



MOTOR NEURON CENTER



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Vision and Objectives

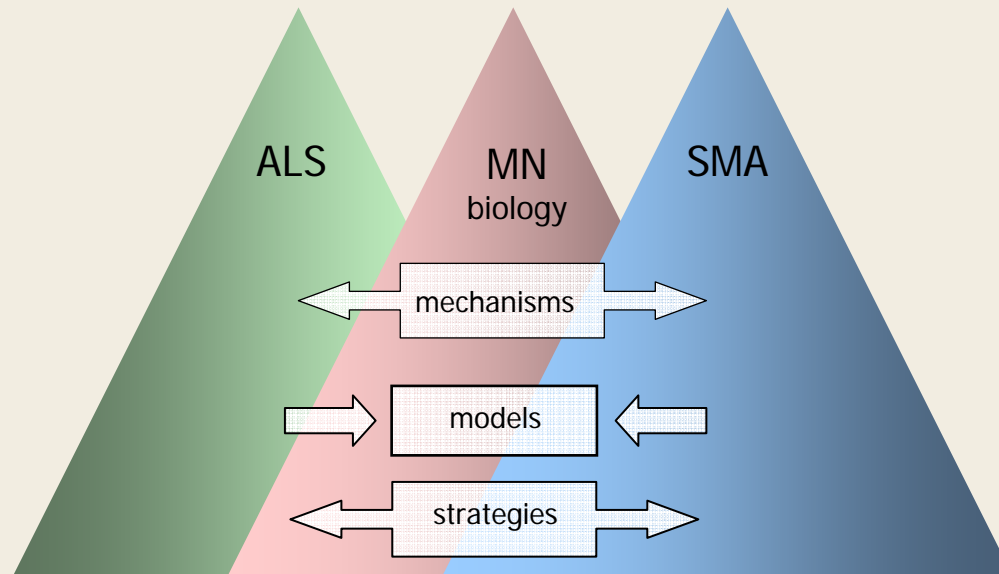
Darryl De Vivo
Christopher E. Henderson
Serge Przedborski



MOTOR NEURON CENTER



Columbia University Center for Motor Neuron Biology and Disease



Translational continuum from basic biology to clinic

Joint research and clinical space

Outreach to clinical and scientific communities

Contacts with industry

Benefits for patients and their families



Biologists discover



Clinicians learn

Basic motor neuron biology



Molecular mechanisms



Cell and animal models of disease



Therapeutic strategies

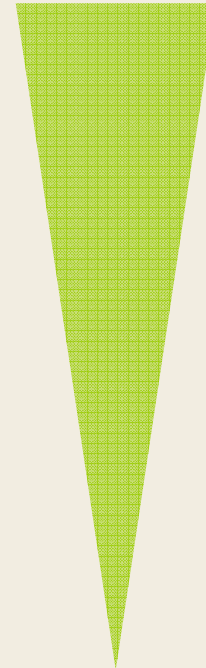


Clinical research



Clinical trials

Biologists learn



Clinicians discover

Week by week at West 168th Street....



Of mice and men: new approaches to a well-established ALS model

Cellular mechanisms

Protein dimerization/aggregation
Oxidative stress and cell death*
Mitochondrial site of action
Role of astrocytes

Disease progression in CNS

Corticospinal degeneration*
Motor control*
Spinal cord imaging*

SOD1 mutant mice
Model for familial ALS

** both mice and men*

Disease mechanisms
Preclinical testing

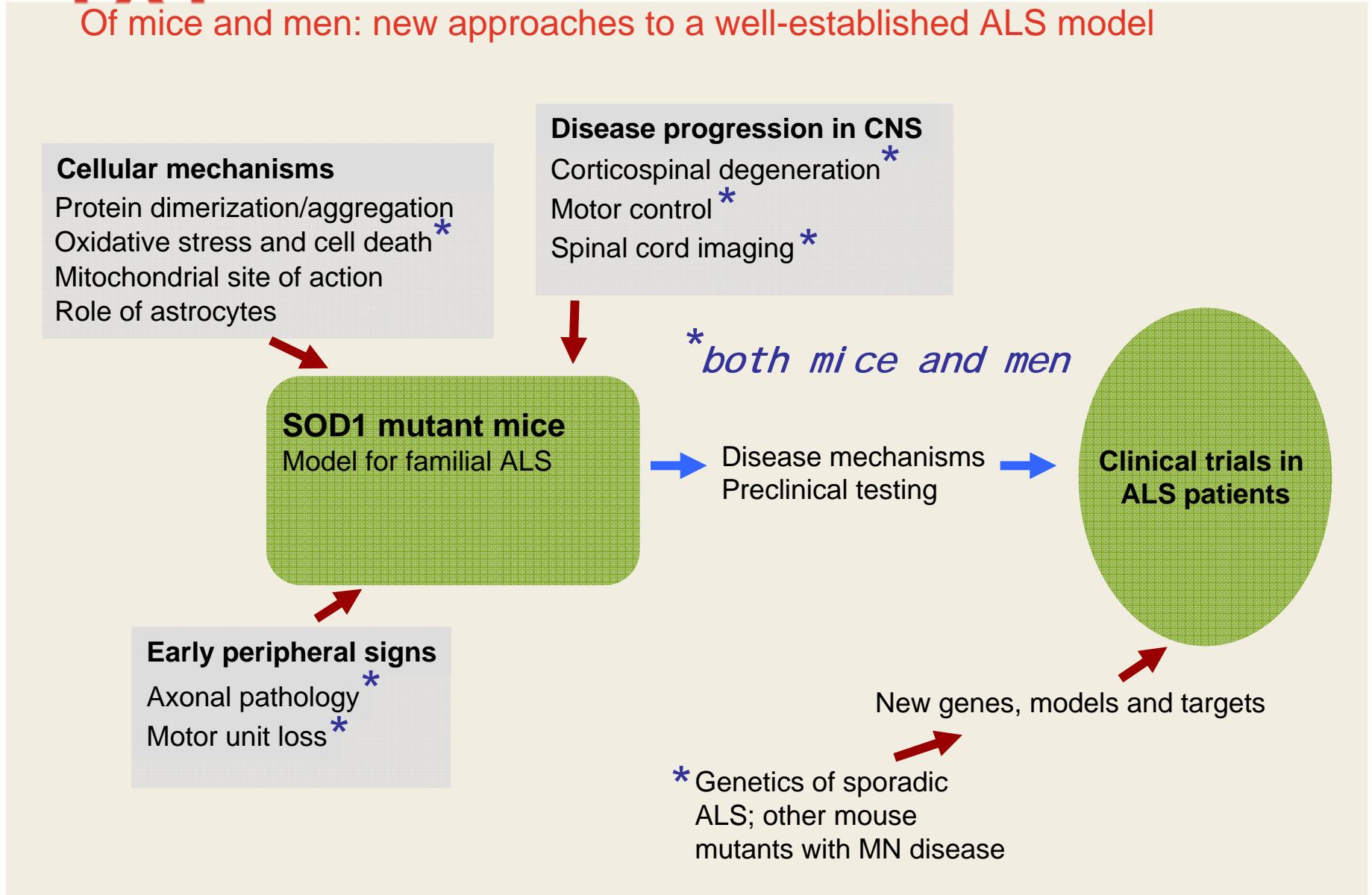
Clinical trials in ALS patients

Early peripheral signs

Axonal pathology*
Motor unit loss*

New genes, models and targets

* Genetics of sporadic ALS; other mouse mutants with MN disease





SMA: animal models representative of all patients

Developmental biology

Motor neuron subtype specification
Axonal guidance and growth
Cell death pathways
RNA maturation in the developing CNS
Axonal functions of SMN
Invertebrate mutants for *smn*



SMA model mice

Human SMN2 expressed on a null background for mouse *smn*



Disease mechanisms
Preclinical testing



**SMA
clinical trials**



Therapeutic strategies

Upregulate SMN2 gene
Correct SMN2 splicing defect
Stabilize synapses
Compensate loss of cholinergic synapses



The Translational SMA Program at Columbia

Input from SMN biology and motor neuron biology
(Jessell, Manley, McCabe, Henderson, Wichterle)

Chemical libraries
(Stockwell, Henderson)

Primary MNs
Wildtype rodents
(Przedborski, Henderson)

Gain-of-function cDNA libraries
(McCabe; MNC Screening Facility)

Primary MNs
SMA mice
(Henderson, Monani)

SMA mice
Burghes model
(Monani, Fischbach, Jessell)

Loss-of-function shRNA
(Stockwell, Scheiffele)

SMA mouse ES-MNs
(Wichterle, Monani, Henderson)

SMA mice
New model
(MNC Animal Core; collabn. SMAF)

Human SMA ES-MNs
(Wichterle, Henderson)

Flies, worms
(McCabe, Hobert)

Compounds and genes from external SMAF partners

Human SMA
Fibroblasts, lymphoid cells
(Chung, Jessell)

Cellular and genetic characterization of disease process

Preclinical testing
(under development)

Clinical research
(De Vivo, Kaufmann, Chung, Hays, Gooch)

Functional testing
Spinal cord imaging
Surrogate markers

SMA clinical trials
(De Vivo, Kaufmann, Chung, Pascual)

Collections to be screened

SMA-related screenable cell phenotype



The Translational ALS Program at Columbia

Chemical libraries
(Stockwell, Henderson)

Gain-of-function cDNA libraries
(McCabe; MNC Screening Facility)

Loss-of-function shRNA
(Stockwell, Scheiffele)

Compounds and genes from external partners

Collections to be screened

Primary MNs
Wildtype rodents
(Przedborski, Henderson)

Primary MNs
SOD1 ALS mice
(Henderson, Przedborski)

SOD1 mouse ES-MNs
(Wichterle, Przedborski, Jessell, Henderson, Kottmann) collabn. Maniatis, Harvard

Human ALS Stem cell-derived MNs
(Wichterle, Henderson, Christiano, Doetsch) collabn. Eggan, Harvard

ALS-related screenable cell phenotype

ALS mice
Mutant SOD1 models
(Przedborski, Henderson)

Other MND mice
(Dauer, Kottmann, Vallee, Liem)

Flies
(McCabe, Mann)

Cellular and genetic characterization of disease process

Input from motor neuron and corticospinal biology
(Jessell, Martin, Krakauer, Liem, McCabe, Schon, Hirano, Henderson, Greene, Troy, Mason, Shapiro)

Preclinical testing
(Przedborski)

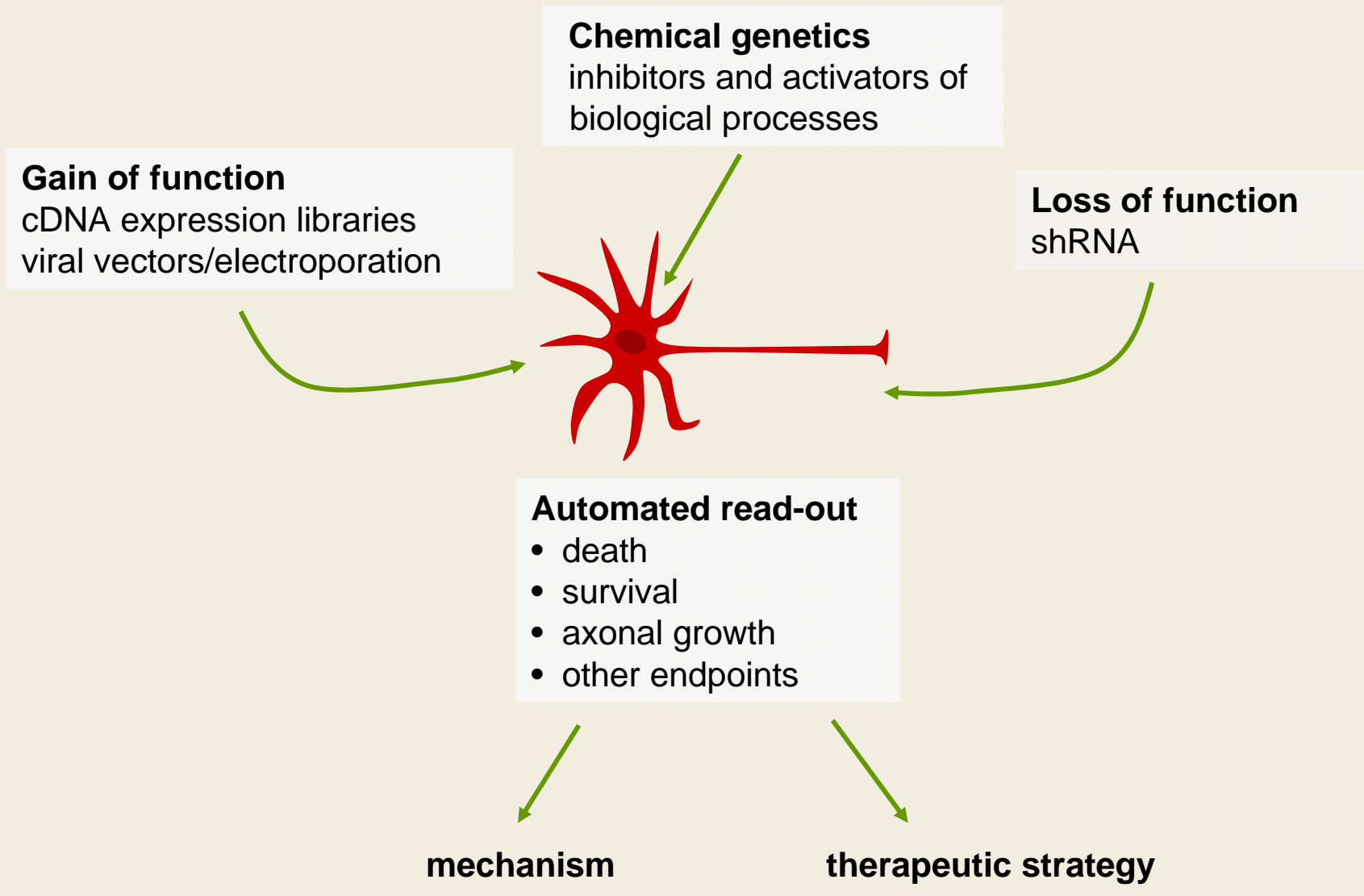
Clinical research
(Mitsumoto, Gordon, Gooch, Hays, Rowland)

ALS genetics
Spinal cord imaging
Surrogate markers

ALS clinical trials
(Mitsumoto, Gordon, Gooch, Rowland)

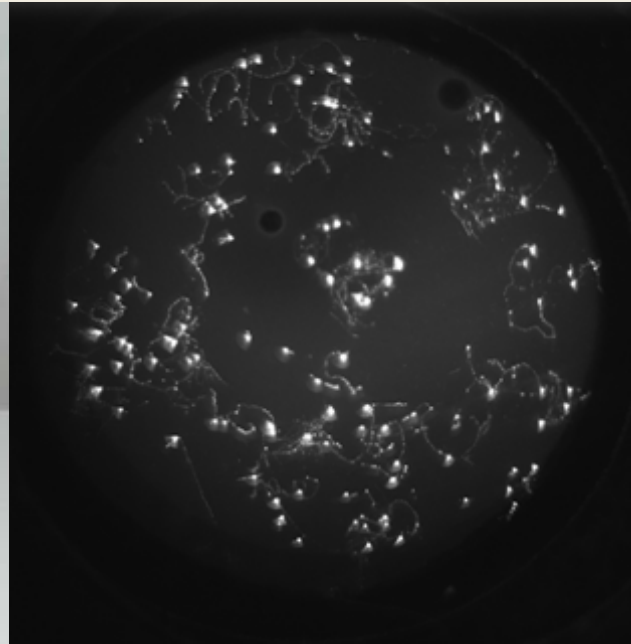


Motor neuron-based screening

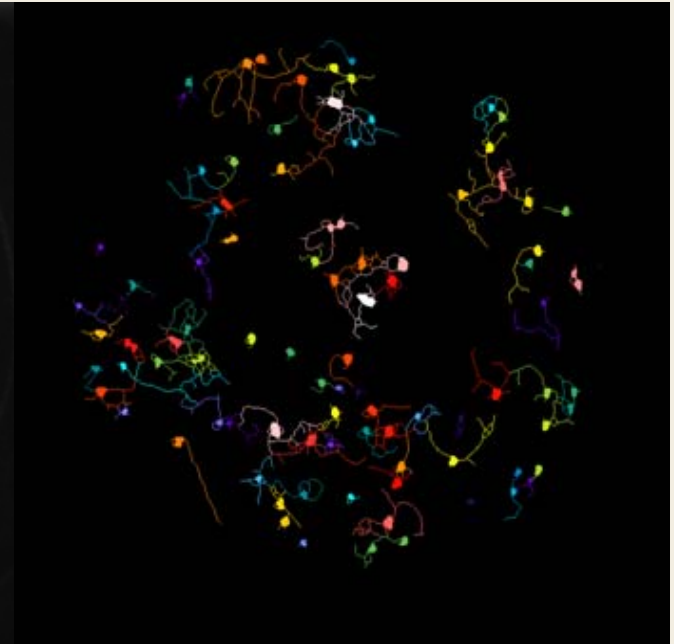




Automated readouts using high-throughput image analysis: the Flash Cytometer



Fluorescent motor neurons

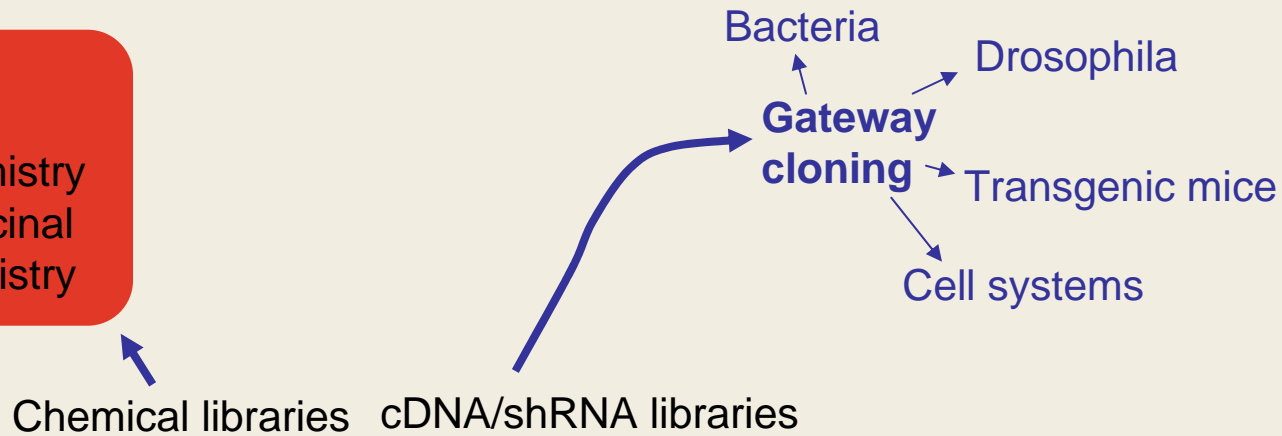


Automatic cell identification and quantification of neurite outgrowth



Screening as a resource for academic and translational research

CU
Chemistry
Medicinal
chemistry



MNC
Neuronal
Screening
Platform

Share libraries & robotics
expertise

Functional hits for profiling

Pathway hits for functional testing

**Genome
Center**
Rothman
Branden



ES cell-derived motor neurons will change the scope and scale of motor neuron biology

Mouse ES-MNs

from HB9::GFP mice
from SMA and ALS model mice
representative of specific motor pools

Human ES-MNs

NIH-approved lines
new cell lines
from SMA and ALS patients

Quantity
Accessibility
Relevance to disease

 cell biology, screening, microarray/proteomics,
regeneration in vivo



THE SCIENCE DRIVES THE STRUCTURE

Research groups with different backgrounds

Need for internal grant system

Cell and animal models of SMA and ALS not easy to set up or access

Need for core facilities and free internal exchange of know-how

Confront new strategies and data with CU and external expertise

MNC meetings and seminars

Internal and external advisory boards



THE SCIENCE DRIVES THE STRUCTURE

MNC success requires strong relationships with patients, their families and associations, other funding agencies and the outside world in general

Need for clear, shared vision and image



GRANTS, CORE FACILITIES

Internal Review Committee:

Competitive internal funding for collaborative (2 or more PIs), translational projects in areas relevant to motor neuron biology and disease: up to 3-year starter grants, milestone-driven

Competitive start-up funding for MNC core facilities: continued support conditional on success as measured by CU and external usage



MEETINGS, SEMINARS

Monthly MNC Meetings for all lab members: two speakers, one clinical and one basic

Monthly MNC Seminars for external speakers

MNC Sabbatical Visit Program



MOTOR NEURON CENTER

YELLOW PAGES REPORTS & FORMS FUNDING



ABOUT US MEMBERS EVENTS NEWS & FEATURES MONTHLY MEETINGS SEMINAR SERIES JOBS MNC SUPPORT

MOVING LIVES. Columbia's Motor Neuron Center will transform our understanding of human health. For the first time, brilliant scientific minds are working together in a common approach to currently incurable motor neuron diseases: spinal muscular atrophy (SMA) in children and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) in adults. New discoveries in the field of motor neuron biology will fuel the search for effective therapy for patients.



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Research Support

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Muscular Dystrophy Association
Wings over Wall Street
ALS Association
NYSTAR
NINDS

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