobiotechnology. 2015 Nov 23;13:87

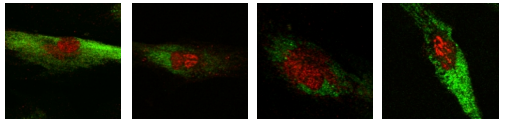
# Effect of nanoparticle surface charge on autophagy



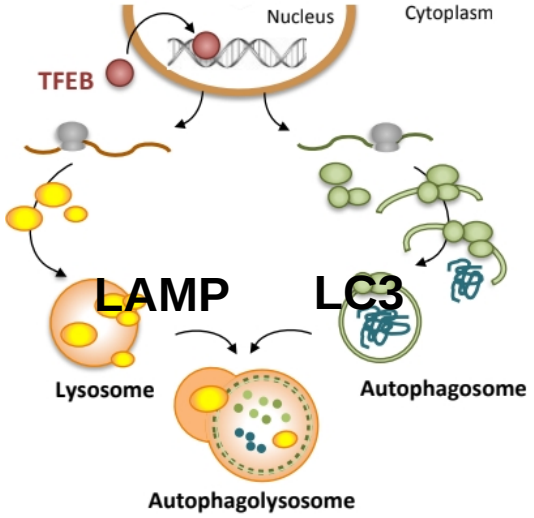



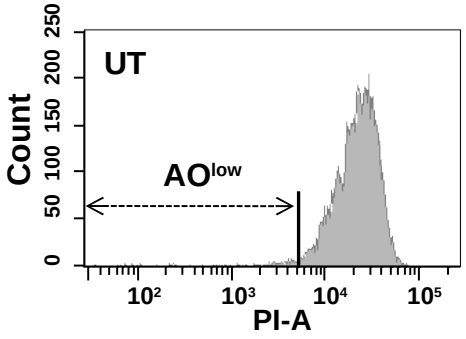



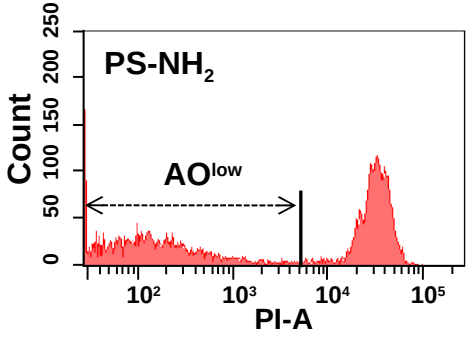



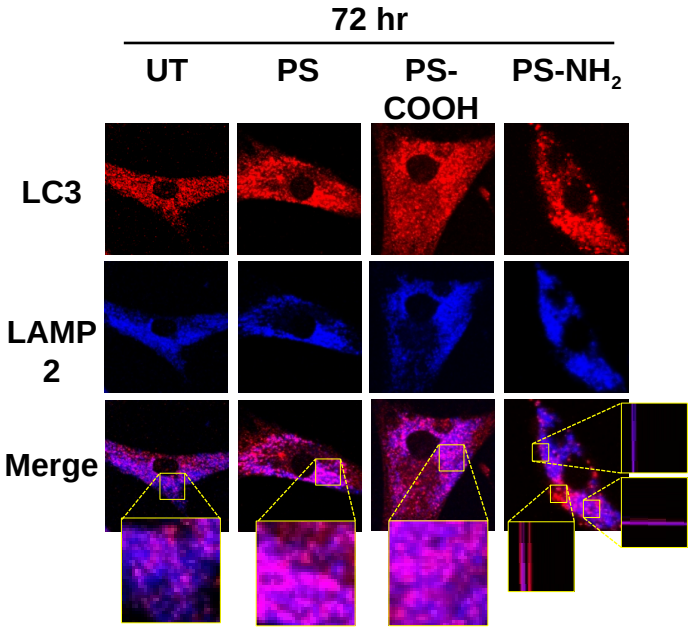
**Nanobiotechnology. 2015 Nov 23;13:87**

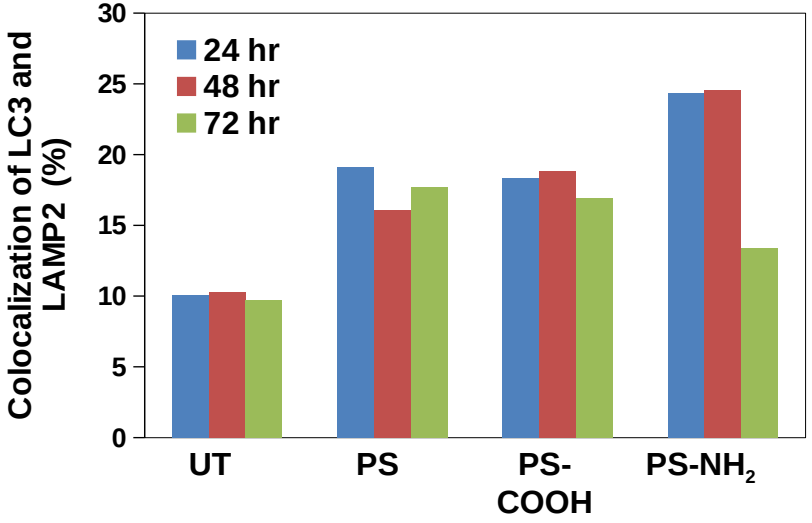
# Cationic PS impair lysosomes



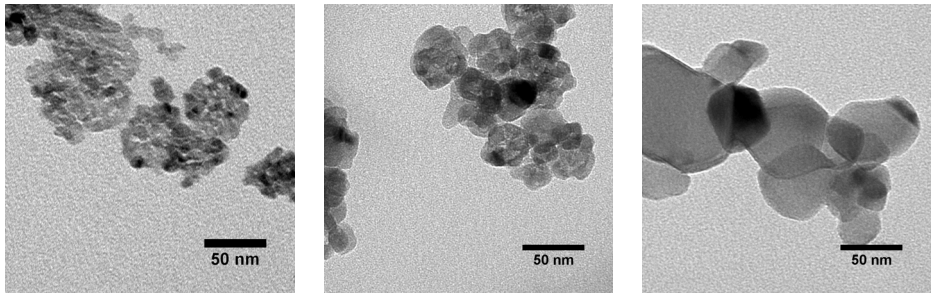




J Nanobiotechnology. 2015 Nov 23;13:87

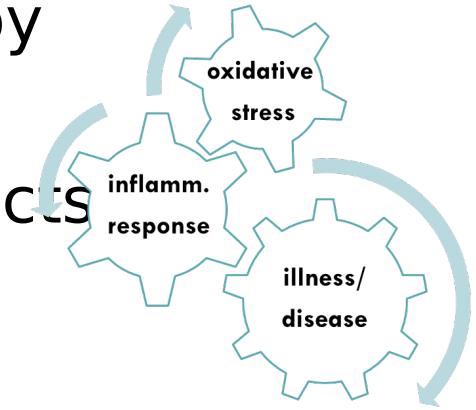
# Autophagic response to cellular exposure to titanium dioxide ($TiO_2$) nanoparticles

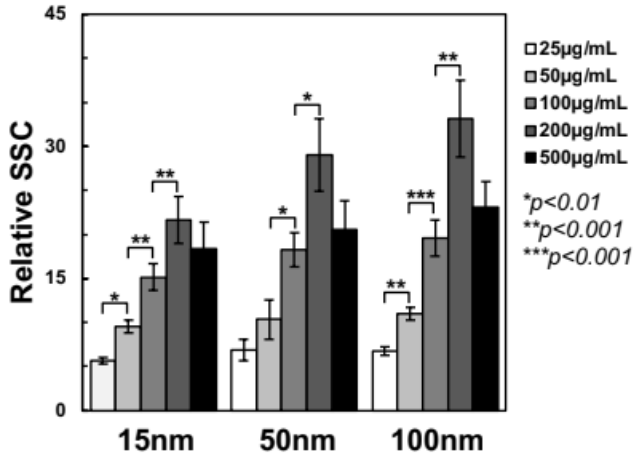
FDA GRAS APPROVED


15 nm 50 nm 100 nm

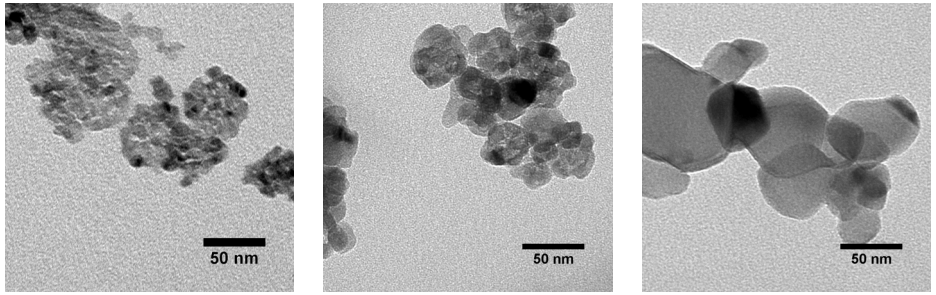
- Generally regarded as safe by FDA
- In consumer/industrial products
- $TiO_2$ NP exposure affects cell function



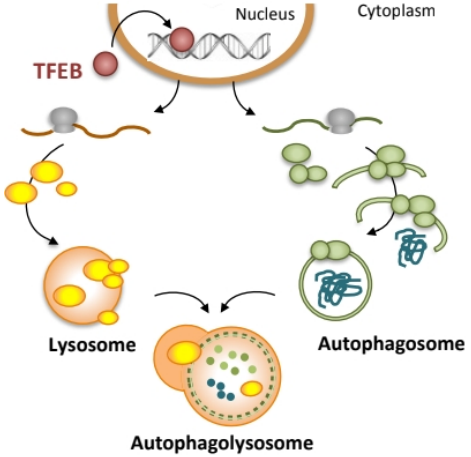



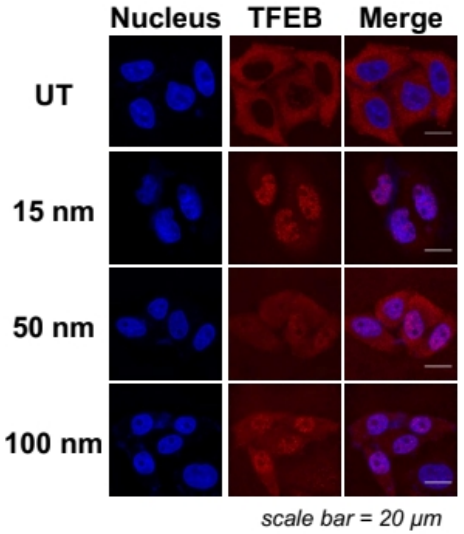

**Acta Biomaterialia 79 (2018) 354–363**

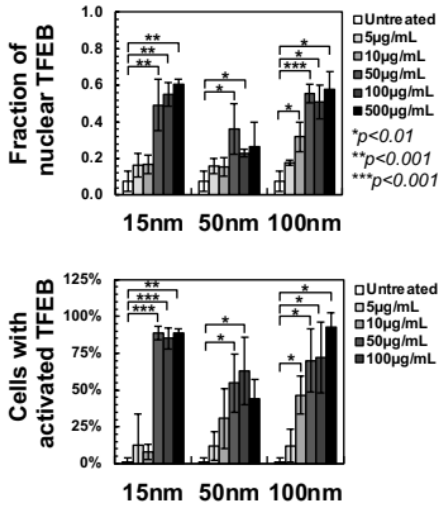
# $TiO_2$ nanoparticles causes lysosomal membrane permeabilization

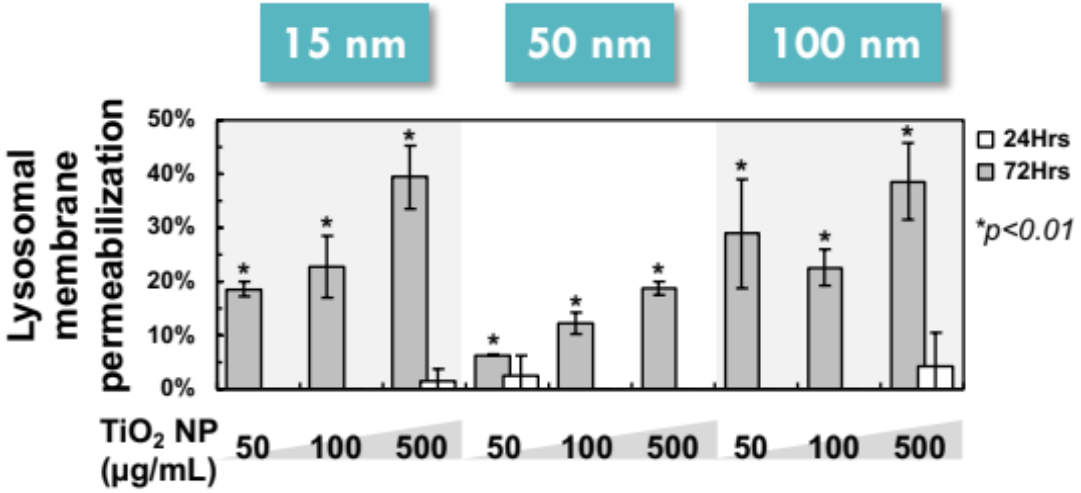



15 nm 50 nm 100 nm

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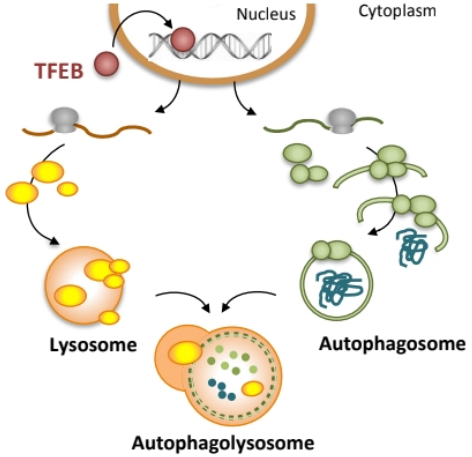
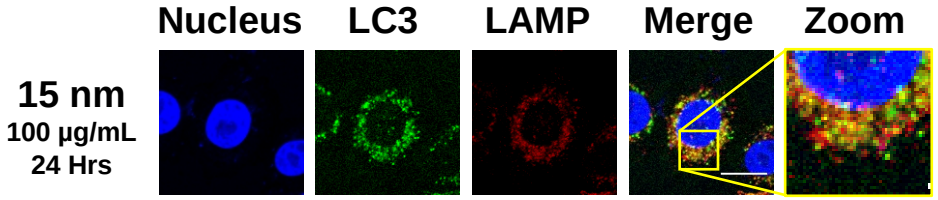
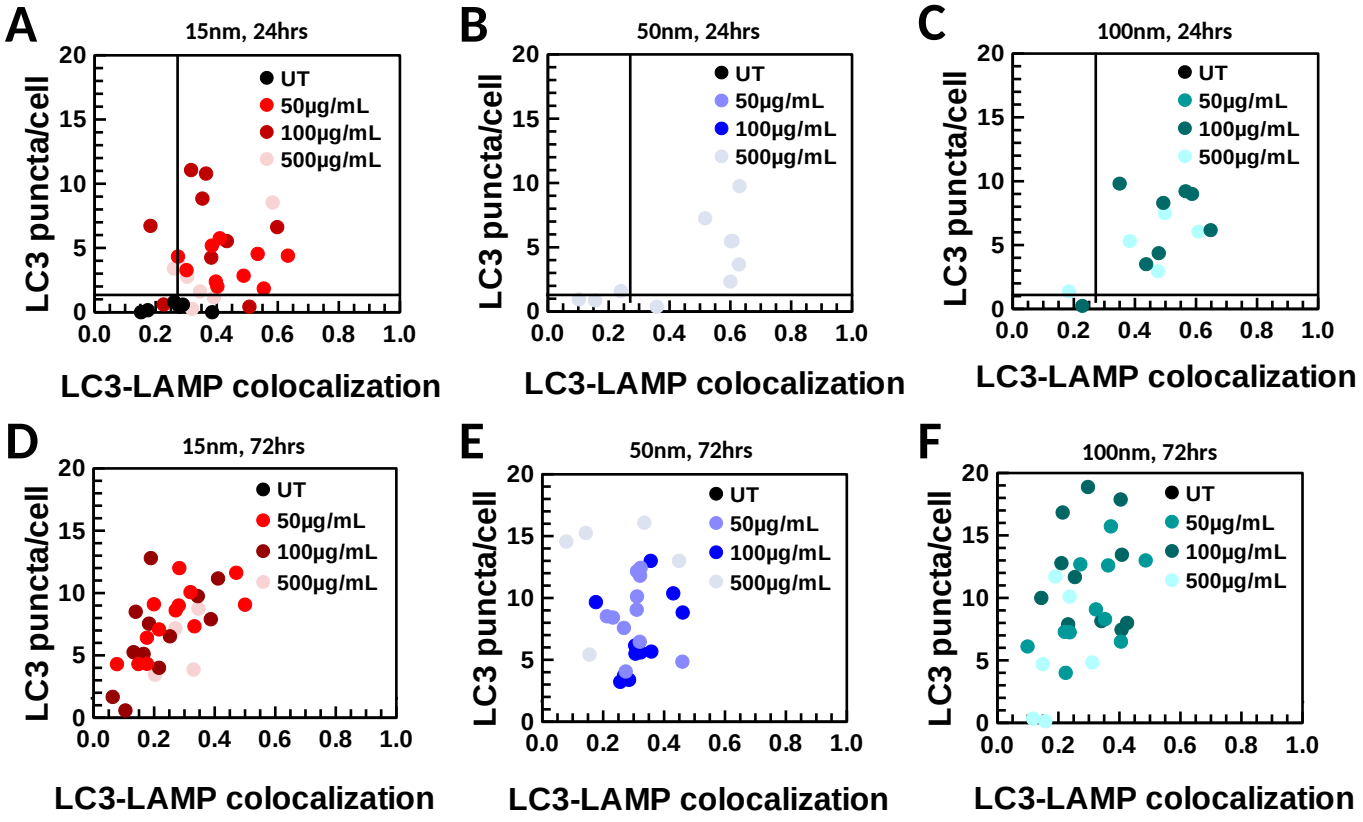
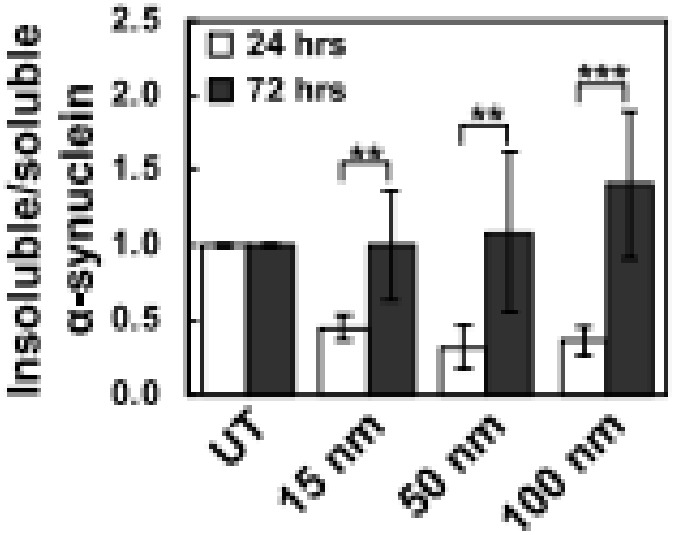
# $TiO_2$ NPs cause blockage of autophagic flux and build up of autophagic substrate over time

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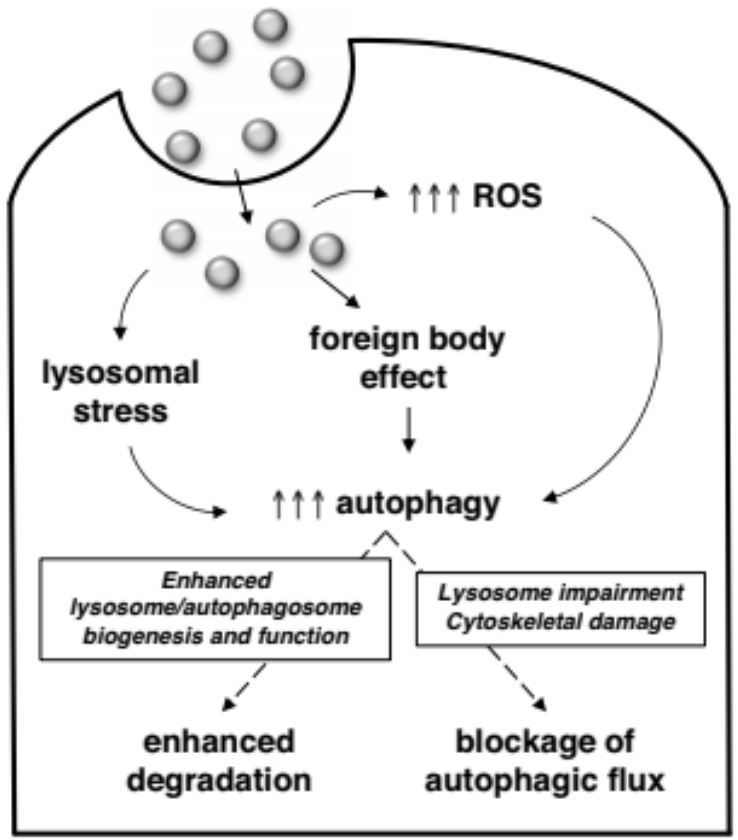
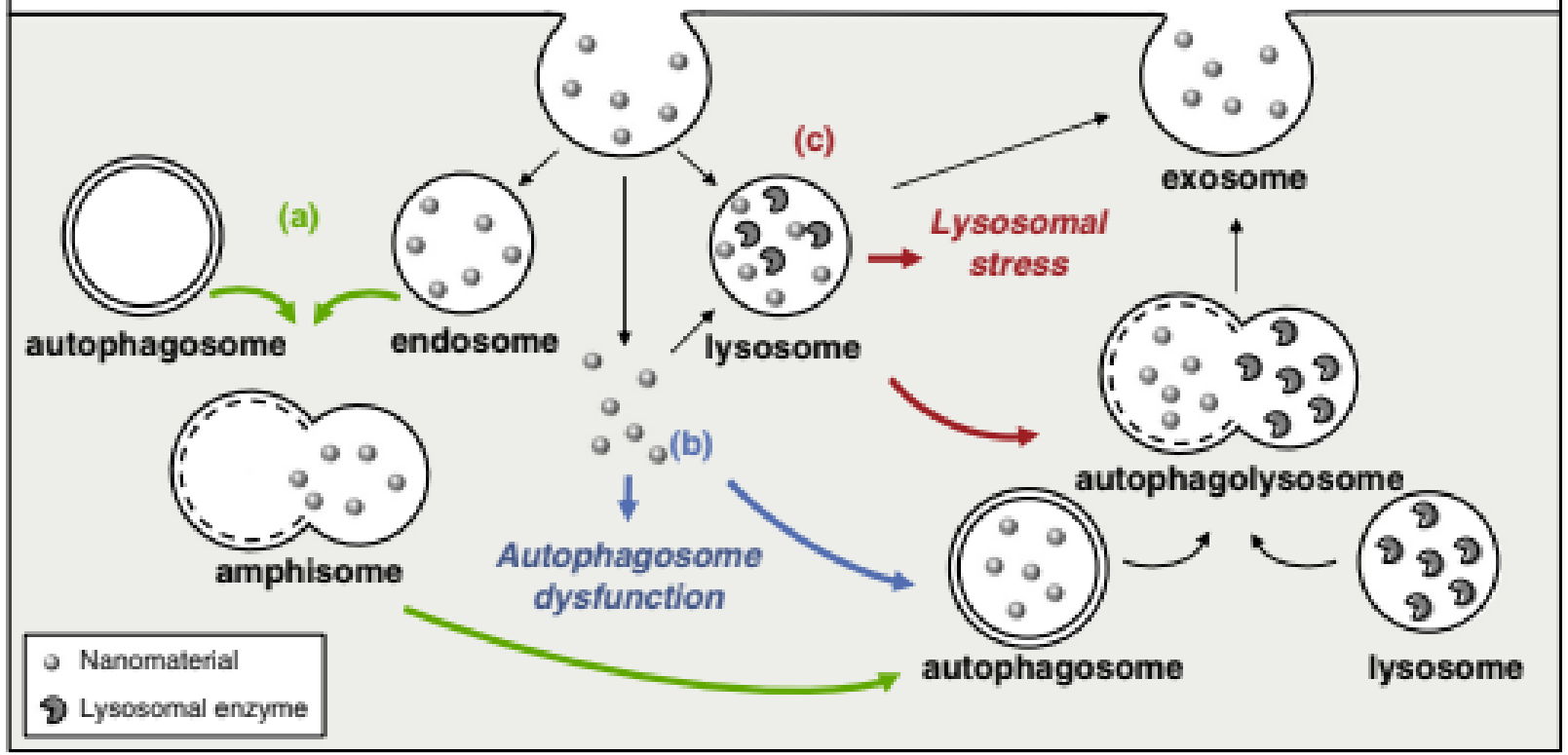
# Nanoparticles as autophagy activators



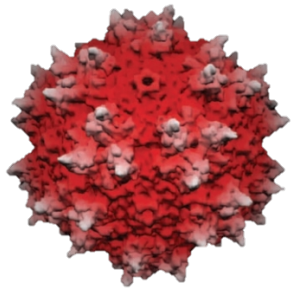

Mechanisms of nanomaterial-induced autophagy activation

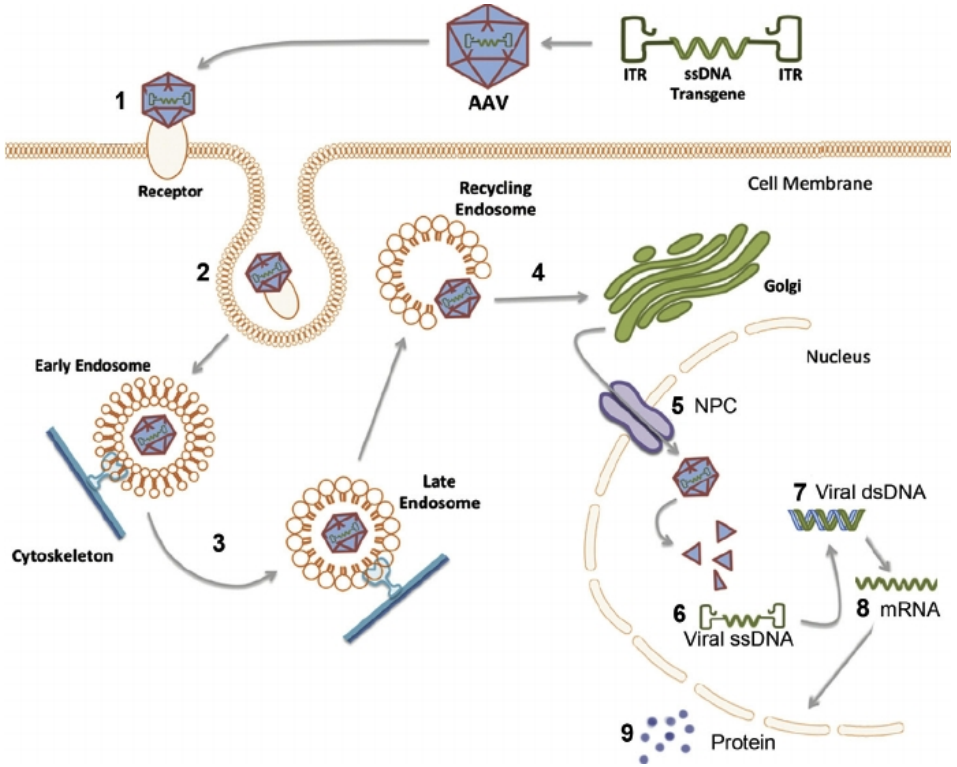
Models of autophagic response to nanomaterials




Curr Opin Biotechnol. 2015 Dec;36:129-3

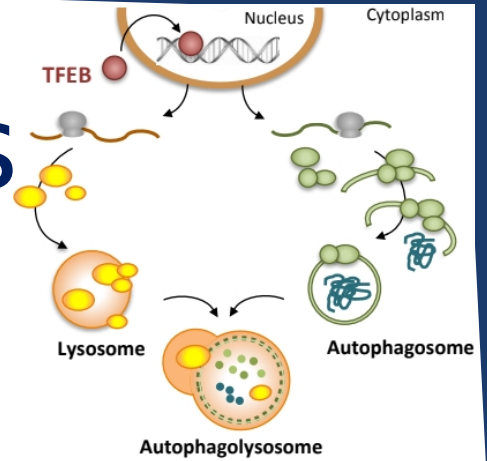
# Adeno-associated virus (AAV)



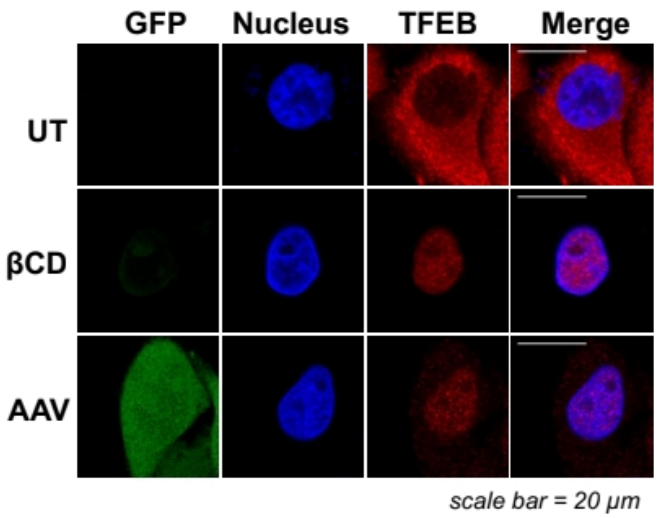



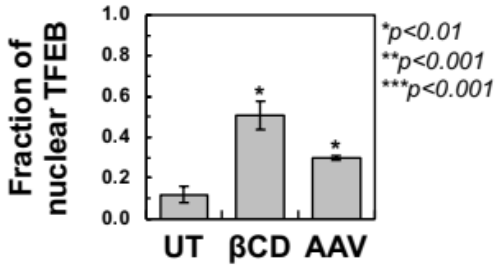

- Naturally occurring, genetically encoded nanomaterial
- ~25 nm diameter
- Used as a gene therapy vector
- Gene delivery requires evasion of cellular clearance mechanisms

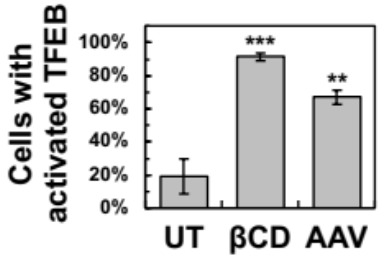
# AAV activates TFEB and enhances cellular clearance



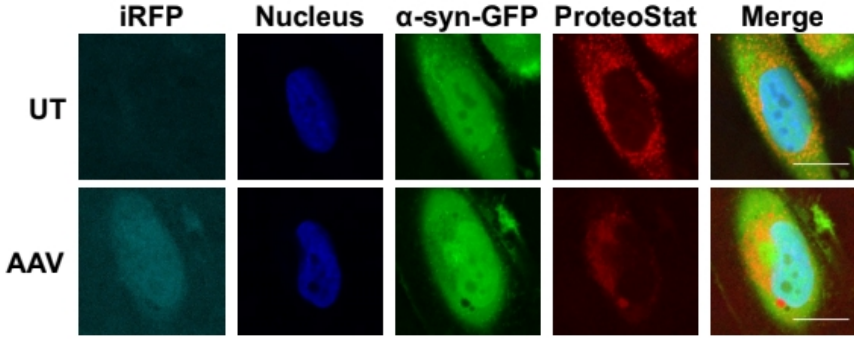

## HeLa/TFEB

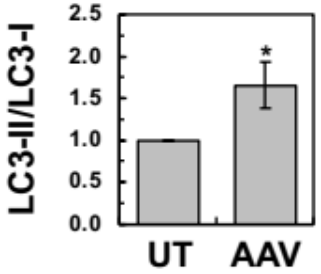


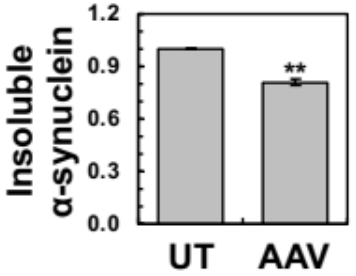




## Neurobalstoma α-synuclein

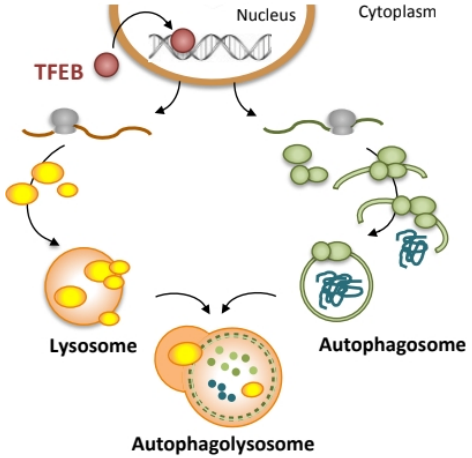


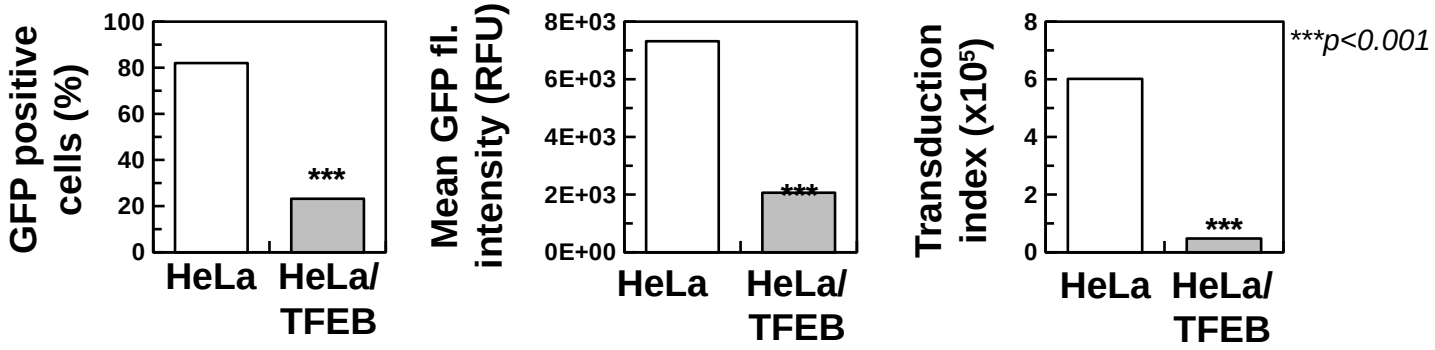



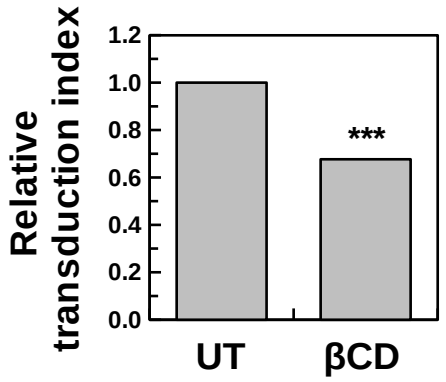

*Virology* **2017 510, 1–8**

# AAV-induced autophagy causes a reduction in AAV transduction efficiency

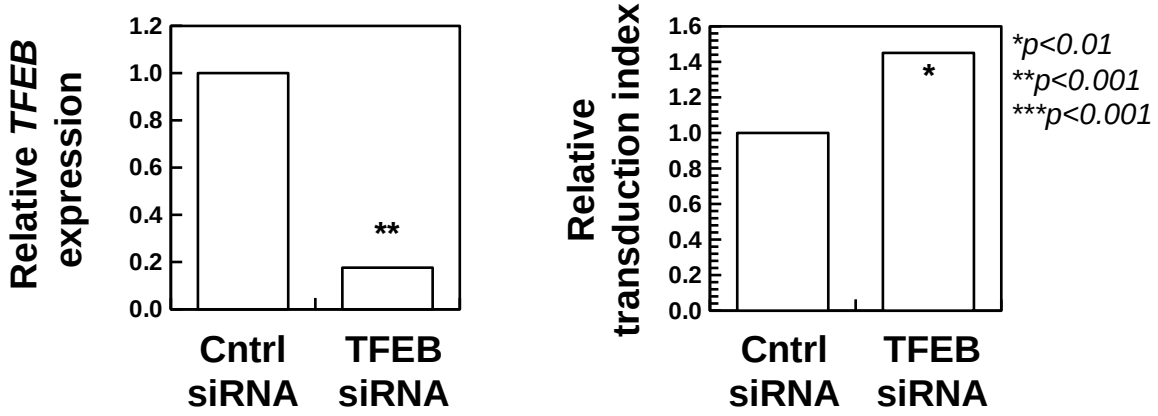



## TFEB pre-activation

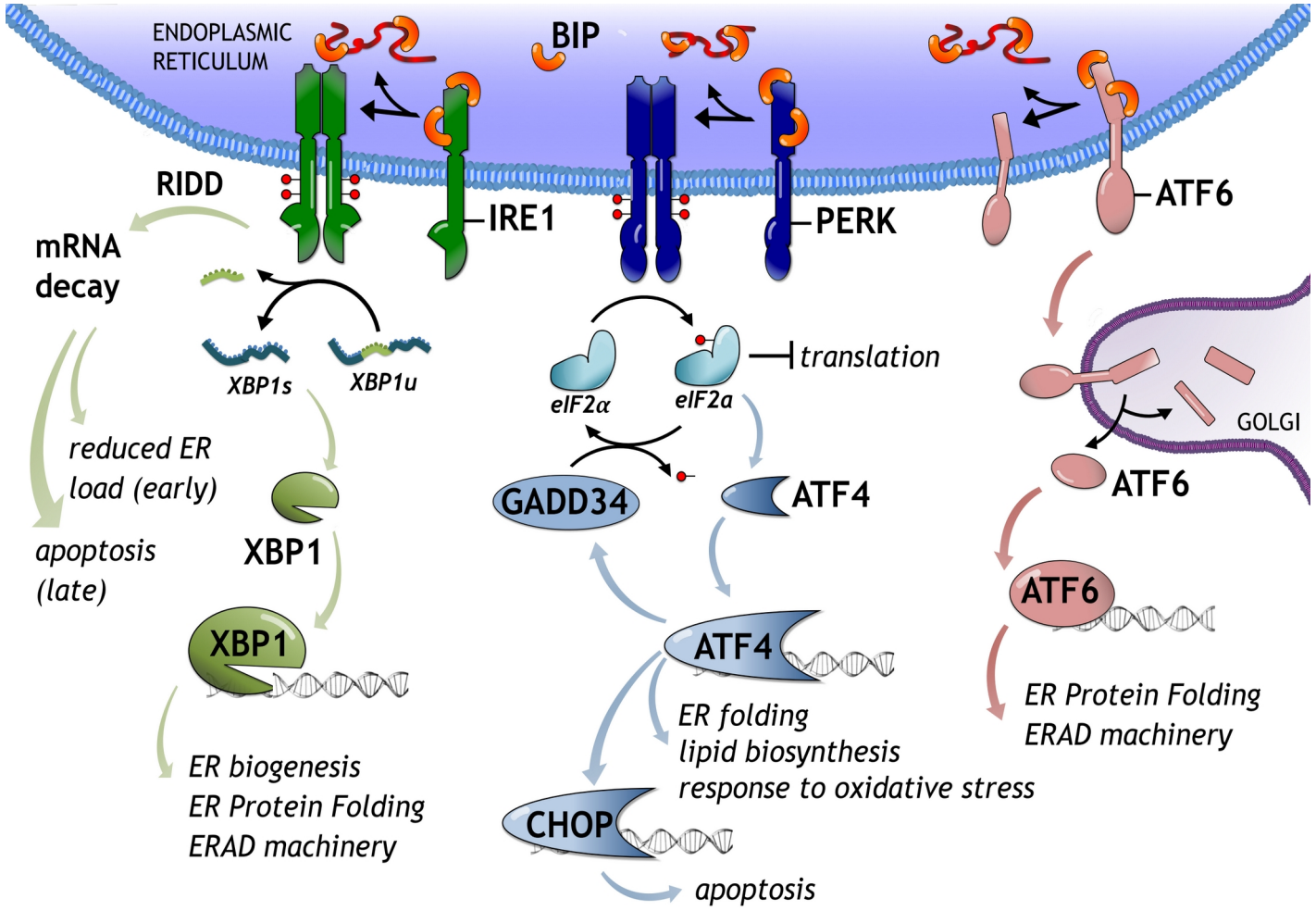


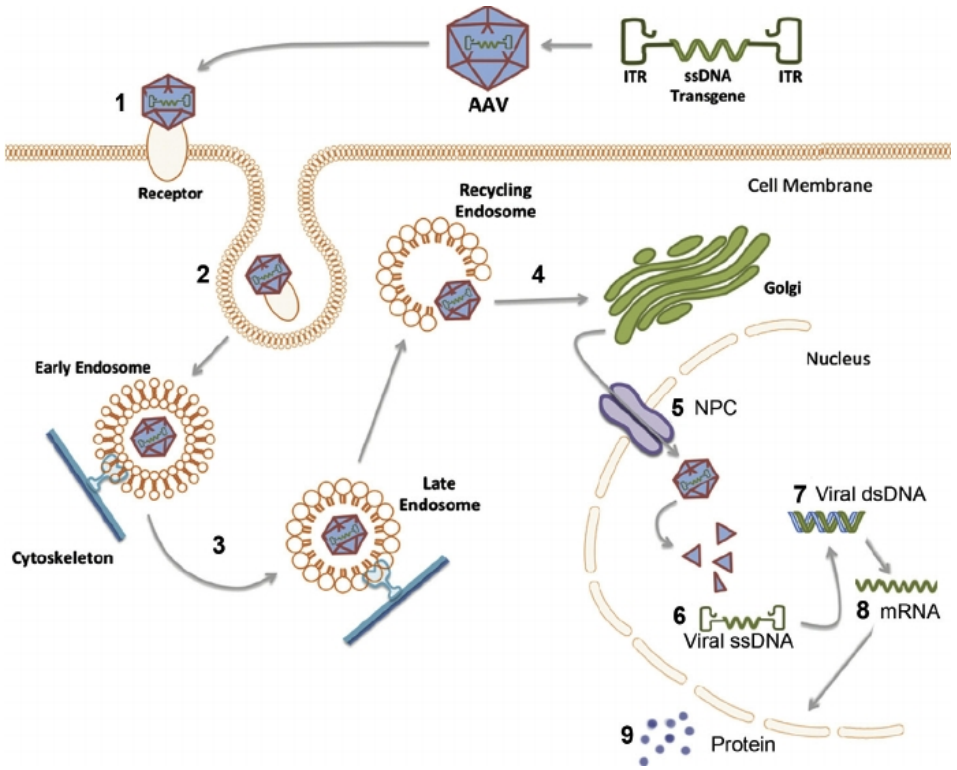

## TFEB silencing



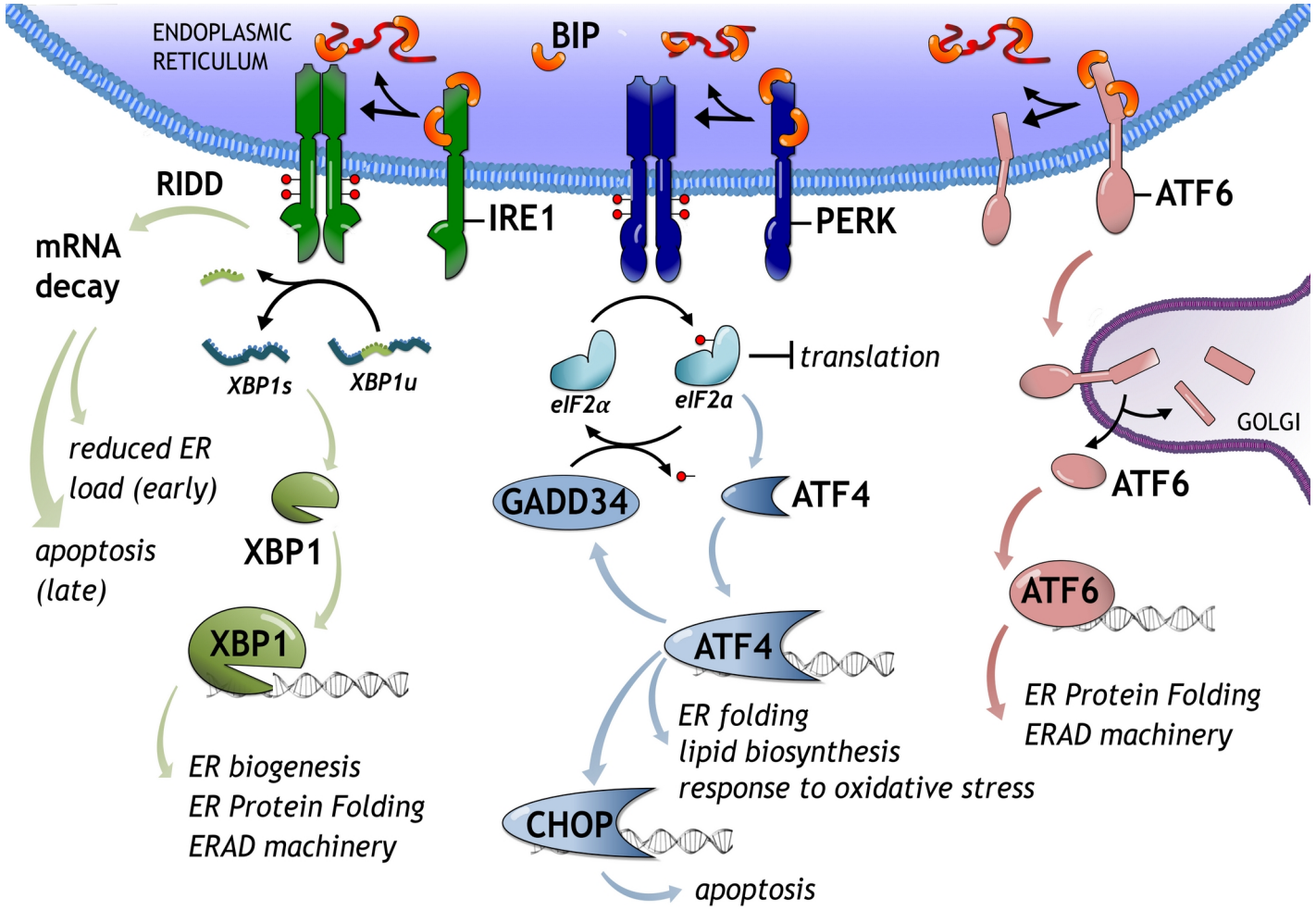

***Virology* 2017 510, 1–8**

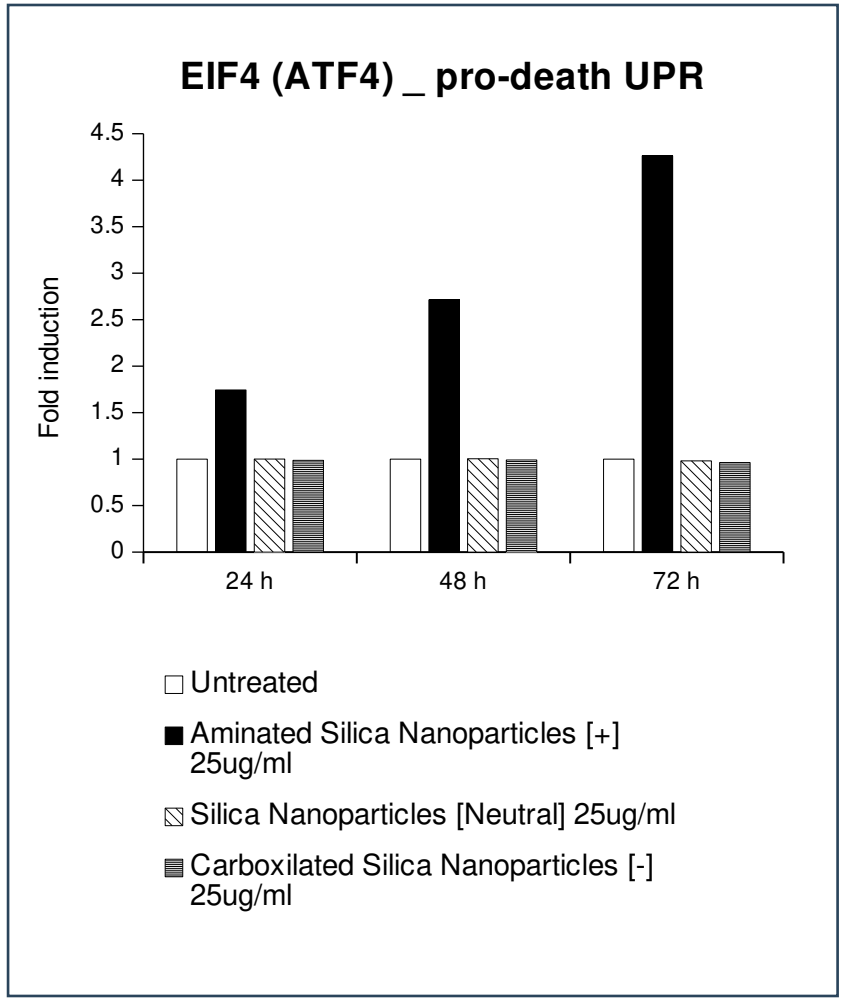
# Unfolded Protein Response (UPR) and AAV



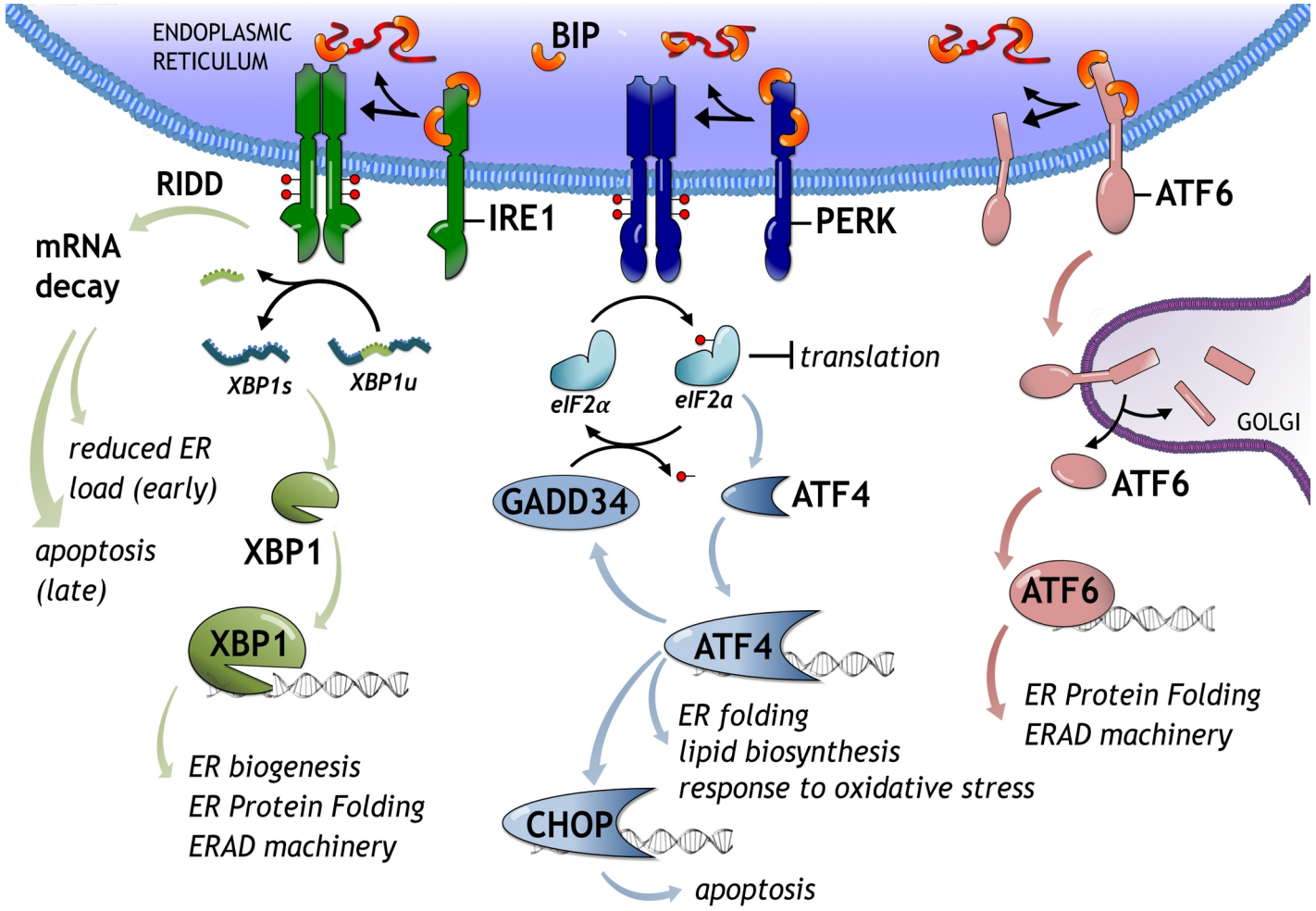



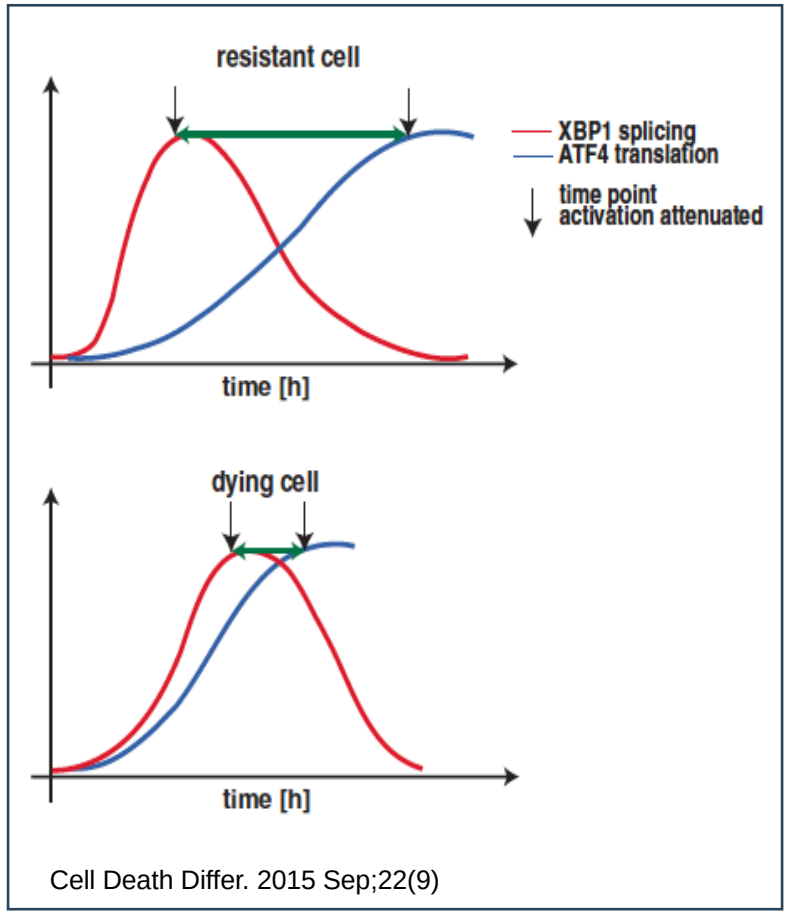
# Unfolded Protein Response (UPR) and nanomaterials



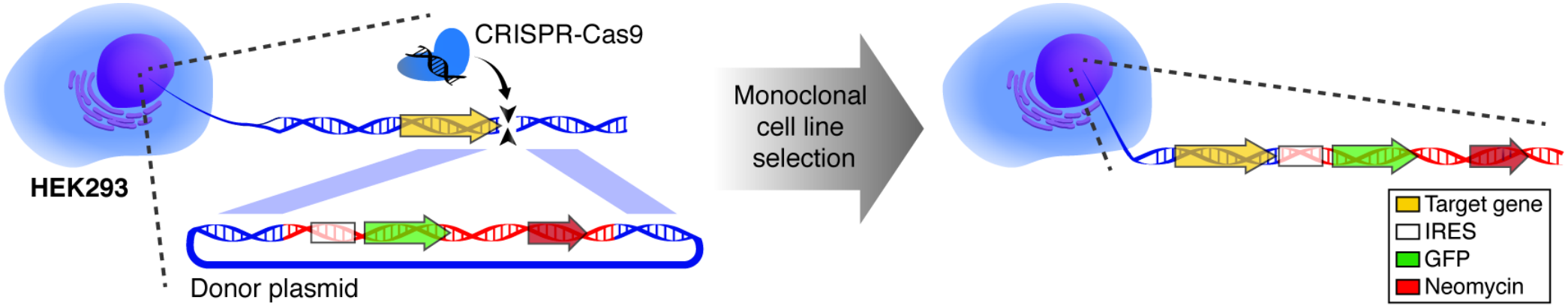
# Unfolded Protein Response (UPR) and nanomaterials




Cell Death Differ. 2015 Sep;22(9)

# Monitoring gene activity from the native chromosomal context

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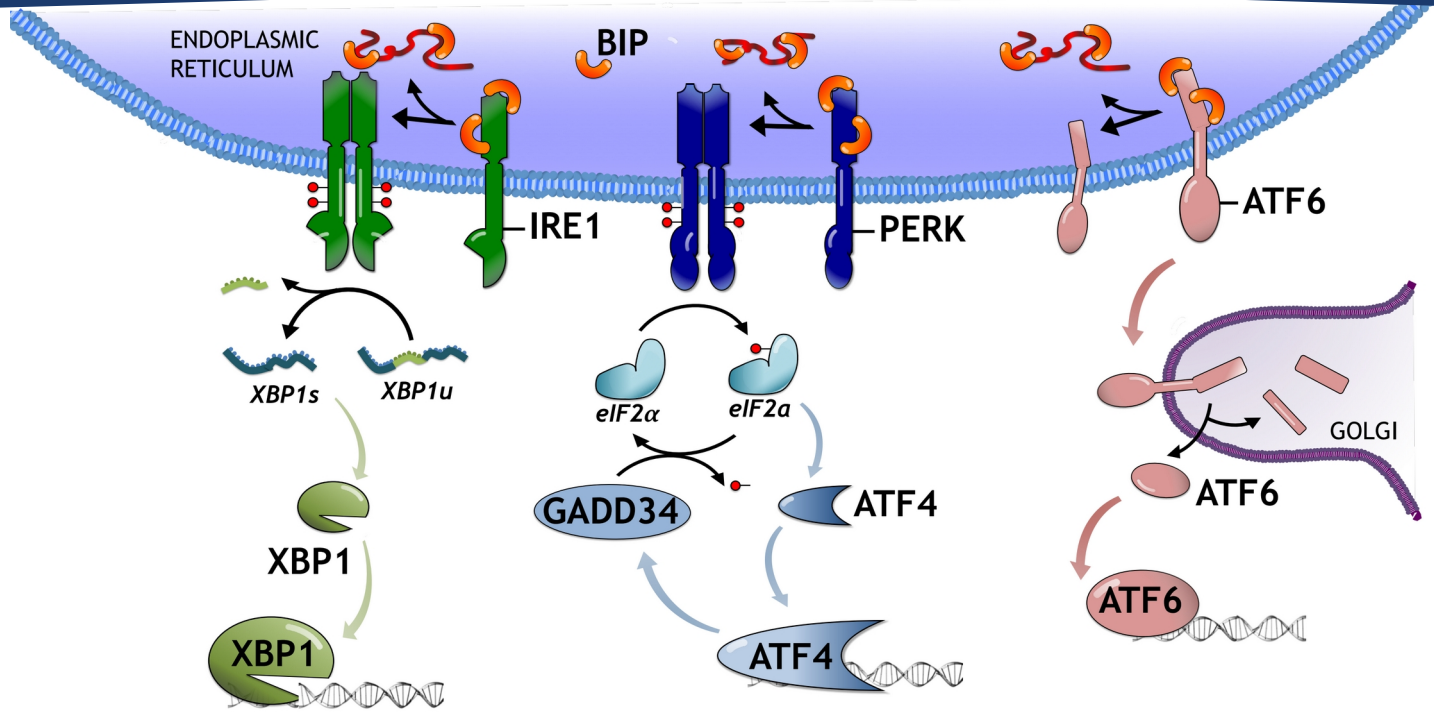
ENDOPLASMIC
RETICULUM
BIP
IRE1
PERK
ATF6
XBP1s
XBP1u
eIF2α
eIF2a
GOLGI
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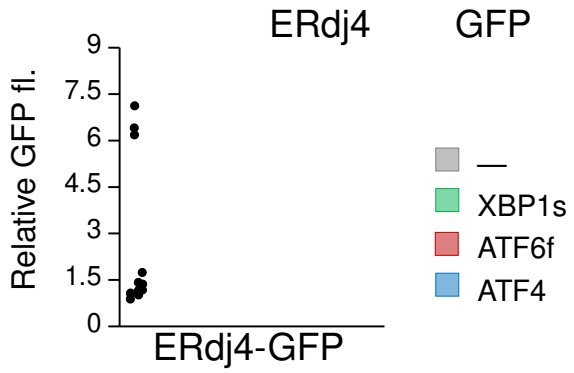
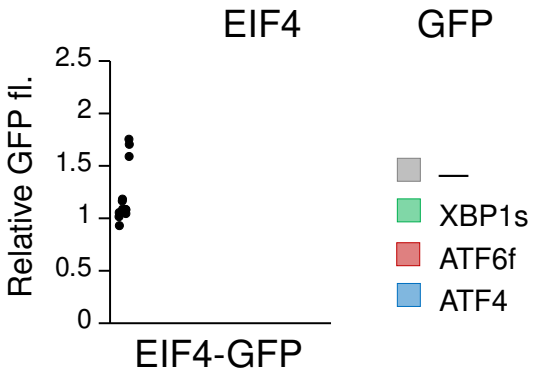
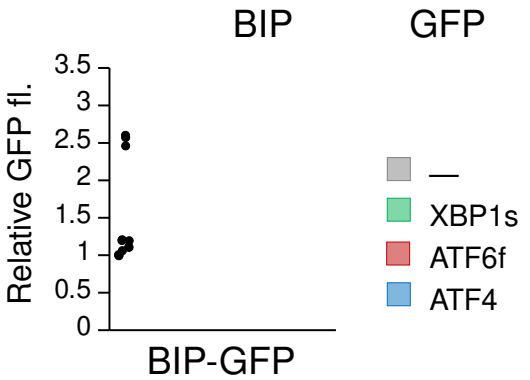
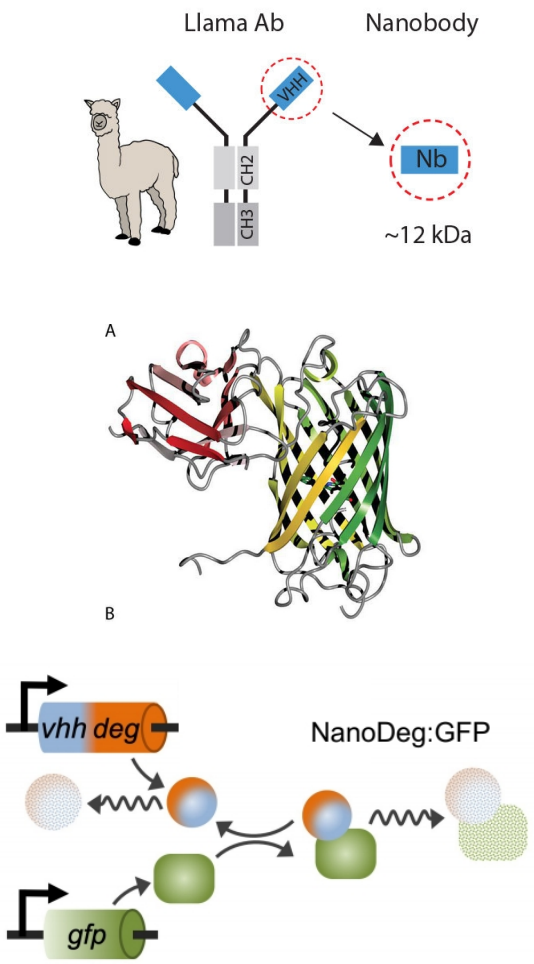
GADD34
ATF4
XBP1
XBP1
ATF4
ATF6

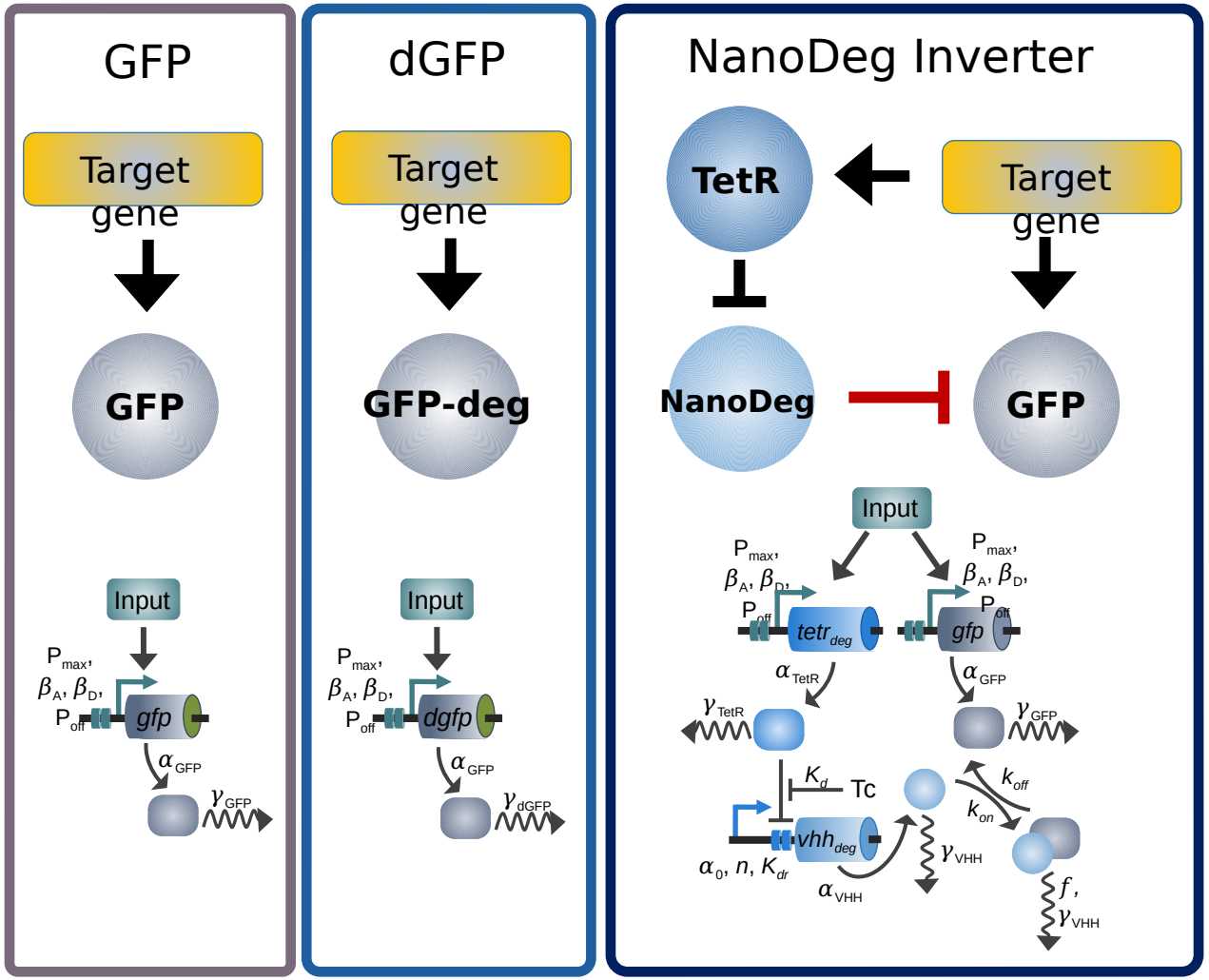

ERdj4
GFP
Relative GFP fl.
9
7.5
6
4.5
3
1.5
0
ERdj4-GFP
—
XBP1s
ATF6f
ATF4

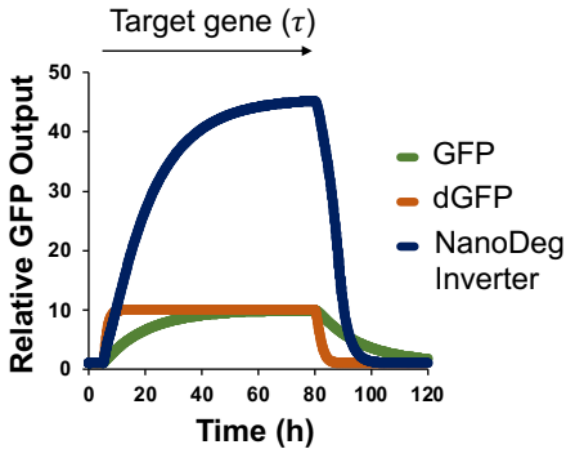

EIF4
GFP
Relative GFP fl.
2.5
2
1.5
1
0.5
0
EIF4-GFP
—
XBP1s
ATF6f
ATF4

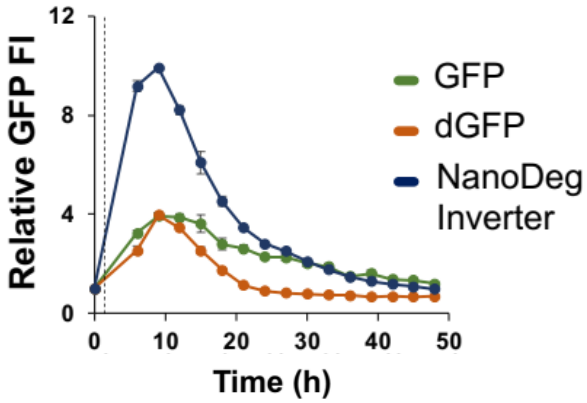

BIP
GFP
Relative GFP fl.
3.5
3
2.5
2
1.5
1
0.5
0
BIP-GFP
—
XBP1s
ATF6f
ATF4

# Post-translational control of the reporter output enhances the dynamic resolution of mammalian signaling systems



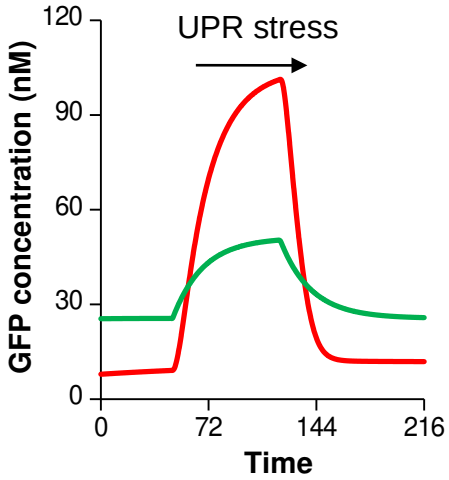



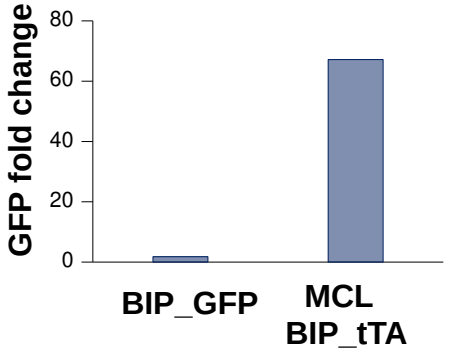



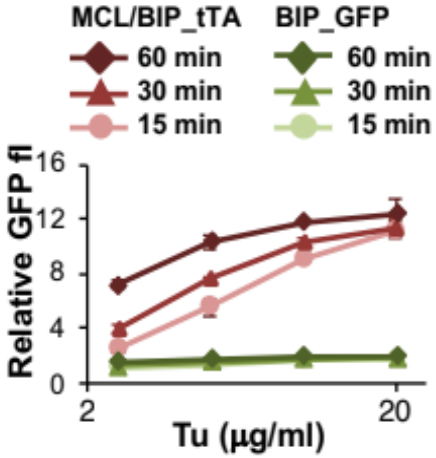

**Methods Enzymol 2019;622:1-27**

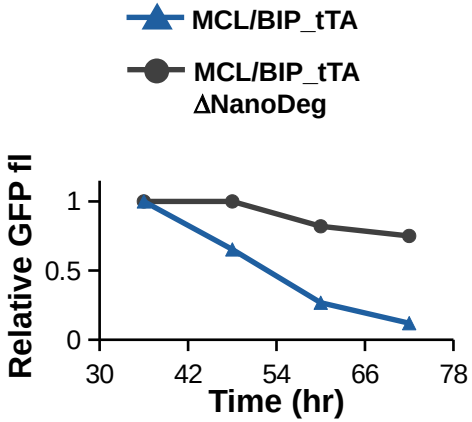
# A gene signal amplifier for monitoring the UPR

***BIP* reporter cell line**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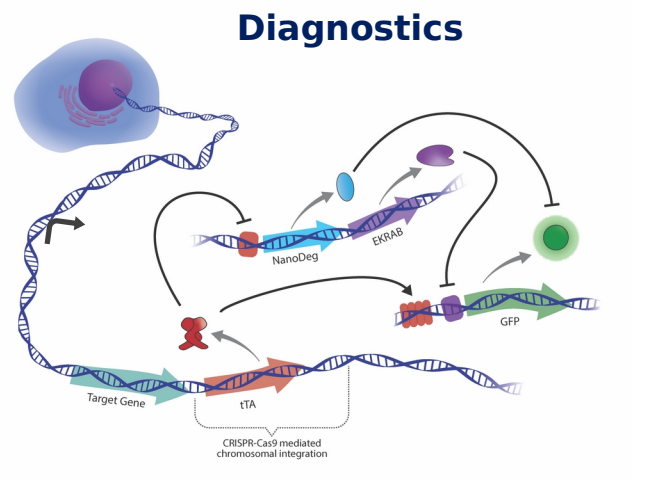
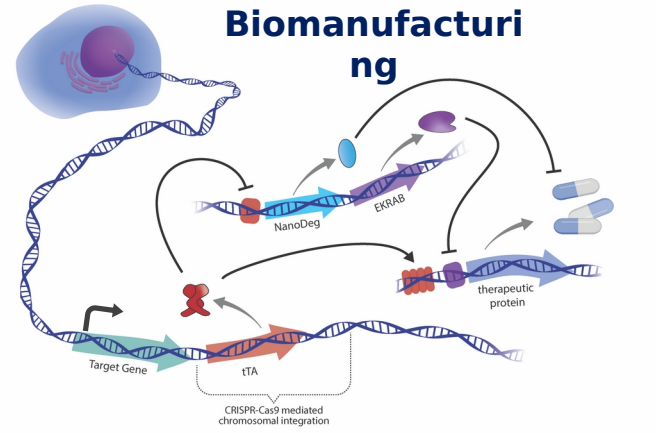
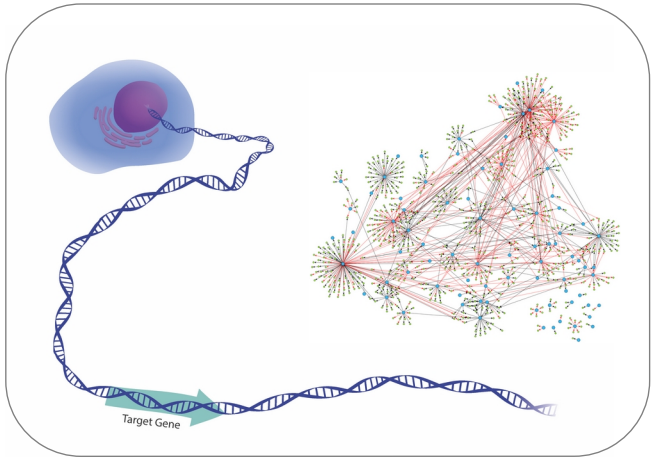
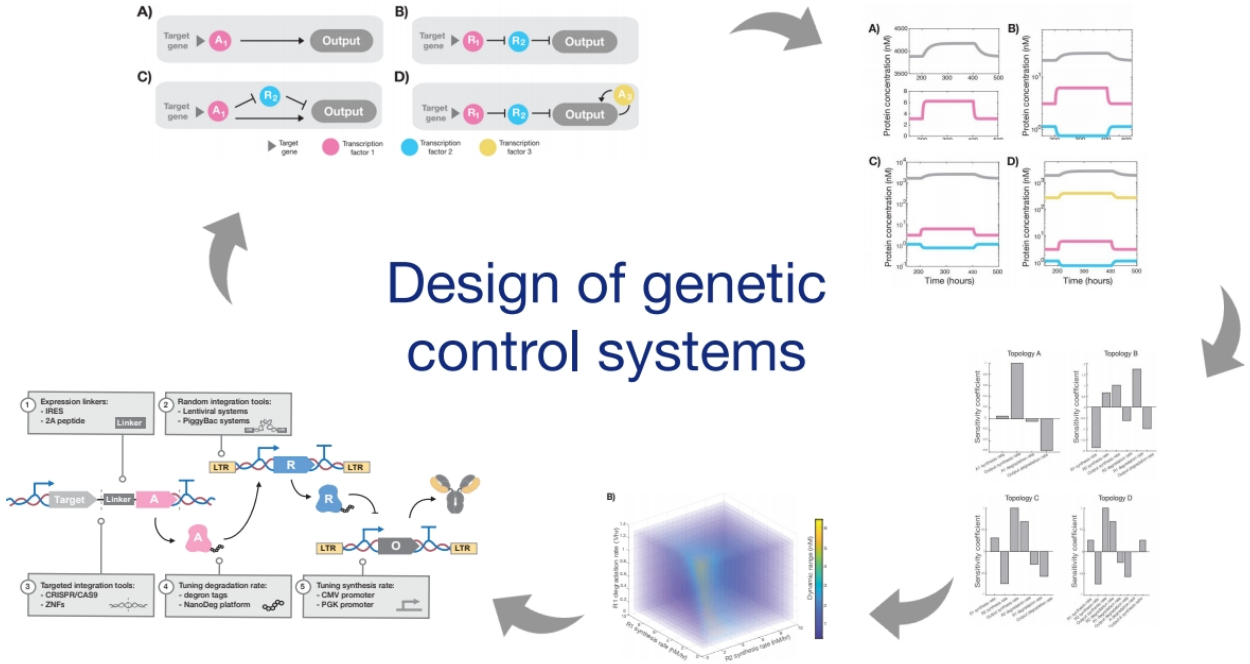
# Programming designer cells




**Methods Mol Biol *in press***

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