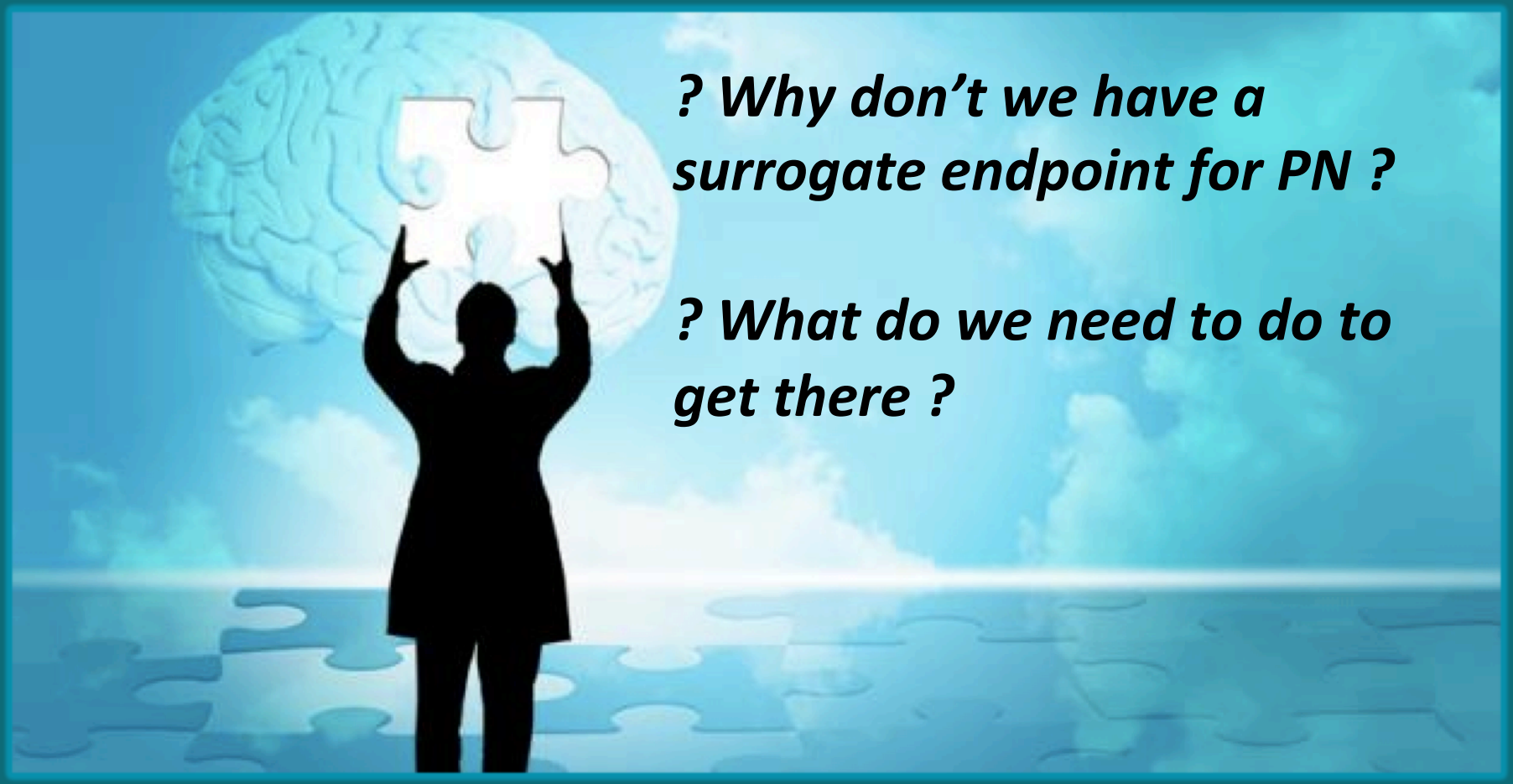
An academic perspective on the role of biomarkers and surrogate endpoints in analgesic clinical trials

Justin C McArthur

Disclosures:

- ***JHU Cutaneous nerve lab***
- ***Unpaid consultant: Biogen, Accentia, Relevare***
- ***Research $ ~ NIH, Pfizer, Biogen***

An academic perspective on the role of biomarkers and surrogate endpoints in analgesic clinical trials



An academic perspective on the role of biomarkers and surrogate endpoints in analgesic clinical trials

- Objectives:
  - Definitions
  - Overview of challenges developing surrogate endpoints
  - FDA's approach
  - Successful examples

- ***Biological Marker (Biomarker)***

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

- ***Clinical Endpoint***

A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

- ***Surrogate Endpoint***

A biomarker intended to substitute for a clinical endpoint. A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm.

Blood pressure
HgbA1C
Plasma HIV RNA copy number
Tumor shrinkage

Why Are Biomarkers Important?

Diagnosis is the foundation of therapy

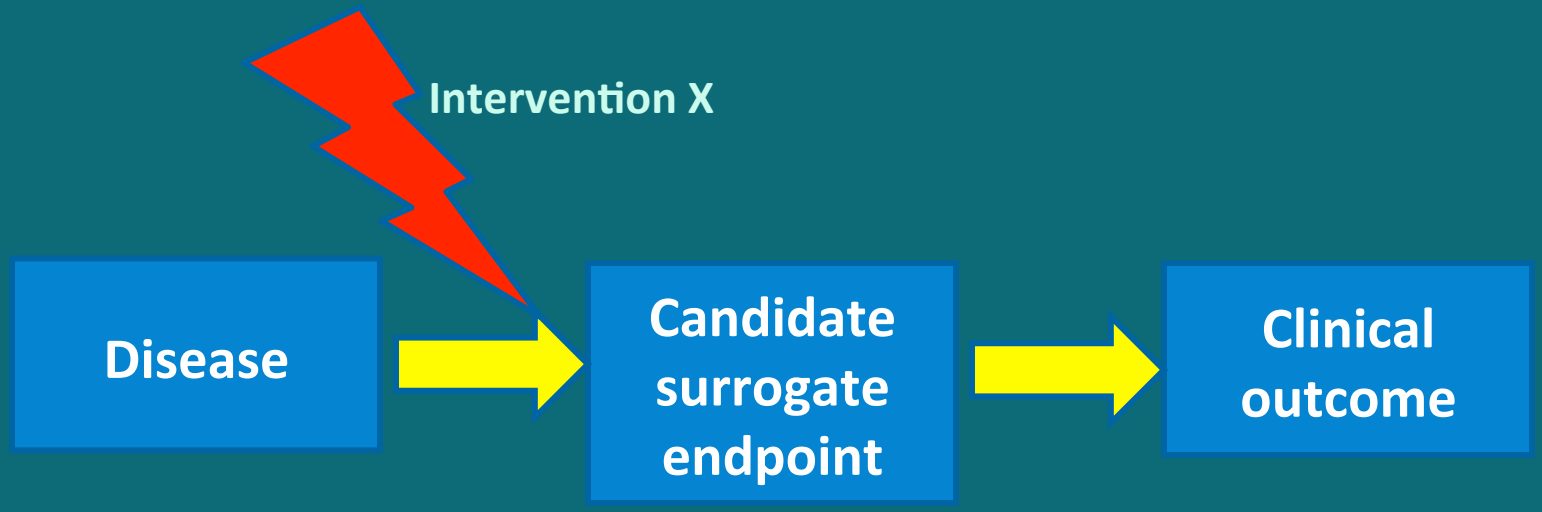
Biomarkers are quantitative measures that allow us to diagnose and assess the disease process and monitor response to treatment

Biomarkers are also crucial to efficient medical product development

As a consequence of scientific, economic and regulatory factors, biomarker development has lagged significantly behind therapeutic development

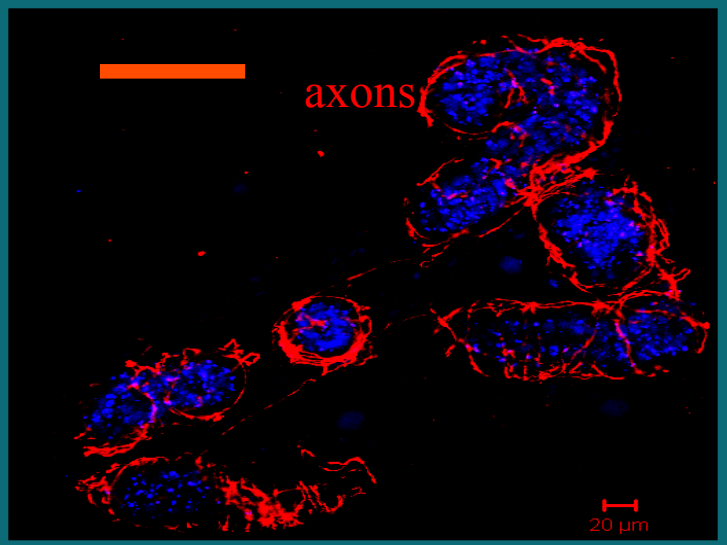
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration

What is the ideal surrogate endpoint ?



Ideal surrogate endpoint

- Predicts clinical endpoint
- Reflects key pathophysiological process
- Responsive to interventions
- Easy to measure: reproducible, cheap, minimally invasive



Why use a surrogate endpoint in a clinical trial ?

- **may allow for more rapid or precise assessment of biological effect ~ *shortening study and reducing n***
- **animal studies have proved to be imperfect predictors of how drugs work in humans**
- **speeds up approval if accepted as a valid surrogate endpoint: eg HIV RNA**

Broader issues in developing a surrogate marker for neuropathic pain trials

- What is the question we are trying to answer with the biomarker ?
  - Early stage trial to inform future design ?
  - FDA approval of NME ?
  - Development of predictive marker ~ either for disease progression or treatment response ?
  - Prediction or detection of adverse effect of drug ??

- Does it matter if a measure is objective or subjective?
- Can one validate an objective measure of pain?

"Validation" of Surrogate endpoints

BIOLOGICAL PLAUSIBILITY

- EPIDEMIOLOGIC EVIDENCE THAT MARKER IS A RISK FACTOR
- MARKER MUST BE CONSISTENT WITH PATHOPHYSIOLOGY
- MARKER MUST BE ON CAUSAL PATHWAY
- CHANGES IN MARKER REFLECT CHANGES IN PROGNOSIS

STATISTICAL CRITERIA

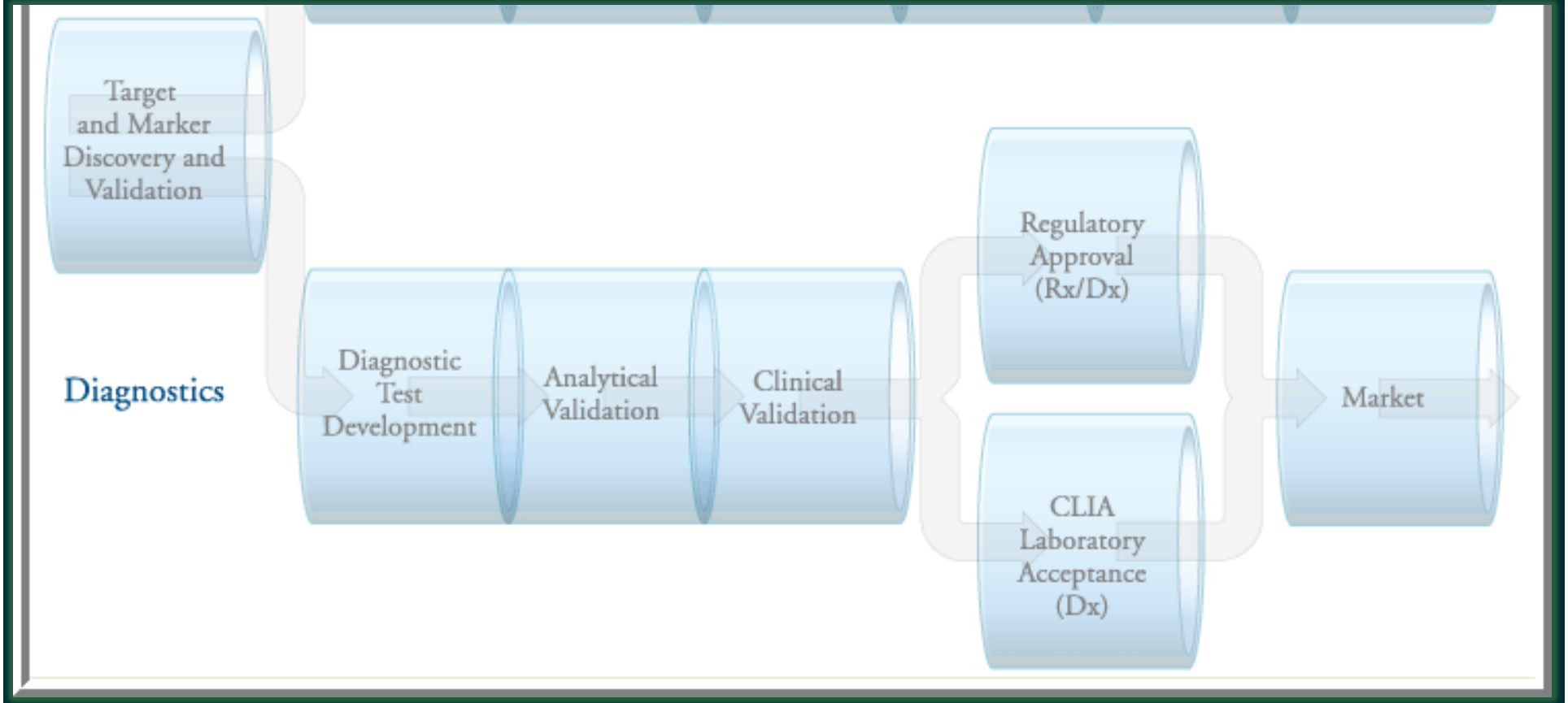
- CHANGES IN MARKER MUST BE CORRELATED WITH CLINICAL OUTCOME

Inclusion of biomarkers in clinical trials: possible trial designs

- Traditional – efficacy only, no biomarker component
- Biomarker Discovery – hitch-hike on mid-development trial, resulting biomarkers are not validated.
- Static Biomarker trial – specific biomarker hypotheses tested as part of trial design, could yield validated biomarkers.
- Adaptive Sampling – a form of adaptive trial in which a biomarker hypothesis is evaluated at an interim point, and subsequent patient selection may be affected by the biomarker.

Rusty Katz, FDA…."no surrogate endpoints are currently accepted for neurological diseases"

Steps in biomarker development



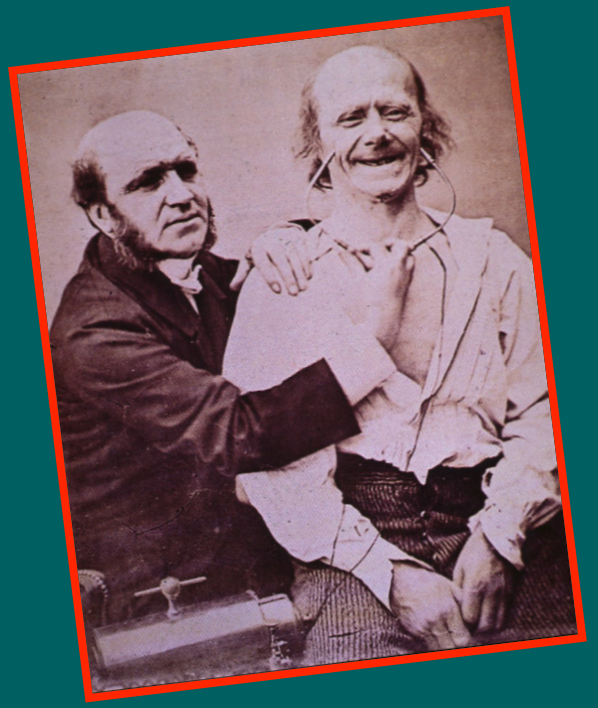
Development of better biomarkers and surrogate endpoints

- FDA's Critical Path Initiative: proposal to use consortia to qualify biomarkers through resource sharing
- Currently such consortia have been set up in many areas eg animal safety testing, disease-specific consortia, NINDS-NEXT, and within Pharma, eg Wyeth
- Safety biomarkers of great interest
- FDA developing a qualification process

Pitfalls of biomarker/surrogate endpoint development

- accurate phenotyping essential
- expensive and difficult to organize in multi-center trials (centralized lab/reading ?)
- difficult to identify disease-specific markers
- accurate quantitation may be difficult and validation is essential ~ to assess analytical validity, clinical validity and clinical utility.
- 'pipeline' problem for diagnostics, lagging behind drug development

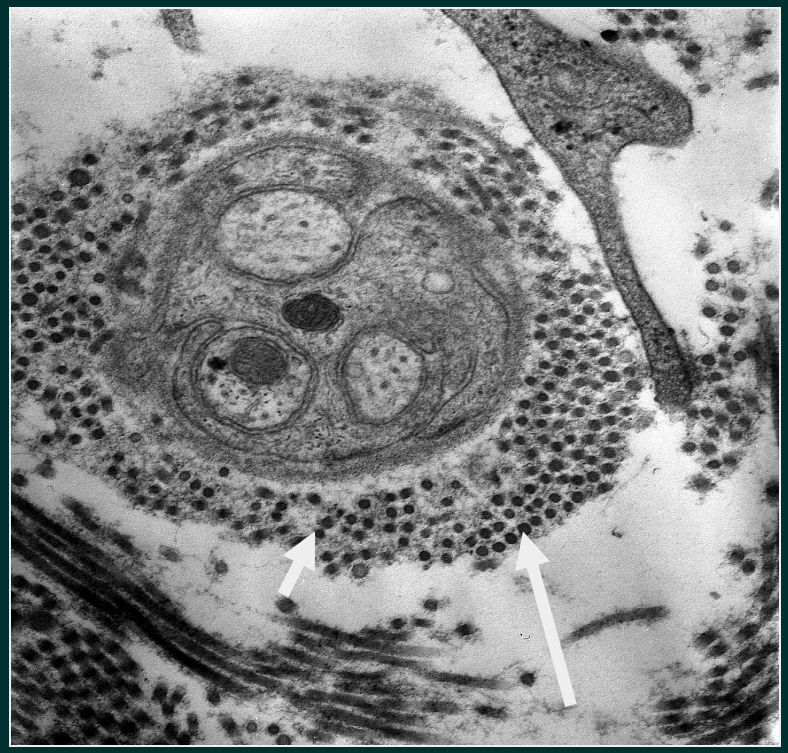
Some examples of surrogate endpoints for neuropathy trials



Example of a tissue biomarker that has now been included in clinical trials as a surrogate endpoint of the severity of epidermal denervation, and to study regeneration

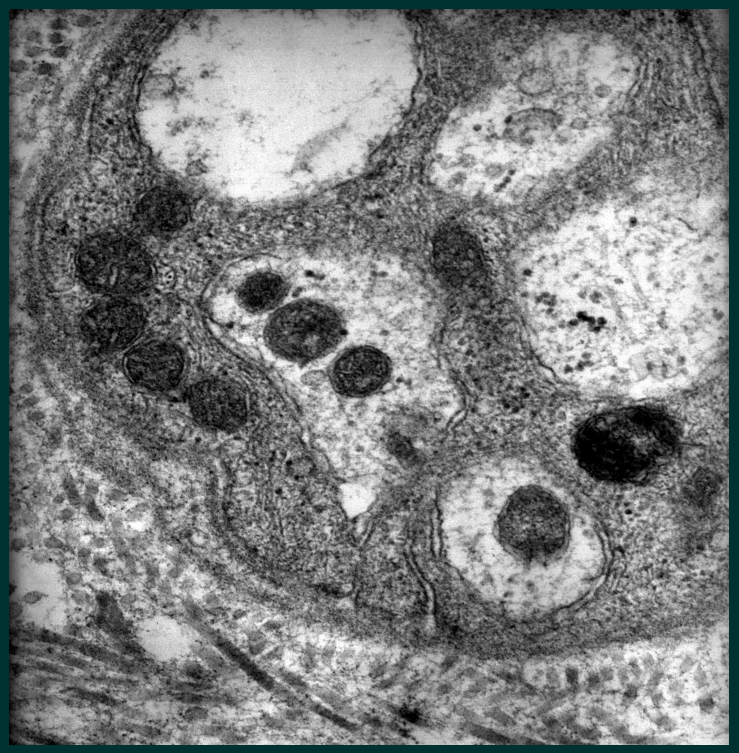
"One day, every neurologist will carry a tuning fork, a reflex hammer…….and a skin biopsy punch"

Jack Griffin



A healthy Remak bundle at the papillary dermis containing 3 axons surrounded by collagen. (x25K)

Healthy control



Remak bundle with dilated unmyelinated axons showing watery axoplasm and granular debris.

HIV neuropathy

EMs courtesy of Dr Gigi Ebenezer

Skin biopsy: applications

- **Marker of early disease**
  - **IGT associated neuropathy**
  - **Chemotherapy neuropathy**
- **Predictor of neuropathy development**
- **Helpful in evaluating proximal sites**
  - **Meralgia paresthetica**
  - **Thoracic neuropathies**
  - **Mononeuritis multiplex**
- **Sensory ganglionopathies, eg Sjogren's syndrome**
- **Sweating / Autonomic dysfunction**
- **Demyelinating neuropathies**
- **Vasculitic neuropathies**

Correlations between epidermal nerve fiber densities, neuropathic features and progression:

(ACTG 5117 Zhou L. Neurology, 2007; Simpson D., Neurology, 2006)

Both an associative and predictive biomarker for HIV SN

ENFD at the DL site correlated with:

- neuropathy severity as gauged by TNS ($p<0.01$)
- neuropathic pain quantified by Gracely Pain Scale ($p=0.01$)
- Visual Analogue Scale ($p=0.01$)
- sural SNAP amplitude ($p<0.01$)
- toe cooling ($p<0.01$)
- vibration detection thresholds ($p=0.02$)

And lower epidermal nerve fiber densities at baseline *predicted* worsening of neuropathy.

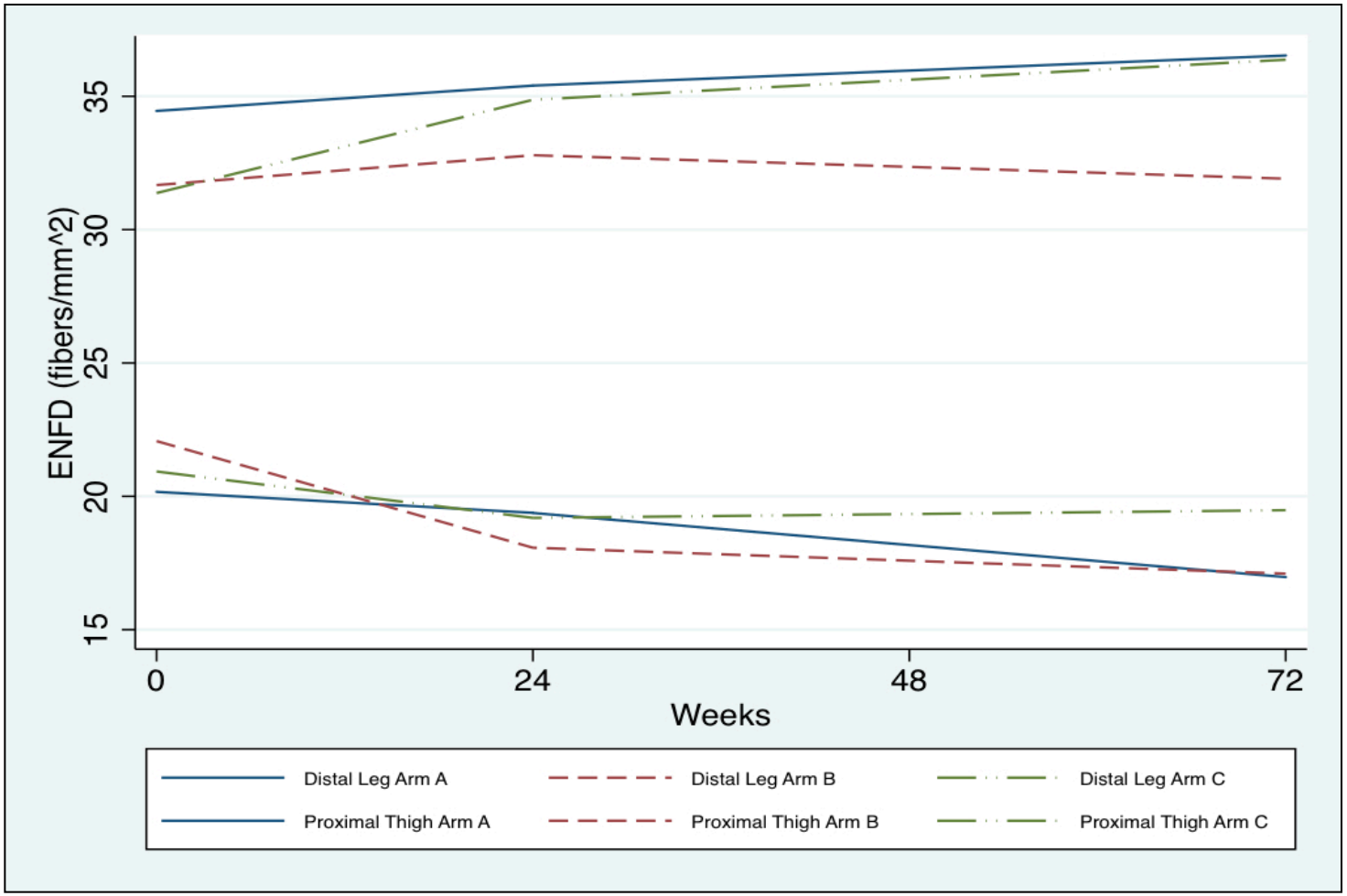
Needs to be replicated in other neuropathies and labs

AAN practice parameters (***Neurology* 2009;72:1–1)**

- "IENF density assessment using PGP 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology. Skin biopsy with IENF density assessment is possibly useful to identify DSP which includes SFSN in symptomatic patients with suspected polyneuropathy (Class III)".

But, ENF may be population specific, and is dependent on lab QC

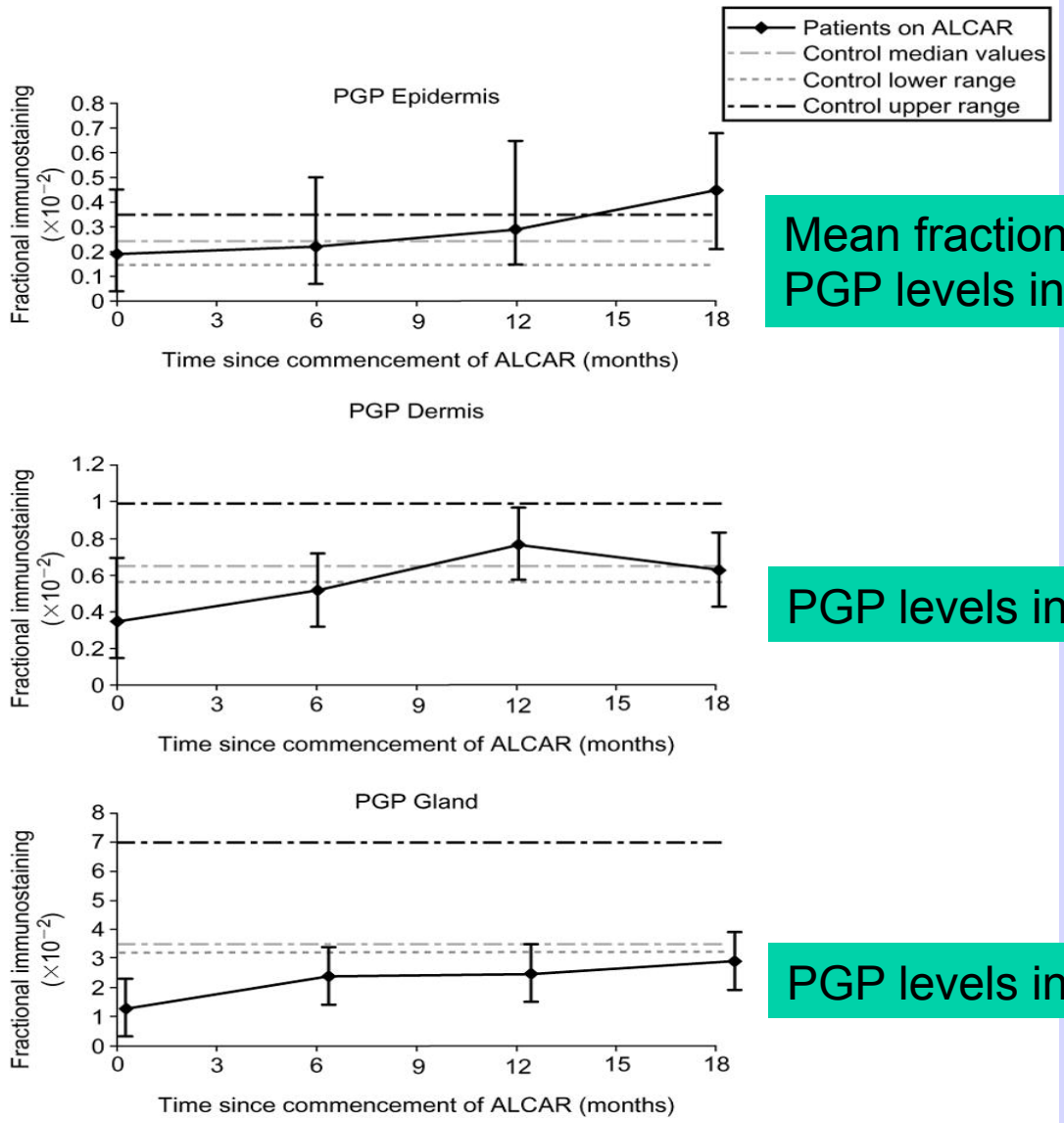
Median ENFD by antiretroviral arms over time
…no correlation with exposure to 'neurotoxic' D4T



Proximal thigh

Distal leg

Controlled trial of acetyl-L-carnitine in HIV SN *Hart et al, 2004*



Mean fractional immunostaining PGP levels in epidermis

PGP levels in dermis

PGP levels in sweat gland

Pathophysiology/Complications

ORIGINAL ARTICLE

Lifestyle Intervention for Pre-Diabetic Neuropathy

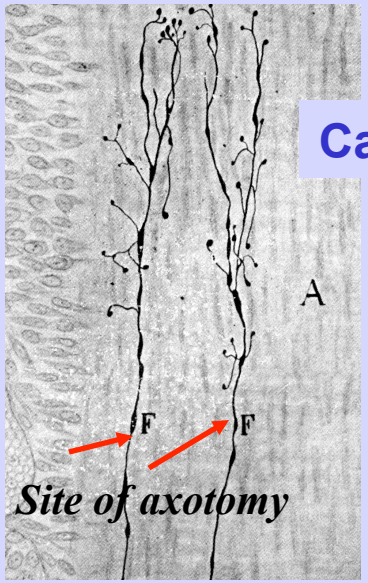
A. Gordon Smith, MD[1,2]
James Russell, MD[3]
Eva L. Feldman, MD, PhD[3]
Jonathan Goldstein, MD[4]
Amanda Peltier, MD[3]
Sheldon Smith, BS[1]
Jouhaina Hamwi, BS[1]
Donald Pollari, BS[1]
Billie Bixby, BS[1]
James Howard, BS[1]
J. Robinson Singleton, MD[1]

athy. One practical test of this hypothesis is to determine whether treatment of IGT results in slowed progression of neuropathy. The Diabetes Prevention Program (DPP) demonstrated that intensive diet and exercise counseling slows progression of IGT to diabetes compared with placebo or metformin (7). We are study-

CONCLUSIONS— These results indicate that skin biopsy is the most sensitive measure of IGTN severity and suggest that treatment with diet and exercise counseling results in partial cutaneous reinnervation.

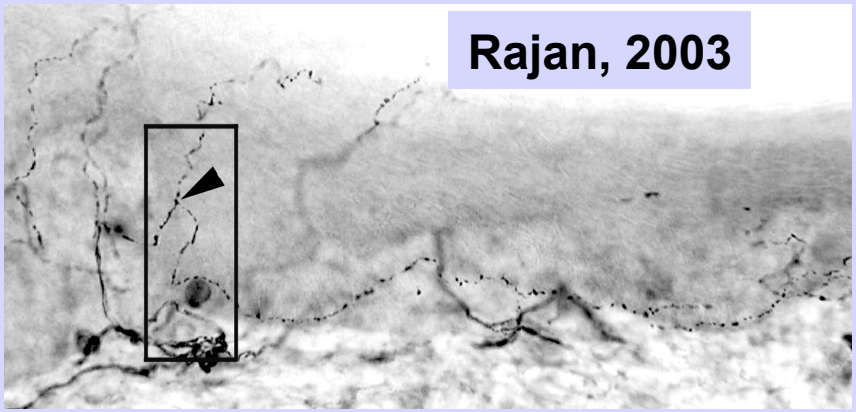
Mechanisms of nerve fiber repair after mechanical cutaneous nerve injury

- Regenerative regrowth ~ from transected nerve fibers along denervated Schwann cell bands



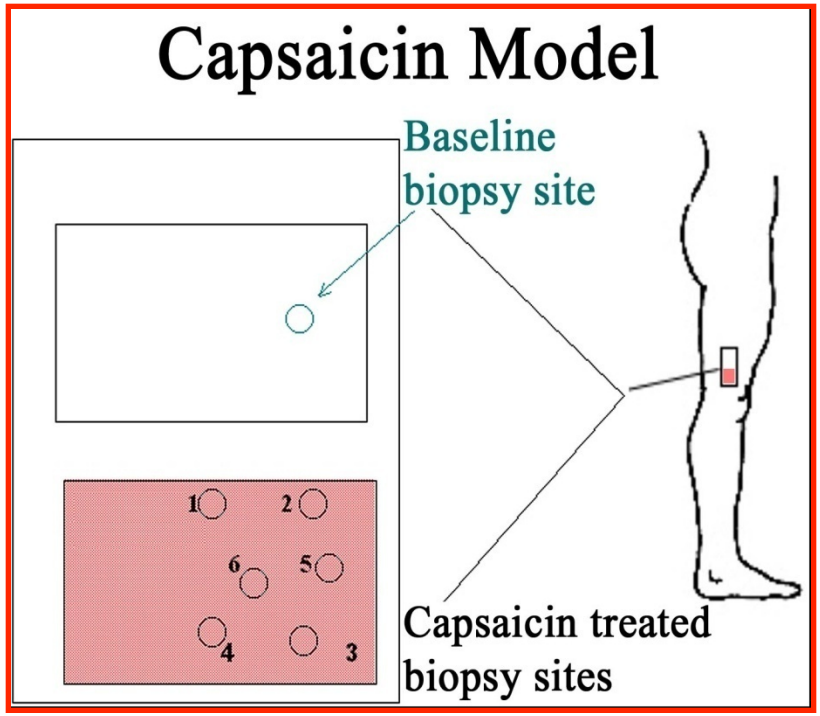
Cajal, 1913

- Collateral sprouting from uninjured nerve fibers in neighboring skin

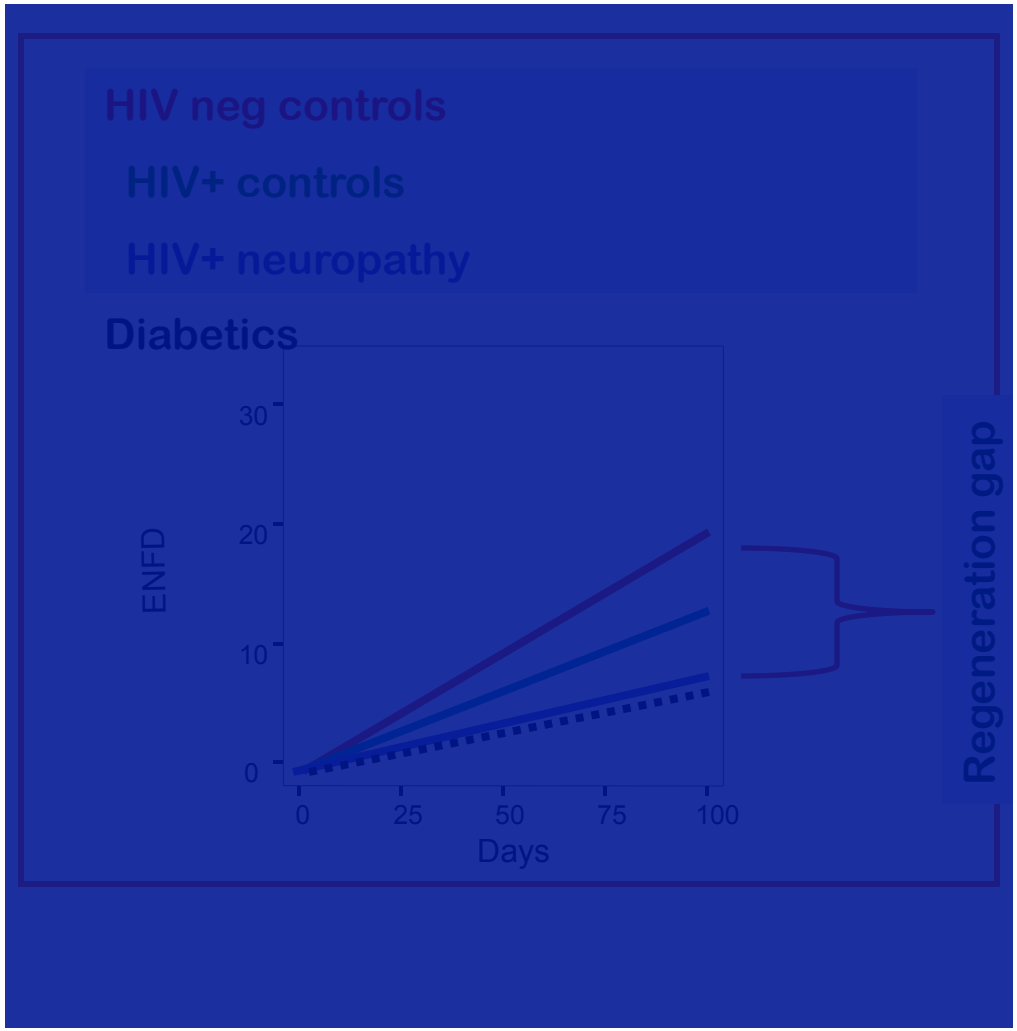


Rajan, 2003

Nerve fiber repair is as impaired in HIV infection as in diabetes

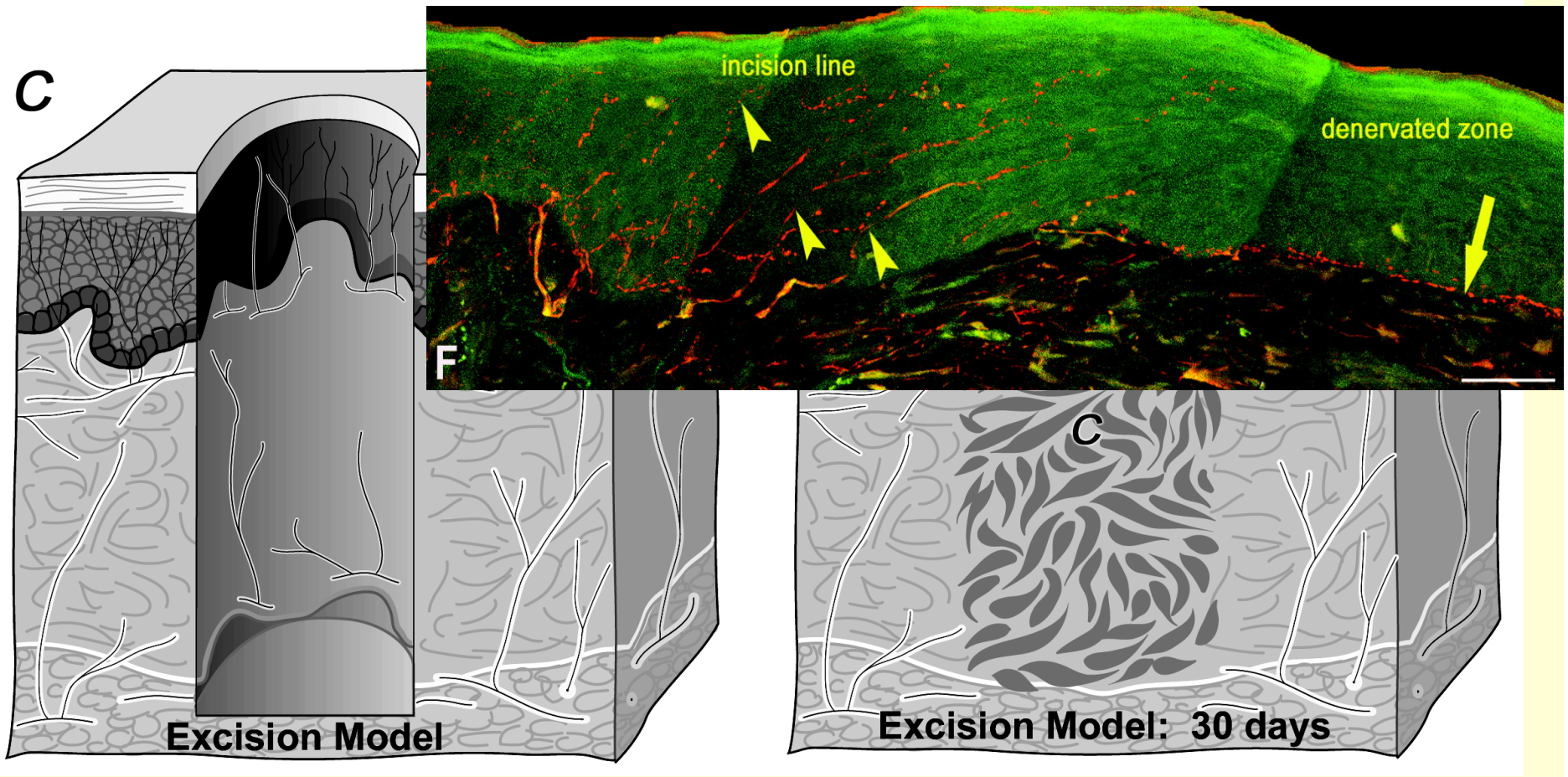


Mike Polydefkis



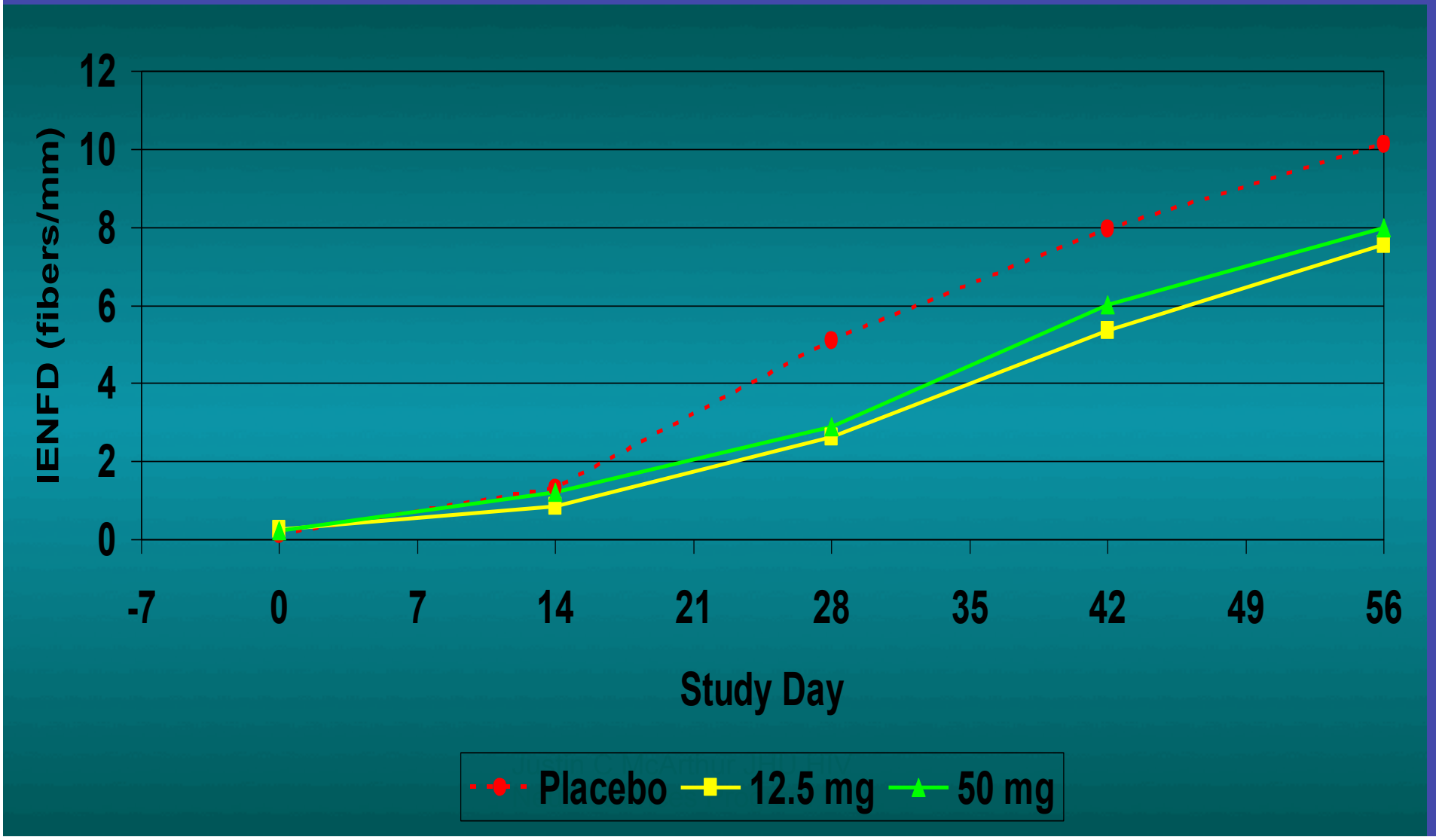
Excision model to study regeneration in human cutaneous nerve injury: *collateral sprouting*

Rajan B., 2003



Recovery of Intraepidermal Nerve Fibers Over Time ~ regenerative regrowth: Timcodar trial

Group Medians by Study Day (Evaluable-for-Efficacy)

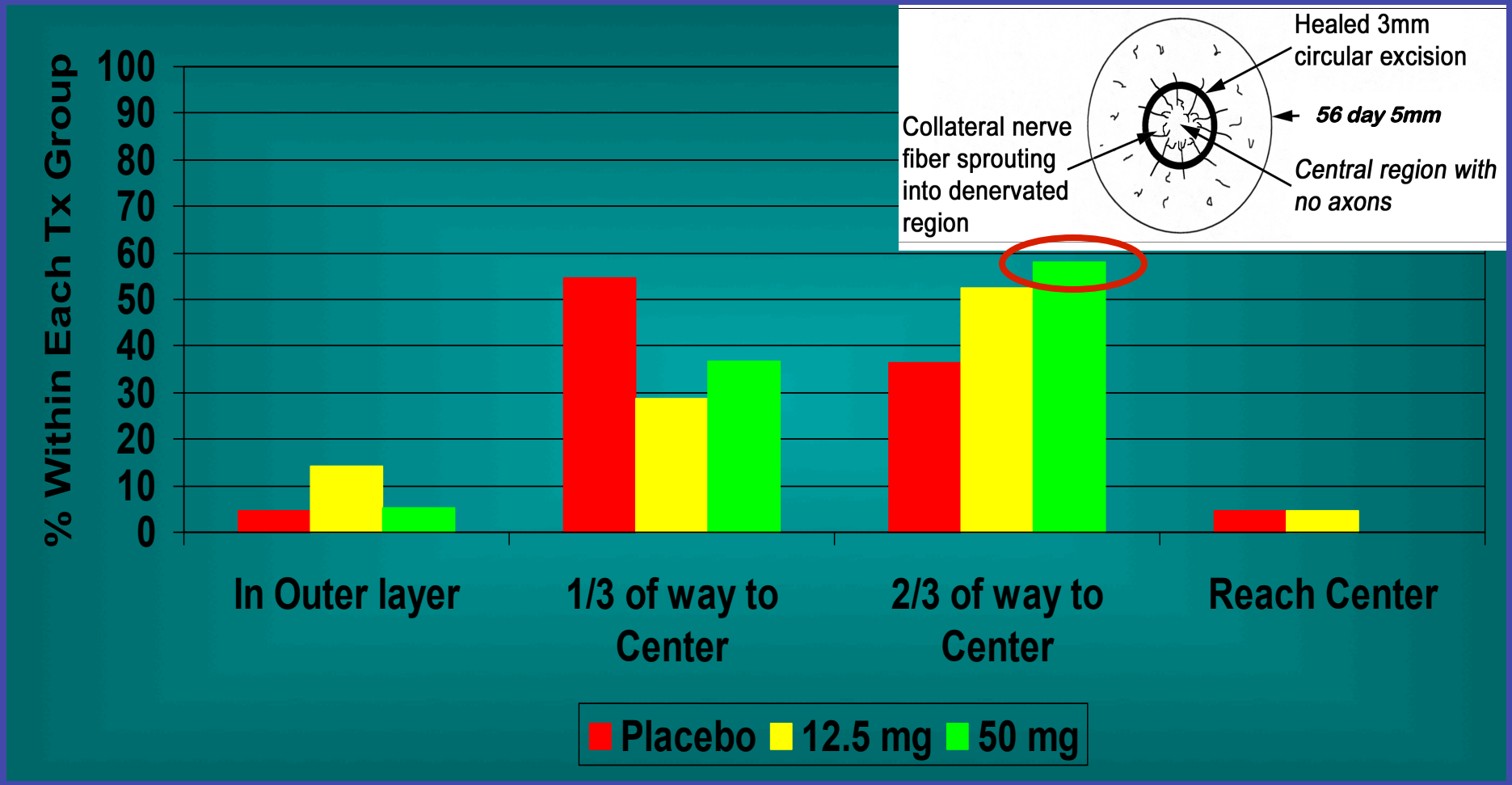


Collateral Nerve Sprouting 56 days after timcodar treatment

Percentage Within Each Treatment Group

Evaluable-for-Efficacy

Polydefkis M, 2004, unpublished.



Implications of these 'regeneration' models for future trial design of 'regenerative' agents

- Fast, efficient mechanism to evaluate the capacity of regenerative or neurotrophic agents to enhance regenerative regrowth or collateral sprouting.
- Sample size potentially 25-50
- Duration of trial 60-120 days
- Argument can be made to include non-neuropathic or mildly symptomatic patients in regenerative PN trials.

Clinical trials using skin biopsy as endpoint

Serial ENFD			Regeneration		
Mitsubishi	DM	?	Centocor	Collateral sprouting	?
Sangamo 901	DM	?	Vertex	Regen/CS	neg
J&J anti NGF	DM	?	Topamax	Regen	?
Merck	DM	?	Astellas	Regen/CS	?
Pfizer FoldRx	DM	?	Sanofi-Aventis	Regen	?
LAC	HIV SN	+	Sangamo 601	Regen	?
rhNGF	HIV SN	neg			
Diet/exercise	Pre-DM	+			

Other techniques *developing* as surrogate endpoints

- Corneal microscopy
- Meissner's corpuscles densities
- Soluble markers ~ CSF or blood
- Sweat gland densities
- Neurophysiology (e.g. EEG, axon reflexes)
- Autonomic testing
- Sleep studies
- Imaging studies
- Electronic pain scoring
- Genomics and genetic markers for pain susceptibility
- Proteomics/lipidomics

Background: neuropathic pain is associated with significant effects upon quality of life, sleep efficacy, symptoms of depression and anxiety, daily activities, and with greater health care utilization. Pain, *2010*

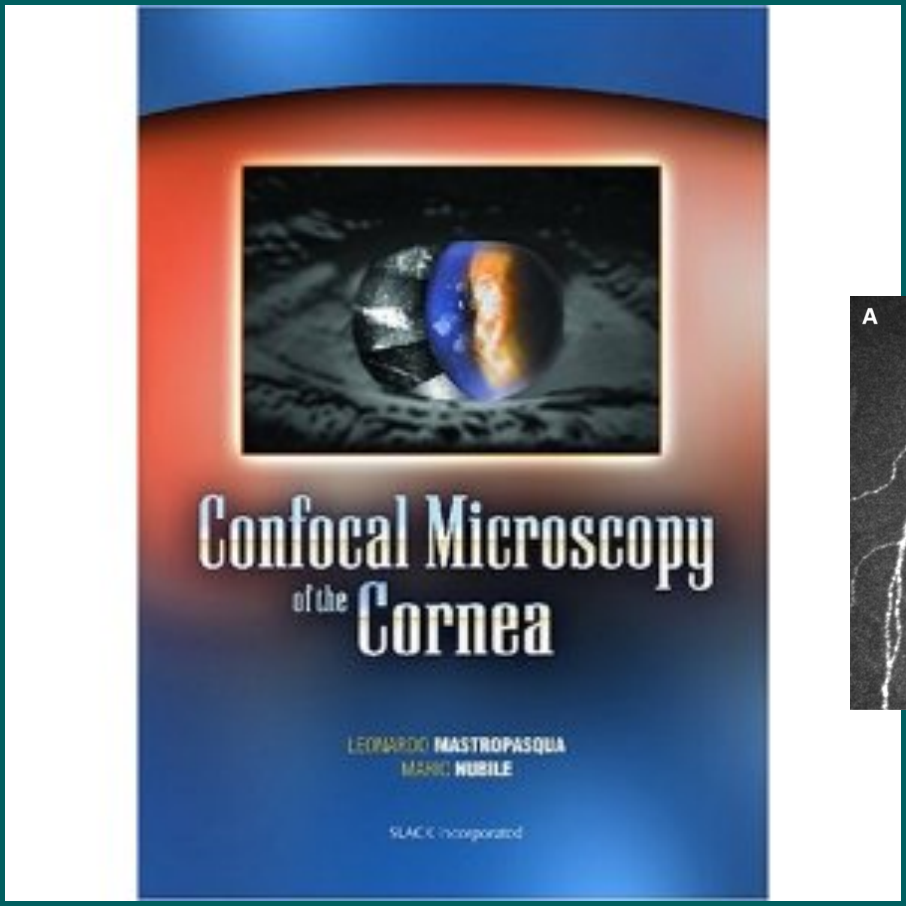
ORIGINAL CONTRIBUTION

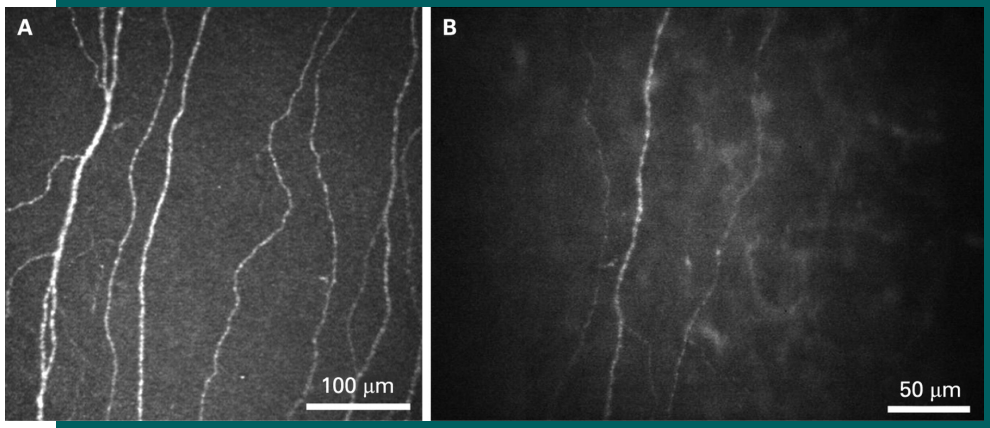
Continued High Prevalence and Adverse Clinical Impact of Human Immunodeficiency Virus–Associated Sensory Neuropathy in the Era of Combination Antiretroviral Therapy

The CHARTER Study

Ronald J. Ellis, MD, PhD; Debralee Rosario, MPH; David B. Clifford, MD; Justin C. McArthur, MBBS, MPH; David Simpson, MD; Terry Alexander, RN; Benjamin B. Gelman, MD, PhD; Florin Vaida, PhD; Ann Collier, MD; Christina M. Marra, MD; Beau Ances, MD, PhD; J. Hampton Atkinson, MD; Robert H. Dworkin, PhD; Susan Morgello, MD; Igor Grant, MD; for the CHARTER Study Group

Arch Neurol. 2010;67(5):552-558.

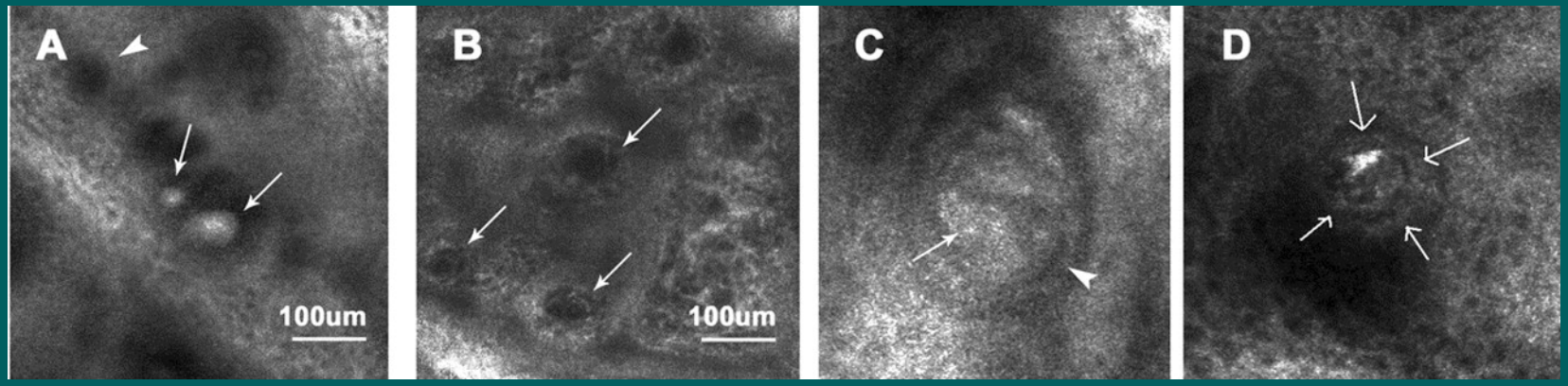




http://ecx.images-amazon.com/images/I/412n4wqKX5L._SL500_AA300_.jpg

Identification of Meissner corpuscles with in vivo reflectance confocal microscopy (RCM)

(A) Glabrous skin from the hand showing a dermal papilla with two Meissner corpuscles (MCs) and an empty papilla (arrow head).
(B) Hairy skin of the forearm showing the expected absence of MCs in papillae.

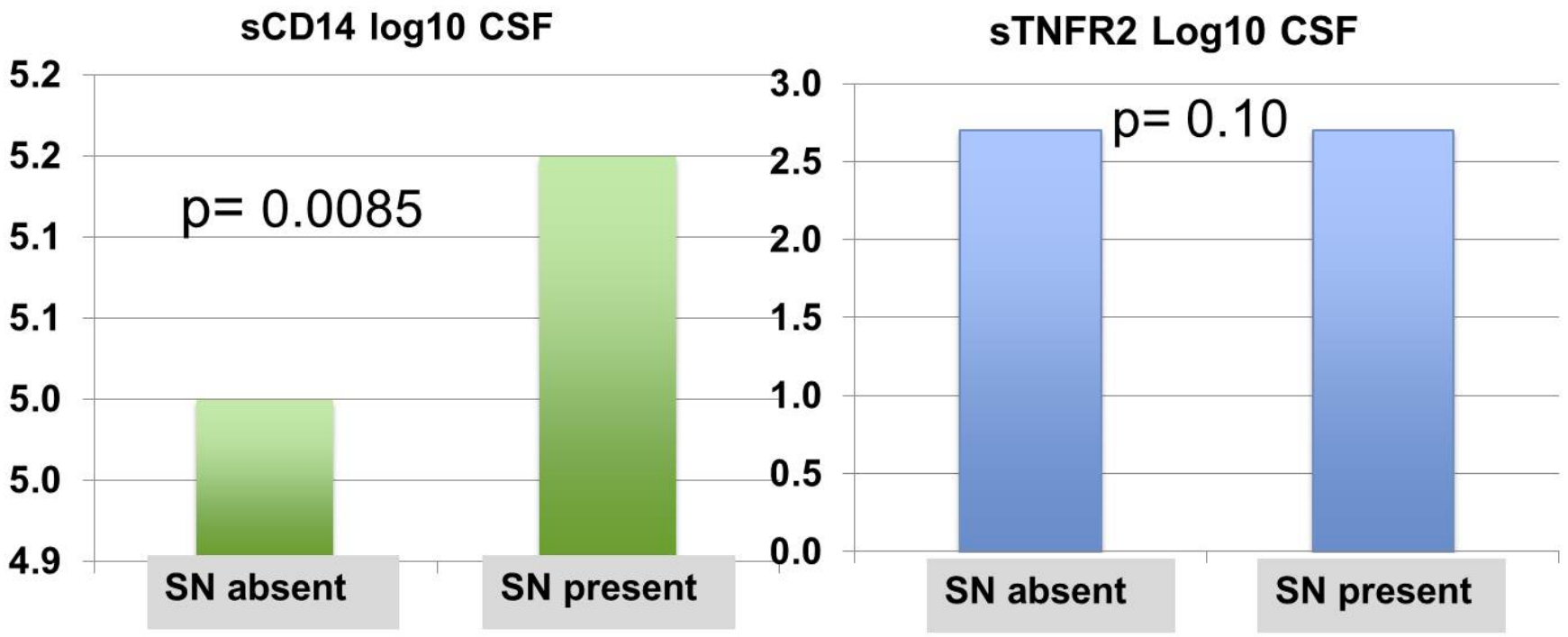


Herrmann D N et al. Neurology 2007;69:2121-2127

AMERICAN ACADEMY OF NEUROLOGY

Soluble biomarkers of inflammation for neuropathy trials ~ HIV-SN

Figure 4. Levels of sCD14, but not sTNFR2, in CSF are elevated in HIV-SN

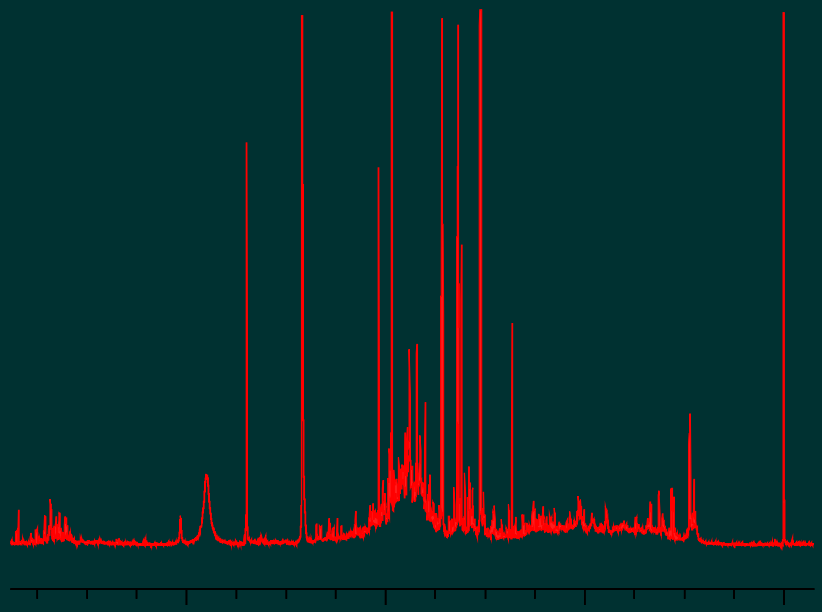


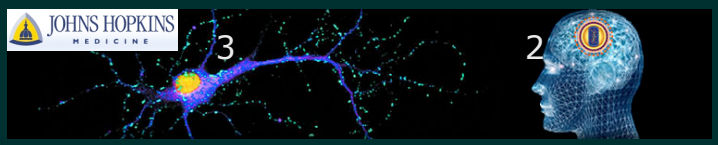
Ellis R. CROI 2012

CHARTER

Metabolite analysis by NMR

- Bruker AVANCE AVIII 700 MH
- 5mm inverted cyroprobe optimised for 1H observation
- 120 sample holder with automatic robot





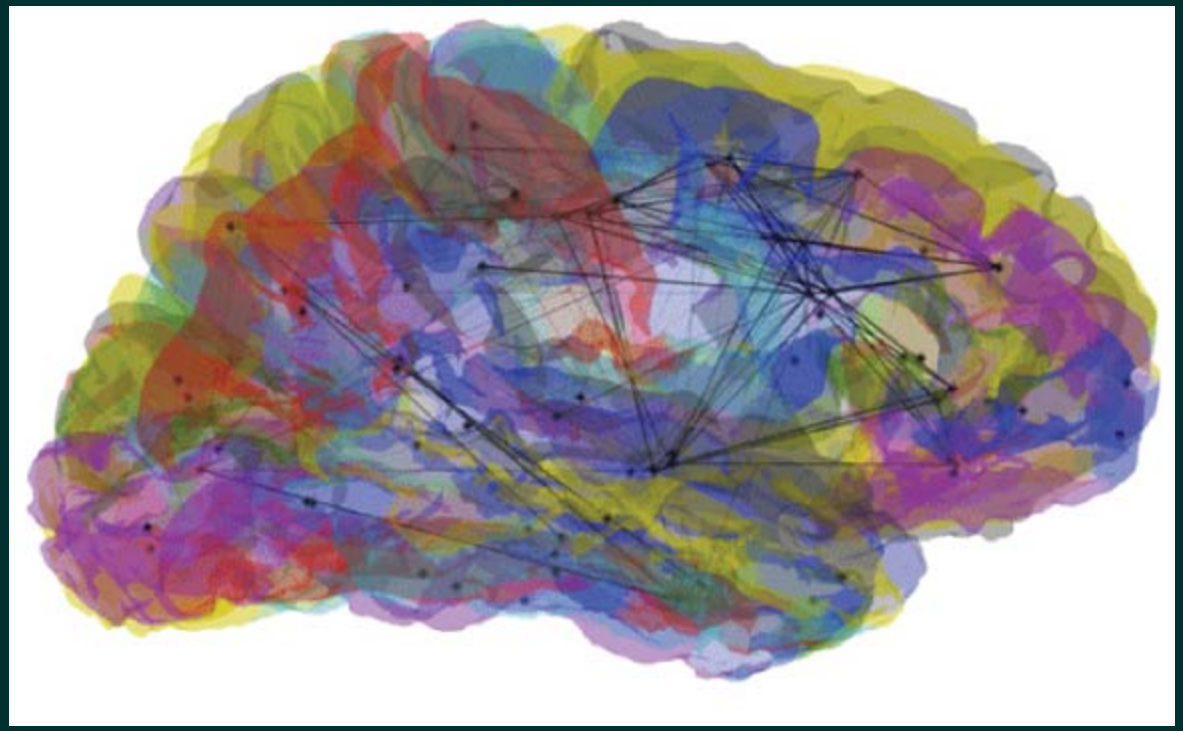
The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders

Biomarker development for HIV-associated neurocognitive disorder

		JHU	UCSD	UNMC
miRNA	Array profiling/individual samples/candidate validation		CSF PBMCs	Plasma
Proteomics	MRM/candidate proteins/ individual samples	CSF Plasma		
	Shotgun discovery/pooling/ validation	CSF		CSF
Lipidomics	Shotgun discovery/pooling/ validation	CSF		
Viral load	High sensitivity determination		CSF	
Multiplex	Targeted protein assays	CSF Plasma	CSF Plasma	

Combinatorial approaches to biomarkers

Eg 1: Recursive partitioning
Eg 2: Combinations of markers



Use of recursive partitioning to identify combinations of markers for prediction

	Diagnostic		Prognostic for Worsening		Prognostic for Improvement	
Misclassification Limit	10%	20%	10%	20%	10%	20%
sCD14	CSF, PL	CSF, PL	CSF	CSF	CSF	-
sTNFR	CSF	CSF	CSF, PL	-	-	-
TNF-α	CSF	-	-	-	CSF, PL	CSF, PL
CXCL10	PL	PL	-	-	-	-
CCL2	CSF, PL	CSF	PL	-	CSF, PL	CSF
CXCL12	-	-	CSF	CSF	-	-
IL-6	-	-	CSF	CSF	-	-
CX3CL1	-	-	-	-	PL	-
Total Assays	7	5	6	3	6	3
R-square	64%	42%	73%	41%	80%	46%
Correct Classification	92%	81%	94%	82%	96%	81%

Correctly classified 100% of Stably Normal

Correctly classified 100% of Stably Impaired

Letendre, et al. 19th CROI, 2012, Abstract E-170

Combinatorial approaches to biomarker development

"Combined automated regional analysis of structural MRI with analysis of plasma cytokines and chemokines and compared these to measures of APOE genotype and clinical assessment to assess which best predict progression. In a total of 205 people with MCI, 77 of whom subsequently converted to Alzheimer's disease, we find **biochemical markers of inflammation to be better predictors of conversion** than APOE genotype or clinical measures (Area under the curve (AUC) 0.65, 0.62, 0.59 respectively). In a subset of subjects who also had MRI scans the combination of serum markers of inflammation and MRI automated imaging analysis provided the best predictor of conversion (AUC 0.78). **These results show that the combination of imaging and cytokine biomarkers** provides an improvement in prediction of MCI to AD conversion compared to either datatype alone, APOE genotype or clinical data and an accuracy of prediction that would have clinical utility."

J Alzheimers Dis 2011;26 Suppl 3:395-405.

Combinatorial markers of mild cognitive impairment conversion to Alzheimer's disease--cytokines and MRI measures together predict disease progression.
Furney SJ, et al

Assessment of pain ~ is there a better way ?

- Clinical evaluation of neuropathic pain is challenging, in part because pain intensity and quality varies considerably within a 24 hour epoch.
- Pain treatment trials often rely on paper and pencil tools that are recorded without observation or verification during treatment, and which typically attempt to 'average' pain during an epoch.
- The development of relatively inexpensive personal EDs make available convenient and affordable technology for prompting observations and recording responses ''in the moment'' throughout a study interval, as well as convenient regular accessing of responses.

OPEN ACCESS Freely available online

PLoS one

A Randomized Trial Evaluating Prosaptide™ for HIV-Associated Sensory Neuropathies: Use of an Electronic Diary to Record Neuropathic Pain

Scott R. Evans[1]*, David M. Simpson[2], Douglas W. Kitch[1], Agnes King[3], David B. Clifford[4], Bruce A. Cohen[5], Justin C. McArthur[3], for the Neurologic AIDS Research Consortium and the AIDS Clinical Trials Group

- This is the first use of an ED in HIV-SN, and we initially hypothesized that the ED might reduce variability of changes in pain measurements over time and might therefore result in more accurate reporting of changes in pain.
-
- However, in our trial, the ED did not appear to decrease the variability of Gracely pain changes (SD =0.32) compared to trials that we have conducted using written diaries (SD = 0.33 in ACTG 291 and ACTG 242.

- Note that the variability of the outcome measure is in part a function of intra-participant variation and also the lack of effectiveness of study medication.

The biomarker world can change quickly….

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION ON PSA TESTING - RESOURCE CENTER

The United States Preventative Services Task Force (USPSTF) made a final recommendation on May 21, 2012 which aligned consistently with the draft recommendation publicly announced on October 7, 2011.

The recommendation is against prostate-specific antigen (PSA) based screening for healthy men, asserting that there is "moderate or high certainty that the service has no benefit or that the harms outweigh the benefits,"

Comparison of Effect Sizes Associated With Biomarkers Reported in Highly Cited Individual Articles and in Subsequent Meta-analyses

John P. A. Ioannidis, MD, DSc
Orestis A. Panagiotou, MD

Context Many biomarkers are proposed in highly cited studies as determinants of disease risk, prognosis, or response to treatment, but few eventually transform clinical practice

COMMENT

This empirical evaluation of 35 top-cited biomarker studies suggests that many of these highlighted associations are exaggerated. In some cases, these markers may have no predictive ability, if one trusts the subsequent replication record, in particular the results of the largest studies on the same associations. Less than half of these biomarkers have shown nominally significant results in the largest studies that have been conducted on them, and only 1 in 5 has shown an RR greater than 1.37.

"This does not mean that no biomarkers of any use are possible to discover, but that the standards for claiming success should be higher. These standards should include not only prospective design, careful analysis plans, and meticulous reporting, but also extensive replication and validation of proposed biomarkers in large independent studies and assessment of their incremental ability. Until such studies are available, emphasis on single studies with highly promising results may be premature".

Ioannidis & Panagiotou, JAMA 2010

Recommendations for surrogate endpoint development ~ an 'academic' perspective:

- Inclusion of skin biopsy for ENFD in trials of potentially regenerative agents for neuropathic pain
- Development of standardized protocols for staining and quantitation
- Pooling samples of blood/CSF to allow systematic examination of soluble biomarkers ~ lipidomics, inflammatory markers, proteomics
- Use of advanced statistics, eg recursive partitioning, and other combinatorial approaches


Thank you