To Know the Road Ahead, Ask Those Who Traveled before You:
A Modified Chinese Proverb Mixed with LINEs

Kenneth S. Ramos, MD, PhD, PharmB, ATS
Texas A&M University Health
TOXICOLOGY IN THE NEWS
ON THE INTERSECTION OF TOXICOLOGY AND MEDICINE

1950s
• Francis Kelsey’s efforts precluded widespread use of thalidomide in the US

1970s
• Dichlorodiphenyltrichloroethane (DDT) was banned for use in Sweden in 1970 and the US in 1972

2000s
• Completion of the Human Genome Project enabled the study of gene-environment interactions in efforts to define the molecular bases of chronic human disease
Marked overexpression of LINE-1 transcripts upon induction of transdifferentiated phenotypes by BaP or its CYP-derived metabolites.

DEMOCRAPHICS OF THE HUMAN GENOME

- Genome is not static, with ~45% of sequences able to mobilize to different locations
- Only 2% of the genome encodes for protein following standard definitions
**LINE-1 RETROELEMENTS**

**5’UTR:** contains a promoter region with regulatory sequences that bind YY1, RunX3, and E2F/Rb

- **ORF1:** encodes an RNA-binding protein that shuttles L1 RNA
- **ORF2:** encodes endonuclease and reverse transcriptase activities

A 3’UTR with a poly A tail

L1 is silenced by DNA methylation and reactivated by reversal of epigenetic marks
IMPACTS OF L1 IN THE HUMAN GENOME

Evolution
Insertion, Duplication, Inversion Mutations
Inhibition of Gene Transcription
Developmental Programming
Alternative Splicing Sites
Exon Skipping
Alternative Promoters
DNA Strand Breaks
DNA Repair
Genetic Reprogramming
“Survival of the Fittest”
Genome-based evaluations for increased diagnostic precision

Targeted therapies to improve pharmacologic efficacy and decrease toxicity

Optimized clinical management based on molecular diagnostics, stratification, and prevention
Catalysts
✓ Health care costs and suboptimal efficiencies
✓ Advances in technology and integration
✓ Reframed expectations, with emphasis on prevention
VISION IS THE ART OF SEEING WHAT MAY BE INVISIBLE TO OTHERS
JONATHAN SWIFT

➢ EDUCATION DEFINES THE PATH FORWARD
➢ MAKING A DIFFERENCE IN THE WORLD (FOR ME THROUGH THE LENS OF SCIENCE)

Be stubborn on vision and flexible on details
TAKING OWNERSHIP AND EMBRACING RESPONSIBILITY

SERVICE DEFINES STRONG LEADERSHIP

A COMMITMENT TO MAKING A DIFFERENCE IN OUR WORLD

People join because of great vision and leave because of poor leadership
ACKNOWLEDGMENTS

Family at home and in the laboratory
Collaborators

AstraZeneca, NAS, NCI, NIEHS, NHLBI