BEFORE THE
TASK FORCE ON NEUROSCIENCE AND MEDICINE TO THE
INDEPENDENT CITIZENS' OVERSIGHT COMMITTEE
TO THE
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
ORGANIZED PURSUANT TO THE
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

REGULAR MEETING

LOCATION: VIA ZOOM

DATE: JULY 17, 2023
1 P.M.

REPORTER: BETH C. DRAIN, CA CSR
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I N D E X

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JULY 17, 2023; 1 P.M.

CHAIRMAN GOLDSTEIN: GREAT. WELCOME, EVERYBODY. WE HAVE TWO ITEMS TODAY. THE FIRST WILL BE A TALK FROM RUSTY GAGE. MARIANNE, CAN YOU CALL THE ROLL PLEASE BEFORE WE MOVE ON?

MS. DEQUINA-VILLABLANCA: YEAH. YOU WERE ON MUTE FOR ONE MINUTE. I'LL GO AHEAD AND CALL THE ROLL NOW.

MARIA BONNEVILLE.

MS. BONNEVILLE: PRESENT.

MS. DEQUINA-VILLABLANCA: LEONDRA CLARK-HARVEY. MARK FISCHER-COLBRIE. FRED FISHER.

DR. FISHER: FRED IS HERE.

MS. DEQUINA-VILLABLANCA: JUDY GASSON.

DR. GASSON: HERE.

MS. DEQUINA-VILLABLANCA: LARRY GOLDSTEIN.

CHAIRMAN GOLDSTEIN: HERE.

MS. DEQUINA-VILLABLANCA: DAVID HIGGINS. VITO IMBASCIANI.

DR. IMBASCIANI: YES. VINI, VIDI, VITO.

MS. DEQUINA-VILLABLANCA: ALL RIGHT. STEVE JUELSGAARD.

MR. JUELSGAARD: PRESENT. PRESENT. PRESENT. SORRY.

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MS. DEQUINA-VILLABLANCA: GOTCHA. GOTCHA. GOTCHA. OKAY. PAT LEVITT.

DR. LEVITT: PRESENT.

MS. DEQUINA-VILLABLANCA: LAUREN MILLER-ROGEN. MARVIN SOUTHARD.

DR. SOUTHARD: PRESENT.

MS. DEQUINA-VILLABLANCA: KEITH YAMAMOTO.

DR. YAMAMOTO: I'M HERE. HI, RUSTY.

DR. GAGE: HEY.

MS. DEQUINA-VILLABLANCA: ALL RIGHT. WE ARE GOOD, AND WE DO HAVE A QUORUM, LARRY. SO YOU MAY PROCEED.

CHAIRMAN GOLDSTEIN: GREAT. THANK YOU.

SO TWO ITEMS TODAY. THE FIRST WILL BE A TALK FROM RUSTY GAGE, THAT I'LL INTRODUCE IN A MOMENT. AND THE SECOND IS WE'LL HEAR A CONCEPT PLAN FROM ROSA CANET-AVILES LAYING OUT A POSSIBLE FUNDING SYSTEM FOR NEUROPSYCHIATRIC STEM CELL RESEARCH.

SO RUSTY WILL SPEAK FOR ABOUT 45 MINUTES, INCLUDING QUESTIONS, AND THEN WE'LL GET ROSA UP.

SO RUSTY GAGE. DR. FRED GAGE HAS BEEN A LONGTIME COLLEAGUE OF MINE. HE HAS A NUMBER OF FIRSTS OVER THE YEARS, INCLUDING EVIDENCE THAT THERE'S NEUROGENESIS IN HUMANS, SOME WONDERFUL STEM CELL WORK OVER THE YEARS. AND THE REASON I THOUGHT

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WE SHOULD HEAR FROM HIM TODAY IS, AS WE LAUNCH INTO NEUROPSYCHIATRIC STEM CELL RESEARCH, IT'S IMPORTANT THAT WE BE ABLE TO ANALYZE WHAT GOES WRONG IN MUTATIONS THAT PREDISPOSE TO SCHIZOPHRENIA OR BIPOLAR DISORDER OR ANY OF THE DISEASES THAT WE MAY TURN OUT TO BE INTERESTED IN. AND RUSTY'S LAB RECENTLY PUBLISHED WHAT I THINK IS ONE OF THE MOST ADVANCED PHENOTYPIC SYSTEMS FOR EVALUATING WHAT IS HAPPENING INSIDE OF BRAIN ORGANOIDS.

AND WITH NO ADDITIONAL VERBIAGE FROM ME, I'M GOING TO TURN IT OVER TO RUSTY. SO TAKE IT AWAY.

DR. GAGE: ALL RIGHT. I'M SCREEN SHARING NOW.

OKAY. WELL, THANKS FOR INVITING ME TO PRESENT. I'LL BE PRESENTING OUR EFFORTS TO DEVELOP A FULLY HUMAN BRAIN ORGANOID MODEL SYSTEM. IT WILL BE MOSTLY METHODOLOGICAL, BUT THERE ARE SOME CONCEPTUAL THINGS THAT I'D LIKE TO ADVANCE AS WELL. BUT HERE'S THE LAYOUT.

WHAT ARE OUR GOALS? WELL, THERE'S A LOT OF FOCUS LATELY IN THE LAST TEN YEARS OR SO ON DEVELOPING HUMAN BRAIN ORGANOIDS IN PART BECAUSE OF THE, LET'S SAY, LACK OF COMPLETE SATISFACTORY EVIDENCE FROM MOUSE MODELS, ESPECIALLY OF

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PSYCHIATRIC DISEASES. AND THE ABILITY TO LOOK AT HUMAN BRAIN TISSUE IN MODELS OF THE HUMAN BRAIN IS HOPED TO ADVANCE OUR ABILITY MAKE NEW DISCOVERIES.

SO WITH THAT TOWARD THE ORGAN TREE OR ORGANOIDS, HUMAN ORGANOIDS, THERE'S A COUPLE OF THINGS THAT ARE PROBLEMATIC SO FAR. AND THAT IS THAT THE ORGANOIDS THAT HAVE BEEN AND ARE BEING USED IN VITRO ARE NOT VASCULARIZED. AND WHAT HAPPENS, BECAUSE OF THE 1 MILLIMETER RULE, THAT MEANS THINGS CAN'T DIFFUSE MORE THAN 1 MILLIMETER INTO THE ORGANOID. ONCE THEY GET LARGER THAN 2 MILLIMETERS IN SIZE, THE CORE BEGINS TO ROT. THE LARGER THEY GET, THE LARGER THE CORE BECOMES. AND IN MY MIND, IN OUR MIND, OUR LAB, IT'S VERY HARD TO MAKE CONCLUSIONS ABOUT THE OUTER RIM OF AN ORGANOID WHEN YOU KNOW THAT THE INNER CORE IS DYING. WE NEED TO ELIMINATE -- WE NEED TO VASCULARIZE THE ORGANOIDS AND ELIMINATE THE NECROTIC CORE.

NEXT IS MOST OF THE ORGANOIDS THAT CURRENTLY EXIST ARE REALLY NEURAL ORGANOIDS. THEY'RE MADE UP OF NEURONS OR NEURAL PRECURSORS AND DON'T REALLY -- THEY'RE NOT REALLY IMBUED NATURALLY WITH OTHER CELL TYPES. AND, OF COURSE, THE BRAIN IS MADE UP OF MANY DIFFERENT CELL TYPES. AND ONCE YOU HAVE THESE -- AS YOU IMBUE THE ORGANOIDS WITH THESE

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DIFFERENT CELL TYPES, YOU NEED TO ESTABLISH THEIR HEALTH AND FUNCTION AND DEMONSTRATE THAT THEY ARE RESPONDING AS ONE MIGHT EXPECT THEM TO RESPOND IN SITU.

I'LL GIVE YOU EVIDENCE TODAY ON NEURONS, MICROGLIA, AND ASTROCYTES AND IN-PROGRESS FOR ENDOTHELIAL CELLS AND PERICYTES, WHICH ARE THE CELLS IN THE BLOOD-BRAIN BARRIER VASCULATURE, AND WITH A LONG-TERM PLAN OF MYELINATING THE AXONS WITHIN THE ORGANOIDS.

NOW, THE GOAL OBVIOUSLY IS ONCE -- AS WE MOVE THROUGH THIS, WE CAN BEGIN TO COMPARE HEALTHY BRAIN TO DISEASED BRAIN. AND REALLY IT'S DISEASE AGNOSTIC BECAUSE WITH IPS TECHNOLOGY YOU CAN GET FIBROBLASTS FROM ANY PATIENT AVAILABLE. ONCE THERE, YOU CAN DO WHAT WE CALL INDUCTIVE EXPERIMENTS WHERE YOU CAN REPLACE A HEALTHY CELL WITH A DISEASED CELL TO DETERMINE IF THAT DISEASE CELL IS DRIVING OR A CONSEQUENCE OR ACTIVATED AS A CONSEQUENCE OF THE ENVIRONMENT THAT THEY FIND THEMSELVES. AND I'LL GIVE YOU AN EXAMPLE OF MICROGLIA IN AUTISM.

RESTORATION IS ANOTHER APPROACH, AND THAT IS WHERE YOU HAVE A DISEASED BRAIN ORGANOID AND YOU REPLACE IT WITH HEALTHY CELLS TO SEE IF YOU CAN ELIMINATE SOME OF THE PATHOLOGY THAT EXISTS WITHIN

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THE ORGANOID DISEASED BRAIN. OF COURSE, WITH THIS SYSTEM, BECAUSE IT'S LIVING AND MODULAR, WE CAN BEGIN TO IDENTIFY CELLULAR ANIMAL MECHANISMS THAT ARE CAUSING OR PREVENTING THESE CELLS TO BECOME HEALTHY.

AND IN THE FINAL CASE, WE THINK OF THIS MODEL SYSTEM AS A TOOL TO TEST THERAPIES IN THE HUMAN BRAIN AND PERHAPS OF THE PATIENT THAT IS BEING TREATED. SO TAKING A FIBROBLAST FROM THE PATIENT THAT'S GOING TO HAVE SOME SORT OF THERAPEUTIC INTERVENTION, YOU CAN ACTUALLY TEST THE DRUG, TEST THE VECTOR, TEST THE GENE THERAPY, TEST THE CELL THERAPY IN THE ORGANOID PRIOR TO GOING INTO THE PATIENT.

SO WITH THAT, WE CAN SAY THAT THERE ARE MANY DIFFERENT CELLS OF THE BRAIN. MOST OF THE ORGANOIDS THAT EXIST HAVE THESE -- CAN YOU SEE MY LITTLE ARROW THERE?

CHAIRMAN GOLDSTEIN: YES.

DR. GAGE: OKAY. WE DO SEE RADIAL GLIA IN THE EXISTING ORGANOIDS, AND THEY GIVE RISE TO NEURONS. THEY'RE LATE IN THE PROCESS. USUALLY FOUR OR FIVE MONTHS INTO IT, YOU WILL SEE ASTROCYTES FORMING IN THE OUTER CORE, BUT THEY DON'T -- THEY HAVEN'T BEEN TESTED YET FOR THEIR FUNCTIONALITY.

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AND NEURAL OPC'S OR OLIGOS HAVE BEEN DETECTED SO FAR.

I'M GOING TO START BY TALKING TO YOU A LITTLE BIT ABOUT MICROGLIA. THESE ARE CELLS THAT ARE NOT EVEN DERIVED IN THE BRAIN, BUT THEY'RE DERIVED IN WHAT'S CALLED THE YOKE SACK, VERY EARLY STAGE IN DEVELOPMENT, WHERE THEY MIGRATE INTO THE PRIMORDIAL BRAIN, TAKE UP RESIDENCE, AND BECOME -- THEY PROLIFERATE ACTUALLY WHEN THEY'RE THERE, AND THEY TAKE UP RESIDENCE. ONCE THE PERICYTES FORM IN THE OUTER EDGES OF THE ENDOTHELIAL CELLS AND PREVENT THE GROWTH OF THESE CELLS OR MOVING THESE CELLS INTO THE BRAIN, YOU RELY PRETTY MUCH ON THE EXISTING MICROGLIA THAT CAME IN EARLY ON. HOWEVER, BONE MARROW-DERIVED MACROPHAGES OR MYELOID ORIGIN CELLS CAN MIGRATE INTO THE BRAIN ALSO UNDER CERTAIN CIRCUMSTANCES. SO WE HAVE TWO SOURCES, EARLY DEVELOPMENT AND LATE DEVELOPMENT ON MICROGLIA. BUT, AGAIN, THEY'RE NOT BRAIN DERIVED. THEY ARE (UNINTELLIGIBLE).

A LOT OF INTEREST IN MICROGLIA LATELY SUGGESTED THEIR ROLE IN A VARIETY OF DISEASES, PARTICULARLY THEIR ROLE IN INFLAMMATION. AND SO A LOT OF WORK HAS BEEN -- I'M TRYING TO CHARACTERIZE. OF COURSE, VERIFIED BY BEN BARRES EARLY ON,

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ESTABLISHING WHAT IS A MICROGLIAL IDENTITY, BOTH DEVELOPMENTAL AND MATURE. WE WERE INVOLVED IN ISOLATING MICROGLIA DIRECTLY OUT OF THE BRAIN. BUT ONE OF THE THINGS THAT HAPPENS WITH MICROGLIA IN VITRO IS THEY'RE VERY SENSITIVE TO THE ENVIRONMENT. AND WHEN THEY GO INTO AN IN-VITRO SETTING, THEY DOWNREGULATE KEY PROTEINS THAT ARE THOUGHT TO BE ESSENTIAL FOR THE FEATURES AND FUNCTION OF MICROGLIA, INCLUDING THESE GENES HERE.

I'M NOT GOING TO GO TOO MUCH INTO SPECIFIC GENES UNLESS THERE'S INTEREST FROM THE GROUP. I CAN GIVE YOU MORE DETAIL IN THE DISCUSSION SECTION. BUT THE FACT IS THEY ARE MICROGLIA IN VITRO, BUT THEY'RE NOT FULLY MATURED.

SO WHAT WE'VE DONE IS WE'VE TAKEN OUR REGULAR ORGANOID AND WE MAKE ERYTHRO-MYELOID CELLS. SO WE TAKE A FIBROBLAST AND TURN IT INTO AN IPS CELL, AND WE GENERATE BASICALLY EARLY DEVELOPMENT OF HEMATOPOIETIC CELLS AND THEN DRIVE THEM SLIGHTLY LESS -- SLIGHTLY INTO THE PHASE WHERE WE KNOW FROM HUMAN DEVELOPMENT THAT THEY MIGRATE INTO THE BRAIN IN ABOUT THREE TO FOUR MONTHS -- WEEKS OF AGE. AND SO HERE WE HAVE THE GREEN AS THE ORGANOID, AND HERE WE HAVE OUR INDUCED MYELOID PROGENITOR CELLS ON THE OUTSIDE. AND YOU CAN SEE IN THE MOVIE THAT THEY'RE

MIGRATING IN OVER A PERIOD OF TIME AND THEY SETTLE IN THE BRAIN.

NOW, I'M NOT GOING TO GO THROUGH IT, BUT WE AND OTHERS HAVE DONE A SERIES OF EXPERIMENTS TRYING TO GET MICROGLIA INTO THE ORGANOIDS, AND THEY DON'T SURVIVE VERY WELL. THEY REQUIRE SEVERAL HUMAN-DERIVED PROTEINS THAT PROTECT THE SURVIVAL OF THE MICROGLIA. WITHOUT THEM, THEY DON'T SURVIVE. AND EVEN WITH THOSE ADDED PROTEINS IN VITRO, THE MICROGLIA DO NOT SURVIVE MORE THAN A MONTH, AND THEY ARE IN WHAT'S CALLED A REACTIVE STATE. SO THEY'RE NOT NATURALLY FORMED.

WE FOUND BACK IN -- WE DEVELOPED A MODEL IN 2018 WHERE WE TAKE AN ORGANOID AND WE CAN FORM IT AND THEN TRANSPLANT IT INTO THE RETROSPLENIAL CORTEX OVERLYING THE VASCULAR BED. AND SO IT'S OVERLYING THIS PERI-COLLICULUS. AND THE BLOOD VESSELS FROM THIS PERI-COLLICULUS GO INTO THE BRAIN, TO THE HUMAN ORGANOID, AND YOU CAN SEE HERE, AFTER AN INTERORBITAL INJECTION OF DYE, THAT THE BLOOD-BRAIN BARRIER IS FORMED AND THERE'S NO LEAKINESS INTO THE HOST.

WHEN WE TRANSPLANT THE MICROGLIA-ENRICHED ORGANOIDS INTO THE BRAIN, WE SEE LIVELY, FULLY MATURE MICROGLIA. THESE ARE LABELED WITH TDTOMATO

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HERE, BUT DOUBLE LABEL WITH IBA1, A MARKER FOR MICROGLIA. WE CAN DO THIS IN SOME DETAIL QUANTITATIVELY. AND NOW WE CAN SEE IN VIVO THAT THESE GENES THAT PREVIOUSLY WERE NOT ON IN VITRO ARE NOW BEING EXPRESSED IN THE MICROGLIA. SO IN VIVO SETTING.

INTERESTINGLY, THE CF1 RECEPTOR, WHICH IS A SURVIVAL RECEPTOR IN THE GENE FOR MICROGLIA IN HUMANS UNIQUELY TO MOUSE, IS BEING EXPRESSED IN OUR ORGANOID, HUMAN ORGANOID. SO WE DO NOT HAVE TO ADD OR ENGINEER THE CELLS IN ANY WAY. THEY'RE NATURALLY SURVIVING. IBA1, HERE ARE THESE MARKERS, ADDITIONAL MARKERS FOR MICROGLIA.

TO SORT OF CONFIRM THAT THEY REALLY ARE IN A MATURED FORM, WE HAVE LOOKED AT SINGLE-CELL SEQUENCING AT 6 WEEKS, 11, AND 24 WEEKS AFTER TRANSPLANTATION. AND WE DO OUR UMAP ANALYSIS HERE, AND YOU CAN SEE THAT THEY -- THESE ARE COLOR CODED FOR THE SENSOME GENOME. SO PICKMAN SOME TIME AGO EXTRACTED HUMAN MICROGLIA FROM THE HUMAN BRAIN AND ANALYZED GENES THAT ARE IMPORTANT FOR WHAT IS CALLED A SENSOME. SO MICROGLIA HAVE THIS INTERESTING PROPERTY WHERE THEY SENSE DANGER OR DAMAGE IN THE ENVIRONMENT AND THEY ATTACK, DESTROY CELLS THAT MAY BE DETRIMENTAL TO THE CELL. WHAT IS CONCEPTUALLY

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BUILT INTO THIS IS THAT WHEN MICROGLIA BECOME OVERACTIVE, THEY BEGIN HARMING OR HURTING THE EXISTING HEALTHY BRAIN AS WELL.

SO WE ARE SEEING THAT THERE'S AN UPREGULATION OF THESE SENSOME GENES. THEY BECOME MORE ACTIVE AND ALSO GENES THAT WE AND OTHERS HAVE DISCOVERED TO BE IMPORTANT FOR MAINTAINING THE ENVIRONMENTAL INTEGRITY OF THE MICROGLIA.

SO ONE OF THE THINGS THAT WE CAN DO WITH THIS MODEL IS WE CAN PUT A GLASS COVERSLIP OVER THE TOP OF THE MOUSE'S BRAIN. THESE ARE NON-SCID MICE. THEY'RE IMMUNOCOMPROMISED. AND WE PUT A 2-PHOTON MICROSCOPE OVER THE TOP OF THE ANESTHETIZED ANIMALS, AND WE CAN WATCH THE MICROGLIA AS THEY SENSE THE ENVIRONMENT. THIS WAS AN EXPERIMENT DONE TEN YEARS AGO IN MICE FOR THE FIRST TIME BY AXEL NIMMERJAHN. AND HE'S NOW A FACULTY MEMBER AT THE SALK. HE WAS ABLE TO SEE HUMAN MICROGLIA BEHAVING IN MANY WAYS THE SAME WAY. WHAT'S INTERESTING, THEY SURVEY THEIR ENVIRONMENT, BUT THEY DON'T TOUCH EACH OTHER, BUT IS SENSING FOR TOXINS IN THE ENVIRONMENT.

WE KNOW THESE CELLS ARE RESPONSIVE. SO WE CAN GIVE AN INFLAMMATORY INJECTION OF WHAT'S CALLED LIPOPOLYSACCHARIDE, WHICH INDUCES AN INFLAMMATORY RESPONSE. AND HERE'S THE CONTROL AND HERE'S 24

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HOURS AFTER INJECTION. AND THEY ROUND UP AND APPEAR MUCH MORE LIKE A PHAGOCYTIC CELL. THESE PHAGOCYTIC CELLS ARE WHAT ARE CALLED REACTIVE MICROGLIA, AND THEY'RE NOT DOING THEIR HEALTHY JOB. THEY'RE ACTUALLY CAUSING TOXICITY, SECRETING A LOT OF UNHEALTHY MOLECULES INTO THE ENVIRONMENT.

NOW, INTERESTINGLY, WHEN WE KILL A CELL RIGHT BETWEEN TWO OF THESE -- FOUR OF THESE MICROGLIA, WE END UP SEEING HOW THE MICROGLIA ACTUALLY RESPOND. SO NORMALLY WHAT WOULD HAPPEN IS THAT THE MOUSE MICROGLIA, AS WE'VE LEARNED IN THE PAST, MIGRATE IN AND SURROUND AND DESTROY THE CELL. BUT HUMAN CELLS BEHAVE DIFFERENTLY. THEY WORK COORDINATELY, RESPONDING TO THEIR ENVIRONMENT AND SEND OUT THEIR PROCESS OF RETAINING THEIR POSITION IN THEIR QUADRANT. SO THIS WAS ACTUALLY A NEW DISCOVERY OF HOW HUMAN MICROGLIA BEHAVE DIFFERENTLY THAN DO MICE, THE ONLY TWO SPECIES IN WHICH WE'VE BEEN ABLE TO SEE LIVING IMAGES OF HOW THEY FUNCTION.

NOW, ONE OF THE ADVANTAGES OF THIS THAT WE KNEW WE COULD EXPLOIT IS TO DETERMINE WHETHER IT IS THE CELLS THEMSELVES, LET'S SAY THE MICROGLIA, WHICH ARE INDUCING A REACTIVITY WITHIN THE HOST, OR IS THE HOST ACTIVATING THE MICROGLIA TO BECOME AN INFLAMED CELL TYPE? WE'VE BEEN PREVIOUSLY WORKING WITH AN

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AUTISTIC SUBGROUP OF INDIVIDUALS THAT HAVE LARGE BRAINS. THESE ARE MACROCEPHALIA. AND ONE OF THE THINGS THAT'S BEEN SHOWN BOTH IN PET AND HISTOLOGY IN THESE PATIENTS IS THEY HAVE AN INCREASE IN MICROGLIA MORPHOLOGICAL RESPONSES, SUGGESTING AN INFLAMED STATE OR A MACROPHAGIC STATE.

SO WE MADE ORGANOIDS FROM OUR CONTROL, AND WE SEE -- AND IMBUED THEM WITH HEALTHY -- THESE ARE ISOGENIC MICROGLIA, AND THEY BEHAVE WELL AND LOOK GOOD. HOWEVER, WHEN WE IMBUED THEM WITH THE -- WHEN WE TOOK THE ASD, THAT'S THE AUTISM SPECTRUM DISORDER, BRAIN ORGANOIDS AND IMBUED THEM WITH THEIR OWN MICROGLIA, THEY WERE INFLAMED. SO THAT'S THE BASELINE. AND THEN THE QUESTION BECOMES IS IT THE BRAIN THAT'S ACTIVATING THE MICROGLIA OR THE MICROGLIA ACTIVATING THE BRAIN?

IN THIS ONE EXPERIMENT, WE JUST DID THE LATTER PIECE, WHICH IS TO TAKE AN ASD ORGANOID AND IMPLANTED THEM WITH NEUROTYPICAL MICROGLIA VERSUS, OF COURSE, CONTROL ORGANOID IN NEUROTYPICAL ORGANOIDS. AND HERE IS THE CONTROL WITH NEUROTYPICAL ORGANOID, HEALTHY LONG BRANCHES. AND IN THIS CASE YOU SEE THAT THEY ARE ACTIVATED. WE CAN NOW SORT THESE MICROGLIA AND THE SURROUNDING BRAIN AREA AND ARE BEGINNING TO UNDERSTAND THE

MOLECULAR SIGNALS FROM THE BRAIN WHICH ARE ACTIVATING THESE MICROGLIA.

SO WHAT I SHOWED YOU SO FAR IS THAT MICROGLIA PROGENITOR CELLS EFFICIENTLY POPULATES THE DEVELOPING HUMAN BRAIN ORGANOID. THE LONG-TERM DIFFERENTIATION WAS ALWAYS HAMPERED IN VITRO, THUS LIMITING THEIR USE. WE DEVELOPED A METHOD FOR CHIMERIC-TRANSPLANTATION PARADIGM, ALLOWING US TO STUDY HUMAN MICROGLIA INSIDE TO OUR HUMAN BRAIN. THEY SURVIVE, MATURE. THEY ACQUIRE IN VIVO-LIKE RESTING PROPERTIES, BUT CAN RESPOND TO STIMULI IN PREDICTED DIRECTION. AND WE CAN LEARN NEW THINGS ABOUT HOW HUMANS ARE DIFFERENT ADULTS, AND WE CAN BEGIN TO TAKE THESE STUDIES INTO A DISEASE CONTEXT AS WELL.

I'D LIKE TO STEP BACK AND SAY WE ARE STILL MISSING MANY OTHER CELLS IN HERE. I'M SHOWING RIGHT NOW SOME UNPUBLISHED RESULTS ON ASTROCYTES. WE DEVELOPED A PROTOCOL WHERE WE CAN USE A SERIES -- WE CAN INCUBATE OUR ORGANOIDS IN GLIAL-PROMOTING FACTORS WHICH CAN INDUCE A RAPID DEVELOPMENT AND MATURATION OF GLIA IN THE ORGANOIDS THEMSELVES.

A GENE THAT HAS BEEN IDENTIFIED VERY EARLY ON BY LAWRENCE STUDER AND HIS TEAM WAS NF1A IS THOUGHT TO BE AN IMPORTANT TRANSCRIPTION FACTOR THAT

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ENABLES ASTROCYTE DIFFERENCES. AND WE FOUND THAT WITH OUR CONDITIONING MEDIA WE GET NF1A EXPRESSION AS EARLY AS 21 DAYS IN VITRO. THIS IS ALL IN VITRO. BY 60 DAYS WE HAVE A FULLY REPRESENTED ASTROCYTE POPULATION THROUGHOUT THE ORGANOID. AND WHEN WE DO SINGLE-CELL SEQUENCING IN TEN-WEEK OLD ENRICHED ORGANOIDS, AGAIN IN VITRO, WE SEE THAT -- OF COURSE, WE SEE EXCITATORY NEURONS, INHIBITORY NEURONS, PRECURSOR ASTROCYTES, AND MATURE ASTROCYTES. I'LL GO INTO THAT IN A LITTLE BIT MORE DETAIL.

BUT FROM THE FUNCTIONAL POINT OF VIEW, YOU CAN SEE THAT THEY CONTINUE TO MATURE FROM THREE MONTHS TO FIVE MONTHS. AND RESEARCH HAS ALL THE MORPHOLOGICAL EVIDENCE ACCORDING TO THE FACT THAT THEY CONTINUE TO GROW AND ELABORATE THE PROCESSES. THEY ARE FUNCTIONAL TO THE EXTENT THAT THEY CAN TAKE UP GLUTAMATE, A TRANSMITTER THAT IS NORMALLY SECRETED BY NEURONS; BUT IN THE ABSENCE OF THIS UPTAKE, GLUTAMATE CAN BE TOXIC TO NEURONS AND MAY, IN OUR ESTIMATE, BE PART OF THE REASON WHY NEURAL ORGANOIDS THEMSELVES HAVE THIS CERTAIN TOXICITY THAT OCCURS OVER TIME BECAUSE THEY'RE NOT ABLE TO TAKE AWAY THE EXCESS GLUTAMATE. THEY ALSO CAN ELICIT CALCIUM SPIKES WITH STIMULATION OF GLUTAMATE AS WELL IN VITRO. THIS IS ALL IN VITRO.

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SO WE TRANSPLANTED THESE CELLS INTO OUR TRANSPLANTATION MODEL. HERE'S THE TRANSPLANT HERE. AND THEY SURVIVE VERY WELL AND THEY CO-LOCALIZE WITH THE HUMAN ANTIBODY. SO WE KNOW THEY'RE HUMAN. QUITE REMARKABLY, THIS IS THE IN VITRO ORGANOID, AND IT HAS A GREATER CONTENT OF ASTROCYTES, BUT THEY'RE REALLY DISORGANIZED. THEY'RE NOT PATTERNED AND DISTRIBUTED LIKE THEY ARE IN VIVO AND LIKE WE SEE IN THE BRAIN. THERE'S ACTUALLY A DECREASE IN VITRO, BUT THEY BEGIN TO PATTERN THEMSELVES.

WHEN YOU LOOK AT THE DIFFERENCE BETWEEN HUMAN AND MOUSE ASTROCYTES, IT'S REALLY QUITE EXTRAORDINARY. NOT ONLY ARE THEY LARGER, BUT THEIR SHAPE IS REALLY QUITE DIFFERENT. THEY HAVE THESE LONG EXTENDED PROCESSES THAT ARE DIRECTLY ATTRACTED; WHEREAS, THE MOUSE ASTROCYTES FORM A SPHERICAL SHAPE. THE LONG PROCESSES THAT EXTEND FROM THE ASTROCYTES ARE OFTEN ASSOCIATED WITH BLOOD VESSELS. IN VIVO THAT'S WHAT ONE SEES AND ALSO WHAT ONE SEES IN VIVO.

AFTER TRANSPLANTATION NOW, WE CAN IDENTIFY NOT JUST THAT THERE'S ASTROCYTES THERE, BUT THE FULL PRINCIPAL TYPES OF ASTROCYTES THAT HAVE BEEN DESCRIBED IN HUMAN LITERATURE CAN BE RECAPITULATED IN THESE ORGANOIDS, SPECIFICALLY UPPER AND -- IT'S

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CALLED THE PEEL LAYER. WE HAVE THESE INTER-LAMINAR ASTROCYTES SEND THEIR PROCESSES DOWN. THEY'RE CLASSIC SORT OF PLASMIC ASTROCYTE IN THE CORE OF THE TISSUE AND THE FIBROUS ASTROCYTES WHERE IT SITS ON THE GLIAL SITE MOVING UP INTO THE TISSUE.

INTERESTINGLY, THERE'S AN ASTROCYTE WHICH IS UNIQUE TO HUMANS CALLED THE VARICOSE PROJECTION ASTROCYTE, AND WE SEE THAT ONE AS WELL. THAT MISSED CELL RIGHT HERE HAS A SINGLE BLIPPY PROTOPLASMIC-LIKE THING WHICH SENDS ON A PROCESS THAT IS BEADED. AND THIS IS A UNIQUE FEATURE OF -- IS A UNIQUE ASTROCYTE ACTIVITY IN HUMANS THAT DOESN'T EXIST IN MOUSE OR LOWER SPECIES. BUT ALL THE OTHER TYPES EXIST IN THERE, AND THEY ARE LAMINATED.

INTERESTING FOR THOSE THAT HAVE WORKED WITH ORGANOIDS IN THE PAST, ONCE THEY'RE TRANSPLANTED AND VASCULARIZED, THEY DON'T -- THEY NO LONGER HAVE A ROSETTE IN THE CORE AND, RATHER, BECOME A FULL LAYERED CORTICAL TISSUE.

SO ONE OF THE FEATURES OF ASTROCYTES THAT WE KNOW IS, AS I POINTED TO YOU BEFORE, THEY SEND THEIR PROCESSES AND EXPRESS A GENE CALLED APOE4 ALONG THE VASCULAR BED. SO HERE IS A BLOOD VESSEL HERE STAINED FOR APOE4A, WHICH IS A PROTEIN FROM THE

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ASTROCYTE. HERE THEY ARE LAMINATED. IN VITRO, OBVIOUSLY THERE'S NO BLOOD VESSELS AND IT'S JUST SORT OF DISTRIBUTED DIFFUSELY AROUND IN THE ASTROCYTE. THEY STILL MAKE IT, BUT IT'S NOT LOCATED TO THE VASCULAR SYSTEM.

HERE IS A 3D -- WHAT THIS IMAGE IS GOING TO SHOW YOU IS WHAT'S CALLED THE VASCULAR UNIT WHICH IS COMPRISED OF ENDOTHELIAL CELLS, PERICYTES, ASTROCYTES, AND ENDOTHELIAL CELLS, AND EXTRACELLULAR MATRIX IN TIGHT JUNCTION. AND THIS IS THE UNIT THAT KEEPS THE OUTSIDE BLOOD FROM COMING INTO THE BRAIN OR WHAT IS CALLED BLOOD-BRAIN BARRIER. HERE'S A THREE-DIMENSIONAL RECONSTRUCTION OF THAT. THESE ARE EM SECTIONS. THEY'RE A SECTION THAT'S VERY THIN AND THEN STACKED, AND THEN WE CAN GO BACK AND LABEL THEM. THEY DON'T COME THIS WAY. WE HAVE TO COLOR THEM. BUT IT NOT ONLY HAS PERICYTES, MEMBRANES, TIGHT JUNCTIONS, AND ENDOTHELIAL CELLS. UNIQUE, AGAIN, TO THE HUMAN IS THE FACT THAT THE ASTROCYTE ABUTS THE UNIT AND COMPLETELY SURROUNDS IT BY ONE ASTROCYTE. IN THE MOUSE THEY GENERALLY SEND PORTIONS OF THEIR PROCESSES AND WOULD HAVE, SAY, AN ASTROCYTE HERE, AN ASTROCYTE PORTION HERE, AND MAYBE A THIRD ASTROCYTE THERE. SO THIS IS A UNIQUE FORM OF THE VASCULAR UNIT IN HUMAN RELATIVE TO THE MOUSE.

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IS THE BLOOD-BRAIN BARRIER INTACT? WE DID THIS BY GIVING DEXTRAN BEADS TO THE INTRAORBITAL -- INJECT THEM INTRAORBITALLY. AND YOU CAN SEE THAT THE DYE WILL -- IN THE LIVER AND THE MUSCLE IT GETS OUT AND SPREADS OUT TO ALL THE TISSUES. HOWEVER, IN THE BRAIN YOU GET NO LEAKAGE OR LITTLE LEAKAGE AND ONLY STAYS WITHIN THE BLOOD VESSELS. SO HERE'S IN OUR ADJACENT MOUSE CORTEX AFTER THE SAME EXPERIMENT, AND HERE'S WITHIN THE TRANSPLANT. SO WE SEE THAT THE BIOTIN TRACER IS EXCLUDED FROM THE TISSUE AND IS MAINTAINED IN THERE, EVIDENCE SUPPORTING THE FACT THAT THIS IS A RELATIVELY INTACT BLOOD-BRAIN BARRIER.

A CAVEAT HERE IS THAT THE ENDOTHELIAL CELLS AND THE PERICYTES THAT MAKE UP THIS BLOOD-BRAIN BARRIER ARE DERIVED FROM THE MOUSE. THEY'RE MIGRATING IN FROM THE MOUSE, AND WE ARE NOT SUPPLYING AT THIS POINT THOSE CELLS. SO THIS IS A LIMITATION.

CHAIRMAN GOLDSTEIN: SO, RUSTY, WE ARE AT ABOUT 25 MINUTES JUST TO GIVE YOU A MARK.

DR. GAGE: PERFECT. I'M TWO MINUTES AWAY OR THREE.

SO WE HAVE -- IN THE SINGLE-CELL SEQUENCING WE CAN LOOK AT THESE ASTROCYTES UNIQUELY,

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AND WE FIND THAT GO CATEGORIES FOR THE GENES IDENTIFY THOSE THINGS THAT WE BELIEVE TO BE IMPORTANT FEATURES LIKE BLOOD-BRAIN BARRIER, PERMEABILITY, POSITIVE REGULATION, VASCULAR PERMEABILITY. ALL THESE GENES ARE UPREGULATED IN THE ASTROCYTE IN THESE EMBEDDED TRANSPLANTED ORGANOIDS.

JUST A LITTLE MORE INFORMATION ABOUT THE MATURATION OF THEM. WE COMPARED THIS TO BEN BARRES' EARLY WORK. WE ISOLATED ASTROCYTES FROM HUMAN FETAL AND ADULT BRAIN, AND WE SEE THAT THE IN VITRO HAS A FEW OF THESE MORE ADULT GENE MARKERS, MORE OF THE FETAL; WHEREAS, IN OUR TRANSPLANT ORGANOIDS, THEY MATURE QUITE DRAMATICALLY OVER TIME.

LARRY, I'M NOT GOING TO TELL TOO MUCH, BUT ALSO PART OF THE STORY IS THAT THE ASTROCYTES EMBED INTO THESE NEURONAL ORGANOIDS, INDUCE A RATHER DRAMATIC MATURATION OF THE NEURONS AS WELL. SO HERE'S THE IN VITRO ORGANOIDS AND HERE ARE NEURAL GENE ONTOLOGY SIGNALS, INDICATING THESE NEURONS, PURIFIED NEURONS, HAVE NOW TAKEN ON A MATURE SET. AND WE CAN SEE THIS BY LOOKING AT AN ELECTRON MICROSCOPE WHERE YOU CAN NOW SEE INTACT SYNAPSES. SO THIS IS A PRESYNAPTIC TERMINAL HERE WITH VESICLES AND POSTSYNAPTIC DENSITY AND POST (UNINTELLIGIBLE),

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WHICH ARE EVIDENT IN THESE CELLS.

FINALLY, WE WANT TO TEST FUNCTIONALITY. SO WE STIMULATED THE ANIMALS WHO HAVE TNF-ALPHA, AN INFLAMMATORY INDUCTION MECHANISM. SO AN INCREASE IN THE SUBSET OF ASTROCYTES IN THE TYPES OF GENES AND NUMBER OF CELLS THAT TOOK PLACE. WE LOOK AT THOSE IN QUITE DETAIL, AND WE SEE THAT THERE'S AN UPREGULATION OF TWO HALLMARKS OF INFLAMMATION, INTERFERON GAMMA, TNF-ALPHA SIGNALING OR NF-KAPPA-B AS WELL, INTERESTINGLY, THE DOWNREGULATION OF OXYGEN PHOSPHORYLATION. SO THE CELLS BECOME MORE GLYCOLYTIC IN THEIR INFLAMED STATE, WHICH IS CHARACTERISTIC OF THE LITERATURE.

FUN NOTE IS WE CAN TAKE THIS SAME ORGANOID AND TEST THINGS IN MORE DETAIL IN VITRO. SO WE TAKE THE ASTROCYTE ORGANOID, TREAT FOR TNF-ALPHA SHORTLY AND LOOK FOR GENES THAT ARE INVOLVED. AND WHAT WE FIND IS THAT CD38, A KEY REGULATOR OF NAD+ LEVELS IN THE BRAIN INVOLVED IN INFLAMMATION AND INTERHUMAN METABOLISM, IS DRAMATICALLY UPREGULATED IN THE BRAIN. IN THE SUBSET OF ASTROCYTES, THERE ARE CANCER DRUGS OUT THERE THAT SPECIFICALLY INHIBIT CD38. WE CAN APPLY THOSE IN THIS IN VITRO MODEL AND WE CAN DRAMATICALLY RETURN NAD+, THE NAD RATIO IN THESE CELLS AFTER REDUCTION.

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AND THIS ALSO IS SHOWN BY LOOKING AT THE FRAGMENTATION OF MITOCHONDRIA. AGAIN, SHOWING THAT THE REESTABLISHMENT OF METABOLIC ACTIVITY WITHIN THESE CELLS. SO WE HAVE RAPIDLY DERIVED FUNCTIONAL ASTROCYTES, BLOOD-BRAIN BARRIER, AND FUNCTIONALITY OF THE GLIAL CELLS.

ONE LAST THING, A COUPLE OF SLIDES JUST TO SHOW THE DIRECTION WE ARE GOING. I TOLD YOU THAT THE ENDOTHELIAL CELLS WERE NOT OF HUMAN ORIGIN. WE HAVE APPLIED THIS PROTOCOL, WHICH IS CALLED "GENERATION OF BLOOD VESSEL ORGANOIDS FROM HUMAN PLURIPOTENT CELLS" BY JOSEF PENNINGER. AND WE APPLIED THIS, AND WE CAN NOW SORT OUT HUMAN PERICYTES AND ENDOTHELIAL CELLS. IT'S QUITE REMARKABLE. THIS IS WHAT THESE ENDOTHELIAL ORGANOIDS LOOK LIKE, AND THEY HAVE PDGF. THEY HAVE ALL THE MARKERS FOR THE CELLS THAT WE WANT.

WE'VE DEVELOPED A PROTOCOL NOW WHERE WE CAN EMBED THE ENDOTHELIAL ORGANOID WITH OUR EXISTING ASTROCYTE AND MICROGLIA ORGANOID, AND WE CAN NOW FOR THE FIRST TIME SEE HUMAN VASCULARIZATION BEGINNING IN THESE HUMAN ORGANOIDS. AND WE'VE JUST BEGUN TO TRANSPLANT THESE CELLS TODAY SO THAT WE CAN SEE IF THE HUMAN ENDOTHELIAL CELL AND PERICYTES WILL ANASTOMOSE WITH THE MOUSE VASCULATURE SO WE CAN GET

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A MORE COMPLETE HUMAN BLOOD-BRAIN BARRIER.

THIS IS THE SUMMARY THAT I STARTED OFF WITH. WE HAVE MICROGLIA AND ASTROCYTES. WE ARE ON THE WAY TO ENDOTHELIAL AND PERICYTES. WE HAVE A STRATEGY FOR OLIGODENDROCYTES THAT I'M HAPPY TO SHARE. AND WE'VE BEGUN DOING THE COMPARISON EXPERIMENTS BY INDUCTING WITH PUTTING THE HEALTHY MICROGLIA INTO A DISEASED ENVIRONMENT TO ASK DIRECTIONALITY. AND WE ARE LOOKING FORWARD TO DEVELOPING THESE MODELS THAT WILL BE USEFUL FOR ADDRESSING HUMAN BRAIN DISEASES HERETOFORE UNTAPPED.

SO WITH THAT, I WANT TO THANK TWO EXTRAORDINARY POST DOCS IN THE LAB, ONE FOR THE ASTROCYTES AND ONE FOR THE MICROGLIA. AND THEY TEAM UP TO WORK ON PUTTING THESE TOGETHER NOW INTO A COMMON SYSTEM.

I'LL STOP THERE, LARRY, AND ESCAPE FROM THIS. AND SHOULD I STOP SHARING? UNLESS YOU WANT TO LOOK AT PICTURES AGAIN.

CHAIRMAN GOLDSTEIN: WELL, ACTUALLY, YEAH. WHY DON'T YOU GO AHEAD AND KEEP CONTROL BECAUSE IT COULD BE THAT A QUESTION WILL ELICIT THE NEED FOR A PARTICULAR SLIDE.

DR. GAGE: OKAY.

CHAIRMAN GOLDSTEIN: SO THAT'S TERRIFIC,

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RUSTY. THIS SYSTEM ALREADY LOOKS LIKE IT'S GOING TO BE INCREDIBLY VALUABLE COMPARED TO PREVIOUS 2D AND NEURAL ONLY SYSTEMS.

ONE QUICK QUESTION. AS THESE BECOME -- AS THESE ORGANOIDS BECOME BETTER VASCULARIZED, WHAT DO YOU THINK IS GOING TO LIMIT THEIR SIZE WHEN TRANSPLANTED INTO THE MOUSE BRAIN?

DR. GAGE: SO WE'VE BEEN DOING THIS NOW FOR ABOUT FIVE YEARS. AND WE DO NOT -- THEY STOP DIVIDING. SO YOU DON'T HAVE -- THEY MATURE ENOUGH. BECAUSE THEY'RE MATURING SO MUCH, THEY DON'T HAVE ANY DIVIDING CELLS. WE PULSE WITH VRDU. AND YOU WILL SEE AN OCCASIONAL DIVIDING CELL, BUT I THINK IT'S A REPLACEMENT RATHER THAN ANY OTHER CELL. THEY REALLY ARE RESTRAINED BY THE CAVITY SIZE.

I THINK THAT'S THE SAME QUESTION YOU WOULD ASK OF YOURSELF, WHY YOUR BRAIN ISN'T BURSTING OUT OF YOUR SKULL, IS THAT IT REACHES A RESTRICTIVE LIMIT.

THERE ARE ABOUT, I WOULD SAY, 3 MILLIMETERS WHEN THEY ARE GRAFTED, AND THEY GET UP TO ABOUT 3.5 TO 4 MILLIMETERS AND THEN THEY STOP AT THAT POINT.

CHAIRMAN GOLDSTEIN: PRETTY REASONABLE SIZE.

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PAT.

DR. LEVITT: THAT'S GREAT, RUSTY. AMAZING TECHNOLOGY. SO TWO RELATED QUESTIONS. ONE IS THE AMOUNT OF WORK IN THESE EXPERIMENTS THAT YOU DESCRIBED IS GINORMOUS. THAT'S LIKE BEYOND ENORMOUS, RIGHT, IS GINORMOUS.

SO FROM THE PERSPECTIVE OF TRYING TO UNDERSTAND BOTH MECHANISM AND ALSO PEOPLE HAVE WRITTEN -- THERE'S BEEN A LOT OF WRITING ABOUT THE USE OF ORGANOIDS AND STEM CELLS FOR TARGETING DRUG SCREENING. WHAT IS YOUR VIEW ON THAT BECAUSE WHAT YOU'VE DESCRIBED IS CERTAINLY TIME-CONSUMING, GNAWING OUT ITS BENEFITS?

AND THEN THE OTHER THING THAT'S RELATED TO THAT IS LIKE IN YOUR BIOLOGICAL PSYCHIATRY PAPER THAT YOU WROTE WITH PAOLA, YOU DID AN INTRODUCTION TO THE SPECIAL ISSUE. ONE OF THE THINGS THAT PAOLA HAS EMPHASIZED IS THE HETEROGENEITY, WHICH I THINK IS BIOLOGICAL. RIGHT? AND SO HOW ARE YOU THINKING ABOUT THAT IN TERMS OF THE NUMBERS THAT YOU'D NEED TO GET TO A POINT WHERE YOU FEEL THE SCREENINGS WOULD ACTUALLY BE VALID AND VALUABLE?

DR. GAGE: I THINK --

DR. LEVITT: TWO VERY EASY QUESTIONS FOR YOU.

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DR. GAGE: YEAH. WELL, FOR ONE, WE DO -- IN A SETTING, IN ONE DAY WE CAN DO 25 TO 30 ANIMALS. SO WE CAN GET GOOD SIZED GROUPS THAT WAY. WE USUALLY DO -- SUBJECT-WISE, WE'LL DO THEM IN DUPLICATE OR TRIPLICATE. THESE ARE ALL REPS. THIS IS ALL THE GRAPHICS. AT THAT POINT, UNLIKE WITH TISSUE CULTURE, YOU DON'T FEED YOURSELVES. YOU JUST PUT THEM IN A CAGE AND THEY FEED THEMSELVES.

DR. LEVITT: SURE.

DR. GAGE: SO I DO THINK THAT THIS IS A MORE COMPLICATED MODEL, BUT -- AND WHAT I WAS TRYING TO SHOW HERE WITH THE IN VITRO EVIDENCE, WE INJECTED TNF-ALPHA AND GOT AN INFLAMMATORY RESPONSE. AND WE COULD THEN PURSUE THAT IN THE SUBPOPULATION IN VITRO FOR THE SHORT-TERM PERIOD THAT WE WANTED. SO I THINK WE ARE NOT SAYING THAT YOU WANT TO THROW OUT ALL IN VITRO WORK; BUT, RATHER, YOU CAN GET A MORE AUTHENTIC REPRESENTATION OF THE INTERACTIONS BETWEEN CELLS IN THE IN VIVO SETTING. AND JUST LIKE WE HAVE DONE IN THE PAST WITH MICE WHERE YOU DO SOME OF THE WORK IN MICE; BUT THEN ONCE YOU ACTUALLY GET TOWARDS THE MECHANISM, THEN YOU WOULD LIKE TO MAKE IT INTO SIMPLER, MORE IN VITRO SYSTEM SO YOU CAN DO MECHANISTIC KINDS OF THINGS OR HIGH THROUGHPUT SCREENING. THIS IS NOT WHERE YOU WOULD DO HIGH

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THROUGHPUT SCREENING. THIS IS WHERE YOU WOULD DISCOVER MECHANISMS AND THEN COME BACK LATER AND MAKE SURE THAT THE COMPOUNDS THAT YOU FOUND THAT ARE DOING THEIR THING DO IT IN THIS CONTEXT AS WELL.

SO I DON'T WANT TO REPRESENT THAT I'M PROMOTING THIS OVER AND ABOVE, BUT AS AN ADDED TOOL TO THE ARSENAL.

DR. LEVITT: OKAY. AND WHAT ABOUT THE HETEROGENEITY ISSUE WHICH --

DR. GAGE: I GUESS I'M -- THERE IS INDIVIDUAL HETEROGENEITY, AND WE EMBRACE HETEROGENEITY AS INDIVIDUAL DIFFERENCES. WE, OF COURSE, ARE INTERESTED IN THAT WITH REGARD TO MOBILE ELEMENTS AND WAYS IN WHICH DIVERSITY CAN BE GENERATED WITH THE TOOLS. WE HAVE FOUND THAT BETWEEN INDIVIDUALS, SO SAME ORGANOIDS TRANSPLANTED IN TWO SEPARATE MICE BUT FROM THE SAME PATIENT, ARE SIMILAR TO EACH OTHER. SO THEY CLUSTER BY SUBJECT RATHER THAN JUST RANDOM VARIATION. SO IT'S NOT RANDOM VARIATION. I BELIEVE, AS YOU SAID, IT'S INDIVIDUAL DIFFERENCES, AND WE EMBRACE THOSE DIFFERENCES.

AND, FOR EXAMPLE, IN THIS AUTISM STUDY THAT WE'VE DONE WITH THE MACROCEPHALIA, THEY ARE CLEARLY DIFFERENT. THEY HAVE -- THE ORGANOIDS GROW

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BIGGER, THEY GROW FASTER, AND THEY HAVE MORE PROLIFERATING CELLS IN THEM RELIABLY ABOVE THE AGE-MATCH CONTROL.

SO WHILE WORKING WITH HUMANS ALWAYS ADDS EXTRA VARIANCE INTO THE SETTING, I BELIEVE THE MORE YOU CAN CONSTRAIN THE CONTEXT IN WHICH YOU'RE GROWING THEM AND ALSO THAT YOU'RE PROVIDING APPROPRIATE NUTRIMENTS, YOU CAN REDUCE THAT AMOUNT OF HETEROGENEITY.

TO BE HONEST WITH YOU, I THINK THAT PART OF THE HETEROGENEITY IS THIS NECROSIS THAT OCCURS IN THE CORE OF THE ORGANOID THAT LEADS TO VARIABLE RESPONSE WITHIN THE HOST. AND EACH ORGANOID IS GOING TO BE SLIGHTLY DIFFERENT DEPENDING UPON HOW MUCH NECROSIS THERE REALLY IS. I THINK SOME OTHERS HAVE ALSO COME TO RECOGNIZE THIS AND THEY'RE SEEING THAT THIS INCREASE IN STRESS RESPONSE IN THE CORE IS IMPACTING THE REST OF THOSE CELLS. I THINK VARIABILITY, I DON'T WANT TO SAY ALL OF IT, BUT I WOULD SAY SOME OF IT COMES FROM THE --

YOU KNOW, THE OTHER THING, JUST TO PLAY ON THAT, YOU CAN GET ASTROCYTES, HUMAN ASTROCYTES, IN THESE ORGANOIDS, BUT IT TAKES ABOUT FIVE MONTHS, AND THEN THEY'RE ONLY IN THE OUTER PORTIONS. AND THAT'S A VARIABLE POINT BECAUSE THEY'RE NOT ALWAYS THERE.

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SO I WOULD ARGUE THAT, LIKE ALL OF US, WE WANT TO HAVE AS MUCH CONTROL OF OUR ENVIRONMENT. THAT'S WHY WE WANT TO DRIVE THE ASTROCYTES AND TAKE OUR TIME. WE WANT TO EMBED THE MICROGLIA AND TAKE THE TIME. WE WANT TO BRING THE ENDOTHELIAL CELLS AND TRY TO MIMIC THE TIME PERIOD WHEN THEY ACTUALLY WOULD GET IN THERE AS BEST WE CAN.

LOT OF WORDS. LOT OF WORDS.

DR. LEVITT: THAT WAS GREAT. THANK YOU.

CHAIRMAN GOLDSTEIN: QUESTIONS FROM THE GROUP?

RUSTY, THE PROGRESS YOU GUYS HAVE MADE, I'M SURE IT'S BEEN AGONIZING AT TIMES, BUT CERTAINLY FROM THE OUTSIDE, OH, IT LOOKS EASY. AND IT WAS REALLY FAST AND YOU KNEW ALL ALONG EXACTLY WHAT YOU ARE GOING TO DO, BUT IT'S A BEAUTIFUL SYSTEM. AND I THINK ALL OF US LOOK FORWARD TO FURTHER DEVELOPMENTS FOR FIGURING OUT WHAT'S GOING WRONG IN ALL THE VARIOUS DISORDERS WE ARE TRYING TO FIGHT, ALS AND ALZHEIMER'S AND THE NEUROPSYCHIATRIC DISORDERS. HAVING A SYSTEM THAT RELIABLY RECAPITULATES FUNCTION -- WHOOPS, THERE'S FRED -- IS GOING TO BE INCREDIBLY USEFUL. SO FRED.

DR. FISHER: THAT'S THE FIRST TIME I'VE HEARD, WHOOPS, THERE'S FRED. HI, RUSTY. IT'S

BEEN --

DR. GAGE: HI.

DR. FISHER: -- A VERY LONG TIME.

SO WHEN YOU WERE DESCRIBING YOUR MODEL AND ITS SEPARATION FROM A VASCULAR SYSTEM, I'M INTERESTED OF WHETHER YOU'VE LOOKED AT CLIVE SVENDSEN'S WORK WHO'S DONE A LOT OF WORK IN THIS AREA ALSO. THEY'VE NOW CREATED SORT OF WHAT THEY CALL BRAIN ON A CHIP WHERE THEY HAVE THE VASCULAR SYSTEM, THEY HAVE THE NEURONS AND THE ASTROCYTES AND ALL OF THAT, AND THEY CAN WATCH THE INTERACTION. I'M WONDERING HOW THAT WORK INFORMS THE FUTURE OF WHAT YOU'RE DOING.

DR. GAGE: I HAVE BEEN FOLLOWING IT. AND WE HAVE A SEPARATE EFFORT USING, IT'S NOT A CHIP, BUT IT'S A FABRICATED, MICROFABRICATED TOOL. WE ARE WORKING WITH THE ENGINEERING DEPARTMENT. AND WE CAN GET -- WHAT YOU HAVE TO DO IS YOU HAVE TO FLOW -- WE MAKE OUR VASCULAR ORGANOIDS AND THEY WILL PENETRATE INTO THE ORGAN. THEIR SURVIVAL LENGTH AND DURATION IS LIMITED, AND YOU'RE RELYING ON PROVIDING ARTIFICIAL CSF AND BLOOD VESSELS THROUGH. THE BLOOD-BRAIN BARRIER IS NOT SO STURDY IN THOSE CASES WHERE YOU CAN SORT OF TEST ORGANOIDS, BUT I'M HOPEFUL THAT THAT TECHNOLOGY WILL COME ALONG AND

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MOVE ALONG AND COMPLEMENT THE TRANSPLANTATION WORK AS WELL.

I WOULD SAY, THOUGH, THAT IRONICALLY THIS MODEL IS GOING TO BE DEPENDENT ON WHERE YOU PUT IT AND HOW OLD THE ANIMALS ARE WHEN YOU DO THE TRANSPLANTATION. THIS IS NOT ADDRESSING YOUR POINT EXACTLY, FRED, BUT I HOPE I ADDRESSED IT. I DON'T FEEL LIKE ANY OF US ARE IN COMPETITION. I FEEL LIKE WE ARE ALL STRIVING TOWARDS IT. AND IF YOU CAN GET AN IN VITRO SYSTEM WHERE IT ACTUALLY HAS AN IMPACT ON THE BLOOD-BRAIN BARRIER WITH PERICYTES AND THEY PENETRATE AND THEY ARE HUMAN AND THEY FULFILL THE OBLIGATORY NUTRIMENTS THAT ARE NECESSARY TO KEEP THEM ALIVE FOR EXTENDED PERIODS OF TIME AND MATURE THE NEURONS, THEN THAT'S GREAT. I THINK THAT WILL BE A GOOD COMPLEMENT TO WHAT'S GOING ON.

ONE INTERESTING THING IS THAT THIS MODEL THAT I PRESENTED TO YOU WAS ACTUALLY DEVELOPED -- I DEVELOPED THIS IN 1984 WHEN I WAS IN SWEDEN. AND WE WERE TRYING TO FIND LOCATIONS IN THE BRAIN WHERE WE COULD TRANSPLANT SUPERIOR CERVICAL GANGLION TO TEST WHETHER OR NOT ANY DIFFERENT AREAS IN THE BRAIN HAD NERVE GROWTH FACTOR, HUMAN NERVE GROWTH. THIS WAS A LONG AGO. SO WE IMPLANTED IT INTO THIS COLLICULUS, WHICH IS (UNINTELLIGIBLE) ACTUALLY, BUT WE TRIED

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LOTS OF DIFFERENT AREAS. AND THERE ARE VERY FEW PORTS IN THE AREA WHERE THEY SURVIVE FOR EXTENDED PERIOD OF TIME AND ARE HIGHLY VASCULARIZED WITHIN THE TISSUE. WE ARE STILL EXPLORING OTHER AREAS, BUT I THINK THAT'S AN ISSUE THAT HAS TO BE CONSIDERED.

THE OTHER ISSUE IS THE AGE OF THE ORGANISM. IF WE TRANSPLANT EARLY ON DURING EARLY DEVELOPMENT, THEN THE ORGANOIDS TEND TO GROW MUCH LARGER. AND WE'VE CHOSEN TO GRAFT INTO THE ADULT SO IT RESTRICTS THE AMOUNT OF GROWTH THAT THE ORGANOID WILL GO THROUGH. BUT REMEMBER, IN THE DEVELOPING BRAIN, THE BRAIN IS GROWING AT THE SAME TIME. AND ONE OF THE FACTORS THAT ARE INVOLVED IN INDUCING ITS OWN CELLS TO GROW ARE IMPACTING ON THE HOST AS WELL.

ANOTHER -- IT'S NOT MORE QUESTIONS. ANOTHER INTERESTING FACT IS THAT IF WE DON'T PUT ASTROCYTES AND MICROGLIA IN THE ORGANOID, THEN THE HOST MICROGLIA AND ASTROCYTES WILL MIGRATE IN. BUT IF YOU PUT HUMAN MICROGLIA INTO THE ORGANOID, IT PREVENTS, YOU WILL SEE THE MICROGLIA ON THE BRAIN SIDE -- ON THE MOUSE SIDE, BUT NONE OF THEM CO-STAIN WITH HUMAN MARKERS. AND THAT'S TRUE FOR ASTROCYTES. THERE IS AN INTERESTING EVOLUTIONARY BARRIER FOR ASTROCYTES AND MICROGLIA THAT WILL NOT PENETRATE INTO THE HUMAN TISSUE IF THE OBLIGATORY OR THEIR

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SISTER CELLS ARE PRESENT.

CHAIRMAN GOLDSTEIN: OKAY. FINAL QUESTION. ABLA.

DR. CREASEY: THANK YOU, DR. GOLDSTEIN. AGAIN, THANK YOU, DR. GAGE. VERY NICE PRESENTATION.

I WANTED TO KNOW JUST PHILOSOPHICALLY THIS BEAUTIFUL SYSTEM, CAN IT BE USED FOR THE STUDY OF BIOLOGY AND THE PATHOGENESIS OF DISEASES OF THE BRAIN? OR IS IT MAINLY A SCREENING METHODOLOGY FOR POTENTIALLY IDENTIFYING AGENTS THAT AFFECT EACH OF THE CELL TYPES?

DR. GAGE: I WANT TO MAKE SURE I UNDERSTAND YOUR QUESTION.

DR. CREASEY: IF WE ARE INTERESTED IN THE BIOLOGY OF UNDERSTANDING MECHANISM OF DISEASE OF THE BRAIN --

DR. GAGE: YES.

DR. CREASEY: -- IS THIS -- DO YOU THINK THIS WILL BE A GOOD SYSTEM TO DO THAT?

DR. GAGE: YES. WELL, SO WE'VE SHOWN, FOR EXAMPLE, THAT -- I'LL GIVE YOU TWO EXAMPLES. IN VITRO IN MONOLAYS WE'VE SHOWN THAT BIPOLAR CELLS, HIPPOCAMPAL BIPOLAR NEURONS FROM PATIENTS WITH BIPOLAR DISEASE, THAT ARE NONRESPONSIVE TO LITHIUM TEND TO BE HYPEREXCITABLE IN A MONOLAYER SETTING.

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BUT WE ARE RESTRICTED IN TERMS OF HOW MUCH MECHANISTICALLY WE CAN UNDERSTAND THAT. AND WHILE WE DO SEE THIS HYPEREXCITABILITY IN THE ORGANOID SETTING AND WE WANT TO UNDERSTAND WHETHER OR NOT WE CAN USE THIS AS A TOOL TO GET A BETTER UNDERSTANDING OF THAT HYPEREXCITABILITY THAT YOU SEE IN THE LITHIUM NONRESPONDING PATIENTS.

SO WE CERTAINLY BELIEVE THAT THE ORGANOIDS WILL BE A VEHICLE FOR UNDERSTANDING PATHOPHYSIOLOGY OF DISEASE, AND THAT'S OUR MAIN GOAL IN DOING THIS. WE ALSO HAVE ANOTHER STUDY IN DEPRESSION WHERE WE FIND THAT PATIENTS THAT ARE RESPONSIVE TO ISSCR'S HAVE A DIFFERENT PROFILE THAN THOSE THAT DO RESPOND TO ISSCR'S. AND, AGAIN, TRYING TO NAIL DOWN THE MECHANISM FOR HOW THAT PATHOPHYSIOLOGY IS MANIFESTED. SO WE BELIEVE THAT THIS IS A GOOD MODEL FOR TRACKING THAT DOWN.

DR. CREASEY: THANK YOU. I WAS MAINLY THINKING ABOUT LIKE WHAT ARE THE TRIGGERS FOR THE PATHOGENESIS OF DISEASE AND HOW THE DISEASE PROGRESSES. BUT IT APPEARS THAT EVENTUALLY YOU HAVE ALL THE CELL TYPES THAT YOU NEED IN ORDER TO ANSWER THAT KIND OF QUESTIONS IN THAT ORGANOID. IS THAT RIGHT?

DR. GAGE: YEAH. I WAS REALLY HOPING THAT

THAT ONE EXAMPLE I SHOWED YOU WHERE YOU TAKE THE NEUROTYPICAL MICROGLIA AND PUT IT INTO A DISEASE ORGANOID AND SHOW THAT IT IS THE HOST THAT'S ACTIVATING THOSE MICROGLIA SUGGESTS THAT THE PATHOGENIC SIGNAL TO GET AN INFLAMED BRAIN IS COMING FROM THE HOST. AND WE ARE LOOKING INTO WHAT FEATURES IN THE HOST, RATHER THAN CONCENTRATING ON THE MICROGLIA, WHAT IS THE HOST DOING TO ACTIVATE AND AGGRAVATE THESE MICROGLIA.

DR. CREASEY: GREAT. THANK YOU.

CHAIRMAN GOLDSTEIN: YEAH. THANK YOU VERY MUCH, RUSTY. THAT WAS REALLY EDIFYING, EXCITING, AND I THINK IT'S GOING TO MAKE A BIG DIFFERENCE MOVING FORWARD IN THE COMING YEARS TO HAVE MODELS LIKE THIS AND OTHERS THAT ARE BEING DEVELOPED. SO THANK YOU VERY MUCH FOR YOUR TIME.

AND WE ARE AT A TRANSITION POINT. RUSTY, YOU'RE WELCOME TO STAY AS LONG AS YOU WANT, BUT OUR NEXT --

DR. GAGE: WOULD YOU RATHER THAT I LEAVE?

CHAIRMAN GOLDSTEIN: NO. IT'S TOTALLY UP TO YOU.

DR. GAGE: I'VE GOT EIGHT MINUTES FOR MY NEXT MEETING. SO I COULD HANG ON.

CHAIRMAN GOLDSTEIN: GOOD.

DR. GAGE: I ALSO THANK YOU ALL FOR INVITING ME AND THANK YOU FOR YOUR SERVICE TO THE COMMITTEE AND TO THE COMMUNITY FOR SERVING ON THIS BOARD.

CHAIRMAN GOLDSTEIN: YOU GOT IT.

SO NEXT UP IS VICE PRESIDENT ROSA CANET-AVILES WHO WILL PRESENT A PROPOSED CONCEPT PLAN THAT, IF WE SIGN OFF ON IT, WILL THEN MOVE TO THE SCIENCE SUBCOMMITTEE AND THEN, IF IT GOES WELL THERE, ON TO THE FULL BOARD. SO, ROSA, PLEASE TAKE IT AWAY.

DR. CANET-AVILES: THANK YOU, DR. GOLDSTEIN. AND THIS PRESENTATION FROM DR. GAGE WAS VERY ON POINT WITH WHAT I'M GOING TO PRESENT. I THINK IT WAS FURTHERING THE EVIDENCE OF THE UTILITY OF HUMAN STEM CELL MODELS IN MODELING THE PATHOLOGY OF NEURO DISEASES, ESPECIALLY THE IMPORTANCE OF THE NEUROIMMUNE AXIS, FOR EXAMPLE. SO WE WILL HEAR ABOUT THIS IN A FEW MINUTES AS I GO ALONG.

SO THIS IS AN OPPORTUNITY THAT WE HAVE TO PRESENT THE FIRST PHASE OF THE CIRM NEUROSCIENCE STRATEGY AND IMPLEMENTATION. AND IT WILL COME IN THE FORM OF THE NEURO DISCOVERY CONCEPT, ALSO KNOWN AS REMIND. AND REMIND STANDS FOR RESEARCH USING MULTIDISCIPLINARY INNOVATIVE APPROACHES IN

NEUROLOGICAL DISEASES.

WHAT I WILL BE PRESENTING TODAY IS ACTUALLY A CONCEPT THAT WILL START WITH A PILOT. AND THIS IS -- WHAT WE ARE PROPOSING IS A PHASED APPROACH THAT I WILL BE EXPLAINING IN LATER SLIDES. AND WE ARE GOING TO PILOT THIS AS A POTENTIAL FRAMEWORK FOR MULTIDISCIPLINARY DISCOVERY RESEARCH AT CIRM WITH A GROWING INVESTMENT ADAPTING TO CIRM'S GROWTH IN OTHER PARTS OF THIS INFRASTRUCTURE. SO I WANT TO CLARIFY THAT THIS IS NOT ONLY FOR, AS YOU WILL SEE LATER, NEUROPSYCHIATRIC DISEASES. IT'S ABOUT DISEASE MECHANISM RESEARCH, AND WE ARE GOING TO PILOT THIS WITH NEUROPSYCHIATRIC DISEASES OR THAT'S WHAT WE ARE PROPOSING. BUT IF THE MODEL OF THIS INITIATIVE IS SUCCESSFUL, WE WILL BE GROWING INTO OTHER DISEASES. I WANTED TO MAKE THIS CLEAR SO THAT THERE IS NO CONFUSION. SO LET'S GET STARTED.

THIS IS -- CIRM'S NEUROSCIENCE STRATEGY HAS BEEN DEVELOPED IN THE CONTEXT OF OUR MISSION STATEMENT. AND IT MAPS OUT AND INTEGRATES WITH THE ELEMENTS OF OUR MISSION AND STRATEGIC PLAN AND SPECIFICALLY WITH THE FIRST THEME OF OUR STRATEGY, ADVANCING WORLD-CLASS SCIENCE AND THE TWO MAIN GOALS, WHICH IS DEVELOP COMPETENCY HUBS AND BUILDING A KNOWLEDGE INFRASTRUCTURE OR THE KNOWLEDGE

NETWORKS.

THE REMIND INITIATIVE CORRESPONDS TO THE DISCOVERY PHASE OF CIRM NEURO STRATEGY. AND THE TRAN AND THE CLIN WILL BE ADDRESSED SEPARATELY. I ALSO WANT TO MAKE SURE THAT WE PROVIDE THE RIGHT CONTEXT FOR TODAY'S DISCUSSION.

THIS IS ALL A REMINDER THAT THIS COMES FROM WITHIN THE CONTEXT OF PROP 14'S MANDATE AND CIRM'S $1.5 BILLION SET ASIDE FOR MENTAL HEALTH RESEARCH WITH THE POTENTIAL TO TRANSFORM THE TREATMENT FOR DISEASES AND CONDITIONS OF THE BRAIN AND THE CNS.

THE GOAL OF THIS SLIDE IS TO PROVIDE A FRAME FOR THE BACKGROUND AND THE RATIONALE FOR THE CONCEPTUALIZATION OF THE CURRENT CONCEPT AND THE VISION OF THE NEURO DISCOVERY STRATEGY HAS BEEN INFORMED BY MULTIPLE LAYERS, AS YOU CAN SEE HERE, OF STAKEHOLDER DISCUSSION AND INPUT THAT STARTED EVEN PRIOR TO THE PASSAGE OF PROP 14 OVER THE PAST TWO YEARS AND IS OUTLINED IN THIS TIMELINE CHART.

AND THERE ARE THREE MAJOR TAKEAWAYS, KEY TAKEAWAYS. ONE IS THAT THERE ARE MAJOR GAPS IN OUR UNDERSTANDING OF MECHANISMS UNDERLYING DISEASE PROCESSES IN THE BRAIN. FOR EXAMPLE, WE KNOW A LOT ABOUT HOW THE HEART WORKS, WHICH HAS BEEN KEY

ACTUALLY FOR DEVELOPING THERAPIES. BUT THE BRAIN IS FAR MORE COMPLICATED, AS WE'VE JUST SEEN WITH DR. GAGE'S PRESENTATION, AND WE KNOW VERY LITTLE. SO THAT HAS BEEN IMPEDING THE PROGRESS IN FINDING THERAPIES FOR PEOPLE WITH MENTAL ILLNESS. AND THE KEY TAKEAWAY IS THAT THE LACK OF UNDERSTANDING OF THESE UNDERLYING MECHANISMS OF DISEASE PROCESSES IN THE BRAIN IS A MAJOR BOTTLENECK IN THE DEVELOPMENT OF SUCCESSFUL THERAPIES.

NOW, IN ORDER TO DISCOVER THESE MECHANISMS, ONE OF THE BEST WAYS IS TO LEVERAGE COLLABORATION. SO THE MOST EFFECTIVE AND PRODUCTIVE WAY THAT WE HEARD WAS THE DEVELOPMENT OF A CONSORTIUM APPROACH WHERE GENOMICS AND BIG DATA, NOVEL STEM CELL MODELS, PATIENT DATA COULD BE COLLECTIVELY LEVERAGED TO ADVANCE THE FIELD OF NEURO RESEARCH IN A COLLABORATIVE MANNER.

IN ORDER FOR A CONSORTIUM TO HAVE ITS MAXIMUM OUTPUT, WE NEED TO PROMOTE KNOWLEDGE SHARING AND EXPAND SHAREABLE RESOURCES TO ACCELERATE RESEARCH OF COMPLEX DISEASES.

SO WHAT HAS CIRM DONE TO COVER THIS LACK OF MECHANISTIC NEURO UNDERSTANDING SINCE ITS INCEPTION? FOR THAT, WE NEEDED A GAP ANALYSIS OF THE PORTFOLIO. AND IN THE PAST NEURO TASK FORCES,

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WE PROVIDED THIS PORTFOLIO GAP ANALYSIS. AT THE LAST TASK FORCE MEETING, WE PRESENTED AN INTERNAL PORTFOLIO GAP ANALYSIS. THIS SLIDE SUMMARIZES THE HISTORICAL FUNDING FOR DISCOVERY, WHICH WAS UP UNTIL NOW $1.2 BILLION. THE NEURO FUNDED DISCOVERY, 28 PERCENT. AND OF THOSE 28 PERCENT, THERE WAS 4 PERCENT IN NEURO DISEASE MECHANISMS. NOW, THAT WASN'T A LOT -- SIGNIFICANT. WHERE DID THE OTHER 24 PERCENT GO? WELL, IT WENT PARTLY TO FUND SCIENTIFIC PROGRESS, REFINING DIFFERENTIATION PROTOCOLS, AND CREATING MORE COMPLEX MODELS IN A DISH, SUCH AS ORGANOIDS, AS WE HEARD, SO THAT THE FIELD COULD BE READY TO STUDY DISEASE MECHANISMS.

SO CIRM INVESTED IN THE INFRASTRUCTURE AND THE BASIC, BASIC FOUNDATIONAL RESEARCH OF THIS TO MAKE THE FIELD READY TO STUDY WITH THE MODELS. AND THAT'S KIND OF WHERE WE ARE NOW.

SO WHAT IS THE FOCUS THAT WE ARE GOING TO HAVE? THE FOCUS THAT WE ARE PROPOSING IS GENERATION OF NOVEL THERAPIES FOR NEURO DISEASES WHICH REQUIRES UNCOVERING THE UNDERLYING MECHANISMS. THEREFORE, THE FIRST GOAL OF CIRM'S NEURO DISCOVERY STRATEGY, WHICH CORRESPONDS TO THE GOAL OF THE CONCEPT FOR THE PROGRAM THAT WE ARE PROPOSING, COULD BE TO ACCELERATE THE DISCOVERY OF MECHANISMS UNDERLYING

CNS DISORDERS LEADING TO THE IDENTIFICATION AND VALIDATION OF NOVEL TARGETS AND BIOMARKERS WITH THE GOAL THAT THESE EFFORTS WOULD PROVIDE NEW AVENUES AND RIGOROUS FOUNDATIONS FOR OTHER TRANSLATIONAL AND CLINICAL DEVELOPMENT WORK.

AS YOU CAN SEE, I MENTIONED HERE NEURO. IT'S NOT NEUROPSYCHIATRIC. WHAT THE GOAL IS IS THE -- REMIND IS A CONCEPT FOR A LARGE INITIATIVE THAT COULD BE PHASED. THE IMPLEMENTATION OF ITS FIRST INSTALLMENT WE ARE GOING TO PROPOSE TO BE NEUROPSYCHIATRIC, BUT IT'S NOT GOING TO BE ALL.

SO HOW ARE WE GOING TO GO ABOUT THIS? WHAT ARE THE SPECIFICS OF HOW WE WILL GO ABOUT ACHIEVING THIS GOAL? THE OBJECTIVES PROPOSED FOR THIS INITIAL PROGRAM ARE TO FIRST ADVANCE FOUNDATIONAL SCIENTIFIC UNDERSTANDING OF NEUROLOGICAL AND DISEASE MECHANISMS. AND THE GOAL IS THAT THESE EFFORTS WILL ULTIMATELY PROVIDE NEW AVENUES AND RIGOROUS FOUNDATIONS FOR OTHER TRANSLATIONAL AND CLINICAL DEVELOPMENT WORK.

THE SECOND COULD BE TO CATALYZE MULTIDISCIPLINARY INNOVATION AND ATTRACT NEW TALENT AND IDEAS INTO THE STUDY OF NEURO DISEASES.

WE NEED TO INCENTIVIZE AND CATALYZE AN OPEN, COLLABORATIVE SCIENCE ECOSYSTEM AND SUPPORT

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THESE KIND OF INTERDISCIPLINARY COLLABORATIVE THEMES, EMPOWERING THE NEXT GENERATION OF SCIENTISTS, AND BRINGING TOGETHER OUTSTANDING, INNOVATIVE, FORWARD-THINKING SCIENTISTS FROM DIFFERENT DISCIPLINES INTO A COLLABORATIVE NETWORK.

ULTIMATELY MULTIDISCIPLINARY TEAMS WITH BIG DATA, COMPUTATIONAL ANALYSIS, FOCUSED DISCOVERY WORK CAN LEAD TO THE IDENTIFICATION OF NOVEL TARGETS AND BIOMARKERS WITH IMMEDIATE IMPLICATIONS FOR CLINICAL TRIALS. AND THIS GOES HAND IN HAND WITH INCENTIVIZING AN OPEN, COLLABORATIVE SCIENTIFIC SYSTEM THROUGH DATA AND KNOWLEDGE SHARING INFRASTRUCTURES.

NOW, ANOTHER OBJECTIVE DERIVED FROM THIS COLLABORATIVE ENVIRONMENT IS TO MOTIVATE AND SUPPORT INNOVATIVE AND BOLD AND INFORMATIVE NEW IDEAS AND TOOLS THAT ADDRESS FUNDAMENTAL CHALLENGES IN CNS DISEASE BIOLOGY. A VERY GOOD EXAMPLE OF THIS WAS, FOR EXAMPLE, OPTOGENETICS. IF WE CAN INVESTIGATE HOW THE NEURONS WORK TOGETHER BY USING LIGHT TO TURN SOME NEURONS ON AND RECORD THE RESPONSE OF OTHER NEURONS, WE'VE ADVANCED A LOT THE FIELD. SO IF WE HAD INVESTED IN THIS AT CIRM, THAT COULD HAVE MADE A BIG TRANSFORMATION FUNDED BY CIRM.

SO THE LAST ONE IS TO LEVERAGE AND CONNECT

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WITH CIRM'S EXISTING INFRASTRUCTURE OF PROGRAMS. AND WE WILL SEE THIS AS WE SHOW HOW EVERYTHING MAPS TOGETHER WITHIN OUR ECOSYSTEM OF CIRM-FUNDED PROGRAMS, BUT WE ARE TALKING ABOUT THE SHARED RESOURCE LABS, THE COMPETENCY HUBS, INFRASTRUCTURE PLATFORMS LIKE THE DATA COORDINATING AND MANAGEMENT CENTER THAT WILL BE -- WE ARE CONCEPTUALIZING IT RIGHT NOW AND OTHERS.

SO WHAT ARE THE OPPORTUNITIES THAT CIRM CAN LEVERAGE TO PUT THIS GOAL IN PLACE? THE FIRST ONE, AS WE MENTIONED, IS THE $1.5 BILLION. AND IT'S NOT ALL THAT COULD GO TO JUST THE NEURO DISCOVERY, OBVIOUSLY, BUT PART OF PROP 14'S $1.5 BILLION EARMARKING SET-ASIDE FOR RESEARCH IN MENTAL HEALTH AND CNS DISEASES. AND THE SECOND COULD BE THE SCIENTIFIC STRENGTH, INNOVATION, AND EXPERTISE IN GENETICS AND STEM CELL BIOLOGY, AND NEUROSCIENCE IN CALIFORNIA. WE HAVE A DEEP POOL OF CALIFORNIA STEM CELL RESEARCHERS, INCLUDING CIRM-SUPPORTED TRAINEES AND INVESTIGATORS.

THE WORLD-CLASS CALIFORNIA STEM CELL RESEARCH INFRASTRUCTURE, INCLUDING CIRM-FUNDED SHARED RESOURCE LABS, THE IPSC BIOBANK, THE PLANNED DATA INFRASTRUCTURE, AND OTHERS. ALSO LARGE AMOUNT OF DATA AND RESOURCES FROM OTHER NEURO-FOCUSED

CONSORTIA INITIATIVES. AND ADVANCES IN STEM CELL TECHNOLOGIES TO STUDY THE ENTIRE DIVERSITY OF CALIFORNIANS WITH DISEASES OF THE BRAIN. AND AS YOU WILL SEE, SOME OF THOSE ADVANCES HAVE BEEN POINTED OUT BY THE TASK FORCE MEETINGS.

NOW, IN ORDER FOR THE COLLABORATIVE RESEARCH TO HAVE AN IMPACT AND ACCELERATE OUR UNDERSTANDING OF THESE DISEASES, THE SCOPE OF THE FIRST INITIATIVE SHOULD BE FOCUSED. THERE ARE MANY NEURO DISEASES WITH A MULTITUDE OF MECHANISMS. AND THESE MECHANISTIC WORLDS DO INTEGRATE, BUT WE NEED TO START FROM THE BOTTOM WITH A FOCUS. AND IN ORDER TO DO THAT, THE BOARD REQUESTED THAT WE DO ANOTHER GAP ANALYSIS. AND WE FOUND THAT WHEN WE MAPPED THE DISCOVERY RESEARCH FROM CIRM'S INCEPTION BY DISEASE TO THE DISEASE BURDEN IN THE U.S. AT THE TIME, WE FOUND THAT NEUROPSYCHIATRIC DISEASES HAD NOT BEEN FUNDED BY CIRM. SO BASICALLY NEUROPSYCHIATRIC DISEASES WERE HISTORICALLY UNDERFUNDED AT CIRM DESPITE THE LARGE BURDEN AND UNMET NEED.

SO WE PROPOSE THAT THIS COULD BE A GOOD PLACE TO START. THEREFORE, THE NEURO TASK FORCE STARTED WITH A SERIES OF MEETINGS THAT MADE THE CASE THAT THE NEUROPSYCHIATRIC SPACE WAS PRIME FOR RAPID PROGRESS DUE TO SEVERAL RECENT ADVANCEMENTS.

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ONE WAS THE GENETIC RISK ARCHITECTURE WAS STARTING TO BEING DEFINED. IT IS STILL FAR FROM THE AGNOSTIC OR PREDICTIVE, BUT WE ARE GETTING CLOSER. AND WE ARE GETTING BETTER AT TRANSLATING LOCI TO GENES TO PATHWAYS.

THE SECOND POINT THAT WE HEARD ABOUT WAS THE DEMONSTRATED UTILITY OF HUMAN STEM CELL MODELS. AND WE HEARD A LITTLE BIT MORE ABOUT THIS TODAY. BASICALLY MOUSE MODELS HAVE REVEALED COMPLEX INTERACTION OF GENES AND CIRCUITS AND BEHAVIOR, BUT THEY HAVE SEVERE LIMITATIONS. FOR EXAMPLE, THEY CAPTURE POORLY THE IMPACT OF NONCODING VARIANTS. AND WE'VE LEARNED FROM KRISTIN BRENNAND'S PRESENTATION THAT IT'S NOT IDEAL.

THERE'S ALSO THE ADVANCEMENT IN RELATED RESEARCH TECHNOLOGIES. WHAT CAN THEY TEACH US ABOUT PSYCHIATRIC DISORDERS? AND WITH ALL THIS EVIDENCE THAT WE HEARD, THE FOCUS OF THE FIRST IMPLEMENTATION FOR THIS CONCEPT WE PROPOSE TO BE NEUROPSYCHIATRIC DISEASE MECHANISMS.

SO HOW DID WE PROPOSE THE STRUCTURE OF THESE RFA PROGRAMS TO FUND ACCELERATION OF DISCOVERY OF DISEASE MECHANISMS IN NEUROPSYCHIATRIC DISORDERS AS THE FIRST PHASE OF THIS PILOT PROGRAM?

SO FOR THIS WE ARE PROPOSING TWO TYPES OF

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AWARDS. A FIRST TYPE OF AWARD, THE LARGE COLLABORATIVE RESEARCH PROJECTS, COULD REQUIRE DATA, PRELIMINARY DATA. IT COULD BE A FOUR-YEAR AWARD WITH A BASE COMPONENT OF $2 MILLION PER YEAR WITH $8 MILLION IN TOTAL OVER THE FOUR YEARS. WE WOULD EXPECT A NUMBER OF SIX AWARDS TO BE FUNDED WITH A TOTAL BUDGET PER CYCLE WHICH WE'LL SEE NOW AND ABOUT FIVE OR MORE INVESTIGATORS, MINIMUM OF FIVE INVESTIGATORS.

NOW, WE THOUGHT THAT WE WOULD LIKE TO INCENTIVIZE COLLABORATION. AND TO DO THAT, WE DECIDED THAT IF WE COULD -- IF THE TEAMS BRING MATCHING FUNDS OF A MINIMUM OF $.5 MILLION A YEAR, THIS CAN BE FROM INDUSTRY, FROM OUTSIDE COLLABORATORS, FROM OTHER CONSORTIA, AND IT DOES NOT NEED TO BE FROM OUTSIDE OF CALIFORNIA. IT CAN BE FROM INSIDE OF CALIFORNIA. SO A GROUP COULD BE COLLABORATING WITH A COMPANY. SO IF YOU BRING $.5 MILLION A YEAR IN FUNDING, CIRM WILL MATCH THOSE FUNDS WITH A TOTAL OF 2 MILLION IN TOTAL FOR THE FOUR YEARS.

SO THIS LED TO A TOTAL FOR THIS TYPE OF PROGRAM OF $2.5 MILLION A YEAR, WHICH COULD BE THREE WITH THE MATCHING, $10 MILLION IN DIRECT FUNDS COST PER AWARD FOR A TOTAL OF FOUR YEARS AND A TOTAL OF

$72 MILLION WITH INDIRECT COSTS AS THE TOTAL THAT WE HAD ASKED FOR THIS PROGRAM.

THE SECOND TYPE OF AWARDS COULD BE MORE EXPLORATORY PROJECTS, MORE PROOF OF CONCEPT OR INITIAL VALIDATION OF THE PROPOSED TOOL, MODEL, HYPOTHESIS. THIS COULD GO WITH THE INNOVATIVE PART OF THE OBJECTIVES. THIS COULD BE WITHOUT REQUIRED PRELIMINARY DATA, TWO YEARS, AND $.5 MILLION A YEAR WITH A MILLION DOLLAR TOTAL FOR THE AWARD, 15 EXPECTED NUMBER OF AWARDS, $18 MILLION IN TOTAL. AND THIS COULD BE TWO OR MORE INVESTIGATORS MINIMUM.

NOW, HOW DO WE SEE THIS FLOWING THROUGH TO THE TIMELINE? SO REMIND-L COULD BE FOUR YEARS. THE LARGE COLLABORATIVE PROGRAMS COULD GO -- AND THEN THERE WOULD BE THE OPPORTUNITY FOR ONE MORE TIME RENEWAL FOR FOUR MORE YEARS IN THE NEXT CYCLE. AND IN CASES WHERE THINGS HAVE ADVANCED THAT CAN BE LEVERAGED BY A TRAN OR CLIN, THERE WOULD BE THE POSSIBILITY OF DYNAMISM TO THIS MECHANISM THAT WE WILL EXPLAIN THROUGH DISCOVERY ADVISORY PANELS. SO, FOR EXAMPLE, IF YOU ARE IN YEAR TWO AND YOU HAVE A DISCOVERY ADVISORY PANEL, YOU'VE ALREADY SHOWN VALIDATION OF A NEW TARGET, YOU COULD ACTUALLY MOVE TOWARD A TRANSLATIONAL AWARD OR APPLICATION OF CIRM FUNDS.

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AND THEN REMIND-X COULD START IN YEAR TWO. SO WE WOULD HAVE AN RFA STARTING -- POSTING NEXT YEAR IN '24, AND THEN IN '25 WE COULD HAVE REMIND-X STARTING AGAIN.

NOW, THIS IS A PILOT. AGAIN, WHAT I WANTED TO SHOW WITH THIS SLIDE IS THAT WE ARE PILOTING A NEW FRAMEWORK. AND THESE AWARDS THAT WE WOULD HAVE, THE EXPLORATORY WITH THE LARGER COLLABORATIVE LARGER AWARDS, AND THEN ALL INTEROPERATING WITH THE DISCOVERY PROGRAMS, ALL OF THESE COULD BE REPEATED. WE WOULD HAVE ANOTHER -- AND I'M NOT SAYING THAT WE ARE GOING TO FUND SPECIFICALLY THIS. THESE ARE ONLY EXAMPLES. BUT THEN WE COULD HAVE ANOTHER ONE IN FOUR YEARS TIME THAT COULD THEN START WITH NEUROVASCULAR AND NEUROIMMUNE AXIS TYPE OF FOCUS OF DISEASE MECHANISMS, OTHER NEUROLOGICAL DISEASES, OTHER FOCUS AREAS OR BOTTLENECKS. WHAT WE ARE TRYING TO SHOW HERE IS THAT WE ARE TRYING TO PILOT A FRAMEWORK FOR A WAY OF FUNDING DISCOVERY RESEARCH IN NEUROLOGICAL DISEASES.

THIS PROGRAM, AS I WAS SHOWING, WE ARE PROPOSING A PHASED APPROACH THAT WILL ALLOW MORE CONTINUITY AND EXPANSION TO OTHER AREAS OF CNS RESEARCH, PILOTING THIS POTENTIAL FRAMEWORK FOR MULTIDISCIPLINARY DISCOVERY RESEARCH AT CIRM AND GROWING AN INVESTMENT, ADAPTING TO CIRM'S GROWTH AND ITS INFRASTRUCTURE KNOWLEDGE NETWORK AND COMPETENCY HUB CAPABILITY.

AGAIN, THIS IS NOT ONLY FOR NEUROPSYCHIATRIC. NEUROPSYCHIATRIC WOULD START THIS YEAR WHERE WE ARE PROPOSING $72 MILLION AND SIX TEAMS AND THEN 15 TEAMS AND $18 MILLION FOR THE INNOVATION. BUT THEN IT COULD -- AS WE MOVE TO THE NEXT ROUND, WE COULD STILL INCLUDE NEUROPSYCHIATRIC, BUT THEN WE WOULD FUND OTHER DISEASES. THESE ARE EXAMPLES ONLY. AND WE COULD ALLOCATE MORE FUNDING AS THE INFRASTRUCTURE WOULD ALREADY BE SETTLED AND IT WOULD ALREADY BE INTEROPERATING WITH THE DATA COORDINATING MANAGEMENT CENTER AND OTHER PARTS OF CIRM'S INFRASTRUCTURE. AND WE WOULD HAVE ALREADY LEARNED HOW TO DO IT WITH OTHER CONSORTIA, AND WE WOULD BE ABLE TO FUND EVEN MORE, AND WE WOULD BE GROWING, AND WE WOULD BE ABLE TO FIGURE OUT COMMON MECHANISMS AMONGST THESE DISEASES AS WELL. AND THEN AS WE GROW EVEN FURTHER, WE COULD BE FUNDING MORE.

THE NEXT SLIDE -- OH, ACTUALLY I FORGOT TO MAKE A POINT HERE. IN HERE YOU CAN SEE THAT THIS PHASED APPROACH COULD BE ALSO COORDINATED, THE PROGRAMS COULD BE COORDINATED ADDING A DISCOVERY ADVISORY PANEL. THE DISCOVERY ADVISORY PANEL COULD BE PROVIDING INPUT TO THE RESEARCHERS, TO THE AWARDEES. SO THIS IS A PART OF THE PROGRAM THAT CIRM COULD PUT IN PLACE. SAME AS WE HAVE TRANSLATIONAL ADVISORY PANELS AND CLINICAL ADVISORY PANELS, WE PROPOSE TO HAVE A DISCOVERY ADVISORY PANEL THAT IS SOME EXPERTS THAT WILL PROVIDE INPUT SO THAT WE CAN LEARN AS WE MOVE FORWARD AND HELP THE AWARDEES LEVERAGE EACH OTHER'S RESEARCH AND IN SOME INSTANCES, IF THINGS ARE ADVANCING FASTER, TO HELP THEM MOVE FASTER TOWARDS TRANSLATION OR CLINICAL. WE COULD ALSO HAVE AN ANNUAL NETWORK CONFERENCE, AND ALL OF THIS DATA COULD BE WORKING AND INTEROPERATING WITH THE DATA COORDINATING AND MANAGEMENT CENTER.

AGAIN, THIS SLIDE IS THE ONE THAT SHOWS HOW THIS PROGRAM BUDGET COULD BE GROWING AS WE ARE GROWING THE PROGRAM AND AS NEW DISEASES ARE COMING INTO PLACE IN THIS INITIATIVE.

AND THEN THIS SLIDE ALSO INTENDS TO SHOW WHAT THE ESTIMATED PROJECTIONS OF MONEY SPENDING COULD BE FOR THIS PROGRAM. SO THE CNS PROJECTS --

THIS IS FOR THE REMIND. SO IT COULD BE $72 MILLION. THEN IF WE MAKE 12 TEAMS, IN FOUR YEARS TIME, 144, 12 MORE TEAMS, $144 MILLION. WE COULD KEEP ABOUT THE SAME LEVEL IN THE REMIND-X. BUT THEN WE ALSO NEED TO TAKE INTO ACCOUNT THAT CNS PROJECTS THAT ARE PART OF OUR DISC-0 AND 2 PILLAR PROGRAMS CURRENTLY, AS WE ARE MAKING CHANGES, CONCEPT AMENDMENTS, WE ARE GOING TO BE INCREASING THE AMOUNT OF FUNDING TO THESE PILLAR PROGRAMS. AND THIS IS AN ESTIMATE BECAUSE THIS HAS NOT YET BEEN PRESENTED OR APPROVED BY THE BOARD.

BUT IMAGINING THAT WE END UP FUNDING AT THE LEVEL THAT WE BELIEVE MIGHT BE FUNDING, THIS COULD CORRESPOND TO ABOUT $235 MILLION IN THE NEXT 12 YEARS, WHICH MEANS THAT THE TOTAL DISCOVERY NEURO FUNDING APPROXIMATELY COULD BE ABOUT $648 MILLION OF THE 1.5 BILLION THAT ARE EARMARKED. SO THIS IS JUST A ROUGH APPROXIMATE.

AGAIN, THIS IS A PRESENTATION OF AN OVERALL CONCEPT FOR A NEW INITIATIVE, NEW WAY OF FUNDING NEURO DISCOVERY SCIENCE AT CIRM.

AGAIN, A REMINDER OF THE KEY PROGRAM DRIVES. THE REMIND PROGRAM DRIVES KEY OBJECTIVES TO ACCELERATE FOUNDATIONAL SCIENTIFIC UNDERSTANDING OF NEUROPSYCHIATRIC, BUT IN GENERAL NEURO DISEASE

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MECHANISMS AND THE DEVELOPMENT OF NOVEL TOOLS. CATALYZING MULTIDISCIPLINARY INNOVATION. YOU'VE SEEN THIS STRUCTURE THAT WE ARE PROPOSING FOR THESE LARGE TEAMS. ATTRACTING NEW TALENT AND IDEAS INTO NEUROPSYCHIATRIC RESEARCH AND SEEDING NEW PARTNERSHIPS.

JUST AS LITTLE BIT OF INFORMATION, WE ARE ALREADY, WE'VE BEEN TALKING TO DIFFERENT PARTNERS, ESPECIALLY THE FEDERAL GOVERNMENT ARE FUNDING, BUT ALSO OTHER PARTNERS SO THAT WE CAN LEVERAGE ALL OF THESE TOGETHER, THEIR INVESTMENT AS WELL INTO THIS INITIATIVE.

AND THEN DRIVING OPEN AND COLLABORATIVE SCIENCE AND ALIGNING BEST PRACTICES THROUGH DATA AND KNOWLEDGE SHARING INFRASTRUCTURE, WHICH IS SOMETHING THAT WE ARE WORKING VERY HARD AND THAT WE WILL BE PROVIDING A CONCEPT. SO THIS COULD BE IMPLEMENTED RIGHT AFTER WE INITIATE. AND WE ARE TAKING INTO ACCOUNT HOW WE COULD MAKE IT WORK GIVEN THAT THE DATA COORDINATING AND MANAGEMENT CENTER COULD HAPPEN RIGHT AFTER.

THIS COULD ALL BE COORDINATED THROUGH THE DATA COORDINATING AND MANAGEMENT CENTER STEERING COMMITTEE. AND, AGAIN, THIS IS JUST A PRESENTATION OF WHAT THIS MODEL IS TAKING INTO ACCOUNT IN TERMS

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OF PROGRAM FOR LARGE RESEARCH TEAMS, PROJECTS, AND THE CIRM DISCOVERY PILLAR PROJECTS.

CHECKING WITH TIME, LARRY, AM I DOING WELL? WE HAVE A FEW MORE SLIDES, ABOUT FIVE MORE SLIDES.

CHAIRMAN GOLDSTEIN: THAT'S FINE. GOT TO LEAVE SOME TIME FOR DISCUSSION THOUGH.

DR. CANET-AVILES: WONDERFUL. YES, ABOUT HALF AN HOUR.

SO THE REMIND HIGH-LEVEL OUTCOMES COULD BE THE NOVEL MECHANISTIC INSIGHTS. SO REMIND-L, WHICH IS THE LARGE COLLABORATIVE PROGRAM, WOULD LEAD TO NOVEL MECHANISTIC INSIGHTS INTO THE BIOLOGY OF NEUROPSYCHIATRIC DISEASES, COULD ALLOW US TO GET FURTHER UNDERSTANDING OF CURRENT MECHANISMS, INCLUDING MECHANISMS CUTTING ACROSS CLASSICALLY DEFINED DISEASE BOUNDARIES. AS YOU CAN SEE, AS WE ADD MORE DISEASES, WE WILL HAVE A CHANCE TO FIND THOSE COMMON MECHANISMS EVEN MORE, BUT WE NEED TO START WITH SOMETHING DEFINED. AND EXTENSION OF VALIDATION OF FINDINGS TO DIVERSE HUMAN POPULATIONS, AS WELL AS IDENTIFICATION AND VALIDATION OF NEW THERAPEUTIC TARGETS OR BIOMARKERS.

AND THEN REMIND-X, HIGH-LEVEL OUTCOMES COULD BE TO PROVIDE PROOF OF CONCEPT OR INITIAL

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VALIDATION OF PROPOSED TOOLS, MODELS, OR HYPOTHESIS.

SO THIS IS A MODEL OF HOW WE SEE IT ALL WORKING. ULTIMATELY THIS IS A MULTIDIMENSIONAL AND LAYERED PROPOSAL THAT PULLS DIFFERENT COMPONENTS TOGETHER IN SERVICE OF THE OVERALL NEURO STRATEGY AND CONSISTENT WITH THE FEEDBACK THAT WE'VE RECEIVED FROM THE MEMBERS OF THE BOARD AND THE TASK FORCE OVER THE PAST FEW MONTHS.

THE GOAL IS TO ACCELERATE THE PACE OF DISCOVERY AND INFORM NEW PATHS TO CURE NEURO DISEASES, LEVERAGING ALREADY EXISTING INFRASTRUCTURE. AS YOU CAN SEE HERE, THERE'S THE DISCOVERY, THE SHARED LABS INFRASTRUCTURE, EVEN THE TRAINING/EDUCATION INFRASTRUCTURE, THEN ALSO LEVERAGING EXTERNAL CONSORTIA, RESOURCE NETWORKS AND DATA PLATFORMS, AND ULTIMATELY LEADING TO THIS OPEN SCIENCE COMMUNITY ECOSYSTEM THAT WILL LEAD TO DISCOVERY OF NOVEL TARGETS AND BIOMARKERS AND INCREASE THE EFFICIENCY AND SUCCESS OF CLINICAL TRIALS. THAT'S WHERE WE ARE ALL TRYING TO LEAD TO.

NOW, IN TERMS OF PROJECT ELIGIBILITY, TO BE ELIGIBLE, REMIND PROJECTS MUST PROPOSE STUDIES THAT ARE FOCUSED ON ELUCIDATION OF MECHANISMS OF NEUROPSYCHIATRIC DISEASES. THAT'S FOR THE FIRST INSTALLMENT OF THIS PROGRAM AGAIN. SO THIS COULD BE

THE CONCEPT THAT WE WOULD COME IN SEPTEMBER WITH. THAT COULD BE THE RFA; BUT AS WE MOVE IN FOUR YEARS TIME, WE COULD BE ADDING OTHER DISEASES. AND INCLUDE THE STUDIES USING HUMAN STEM CELLS OR GENETIC RESEARCH.

NOTE THAT ANY STUDIES USING NONHUMAN SYSTEMS MUST BE VALIDATED WITH A RELEVANT HUMAN CELL EQUIVALENT.

IN TERMS OF PRINCIPAL INVESTIGATOR ELIGIBILITY, FOR BOTH TYPES, ALL PRINCIPAL INVESTIGATORS SHOULD BE EMPLOYED AT CALIFORNIA NONPROFIT OR FOR-PROFIT RESEARCH INSTITUTION. THERE HAS TO BE ONE PI THAT'S GOING TO BE DESIGNATED AS THE COORDINATING PI WHO WILL MANAGE THE COLLABORATION AND WILL BE THE ADMINISTRATIVE CONTACT FOR CIRM AND ANY GRANT PARTNERS. THE MINIMUM PERCENT EFFORT FOR THE COORDINATING PI IN THE REMIND-L, THE LARGE COLLABORATIVE, IS 20 PERCENT. AND FOR THE REMIND-X, WHICH IS THE EXPLORATORY, HIGH-RISK PROJECTS, IS GOING TO BE 10 PERCENT. OTHER PI'S WE ARE ASKING FOR A 10-PERCENT MINIMUM.

THE TEAM SIZE, FIVE MINIMUM FOR REMIND-L AND REMIND-X IS TWO MINIMUM. AND FOR REMIND-L WE ARE ASKING THAT AT LEAST ONE MEMBER OF THE COLLABORATION SHOULD HAVE RELEVANT CLINICAL

EXPERTISE, AND ONE MEMBER SHOULD HAVE RELEVANT COMPUTATIONAL BIOLOGY EXPERTISE GIVEN THE NEED TO LINK TO CLINICAL AND ALSO TO BE ABLE TO LEVERAGE THE DATA. CIRM WILL ENCOURAGE FAVORABLE CONSIDERATION OF APPLICATIONS THAT INCLUDE AT LEAST ONE TO TWO EARLY CAREER FACULTY.

FOR THE REMIND-X WE STRONGLY ENCOURAGE APPLICATIONS FROM INVESTIGATORS WHO CAN BRING NEW TECHNOLOGY, RESOURCES, OR FRAMEWORKS TO THE STUDY OF NEUROPSYCHIATRIC DISEASE AND IN VITRO MODELING OF CNS.

NOW, IN TERMS OF DATA SHARING, ALL PROPOSALS WILL NEED TO INCLUDE THE DATA SHARING AND MANAGEMENT PLAN AND DESCRIBE AN APPROACH TO SHARING AND MANAGEMENT OF DATA GENERATED CONSISTENT WITH FAIR PRINCIPLES, FINDABLE, ACCESSIBLE, INTEROPERABLE, AND REPRODUCIBLE PRINCIPLES, AND IT ALSO MUST COORDINATE WITH THE DATA COORDINATING AND MANAGEMENT CENTER THAT WILL BE PRESENTED THE CONCEPT IN MARCH OF 2024.

NOW, HERE THERE IS A TIMELINE SITUATION BECAUSE THE DCMC IS COMING LATER. BUT GIVEN THAT THIS RFA, IF APPROVED THE CONCEPT, THE APPLICATIONS COULD BE REVIEWED IN MAY OF 2024. WE WILL BE CREATING A PROCESS BY WHICH CIRM WILL MEET WITH THE

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AWARDEES DURING THE FUNDING ADMINISTRATIVE REVIEW TO MAKE SURE THAT THEIR DATA SHARING AND MANAGEMENT WILL ALIGN WITH WHAT WE NEED FOR THE DATA COORDINATING AND MANAGEMENT CENTER. SO WE'VE BEEN THINKING ABOUT HOW THIS COULD BE DOING, AND THIS IS BRINGING ALSO ADVICE THAT WE GATHERED FROM COLLEAGUES FROM THE FEDERAL GOVERNMENT THAT ARE DOING SIMILAR INITIATIVES.

AND THEN DIVERSITY, EQUITY, AND INCLUSION, THE APPLICATIONS NEED TO INCLUDE PLANS TO ADDRESS DEI.

THE DISCOVERY ADVISORY PANEL, CIRM, THIS IS VERY IMPORTANT, WILL COORDINATE THE DISCOVERY ADVISORY PANEL THAT WILL BE COMPOSED OF NON-CALIFORNIA EXPERTS TO PROVIDE INDEPENDENT, CONFIDENTIAL, EXPERT ADVICE ON REMIND PROGRAMS. THIS IS WHAT I WAS TRYING TO SAY EARLIER, BUT THIS IS A BIT BETTER ARTICULATED.

THE SPECIFIC ACTIVITIES OF THIS COMMITTEE COULD INCLUDE REVIEW OF THE PROGRESS REPORTED BY THESE LARGE COLLABORATIVE TEAM AWARDEES AND PROVIDE NONBINDING ADVICE TO THE AWARDEES AND CIRM. SO BASICALLY WE WILL PROVIDE THIS AS AN EXTRA RESOURCE FOR OUR APPLICANTS. AND THIS FROM OUR COLLEAGUE, ABLA CREASEY, SHE HAS TOLD US THAT THESE ARE AN

EXTREMELY HELPFUL RESOURCE FOR THE TRANSLATIONAL AND CLINICAL RESEARCHERS. AND THAT ALSO WILL HELP US IDENTIFY AND LEVERAGE EXTERNAL RESOURCES TO FURTHER COLLABORATIVE RESEARCH.

NOW, THE BUDGET. SO THE OVERALL CONCEPT, WE ARE NOT ASKING FOR MONEY HERE. THIS IS JUST AN ESTIMATE OF WHAT WE COULD BE INVESTING ON THE FIRST PHASE. WE ARE ONLY GIVING A PROJECTION OF THE FUNDS THAT WILL BE REQUIRED BECAUSE THE BUDGET FOR EACH ONE OF THESE RFA'S IS BEING ASKED SEPARATELY AT THE CORRESPONDING JOINT ICOC. SO THE BUDGET FOR THE REMIND-L WAS INCLUDED IN THE DISCOVERY BUDGET FOR FISCAL YEAR 23/24 THAT WAS PRESENTED BY OUR COLLEAGUE, POUNEH SIMPSON, AT THE LAST JUNE MEETING.

SO WHAT WE ARE ASKING IS THE REQUEST OF THE BOARD TO APPROVE THE PROPOSED REMIND PROGRAM CONCEPT AS AN INITIATIVE THAT WILL HELP US FURTHER THE DISCOVERY OF DISEASE MECHANISMS IN NEURO DISEASES AND WE WILL BE IMPLEMENTING IN ITS FIRST PHASE WITH NEUROPSYCHIATRIC DISEASES AS A FOCUS. THANK YOU.

CHAIRMAN GOLDSTEIN: THANK YOU, ROSA. THAT WAS A TERRIFIC PRESENTATION.

SO QUESTIONS AND/OR DISCUSSION FROM THE TASK FORCE? STEVE.

MR. JUELSGAARD: WONDERFUL PRESENTATION, ROSA. THANK YOU VERY MUCH. CAN YOU GO BACK TO SLIDE 15 PLEASE?

DR. CANET-AVILES: YES. GIVE ME A SEC. THERE YOU GO.

MR. JUELSGAARD: NO, IT'S THE NEXT ONE OR THE ONE BEFORE IT. IT'S THE ONE THAT SHOWS THE USE OVER TIME OF EXPANDING THE PROGRAM. SO I COUNTED --

DR. CANET-AVILES: YES. THIS ONE, CORRECT?

MR. JUELSGAARD: RIGHT. SO THIS IS MORE OF A QUESTION, I GUESS, GLOBALLY AND MAYBE FOR MARIA MILLAN. BUT THIS SUGGESTS THAT WE COULD BE FUNDING THESE PROGRAMS ON THROUGH 2035. AND WE HAVE THIS NEURO BUDGET OF 1.5 BILLION WHICH LEAVES THEN, WHAT, 4 MILLION FOR THE REMAINDER OF THINGS THAT CIRM DOES.

DO WE HAVE A TIMELINE PLAN FOR THE EXISTENCE OF CIRM OUTSIDE OF THE CNS AREA? IN OTHER WORDS, IS CIRM GOING TO BE AROUND IN -- AS BEFORE, WHEN WE WERE THINKING ABOUT WHAT WAS GOING TO HAPPEN WITH PROPOSITION 14 AND IT WAS A VERY CLOSE CALL, WE HAD TO HAVE A PLAN OF WHAT WOULD HAPPEN IF WE DIDN'T GET REFUNDED. AND I THINK THAT'S ALWAYS WISE TO KEEP IN THE BACK OF OUR MIND, THAT THE THIRD TIME

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MAY NOT BE THE CHARM.

AND SO THE INTEGRATION OF SPENDING $1.5 BILLION IN THE CNS AREA AND THE EXISTENCE OF CIRM WRIT LARGE SPENDING MONEY OTHERWISE, I DON'T KNOW, IS THAT BEING THOUGHT OF AS WE GO ALONG SO THAT WE'RE GOING TO KEEP CIRM GOING INDEPENDENT OR IN CONJUNCTION WITH THE CNS AREA ON UP INTO 2032, 2035?

DR. MILLAN: THANK YOU SO MUCH FOR THAT QUESTION, STEVE. SO POUNEH SIMPSON AND THE TEAM HAVE BEEN, SINCE THE PASSAGE OF PROP 14, HAVE BEEN DEPLOYING A FORECASTING TOOL IN TERMS OF EXPENDITURES OVER TIME, BOTH FOR THE RESEARCH AND ADMINISTRATIVE BUDGET. THERE ARE A VARIETY OF DIFFERENT MODELS TO THAT, BUT LET'S SAY THE BASE CASE IS AN EXPENDITURE OF WHAT THE MAXIMUM ALLOWABLE FUNDING IS ACCORDING TO PROP 14 -- THERE ARE SOME EXCEPTIONS TO THAT -- AND THEN ALSO CALCULATING INTO IT RETURNED FUNDS, ET CETERA.

AND SO THE TIMELINE THAT ROSA PRESENTED IS COMPATIBLE WITH THE PROJECTION IN TERMS OF THE ADMINISTRATIVE RUNWAY ACCORDING TO THIS MODELING AS WELL AS THE RESEARCH RUNWAY WITH THOSE FUNDS. SO THERE'S KIND OF THESE PARALLEL TYPE OF FORECASTING. THIS FORECASTING TOOL IS FED BY WHAT OUR ACTUALS ARE, OUR ACTUAL PERFORMANCE IS. SO IT'S A PRETTY --

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THE ASSUMPTIONS THAT ARE BUILT IN ARE BUILT IN WITH A VERY AGGRESSIVE EXPENDITURE OF THE ACTUAL BUDGETS WE BUDGET PER YEAR. AND AS YOU KNOW, THERE'S VARIANCE. SO SHE HAS A BUNCH OF DIFFERENT MODELS.

SO I HOPE THAT ANSWERS YOUR QUESTION. SO IT IS -- THE TIMELINES THAT ROSA PRESENTED ARE REASONABLE TO THOSE PROJECTIONS, ESPECIALLY A 2032 TIMELINE. SO THAT'S KIND OF -- HOPEFULLY THAT'S RESPONSIVE TO YOUR QUESTION.

MR. JUELSGAARD: YES, IT IS. THANK YOU, MARIA. I THINK IT'S SOMETHING WE JUST NEED TO KEEP AN EYE ON AS WE GO FORWARD. MY WORRY IS THAT WE WILL GET TO A POINT WHERE THE ONLY FUNDS THAT ARE LEFT ARE FOR THIS AREA, THE CNS AREA, AND WE DON'T HAVE ANY FUNDS AVAILABLE FOR FUNDING OTHER PROJECTS. AND THEN HOW DO WE RUN THE ORGANIZATION AT THAT POINT? BUT THAT'S A LONG WAYS DOWN THE ROAD, BUT I THINK IT'S JUST SOMETHING AS WE MOVE ALONG WE NEED TO KEEP AN EYE ON BECAUSE WE HAVE A HUGE RESEARCH BUDGET THIS TIME AROUND. THE APPROVAL WAS UP CLOSE TO $500 MILLION, SOMETHING LIKE THAT. SO IF WE SPEND ALL THAT, THAT'S GOING THROUGH MONEY AT A VERY FAST PACE.

DR. MILLAN: ABSOLUTELY. WHAT ROSA PRESENTED IN TERMS OF WHAT OUR HISTORICAL

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EXPENDITURES HAVE BEEN ON OUR PILLAR PROGRAMS, GIVEN THE PERCENT OF THOSE KIND OF ORGANIC PROGRAMS THAT ARE COMING IN, SHE PRESENTED AN ESTIMATE OF HOW THAT COULD STILL BE FUNDED. AND THEN I THINK SHE -- ROSA IS RIGHT HERE. I'M SAYING LIKE SHE'S NOT IN THE ROOM. BUT I THINK THE ESTIMATE OF THESE MEGA PROGRAMS THAT SHE'S PRESENTING, I THINK AT LEAST FOUR OR FIVE OF THESE BIG CONSORTIA-TYPE APPROACHES COULD THEN BE FUNDED, NOT ONLY FOR NEUROPSYCH, BUT OTHER TYPES OF NEURAL FIELDS. AND THEN IN TOTAL THAT WOULD COMPOSE THE 1.5 BILLION IN TERMS OF THE EARMARK FOR NEURO, FOR CNS, THE COMBINATION OF THE ORGANIC THINGS THAT COME IN THROUGH THE PILLAR PLUS THIS SPECIAL PROGRAM PROJECT OR CONSORTIUM. AND THEN THE REMAINDER OF THE FUNDING WOULD BE THEN AVAILABLE FOR OTHER NON-CNS TYPES OF INITIATIVES ACROSS THE DIFFERENT TYPES OF RESEARCH PROGRAMS.

CHAIRMAN GOLDSTEIN: GOOD. THANK YOU. GREAT QUESTION, STEVE. PAT.

DR. LEVITT: THANKS, ROSA. THAT WAS GREAT AND I LOVE THE CONCEPTS. I WANT TO TALK A LITTLE BIT ABOUT THOSE ISSUES AROUND SORT OF THE CONTENT OF REMIND-L AND REMIND-X. I LOVE THE CONCEPTS.

CAN YOU GO TO THE SLIDE WHERE YOU GOT -- I DON'T KNOW WHAT THE NUMBER IS. IT'S THE SLIDE THAT

HAS THE REQUIREMENTS IN TERMS OF INVESTIGATORS AND EFFORT. IF YOU CAN GO TO THAT.

DR. CANET-AVILES: YEAH. LET ME SEE. IS THIS THE ONE?

DR. LEVITT: THAT'S GOOD. SO PRINCIPAL INVESTIGATORS, FOR THE REMIND-L, YOU WANT ONE WHO HAS CLINICAL EXPERTISE AND ONE WHO HAS COMPUTATIONAL EXPERTISE, RIGHT?

DR. CANET-AVILES: YES. ONE SECOND.

DR. LEVITT: THAT'S FINE. THAT'S GOOD. I JUST NEED MORE CLARIFICATION ABOUT WHAT YOU MEAN BY THE TEAM. SO WHEN YOU TALK ABOUT FIVE PI'S FOR A MODEL LIKE THE P50 AT NIH, A PI IS A PROJECT. THESE ARE ALL INTEGRATED, OF COURSE, AROUND A SPECIFIC THEME OR HYPOTHESIS FOR DISCOVERY. IS THAT WHAT YOU'RE TALKING ABOUT HERE? FIVE PROJECTS AND ONE OF THOSE FIVE WOULD BE THE COORDINATING PI, OR ARE YOU TALKING ABOUT FIVE INVESTIGATORS, SOME OF WHOM MIGHT BE SERVING THE PURPOSE OF GENERAL LEADERSHIP IN A CLINICAL AREA FOCUS, AND ONE WOULD BE SERVING IN GENERAL ALL THE PROJECTS THAT ARE DOING -- THAT HAVE COMPUTATIONAL COMPONENTS TO THEM?

DR. CANET-AVILES: WE ARE TALKING ABOUT -- THANK YOU, PAT, FOR THE QUESTION. VERY RELEVANT. WE ARE TALKING ABOUT NOT FIVE DISTINCT PROJECTS. WE

ARE TALKING ABOUT ONE LARGE COLLABORATIVE PROJECT THAT CAN HAVE DIFFERENT AIMS, THAT DIFFERENT PEOPLE MIGHT BE WORKING ON, DIFFERENT PI'S. THERE SHOULD BE ONE PI THAT COORDINATES AND WILL BE THE ADMINISTRATIVE POINT TO THE AWARD WITH CIRM. AND IT WILL BE THE PERSON THAT WILL BE RESPONSIBLE FOR IF WE HAVE A DISCOVERY ADVISORY PANEL AND THERE IS SOMETHING THAT NEEDS TO BE IMPLEMENTED, HE WILL BE RESPONSIBLE TO COORDINATE THINGS. IT WILL BE THE ONE THAT WILL WRANGLE EVERYBODY TOGETHER TOWARDS MAKING SURE THAT WE GET TO THE OUTCOMES, THE GOALS.

IT DOESN'T NEED TO BE -- WE DON'T NEED ONE LEAD THAT'S CLINICAL, ONE LEAD THAT'S COMPUTATIONAL. WHAT WE WANT IS THE EXPERTISE. IT COULD BE THAT THE OTHER PI, SO WE HAVE FIVE PI'S IS MINIMUM, IT COULD BE THAT THERE ARE SEVEN, FIVE WE THINK IS A GOOD NUMBER FOR THESE KIND OF COLLABORATIVE PROJECTS. IT COULD BE THAT ONE OF THE OTHER PI'S, THE 10 PERCENT IS A CLINICIAN OF THE DISEASE. THAT WILL BE THE ONE THAT'S GOING TO BRING THE RELEVANT TYPE OF QUESTIONS THAT ARE RELEVANT TO THE DISEASE MECHANISMS THAT WE'LL BE DISCOVERING FOR THE CLINICAL TRIALS, RIGHT. AND THAT WILL ALSO BE THE CONTACT TO THE PATIENT POPULATIONS. WE NEED TO HAVE THE END GOAL, AND I THINK HAVING A CLINICIAN IN THE TEAM IS VERY

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RELEVANT.

THE COMPUTATIONAL BIOLOGY EXPERTISE HAS TO DO WITH BEING MORE -- HAVING A COMPUTATIONAL BIOLOGIST WILL MAKE SURE THAT THERE IS SOME VOICE THERE THAT KEEPS EVERYBODY THINKING ABOUT WHAT METADATA DO WE NEED TO GATHER. WHAT ARE THE STANDARDS THAT WE NEED TO HAVE? WHO DO WE NEED TO TALK? SO THAT'S WHAT WE WANT TO HAVE.

DR. LEVITT: THAT ALL MAKES SENSE. THIS IS ABOUT THE ARCHITECTURE OF THIS, WHICH I THINK IS REALLY IMPORTANT SO THAT INVESTIGATORS ARE CLEAR ABOUT IT. IF YOU'VE GOT COLLABORATIONS ACROSS SITES, IT MEANS EACH SITE IS GOING TO HAVE A STATEMENT OF WORK, A SET OF RESPONSIBILITIES THAT THEY HAVE WITH SEPARATE BUDGETS. IT'S UNLIKELY WHAT YOU'RE LOOKING FOR, IS IT LIKELY THAT IT'S GOING TO BE AT ONE INSTITUTION? THIS MATTERS BECAUSE OF HOW YOU WOULD STRUCTURE THIS.

AND SO THE REASON -- THERE'S A THEME AROUND A PROGRAM PROJECT GRANT THAT HAS A SINGULAR THEME, AND THEN THERE ARE ELEMENTS TO IT. ONE MIGHT BE EXPERT IN IMAGING THAT'S GOING TO BE DONE, ONE MIGHT BE EXPERT IN ELECTROPHYSIOLOGY, ET CETERA, BUT THEY ALL ADDRESS THE CORE THEME, THE CORE QUESTION.

AND IT SOUNDS LIKE HERE YOU'VE GOT ONE

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LARGE PROJECT THAT'S GOING TO HAVE MULTIPLE PI'S TO IT. BUT IF THEY'RE AT DIFFERENT INSTITUTIONS, THE LOGISTICS OF DIVIDING THAT PIE THE WAY THAT PI'S ARE USED TO OPERATING IS GOING TO BE AN ISSUE. SO I THINK YOU MAY WANT TO THINK ABOUT HOW YOU WANT TO STRUCTURE THIS SO THAT IT'S CLEAR WHAT CIRM IS LOOKING FOR.

THE OTHER IS THAT -- AND WE HEARD THIS FROM SEVERAL PRESENTATIONS. 20-PERCENT EFFORT FOR LET'S SAY, A SENIOR SCIENTIST WHO HAS THE ABILITY TO COORDINATE A PROGRAM LIKE THIS IS A HIGH PERCENTAGE, AND IT'S LIKELY TO ELIMINATE A NUMBER OF INDIVIDUALS WHO WE KNOW, SOME OF WHOM PRESENTED TO US, WHERE THEY JUST DON'T HAVE THE EFFORT. AND AS YOU KNOW, LEGALLY WE CAN'T GO OVER A HUNDRED PERCENT. OF COURSE, WE ALL DO GO OVER A HUNDRED PERCENT, BUT WE CAN'T LEGALLY GO OVER A HUNDRED PERCENT.

SO ONE THOUGHT THAT I HAD AS GOING THROUGH THE SLIDES IS A COORDINATING PI WOULD HAVE TO CERTAINLY DESIGNATE 10 PERCENT, BUT THE OTHER PI'S MIGHT BE AT 5 PERCENT. AND THERE WERE LIKE, FROM WHAT I CAN RECALL, AT LEAST THREE PRESENTERS WHO TALKED ABOUT THE EFFORT REQUIREMENTS.

I THINK FOR THE REMIND-X FOR THE DISCOVERY PHASE, I DON'T THINK 10 PERCENT IS AN ISSUE. I

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THINK THOSE ARE FINE. SO THINK ABOUT THAT.

I THINK THE DOLLAR AMOUNTS ARE REALLY ALIGNED WELL WITH WHAT INVESTIGATORS ARE USED TO WHEN THEY'RE PUTTING TOGETHER A PROGRAM PROJECT, A P50. AND I THINK I MENTIONED THIS TO YOU BEFORE. DIFFERENT INSTITUTES AT NIH DO IT IN DIFFERENT WAYS; BUT WHEN THEY DO THEIR ANALYSES OF RETURN ON INVESTMENT, THESE PROGRAMS GENERALLY DO REALLY WELL BECAUSE THEY'RE STRUCTURED AND ORGANIZED WELL.

THE OTHER THING TO THINK ABOUT IS FOR THE ADVISORY PANEL, AND THAT WAS SINGULAR, SO I'M ASSUMING AN ADVISORY PANEL, BUT YOU'RE LOOKING AT 16 PROJECTS HERE, AND THAT'S A LOT.

DR. CANET-AVILES: IT WOULD ONLY BE FOR THE LARGE ONES. THE SMALLER ONES DON'T NEED AN ADVISORY PANEL. IT'S FOR THE REMIND-L. IT'S THE SIX PROJECTS.

DR. LEVITT: SO I'M JUST SAYING FROM EXPERIENCE THEY'RE THERE TO JUST SERVE WHEN SOMEBODY WOULD SEND THEM A QUESTION OR THEY'RE MEETING TO REVIEW THE PROGRESS OF THE PROGRAMS. ARE THEY THERE TO PROVIDE CIRM WITH FEEDBACK AND HOW THINGS ARE GOING, OR ARE THEY THERE JUST TO BE EXPERT SOURCES?

DR. CANET-AVILES: WE WILL USE THEM MAINLY FOR A YEARLY PROGRESS REVIEW AND PROVIDE ADVICE TO

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THE GRANTEE, THE AWARDEES, AND TO CIRM RECOMMENDATIONS. BUT I THINK WE WILL ALSO USE THEM AD HOC. WE MIGHT NOT HAVE ALL THE EXPERTISE INTERNALLY. IF WE NEED TO USE THEM AS CONSULTANTS FOR CERTAIN QUESTIONS WHEN WE NEED TO MAXIMIZE THE OUTCOME OF THESE RESEARCH PROJECTS, WE WILL. SO THAT COULD BE THE IDEA.

DR. LEVITT: YEAH. I DON'T KNOW HOW -- SOME OF US ON THIS CALL HAVE SERVED ON THESE KINDS OF SCIENTIFIC ADVISORY BOARDS. AND SIX PROJECTS OF THIS SIZE IS A VERY HEAVY LIFT FOR A SINGLE COMMITTEE. EVEN IF YOU -- YOU CAN HAVE A LARGE COMMITTEE AND THEN EACH PERSON GETS ONE OR TWO, BUT --

DR. CANET-AVILES: YEAH. IT'S NOT ONE COMMITTEE. DISCOVERY ADVISORY PANEL, WE ARE GOING TO HAVE -- IT'S LIKE THE CLINICAL ADVISORY PANELS OR THE TRANSLATION ADVISORY PANELS. IT'S NOT THE SAME THREE PEOPLE FOR ALL THE AWARDEES AND FOR ALL THE AWARDS. IT'S A COMBINATION. SO WE'LL HAVE A POOL OF, SAY, 15 EXPERT CONSULTANTS, AND WE WILL MIX AND MATCH DEPENDING ON WHAT'S THE PROJECT THAT WE ARE LOOKING AT. SO PROBABLY EACH ONE OF THEM MIGHT HAVE A MAXIMUM OF TWO PROJECTS THAT THEY WILL BE ADVISING ON.

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DR. LEVITT: OKAY. ONE THING TO THINK ABOUT IS THAT FOR ALL P50S THAT I'M AWARE OF, THEY HAVE TO HAVE A SCIENTIFIC ADVISORY COMMITTEE AND THEY'RE THE ONES WHO DEFINE IT. A SCIENTIFIC ADVISORY COMMITTEE ESSENTIALLY DOES WHAT YOU JUST SAID. THEY MEET ANNUALLY. AND THAT'S ANOTHER MODEL WHERE EACH OF THE LARGE PROGRAMS WOULD HAVE AN ADVISORY COMMITTEE THAT WOULD SEND A REPORT TO CIRM. AND THEY MAY BE AS OR MORE EFFECTIVE BECAUSE THEN YOU HAVE THE INVESTIGATORS HAVING SOME INPUT INTO THE EXPERTISE THAT THEY FEEL IS GOING TO BE MOST IMPORTANT.

THE ONLY THING I JUST WANTED TO MENTION, I HAVE SOME WORDSMITHING THAT I'LL SEND YOU. I'M NOT GOING TO BRING IT UP NOW. IT MAY BE WORTH THINKING ABOUT, PARTICULARLY FOR THE LARGE PROJECTS THAT HAVE A BRIDGE WITH CLINICAL DISORDERS, HAVING, IN ADDITION TO A DEI PLAN, A COMMUNITY ADVISORY COMMITTEE MAY BE WORTH THINKING ABOUT. CAC'S ARE REALLY HELPFUL IN THINKING ABOUT, PARTICULARLY SINCE A LOT OF THIS INVOLVES PATIENT MATERIAL THAT IS BEING USED, ET CETERA, AND HAVING A CAC, A SMALL CAC, FOR THE PROGRAMS MIGHT BE REALLY, I THINK, IMPORTANT. AND WE HAVE PATIENT ADVOCATES ON OUR BOARD THAT I THINK MAY FEEL THE SAME WAY. FOR US

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AND MY OWN PROJECTS, IT'S BEEN INCREDIBLY HELPFUL TO GET INSIGHT FROM A COMMUNITY ADVISORY COMMITTEE THAT'S RELEVANT TO THE STUDIES THAT WE ARE DOING. SO THAT'S SOMETHING TO THINK ABOUT. THANK YOU.

DR. CANET-AVILES: THANK YOU, PAT. SO LET ME JUST TOUCH SOMETHING. WHEN YOU SAID THE PI COMMITMENT, WHAT WERE YOU SUGGESTING FOR REMIND-L?

DR. LEVITT: SO EVERY P50, WHICH IS THE NIH TERM FOR WHAT YOU'RE DESCRIBING, HAS A SCIENTIFIC ADVISORY COMMITTEE. IT'S USUALLY THREE OR FOUR.

DR. CANET-AVILES: NO. NO. NO. THE PERCENTAGE OF THE PI.

DR. LEVITT: I WAS GOING TO RECOMMEND, BASED ON THE FEEDBACK WE GOT AND BASED ON MY UNDERSTANDING OF WHERE -- THIS IS GOING TO DRAW -- CIRM WANTS TO DRAW THE MOST IMPRESSIVE SCIENTISTS INTO THIS PROGRAM. WE HEARD FROM ONE TODAY. DOES HE HAVE 20 PERCENT TO COMMIT? HE'S NOT ON THE CALL NOW. I'M NOT ASKING HIM. EVEN IF HE WAS, I'M NOT ASKING HIM TO REVEAL. BUT 20 PERCENT FOR THAT KIND OF A LABORATORY FOR THE PI IS A LOT TO ASK. AND I DON'T KNOW HOW OTHERS ON OUR TASK FORCE FEEL, BUT --

DR. CANET-AVILES: COULD IT BE THAT WE ALLOW -- WE ARE ASKING FOR SOMEONE THAT'S MORE NEW

TO THE FIELD, BUT IS A PI BE THE COORDINATING PI AT A 20 PERCENT? AND THEN THE MORE -- I'M JUST THINKING. WE ARE ASKING FOR AT LEAST FIVE PEOPLE. WE CAN DISCUSS. WE CAN DISCUSS. I HEAR YOU. AND WE WERE THE SAME AS YOU. 15 PERCENT, COULD THAT BE FAIR, 15 PERCENT, A COORDINATING PI?

DR. LEVITT: IF YOU HAVE FOUR AT 5 PERCENT -- LET'S SAY YOU HAVE TWO AT 10 PERCENT AND THREE AT 5 PERCENT. THAT'S 20. THAT'S 35 PERCENT. THAT'S .35 FOR A FACULTY COMMITMENT. THAT'S PRETTY SUBSTANTIAL FOR A PROGRAM. I LOOK AT IT AS A SUM, NOT AS INDIVIDUALS. AND I DON'T KNOW. THE GROUP WILL HAVE TO CONTEMPLATE THIS. I HAVE MY OWN VIEWS, THAT 10 PERCENT FOR THE COORDINATING PI, AND I WOULD SAY THAT IT WOULD NOT BE A GOOD IDEA TO HAVE A JUNIOR INVESTIGATOR TO BE THE COORDINATING PI.

DR. CANET-AVILES: I HEAR YOU.

DR. LEVITT: IT'S A LOT OF WORK. IT TAKES SOME JUGGLING TO DO IT WELL BECAUSE THERE'S ALWAYS CONFLICTS THAT ARISE, NOT BAD CONFLICTS, BUT THERE'S ALWAYS ISSUES THAT ARISE. AND I THINK IT'S CHALLENGING FOR A JUNIOR PERSON TO DO THAT. I SHOULD LET OTHERS SPEAK.

DR. CANET-AVILES: LET ME SEE. I WAS JUST TRYING TO SEE IN COMPARISON WITH OTHER.

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CHAIRMAN GOLDSTEIN: ROSA, WE'LL HAVE TO CONTINUE THIS CONVERSATION OFFLINE, I THINK, BUT IT'S AN IMPORTANT POINT. FRED.

DR. FISHER: THANKS. I WON'T BELABOR IT, BUT I THINK THIS SLIDE, I REALLY WANT TO THANK PAT AND STEVE FOR KICKING THIS OFF BECAUSE I THINK THEY ALSO STARTED WHERE I WANTED TO START.

IT ISN'T CLEAR, BUT I'D LIKE TO SEE, NOT TODAY AND I DON'T EVEN WANT TO HEAR ABOUT IT TODAY BECAUSE THERE ISN'T TIME, BUT I WANT TO UNDERSTAND HOW THE STAFF AND ANY OTHER OTHERS INVOLVED IN PUTTING ALL OF THIS TOGETHER ACTUALLY TOOK IN THE REASON WHY THERE IS NOT MORE NEUROPSYCH MONEY BEING SPENT. IT'S NOT BECAUSE THEY DON'T KNOW ABOUT US. IT'S NOT BECAUSE THEY DON'T WANT THE MONEY. WHAT WE HEARD WAS IT'S TOO MUCH EFFORT FOR TOO LITTLE DOLLARS.

SO HOW DID THE CIRM TEAM TAKE THAT FEEDBACK AND BUILD IT INTO THIS PLAN SO THAT IN THE END WE DON'T FIND OURSELVES LOOKING AT ANOTHER PIE CHART THAT SAYS, OH, NEUROPSYCH WAS STILL UNDERFUNDED AND WE PUT THIS WHOLE GREAT PROGRAM TOGETHER BECAUSE WE DIDN'T PAY ATTENTION TO THE FEEDBACK WE GOT FROM THEM, THAT IT'S TOO MUCH WORK FOR TOO LITTLE DOLLARS. AGAIN, I DON'T WANT TO TAKE

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THE TIME NOW. THAT'S ONE.

IF YOU COULD GO BACK TO THE SLIDE THAT STEVE TALKED ABOUT THAT SHOWED ALL THE ARROWS AND THE SPENDING. IT'S AFTER THAT BECAUSE IT GETS DOWN TO A TOTAL OF BARELY...

SO WHAT'S NOT HELPFUL ABOUT THIS SLIDE IS YOU'RE TALKING ABOUT A NEUROPSYCH PROGRAM, AND YOU NEVER -- AND IT'S -- SO DO I UNDERSTAND WE'RE TALKING ABOUT 240 MILLION OUT OF 1.5 BILLION? IS THAT WHAT WE ARE TALKING ABOUT SPENDING ON NEUROPSYCH?

DR. CANET-AVILES: NO. AS I MENTIONED IN THE PREVIOUS SLIDE, LET ME JUST SHOW HERE, WHAT WE WERE PROPOSING IS THAT WE WOULD BE STARTING WITH NEUROPSYCHIATRIC AS A PILOT. AS WE MOVE FORWARD, WE WOULD BE INCLUDING OTHER DISEASES AND MORE WORKING FOCUSED ON SYSTEMS. SO RESEARCH MECHANISMS, DISEASE MECHANISMS, NEUROIMMUNE AXIS, AND INCLUDE NEURODEGENERATIVE, NEUROPSYCHIATRIC, NEURODEVELOPMENTAL, FOR EXAMPLE, NEUROVASCULAR, THE SAME. THOSE ARE EXAMPLES, BUT WE COULD START -- WE COULD INCREASE THE SCOPE OF DISEASES BY FOCUSING ON SYSTEMS. THAT'S HOW WE WERE PROPOSING TO MOVE FORWARD.

SO, NO, THE $648 MILLION COULD ACTUALLY BE

FOR NEUROLOGICAL DISEASES, DISCOVERY OF DISEASE MECHANISMS, NEUROLOGICAL DISEASES. ONLY THE FOUR FIRST YEARS COULD BE FOCUSED ON NEUROPSYCHIATRIC. THANK YOU.

DR. FISHER: SO REMIND-L AND REMIND-X ARE NOT EXCLUSIVELY NEUROPSYCH. THEY ARE --

DR. CANET-AVILES: CORRECT.

DR. FISHER: THIS IS WHAT YOU'RE CALLING THIS WHOLE EXPANSION. AND NOW MY QUESTION IS WHERE DID THESE OTHER INDICATIONS COME FROM BECAUSE TO MY KNOWLEDGE THEY HAVEN'T BEEN DISCUSSED BY THIS COMMITTEE.

DR. CANET-AVILES: NO.

DR. FISHER: THESE ARE THE THINGS THAT WE SHOULD BE FOCUSING ON IN FUTURE YEARS.

DR. CANET-AVILES: CORRECT. CORRECT. WE WOULD BE COMING IN FOUR YEARS OR THREE YEARS TIME. AS WE ARE MOVING TOWARDS THE NEXT SET OF RFA'S, WE WOULD COME TO THE BOARD WITH THE SPECIFICATION -- WE COULD COME WITH AN OUTCOMES ANALYSIS OF WHAT WE HAVE DONE WITH THE MONEY OF NEUROPSYCH AND WHAT WE THINK THAT MIGHT BE BEST TO LEVERAGE IT WITH, BUT UP TO YOU TO DECIDE WHERE YOU WANT US TO FOCUS BASED ON WHATEVER ANALYSIS YOU WANT US TO DO.

SO THIS IS JUST TO SHOW THAT THE REMIND-L

AND X, THIS REMIND CONCEPT STRUCTURE IS FOR DISCOVERY IN NEUROLOGICAL DISEASES. AND WE ARE GOING TO APPLY IT FIRST TO NEUROPSYCHIATRIC, AND THEN WE WILL COME TO YOU TO TELL US WHAT ELSE YOU WANT US TO START BRINGING IN, BUT GIVING YOU OUTCOMES, GIVING YOU WHAT IS IT THAT WE'VE ACHIEVED IN THE NEXT THREE TO FOUR YEARS.

DR. FISHER: SO YOU HAVE TO TAKE OFF ANY OTHER DISEASE INDICATIONS, CALL IT INDICATION X, INDICATION Y, INDICATION Z. WHEN YOU START PUTTING THINGS IN WRITING, YOU CREATE THE EXPECTATION THAT THAT'S WHERE THIS IS STARTING. JUST LIKE IT STILL REMAINS A MYSTERY HOW WE ENDED UP STARTING ON NEUROPSYCH, BUT IT IS WHAT IT IS. AND WHEN YOU START PUTTING THINGS DOWN, IT SEEMS TO HAVE THE SETTING-IN-STONE FUNCTION.

SO IF YOU'RE JUST TALKING ABOUT ADDING DISEASE INDICATION, HAVE IT JUST SAY LITERALLY DISEASE INDICATION NO. 1, NO. 2, NO. 3 SO YOU SHOW IT GROWING.

SO WHAT YOU STARTED WITH HERE WAS WE ARE LOOKING AT A PROGRAM THAT APPARENTLY HAS A SUBSET OF COST. NOW, IF YOU CLICK ON ANOTHER SLIDE WHERE YOU GET TO THE 648 MILLION, WE GET TO 648 MILLION OF TOTAL COSTS FOR THIS NEW INITIATIVE, WHICH IS 43

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PERCENT OF THE TOTAL MINIMUM FOR NEURO. GIVEN THAT MY UNDERSTANDING IS THAT CIRM HAS ALREADY SPENT IN THE PRIOR FUNDING CYCLE 1.5 BILLION OR MAYBE IT DID OR MAYBE IT DIDN'T, I DON'T KNOW. I DON'T WANT TO REHASH THIS, BUT I NEED TO UNDERSTAND WHETHER WE ARE ACTUALLY GOING TO NOT BE ABLE TO FUND THINGS THAT WE WOULD WANT TO FUND BECAUSE WE ARE LOOKING AT CARVING OUT 43 PERCENT OF THE 1.5 BILLION FOR NEURO, WHICH I WANT TO KNOW WHAT THAT TOTAL IS FOR NEUROPSYCH, PLUS SOME OTHER THINGS.

SO THIS SLIDE WHERE YOU HAVE THESE ARROWS, LIKE, IT'S MISLEADING BECAUSE YOU'RE TALKING ABOUT REMIND-L AND REMIND-X, WHICH IN THESE FUTURE YEARS IS GOING TO BE SOMETHING OTHER THAN NEUROPSYCH, BUT WHAT YOU'VE PUT UNDER THE ARROWS, I THINK, IS FUNDING STRICTLY CONNECTED TO NEUROPSYCH.

DR. CANET-AVILES: NO. NO.

DR. FISHER: IT'S 12 TEAMS, 144 MILLION. YOU'RE TALKING ABOUT NEUROPSYCH.

DR. CANET-AVILES: NO. NO. NO. FOR REMIND-L, IT COULD BE FOR DIFFERENT DISEASES. IT COULD BE THAT IN YEARS 2028 TO 2031 WE DECIDE THAT WHAT CIRM IS GOING TO FUND IS RESEARCH AROUND THE NEUROIMMUNE AXIS. THIS IS MECHANISMS ACROSS ALL NEURO DISEASES, AND THAT WOULD BE THE FUNDING.

TWELVE TEAMS COULD BE REALLY LARGE BECAUSE THOSE ARE $2.5 MILLION-A-YEAR TEAMS. SO IT'S LIKE $10 MILLION-A-YEAR AWARDS, $10 MILLION AWARDS, 12 OF THEM. THAT'S A LOT OF MONEY THAT WE WOULD BE FUNDING, BUT IT'S NOT NEUROPSYCH. IT'S TO DO WITH ALL NEURO.

AND I TOOK YOUR POINT THAT WE NEED TO REMOVE FROM THIS SLIDE 17 THE INDICATIONS. WE ARE STARTING WITH NEUROPSYCH NOW. THE TOTAL WILL BE $168 MILLION FOR NEUROPSYCH, BUT THE 648 MILLION COULD BE FOR ALL NEURO DISEASES AND DISCOVERY. SO THIS COULD BE WHAT WE ARE ASKING FOR THE NEURO STRATEGY AT CIRM. THE DISCOVERY PART WE ESTIMATE MIGHT TAKE ABOUT 42 PERCENT OF THE FUNDING, INCLUDING WHAT WE WILL SPEND IN THE DISC PILLAR PROGRAM AS WELL.

DR. FISHER: IF YOU WANT TO KNOW MORE ABOUT THE CONFUSION OF THIS SLIDE, I WON'T TAKE THE TIME HERE BECAUSE I SEE LEONDRA HAS HER HAND UP. THIS IS A VERY CONFUSING SLIDE. I DON'T UNDERSTAND WHAT THE SALMON ARROW IS AT 235 MILLION. AND IF I UNDERSTAND WHAT YOU'RE SAYING, THE TOTAL COMMITMENT OF 1.5 BILLION DEDICATED TO NEUROPSYCH IS 168 MILLION, WHICH IS 11.2 PERCENT OF THE 1.5 BILLION. THAT'S WHAT I WANT TO UNDERSTAND BECAUSE WHEN YOU'RE

TALKING ABOUT STARTING WITH A PILOT AROUND NEUROPSYCH, THE QUESTION IS HOW MUCH ARE YOU GOING TO DEVOTE TO THAT? AND THE ANSWER IS 11.2 PERCENT BASED ON WHAT YOU'RE TELLING ME TODAY, BUT I COULD NOT DERIVE THAT FROM ANY OF THESE SLIDES.

AND THEN THERE NEEDS TO BE A RATIONALE FOR WHY 11.2 PERCENT IS THE RIGHT NUMBER, PARTICULARLY SINCE WHAT WE HEARD IS THE OBSTACLE IS NOT THE ABSENCE OF A PROGRAM. THE OBSTACLE IS CIRM DOESN'T PAY ENOUGH MONEY AND REQUIRES TOO MUCH EFFORT. AND I DON'T SEE THAT ADDRESSED, AND YOU'VE CREATED A MASSIVE PROGRAM THAT ACTUALLY I DON'T HAVE ANY EVIDENCE THAT YOU'VE ACTUALLY SOLVED THE PROBLEM. I'LL STOP THERE.

CHAIRMAN GOLDSTEIN: THANK YOU. FRED AND ROSA, PERHAPS YOU CAN GET THROUGH SOME OF THESE ISSUES OFFLINE. LEONDRA.

DR. CLARK-HARVEY: THANK YOU. I'LL BE QUICK.

FIRST, THANK YOU. THANK YOU FOR THE CONCEPTUALIZATION AND THE TIME THAT STAFF PUT INTO THIS REMIND. I LOVE IT, BY THE WAY, THE WAY IT'S LABELED.

I DO AGREE WITH FRED. THERE IS SOME CONFUSION HERE, AND I WOULD LIKE CLARITY. SO

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WHATEVER CONVERSATION OR WHATEVER YOU WORK THROUGH OFFLINE, IF YOU COULD REPORT BACK TO THE REST OF US. FOR THOSE OF US THAT ARE NOT QUITE CAUGHT UP, I WOULD APPRECIATE THAT.

AND ALSO TO FRED'S POINT AROUND THE MONEY AND THE EFFORT, THAT TRULY WAS WHAT STOOD OUT TO ME AT ONE OF OUR LAST MEETINGS. I KNOW IT WAS REITERATED AT OUR ICOC MEETING A FEW WEEKS AGO. AND SO I WANT TO MAKE SURE THAT THAT DOESN'T GET LOST IN ALL OF THIS. AND SO I THINK THAT THERE'S OPPORTUNITIES TO CONTINUE THE DISCUSSION.

ALSO TO PAT'S POINT AROUND THE COMMUNITY ADVISORY COMMITTEE, IT'S SOMETHING THAT I RAISED AT OUR LAST MEETING, AND I'M GLAD TO HEAR IT RAISED HERE AGAIN. I THINK THERE REALLY NEEDS TO BE SPACE AND ROOM FOR IT, ESPECIALLY CONSIDERING THE DIRECT FEEDBACK THAT WE'VE RECEIVED, SOME OF WHICH FRED JUST RELAYED. SO I DO HOPE THAT THERE'S GOING TO BE SOME EFFORTS TO DO THAT. BUT, AGAIN, THANK YOU FOR THIS. I KNOW YOU ALL ARE WORKING THIS OUT. I'M GLAD WE'RE HAVING THIS MEETING SO YOU CAN HEAR DIRECTLY FROM US WHAT SOME OF THE KINKS MIGHT BE OR BETTER WAYS TO MAKE IT CLEAR SO THAT EVERYBODY, BECAUSE IF WE'RE NOT CLEAR, BELIEVE YOU ME, OTHERS WON'T BE EITHER AS THIS MOVES FORWARD. SO

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APPRECIATE THAT. THANK YOU.

DR. CANET-AVILES: THANK YOU. GREAT FEEDBACK.

DR. SOUTHARD: I JUST WANTED TO SAY THAT I THINK THIS IS A REALLY GOOD START AT AN ISSUE THAT WE WERE TRYING TO GET TO IS UNDERSTANDING WHY NOTHING HAD BEEN DONE AT ALL ON NEUROPSYCH. AND THIS IS AN EFFORT TO BEGIN TO CURE THAT, THAT I THINK IS ACTUALLY PRETTY CLEAR AND OUTSTANDING.

AND MY ONLY QUESTION WOULD BE IS THERE ANY POSSIBILITY OF ACCELERATING THE TIMELINE ON THIS? BECAUSE AS -- IT'S A LOT, BUT IT'S A LONG TIME, AND NEUROPSYCH HAS BEEN SO UNDERFOCUSED ON, THAT WHATEVER WE CAN DO TO MOVE IT FORWARD, I THINK, WOULD BE A GREAT THING. BUT I THINK THIS IS A GOOD START PERSONALLY.

CHAIRMAN GOLDSTEIN: THANK YOU, MARV.

CAN I ASK SOMEBODY A PROCESS QUESTION? WE ARE HAVING TO WRAP UP HERE. DO WE FORMALLY VOTE TO SEND THIS ON TO THE SCIENCE SUBCOMMITTEE, OR DO WE MAKE A RECOMMENDATION, OR DO WE HAVE ANY RULE AT ALL ABOUT WHAT OUR FINAL ACT IS HERE TODAY?

MR. TOCHER: SURE, LARRY. THIS IS SCOTT BACK AT CIRM. IT'S THE PLEASURE OF THE COMMITTEE, BUT IN NORMAL COURSE THE RECOMMENDATION WOULD BE TO

FORWARD TO THE SCIENCE SUBCOMMITTEE WITH A RECOMMENDATION TO THE COMMITTEE AND FULL BOARD TO ADOPT IT.

CHAIRMAN GOLDSTEIN: GREAT. SO WE CAN MAKE A VOTED RECOMMENDATION. SO CAN SOMEBODY MAKE A MOTION PLEASE?

DR. SOUTHARD: I WOULD MOVE WITH -- AFTER CLARIFICATIONS AS TO THE SLIDE, THAT THIS MOVE FORWARD TO THE SCIENTIFIC COMMITTEE.

DR. GASSON: I SECOND.

CHAIRMAN GOLDSTEIN: THANK YOU. LET'S SEE. A ROLL CALL VOTE. MARIANNE.

MR. TOCHER: JUST A SECOND. LARRY, THERE'S BOARD COMMENT ON THE MOTION. WE'LL TAKE THAT NOW. LOOKS LIKE STEVE'S HAND IS RAISED, AND THEN WE WOULD HAVE PUBLIC COMMENT AFTER THAT.

CHAIRMAN GOLDSTEIN: OKAY.

MR. JUELSGAARD: SO MARV'S MOTION ACTUALLY OPENS THE DOOR TO THIS QUESTION BECAUSE HE DIDN'T APPROVE -- HE DID MOVE THAT THIS PRESENTATION PER SE BE FORWARDED TO THE SCIENTIFIC SUBCOMMITTEE, BUT WITH MODIFICATIONS. AND I GO BACK TO SOMETHING THAT FRED WAS TALKING ABOUT AND PAT TOO, FOR THAT MATTER. ARE WE READY FOR PRIME TIME WITH THIS? I DON'T WANT TO GO RECOMMENDING SOMETHING TO THE SCIENTIFIC

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SUBCOMMITTEE, AND LEONDRA SAID THE SAME THING, THAT'S NOT QUITE FULLY BAKED. THIS IS PRETTY IMPORTANT WHAT WE ARE PLANNING ON DOING, AND IT'S NOT CLEAR TO ME THAT WE ARE AT THAT POINT. I'D RATHER TAKE A LITTLE BIT MORE TIME AND BEG THE ICOC'S INDULGENCE ULTIMATELY IN ORDER TO HAVE SOMETHING THAT WE ARE ALL SETTLED AS A GOOD PLAN TO MOVE FORWARD.

CHAIRMAN GOLDSTEIN: FRED.

DR. FISHER: WHAT STEVE SAID. AND IF IT -- IF THIS MOTION DOES COME TO A VOTE, I WILL UNFORTUNATELY HAVE TO VOTE NO. IT'S NOT READY.

CHAIRMAN GOLDSTEIN: MARIA MILLAN.

DR. MILLAN: IT MAY NOT ANSWER ALL THE QUESTIONS, BUT I WANTED TO, I THINK, ANSWER THE QUESTION ABOUT THIS 11 PERCENT. THE 235 MILLION THAT IS ON THE SALMON ARROW, I BELIEVE, IS THE TOTAL EXPENDITURES FOR ALL DISCOVERY PROGRAMS COMING THROUGH THE USUAL PILLARS FOR NEURO, NOT NEUROPSYCH, ALL OF NEURO. AND I BELIEVE THAT THAT GOT ADDED TO THE PROPOSED EXPENDITURES FOR THESE BIGGER PROGRAMS AND THAT GAVE RISE TO THE 648 MILLION. AND THE BALANCE OF THAT WOULD BE WHAT'S AVAILABLE FOR OTHER PROGRAMS, INCLUDING TRANSLATIONAL AND CLINICAL.

SO IT MAY NOT MAKE A DIFFERENCE, BUT I

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JUST WANTED TO POINT OUT MY UNDERSTANDING OF THIS 235 MILLION. SO THE --

DR. CANET-AVILES: I CAN EXPLAIN. I DECIDED THAT WE CLARIFY --

DR. FISHER: I NEED TO GO BACK. WE DON'T HAVE TIME TO GO BACK AND GET INTO THE GRANULAR DETAIL. IT'S A GOOD EXAMPLE OF WHY WE NEED ANOTHER MEETING TO TALK THROUGH ALL OF THIS BECAUSE 235 MILLION ON NEURO IN THE PAST CYCLE DOESN'T MAKE SENSE EITHER.

DR. CANET-AVILES: I CAN EXPLAIN, BUT I DIDN'T THINK WE HAD THE TIME. SO I THINK PERHAPS WE HAVE ANOTHER MEETING, AND I CAN MAKE THE CLARIFICATIONS THAT EVERYBODY IS ASKING. THIS IS EASY. THIS WAS A BIG BITE TO BRING INTO THE TASK FORCE, AND I'M HAPPY TO CLARIFY. IT'S EASY. IT'S VERY EASY ALL THESE QUESTIONS. AND I APPRECIATE THEM. IT MAKES ME REALIZE WHAT'S NOT UNDERSTANDABLE.

CHAIRMAN GOLDSTEIN: MARIA BONNEVILLE.

VICE CHAIR BONNEVILLE: I WAS JUST GOING TO ADD I THINK IT'S IMPORTANT AT THE NEXT MEETING, MARIA AND TEAM, IS TO COME BACK WITH THE ANSWERS TO SOME OF THE THINGS THAT WERE BROUGHT UP OUTSIDE OF THIS SPECIFICALLY, BUT ALSO ARE WE -- IS IT ENOUGH

MONEY? HOW DID WE COME TO THOSE CONCLUSIONS? WHAT'S THE PERCENT EFFORT? HOW DID WE ARRIVE AT ALL OF THAT BECAUSE I THINK THERE HAS BEEN IN THE PAST SEVERAL MEETINGS A CALL TO RESEARCH SOME OF THESE ISSUES THAT HAVE BEEN BROUGHT UP ON MORE THAN ONE OCCASION. SO I THINK IT WOULD BE REALLY HELPFUL.

CHAIRMAN GOLDSTEIN: STEVE.

MR. JUELSGAARD: YES. I'M JUST GOING TO BASICALLY REINFORCE SOMETHING THAT FRED SAID DURING THE COURSE OF HIS SOLILOQUY. HAVE WE SOCIALIZED WHAT WE WOULD LIKE TO DO IN TERMS OF FUNDING WITH ANY OF THE FOLKS THAT HAVE MADE PRESENTATIONS BEFORE OR OTHER RESEARCH INSTITUTIONS OR ACADEMIC INSTITUTIONS WITHIN THE STATE? IN OTHER WORDS, THE QUESTION ON THE TABLE IS ARE WE WILLING TO GRANT ENOUGH MONEY TO MAKE A DENT IN THIS? DO WE KNOW THAT? WE PROVIDED SOME AMOUNT OF MONEY AND SOME TIME PERIOD. IS THAT REALLY SUFFICIENT OR NOT? I WOULD LIKE TO KNOW THAT PEOPLE FROM OUTSIDE OF THIS GROUP SAY YES. THAT'S GREAT. THAT'S PERFECT. THAT'S EXACTLY WHAT WE NEED. OR, NO, WAIT A MINUTE. THAT'S NOT QUITE ENOUGH. WE WOULDN'T TAKE OUR TIME TO APPLY FOR A GRANT. BECAUSE I DON'T WANT TO RUN INTO THAT PROBLEM AGAIN. I WANT TO MAKE SURE THAT WHAT WE DO WE ARE GOING TO BE SUCCESSFUL AT DOING.

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DR. CANET-AVILES: THE ANSWER, STEVE, IS YES, WE HAVE. WE HAVE ALSO BEEN TALKING TO THE NIMH WHICH WOULD BE THE FUNDING AGENCY AT THE FEDERAL LEVEL THAT HAS BEEN GRANTING AWARDS LIKE THIS. WE'VE BEEN DOING LANDSCAPE ANALYSIS OF WHAT'S FUNDED OUT THERE. WE'VE BEEN TALKING TO RESEARCHERS. WE HAVE TO BE CAREFUL BECAUSE THIS IS NOT A CONCEPT EVEN. SO IF WE PUT TOO MUCH SWEETNESS IN THEIR MOUTH AND THEN WE DON'T GIVE IT TO THEM, THEY WILL THINK THAT, BUT WE HAVE. WE HAVE ACTUALLY BEEN TALKING TO THE PEOPLE THAT SPOKE AND OTHERS, AND WE'VE BEEN GOING TO MEETINGS AS WELL. AND EVERYBODY IS VERY EXCITED AND WAITING FOR THIS TO BE OUT.

MR. JUELSGAARD: GREAT. THANK YOU, ROSA.

CHAIRMAN GOLDSTEIN: PAT.

DR. LEVITT: I WAS JUST GOING TO COMMENT THAT THERE'S ENOUGH EXPERTISE ON THIS COMMITTEE TO -- THERE'S NOT A FORMULA. THERE'S NOT GOING TO BE A FORMULA THAT SAYS WE NEED EXACTLY THIS AMOUNT OF MONEY TO ADDRESS THE GAPS THAT HAVE BEEN IDENTIFIED BY THOSE WHO HAVE PRESENTED AND WHAT THIS TASK FORCE HAS ADDRESSED. THERE'S GAPS IN EVERY AREA OF BRAIN DISEASES AND DISORDERS EVERYWHERE. SO WE'VE GOTTEN INPUT. THERE'S CERTAIN PRESSURE POINTS THAT WE KNOW ABOUT, AND THE FUNDING LEVELS ARE GOING

TO BE TO SOME DEGREE SUBJECTIVE. IT'S JUST THE WAY IT IS. WE CAN'T PREDICT THAT IT'S GOING TO BE 550 VERSUS $750 MILLION. AND IF WE GO TO 750, THAT WILL BE ENOUGH. WHO KNOWS WHAT'S GOING TO BE ENOUGH? IS THERE ANYONE ON THIS COMMITTEE WHO CAN TELL ME WHAT THE FORMULA IS?

SO I THINK WE DO HAVE TO HAVE ANOTHER MEETING TO GIVE ROSA AND THE TEAM A CHANCE TO MAKE THE EDITS AND SUGGESTIONS. AND MAYBE BETWEEN NOW AND THAT MEETING, SOME OFFLINE CONVERSATIONS WITH SOME FOLKS HERE ABOUT UNDERSTANDING THE DOLLAR AMOUNTS, WHICH I THINK CAN BE SOMEWHAT CONFUSING.

THAT'S MY RECOMMENDATION AND THEN WE HAVE TO GET ON WITH THE VOTE. THE EXPECTATION THAT WE'RE GOING TO COME UP WITH A FORMULA THAT'S GOING TO TELL US EXACTLY HOW MUCH MONEY IS GOING TO BE THE RIGHT AMOUNT OF MONEY IS JUST NOT GOING TO HAPPEN. THAT'S IT.

CHAIRMAN GOLDSTEIN: THANK YOU, PAT.

SCOTT, PROCESS QUESTION. WHERE DO WE GO FROM HERE?

MR. TOCHER: WELL, THE MOTION THAT HAS BEEN MADE AND SECONDED ACTUALLY, TECHNICALLY BELONGS TO THE WHOLE OF THE TASK FORCE NOW. LISTENING TO THE COMMENT, I THINK MAYBE PROCEDURALLY YOU COULD

JUST ASK, IF THERE'S NO OBJECTION, THAT WE TABLE THE MOTION UNTIL ANOTHER MEETING OF THE TASK FORCE TO SEE A REFINED PROPOSAL AND TAKE UP THE MOTION AT THAT TIME AFTER THE PRESENTATION AT THAT MEETING. AND THAT WE WOULD SCHEDULE THAT MEETING, OF COURSE, BEFORE THE SCIENCE SUBCOMMITTEE MEETING.

CHAIRMAN GOLDSTEIN: AND DO WE DO THAT BEFORE OR AFTER WE GET PUBLIC COMMENT?

MR. TOCHER: YOU CAN DO THAT AFTER YOU RECEIVE PUBLIC COMMENT OR NOW. EITHER IS FINE.

CHAIRMAN GOLDSTEIN: IS THERE ANYBODY ON THE LINE FOR PUBLIC COMMENT? BECAUSE IF THERE'S SOMEBODY WHAT WANTS TO ADDRESS THESE ISSUES, THAT COULD BE HELPFUL.

MS. DEQUINA-VILLABLANCA: THERE LOOKS LIKE THERE MIGHT BE A COUPLE. BUT IF YOU ARE, YOU CAN DO STAR NINE TO BE PUT IN THE QUEUE IF YOU'D LIKE TO MAKE A COMMENT. THERE ARE NONE POPPING UP, LARRY.

CHAIRMAN GOLDSTEIN: NO COMMENT. SO THEN I THINK WE SHOULD DO WHAT SCOTT SUGGESTED. IF THOSE WHO PROPOSED THE ORIGINAL MOTIONS ARE IN AGREEMENT, PLEASE LET US KNOW.

DR. SOUTHARD: FINE WITH ME.

DR. GASSON: YES.

CHAIRMAN GOLDSTEIN: OKAY. GREAT. NEXT

STEP IS ANOTHER TASK FORCE MEETING THAT WILL ADDRESS THE ISSUES THAT HAVE BEEN RAISED ABOUT DOLLARS, EFFORT, SOCIALIZING WITH THE COMMUNITY, AND SOME CLARIFICATION OF THE TIMING AND GROWTH OF REMIND-L AND REMIND-X. DO I HAVE THAT RIGHT?

MR. JUELSGAARD: YES.

CHAIRMAN GOLDSTEIN: GOOD. OKAY. ROSA, OKAY?

DR. CANET-AVILES: FANTASTIC. YES, WE'LL BE THERE.

CHAIRMAN GOLDSTEIN: OKAY. I THINK WITH THAT --

DR. CANET-AVILES: THANK YOU, LARRY, AND THANK YOU, EVERYBODY, FOR THE FEEDBACK. VERY USEFUL.

CHAIRMAN GOLDSTEIN: OKAY. I THINK WITH THAT, WE CAN ADJOURN AND SEE YOU ALL SOON WITH ADDITIONAL INFORMATION.

(THE MEETING WAS THEN CONCLUDED AT 3:13 P.M.)

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REPORTER'S CERTIFICATE

I, BETH C. DRAIN, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT OF THE VIRTUAL PROCEEDINGS BEFORE THE TASK FORCE ON NEUROSCIENCE AND MEDICINE OF THE INDEPENDENT CITIZEN'S OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD ON JULY 17, 2023, WAS HELD AS HEREIN APPEARS AND THAT THIS IS THE ORIGINAL TRANSCRIPT THEREOF AND THAT THE STATEMENTS THAT APPEAR IN THIS TRANSCRIPT WERE REPORTED STENOGRAPHICALLY BY ME AND TRANSCRIBED BY ME. I ALSO CERTIFY THAT THIS TRANSCRIPT IS A TRUE AND ACCURATE RECORD OF THE PROCEEDING.

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