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: MAY 15, 2023
1 P.M.

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

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I N D E X

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MAY 15, 2023; 1:00 P.M.

CHAIRMAN GOLDSTEIN: OKAY. GREAT. THANK YOU, MARIANNE.

LET'S SEE. SO LET ME CALL US TO ORDER, AND THEN THE FIRST ITEM OF BUSINESS IS MARIANNE IS SUPPOSED TO CALL THE ROLL.

MS. DEQUINA-VILLABLANCA: LET'S MAKE SURE WE GET THE RECORDING. ALL RIGHT.

LEONDRA CLARK-HARVEY.

DR. CLARK-HARVEY: PRESENT.

MS. DEQUINA-VILLABLANCA: MARIA BONNEVILLE. MARK FISCHER-COLBRIE. FRED FISHER.

DR. FISHER: GOOD AFTERNOON.

MS. DEQUINA-VILLABLANCA: JUDY GASSON.

DR. GASSON: HERE.

MS. DEQUINA-VILLABLANCA: LARRY GOLDSTEIN.

CHAIRMAN GOLDSTEIN: HERE.

MS. DEQUINA-VILLABLANCA: DAVID HIGGINS.

DR. HIGGINS: HERE.

MS. DEQUINA-VILLABLANCA: VITO IMBASCIANI.

DR. IMBASCIANI: HERE.

MS. DEQUINA-VILLABLANCA: STEVE JUELSGAARD.

DR. JUELSGAARD: PRESENT.

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MS. DEQUINA-VILLABLANCA: PAT LEVITT.
DR. LEVITT: HERE.
MS. DEQUINA-VILLABLANCA: LAUREN MILLER-ROGEN.
MS. MILLER-ROGEN: HERE.
MS. DEQUINA-VILLABLANCA: AL ROWLETT.
MR. ROWLETT: PRESENT.
MS. DEQUINA-VILLABLANCA: MARVIN SOUTHARD.
DR. SOUTHARD: PRESENT.
MS. DEQUINA-VILLABLANCA: KEITH YAMAMOTO.
ALL RIGHT. WE ARE GOOD. WE HAVE QUORUM.
CHAIRMAN GOLDSTEIN: THANK YOU, MARIANNE. AND DO WE HAVE OUR SPEAKERS PRESENT?
DR. GESCHWIND: YES.
MS. DEQUINA-VILLABLANCA: BOTH SPEAKERS ARE PRESENT, YES.
CHAIRMAN GOLDSTEIN: AND LILIA?
DR. IAKOUCHEVA: HERE.
CHAIRMAN GOLDSTEIN: GOOD. OKAY. GREAT.
SO I WANT TO TAKE A FEW MINUTES BEFORE TURNING THE MICROPHONE OVER TO DAN AND LILIA. AND I THOUGHT IT WOULD BE USEFUL IF I JUST REVIEWED WHERE WE'VE BEEN AND HOW WE GOT TO WHERE WE ARE WITH THIS TASK FORCE. YOU MAY RECALL THAT OUR FIRST MEETING WAS ON FEBRUARY THE 22D. AND ONE OF THE THINGS WE

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DID THERE IS WE GOT A VERY BRIEF OVERVIEW OF THE CIRM PORTFOLIO, WHAT KINDS OF GRANTS ARE BEING FUNDED, WHERE WERE THEY, WHAT TOPICS. AND AFTER SOME DISCUSSION AMONGST OURSELVES AND WITH THE CIRM STAFF, WE REALIZED THAT MANY OF THE TRADITIONAL AREAS OF NEUROSCIENCE AND NEURO DISEASE WERE ACTIVELY BEING FUNDED AND WERE MOVING ALONG, I DON'T KNOW, BUT HEALTHY WAYS IS THE RIGHT WAY TO SAY IT FOR SOME OF THE AREAS WHICH ARE VERY HARD, BUT PROGRESS WAS BEING MADE.

ONE OF THE THINGS THAT WE COLLECTIVELY NOTICED WAS THAT THE AREA OF NEUROPSYCHIATRIC DISEASE, SO DISEASES SUCH AS DEPRESSION, ANOREXIA, BIPOLAR, WHAT HAVE YOU, WERE ACTIVELY -- WERE PRIMARILY MISSING FROM OUR PORTFOLIO. AND AFTER A CONSIDERABLE AMOUNT OF DISCUSSION AT THAT MEETING, WE AGREED ON TWO THINGS. ONE IS THAT WE WANTED TO WORK WITH THE CIRM TEAM TO LEARN MORE ABOUT THE NEUROPSYCHIATRIC AREA TO SEE IF WE THOUGHT THAT THERE WERE GOOD AVENUES OF APPROACH USING STEM CELLS OR GENE THERAPY. AND I'LL JUST BLOW THE SUSPENSE. I THINK THAT WE'VE LEARNED THAT, IN FACT, THERE'S SOME GOOD THINGS TO DO. AND THE SECOND THING WE AGREED IS THAT WE WOULD PICK UP AND CONTINUE OUR DISCUSSION OF THE GENERAL PORTFOLIO AT CIRM AND IN

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THE STATE OF CALIFORNIA AND ASK WHETHER THERE ARE OTHER AREAS OF OPPORTUNITY THAT WERE UNDERFUNDED AND EVENTUALLY TO TRY TO TANGLE WITH THE QUESTION OF WHETHER A BILLION AND A HALF, SOME FOLKS THINK IT'S A SET ASIDE, SOME FOLKS THINK IT'S A TARGET, BUT APPROXIMATELY A BILLION AND A HALF, WERE WE ADEQUATELY TAKING ADVANTAGE OF THAT OPPORTUNITY TO MAKE AN IMPACT IN ALL AREAS OF NEUROSCIENCE AND NEUROMEDICINE.

I'LL SAY THAT OF THOSE TWO AREAS, WE HAVEN'T BEEN AS ACTIVELY DISCUSSING THE GENERAL PORTFOLIO ISSUES AT CIRM. AND I THINK THAT'S SOMETHING WE NEED TO TAKE UP AGAIN ACTIVELY AT THE NEXT MEETING OR THE ONE BEYOND. BUT I WILL SAY THAT I THINK WE'VE DONE A PRETTY GOOD JOB OF EDUCATING OURSELVES ABOUT THE STATE OF THE NEUROPSYCHIATRIC DISEASE FIELD. AND LET ME JUST GIVE YOU A QUICK SUMMARY OF THAT.

AT THE FIRST MEETING, WHICH WOULD HAVE BEEN OUR MARCH MEETING, WE HAD TWO SPEAKERS, JONATHAN SABAT FROM UC SAN DIEGO, AND I FORGET THE GUY'S NAME, BUT DR. PIERCE FROM MASS GENERAL. AND WHAT WE LEARNED FROM THEM WAS A GOOD DEAL ABOUT NEUROPSYCHIATRIC GENETICS. AND WE LEARNED THAT THERE WAS CONSIDERABLE GENETIC INFLUENCES ON DISEASE

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AND, IN GENERAL, THE PATTERNS OF VARIATION THAT SEEM TO BE SUPPORTING THE DEVELOPMENT OF NEUROPSYCHIATRIC DISEASE WERE SIMILAR TO WHAT'S SEEN IN OTHER DISORDERS OF THE BRAIN, WHICH IS THAT THERE WERE A COUPLE OF RARE, HIGHLY ACTIVE VARIANTS THAT PREDISPOSE STRONGLY TO DISEASE AS ONE CATEGORY. AND THEN AS A SECOND CATEGORY THERE WERE CLEARLY CASES WHERE LOTS OF VARIANTS, EACH OF SMALL EFFECT, WORKED TOGETHER TO GENERATE DISEASE. AND THOSE VARIANTS TENDED TO BE COMMON IN THE HUMAN POPULATION, AND EACH ONE OF THEM WAS OF RELATIVELY SMALL EFFECT, BUT THIS IS SORT OF THE PATTERN FOR A LOT OF DISEASES OF THE BRAIN AND OF OTHER PARTS OF THE ANATOMY.

IN THE APRIL MEETING, WHICH WAS LAST MONTH, WE HEARD FROM TOM SUDHOF AND KRISTEN BRENNAND, AND WE LEARNED THAT, IN FACT, STEM CELLS LOOKED AS THOUGH THEY COULD BE ACTIVELY USED IN THE FIGHT AGAINST NEUROPSYCHIATRIC DISEASE AND HOPEFULLY IN THE DEVELOPMENT OF THERAPEUTIC AVENUES. AND IN PARTICULAR WE HEARD FROM TOM A REALLY BEAUTIFUL SERIES OF EXPERIMENTAL OBSERVATIONS MADE IN HIS LAB WHERE THEY DISSECT3ED ONE OF THE NEUROPSYCHIATRIC DISORDERS USING STEM CELLS AND OTHER APPROACHES AND WERE ABLE TO TRACK THE DISORDER DOWN TO A DEFECT IN THE BEHAVIOR OF A MAJOR PROTEIN AT THE CONNECTION

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BETWEEN NEURONS OR SYNAPSES, WHICH MAKES SOME SENSE. BUT TOM'S'S WORK, I THINK, WAS REALLY A GREAT EXAMPLE OF WHAT MAY BE ACHIEVABLE IN THIS FIELD IF THERE'S ADEQUATE INVESTMENT.

AND THEN, FINALLY, WE HAVE TODAY'S MEETING WITH DAN GESCHWIND AND LILIA -- OH, I'M GOING TO MESS THIS UP, LILIA -- IAKOUCHEVA. I'M CLOSE AT LEAST.

DR. IAKOUCHEVA: GOOD ENOUGH.

CHAIRMAN THOMAS: GOOD ENOUGH. OKAY. THANK YOU.

AND THEY'LL TELL US ABOUT ADDITIONAL IT PHENOTYPIC METHODS AND APPROACHES THAT CAN BE USED TO FURTHER EVALUATE THE INFLUENCE OF GENETICS ON THESE DISORDERS AND TO IMPROVE OUR UNDERSTANDING. AND SO WITH THAT AS BACKGROUND, I NOW WANT TO TURN THE FLOOR OVER TO OUR TWO SPEAKERS, EACH OF WHOM WILL SPEAK FOR ON THE ORDER OF 20 MINUTES AND THEN GIVE US FIVE OR TEN MINUTES OF DISCUSSION APIECE.

OUR FIRST SPEAKER IS DAN GESCHWIND, WHO IS A FACULTY MEMBER AT UC LOS ANGELES. HE'S WELL-KNOWN FOR HIS WORK IN AUTISM AND A NUMBER OF OTHER NEUROGENETIC DISORDERS USING NOT JUST MEASUREMENTS OF RNA, BUT SOPHISTICATED MATHEMATICS TO TRY TO UNDERSTAND HOW THESE DISORDERS ARE GENERATED.

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AND OUR SECOND SPEAKER IS, AS I MENTIONED, LILIA IAKOUCHEVA, WHO'S A FACULTY MEMBER AT UC SAN DIEGO, WHO I DON'T KNOW WELL, BUT WAS RECOMMENDED TO ME BY A COLLEAGUE FOR HER WORK ON SINGLE-CELL RNA METHODS AND RELATED TECHNOLOGIES.

BOTH OF OUR SPEAKERS AND PARTICIPANTS ARE WELL-RESPECTED IN THE NEUROPSYCHIATRIC GENETICS COMMUNITY. AND I THINK WITH NO FURTHER FUSS, LET ME TURN THE PODIUM OVER TO WHICHEVER ONE OF YOU WOULD LIKE TO GO FIRST.

DR. GESCHWIND: OKAY. HOW DO YOU WANT TO RUN IT? SHOULD I GO -- SHALL WE JUST GO BY THE ORDER?

DR. IAKOUCHEVA: YES, PLEASE. I'LL GO AFTER YOU, DAN.

DR. GESCHWIND: OKAY.

SO CAN YOU GUYS SEE THIS? I'LL PUT IT ON SCREEN. CAN YOU GUYS SEE THIS?

CHAIRMAN GOLDSTEIN: YEAH. GREAT.

DR. GESCHWIND: GREAT. OKAY. SO I'LL BE BRIEF AS THIS IS A BRIEFING, AS BRIEF AS I CAN BE.

SO HERE IS JUST A QUICK DISCLOSURE. I'M NOT TALKING ABOUT WORK RELATED TO THESE, BUT I DO WANT TO DISCLOSE THEM.

SO WHAT I'M GOING TO SAY TODAY IS THAT

GENETIC STUDIES HAVE YIELDED HUNDREDS OF LOCI AND IN SOME CASES GENES THAT A CAUSE NEUROPSYCHIATRIC DISEASE. AND THE REASON THIS IS SO IMPORTANT IS THAT GENETICS GIVES YOU A CAUSAL ANCHOR. IT TELLS YOU WHAT IS CAUSAL, WHERE TO START IN A WAY. BUT THIS SUCCESS HAS BRED CHALLENGES. IT'S SHOWN THAT ALL THESE DISORDERS ARE VERY HETEROGENEOUS.

SO THE OTHER POINT I'M GOING TO MAKE IS THAT THE HUMAN IPSC-BASED MODELS ARE NOT ONLY UNIQUE IN ALLOWING US TO STUDY THE FUNCTION OF HUMAN GENETIC VARIATION, DISEASE-ASSOCIATED CAUSAL VARIATION ON HUMAN NEURO -- DEVELOPMENT OF NEURAL FUNCTION, BUT THEY'RE REALLY, REALLY EFFICACIOUS AND THEY PERMIT HIGH THROUGHPUT ASSESSMENT. AND THAT'S REALLY A KEY POINT HERE TOO IF WE ARE THINKING ABOUT THE FUTURE OF DRUG DEVELOPMENT AS WELL.

SO LET ME JUST GIVE A QUICK PRIMER BECAUSE I'M NOT SURE WHAT'S BEEN DISCUSSED AND I DON'T KNOW EVERYBODY'S BACKGROUND. BUT THERE'S BASICALLY AN A TRADE-OFF DUE TO EVOLUTION BETWEEN EFFECT SIZE AND FREQUENCY. THINGS THAT HAVE VERY LARGE EFFECT SIZES ARE WEEDED OUT BY NATURAL SELECTION. EFFECT SIZES MEANS IF YOU HAVE THE MUTATION, YOU GET A BAD DISEASE. AND SO IN MOST CASES RARE MUTATIONS, SUFFICIENT TO BE CAUSAL -- SINGLE MUTATION CAUSES A

DISEASE. SO IT HAS A LARGE EFFECT, BUT THEY'RE VERY RARE. AND THEY'RE TYPICALLY IDENTIFIED NOW BY SEQUENCING, EITHER WHOLE EXOME OR WHOLE GENOME SEQUENCING. THERE WERE OTHER METHODS TO DEFINE THEM IN THE PAST.

COMMON GENETIC VARIANTS, THAT IS WHAT WE ALL SHARE, IS ACTUALLY, AS LARRY MENTIONED, MOST OF THE RISK FOR COMMON DISEASES AND COMMON DISORDERS, BUT NONE OF THE INDIVIDUAL VARIANTS CAUSE THE DISEASE IN THE WAY THEY'RE SUFFICIENT TO CAUSE IT ALONE, BUT THEY'RE CAUSAL IN THAT THEY INCREASE RISK AND THEY CONTRIBUTE TO THE DISEASE IN AN ADDITIVE AGGREGATE FASHION. SO THEY ADD UP TO CAUSE OF DISEASE, SO YOU NEED A BUNCH OF THEM. AND SO I'VE DICHOTOMIZED THEM. OF COURSE, THEY CAN ACT TOGETHER AS WELL.

SO GENETICS GIVES YOU KIND OF WHAT IN QUOTES IN A KIND OF SILLY WAY IS A SIMPLE PARADIGM. YOU KNOW THAT SOMETHING IS HERITABLE IN B, AND THIS IS A PAPER THAT JONATHAN FLINT AND I WROTE A REVIEW IN *SCIENCE* A FEW YEARS AGO JUST SAYING THESE DISORDERS, THESE NEUROPSYCHIATRIC DISORDERS, ON THE LEFT, A, ARE INCREDIBLY COMMON. THEIR PREVALENCE IS HIGH FROM ANXIETY AND MAJOR DEPRESSION AT THE TOP DOWN EVEN TO SCHIZOPHRENIA AND AUTISM, WHICH ARE

AROUND 1 PERCENT AT THE BOTTOM.

YOU CAN CALCULATE HERITABILITY IN A LOT OF WAYS. I'M NOT GOING TO GO INTO TO THIS. BUT SUFFICE IT TO SAY THESE DISORDERS ARE HIGHLY HERITABLE. IN AUTISM THE MOST RECENT TWIN STUDIES ESTIMATE BETWEEN 80 AND 85 PERCENT. THESE ARE LARGE-SCALE POPULATION STUDIES IN SWEDEN. SO ONCE YOU FIND HERITABILITY, THEN YOU CAN GO AND DO ASSOCIATION STUDIES TO FIND LOCI. YOU COMPARE CASES AND CONTROLS AND FIND THINGS THAT ARE ASSOCIATED WITH DISEASE.

THE ISSUE WITH COMMON GENETIC VARIATION IN THIS KIND OF GWAS PARADIGM OF FINDING GENES IS THAT YOU'RE ACTUALLY FINDING REGIONS OF THE CHROMOSOME THAT ARE ASSOCIATED WITH DISEASE, AND THEN YOU HAVE TO ATTACH THAT TO A DISEASE GENE. AND SO FINDING GENES IS NOT NECESSARILY DIRECTLY FALL OFF EASILY FROM FINDING GWAS LOCI. AND THEN, OF COURSE, THE NEXT STEP IS TO DETERMINE HOW THEY CAUSE DISEASE. SO FROM A LOGICAL STANDPOINT, THIS IS A SIMPLE PARADIGM. OF COURSE, EACH OF THESE STEPS ARE DIFFICULT. BUT WHAT'S HAPPENED IS, BECAUSE OF THE POWER OF GENETICS AND LARGE SAMPLE SIZES, LOCI HAVE BEEN FOUND, IN FACT HUNDREDS OF THEM. AND THIS IS JUST SHOWING FROM THAT ORIGINAL REVIEW THAT

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STRUCTURAL VARIATIONS IN RED, IT DEPENDS ON WHAT DISEASE YOU'RE LOOKING AT. THIS IS JUST A CROSS-SECTION OF ALL THESE DIFFERENT DISORDERS IN A. AND IT SHOWS THAT AS YOU GET LARGER AND LARGER CASE STUDIES, LARGER AND LARGER STUDIES, YOU IDENTIFY MORE AND MORE LOCI. SO AS WE INCREASE SAMPLE SIZE, WE'RE GOING TO GET MORE AND MORE LOCI, AND THAT'S WHAT'S HAPPENED. AND NOW HUNDREDS HAVE BEEN IDENTIFIED IN SCHIZOPHRENIA, ET CETERA, AS THE SAMPLE SIZES GROW.

WHAT WAS POINTED OUT BY THE DIFFERENCE BETWEEN THE BLUE AND THE RED IS THAT THE GENETIC ARCHITECTURE OF THESE DISORDERS IS A LITTLE BIT DIFFERENT IN THAT SOME OF THEM, LIKE THE CHILDHOOD DISORDERS, HAVE VERY RARE MUTATIONS. THESE STRUCTURAL CHROMOSOMAL VARIATIONS ARE RARE CAUSAL SINGLE HIT MUTATIONS AND MORE SO THAN THE COMMON GENETIC DISORDERS IN A WAY. YOU'LL SEE THAT IN A SECOND. BUT THE THINGS LIKE SCHIZOPHRENIA, ANOREXIA, MAJOR DEPRESSION, BIPOLAR, THOSE HAVE VERY LIMITED CONTRIBUTION FROM RARE MUTATIONS. IT'S MOSTLY COMMON; WHEREAS, AUTISM IT'S KIND OF 50-50, FOR EXAMPLE.

AND THIS IS JUST SHOWING FROM A REVIEW THAT'S ABOUT FIVE YEARS PAST THAT OTHER ONE THAT

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THIS IS WHAT'S HAPPENING AS SAMPLE SIZES INCREASE THE LOCI. SO LIKE WHAT I SHOWED YOU IN 2015 OF ABOUT A HUNDRED SCHIZOPHRENIA LOCI, IT'S NOW ALMOST 300. AND SAME THING WITH BIPOLAR, MAJOR DEPRESSION. BUT, AGAIN, YOU CAN SEE AT THE BOTTOM THE THINGS LIKE AUTISM, ADHD, FEWER COMMON GENETIC ASSOCIATIONS; BUT STILL AS SAMPLE SIZE INCREASES, THIS HAS BEEN MASSIVELY POWERFUL. SO IT TELLS US ONE REALLY IMPORTANT THING IS THAT NOT ONLY IS THE HERITABILITY STUFF KIND OF RIGHT IN THAT THESE HAVE A GENETIC COMPONENT, BUT THAT WE CAN IDENTIFY THE GENETIC COMPONENT AND, EVEN THOUGH OUR CONCEPTUALIZATION OF THESE DISEASES IS BASED ON BEHAVIOR AND COGNITION, IT'S NOT LIKE A NEUROLOGIC DISEASE WHERE WE CAN MEASURE NEUROPATHOLOGY AND HAVE SOMETHING A LITTLE BIT MORE SPECIFIC. EVEN DESPITE THAT KIND OF HAZINESS IN DIAGNOSIS, THERE STILL IS SOME BIOLOGICAL UNDERPINNING TO THOSE DIAGNOSES WHICH IS KIND OF REMARKABLE.

SO I'LL SWITCH TO AUTISM A LITTLE BIT TO GIVE YOU AN EXAMPLE OF WHERE WE ARE THERE. SO AUTISM IS CLINICALLY AND GENETICALLY HETEROGENEOUS. THERE ARE MANY FORMS OF GENETIC VARIATION AND MODES OF INHERITANCE. AUTISM IS DEFINED BY DEFECTS IN SOCIAL COGNITION AND MENTAL FLEXIBILITY AND OVERLAPS

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ABOUT 5 TO 10 PERCENT OF EPILEPSY, ABOUT 30 PERCENT OF INTELLECTUAL DISABILITY, BUT THEY DON'T HAVE TO HAVE INTELLECTUAL DISABILITY. BUT AUTISM OVERLAPS WITH OTHER NEURODEVELOPMENTAL DISORDERS AND CAN HAVE COMORBIDITY.

AND SO, AGAIN, WHEN WE LOOK AT AUTISM, THIS IS GETTING MORE SPECIFIC ABOUT WHAT CAUSES AUTISM. STARTING AT THE RIGHT, ABOUT 40 PERCENT, AGAIN, THIS IS ABOUT SIX YEARS AGO, IS UNACCOUNTED FOR. ABOUT 50 PERCENT IS PREDICTED TO BE THESE COMMON GWAS HITS, COMMON GENETIC VARIATION, THINGS THAT ARE SHARED IN MORE THAN 1 PERCENT OF THE POPULATION. AND ABOUT 10 PERCENT WAS KNOWN TO BE CAUSED BY RARE MUTATIONS, EITHER STRUCTURAL CHROMOSOMAL VARIATION CALLED COPY NUMBER VARIATION. IN THE MIDDLE, KNOWN MEDICAL GENETIC CONDITIONS LIKE FRAGILE X OR NEWLY DISCOVERED THINGS. AND HERE AT THIS TIME THERE WERE ABOUT A DOZEN OR 20 OF THOSE, AND NOW THERE ARE ALMOST 200 OF THESE TO FILL IN.

AS THESE HAVE GOTTEN FILLED IN, THE UNACCOUNTED FOR IS SHRINKING MORE AND MORE AND MORE IN THE LAST SIX YEARS. SO GENE DISCOVERY HAS BEEN OFF THE CHARTS. SO THERE'S A PROPORTION OF AUTISM, ABOUT 15 PERCENT, LET'S SAY, MAYBE 20 PERCENT, THAT'S CAUSED BY RARE SINGLE MUTATIONS THAT COULD

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INVOLVE, IF THEY'RE STRUCTURAL, LIKE A CHROMOSOMAL GENE, AND SO THAT PROPORTION OF AUTISM IS A COLLECTION OF RARE DISORDERS.

AND CURRENTLY, CLINICALLY GENETIC TESTING CAN IDENTIFY 10 TO 20 PERCENT OF MUTATIONS CONTRIBUTING TO AUTISM. IN OTHER WORDS, YOU HAVE A HUNDRED PEOPLE IN THE CLINIC, YOU DO GENETIC TESTING, YOU'RE GOING TO FIND A MUTATION, A CAUSAL VARIANT IN 10 TO 20 PERCENT DEPENDING ON HOW THAT IS. SO REALLY MASSIVELY -- GENETICS HAS BEEN MASSIVELY IMPORTANT HERE.

BUT WE HAVE A CHALLENGE THAT COMES FROM ALL THIS SUCCESS. ADVANCES IN GENETICS AND GENOMICS HAVE IDENTIFIED MANY GENES THAT ARE INVOLVED IN THESE DISORDERS AND AUTISM. AND THEY PROVIDE TARGETS FOR MECHANISTIC UNDERSTANDING AND THERAPY JUST LIKE CANCER. HOWEVER, THESE FINDINGS HIGHLIGHT EXTREME HETEROGENEITY EVEN IN THESE RARE DISORDERS. AND SO ONE OF THE QUESTIONS IS DO WE HAVE TO DEVELOP A SPECIFIC TREATMENT FOR EACH LIKE FORM? OR IS THERE GOING TO BE CONVERGENCE ON SPECIFIC BIOLOGICAL PATHWAYS, DEVELOPMENTAL STAGES OR PROCESSES OR BRAIN CIRCUITRY? AGAIN THE ANALOGY, IN CANCER THERE'S -- EVERY CANCER PROLIFERATES, METASTATIC CANCER, OR INVADES. SO THAT'S A CONVERGENT PART OF

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THEIR BIOLOGY. OF COURSE, THEY DO IT VIA DIFFERENT MECHANISMS.

AND SO ONE OF THE KEY POINTS HERE AS WELL IS THAT GENES DON'T ACT ALONE. THEY ACT IN CONCERT WITH OTHER GENES. AND SO IT'S REALLY KEY TO TAKE A SYSTEMATIC, UNBIASED KIND OF SYSTEMS BIOLOGY APPROACH, GOING FROM SEQUENCE DATA TO ALL THESE OTHER LEVELS OF GENETIC, GENOMIC, EPIGENETIC DATA. AND WE NOW ACTUALLY HAVE TOOLS TO INTEGRATE AT ALL THESE LEVELS AND TO TAKE THIS FORWARD AND HAVE A REAL MECHANISTIC, MULTILEVEL UNDERSTANDING OF THESE DISORDERS, MOVING FROM SEQUENCE TO CELL.

ANOTHER CHALLENGE, THOUGH, AND I'VE BEEN TALKING ABOUT AUTISM, RIGHT, BECAUSE AUTISM WE HAVE 200 RARE GENES THAT WE CAN WORK ON. BUT IN SCHIZOPHRENIA, BIPOLAR, AND MAJOR DEPRESSION WHICH DON'T HAVE MANY OF THOSE RARE GENES, THERE ARE A HANDFUL, A DOZEN OR SO FOR SCHIZOPHRENIA, MOST DISEASE CAUSING HUMAN GENETIC VARIATION, MOST OF THE GWAS HITS THAT I SHOWED YOU LIE IN NONCODING GENETIC REGIONS WHOSE FUNCTION IS NOT KNOWN, BUT THEY GENERALLY REGULATE GENE EXPRESSION. THESE ARE REGULATORY REGIONS. THEY TURN GENES ON AND OFF OR THEY REGULATE THE SPLICING OF GENES. THINGS THAT TURN GENES ON ARE CALLED ENHANCERS.

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NOW, THERE ARE ALL KINDS OF PROBLEMS -- THIS CAN CAUSE ALL KINDS OF CHALLENGES BECAUSE MOST GENE REGULATION OCCURS AT A DISTANCE. SO I'M GOING TO GIVE YOU AN EXAMPLE OF THE 108 SCHIZOPHRENIA-ASSOCIATED GENETIC LOCI IN 2014, WHICH WAS A MAJOR LANDMARK IN THE FIELD, ONLY ABOUT TEN CHANGED THE CODING REGION OF A PROTEIN. THE REST WERE IN NONCODING REGIONS THAT ARE REGULATORY. SO ASSIGNING THEM TO GENES WAS REALLY, REALLY HARD.

AND ONE OF THE KEY THINGS IS THAT THESE NONCODING REGIONS ARE A BIG PART OF WHAT MAKES US HUMAN, AND THEY'RE NOT WELL CONSERVED IN OTHER SPECIES, CERTAINLY NOT IN RODENTS. THERE'S SOME, BUT THEY'RE NOT WELL CONSERVED LIKE PROTEINS ARE. SO THIS MEANS THAT WE NEED HUMAN MODELS IF WE'RE GOING TO UNDERSTAND THIS. WE CANNOT DO ALL OF THIS IN MOUSE OR OTHER SPECIES.

SO WHAT DO NONCODING REGIONS DO? THEY TURN GENES ON AND OFF. BUT HOW DO WE KNOW THAT? THEY ALTER SPLICING AND EXPRESSION OF TARGET GENES, AND WE CAN FIGURE THIS OUT BY MAKING MAPS OF FUNCTIONAL ANNOTATION OF THE GENOME. AND THIS IS JUST SHOWN HERE ON THE LEFT WITH A VARIETY OF TECHNIQUES, DNA METHYLATION, HISTONE MODIFICATIONS, CHROMATIN ACCESSIBILITY. ONCE WE MAKE THIS MAP, WE

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CAN SAY, AHA, THIS IS AN ENHANCER PROBABLY. AND THIS IS AN ENHANCER IN THE BRAIN BECAUSE MOST OF THIS HAPPENS IN A TISSUE-SPECIFIC, CELL TYPE-SPECIFIC MANNER. AND, AGAIN, AND IT'S SPECIES SPECIFIC BECAUSE IT'S A NONCODING REGION IN MANY CASES. ALSO, THESE REGIONS AREN'T SITTING IN GENES. SO UNLESS THEY'RE VERY, VERY CLOSE TO A GENE, YOU CAN'T REALLY ASSIGN THEM TO A GENE. YOU HAVE TO USE OTHER METHODS, AND THAT'S SHOWN THE TARGET IDENTIFICATION WITH THESE OTHER NEW METHODS CALLED CHROMOSOMAL CONFIRMATION METHODS OR EXPRESSION QUANTITATIVE TRAIT. THERE ARE A LOT OF DIFFERENT WAYS TO ASSIGN FUNCTION, LIKE ONCE YOU IDENTIFY A REGION THAT'S FUNCTIONAL THAT CONTAINS A GWAS HIT TO ASSIGN IT TO A GENE, BUT IT'S NONTRIVIAL. AND SO YOU HAVE TO HAVE MAPS OF EACH TISSUE IN EACH CELL IN EACH DEVELOPMENTAL STAGE TO UNDERSTAND HOW GENETIC VARIATION ACTUALLY WORKS.

AND SO THERE'S BEEN THIS THING CALLED PSYCHENCODE WHICH IS BUILDING REFERENCE MAPS OF GENE REGULATION, ENCODE EXPRESSION IN DEVELOPING AN ADULT HUMAN BRAIN. AND THESE ARE JUST SOME OF THE PAPERS THAT WE'VE BEEN INVOLVED IN IN DRIVING THIS FORWARD. SOME OF THE NEW PAPERS ARE IN BIOARCHIVE AND MEDARCHIVE.

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JUST TO SAY THAT MAKING THESE MAPS HAS BEEN ESSENTIAL; BUT NOW THAT WE HAVE THESE MAPS, ONE CAN ASK HOW DO THEY WORK IN MODEL SYSTEMS LIKE STEM CELLS. RIGHT? WE HAVE FUNCTIONAL GENOMIC MAPS. KNOWING WHAT RNA IS EXPRESSED, WHAT GENES ARE TURNED ON, WHAT IS ACTUALLY TURNING THEM ON AND OFF, AND WE CAN ASK IN A NEUROTYPICAL BRAIN WHAT'S GOING ON IN THESE IN VITRO MODELS. SO WE HAVE THE MAPS TO BE ABLE TO DO ALL THE HARD CARTOGRAPHY THAT'S NECESSARY.

AND SO THE IDEA IS WE FIND LOCI, RIGHT; AND IF WE DO A WHOLE GENOME SEQUENCING OR WHOLE EXOME SEQUENCING SHOWN ON THE LEFT, WE CAN ACTUALLY IDENTIFY A GENE THAT'S MUTATED OR KNOCKED OUT OR CHANGED IN SOME WAY. BUT FOR GWAS WE ARE NOT IDENTIFYING A GENE. WE ARE JUST IDENTIFYING A LOCUS THAT CONTAINS A LOT OF GENES. AND WE HAVE TO DO ALL THIS OTHER WORK HERE UNDER FUNCTIONAL ARCHITECTURE TO FIND THE GENES. SO WE MAKE ALL THESE GENOMIC MEASUREMENTS, RNA SEQUENCING, CHROMATIN STATE, ET CETERA. NOW, OF COURSE, GENES DON'T ACT ALONE. THEY ACT TOGETHER AND THEY ACT WITHIN CELLS. SO TO UNDERSTAND MECHANISMS, WE HAVE TO UNDERSTAND HOW GENES ACT TOGETHER IN PATHWAYS AND IN NETWORKS IN CERTAIN CELL TYPES, ET CETERA. SO THAT'S REALLY THE

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CHALLENGE, BUT WE HAVE ALL THE TOOLS TO ACTUALLY DO THIS NOW.

SO WE CAN ASK WHEN DO AUTISM RISK GENES ACT AND IN WHAT CELL TYPES DO THEY ACT? AND SO WE'VE DONE THAT AND OTHER PEOPLE HAVE, AND HERE ARE SOME OF THE CITATIONS BELOW. THEY ACT PRENATALLY. AUTISM IS CAUSED BY PRENATAL DISRUPTION OF BRAIN DEVELOPMENT. THIS WAS THE FIRST PAPER TO SHOW IT. IT WAS PUBLISHED IN 2013 WHEN WE JUST HAD A HANDFUL OF GENES, BUT IT'S BEEN REPLICATED OVER AND OVER AGAIN. AND THESE GENES FALL INTO DIFFERENT PROSTHESES OR CLUSTERS, MODULES. WE JUST NUMBER THEM, CALLED M2 AND M3. MOST AUTISM GENES SIT, MANY OF THE ONES THAT WE'RE GOING TO TALK ABOUT, SIT IN THAT M2 AND M3 AND REGULATE NEURAL DEVELOPMENT VIA THEIR IMPACT ON TRANSCRIPTIONAL REGULATION.

AND THIS IS JUST SHOWING -- THAT'S RARE GENES. THIS IS SHOWING FROM THE MOST RECENT AUTISM GWAS HYEJUNG WON AND I TOOK A LOOK AT THOSE GENES IN THAT PAPER AND SHOWED, AGAIN, THAT THEY PEAK AT ABOUT RIGHT AT MID-GESTATION, VERY SIMILAR TO THE PEAKING OF EXPRESSION OF THE RARE MUTATIONS. SO COMMON AND RARE GENETIC VARIATION IN AUTISM PEAKS DURING FETAL HUMAN DEVELOPMENT TO THEN IMPACT THINGS LATER. DOESN'T MEAN EVERY GENE IS EXPRESSED THEN,

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BUT IT'S JUST LIKE IF YOU WANT TO KNOW WHERE THINGS CONVERGE, WHERE THEY'RE ADDING UP, THIS IS WHAT IT'S TELLING US.

SO HERE'S ANOTHER REALLY WILD THING IS THAT PSYCHIATRIC DISEASES ARE DIFFERENTIATED FROM THE NEUROLOGIC DISEASES THAT LARRY WAS REFERRING TO BECAUSE THEY HAVE NO VISIBLE PATHOLOGY. IF YOU HAVE A STROKE, YOU CAN SEE IT ON AN MRI. IF YOU HAVE MS, YOU CAN SEE IT ON THE TISSUE ON AN MRI. ALZHEIMER'S DISEASE, THERE'S A PATHOLOGY, ALS, ET CETERA, PARKINSON'S DISEASE. BUT PSYCHIATRIC DISEASES WERE CONSIDERED SEPARATE BECAUSE THERE'S NO VISIBLE OR MICROSCOPIC PATHOLOGY OR PROTEIN PATHOLOGY. BUT ONCE WE WERE ABLE TO MEASURE RNA AT A GENOMEWIDE LEVEL CHEAPLY, WE ARE WERE ABLE TO SHOW THAT THERE IS A MOLECULAR PATHOLOGY OF PSYCHIATRIC DISEASES AND THAT IT'S DEFINABLE, BUT IT'S JUST NOT VISIBLE UNDER A MICROSCOPE. IT'S VISIBLE WHEN YOU LOOK AT RNA.

SO THIS WAS THE FIRST PAPER IN 2011. IN 2016 WE AGAIN EXPANDED THIS ABOUT FIVEFOLD USING DIFFERENT METHODS, LOOKING AT MICRO RNA, LOOKING AT CHROMATIN. WE SEE THE SAME THING OVER AND OVER AGAIN, THAT IN CEREBRAL CORTEX THERE IS -- AND THIS IS ONE OF THE MOST RECENT PAPERS WITH A HUGE DATASET WHERE WE'VE EXPANDED THIS TO AUTISM, SCHIZOPHRENIA,

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BIPOLAR COMPARISON TO CONTROL ALMOST 2,000 CASES AND CONTROLS, AND IT VALIDATES WHAT'S FOUND BEFORE BUT REALLY EXTENDS IT SUBSTANTIALLY TO THESE OTHER DISORDERS AND SHOWS WHERE THEY OVERLAP AND WHERE THEY DON'T OVERLAP.

AND THE LAST PAPER ON THE BOTTOM THERE, THE WAMSLEY, ET AL. IN BIOARCHIVE IS ACTUALLY SHOWING THAT AT A SINGLE CELL LEVEL.

SO THIS IS A ROBUST PATTERN. DOWN-REGULATION OF GENES RELATED TO SYNAPTIC SIGNALING, UP-REGULATION OF ASTROCYTES, MICROGLIA, AND NEURAL IMMUNE PATHWAYS. BUT THE GENETIC RISK IS DRIVING THE SYNAPTIC GENES. IT'S NOT DRIVING THE UP-REGULATION OF MICROGLIA AND ASTROCYTE GENES. THEY ARE A CONSEQUENCE OF THE GENETIC RISK.

SO WHAT WE HAVE NOW ARE RNA AND EPIGENETIC PROFILING THAT DEFINES A PATHWAY. IT GIVES US LIKE A GOLD STANDARD. THIS IS WHAT HAPPENS IN THE BRAIN. WE CAN UNDERSTAND AS A STARTING POINT FOR UNDERSTANDING DISEASE MECHANISMS AND THERAPEUTIC DEVELOPMENT. IT'S DEFINITELY NOT AN ENDING POINT. IT'S JUST A SIGNPOST ALONG THE WAY.

SO REALLY THE KEY QUESTION IS, AND I KNOW LILIA IS GOING TO GET INTO THIS MORE, I'M JUST GOING TO GIVE A VERY, VERY QUICK SHOT AT THIS, IS WE HAVE

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THESE MOLECULAR CHANGES THAT ARE ROBUSTLY SHOWN IN POSTMORTEM BRAIN IN AUTISM AND OTHER SEVERE NEUROPSYCHIATRIC DISORDERS. WE KNOW THAT GENETIC RISK IS HAPPENING PRENATALLY. SO HOW DO THE MOLECULAR CHANGES EMERGE? HOW DO WE UNDERSTAND WHAT HAS HAPPENED IN BETWEEN NEUROGENESIS AND FUNCTIONING TO ACTUALLY GET THERE, AND WHAT DOES THIS ACTUALLY MEAN? SO WE NEED TO BE ABLE TO MODEL THIS.

SO THE QUESTION IS HOW DO WE CONNECT THE MULTITUDE OF GENETIC RISK FACTORS TO THE ROBUST MOLECULAR PATTERNS OBSERVED IN BRAIN? AND CAN WE USE IN VITRO IPSC-BASED MODELS TO UNDERSTAND HOW GENETIC RISK WOULD KIND OF PERCOLATE THROUGH DEVELOPMENT TO LEAD TO THESE PATTERNS? AND SO THE ANSWER IS YES. AND I'M JUST GOING TO REALLY FLASH THROUGH THESE VIGNETTES TO GIVE LILIA MORE TIME TO TALK.

SO ONCE YOU HAVE AN RNA PROFILE OF IN VIVO BRAIN DEVELOPMENT, YOU HAVE A GENOMIC PROFILE OF WHAT'S ACTIVE, WHAT'S TURNED ON, WHAT'S TURNED OFF, YOU CAN USE THAT TO ASK HOW WELL DO MY CELLS ACTUALLY MODEL THAT? YOU HAVE A QUANTITATIVE WAY OF ASKING HOW DO NEURAL STEM CELLS MODEL IN VIVO BRAIN DEVELOPMENT? SO WE'VE DEVELOPED TOOLS TO DO THAT.

THIS WAS THE FIRST ONE IN 2014 USING

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TWO-DIMENSIONAL CULTURES, AND WE COULD SEE THAT THE PATTERN OF HOW GENES ARE CO-REGULATED, TURNED ON AND OFF, THAT WE SEE IN VIVO IS PRESERVED IN VITRO IN THESE MODELS. SO THAT TELLS US THAT WE HAVE A LOT -- THAT FOR MODELING THESE EARLY CHANGES, WE ARE IN PRETTY GOOD SHAPE.

SUBSEQUENTLY WE'VE BEEN WORKING WITH SERGIU PASCA'S LAB AT STANFORD TO REALLY UNDERSTAND THIS MORE DEEPLY IN TERMS OF HOW MUCH BETTER ARE THREE-DIMENSIONAL MODELS. AND, AGAIN, THIS PAPER IS PUBLISHED. WHAT THIS SHOWS UP AT THE TOP IS THESE CULTURES CAN BE CULTURED VERY REPRODUCIBLY USING GENOMIC -- WE HAVE A QUANTITATIVE METHOD FOR MEASURING ALL THE GENES EXPRESSED. AND WE CAN SEE OVER AND OVER AGAIN WE GET BETWEEN AND WITHIN INDIVIDUAL CO-EXPRESSION THAT'S REPRODUCIBLE.

THE OTHER THING, THOUGH, IS THAT WHAT SERGIU'S LAB, SE-JIN YOON SHOWED, SHE CULTURED THESE FOR SOMETIMES UP TO 600 DAYS. AND WHAT WE COULD SHOW IS, ONCE WE HIT BETWEEN AROUND 280 DAYS, THE TRANSITION TO LOOKING POSTNATAL USING THAT TOOL THAT I SHOWED IN THE LAST SLIDE, A MACHINE LEARNING TOOL THAT ACTUALLY TELLS YOU WHAT TRANSITIONS YOU'VE ACTUALLY SEEN IN VIVO.

WE ALSO USED EPIGENETIC AGING, THE DNA

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METHYLATION CLOCK THAT STEVE HORVATH DEVELOPED, TO LOOK AT THIS AND ASK IS MATURATION OCCURRING AT THE NORMAL PATTERN IN VITRO? AND IT IS. SO THERE'S LIKE AN INTERNAL CLOCK THAT'S TICKING. AND THAT WHEN WE PUT THESE CELLS IN VITRO, THEY'RE MODELING IN VIVO DEVELOPMENT AT THE TRANSCRIPTIONAL LEVEL AND AT THE EPIGENETIC LEVEL. SO THAT'S PRETTY REMARKABLE.

WE CAN ALSO THEN LOOK AND ASK WHEN ARE SCHIZOPHRENIA GENES EXPRESSED? HOW WERE THEY EXPRESSED? WE DID THIS WITH AUTISM GENES, INTELLECTUAL DISABILITY, SCHIZOPHRENIA IN THIS PAPER. AND WE SAW THAT AUTISM GENES KIND OF FELL INTO FIVE CLUSTERS, ALL OF WHICH ARE EXPRESSED KIND OF VERY, VERY EARLY IN DEVELOPMENT. AND THEN THERE WAS ONE SMALLER CLUSTER RELATED MOSTLY TO GLIAL DEVELOPMENT AND SOME OTHER THINGS THAT EXPRESSED PRENATALLY, BUT KIND OF KEEPS GOING UP A LOT.

AND WE CREATED A BROWSER WHERE ONE CAN LOOK AT THIS AND ASK IS MY GENE EXPRESSED? WHEN IS IT HIGHEST? WHEN SHOULD I BE LOOKING AT IT, ET CETERA?

SO WE'VE ALSO -- AGAIN, THIS WAS A CIRM GENOMICS FUNDED PROJECT, FUNDED THROUGH CIRM ABOUT FIVE, SIX YEARS AGO TO MY LAB AND SERGIU PASCA'S

LAB. AND SERGIU'S LAB TOOK PATIENTS WITH ALL OF THESE MUTATIONS, 70 LINES TOTAL, 464 SAMPLES AND DIFFERENTIATED THEM OVER A HUNDRED DAYS. AND WE MEASURED GENE EXPRESSION. AND WE'VE BEEN ASKING WHAT'S GOING ON? AND WHAT WE FIND IS THAT, ALTHOUGH THERE IS SOME CLUSTERING BY TIME, OF COURSE, BECAUSE TIME IS A BIG DEAL HERE, YOU GO FROM PROGENITORS ALL THE WAY TO DIFFERENTIATED NEURONS AND STUFF IN A DISH. BUT THE MUTATIONS CLUSTER TOGETHER IN VERY, VERY SPECIFIC PATTERNS THAT ARE ROBUST TO WHATEVER METHOD WE USED TO CLUSTER THEM. AND THIS IS JUST SHOWING ONE. SO THERE ARE SHARED CONVERGENT PATHWAYS THAT WE CAN SEE HERE.

AND I'M JUST GOING TO END BY SAYING THAT THIS IS JUST LOOKING AT SOME OF THAT OVERLAP. AND, AGAIN, IT GETS BACK TO THIS ISSUE OF CHROMATIN. CHROMATIN IS HOW GENE TRANSCRIPTION AND GENE REGULATION IS TURNED ON AND OFF. AND SO THESE MUTATIONS OVERLAP IN THAT AREA, AND IN FACT THEY OVERLAP QUITE SPECIFICALLY. WE'VE BEEN ABLE TO IDENTIFY IN BLACK HERE IN THE MIDDLE ARE A MODULE THAT WE CALL M5 THAT IS A BUNCH OF CHROMATIN REGULATORS THAT DRIVE THE AUTISM RISK GENES AND ALL THE DIFFERENT DISORDERS. AND IT'S REALLY QUITE REPRODUCIBLE AND QUITE REMARKABLE.

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WHAT'S AMAZING IS THAT THESE FORM A PROTEIN INTERACTION NETWORK IN NEURONAL PROGENITORS AND IT'S SPECIFIC. IT'S NOT -- IF WE TAKE THE SCHEMA SCHIZOPHRENIA RISK GENES OR INTELLECTUAL DISABILITY GENES, THIS NETWORK IS NOT DRIVING THEM. SO WE FOUND THIS KIND OF AUTISM.

SO YOU MAY SAY OKAY. SO YOU HAVE THIS NETWORK. WHAT CAN YOU DO WITH IT? WELL, NO. 1, IT GIVES US A SENSE OF WHEN AND WHERE THINGS ARE BEING TURNED ON AND OFF, WHAT CELL TYPES WE NEED TO LOOK AT, ET CETERA, AND WHAT BIOLOGICAL PROCESSES ARE BEING DISRUPTED? AND SO IT GIVES US REALLY A STARTING PLACE FOR MECHANISTIC UNDERSTANDING.

BUT ONE OF THE QUESTIONS WE'VE ALWAYS HAD IN THE BACK OF OUR MIND IS CAN ONE ACTUALLY TARGET A NETWORK, EVEN IF WE DIDN'T KNOW THE BIOLOGY, THE IDEA BEING THAT IF THIS NETWORK IS UP IN AUTISM AND DOWN IN CONTROLS, IF WE JUST MOVE IT TOWARDS CONTROL, COULD THAT ACTUALLY BE THERAPEUTIC EVEN WITHOUT KNOWING THE MECHANISMS?

AND SO YOU PROBABLY ARE FAMILIAR WITH THE BROAD CONNECTIVITY MAP. WHAT THEY HAVE DONE IS THEY'VE GIVEN DRUGS TO CELLS AND THEN THEY MEASURED THE RNA NETWORKS THAT ARE EXPRESSED AFTER EACH DRUG. SO IT'S CONNECTING A DRUG TO A GENE EXPRESSION

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PROFILE. SO WE CAN USE THAT GENE EXPRESSION PROFILE THEN TO MAP TO OUR GENE EXPRESSION PROFILES IN OUR DISEASE MODELS OF PATIENT TISSUES AND TRY TO FIND SOMETHING, A DRUG THAT HAS THE REVERSE PATTERN BY PATTERN MATCHING. AND WE'VE DONE THIS IN SOME OF THOSE PAPERS THAT ARE DOWN TO THE RIGHT IN OTHER DISORDERS, NOT IN AUTISM YET FOR VARIOUS REASONS THAT I'M HAPPY TO DISCUSS. BUT YOU IDENTIFY DRUGS THAT REVERSE THE PATTERN AND YOU TEST THE DRUGS IN MODEL SYSTEMS, AND WE'VE SHOWN THAT THAT CAN ACTUALLY BEGIN TO WORK.

SO THIS GIVES YOU A NUMBER OF DIFFERENT WAYS THAT YOU CAN BEGIN TO APPROACH THIS. YOU CAN DEEPLY UNDERSTAND THE BIOLOGY AND TRY TO FIND DRUGS THAT MODIFY CHROMATIN AND MODIFY THE CHANGES THAT ARE GOING ON, AND YOU CAN ALSO AT THE SAME TIME TRY TO REVERSE THESE TRANSCRIPTIONAL CHANGES AND SEE IF YOU CAN REVERSE THE BIOLOGY.

AND, LASTLY, ONE OF THE REASONS WE DO ALL THE TRANSCRIPTOMES AND ALL OF THIS IS BECAUSE IT'S VERY HIGH THROUGHPUT. IT'S UNBIASED. WE CAN LOOK AT HUNDREDS OF GENES AND THOUSANDS OF SAMPLES IN PARALLEL. WE HAVE TO BE ABLE TO DO THAT WITH OTHER BIOLOGY. SO WITH OUR COLLEAGUES AT UCLA WE ARE BUILDING A HIGH THROUGHPUT PHENOTYPING CENTER THAT

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ALLOWS US TO NOT ONLY DO THIS WITH GENE EXPRESSION, BUT ALSO WITH PHYSIOLOGY NETWORKS. AND WE CAN IMAGE NOW WHOLE 96-WELL PLATES OF SAMPLES AND WITH 96 DIFFERENT MUTATIONS KIND OF SIMULTANEOUSLY AND BEGIN TO UNDERSTAND WHAT'S GOING ON AT A PHYSIOLOGIC LEVEL THERE. ONE CAN DO THE SAME THING WITH ANATOMY.

SO I'M VERY EXCITED ABOUT COUPLING THE KIND OF GENOMICS AND GENETICS ALL THE WAY THROUGH TO BIOLOGY IN A HIGH THROUGHPUT WAY TO BEGIN TO GET A COHERENT PICTURE OF WHAT'S GOING ON IN A HETEROGENEOUS DISTORTER LIKE THESE NEUROPSYCHIATRIC DISORDERS.

SO I'LL CONCLUDE BY SAYING GENETICS PROVIDES A CAUSAL ANCHOR FOR UNDERSTANDING DISEASE MECHANISMS, THAT THE GENOMIC DATA AND OTHER OMICS, LIKE PROTEOMICS, PROVIDE A QUANTITATIVE PLATFORM FOR UNDERSTANDING HOW WELL MODEL SYSTEMS RECAPITULATE HUMAN IN VIVO BRAIN DEVELOPMENT AND FUNCTION. THEY ALSO PROVIDE A MEANS FOR DISCOVERY, AND THEY STRONGLY SUPPORT THE USE OF THESE IPSC-DERIVED SYSTEMS SO STUDY NEUROPSYCHIATRIC DISEASE MECHANISMS. AND COUPLED WITH OTHER HIGH THROUGHPUT BIOLOGY APPROACHES, THIS IS GOING TO BE AN INCREDIBLY POWERFUL FRONTIER. SO THANK YOU FOR YOUR ATTENTION.

I HAVE TO THANK ALL THE PEOPLE IN MY LAB WHO HAVE CONTRIBUTED TO THIS. THE PEOPLE IN PARENTHESES -- ALL THE PEOPLE WITH STARS HAVE GONE OFF. PEOPLE IN PARENTHESES ARE RUNNING THEIR OWN LABS AT OTHER PLACES. AARON GORDON DROVE THAT LAST PIECE OF WORK WITH LUCY BICKS AND SE-JIN YOON IN SERGIU PASCA'S LAB. SO THANKS FOR YOUR ATTENTION.

CHAIRMAN GOLDSTEIN: GREAT STUFF, DAN. THAT'S REALLY TERRIFIC. THANK YOU FOR TAKING THE TIME. WILL YOU BE ABLE TO STAY FOR A GENERAL DISCUSSION AFTER LILIA'S TALK?

DR. GESCHWIND: YES. YES, SURE. THANK YOU.

CHAIRMAN GOLDSTEIN: OKAY. GREAT. THANKS.

SO WHAT I'D LIKE TO DO IS ANY BURNING QUESTIONS, LET'S GET THEM OUT THERE NOW. OTHERWISE LET'S WAIT FOR LILIA TO FINISH AND THEN WE'LL HAVE A GENERAL DISCUSSION WITH BOTH OF OUR GUESTS.

DR. SOUTHARD: JUST WONDERED IF THERE ARE SIMILAR DEVELOPMENTS FOR ADDICTION ISSUES THAT ARE COMING UP?

DR. GESCHWIND: I'M NOT AS FAMILIAR WITH THAT LITERATURE, BUT IN TERMS OF GWAS, ET CETERA, THERE ARE GWAS LOCI FOR DIFFERENT SUBSTANCE USE

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DISORDERS. AND SO ONE COULD BEGIN TO IDENTIFY THE GENES AND BEGIN TO WORK ON THAT AND DO THE SAME -- A SIMILAR TYPE OF WORK. IT'S JUST IT HASN'T BEEN QUITE AS PRODUCTIVE AS AUTISM OR SCHIZOPHRENIA YET.

CHAIRMAN GOLDSTEIN: ALTHOUGH THERE IS A COMPANY THAT'S TRYING TO MARKET AND GET APPROVAL FOR A GENETIC TEST FOR SUBSTANCE ABUSE DISORDERS. A LOT OF THOSE MARKERS ARE IN THE REWARD PATHWAYS IN THE BRAIN.

DR. GESCHWIND: THAT'S RIGHT. THAT'S RIGHT.

CHAIRMAN GOLDSTEIN: LET ME JUST ASK ONE FINAL QUESTION BEFORE WE MOVE TO LILIA, DAN. YOU SAID SOMETHING THAT REALLY SURPRISED ME, WHICH IS THAT YOU THINK THAT MOST OR ALL OF THE GENES THAT ARE ACTIVE IN THESE NEUROPSYCHIATRIC DISORDERS ARE ACTING IN THE NEURON AND THAT THE INFLAMMATORY EFFECTS ARE SECONDARY AND THAT THERE'S NO DISEASE WHERE THE FIRE IS STARTED IN THE INFLAMMATORY CELLS AND SPREAD TO NEURONS.

DR. GESCHWIND: THAT IS THE CASE FOR AUTISM. THERE ARE A HANDFUL OF GENES THAT ARE EXPRESSED IN GLIA AND STUFF. BUT IF YOU LOOK AT THE CONFLUENCE OF WHERE THE GENETIC RISK IS ADDING UP, THE VAST MAJORITY IS IN EARLY NEURAL DEVELOPMENT,

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NEUROPROGENITORS, EARLY KIND OF ACTUALLY SPECIFIC CLASSES OF PROJECTION IN INTERNEURONS. SO THAT'S AUTISM. SCHIZOPHRENIA IS A LITTLE BIT DIFFERENT. SCHIZOPHRENIA SHARES ENRICHMENT NEURONS AS WELL VERY STRONGLY, BUT ALSO HAS AN MHC COMPONENT AND SOME OTHER INFLAMMATORY COMPONENTS. SO THEY'RE DIFFERENT. THESE DISORDERS AREN'T THE SAME. AND, IN FACT, THE SHARING OF GENETIC RISK BETWEEN AUTISM AND SCHIZOPHRENIA IS SOMEWHERE, IF YOU LOOK AT COMMON GENETIC VARIATION, AROUND .2. SO .8 IS LIKE NOT SHARED. SO MOST IS NOT SHARED. THERE'S SOME SHARING OF NEURONAL THINGS. SO LIKELY SCHIZOPHRENIA INVOLVES GENES THAT ARE EXPRESSED A LITTLE BIT LATER IN DEVELOPMENT AND MUCH MORE LIKELY TO BE INVOLVED IN SYNAPTIC FUNCTION THAN CHROMATIN.

SO AUTISM VERY, VERY EARLY DURING FETAL DEVELOPMENT. SCHIZOPHRENIA, SOME FETAL KIND OF DEVELOPMENTAL GENES, BUT KIND OF MORE OF IT IS KIND OF IN NEURONAL AND POSTNATAL AND A LITTLE BIT MORE MIXED BETWEEN NEURONS AND GLIA THAN AUTISM IS. BUT THE GLIAL COMPONENT IN AUTISM IS REALLY KEY. MICROGLIA ACTIVATION IS MASSIVE IN AUTISM POSTMORTEM BRAIN, WAY MORE SO THAN IN BIPOLAR OR SCHIZOPHRENIA. AND WE THINK IT'S A KEY COMPONENT OF THE DISORDER AND MAY BE ONE OF THE THINGS THAT KIND OF

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PROPAGATES. LIKE YOU CAN IMAGINE A SNOWBALL KIND OF GOING DOWNHILL. SO WE DON'T THINK IT'S A GOOD THING, BUT MOST OF THE GENETIC RISK, IT'S A NEURON, THERE'S PROBABLY SYNAPTIC DYSFUNCTION, CHANGES IN CIRCUITRY, GLIA UP-REGULATION. TO CREATE MORE HOMEOSTATIC PLASTICITY WOULD BE THE MODEL. AND THAT'S KIND OF WHAT'S GOING ON.

AND I THINK IN THE NEXT THREE OR FOUR YEARS WE'RE GOING TO HAVE A REALLY -- USING THESE MODELS, ACTUALLY WE'RE GOING TO HAVE A REALLY MUCH BETTER SENSE OF THAT BECAUSE WE CAN ADD MICROGLIA TO THESE MODELS AND SEE HOW THEY IMPACT. WE ARE DOING STUDIES NOW WHERE WE HAVE THE GENETIC RISK IN A STEM CELL-DERIVED NEURON AND IN A STEM CELL-DERIVED MICROGLIA FROM THE SAME PATIENT. WE CAN MIX AND MATCH AND REALLY BEGIN TO SHOW THIS AND SHOW HOW IT'S AN INTERACTION BETWEEN THESE DIFFERENT CELL TYPES.

CHAIRMAN GOLDSTEIN: AMAZING. TERRIFIC STUFF. OKAY. LILIA, ARE YOU READY?

DR. IAKOUCHEVA: YES. LET ME SHARE MY SCREEN.

CHAIRMAN GOLDSTEIN: OKAY. TAKE IT AWAY.

DR. IAKOUCHEVA: I'M SHARING MY SCREEN. SO YOU GUYS SEE A FULL SCREEN AND MY MOUSE?

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CHAIRMAN GOLDSTEIN: VERY GOOD.

DR. IAKOUCHEVA: SO I THINK DAN REALLY SET UP NICELY THE STAGE FOR MY TALK. AND I ALSO AM REPEATING A COUPLE OF SLIDES ABOUT GENETICS OF AUTISM SPECIFICALLY, BUT I'LL JUST GO FAST THROUGH THEM SINCE YOU GUYS ALREADY SAW DAN'S BEAUTIFUL WORK ON THE GENETICS OF AUTISM.

BUT MY LAB BASICALLY IS MAINLY FOCUSED ON THE AUTISM SPECTRUM DISORDERS. WE ALL KNOW THAT THE PREVALENCE OF AUTISM IS STEADILY INCREASING AND NOW IS 1 IN 36 PREVALENCE ACCORDING TO THE LATEST CDC REPORT. AUTISM HAS 4 TO 1 BOYS TO GIRLS RATIO AND TYPICALLY DIAGNOSED BEFORE THE AGE OF THREE.

UNFORTUNATELY, DESPITE THE VERY STRONG EFFORTS FROM SCIENTIFIC COMMUNITY, WE STILL DO NOT HAVE A RELIABLE DIAGNOSTIC BIOMARKER TO DIAGNOSE AUTISM. AND EVEN MORE UPSETTING, WE DON'T HAVE A SINGLE FDA-APPROVED DRUG THAT TARGETS CORE SOCIAL DEFICITS OF THE DISEASE.

SO, AGAIN, REPEATING WHAT DAN HAS ALREADY ALLUDED TO, AUTISM FIELD RAN FROM ALMOST NO CANDIDATES ABOUT A DECADE, A LITTLE BIT OVER A DECADE AGO TO ALMOST, I WOULD SAY, TOO MANY CANDIDATE GENES THANKS TO THE GENETICS. BUT AUTISM IS VERY HIGHLY GENETIC HETEROGENEOUS.

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SO WHAT GENES ARE INVOLVED IN AUTISM? FROM THE WHOLE GENOME AND WHOLE EXOME SEQUENCING, WE KNOW THAT RARE DE NOVO VARIANTS IN THE GENES ARE STRONGLY IMPLICATED IN AUTISM SPECTRUM DISORDER.

AND COMMON VARIANTS, AS DAN ALREADY MENTIONED, ARE ALSO INVOLVED, ALTHOUGH THE GWAS STUDIES IN AUTISM DID NOT PRODUCE AS MANY GOOD TARGETS AS, SAY, SCHIZOPHRENIA GWAS. CURRENTLY, WE KNOW OF ABOUT 12 GENES THAT ARE HID BY COMMON VARIANTS, BUT IT'S BASICALLY MAINLY BECAUSE OF THE SMALL SAMPLES THAT WE HAVE FOR AUTISM.

AND AS THE GENES THAT ARE INVOLVED IN AUTISM ARE SYNDROMIC GENES, SUCH AS FRAGILE X AND RAD SYNDROME, ARE CAUSED BY MUTATIONS IN JUST ONE SPECIFIC GENE THAT WE KNOW. AND A LOT OF CHILDREN WITH THE SYNDROME ALSO HAVE FEATURES OF AUTISM. AND, FINALLY, A LARGE ROLE IN AUTISM COPY NUMBER VARIANTS PLAY, ITS REGIONS OF GENOMES THAT COULD BE EITHER DUPLICATED OR DELETED AND ALSO STRONGLY IMPLICATED IN AUTISM.

NOW THAT WE HAVE ALL THIS BREADTH OF AUTISM CANDIDATE GENES THAT ARE NOW APPROACHING TO, I WOULD SAY, MAYBE A THOUSAND EVEN WITH ABOUT A HUNDRED THAT ARE VERY STRONGLY IMPLICATED, WHAT WE WANT TO KNOW, OF COURSE, IS WHAT PATHWAYS ARE

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DISRUPTED BY THESE GENES AND AT WHAT PERIOD OF BRAIN DEVELOPMENT?

THE GREAT RESOURCE FOR IDENTIFYING THE SPECIFIC PERIODS OF BRAIN DEVELOPMENT THAT COULD BE IMPACTED BY AUTISM MUTATIONS IS THIS RESOURCE THAT'S CALLED BRAINSPAN. IT'S BASICALLY A TRANSCRIPTOME OF THE DEVELOPING HUMAN BRAIN STARTING FROM FETAL STAGES TO ADULT, BUT THIS IS NOT BRAIN WITH AUTISM. IT'S A TYPICALLY DEVELOPING HUMAN BRAIN. BUT WHAT WE CAN DO WITH THIS, WE CAN ACTUALLY BUILD SO-CALLED SPECIAL TEMPORAL BRAIN TRANSCRIPTOME NETWORKS. AND THEN WHAT WE CAN DO WITH THIS NETWORK, WE CAN TAKE GENES THAT ARE HIT BY THE AUTISM MUTATIONS AND MAP THOSE GENES COMPUTATIONALLY TO THESE NETWORKS TO IDENTIFY WHICH SPECIFIC PERIOD THESE GENES ARE EXPRESSED THAT ARE HID BY AUTISM MUTATIONS AND AT WHAT REGIONS, AT WHAT DEVELOPMENTAL STAGES.

AND DAN'S LAB, THIS PAPER THAT DAN ALREADY SHOWED AS WELL AS MATT STATE AND SOME PAPERS FROM MY LAB AS WELL, IDENTIFIED LATE MID-FETAL PERIOD OF CORTICAL DEVELOPMENT AS BEING VERY CRUCIAL FOR THE AUTISM DEVELOPMENT. AND DAN ALREADY ALSO MENTIONED THAT.

SO NOW THAT WE KNOW THAT BRAIN KIND OF DERAILMENT IN AUTISM HAPPENS IN LATE MID-FETAL

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DEVELOPMENT, HOW CAN WE STUDY THEN AUTISM? SO WHAT WE NEED ACTUALLY IS BASICALLY FETAL BRAIN WITH AUTISM DIAGNOSIS; BUT, OF COURSE, IS NOT AVAILABLE BECAUSE THE AUTISM IS DIAGNOSED AFTER BIRTH. SO HOW CAN WE STUDY, THEN, LATE MID-FETAL PERIOD IN AUTISM IF WE DON'T HAVE THE SAMPLES? SO IT'S A HUGE BOTTLENECK OBVIOUSLY IN AUTISM RESEARCH IS A LACK OF FETAL BRAIN SAMPLES WITH AUTISM DIAGNOSIS. I GUESS THE ONLY THING THAT WE CAN DO IS TO RELY ON OTHER MODELS TO STUDY FETAL BRAIN AND AUTISM. AND, OF COURSE, THE GREAT MODELS THAT WE ARE USING NOW ARE GENOME-EDITED ANIMAL MODELS WHERE WE CAN ACTUALLY INTRODUCE THE MUTATION THAT IS FOUND IN THE PATIENT INTO THE MOUSE OR RAT MODELS AND THEN WE CAN EXTRACT THE FETAL BRAIN FROM THIS MODEL WITH THE MUTATION FROM HUMAN AND INVESTIGATE THIS ANIMAL FETAL BRAIN.

ANOTHER AVENUE OF RESEARCH IS THE PATIENT IPC-DERIVED ORGANOIDS. SO THIS MODEL COULD BE DERIVED FROM THE TISSUES FROM AUTISM PATIENTS SUCH AS BLOOD AND ALSO SKIN. AND THE ADVANTAGE OF THIS MODEL IS THAT, FIRST OF ALL, THEY'RE DERIVED FROM THE AUTISM PATIENT. SO THEY'RE BASICALLY GENETICALLY IDENTICAL TO THE PATIENTS. AND SECONDLY, AS I WILL SHOW LATER, THEY RECAPITULATE HUMAN FETAL BRAIN DEVELOPMENT. AND ANOTHER

ADVANTAGE OF THIS MODEL IS THAT WE CAN ACTUALLY STRATIFY THE PATIENTS WITH SPECIFIC MUTATIONS TO INCREASE THE STATISTICAL POWER OF OUR FINDING RATHER THAN LOOKING AT THE IDIOPATHIC AUTISM WITH DIFFERENT TYPES OF MUTATIONS. WE CAN ACTUALLY FOCUS ON PATIENTS WITH SPECIFIC MUTATION AND MAYBE IDENTIFY MECHANISM OF DISEASE.

AND MY LAB STUDIED BOTH OF THESE MODELS, AND TODAY I'M JUST GOING TO FOCUS ON THIS PATIENT-DERIVED IPC ORGANOIDS THAT WE USE FOR ONE SPECIFIC MUTATION. AND I SHOW HOW WE IDENTIFIED THE PATHWAY THAT CAN BE IMPACTED BY THIS MUTATION.

SO WE STUDIED THE SPECIFIC MUTATION THAT IS HIGHLY IMPLICATED IN AUTISM. IT'S CALLED 16P11.2 COPY NUMBER VARIANTS. THESE COPY NUMBER VARIANTS CAN BE EITHER DELETED OR DUPLICATED FROM THE GENOMES OF CHILDREN WITH AUTISM. AND IT CONSISTS OF 29 GENES. IT'S NOT ONE GENE. IT'S 29 GENES. AND IT'S THE MOST FREQUENT AMONG ALL RARE COPY NUMBER VARIANTS THAT ARE IMPLICATED IN AUTISM.

BUT WHAT IS VERY INTERESTING ABOUT THIS VARIANT IS THAT THIS IS RISK -- THIS VARIANT CONFERS RISK TO MULTIPLE NEUROPSYCHIATRIC DISORDERS. FOR EXAMPLE, THE DELETIONS SHOWN IN RED HERE OF THIS VARIANT HAVE A HIGH ODDS RATIO FOR INTELLECTUAL

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DISABILITY AND AUTISM; WHEREAS, DUPLICATIONS OF EXACTLY THE SAME 29 GENES CONFER HIGH RISK AGAIN FOR AUTISM, BUT ALSO FOR SCHIZOPHRENIA. IT'S REALLY INTRIGUING HOW THIS VARIANT BASICALLY WITH THE SAME 29 GENES WOULD PLAY A ROLE IN AUTISM AND SCHIZOPHRENIA AND INTELLECTUAL DISABILITY AS WELL.

ANOTHER INTERESTING FEATURE OF THIS VARIANT IS THAT DELETIONS ARE ASSOCIATED WITH ENLARGED HEAD SIZE AND ALSO HIGHER BODY MASS INDEX IN THE PATIENTS. AND DUPLICATIONS HAVE OPPOSITE EFFECT. SO CHILDREN WITH DUPLICATIONS HAVE MICROCEPHALY OR REDUCED HEAD SIZE AND ALSO THEY ARE SKINNIER. AND THIS WAS ALSO CONFIRMED BY THE BRAIN MRI OF THE PATIENTS WITH THESE MUTATIONS. NOT ONLY HEAD SIZE, BUT ALSO BRAIN SIZE RECAPITULATES THIS MACROCEPHALY AND MICROCEPHALY.

SO THERE ARE THREE MOUSE MODELS THAT WERE DEVELOPED WITH THIS SPECIFIC COPY NUMBER VARIANT. AND WHAT'S INTERESTING -- AND THOSE THREE MODELS, THEY WERE DESIGNED LIKE ON DIFFERENT GENETIC BACKGROUND AND MAYBE THEY HAVE A LITTLE BIT DIFFERENT BREAKPOINT OF THIS COPY NUMBER VARIANT, BUT WHAT'S INTERESTING ABOUT THESE THREE DIFFERENT MOUSE MODELS, THAT SOME OF THE PHENOTYPES OF THE THESE MICE ARE CONCORDANT BETWEEN MODELS. FOR

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EXAMPLE, IN ALL THREE MODELS THE DELETION MICE HAVE HYPERACTIVITY, AND ALSO THERE ARE SOME BRAIN REGION SIZE DIFFERENCES THAT ARE SHARED BETWEEN THOSE MODELS.

BUT ANOTHER INTERESTING FEATURE OF THIS MODEL IS THAT SOME PHENOTYPES IN THESE MODELS ARE DISCORDANT BETWEEN EACH OTHER. SO THERE IS HERE DEFICITS IN ONE MODEL, BUT NOT IN THE OTHER. BUT THE MOST KIND OF PROBLEMATIC THING ABOUT THESE MODELS IS THAT SOME PHENOTYPES BETWEEN MOUSE MODELS AND HUMANS ARE DISCORDANT. AS I MENTIONED BEFORE, YOU KNOW THAT DELETIONS ARE ASSOCIATED WITH MACROCEPHALY AND HIGH BMI AND DUPLICATIONS ARE OPPOSITE. SO WHEN YOU LOOK AT THE MICE, IN AT LEAST TWO OF THESE MODELS, WE SEE ACTUALLY OPPOSITE. WE SEE DECREASED TOTAL BRAIN VOLUME IN DELETIONS AND DELETION MICE ALSO LEAN AND DUPLICATIONS OBESE, WHICH IS COMPLETELY OPPOSITE TO THE HUMAN PHENOTYPE.

THEN THERE WAS ALSO THE BRITISH MODEL THAT WERE DESIGNED FOR THESE COPY NUMBER VARIANTS. AND THE BRITISH MODEL, ONE OF THE PAPERS THAT DELETED ONE BY ONE ALL THESE 29 GENES SHOWED THAT ONE OF THE GENES THAT'S CALLED KCTD13 HAS IMPACT ON THE FISH HEAD SIZE IN THE SAME DIRECTION AS THE COPY NUMBER VARIANT IN HUMAN. HOWEVER, THE PAPER -- A RECENT

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PAPER THAT TRIED TO REPLICATE THESE RESULTS COULD NOT REPLICATE THESE RESULTS. AND SO DESIGNED A MOUSE MODEL WITH THIS SPECIFIC GENE FROM THIS COPY NUMBER VARIANT DELETED, AND THEY DID NOT SEE ANY HEAD SIZE PHENOTYPE IN THIS MOUSE MODEL.

SO JUST TO SUMMARIZE, ALTHOUGH ANIMAL MODELS CAN BE A GOOD MODEL FOR SOME OF THE GENES FOR AUTISM, IT LOOKS LIKE FOR THIS SPECIFIC COPY NUMBER VARIANT, THEY'RE NOT AS GREAT BECAUSE OF THIS, LIKE, DISCORDANT PHENOTYPES BETWEEN HUMAN AND MOUSE BECAUSE OF INCONSISTENCY BETWEEN DIFFERENT MOUSE MODELS. THAT'S WHY WE DECIDED ACTUALLY TO RESORT TO STUDYING ORGANOIDS.

SO WE DECIDED TO INVESTIGATE -- TO CREATE THE ORGANOIDS FROM THE PATIENT'S SKIN FIBROBLAST WITH THE 16P DUPLICATIONS AND DELETIONS. AND THEN WE SELECTED SPECIFICALLY PATIENTS ACTUALLY THAT HAVE THESE MACROCEPHALY AND MICROCEPHALY PHENOTYPES. AND THEN WE PERFORMED THE MOLECULAR CELLULAR PHENOTYPE CHARACTERIZATION AS WELL AS WE USED PHARMACOLOGICAL INHIBITORS TO RESCUE THOSE PHENOTYPES.

SO FIRST QUESTION THAT WE ASKED WAS WERE THE ORGANOIDS THAT THEY DERIVED FROM THESE PATIENTS WITH MACROCEPHALY AND MICROCEPHALY AND THIS COPY NUMBER VARIANT CAN RECAPITULATE THE HEAD SIZE

PHENOTYPES OF THE PATIENTS. AND WE WERE VERY PLEASED TO SEE THAT, IN FACT, WHEN WE GREW THOSE ORGANOIDS, WE SAW THAT DELETIONS HAVE HIGHER -- LARGER DIAMETER AND DUPLICATIONS HAVE SMALLER DIAMETER, WHICH IS RECAPITULATION THAT HUMAN HEAD SIZE PHENOTYPES. AND WE ALSO SAW THAT THE PROPORTIONS OF THE SMALL ORGANOIDS IS HIGHER IN DUPLICATIONS AND PROPORTION OF LARGE ORGANOIDS IS HIGHER IN DELETIONS.

SO WHAT THIS MEANS IS THAT OUR ORGANOIDS, UNLIKE MOUSE MODELS, ACTUALLY DO RECAPITULATE THE HEAD SIZE PHENOTYPES OF THE PATIENTS.

NEXT, WE PERFORMED GENE EXPRESSION AND ALSO PROTEIN EXPRESSION ANALYSIS OF THE ORGANOIDS THAT ARE DERIVED FROM THESE PATIENTS AND CONTROLS AT THREE STAGES, AT THE STAGE OF IPSC ONE MONTH ORGANOIDS AND THREE MONTH ORGANOIDS.

AGAIN, THE NEXT QUESTION THAT WE ASKED AND IS REALLY IMPORTANT IN THE FIELD, WHETHER THE EXPRESSIONAL PROFILES OR MOLECULAR PROFILES OF THOSE ORGANOIDS ACTUALLY RECAPITULATE WHAT'S GOING ON IN HUMAN BRAIN. SO WHAT WE DID, WE ACTUALLY USED, AGAIN, THIS RESOURCE BRAINSPAN, AND ACTUALLY THE TOOL THAT WAS DEVELOPED BY JASON STEIN IN DAN'S LAB THAT IS CALLED CONTEXT, WHICH CAN COMPARE, USING

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MACHINE LEARNING, IT CAN COMPARE HOW DIFFERENT OR HOW SIMILAR YOUR ORGANOIDS ARE TO THE HUMAN BRAIN. AND WHAT WE SAW WAS ABSOLUTELY STUNNING, I THINK.

SO YOU CAN SEE ON THIS FIGURE, SO RED COLOR MEANS THAT THIS IS MORE SIMILAR TO HUMAN BRAIN; WHEREAS, BLUE COLOR MEANS LESS SIMILAR TO HUMAN BRAIN. AND THIS IS THREE DIFFERENT STAGES OF ORGANOIDS. THIS IS VERY EARLY STAGE, JUST IPC'S FROM THIS PATIENT, AND THEN THERE IS ONE MONTH ORGANOIDS, AND THEN WE KEEP THEM LONGER FOR THREE MONTHS. AND WHAT YOU CAN ACTUALLY APPRECIATE HERE IS THAT AT THE IPSC STAGE -- I'M SORRY -- ORGANOIDS PRETTY MUCH RECAPITULATE THE GLOBAL EXPRESSIONAL PROFILES OF EMBRYONIC AND EARLY FETAL BRAIN DEVELOPMENT; WHEREAS, AS ORGANOIDS MATURE AND GO MORE INTO ONE MONTH, YOU CAN SEE THAT IT'S MORE SIMILAR TO LIKE EARLY MID-FETAL AND EVEN LATE MID-FETAL DEVELOPMENT. AND, AGAIN, WHEN WE KEEP CULTURING THEM FOR ANOTHER TWO MONTHS, THEY SHIFT EVEN MORE IN TERMS OF GLOBAL EXPRESSIONAL PROFILES TO MORE LIKE LATE MID-FETAL, LATE FETAL, AND EVEN KIND OF NEONATAL.

SO WHAT THIS SLIDE SHOWS, THAT ORGANOIDS THAT WE ARE PRODUCING ARE ACTUALLY SIMILAR TO THE HUMAN FETAL BRAIN DEVELOPMENT. AND, AGAIN, YOU

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ALREADY SAW THIS QUOTE FROM DAN'S TALK ACTUALLY. SO, AGAIN, USING THIS TOOL THAT DAN CREATED, WE ALSO COMPARED THE LAYERS. SO OUR ORGANOIDS DO NOT HAVE A SPECIFIC LAYER. IT'S KIND OF A MIXTURE OF THE CELLS, BUT WE STILL CAN LOOK AT THIS EXPRESSION PROFILE AND ASK A QUESTION, WHETHER THIS EXPRESSION PROFILE FROM OUR ORGANOIDS, WHICH OF THE BRAIN LAYERS IT CORRESPONDS TO. AND YOU COULD APPRECIATE THAT AT ONE MONTH ORGANOIDS ACTUALLY RECAPITULATE IN MORE LIKE EARLY LAYERS THAT ARE MORE LIKE AN EARLY FETAL BRAIN AND THEN -- I'M SORRY. IT'S JUMPING ALL OVER THE PLACE. I SHOULDN'T USE MY MOUSE. AND THEN AT THREE MONTHS, YOU CAN SEE IT'S HIGHLIGHTED HERE MORE IN RED, THAT IN THREE MONTHS THE RESEMBLANCE IS MOVING TO UPPER CORTICAL LAYERS OF THE HUMAN BRAIN, WHICH IS REALLY NICE, WE THOUGHT.

THEN WE PERFORMED TWO DIFFERENT OTHER ANALYSIS. WE WANTED TO KNOW WHAT THE DIFFERENCES, WHAT GENES ARE DIFFERENTIALLY KIND OF IMPACTED BETWEEN DELETIONS AND DUPLICATIONS. AND WE OBSERVED THIS VERY INTERESTING SET OF GENES. FIRST, WE OBSERVED GENES THAT ARE RESPONSIBLE FOR THE NEURON MIGRATION AND ACTIN CYTOSKELETON IN ORGANOIDS THAT ARE DIFFERENTIALLY EXPRESSED BETWEEN DUPLICATIONS AND DELETIONS. AND THE SECOND SET OF GENES THAT

PROBABLY UNSURPRISING THAT WE OBSERVED ARE THESE NEURONAL AND -- GENES THAT PERFORM THIS NEURONAL AND SYNAPTIC FUNCTIONS.

AND WE ALSO PERFORMED ANOTHER TYPE OF ANALYSIS WHERE WE WANTED TO SEE WHICH OF THE GENES ARE KIND OF EXPRESSED TOGETHER AND WHICH ARE DIFFERENT BETWEEN CASES AND CONTROLS. AND, AGAIN, WE SAW THIS MIGRATION MODULE, AGAIN, RECAPITULATION OF OUR PREVIOUS ANALYSIS, AND ALSO NEURONAL AND SYNAPTIC MODULE. AND WE ALSO SAW ANOTHER MODULE, WHICH IS CHROMATIN MODULE, WHICH DAN ALSO MENTIONED THAT CHROMATIN PROCESSES ARE ALSO VERY FREQUENTLY IMPACTED IN AUTISM.

SO AFTER WE OBSERVED THESE MODULES AND THE DIFFERENTIALLY EXPRESSED GENES FROM COMPUTATIONAL ANALYSIS, WE REALLY WANTED TO KNOW WHETHER WE CAN ACTUALLY OBSERVE THEM EXPERIMENTALLY. SO WHAT WE DID, WE TOOK OUR ORGANOIDS FROM CONTROL, DELETION, AND DUPLICATION AND WE SLICE THEM INTO THESE LIKE THIN SLICES, PUT THEM ON THE SLIDES, AND THEN WE STAINED THEM WITH DIFFERENT MARKERS, IMMUNOFLUORESCENT MARKERS, AND WE SAW A REALLY INTERESTING THING. SO YOU SEE THOSE GREEN DOTS IN DELETION ORGANOIDS, THOSE ACTUALLY ARE MATURE NEURONS THAT ARE LABELED HERE.

SO WE WHAT WE SAW, THAT IN THESE DELETIONS, RIGHT, WHERE THE GENES ARE DELETED, WE SEE MORE THESE IMMATURE NEURONS OR IMMATURE CELLS WHICH ARE NEUROPROGENITORS. SO THEY WERE DECREASED IN DELETIONS, AND AT THE SAME TIME THEY WERE INCREASED IN DUPLICATIONS; WHEREAS, MATURE NEURONS WERE OPPOSITE. SO WE SAW THAT THESE DELETION ORGANOIDS HAVE MORE OF THESE MATURE NEURONS AND DUPLICATIONS HAVE LESS. WHAT THIS TELLS US, THAT WE ACTUALLY SEE IS THAT THESE COPY NUMBER VARIANTS CAUSES ACCELERATED NEUROGENESIS IN DELETIONS AND KIND OF DELAYED NEUROGENESIS IN THOSE DUPLICATIONS.

SO IF WE SEE MORE NEURONS IN DELETIONS, WE THEN ASK THE QUESTION: ARE THERE MORE SYNAPSES? WHEN THERE ARE MORE NEURONS, THERE COULD BE ALSO MORE SYNAPSES IN THOSE ORGANOIDS. AND, INDEED, WHEN WE STAINED THOSE SLICES OF ORGANOIDS WITH THE MARKERS FOR THE SYNAPTIC PUNCTA, WE SAW THAT IN DELETION, ORGANOIDS CONCORDANT WITH THE HIGHER NUMBER OF NEURONS. WE ALSO SEE A HIGHER NUMBER OF SYNAPTIC PUNCTA AS WELL.

NEXT, YOU REMEMBER THAT I TOLD YOU THAT WE ALSO OBSERVED THIS MIGRATION MODULE. SO WHAT CAN BE HAPPENING IN THE FETAL BRAIN WE THOUGHT IS THAT MAYBE THERE IS DISRUPTIVE -- NEURONS HAVE TO MIGRATE

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TO SPECIFIC PLACES IN THE BRAIN, AND CERTAIN NUMBER OF NEURONS. BUT HERE WE SAW THIS MIGRATION MODULE. SO WE WANTED TO SEE WHETHER, IF WE PLANT ORGANOIDS ON THE SPECIFIC MEDIA AND WE LOOK HOW NEURONS ARE MIGRATING OUT OF ORGANOIDS, WHETHER WE CAN SEE ANY OF THIS MIGRATION DEFECT. AND, INDEED, WHEN WE PLATED ORGANOIDS CONTROL, AGAIN DELETION AND DUPLICATION, ON THE MATRIGEL AND WE RECORDED FOR 72 HOURS, WE RECORDED A MOVIE, HOW THESE NEURONS ARE MIGRATING. SO I'M GOING TO START THE MOVIE. I DON'T KNOW IF YOU GUYS CAN SEE IT. BUT HERE IT GOES. SO YOU CAN SEE HOW FROM CONTROL THOSE NEURONS ARE MIGRATING AND THERE IS DELETION AND DUPLICATION. YOU CERTAINLY CAN SEE THAT THOSE CELLS ARE JUST LIKE HOVERING AROUND DELETIONS AND DUPLICATIONS AND NOT MIGRATING AS FAR AS FROM CONTROLS. AND WHEN WE QUANTIFIED THAT, WE DEFINITELY SAW THAT DELETIONS AND DUPLICATIONS BOTH HAVE THIS DISRUPTIVE NEURONAL MIGRATION. AND IN DELETIONS ACTUALLY YOU CAN SEE IT'S EVEN MORE SEVERE THAN IN DUPLICATIONS.

AND THEN WHEN WE STAINED, AGAIN, THESE PICTURES, YOU CAN CERTAINLY SEE THAT THESE FIBERS HERE ARE DEFINITELY PROTRUDING FROM CONTROLS FURTHER, AND YOU SEE THOSE NEURONS THAT ARE BLUE OR WHITE, BLUE ON THE LEFT AND WHITE ON THE RIGHT, AND

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YOU SEE MUCH LESS OF THESE NEURONS MIGRATING OUT OF THE MUTANT DELETIONS AND DUPLICATIONS.

SO NOW WE CONFIRMED THAT WHAT WE SAW FROM OUR COMPUTATIONAL ANALYSIS, THAT INDEED THIS MIGRATION AND ALSO SYNAPTIC AND NEURONAL PROCESSES ARE DISRUPTED BY THIS MUTATION. BUT WE WERE NOT SATISFIED WITH THIS RESPONSE BECAUSE WE REALLY WANTED TO KNOW WHAT EXACTLY CAUSES THIS DELAYED MIGRATION AND THOSE SYNAPTIC DEFICITS. SO WE LOOKED AT THE MIGRATION MODULE IN MORE DETAIL BECAUSE FROM OUR MOLECULAR ANALYSIS WE CAN ACTUALLY IDENTIFY WHAT SPECIFIC GENES DYSREGULATE THIS MIGRATION.

AND WE SAW THAT ONE OF THE PROCESSES SAY THAT THIS REGULATION OF SMALL GTPASE OR REGULATION OF RAW PROTEIN SIGNAL TRANSDUCTION, SO ONE OF THE GENES WITHOUT THIS FUNCTION IS SO-CALLED SMALL GFPASE RHOA. SO THIS RHOA IS VERY HIGHLY UP-REGULATED IN BOTH ACTIVE RHOA IN BOTH DELETIONS AND DUPLICATIONS. WHEN WE LOOKED AT THE (UNINTELLIGIBLE), WE SAW THAT THIS OVER-ACTIVATION OF RHOA HAS ACTUALLY BEEN SHOWN THAT IT CAN STALL MIGRATION OF THE NEURONS. SO WE KIND OF IMPLICATED THAT PROBABLY THESE MIGRATION DEFECTS ARE HAPPENING BECAUSE OF THIS OVERACTIVE -- THIS RHOA MOLECULE.

SO WE WERE LUCKY ACTUALLY BECAUSE THERE IS

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ALREADY AN INHIBITOR OF THE RHOA THAT WAS DEVELOPED THAT IS CALLED RHOSIN. SO WHEN WE TREATED -- IT'S A VERY SPECIFIC INHIBITOR. SO WHEN WE TREATED OUR ORGANOIDS STARTING FROM DAY SIX UP TO THE MONTH WITH THIS RHOSIN, WHAT WE SAW WAS THAT IT ACTUALLY RESCUES THE MIGRATION. SO YOU SEE IN THE BOTTOM ROW THERE IS ALMOST NO DIFFERENCE BETWEEN THE DUPLICATION AND DELETIONS THAT ARE TREATED WITH THIS RHOSIN. SO TREATING ORGANOIDS WITH THIS INHIBITOR ACTUALLY RESCUED THESE MIGRATION PHENOTYPES IN ORGANOIDS.

SO YOU MIGHT THINK LIKE WHAT DOES RHOA EVEN HAVE TO DO WITH THE 16P COPY NUMBER VARIANT THAT IMPACTS 29 GENES? WELL, WE WONDERED THAT OURSELVES AS WELL. AND ONE THING THAT ACTUALLY WE DISCOVERED IS THAT ONE OF THE GENES WITHIN THIS 16P COPY NUMBER VARIANT CALLED KCDT13 ACTUALLY INTERACTS AT THE PROTEIN LEVEL WITH THIS OTHER MOLECULE WHICH IS CULLIN3 UBIQUITIN LIGASE. SO IT'S A DIFFERENT GENE THAT'S COMPLETELY IN DIFFERENT CHROMOSOME, BUT THOSE TWO PROTEINS FORM A COMPLEX. AND ACTUALLY RHOA IS A SUBSTRATE OF THIS COMPLEX. SO THIS CULLIN3, A NEW GENE, A NEW PROTEIN, UBIQUITIN RHOA, AND THEN THEY REACTED CHROMOSOMAL DEGRADATION. SO IT REGULATES THE LEVELS OF RHOA. AND RHOA IS KNOWN

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TO BE INVOLVED IN, LIKE, ACTIN CYTOSKELETAL MIGRATION. SO THERE IS A TIGHT CONNECTION BETWEEN THE 16P COPY NUMBER VARIANT AND THIS RHOA THAT WE OBSERVED TO BE UP-REGULATED AND THAT'S CORRECTED BY THE RHOSIN TREATMENT.

SO WHAT WE DECIDED TO DO, WE DECIDED TO MAKE A MOUSE WITH THIS MUTATION IN THIS CULLIN3 GENE JUST BECAUSE WE DIDN'T HAVE THE PATIENT'S ORGANOIDS FROM THIS CULLIN3. AND ANOTHER THING ABOUT THIS CULLIN3 IS THAT IT'S ALSO AUTISM GENE. SO INTERESTINGLY, CULLIN3 IS ALSO MUTATED IN AUTISM AS WELL.

SO WE MADE A MOUSE USING CRISPR FROM THESE CULLIN3 GENES AND WE CORRECTED THIS MOUSE. AND THIS MOUSE HAD A LOT OF VARIOUS DEFICITS. IT WAS SMALLER. THE BRAIN WAS DIFFERENT. BUT THE MOST KIND OF REWARDING THING FROM THIS WORK WAS THAT ACTUALLY THIS CULLIN3 MOUSE ALSO HAS THE SAME RHOA BEING UP-REGULATED. SO 16P COPY NUMBER VARIANT OR KCDT13 IS A MEMBER OF THIS COPY VARIANT AND CULLIN3 IS ALSO MUTATED IN AUTISM. THEY BOTH INTERACT, AND RHOA IN THE UP-REGULATED THIS RHOA MOLECULE.

AND THEN WE WANTED TO SEE WHETHER THIS RHOSIN CAN ACTUALLY RESCUE SOME OF THE PHENOTYPES OF THIS MOUSE. SO THIS CULLIN3 MOUSE ALSO HAS DEFECTS

IN THE FIRING RATE AND BURST OF THE NEURONS. SO YOU SEE THAT THE TRACKS OF LIKE NEURONAL ACTIVITY IS LOWER ACTUALLY HERE. AND WHEN WE TREATED THOSE NEURONS FROM THE MOUSE BRAIN THAT WE PLATED ON THE SO-CALLED MICROELECTRODE ARRAYS AND WE TREATED WITH RHOSIN. SO RHOSIN COMPLETELY RESTORED THIS IMPAIRED NEURONAL ACTIVITY OF THIS CULLIN3 MOUSE BRAIN.

SO NOW WE KIND OF HAVE A MODEL WITH TWO DIFFERENT AUTISM VARIANTS THAT CONVERGE ON THE SAME PATHWAY. SO WHEN WE HAVE A NORMAL COPY NUMBER OF 16P, RIGHT, THEN THIS CULLIN3, KCDT13, INTERACTS WITH CULLIN3, AND THERE IS SUBSTRATE OF THIS COMPLEX, WHICH IS RHOA, COMPLEX UBIQUITIN A TRAY AND THEY REACTED TO CHROMOSOMAL DEGRADATIONS AND EVERYTHING IS FINE. HOWEVER, WHEN EITHER DELETION OR DUPLICATION HAPPENS OF THIS VARIANT, AND KCTD13 IS IMPACTED, IT'S MUTATED. OR WHEN CULLIN3 IS MUTATED IN AUTISM, THEN THIS RHOA IS NOT GETTING UBIQUITIN A, THEN IT ACCUMULATES WHICH THEN CAUSES ALL THESE DEFECTS THAT WE SEE, NEURONAL DEFECTS, MIGRATION DEFECTS, AND OTHER DEFICITS.

SO NOW WE HAVE A MODEL WHERE THESE TWO DIFFERENT MUTATIONS CONVERGE ON THE SAME PATHWAY. AND NOW WE EVEN HAVE A DRUG THAT WE CAN TEST IN THE FUTURE IN OTHER MODELS, FOR EXAMPLE, CULLIN3

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ORGANOIDS, AND SEE WHETHER IT RESCUES ALL THESE DEFICITS.

SO JUST TO SUMMARIZE, I HOPE I CONVINCED YOU THAT ORGANOIDS CAN RECAPITULATE PATIENTS' PHENOTYPES, AT LEAST THE HEAD AND BRAIN SIZE PHENOTYPES. THEN WE SAW THAT ORGANOIDS HAVE SIGNATURES THAT ARE VERY SIMILAR TO DEVELOPING HUMAN BRAIN. AND THEY HELP US TO IDENTIFY POTENTIAL MECHANISMS SUCH AS DEFECTS IN MIGRATION AND NEUROGENESIS THAT MAY BE DYSREGULATED BY TWO DIFFERENT MUTATIONS IN AUTISM. AND ORGANOIDS HELPED US ALSO TO IDENTIFY THE POTENTIAL CANDIDATE DRUGS THAT COULD BE USED AS A POTENTIALLY THERAPEUTIC TARGET.

AND, MOST IMPORTANTLY, I SHOWED YOU THAT THERE COULD BE A CONVERGENCE OF DIFFERENT AUTISM MUTATIONS ON THIS DOWNSTREAM PATHWAY. AND THIS IS VERY IMPORTANT BECAUSE IN AUTISM AREA, MAYBE WE CAN TREAT AUTISM WHEN ONE GENE IS INVOLVED, MAYBE WE CAN UP-REGULATE IT, CREATE ANTISENSE OLIGOS OR SOMETHING. BUT IF THERE IS A CNV, COPY NUMBER VARIANT, IN THESE 29 GENES, THERAPEUTIC STRATEGIES SEEM TO BE VERY LIMITED BECAUSE IT WOULD BE VERY HARD TO KIND OF UP-REGULATE ALL 29 GENES OR SOMETHING LIKE THIS. SO MAYBE FOR THE CNV IS WE

NEED TO FOCUS OR FIND THOSE DOWNSTREAM PATHWAYS THAT CAN BE TARGETED BY THE THERAPIES.

AND JUST TO HIGHLIGHT FUTURE DIRECTIONS, OF COURSE, MIGRATION AND SYNAPTIC DEFICITS IS ONLY ONE PATHWAY THAT WE SAW. AND WE THINK THERE ARE OTHER PATHWAYS THAT COULD BE DYSREGULATED, SUCH AS I SHOWED YOU THIS CHROMATIN-RELATED MODULE. SO I THINK WE ARE JUST MAYBE SCRATCHING THE SURFACE OF THE MECHANISMS OF DISEASE AT THIS POINT.

AND BECAUSE WE DID BULK RNASEQ, WE STILL HAVE TO IDENTIFY WHAT SPECIFIC CELL TYPES ARE IMPACTED BY THESE COPY NUMBER VARIANTS. AND WE'LL BE DOING A SINGLE-CELL RNASEQ ON THOSE ORGANOIDS IF WE CAN GET FUNDING FOR THAT.

THEN RHOA IS ACTUALLY -- COULD BE IMPLICATED IN THE PATHWAY FOR OTHER AUTISM MUTATIONS. FOR EXAMPLE, ONE OF THE PAPERS FROM RICARDO DOLMA'S LAB WHERE COMPLETELY DIFFERENT GENE IS MUTATED. CACNA1C IS A CALCIUM CHANNEL IN THE TIMOTHY SYNDROME. THERE IS ALSO A POSSIBILITY THAT IT'S REGULATED BY RHOA AS WELL. AND WE ARE WORKING ON THERAPEUTIC STRATEGIES FOR THE DISEASE NOW. MAYBE IN MOUSE, CULLIN3 MOUSE, ACTIVATE WITH CRISPR A OR USING RHOSIN TO RESCUE THOSE PHENOTYPES. AND WE ARE ALSO LOOKING TO RECRUIT THE PATIENTS WITH

CULLIN3 MUTATIONS NOW TO CREATE THE ORGANOIDS AND SEE WHETHER OUR 16P FINDINGS ARE SIMILAR WITH RHOA AND OTHER PATHWAYS IN CULLIN3 PATIENTS AS WELL.

SO I WOULD LIKE TO THANK PEOPLE IN MY LAB, ESPECIALLY ALYSSON MUOTRI. IT'S A TIGHT COLLABORATION WITH ALYSSON'S GROUP WHO ACTUALLY TAUGHT US HOW TO MAKE ORGANOIDS. JOHN YATES' LAB WHO DID PROTEOMIC ANALYSIS AND THE SIMONS FOUNDATION FOR AUTISM RESEARCH AND FUNDED THIS WORK. AND THANK YOU FOR YOUR ATTENTION.

CHAIRMAN GOLDSTEIN: THANK YOU, LILIA. THAT'S REALLY AMAZING AND IMPRESSIVE.

WHAT I'D LIKE TO DO NOW IS TAKE JUST A COUPLE MINUTES FOR SPECIFIC QUESTIONS TO LILIA AND THEN EVOLVE INTO A MORE GENERAL DISCUSSION OF ARE ANY OF THESE TARGETS REALLY GOING TO BE THERAPEUTICALLY READY IF THERE WERE APPROPRIATE CELL LINES AND COLLECTIONS AND RELATED ISSUES.

I THINK THE FIRST QUESTION I WANT TO JUST LAUNCH TO GET US GOING, LILIA, IS IT SEEMS TO ME THAT, ALTHOUGH YOU'VE DEVELOPED POTENTIAL TREATMENT STRATEGIES, DON'T THEY HAVE TO BE ADMINISTERED AT EXACTLY THE RIGHT TIME OF IN-UTERO DEVELOPMENT SO THAT YOU WOULD NEED TO HAVE A DIAGNOSTIC THAT SAID THE FETUS IN UTERO IS DESTINED TO HAVE SEVERE

AUTISM, SAY. AND THEN YOU'D REALLY HAVE TO DO THE TREATMENT AT EXACTLY THE RIGHT MOMENT. AND CERTAINLY YOU COULD NOT DO IT AFTER BIRTH IN MOST CASES.

DR. IAKOUCHEVA: OF COURSE. NOT ONLY THAT, LARRY, BUT WE ALSO NEED TO KNOW THE CELL TYPES THAT ARE IMPACTED. MAYBE WE DON'T WANT TO TREAT BEFORE WE KNOW WHAT EXACTLY CELL TYPES ARE IMPACTED. THAT'S WHY WE ARE DOING THE SINGLE-CELL STUDIES.

I'M NOT SUGGESTING THAT WE ARE GOING TO START TREATING RIGHT NOW. I THINK THERE IS MORE WORK NEEDS TO BE DONE TO ACTUALLY IDENTIFY THE MECHANISMS. BUT IN PRINCIPLE, YOU CAN IMAGINE THAT THE DIAGNOSIS OF 16P, IT'S A BIG COPY NUMBER VARIANT. AND IN PRINCIPLE IT COULD BE MADE -- DIAGNOSIS COULD BE MADE FROM THE EITHER AMNIOTIC FLUID DEFINITELY WHETHER BABY CARRIES 16P OR NOT.

AND I'M NOT PROPOSING THAT -- MAYBE THAT'S WHY WE WOULD LIKE TO KNOW, MAYBE TREATING RIGHT AFTER THE BIRTH IN THE FIRST WEEK AFTER THE BIRTH COULD BE ACTUALLY A POSSIBILITY. WE DEFINITELY NEED TO WORK MORE TO DETERMINE THE WINDOWS OF THE THERAPEUTIC TREATMENT, FOR SURE, CORRECT WINDOW AND SO FORTH. BUT I THINK DIAGNOSIS IN UTERO IS NOW NOT

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A BIG PROBLEM ESPECIALLY FOR COPY NUMBER VARIANTS. BECAUSE THEY'RE BIG, YOU CAN SEE THEM JUST BY ARRAY CGH.

CHAIRMAN GOLDSTEIN: OTHER QUESTIONS FOR LILIA BEFORE WE MOVE INTO A JOINT DISCUSSION? OKAY.

SO LET ME LAUNCH THE JOINT DISCUSSION WITH A SET OF QUESTIONS FOR LILIA AND DAN. AND THE ISSUE, I THINK, IS ONE OF HAVE WE -- HAS THE COMMUNITY ADEQUATELY ANALYZED THE VARIOUS TYPES OF HUMAN POPULATIONS? AND, OF COURSE, IN PARTICULAR IN THE U.S., HAVE UNDERSERVED POPULATIONS BEEN SAMPLED? AND DO WE KNOW TO WHAT EXTENT DIFFERENT GENETIC VARIANTS ARE ACTIVE IN DIFFERENT GENETIC BACKGROUNDS?

DR. GESCHWIND: THAT'S A GREAT QUESTION. SO ABOUT TEN YEARS AGO, KIND OF SEEING THE EXPLOSION OF SUCCESS IDENTIFYING GENES IN MOSTLY EUROPEAN POPULATIONS, WE STARTED A PROJECT, ACTUALLY A NETWORK FUNDED BY NIMH CALLED, IT'S AN AUTISM CENTER OF EXCELLENCE, TO RECRUIT AFRICAN-AMERICANS WITH AUTISM TO LOOK AT THOSE WITH AFRICAN ANCESTRY AND TO SEE TO WHAT EXTENT GENETIC VARIATION WAS ON THE AFRICAN OR EUROPEAN PARTS AND ALL OF THAT. THAT'S AN ONGOING PROJECT THAT IS -- THAT'S THE ONLY ONE OF ITS TYPE IN PSYCHIATRIC DISEASES THAT I'M AWARE OF

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THAT'S NIH FUNDED.

I'M ANTICIPATING THAT WITHIN THE NEXT YEAR WE'LL HAVE A SERIES OF OUR FIRST PAPERS OUT WHERE -- YOU KNOW, WE HAVE TO GET THE SAMPLES TO A LARGE ENOUGH COHORT, AND THEY'RE STILL NOT SUPER LARGE RELATIVE TO THE EUROPEAN COHORTS, BUT SO FAR WE DON'T HAVE ANY EVIDENCE THAT THE VAST MAJORITY -- THE KIND OF DE NOVO MUTATIONS ARE OCCURRING ANY DIFFERENTLY. IT'S JUST THAT AFRICAN CHROMOSOMES, AS YOU PROBABLY KNOW, WE ALL CAME OUT OF AFRICA. IN OTHER WORDS, IF WE ALL LOOK FOR OUR COMMON ANCESTORS AS HUMANS, IT'S IN AFRICA, THERE'S A BOTTLENECK. AND SO IF YOU ACTUALLY LOOK -- AND SO THERE'S A BOTTLENECK COMING OUT OF AFRICA. THAT MEANS ONLY A SMALL PROPORTION OF REAL HUMAN GENETIC VARIATION CAME OUT OF AFRICA. AND THE REST OF IT HAS STAYED IN AFRICA.

SO WHEN YOU LOOK AT AFRICAN CHROMOSOMES, YOU SEE A LOT MORE RARE GENETIC VARIATION. AND SO WE ARE KIND OF EXPLORING THAT. BUT SO FAR WE HAVE NO EVIDENCE TO SUGGEST THAT THE ACTUAL TYPES OF GENETIC VARIATION ARE DIFFERENT. IT'S JUST THAT BECAUSE THE MARKERS ARE A LITTLE DIFFERENT, THEY'RE HARDER TO DETECT IF YOU HAVEN'T -- LIKE, WE CAN'T COURT THE SCORE FROM EUROPEANS OR FROM CHINESE OR

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ANYBODY INTO ANOTHER POPULATION EASILY. BUT THE MARKERS AND THE DISEASE THINGS ARE LIKELY TO BE THE SAME.

JOE BUXBAUM AND BERNIE DEVLIN AND OTHERS HAVE STARTED A PROJECT WITH PEOPLE OF HISPANIC, SELF-IDENTIFIED HISPANIC BACKGROUND IN AUTISM THAT'S MOVING FORWARD TOO. AND OURS IS A NETWORK THAT ACTUALLY INVOLVES EMORY AND EINSTEIN AND WASH U IN ST. LOUIS AND L.A. BUT THERE ISN'T A LOT GOING ON THERE. AND IT'S VERY EXPENSIVE TO BE COLLECTING -- AND SO NIH HAS GOTTEN LESS INTERESTED. AND SO AT THE SAME TIME, THEN HAVING DIVERSE BIOBANKS THAT HAVE THIS GENETIC DIVERSITY IN THEM FOR IPSC'S IS ALSO ANOTHER BIG DEAL. SO ONCE WE IDENTIFY MUTATIONS IN PATIENTS, WE'RE GOING TO CALL THEM BACK IN, SELF-IDENTIFIED AFRICAN-AMERICAN PATIENTS WHO HAVE AFRICAN ANCESTRY, AND TRY TO BANK THEIR CELLS AS WELL. THAT'S ONE OF OUR GOALS. BUT IT'S -- YEAH. IT'S AN IMPORTANT ISSUE.

AND WE STARTED IT ABOUT EIGHT OR NINE YEARS AGO, ALMOST TEN, WHEN IT WASN'T REALLY AS WELL APPRECIATED HOW IMPORTANT THAT IS AS IT IS NOW. SO WE'VE JUST BEEN PLUGGING ALONG.

CHAIRMAN GOLDSTEIN: LILIA, DO YOU WANT TO ADD ANYTHING TO THAT BEFORE I CALL ON ROSA AND THEN

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PAT?

DR. IAKOUCHEVA: WELL, I'M A MEMBER OF THIS SO-CALLED NEW CONSORTIUM THAT NIH IS FUNDING CALLED IGVF, IMPACT OF GENETIC VARIATION ON FUNCTION. AND ONE OF -- WELL, THE GOAL OF THIS CONSORTIUM IS TO CHARACTERIZE FUNCTIONAL IMPACT OF EVERY SINGLE SNP, CHARACTERIZE OR PREDICT A FUNCTIONAL IMPACT OF EVERY SNP THAT ACTED IN HUMAN GENOME. AND ONE OF THE LEADS OF THIS CONSORTIUM IS ALSO LOOK AT THE VARIANTS IN DIFFERENT POPULATIONS AS WELL. AND I THINK IT WILL BE VERY IMPACTFUL. IT'S JUST AT THE VERY BEGINNING. SO I THINK IT'S GOING TO TAKE ANOTHER FIVE TO TEN YEARS TO ACTUALLY GET SOME RESULTS FROM THIS. BUT I AGREE. IT'S VERY MUCH NEEDED.

DR. GESCHWIND: IT'S SOMETHING WE CAN ACCELERATE HERE IN CALIFORNIA THOUGH.

DR. IAKOUCHEVA: RIGHT. YEAH. THAT'S SOMETHING THAT'S NEEDED TO LOOK AT THE VARIANTS IN DIFFERENT POPULATIONS, ABSOLUTELY.

CHAIRMAN GOLDSTEIN: GREAT. THANK YOU. ROSA.

DR. CANET-AVILES: THANK YOU, DR. GOLDSTEIN. I JUST WANTED TO SPEAK ALSO ABOUT MORE HIGH INCIDENCE DISEASES LIKE SCHIZOPHRENIA, BIPOLAR

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AS WELL. I JUST WANTED TO BRING UP A VERY LARGE NIMH ANCESTRAL POPULATION NETWORK THAT LAUNCHED LAST YEAR. AND WE'VE BEEN SPEAKING TO THEM. DR. PANCHISION AT NIMH IS THE PROGRAM DIRECTOR ON THIS AND HE HAS SOME SITES IN CALIFORNIA. AND THEY ARE CURRENTLY -- THEY HAVE THOUSANDS OF DIVERSE POPULATIONS FROM LATIN AMERICA AND AFRICAN ANCESTRIES AS WELL AS SOUTH AFRICA AND ASIA.

AND THEIR GOAL IS TO RECRUIT -- THEY ARE DOING BIOSPECIMEN COLLECTION, CLINICAL PHENOTYPING, GENOMICS. AND THEY DON'T HAVE AN IPS CELL COMPONENT. SO THAT'S SOMETHING THAT COULD BE OF INTEREST. AND THAT INCLUDES MOSTLY SCHIZOPHRENIA AND BIPOLAR POPULATION. JUST WANTED TO BRING THIS UP AND RAISE IT TO THE TASK FORCE.

DR. GESCHWIND: YEAH. IN FACT, NELSON FREIMER, HERE. I'M SORRY. YEAH. I TOTALLY SPACED OUT ON THAT. THANKS, ROSA, FOR BRINGING THAT UP BECAUSE THEY'VE BEEN DRIVING THAT STARTING IN COSTA RICA, BUT NOW IN COLUMBIA AND OTHER PLACES AS WELL. THANK YOU.

CHAIRMAN GOLDSTEIN: THANK YOU. PAT.

DR. LEVITT: YEAH, THANKS FOR BOTH GREAT PRESENTATIONS. SO I'LL ASK A MORE GENERAL QUESTION. THERE'S SORT OF IN THIS STANDARD PATH TO FOLLOW THAT

GOES FROM DISCOVERY TO ALL SORTS OF IN VITRO EXPERIMENTAL MODELS ULTIMATELY BEING TESTED IN ANIMALS BEFORE IT GOES TO HUMANS. SO MAYBE YOU CAN EACH SPEAK TO WHETHER YOU ENVISION A PARADIGM SHIFT WHERE WE GO FROM ORGANOIDS TO CLINICAL TRIAL. GIVEN SOME OF THE QUEASINESS AROUND SOME OF THE PARTICULARLY RODENT MODELS, ALTHOUGH I WOULD CAUTION THAT PUTTING A MUTATION ONTO A SINGLE BACKGROUND STRAIN DOESN'T NECESSARILY SAY THAT YOU CAN'T RECAPITULATE THE MAJOR PHENOTYPES. WE KNOW THAT NOW, RIGHT? BUT I'M MORE INTERESTED IN YOUR THOUGHTS ABOUT WHETHER YOU ENVISION A PARADIGM SHIFT IN TERMS OF HOW ONE VIEWS GOING FROM DISCOVERY USING HUMAN PLATFORMS TO DRUG DEVELOPMENT.

DR. GESCHWIND: I WAS GOING TO SAY TOXICITY IS STILL A MAJOR ISSUE. SO YOU'D HAVE TO USE ANIMALS FOR TOX STUDIES. BUT I THINK IN TERMS OF FACE AND CONSTRUCT AND PREDICTIVE VALIDITY, THERE'S STILL SOME WORK THAT HAS TO BE DONE TO ACTUALLY REALLY SHOW THAT. AND THAT'S SOMETHING THAT NEEDS TO BE DONE, BUT I'M OPTIMISTIC THAT THESE MODELS WILL BE USEFUL TO THAT AND MAYBE BE MORE TRANSLATABLE THAN SOME OF THE SINGLE BACKGROUND MOUSE WORK THAT'S BEEN DONE TO DATE.

AND ONE THING THAT'S NICE IS IT'S EASY TO

PUT MUTATIONS INTO MANY BACKGROUNDS AND STUDY THEM IN PARALLEL SO THAT YOU CAN ACTUALLY STUDY THE IMPACT OF THE MUTATION AND ITS FUNCTION IN THE DRUG ACROSS DIVERSE POPULATIONS IN A DISH WHICH IS MUCH MORE DIFFICULTY OTHERWISE. AND SO I DO THINK THAT THERE WILL BE A SHIFT TOWARDS DRUG DEVELOPMENT USING THESE METHODS, BUT STILL TOXICITY IS GOING TO HAVE TO BE IN LARGE ANIMALS BECAUSE MOST DRUGS FAIL BECAUSE OF TOXICITY.

DR. IAKOUCHEVA: I CAN SEE A BIG PROMISE OF STEM CELL-DERIVED MODELS OR ORGANOIDS OR WHATNOT FOR INITIAL DRUG SCREENING. FOR EXAMPLE, IF YOU ALREADY HAVE FROM THE RESEARCH AND SUSPECTED PATHWAY OR EVEN TAKE LIKE, AS DAN SAID, THE BROAD INSTITUTE, RIGHT, THE DRUG AND SCREEN THEM IN NPC MODELS OR ORGANOIDS FOR INITIAL SCREEN. BUT I THINK WE WOULD NOT BE ABLE TO GO FROM THE ORGANOIDS MODELS STRAIGHT INTO THE PATIENTS. THERE SHOULD BE EITHER NONHUMAN PRIMATE, SUCH AS MARMOSET, IS A REALLY NICE MODEL. MAYBE NOT EVEN MOUSE BECAUSE MOUSE IS TOO DIFFERENT FROM HUMAN. AND ALSO THE CHIMPANZEE IS MORE SIMILAR TO HUMANS.

BUT I THINK ORGANOIDS AND STEM CELL-DERIVED MODELS COULD BE A FIRST STEP. AND THEN ONCE THE DRUGS, THE MOST PROMISING TARGET, IS

IDENTIFIED, GO TO MARMOSET OR NONHUMAN OR HUMAN PRIMATES FOR, AGAIN, TOXICITY OR EFFECTIVENESS OR OTHER STUDIES.

DR. GESCHWIND: I GUESS I WOULD SAY I DO SEE A PARADIGM SHIFT IN THAT WE ARE NOT GOING TO BE RELYING AS MUCH ON ANIMAL MODELS FOR EFFECTIVENESS BECAUSE THEY HAVEN'T PROVEN TOO VALUABLE YET. SO MY PUSH WOULD BE, MY THINKING WOULD BE THAT FOR EFFECTIVENESS, I THINK EVENTUALLY WHEN THERE'S A LITTLE MORE DATA, I CAN SEE A TIME WHEN WE GO FROM DEVELOPING A DRUG SHOWING IMPACT IN MULTIPLE BACKGROUNDS IN A STEM CELL MODEL ACROSS HUMAN POPULATIONS AND MULTIPLE MODELS TO THEN JUST CHECKING FOR TOXICITY IN LARGE ANIMALS AND MOVING INTO A PHASE 1 TRIAL, MUCH FASTER, MUCH BETTER, AND OF COURSE, LESS RISK IF YOU'VE CHECKED IT IN LARGE ANIMALS TOO.

CHAIRMAN GOLDSTEIN: FRED.

DR. FISHER: CAN YOU HEAR ME?

MR. TOCHER: YES, WE CAN HEAR YOU, FRED.

DR. FISHER: GREAT. THANKS FOR THE PRESENTATIONS. AS A BOARD MEMBER AND PATIENT ADVOCATE, NOT A SCIENTIST, I'M ILL PREPARED TO ASK SCIENTIFIC QUESTIONS, BUT YOU'VE DONE A GREAT JOB HELPING US UNDERSTAND THE OPPORTUNITY FOR INVESTMENT

IN STEM CELL AND GENETIC RESEARCH IN A NUMBER OF NEUROPSYCHIATRIC AREAS. YOU AND THE COLLEAGUES THAT PRESENTED BEFORE YOU OVER THE LAST FEW MEETINGS ALSO DID A GREAT JOB OF DOING THAT.

SO THE OPPORTUNITY TO INVEST MORE IN NEUROPSYCHIATRIC RESEARCH WITH CIRM FUNDING SEEMS SELF-EVIDENT AT THIS POINT. I'M HOPING THE TWO OF YOU CAN LEND SOME INSIGHT INTO WHY NEUROPSYCH RESEARCH IS UNDERREPRESENTED IN THE APPLICATIONS THAT CIRM RECEIVES. WITHIN YOUR COMMUNITIES, IS CIRM NOT SEEN AS POTENTIAL FUNDER OF THE KIND OF WORK THAT YOU'VE BEEN DOING OR SEE NEEDS TO BE DOING? HELP US UNDERSTAND WHY IT IS THAT PERHAPS THOSE DOING GENETIC AND STEM CELL RESEARCH IN THE NEUROPSYCH AREA AREN'T SEEKING FUNDING FROM CIRM TO DO IT.

CHAIRMAN GOLDSTEIN: GREAT QUESTION.

DR. GESCHWIND: I MEAN I CAN SPEAK PERSONALLY. THE EFFORT REQUIREMENT IS TOO MUCH FOR THE AMOUNT GIVEN. SO WE DID HAVE A CIRM GRANT THAT WAS PART OF THE GENOMICS PIECE, AND IT WAS SEVERAL MILLION DOLLARS. IT WAS ENOUGH TO DO THAT HUGE STUDY WITH SERGIU THAT IS ABOUT TO BE SUBMITTED THAT'S AN INCREDIBLE COLLABORATION BETWEEN OUR GROUPS.

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BUT OTHER THAN THAT, I THINK THE FUNDING, IF I REMEMBER, LET'S JUST SAY ON THE ORDER OF 300 K A YEAR AND THEN IT REQUIRES AT LEAST 10-PERCENT EFFORT OR SOMETHING LIKE THAT. AND IN OUR GENOMICS LABS, THAT'S WAY TOO MUCH EFFORT FOR A GRANT THAT SMALL. YOU CAN'T DO ANYTHING WITH IT. SO THAT'S LIKE A 1-PERCENT EFFORT GRANT. BECAUSE WE HAVE LABS THAT ARE IDENTIFYING GENETIC VARIATION, WHICH IS ONE TYPE OF RESEARCH, AND THEN WE ARE TRANSLATING THAT GENETIC VARIATION INTO MODEL SYSTEMS. THAT'S ANOTHER TYPE OF RESEARCH. SO WE HAVE BIG LABS TO KIND OF CONNECT THOSE THINGS TOGETHER IN-HOUSE.

AND SO IT TAKES A LOT OF DIFFERENT FUNDING STREAMS TO DO THAT. SO AN AVERAGE NIH GRANT FOR SOMEBODY IS GOING TO BE MULTIPLES OF THAT AND YOU'RE GOING TO PUT IN A LOT LESS EFFORT. SO I THINK REDUCING THE EFFORT REQUIREMENT SUBSTANTIALLY OR BASICALLY LEAVING IT OFF, UNLESS THE GRANT IS HUGE. I CAN UNDERSTAND IF YOU HAVE 1 $2 MILLION A YEAR GRANT TO AN INDIVIDUAL LAB OR A SERIES OF TWO OR THREE LABS, THAT YOU'LL SAY, WELL, OKAY, EACH PI HAS TO PUT IN 10-PERCENT EFFORT. THAT MAKES SENSE, BUT OTHERWISE PI'S LIKE ME AND OTHERS IN MY FIELD CAN'T AFFORD TO GIVE UP THE EFFORT FOR SUCH A SMALL AMOUNT OF FUNDING FOR THAT GRANT.

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SO WE'VE SEEN THEM COME ALONG, AND I'VE SAID, OH, WE SHOULD APPLY FOR THAT. AND THEN WE -- BECAUSE IT'S RIGHT UP OUR ALLEY. AND WE HAVE HAD INTERNAL BROAD STEM CELL FUNDING FOR SOME OF THESE PILOT GRANTS TO ACTUALLY BUILD THERAPEUTICS IN THESE MODELS, AND THEN I CAN'T APPLY TO CIRM FUNDING FOR IT BECAUSE IT'S NOT -- BECAUSE THE MECHANISM DOESN'T FIT. SO I THINK IT HAS TO DO WITH MECHANISMS AND EFFORT. MAYBE LILIA.

DR. IAKOUCHEVA: FOR ME IT WAS A DIFFERENT REASON. ACTUALLY I APPLIED ONLY ONCE TO CIRM, AND I DID NOT GET FUNDED. AND IT WAS ABOUT RHOSIN, ABOUT RESCUING PHENOTYPES IN THE STEM CELLS AND SO FORTH. IT WAS A STUDY I PRESENTED. FOR ME IT'S A BUREAUCRATIC BURDEN, LIKE ASSEMBLING THIS APPLICATION WAS A HUGE DRAIN ON MY TIME. ACTUALLY THERE IS SO MUCH PAPERWORK THAT NEEDS TO BE, FORMS THAT NEEDS TO BE FILLED IN, IT'S JUST INSANE. IT WAS ABSOLUTELY INSANE FOR ME. THE AMOUNT OF EFFORT THAT I PUT INTO ASSEMBLING THE APPLICATION WAS ENORMOUS COMPARED TO NIH.

ACTUALLY ONE OF MY SUGGESTIONS, IF CIRM CAN ACTUALLY SIMPLIFY THE APPLICATION PROCESS AND MAKE IT MORE SIMILAR TO NATIONAL INSTITUTE OF HEALTH WHERE IT'S ONLY FIVE DOCUMENTS THAT I NEEDED, YOUR

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BIO, YOUR RESEARCH PLAN, THE DATA SHARING, THE REFERENCES, AND THE SUMMARY, IT WOULD BE SO MUCH BETTER BECAUSE THE AMOUNT OF BUREAUCRACY THAT'S NEEDED TO SUBMIT CIRM, I HAVE NOT APPLIED AFTER THAT.

ANOTHER THING, FRED, DO YOU THINK THAT YOU DON'T GET APPLICATIONS IN NEURO? OR YOU GET THEM, THEY'RE NOT FUNDED WITH THE HIGHER -- AS HIGH EFFICIENCY AS OTHER DISEASES? ONE OF THE REASONS COULD BE THAT YOU GUYS, FROM MY UNDERSTANDING, ARE LOOKING AT, LIKE, THE FINAL PRODUCT. AND NEUROSCIENCE, WE ARE NOT KIND OF THERE YET. I THINK WE ARE MORE STILL AT THE DISCOVERY AND MAKING MORE LIKE R & D, RESEARCH AND DEVELOPMENT, JUST LOOKING FOR TARGETS. MAYBE I'M WRONG, BUT TO ME IT SEEMS LIKE THAT WAS THE REASON THAT MY APPLICATION WASN'T FUNDED BECAUSE I WAS NOT PROPOSING TO PUT MY RHOSIN INTO THE PATIENTS. THAT BASICALLY WAS THE REASON. SO I DON'T KNOW.

CHAIRMAN GOLDSTEIN: INTERESTING. MARIA MILLAN. FRED, WERE YOU GOING TO FOLLOW UP?

DR. FISHER: YEAH. I WAS JUST GOING TO SAY THANK YOU FOR THAT INSIGHT BECAUSE THAT'S NOT SOMETHING THAT WE HAVE ADDRESSED. AND WHEN WE ARE LOOKING AT AREAS THAT ARE UNDERREPRESENTED IN OUR

NEURO FUNDING PORTFOLIO, IT'S INTERESTING THAT AWARENESS OF CIRM FUNDING, IF I UNDERSTOOD THE RESPONSE, AWARENESS OF CIRM FUNDING IS THERE, BUT THE BURDEN IMPOSED FOR THE DOLLARS RECEIVED, TO PUT IT VERY GENERALLY, IS OUT OF PROPORTION. AND IF WE WANT MORE APPLICATIONS IN UNDERREPRESENTED NEUROINDICATIONS, PERHAPS WE NEED TO BE LOOKING INWARD AT OUR OWN PROCESS. AND I'M GATHERING THAT THE PEOPLE WHO HAVE PRESENTED TO US, LIKE THE TWO DISTINGUISHED SCIENTISTS PRESENTED TODAY, COULD PROVIDE US FURTHER INSIGHT IN HOW WE COULD IMPROVE OUR INTERNAL PROCESS AND OUR EXPECTATIONS AND OUR OUTREACH PROCESS THAT WE MAY FIND THAT WE SOLVE THE, AT LEAST IN THE NEUROPSYCH SPACE, WE SOLVE SOME OF THE PROBLEM WE SEEM TO HAVE IDENTIFIED. THANK YOU.

CHAIRMAN GOLDSTEIN: GOOD POINTS. MARIA MILLAN.

DR. MILLAN: THANK YOU SO MUCH. AND THANK YOU, FRED, FOR ASKING THAT QUESTION. I JUST HAD A FOLLOW-UP TO THAT QUESTION, AND THEN ALSO I WANTED TO SPEAK TO THE ANIMAL -- TO THE ORGANOID MODELS AND WHERE THE FDA IS GOING WITH THAT.

LILIA, HAD YOU APPLIED TO CIRM SINCE THE 2016 REVAMP OF THE PROGRAM OPPORTUNITIES?

DR. IAKOUCHEVA: YEAH. I APPLIED AFTER

2016, YES. IT WAS A DISC, I DON'T REMEMBER, 1 OR 2, ONE OF THE DISC GRANTS. AND I APPLIED ONLY ONCE. THIS IS THE REASON. I DIDN'T EVEN RESUBMIT IT BECAUSE OF THE PAPERWORK BURDEN.

DR. MILLAN: ONE THING THAT CHANGED IS THAT, AND I'M SURE ROSA CAN SPEAK TO THIS, IS THAT WE JUST RELAUNCHED THE BASIC DISCOVERY AWARDS JUST IN THE PAST YEAR, WHICH IS VERY, VERY BASIC. THE OTHER -- THE DISC2 IS INTENDED TO COME UP WITH A CANDIDATE, A THERAPEUTIC CANDIDATE. SO YOU'RE ABSOLUTELY RIGHT, ESPECIALLY IN THE TAIL END OF CIRM UNDER PROPOSITION 71, WHAT HAPPENED WAS THAT WE HAD TO KIND OF REFINE OUR OFFERINGS. AND IT WAS MORE TOWARD KIND OF THE DISCOVERY PROGRAMS THAT LED TO A CANDIDATE. BUT NOW WE ALWAYS HAVE THE DISCOVERY0 AWARDS, WHICH ARE -- ROSA, YOU CORRECT ME -- $2 MILLION AWARDS; IS THAT CORRECT? OKAY. OR 1.8.

BUT ONE OF THE THINGS -- I'M GOING TO TURN IT OVER TO ROSA BECAUSE SHE KNOWS MORE ABOUT THAT. BUT ABOUT THE FDA, THAT WAS AN EXCELLENT QUESTION. AND I DO AGREE BECAUSE EVEN MOST RECENTLY IN JANUARY 2023 AN ARTICLE IN *SCIENCE* HAD COME OUT SPECIFICALLY WITH THE TITLE "FDA NO LONGER NEEDS TO REQUIRE ANIMAL TESTS BEFORE HUMAN DRUG TRIALS" WAS THE TITLE. AND THAT IS WHERE THE FDA IS GOING. AND THE

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COMMISSIONER, ROB CALIFF, JUST BROUGHT ON A NEW CHIEF SCIENTIST TO THE FDA, WHO I GOT TO MEET A COUPLE OF MONTHS AGO WHEN SHE PRESENTED ON THE ROLE OF HUMAN MODELS IN DRUG DEVELOPMENT, NAMANDJE BUMPUS, WHO COMES FROM HOPKINS, IS NOW THE NEW CHIEF SCIENTIST. AND SHE REALLY HIGHLIGHTED HOW MOST OF THE TIME ANIMAL MODELS JUST DO NOT EVEN REFLECT THE BIOLOGY AND ARE NOT PREDICTIVE AND HAVE NOT BEEN REALLY HELPFUL.

SO I THINK THE PRESENTATION THAT YOU GAVE IN TERMS OF THE RELEVANCE OF HUMAN INFORMATION IN TERMS OF BOTH DISCOVERY AND THEN LATER ON IS REALLY KEY. AND IT SEEMS THAT THE FDA IS TRENDING IN THAT DIRECTION. SO I THINK THERE ARE OPPORTUNITIES THERE. I WANTED TO JUST BRING THAT UP. THANK YOU SO MUCH.

CHAIRMAN GOLDSTEIN: THANK YOU, MARIA. ROSA.

DR. CANET-AVILES: THANK YOU, DR. GOLDSTEIN. JUST SPEAKING TO -- THIS IS A QUESTION THAT HAS COME UP COMING FROM DIFFERENT STAKEHOLDERS: WHY HAS CIRM NOT FUNDED NEUROPSYCHIATRIC? SO THE FUNDING MODEL UP UNTIL NOW WAS WE DIDN'T HAVE A SCOPE. THE SCOPE WAS THE WHOLE DISEASE PORTFOLIO BASICALLY.

NOW, WHEN I PRESENTED BACK IN JANUARY OR FEBRUARY IN THE TASK FORCE, I PROVIDED AN OVERVIEW OF WHAT ARE THE NEEDS, WHAT ARE THE NEEDS THAT WE HAD IDENTIFIED BASICALLY IF WE WERE GOING TO INVEST IN DISCOVERY TOWARDS CNS DISEASES. AND THE MAIN GAP IS OUR UNDERSTANDING OF THE MECHANISMS UNDERLYING NORMAL DISEASE PROCESSES IN THE BRAIN. AND WE HEARD IN OUR LAST TASK FORCE AND IT'S REITERATED, IT WAS REITERATED TODAY, AND THAT WAS THE WAY THAT WE WERE BUILDING OUR CONCEPT.

SO THE FOUNDATIONAL AWARDS THAT WE HAVE, THE FOUNDATIONAL AWARDS, THEY ARE ACTUALLY $1 MILLION, THEY ARE SMALLER AWARDS. AND IN ORDER TO ADVANCE INNOVATION AND UNDERSTANDING OF DISEASE MECHANISMS WHICH COULD BE PILOTED IF THIS BOARD GREASE WITH NEUROPSYCHIATRIC, NEURODEVELOPMENTAL TYPE OF DISORDERS, WE WOULD HAVE TO ENGAGE IN A NEW FORM OF -- A NEW TYPE OF PROGRAM AS OUR PRESENTERS ARE TELLING US TODAY. AND ONE OF THEM COULD BE CATALYZING MULTIDISCIPLINARY INNOVATION AND ATTRACT NEW TALENT AND IDEAS, ENGAGING WITH COLLABORATIVE SCIENCE.

SO I JUST WANTED TO MAKE THIS DIFFERENTIATION WHY WE HAVEN'T GOTTEN IT IS BECAUSE OUR FOCUS WAS NOT DISEASE MECHANISMS. OUR FOCUS WAS

ACTUALLY MECHANISMS OF PLURIPOTENCY IN STEM CELLS AND REGENERATIVE MEDICINE, WHICH IS VERY DIFFERENT.

MS. DEQUINA-VILLABLANCA: LARRY, THERE ARE NO MORE HANDS RAISED.

DR. LEVITT: I'LL RAISE MY HAND AGAIN. SO, DAN, ARE YOU STILL THERE?

DR. GESCHWIND: YES, BUT I WAS MUTED.

DR. LEVITT: PERFECT. SO YOU PRESENTED ELOQUENTLY ABOUT THE MULTIGENE COMPONENTS, THE COMBINATORIAL COMPONENTS THAT ACCOUNT FOR MOST OF THE DIAGNOSES. SO MAYBE YOU CAN SPEAK TO THAT IN TERMS OF THE MODEL SYSTEMS THAT YOU'RE TALKING ABOUT. HOW DO WE ACCOUNT FOR THAT? BECAUSE CURRENTLY A LOT OF WHAT'S OCCURRING, AT LEAST IN TERMS OF THE DISEASE MODELS AND DISORDER MODELS, HAS BEEN BEAUTIFUL WORK OF CHROMOSOMAL DISRUPTIONS OR SINGLE GENE MUTATIONS THAT WE KNOW ARE CAUSAL, ET CETERA. SO MAYBE YOU CAN SPEAK TO THIS ISSUE OF WHERE YOU THINK WE ARE GOING WITH TRYING TO UNDERSTAND AND MODEL THE COMBINATORIAL MULTIGENE COMPONENTS THAT ARE ACCOUNTING FOR MOST OF THESE DIAGNOSES.

DR. GESCHWIND: YEAH. IT'S REALLY A GREAT, GREAT QUESTION. I DON'T THINK ANYBODY HAS A CONCLUSIVE -- I CAN'T GIVE YOU A HUNDRED PERCENT

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ANSWER TO THAT, BUT I CAN TELL YOU THAT THIS IS ONE OF THE REASONS WHY A HUMAN MODEL IS SO ESSENTIAL TO ACTUALLY -- IF WE'RE GOING TO BE ABLE TO LOOK AT THAT. SO THERE WAS A RECENT PAPER IN *AMERICAN JOURNAL OF HUMAN GENETICS* WITH TONY WYNSHAW-BORIS' GROUP PUT A MUTATION ON DIFFERENT GENETIC BACKGROUND HIGH AND LOW RISK. AND WE'VE BEEN DOING THAT FOR A LITTLE WHILE JUST THE JURY ISN'T OUT YET. BUT YOU CAN GET LINES FROM PEOPLE WITH INCREDIBLY HIGH, IN THE TOP 1 OR 2 PERCENT OF POLYGENIC RISK FOR DISORDER.

AND IN CARDIAC DISEASES AND IN CANCER, SOMETIMES THAT'S BIGGER -- THE SAME SIZE AS ONE OF THESE MONOGENIC RISK FACTORS. SO THAT YOU CAN GET PATIENTS WITH INCREDIBLY HIGH RISK THAT PUTS THEM IN THE TOP 5 PERCENT OF RISK AND YOU CAN MAKE MODELS FROM THEM. AND ACTUALLY THE CIRM BANK CONTAINS THEM. AND WE HAVE TRIED TO MAKE MODELS OUT OF HIGH AUTISM RISK AND LOW AUTISM RISK. ACTUALLY ONE OF THE ISSUES, JUST FOR THE BOARD, JUST SO YOU KNOW, IS THAT THE QUALITY OF THOSE LINES WAS HIGHLY, HIGHLY VARIABLE SO THAT OUT OF THE TEN THAT WE USED, ONLY 30 OR 40 PERCENT REALLY WORKED GREAT. AND WE HAD A LOT OF DIFFICULTY WITH SOME OF THEM. PROBABLY A LITTLE MORE WORK THAT NEEDS TO BE DONE THERE TO

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DEVELOP LINES.

BUT I'D SAY YOU GET PATIENTS, SO PATIENTS HAVE BEEN GENOTYPED. AND THIS IS WE ARE WORKING WITH PEOPLE WHO HAVE THESE PSYCHIATRIC DISEASE COHORTS OR I WON'T CALL THEM DISEASES, BUT DISORDERS, CONDITIONS BECAUSE IT'S JUST PART OF THE HUMAN CONDITION. SO LIKE IF WE JUST TAKE THAT -- TAKE THOSE FOLKS WHO ARE AT VERY HIGH POLYGENIC RISK DUE TO THEIR GENOTYPE, AND WE HAVE ALL THAT INFORMATION, YOU MAKE LINES FROM THEM. THEN YOU CAN USE THOSE MODELS. AND THE EFFECT SIZE, THE IMPACT SHOULD BE SIMILAR TO SOMEBODY WITH A MONOGENIC BIG EFFECT SIZE MUTATION. SO THAT'S ALL DOABLE. AND YOU OBVIOUSLY CAN'T DO THAT IN MOUSE, ET CETERA. SO, YEAH. I HOPE THAT ANSWERS THAT, PAT.

DR. LEVITT: YEAH. THAT WAS GREAT. YEAH. THANK YOU.

CHAIRMAN GOLDSTEIN: SO WE ARE STARTING TO RUN A LITTLE SHORT ON TIME. SO, STEVE, WHY DON'T WE LET YOU DO THE LAST QUESTION, AND THEN WE'LL DO PUBLIC COMMENT AND I'LL LAY OUT A PROPOSED MAP FOR MOVING FORWARD.

MR. JUELSGAARD: THANK YOU, LARRY. THIS ISN'T REALLY A QUESTION, BUT AN OBSERVATION. SO IF YOU READ THE LANGUAGE OF PROPOSITION 14 IN THIS

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AREA, IT TALKS ABOUT THE FACT THAT THE INSTITUTE SHALL ALLOCATE AT LEAST $1.5 BILLION OF PROCEEDS FOR BASICALLY DISEASES AND CONDITIONS OF THE BRAIN AND CENTRAL NERVOUS SYSTEM. NOWHERE ELSE IN EITHER PROPOSITION 71 OR PROPOSITION 14 WAS SUCH LANGUAGE AROUND AN AREA OF THE HUMAN EXISTENCE CREATED. SO THIS FOR ME IS A SPECIAL CASE. AND THE FACT IT WAS POINTED OUT SO UNIQUELY IN PROPOSITION 14 SUGGESTS THAT THIS MAY WELL BE AN AREA THAT WE CAN TREAT DIFFERENTLY THAN HOW WE HAVE BEEN TREATING OTHER THERAPEUTIC AREAS OR OTHER CONDITIONS IN THIS ORGANIZATION.

I'M SPEAKING NOW SPECIFICALLY ABOUT FUNDING WHICH WE JUST HEARD SOME OF THE ISSUES ASSOCIATED WITH. REMEMBER THAT THESE FUNDING LIMITATIONS WERE CREATED QUITE SOME TIME AGO, WELL BEFORE THIS PARTICULAR PROPOSITION CREATED THE $1.5 BILLION FUNDING. SO ONE OF THE THINGS WE OUGHT TO THINK ABOUT IS WHETHER WE WANT TO CREATE FOR THIS AREA, IN ESSENCE, DIFFERENT LEVELS OF FUNDING ASSOCIATED WITH THE DIFFERENT KINDS OF RESEARCH THAT MIGHT BE NECESSARY TO REALLY BETTER UNDERSTAND THIS AREA. WE ARE REALLY AT THE VERY FRONT END OF UNDERSTANDING THIS AREA. SO IT'S GOING TO BE A LOT OF WHAT WE'VE CALLED DISCOVERY RESEARCH, ESSENTIALLY

THESE SMALLER GRANTS OF EITHER, RIGHT NOW, ONE MILLION OR ONE AND A HALF MILLION.

I WOULD THINK THAT ONE OF THE THINGS WE MIGHT THINK ABOUT AND PRESENT TO THE ICOC IS THAT WE REVISIT FOR THIS AREA AND THIS AREA ONLY EXPANDING THOSE GRANTS SO THAT THEY'RE SUFFICIENTLY LARGE TO REALLY DEAL WITH SOME OF THE ISSUES THAT HAVE BEEN RAISED BY THE TWO PRESENTERS TODAY. THANK YOU FOR THE TIME.

CHAIRMAN GOLDSTEIN: IT'S A GREAT POINT, STEVE. BECAUSE THE TECHNOLOGY THAT'S IN USE TO MAKE THE KIND OF PROGRESS THAT DAN AND LILIA TALKED ABOUT, IT'S AMAZING TECHNOLOGY. AND IT IS NOT CHEAP. SO THIS MAY BE AN OPPORTUNE TIME TO TACKLE THAT EXACT ISSUE.

DR. IAKOUCHEVA: YEAH. I TOTALLY SUPPORT THAT. I DON'T KNOW, GUYS, IF YOU KNOW, BUT ORGANOID RESEARCH IS MUCH MORE EXPENSIVE THAN MOUSE RESEARCH. LIKE, FOR US TO MAKE THE MOUSE, IT'S REALLY CHEAP. IT'S LIKE 3K TO MAKE A MOUSE. AND TO PRODUCE ORGANOIDS AT DIFFERENT TIME POINTS IN DEVELOPMENT, ESPECIALLY SINGLE CELL SEQUENCING TECHNOLOGIES THAT ARE VERY MUCH NEEDED, IF YOU HAVE ORGANOID, YOU WANT TO DO SINGLE CELL SEQUENCING. IT'S 3K PER SAMPLE. SO TO MAKE A MOUSE IS 3K. AND THEN MOUSE JUST

REPRODUCES AND COSTS NOTHING TO MAINTAIN. WHEREAS, TO SEQUENCE ONE ORGANOID SAMPLE, SINGLE CELL, IS 3K. AND TO BE STATISTICALLY ROBUST, WE NEED HUNDREDS OF THOSE SAMPLES.

SO RAISING THE CEILING FOR THE FUNDING FOR STEM CELL RESEARCH, AT LEAST FOR THE NEURO, I DON'T KNOW ABOUT OTHER ORGANS, I THINK IS VERY IMPORTANT.

CHAIRMAN GOLDSTEIN: THANK YOU. MARIA MILLAN.

DR. MILLAN: I DON'T WANT -- THAT WAS A REALLY GREAT -- GIVING US SOME QUANTITATIVE MEASURES THERE IS REALLY IMPORTANT. AND I THINK I JUST WANT TO HIGHLIGHT WHAT ROSA HAD SAID, WHICH IS THE VALUE OF -- IF YOU WERE TO DO THAT FOR EVERY SINGLE RESEARCHER, HOW MUCH WOULD THAT COST, BUT IT'S THE VALUE OF KIND OF THAT NETWORKED APPROACH. AND SOME OF THE ABILITY TO LEVERAGE THE MODEL DEVELOPMENT I THINK IS A REALLY KEY THING FOR THIS TASK FORCE TO CONSIDER IN TERMS OF A VALUE OF A CONSORTIUM APPROACH TO THIS BECAUSE IT DOES BRING VALUE TO THE INVESTMENT IN CREATING THESE ORGANOID MODELS AND ALSO LEVERAGES SOME OF THE OTHER CIRM PROGRAMS, INCLUDING THE SHARED RESOURCES LABS THAT WILL DEVELOP CELL AND ORGANOID MODELS. I JUST WANTED TO MAKE THAT LINKAGE. THANK YOU.

CHAIRMAN GOLDSTEIN: THANK YOU, MARIA.

SO WE ARE RUNNING QUITE SHORT ON TIME. I'D LIKE TO SUGGEST THAT WHAT WE DO AT OUR NEXT MEETING IN JUNE IS TO CONTINUE A DISCUSSION THAT ROSA INITIATED ABOUT WHAT AN INTERDISCIPLINARY GRANTS PROGRAM MIGHT LOOK LIKE OR WHAT A CONCEPT PLAN FOR SUCH PROGRAMS MIGHT LOOK LIKE. AND I THINK TODAY'S DISCUSSION WILL HAVE A BIG IMPACT ON WHAT ROSA BRINGS TO US. SO THAT WOULD BE ONE TOPIC WE WOULD TAKE ON AT THE NEXT MEETING.

AND THEN THE OTHER IS TO DO ANOTHER LOOK AT OUR PORTFOLIOS TO ASK THE QUESTION: IS THERE ANYTHING ELSE THAT WE ARE MISSING IN OUR CURRENT NEURO PORTFOLIO? AND PERHAPS THEN A RELATED QUESTION: HAVE WE ADEQUATELY ADDRESSED NEURO PROBLEMS THAT ARE IN UNDERSERVED COMMUNITIES WHERE WE MIGHT MAKE A SIGNIFICANT IMPACT? AND THAT CAN BE IN PART A BEGINNING OF FURTHER PLANNING FOR WHAT WE MIGHT DO WITH THIS UNIQUE OPPORTUNITY IN NEURO. SO ANY OBJECTIONS TO PROCEEDING IN THAT WAY?

DR. SOUTHARD: WELL, I COMPLETELY SUPPORT IT, PARTICULARLY IF WE TAKE A CAREFUL LOOK AT THE ADDICTION ISSUES THAT I RAISED EARLIER BECAUSE THEY AFFECT BOTH OF THE AREAS THAT YOU JUST MENTIONED.

CHAIRMAN GOLDSTEIN: ABSOLUTELY.

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LILIA, YOU HAVE YOUR HAND UP.

DR. IAKOUCHEVA: I DON'T HAVE AN OBJECTION. BUT CAN I MAKE ANOTHER SUGGESTION? SO CIRM IS SUPPOSED TO BE A RESOURCE, RIGHT, FOR THE INDUCED PLURIPOTENT STEM CELLS. SO FOR MY RESEARCH IN AUTISM, LIKE, I WENT TO CIRM, I WANTED TO FIND MORE PATIENTS WITH THIS COPY NUMBER VARIANT OR CULLIN3 MUTATIONS THAT I WAS STUDYING. AND I SAW THAT THERE ARE A LOT OF IPC'S. I WAS ACTUALLY STUNNED. IT WAS LIKE 150, 200 IPC OF AUTISM. BUT THE PROBLEM IS THAT THERE WERE NO GENETICS ASSOCIATED WITH IT. SO I COULDN'T USE THIS RESOURCE.

I REACHED OUT TO CHRIS AND TO PEOPLE WHO DEPOSITED THOSE RESOURCES AND SAID, OH, GENETIC IS SOMEWHERE THERE. BUT THE RESOURCE WAS LITERALLY UNUSABLE BECAUSE IT DIDN'T HAVE -- AND IT WAS GENOTYPED. ALL THE SAMPLES WERE ACTUALLY GENOTYPED, BUT IT'S JUST IMPOSSIBLE TO FIND THE GENETICS.

SO THAT'S ANOTHER THING. WHEN YOU GUYS ARE CREATING THOSE RESOURCES, I THINK YOU SHOULD REQUIRE THE GENOTYPES TO BE ABLE TO SHARE WITH RESEARCHERS BECAUSE THIS IS VERY, VERY IMPORTANT. I CAN'T OVEREMPHASIZE THIS.

CHAIRMAN GOLDSTEIN: IT'S A GREAT POINT.

I'M GUESSING THAT THERE'S PARTLY A CONSENT ISSUE FLOATING AROUND IN THERE.

OKAY. IS THIS THE TIME FOR PUBLIC COMMENT, MARIA?

MS. DEQUINA-VILLABLANCA: YES.

CHAIRMAN GOLDSTEIN: OKAY. PUBLIC COMMENT.

MS. DEQUINA-VILLABLANCA: I DON'T SEE ANY AT THE MOMENT, LARRY.

CHAIRMAN GOLDSTEIN: OKAY. SO UNLESS THERE'S AN OBJECTION, WE HAVE A PLAN FOR MOVING FORWARD. AND WE WILL ADJOURN ONE AND A QUARTER MINUTES EARLY. SO USE THE TIME WISELY.

(THE MEETING WAS THEN CONCLUDED AT 2:58 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 MAY 15, 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, CA CSR 7152
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