NOVEL ANTI-RETROVIRAL DRUG TARGETS

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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

CAN ACCESS ANCIENT STRESS RESPONSES

REGULATE MASTER MOLECULES: TERT

TRIGGER STRESS RESPONSE: MIMETICS
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)
R E V E R S E  T R A N S C R I P T A S E

PROMICIOUS “PARTNERS”

RNA DEPENDENT DNA POLYMERASE

RNA DEPENDENT RNA POLYMERASE

CONTROLS MASTER SWITCHES OF GENE EXPRESSION

DETERMINES CELL DEATH VS SURVIVAL

TERT NON TELOMERE

PLAY TIME ACTIVITIES
PROMISCUOUS TERT INTERACTIONS

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

MASTER REGULATOR PATHWAYS CONTROLS

(I.E. WNT/CATENIN, NFκB, NOTCH, P53, STRESS, APOPOPOTOSIS, P15ink4b)

TARGETS TO REGULATE TERT
TERT LIKE RETRO-TRANSPIRTASE

TERT RNA DEPENDENT cDNA POLYMERASE:

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

NUCLEUS TERT: USES TERC FOR cDNA for TELOMERS
TERT IS, NOT ONLY TELOMERES: ALSO MITOCHONDRIA 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
CD4+ CELL DEPLETION GREATLY EXCEEDS NUMBER OF INFECTED CELLS
TERT IN CD4+ CELLS

TERT IS DOWNREGULATE 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

MDM : CD4 ASSOCIATION TOXIC

EXOSOMES FROM MDM TOXIC

ABORTIVE HIV INFECTION

APOPTOSIS OF CD4+
ANTIVIRAL THERAPY: ACCELERATED AGING

侧效应：TERT 缺乏

与 HIV 治疗相关的年龄相关症状的发病率。

干预：TERT 激活药物
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”)

IMMUNOLIPOPOSOMES 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 $\uparrow$ CD4 BYSTANDER CELLS

INHIBIT TERT $\downarrow$ MDM INFECTED RESERVOIR
CD4+ therapy upregulates TERT; siRNA downregulates TAT, NOTCH.

Upregulate TERT (AGS 499, Saquinavir, protease inhibitor); downregulate TAT (siRNA): 1. Saquinavir (protease inhibitor); 2. SiRNA for TAT.

Notch expression downregulated by GSIXX, gamma secretase inhibitor, blocks Notch signaling (Notch signal upregulated 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)
DELTA OPIOIDS AGONIST TRIGGER

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

BENEFICIAL: ISCHEMIC SHOCK, HEMORRAGE, STROKE,
T-OLIGOS DAMAGE MIMETIC


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

AICAR substitutes for exercise

AICAR extends golden hour after hemorrhagic shock

AICAR inhibited Tat-induced HIV-transactivation.
DRUG RESERVOIRS: MIMETICS OF STRESS

UNIVERSAL STRESS RESPONSE TRIGGERS

DISEASE CELLS: ↓ STRESS PATHWAYS

Bystanders ↑ STRESS RESPONSE
- ALZHEIMERS, STROKE, SHOCK, NEUROLOGICAL DISORDERS, CANCER, HIV
TARGETED STRESS RESISTANCE

- STIMULATE CELL-SPECIFIC BENEFIT
- PREVENT INFECTION
- MODIFY CANCER UNIVERSAL PEPTIDE
- USE MIMETICS OF CONSERVED RESISTANCE

STRESS RESISTANCED BYSTANDER TRIGGERS: RECIPROCAL DRUGS: CANCER, HIV, ALZHEIMERS, SHOCK, HEART ATTACK, NEUROLOGICAL DISEASES, AND DIABETES,
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