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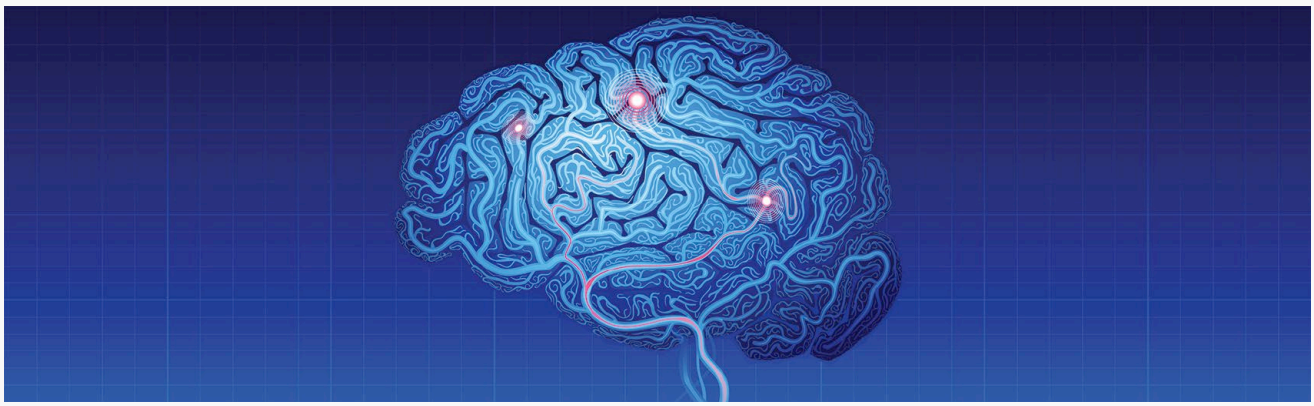

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STRATEGY

HEAL-ING PAIN AT NIH

By Emily Cukier, Senior Writer

In a move that could change how pain is studied and treated, NIH is planning a series of projects to build a platform for translational research that is more predictive and reproducible than the current paradigms. The agency hopes to find new strategies to intercept chronic pain as it develops and spur development of non-addictive therapies.

NIH's Helping to End Addiction Long-Term (HEAL) Initiative, launched in April and described in a June *Journal of the American Medical Association* viewpoint, offers a path to a coordinated effort to capitalize on emerging ideas and new technologies in the field. The interdisciplinary program is part of the institute's response to the opioid crisis and seeks solutions through preclinical, clinical and community-based research.

Increasingly, researchers are putting forward new hypotheses about the biology of pain that incorporate the whole brain, rather than specific circuits that travel through the spinal cord, and that take into account cognitive and mental state as well as physiology.

"The classic idea of pain dependent on a single receptor is just not true. The whole brain is involved," said A. Vania Apkarian, a professor of physiology at Northwestern University's Feinberg School of Medicine.

In addition, emerging technologies, from imaging to induced pluripotent stem (iPS) cells, are generating opportunities to upend the classical animal models of pain that have been poor predictors of clinical activity.

Rebecca Baker, special assistant to the NIH Director on Pain and Opioids, told BioCentury there's been a long history of poor translation to the clinic that has held back progress in understanding and treating pain.

"When they went into human trials, the candidate drugs were not effective even though they were hitting the target. Meaning our models for understanding the neurobiology of pain in animals had not been helpful," said Baker.

Baker is HEAL's point person in the Office of the Director.

The HEAL initiative draws on funding from an FY18 $500 million Congressional appropriation for research on opioid addiction, development of opioid alternatives, pain management and addiction treatment. Of HEAL's $266 million planned budget, over $48 million is tagged for research on enhanced pain management, covering discovery biology, preclinical screening, data and asset sharing, biomarkers and a clinical trials network (see "Table: HEAL Funding FY18").

The initiative's plan reflects a yearlong collaboration with patients, advocates, academics, industry and government to identify unmet needs and areas of greatest opportunity to combat the opioid crisis, and includes measures to improve treatments for opioid misuse and addiction, as well as alternative methods for pain management.

HEAL's initiatives will feed into a series of public-private partnerships to promote development of new non-addictive pain treatments.

Linda Porter, director of the Office of Pain Policy at NIH's National Institute of Neurological Disorders and Stroke (NINDS), said one important goal is to uncover imaging or other biomarkers that can distinguish different pain conditions.

"Does osteoarthritis look different from fibromyalgia or neuropathic pain? And looking at those chronic states, is it helping us understand mechanistically how best to treat them?" she told BioCentury.

NIH has allocated $20.1 million of the proposed HEAL budget to fund research into human cell-based screening models for pain, and an additional $3 million for preclinical animal models. The agency hopes to use the results to build a coordinated set of standardized preclinical tests that will increase understanding of why certain candidates fail and enable comparisons among existing and new compounds for pain.

An additional $20 million will go to projects to discover and validate new pain targets.

One of the most forward-thinking ideas in HEAL is the Acute to Chronic Pain Signatures Program, which aims to find a signature in patients with acute pain who are at greater risk of developing chronic pain. This opens up the possibility of developing preventive treatments as well as therapies for established disease. It is funded through the NIH Common Fund.

The remaining roughly $5 million will go to public-private partnerships targeting data and asset sharing, biomarker discovery and validation, and a clinical trials network.

The trials network will conduct Phase II studies of compounds contributed by companies, and will be open to contributions from academia and other sources. Baker said NIH and partners can use the preclinical platform to prioritize compounds to study in the network based on the odds of successful translation.

Biomarkers discovered in the pain signatures program and elsewhere in HEAL will also be tested in the clinical trials network.

NIH initially plans to prioritize projects that look at pain pathways shared across multiple conditions so that the resulting products could be used for a broad population.

ANIMAL TRAINERS

Robert Gereau, a professor of anesthesiology at Washington University School of Medicine in St. Louis, thinks both the funding areas and the priorities that NIH outlined in the HEAL research plan are on the right track to address key challenges in developing pain therapies.

"As a basic scientist working for a couple of decades trying to identify new things to treat pain, I feel there's a path forward now," he said.

According to Baker, one of NIH's first goals is to learn more about why animal models have failed, by studying why they were poorly predictive and using that knowledge to standardize how they are used in future therapeutic programs.

Multiple factors play into the problems with preclinical pain models. Animal and human neurons can differ in their protein

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NIGHT MOVES

Vium Inc. has found at least one way to get better data from preclinical pain models using its platform for automated continuous animal observation: watching mouse activity at night.

The company's Vium Smart Housing cages use sensors and high-definition cameras to continuously capture data such as breath rate, activity and circadian rhythms, plus changes to the animals' environment.

CSO Laura Schaevitz said Vium chose to study the platform in pain because assessing pain in animal models has been labor intensive, and because it can capture behaviors that are useful measures without having to disturb the animals.

She said so far gross motion — measured by how fast animals move about their enclosures — best correlates to pain and pain relief among models the company has tested. She added that Vium has shown that animals thought to be in pain are less active than control mice, and become more active again when given analgesics.

Schaevitz said video capture is particularly helpful because the activity difference is most pronounced at night, when it is less likely to be observed.

"At the time when an experimenter would not be in the room, that's when they would be the most active, and that's when you see them not running around as much," she said.

Vium has partnered with an undisclosed company to use the platform to assess a mouse model of neuropathic pain. According to Schaevitz, the company has seen changes in animal behavior with induced neuropathic pain that it plans to describe in an upcoming publication.

— *Emily Cukier*

makeup, with versions that lack strong homology or carry different post-translational modifications. Target proteins in animals may not be expressed in the same neuronal circuits as in humans.

On top of that, said Gereau, findings from animal pain models can be difficult to replicate because behavioral testing requires a high level of operator training to perform consistently. Plus, small variations in experimental conditions can greatly affect the results.

"Little tiny details of experimental procedures that are not reproduced 100% from lab to lab can cause a great deal of variability," he said.

For chronic pain, the models fail because there are many different underlying pathologies, whose biological basis is largely unknown. "It's very difficult to develop an animal model if you don't know what causes the disease condition in a human," said Gereau.

Baker agreed that even where the lack of translation is well documented, the reasons can be difficult to deconvolute.

For example, animal models suggested a role for substance P in pain because inhibitors of its receptor, TACR1, could alleviate pain — as well as other neurological disorders. But clinical studies of TACR1 antagonists failed to recapitulate the results. Hypotheses for the difference include poor animal models, differences in blood-brain barrier penetration, or an unexpected role for TACR1 signaling after it is internalized into endosomes (see "Insider Signaling").

Baker said with the platform, NIH hopes the community can test pain compounds known to work alongside those that didn't translate, and use the resulting knowledge base to make better choices about which experimental compounds to advance.

She said animal models will also be important for studying devices, which NIH thinks will have their own place in a new pain treatment arsenal.

While Gereau thinks the initiative is headed in the right direction, he hoped NIH would go a step further and help create centralized preclinical pain testing facilities to run the standardized batteries more quickly and consistently than individual laboratories can.

"If you can get access to trained people with all the equipment and space to get things done quickly, you can accelerate a program by a year," he said.

Clifford Woolf, director of the F. M. Kirby Neurobiology Center at Boston Children's Hospital, thinks HEAL should place more emphasis on animal models of chronic pain states, such as the conditioned place preference model.

HEAL FUNDING FY18

The tentative FY18 budget for the **National Institutes of Health (NIH)** Helping to End Addiction Long-term (HEAL) Initiative comes from a $500 million Congressional appropriation for research on opioid addiction support. The planned budget earmarks over $200 million to improve treatments for opioid misuse and addiction, and around $50 million for research into pain management, with $10 million for supplemental expenses and the remainder carried into the following year. NIH's fiscal year 2018 started on Oct. 1, 2017.

NIDA = National Institute on Drug Abuse; *Source: NIH*

Improve Treatments for Opioid Misuse and Addiction	
Focused medication development to treat opioid use disorder (OUD) and prevent/reverse overdose	$70.3
Development of novel immunotherapies for OUD	$5.0
Reduction of drug craving and harm in people with OUD	$1.0
Advancing clinical trials for neonatal opioid withdrawal	$10.0
Enhanced NIDA clinical trials network for opioid research	$29.0
Justice community opioid innovation network	$5.8
HEALing communities study	$96.3
Enhance Pain Management	
Discovery and validation of novel targets for safe and effective pain treatment	$20.0
Human cell-based screening models to identify and profile non-addictive therapeutics for pain	$20.1
Preclinical animal models to identify and profile non-addictive therapeutics for pain	$3.0
Data and asset sharing for new pain therapies	$2.1
Biomarkers for new pain therapies	$1.2
Clinical trials network for new pain therapies	$1.8
Consortia management	$0.2
Total FY18 (tentative)	**$265.6**

"That may be more complicated, but that's what we need," said Woolf.

He said one way to get better data out of that and similar models is to apply neural network learning to videos of the animals.

Networks would be trained to automatically detect when animal behavior starts to reflect disease processes, or when an intervention is helping resolve them. This could give an unbiased and continuous assessment of animal behavior, compared to periodic observations made by a technician.

At least one company is already doing so to study pain. Vium Inc. is using its Smart Housing cages to continuously monitor and record animal behavior and has found that mouse nighttime activity correlates with pain (see "Sidebar: Night Moves").

> "The classic idea of pain dependent on a single receptor is just not true. The whole brain is involved."
>
> A. Vania Apkarian, Northwestern University

ORTHOGONAL SUPPORT

The initiative also calls for better early stage tools such as cell-based models of human neurons that can boost or verify data from animals and provide additional information about underlying biology before candidates are moved into human testing.

Baker said NIH is interested in engineered iPS cell models of neurons that play roles in pain or reward circuits, as the latter play a role in therapies' addictive potential. It would also like to see projects to develop multicellular models, such as tissue chips or bioprinted tissue models, to study more elaborate neuronal interactions.

NIH's National Center for Advancing Translational Sciences (NCATS) has been working on chip and bioprinted models of neuronal tissue for the "past several years," said Baker, but it has not yet used them to investigate pain or addiction.

"We're taking those models that we've developed and asking specific scientific questions for these new targets that we seek to identify, or have identified in preliminary studies," she said.

NCATS will make the chip and bioprinted tissue models available to outside researchers who seek HEAL grants.

Gereau said having good human cell models could resolve problems with tissue scarcity, which is a major practical hurdle for researchers. His lab has used donated human tissue to confirm whether a pain target in rodents is expressed by the same neurons in humans, but getting the samples was slow, whereas engineered cells would be easier to access.

In addition, engineered human neurons open up new types of experiments for probing how pain arises and propagates through different pathologies.

Woolf said models of individual neurons can tease out the mechanisms that underlie susceptibility to pain, and probe how compounds could affect them. For example, he said his group has made gene-edited neurons using CRISPR that express hyperexcitable Nav1.7 channels, and screened them for compounds that restore normal excitability.

Cell-based models could also recapitulate different disease processes that lead to pain.

"If we can take inflammatory mediators and add them to neurons, they become sensitive and hyperexcitable. That may reflect the process that occurs," said Woolf.

PREVENTING THE PROBLEM

The initiative's goal to find a signature that predicts who is at risk of developing chronic pain from acute insult is rooted in the fact that most opioid misuse stems from improper use during outpatient treatment for chronic pain (see "Perception into Pain").

HEAL's Acute to Chronic Pain Signatures Program will fund prospective longitudinal studies of patients with acute pain associated with surgery or musculoskeletal trauma.

The signature could include factors like protein expression levels, metabolites, differences in neuronal circuits, sensory testing and psychosocial assessments.

NINDS's Porter said NIH is particularly interested in how imaging can contribute to the signatures, in light of data from Apkarian's and other labs showing differences in the brains of acute pain patients whose pain turns chronic, and changes as chronic pain develops or recedes.

In a longitudinal study of 24 patients with subacute back pain published in *Neuron* in 2015, Apkarian's lab showed that properties of brain white matter and corticostriatal functional connectivity could each predict development of chronic pain over one year with at least 80% accuracy. The study used T1 imaging, diffusion tensor imaging (DTI) and fMRI.

"What we're seeing is the brain is already predisposed to take one route or the other," Apkarian told BioCentury.

He said combining multiple imaging techniques of brain anatomy and function with genetic information improves predictive power.

Porter said the resulting signatures could change how pain is treated, as well as the therapeutic goals. Rather than simply

managing acute pain, interventions should also try to prevent the changes in neural circuitry that underlie chronic pain.

"Maybe they need more coping skills, or chronic medicine, or physical therapy. If successful, that study will help us perhaps figure out how better to treat acute pain to prevent chronic," she said.

Porter said NIH will be looking for studies that test potential pain signature elements where there is already some evidence of a role in chronic pain.

Apkarian thinks the signatures could also encourage pursuit of a broader set of pain targets than currently being investigated.

Until recently, the brain's role in pain has been underappreciated as research focused on sensory neurons and the spinal cord, he said.

Longitudinal studies that show how the brain changes in chronic pain could broaden the types of targets one might pursue beyond individual ion channels associated with skin or spinal cord neurons to those that can modulate brain circuits involved in pain.

COMPANIES AND INSTITUTIONS MENTIONED

Boston Children's Hospital, Boston, Mass.
National Center for Advancing Translational Sciences (NCATS), Bethesda, Md.
National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, Md.
National Institutes of Health (NIH), Bethesda, Md.
Northwestern University Feinberg School of Medicine, Chicago, Ill.
Vium Inc., San Mateo, Calif.
Washington University School of Medicine in St. Louis, St. Louis, Mo.

TARGETS

Nav1.7 (SCN9A) - Sodium voltage-gated channel α subunit 9
Substance P (NK1)
TACR1 (NK1R) – Neurokinin 1 receptor

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