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: MARCH 22, 2024
10 A.M.

REPORTER: BETH C. DRAIN, CA CSR
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FILE NO.: 2024-15

I N D E X

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MARCH 22, 2024; 10 A.M.

(THE MEETING WAS DULY CALLED TO ORDER BY CHAIRMAN GOLDSTEIN, AND THE ROLL CALLED AS FOLLOWS:)

MS. MANDAC: LEONDRA CLARK-HARVEY.

DR. CLARK-HARVEY: HERE.

MS. MANDAC: MARIA BONNEVILLE. MARK-FISCHER-COLBRIE. FRED FISHER.

DR. FISHER: HERE.

MS. MANDAC: JUDY GASSON.

DR. GASSON: HERE.

MS. MANDAC: LARRY GOLDSTEIN.

CHAIRMAN GOLDSTEIN: HERE.

MS. MANDAC: DAVID HIGGINS.

DR. HIGGINS: HERE.

MS. MANDAC: VITO IMBASCIANI.

CHAIRMAN IMBASCIANI: HERE.

MS. MANDAC: STEVE JUELSGAARD. PAT LEVITT. LAUREN MILLER-ROGEN. MARV SOUTHARD.

DR. SOUTHARD: HERE.

MS. MANDAC: THANK YOU SO MUCH, MARV. LARRY, BACK TO YOU.

CHAIRMAN GOLDSTEIN: OKAY. GREAT. THANK YOU. SO LET ME JUST GIVE A COUPLE OF BRIEF REMARKS BEFORE WE GET GOING, AND THEN I'LL TURN IT OVER TO

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ROSA. WE'RE JUST COMING BACK FROM A BRIEF HIATUS. OUR NEXT TOPIC IS NEURODEGENERATION. AND SO WE'LL PROCEED BY GETTING A HANDLE ON WHAT WE CURRENTLY HAVE IN OUR PORTFOLIO, WHICH IS WHAT ROSA WILL COVER THIS MORNING. AND THEN THIS MONTH WE'LL HEAR FROM ALS EXPERT JEFF ROTHSTEIN AND PARKINSON EXPERT LORENZ STUDER, BOTH PATHFINDERS AND RESEARCHERS AT THE CUTTING-EDGE OF THEIR FIELDS SCIENTIFICALLY AND MEDICALLY. AND THEN NEXT MONTH WE'LL HEAR, I HOPE, FROM ALISON GOATE ON ALZHEIMER'S DISEASE AND SARAH TABRIZI ON POLYGLUTAMINE DISEASES, IN PARTICULAR HUNTINGTON, AND WE'LL HAVE SOME TIME TO BEGIN DISCUSSING WHAT OUR NEXT STEPS MIGHT BE IN THIS AREA.

SO WITHOUT FURTHER ADO, LET ME GIVE YOU ROSA. ROSA, YOU'VE GOT ABOUT 25 MINUTES TO WORK ON THE NEURODEGENERATIVE REVIEW PLEASE.

DR. CANET-AVILES: OKAY. THANK YOU, LARRY. KELLY, CAN YOU SHARE THE SLIDES PLEASE. WE HAVE A TANDEM SITUATION SO THAT I COULD ACCESS MY SCREEN. THANK YOU, KELLY. FANTASTIC.

SO THANK YOU, DR. GOLDSTEIN, MEMBERS OF THE NEURO TASK FORCE, DR. STUDER AS WELL, IT IS AN HONOR TO HAVE YOU WITH US, AND THE PUBLIC. I WILL BE PROVIDING A COMPREHENSIVE OVERVIEW OF OUR

NEURODEGENERATION PORTFOLIO ANALYSIS THAT HAS BEEN DEVELOPED THROUGH CONCERTED EFFORTS FROM DR. CREASEY, MYSELF, AND OUR DEDICATED PROGRAM TEAMS.

BEFORE WE DIVE INTO THE SPECIFICS, I ACTUALLY WOULD LIKE TO TAKE A MOMENT TO ACKNOWLEDGE THE WORK OF OUR COLLEAGUES, DR. JANIE BYRUM, DR. KELLY SHEPARD, DR. SARA TAYLOR, DR. LISA MCGINLEY, FOR THEIR METICULOUS WORK IN PUTTING ALL OF THIS TOGETHER OVER THE PAST MONTH AND FOR THEIR COMPILATION OF THE ANALYSIS. I'D ALSO LIKE TO GIVE A SPECIAL THANKS TO DR. SHYAM PATEL FOR PROVIDING THE PARTNERING DATA IN THE LAST SLIDE WHICH HELPS US EMPHASIZE THE IMPACT OF SOME OF OUR WORK.

SO WITHOUT FURTHER ADO, LET'S GET THIS STARTED. NEXT SLIDE.

THIS IS ONE OF THREE SLIDES, AND I'M GOING TO FOCUS ON THIS ONE. THE TWO OTHERS ARE BASICALLY, THIS ONE REPRESENTS PROPOSITION 14 AND PROPOSITION 71 NUMBERS, AND THE NEXT ONE IS JUST PROP 14 AND THE OTHER IS PROP 71. SO I'LL BE GOING QUICK THROUGH THOSE ESPECIALLY AS WE HAVE ONLY 25 MINUTES.

SO THIS SLIDE REPRESENTS THE SCOPE OF CIRM'S INVESTMENT IN NEURODEGENERATION, COMBINING THE EFFORTS OF BOTH PROPOSITIONS WITH THE YEARS FROM 2007 TO 2023. WE HAVE DIVIDED THIS THESE IN THREE

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MAIN COLUMNS, THE DISEASES LEFT, THE NUMBER OF AWARDS GIVEN ON THE LEFT, AND THE FUNDS ALLOCATED AS DENOTED IN MILLIONS OF DOLLARS ON THE RIGHT.

THE COLOR CODING, WHICH IS GOING TO BE CONSISTENT ACROSS THE PRESENTATION FOR BETTER VISUALIZATION, SHOWS DISCOVERY AWARDS IN YELLOW-GREEN, TRANSLATION IN ORANGE, AND CLINICAL AWARDS ARE IN BLUE.

SO TO THE LEFT WITH THE NUMBER OF AWARDS, WHAT THAT HIGHLIGHTS IS THAT PARKINSON'S DISEASE HAS RECEIVED A TOTAL OF 28 AWARDS WITH DISCOVERY BEING THE FOCUS. ALZHEIMER'S FOLLOWS WITH 17 AWARDS, ALSO HEAVILY FOCUSED ON DISCOVERY AND SOME TRANSLATION, NO CLINICAL. ALS HAS A NOTABLE NUMBER OF 29 AWARDS, AGAIN WITH A FOCUS ON DISCOVERY, BUT ALSO WITH A SIGNIFICANT PORTION IN CLINICAL TRIALS. AND THEN WE HAVE HUNTINGTON'S AND SPINAL MUSCULAR ATROPHY WHICH HAVE RECEIVED A COMBINED NUMBER OF 23 AND 4 AWARDS RESPECTIVELY.

LOOKING AT THE NUMBER OF FUNDS, ALS HAS THE HIGHEST INVESTMENT WITH OVER $106 MILLION, EMPHASIZING THE FOCUS ON BOTH EQUALLY, MORE OR LESS, DISCOVERY AND CLINICAL TRIALS. PARKINSON'S HAS ALSO RECEIVED A CONSIDERABLE AMOUNT OF FUNDING WITH A TOTAL OF $63.9 MILLION WHERE 44.6 IS DIRECTED TOWARD

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DISCOVERY RESEARCH AND 15.3 TO CLINICAL.

ALZHEIMER'S DISEASE HAS $50.2 MILLION IN FUNDING WITH A BALANCE DISTRIBUTION BETWEEN DISCOVERY AND TRANSLATIONAL RESEARCH. AND HUNTINGTON'S DISEASE HAS BEEN ALLOCATED 49.1 MILLION, AGAIN, WITH A STRONG CLINICAL TRIAL INVESTMENT.

THE LOWER SECTION OF THE SLIDE IDENTIFIES A FOCUS ON RARE DISEASES, SUCH AS TAY-SACHS, PML, AND LYSOSOMAL STORAGE DISEASES. MOST OF THEM HAVE ONE TO TWO AWARDS EACH AND CORRESPONDING FUNDING. AND THIS INDICATES THAT, WHILE THESE CONDITIONS ARE LESS COMMON, THEY ARE ALSO A FOCUS OF CIRM'S EFFORTS, AS WE ALL KNOW.

SOME OF THE INVESTMENT ON NEURODEGENERATIVE DISEASE, AS YOU CAN SEE, IS IN DISCOVERY RATHER THAN CLINICAL; FOR EXAMPLE, ALZHEIMER'S DISEASE VERSUS ALS. AND THIS IS DUE TO SOME OF THE FACTORS. BUT ALZHEIMER'S DISEASE COMPARED TO ALS, ALS HAS SEEN MORE SIGNIFICANT ADVANCES IN CELL AND GENE THERAPY APPROACHES GIVEN ITS CLEARER GENETIC COMPONENTS IN SOME OF THE CASES WHICH HAS ALLOWED MORE TARGETED THERAPIES. AND WE WILL HEAR ABOUT THESE TODAY FROM DR. ROTHSTEIN LATER ON, I'M SURE.

BUT, IN ESSENCE, THIS SLIDE PROVIDES A COMPREHENSIVE OVERVIEW OF OUR STRATEGIC FUNDING DISTRIBUTION ACROSS A RANGE OF NEURODEGENERATIVE DISEASES ACROSS A 16-YEAR PERIOD WITH SIGNIFICANT INVESTMENTS IN BOTH EARLY STAGE AND CLINICAL RESEARCH, WHICH HIGHLIGHTS OUR COMMITMENT TO NEURODEGENERATIVE DISEASES. NEXT SLIDE, KELLY. THANK YOU.

SO THESE SLIDE REPRESENTS -- NO. 2 AND 3, AS I SAID EARLIER ON, IS THE CIRM NEURODEGENERATION PORTFOLIO OF AWARDS DATA UNDER PROP 71 IN THIS CASE. AND THE MAIN OBSERVATION IS THAT THE UNDERLYING TRENDS IN FUNDING AND AWARD DISTRIBUTION REMAIN CONSISTENT ACROSS BOTH TIMEFRAMES AND WITH THE PREVIOUS THAT WAS THE OVERALL FEATURE BETWEEN BOTH PROPOSITIONS.

SO LET'S GO PAST, AGAIN, THE NEXT SLIDE. THIS IS PROP 14, AND AGAIN SHOWING THAT THE UNDERLYING TRENDS IN FUNDING AND AWARD DISTRIBUTION REMAIN CONSISTENT AS WELL RIGHT NOW. GIVEN THAT WE ARE ONLY A COUPLE OF YEARS ON THIS PROPOSITION, WE HAVE LESS NUMBER OF AWARDS AND LESS AMOUNT OF FUNDING INVESTED. NEXT SLIDE.

ON THIS SLIDE WE ARE LOOKING AT THE CIRM NEURODEGENERATION PORTFOLIO SPENDING BY DISEASE,

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COMPARING PROPOSITIONS, CONTRASTING THE ALLOCATIONS UNDER PROP 71 ON THE LEFT AND PROP 14 ON THE RIGHT. THIS SLIDE HIGHLIGHTS THE DISTRIBUTION OF FUNDS ACROSS THE SPECTRUM OF NEURODEGENERATIVE DISEASES WITH A FOCUS ON HOW FINANCIAL RESOURCES HAVE BEEN DIRECTED TOWARDS EITHER DISCOVERY, TRANSLATION, AND CLINICAL RESEARCH. AND, AGAIN, IT'S YELLOW-GREEN, DISCOVERY; ORANGE, TRANSLATION; AND BLUE IS CLINICAL.

SO ON THE LAST UNDER THE PROPOSITION 71, YOU CAN SEE THAT PARKINSON'S DISEASE RECEIVED THE HIGHEST FUNDING IN DISCOVERY WITH A SIGNIFICANT PORTION CHANNELED INTO CLINICAL RESEARCH AS WELL, DEMONSTRATING CIRM'S COMMITMENT TO TRANSLATING ALSO THE DISCOVERY OF EVENTUAL TREATMENTS.

ALZHEIMER'S DISEASE ALSO SAW A SUBSTANTIAL INVESTMENT, ESPECIALLY IN DISCOVERY AND TRANSLATIONAL RESEARCH, WHICH REFLECTS THE STRATEGIC EMPHASIS ON UNRAVELING THE COMPLEXITIES OF THE DISEASE.

AND ALS HAS A NEARLY EQUAL DISTRIBUTION OF FUNDS ACROSS DISCOVERY AND CLINICAL STAGES, WHICH RECEIVED -- AND ALS RECEIVED THE HIGHEST AMOUNT OF FUNDING. THE EQUAL DISTRIBUTION UNDERSCORES A BALANCED APPROACH TOWARDS DEVELOPING AS WELL AS

UNDERSTANDING THE DISEASE MECHANISMS AND PUSHING THE PROMISING TREATMENT INTO THE CLINICAL. AND A SIGNIFICANT CLINICAL INVESTMENT IS LIKELY A RESPONSE OF THE URGENT NEED TO FIND THERAPEUTIC OPTIONS FOR THIS RAPIDLY PROGRESSING CONDITION, I WOULD SAY.

SO MOVING ON TO PROPOSITION 14, THE FUNDING PATTERN HERE SHOWS THE CONTINUED FOCUSED BOOST IN CLINICAL RESEARCH FOR ALS. AND TO NOTE, WE ARE COMPARING 17 YEARS VERSUS 2 YEARS. SO PROP 71 VERSUS PROP 14. SO WE CANNOT REALLY MAKE ANY CONCLUSIONS YET. NEXT SLIDE.

AND FEEL FREE IF ANYBODY HAS A QUESTION, WANTS TO CLARIFY, PLEASE STOP ME. WE ARE GOING TO MOVE INTO FUNDING. THE NEXT THREE SLIDES ARE GOING TO BE ABOUT PROP 71 AND PROP 14 TOGETHER. SO THIS SLIDE DISPLAYS CIRM'S R&D FUNDING IN NEURODEGENERATIVE PORTFOLIO AS A PERCENTAGE OF THE TOTAL IN EACH PILLAR UNDER BOTH PROPOSITIONS OVER THE LAST 17 YEARS AND SHOWCASES THE ALLOCATION ACROSS DISCOVERY. SO 43 PERCENT OF THE FUNDING OF NEURO FOR DISCOVERY HAS BEEN IN NEURODEGENERATION, 26 PERCENT HAS BEEN FOR TRANSLATIONAL, AND 23 PERCENT OF THE FULL NEURO FUNDING IN CLINICAL HAS BEEN IN NEURODEGENERATION.

DISCOVERY SHOWS THE LARGEST SHARE OF THE

NEURODEGENERATION-SPECIFIC FUNDING AT $169.8 MILLION, WHICH EMPHASIZES THE IMPORTANCE OF FOUNDATIONAL RESEARCH, AND I COULD GO FURTHER AND SAY THIS MECHANISM -- DISCOVERY OF NEURODISEASE MECHANISMS THAT ARE VERY NEEDED FOR ALL THESE DISEASES, COMPLEX DISEASES.

TRANSLATIONAL EFFORTS HAVE RECEIVED 61.8 MILLION, WHICH BRIDGES THE LAB FINDINGS INTO THE CLINICAL APPLICATIONS, WHILE CLINICAL RESEARCH IS THE MOST RESOURCE INVESTMENT SPACE, AND IT HAS ALLOCATED 96.2 MILLION, REFLECTING THE SIGNIFICANT COST OF BRIDGING THERAPIES TO PATIENTS.

LET'S MOVE TO THE NEXT SLIDE. THE NEXT SLIDE SHOWS -- SHIFTS OUR FOCUS FROM FUNDING TO THE DISTRIBUTION OF AWARDS WITHIN CIRM'S R&D NEURODEGENERATION PORTFOLIO FROM THE DURATION OF THE LAST PROPOSITIONS OF 17 YEARS. IT OUTLINES THE NUMBERS OF AWARDS GIVEN IN THE THREE CATEGORIES AGAIN. AND THIS IS WHAT WE HAVE SPENT IN TOTAL NEURO.

YOU CAN SEE THAT IN THE DISCOVERY CATEGORY, THERE HAVE BEEN 90 AWARDS SPECIFICALLY TARGETING NEURODEGENERATION, WHICH COMBINED WITH OTHER NEUROLOGICAL AWARDS TOTALS 218 AWARDS. THIS HIGHLIGHTS CIRM'S STRONG EMPHASIS ON FOUNDATIONAL

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RESEARCH IN NEURODEGENERATION. TRANSLATIONAL RESEARCH HAS SEEN 11 AWARDS DEDICATED TO NEURODEGENERATION OUT OF 37 TOTAL NEURO AWARDS AND REFLECTS THE FOCUSED EFFORTS TO BRIDGE THE GAP BETWEEN LEVEL OF FINDINGS AND POTENTIAL CLINICAL APPLICATIONS, BUT IT ALSO SHOWS THAT MANY OF THE DISCOVERY MIGHT NOT BE SUCCESSFUL, NOT BECAUSE WE ARE NOT TRANSLATING THEM, OR THEY MIGHT BEING THE RISK SOMEWHERE ELSE IN FOR-PROFIT INDUSTRY.

IN THE CLINICAL SPACE THERE ARE TEN NEURODEGENERATION-SPECIFIC AWARDS FROM A TOTAL OF 41, AND THIS SHOWS THE STRATEGIC PUSH TOWARDS BRINGING THE THERAPIES FROM THE LAB INTO THE CLINICAL TESTING PHASE. AND THIS AWARD DISTRIBUTION, I THINK, COMPLEMENTS THE FUNDING PATTERN THAT WE DISCUSSED EARLIER, DEMONSTRATING CIRM'S BALANCED INVESTMENT IN EACH RESEARCH STAGE TO ADVANCE THE UNDERSTANDING OF THESE DEVASTATING DISEASES.

LET'S MOVE TO THE NEXT SLIDE. THE NEXT SLIDE IS AN ALTERNATIVE WAY TO VISUALIZE THE NO. 5. AND INSTEAD OF PERCENTAGES, IT'S BY AMOUNT SPENT RELATIVE TO EACH OTHER. SO IT'S ALL THE SAME AS THE FIRST SLIDE ON THIS TREND. NEXT SLIDE.

THIS SLIDE PROVIDES AN ANALYSIS OF THE

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PERCENTAGES OF NEURODEGENERATION SPENDING COMPARED TO THE OTHER NEUROLOGICAL AREAS IN THE MOST RECENT FUNDING PHASE UNDER PROP 14. SO THE LAST THREE SLIDES WERE BOTH PROPOSITIONS. THIS IS JUST SO WE CAN SEE WHAT PROP 14 -- WHAT'S HAPPENING WITH PROP 14. AND HERE WE OBSERVE THAT THE STRATEGIC ALLOCATION OF FUNDS PARALLELS THE TRENDS OF BOTH PROPS TOGETHER. NEXT SLIDE.

THIS IS THE NUMBER OF AWARDS, AND THE DISTRIBUTION ALSO PARALLELS THE TRENDS THAT WE HAD UNDER PROP 71 AND PROP 14 TOGETHER. NEXT SLIDE.

AND THIS IS BY SPENDING, ANOTHER ALTERNATIVE WAY TO VISUALIZE SLIDE 8 INSTEAD OF PERCENTAGES BY AMOUNT OF SPEND RELATIVE TO EACH OTHER.

NOW, ANY QUESTIONS SO FAR? OKAY.

CHAIRMAN GOLDSTEIN: ACTUALLY ONE QUESTION, ROSA. WHAT FRACTION OR APPROXIMATE FRACTION OF THE CLIN AWARDS ARE PARTNERED WITH INDUSTRY?

DR. CANET-AVILES: WE WILL SEE THAT AT THE END. YOU ARE GOING TO SEE THAT AT THE END. SO WE ARE GOING TO SEE A COUPLE THINGS. THANK YOU, LARRY, FOR THE QUESTION. SO ONE OF THEM, WE ARE GOING TO SEE THE PROGRESSION. SO THOSE AWARDS THAT HAVE

STARTED WITH FUNDING FROM CIRM AT THE STAGE OF DISCOVERY OR TRANSLATIONAL AND THEY'VE MOVED TO THE NEXT STAGE ALSO FUNDED BY CIRM. AND ANOTHER SET OF DATA IS GOING TO BE ABOUT PARTNERING ACTIVITIES. AND THAT'S WHAT DR. PATEL PROVIDED AND WE WILL BE DISCUSSING.

SO LET'S MOVE ON TO THE NEXT SLIDE PLEASE. IT'S A BUSY SLIDE.

DR. YAMAMOTO: ROSA.

DR. CANET-AVILES: YEAH.

DR. YAMAMOTO: THIS IS KEITH. I'M SORRY TO BE LATE, SO YOU MAY HAVE ALREADY TALKED ABOUT THIS. BUT WHAT FRACTION -- I ASSUME THAT THE CLINICAL AWARDS INCLUDE TRIALS.

DR. CANET-AVILES: CORRECT.

DR. YAMAMOTO: AND SO WHAT FRACTION OF THE EXPENDITURE ON THE CLIN SIDE IS SPECIFICALLY FOR SUPPORTING CLINICAL TRIALS?

DR. CANET-AVILES: SO WE COULD BE -- LET ME SEE. UNDER CLINICAL. ABLA, CAN YOU MOVE TO -- KELLY, CAN YOU MOVE TO SLIDE NO. 5. AND, ABLA, I WILL DEFER TO YOU BECAUSE I COULD SAY THAT IT'S 23 PERCENT. NO. 5, SLIDE NO. 5, KELLY. THIS ONE.

ABLA, WOULD YOU LIKE TO ANSWER THE

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QUESTION? I COULD SAY IT'S 23 PERCENT, BUT I DON'T KNOW EXACTLY. ABLA, YOU MIGHT BE MUTED, ABLA.

DR. CREASEY: I'M NO LONGER MUTED. YES, AS REPRESENTED ON THAT SLIDE, IT'S 23 PERCENT IN CLINICAL TRIALS.

MR. JUELSGAARD: I THINK SAYING THEY'RE IN CLINICAL TRIALS IS JUST A LITTLE MISLEADING BECAUSE THE CLIN AWARDS INCLUDE THE STUDIES LEADING UP TO AN IND FILING. SO YOU HAVE TO HAVE AN IND IN ORDER TO ACTUALLY BEGIN CLINICAL TRIALS. IF YOU GO TO THOSE SLIDES BEFORE, YOU WILL SEE THAT THERE ARE TWO $4 MILLION AMOUNTS. THOSE WERE ALL STUDIES LEADING TO AN IND. THERE'S ONLY ONE -- YEAH, SO THAT SLIDE, FOR EXAMPLE, THE BLUE ONES. THE TWO BLUE FOURS HAVE TO BE TRIALS LEADING UP TO AN IND. SO WHETHER THEY GET THE IND OR NOT IS STILL AN OPEN ISSUE.

SO THEN THERE'S ONE FOR 12 MILLION, WHICH SUGGESTS, UNLESS THERE'S MORE THAN ONE INVOLVED THERE, THAT THAT'S PROBABLY A CLIN AWARD, PROBABLY A PHASE 1.

DR. CANET-AVILES: YES, YOU ARE CORRECT, STEVE. I THINK WE DID THAT ANALYSIS. I WOULD NEED TO GO INTO OTHER SLIDES, BUT WE COULD FOLLOW UP WITH PROVIDING THIS INFORMATION.

MR. JUELSGAARD: OKAY.

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DR. CANET-AVILES: BUT I DON'T THINK WE -- SOMEBODY IS SPEAKING. SORRY.

CO-CHAIRMAN FISHER: I THINK THE FOCUS OF THIS TASK FORCE IS ON PROP 14. SO ARE YOU GOING TO BE FOCUSING WHAT WE'VE DONE SO FAR RELATED TO PROP 14, OR ARE WE LOOKING AT A COMBINATION AND THEN WE HAVE TO PARSE OUT HOW MUCH IS PROP 14 AND HOW MUCH IS PROP 71, WHICH IS NOT REALLY PART OF THE SCOPE OF WHAT OUR TASK FORCE IS CHARGED WITH. I'M WONDERING HOW WE'RE GOING TO GET TO THAT WHEN ALL OF THESE NUMBERS ARE COMBINED.

DR. CANET-AVILES: THANK YOU, FRED, FOR YOUR COMMENT. ACTUALLY THE NUMBERS ARE SEPARATED. WE'VE DONE THE THREE ANALYSES. WE'VE DONE COMBINED AND ONE BY ONE SO THAT WE COULD SEE, A, WHAT HAS HAPPENED SO FAR, WHAT HAPPENED DURING PROP 71, AND WHAT'S HAPPENING DURING PROP 14 SO WE CAN SEE WHETHER THE TRENDS ARE STILL THE SAME. AND FOR NOW WE CAN SEE -- WHAT WE ARE CONCLUDING IS THAT THE TRENDS ARE THE SAME DURING PROP 14.

CO-CHAIRMAN FISHER: OKAY. THANK YOU SO MUCH.

DR. CANET-AVILES: OF COURSE. OF COURSE. AND I THINK THAT'S A VERY RELEVANT QUESTION. SO YOU'RE ABSOLUTELY ON THE SPOT. THE THING IS THIS IS

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A LOT OF INFORMATION. THAT'S WHY IT WAS POSTED SO THAT PEOPLE COULD DIGEST IT BEFORE THE MEETING BECAUSE GOING THROUGH ALL THESE SLIDES IS KIND OF A LITTLE BIT TOO MUCH INFORMATION, RIGHT.

SO I AM GOING TO GO -- WE WERE GOING TO GO TO SLIDE NO. 11 WHERE WE ARE PRESENTING. SO, AGAIN, THE QUESTION THAT WAS ASKED IN TERMS OF THE PROPORTION BY KEITH YAMAMOTO AND STEVE JUELSGAARD, IN TERMS OF CLINICAL, WE CAN SAY THAT WE HAVE FUNDED 23 PERCENT OF THE WHOLE NEURO PORTFOLIO WITH THE CORRESPONDENCE OF $96.2 MILLION HAVE BEEN INVESTED IN CLINICAL. AND OF THOSE, ABOUT HALF HAVE BEEN IN ALS.

SO WE CAN -- THAT'S WHAT WE CAN SAY. AND THEN WE WILL HAVE -- IN TERMS OF ALS, FOR EXAMPLE, WE CAN SEE HERE THAT IN TERMS OF NUMBER OF AWARDS, WE HAVE THREE IN THE CLINICAL. THIS SLIDE IS ACTUALLY SHOWING BY APPROACHES. IT'S PROBABLY -- AND IT'S A COMPREHENSIVE OVERVIEW OF THE NEURODEGENERATION PORTFOLIO OF AWARDS BY APPROACH UNDER PROP 71. WE ALSO HAVE PROP 14. AND WE HAVE CATEGORIZED THESE IN FOUR COLUMNS REPRESENTING DISEASE ON THE LEFT AND THEN THE THREE STAGES: DISCOVERY, TRANSLATIONAL, AND CLINICAL.

AND IT BREAKS DOWN, THE CHART BREAKS DOWN

THE NUMBER OF AWARDS GIVEN TO VARIOUS NEURODEGENERATIVE DISEASES. FOR EXAMPLE, WE CAN SEE THAT FOR PARKINSON'S DISEASE, THEY HAD, I THINK, 23 AWARDS IN THE DISCOVERY PHASE, ONE IN THE TRANSLATIONAL PHASE, AND THEN WE HAD TWO IN THE CLINICAL PHASE.

AND THEN WE HAVE -- THE COLOR-CODED LEGEND AT THE BOTTOM SHOWS THE DIFFERENT RESEARCH MODALITIES, SUCH AS ALLOGENEIC, AUTOLOGOUS, GENE-MODIFIED, SMALL MOLECULES, CELL FREE GENE THERAPY, FOUNDATIONAL RESEARCH, AND AUTOLOGOUS, BIOLOGIC. AND THESE MODALITIES WILL HELP US UNDERSTAND WHERE THE FOCUS OF OUR RESEARCH ALSO HAS BEEN.

I WOULD LIKE TO DRAW ATTENTION TO ALS. IT HAS 13 AWARDS IN DISCOVERY PHASE, WHICH ARE HIGHLIGHTED IN -- NOT 13 -- 17 AWARDS IN THE DISCOVERY PHASE, AND WE ALSO HAVE THREE IN THE CLINICAL. BUT GIVEN THAT IT HAS -- SO THOSE ARE PROBABLY CLINICAL TRIALS BECAUSE OF THE NUMBER OF AWARDS AND THE AMOUNT THAT WE'VE SPENT IN ALS CLINICAL.

DR. CREASEY: CAN I COMMENT HERE? WHEN YOU TALK ABOUT THE CLINICAL, IT'S ACTUALLY JUST PHASE 1. AND SO IT IS A LIKE UNCONTROLLED CLINICAL

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RESEARCH IN ALS. THERE ARE NO PLACEBOS, WHATEVER. SO WHENEVER YOU CALL A TRIAL, I THINK IT'S FAIR TO SAY THAT YOU NEED A COMPARATOR. AND IN OUR SITUATION WITH ALS, OTHER THAN BRAINSTORM THERAPEUTICS, THE OTHER TWO WERE ONLY RESEARCH, OPEN LABEL TRIALS, OPEN LABEL RESEARCH.

DR. CANET-AVILES: GREAT. THANK YOU FOR THE CLARIFICATION, ABLA.

SO THE NEXT SLIDE ACTUALLY SHOWS, INSTEAD OF NUMBER OF AWARDS, IT REPRESENTS THE PORTFOLIO BY FUNDING BY APPROACH. AND THIS IS THE STAGE AND, AGAIN, ALSO THE DIFFERENT COLOR-CODED MODALITIES. AND AS YOU CAN SEE, THIS KIND OF PARALLELS THE AMOUNT OF FUNDING THAT YOU WERE TALKING ABOUT IN CLINICAL. WE CAN SEE THAT WE'VE SPENT MOST OF OUR FUNDING IN CLINICAL IN PARKINSON'S, ALS, AND HUNTINGTON'S DISEASE IN PROP 71. NEXT SLIDE.

THIS SLIDE IS THE SAME, BUT JUST FOR PROP 14. SO FOR PROP 14, WE CAN SEE THAT SO FAR WE HAVE HAD QUITE A BIT OF INVESTMENT IN CLINICAL AS WELL. SO PARKINSON'S DISEASE, WE HAVE ONE AWARD IN CLINICAL, WE HAVE ONE IN ALS, AND WE HAVE ONE IN TAY-SACHS. WE HAVE SOME TRANSLATIONAL APPROACHES FOR PARKINSON'S AGAIN AND FRIEDREICH'S ATAXIA, AND THEN WE HAVE IN DISCOVERY ONE AWARD FOR ALZHEIMER'S,

MULTIPLE SCLEROSIS, A LOT OF FUNDING OR A LOT OF AWARDS IN ALS. SO IT'S LIKE -- IT'S ONE OF THE CANDIDATE NEURODEGENERATIVE DISEASES THAT WE HAVE INVESTED THE MOST. IT'S ACTUALLY THE ONE THAT WE'VE INVESTED THE MOST, ALSP AND PML. AND YOU CAN SEE THE DIFFERENT APPROACHES WITH THE CODE AT THE BOTTOM.

THE NEXT SLIDE SHOWS THE SAME INFORMATION, BUT BY FUNDS SPENT. AND WE CAN AGAIN SEE THAT ALS IS THE ONE THAT HAS RECEIVED THE MOST FUNDING, AND IT'S FOCUSED ON EARLY RESEARCH, FOUNDATIONAL, OR SMALL MOLECULE, BIOLOGIC, AND GENE THERAPY, CELL FREE GENE THERAPY. SO THESE TWO AWARDS ARE TRYING TO DEVELOP NEW CANDIDATES THAT WILL MOVE INTO TRANSLATION AND CLINICAL, NOT SO MUCH FOUNDATIONAL DISCOVERY. AND IN THE CLINICAL WE HAVE 12 MILLION, AND I THINK IT'S ALLOGENEIC, CORRECT, ALLOGENEIC, GENE-MODIFIED THERAPY. AND I THINK WE WILL SEE AN EXAMPLE SOON IN THE SLIDES. ANY QUESTIONS?

CHAIRMAN GOLDSTEIN: ROSA, YOU'RE GETTING TIGHT ON TIME.

DR. CANET-AVILES: OKAY. SO I WILL JUST GO -- THANK YOU. NEXT SLIDE, KELLY.

THIS SLIDE PROVIDES AN OVERVIEW. I'M NOT GOING TO GO THROUGH THIS ONE. I'M GOING TO GO

THROUGH THE NEXT, BUT WHAT I WANT TO PRESENT IS WHAT THIS SLIDE AND THE NEXT REPRESENT. THESE ARE THE OVERALL NEURO PORTFOLIO PROGRESSION OF EVENTS FOR BOTH PROPOSITIONS.

WHAT A PROGRESSION EVENT IS IS A MEASURE OF THE SUCCESS OF OUR PROGRAMS AND FUNDING AND MOVING TO THE NEXT STAGES. NOW, WHAT WE CAPTURE HERE IS WHAT MOVES TO THE NEXT STAGE WITHIN OUR CIRM PORTFOLIO OF FUNDING. SO WHAT WE HAVEN'T CAPTURED HERE, WHICH WE WILL TRY TO CAPTURE NEXT, IS WHAT MIGHT BE THE RISK AND IS FUNDED THROUGH INDUSTRY, RIGHT.

SO A PROGRESSION EVENT IS WHEN THE CIRM AWARD COMPLETES ONE STAGE OF RESEARCH AND IS SUCCESSFUL AND GETS CIRM FUNDING TO MOVE ON TO THE NEXT STAGE TO DEVELOP EITHER A SECOND GENERATION OF THE SAME DEVICE OR THERAPY.

SO IN HERE I WOULD LIKE TO HIGHLIGHT A CASE STUDY TO DEMONSTRATE HOW OUR FUNDING WHEN IT APPLIES TO PROGRAMS SUCH AS THE ONE PIONEERED BY UCSF UNDER DR. KRIEGSTEIN AND DR. RUBENSTEIN THAT MOVED TO DR. CORY NICHOLAS AND NEURONA THERAPEUTICS. THEY DEVELOP -- THROUGH FIVE BASIC AND DISCOVERY AWARDS, THEY DEVELOPED THE PROTOCOLS FOR DERIVATION, CHARACTERIZATION, SELECTION, AND PRODUCTION OF

INTRAMURAL PRECURSORS. AND THEY GOT A TRAN AWARD WHERE THEY DEVELOPED THE INHIBITORY NEURONS AS A THERAPEUTIC FOR FOCAL EPILEPSY, AND THEN THEY MOVE ON TO PHASE 1/2 TRIAL TO TEST SAFETY AND EFFICACY OF THE POTENTIAL TREATMENT FOR DRUG RESISTANT UNILATERAL MEDIAL TEMPORAL LOBE EPILEPSY.

SO THIS IS A VERY NICE EXAMPLE OF HOW SUCCESSFUL SOME OF OUR NEUROTHERAPIES HAVE BEEN EVOLVING THROUGH OUR PORTFOLIO.

NEXT SLIDE IS A FOCUS ON OUR NEURODEGENERATION, AND I WILL SAY WE HAVE MADE A MISTAKE THAT WE RECTIFIED. WE HAD MISSED A COUPLE, AND WE ADDED THEM. SO THAT WAS WHAT THE REVISION OF THE SLIDES WAS.

AND WE CAN SEE HERE THAT WE HAVE A FAIR AMOUNT OF PARKINSON'S DISEASE. WE HAVE THREE PROJECTS THAT HAVE MOVED FROM DISCOVERY EITHER TO TRAN OR TO CLIN OR THAT THEY ARE MOVING FROM DISCOVERY FOUNDATIONAL TO A DEVELOPMENT CANDIDATE AND SO ON. SO THIS IS JUST FOR REFERENCE.

I JUST WANT TO MOVE TO THE LAST SLIDE BECAUSE I'M SHORT ON TIME. AND THIS LAST SLIDE PROVIDES A COMPREHENSIVE OVERVIEW OF THE NEURODEGENERATION PARTNERING ACTIVITIES FROM 2007 TO 2024. AND BY PARTNERING, WHAT WE MEAN HERE IS THAT

A PROGRAM THAT HAD STARTED WITH CIRM FUNDING HAS EITHER RAISED MONEY THROUGH A VC, SPUN OUT OF ACADEMIA INTO A FOR-PROFIT, AND/OR RAISED VC FUNDING OR LICENSED OR BEING ACQUIRED.

THIS IS A MEASURE OF THE IMPACT OF CIRM FUNDING. THESE PARTNERSHIPS, I THINK, ARE VITAL FOR ADVANCING RESEARCH FROM THE LAB TO THE CLINIC, EMPHASIZING THE IMPORTANCE OF COLLABORATION BETWEEN PUBLIC INSTITUTIONS AND PRIVATE ENTITIES IN TACKLING THESE DEVASTATING NEURODEGENERATIVE DISEASES. AND I THINK IT WAS -- I CAN'T REMEMBER WHO ASKED THE QUESTION, BUT YOU CAN SEE THAT, YES, IN THE CLINICAL WE HAVE SOME PROGRAMS THAT STARTED IN THE CLINICAL AND THAT HAVE HAD PARTNERING ACTIVITIES. SO YOU CAN SEE IN HUNTINGTON'S, PARKINSON'S, ALS, PARKINSON'S DISEASE WE HAVE DETAILS, BUT WE HAVE SOME IN EACH.

STEPHEN.

MR. JUELSGAARD: YEAH. SO SOME OF THESE DESCRIPTIONS OF WHERE THINGS STAND ARE A LITTLE MISLEADING. I DID MY OWN INDEPENDENT RESEARCH ON ALL OF THESE COMPANIES.

I WANT TO START WITH BRAINSTORM BECAUSE ACTUALLY THEY COMPLETED A PHASE 3 CLINICAL TRIAL, BUT HAD AN FDA ADVISORY COMMITTEE MEETING WHICH VOTED 17 TO 1 NOT TO PROCEED, FOR THE FDA NOT TO

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PROCEED WITH APPROVAL BASED ON THEIR PHASE 3 TRIAL. SO THEY'RE BACK TO THE DRAWING BOARD.

THE ACUREX -- I'M SORRY. LET'S DO THIS. ASPEN NEUROSCIENCE, THEY HAVE AN IND APPROVED, BUT THEY'RE NOT IN CLINICAL TRIALS YET EVEN THOUGH IT SAYS CLINICAL TRIALS ONGOING. THEY'RE NOT THERE YET.

THERE'S ANOTHER ONE THAT SAYS THAT THEY'RE IN CLINICAL TRIALS. SO THAT'S THE ACUREX, THE SECOND ONE DOWN, SAYS CLINICAL TRIALS ONGOING. THAT'S NOT QUITE THE CASE. THEY'RE TRYING TO RAISE MONEY RIGHT NOW TO GET INTO THEIR FIRST CLINICAL TRIAL.

ANYWAY, MY POINT IS THAT I DON'T THINK WE'RE NEARLY AS FAR ALONG WITH RESPECT TO INDUSTRY PARTNERS AS THIS SLIDE MIGHT SUGGEST. WE'RE STILL WAY, WAY BACK AT THE VERY BEGINNING OF THINGS. AND THE ONE THAT WAS THE FURTHEST ALONG ACTUALLY FAILED IN TERMS OF ITS PHASE 3 CLINICAL TRIAL. SO WE HAVE A LONG WAYS TO GO IN THE CLINICAL AREA, WHETHER IT'S WITH ACADEMIA OR PARTNERS, BEFORE WE'RE GOING TO GET ANYWHERE IN THIS ENTIRE AREA.

DR. CREASEY: CAN I ANSWER STEPHEN? STEPHEN, YOU'RE ABSOLUTELY CORRECT. BRAINSTORM, THE PHASE 3 TRIAL FAILED. THEY'RE STILL DISCUSSING --

THEY ARE GETTING A SPECIAL KIND OF MANAGEMENT OF A NEW TRIAL WITH THE FDA. SO YOU'RE RIGHT. THERE ARE NO CLINICAL TRIALS ONGOING REGARDING THAT. I THINK THAT MAY -- THE CLINICAL TRIALS ONGOING WAS FOR MS. MAYBE THE WORD "MS" WAS MISSED.

THE ASPEN NEUROSCIENCE HAS APPLIED FOR A CIRM GRANT AND WAS APPROVED. IT'S ALREADY -- IT'S STARTING A CLINICAL TRIAL WITH US, AND THAT'S PUBLIC.

SO JUST TO CORRECT THOSE TWO. SO, AGAIN, ASPEN IS, AGAIN, WITHIN -- STARTED THEIR PHASE 1 CLINICAL TRIAL WITH CIRM FUNDING.

MR. JUELSGAARD: WELL, THEY'VE OPENED THE PHASE 1 CLINICAL TRIAL, ABLA, BUT THEY HAVEN'T RECRUITED ANY PATIENTS YET. THAT'S THE ISSUE THERE.

DR. CREASEY: STEVE, THE DESIGN THERE IS THESE ARE IPS CELLS WHERE THEY ALREADY HAVE IDENTIFIED THE PATIENTS. THEY HAVE ALREADY BANKED THEIR IPSC CELLS, AND THEY ARE GOING THEN TO TREAT THEM PER -- SO IT'S AUTOLOGOUS. AND THAT'S WHAT'S GOING ON. SO THE RECRUITMENT OF THE PATIENTS IS PART OF THE MODALITY BY WHICH THEY'RE WORKING WITH.

CHAIRMAN GOLDSTEIN: SO GIVEN THE TIME, I'M GOING TO ASK THAT ABLA AND STEVE GET ON THE SAME PAGE BETWEEN NOW AND THE NEXT MEETING, AND WE'LL

HAVE TIME AT THE NEXT MEETING FOR FURTHER DISCUSSION OF THE PORTFOLIOS. BUT UNLESS SOMEBODY HAS A BURNING QUESTION, I'D LIKE TO MOVE ON TO OUR PRESENTATION FROM LORENZ STUDER SO WE DON'T GET TOO FAR BEHIND ON OUR SCHEDULE.

SO ANYTHING BURNING, GUYS? OKAY. GOOD. ROSA, THANK YOU VERY MUCH. THAT WAS A VERY COMPREHENSIVE PRESENTATION, AND I WOULD ENCOURAGE FOLKS TO WORK OUT SOME OF THE DIFFERENCES BEHIND THE SCENES, AND THEN WE'LL HAVE ANOTHER DISCUSSION OF THIS PERHAPS MORE IN-DEPTH AT OUR NEXT MEETING IN -- LET'S SEE. WHAT MONTH ARE WE IN, MARCH -- SO APRIL.

OKAY. SO OUR NEXT PRESENTER IS LORENZ STUDER, WHO I'M SURE IS KNOWN TO MOST OF THE MEMBERS OF THIS GROUP. LORENZ HAS WORKED ON DIFFERENTIATION OF DOPAMINERGIC CELLS AND NEURONS FOR MANY YEARS THROUGH ALL PHASES OF HIS TRAINING. OF NOTE, HE'S RECEIVED A MACARTHUR FELLOWSHIP, IS A CO-FOUNDER OF BLUE ROCK THERAPEUTICS, AND HAS DONE A GREAT DEAL OF WORK ON THE DEVELOPMENT OF DOPAMINERGIC NEURONS FOR TREATMENT OF PARKINSON'S DISEASE.

I'VE ALSO ASKED HIM AT THE END TO COVER SOME AREAS OTHER THAN DOPAMINERGIC TREATMENT FOR PARKINSON'S DISEASE WHERE HE THINKS THERE ARE

OPPORTUNITIES THAT ARE UNDERRECOGNIZED AND UNDERRESOURCED FOR US TO THINK ABOUT.

SO, LORENZ, I HOPE I GOT MOST OF THAT RIGHT, AND I'LL TURN THE MICROPHONE AND PRESENTATION OVER TO YOU.

DR. STUDER: THANKS SO MUCH FOR THE INVITATION. I HOPE YOU CAN SEE MY SLIDES. IS THAT OKAY?

CHAIRMAN GOLDSTEIN: PERFECT.

DR. STUDER: OKAY. EXCELLENT.

WHAT I WOULD LIKE TO DO WITH THE NEXT 30 MINUTES, IF I HAVE THIS CORRECT, FOLLOWED BY 15 MINUTES OF DISCUSSION, GIVE YOU A LITTLE BIT OF AN UPDATE ON CELL THERAPY DEVELOPMENT, FOCUSING, AS AN EXAMPLE, OBVIOUSLY ON OUR OWN WORK, BUT ALSO BROADER STATUS OF THE FIELD. AND AS LARRY MENTIONED, GO A LITTLE BIT BEYOND JUST DOPAMINE NEURON REPLACEMENT TOWARDS THE END.

SO JUST TO GET STARTED, I HAVE TO PUT UP MY DISCLOSURE SLIDES BECAUSE WE DID ACTUALLY SPIN OUT A COMPANY, WHICH IS BLUE ROCK THERAPEUTICS. IT WAS ACQUIRED BY BAYER A COUPLE OF YEARS AGO AND THAT SPONSORS THE WORK AND NOW MOVING FORWARD, INCLUDING THE CLINICAL WORK.

SO THIS IS, AGAIN, THE BROADER OUTLINE OF

WHAT I WANT TO DO. SO REALLY SPEND MAYBE ABOUT TEN MINUTES OR 15 MINUTES REALLY ON KIND OF THE CORE OF WHERE WE STAND WITH CLASSIC DOPAMINE NEURON CELL REPLACEMENT THERAPY, BUT THEN TALK ABOUT SOME OF THE REMAINING CHALLENGES OF THAT APPROACH, POSSIBLE NEXT GENERATION PRODUCTS, SOME OF THE LIMITATIONS OF THE FIELD, LIKE ANIMAL MODELS, AND THEN, AGAIN, GO HOPEFULLY A LITTLE BIT INTO THE NON-DOPAMINERGIC FEATURES THAT POTENTIALLY COULD BE TREATED BY CELL THERAPY APPROACHES.

I ALSO WANT TO STATE FROM THE BEGINNING THAT I REALLY FOCUS PRETTY MUCH EXCLUSIVELY ON CELL-BASED APPROACHES. AND I'M NOT GOING TO DISCUSS DISEASE MODELING NOW USING STEM CELLS AND SO FORTH, WHICH IS AN AREA WE'RE ALSO VERY MUCH INVOLVED. HAPPY TO DISCUSS, BUT FOR TODAY I'M GOING TO BE FOCUSED ON CELL-BASED THERAPIES.

JUST FOR AN INTRODUCTION, I'M NOT GOING TO SPEND MUCH TIME HERE. NOW, THE RATIONALE IS PRETTY CLEAR, THAT WHAT YOU WANT TO DO IS YOU WANT TO REPLACE THE DOPAMINE NEURONS THAT ARE LOST IN THE DISEASE. AND THE REASON WHY IT'S A WIDELY DISCUSSED APPROACH IS BECAUSE YOU ACTUALLY HAVE RELATIVELY FEW OF THOSE IN A HEALTHY PERSON. YOU HAVE ABOUT HALF A MILLION ROUGHLY ON EACH SIDE OF THE BRAIN. ONCE YOU

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LOSE HALF OF THEM, YOU START GETTING SOME OF THOSE MOVEMENT-RELATED SYMPTOMS. AND YOU ALL KNOW IT'S A VERY COMMON DISEASE. IT'S A BIG SOCIOECONOMIC BURDEN ON THE SOCIETY.

IT'S IMPORTANT TO SAY, AND THAT'S LISTED HERE, THAT IT'S NOT A PURELY DOPAMINERGIC DISEASE. AND, AGAIN, THAT'S WHY I WANT TO DISCUSS MAYBE WHAT YOU CAN DO THERE. IT'S ALSO IMPORTANT HOW TO STATE WHAT THE DOPAMINE NEURON REPLACEMENT THERAPY COULD ACHIEVE. AND, AGAIN, THAT'S WHY I WANT TO DISCUSS MAYBE WHAT YOU CAN DO THERE. IT'S ALSO IMPORTANT HOW TO STATE WHAT A DOPAMINE NEURON REPLACEMENT THERAPY COULD ACHIEVE IN PARKINSON'S DISEASE. EVEN IN THE BEST DREAM SCENARIO, IT WOULD BE BASICALLY A CURE, QUOTE, OF THE MOVEMENT DISORDER; BUT IT WOULD NOT BE A CURE OF PARKINSON'S DISEASE BECAUSE, AGAIN, PARKINSON'S HAS SOME OF THOSE OTHER SYMPTOMS SHOWN HERE THAT CAN OFTEN PRECEDE MOVEMENT DISORDER-RELATED SYMPTOMS BY MANY YEARS ACTUALLY.

AND SOME OF THEM ARE OBVIOUSLY VERY FEARED. HAPPENS NOT IN ALL THE PATIENTS, BUT QUITE A FEW OF THE PATIENTS ACTUALLY DEVELOP MAJOR COGNITIVE PROBLEMS AT LATER STAGES OF THE DISEASE.

SO THIS FIELD REALLY STARTED MANY, MANY YEARS BACK OF AN ID, WHICH IS THE CELL REPLACEMENT

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IDEA, WHICH IS THE CELL REPLACEMENT IDEA. AND IT WAS VERY IMPORTANT PIONEERING BASIC WORK DONE USING AT THAT TIME FETAL DOPAMINE NEURONS, WORK IN THE LATE '80S, '90S. THOSE STUDIES ARE IMPORTANT BECAUSE IT KIND OF SHOWS THE PARADIGM THAT WE REALLY WANT TO PURSUE. THEY SHOWED THAT YOU CAN HAVE FETAL DOPAMINE NEURONS ISOLATED FROM FETAL TISSUE. THEY SHOW THAT THOSE CELLS CAN SURVIVE IN A PARKINSON'S BRAIN. AND THESE RED BLOBS HERE IS A TRACER THAT LABELS THE DOPAMINES CELLS. AND IMPORTANTLY, EVEN THOUGH, THIS PATIENT FOR 23 YEARS OF THE LIFE OF THE GRAFTING DID NOT RECEIVE ANY IMMUNE SUPPRESSION. YOU CAN SEE A VERY NICE SURVIVING GRAFT AT A VERY LATE STAGE OF THAT PATIENT'S LIFE.

SO THE POINT THAT I'M TRYING TO MAKE, UNLIKE MANY ORGAN TRANSPLANTATION APPROACHES, IN THE BRAIN YOU'RE PROBABLY GOING TO GET AWAY WITH VERY LITTLE IMMUNOSUPPRESSION. AND THAT MAKES IT ACTUALLY, AGAIN, ALSO A GOOD TARGET.

NOW, MANY OF YOU PROBABLY HAVE HEARD OF FETAL TISSUE, AND CLEARLY IT'S NOT SOMETHING THAT'S ROUTINELY USED IN THE CLINIC. AND IT HAS TO SOME EXTENT FAILED ONCE IT CAME TO PLACEBO CONTROLLED TRIALS. HAPPY TO GO INTO MORE DETAIL IF ANYONE IS INTERESTED, BUT A BIG PART OF IT IS THAT THE WAY THE

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CLINICAL TRIALS WERE DESIGNED, THEY HAD THE READOUT PROBABLY TOO EARLY BECAUSE THIS IS, LIKE CALL IT LIKE A LIVING DRUG. THE CELLS, THEY'RE ALIVE, AND THEY ACTUALLY GET THEIR FULL FUNCTIONALITY ONLY BY TWO TO THREE YEARS AFTER WE INJECT THOSE. SO IT'S VERY, VERY SLOWLY BECOMING FULLY FUNCTIONAL.

AND SOME PATIENTS ALSO DEVELOP SIDE EFFECTS, AND THAT REALLY WHAT KILLS THE APPROACH, SO-CALLED GRAFT-INDUCED DYSKINESIA. SO THE COMBINATION OF THOSE QUESTIONABLE EFFICACY AND POTENTIAL SIDE EFFECTS KIND OF STOPPED THE FIELD, BUT NOT COMPLETELY BECAUSE NEUROLOGISTS FOLLOWED THOSE PATIENTS STILL LONG TIME AND FOUND AT LEAST A SUBSET OF THOSE SEEM TO BE DOING VERY UNUSUALLY WELL.

NOW, ADMITTEDLY, THIS WERE A VERY FEW PATIENTS, BUT THERE ARE SOME PATIENTS WHERE CONTACT WOULD STOP THE DOPAMINE THERAPY FOR MANY YEARS. AND THAT'S SOMETHING THAT'S VERY RARE IN A DISEASE THAT'S CONSTANTLY PROGRESSING.

NOW, WE SHOULD SOON HEAR FROM A STUDY THAT WAS DONE BY ROGER BARKER THAT ACTUALLY WENT BACK AND SAY, OKAY, DID WE LEARN FROM THOSE EARLY STUDIES BEFORE 2000? CAN WE SELECT THE PATIENTS BETTER? AND THEN SHOW, NO, THAT THIS WAS REALLY THE PROBLEM

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WHY THE STUDY FAILED, MAYBE DIFFERENT CLINICAL TRIAL DESIGN. AND, AGAIN, THIS IS STILL UNPUBLISHED DATA, SO I CANNOT GO INTO TOO MUCH DETAIL, BUT I DON'T THINK, AGAIN, THAT THE STUDY IS GOING TO RESOLVE IT BECAUSE I THINK EVEN THERE IT'S KIND OF UNCLEAR HOW COULD IT REALLY WORK. IT'S STILL AN UNCONTROLLED STUDY. AND THEY HAD ALSO NUMBER OF CHALLENGES THAT HAD TO DO WITH DEVICES, WITH CONSISTENCY OF THE FUNCTION, AND SO FORTH. SO I DON'T THINK THIS IS A RESOLVED ISSUE. AND I THINK THE MAIN THING WE LEARNED, AND ROGER COULD SPEAK MORE TO THAT, IS THAT IT'S REALLY CURRENTLY NEARLY IMPOSSIBLE TO DO WITH THIS FETAL TISSUE. BECAUSE YOU APPLY SIMILAR STANDARDS OF QUALITY CONTROL TO FETAL TISSUE, IT'S VERY, VERY DIFFICULT TO DO THAT IN A WAY TO ROUTINELY TREATING PATIENTS.

SO THAT'S WHY WE AND OTHERS TRIED TO DEVELOP PLURIPOTENT-BASED APPROACHES. THAT GOES TEN YEARS BACK WHERE WE SHOWED WE COULD MAKE THOSE DOPAMINE CELLS IN A WAY THAT THEY CAN RESCUE AND SURVIVE IN A MOUSE BRAIN, IN A RAT BRAIN, OR IN A MONKEY BRAIN. THEY CAN DO THAT IN QUITE LARGE NUMBERS. THEY CAN RESTORE SOME OF THE BEHAVORIAL ASSAYS. WE COME BACK TO A LITTLE BIT WHAT'S THE PROBLEM WITH SOME OF THOSE MODELS. BUT THERE'S ONE

MODEL WHERE THE MOUSE HAS KIND OF PARKINSON'S, THEY'RE GOING TO CALL IT, ON ONE SIDE OF THE BRAIN, AND THEN IT SPINS AROUND ITS OWN AXIS IF YOU STIMULATE IT, AND WE CAN USE THAT AS A READOUT. SO THEN ON THE ONE SIDE THAT HAS THE DISEASE GETS GRAFTED, IT BECOMES SYMMETRIC.

THIS IS A RAT WHERE YOU SEE ON THE LEFT OF THAT -- IF YOU LOOK AT THIS SIDE, YOU CANNOT REALLY PROPERLY INITIATE MOVEMENT IN THIS PAW; BUT AFTER GRAFTING, IT CAN DO THAT AGAIN.

AND FINALLY, I'M NOT GOING TO SPEND TOO MUCH TIME ON THAT BECAUSE IT'S A BIT TECHNICAL, BUT WE ALSO KNOW EXACTLY HOW THESE CELLS FUNCTION. SO IT'S NOT JUST SOME KIND OF A WEIRD CELL WHERE WE HOPE THAT IT'S POSITIVELY INFLUENCING THE BRAIN. WE CAN ACTUALLY PUT THE CELLS IN WITH LIKE A LIGHT SWITCH WHERE THE CELLS GO INTO THE BRAIN. THEY RESCUE ALL THOSE BEHAVIORS, BUT THEN THEY CAN LITERALLY FLIP THE LIGHT SWITCH AND SWITCH THEM OFF. AND THEY SHOWED THAT THE ANIMAL IS AGAIN FULLY PARKINSONIAN.

SO THOSE STUDIES SHOW IN THIS CASE IT'S REALLY THE NERVE CELLS THAT INTEGRATE INTO THE BRAIN, THEY SECRETE DOPAMINE, AND THEY SECRETE IT TO THE RIGHT CELL. AND SO THAT'S, AGAIN, ONE OF THE

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FEW DISEASES WHERE WE ACTUALLY HAVE A LOT OF THIS MECHANISM WHERE WE KNOW EXACTLY HOW THE CELLS FUNCTION.

FROM THERE IT TOOK US ABOUT ANOTHER TEN YEARS TO REALLY GET THAT PROTOCOL THAT WORKED IN THOSE MOUSE, RAT, AND MONKEY IN A WAY THAT WE CAN USE IT IN PATIENTS. BUT THERE'S ALL THESE MANUFACTURING ISSUES THAT WE RESOLVED. WE GOT AN AWARD FROM THE NEW YORK STATE PROGRAM, WHICH IS A $15 MILLION AWARD TO REALLY MAKE A CLINICAL GRADE PRODUCT. WE CALLED IT MSK-DA01. AND AS YOU PROBABLY ALL KNOW, YOU HAVE TO DO A LOT OF TESTING IN ANIMALS. YOU DO TUMORIGENICITY TESTING, BIODISTRIBUTION, TOXICOLOGY, HUNDREDS OF ANIMALS. SO THIS IS MILLION DOLLARS OF STUDIES.

WE DO IT IN THE RAT WHERE WE HAD SOMETHING LIKE 50 RATS WHERE WE HAD TO SHOW THAT WE CAN RESCUE THE BEHAVIOR. AND WE DID ALSO A NUMBER OF MONKEYS TO SHOW THAT THE DEVICE WE'RE GOING TO USE IN THE PATIENT ACTUALLY CAN RELIABLY DELIVER THE CELLS IN A LARGE BRAIN SUCH AS IN A MONKEY.

AND I'LL SHOW YOU JUST ONE PICTURE HERE BECAUSE IT'S VERY EASY TO UNDERSTAND. SO IT'S, AGAIN, THIS MODEL WHERE YOU HAVE PARKINSON'S-LIKE ISSUES FOR MOVEMENT ON ONE SIDE OF THE BRAIN. SO

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YOU LACK THIS BROWN COLOR WHICH IS THE DOPAMINE FIBERS. BUT ONCE YOU GRAFT OUR CELLS THAT WERE COMPLETELY GENERATED IN A DISH, HUMAN-DERIVED CELLS, YOU CAN SEE NOT ONLY THE CELLS HERE, THIS DARK AREA ARE THE CELLS, BUT THEN THEY RECONNECT WITH THE WHOLE BRAIN. AND, AGAIN, WE DO THAT EFFECTIVELY HERE IN MANY, MANY MALE OR FEMALE PARKINSONIAN ANIMALS.

SO THAT LED US, THEN, IN 2021 TO REALLY GRAFT THE FIRST PATIENT. IN LATE 2020 WE GOT APPROVAL FROM THE FDA THAT SHOWS YOU JUST HOW THAT WORKS. SO THEY COME FROM THE GMP FACILITY WHERE THEY ARE PREPARED, THEY'RE BROUGHT INTO THE SURGERY ROOM, THEY ARE LOADED INTO A DEVICE THAT WE ADJUST AND OPTIMIZE FOR DELIVERY OF THOSE CELLS BY DR. TABAR, WHO'S THE NEUROSURGEON IN THIS STUDY AND ALSO DID MOST OF THE PRECLINICAL WORK. YOU HAVE TO CAREFULLY CHECK THAT THE CELLS ARE PROPERLY DELIVERED, AND EVENTUALLY INJECT IT DIRECTLY INTO THE BRAIN.

SO YOU ACTUALLY HAVE TO INJECT IT INTO THE BRAIN PARENCHYMA VERY, VERY CAREFULLY OBVIOUSLY TO MAKE SURE YOU DON'T CAUSE ANY BLEEDING AND SO FORTH. AND YOU INJECT BASICALLY IN EACH PATIENT ON EACH SIDE OF THE BRAIN THREE TRACTS. AND EACH OF THOSE

TRACTS ARE THREE DEPOSITS OR NINE DEPOSITS ON EACH SIDE AND 18 DEPOSITS THEN IN TOTAL PER PATIENT. WE DID THAT IN TOTAL OF 12 PATIENTS, SO IT'S SOMETHING LIKE MORE THAN 200 DEPOSITS WERE DONE IN THIS CLINICAL TRIAL. AND I'M HAPPY TO SAY THAT WE DIDN'T GET ANY COMPLICATION WITH REGARD TO BLEEDING, HEMORRHAGING, OR ANYTHING LIKE THAT.

NOW, THIS MSK-DA01 PRODUCT HAS NOW THIS LITTLE BIT UNPRONOUNCEABLE NAME, BEMDANEPROCEL. THAT'S NOW THE PRODUCT NAME THAT BLUE ROCK TAKES IT FORWARD. AND WHAT I CAN TELL YOU, AND AGAIN I'M NOT GOING TO SPEND MUCH TIME ON THAT, THESE ARE SOME OF THE RESULTS FROM THIS PHASE 1 STUDY THAT IS NOT PUBLISHED, BUT THEY HAVE BEEN PUBLICLY RELEASED BY THE COMPANY SHOWING JUST THAT IT GENERALLY WAS SAFE AND WELL TOLERATED IN ALL 12 PATIENTS. FIVE OF THOSE PATIENTS RECEIVED THE LOWER DOSE, SEVEN A SLIGHTLY HIGHER DOSE. WE COULD SHOW THAT THIS DELIVERY CAN BE DONE SAFELY, I MENTIONED AGAIN, WITH NO BLEEDING. IT TRANSIENTLY IMMUNOSUPRESSED THE PATIENT, BUT, AGAIN, ONLY TRANSIENTLY; AND IT WAS, AGAIN, VERY WELL TOLERATED.

WE HAVE EVIDENCE THAT THE CELLS SURVIVED. REMEMBER THIS RED COLOR ON THE FETAL GRAFTING, SO WE HAVE SIMILAR DATA FOR THOSE FOR THOSE SHOWING THAT

THEY CAN INCREASE THIS DOPAMINE SIGNAL. AND WE HAVE SOME SUGGESTION, THIS IS A PHASE 1 STUDY, SMALL GROUPS, BUT YOU HAVE SUGGESTION THAT THERE MIGHT BE ACTUALLY AN EFFECT ON CLINICAL IMPACT, AND IT MADE A GREATER EFFECT IN THE PATIENTS THAT GOT MORE CELLS.

I'LL SHOW YOU ONE SLIDE AFTER THAT TO ILLUSTRATE THAT THEY DIDN'T SEE THE SIDE EFFECTS THAT WERE SEEN IN THOSE FETAL GRAFTS IN THE PAST. AND, AGAIN, THE CAVEAT, THIS IS STILL A SMALL SAMPLE SIZE, THE PRIMARY GOAL WAS SAFETY AND FEASIBILITY. AND, IN FACT, IN THIS REGARD, THE STUDY HAS ALREADY MET, SO-CALLED TECHNICALLY MET ITS PRIMARY ENDPOINT AND CAN NOW MOVE ON TO A LATER STAGE STUDY.

AGAIN, I'LL SHOW YOU TWO SLIDES WITH REGARD TO THE EARLY SIGNS OF POTENTIAL EFFICACY. COHORT A IS THE LOWER DOSE GROUP, THE COHORT B THE HIGHER DOSE GROUP. AND THIS IS ONE OF THOSE MEASURES, SO THESE ARE PATIENTS RELATIVELY SEVERE. AND EVEN WITH THE BEST TREATMENT, THEY SPEND ABOUT FOUR, FIVE HOURS OF THE DAY SO-CALLED OFF. SO THEY CANNOT PROPERLY DO THEIR ACTIVITY OF DAILY LIFE, PROPERLY MOVE AROUND, AND SO FORTH, SO THEY ARE OFF.

BUT YOU CAN SEE THEY GOT NEARLY AN ADDITIONAL -- THEY COULD REDUCE THAT FOUR TO FIVE HOURS BY ABOUT TWO HOURS IN THE HIGHER DOSE. AND

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THIS IS THE CONVERSE ONE SO-CALLED ON TIME. OBVIOUSLY IF THEY'RE NOT OFF, THEY'RE ON, BUT THEY'RE ON NOW WITHOUT ANY OF THOSE DYSKINESIA THAT YOU SOMETIMES SEE IF YOU GET ON WITH A DRUG.

WHAT'S ALSO EXCITING IS THAT TREND SEEMS TO CONTINUE. SO THESE ARE THE DATA JUST RELEASED ABOUT A MONTH OR A FEW WEEKS ACTUALLY, LESS THAN A MONTH AGO, FROM THE 18TH MONTHS DATA. AND NOW IT'S ACTUALLY 2.7 HOURS IN THE HIGH DOSE TO OFF IMPROVED AND 2.7 HOURS IN THE ON. AND SO THAT'S REALLY IMPORTANT BECAUSE BY 12 MONTHS WE REMOVE THE IMMUNOSUPPRESSION. BUT THAT SUGGESTS, AGAIN, IF YOU BELIEVE THIS IS A REAL MEANINGFUL EFFECT, GOES IN THE RIGHT DIRECTION, CELLS CONTINUE TO MATURE, SEEMS TO HAVE BETTER EFFECT ON THE IMMUNOSUPPRESSION, DID NOT IMPACT THE LOSS OF IMMUNOSUPPRESSION.

THAT'S ANOTHER SCORE. AGAIN, MANY OF YOU MIGHT NOT KNOW EXACTLY PARKINSON'S SCORE, BUT IT'S THE MOST WIDELY USED PARKINSON'S SCORE. ON THE SCALE, THESE PATIENTS HAVE TYPICALLY ABOUT 40 TO 50 POINTS. THE MORE POINTS YOU HAVE, THE MORE SEVERE YOU ARE. YOU SEE THAT BY 12 MONTHS, PARTICULARLY IN THE HIGH DOSE GROUP, THERE SEEMS TO BE A TREND THAT THIS GETS BETTER BY 13 POINTS. AND EVEN THE WORST PATIENT SHOWN HERE WAS GOING A LITTLE BIT DOWN.

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AND, AGAIN, USUALLY AS THE DISEASE PROGRESSES, YOU SLOWLY INCREASE THE SCORE.

BUT WHAT'S REALLY EXCITING IS BY 18 MONTHS THE HIGH DOSE COHORT WENT ALL THE WAY TO MINUS 23 POINTS, WHICH IS A QUITE A BIG POINT CHANGE. AGAIN, WE HAVE TO BE VERY CAREFUL BECAUSE IT'S A SMALL GROUP OF PATIENTS, BUT IT'S AT LEAST AS GOOD AS WE COULD HAVE EXPECTED FROM A PHASE 1 STUDY. AND SO WE'RE REALLY EXCITED TO SEE HOW THAT MOVES FORWARD.

SO THE WAY IT'S SUPPOSED TO MOVE FORWARD IS THAT WE'RE NOW MOVING TO NEXT PHASE OF STUDY, WHICH IS SUPPOSED TO START IN Q3 OF THIS YEAR, AND THAT WILL BE A PLACEBO CONTROLLED STUDY. AND THERE'S, AGAIN, SOME CHALLENGES HOW YOU ACTUALLY DO THAT FOR A SURGICAL TRIAL, PUTTING CELLS INTO THE BRAIN AND SO FORTH. SO HAPPY TO DISCUSS THAT, BUT THIS WILL, AGAIN, START VERY, VERY SOON ON A LARGE SET OF PATIENTS AND MANY MORE CENTERS THAN THE EARLY STUDY.

HERE WE GET, THEN AGAIN, HOW THIS COMPARED TO OTHER ONGOING EFFORTS IN THE FIELD, AND I THINK YOU DISCUSSED A LITTLE BIT WHAT CIRM ALREADY FUNDED. SO THERE HAS BEEN A TRIAL STARTED IN JAPAN ACTUALLY QUITE A LONG TIME AGO, BUT THEY HAVE A SLIGHTLY DIFFERENT APPROACH. SO UNLIKE OUR GROUP WHERE WE

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MAKE SOMETHING LIKE TEN BILLION CELLS OFF THE SHELF, THEN WE JUST GO BACK TO THE FREEZER AND TAKE CELLS FOR EVERY PATIENT, THEY HAD TO PREPARE THE CELLS FOR INDIVIDUAL PATIENTS BECAUSE THEY COULDN'T FREEZE THE CELLS AT THE ENDPOINT. SO THEY HAVEN'T REALLY REPORTED THEIR RESULTS YET, BUT THEY HAVE THOSE SEVEN PATIENTS. AND I THINK THEY'RE AT THE ONE- OR TWO-YEAR MARK. SO HOPEFULLY SOON WE'LL HEAR FROM THEM. AND THEY ACTUALLY WANT TO DO A SIMILAR EARLY STAGE, I THINK A PHASE 1 TRIAL, THEY APPLIED FOR FDA DOING THAT IN THE U.S.

THERE'S ANOTHER GROUP IN LUND, AND ACTUALLY THOSE THREE GROUPS TOGETHER WITH OUR GROUP, SO-CALLED FOUNDER OF GFORCE-PD, WHERE AS A COMMUNITY WE TRIED TO HELP EACH OTHER NOW MOVING THE FIELD FORWARD IN KIND OF A NONCOMPETITIVE, COLLABORATIVE MANNER EVEN THOUGH WE ALL STARTED OUR OWN COMPANIES IN ORDER TO TAKE THIS WORK FORWARD.

SO THIS HAVE SO FAR GRAFTED TWO PATIENTS, AND THEY USE A VERY SIMILAR TYPE PRODUCT, WHICH IS ALSO OFF THE SHELF, LARGE-SCALE. THERE WAS ONE PATIENT REPORTED IN THE PAST THAT WAS BASICALLY TREATED IN A WAY THAT DIDN'T REALLY REQUIRE THE STANDARD FDA APPROVAL BECAUSE THEY'RE A ONE-OFF CASE, NOT A REAL CLINICAL TRIAL. BUT IT'S NOT CLEAR

HOW MUCH THE PATIENT REALLY BENEFITED, BUT IT WAS THE FIRST AUTOLOGOUS STUDY. SIMILAR TO WHAT ASPEN WANTED TO DO IN CALIFORNIA, WAS MENTIONED BEFORE, I DON'T THINK THEY GRAFTED ANY PATIENT YET, BUT THEY HAVE CLEARANCE.

THERE'S ANOTHER GROUP IN SOUTH KOREA THAT HAS, I THINK, BY NOW DOSED 12 PATIENTS. BUT, AGAIN, THEY'VE JUST FINISHED THE DOSING. SO THEY'RE NOW MAYBE ABOUT ROUGHLY TWO YEARS BEHIND OUR STUDY TO REPORT ON THEIR DATA.

AND THEN THERE ARE ADDITIONAL TRIALS PLANNED. I THINK WE HEARD ABOUT KENAI WAS MENTIONED BEFORE. OLE ISAACSON AT HARVARD RECENTLY GOT APPROVAL FOR ANOTHER AUTOLOGOUS TRIAL.

SO THE POINT I'M TRYING TO MAKE HERE IS THAT OBVIOUSLY THERE'S A HIGH LEVEL OF SATURATION ALREADY IN THE FIELD, NOT TO SAY THERE SHOULDN'T BE MORE, BUT I THINK IT'S IMPORTANT THAT NEW TRIALS, I THINK, GO A LITTLE BIT BEYOND WHAT HAS BEEN ALREADY DONE. AND I THINK THAT'S GOING TO BE NOW ON A MUCH QUICKER PACE, SOME OF THE OTHER TOPICS I WANT TO TOUCH UPON.

SO WHAT ARE THE CHALLENGES OF THE APPROACH, KIND OF THE APPROACH THAT I MENTIONED FOR OURSELVES, FOR EXAMPLE? SO I SHOWED YOU THAT MAYBE

THE HIGHER DOSE OF PATIENTS DOES BETTER, BUT IS THIS REALLY THE BEST DOSE? HOW DO YOU FIGURE IT OUT IS ACTUALLY QUITE CHALLENGING. I MENTIONED ALSO SOME TRIALS ARE ALLOGENEIC, OFF THE SHELF, SOME ARE AUTOLOGOUS PATIENT BY PATIENT. SOME GROUPS WANT TO MAKE IMMUNE-COMPATIBLE CELLS, UNIVERSAL CELLS, SO-CALLED HYPER-IMMUNE CELLS. BUT THERE'S QUESTIONS. RIGHT NOW ALL THE GROUPS PUT THE CELLS INTO THE TARGET REGION WHERE THE DOPAMINE IS MISSING, BUT THEY DON'T PUT THEM EXACTLY AT THE PLACE WHERE THEY NORMALLY ARE. SHOULD THAT BE DONE? IT'S AN INTERESTING QUESTION.

THEY ARE ALSO DIFFERENT STAGES OF CELLS THAT ARE USED THAT MIGHT HAVE DIFFERENT POTENCY. AND THERE'S ALSO STILL THIS ISSUE OF GRAFT SURVIVAL, THAT MANY CELLS ACTUALLY DIE WHEN YOU INJECT THEM, AND THAT CAN LEAD TO VARIABILITY EVEN IF YOU JUST SIMPLY ADD MORE CELLS TO COMPENSATE FOR THAT.

THERE'S ALSO AN IMPORTANT ISSUE. NOW, IF YOU THINK ABOUT ACTUAL TRANSLATION, I WANT TO DO THAT ROUTINELY, HUNDREDS OF THOUSANDS OF PATIENTS ON THE THERAPY, WHAT IS THE DEVICE YOU ARE GOING TO USE? YOU'RE NOT ALWAYS GOING TO HAVE AN EXPERT LIKE VIVIANE WHO WORKED ON THAT FOR MANY YEARS IN ANIMAL MODELS AND CAN LOAD THIS COMPLICATED WAY THE NEEDLE.

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SO A LOT OF EFFORT BY MANY WHO SAY THEY NEED TO INVEST INTO DEVICES TO MAKE THAT KIND OF FOOLPROOF. AND SO I THINK THAT'S AN AREA THAT'S GOING TO BE QUITE IMPORTANT, BUT THAT'S GOING TO BE SPONSORED BY ORGANIZATIONS LIKE CIRM OR DONE IN THE INDUSTRY. WE'LL HAVE TO SEE.

THERE'S ALSO NEW WAYS TO TRACK PATIENTS. RIGHT NOW WE DO UPDRS TIME OFF. THESE ARE VERY CRUDE MEASURES. AND SO YOU CAN IMAGINE THAT A LOT OF INFORMATION THAT YOU CAN GET FROM WEARABLES, APPLE WATCHES; FITBITS, AND SO FORTH. THERE'S A SYSTEM THAT ACTUALLY BLUE ROCK OR BAYER IS USING CALLED EMERALD WHERE YOU DON'T NEED TO EVEN WEAR A DEVICE. YOU CAN INSTALL IT AT HOME, AND THEY CAN REMOTELY KEEP TRACK OF THE MOVEMENT OF PATIENTS.

AND THEN THERE'S ALSO THE QUESTION OF PATIENT STRATIFICATION. WE KNOW SO MUCH MORE ABOUT THE DISEASE. MICHAEL J. FOX FOUNDATION TOGETHER WITH OTHERS INVEST HUNDREDS OF MILLIONS TO REALLY DO THIS TRACKING OF PATIENTS. AND SO WE CAN NOW ASK WHAT ARE THE BEST PATIENTS THAT MIGHT BENEFIT FROM THIS APPROACH? WHAT ARE THE ONES MAYBE THAT ARE LESS SUITED? AND HOW CAN WE HAVE MAYBE BIOMARKERS THAT HELP US TO STUDY THAT?

WHAT ABOUT ON THE CELL SIDE? WHAT'S THE

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NEXT GENERATION CELLS? SO THERE IS ALWAYS -- YOU CAN MAKE CELLS ALWAYS BETTER, NO? YOU CAN ALWAYS MAKE THEM MORE POTENT. WE THINK MAYBE IT COULD MAKE THEM FULLY MORE MATURE WHEN YOU INJECT THEM. MAYBE THEY NEED LESS CELL TO MATURE. THERE WOULD BE REALLY NO RISK AT ALL THAT THE CELLS COULD FORM TUMORS IF THEY'RE ALL POSTMITOTIC.

SO THESE ARE AREAS WHERE YOU COULD DEVELOP, BUT SOME PEOPLE WILL SAY WHY DO YOU NEED IT IF THE OTHER STUFF ALREADY WORKS. BUT THAT'S AN AREA THAT CONTINUES TO BE DEVELOPED, PARTICULARLY IF YOU GET SOME OF THE RIGHT SUBTYPES.

THIS ISSUE OF SURVIVAL, WE MADE ACTUALLY SOME MAJOR PROGRESS. THERE'S A PAPER COMING OUT SOON WHERE WE FIGURED OUT SOME OF THE MECHANISM WHY CELLS DIE WITHIN ACTUALLY THE FIRST FEW DAY AFTER GRAFTING. AND WE HAVE A VERY SIMPLE FIX THAT HAS TO DO WITH TNF ALPHA SIGNALING THAT CAN BASICALLY OVERCOME THAT THAT COULD BE ADDED TO SUCH GRAFT, MAYBE MAKE THEM MORE RELIABLE AND REQUIRING LESS CELLS.

AND THEN, FINALLY THAT'S REALLY A BIG TOPIC, NO, FOR THE FIELD. CAN WE DO CELL PLUS GENE? SO CAN WE ADD A GENE THAT HELPS THE CELLS TO BE EVEN BETTER THAN THE NATURAL VERSION?

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SO I ALREADY MENTIONED, FOR EXAMPLE, YOU COULD MAKE THEM SUCH THAT MAYBE DON'T EVEN NEED INITIAL 12 MONTHS OF IMMUNE SUPPRESSION. TECHNICALLY YOU CAN DO IT, BUT YOU MAKE CELLS THAT ARE IMMUNE EVASIVE, BUT THEY HAVE THEIR OWN RISKS.

THE OTHER OPTION IS YOU GRAFT THE CELLS INTO A PATIENT THAT HAS AN ONGOING DISEASE, AND THERE ARE WAYS YOU MIGHT ACTUALLY BE ABLE TO PROTECT THOSE CELLS MORE EFFECTIVELY. AND, AGAIN, WE DON'T GO TOO MUCH IN TECHNICAL DETAILS, BUT (CORRUPTED TRANSMISSION) THAT'S GOING TO BE REQUIRED TO TRANSMIT THE DISEASE TO THE GRAFT.

BUT THERE'S ALSO THE IDEA THAT YOU CAN INTRODUCE CERTAIN GENE MUTATIONS THAT ARE ACTUALLY NOT ONLY NOT CAUSING THE DISEASE, BUT MIGHT PROTECTIVE IN THOSE NEURONS. YOU MAKE A SPLIT OF THE NEURONS THAT MIGHT DO MUCH, MUCH BETTER IN THE DISEASE CONTEXT.

YOU COULD ALSO USE GLIAL CELLS. THESE ARE VERY INTERESTING AREAS THAT COULD BE PURSUED FOR THE NEXT GENERATION. THERE'S ALSO CLINICIAN T HAT COMES THERE AND HAS TO DO, AS I SAID BEFORE, IF IT ALREADY WORKS, HOW DO YOU KNOW IT WORKS BETTER? AND SO SOMETIMES YOU CAN JUST GO TO LARGER ANIMAL MODELS. AND ONE AREA, FOR EXAMPLE, THAT YOU WANT TO STUDY:

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IS IT A GOOD IDEA TO PUT THE CELLS ALSO BACK INTO THE LOCATION WHERE THEY NORMALLY ARE IN THE MIDBRAIN? BUT FROM THERE THEY NEED TO MAKE VERY, VERY LONG CONNECTIONS BACK TO THE TARGET REGION.

SO THE IDEA WOULD BE TO MAKE TWO SITES. ONE SITE WHERE THE CELLS ARE IMPLANTED CURRENTLY LIKE IN THE CLINICAL TRIAL, BUT ANOTHER SITE WHERE THEY ARE NORMALLY LOCATED. BUT WE NEED TO HAVE A LARGE ANIMAL MODEL TO SHOW THAT THIS APPROACH REALLY CAN WORK OVER VERY LARGE DISTANCES.

THE OTHER POINT IS, AGAIN, NOT VERY SENSITIVE TO POTENCY. SOME OF THOSE ASSAYS IN THE ANIMAL ROTATE ON THEIR AXIS. THEY RECOVER VERY EASILY. IF YOU HAVE NOW A CELL THAT'S THREE TIMES MORE POTENT, THEY'RE STILL GOING TO RECOVER THE SAME WAY. THEY'RE ALREADY FULLY RECOVERED. SO WE NEED TO THINK MORE SENSITIVE ASSAYS THAT PEOPLE TRY TO DEVELOP. FOR EXAMPLE, THEY USE DEEP LEARNING IN THE MOUSE BEHAVIOR, BUT THEY HAVE THE ANIMALS DOING TASKS AND SO FORTH. SO IT'S GOING TO BE VERY IMPORTANT TO LOOK AT MUCH MORE FINE BEHAVIORAL FUNCTION OR FUNCTIONS RELATED TO LEARNING AND SO FORTH.

AND THESE ARE OTHER ANIMALS THAT MAYBE MIMIC THE DISEASE A LITTLE BIT BETTER. THIS IS AN

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ANIMAL MODEL FROM JIM SURMEIER THAT'S VERY CHRONIC PROGRESSIVE. FIRST YOU LOSE THE DOPAMINE FIBERS WHERE THEY CONNECT IN THE BRAIN AND ONLY LATER THE CELL BODIES. AND THAT'S EXACTLY WHAT HAPPENS NORMALLY IN THE DISEASE UNLIKE THE MODELS THAT WE'VE USED FOR OUR CLINICAL DEVELOPMENT WHERE WE JUST WIPE OUT THE DOPAMINE CELLS IN ONE SHOT.

THERE'S ANOTHER ANIMAL THAT NOW VIVIANE TABAR, I MENTIONED HER NAME BEFORE, WE WORK A LOT WITH HER. SHE USES AN ANIMAL MODEL THAT ACTUALLY HAS KIND OF A TREMOR-LIKE SYMPTOM SIMILAR TO THE PATIENTS AND THAT HAS ALSO DISEASE SYMPTOMS, THIS ALPHA-SYNUCLEIN IN THE BRAIN. AND TO SEE HOW THE CELLS BEHAVE IN THIS DISEASE ENVIRONMENT WILL BE VERY INTERESTING. BUT, AGAIN, AN AREA I THINK THAT IS INTERESTING TO ACTUALLY BETTER UNDERSTAND INTERACTION OF THE CELLS IN SUCH A BRAIN.

NOW, THAT LEADS ME THEN TO THE NEXT POINT, WHICH IS WHAT CAN WE DO MAYBE BEYOND DOPAMINE? SO EVERYTHING THAT I TALKED TO YOU ABOUT HAS BEEN TO MAKE THE DOPAMINE APPROACH BETTER, MAYBE MAKE IT MORE POTENT, MAYBE DOESN'T REQUIRE IMMUNE SUPPRESSION, AND SO FORTH. I THINK THESE ARE ALL IMPORTANT AREAS.

AND, AGAIN, THIS IS GOING TO BE VERY SHORT

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BECAUSE, AGAIN, WE DON'T REALLY KNOW TOO MUCH YET, BUT I LISTED WHEN I GAVE YOU THE PICTURE NOW WITH THE PATIENT AND WITH THE SYMPTOMS, IT HAD SOME OF THOSE POINTS, LOSS OF SMELL, SLEEP DISORDERS, GASTROINTESTINAL DISORDER. AND IF YOU TALK TO SOME OF THE PATIENTS, THEY CAN ACTUALLY BE QUITE DEBILITATING, PARTICULARLY THE GI COMPONENT. THEY OFTEN REALLY COMPLAIN QUITE SEVERELY. IT'S NOT JUST A LITTLE BIT BEING DISCOMFORT WHERE IT CAN BE REALLY QUITE DEBILITATING. BUT OBVIOUSLY EVEN MORE DEBILITATING EVENTUALLY IS THE COGNITIVE LOSS OF FUNCTION.

AND SO, AGAIN, RIGHT NOW WE DON'T HAVE ANY GOOD APPROACH AT THIS POINT, AND WE DON'T ALSO KNOW EXACTLY EVERYTHING ABOUT COGNITIVE LOSS IN PD. BUT THERE'S PROBABLY TWO COMPONENTS TO IT. ONE HAS TO DO MORE WHERE WE ACTUALLY MIGHT HAVE A SHOT TO HAVE SOME IMPACT WITH THE DOPAMINE NEURONS. IF THERE IS SOME DOPAMINERGIC INNERVATION OF THE FOREBRAIN, FRONTAL CORTEX, THAT MIGHT ACTUALLY BENEFIT FROM THE NEW DOPAMINE NEURONS. AND IT HAS TO DO WITH KIND OF WHAT YOU CALL EXECUTIVE FUNCTION THAT GETS WORSE IN PATIENTS. SO THERE MIGHT BE SOME HOPE THAT CERTAIN SMALL AREA OF SYMPTOMS MIGHT IMPROVE COGNITIVELY. BUT THE MUCH BIGGER PROBLEM IS THIS DIFFUSE LEWY

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BODY DISEASE, BUT THERE'S NO REASON TO BELIEVE THAT DOPAMINE NEURON REPLACEMENT WOULD ADD TO ANYTHING MAJOR ABOUT THAT AND CAN AFFECT MANY NEURON POPULATION.

NOW, ONE POPULATION THAT GETS AFFECTED ALSO QUITE EARLY ARE NOT JUST DOPAMINE NEURONS. THEY ARE ACTUALLY FOREBRAIN CHOLINERGIC NEURONS. SO THEY ARE SITTING, AGAIN, IN THE NUCLEUS IN THE BRAIN AS YOU CAN SEE HERE. THAT BASICALLY IS AN AREA THAT PROTECTS VERY, VERY WIDELY WITHIN THE BRAIN TO ALL KIND OF AREAS, THE HIPPOCAMPUS, THE CORTEX, AND SO FORTH. AND THEY ACTUALLY DIE QUITE EARLY OR ARE AFFECTED DYSFUNCTIONAL ALSO QUITE EARLY IN PARKINSON'S DISEASE. AND THERE'S A LONG HISTORY ACTUALLY GOING BACK TO FETAL GRAFT AND SIMILAR TO DOPAMINE NEURON FETAL GRAFTING, WHERE PEOPLE TRIED TO HAVE MODELS TO KIND OF HAVE A DEGENERATION OF THOSE CELLS AND SEE WHERE THEY CAN BE REPLACED USING FETAL ISSUE.

I SHOW YOU HERE ONE SUCH STUDY THAT WAS ONE OF THE MAJOR ONES. IT'S SO-CALLED A COGNITIVE TEST, A WATER MAZE TEST WHERE THE MOUSE NEEDS TO KNOW WHERE BASICALLY A SAFE EXIT IS ON THE PLATFORM. AND THE RED ONE IS THE SAFE AREA. YOU CAN SEE NORMAL MOUSE FINDS THIS PLATFORM QUITE ROUTINELY. A

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LESIONED ONE DOESN'T. THE GRAFTED ONE IS NEARLY AS GOOD AS THE NORMAL ONE. AND SO THIS IS GRAFT OF THOSE BASAL FOREBRAIN CHOLINERGIC NEURONS.

AND WE HAVEN'T REALLY DONE MUCH ON THAT WORK, BUT I KNOW THE SWEDISH GROUP UNDER S. LUND AND AGNETE KIRKEBY AND OTHERS, THEY ACTUALLY NOW GO BACK AND USE SOME OF THE PROTOCOLS WE AND (UNINTELLIGIBLE) CHUNG DEVELOPED, REFINED THEM FURTHER, AND ACTUALLY TRIED LISTING PRECLINICALLY, SEE CAN WE HAVE A COMBINED APPROACH. COULD YOU HAVE DOPAMINE NEURONS FOR THE CLASSIC MOTOR DISEASE? AND COULD YOU HAVE THOSE FOREBRAIN CHOLINERGIC NEURONS FOR SOME OF THE COGNITIVE SYMPTOMS THAT YOU SEE IN AD? AGAIN, CLEARLY WOULDN'T TREAT ALL THE SYMPTOMS, BUT THAT'S SOMETHING THAT IS CURRENTLY ACTUALLY BEING KIND OF RE-PURSUED WITHIN THE FIELD.

NOW, AGAIN, THERE ARE OBVIOUSLY OTHER WAYS THAT CAN BE THOUGHT ABOUT AND OTHER CELL TYPES THAT PEOPLE HAVE THOUGHT ABOUT IS PARTICULARLY CELLS THAT WOULD JUST SIMPLY AFFECT THE DISEASE PROCESS, MAYBE A LITTLE BIT, AGAIN, IN THE CELL PLUS GENE; BUT IN THIS CASE, PROBABLY NOT THE DOPAMINE NEURONS, BUT MAYBE MORE ASTROCYTES OR MICROGLIA THAT COULD PRODUCE ANTIBODIES OR COULD BE ANTI-INFLAMMATORY TO AFFECT THE DISEASE PROCESS.

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NOW, AND EVEN MORE KIND OF OUT THERE AND, AGAIN, NOT SOMETHING WHICH CAN HAPPEN IMMEDIATELY, BUT TECHNICALLY FEASIBLE IS TO TREAT THE GASTROINTESTINAL SYMPTOMS IN PD. SO WE, FOR EXAMPLE, HAVE SHOWN COUPLE OF YEARS AGO THAT IN A VERY SEVERE MODEL IN A MOUSE WHERE A MOUSE ACTUALLY DOESN'T HAVE THE NERVE CELLS OF THE GUT PROPERLY FUNCTIONING, THE SAME NERVE CELLS THAT DON'T PROPERLY FUNCTION IN PARKINSON'S DISEASE BECAUSE THEY'RE AFFECTED BY THE DISEASE, YOU CAN LITERALLY REPLACE THEM.

SO THESE RED SPOTS ALONG THE COLON ARE NOW HUMAN CELLS THAT TAKE UP SHOP QUITE QUICKLY IN A MOUSE. AND THIS IS NOW MUCH, MUCH LATER, SOMETHING LIKE, I THINK IT WAS, NINE MONTHS LATER, YOU CAN SEE THIS BEAUTIFUL FIBER THAT'S A NETWORK THAT CORRESPONDS TO THE ENTERIC NERVOUS SYSTEM, BUT IT'S COMPLETELY HUMAN DERIVED IN A MOUSE.

WHAT YOU CAN SHOW THEN IS THAT NOW THE GUT, THE COLON ACTUALLY CONTRACTS AND RELEASES. AS YOU KNOW, WHEN YOU PUSH THE FOOD FORWARD, WHICH IS THIS BLUE, ORANGE, RED PERISTALTIC MOVEMENT OVER TIME, THERE'S A TIME AXIS, YOU CAN SEE THAT YOU CAN TRIGGER THESE NICE WAVES OF PERISTALTIC IN COLON COMPLETELY WITHIN THIS HUMAN ENTERIC NERVOUS SYSTEM.

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AGAIN, HERE THE IDEA WOULD BE THAT YOU WOULD FIRST GO TO VERY SEVERE DISEASE, LIKE HIRSCHSPRUNG, SHOWS THAT THIS CAN BE ROUTINELY AND SAFELY DONE, BUT MAYBE THAT IS NO LONGER COMPLETELY CRAZY. NOW THEY USE THESE CELLS IN OTHER DISORDERS MAYBE IN THE CONTEXT OF (CORRUPTED TRANSMISSION) DISEASE, MAYBE IN THE CONTEXT EVEN OF PARKINSON'S DISEASE.

SO THEN LAST BUT NOT LEAST, THE QUESTION IS REALLY BEYOND PARKINSON'S. I'M NOT GOING TO SPEND MORE THAN LIKE ONE MINUTE ON THAT BECAUSE THAT WAS NOT THE TOPIC OF TODAY. BUT I MENTIONED SOME OF THOSE CELLS NOW THAT WE COULD PUT IN LIKE GLIAL CELLS, FOR EXAMPLE, THAT COULD HAVE A DISEASE MODIFYING ROLE, THAT'S CLEARLY THE CASE IN PARKINSON'S DISEASE, BUT I THINK WHERE IT'S ALREADY GETTING PURSUED IS IN ALZHEIMER'S DISEASE. THIS IS FROM WORK YOU PROBABLY KNOW, (UNINTELLIGIBLE) BUT YOU CAN ACTUALLY LITERALLY SWAP MICROGLIA. THESE ARE HUMAN MICROGLIA IN THE MOUSE BRAIN. WE ARE DOING SOME OF THOSE STUDIES TOO. AND YOU CAN THEN HAVE A REJUVENATED POPULATION BECAUSE THE MICROGLIA YOU HAVE IN YOUR BRAIN THAT CAME DURING DEVELOPMENT INTO THE BRAIN, THEY HAVE BEEN THERE FOR 50, 60 YEARS, WHATEVER YOUR AGE IS. YOU CAN GIVE THEM EASILY A CARGO OR AS WE CALL YOU CAN MAKE THEM

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STEALTHS. YOU CAN GIVE THEM SUPRAPHYSIOLOGICAL FUNCTIONS THAT WOULD MAKE THEM BEING NOT ONLY NOT SO MUCH AFFECTED BY THE DISEASE, BUT HELP THE DISEASE.

AND SO I THINK THESE ARE ALL VERY EXCITING AREAS, AND YOU CAN JUST SIMPLY SWITCH THE CARGO AND CONDITIONS AND THEN APPLY THAT BACK, FOR EXAMPLE, TO PARKINSON'S DISEASE WHERE THE MECHANISMS ARE SLIGHTLY DIFFERENT, BUT MICROGLIA AND ASTROCYTES PLAY ALSO A VERY IMPORTANT ROLE AND, AGAIN, COULD BE SIMILARLY SWAPPED, SO TO SAY.

ANOTHER AREA THAT'S BEING DONE, THERE IS THE SAME APPROACH THAT I MENTIONED WHICH IS BASAL FOREBRAIN NEURONS OBVIOUSLY YOU COULD TRY. IN AD IT HAS BEEN DONE BEFORE. AND I THINK I MENTIONED THAT THOSE INTERNEURON APPROACHES ARE ACTUALLY ALSO QUITE INTERESTING IN THE CONTEXT OF AD BECAUSE THERE ARE CERTAIN NEUROPHYSIOLOGICAL CHANGES THAT HAPPEN THAT ARE IMPORTANT FOR COGNITION. THERE'S LI-HUEI TSAI AT MIT THAT ACTUALLY TRIES TO PURSUE THAT LESS WITH INTERNEURON, BUT BY STIMULATING THEM, MIMICKING INTERNEURON LIKE TO PHYSIOLOGICALLY.

AND THEN, FINALLY, WE ALREADY HEARD FROM NEURONA. THERE WAS REALLY BEAUTIFUL WORK WITH INTERNEURONS IN CALIFORNIA FOR SEIZURES. I THINK THEY'RE ALSO INTERESTED IN PAIN. AND THERE ARE

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OTHER TYPES OF INTERNEURONS THAT COULD BE INTERESTING FOR SPINAL CORD INJURY.

SO THIS IS JUST A KIND OF A LITTLE BIT OF AN EXCURSION BEYOND PD, BUT I THINK, AGAIN, THIS GOES FORTH AND BACK TO SEE WHAT ARE THE RIGHT CELL TYPES THAT CAN BE PURSUED BY CELL THERAPY.

LAST BUT NOT LEAST, HERE'S SOME OF THE CONCLUSIONS FOCUSING ON PARKINSON'S. SO, AGAIN, DOPAMINE NEURON REPLACEMENT IS NOW IN THE CLINIC, AT LEAST IN THE EARLY STAGE TRIAL WITH LATER STAGE TRIAL GETTING STARTED, PROMISING EARLY RESULTS. MANY GROUPS ARE PURSUING IT, INCLUDING BIG PHARMA. SO BAYER ACQUIRED BLUE ROCK. NOVO NORDISK IS SPONSORING THE TRIALS IN EUROPE. AND MULTIPLE START-UPS. WE HEARD FROM KENAI AND ASPEN AND SO FORTH IN ADDITION TO SOME ACADEMIC CENTERS.

MY POINT IS THAT THERE COULD BE A BIG IMPACT THAT REALLY TRY TO DEVELOP NEURAL APPROACHES, NOT JUST DOING THE EXACT SAME CELLS AT MANY MORE PLACES, BUT SEE WHERE ARE THE BOTTLENECKS THAT I TRIED TO HIGHLIGHT. CELL PLUS GENE IS ONE OF THOSE APPROACHES. BUT, AGAIN, MAYBE WON'T BE VERY BOLD. MAYBE YOU CAN ALSO THINK AND INVEST IN THE AREAS TO ACTUALLY TARGET SOME OF THE NON-DOPAMINE-RELATED SYMPTOMS IN PARKINSON'S, APPROACHES THAT COULD

BENEFIT NEURODEGENERATION BEYOND PARKINSON'S.

AND THEN FINALLY THERE'S JUST SOME OF THE PEOPLE. I'M NOT GOING TO SPEND MUCH TIME, BUT THIS IS SOME OF THE CREW IN MY LAB THAT REALLY DOES THE DOPAMINE WORK CURRENTLY, BUT THEN ALSO IT'S THE WHOLE TEAM NEEDED THAT'S NOW MOVED FROM MY LAB, AT LEAST SOME OF THEM, TO BLUE ROCK THERAPEUTICS AND LEADS THE EFFORTS OVER THERE.

I'M GOING TO STOP HERE AND OBVIOUSLY BE HAPPY TO TAKE ANY OF THE QUESTIONS YOU MIGHT HAVE.

CHAIRMAN GOLDSTEIN: THANK YOU, LORENZ. THAT'S REALLY TERRIFIC. LET ME LAUNCH THE QUESTIONS BY ASKING A FAIRLY SIMPLE ONE. IS THE BASAL FOREBRAIN ORDINARILY RECEIVING DOPAMINERGIC INPUT FROM THE SUBSTANTIA NIGRA, OR IS ITS FAILURE AN AUTONOMOUS DEFECT RELATIVE TO THE SUBSTANTIA NIGRA, OR IS IT JUST UNCLEAR?

DR. STUDER: I THINK IT'S NOT COMPLETELY CLEAR, BUT I WOULD GUESS, PRETTY HEAVILY GUESS THAT IT'S UNRELATED BECAUSE THERE ARE MANY OTHER BRAIN REGIONS THAT ARE AFFECTED. I DIDN'T TALK, FOR EXAMPLE, ABOUT LOCUS COERULEUS. THAT'S ANOTHER POPULATION VERY EARLY AFFECTED, NOT A POPULATION CAN BE GRAFTED, AND CAN BE ACTUALLY GENERATED BY -- CHUN-LI ZHANG JUST PUBLISHED A PAPER ON MAKING

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LOCUS COERULEUS NEURONS. VERY IMPORTANT FOR SOME OF THE SLEEP-RELATED, MOTOR-RELATED SYMPTOMS IN PD, BUT THAT'S EVEN FURTHER BEHIND TRYING TO DEVELOP THAT. BUT I THINK THESE ARE ALL INTERESTING AREAS.

CHAIRMAN GOLDSTEIN: YEAH. THAT'S QUITE A LOT OF OVERLAP WITH ALZHEIMER'S DISEASE ACTUALLY BECAUSE THE LOCUS COERULEUS GOES -- IT FAILS EARLY IN AD AS WELL.

QUESTIONS FROM THE REST OF THE GROUP?

MS. MANDAC: J.T. HAS HIS HAND RAISED.

CHAIRMAN GOLDSTEIN: J.T., PLEASE.

CHAIRMAN IMBASCIANI: J.T., UNMUTE.

DR. THOMAS: SORRY ABOUT THAT. LORENZ, OUTSTANDING PRESENTATION. THANK YOU SO MUCH. REALLY APPRECIATE IT.

QUESTION ON IPS WORK THAT'S USED IN CONNECTION WITH HIGH THROUGHPUT SCREENING AGAINST NEURONS IN THE DISH. I KNOW THIS IS SOMETHING YOU WERE WORKING ON A LITTLE WHILE AGO, BUT I'M JUST CURIOUS WHAT THE LATEST IS. SO ONE OF THE ISSUES WHEN YOU OBVIOUSLY REPROGRAM IPS CELLS INTO NEURONS, THEY'RE SORT OF YOUNG NEURONS, IF YOU WILL, IN THE DISH AND HAVEN'T FULLY ADVANCED TO MATURITY WHERE THEY'D HAVE FULL MANIFESTATION OF WHATEVER THE PHENOTYPIC CONDITION IS YOU'RE TRYING TO STUDY,

WHETHER IT'S PARKINSON'S OR ALZHEIMER'S OR WHATEVER.

WHAT'S BEEN DONE TO ACCELERATE THAT PROCESS TO MAKE DRUG SCREENING SORT OF MORE RELEVANT TO LATER STAGE DISEASE?

DR. STUDER: I THINK THERE'S A LOT OF EARLY STAGE DEVELOPMENTS IN THOSE AREA. WE ACTUALLY -- IT'S AN AREA THAT WE ARE REALLY INTERESTED IN. AND SO WE JUST PUBLISHED TWO PAPERS ON WHAT WE REFER TO AS IMPROVING THE MATURATION STAGE. THERE WAS ONE PAPER IN *NATURE*, ONE PAPER IN *NATURE BIOTECH* EARLY THIS YEAR. THAT HAS TO DO WITH NEURONAL MATURATION. SO WE CAN ADD COMPOUNDS THAT AFFECT THE CHROMATIN STATE TEMPORARILY. IT LOOKS LIKE THE TIMING IS CONTROLLED BY A CLOCK, THE HUMAN CLOCK, BECAUSE IT TICKS MUCH LOWER THAN THE MOUSE, AND IT HAS TO DO WITH CERTAIN CHROMATIN STATE OF THE CELL. SO WE CAN TEMPORARILY DISRUPT THAT, AND THEN THE CELLS THAT RESULT AFTER THE DISRUPTION ACTUALLY MOVE MUCH FASTER THROUGH THE MATURATION STAGES.

NOW, WE HAVEN'T REALLY USED THAT EITHER IN IN VIVO STUDIES OR EVEN FOR DRUG DISCOVERY. THAT'S ACTUALLY SOMETHING WE'RE DOING RIGHT NOW WHERE WE TRY TO SEE CAN WE INTEGRATE THAT. AND SO THAT'S ONE COMPONENT, ACTUALLY TWO COMPONENTS. ONE IS REMOVING WE CALL THE EPIGENETIC BARRIER. AND THE OTHER ONE

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IS ACTIVITY RELATED. SO YOU CAN ADD FACTORS THAT CONTROL THOSE TWO COMPONENTS TO MAKE THE NEURONS GO FASTER. THEN WE HAVE ALSO NEW STUDY THAT SHOULD COME OUT SOON, IT'S NOT COMPLETELY OUT YET, THAT HAS TO DO WITH THE WAY WHERE WE START WITH ALZHEIMER'S DISEASE, BUT ALSO IN PARKINSON'S WHERE WE SCREENED EVERY SINGLE GENE IN THE HUMAN GENOME THAT CAN SYNERGIZE WITH THE DISEASE SUSCEPTIBILITY TO TRIGGER DISEASE.

WE FOUND A PATHWAY WHERE WE CAN JUST WITH A COMPOUND WE CAN STIMULATE THOSE CELLS AND THEY KIND OF IN ABOUT TEN DAYS TRIGGER AGE-LIKE FEATURES, BUT THEY'RE NOT FULLY MATURE. SO IT'S A BIT OF A DIFFERENT THING BETWEEN MATURATION AND AGING, BUT THEY ARE GETTING THESE AGING FEATURES THAT MAKES THEM NOW VULNERABLE TO DISEASE THAT MIMICS WHAT HAPPENS LATER IN LIFE.

AGAIN, THOSE ARE JUST AREA OF MATURATION AND AGING IN OUR LAB, AND I'M SURE OTHER PEOPLE DO THAT TOO, TRY TO INTEGRATE TO DO DRUG SCREENING. AND I THINK THAT'S, AGAIN, AN AREA THAT'S VERY INTERESTING.

BUT THE OTHER THING IS THAT A LOT OF EFFORTS ARE NOW DONE TO DO THAT NOT JUST IN ONE PATIENT. AS I MENTIONED, FOR PATIENT

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STRATIFICATION, THIS PPMI COHORT, WE AND OTHERS HAVE NOW IPS CELLS FROM THOSE HUNDREDS OF INDIVIDUALS. AND WE CAN GROW IT NOT ONLY ONE BY ONE, BUT WE MAKE POOLS OF THEM. WE CALL THEM A VILLAGE IN A DISH. THEY HAVE A WHOLE VILLAGE OF, LET'S SAY, HUNDRED TO 200 PATIENTS, AND YOU GIVE THEM A DRUG. YOU DO THE AGING, WHATEVER YOU DO, AND THEN THEY SHOULD HAVE THE DISEASE MANIFESTATION. YOU CAN NOW LITERALLY SEE NOW WHICH OF THE PATIENTS RESPOND TO INTERVENTION.

IN THE PAST THAT WAS VERY, VERY DIFFICULT BECAUSE, AS YOU KNOW, GROWING HUNDRED, 200 CELLS IN EACH WELL IN A SYNCHRONIZED MANNER IS VERY DIFFICULT FOR SOME OF THOSE CELL TYPES. BUT SO THIS VILLAGE IN A DISH, I THINK, IS NOW THE RECENT DEVELOPMENT, I THINK THAT'S GOING TO CHANGE HOW PEOPLE ARE GOING TO DO SOME OF THOSE DISEASE MODELING STUDIES. SO THERE ARE A LOT OF DEVELOPMENT, I THINK, ON THIS AREA AS WELL FOR DRUG DISCOVERY THAT WE ARE VERY EXCITED. AND, AGAIN, FOR FULL DISCLOSURE, WE STARTED ANOTHER COMPANY WHICH IS CALLED DACAPO BRAINSCIENCE, WHICH IS NOW JUST GETTING INTO THIS AREA THAT USES SOME OF THOSE TOOLS TOGETHER WITH MACHINE LEARNING TOOLS. FROM THE PATIENT DATA, WE TRY TO INTEGRATE AND KNOW HOW DO YOU PREDICT PROGRESSION? HOW DO YOU RESPOND

TO GENETIC PERTURBATION? HOW DO YOU RESPOND TO DRUGS?

SO IT'S AN AREA I'M VERY EXCITED ABOUT ACTUALLY, WHICH IS ALWAYS INDEPENDENT OF CELL THERAPY, BUT IS ACTUALLY DRUG DISCOVERY.

DR. THOMAS: THANK YOU. VERY EXCITING.

CHAIRMAN GOLDSTEIN: YEAH. A LOT OF GREAT WORK GOING ON, LORENZ.

OTHER QUESTIONS FROM THE TASK FORCE? OKAY. SO HAS JEFF ROTHSTEIN JOINED US?

MS. MANDAC: YES.

DR. ROTHSTEIN: YES, I'M HERE.

CHAIRMAN GOLDSTEIN: ALL RIGHT. SO, JEFF, YOU'VE GOT A TOUGH ACT TO FOLLOW HERE, BUT I'M SURE YOU'LL BE MORE THAN CAPABLE OF IT.

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JEFF IS AN M.D./PH.D. HE'S MOVED AROUND TO A LOT OF PLACES, BUT HE'S REALLY SPENT THE BULK OF HIS CAREER AT HOPKINS WHERE HE HAS LED THE DEPARTMENT OF NEUROSCIENCES FOR PART OF HIS TIME THERE, AND PERHAPS MOST IMPORTANT HE DEVELOPED THE PACKARD ALS CENTER, WHICH I HAD SOME ASSOCIATION WITH SOME YEARS AGO, AND IT IS A TRULY POWERFUL DISCOVERY ENGINE IN THE AREA OF ALS. AND SO JEFF WILL GIVE US SOME UNDERSTANDING OF WHAT'S CURRENT IN ALS AND PERHAPS WHERE TO GO NEXT WITH RESEARCH.

SO, JEFF, YOU'RE UP.

DR. ROTHSTEIN: GREAT. THANKS, LARRY. NICE TO SPEND SOME TIME WITH YOU. I ACTUALLY WAS INVOLVED WITH CIRM WHEN YOU FIRST STARTED MANY YEARS AGO AS AN EXTERNAL REVIEWER.

I'M GOING TO TRY MOVE FAST. I KNOW THIS IS A MIXED GROUP. ONE OTHER BIT OF BACKGROUND, I'M BOTH A NEUROLOGIST. I FOUNDED THE ALS CLINIC AT HOPKINS. SO I'VE RUN MOST, IF NOT ALL, OF THE ALS CLINICAL TRIALS OVER THE YEARS, BUT I RUN A BASIC SCIENCE LAB WORKING ON BASIC CELL BIOLOGY UNDERLYING ALS, OF COURSE, WITH THE HOPES OF FINDING DRUGS.

WHAT I'M NOT GOING TO TELL YOU ABOUT IS CELL THERAPY. AND I'M FROM THE EAST COAST, AND I'M NOTHING BUT BLUNT. SO CELL THERAPY FOR ALS IS A

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BUNCH OF BULLSHIT. IT'S A WASTE OF TIME. THE REAL VALUE IN CELLS IN ALS, WHICH IS LARGELY A SPORADIC DISEASE, NOT UNLIKE PARKINSON'S. AND, OF COURSE, YOU JUST HEARD THE ELEGANT WORK BY LORENZ. AND ALZHEIMER'S IS TRYING TO FIND APPROACHES TO SPORADIC ALS, AND THERE IS NO ANIMAL MODEL FOR SPORADIC ALS. AND SO THIS IS WHERE IPS CELLS BECOME A REAL PLATFORM.

SO I'M GOING TO FIRST VERY QUICKLY TELL YOU ABOUT A PATHWAY, AND BURIED IN THAT WILL BE HOW YOU CAN USE IPS CELLS AS A PLATFORM TO UNDERSTAND THE PATHOGENESIS CASCADE THROUGH THE DISEASE AS WELL AS THERAPIES AND WHERE WE'RE GOING IN THE FUTURE.

SO THE START OF THIS IS VERY BASIC, AND IT'S ABOUT A NEW PATHWAY THAT UNDERLIES ALMOST ALL OF SPORADIC ALS. REAL QUICK BACKGROUND BECAUSE I DON'T KNOW THE BACKGROUND OF YOU. ALS LIKE ALZHEIMER'S AND PARKINSON'S, THIS IS A LARGELY A SPORADIC DISEASE. THIS DISEASE LARGELY AFFECTS YOUR VOLUNTARY MOTOR SYSTEM. IT'S DUE TO THE LOSS OF CORTICAL MOTOR NEURONS, WHICH INTERACT WITH SPINAL MOTOR NEURONS AND CONTROL THE CONTRACTION OF MUSCLES, BOTH VOLUNTARY MUSCLES, SUCH AS, OF COURSE, YOUR ARMS AND YOUR LEGS, BUT ALSO YOUR DIAPHRAGM AND THE FIRST PART OF YOUR SWALLOWING MUSCLES. AS SUCH,

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ALS IS A UNIFORMLY FATAL DISEASE. THERE ARE NO ESCAPEES FROM THIS DISEASE.

AND TYPICALLY IT PROGRESSES OVER TWO TO THREE YEARS; BUT LIKE ALL MEDICAL DISEASES, THERE ARE EXCEPTIONS. I'VE SEEN WELL OVER 10,000 PATIENTS, AND MY FASTEST PATIENT HAS BEEN SOMETHING ON THE ORDER OF THREE MONTHS FROM ONSET. NOW THERE ARE THOSE THAT ARE 20 AND 30 YEARS. SO HIGHLY VARIABLE. WHY THAT'S VARIABLE IS A DIFFERENT ISSUE, BUT IT'S ALWAYS FATAL.

WE USED TO THINK OF ALS AS ONLY A MOTOR SYSTEM DISEASE. IT IS NOT. 50 PERCENT OF PATIENTS CAN DEVELOP A MILD DEMENTIA, AND A SMALL PERCENTAGE, ABOUT 10 PERCENT, OVERLAP WITH HAVING A FRONTAL TEMPORAL DEMENTIA AS WELL AS ALS. AND WE NOW KNOW SOME OF THE GENES THAT CAUSE FRONTAL TEMPORAL DEMENTIA ARE THE SAME GENES THAT CAUSE ALS. ALTHOUGH WE THINK OF IT AS A MOTOR SYSTEM DISEASE, IN THE EARLY DAYS OF EVEN THE USE OF STEM CELLS FOCUSED ON MOTOR NEURONS, THAT MISSES THE BOAT. THERE ARE MANY OTHER CELL TYPES THAT DEGENERATE IN ALS THAT CONTRIBUTE TO THE CLINICAL SYNDROME OF THE DISEASE.

THE FIRST GENE DISCOVERED WAS SOD1, AN ANTIOXIDANT GENE DISCOVERED IN THE EARLY '90S BY BOB

BROWN AND TEEPU SIDDIQUE. AND THAT LED TO THE FIRST MOUSE MODELS IN ANY NEURODEGENERATIVE DISEASE, WHAT'S KNOWN AS THE SOD1 MOUSE. IT'S USED FOR MORE THAN TWO DECADES TO GRADE MOUSE IN THAT IT LOOKS LIKE ALS, AND IT'S A TERRIBLE MOUSE FOR DETERMINING WHAT DRUGS WORK IN PATIENTS. IN FACT, NO MODEL TO DATE HAS BEEN AN EXACT PREDICTOR OF WHAT WORKS IN PATIENTS OTHER THAN THE SOD1 MOUSE BECAUSE TURNING OFF THAT GENE, WHICH IS A THERAPY THAT WAS JUST APPROVED BY THE FDA, SHOWS REMARKABLE EFFICACY IN HUMANS. SO KNOW THE MUTATION, YOU CAN HAVE A GREAT OUTCOME. AND WHEN TIME PERMITS, I'LL TALK ABOUT OTHER MUTATIONS.

A REAL CHANGE IN THE DISEASE CAME WITH THE DISCOVERY OF A GENE CALLED C9ORF-72, LONG NAME, A GENE WHOSE PROTEIN WE DON'T ENTIRELY KNOW WHAT IT DOES, BUT IT'S AN UNUSUAL MUTATION BECAUSE IT'S IN THE FIRST INTRON. AND THAT CAUSES A VARIETY OF OTHER PROBLEMS, INCLUDING ABERRANT RNA SPECIES AS WELL AS ABERRANT POLYPEPTIDES THAT ARE MADE FROM THAT GENE. THAT GENE IS ACTUALLY VERY COMMON. UP TO 20 TO 40 THE PERCENT OF ALS PATIENTS THAT INHERITED ALS HAVE THAT GENE MUTATION. AND UP TO 10 TO 20 PERCENT OF SPORADIC PATIENTS WITH NO FAMILY HISTORY HAVE THAT MUTATION AS WELL. AND IT'S

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EQUALLY COMMON IN FRONTAL TEMPORAL DEMENTIA.

IT'S THE MOST COMMON DISEASE CAUSING GENE IN FTD AS WELL. YOU CAN HAVE A FAMILY WITH A SISTER WITH FTD WITH THE GENE MUTATION AND A BROTHER WITH ALS. REALLY A PHENOMENAL FOCUS OF RESEARCH IN THE LAST DECADE OR SO. NEVERTHELESS, MOST OF THE DISEASE IS SPORADIC, AND THAT BECOMES AN IMPORTANT POINT WHEN WE'RE THINKING ABOUT HOW DO WE UNDERSTAND WHAT'S THE MOST EFFECTIVE THERAPY FOR THE DISEASE.

OVER THE YEARS USING MOUSE MODELS, AND IN FACT FROM THE MID-1990S WHEN THE MOUSE MODELS WERE FIRST DEVELOPED HEAVILY HERE AT HOPKINS, WE, THE COMMUNITY, IT'S A ROYAL WE, USE THOSE MICE TO TRY TO UNDERSTAND PATHWAYS. BECAUSE UNDERSTANDING THE PATHWAYS, AS SHOWN IN THIS SLIDE FROM A COUPLE YEARS AGO FROM COLLEAGUES IN EUROPE, ARE THE WAYS YOU FIND DRUGS FOR THE DISEASE. AND NO MATTER WHAT YOU WANT TO STUDY, ULTIMATELY IT'S KNOWING THE DISEASE CAUSING PATHWAYS. AND EACH OF THESE PATHWAYS HAVE BEEN DESCRIBED IN MICE.

NOW, THE UNFORTUNATE PART OF THIS, AND I'M GOING TO COME BACK TO THIS IN JUST A FEW MINUTES, IS THAT MOUSE MODELS ARE GREAT. THEY LOOK LIKE THE DISEASE, BUT THEY MAY NOT RECAPITULATE WHAT REALLY HAPPENS IN HUMAN. AND QUITE HONESTLY, THE ONLY

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THING THAT COUNTS -- I'M NOT INTERESTED IN CURING A MOUSE OR ANY OTHER ORGANS IN A FLY, A FISH. I NEED TO KNOW THIS IS A PLATFORM FOR FINDING THERAPIES IN HUMAN.

AND THE REASON I POINT THAT OUT IS BECAUSE OVER THE YEARS THE MOUSE MODEL WHICH WAS DISTRIBUTED WORLDWIDE, GREAT TOOL, WAS NOT ALWAYS MATCHED WITH HUMAN STUDIES TO PROVE THAT THE PATHWAY OF DISCOVERY, WHEREVER IT MIGHT BE, WAS ALSO PRESENT IN HUMANS. AND IF IT'S NOT PRESENT IN HUMANS, QUITE FRANKLY, WHO GIVES A SHIT? IT ONLY COUNTS WHEN IT'S PRESENT IN HUMANS.

MANY OF THESE HAVE BEEN ULTIMATELY DESCRIBED IN HUMANS. ACTUALLY STARTED WITH WORK IN MY OWN LAB STUDYING ASTROCYTES AND EXCITOTOXICITY, AND THAT ACTUALLY LED TO THE FIRST FDA-APPROVED DRUG FOR ALS. WE'VE ONLY HAD ABOUT TWO OTHER DRUGS APPROVED, AND NONE OF THEM WORK ANY BETTER THAN THAT FIRST DRUG UNFORTUNATELY.

I'M JUST GOING TO SKIP THROUGH THIS FOR THE SAKE OF TIME.

WHAT HAPPENED WAS ABOUT A DECADE AGO, MORE THAN A DECADE AGO, ONCE C9 WAS DISCOVERED, WE WERE FORTUNATE THAT THE NIH SPONSORED EFFORTS TO DEVELOP IPS CELLS FOR ALS, HUNTINGTON'S DISEASE, AND

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PARKINSON'S DISEASE. AND I RAN THE ALS PROGRAM ALONG WITH -- THEN I BROUGHT IN COLLABORATORS, KEVIN EGGAN AND CHRIS HENDERSON, THEN STILL IN ACADEMICS, NO LONGER UNFORTUNATELY, BUT THEY'RE STILL GREAT SCIENTISTS. AND FROM THOSE IPS CELLS, WE BEGAN TO HAVE A SENSE OF WHAT'S REALLY GOING ON IN HUMAN TISSUES, EVEN THOUGH IT'S NOT A COMPLETE SYSTEM, AND SOME DISEASES CLEARLY YOU CAN'T JUST USE SIMPLE 2D IPS CELLS. BUT IF YOU'RE TRYING TO UNDERSTAND THE CELL BIOLOGICAL PATHWAY, YOU CAN USE THAT SYSTEM.

AND IN THOSE DAYS A MOUSE, IT TOOK YEARS BEFORE A MOUSE COULD EVER BE BUILT AROUND THIS MUTATION. AND WE BEGAN TO DISCOVER THAT FUNDAMENTAL TO SOME OF THESE MUTATIONS, ESPECIALLY ALS, WAS INVOLVEMENT UNDER THE NUCLEAR PORE, WHICH I'M GOING TO TALK ABOUT IN A MINUTE.

SO THE NUCLEAR -- EVERY NUCLEUS HAS NUCLEAR PORES. THINK OF IT AS A TENNIS BALL WITHIN A TENNIS BALL. AND THEY HAVE ABOUT 2,000 TO 3,000 NUCLEAR PORES. THIS ALLOWS THE MOVEMENT OF MOLECULES IN AND OUTSIDE THE NUCLEUS. REMEMBER WITHIN THE NUCLEUS IS YOUR DNA, WHICH EVENTUALLY CODES FOR RNA, WHICH EVENTUALLY LEADS TO THE PROTEINS THAT ARE MADE IN EVERY CELL. AND OUR BODY'S BIOLOGY IS ULTIMATELY ABOUT PROTEINS. THAT

ENTIRE PROCESS OF MOVING IN AND OUT IS CONTROLLED BY THE NUCLEAR PORE. IT'S ONE OF THE LARGEST COMPLEXES IN THE HUMAN BODY. THAT NUCLEAR PORE OR COMPLEX IS A THOUSAND PROTEIN MOLECULES ASSEMBLED IN SORT OF LIKE A DONUT. THIS IS ACTUALLY A SCHEMA OF WHAT THAT LOOKS LIKE.

THIS SCHEMA OF THE HUMAN NUCLEAR PORE STRUCTURE WAS ACTUALLY PUT TOGETHER BY SOMEONE IN YOUR STATE, ANDRE HOELZ AT CALTECH, A COLLABORATOR OF OURS, AND HE COULD DETERMINE THE ACTUAL ASSEMBLY OF ALL OF THESE PROTEINS THAT MAKE UP DIFFERENT DOMAINS OF THIS NUCLEAR PORE.

THE NUCLEAR PORE NOT ONLY REGULATES WHAT MOVES IN AND OUT OF THE NUCLEUS RNA'S AND PROTEINS, BUT IT INTERACTS DIRECTLY WITH THE DNA AS WELL TO REGULATE GENE ACTIVATION. SO IT'S A REALLY IMPORTANT STRUCTURE IN THE CELLS.

AND WE LEARNED EARLY ON, NOW ALMOST ABOUT EIGHT YEARS AGO, THAT THERE WERE DEFECTS IN THE NUCLEAR PORE. I'M NOT GOING TO WORK YOU THROUGH ALL OF THOSE EXPERIMENTS, BUT THE NUCLEAR PORE STRUCTURE IS BOUND TO THE NUCLEAR MEMBRANE. SO THINK OF THESE INDIVIDUAL LITTLE DONUTS ON A SURFACE OF A TENNIS BALL HAS TO BE BOUND TO THE TENNIS BALL, AND THOSE ARE WHAT ARE KNOWN AS TRANSMEMBRANE NUCLEAR PORE

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PROTEINS. AND WE LEARNED THAT A NUMBER OF THESE NUCLEAR PORES WERE MISSING IN SPORADIC ALS AS WELL AS C9 ALS. AND I'LL TELL YOU MORE ABOUT THAT IN JUST A SECOND.

AND IT ALL BEGAN WITH THE LOSS OF ONE THAT LED TO A CASCADE, KIND OF LIKE A DOMINO EFFECT, OF OTHERS THAT BEGAN WITH ONE PROTEIN KNOWN AS POM121. WHEN IT'S LOST FROM THE NUCLEAR PORE, THERE'S A SERIES OF OTHER NUCLEOPORINS THAT ARE LOST AS WELL. THAT EVENTUALLY AFFECTS THE TRANSPORT IN AND OUT OF CELLS AND MAKES THOSE NEURONS, ESPECIALLY MOTOR NEURONS, MUCH MORE SUSCEPTIBLE TO DEATH.

THIS IS AN IMPORTANT CASCADE BECAUSE, SEPARATE FROM THE STUDIES WE WERE DOING, OTHERS IN THE FIELD WAY BACK IN 2005 HAD DETERMINED THAT FIRST IN ALS, AND I'LL COME BACK TO OTHER DISEASES IN A MINUTE, THERE'S A NUCLEAR PROTEIN KNOWN AS TDP-43. FIRST WE DIDN'T KNOW MUCH ABOUT WHAT IT DOES. AGAIN, WHEN I SAY WE, IT'S THE ROYAL WE. BUT WE LEARNED THAT IN DISEASES LIKE ALS AND LATER FRONTAL TEMPORAL DEMENTIA AND EVEN HALF OF ALZHEIMER'S DISEASE, THIS PROTEIN IS CLEARED FROM THE NUCLEUS OR PARTIALLY CLEARED. IT BECOMES VERY CYTOPLASMIC AND IT EVENTUALLY AGGREGATES. AND WHEN IT'S NO LONGER IN THE NUCLEUS, WE'VE LEARNED THAT ITS FUNCTION TO

REGULATE MANY, MANY, HUNDREDS, IF NOT THOUSANDS, OF RNA'S ARE LOST. AND IF YOU ARTIFICIALLY TURN OFF THAT PROTEIN, THIS WAS DONE BY ANOTHER MEMBER OF YOUR STATE, DON CLEVELAND AND COLLABORATORS AS WELL AS KEVIN EGGAN INDEPENDENTLY, A WHOLE SERIES OF GENES ARE MISHANDLED. IN FACT, TODAY INDIVIDUAL BIOTECH COMPANIES ARE TARGETING SINGLE GENES TO REPLACE THEM. BUT THE REALITY IS ALL OF THESE GENES ARE MISHANDLED BECAUSE OF THIS PROTEIN NOT BEING IN THE NUCLEUS.

OF COURSE, A QUESTION WOULD BE WHY IS IT NOT IN THE NUCLEUS? IT'S NOT IN THE NUCLEUS BECAUSE OF NUCLEAR PORE DEFECTS. AND WE DISCOVERED THAT NOW ENTIRELY BASED, STARTING FROM ABOUT 2013, USING IPS CELLS, CAN'T STUDY THIS IN MOUSE, NO MOUSE DEVELOPS THIS DEFECT. THIS IS A COMMON DEFECT OF SPORADIC ALS. NO RODENT MODEL SHOWS THAT. BUT HUMAN IPS CELLS -- AND I'LL GET TO THE QUESTION THAT JON ASKED EARLIER AND LORENZ IS TALKING ABOUT MATURATION IN JUST A MOMENT.

TURNS OUT WHEN YOU HAVE THESE CELLS, AND WE'RE LOOKING HERE AT IPS CELLS THAT ARE VERY YOUNG. SORRY. I SAID THAT WRONG. THESE ARE IPS CELLS TURNED INTO EARLY MOTOR NEURONS ONLY ABOUT A WEEK OR TWO OF AGE. THESE LITTLE GREEN DOTS ARE THE NUCLEAR

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PORES ON THE SURFACE OF THE NUCLEUS. AND WHAT HAPPENS IS THERE'S A PROTEIN CALLED CHMP7, WHICH REGULATES SORT OF THE STRUCTURE OF NUCLEAR PORES, CLEANS THEM OUT, PUTS THEM BACK IN.

AND WE LEARNED EARLY ON WELL BEFORE THERE'S ANY DISEASE IN THESE IPS CELLS THAT THIS CHMP7 IS RELOCALIZED TO THE NUCLEUS. SHOULDN'T BE THERE. SHOULD LOOK LIKE CONTROLS. YOU WAIT A COUPLE WEEKS LONGER, AND THE NUCLEAR PORE MAY LOOK LIKE THE SAME GREEN DOT -- IT'S NOT. THESE ARE NUCLEAR PORES -- ARE THEN MISSING IN ALS. THIS IS ONE OF EIGHT THAT ARE MISSING.

AND THEN WE WAIT LONGER, AND THEN THERE'S A DEFECT IN NUCLEAR TRANSPORT, THE FUNCTION OF THE NUCLEAR PORE. AND THEN WE WAIT EVEN LONGER AND NOW THAT WHOLE TDP-43 PROCESS IS COMPLETELY ABNORMAL.

SO THE POINT OF THIS IS IF THIS IS A MOUSE EXPERIMENT, THIS MIGHT BE A MOUSE AT 30 DAYS OF AGE, 60 DAYS OF AGE, A YOUNG ADULT, AND FINALLY A MORE SENIOR ADULT THAT DEVELOPS THE DISEASE PHENOTYPE.

SO GETTING BACK TO WHAT YOU WERE TALKING ABOUT EARLIER WITH LORENZ, WE ACTUALLY DO HAVE A PATHOGENIC CASCADE. I DON'T CARE IF THESE ARE YOUNG CELLS. THEY'RE MATCHING, AS YOU WILL SEE IN A MOMENT, THE PATHOGENIC CASCADE THAT OCCURS IN

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HUMANS. THIS IS NOT ABOUT SYNAPTIC BIOLOGY. IN ALS IT'S NOT ABOUT SYNAPTIC BIOLOGY. IT'S MORE ABOUT THE CELL BIOLOGY OF THE CELL AND CAN WE SEE THAT PHENOTYPE. SO ALTHOUGH PEOPLE BANTER AROUND ABOUT EPIGENETIC MODIFICATIONS AND STUFF, IT'S ALL BULLSHIT WHEN IT COMES TO THIS. WE SEE THE CASCADE THAT'S PRESENT IN PATIENTS IN THE CELLS AS THEY MATURE. AS YOU WILL SEE, THIS IS VERY RELEVANT TO OUR PATIENTS AS WELL.

WHY DOES THIS OCCUR IS A BIG QUESTION. SO LET ME GO BACK A STEP AND TELL YOU A PROGRAM THAT WAS ESSENTIAL FOR ALL OF THIS. IF YOU'RE LOOKING AT A SPORADIC DISEASE, YOU CAN'T LOOK AT ONE OR TWO IPS LINES. IT'S NONSENSE. IT'S ME IN THE CLINIC LOOKING AT ONE OR TWO PATIENTS. I CAN MAKE NO CONCLUSIONS FROM LOOKING AT ONE OR TWO PATIENTS. I NEED HUNDREDS OF PATIENTS, CERTAINLY DOZENS. AND WHEN WE DESIGNED -- WHEN I DESIGNED THE PROGRAM BACK IN 2013 CALLED ANSWER ALS, THE IDEA THERE WAS LET'S BUILD IPS LINES FROM NOT ONE OR TWO OR THREE PATIENTS, BECAUSE THIS IS A SPORADIC DISEASE, FROM A THOUSAND PATIENTS. AND ANSWER ALS WAS A PROGRAM THAT WE ACTUALLY STARTED ENROLLING IN 2016, FINISHED ENROLLING BY ABOUT 2021. AND IT'S A BIG CONSORTIUM AND HEAVILY INVOLVES ACTUALLY MEMBERS OF YOUR --

ACADEMIC MEMBERS IN YOUR STATE.

WE ENROLLED AT EIGHT CLINICS AROUND THE COUNTRY. THE CLINICS ARE SHOWN HERE. OBVIOUSLY A LITTLE HEAVY ON THE EAST COAST. AND WE REALLY ENROLLED IN CLINICS THAT WE KNEW WE COULD ENROLL FAST. WE ENROLLED A THOUSAND PATIENTS IN A LITTLE OVER A YEAR.

EVERY PATIENT HAD WHOLE GENOME SEQUENCING. IN EVERY PATIENT WE MADE IPS CELLS FROM THEIR BLOOD. THAT WAS DONE WITH CLIVE SVENDSEN AT CEDARS-SINAI. AND IN DOING A THOUSAND, WE UNIFORMLY CREATED THE SAME LINES WITH RIGOROUS QUALITY CONTROL BUILT INTO THAT, REPRODUCIBILITY BUILT INTO THAT, AND EACH OF THOSE LINES WERE THEN DIFFERENTIATED TO EARLY STAGE MOTOR NEURONS OR SPINAL NEURONS, NOT JUST PURE MOTOR NEURONS. AND BY THE WAY, THAT'S IMPORTANT. SOME PEOPLE WANT TO LOOK AT A SINGLE CELL TYPE. ALS IS NOT ABOUT JUST MOTOR NEURONS. I ALREADY TOLD YOU IT INVOLVES OTHER CELLS AS WELL AS GLIAL CELLS. WE WANTED SORT OF A SAMPLE EQUIVALENT OF A BIOPSY OF THE SPINAL CORD.

SO WE DID SPINAL DIFFERENTIATIONS. AND EACH OF THOSE BATCHES OF DIFFERENTIATIONS FROM EACH CELL THEN UNDERWENT PROTEOME, EPIGENOME, AND RNA SEQ.

IN AGGREGATE, ALONG WITH LONGITUDINAL CLINICAL DATA FROM EVERY SINGLE PATIENT USING AN IPHONE APP -- IBM WATSON WAS A PARTNER IN THIS -- AND IT AMOUNTED TO ABOUT -- AMOUNTS TO ABOUT 6 BILLION DATA POINTS PER PATIENT. WE'LL GET TO THAT LATER, BUT WHAT IT ALSO MEANT IS THAT WE HAVE AN ENORMOUS BANK OF WELL-DIFFERENTIATED OR WELL-DESCRIBED IPS LINES WITH FULL CLINICAL DATA THAT WE CAN PICK AMONG TO DO OUR ANALYSIS. AND THE HOPES WERE WOULD WE FIND SUBGROUPS OF THIS SPORADIC DISEASE BECAUSE PATIENTS, I GOT TO TELL YOU, ARE ALL OVER THE PLACE. I ALREADY TOLD YOU AT THE BEGINNING THREE MONTHS SURVIVAL, 30-YEAR SURVIVAL. WHAT ARE THESE DIFFERENCES BECAUSE IN CLINICAL TRIALS WE LUMP EVERYONE TOGETHER. AND AS YOU WILL SEE LATER IN THE TALK, WE OBVIOUSLY FAIL AT OUR CLINICAL TRIALS, BUT UNDERSTANDING THE MOLECULAR PATHWAYS, AND IPS CELLS HAS THAT POTENTIAL, IN FACT, IT DOES SHOW THAT POTENTIAL, WE CAN POTENTIALLY TARGET THE RIGHT DRUGS TO THE RIGHT PATIENT.

SO HERE'S A REAL-WORLD EXAMPLE. I'VE JUST TOLD YOU ABOUT THESE PATHWAYS. TDP-43 AND CHMP7, WHICH IS AN EARLY INJURY TO THE NUCLEAR PORE, THIS IS A REALLY BUSY SLIDE, BUT THERE'S A TON OF DATA. WHAT YOU'RE SEEING HERE IS SOMETHING WE COMPLETED

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RECENTLY. THIS IS 200 PATIENTS, INDIVIDUAL IPS LINES, GREAT REPRODUCIBILITY IN PRODUCING AND WE WAIT -- IT'S NOT SHOWING HERE. WE CAN LOOK AT DIFFERENT TIME POINTS, 30 DAYS, 45 DAYS, 60 DAYS. AND WHEN WE DO THAT, WE ACTUALLY SEE THE DEVELOPMENT OF WHAT YOU'RE SEEING HERE. THIS IS KNOWN AS A HEAT MAP FOR THOSE NOT FAMILIAR. AND THE DARKER THE COLOR THE MORE DYSFUNCTIONAL THAT PATHWAY IS. YOU CAN OBVIOUSLY SEE THERE ARE NOT A LOT OF CHANGES HERE BECAUSE THESE 30-ODD CONTROL PATIENTS, YOU AND ME, IF YOU WILL, YEAH, THERE'S NO ABNORMALITIES.

AND BY THE WAY, WHEN I SAY ABNORMALITIES, YOU PROBABLY WOULD HAVE A HARD TIME SEEING THAT, BUT THIS FIRST COLUMN IS A DEFECT IN THE PATHWAY THAT'S INJURING THE NUCLEAR PORE COMPLEX. ALL OF THE C9, FTD/ALS, SPORADIC ALS ALL HAVE JUST -- ALMOST ALL OF THEM HAVE ABNORMALITIES OR AT LEAST 85 PERCENT IN CHMP7, THEY ALL HAVE ABNORMALITIES IN THE NUCLEAR PORE. AND MOST OF REST OF THESE ARE THOSE TDP-43 PRODUCTS. REMEMBER I TOLD YOU THERE'S ONE OR TWO OR A HUNDRED DIFFERENT, IF NOT A THOUSAND. HERE WE'RE PICKING 18 DIFFERENT ONES.

AND VERY QUICKLY, YOU CAN SEE THAT, GEEZ, THERE'S A BUNCH OF RED HERE. THAT'S BECAUSE C9 PATIENTS, THEY HAVE A DEFECT IN THIS PATHWAY THAT

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THE REMAINING PATIENTS AREN'T AS DEFECTIVE IN. EVEN THOUGH IT'S TDP-43, SOMETHING IS DIFFERENT ABOUT THEM. ALL OF THE ALS PATIENTS IN AGGREGATE HAVE TDP-43 DEFECTS, BUT IT'S VARIABLE. SO RIGHT NOW, FOR EXAMPLE, BIOTECH COMPANIES ARE FOCUSING ON ONE OF THEM CALLED STATHMIN. THAT'S THIS COLUMN HERE, BUT YOU CAN SEE THE RED ONE STATHMIN, THERE'S ONLY ABOUT 10 PERCENT OF PATIENTS. THIS WOULD TEACH US THAT THE IPS PLATFORM ALLOWS US TO TELL US MAYBE WHICH OF THE PATIENTS ARE BETTER TIED TO A DISEASE THERAPY THAN OTHERS. THIS IS REALLY IMPORTANT WHEN WE PUT OUR TRIALS TOGETHER BECAUSE TRIALS TAKE A LONG TIME, IT'S A FATAL DISEASE, YOU'D LIKE TO BE ASSURED OF POSITIVE OUTCOMES.

AND SOME PATIENTS ACTUALLY HAVE VERY LITTLE CHANGE THAT ARE SPORADIC ALS, WHICH MEANS SOMETHING IS DIFFERENT ABOUT THEM. THERE'S NOT A NUCLEAR PORE. THERE'S NOT A TDP-43 ABNORMALITY EVEN THOUGH MOST PEOPLE THINK THAT EVERYONE HAS A TDP-43 ABNORMALITY. SO THIS IS PLATFORM, WHICH, BY THE WAY, IS SHOWING YOU THE SAME THING WE CAN SEE IN PATIENTS. I'LL SHOW YOU THAT IN A MINUTE.

IT TEACHES US THAT FOR THIS PATHWAY, YOU DON'T NEED A MOUSE MODEL. YOU DON'T NEED ALL THAT STUFF ABOUT AGING EPIGENETICS, NOT THAT THAT CAN'T

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BE IMPORTANT. THIS PATHWAY IS DETECTABLE IN AN IPS PLATFORM.

NOW, DOES IT MATCH, THOUGH, HUMAN BRAIN? EARLIER I TOLD YOU IT'S REALLY IMPORTANT WHATEVER MODEL YOU USE MATCHES HUMAN BRAIN. FORTUNATELY, BECAUSE OF THAT LARGE ANSWER ALS PROGRAM, WE ACTUALLY HAVE AUTOPSIES FROM THE SAME PATIENTS THAT WE GENERATED IPS CELLS FROM, AND WE CAN MAKE THE COMPARISON. DID THAT IPS CELL FOR THESE PATHWAYS TEACH US THE SAME THING YOU SEE AT THE OTHER END OF LIFE, DEATH? AND THE ANSWER IS YOU BET IT DID. SO THESE ARE A HANDFUL OF PATIENTS THAT WE'VE STUDIED, AND I'M NOT GOING TO GO THROUGH ALL OF THESE. THESE ARE THE SAME RNA PROCESSING PRODUCTS, BUT BASICALLY THE CHANGES THAT WE SEE IN IPS CELLS WE SEE IN THE SAME PATIENT'S BRAIN AT DEATH. AND THAT MEANS FOR THIS PATHWAY, THIS MODEL SYSTEM, AND NOT ALL MODEL SYSTEMS WILL THIS APPLY TO, IS A GREAT REPRODUCER OF WHAT'S GOING ON IN PATIENTS. IT RECAPITULATES THE SAME CHANGES WE SEE IN PATIENTS.

AND WE'VE EVEN DONE MULTIPLE -- IT'S HARD FOR YOU TO SEE -- BUT MULTIPLE TISSUE SAMPLES FROM THE SAME PATIENT'S CORTEX, AND IT'S VERY REPRODUCIBLE. DEFECTS IN IPS MATCH DEFECTS WE SEE IN PATIENTS.

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THIS IS REALLY IMPORTANT IF YOU ARE GOING TO USE A MODEL SYSTEM. I'M NOT GOING TO TELL YOU THIS APPLIES TO OTHER PATHWAYS THAT MAY APPLY TO ALS, BUT THIS IS A MAJOR PATHWAY THAT UNDERLIES SPORADIC ALS, THE VAST AND COMMON FORM OF ALS. IS THIS MODEL SYSTEM GOING TO TEACH US ABOUT INFLAMMATION? NO. THERE'S NO MICROGLIA IN THIS PATHWAY, BUT DO I CARE ABOUT THAT? NO. AND I'LL TELL YOU WHY IN A MINUTE.

CAN WE LEARN THE RELATIONSHIP BY USING THESE LARGE NUMBERS OF IPS CELLS TO ACTUAL CLINICAL INDICES? WELL, WE'RE JUST BEGINNING TO DO THAT. THIS IS WHERE YOU NEED AI TO COME IN, AND WE HAVE COLLABORATORS HERE AT HOPKINS, AND IT'S PART OF THE ANSWER ALS PROGRAM AT MIT. WE BEGIN TO LOOK AT THAT, AND SOME OF THESE PATHWAYS IN IPS CELLS DO MATCH THE CLINICAL INDICES THAT WE'RE SEEING. IN THIS CASE, AGE OF ONSET SEEMS TO MATCH THE CHANGES WE'RE SEEING IN THE IPS CELLS THAT WE'VE LOOKED AT SO FAR.

NOW, BY THE WAY, THAT VARIABILITY I SHOWED YOU IN IPS CELLS, WE CAN TAKE A DOZEN OR TWO DOZEN HUMAN BRAINS AT AUTOPSY AND SHOW ACTUALLY THAT SAME VARIABILITY. SO STATHMIN OR UNC13, THESE ARE THE SINGLE TARGETS THAT ARE OF GREAT IMPORTANCE. RIGHT

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NOW THERE'S SOME NEW BIOTECHS. THEY'RE CHANGED, BUT, YEAH, NOT EVERY PATIENT HAS CHANGES. SO, AGAIN, A RECAPITULATION OF WHAT WE SEE IN IPS CELLS CAN BE SEEN IN HUMAN BRAIN, TEACHING US THAT THE REAL VALUE OF IPS CELLS, STEM CELLS, IS ACTUALLY IN HUMAN BRAIN.

BY THE WAY, I HAVEN'T TOLD YOU WHY IT'S NOT SO VALUABLE FOR THERAPY. STEM CELL THERAPY IN ALS HAS BEEN, QUITE FRANKLY, A DEAD END, TERRIBLE COMPANIES HAVE BEEN INVOLVED, AND IT'S JUST NOT THE WAY OF GETTING AT THE HEART OF THE DISEASE. AND PART OF THAT IS THE COMPLEXITY. IT WOULD TAKE -- IF I COULD PUT A MOTOR NEURON INTO SOMEONE'S SPINAL CORD, IT WOULD TAKE A MINIMUM OF THREE YEARS TO GROW THAT AXON TO TARGET EVEN IF IT COULD EVER FIND ITS TARGET. IT'S NOT THE WAY TO GO. THE POWER OF THIS HUMAN PLATFORM IS IN DISCOVERING PATHWAYS AND THEN USING THESE PLATFORMS FOR DRUG DISCOVERY.

IN FACT, THE NEXT SLIDE SHOWS THAT. SO HERE'S -- WE NOW KNOW THE PATHWAY. BY THE WAY, THIS IS ONLY ONE OF MANY PATHWAYS, BUT HERE'S A PATHWAY THAT INVOLVED THAT PROTEIN CHMP7 THAT IS INVOLVED IN THE DEGRADATION OF THE NUCLEAR PORE. WE CAN NOW TAKE 30 IPS LINES THAT HAVE THAT DEFECT AS SHOWN HERE, TREAT THEM WITH AN ANTISENSE OLIGONUCLEOTIDE,

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THE FASTEST THERAPY TO GO FROM LABORATORY TO CLINIC IN NEUROLOGIC DISEASES.

AND WE CAN SHOW IN 30 DIFFERENT PATIENTS THAT WE COMPLETELY REPAIR THAT PATHWAY. THIS IS LIKE A HUMAN TRIAL IN CULTURE. IT'S JUST PHENOMENAL. AND THIS IS AN EXAMPLE OF ACTUALLY A PATHWAY THAT'S BEING WORKED ON BY, AGAIN, ANOTHER COMPANY IN YOUR STATE, IMS PHARMACEUTICALS, TO DEVELOP THIS ASO FOR PATIENTS.

BY THE WAY, I STRESS THAT THAT'S FAST. ONE OF THE NEWER THERAPIES, WHETHER THEY'LL WORK OR NOT I DON'T KNOW FOR ALS, IS ONE OF THOSE TDP-43 DEFECTS KNOWN AS STATHMIN2. THOSE FIRST PAPERS CAME OUT IN 2019 BY THE CLEVELAND LAB AND THE EGGAN GROUP. AND WITHIN THREE YEARS A CLINICAL TRIAL HAD STARTED USING THOSE ASO'S. THERE'S NOTHING THAT FAST. HIGHLY SPECIFIC TARGETING AGENT, AND INCREDIBLY FAST MOVING FROM THE LAB TO THE CLINIC. THAT'S WHY MANY OF US ARE QUITE EXCITED ABOUT THIS APPROACH. THERE ARE GOING TO BE FOLLOW-ON APPROACHES, BUT IT'S WONDERFUL TO UNDERSTAND THE MOLECULAR PATHWAYS TO DEVELOP A DRUG-TARGETED MOLECULAR PATHWAY AND BRING IT TO PATIENTS.

AND BY THE WAY, DO WE KNOW THIS APPROACH CAN WORK? SOD1, THE FIRST GENE DISCOVERED, FDA

APPROVED THE SOD1 ANTISENSE. REMEMBER THIS IS A FATAL DISEASE. CERTAIN FORMS OF THE SOD1 MUTATION PROGRESS OVER NINE MONTHS. THOSE PATIENTS WHO HAVE GOTTEN THE ASO TO SOD1 ARE ALIVE TWO YEARS LATER, AND THEY'RE ACTUALLY IMPROVING IN STRENGTH. THAT'S UNHEARD OF IN AN ADULT NEURODEGENERATIVE DISEASE. AND IT REALLY IS THE SPEED BY WHICH WE CAN TARGET A WELL-DEFINED MOLECULAR PATHWAY. IT'S WHY THE FOCUS ON USING IPS CELLS FOR FINDING THOSE PATHWAYS BECOMES SO IMPORTANT.

WHY THIS PROCESS BEGINS IN ALS THEN GOES BACK TO REALLY TRYING TO UNDERSTAND THE DEFECTS IN THE NUCLEAR PORE. WHAT INITIATES THIS DEFECT? AND WE HAVE LEARNED THAT THOSE INDIVIDUAL PROTEINS CAN HAVE -- EACH PROTEIN HAS A MOLECULAR CODE TO IT, AND THERE CAN BE CODING VARIATIONS. SO THIS IS A THOUSAND MOLECULES ALL ASSEMBLED TOGETHER. YOU MIGHT IMAGINE THAT IF THEY DON'T ASSEMBLE PROPERLY JUST BECAUSE OF A SMALL DEFECT, THAT COULD ACTIVATE THAT DEGRADATION PATHWAY. AND WE HAVE NOW DISCOVERED THAT, IN FACT, THAT CAN HAPPEN. AND THIS IS ACTUALLY A HEAT MAP FROM ANDRE HOELZ. THE DARKER THE BROWN, THE GREATER THE FREQUENCY OF DEFECTS IN THOSE NUCLEOPORINS IN SPORADIC ALS CAN BE FOUND. SO THESE AREN'T MUTATIONS. THEY'RE CALLED CODING

VARIANTS. AND WE'RE BEGINNING TO THEN LOOK FOR THEM IN THOSE IPS CELLS.

AND THIS IS COMING BACK TO WHERE I SHOWED YOU. ALL OF THE IPS CELLS THAT WE HAVE ALREADY, A NUMBER OF THEM HAVE THESE CODING VARIANTS. WE CAN THEN USE THE IPS CELLS TO CORRECT THOSE CODING VARIANTS USING CRISPR METHODOLOGY TO REPAIR THEM. AND WHEN WE REPAIR THEM IN PATIENTS, WILL WE SEE AN IMPROVEMENT IN THE LOSS OF THE NUCLEAR PORE DEFECT AND, THEREFORE, A GREATER SURVIVAL? AND IT WILL GIVE US AN UNDERSTANDING WHAT WAS THE ACTUAL INITIATING EVENT IN SPORADIC ALS. AND THIS IS THE KIND OF ANALYSIS THAT'S DONE. THIS IS THAT NUCLEAR PORE COMPLEX. ANDRE HOELZ CAN LOOK AT INDIVIDUAL PROTEINS AND SAY, WELL, THERE'S A CODING VARIANT HERE, IT MAY BE HERE, AND THIS PREDICTS THAT IT WON'T INTERACT WITH ITS NEIGHBOR PROTEIN, AND THOSE BECOME CANDIDATES FOR US TO ATTEMPT TO REPAIR.

ALL OF THIS IS NOT POSSIBLE IF NOT FOR AN IPS-BASED PLATFORM. I'M GOING TO SKIP THROUGH THAT.

SO I MENTIONED BEFORE HOW IMPORTANT HAVING LARGE NUMBERS OF IPS CELLS ARE, ESPECIALLY FROM THE SPORADIC ALS POPULATION. THIS COULD EQUALLY APPLY TO ANY OTHER DISEASE. A RELATIVELY LARGE POPULATION OF IPS CELLS HAVE ALSO BEEN DEVELOPED FOR FRONTAL

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TEMPORAL DEMENTIA. I THINK THE LARGEST ONE WORLDWIDE, THOUGH, IS REALLY IN ALS BECAUSE OF THE ANSWER ALS PLATFORM. THAT DATA, BY THE WAY, EVERYTHING DONE IN THE ANSWER ALS PLATFORM, COMPLETELY, FREELY AVAILABLE TO COMPANIES AND ACADEMICS ALIKE. YOU HAVE TO PAY A SMALL FEE TO CLIVE AT CEDARS-SINAI TO BUY THE CELLS ONLY BECAUSE THEY HAVE TO GROW UP A NEW BATCH. BUT THE DATA FROM THAT PLATFORM, ALL THOSE ANALYTICS CAN BE FILTERED ONLINE, COMPLETELY FREE. YOU CAN DOWNLOAD THE WHOLE GENOME SEQUENCES. YOU CAN DOWNLOAD THE RNA SEQ. YOU CAN CHOOSE BETWEEN WHAT AGES OF PATIENTS, HOW FAST THEY'RE PROGRESSING, WHETHER THEY HAVE MUTATIONS OR NOT, AND DOWNLOAD THAT DATA FOR FREE.

AND, IN FACT, TODAY ALMOST ALL 1,000 IPS LINES ARE AVAILABLE, NOT QUITE ALL AVAILABLE. THEY'RE GENERATED IN BATCHES. FROM THOSE IPS CELLS, WE ROLL OUT NEW DATASETS ON THE EPIGENOMICS, THE PROTEOMICS, THE TRANSCRIPTOMICS, AND, OF COURSE, WHOLE GENOME IS REALLY KNOWN ON ALL OF THEM, ALL ACCESSIBLE. AND TO DATE THE DATA HAS BEEN SHARED THROUGH COUNTRIES REALLY WORLDWIDE. THIS IS A LITTLE OUTDATED. AND PROJECTS ARE STARTED BASED ON THOSE DATASETS. SO WE'VE NOW ALREADY, AGAIN THIS IS A LITTLE OUTDATED, MORE THAN 95 TERABYTES OF OMICS

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DATA HAVE BEEN RELEASED TO THE WORLD. HUNDREDS OF PROJECTS HAVE BEEN STARTED, AND HUGE NUMBERS OF CELL LINES HAVE BEEN DISTRIBUTED BOTH TO PHARMA AND TO ACADEMICS. THERE ARE NO INTELLECTUAL PROPERTY RESTRAINTS ON ANY OF THIS. NO OWNERSHIP. WE CONSENTED PATIENTS FROM THE VERY BEGINNING KNOWING THAT'S EXACTLY HOW WE WANTED THIS DATA USED.

AND I THINK THAT'S -- OH, ONE FINAL POINT, THOUGH ALMOST TO END, IS THAT OVER THE YEARS IN ALS, THIS IS A LIST FROM ABOUT A YEAR AGO OF STUDIES OF MORE THAN A HUNDRED PATIENTS IN ALS. JUST ABOUT ALL OF THESE STUDIES BUT ONE REALLY HAVE ALL BEEN FAILURES. THEY'RE ALL BASED ON SOME PATHWAY ANALYSIS, MANY FROM THE ALS MOUSE, ESSENTIALLY NONE FROM THE IPS CELLS, THEY'RE RELATIVELY NEW, A HIGH RATE OF FAILURES. IT'S INCREDIBLY DEPRESSING.

HOWEVER, BEGINNING TO LOOK AT THE GENES THAT CAUSE ALS EITHER FROM GENETIC MODELS OR FROM IPS CELLS, WE'RE ALREADY BEGINNING TO SHOW SUCCESS. SOD1, WE ALREADY HAVE AN FDA APPROVED. THE NEXT ONE SOMEWHERE HERE FUS, A RELATIVELY RARE MUTATION, IS LOOKING ALMOST AS GOOD AS SOD1 IN SLOWING THE DISEASE. IN THIS CASE, FUS IS VERY YOUNG PATIENTS WITH THE DISEASE. ALL OF THESE ARE, I'M GOING TO ARGUE, EASY TARGETS BECAUSE WE KNOW THE MUTATION.

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IT'S SPORADIC DISEASE WHICH IS THE VAST MAJORITY OF DISEASE THAT WE HAVE TO MAKE A DIFFERENCE IN.

NOW, RECENTLY, IF WE LOOK AT WHAT'S COMING FROM BOTH IPS CELLS AND SOME MODEL SYSTEMS AND HUMAN TISSUE, THERE ARE A SERIES OF PATHWAYS THAT HAVE BEEN DISCOVERED MORE RECENTLY THAT ALL ARE POTENTIAL TARGETS FOR THERAPIES. AND THIS COMES BACK TO WHERE DO WE WANT TO GO IN THE FUTURE. AND I WOULD ARGUE WHERE WE WANT TO GO IN THE FUTURE IS WITH IPS. BY THE WAY, NOT ALL OF THESE ARE GOING TO BE AMENABLE TO IPS PREPARATIONS, ESPECIALLY INFLAMMATORY PATHWAYS. THERE YOU MAY NEED ORGANOIDS. I WON'T SPEAK TO ORGANOIDS BECAUSE THERE'S VERY LITTLE WORK IN ALS IN ORGANOIDS. I DON'T KNOW IF THEY'RE ANY BETTER THAN WHAT WE'VE SEEN IN TISSUE. I CAN TELL YOU ALL OF THESE LISTS OF PATHWAYS, INFLAMMATION HAS BEEN THE GREATEST -- I WENT BACK TWO SLIDES EARLIER TO SHOW ALL THOSE HUMAN TRIALS. INFLAMMATION IS THE MOST COMMON APPROACH TO ALS. EVERY NEURODEGENERATIVE DISEASE HAS INFLAMMATION, EVERY NEURODEGENERATIVE DISEASE, AT LEAST AT END STAGE.

NOW, TWO WEEKS PRIOR TO THE PATIENT'S DEATH, DID THEY HAVE THAT MUCH INFLAMMATION? DON'T KNOW. WE DON'T TEND TO LOOK AT HUMANS THAT EARLY. SOME COMPANIES ARE BEGINNING TO LOOK AT BIOMARKERS,

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BUT I CAN TELL YOU ALL OF THESE INFLAMMATORY PATHWAYS WHERE OFTEN COMPANIES HAVE VERY LITTLE DATA, A LITTLE HISTOLOGY AT DEATH AND THAT'S IT, THEY'VE ALL BEEN FAILURES. THE GREATEST LIST OF FAILURES IN NEURODEGENERATION ARE INFLAMMATORY PATHWAYS. THE GREATEST LIST OF CANDIDATE DRUGS ARE INFLAMMATORY PATHWAYS BECAUSE MOST OF THESE COMPANIES ARE ALREADY DEALING WITH INFLAMMATION FROM PERIPHERAL TARGETS, PERIPHERAL INFLAMMATION. SO THEY HAVE A DRUG ALREADY AND THEY'LL COME TO US.

EVEN THOUGH THERE'S A HIGH FAILURE RATE, I'M NOT GOING TO TURN A COMPANY DOWN AS LONG AS THE DESIGN IS DONE WELL BECAUSE I CAN'T TELL YOU I CAN PREDICT WHAT WORKS IN ALS. BUT I CAN TELL YOU THERE'S A LONG HISTORY, TWO PLUS DECADES OF INFLAMMATORY MEDIATORS ALL BEING FAILURES.

THE SUCCESSES ARE COMING FROM UNDERSTANDING PATHWAYS. OBVIOUSLY GENE TARGETS ARE PATHWAYS. THERE ARE NOW TARGETS FOCUSING ON ASTROCYTES, OLIGODENDROGLIA. SOME ARE NOT AS WELL WORKED OUT. MANY GENETIC SUBTYPES ARE GOING TO BE TARGETS. THAT MAKES PERFECT SENSE. AND WHAT WE'RE LEARNING FROM IPS CELLS, RNA BINDING PROTEINS, NUCLEAR PORES, NUCLEAR TRANSPORT ARE SORT OF THE UPCOMING PATHWAYS. DNA DAMAGE IS OF INTEREST, AND

CERTAINLY AXON REGROWTH, THERE ARE COMPANIES THAT ARE DEVELOPING DRUGS FOR AXON REGROWTH. AGAIN, GREAT PATHWAYS FOR STUDYING IN IPS CELLS DUE TO GROWTH OF AXONS.

THESE ARE NOT PLATFORMS PARTICULARLY GOOD FOR MULTIPLE SYNAPTIC INTERACTIONS, BUT ALS IS NOT GENERALLY THOUGHT TO BE A MULTISYNAPTIC INTERACTION DISEASE. IT'S HEAVILY BASED ON TRUE CELL BIOLOGY OF INDIVIDUAL CELLS. OTHER THAN CELL-CELL INTERACTIONS, LIKE GLIAL CELLS INTERACTING WITH NEURONS, THAT MAY BE WHERE IPS CELLS FALL SHORT. ORGANOIDS MIGHT BE BETTER.

SO THIS IS SORT OF JUST A CURRENT LIST OF WHAT WE AS A COMMUNITY THINK ARE INTERESTING PATHWAYS. MOST OF THESE, THOUGH, CAN BE OPTIMIZED THROUGH THE USE OF PATIENT IPS LINES. AND I WOULD ARGUE, DEPENDING ON AS YOU LOOK FORWARD, I WOULDN'T WASTE -- I'M GOING TO BE HARSH HERE. I WOULD NOT WASTE YOUR MONEY ON CELL THERAPIES. I CAN ANSWER QUESTIONS ABOUT THAT. THIS IS WHAT YOU USE IPS CELLS FOR, FOR FINDING PATHWAYS. AND THE QUESTION EARLIER ABOUT DRUG SCREENING, NO QUESTION. INSITRO IN SAN FRANCISCO IS ALREADY USING LARGE NUMBERS OF ANSWER ALS IPS LINES ULTIMATELY FOR DRUG PATHWAY AND DRUG SCREENING. THERE'S NO QUESTION THAT'S AN

EXCITING PLATFORM FOR COMPANIES, TO A LESSER EXTENT ACADEMICS, TO USE.

I WENT KIND OF FAST, BUT I WANTED TO MAKE SURE WE HAD TIME FOR QUESTIONS. I SHOULD POINT OUT THAT, LIKE LORENZ, MUCH OF WHAT WE DO IN THE FIELD IS HEAVILY BASED ON COLLABORATIVE INTERACTIONS BETWEEN MY LAB, DR. COYNE'S LAB HERE FOR SOME OF THE NUCLEAR PORE BIOLOGY, BUT MANY RESEARCHERS, BOTH WEST, EAST COAST, AND EUROPE, THAT HELP MAKE ALL OF THIS RESEARCH POSSIBLE, AND ALL OF US, I BELIEVE, RELY ON MANY DIFFERENT SOURCES OR FUNDING TO MAKE SURE WE CAN MOVE FORWARD RAPIDLY. THANKS.

CHAIRMAN GOLDSTEIN: JEFF, THAT WAS ABSOLUTELY TERRIFIC. SO A COUPLE OF COMMENTS AND THEN A QUESTION.

THE COMMENT IS YOU AND CLIVE AND COLLABORATORS DESERVE A GREAT THANK-YOU FOR NOT ONLY CREATING THIS LIBRARY, BUT MAKING IT VERY STRAIGHTFORWARD FOR THE REST OF THE COMMUNITY TO ACCESS IT. IT'S A REALLY POWERFUL DISCOVERY TOOL, I THINK.

MY SECOND COMMENT IS ACTUALLY A QUESTION. THIS MAY BE LOONEY, BUT THE DEFECTS IN THE NUCLEAR PORE IN SOME WAYS ARE REMINISCENT OF THE DEFECTS IN PROGERIA.

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DR. ROTHSTEIN: YES.

CHAIRMAN GOLDSTEIN: AND I GUESS THE QUESTION IS WOULD ALL OF THESE NUCLEAR PORE DEFECTS IN ALS BENEFIT FROM A SHOT OF THE NORMAL PROGERON GENE?

DR. ROTHSTEIN: DIFFERENT. SO PROGERIA, I BELIEVE, AFFECTS LAMINS. I CAN'T REMEMBER IF IT'S LAMINATORS. I NEVER REMEMBER THIS.

CHAIRMAN GOLDSTEIN: FAIR ENOUGH. RIGHT.

DR. ROTHSTEIN: NUCLEAR MEMBRANES ARE ACTUALLY NOT THE DEFECT IN ALS. WE BELIEVE IT. WE'VE DONE A STRUCTURAL LAMINATION MICROSCOPY. WE'D LOVE TO DO CRYO EM. IT'S VERY DIFFICULT IN IPS CELLS, BUT WE'VE EXTENSIVELY LOOKED. SO NUCLEAR LAMINS ARE NOT REALLY DEFECTIVE IN ALS. IT'S THE PORE ITSELF. BUT IT WAS A VERY IMPORTANT QUESTION FOR US TO LOOK AT EARLIER.

ON THE OTHER HAND, COULD I TELL YOU THAT IF WE DID SOMEHOW ENHANCE LAMINS OR FOR THAT MATTER, THIS MAYBE WILL GO BEYOND MANY OF YOU IN THE AUDIENCE, THE LINK COMPLEX. THERE ARE CERTAIN LINK COMPLEX PROTEINS THAT INTERACT WITH THE NUCLEAR PORE SUCH AS SUN1. THERE MAY BE A HINT THERE. RIGHT NOW MOST OF IT'S COMING FROM THIS ESCRT-III PATHWAY, WHICH IS CHMP7, AND ITS INTERACTION. WE DON'T KNOW

WHAT STARTS THAT. WE GUESS RIGHT NOW IT'S THESE CODING VARIANTS THAT WE THINK SOMEHOW OVER TIME BUILD UP SOME SLOWLY DEVELOPING INJURY. ONE OF THE THINGS, AGAIN, FOR ANY OF THE SCIENTISTS IN THE ROOM, AGAIN, THIS WORK COMES FROM THE SALK, IS THAT NUCLEAR PORE PROTEINS ARE SOME OF THE LONGEST LIVED PROTEINS IN THE HUMAN BODY. SOME OF THOSE NUCLEOPORINS HAVE HALF-LIFE MEASURED IN YEARS, NOT HOURS, NOT DAYS, BUT YEARS.

IN FACT, WHEN WE FIRST PUBLISHED OUR FIRST STUDIES IN 2015 ON NUCLEAR PORE -- NUCLEAR TRANSPORT DEFECTS, IT WAS RUSTY GAGE WHO SEPARATELY THAT SAME YEAR HAD A PAPER IN *SCIENCE* ON SORT OF DEFECTS ASSOCIATED WITH AGING. ONE OF THE HIGHEST ONES WAS A NUCLEOPORIN. I CAN'T REMEMBER IF IT WAS NUKE 62 OR GROUP 98. SO AGING, YES, IN SOME WAY IS THAT COMPONENT. BUT I CAN ONLY HANDWAVE AT THIS POINT, LARRY.

CHAIRMAN GOLDSTEIN: INTERESTING. QUESTIONS FROM THE GROUP?

DR. ROTHSTEIN: BY THE WAY -- GO RIGHT AHEAD. SOMEONE HAS QUESTIONS.

CHAIRMAN GOLDSTEIN: WELL, I WAS JUST GOING TO MENTION ON THE ONE HAND IT'S A TREMENDOUSLY DISAPPOINTING THERAPY DISCOVERY EFFORT SO FAR.

DR. ROTHSTEIN: YES.

CHAIRMAN GOLDSTEIN: I'VE CERTAINLY SEEN THOSE FIRSTHAND.

DR. ROTHSTEIN: GO AHEAD.

CHAIRMAN GOLDSTEIN: I THINK WHERE YOU ARE WITH THE NUCLEAR PORE IS A REALLY INCREDIBLE OPPORTUNITY TO MAKE A DIFFERENCE FOR A SUBSET OF ALS PATIENTS IF YOU CAN FIND ASO'S OR DRUGS THAT HELP.

DR. ROTHSTEIN: I WANT TO MAKE SURE. I DID THIS FAST. THERE ARE OTHER LABORATORIES THAT ARE VERY MUCH IPS BASED. A LOT OF LABORATORIES IN ALS ARE BEGINNING TO MOVE AWAY FROM MICE USING IPS. AND YOU HEARD ME BEING VERY BLUNT AT THE BEGINNING. IT'S NOT ABOUT THERAPY. WHAT I MEAN BY THAT IT'S NOT ABOUT CELLULAR THERAPY. IT'S REALLY ABOUT USING THE VALUE OF A TRUE HUMAN MODEL SYSTEM TO UNDERSTAND DISEASE. AS LONG AS YOU MAKE SURE YOU TRY TO REPLICATE THAT IN HUMAN BRAIN, KNOWING YOU MIGHT NOT, THAT'S END STAGE DISEASE. A LOT OF OTHER THINGS HAPPEN AT THE END STAGE, BUT NOT CELLULAR THERAPY.

I KNOW MY COLLEAGUE CLIVE HAS BEEN TRYING CELL THERAPY, BUT IT'S -- THE COMPLEXITY IN A DISEASE LIKE ALS, THIS IS VERY DIFFERENT THAN LORENZ'S DISCUSSIONS AROUND, SAY, PARKINSON'S

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DISEASE, WHICH IS VERY FOCAL. WE'RE TALKING ABOUT THE ENTIRE MOTOR CORTEX, THE ENTIRE NEURO AXIS, YOUR ENTIRE SPINAL CORD MOTOR NEURONS, WHICH HAVE VERY LONG PROCESSES, THE SOMA, THE CELL BODY, AS YOU KNOW.

JUST FOR THOSE OF YOU WHO DON'T KNOW, THE CELL BODY OF A MOTOR NEURON THAT ALLOWS YOU TO WIGGLE YOUR BIG TOE STARTS AT YOUR BELLY BUTTON. AND THAT LONG AXON GOES FROM THERE ALL THE WAY DOWN THREE OR FOUR FEET, DEPENDING HOW TALL OR SHORT YOU ARE, AND THAT'S JUST INCREDIBLY COMPLEX. NOT TO SAY ONE DAY SOMEONE MIGHT KNOW HOW TO DO THAT, BUT THOSE DAYS OF FOCUSING ON THAT, I THINK, ARE PAST. THERE ARE A FEW COMPANIES IN OUR FIELD THAT HAVE BEGUN TO DEAL WITH CELLULAR-BASED THERAPIES THAT HAVE BEEN TERRIBLE. I CAN ONLY SAY -- I CAN'T SAY ANYTHING NICE ABOUT THEM. THEY'RE NOT GOOD COMPANIES.

JON, YOU HAVE YOUR HAND UP.

CHAIRMAN GOLDSTEIN: J.T., YEAH.

DR. THOMAS: HI, JEFF. ANOTHER JUST OUTSTANDING PRESENTATION. THANK YOU.

IF YOU HAD TO SPECULATE, WHAT IS IT THAT ALLOWS THE PATIENTS WITH THE CONDITION FOR 25 TO 30 YEARS TO MAKE IT THAT FAR, LET ALONE STEVEN HAWKING WHO CLIVE HOSTED AT CEDARS A NUMBER OF YEARS AGO,

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WHICH WAS A FASCINATING EVENT, WHY IS THAT HAPPENING?

DR. ROTHSTEIN: YES. IT'S A GREAT QUESTION. AND THE SIMPLE ANSWER IS, SHIT, I DON'T KNOW. NO ONE KNOWS. ALL DEGENERATIVE DISEASES ARE LATE ONSET, ALZHEIMER'S, PARKINSON'S. YOU COULD POSE THAT QUESTION TO ANY ONE OF US, AND WE DON'T KNOW THAT ANSWER. WE KNOW -- THIS IS WHERE ANIMAL MODELS ARE USEFUL OR EVEN IPS. WE KNOW THEY CAN HAVE AN INJURY CASCADE EARLY ON, BUT WHAT TIPS THAT OVER TO CELL DEATH WE DON'T KNOW YET. IS THAT AN ENVIRONMENTAL STRESSOR? WE KNOW THE IPS CLEARLY HAS A DEFECT. I CAN SHOW THE SAME DEFECTS IN BRAIN. SO I KNOW I CAN BRIDGE THOSE TWO. EVEN IN MOUSE MODELS WE KNEW YOU CAN SEE A DEFECT. MOUSE MAY DIE AT 120 DAYS OF AGE; BUT, GEE, AT TWO WEEKS OF AGE? WE CAN FIND ALREADY EARLY RNA CHANGES AND PROTEIN CHANGES. WHY THAT ACCUMULATES TO REACH A THRESHOLD, I DON'T THINK ANY OF US REALLY FULLY UNDERSTAND. I CAN HANDWAVE, BUT SAY, WELL, NUCLEAR PORE PROTEINS HAVE SUCH A LONG HALF-LIFE AND THEY'RE NOT DIVIDING CELLS, SO CAN TAKE TIME TO BUILD UP AN INJURY. I'M REALLY HANDWAVING THERE.

SO THAT WAS A REALLY CRAPPY ANSWER TO YOUR QUESTION, BUT IT'S THE BEST I CAN DO.

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STEVEN HAWKING, THOUGH, PEOPLE DON'T REALIZE HE WAS ON A VENTILATOR. IF YOU'RE ON A VENTILATOR, YOU DON'T DIE OF ALS. YOU DIE BECAUSE THE VENTILATOR, YOU GET A BAD INFECTION. I'VE HAD PATIENTS WHO LIVE 20 PLUS TO 30 YEARS WHEN THEY SHOULD HAVE DIED WHEN THEY WERE TEN YEARS INTO THE DISEASE, BUT THEY ARE ON A VENTILATOR.

THE DISEASE DOES NOT STOP, AND YOU CAN SEE STEVEN HAWKING COULDN'T DO MUCH. IN FACT, IN THE BEGINNING, AS THE DISEASE MOVES ON, THE ONLY THING PRESERVED ARE YOUR EYE MOVEMENTS, AND WE USE COMPUTER SCREENS TO READ LETTERS, BUT EVENTUALLY EVEN THAT CAN GO AWAY FOR MOTOR NEURONS. BUT AS LONG AS YOU'RE BREATHING, YOU DON'T DIE. AND YOU'LL ONLY DIE BECAUSE THE VENTILATOR COMES OFF ACCIDENTALLY. IT HAPPENS IN PATIENTS OCCASIONALLY. POWER TO THE VENTILATOR, OR YOU CAN HAVE A SEVERE INFECTION. AND THE FOURTH REASON IS YOU FINALLY SAY, "I DON'T WANT TO BE ON A VENTILATOR ANYMORE. HELP ME END MY LIFE." ALL OF THOSE ARE REAL-WORLD EXAMPLES. BUT HE LIVED LONGER BECAUSE HE WAS ARTIFICIALLY VENTILATED.

DR. THOMAS: INTERESTING.

CHAIRMAN GOLDSTEIN: VITO, YOU HAVE A QUESTION?

CHAIRMAN IMBASCIANI: HI. I HAVE A QUESTION FOR JEFFREY. JEFFREY, I GOT TO TELL YOU THAT MY PH.D. FROM CORNELL IS IN THE HUMANITIES. OKAY. SO BUT A QUESTION I READ IN THE NEWSPAPERS THAT POLIO IS RESURGENT IN NEW YORK CITY'S WATERS. AND I'M THINKING IS THERE ANY INTEREST IN YOUR COMMUNITY TO UNDERSTAND HOW THE ANTERIOR HORN CELLS THAT ARE KILLED OFF BY THE POLIO VIRUS AND THEN THE SURVIVING NEURONS, I PRESUME, ARBORIZE TO PICK UP ORPHAN NEUROMUSCULAR. IS THERE ANYTHING IN THAT AREA? I DON'T READ ANYTHING IN THE POST-POLIO.

DR. ROTHSTEIN: YEAH. WHAT YOU ARE REFERRING TO IS WHAT'S CALLED POST-POLIO. FIRST OF ALL, IT'S EXTREMELY RARE. I HAVE, I THINK, THREE PATIENTS IN MY CAREER THAT ARE POST-POLIO. ONE WAS A SENATOR. AND THERE WAS -- ACTUALLY THE ONLY RESEARCH I KNOW IN THE U.S. WAS A GUY NAMED BURT JUBELT AT SYRACUSE WHO USED TO DO WORK ON THAT. BEYOND THAT I KNOW NO ONE ELSE DOING IT.

THERE'S A VERSION OF THAT, SOME OF THE CHILDHOOD ENCEPHALITITIES, BOTH WEST NILE AND -- SHIT, I'M BLOCKING ON THE OTHER ONE. THERE'S ACTUALLY A COLLEAGUE WHO WAS A YOUNG M.D./PH.D. PEDIATRIC NEUROLOGIST WHO'S WORKING ON ONE OF THOSE WHERE IT LOOKS LIKE POLIO. IT'S A RESURGENCE OF A

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VIRUS LIKE POLIO, IT'S NOT POLIO, THAT AFFECTED CHILDREN PREDOMINANTLY MOTOR NEURONS SPECIFICITY THAT THERE HAD TO DO MORE WITH THE VIRUS GETTING INTO MOTOR NEURONS. AND BY THE WAY, AFFECTING THE NUCLEUS INCLUDING NUCLEAR PORE PROTEINS. AND THAT'S ACTUALLY WHAT HE WAS STUDYING IN MY LAB.

BUT THE POST-POLIO SIDE OF THINGS, I DON'T KNOW OF ANYONE STUDYING IT. IT'S EXACTLY AS YOU DESCRIBE. IT'S THE ARBORIZATION. AND IT COMES -- ACTUALLY AS YOU SAID THAT, IT REMINDS ME. AS WE'RE KEEPING SOD1 PATIENTS ALIVE NOW WHO LOST HALF THEIR MOTOR NEURONS, WE'RE SEEING WHAT WE THINK IS THAT SAME EFFECT. THE REMAINING MOTOR NEURONS BRANCH OUT NOW.

AND FOR THOSE IN THE AUDIENCE WHO DON'T KNOW THIS, POST-POLIO WAS THE FACT THAT YOU HAVE POLIO AND YOU'RE VERY WEAK, YOUR OTHER MOTOR NEURONS ARE SORT OF COMPENSATING, THEY'RE HELPING OUT KEEPING THINGS MOVING A LITTLE BIT, BUT EVENTUALLY THEY DIE AS WELL. AND THAT WAS WHAT WAS CALLED POST-POLIO. EVENTUALLY YOU'RE STABLE AND THEN YOU START GETTING WEAK AGAIN. THE SAME COULD OCCUR WITH THE SOD1 PATIENTS EXCEPT THEY'RE GETTING THEIR THERAPIES TODAY MUCH LATER IN LIFE, THEIR FIFTIES.

I HAVE TO TELL YOU ONE OTHER THING THAT'S

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THE MOST EXCITING TO MANY OF US. AS WE DEVELOP GENE THERAPIES, IT'S NOT AS MUCH ABOUT STEM CELLS, BUT DERIVES FROM THEM. AS WE DEVELOP GENE THERAPIES FOR PATIENTS WHO HAVE DISEASE NOW, WHAT WE'RE DOING IS THINKING ABOUT THE NEXT STEP. SO WHAT IF YOU HAVE ALS, UNFORTUNATELY, BUT YOUR SON CARRIES THE MUTATION. HE'S GOING TO GET DISEASE ONE DAY. SOME OF THESE ARE A HUNDRED PERCENT PENETRANT. WE'RE ACTUALLY FOLLOWING THOSE INDIVIDUALS NOW. AND THERE'S A PROTEIN IN THE BLOOD THAT SAYS THE NERVOUS SYSTEM IS STARTING TO GET AFFECTED. THEY'RE GETTING THE GENE THERAPY BEFORE THEY GET DISEASE. BUT THE IDEA IS THEY WILL NEVER ACTUALLY GET ALS BECAUSE WE'RE TURNING OFF THAT GENE WITH THIS THERAPY.

AND THE NEXT GENERATION OF THAT, AND THIS IS GOING ON HEAVILY ACTUALLY BY SOME OF THE PEOPLE IN YOUR STATE, SOMEONE I'M TRYING TO RECRUIT TO HOPKINS, IS USING CRISPR TO COMPLETELY FIX THE GENE. BUT RIGHT NOW ASO'S ARE THAT NEXT GREAT HOPE, AND THAT'S PREVENTIVE NEUROLOGIC MEDICINE, UNHEARD OF IN NEUROLOGY UNTIL THERAPIES. AND I'M GOING TO ARGUE THIS IS WHERE IPS PLATFORM, YOU'RE GOING TO INVEST LOCALLY IN YOUR STATE, THOSE ARE THE THINGS TO THINK ABOUT.

CHAIRMAN IMBASCIANI: THANK YOU.

CHAIRMAN GOLDSTEIN: SO IF THERE'S NOTHING BURNING, WE SHOULD PROBABLY WRAP UP THIS DISCUSSION. JEFF, FASCINATING AS ALWAYS. WE DO HAVE A COUPLE MINUTES FOR PUBLIC COMMENT. CLAUDETTE, DO WE HAVE ANY OF THAT?

MS. MANDAC: WE ACTUALLY DO HAVE A PUBLIC COMMENT FROM A PERSON IN OUR ROOM.

DR. CHAMBERS: HELLO. MY NAME IS STUART CHAMBERS. IF THAT RINGS A BELL, I WAS A POST-DOC IN LORENZ STUDER'S LAB. AND I DEVELOPED MANY OF THE PROTOCOLS THAT WERE FOR MAKING NEURONS IN THE NERVOUS SYSTEM FROM PLURIPOTENT STEM CELLS. AND THAT'S THE BASIS FOR WHAT NOW PROPELS BLUE ROCK, NEURONA, AND ASPEN NEUROSCIENCE AS MANY OTHERS TOWARDS THE CLINIC.

I'M HERE TO ADVOCATE FOR EARLY SEED START-UPS AND THEIR APPLICATION PROCESS AS PART OF APPLYING TO CIRM. I WANTED TO BRING THIS TO THE TASK FORCE'S ATTENTION BECAUSE THERE'S A BIG CHALLENGE WITH PRE-SEED COMPANIES IN PARTICULAR IN REGARDS TO APPLYING FOR CIRM FUNDING. THERE'S A SOLVENCY CHECK IN PLACE THAT MAKES IT TRICKY, BASICALLY MAKES IT A BURDEN.

IN MY PERSONAL CASE, I COULD NOT APPLY AT ALL. AND I JUST SIMPLY WANTED TO SAY THAT THIS IS

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IMPORTANT. IT'S IMPORTANT THAT WE FIGURE OUT WAYS FOR PRE-SEED AND EARLY SEED COMPANIES TO CONTINUE TO BE ABLE TO APPLY FOR CIRM. I RECOGNIZE THE PURPOSE OF THE SOLVENCY CHECK IN TERMS OF MAKING GOOD INVESTMENTS AND BEING GOOD STEWARDS OF THE CALIFORNIA STATE'S MONEY, BUT AT THE SAME TIME I WONDER IF THERE ARE CREATIVE SOLUTIONS TO THIS PROBLEM.

I JUST SIMPLY WANT TO BRING IT UP TO THIS AUDIENCE AND CIRM AS A WHOLE SO THAT WE CAN TALK ABOUT THIS IN THE FUTURE.

CHAIRMAN GOLDSTEIN: GREAT POINT. CAN SOMEBODY MAKE SURE THAT SHYAM PATEL GETS ON THIS TO THINK ABOUT IT?

MR. TOCHER: WILL DO, LARRY.

CHAIRMAN GOLDSTEIN: GREAT. ANY OTHER PUBLIC COMMENT?

MS. MANDAC: NO HANDS RAISED.

CHAIRMAN GOLDSTEIN: OKAY. IF NOT, I'M GOING TO ADJOURN US TWO MINUTES LATE. SORRY FOR THE EXTRA TIME. AND THANK YOU ALL FOR YOUR PARTICIPATION. FASCINATING DISCUSSIONS TODAY. JEFF AND LORENZ, THANK YOU FOR HELPING US. VITO HAS GOT IT RIGHT.

DR. THOMAS: THANK YOU, GUYS.

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(THE MEETING WAS THEN CONCLUDED AT 12:02 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 MARCH 22, 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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