



Déclaration d'intérêts en rapport avec la présentation

➤ **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

Non

➤ **Essais cliniques, autres travaux, communications de promotion**

Non

➤ **Intérêts financiers (actions, obligations)**

Non

➤ **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

Non

➤ **Réception de dons sur une association dont je suis responsable**

Non

➤ **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

Non

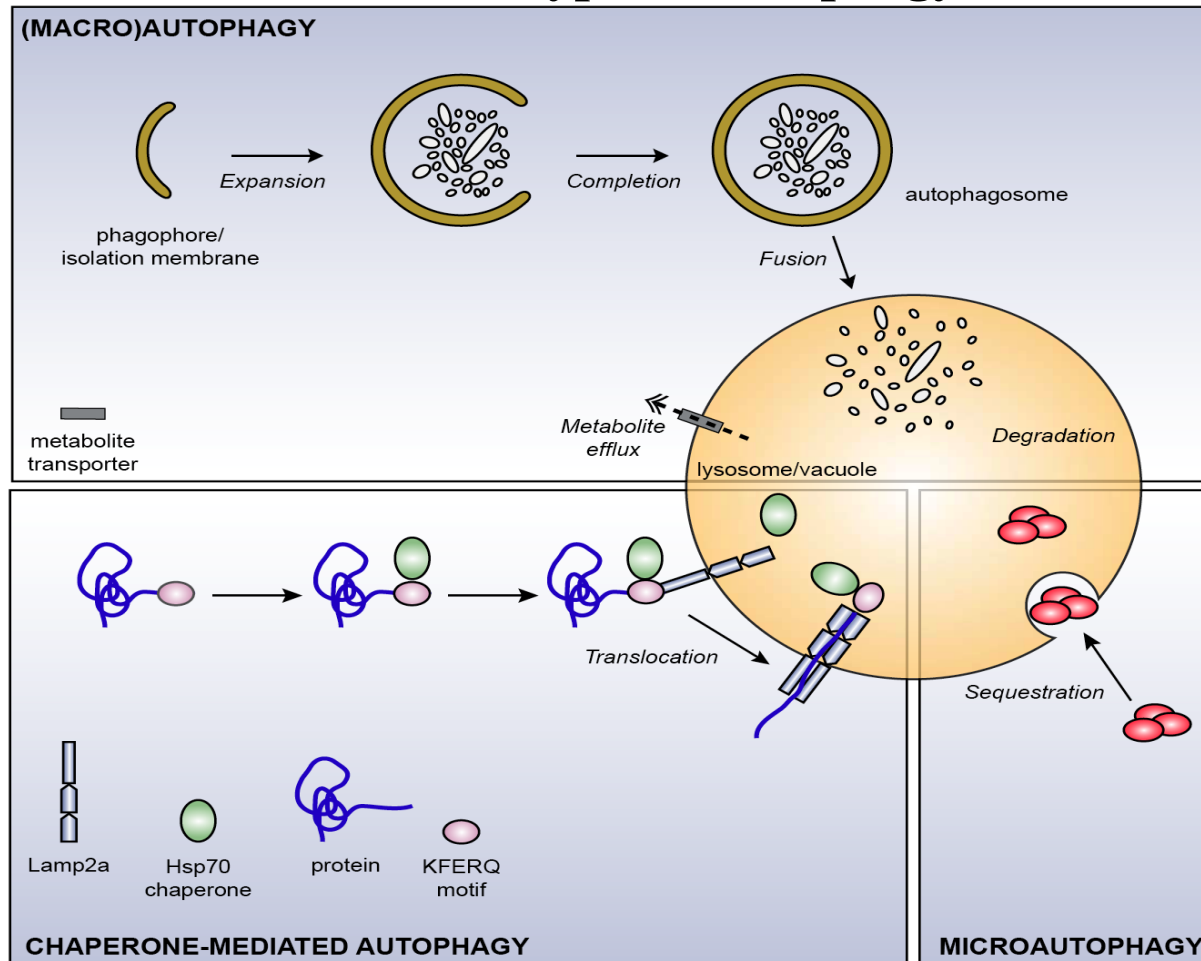


Autophagy: Self-eating is good for you

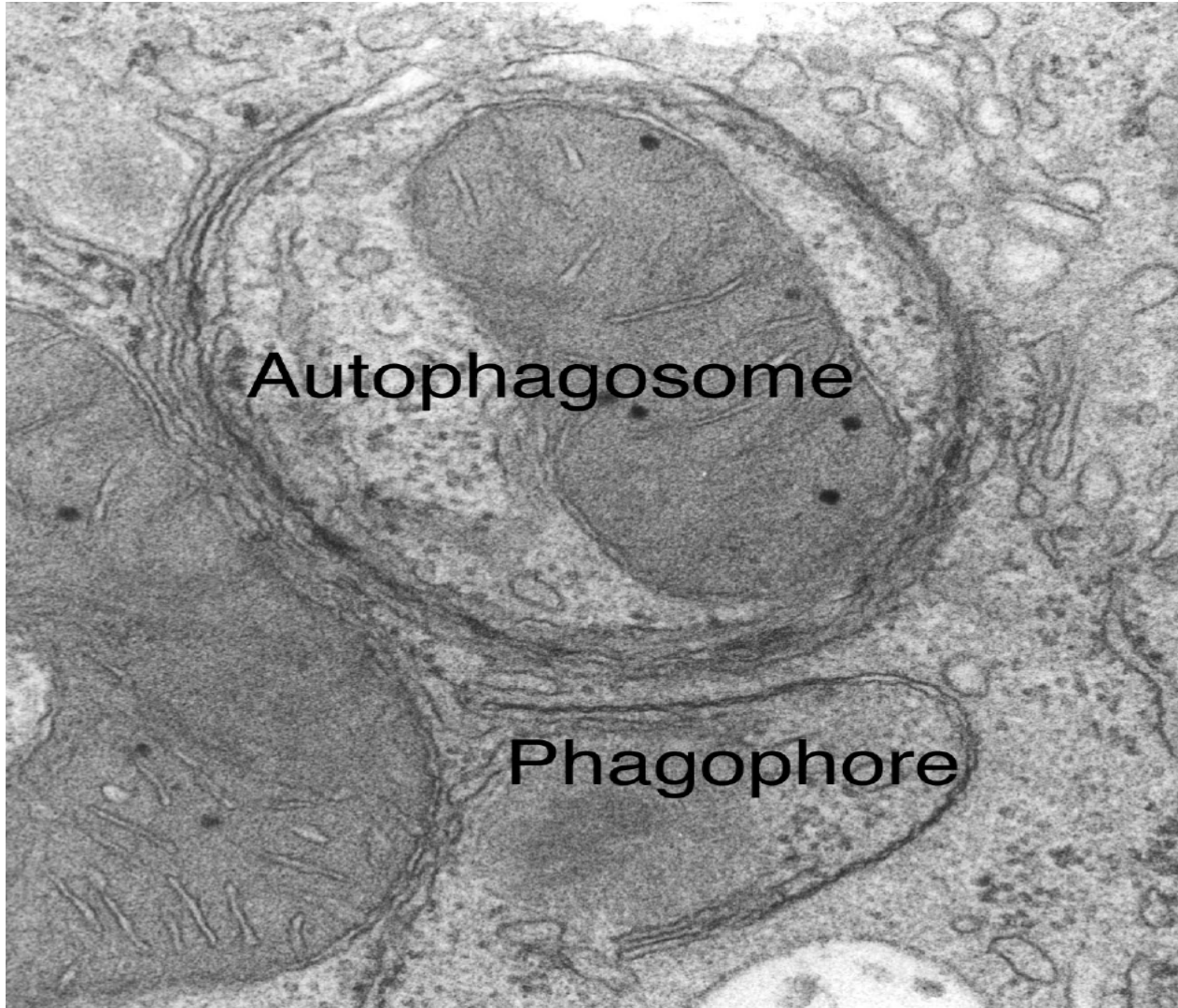
**Patrice Codogno
Necker Growth and Signaling Research Center
INSERM U845
University René Descartes/Paris 5**

Bordeaux December 2013

The different types of autophagy



From *Boya, Reggiori and Codogno 2013 Nat Cell Biol 15, 713*

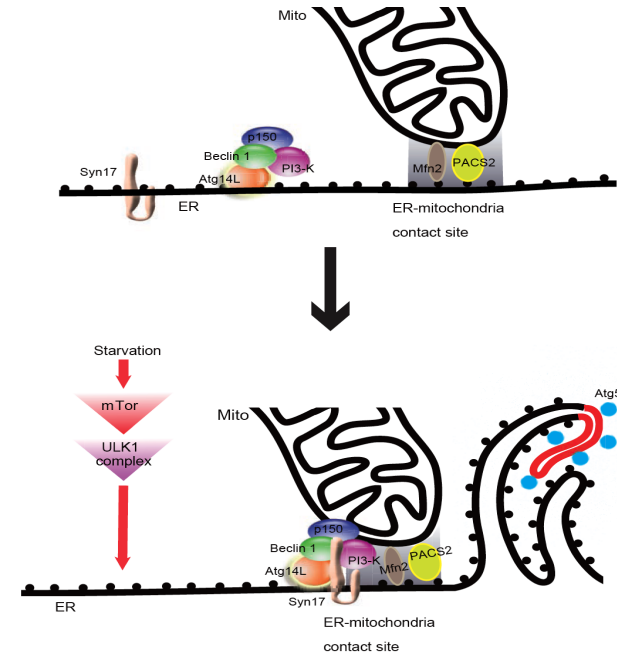
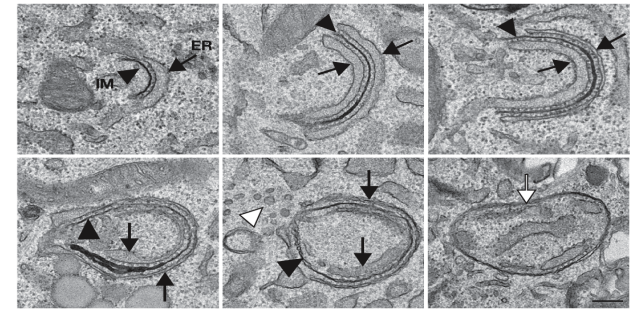
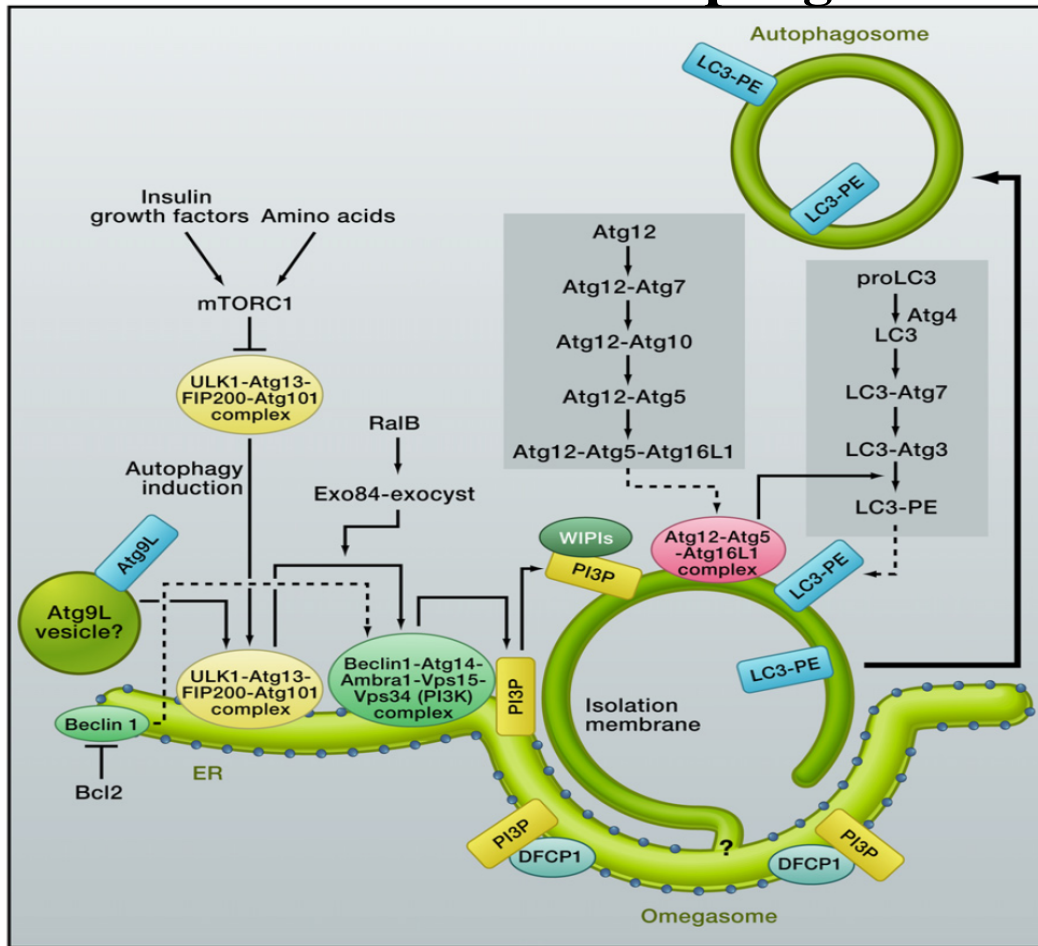


Autophagosome

Phagophore

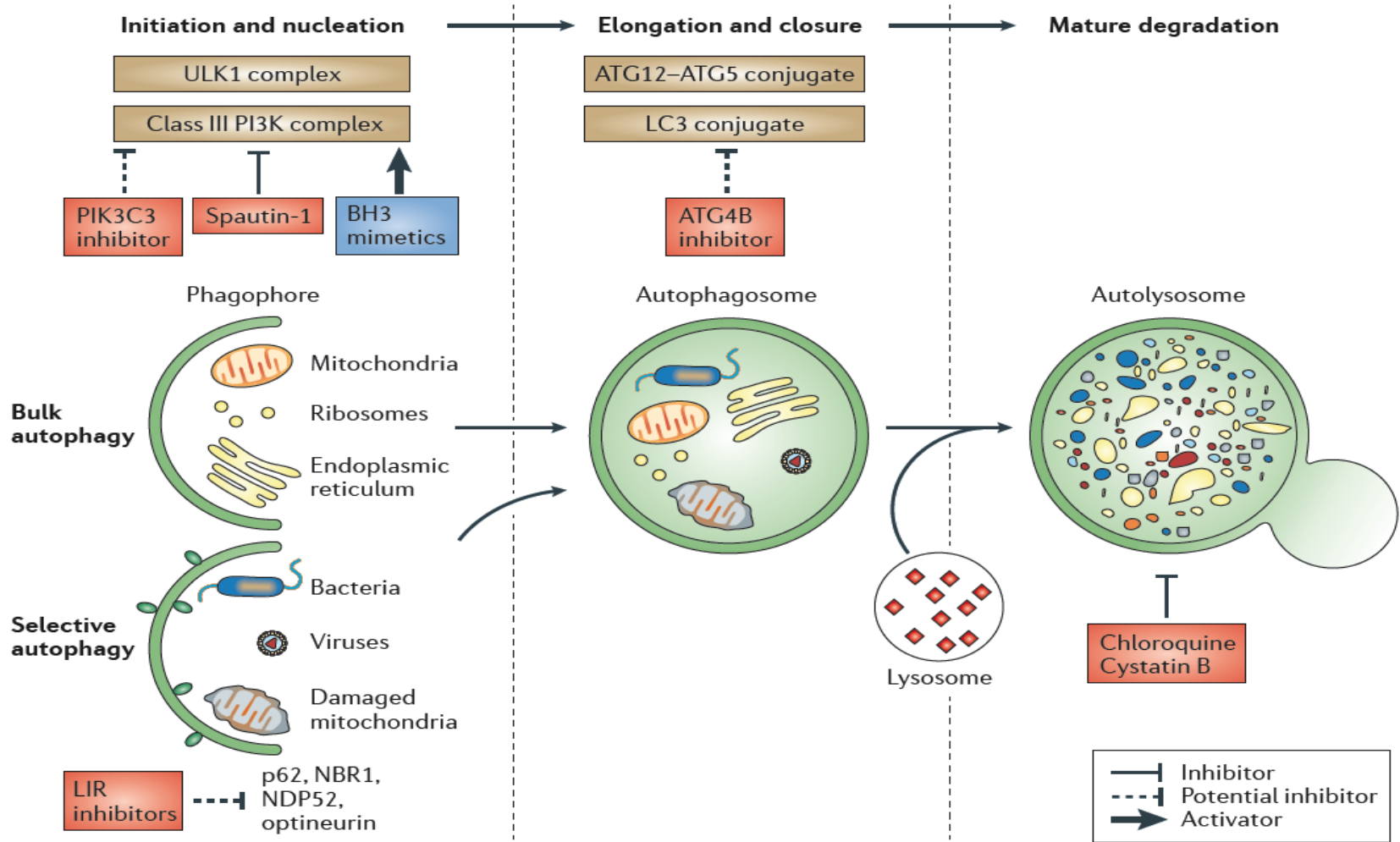
Eskelinen 2005

Autophagosome formation



Mizushima and Komatsu 2011 Cell 147, 728

Hamasaki et al 2013 Nature 495, 389



Rubinsztein, Codogno and Levine 2012 Nat Drug Discov 11, 709

Physiology

Differentiation

Erythrocyte
Adipocyte
Lymphocyte
Neurons

Homeostasis of differentiated cells

Tissue
homeostasis

Development

Pre-implantation of fertilized oocyte
Elimination of maternal mRNAs
Apoptotic cell removal
Hyaloid vessel regression
Neonate survival

Immunity

Thymic selection
Effector of TLR signaling
Effector of Th1/Th2 polarization
Antigen presentation

Basal autophagy

Prevents accumulation of aggregation-prone proteins
Reduces ER stress

Limits ROS production (elimination of damaged mitochondria)

Longevity

Inflammation

Crohn's disease

Cardiac and muscle disease

(Cardio) Myopathy
Pompe's disease

Infectious disease

Pathology

Diabetes
Obesity
Pancreatitis

Liver disease
Hepatocarcinoma
Hepatitis
Fibrosis (Alpha1-antitrypsin mutations)

Neurodegenerative disease

Huntington
Parkinson
Alzheimer
Lafora
Lysosomal Storage Diseases

Cancer

Stimulated autophagy during nutrient starvation

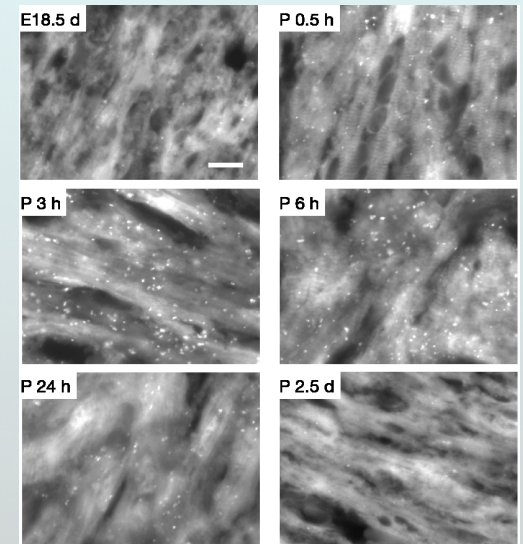
Role in intermediate metabolism

Nutrient supply

Energy supply

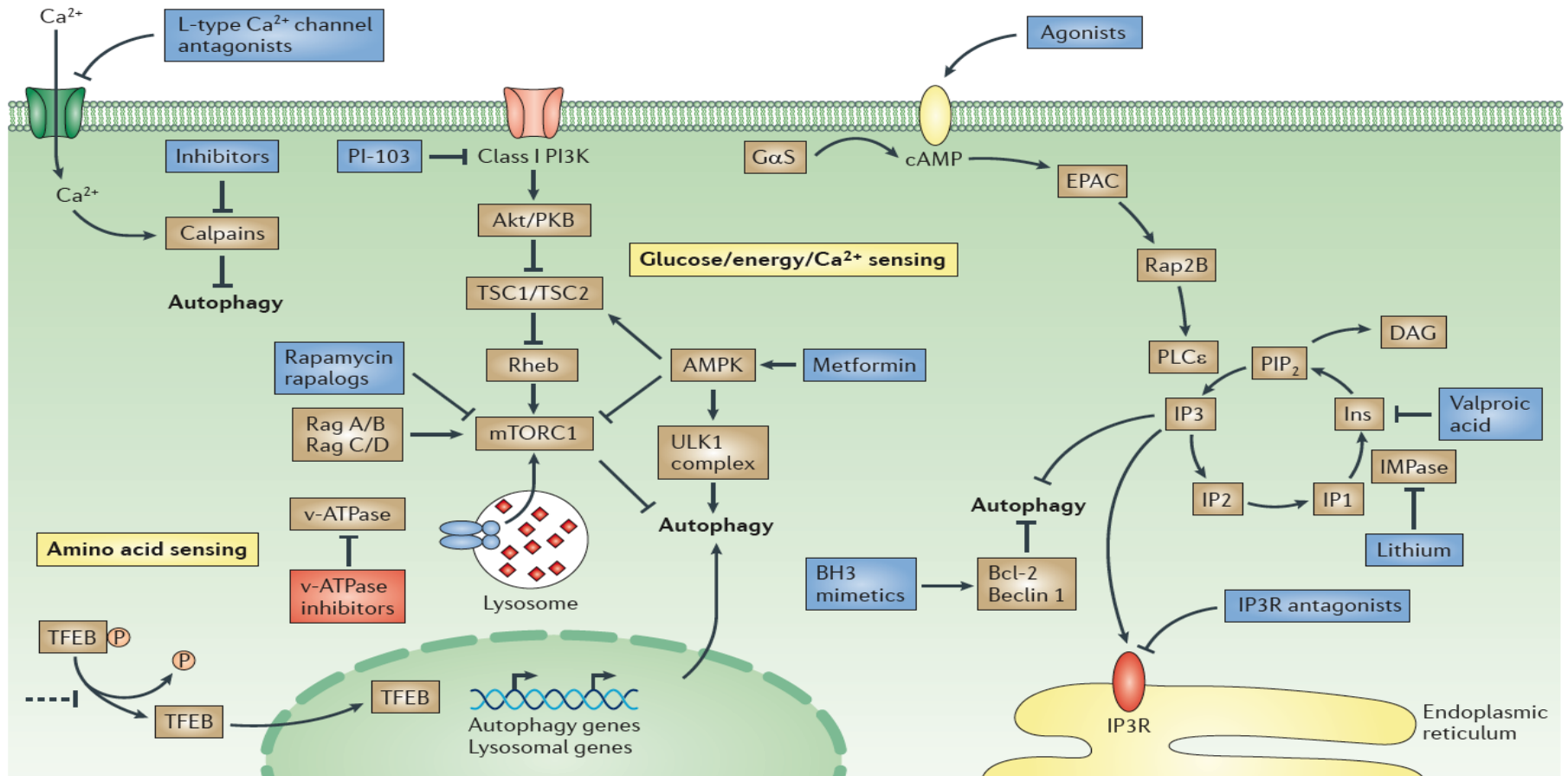


GFP-LC3



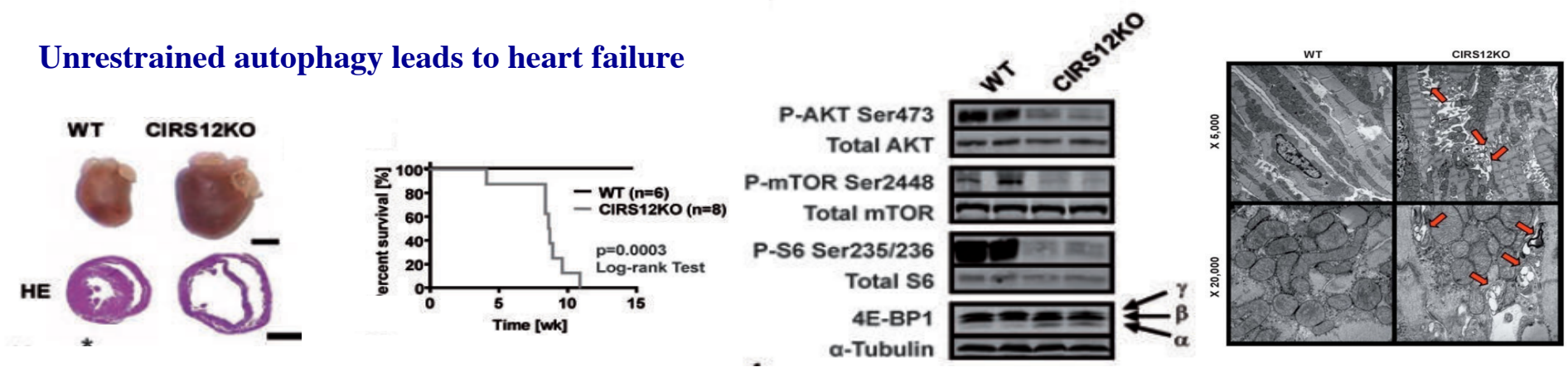
Kuma et al 2004 Nature 432, 1032

The signaling autophagic pathway

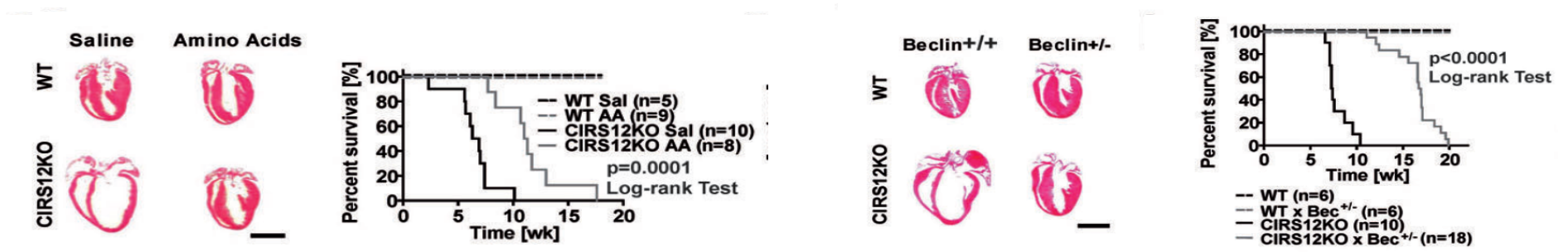


Suppression of neonatal autophagy in the heart

Unrestrained autophagy leads to heart failure

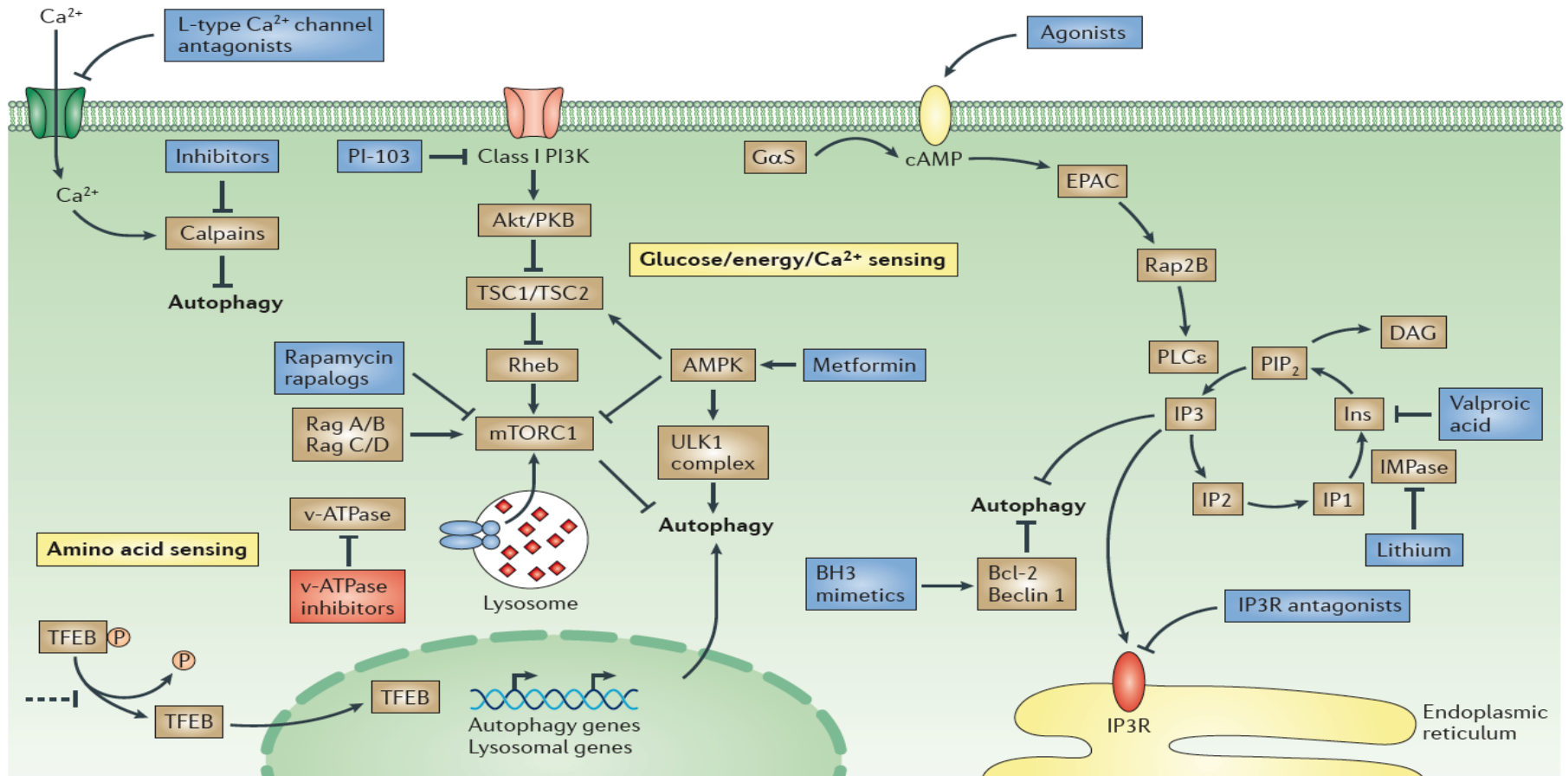


Decrease autophagy attenuates heart failure



From Riehle et al 2013 J Clin Invest 123, 5319

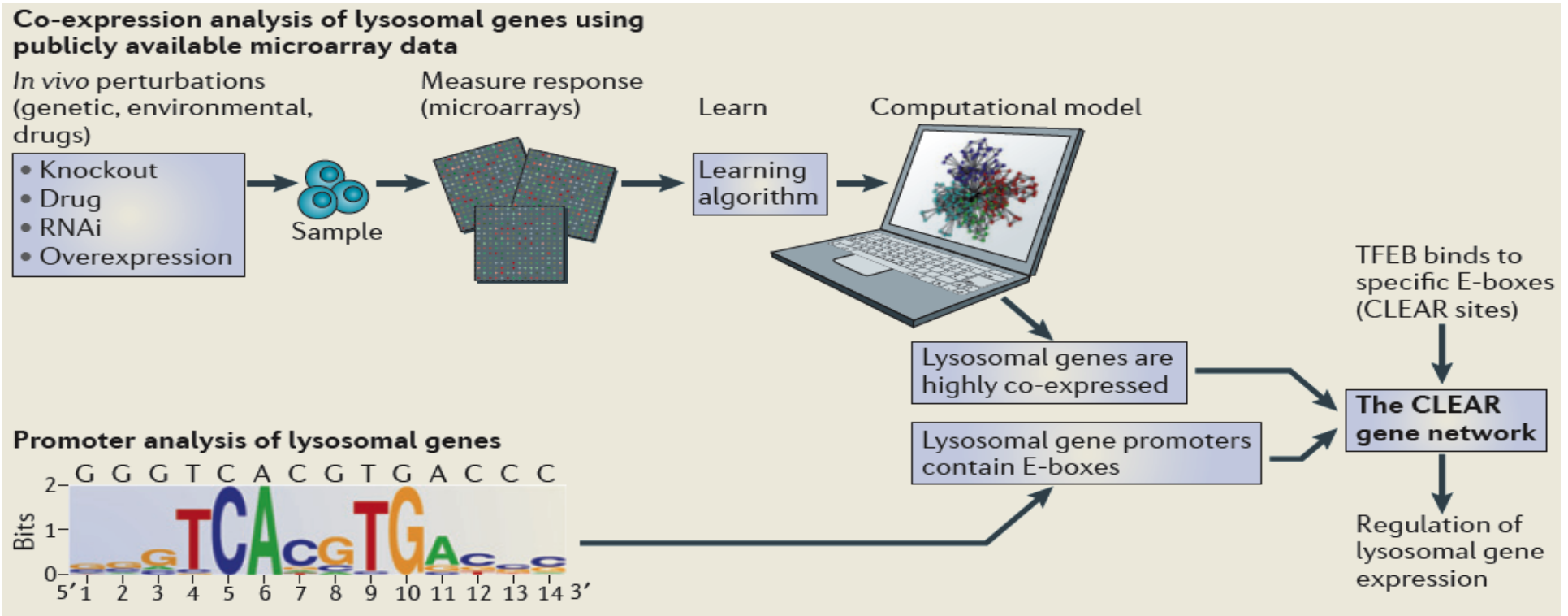
The signaling autophagic pathway



Rubinsztein, Codogno and Levine 2012 *Nat Drug Discov* 11, 709

The identification of the CLEAR gene network

CLEAR: Coordinated lysosomal expression and regulation

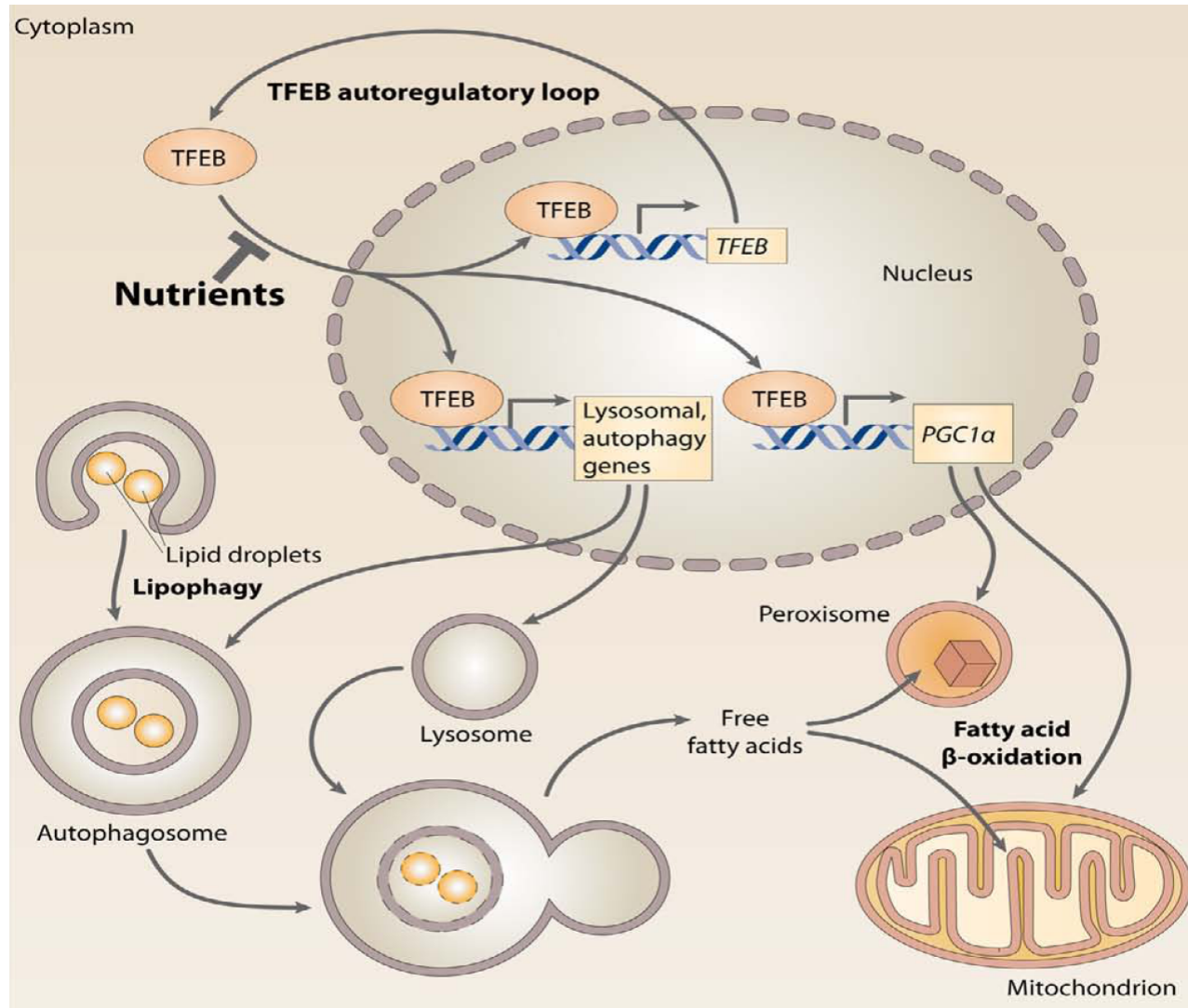


TFEB: member of the MITF (microphthalmia-associated transcription factor) subfamily

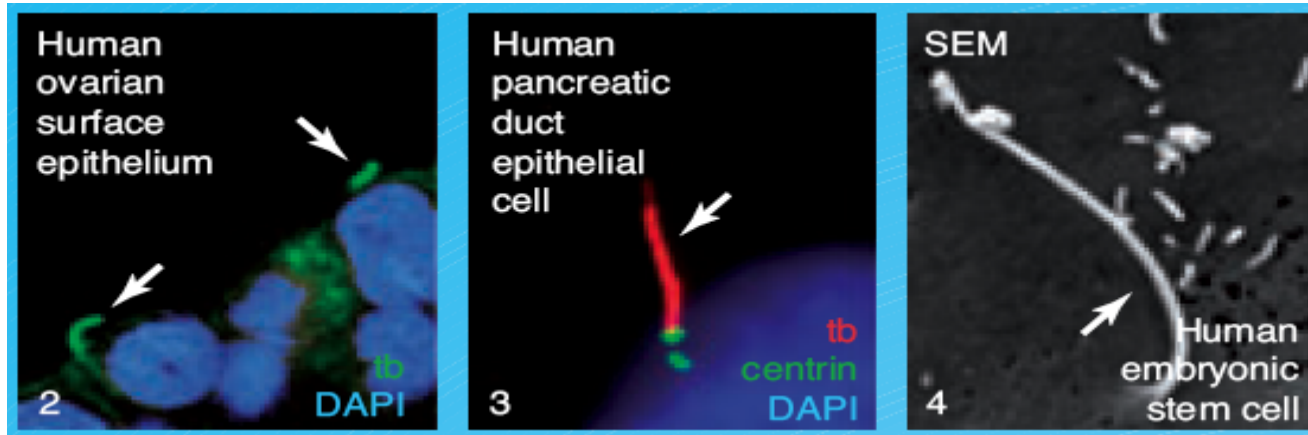
Settembre et al 2013 Nat Rev Mol Cell Biol 14, 283. See also Sardiello et al 2009 Science 325, 473

TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop

Carmine Settembre^{1,2,3,4,11}, Rossella De Cegli^{1,10}, Gelsomina Mansueto^{1,10}, Pradip K. Saha^{5,10}, Francesco Vetrini^{2,3,10}, Orane Visvikis^{6,10}, Tuong Huynh^{2,3}, Annamaria Carissimo¹, Donna Palmer², Tiemo Jürgen Klisch^{2,3}, Amanda C. Wollenberg⁶, Diego Di Bernardo^{1,7}, Lawrence Chan^{5,8,9}, Javier E. Irazoqui⁶ and Andrea Ballabio^{1,2,3,4,11}

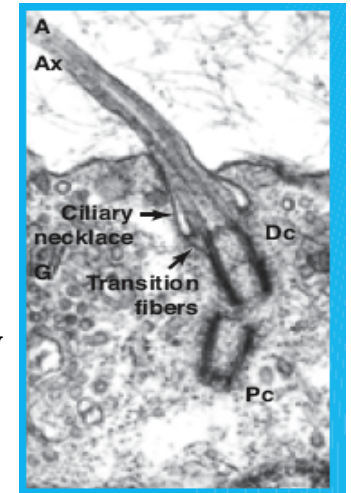


Autophagy and primary cilium



Axoneme

Basal Body



From Satir, Pedersen and Christensen 2010 J Cell Sci 123, 499

Idil Orhon, Chantal Bauvy, Isabelle Beau

Collaboration: Ana Maria Cuervo A. Einstein College of Medicine (Bronx, NY, USA)

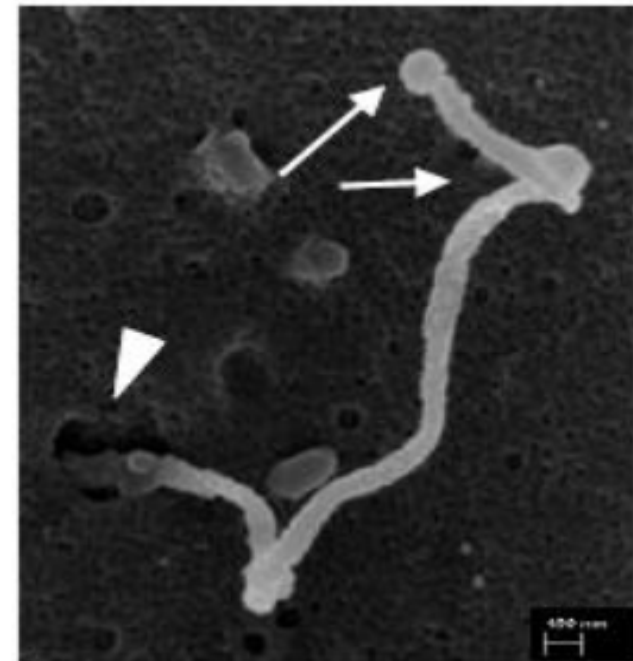
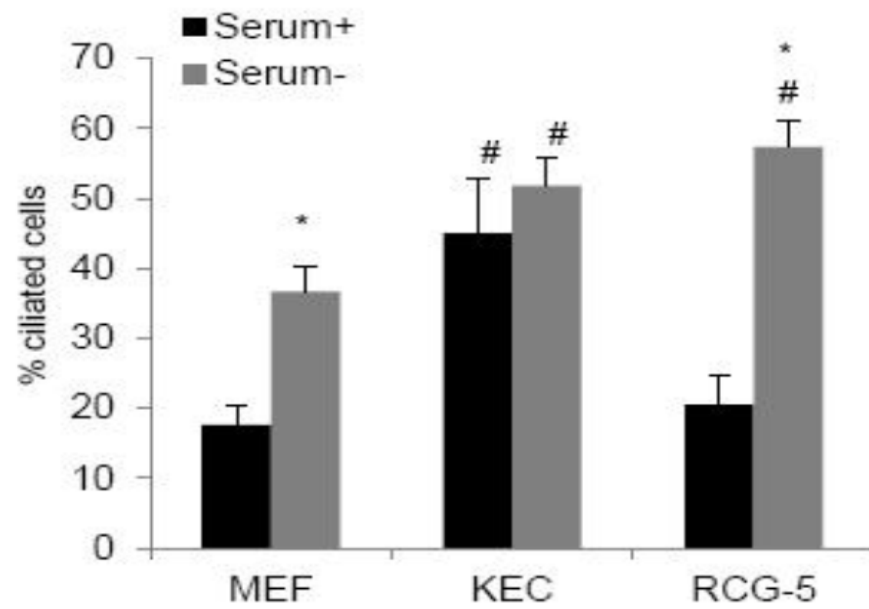
Collaboration: Satir P A. Einstein College of Medicine (Bronx, NY, USA)

Functions of mammalian primary cilium

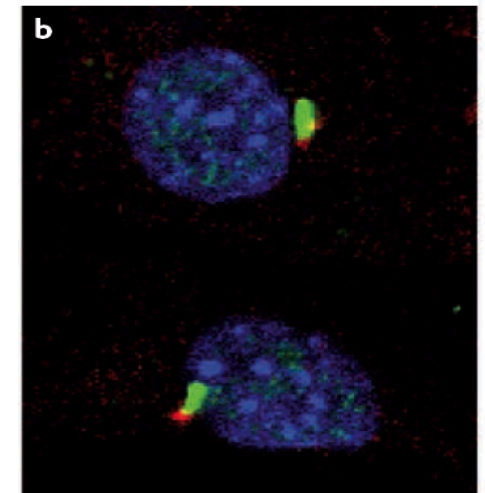
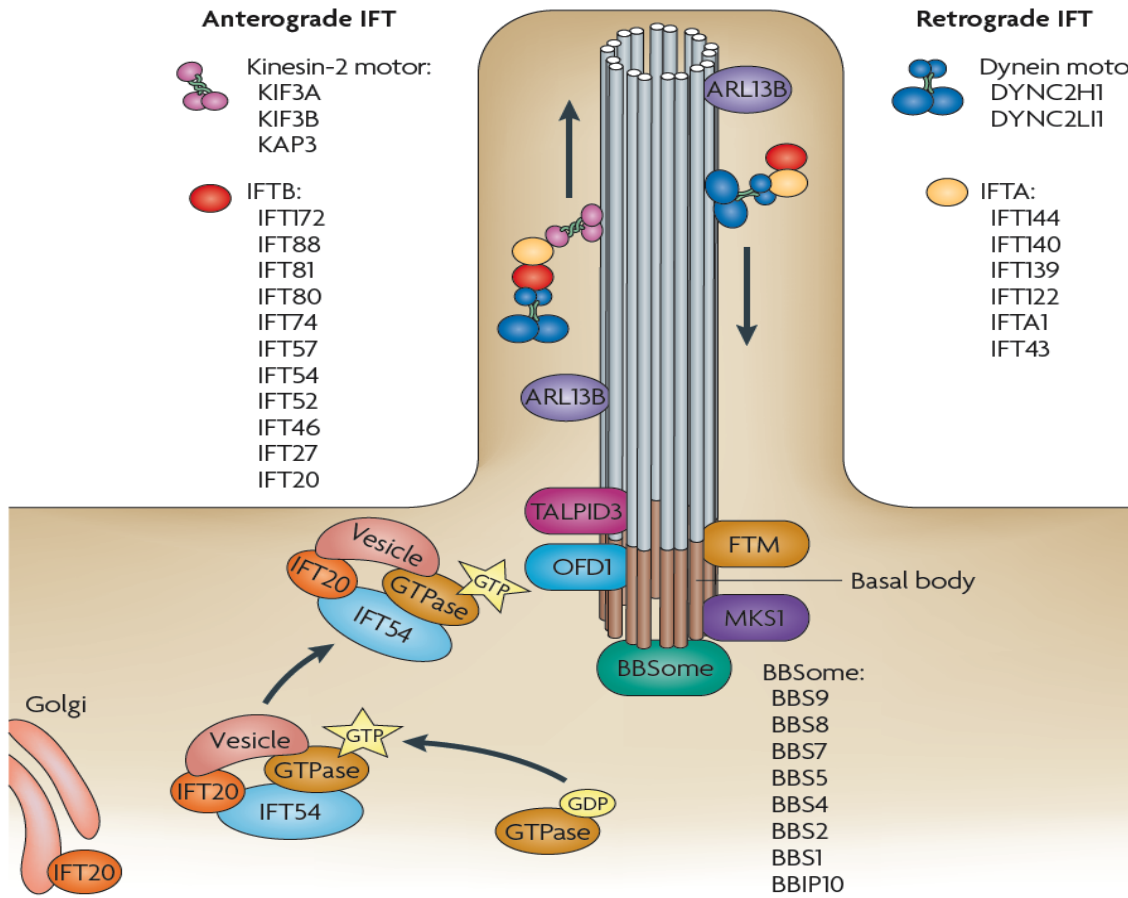
- ✓ **Coordinator of signaling pathways: Hedgehog, PDGF, Wnt... during development and in tissue homeostasis**
- ✓ **Sensory modalities:**
 - Mechanical stimulation (bending)**
 - Chemosensation (ligand, growth factor, morphogen)**
- ✓ **Ciliopathies: human diseases and developmental disorders**

Ciliogenesis in different cell types

MEF Serum-

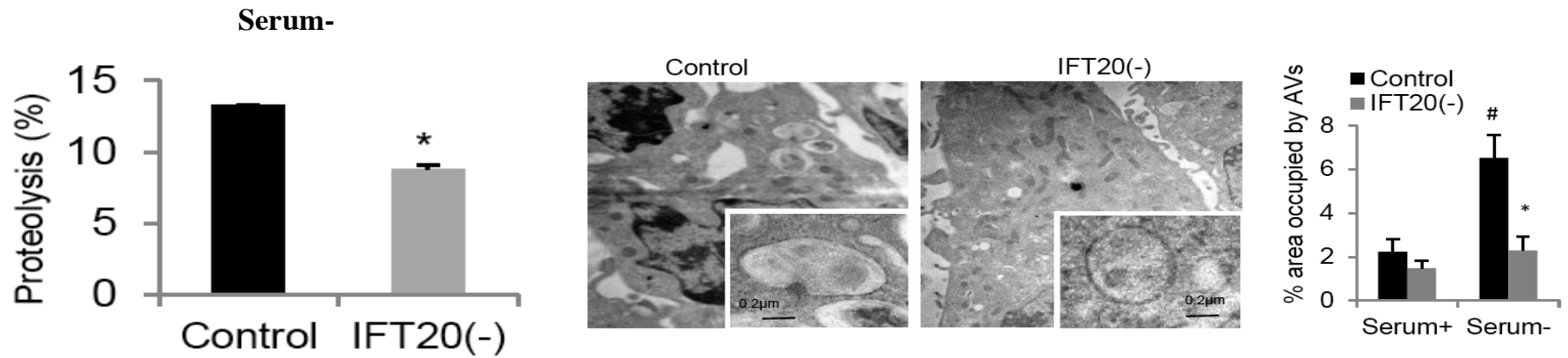
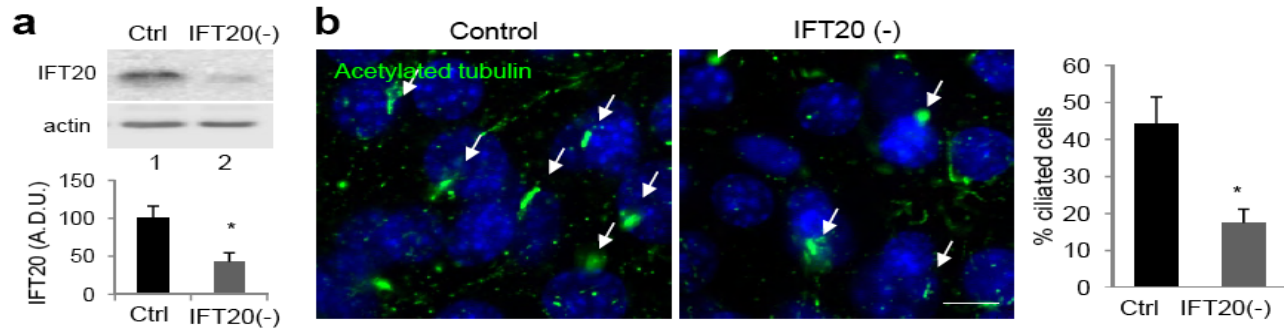


Cilia structure and intraflagellar transport



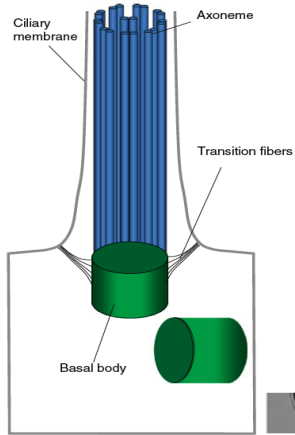
From Goetz and Anderson (2010) *Nat Rev Genet* 11, 331

Knock-down of IFT20 reduces autophagic activity (Mouse Embryo Fibroblats)



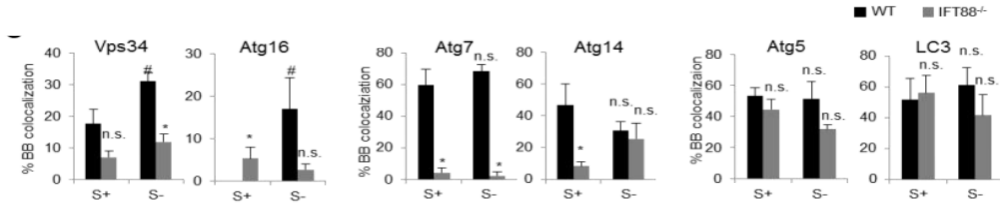
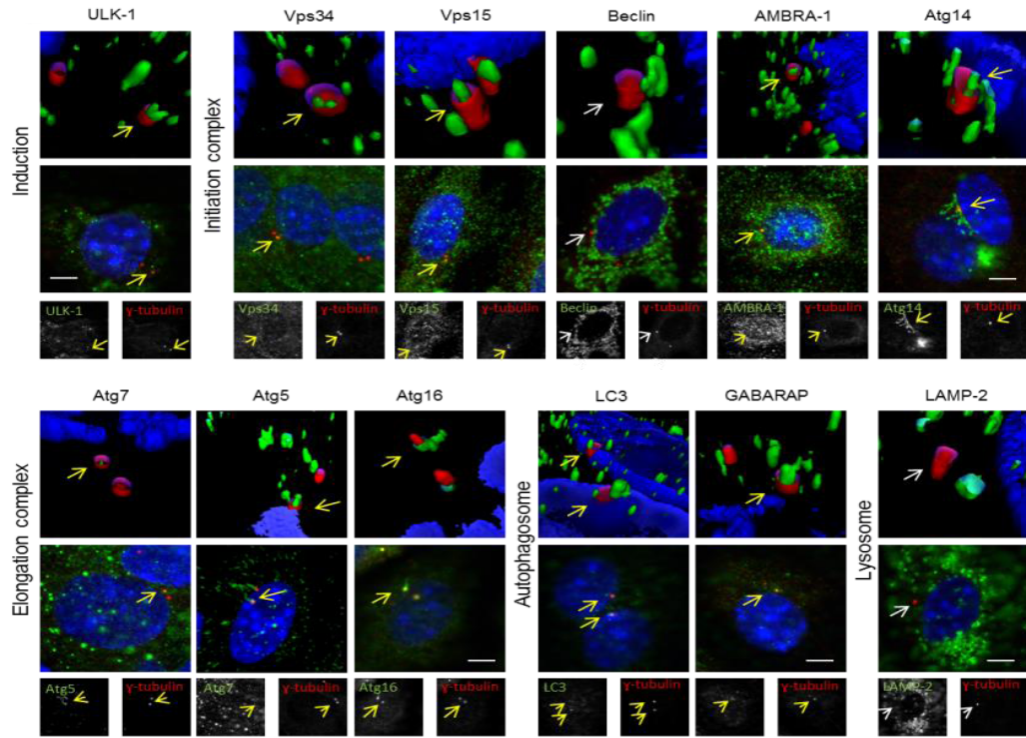
Distribution of autophagy machinery at the basal body

Serum-

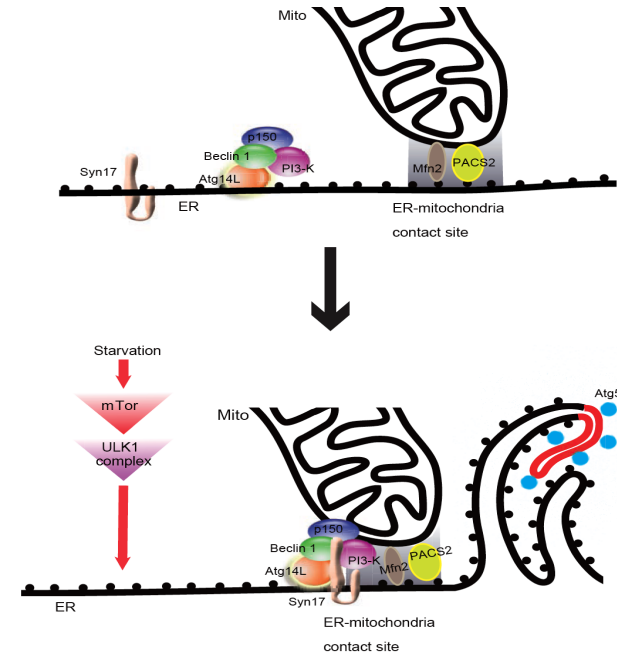
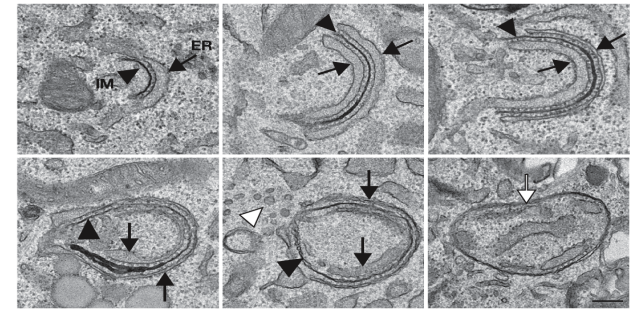
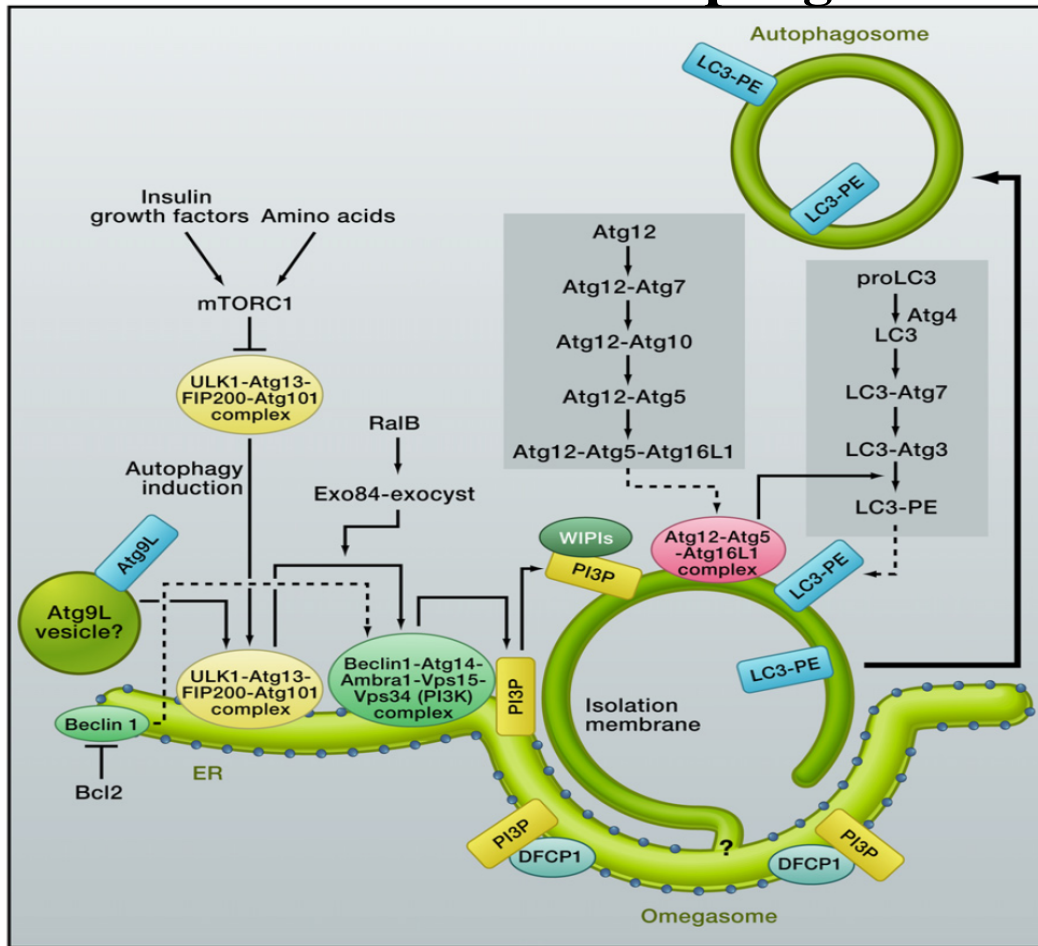


γ -tubulin (red)

ATG (green)



Autophagosome formation

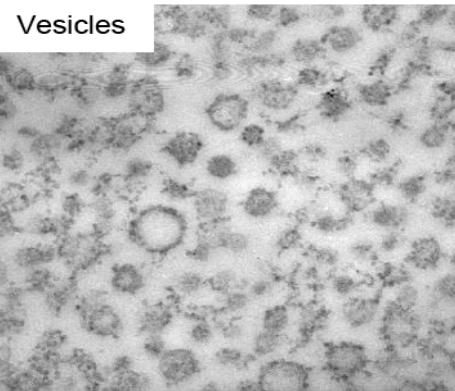
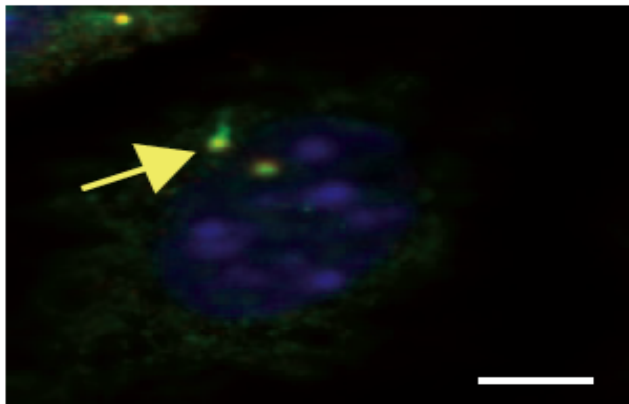
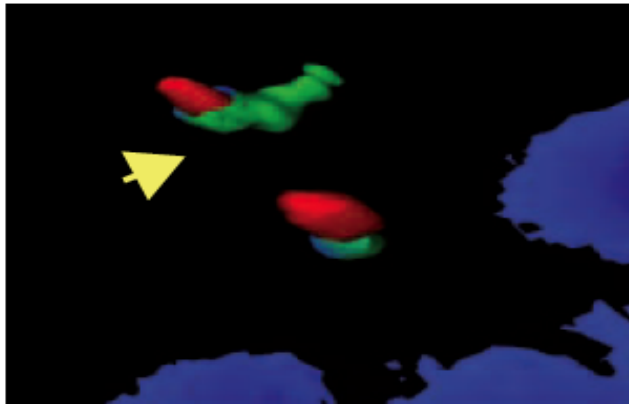


Mizushima and Komatsu 2011 Cell 147, 728

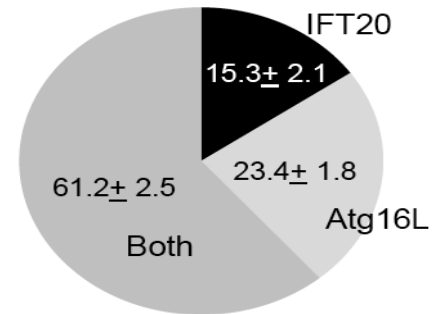
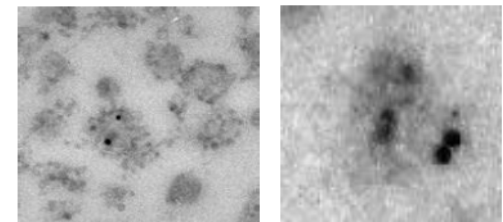
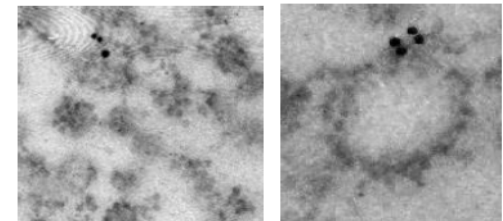
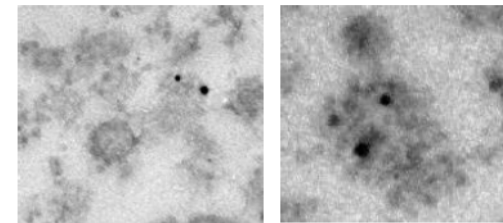
Hamasaki et al 2013 Nature 495, 389

IFT20 regulates the trafficking of ATG16L to the cilium

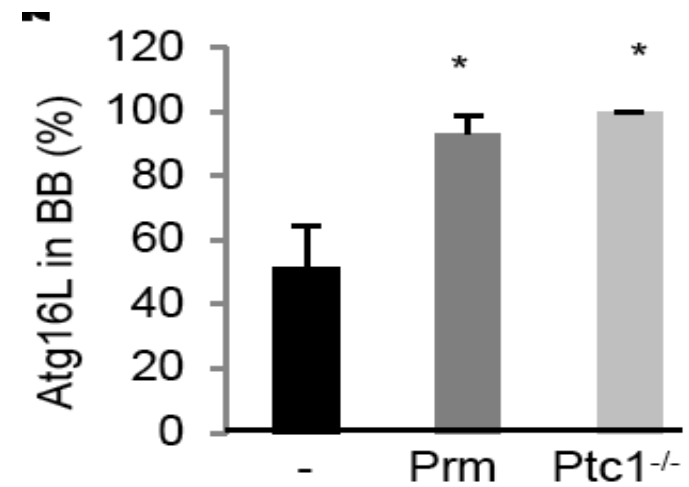
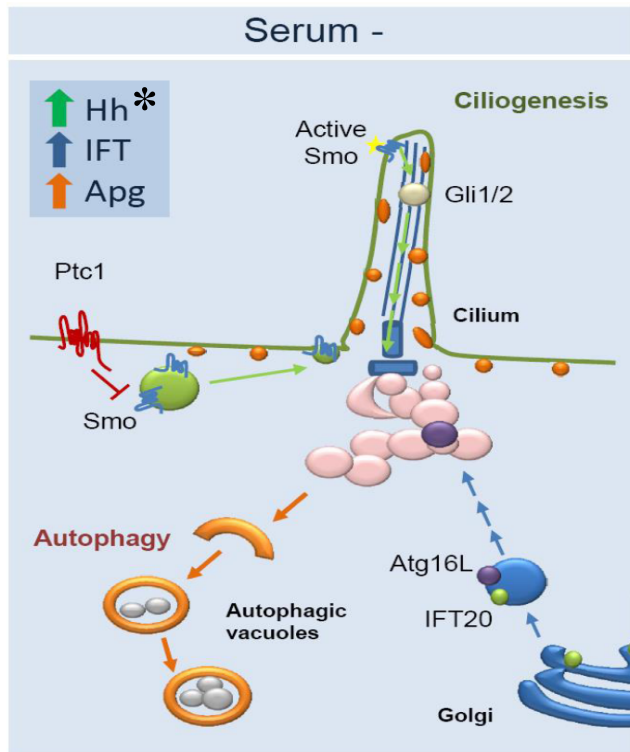
ATG16L



Atg16 (15nm) + IFT20(10nm)



Interplay between autophagy and ciliogenesis



KEYS



Atgs



Lipid-binding Atgs



IFT20



Smo



Atg16L



Ptc1

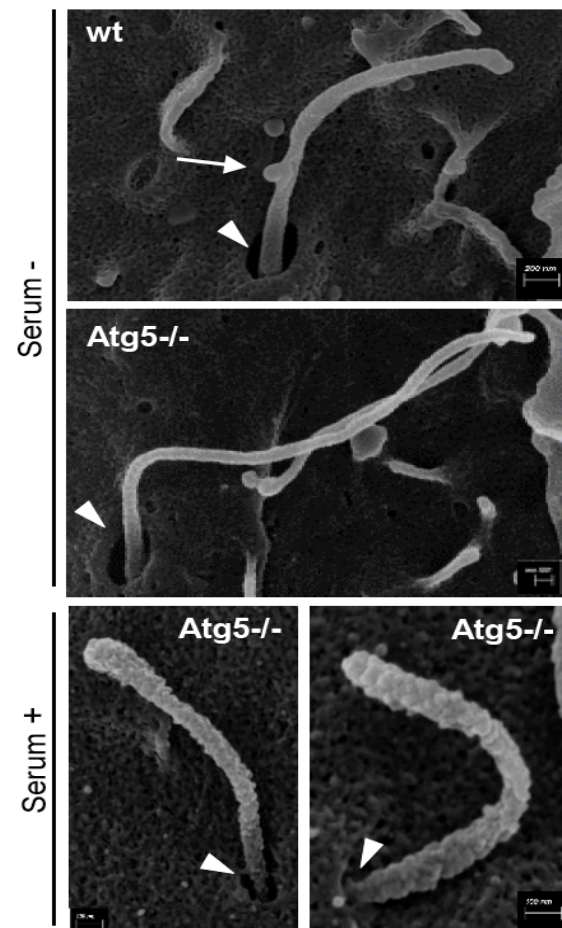
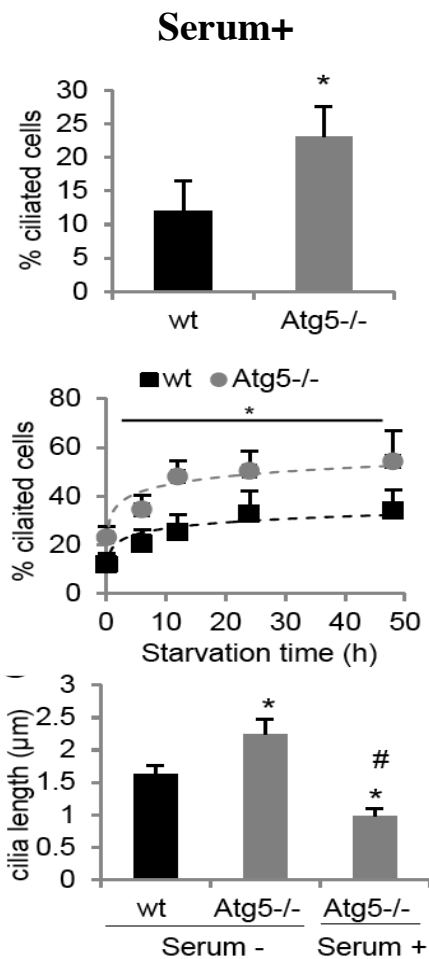
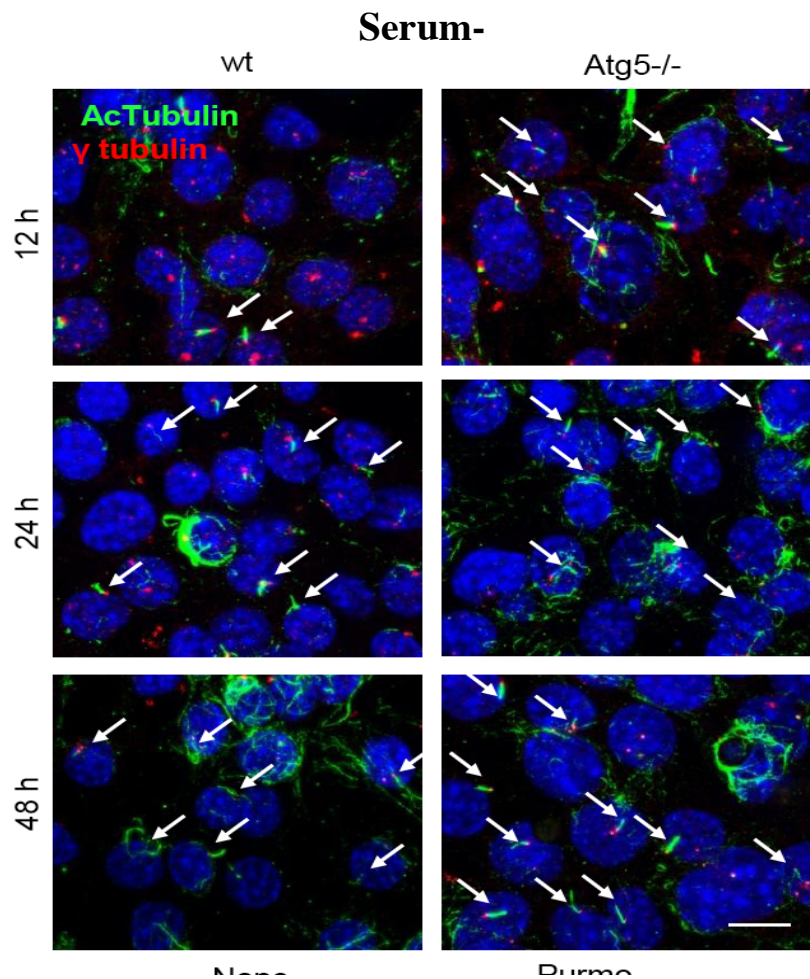


Gli1/2



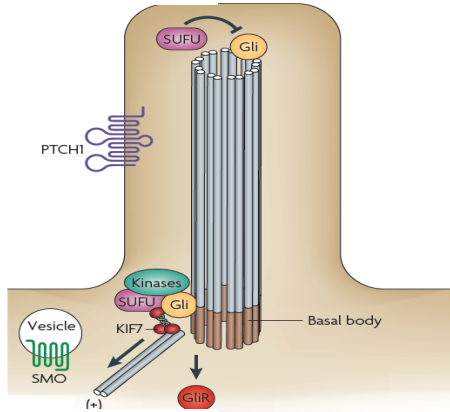
**Autophagy
regulates cilia growth**

Ciliogenesis is enhanced in autophagy-defective cells

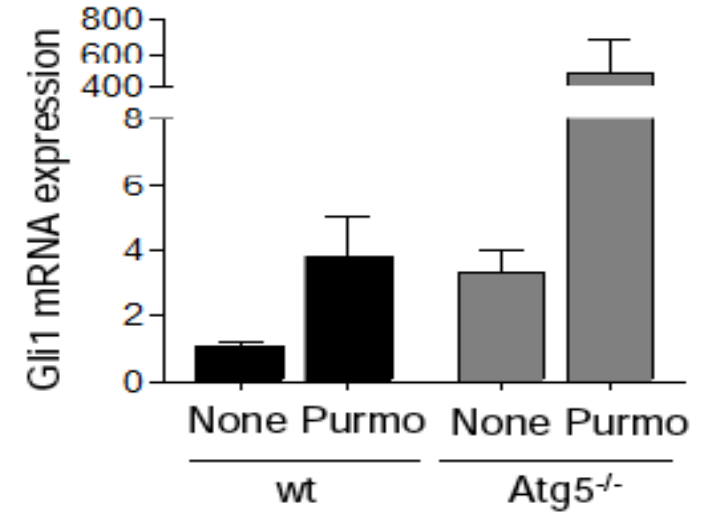
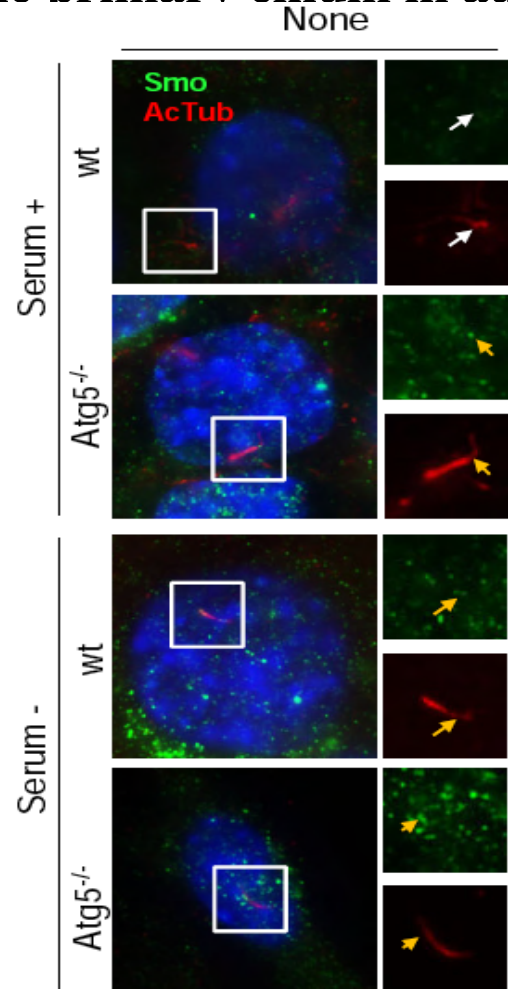
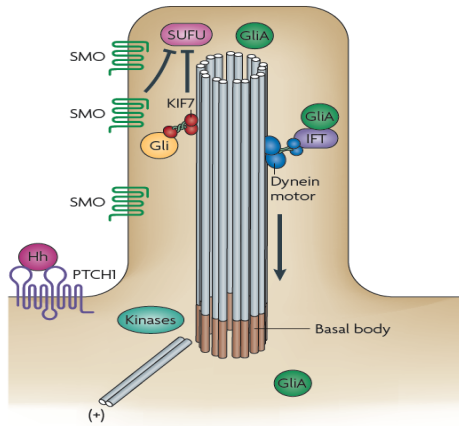


Functionality of the primary cilium in autophagy-deficient cells

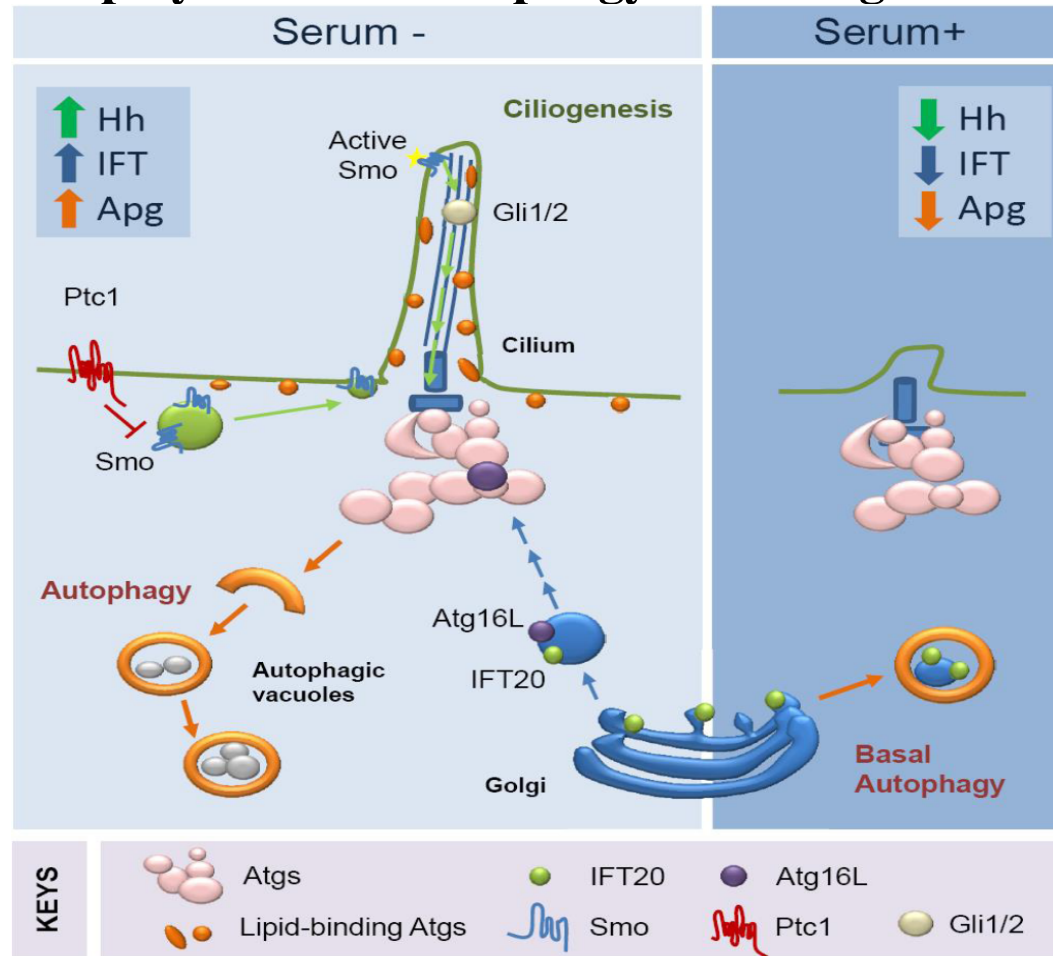
Unstimulated



Hh stimulated



Interplay between autophagy and ciliogenesis



Pampliega, Orhon et al 2013 Nature 502: 194-200

Present

**Chantal Bauvy
Joëlle Botti
Nicolas Dupont
Anne Greffard
Ahmed Hamai
Maryam Mehrpour
Etienne Morel
Idil Orhon**

Past

**Isabelle Beau
Matthieu Bertrand
Mojgan Djavaheri-Mergny
Audrey Esclatine
Séverine Lorin
Sophie Pattingre
Francesca Scarlatti**

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**Birgit Satir
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**Department of Development and Molecular
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**Albert Einstein College of Medicine
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**Olatz Pampliega
Bindi Patel
Ana Maria Cuervo**