THE TURKISH JOURNAL OF
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From the Editor

MOVING BEYOND ANIMAL MODELS

Since I became the Editor in Chief of the Turkish Journal of Gastroenterology 18 months ago, this publication has only accepted manuscripts reporting research that did not directly involve the use of animals. This policy is still in effect, and will continue to be because it embodies the high scientific and ethical standards that researchers expect from our journal.

There is a growing concern about the lack of applicability of animal research to humans. The U.S. Food and Drug administration, for example, reports a 92% failure rate of clinical trials following preclinical success in animal studies (1), and this number was reported to be as high as 95% more recently (2).

> ***Animal models may not be the right way to go***

Many reasons for this overwhelming failure have been discussed, including reporting and publication bias, poor study design, inadequate sample size and inappropriate statistical analysis, and low reproducibility in animal studies, leading researchers to conclude that "it is nearly impossible to rely on most animal data to predict whether or not an intervention will have a favorable clinical benefit-risk ratio in human subjects." (3). These concerns should be taken seriously, and measures should be implemented accordingly, including journal editors avoiding publishing this misleading work.

Aside from the limitations of preclinical study design and reporting, however, there is a bigger and deeper problem that does not have any easy solution, and that is the influence of intrinsic species differences. Several systemic reviews have pointed out that animals are poor models for human pathophysiology. For example, "Animal models of stroke mimic at best less than 25% of all strokes", and all of the 100 experimental neuroprotective drugs failed in clinical trials despite promising results in animal models (4). Furthermore, it has been more than 10 years since the recommendations of Stroke Therapy Academic Industry Roundtable criteria, yet even with the best studies that adhere to the criteria "the ultimate proof that plain standardization of procedures in fact increases the rate of successful translation from bench to bedside in stroke research is still missing." (4). Genetic differences have contributed to the failure of acute inflammation (such as sepsis, trauma and burns) research using mice (5). It has been shown that "Among genes changed significantly in humans, the murine orthologs are close to random in matching their human counterparts" (5). There have been nearly 150 clinical trials testing inflammatory drugs in critically ill patients, and all of them have failed, prompting researchers to suggest the need of "higher priority for translational medical research to focus on the more complex human conditions rather than relying on mouse models to study human inflammatory diseases" (5). The influence of genetic differences is not limited to species that are less similar to humans. In fact, even chimpanzees and other primates have critical genetic differences that make translation to humans unreliable (6-8). There have been more than 200 clinical trials for vaccines against human immunodeficiency virus (HIV), but none of them made it through despite preclinical success in chimpanzees and other non-human primates (9). The Institute of Medicine has determined that "most current biomedical use of chimpanzees is unnecessary" (10) and the National Institute of Health (NIH) of the United States has stated that experiments on chimpanzees—who are more genetically similar to humans than any other animals— "rarely accelerated new discoveries or the advancement of human health for infectious diseases." (11). The list goes on and on.

The problems with the use of animals in biomedical research are widely recognized. Dr. Don Nicholson, former vice president of the pharmaceutical giant Merck, acknowledged that "The limitations of animals as stand-ins for human

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patients are a major reason [for failure]. Animal disease doesn't faithfully replicate asthma, for instance. The condition is uniquely human, and animal models can't capture the constriction of airways and all of the other characteristics of the disease." "We have found great mechanisms that can control asthma in an animal," he says. "And most of them have failed" in humans (12). Dr. Richard Klausner, former director of the National Cancer Institute, said "The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades—and it simply didn't work in humans." (13). Dr. Elias Zerhouni, former director of the U.S. NIH has stated: "We have moved away from studying human disease in humans," he lamented. "We all drank the Kool-Aid on that one, me included." With the ability to knock in or knock out any gene in a mouse—which "can't sue us," Zerhouni quipped—researchers have over-relied on animal data. "The problem is that it hasn't worked, and it's time we stopped dancing around the problem...We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans." The current director of NIH, Dr. Francis Collins, has also agreed that the failure of animal

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models in the area of sepsis, for example, is "a heartbreaking loss of decades of research and billions of dollars" and announced NIH's commitment to developing novel non-animal methods known as organs on chips (14).

A 2014 BMJ article discussing systematic reviews of the translation of animal research concluded, "if animal researchers continue to fail to conduct rigorous studies and synthesise and report them accurately, if research conducted on animals continues to be unable to reasonably predict what can be expected in humans, the public's continuing endorsement and funding of preclinical animal research seems misplaced." (15).

The history of cancer research has been a history of curing cancer in the mouse

I agree. The scientific community has been too content with animal experiments and even applauded serendipitous findings from animal studies, not realizing that the opportunistic approach is dangerous and misleading.

When we recognize that the reliance on inherently flawed animal models of human disease are largely responsible for clinical failure—beyond the limitations of study design and reporting and selective use of species that are genetically further from humans—it does not make sense to continue to promote this practice. Human-relevant approaches should be more aggressively developed and utilized instead. Fortunately, non-animal research methods like established clinical, computational and in vitro models abound, (16) and new technologies like guts (17) and other organs-on-chips (18) are constantly being developed and validated. With the implementation of these modern technologies, scientists do not need to rely on experiments that harm animals and that we know will likely never improve human health.

We challenge other scientific journals to do the same!

As a scientific publication, we have a special role in steering the direction of future endeavor. Researchers have warned that "Each time... potential treatments is observed to be effective based upon animal research, it propagates numerous further animal and human studies consuming enormous amounts of time and effort to prove that the observation has little or no relevance to human disease or that it may have been an artifact of the animal model itself." (19).

Given the limitations of animal models, publishing animal studies would mislead the scientific community into futile research and give the general public false hope. This is unethical. We encourage submissions of studies with human-relevant approaches such as clinical, in vitro, in silico, and other non-animal methods, and we challenge other scientific journals to do the same. The Turkish Journal of Gastroenterology is a "cruelty-free journal", to both humans and non-human animals, and we believe that this policy would foster positive changes in the current research system and facilitate much-needed medical progress.

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Editor in Chief

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