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WEIZMANN INSTITUTE SCIENTISTS DISCOVER THAT PHEROMONES REGULATE AGGRESSION OF NON-MOTHER FEMALE MICE TOWARD PUPS IN WILD-DERIVED MICE

REHOVOT, ISRAEL—August 5, 2014—Laboratory mice are one of the most common animal models used in biological and medical research. Thousands of laboratory mouse strains are produced by artificial selection – the process by which humans breed animals over dozens of generations for particular traits. This has led to the domestication of mice: strengthening specific qualities that make them well-adapted for research under laboratory conditions, such as rapid reproduction, while eliminating characteristics that are not conducive to research, for example, aggression, the desire and ability to escape from danger, and anxiety caused by environmental disturbances.

However, the artificial selection process also caused the mice to lose the very important trait of being able to survive in the wild. Besides these lost traits, the female lab mice developed the tendency to immediately mate with every male in their vicinity, including siblings and parents. That is, they lost the ability to selectivity choose a mate according to traits that "promise" the offspring better genes and a higher survival rate than those who share a common descent. At the same time, they evolved the willingness to take care of pups belonging to "strangers" (even if they are not themselves mothers). The strains of lab mice chosen to undergo further artificial selection are those who are not "fussy eaters," grow faster, and reach sexual maturity more quickly relative to wild mice. That is how we ended up with larger, less aggressive mice that reproduce at a younger age and are less particular when it comes to choosing a mate. In other words, these strains are quite different from wild mice with regard to structural, physiological, and behavioral features.

Dr. Tali Kimchi of the Weizmann Institute of Science's Department of Neurobiology understood that these laboratory mouse strains are not suitable for answering some types of questions posed by her research, which focuses on the neural

and genetic roots of social behavior, including reproduction and maternal instinct (for example, a mother's aggression toward another's offspring, and the role of odors – pheromones – in mate selection and caring for offspring). Therefore, Dr. Kimchi had to develop a unique mouse strain, restoring those properties removed from the laboratory mouse strains, while retaining the ability to employ genetic engineering tools to create mutant strains (a genetic change that disables the function of a particular gene).

To do this, Dr. Kimchi and her research group backcrossed strains of laboratory mice that had a specific mutation in the gene responsible for detecting pheromone signals, with wild-derived (undomesticated) mice for ten generations. As a result, in these new backcrossed strains of mice, the scientists managed to reinstate traits typical of wild mice, which were lost through the domestication process and, thus, are absent in laboratory strains. These include traits pertaining to behavior, body structure, hormones, various biological processes, and genetic functions. More specifically, the team restored, among other things, the ability to react to and escape from danger, spontaneous anxiety-related jumping and freezing behavior, and aggressive attacks toward other females. Another important feature that was restored in the new breed of mice was maternal instinct: Naïve (not yet mated and maternal), backcrossed, wild-derived female mice were less likely to nurture another's pup; they were also aggressive toward those pups, as well as among themselves – just like wild mice.

The new mouse model created by Dr. Kimchi and her team has allowed them to explore, for the first time, the biological roots of aggressive behavior in females, both toward each other and, especially, toward the pups of others. It also enabled them to locate a particular gene, which is responsible for the perception of pheromone signals, and to determine this to be the main cause for rejecting a stranger's pup, as well as the aggressive behavior displayed toward such pups. A pup's mother, it turns out, is the one and only, and stepmothers, naturally, are more aggressive toward others' offspring. Their findings, published in the journal *Nature Communications*, provide the basis for developing additional mouse strains that will enable a better understanding of the

neural and genetic basis of behavior relating to reproduction in females, and the differences between males and females.

Dr. Kimchi hopes that further research will lead, in the future, to improved understanding of the biological mechanisms underlying social and reproductive processes that have – until now – been impossible to explore in standard lab mice. Her work may also lead to a better understanding of the social component of neuropsychiatric diseases, which is manifested in different ways in men and women. Such knowledge will contribute to improving the development of drugs targeted to the different sexes and, in particular, will enable analysis of the effect of certain drugs on women.

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