BEFORE THE
TASK FORCE ON NEUROSCIENCE AND MEDICINE
OF 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: APRIL 24, 2023
12 P.M.

REPORTER: BETH C. DRAIN, CA CSR
CSR. NO. 7152

FILE NO.: 2023-14

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APRIL 24, 2023; 12 P.M.

CHAIRMAN GOLDSTEIN: OKAY. GOOD AFTERNOON, EVERYBODY, AND WELCOME TO THE THIRD MEETING OF THE CIRM TASK FORCE ON NEUROSCIENCE AND NEUROMEDICINE. AND WHAT I WANT TO DO IS JUST TAKE A COUPLE MINUTES TO REVIEW WHERE WE'VE BEEN THUS FAR IN OUR MEETINGS, AND THAT WILL FRAME THE TOPICS THAT TODAY'S SPEAKERS WILL DISCUSS WITH US.

SO THE FIRST MEETING THAT WE DID BACK IN FEBRUARY --

MS. DEQUINA-VILLABLANCA: LARRY, SHOULD I DO ROLL CALL REAL QUICK?

CHAIRMAN GOLDSTEIN: OH, YES. I FORGOT ABOUT ROLL CALL. THANK YOU, MARIANNE.

MS. DEQUINA-VILLABLANCA: OKAY. HERE WE GO --

CHAIRMAN GOLDSTEIN: I'M NOT MUCH FOR FORMALITIES, AS YOU CAN SEE.

MS. DEQUINA-VILLABLANCA: NO WORRIES.

LEONDRA CLARK-HARVEY. MARIA BONNEVILLE.

MS. BONNEVILLE: PRESENT.

MS. DEQUINA-VILLABLANCA: MARK FISCHER-COLBRIE.

DR. FISCHER-COLBRIE: HERE.

MS. DEQUINA-VILLABLANCA: FRED FISHER.
DR. FISHER: YEP.
MS. DEQUINA-VILLABLANCA: JUDY GASSON. I SAW JUDY. SHE IS ON MUTE. JUDY, YOU'RE ON MUTE. ALL RIGHT. I'LL GO BACK.
LARRY GOLDSTEIN.
CHAIRMAN GOLDSTEIN: HERE.
MS. DEQUINA-VILLABLANCA: DAVID HIGGINS.
DR. HIGGINS: HERE.
MS. DEQUINA-VILLABLANCA: VITO IMBASCIANI.
DR. IMBASCIANI: PRESENT.
MS. DEQUINA-VILLABLANCA: STEVE JUELSGAARD.
MR. JUELSGAARD: PRESENT.
MS. DEQUINA-VILLABLANCA: PAT LEVITT.
DR. LEVITT: HERE.
MS. DEQUINA-VILLABLANCA: LAUREN MILLER-ROGEN.
MS. MILLER-ROGEN: HERE.
MS. DEQUINA-VILLABLANCA: AL ROWLETT.
CHAIRMAN GOLDSTEIN: I THOUGHT I SAW AL A COUPLE MINUTES AGO.
MS. DEQUINA-VILLABLANCA: HE WAS THERE. YES, HE WAS. OKAY.
MARVIN SOUTHARD. AND SEEMS LIKE MARVIN IS

ON, BUT I THINK HE WAS HAVING PROBLEMS WITH HIS AUDIO. I DO SEE HIM.

KEITH YAMAMOTO.

DR. YAMAMOTO: HERE.

MS. DEQUINA-VILLABLANCA: LET ME CHECK AGAIN. JUDY GASSON. AND THEN AL ROWLETT. ALL RIGHT. WE CAN PROCEED.

CHAIRMAN GOLDSTEIN: PROCEED. THANK YOU.

SO WHAT I WANT TO DO IS JUST REVIEW WHERE WE'VE BEEN TO SET UP TODAY'S SPEAKERS AND TOPICS. SO THE FIRST MEETING OF THIS TASK FORCE DID A PORTFOLIO REVIEW OF CIRM'S PRESENCE IN NEUROSCIENCE, NEUROMEDICINE, AND ALSO WHAT THE BUSINESS LANDSCAPE LOOKED LIKE. AND WHAT WE DISCOVERED WAS THAT, WHILE CIRM HAS PRETTY GOOD EFFORTS GOING IN VARIOUS NEURODEGENERATIVE DISORDERS USING STEM CELLS IN DIFFERENT WAYS RANGING FROM MECHANISM DISCOVERY TO CELL THERAPIES, WE HAD VIRTUALLY NO REPRESENTATION IN NEUROPSYCHIATRIC DISORDERS EVEN THOUGH THERE ARE GOOD ARGUMENTS TO BE MADE THAT STEM CELL TECHNOLOGY WILL BE VERY HELPFUL FOR TACKLING THE PROBLEM OF NEUROPSYCHIATRIC DISORDERS, THAT THESE ARE RELATIVELY COMMON IN THE POPULATION WITH TREMENDOUS DISEASE BURDEN ON SOCIETY.

AND SO WE HAD A DISCUSSION ABOUT THESE

PORTFOLIO ISSUES AND AGREED THAT THE FIRST PROBLEM WE WOULD ATTACK IN OUR PLANNING, AND AS YOU WILL SEE IN EARLY FUNDING INITIATIVE, WAS TO TACKLE THIS PROBLEM WHILE WE CONTINUE OUR EDUCATION ABOUT WHAT'S GOING ON IN DIFFERENT NEURO DISORDERS AND WHERE WE MIGHT MAKE UNIQUE IMPACT. AND IN FACT, TODAY'S SPEAKERS, YOU'LL SEE, HAVE BEEN USING STEM CELL TECHNOLOGY TO TACKLE THE PROBLEM OF NEUROPSYCHIATRIC DISORDERS. AND THEY'VE GOT SOME VERY INTERESTING INSIGHTS AND PROJECTS TO TELL US ABOUT.

THE SECOND MEETING LAST MONTH FURTHER POSITIONED HOW WE MIGHT THINK ABOUT THINGS BECAUSE IT WAS A SET OF PRESENTATIONS BY TWO PSYCHIATRIC GENETICISTS THAT REVEALED THAT IN MANY OF THESE DISORDERS THERE ARE SIGNIFICANT IMPACT OF THE GENETIC CONSTITUTION THAT INDIVIDUALS HAVE AND THAT, LIKE MANY DISEASES IN HUMANS, WHAT ONE SEES IS THAT THERE'S SORT OF A BREAKDOWN BETWEEN TWO MAJOR WAYS THAT ONE SEES GENETIC EFFECTS ON NEUROPSYCHIATRIC DISORDERS.

ONE IS BY THE ACTION OF RARE VARIANTS IN THE POPULATION THAT HAVE STRONG IMPACT, AND THE OTHER CLASS, IF YOU WILL, ARE MORE COMMON VARIANTS, EACH OF SOMEWHAT WEAKER IMPACT, BUT TOGETHER CAN LEAD TO THE DEVELOPMENT OR ENHANCE THE PROBABILITY

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OF DEVELOPMENT OF NEUROPSYCHIATRIC DISEASE.

IN FACT, AS IT TURNS OUT, AT PUBLIC COMMENT OF ONE OF OUR MEETINGS ABOUT TECHNOLOGIES THAT CIRM SHOULD USE OR COULD USE TO TACKLE DISEASE, TOM SUDHOF, ONE OF OUR SPEAKERS TODAY, SENT IN A VERY THOUGHTFUL LETTER. AND I THOUGHT I WOULD JUST READ THE LAST PARAGRAPH OF TOM'S LETTER. THERE WE GO. IT'S SHORT, SO BEAR WITH ME.

AND WHAT TOM SAID WAS, "CALIFORNIA HAS FANTASTIC NEUROSCIENCE AND GREAT NEUROSCIENTISTS. BY ENGAGING THE CREATIVE ENERGY OF CALIFORNIA'S NEUROSCIENTISTS TO DEVELOP AMBITIOUS RESEARCH INITIATIVES FROM MOLECULES TO THE TREATMENT OF PATIENTS, CIRM HAS THE OPPORTUNITY TO TRANSFORM THE TREATMENT OF MENTAL ILLNESS AND REDUCE THE SUFFERING OF MILLIONS OF CALIFORNIANS."

AND I PERSONALLY THINK THAT TOM IS CORRECT IN THAT SENTIMENT. AND, OF COURSE, WE WILL BE TALKING ABOUT THAT FURTHER TODAY AND IN FUTURE MEETINGS.

SO WHAT I WANT TO DO NOW IS JUST GIVE YOU A BRIEF INTRODUCTION TO THE TWO SPEAKERS TODAY. THEY'RE BOTH WELL-KNOWN TO MANY OF YOU. ONE, KRISTEN BRENNAND, WHO IS A FACULTY MEMBER AT YALE USING STEM CELL TECHNOLOGIES TO TACKLE

NEUROPSYCHIATRIC DISORDERS. KRISTEN DID HER PH.D. WORK WITH DOUG MELTON AT HARVARD WORKING ON PANCREATIC DEVELOPMENT. SHE THEN DID A POST-DOC WITH RUSTY GAGE, WHO MANY OF YOU KNOW, WHO'S DONE REALLY TERRIFIC WORK IN NEUROPSYCHIATRIC DISORDERS AND USING STEM CELLS TO TACKLE THEM. AND KRISTEN TOOK A PART OF THAT PORTFOLIO WITH HER WHEN SHE MOVED TO HER FACULTY POSITION WHERE SHE CURRENTLY IS AT YALE.

TOM SUDHOF DID HIS PH.D. WORK IN GERMANY, BUT THEN POST-DOC'D WITH MIKE BROWN AND JOE GOLDSTEIN, NO ACTUAL RELATIVE OF MINE, BUT A TERRIFIC GUY NONETHELESS. AND THAT'S WHERE TOM REALLY BEGAN HIS INITIATIVES ON TRYING TO UNDERSTAND THE MECHANICS AND BIOCHEMISTRY OF SYNAPTIC TRANSMISSION. AND TO SAY THAT TOM IS A WORLD LEADER IN THIS FIELD WOULD BE AMAZINGLY AN UNDERSTATEMENT.

WILL JUST NOTE THAT A FEW YEARS AGO HE WAS AWARDED THE NOBEL PRIZE WITH RANDY SCHEKMAN AND JIM ROTHMAN. AND TOM WAS RECOGNIZED IN PARTICULAR FOR HIS WORK ON UNDERSTANDING HOW THE SYNAPSE WORKED AND HOW NEURONS TALK TO EACH OTHER.

SO THE FINAL THING WE'LL DO IN TODAY'S MEETING AFTER TOM AND KRISTEN'S PRESENTATIONS AND Q AND A ABOUT THOSE PRESENTATIONS, WE'LL TACKLE TWO

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THINGS. ONE IS I'LL REMIND YOU THAT WE ASKED AT THE LAST MEETING ROSA CANET-AVILES TO BEGIN WORKING ON A CONCEPT PLAN THAT WOULD COME TO THIS TASK FORCE FORMALLY AT OUR NEXT MEETING IN MAY, THEN TO THE SCIENCE SUBCOMMITTEE AT THE END OF MAY, AND THEN ON TO THE FULL ICOC OR BOARD OF DIRECTORS AT OUR MEETING AT THE END OF JUNE.

AND THE IDEA IS TO KICK-START OUR EFFORTS IN THIS FIELD BY PROVIDING AWARDS TO INTERDISCIPLINARY GROUPS OF INVESTIGATORS WHO ARE TACKLING DIFFERENT NEUROPSYCHIATRIC DISORDERS. AND YOU'LL SEE THE DETAILS AT OUR NEXT MEETING.

THE OTHER THING THAT ROSA HAS BEEN WORKING ON AND THAT I'LL ASK HER TO PRESENT TO YOU TODAY IS A SURVEY OF CALIFORNIA NEUROSCIENTISTS TO DEVELOP A BETTER UNDERSTANDING OF WHAT DOES THE COMMUNITY OF NEUROSCIENTISTS WORKING WITH STEM CELLS IN CALIFORNIA LOOK LIKE AND WHERE ARE IMPORTANT THERE OPPORTUNITIES AND WHAT DO THESE COMMUNITIES THEMSELVES THINK OF THE BEST WAY TO MAKE PROGRESS ON THESE DISORDERS USING STEM CELL TECHNOLOGY.

SO WITH NO FURTHER ADO, UNLESS SOMEBODY HAS OTHER QUESTIONS OR COMMENTS THAT THEY WANT TO MAKE, IF YOU DO PLEASE RAISE YOUR HAND, AND I DO NOT SEE ANY RAISED HANDS HERE. AND SO -- FRED, YES,

PLEASE.

DR. FISHER: SO, NOW, YOU'VE LAID OUT WHAT IS BASICALLY, INCLUDING THE NEXT MEETING, OR THE FIRST FOUR MEETINGS OF THIS WORK GROUP ESSENTIALLY BEING FOCUSED ON NEUROPSYCHIATRIC OPPORTUNITIES FOR CIRM'S INVESTMENT. I'M WONDERING WHEN WE'RE GOING TO GET TO THE OTHER PRIORITIES BECAUSE TO SPEND THE FIRST FOUR MEETINGS ON NEUROPSYCHIATRIC SORT OF BEGS THE QUESTION: IS THIS NOW THE PRIORITY OF THIS WORK GROUP, OR ARE WE ACTUALLY GOING TO BE LOOKING AT THE ENTIRE LANDSCAPE OF WHAT THOSE NEURO INVESTMENTS ARE OR ARE SUPPOSED TO BE? BECAUSE RIGHT NOW IT SEEMS VERY HEAVILY WEIGHTED IN THE DIRECTION OF NEUROPSYCHIATRIC. AND I'M TRYING TO CONTEXTUALIZE THAT INTO THE BIGGER UNIVERSE OF NEURO ISSUES.

CHAIRMAN GOLDSTEIN: YES. SO, FRED, THAT'S REALLY A GREAT QUESTION. AND THANK YOU FOR BRINGING IT UP. IT'S AN IMPORTANT ISSUE. AND I THINK THE WAY I WOULD LOOK AT IT, AT LEAST, AND I THINK THIS IS THE SENTIMENT OF THE TASK FORCE, IS THAT WE HAVE TO START SOMEWHERE. NEUROPSYCHIATRIC DISORDERS HAVE A TREMENDOUS BURDEN ON BOTH MAJORITY AND MINORITY POPULATIONS IN CALIFORNIA. AND AS TODAY'S PRESENTATION AND THE NEXT AND PROBABLY LAST ONE ON NEUROPSYCHIATRIC IS MY GUESS, ALTHOUGH

ULTIMATELY IT IS UP TO THIS TASK FORCE, THAT THERE IS AN OPPORTUNITY TO MAKE A REAL IMPACT HERE AND THAT WE'VE BEEN SUBSTANTIALLY UNDERREPRESENTED IN THIS AREA.

I THINK FOLLOWING THE DEVELOPMENT OF SOME INITIAL ATTACKS ON NEUROPSYCHIATRIC, WHICH IS WHAT WE ARE DOING NOW, THEN I THINK I AGREE WITH THE ISSUE YOU'RE BRINGING UP, WHICH IS WE HAVE TO LOOK AT SOME OF THE OTHER DISORDERS AND ASK THE QUESTION MORE FORMALLY, IF YOU WILL: ARE WE ADEQUATELY REPRESENTED SCIENTIFICALLY AND MEDICALLY IN THE STUDY OF THESE OTHER DISORDERS AND THE DEVELOPMENT OF THERAPIES OF THESE OTHER DISORDERS? AND WHAT IS THE BEST WAY TO MAKE A SIGNIFICANT IMPACT ON SOME OF THESE OTHER DISORDERS AS PART OF THIS LONG-RANGE PLANNING EFFORT?

SO I THINK THE ANSWER IS STAY TUNED. WE ARE NOT ONLY GOING TO BE LOOKING AT NEUROPSYCHIATRIC DISORDERS. WE ARE TAKING ADVANTAGE OF A UNIQUE AND, I WOULD ARGUE, SOMEWHAT POWERFUL PORTION OF THE LANDSCAPE WHERE I THINK WE ARE, AND IT HAS BEEN THE SENTIMENT OF THE TASK FORCE, THAT WE ARE COLLECTIVELY AWARE THAT WE ARE SUBSTANTIALLY UNDERREPRESENTED IN THIS AREA, THAT IT'S WORTHY OF THE BEGINNING OF AN ATTACK VIA FUNDING, WHICH IS ONE

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OF THE MAJOR METHODS WE USE TO HAVE AN IMPACT ON FIELDS, BUT WE WILL THEN COME BACK TO DISORDERS SUCH AS ALS, YOUR PARTICULAR PRIMARY INTEREST, ALZHEIMER'S DISEASE, PARKINSON'S, AND SOME OF THE OTHER NEURODEGENERATIVES. AND WE'RE GOING TO HAVE TO DEVELOP SOME IDEAS WHERE WE THINK ABOUT HOW DO WE FAIRLY WEIGHT OUR EFFORTS AMONG THESE DIFFERENT DISEASES AND WHERE ARE THERE THE BEST OPPORTUNITIES, AND HAVE WE SATURATED OR NOT OUR EFFORTS IN THESE OTHER DISORDERS?

SO THAT WOULD BE MY ANSWER. IT'S NOT A PERFECT ANSWER, I RECOGNIZE, BUT I THINK IT FAIRLY SUMMARIZES THE VIEWS OF THE GROUP AS WE'VE TALKED ABOUT THESE THINGS, THESE DISORDERS, AND IN PARTICULAR WHAT WE DISCUSSED FOLLOWING THE PORTFOLIO REVIEW BACK AT OUR FIRST MEETING.

STEVE JUELSGAARD.

DR. FISHER: IF WE GO AS DEEPLY INTO ALL OF THE OTHER NEURO OPPORTUNITIES AS WE ARE NOW DELVING INTO THE MENTAL HEALTH SIDE OF THINGS, WE'RE GOING TO BE AT THIS DISCOVERY PROCESS FOR A VERY LONG TIME AND LIKELY WILL NOT HAVE ANY RECOMMENDATIONS REGARDING HOW TO ALLOCATE 1.5 BILLION ACROSS THOSE UNTIL WE HAVE THOROUGHLY VETTED ALL OF THEM. AND AT THIS PACE, THAT COULD TAKE A

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VERY LONG TIME TO DO ALL THE OTHERS JUSTICE.

CHAIRMAN GOLDSTEIN: I'LL DISAGREE WITH THAT POINT, FRED. I MEAN I UNDERSTAND THE SENTIMENT AND WHERE IT'S COMING FROM. YES, WE DON'T WANT TO SPEND THE NEXT SIX YEARS PLANNING. I'M IN COMPLETE AGREEMENT WITH THAT EXTREME VERSION OF THE ARGUMENT.

MY SENSE, HOWEVER, BASED ON THE CONVERSATIONS WE'VE HAD THUS FAR, IS THAT WE AS A GROUP ARE SUBSTANTIALLY UNDERREPRESENTED IN OUR UNDERSTANDING OF NEUROPSYCHIATRIC DISORDERS IN PARTICULAR AND HOW TO TACKLE THEM USING STEM CELL TECHNOLOGY. AND THAT USING STEM CELL TECHNOLOGIES, THERAPIES, GENE THERAPIES, WHAT HAVE YOU, FOR THE VARIOUS NEURODEGENERATIVES, WE ACTUALLY DO AS A GROUP HAVE A MUCH BETTER UNDERSTANDING OF THOSE FROM THE START HERE. AND I THINK WE CAN BRING IN PLANNING EFFORTS IN THOSE AREAS RELATIVELY QUICKLY WITH RESPECT TO HOW QUICKLY OR NOT THAT WE ARE MOVING IN THIS ONE UNDERREPRESENTED AREA.

I'LL JUST POINT OUT THAT IT'S NOT AS THOUGH WE ARE DOING NOTHING ON THESE OTHER AREAS. IN FACT, WE HAVE SIGNIFICANT FUNDING GOING INTO STUDIES OF A VARIETY OF OTHER NEURODEGENERATIVE DISORDERS THAT IS CONTINUING. IT'S COMING IN THROUGH A MORE CONVENTIONAL MECHANISM. AND I THINK

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AT THE MOMENT, AT LEAST, IF ANYTHING, WE ARE TRYING TO GET THE NEUROPSYCHIATRIC DISORDERS CAUGHT UP TO WHERE THE NEURODEGENERATIVES ARE BECAUSE AN UNDERRECOGNIZED SET OF TECHNOLOGIES FOR ATTACKING NEUROPSYCHIATRIC DISORDERS ARE, IN FACT, THE STEM CELL TECHNOLOGIES. WE'LL GET A BITE OF THAT TODAY FROM TOM AND KRISTEN. AND I THINK AT OUR NEXT MEETING OR THE ONE THEREAFTER, WE CAN INTELLIGENTLY AND IN A BETTER INFORMED WAY DISCUSS HOW DO WE WANT TO GO ABOUT PRIORITIZATION RELATIVE TO EACH OTHER OF THESE DIFFERENT DISORDERS.

THE PROBLEM IN AN AGENCY LIKE THIS IS, AS I'M SURE YOU AND OTHERS RECOGNIZE, IS YOU'RE OFTEN LOOKING FOR A BALANCE BETWEEN, IN A SENSE, PICKING AREAS THAT YOU THINK THERE ARE OPPORTUNITIES FOR INVESTMENT. AND THAT NEEDS TO BE BALANCED WITH THE TRADITIONAL GRANTMAKING MECHANISM, WHICH IS ONGOING EVEN AS WE SPEAK FOR MOVING POTENTIAL THERAPIES THROUGH ANIMAL MODELS, DOING ENOUGH BASIC SCIENCE TO DEVELOP NEW IDEAS, AND TO LAUNCH CLINICAL TRIALS. AND THOSE ACTIVITIES ARE ONGOING. AND THE DISCUSSION OF RELATIVE PRIORITIES OF THESE VARIOUS DISORDERS TO EACH OTHER AND TO NEUROPSYCHIATRIC DISORDERS THAT WE ARE DISCUSSING CURRENTLY, THAT KIND OF PRIORITIZATION IS ALWAYS CHALLENGING TO DO.

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AND IN SOME WAYS THE GRANTMAKING MECHANISM DOES PART OF THAT FOR US SIMPLY BASED ON WHAT DO REVIEWERS SEE AS HIGH QUALITY, HIGH LIKELIHOOD OF SUCCESS PROJECTS.

SO I THINK WE'LL GET TO WHERE YOU WANT US TO BE ACROSS THIS SUMMER. WE AGREED AT THE FIRST MEETING NOT TO TRY A MAD RUSH TO TRY TO GET A COMPLETE PLAN WITH ALL OF THE DISORDERS AND ALL OF THE SCIENTIFIC AREAS WE MIGHT WANT TO EMBRACE BY THE JUNE MEETING OF THE ICOC AS BEING UNREALISTIC. AND SO, YES, WE ARE GIVING OURSELVES MORE TIME THAN JUST GOING TO THE JUNE MEETING, WHICH HAD BEEN MY INITIAL HOPE. AND I THINK, UPON THINKING THROUGH WITH THIS GROUP THE MAGNITUDE OF THAT CHALLENGE, WE'RE GOING TO HAVE TO GO A LITTLE BIT SLOWER AND A LITTLE BIT MORE DELIBERATELY. AND I THINK THAT'S WHAT WE ARE DOING.

I DON'T KNOW IF THAT SATISFIES YOU OR NOT, BUT IT'S A PARTIAL ONE.

DR. FISHER: THAT'S FINE. I APPRECIATE THE RESPONSE.

CHAIRMAN GOLDSTEIN: OKAY. GREAT. THANK YOU, FRED. STEVE.

MR. JUELSGAARD: YES. SO FIRST LET ME APOLOGIZE THAT MY IMAGE IS NOT SHOWING UP ON THE

SCREEN. OUR INTERNET WENT OUT THIS MORNING, SO I'M RELYING ON MY IPAD HOT SPOT. SO HOPEFULLY WHAT I'M SAYING WILL COME THROUGH.

SO AN OBSERVATION AND A QUESTION. SO STARTING AT THE GRAND SCALE, THE PURPOSE OF CIRM AND ITS MISSION, IF YOU WILL, IS TO MARRY REGENERATIVE MEDICINE AND GENE THERAPY WITH THE TREATMENT OF UNMET MEDICAL NEEDS. SO NOW DIVING A LITTLE DEEPER INTO THAT, I'LL BE REALLY INTERESTED IN ABLA'S SURVEY OF THE GRANT INSTITUTIONS IN CALIFORNIA AND FIND OUT HOW MANY ARE DEALING WITH THE ISSUE OF NEUROPSYCHIATRIC DISORDERS USING EITHER REGENERATIVE MEDICINE OR GENE THERAPY AS THE TOOLS TO STUDY IT.

I WOULD JUST NOTE, I AM NOT AWARE OF, IT MAY BE THAT THERE ARE SOME, BUT I'M NOT AWARE OF ANYBODY COMING FORWARD WITH GRANT APPLICATIONS THAT DEAL WITH NEUROPSYCHIATRIC DISORDERS USING THOSE TOOLS THAT I JUST DESCRIBED. IT SEEMS TO ME WE'VE HAD A -- AND WE'VE BEEN OPEN-MINDED ABOUT THIS -- WE'VE HAD A DEARTH OF APPLICATIONS SO FAR, WHICH BEGS THE QUESTION OF TO WHAT EXTENT ARE SCIENTISTS IN CALIFORNIA REALLY FOCUSED ON USING THESE TOOLS OF REGENERATIVE MEDICINE, GENE THERAPY TO DEAL WITH NEUROPSYCHIATRIC DISEASE.

MORE PARTICULARLY, SO WE'RE GOING TO HEAR

FROM THOMAS SUDHOF. THOMAS IS AT STANFORD UNIVERSITY, SO HE'S LOCATED IN CALIFORNIA. MY QUESTION OF THOMAS: HAS HE EVER APPLIED FOR A CIRM GRANT FOR ANY OF HIS WORK THAT HE'S DONE BECAUSE HE'S GOING TO BE SPEAKING TO THE ISSUE OF STEM CELL THERAPY AND NEUROPSYCHIATRIC DISORDERS. AND IF HE HAS, WHAT HAVE THOSE RELATED TO? AND IF NOT, WHY NOT?

SO MY CONCERN IS THE FOUNDATION ON WHICH WE ARE TRYING TO BUILD A NEUROPSYCHIATRIC PROGRAM AND HOW SOLID IS THAT FOUNDATION TO BEGIN WITH, OR IS IT REALLY SOMETHING THAT WE HAVE TO CREATE OUT OF WHOLE CLOTH HERE COMING OUT OF THIS GROUP? DONE.

CHAIRMAN GOLDSTEIN: SO, STEVE, I THINK THOSE ARE EXCELLENT QUESTIONS. IN FACT, THOSE ARE THE KINDS OF QUESTIONS WE ARE IN THE PROCESS OF TRYING TO TANGLE WITH. THE SURVEY THAT ROSA IS BUILDING WILL GIVE US A LITTLE BIT MORE INFORMATION ON THE QUESTIONS YOU'VE POSED. TOM, I THINK, WILL ADDRESS THE QUESTIONS YOU'VE JUST RAISED IN HIS PRESENTATION HOPEFULLY. SO WE'LL FIND OUT WHAT THE ANSWER IS.

I'LL JUST NOTE THAT YOU'RE RIGHT. THE CONVENTIONAL GRANTMAKING MECHANISM HAS DONE A PRETTY GOOD JOB OF IDENTIFYING NEURODEGENERATIVE PROJECTS

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AND SOME NEURODEVELOPMENTAL PROJECTS. WHY WE DON'T HAVE AN EXISTING INVESTMENT IN NEUROPSYCHIATRIC, ESPECIALLY GIVEN HOW COMMON THESE DISORDERS ARE, IS NOT SO CLEAR TO ME AS YET. AND I THINK THIS IS SOMETHING THAT WE WILL BE FINDING OUT VIA ROSA'S SURVEY AND HEARING FROM TWO OF THE LEADING USERS OF STEM CELL TECHNOLOGY TO TACKLE NEUROPSYCHIATRIC DISORDERS. I THINK THEY'LL BOTH BE SCHIZOPHRENIA IS MY RECOLLECTION, BUT WE'LL FIND OUT. AND WE'LL TAKE IT FROM THERE.

I DO FIND IT HARD TO BELIEVE THAT IT'S ONLY A QUALITY ISSUE. OUR GRANTMAKING SYSTEM REALLY PUTS QUALITY FIRST AND AREAS OF ENDEAVOR A CLOSE SECOND HAS BEEN MY OBSERVATION OVER THE YEARS, BUT WE'LL DELVE INTO THIS ISSUE MORE DEEPLY AS WE GO.

OKAY. AL, PLEASE.

MR. ROWLETT: I WANTED TO FIRST ACKNOWLEDGE THAT I GOT DROPPED, AND SO I'M GOING TO LEAVE MY CAMERA OFF UNTIL I CAN FIGURE OUT MY INTERNET ISSUES. SO MY APOLOGIES FOR ONLY HEARING MY AUDIO.

I AM A SUPPORTER OF THE NEUROPSYCHIATRIC APPROACH. ONE OF THE REASONS IS THAT OFTENTIMES I HAVE THE UNIQUE PRIVILEGE OF WORKING WITH A LOT OF PEOPLE WHO HAVE BEEN DIAGNOSED WITH DIFFERENT FORMS

OF SCHIZOPHRENIA. AND SELDOM ARE THE APPROACHES FOR TREATMENT LIKE THOSE THAT ARE SPONSORED BY THE AGENCY, REGENERATIVE MEDICINE, OR REALLY LOOKING AT APPROACHES THAT COULD AMELIORATE SOME OF THE ORGANIC CAUSES OF SCHIZOPHRENIA TYPICALLY AREN'T TALKED ABOUT. WHAT IS DISCUSSED IS THERE'S A PLETHORA OF DATA ASSOCIATED WITH THE SOCIAL DETERMINANTS AND OTHER FACTORS THAT INFLUENCE THE TRAJECTORY OR THE COURSE OF THE DISEASE.

THAT INFORMATION COUPLED WITH WHAT CIRM MIGHT BE DOING, I THINK, WOULD RESULT IN SOME WONDERFUL GRANTMAKING OPPORTUNITIES AND ACTUALLY SOME THINGS THAT ARE QUITE INTRIGUING IN THE AREA OF ADVANCING THE INITIATIVES ASSOCIATED WITH THE PATIENT PERSPECTIVE THAT CIRM IS EMBRACING AND ENSURING THAT DIVERSITY, EQUITY, INCLUSION IS INCULCATED INTO ANY RESPONSE THAT WE MIGHT CONSIDER.

THERE'S A LOT OF WORK IN THAT AREA WITH NEUROPSYCHIATRIC DISORDERS BECAUSE THE APPROACH HAS BEEN TYPICALLY SUPPORTING PEOPLE CLINICALLY WITH HOW TO LIVE WITH THE DISEASE AND AMELIORATING SOCIAL DETERMINANTS. SO FOR FEAR OF REPEATING MYSELF AGAIN, I JUST WANT TO SAY, LARRY, I THINK YOU GOT TO START SOMEWHERE. I HEARD SOMEONE SAY A MILE WIDE OR A MILE DEEP, AND WE'RE GOING TO GO A MILE DEEP AND

AN INCH WIDE AND SEE WHAT WE GET. I SUPPORT THE EFFORT.

CHAIRMAN GOLDSTEIN: GREAT. THANK YOU, AL.

I'LL JUST ADD THAT MY READING OF THE LITERATURE SUGGESTS THAT THESE DISORDERS ARE NOT PARTICULARLY RARE. THEY MAY BE MORE COMMON IN UNDERSERVED COMMUNITIES, ALTHOUGH I THINK WE DON'T REALLY KNOW THAT. AND MY GUESS WOULD BE THAT MOST YOUNG SCIENTISTS, WHEN THEY'RE STARTING THEIR CAREERS, HAVE A LOOK AT THE MAGNITUDE OF THIS PROBLEM AND THE COMPLEXITY OF IT AND SWITCH TO OTHER AREAS OF RESEARCH. BUT I DON'T KNOW THAT. THAT IS SPECULATION ON MY PART.

OKAY. ANYBODY ELSE BEFORE WE HEAR FROM KRISTEN?

DR. SUDHOF: ONE THING.

CHAIRMAN GOLDSTEIN: YES, PLEASE.

DR. SUDHOF: I JUST WANT TO REMIND YOU I HAVE A HARD STOP AT 1 O'CLOCK.

CHAIRMAN GOLDSTEIN: OH, RIGHT. SORRY. YES. OKAY. I'LL INVERT THE ORDER. THANK YOU FOR REMINDING ME, TOM. MUCH APPRECIATED.

OKAY. SO, TOM, YOU'RE UP WITH NO FURTHER ADO.

DR. SUDHOF: OKAY. LET ME SHARE MY SCREEN.

SO IT'S REALLY AN HONOR FOR ME TO PRESENT TO YOU HERE TODAY WHY I BELIEVE, AND I HOPE I CAN MAKE THIS CLEAR, THAT CIRM WOULD BE WELL PLACED TO SUPPORT VIA A SOLID GRANTING MECHANISM RESEARCH INTO THE BASIC PROCESSES THAT UNDERLIE NEUROPSYCHIATRIC DISORDERS.

THE QUESTIONS REALLY ARE WHY DO WE NEED STEM CELL BIOLOGY TO STUDY NEUROPSYCHIATRIC DISEASES AND HOW CAN STEM CELL BIOLOGY HELP US UNDERSTAND WHAT IS ARGUABLY A MAJOR CRISIS IN OUR HEALTHCARE SYSTEM? AND I THINK THERE CAN BE NO DOUBT, AS LARRY ALREADY ARTICULATED, THAT NEUROPSYCHIATRIC DISORDERS ARE NOT RARE. AND, FOR EXAMPLE, THE HOUSING CRISIS, THE HOMELESS CRISIS THAT WE HAVE IN CALIFORNIA IS PARTLY, AT LEAST, I BELIEVE, DUE TO THE PROBLEM OF NEUROPSYCHIATRIC DISORDERS. THIS IS A WIDELY DISTRIBUTED, UNFORTUNATELY, QUITE HIGH FREQUENCY SET OF DISEASES.

NOW, NEUROPSYCHIATRIC DISORDERS ARE NEURODEVELOPMENTAL. THAT IS, THE IDEA IS THAT MOST PEOPLE IN THE FIELD FEEL THAT THEY ARE EMERGING FROM SOME KIND OF MISALIGNMENT DURING THE PROCESS OF HOW THE BRAIN IS WIRED DURING DEVELOPMENT. AND,

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THEREFORE, STEM CELL BIOLOGY, WHICH IS IDEALLY SUITED, ESPECIALLY FOR DEVELOPMENTAL QUESTIONS, IS ACTUALLY A VERY GOOD WAY OF APPROACHING THIS, ESPECIALLY SINCE IT CAN BE DONE WITH HUMAN MATERIAL.

AND WHAT I WANT TO DO IS TALK ABOUT SCHIZOPHRENIA AS AN EXAMPLE, BUT MY LAB, AS WELL AS KRISTEN'S AND OBVIOUSLY MANY OTHERS, HAVE ALSO USED STEM CELL BIOLOGY FOR OTHER NEUROPSYCHIATRIC DISORDERS. AND SCHIZOPHRENIA I WANT TO USE AS AN EXAMPLE BECAUSE THE GENETICS OF SCHIZOPHRENIA ARE SO WELL UNDERSTOOD.

WHAT YOU SEE HERE IS TAKEN FROM A PAPER FROM ONE OF THE LEADING LABS AT THE BROAD ON THE GENETICS OF SCHIZOPHRENIA. AND YOU CAN SEE HERE THE PLOT OF THE FREQUENCY WITH WHICH A CERTAIN POLYMORPHISM GENETIC CHANGE HAPPENS IN THE GENERAL POPULATION VERSUS THE CHANCE, THE ODDS RATIO OF GETTING SCHIZOPHRENIA. YOU CAN SEE THAT THOSE POLYMORPHISMS THAT HAVE A VERY LOW IMPACT ARE SHOWN ON THE RIGHT. THEY ARE MUCH MORE FREQUENT OBVIOUSLY. AND THEN YOU CAN ALSO SEE THAT ON THE LEFT THERE'S THESE HIGH IMPACT GENE MUTATIONS GENERALLY THAT ARE EXTREMELY RARE.

THE PROBLEM IS THAT WE HAVE HAD ENORMOUS PROGRESS IN HUMAN GENETICS, BUT ALMOST NONE IN

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MECHANISTIC SCIENCE. IN OTHER WORDS, WE DON'T ACTUALLY KNOW HOW THESE GENETIC CHANGES PREDISPOSE TO NEUROPSYCHIATRIC DISORDERS SUCH AS SCHIZOPHRENIA. AND A SIMILAR PICTURE EMERGES FOR AUTISM. THE REASON WHY, AND WE CAN TALK ABOUT THIS AT THE END, WHY THERE HAS BEEN SO LITTLE PROGRESS IN THERAPEUTICS AND PRESUMABLY WHY THERE ARE FEW GRANT APPLICATIONS TO CIRM OR OTHERS THAT ARE DIRECTLY TRANSLATIONAL IS THAT WE HAVE FANTASTIC GENETICS, BUT THE GENETICS DOESN'T ACTUALLY TELL US HOW IT WORKS. IT ONLY TELLS US THAT THERE'S A GENETIC PREDISPOSITION.

SO INSTEAD OF GOING THROUGH ALL THESE GENES AND TALKING ABOUT WHAT WE AND OTHERS HAVE DONE ON THEM, I THOUGHT THAT MY BEST SERVICE TO THE COMMITTEE WOULD BE TO EXPLAIN TO YOU ABOUT HOW OUR LAB HAS WORKED ON ONE PARTICULAR GENE, A GENE CALLED NRXN1, THAT IS NOW HIGHLIGHTED HERE WITH THE CIRCLE, AND THAT IS CRUCIALLY INVOLVED IN SCHIZOPHRENIA BECAUSE TO THIS POINT IT IS STILL THE ONE GENE THAT PROVIDES THIS AS A SINGLE GENE MUTATION PROVIDES THE MOST FREQUENT PREDISPOSITION TO SCHIZOPHRENIA.

YOU CAN ALSO SEE THAT IT HAS QUITE A HIGH ODDS RATIO, MEANING IT HAS A VERY LARGE EFFECT SIZE. IT'S NOT A SMALL EFFECT SIZE.

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AND SO WHAT I'M GOING TO DO TODAY IS TRY TO ILLUSTRATE FOR YOU WITH THIS STUDY HOW WE CAN ACTUALLY GET CLOSER TO MECHANISMS ALTHOUGH I HAVE TO TELL YOU WE DON'T YET UNDERSTAND EXACTLY. WE ARE NOT THERE YET AND WILL TAKE EVEN MORE BASIC STUDIES. BASIC STUDIES ARE, THIS IS MY MESSAGE, THE CRUCIAL REQUIREMENT AT THIS POINT IN UNDERSTANDING NEUROPSYCHIATRIC DISEASES IN ORDER TO MAKE PROGRESS TOWARDS THERAPEUTICS.

SO NRXN1 IS A GENE THAT BELONGS TO A FAMILY CALLED NEUREXINS. AND WHAT YOU SEE HERE VERY SCHEMATICALLY IS WHAT THESE PROTEINS LOOK LIKE. THEY'RE CELL SURFACE PROTEINS. THEY HAVE MULTIPLE DOMAINS THAT ARE NOT VERY RELEVANT AS SHOWN HERE CALLED L AND E. AND THEY BIND ACROSS THE SYNAPSE, WHICH IS SCHEMATICALLY ILLUSTRATED HERE AS LEFT AND RIGHT, ON THE POSTSYNAPTIC SIDE TO A NUMBER OF LIGANDS. SO THEY HAVE LOTS OF DIFFERENT FUNCTIONS BY BINDING LOTS TO LOTS OF DIFFERENT PROTEINS.

THERE ARE THREE GENES THAT HAVE INDEPENDENT PROMOTERS BECAUSE THE NEUREXINS COME IN TWO FLAVORS, ALPHA, LONGER, BIGGER PIECES THAT ARE SHORTER. THEY HAVE, AS I ALREADY MENTIONED, DIVERSE TRANS-SYNAPTIC LIGANDS AND EXTENSIVE ALTERNATIVE SPLICING. AND HERE'S WHY WE ARE TALKING ABOUT THIS.

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THERE'S THOUSANDS OF GENE MUTATIONS IN NEUREXINS, NOT ONLY NRXN1, BUT BY FAR THE MOST FREQUENTLY, NRXN1, THAT PREDISPOSE TO MULTIPLE NEUROPSYCHIATRIC DISORDERS. SO WHAT I'M GOING TO TELL YOU ABOUT TODAY IS ACTUALLY NOT ONLY ABOUT SCHIZOPHRENIA. IT'S ABOUT NEUROPSYCHIATRIC DISORDERS IN GENERAL.

WHAT YOU SEE HERE IS A SLIDE TAKEN FROM A PAPER BY COSEMANS, ET AL. WHERE THEY HAVE MAPPED THE DELETIONS IN THE NRXN1 GENE AND COMPARED THEM WHETHER OR NOT THEY HAVE A SPECIFIC PHENOTYPE IN TERMS OF THE CLINICAL PRESENTATION OR NOT. AND IN BLACK YOU SEE THOSE THAT DO CAUSE OF CLINICAL PHENOTYPE, IN GREEN THOSE THAT DON'T. THE POINT OF THIS SLIDE IS NOT TO LET YOU KNOW ABOUT THE DETAILS OF THESE MUTATIONS. THAT'S IRRELEVANT. THE POINT OF THE SLIDE IS THAT THESE MUTATIONS, INDEPENDENT OF WHERE THEY ARE, ARE ASSOCIATED WITH A DIVERSE SET OF CLINICAL PRESENTATIONS, AUTISM, SCHIZOPHRENIA, TOURETTE, INTELLECTUAL DISABILITY. THOUSANDS OF CASES, ENORMOUS DIVERSITY.

AND SO THE CHALLENGE HERE, AND THE SAME ACTUALLY APPLIES FOR OTHER GENE MUTATIONS, IS NOT THAT WE HAVE THE GENE MUTATIONS. THE CHALLENGE IS TO UNDERSTAND WHY THE SAME MUTATIONS ARE SO HIGHLY PREDISPOSING TO DIFFERENT NEUROPSYCHIATRIC DISEASES.

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AND JUST TO ILLUSTRATE THIS POINT EVEN FURTHER, AGAIN FROM THE SAME PAPER ON THIS CLINICAL PRESENTATION OF THE PATIENTS, WHAT IT MAPS IS THE FREQUENCY OF DELETERIOUS VERSUS NON-DELETERIOUS MUTATIONS SHOWN ON TOP. AND THE BOTTOM EXHIBITS THE TYPES OF PRESENTATIONS THAT ARE OBSERVED IN PATIENTS WITH THESE DELETIONS IN THE NRXN1 GENE. AND YOU CAN SEE THERE'S A WHOLE GAMUT OF PRESENTATIONS THAT SHIFT SLIGHTLY DEPENDING ON WHERE THE DELETIONS ARE IN THIS HUGE GENE.

BUT THE POINT HERE IS THAT IN THE MAJORITY OF THE CASES, IT'S A PSYCHIATRIC DISORDER THAT IS THE MANIFEST OF THIS PARTICULAR MUTATION, RESULTING IN A SEVERE IMPAIRMENT IN HOW THESE PATIENTS CAN DEAL WITH EVERYDAY LIFE. AND THIS IS SORT OF AN EXAMPLE, I THINK IN MANY WAYS A PARADIGM OF HOW NEUROPSYCHIATRIC DISORDERS ARE CURRENTLY VIEWED IN THE FIELD.

MOST OF THESE MUTATIONS ARE ACTUALLY INHERITED BECAUSE THEY ONLY PARTIALLY MANIFEST, BUT A SIGNIFICANT PART IS ALSO DE NOVO AS SHOWN HERE AT THE BOTTOM. SO THIS IMPACT OF THESE NEUREXIN DELETIONS IS HUGE. AND AS I ALREADY MENTIONED, THE NEUREXIN DELETIONS ARE THE MOST PREVALENT SINGLE-GENE MUTATIONS PREDISPOSING TO SCHIZOPHRENIA

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AND AMONG THE MOST PREVALENT PREDISPOSING TO TOURETTE AND TO AUTISM.

AND SO WHAT I'M GOING TO TELL YOU NEXT IS HOW WE APPROACHED AN UNDERSTANDING OF WHY THESE MUTATIONS MIGHT BE PREDISPOSING TO NEUROPSYCHIATRIC DISORDERS USING STEM CELL BIOLOGY. AND I'M GOING TO TRY TO LEAD YOU THROUGH SOME OF THE STUDIES VERY BRIEFLY AND VERY SCHEMATICALLY TO TRY TO GIVE YOU A FLAVOR FOR WHAT NEEDS TO BE DONE, AT LEAST IN OUR VIEW, IN ORDER TO UNDERSTAND HOW THIS CAN POTENTIALLY BE ANALYZED.

SO AS A STARTING POINT, SOME YEARS AGO, ABOUT TEN YEARS AGO, WE DEVELOPED A METHOD OF RAPIDLY GENERATING HUMAN NEURONS FROM STEM CELLS, AND WE USED THIS METHOD TO ANALYZE NRXN1 MUTATIONS.

NOW, THIS METHOD, I BELIEVE, IS NOW WIDELY USED BY MANY DIFFERENT LABS. AND MAYBE KRISTEN WILL ALSO TALK ABOUT IT. AND THE METHOD DEPENDS ON TRANSDUCING STEM CELLS, IPS CELLS, ES CELLS, ANY KIND OF STEM CELL, WITH VIRUSES THAT EXPRESS A TRANSCRIPTION FACTOR. AND BY EXPRESSING THE SINGLE TRANSCRIPTION FACTOR NGN2, WE CAN MAKE THESE STEM CELLS BECOME NEURONS WITHIN WEEKS. AND THESE NEURONS ARE TRUE NEURONS. THEY DON'T ONLY LOOK LIKE NEURONS, BUT THEY ACTUALLY FORM SYNAPSES. AND THIS

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IS ILLUSTRATED DOWN HERE WHERE YOU CAN SEE THAT EVEN AFTER TWO WEEKS AND CERTAINLY AFTER THREE WEEKS THERE'S ROBUST SYNAPTIC RESPONSES. AND AS THESE NEURONS MATURE IN THE DISH WHERE THEY CAN BE KEPT FOR MONTHS AND EVEN YEARS, THESE SYNAPTIC RESPONSES BECOME BIGGER AND BIGGER AND BIGGER. SO THEY CONTINUE TO MATURE AS A FUNCTION OF TIME. AND BECAUSE THESE SYNAPTIC RESPONSES RESEMBLE THOSE THAT ARE OBSERVED IN AN ADULT, THESE SYNAPTIC RESPONSES AND THE SYNAPSES CAN BE USED TO ANALYZE DISEASE PROCESSES.

SO USING THIS SYSTEM, WE ENGINEERED CONDITIONAL NRXN1 MUTATIONS INTO STEM CELLS. AND WE USED CONDITIONAL MUTATIONS BECAUSE WE WANTED TO HAVE A SITUATION WHERE WE COULD ANALYZE THE MUTATION INDEPENDENT OF THE GENETIC BACKGROUND. SO THE GENETIC BACKGROUND WOULD ALWAYS BE THE SAME FOR BOTH THE TEST AND THE CONTROL, THE MUTANT AND THE WILD TYPE. THEN WE ANALYZED GENETICALLY IDENTICAL WILD TYPE AND MUTANT HUMAN NEURONS.

WHAT YOU SEE HERE ON TOP IS A PICTURE OF WHAT THESE NEURONS LOOK LIKE. THEY LOOK LIKE ANY KIND OF NEURON. IT DOESN'T MATTER IF THEY HAVE A HETEROZYGOUS NRXN1 LOSS-OF-FUNCTION OR NOT. BUT AS EXPECTED, THEY EXPRESS LESS NRXN1 BECAUSE THEY HAVE

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A HETEROZYGOUS DELETION.

AND THEN WE ASKED, WELL, WHAT DOES THIS DO TO NEURONAL DEVELOPMENT AND SYNAPSE NUMBERS? AND IT DOESN'T DO ANYTHING TO EITHER. AND WE ASKED WHETHER THERE ARE ANY FUNCTIONAL EFFECTS SINCE THERE'S NO EFFECT ON THE ACTUAL MORPHOLOGY ON THE ABILITY OF THESE NEURONS TO FORM SYNAPSES IN THE FIRST PLACE. AND WE OBSERVED A VERY ROBUST IMPAIRMENT IN SYNAPTIC TRANSMISSION THAT IS ILLUSTRATED HERE. IN OTHER WORDS, THESE NEURONS, THEY MAKE SYNAPSES WHICH LOOK PERFECTLY NORMAL WHEN YOU LOOK AT THEM IN A MICROSCOPE, EM OR LIGHT; BUT WHEN YOU MEASURE THEIR FUNCTION, THEIR FUNCTION IS IMPAIRED. THEY HAVE A DISCRETE PHENOTYPE, THEY FLEX, DECREASE IN RELEASE PROBABILITY, SO PRESYNAPTIC FUNCTION, THE WAY HOW A PRESYNAPTIC NEURON SENDS OUT A SIGNAL DURING SYNAPTIC TRANSMISSION TO THE POST-SYNAPTIC SIDE. AND THIS PARTICULARLY DISCRETE PHENOTYPE IS ROBUSTLY OBSERVED.

WE WONDERED WHAT THE MOLECULAR CORRELATE, AND THIS IS WHERE WE DON'T REALLY KNOW HOW THIS PRESYNAPTIC DECREASE HAPPENS, HOW THIS IMPAIRMENT HAPPENS, BUT WE FOUND AS A MAJOR SIGNATURE THAT THERE WAS ONE PARTICULAR PROTEIN THAT WAS CHANGED IN LEVELS AND, IN FACT, INCREASED A PROTEIN CALLED

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CASK. I WON'T DISCUSS THIS ANY FURTHER. IT MAKES SENSE THOUGH BECAUSE WE KNOW THAT THIS PROTEIN ACTUALLY BINDS TO NEUREXINS.

SO THE ROBUST AND SELECTIVE FUNCTIONAL IMPAIRMENT OF HETEROZYGOUS NRXN1-MUTANT NEURONS WERE UNEXPECTED. WE DIDN'T EXPECT THAT SUCH A HETEROZYGOUS DELETION WOULD CAUSE A MAJOR CHANGE. AND WE WONDERED WOULD THIS ALSO BE OBSERVED IN PATIENT-DERIVED NEURONS? IS THIS SOMETHING THAT IS ONLY OBSERVED IN A RATHER ARTIFICIAL OR THE WELL-CONTROLLED CONDITIONAL MUTATION, OR CAN THIS ALSO BE OBSERVED IN A MORE TRANSLATIONAL RELEVANT PATIENT DIRECT NEURON SITUATION?

AND SO WE INITIATED A LARGE-SCALE VALIDATION PROJECT THAT TESTED THE POTENTIAL TRANSLATABILITY OF WHAT WE HAD OBSERVED. AND THIS WAS SPONSORED BY NIMH BECAUSE NIMH WAS VERY CONCERNED ABOUT REPRODUCIBILITY AND ABOUT THE ROBUSTNESS OF MANY NEUROPSYCHIATRIC-ASSOCIATED PHENOTYPES THAT HAVE BEEN REPORTED IN THE LITERATURE OVER THE YEARS.

SO THE PROJECT THAT WE INITIATED IS ILLUSTRATED HERE SCHEMATICALLY. WE GENERATED, IN COLLABORATION WITH NIMH, IPS CELLS FROM PATIENTS AND MATCHED CONTROLS. AND THIS IS FROM SCHIZOPHRENIA

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PATIENTS. AND WE ANALYZED THREE PAIRS, NOT A LARGE SAMPLE. BUT BECAUSE OF THE DEPTH OF ANALYSIS, WHICH REQUIRES A HUGE AMOUNT OF INVESTMENT OF LABOR, THREE PAIRS WAS ALL WE COULD DO WITH THE AVAILABLE FUNDING.

WE THEN USED THESE HUMAN IPS CELLS AND WE DISTRIBUTED THEM INTO TWO SITES IN THE COUNTRY, STANFORD AND RUTGERS. AND THERE THESE IPS CELLS WERE INDEPENDENTLY TRANSFORMED INTO NEURONS USING OUR NGN2 METHOD AND THEN ANALYZED FUNCTIONALLY AND THE RESULTS WERE COMPARED. I'M NOT GOING TO TELL YOU IN DETAIL WHAT WE FOUND. SUFFICE IT TO SAY THAT WE FOUND IDENTICAL PHENOTYPES IN RUTGERS AND STANFORD DESPITE THE FACT THAT THEY WERE SEPARATELY ANALYZED. AND THIS PHENOTYPE IS SUMMARIZED HERE, WHICH IS A SELECTIVE LOSS OF SYNAPTIC STRENGTH INDEPENDENT, WITHOUT ANY CHANGE IN THE MORPHOLOGY, WITHOUT CHANGE IN SYNAPSE NUMBERS OF MAKING SYNAPSES. ONLY THE STRENGTH OF THE SYNAPSE, OF THESE EXCITATORY SYNAPSES, IN THESE HUMAN NEURONS WAS IMPAIRED IN PATIENT-DERIVED NEURONS COMPARED TO MATCHED OBVIOUSLY NONIDENTICAL CONTROLS.

AND THIS IS SHOWN HERE FOR THE THREE PAIRS IN THREE DIFFERENT COLORS TO ILLUSTRATE TO YOU THAT IN EACH CASE THE DECREASE IN SYNAPTIC STRENGTH WAS

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VERY, VERY SIMILAR, ACTUALLY AMAZINGLY SIMILAR. AND WE ALSO OBSERVED AN INCREASE IN WHAT'S CALLED THE C.V. IT DOESN'T REALLY MATTER WHAT THAT MEANS. SUFFICE IT TO SAY THAT IT'S A REFLECTION OF THE RELEASE PROBABILITY, SORT OF TELLS YOU OF HOW WELL THE PRESYNAPTIC NEURON IS ABLE TO SEND OUT A SIGNAL.

SO THIS LARGE DECREASE IN RELEASE PROBABILITY CAUSES A MAJOR LOSS OF SYNAPTIC STRENGTH, AND THIS WAS REPLICATED, SUGGESTING THAT THIS PROVIDES A SUBSTRATE FOR UNDERSTANDING WHY THIS MUTATION IS NOT GOOD FOR PEOPLE, WHY IT PREDISPOSES IN A SUBSET OF PEOPLE, ACTUALLY IN THE MAJORITY, TO SOME NEUROPSYCHIATRIC DISORDER. AND THESE MUTATIONS IN THESE PAIRS WAS ALSO ASSOCIATED WITH THE CASK INCREASE THAT I OBSERVED ALREADY, TOLD YOU ABOUT IN THE ENGINEERED NEURONS WHERE WE OBSERVED AN INCREASE IN THE PROTEIN CALLED KYAT3. AND KYAT3 IS THE KYNURENINE AMINOTRANSFERASE 3 THAT SYNTHESIZES KYNURENIC ACID, WHICH IS A GLUTAMATE RECEPTOR ANTAGONIST. SO IT FITS INTO THE GENERAL THEME OF HAVING SYNAPTIC TRANSMISSION ABNORMALITY.

SO WE WONDERED ARE THESE CHANGES IN PROTEIN LEVELS AND SYNAPTIC STRENGTH DUE TO A TRANSCRIPTIONAL CHANGE IN RESPONSE TO THE NRXN1 DELETION? AND WE ASKED THIS BECAUSE NOWADAYS IT'S

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REALLY COMMON TO DO RNASEQ EXPERIMENTS. IT'S EASY. IT PROVIDES HUGE AMOUNTS OF DATA QUICKLY. SO EVERYBODY DOES IT. AND MOST OF THE CASES PEOPLE FIND SOMETHING THAT'S DIFFERENT, AND WE ALSO FOUND SOMETHING THAT'S DIFFERENT. BUT THE MAJOR DIFFERENCE WE FOUND IS SHOWN HERE IN THIS HEAT MAP IS BETWEEN THE IPS AN ES CELLS AND THE NEURONS. THERE THE DIFFERENCE WAS BASICALLY RED AND BLUE AS YOU CAN SEE HERE AT THESE TWO HIGHLIGHTED AREAS. WHEREAS, WHEN WE COMPARED EITHER PATIENT-DERIVED NEURONS WITH CONTROL NEURONS OR ENGINEERED TEST NEURONS WITH ENGINEERED CONTROL NEURONS, WE FOUND VERY, VERY LITTLE DIFFERENCES. THE DIFFERENCES WERE STATISTICALLY SIGNIFICANT, BUT THAT IS ONLY BECAUSE IN TRANSCRIPTOMICS EVERYTHING IS STATISTICALLY SIGNIFICANT.

IT'S ACTUALLY THE CASE THAT THERE IS MORE DIFFERENCE, AS SHOWN HERE, IN THE PRINCIPAL COMPONENT ANALYSIS BETWEEN THE PARENTAL IPS CELLS AND THE NEURONS WHERE THE DIFFERENCES ARE HUGE. THEN THERE IS BETWEEN THE NEURONS FROM WILD TYPE OF CONTROLLED PATIENTS AND FROM PATIENTS, FROM CONTROL INDIVIDUALS, SORRY, AND PATIENTS, AND ALSO WE OBSERVED VERY LITTLE DIFFERENCE BETWEEN THE CONTROL NEURONS AND TEST NEURONS WITH THE ENGINEERED

MUTATIONS.

SO THE CONCLUSIONS FROM THE RNASEQ EXPERIMENTS IN OUR CASE ARE THAT THE ABNORMALITIES THAT WE OBSERVE IN SYNAPTIC STRENGTH ARE NOT DUE TO GENE EXPRESSION CHANGES. THEY'RE DUE TO CHANGES OF HOW NRXN1 BASICALLY ORGANIZES SYNAPSES. NRXN1 MUTATION HAS A MINIMAL IMPACT ON GENE EXPRESSION. IT BASICALLY ACTS AT THE SYNAPSE AS WE HAVE SHOWN IN OTHER STUDIES THAT I DON'T HAVE TIME TO DISCUSS IN ORDER TO ENABLE A SYNAPSE TO FUNCTION PROPERLY. AND YOU CAN IMAGINE THAT IF YOU HAVE A WHOLE BRAIN WHERE THE SYNAPSES, MOST OF THE SYNAPSES, HAVE A DEFICIENCY IN SOME KIND OF SYNAPTIC TRANSMISSION, THAT THIS DOES HAVE OVERALL CONSEQUENCES FOR NEURAL CIRCUITS.

FINALLY, I WANT TO BRIEFLY DISCUSS THE NEED TO ACTUALLY DO SUCH EXPERIMENTS IN HUMAN NEURON CELLS DERIVED FROM STEM CELLS BECAUSE I THINK THAT, ALTHOUGH MOUSE MODELS ARE TERRIFIC, WE NEED THEM, THEY'RE ESSENTIAL FOR REALLY SCIENCE TRANSLATION, FOR EVERYTHING. IN THE END WE HAVE TO UNDERSTAND WHAT HAPPENS IN HUMAN NEURONS AT THE MOST BASIC LEVEL WHICH WILL ALLOW US TO IDENTIFY POTENTIAL THERAPEUTIC TARGETS, DEVELOP DRUGS, SCREEN FOR DRUGS, AND EVENTUALLY GO INTO CLINICAL TRIALS.

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AND THIS, WHAT I WANT TO TELL YOU ABOUT HERE NOW IS A DIRECT COMPARISON OF HUMAN VERSUS MOUSE NEURONS. SO WHEN WE GOT THE RESULTS THAT I TALKED TO YOU UP TO NOW, WE WONDERED WHY IS IT THAT WE DID NOT OBSERVE A COMPARABLE RESULT WITH HETEROZYGOUS MUTATIONS THAT WE PREVIOUSLY ANALYZED IN MOUSE NEURONS? AND THE POTENTIAL REASON COULD HAVE BEEN THAT WE NEVER REALLY COMPARED THE SAME PREPARATIONS, THE SAME APPROACHES. IN THE MOUSE NEURONS YOU ALWAYS USED NEURONS THAT WERE ACTUALLY GENERATED BY THE MICE AS THEY WERE DEVELOPING AS A REAL ORGANISM. WHEREAS, IN THE CASE OF THE HUMAN NEURONS, WE WERE MAKING THE HUMAN NEURONS --

(INTERRUPTION.)

I'M ALMOST DONE. SO WHAT WE DID IN THESE STUDIES IS WE MADE MOUSE AND HUMAN IPS CELLS THAT WERE ES CELLS AND IPS CELLS THAT WERE EXACTLY IDENTICAL, WITH THE IDENTICAL MUTATIONS, HETEROZYGOUS MUTATIONS. EVERYTHING WAS EXACTLY THE SAME. AND THEN WE ANALYZED THEM IN PARALLEL. AND THIS ALLOWED US TO ACTUALLY COMPARE EXACTLY THE SAME SITUATIONS AND TO TEST RIGOROUSLY WHERE THE MOUSE MODELS ARE ULTRALY RELIABLE OR PARTIALLY RELIABLE. AND WHAT WE FOUND, AS SHOWN HERE IN THIS VERY BUSY SLIDE, SO I'M NOT GOING TO GO THROUGH THIS, JUST

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FOCUS ON THE TOP, A AND D, IS THAT THE MOUSE NEURONS DO NOT HAVE THE PHENOTYPE THAT THE HUMAN NEURONS HAVE WHERE THERE IS A DECREASE IN SYNAPTIC ACTIVITY CALLED MEPSC FREQUENCY; WHEREAS, IN THE MOUSE NEURONS THAT ISN'T OBSERVED. AND MAYBE NOT SURPRISINGLY, MICE AND HUMANS ARE THUS DIFFERENT.

SO THEN WHAT I'VE TRIED TO TELL YOU HERE WITH THIS PART IS THAT HETEROZYGOUS HUMAN, BUT NOT MOUSE NRXN1-MUTANT NEURONS EXHIBIT A ROBUST SYNAPTIC IMPAIRMENT THAT COULD SERVE AS THE BASIS FOR MECHANISTIC AND TRANSLATIONAL STUDIES WHICH ARE HOPEFULLY GOING TO BE IDENTIFYING TARGETS THAT WE CAN USE TO MORE SPECIFICALLY TREAT PATIENTS THAN THE CURRENTLY AVAILABLE MEDICATIONS, WHICH ARE NOT SUFFICIENT, WHICH ARE REALLY NOT WORKING WELL.

AND THE BIGGER PICTURE HERE IS THAT MECHANISTIC STUDIES ON A DISEASE PROCESS ARE ESSENTIAL FOR IDENTIFYING DRUG TARGETS AND DEVELOPING THERAPIES. THE REASON, MAYBE ONE OF THE REASONS WHY CIRM HASN'T GOTTEN APPLICATIONS IN THIS AREA IS THAT, IN MY VIEW AT LEAST, WE ARE AT THE BEGINNING OF AN UNDERSTANDING OF HOW NEUROPSYCHIATRIC DISEASE ACTUALLY OCCURS. AND I THINK THE SAME IS ACTUALLY TRUE FOR NEURODEGENERATIVE DISEASES, BUT THAT'S A DIFFERENT

SUBJECT. WE KNOW THE GENES, BUT WE DON'T KNOW HOW THE GENES ACTUALLY OPERATE IN THE DISEASE AND, IN FACT, IN THE NORMAL. WE NEED STEM CELL BIOLOGY TO BASICALLY DECONSTRUCT WHY CHANGES IN THESE GENES PREDISPOSE, AND THEY ALWAYS PREDISPOSE, TO NEUROPSYCHIATRIC DISORDERS, AND THEN WE CAN MOVE FORWARD TOWARD STUDIES WHERE WE DEVELOP DRUGS AND WHERE WE TRY TO PUT THESE DRUGS INTO PEOPLE.

LET ME TELL YOU I AM EXTREMELY INTERESTED IN DEVELOPING DRUGS. I WORK WITH MULTIPLE COMPANIES IN THIS ENDEAVOR, AND I KNOW FROM MY EFFORTS WITH THESE COMPANIES HOW DIFFICULT IT IS TO DEVELOP DRUGS WHEN YOU DON'T ACTUALLY UNDERSTAND THE DISEASE. AND THIS IS REALLY WHAT WE WANT TO DO IN APPROACHING THESE QUESTIONS USING HUMAN STEM CELL BIOLOGY. HAPPY TO TAKE ANY QUESTIONS YOU MIGHT HAVE.

CHAIRMAN GOLDSTEIN: TOM, THANK YOU VERY MUCH. LOVELY PIECE OF WORK, JUST EXTRAORDINARILY IMPRESSIVE.

SO LET ME JUST ASK A SIMPLE QUESTION TO START, WHICH IS WHAT FRACTION OF SCHIZOPHRENIA DO YOU THINK IS ACCOUNTED FOR BY NEUREXIN MUTATIONS OR PERHAPS PROTEINS THAT ARE INVOLVED IN WHAT YOU MIGHT CALL THE NEUREXIN PATHWAY; THAT IS, WHAT THIS MOLECULE IS ACTUALLY DOING AT THE SYNAPSE?

DR. SUDHOF: THE ACTUAL MUTATIONS ARE VERY RARE. SO THERE'S THOUSANDS OF PATIENTS, BUT THERE'S MILLIONS AND MILLIONS OF SCHIZOPHRENICS. AND SO IT IS SUCH A DEVASTATING, PREVALENT DISEASE. IT IS TRULY -- I DON'T KNOW -- I WAS ACTUALLY TRAINED AS AN M.D. ORIGINALLY. IT IS ONE OF THE MOST DEVASTATING DISEASES YOU CAN HAVE AS A HUMAN. IT IS HORRIBLE FOR THE PEOPLE. AND THE SUICIDE RATE AMONGST SCHIZOPHRENICS IS HIGHER THAN AMONG DEPRESSION. IT IS VERY, VERY, VERY -- YEAH.

BUT HAVING SAID THAT, EVERYBODY IN THAT FIELD, IN SCHIZOPHRENIA FIELD, IS NOW FOCUSING ON NMDA RECEPTORS AS A KEY POINT. AND, IN FACT, EVEN RARE MUTATIONS HAPPEN IN NMDA RECEPTORS. IN OTHER WORK THAT WAS ACTUALLY DONE IN MICE, BUT WHICH WE HOPE TO EXTEND TO HUMAN STEM CELLS, WE HAVE SHOWN THAT NRXN1 IS A REGULATOR OF NMDA RECEPTORS. OKAY.

AND SO WE THINK THAT THIS WHOLE PATHWAY IS ONE PATHWAY IN SCHIZOPHRENIA THAT GOES FROM PRESYNAPTIC SITES, CASK, OR NEUREXINS, OR NMDA RECEPTORS ALL THE WAY, KYNURENIC ACID, BUT THIS IS ONE BIG, HUGE PATHWAY WHICH CAN BE HIT INDEPENDENTLY BY DIFFERENT GENE MUTATIONS OR IN SPORADIC CASES BY SOME NEURODEVELOPMENTAL ACCIDENT THAT MAY HAVE HAPPENED FOR WHATEVER REASON THAT WE DON'T

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UNDERSTAND THAT PREDISPOSES PATIENTS TO DEVELOP THE DISEASE.

AND SO MY SPECULATION, AND THIS IS PURE SPECULATION, THIS IS NOT SCIENTIFIC, THIS IS BASED ON THE FACT THAT NMDA RECEPTORS ARE THE KEY CENTRAL POINT OF SCHIZOPHRENIA CLINICALLY -- KETAMINE, FOR EXAMPLE, IS AN EXAMPLE -- IS THAT THIS PATHWAY IS LIKELY GOING TO BE INVOLVED BROADLY IN SCHIZOPHRENIC PATIENTS FAR BEYOND THE NUMBERS THAT CARRY THE ACTUAL NRXN1 MUTATIONS.

CHAIRMAN GOLDSTEIN: BOY. ABSOLUTELY REMARKABLE. LET'S SEE. QUESTIONS FROM OTHER MEMBERS OF THE GROUP PLEASE. PAT.

DR. LEVITT: HI, TOM.

DR. SUDHOF: HI, PAT.

DR. LEVITT: HOW ARE YOU? GOOD.

SO YOU MENTIONED AT THE BEGINNING, WHICH I THINK IS REALLY AN IMPORTANT ISSUE TO ADDRESS, IS THAT, AND THIS IS A POSTER CHILD FOR THE COMPLEXITY IN WHICH YOU HAVE MUTATIONS IN THE SAME GENE, AND YET THE PHENOTYPES CAN VARY QUITE A BIT. AND YOU SHOWED THAT GRAPHIC THAT INCLUDED INTELLECTUAL DISABILITY, AUTISM, SCHIZOPHRENIA, AND OTHER. SO I'M WONDERING WHAT YOUR THOUGHTS ARE ABOUT HOW THIS MIGHT WORK. YOU HAVE THESE FUNDAMENTAL CHANGES IN

EXCITATORY NEUROTRANSMISSION, PRESUMABLY IN SPECIFIC CIRCUITS AND SPECIFIC NEURAL SUBTYPES. AND MAYBE YOU THOUGHT MORE ABOUT WHY YOU WOULD GET THIS ARRAY OF THE PHENOTYPES THAT WOULD BE EXPRESSED DIFFERENTLY FROM ONE INDIVIDUAL TO THE NEXT.

DR. SUDHOF: IT'S A GREAT QUESTION, SOMETHING THAT WE HAVE GRAPPLED WITH, I THINK THE PERSON HAS GRAPPLED WITH AS WELL. MY PERSONAL HYPOTHESIS IS THAT WE CAN LEARN A LOT FROM CANCER. IN CANCER YOU HAVE A COMBINATION OF GENETIC PREDISPOSITION WITH ACCIDENTS, AND THEY HAPPEN STOCHASTICALLY. IN SCHIZOPHRENIA, I THINK IN NEURODEVELOPMENTAL DISORDERS, THERE'S MANY, MANY SPORADIC CASES. THEY HAVE VERY FEW PREDISPOSING GENETIC FACTORS. GENETICS ONLY PROVIDES ONE PIECE. WHEN AN ORGANISM DEVELOPS, THERE'S ALL KINDS OF THINGS THAT CAN GO WRONG DURING DEVELOPMENT. THERE ARE SO MANY POINTS OF DECISIONS WHERE THINGS CAN GO WRONG.

I THINK ANY ACCIDENT, IF YOU WANT TO CALL IT THAT, ANYTHING WHERE SOMETHING HAPPENS DURING DEVELOPMENT WHERE THIS PATHWAY IS AFFECTED WILL PREDISPOSE TO SCHIZOPHRENIA. SO I DON'T THINK THAT GENETICS ALONE WILL EXPLAIN NEUROPSYCHIATRIC DISORDERS. I THINK GENETICS TEACHES US TO LOOK FOR

WHAT PATHWAYS TO STUDY AND TO TRY TO IDENTIFY, BASED ON THE GENETIC PATHWAYS, TARGETS THAT WE CAN USE TO DEVELOP DRUGS. BUT IN THE HUMAN CLINICAL SITUATION, I BELIEVE, IN ADDITION TO THE GENETICS, THERE'S ALWAYS A NONGENETIC COMPONENT, A DEVELOPMENTAL COMPONENT IN THIS CASE, AND WE NEED TO UNDERSTAND BETTER THERE COULD BE ENVIRONMENTAL, FOR EXAMPLE, VERY WELL POSSIBLE. IT COULD BE AN INFLAMMATORY EVENT DURING PREGNANCY, FOR EXAMPLE, WHICH IS ABSOLUTELY, I THINK, PLAUSIBLE. IT COULD BE SOMETHING ELSE EARLY IN CHILDHOOD. YEAH. I THINK IT'S NOT JUST GENETICS.

DR. LEVITT: THANK YOU.

CHAIRMAN GOLDSTEIN: THAT'S REASONABLY TYPICAL FOR A LOT OF THESE KINDS OF DISORDERS, THAT YOU HAVE ABOUT HALF OF THE PHENOTYPE CONTROLLED BY THE GENETIC CONSTITUTION OF THE INDIVIDUAL AND THE OTHER HALF OF THE PHENOTYPE COMING FROM ENVIRONMENTAL FACTORS THAT, AS YOU NOTE, ARE REALLY POORLY UNDERSTOOD AND HARD TO GET A HANDLE ON.

ON THE OTHER HAND, IF HALF OF THE PHENOTYPIC BEHAVIOR COMES FROM THIS COLLECTION OF GENES, THAT IS HOPEFUL FOR THERAPY DISCOVERY. I MEAN IT'S GIVEN YOU A CLUE ABOUT WHERE TO LOOK AND WHAT TO MODULATE. SO WHILE COMPLICATED, IT'S A

TERRIFIC OPPORTUNITY FOR, AS YOU POINT OUT, A TERRIBLE DISORDER.

WE ARE AT ONE ZERO ZERO, TOM. YOU'RE FREE FOR THE TIME BEING, BUT I RESERVE THE RIGHT FOR US TO COME BACK TO SEEK ADDITIONAL ADVICE FROM YOU.

DR. SUDHOF: PLEASE DO. ANYTHING I CAN DO. I THINK THIS IS SO IMPORTANT FOR CALIFORNIA AND ACTUALLY FOR THE PATIENTS. I DO THINK THAT WE NEED TO MAKE PROGRESS.

CHAIRMAN GOLDSTEIN: GREAT.

DR. SUDHOF: THANK YOU.

CHAIRMAN GOLDSTEIN: THANK YOU, TOM.

OKAY. NEXT UP, KRISTEN, CAN YOU SHED SOME LIGHT ON THESE DISORDERS FOR US PLEASE?

DR. BRENNAND: YEAH. I'M REALLY, REALLY EXCITED TO GET THE CHANCE TO CHAT WITH THIS GROUP. I'VE GOT TO SAY I WAS ONE OF THE FIRST CLASS OF CIRM POST-DOC FELLOWS BACK IN 2008. AND CIRM HAS ALWAYS BEEN A DEAR PART OF MY TRAINING IN MY COMMUNITY. AND SO WHEN LARRY ASKED ME TO SPEAK WITH YOU, I SHOULD ADD HE GAVE A VERY LONG LIST OF QUESTIONS THAT HE WANTED US TO ADDRESS IN JUST 15 MINUTES. AND SO I'M GOING TO DO MY BEST TO HIT A FEW OF THEM IN THE TALK, AND THEN POST THE REST OF THEM AT THE END SO WE CAN DISCUSS THEM AND MAKE SURE WE HIT

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EVERYTHING THAT HE ASKED.

AND SO I'M GOING TO TALK TO YOU ABOUT SOME OF THE WORK THAT MY LAB HAS BEEN DOING USING STEM CELLS TO EXPLORE THE GENETICS OF NEUROPSYCHIATRIC DISORDERS. AND THE FIRST THING THAT I THINK IS SO IMPORTANT TO TALK ABOUT IS HOW COMMON THESE DISORDERS ARE.

SO ONE IN FIVE PEOPLE ACROSS THE U.S. WILL EXPERIENCE A PSYCHIATRIC DISORDER THIS YEAR. YOUR LIFETIME RISK IS ACTUALLY ONE IN THREE. AND SO IT'S SO IMPORTANT THAT WE TALK ABOUT THESE DISORDERS AND MOVE THEM OUT OF STIGMA AND INTO TREATMENT. NOT JUST ARE THEY COMMON; THEY'RE SEVERE. SO IF YOU LOOK AT THE DISABILITY ADJUSTED LIFE YEARS THAT WE LOSE BECAUSE OF PSYCHIATRIC DISORDERS, THEY'RE ACTUALLY MORE IMPACTFUL THAN THINGS LIKE DIABETES AND NEURODEGENERATIVE DISEASE THAT I KNOW CIRM HAS DONE A LOT TO STUDY. THESE ARE IN THE TOP FIVE CAUSES OF DISABILITY WORLDWIDE.

THEY ARE VERY HETEROGENEOUS. WHEN WE TALK ABOUT NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS, WE ARE TALKING ABOUT A SPECTRUM THAT STARTS WITH AUTISM AND DEVELOPMENTAL DELAY, INCLUDES PSYCHOSIS, BIPOLAR, EATING DISORDERS, ANXIETY, DEPRESSION, AND SUBSTANCE ABUSE. AND SO WE HAVE A HUGE COLLECTION

OF PRESENTATIONS HERE. AND WHAT I REALLY WANT YOU TO SIT ON FOR A MOMENT IS THESE TWO REALLY IMPORTANT CLINICAL FACTS.

AND THE FIRST IS THAT THE DELAY, THE AVERAGE DELAY BETWEEN SYMPTOM ONSET AND TREATMENT IN THE U.S. IS EIGHT TO TEN YEARS. PEOPLE ARE EXPERIENCING AND SUFFERING FROM THE DISABILITY THAT COMES WITH PSYCHIATRIC DISORDERS FOR UP TO TEN YEARS BEFORE THEY'RE GETTING ANY HELP WITH THE SYMPTOMS. AND SECOND OF ALL, EVEN AFTER DIAGNOSIS, MANY PEOPLE ARE NOT BEING TREATED. THE PERCENTAGE OF ADULTS WITH A PSYCHIATRIC DISORDER WHO DID NOT RECEIVE TREATMENT LAST YEAR WAS 60 PERCENT.

THIS REFLECTS A LOT OF TRUTHS, ONE THAT WE ARE BAD AT DIAGNOSING, TWO, THAT OUR DRUGS TEND TO BE REALLY TERRIBLE AND THEY HAVE A LOT OF SIDE EFFECTS, AND SOME PATIENTS CHOOSE NOT TO TAKE THEM; THREE, THAT SOME OF THE DRUGS ARE JUST -- THERE ARE ABOUT A THIRD OF CASES OF SCHIZOPHRENIA AND BIPOLAR, FOR EXAMPLE, THAT IS NOT TREATMENT RESPONSIVE. SO THERE'S A LACK OF TREATMENTS, A LACK OF GOOD TREATMENTS, A LACK OF TREATMENTS WITHOUT SIDE EFFECTS, AND THEN A LACK OF ACCESS.

PATIENTS WITH PSYCHIATRIC DISORDERS ARE OVERREPRESENTED IN OUR CRIMINAL, HOMELESS, AND

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INSTITUTIONALIZED POPULATIONS AND UNDERREPRESENTED IN OUR DAY-TO-DAY LIVES.

THE GENETICS, AND TOM AND LARRY HAVE HINTED AT THIS ALREADY, BUT THE COMPLEX GENETIC RISK ARCHITECTURE IS VERY FAR FROM DIAGNOSTIC OR PREDICTIVE.

I'LL START HERE WITH SCHIZOPHRENIA BECAUSE IT'S WHAT MY LAB FOCUSES ON, BUT ALSO IT'S THE MOST HERITABLE PSYCHIATRIC DISORDER, WHICH IS A BIG PART OF WHY MY LAB FOCUSES ON IT. SO THE HERITABILITY FROM TWIN STUDIES FOR SCHIZOPHRENIA IS ACTUALLY ESTIMATED AT 80 PERCENT. SO A HUGE AMOUNT OF WHETHER OR NOT PEOPLE HAVE SCHIZOPHRENIA CAN BE PREDICTED OR OUGHT TO BE ABLE TO BE PREDICTED FROM THE DNA THAT THEY ARE BORN WITH.

NOW, THAT'S NOT TO SAY THAT WE CAN DO THAT YET. WE DON'T UNDERSTAND, IN FACT, MOST OF THE HERITABILITY FOR SCHIZOPHRENIA. SO ABOUT A THIRD OF THAT KNOWN HERITABILITY WE CAN EXPLAIN FROM GENOMEWIDE ASSOCIATION STUDIES. BUT TWO-THIRDS OF IT IS TERMED MISSING HERITABILITY. WE KNOW IT MUST BE THERE FROM TWIN STUDIES, BUT WE DON'T KNOW HOW TO EXPLAIN IT YET.

NOW, IF WE EXPAND THIS ACROSS THE SPECTRUM OF PSYCHIATRIC DISORDERS I WANT YOU TO SEE. SO AT

THE TOP WE HAVE SCHIZOPHRENIA, AUTISM, ADHD, BIPOLAR. THEY'RE EXTREMELY HERITABLE. BUT THREE-QUARTERS ARE HERITABILITY; BUT ACROSS ALL OF THEM, OUR ABILITY TO EXPLAIN THAT HERITABILITY IS ABOUT A THIRD TO A QUARTER.

THE OTHER END OF THE SPECTRUM, WE HAVE ANXIETY DISORDER, DEPRESSION, PTSD. THESE ARE EXTREMELY DRIVEN BY ENVIRONMENT. NOW, THIS MAKES SENSE. PTSD IS DEFINED BY BEING A DISORDER THAT OCCURS IN RESPONSE TO A TRAUMATIC EVENT. SO THERE HAS TO BE A HUGE ENVIRONMENTAL COMPONENT HERE.

AND SO ONE OF LARRY'S QUESTIONS WAS REALLY WHICH DISEASES ARE APPROPRIATE FOR STEM CELL MODELS. AND I THINK IT DEPENDS A LOT ON THE EXTENT TO WHICH WE UNDERSTAND THE GENETICS AND/OR THE EXTENT TO WHICH WE UNDERSTAND THE BIOLOGICAL EFFECTORS DRIVING THE ENVIRONMENTAL EXPOSURES.

BUT I'M GOING TO DIVE IN, BACK-DIVE TO SCHIZOPHRENIA HERE TO TAKE YOU THROUGH SOME EXAMPLES OF HOW WE CAN USE STEM CELLS, ESPECIALLY WHEN COMBINED WITH CRISPR, TO INVESTIGATE A PSYCHIATRIC DISORDER.

AND SO HERE'S EVERYTHING THAT WE KNOW ABOUT THE GENETICS OF SCHIZOPHRENIA AS OF LATE LAST YEAR. SO THERE ARE THREE TYPES OF VARIANTS ON THIS

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PLOT. THESE GREEN ONES WERE ACTUALLY THE FIRST ONES LINKED TO SCHIZOPHRENIA. THESE ARE COPY NUMBER VARIANTS. THEY TEND TO BE VERY LARGE DELETIONS OR DUPLICATIONS. HERE'S 2P16.3, THE ONE THAT THOMAS JUST SPOKE WITH US ABOUT. SO THIS PLOT IS PLOTTING THE ODDS RATIOS OR THE PENETRANCE OF THE VARIANT, HOW LIKELY YOU ARE NOT TO BE A CONTROL IF YOU INHERIT THIS VARIANT. WHEREAS, THE X AXIS IS LOOKING AT HOW COMMON IT IS IN THE POPULATION. AND SO THIS 3Q29 DELETION IS THE MOST PENETRANT. YOU ARE INCREDIBLY UNLIKELY TO BE A CONTROL IF YOU INHERIT IT, BUT IT'S EXTREMELY RARE IN LIKE LESS THAN A HUNDREDTH OF A PERCENTAGE OF PATIENTS.

IN AGGREGATE, THESE GREEN DOTS EXPLAIN ABOUT 5 PERCENT OF CASES. SO THEY ARE NOT EXPLAINING THE MAJORITY OF THE GENETICS, BUT THEY ARE A VERY SIGNIFICANT RISK GENE. THEY ALSO CAN BE PLEIOTROPIC. SO IF YOU HAVE, FOR EXAMPLE, A DELETION IN 22Q11, YOU'RE EXTREMELY LIKELY TO HAVE INTELLECTUAL DISABILITY, BUT ONLY ABOUT ONE-THIRD LIKELY TO HAVE SCHIZOPHRENIA. THE DELETIONS ASSOCIATED WITH NRXN1 THAT THOMAS WAS TALKING ABOUT, THEY'RE SIGNIFICANTLY ASSOCIATED WITH SCHIZOPHRENIA, BUT ALSO AUTISM, EPILEPSY, OCD. AND SO YOU SEE THESE PLEIOTROPIC EFFECTS OF THESE RARE VARIANTS

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LIKELY CAUSED BY THEIR INTERACTION WITH THE OTHER VARIANTS YOU MIGHT INHERIT.

SO THESE RED VARIANTS ARE ALSO RARE. THEY'RE, IN FACT, MORE RARE THAN THE GREEN VARIANTS THAT ARE LEFT SHIFT IN THIS PLOT. THEY'RE NOW PROTEIN-TRUNCATING VARIANTS. THEY'VE ONLY BEEN IDENTIFIED IN THE LAST YEAR, SO THEY'RE MUCH NEWER TO US. THEY'RE JUST AS PENETRANT AS THESE COPY NUMBER VARIANTS, BUT IN A SMALLER PERCENTAGE OF PATIENTS.

AND THEN, FINALLY, OVER HERE ON THE OPPOSITE SIDE OF THE GRAPH, WE HAVE THESE COMMON VARIANTS. AT PRESENT THE MOST RECENT GENETIC STUDY HAS ABOUT 250 OF THESE COMMON VARIANTS. EACH OF THEM CONFERS PERHAPS A 1-PERCENT INCREASED RISK OF SCHIZOPHRENIA. AND SO IN ISOLATION THESE VARIANTS DO ALMOST NOTHING TO PREDICT OR MAYBE EVEN CAUSE DISEASE; BUT IN AGGREGATE, WHEN YOU CONSIDER THE DOZENS THAT EACH OF US INHERIT, THE INTERACTIONS BETWEEN THEM DO LEAD TO LARGE PHENOTYPIC EFFECTS.

AND SO DIVING INTO THESE COMMON VARIANTS HERE, THIS IS THE MOST RECENT GWAS FOR SCHIZOPHRENIA. THE Y AXIS HERE IS THE P-VALUE, SO THE LIKELIHOOD THAT A VARIANT IS ASSOCIATED WITH SCHIZOPHRENIA. AND THIS RED LINE IS GENOMEWIDE

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SIGNIFICANCE. SO EVERYTHING ABOVE THAT LINE IN THIS MANHATTAN PLOT IS SIGNIFICANTLY ASSOCIATED WITH SCHIZOPHRENIA.

NOW, THIS IS A PLOT OF SINGLE NUCLEOTIDE POLYMORPHISMS. YES, SOME OF THESE LOOK LIKE LINES, BUT SOMETIMES IT'S MORE CLEAR THAT THEY'RE JUST COLLECTIONS OF VARIANTS THAT MAY OR MAY NOT BE CLOSE TOGETHER IN SPACE. SOMETIMES WE CAN ENCOMPASS KILOBASES OF SPACE IN BETWEEN THE VARIANTS AT A GIVEN LOCI.

SO HOW DO YOU TRANSLATE A BIG GENETIC PLOT LIKE THIS INTO SCHIZOPHRENIA? WHAT ARE SOME BIG CHALLENGES? FIRST OF ALL, EACH OF THESE LOCI, AGAIN, CAN BE COMPRISED OF DOZENS OR HUNDREDS OF THOUSANDS OF SINGLE NUCLEOTIDE POLYMORPHISMS. AND RESOLVING WHICH ONE OR ONES IS LINKED TO DISEASE CAUSALLY IS CHALLENGING. FIGURING OUT WHICH GENES ARE THE TARGETS OF EACH OF THESE LOCI IS MORE CHALLENGING. I'M SORRY. THE PATHWAYS THAT ARE IMPACTED DOWNSTREAM OF THESE NONCODING SNP'S IS EVEN HARDER. SO TRANSLATING GENETIC HITS TO BIOLOGY IS REALLY CHALLENGING WHEN THEY'RE NOT IN THE CODING REGION. IT'S VERY EASY TO ASSIGN A DELETION OR A TRUNCATION IN THE CODING GENE TO THE GENE TARGET. IT'S VERY HARD TO ASSIGN A NONCODING PUTATIVE

REGULATORY ELEMENT TO A DOWNSTREAM GENE TARGET.

SECOND OF ALL, NONE OF THESE VARIANTS ACT IN ISOLATION. AGAIN, ALL OF US INHERITED DOZENS OF THEM. PATIENTS MIGHT HAVE JUST INHERITED A DOZEN MORE. SO THE INTERACTIONS BETWEEN THESE VARIANTS IS CRITICALLY IMPORTANT AND MIGHT ACTUALLY BE THE ANSWER TO THIS MISSING HERITABILITY.

AND FINALLY, HOW DOES ALL OF THIS TOGETHER, THE INTERACTION OF RARE VARIANTS AND COMMON VARIANTS AND COMMON VARIANTS AND COMMON VARIANTS WITH COMMON VARIANTS AND COMMON VARIANTS WITH ENVIRONMENT, HOW DOES THIS IMPACT CLINICAL PENETRANCE AND EXPRESSIVITY? AND SO THESE ARE EXACTLY THE QUESTIONS MY LAB HAS BEEN ASKING.

I DO WANT TO BACK UP AND FOR, LIKE, ONE MINUTE TALK TO YOU ABOUT SCHIZOPHRENIA AND WHAT WE KNOW FROM HUMAN STUDIES. MUCH LIKE NEURODEGENERATIVE DISEASE, POSTMORTEM STUDIES HAVE LONG SHOWN THAT THE BRAINS OF INDIVIDUALS WITH SCHIZOPHRENIA ARE SMALLER. WE'VE KNOWN THIS FROM AUTOPSY STUDIES WHERE THE BRAINS WERE WEIGHED AND WHERE WE CERTAINLY KNOW THIS FROM BRAIN IMAGING SCANS. HERE THIS IS A STUDY BY JUDY RAPOPORT WHERE THE REGIONS IN RED ARE SMALLER. BUT UNLIKE NEURODEGENERATIVE DISEASE, THE REGIONS ARE NOT

SMALLER BECAUSE THE NEURONS ARE DEAD OR THE CELLS ARE MISSING. THE NEURONS THEMSELVES ARE SMALLER. SO WE KNOW FROM POSTMORTEM PATHOLOGY THERE'S FEWER DENDRITES, SO FEW BRANCHING FROM NEURONS AND FEWER CONNECTIONS BETWEEN THEM, FEWER SYNAPSES IN POSTMORTEM BRAINS.

AND SO WE CAN SEE AT END-STAGE DISEASE HUMAN BRAINS ARE LESS WELL CONNECTED, BUT THERE ARE SO MANY QUESTIONS THAT WE DON'T KNOW. WHICH CELL TYPE IS IMPACTED FIRST IN SCHIZOPHRENIA? WE HAD LONG ASSUMED THAT NEURONS FOR THE CELL TYPE OF ORIGIN IN ALZHEIMER'S, AND THE GENETIC STUDIES HAVE MUCH MORE RECENTLY TAUGHT US THAT MICROGLIA ARE HUGELY DRIVING THE SUBSEQUENT NEURONAL DEATH.

LIKEWISE, IN SCHIZOPHRENIA WE HAVE FOR DECADES TREATED DOPAMINE RECEPTOR ACTIVITY, BUT THE GENETIC STUDIES DON'T KEEP HIGHLIGHTING DOPAMINE ROBUSTLY. INSTEAD, THEY'RE HITTING GLUTAMATERGIC AND GABAMINURGIC SIGNALING. SO ARE THOSE THE CELL TYPES OF ORIGIN FOR DISEASE? AND IF THEY ARE, WHEN IN DEVELOPMENT ARE THEY BEING IMPACTED? AGAIN, THE GENETICS STUDIES SUGGEST IT'S SECOND AND THIRD TRIMESTER, BUT THE THINGS THAT ARE GOING WRONG IN THE BRAIN OF SOMEBODY WHO'S GOING TO HAVE SCHIZOPHRENIA THREE DECADES FROM NOW OR TWO DECADES

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FROM NOW ARE GOING WRONG IN UTERO.

WHY DO WE KNOW SO LITTLE? WELL, JUST LIKE IN NEURODEGENERATION, BUT UNLIKE IN CANCER, THERE'S JUST INSUFFICIENT LIVE HUMAN TISSUE FOR STUDIES OF PSYCHIATRIC DISORDER RISK AND DRUG DISCOVERY. AND WHILE MOUSE MODELS HAVE BEEN HUGELY INFORMATIVE ACROSS A NUMBER OF DISEASES, I LIKE TO JOKE THAT I WASN'T TRAINED AS A NEUROSCIENTIST, AND EVEN I CAN TELL THE DIFFERENCE BETWEEN THIS MOUSE BRAIN AND THIS HUMAN BRAIN. AND THAT REMAINS TRUE WHEN WE SCALE FOR SIZE.

NOW, MOUSE MODELS ARE REALLY GOOD AT LOOKING AT THE COMPLEX INTERACTIONS OF GENES, CIRCUITS, AND BEHAVIORS. WHAT HAPPENS IF YOU KNOCK OUT THIS GENE ON THAT CIRCUIT AND THAT BEHAVIORAL TASK? BUT LIKE ALL MODELS, THEY HAVE LIMITATIONS. AND I THINK TWO OF THE MAJOR LIMITATIONS OF MOUSE MODELS ARE THEY POORLY CAPTURE THE IMPACT OF NONCODING COMMON VARIANTS BECAUSE THEY'RE INFREQUENTLY CONSERVED BETWEEN RODENTS AND HUMANS.

I JUST SHOWED YOU THAT MUCH, IN FACT, MOST OF THE GENETIC RISK THAT WE HAVE IDENTIFIED TO DATE FOR PSYCHIATRIC DISEASES IS IN THE FORM OF NONCODING COMMON VARIANTS THAT ARE INFREQUENTLY CONSERVED IN RODENTS. AND SECOND OF ALL, IT'S VERY DIFFICULT TO

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STUDY THE INTERACTIONS BETWEEN VARIANTS IN MICE BECAUSE, ONE, IT'S DIFFICULT TO ENGINEER MANY VARIANTS. AND SECOND, IT'S EVEN HARDER TO BREED THEM TRUE.

SO WHAT DO I THINK STEM CELLS ARE USEFUL FOR TEACHING US ABOUT PSYCHIATRIC DISORDERS? WELL, I THINK THERE'S TWO WAYS THAT THEY'RE REALLY GOING TO HELP ADVANCE OUR UNDERSTANDING AND TREATMENT OF PSYCHIATRIC DISORDERS. AND THE FIRST IS IMPROVING DIAGNOSIS. THERE ARE NO BLOOD TESTS TO DIAGNOSE PSYCHIATRIC DISORDERS. THERE'S NO BIOPSIES. THERE'S, IN FACT, NO BRAIN IMAGING SCANS. SO WE TALK A LOT ABOUT HOW THE TOOLS ARE DIFFICULT IN NEURODEGENERATION TO DIAGNOSE. WELL, THEY'RE ARGUABLY MUCH FURTHER BEHIND IN PSYCHIATRY. IT CAN BE EXTREMELY CHALLENGING TO ACCURATELY DIAGNOSE SOMEBODY WITHIN YEARS OF SYMPTOM ONSET. AND SECOND OF ALL, THERE'S A LACK OF ADEQUATE TREATMENTS FOR PSYCHIATRIC DISORDERS AND, MORE SO, A LACK OF METHODS TO PREVENT DISORDER. AND IF WE COULD GET BETTER AT DIAGNOSIS, IF WE COULD PREDICT WHO WAS AT HIGH RISK PRIOR TO SYMPTOM ONSET, I THINK WE REALLY ARE CHANGING THE WINDOW OF THERAPEUTIC INTERVENTION.

JUST LIKE I'D MUCH RATHER TREAT MY FUTURE ALZHEIMER'S WHEN I'M 40 OR 50 WITH TARGETING

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ABERRANT MICROGLIA FUNCTION THAN WHEN I'M 80 OR 90 AND FACING SEVERE COGNITIVE DEFICITS AND NEURONAL DEATH. LIKEWISE, WE'D LIKE TO TREAT PSYCHIATRIC DISORDERS PRIOR TO SYMPTOM ONSET AND PRIOR TO THIS REINFORCEMENT OF ABERRANT CIRCUIT FUNCTION.

AND SO WHAT I'M REALLY TALKING ABOUT IN THIS PRECISION MEDICINE, THAT IF WE COULD UNDERSTAND WHY ALL OF THE DOZENS OF RISK VARIANTS THAT A GIVEN PATIENT HAS INHERITED, WHAT THEY DO AND HOW THEY INTERACT WITH EACH OTHER, THEN MAYBE WE CAN IDENTIFY THE RIGHT, THE PRECISE THERAPEUTIC TO INTERVENE WITH. AND I THINK THE BIG DIFFERENCE HERE IN PSYCHIATRY VERSUS NEURODEGENERATION IS THAT GOAL COULD JUST BE PHARMACOLOGY. WE DON'T NECESSARILY NEED CELL REPLACEMENT THERAPY TO DO BETTER BY OUR PATIENTS IN PSYCHIATRY. WE DON'T EVEN NEED A CURE. WE JUST NEED TO LESSEN THE IMPACT OF THEIR SYMPTOMS.

AND SO THINKING ABOUT HOW WE CAN USE STEM CELLS TO UNDERSTAND THE COMPLEX GENETICS OF SCHIZOPHRENIA, I WANT TO SHOW YOU ONE EXAMPLE OF HOW WE TRACK GENOTYPE TO PHENOTYPE. THIS IS WORK LED BY A FORMER POST-DOC OF MINE, NADINE SCHRODE.

WE LOOKED AT THE GWAS BACK IN 2015, AND WE WERE TRYING TO PRIORITIZE WHICH LOCI TO EDIT USING CRISPR, NONCODING SNP. THIS WAS BACK WHEN CRISPR

EDITING REMAINED REALLY CHALLENGING. WHICH ONE DO YOU PICK? DO YOU PICK THE TALLEST ONE? DO YOU PICK THE SPARSEST ONE? AND IN TRUTH WE WORKED REALLY CLOSELY WITH GENETICISTS TO UNDERSTAND WHICH ONE THEY WOULD PICK. AND THEY WERE REALLY EXCITED ABOUT THIS SNP OVER HERE IN THE THREE PRIME UTR OF A GENE CALLED FURIN. AND THE REASON THEY WERE EXCITED ABOUT IT IS SOMETHING HAPPENED AT THIS SNP THAT DIDN'T HAPPEN ANYWHERE ELSE IN THE GWAS PLOT.

SO HERE IN THIS PLOT WE'VE GOT THE Y AXIS BEING P-VALUE, SAME AS OVER HERE. SO THE STRENGTH OF THE ASSOCIATION BETWEEN A GIVEN VARIANT AND SCHIZOPHRENIA DIAGNOSIS. BUT WE HAVE CROSSED IT WITH A BRAIN EQTLKEY VALUE, WHICH IS TO SAY WHAT IS THE PROBABILITY THAT ANY GIVEN SNP AT THAT LOCI IS REGULATING EXPRESSION OF THE NEAREST TARGET GENE? AND WHAT YOU GET AT THIS LOCUS IS A SINGLE SNP IN THE TOP RIGHT-HAND CORNER, A SNP TERMED RS4702. SO THIS SNP WAS THE SNP MOST LIKELY TO BE CONFERRING RISK FOR SCHIZOPHRENIA AND ALSO MOST LIKELY TO BE REGULATING EXPRESSION OF FURIN.

AND SO THIS WAS THE SNP THAT WE CHOSE FOR CRISPR EDITING. THE SECOND BEST CANDIDATE GENE, THE SECOND BEST ONE LOOKED LIKE THIS WHERE WE'VE GOT 20 OR 30 DOTS IN THE TOP RIGHT-HAND CORNER. AND SO IT

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WASN'T CLEAR TO US WHETHER ALL OF THESE SNP'S WERE CONFERRING 1 OR 2 PERCENT OF THE RISK AT THIS LOCI OR WHETHER THERE WAS ONE REALLY IMPORTANT SNP IN THAT CLUSTER THAT WE JUST COULDN'T DISCERN YET. AND SO WE'LL USE CRISPR EDITING TO LOOK AT RS4702, AND WE'LL USE A DIFFERENT CRISPR TOOL, CRISPR ACTIVATION, TO LOOK AT SNAP91.

AND SO THIS WAS THE EDIT THAT NADINE ACHIEVED. SHE STARTED, I BELIEVE, TWO CONTROLLED DONORS, MANIPULATED THE AA GENOTYPE TO A GG GENOTYPE, AND COULD SHOW THAT THE GG SAT WHERE THEY'RE ISOGENIC TO EACH OTHER EXCEPT THAT ONE NONCODING SNP. THE GG CELLS WHEN THEY WERE INDUCED INTO NEURONS SHOWED REDUCED FURIN EXPRESSION. OVER THE TIME IT TOOK HER TO DO THE EDIT, IT WAS ACTUALLY SHOWN THAT THIS SNP, RS4702, WAS IN A BINDING SITE FOR MIR338. AND WHEN SHE ELIMINATED MIR338 ACTIVITY THROUGH AN INHIBITOR, SHE ELIMINATED THE REGULATORY EFFECT OF THIS SNP. NOW THIS MAKES SENSE. WITHOUT MIR338 BINDING, IT CAN'T REGULATE THE EXPRESSION OF FURIN. AND SO THIS BECOMES NOW A CONTEXT-SPECIFIC REGULATORY ELEMENT WHERE ONLY IN THOSE CELL TYPES THAT MIR338 EXPRESSED WOULD RS4702 BE PREDICTED TO INFLUENCE YOUR RISK FOR SCHIZOPHRENIA.

NADINE TOOK IT FURTHER. SHE WAS ABLE TO

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SHOW THAT GG NEURONS WITH THEIR REDUCED FURIN EXPRESSION HAD A REDUCED NEURITE OUTGROWTH CONSISTENT WITH FURIN KNOCKOUT MICE AND ALTERED PATTERNS OF NEURONAL ACTIVITY.

BUT, AGAIN, THIS IS JUST ONE SNP IN ISOLATION. AND WE REALLY WANTED TO KNOW WHAT WOULD HAPPEN IF WE MANIPULATED MORE RISK GENES AT THE SAME TIME. AND SO WE PRIORITIZED AGAIN BY INTERSECTING GWAS AND BRAIN EXPRESSION, AND WE ENDED UP WITH A SLIGHTLY LONGER LIST OF FOUR GENES: FURIN, NRX2, SNAP91, AND T-SNARE. WE ARE USING CRISPR A AND CRISPR I TO ACTIVATE AND INHIBIT EXPRESSION OF THESE GENES. AND SO HERE YOU CAN SEE THAT THE MOST PERTURBED GENE IS THE GENE WE ARE TARGETING. THOSE OTHER GENES CHANGING DOWNSTREAM, AND THOSE DOWNSTREAM GENES, THEY DON'T SEEM TO BE OFF-TARGET EFFECTS BECAUSE THEY'RE SPECIFICALLY IMPACTING SYNAPTIC FUNCTION. AND, IN FACT, IF WE MANIPULATE SNAP91, WE CAN SEE RECIPROCAL EFFECT BY ELECTROPHYSIOLOGY LOOKING AT THE FREQUENCY OF SYNAPTIC ACTIVITY. SO INCREASING SNAP91, INCREASING SYNAPTIC ACTIVITY, DECREASING IT DECREASES SYNAPTIC ACTIVITY. BUT, AGAIN, ONE GENE AT A TIME. THAT WAS NOT THE GOAL. WE WANTED TO KNOW HOW THESE RISK VARIANTS INTERACT.

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SO HERE NADINE HAS TAKEN THESE FOUR GENES, DONE WITH SINGLE GENE PERTURBATIONS FOLLOWED BY RNASEQ, GENERATED COMPUTATIONALLY AND EXPECTED ADDITIVE MODEL COMBINING THE RNASEQ, AND THEN ASKING EXPERIMENTALLY HOW GOOD THE MODEL WAS COMPARED TO THE PREDICTION. AND IT TURNED OUT THE MODEL WAS PRETTY GOOD. GENOMEWIDE ABOUT 82 PERCENT OF GENES ARE ACCURATELY PREDICTED BY THE EXPECTED ADDITIVE MODEL, BUT 7 PERCENT OF GENES ARE MORE DOWN THAN EXPECTED. THEY WERE ENRICHED FOR NEUROTRANSMITTER GENES, AND 11 PERCENT OF GENES WERE MORE UP THAN EXPECTED, MIR ENRICHED FOR THE RARE AND COMMON VARIANTS LIKE SCHIZOPHRENIA AND BIPOLAR. AND SO REALLY THIS IS HINTING AN EMERGENT BIOLOGY THAT YOU CAN ONLY DETECT WHEN YOU MANIPULATE GENES IN COMBINATION THAT YOU CANNOT PREDICT BY ADDING UP THE EFFECTS OF SINGLE-GENE PERTURBATIONS.

WE WANTED TO VALIDATE THIS ACROSS A LARGER NUMBER OF GENES, SPECIFICALLY CONSIDERING PATHWAY BIOLOGY. SO USING AN UPDATED GENETICS STUDY AND AN UPDATED POSTMORTEM BRAIN STUDY, WE WERE ABLE TO NOW FILTER TO THE TOP FIVE GENES THAT ARE SYNAPTIC IN FUNCTION, THE TOP FIVE EPIGENETIC, THE REGULATORY GENES, BECAUSE THESE ARE THE TWO MAJOR FUNCTIONS LINKED TO SCHIZOPHRENIA RISK, AND THEN THE TOP FIVE

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GENES THAT WERE NOT SYNAPTIC, NOT REGULATORY, AND NOT RELATED TO EACH OTHER.

AND MICHAEL WAS NOW ABLE TO SHOW THAT HE COULD SEE THE SYNERGY IN THE SYNAPTIC SET, IN THE REGULATORY SET, BUT NOT IN THE MULTIPATHWAY SET. SO SYNERGY SEEMED TO BE DEPENDENT ON THE GENES HAVING A SHARED BIOLOGY. AND THIS SHARED BIOLOGY ACTUALLY REFLECTED THE CONVERGENT DOWNSTREAM TARGETS OF THE INDIVIDUAL FIVE GENES IN EACH CLUSTER. SO WE SAW STRONG OVERLAP OF CONVERGENT GENES AND SYNERGY GENES AND SYNAPTIC AND REGULATORY AND NOT AT ALL IN THE MULTIFUNCTION.

THIS IDEA, I THINK, IS REALLY COOL AND IT GETS TO THIS UNIQUELY HUMAN ELEMENT OF COMPLEX GENETIC DISORDERS. SO IF WE'VE GOT, FOR EXAMPLE, TEN GENES IN THIS MODEL THAT IN ISOLATION HAVE THESE SMALL EFFECTS, YOU MIGHT PREDICT AN EXPECTED ADDITIVE MODEL THAT JUST SUMS THESE EFFECTS. BUT IF YOU DO THE EXPERIMENT, YOU MIGHT SEE SOMETHING LESS. AND WHAT WE ARE BEGINNING TO SEE NOW IS THAT IF YOU LOOK AT THE SHARED IMPACTS DOWNSTREAM OF THESE SINGLE-GENE PERTURBATIONS, YOU CAN USE THOSE TO EXPLAIN THE DIFFERENCE BETWEEN THE EXPECTED AND THE OBSERVED COMBINATORIAL EFFECTS.

AND WHY IS THIS IDEA OF CONVERGENCE SO

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IMPORTANT? WELL, WE ARE INCREASINGLY SEEING IT ACROSS BRAIN DISORDERS. SO THERE'S A HUGE AMOUNT OF CONVERGENCE IN THE VARIANTS LINKED TO SCHIZOPHRENIA AND BIPOLAR. THIS HAS BEEN KNOWN FOR A DECADE NOW. BUT AS THE GENETICS STUDIES GET LARGER, WE CAN ALSO SEE CONVERGENCE ACROSS ANXIETY, PTSD, AND DEPRESSION. AND WE CAN SEE THIS ACROSS THE NEURODEGENERATIVE DISORDERS.

BUT THEN MORE RECENTLY, WE ARE ALSO BEGINNING TO SEE CONVERGENCE ACROSS PSYCHIATRIC AND NEURODEGENERATIVE DISORDERS. SO YOU CAN SEE HERE SOME RICH GENES LINKED TO SCHIZOPHRENIA THAT ARE ALSO LINKED TO PARKINSON'S, RISK GENES LINKED TO BIPOLAR THAT ARE ALSO LINKED TO ALZHEIMER'S. AND YOU CAN LOOK AT THE PATHWAY LEVEL. AND VERY FEW GENES ARE BOTH YELLOW AND PINK. I THINK IT'S THE CONNECTION BETWEEN THESE PSYCHIATRIC DISORDER GENES AROUND HOW THE NEURODEGENERATIVE DISORDER GENES IS REALLY STRIKING AND I THINK SHOULD ENCOURAGE YOU TO REALIZE THAT THIS HUGE GROUP OF NEURODEGENERATIVE RESEARCHERS THAT YOU ALREADY HAVE IN CALIFORNIA SHOULD BE ABLE TO HELP EXPAND INTO PSYCHIATRIC DISORDERS WITH A LITTLE BIT OF INCENTIVE.

AND SO THE OVERARCHING IDEA THAT I WANT TO SHARE IS THAT, YES, WE KNOW THAT GENOTYPES REGULATE

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PHENOTYPES, BUT IT'S NEVER THAT SIMPLE. THE ENVIRONMENT THAT YOU LIVE IN CAN MAKE A PHENOTYPE WORSE. SO LIVING IN A STRESSED ENVIRONMENT, AN ENVIRONMENT THAT CAUSED A LOT OF INFLAMMATION HAS MORE PENETRANCE. WHEREAS, THE ASSUMPTION IS THERE ARE LIKEWISE PRO, GOOD ENVIRONMENTS THAT MIGHT AMELIORATE IT. IT COULD BE A DRUG. IT COULD BE JUST AN UNSTRESSED ENVIRONMENT THAT ALLOWS YOU TO ACHIEVE YOUR GENETIC MAXIMUM TOWARDS THIS IDEA -- THIS WILL BE MY LAST DATA SLIDE, I THINK. I'VE WORKED WITH RACHEL YEHUDA, THE NEW YORK STEM CELL FOUNDATION, TO LOOK AT THE IMPACT OF STRESS ON GENE EXPRESSION.

AND SO HERE WE HAVE STEM CELLS FROM 39 DONORS. WE'VE STRESSED THEM WITH A LOW DOSE OF THE STRESS HORMONE HYDROCORTISOL AND A HIGH DOSE. AND WHAT I THINK IS PRETTY OBVIOUS TO EVERYBODY IS THAT THERE'S MORE BLUE, THERE'S MORE CHANGES IN GENE EXPRESSION WHEN YOU STRESS NEURONS MORE. IF, HOWEVER, YOU BREAK THOSE 39 DONORS -- THEY WERE ALL COMBAT EXPOSED VETERANS, BY THE WAY -- INTO THE 19 WHO HAD PTSD AND THE 20 WHO DID NOT. WHAT YOU CAN NOW SEE IS THAT THE PTSD-SPECIFIC DIFFERENCES OCCURRED HERE AT THE LOW DOSE, WHICH IS TO SAY THE NEURON FROM INDIVIDUALS WITH PTSD WERE HYPER STRESS

RESPONSIVE. THEY WERE MORE LIKELY TO RESPOND TO STRESS AT LOW DOSE THAN THOSE FROM CONTROLS.

YOU CAN USE THAT LOW DOSE STRESS RESPONSE TO PREDICT WHO HAD PTSD AND WHO DID NOT. AND THE TYPES OF GENES THAT WERE DIFFERENTIALLY EXPRESSED IN THE PTSD NEURONS IN LOW STRESS CONDITIONS ARE ACTUALLY ENRICHED, NOT JUST FOR THE PTSD RISK GENES, BUT ALSO FROM POSTMORTEM SIGNATURES. BUT THEY'RE NOT SPECIFIC TO PTSD. YOU CAN SEE HERE WE ALSO HAVE A LOT OF AUTISM AND SCHIZOPHRENIA GENES. AGAIN, SUGGESTING THAT STRESS NONSPECIFICALLY INCREASES YOUR RISK FOR PSYCHIATRIC DISORDERS. AND SO IT ADDS TO THE RISK THAT YOU WERE BORN WITH.

AND SO MY LAB IS JUST SO INTERESTED IN THESE GENE-GENE AND GENE-ENVIRONMENT INTERACTIONS TRYING TO UNDERSTAND GENETIC RESILIENCE. HOW DO WE ALLOW PEOPLE TO ACHIEVE THEIR GENETIC BEST TO MINIMIZE THE IMPACT AND THE INTERACTIONS BETWEEN THEIR RISK GENES AND RISK ENVIRONMENTS?

AND SO TO ANSWER LARRY'S QUESTIONS, I THINK IT REALLY IS TIME TO TALK ABOUT DISCUSSION OF WHICH DISORDERS TO PRIORITIZE IN COMING BACK TO THIS IDEA OF CONVERGENCE, THAT I THINK WE CAN PRIORITIZE ALL OF THEM.

CELL TYPES TO STUDY? I THINK THIS HAS TO

BE BASED ON THE GENETICS WHETHER THEY STUDY COMMON OR RARE VARIANTS AND POWER LIMITATIONS. AND SO WITH THAT, I'M REALLY HAPPY TO STOP SHARING AND TO TALK ABOUT THESE QUESTIONS WITH YOU.

CHAIRMAN GOLDSTEIN: KRISTEN, THANK YOU. LOVELY STUFF. REALLY THOUGHT PROVOKING. I'LL LAUNCH THE FIRST QUESTION AS PEOPLE THINK THROUGH WHAT THEY WANT TO KNOW ABOUT.

I GUESS THE QUESTION REALLY DOES BECOME WHAT IS THE DEGREE OF RELATIONSHIP BETWEEN SOMETHING THAT WE WOULD CALL, OH, THAT'S A NEURODEGENERATIVE DISORDER VERSUS SOMETHING LIKE SCHIZOPHRENIA WHERE YOU SAY, OH, THAT HAS NOTHING TO DO WITH NEURODEGENERATION. THAT'S JUST THE PSYCHIATRIC DISORDER. YOU AND ACTUALLY TOM HAVE BOTH RAISED THE POSSIBILITY THAT THESE DISORDERS ARE ENORMOUSLY OVERLAPPING. AND I GUESS THE QUESTION THAT IS MAYBE A SLIGHTLY MORE PRECISE WAY OF ASKING WHAT I'D LIKE TO KNOW IS WHAT REALLY IS THE EXTENT OF OVERLAP BETWEEN THOSE TWO BROAD CLASSES?

DR. BRENNAND: I THINK EVEN FIVE YEARS AGO PEOPLE WOULD HAVE SAID THERE WASN'T ONE. YOU HAD TO HAVE A HUGE AMOUNT OF GENETIC KNOWLEDGE TO BE ABLE TO BEGIN TO SEE IT. THERE WAS A STUDY IN *SCIENCE*, I THINK, IN 2018 SAYING THERE WAS NO OVERLAP BETWEEN

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NEURODEGENERATION AND PSYCHIATRIC DISORDERS AT THE GENETIC RISK LEVEL. AND THERE'S BEEN TWO IN THE LAST SIX MONTHS SAYING THERE IS. AND SO I THINK THAT THE ISSUE IS THAT THE GENETICS ARE SO COMPLEX. IT'S NOT THAT THERE'S THREE ALZHEIMER'S GENES AND THERE'S FIVE SCHIZOPHRENIA GENES AND EITHER THEY OVERLAP OR THEY DON'T. AND IT IS THAT PEOPLE ARE REALLY COMPLEX. AND SO AT THE LEVEL OF EVEN THESE NONCODING COMMON VARIANTS AND RARE VARIANTS, IT'S VERY RARE EVEN IN SCHIZOPHRENIA TO HAVE THE COMMON VARIANT TARGETS DIRECTLY OVERLAP WITH THE RARE VARIANT TARGETS. AND THAT CAN SEEM REALLY INCONSISTENT AND REALLY HARD TO WRAP YOUR HEAD AROUND UNTIL YOU PAUSE AND THINK ABOUT THE FACT THAT A COMMON VARIANT MIGHT BE CHANGING EXPRESSION IN THE BRAIN BY 5 OR 10 PERCENT. AND A RARE VARIANT IS 50 PERCENT. AND YOU HAVE TO SURVIVE DEVELOPMENT TO BE A PERSON.

SO THERE'S A HUGE SELECTIVE PRESSURE. AND WHILE OUR ASSUMPTION, I THINK, IS THAT THESE RARE VARIANTS ARE THE MORE IMPORTANT DISEASE GENES, WE SURVIVE WITH THOSE MISSING HALF THE DOSE. AND SO THESE COMMON VARIANTS THAT I THINK GOT DISMISSED FOR A LONG TIME BECAUSE THEIR EFFECT SIZES WERE SO SMALL MIGHT ACTUALLY HINT AT SOME OF THE FUNDAMENTAL

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BIOLOGY BECAUSE WE TOLERATE VERY SMALL CHANGES THERE. AND SO I THINK UNDERSTANDING THAT EVERY CELL TYPE MIGHT HAVE DIFFERENT RISK VARIANTS OR THAT IMPACT DIFFERENT GENES AT DIFFERENT STAGES OF DEVELOPMENT AND IN DIFFERENT CELL TYPES. LIKE THE SAME RISK GENE MIGHT IMPACT GLUTAMINURGIC NEURONS TO CAUSE SCHIZOPHRENIA AND ASTROCYTES TO CAUSE ALZHEIMER'S. IT REALLY DEPENDS ON THE CELL TYPE SPECIFIC AND CONTEXT DEPENDENT REGULATORY ACTIVITY OF THESE NONCODING SNPS. IT'S BECAUSE BIOLOGY IS LAZY AND REUSES ALL THESE VARIANTS I THINK IS WHY THE ANSWER IS SO HARD.

CHAIRMAN GOLDSTEIN: INTERESTING STATEMENT. BIOLOGY IS LAZY. YES. IT REUSES THINGS IMMENSELY.

DR. BRENNAND: OR INEFFICIENT OR I DON'T KNOW.

CHAIRMAN GOLDSTEIN: I MEAN I GUESS THE OTHER FACTOR IS WE TEND TO THINK OF, FOR EXAMPLE, LETHAL MUTATIONS ARE ONLY ELIMINATED FROM POPULATIONS WHEN THEY'RE HOMOZYGOUS. AND THAT'S ACTUALLY JUST NOT TRUE. DICK LEWINGTON ARGUED A LONG TIME AGO VERY EFFECTIVELY THAT WHEN YOU HAVE DISORDERS -- SORRY -- WHEN YOU HAVE MUTATIONS PRESENT IN HETEROZYGOUS CONDITION, THE EFFECT ON

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NATURAL SELECTION AND THE VIABILITY IN THE POPULATION IS, IN FACT, OVER EVOLUTIONARY TIME, AT LEAST, VERY SUBSTANTIAL. AND WHEN YOU COMBINE THAT WITH THE BIG SURPRISE OF THE LAST 20 YEARS WHICH IS THAT THE NUMBER OF HUMAN GENES IS FAR SMALLER THAN WE EXPECTED, OF COURSE, THEY'RE REUSED IN MULTIPLE TISSUES, ORGANS, AND HAVE AN IMPACT ON DIFFERENT DISORDERS. AMAZING CONCEPT YOU'VE RAISED THERE.

PAT.

DR. LEVITT: HI, KRISTEN. THAT WAS GREAT. AND ACTUALLY THE LAST THING YOU SAID WAS A PART OF WHAT I WAS GOING TO ADDRESS IS THAT THERE ARE -- GENES ARE NOT DISEASE GENES PER SE, LIKE THEY DON'T EXIST TO CAUSE DISEASE. THEY EXIST TO ENCODE PROTEINS TO PERFORM FUNCTIONS FOR THE ORGANISM, RIGHT. AND SO THE INCREASING AMOUNT OF DATA NOW SHOWING THAT GENES THAT HAVE BEEN ASSOCIATED WITH NEURODEGENERATION CLEARLY PLAY A ROLE IN DEVELOPMENT. RIGHT. THE LATEST WAS THIS PAPER THAT CAME OUT IN *SCIENCE* ON HUNTINGTON'S DISEASE IN A MOUSE MODEL IN WHICH THEY WERE ABLE TO TREAT WITH A GLUTAMATE RECEPTOR STIMULATOR AGONIST FOR JUST A SHORT PERIOD OF TIME IN DEVELOPMENT AND CAUSED MAJOR INCREASES IN LIFE SPAN IN THOSE MICE FROM JUST A SEVEN-DAY DEVELOPMENTAL TREATMENT.

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SO THE QUESTION I HAVE IS, GIVEN WHAT YOU JUST SAID, WHICH IS A CORE BELIEF SYSTEM THAT I'VE HAD FOR A LONG PERIOD OF TIME, THAT EVERYTHING IS DEVELOPMENTAL ANYWAY, WHAT CAN YOU TELL US ABOUT HOW STEM CELLS CAN BE USED DIFFERENTLY TO TRY TO UNDERSTAND THE INTERACTIONS THAT YOU DISCUSSED WHICH MAY BE OVERLAPPING BUT NOT IDENTICAL TO CAUSE A PSYCHIATRIC DISORDER THAT EMERGES, LET'S SAY, IN ADOLESCENTS AND A DISORDER OF CELL SURVIVAL OR DEGENERATION WHICH MAY OCCUR DECADES LATER? WHAT'S YOUR TAKE ON HOW STEM CELLS CAN BE USED TO TRY TO DIFFERENTIATE THOSE FROM A MECHANISTIC PERSPECTIVE?

DR. BRENNAND: I THINK WE FEEL LIKE THE GENETICISTS HAVE DONE AN AMAZING JOB AT CATALOGING LISTS OF VARIANTS AND GENES. AND SO WE HAVE THIS WEALTH OF INFORMATION ACROSS MOST DISEASES THAT I WOULD ARGUE WE FAILED TO TURN INTO CLINICAL PRACTICE. IT'S HARD TO ANNOTATE NONCOMMON VARIANT -- NONCODING VARIANTS ESPECIALLY IF THEY'RE GOING TO HAVE DIFFERENT EFFECTS IN DIFFERENT DONORS AND CELL TYPES AND CONTEXT. AND SO I THINK THAT STEM CELLS REPRESENT THIS PLACE TO TEST HYPOTHESIS AND LEARN ABOUT HOW TO INTERPRET NONCODING VARIANTS. AND SO WHAT I MEAN BY THAT IS THAT I DON'T THINK WE ARE EVER GOING TO FIND ONE CURE FOR ALZHEIMER'S OR

ONE CURE FOR AUTISM, MUCH LIKE THERE'S NOT GOING TO BE ONE CURE FOR CANCER. BUT WE ARE GOING TO FIND A LOT OF TREATMENTS THAT WORK IN SOME PEOPLE.

AND SO YOU ARE GOING TO CHIP AWAY -- I'VE HAD PEOPLE ASK, LIKE, HOW LONG ARE WE GOING TO HAVE TO KEEP SEQUENCING PEOPLE WITH DISEASES? AND I SAY, WELL, HONESTLY, TILL WE HAVE ONE TREATMENT THAT WORKS DEPENDENT ON IT. AND THEN THE PHARMA COMPANIES WILL DO ALL THE SEQUENCING FOR US, RIGHT. LIKE WE JUST NEED THAT FIRST PIZZA SLICE. AND WE ARE THERE WITH CANCER. WE HAVE A LOT OF THE PIZZA SLICES. RIGHT. WE DON'T UNDERSTAND EVERYTHING ABOUT CANCER, BUT THERE ARE A LOT OF MUTATIONS NOW THAT IF THIS, THEN THAT DRUG. IF THESE TWO, THEN THIS OTHER DRUG GETS ADDED IN.

AND I THINK WE NEED TO BEGIN TO START, FOR LACK OF A MORE TECHNICAL WORD, BUCKETING PEOPLE. WHO BELONGS TOGETHER? AND IT TURNS OUT IT'S PROBABLY NOT BY CLINICAL PRESENTATION. WE'VE BUCKETED PEOPLE INTO NEURODEGENERATION AND PSYCH BY PHENOTYPES. WE'VE BUCKETED THEM INTO SCHIZOPHRENIA AND AUTISM BY CLINICAL PRESENTATION. BUT IF YOU HAVE A NRXN1 DELETION AND YOU HAVE AUTISM OR SCHIZOPHRENIA, ARE YOU LESS ALIKE THAN TWO SCHIZOPHRENIA PATIENTS OR TWO AUTISM PATIENTS? AND

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I WOULD ARGUE THAT UNDERSTANDING THESE COMMON VARIANT BUCKETS IS JUST AS IMPORTANT AS UNDERSTANDING THAT RARE VARIANT BUCKET.

DR. LEVITT: THANK YOU.

CHAIRMAN GOLDSTEIN: THE OTHER RELEVANT BIT IS THAT IT HAS BEEN RECOGNIZED FOR SOME TIME AND NOBODY HAS BEEN QUITE SURE WHAT TO DO WITH IT, THAT THE NEURODEGENERATIVES OFTEN HAVE PSYCHIATRIC PHENOTYPES. HYPERACTIVITY THAT LOOKS IN SOME WAYS LIKE THE MANIA IN BIPOLAR DISORDER. AND, IN FACT, IT'S -- IN SOME WAYS IT'S AN EASIER TREATMENT OPPORTUNITY THAN THE DEGENERATION BECAUSE MEASURING COGNITIVE DECLINE OR ARREST OF COGNITIVE DECLINE WITH A DRUG CANDIDATE OVER A PERIOD OF YEARS VERSUS DEVELOPING A DRUG THAT HELPS WITH THE BEHAVIORAL PROBLEMS IN ALZHEIMER'S AND PARKINSON'S -- I DON'T KNOW IF FRED KNOWS WHAT IT IS -- WHETHER THERE'S SOMETHING LIKE THIS IN ALS OR NOT -- THOSE ARE MUCH MORE STRAIGHTFORWARD TREATMENT OPPORTUNITIES THAT ACTUALLY WOULD BE VERY HELPFUL TO CAREGIVERS WHO HAVE TO MANAGE PEOPLE WITH THESE TERRIBLE DISORDERS.

SO, FRED, DO YOU KNOW? ARE THERE BEHAVIORAL CHANGES IN ALS PATIENTS THAT ARE BEYOND JUST THE SORT OF OBVIOUS DEPRESSION THAT COMES FROM HAVING A DISORDER LIKE THAT?

DR. FISHER: A HUNDRED PERCENT. THE SAME GENE THAT CAUSES ALS CAUSES FRONTAL TEMPORAL DEMENTIA. SO YES. IT'S ESTIMATED THAT AS HIGH AS 30 PERCENT OF THE PATIENT POPULATION WITH ALS DEVELOP SOME KIND OF COGNITIVE DISORDER, WHICH IS WHY IT'S IMPORTANT TO TALK ABOUT TREATMENT OPTIONS AND END-OF-LIFE OPTIONS VERY EARLY ON WHILE PEOPLE STILL HAVE THE ABILITY TO PARTICIPATE IN THOSE DECISIONS.

CHAIRMAN GOLDSTEIN: YEAH. GREAT POINT. OKAY. OTHER QUESTIONS FOR KRISTEN BEFORE WE WRAP UP THIS PART OF THE MEETING? GOING ONCE, TWICE. KRISTEN, THANK YOU VERY MUCH FOR YOUR TIME TODAY. VERY ILLUMINATING. AND I THINK THE COMBINATION WITH TOM REALLY GAVE US A GREAT WAY TO START THINKING ABOUT THESE DISORDERS IN A SOMEWHAT DIFFERENT WAY.

DR. BRENNAND: IT WAS SO MUCH FUN. AND I'M HAPPY TO COME BACK ANY TIME.

CHAIRMAN GOLDSTEIN: OKAY.

DR. BRENNAND: THANK YOU.

CHAIRMAN GOLDSTEIN: YOU'LL BE COMING BACK INTO CALIFORNIA.

DR. BRENNAND: ASK ME ANY YEAR IN JANUARY.

CHAIRMAN GOLDSTEIN: GOT IT.

DR. BRENNAND: BYE.

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CHAIRMAN GOLDSTEIN: OKAY. SO THE LAST PART OF TODAY'S MEETING, IF I'VE GOT THIS RIGHT -- WELL, OTHER THAN PUBLIC COMMENT, WHICH I SEEM TO BE IN THE HABIT OF FORGETTING, THE LAST ISSUE WE WANT TO TALK ABOUT IS SOMETHING THAT ROSA HAS BROUGHT UP, WHICH IS THE VALUE OF A SURVEY IN CALIFORNIA OF POTENTIAL GRANTEES. THIS MAY ALSO HELP US THINK ABOUT THE QUESTION THAT FRED RAISED, WHICH IS WHY IS THERE SUCH A PAUCITY OF NEUROPSYCHIATRIC PROGRAMS WITHIN THE CIRM PORTFOLIO.

SO, ROSA, IF YOU ARE READY, I'LL TURN THE MIC OVER TO YOU TO TALK ABOUT SURVEYS.

DR. CANET-AVILES: THANK YOU, LARRY. MARIANNE, DO YOU HAVE THOSE TWO SLIDES?

MS. DEQUINA-VILLABLANCA: YES, I DO.

DR. CANET-AVILES: THANK YOU, LARRY. AND THIS WAS ALIGNED WITH WHAT YOU INTRODUCED US WITH AROUND DEVELOPING A BETTER UNDERSTANDING OF WHAT THE COMMUNITY IN CALIFORNIA LOOKS LIKE AND WHAT DO WE THINK THAT WE ARE MORE PRIMED FOR. AND THIS IS ALSO IN REFERENCE TO STEVE JUELSGAARD'S QUESTION ABOUT THAT.

THERE WAS SOMETHING ELSE THAT I WANTED TO MENTION, AND AS STEVE MENTIONED, WHY DON'T WE HAVE AN INVESTMENT SO FAR IN THE RFA NEUROPSYCHIATRY?

AND I THINK THAT WAS ALIGNED -- IF YOU CAN GO TO NO. 3, SLIDE NO. 3. I JUST WANTED TO MENTION THAT THE FIRST PRESENTATION I PRESENTED TO THE TASK FORCE DID AN ANALYSIS OF WHAT KIND OF DISEASE MECHANISMS WORK HAVE WE FUNDED SO FAR. ONE OF THE THINGS THAT CIRM HAD NOT DONE WAS WE DID NOT FOCUS ON WORK AROUND DISEASE MECHANISMS. SO WE DID NOT ASK FOR THESE SPECIFICALLY IN OUR PROGRAM ANNOUNCEMENTS.

SO THIS IS WHAT WE ARE CHANGING HERE. THIS IS WHAT WE WILL BE PROPOSING, AND THIS IS ALIGNED WITH WHAT DR. SUDHOF AND DR. BRENNAND JUST PRESENTED.

SO WITHOUT FURTHER ADO, THE SURVEY IS TO GATHER INPUT FROM MEMBERS OF THE CALIFORNIA SCIENTIFIC COMMUNITY TO ENSURE THAT THE PROGRAM DESIGN WILL LEAD TO PHYSICAL MULTIDISCIPLINARY RESEARCH PROJECTS WITH THE HIGHEST IMPACT AROUND FOUNDATIONAL RESEARCH TO ACCELERATE THE DEVELOPMENT OF THERAPIES FOR NEUROPSYCHIATRIC DISORDERS. AND AS WE WERE JUST MENTIONING, THERE ARE ALSO COMPONENTS, NEUROPSYCHIATRIC COMPONENTS, IN OTHER CNS DISEASES LIKE ALZHEIMER'S, ALS, AND OTHERS.

SO THE DISCUSSION OBJECTIVE OF THE NEXT SLIDE IS NOT TO DISCUSS ANSWERING THE QUESTIONS, BUT TO GATHER FEEDBACK FROM THE TASK FORCE AROUND THE

DESIGN OF THE QUESTIONS TO ACHIEVE THE GOAL THAT WE HAVE HERE. WE AT CIRM HAVE DONE AN ANALYSIS OF POTENTIAL APPLICANTS. SO WE HAVE A LIST OF AROUND 240 RESEARCHERS IN THE STATE OF CALIFORNIA THAT HAVE AT A TIME OR OTHER BEEN WORKING IN NEUROPSYCHIATRIC DISORDERS AND SOME OF THEM ALSO HAVE BEEN WORKING WITH STEM CELLS.

SO WITH THAT SAID, THE FIRST QUESTION, IF YOU COULD MOVE TO THE NEXT SLIDE, MARIANNE, THE FIRST ONE IS ALIGNED WITH WHAT WE HAVE BEEN DISCUSSING IN THE LAST DISCUSSION AFTER KRISTEN'S PRESENTATION. WHICH NEUROPSYCHIATRIC DISEASE AREAS COULD BE MOST PRIME FOR DISEASE MECHANISM RESEARCH WITH STEM CELL MODELS IN NEUROPSYCHIATRIC DISEASES AND WHY? AND THIS COULD BE A MULTIPLE CHOICE TYPE OF QUESTION THAT WE WOULD BE ASKING CALIFORNIA RESEARCHERS.

AND THE GOAL OF THIS QUESTION COULD BE TO FIGURE OUT WHETHER THERE IS -- WHAT'S THE LEVEL OF INTEREST AND ALSO OF RESEARCHERS ALREADY WORKING IN SOME OF THESE DISEASES. SO WE COULD ADD ADDICTION, ANXIETY DISORDERS, INCLUDING PTSD, ATTENTION DEFICIT HYPERACTIVITY DISORDER, AUTISM SPECTRUM DISORDERS, INTELLECTUAL DISABILITY DISORDERS, BIPOLAR, EATING DISORDERS, SCHIZOPHRENIA. SO THESE COULD BE

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MULTIPLE CHOICE SO THAT WE MIGHT BE ABLE TO SEE WHAT'S THE LANDSCAPE OF APPETITE AND OF THE REALITY.

SO I WILL STOP HERE TO SEE IF THERE IS DISCUSSION, FEEDBACK ABOUT THESE QUESTIONS. I DON'T KNOW, LARRY, YOU HAVE ANY INPUT ABOUT HOW DO YOU WANT TO RUN THIS, IF YOU WANTED TO GO THROUGH ALL OF THEM OR IF YOU WANTED TO STOP ONE BY ONE.

CHAIRMAN GOLDSTEIN: I THINK HITTING THEM ONE BY ONE IS FINE, ROSA. I'LL KEEP AN EYE ON THE TIME. AND IF IT LOOKS LIKE WE ARE TAKING TOO MUCH, THEN I CAN MOVE US ALONG A BIT MORE QUICKLY.

DR. CANET-AVILES: OKAY.

CHAIRMAN GOLDSTEIN: I THINK, AS LONG AS I'VE GOT THE MICROPHONE ON HERE, BASED ON WHAT WE'VE JUST HEARD AND WHAT I'VE READ IN THE PAST, THE QUESTION WOULD BE, IN MY MIND, IT SEEMS TO ME A VERY STRONG ARGUMENT FOR STRATIFICATION OF OUR LEVEL OF ATTENTION SHOULD BE RELATED TO THE MAGNITUDE OF THE GENETIC CONTRIBUTION. IF YOU'RE DEALING WITH A HUMAN DISORDER THAT IS PRIMARILY ENVIRONMENTAL, WELL, THAT'S GOING TO BE PRETTY HARD TO MODEL IN STEM CELLS AND ORGANOIDS AND THAT SORT OF TECHNOLOGY. WHEREAS, SOMETHING LIKE SCHIZOPHRENIA WHERE WE JUST HEARD A GREAT DEAL, NOT ONLY IS THERE A VERY STRONG COMPONENT, THE GENETIC ARCHITECTURE IN

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MEASURING RISK, BUT THEY ACTUALLY AFFECT THE CHARACTER OF THE DISEASE, PSYCHIATRIC VERSUS DEGENERATIVE, FROM ALLELES OF THE SAME GENE.

SO IT SEEMS TO ME YOU'D ALMOST WANT TO CALL THE QUESTION OR WE WOULD BE INTERESTED IN HEARING WHAT THE COMMUNITY HAS TO SAY. ARE THERE STRONG ARGUMENTS FOR WORKING ON DISORDERS THAT ARE PRIMARILY ENVIRONMENTAL IN STEM CELL MODELS AS OPPOSED TO, IT SEEMS TO ME, A VERY STRONG ARGUMENT THAT OUR RESEARCHERS ARE GOING TO COME BACK AND TELL US IF THERE'S A STRONG GENETIC COMPONENT, THAT'S WHAT YOU'RE TRAPPING IN THESE CELLS EITHER BY GENOME CAPTURE OR BY CRISPR-INDUCED MUTATIONS. WE'RE GOING TO HEAR THAT.

I'D LOVE TO KNOW IF THERE'S A STRONG ARGUMENT COMING BACK FOR DISORDERS THAT ARE PRIMARILY ENVIRONMENTAL.

DR. LEVITT: LARRY, I WOULD SAY THAT THE TARGETS AND THE TREATMENTS ARE GOING TO BE BASED ON THE STEM CELL BIOLOGY. THE PICTURE, I THINK, AS TOM REALLY FOCUSED ON IS THAT THERE'S A FUNDAMENTAL CHANGE IN HOW THE PRIMARY SOURCE OF INFORMATION PROCESSING, THE SYNAPSE, IS FUNCTIONING. IT'S NOT REFLECTED IN GENE EXPRESSION. IT'S CAUSED -- IN HIS CASE HE USED GENETIC MODELS FOR THAT, AND THAT'S

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PERFECTLY FINE. BUT IT'S CLEAR THAT ENVIRONMENTAL CONTRIBUTIONS CAN END UP DRIVING THE SAME CHAIN BIOLOGICALLY, AND THAT'S THE TARGET FOR THERAPEUTICS.

I'M NOT SUGGESTING THAT -- AN IPS CELL DERIVED FROM SOMEBODY WHO HAS DEPRESSION AND DEPRESSION IS RELATIVELY LOW ON THE SCALE IN TERMS OF HERITABILITY COMPARED TO OTHER PSYCHIATRIC DISORDERS; BUT, NONETHELESS, THE CELLS THAT ARE DERIVED FROM AN INDIVIDUAL WITH MONOPOLAR DEPRESSION MIGHT BE QUITE INFORMATIVE IN TERMS OF UNDERSTANDING WHAT THE CHANGES ARE IN TERMS OF HOW THAT NEURON FUNCTIONS, WHICH WE CAN'T GET FROM A MOUSE.

SO TO ME THE FIRST QUESTION IS WHETHER, FOR ME -- IT'S A FINE QUESTION AND THE DESIGN IS GREAT. DO WE WANT TO SAY MOST PRIMED OR PRIMED? SOMETIMES WHEN YOU SAY MOST PRIMED, YOU GET ANSWERS BACK FROM INDIVIDUALS WHO ARE FOCUSING ON WHAT THEY FEEL IS THE MOST PRIMED. IF YOU USE THE BROADER TERM LIKE PRIMED, THEY MIGHT BE MORE INCLUSIVE OF MENTIONING OTHERS THAT THEY MAY NOT BE FOCUSING ON RIGHT AWAY.

I THINK THE FIRST QUESTION IS OBVIOUSLY A VERY IMPORTANT ONE FROM OUR PERSPECTIVE.

DR. CANET-AVILES: THANK YOU, PAT. AND

ALSO ONE THING TO TAKE INTO ACCOUNT IS IN GENERAL MOST PROJECTS WITH HIGH HERITABILITY AND INCIDENCE OF THE NUMBER OF MUTATIONS ARE THE ONES THAT WILL LEAD TO MORE SUCCESSFUL PROJECTS IN GENERAL. AND WE NEED TO TAKE INTO ACCOUNT THAT THIS HERITABILITY IS MAINTAINED IN THE CELLS AFTER RECOMBINING AS WELL AND DIFFERENTIATION. SO THAT SHOULD BE ALSO SOMETHING TO TAKE INTO ACCOUNT.

DR. LEVITT: YEAH.

CHAIRMAN GOLDSTEIN: THE OTHER ISSUE THAT I DON'T KNOW THAT WE'VE YET -- I DON'T KNOW THAT WE'VE YET CAPTURED IN THE QUESTIONS HERE AND THAT WE'VE SEEN IS TO WHAT EXTENT ARE DIFFERENT NEURODEGENERATIVE OR NEUROCOGNITIVE DISORDERS ENRICHED IN THE DIFFERENT TYPES OF ENVIRONMENTS WE HAVE IN CALIFORNIA. SO UNDERSERVED COMMUNITIES HAVE ONE SET OF PRESSURES THAT THEY HAVE TO DEAL WITH IN THEIR LIVES. WEALTHIER COMMUNITIES, I GUESS, HAVE SOMEWHAT DIFFERENT PROBLEMS. AND IF WE ARE THINKING ABOUT ENVIRONMENTAL STRESSORS, FOR EXAMPLE, EXPOSURE TO LARGE AMOUNTS OF VINYL CHLORIDE BECAUSE YOU LIVE NEAR RAILROAD TRACKS, IS THERE SOME WAY OF CAPTURING THAT IN RESEARCH AREAS THAT OUR COMMUNITIES THINK ARE ACTUALLY TRACTABLE PROBLEMS?

DR. LEVITT: SO I DON'T WANT TO HOG THE

CONVERSATION, BUT I THINK ONE OF THE REALLY IMPORTANT THINGS THAT I DIDN'T QUITE GET A SENSE OF, BUT YOU GET IT FROM READING PAPERS IS THE DEPTH AT WHICH -- AND JONATHAN SABBAT TALKED ABOUT THIS -- THE DEPTH OF INFORMATION YOU GET FROM THOSE PATIENTS FROM WHOM YOU'RE OBTAINING PLURIPOTENTIAL STEM CELLS TO DO YOUR WORK, THAT THAT INFORMATION IS REALLY IMPORTANT, FOR ME ALMOST A REQUISITE, WHICH WOULD ADDRESS, FOR EXAMPLE, LARRY, THE PATIENT COMES FROM WHAT ZIP CODE. RIGHT? INFORMATION THAT'S HARDLY EVER PROVIDED WHEN YOU GET -- THE SOURCES DON'T PROVIDE A BUNCH OF INFORMATION.

SO I THINK EMPHASIZING DIVERSITY IN TERMS OF THE ORIGINS OF THE EXPERIMENTAL CELLS AND WHAT WE MEAN BY DIVERSITY, I THINK, WHICH INCLUDES ANCESTRY, IT INCLUDES THE BUILT AND LIVED ENVIRONMENT, THOSE SORTS OF THINGS. OBVIOUSLY IT'S VERY DIFFICULT TO GET AN ENTIRE LIFE HISTORY, BUT I THINK IT'S IMPORTANT TO EMPHASIZE THAT THE MORE INFORMATION WE GET OR THAT THEY HAVE, THE BETTER THE STUDY IS GOING TO BE IN TERMS OF BEING ABLE TO CORRELATE OUTCOMES WITH FACTORS THAT MAY BE DRIVING IT.

CHAIRMAN GOLDSTEIN: IT'S A GREAT POINT. BECAUSE FOR ALS, FOR EXAMPLE, THERE HAVE BEEN ON-AND-OFF SUPPORT FOR THE IDEAS THAT ENVIRONMENTAL

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EXPOSURE IS A PRIMARY CAUSE VERSUS SOMEWHAT LOWER DOWN. SO MAYBE THE SURVEY QUESTION WOULD BE WHAT DOES THE USER COMMUNITY THINK IS THE RIGHT WAY TO CAPTURE ENVIRONMENTAL INFORMATION IN CONTRIBUTIONS.

DR. LEVITT: YEAH. THERE'S OTHER -- FOR EXAMPLE, PERINATAL COMPLICATIONS INCREASES RISK FOR SCHIZOPHRENIA. IT'S THE MOST DRAMATIC NONGENETIC, SO-CALLED NONGENETIC, CERTAINLY INHERITED FROM THE OFFSPRING, LARGE GENETIC COMPONENT OF INCREASING RISK. IT'S ENORMOUS. AND YET THAT KIND OF INFORMATION MAY OR MAY NOT BE AVAILABLE IN A BANK WHERE YOU MIGHT BE ABLE TO ACCESS STEM CELLS FOR -- PLURIPOTENTIAL STEM CELLS FOR INDUCING WHATEVER CELL TYPE YOU WANT TO STUDY.

AND SO THOSE ARE THE KINDS OF THINGS THAT I THINK ARE REALLY HELPFUL BECAUSE NOT EVERYBODY WITH SCHIZOPHRENIA EXPERIENCE PERINATAL COMPLICATIONS. BUT THOSE WHO EXPERIENCE PERINATAL COMPLICATIONS HAVE AN INCREASED RISK FOR PSYCHIATRIC DISORDERS.

SO THIS IS THE KIND OF THING, NOT MAYBE PART OF THE SURVEY QUESTIONS, BUT CERTAINLY IN TERMS OF ANY KIND OF REQUEST FOR APPLICATION WHERE THE DEPTH OF INFORMATION IS REALLY IMPORTANT.

ONE THING, ROSA, THAT I THOUGHT OF WHEN

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YOU SAY MULTIDISCIPLINARY TEAMS, WOULD YOU WANT INFORMATION ON WHETHER PEOPLE -- ABOUT WHETHER INVESTIGATORS FEEL IT WOULD BE MOST PRODUCTIVE TO WORK AS PART OF A NETWORK, OR ARE WE TALKING ABOUT PROMOTING INDEPENDENT, THE WAY THAT NIH MOSTLY DOES IT EXCEPT IN BIG EFFORTS LIKE GENETICS OR IN BRAIN IMAGING, ARE WE TALKING ABOUT NETWORKS THAT WE WOULD SUPPORT OR INDIVIDUALS OR BOTH?

DR. CANET-AVILES: WE ARE TRYING TO DO A COUPLE OF THINGS HERE WITH THIS. ONE IS TO CATALYZE COLLABORATIVE EFFORTS BETWEEN DISCIPLINES THAT ARE NOT PER SE WORKING CURRENTLY IN NEUROPSYCHIATRIC DISORDERS. SO WE ARE TRYING TO BRING IN COMPUTATIONAL BIOLOGIES WITH NEUROBIOLOGIES WITH IMMUNOLOGISTS TOGETHER AND AT THE SAME TIME WITH CLINICIANS, WHICH ULTIMATELY COULD HAVE THE KNOWLEDGE OF THE CLINICAL ASPECTS OF THE DISEASE, BUT ALSO ACCESS TO THE PATIENTS. SO WE ARE TRYING TO CATALYZE THOSE MULTIDISCIPLINARY THREE TO FOUR, LIKE THAT'S INITIALLY WHAT WE ARE THINKING, AND THAT'S WHY WE WANT TO SEE WHAT PEOPLE ARE READY TO OR INCENTIVIZED TOWARDS OR LOOKING FORWARD TO. SO WE WOULD LIKE TO ASK THIS. SO HOPEFULLY THAT ANSWERS YOUR QUESTION.

WE WANT TO KNOW WHAT DISCIPLINES ARE

LACKING TO FURTHER OUR UNDERSTANDING OF FOUNDATIONAL MECHANISMS OF THESE DISEASES.

CHAIRMAN GOLDSTEIN: GREAT POINT. FRED.

DR. FISHER: I REALLY FEEL LIKE I'M IN THE WRONG GROUP. WHY DO WE NEED A SURVEY TO TELL THIS INFORMATION WHEN APPARENTLY THERE ARE EXPERTS IN THE FIELD THAT UNDERSTAND THE USE OF STEM CELLS IN GENETICS IN THE EXPLORATION OF UNDERSTANDING NEUROPSYCHIATRIC DISEASE? AND THOSE PEOPLE HAVE AN OPEN INVITATION TO APPLY TO ANY NUMBER OF OUR BUCKETS OF FUNDING. HERE I THINK I'M IN A WORK GROUP THAT'S SUPPOSED TO BE LOOKING AT HOW TO DEPLOY OR EVALUATE OUR DEPLOYMENT OF NEURO FUNDING. AND WE ARE NOW CREATING A SURVEY TO ASK QUESTIONS THAT, IN MY MIND, THAT THE PEOPLE REQUESTING THE FUNDING SHOULD BE ABLE TO TELL US. I DON'T UNDERSTAND THE PURPOSE OF THIS AT ALL.

SO THAT'S WHY I FEEL LIKE I'M COMPLETELY LOST AND REALLY NOT UNDERSTANDING WHAT I'M DOING HERE BECAUSE I KEEP BEING SURPRISED BY WHAT WE ARE DOING.

DR. LEVITT: FRED, I'LL ANSWER THAT AS SOMEBODY WHO'S BEEN WORKING IN THIS FIELD FOR A LONG TIME. MANY SHIFT CHANGES IN EFFORTS THAT INVESTIGATORS MAKE IS BASED ON, AND MOST OF OUR

FUNDING COMES FROM THE NATIONAL INSTITUTES OF HEALTH FOR THIS KIND OF RESEARCH, COMES FROM NATIONAL INSTITUTES OF HEALTH WORKSHOPS THAT ARE RUN OR SURVEYS THAT ARE GENERATED TO GET THIS KIND OF INFORMATION AND THEN SCULPT REQUESTS FOR APPLICATIONS THAT ADDRESS THE THOUGHT PROCESSES OF INVESTIGATORS WHO MAY BE WORKING IN A CERTAIN AREA THAT IS NOT PARTICULARLY RELEVANT TO USE OF STEM CELLS, BUT MIGHT FIND A REQUEST FOR APPLICATION IN THE EMPHASIS AREAS IN PARTICULAR SOMETHING THAT ALIGNS WITH WHAT THEY FEEL THEY COULD ACCOMPLISH WITH FUNDING.

IT DOESN'T NECESSARILY COME FROM THE INVESTIGATOR INDEPENDENT OF THE FUNDING AGENCY IN TERMS OF WHAT THE PRIORITIES ARE FOR THE FUNDING AGENCY. THE NIH DOES THIS ALL THE TIME. THE DEPARTMENT OF EDUCATION DOES IT ALL THE TIME. HRSA, SAMHSA, ALL THESE FEDERAL AGENCIES OFTEN GET THIS KIND OF INFORMATION BECAUSE THEY WANT TO TRY TO ALIGN THEIR NEW INITIATIVES WITH WHAT INVESTIGATORS MIGHT FEEL WOULD BE RELEVANT FOR THE KINDS OF INCREASED ACTIVITY THAT THEY MAY NOT BE PURSUING AT THE TIME.

THAT'S MY OWN BELIEF SYSTEM AND MY OWN EXPERIENCE AS AN INVESTIGATOR. THAT'S WHAT I'VE

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EXPERIENCED FOR A LONG TIME. SO THIS IS PRETTY USUAL, NOT UNUSUAL. AND ALSO FOUNDATIONS DO THIS AS WELL. PRIVATE FOUNDATIONS OFTEN TRY TO UNDERSTAND THE NATURE OF THE PLAYING FIELD IN TERMS OF THE INVESTIGATORS. AND NOT DEVIATING FROM THEIR MISSION, BUT TRYING TO ALIGN WHAT THEY ARE TRYING TO SUPPORT AND DO IT IN A WAY THAT ALIGNS WITH HOW THEY FEEL THEY CAN GET INVESTIGATORS TO SPEND MORE TIME ON THEIR PARTICULAR GOALS, ON THE GOALS OF THE FOUNDATION.

CHAIRMAN GOLDSTEIN: YEAH. I WOULD JUST ADD TO THAT TWO POINTS, AND THEN WE SHOULD MOVE ON TO THE NEXT QUESTION, I THINK. ONE IS THAT THE WAY YOU WRITE AN RFA HAS A BIG IMPACT, AS I'M SURE YOU'VE EXPERIENCED IN BEING HEAD OF YOUR ORGANIZATION, FRED. HOW YOU WRITE THE RFA HAS A BIG IMPACT ON WHAT SORTS OF GRANTS YOU GET BACK IN AND WHAT SORTS OF PROPOSALS YOU GET TO SEE. AND IF YOU WANT TO SEE A LOT OF MULTIDISCIPLINARY PROPOSALS, YOU NEED TO STRUCTURE THINGS APPROPRIATELY IF YOU THINK THAT'S THE MOST INTERESTING KIND OF APPLICATION TO COME IN.

THE OTHER THING IS ACADEMIC INSTITUTIONS MOSTLY ARE EXTREMELY SILOED. AND SO IF YOU DON'T HAVE INCENTIVES TO TRY TO INCLUDE, FOR EXAMPLE,

HIGHLY RIGOROUS, SOPHISTICATED STATISTICIANS IN THE FACE OF A DISORDER THAT'S ENORMOUSLY VARIABLE LIKE ALS, IT'S HARD TO MAKE SURE YOU'RE FINANCING THE RIGHT KINDS OF INVESTIGATIONS.

BUT WE BETTER MOVE ON TO THE NEXT COUPLE OF QUESTIONS. WE ONLY HAVE A FEW MINUTES LEFT, ROSA.

DR. CANET-AVILES: YES. SO I THINK WE TALKED A LITTLE BIT ABOUT THE MULTIDISCIPLINARY TEAM ALREADY. SO UNLESS THERE IS ANY. AND THE NEXT ONE, NO. 3, WOULD BE WHAT'S THE IDEAL SIZE OF A MULTIDISCIPLINARY TEAM? THE GOAL HERE WAS THINKING -- OUR THINKING RIGHT NOW IS THAT THREE TO FOUR, NO MORE THAN THAT, BETWEEN STATISTICIAN, COMPUTATIONAL BIOLOGIES, THE STEM CELL SCIENTISTS, CLINICIANS, THAT SHOULD BE. BUT THEN IF WE SEE THAT THE ANSWER IS LIKE MULTIDISCIPLINARY TEAMS OF SEVEN, THAT WILL GIVE US A GUIDANCE TO INCLUDE UP TO SEVEN, FOR EXAMPLE, IN THE PROGRAM ANNOUNCEMENT. THAT'S WHAT THE IDEA OF THIS WAS.

I THINK AL HAS A COMMENT, LARRY.

MR. ROWLETT: SO, FIRST, I WANT TO SAY I REALLY DO APPRECIATE YOUR COMMENTS, LARRY, ABOUT ACADEMIC INSTITUTIONS BEING SILOED. THAT EXPLAINS SOME OF THEIR ANSWERS TO THE QUESTIONS RELATED TO

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DEI. BUT AS IT REFERENCES THE IDEAL SIZE, SO I THOUGHT I WAS APPRECIATING, PAT, YOUR POINT WAS THAT WE MIGHT ACTUALLY INVOLVE OR APPLYING ENTITIES MIGHT ACTUALLY INVOLVE INDIVIDUALS WHO HAVE BEEN IMPACTED BY NEUROPSYCHIATRIC DISORDERS AS A PART OF THEIR MULTIDISCIPLINARY TEAM. AND I SAY THAT BECAUSE ON THE SOCIAL SCIENCE SIDE, IT IS QUITE COMMON, ESPECIALLY WHEN WE ARE APPLYING TO ENTITIES THAT HAVE MORE OF A SOCIAL DETERMINANT FOCUS TO BE REQUIRED TO INCLUDE PEOPLE WHO HAVE EXPERIENCED THE DISORDER OR TO REALLY FOCUS ON ACTIVITIES IN GEOGRAPHIC LOCATIONS WHERE THERE'S A DISPROPORTIONATE CONCERNS OF SPECIFIC FACTORS THAT LEAD TO WHAT WE ARE STUDYING, NEUROPSYCHIATRIC SYMPTOMS.

SO IT'S COMMON FOR US, AND SO I'M A LITTLE BIT CHALLENGED BY US PRESCRIBING AN IDEAL SIZE. IF I'M UNDERSTANDING THE THOUGHT PROCESS IN THAT IT WOULD BE UP TO THE APPLICANT TO DETERMINE THAT.

DR. CANET-AVILES: SO JUST TO CLARIFY, THE TEAM, IT COULD BE THE RESEARCHERS. SO WE USUALLY HAVE A TEAM THAT'S ONE PI, AND THEN THAT'S WHERE WE ARE GEARING THE FUNDING. WHAT WE ARE THINKING ABOUT HERE IS POTENTIALLY A PI -- WE HAVE TWO OR THREE PI'S AT THE SAME LEVEL OF COMMITMENT AND

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COLLABORATIVE EFFORT IN AN AWARD. THESE ARE GOING TO BE POTENTIALLY LARGE AWARDS TO ADVANCE THE FUNDAMENTAL UNDERSTANDING OF THESE DISEASES. SO THAT'S WHERE WE ARE GOING, AND THAT'S WHY WE ARE ASKING.

MR. ROWLETT: SO THAT DOESN'T PROHIBIT OTHER INDIVIDUALS AS BEING A PART OF WHAT I TECHNICALLY DESCRIBE AS A MULTIDISCIPLINARY TEAM. AND, AGAIN, I HAVE A DIFFERENT PERSPECTIVE AROUND THIS, THAT WHAT YOU'RE DESCRIBING TO ME IS AN APPLICATION WHERE YOU WOULD ASK THE APPLICANT TO IDENTIFY MULTIPLE PI'S AS PART OF THE MULTIDISCIPLINARY TEAM.

DR. CANET-AVILES: CORRECT. WE DON'T KNOW IF WE WILL BE ABLE TO CALL THEM PI'S BECAUSE THAT'S PER THE GRANT ADMINISTRATION POLICY. CO-PI'S DO NOT EXIST. SO WE MIGHT HAVE TO ASK THE BOARD TO ALLOW FOR THAT. BUT THAT'S WHERE WE WERE GOING. WE WANT TO HAVE A MULTITYPE OF PI EFFORT SO THAT PEOPLE FEEL RESPONSIBLE FOR DIFFERENT PARTS OF A VERY MULTIDISCIPLINARY EFFORT.

DR. LEVITT: BUT I WOULD SAY -- I KNOW WE'RE GOING TO GO OVER TO ADDRESS AL'S COMMENT. AL, SO WHAT YOU DESCRIBE IS VERY COMMON IN CLINICAL RESEARCH PROJECTS, WHETHER THEY'RE DESCRIPTIVE OR

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WHETHER THEY'RE CLINICAL TRIALS. IT'S VERY, VERY COMMON TO BE INCLUSIVE. THAT WOULD INCLUDE COMMUNITY MEMBERS IMPACTED IN THE SPECIFIC AREA OF BIOMED MEDICAL RESEARCH THAT'S BEING DONE. IT'S VERY UNCOMMON IN WHAT WE WOULD DEFINE AS BASIC RESEARCH, BUT SOMETHING THAT I THINK WE SHOULD CONSIDER.

WE DO WITH OUR RESEARCH INSTITUTE AND THERE'S A LOT OF BASIC STUDIES AND WE HAVE COMMUNITY MEMBERS WHO ARE INVOLVED AND THERE ARE FOUNDATIONS THAT DO THAT AS WELL. I THINK IT'S AN INTERESTING POINT TO BRING UP. BUT CERTAINLY IN TERMS OF CLINICAL RESEARCH, IT'S VERY COMMON TO DO EXACTLY WHAT YOU DISCUSS AND THEY'RE PART OF THE TEAM.

MR. ROWLETT: THANK YOU, PAT.

CHAIRMAN GOLDSTEIN: SO, LOOK, THIS IS A FASCINATING CONVERSATION THAT I DO THINK IS VERY USEFUL. BUT WE'VE HIT OUR TIME LIMIT FOR THE DAY. I DON'T WANT TO MESS UP ANYBODY ELSE'S CALENDAR. FOLKS --

DR. LEVITT: LARRY, CAN I JUST MAKE ONE SUGGESTION?

CHAIRMAN GOLDSTEIN: SURE.

DR. LEVITT: TO ALIGN THE TERM WE USE WITH OUR FUNDING, INSTEAD OF SAYING -- I JUST PUT THIS

OUT THERE. INSTEAD OF BASIC RESEARCH, CAN WE SAY DISCOVERY RESEARCH BECAUSE THAT'S WHAT OUR GRANTS ARE CALLED AT THE MECHANISTIC LEVEL. THEY'RE DISCOVERY RESEARCH, NOT TO BE CONFUSED WITH -- BECAUSE THE INTERPRETATION OF BASIC RESEARCH MAY BE SO FUNDAMENTAL AND NOT TRANSLATABLE INTO THE TRANS GRANTS. THAT IS MY ONLY WORRY ABOUT THAT TERM.

DR. CANET-AVILES: WELL, THAT'S FINE. THAT'S OKAY. YEAH. THAT'S OKAY. WE CAN SAY DISCOVERY RESEARCH.

CHAIRMAN GOLDSTEIN: WE ARE PARTLY THERE.

DR. CANET-AVILES: IT'S DISCOVERY AND VALIDATION TYPE OF RESEARCH, IDENTIFICATION, DISCOVERY VALIDATION. SO THAT'S WHY WHERE WE ARE GOING IS FUNDAMENTAL MECHANISTIC RESEARCH. WE ARE KIND OF BEING A LITTLE BIT DIFFERENT FROM THE WAY WE'VE BEEN THINKING ABOUT DISCOVERY. BUT THAT'S FINE. THIS IS EARLY RESEARCH, BASIC DISCOVERY. WE WILL CALL IT DISCOVERY SO IT ALIGNS WITH THE PILLAR OF FUNDING.

CHAIRMAN GOLDSTEIN: SO, TASK FORCE MEMBERS, YOU'VE ALL SEEN THE QUESTIONS. PLEASE EMAIL ROSA WITH ANY OTHER QUESTIONS OR SUGGESTIONS THAT YOU HAVE. WE WON'T GET THIS TO BE IDEAL, BUT LET'S GO FOR BEST POSSIBLE.

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DR. CANET-AVILES: THANK YOU, LARRY. WE WERE INTENDING TO SEND IT BY WEDNESDAY BECAUSE WE NEED THE CONCEPT TO FINALIZE FOR THE TASK FORCE MEETING ON THE 15TH OF MAY. SO WE WANT TO MAKE SURE THAT WE GATHER UP THE INPUT. THANK YOU, LARRY.

CHAIRMAN GOLDSTEIN: SURE. SO EMAIL ROSA QUICKLY IF YOU HAVE ANY THOUGHTS.

OKAY. SO THAT'S IT FOR TODAY. I THINK WE SHOULD WRAP UP. NEXT MEETING WILL INCLUDE TALKS BY DAN GESCHWIND AND LILY YESHQAVA (PHONETIC) PRIMARILY ON SINGLE-CELL METHODS OF ANALYSIS AND THE TECHNOLOGIES THAT ARE BEING DEVELOPED TO MAKE THAT POSSIBLE. IT'S A VERY IMPORTANT AREA THAT'S DEVELOPING. AND ROSA WILL HAVE A DETAILED CONCEPT PLAN FOR US TO TALK ABOUT AS WELL. SO IT WILL BE A LIVELY MEETING, UNLIKE ALL THE OTHERS WHICH HAVE BEEN SLOW. SO THANK YOU ALL FOR YOUR TIME.

MS. DEQUINA-VILLABLANCA: LARRY.

CHAIRMAN GOLDSTEIN: OH, PUBLIC COMMENT, RIGHT.

MS. DEQUINA-VILLABLANCA: YES. AND THERE WAS TWO THAT WERE RECEIVED EARLIER IF I CAN READ THOSE REAL QUICKLY.

CHAIRMAN GOLDSTEIN: GO FOR IT.

MS. DEQUINA-VILLABLANCA: OKAY. GREAT.

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THIS ONE IS FROM DR. YE ZHANG FROM UCLA. "STUDYING THE BASIC BIOLOGY OF NEURAL STEM CELLS AND BASIC DEVELOPMENTAL NEUROBIOLOGY IS VITAL FOR UNDERSTANDING THE NEUROLOGICAL AND PSYCHIATRIC DISORDERS BECAUSE IT HELPS US UNLOCK POTENTIAL THERAPEUTIC TARGETS AND DEVELOP MORE EFFECTIVE TREATMENTS. BY UNDERSTANDING THE FULL MECHANISMS OF NEURAL STEM CELL BEHAVIOR, SUCH AS THEIR GENERATION, DIFFERENTIATION, AND DEPLETION, WE CAN GAIN INSIGHTS INTO A WIDE RANGE OF DISORDERS.

"WHILE IT'S TRUE THAT INVESTIGATING NEUROLOGICAL AND PSYCHIATRIC DISEASES DIRECTLY CAN LEAD TO SHORT-TERM PROGRESS, WE ALSO NEED BASIC NEURAL STEM CELL AND NEURAL DEVELOPMENT RESEARCH TO BUILD A CONTINUOUS PIPELINE FOR NEW THERAPEUTIC TARGETS. BY UNDERSTANDING HOW NEURAL STEM CELLS RESPOND TO DIFFERENT SIGNALS DIFFERENTIATE INTO SPECIALIZED CELL TYPES AND CONTRIBUTE TO THE REPAIR AND REGENERATION OF DAMAGED TISSUES, WE CAN DEVELOP NOVEL THERAPIES TARGETING THE UNDERLYING CAUSE OF THESE DISEASES.

"MOUSE MODELS HAVE BEEN INVALUABLE FOR STUDYING THE COMPLEX PROCESSES INVOLVED IN NEURAL STEM CELL BIOLOGY. THEY ALLOW US TO MANIPULATE SPECIFIC GENES OR TRUSTED ENVIRONMENTAL STRESSORS IN

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A CONTROLLED, REPRODUCIBLE MANNER. THIS PROVIDES INSIGHTS INTO HOW THESE FACTORS IMPACT NEURAL STEM CELL BEHAVIOR AND CONTRIBUTE TO THE DEVELOPMENT OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS. MOUSE MODELS ALSO ENABLE US TO STUDY NEURAL STEM CELL TRANSPLANTATION AND THE POTENTIAL FOR CELL REPLACEMENT THERAPIES IN THE CONTEXT OF NEURODEGENERATIVE DISEASES.

"INVESTING IN BASIC NEURAL STEM CELL RESEARCH, INCLUDING STUDIES USING MOUSE MODELS, IS AN EXCELLENT LONG-TERM STRATEGY. IT CAN PAVE THE WAY FOR MORE EFFECTIVE AND TARGETED TREATMENTS. IT'S ESSENTIAL THAT CIRM INVEST IN THE STUDY OF THE BASIC BIOLOGY OF NEURAL STEM CELLS AND BASIC DEVELOPMENTAL NEUROBIOLOGY, INCLUDING USING MOUSE MODELS, AS THIS KNOWLEDGE HAS THE POTENTIAL TO IMPROVE OUR APPROACH TO UNDERSTANDING AND TREATING A VAST ARRAY OF NEUROLOGICAL AND PSYCHIATRIC CONDITIONS."

AND THEN THE LAST ONE IS FROM PAUL KNOEPFLER FROM UC DAVIS. "CEREBRAL PALSY OR CP IS A COMMON NEUROLOGICAL CONDITION PRESENT IN ABOUT THREE OUT OF THOUSAND CHILDREN, AND MORE THAN 750,000 PEOPLE ARE LIVING WITH THIS CONDITION IN THE U.S. TODAY. CP GENERALLY RESULTS FROM BRAIN INJURY

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DURING PREGNANCY OR AT BIRTH. TWO MAIN, MORE SPECIFIC CAUSES OF CP-RELATED BRAIN ISSUES ARE HYPOXIA OR LACK OF OXYGEN AND GENETIC VARIANTS, INCLUDING MUTATIONS.

"CP MANIFESTS WITH NUMEROUS SYSTEMS, INCLUDING MOVEMENT DISORDERS AND DELAYED COGNITIVE DEVELOPMENT. "THERE IS A GROWING APPRECIATION OF THE PSYCHIATRIC ELEMENTS TO CP TOO. FOR EXAMPLE, PEOPLE WITH CP ARE ANYWHERE FROM TWO TO TENFOLD MORE LIKELY TO HAVE ANXIETY AND DEPRESSION AS WELL AS OTHER PSYCHIATRIC CONDITIONS.

"THERE ARE RELATIVELY FEW EFFECTIVE TREATMENT AND PREVENTION OPTIONS FOR CP, LEAVING AN IMPORTANT HEALTH GAP. IN PART THIS GAP IS DUE TO THE MANY OPEN QUESTIONS SURROUNDING QUESTIONS OF CP CAUSE AND MECHANISMS. RESEARCH ON THE GENETIC ELEMENTS OF CP IS A PARTICULARLY EXCITING NEW AREA THAT REQUIRES MORE EMPHASIS AND SUPPORT. DESPITE THE LARGE SCOPE OF HEALTH PROBLEMS WITH CP, IN GENERAL THERE HASN'T BEEN ENOUGH RESEARCH INTO THE CONDITION, AND CIRM ITSELF HISTORICALLY HAS FUNDED RELATIVELY FEW CP FOCUSED GRANTS.

"I STRONGLY SUPPORT THE CIRM NEUROPSYCHIATRIC PROGRAM AND BELIEVE THAT CP IS ONE IMPORTANT AREA THAT SHOULD BE A FOCUS WHERE CIRM

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COULD HAVE DISPROPORTIONATELY LARGE POSITIVE IMPACT MOVING FORWARD."

CHAIRMAN GOLDSTEIN: THANK YOU, MARIANNE. OKAY. IS THERE ANYTHING ELSE I'VE MISSED BEFORE WE ADJOURN HERE? OTHERWISE, WE ARE OUT OF THERE. HAVE A GOOD EARLY MAY. TALK TO YOU SOON, GUYS. BYE.

(THE MEETING WAS THEN CONCLUDED AT 2:09 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 APRIL 24, 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.

BETH C. DRAIN, CSR 7152
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