Bericht aus der Charité-Grundlagenforschung

Wie dicht sind wir an den Ursachen der ALS?

ALS-Tag an der Charité 2017
Christopher Secker

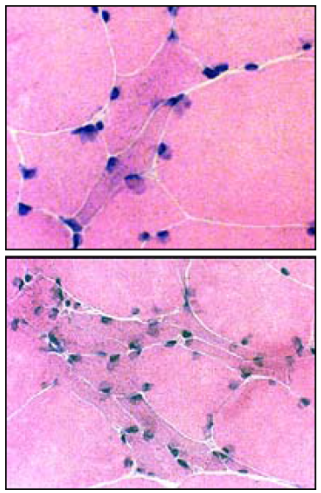
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

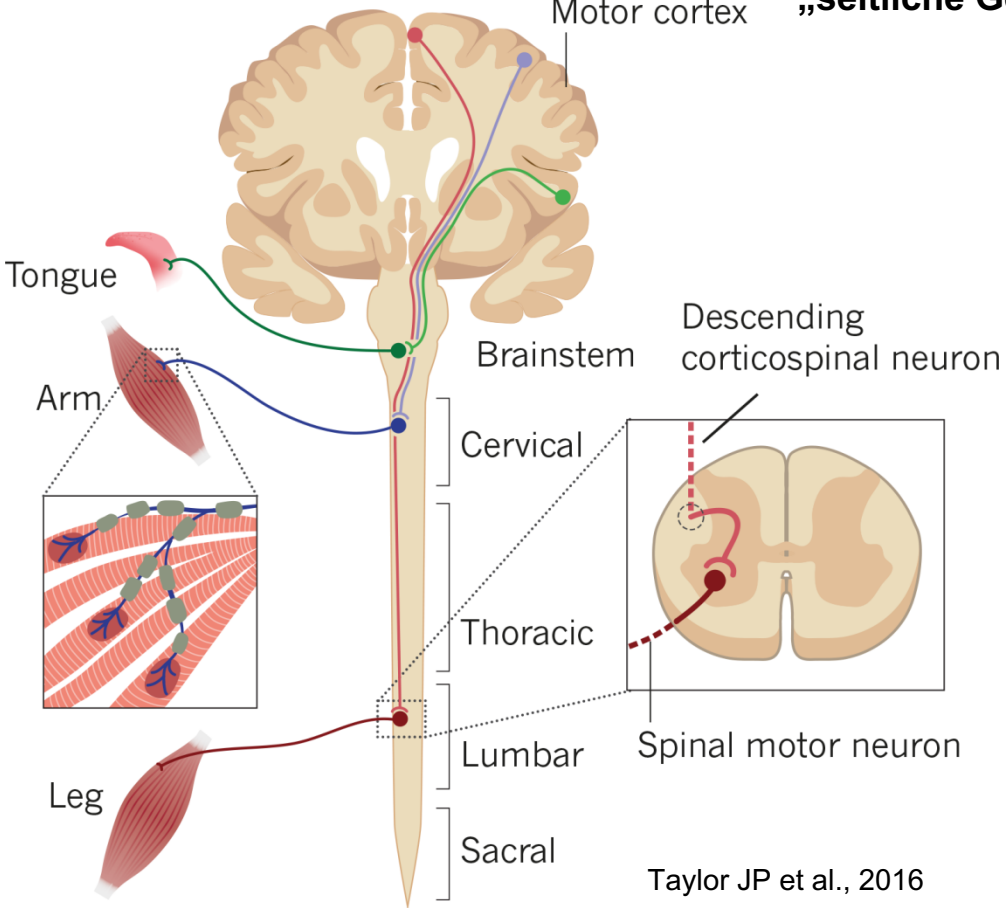
Hilfe für ALS-kranke Menschen

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT

Charakteristische Schädigung des 1. und 2. Motoneurons

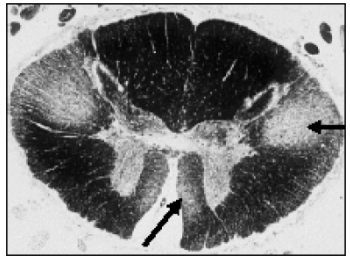
A-myo-trophie (My-a-trophie): „Muskelschwund“





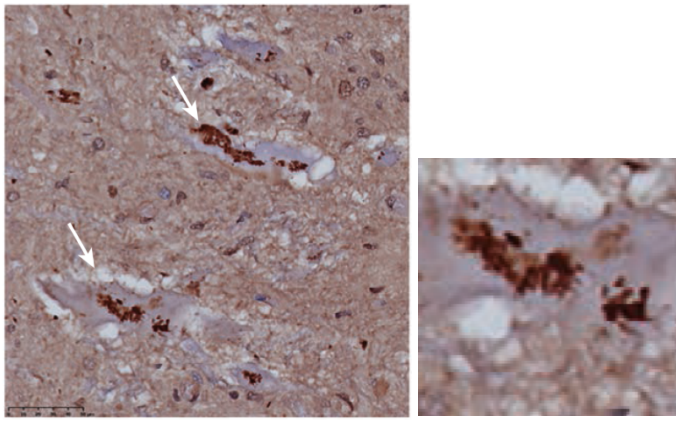
Taylor JP et al., 2016

Lateral-sklerose: „seitliche Gewebeverhärtung“

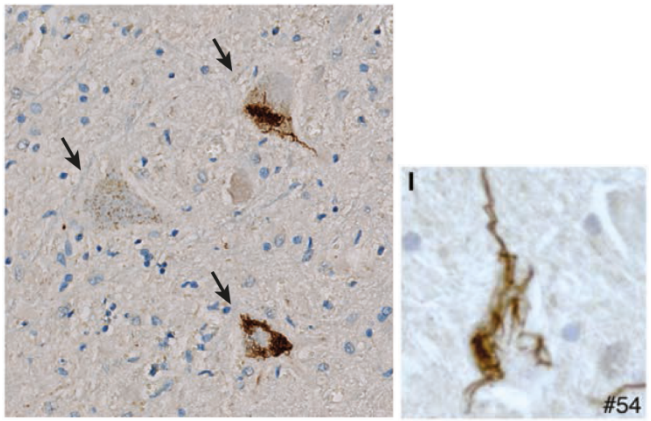


Neuronale Proteineinschlüsse in betroffenen Zellen bei der ALS

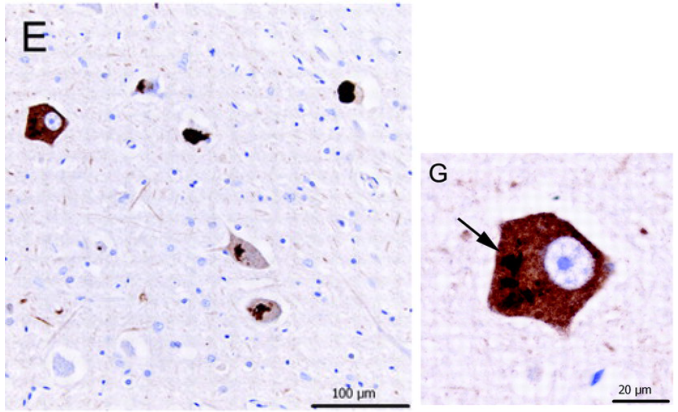
SOD1



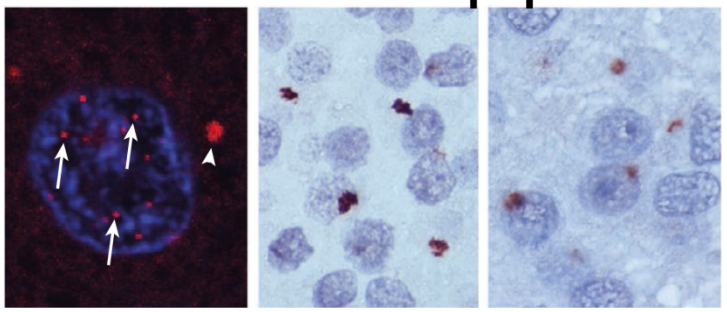
TDP-43



FUS



C9orf72 RNA und Dipeptide

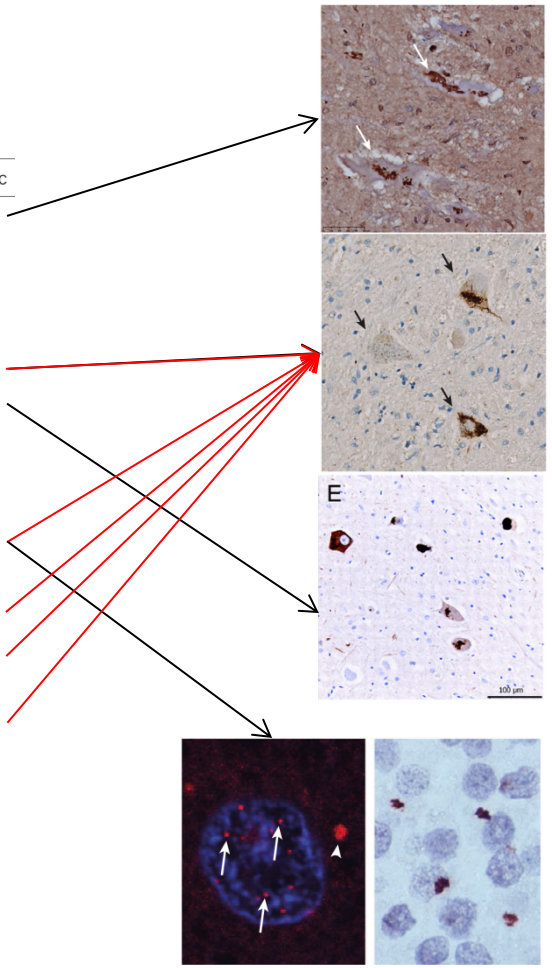


Taylor JP et al., 2016

Neuronale Proteineinschlüsse bei der familiären und sporadischen ALS

sporadische ALS: **~90%**
familiäre ALS: **~10%**

Gene	Protein	Protein function	Mutations	Proportion of ALS	
				Familial	Sporadic
SOD1	Cu–Zn superoxide dismutase	Superoxide dismutase	>150	20%	2%
DCTN1	Dynactin subunit 1	Component of dynein motor complex	10	1%	<1%
ANG	Angiogenin	Ribonuclease	>10	<1%	<1%
TARDBP	TDP-43	RNA-binding protein	>40	5%	<1%
FUS	FUS	RNA-binding protein	>40	5%	<1%
VCP	Transitional endoplasmic reticulum ATPase	Ubiquitin segregase	5	1–2%	<1%
OPTN	Optineurin	Autophagy adaptor	1	4%	<1%
C9orf72	C9orf72	Possible guanine nucleotide exchange factor	Intronic GGGGCC repeat	25%	10%
UBQLN2	Ubiquilin 2	Autophagy adaptor	5	<1%	<1%
SQSTM1	Sequestosome 1	Autophagy adaptor	10	<1%	?
PFN1	Profilin-1	Actin-binding protein	5	<1%	<1%
HNRNPA1	hnRNP A1	RNA-binding protein	3	<1%	<1%
MATR3	Matrin 3	RNA-binding protein	4	<1%	<1%
TUBA4A	Tubulin α-4A chain	Microtubule subunit	7	<1%	<1%
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10	Mitochondrial protein of unknown function	2	<1%	<1%
TBK1	Serine/threonine-protein kinase TBK1	Regulates autophagy and inflammation	10	?	?



SOD1

TDP-43

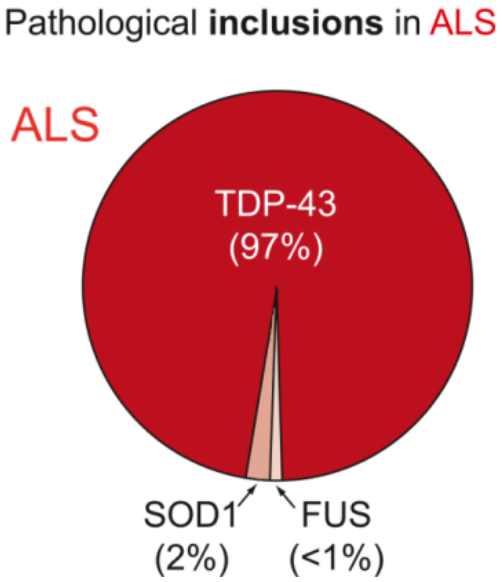
FUS

C9orf72
RNA und
Dipeptide

Taylor JP et al., 2016

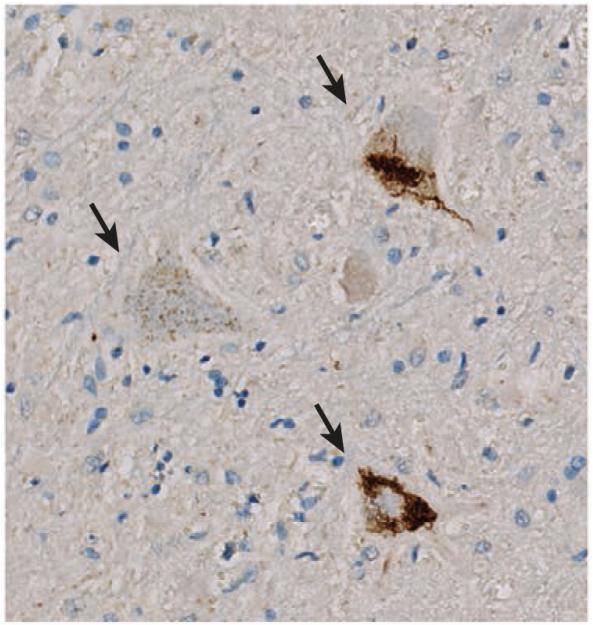
Neuronale Proteineinschlüsse bei der ALS: in 97% der Fälle TDP-43

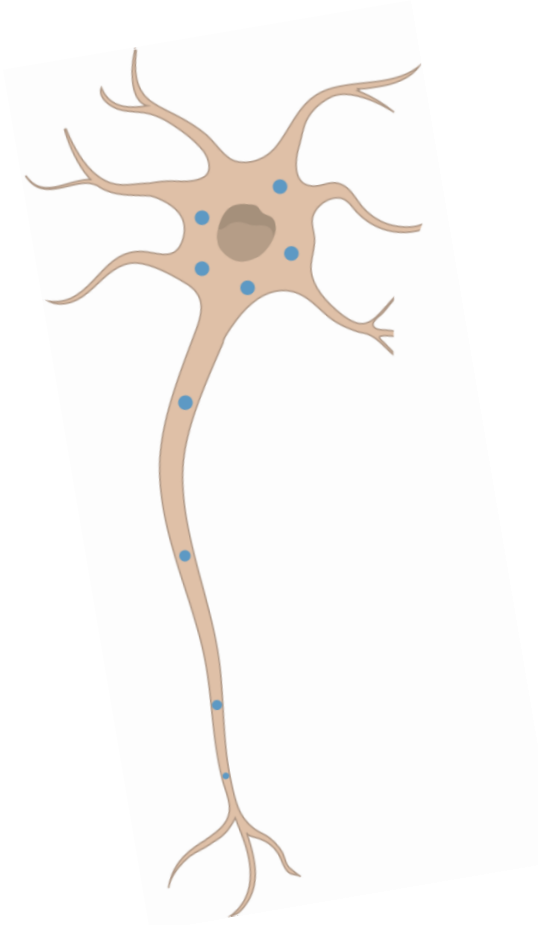
sporadische ALS: **~90%**
familiäre ALS: **~10%**



Ling S-C,
Polymenidou M., *2013*

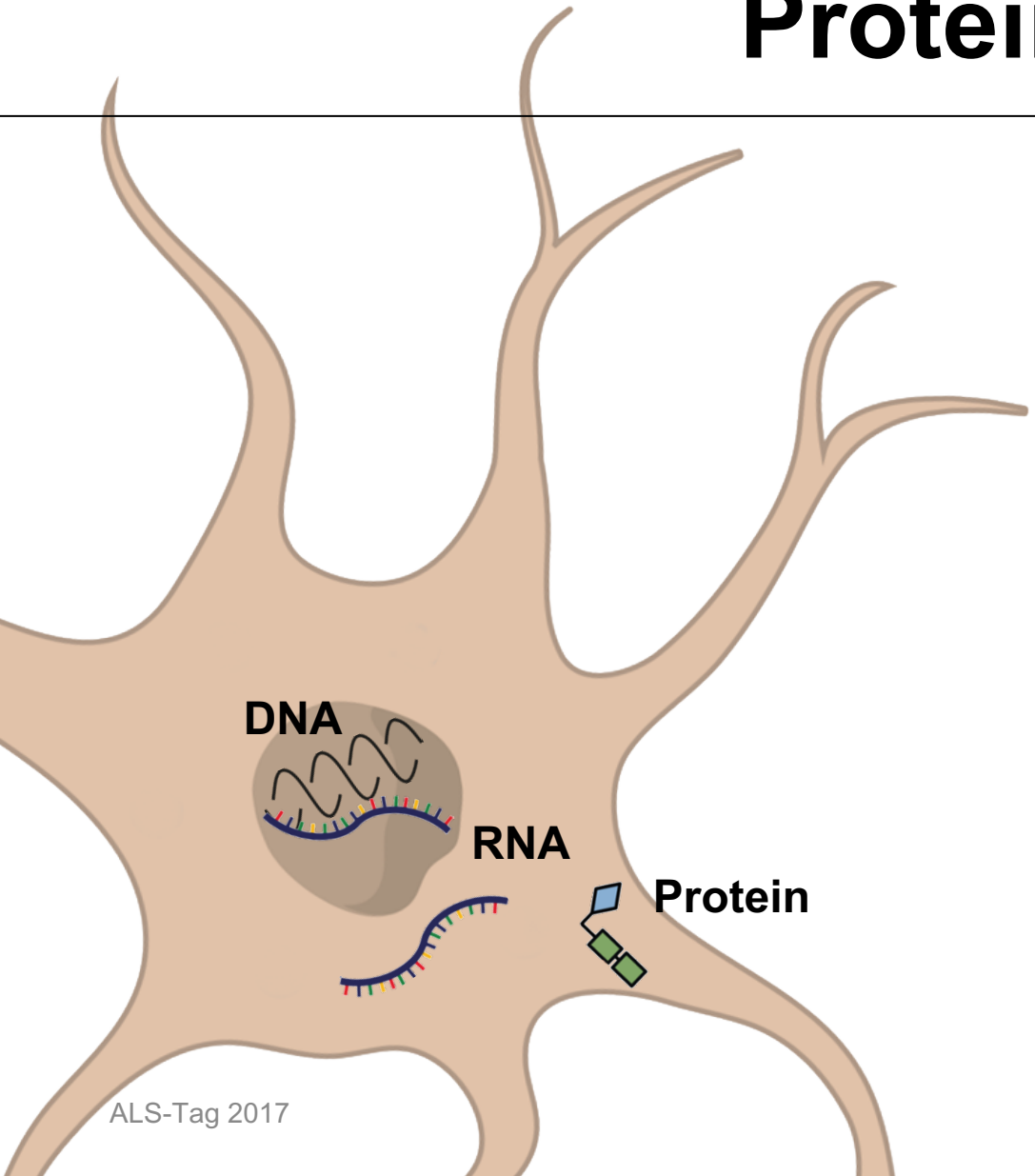
TDP-43





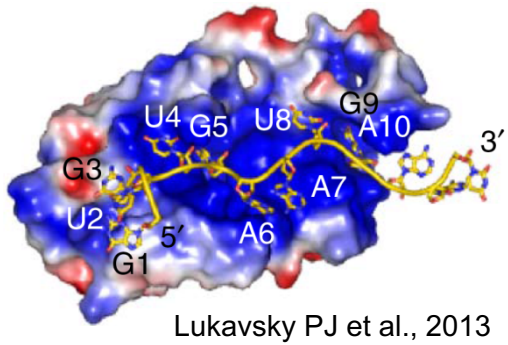
Taylor JP et al., 2016

TDP-43: Ein RNA-bindendes Protein



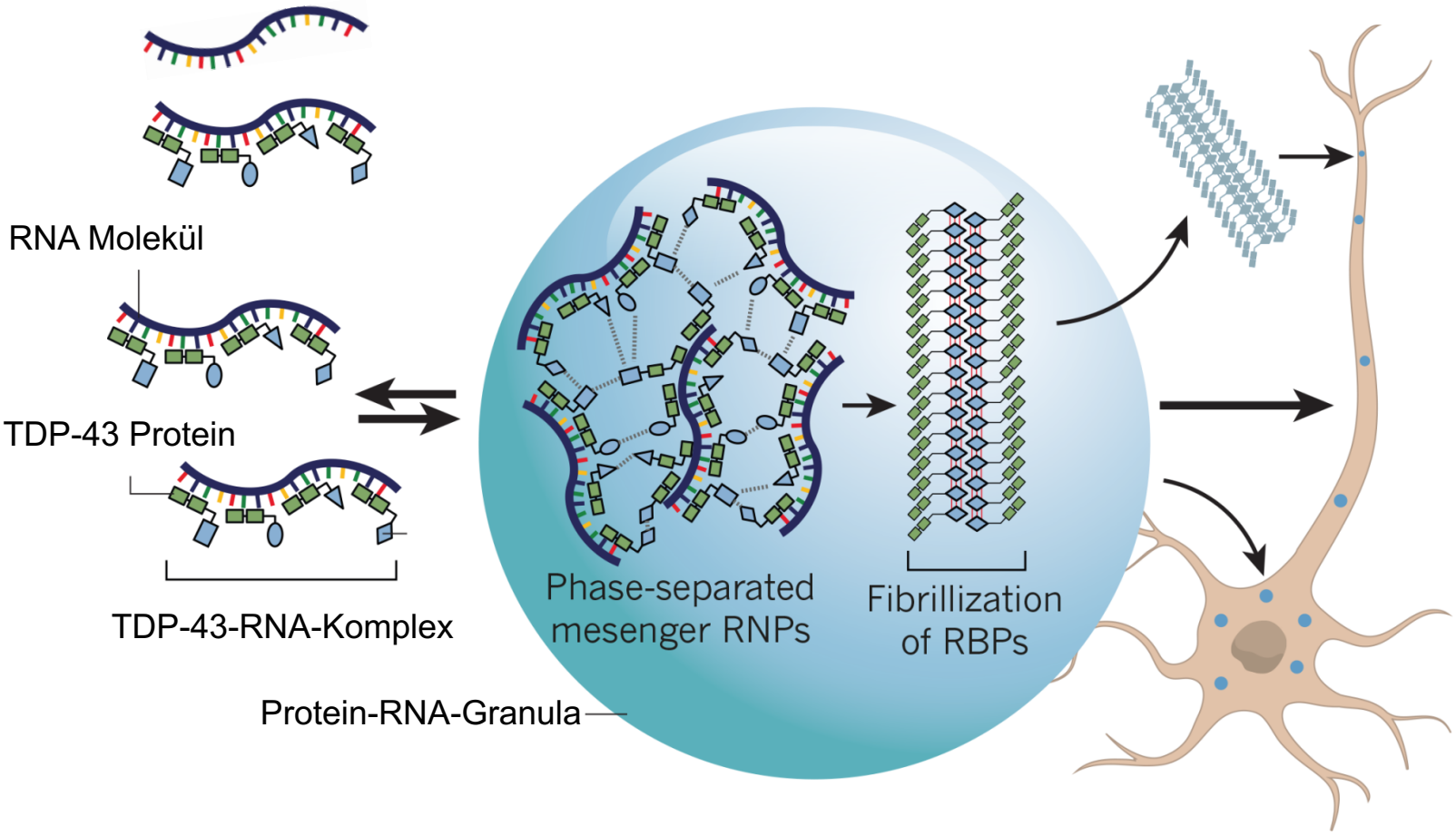
TDP-43: Ein **RNA bindendes** Protein

TDP-43 im **Komplex** mit **RNA**



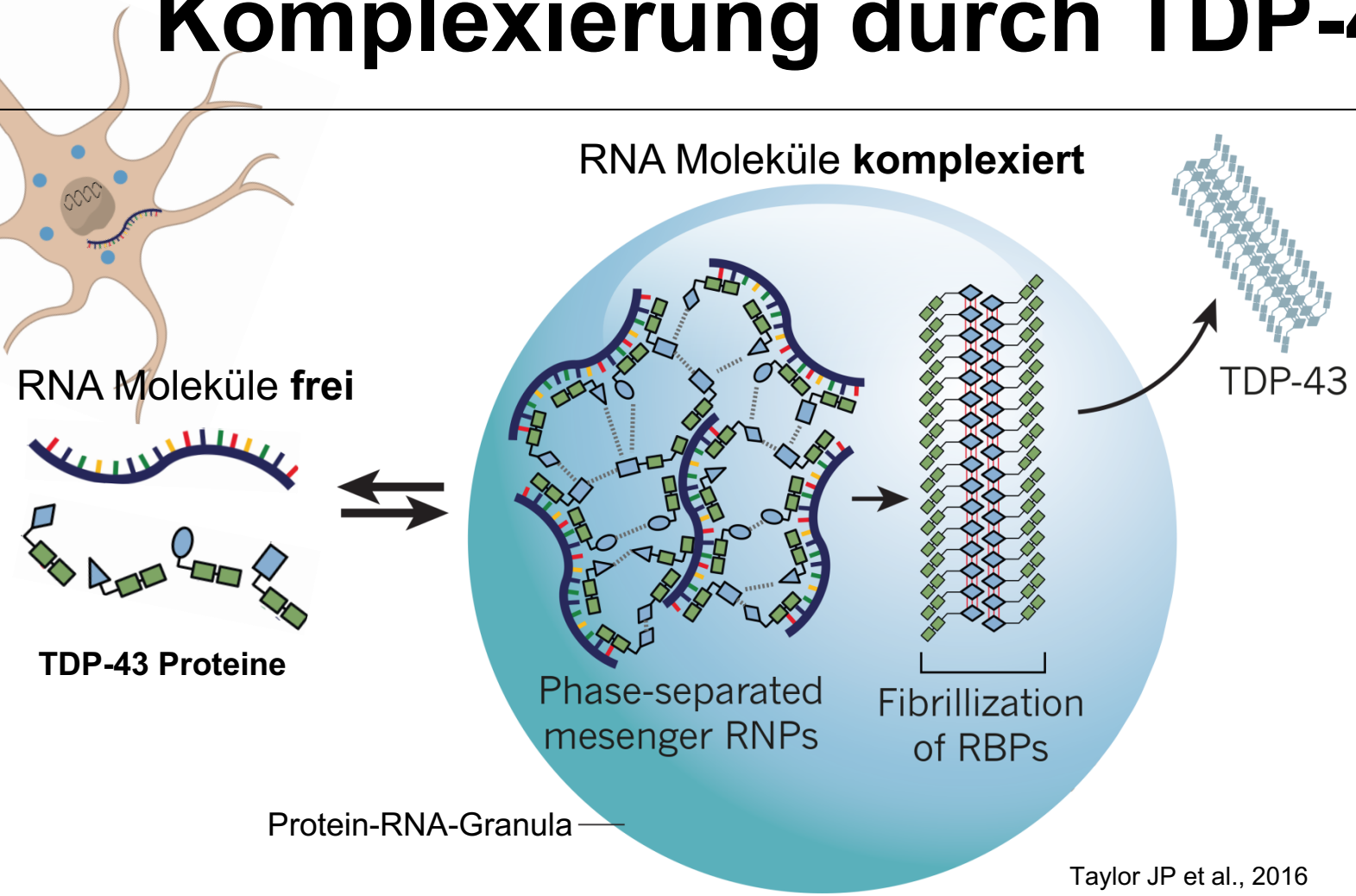
Lukavsky PJ et al., 2013

TDP-43 komplexiert RNA Moleküle



Taylor JP, Nature 2016

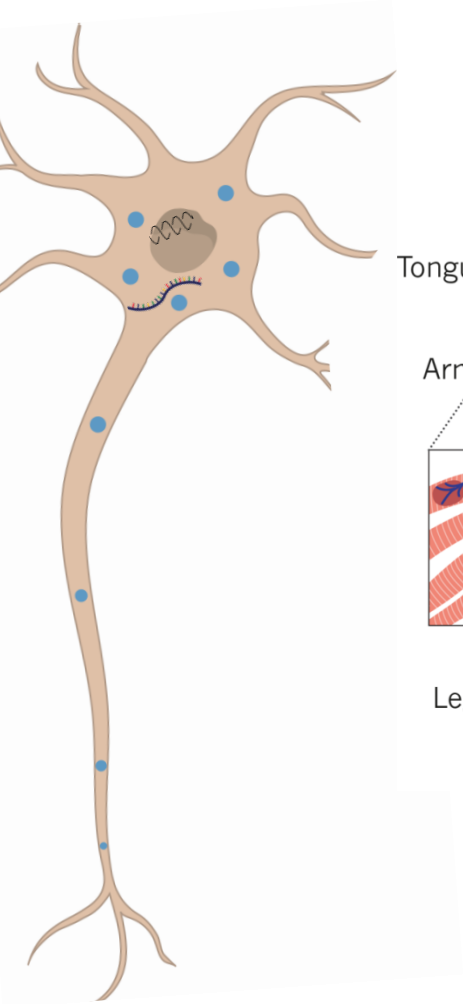
Was sind die Folgen von RNA Komplexierung durch TDP-43?

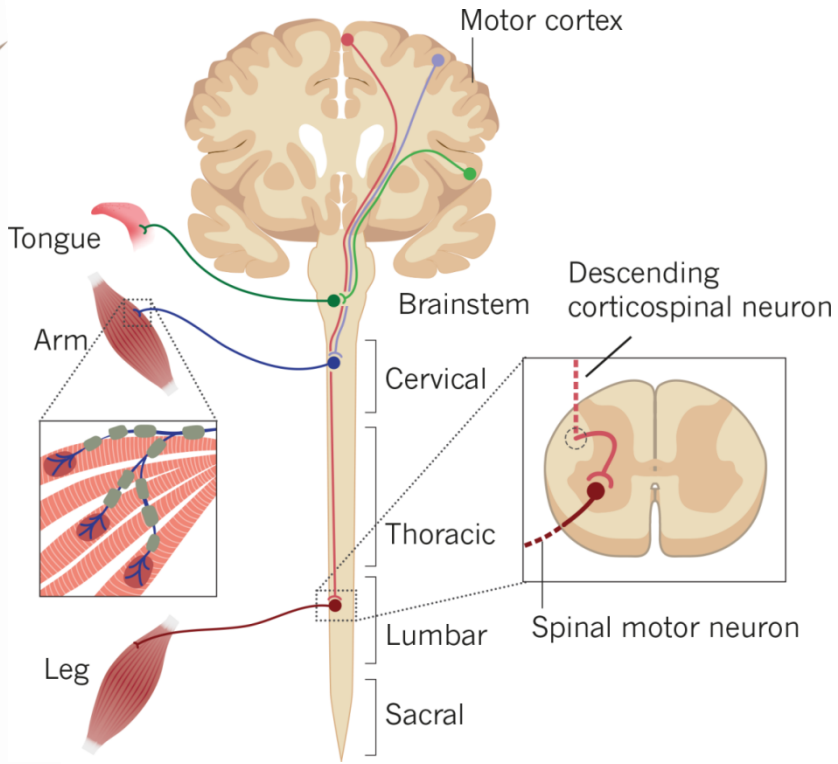


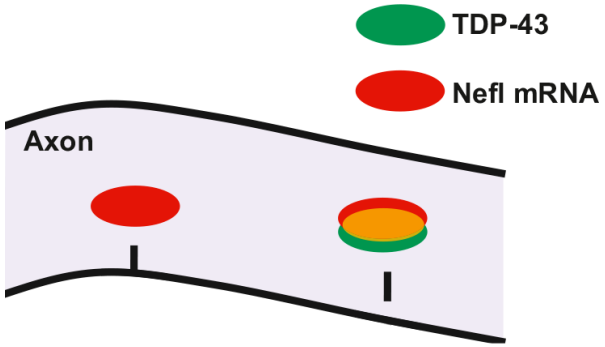
Taylor JP et al., 2016

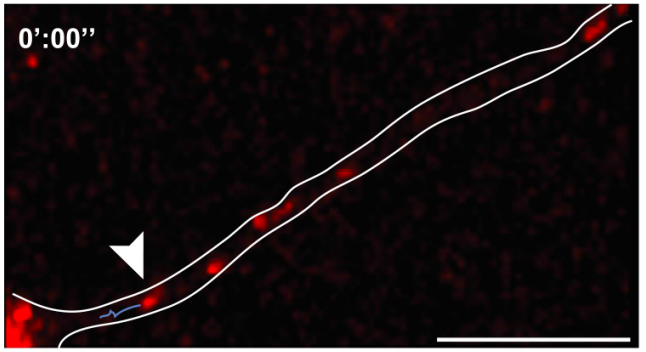
Proteinproduktion ↑ ⇌ **Proteinproduktion ↓**

Komplexierung durch TDP-43 als Transportmittel für RNA Moleküle



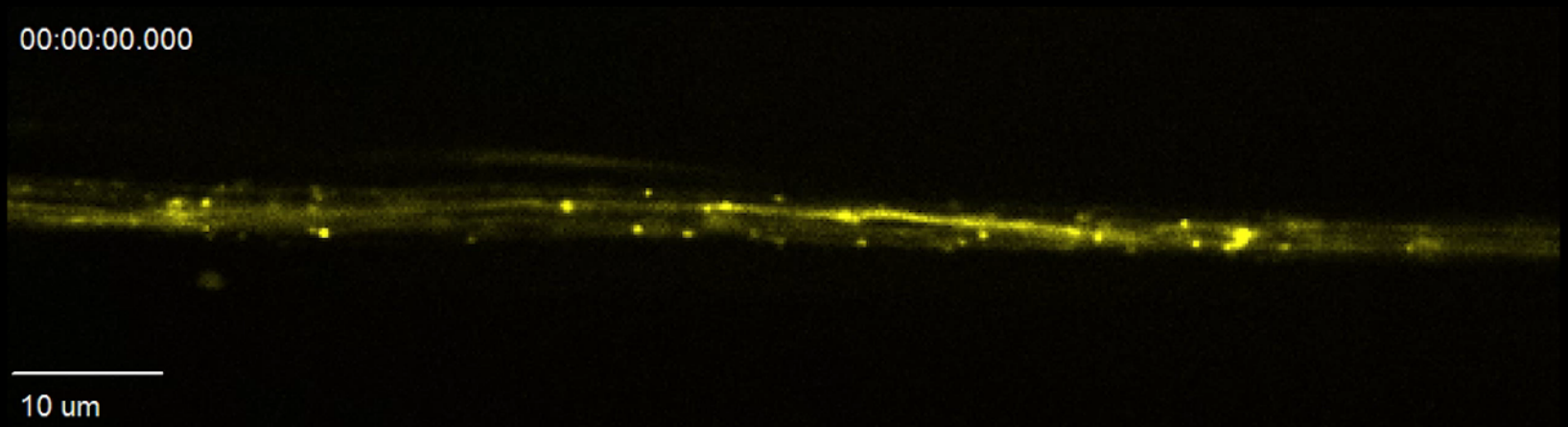


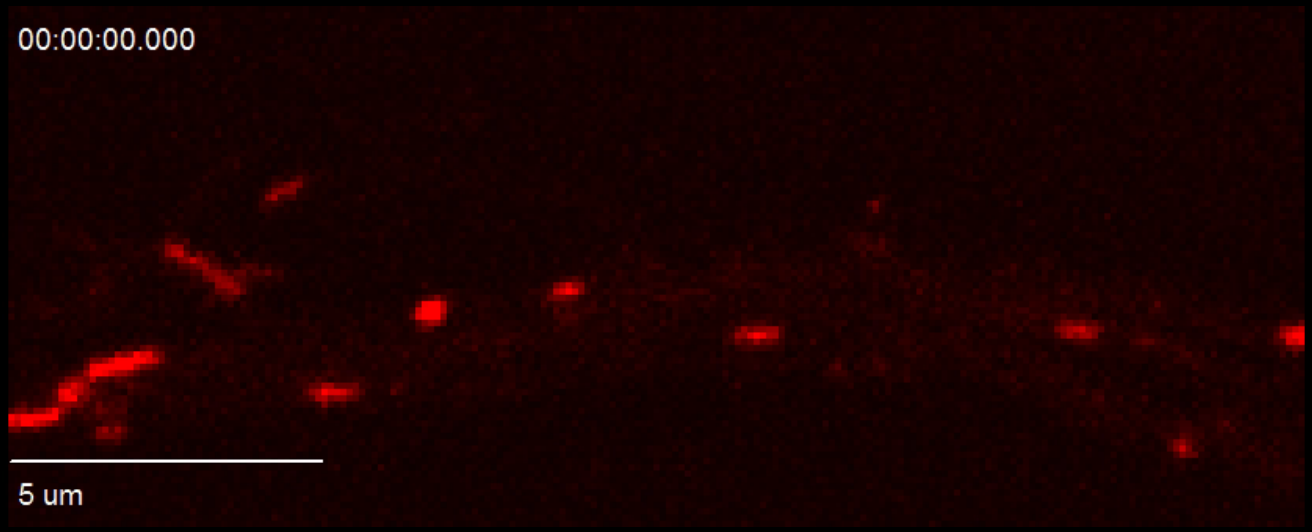




Alami et al., 2014.

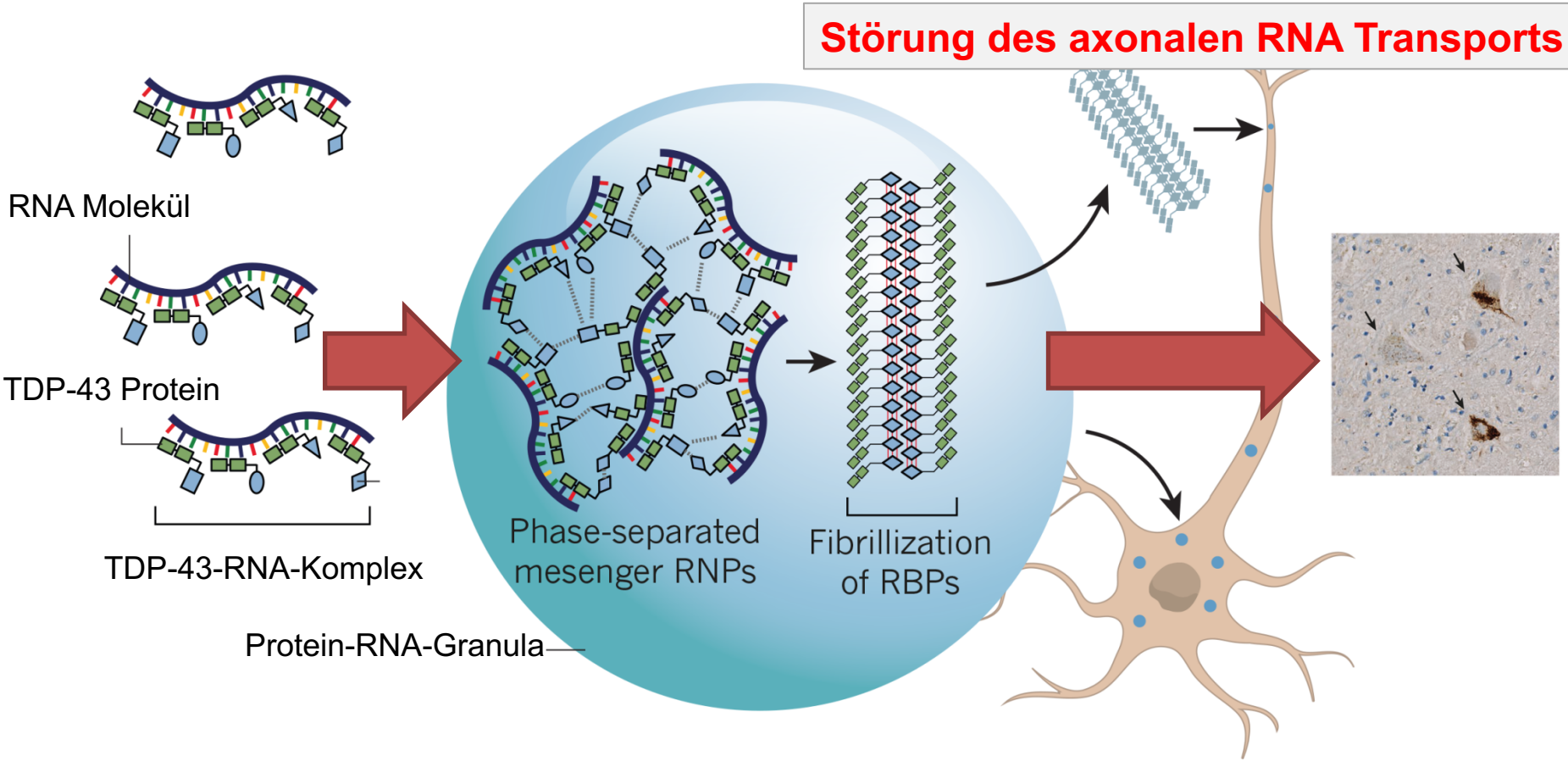
Komplexierung durch TDP-43 als Transportmittel für RNA Moleküle





Alami et al., 2014.

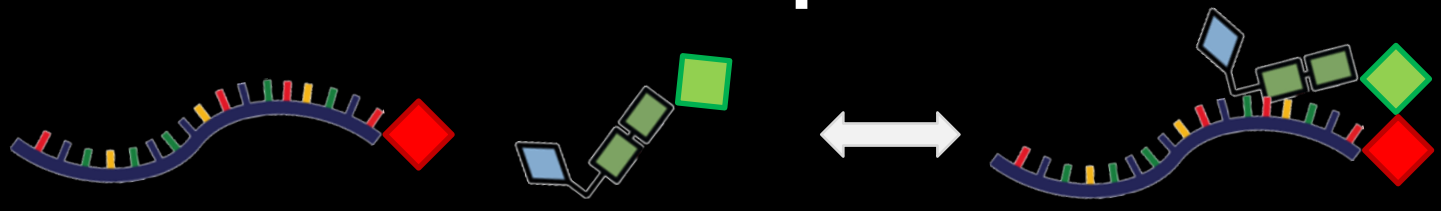
Neuronale Proteineinschlüsse bei der familiären und sporadischen ALS

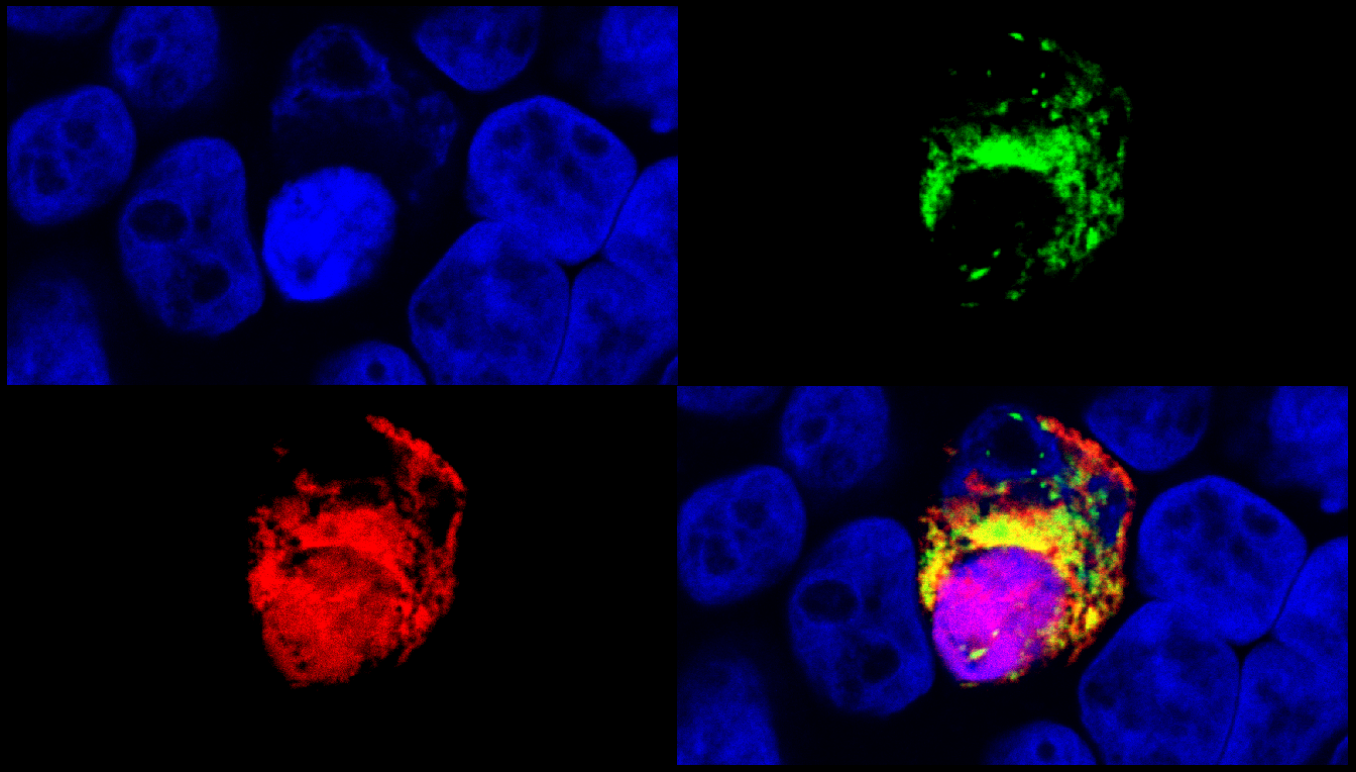


Fehlregulation der Proteinproduktion ↓

Taylor JP et al., 2016

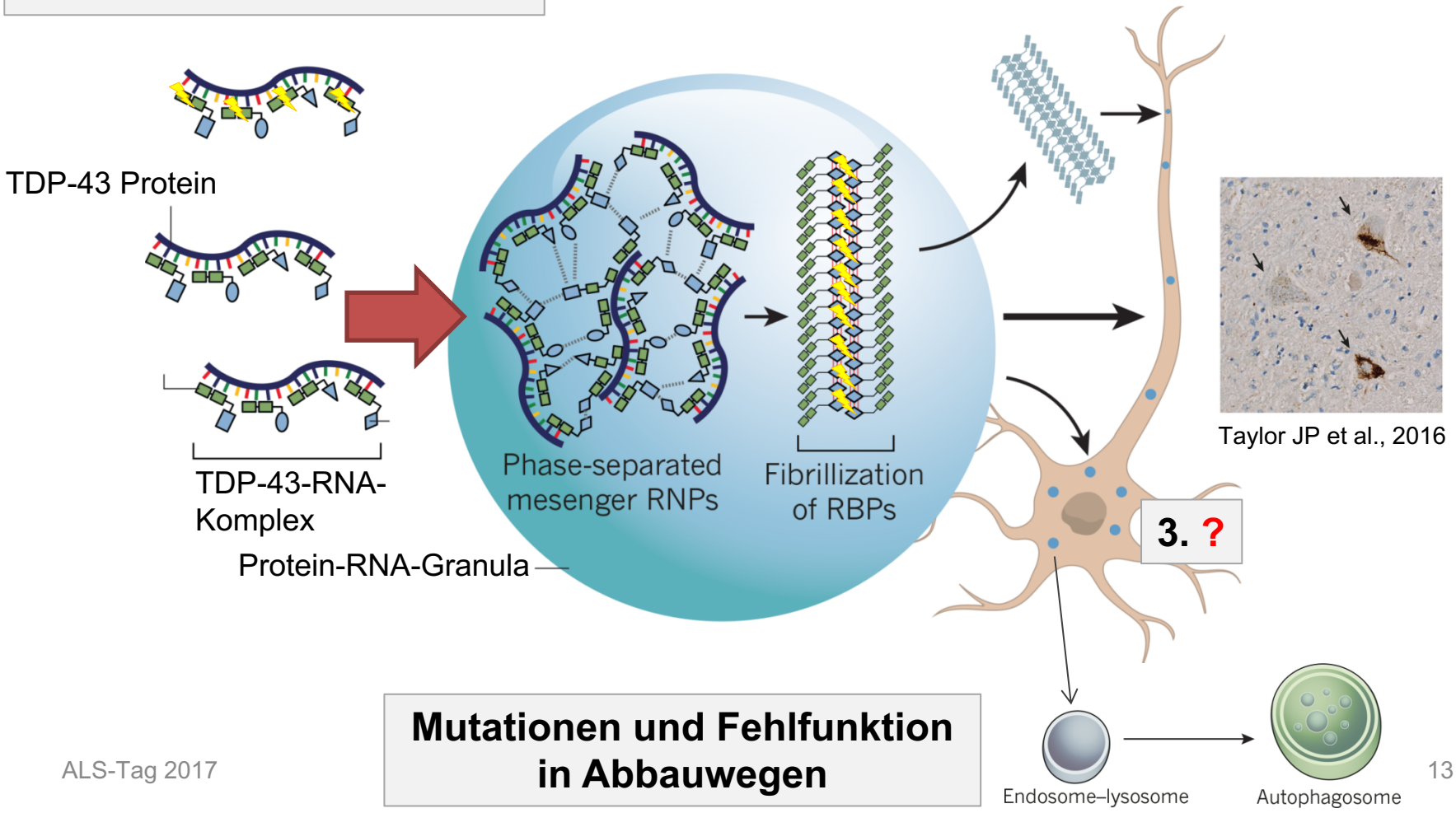
Welche RNA Moleküle werden durch TDP-43 komplexiert?





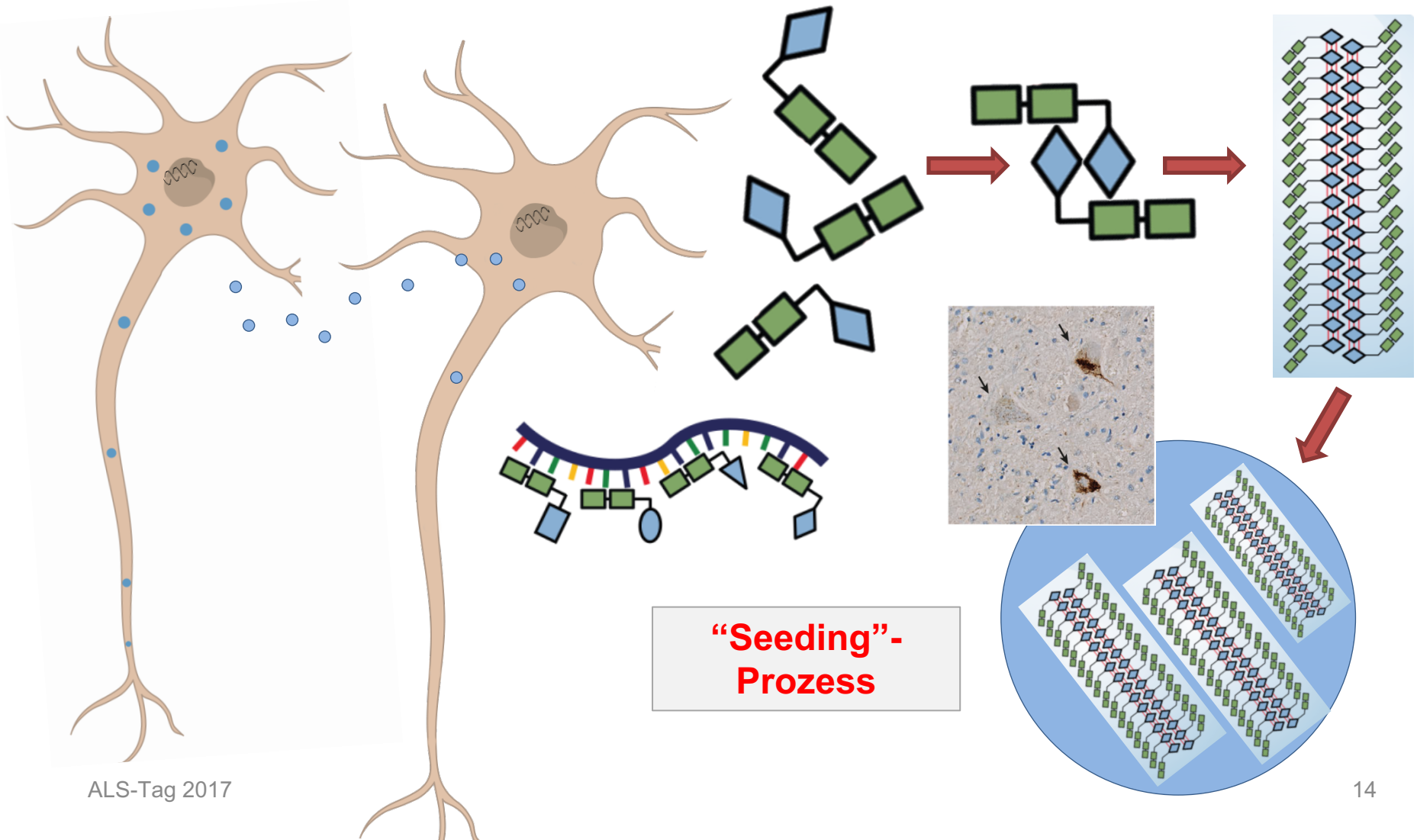
Welche Ursachen führen zur verstärkten Ablagerung („Aggregation“) von TDP-43?

Mutationen im TDP-43 Gen

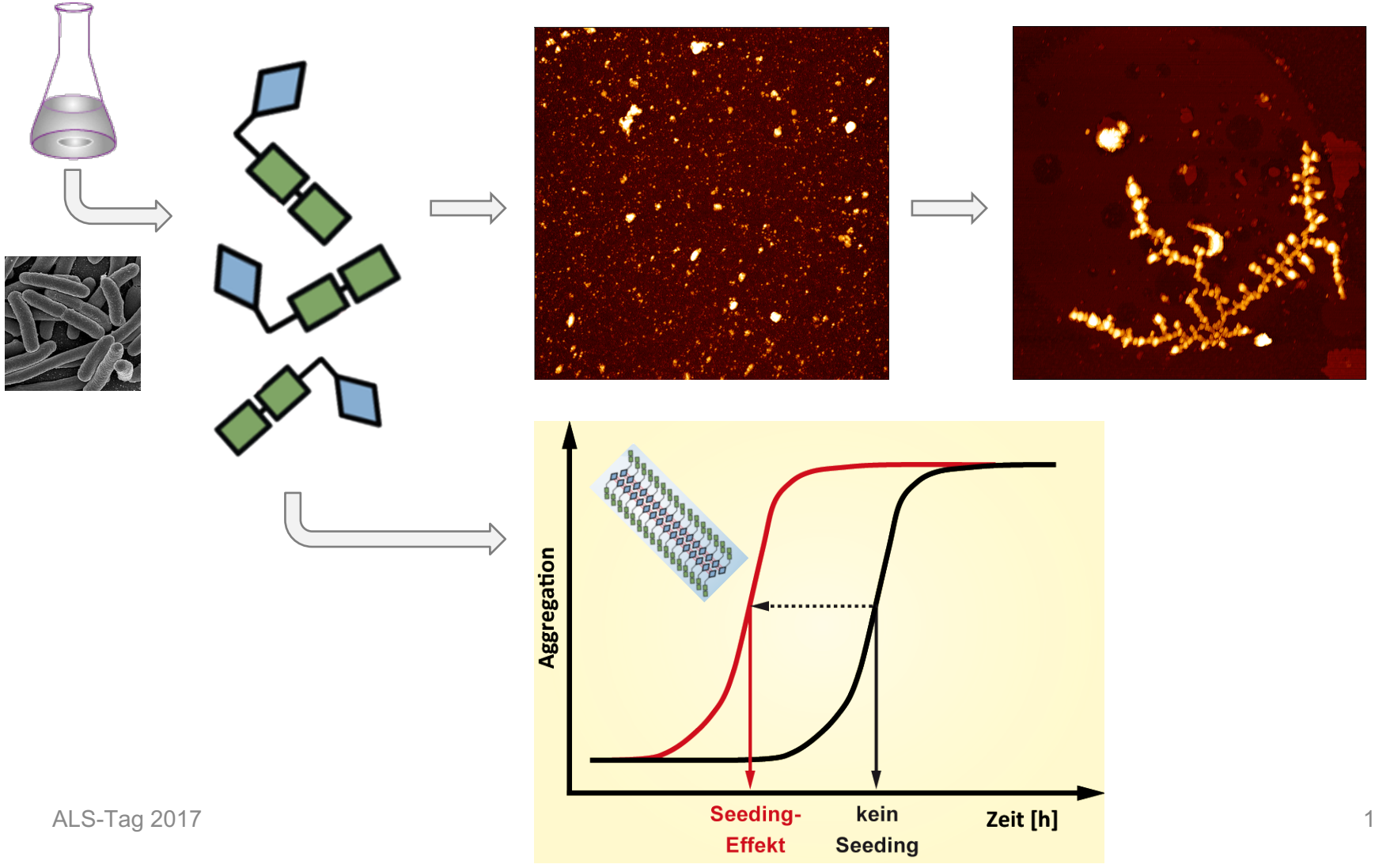


Mutationen und Fehlfunktion in Abbauwegen

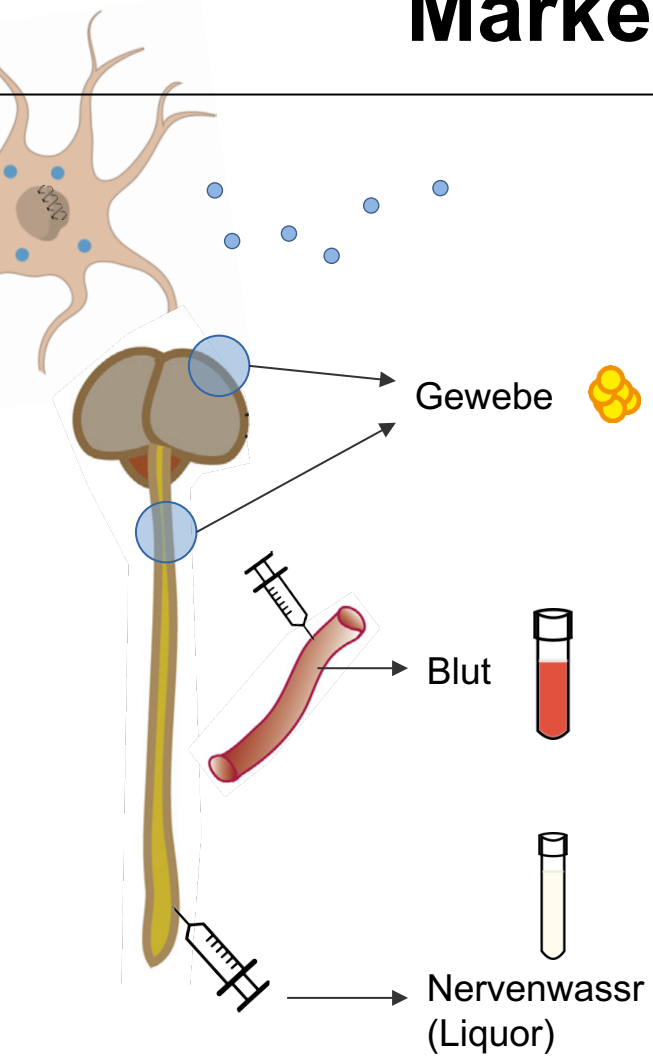
Wie schreitet die Pathologie und damit die ALS voran?

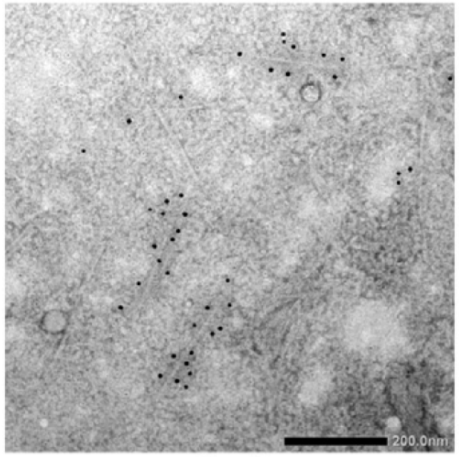


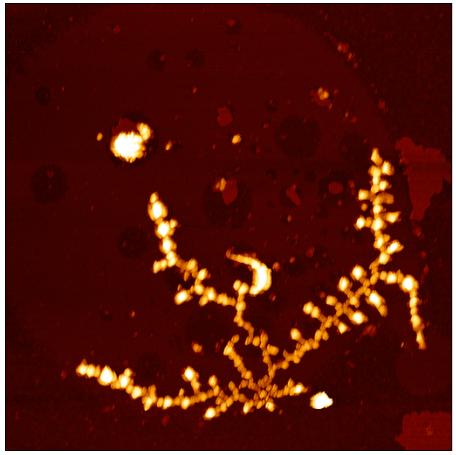
Wie können wir die Mechanismen der Proteinaggregation untersuchen?

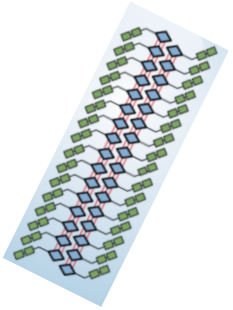


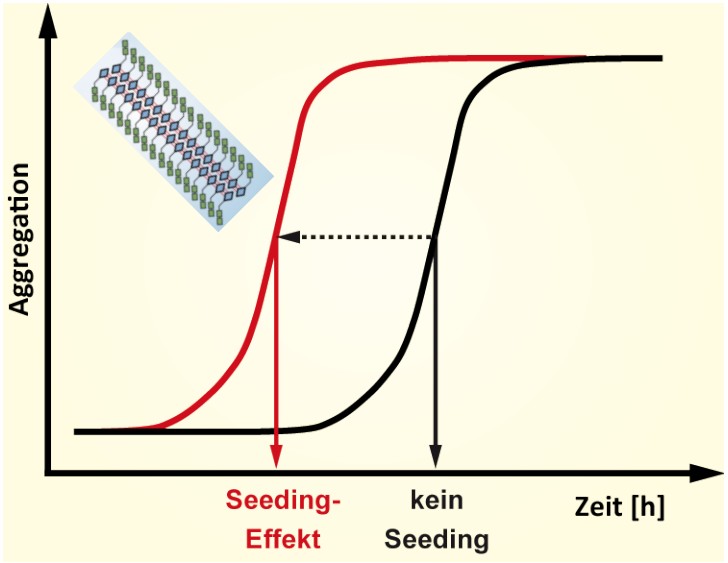
Seeding-Kapazität als ein biologischer Marker im Verlauf der ALS?











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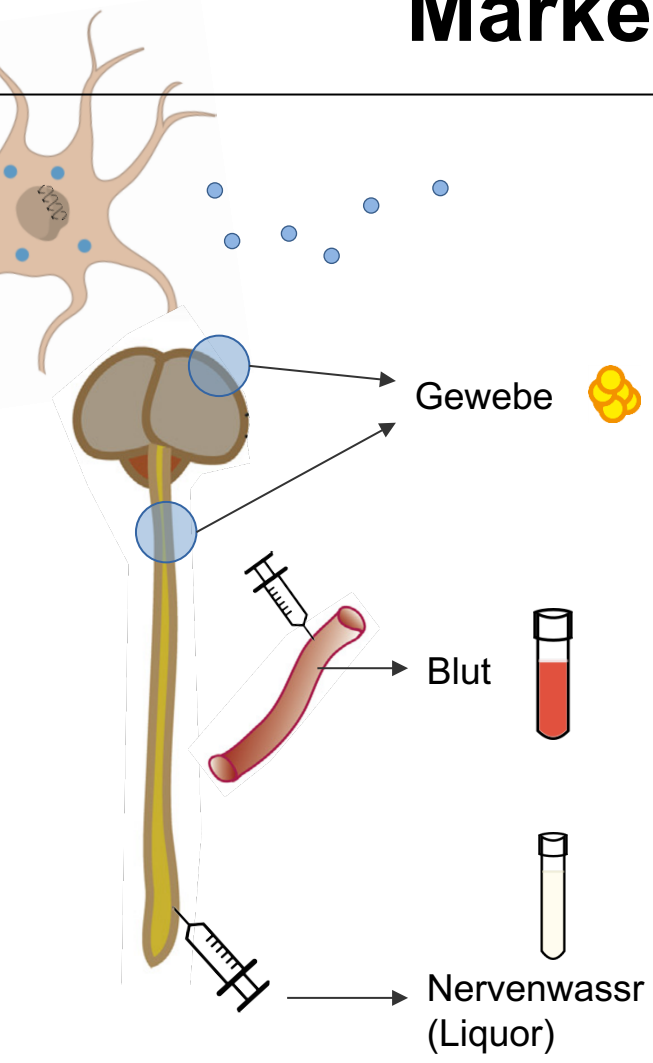
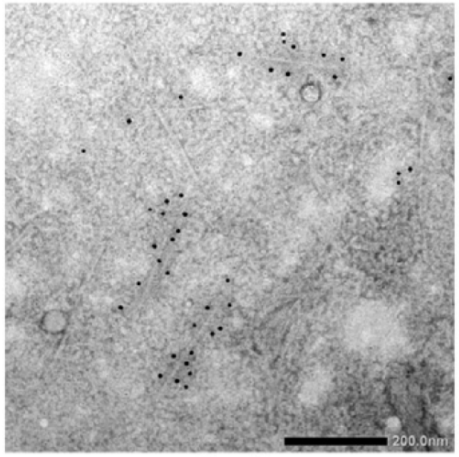
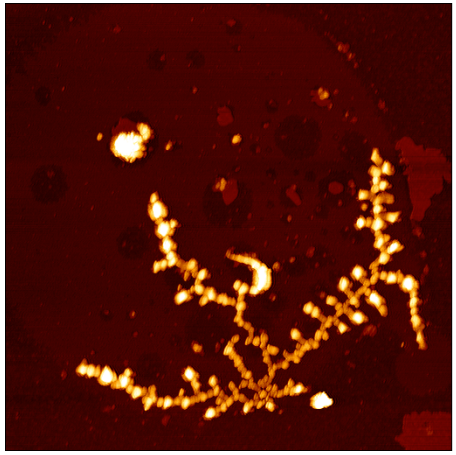
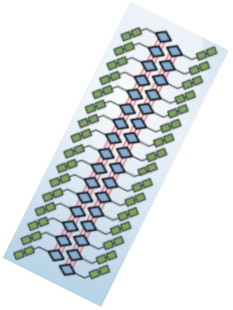
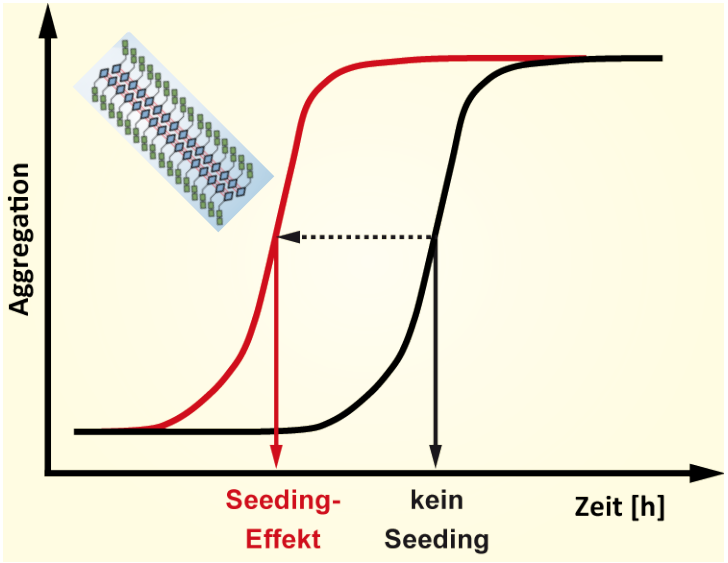


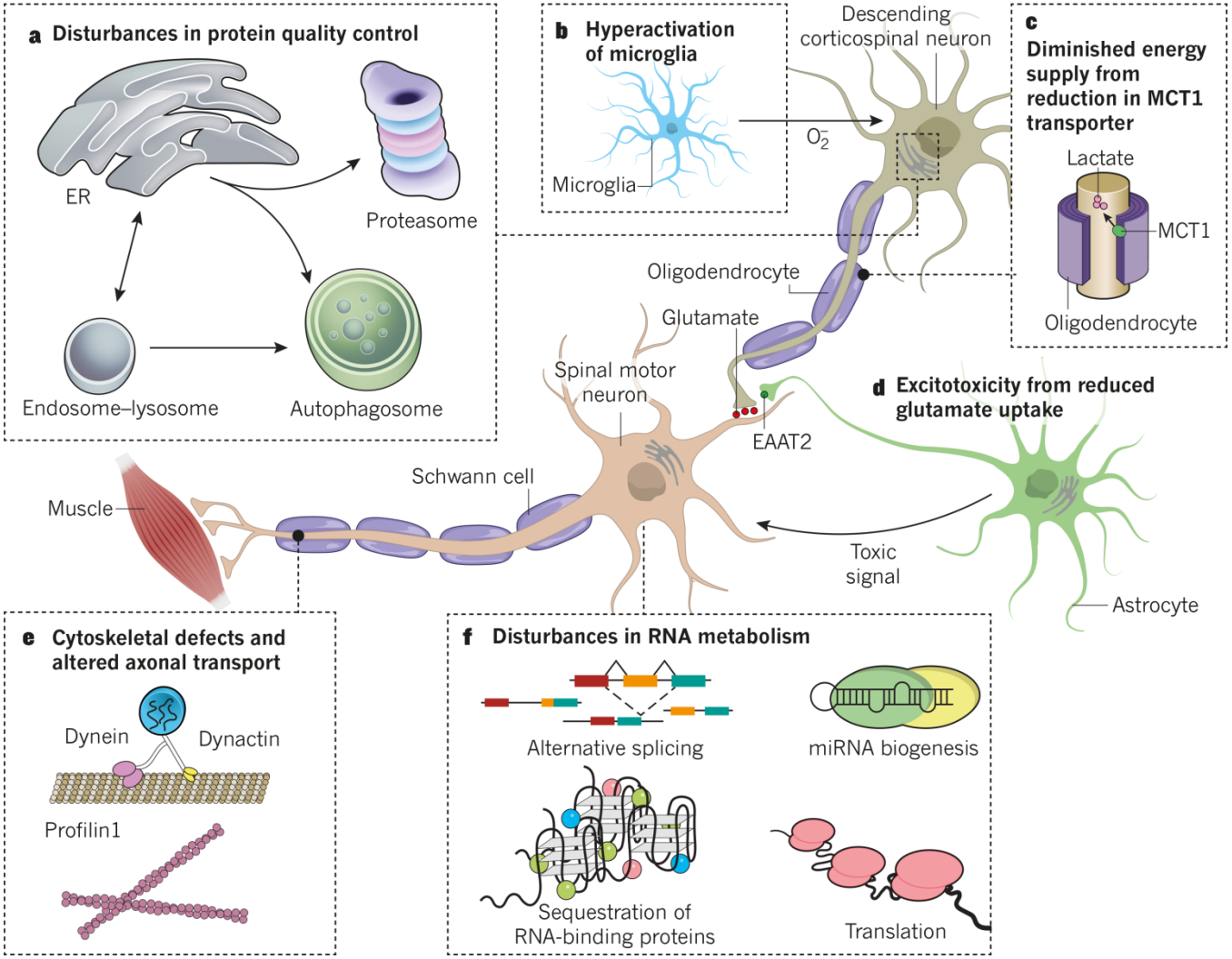




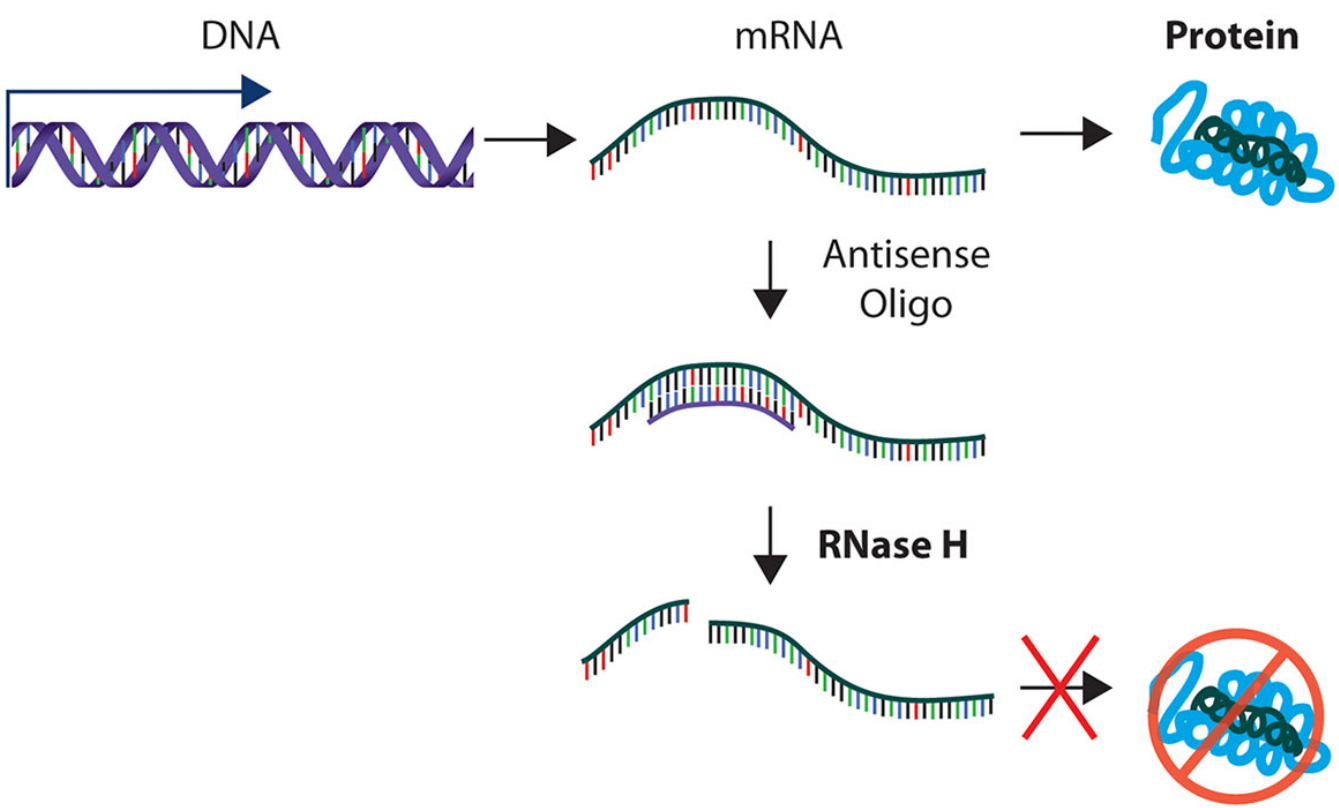




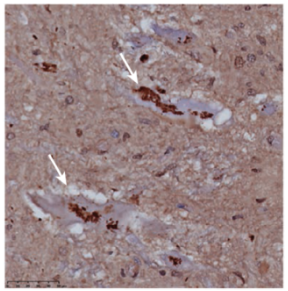
Wie dicht sind wir an den Ursachen der ALS?



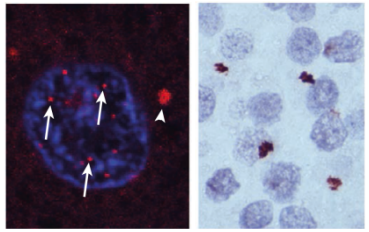
Antisense-Oligonukleotide zur Reduktion von aggregierenden Protein



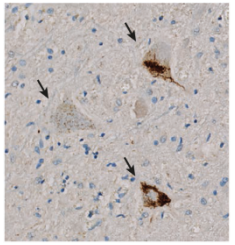
SOD1



C9orf72 **RNA** und **Dipeptide**



TDP-43



Reduktion der Proteinproduktion aggregierender, ALS-assoziierter Proteine

ALS-Forschung ist Teamarbeit

CharitéCentrum für Neurologie, Neurochirurgie und Psychiatrie	Prof. Dr. Matthias Endres Prof. Dr. Thomas Meyer PD Dr. Harald Prüß Team der ALS Ambulanz
MDC - AG Wanker ‚Neuroproteomics‘	Prof. Dr. Erich Wanker Dr. Alex Buntru Dr. Philipp Trepte Simona Kostova Mirjam Groh
Initiative ‚Hilfe für ALS-kranke Menschen‘	Dr. Martin Herrenknecht

Vielen Dank für
Ihre Aufmerksamkeit!