Behind the lab coat: How medical research really works

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Foundation for Peripheral Neuropathy, March 2026

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Peripheral Nervous System (PNS):

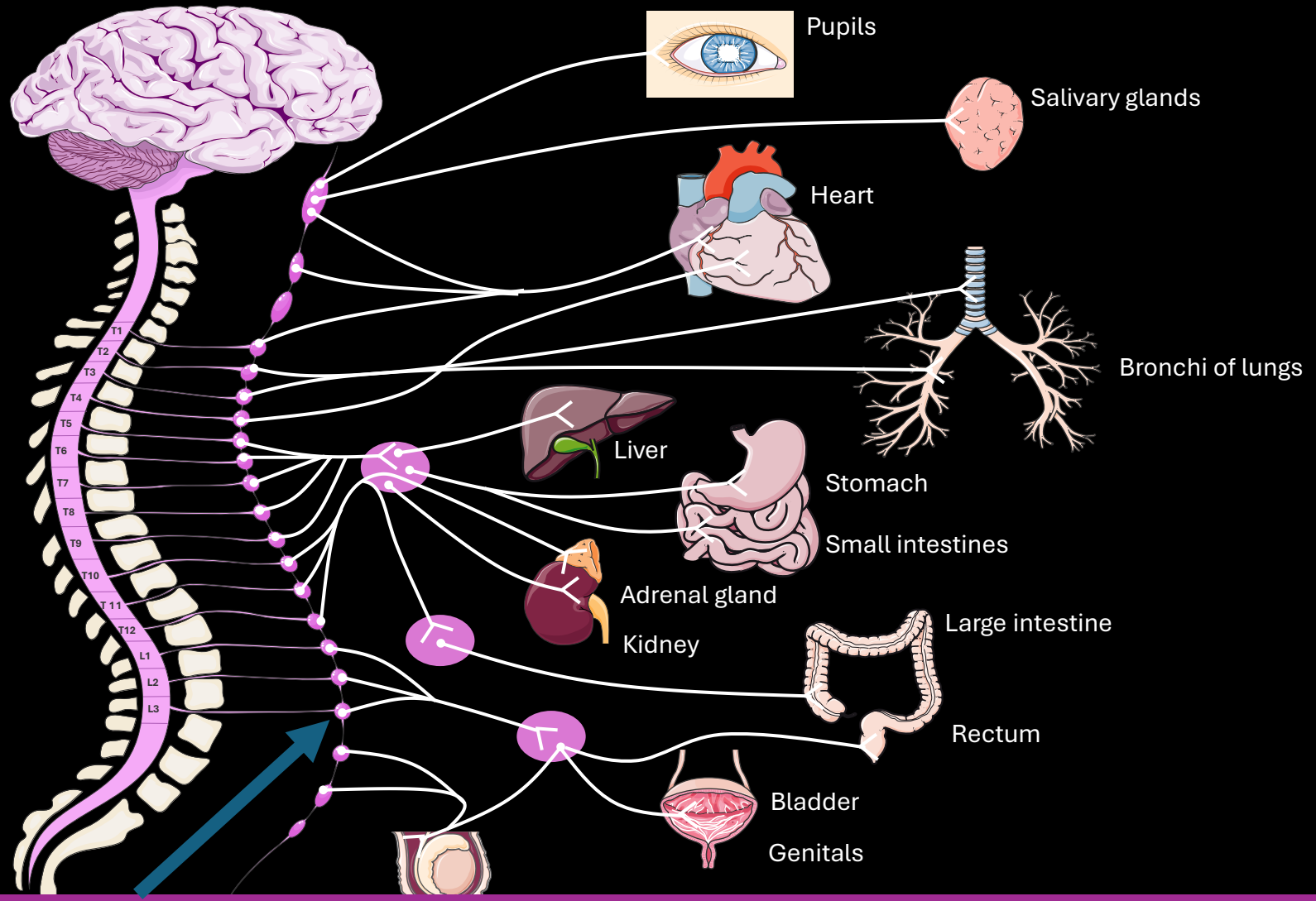
-- Peripheral nerves enable bi-directional neural communication between the brain & tissues and organs

Efferent nerves:

from brain to tissues
(ex: sympathetic)

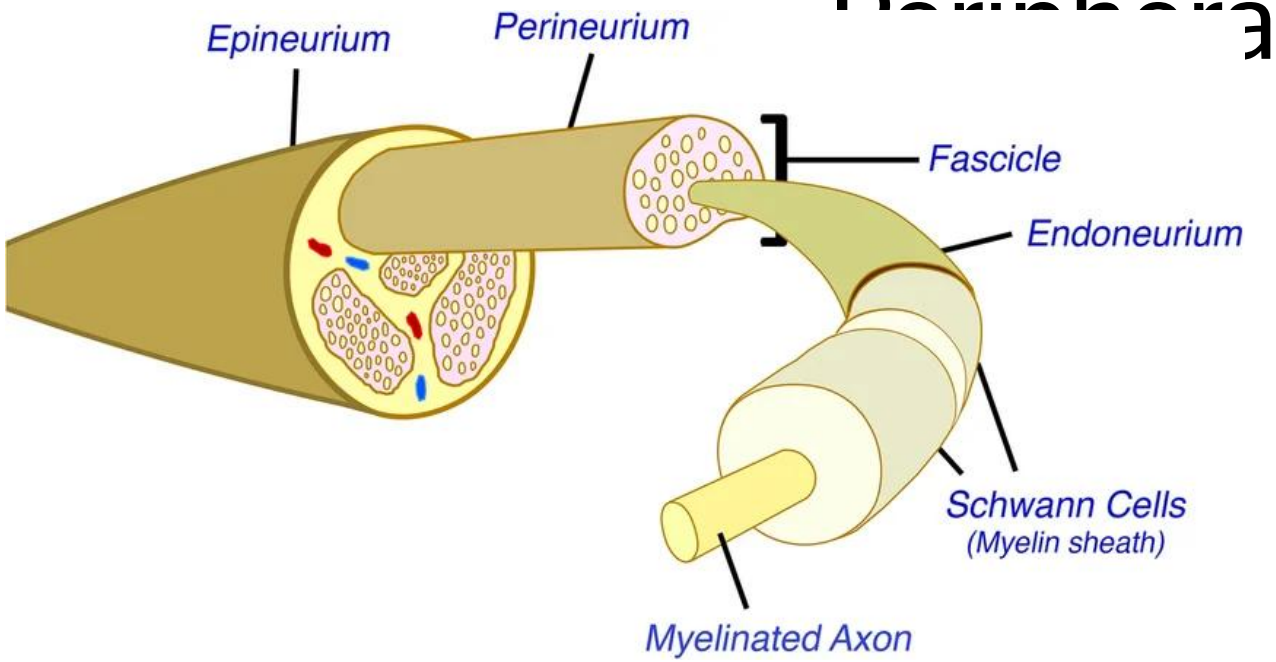
Afferent nerves:

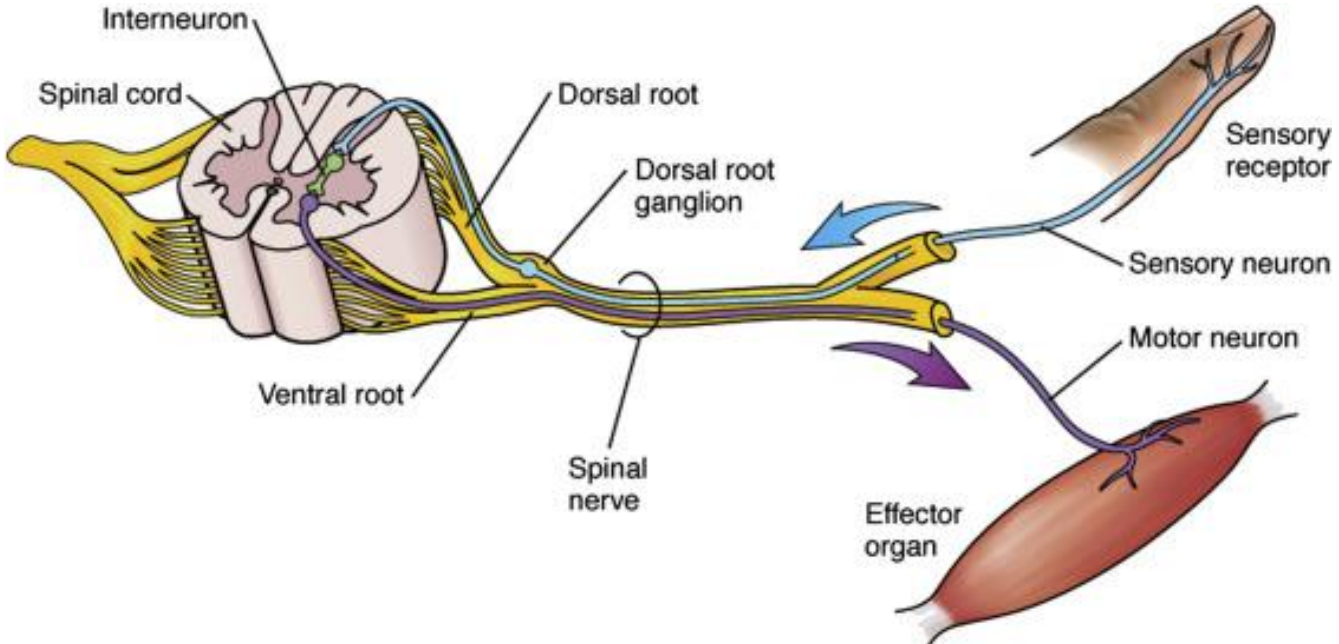
from tissues to brain
(ex: sensory)

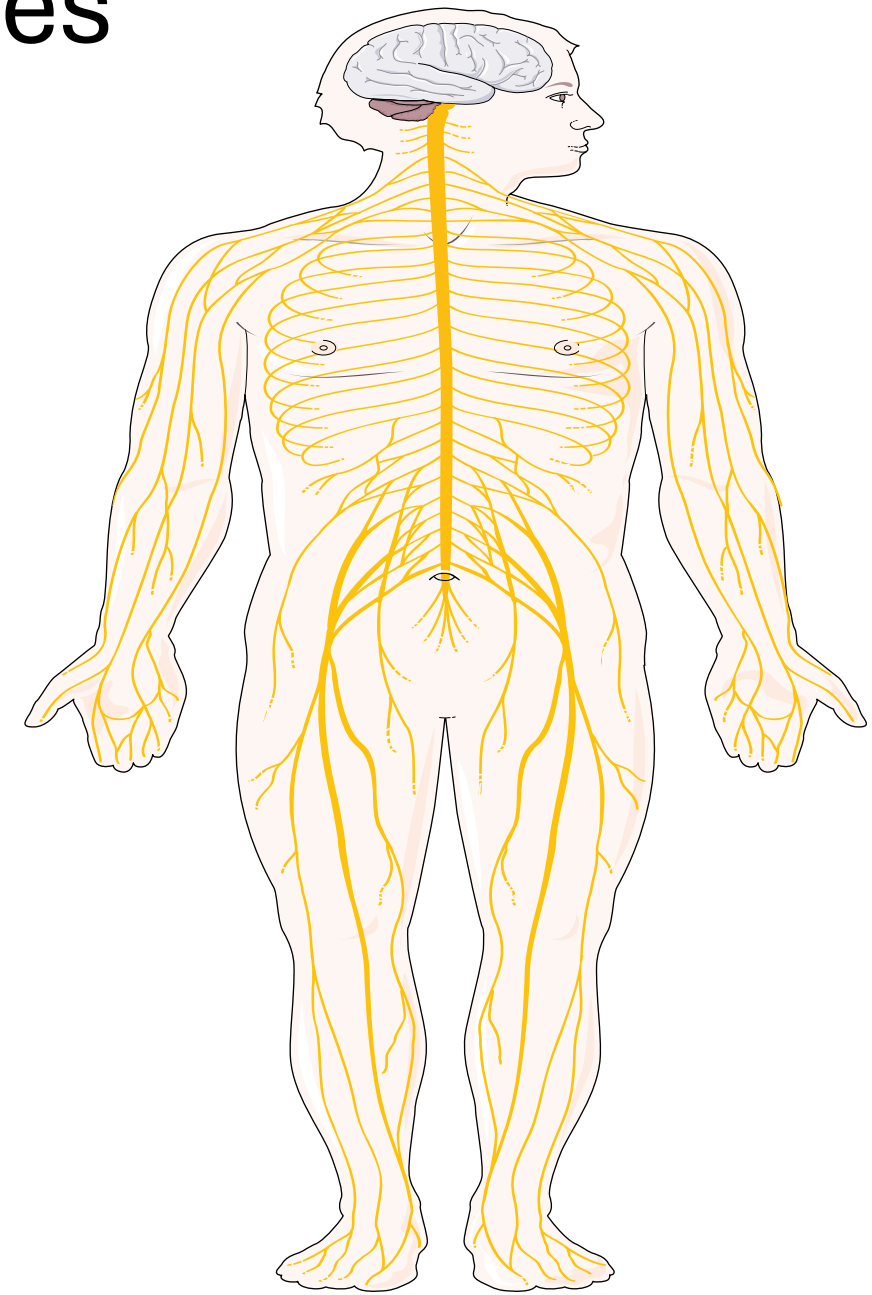


Cell bodies of peripheral nerves mostly reside in ganglia outside the spine, long axons reach out to the tissues and organs

Peripheral Nerves







Peripheral Neuropathy (PN)

- **Degeneration of peripheral nerves** → loss of innervation and blunted neural communication between tissues and brain (often length-dependent)

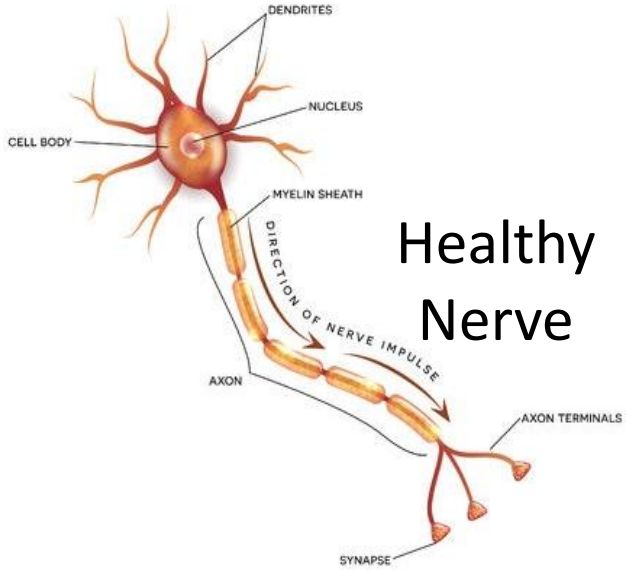
- Affects **~30+ million adults** in the United States
  - 13.5% of persons over 40 *(Hicks et al…Selvin, Sci Rep, 2021)*

- Variety of etiologies – including **metabolic (top cause)**
  - Affects **up to 70% patients with diabetes** eventually
  - Can manifest early in the **pre-diabetes stage**
  - **Obesity -**associated PN
  - **Aging-**associated PN (under-studied), associated with age-related metabolic disease

- Key symptoms – motor, sensory, autonomic nerves can be affected:
  - ➢ Numbness, tingling, burning, **pain**
  - ➢ Loss of sensory, autonomic and motor functions
  - ➢ Can lead to ulcers, fall fractures, foot amputation, **significantly worsened quality of life**

- **Often goes undiagnosed (80%)** *(Rodriguez-Saldana et al…Weiser, Curr Med Res Opin, 2024)*

- Treatments address symptoms, ***no therapies*** to reverse nerve degeneration or regrow axons, **no cure**



Healthy Nerve

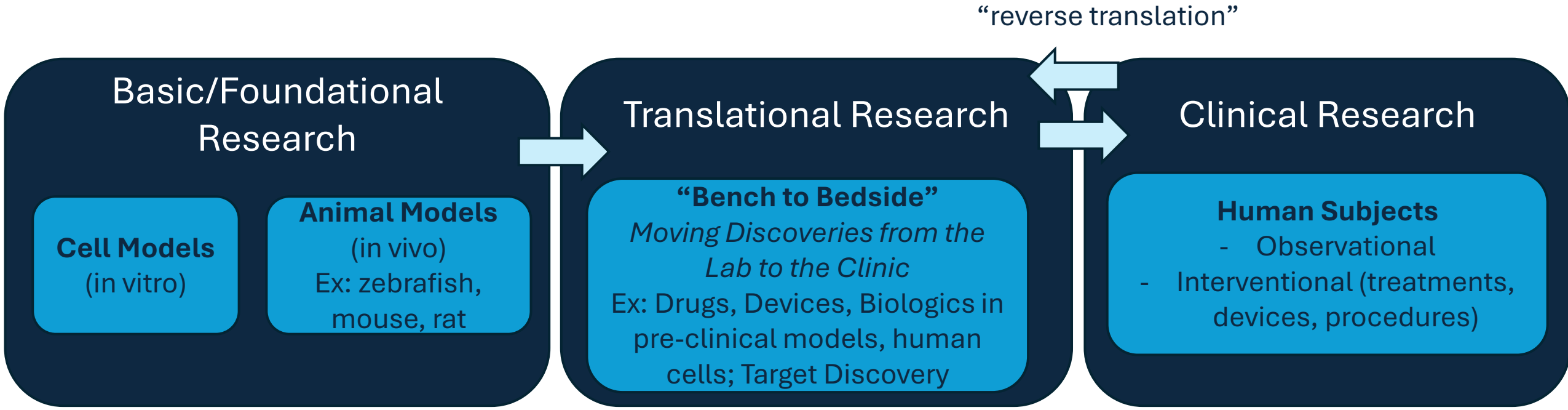
Damaged myelin sheath; axon degradation

Unhealthy Nerve

Research is Required to Improve Diagnosis and Treatment of Neuropathies

Townsend Lab for Neurobiology & Energy Balance

Understanding Peripheral Neuropathy Through Translational Research



~~How do peripheral nerves function~~ when they're healthy, across the body?
What happens to cause death of peripheral nerves with disease?
What helps nerves regenerate and regrow?

~~Is this treatment or device safe and~~ effective, before we try it in humans?
Does the mechanism of action point to a targetable protein?

~~Research across T0-T4~~

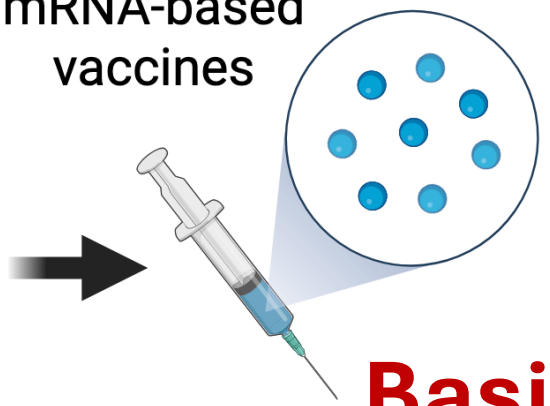
- First in Human
- Clinical Studies
- Clinical Trials; Phase 1-4

Basic/Foundational Research:

- We study:
  - How the sensory nerves in our fat (adipose) tissue function
  - How lipids impact peripheral nerve activity
  - How support cells help peripheral nerves function (ex: immune cells, glia)
  - And More…

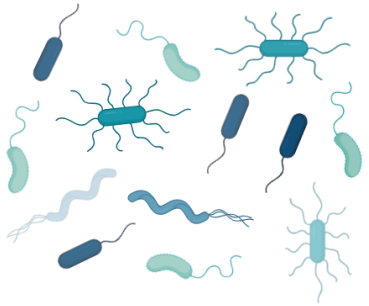
mRNA-based vaccines

mRNA



Basic/Foundational Research: Long Term Impacts for Human Health are Plentiful, but Challenging to Predict

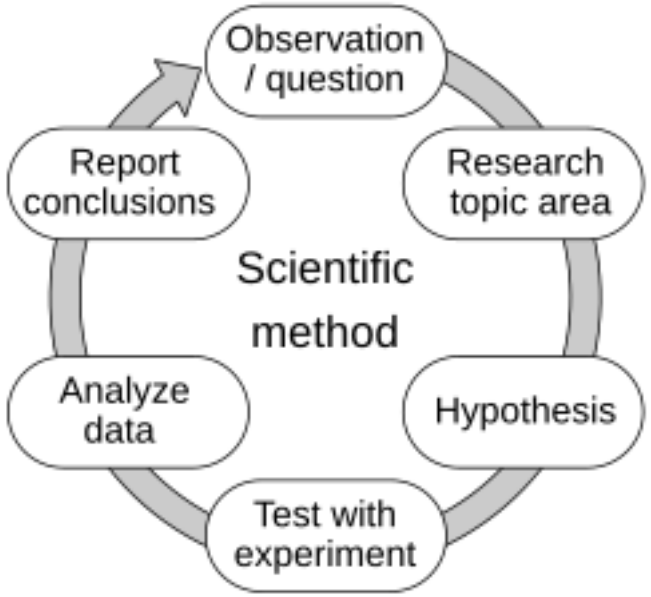
CRISPR-Cas9 in bacteria

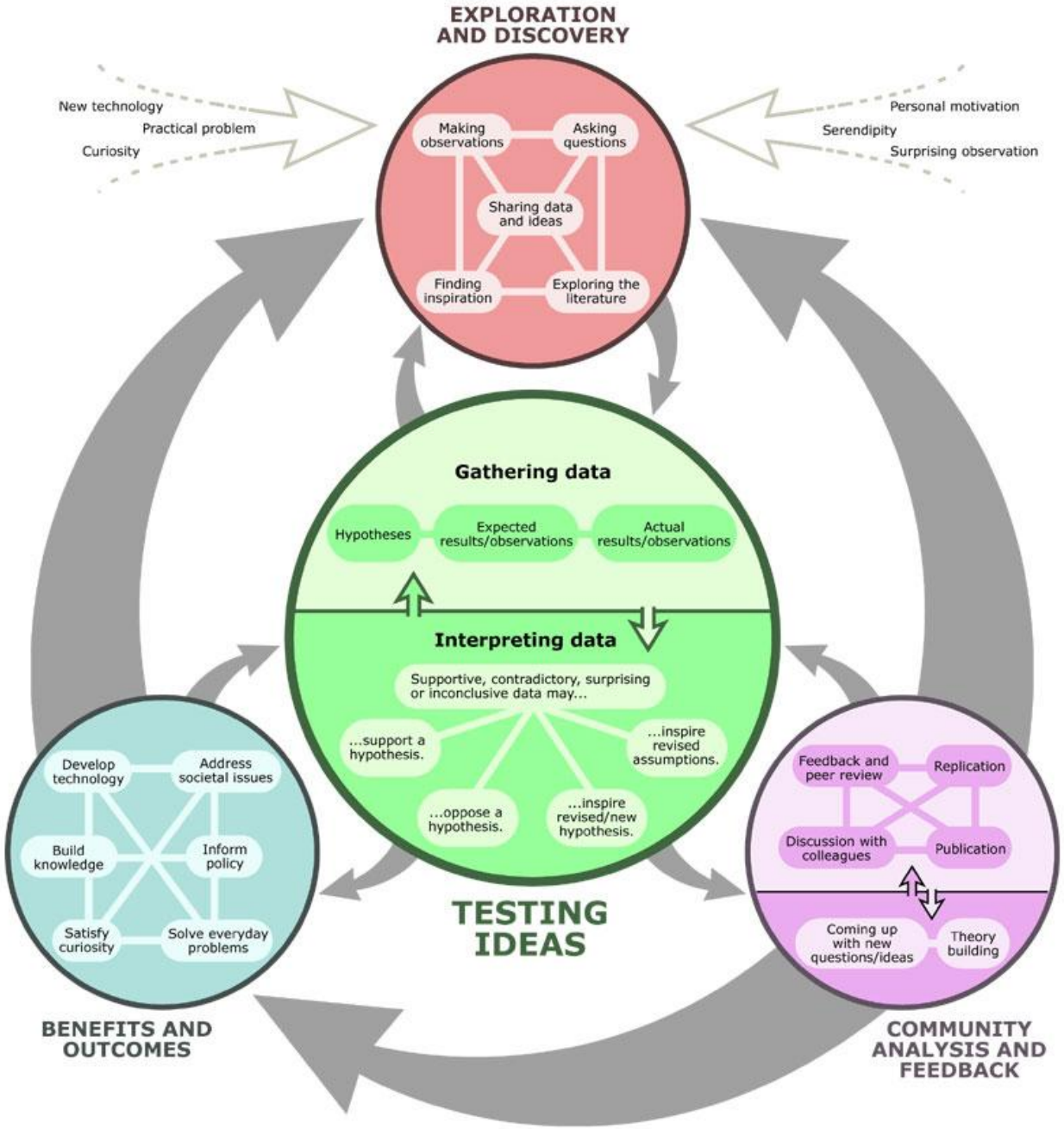


CRISPR-based gene editing

How it works...

1) The Scientific Method





https://usef.utah.edu/resource-center/the-scientific_method

2) Designing rigorous experiments to gain evidence-based insights

- “Powering” the study – enough data points to interpret with biostatistics?
- A priori experimental plans, statistics plans
- Optimized protocols and SOPs
- Validated research tools
- Which model? (even if mouse or rat, which strain/genotype?)
- How/what to phenotype or assess? Primary vs secondary outcomes
  - Functional neuropathy tests
  - Validated clinical scales or questionnaires
  - Molecular assessments (ex: skin punch)
  - Etc…

How it works…

3) Peer-Review to Dissemination

- Peer reviewed journals (avoid predatory journals)
- “Impact Factor” of the journal title
- “Open Access” articles
- Altmetrics and citation index
- Press coverage

How it works…

4) Reproducibility

- Across experimental sites, labs, or population groups…can the work be reproduced and replicated?
- (Importance of Methods reported for prior studies)

- Rare instances: retractions or corrections

Healthy Adipose (fat) – Role of Innervation by Sensory/Sympathetic Peripheral Nerves

Nerves

Anti-Tyrosine Hydroxylase

Healthy Adipose – Role of Innervation by Sensory/Sympathetic Peripheral Nerves

Nerves
Anti-Tyrosine Hydroxylase

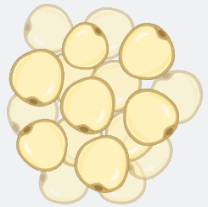
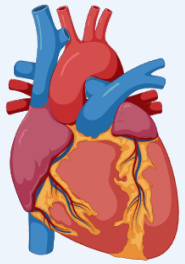
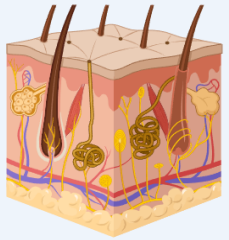
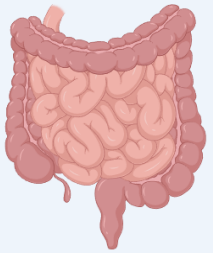
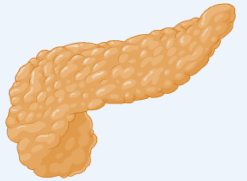
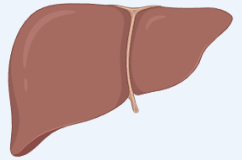
What do nerves in adipose do to contribute to healthy functions?

How does neuropathy in adipose impact our metabolic health?

Does metabolic disease (obesity, pre-diabetes, diabetes, cardiometabolic disease, aging, etc.) impact the function of our nerves?

Broad tissue neuropathy with metabolic disease

Diabetes/Obesity- induced peripheral neuropathy (representative papers cited) :

WAT	Heart	Skin	Muscle	Intestine	Pancreas	Liver
						
Adipose neuropathy PMID: 31509546 PMID: 32699414	Cardiac autonomic neuropathy (CAN) PMID: 30788010	Skin polyneuropathy PMID: 29484103	Neuromuscular junction (NMJ) denervation PMID: 28571613	Gastrointestinal autonomic neuropathy PMID: 32550939	Increased innervation followed by neuropathy PMID: 33036983	Liver neuropathy (sympathetic) PMID: 33545051 PMID: 34290096

Modified from Townsend “One Nervous System”, Diabetes 2025

REVIEW June 2024

CURRENT OPINION

Obesity-related neuropathy: the new epidemic

Melissa A. Elafros[a], Evan Lee Reynolds[b] and Brian C. Callaghan[a]

A Basic Science Finding From Our Lab:
Axon Outgrowth Pathways Impact Adipose Innervation

Take Home Message:
Semaphorin 7a is needed for proper tissue innervation and response of those nerves to stimuli

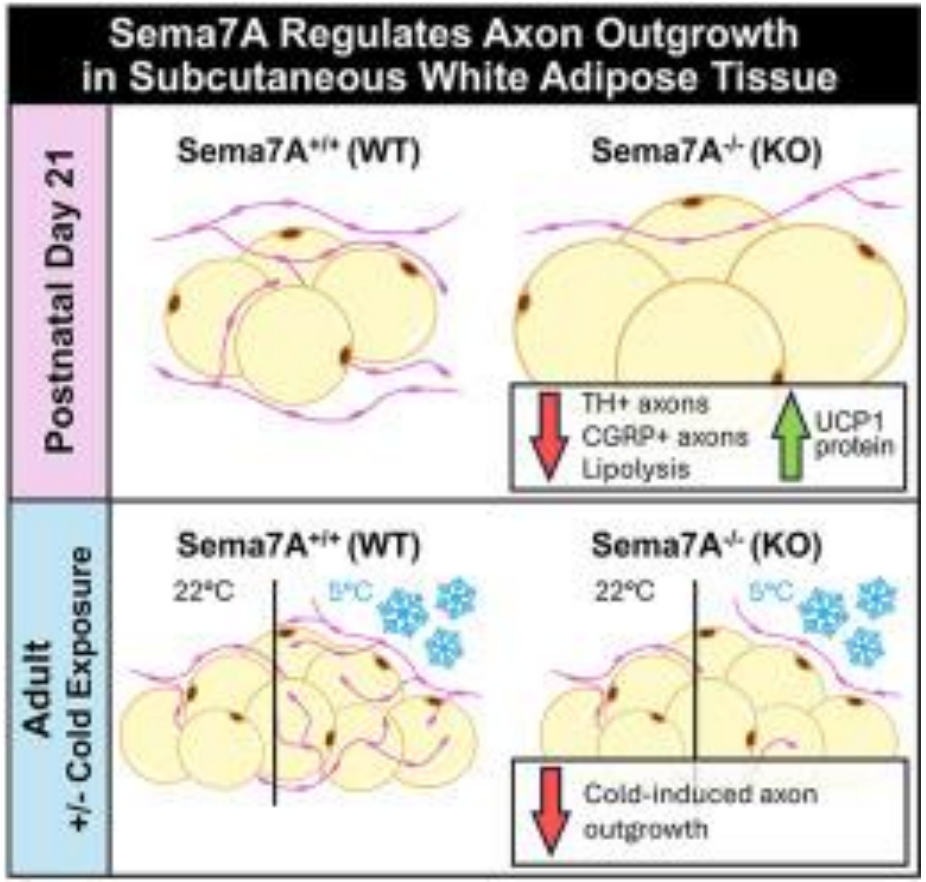
It is a signal that controls axon outgrowth and may be impacted in neuropathy

Brief Communication

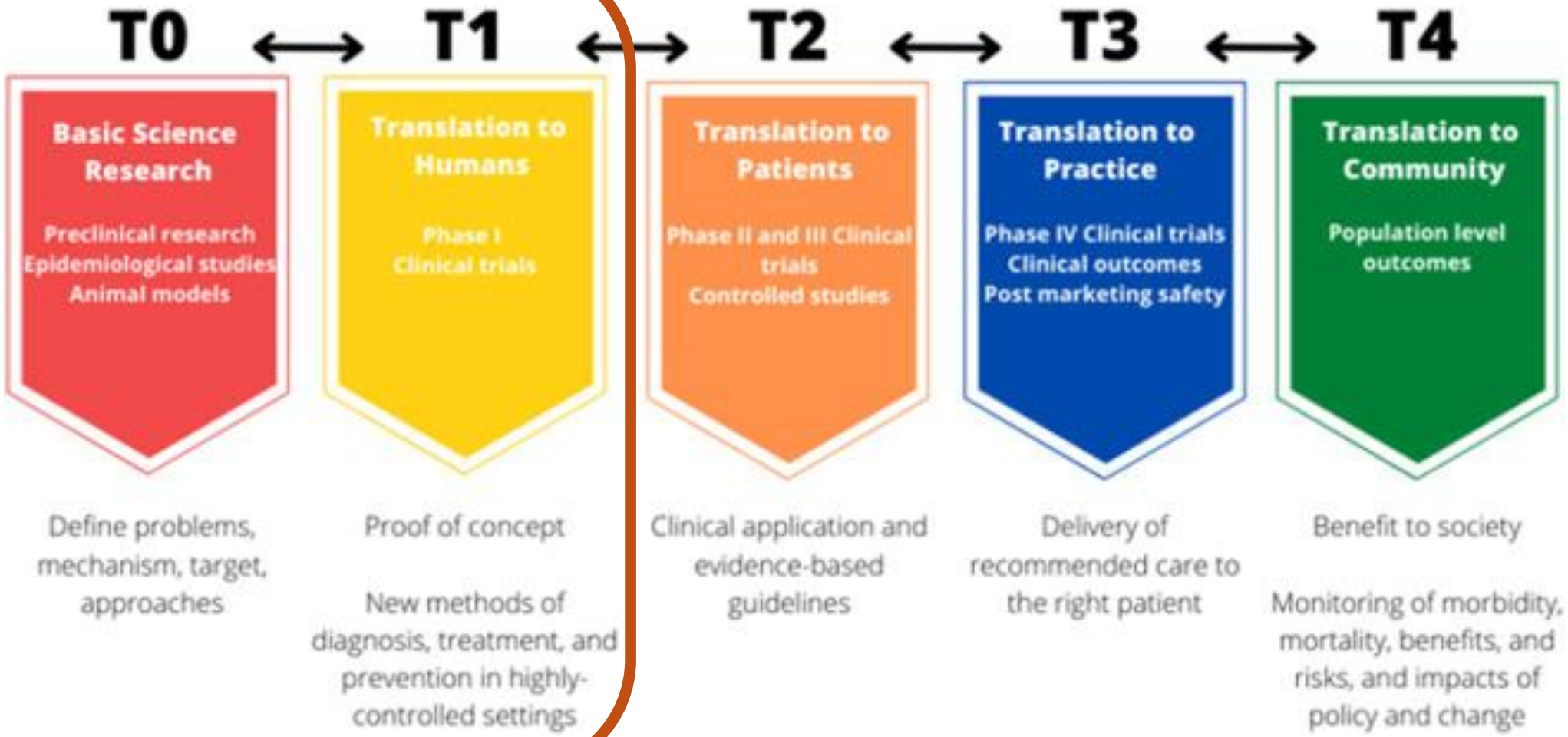
MOLECULAR METABOLISM

Semaphorin 7A regulates axon outgrowth in subcutaneous white adipose tissue 2026

Jake W. Willows[1], Lindsey M. Lazor[1], Gabriela Wandling[2], William Butke[1], Fatma Fenesha[2], Kara N. Corps[3], Sarah B. Peters[2], Kristy L. Townsend[1,*]



Translational Research:



Learn More:
https://ncats.nih.gov/about/about-translational-science

Translational Research:

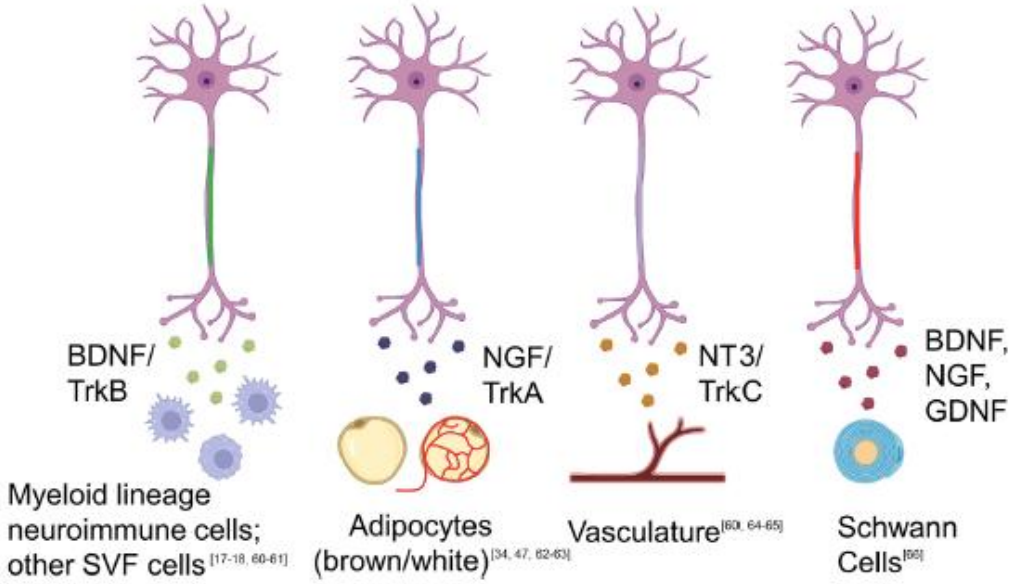
- We study:
  - Mechanistic links between age-related metabolic disease and neurodegeneration with Alzheimer's and Neuropathy
  - Moving new neuropathy biomarkers and treatments from pre-clinical models to human
  - Identifying new pathways impacting peripheral nerves in health vs disease – target discovery for new therapies
  - And More…

Translational Research From Our Lab: Neurotrophic Factors To Improve Tissue Innervation

Neurotrophic factors – growth signals for our peripheral nerves

Can be lost or reduced with neuropathy

Systemic treatment to increase neurotrophic factors in the whole body would not be good (ex: increased pain) → need to target the treatments to the nerve endings (ex: gene therapy)

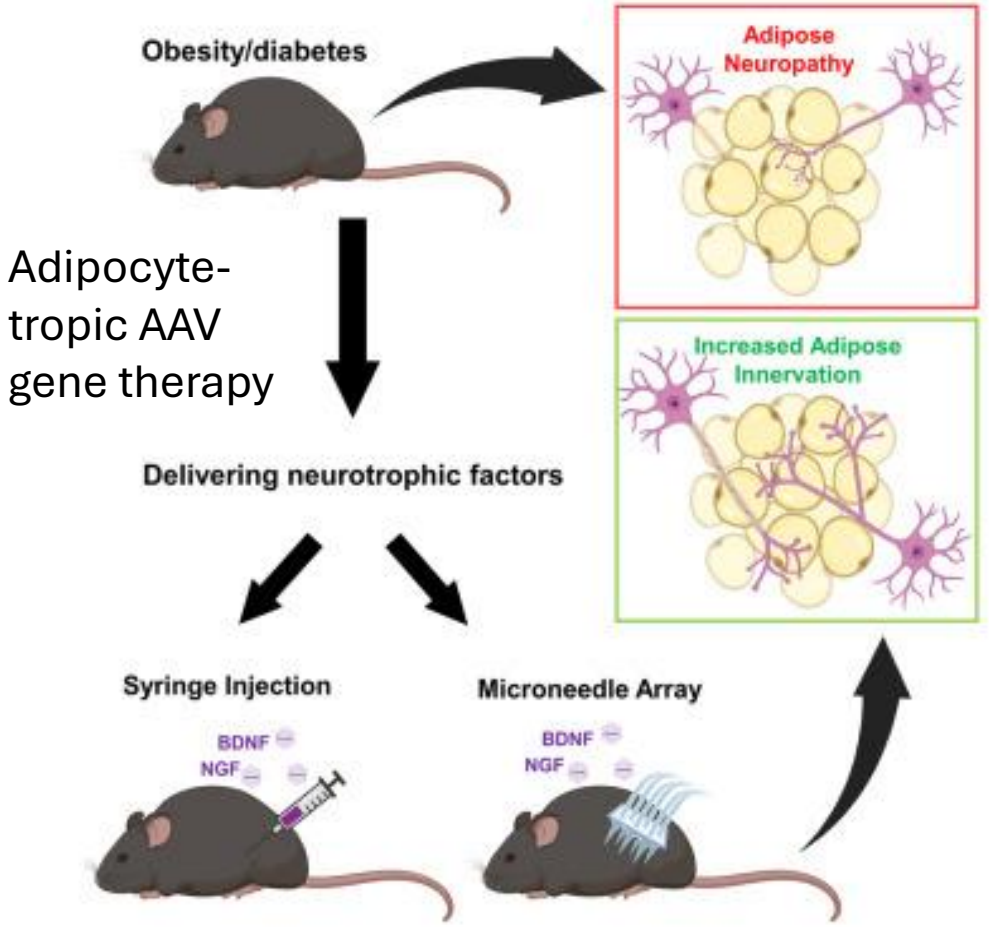


Molecular Therapy
Original Article

2024

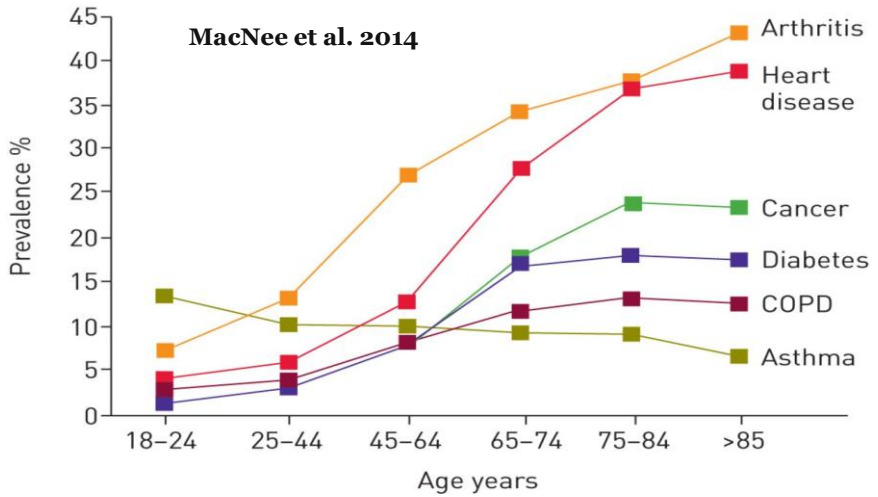
Gene therapy approaches for obesity-induced adipose neuropathy: Device-targeted AAV-mediated neurotrophic factor delivery to adipocytes in subcutaneous adipose

Magdalena Blaszkiewicz,[1] Tianyi Tao,[1] Kofi Mensah-Arhin,[1] Jake W. Willows,[1] Rhiannon Bates,[2] Wei Huang,[2] Lei Cao,[2] Rosemary L. Smith,[3] and Kristy L. Townsend[1,3]



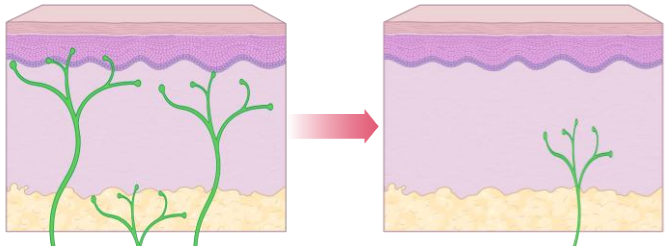
Aging - Numerous Negative Impacts on Metabolic & Nerve Health

Age is the Predominant Risk Factor for Disease



Aging Impacts on Nervous System – beyond the brain

Peripheral Neuropathy



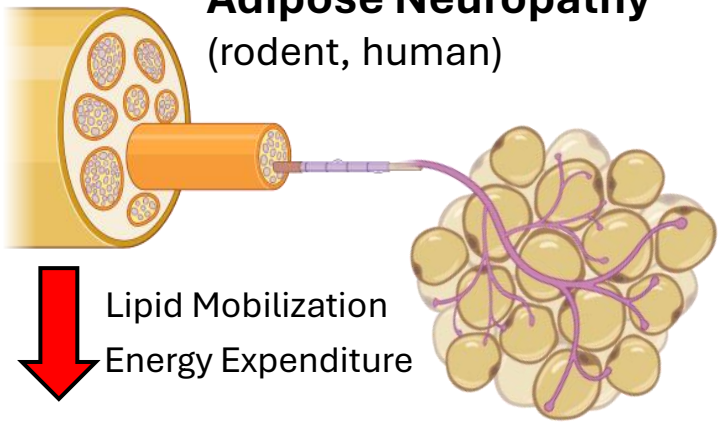
Prevalence of PN 2.4% → to 8% over age 55

(England & Asbury (2004); NHANES & ARIC studies defined PN by monofilament insensitivity, prevalence in US

Aged ≥ 40 13.5%, → as high as 42.4% in

Adipose Neuropathy

(rodent, human)

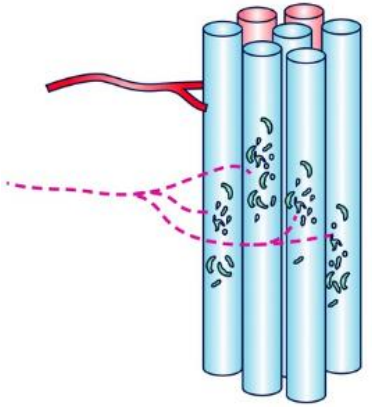


Lipid Mobilization
Energy Expenditure

Blaszkiewicz, et al. 2019 PLoS One

Neuromuscular Denervation

(loss NMJ occupation)



Strength
Coordination
Muscle Mass

Hepple et al. 2016, J Physiol

Pre-Clinical Mouse Models of PN

High fat/high sugar diet-induced, genetic (leptin deficient), aging (HET3), etc. → **multi-tissue** peripheral neuropathy

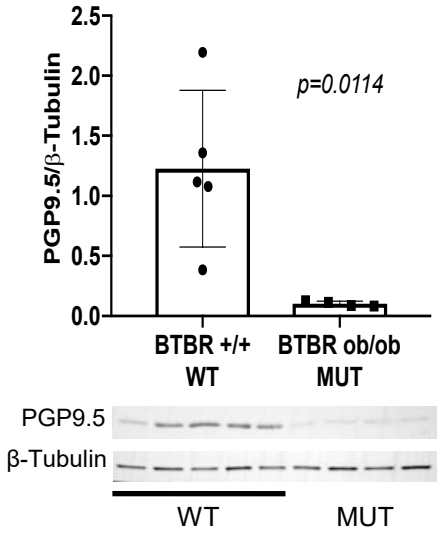
A. Skin - reduced intraepidermal nerve fiber density (IENFD)

B. Loss of occupation of neuromuscular junction (NMJ) of muscle

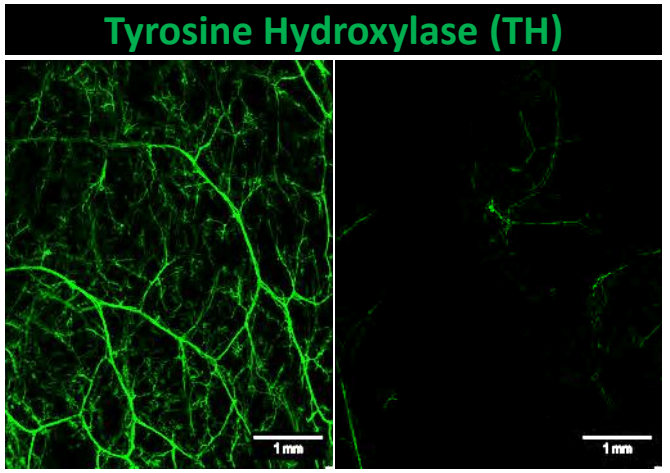
C. Adipose tissue neuropathy

Adipose neuropathy with obesity/diabetes

Inguinal scWAT PGP9.5

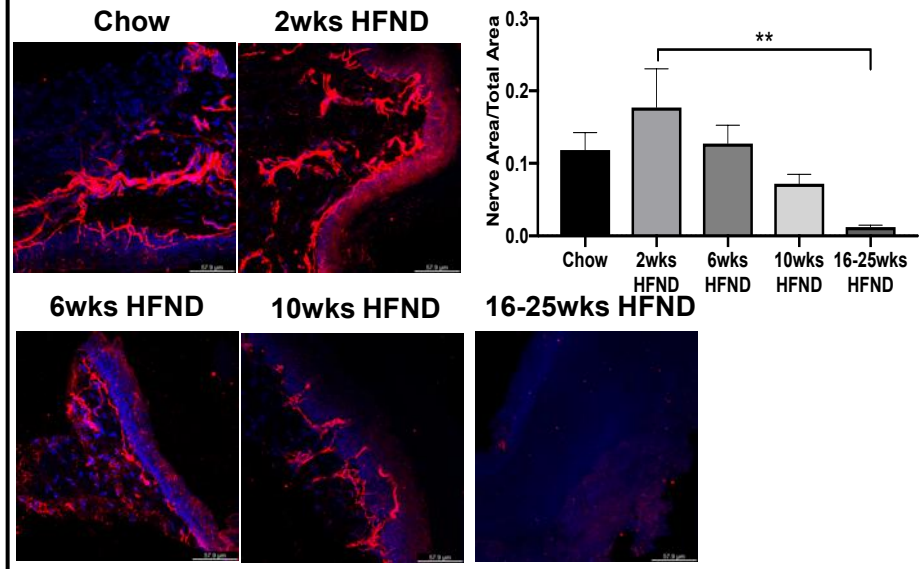


BTBR *ob/ob*: Loss of Small Nerve Fibers



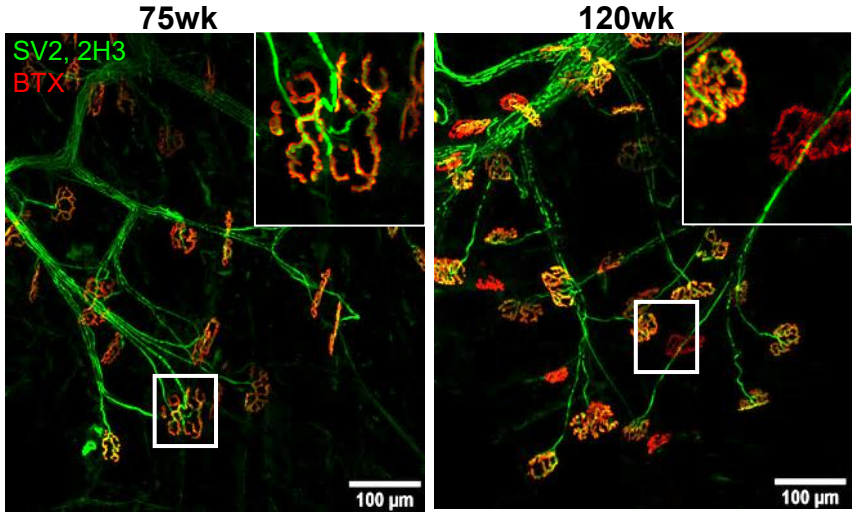
Blaszkiewicz, et al...Townsend, PloS One 2019;
Willows, et al...Townsend, iScience. 2023

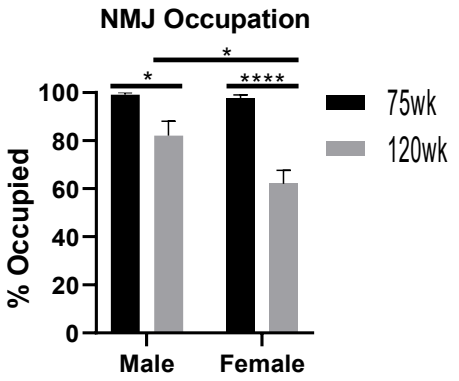
Intra-Epidermal Nerve Fiber Density (IENFD) Staining (PGP9.5)



Blaszkiewicz, et al...Townsend, Front. BioEng. 2025

Neuromuscular Junction (NMJ) Occupation





Willows, et al...Townsend, Aging Cell,. 2023

Longevity Treatments Tested by the National Institute on Aging's Intervention Testing Program (ITP)

Aspirin	Simvastatin	Med. Chain Triglyceride Oil	Metformin
NFP	Resveratrol	**17α-Estradiol**	**Protandim**
NDGA	**Rapamycin**	Methylene Blue*	INT-767
4-OH-PBN	Oxaloacetic Acid	**Acarbose****	HBX
CAPE	Green Tea Extract	Fish Oil	UDCA
Enalapril	Curcumin	**Supplemental Glycine**	Bile Acids
TM5441	Insulin	17-DMAG	MitoQ
Minocycline	B-GPA	MIF098	Nicotinamide riboside
Canagliflozin	Candesartan Cilexetil	Geranylgeranyl Acetone	Hydrogen Sulfide
1,3-butanediol	**Captopril**	L-Leucine	PB125
Sulindac	Syringaresinol	Astaxanthin	Dimethyl Fumurate
Meclizine	Mycophenolic Acid	4-Phenylbuturate	Hydrogen Sulfide
16 alpha-hydroxyestradiol	2,4,-Dinitrophenol	Hydralazine	Nebivolol
Sodium Theosulfate			

NIH: National Institute on Aging – Compounds in Testing

*MP no effect on median LS but increase max LS in females only
**Acarbose – improves health and lifespan, Male and females

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Sodium Theosulfate			

We *consistently* see female mice protected from neuropathy phenotypes compared to males until late age. Female neuropathy is worse after reproductive senescence and loss of estrogens; or mouse 'menopause'.

Is estrogen protective for metabolic *and* nervous system health?

Can we target a *safe estrogen signaling axis* for treatments in males and females?

Translational Research – underway in our lab.

NIH: National Institute on Aging – Compounds in Testing

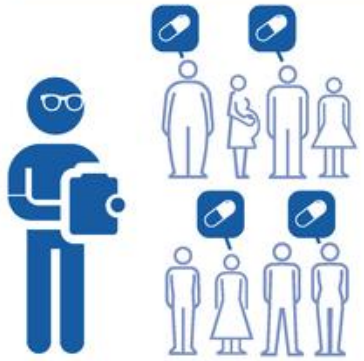
*MP no effect on median LS but increase max LS in females only
**Acarbose – improves health and lifespan, Male and females

Clinical Research:

What is the main difference between the types of clinical research studies?

The main difference is if researchers assign participants to get an **intervention**, such as a drug, behavior, or medical device.

Clinical trial



In **clinical trials**, researchers do **assign participants** to one or more interventions.

Sometimes, researchers randomly assign participants to interventions.

Observational study

In **observational studies**, researchers **do not assign** participants to an intervention.

If there is an intervention, participants were already using it as part of their regular health care or daily life.

+ Medical Record/ Data Research

Source: NIH

Who does the research and who funds it?

Clinical Research:

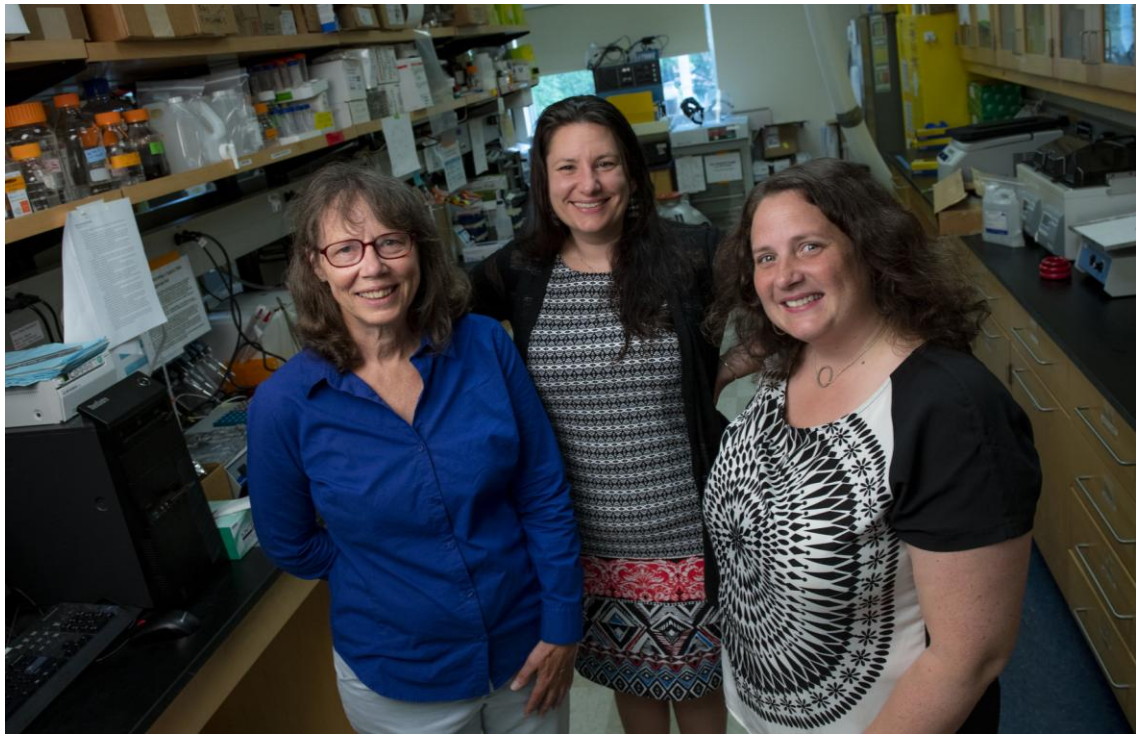
- We study:
  - How does fat (adipose) tissue impact nerve health, such as with nerve repair surgeries?
  - Is there neuropathy in adipose of humans with metabolic disease, like we see in mouse?
  - Can we more effectively diagnose small fiber neuropathies, and can spinal cord stimulation help regenerate axons?
  - And more…

Compliance and Regulatory Safeguards for Clinical Research

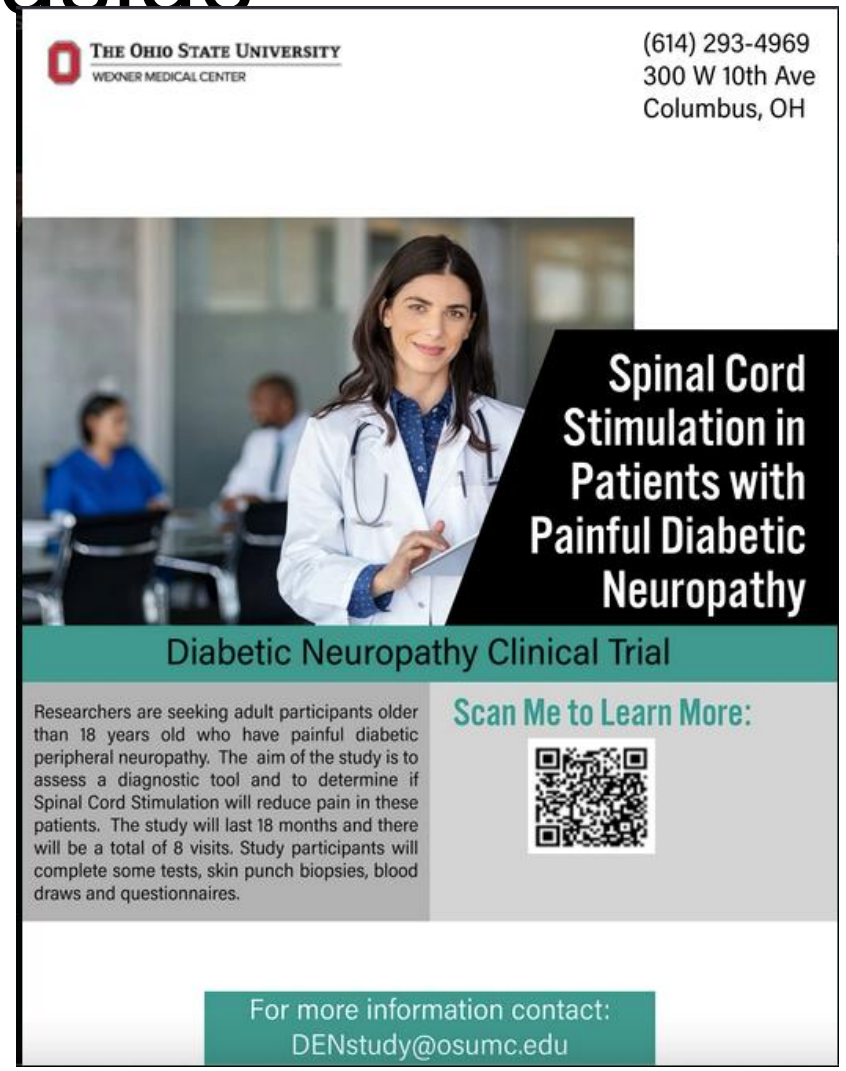
- **Institutional Review Board (IRB) -** formally designated to review and monitor biomedical research involving human subjects (IRB protocols)
- **Informed Consent -** provider explains what the intervention/process is, what it can do and what risks it may have. You get to ask questions, and can give or decline your consent.
- **HIPAA -** a law, called the Health Insurance Portability and Accountability Act of 1996 (HIPAA), gives you rights over your health information, including the right to get a copy of your information, make sure it is correct, and know who has seen it
- **Food and Drug Administration (FDA) -** responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

Learn More: https://clinicaltrials.gov/study-basics/learn-about-studies
Find a Neuropathy Clinical Trial: https://clinicaltrials.gov/
Glossary: https://clinicaltrials.gov/study-basics/glossary
Your Rights: https://www.hhs.gov/hipaa/for-individuals/guidance-materials-for-consumers/index.html

Diagnostics – from Bench to Bedside

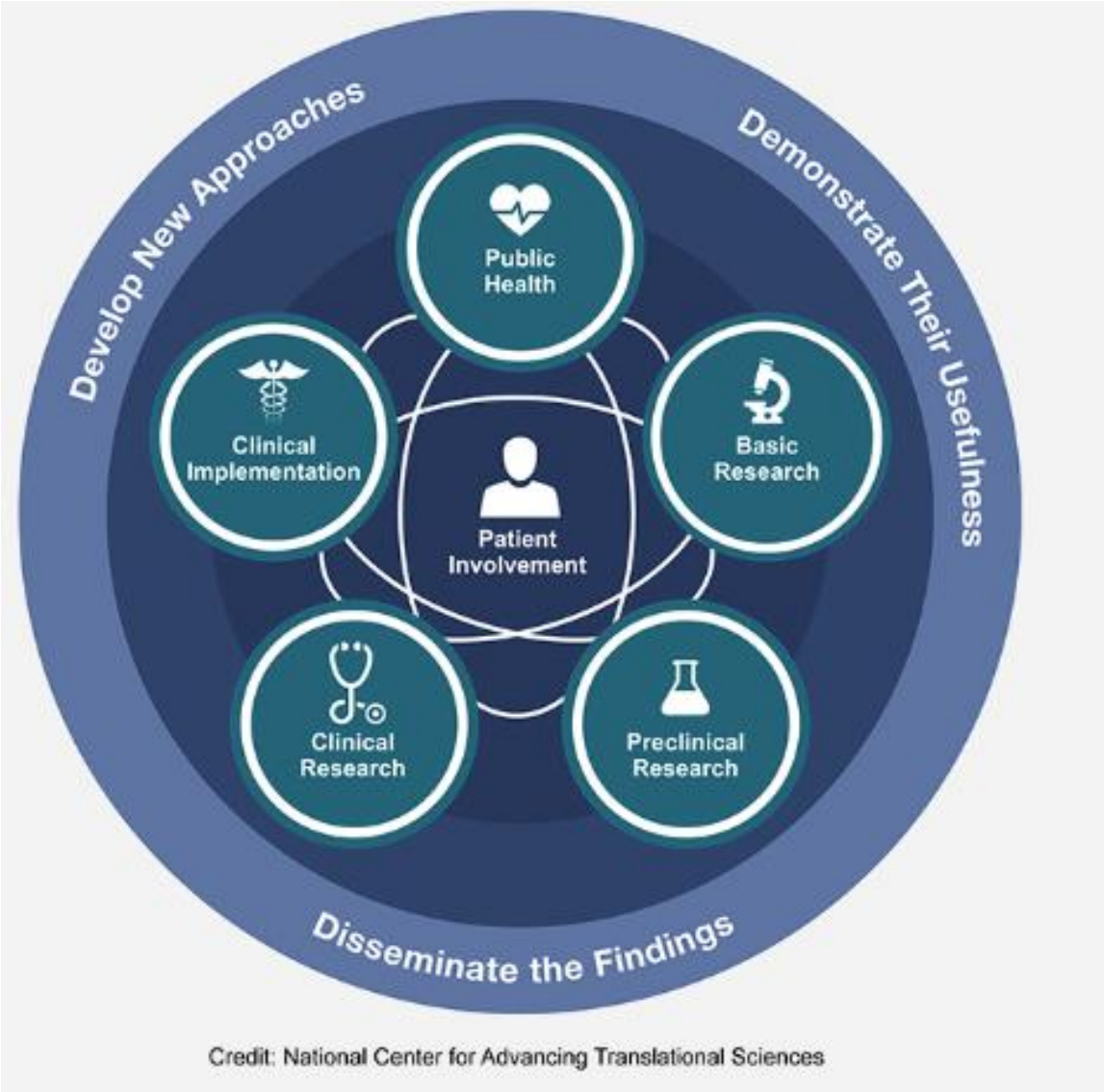


Bioengineering collaboration – diagnostic device development for use in pre-clinical research to detect transdermal nerve electrical activity (small fiber neuropathy)
(Dr. Smith, Dr. Blaszkiewicz, Dr. Townsend)



First In-Human (FIH) clinical trial underway at The Ohio State University:

Improving Diagnosis and Treatment of Neuropathies Requires Research



Credit: National Center for Advancing Translational Sciences

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Townsend Lab Contributors:

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Jake Willows
Gilian Gunsch
Dr. Erica DeSousa
Dr. Magda Blaszkiewicz
Tianyi Tao
Dr. Holly Sucharski-Argall
+ *Previous Lab Members*
+ *Many Talented Undergraduates*!

April 2025

ktownsendlab.com

Collaborators/Consultants for Projects Discussed Today: Martha Belury, Ben Harrison, Andrea Tedeschi, Lori Zeltser, Sandra Rieger, Lauren Sparks, John McGregor, Eva Feldman, David Harrison, Lei Cao, Mike Iadarola, Nandini Archana, Tim Shay, Andy Steele, Sarah Peters, Masticks, Matt Lynes, Andrew Sas, and more.

@neuroadipo

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+ UMaine/Ohio State Internal Funds

Lisa Dean Moseley Foundation

NIDDK Pilot Award

www.diacomp.org