NOVEL ANTI-RETROVIRAL DRUG TARGETS

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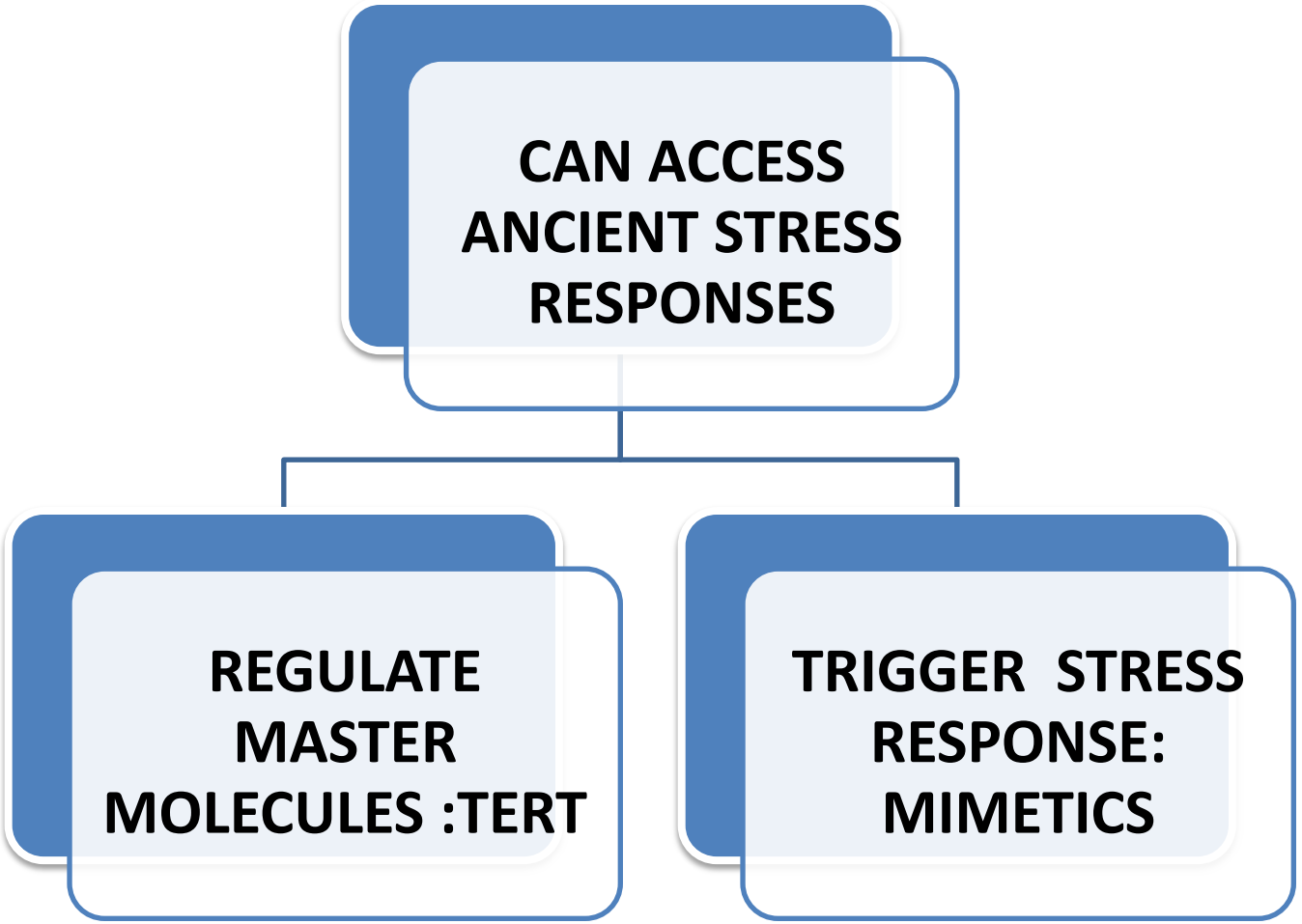
GOAL: PROPOSAL

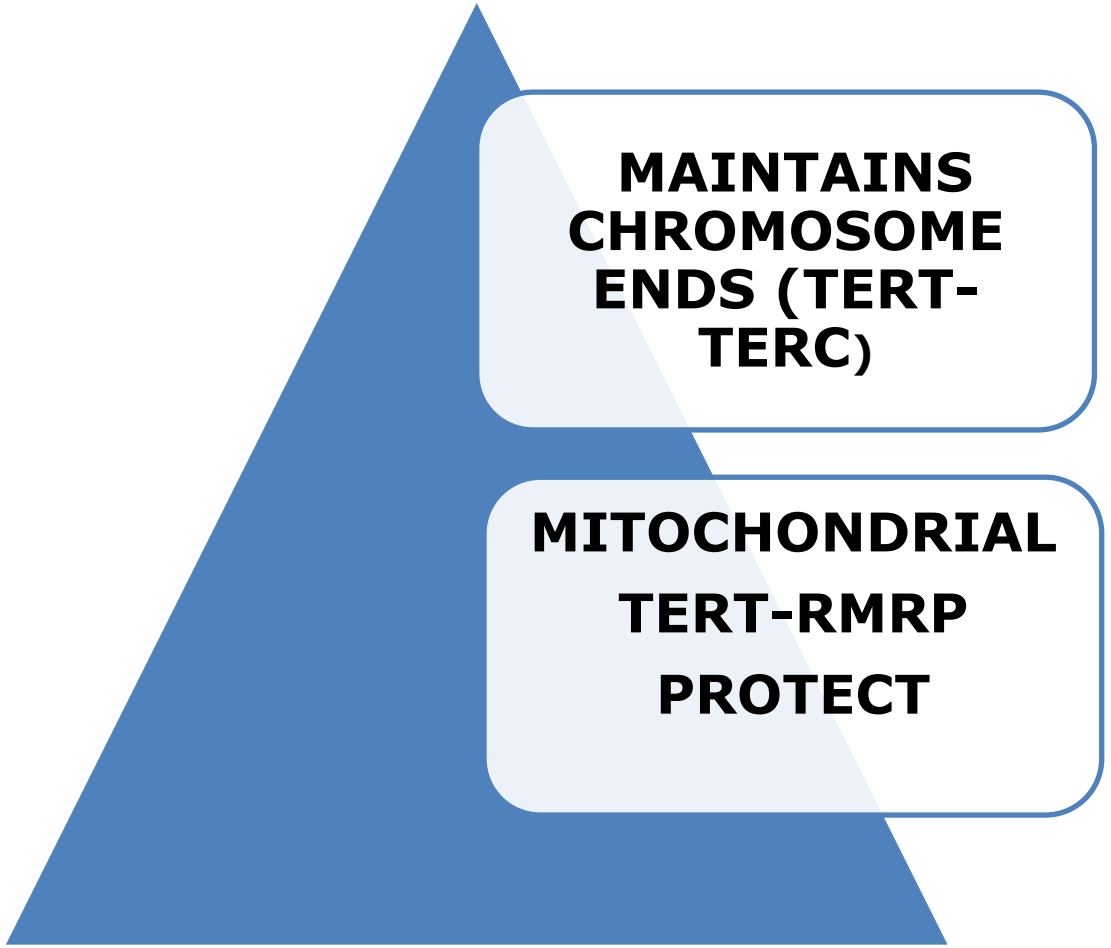
ACCESS ANCIENT ANTISTRESS PATHWAYS FOR HIV THERAPEUTICS

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

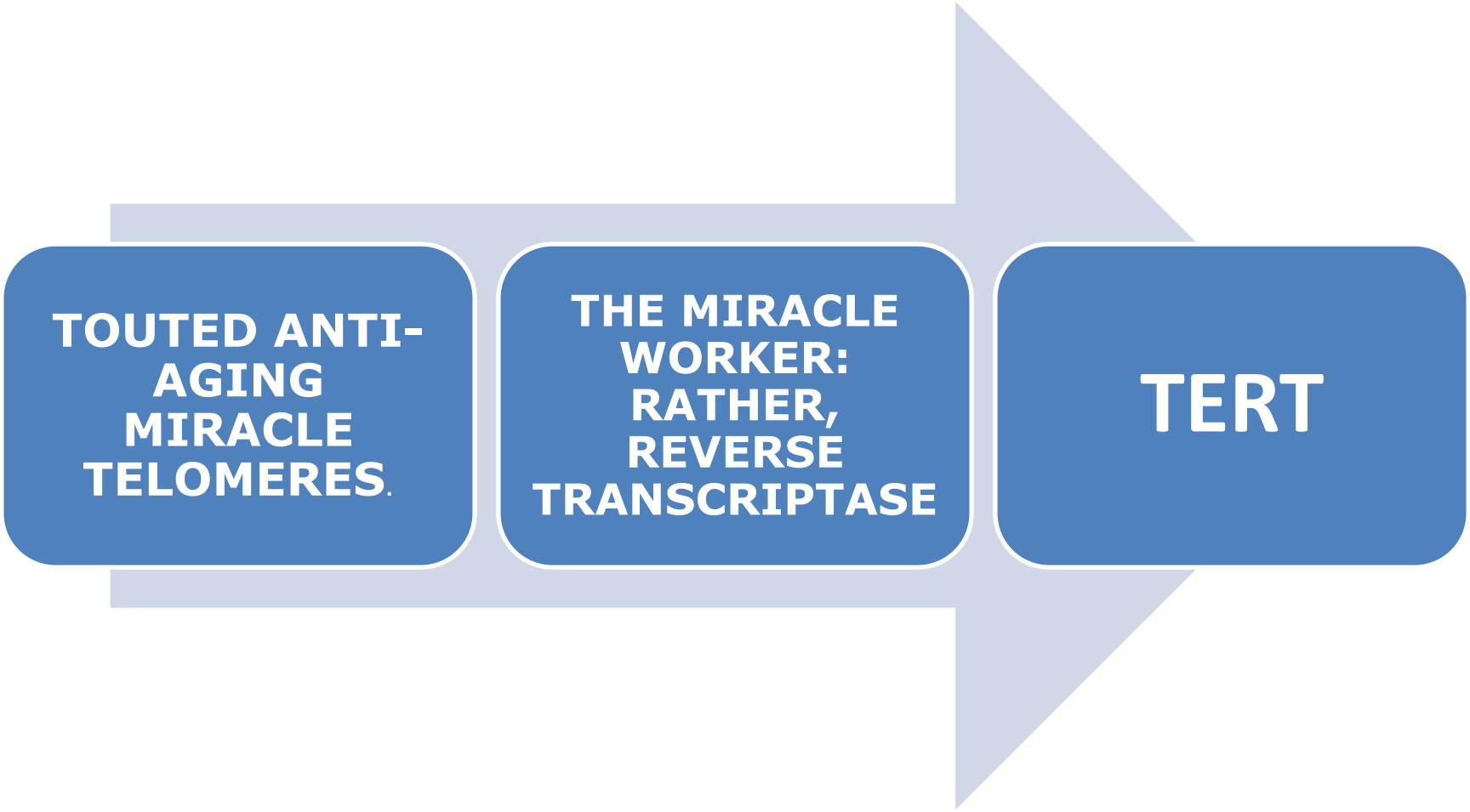
STRATEGY: ACCESS CONSERVED STRESS RESISTANCE FOR HIV THERAPY



WHY MASTER SURVIVAL REGULATOR: TELOMERASE



TELOMERASE: SUBUNIT FOR HIV?



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

R E V E R S E T R A N S C R I P T A S E

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, NFκB, NOTCH, P53, STRESS, APOPOTOSIS, P15ink4b)

TARGETS TO REGULATE TERT

TERT LIKE RETRO-TRANSCRIPTASE

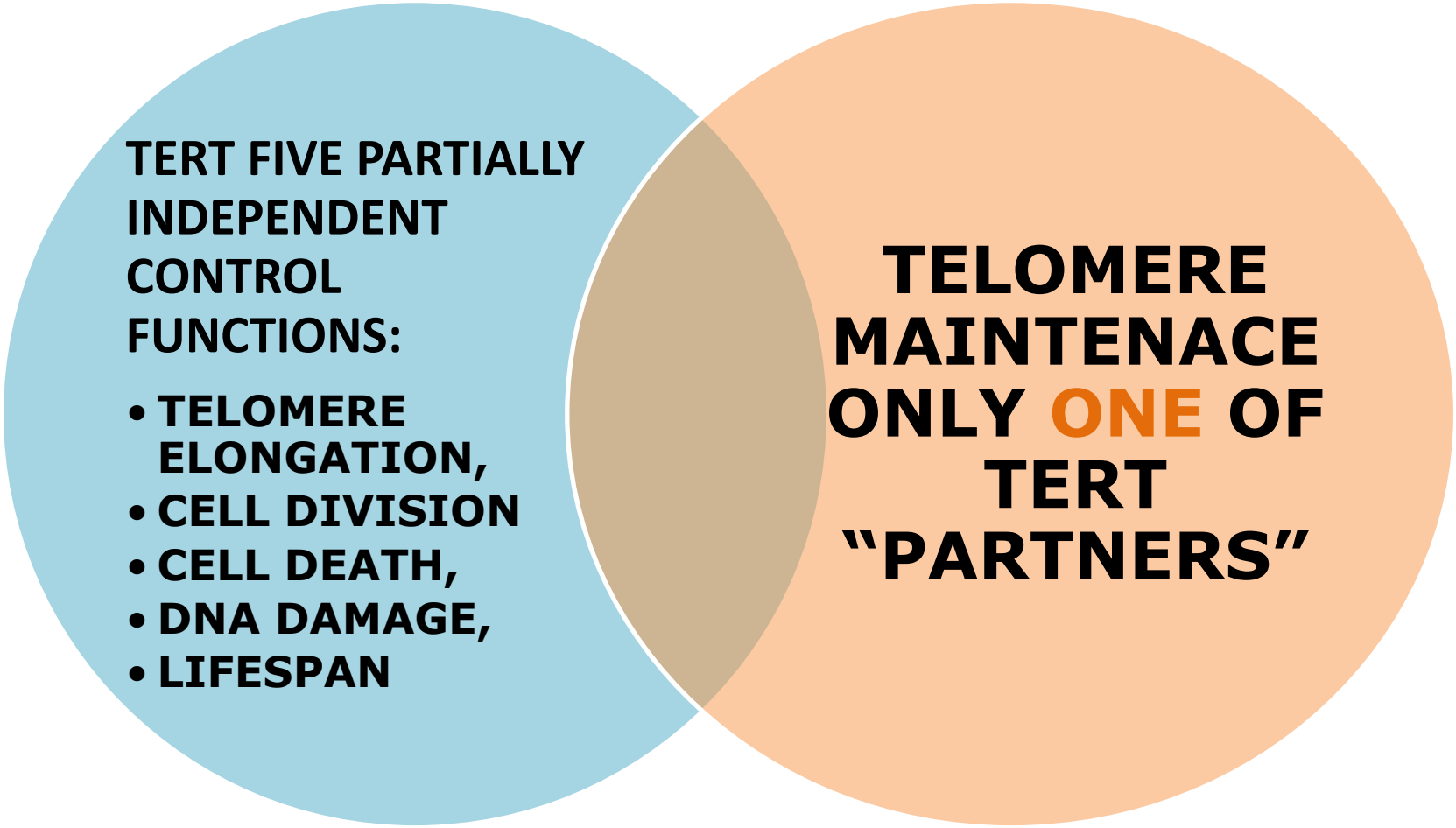
TERT RNA DEPENDENT cDNA POLYMERASE:

MITOCHONDRIAL TERT:

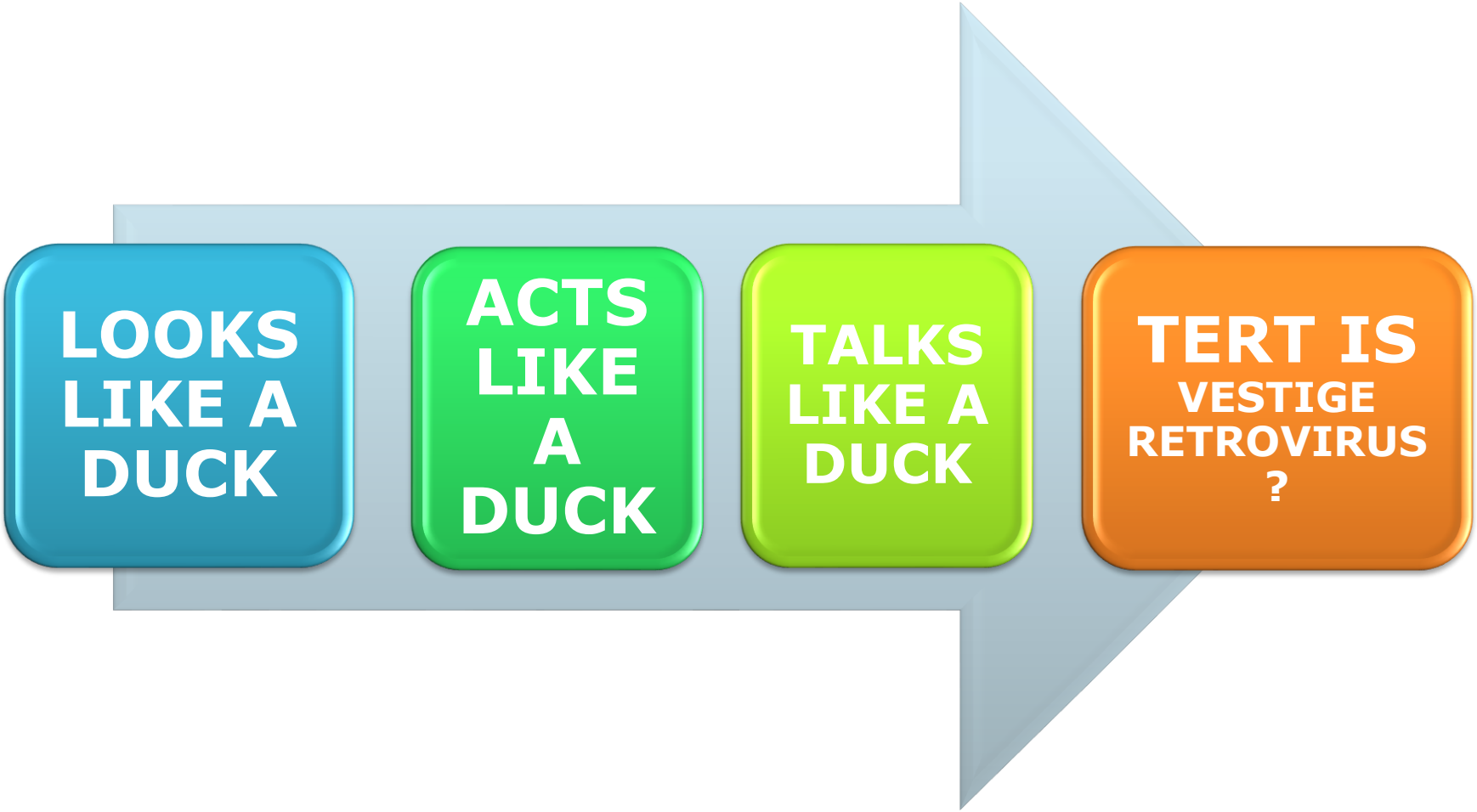
tRNA FOR cDNA SYNTHESIS (LIKE COMMERCIAL RETRO-TRANSCRIPTASE).

NUCLEUS TERT: USES TERC FOR cDNA for TELOMERES

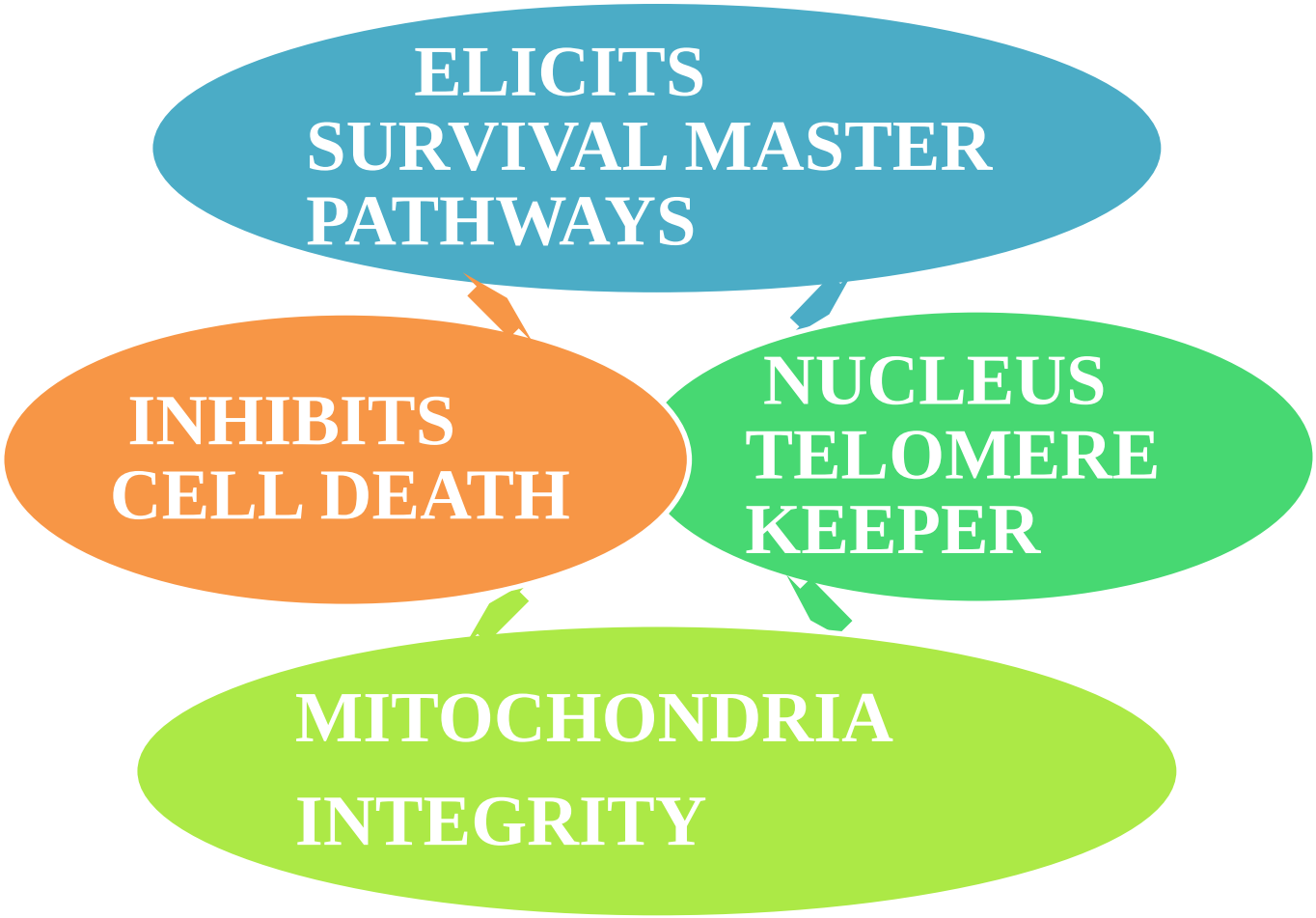
TERT IS, NOT ONLY TELOMERES : ALSO MITOCHONRIA DICTATOR



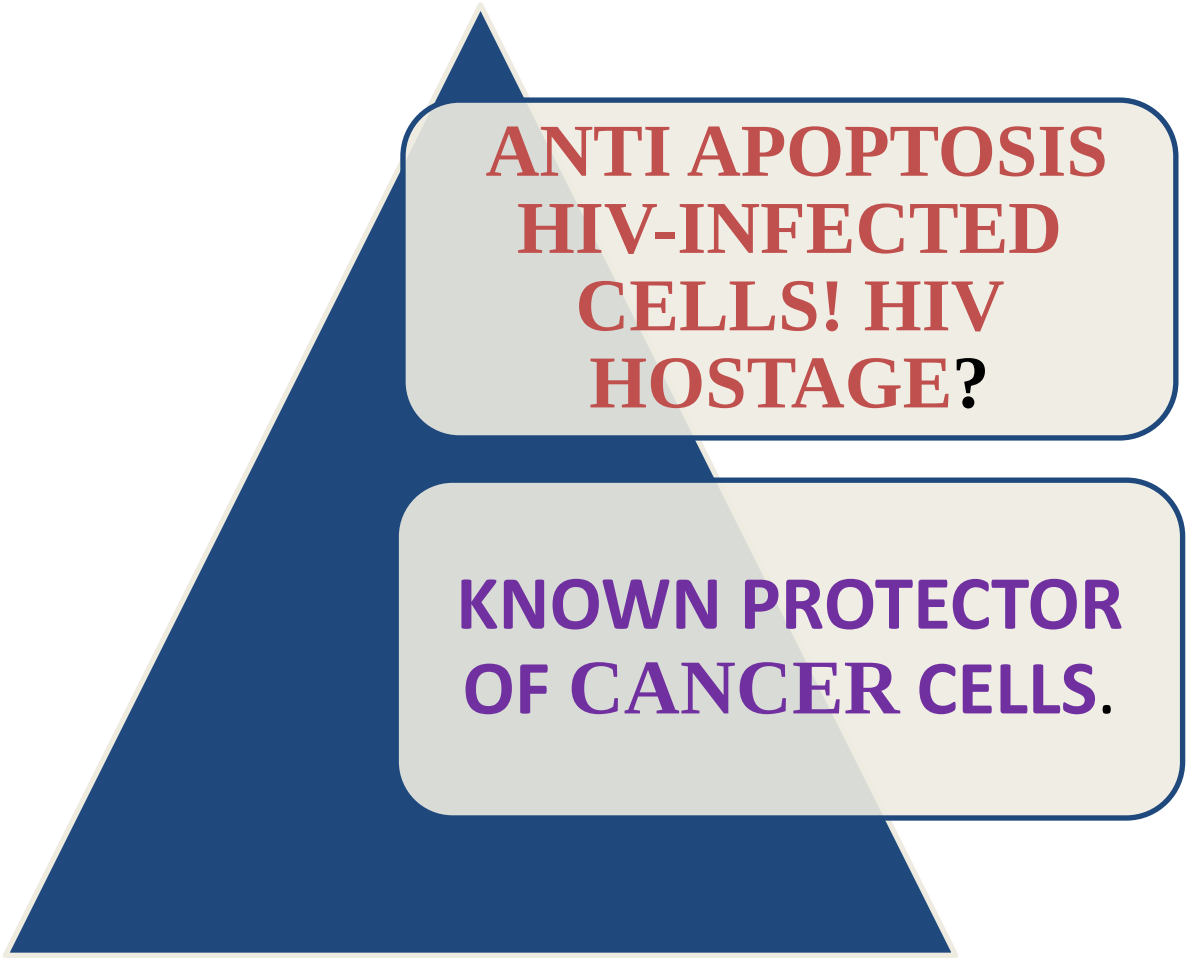
TERT & MITOCHODRIA RETROVIRUS



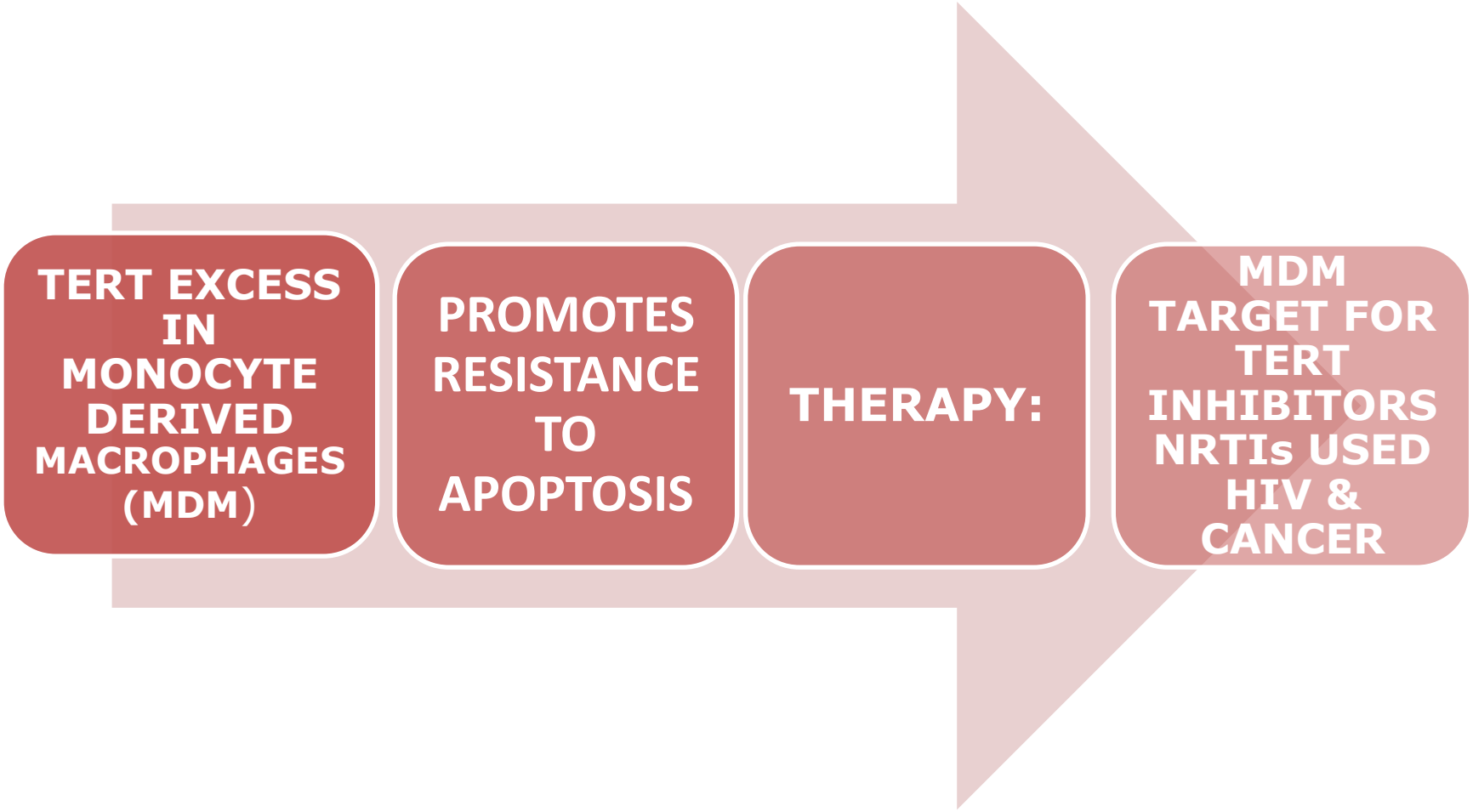
TERT AS PROTECTIVE STRESS HERO



TERT DARK SIDE (0VEREXPRESSED)



TERT ROLE IN MDM VIRAL RESERVOIRS



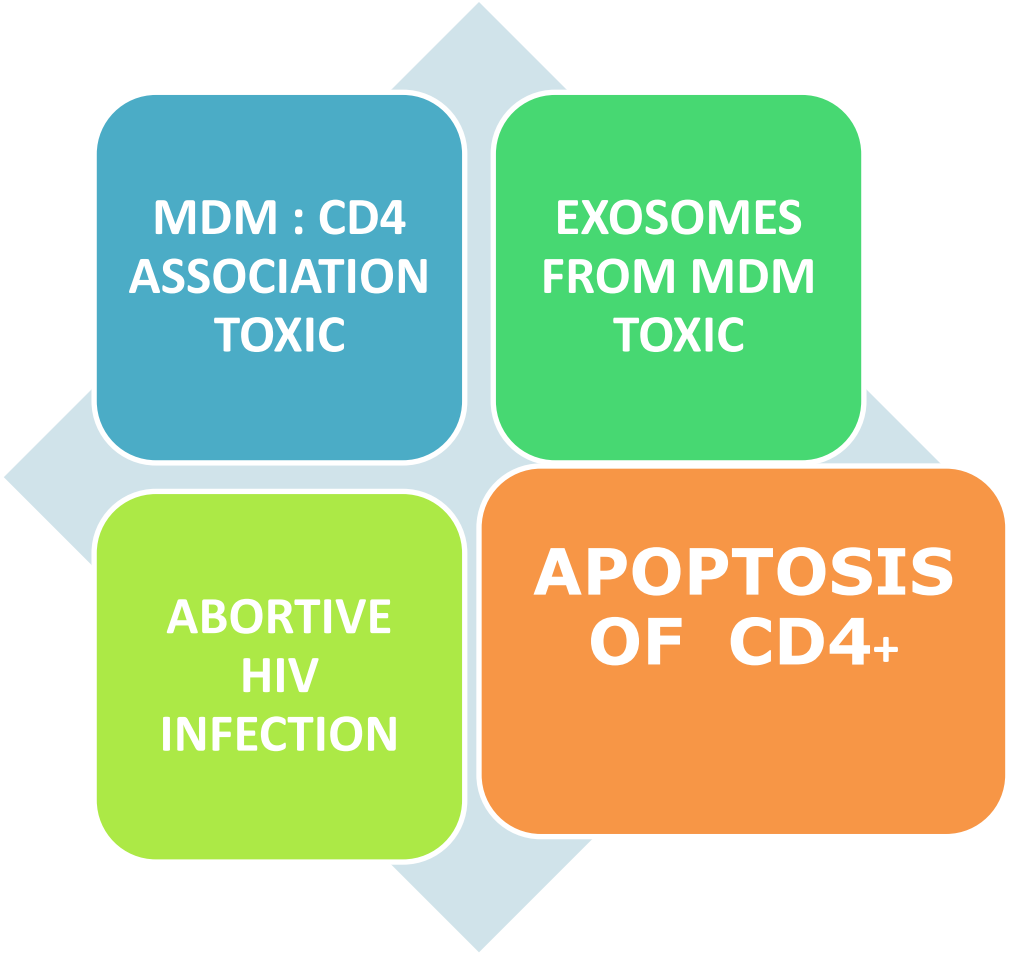
AQUIRED IMMUNE DEFICIENCY

CD4+ CELL DEPLETION GREATLY EXCEEDS NUMBER OF INFECTED CELLS

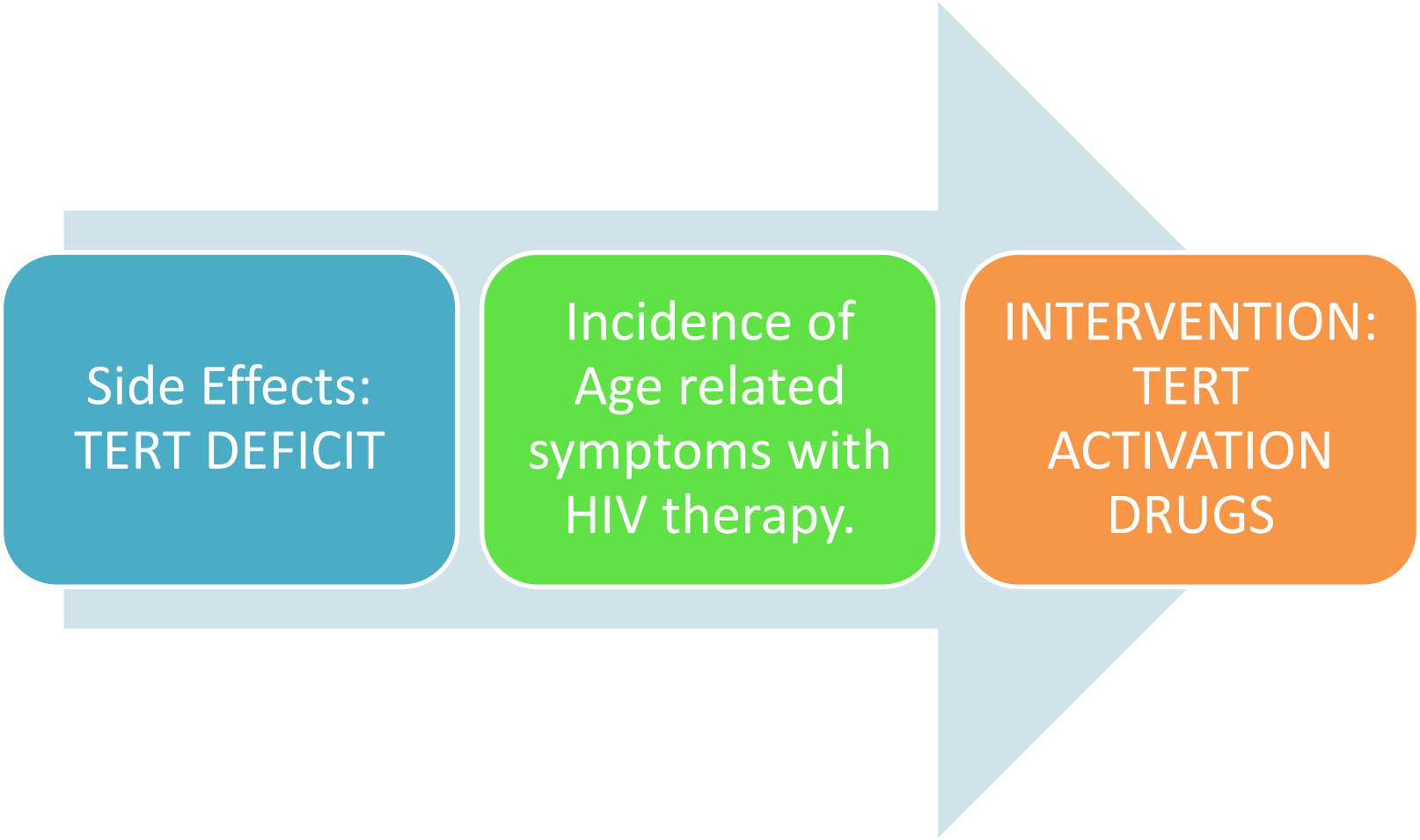
TERT IN CD4+ CELLS

- 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 ACIVATION OF IMMUNE RESPONSE

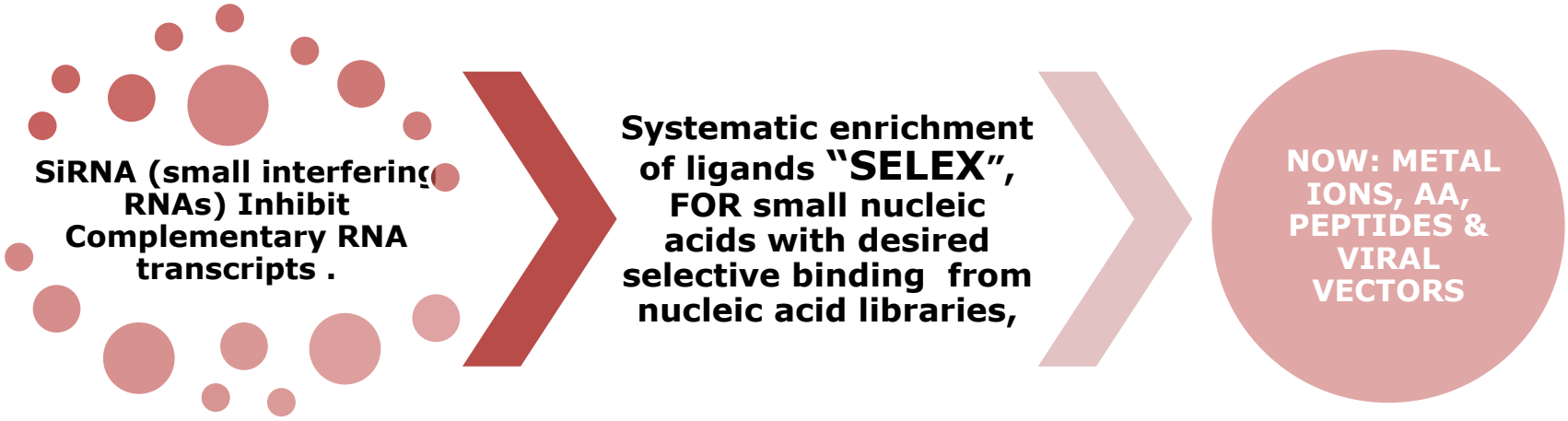
CD4+ BYSTANDER TOXIC ATTACKS



ANTIVIRAL THERAPY : ACCELERATED AGING



HOW? HIV SPECIFIC DELIVERY VEHICLE SYSTEM: APTAMERS

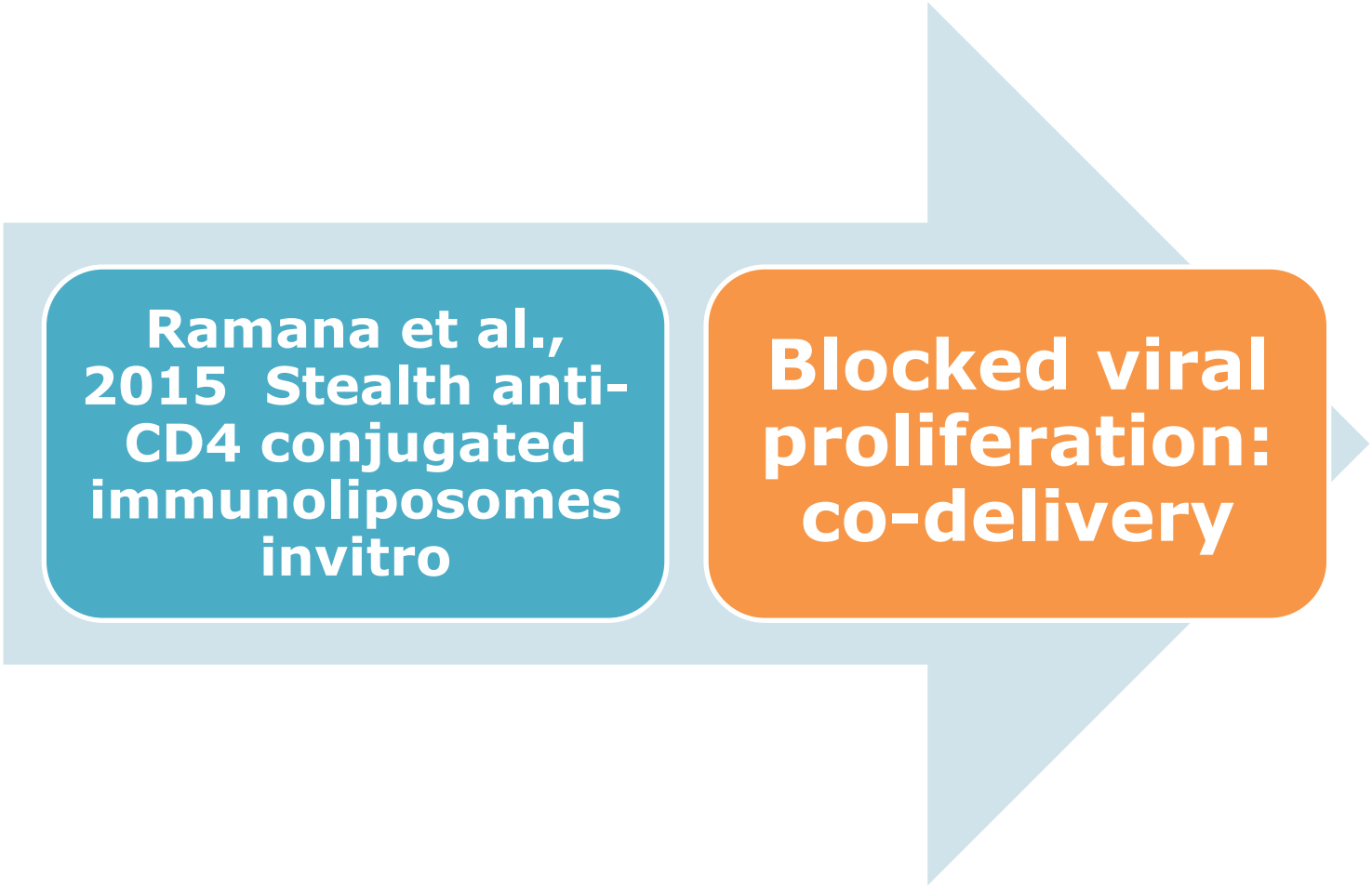


AVAILABLE MAJIC BULLETS

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



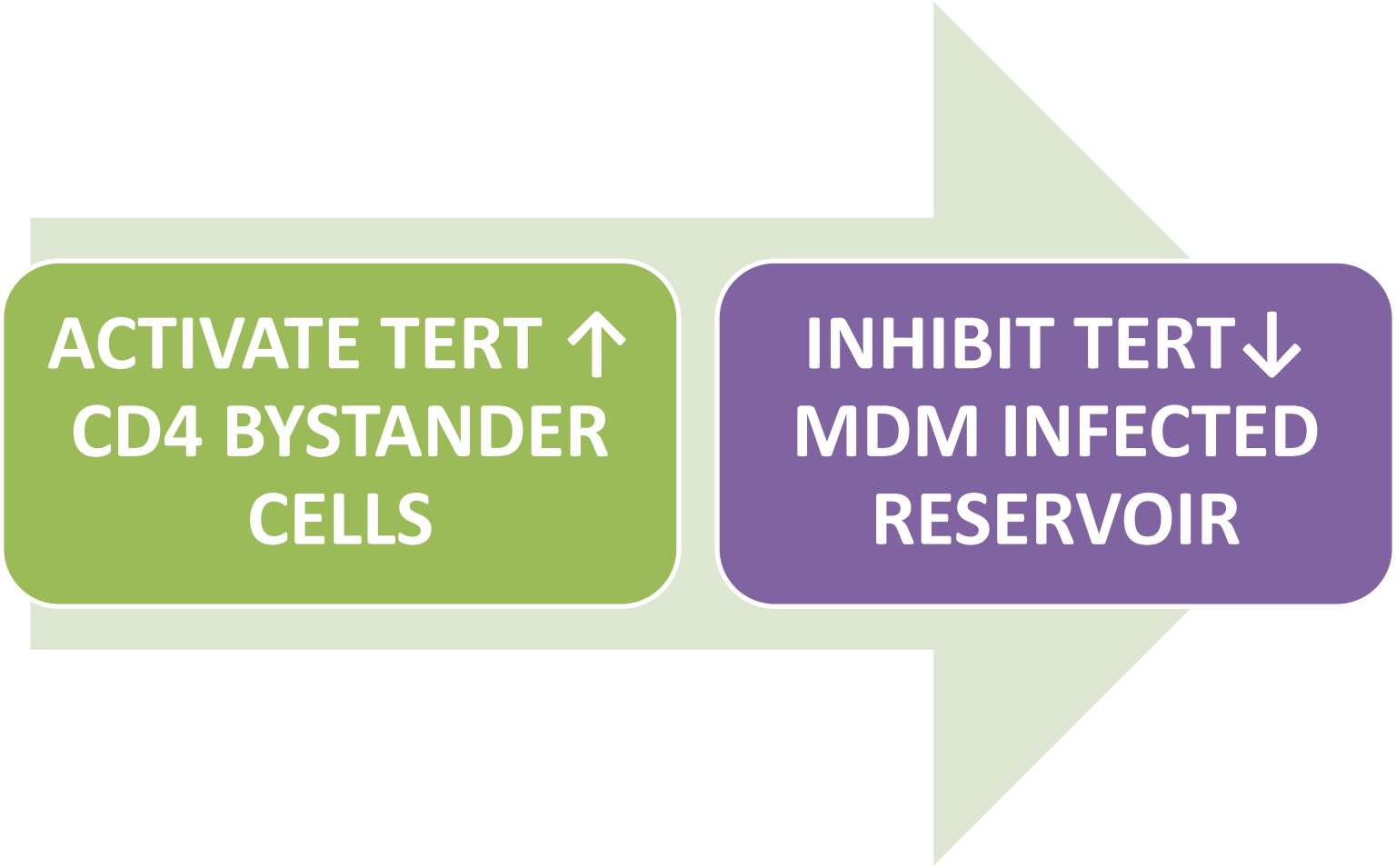
TAR siRNA DECOY VEHICLE

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



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: REGERERATIVE 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

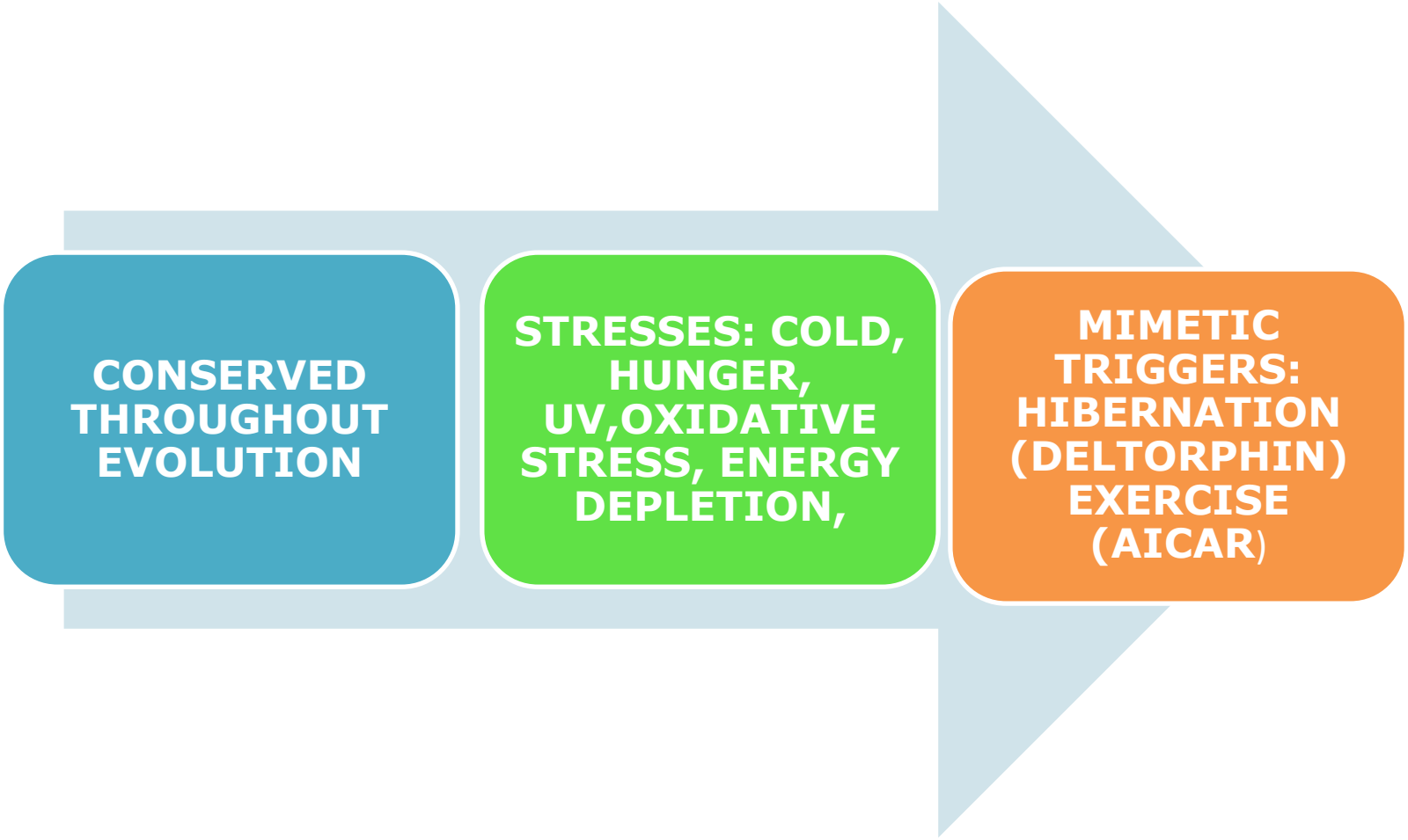
HORMESIS A LITLE BAD IS GOOD

LOW DOSES OF OTHERWISE HARMFUL AGENTS,

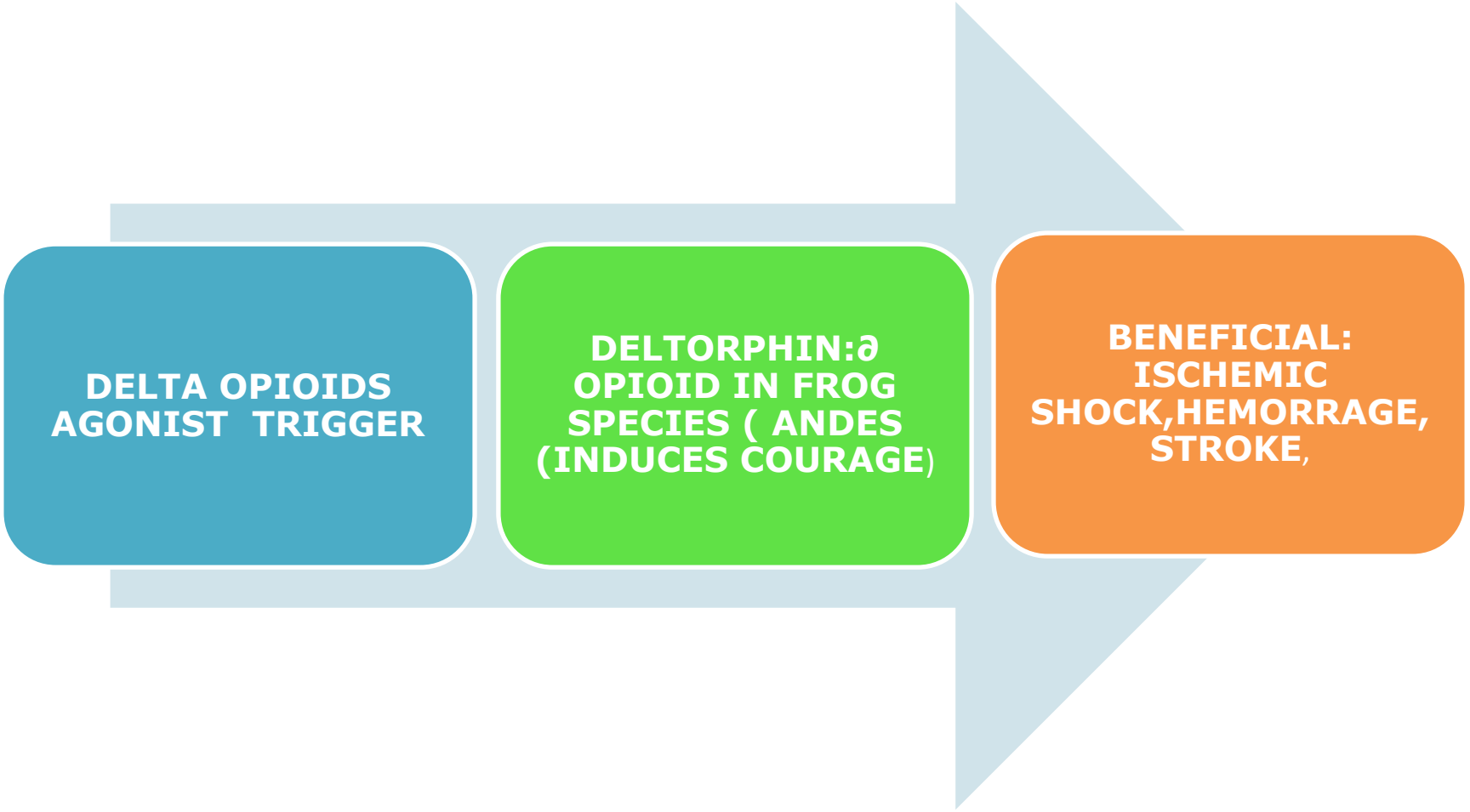
ACTIVATE STRESS RESPONSES.

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

STRESS RESPONSE TRIGGERS



HIBERNATION INDUCTION (BEARS, WOOCHUCKS, FROG) TRIGGER



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 PLASTICISITY

PROTECTIVE: NEURODEGENERATION

HIV BRAIN INJURY ?

Hibernation and HIV RESPONSE

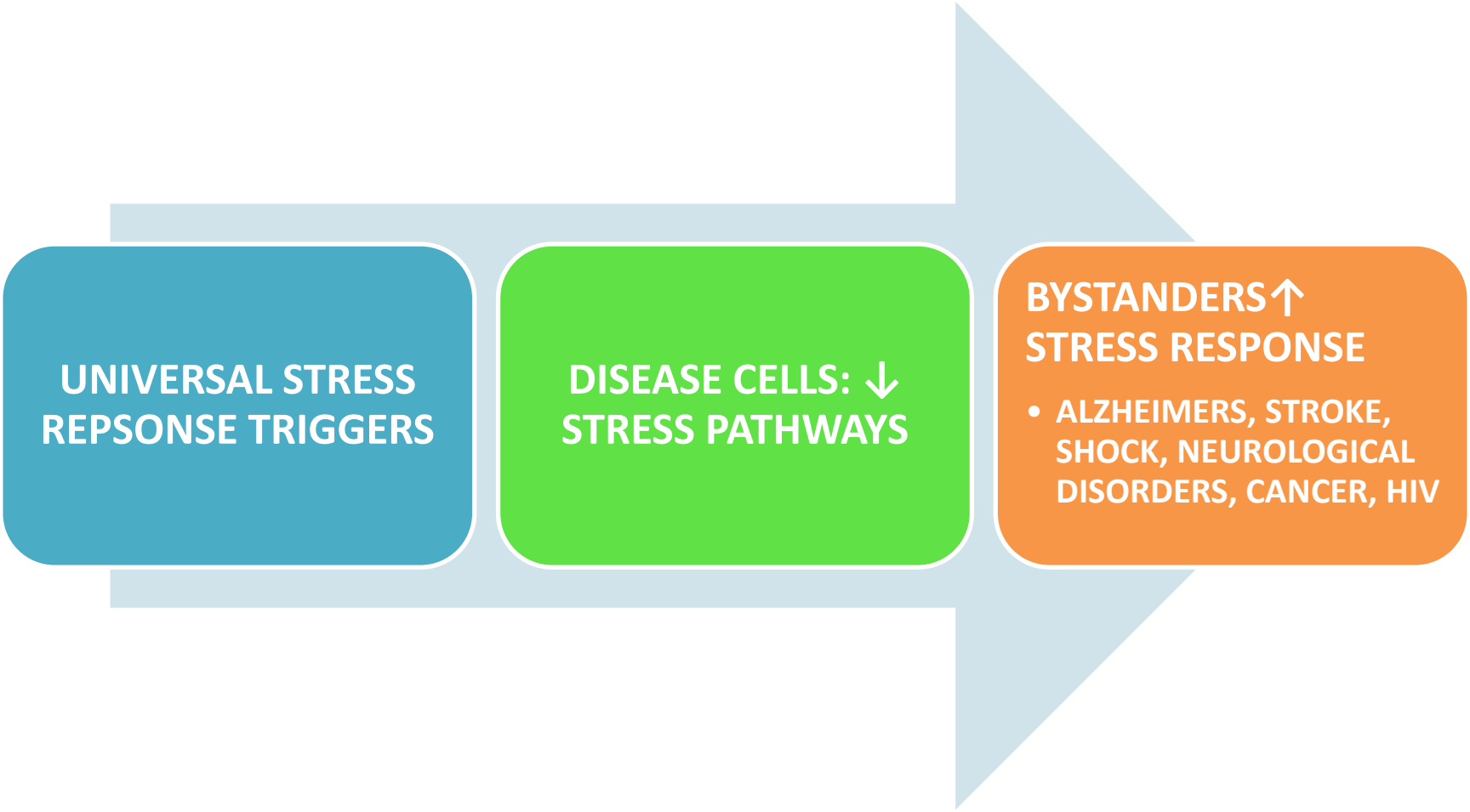
OPIOID RECEPTORS STIMULATION ACTIVATED CD4+ T cells SUPPRESSED HIV-1 EXPRESSION.

DELTORPHIN ↓ MARK 38 IN MACROPHAGES

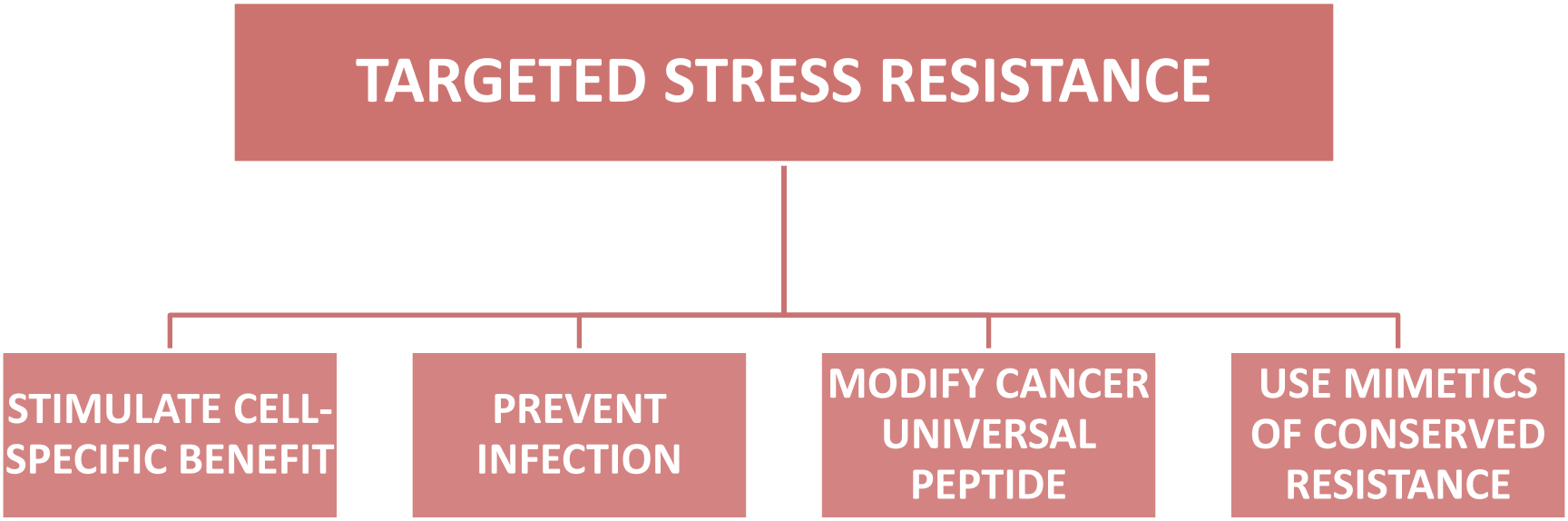
MARK38 ↑ HIV BRAIN INJURY: deltorphin ?

EXERCISE MIMETIC AICAR & HIV

DRUG RESERVOIRS: MIMETICS OF STRESS



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



Bibliography RETROVIRUS 2015

- Adotévi O et al. Hum Vaccin Immunother. 2013 May;9(5):1073-7
- Ahr B et al., J Cell Sci 2008 Apr 1;121(Pt 7):1046-53
- Autexier C et al., EMBO J. 1996;15:5928–5935
- Blackburn E H et al. Genome. (1989);31:553–560
- Calabrese EJ et al., Hum and Exper Toxic. 2000;19(1):41–75
- Comandini FA et al., Mol Immunol. 2013 Jun;54(2):181-92.
- Del Bufalo D, et al., Cell Death Differ. 2005;12:1429–1438
- de Carvalho JV et al. PLoS One. 2014 Nov 25;9(11):e1136.
- Doitsh G et al., Cell. 2010 Nov 24;143(5):789-801
- Edrey YH et al., Aging Cell. 2012;11(2):213–222
- Eitan E et al.,,. EMBO Mol Med 4: 313
- Février M et al.. Viruses. 2011 May;3(5):586-612.
- Franzese O et al., J Med Virol. 2007 May;79(5):639-46.
- Garg H et al.,. Viruses. 2012 Nov 9;4(11):3020-43
- Garbarino VR et al., Arch Biochem Biophys. 2015 1. pii: S0003-986136-8.
- Ghosh A et al., Nat. Cell Biol. (2012);14:1270–1281
- Gillis AJ et al., Nature 455 (7213): 633–7
- Govindaswami M et al., Acad Emerg Med. 2008 Mar;15(3):250-7.
- Husted TL et al., J Surg Res. 2005 Sep;128(1):45-9.
- Kovalenko OA et al., PLoS One. 2010 May 25;5(5):e10812
- Leeansyah E et al., J Infect Dis. 2013 Apr;207(7):1157-65.
- Lue NF et al., Proc Natl Acad Sci U S A. 2005 Jul 12;102(28):9778-83.
- Garg H et al., Viruses. 2012 Nov 9;4(11):3020-43
- Maida Y et al., Nature. 2009 Sep 10;461(7261):230-5.
- Medders KE et al J Neuroimmune Pharmacol. 2011 Jun;6(2):202-15.
- Murugaiyah V et al., Neurochem Int. 2015 Apr 7. pii: S0197-0186(15)00060-1
- Muthumani K et al., Blood. 2005 Sep 15;106(6):2059-68
- Mukherjee E et al., Proc Natl Acad Sci USA 2011;108 E11363-7
- Narkar VA et al., Cell. 2008 Aug 8;134(3):405-15.
- Overhoff MG et al., Nucleic Acids Res. 2014 Feb;42(3):1606-18.
- Peretti D et al., Nature. 2015 Feb 12;518(7538):236-9.
- Ramana LN et al., Eur J Pharm Biopharm. 2015 Jan;89:300-11.
- Rutten M et al., Shock. 2008 Jan;29(1):42-8
- Sharp BM et al., J Immunol. 2001 Jul 15;167(2):1097-102.
- Saretzki G. Curr Pharm Des. 2014;20:6386–6403
- Sharma M et al., Am J Physiol Renal Physiol. 2013 Apr 15;304(8):F1127-36.
- Shkreli M et al., Nat Med. 201118(1):1
- Smith-Sonneborn J. Science. 1979:203(4385):1115-7.
- Smith Sonneborn J. Int J Alzheimers Dis. 2012;2012:684283.
- Smith Sonneborn J et al., Shock. 2011;36(2):191-5
- Reynoso R et al., J Viol. 2012 ;86(19):10327-37
- Rutten M et al., Shock. 2008:42-8.
- Sonneborn JS. Dose-Response. 2010;97–121
- Sonneborn JS. Annals of the New York Academy of Sciences. 2005;1057:165–176
- Sonneborn JS et al., J Gerontol A Biol Sci Med Sci. 2004 May;59(5):433-40.
- Spilsbury A, J Neurosci. 2015 Jan 28;35(4):1659-74
- Stampfer MR et al., Proc Natl Acad Sci U S A. 2001 Apr 10;98(8):4498-503.
- Takahashi M et al.,. Adv Exp Med Biol. 2015;848:211-34
- Tawaraya Y etal., Biol Pharm Bull. 2014;37(8):1411-5.
- Torres RA &, Lewis W. Lab Invest. 2014 Feb;94(2):120-8
- Stampfer MR et al., Proc Natl Acad Sci U S A. 2001 10;98(8):4498-503..
- Unwalla HJ &, Rossi JJ. Virol J. 2010 Feb 10;7:33
- Xiang T et al., Cancer Lett. 2015 Apr 29. pii: S0304-3835(15)00306-7
- Wang X et alJ Biol Chem. 2013;288(22):15474-80.
- Yin L et al., J Biol Chem. 2000 Nov 24;275(47):36671-5.
- Zhang HS et al., Wu MR. Virus Res. 2009 Dec;146(1-2):51-7
- Zhou J & Rossi JJ. Mol Ther Nucleic Acids.2014 Jun 17;3:e169.
- Zhou J. et al., BMB REP.2014 Jan 47 (1):