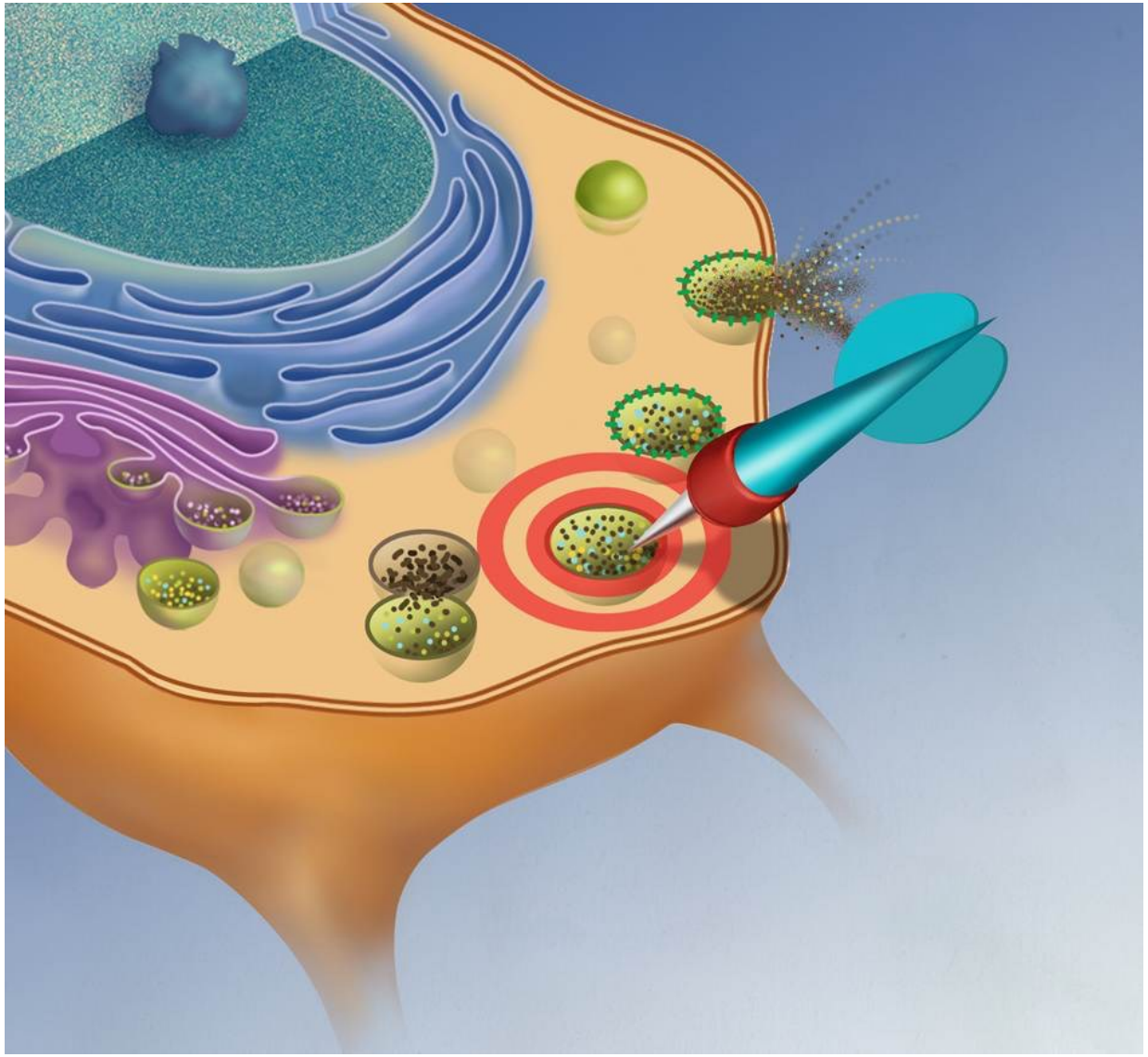
NY ANVENDELSE AF GAMMEL MEDICIN: KATIONISKE OG AMFIFILISKE STOFFER

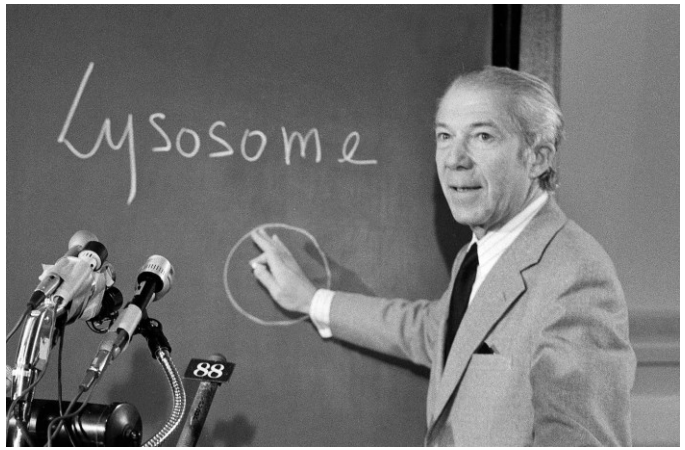


https://beyondbatten.org/wp-content/uploads/2014/10/Drug-Targeting-the-Lysosome.jpg

- INTRODUCTION TIL LYSOSOMER OG DERES ROLLE I KRÆFT
- KATIONISKE OG AMFIFILISKE STOFFER RAMMER LYSOSOMER
- EFFEKTEN AF KATIONISKE OG AMFIFILISKE ANTIHISTAMINER PÅ KRÆFT DØDLIGHED

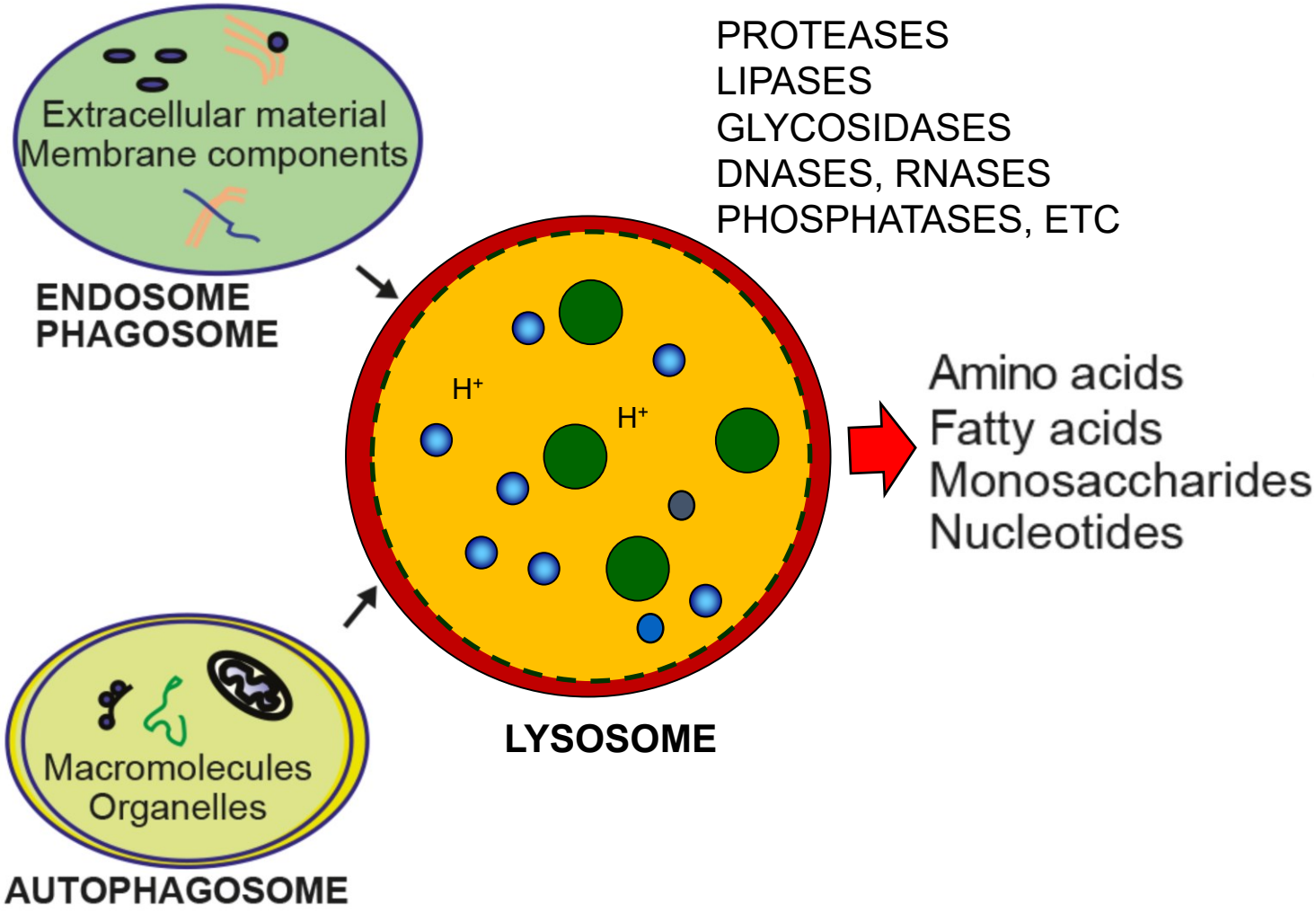
MARJA JÄÄTTELÄ
CELL DEATH AND METABOLISM
CENTER FOR AUTOPHAGY, RECYCLING AND DISEASE
DANISH CANCER SOCIETY RESEARCH CENTER

LYSOSOM – CELLENS MAVE

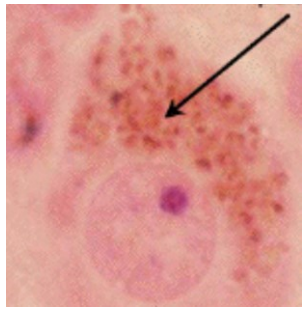


Christian de Duve
Belgisk biokemiker (1917-2013)
Nobel Pris 1974

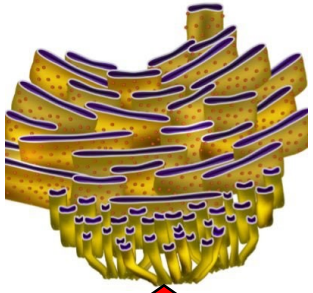
- SURE VESIKLER
- >60 HYDROLASER
- CELLULAR GENBRUGSSTATIONER



LYSOSOM – MEGET MER END CELLENS MAVE

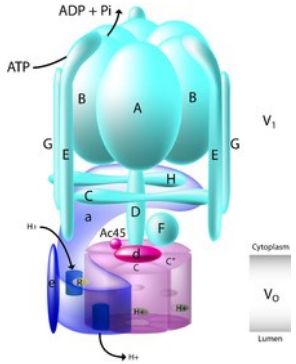


Lipofuscin

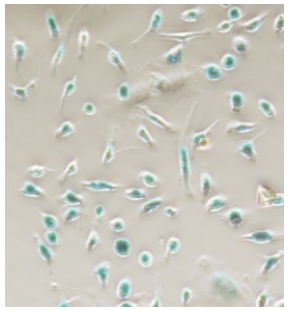


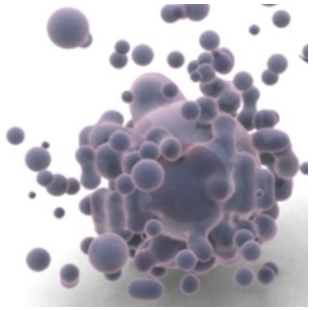
Ca^{++} HOMEOSTASE & SIGNALERING

HÆMNING AF ALDRINGSPROCESSEN & DEGENERATIVE SYGDOMME

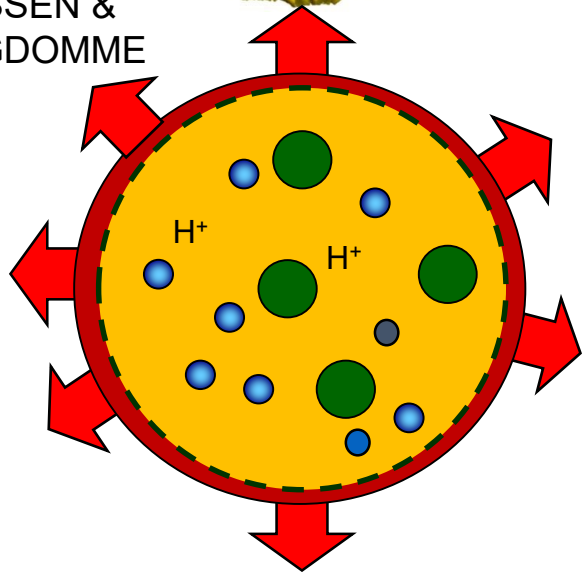


INTRACELLULÆR pH (V-ATPase / STAT3)

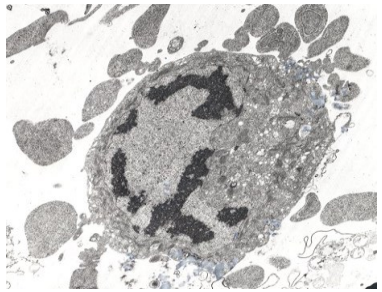




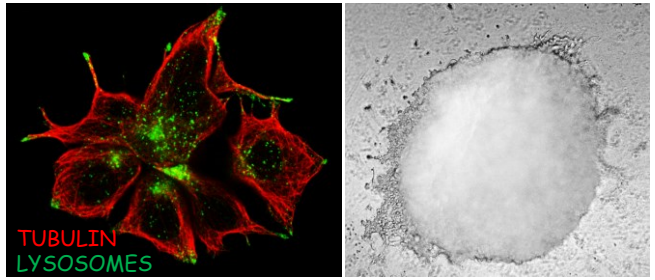
APOPTOSE SENESENS



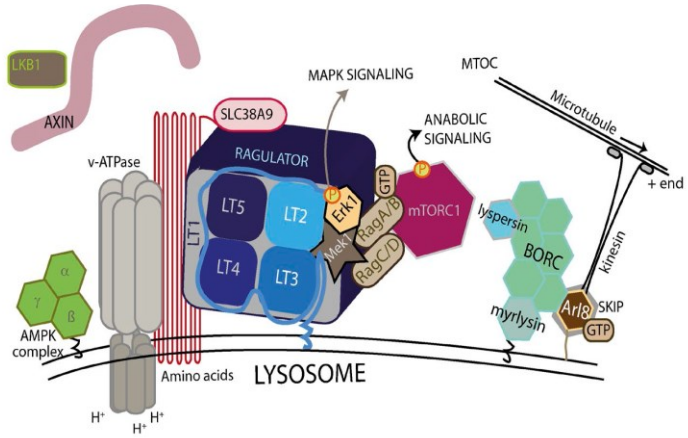
LYSOSOMAL CELLEDØD



INVASION & METASTASERING

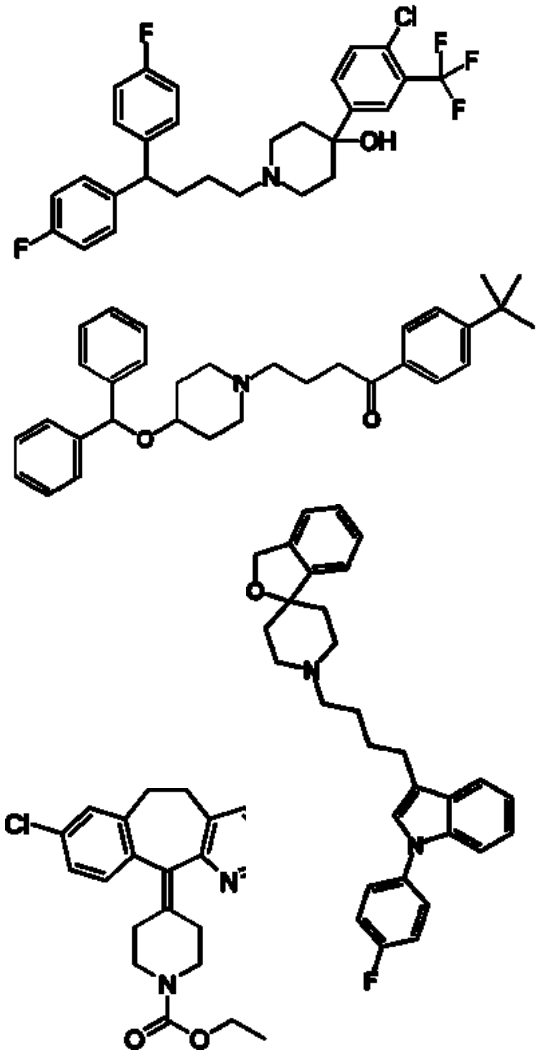


CELLE VÆKST & METABOLISME (mTORC1,AMPK, LKB1, MAPKs. DNAPK, etc)



Ellegaard, Bach & Jäättelä, *Rev Physiol Biohem Pharmacol*, 2021

KATIONISKE OG AMFIFILISKE STOFFER RAMMER LYSOSOMER



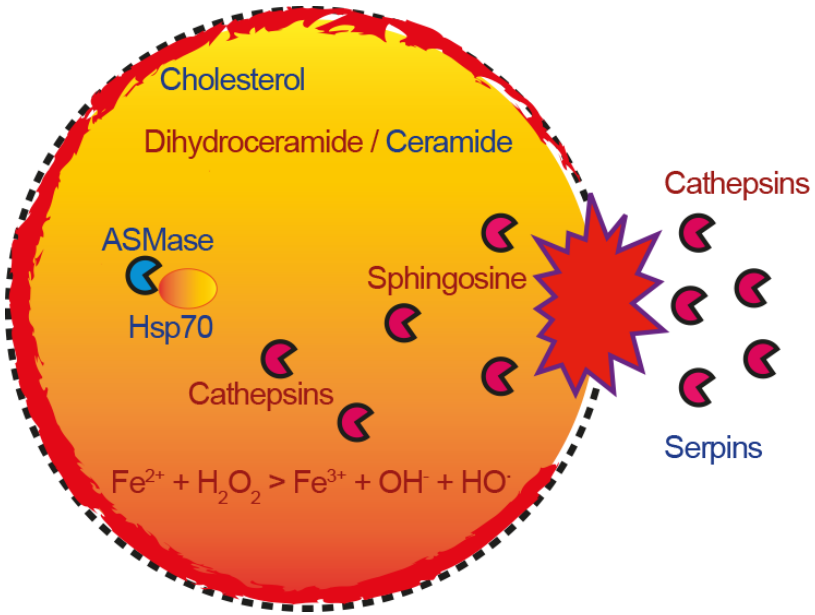
- SMÅ MOLEKYLER MED HØJ LogP OG pKa
- DIFFUNDERER FRIT GENNEM BIOLOGISKE MEMBRANER
- AKKUMULERER OP TIL 1000 GANG I DE SYRE LYSOSOMER
- ØGER LYSOSOMAL pH OF FORSTYRER LYSOSOMERNES FUNKTION

- ANTIDEPRESSANTER
- ANTIPSYKOTIKA
- ANTIHISTAMINER
- MALARIA MEDICIN
- KINASE HÆMMERE
- ANTIBIOTIKA
- ANTIKOLINERGIKA
- CALCIUM KANAL HÆMMERE

Ellegaard, Bach & Jäättelä, *Rev Physiol Biohem Pharmacol*, 2021

KATIONISKE OG AMFIFILISKE STOFFER SOM KRÆFT MEDICIN

- KRÆFT-SPECIFIK CYTOTOXICITET: >60 KRFTCELLELINJER TESTET *IN VITRO*
- HÆMNING AF TUMOR VÆKST: >50 KRÆFTMODELLER I MUS OG ROTTER

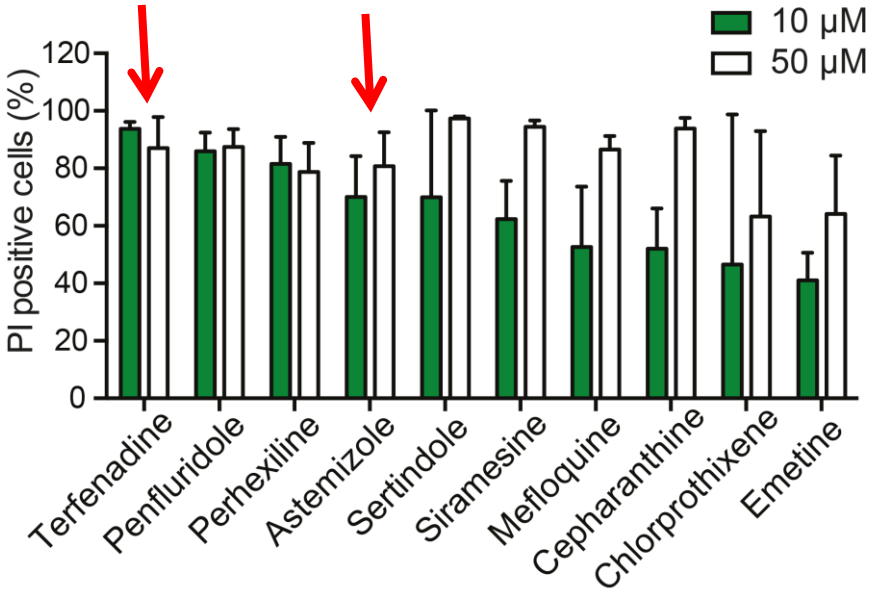


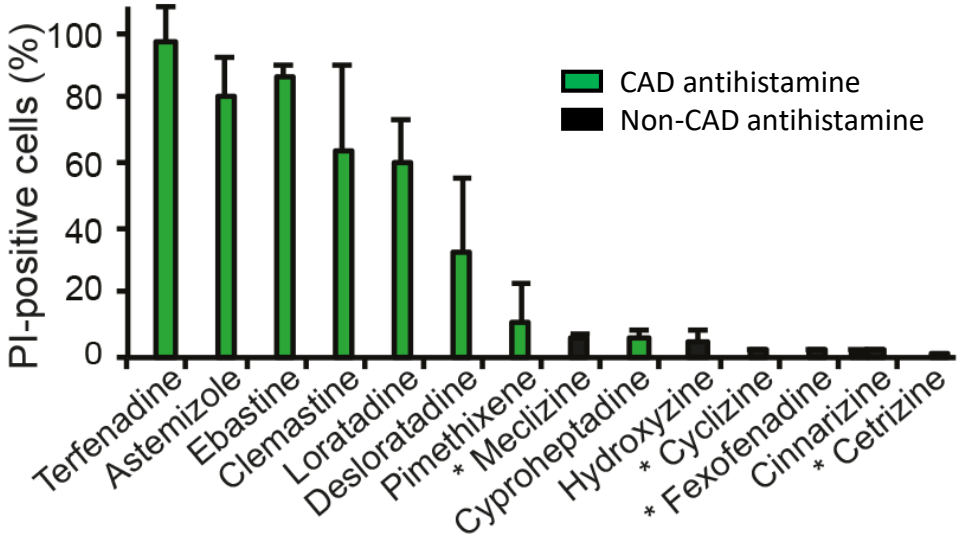
- LYSOSOMAL LÆKAGE & CELLEDØD
- HÆMNING AF LYSOSOMERNES FUNKTION
- HÆMNING AF CELLEVÆKST (mTORC1)
- SENSITERING TIL KEMOTERAPI
- HÆMNING AF MULTIDRUG RESISTENS
- NEDSÆTTELSE AF CYTOSOLISK pH
- HÆMNING AF STAT3 AKTIVITET
- HÆMNING AF AUTOFAGI OG ENDOCYTOSE
- INFLAMMATION

Ellegaard, Bach & Jäättelä, *Rev Physiol Biohem Pharmacol*, 2021

HVILKEN KATIONISK OG AMFIFILISK STOF ER BEDST TIL KRÆFTBEHANDLING?

DRUG LIBRARY SCREEN FOR
CYTOTOXICITET MOD NSCLC CELLER





Ellegaard et al, *EBioMedicine, 2016*

Pharmaco-epidemiologisk studie af effekten af KA-antihistaminer på cancer prognose

- 185.000 patienter diagnostiseret med non-localiseret kræft i Denmark mellem 1995 og 2011
- Stratificeret ifølge KA versus ikke-KA-antihistamin brug 0-6 mdr efter diagnosen
- Stratificeret ifølge kemoterapi (tilgænglig efter 2002)
- Stratificeret ifølge kræft type (NSCLC)
- Cox proportional hazard ratio (HR)

Ellegaard et al, *EBioMedicine, 2016*

KATIONISKE OG AMFIFILISKE ANTIHISTAMINER REDUCERER HR FOR MORTALITET BLANDT PATIENTER MED IKKE-LOKALISERET KRÆFT

Drug	HR	2.5%	97.5%	P	N
Astemizole	**0.67**	**0.46**	**0.98**	**0.040**	**38**
Desloratadine	**0.94**	**0.79**	**1.13**	**0.524**	**280**
-Chemo (+)	0.79	0.61	1.02	0.071	123
-Chemo (-)	0.97	0.73	1.28	0.832	150
Ebastine	**0.82**	**0.62**	**1.09**	**0.181**	**87**
-Chemo (+)	0.81	0.43	1.51	0.505	18
-Chemo (-)	0.94	0.58	1.53	0.806	38
Loratadine	**0.90**	**0.82**	**0.99**	**0.042**	**854**
-Chemo (+)	0.76	0.63	0.93	0.009	209
-Chemo (-)	0.85	0.70	1.04	0.125	270
Terfenadine	**1.00**	**0.83**	**1.20**	**0.988**	**166**

SAMLIGNET MED MATCHEDE KONTROLLER MED LIGNENDE BRUG AF IKKE-KA-ANTIHISTAMINER (CETRIZINE AND FEXOFENADINE)

Ellegaard et al, *EBioMedicine, 2016*

LORATADINE REDUCERER HR FOR MORTALITET BLANDT PATIENTER MED AVANCERET **NSCLC**

Drug	HR	2.5%	97.5%	P	N
Loratadine	0.69	0.49	0.96	0.030	60
Chemo (+)	0.64	0.42	0.97	0.035	34
Chemo (-)	0.81	0.46	1.41	0.457	26

SAMLIGNET MED MATCHEDE KONTROLLER MED LIGNENDE BRUG AF IKKE-KA-ANTIHISTAMINER (CETRIZINE AND FEXOFENADINE)

Ellegaard et al, *EBioMedicine, 2016*

KATIONISKE OG AMFIFILISKE ANTIHISTAMINER REDUCERER HR FOR MORTALITET BLANDT PATIENTER MED ÆGGESTOK KRÆFT

JNCI J Natl Cancer Inst (2020) 112(9): djz217

doi: 10.1093/jnci/djz217
First published online November 5, 2019
Brief Communication

BRIEF COMMUNICATION

Antihistamines and Ovarian Cancer Survival: Nationwide Cohort Study and in Vitro Cell Viability Assay

Freija Verdoodt, Christian Dehlendorff, Marja Jäättelä, Robert Strauss, Anton Pottegård, Jesper Hallas, Søren Friis, Susanne K. Kjaer

Table 1. Association between antihistamine use and ovarian cancer–specific mortality: use of CAD antihistamines compared with non-CAD antihistamine use as an active comparator (upper panel), and compared with nonuse of any antihistamines (lower panel)

Analysis	Antihistamine use	No.	Events	HR (95% CI)*	HR (95% CI)†
1-y baseline	Non-CAD antihistamine‡	346	168	1.00 (Referent)	1.00 (Referent)
	CAD antihistamine§	138	58	0.77 (0.57 to 1.05)	0.74 (0.51 to 1.06)
	Cumulative amount (/100 DDD)‖				0.92 (0.76 to 1.12)
3-y baseline	Non-CAD antihistamine‡	304	111	1.00 (Referent)	1.00 (Referent)
	CAD antihistamine§	133	37	0.74 (0.51 to 1.09)	0.63 (0.40 to 0.99)
	Cumulative amount (/100 DDD)‖				0.95 (0.85 to 1.05)

KATIONISKE OG AMFIFILISKE ANTIHISTAMINER REDUCERER HR FOR MORTALITET BLANDT PATIENTER MED BRYST KRÆFT

ACTA ONCOLOGICA
2020, VOL. 59, NO. 9, 1103–1109
https://doi.org/10.1080/0284186X.2020.1769185

Taylor & Francis
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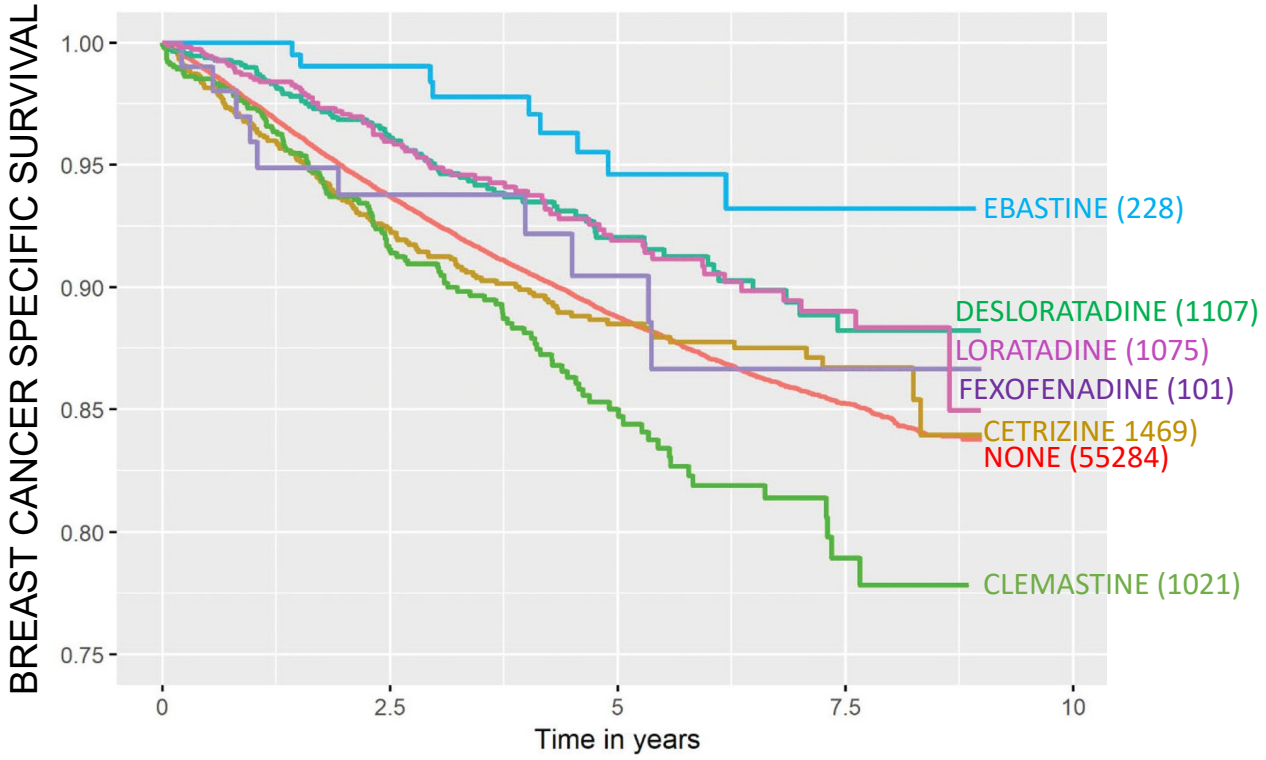
ORIGINAL ARTICLE

OPEN ACCESS Check for updates

Desloratadine and loratadine stand out among common H_1-antihistamines for association with improved breast cancer survival

Ildikó Fritz[a], Philippe Wagner[a], Per Broberg[a], Rickard Einefors[a] and Håkan Olsson[a,b]



Peridiagnostic antihistamine use and breast cancer specific mortality

Antihistamine type	HR[b]	2.5 %	97.5 %	*p*
Cetirizine	1.16	0.99	1.35	.067
Clemastine	1.34	1.14	1.59	<.001
Desloratadine	0.69	0.55	0.86	.001
Ebastine	0.49	0.27	0.88	.018
Fexofenadine	1.06	0.57	1.97	.856
Loratadine	0.78	0.63	0.96	.021

Note the effect of ebastine!!!

KATIONISKE OG AMFIFILISKE ANTIHISTAMINER REDUCERER HR FOR MORTALITET BLANDT KRÆFTPATIENTER

Translational Oncology 14 (2021) 101029

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

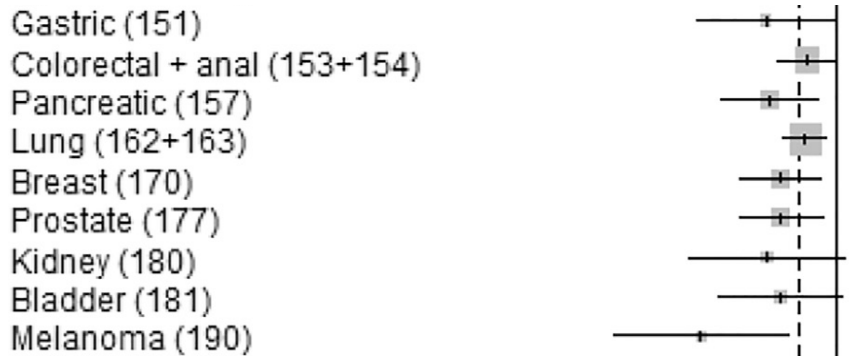
Original Research

Improved survival in several cancers with use of H_1-antihistamines desloratadine and loratadine

Ildikó Fritz[a,*], Philippe Wagner[a], Håkan Olsson[a,b]

[a] Department of Cancer Epidemiology, Clinical Sciences, Lund University, Lund, Sweden
[b] Department of Oncology and Pathology, Clinical Sciences, Lund University, Lund, Sweden

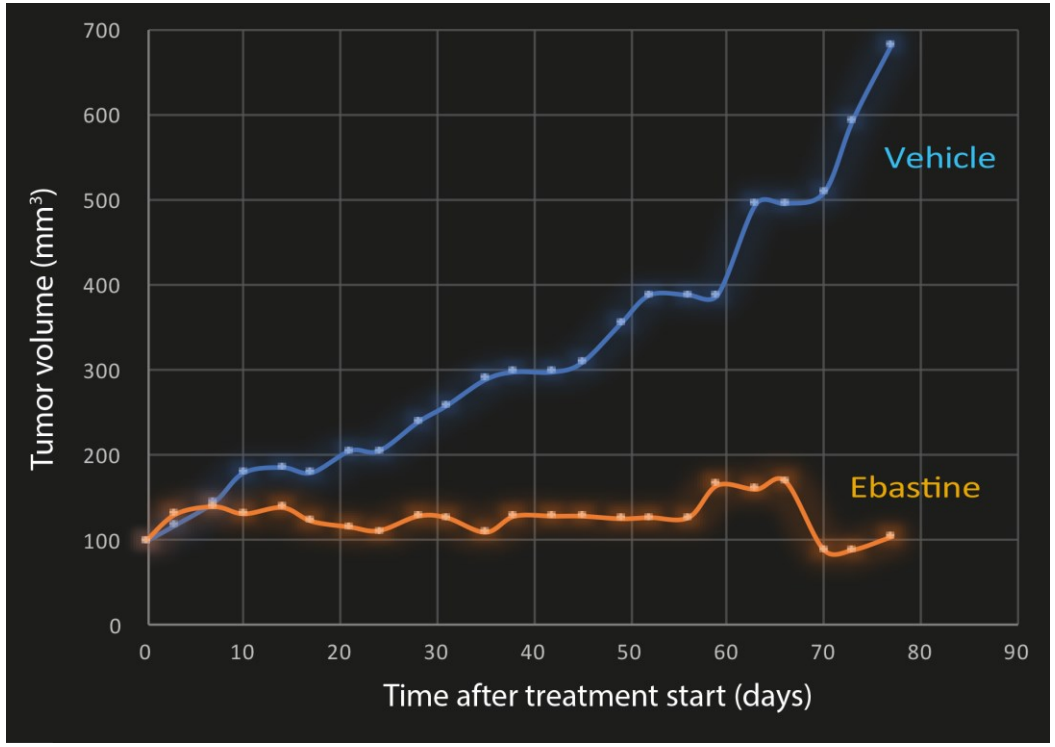
Effect of peridiagnostic **desloratadine** use on cancer mortality



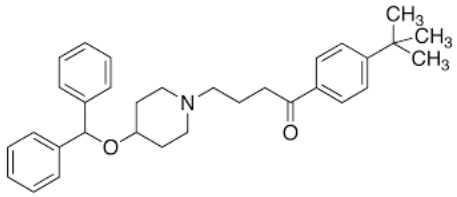
NÆSTE SKRIDT: KLINISKE FORSØG MED KA-ANTIHISTAMINER

BEHANDLING AF BEHANDLINGSRESISTENT KRÆFT MED EBASTINE OR LORATADINE

ORTHOTOPIC MCF7 BREAST CANCER XENOGRAFT



- GOD ANTI-KRÆFT EFFEKTIVITET IN VIVO
- AKKUMULERING I KRÆFT VÆV
- UFARLIGE OG BILLIGE
- PROBLEMET: - HVEM BETALER REGNINGEN?



TAK!

Cell Death & Metabolism, DCRC:
-Anne Marie Ellegaard & Mikkel Rohde

Statistics & Pharmacoepidemiology, DCRC:
-Christian Dehlendorff & Søren Friis

Virus, Lifestyle & Genes, DCRC:
-Freija Verdoot & Susanne Krüger Kjær

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