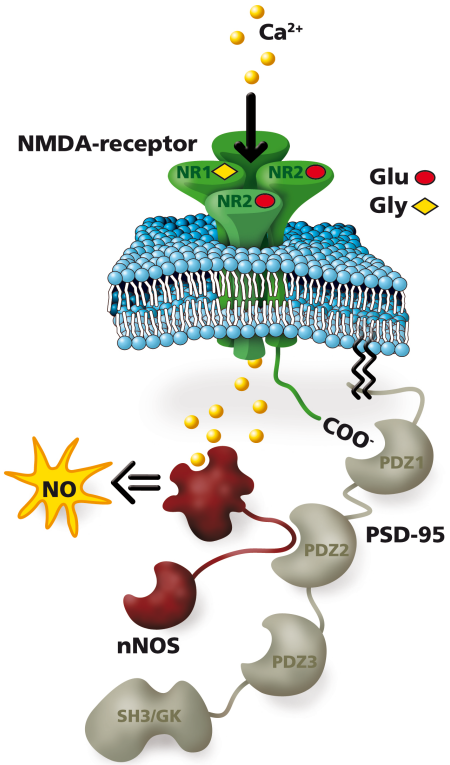
Avilex Pharma

Dimeric PSD-95 inhibitors as novel drugs against ischemic stroke - From PhD to Biotech

Innovation and intellectual property rights in biotechnology
February 2, 2017



Anders Bach, Associate Prof.
Faculty of Health and Medical Sciences
Dept. of Drug Design and Pharmacology
University of Copenhagen

Co-founder and Consultant of Avilex Pharma

2002: B.Sc. Biochemistry
2005: M.Sc. Human biology
2009: Ph.D. Medicinal Chemistry

Outline

1. **The Science**
   - Target, disease, compounds, competition

2. **Business**
   - IP and funding prior to Avilex Pharma
   - Avilex Pharma
     - Founding
     - Current Strategy and Status

3. **Conclusions**

Joint forces

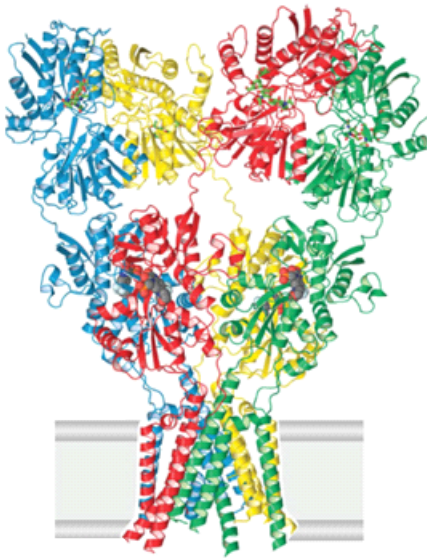
Get advice

Soft-money - to get as far as possible

Spin-outs = The link between Academia and Pharma

Innovate at University and as a PhD student

PSD-95 inhibition - the principle

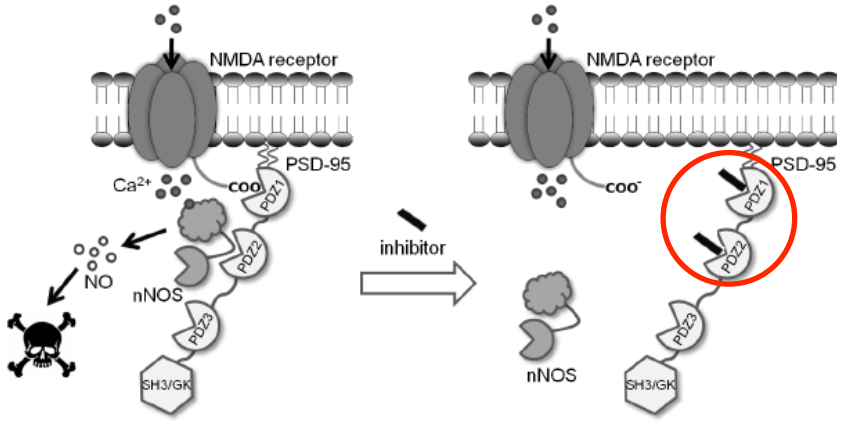


Glutamate Receptors

- Key role in normal brain function
- Ischemic stroke and Pain
- Antagonists: Affects normal activity and neurotransmission
- Severe side effects (and lack of efficacy)

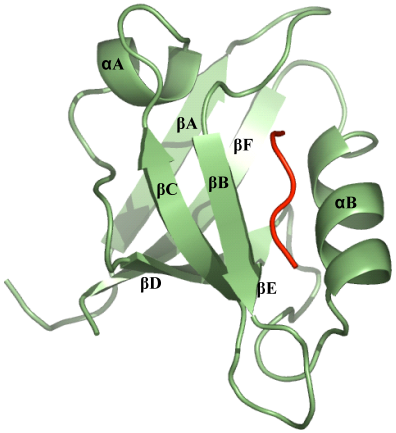
Alternative Strategy: Targeting PSD-95

- Normal NMDA receptor function not affected
  - Normal neurotransmission
  - Ca^{2+} dependent pro-survival pathways maintained
- Tat-NR2B9c (**NA-1**): YGRKKRRQRRR-KLSSIESDV
  - Micromolar affinity (Ki ~5 µM)
  - Tat: BBB permeability
  - Primate study and Phase II/III clinical trials (ischemic stroke)



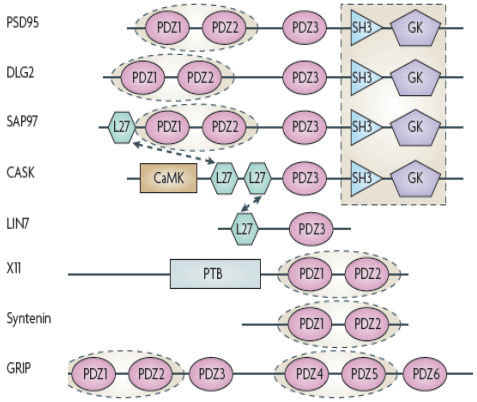
Aarts et al, *Science* **2002**
Cook et al, *Nature* **2012**
Hill et al, *Lancet Neurol.* **2012**

PDZ Domains



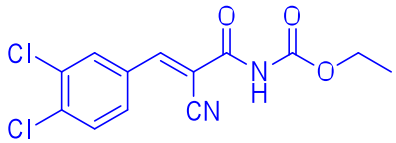
Structure and Function

- Size: ~90 amino acid residues
- Binds C-terminus of interacting protein (β-strand)
- Organizing signal transduction complexes, clustering membrane receptors, trafficking

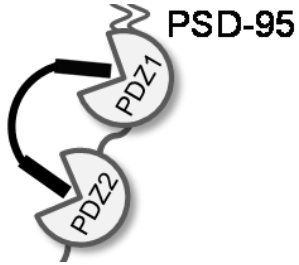


The PDZ binding pocket

- Small and narrow pocket (**Peptide-biased**)
  - PSD-95: Screening 12.000 fragments by NMR → No Hits
  - Mint: Screening 100.000 cmpds → No Hits
  - PICK1: Screening 44.000 cmpds → 3-5 hits (K_i ~7 µM)
- No small molecule inhibitors against PDZ domains with K_i < 5 µM



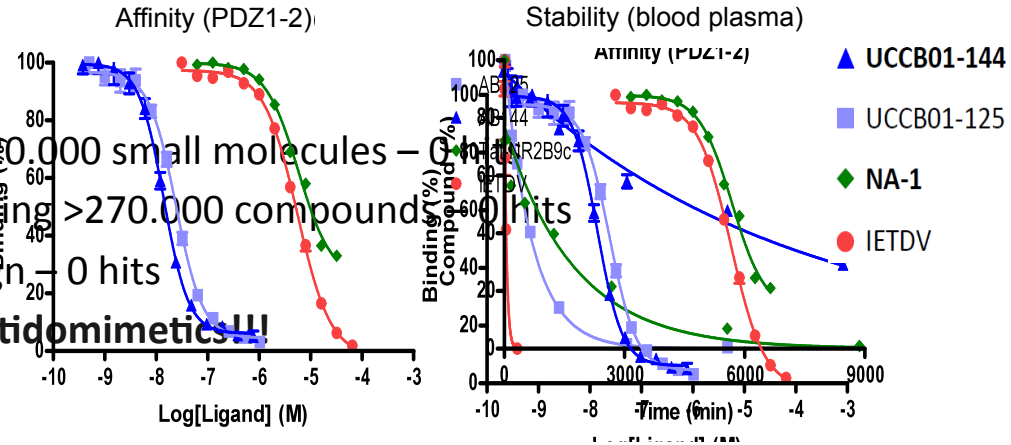
PhD Project and Dimeric PSD-95 inhibitors



Finding inhibitors

- Screening >320.000 small molecules – 0 hits
- Virtual screening >270.000 compounds – 0 hits
- Rational design – 0 hits

=> Peptidomimetics !!!

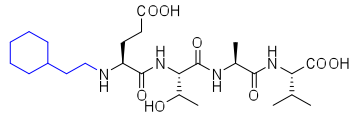


YGRKKRRQRRRKLSSIESDV

NA-1

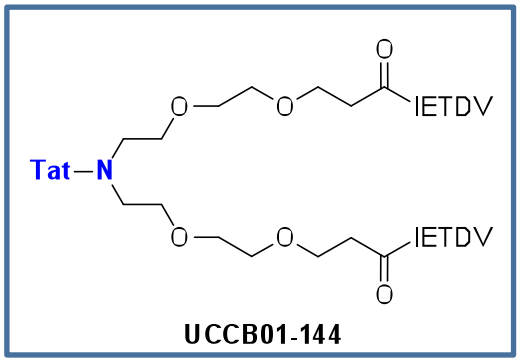
Science **2002**

IETDV +



J. Med. Chem. **2008**

Medium affinity and stability

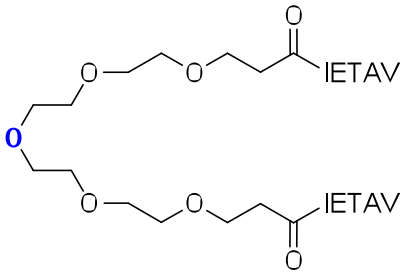


UCCB01-144

Proc. Natl. Acad Sci. USA **2012**

High affinity, high stability

+ BBB permeability



UCCB01-125

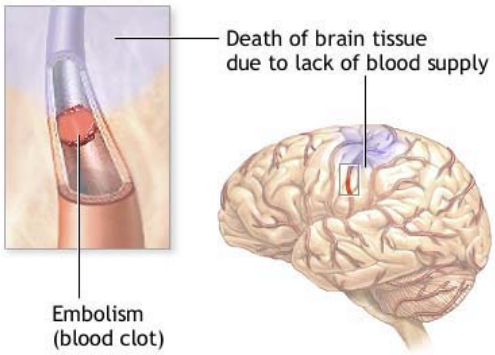
Angew. Chem. Int. Ed. **2009**

High affinity, medium stability

Ischemic stroke - a major unmet medical need

Ischemic Stroke

- **Second leading cause of death**, major cause of disability
- **Neuroprotection** – excitotoxicity – toxic levels of glutamate



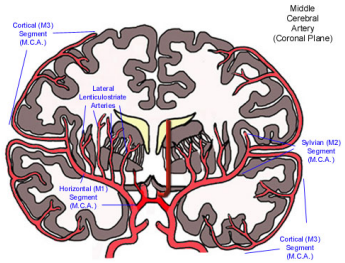
Current treatment

- Prevention and rehabilitation therapy
- Thrombolysis - rtPA, but **<10% of patients benefit from rtPA**
- No neuroprotective drugs (>114 negative trials)
- 'Graveyard of biotech'

Key on-going clinical trials – stroke

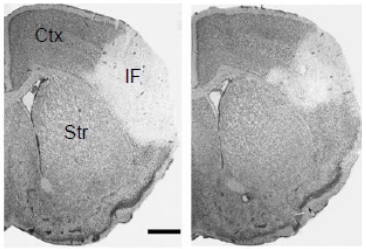
Compound	Sponsor	Mechanism	Status
NA-1	NoNO Inc.	PSD-95, neuroprotection	Phase II
Lovastatin	Mitchell S. Elkind	Inflammation, Blood flow, antioxidant	Phase II
Simvastatin	Vall d'Hebron Hosp	Inflammation, Blood flow, antioxidant	Phase IV
Edaravone	Mitsubishi	Antioxidant, scavenger	Phase II
GM602	Genervon	Apoptosis, inflammation	Phase II

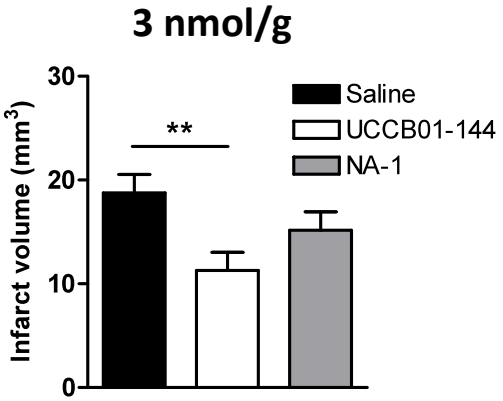
UCCB01-144 – in vivo models of stroke



Permanent Middle Cerebral Artery Occlusion (pMCAO) model

- SINGLE dose (3 nmol/g), 30 min AFTER infarct
- Infarct reduction *and* Motor functions improved
- Dose-response studies





Dose	NA-1	144
1 nmol/g	-	NA
3 nmol/g	NA	37%
9 nmol/g	32%	37%
30 nmol/g	death	NA

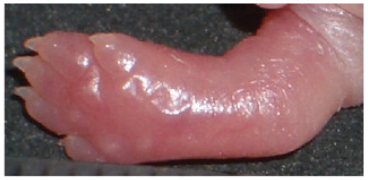
NA: No Activity

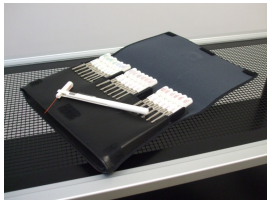
UCCB01-144 – benchmarking vs. NA-1

	UCCB01-144	NA-1
Affinity to PSD-95 (K_i)	4.6 nM	4,600 nM
Plasma stability ($T_{1/2}$)	4,900 min	1,100 min
Infarct reduction[1]	40%	No significant effect
Toxicity[2]	No effect on heart rate, blood pressure, or behaviour	Drop in heart rate and blood pressure leading to death
MTD, human	-	2.6 mg/kg[3]

[1]pMCAO, mice, dose: 3 nmol/g.
[2]mice, dose: 30 nmol/g.
[3]low due to histamine release (equivalent to 3 nmol/g in rats).

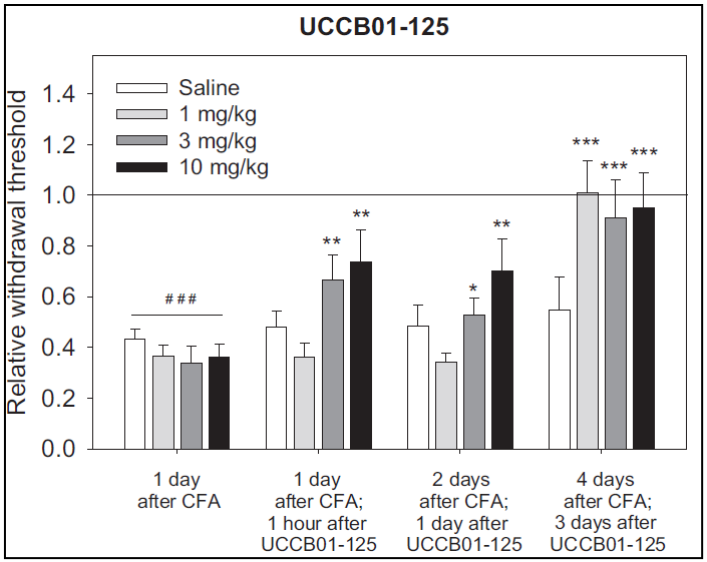
UCCB01-125/144 – Pain

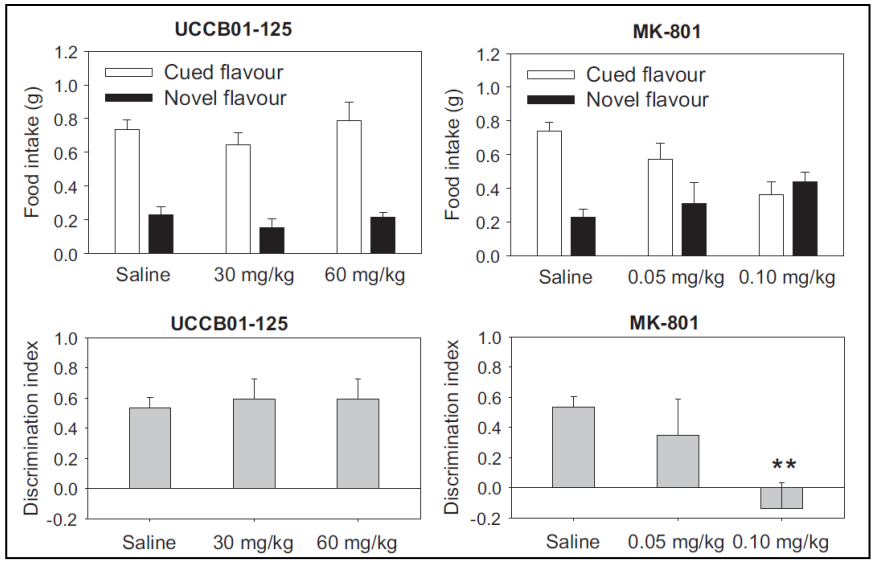




Model of inflammatory pain: Complete Freund's adjuvant (CFA)

- UCCB01-125 at 3 and 10 mg/kg (i.p.) reduces CFA-induced hyperalgesia
- The effect is preserved at 72 h
- Also when cmpd is given 24 h after CFA
- No cognitive or motor side effects seen (as for MK-801)





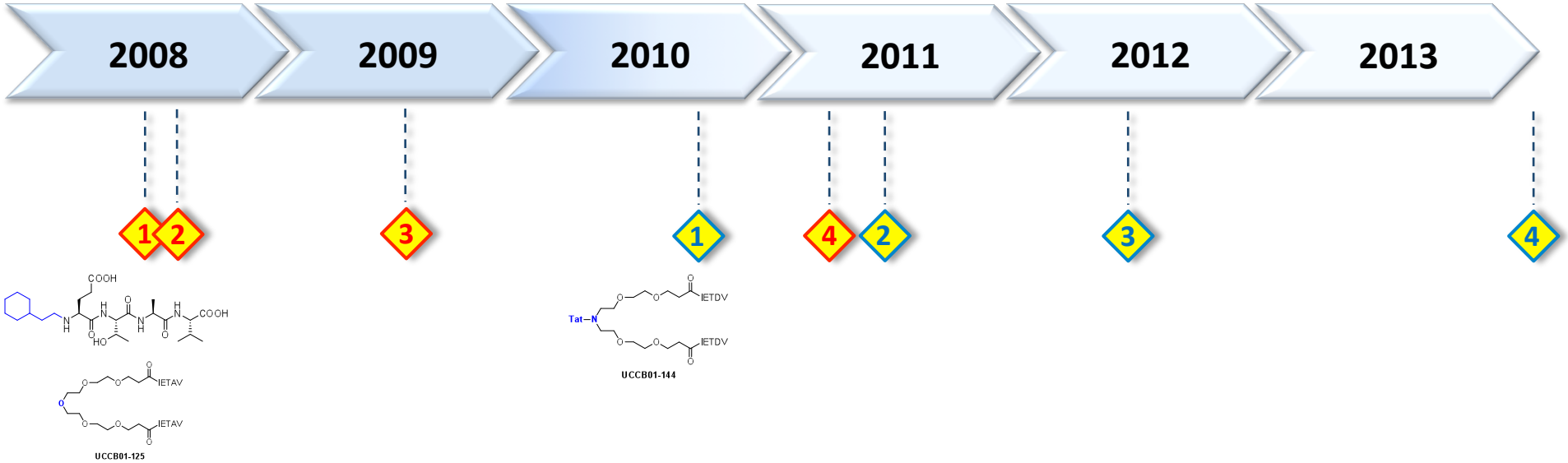
Andreasen et al, *Neuropharmacology* **2013**

Patents, Funding, and Founding Avilex

The Patent Process

Key Patenting Steps – Patent 1 (*N*-alkylated tetrapeptides and 1st gen. dimeric ligands)

Key Patenting Steps – Patent 2 (2nd gen. dimeric ligands)



1: Invention Disclosure:

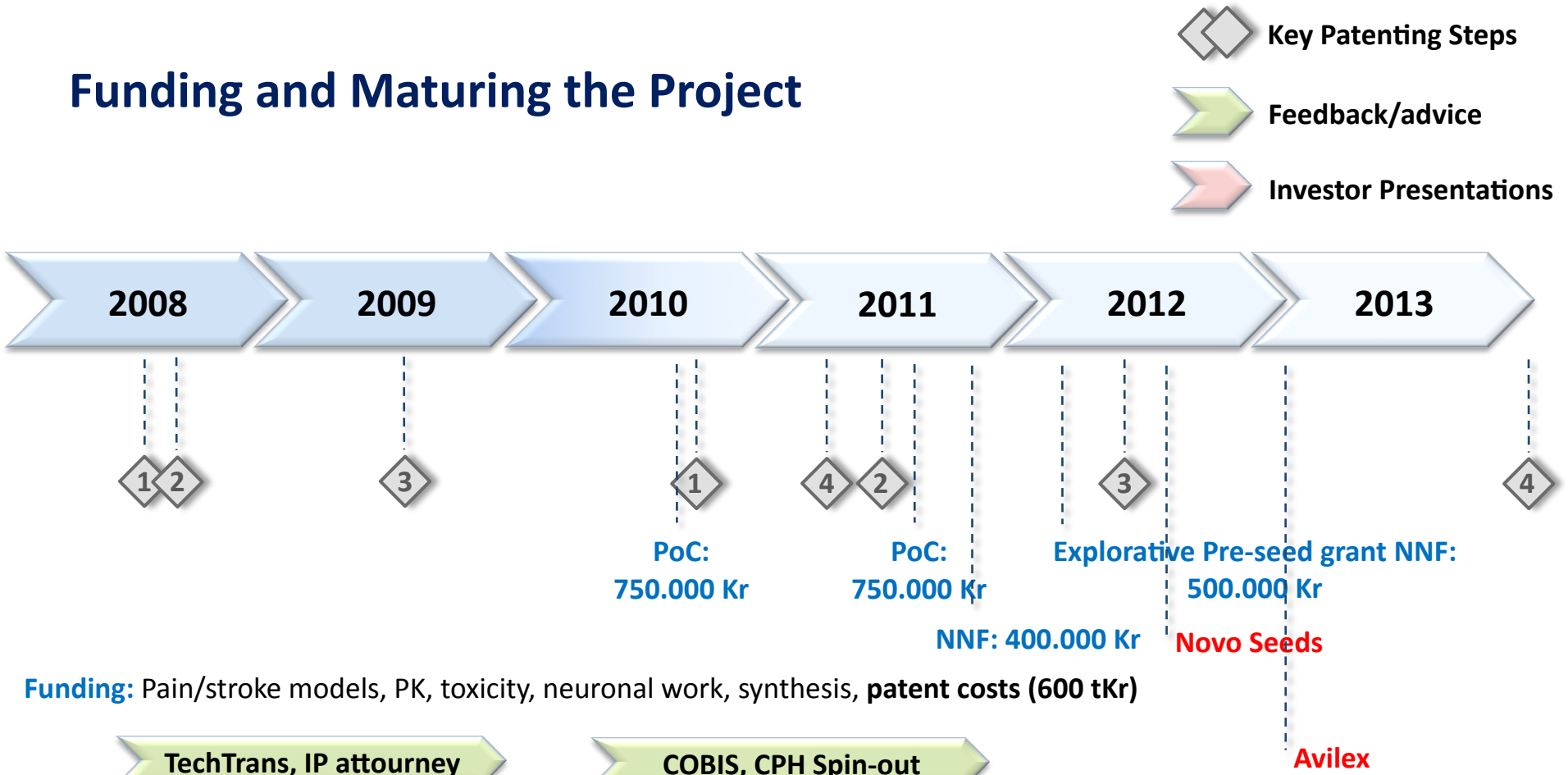
e series of dim

atents

1: Invention Disclosure; **2:** Filing of 1st pa

ng of AU, BR, CA, CN, EP, IN, IL, JP, KR, MX, SG and US

Funding and Maturing the Project



Funding: Pain/stroke models, PK, toxicity, neuronal work, synthesis, **patent costs (600 tKr)**

TechTrans, IP attourney

Analogues
Biological results

COBIS, CPH Spin-out

Indication (+Pain)
Investor material/presentations

~ 12 Investor Presentations

Pharma Companies and Venture Fonds
Out-licensing

Avilex Pharma

Founding

- Autumn 2012: Settling strategy, conditions, and structure with Novo Seeds
- Jan 2013: Launch (5 mill DKK seed investment) (www.avilexpharma.com)

Strategy

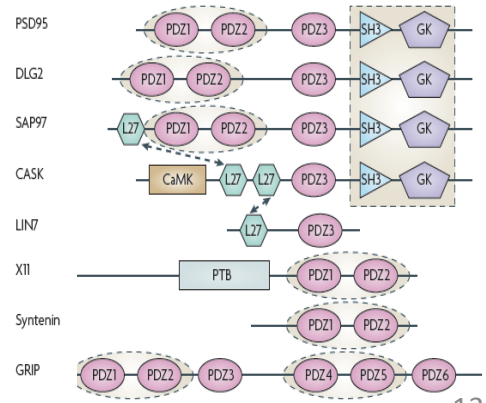
- Treat **neuropathic pain** with dimeric peptide-based inhibitors of PDZ tandem targets
  - Lead structure: UCCB01-125. Backup: UCCB01-144

Goals

1. Proof-of concept data in a neuropathic pain models
2. PK and Biodistribution: Sub cut. delivery => Relevant concentrations in spinal cord
3. Toxicity (cf. SAP-97): Heart, cells, selectivity

Secondary activities - academically driven

- Stroke (UCCB01-144) ('Graveyard of Biotech')
- Platform: Other tandem PDZ targets
- Other diseases: TBI, Depression, Angelman Syndrome
- Other compounds: Trimers, fatty acid dimers



…4 years later

Avilex Pharma - revised

Goals (Experiments in 2013)

1. Proof-of concept data in a neuropathic pain models ÷
2. PK and Biodistribution: Sub cut. delivery => Relevant concentrations in spinal cord √
3. Toxicity (cf. SAP-97): Heart, cells, selectivity √

Strategy (2014)

- Treat **Ischemic Stroke** ~~neuropathic pain~~ with dimeric peptide-based inhibitors of PDZ tandem targets
  - Lead structure: ~~UCCB01-125. Backup:~~ UCCB01-144

Funding going ahead (2015-18)

- Welcome Trust Translational Award (~ 3.2 mill Euro)
  - Bring UCCB01-144 ready for human trials
    - Animal stroke models
    - CMC
    - Safety and toxicity (PK/ADMET)

The Team

Mark Treherne – CEO

- Expertise: Biotech, Clinical development, CNS, funding

Kristian Strømgaard - Co-founder & CSO

- H. Lundbeck Professor, Dept. Drug Design and Pharmacology, University of Copenhagen

Mikael Thomsen – CDO

- ADMET/Safety (Preclinical and clinical), CSO Contera Pharma

Anders Bach - Co-founder & Consultant

- Associate Prof, Dept. Drug Design and Pharmacology, University of Copenhagen

Board

- **Emanuelle Coutanceau** (Chairman), Investment director, Novo Seeds
- **Raymond Hill**, Visiting Prof. of Pharmacology, Imperial College, UK, Executive Director, Neuroscience Research Merck/MSD 1990-2002

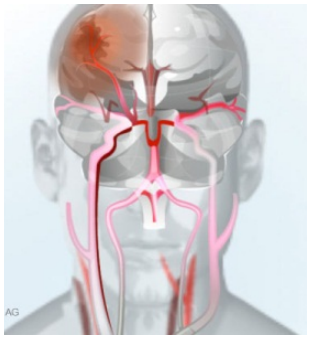
Advisors

- **Ulrich Dirnagl - Clinical Advisor,** Professor, Charité, Berlin (leading stroke expert, >17.000 citations, H index 72)

Executive Summary

Ischemic stroke

- Major unmet medical need

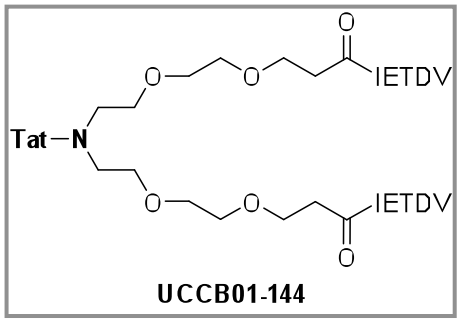


UCCB01-144

- Dimeric PSD-95 inhibitor – novel mode of action - unprecedented affinity (K_i = 4.6 nM)

Benchmarking

- **NA-1** – monomeric PSD-95 inhibitor (K_i = 4,600 nM)
- Successful phase II clinical trial – Phase III trial (2016/17)



UCCB01-144

Ambition

- To make **UCCB01-144** ready for Phase II clinical trials for treatment of patients suffering from ischemic brain damage.

YGRKKRRQRRRKLSSIESDV

NA-1

Timeline

- Finalize Phase I trial – ultimo 2018
- Find business partner (Pharma?)

How will UCCB01-144 break the cycle of failures in ischemic stroke?

Novel promising target

- **PSD-95** – no effect on normal NMDA receptor function
- Principle and safety demonstrated by NA-1

Novel mechanism of action

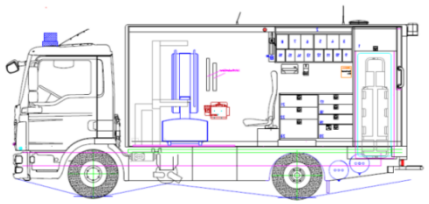
- Dimeric ligand - **UCCB01-144**

Comprehensive preclinical efficacy studies

- Rodents (male/female, aged, mice/rats, transient/permanent models)
- Rabbit model – high translatory value: co-adm. and comparison with rtPA; time-window

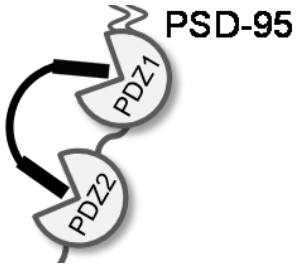
Phase I clinical studies

- CSF sampling and/or PET studies



Improved design of Phase II clinical study

- Ambulance treatment (Golden hour!)
- Hospital treatment (iatrogenic stroke) under optimized conditions



Conclusions

Science and Avilex' case

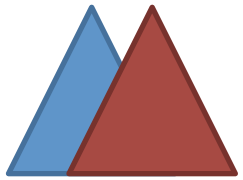
- PSD-95 - a promising target against ischemic stroke (but not neuropathic pain)
- Dimeric peptide, **UCCB01-144**, is a novel and promising lead against ischemic stroke
- Big market potential and strong IP
- CMC, PK and toxicity studies of **UCCB01-144** support further development
- **UCCB01-144** is better than clinical front-runner NA-1 (affinity, neuroprotection, toxicity)
- Plan and funding in place to make **UCCB01-144** ready for phase 1 in 2018

Innovation at University – Key Steps

- Tech Trans Unit - Market potential (usefulness and competition) and Feasibility
- Maturation of project and commercialization
  - Feedback: TechTrans, IP lawyers, Innovation camps, Investor presentations
  - Funding: Proof-of-Concept and Innovation-focused (NNF, Ministry of Research, EU, WT)
- Spin-out or out-licensing?

Doing biotech as an academic - why?

- Realise your research + Gives you a new set of skills
- Gives a clear direction to your research (shared goals)
- Opens up for other funding types



Academic goal: Is PSD95 a valid stroke target?

Avilex goal: Make a drug against PSD95 and stroke

Acknowledgements

Academic Collaborators
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Natasha Fauerby

Seth Grant
Maksym Kopanitsa

Lars K. Poulsen
Bettina M. Jensen
Per S. Skov

Commercial Collaborators
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Verena Simpson
Mai-Britt Zocca
Morten Albrechtsen

Robert Tansley
Ingelise Saunders
Nanna Lüneborg
Henrijette Richter

Bobby Soni
Raymond Hill
Peter Holm
Mikael Thomsen
Ulrich Dirnagl
Mark Treherne

Foundations
The Danish Research Councils
GluTarget
The Lundbeck Foundation
Proof-of-concept (PoC)
Novo Nordisk Foundation
Novo Seeds

Thank you!

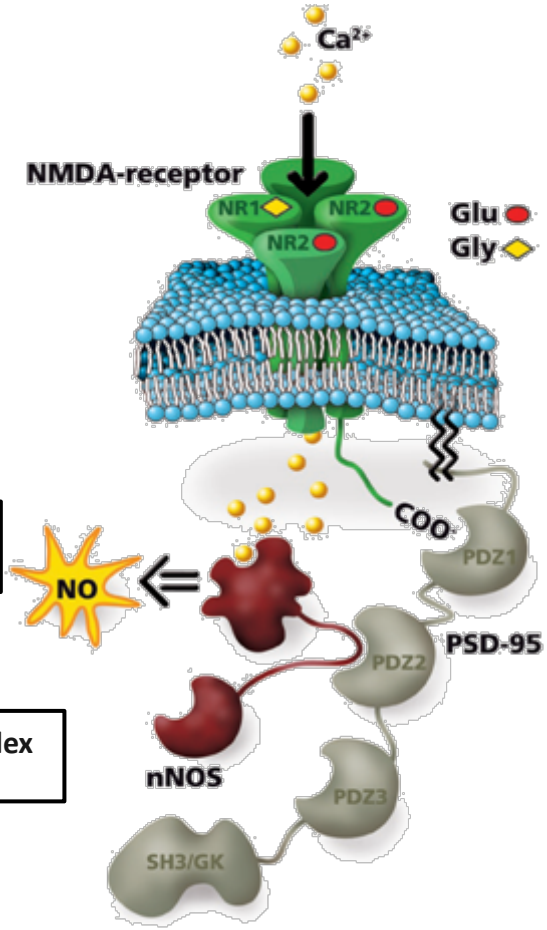
APPENDIX

PSD-95 inhibition - Target validation

nNOS essential for neurotoxicity
Huang et al., *Science*, 1994
Dawson et al. *J. Neurosci.*, 1996

Source specificity of Ca^{2+} neurotoxicity
Sattler *et al. J. Neurosci.*, 1998

nNOS/PSD-95/NMDA receptor complex
Christopherson et al. *JBC.* 1999

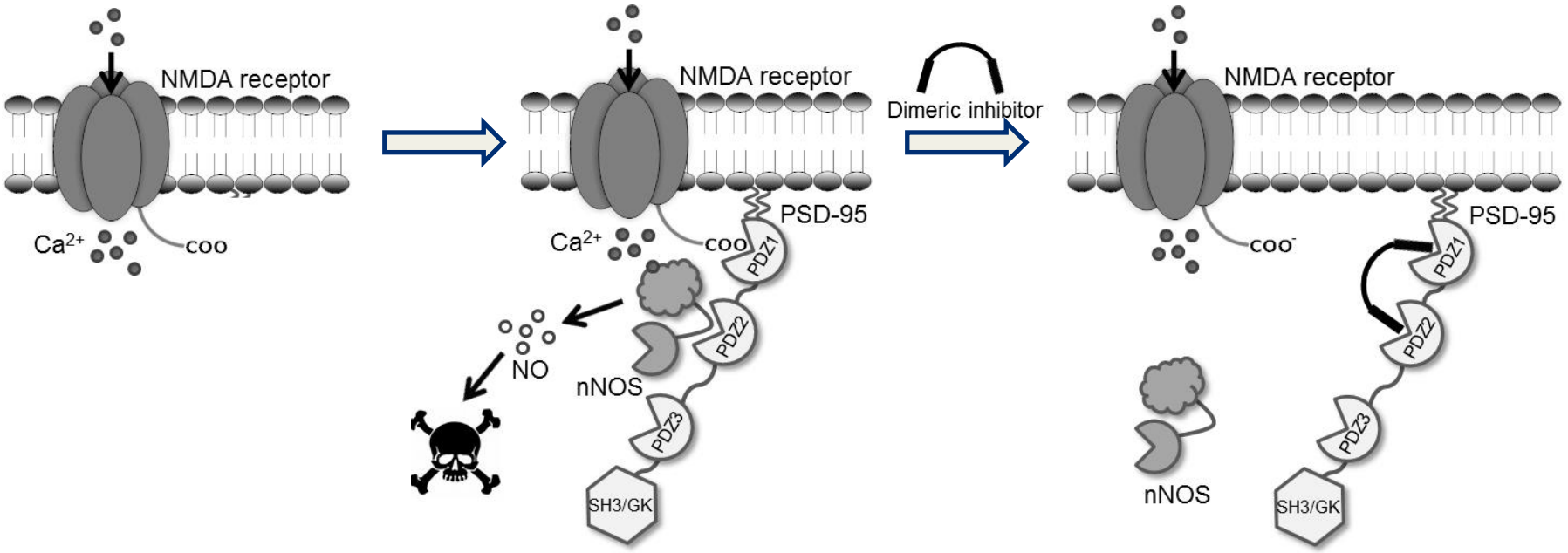


Effect in advanced monkey model. Correlation with effects in humans Phase II clinical trials
Cook et al. *Nature*, 2012
Cook et al. *Science Trans. Med.* 2012
Hill et al. *Lancet Neurol.* 2012

NA-1 reduces ischemic brain damage *in vivo*, improve neurological function and no effect on Ca^{2+}-pro-survival pathways
Aarts et al. *Science*, 2002
Soriano et al. *J. Neurosci.*, 2008
Sun et al. *Stroke*, 2008

Suppressing PSD-95 → Reduction of excitoxic cell death and NO, no effect on NMDA receptor function
Sattler et al. *Science*, 1999

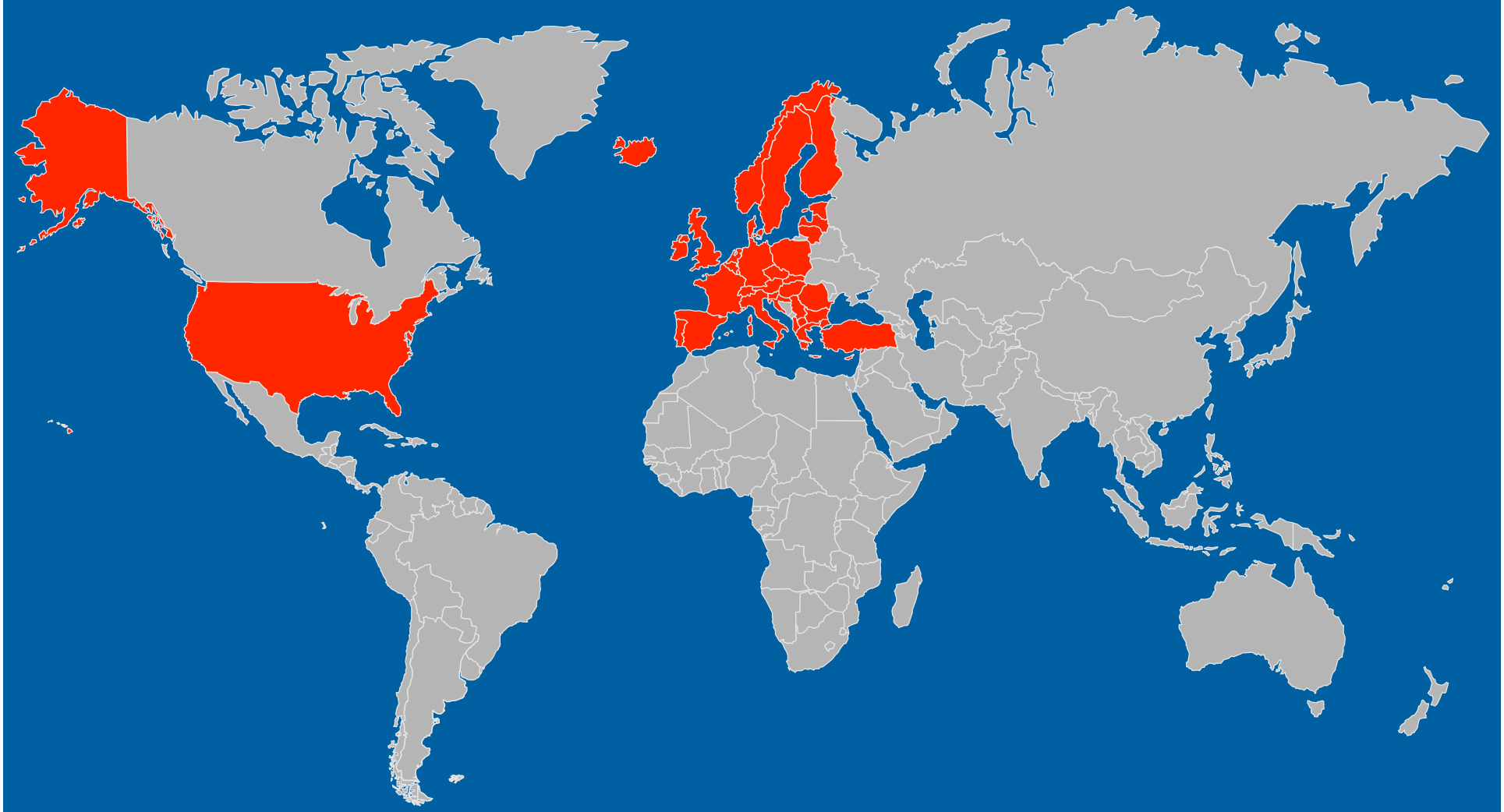
PSD-95 inhibition – novel principle in treatment of ischemic stroke



Compound	Sponsor	Mechanism	Status
Desmoteplase	H. Lundbeck A/S	Anti-thrombolytic	Phase III (Negative data)
Transcranial laser therapy	PhotoThera, Inc	Mitochondrial stimulation	Phase III (Negative data)
Magnesium Sulfate	Jeffrey L. Saver, NINDS	Anti-excitotoxic, NMDA ion channel blocker	Phase III (Negative data)
Albumin	Seoul St. Mary's Hosp.	Antioxidant, Hemodiluiting agent	Phase III (Negative data)
Spheno-Palatine Ganglion (SPG) stimulation	BrainsGate	Induction of cerebral vasodilatation	Phase III (Recruiting)
THR-18	D-Pharm Ltd.	Synthetic plasminogen activator inhibitor	Phase II (on-going)
NA-1	NoNO Inc.	PSD-95, neuroprotection	Phase IIb (Recruiting)
Hypothermia	Univ. California, NINDS	Reduce cerebral oxygen metabolism, synaptic inhibitor	Phase II/III (Recruiting)
Simvastatin	Vall d'Hebron Hosp	HMGCoA inhibitor, Inflammation, Blood flow, antioxidant	Phase IV (Recruiting)
Lovastatin	Mitchell S. Elkind	HMGCoA inhibitor, Inflammation, Blood flow, antioxidant	Phase II (Recruiting)
GM602	Genervon	Apoptosis, inflammation	Phase II (Recruiting)
PG2 (Polysaccharides)	China Medical Univ. Hosp.	antioxidative and antiinflammatory	Phase II (Recruiting)
Edaravone	Mitsubishi	Antioxidant, scavenger	Phase II (Results, ?)
Cyclosporin A	Hospices Civils de Lyon	Anti-inflammatory, anti-excitotoxic	Phase II (Results, ?)
Deferoxamine mesylate	Germans Trias Pujol Hosp	Iron chelator, antioxidant	Phase II (Results, ?)
Dapsone	Cidat, S.A. de C.V.	Anti-inflammatory, antioxidant	Phase II/III (?)
Minocycline	Singhealth Foundation	Anti-inflammatory, antioxidant	Phase IV (?)
Ebselen	Daiichi Pharmaceutical	Antioxidant, free radical scavenger	Phase III (?)

Based on Minnerup et al, *Int. J. Mol. Sci.* **2012** and checks (Dec 8, 2014) on public domains (e.g. www.clinicaltrials.gov; www.strokecenter.org/trials)

WO 2010/004003 - "1st application" Geographical coverage



WO 2012/156308 - "2nd application" Geographical coverage