AD/PD Conference, Nice, Fr, 2015

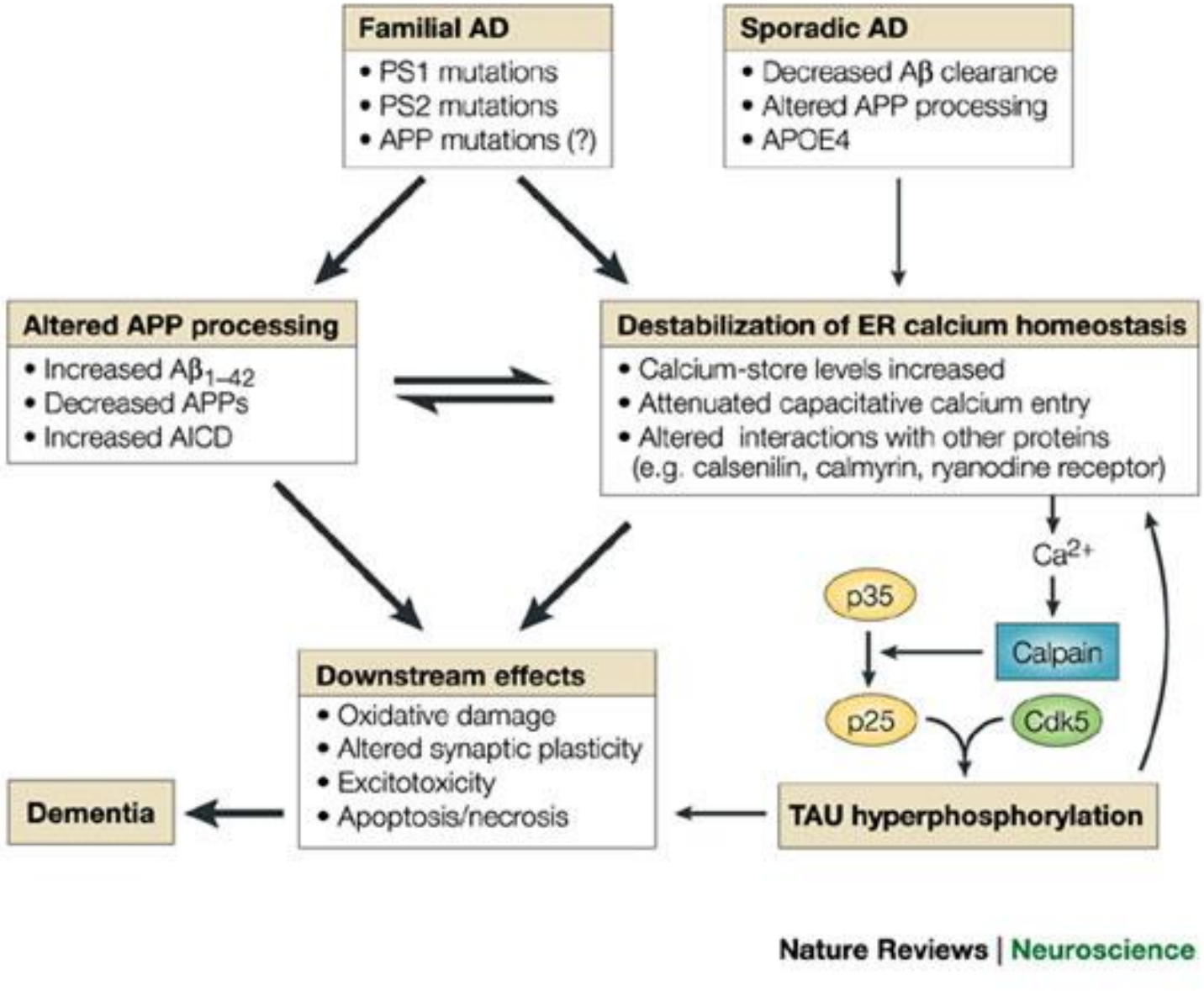
Overview, novelties and conclusions for domestic research

NAP B MTA TTK MS Neuroproteomics Group

Overlaping molecular mechanisms of miss-folded protein based neurodegenerative diseases

LIST OF DISEASES	MISFOLDED PROTEINS
Alzheimer's disease, AD	β-amyloid
	hyperphosphorylated Tau
	α-synuclein
	TDP-43
Parkinson's disease, PD	α-synuclein
Huntington disease, HD	huntingtin
Lewy-body dementia, DLB	α-synuclein
Amyotrophic lateral selerosis, ALS	TDP-43
	superoxide dismutase
Prion diseases	prion protein (PrP^{sc})

Actual stage of knowledge about AD development



ANAVEX 3-71, previously AF710B, is a unique and promising preclinical drug candidate with a novel mechanism of action shown to enhance neuroprotection and cognition in Alzheimer's disease. It is a CNS-penetrable mono-therapy that bridges treatment of both cognitive impairments with disease modifications. ANAVEX 3-71 is highly effective in very small doses against the major Alzheimer's hallmarks in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathologies, and also has beneficial effects on inflammation and mitochondrial dysfunctions.

Cutting edge scientific breakthroughs presented at AD/PD 2015 included emerging technologies for manipulating the immune response to treat neurological diseases, novel molecular brain imaging technologies and biomarkers of disease.
New insights into disease mechanisms include seeding and spreading of misfolded proteins, as well as epigenetic and genetic effects in neurodegenerative diseases. The role of receptors and enzymes as potential novel therapeutic targets were also discussed.

Main trends in early diagnosis, behavior and psychology

1. Complex behavioral tests as spatial navigation (Jan Hort Cz)
2. Neuropsychological deficit profile (D. Salmon,USA)
3. Biomarkers, CSF biomarkers in EU cohorts (J. Steenoven Swe)
4. CSF biomarkers in AD (G.B. Stokin, Cz)
5. Retinal imaging and pre-symptomatic AD (P.J.Snyder, USA)
6. PET bimarkers (Swe groups)
7. APOE based prediction and immunotherapy (USA, Israel)

New trends in basic mechanisms

1. APP synaptic processing (Swe, USA)
2. TOR pathway (USA, Vellai)
3. Diabetes and AD (USA)
4. Mitochondria and MAM (Swe, Spa, Hu)
5. Microglia (Haass, Ger, links to Kardos)
6. Lipids, P-lipids (USA, links to Szeged)
7. Inflammation (UK and USA, links to Kardos)

Treatment trends and advances

1. No breakthrough in therapy
2. Raise Sterling clinical programs A4 is running
3. Focal model (R. Sterling, USA)
4. Immunotherapy against Abeta (Biogen Idec, Marion Wittmann)
5. iPC based therapy ideas still in early stage (USA)

Aducanumab (BIIB037) reduced brain amyloid plaque levels and slowed cognitive decline in patients with prodromal or mild Alzheimer's disease in Phase 1b study.

Aducanumab (BIIB037) is a recombinant human monoclonal antibody targeting Abeta aggregates that plays a role in the neurodegenerative process in Alzheimer's disease. Aducanumab (BIIB037) is currently being investigated in patients with prodromal and mild Alzheimer's disease and with a positive PET amyloid scan at baseline. Neuroimmune licensed aducanumab to Biogen Idec in 2007 under a collaborative development and license agreement. Neuroimmune and Biogen Idec expanded their collaboration in 2010 with recombinant human RTM™ technology-derived antibodies targeting tau, alpha-synuclein and TDP-43 for the treatment of related neurodegenerative diseases.

ANAVEX 2-73 and ANAVEX 3-71, at the 12th International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD 2015).

ANAVEX 3-71, previously AF710B, is a unique and promising preclinical drug candidate with a novel mechanism of action shown to enhance neuroprotection and cognition in Alzheimer's disease. It is a CNS-penetrable mono-therapy that bridges treatment of both cognitive impairments with disease modifications. ANAVEX 3-71 is highly effective in very small doses against the major Alzheimer's hallmarks in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathologies, and also has beneficial effects on inflammation and mitochondrial dysfunctions.

http://globenewswire.com/

Experimental systems

1. Animal models of non-rodents (marmoset, dog, polar bear)
2. Rodent models are big problems
3. Behavioral tests, Morris watermaze is limited, novel complex tests
4. iPC models are in focus and pushed by USA
5. Systems biology approach is growing, few lipidomics
6. Human MRI studies on memory just started
7. Psychological approaches are growing, early symptoms search
8. Forcing of novel approaches (Karl Deisseroth was invited)

Conclusive remarks

1. Paradox: USA and EU sponsorship is high, Hungarian AD reseach activity is low.
2. There are AD research initiatives in HU in cutting edge: Abeta chemistry, Lipidomics, C1Q-synaptic pruning, memory proteomics, iPC, MAM.
3. All HU efforts are atomized, no support from the state (we are the only country in EU behaving so).
4. Equipment and human resources are good, unified effort is missing: HU ready for making an AD/PD research initiative.
5. HU Pharma Industry is not able to lead a National AD/PD initiative, only one company is doing real research.
6. Low activity in AD/PD research makes impossible to use novel therapies and personalized medicine soon.
7. Social pressure on science to concern with AD/PD is high, we could not stay away and neglect the need of tax payers.
8. Biomarkers and epigenetic background of AD/PD are race specific, we can not apply US and EU data blindly.
9. Our proposal is to create a Hungarian AD/PD Initiative, ready to receive money form the budget.

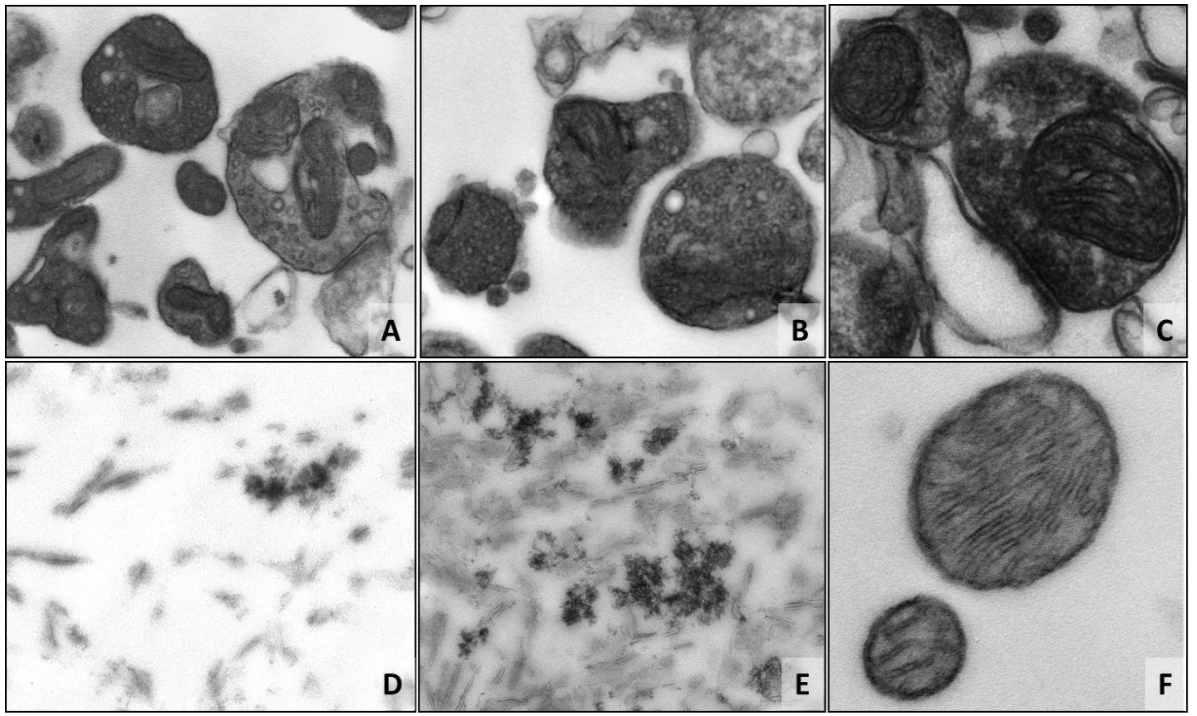
New technologies

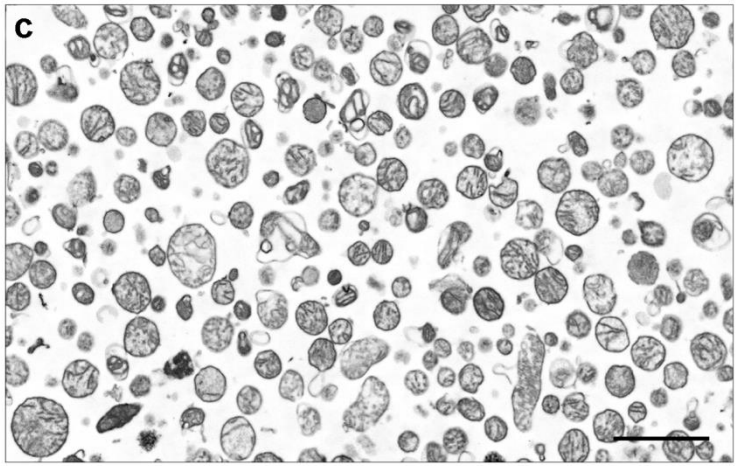
Cell compartment isolation:

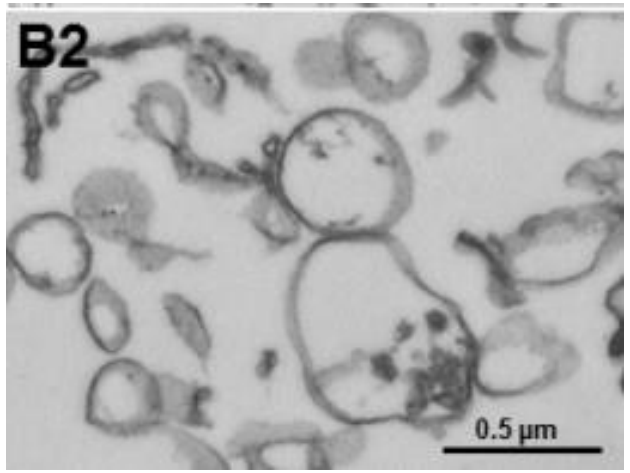
Isolation of synaptosomes,
pre- and post-synaptic membrane

Isolation of mitochondria,
synaptic mitochondria

Isolation of MAM membrane

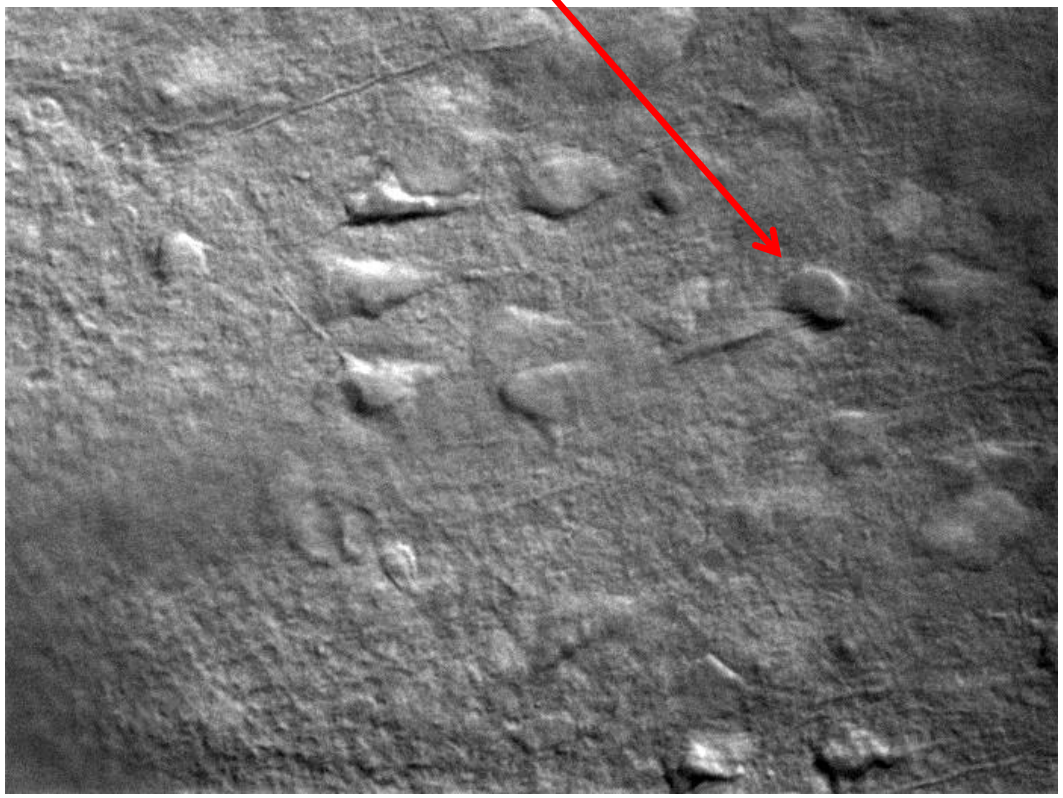


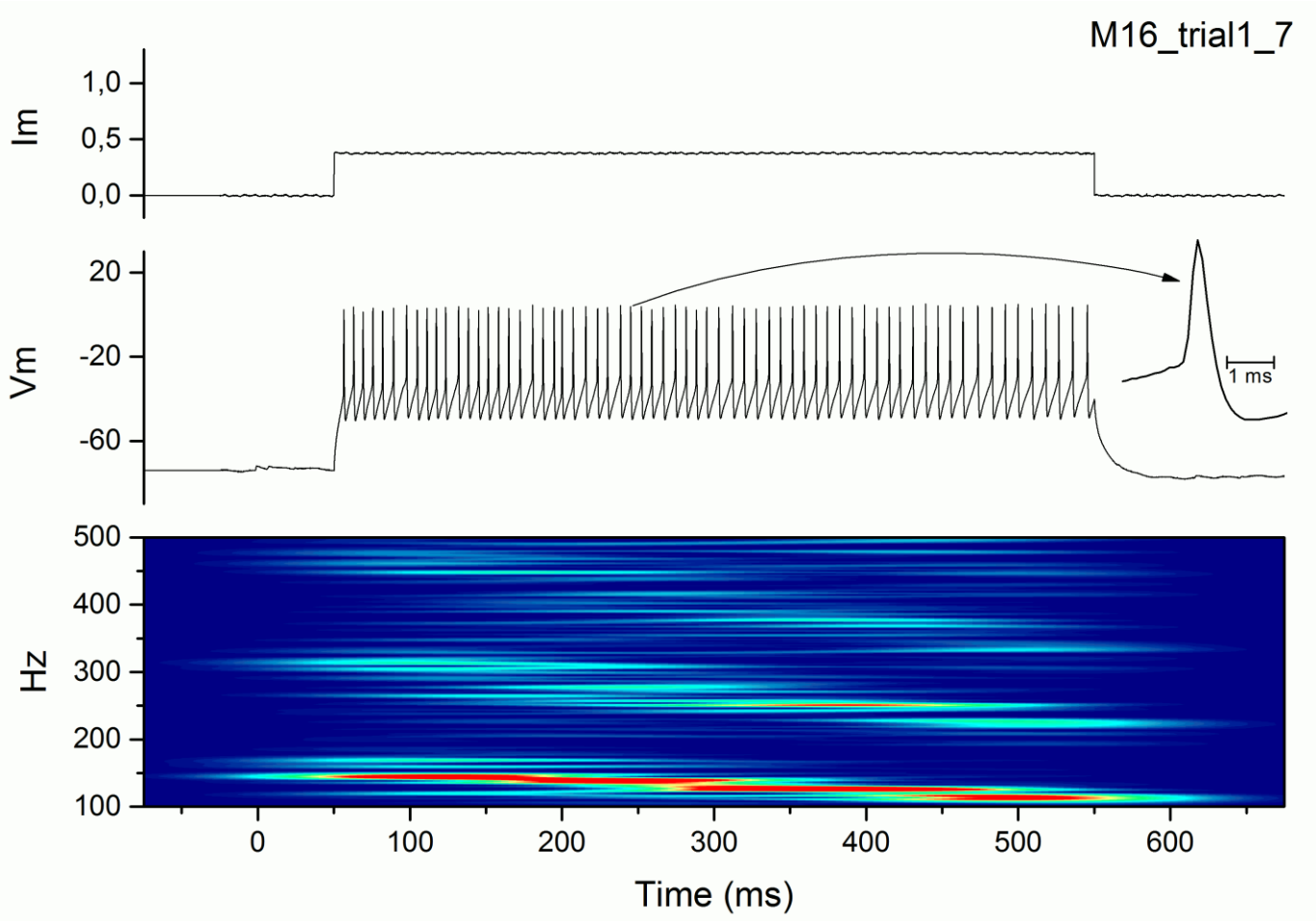


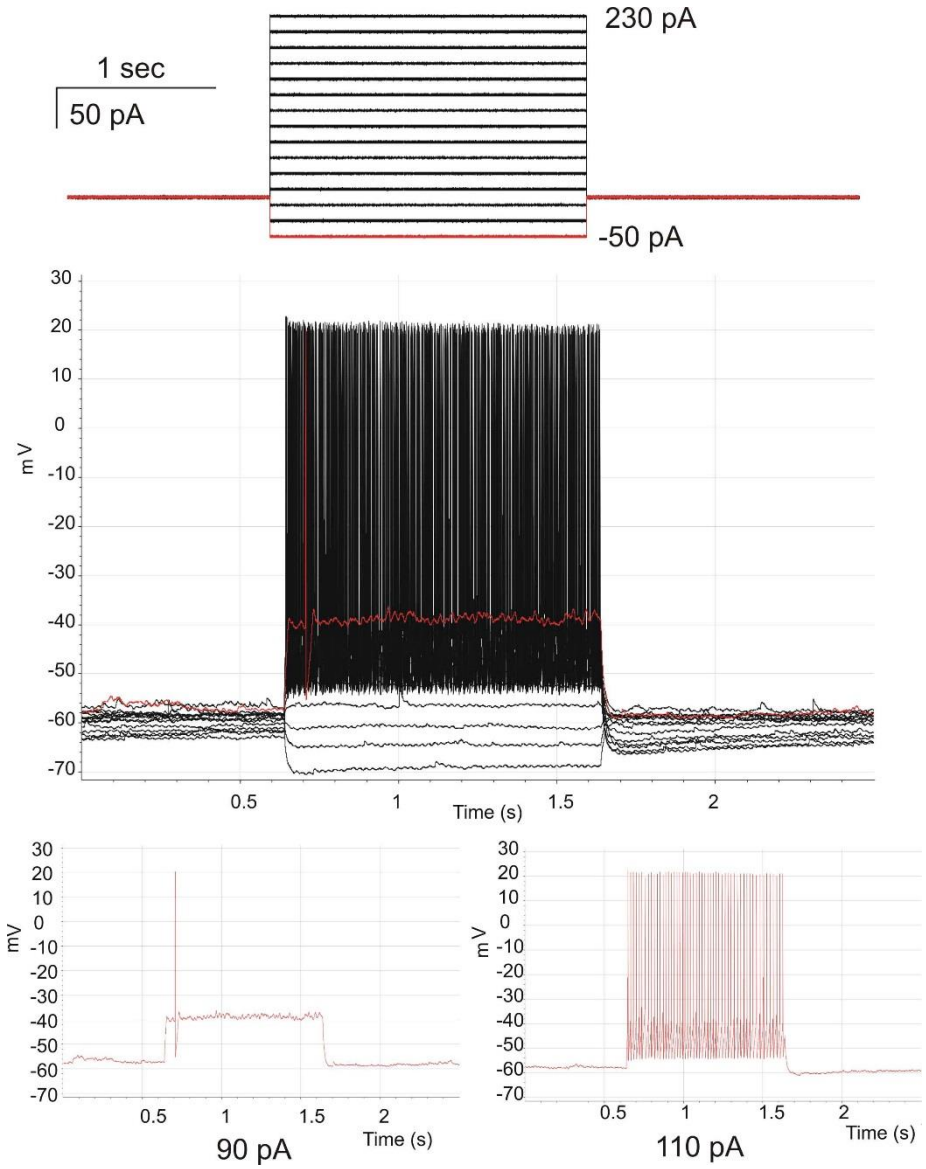


Single cell transcriptomics: step toward full scale proteomics of nerve cells

FS neuron







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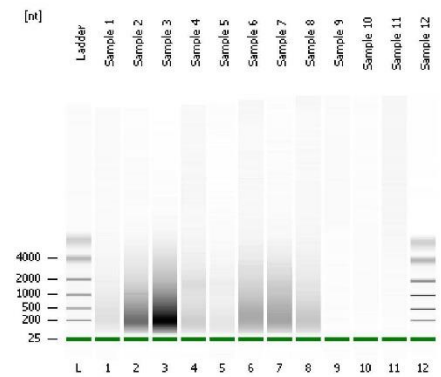

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Assay Comments: mRNA Analysis ng sensitivity

Chip Information:
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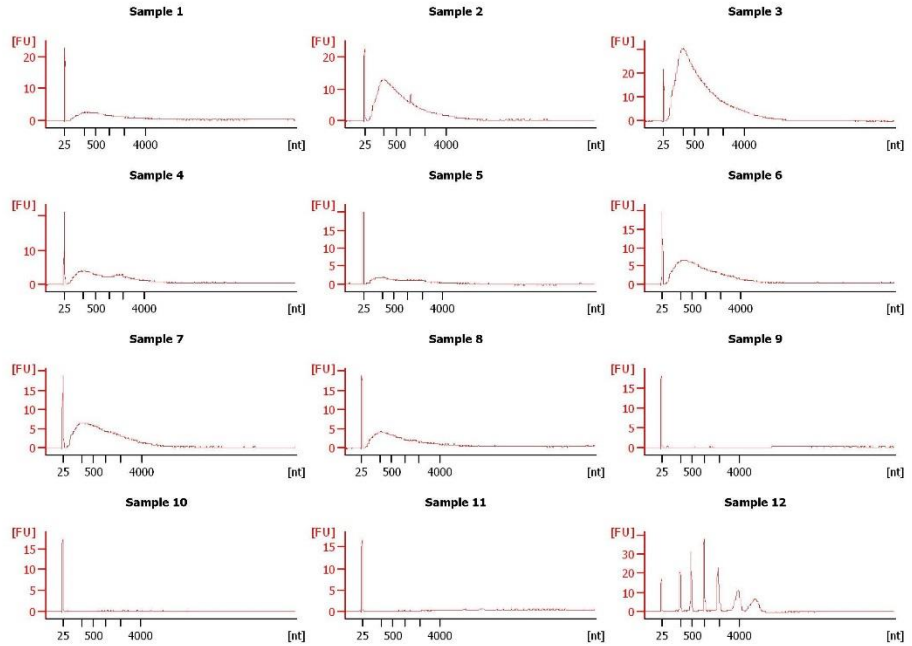
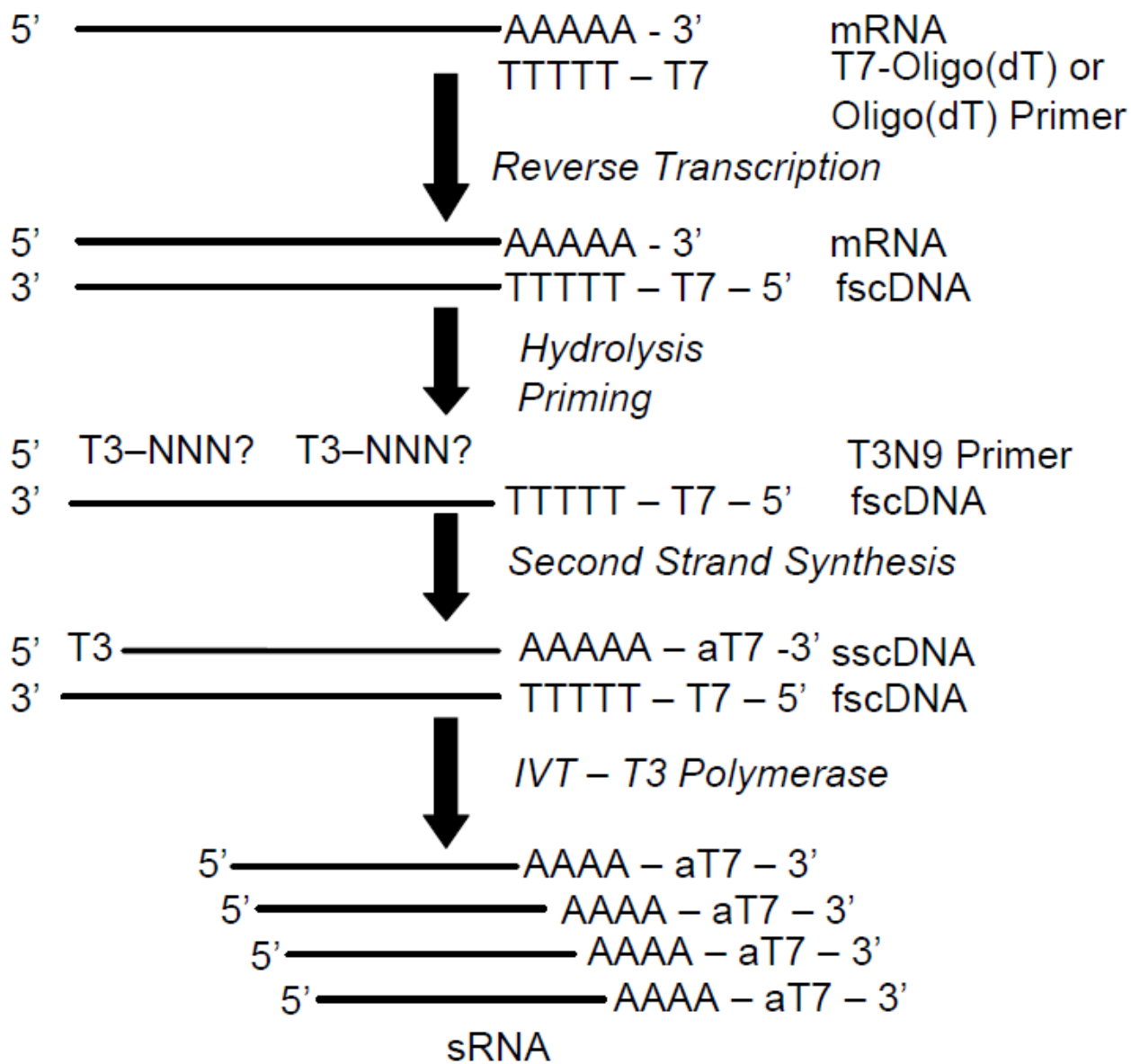
Reagent Kit Lot #:
Chip Comments:




5’
AAAAA - 3’
TTTTT – T7
mRNA
T7-Oligo(dT) or
Oligo(dT) Primer
Reverse Transcription
5’
AAAAA - 3’
mRNA
3’
TTTTT – T7 – 5’
fscDNA
Hydrolysis
Priming
5’ T3–NNN? T3–NNN?
T3N9 Primer
3’
TTTTT – T7 – 5’
fscDNA
Second Strand Synthesis
5’ T3
AAAAA – aT7 -3’
sscDNA
3’
TTTTT – T7 – 5’
fscDNA
IVT – T3 Polymerase
5’
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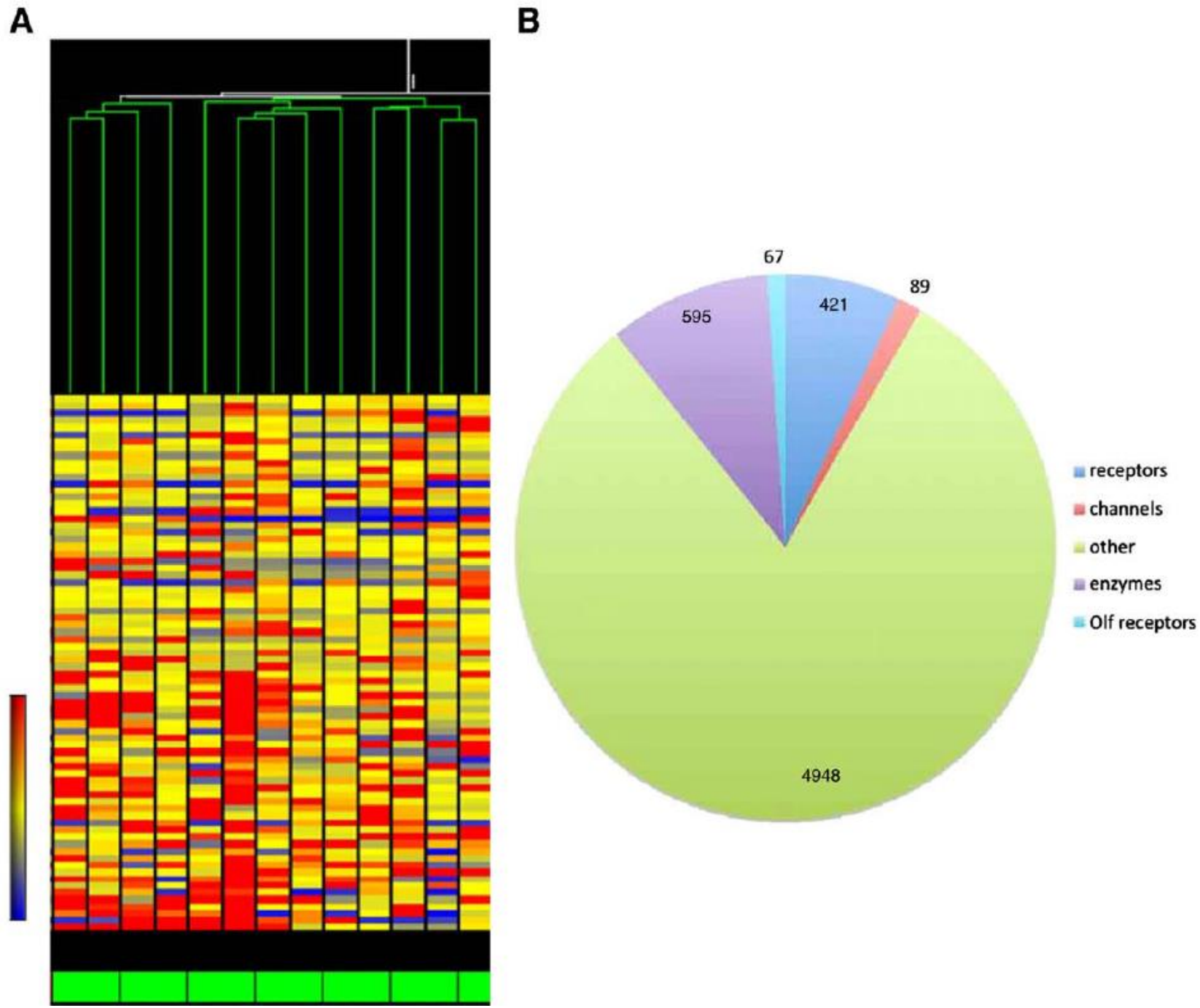
sRNA


A
B
67
89
421
595
4948
receptors
channels
other
enzymes
Olf receptors

Actual stage of development:

We can harvest single cells after a physiological study (FS cell isolation).

We are ready for single cell PCR, already done for GAPDH.

Sequencing is planned under a common research contract with Genetica Ltd.

Sequencing will be done in Olomouc Cz at Illumina Lab of Genetica Ltd.

First transcriptome wide studies on MySeq planned in July or August
by Petra Widenska (we already visited her).