

# NOVEL ANTI-RETROVIRAL DRUG TARGETS

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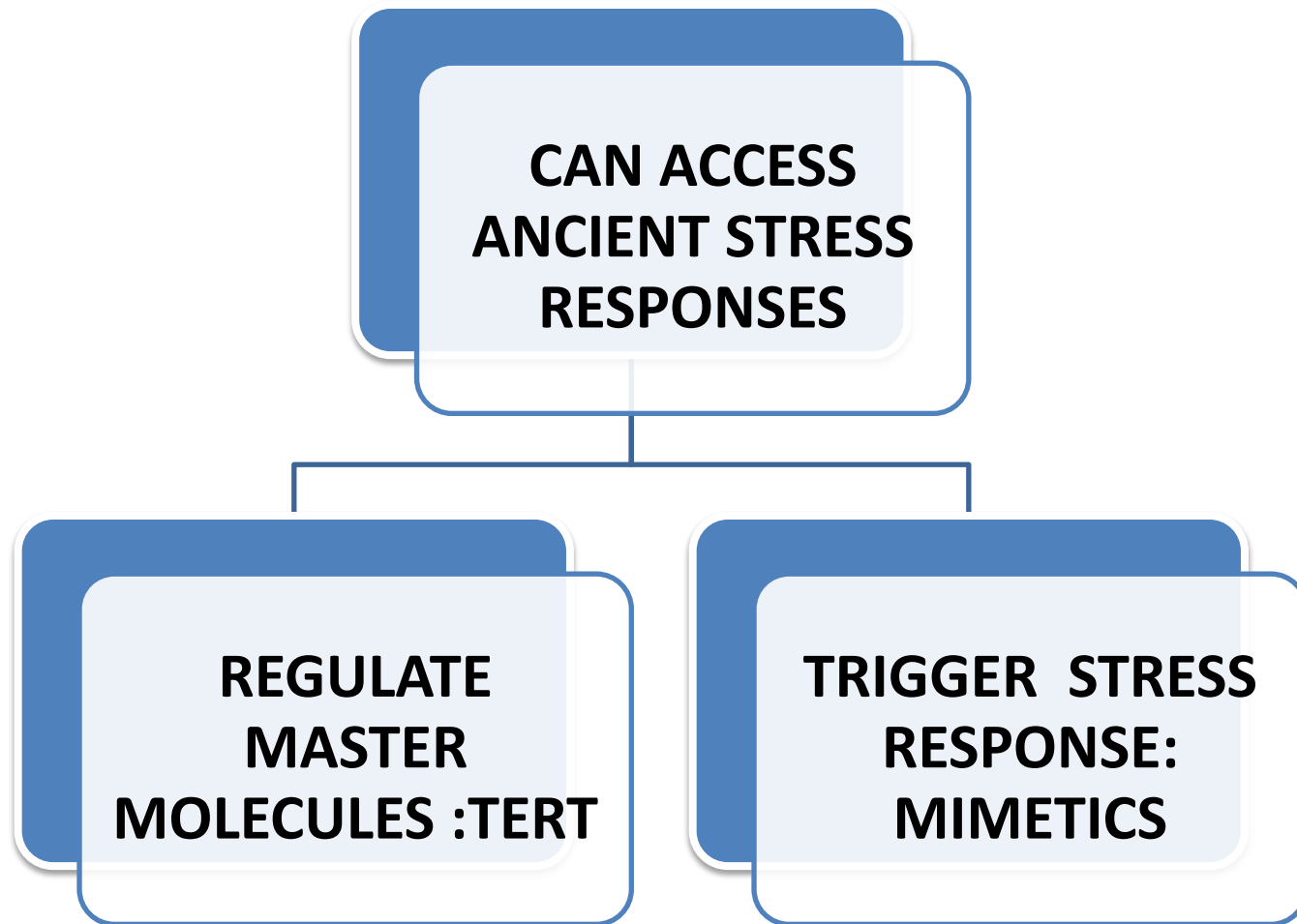
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# GOAL: PROPOSAL

**ACCESS ANCIENT  
ANTISTRESS  
PATHWAYS FOR HIV  
THERAPEUTICS**

**UTILIZE ANTI-STRESS  
DRUGS USED FOR CANCER,  
ALZHEIMERS, STROKE,  
HEART ATTACK,  
NEUROLOGICAL DISEASES,  
WOUND HEALING**

# STRATEGY: ACCESS CONSERVED STRESS RESISTANCE FOR HIV THERAPY



# WHY MASTER SURVIVAL REGULATOR: TELOMERASE

**MAINTAINS  
CHROMOSOME  
ENDS (TERT-  
TERC)**

**MITOCHONDRIAL  
TERT-RMRP  
PROTECT**

# TELOMERASE: SUBUNIT FOR HIV?

**TOUTED ANTI-  
AGING  
MIRACLE  
TELOMERES.**

**THE MIRACLE  
WORKER:  
RATHER,  
REVERSE  
TRANSCRIPTASE**

**TERT**

# STRUCTURE TERT LIKE RETROVIRUS & BACTERIOPHAGE

**HIGH RESOLUTION TERT  
STRUCTURE:**

**COMMON RNA-BINDING  
RING CONFIGURATION  
DOMAIN OF FINGERS  
PALM AND THUMB  
ORGANIZATION**  
**(retroviral reverse  
transcriptase, viral RNA  
polymerases, and  
bacteriophage B-family DNA  
polymerases)**

**TERT NON TELOMERE**

**PLAY TIME ACTIVITIES**

**REVERSE TRANSCRIPTASE**

**PROMICUOUS “PARTNERS”**

**RNA DEPENDENT DNA POLYMERASE**

**RNA DEPENDENT RNA P OLYMERASE**

**CONTROLS MASTER SWITCHES OF GENE  
EXPRESSION**

**DETERMINES CELL DEATH VS SURVIVAL**

# PROMISCUOUS TERT INTERACTIONS

**GENERATES MITOCHONDRIA (siRNA), tRNA, double stranded RNA (TERT-RMRP)**

**MASTER REGULATOR PATHWAYS CONTROLS**

**(I.E. WNT/CATENIN, NF $\kappa$ B, NOTCH, P53, STRESS, APOPTOSIS, P15ink4b)**

**TARGETS TO REGULATE TERT**



# TERT LIKE RETRO-TRANSCRIPTASE

**TERT RNA  
DEPENDENT  
cDNA  
POLYMERASE:**

**MITOCHONDRIAL  
TERT:  
tRNA FOR cDNA  
SYNTHESIS (LIKE  
COMMERCIAL  
RETRO-  
TRANSCRIPTASE).**

**NUCLEUS  
TERT: USES  
TERC FOR  
cDNA for  
TELOMERES**

# TERT IS, **NOT** ONLY TELOMERES : ALSO MITOCHONRIA DICTATOR

TERT FIVE PARTIALLY  
INDEPENDENT  
CONTROL  
FUNCTIONS:

- TELOMERE  
ELONGATION,
- CELL DIVISION
- CELL DEATH,
- DNA DAMAGE,
- LIFESPAN

TELOMERE  
MAINTENANCE  
ONLY **ONE** OF  
TERT  
"PARTNERS"

# TERT & MITOCHONDRIA RETROVIRUS

**LOOKS  
LIKE A  
DUCK**

**ACTS  
LIKE  
A  
DUCK**

**TALKS  
LIKE A  
DUCK**

**TERT IS  
VESTIGE  
RETROVIRUS  
?**

# TERT AS PROTECTIVE STRESS HERO

**ELICITS  
SURVIVAL MASTER  
PATHWAYS**

**INHIBITS  
CELL DEATH**

**NUCLEUS  
TELOMERE  
KEEPER**

**MITOCHONDRIA  
INTEGRITY**

# TERT DARK SIDE (OVEREXPRESSED)

**ANTI APOPTOSIS  
HIV-INFECTED  
CELLS! HIV  
HOSTAGE?**

**KNOWN PROTECTOR  
OF CANCER CELLS.**

# **TERT** ROLE IN MDM VIRAL RESERVOIRS

**TERT EXCESS  
IN  
MONOCYTE  
DERIVED  
MACROPHAGES  
(MDM)**

**PROMOTES  
RESISTANCE  
TO  
APOPTOSIS**

**THERAPY:**

**MDM  
TARGET FOR  
TERT  
INHIBITORS  
NRTIs USED  
HIV &  
CANCER**

# AQUIRED IMMUNE DEFICIENCY

CD4+ CELL DEPLETION  
GREATLY EXCEEDS  
NUMBER OF  
INFECTED CELLS

# TERT IN CD4+ CELLS

**TERT IS DOWNREGULATED IN HELPER CELLS**

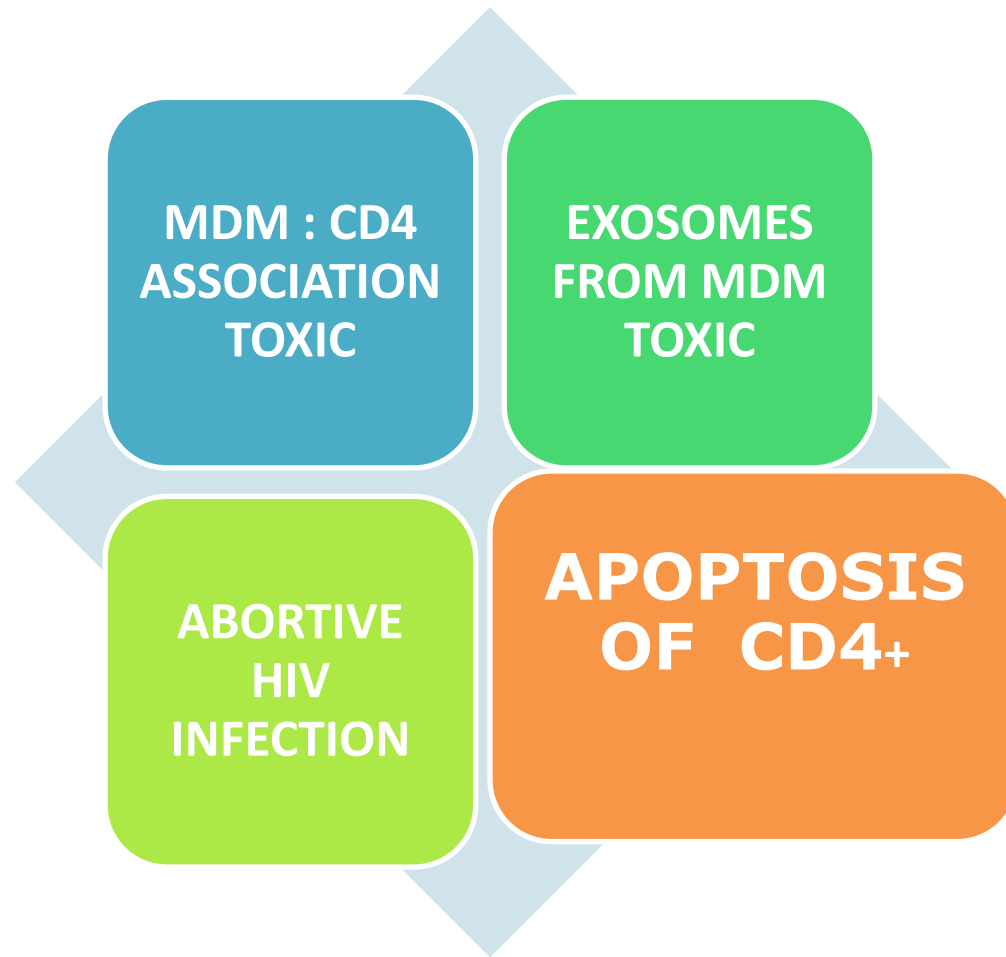
**THERAPY**

**TARGETED UPREGULATION OF TERT AGS 499 (Eitan et al 2012), siRNA of TAT (TAT INHIBITS TERT)**

**UNIVERSAL PEPTIDE FOR MDM SURFACE TO TRIGGER ACTIVATION OF IMMUNE RESPONSE**



# CD4+ BYSTANDER TOXIC ATTACKS



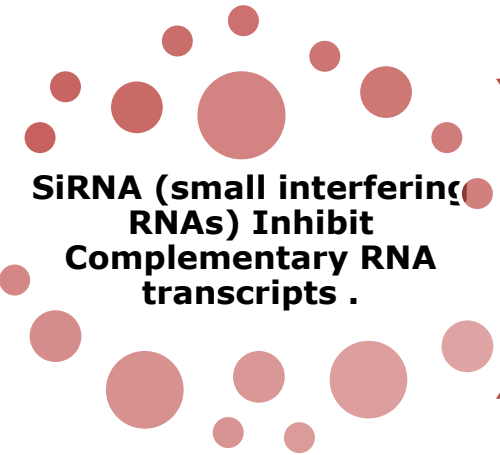
# ANTIVIRAL THERAPY : ACCELERATED AGING

Side Effects:  
TERT DEFICIT


Incidence of  
Age related  
symptoms with  
HIV therapy.

INTERVENTION:  
TERT  
ACTIVATION  
DRUGS

# HOW? HIV SPECIFIC DELIVERY VEHICLE SYSTEM: APTAMERS



**SiRNA (small interfering RNAs) Inhibit Complementary RNA transcripts .**



**Systematic enrichment of ligands "SELEX", FOR small nucleic acids with desired selective binding from nucleic acid libraries,**



**NOW: METAL IONS, AA, PEPTIDES & VIRAL VECTORS**

# AVAILABLE MAJIC BULLETS

Aptamers covalently linked with siRNA, micro RNA, DRUGS, toxins, SOS TRIGGERS. (“DRONES WITH BULLETS”)

IMMUNOLIPOSOMES ATTACHED TO DUAL ANTI VIRAL DRUGS AS STEALTH “TROJAN HORSE”(Ramana et al 2015)

# Dual antiretroviral drugs--modern Trojan horses to combat HIV

**Ramana et al.,  
2015 Stealth anti-  
CD4 conjugated  
immunoliposomes  
invitro**

**Blocked viral  
proliferation:  
co-delivery**

# TAR siRNA DECOY VEHICLE

**TAR microRNA is  
ANTI APOPTOSIS:  
PROTECTS VIRAL  
RESERVOIR.**

**ENGINEERED TAR RNA  
siRNA of HIV.  
TAR DECOY INHIBITED  
HIV EXPRESSION IN  
CHALLENGE . (TROJAN HORSE)**

# CELL-SPECIFIC OPPOSITE TERT THERAPY

ACTIVATE TERT ↑  
CD4 BYSTANDER  
CELLS

INHIBIT TERT ↓  
MDM INFECTED  
RESERVOIR

CD4+ THERAPY ↑TERT; siRNA ↓TAT, ↓ NOTCH

UPREGULATE TERT ↑(AGS 499,

DOWNREGULATE TAT↓ (siRNA): 1.Saquinavir (protease inhibitor); 2.SiRNA for TAT

NOTCH EXPRESSION ↓: GSIXX, (gamma secretase inhibitor) blocks Notch signaling (notch signal ↑ in kidney HIV & disease.)



# TERT OUT OF BALANCE

OVEREXPRESSION: PERMISSIVE TO  
HIV INFECTED AND CANCER CELLS,

NORMAL EXPRESSION:  
REGENERATIVE AND PROTECTIVE  
AGAINST TOXIC STRESSES IN CD4+.

# DISEASES WITH COMMON STRESS

## CAN USE COMMON DRUGS!!

DESPITE SYMPTOMS  
DIVERSITY  
-ROS & ENERGY  
DEPLETIONS

HIV,CANCER,  
ALHEIMERS, STROKE ,  
HEART ATTACK,  
NEUROLOGICAL  
DISEASES

TARGETED  
THERAPEUTIC DRUGS  
RESERVOIR FOR EACH  
OTHER

# HORMESIS A LITTLE BAD IS GOOD

LOW DOSES OF OTHERWISE HARMFUL AGENTS,

ACTIVATE STRESS RESPONSES.

MIMETICS OF THE NATURAL STRESSES :SERVE TO  
ACTIVATE SURVIVAL & LONGEVITY PATHWAYS

# STRESS RESPONSE TRIGGERS

**CONSERVED  
THROUGHOUT  
EVOLUTION**

**STRESSES: COLD,  
HUNGER,  
UV, OXIDATIVE  
STRESS, ENERGY  
DEPLETION,**

**MIMETIC  
TRIGGERS:  
HIBERNATION  
(DELTORPHIN)  
EXERCISE  
(AICAR)**

# HIBERNATION INDUCTION

(BEARS, WOCHUCKS, FROG ) TRIGGER

**DELTA OPIOIDS  
AGONIST TRIGGER**

**DELTORPHIN:δ  
OPIOID IN FROG  
SPECIES ( ANDES  
(INDUCES COURAGE)**

**BENEFICIAL:  
ISCHEMIC  
SHOCK,HEMORRAGE,  
STROKE,**

# T-OLIGOS DAMAGE MIMETIC

T-oligo, TELOMERE DAMAGE MIMETIC: CANCER therapeutic. ↑ p53 DIFFERENTIATION & caspase-mediated apoptotic cascade.

T-oligo ↑ antioxidant enzymes superoxide dismutase 1 and 2, protects cells from oxidative damage;

# COLD SHOCK RBM3: HIV THERAPY?

MEDIATES STRUCTURAL  
PLASTICITY

PROTECTIVE:  
NEURODEGENERATION

HIV BRAIN INJURY ?

# Hibernation and HIV RESPONSE

OPIOID RECEPTORS STIMULATION ACTIVATED CD4+ T cells SUPPRESSED HIV-1 EXPRESSION.

DELTORPHIN ↓ MARK 38 IN MACROPHAGES

MARK38 ↑ HIV BRAIN INJURY: deltorphin ?



# EXERCISE MIMETIC AICAR & HIV



# DRUG RESERVOIRS: MIMETICS OF STRESS

UNIVERSAL STRESS  
RESPONSE TRIGGERS

DISEASE CELLS: ↓  
STRESS PATHWAYS

BYSTANDERS ↑  
STRESS RESPONSE

- ALZHEIMERS, STROKE,  
SHOCK, NEUROLOGICAL  
DISORDERS, CANCER, HIV

**STRESS RESISTANCED BYSTANDER TRIGGERS: RECIPROCAL DRUGS:  
CANCER, HIV, ALZHMERS, SHOCK, HEART ATTACK, NEUROLOGICAL  
DISEASES, AND DIABERTES,**

## **TARGETED STRESS RESISTANCE**

**STIMULATE CELL-  
SPECIFIC BENEFIT**

**PREVENT  
INFECTION**

**MODIFY CANCER  
UNIVERSAL  
PEPTIDE**

**USE MIMETICS  
OF CONSERVED  
RESISTANCE**

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