

TRANSCRIPT FOR: NEW FUNDING ANNOUNCEMENT FOR HIGH RISK - HIGH REWARD PROGRAM: NIH DIRECTOR'S TRANSFORMATIVE RESEARCH AWARD

RAVI BASAVAPPA: HELLO AND WELCOME. THIS IS THE NIH HIGH RISK-HIGH REWARD PROGRAM AWARD WEBINAR. I AM RAVI BASAVAPPA AND I'M PROGRAM DIRECTOR OF THE OFFICE OF STRATEGIC COORDINATION OF THE NATIONAL INSTITUTES OF HEALTH. HERE'S THE AGENDA FOR TODAY'S MEETING.

WE WILL BEGIN WITH A SERIES OF PRESENTATIONS ON THE HR-HR OR HIGH RISK-HIGH REWARD PROGRAM AND FUNDING OPPORTUNITY ANNOUNCEMENT FOR THE TRANSFORMATIVE RESEARCH AWARD. THEN, MEMBERS OF THE TRANSFORMATIVE RESEARCH AWARD PROJECT TEAM WILL ANSWER QUESTIONS WE RECEIVED IN ADVANCE OR DURING THIS WEBINAR VIA INTERNET OR BY PHONE. THE PHONES WILL BE OPEN ONLY DURING THE QUESTION/ANSWER SESSION. SO LET'S MOVE ON TO THE NEXT AGENDA ITEM.

THIS WILL BE A BRIEF OVERVIEW OF THE TRANSFORMATIVE RESEARCH AWARD. FIRST OFF, I'D LIKE TO BEGIN BY ACKNOWLEDGING THE NIH COMMON FUND PROJECT TEAM THAT HELPS TO OVERSEE THE TRANSFORMATIVE RESEARCH AWARD INITIATIVE. THIS PROJECT TEAM IS ACTUALLY A SUBSET OF LARGER WORKING GROUP THAT HELPS TO OVERSEE THE COMMON FUND HIGH RISK-HIGH REWARD PROGRAM. AS YOU CAN SEE BY THE TEAM ROSTER, THIS REALLY IS A TRANS-NIH EFFORT. FORTUNATELY, MOST OF THOSE ON THE TEAM ARE PRESENT HERE AND WILL HELP TO FIELD QUESTIONS AND PROVIDE COMMENTS. SO IN THIS PRESENTATION, I WILL PROVIDE A BRIEF HISTORY OF THE INITIATIVE, DESCRIBE THE CHARACTERISTICS OF THE APPLICATIONS AND THE STRUCTURE OF THE TRANSFORMATIVE RESEARCH AWARD APPLICATION, THEN DESCRIBE WHAT WE THINK ARE CHARACTERISTICS OF STRONG APPLICATIONS, AND THEN PROVIDE EXAMPLES OF WHAT WE THINK ARE TRANSFORMATIVE IDEAS AND IDEAS THAT ARE NOT SO TRANSFORMATIVE.

SOON AFTER DR. ZERHOUNI BECAME NIH DIRECTOR, HE SOUGHT INPUT FROM THE SCIENTIFIC COMMUNITY TO DETERMINE HOW THE NIH FUNDING PROCESS MIGHT BE IMPROVED. ONE PROMINENT THEME THAT EMERGED WAS THAT TRADITIONAL NIH REVIEW TENDED TO BE TOO CONSERVATIVE. THE BIG, BOLD IDEAS WITHOUT COMPELLING DEMONSTRATIONS AND FEASIBILITY DID NOT TYPICALLY FAIR WELL IN THE REVIEW PROCESS. THAT IS, THE REVIEW PROCESS TENDS TO BE RISK AVERSE. THEREFORE, BECAUSE THE REVIEW PROCESS TENDS TO AVOID RISK, OPPORTUNITIES FOR MAKING LEAPS IN SCIENCE AND PUBLIC HEALTH MIGHT BE LOST. IN RESPONSE TO THIS PERCEIVED SHORT COMING BY THE COMMUNITY, THE TRANSFORMATIVE RESEARCH INITIATIVE WAS STARTED IN 2009, SPECIFICALLY TO SUPPORT BOLD, RISKY RESEARCH THAT HAS A POTENTIAL FOR UNUSUALLY LARGE IMPACT. AN ANNUAL FOA OR FUNDING OPPORTUNITY ANNOUNCEMENT HAS BEEN ISSUED SINCE THEN. SINCE THE INITIATIVE WAS STARTED, THE OVERALL PARAMETERS HAVE STAYED PRETTY MUCH THE SAME, NAMELY, ALL AREAS OF RESEARCH RELEVANT TO THE MISSION OF NIH ARE WELCOME, THE BUDGETS ARE FLEXIBLE UP TO \$25 MILLION PER YEAR, WHICH IS AN ENTIRE POT OF MONEY SET ASIDE FOR THIS INITIATIVE. MULTI-PI APPLICATIONS ARE ACCEPTED AND ACTUALLY ENCOURAGED. FINALLY THE STRUCTURE OF THE APPLICATION, THE LANGUAGE OF THE FUNDING OPPORTUNITY ANNOUNCEMENT

INSTRUCTIONS GIVEN TO REVIEWERS, AND THE REVIEW PROCESS ALL EMPHASIZE SIGNIFICANT POTENTIAL IMPACT AND INNOVATION.

SO, WHAT'S NEW FOR THIS YEAR? THIS YEAR, WE HAVE RENAMED THE TRO1S THE TRANSFORMATIVE RESEARCH AWARDS. THIS CHANGE IS BEING MADE TO EMPHASIZE UNIQUENESS OF THE TRANSFORMATIVE RESEARCH AWARD AND TO EMPHASIZE THE FACT THAT IT'S COMPLEMENTARY TO THE TRADITIONAL RO1, BUT DIFFERENT IN SEVERAL KEY WAYS, AS A WAY TO STIMULATE BIG IDEAS THAT MAY REQUIRE LARGE BUDGETS AND MULTIDISCIPLINARY TEAMS. AS PART OF THIS NEW EFFORT, WE ARE SEEKING TO INCREASE THE AWARENESS OF THIS FUNDING OPPORTUNITY ANNOUNCEMENT TO THE SCIENTIFIC COMMUNITY.

SO WHAT IS A STRUCTURE OF THE TRO1, THE TRANSFORMATIVE RESEARCH AWARD? SO WHAT'S IN A NAME? AS WE WERE TRYING TO REBRAND THIS TRANSFORMATIVE RESEARCH AWARD INITIATIVE, WE WERE TRYING TO THINK OF WAYS TO SORT OF TAG THE INITIATIVE. SOME THINGS THAT CAME UP WERE, "IT'S NOT YOUR MENTOR'S RO1," OR WHEN TRADITIONAL STUDY SECTIONS WOULD SAY "NO WAY, GO TAKE A FLYING LEAP," THE TRANSFORMATIVE RESEARCH STUDY SECTION MIGHT SAY THE SAME THING IN A POSITIVE WAY, LIKE "GO TAKE A LEAP INTO THE UNKNOWN, WE'RE READY TO RATE THIS RESEARCH AS BEING VERY MERITORIOUS."

WHAT IS THE STRUCTURE OF THE TRA APPLICATION? THE TRA APPLICATION USES THE RO1 ACTIVITY CODE. THE OVERALL FRAMEWORK IS THE SAME AS THE TRADITIONAL RO1, BUT WITHIN THAT FRAMEWORK, CRITICAL DIFFERENCES HAVE BEEN IMPLEMENTED TO EMPHASIZE SIGNIFICANCE, INNOVATION, AND IMPACT. WHAT ARE SOME OF THESE CRITICAL DIFFERENCES? WELL, IN THE RESEARCH STRATEGY, APPLICANTS ARE REQUESTED TO PROVIDE IN ONE PAGE, THE CHALLENGE, INNOVATION AND IMPACT STATEMENT, AS WELL AS A RATIONALE SECTION. FOR THE CHALLENGE, INNOVATION AND IMPACT STATEMENT, YOU'RE ASKED TO EXPLAIN TO THE REVIEWERS WHAT THE PARTICULAR CHALLENGE IS THAT YOU'RE ADDRESSING, WHY IT'S AN IMPORTANT CHALLENGE, WHY THE PROPOSED RESEARCH IS EXCEPTIONALLY INNOVATIVE, AND WHETHER IT WILL CHALLENGE FUNDAMENTAL PARADIGMS. ALSO, WHAT THE EXPECTED IMPACT IS OF THE RESEARCH IF IT'S SUCCESSFUL. SO THAT'S ALL IN ABOUT TWO HUNDRED WORDS. CHOOSE YOUR WORDS CAREFULLY. THEN IN THE RATIONALE SECTION, YOU'RE ASKED TO ADDRESS QUESTIONS SUCH AS "WHAT LOGIC LED YOU TO THIS IDEA?, AND WHAT INNOVATIONS WILL BE NECESSARY DURING THE COURSE OF THE RESEARCH TO MAKE YOUR PROPOSAL SUCCESSFUL?" IT IS IMPORTANT TO NOTE THAT THIS PAGE PROVIDES AN OVERVIEW OF THE ENTIRE APPLICATION. NEXT ITEM IN THE RESEARCH STRATEGY IS APPROACH. IN THIS SECTION, THE APPLICANTS ARE ASKED TO ADDRESS QUESTIONS SUCH AS: "HOW WILL YOU ATTEMPT TO TEST THE NOVEL PARADIGMS OR ATTACK THE PROBLEM? HOW DOES YOUR APPROACH DIFFER FROM THE CURRENT STATE OF THE ART IN THE FIELD? AND IS YOUR METHODOLOGY NOVEL?" SO, HERE, PROVIDE ENOUGH INFORMATION FOR THE REVIEWERS TO DETERMINE WHAT YOU'RE PROPOSING TO DO, BUT DO NOT INCLUDE A DETAILED EXPERIMENTAL PLAN. NOTE THAT PRELIMINARY DATA ARE NOT REQUESTED. THIS IS BECAUSE THE INITIATIVE TOLERATES MORE RISK THAN IN CONVENTIONAL RO1 REVIEW. WHILE CONVENTIONAL REVIEW TENDS TO BE RISK AVERSE, WE WANT THIS INITIATIVE TO EMBRACE RISK. YOU ARE THEN EXCLUSIVELY ASKED TO ADDRESS WHY YOU

THINK THIS PROPOSAL IS BETTER SUITED TO THIS INITIATIVE THAN TO CONVENTIONAL NIH PROGRAMS. FINALLY, IN HALF A PAGE, YOU'RE ASKED TO PROVIDE A TIMELINE FOR THE PROPOSED RESEARCH. THE OTHER SECTION IN WHICH THERE ARE SIGNIFICANT DIFFERENCES FROM THE TRADITIONAL RO1 APPLICATION IS IN THE BIOSKETCH FOR THE PI OR PIs. IT HAS BEEN MODIFIED TO VERY MUCH FOCUS ON YOUR HISTORY OF BEING UNUSUALLY CREATIVE IN OVERCOMING SIGNIFICANT TECHNICAL AND CONCEPTUAL CHALLENGES. FOR EXAMPLE, YOU'RE ASKED TO LIMIT THE NUMBER OF PUBLICATIONS, PATENTS AND/OR MEETING ABSTRACTS TO TEN OR LESS ITEMS. THESE, OF COURSE, SHOULD BE CHOSEN TO HIGHLIGHT YOUR ABILITY TO BE UNUSUALLY INNOVATIVE AND DO NOT NECESSARILY NEED TO BE RELATED TO THE TOPIC OF THE PROPOSAL. IN ANOTHER UNUSUAL ASPECT OF THIS APPLICATION BIOSKETCH, YOU HAVE THE OPPORTUNITY TO ANNOTATE EACH CITATION BRIEFLY TO EXPLAIN WHY YOU THINK THAT PARTICULAR CITATION DEMONSTRATES EXCEPTIONAL INNOVATION AND/OR BROAD SCIENTIFIC IMPACT. WITH THIS BIOSKETCH AND RESEARCH STRATEGY SECTIONS, AS I'VE DESCRIBED BRIEFLY, YOU HAVE THE OPPORTUNITY TO REALLY CAST YOUR PROPOSAL SUCH THAT YOU REALLY ARE ABLE TO HIGHLIGHT SIGNIFICANCE, INNOVATION, AND IMPACT.

SO WHAT ARE THE CHARACTERISTICS OF AWARDED TRA GRANTS? FIRST OFF, THEY GO TO A WIDE VARIETY OF INSTITUTIONS. THE DIVERSITY OF INSTITUTIONS SUPPORTED BY THIS INITIATIVE IS ACTUALLY QUITE LARGE: 44 DIFFERENT INSTITUTIONS AND AFFILIATES ARE SUPPORTED BY THE TRA INITIATIVE. BY INSTITUTION/AFFILIATES, I MEAN "UNIVERSITY" AS WELL AS "AFFILIATED MEDICAL SCHOOL OR SCHOOL OF PUBLIC HEALTH" ALL COUNT AS ONE ENTITY. THE GEOGRAPHIC DISTRIBUTION IS ALSO QUITE IMPRESSIVE AS SHOWN IN THE MAP HERE. I'D LIKE TO NOTE THAT THIS COUNTS ONLY THE CONTACT PI'S INSTITUTION. SO THE ACTUAL DISTRIBUTION OF INSTITUTIONS IS ACTUALLY GREATER THAN WHAT IS SHOWN HERE, CONSIDERING THE APPLICATIONS WITH MULTIPLE PIs. SPEAKING OF MULTIPLE PIs, YOU'LL NOTE THAT A MUCH GREATER FRACTION OF THE TRA AWARDS GO TO MULTI-PI GRANTS. FOR THE TRA, 31% OF THE TRA APPLICATIONS ARE ACTUALLY TO MULTI-PI PROPOSALS AS COMPARED TO UNSOLICITED RO1 APPLICATIONS, IN WHICH ONLY ABOUT 10% OF FUNDED AWARDS GO TO MULTI-PI PROPOSALS. SO THIS UNDERSCORES THE FACT THAT WHAT WE'RE SEEKING FOR PROJECTS TEND TO BE VERY BROAD, AMBITIOUS, AND REQUIRES EXPERTISE IN MORE THAN ONE DISCIPLINE. SO, I THINK A QUESTION THAT IS IN THE MIND OF MANY POTENTIAL APPLICANTS IS, "WHAT IS A TYPICAL BUDGET FOR A TRA AWARD?" THIS TENDS TO VARY QUITE A BIT, BUT A LITTLE OVER A QUARTER OF THE TRA AWARDS HAVE A BUDGET WITH TOTAL DIRECT COSTS PER YEAR BUDGET OF \$250,000 OR LESS, AND THEN THERE'S ANOTHER PEAK AT ABOUT \$500,000 PER YEAR DIRECT PER YEAR, AND IT TAILS OFF QUITE SLOWLY AS THE BUDGET INCREASES. THERE ARE ONLY ABOUT FIVE OR SO AWARDS IN WHICH THE ANNUAL DIRECT COST BUDGET IS GREATER THAN OR EQUAL TO ABOUT ONE 1 TO 1.25 MILLION PER YEAR.

SO WHAT ARE THE CHARACTERISTICS OF STRONG TRA APPLICATIONS? MUCH OF WHAT I'M ABOUT TO DESCRIBE IS ACTUALLY TAKEN FROM AN EVALUATION THAT WAS CONDUCTED FOR THE CENTER FOR SCIENTIFIC REVIEW, AS A COMMISSIONED REPORT. THE REPORT IS AVAILABLE ONLINE. I THINK THE EASIEST WAY TO FIND THIS REPORT IS TO SEARCH USING YOUR FAVORITE SEARCH ENGINE FOR "T-RO1 EVALUATION REPORT." IN THIS EVALUATION, MANY OF THE INVESTIGATORS WHO APPLIED FOR THE TRA AWARD WERE ASKED: "WHAT COMPONENTS DID YOU USE TO EMPHASIZE THAT THEIR PROPOSAL

WAS OF HIGH SIGNIFICANCE, AND HAD HIGH INNOVATION WITH BROAD POTENTIAL IMPACT?" YOU'LL SEE THAT MOST OF THE RESPONDANTS, ACCORDING TO THIS GRAPH, CONSIDERED THE "CHALLENGE" AND "IMPACT STATEMENT" AS BEING VERY IMPORTANT IN THE APPLICATION. WHEN THE SAME QUESTION WAS ASKED FOR THE REVIEWERS: "WHAT MAKES A STRONG TRA APPLICATION?" MOST OF THE REVIEWERS DIDN'T FOCUS ON JUST ONE PARTICULAR COMPONENT OF THE "RESEARCH STRATEGY", LIKE THE "CHALLENGE" AND "IMPACT STATEMENT" OR THE "RATIONALE", RATHER THEY USED MANY ASPECTS OF THE APPLICATION, BUT PRIMARILY THE "RESEARCH STRATEGY", THE "CHALLENGE" AND "IMPACT STATEMENT" PAGE, AS WELL AS THE BIOSKETCH OF THE PI OR PIs.

WHEN THE APPLICANTS IN THE SURVEY THEN WERE ASKED, "WHAT ARE THE CHARACTERISTICS OF TRANSFORMATIVE RESEARCH?" THE APPLICANTS RESPONDED ACCORDINGLY: TRANSFORMATIVE RESEARCH: 1) TAKES A DISCIPLINE IN NEW DIRECTIONS, 2) OPENS NEW METHODOLOGY OR NEW MECHANISMS, 3) GENERATES NEW TECHNOLOGY, 4) ACCELERATES A GIVEN FIELD, 5) CHALLENGES, 6) CLOSES KNOWLEDGE GAPS, 7) ADDRESSES IMPORTANT PROBLEMS, 8) CAN ONLY BE KNOWN IN RETROSPECT AND YOU KNOW IT WHEN YOU SEE IT, AND/OR 9) STILL REMAINS A FUZZY CONCEPT.

WHEN PAST APPLICANTS WERE ASKED TO PROVIDE EXAMPLES OF WHAT THEY CONSIDERED TO BE TRANSFORMATIVE RESEARCH, THOSE RESPONDING GAVE EXAMPLES SUCH AS: 1) POLYMERASE CHAIN REACTION, 2) INTERFERENCE RNA OR MICRO-RNA, 3) DNA METHYLATION, 4) INDUCED STEM CELLS, AND 5) CONTROLLED GENE KNOCKOUT IN MICE.

SO CONTINUING THIS IDEA OF WHAT REALLY CONSTITUTES TRANSFORMATIVE RESEARCH, WE MIGHT ALSO LOOK AT WHAT APPLICATIONS HAVE BEEN FUNDED. ALL THE TRANSFORMATIVE RESEARCH AWARDS THAT HAVE BEEN FUNDED ARE SHOWN ON OUR WEB SITE -- COMMONFUND.NIH.GOV— WHICH WILL GIVE YOU AN IDEA OF THE SCOPE AND TOPICS THAT HAVE BEEN SUPPORTED TO DATE. BUT I'D LIKE TO POINT OUT THREE EXAMPLES. ONE PROJECT IS BY VEMSI MOOTHA, ON "MOLECULAR PROSTHESIS FOR MITOCHONDRIAL DISORDERS." IN THIS PROJECT, THE PI PROPOSED TO SCAN SEQUENCED BACTERIAL GENOMES FOR BACTERIA THAT HAVE INCOMPLETE RESPIRATORY GENES TO IDENTIFY GENES OR SMALL MOLECULES AND THEN USE THIS KNOWLEDGE TO TREAT A VARIETY OF MITOCHONDRIAL MYOPATHIES. SO IT HAS, YOU KNOW, CLEARLY BROAD POTENTIAL IMPACT, BUT IT IS INHERENTLY RISKY. ANOTHER EXAMPLE IS "BUILDING NOVEL VACCINES ON A BORROWED COAT" BY NINA PAPAVALIOUS. IN THIS PROJECT, SHE USES COAT PROTEINS TO PRODUCE SPECIFIC LONG-TERM B CELL MEMORY CELLS AND WITH THIS, HOPE TO GET RESPONSES FOR INDIVIDUALIZED TARGETS. A THIRD AND FINAL EXAMPLE IS "INTEGRATED BRAIN, BODY, AND SOCIAL INTERVENTION FOR ADHD" BY JAMES LECKMAN AND BRUCE WEXLER. IN THIS MULTI-PI AWARD, THEY PROPOSED TO COMBINE COGNITIVE, PHYSICAL, AND PSYCHOSOCIAL APPROACHES FOR THE TREATMENT OF ADHD.

SO, WHAT ARE SOME NOT SO SUCCESSFUL EXAMPLES OF IDEAS FOR TRANSFORMATIVE RESEARCH PROJECTS WE'VE RECEIVED? WELL, SOME THINGS THAT COME TO MIND ARE IDEAS THAT MIGHT TYPICALLY BE SUPPORTED THROUGH THE CONVENTIONAL RO1 AWARD, BUT VERY UNLIKELY TO BE SUPPORTED THROUGH THIS INITIATIVE. FOR EXAMPLE, THE IDEA OF USING RNAI TO KNOCKDOWN EXPRESSION OF PROTEINS IN A NEW SYSTEM IF THERE'S NO COMPELLING HYPOTHESIS TO DO IT. JUST

BECAUSE IT ANSWERED A VERY FOCUSED QUESTION WITH RELATIVELY LITTLE POTENTIAL IMPACT, IT WOULD NOT FAIR WELL IN A REVIEW FOR THIS INITIATIVE. OR THE IDEA OF EXPANDING A CLINICAL RESEARCH NETWORK WITHOUT INTRODUCING NEW CONTENT, THAT IS, LEVERAGING AN ONGOING EFFORT, USUALLY WOULD NOT DO WELL IN REVIEW FOR THIS INITIATIVE. LASTLY, AN IDEA TO USE A RARE BACTERIUM THAT EMPLOYS A NOVEL MECHANISM FOR WHOLE CELL ENTRY IN NEWTS WITHOUT PROPOSING POTENTIALLY BROADER IMPLICATIONS. IT'S VERY FOCUSED ON A PARTICULAR BACTERIUM OR PARTICULAR ORGANISM, OR EVEN A MODEL ORGANISM, BUT WOULD NOT DO WELL FOR THIS INITIATIVE UNLESS IT'S EXPLAINED COMPELLINGLY WHY THIS RESEARCH WOULD HAVE BROAD IMPACT.

SO, WITH THAT, I WOULD LIKE TO INTRODUCE NED TALLEY OF THE NEUROLOGICAL DISEASES AND STROKE AT NIH TO TALK ABOUT THE AREAS OF SCIENCE BEING ADDRESSED BY THE TRANSFORMATIVE RESEARCH AWARDS.