COX INHIBITORS AND NGF ANTIBODIES AS TARGETS FOR PRECISION PAIN MEDICINE

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TERMINOLOGY

- PHENOTYPE to refer to a stable patient characteristic that may impact safety or efficacy of a treatment
  - Sensory profile
  - Biomarkers of disease state or pain processing
- I am IGNORING (even though they may be important):
  - Other patient characteristics that may impact observed effect sizes, such as age, gender, medical or psychiatric comorbidities, pain intensity or variability, ability to report pain accurately, placebo responsiveness, compliance, etc.
  - Clinical diagnostic phenotyping; e.g. LBP includes disk herniation, arthritis, spinal stenosis, etc.
  - PK phenotypes – obviously drug exposure affects efficacy
- I am only focused on group characteristics that modify treatment effect (drug vs. placebo)

MAIN QUESTION

Do phenotypes act as effect modifiers of drug treatments for pain?

CLINICAL TRIAL PARADIGM:

	Drug	Placebo	Effect
Phenotype 1	d_1	p_1	(d_1-p_1)
Phenotype 2	d_2	p_2	(c_2-d_2)

HYPOTHESIS: $(d_1-p_1) \neq (d_2-p_2)$

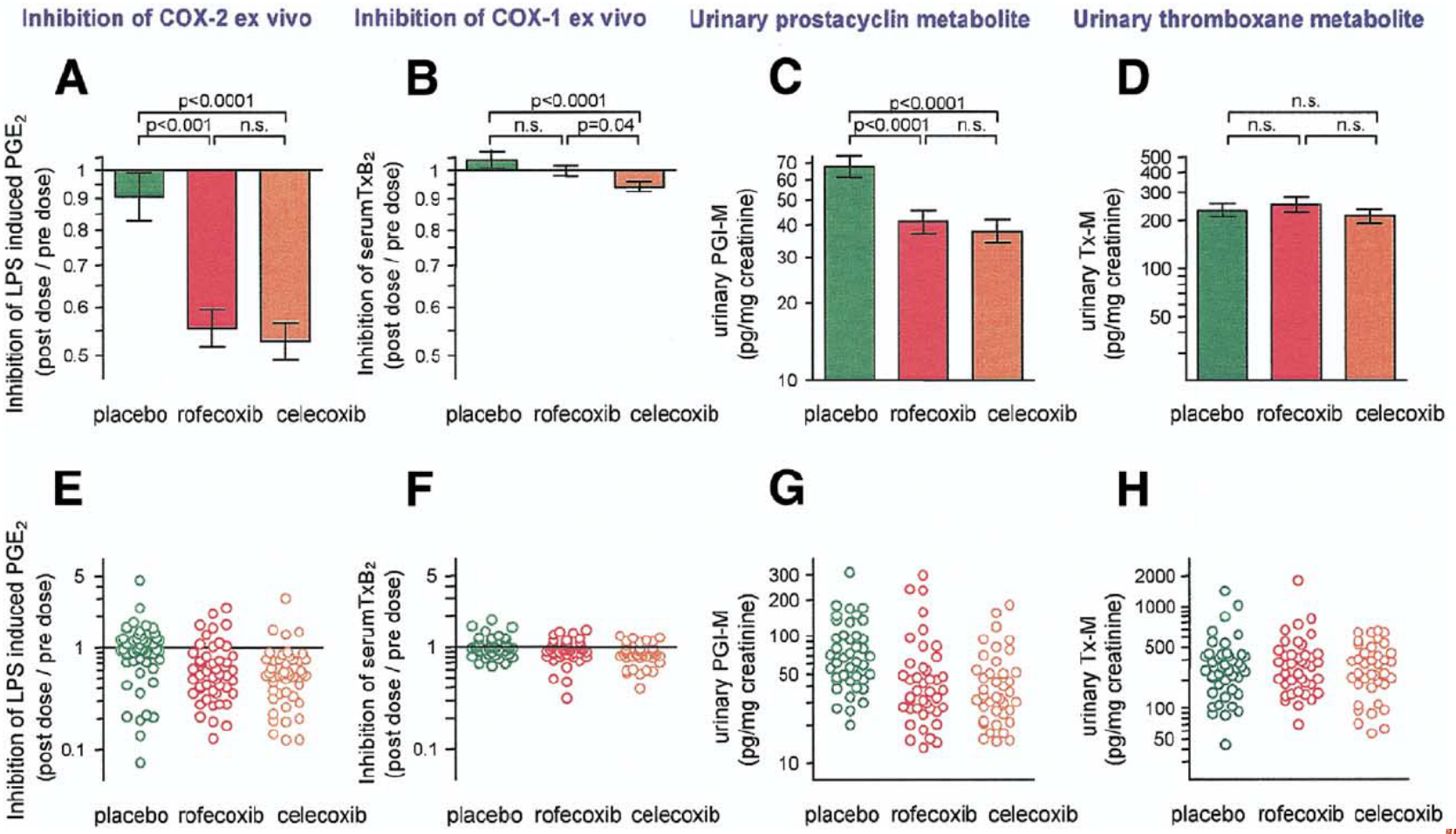
COX INHIBITORS

NSAIDS DIFFER FROM EACH OTHER IN WAYS THAT IMPACT RESPONSE

- COX-2 vs. COX-1 selectivity
- Degree of penetration and residence in inflamed tissues (related to acidity)
- Protein binding
- Rate of absorption and elimination
- CNS penetration

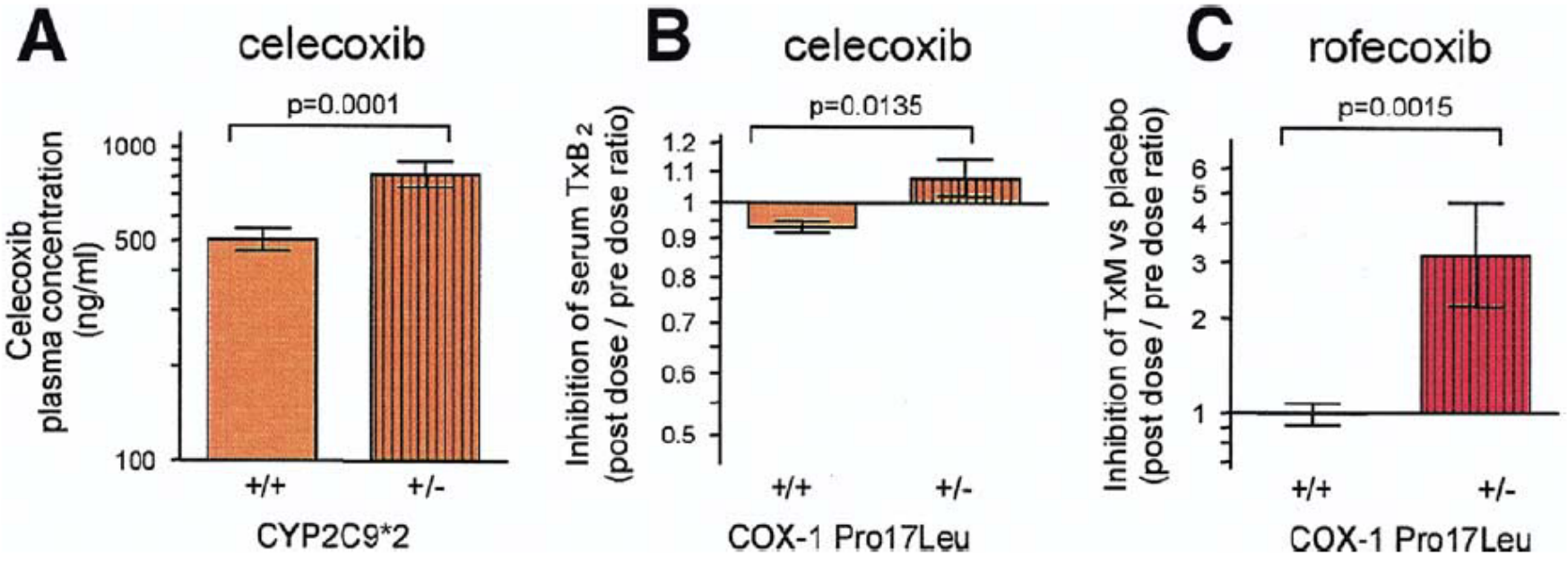
Therefore it is conceivable that patient-specific factors could influence the impact of these factors on clinical response

INTERINDIVIDUAL VARIABILITY IN BIOMARKERS FOR NSAID EFFECTS



Fries S, Gastroenterology, 2006

VARIATIONS IN GENES CODING FOR COXIB METABOLISM IMPACT COXIB EFFECTS



Fries S, Gastroenterology, 2006

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER, EXPLORATORY TRIAL OF NAPROXEN TO EVALUATE VARIOUS METHODS OF MEASURING ANALGESIC EFFECT IN OA PAIN OF THE KNEE

- Objective 3
  - **Phenotyping:** To confirm the ability of the Bedside Sensory Testing Kit for Osteoarthritis (BSTK-OA) to classify subjects with OA (osteoarthritis) into distinct subgroups; to compare the efficacy of naproxen versus placebo in these subgroups
- Design
  - 2-treatment, 2-period crossover (naproxen vs. placebo)
  - 1 week screening, 1-week washout, 1-week treatment periods
  - Phenotyping at baseline using published technique

Osgood E, et al, Rheumatol Int. 2015

BEDSIDE SENSORY TESTING KIT (BSTK)

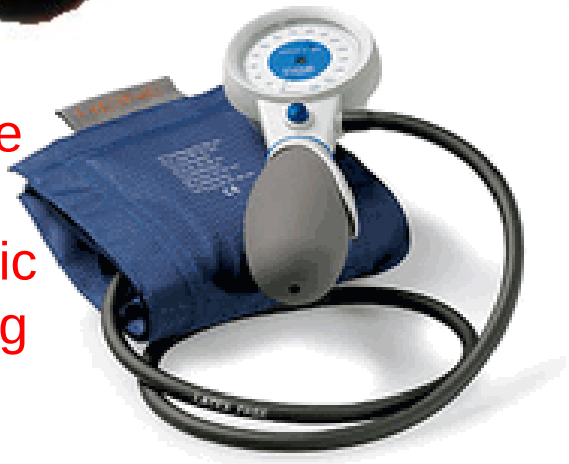
Pressure Algometer kg/cm^2

Non-toxic water soluble marker

2lb weight to help induce ischemic pain (HNCS) through exercise

von Frey Filament set

Blood Pressure Cuff to help induce ischemic arm pain during exercise



2” x 6” Brass Rod for cold pain

RESULTS: SENSORY PHENOTYPES

Subgroup	Primary HA	Secondary HA	DNIC	N
A	No	No	Intact	19
B	No	No	Dysfunctional	5
C	No	Yes	Intact	8
D	No	Yes	Dysfunctional	4
E	Yes	No	Intact	3
F	Yes	No	Dysfunctional	1
G	Yes	Yes	Intact	4
H	Yes	Yes	Dysfunctional	7
				51

Analgesic Solutions, data on file

SES of Naproxen vs Placebo for WOMAC Pain	n	SES
Subgrouping based on all BSTK tests		
All Normal Sensory Findings (Subgroup A)	19	0.44
All Abnormal Sensory Findings (Subgroup H)	7	0.75
Mixed Sensory Findings (Subgroups B + C + D + E + F + G)	25	0.33
Subgrouping based on the DNIC test		
Intact DNIC (Subgroups A + C + E + G)	34	0.33
Dysfunctional DNIC (Subgroups B + D + F + H)	17	0.67
Subgrouping based on Hyperalgesia		
Both Local and Distant Positive (Subgroups G + H)	11	0.80
Both Local and Distant Negative (Subgroups A + B)	24	0.42
Mixed Local and Distant (Subgroups C + D + E + F)	16	0.12
Subgrouping based on S-LANSS Score		
S-LANSS Score < 12	41	0.24
S-LANSS Score ≥ 12	14	1.00

Analgesic Solutions, data on file

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000000562

Evidence for a central mode of action for etoricoxib (COX-2 Inhibitor) in patients with painful knee osteoarthritis

Lars Arendt-Nielsen[1, 2], Line Lindhardt Egsgaard[1, 2], and Kristian Kjær Petersen[1]

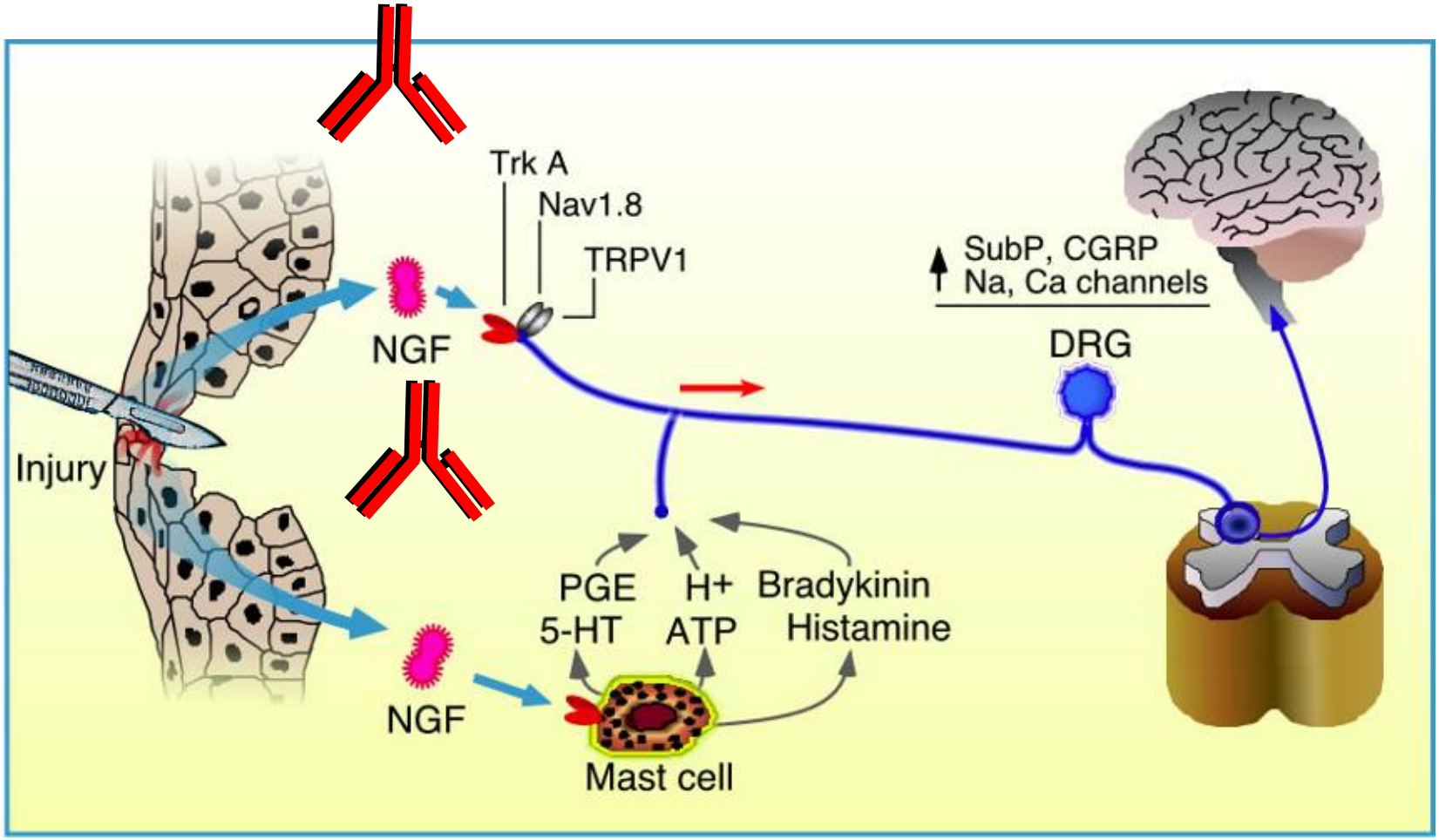
- Randomized, placebo-controlled, crossover study
- Etoricoxib vs. placebo, 4 weeks of each
- Multiple QST "phenotyping" measures
- Data not presented as active vs. placebo differences by baseline characteristic, and therefore does not directly address effect modification by phenotype

CONCLUSIONS: PHENOTYPING FOR NSAIDS

- Biomarkers exist for inter-individual variability in NSAID effects although these have not been used to predict efficacy
- One small unpublished study suggests that sensory profile in patients with OA predicts naproxen effects (vs. placebo)
  - Patients with abnormal sensory function responded better to naproxen vs. placebo than patients with normal sensory function
  - Another completed study has the potential for addressing this issue
- It seems to me that further research on using phenotypes and genotypes to predict safety and efficacy of NSAIDs is worthwhile
  - Main hook is safety since it's cheap and easy to try the drug as the best test for efficacy

ANTIBODIES TO NERVE GROWTH FACTOR

ROLE OF NGF IN PAIN



NGF blockade modifies signaling of a variety of other mediators

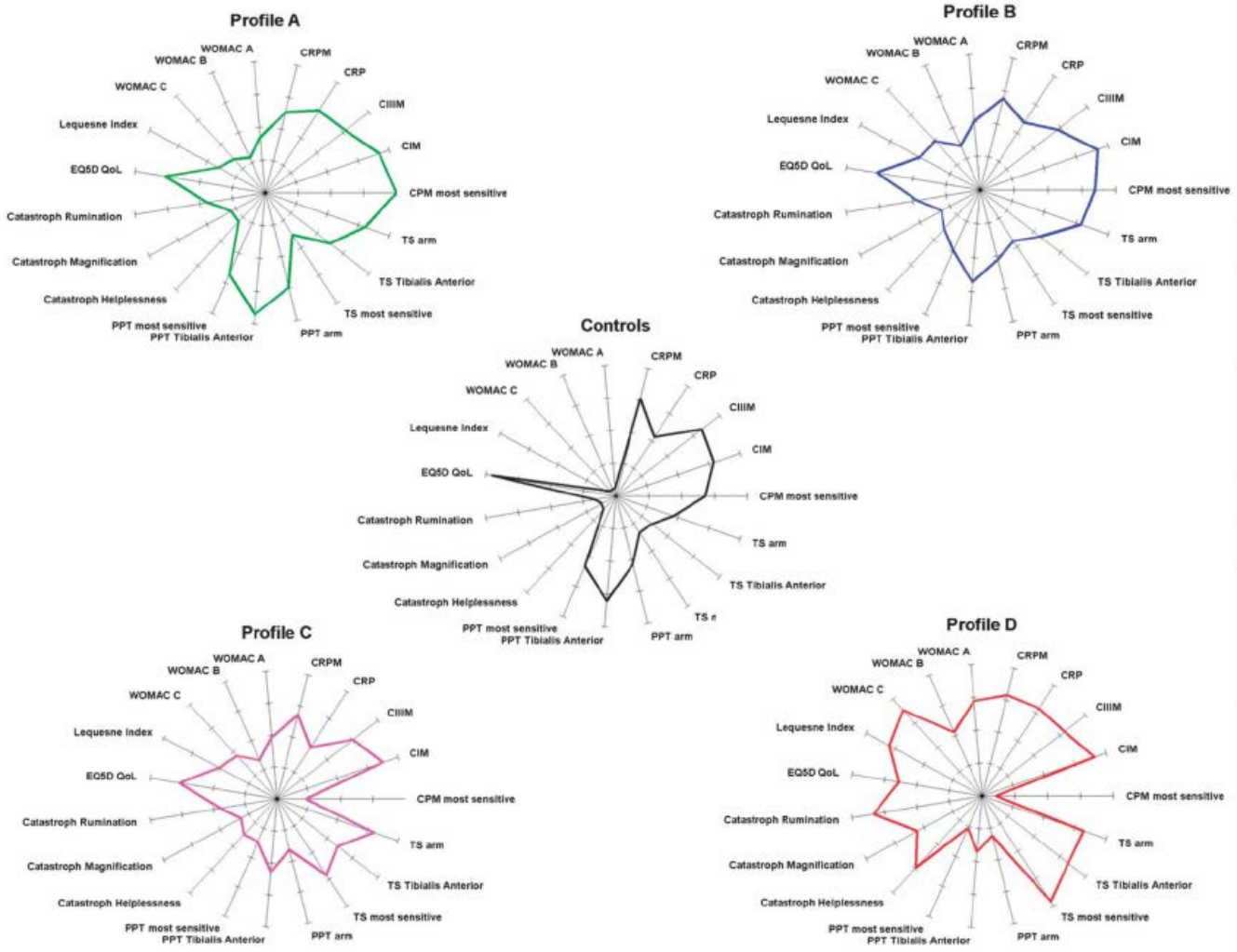
Slide courtesy of Dave Shelton, Pfizer

SUMMARY OF ANTI-NGF ANTIBODIES

- Efficacy convincingly demonstrated in multiple RCTs in multiple pain indications: OA, LBP, various types of neuropathic and visceral pain
- Several products in Phase 3
- Strongest data in musculoskeletal pain
- Uncommon but severe safety issues:
  - Rapidly progressive OA (leading to joint replacements)
  - Peripheral neuropathy (mostly but not all transient)
- Antibodies have prolonged effects
- New treatments may be expensive
- **Thus prediction of either efficacy or safety would be an important clinical achievement**

I AM NOT AWARE OF ANY CLINICAL TRIAL DATA EXAMINING THE IMPACT OF PHENOTYPES ON EFFICACY OF ANTI-NGF ANTIBODIES

MULTIDIMENSIONAL OA PHENOTYPES



Egsgaard LL, Pain, 2015

CONCLUSIONS

- A small literature indicates early explorations of various approaches to categorizing patients with select chronic pain syndromes based on:
  - Soluble biomarkers of disease activity
  - Sensory profiles
  - Genes that impact pharmacokinetics and pharmacodynamics of certain analgesics
- Studies using these categories to predict efficacy of NSAIDs or anti-NGFs are virtually non-existent, with most of the few reports focused on safety
- Predicting anti-NGF efficacy and safety are of high scientific and practical interest since the consequences of administering the treatments to the wrong patients are high
- Progress will require a thoughtful evaluation of the biology of the painful disorder, the pharmacology of the test drug, and a systematic approach to phenotyping patients, trial by trial