Research team describes new preclinical system to better turn lab discoveries into effective treatments

September 20 2023

Credit: CC0 Public Domain

It is an all-too-common fact that potential drugs can look extremely promising in preclinical laboratory testing but fail when it comes to

effectively treating humans. To better translate promising lab findings into effective new treatments, a team of researchers from the Keck School of Medicine of USC has developed and tested an innovative new system for conducting preclinical research on six potential new stroke treatments, identifying the strongest candidate for further study.

"We now have a feasible preclinical research system to find promising stroke therapies with a higher chance of success in clinical trials," said Walter J. Koroshetz, MD, director of NIH's National Institute of Neurological Disorders and Stroke (NINDS).

Rather than relying on a single laboratory led by one investigator to test a potential new drug, Patrick D. Lyden, MD, professor of physiology and neuroscience and of neurology at the Keck School of Medicine of USC, coordinated the efforts of a network of laboratories to conduct preclinical research on potential stroke treatments combined with intravascular thrombectomy. A central coordinating body at the Keck School of Medicine developed detailed protocols for the labs to follow to ensure higher levels of scientific rigor than traditional preclinical testing models.

"For years, we have tested drugs on animals first, but we often get it wrong," said Lyden, who is lead author of a study about this network and the research it carried out which was just published in *Science Translational Medicine.* "Our primary goal with this research was to show there is a better way to do preclinical testing and that this is one way to get better results that can be replicated."

Better models, more rigor

The network, dubbed the Stroke Preclinical Assessment Network, or SPAN, consisted of six laboratories in different locations across the U.S. The team at the Keck School of Medicine was not directly involved in

any of the testing. Lyden and his team developed the protocols and procedures the network had to follow; handled the preparation and distribution of the study drugs; collected and analyzed all outcome data; and created a unique system of blinding the testing to prevent bias.

One critical innovation the team instituted, in addition to increasing the number of laboratories involved, was to use animal models that resembled typical stroke patients. Instead of testing drugs mostly on young male mice and rats, as Lyden says is often the case in preclinical research, the researchers also included older mice, mice with diet-induced obesity or hyperglycemia, and rats that were spontaneously hypertensive. The rodents were also evenly split between male and female.

Lyden's team also developed new ways to build more scientific rigor into preclinical testing, standardizing the randomization and blinding practices among the different labs.

All animals in SPAN were logged at USC by the research laboratories using an online database. The animals were randomly assigned to treatment by the USC team and then treated at the appropriate research laboratory. When it came to blinding the study, the team at USC turned all the substances into identical looking powders, assigned them numbers as their only identification and shipped them to the various labs. One of the six treatments involved a medical device that could not be concealed.

"We showed that it is feasible to improve the scientific rigor of preclinical testing and how it can be done," said Lyden. "If research is being done without as much rigor as possible, it is a waste of time, taxpayer money and animal lives."

A possible candidate

The central coordinating team at the Keck School of Medicine also employed a novel statistical method to evaluate the six treatments at four points in the process. While all the substances had been selected for inclusion based on prior research showing promise as a stroke treatment, the USC team analyzed the efficacy of each of the substances at these four points by giving the animals a series of functional tests.

Based on the results of those tests, substances that failed to show sufficient efficacy were dropped. Using this new statistical method, three substances were dropped after the second evaluation, and two more were dropped after the third. Only one substance, uric acid, showed efficacy through all four phases of analysis.

Although uric acid appeared promising in the SPAN trial using the primary endpoint, there were no signs of benefit using the other secondary endpoints. Hence, the SPAN investigators recommend additional animal studies of uric acid before recommending clinical trials in human stroke patients.

"The study acted as we intended it to by sequentially eliminating the futile drugs until we were left with one," said Lyden. "We believe uric acid, based on this evaluation, should be studied further."

More information: Patrick D. Lyden et al, A multi-laboratory preclinical trial in rodents to assess treatment candidates for acute ischemic stroke, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.adg8656

Provided by Keck School of Medicine of USC

effective treatments (2023, September 20) retrieved 27 April 2024 from https://medicalxpress.com/news/2023-09-team-preclinical-lab-discoveries-effective.html