Repurposing – fresh perspectives on known components

Technical Journal Club

Johanna Schaffenrath

15.05.2018

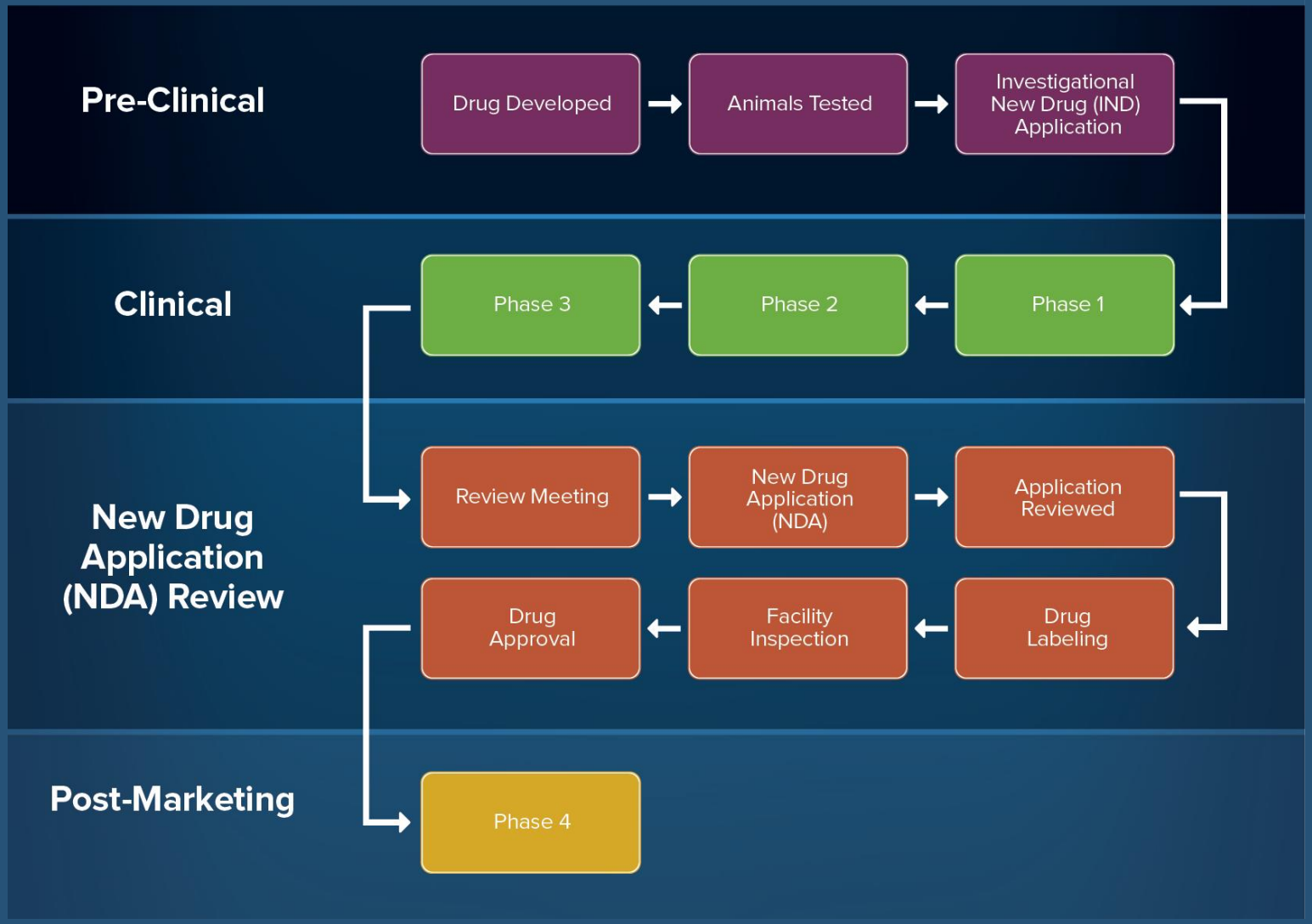
About drug specificity…

"My feeling is that the proportion of drugs that in theory could be repositioned is probably around 75%."

Bernhard Munos, FasterCures

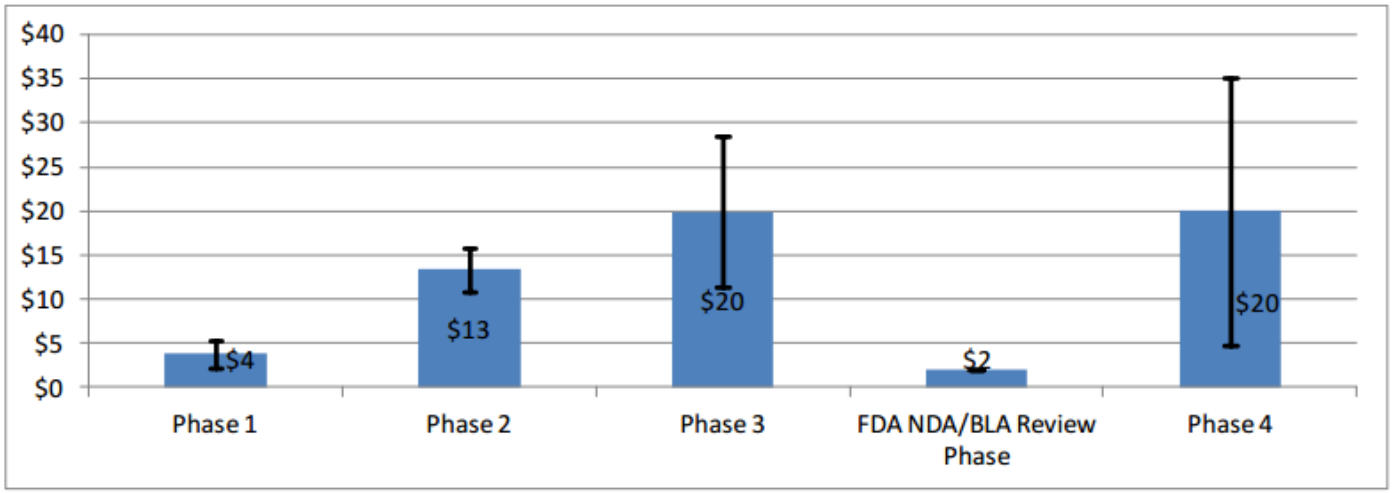
https://lumiere-a.akamaihd.net/v1/images/open-uri20160107-21163-hs6ze2_eb82ef95.jpeg

Food and Drug Administration (FDA) Drug Approval Process



Average Per-Study Costs by Phase

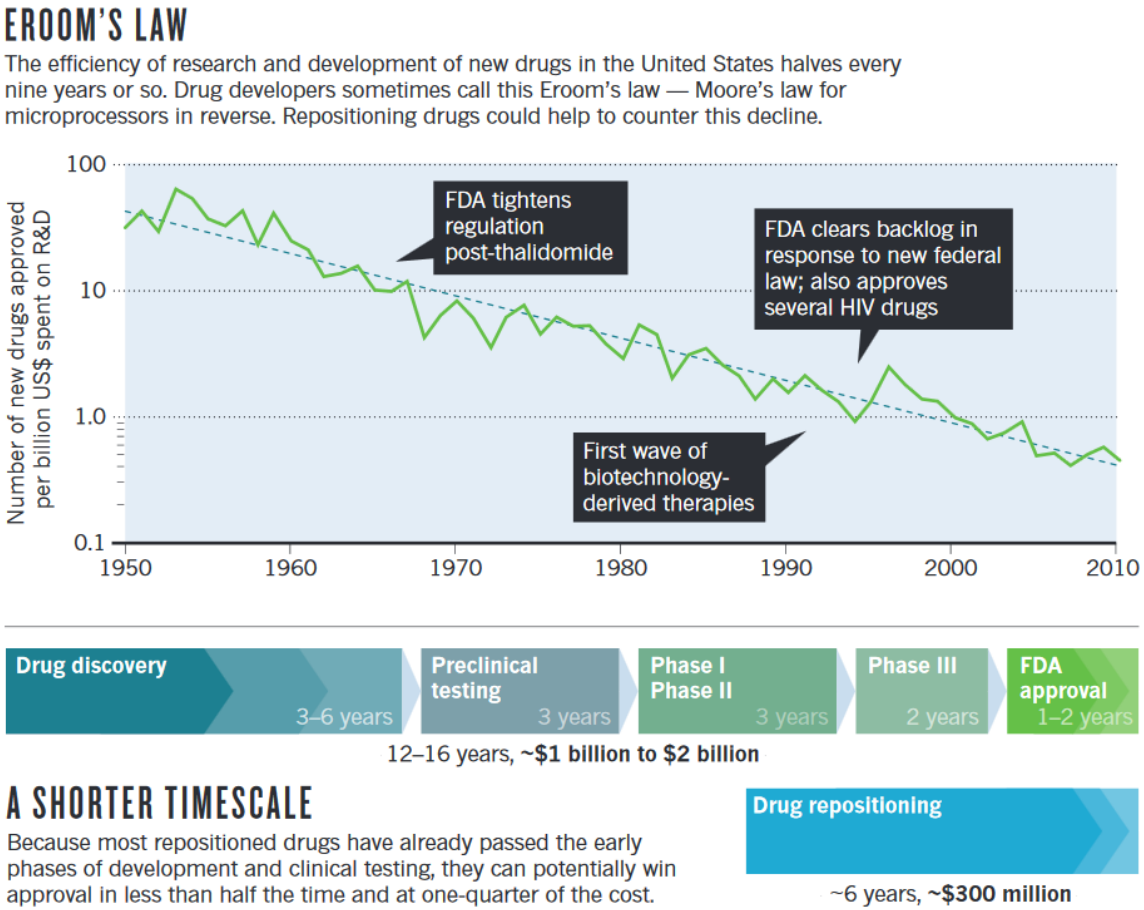
Figure 4: Average Per-Study Costs by Phase (in $ Millions) Across Therapeutic Areas



Phase 1: testing on 20-80 healthy volunteers using subtherapeutic dose
Phase 2: testing on 100s of patients using therapeutic dose
Phase 3: testing on 1000s of patients using therapeutic dose
Review Phase: Prior to New Drug Application
Phase 4: surveillance phase – assessing long term effects

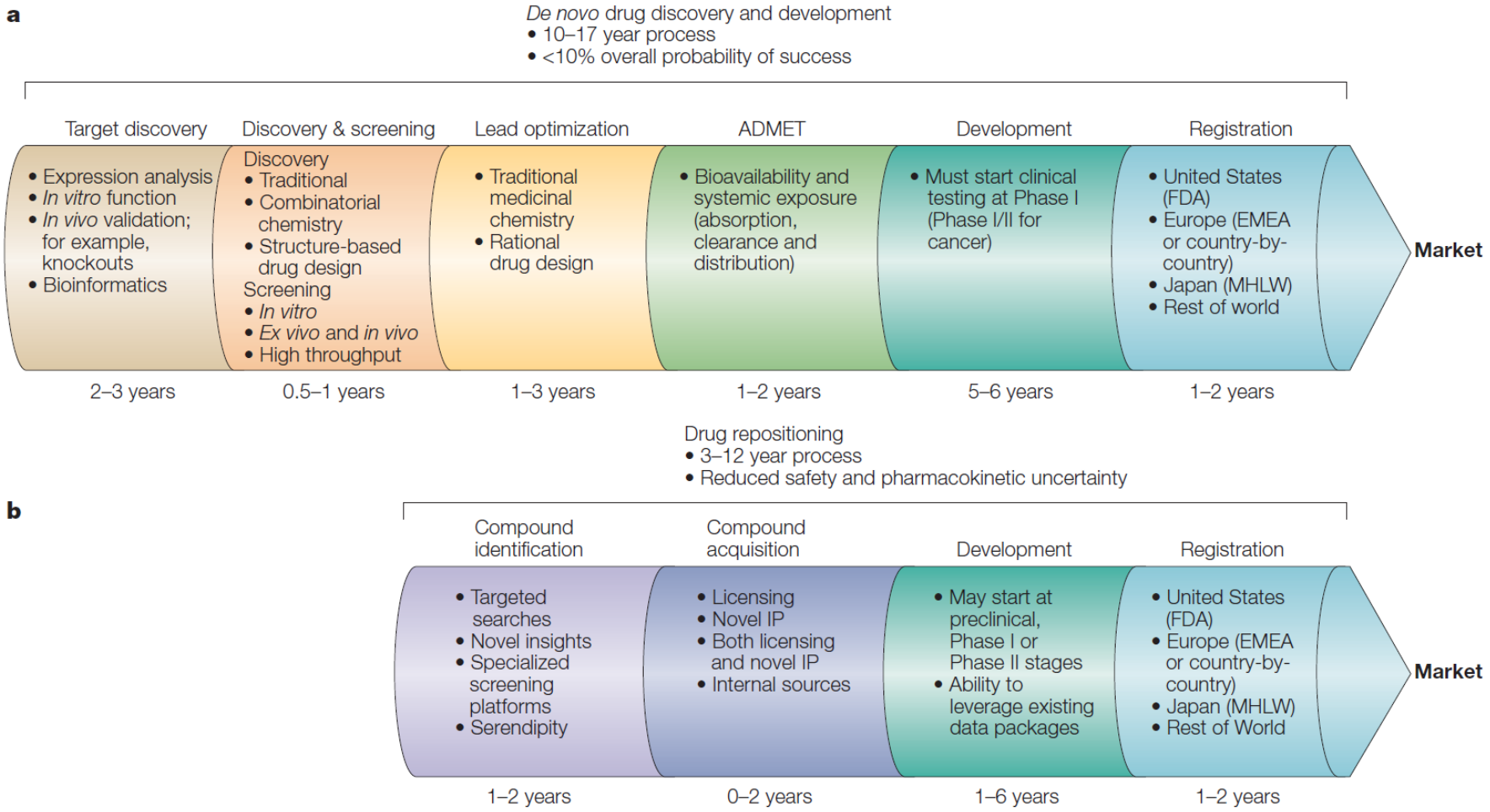
https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development

Eroom`s law



- High cost
- Long timelines
- Difficulties in recruiting and retaining participants
- Administrative barriers
- Financial barriers – sponsors
- About 30% of drugs entering approval pipeline are repurposed

De novo drug discovery vs. Drug repurposing



ADMET, absorption, distribution, metabolism, excretion and toxicity

Increasing trend for repurposing

- Financial advantages are massive
    - Relaunching a repurposed drug: ~8.4 million $
    - Relaunching a new formulation of an existing drug: ~41.3 million $
    - Successfully releasing a new drug: ~1.3 billion $
- Lower risks
- Companies rise business centres exploring repositioning opportunities
    - Pfizer´s indication discovery unit
    - Bayer Healthcare´s common mechanisms research group
    - Novartis´ new indications discovery unit
    - virtual proof of concept units
    - 3-4 drug repurposing companies open per year (data 2016)

http://www.ddw-online.com/business/p142737-the-benefits-of-drug-repositioning-spring-11.html

Increasing trend for repurposing

- easiest to repurpose: generic drugs
  - Well known safety profile
  - Expried original patents
- Failed drugs which passed phase 1 but not 2 & 3
- Scanning thorugh generic drugs to find connections involved in
  - Genes
  - Pathways
  - Targets
- Repurposing often start at physicians
  - Repurposed prescriptions

Repurposing and basic research

- Repurposing used in basic research
  - Acceleration of discoveries and understanding of new biology
  - uncover new pathways and mechanisms by «off-target» effects
- Vendors and CROs offering repositioning services
  - widescale in vitro binding
  - cell line screening
  - protein-protein interaction studies
  - phenotypic screening of animal model sets
  - pathway and data mining approaches
- Good for commercial and reserach sense
- Innovation in understanding of basic disease biology

http://www.ddw-online.com/business/p142737-the-benefits-of-drug-repositioning-spring-11.html

Repurposing platforms

The Drug Repurposing Hub: a next-generation drug library and information resource

Steven M. Corsello[1,2,3], **Joshua A. Bittker**[1], **Zihan Liu**[1], **Joshua Gould**[1], **Patrick McCarren**[1], **Jodi E. Hirschman**[1], **Stephen E. Johnston**[1], **Anita Vrcic**[1], **Bang Wong**[1], **Mariya Khan**[1], **Jacob Asiedu**[1], **Rajiv Narayan**[1], **Christopher C. Mader**[1], **Aravind Subramanian**[1], and **Todd R. Golub**[1,3,4,5,*]

http://www.excelra.com/d-repurposing-platform.php

Review

Informatics

Uncovering novel repositioning opportunities using the Open Targets platform

Mugdha Khaladkar [1], Gautier Koscielny [2, 3], Samiul Hasan [2], Pankaj Agarwal [1], Ian Dunham [3, 4], Deepak Rajpal [1], Philippe Sanseau [2, 3]

Received: 26 February 2018 | Accepted: 28 February 2018
DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

WILEY Journal of Cellular Physiology

Possible repurposing of pyrvinium pamoate for the treatment of mesothelioma: A pre-clinical assessment

Marcella Barbarino[1,2] | Daniele Cesari[1] | Riccardo Intruglio[1] | Paola Indovina[2] | Asadoor Namagerdi[1] | Franca Maria Bertolino[1] | Maria Bottaro[1] | Delaram Rahamani[1] | Cristiana Bellan[3] | Antonio Giordano[1,2]

Received: 26 February 2018 | Accepted: 28 February 2018
DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

WILEY Journal of Cellular Physiology

Possible repurposing of pyrvinium pamoate for the treat
of mesothelioma: A pre-clinical assessment

Marcella Barbarino[1,2] | Daniele C
Asadoor Namagerdi[1]
Delar

Published online: April 17, 2018

Research Article

TRANSPARENT PROCESS
OPEN ACCESS
EMBO Molecular Medicine

Identification of circadian clock modulators from existing drugs

T Katherine Tamai[1], Yusuke Nakane[1,2], Wataru Ota[1,2], Akane Kobayashi[1,2], Masateru Ishiguro[1,2], Naoya Kadofusa[1], Keisuke Ikegami[3], Kazuhiro Yagita[4], Yasufumi Shigeyoshi[3], Masaki Sudo[1], Taeko Nishiwaki-Ohkawa[1,2], Ayato Sato[1] & Takashi Yoshimura[1,2,5,6,*]

Received: 26 February 2018 | Accepted: 28 February 2018
DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

WILEY Journal of Cellular Physiology

Possible repurposing of pyrvinium pamoate for the treat… of m… : A pre-clinical assessment

Mar…
Asa…
De…

Accepted: 5 February 2018
DOI: 10.1111/epi.14037

FULL-LENGTH ORIGINAL RESEARCH

A comprehensive approach to identifying repurposed drugs to treat *SCN8A* epilepsy

Talia A. Atkin[1] | Chani M. Maher[1] | Aaron C. Gerlach[2] | Bryant C. Gay[1] | Brett M. Antonio[2] | Sonia C. Santos[2] | Karen M. Padilla[2] | JulieAnn Rader[1] | Douglas S. Krafte[2] | Matthew A. Fox[1] | Gregory R. Stewart[1] | Slavé Petrovski[1,3] | Orrin Devinsky[1,4] | Matthew Might[1,5] | Steven Petrou[1,3] | David B. Goldstein[1,6]

T Katherin…
Naoya Kadofusa…
Taeko Nishiwaki-Ohkaw…

Epilepsia®

OPEN ACCESS

EMBO Molecular Medicine

…rs from

Received: 26 February 2018 | Accepted: 28 February 2018
DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

WILEY Journal of Cellular Physiology

Possible repurposing of pyrvinium pamoate for the treat
of m : A pre-clinical assessment

Mar

Accepted: 5 February 2018
DOI: 10.1111/epi.14037

FULL-LENGTH

OPEN ACCESS

EMBO Molecular Medicine

SCIENTIFIC REPORTS

OPEN

Sertraline, Paroxetine, and Chlorpromazine Are Rapidly Acting Anthelmintic Drugs Capable of Clinical Repurposing

Received: 9 March 2017
Accepted: 12 December 2017
Published online: 17 January 2018

Janis C. Weeks[1], William M. Roberts[1], Caitlyn Leasure[2], Brian M. Suzuki[3], Kristin J. Robinson[1], Heather Currey[4], Phurpa Wangchuk[5], Ramon M. Eichenberger[5], Aleen D. Saxton[4], Thomas D. Bird[4,6,7,8], Brian C. Kraemer[4,7,9,10], Alex Loukas[5], John M. Hawdon[2], Conor R. Caffrey[3] & Nicole F. Liachko[4,9]

Received: 26 February 2018 | Accepted: 28 February 2018
DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

Possible repurposing of
of m

Received: 3 January 2018 | Revised: 27 February 2018 | Accepted: 13 March 2018
DOI: 10.1111/cns.12855

ORIGINAL ARTICLE

Repurposing carbamazepine for the treatment of amyotrophic lateral sclerosis in SOD1-G93A mouse model

Jing-Jing Zhang[1,2,3] | Qin-Ming Zhou[4] | Sheng Chen[5] | Wei-Dong Le[1,2,6]

WILEY CNS Neuroscience & Therapeutics

REPORTS

Sertraline, Paroxetine, and Chlorpromazine Are Rapidly Acting Anthelmintic Drugs Capable of Clinical Repurposing

Received: 9 March 2017
Accepted: 12 December 2017
Published online: 17 January 2018

Janis C. Weeks[1], William M. Roberts[1], Caitlyn Leasure[2], Brian M. Suzuki[3], Kristin J. Robinson[1], Heather Currey[4], Phurpa Wangchuk[5], Ramon M. Eichenberger[5], Aleen D. Saxton[4], Thomas D. Bird[4,6,7,8], Brian C. Kraemer[4,7,9,10], Alex Loukas[5], John M. Hawdon[2], Conor R. Caffrey[3] & Nicole F. Liachko[4,9]

Received: 26 February 2018 | Accepted: 28 February 2018
DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

Poss repurposing of
of n

Received: 9 March 2017
Accepted: 12 December 2017
Published online: 17 January 2018

Chlorp
Anthelmintic Dr
Clinical Repurposing

Janis C. Weeks[1], William M. Roberts[1], Caitlyn Leasure[2], Brian M. Suzuki[3], Kristin J. Robinson[1], Heather Currey[4], Phurpa Wangchuk[5], Ramon M. Eichenberger[5], Aleen D. Saxton[4], Thomas D. Bird[4,6,7,8], Brian C. Kraemer[4,7,9,10], Alex Loukas[5], John M. Hawdon[2], Conor R. Caffrey[3] & Nicole F. Liachko[4,9]

Journal of Neurology (2018) 265:446–448
https://doi.org/10.1007/s00415-018-8732-z

JOURNAL CLUB

Repurposing drugs to treat neurological diseases

T. H. Massey[1] · N. P. Robertson[1]

Published online: 10 January 2018

Received: 13 March 2018 | Accepted: 13 March 2018

WILEY CNS Neuroscience & Therapeutics

the treatment of amyotrophic
e model

Dong Le[1,2,6]

Jing-Jing

Received: 26 February 2018 | Accepted: 28 February 2018
DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

Poss repurposing of

of amyotrophic

Journal of Neurology (201 ruary 2018 | Accepted: 13 March 2018
https://doi

WILEY CNS Neuroscience & Therapeutics

Published in final edited form as:
Nat Med. 2017 April 07; 23(4): 405–408. doi:10.1038/nm.4306.

The Drug Repurposing Hub: a next-generation drug library and information resource

Steven M. Corsello[1,2,3], **Joshua A. Bittker**[1], **Zihan Liu**[1], **Joshua Gould**[1], **Patrick McCarren**[1], **Jodi E. Hirschman**[1], **Stephen E. Johnston**[1], **Anita Vrcic**[1], **Bang Wong**[1], **Mariya Khan**[1], **Jacob Asiedu**[1], **Rajiv Narayan**[1], **Christopher C. Mader**[1], **Aravind Subramanian**[1], and **Todd R. Golub**[1,3,4,5,*]

Accepted: 12 December 2017
Published online: 17 January 2018

Clinical Repurposing

Janis C. Weeks[1], William M. Roberts[1], Caitlyn Leasure[2], Brian M. Suzuki[3], Kristin J. Robinson[1], Heather Currey[4], Phurpa Wangchuk[5], Ramon M. Eichenberger[5], Aleen D. Saxton[4], Thomas D. Bird[4,6,7,8], Brian C. Kraemer[4,7,9,10], Alex Loukas[5], John M. Hawdon[2], Conor R. Caffrey[3] & Nicole F. Liachko[4,9]

nature COMMUNICATIONS

ARTICLE

Received 9 Dec 2014 | Accepted 24 Aug 2015 | Published 27 Oct 2015

DOI: 10.1038/ncomms9466 OPEN

Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug

Julia Marschallinger[1,2], Iris Schäffner[3], Barbara Klein[1,2], Renate Gelfert[1,2], Francisco J. Rivera[1,2], Sebastian Illes[1,2], Lukas Grassner[1,2,4], Maximilian Janssen[1,2], Peter Rotheneichner[1,2,5], Claudia Schmuckermair[6], Roland Coras[7], Marta Boccazzi[8], Mansoor Chishty[9], Florian B. Lagler[10], Marija Renic[11], Hans-Christian Bauer[2,12], Nicolas Singewald[6], Ingmar Blümcke[7], Ulrich Bogdahn[13], Sebastien Couillard-Despres[2,5], D. Chichung Lie[3], Maria P. Abbracchio[8] & Ludwig Aigner[1,2]

Steven M. Corsello[1,2,3], Joshua A. Bittker[1], Zihan Liu[1], Joshua Gould[1], Patrick McCarren[1], Jodi E. Hirschman[1], Stephen E. Johnston[1], Anita Vrcic[1], Bang Wong[1], Mariya Khan[1], Jacob Asiedu[1], Rajiv Narayan[1], Christopher C. Mader[1], Aravind Subramanian[1], and Todd R. Golub[1,3,4,5,*]

Accepted: 12 December 2017

Published online: 17 January 2018

Clinical Repurposing

Janis C. Weeks[1], William M. Roberts[1], Caitlyn Leasure[2], Brian M. Suzuki[3], Kristin J. Robinson[1], Heather Currey[4], Phurpa Wangchuk[5], Ramon M. Eichenberger[5], Aleen D. Saxton[4], Thomas D. Bird[4,6,7,8], Brian C. Kraemer[4,7,9,10], Alex Loukas[5], John M. Hawdon[2], Conor R. Caffrey[3] & Nicole F. Liachko[4,9]

nature COMMUNICATIONS

ACCEPTED MANUSCRIPT

Repurposing sex steroids and related drugs as potential treatment for Parkinson's disease

Mélanie Bourque[a,b], Marc Morissette[a] and Thérèse Di Paolo[a,b]*

[a]Neuroscience Research Unit, Centre Hospitalier Universitaire de Québec, CHUL, Quebec City, CANADA, G1V 4G2 and

[b]Faculty of Pharmacy, Université Laval, Quebec City, CANADA, G1K 7P4.

Jodi E. Hirschman[1], Stephen E. Johnston[1], Anita Vrcic[1], Bang Wong[1], Mariya Khan[1], Jacob Asiedu[1], Rajiv Narayan[1], Christopher C. Mader[1], Aravind Subramanian[1], and Todd R. Golub[1,3,4,5,*]

Accepted: 12 December 2017
Published online: 17 January 2018

Clinical Repurposing

Janis C. Weeks[1], William M. Roberts[1], Caitlyn Leasure[2], Brian M. Suzuki[3], Kristin J. Robinson[1], Heather Currey[4], Phurpa Wangchuk[5], Ramon M. Eichenberger[5], Aleen D. Saxton[4], Thomas D. Bird[4,6,7,8], Brian C. Kraemer[4,7,9,10], Alex Loukas[5], John M. Hawdon[2], Conor R. Caffrey[3] & Nicole F. Liachko[4,9]

ARTICLE

Received 9 Dec 2014 | Accepted 24 Aug 2015 | Published 27 Oct 2015

DOI: 10.1038/ncomms9466 OPEN

Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug

Julia Marschallinger[1,2], Iris Schäffner[3], Barbara Klein[1,2], Renate Gelfert[1,2], Francisco J. Rivera[1,2], Sebastian Illes[1,2], Lukas Grassner[1,2,4], Maximilian Janssen[1,2], Peter Rotheneichner[1,2,5], Claudia Schmuckermair[6], Roland Coras[7], Marta Boccazzi[8], Mansoor Chishty[9], Florian B. Lagler[10], Marija Renic[11], Hans-Christian Bauer[2,12], Nicolas Singewald[6], Ingmar Blümcke[7], Ulrich Bogdahn[13], Sebastien Couillard-Despres[2,5], D. Chichung Lie[3], Maria P. Abbracchio[8] & Ludwig Aigner[1,2]

Received: 3 January 2018 | Revised: 27 February 2018 | Accepted: 13 March 2018

DOI: 10.1111/cns.12855

ORIGINAL ARTICLE

WILEY CNS Neuroscience & Therapeutics

Repurposing carbamazepine for the treatment of amyotrophic lateral sclerosis in SOD1-G93A mouse model

Jing-Jing Zhang[1,2,3] | Qin-Ming Zhou[4] | Sheng Chen[5] | Wei-Dong Le[1,2,6]

Received: 26 February 2018 | Accepted: 28 February 2018

DOI: 10.1002/jcp.26579

ORIGINAL RESEARCH ARTICLE

WILEY Journal of Cellular Physiology

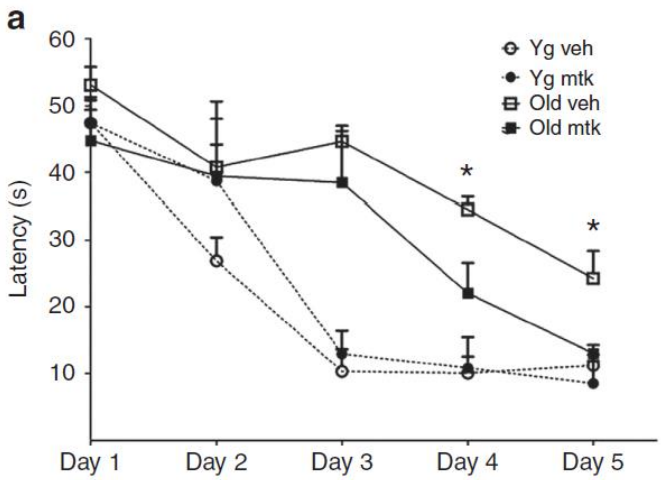
Possible repurposing of pyrvinium pamoate for the treatment of mesothelioma: A pre-clinical assessment

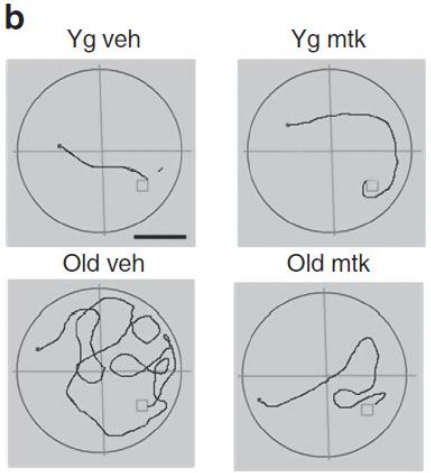
Marcella Barbarino[1,2] | Daniele Cesari[1] | Riccardo Intruglio[1] | Paola Indovina[2] | Asadoor Namagerdi[1] | Franca Maria Bertolino[1] | Maria Bottaro[1] | Delaram Rahamani[1] | Cristiana Bellan[3] | Antonio Giordano[1,2]

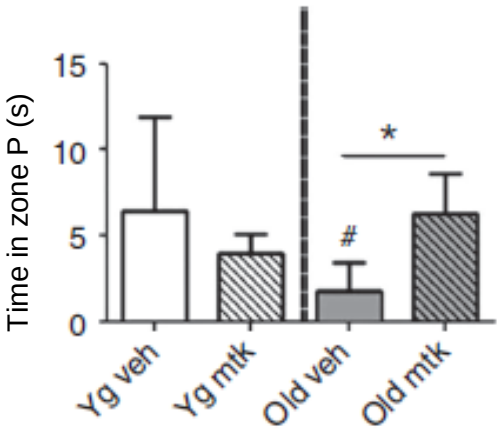
Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug

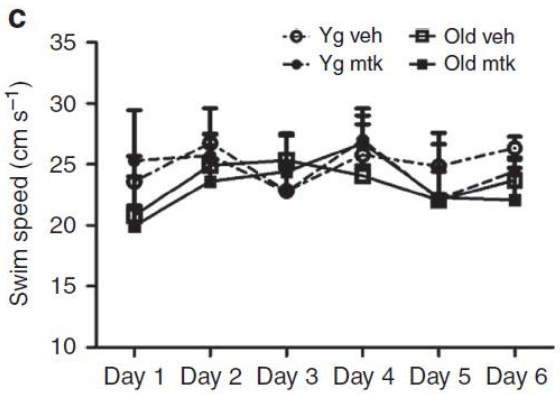
- Aim: target histopathological processes correlating with age-related cognitive declines to structurally and functionally rejuvenate the aged brain
  - Neuroinflammation
  - Low levels of neurogenesis
  - Disrupted BBB
  - Altered neuronal activity
- 6 weeks of 10mg/kg Montelukast treatment of young (4 month) and aged (20 month) old rats
- Montelukast: Leukotriene receptor antagonist

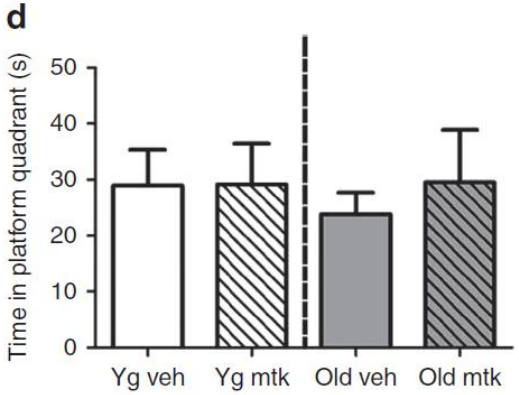
Montelukast treatment improved learning and memory in aged rats

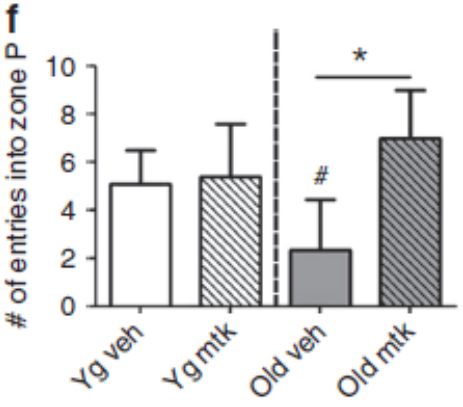




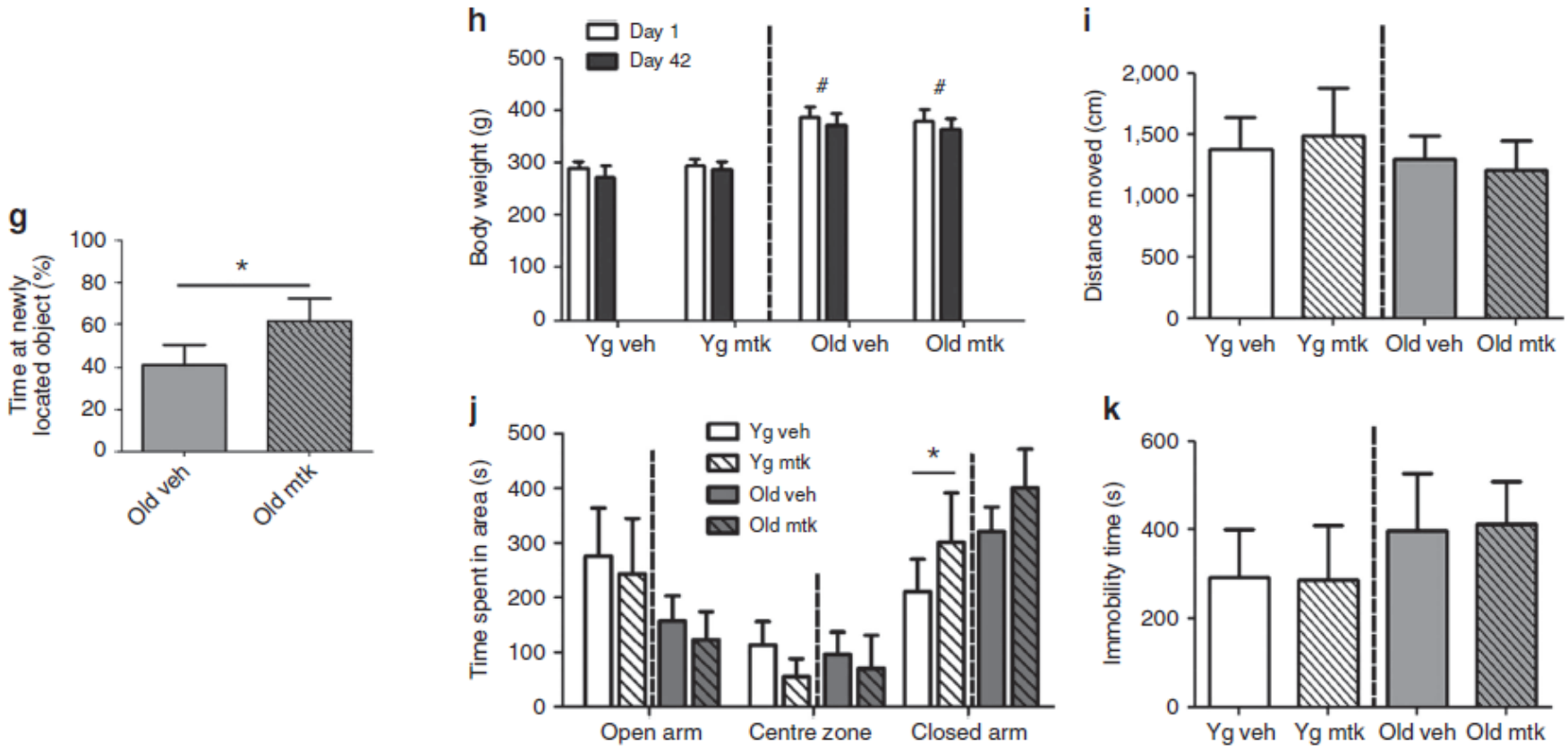




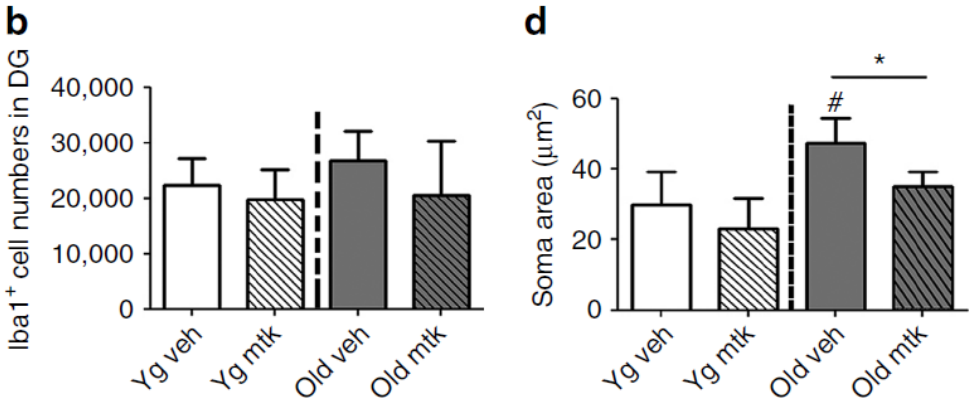


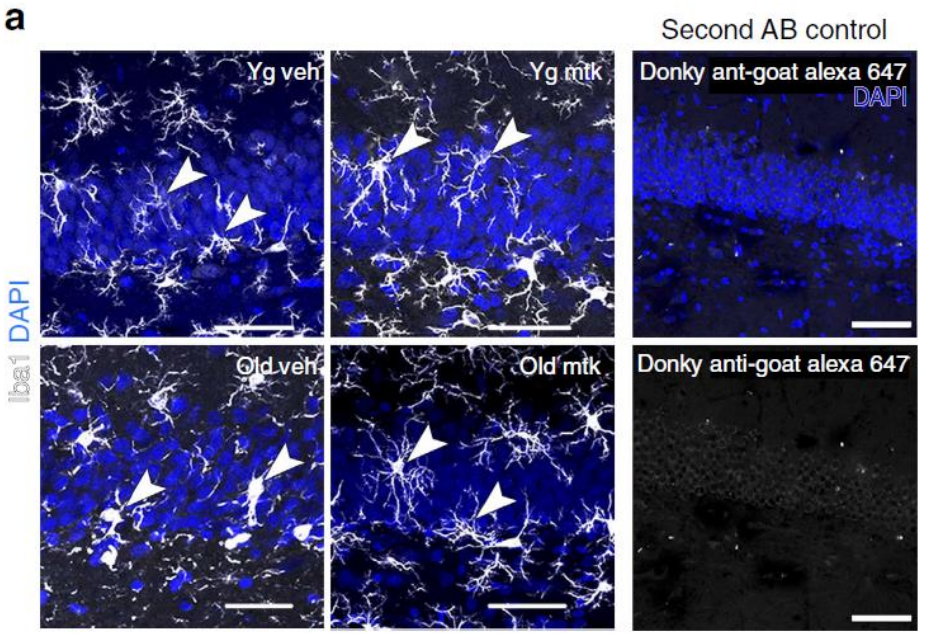


Montelukast treatment improved learning and memory in aged rats

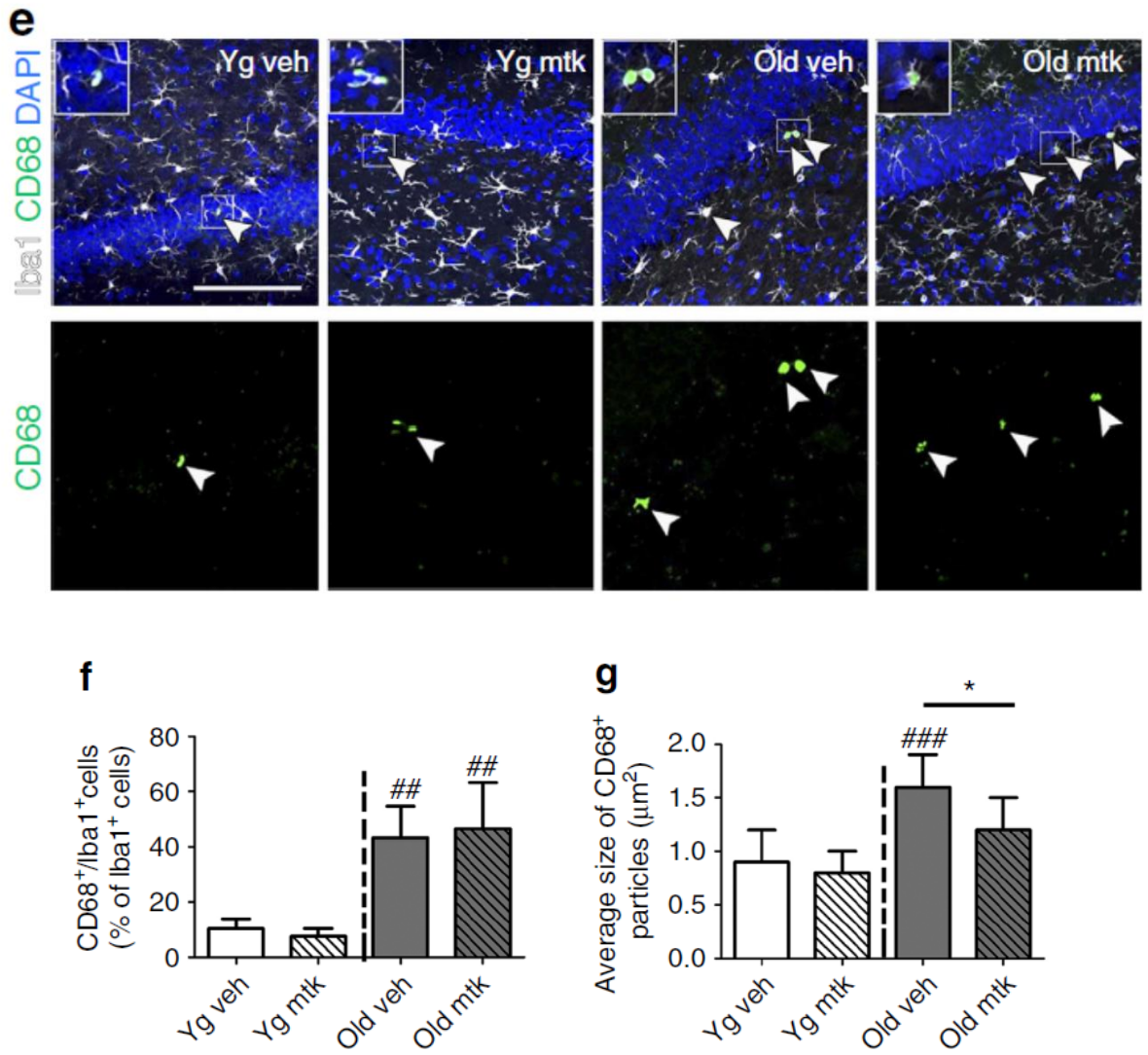


Montelukast modulates microglia in aged rats

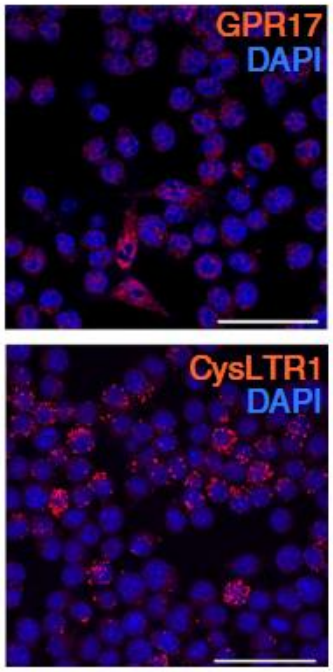


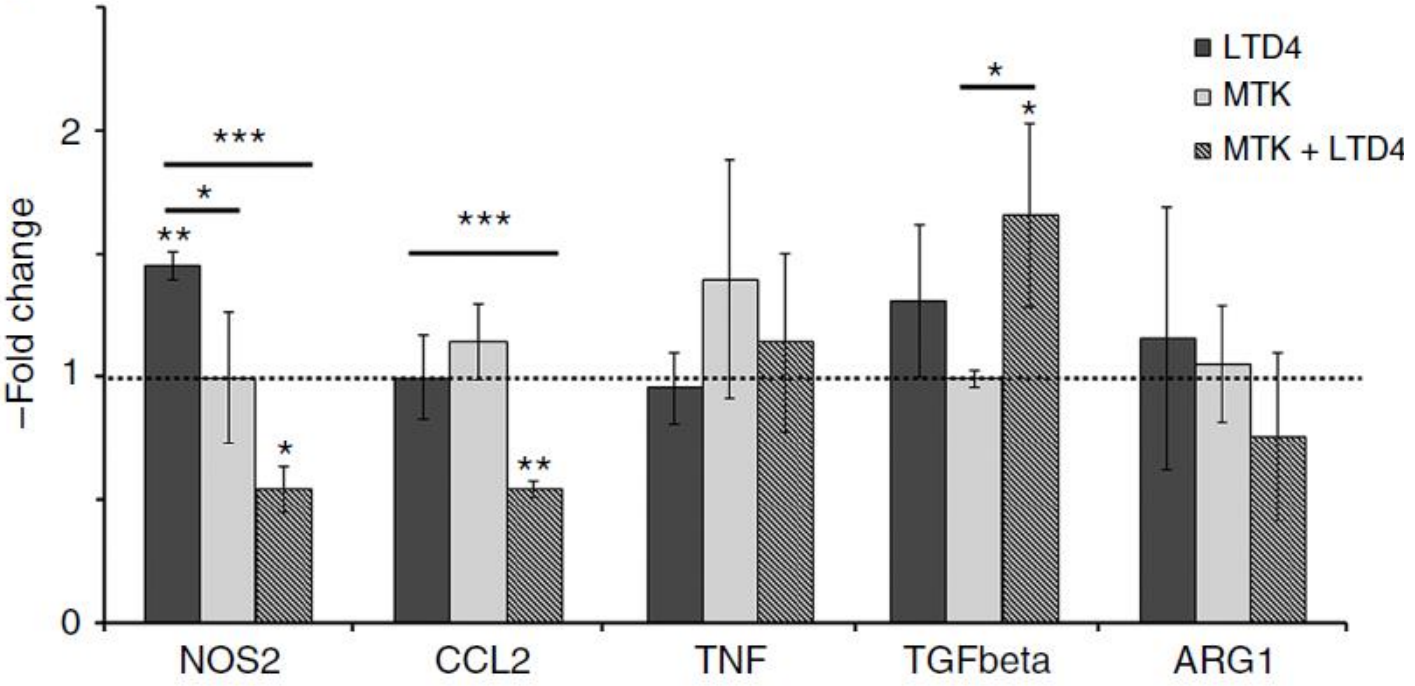


Montelukast modulates microglia in aged rats



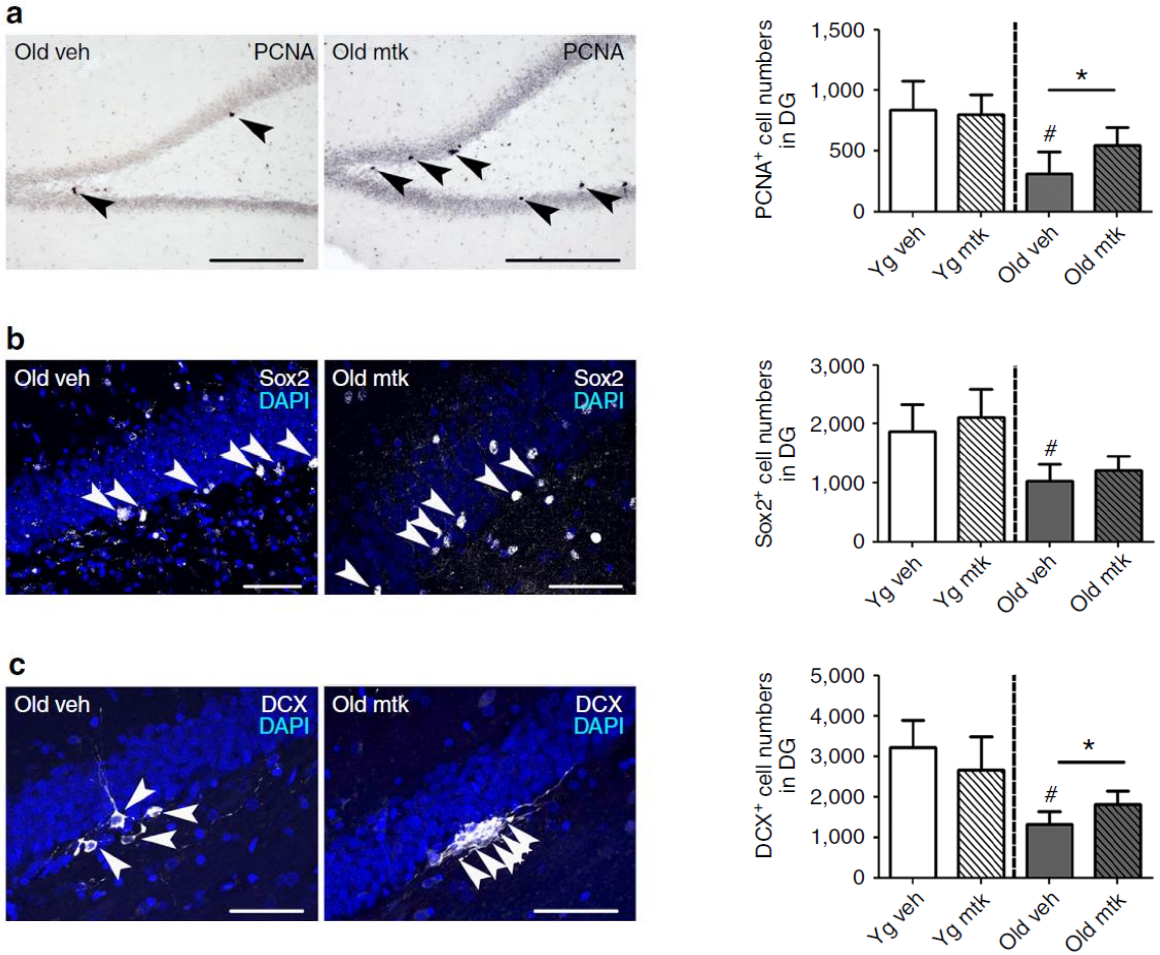
Montelukast modulates neuroinflammatory gene expression in BV-2 microglia cell line





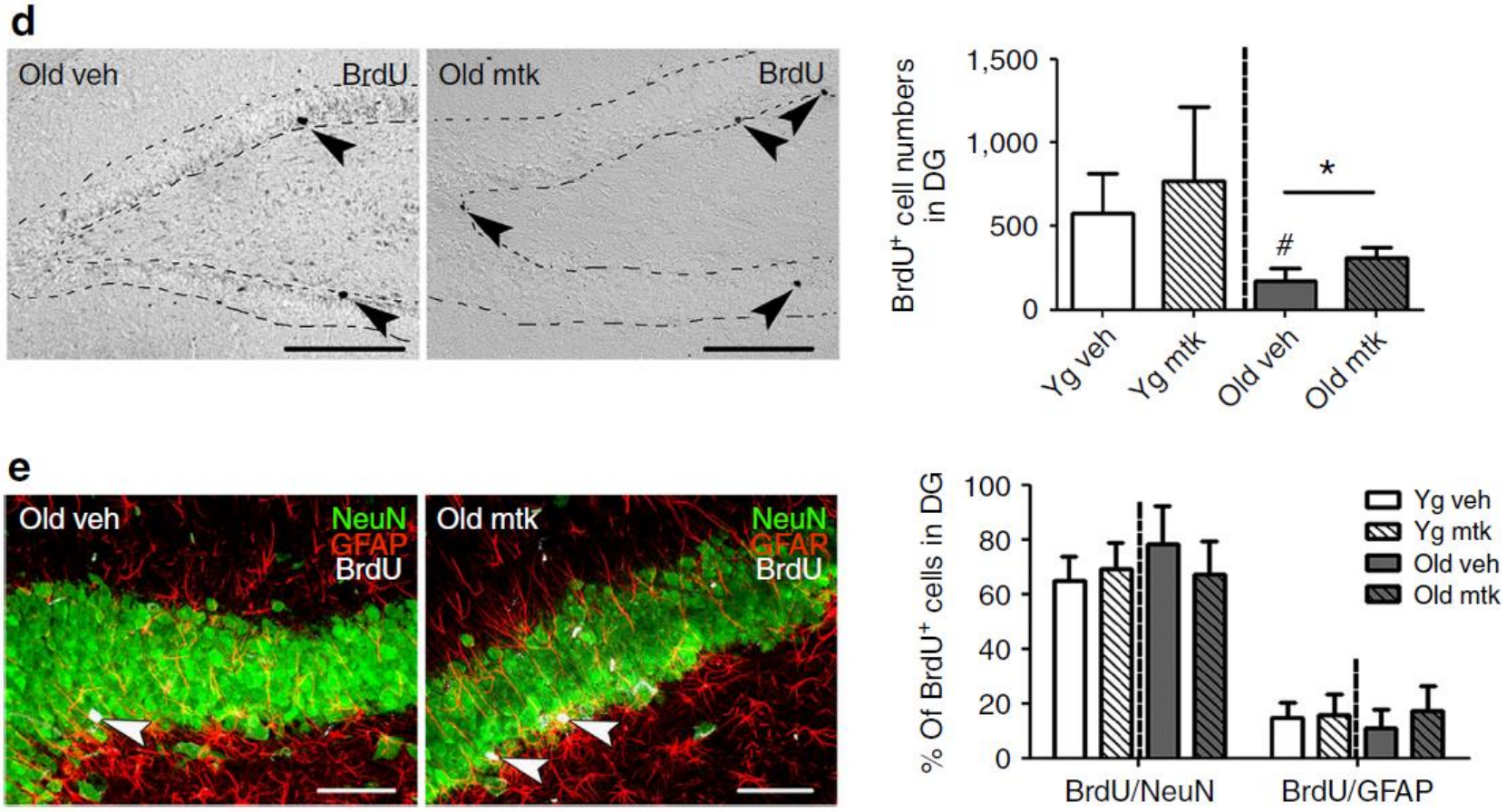
LTD4 100nM, MTK 15µM

Montelukast increases dentate gyrus neurogenes in aged rats

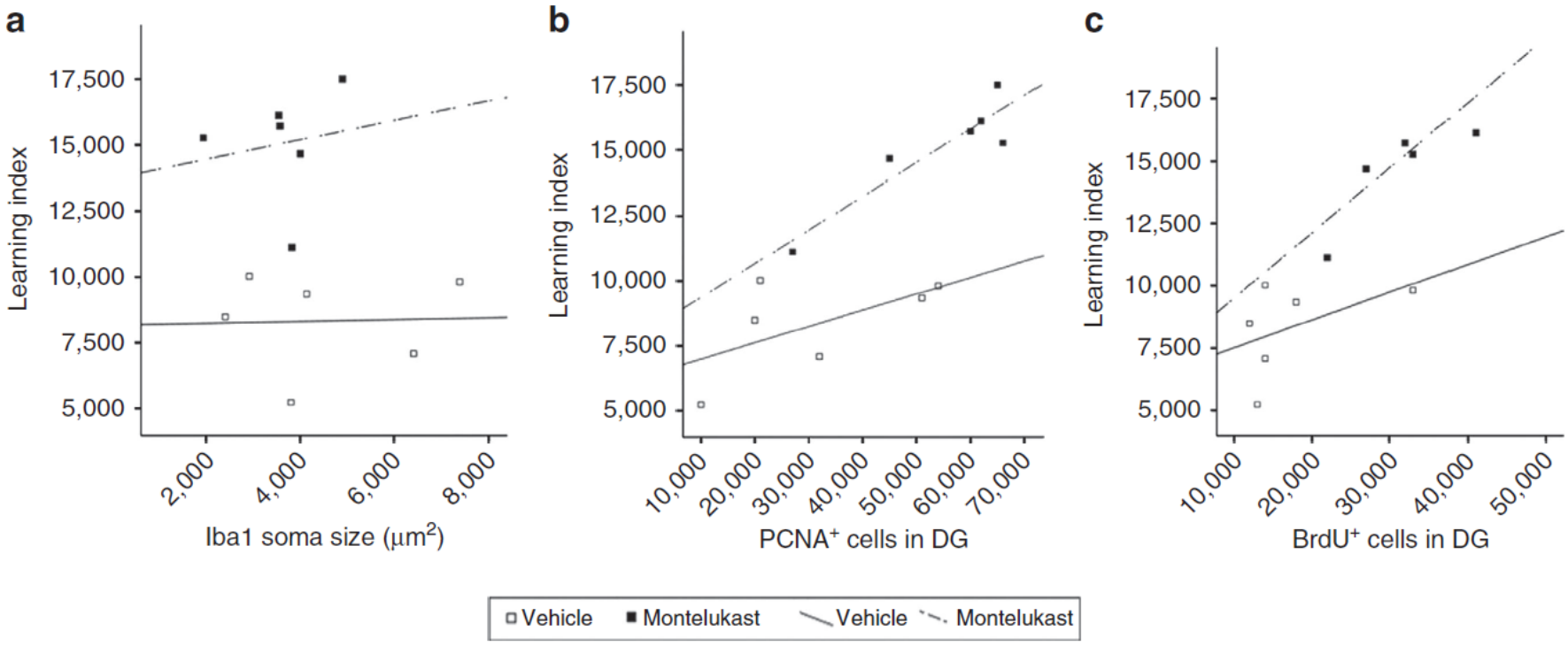


→ Elevated PCNA signal not due to enlarged neural stem cell pool

Montelukast increases dentate gyrus neurogenesis in aged rats

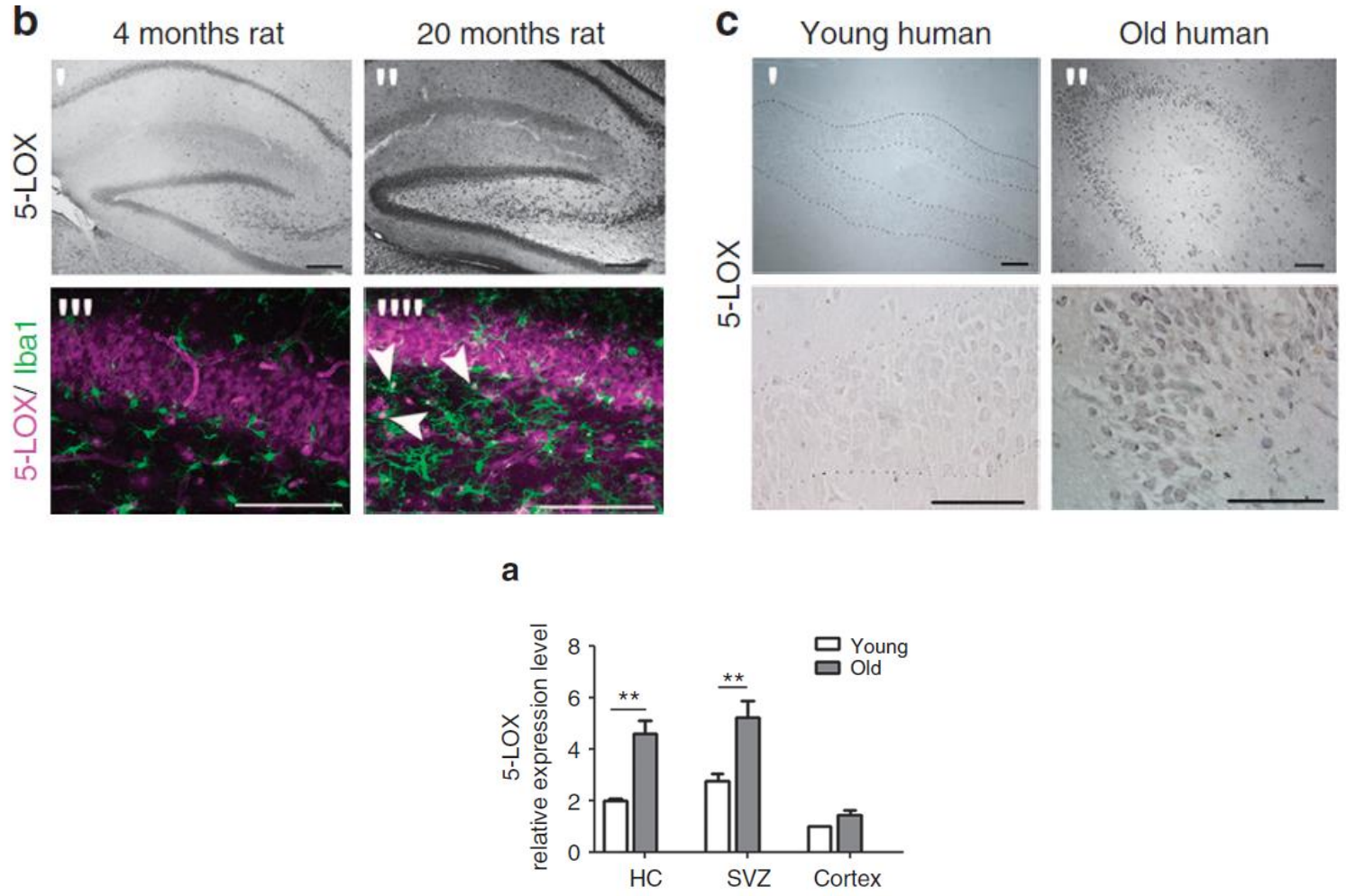


Montelukast-mediated cognitive improvements in old rats correlate with increased neurogenesis

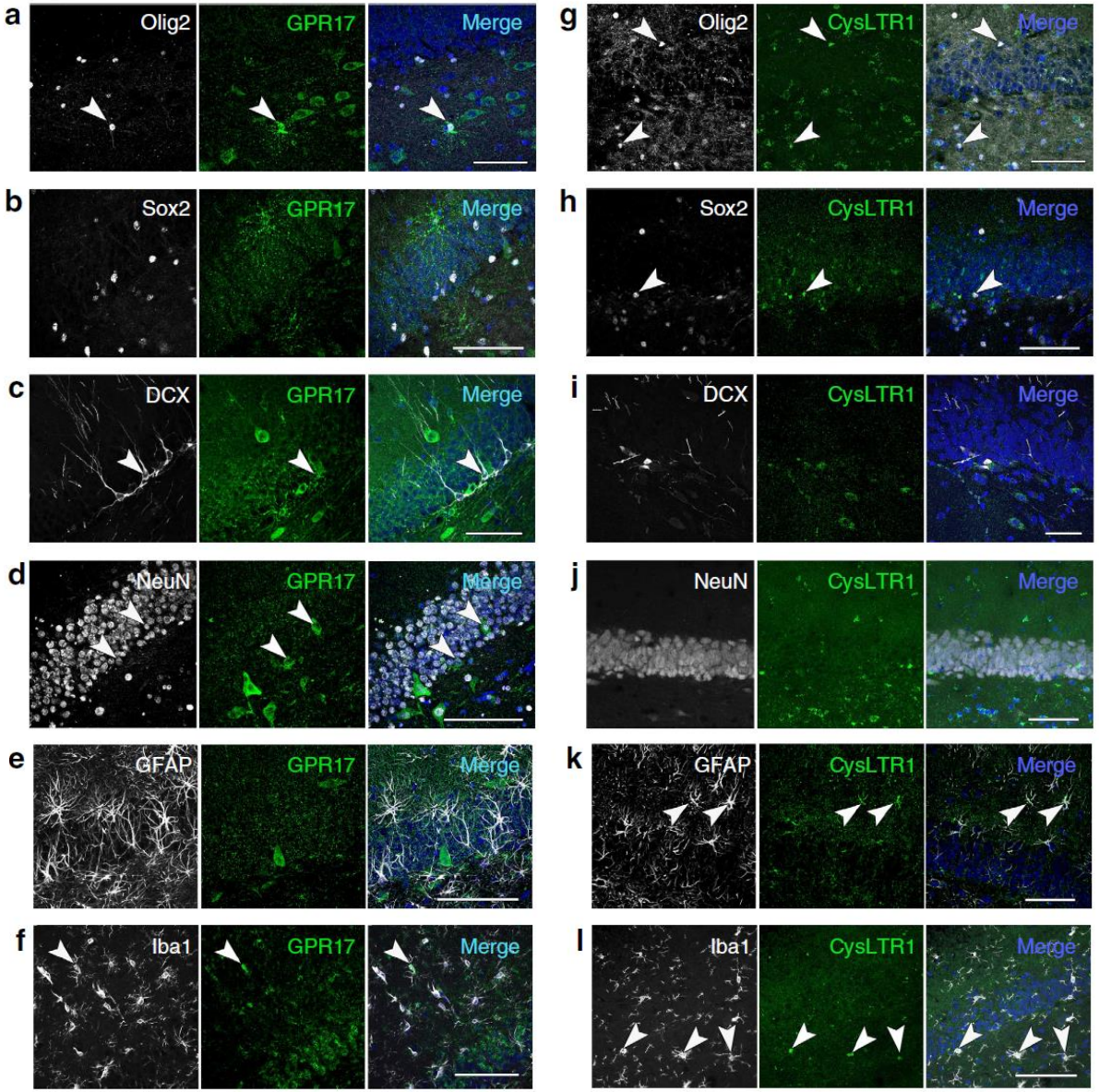


→ Increased neurogenesis might be the reason for better learning of aged rats

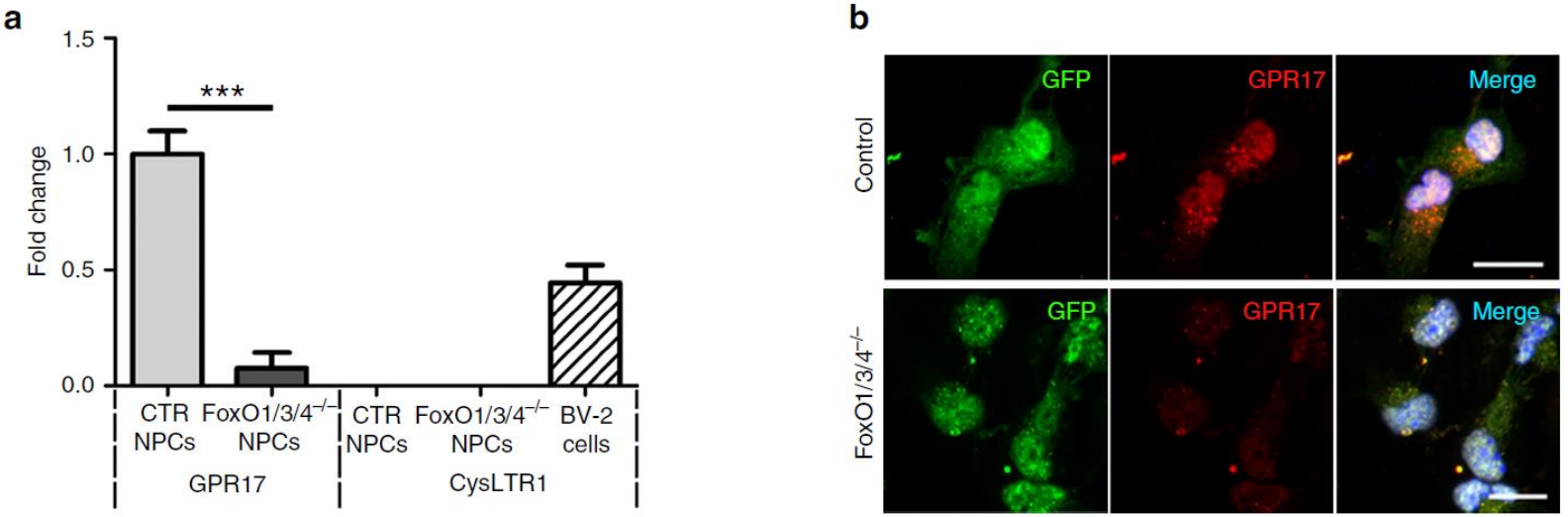
5-LOX expression is upregulated in the hippocampus of old rats and elderly humans



GPR17 and CysLTR1are expressed within the dentate gyrus of aged rats

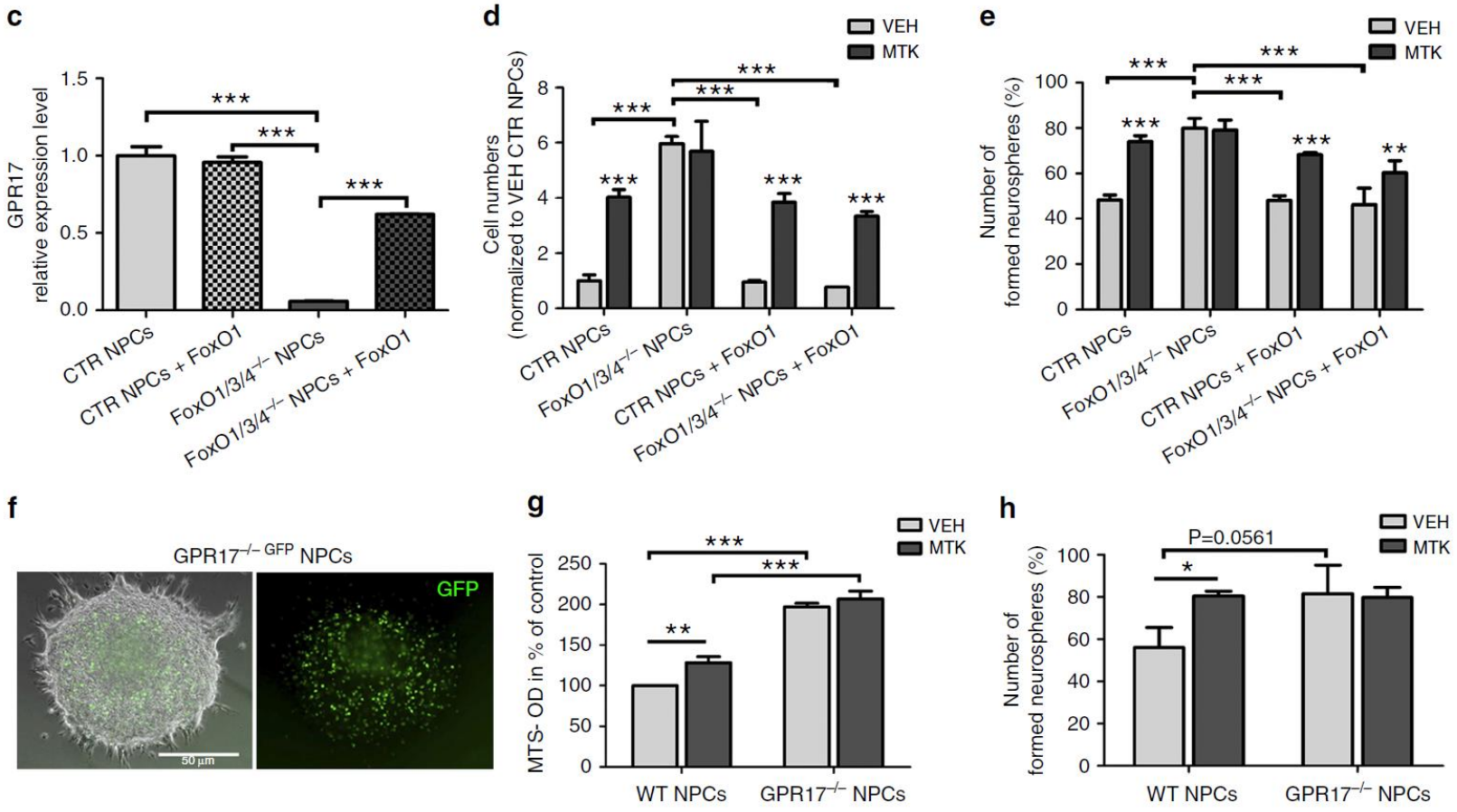


GPR17 and CysLTR1 expression in FoxO1/3/4 $^{-/-}$ NPCs



GPR17 is a target of FoxO transcription factors
Mouse line: FoxO1,3,4 fl/fl recombined with GFP/Cre retrovirus (FoxoO1/3/4 -/- NPCs)
Controls: neurospheres with GFP-only retrovirus

GPR17 k.o. in neurospheres induced hyperproliferation and abolished the effects of montelukast



Conclusion 1

- Montelukast: anti-asthmatic drug which antagonizes leukotriene receptors caused
  - Reduced neuroinflammation
  - Elevated hippocampal neurogenesis
  - Improved learning and memory of aged rats
- Gene knockout and knockdown approaches to find inhibition of GPR17 as effect mediating
- Inhibition of leukotriene receptor signaling via Montelukast could be a safe and druggable option to restore cognitive function in old individuals → treatment of dementia etc.

Repurposing carbamazepine for the treatment of amyotrophic lateral sclerosis in SOD1-G93A mouse model

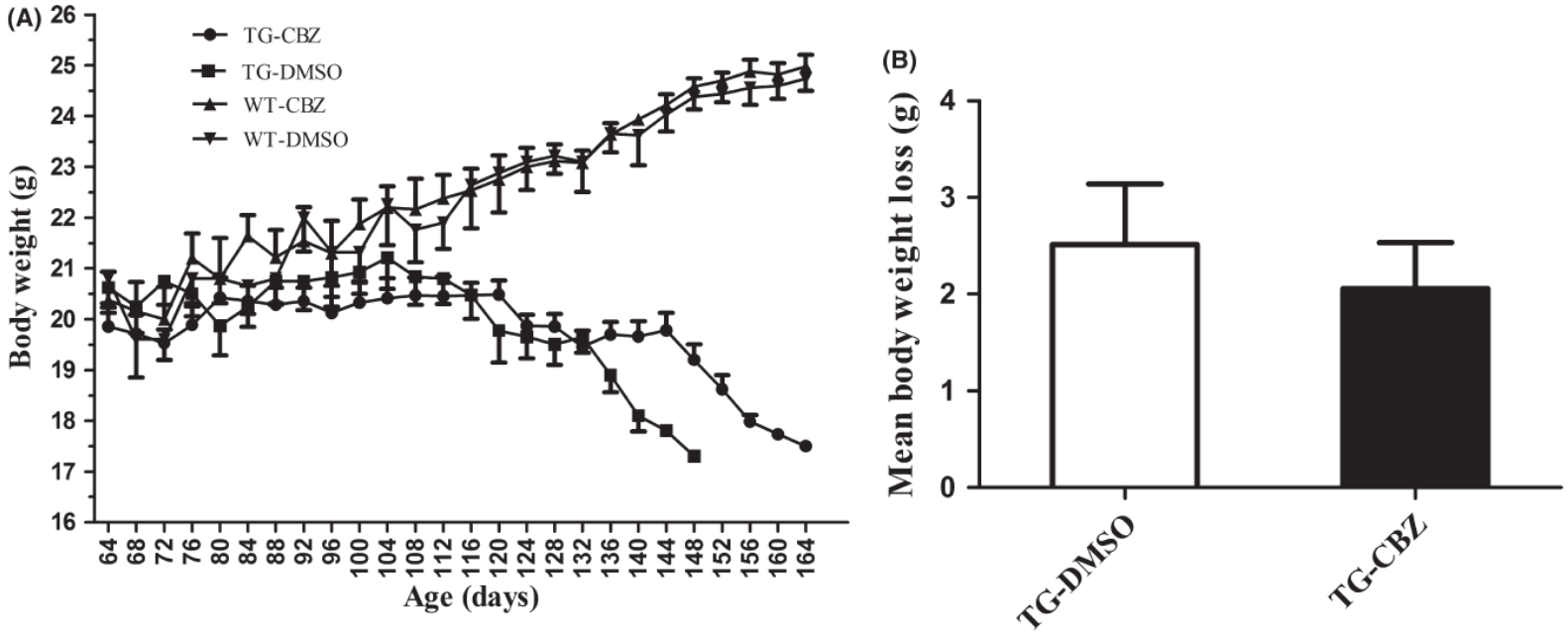
- Aim: Investigation of the effect and mechanisms of carbamazepine (CBZ) on the onset and progression of ALS in SOD1-G93A mouse model

- daily oral administration of 200 mg/kg CBZ in DMSO from 64 days of age to death

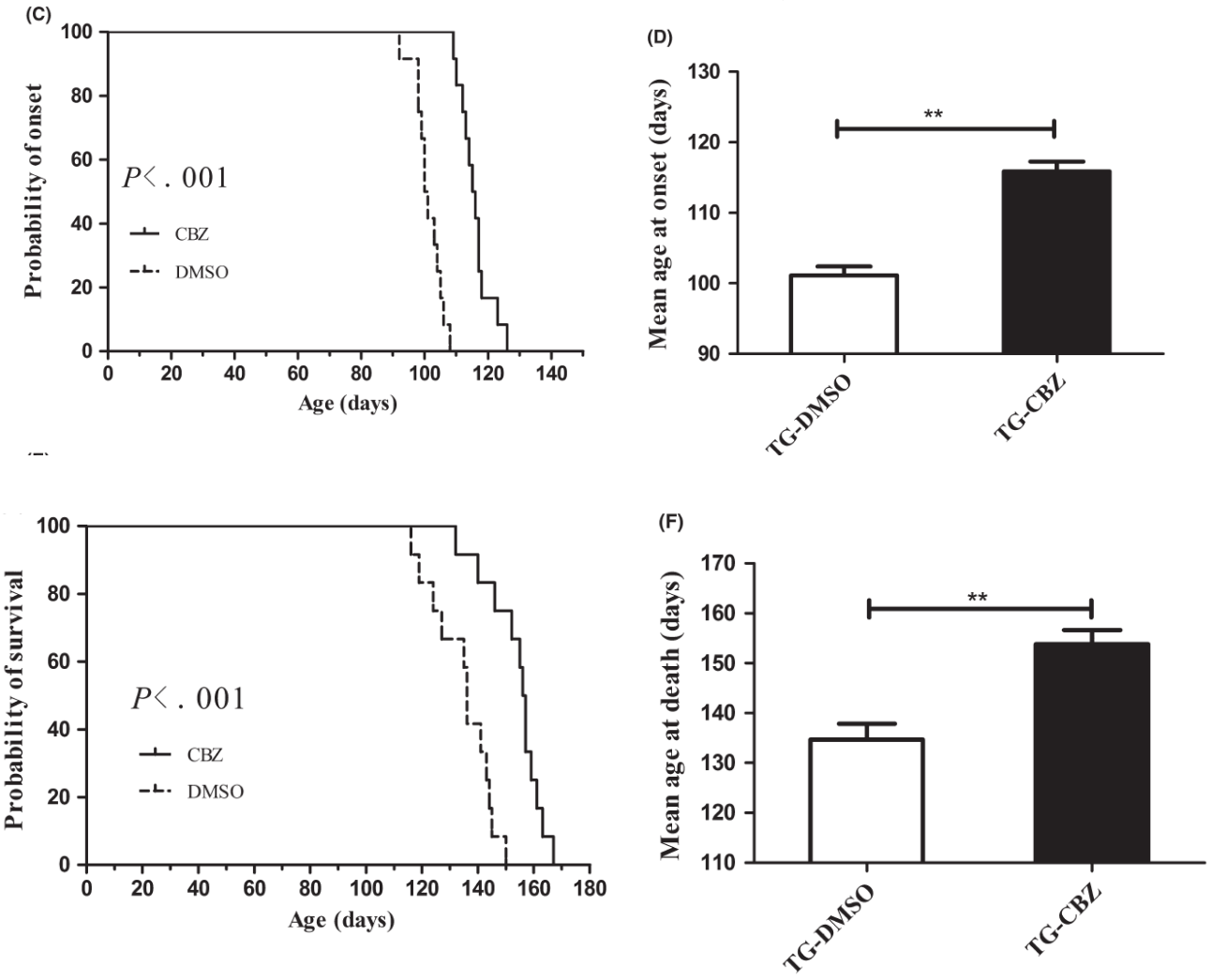
SOD1-G93A mice overexpressing high-level human mutant SOD1-G93A gene and show hindlimb paralysis in average 99.2 days of life plus MN loss after 60 days of life

Carbamazepine is an anti-epileptic drug can stimulate autophagy by decreasing the intracellular level of inositol

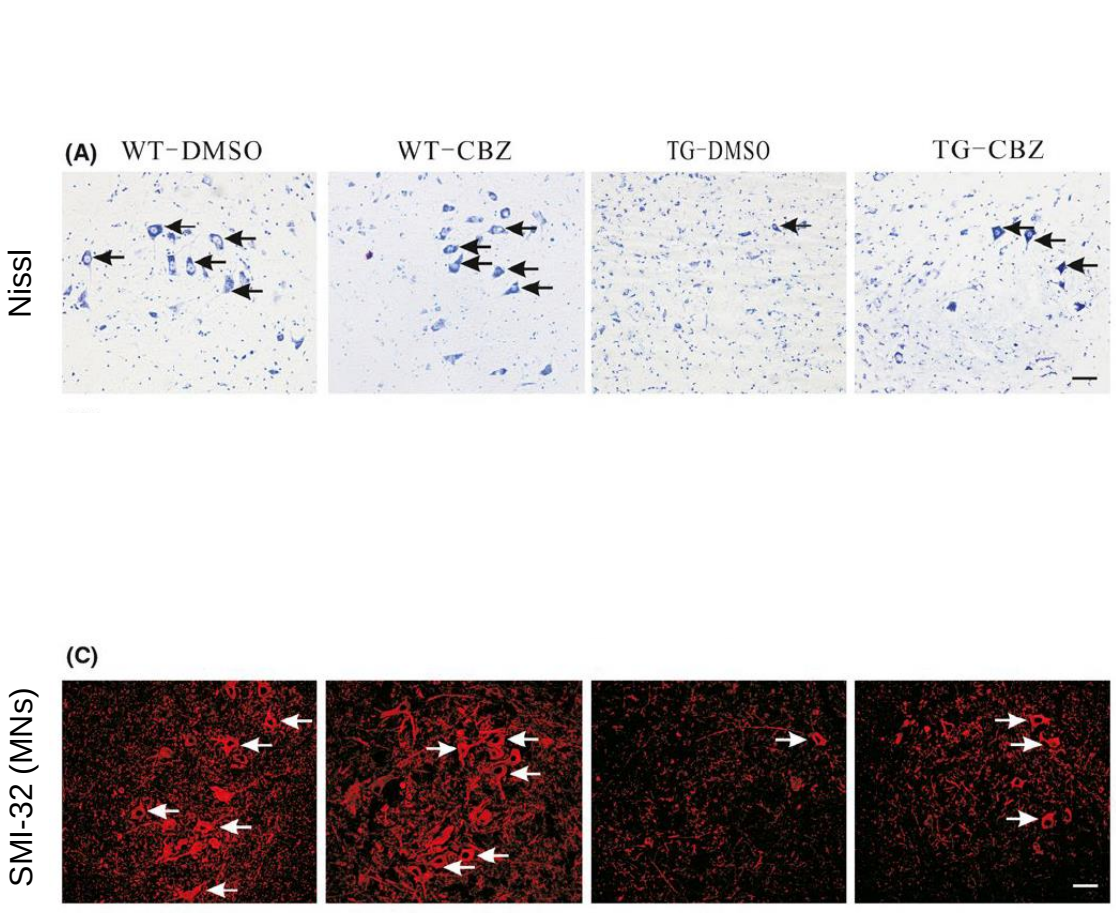
Carbamazepine treatment delayed disease onset and extended life span

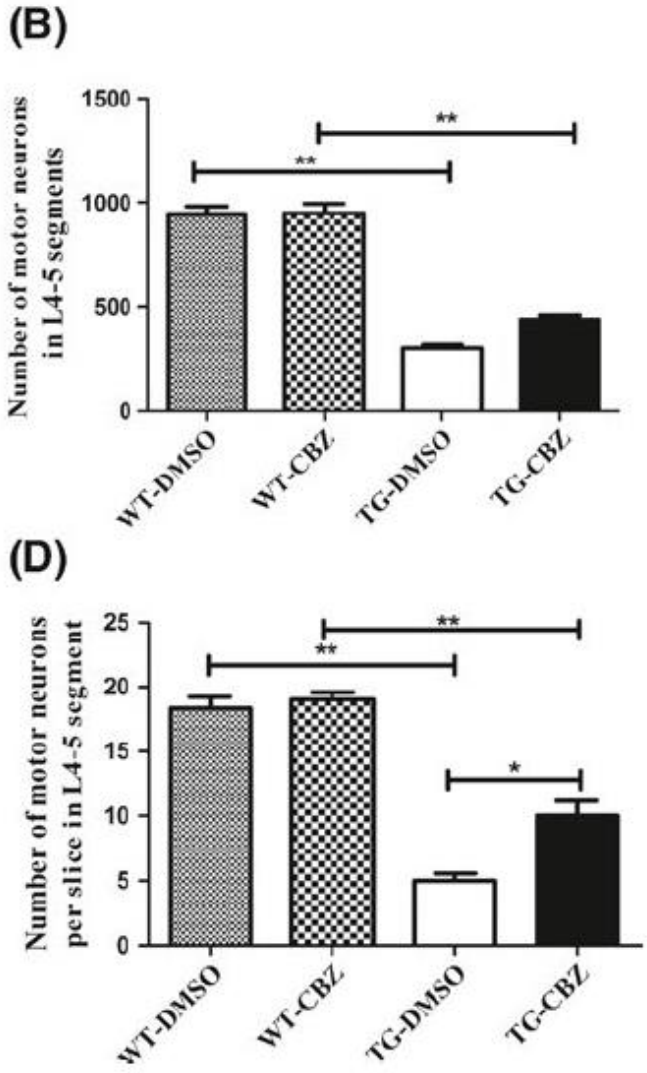


Carbamazepine treatment delayed disease onset and extended life span

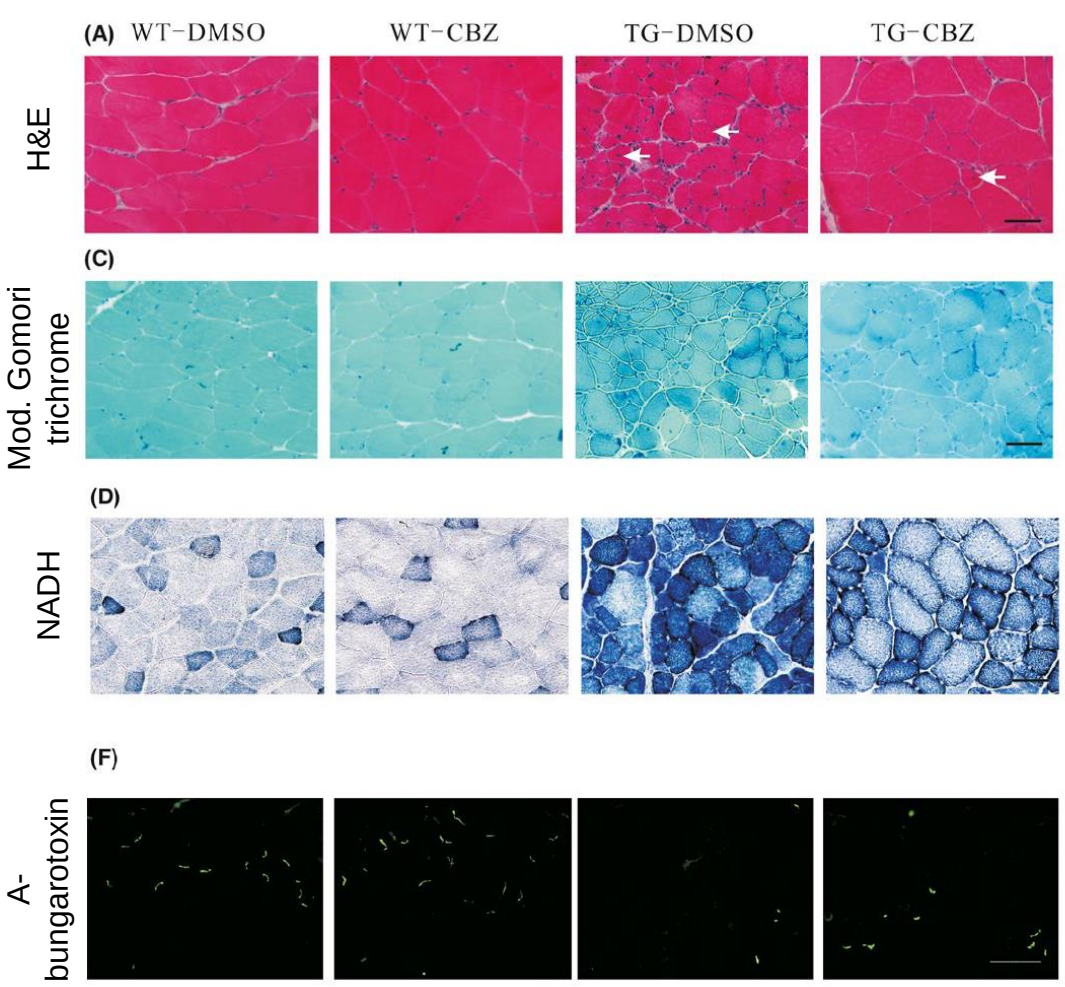


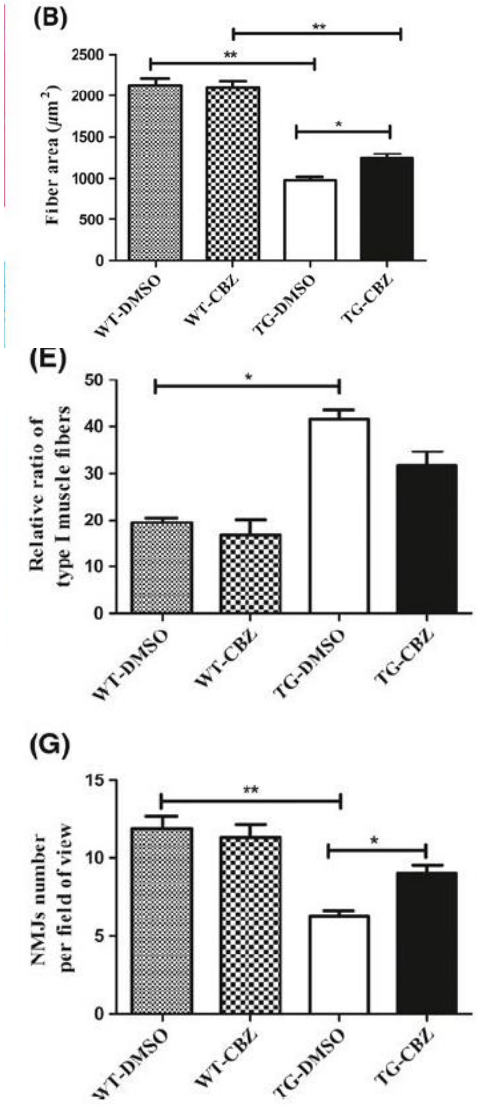
Carbamazepine treatment alleviated motoneuron loss



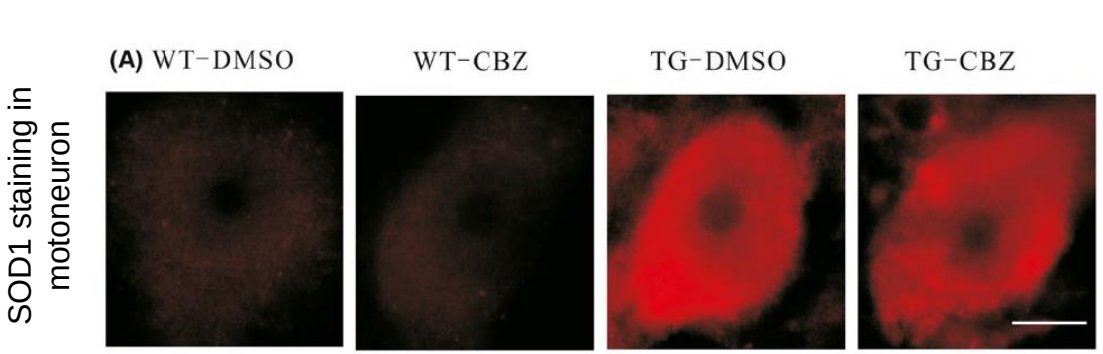


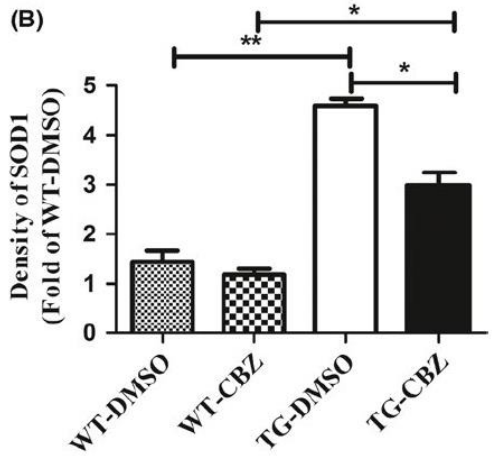
Carbamazepine treatment ameliorated morphological muscle damage

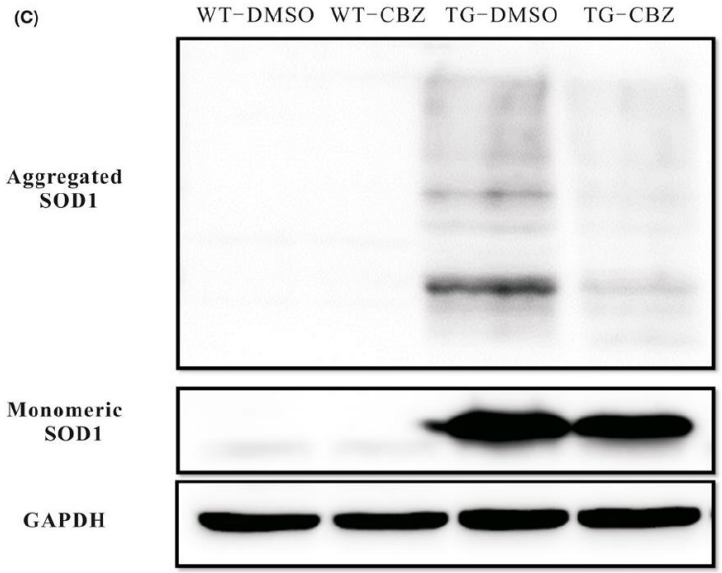


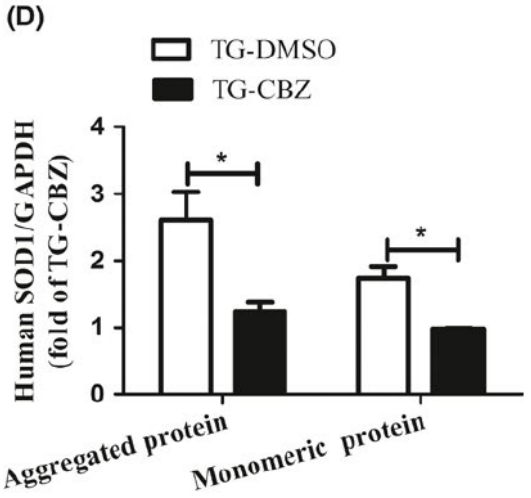


Carbamazepine effect on SOD1 aggregation in SOD1-G93A mice

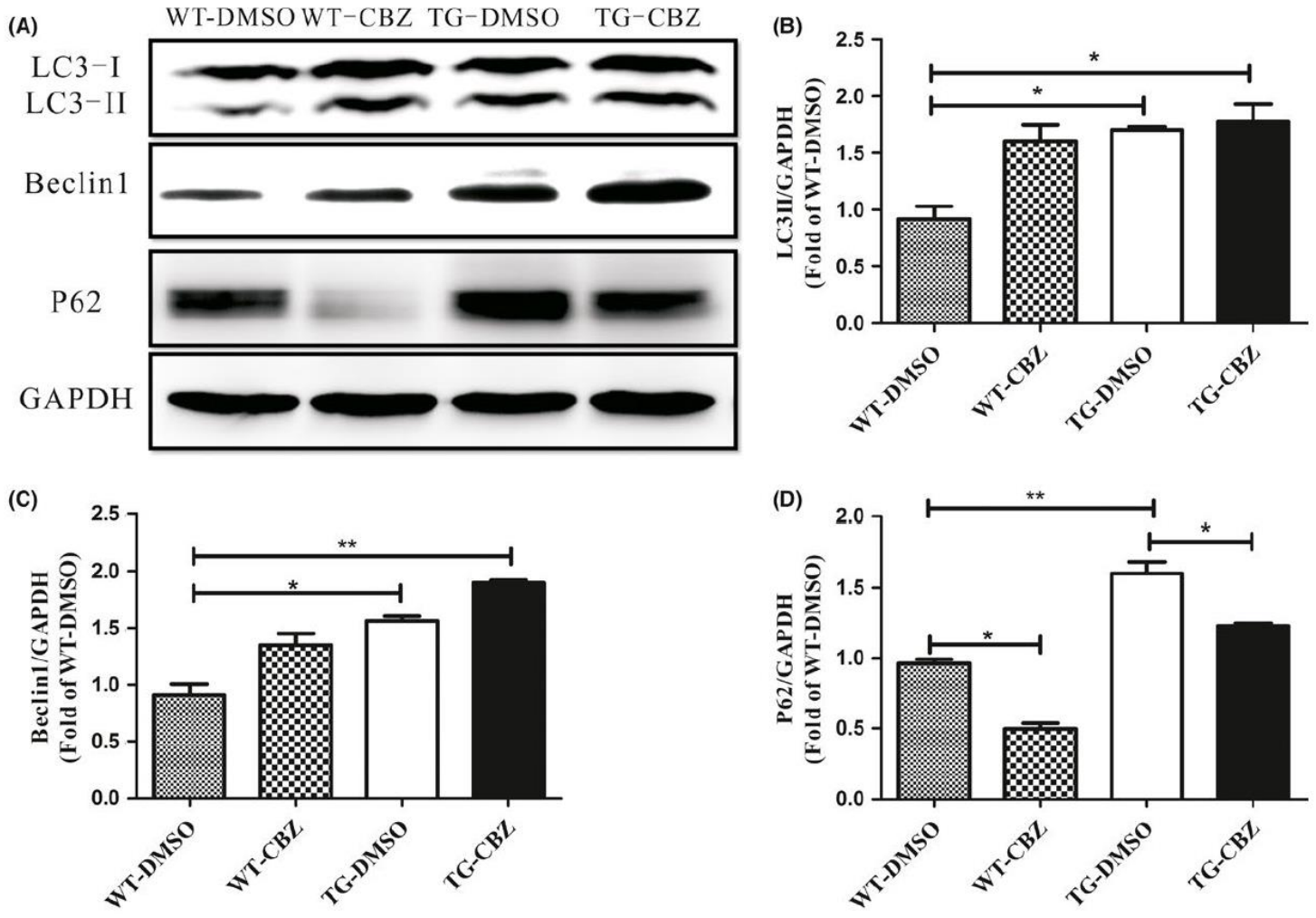




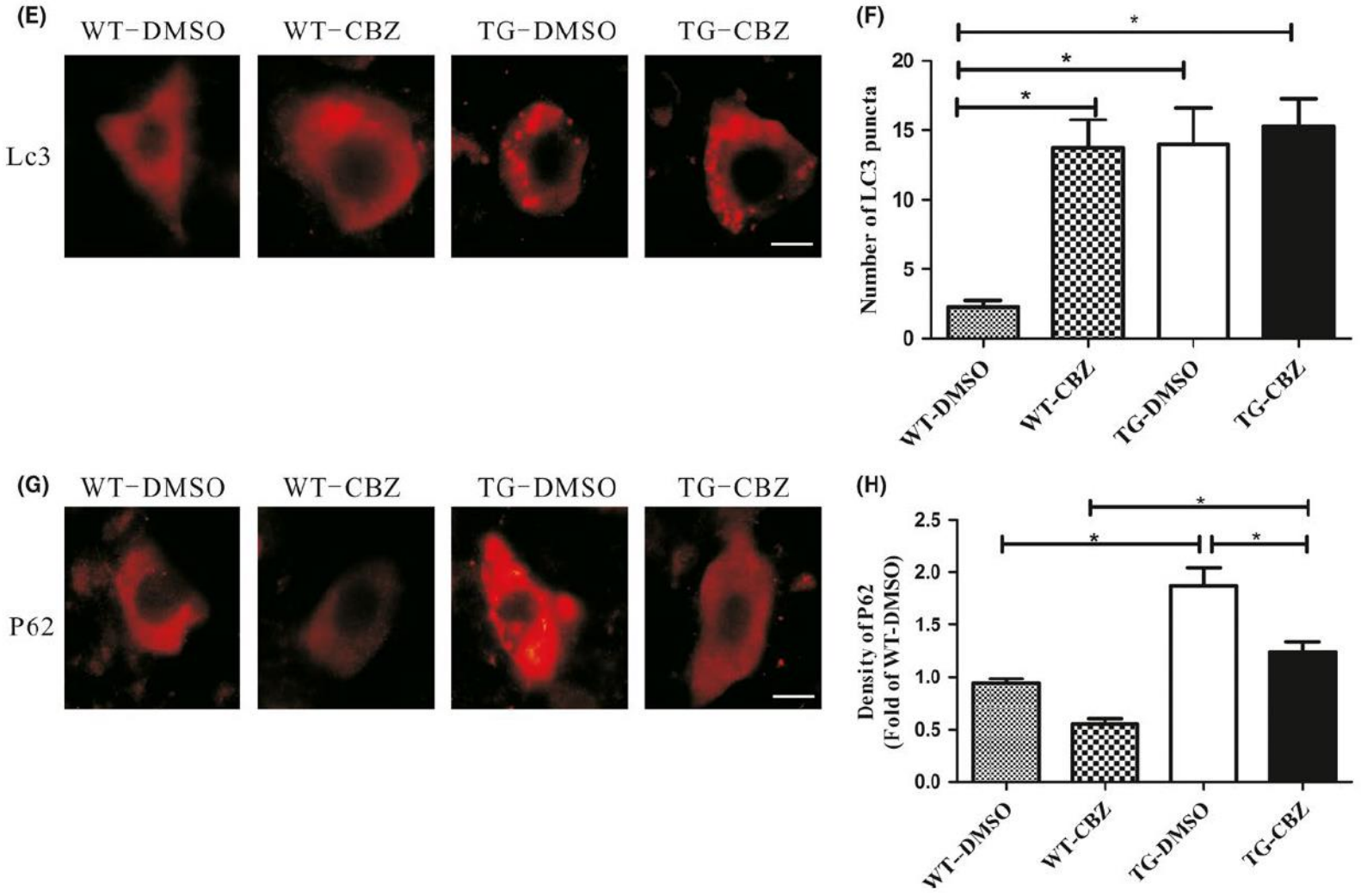




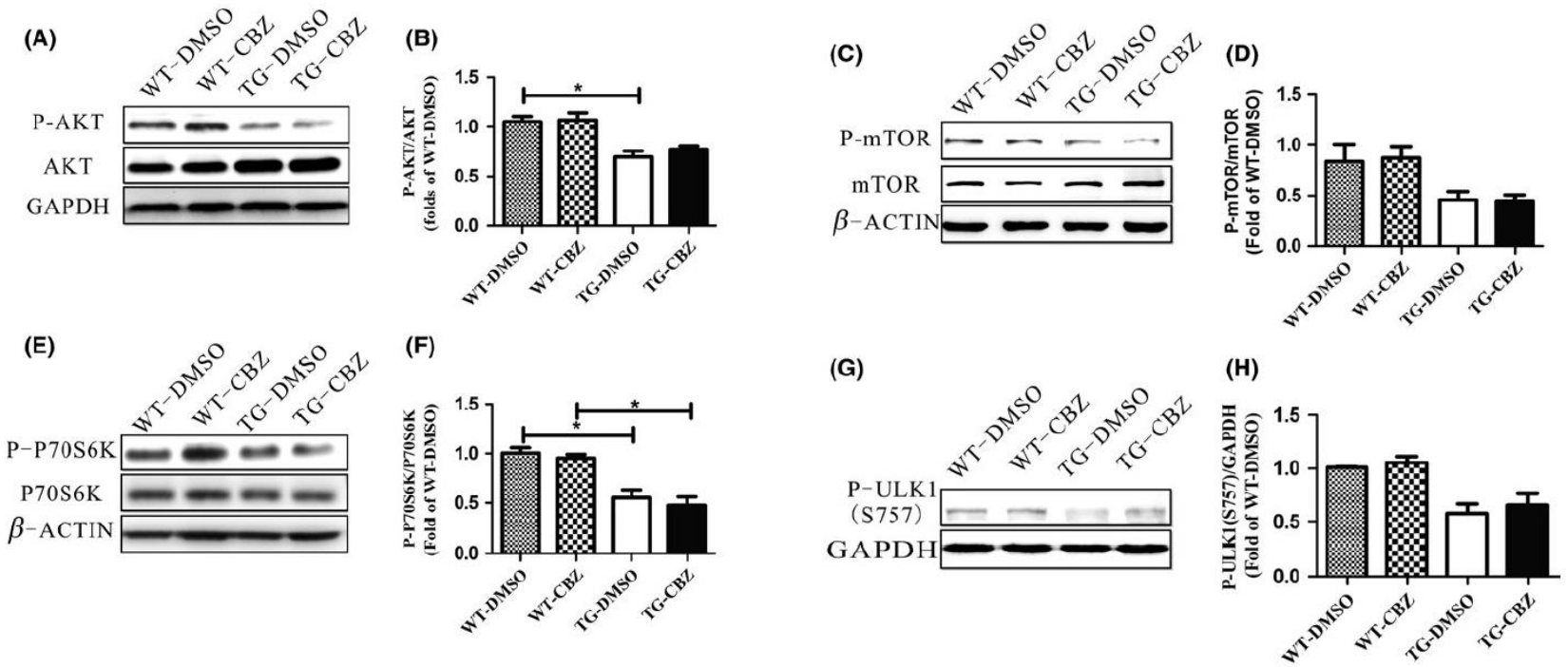
Carbamazepine regulated autophagic flux in SOD1-G93A mice



Carbamazepine regulated autophagic flux in SOD1-G93A mice



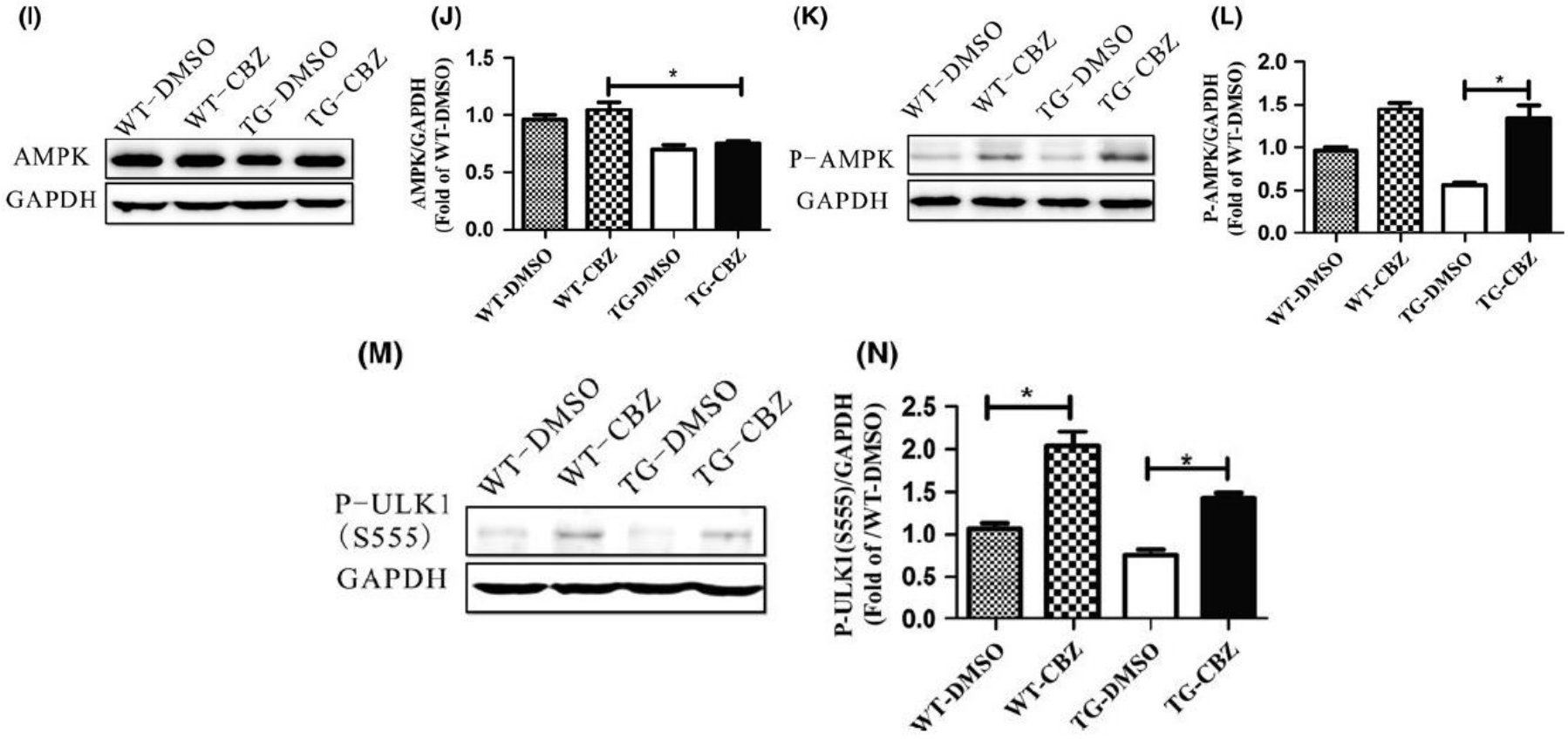
Carbamazepine activated autophagy by AMPK-ULK1 pathway



Ratio pAKT/AKT ↓
Ratio P-P70S6K ↓
P-ULK ↓

→ m-TOR independent pathway
→ AMPK regulation of ULK1

Carbamazepine activated autophagy by AMPK-ULK1 pathway



→ CBZ induces autophagy via AMPK-ULK1-Beclin1 pathway

Conclusion 2

- CBZ treatment
  - Delayed disease onset and extented lifespan of mice by 14.5% and 13.9% respectively
  - Reduced motoneuron loss by about 46.6% and ameliorated altered muscle morphology and neuromuscular junctions
  - Activated autophagy and clearance of mutant SOD1 aggregation

- Therapeutic effect on disease pathogenesis in SOD1-G93A mice → clinical utilization in ALS therapy

Possible repurposing of pyrvinium pamoate for the treatment of mesothelioma: A pre-clinical assessment

- Aim: investigate the role of the Wnt/ β-catenin inhibitory drug pyrvinium pamoate for potential anti-tumor activity on malignant mesothelioma cell lines
- Effect of different concentrations of pyrvinium pamoate on different Mesothelioma cell lines when treated 72hours

- Pyrvinium pamoate used as anthelminthic drug inhibiting different molecular oncogenic pathways.

Dose-response curves of mesothelioma cells treated with pyrvinium pamoate

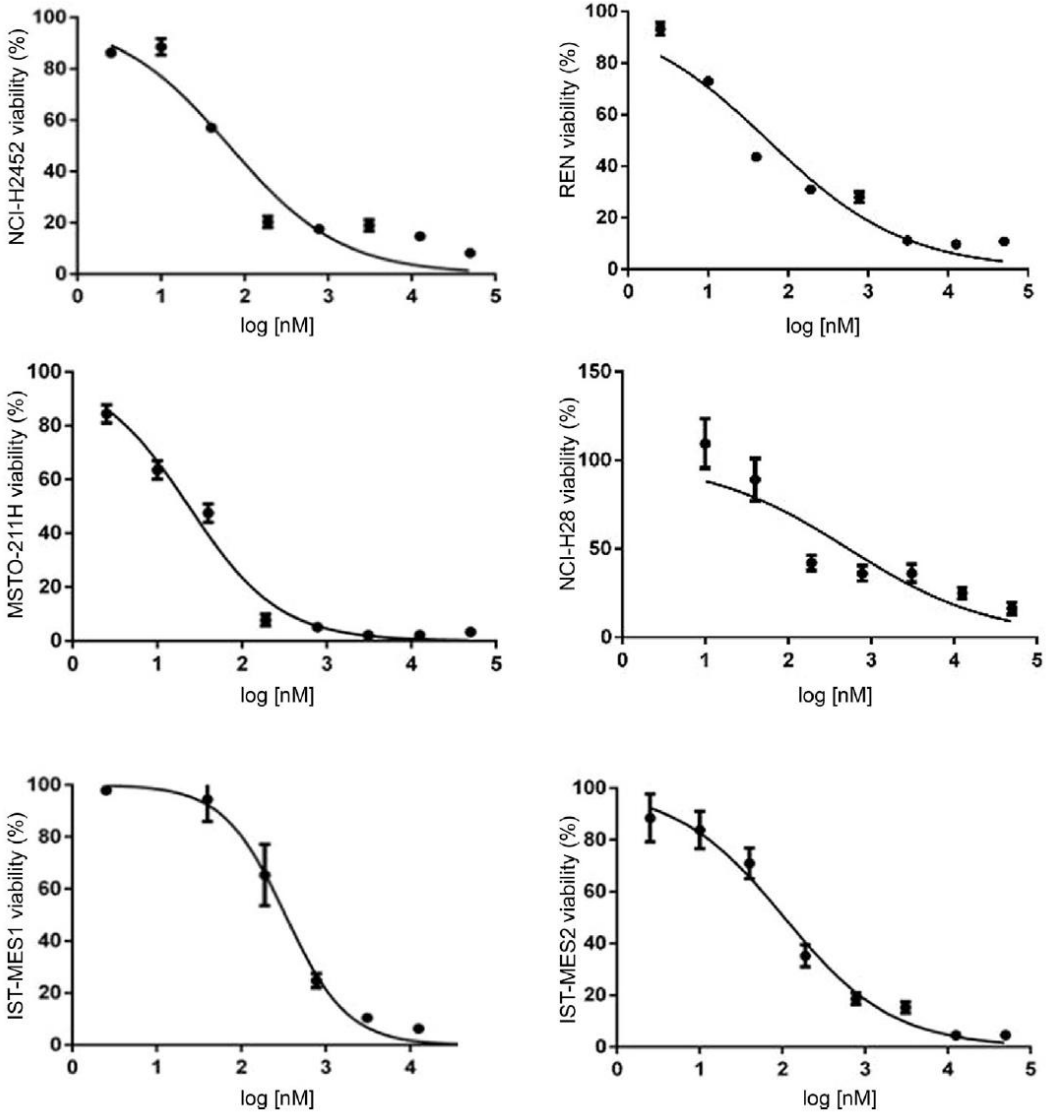
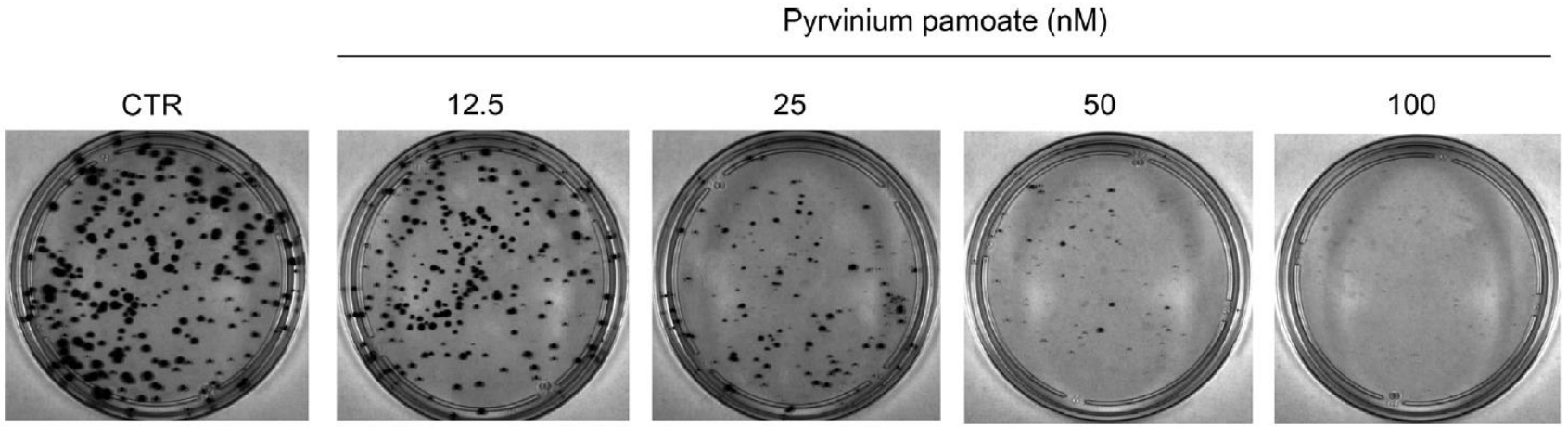


TABLE 2 IC50 values of pyrvinium pamoate in mesothelioma cell lines

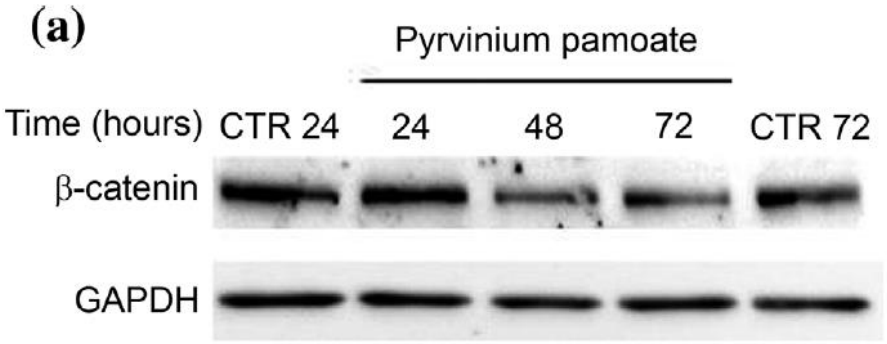
Cell line	IC50 (nM)
NCI-H2452	65.59
REN	56.3
MSTO-211H	23.58
NCI-H28	535.6
IST-MES1	332.3
IST-MES2	105.7

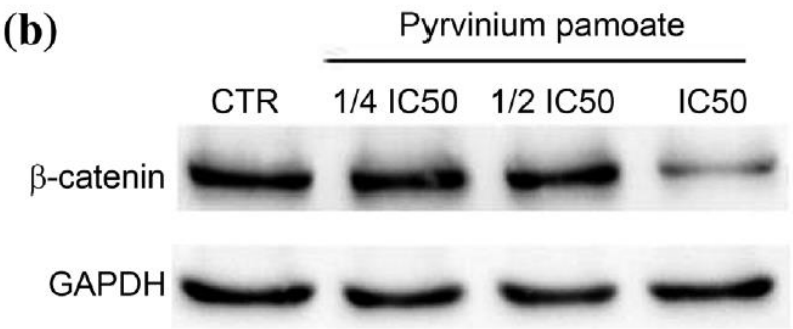
Long term effect of pyrvinium pamoate

Clonogenic assay

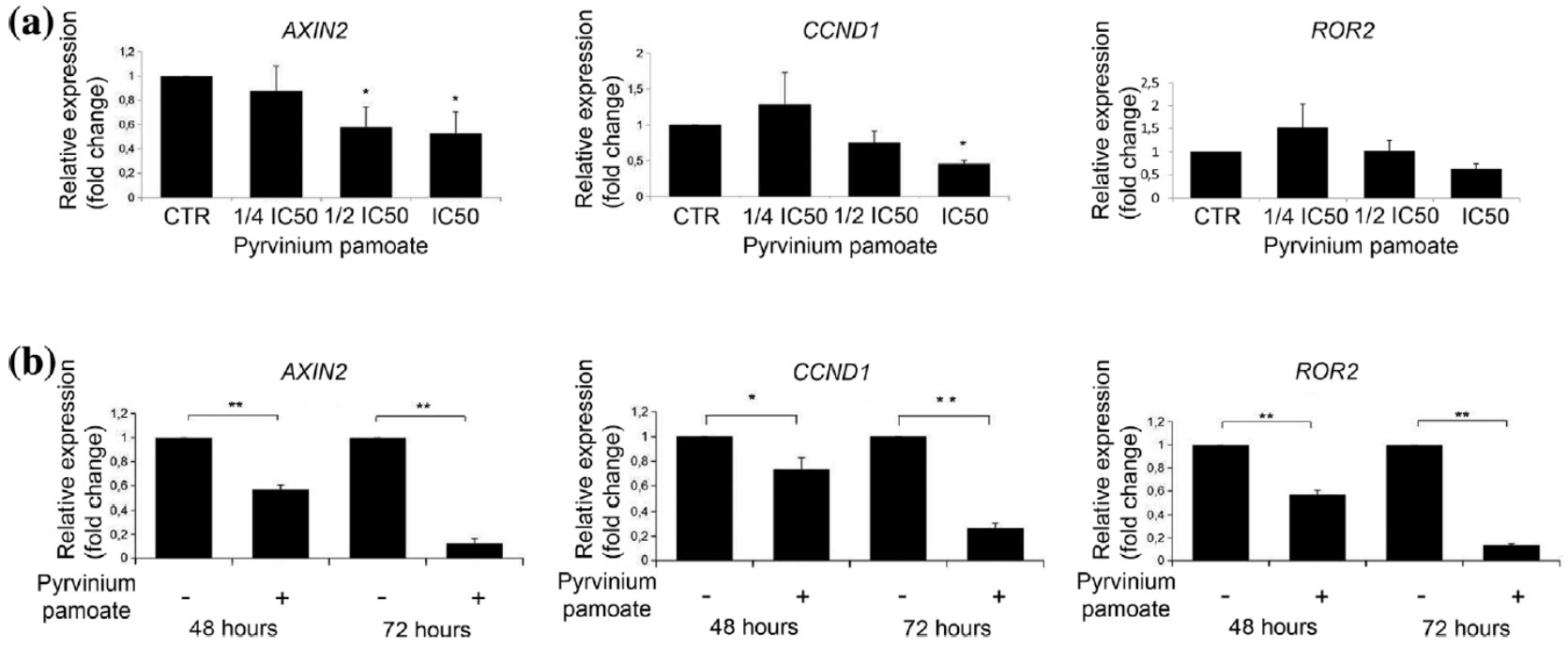


Oncoprotein analysis

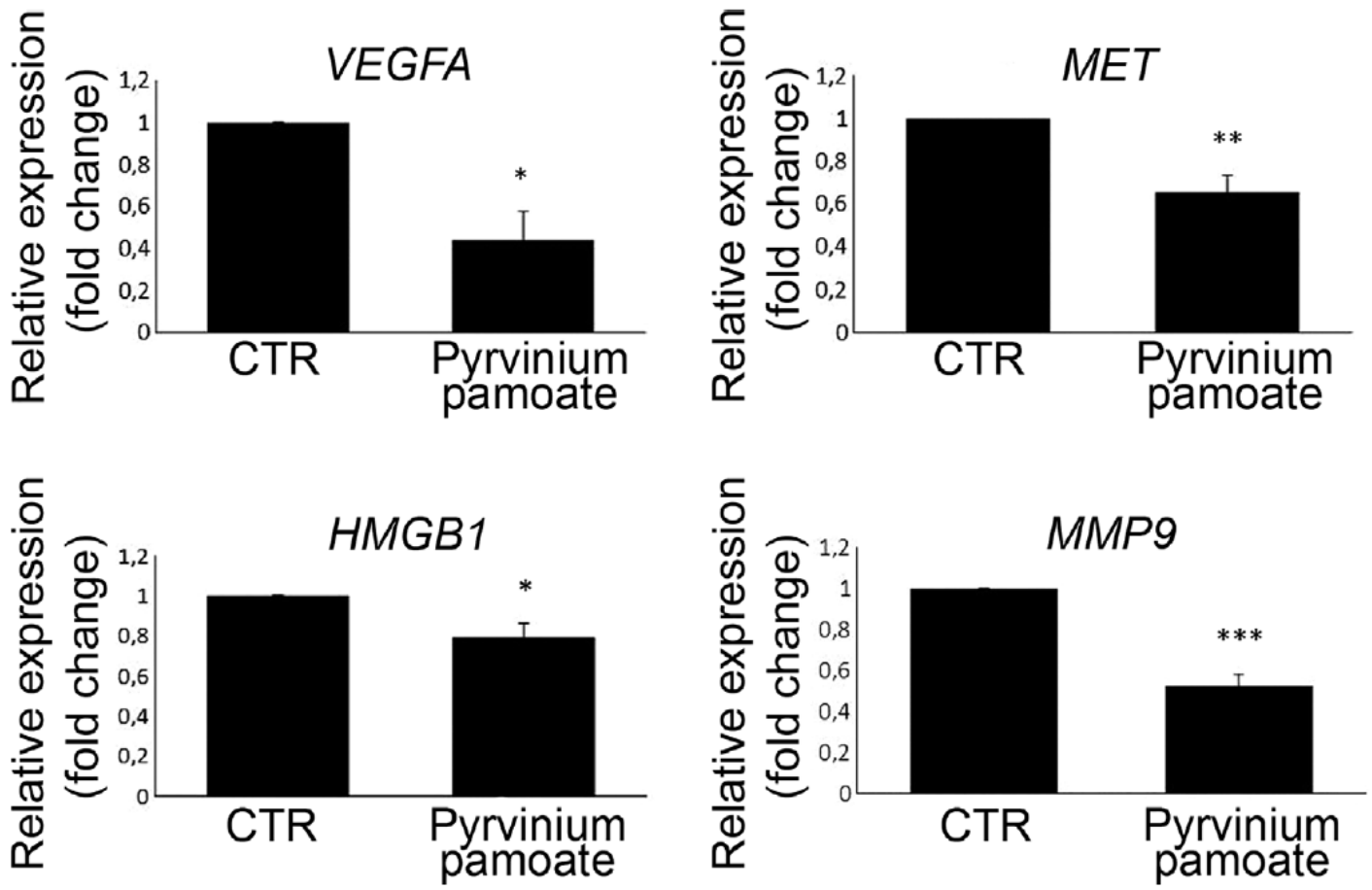




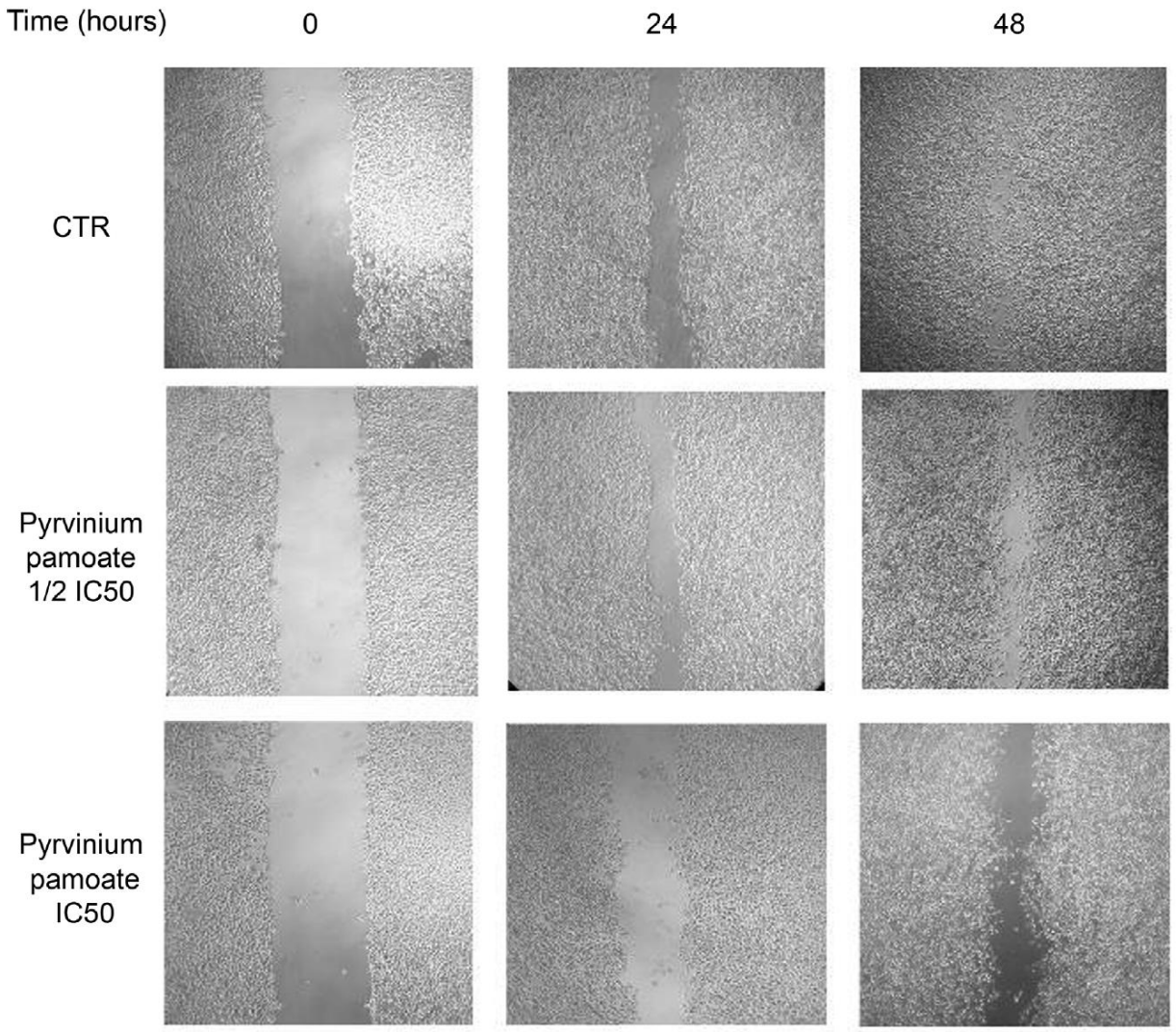
Decreased expression of downstream genes of Wnt pathway in dose- and time- dependent manner



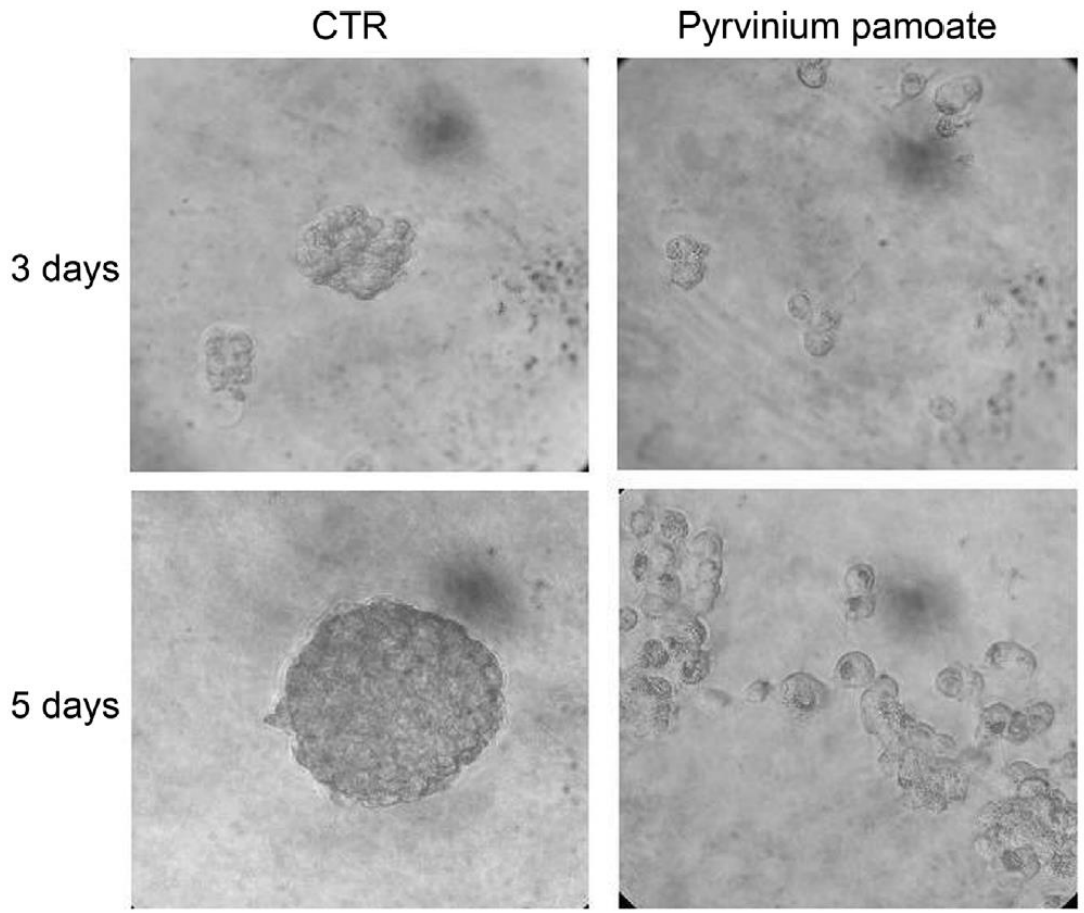
Decreased transcripts of key genes in mesothelioma



Impaired mesothelioma cell migration ability



Pyrvinium pamoate inhibits spheroid formation in 3D culture



Conclusion 3

- Pyrvinium pamoate affects hallmarks of mesothelioma cell lines
  - impairs growth
  - impairs migration
- Impairment of tumor spheroid formation
- Down-regulation of β-catenin and Wnt -regulating genes

Thank you for your interest!