

# Kjøreregler for Forelesningen

**NB: Forelesningen vil bli tatt opp og lagt ut på YouTube etterpå. Hvis du ikke ønsker å komme med på opptaket, skru av mikrofon og video, og ikke del skjermen din. Du kan også velge å forlate denne forelesningen nå.**

**Stille spørsmål?** Du kan når som helst bruke **Chat feltet på Skype** til å stille spørsmål. Du kan også **melde deg med navn** i feltet til å muntlig stille spørsmål med påsatt lyd og video. Men jeg følger ikke med på dette feltet mens jeg gir forelesning. Etter forelesningen, kan jeg besvare spørsmål (skriftlig & muntlig).

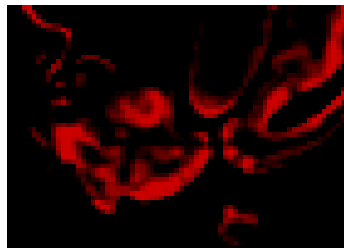
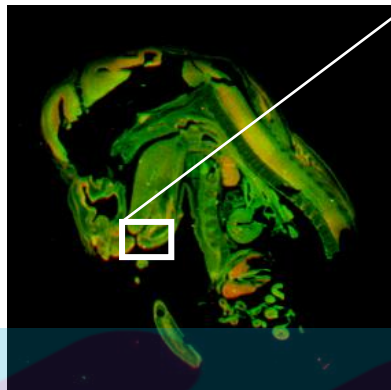


# *En ny rolle for vårt medfødte immunforsvar*

Geir Bjørkøy

Daglig leder, Vitensenter Nordland

Dr. scient, professor NTNU

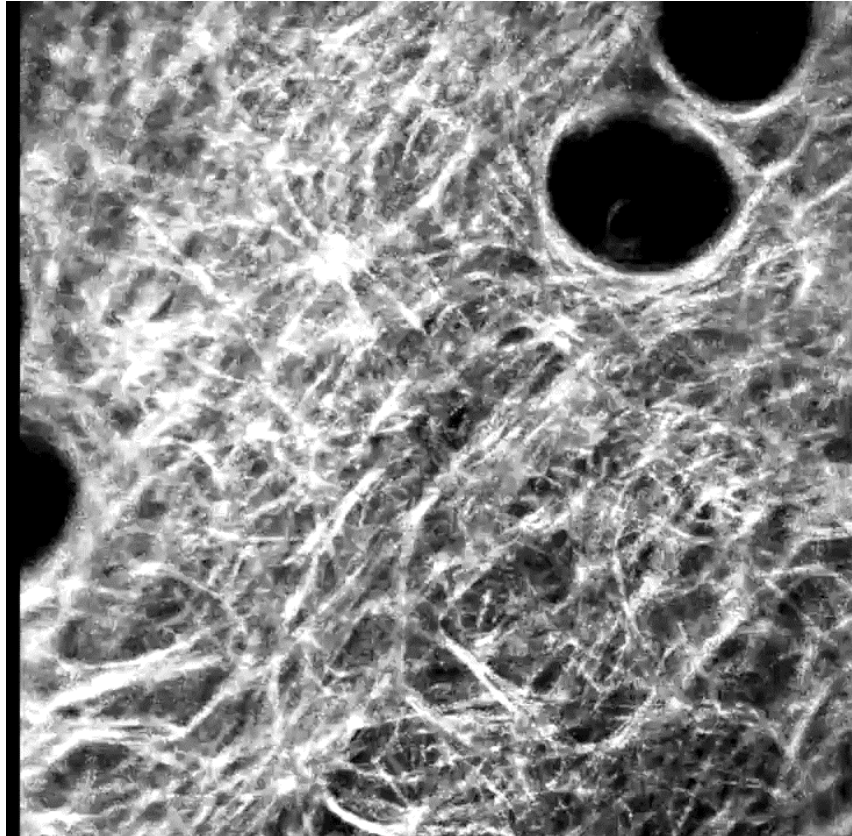
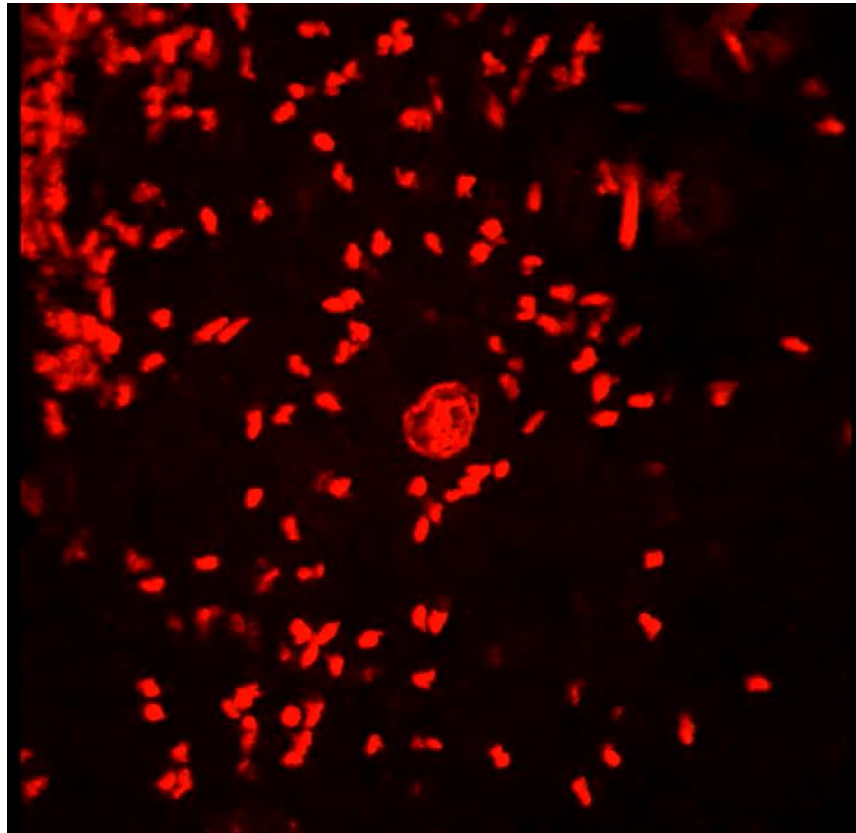


# Akkurat nå, bakgrunn og frempek....



<https://www.wibbitz.com/watch/bcc90a21819614d2aaee7d7f3f7fc9230/?cl=#7f8790&cl4=#15324e&lg=8132e369779d4f878702ab25f531c8cf&type=produced>

# Umiddelbar immunreaksjon – nøytrofile



Ronald Germain, NIH, Laboratory of Immune System Biology

<https://www.youtube.com/watch?v=BdYcmcVI99E>

<https://www.youtube.com/watch?v=HPeEyfgt8hY>



# Kalori-restriksjon og helse...

27 år gammel  
Redusert kalori-inntak  
Diett: Prosessert mat  
Høyt sukkerinnhold  
Denne gruppen:  
- Levde lengre  
- Var mindre syk



A 2009 image of rhesus monkeys in a landmark study of the benefits of caloric restriction. The 27-year-old monkey on the left was given a diet with fewer calories while the 29-year-old monkey on the right was allowed to eat as much as it liked. Both animals have since died of natural causes. PHOTO: JEFF MILLER

Mindre effekt med mer naturlig kosthold  
Hunnene tåler overvekt bedre  
Kalorirestriksjonen bør ikke starte for tidlig

29 år gammel  
Ubegrenset kalori-inntak  
Diett: Prosessert mat  
Høyt sukkerinnhold  
Denne gruppen hadde:  
- Økt kreft  
- Økt insulinresistens  
- Økte hjerte-kar lidelser

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DOI: 10.1038/ncomms14063

OPEN

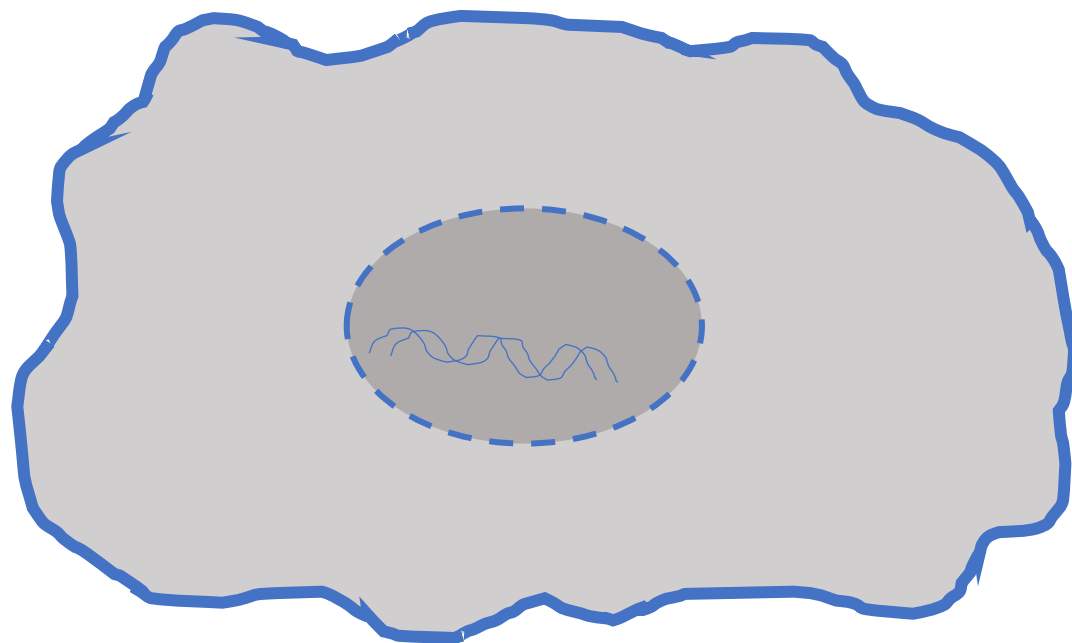
Caloric restriction improves health and survival of rhesus monkeys

Julie A. Mattison<sup>1,\*</sup>, Ricki J. Colman<sup>2,\*</sup>, T. Mark Beasley<sup>3,4,\*</sup>, David B. Allison<sup>3</sup>, Joseph W. Kemnitz<sup>2,5</sup>, George S. Roth<sup>6</sup>, Donald K. Ingram<sup>7</sup>, Richard Weindruch<sup>8,9</sup>, Rafael de Cabo<sup>1,\*\*</sup> & Rozalyn M. Anderson<sup>8,9,\*\*</sup>

# Flercellede organismer er avhengig av at cellene fungerer og samarbeider

Sykdommer som skyldes at (noen) celler blir taper funksjoner:

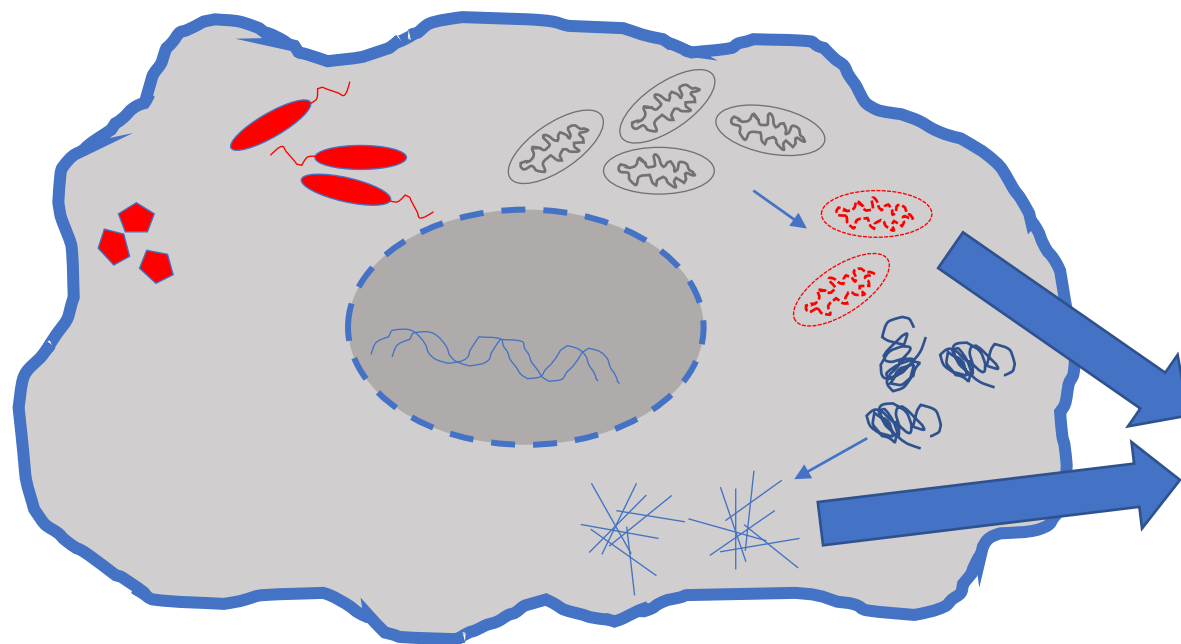
- kreft, hjerte-kar lidelser, demens, auto-immune sykdommer .....



Kroppen består av  $1300 \times 10^9$  celler  
Mange ulike typer celler organisert i vev  
Ulike funksjoner og levetid

# Våre celler må fjerne uønsket innhold – eller dø

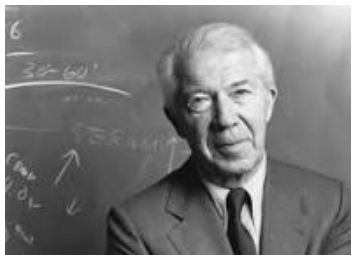
Virus – intracellulære bakterier – ødelagte cellekomponenter – feilfoldede proteiner ++++++



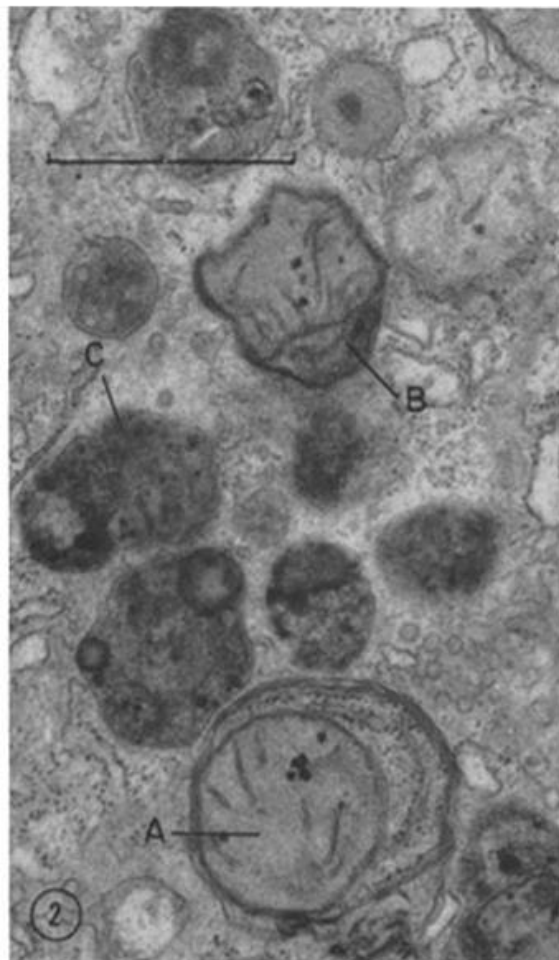
Kan «søppelfjerningen» være kontrollert av immunceller?

Immunstimulerende alarmsignaler

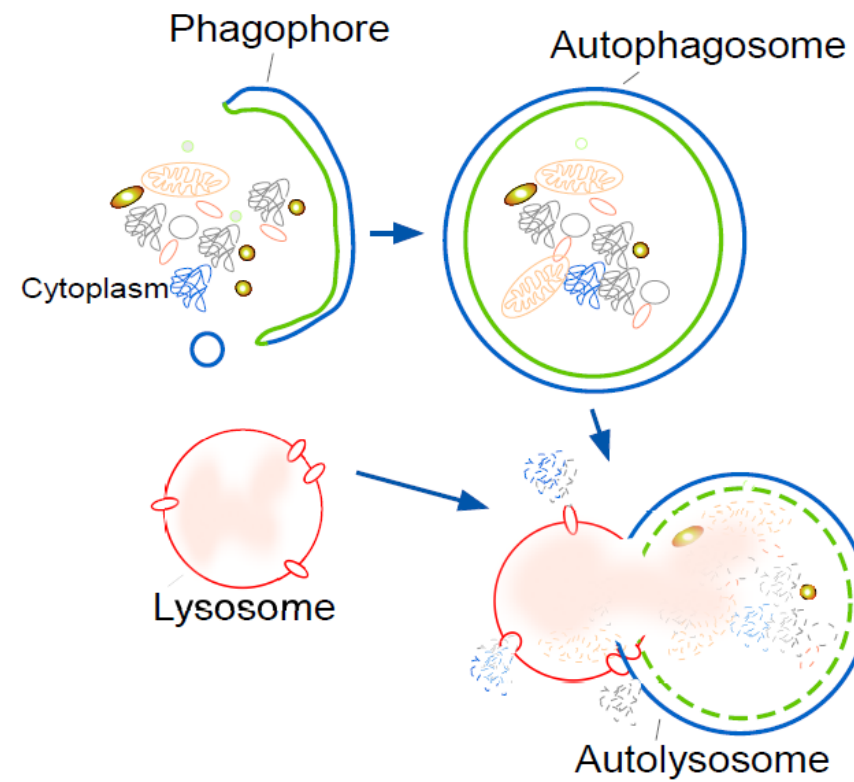
# Autophagy (selv-degradering inne i våre celler)



Christian de Duve



ASHFORD, T.P. and PORTER, K.R. 1962, J Cell Biol





# Identifisering av genene som driver autofagi



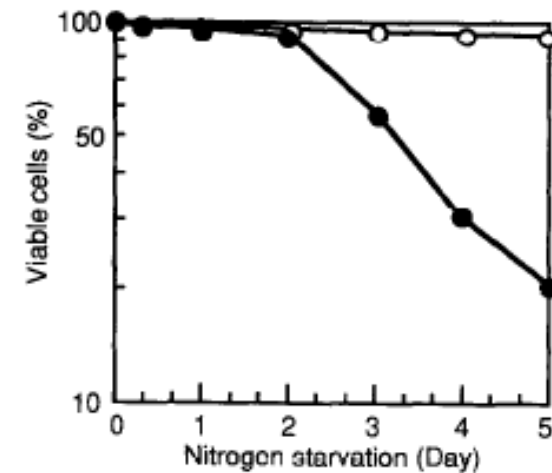
Yoshinori Ohsumi

**The Nobel Prize in Physiology or Medicine 2016**



Vacuoles in lysosomal protease deficient yeast under nitrogen starvation

Takeshigi K. et al 1992 J Cell Biol

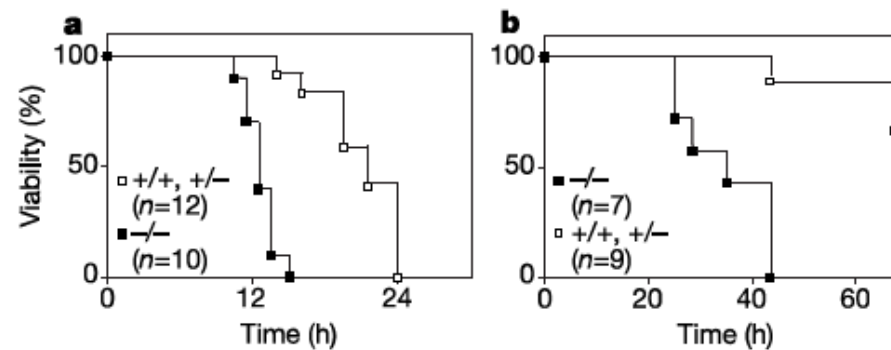


Loss of viability of the *apg1* mutant in nitrogen starvation medium.

Miki Tsukada and Yoshinori Ohsumi, (1993) FEBS

# 1. generasjon autofagi KO-mus

Kuma, A. et al. The role of autophagy during the early neonatal starvation period. *Nature* 432, 1032--1036 (2004).



**Figure 3** Early postnatal lethality of *Atg5*<sup>-/-</sup> mice. Neonates were obtained by caesarean delivery. **a, b**, Successfully resuscitated pups were monitored in a humidified chamber without milk feeding (**a**) or with artificial milk feeding provided every 3–6 h through a tube inserted into the stomach (**b**).

Kuma et al *Nature* 2004

## 2. generasjon autofagi KO-mus – defekt autofagi i CNS

- Engstelige, tap av reflekser og balanse
- Død av neurodegenerering

### Loss of autophagy in the central nervous system causes neurodegeneration in mice

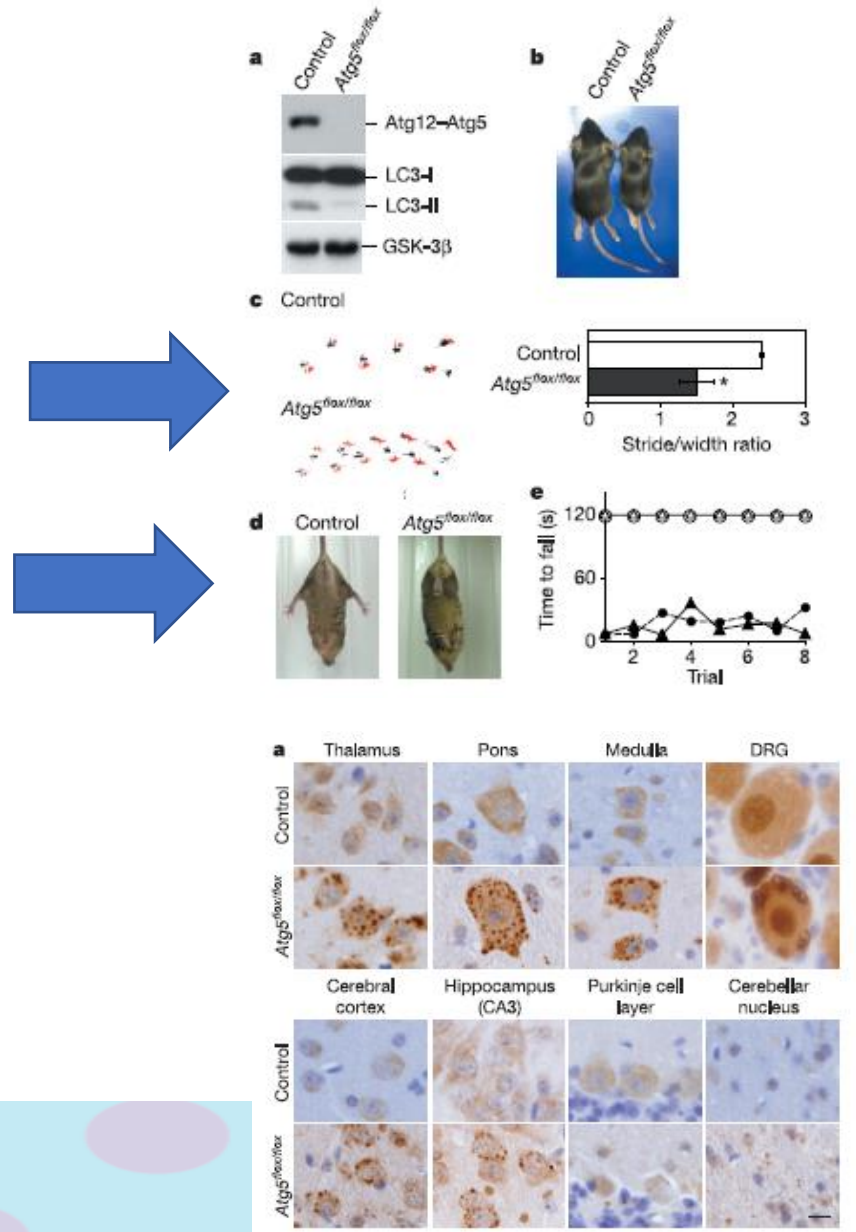
Masaaki Komatsu<sup>1,2\*</sup>, Satoshi Waguri<sup>3\*†</sup>, Tomoki Chiba<sup>1</sup>, Shigeo Murata<sup>1</sup>, Jun-ichi Iwata<sup>1,2</sup>, Isei Tanida<sup>2</sup>, Takashi Ueno<sup>2</sup>, Masato Koike<sup>3</sup>, Yasuo Uchiyama<sup>3</sup>, Eiki Kominami<sup>2</sup> & Keiji Tanaka<sup>1</sup>

NATURE, Vol 441, 15 June 2006

### Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice

Taichi Hara<sup>1</sup>, Kenji Nakamura<sup>2</sup>, Makoto Matsui<sup>1,3,4</sup>, Akitsugu Yamamoto<sup>5</sup>, Yohko Nakahara<sup>2</sup>, Rika Suzuki-Migishima<sup>2</sup>, Minesuke Yokoyama<sup>6</sup>, Kenji Mishima<sup>7</sup>, Ichiro Saito<sup>7</sup>, Hideyuki Okano<sup>8,9</sup> & Noboru Mizushima<sup>1,10</sup>

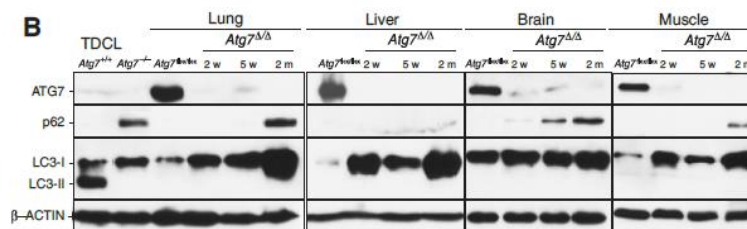
NATURE, Vol 441, 15 June 2006



# Systemisk tap av autofagi i voksne mus

Indusert, systemisk KO i unge voksne

*Cancer Discovery* 2014;4:914-927. Published OnlineFirst May 29, 2014.

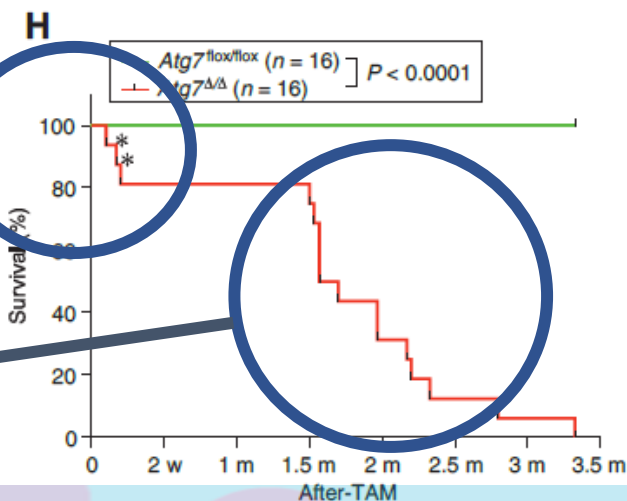


## Autophagy Is Required for Glucose Homeostasis and Lung Tumor Maintenance

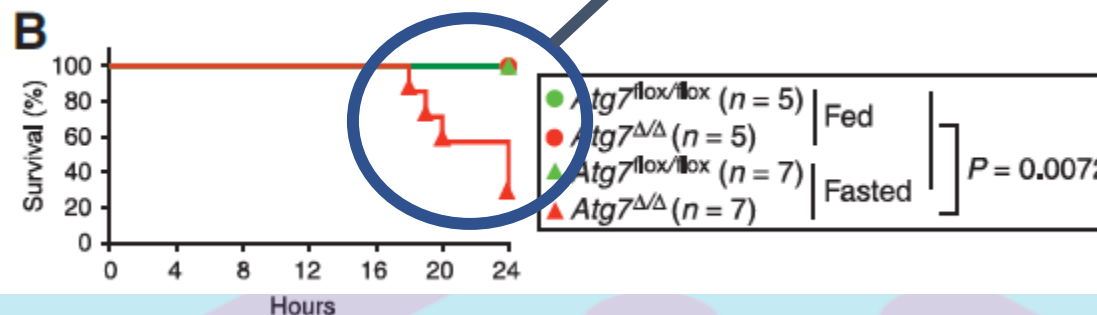
Gizem Karsli-Uzunbas<sup>1,2</sup>, Jessie Yanxiang Guo<sup>1,2</sup>, Sandy Price<sup>1</sup>, Xin Teng<sup>3</sup>, Saurabh V Laddha<sup>1</sup>, Sinan Khor<sup>1,2</sup>, Nada Y. Kalaany<sup>4</sup>, Tyler Jacks<sup>5,6</sup>, Chang S. Chan<sup>1,7</sup>, Joshua D. Rabinowitz<sup>1,3</sup>, and Eileen White<sup>1,2</sup>

Døde av Intracellulære bakterier

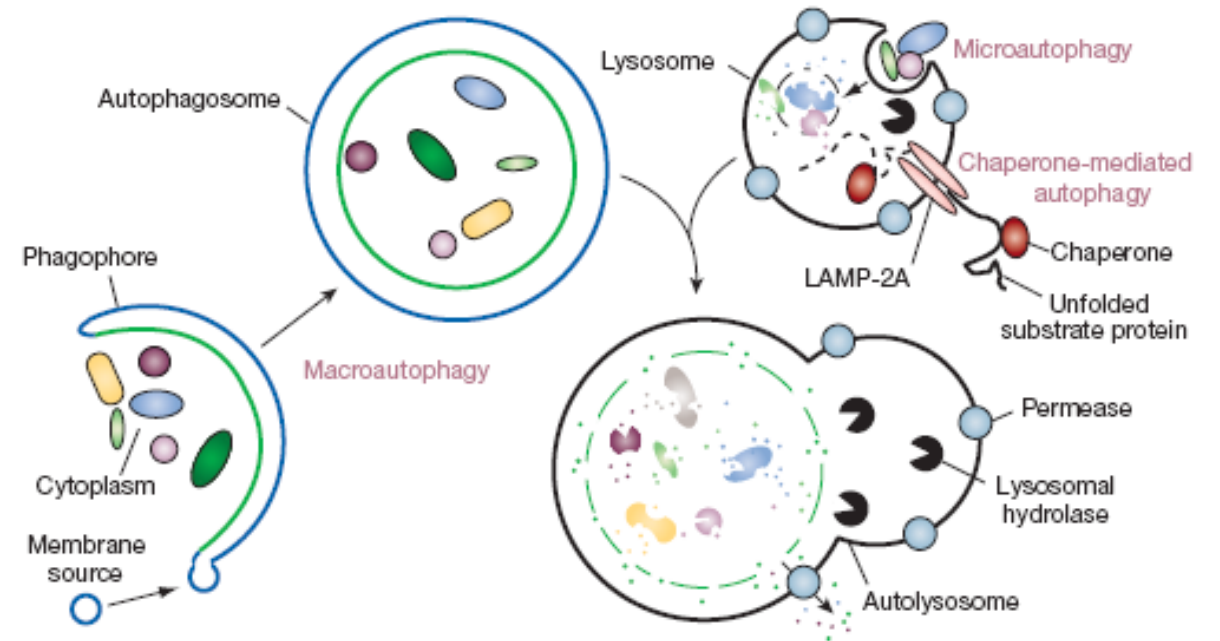
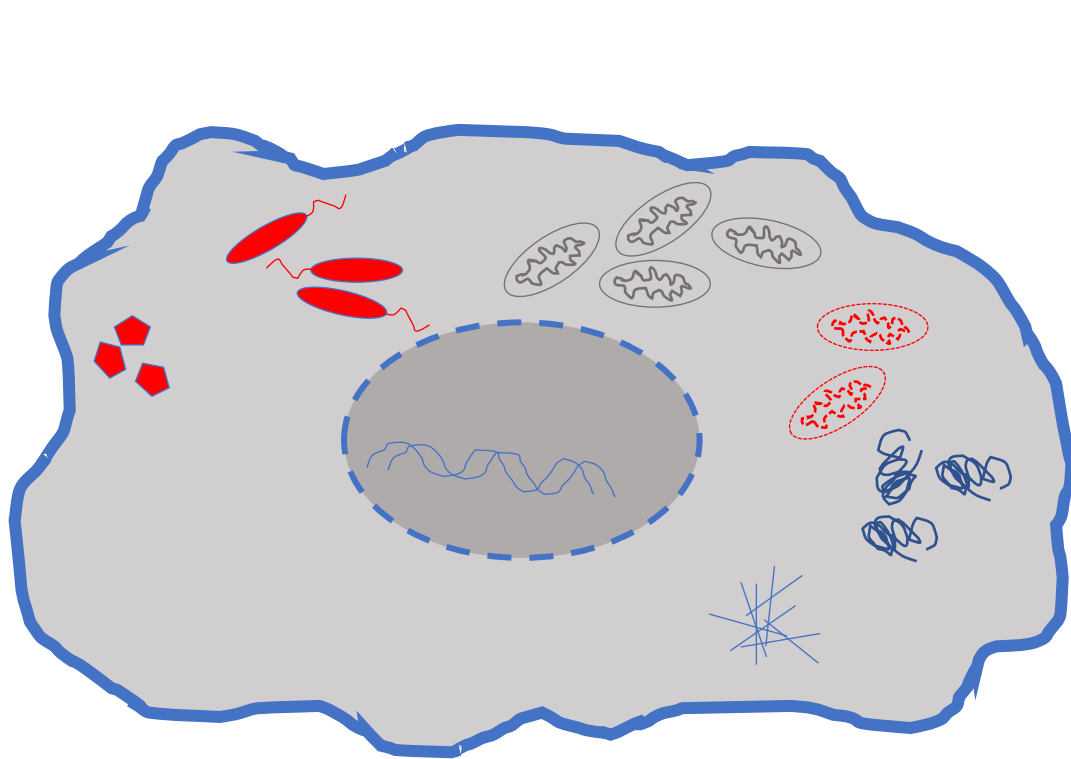
Døde av neurodegenerering



Døde av sult (maten fjernet på tid «0»)



# Kan autofagi være en tilfældig proces?



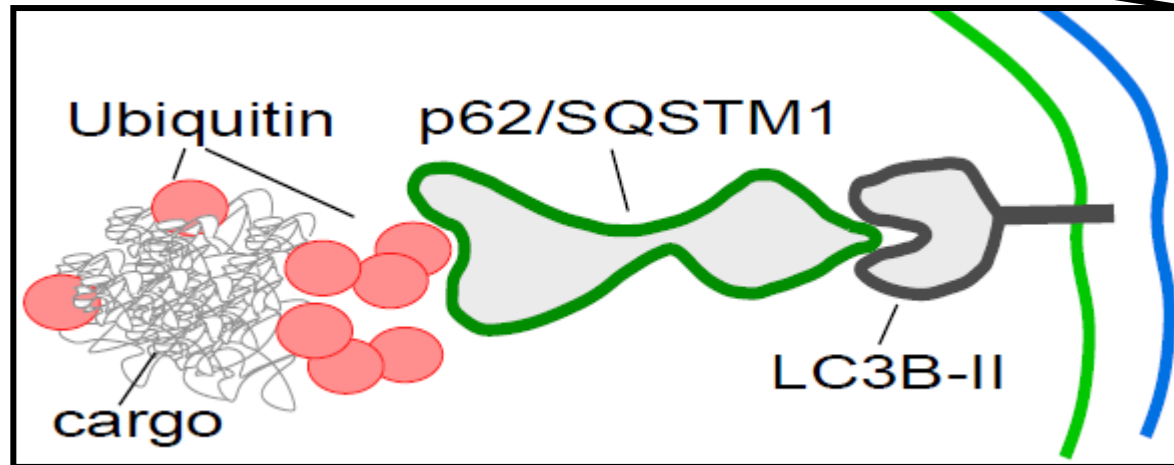
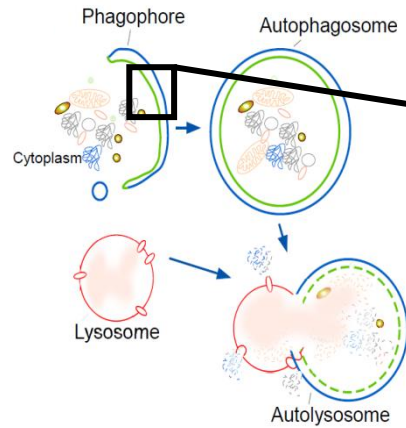
Mizushima N. *et al.* (2008) NATURE Vol 451



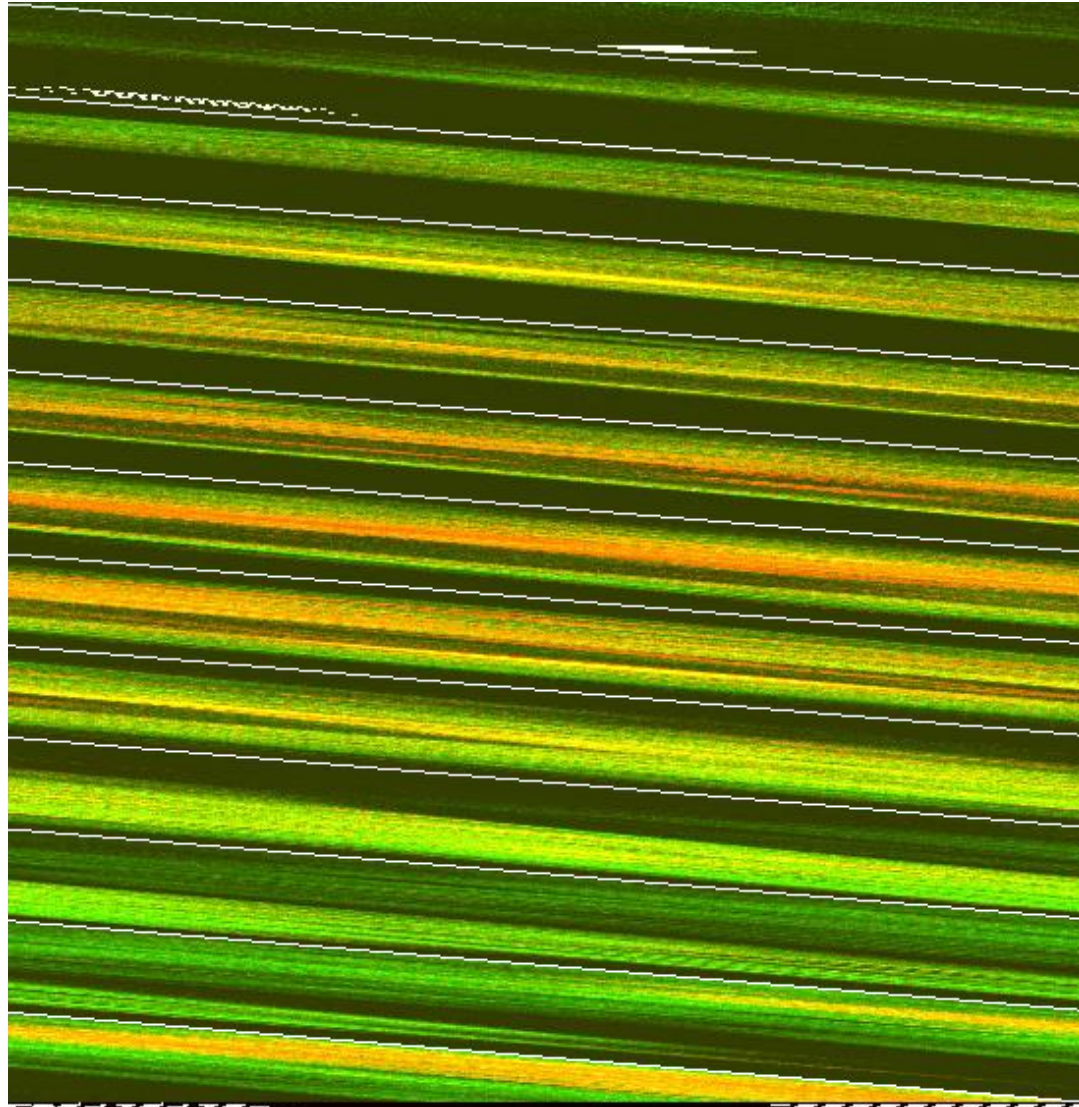
# Ødelagte celle-deler blir gjenkjent og fjernet ved hjelp av autofagi-reseptorer

Bjørkøy G, Lamark T, Brech A, Outzen H, Perander M, Øvervatn A, Stenmark H, Johansen T. (2005) J Cell Biol. 171(4):603-14

Pankiv S, Clausen TH, Lamark T, Brech A, Bruun JA, Outzen H, Øvervatn A, Bjørkøy G, Johansen T. (2007) J Biol Chem. 282(33):24131-45



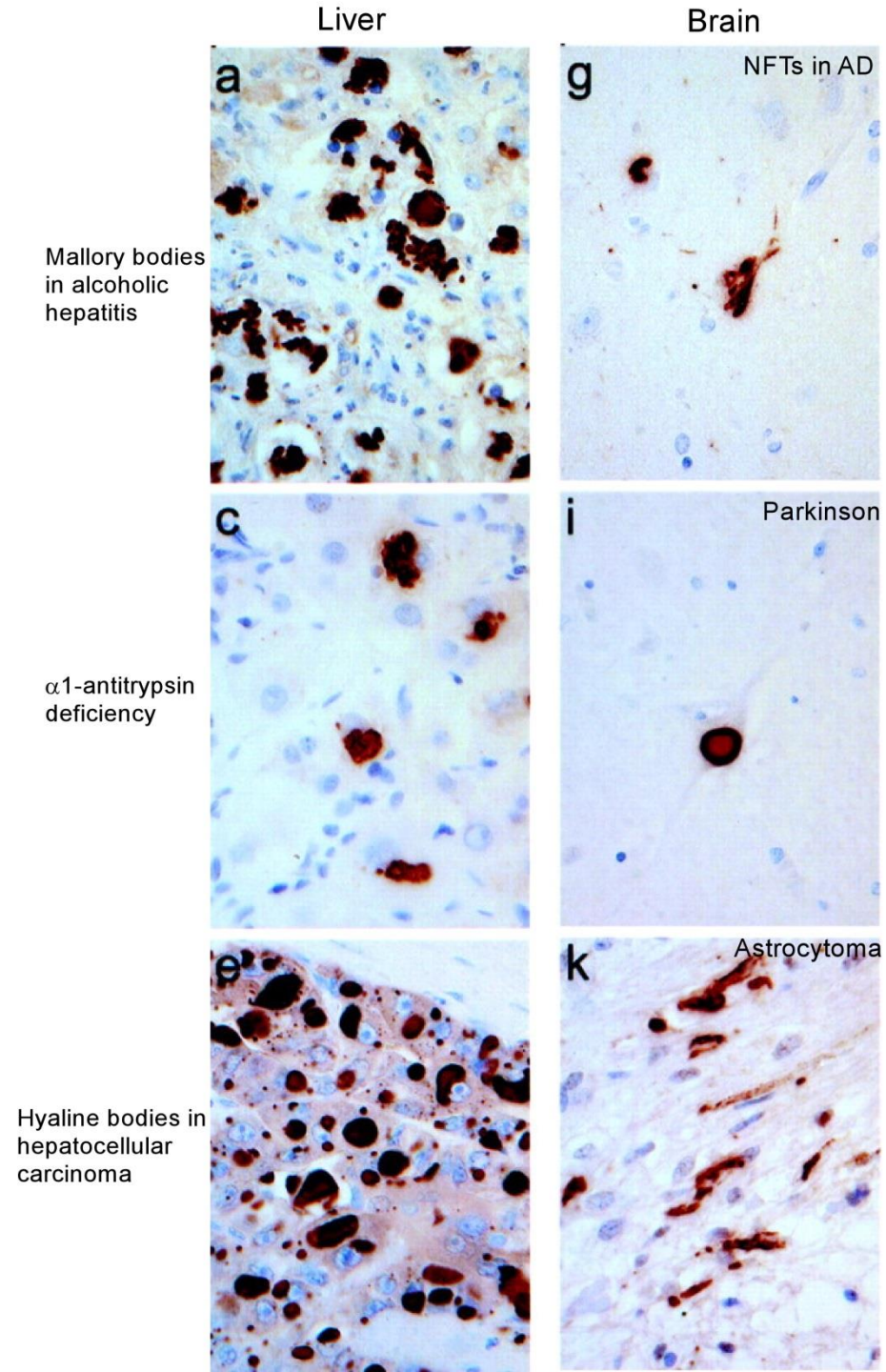
## Transport av “søppel” i cella



**mCherry-p62**

**GFP-MAP1S**

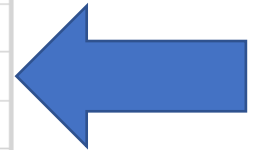
Akkumulering av protein-  
aggregater (SQSTM1/p62) er  
kjennetegn for en lang rekke  
sykdommer



## Table 1 Neurodegenerative disorders (except PD, AD and HD) and correlated core ATG genes with genetic mutations.

From: [Autophagy and disease: unanswered questions](#)

Disease	Gene(s)	Reference
β-propeller protein-associated neurodegeneration (BPAN)	<i>WDR45/WIPI4</i>	[115]
Amyotrophic lateral sclerosis (ALS)	<i>PINK1, PRKN/PARK2, SQSTM1/p62, OPTN, and TBK1</i>	[116,117,118]
Ataxias	<i>ATG4D, ATG5, VPS13D</i>	[119,120,121]
Atypical apraxia of speech (AAS)	<i>SQSTM1/p62</i>	[122]
Childhood-onset neurodegeneration	<i>SQSTM1/p62</i>	[123]
Developmental and epileptic encephalopathy (DEE)	<i>WDR45/WIPI4</i>	[124]
Early-onset epileptic encephalopathy (EOEE)	<i>WDR45/WIPI4</i>	[125]
Frontotemporal dementia (FTD)	<i>SQSTM1/p62</i>	[118]
Hereditary sensory and autonomic neuropathy II (HSANIIB)	<i>RETREG1</i>	[126]
Neuromyelitis optica (NMO)	<i>ATG5</i>	[127]
Normal-tension glaucoma (NTG)	<i>OPTN, TBK1</i>	[128]
RETT-like syndrome	<i>WDR45</i>	[129]

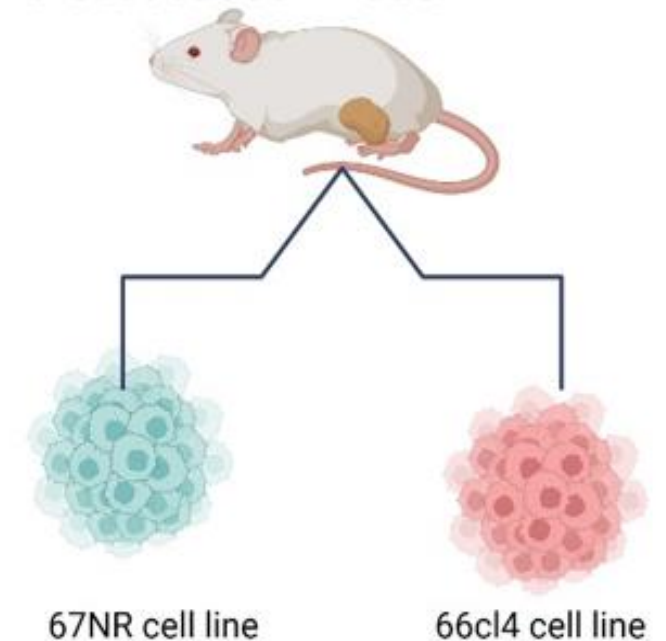




# Celle-søppel og aggressiv kreftutvikling?

1. Akkumulering av intracellulært søppel induserer lokal inflammasjon
  2. Aggressive kreftceller dyrket i kultur inneholder mye celle-søppel
  3. Aggressive tumorer er karakterisert med lokal immunsuppresjon
  4. Hypotese: Aggressive kreftceller kan rekruttere immunceller som:
    - 1) Stimulerer søppeldegradering i kreftcellene
    - 2) Demper det lokale immun-mikromiljøet i tumor
- Er immuncellene ulike i benigne og aggressive tumor?
  - Om det er forskjeller – hvordan rekrutteres de?
  - Om det er forskjeller – hvordan kan immuncellene stimulere autofagi?

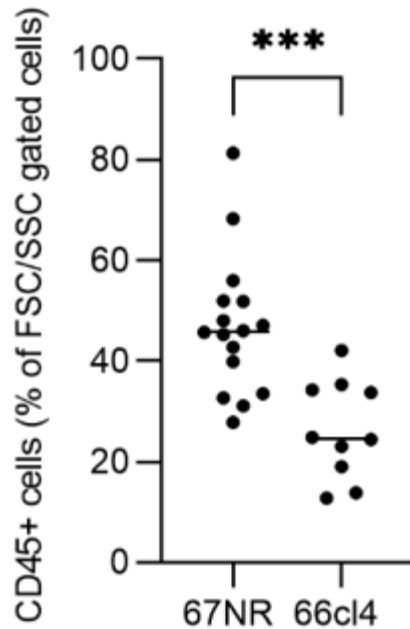
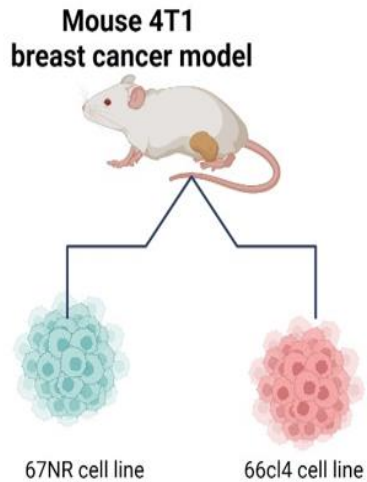
## Mouse 4T1 breast cancer model



+ Data mining in big data  
Cancer Genome Project  
CCLE +++++

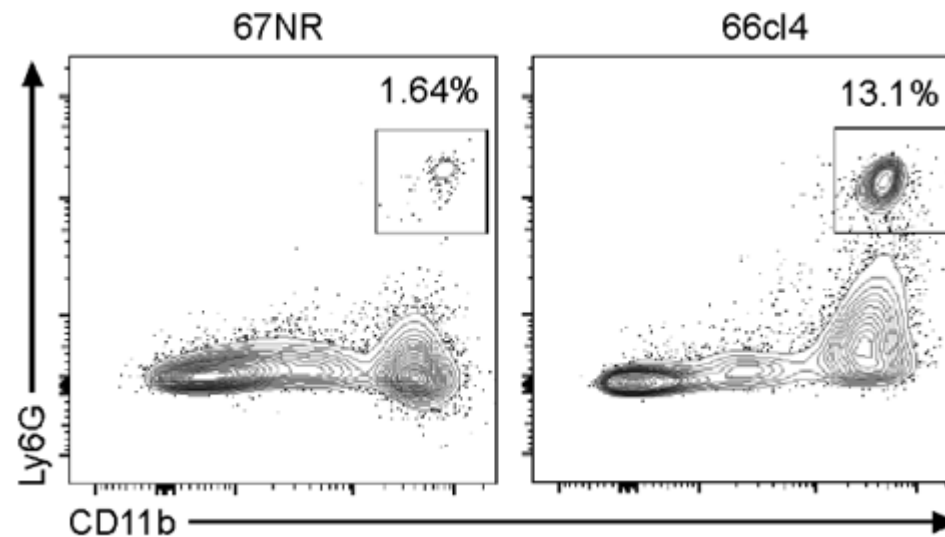


# I. Aggressive tumorer inneholder mer nøytrofile celler



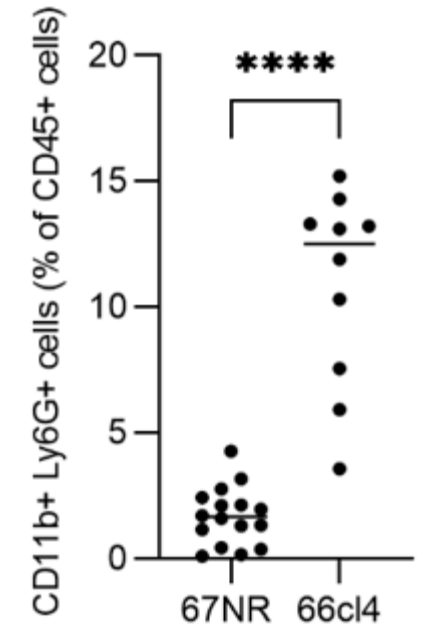
↓

Færre  
Immunceller  
i aggressiv tumor

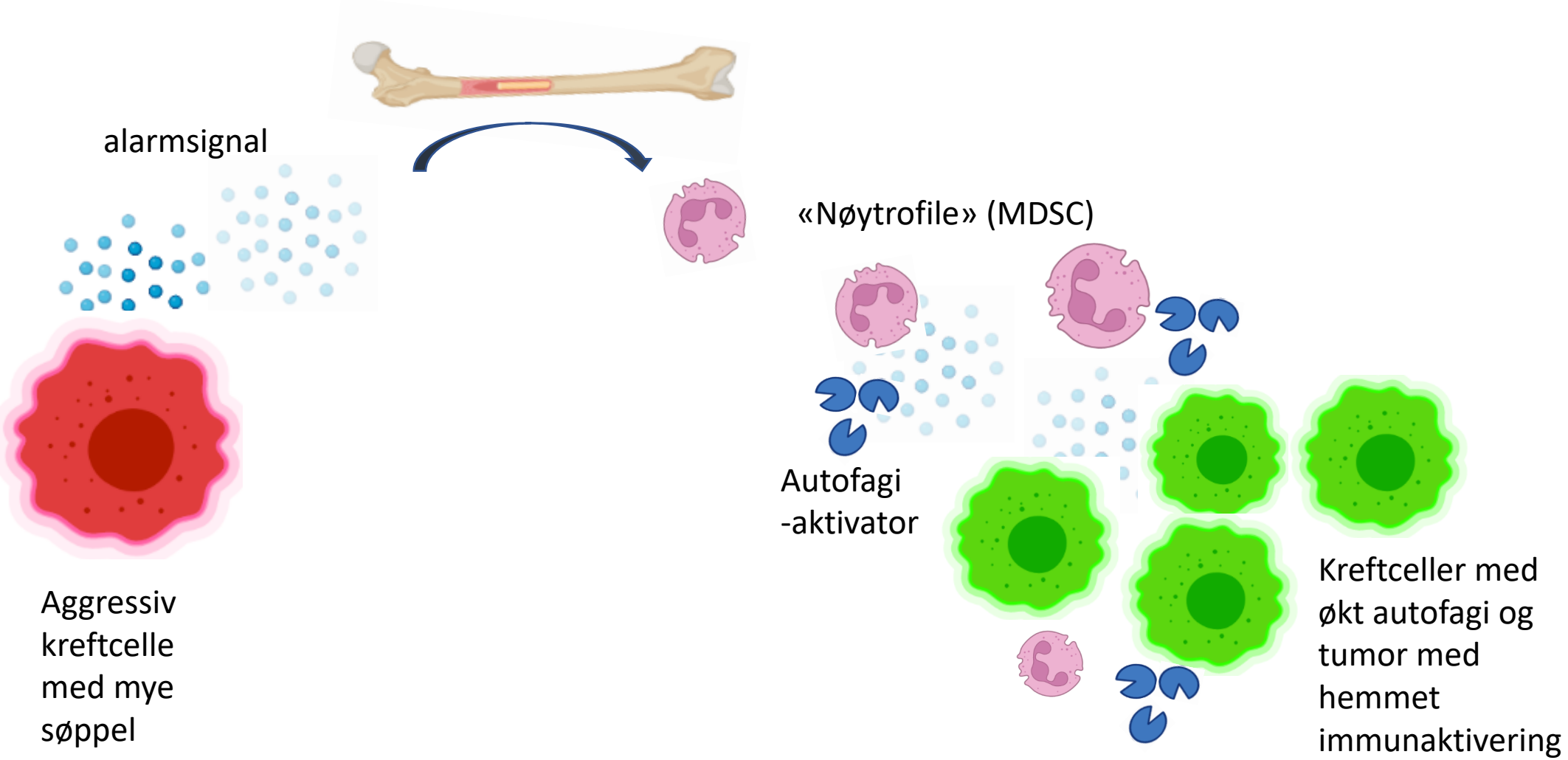


↓

MEN – det er flere nøytrofile celler i aggressive tumor (66cl4)



# Grafisk oppsummering



# Acknowledgement



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Takk for oppmerksomheten!  
Velkommen til Vitensenter Nordland 😊