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

REGULAR MEETING

LOCATION: VIA ZOOM

DATE: APRIL 17, 2024
12 P.M.

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

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APRIL 17, 2024; 12 P.M.

CHAIRMAN GOLDSTEIN: WE HAVE A VERY PACKED AGENDA AND SO WELCOME, EVERYBODY, TO TODAY'S MEETING. I THINK CLAUDETTE IS GOING TO CALL THE ROLL AS THE NEXT ACTION.

MS. MANDAC: LEONDRA CLARK-HARVEY. MARIA BONNEVILLE.

VICE CHAIR BONNEVILLE: PRESENT.

MS. MANDAC: MARK FISCHER-COLBRIE.

MR. FISCHER-COLBRIE: HERE.

MS. MANDAC: FRED FISHER. JUDY GASSON.

DR. GASSON: HERE.

MS. MANDAC: LARRY GOLDSTEIN.

CHAIRMAN GOLDSTEIN: HERE.

MS. MANDAC: DAVID HIGGINS.

DR. HIGGINS: PRESENT.

MS. MANDAC: VITO IMBASCIANI.

CHAIRMAN IMBASCIANI: HERE.

MS. MANDAC: STEVE JUELSGAARD. PAT LEVITT.

DR. LEVITT: PRESENT.

MS. MANDAC: LAUREN MILLER-ROGEN. MARV SOUTHARD.

DR. SOUTHARD: PRESENT.

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MS. MORALEZ: LAUREN AND FRED FISHER ARE ON.

MS. MANDAC: LAUREN MILLER-ROGEN.

CHAIRMAN GOLDSTEIN: I SEE HER.

MS. MANDAC: FRED. FRED FISHER.

CO-CHAIR FISHER: I'M HERE.

MS. MANDAC: AND THEN ONE LAST CALL FOR LAUREN, BUT WE DO SEE YOU.

WE DO HAVE QUORUM, LARRY, SO WE CAN MOVE FORWARD.

CHAIRMAN GOLDSTEIN: GREAT. WHOSE HAND IS UP?

MS. MANDAC: THERE IS A HAND UP FOR 760. WE ARE NOT YET READY FOR PUBLIC COMMENT. SO WE WILL NOTIFY YOU WHEN WE ARE READY.

CHAIRMAN GOLDSTEIN: GOOD. ALL RIGHT. SO WE HAVE A VERY BUSY AGENDA TODAY. WE HAVE TWO TERRIFIC EXPERTS, JIM GUSELLA AND ALISON GOATE TALKING ABOUT HUNTINGTON'S DISEASE AND ALZHEIMER'S DISEASE RESPECTIVELY. AND AT THE VERY BEGINNING 15 MINUTES, ROSA WILL GIVE US A QUICK OVERVIEW OF WHERE WE HAVE BEEN AS A TASK FORCE. AND THEN AT THE END FOR ANOTHER 15 MINUTES, SHE WILL GIVE US SOME THOUGHTS ON HOW WE'RE GOING TO INTERFACE WITH THE PRIORITIZATION EFFORT THAT IS ONGOING AT CIRM. SO

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LET ME TURN IT OVER TO ROSA.

DR. CANET-AVILES: THANK YOU, DR. GOLDSTEIN. CAN YOU ALL HEAR ME?

CO-CHAIR FISHER: YES.

DR. CANET-AVILES: FANTASTIC. SO AS DR. GOLDSTEIN MENTIONED, IN THE UPCOMING 15 MINUTES, I'LL TRY TO BE BRIEF AS WE HAVE VERY EXCITING PRESENTATIONS, I'LL BE SUMMARIZING THE EFFORTS UNDERTAKEN BY THE NEURO TASK FORCE TO DATE, AND THIS WILL HELP ENSURE ALIGNMENT WITH ALL ACTIVITIES, AND SET THE STAGE FOR TODAY'S PRESENTERS. NEXT SLIDE.

SO THE FIRST PART OF THE PRESENTATION IS ABOUT THE BACKGROUND AND THE PROGRESS THAT WE'VE MADE WITHIN THE NEURO TASK FORCE. NEXT SLIDE.

THIS SLIDE SHOWS THE STEPS THAT LED TO THE CREATION OF THE NEURO TASK FORCE BACK IN JANUARY OF 2023. AND SINCE THEN, THE TASK FORCE WAS HARD AT WORK LEADING TO THE DEVELOPMENT OF THE CONCEPT FOR THE REMIND INITIATIVE. NEXT SLIDE.

THE REMIND INITIATIVE -- SORRY. THE MAIN OUTCOMES TO DATE WERE AFTER THE REVIEW OF OUR GRANT PORTFOLIO, WE HAVE CONFIRMATION OF COMPLIANCE WITH THE PROPOSITION 14 ALLOCATION MANDATE, BUT WE ALSO REALIZED THAT WE HAD UNDERREPRESENTATION OF NEUROPSYCHIATRIC DISEASE RESEARCH. AND THE

SCIENTIFIC SESSIONS THAT WE HAD OVER THE PAST YEAR LED BY SEVERAL SCIENTISTS UNDERSCORED THE ADVANTAGES OF UTILIZING GENETIC AND STEM CELL TECHNOLOGIES TO STUDY THOSE DISORDERS. THIS LED TO THE CURRENT CONCEPT PLAN TO SUPPORT RESEARCH USING MULTIDISCIPLINARY INNOVATIVE APPROACHES IN NEURO DISEASES, THE REMIND PROGRAM INITIATIVE THAT WAS DEVELOPED AND APPROVED.

NEXT SLIDE. AFTER THE REMIND CONCEPT WAS APPROVED, THE IMPLEMENTATION OF THE PROGRAM GOT STARTED WITH THE FIRST RFA REMIND-L FOR LARGE COLLABORATIVE PROJECTS LAUNCHED AT THE END OF 2023. AND WE ARE EXCITED TO LET YOU ALL KNOW THAT WE HAVE NOW RECEIVED APPLICATIONS FOR THAT PROGRAM WHICH WILL BE SOON UNDER REVIEW.

THE NEURO TASK FORCE CONTINUED ITS WORK; AND IN JANUARY OF THIS YEAR, WE HAD THE FIRST MEETING OF A NEW SERIES -- NEXT SLIDE -- DURING WHICH THE NEURO TASK FORCE OUTLINED A COMPREHENSIVE PLAN FOR THE NEXT FEW MONTHS. THIS PLAN FOCUSED ON ADVANCING RESEARCH IN THE AREA OF NEURODEGENERATION AND INCLUDES ENGAGING WITH A VARIETY OF EXPERTS, SUCH THE ONES THAT WE HAVE THE HONOR TO HAVE TODAY IN THIS MEETING TO GAIN INSIGHTS INTO CUTTING-EDGE PROJECTS AND AREAS THAT ARE EITHER INNOVATIVE OR

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UNDERRESEARCHED AND ARE RIPE FOR EXPLORATION.

THE TASK FORCE, ANOTHER ONE OF THE DISCUSSION OUTCOMES OF THE JANUARY NEURO TASK FORCE WAS THAT THE TASK FORCE THROUGH THESE EXPERT EDUCATIONAL SESSION COULD LEVERAGE THE INSIGHTS TO IDENTIFY AND PRIORITIZE RESEARCH IN AREAS THAT HOLD THE MOST PROMISE FOR GROUNDBREAKING DISCOVERIES.

THIS PROCESS INCLUDES ASSESSING WHERE CIRM'S FUNDING COULD HAVE THE MOST SIGNIFICANT IMPACT, ESPECIALLY IN AREAS THAT ARE NOT ALREADY HEAVILY FUNDED BY OTHER FUNDERS OR SOURCES. WE ALSO DISCUSSED THE FUNDING MECHANISM AND STRUCTURE. A KEY COMPONENT OF THE PLAN COULD BE THROUGH THE PROPOSED FUNDING MECHANISM MODELED AFTER THE REMIND PROGRAM STRUCTURE. THAT COULD BE PART OF IT BECAUSE IT LEADS TO CROSS-DISCIPLINARY WORK AND CATALYZING COLLABORATION.

AND IN TERMS OF BUDGET AND FUNDING ALLOCATION, THE TASK FORCE DISCUSSED THAT WE NEED TO ENSURE THAT THERE IS A BALANCED INVESTMENT ACROSS VARIOUS ASPECTS OF NEURO RESEARCH.

WITH THAT IN MIND, IN ORDER TO -- NEXT SLIDE -- IN ORDER TO ACHIEVE THE GOAL SET IN JANUARY, THE TASK FORCE DEVELOPED A DESIGN BRIEF WITH INTENT TO IDENTIFY THOSE BOTTLENECKS AND

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KNOWLEDGE GAPS, TO FIGURE OUT HOW INSIGHTS FROM STEM CELL AND GENETIC RESEARCH COULD BENEFIT THE DISCOVERY IN NEURODEGENERATIVE DISEASES THAT COULD BE APPLIED. SO HOW THE DISCOVERIES IN ONE DISEASE CAN BE APPLIED TO OTHERS, CROSS-DISEASE ANALYSIS. WE ALSO -- ANOTHER OF THE INTENTS IS TO DISCUSS HOW INSIGHTS AND INNOVATIVE TOOLS AND TECHNOLOGIES CAN BE APPLIED ACROSS THOSE DISEASE. AND TO DISCUSS A POTENTIAL ROLE FOR CIRM IN ADDRESSING THE ABOVE POINTS.

FOR THAT WE DEVELOPED THIS TABLE. AND THE GOAL WAS THAT WE COULD COMPLETE THIS TABLE FOR EACH ONE OF THE TALKS. SO WE CAN HAVE A REFERENCE WHEN WE HAVE THE DISCUSSIONS AT THE END. NEXT SLIDE.

SOME OF THE GUIDING QUESTIONS FOR THE TALKS WERE HERE, AND THAT'S BEEN COVERED THROUGHOUT THE DIFFERENT TALKS THAT WE'VE HAD.

SO THE FIRST TALKS THAT WE HAD -- NEXT SLIDE -- WE HAD MUST HONOR TO HAVE DR. LORENZ STUDER WHO'S THE DIRECTOR OF THE CENTER FOR STEM CELL BIOLOGY AT SLOAN KETTERING FOR CANCER RESEARCH IN NEW YORK. AND HE GAVE US A GOOD OVERVIEW OF SOME OF THE CHALLENGES IN PARKINSON'S DISEASE. AND DR. JEFF ROTHSTEIN, WHO'S PROFESSOR OF NEUROLOGY AND NEUROSCIENCE, DIRECTOR OF BRAIN SCIENCE INSTITUTE AT

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JOHN HOPKINS SCHOOL OF MEDICINE. HE PROVIDED HIS PERSPECTIVE ON ALS. SO WE COMPLETED THESE -- WE TOOK THE TALKS AND WE COMPLETED THIS OVERVIEW. NEXT SLIDE.

SO FOR PARKINSON'S DISEASE, WE HEARD A LOT OF THINGS, BUT THREE OF THE MAIN KNOWLEDGE GAPS THAT WE THOUGHT SHOULD BE PRIORITIZED FROM WHAT DR. STUDER WAS TALKING WAS THE NON-DOPAMINERGIC FEATURES AND THEIR TREATMENT, THERE'S A NEED FOR EXPLORATION OF POTENTIAL TREATMENTS FOR NON-DOPAMINERGIC FEATURES IN PARKINSON'S DISEASE, INCLUDING SLEEP DISORDERS, LOSS OF SMELL, GASTROINTESTINAL DISORDERS, AND COGNITIVE DECLINE. AND THE FIELD IS STILL UNCERTAIN ABOUT THE BEST APPROACHES TO THESE SYMPTOMS. AND TO ADDRESS THESE, ONE OF THE POSSIBILITIES FOR CIRM COULD BE TO FOCUS AROUND PROGRAMS USING INTERDISCIPLINARY RESEARCH THAT FOCUSES AROUND THE UNDERLYING MECHANISMS OF THE SYMPTOMS AND DEVELOP COGNITIVE THERAPIES THAT GO BEYOND DOPAMINE NEUROREPLACEMENT. AND THIS IS SOMETHING THAT COULD BE COVERED THAT THE STRUCTURE THAT WE HAVE UNDER REMIND DISC4 INITIATIVE, FOR EXAMPLE. JUST AS AN EXAMPLE.

THE SECOND BOTTLENECK THAT WE HEARD WAS ABOUT BIOMARKER, NOT ONLY ABOUT JUSTIFICATION, BUT

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ONE OF THE MAIN ONES THAT HE SPOKE ABOUT WAS PATIENT STRATIFICATION AND PERSONALIZED THERAPY. HE HIGHLIGHTED IMPORTANCE OF THESE TYPE OF BIOMARKERS WHERE BETTER UNDERSTANDING OF THE DISEASE PROGRESSION IN DIFFERENT INDIVIDUALS CAN LEAD TO MORE PERSONALIZED AND EFFECTIVE TREATMENTS. AND THIS CAN INVOLVE UTILIZING BIOMARKERS FOR BETTER SELECTION OF PATIENTS FOR SPECIFIC THERAPIES.

SO CIRM COULD SUPPORT THE INTEGRATION OF THE DATA AND ARTIFICIAL INTELLIGENCE IN CLINICAL RESEARCH TO BETTER CATEGORIZE PATIENTS BASED ON THEIR SUSCEPTIBILITY, DISEASE PROGRESSION, AND RESPONSE TO TREATMENTS. AND THIS COULD LEAD TO THE DEVELOPMENT OF NEW BIOMARKERS. ALSO I JUST WANT TO HIGHLIGHT WE JUST HAD A WEBINAR FOR THE DISC2 PROGRAM THAT HAS A NEW TRACK OF NOT ONLY WE HAVE NOW DEVELOPMENT OF THERAPEUTIC CANDIDATES, BUT ALSO A BIOMARKER PATH. SO THAT COULD BE ALSO SOMETHING THAT WE COULD ENTERTAIN WITHIN THAT PROGRAM OR THROUGH A DISC4 TYPE OF PROGRAM STRUCTURE.

AND LASTLY, ANOTHER KEY KNOWLEDGE GAP THAT DR. STUDER RAISED IS WITHIN THE CONTEXT OF GRAFTED CELL DELIVERY AND SURVIVAL. CRITICAL TO THE SUCCESS OF CELL REPLACEMENT THERAPIES IS THE INTEGRATION AND SURVIVAL OF THE CELLS POST-TRANSPLANTATION. AND

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THIS CAN BE TACKLED THROUGH A TRANSLATIONAL BOTTLENECK, EARLY CLINICAL PROGRAM FOCUSED, BUT MOSTLY TRANSLATIONAL. SO THOSE WERE THE BOTTLENECKS THAT WE HEARD ABOUT. NEXT SLIDE.

I'M GOING VERY FAST BECAUSE I WANT TO MAKE SURE THAT WE HAVE TIME TO HEAR ABOUT OUR SPEAKERS TODAY. THE NEXT SLIDE, SARA.

SO DR. ROTHSTEIN PROVIDED THREE -- HE GAVE A VERY THOROUGH OVERVIEW OF THE CHALLENGES IN ALS AND THE POTENTIAL PATHS MOVING FORWARD -- WE WERE JUST ADDING SOME VIDEO IN THE ROOM FOR THE PUBLIC THAT'S ATTENDING AT THE CIRM HEADQUARTERS.

SO THE THREE PRIORITIZED KEY KNOWLEDGE GAPS FOR ALS WERE THAT SPORADIC ALS AND PATHWAY ANALYSIS. THE MAJORITY OF ALS CASES ARE SPORADIC WITH NO CLEAR GENETIC CAUSE. AND CIRM COULD SUPPORT STUDIES UTILIZING IPS LINES FROM LARGE COHORTS OF ALS PATIENTS TO DISCOVER NEW PATHWAYS INVOLVED IN THE DISEASE, WHICH COULD LEAD TO NOVEL THERAPEUTIC APPROACHES. AND THIS CAN BE DONE NOT ONLY WITH ALS. WE CAN DO IT WITH OTHER DISEASES. AND IT CAN BE DONE WITHIN THE CONTEXT OF EITHER THE DISCOVERY -- ANY OF THE DISCOVERY PROGRAMS THAT WE HAVE, BUT ESPECIALLY PROBABLY DISC4, THE REMIND PROGRAM.

THE SECOND BOTTLENECK IS THE VARIABILITY IN ALS PROGRESSION. ALS PROGRESSION IS HIGHLY VARIABLE WITH FEW PATIENTS SURVIVING 30 YEARS WITH THE DISEASE. SO WE NEED TO FUND RESEARCH INTO GENETIC, MOLECULAR, OR ENVIRONMENTAL FACTORS CONTRIBUTING TO THE VARIABILITY POTENTIALLY THROUGH A COMPREHENSIVE PATIENT-DERIVED IPS LIBRARY OR BIOMARKER DEVELOPMENT.

AND LASTLY, WE NEED TO THINK BEYOND MOTOR NEURONS. THERE ARE OTHER CELL TYPES, SUCH AS GLIAL CELLS, THAT ALSO DEGENERATE AND CONTRIBUTE TO THE DISEASE CLINICAL SYNDROME. SO WE NEED TO BROADEN THE FOCUS OF ALS TO THESE OTHER CELL TYPES, WHICH COULD LEAD TO A MORE COMPREHENSIVE UNDERSTANDING OF THE DISEASE AND POTENTIAL NEW THERAPEUTIC TARGETS. NEXT SLIDE.

SO WE HAVE THE HONOR TODAY OF -- I HOPE THAT ALISON, DR. GOATE AND DR. GUSELLA LIKE THE PICTURES. I JUST FOUND THOSE. I THOUGHT THEY WERE THE NICEST. THE DANGERS OF THE ONLINE SEARCH IS RIGHT.

BUT THEY ARE OUR EXPERTS IN EDUCATIONAL SESSIONS IN AD AND HD. AND I FEEL HONORED TO INTRODUCE DR. ALISON GOATE WHO OVER THE LAST THREE DECADES HAS BEEN PART OF MANY GENE FINDING THEMES

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THAT HAS SUCCESSFULLY IDENTIFIED DISEASE-CAUSING VARIANTS FOR BOTH ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA.

WHILE WORKING AT THE IMPERIAL COLLEGE LONDON, AND SHE PROBABLY DOESN'T KNOW, BUT I WAS ALSO WITH JOHN HARVEY WHEN HE WAS IN JACKSONVILLE. SO SHE WAS WITH DR. HARVEY, AND SHE REPORTED THE FIRST MUTATION TO CAUSE FAMILIAL ALZHEIMER'S DISEASE, AND HER EARLY STUDIES AT WASHINGTON UNIVERSITY IN ST. LOUIS ALSO IDENTIFIED A MUTATION IN COLOMBIAN FAMILIES THAT ARE NOW PART OF THE ALZHEIMER'S DISEASE PREVENTION INITIATIVE LIKE CLINICAL TRIAL. HER LAB WAS ALSO PART OF THE TEAM THAT FIRST REPORTED MUTATIONS IN FRONTOTEMPORAL DEMENTIA.

SO DR. GOATE IS ALSO A LEADER IN THE STUDY OF LATE ONSET AD GENETICS, USING GENOMIC APPROACHES TO IDENTIFYING ALL GENETIC RISK FACTORS. AND HER WORK LED TO THE IDENTIFICATION OF TREM2, WHICH IS A TARGET THAT MANY ARE PURSUING RIGHT NOW, AS A RISK FACTOR FOR AD AND HAS HIGHLIGHTED THE ENRICHMENT OF AD RISK VARIANTS IN MICROGLIAL ENHANCERS, REGULATORY ELEMENTS IN DNA THAT COULD HELP WITH EXPRESSION IN IMMUNE CELLS OF THE BRAIN.

DR. GOATE IS NOW BUILDING OPEN DISEASE

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SITES USING GENOME EDITING IN IPS CELLS TO UNDERSTAND THE MOLECULAR MECHANISMS OF DISEASE AND TO DEVELOP NOVEL THERAPEUTICS. THANK YOU, DR. GOATE.

AND I'M GOING TO INTRODUCE -- LARRY, WOULD YOU LIKE ME TO INTRODUCE DR. GUSELLA NOW, OR WE DO IT AFTERWARDS WHEN HE'S ABOUT TO TALK?

CHAIRMAN GOLDSTEIN: GO AHEAD. YOU'RE ON A WILL ROLL, ROSA.

DR. CANET-AVILES: OKAY. AND I'M WITHIN THE 15 MINUTES THAT YOU GAVE ME. OKAY.

SO DR. GUSELLA IS THE BULLARD -- AND I HOPE I'M MAKING THE RIGHT PRONUNCIATION. SEE, I ALWAYS HAVE AN EXCUSE WITH MY CATALAN ACCENT. BUT DR. GUSELLA IS THE BULLARD PROFESSOR OF NEUROGENETICS IN THE DEPARTMENT OF GENETICS AT HARVARD MEDICAL SCHOOL. AND HIS LABORATORY, AMONGST MANY THINGS, IS CURRENTLY PURSUING COLLABORATIVE STUDIES OF ALL STAGES OF THE GENETIC RESEARCH CYCLE AIMED AT DISCOVERING GENES THAT CAUSE OR PREDISPOSE TO A MODIFYING NEUROLOGICAL AND BEHAVORIAL DISORDERS, ALSO CAUSE OF NORMAL DEVELOPMENT IN SUBJECTS WITH CHROMOSOMAL ABERRATIONS AND DEVELOPMENTAL PHENOTYPES, DELINEATING MECHANISMS OF PATHOGENESIS AND MODIFIERS IN HUNTINGTON'S DISEASE,

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THE NEUROFIBROMATOSIS AND AUTISM AND EXPLORING THE POTENTIAL FOR MECHANISM-BASED TREATMENTS.

SO THANK YOU. WELCOME. AND WE ARE HONORED TO HAVE YOU HERE. LARRY, BACK TO YOU.

CHAIRMAN GOLDSTEIN: THANK YOU. SO I'M NOT GOING TO TAKE ANY MORE TIME HERE. ALISON, ARE YOU READY TO GO? ALISON.

MS. MANDAC: YOU'RE JUST MUTED, DR. GOATE. LET ME TRY TO UNMUTE.

DR. GOATE: YEAH. THERE WE GO. SORRY ABOUT THAT.

CHAIRMAN GOLDSTEIN: GREAT. GO AHEAD PLEASE. THANK YOU.

DR. GOATE: LET ME GO AHEAD AND SHARE MY SCREEN. SO HOPEFULLY YOU CAN SEE MY SLIDES.

CHAIRMAN GOLDSTEIN: PERFECT.

DR. GOATE: OKAY. SO I WILL, FIRST OF ALL, JUST PRESENT SOME BACKGROUND FOR YOU ABOUT ALZHEIMER'S DISEASE AND GENETICS AND WHAT WE'VE LEARNED SO FAR, AND THEN GO ON AND TALK ABOUT SOME OF THE KEY KNOWLEDGE GAPS. OKAY.

SO I THINK, FIRST OF ALL, THE MOST IMPORTANT THING TO POINT OUT IS THAT AD IS A HUGE UNMET MEDICAL NEED IN THAT WE REALLY DON'T HAVE A TREATMENT FOR THE DISEASE CURRENTLY, AND IT'S THE

ONLY TOP TEN CAUSE OF DEATH IN THE U.S. THAT CAN'T BE PREVENTED OR CURED WITH A LOOMING BILL OF OVER A TRILLION DOLLARS BY 2050 AND MORE THAN 14 MILLION PEOPLE BEING AFFECTED WITH ALZHEIMER'S DISEASE. SO REALLY A PRESSING MEDICAL NEED.

I WAS TOLD THAT THE AUDIENCE IS VERY BROAD, SO I HAVE A COUPLE OF SOME INTRODUCTORY SLIDES JUST TO DESCRIBE ALZHEIMER'S DISEASE.

SO THIS IS A LATE ONSET, GENERALLY, DEMENTIA. IT WAS FIRST DESCRIBED BY ALOIS ALZHEIMER, AND SO IT'S REALLY CHARACTERIZED BY PROGRESSIVE MEMORY LOSS AND DISORIENTATION FOR TIME AND PLACE WITH USUALLY A TIME COURSE FOR DISEASE ANYWHERE FROM 5 TO 20 YEARS, DEPENDING ON THE AGE OF THE PERSON AND THE OTHER COMORBIDITIES THAT THEY HAVE.

AND IT'S CHARACTERIZED NEUROPATHOLOGICALLY OBVIOUSLY BY EXTENSIVE NEURONAL LOSS AND GLIOSIS, WHICH YOU CAN SEE ILLUSTRATED HERE IN JUST THAT THE SHRINKAGE OF AN ALZHEIMER BRAIN COMPARED WITH A HEALTHY BRAIN AT AUTOPSY; BUT ALSO WHEN YOU LOOK AT A MICROSCOPIC LEVEL, YOU HAVE THESE EXTRACELLULAR BETA AMYLOID PLAQUES AND INTRANEURONAL NEUROFIBRILLARY TANGLES. AND THESE ARE -- THE PLAQUES ARE COMPOSED LARGELY OF BETA AMYLOID, BUT

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THERE ARE MANY OTHER PROTEINS IN THEM AS WELL, AND THE NEUROFIBRILLARY TANGLES ARE LARGELY MICROTUBULAR ASSOCIATED PROTEIN, TAU. SO THOSE ARE THE TWO KEY PROTEINACEOUS COMPONENTS THAT FORM THESE INCLUSIONS THAT DEFINE THE DISEASE.

BUT THERE'S ALSO A LOT OF OTHER COMORBID PATHOLOGIES, PARTICULARLY IN LATE ONSET ALZHEIMER'S DISEASE, WHERE YOU SEE VASCULAR PATHOLOGY, YOU SEE LEWY BODIES THAT ARE CHARACTERISTIC OF PARKINSON'S DISEASE AND LEWY BODY DISEASE, BUT YOU ALSO SEE THEM IN ALZHEIMER'S DISEASE, AND YOU SEE TDP-43 INCLUSIONS THAT ARE TRADITIONALLY ASSOCIATED WITH FTD AND ALS, BUT ALSO SEEN HERE. AND SO I THINK IT'S A REALLY IMPORTANT POINT THAT A LOT OF PARTICULARLY LATE ONSET ALZHEIMER'S DISEASE OVER THE AGE OF 70 HAS ALL OF THESE PATHOLOGIES PRESENT. AND THAT IF WE'RE GOING TO SUCCESSFULLY TREAT THESE DISEASES, WE'RE PROBABLY GOING TO NEED TO TREAT, NOT JUST ONE OF THESE PATHOLOGIES, BUT MULTIPLE PATHOLOGIES. AND, THEREFORE, I THINK THAT THAT'S -- IF YOU'RE THINKING ABOUT OTHER NEURODEGENERATIVE DISEASES, THINK ABOUT THE FACT THAT THERE ARE MANY THINGS THAT ARE SHARED IN COMMON ACROSS THESE DISORDERS, INCLUDING THESE VARIOUS INCLUSIONS THAT I DESCRIBED.

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ANOTHER THING THAT'S OFTEN SHARED ACROSS THESE DISORDERS IS AN IMMUNE RESPONSE TO THE PRESENCE OF MISFOLDED PROTEINS. IT'S LARGEST IN ALZHEIMER'S DISEASE PROBABLY BECAUSE BETA AMYLOID IS AN EXTRACELLULAR INCLUSION, AND THE OTHER INCLUSIONS IN OTHER DISEASES AND ALZHEIMER'S DISEASE ARE INTRACELLULAR. BUT HERE YOU CAN SEE ON THE BOTTOM THAT THIS IS AN AMYLOID PLAQUE IN GREEN, AND ALL OF THE RED REPRESENTS MICROGLIA AROUND THE PLAQUES. SO THIS IS A -- PEOPLE HAVE ALWAYS HAVE TRADITIONALLY THOUGHT ABOUT THIS AS BEING SECONDARY TO DISEASE, BUT THE GENETICS NOW REALLY SAYS THAT IN LATE ONSET ALZHEIMER'S DISEASE THAT THIS IS PROBABLY AN IMPORTANT DRIVER OF THE PATHOLOGY.

SO THIS IS JUST A LITTLE SCHEMATIC CARTOON OF WHAT GENETIC ARCHITECTURE OF ANY HUMAN TRAIT LOOKS LIKE. I'M GOING TO WORK MY WAY AROUND THIS. AND WE'LL START OFF LOOKING AT THE RARE ALLELES THAT CAUSE MENDELIAN FORMS OF ALZHEIMER'S DISEASE. THESE REPRESENT PROBABLY LESS THAN 1 PERCENT OF ALL ALZHEIMER'S DISEASE. BUT WHEN THEY OCCUR, YOU SEE THEM IN MULTIGENERATION PEDIGREES LIKE THE ONE THAT'S ILLUSTRATED HERE. AND THIS WAS REALLY THE FIRST INROADS INTO THE GENETICS OF ALZHEIMER'S DISEASE WITH STUDYING PEDIGREES WITH THESE INHERITED

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FORMS OF DISEASE. AND, INDEED, THAT WAS TRUE FOR ALS AND FOR PARKINSON'S DISEASE AS WELL. THE FIRST GENETICS WERE REALLY DONE WERE THESE MENDELIAN FORMS OF THE DISEASE.

AND THAT LED TO THE IDENTIFICATION OF THREE GENES THAT ARE IDENTIFIED HERE, THE AMYLOID PRECURSOR PROTEIN GENE AND THEN PRESENILIN1 AND PRESENILIN2. AND YOU CAN SEE THAT THESE GENE DISCOVERY PROGRAMS OCCURRED IN THE '80S AND '90S. SINCE THAT TIME, NO ADDITIONAL GENE HAS BEEN ADDED TO THIS LIST AS BEING AN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE GENE.

THERE'S SOME MUTATIONS DESCRIBED IN A FOURTH GENE CALLED SORL1 WHERE IN SOME FAMILIES THEY DO APPEAR TO BE HIGHLY PENETRANT. I DIDN'T INCLUDE IT ON THIS LIST; BUT JUST FOR COMPLETENESS SAKE, I DEFINITELY WANT TO POINT THAT OUT BECAUSE THAT MIGHT POTENTIALLY BE AN AREA WHERE ADDITIONAL WORK COULD BE BENEFICIAL.

THE OTHER THING TO SAY ABOUT THESE MUTATIONS IS THAT THE ORIGINAL STUDIES WERE ALL DONE IN THESE POLYPENETRANT DOMINANT-LOOKING FAMILIES. AND OVER THE YEARS SINCE THEN, YOU CAN SEE THAT ABOUT 80 PERCENT OF FAMILIES AND MUTATIONS ARE IN PRESENILIN1, ABOUT 15 PERCENT OF THESE MUTATIONS ARE

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IN APP, AND THEN ABOUT 5 PERCENT ARE IN PRESENILIN2. AND THESE NUMBERS REALLY HAVEN'T CHANGED OVER THE LAST 20, 25 YEARS, BUT THIS SEEMS TO BE THE APPROXIMATE BREAKDOWN OF MUTATIONS ACROSS THESE THREE GENES.

INTERESTINGLY, IF ONE LOOKS AT LATE ONSET FAMILIES, SO THIS IS OBVIOUSLY A SOMEWHAT ARBITRARY DEFINITION, BUT PEOPLE OFTEN USE 60 OR 65 AS A CUTOFF AND CALL EVERYTHING ABOVE THOSE NUMBERS LATE ONSET AND EVERYTHING BELOW EARLY ONSET. WHAT THIS STUDY SHOWS WAS THAT WHEN WE LOOKED AT 440 APPROXIMATELY LATE ONSET AD FAMILIES, SO WITH ONSET ABOVE 60, WE IDENTIFIED ABOUT 3.5 PERCENT OF THOSE CLINICALLY DIAGNOSED FAMILIES AS CARRYING MUTATIONS IN GENES THAT WERE TRADITIONALLY ASSOCIATED WITH EARLY ONSET ALZHEIMER'S DISEASE. AND GIVEN THAT THIS IS A MUCH MORE COMMON FORM OF THE DISEASE, THERE ARE PROBABLY NUMERICALLY MORE FAMILIES WITH A LATE ONSET THAN THERE ARE WITH AN EARLY ONSET EVEN THOUGH IT'S A SMALL PERCENTAGE. SO 1 PERCENT -- 1.6 PERCENT OF THESE FAMILIES HAD A PRESENILIN1 MUTATION THAT WAS KNOWN FROM THE EARLY ONSET LITERATURE. SO JUST SAYING THAT THE PENETRANCE ISN'T SOLELY DRIVEN BY THE MUTATION. THERE MAY BE OTHER THINGS THAT INFLUENCE THE AGE AT WHICH DISEASE IS DEVELOPING.

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SO ANOTHER IMPORTANT POINT ILLUSTRATED BY THE BOTTOM OF THE SLIDE IS THAT WHEN YOU'VE GOT CLINICALLY DIAGNOSED CASES, THERE'S ALWAYS SOME LEVEL OF MISDIAGNOSIS. AND YOU CAN SEE HERE THAT FOUR -- WELL, C9ORF72 IS AN EXPANSION, BUT THREE DIFFERENT MUTATIONS IN GRANULIN THAT WERE FOUND IN THESE LATE ONSET AD FAMILIES. AND SO ACTUALLY A SIMILAR PERCENTAGE, 1.8 PERCENT OF THE FAMILIES HAD A MUTATION THAT ACTUALLY LEADS TO FRONTOTEMPORAL DEMENTIA, NOT ALZHEIMER'S DISEASE EVEN THOUGH THEY WERE CLINICALLY DIAGNOSED AS ALZHEIMER'S DISEASE.

SO IT'S IMPORTANT TO NOTE THAT THERE'S REALLY A SPECTRUM OF CLINICAL PHENOTYPES, AND A LOT OF THESE DISEASES OVERLAP IN THE PHENOTYPES.

LASTLY, IN THE SAME VEIN HERE, SPORADIC CASES OF EARLY ONSET ALZHEIMER'S DISEASE CAN RESULT FROM DE NOVO MUTATIONS IN THESE KNOWN GENES. AND THIS STUDY JUST SHOWED THAT AMONG 129 SPORADIC CASES, 18 OF THEM CARRIED A MUTATION IN ONE OF THESE THREE GENES, AND 11 OF THE 18 MUTATIONS WERE ALREADY KNOWN MUTATIONS THAT PEOPLE HAVE REPORTED IN FAMILIES, SO EXTREMELY LIKELY TO BE CAUSATIVE. AND AMONG THE TEN WHERE THEY WERE ABLE TO TEST WHETHER IT WAS A DE NOVO MUTATION BECAUSE THEY HAVE PARENTS, SEVEN OF THEM WERE DEFINITELY DE NOVO MUTATIONS. SO

133 HENNA COURT, SANDPOINT, IDAHO 83864
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EVEN THOUGH THESE APP AND PRESENILIN MUTATIONS WERE ORIGINALLY ASSOCIATED WITH AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE WITH AN EARLY ONSET, THEY'RE ALSO PRESENT IN LATE ONSET ALZHEIMER'S DISEASE AND IN SPORADIC EARLY ONSET AD CASES. THAT'S REALLY WHAT'S SUMMARIZED HERE.

SO IDENTIFYING THESE MUTATIONS REALLY LED TO THE AMYLOID CASCADE HYPOTHESIS, WHICH BASICALLY SAYS THAT IT'S THE FORMATION OF AMYLOID PLAQUES OR THE ACCUMULATION OF BETA AMYLOID THAT LEADS TO ALL THE DOWNSTREAM EFFECTS, INCLUDING FORMATION OF TANGLES, NEURODEGENERATION, IMMUNE RESPONSE DEMENTIA. ALL OF THESE DIRECTLY RESULT FROM ACCUMULATION OF Aß. AND THIS HAS REALLY BEEN THE DOMINANT MODEL IN THE FIELD FOR MAYBE 40 YEARS NOW. APP OBVIOUSLY IS THE SUBSTRATE FOR BETA AMYLOID. AND INTERESTINGLY, THE PRESENILINS ARE PART OF THE CATALYTIC SITE OF THE ENZYME THAT CLEAVES HERE TO RELEASE Aß.

SO THESE MUTATIONS IN THESE THREE GENES REALLY SUPPORT THE IDEA OF THE AMYLOID AS BEING A DRIVING FORCE IN DISEASE.

SO NOW MOVING ON THIS HIGH EFFECT COMMON VARIANTS, THESE ARE ACTUALLY PRETTY RARE IN THE POPULATION ASSOCIATED WITH DISEASE. BUT IN

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ALZHEIMER'S DISEASE, WE HAVE AN EXAMPLE OF ONE OF THESE GENES, AND THAT'S APOLIPOPROTEIN E OR APOE. IT IS REALLY THE MAJOR GENETIC RISK FACTOR FOR ALZHEIMER'S DISEASE ACROSS ALL FORMS OF DISEASE EXCEPT THOSE EARLY ONSET MENDELIAN FORMS OF THE DISEASE. AND THIS SHOWS YOU SURVIVAL CURVES FOR EACH OF THE GENOTYPES THAT WE SEE ACROSS APOE.

SO THERE ARE THREE ALLELES, E2, E3, AND E4. E3 IS ALWAYS THE MOST COMMON ALLELE IN ANY POPULATION THAT YOU LOOK AT. AND THIS IS A SURVIVAL CURVE FOR THAT GENOTYPE WHERE YOU SEE ABOUT 50 PERCENT OF PEOPLE WITH THE 3/3 GENOTYPE HAVE DEVELOPED ALZHEIMER'S DISEASE BY THE AGE OF 80.

AND THE STRIKING THING ABOUT THE IMPACT OF THE E4 ALLELE, WHICH IS A RISK FACTOR, IS THAT 50 PERCENT OF PEOPLE WITH THIS 4/4 GENOTYPE HAVE ALZHEIMER'S DISEASE BY THE AGE OF 70. SO A STRONG INCREASE IN RISK FOR DISEASE; WHEREAS, THE E2, THE E2 HOMOZYGOTES, WHICH IS A PRETTY RARE GENOTYPE, THERE'S NEVER 50 PERCENT OF PEOPLE AFFECTED WITH ALZHEIMER'S DISEASE AS YOU CAN SEE HERE. ONLY PROBABLY ABOUT 20 PERCENT OF PEOPLE WITH THIS GENOTYPE EVER DEVELOP WILL ALZHEIMER'S DISEASE.

RECENT EFFORTS IN SEQUENCING HAVE IDENTIFIED ADDITIONAL RARE PROTECTIVE AND RISK

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ALLELES OF APOE. SO NOW THAT THERE ARE PROBABLY SIX OR SEVEN TOTAL VARIANTS THAT HAVE BEEN DESCRIBED, PROBABLY THE ONE THAT'S RECEIVED THE MOST PRESS COVERAGE AND RECENTLY PAPERS IS APOE CHRISTCHURCH, WHICH WAS FOUND IN A PERSON WITH A PRESENILIN MUTATION WHO DIDN'T DEVELOP ALZHEIMER'S DISEASE UNTIL THEY WERE IN THEIR 70S. SO THERE WAS PROBABLY A 30-YEAR PROTECTION FROM DEVELOPING DISEASE BY CARRYING THIS APOE CHRISTCHURCH VARIANT.

SO I THINK THAT THAT'S AN AREA THAT'S VERY INTERESTING ABOUT THE PROTECTIVE VARIANTS IN APOE.

BECAUSE OF THE BIAS IN THE FIELD AROUND THE AMYLOID CASCADE HYPOTHESIS, A LOT OF THE WORK ON APOE HAS FOCUSED ON APOE'S RELATIONSHIP TO BETA AMYLOID. AND IT'S DEFINITELY TRUE THAT Aß AGGREGATION IS INCREASED BY THE E4 ALLELE AND Aß CLEARANCE IS DECREASED. SO THAT CERTAINLY CONTRIBUTES TO AD RISK; BUT AS YOU CAN SEE IN THIS FIGURE HERE, THERE ARE MANY OTHER PHENOTYPES THAT HAVE BEEN ASSOCIATED WITH AD RISK AND APOE4 EFFECTS. AND SOME OF THEM ARE DUE TO A LOSS-OF-FUNCTION POTENTIALLY ON THE RIGHT WHILST OTHERS ARE A GAIN-OF-FUNCTION. AND SO THIS HAS SORT OF PARALYZED THE FIELD FOR A NUMBER OF YEARS IN TERMS OF IF WE WANT TO TARGET APOE AS A THERAPY, WHAT DO WE REALLY

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NEED TO DO? AND IT KIND OF MATTERS WHETHER IT'S A TOXIC GAIN-OF-FUNCTION OR A LOSS-OF-FUNCTION AS TO WHAT STRATEGY YOU WOULD USE THERAPEUTICALLY.

IN THE LAST COUPLE OF YEARS, THERE HAVE NOW BEEN TWO FDA APPROVALS: ADUHELM, WHICH WAS QUITE CONTROVERSIAL, AND THEN LATER LECANEMAB OR LEQEMBI. WE'RE CURRENTLY WAITING FOR FDA APPROVAL OF ELI LILLY'S DONANEMAB ANTIBODY. SO THESE ARE ALL IMMUNOTHERAPIES BASED ON CLEARANCE OF Aß. AND THEY DO SEEM TO -- THE DRUGS SEEM TO BE VERY GOOD AT REMOVING Aß FROM THE BRAIN; BUT SO FAR IN THE CLINICAL TRIALS, I WOULD SAY THERE'S ONLY MODEST EFFECTS ON COGNITIVE DECLINE. AND SO I THINK WE WILL FIND OUT THROUGH THE CLINICAL MANAGEMENT OF PATIENTS IS HOW LONG TERM IS THAT SLOWING OF COGNITIVE DECLINE AND HOW UNIVERSAL IS IT? DOES IT HAPPEN IN ALL PATIENTS OR ONLY SUBSETS OF PEOPLE?

FROM THE CLINICAL TRIALS, IT WAS VERY CLEAR THAT THE EARLIER PEOPLE WERE TREATED, PARTICULARLY HAVING FEWER TANGLES, WAS WHEN THEY SAW THE MOST BENEFICIAL EFFECTS ON COGNITION. SO THERE'S STILL QUITE A BIT TO LEARN ABOUT THE IMPACT OF THESE DRUGS. CERTAINLY IN THE CLINICAL TRIALS, IT LOOKS LIKE WOMEN SHOW LESS BENEFIT THAN MEN, BUT THE STUDIES WERE NOT REALLY POWERED TO ADDRESS THIS.

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AND E4/4 CARRIERS SHOW THE MOST SIDE EFFECTS AND THE LEAST BENEFIT. SO THERE'S A BLACK LABEL WARNING ON THE DRUGS ABOUT THIS. AND, INDEED, SOME PHYSICIANS ARE NOT EVEN GIVING PEOPLE WHO ARE E4 HOMOZYGOTES THE DRUG; WHEREAS, OTHERS ARE TREATING THEM, BUT MONITORING CLOSELY. AND AS I SAY, THERE'S A RECOMMENDATION TO DO APOE GENOTYPING BEFORE INITIATING THE TRIAL.

SO THIS IS THE STATE OF THE ART AS FAR AS TREATMENTS IS CONCERNED RIGHT NOW. SO I WOULD SAY WE'RE IN VERY EARLY DAYS IN LOOKING AT DISEASE-MODIFYING TREATMENTS IN ALZHEIMER'S DISEASE.

SO DATING BACK ABOUT A DECADE, PEOPLE STARTED TO DO WHOLE GENOME AND WHOLE EXOME SEQUENCING LOOKING FOR RARE VARIANTS TO IDENTIFY ADDITIONAL GENES THAT MIGHT BE INVOLVED. AND THIS IS A COUPLE OF PAPERS THAT CAME OUT AT THE SAME TIME ARE EARLY 2013. THIS WAS THE FIRST INDICATION OF VARIANTS IN IMMUNE-RELATED PROTEINS AFFECTING RISK FOR ALZHEIMER'S DISEASE. AND SO THIS TRIGGERING RECEPTOR ON MYELOID CELLS 2 OR TREM2, AS IT'S CALLED, HAS AN IMPACT ON RISK FAIRLY SIMILAR TO CARRYING ONE E4 ALLELE. SO ABOUT A THREEFOLD INCREASE IN RISK FOR DISEASE.

AND THAT WAS SUBSEQUENTLY FOLLOWED BY A

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NUMBER OF OTHER SEQUENCING PROJECTS THAT IDENTIFIED SEVERAL OTHER GENES HERE, MANY OF WHICH ARE -- WELL, THEY'RE ALL MICROGLIAL EXPRESSED GENES. SOME OF THEM ARE UNIQUELY EXPRESSED IN MYELOID CELLS. AND THE ONES IN THE PURPLE COLOR ARE GENES THAT ARE ALSO IDENTIFIED WITHIN GWAS LOCI. SO PROBABLY CONTAIN NONCODING VARIANTS THAT AFFECT -- THAT ARE COMMON IN THE POPULATION AND PROBABLY AFFECT THE SAME GENE.

SO YOU CAN SEE THIS GENE I MENTIONED EARLIER. SORL1 WAS IDENTIFIED IN THIS GROUP AS WELL AS HAVING RARE CODING VARIANTS IN LATE ONSET ALZHEIMER'S DISEASE AS WELL. AND THEN ABCA7, ABI3, AND PLCG2 HAS ONE PROTECTIVE ALLELE IN THE POPULATION OF I THINK ABOUT 2 PERCENT. SO THERE'S ANOTHER EXAMPLE OF A PROTECTIVE ALLELE.

MOVING ON TO THE BOTTOM RIGHT CORNER HERE, THIS IS WHAT GENOMEWIDE ASSOCIATION WITH SNP ARRAYS IDENTIFY. AND YOU CAN SEE NOW WE HAVE ABOUT 75 LOCI THAT HAVE BEEN DESCRIBED. AND HERE THIS IS REPORTING, IN GENERAL, THE NEAREST GENE TO THESE SIGNALS. ONE OF THE COMPLICATIONS FOR GWAS IS IT IDENTIFIES A REGION OF DISEQUILIBRIUM WHERE THERE'S CO-SEGREGATION. AND YOU CAN SEE THAT THERE ARE OFTEN MANY GENES UNDERNEATH THE LOCUS. AND SO IT'S OFTEN HARD TO FIGURE OUT WHICH GENE IS REALLY THE

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CAUSAL GENE.

SO THIS IS SOME WORK FROM CHRIS GLASS' LAB WHICH WAS LOOKING AT ENRICHMENT OF THESE AD RISK ALLELES FROM THESE GWAS STUDIES IN DIFFERENT PROMOTER AND ENHANCER ANNOTATIONS IN DIFFERENT CELL TYPES IN THE BRAIN REALLY IDENTIFYING THAT MICROGLIAL ENHANCERS ARE SPECIFICALLY ENRICHED FOR AD RISK ALLELES OVER ALL OTHER CELL TYPES. AND SO THIS THEN POINTS TO MICROGLIA AS BEING AN IMPORTANT CELL TYPE IN ALZHEIMER'S DISEASE.

MY OWN GROUP DID A SIMILAR ANALYSIS, BUT COMING FROM A SLIGHTLY DIFFERENT DIRECTION, WAS THAT IN THAT WHEN WE LOOKED IN THE GTEX TISSUES, WE REALIZED ACTUALLY THAT BLOOD SHOWED THE STRONGEST RESPONSE, AND THAT IT WAS ACTUALLY MYELOID CELLS THAT WERE DRIVING THE SIGNAL. AND SO WE LOOKED IN MICROGLIA FROM THE BRAIN, MACROPHAGES FROM PERIPHERAL TISSUES, AND MONOCYTES, AND WE SEE ACTIVE ENHANCERS ALSO SHOW US THE ENRICHMENT FOR AD RISK ALLELES, BUT WE COULDN'T DISTINGUISH BETWEEN MONOCYTES, MACROPHAGES, AND MICROGLIA. THEY ALL SHOW SIMILAR ENRICHMENT.

SO ONE POTENTIAL FROM THIS IS THAT PART OF ALZHEIMER'S DISEASE IS ACTUALLY PERIPHERAL RISK RATHER THAN THE CENTRAL NERVOUS SYSTEM. SO I THINK

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THAT'S AN OPEN QUESTION. WE DON'T KNOW HOW MUCH OF THE SIGNAL IS ACTUALLY DUE TO THIS ENRICHMENT IN PERIPHERAL CELLS VERSUS MICROGLIA.

ALL THIS TO SAY FROM BOTH CHRIS' DATA AND OUR DATA REALLY SUPPORTS THE IDEA THAT MOST AD RISK ALLELES THAT ARE NONCODING OCCUR IN ENHANCERS IN MYELOID CELLS AND THAT THEY COULD BE REGULATING GENES AT SOME DISTANCE FROM THE GWAS SIGNAL.

SO WE HAVE TAKEN THIS INFORMATION THEN AND INTEGRATED EXPRESSION DATA FROM MYELOID CELLS WITH GENETIC -- FROM THE GWAS SIGNALS, LIKE THE ONE I JUST SHOWED YOU, AND THIS ALLOWED US TO IDENTIFY SEVERAL HUNDRED GENES WHERE EITHER IN RED HIGH EXPRESSION IS ASSOCIATED WITH RISK, OR ON THE BOTTOM, LOWER EXPRESSION IS ASSOCIATED WITH INCREASED RISK. AND THEN IF YOU NOW DO PATHWAY-BASED ANALYSES ON THESE SEVERAL HUNDRED GENES AND ASK WHAT PATHWAYS ARE IMPORTANT FOR AD RISK, WE IDENTIFY BASICALLY A SINGLE PATHWAY, WHICH IS PHAGOCYTIC PATHWAY GENES, IN PHAGOCYTIC CELLS OF WHICH IN THE BRAIN MICROGLIA WOULD BE THE MOST PHAGOCYTIC CELL, BUT MACROPHAGES ARE ALSO IMPORTANT PHAGOCYTIC CELLS.

AND SO THIS SUGGESTS THAT LATE ONSET AD RISK IS REALLY SOLELY WITHIN THIS ONE PATHWAY. AND

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I THINK A BIG QUESTION FOR THE FIELD IS HOW THAT RELATES TO THE EARLY ONSET GENES IN THIS Aß METABOLISM. THEY MAY BE RELATED, BUT I WOULD ARGUE THAT AT THE PRESENT TIME THE JURY IS STILL OUT ON THAT.

SO THIS TRIES TO PUT ALL OF THAT TOGETHER IN SAYING THAT BOTH COMMON AND RARE AD RISK VARIANTS FROM EVERYTHING OTHER THAN THOSE AUTOSOMAL DOMINANT CASES IDENTIFIED THESE THREE PATHWAYS: LIPID METABOLISM, INNATE IMMUNITY, AND ENDOLYSOSOMAL BIOLOGY. AND TOGETHER THEY ALL POINT TO THE SINGLE BIOLOGICAL PATHWAY EFFEROCYTOSIS IN THE PHAGOCYTIC CELLS. AND SO I THINK THAT THERE'S SOME NOW I WOULD ARGUE AT LEAST A COHERENT HYPOTHESIS THAT PUTS ALL OF AD RISK IN LATE ONSET AD INTO A SINGLE FRAMEWORK THAT COULD BE USED TO THINK ABOUT THERAPEUTIC TARGETS.

AND SO I THINK WITH THAT, IT'S PRETTY CLEARLY ONSET AD IS HIGHLY POLYGENIC, ALTHOUGH IT DOES HAVE THIS MAJOR RISK FACTOR APOE. AND I THINK THAT'S REALLY NOT BEEN EXPLOITED AS MUCH IN THE FIELD AS IT PROBABLY SHOULD HAVE BEEN. AND THAT RARE AND COMMON AD RISK ALLELES IMPLICATE THIS -- FIRST OF ALL, IMPLICATE MYELOID CELLS AND SPECIFICALLY THIS BIOLOGICAL PROCESS OF

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EFFEROCYTOSIS OR CLEARANCE OF DEBRIS IN DYING CELLS AS A CAUSAL PATHWAY IN ALZHEIMER'S DISEASE. SO EVEN THOUGH IT'S A NEURODEGENERATIVE DISEASE, THE GENETICS SAYS THAT THE CAUSAL RISK IS ACTUALLY WITHIN MYELOID CELLS, NOT NEURONS.

SO THAT'S MY SUMMARY. AND THEN IN THE LAST FEW MINUTES, JUST TO TALK ABOUT SOME OF THE THINGS ABOUT THE KNOWLEDGE GAPS. THESE ARE BROAD ONES HERE, AND I HAVE ON ANOTHER SLIDE THINGS DIRECTLY COMING OUT OF THE GENETICS. BUT AS YOU SEE, WE HAVE NO EFFECTIVE TREATMENT FOR THE DISEASE, AND THERE ARE FEW TARGETS BEYOND Aß AND TAU. SO WE REALLY SHOULD BE USING THE GENETICS TO GUIDE DEVELOPMENT OF NOVEL TARGETS.

I THINK A REALLY IMPORTANT POINT IS THAT MOST AD CASES ARE MIXED DEMENTIAS, AND WE NEED BETTER MARKERS FOR THE COMMON MISFOLDED PROTEINS. WE HAVE AMYLOID. NOW THERE'S SOME FOR TAU. THERE ARE SOME BEING DEVELOPED FOR THESE OTHER ONES, BUT WE REALLY NEED THAT. AND THAT'S GOING TO BE USEFUL ACROSS ALL NEURODEGENERATIVE DISEASES TO HAVE BOTH IMAGING AND FLUID BIOMARKERS FOR ALL OF THE MAJOR MISFOLDED PROTEINS IN THESE DISEASES.

I THINK ONE QUESTION FOR ME, IF TAU IS PART OF THE PATHOLOGY OF A LOT OF THESE DISEASES AND

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IS INDICATED GENETICALLY IN SEVERAL OF THEM, IS TAU A TARGET THAT COULD BE VALUABLE ACROSS DISEASES?

AND THEN I THINK, AS WAS MENTIONED, I CAN'T REMEMBER WHETHER IT WAS THE PD OR THE ALS, I THINK IT WAS PD, PATIENT STRATIFICATION FOR PERSONALIZED MEDICINE, I THINK, IS SOMETHING THAT'S GOING TO BE IMPORTANT. AND WE COULD STRATIFY ON APOE. IT'S CLEARLY A MAJOR RISK FACTOR, AND THINGS MIGHT BE DIFFERENT IN E4 NEGATIVE PEOPLE VERSUS E4 POSITIVE. AND PATIENT STRATIFICATION BASED ON BIOMARKERS, AND I THINK IN PARTICULAR, RELATED TO WHAT MISFOLDED PROTEINS ARE PRESENT IN SOMEBODY WITH DEMENTIA, BECAUSE I THINK THAT THE STRATEGIES FOR TREATMENT MIGHT BE VERY DIFFERENT FROM SOMEONE WHO HAS ONLY Aß AND TAU VERSUS SOMEONE WHO HAS A LOT OF TDP-43 OR A LOT OF A-SYNUCLEIN IN ADDITION TO THOSE OTHER THINGS.

FROM THE GENETICS, SO THIS IS MUCH MORE SPECIFIC, BUT I THINK DEFINITELY RELEVANT TO CIRM INITIATIVES, APOE HAS BOTH RISK-INCREASING AND PROTECTIVE ALLELES. AND EVEN THOUGH WE'VE KNOWN ABOUT E2 AND E3 AND E4, BUT SINCE THE EARLY '90S, WE DON'T KNOW IF THE SAME PATHWAYS ARE AFFECTED BUT IN OPPOSITE DIRECTIONS FOR E2 AND E4 OR WHETHER THEY AFFECT DIFFERENT PATHWAYS, WHETHER THERE'S DIFFERENT

133 HENNA COURT, SANDPOINT, IDAHO 83864
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BIOLOGY BEHIND PROTECTION VERSUS RISK, WHICH IS A REALLY FUNDAMENTAL QUESTION. AND IT'S CRAZY THAT WE DON'T KNOW THE ANSWER TO THAT. AND NOW THAT WE HAVE MORE PROTECTIVE ALLELES, AND I GIVE AN EXAMPLE OF THREE HERE, DO ALL OF THESE PROTECTIVE ALLELES WORK IN THE SAME WAY? NATURE HAS DONE AN EXPERIMENT HERE FOR US. WE KNOW HOW TO PROTECT PEOPLE FROM ALZHEIMER'S DISEASE BASED ON THESE VARIANTS, BUT WE NEED TO UNDERSTAND HOW THEY WORK.

I MENTIONED BRIEFLY SORL1 EARLIER. I THINK IT CAN AFFECT TRAFFICKING OF APP, BUT WE DON'T KNOW FOR SURE THAT THAT IS THE MAJOR BIOLOGY BEHIND SORL1 AS A RISK FACTOR FOR DISEASE.

DO RISK AND PROTECTIVE ALLELES FOR LATE ONSET AD GENES AFFECT MICROGLIAL FUNCTION? OR DO THEY ALSO AFFECT OTHER MACROPHAGE POPULATIONS? AND I THINK THESE ARE PARTICULARLY IMPORTANT IN THINKING ABOUT THERAPEUTICS. IS IT NECESSARY TO GET A DRUG ACROSS THE BLOOD-BRAIN BARRIER TO TREAT THE DISEASE? IF IT'S MICROGLIAL FUNCTION THAT HAS TO BE CORRECTED, THEN THAT WILL BE THE CASE. BUT OTHER MACROPHAGE POPULATIONS MIGHT BE ACCESSIBLE BECAUSE THEY'LL BE OUTSIDE THE BLOOD-BRAIN BARRIER. AND IF THAT'S THE CASE, THAT WOULD CERTAINLY MAKE DEVELOPMENT OF ANY DRUGS EASIER IF YOU DON'T HAVE TO

133 HENNA COURT, SANDPOINT, IDAHO 83864
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GET THEM INTO THE BRAIN.

AND THEN JUST THINKING ABOUT THE FACT THAT THERE SEEMS TO BE ONE MAJOR PATHWAY THAT'S INVOLVED, WHICH GENES ARE THE MOST TRACTABLE DRUG TARGETS WITHIN THIS PATHWAY FOR TREATMENT FOR DISEASE? AND I THINK THAT MECHANISTIC STUDIES AROUND ANY OR ALL OF THESE AREAS THAT COMBINE RESEARCH ON STEM CELLS WITH MOUSE AND HUMAN STUDIES WOULD BE TREMENDOUSLY IMPORTANT IN ADVANCING OUR UNDERSTANDING OF DISEASE.

SO WHAT ARE THE MOST IMPORTANT BOTTLENECKS IN THE DEVELOPMENT PROCESS FOR --

CHAIRMAN GOLDSTEIN: ALISON, COULD YOU THINK ABOUT FINISHING UP REASONABLY QUICKLY SO THERE'S TIME FOR QUESTIONS?

DR. GOATE: YEAH. I DON'T KNOW WHETHER YOU WANT ME TO GO THROUGH THESE LAST COUPLE OF SLIDES OR WHETHER YOU WANT TO JUST ASK THE QUESTIONS. AND I CAN LEAVE YOU WITH THE SLIDES, AND YOU CAN HAVE THESE THINGS AS WELL. I'M HAPPY TO DO THAT.

CHAIRMAN GOLDSTEIN: I THINK THAT WOULD BE GOOD BECAUSE I ALREADY SEE A HAND UP, AND I DO HAVE A QUESTION OR TWO FOR YOU AS WELL.

DR. GOATE: OKAY. LET ME --

CHAIRMAN GOLDSTEIN: THANK YOU. THAT WAS

A WONDERFUL SUMMARY OF HOW GENETICS IS DISSECTING HOW WE THINK ABOUT THIS AWFUL DISEASE, AND I THINK IS VERY USEFUL FOR CIRM IN THINKING ABOUT HOW TO MOVE AHEAD.

MARK.

MR. FISCHER-COLBRIE: THANKS FOR THE QUESTION OPPORTUNITY. I AM FASCINATED WITH THE OVERLAP OF OTHER DISEASE CONDITIONS IN THE RISK CONTEXT. BOTH LIPIDS AND GLUCOSE METABOLISM MAY HAVE SOME ROLE POTENTIALLY RELATED TO ALZHEIMER'S FROM WHAT I UNDERSTAND. I'D LIKE TO GET YOUR PERSPECTIVE ON WHERE THERE MIGHT BE PATHWAYS OR MECHANISMS THAT MIGHT EVEN HAVE IMPACT IN OTHER DISEASE AREAS AS A CONSEQUENCE.

DR. GOATE: YEAH. I MEAN I THINK THAT LIPID METABOLISM AND ENDOLYSOSOMAL BIOLOGY SHOW UP AND OVERLAP IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE, MAYBE TO A LESSER EXTENT IN ALS, BUT DEFINITELY THERE AS WELL. AND REALLY THE LIPID METABOLISM SIDE OF THINGS HAS ONLY REALLY RECENTLY BEEN EXAMINED TO ANY GREAT LEVEL DESPITE THE FACT THAT WE'VE KNOWN ABOUT APOE FOR SUCH A LONG TIME.

SO I DEFINITELY -- LYSOSOMAL GENES COME OUT IN AD GENETIC RISK AND IN AD GENETIC RISK, BUT THEY'RE DIFFERENT GENES. AND IT MIGHT BE THAT IT

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ENDS UP BEING DIFFERENT CELL TYPES THAT ARE IMPORTANT BECAUSE I THINK THERE'S BOTH DIMENSIONS THERE, BUT I DO THINK ENDOLYSOSOMAL BIOLOGY IS GOING TO BE IMPORTANT. I THINK TRAFFICKING AND CLEARANCE OF PROTEINS AND LIPIDS IS GOING TO BE IMPORTANT ACROSS ALL OF THESE DISEASES.

MR. FISCHER-COLBRIE: THANK YOU.

CHAIRMAN GOLDSTEIN: SO PERHAPS I COULD FOLLOW UP, ALISON, BY JUST HIGHLIGHTING SOMETHING AND GETTING YOUR THOUGHTS ABOUT IT. I MEAN THE NORMAL FUNCTION OF APOE, AS I UNDERSTAND IT, IS TO BE THE MAJOR CARRIER OF CHOLESTEROL IN THE BRAIN, BUT NOT IN THE PERIPHERY. AND SO THE QUESTION IS TO WHAT EXTENT IS IT MANAGEMENT OF CHOLESTEROL THAT THESE ALLELES ARE IMPACTING?

DR. GOATE: I THINK THAT THAT'S A REALLY IMPORTANT QUESTION, LARRY. AND -- SO I WOULD SAY THAT APOE IS A TRANSPORTER OF LIPIDS IN BOTH THE PERIPHERY AND IN THE BRAIN, BUT IN THE BRAIN THERE'S NOTHING ELSE. SO IT'S ONLY APOE. AND THAT'S WHY IT'S PARTICULARLY IMPORTANT. AND I THINK IF YOU LOOK AT DISEASES LIKE NEIMAN PICT DISEASE, FOR EXAMPLE, THE GENE THERE AFFECTS -- CAUSES CHOLESTEROL ACCUMULATION AS A LOSS-OF-FUNCTION, AND THAT IS A DISEASE THAT HAS TANGLES IN IT TOO. AND

IT'S A CHILDHOOD DISEASE, AND THAT'S A LYSOSOMAL STORAGE DISEASE.

SO I BELIEVE THERE ARE MANY CONNECTIONS A CROSS THESE DISEASES, BOTH LATE ONSET NEURODEGENERATIVE DISEASES AND EARLY ONSET LYSOSOMAL STORAGE DISEASES IN CHILDREN WHERE THERE ARE A LOT OF SIMILARITIES MECHANISTICALLY BEHIND THESE DISEASES AND THAT THEY'VE BEEN UNDEREXPLORED. BUT I THINK PEOPLE NOW RECOGNIZE THAT THERE'S BEEN A TREMENDOUS BIAS IN WHAT WE'VE LOOKED AT OVER THE LAST 20, 30 YEARS IN TERMS OF FOCUSING ON AMYLOID IN PARTICULAR AND THAT WE NEED -- SO I THINK THERE'S NOW MORE RECOGNITION THAT WE NEED TO BE LOOKING AT OTHER PATHWAYS. AND SO PEOPLE ARE LOOKING MORE AT CHOLESTEROL METABOLISM IN PARTICULAR, WHICH I THINK -- THE BRAIN IS THE MOST CHOLESTEROL RICH ORGAN IN THE BODY. SO IF SOMETHING GOES WRONG WITH LIPID METABOLISM, IT'S GOING TO HAVE A BIG IMPACT ON THE BRAIN.

CHAIRMAN GOLDSTEIN: YES. THANK YOU. PAT.

DR. LEVITT: YES. THANKS MUCH, ALISON. SO THE OVERLAP IN SOME OF THESE PATHWAYS FOR NEURODEGENERATIONS IS INTERESTING, BUT THEY ALL HAVE ONE THING IN COMMON, WHICH IS THERE'S SELECTIVITY

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WITHIN EACH OF THE CATEGORIES IN TERMS OF THE NEURONS THAT ARE TARGETED FOR DEGENERATION. AND IN THE CONTEXT OF US BEING A STEM CELL REGENERATIVE MEDICINE AGENCY, AND SOME OF THE INTRIGUING THINGS YOU TALKED ABOUT IN TERMS OF NON-NEURONAL COMPONENTS THAT MAY BE EITHER MODULATING THE DISRUPTIONS OR BEING CAUSAL, WHAT IS YOUR THINKING ABOUT HOW YOU BLEND THOSE FINDINGS, THOSE NEWER FINDINGS, WITH SPECIFICITY THAT WE NEED TO THINK ABOUT IN TERMS OF THE AGENCY LOOKING AT FUNDING THAT WOULD ADDRESS THIS ISSUE ABOUT SPECIFICITY WITHIN EACH OF THESE NEURODEVELOPMENTAL DISORDERS? SORRY. NEURODEGENERATIVE. I HAVE NEURODEVELOPMENT ON MY MIND ALL THE TIME, SO I APOLOGIZE FOR THAT.

DR. GOATE: I MEAN IT'S DEFINITELY TRUE THAT IN EACH DISEASE THERE'S SELECTIVE NEURONAL VULNERABILITY, RIGHT? AND THAT'S WHY PHENOTYPICALLY THEY LOOK DIFFERENT. EVEN THOUGH WE'RE KILLING NEURONS IN ALL OF THESE DISEASES, IT'S DIFFERENT POPULATIONS OF NEURONS.

I THINK WHAT WAS REALLY STRIKING TO ME IN THE AD GENETICS IS THAT THE VULNERABILITY DOESN'T -- GENETICALLY DOESN'T HAVE TO RESIDE IN THE NEURONS, RIGHT, BUT IN ALZHEIMER'S DISEASE IT APPEARS THAT THE GENETIC RISK IS ACTUALLY IN GLIA,

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AND THAT IT'S COMMUNICATION BETWEEN NEURONS AND MICROGLIA THAT LIKELY GOES AWRY AND THAT IT'S THAT THAT LEADS TO I DON'T KNOW WHETHER IT'S INADEQUATE TROPHIC SUPPORT OR WHAT THE EXACT MECHANISM IS, BUT THAT IT REQUIRES MORE THAN ONE CELL TYPE. RIGHT. AND I THINK THAT THAT'S SOMETHING THAT WE SHOULD BE MINDFUL ACROSS DISEASES, RIGHT. HOW OFTEN IS IT THAT IT'S A BREAKDOWN IN COMMUNICATION BETWEEN DIFFERENT CELL TYPES IN THE BRAIN THAT LEADS TO ONE PARTICULAR CELL TYPE DYING RATHER THAN EVERYTHING BEING INTRINSIC TO THAT CELL TYPE AND IT DIES BECAUSE IT HAS THE WRONG INFORMATION RATHER THAN BECAUSE IT HAS POOR COMMUNICATION WITH SURROUNDING CELLS?

DR. LEVITT: I JUST WANT TO FOLLOW UP.

DR. GOATE: I THINK THAT'S IMPORTANT TO THINKING ABOUT MODELS, RIGHT?

DR. LEVITT: YEAH, EXACTLY. I WANT TO FOLLOW UP ON THAT BECAUSE THERE'S BEEN THIS VERY NEUROCENTRIC APPROACH TO UNDERSTANDING DIVERSITY IN THE NERVOUS SYSTEM. AND WE HAVE A PRETTY SUBSTANTIAL UNDERSTANDING OF THAT NOW, AND THERE'S BEEN MUCH LESS ATTENTION FROM IPSC TO DIFFERENTIATE A CELL TYPE WITH RESPECT TO THE TERMS OF THESE OTHER CELL TYPES. AND THERE'S LOTS OF EVIDENCE THAT

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ASTROCYTES AND MICROGLIA, DEPENDING UPON THE BRAIN AREA, ACTUALLY HAVE SOME DIFFERENT PROPERTIES AT A MOLECULAR LEVEL AND AT A FUNCTIONAL LEVEL AS WELL. SO IT'S NOT LIKE THEY'RE ALL THE SAME. A MICROGLIAL CELL IS NOT NECESSARILY LIKE A GLIAL CELL IF YOU'RE IN THE CORTEX OR IF YOU'RE IN THE SUBSTANTIA NIGRA.

SO I'M WONDERING WHETHER YOU KNOW OF FOLKS WHO ARE LOOKING AT THE DIVERSITY OF THESE OTHER CELL TYPES THAT COULD BE RESPONSIBLE FOR THIS COMMUNICATION DISRUPTION AND THAT THERE WOULD BE SPECIFICITY TO LOOK AT THEM? I'M JUST TRYING TO CONNECT SOME OF THIS TO WHAT WE DO AS CIRM BECAUSE WE'RE NOT NIH, RIGHT, WE HAVE A FOCUS, HOW TO CONNECT IT IN A WAY THAT WOULD BE USEFUL FOR THE FIELD.

DR. GOATE: RIGHT. I MEAN SO I GUESS I THINK THAT SINGLE CELL SEQUENCING HAS REALLY OPENED OUR EYES OVER THE LAST FEW YEARS IN THIS REGARD IN THAT, AS YOU SAID, WE'VE KNOWN ABOUT NEURONAL DIVERSITY FOR DECADES, RIGHT, BUT PEOPLE ALWAYS JUST USED TO THINK ABOUT ASTROCYTES OR MICROGLIA WITHOUT THINKING ABOUT WHETHER BRAIN REGION MATTERED OR EVEN FINER DEFINITIONS. BUT NOW FROM SEQUENCING, IT'S VERY CLEAR THAT IN SINGLE CELL DATA, THAT THERE ARE MULTIPLE CLUSTERS BOTH IN MICROGLIA AND IN

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ASTROCYTES FOR CELLS WHICHEVER BRAIN REGION YOU TAKE THESE FROM, BUT THAT THEY MAY DIFFER FROM BRAIN REGION TO BRAIN REGION. AND THINKING ABOUT IPS CELLS, YOU CAN CREATE SOME OF THAT DIVERSITY, EVEN GROWING THEM IN A DISH FROM IPS CELLS. BUT YOU GET DIFFERENT LEVELS OF MATURITY, NOT SURPRISINGLY, IF YOU HAVE A MIXED CULTURE OF CELLS VERSUS A MONOCULTURE.

SO IF YOU'RE GROWING MICROGLIA WITH NEURONS AND ASTROCYTES, THEY GET TO BE MORE MATURE. AND MAYBE YOU WILL HAVE MORE OF CERTAIN OF THESE FUNCTIONAL SUBCLUSTERS BY DOING THAT.

SO I WOULD SAY TO CIRM, YEAH, I THINK THERE'S A LOT THAT COULD BE DONE TO STUDY THE DIFFERENT COMPONENTS, SUBSETS OF GLIA AND THEIR RELEVANCE TO DIFFERENT BRAIN REGIONS AND TO DIFFERENT DISEASE STATES.

CHAIRMAN GOLDSTEIN: SO LET ME WIND UP THE QUESTIONING, ALISON, WITH ONE FINAL QUESTION. ONE OF CIRM'S CORE INTERESTS HAS ALWAYS BEEN CELL REPLACEMENT THERAPY. AND I GUESS THE QUESTION IS WHETHER -- THERE'S BEEN THIS IDEA THAT WE WOULD NEVER BE ABLE TO REPLACE NEURONS IN SOME OF THESE DISEASES BECAUSE THE DAMAGE IS SO WIDESPREAD. BUT I WONDER WHETHER THE REPLACEMENT OF MICROGLIAL CELLS,

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ESPECIALLY SINCE THEY MIGHT BE MOTILE, WOULD BE SOMETHING THAT WOULD BE A REASONABLE STRATEGY TO CONSIDER.

DR. GOATE: WELL, I MEAN I THINK OF ONE PERSON IN PARTICULAR. I KNOW MATT BLURTON-JONES AT UC IRVINE IS DEFINITELY TRYING TO TAKE THAT APPROACH, AND ALSO ONE OF THE COMPANIES, RIGHT, BLUEROCK, I THINK IT IS, IS DOING THAT. SO THERE ARE DEFINITELY PEOPLE OUT THERE WHO BELIEVE THAT THIS COULD BE AN ALTERNATIVE STRATEGY FROM A CELL REPLACEMENT THERAPY POINT OF VIEW.

CHAIRMAN GOLDSTEIN: LET'S SEE. WE HAVE A QUESTION FROM THE CONFERENCE ROOM, IT LOOKS LIKE. WHO'S GOT THEIR HAND UP?

DR. THOMAS: IT'S J.T., LARRY. SO, ALISON, THANKS VERY MUCH FOR THAT MOST INFORMATIVE TALK. I HAVE SORT OF A MACRO QUESTION. WHAT IS THE LATEST THINKING ABOUT THE VIABILITY OF MODEL SYSTEMS AS PREDICTORS FOR ACTUAL HUMAN RESULT THESE DAYS? THERE'S BEEN A LOT OF PROBLEMS WITH FINDING MODEL SYSTEMS THAT ARE SUFFICIENTLY ALIKE TO GET ANYTHING OF GREAT VALUE. WHAT'S THE LATEST ON THAT?

DR. GOATE: YEAH. I THINK THERE IS STILL A PROBLEM, RIGHT, IN THAT ALL OF THE MOUSE MODELS THAT PEOPLE ARE USING, THEY EITHER HAVE AMYLOID

133 HENNA COURT, SANDPOINT, IDAHO 83864
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DEPOSITION AND NOT VERY MUCH NEURODEGENERATION OR THEY HAVE TAU WITHOUT AMYLOID AND A LOT OF NEURODEGENERATION. SO NEITHER OF THOSE MODELS ACTUALLY REALLY REFLECT THE HUMAN DISEASE. AND WE WERE DEFINITELY LED ASTRAY WITH THE AMYLOID THERAPIES FOR A LONG TIME WITH THESE POOR ANIMAL MODELS.

I THINK THERE'S A GREATER UNDERSTANDING THAT THEY ARE IMPERFECT MODELS AND YOU HAVE TO BE VERY CAREFUL ABOUT WHAT QUESTIONS YOU ASK IN WHICH MODEL. SO MAYBE, AT LEAST FROM THE INVESTIGATOR'S STANDPOINT, PEOPLE ARE MORE CAREFUL NOW ABOUT HOW THEY USE THESE MODELS.

PEOPLE LIKE MATT BLURTON-JONES AND MYSELF AND OTHERS ARE DEFINITELY TAKING IPS CELLS AND PUTTING THEM AND DOING XENOTRANSPLANTATION EXPERIMENTS SO WE CAN HAVE HUMAN IMMUNE CELLS IN THESE MOUSE MODELS TO SEE HOW THEY REACT. SO I THINK THAT THE MODELS ARE BECOMING BROADER, AND OBVIOUSLY YOU CAN USE ORGANOIDS. PEOPLE HAVE PUT ORGANOIDS BACK INTO MOUSE BRAINS AS WELL. SO I THINK THERE'S A PLACE FOR USING MORE COMPLEX MODELS THAT START OFF FROM HUMAN CELLS. WHETHER YOU DO IT WHOLLY IN THE DISH, OR WHETHER YOU DO IT IN COMBINATION THROUGH XENOTRANSPLANTATION, I THINK

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BOTH HAVE THEIR USES AND VALUES. BUT I THINK IT'S DEFINITELY IMPORTANT TO DO SOME OF THESE EXPERIMENTS IN HUMAN CELLS AS JUST IN MOUSE MODELS.

CHAIRMAN GOLDSTEIN: SO THANK YOU VERY MUCH, ALISON. THAT WAS TREMENDOUSLY INTERESTING AND PROVOCATIVE. WE REALLY APPRECIATE YOUR TIME. AND I THINK --

DR. GOATE: AND I'M HAPPY TO SEND THE FULL DECK OF SLIDES TO YOU GUYS SO THAT YOU CAN LOOK THROUGH THEM.

CHAIRMAN GOLDSTEIN: PLEASE DO. THAT WOULD BE VERY HELPFUL. I THINK WE'LL HAVE A LOT TO TALK ABOUT AT OUR NEXT MEETING ABOUT SOME OF THE POINTS YOU RAISED.

SO AT THIS POINT, ROSA, DO YOU WANT TO GO AHEAD AND INTRODUCE JIM GUSELLA?

DR. CANET-AVILES: I'M HAPPY TO DO SO. I THINK YOU KNOW HIM BETTER THAN I DO, BUT WE ARE HONORED TO HAVE DR. GUSELLA. I DIDN'T KNOW THAT YOU WERE A MENTOR OF DR. TANSY AS WELL. SO I'M LOOKING AT YOUR BACKGROUND. I FOUND LOTS OF VERY AMAZING ACHIEVEMENTS.

BUT DR. GUSELLA IS THE BULLARD PROFESSOR OF NEUROGENETICS AT THE DEPARTMENT OF GENETICS AT HARVARD MEDICAL SCHOOL. AND AS WE MENTIONED, HIS

LAB IS PURSUING COLLABORATIVE STUDIES AT ALL STAGES OF GENETIC RESEARCH CYCLE AIMED TO DISCOVER GENES THAT CAUSE, PREDISPOSE, OR MODIFY NEUROLOGICAL AND BEHAVORIAL DISORDERS IN SUBJECTS WITH BALANCED CHROMOSOMAL ABERRATIONS AND DEVELOPMENTAL PHENOTYPES. AND HE'S FOCUSED ON DELINEATING MECHANISMS OF PATHOGENESIS, WHICH IS VERY ALIGNED WITH WHAT WE'VE BEEN FOCUSED ON IN OUR LAST YEAR OF INTEREST IN THIS NEURO TASK FORCE.

AND HE'S GOING TO TALK TO US ABOUT, I BELIEVE, HUNTINGTON'S DISEASE. IS THAT RIGHT, DR. GUSELLA?

DR. GUSELLA: THAT'S RIGHT.

DR. CANET-AVILES: GREAT.

DR. GUSELLA: OKAY. LET'S SEE. I GOT TO GET MY PICTURE OUT OF THE WAY HERE. ALL RIGHT. IS THAT SHOWING UP PROPERLY?

MS. MANDAC: YES.

DR. GUSELLA: OKAY. WELL, I HAVE TO MAKE DISCLOSURES EVEN THOUGH THE COMPANY I'M MAINLY DISCLOSING HAS BEEN DEFUNCT FOR A COUPLE YEARS. MY INSTITUTION INSISTS THAT I CONTINUE TO DISCLOSE IT UNTIL MY NIH GRANT ENDS.

SO HUNTINGTON'S DISEASE, JUST AS BACKGROUND, WAS DESCRIBED A 150 YEARS AGO BY GEORGE

HUNTINGTON. AND IT WAS -- WHAT WAS REMARKABLE ABOUT HIS DESCRIPTION WAS NOT JUST THIS WRITHING LUMEN DISORDER THAT ONSET IN MIDLIFE. IT WAS THE FACT THAT HE CAPTURED THE INHERITANCE PATTERN FROM THE DISEASE AS AUTOSOMAL DOMINANT BEFORE MENDEL HAD ACTUALLY DESCRIBED WHAT THAT MEANT OR BEFORE MENDEL WAS UNDERSTOOD TO HAVE DESCRIBED WHAT THAT MEANT.

THE DISORDER INVOLVES MOVEMENTS AS ITS CHARACTERISTIC FEATURE, CHOREIC MOVEMENTS, BUT HAS INTELLECTUAL DECLINE, IT HAS PSYCHIATRIC SYMPTOMS, AND THEY'RE ALL DUE TO SELECTIVE NEURONAL LOSSES IN THE BRAIN. AND IT IS A DEBILITATING DISEASE THAT PROGRESSIVELY DETERIORATES OVER TIME IN THE INDIVIDUAL SO THAT THEY DIE ABOUT 15 YEARS AFTER THEIR ONSET INITIALLY.

NOW, UNLIKE THE OTHER NEURODEGENERATIVE DISEASES YOU'VE HEARD ABOUT, EVERY INDIVIDUAL WITH HUNTINGTON'S DISEASE HAS A MUTATION IN THE SAME GENE AND THE SAME TYPE OF MUTATION. AND THAT MUTATION CAUSES THE LOSS OF NEURONS THAT, IN FACT, OCCUR THROUGHOUT THE BRAIN. THE RIGHT-HAND SIDE OF THIS SLIDE WILL -- IF I CAN GET A POINTER, I'D BE ABLE TO POINT TO IT. HERE WE GO -- SHOWS YOU THAT THERE IS LOSS IN THE STRIATAL REGION, BUT THERE'S LOSS THROUGHOUT THE BRAIN IF YOU JUST COMPARED THE HD

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208-920-3543 DRAIBE@HOTMAIL.COM

BRAIN TO THE NORMAL. WHAT IS BEST CHARACTERIZED HAS BEEN THE LOSS IN THE STRIATAL REGION BECAUSE THE ENTIRE ARCHITECTURE OF THE REGION IS DESTROYED. AND THAT IS BECAUSE IT'S MAINLY MADE UP OF MEDIUM SPINY NEURONS WHICH ARE LOST OVER TIME, AND THEY'RE LOST WITH A PARTICULAR GRADIENT ACROSS THE TISSUE.

NOW, HUNTINGTON'S DISEASE IS CAUSED BY THIS ONE MUTATION AND THIS ONE GENE NOW CALLED HTT, A VERY UNFORTUNATE NAME CHANGE ON THE PART OF THE GENETICS COMMUNITY SINCE HTT WAS ALREADY BEING USED AS A SHORT FORM FOR A RECEPTOR IN THE BRAIN, BUT THEY DECIDED THAT HTT WOULD MAKE SENSE FOR A LOCUS NAME.

THE MUTATION IS AN EXPANDED CAG REPEAT IN THE FIRST EXON. AND I'VE SHOWN THE CAG REPEAT HERE AS 21. THIS COMES FROM A NORMAL CHROMOSOME. AND ON A CANONICAL HD CHROMOSOME, THAT 21 OR THE CAG REPEAT WOULD BE FOLLOWED BY A CAA AND A CAG. BUT IF IT WAS AN HD CHROMOSOME, THIS WOULD BE EXPANDED TO OVER 34, 35 UNITS. IT ENCODES A GLUTAMINE TRACK WITHIN THE BEGINNING OF THIS VERY LONG PROTEIN THAT IS NOW CALLED HUNTINGTIN. AND THE EXACT FUNCTION OF THIS PROTEIN IS NOT KNOWN. IT INTERACTS WITH LOTS AND LOTS OF OTHER PROTEINS. IT APPEARS TO OPERATE AS A FACILITATOR IN DIFFERENT PROCESSES WITHIN THE CELL.

133 HENNA COURT, SANDPOINT, IDAHO 83864
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AND IT IS AN ESSENTIAL PROTEIN AT THE LEVEL OF THE ORGANISM, BUT NOT AT THE LEVEL OF THE CELL.

MY SLIDE IS NOT MOVING. THERE WE GO. SO I MENTIONED THAT THE REPEAT WAS EXPANDED ON HD CHROMOSOMES. THIS IS A PLOT OF A VERY LARGE NUMBER THAT HAVE BEEN STUDIED HERE AT MASS GENERAL WHERE EVERY INDIVIDUAL CARRYING TWO CHROMOSOME4S TYPICALLY HAS ONE EXPANDED ALLELE AND ONE NORMAL ALLELE BECAUSE THIS IS A DOMINANT DISORDER. AND SO YOU CAN LOOK AT THE REPEAT DISTRIBUTION OF BOTH SETS OF CHROMOSOMES. WHAT YOU FIND, IF YOU LOOKED AT THAT LARGE POPULATION, IS THAT THIS REPEAT IS POLYMORPHIC IS NORMAL PEOPLE, VARYING BETWEEN JUST FOUR OR FIVE REPEATS UP INTO THE 20S. AT THE HIGH END OF THE RANGE FROM 27 TO 35, WE COLOR IT DIFFERENTLY BECAUSE, IN FACT, IT IS OCCASIONALLY UNSTABLE THROUGH MYOTIC TRANSMISSION, GIVING RISE TYPICALLY TO A SLIGHTLY LARGER REPEAT. IN THE RANGE OF 36 TO 39, YOU WILL FIND PEOPLE IN THE POPULATION AT A FREQUENCY OF PROBABLY 1 IN 500 OR MORE WHO CARRY REPEATS IN THIS RANGE, BUT DON'T ALWAYS SHOW SYMPTOMS OF HUNTINGTON'S DISEASE BECAUSE IT'S A NONPENETRANT RANGE. AND ONCE YOU GET TO 40, IF YOU LIVE A NORMAL LIFESPAN, YOU'RE GOING TO SHOW SYMPTOMS OF HUNTINGTON'S DISEASE. BUT YOU COULD

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HAVE A MUCH LONGER REPEAT BEING INHERITED IN A VERY SMALL NUMBER OF CASES.

THAT'S IMPORTANT BECAUSE THE EXPANDED REPEAT LENGTH THAT YOU INHERIT IS CORRELATED WITH YOUR EXPECTED AGE OF ONSET SO THAT THOSE PEOPLE WHO INHERIT EXTREMELY LONG REPEATS HAVE JUVENILE ONSET AS YOUNG AS TWO YEARS OF AGE OR YOUNGER. AND THE COURSE OF THE DISEASE IS A LITTLE BIT DIFFERENT IN THOSE PEOPLE. YOU GET GREATER ONSET OF RIGIDITY EARLY IN THAT DISEASE OF JUVENILE ONSET; BUT IN NORMAL, TYPICAL HD ONSET, ADULT ONSET, THE FIRST SYMPTOMS ARE ABNORMAL CHOREIC MOVEMENTS AND THEN A GRADUAL PROGRESSION UNTIL A PERSON IS TOTALLY DISABLED.

OKAY. SO HD IS ACTUALLY ONE OF THE EARLIEST DISEASES DISCOVERED THAT'S CAUSED BY ONE OF THESE REPEATS, BUT THE NUMBER OF THESE DISEASES HAS EXPANDED DRAMATICALLY OVER TIME. AND THIS IS FROM A REVIEW ARTICLE BY JEAN-LOUIS MANDEL ALREADY THREE YEARS AGO NOW. AND YOU CAN SEE FROM THE LONG RESEQUENCING ANGLE THAT MORE AND MORE OF THESE DISEASE GENES ARE BEING DISCOVERED. SO THERE IS A COMMONALITY ACROSS DISEASES. MANY OF THESE ARE NEURODEGENERATIVE DISEASES WHERE AN EXPANDED REPEAT IS THE SOURCE OF THE DISORDER. AND HUNTINGTON'S

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DISEASE EFFECTIVELY, BECAUSE OF ITS HIGHER FREQUENCY THAN MANY OF THESE OTHERS, ACTS AS A MODEL FOR UNDERSTANDING THE PROCESSES THAT MAY BE GOING ON IN THEM AS WELL.

I SAID THERE WAS OVER 50 OF THEM AT THIS POINT. THESE REPEATS CAN OCCUR IN VARIOUS PLACES. WHEN THEY OCCUR AND THEY ARE A CAG REPEAT IN AND EXON, THEY BECOME KNOWN AS A POLYGLUTAMINE REPEAT BECAUSE THAT'S WHAT THEY ENCODE. AND SO THE DISEASE BECOMES A POLYGLUTAMINE DISEASE, BUT THAT'S BY NO MEANS CERTAIN THAT THE POLYGLUTAMINE ACTUALLY PLAYS ANY ROLE AT ALL IN THE PATHOGENESIS OF THE DISEASE, WHICH I WILL GET TO TOWARDS THE END.

SO EACH OF THESE DIFFERENT REPEATS CAN CAUSE A PROBLEM. WHETHER THEY ALL CAUSE IT IN THE SAME WAY, NOT COMPLETELY CLEAR, BUT THERE ARE CERTAIN COMMONALITIES THAT CROSS MANY OF THESE DISEASES THAT WILL SHOW UP RELATIVE TO WHAT I'M TALKING ABOUT NEXT.

SO THE FIRST THING THAT IS IMPORTANT TO KNOW ABOUT HUNTINGTON'S DISEASE WITH RESPECT TO THIS AGE OF ONSET AND NUMBER OF CAG REPEATS THAT SPEAKS TO THE MECHANISM IS THAT IF YOU HAVE A SECOND COPY OF THE EXPANDED REPEAT BECAUSE BOTH OF YOUR PARENTS HAD HUNTINGTON'S AND YOU WERE UNFORTUNATE ENOUGH TO

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HAVE INHERITED THE EXPANDED ALLELE FROM BOTH OF THEM, IF YOU HAVE TWO COPIES, YOU DON'T HAVE ONSET OF THE DISEASE EARLIER THAN IF YOU JUST HAVE ONE. YOUR ONSET IS CORRELATED WITH THE LONGER OF THE TWO REPEATS. SO THE SECOND COPY THAT IS EXPANDED IS NOT CONTRIBUTING AND, IN FACT, IF YOU ARE A TYPICAL HD HETEROZYGOTE, THE NORMAL COPY OF THE REPEAT IN THE INDIVIDUAL IS NOT CONTRIBUTING AT ALL TO DETERMINING THE TIMING OF ONSET. SO HUNTINGTON'S DISEASE IS A TRUE DOMINANT DISORDER. ONE COPY OF THE GENE IS SUFFICIENT TO CAUSE THE ENTIRE PROCESS WITH THE SAME RATE AS IF YOU HAD TWO COPIES.

THIS ARGUES AGAINST THE IDEA THAT CONTINUOUS DOSE DEPENDENT NEURONAL DAMAGE AT PHYSIOLOGICAL LEVELS OF EXPRESSION. AND SO ONE OF THE THINGS THAT WAS NOTED EARLY ON WAS THAT POLYGLUTAMINE IS VERY PRONE TO PRODUCING DELETIONS AND CELLULAR INCLUSIONS. THIS CAME FROM AN EARLY MOUSE MODEL. BUT THE IDEA THAT THIS SIMPLE AGGREGATION PROCESS WAS THE SOURCE OF THE DISEASE WHICH LED TO A COUPLE OF DECADES WORTH OF WORK REALLY ISN'T SUPPORTED BY THE HUMAN GENETICS BECAUSE OF THIS EFFECTIVE HOMOZYGOSITY LACK THEREOF.

BUT THE GENETICS ACTUALLY COULD TELL YOU MORE ABOUT THE DISEASE MECHANISM IF YOU THOUGHT NOT

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IN TERMS OF WHAT'S CAUSING THE DISEASE, BUT WHAT MODIFIES IT. BECAUSE WHEN YOU LOOK AT THAT CURVE OF AGE OF ONSET, NOT EVERYBODY'S HAD THEIR ONSET RIGHT THE LINE. SOME PEOPLE HAD ONSET EARLIER THAN EXPECTED, SOME HAD ONSET LATER THAN EXPECTED. AND IT WAS SHOWN 20 YEARS AGO THAT A SIGNIFICANT COMPONENT OF THAT VARIATION WAS GENETIC, VARYING WITHIN FAMILIES TO A LESSER DEGREE THAN IT DID ACROSS FAMILIES.

AND SO YOU COULD THINK OF THIS MODIFICATION AS BEING A NATURAL CLINICAL TRIAL WHERE AN INDIVIDUAL COULD BE CONCEIVED WITH A PARTICULAR REPEAT LENGTH, IN THIS CASE, CAG43, AND THEY'D HAVE A PARTICULAR EXPECTED TIME OF CLINICAL DIAGNOSIS, AND 15 YEARS LATER THEY WOULD DIE. BUT IF THEY HAD A PARTICULAR INTERVENTION, IN THIS CASE A PARTICULAR GENETIC MODIFIER, IT MIGHT DELAY THAT CLINICAL DIAGNOSIS AND LEAD TO DEATH LATER. YOU COULD ALSO IMAGINE MODIFIERS DOWN HERE THAT DELAY THINGS, BUT WHAT THE RESEARCH COMMUNITY AIMED AT WAS TRYING TO FIND VARIATION THAT IMPACTED ON THE TIMING OF CLINICAL DIAGNOSIS.

AND SO A CONSORTIUM WAS FORMED CALLED THE GENETIC MODIFIERS OF HUNTINGTON'S DISEASE CONSORTIUM HD, TO CARRY OUT GENOMEWIDE ASSOCIATION STUDIES

133 HENNA COURT, SANDPOINT, IDAHO 83864
208-920-3543 DRAIBE@HOTMAIL.COM

WHERE GENETIC VARIANTS WERE LOOKED AT ALL ACROSS ALL OF THE CHROMOSOMES FOR ANYTHING THAT WAS ASSOCIATED WITH AN EARLIER AGE OF ONSET THAN EXPECTED OR A LATER AGE OF ONSET THAN EXPECTED. AND IN THIS FIRST STUDY THAT WAS PUBLISHED BACK IN 2015, THIS ACTED AS THE PROOF OF PRINCIPLE THAT HUNTINGTON'S DISEASE CAN BE MODIFIED BEFORE ONSET BECAUSE THE GENETIC VARIATION OF THESE TWO GENES DID MODIFY. IN THE CASE OF RRM2B HAS CAUSED ONSET TO BE EARLIER THAN EXPECTED. BUT IN THE CASE OF FAN1, THERE WERE TWO DIFFERENT EFFECTS. ONE EFFECT, ONE VERSION WILL OF FAN1, CAUSED ONSET TO BE LATER THAN EXPECTED. AND THE OTHER CAUSED IT TO BE EARLIER THAN EXPECTED.

SO WE KNEW THEREFOR THIS THAT YOU COULD MODIFY HUNTINGTON'S DISEASE. IF YOU COULD FIGURE OUT WHAT THE MODIFIER WAS, YOU THEN WOULD HAVE A CLUE TO WHAT WOULD BE THERAPEUTIC IN TERMS OF A PHARMACEUTICAL INTERVENTION OR ANY OTHER ATTEMPT TO REPRODUCE BUT THE MODIFIER IS DOING EXCEPT PERHAPS DO IT EVEN STRONGER. AND SO THESE KINDS OF STUDIES EXPANDED FURTHER. AND IN 2019 ANOTHER VERSION WAS PUBLISHED BY THE GEM CONSORTIUM, AND NOW THERE WERE MANY MORE GENES THAT WERE ON THE LIST. BUT YOU WILL NOTICE THAT A NUMBER OF THEM ARE COLORED. AND THE REASON THAT THEY'RE COLORED IS THEY ALL TAKE PART IN

133 HENNA COURT, SANDPOINT, IDAHO 83864
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THE SAME GENERAL PROCESS, WHICH IS DNA DAMAGE REPAIR.

NOW, PMS1, MLH1, MSH3, AND PMS2 ARE ALL CLASSIFIED AS MISMATCH REPAIR PROTEINS. FAN1 WAS A GENE THAT WAS KNOWN TO BE INVOLVED IN CROSS-LINK REPAIR, BUT SUBSEQUENT RESEARCH HAS ALSO SHOWN THAT IT INTERACTS WITH MLH1 AND MSH3 IN A COMPETITIVE MANNER. IN FACT, WHERE FAN1 ACTS TO -- WE'LL GET TO IT -- ACTS TO SUPPRESS WHAT I'M GOING TO GET TO. LIG1 IS THE ENZYME THAT CLOSE UP GAPS IN DNA AFTER THEY'VE BEEN REPAIRED. AND SO YOU HAVE A NUMBER OF THINGS THAT REALLY POINT TO THE SAME PROCESS AS BEING A MODIFIER OF HD. AND THAT PROCESS CAN MODIFY EITHER BY CAUSING ONSET TO BE EARLIER THAN EXPECTED OR ONSET LATER THAN EXPECTED.

YOU WILL ALSO NOTICE THAT THERE ARE A COUPLE OF GENES IN BLACK HERE OTHER THAN THE HTT ITSELF WHICH DON'T FIT CLEANLY INTO THAT DNA REPAIR PATHWAY. AND SO WE'LL TALK A BIT MORE ABOUT THEM LATER, BUT THEY MUST ACT IN A DIFFERENT WAY, EITHER IN DIRECTLY ON THE DNA REPAIR OR ON SOME OTHER PROCESS.

SO THE DNA MISMATCH REPAIR IS A WELL-KNOWN PROCESS STUDIED IN DIVIDING CELLS WHERE IT PARTICIPATES IN EITHER REPAIRING DNA MISMATCHES OR

133 HENNA COURT, SANDPOINT, IDAHO 83864
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SMALL DELETIONS THAT OCCUR, INSERTIONS OR DELETIONS. SO IT'S THOUGHT, IN FACT, THAT WHAT'S GOING ON IN HUNTINGTON'S DISEASE IS THAT THE REPEAT THAT FORMS AS IT BECOMES LONG CAN OCCASIONALLY LOOP OUT DURING A TIME WHEN THE DNA IS OPEN, BASICALLY WHAT HAPPENED DURING REPAIR OF SOME KIND OF DAMAGE, BUT WHEN IT IS OPEN AND LOOPS OUT, IT MIGHT NOT COALESCE PROPERLY BACK TO A CLEANLY ANNEALED STRAND. AND SO THIS PROCESS IS PERHAPS BROUGHT IN TO TRY AND REPAIR IT. AND IN DOING THE REPAIR, WHAT HAPPENS IS IT ACTUALLY CHANGES THE LENGTH OF THE CAG REPEAT.

SO THE CAG REPEAT SHOWS SOMATIC INSTABILITY. YOU ARE INHERITED -- YOU HAVE AN INHERITED REPEAT LENGTH OF A PARTICULAR NUMBER OF CAG'S, BUT DURING YOUR LIFETIME IN PARTICULAR CELLS THE REPEAT IS PRONE TO EXPAND. AND THESE PROTEINS ARE IN SOME WAY INVOLVED IN THAT EXPANSION.

SO THIS HAS LED TO A MODEL OF HUNTINGTON'S DISEASE PATHOGENESIS THAT INVOLVES A MINIMUM OF TWO PARTS, ONE WHICH IS THE SOMATIC INSTABILITY OF THE REPEAT, AND THE OTHER IS THE OUTCOME OF THAT SOMATIC INSTABILITY. BASED ON SOME CALCULATIONS THAT HAVE BEEN DONE FROM HUMAN STUDIES, WHICH I'LL GET TO IN A SECOND, THIS MODEL IS PREDICTED WHERE CAG EXPANSION OCCURS BUT NO DAMAGE IS ACTUALLY OCCURRING UNTIL YOU

133 HENNA COURT, SANDPOINT, IDAHO 83864
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HIT SOME THRESHOLD WHERE NEURONAL DAMAGE IS TRIGGERED, AND AFTER THAT THE NEURON BEGINS TO DIE. SO THIS IS VIEWED AS A CELL AUTONOMOUS EFFECT IN WHICH THE REPEAT WITHIN A GIVEN NEURON DETERMINES WHETHER THAT NEURON IS GOING TO DIE. WHEN YOU GET TO A PARTICULAR THRESHOLD, THE NEURON DOES DIE. IF YOU HAVE HAPPEN TO HAVE AN ONSET HASTENING MODIFIER, THAT REPEAT EXPANSION HAPPENS FASTER. SO YOU GET TO THE THRESHOLD SOONER. AND IF YOU HAVE AN ONSET DELAYING MODIFIER, IT HAPPENS MUCH MORE SLOWLY AND YOU GET THERE LATER.

SO THIS DOESN'T HAPPEN IN ALL NEURONS. THERE ARE PARTICULAR NEURONS THAT ARE PRONE TO THIS EXPANSION HAPPENING. AND IT TURNS OUT THAT THE STRIATUM IS PARTICULARLY PRONE, THE MEDIUM SPINY NEURONS ARE PARTICULARLY PRONE TO THIS PROCESS. BUT THERE ARE NEURONS IN OTHER REGIONS OF THE BRAIN THAT ARE ALSO PRONE TO IT.

WHEN THE THRESHOLD IS HIT AND YOU TRIGGER WHATEVER THE PROCESS IS THAT IS GOING TO CAUSE DAMAGE IS A LINK IS THAT IS JUST NOW BEING DETERMINED IN RESEARCH STUDIES BOTH IN HUMANS AND MODEL SYSTEMS. IT IS PROBABLY OVER A HUNDRED TO A HUNDRED FIFTY REPEATS LONGER THAN WHAT YOU STARTED WITH. SO YOU'RE GETTING QUITE DEGREE OF EXPANSION.

133 HENNA COURT, SANDPOINT, IDAHO 83864
208-920-3543 DRAIBE@HOTMAIL.COM

BUT YOU CAN SEE MANY MORE REPEATS THAN THAT IN HUMAN NEURONS. FROM POSTMORTEM BRAIN, YOU CAN SEE REPEATS UP INTO THE HUNDREDS. SO THIS EXPANSION PROCESS REALLY CARRIES IT OVER QUITE A NUMBER OF REPEATS RELATIVE TO THE STARTING POINT.

ONCE IT HITS THAT THRESHOLD, IT TRIGGERS TOXICITY. AND ONE OF THE BIG ISSUES IS WE DON'T KNOW WHAT THAT TOXICITY IS AT THIS POINT. IT MIGHT INVOLVE POLYGLUTAMINE, BUT IT MIGHT NOT. IT MIGHT INVOLVE OTHER EFFECTS AT EITHER THE RNA OR ALTERNATIVE PEPTIDE LEVELS OR EVEN AT THE DNA LEVEL. THIS ALL REMAINS TO BE DETERMINED; BUT WHAT SEEMS CLEAR, ALTHOUGH, AGAIN, NOT COMPLETELY QUANTITATED TO THE POINT WHERE I CAN GIVE YOU SPECIFIC NUMBERS, IS THAT THE TIME THAT IT TAKES TO GET TO THIS POINT IS MUCH, MUCH LONGER THAN THE TIME IT TAKES TO GET FROM THIS POINT TO THE CELL DYING.

SO IF YOU'RE GOING TO TREAT, IT WOULD BE NICE TO TREAT DURING THIS PHASE RATHER THAN DURING THE DOWNSTREAM PHASE EVEN THOUGH BOTH ARE POTENTIAL TARGETS.

OKAY. SO I SAID THAT THIS MODEL CAME LARGELY FROM THE OBSERVATION THAT DNA REPAIR GENES WERE INVOLVED IN MODIFYING THE DISEASE. IN A PRIOR MATHEMATICAL MODELING EFFORT THAT HAD TAKEN THE AGE

133 HENNA COURT, SANDPOINT, IDAHO 83864
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OF ONSET AND LOOKED AT IT AND CAME TO THE CONCLUSION WITHOUT ANY EXPERIMENTAL DATA, JUST TAKING THE HUMAN DATA, THAT THE WHOLE THING WAS CONSISTENT WITH A PROCESS WHERE YOU STARTED WITH A REPEAT AT BIRTH AND THEN IN A STOCHASTIC WAY, THE REPEATS GREW SO THAT CELL REPEATS GREW AT DIFFERENT RATES BASED ON WHAT JUMPS HAPPENED UNTIL SOME STARTED TO CROSS THE LINE, AND THEN THOSE CELLS STARTED TO DIE.

AT THAT POINT YOU'D SEE THE REST OF THE CELLS POTENTIALLY REACTING IN TERMS OF THEIR OVERALL EXPRESSION TO THE FACT THAT THE TISSUE'S NOW CHANGED. AND WHILE YOU DO SEE THAT, IF YOU LOOK IN POSTMORTEM BRAIN, A COMPARISON OF THE CELLS THAT HAVE HIGH REPEATS OR LOWER REPEATS DOESN'T SHOW A LOT OF DIFFERENCE. IT'S REALLY ONLY THE CELLS THAT HAVE CROSSED THE THRESHOLD THAT ARE NOW REALLY SHOWING THE DAMAGE. SO A LONG-RANGE OVER WHICH ONE COULD POTENTIALLY TREAT.

SO IF YOU GO BACK AND PLOT THE DISEASE TRAJECTORY OF AN INDIVIDUAL, IN THIS CASE WE'VE TAKEN AN INDIVIDUAL WHO HAS A CAG OF 42, YOU CAN MEASURE ALL ALONG THE WAY VARIOUS MEASURES OF COGNITIVE ABILITY OR OF MOVEMENT DISTURBANCE. AND THESE COME FROM WHAT'S CALLED THE UNIFIED HUNTINGTON'S DISEASE RATING SCALE THAT THE

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CLINICIANS USE, THE UHDRS, AND THEY'RE THE TYPICAL TESTS THAT ARE USED. OTHERS ARE USED AS WELL. FOR EACH ONE OF THESE, YOU CAN DEVISE A TRAJECTORY THAT GOES OVER THE LIFE OF THE INDIVIDUAL. AND THIS POINT, DCL4, IS A LANDMARK KNOWN AS DIAGNOSTIC CONFIDENCE LEVEL 4. THIS IS THE POINT AT WHICH A CLINICIAN IS GREATER THAN 99 PERCENT CERTAIN THAT HE'S DEALING WITH HUNTINGTON'S DISEASE JUST BASED ON CLINICAL GROUNDS. USED TO BE COMPLETELY BASED ON MOTOR, BUT WITH A RECOGNITION THAT THERE ARE COGNITIVE EFFECTS AS WELL. THOSE HAVE COME INTO PLAY IN TERMS OF THEIR DETERMINATION.

ABOUT A DOZEN YEARS LATER IS THIS LANDMARK CALLED TFC6. THAT MEANS A SCORE OF SIX ON A TOTAL FUNCTIONAL CAPACITY SCALE. TOTAL FUNCTIONAL CAPACITY SCALE GOES FROM A STARTING POINT OF 13 WHERE YOU'RE INDISTINGUISHABLE FROM ANYBODY ELSE IN THE WORLD TO ONE WHERE SIX IS THE POINT AT WHICH YOU ARE JUST BEGINNING TO HAVE TROUBLE WITH THE ACTIVITIES OF DAILY LIFE. SO YOU CAN SEE THAT FROM THE TIME YOU HAVE ONSET TO THE TIME YOU BEGIN TO HAVE ISSUES WITH DAILY LIFE, YOU'RE DEALING WITH ABOUT A DOZEN YEARS ON AVERAGE IF YOU HAVE A CAG REPEAT ABOVE 42, AND THEN YOU'RE GOING TO LIVE DOWNSTREAM FROM THIS ANOTHER FEW YEARS AS

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DETERIORATION PROGRESSES AND YOU DIE. BUT EACH OF THESE IS MEASURABLE DURING THIS PHASE; BUT AT THIS POINT HERE, YOU CAN'T DIAGNOSE BASED ON THEM, AND CERTAINLY MORE THAN TEN YEARS BEFORE ONSET, YOU CAN'T REALLY EVEN DISTINGUISH OTHER THAN AT THE GROUP LEVEL THAT ANYTHING IS GOING ON.

SO GIVEN THIS MODEL, WHAT ARE THE OPPORTUNITIES FOR DISEASE-MODIFYING TREATMENTS? YOU COULD POTENTIALLY INHIBIT OR SUPPRESS THOSE DNA MISMATCH REPAIR PROTEINS THAT ARE INDICATED LIKE MSH3 OR PMS1. THE MSH3 IS WELL CHARACTERIZED AND DOESN'T HAVE THE SAME INVOLVEMENT WITH COLORECTAL CANCER THAT SOME OF THE OTHER GENES DO. IT DOESN'T PRESENT SEEMINGLY AS MUCH OF A CANCER RISK IF YOU INHIBITED IT. AND THERE ARE PEOPLE OUT IN THE POPULATION WHO ARE HETEROZYGOUS FOR INACTIVATING MUTATIONS OF MSH3. SO CERTAINLY KNOCKING IT DOWN TO 50 PERCENT DOESN'T SEEM TO BE A PROBLEM. AND YET IN THE HUMANS, THE EFFECTS OF THESE MODIFIERS, WHICH ARE TYPICALLY ONE TO THREE YEARS, INVOLVE FAR LESS THAN A 50-PERCENT CHANGE IN THE EXPRESSION LEVEL OF THE PARTICULAR PROTEIN.

PMS1, IT'S NOT AT ALL CLEAR WHAT IT DOES IN MISMATCH REPAIR. IT'S LABELED BASED ON ITS FORMING DIMERS WITH THESE OTHER PROTEINS, BUT

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EXACTLY WHAT ITS ROLE IS IS NOT CLEAR.

SO ONE WAY WOULD BE TO INHIBIT THE GENES WHOSE PRESENCE PROMOTES SOMATIC EXPANSION. THE OTHER WOULD BE TO OVEREXPRESS OR TO INCREASE THE EXPRESSION GENES THAT NORMALLY SUPPRESS SOMATIC EXPANSION LIKE FAN1.

ANOTHER WAY TO LOOK AT IT IS TO LOOK AT THE REPEAT ITSELF BECAUSE THE DEGREE TO WHICH THE REPEAT IS PRONE TO SOMATIC EXPANSION IS DEPENDENT ON ITS LENGTH. THE LOWER REPEATS HAVE LATER ONSET PURELY BECAUSE THEY START OUT LOWER AND HAVE TO EXPAND FARTHER TO GET DO THE THRESHOLD. SO IF YOU COULD REDUCE THE PURE LENGTH OF THE REPEAT BY DELETION OR INTERRUPTION, YOU WOULD HAVE EFFECTIVELY TREATED AND PREVENTED ONSET OF THE DISEASE. IF YOU OTHERWISE INTERFERE WITH THE SUBSTRATE IN A WAY THAT DOESN'T ALLOW IT TO REPEAT OR ITS SURROUNDINGS BECAUSE, OF COURSE, THIS EXPANSION IS OCCURRING PREFERENTIALLY IN CERTAIN CELLS. EVERY CELL IS SOMEWHAT PRONE TO EXPANSION. YOU CAN MEASURE CAG IN STABILITY EVEN IN BLOOD DNA. BUT TO GET THESE MUCH LARGER EXPANSIONS, ONLY CERTAIN CELLS ARE PRONE. AND THEN ONLY CERTAIN CELLS ARE PRONE TO GETTING TO A POINT WHERE THERE IS A TOXICITY THAT'S INVOLVED. SO THE CAG REPEAT, FOR EXAMPLE, WILL EXPAND QUITE A

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BIT IN LIVER CELLS; BUT LIVER TOXICITY IS NOT ASSOCIATED WITH HUNTINGTON'S DISEASE. IT WILL EXPAND QUITE A BIT IN STRIATAL CELLS, AND STRIATAL CELLS DIE AS A RESULT OF HUNTINGTON'S DISEASE. AND SIMILARLY, CORTICAL NEURONS, CERTAIN TYPES ARE PRONE TO THAT EXPANSION.

SO THERE ARE A WHOLE VARIETY OF WAYS THAT PREVENTING THAT SOMATIC EXPANSION WOULD MAKE IT A GREAT TARGET BECAUSE YOU WOULD EITHER DELAY THE ONSET OF THE DISEASE OR PREVENT THE ONSET ENTIRELY IF YOU GOT ENOUGH OF THE CELLS TO PREVENT EXPANSION.

AND AT THAT POINT, THEN YOU'D WONDER IF WE'VE NOW DEALT WITH THIS DISEASE, WE'VE TREATED IT, YOU'D BE IN A GOOD POSITION OF THEN FIGURING OUT IF THERE'S ANY PERIPHERAL EFFECTS INVOLVED IN THE DISEASE BECAUSE AS OF NOW EVERYTHING IS PREDOMINANTLY BRAIN DRIVEN.

A SECOND WAY YOU COULD LOOK AT TRYING TO TREAT WOULD BE TO ALTER THAT THRESHOLD, BUT YOU NEED TO UNDERSTAND WHAT THE THRESHOLD IS. WHAT ARE THE PROTECTIVE RESPONSES THAT ARE KEEPING THE CELL AT A PARTICULAR POINT OF NO DAMAGE BECAUSE THEY HAVEN'T HIT THE THRESHOLD VERSUS DAMAGE AFTERWARDS. CAN YOU ENHANCE THE PROTECTIVE RESPONSES TO MOVE IT UP? AND THAT DEPENDS IN PART ON UNDERSTANDING WHAT THAT

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TOXICITY MECHANISM IS, AND WE REALLY DON'T KNOW.

REDUCED EXPRESSION OF MUTANT HUNTINGTIN BECAUSE, OF COURSE, IN A DOMINANT DISEASE, THE NATURAL THING YOU THINK ABOUT IS GETTING RID OF THE GENE PROTEIN THAT SEEMS TO BE CAUSING IT. SO REDUCED EXPRESSION OF HUNTINGTIN HAS BEEN TRIED. THERE HAVE BEEN CLINICAL TRIALS BASED ON ANTISENSE OLIGOS TO REDUCE THE EXPRESSION OF HUNTINGTIN. THERE HAVE BEEN TRIALS BASED ON SPLICE MODULATORS THAT INCORPORATE A PSEUDOEXON INTO HUNTINGTIN AND STOP IT FROM BEING EXPRESSED PROPERLY. AND TO DATE NOTHING HAS YET BEEN SUCCESSFUL, AND TO SOME DEGREE THEY'VE BEEN PRONE TO SIDE EFFECTS THAT HAVE LED TO HALTING IN AT LEAST SOME OF THE TRIALS.

NOW, ANOTHER THING THAT'S SHOWN UP IN THE LAST FEW YEARS IS THAT YOU CAN MAKE A PRODUCT ONLY FROM EXON1. AND THAT PRODUCT MAY BE MADE MORE FREQUENTLY AS THE REPEAT LENGTH GETS LONGER. SO IT MAY WELL BE THAT THE REPEAT EXPANDING TO A THRESHOLD INVOLVES GETTING TO THE POINT WHERE YOU MAKE A SUFFICIENT AMOUNT OF EXON1 TO NOW TRIGGER THE POLYGLUTAMINE PATHOLOGY THAT EVERYBODY HAS STUDIED FOR YEARS, BUT WAS STUDYING AT MUCH LOWER REPEAT LENGTHS. POSSIBLE, BUT KNOCK-DOWN OF THAT PRODUCT HAS NOT YET BEEN TESTED. PEOPLE HAVE TRIED TO

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PREVENT JUST EXPRESSION OF THE TRANSCRIPT ENTIRELY, BUT THE IDEA THAT THE HUNTINGTIN PROTEIN OR SOME PORTION OF IT IS ACTUALLY INVOLVED IN TRIGGERING PATHOGENESIS IS STILL REALLY UNCLEAR. IT'S POSSIBLE THAT THERE IS RAN TRANSLATION THAT HAPPENS WHERE OTHER PEPTIDES ARE MADE FROM THE REPEAT AS IT EXPANDS. IT'S POSSIBLE THAT THERE ARE EFFECTS OF THE EXPANDED REPEAT IN THE RNA THAT ARE ACTING ELSEWHERE. IT'S POSSIBLE THAT THERE'S EFFECTS AT THE DNA LEVEL ON THE CHROMAN IN THE REGION. NONE OF THIS IS AT ALL CERTAIN. WHAT IS CERTAIN IS YOU HAVE TO EXPAND THE REPEAT BEFORE YOU GET TO THE POINT WHERE THESE ARE A PROBLEM.

AND SO THE TAKE-HOME MESSAGE IS THAT BLOCKING THAT SOMATIC CAG EXPANSION AS EARLY AS POSSIBLE WOULD PROVIDE A RATIONAL DISEASE-MODIFYING TREATMENT. YOU THEN ARE FACED WITH THE QUESTION OF HOW DO YOU ACTUALLY GO ABOUT DOING SUCH A TRIAL BECAUSE YOU NEED A BIOMARKER, AND YOU DON'T HAVE THE ABILITY TO MEASURE THE REPEAT LENGTH IN THE NEURONS OF THE LIVING INDIVIDUALS. SO PEOPLE ARE LOOKING AT VARIOUS WAYS OF TRYING TO HAVE PERIPHERAL SOURCES OF THE REPEAT AS PROXIES, MORE REASONABLE FOR THINGS WHERE YOU'RE DOING A SMALL MOLECULE THERAPY THAT'S INTRODUCED SYSTEMICALLY. IF YOU'RE DOING A THERAPY

133 HENNA COURT, SANDPOINT, IDAHO 83864
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THAT INVOLVES MANIPULATING THE NERVE CELLS WITHIN THE BRAIN WITH CRISPR OR ANY OTHER APPROACH, YOU ARE FACED WITH THE DIFFICULTY OF HAVING THE BIOMARKER THAT TELLS YOU HOW YOU'RE PROGRESSING.

NOW, PEOPLE HAVE MEASURED HUNTINGTIN ITSELF IN THE EXTRACELLULAR FLUID. AND YOU CAN SHOW, FOR EXAMPLE, IN THE ASO TRIAL THAT YOU DID GET TARGET ENGAGEMENT BECAUSE YOU COULD REDUCE THE LEVEL OF EXPRESSION OF HUNTINGTIN IN THE CSF MEASURABLY. BUT WHETHER THAT WILL BE USEFUL IN A WAY THAT ALLOWS YOU TO JUDGE CHANGES IN REPEAT LENGTH IS NOT AT ALL CLEAR YET, SOMETHING THAT NEEDS TO BE LOOKED AT.

NOW, I WILL GO BACK TO THE POINT THAT THERE ARE A LOT OF DISEASES THAT INVOLVE REPEATS, AND SOMATIC EXPANSION --

CHAIRMAN GOLDSTEIN: CAN YOU START WRAPPING UP REASONABLY QUICKLY?

DR. GUSELLA: ALMOST THERE. SO SOMATIC EXPANSION IS A THERAPEUTIC STRATEGY ACROSS ALL OF THESE, THE ONES THAT SHOW EXPANSION. SO ANYTHING THAT HAPPENS IN HUNTINGTON'S COULD WELL IMPACT ON ALL THESE OTHERS AND, IN FACT, STUDIES IN SOME OF THESE OTHERS COULD IMPACT ON HUNTINGTON'S BECAUSE THE THING THAT'S DIFFERENT, AS WAS POINTED OUT AT THE END OF THE LAST TALK, IS WHICH CELLS DIE, WHICH

IMPLIES THAT THE TOXICITY THEY CAN HIT IS DIFFERENT EVEN IF THE EXPANSION PROCESS IS THE SAME.

SO THAT'S MY END POINT. YOU COULDN'T DO THIS WITHOUT HD PEOPLE, AND THEY'VE BEEN TERRIFIC ABOUT PARTICIPATING IN RESEARCH.

CHAIRMAN GOLDSTEIN: GREAT. THANK YOU VERY MUCH, JIM.

SO LET ME INITIATE THE QUESTIONS WITH ONE IMPLICATION OF WHAT YOU'RE SAYING IS THAT THE DISEASE MAY BE NEURON SPECIFIC, BUT ON THE OTHER HAND MY TAKE ON THE HUMAN NEURODEGENERATIVE PATHOLOGY LITERATURE IS THAT ULTIMATELY ALL CELL TYPES IN THE BRAIN ARE INVOLVED, AND THE GLIA WILL PLAY A MAJOR ROLE. BUT IS HUNTINGTIN AN EXCEPTION TO THAT IN NOT MAKING GLIA A MAJOR PLAYER, OR IS IT JUST UNDERSTUDIED?

DR. GUSELLA: I THINK THAT IT'S AN EXCEPTION IN THE SENSE THAT THE DRIVER OF THE PATHOLOGY IS THE NEURON. BUT, OF COURSE, ONCE YOU'VE GOT PATHOLOGY GOING ON TO THE POINT WHERE YOU UPSET THE TISSUE. AND SO AT THE TIME, FOR EXAMPLE, THAT YOU HAVE ONSET OF HUNTINGTON'S DISEASE, YOU'VE ALREADY LOST 30 TO 40 PERCENT OF THE NEURONS IN THE STRIATUM. SO AT THAT POINT YOU'RE REACTING TO THAT, AND IT'S VERY CLEAR IN MANY DISEASES THAT REACTION

133 HENNA COURT, SANDPOINT, IDAHO 83864
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CAN BE BAD AND CONTRIBUTE TO THEN FURTHER DETERIORATION. BUT I THINK IT IS AN EXCEPTION IN THE SENSE THAT IT SEEMS LIKE IT IS THE NEURON PATHOGENESIS AS A RESULT OF EXPANDED REPEAT THAT DRIVES IT AND THEN OTHER THINGS PARTICIPATE DOWNSTREAM, WHICH IS WHY, IN FACT, WHEN YOU START WITH A HIGHER REPEAT LENGTH, YOU START BRINGING IN MORE NEURONS IN OTHER PARTS OF THE BRAIN BECAUSE THEY GET LONGER EXPANSIONS THAN THEY WOULD OTHERWISE IN THAT PERIOD OF TIME.

CHAIRMAN GOLDSTEIN: INTERESTING. PAT.

DR. LEVITT: UNMUTE. I WAS GOING TO SAY THE BRAIN -- THINGS ARE CONNECTED TO THINGS. NEURONS CONNECT TO NEURONS. AND WHEN YOU DISRUPT THE PRIMARY TARGET, THOSE THAT PROJECT TO THE PRIMARY TARGET MAY BE AFFECTED. SO IT'S REALLY DIFFICULT TO DISENTANGLE THAT, RIGHT, BECAUSE YOU CAN GET TRANSSYNAPTIC NEURODEGENERATION AND GO ALL OVER THE PLACE. IT ONLY TAKES SYNAPSES, SIX SYNAPSES TO CONNECT EVERYTHING TO EVERYTHING IN THE BRAIN. THAT'S NOT MY QUESTION. THAT WAS GREAT, JIM. I JUST WANT TO POINT THAT OUT. IT DOESN'T TAKE MUCH TO GET EVERYTHING CONNECTED.

DR. FISHER: CAN WE STOP THE SLIDE SHARE?

DR. GUSELLA: I CAN.

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DR. LEVITT: THERE HAVE BEEN SEVERAL PAPERS PUBLISHED ON EXPANSION AND REPEAT NEURODEGENERATIVE DISORDERS THAT SPEAK TO THIS ISSUE AROUND EARLY DEVELOPMENTAL PROCESSES BEING DISRUPTED, SORT OF SETTING THE BRAIN UP FOR -- AND THERE MAY BE OTHER FACTORS THAT FINALLY GENERATE THE CLINICAL PRESENTATION, BUT THAT THERE'S A DEVELOPMENTAL COMPONENT TO THESE. THERE'S A FRONTOTEMPORAL DEMENTIA PUBLICATION THAT CAME OUT OF THE (UNINTELLIGIBLE) LAB, THERE WAS A *SCIENCE* PAPER THAT CAME OUT IN 2020 ABOUT HD.

WHAT'S YOUR FEELING ABOUT THAT BECAUSE, AGAIN, THAT RELATES TO BEING ABLE TO AT LEAST MAKE DISCOVERIES ABOUT THE POTENTIAL FOR USING, FOR EXAMPLE, IPS LINES TO UNDERSTAND THE TRAJECTORY OF THOSE DIFFERENTIATED NEURONS THAT HAVE THESE EXPANSION REPEATS?

DR. GUSELLA: YEAH. I RECOGNIZE THAT THERE ARE DIFFERENCES THAT CAN BE MEASURED. AND IT'S REALLY -- IT'S JUST REALLY HARD FOR ME TO BELIEVE WHEN I DEAL WITH THE PEOPLE FOR 40 YEARS WHO ARE CARRYING REPEATS THAT THOSE DIFFERENCES WAY BACK WHEN SET THE BRAIN UP TO BE PARTICULARLY SUSCEPTIBLE TO A PROCESS THAT ONLY OCCURS MUCH LATER WHEN THE REPEAT EXPANDS. I THINK THAT THINGS PARTICIPATE IN

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DEVELOPMENT IN DIFFERENT WAYS, AND I THINK THAT THEY CAN HAVE CONSEQUENCES AT THE TIME THAT YOU'RE MEASURING THEM THAT THEN ARE NOT IMPARTED LATER ON AS SUSCEPTIBILITY TO DISEASE. AND IF YOU DEAL WITH THESE PEOPLE, THERE'S ABSOLUTELY NO WAY TO DISTINGUISH THEM. YOU WOULD NEVER CALL THEM IN ANY WAY DEVELOPMENTALLY DIFFERENT THAN ANYONE ELSE.

SO I THINK THE PROBLEM IS IN PART IN THE SENSITIVITY OF YOUR MEASURES.

DR. LEVITT: OKAY. ALL RIGHT. THANKS.

CO-CHAIR FISHER: LARRY, I HAVE A QUESTION. OKAY. LARRY IS MUTED.

CHAIRMAN GOLDSTEIN: GO AHEAD, YES.

CO-CHAIR FISHER: I ALWAYS THOUGHT OF HUNTINGTON'S DISEASE AS A SINGLE GENE MUTATION DISEASE. AND BASED ON WHAT YOU PRESENTED, I'M STARTING TO RETHINK THAT. BUT I'M WONDERING WHAT YOUR THOUGHTS ARE ABOUT ANTISENSE OLIGONUCLEOTIDES APPROACH TO TREATING HUNTINGTON'S. I DON'T RECALL SEEING YOU MENTION THAT, AND IT SEEMS LIKE A CLEAR MUTATION TO TARGET. ANTISENSE MIGHT BE AN INTERESTING THERAPEUTIC APPROACH.

DR. GUSELLA: YEAH. SO IT'S BEEN TRIED IN TERMS OF KNOCKING OUT OR A REDUCED SUPPRESSANT FOR THAT. SO BY LOWERING THE EXPRESSION OF THE

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FULL-LENGTH PROTEIN. IT HAS BEEN TRIED. THE TRIAL WAS HALTED BECAUSE THE INDIVIDUALS RECEIVING THE TREATMENT WERE DOING A LITTLE BIT WORSE THAN THE PEOPLE WITH THE PLACEBO. AND IT IS NOW BEING TRIED AGAIN IN YOUNGER INDIVIDUALS, BUT THAT'S BASED ON THE ASSUMPTION THAT IT'S THE FULL-LENGTH PROTEIN THAT MATTERS. I THINK THERE WILL PROBABLY BE AN EFFORT TO TARGET THE ANTISENSE OLIGONUCLEOTIDE APPROACH ONLY TO EXON1 BECAUSE IF YOU BELIEVE IN THE POLYGLUTAMINE AGGREGATION HYPOTHESIS FOR ULTIMATE CELL DEATH, YOU COULD TARGET THAT WHETHER IT'S A FULL-LENGTH PROTEIN OR NOT AND STILL HAVE TWO SHOTS ON GOAL INSTEAD OF ONE.

I THINK WE'RE NOT CERTAIN THAT THAT'S GOING TO WORK, BUT THERE ARE TWO PROBLEMS I HAVE WITH IT ULTIMATELY. ONE IS THAT UNLESS THE ANTISENSE OLIGO SOMEHOW ALSO INTERFERES WITH SOMATIC EXPANSION, THAT EVEN IF YOU ARE ABLE TO TEMPORARILY DEAL WITH THE PRODUCT OF THAT EXPANSION, THE EXPANSION IS ONLY GOING TO GET BIGGER AND BIGGER AND BIGGER AND MAY WELL OVERCOME YOUR ABILITY TO TREAT IT.

THE OTHER IS THAT I THINK THAT BY THE TIME YOU REACH THE POINT AT WHICH THE POLYGLUTAMINE PEPTIDE FROM THE FIRST EXON COULD BE A PROBLEM, YOU

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DON'T HAVE THAT MUCH LONGER TO LIVE AS A NEURON. AND SO I JUST THINK IN TERMS OF ULTIMATE TREATMENT, YOUR TARGET WINDOW MAY BE A LOT SHORTER THAN IF YOU'RE ABLE TO BLOCK EVER GETTING TO THAT POINT.

CHAIRMAN GOLDSTEIN: SO, JIM, MAYBE ONE FINAL QUESTION. I DIDN'T GET A CLEAR PICTURE FROM WHAT YOU SAID. WOULD TARGETING THE EXPRESSION OF THE HUNTINGTIN GENE BE A BETTER STRATEGY? I MEAN AS KNOWLEDGE INCREASES OF HOW THE PROMOTER AND ENHANCER ELEMENTS WORK AND INTERACT, THERE WILL BE BIOCHEMICAL WAYS OF LEARNING TO INTERFERE WITH THAT. SO WOULD THAT BE A REASONABLE APPROACH FOR HUNTINGTON?

DR. GUSELLA: IT'S A REASONABLE APPROACH. WHETHER I THINK IT HAS A HIGH LIKELIHOOD OF SUCCESS IS A DIFFERENT QUESTION.

CHAIRMAN GOLDSTEIN: UNFORTUNATE. OKAY. GREAT. SO THANK YOU VERY MUCH FOR YOUR TIME, JIM. THAT WAS TRULY ENLIGHTENING, AND I THINK HAS PROBABLY CHANGED EVERYBODY'S CONCEPTION OF HOW HUNTINGTIN MAY WORK TO CAUSE DISEASE. SO I THINK THAT'S VERY USEFUL.

DR. GUSELLA: THANK YOU.

CHAIRMAN GOLDSTEIN: THANK YOU. YES. SO, ROSA, YOU HAD SOME PRIORITIZATION WORK THAT YOU

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WANTED TO GET THE NEURO TASK FORCE LOOPED IN ON. SO IF YOU'RE READY TO GO, PLEASE TAKE OVER THE SCREEN.

DR. CANET-AVILES: YEAH. THANK YOU. THIS IS FRUIT OF THE LABOR OF THE CIRM TEAM IN COLLABORATION WITH MEMBERS OF THE TASK FORCE. SORRY. I'M JUST WARMING UP.

GREAT PRESENTATION, BY THE WAY.

SO WHAT WE'RE GOING TO DO NOW IS WE'RE GOING TO TALK ABOUT HOW WHAT I PRESENTED EARLIER ON THAT WAS FOLLOWED BY THESE TWO WONDERFUL PRESENTATIONS, HOW DOES IT FEED INTO THIS STRATEGY AND THE NEXT STEPS?

SO DURING THE ICOC MEETING OR LAST ICOC MEETING BACK IN MARCH, THE STAFF PRESENTED TO THE BOARD THE STRATEGIC ALLOCATION FRAMEWORK, THE PROCESS, THE STEPS, WHICH IS A DATA-DRIVEN APPROACH THAT WILL ENABLE CIRM TO REASSESS OUR FUNDING ALLOCATIONS FOCUSING ON POTENTIAL, IMPACT POTENTIAL, PATIENT REACH, TECHNOLOGICAL FEASIBILITY, AND PROSPECTS OF REGULATORY APPROVAL AMONGST OTHERS.

WHAT WE ARE PRESENTING TODAY IS HOW DOES THE NEURO TASK FORCE EFFORTS, HOW DO THEY FIT WITHIN THESE? NEXT.

SO THIS WAS THE KICKOFF WITH THE STAFF IS THE STRATEGIC ALLOCATION FRAMEWORK, WHICH STANDS FOR

PRIORITIZATION, BUT LITTLE BIT MORE SPECIFIC NAMING. AND WE ARE CURRENTLY UNDERGOING THE DATA -- WELL, THE GUIDING QUESTIONS WE ARE GATHERING AND GATHERING DATA AS WELL. AND WE ARE HOPING TO -- NOT HOPING -- WE ARE COMING TO THE BOARD WITH RECOMMENDATIONS IN SEPTEMBER, AND THEN WE'LL HAVE THE IMPLEMENTATION. NEXT SLIDE.

SO THIS SLIDE PROVIDES A SNAPSHOT OF CIRM'S REMAINING FUNDS THAT WE SAW BACK IN MARCH FOR THE STRATEGIC ALLOCATION, WHICH IS THE FOCUS OF THE STRATEGIC ALLOCATION FRAMEWORK EXERCISE AS WE PRESENTED DURING THE ICOC. THE FIELD OF REGENERATIVE MEDICINE HAS GROWN EXPONENTIALLY. IT'S STILL GROWING IN THE PAST 17 YEARS, AND WE HAVE FINITE RESOURCES. THEREFORE, WE ARE LEADING TO THIS PRIORITIZATION.

FOR THE NEURO RESEARCH SPECIFICALLY, WE HAVE 1.11 BILLION LEFT FOR THE ALLOCATION. SO WITHOUT SPECIFIC ACTION, WE ACTUALLY ARE SPENDING AT A HIGHER RATE THAN WHAT WAS EARMARKED BY THE PROPOSITION 14. NEXT SLIDE.

SO THE FOLLOWING IS THE PROCESS THAT WE PRESENTED BACK AT THE ICOC IN MARCH. THIS IS THE PROCESS THAT OUR TEAM IS INTEGRALLY INVOLVED IN FOLLOWING FOR THE STRATEGIC ALLOCATION FRAMEWORK,

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DEFINING THE IMPACT GOALS. CURRENTLY WE ARE DESIGNING CATEGORIES. THE IMPACT GOALS WILL BE FINALIZED ONCE WE HAVE THE RECOMMENDATIONS. WE HAVE SOME IDEA, BUT WE ARE HAVING AN ITERATIVE PROCESS. SO I'M GOING TO CALL THEM CATEGORIES; BUT WHEN I SAY CATEGORIES, THINK ABOUT MEASURABLE GOALS THAT WE WILL BE COMING WITH AT THE END.

THEN WE HAVE THE GUIDING QUESTIONS. THAT'S THE FORMULA THAT WE'VE DESIGNED TO PROBE DEEPLY INTO THE POTENTIAL IMPACT FEASIBILITY AND ALIGNMENT WITH OUR MISSION. AND THEY SERVE, THESE QUESTIONS, AS A CRITICAL TOOL FOR DECISION-MAKING, HELPING TO CLARIFY OBJECTIVES AS WE DEFINE OUR STRATEGIC DIRECTION. WHY AM I MENTIONING THIS IS BECAUSE THE NEURO TASK FORCE HAS ALSO DEVELOPED QUESTIONS THAT I'M GOING TO GO THROUGH. AND WE WILL BE GATHERING DATA AS WELL THAT WILL LEAD TO RECOMMENDATIONS. SO THE NEURO TASK FORCE WILL INFORM SPECIFIC ASPECTS OF THE RECOMMENDATION FOLLOWING THIS PROCESS. NEXT SLIDE.

THESE ARE THE FOUR CATEGORIES. AS I WAS SAYING, THE GOALS, THE IMPACT GOALS, WILL BE FRAMED WITHIN THESE CATEGORIES. THE FIRST ONE IS APPROVAL OF CELL AND GENE THERAPIES, THE SECOND IS THE ACCESSIBILITY AND AFFORDABILITY OF CIRM-FUNDED CELL

AND GENE THERAPIES. THE THIRD ONE IS THE DISCOVERY OF NOVEL DISEASE MECHANISMS. AND THE FOURTH ONE IS DIVERSE WORKFORCE DEVELOPMENT.

AND THE FIRST THREE ARE ACTUALLY CATEGORIES AND GOALS IN WHICH THE NEURO TASK FORCE HAS DIRECT RECOMMENDATIONS WITHIN.

SO NEXT SLIDE IS THE DESIGN QUESTIONS. AS YOU CAN SEE, IT'S A VERY PARALLEL INTEGRATED EXERCISE. THE ORIGINAL QUESTIONS FOR THE STRATEGIC ALLOCATION FRAMEWORK WERE THESE QUESTIONS WITHOUT THE SPECIFICATION OF NEURO, AND THE BUDGET WAS THE FULL BUDGET OF 3.54 BILLION. SO OUR SPECIFIC QUESTIONS FOR THE NEURO TASK FORCE IS TO DETERMINE HOW CAN CIRM MAKE THE GREATEST IMPACT OF ITS MISSION IN THE NEURO SPACE WHICH WILL FEED TO THOSE THREE CATEGORIES, THREE GOALS? AND HOW MIGHT CIRM EFFECTIVELY ALLOCATE ITS REMAINING NEURO BUDGET FOR $1.11 BILLION. NEXT SLIDE.

SO THE QUESTIONS, THESE ARE THE POTENTIAL ELEMENTS THAT WILL HAVE AN IMPACT THAT THE PLAN SHOULD ADDRESS, THE RECOMMENDATION SHOULD ADDRESS. AND THESE ARE A CRITICAL TOOL FOR DECISION-MAKING, HELPING US CLARIFY THE OBJECTIVES AND REFINE THE STRATEGIC DIRECTION WITHIN NEURO, BUT ALSO WITHIN OUR OVERALL STRATEGIC ALLOCATION FRAMEWORK.

THEY FIT INTO THE THREE CATEGORIES, AS I MENTIONED, AND I'LL JUST GO THROUGH THERE. SO THE FIRST ONE IS SHOULD ANY AREAS OF NEURO BE SINGLED OUT FOR ENHANCED FUNDING, FOR EXAMPLE? ANOTHER QUESTION COULD BE WHAT CRITERIA SHOULD GUIDE ANY REVISIONS TO OUR CURRENT PORTFOLIO, FUNDING PORTFOLIO? AND WHAT ADJUSTMENTS MIGHT BE NEEDED?

THE STRATEGIC DIRECTION IN RESEARCH PHASES. HOW SHOULD WE DELINEATE OUR FOCUS BETWEEN TRANSLATIONAL, CLINICAL, AND DISCOVERY STAGES WITHIN NEURO RESEARCH?

SHOULD WE HAVE ANY SPECIFIC PROJECTS, SPECIAL PROJECT FUNDING ALLOCATION? WHAT PROPORTION AND, IF ANY, OF OUR NEURO BUDGET SHOULD BE EARMARKED FOR TASK FORCE IDENTIFIED PROJECTS? ONE OF THE QUESTIONS HAS BEEN WHETHER WE SHOULD SET ASIDE ANY FUNDING FOR REPURPOSING SMALL MOLECULES FOR CLINICAL TRIALS IN NEURO.

WHAT'S THE NEURO TASK FORCE SCOPE? THE FIELD OF NEURODEGENERATION AND NEURO-INJURY. ARE THERE OTHER AREAS THAT THE NEURO TASK FORCE SHOULD CONSIDER BEFORE FINALIZING OUR PLAN? AND WHAT'S THE PROCESS THAT WE WILL FOLLOW TO DO THIS?

SO THE NEXT STEP IN MAKING THESE RECOMMENDATIONS IS TO ANSWER THOSE QUESTIONS, BUT WE

NEED TO ANSWER THOSE QUESTIONS BASED ON A RIGOROUS ANALYSIS TO UNDERSTAND THE LANDSCAPE, TO EVALUATE OPPORTUNITIES, TO ASSESS RISKS. AND THIS STEP IS ESSENTIAL IN ORDER TO MAKE INFORMED DECISIONS THAT ARE BACKED EMPIRICALLY BY EVIDENCE, RIGHT.

SO WHAT WE'VE DONE IS WE HAVE TRANSLATED THE QUESTIONS AND DEVELOPED THE TYPE OF DATA THAT WE NEED IN ORDER TO ANSWER THOSE QUESTIONS. AND THE CIRM TEAM TOGETHER WITH THE NEURO TASK FORCE WOULD BE -- WELL, THE CIRM TEAM COULD BE GATHERING THE DATA. WE COULD PROVIDE THE ANALYSIS. AND IT COULD FIT INTO THE STRATEGIC ALLOCATION FRAMEWORK, RIGHT, WITH THE NEURO TASK FORCE.

SO THE FIRST ONE IS TO FIGURE OUT WHAT THE PREVALENCE OF BURDEN OF NEUROLOGICAL CONDITIONS IN CALIFORNIA TO ANSWER THE FOCUSED NEURO INVESTMENT, RIGHT. TO HAVE A LANDSCAPE ANALYSIS OF OUR CURRENT RESEARCH FUNDING AND GAPS -- CURRENT RESEARCH FUNDING AND GAPS IN THE NEURO FIELD, NOT ONLY OURS, BUT ALSO EXTERNAL TO SEE WHAT ARE THE GAPS, ET CETERA. TO GATHER EXPERT CONSENSUS ON EMERGING AREAS WITHIN NEUROSCIENCE WITH HIGH POTENTIAL FOR BREAKTHROUGHS. THIS IS WHAT WE ARE DOING THROUGH THESE DIFFERENT MEETINGS THAT WE HAVE HAD WITH THESE FOUR SPECIALISTS THAT WE HAVE HAD SO FAR.

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TO HAVE A PORTFOLIO REASSESSMENT. GATHERING HISTORICAL PERFORMANCE DATA OF FUNDED PROJECTS. A COMPARATIVE ANALYSIS OF OUR FUNDING PORTFOLIOS AND STRATEGIES WITH PEER ORGANIZATIONS. THERE ARE MANY OTHER ORGANIZATIONS, NON-PROFIT AND FOR-PROFIT, THAT ARE FUNDING, ALSO THE NIH, OTHER NEURODEGENERATION AND NEURODEVELOPMENTAL AND PSYCHIATRIC ORGANIZATIONS. I DON'T WANT TO SAY SPECIFIC NAMES, NOT TO GATHER BAD ATTENTION, BUT THE NEXT ONE COULD BE DATA ON INDUSTRY TRENDS --

CHAIRMAN IMBASCIANI: ROSA, COULD I ASK YOU TO FINISH UP RELATIVELY QUICKLY? I THINK PEOPLE CAN READ IT IF WE CIRCULATE IT.

DR. CANET-AVILES: GOT IT. GOT IT.

CHAIRMAN GOLDSTEIN: WE HAVE MULTIPLE MEMBERS OF THE PUBLIC.

DR. CANET-AVILES: YES. GOING DO THE LAST SLIDE WHICH IS THE IMPORTANT ONE. SO I JUST WENT THROUGH THAT. HOW DOES THIS FIT WITH THE NEXT STEPS? SO AS YOU CAN SEE, THE STRATEGIC ALLOCATION FRAMEWORK AND THE NEURO TASK FORCE ARE CURRENTLY DEVELOPING QUESTIONS, GATHERING ANALYSIS, AND BY SEPTEMBER WE COULD COME WITH RECOMMENDATIONS THAT WOULD FIT INTO THE SAF. AND THEN IMPLEMENTATION, WE WOULD IMPLEMENT THE NEURO TASK FORCE RECOMMENDATIONS

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POTENTIALLY THROUGH EXPANDING, FOR EXAMPLE, THE DISC4 PROGRAM, INPUT AND PRIORITIZATION OF NEURODISEASES FOR CLINICAL PROGRAMS AND POTENTIALLY SPECIFIC CALLS. THOSE ARE JUST SOME OF THE POTENTIAL WAYS THAT WE COULD MOVE FORWARD. AND WITH THAT, WE ARE DONE HERE. THANK YOU, LARRY.

CHAIRMAN GOLDSTEIN: THANK YOU VERY MUCH, ROSA. THAT'S A VERY HELPFUL FRAMEWORK. LET ME JUST TELL THE TASK FORCE WE WILL SPEND THE NEXT MEETING, WHICH WILL BE LATE MAY OR EARLY JUNE, ON DISCUSSING THESE ISSUES. OBVIOUSLY IT WILL BE A STRUCTURED DISCUSSION, BUT IT IS TIME TO START ASKING THAT, AND AT AN INTERMEDIATE POINT, THEN WE'LL LOOK AT NEURO-INJURY AS AN ADDITIONAL AREA.

SO, CLAUDETTE, CAN YOU CALL ON THE MEMBERS OF THE PUBLIC? I THINK YOU HAVE THEIR IDENTITIES OR CONTACT INFORMATION.

MS. MANDAC: YES. GIVE ME JUST A SECOND TO SWITCH OVER THE AUDIO TO A DIFFERENT ROOM.

CHAIRMAN GOLDSTEIN: THANK YOU.

MS. MANDAC: CAN YOU HEAR US, LARRY?

CHAIRMAN GOLDSTEIN: YES.

MS. MANDAC: YES. OKAY. ALL RIGHT. SO THE FIRST ONE OF OUR PUBLIC COMMENTERS IS JARY LARSEN FROM AFTD. YOU HAVE THREE MINUTES. I WILL

STOP YOU WHEN THE CLOCK IS UP.

DR. LARSEN: THANK YOU. MY NAME IS JARY LARSEN. I'M A CLINICAL NEUROPSYCHOLOGIST, AND I WORK AT A LARGE TEACHING HOSPITAL. AND I ALSO WANT TO JUST FOR TRANSPARENCY, I DO KNOW A FEW PEOPLE WHO EITHER ARE IN THE ROOM OR WERE ALSO SPEAKING EARLIER. AND I DID COME WITH SOME THINGS THAT WERE PREPARED, BUT A LOT OF THIS HAS CHANGED LISTENING TO ALISON GOATE SPEAK.

SO I AM HERE TO ADVOCATE FOR THE INCLUSION OF FRONTOTEMPORAL DEGENERATION OR FTD AS ONE OF THE NEURODEGENERATIVE DISEASES THAT CAN POSSIBLY RECEIVE CIRM FUNDING.

I SERVE ON THE BOARD OF THE ASSOCIATION FOR FRONTOTEMPORAL DEGENERATION OR AFTD. IN ADDITION, AND I THINK MORE IMPORTANTLY, I COME FROM A LARGE FAMILY THAT HAS A LOT OF PROGRANULIN FTD. MY BROTHER DIED FROM FTD. I HAVE A SISTER WHO IS CURRENTLY IN CARE FOR FTD. MY FATHER, MY UNCLE, THEIR FATHER AND GRANDFATHER ALL DIED FROM FTD, OR AT LEAST WHAT WOULD BE CONSIDERED FTD AT THIS POINT.

AS MOST OF YOU -- AS SOME OF YOU MAY KNOW, FTD IS PARTICULARLY DEVASTATING BECAUSE OF THE EARLY ONSET OF THE DISEASE AND HOW IT FREQUENTLY IS IMPACTING INDIVIDUALS WHEN THEY ARE AT THE HEIGHT OF

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THEIR CAREERS ONLY TO HAVE EVERYTHING COME CRASHING DOWN, ESPECIALLY AROUND THE FAMILY. IN ADDITION, THE PATH TO DIAGNOSE, ESPECIALLY FOR THOSE WITH SPORADIC FORMS OF FTD, CAN BE VERY LONG AND ARDUOUS AND TYPICALLY INVOLVES MULTIPLE CLINICIANS WITH MULTIPLE DIFFERENT DIAGNOSES, FREQUENTLY INCLUDING A DIAGNOSIS OF SOME SORT OF LATE ONSET MENTAL HEALTH DISORDER. I THINK AT THIS POINT WE REALLY UNDERSTAND THAT IF THERE'S A LATE ONSET MENTAL HEALTH DISORDER, IT IS ALMOST ALWAYS NEURODEGENERATIVE. IT'S NOT A MORE PRIMARY CLASSIC MENTAL HEALTH DISORDER.

I KNOW THAT THERE'S SOME OTHER LETTERS THAT HAVE BEEN SUBMITTED. I DON'T WANT TO SPEAK TO THAT, BUT I DO JUST WANT TO TALK ABOUT SOME OF THE STUFF THAT ALISON GOATE HAD BEEN TALKING ABOUT. AND I MET HER AT A CONSORTIUM MEETING ABOUT A MONTH AGO WHEN I WAS INVITED A GUEST THERE. FOR THOSE OF YOU WHO DON'T KNOW, ALISON GOATE'S LAB WAS ONE OF THE LABS THAT WAS INVOLVED IN THE IDENTIFICATION OF THE MAP TEACHING, WHICH IS IMPLICATED IN FTD. I'D BE REALLY CURIOUS TO KNOW WHAT HER THOUGHTS ARE ABOUT INCLUDING FTD. BUT I THINK SHE TOUCHED ON SOME REALLY IMPORTANT POINTS, AND THAT IS THERE IS A LOT WITH FTD AND ESPECIALLY THE GENETIC FORMS. THERE'S

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A LOT OF MISDIAGNOSIS. AND LOT OF THESE INDIVIDUALS ARE DIAGNOSED WITH ALZHEIMER'S DISEASE. MY BROTHER WAS DIAGNOSED WITH ALZHEIMER'S DISEASE AT 54. I HAD TO FIGHT BACK, AND I'M GOING TO LEAVE IT AT THAT. SO THANK YOU VERY MUCH.

MS. MANDAC: THANK YOU SO MUCH.

CHAIRMAN GOLDSTEIN: THANK YOU VERY MUCH. LET ME JUST INTERJECT. DURING THE PROP 71 ERA, WHICH WAS OUR INITIAL TIME, I LOOKED IT UP AND THERE WERE TWO FTD GRANTS THAT WERE FUNDED. AND I CERTAINLY DON'T HAVE THE SENSE THAT OUR REVIEWERS WOULD HAVE ANY PREJUDICE AGAINST GOOD PROJECTS IN THIS AREA. SO I DO APPRECIATE THE NEED FOR FTD RESEARCH, BUT IT'S NOT OBVIOUS TO ME THAT WE'VE NEGLECTED IT WHEN THERE HAVE BEEN GOOD PROJECTS SUBMITTED.

WHO'S NEXT PLEASE?

MS. MANDAC: WE HAVE PURVI KUNWAR FROM PRECISION NEURO MEDICINE.

DR. KUNWAR: THANK YOU VERY MUCH. MY NAME IS PURVI KUNWAR. I'M REPRESENTING PRECISION NEURO MED. WE ARE A CNS THERAPEUTICS COMPANY THAT STARTED IN 2022. INITIALLY WE ARE GOING TO BE LOOKING AT ALS, BUT WE ARE ACTUALLY STARTING TO BUILD OUT A (INAUDIBLE) DELIVERY MECHANISM TO THE BRAIN.

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SO ONE INITIAL QUESTION I HAVE IS ARE (UNINTELLIGIBLE) CONSIDERED PART OF THE MARKETING RFP, THE FIRST ONE?

AND THE SECOND ONE IS WHEN DO WE THINK THAT CLIN1 AND CLIN2 MIGHT COME BACK? THE QUESTION IS GLIA MUST BE CONSIDERED PART OF THE REMIND RFP THAT WE HAVE OUT RIGHT NOW?

DR. CANET-AVILES: IT'S AN RFA. DISC4 IS ONE THAT I MENTIONED AS A FOCUS OF NEUROPSYCHIATRIC DISEASES. SO WE WILL BE FOLLOWING THAT TO DEVELOP ALL THESE QUESTIONS FOR THE NEURO TASK FORCE, AND WE'LL SEE WHAT HAPPENS IN THE NEXT ITERATIONS IF THERE ARE. THANK YOU.

DR. THOMAS: I'LL TAKE THE SECOND QUESTION. SO WE'RE GOING TO BE GOING BACK TO THE BOARD IN JUNE TO DISCUSS A NUMBER OF THINGS WITH RESPECT TO THE PRIORITIZATION. ALSO, WE JUST DO FLOW CONTROL WITH RESPECT TO CLIN1 AND CLIN2S AT THAT TIME. SO THE ANSWER WILL BE COMING AT THAT MEETING.

CHAIRMAN GOLDSTEIN: THANK YOU, J.T. CLAUDETTE, IS THERE ANYBODY ELSE WHO WANTS TO ADDRESS US?

MS. MANDAC: YES. WE HAVE TWO MORE INDIVIDUALS ON THE ZOOM LINE. BOTH ARE PHONE

NUMBERS. SO I'M GOING TO READ OFF THE NUMBER. (212) 390-1392. IF YOU COULD UNMUTE. THE PHONE NO. (212) 390-1392. OKAY. WE'RE GOING TO MOVE ON TO THE NEXT NUMBER. (760) 807-6696, IF YOU'D STILL LIKE TO MAKE PUBLIC COMMENT, PLEASE UNMUTE.

MS. SMITH: THANK YOU. CAN YOU HEAR ME?

MS. MANDAC: YES.

MS. SMITH: ALL RIGHT. GREAT. GOOD AFTERNOON, DR. GOLDSTEIN AND THE MEMBERS OF THE CIRM AND NEURO TASK FORCE. MY NAME IS WANDA SMITH. AND IT'S A VERY DEEP PLEASURE TO SPEAK WITH YOU.

AS A CALIFORNIA RESIDENT, I WOULD ENCOURAGE THE TASK FORCE TO INCLUDE FTD AS A NEURODEGENERATIVE DISEASE IN YOUR FUNDING. I BELONG TO A LARGE DEMENTIA FAMILY WITH FIVE-GENERATION PEDIGREE, WELL CHARACTERIZED AND STUDIED FOR MORE THAN 40 YEARS. WE'VE SUFFERED GREAT LOSSES DUE TO FTD PROGRANULIN, ALZHEIMER'S DISEASE, AND PARKINSON'S.

SYMPTOMS PRESENT AS A SINGLE DISEASE CAUSING MUCH CONFUSION AMONG THE NEUROLOGISTS AND FAMILY MEMBERS. HOWEVER, GENETIC TESTING IS THE ONLY WAY TO ACCURATELY IDENTIFY DISEASE. THE DISEASES AFFECT US AT DIFFERENT AGES AND DIFFERENT LENGTHS OF TIME. PROGRANULIN AGES 40 TO 84,

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ALZHEIMER'S IN THEIR '80S, PARKINSON'S 60 YEARS AND OVER, WITH A VARYING LENGTH OF TIME FROM THREE TO NINE YEARS.

FTD PROGRANULIN FAMILY MEMBERS UNDERSTAND THAT THEY ARE DEFICIENT IN THE PROTEIN OF PROGRANULIN. WHY THE DIFFERENT AGES AND LENGTH OF THE DISEASE WE DO NOT KNOW. BUT WE DO KNOW THAT PROGRANULIN MAY PLAY A ROLE IN ALZHEIMER'S DISEASE AND OTHER DISEASES TOO. TO ME IT'S ALL ABOUT THE PROTEINS.

CLINICAL DIAGNOSIS FOCUSING ON MEMORY AND MOVEMENT ARE CHALLENGING, BUT IDENTIFYING CLEAR BIOMARKERS OF THESE NEURODEGENERATIVE DISEASES ACROSS THE LANDSCAPE OF MY FAMILY IS VERY IMPORTANT. I LEAD AN ALZHEIMER'S SUPPORT GROUP AND ENCOURAGE CAREGIVERS TO CONSIDER GETTING THEIR LOVED ONES GENETICALLY TESTED IF THEY SEE MULTIPLE DISEASES OCCURRING WITHIN THE FAMILY. LAST YEAR SIX FAMILIES CLINICALLY DIAGNOSED WITH ALZHEIMER'S DISEASE RECEIVED STARTLING GENETIC REPORTS. THEY WEREN'T ALZHEIMER'S AT ALL. THREE FAMILIES HAD FTD CAUSED BY C9ORF72, AND TWO FAMILIES HAD LEWY BODY, AND ONE WAS UNKNOWN.

THE NUMBER OF FTD MAY NOT BE ACCURATE DUE TO THE LACK OF EPIDEMIOLOGICAL STUDIES AND USING

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LANGUAGE THAT CURRENTLY IS 115 YEARS OLD CREATES MUCH CONFUSION AND CHAOS TO OUR FAMILY.

IN SUMMARY, DR. BOB KATZMAN, THE PIONEER OF ALZHEIMER'S DISEASE IN 1984 SAID IT BEST. "GENETIC FAMILIES WILL BE THE GUIDING LIGHT INTO THE MECHANISMS OF CELLULAR DISCOVERY AND MAY HOLD THE KEY TO UNRAVELING MOST, IF NOT ALL, OF THE NEUROLOGICAL DISEASES."

SO IN CLOSING, THANK YOU FOR YOUR TIME, AND I ENCOURAGE YOU TO PUT FTD AS THE CENTERPIECE IN THE FUNDING. THANK YOU.

CHAIRMAN GOLDSTEIN: OKAY. THANK YOU VERY MUCH FOR THAT. CLAUDETTE, DOES 212 HAVE THEIR HAND BACK UP?

MS. MANDAC: YES. THEY'VE RAISED THEIR HAND AGAIN. (212) 390-1392. OKAY. PLEASE START NOW.

SPEAKER: THANK YOU. CAN YOU HEAR ME NOW? I TRIED TO UNMUTE LAST TIME, BUT FAILED. I APOLOGIZE.

MS. MANDAC: NO WORRIES.

SPEAKER: THANK YOU SO MUCH. THIS IS PENNY DACKS ALSO WITH THE ASSOCIATION FOR FRONTOTEMPORAL DEGENERATION. I AM NOT GOING TO REPEAT WHAT YOU JUST HEARD FROM WANDA AND FROM JARY

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WHO SPOKE ELOQUENTLY ABOUT THE MANY DIFFERENT ASPECTS OF FTD. AS THE HEAD OF THE AFTD SCIENCE TEAM, I'LL CALL OUT A COUPLE ASPECTS OF THE SCIENCE HERE THAT I THINK SHOULD BE REALLY CONSIDERED. WELL, FRANKLY, WE'RE URGING YOU TO CONSIDER FTD IN YOUR FUNDING FOCUS AT A STRATEGIC LEVEL.

SO I USED TO WORK IN THE ALZHEIMER'S AND DEMENTIA SPACE AS WELL. AND I THINK ONE THING I THINK YOU SHOULD CONSIDER IS THAT FTD IS ALSO AN EARLIER ONSET DISEASE. IN ALZHEIMER'S DISEASE AND MOST OTHER CAUSES OF DEMENTIA THAT HAPPEN LATER IN LIFE, CO-PATHOLOGY IS THE NORM, NOT THE EXCEPTION.

WE HAVE INCREDIBLE FAILURE RATES IN THE CLINICAL TRIALS FOR THE THERAPIES DESPITE MASSIVE INVESTMENT IN ALZHEIMER'S DISEASE IN PARTICULAR. AND IF YOU LOOK AT THE ACTUAL STAGE AT THE AUTOPSY, IT IS THE COMBINATION OF PATHOLOGY IN THOSE LATER ONSET DEMENTIAS, COMBINATIONS OF PATHOLOGY EVEN IN PEOPLE DIAGNOSED WITH ALZHEIMER'S. IT IS THE MOST STRONG CORRELATE WITH THE SEVERITY OF SOMEBODY'S COGNITION AND FUNCTION AT THE TIME OF THEIR DEATH.

IT'S NOT REALLY SURPRISING TO ME THAT WHEN YOU HAVE A TREATMENT THAT TARGETS ONE FORM OF ALZHEIMER'S PATHOLOGY, YOU'RE NOT SEEING THE BENEFIT THAT YOU MIGHT SEE BECAUSE THERE ARE OTHER FORMS OF

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PATHOLOGY DRIVING THIS AS WELL. THAT'S A THEORY. I DON'T KNOW IF THAT'S THE ANSWER. NOBODY REALLY DOES. BUT THE REALITY IS THAT THE EARLIER ONSET DEMENTIAS ARE PARTICULARLY TRAUMATIC. THEY'RE ALSO RELATIVELY SINGLE PATHOLOGY, WHICH IS AN OPPORTUNITY FOR THE WHOLE FIELD OF NEURODEGENERATION TO SEE IF WE CAN GET OVER THIS INCREDIBLE CONTINUED FAILURE RATE IN BEING ABLE TO HAVE THE TRANSFORMATIVE IMPACT THAT WE WANT TO HAVE ON THE FAMILIES.

THE SECOND REASON TO CONSIDER IT IS THAT FTD RESEARCH AND CIRM INVESTMENT COULD BE EXTREMELY TIMELY AND INFLUENTIAL FOR A FIELD THAT GETS DRASTICALLY LESS FUNDING. SO I'M A HUGE ADVOCATE FOR ALZHEIMER'S RESEARCH AS WELL, BUT ALZHEIMER'S ALSO GETS MORE MONEY FROM THE NIH THAN ALL OTHER FORMS OF DEMENTIA COMBINED, AND IT HAS FOR MANY, MANY YEARS.

SO IF YOU THINK ABOUT THE INFLUENCE OF ADDITIONAL INVESTMENT FROM CIRM, CIRM'S IMPACT COULD BE TRANSFORMATIVE FOR THE FIELD OF FTD. WE HAVE HAD INCREDIBLE PROGRESS OVER THE LAST TEN YEARS DUE TO CHANGE IN PROGRESS OF BIOMARKERS AND UNDERSTANDING OF THE DISEASE AND THE CLINICAL RESEARCH INFRASTRUCTURE. OUR NON-PROFIT HAS A RECENT ROUNDTABLE RIGHT NOW WITH 12 COMPANIES WITH ACTIVE

PARTICIPATION FROM THE FDA AND THE EMA. BUT THE BASE OF SCIENTIFIC KNOWLEDGE IS STILL VERY LIMITED COMPARED TO WHAT IT IS FOR ALS, FOR ALZHEIMER'S, AND FOR MANY OTHER FIELDS.

SO WE HAVE SPECIFIC KNOWLEDGE GAPS THAT WE'D BE HAPPY TO SHARE WITH YOU IF AND WHEN THAT IS HELPFUL, BUT IN THREE MINUTES WE DIDN'T WANT TO GO INTO THAT. SO BE HAPPY TO SHARE MORE. THANK YOU VERY MUCH FOR LISTENING.

MS. MANDAC: THANK YOU SO MUCH. TERRY, WE ARE SEEING YOU ON VIDEO. WE'RE NOT QUITE SURE IF YOU'VE BEEN TRYING TO RAISE YOUR HAND.

CHAIRMAN GOLDSTEIN: NO, I DON'T SEE ANY HANDS UP.

MS. MANDAC: WE DO HAVE A VIDEO FROM TERRY'S IPHONE WHERE I THINK SHE MAY HAVE TROUBLE WITH AUDIO. TERRY, CAN YOU HEAR US?

CHAIRMAN GOLDSTEIN: I THINK WE'RE GOING TO HAVE TO ADJOURN UNLESS THIS PERSON FIGURES OUT HOW TO GENERATE IPHONE FROM THEIR WORKSTATION.

DR. LARSEN: VERY QUICKLY, TERRY IS AN ADVOCATE FROM THE C9 COMMUNITY FOR THE SACRAMENTO AREA. HER HUSBAND AND HIS TWO BROTHERS ALL DIED FROM FTD/ALS. AND I THINK THAT'S ONE OF THE THINGS THAT SHE WANTED TO TALK ABOUT WAS WITH THE C9

MUTATION, YOU NEVER KNOW EXACTLY WHAT YOU'RE GOING TO GET. AND I THINK SHE WANTED TO MAKE THE CASE THAT IT'S IMPORTANT TO FUND ALS. IT'S ALSO REALLY IMPORTANT TO FUND THE FTD COMPONENT. AND I HOPE THAT'S CORRECT, TERRY. I APOLOGIZE IF I GOT IT WRONG.

CHAIRMAN GOLDSTEIN: THANK YOU. IT'S A GREAT POINT. IT SPEAKS TO THE INTERRELATEDNESS OF THESE DISORDERS AND HOW FINDING A THERAPY FOR ONE MAY HELP THE OTHERS. SO WE APPRECIATE IT. THANK YOU.

I THINK WE'RE GOING TO NEED TO ADJOURN. WE'RE OVER TIME. VERY SUBSTANTIVE MEETING TODAY. THANK YOU ALL FOR YOUR PATIENTS IN STICKING IT OUT TO THE END HERE. WE WILL SEE YOU IN A BIT OVER A MONTH.

VICE CHAIR BONNEVILLE: THANKS.

MS. MANDAC: THANK YOU ALL.

(THE MEETING WAS THEN CONCLUDED AT 2:06 P.M.)

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REPORTER'S CERTIFICATE

I, BETH C. DRAIN, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT OF THE VIRTUAL PROCEEDINGS BEFORE THE TASK FORCE ON NEUROSCIENCE AND MEDICINE OF THE INDEPENDENT CITIZEN'S OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD ON APRIL 17, 2024, 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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