



Amarantus
BioScience

Mesencephalic Astrocyte-derived Neurotrophic Factor (MANF)

A novel neurotrophic factor with potential for treatment of retinal disorders

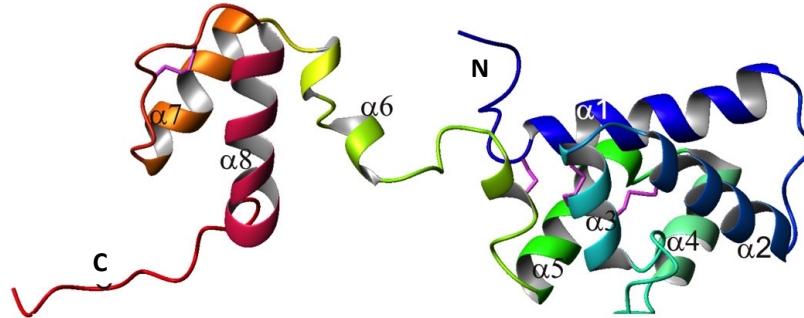
OTCQB: AMBS

Targeting Ocular Disorders 2014

Forward-Looking Statements

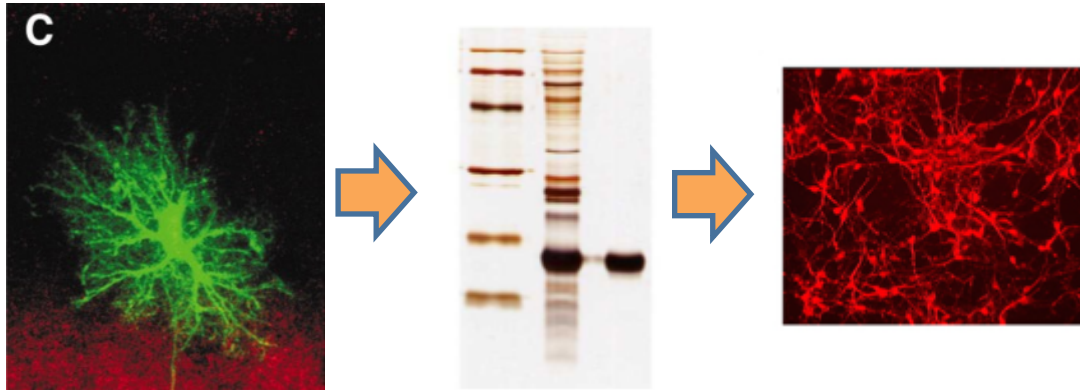
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MANF: A Novel Growth Factor

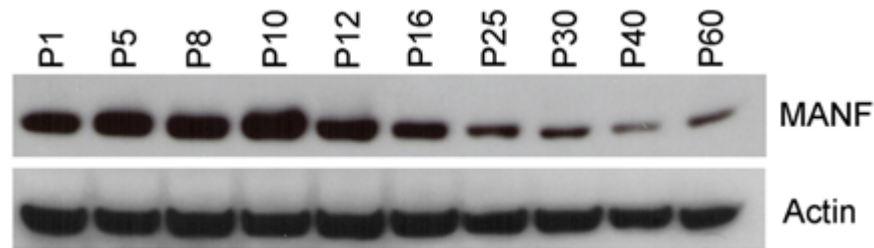


- MANF: Mesencephalic astrocyte-derived neurotrophic factor
- Original discovery by Amaranthus' CSO
- Prototype of emerging family of novel growth factors
- Evolutionary highly conserved structure and function
- Expressed in response to cellular stress
- Cell protective and anti-apoptotic
- Potential therapy for Retinitis Pigmentosa, Parkinson's Disease, Diabetes and Myocardial Infarction

From Astrocytes to DA Neurons to the Retina



Figures from Bushong et al. 2003; Petrova et al., 2003



Data generated by Prof. Rong Wen, PCT application WO 2012/170918 A2; University of Miami

- Astrocytes were the initial source for MANF discovery
- MANF supports survival of dopaminergic neurons
- MANF expression in the retina peaks at P10
- MANF expression steadily decreases as the retina matures
- Re-activation of developmental genes observed as a mechanism of tissue repair
- Regenerative / protective potential of MANF in retinal disorders

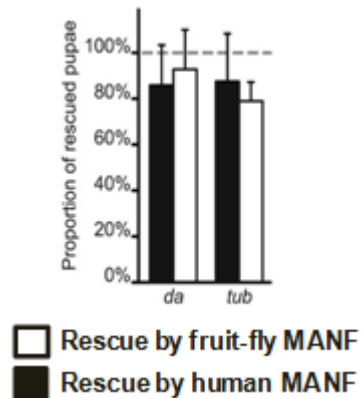
MANF Structure and Function is Evolutionarily Highly Conserved

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H. s. MANF MWATQGLA-VALALSVLPGSRALRPG-----DCEVCISYLGRFYQD 40
M. m. MANF MWATRGLA-VALALSVLPPSRALRPG-----DCEVCISYLGRFYQD 40
D. m. MANF MKTWYVVVVVIGFLATLAQTSALKEE-----DCEVCVKTVRRFADS 41
C. e. MANF MS--RLVLLISLVIVVASAAP-----DCEVCKVLDLDDVMAX 35
*      : : : : : : : : : : : : : : : : : : : : : : : : : : : :
H. s. MANF LKDRDVTFFSPATIENELIKFCREARGKENRICYIIGATDDAATKIINEVS 90
M. m. MANF LKDRDVTFFSPATIEEELIKFCREARGKENRICYIIGATDDAATKIINEVS 90
D. m. MANF LDDSTKK-DYKQIETAFKFKCAQKNKEHRHCYIYLGGLAESATGILNELS 90
C. e. MANF VPAGDKS-KPDAIGKVIREHCETTRNKENKCFYIIGALPESATSIMNEVT 84
:      * : : : : : : : : : : : : : : : : : : : : : : : : : : :
H. s. MANF KPLAHHIPVEKIC-EKLLKKDSQICELKYDKQIDLSTVDLKKLRVKELKK 139
M. m. MANF KPLAHHIPVEKIC-EKLLKKDSQICELKYDKQIDLSTVDLKKLRVKELKK 139
D. m. MANF KPLSWSMPAEKIC-EKLLKKDAQICDLRYEKQIDLSVDLKKLRVLDLKK 139
C. e. MANF KPLSWSMPTEKICLEKLGKDAQICELKYDKPLDWKTIDLKMRVKELKN 134
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H. s. MANF ILDDWGETCKGCAEKSDYIRKINELMPKYAPKAASARTDL 179
M. m. MANF ILDDWGEMCKGCAEKSDYIRKINELMPKYAPKAASARTDL 179
D. m. MANF ILNDWDESCDGGLEKGFIRKRIEELKPKYS-----RSEL 173
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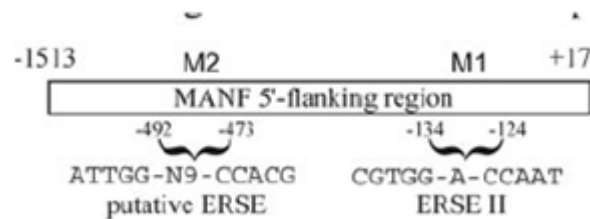
- Sequence is highly conserved from human to fruit-fly to nematode
- Human MANF can compensate the function of fruit-fly MANF
- MANF acts through an evolutionarily conserved pathway
- High probability of translational success from animal models to humans

- ✓ MANF deletion is lethal in fruit-fly
- ✓ Rescue by expression of fruit-fly or human MANF

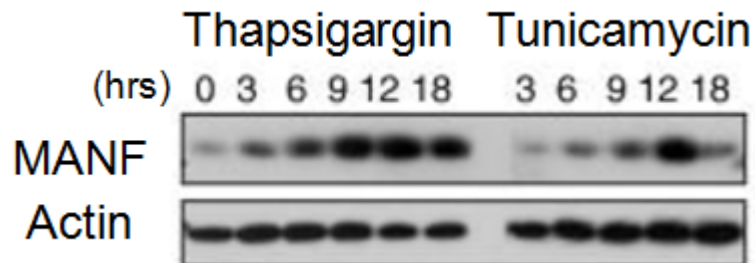


MANF Prevents Stress-induced Apoptosis

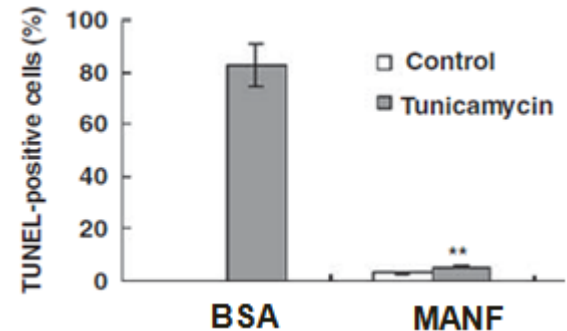
MANF promoter contains ER stress response element



MANF expression is induced by ER stressors



ER stress (Tunicamycin)
Primary neurons
Apoptosis – TUNEL⁺



MANF prevents ER stress-induced apoptosis

Reduction of TUNEL⁺ cells

MANF Potential Therapeutic Areas

Neurology

Cardiovascular

MANF

Diabetes

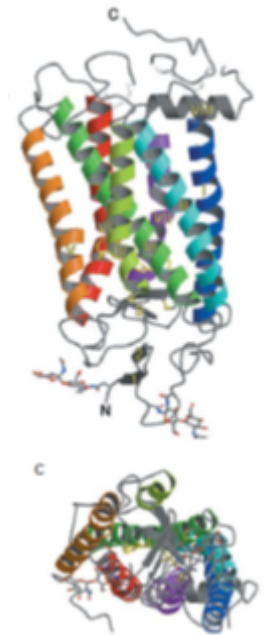
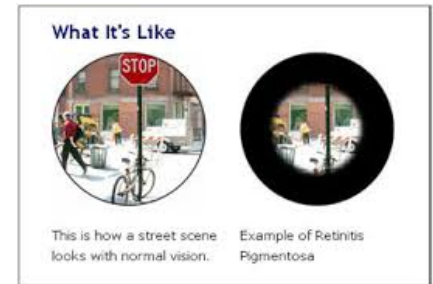


Ophthalmology

Retinitis Pigmentosa
Optic Nerve Ischemia (CRAO, CRVO)
Glaucoma

Retinitis Pigmentosa

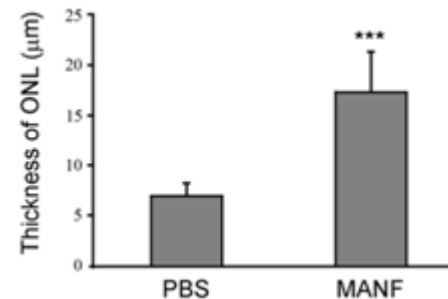
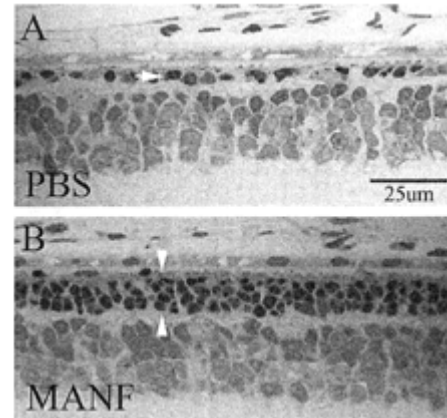
- Genetic disease of the retina
 - ✓ 1:3500 subjects; Est. China 400k, US 100k, EU 100k, JP 50k
 - ✓ No treatment currently approved
- Progressive vision loss
 - ✓ Rod photoreceptors followed by cone degeneration
 - ✓ Night vision loss followed by loss of peripheral vision
 - ✓ Progression to legal blindness in adulthood
- Mutations in the rhodopsin gene
 - ✓ Single most common cause of retinitis pigmentosa
 - ✓ Mutated rhodopsins misfold and aggregate
 - ✓ Unfolded protein response, cellular stress and cell death



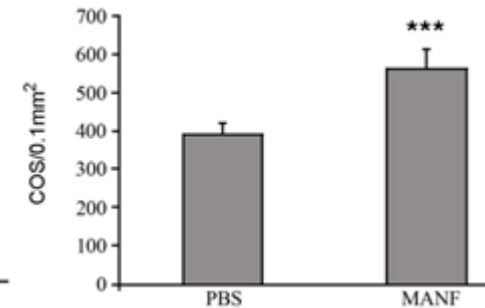
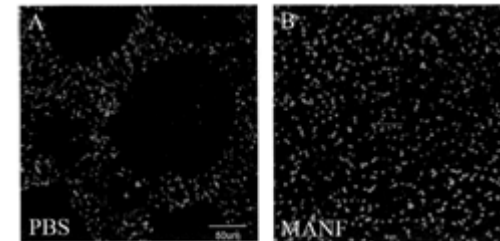
MANF Protects Photoreceptors in the RP Model S334ter Line 3

- Rhodopsin termination mutation at position 334
- Protein aggregation, unfolded protein response, apoptosis
- Primary rod photoreceptor degeneration
- Secondary cone degeneration
- Single MANF admin on Day 9 for rod protection
- Single MANF admin on Day 20 for cone protection

Rod photoreceptors Day 21



Cone photoreceptors Day 30



MANF protects rod photoreceptors
MANF protects cone photoreceptors

MANF Protects the Retina in two Additional Models of RP

Crx^{tvrm65} RP model

- Photoreceptor-specific transcription factor (CRX: cone-rod homeobox)
- Controls expression of retinal genes (rhodopsin)
- Mutations associated with RP
- Crx^{tvrm65}: recessive mutation, homozygous animals
- Single admin of MANF at P14
- Reduced TUNEL⁺ cells
- Preserved ONL thickness

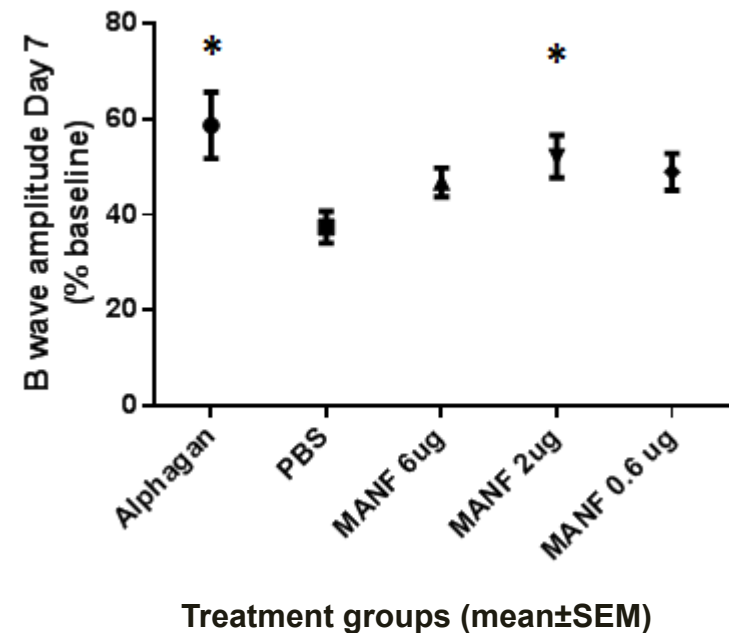
Rd1 RP model

- PDE6 is a protein complex composed of α , β and two γ subunits
- Hydrolyzes cGMP in response to light activation of G protein coupled receptors
- Pde6b^{Rd1}: Rd (Rodless retina mutation); Recessive mutation, homozygous animals
- Single admin of MANF at P7
- Reduced TUNEL⁺ cells
- Preserved ONL thickness

MANF protects photoreceptors against apoptosis
MANF preserves photoreceptors in the outer nuclear layer of the retina

Functional Protective Effect of MANF in an Optic Nerve Ischemia Model – CRAO/CRVO/Glaucoma

- Retinal ischemia is a cause of visual impairment and blindness
- Occlusion / reperfusion model
 - ✓ Central retinal artery occlusion (CRAO)
 - ✓ Central retinal vein occlusion (CRVO, orphan)
 - ✓ Glaucoma
- Single intravitreal MANF administration immediately after occlusion / reperfusion
- ERG, b-wave amplitude on Day 7



First observation of a functional benefit with MANF

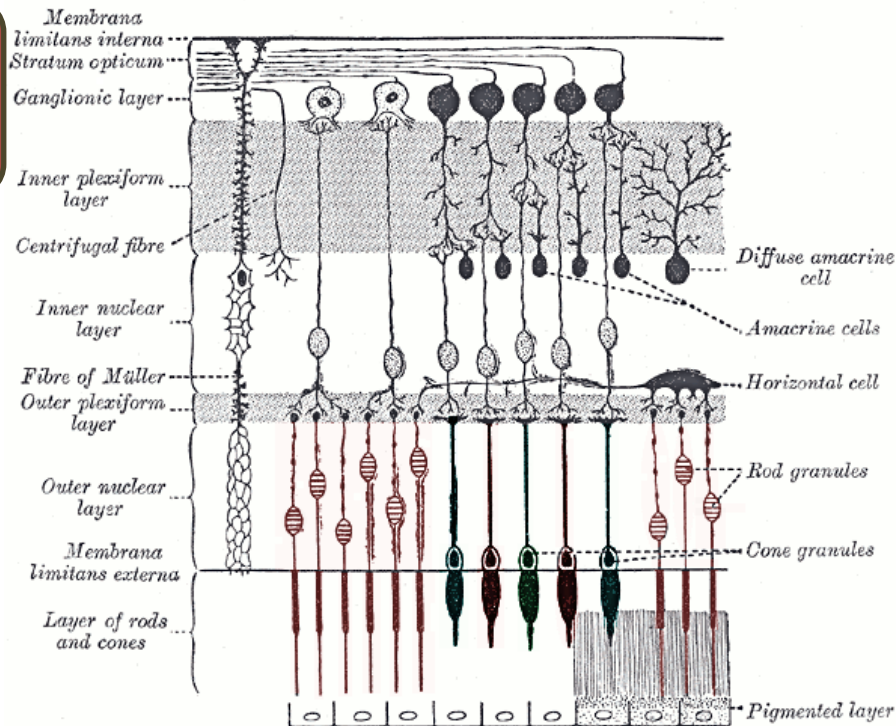
Dose-effect relationship mirrors effects in Parkinson's disease model

Most effective dose has a safety margin compared to the ocular tolerance study dose

MANF effect similar to Alphagan despite completely different MOA

MANF Protects Retinal Cells from Injury

Retinal Ganglion Cells
Nerve crush model
Glaucoma



Mueller Glia
ERG data
CRAO, CRVO,
glaucoma

Photoreceptors
S334ter, crx, rd1
Retinitis Pigmentosa

MANF exhibits broad protective activity in retinal injury models

MANF Safety Data

- Single MANF admin by intravitreal injection to pigmented rabbits
- Dose level scaled from highest rat ONI dose to rabbit vitreous volume
- Adequate number of animals for pilot ocular tolerance study
- 15-day follow-up
 - ✓ Split lamp examination (McDonald-Shadduck's scale)
 - ✓ General clinical examination; Animal weights
 - ✓ Histopathology at Day 15
- No treatment- or administration-related effects on body weight, clinical observations or ophthalmic examinations
- No pathological findings related to treatment in any of the eyes observed during histopathology evaluation.

A single intravitreal administration of MANF (300 µg) in pigmented rabbits was macroscopically and microscopically very well tolerated

MANF Summary

- Protein drug with breakthrough biology
- Conserved structure and biology
- Counteracts cellular stress
- Prevents retinal degeneration in models of retinitis pigmentosa
- Provides functional benefit in optic nerve ischemia model
- Safe and well tolerated in pilot ocular tolerance study
- Poised to initiate manufacturing and to move into IND enabling