Role of preclinical pain models in developing and deploying biomarkers

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Making Cancer History®

Preclinical models are vital to pain research

Tools to understand cellular and molecular mechanisms of pain

- Cells and molecules can be precisely manipulated and studied *in vivo*
- Otherwise inaccessible tissues can be assayed with advanced techniques

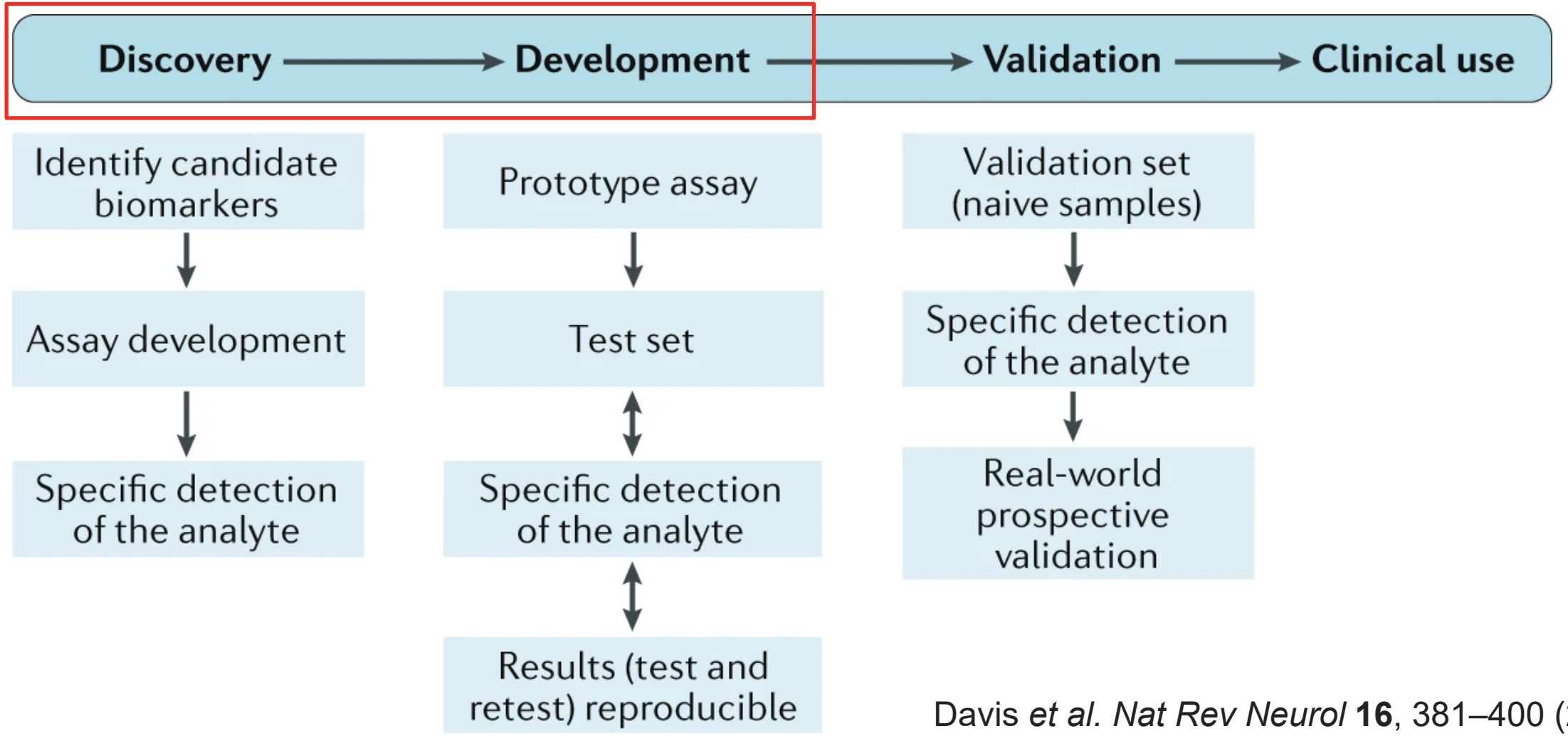
These features can be applied to biomarker discovery and development

Experimental interventions can be evaluated in preclinical studies

- Ethical and cost-effective

Biomarkers may serve as translational tools for preclinical drug development

Preclinical models in biomarker discovery and development



Davis *et al. Nat Rev Neurol* **16**, 381–400 (2020)

Biomarker discovery in preclinical models

Preclinical models offer advantages for biomarker discovery

- Homogeneous study population, controlled induction of pain, fewer confounding variables (co-morbidities, treatments, etc)
- Access to CNS tissue

Journal of Neurochemistry JNC

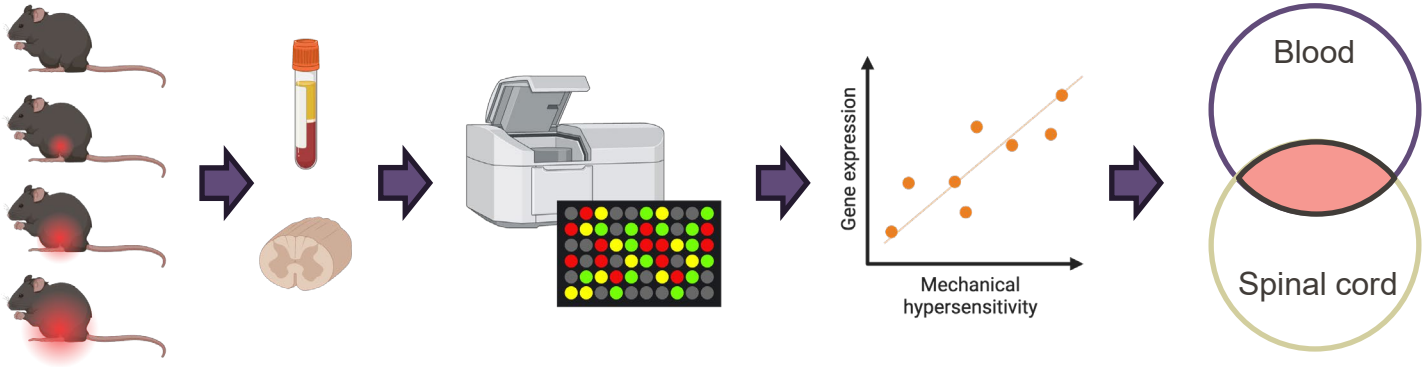
JOURNAL OF NEUROCHEMISTRY | 2012 | 122 | 976–994 doi: 10.1111/j.1471-4159.2012.07833.x

ORIGINAL ARTICLE

Harnessing pain heterogeneity and RNA transcriptome to identify blood-based pain biomarkers: a novel correlational study design and bioinformatics approach in a graded chronic constriction injury model

Peter M. Grace,*·† Daniel Hurley,‡·§·¶ Daniel T. Barratt,* Anna Tsykin,** Linda R. Watkins,† Paul E. Rolan* and Mark R. Hutchinson*·†·††

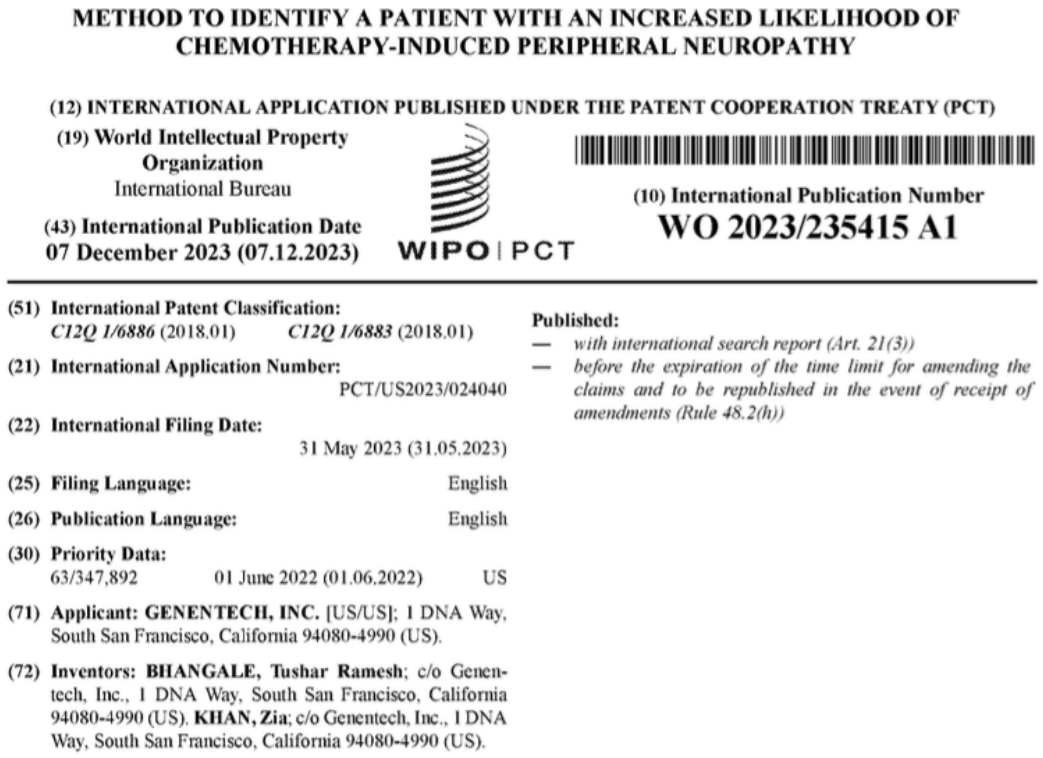
Gene expression correlated with mechanical pain



"Hits" can be followed up in subsequent preclinical and clinical studies

Development of biomarkers using preclinical models

- Clinical studies have identified potential biomarkers
  - *MFAP3*; *GRID2, SCG2, GPR68*; anti-GFAP and anti-CRMP2 IgG
  - Could serve as prognostic, diagnostic, pharmacodynamic, and/or predictive biomarkers
- Putative biomarkers have yet unknown functions in chronic pain



METHOD TO IDENTIFY A PATIENT WITH AN INCREASED LIKELIHOOD OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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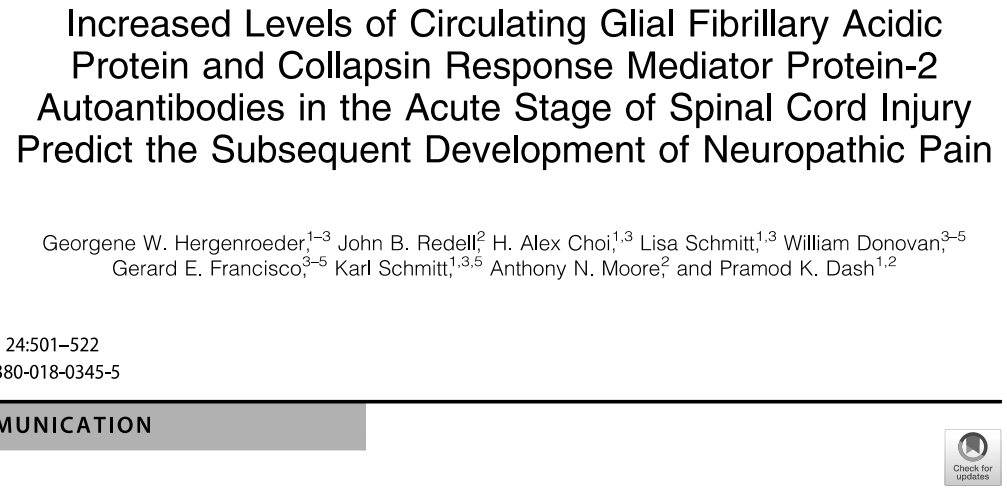

Increased Levels of Circulating Glial Fibrillary Acidic Protein and Collapsin Response Mediator Protein-2 Autoantibodies in the Acute Stage of Spinal Cord Injury Predict the Subsequent Development of Neuropathic Pain

Georgene W. Hergenroeder[1–3] John B. Redell[2] H. Alex Choi[1,3] Lisa Schmitt[1,3] William Donovan[3–5] Gerard E. Francisco[3–5] Karl Schmitt[1,3,5] Anthony N. Moore[2] and Pramod K. Dash[1,2]

Molecular Psychiatry (2019) 24:501–522
https://doi.org/10.1038/s41380-018-0345-5

IMMEDIATE COMMUNICATION

Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs

A. B. Niculescu[1,2,3] · H. Le-Niculescu[1] · D. F. Levey[1] · K. Roseberry[1] · K. C. Soe[1] · J. Rogers[1] · F. Khan[1] · T. Jones[3] · S. Judd[1] · M. A. McCormick[1] · A. R. Wessel[1] · A. Williams[3] · S. M. Kurian[4] · F. A. White[2,3,5]

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- Putative biomarkers have yet unknown functions in chronic pain
- Understanding the biological function of putative biomarkers is necessary to define their **context of use** and **specificity**

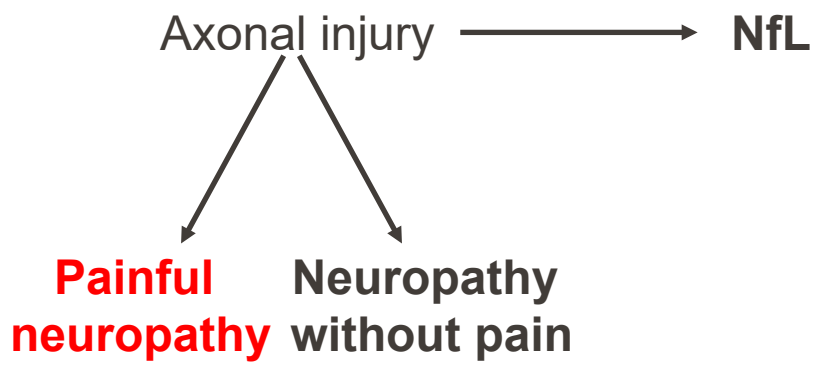
CellPress

ciences

Opinion

Neurofilament light chain as a biomarker of chemotherapy-induced peripheral neuropathy

Nanna E. Andersen [1], Wolfgang Boehmerle[2,3,4,5], Petra Huehnchen[2,3,4], and Tore B. Stage[1,*]



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The function of putative biomarkers can be determined in preclinical studies

Biomarkers as translational tools for drug development

Poor translation of analgesics developed in preclinical models

- Endpoints and outcomes often vary between preclinical and clinical studies
  Patient-reported outcomes, quantitative sensory testing, biochemical markers, etc.

Biomarkers could serve as unified measures

doi:10.1093/brain/awu377 BRAIN 2015: 138; 604–615 | 604

BRAIN
A JOURNAL OF NEUROLOGY

Evidence for brain glial activation in chronic pain patients

Marco L. Loggia,[1,2,*] Daniel B. Chonde,[1] Oluwaseun Akeju,[3] Grae Arabasz,[1] Ciprian Catana,[1] Robert R. Edwards,[2,4] Elena Hill,[5] Shirley Hsu,[1] David Izquierdo-Garcia,[1] Ru-Rong Ji,[2,6] Misha Riley,[1] Ajay D. Wasan,[2,4,7] Nicole R. Zürcher,[1] Daniel S. Albrecht,[1] Mark G. Vangel,[1] Bruce R. Rosen,[1,8] Vitaly Napadow[1,2,9] and Jacob M. Hooker[1]

Brain, Behavior, and Immunity 123 (2025) 11–27

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18 kDa Translocator protein (TSPO) is upregulated in rat brain after peripheral nerve injury and downregulated by diroximel fumarate

Rafael A. Cazuza [a], Sever M. Zagrai [a], Anamaria R. Grieco [a], Thomas D. Avery [b], Andrew D. Abell [b], Hsiao-Ying Wey [c], Marco L. Loggia [c,d], Peter M. Grace [a,*]

Biomarkers as translational tools for drug development

Poor translation of analgesics developed in preclinical models

- Endpoints and outcomes often vary between preclinical and clinical studies
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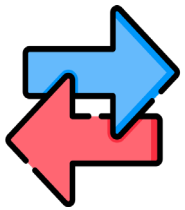
Biomarkers could serve as unified measures

Gain mechanistic insights into the results from interventional clinical trials

Summary and conclusions



Preclinical models can support discovery and development of human biomarkers of pain

- Biomarkers may be discovered in preclinical studies
- Preclinical models can be used to develop biomarkers and guide their application

Translational biomarkers may enhance preclinical and clinical drug development