EDITORIAL

Translational Research in Headache: From Bench to Bedside and Back Again

Investigação Translacional em Cefaleias: Do Laboratório à Prática Clínica e Regresso ao Laboratório

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Introduction

Over the last three decades, discoveries originating from experimental models have progressively shaped clinical investigation and transformed therapeutic strategies. Conversely, clinical observations have generated hypotheses that can be addressed by laboratory research. This bidirectional process embodies the essence of translational research, and migraine represents one of the most successful examples of translational neuroscience. In headache medicine, this "bench-to-bedside-and-back" paradigm has produced remarkable examples of how fundamental neurobiological insights can lead to targeted therapies, diagnostic and prognostic tools and how patients themselves can become the source of new scientific questions.

Among neurological disorders, headache is a global health challenge which accounts for adequate diagnosis and treatment management strategies to reduce its burden.[1,2] Once largely interpreted through vascular theories, migraine is now recognized as a complex brain disorder involving neuronal excitability, neuropeptide signaling, sensory processing, immune system involvement, and genetic susceptibility.[3,4] Continued dialogue between experimental science and clinical observation will remain essential to drive future discoveries and disease management, with physician-scientists occupying the critical interface between both worlds, making headache medicine a paradigm for translational neuroscience (**Fig. 1**).

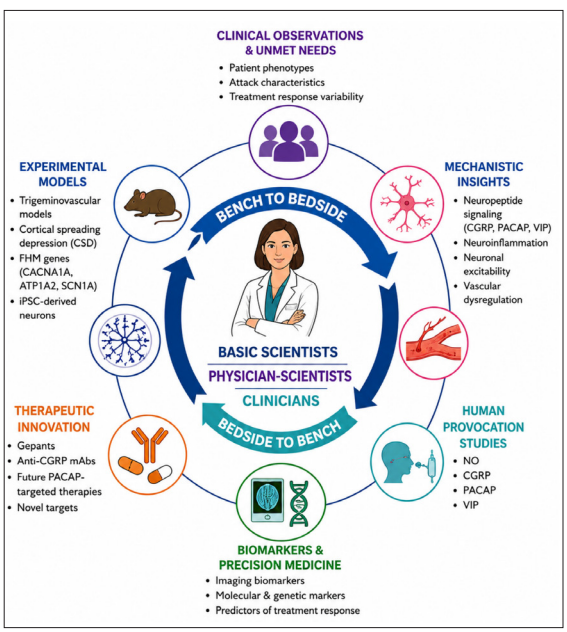

Figure 1. Translational research cycle in headache research. Clinical observations and unmet needs generate hypotheses that are investigated through experimental models. Mechanistic discoveries are subsequently tested in human provocation studies, leading to biomarker development and therapeutic innovation. Real-world clinical outcomes generate new hypotheses, completing a continuous bench-to-bedside and bedside-to-bench cycle where physician-scientists occupy the central interface connecting all stages.

CGRP, calcitonin gene-related peptide; PACAP, pituitary adenylate cyclase-activating polypeptide; VIP, vasoactive intestinal peptide; CSD, cortical spreading depression; FHM, familial hemiplegic migraine; CACNA1A, calcium voltage-gated channel subunit alpha1 A; ATP1A2, ATPase Na+/K+ transporting subunit alpha 2; SCN1A, sodium voltage-gated channel alpha subunit 1; iPSC, induced pluripotent stem cell; mAbs, monoclonal antibodies; NO, nitric oxide. Image generated using ChatGPT (OpenAI) with DALL·E.

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Experimental Models of Headache

Animal models have been fundamental for understanding migraine pathophysiology.[2,4] Despite the inherent difficulties associated with pain research, including the subjective nature of symptoms such as pain and photophobia, available models reproduce selected biological components of migraine and have enabled a better understanding of the molecular and signaling pathways underlying this condition.[4]

Among the most widely used approaches are trigeminovascular activation models, inflammatory stimulation of the meninges, nitroglycerin-induced hyperalgesia, and cortical spreading depression models that reproduce mechanisms underlying migraine aura.[4,5] These paradigms have established the importance of trigeminal afferents, central sensitization, neurogenic inflammation, and altered neuronal excitability. Furthermore, migraine is increasingly recognized as the consequence of multiple interacting biological processes and pathways rather than a single mechanism.[6,7]

Genetic models have provided additional insights into migraine pathophysiology. Studies of familial hemiplegic migraine mutations involving *CACNA1A*, *ATP1A2*, and *SCN1A* genes have improved our understanding of cortical spreading depression, ion channel dysfunction, and glutamatergic neurotransmission, reinforcing the concept that migraine is fundamentally a disorder of brain excitability.[4] These models have also contributed to elucidating the molecular mechanisms linking genetic susceptibility with altered neuronal and network function.

More recently, advances in translational neuroscience have expanded beyond traditional animal models. Human-derived cellular systems, induced pluripotent stem cells, and multimodal approaches integrating molecular, electrophysiological, and imaging techniques offer unprecedented opportunities to investigate migraine mechanisms in human tissues. These emerging technologies may enhance translational validity and facilitate the development of more precise and individualized therapeutic strategies.[7,8]

Provocation Studies: A Unique Human Translational Model

One of the most distinctive contributions of headache research to translational medicine is the development of human provocation studies. Unlike most neurological disorders, migraine attacks can be experimentally induced in susceptible individuals through administration of specific molecules. Beginning with nitric oxide donors and subsequently extending to calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide (PACAP), vasoactive intestinal peptide (VIP), prostaglandins, and other mediators, provocation paradigms have provided a controlled model of migraine attacks in humans.[8,9]

Importantly, these studies demonstrated that vasodilation alone does not fully explain migraine generation, challenging traditional theories and shifting attention toward neuronal and neuropeptide mechanisms.[6] Provocation studies have therefore become a powerful translational platform capable of validating therapeutic targets before starting drug development programs.[8-10]

The CGRP Revolution: A Model of Successful Translational Research

Perhaps one of the most relevant examples of successful translational research in neurology is the development of therapies targeting CGRP. Experimental studies demonstrated the presence of CGRP within trigeminal neurons and its release during migraine attacks.[4,9] Clinical investigations subsequently showed that intravenous CGRP administration could trigger migraine attacks in susceptible individuals.[8,9] These observations culminated in the development of monoclonal antibodies and gepants targeting the CGRP pathway.[11,12] The success of these therapies has revolutionized migraine management and validated decades of mechanistic research.

Following the success of CGRP-targeted therapies, increasing attention has focused on PACAP. Experimental evidence suggests that PACAP participates in trigeminovascular activation, nociceptive transmission, and autonomic responses associated with migraine.[13] Human provocation studies have shown that PACAP38 infusion induces migraine-like attacks in susceptible individuals, providing strong translational evidence for its biological relevance.[14,15]

Although initial therapeutic trials have produced mixed results, PACAP research exemplifies the iterative nature of translational medicine, in which negative findings often refine rather than invalidate mechanistic hypotheses.

Clinical Cohorts, Biomarkers, and Precision Medicine

The emergence of large prospective cohorts and real-world registries has expanded translational research

beyond target identification.[16] Longitudinal studies now provide opportunities to investigate disease progression, treatment response, and safety in populations often underrepresented in randomized clinical trials.[17]

Biomarkers represent one of the greatest unmet needs in headache medicine both for classification and treatment response prediction. Candidate biomarkers include circulating neuropeptides, inflammatory mediators, genetic variants, neuroimaging signatures, electrophysiological measures, and digital phenotyping. This challenge likely reflects the biological complexity of migraine. Rather than representing a single disease entity, migraine probably encompasses multiple endophenotypes with distinct mechanisms and therapeutic susceptibilities, which further highlights the importance of disease-specific biological profiles and treatment safety considerations in this population.[18] Similarly, advances in neuroimaging have highlighted the potential role of imaging biomarkers in improving diagnostic accuracy and deepening our understanding of migraine pathophysiology.[19] Therefore, integrating clinical, molecular, imaging, and omics data may facilitate the development of precision medicine approaches in migraine.[16]

Predicting Treatment Response: Challenging Assumptions and Future Perspectives

One of the most relevant translational questions concerns prediction of therapeutic response, where there is a clear need for larger studies integrating clinical and biological variables.[16] Beyond efficacy prediction, contemporary cohorts increasingly address treatment safety and disease-specific phenotypes, illustrating the expanding scope of translational headache research. These efforts are progressively moving the field toward precision medicine, where treatment decisions may eventually rely on integrated clinical, biological, and imaging signatures rather than isolated clinical variables.

The future of translational headache research will likely rely on multidimensional approaches integrating basic neuroscience, human provocation models, neuroimaging, genetics, artificial intelligence, and large clinical datasets accessible to researchers worldwide. Advances in single-cell technologies, multi-omics platforms, and machine learning may allow identification of biologically meaningful migraine subtypes and facilitate individualized treatment decisions.[20] Simultaneously, patient-derived models and biomarkers may strengthen the connection between experimental findings and clinical outcomes, with physician-scientists playing a central role in this process.[16]

Migraine has evolved from one of the least understood neurological disorders to one of the most successful examples of mechanism-based therapeutics in neurology. The field is now entering a new era in which biomarkers, multimodal phenotyping, and precision medicine may allow treatments to be tailored to individual biological profiles. Continued dialogue between laboratory science and clinical observation will remain essential to drive the next generation of discoveries in Neurology. Headache medicine continues to demonstrate the transformative power of translational research, with physician-scientists occupying the critical interface between bench and bedside. ■

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