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Island Eradications of the Future: RNAi as a Selective Tool

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ABSTRACT: Rodents cause devastating damage to both agriculture and ecosystems worldwide. Invasive rodents are commonly found on islands, historically free of these animals, and have significant negative impacts on both native plant and animal species. Rodents are exceptionally well adapted to their environments and therefore, quite challenging to control. Current control strategies often include large scale applications of toxicants, which have potential adverse effects on non-target wildlife. In island ecosystems, these adverse effects are a major hurdle to eradication efforts. The time and financial resources required to minimizing risks to non-target species and performing post-eradication exposure monitoring can limit the number of islands from which rodents are successfully eradicated. Therefore, the development of new species-specific rodenticides would be a valuable advancement in the effort to control these pest species, especially for island eradications. To that end, USDA Wildlife Services is investigating the use of interfering RNA (RNAi) as a novel way to control rodent species.

RNAi reduces the amount of a specific protein that is made by a cell. This is done through post-transcriptional gene-silencing. The RNAi pathway is initiated when a small section of double stranded RNA is introduced into the cytoplasm of a cell. This double stranded RNA comprises a guide strand and a passenger strand. In the first step of the RNAi pathway, the foreign RNA is incorporated into an enzyme complex called RNA-induced silencing complex (RISC) at which time the passenger strand is degraded. The RISC/RNA complex then finds the complementary mRNA made by the cell and binds to it. Subsequently, the RISC complex degrades the complementary mRNA. This breaking down of the mRNA prevents the synthesis of the corresponding protein. The reduction in protein synthesis is the benchmark of RNAi and is how it will be used to elucidate lethal physiological changes in pest species.

The species specificity of RNAi depends on the selection of portions of genes that are unique to the target animal species. By screening the rodent genome and comparing sequences of rodent genes to non-target species, we can choose sections of genes that are present in the pest species and absent in the non-target species. Previous research has established guidelines for both the nucleic acid composition of RNAi sequences and their location in the corresponding mRNA that facilitate maximum inhibition of protein synthesis while maintaining species specificity. Therefore, unlike current rodenticides, if non-target species consume the RNAi they will not be affected. This specificity could allow for the eradication of rodents from islands that have historically not been feasible.

For RNAi to be useful as a rodenticide, it will likely have to be formulated in a bait for oral consumption. This is a significant hurdle: most RNAi based therapeutics for human use are formulated for intravenous or subcutaneous injection. Like all rodenticide baits, an RNAi-based bait will have to be stable in a wide range of environmental conditions and have a long shelf life. However, once consumed by the target animal, RNAi-based baits will have to be significantly more complex than traditional toxicant baits. The double stranded segments of RNA will have to be protected from the changing pH of the digestive tract and absorbed into the systemic circulation while maintaining viability. Once in circulation, RNAi molecules must be delivered to the target tissues at concentrations high enough to elucidate a physiological response. Advances in bioengineering have given researchers products that both hide RNAi inside stable exterior shells and direct these carrier molecules to the site of action. These cutting-edge technologies make the development of a RNAi-based rodent bait a feasible option.

The use of RNAi for rodent control shows promise because of its species specificity and low non-target impact. RNAi sequences are selected to sections of the rodent genome that are significantly different from non-target species genes and therefore do not bind to and degrade the non-target mRNA. Formulating RNAi into oral baits presents challenges but recent advances in bioengineering have led to the development of mechanisms for delivery useful for this application of RNAi. RNAi-based baits will be a great benefit to efforts to eradicate rodents off islands because they will reduce the time and funding necessary to mitigate risks to non-target species and the environment.

KEY WORDS: eradication, gene silencing, interfering RNA, island, non-target species, novel toxicant, rodent control, RNAi, species-specific toxicant

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