A Risk Assessment Framework for Paratransgenesis

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Paratransgenesis is a novel approach to control of vector-borne disease. In the paratransgenic approach, symbiotic bacteria of a disease-transmitting arthropod vector are genetically transformed to export molecules with activity against a targeted pathogen. We developed a system for control of Chagas disease using the vector *Rhodnius prolixus* and its symbiont, *Rhodococcus rhodnii.* In this system *R. rhodnii* is genetically transformed to express cecropin A, an insect immune peptide with activity against *Trypanosoma cruzi*, the parasite causing Chagas disease. Field application of the paratransgenic approach would involve environmental release of a genetically modified bacterium, an event associated with potentially significant risks. We have developed a comprehensive framework for evaluating risks associated with paratransgenic disease control. We contend that the principles informing this framework can be applied to a spectrum of transgenic disease interventions.

For purposes of explanation, our risk assessment framework will be presented in four stages. The first stage involves identification of adverse outcomes. Here adverse outcomes were identified and considered for assessment of risk on the basis of four criteria: (1) documentation in the scientific literature as a hazard associated with introduction of a novel or genetically modified organism, (2) concern expressed by regulatory, advocacy, or scientific organizations, (3) biological plausibility, and (4) magnitude of effect.

This process selected four adverse outcomes for assessment: toxicity, fitness alteration, transfer to non-target organisms, and transgene instability. In the second stage of the framework, these outcomes were assessed for risk. Assessments were designed and executed pursuant to the following objectives: (1) evaluation under conditions of maximal probability, (2) laboratory simulation of environmental conditions, (3) scale invariance, and (4) uniform spatial and temporal extension. Examples of these will be discussed.

Initial assessment of the risk of adverse outcomes perforce treats these as discrete events detectable in identified populations. There are, however, potential impacts of the paratransgenic approach not amenable to this methodology. Release of large numbers of engineered microbes has the potential to disrupt ecosystems by displacing established organisms, decrementing biodiversity, and altering equilibria of microbial communities. Assessment of these impacts involves biotic communities and requires investigation in the context of microbial and vector ecology. Therefore, assessment of community ecology impacts is the focus of the fourth stage of our risk assessment framework. The emphasis here is on the extrapolation of assessment of discrete events to the community level using cognate methodologies. Examples of environmental simulations, predictive models, and post-release monitoring and rescue strategies will be presented.

The fourth and final stage of our risk assessment framework involves stakeholder oversight. Fellow researchers, regulatory personnel, public health officials, and members of at-risk groups all have a stake in risk assessment of paratransgenic intervention. Presenting results of a risk assessment program in a setting where dialogue can take place will facilitate incorporation of the concerns and insights of these groups in an ongoing risk assessment program. A proposal for a forum for constructive dialogue between researchers, regulatory agencies, advocacy groups, and representatives of at-risk groups will be presented. Principles of milestone-gated communication will be reviewed and illustrated with examples. How such a forum could be used to facilitate transfer of the research and assessment apparatus to stakeholders in the endemic region will be discussed.

The concluding section of the presentation will emphasize the fundamentally heuristic nature of transgenic risk assessment. Special attention will be paid to the inverse relationship of efficacy and risk. The importance of establishing a minimum effective release (MER) will be illustrated. The potential for applications of network theory models, remote sensing data, and nanotechnology in risk mitigation will be introduced.