BEFORE THE

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

SCIENTIFIC STRATEGY ADVISORY PANEL

LOCATION: VIA ZOOM

DATE: FEBRUARY 22, 2021
7 A.M.

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

FILE NO.: 2021-04

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

MONDAY, FEBRUARY 22, 2021

7 A.M.

DR. MILLAN: SO NOW IT'S 7:05. THANK YOU AGAIN FOR JOINING US. I'M MARIA MILLAN. I'M NOW TURNING IT OVER TO JONATHAN THOMAS WHO WILL OPEN THE MEETING. CHAIRMAN THOMAS.

CHAIRMAN THOMAS: GOOD MORNING, EVERYBODY. WELCOME TO THIS MOST SPECIAL EDITION OF THE ICOC AND APPLICATION REVIEW SUBCOMMITTEE. MARIA, WILL YOU PLEASE CALL THE ROLL?

DR. MILLAN: I DON'T KNOW IF MARIA BONNEVILLE IS ON SPEAKER MODE.

CHAIRMAN THOMAS: WE'LL GET TO OUR BOARD MEMBERS AS WE GO THROUGH THE MEETING. SO WELCOME, EVERYBODY, WELCOME TO OUR MOST DISTINGUISHED MEMBERS OF OUR SCIENTIFIC STRATEGY ADVISORY PANEL AND OUR DISTINGUISHED GRANTEES WHO WILL BE PRESENTING AT THIS MEETING.

THIS IS A FIRST OF ITS KIND FOR THE NEW ITERATION OF CIRM WHICH RESULTED FROM THE PASSAGE OF PROPOSITION 14 LAST NOVEMBER. WE ARE DELIGHTED TO HAVE EVERYBODY HERE.

JUST TO BRIEFLY SUMMARIZE, AS YOU KNOW, OF COURSE, THE FIRST ITERATION, WHICH BEGAN IN 2004,

HAD CIRM WITH $3 BILLION TO DEPLOY ACROSS THE STATE OF CALIFORNIA FOR A VARIETY OF PROGRAMS THAT DR. MILLAN WILL GET INTO BRIEFLY IN HER PRESENTATION. BY ANY METRIC, THE FIRST ITERATION WAS A GREAT SUCCESS AND HAS POSITIONED CIRM WITH A PORTFOLIO OF WORLD-CLASS PROJECTS THAT ARE PROCEEDING TOWARDS THE CLINIC AND A NUMBER, OF COURSE, WE ARE CERTAIN WILL BE REACHING COMMERCIALIZATION AND BE AVAILABLE TO PATIENTS EVERYWHERE.

CIRM, AS YOU KNOW, AS WE HIT 2020, WHICH WAS A MOST DIFFICULT YEAR FOR MANY DIFFERENT REASONS, WAS RUNNING OUT OF CASH AS WE HAD LAST YEAR BASICALLY ONLY ENOUGH FOR A SMALL ROUND WHICH WE IMPLEMENTED AS PART OF THE WORLDWIDE COLLABORATION ON COVID RESEARCH IN THE MIDDLE OF THE YEAR WHICH RESULTED IN 17 AWARDS, WHICH WE ARE VERY PROUD OF, WITH A MINIMAL FUNDING. WE ALSO HAD A SMALL AMOUNT AVAILABLE WHICH WE'RE USING FOR AN ONGOING COLLABORATION IN SICKLE CELL RESEARCH WITH NHLBI. BESIDES IS THAT, WE BASICALLY WERE OUT OF FUNDS. CIRM HAD TO STREAMLINE DOWN TO A SMALL TEAM, AND WE WERE HOPING, OF COURSE, THAT PROPOSITION 14 WOULD PASS TO RENEW THE ENTIRE EFFORT.

ONE OF THE THINGS THAT WE DID DO OVER THE COURSE OF THE YEAR, LED BY DR. MILLAN AND OUR

EXCELLENT TEAM, WAS TO BEGIN, NOT JUST BEGIN, BUT GET QUITE A WAYS INTO THE DEVELOPMENT OF STRATEGIC PLAN CONCEPTS THAT WOULD, IF PROP 14 WERE TO PASS, SET THE TABLE FOR THE NEXT FIVE-YEAR STRATEGIC PLAN WHICH WAS NORMALLY TO BEGIN IN 2021.

HAD DISCUSSIONS WITH MANY STAKEHOLDERS ABOUT THAT, AND MARIA WILL BE GETTING INTO THAT IN MORE DETAIL A LITTLE BIT LATER HERE.

THE PROPOSITION, AS YOU KNOW, THANKFULLY DID PASS IN NOVEMBER. IT WAS A CLOSE AFFAIR. MOST OF THE TIME YOU THINK THAT WHEN YOU HAVE AN ELECTION, YOU ARE GOING TO GET RESULTS ON THE DAY OF THE ELECTION. IT TURNS OUT IT TOOK TEN DAYS OF VOTE COUNTING IN CALIFORNIA TO ESTABLISH THAT, IN FACT, IT HAD PASSED 51/49, 51.2 TO BE PRECISE, WHICH WAS A HUGE WIN FOR ALL PATIENTS FIRST AND FOREMOST, FOR WHICH WE ARE DELIGHTED. AND, OF COURSE, A MAJOR SHOUT OUT GOES TO BOB KLEIN WHO WAS THE ARCHITECT BOTH OF PROPOSITION 71 AND PROPOSITION 14 WITH AN ASSIST FROM OUR LONGTIME COUNSEL JAMES HARRISON. I DON'T KNOW IF JAMES IS ON THE LINE OR NOT. JAMES AND BOB WROTE BOTH INITIATIVES. AND BOB AND HIS TEAM COORDINATED THE ELECTION EFFORTS FOR BOTH. AND AS HISTORY WILL LOOK BACK OVER TIME, BOB'S EFFORTS IN ENVISIONING AND CREATING AND MAKING HAPPEN CIRM

WILL BE SOMETHING THAT WILL BE FEATURED LARGELY IN THE ANNALS OF MEDICAL RESEARCH.

THE PROPOSITION ITSELF ADDED TO A NUMBER OF THE LONGSTANDING PROGRAMS THAT CIRM HAD IN PLACE. IT AUTHORIZED AN ADDITIONAL $5.5 BILLION AND HAD A HOST OF DIFFERENT OTHER PROGRAMS THAT WILL BE IMPLEMENTED OVER TIME.

ONE OF THE MORE UNUSUAL ONES OF WHICH WAS IT CREATED A WORKING GROUP FOR ACCESSIBILITY AND AFFORDABILITY ISSUES TO MAKE SURE THAT CIRM IS GOING TO BE ABLE TO CARRY FORWARD IN THE FUTURE IN A WAY THAT HELPS ALL CALIFORNIANS GET ACCESS TO CIRM-FUNDED PRODUCTS AS THEY HIT THE MARKET IN AN AFFORDABLE WAY.

THE MEASURE ALSO PROVIDED FOR EXPANDING OUR ALPHA STEM CELL CLINICS NETWORK, WHICH YOU MAY RECALL IS A FIVE-ENTITY NETWORK THAT PROVIDES START-TO-FINISH STEM CELL CLINICAL TRIALS FOR PATIENTS, NOT JUST FOR CIRM-FUNDED PROJECTS, BUT ALSO FOR PROJECTS THAT ARE FUNDED ELSEWHERE. IT'S RETURNING OUR SHARED LABS PROGRAMS AND TRAINING PROGRAMS THAT WE HAD IN THE EARLIER DAYS OF CIRM. IT'S CREATING A HOST OF NEW OPPORTUNITIES FOR A VARIETY OF DIFFERENT SORTS OF PROJECTS.

AND ONE OF THE THINGS THAT IT CREATED WAS



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THE ABILITY OF THE CHAIR AND THE PRESIDENT TO CALL TOGETHER A STRATEGIC ADVISORY PANEL THAT COULD ADVISE CIRM FOR VARIOUS REASONS THAT ARE OF IMPORTANCE TO THE AGENCY. AND IT WAS AS A RESULT OF THIS PARTICULAR PROVISION THAT DR. MILLAN AND I DECIDED THAT, AS THE NEW STRATEGIC PLAN WAS ABOUT TO BE DEVELOPED FURTHER AND IMPLEMENTED LATER THIS YEAR, THAT IT MADE A GREAT DEAL OF SENSE TO PULL TOGETHER KNOWN OPINION LEADERS FROM LITERALLY ALL OVER THE WORLD TO ADVISE US ON WHAT YOU THINK MIGHT BE THE BEST IDEAS TO USE TO DEPLOY THE ADDITIONAL $5.5 BILLION THAT WE HAVE GOING FORWARD.

SO TOWARDS THAT END, WE HAVE BROUGHT TOGETHER WHAT IS A HIGHLY DISTINGUISHED GROUP OF EXPERTS THAT BRING A VARIETY OF EXPERTISE TO THE TABLE FOR PURPOSES OF THIS DISCUSSION. WE ARE MOST GRATEFUL THAT EVERYBODY HAS THE INTEREST AND THE TIME TO JOIN US TODAY. I THINK YOU WILL FIND THIS A MOST INTERESTING EVENT AND SOMETHING THAT WILL BE OF GREAT IMPORTANCE AND WILL HELP CIRM FACTOR IN ALL OF YOUR THOUGHTS INTO THE STRATEGIC PLAN AS WE GO FORWARD.

SO WITH THAT, I WANT TO TURN IT OVER TO DR. MILLAN WHO'S GOING TO GIVE A PRESENTATION ON TODAY'S SESSION. AND, ONCE AGAIN, THANK YOU SO



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MUCH, EVERYBODY, FOR JOINING. I HOPE YOU FIND THIS TO BE AN INTERESTING AND MOST WORTHWHILE EFFORT. DR. MILLAN.

DR. MILLAN: THANK YOU SO MUCH, CHAIRMAN THOMAS. AGAIN, I WANT TO THANK EVERYBODY FOR BEING HERE TODAY. THOUGH WE DON'T HAVE THE OPPORTUNITY TO INTRODUCE EVERYBODY INDIVIDUALLY, THE SPEAKER BIOS AS WELL AS THE BIOS FOR OUR DISTINGUISHED PANELISTS IS PROVIDED WITH THE MEETING PACKET AND ON OUR WEBSITE FOR THIS MEETING.

SO WITHOUT FURTHER ADO, I'M GOING TO GO AHEAD AND DO A VERY SHORT INTRODUCTION. WE ARE VERY TIME CONSTRAINED, SO I'M HAVING KOLEY HELP US WITH TIME CHECKS. SO I'LL PROCEED NOW BY JUST GIVING KIND OF A BASIC INTRO AND STRUCTURE FOR THE MEETING.

SO AS J.T. MENTIONED, CIRM WAS CREATED ORIGINALLY IN 2004 UNDER A $3 BILLION BOND INITIATIVE. AND UNDER THAT BOND INITIATIVE, OVER A THOUSAND PROGRAMS HAVE BEEN FUNDED IN THE FOLLOWING PILLARS: EDUCATION, INFRASTRUCTURE, DISCOVERY, TRANSLATIONAL, AND CLINICAL. AND YOU'LL HEAR A LITTLE BIT MORE ABOUT THAT FROM DR. SAMBRANO, WHO WILL GIVE AN OVERVIEW OF OUR REVIEW PROCESS AND OUR PORTFOLIO AND THE STATE OF THAT PROGRAM TODAY.

WE FUNDED 68 MOSTLY FIRST-IN-HUMAN

CLINICAL TRIALS. MOST OF THESE HAD COME IN OVER THE PAST FIVE YEARS WITH 51 TRIALS BEING ADDED TO THE PORTFOLIO IN THE PAST FIVE YEARS. AND NOW WITH THE $5.5 BILLION BOND INITIATIVE UNDER PROP 14, WE ARE ASSEMBLING THIS GROUP AND UNDERGOING A STRATEGIC PLANNING.

FIRST I'D LIKE TO GIVE A REPORT CARD ON WHAT HAPPENED WITH OUR FINAL LEG OF PROP 71, THE PROP 71 ERA, AND THE MOST RECENT FIVE-YEAR STRATEGIC PLAN 2016 THAT ENDED AT THE END OF 2020.

WE HAD SIX, WE CALL THEM THE BIG SIX GOALS: BUILD A PORTFOLIO, ADVANCE PROGRAMS, ACCELERATE THEM THROUGH THE DEVELOPMENT PATH, TO BUILD A CLINICAL PORTFOLIO, AND ATTRACT INDUSTRY PULL BECAUSE WITH INDUSTRY ONLY CAN WE COMMERCIALIZE SOME BUT NOT ALL PROGRAMS -- YOU WILL HEAR A LITTLE BIT OF SOME IDEAS OF THAT LATER -- AND TO CREATE PROGRAMS THAT WILL ALSO COORDINATE WITH THE REGULATORY PATHWAYS. DR. PETER MARKS JOINS US TODAY. THE 21ST CENTURY CURES ACT PROVIDED FOR AN EXPEDITED REGULATORY PATHWAY FOR REGENERATIVE MEDICINE. WE ARE PROUD THAT EIGHT OF CIRM PROGRAMS, SOME OF THE FIRST RMAT DESIGNATIONS WERE ACTUALLY CIRM PROGRAMS, REALLY ASSISTED GREATLY IN ACCELERATING BY PROVIDING FOR VERY FREQUENT

INTERACTIONS AND A COLLABORATIVE APPROACH TO THESE NOVEL TYPES OF CLINICAL TRIALS.

WE'VE ALSO HAD A BOLD GOAL TO SHORTEN DEVELOPMENT TIME BY MAKING SURE THAT BOTH THE REVIEW PROCESS AND THE WAY WE ASSIST OUR PROGRAMS WITH ADVISORY PANELS AND MILESTONE-BASED FUNDING WOULD PROGRESS IN A TIMELY FASHION. AND BY DOING SO, WE SHORTENED TIMELINES WITH 73 PERCENT OF OUR PRECLINICAL PROGRAMS IN THE IND-ENABLING STATE, ACHIEVING AN IND WITHIN TWO YEARS FROM THE TIME THAT THEY PRESENTED TO US THE APPLICATION, THEIR PROPOSAL, WITH THEIR IND-ENABLING STUDIES, AND A PRE-IND FEEDBACK FROM THE FDA, MANY WITHIN 18 MONTHS.

AND KIND OF A MEASURE OF THAT IS THE INCREASE IN INDUSTRY UPTAKE. THIS IS BOTH A MEASURE OF THE MATURATION OF THIS SECTOR IN THE FIELD. BOB NELSEN ON THIS PANEL CAN SPEAK TO THAT, THAT THERE'S BEEN -- IT CAPTURED THE ATTENTION OF INVESTORS AND INDUSTRY. AND JUST OVER THE PAST FIVE YEARS, YOU CAN SEE THIS TRAJECTORY OF INDUSTRY INVESTMENT BY WAY OF LICENSING, ACQUISITION, FINANCING, AND WE HAD OVER 40 PROGRAMS SPINNING OUT FROM OUR PORTFOLIO PROGRAMS AND THREE IPO'S FROM PROGRAMS WE FUNDED. AND MOST OF THE INVESTMENTS HAVE COME IN OVER THE

PAST THREE YEARS, AMASSING OVER $13 BILLION IN VALUE AND DEALS. AGAIN, IT'S AN INDICATOR THAT THE FIELD IS STARTING TO MATURE.

THE TOTAL OF THE CIRM INVESTMENTS UNDER PROP 71 ARE SUMMARIZED BELOW. ALMOST HALF A BILLION DOLLARS INTO INFRASTRUCTURE, ALMOST A BILLION DOLLARS INTO DISCOVERY, OVER 200 MILLION INTO EDUCATION PROGRAMS, 316 FOR TRANSLATION, AND 740 MILLION INTO CLINICAL STAGE PROGRAMS. DR. SAMBRANO WILL GIVE YOU JUST A LITTLE BIT MORE DETAIL ON THAT.

SO THAT LEADS US TO WHERE WE ARE TODAY. HOW DO WE GO ABOUT THE STRATEGIC PLANNING? WHILE WE WERE AWAITING THE OUTCOME OF PROP 14, WE WERE ENGAGED IN ACTIVITIES LOOKING AT WHAT WE'D ACCOMPLISHED, SPEAKING TO OUR STAKEHOLDERS, ASSEMBLING WORKSHOPS, REACHING OUT TO KEY OPINION LEADERS, ATTENDING MEETINGS SUCH AS NATIONAL ACADEMY OF MEDICINE MEETING -- DR. VICTOR DZAU IS ON THE CALL TODAY -- WHICH WERE BOTH ALIGNED AND INSPIRED THAT SOME OF THE CONCEPTS THAT WE WERE STARTING TO LOOK AT AS HOW CAN WE DO THINGS EVEN BETTER IF WE WERE TO BE REFUNDED.

SO CIRM TODAY HAS ESTABLISHED A VALUE PROPOSITION OF A FUNDING MODEL THAT ALLOWED FOR ACCELERATION, YET SAFE AND REGULATED ACTIVITIES,

PATIENT CENTRIC, IT'S A FUNDER, A PARTNER AND A DERISKER THAT ALLOWED FOR US TO FUND AND DERISK EARLY STAGE PROGRAMS FOR WHICH THERE ORIGINALLY WAS NOT A REAL PATHWAY TOWARDS SIGNIFICANT INVESTMENT AND THEN ATTRACTED INDUSTRY AND OTHER INVESTMENT LATER ON ONCE THERE WAS PROOF OF CONCEPT, AND FUNDING BASIC, TRANSLATIONAL, AND CLINICAL RESEARCH, AS WELL AS ESTABLISHMENT OF CRITICAL INFRASTRUCTURE AND EDUCATION PROGRAMS, EXAMPLES OF WHICH YOU WILL HEAR IN A LITTLE BIT AND MAYBE THROUGHOUT THE DISCUSSION TODAY.

SO THE IDEA IS TO BUILD ON THIS VALUE PROPOSITION AND ESTABLISH A FUNDING MODEL. AND TO DO THIS, WE FOCUSED ON FOUR STRATEGIC THEMES OF ADVANCE WORLD-CLASS SCIENCE, WHICH IS THE TOPIC OF TODAY. WE WILL FULLY BE FOCUSED ON THIS THEME. BUT ALSO BUILDING PATHWAYS TO COMMERCIALIZATION, AND THERE WILL BE OTHER WORKSHOPS, INCLUDING A MANUFACTURING WORKSHOP, THAT THE TEAM WILL BE ASSEMBLING TO LOOK AT SOME OF THE HURDLES TOWARD TAKING EARLY STAGE PROGRAMS THROUGH TO COMMERCIALIZATION OR INTO TREATMENT MODELS WHERE THEY CAN REACH PATIENTS. INCREASE EQUITABLE PATIENT ACCESS TO INNOVATIVE TREATMENTS. AND THAT DOESN'T JUST MEAN A DELIVERY SYSTEM. IT MEANS TAKING INTO

ACCOUNT DIVERSITY, EQUITY, AND INCLUSION AND REALITIES OF WHAT IT TAKES TO GET INNOVATIVE PROGRAMS OUT INTO THE COMMUNITY.

AND AS J.T. HAD SUMMARIZED, THERE ARE PROVISIONS WITHIN PROP 14 THAT ACCOUNT FOR THIS, SUCH AS ESTABLISHMENT OF COMMUNITY CARE CLINICS, EXPANSION OF OUR CLINICAL DELIVERY SYSTEM, BUT ALSO ESTABLISHMENT OF ACCESSIBILITY AND AFFORDABILITY. THOSE WILL NOT BE DISCUSSED TODAY, THOUGH THOSE ARE SUBJECTS FOR OTHER MEETINGS. AND THEN MAXIMIZE OUR IMPACT THROUGH OPERATIONAL EXCELLENCE. THIS IS ONE WHERE WE HAVE ESTABLISHED A MODEL THAT GIL WILL SUMMARIZE IN A BIT THAT HAS ALLOWED US TO BUILD THIS PORTFOLIO, ACCELERATED THE PROGRESS OF OUR PROGRAMS AND BUILD THE CLINICAL PORTFOLIO.

WHAT ARE SOME OF THE THEMES THAT WE HAVE BEEN DRIVING AT OR DISCUSSING IN OUR VARIOUS MEETINGS AND IN OUR INTERNAL DISCUSSIONS? ACCELERATING SCIENTIFIC ADVANCEMENTS THROUGH TEAM SCIENCE AND FOR REAL DEPLOYING A CONSORTIUM APPROACH THAT'S REALLY AN INTEGRATED APPROACH TO HOW WE FUND SCIENCE AND PROVIDES INTERCONNECTIVITIES OF OUR SCIENCE ALONG THE VARIOUS STAGES OF RESEARCH. SO, FOR INSTANCE, IT'S NOT JUST A LINEAR PATH THEN FROM GOING FROM DISCOVERY, TRANSLATIONAL, CLINICAL, BUT

THERE WILL BE DISCOVERY PROGRAMS THAT MAY NOT LEAD TO THE DEVELOPMENT PROGRAMS, BUT THERE ARE BASIC DISCOVERY THAT ARE KNOWLEDGE GENERATING THAT ARE ESSENTIAL TO TACKLING THE BROADER CHALLENGES BOTH IN DEVELOPMENT OF SCIENCE BUT IN DISEASES AND UNDERSTANDING DISEASE BETTER. AND THEN ALSO PROVIDING A WAY THAT KNOWLEDGE IS MORE EFFICIENTLY SHARED THROUGH DATA KNOWLEDGE NETWORKS. AND THAT IS A VERY IMPORTANT TOPIC THAT ALL OF US ARE INVOLVED IN. THE NATIONAL ACADEMY OF MEDICINE WAS REALLY -- THEY HAD ASSEMBLED, DR. VICTOR DZAU IS HERE, AN AMAZING PANEL OF KOL'S WHO ARE WORKING ON THIS BOTH FROM INDUSTRY AND ACADEMIA. AND THE NIH HAS JUST LAUNCHED THEIR STRATEGIC OR IN THE MIDST OF STRATEGIC PLANNING ABOUT THE LAUNCH.

SO WE ARE VERY MUCH IN TOUCH WITH ALL THE DIFFERENT PARTIES INVOLVED WITH THIS BECAUSE THIS IS CRITICAL FOR US AS A SCIENTIFIC COMMUNITY. AND THEN EMBEDDING SYSTEMICALLY WITHIN OUR SYSTEM PRINCIPLES OF DIVERSITY, EQUITY, AND INCLUSION BECAUSE, AFTER ALL, IF WE DO SCIENCE TOWARD ONLY A LIMITED DATASET, WHAT ARE WE GOING TO GET IN THE END? IF WE DEVELOP PROGRAMS ONLY FOR A SLICE OF THE COMMUNITY, WHERE ARE WE GOING TO BE IN THE END IN TRULY ADDRESSING THE UNMET MEDICAL NEEDS THAT WE SEE?

AND THEN IN ADDITION, EXPLORING CLINICAL PARADIGMS THAT MAY BE MORE COMPATIBLE OR NECESSARY FOR THE TYPES OF TECHNOLOGIES AND SCIENCE THAT WE ARE EXPLORING. SO SOME OF THOSE EXAMPLES ARE NOTED HERE. YOU MAY HEAR ABOUT SOME OF THOSE MODELS THAT HAVE BEEN -- THESE ARE NOT NEW. IT'S A MATTER OF COORDINATING THEM AND REFINING THEM FOR THE PURPOSES OF THE TYPES OF PROGRAMS THAT WE WOULD BE INVOLVED IN OR WOULD BE FUNDING.

AND THEN LEVERAGING STRATEGIC PARTNERSHIPS. WE ALREADY HAVE SOME VERY GOOD EXAMPLES OF WHERE THIS WORKS OUT VERY NICELY. FOR INSTANCE, WE HAVE AN MOU WITH THE HEART LUNG BLOOD INSTITUTE OF NIH FOR A SICKLE CELL INITIATIVE, AND THAT HAS BEEN AN AMAZING EXAMPLE OF HOW TWO AGENCIES CAN REALLY WORK TOGETHER. WE HAVE A SHARED APPLICATION, AND THE CONTRACTING ARE ALL ALIGNED WITH IDENTICAL MILESTONES. SO IT'S VERY TRANSPARENT, VERY CLEAR. AND THEN BOTH AGENCIES ARE ABLE TO DEPLOY, NOT JUST FUNDING, BUT THEIR INFRASTRUCTURE AND THEIR ASSETS TOWARD THAT PROJECT TO GIVE US THE BEST CHANCE OF SUCCESS.

AND THEN TRAINING THE WORKFORCE OF TOMORROW WITH OUR EDUCATION PROGRAMS. THOUGH THIS WILL BE SUMMARIZED BY DR. SAMBRANO, IT WILL NOT BE A



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MAJOR TOPIC. IT'S AN IMPORTANT TOPIC, BUT IT, AGAIN, A SUBJECT OF OTHER TYPES OF MEETINGS. BUT IT'S CONNECTED TO THE SCIENTIFIC PROGRAMS IN THAT THE VERY LABS WHERE THE RESEARCH IS BEING DONE, THE CLINICAL SITES WHERE THE CLINICAL RESEARCH IS BEING DONE WILL BE THE SETTINGS WHERE OUR TRAINEES WILL BE INVOLVED. AND THE MANUFACTURING, FUTURE MANUFACTURING, PROGRAMS, FOR INSTANCE, WILL BE WHERE THEY DO THEIR INTERNSHIPS BOTH IN ACADEMIA AND IN INDUSTRY.

SO WE DO BELIEVE THAT THE CIRM ACCELERATION MODEL UTILIZING THE FUNDING PILLARS THAT ARE ALREADY ESTABLISHED AND HAVE BEEN SUCCESSFUL IN FUNDING INDIVIDUAL PROGRAMS, WE DO BELIEVE THAT STRUCTURING THIS IN A WAY THAT ALLOWS FOR A CONSORTIUM MODEL WILL TRULY ALLOW US TO REALIZE THE ASPIRATIONS AND THE GOALS OF KNOWLEDGE NETWORKS, BUILT-IN EFFICIENCIES THROUGH SHARE OF SPECIALTY CORES BOTH IN BASIC SCIENCE AS WELL IN CLINICAL RESEARCH, AND WILL BE AN IDENTIFIABLE, GO-TO PARTNERSHIP HUB AND PLATFORM TO REALLY LEVERAGE AND COLLECT FROM A MULTIPLIER EFFECT OF INVESTMENT IN SCIENCE.

SO WITH THAT LIGHTNING PRESENTATION, I'M GOING TO JUST LAY OUT THE MEETING FORMAT FOR TODAY.

WHAT WE REALLY DO HOPE TO ACCOMPLISH IN TODAY'S CONVERSATIONS AND YOUR INPUT IS TO GET A REAL SENSE OF WHAT IS THE GREATEST IMPACT THAT CIRM CAN MAKE IN THE NEXT TEN YEARS FOR STEM CELL REGENERATIVE MEDICINE RESEARCH? AND WHAT TYPES OF VITAL RESEARCH OPPORTUNITIES ARE IN NEED OF FUNDING WITHIN THE STEM BIOLOGY, GENOMICS, GENE THERAPY FIELD, AND PARTICULARLY NEUROSCIENCE BECAUSE THERE IS A SPECIFIC EARMARK FOR 1.5 BILLION OUT OF THE 5.5 BILLION IN PROP 14. ARE THERE VITAL RESEARCH OPPORTUNITIES THAT FALL OUTSIDE OUR TRADITIONAL CATEGORIES? AND WHAT ARE THE ADVANTAGES AND DISADVANTAGES OF CONSORTIA MODELS? WHAT IS THE LARGEST GAP IN STEM CELL RESEARCH BASIC AND TRANSLATIONAL? WHAT ARE THE KEY SCIENTIFIC AND CLINICAL RESEARCH INFRASTRUCTURE GAPS THAT EXIST OUT THERE THAT COULD BE FUNDED UNDER OUR INFRASTRUCTURE PROGRAMS OR THROUGH A CONSORTIA MODEL?

AND I'D LIKE TO SAY THAT MANUFACTURING IS A BIG TOPIC AND WE REALIZE THAT. WE ARE GOING TO TOUCH ON THE ACADEMIC PORTION OF IT; HOWEVER, KIND OF THE BIGGER QUESTION IS GOING TO BE ADDRESSED IN OTHER SETTINGS.

TODAY YOU WILL SEE IN THE AGENDA THAT WE HAVE REPRESENTATIVES FROM OUR CIRM SCIENTIFIC

COMMUNITY AND FROM OUR GRANTS WORKING GROUP WHO WILL INTRODUCE A VARIETY OF TOPIC AREAS. AND THESE ARE MEANT TO FRAME AND SPUR DISCUSSION. THEY WILL GIVE TEN-MINUTE TALKS FOLLOWED BY 15 MINUTES OF DISCUSSION. WE HOPE THE DISCUSSION WILL BE PRIMARILY BETWEEN PANELISTS, BUT ALSO WHERE IT'S HELPFUL TO BRING IN THE INVITED SPEAKERS AS WELL. THERE ARE NO SPECIFIC PROPOSALS THAT WILL BE PRESENTED TODAY. THESE PRESENTERS WILL NOT BE PRESENTING THEIR PROJECT, THEY WILL NOT BE PITCHING FOR PROJECTS IN PARTICULAR TODAY. THEY WILL BE TALKING ABOUT BROAD AREAS OF OPPORTUNITY IN SCIENTIFIC RESEARCH.

AND RELATED TO THAT, WE WILL NOT BE SEEKING PROJECT OR PROGRAM-RELATED FUNDING RECOMMENDATIONS FROM THIS PANEL TODAY. SO I WANTED TO POINT OUT THAT NEUROSCIENCE IS SPECIFICALLY HIGHLIGHTED. YOU CAN SEE IN THE AGENDA THAT IT'S VERY WELL REPRESENTED, BUT IT'S NOT MEANT TO BE A NEUROSCIENCE ONLY DISCUSSION. NEUROSCIENCE HAS PROVED TO BE AN ACCESS OR AN EXAMPLE FOR BROADER CONSIDERATION IN STEM CELL GENOMICS AND REGENERATIVE MEDICINE EVEN IN NON-NEUROSCIENCE AREAS.

SO WITH THAT, I'M GOING TO TURN IT OVER NOW TO MY COLLEAGUE DR. GIL SAMBRANO, VP OF

PORTFOLIO DEVELOPMENT AND REVIEW, TO GIVE AN OVERVIEW OF OUR FUNDING PROGRAMS AND OUR CURRENT PORTFOLIO. DR. SAMBRANO.

DR. SAMBRANO: THANK YOU, DR. MILLAN. SO GOOD MORNING AND WELCOME TO EVERYBODY. I'M GOING TO SHARE MY SCREEN HERE JUST TO GO THROUGH A SET OF SLIDES. AND I WILL TRY TO MAKE THIS AS QUICK AS POSSIBLE. THERE'S REALLY A LOT TO SAY ABOUT WHAT CIRM HAS DONE OVER THE LAST 15 YEARS, AS YOU CAN IMAGINE. SO I WILL TRY TO BE BRIEF ABOUT THIS TO THE EXTENT THAT I CAN.

SO AS MENTIONED BEFORE, THE CIRM INVESTMENTS ACROSS OUR PORTFOLIO CAN BE DIVIDED INTO THESE FIVE MAJOR PILLARS. SO THE DISCOVERY, TRANSLATION, AND CLINICAL HAVE FORMED SORT OF THE CORE OF OUR FUNDING PROGRAMS, THE BASIC RESEARCH ALL THE WAY THROUGH CLINICAL TRIALS AS WELL AS THE SUPPORTING PILLARS, SUCH AS THE INFRASTRUCTURE AND EDUCATION WHICH PROVIDES MANY OF THE RESOURCES THAT WILL SUPPORT THOSE PROJECTS.

NOW, THIS DIAGRAM IS ONE THAT WE GENERATED AT THE END OF 2019. AND SO THE NUMBERS THAT YOU WILL SEE ARE PROBABLY NOT EXACTLY UP TO DATE, BUT THE POINT OF THIS FIGURE IS TO SHOW YOU HOW WE HAVE TRANSITIONED FROM WHERE WE STARTED BEFORE 2015 IN

TERMS OF THE INVESTMENTS. YOU CAN SEE THAT OUR INVESTMENTS WERE MOSTLY IN THE DISCOVERY AREA AND THE INFRASTRUCTURE. AND A LOT OF THIS WAS SIMPLY BECAUSE, AT THE TIME IN 2005, WE ARE TRYING TO SEED THE FIELD AND PROMOTE RESEARCH IN HUMAN EMBRYONIC STEM CELL RESEARCH IN PARTICULAR. AND SO A LOT OF THE WORK AND SUPPORT WENT INTO VERY BASIC PROGRAMS, CREATING LABORATORY SPACE, PARTICULARLY SAFE HAVENS WHERE SUCH WORK COULD BE DONE.

IN LATER YEARS, SO BETWEEN 2015 AND 2019, YOU CAN SEE THAT OUR INVESTMENT WAS, EVEN THOUGH WE CONTINUED TO FUND ACROSS THE FIVE PILLARS, IT REALLY WAS MOSTLY IN THE CLINICAL ARENA WHERE WE FELT THE FIELD HAD ADVANCED NOW TO A POINT WHERE WE COULD SUPPORT CLINICAL TRIALS AND WE COULD MAKE A GREAT INVESTMENT THERE. SO THAT'S WHERE WE WERE AT THE END OF 2019.

HERE IS JUST A PIE CHART THAT SHOWS YOU JUST BROADLY LOOKING AT OUR R&D PORTFOLIO WHAT IT LOOKS LIKE. SO THIS IS FROM BASIC DISCOVERY RESEARCH ALL THE WAY THROUGH CLINICAL, KIND OF THE BROAD DISEASE CATEGORIES THAT OUR RESEARCH FALLS INTO. AND YOU WILL SEE THAT A BIG PORTION OF THAT PIE IS IN THE NEUROLOGICAL AREA, THE NEUROFIELD, A BIG SEGMENT IN CARDIOVASCULAR, BLOOD DISEASES, AND



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SO ON.

IF YOU DIVE DEEPER INTO THE NEUROSCIENCE PORTFOLIO, YOU WILL ALSO SEE THAT WITHIN THAT WE HAVE MANY PROJECTS WITHIN THE PARKINSON'S DISEASE AREA, ALS, ALZHEIMER'S, AND SPINAL CORD INJURY.

IF YOU LOOK AT THE CLINICAL TRIALS, AS MENTIONED, WE HAVE HAD 68 CLINICAL TRIALS TO DATE THAT CIRM HAS BEEN ABLE TO SUPPORT DIRECTLY THAT ADDRESS OVER 35 DIFFERENT INDICATIONS AND UNMET NEEDS. SO HERE IS JUST A LISTING TO GIVE YOU A FLAVOR OF THE BREADTH THAT WE HAVE HAD IN THIS ARENA, INCLUDING COVID-19, WHICH IS BASED ON THE PROGRAM THAT WE INSTITUTED LAST YEAR IN RESPONSE TO THE NEEDS FOR COVID-19.

JUST A SNAPSHOT HERE OF OUR EDUCATION PILLAR. WE HAVE HAD TRAINING PROGRAMS, AND TRAINING WAS WHERE WE FIRST STARTED IN 2005 AS A PLACE TO BEGIN SUPPORT OF STEM CELL RESEARCH AS A WHOLE. AND NOW LOOKING BACK, WE HAVE TRAINED WELL OVER 2,700 TRAINEES ACROSS ALL THESE DIFFERENT PROGRAMS THAT WILL SUPPORT STUDENTS FROM HIGH SCHOOL LEVEL TO UNDERGRAD AND MASTER'S MOSTLY AT CAL STATE, COMMUNITY COLLEGES, AS WELL AS PREDOC AND POSTDOCTORAL AND CLINICAL RESIDENTS. SO THOSE HAVE BEEN OUR TRAINING PROGRAMS.



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A SNAPSHOT OF OUR INFRASTRUCTURE. SO WE HAVE HAD MANY INFRASTRUCTURE PROGRAMS IN PLACE. MANY OF THEM STARTED, AS I MENTIONED EARLIER, WITH HELPING THE CONSTRUCTION OF BUILDINGS, OR AT LEAST FLOORS WITHIN BUILDINGS, THAT WOULD SUPPORT STEM CELL RESEARCH AND CREATE LABORATORY SPACE. WE HAD A SHARED LABS PROGRAM THAT CREATED THOSE SAFE HAVENS FOR HUMAN EMBRYONIC STEM CELL RESEARCH. SO THOSE WERE EARLY ON.

IN LATER YEARS WE DEVELOPED THE ALPHA STEM CELL CLINICS NETWORK, WHICH INCLUDES SEVERAL SITES THAT SUPPORT THE CONDUCT AND COORDINATION OF CLINICAL TRIALS, PARTICULARLY IN CELL AND GENE THERAPY. SO THAT KNOWLEDGE BASE IN CELL AND GENE THERAPY, WE FELT, WAS IMPORTANT TO FACILITATE SUCH TRIALS AS WE BEGIN TO EMBARK IN THAT AREA.

AN ACCELERATING AND TRANSLATING CENTER TO HELP OUR PROJECTS WITH CLINICAL TRIAL COORDINATION, WITH REGULATORY AFFAIRS, WITH THE CONDUCT OF TOXICOLOGY, PHARMACOLOGY STUDIES, AND SO ON. WE ALSO CREATED AN IPSC REPOSITORY SO THERE IS AN IPSC BANK THAT HAS MANY CELL LINES THAT WERE ALL CREATED IN A UNIFORM FASHION ACROSS MANY PATIENT TYPES AND DISEASE AREAS. A GENOMICS INITIATIVE WHICH CREATED A STEM CELL HUB THAT SUPPORTS DATA SHARING AND DATA



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ANALYSIS.

OKAY. SO WHEN YOU LOOK ACROSS THIS PORTFOLIO, MOST OF IT YOU MAY UNDERSTAND IS A REFLECTION OF THE OPPORTUNITIES THAT WE CREATED, OBVIOUSLY, BUT IT'S ALSO THE RESPONSE THAT WE GOT. SO THAT IS THE PROPOSALS THAT WERE SUBMITTED TO CIRM BASED ON WHAT WE WERE HOPING TO GET BACK. AND SO WE SET UP INITIALLY A LOT OF DIFFERENT RFA'S TRYING TO STAY UP WITH THE FIELD AND TRYING TO ADDRESS NEEDS AS THEY WERE. BUT THAT SET UP A RATHER UNPREDICTABLE SYSTEM. FOLKS DIDN'T KNOW EXACTLY WHEN THE NEXT RFA WOULD COME UP. SO ABOUT FIVE YEARS AGO WE SET UP A MORE PREDICTABLE AND RECURRING OPPORTUNITY SET IN ORDER TO SUPPORT AT THE VERY LEAST THE THERAPY DEVELOPMENT PIPELINE. SO WE WANTED TO CREATE SOMETHING THAT WAS SEAMLESS WHERE PROJECTS COULD COME IN AT ANY TIME POINT ALONG THIS PIPELINE FROM DISCOVERY TO THE CLINIC AND HAVE THESE OPPORTUNITIES OCCUR ON MULTIPLE TIMES OVER THE YEAR. SO, FOR EXAMPLE, WITH DISCOVERY WE HAD THAT OPPORTUNITY AVAILABLE TWICE A YEAR, TRANSLATION PROGRAM AVAILABLE THREE TIMES PER YEAR, AND OUR CLINICAL PROGRAM BASICALLY ONCE A MONTH.

AND SO WE HAVE ACTUALLY RELAUNCHED THIS KNOWING THAT THIS HAS BEEN A CRITICAL PROGRAM FOR US

BOTH IN BRINGING PROJECTS IN AND ALSO PROVIDING AN OPPORTUNITY TO CAPTURE PROJECTS AS SOON AS THEY ARE READY TO COME IN. SO IN JANUARY WE BEGAN THE RELAUNCH OF THIS PROGRAM. ALTHOUGH WE ANTICIPATE THAT OVER TIME WE WILL PROBABLY SEE A NEED TO TWEAK IT, CERTAINLY IN RESPONSE TO OUR STRATEGIC PLAN AS WE DEVELOP IT AS WELL.

AND THEN THIS IS JUST A VERY QUICK LOOK AT OUR REVIEW PROCESS JUST SO YOU HAVE AN UNDERSTANDING OF HOW ALL OF OUR APPLICATIONS THAT COME IN GO THROUGH REVIEW.

SO IT'S SET UP IN THREE BASIC STAGES. WE ASSESS ELIGIBILITY AT CIRM AND DETERMINE WHETHER THIS IS AN APPLICATION THAT CAN BE REVIEWED. IT GOES TO OUR GRANTS WORKING GROUP, OUR EXPERT PANEL, WHO ASSESSES SCIENTIFIC MERITS AND DETERMINES WHETHER THE APPLICATION IS SCIENTIFICALLY MERITORIOUS. AND THEN, FINALLY, RECOMMENDATIONS FROM THAT PANEL GO TO OUR BOARD WHERE A FINAL DECISION TO FUND IS MADE AND WHERE A PROGRAMMATIC REVIEW OF WHETHER SUCH PROJECTS SHOULD BE FUNDED BY CIRM.

AND SO THIS CYCLE IS ABOUT 80 TO 90 DAYS FOR OUR CLINICAL PROGRAM. SO NOT MORE THAN THREE MONTHS IF EVERYTHING GOES WELL. FOR OUR DISCOVERY



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AND TRANSLATION PROGRAM, IT'S ABOUT 120 DAYS FOR THAT CYCLE.

AND THEN HERE THIS IS JUST A SUMMARY OF THE SCOPE OF PROJECTS THAT WE HAVE SUPPORTED AT CIRM OVER THE LAST 15 YEARS. SO OBVIOUSLY WE BEGAN AND HAVE BEEN PRIMARILY A STEM CELL ORGANIZATION. SO STEM CELL AND PROGENITOR CELL-BASED PROJECTS HAVE BEEN THE CORE OF WHAT WE HAVE SUPPORTED, LOOKING AT, FOR EXAMPLE, CELL THERAPY DEVELOPMENT WHICH SUPPORTS ANYTHING FROM HUMAN EMBRYONIC STEM CELLS TO IPSC, MESENCHYMAL STEM CELLS, AND OTHERS. WE HAVE ALSO SUPPORTED PROJECTS THAT DIRECTLY STUDY STEM PROGENITOR CELLS, SUCH AS MECHANISMS OF DIFFERENTIATION; PROJECTS THAT USE STEM CELLS AS A TOOL, SUCH DISEASE IN A DISH MODELS; OR EVEN DIRECTLY REPROGRAMMED CELLS.

WE WERE ALSO QUITE BROAD IN OUR APPROACH INCLUDING SMALL MOLECULES OR OTHER BIOLOGICS THAT WOULD ACT ON OR WOULD BE DEPENDENT ON STEM CELLS FOR THEIR ACTION. BUT IN SOME WAY THERE HAS ALWAYS BEEN A CONNECTION TO STEM CELLS IN SOME WAY.

BUT WE HAVE SINCE BROADENED OUR SCOPE SOMEWHAT. AND WE BEGAN THIS EVEN BEFORE PROP 14. BUT UNDER PROP 14, GENETIC RESEARCH OR GENE THERAPY HAS BEEN PLACED UNDER OUR SCOPE. AND SO WE HAVE

CREATED A DEFINITION AROUND GENE THERAPY WHERE GENE THERAPY AS YOU MAY KNOW, BUT ALSO THAT HAS A REGENERATIVE MEDICINE INTENT. SO HERE A DEFINITION OF REGENERATIVE MEDICINE THAT WE USE WHERE THE GENE THERAPY IS INTENDED TO REPLACE, REGENERATE, OR REPAIR THE FUNCTION OF AGE, DISEASE, DAMAGE, OR DEFECTIVE CELLS, TISSUES, OR ORGANS. SO IT IS PRETTY BROAD, AND WE HAVE BEGUN TO LOOK AT PROJECTS AND SUPPORT PROJECTS IN THIS ARENA.

BUT JUST BROADLY SPEAKING, AND DR. MILLAN BROUGHT THIS UP, WE ALSO OFTEN REFERENCE WHAT ARE CALLED VITAL RESEARCH OPPORTUNITIES. SO THIS IS SPECIFIC REFERENCE IN PROP 14 AS WELL AS IN PROP 71 THAT ALLOWED CIRM TO BROADEN ITS PURVIEW AS IT DEEMS NECESSARY BY THE BOARD IN ORDER TO ADDRESS AREAS THAT MAYBE WERE NOT ORIGINALLY THOUGHT OF OR HIGHLIGHTED BY THE PROPOSITION ITSELF. IT ALLOWS US TO MOVE INTO AREAS AS WE DID BEFORE GENE THERAPY AND POTENTIALLY OTHERS. AND SO IN THINKING ABOUT HOW IT IS THAT WE WANT TO MAKE AN IMPACT GOING INTO THE FUTURE, IT'S WORTH CONSIDERING IF THERE ARE ADDITIONAL AREAS THAT CIRM COULD SUPPORT UNDER A VITAL RESEARCH OPPORTUNITY.

SO THE LAST THING THAT I'M GOING TO TALK ABOUT IS JUST SUMMARIZE A COUPLE OF MEETINGS THAT WE

HAD. WE HAVE BEEN SEEKING FEEDBACK EVEN BEFORE THIS MEETING, AS WAS MENTIONED BY CHAIRMAN THOMAS. WE BEGAN TO LOOK FOR WAYS IN WHICH WE COULD START THINKING ABOUT THE IMPACT THAT WE COULD MAKE VERY EARLY ON.

SO WE HAD A MEETING WITH OUR GRANTS WORKING GROUP THAT IS OUR EXPERT REVIEW PANEL. WE INVITED ABOUT 25 MEMBERS TO COME TO THE BAY AREA TO HELP US THINK ABOUT HOW WE COULD PREPARE AT THE TIME FOR A POSSIBLE LIFE BEYOND 2020. SO THESE ARE THE KINDS OF QUESTIONS WE ASKED. HOW CAN CIRM DELIVER THE GREATEST IMPACT IN THE FUTURE? WHAT OPPORTUNITIES MIGHT CIRM SEE TO ACCELERATE THE FIELD? AND SO ON. AND SO AT THE END OF THAT MEETING, THERE WERE SOME MAJOR THEMES THAT CAME OUT OF IT AND WHICH HAVE FED INTO OUR THINKING ABOUT STRATEGIC PLANNING.

SO PRIORITIZING FUNDING OF WORK THAT CANNOT BE FUNDED ELSEWHERE OR THAT IS UNDERFUNDED WAS ONE. TO EXPLORE WAYS TO ENCOURAGE COLLABORATIVE OR TEAM-BASED APPROACHES, TO ESTABLISH AND MAINTAIN CORE SERVICES, ENCOURAGE STANDARDIZATION, IMPLEMENT DATA SHARING, AND ALSO TO FUND ALL REGENERATIVE MEDICINE APPROACHES AND TO NOT LIMIT FUNDING TO STEM CELLS.

SOME ADDITIONAL RECOMMENDATIONS WERE TO SUPPORT INFRASTRUCTURE AND TECHNOLOGY DEVELOPMENT FOR CELL AND GENE THERAPY MANUFACTURING. THAT WAS SEEN AS AN IMPORTANT AREA. TO ENHANCE TRAINING ACROSS ALL LEVELS. TO CONTINUE TO INNOVATE IN THE PEER REVIEW PROCESS AND EVEN TO ESTABLISH SOME MOONSHOT PROJECTS OR ATTEMPTS IN OUR FUNDING.

AND THEN WE HAD ANOTHER MEETING WHICH WAS FOCUSED IN THE AREA OF NEURODEGENERATION ALSO THAT TOOK PLACE IN 2019. THIS WAS A TWO-DAY WORKSHOP THAT BROUGHT TOGETHER ABOUT 50 KEY OPINION LEADERS ACROSS THE FIELD AND INCLUDED INDUSTRY, FUNDING AGENCIES, THE FDA, AND OTHERS TO TRY TO ADDRESS ISSUES SPECIFIC TO NEURODEGENERATION THERAPY DEVELOPMENT AND THINK ABOUT HOW THE STATE OF THE SCIENCE AT THE TIME COULD BE CONFIGURED TO ADDRESS ISSUES IN DISCOVERY AND LATER DEVELOPMENT OF THERAPIES.

SO SOME OF THE RECOMMENDATIONS THAT CAME OUT OF THAT MEETING ARE SUMMARIZED HERE. AGAIN, COLLABORATIVE SCIENCE WAS ANOTHER THEME THAT EMERGED FROM HERE AS WELL AS ADDRESSING PRECISION MEDICINE AND GENOMIC ATTEMPTS TO TRY TO UNDERSTAND HOW TO ADDRESS THIS FOR INDIVIDUAL PATIENTS, STANDARDIZATION OF PRACTICES, TO ENABLE DATA AND

DEVELOPMENT COMPARABILITY FROM EARLY DISCOVERY THROUGH THE CLINIC. TO IDENTIFY NOVEL TARGETS IN DISCOVERY AND FOR VALIDATION. EXPAND BIOMARKER DISCOVERY AND VALIDATION. DATA HARMONIZATION AND SHARING WHICH, AGAIN, WAS ANOTHER IMPORTANT THEME. AND ALSO ADDRESSING DIVERSITY AND UNDERREPRESENTED POPULATIONS IN THE AREA OF NEURODEGENERATION.

SO THAT CONCLUDES MY PRESENTATION. AND SO IF THERE ARE QUESTIONS, I'M HAPPY TO TAKE THEM; OR IF WE NEED TO GO ON, HAPPY TO DO THAT AS WELL.

DR. MILLAN: GIL, THANK YOU SO MUCH FOR THE PRESENTATION. TO THE PANEL, THANK YOU FOR YOUR QUESTIONS. I'VE RESPONDED TO MOST OF THEM, I BELIEVE. DR. WAGERS ASKED ABOUT KIND OF A BREAKDOWN OF THE TYPES OF STEM CELLS AND CELL THERAPIES, AND WE'LL GET YOU THAT BREAKDOWN. WE DO HAVE THAT INFORMATION. SO AS SOON AS WE GET IT, WE WILL SHARE IT WITH ENTIRE PANEL.

AND THEN THERE WAS A QUESTION FROM DR. MUMMERY ABOUT WHERE THE REVIEWS ARE HELD. THEY ARE HELD BY CIRM IN CALIFORNIA, ALTHOUGH OUR REVIEWERS ARE FROM OUTSIDE OF CALIFORNIA. WE ALSO HAVE SPECIALTY REVIEWERS WHO COME IN FOR A VARIETY OF TOPICS THAT CAN BE FROM WITHIN OR OUTSIDE OF CALIFORNIA, BUT THE VOTING REVIEWERS ARE FROM

OUTSIDE OF CALIFORNIA.

THERE'S A QUESTION ABOUT -- I THINK THAT'S PRETTY MUCH IT. THERE MAY BE AN ADDITIONAL ONE THAT WE'LL GET INTO. DR. DZAU HAD HIS HAND UP. DR. DZAU.

DR. DZAU: I THINK I'M FASTER SPEAKING THAN TYPING. ANYWAY, MY QUESTION HAS TO DO WITH PARTNERSHIP AND COLLABORATION OUTSIDE CALIFORNIA AND EVEN OUTSIDE THE COUNTRY. I KNOW THAT YOU DO HAVE THEM. WHAT IS THE CIRCUMSTANCE, RELATIONSHIP THAT NEEDS TO ESTABLISHED FOR SUCH PARTNERSHIP AND COLLABORATION?

DR. MILLAN: DR. DZAU, MAYBE ONE OF THE EXAMPLES THAT WE ACTUALLY ACTIVE RIGHT NOW IS SOME OF THE MOU'S WE HAVE IN PLACE. SO THE MOU WITH THE HEART LUNG BLOOD INSTITUTE AT NIH FUNDS PROGRAMS BOTH WITHIN CALIFORNIA AND OUTSIDE OF CALIFORNIA. WE HAVE PUT TOGETHER KIND OF THE PARAMETERS OF HOW WE'RE GOING TO DO BUSINESS TOGETHER, HOW WE WILL ALIGN AND COORDINATE SO THERE'S NO DUPLICATION. AND THAT IS ALL -- WE DON'T HAVE PARALLEL REVIEWS THAT GIVE DIFFERENT DECISIONS, FOR INSTANCE, THAT WE CAN'T DEAL WITH. SO THERE'S PARALLEL REVIEW PROCESSES THAT USE THE SAME APPLICATION, AND IT'S SO WELL COORDINATED, THAT WITHIN TEN DAYS OF OUR GWG

GIVING RECOMMENDATION, THAT NHLBI WILL GIVE US FROM THEIR EXECUTIVE COMMITTEE AND FROM THEIR DIRECTOR A DECISION AS TO WHETHER OR NOT THEY WILL BE ABLE TO CO-FUND THE PORTION OF THAT GRANT FROM THE NON-CIRM COVERED COSTS. SO THAT'S WORKED OUT WELL.

WE DO FUND PROGRAMS OUTSIDE OF CALIFORNIA. IT'S JUST THAT THE CALIFORNIA COSTS, THE CALIFORNIA PORTION OF THAT PROJECT, ARE THOSE THAT ARE ELIGIBLE FOR CIRM DOLLAR FUNDING. AND SO WE HAVE A VARIETY OF EXAMPLES OF CO-FUNDING RELATIONSHIPS, NOT ONLY WITH AGENCIES, BUT WE HAVE INDUSTRY WHO CO-FUND PROGRAMS AS WELL AS OTHERS. AND SO WE DO BELIEVE THAT WE HAVE SOME DEMONSTRATION CASES OF WHERE THIS RUNS REALLY EFFICIENTLY. AND THE PARTNERING ORGANIZATION HAS FOUND IT TO BE BENEFICIAL FOR THEM AS AN ACCELERATION AND KIND OF AN ORGANIZED APPROACH WHERE WE CAN PUT ALL OF OUR ASSETS INTO EVALUATION AND SUPPORT OF THOSE PROGRAMS.

DR. DZAU: THANK YOU.

DR. MILLAN: THERE WAS A QUESTION FROM DR. AUSTIN ABOUT THE PRIORITIES. SO JUST WHAT HAPPENS IS THAT THE PILLAR PROGRAMS THAT GIL HAD TALKED ABOUT, THE DISC, EDU, INFRASTRUCTURE, TRANSLATIONAL, AND CLINICAL. WHAT HAPPENS WITH THOSE ARE THAT PROGRAMS COME IN WITHOUT ANY PARTICULAR -- THERE'S

JUST A SCOPE OF TYPES OF PROGRAMS THAT CIRM CAN FUND. AND AS LONG AS THEY MEET ELIGIBILITY AND SCOPE, APPLICATIONS COME IN IN OUR CURRENT MODEL AT ANY GIVEN TIME, AND THERE'S A PERIODIC REVIEW. AND IT'S KIND OF A RECURRING AND SCHEDULED OPPORTUNITY. AND I THINK THERE ARE THREE OPPORTUNITIES FOR DISC TRADITIONALLY OR TWO AND TWO FOR TRANSLATION, MAYBE THREE, AND FOR CLINICAL EVERY MONTH, MEANING FOR IND-ENABLING AND CLINICAL TRIALS.

WHAT HAPPENS IS THOSE PROGRAMS COME IN AND THEY GET EVALUATED ON SCIENTIFIC MERIT. WITHIN THE REVIEW THERE IS A REVIEW CRITERIA CALLED SIGNIFICANCE AND IMPACT. BUT AS OF NOW IN THE CURRENT MODEL, THERE'S NO SPECIFIC PRIORITIZATION. SHOULD WE GO TO A DIFFERENT TYPE OF SPECIAL CALL? FOR INSTANCE, WE HAD A SPECIAL CALL FOR COVID. IN THOSE CASES WE SPECIFICALLY SOUGHT APPLICATIONS AND VARIOUS APPROACHES TO COVID THERAPEUTIC, VACCINE DEVELOPMENT, DISCOVERY TYPE PROGRAMS. SO WE HAVE BEEN ABLE TO CARRY OUT REVIEWS UNDER BOTH TYPES OF SCENARIOS, BUT THE STANDING PROGRAM ANNOUNCEMENTS CURRENTLY ARE BASED ONLY ON SCIENTIFIC, NOT ONLY, BUT PRIMARILY ON SCIENTIFIC MERIT AND ARE NOT SPECIFICALLY SEEKING ANY PARTICULAR DISEASE INDICATION.



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AND DR. TEMPLE ASKED CAN CIRM FUNDING BE USED TO SUPPORT NON-NIH PORTION OF SUCCESSFUL NIH REGENERATIVE MEDICINE PRODUCT APPLICATIONS TO PROVIDE MATCHING FUNDS? YES. WE'VE DONE THAT WITH THE CURE SICKLE CELL INITIATIVE. FOR INSTANCE, ONE OF THE RECENT ONES WAS OUT OF BOSTON CHILDREN'S HOSPITAL, DR. DAVID WILLIAMS' TRIAL FOR SICKLE CELL, AND CIRM IS FUNDING THE CALIFORNIA PORTION OF THAT MULTICENTER PROPOSED PHASE 2 TRIAL. SO CALIFORNIA ENROLLMENT, MANUFACTURING, AND ANY RESEARCH THAT HAPPENS IN CALIFORNIA IS FUNDED BY THE CIRM PORTION OF THE AWARD. AND ALSO CIRM DEPLOYS ITS CLINICAL ADVISORY PANEL, AND IT'S MILESTONE BASED KIND OF PROJECT MANAGEMENT. AND THE NIH HAS BEEN MIRRORING THOSE -- WE WORK COLLABORATIVELY ON NEGOTIATING MILESTONES, AND THEY'VE BEEN PARTICIPATING IN OUR ADVISORY PANELS. AND THE CIRM OPERATIONS TEAM AND THE NHLBI OPERATIONS TEAM WORK TOGETHER IN MAKING SURE THAT THIS IS EXECUTED EFFICIENTLY.

THERE ARE SOME GREAT QUESTIONS HERE. I KNOW, DR. CLARK, WE'RE CUTTING INTO YOU, BUT WE'RE NOT GOING TO CUT YOU SHORT IN TERMS OF WHAT YOU HAVE. WHAT WE'LL DO NOW IS MAYBE I WILL CONTINUE, THE TEAM WILL HELP ME COLLECT THESE QUESTIONS AND MAKE SURE WE GET TO ALL OF THEM. AND THEN YOU CAN

ALSO HOLD YOUR QUESTIONS TO THE NEXT SESSION, THE NEXT QUESTION AND ANSWER SESSION.

SO I'M GOING TO NOW TURN IT OVER TO DR. AMANDER CLARK. AS STATED IN THE BEGINNING, I WON'T BE INTRODUCING EVERYBODY BY TITLE OR ANYTHING ELSE. THEY'RE JUST GOING TO KIND OF COME IN THERE AND SET UP THE STAGE FOR DISCUSSION, AND THEN WE WILL GO FROM THERE. WE WILL DO A TIME CHECK. DR. CLARK IS STARTING AT 7:54. SO YOU'RE SCHEDULED UNTIL 8:04 FOR YOUR PORTION OF THE TALK. THANK YOU SO MUCH.

DR. CLARK: THANK YOU, DR. MILLAN AND CIRM LEADERSHIP FOR INVITING ME TO FRAME THE DISCUSSION ON THE STRATEGIC DIRECTION OF BASIC SCIENCE STEM CELL RESEARCH BY CIRM. SO AS DR. MILLAN SAID, MY NAME IS AMANDER CLARK. I'M PROFESSOR AND CHAIR OF MOLECULAR CELL AND DEVELOPMENTAL BIOLOGY AT UCLA.

I'M GOING TO FRAME MY DISCUSSION TODAY IN THREE AREAS. ONE IS CIRM'S CRITICAL ROLE IN SUPPORTING BASIC SCIENCE RESEARCH AND COLLABORATION, AS WE'VE ALREADY HEARD ABOUT THIS MORNING, THE IMPORTANCE OF CIRM IN TAKING A LEADERSHIP ROLE IN REGULATION AND POLICY OF NEW STEM CELL SCIENCE AS IT EMERGES, AND, THREE, THE ROLE OF CIRM IN ORIENTING BASIC STEM CELL RESEARCH TOWARDS IMPROVING THE

HEALTH OF CHILDREN AND YOUNG ADULTS.

SO I'LL BEGIN WITH BASIC SCIENCE RESEARCH AND COLLABORATION. ONE THING WE CAN ALL AGREE UPON IS THAT BASIC SCIENCE DISCOVERIES HAVE A PROFOUND AND LONG-LASTING IMPACT ON BIOMEDICAL RESEARCH AND TRANSLATION. THESE DISCOVERIES CAN COME FROM THE UNLIKELIEST OF PLACES. GIVEN THIS, LEVERAGING AND SUPPORTING EXCELLENT BASIC SCIENCE RESEARCH IN CALIFORNIA IRRESPECTIVE OF DISCIPLINE SHOULD BE THE VERY FOUNDATION OF THE CIRM SCIENTIFIC PIPELINE.

CALIFORNIA IS HOME TO A WIDE VARIETY OF TIER I RESEARCH INSTITUTIONS CONTAINING LABORATORIES AND FACULTY WHO DEDICATE THEIR CAREERS TO FUNDAMENTAL SCIENTIFIC DISCOVERY. CIRM IS IN THE UNIQUE POSITION TO HARNESS THIS TALENT THROUGH RESEARCH GRANTS THAT SUPPORT SCIENTIFIC EXCELLENCE ABOVE AND BEYOND WHAT CAN BE ACHIEVED WITH FUNDS FROM THE NIH AND NSF. FOR EXAMPLE, CIRM COULD FOCUS ON BOLD COLLABORATIVE, MULTI-PI STEM CELL GRANTS THAT WOULD BE CONSIDERED HIGH RISK COMPARED TO THOSE TRADITIONALLY FUNDED THROUGH THE NIH SYSTEM.

CONSISTENT WITH BUILDING THIS PIPELINE, CIRM IS IN A KEY POSITION TO PROVIDE RESOURCES TO ATTRACT THE BEST AND BRIGHTEST TO THE STATE THROUGH A RECRUITMENT PROGRAM THAT COULD INVOLVE MATCHING



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FUNDS WITH RECRUITING INSTITUTIONS. CIRM IS ALSO IN A POSITION TO STABILIZE FUNDING IN CRITICAL AREAS OF STEM CELL RESEARCH THAT TEND TO GET CAUGHT IN SHIFTING POLITICAL WHIMS. THIS INCLUDES HUMAN EMBRYONIC STEM CELLS, FETAL TISSUE RESEARCH, STEM CELL-BASED EMBRYO MODELS, AND HUMAN EMBRYO AND GAMETE RESEARCH, WHICH IS THE FUNDAMENTAL SCIENCE BEHIND HEALTHY FAMILIES.

TODAY IT IS RARE FOR TRANSFORMATIVE STEM CELL SCIENCE TO OCCUR AT A SINGLE LABORATORY. INSTEAD, IT DEMANDS COLLABORATION AND IN MANY CASES THE NEED TO WORK WITH SCIENTISTS AND CLINICIANS OUTSIDE OF THE STATE. THEREFORE, CIRM SHOULD LEVERAGE TAXPAYER DOLLARS TO DEVELOP A FRAMEWORK THAT ENABLES CALIFORNIA STEM CELL SCIENTISTS TO FREELY WORK WITH COLLEAGUES AROUND THE NATION AND WORLD WHILE PROTECTING IP DEVELOPED WITH CIRM FUNDING. THIS COULD INCLUDE EVALUATING PREVIOUS MOU AGREEMENTS, ESTABLISHING NEW AGREEMENTS, OR POSSIBLY CREATING A FELLOWS PROGRAM TO FUND OUTSTANDING EARLY CAREER STEM CELL RESEARCHERS INSIDE AND OUTSIDE OF THE STATE.

A MAJOR SHIFT IN STEM CELL SCIENCE IS THE NEED FOR INCREASING FUNDING TOWARDS QUANTITATIVE DATA SITES AND MACHINE LEARNING. CIRM SHOULD TAKE A



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LEADERSHIP ROLE IN ESTABLISHING THE INFRASTRUCTURE SO THAT DATASETS CREATED WITH CIRM FUNDING ARE CENTRALIZED AND ACCESSIBLE FOR SCIENTISTS WITH A RANGE OF SKILL SETS AND NOT JUST THE EXPERTS IN THE PARTICULAR AREA.

IN ADDITION AND WHERE POSSIBLE, THE COLLECTION OF LARGE DATASETS THAT UTILIZE HUMAN SAMPLES SHOULD BE INCLUSIVE OF THE DIVERSITY WITHIN THE STATE OF CALIFORNIA SO THAT TREATMENTS AND CURES CAN BE DEVELOPED FOR EVERYONE. THEREFORE, CIRM SHOULD CONSIDER A DIVERSITY REQUIREMENT WHEN SUPPORTING BASIC SCIENCE STUDIES THAT INVOLVES HUMAN SUBJECTS RESEARCH. THIS IS BECAUSE PROMOTING INCLUSION OF DIVERSE SAMPLES AT THE BEGINNING OF THE BASIC SCIENCE PIPELINE COULD BE A STRONG STEP TOWARDS ELIMINATING HEALTH DISPARITIES AS THE PIPELINE BUILDS TOWARDS TREATMENT.

NO. 2, TAKING A LEADERSHIP ROLE IN REGULATION AND POLICY. AS CIRM CONTINUES TO BUILD ON THE STEM CELL-BASED SCREENING AND THERAPEUTIC PIPELINES CREATED UNDER PROP 71, IT IS IMPERATIVE THAT CIRM CONTINUES UNDER PROP 14 FUNDING TO TAKE A LEADERSHIP ROLE AND ALSO A GLOBAL VIEW IN COORDINATING NATIONAL ACADEMIES, SOCIETIES, GOVERNMENTS, AND FUNDING AGENCIES WORLDWIDE TO



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ENSURE THAT NEW FORMS OF SCIENCE MOVE FORWARD UNDER A COORDINATED SCIENTIFIC AND ETHICAL FRAMEWORK.

SPECIFIC EXAMPLES OF THE NEW STEM CELL-BASED EMBRYO MODEL, THIS WOULD BE ESSENTIAL TO ENSURE THAT STEM CELL THERAPIES MOVE SAFELY AND SWIFTLY FROM BENCH TO BEDSIDE IN CALIFORNIA AND AROUND THE WORLD.

AND, FINALLY, I'D LIKE TO TURN TO THE FUTURE. WITH NOTABLE EXCEPTIONS, SCID BEING ONE, THE LAST 14 YEARS OF CIRM FUNDING UNDER PROP 71 HAS PLACED SIGNIFICANT EMPHASIS ON THE USE OF STEM CELLS TO IMPROVE THE HEALTH AND DEVELOP CURES FOR ADULTS, INCLUDING A FOCUS ON CANCER AS WELL AS DEGENERATIVE DISEASE. IT IS IMPORTANT THAT IN THE NEXT PHASE OF CIRM FUNDING THERE IS AN INTENTIONAL FOCUS ON THE HEALTH OF FUTURE CALIFORNIANS, INCLUDING UNDERSTANDING THE DEVELOPMENTAL ORIGINS OF DISEASE WITH A FOCUS ON DEVELOPMENTAL BIOLOGY, CHILD HEALTH, AND THE HEALTH OF YOUNG ADULTS. THIS IS PARTICULARLY CRITICAL AS CIRM TURNS ITS FOCUS TOWARDS THE USE OF STEM CELLS TO UNDERSTAND AND TREAT DISEASES OF THE BRAIN AND CENTRAL NERVOUS SYSTEM.

CIRM SHOULD BE APPLAUDED FOR TAKING A LEADERSHIP ROLE IN THIS AREA, AND TODAY WE WILL HEAR



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A NUMBER OF TALKS ABOUT USE OF STEM CELLS TO TREAT DEGENERATIVE BRAIN DISORDERS. HERE I WOULD ALSO LIKE TO ADVOCATE FOR OTHER DISEASES OF THE BRAIN, INCLUDING PSYCHIATRIC OR MENTAL DISORDERS WHICH DISPROPORTIONATELY AFFECT CHILDREN AND YOUNG ADULTS AND IN MANY CASES DISPROPORTIONATELY AFFECT MINORITY POPULATIONS. TO MAKE AN IMPACT IN THIS AREA, HOWEVER, WILL REQUIRE AN INVESTMENT IN BASIC SCIENCE. FOR EXAMPLE, DUE TO THE LARGE AND DIVERSE POPULATION IN CALIFORNIA, CIRM IS UNIQUELY POSITIONED TO DEVELOP THE FRAMEWORK FOR IDENTIFYING GENES IN CHILDREN WHO ARE AT HIGH RISK FOR AUTISM, BIPOLAR DISORDER, AND OTHER PSYCHIATRIC DISEASES, AND UTILIZING IPS TECHNOLOGY TO UNDERSTAND THE ROLE OF THESE GENES IN BRAIN CELL DEVELOPMENT.

FURTHERMORE, GIVEN THERE IS A DEVELOPMENTAL ETIOLOGY TO MANY SEVERE PSYCHIATRIC CONDITIONS, IT IS ESSENTIAL THAT CIRM CONSIDERS INVESTMENT IN BASIC RESEARCH ON PRENATAL AND POSTNATAL BRAIN DEVELOPMENT, INCLUDING NONINVASIVE STUDIES IN CHILDREN, IN ORDER TO UNDERSTAND CIRCUITS AND WIRING.

FINALLY, A MISSED OPPORTUNITY SO FAR AND AN AREA THAT I HOPE CIRM WILL CONSIDER AS IT MOVES FORWARD IS A FOCUS ON THE ENVIRONMENT AND HOW THE



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ENVIRONMENT CAN AFFECT BRAIN DEVELOPMENT AND HOW THE ENVIRONMENT AND THE CHANGING ENVIRONMENT COULD BE ASSOCIATED WITH THE EMERGENCE OF PSYCHIATRIC DISORDERS AND NEUROLOGICAL DISEASE. ONCE FUNDAMENTAL DISCOVERIES ARE MADE IN THESE AREAS, THE UTILITY OF STEM CELLS TO UNDERSTAND AND TREAT DISEASES OF THE BRAIN AND CENTRAL NERVOUS SYSTEM WILL BEGIN TO EMERGE.

IN SUMMARY, CIRM IS IN A UNIQUE POSITION TO MAKE A SIGNIFICANT IMPACT IN STEM CELL SCIENCE IN THE STATE OF CALIFORNIA, THE NATION, AND AROUND THE WORLD. THIS BEGINS WITH AN INVESTMENT IN BASIC SCIENCE, IN COLLABORATION, A FOCUS ON REGULATION AND POLICY, AND AN INTENTIONAL FOCUS ON THE HEALTH OF CURRENT AND FUTURE GENERATIONS OF CALIFORNIANS. THANK YOU.

DR. MILLAN: THANK YOU SO MUCH, DR. CLARK. YOU'RE AHEAD OF SCHEDULE. BECAUSE OF THAT, I'M ABLE TO RESPOND TO TWO MORE QUESTIONS BEFORE WE DISCUSS THIS PARTICULAR SUBJECT MATTER.

SO DR. WAGERS HAD ASKED EARLY ON IN THE PIE CHART THAT DR. SAMBRANO HAD PRESENTED REGARDING THE DISEASE AREAS. THOSE ARE PERCENT OF PROJECTS, NOT PERCENT OF DOLLARS.

AND THEN, DR. AUSTIN, WE WILL BE GETTING

YOU THE BREAKDOWN AND TYPES OF STEM CELLS SHORTLY.

AND WITH THAT, I'D LIKE TO OPEN IT UP FOR DISCUSSION AMONG THE PANELISTS THIS TOPIC THAT DR. AMANDER CLARK HAD KIND OF PROPOSED TO US REGARDING A CONSORTIUM APPROACH TO BASIC DISCOVERY AND SPECIFICALLY IDEAS REGARDING KIND OF DEVELOPMENTAL BIOLOGY AND ALL OF THE OTHER TOPIC AREAS. CAN I GO AHEAD AND JUST OPEN IT UP TO THE PANEL. AND I GUESS WE'LL GO AHEAD AND JUMP IN, AND THEN WE'LL HAVE HAND RAISING ONCE THERE ARE MORE PEOPLE ON THE LINEUP TO GIVE COMMENTS OR QUESTIONS.

THE FIRST PERSON CAN JUMP IN AND TAG THE NEXT PERSON. HOW DOES THAT SOUND?

DR. MC CUNE: THIS IS MIKE MCCUNE. I'M HAPPY TO JUMP IN. I THINK ONE THING THAT CIRM COULD DO IMMEDIATELY IS TO OPEN UP THE GATES FOR CONTINUED WORK ON FETAL TISSUE. SHUTDOWN, AS WE ALL KNOW, IN PREVIOUS ADMINISTRATION, SOMETHING THAT MAY CHANGE, BUT PROBABLY NOT QUICKLY WITH THE CURRENT ADMINISTRATION. AND ESPECIALLY IMPORTANT, I THINK, FROM THE STANDPOINT OF LOOKING AT DISEASES THAT AFFECT CHILDREN AND BABIES.

I'M NOT SURE HOW TO TAG ANYBODY, MARIA. IF SOMEBODY ELSE WANTS TO JUMP IN.

DR. DALEY: I MIGHT SECOND THAT. I JUST

SORT OF RAISE THE GENERAL QUESTION THAT CIRM WAS FOUNDED TO DO THINGS THAT NIH AND THE FEDERAL GOVERNMENT COULDN'T OR WOULDN'T PRIORITIZE. AND SORT OF THE GENERAL QUESTION IS IS THAT PHILOSOPHY STILL DOMINANT? OBVIOUSLY, THERE'S CRITICAL IMPORTANCE OF BEING ABLE TO DEMONSTRATE IMPACT. AND ALL OF THE CLINICAL PROGRAMS CERTAINLY HAVE DONE THAT; AND IN MOST OF THOSE TRANSLATIONAL CONTEXTS, IT'S NOT THE EMBRYONIC STEM CELLS OR CLONING OR FETAL TISSUE RESEARCH OR THAT SORT. THERE OBVIOUSLY HAS TO BE SOME BALANCE, BUT I WOULD SAY THAT THERE ARE DEFINITELY AREAS WHERE CRITICAL INVESTMENTS HAVE TO CONTINUE. I THINK AMANDER MENTIONED SOME OF THEM, BUT THEY'RE THE KIND OF NONPRESIDENTIAL TOPICS FROM THE PAST, FETAL TISSUE, HUMAN EMBRYOLOGY, MITOCHONDRIAL REPLACEMENT, HUMAN GAMETOGENESIS, THE EMBRYO CHIMERA WORK THAT'S STILL SOMEWHAT STALLED IN ETHICAL REVIEW AT THE NIH. THESE EMBRYO MODELS.

AND THEN ANOTHER TISSUE THAT MAY COME UP IS WHETHER IT'S TIME, IN THE AFTERMATH OF THIS RE-FUNDING OF CIRM, FOR CIRM TO BE A PLATFORM FOR TALKING ABOUT THE 14-DAY RULE AND BEING ABLE TO DO THINGS THAT PUSH THE ENVELOPE IN THAT DIRECTION.

DR. MILLAN: THANK YOU, DR. DALEY.

ADDITIONAL COMMENTS OR QUESTIONS RELATED

TO? SO WHAT DOES THE PANEL -- SO EMBRYONIC STEM CELL RESEARCH IS ONE OF THOSE AREAS IN ADDITION TO FETAL THAT I WOULD SAY THERE IS A KIND OF CONSENSUS THAT THOSE ARE ALWAYS AT RISK IN TERMS OF WHAT TYPE -- THE FUNDING AND THE SUPPORT THEY CAN GAIN. AMANDER HAD MENTIONED THIS IDEA OF SOME SORT OF COLLABORATIVE CONSORTIUM AND CREATING DEVELOPMENTAL BIOLOGY, EMBRYOLOGY MODELS THAT COULD BE EMPOWERED. ARE THERE ANY OTHER THOUGHTS? DR. MUMMERY, WOULD YOU, AS THE PRESIDENT IF ISSCR AND A SPECIALIST IN THE FIELD, DO YOU HAVE ANY THOUGHTS ON THAT TYPE OF MODEL?

DR. MUMMERY: ABSOLUTELY. I THINK IT'S ONE OF THE OPPORTUNITIES FOR CALIFORNIA IS TO DO GAMETE RESEARCH, HUMAN GAMETE RESEARCH, COMPARE THEM WITH GAMETES IN EARLY EMBRYOS. AND EVEN CREATING EMBRYOS FOR RESEARCH, SIMPLY PUT THE FERTILIZATION PROCESS. AND IN MANY COUNTRIES THIS IS NOT ALLOWED. IT WOULD BE ALLOWED IN CALIFORNIA AS FAR AS I KNOW. THESE ARE REAL OPPORTUNITIES TO ADDRESS ISSUES OF INFERTILITY. AGAIN, THE 14-DAY RULE FALLS INTO THAT CATEGORY.

ONE OF THE THINGS THAT COULD BE CONSIDERED IS LOOKING AT GENETIC MODIFICATION OF EARLY EMBRYOS TO SEE WHERE THINGS GO WRONG. AND THIS WOULD BE A



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UNIQUE OPPORTUNITY TO BE ABLE TO DO THIS IN A PROTECTED ENVIRONMENT IN CALIFORNIA. AND THE EXPERTISE TO DO IT IS CERTAINLY PRESCIENT. SO IT WOULD BE GREAT TO FOLLOW THAT PART OF EARLY HUMAN DEVELOPMENT THROUGH.

DR. MILLAN: THANK YOU, DR. MUMMERY.

DR. TEMPLE, YOU HAD MENTIONED SOMETHING ABOUT SOME REFERENCE SAMPLES THAT COULD BE A COMPONENT OF WHAT DR. CLARK HAD DESCRIBED AS A POSSIBILITY. DID YOU WANT TO TALK ABOUT THAT A LITTLE BIT MORE?

DR. TEMPLE: I THOUGHT THAT WAS A GREAT PRESENTATION. THANK YOU, AMANDER.

THIS CONCEPT THAT WE NEED REFERENCE SAMPLES THAT ARE GROUNDED IN REAL BIOLOGY IS CRITICAL. WE ALREADY TALKED ABOUT THE NEED TO HAVE FETAL TISSUE SO THAT WE KNOW THAT WHAT WE ARE MAKING IS FOLLOWING THE TRAJECTORY OF NONDEVELOPMENT. I THINK IT'S CRUCIAL. AND THAT HAS BECOME ALMOST IMPOSSIBLE TO DO NOW WITH NIH FUNDING RESTRICTIONS IN PLACE.

BUT I'D ALSO ADVOCATE FOR SAMPLES THAT ARE COMING FROM DISEASES OF THE BRAIN NEURODEGENERATIVE DISEASES WHICH IS A FOCUS AND ALL STAGES APPLIES BECAUSE IF WE DON'T HAVE THOSE REFERENCE SAMPLES, WE

DON'T KNOW IF WE ARE REALLY FOLLOWING THE DISEASE COURSE. SO WE NEED THAT. OFTEN THEY'RE RARE DISEASES, AND I KNOW FROM OUR OWN WORK THAT THE BRAIN IN THE NETHERLANDS AND THE BRAIN AT UCSF AND WE ARE TRYING TO COORDINATE TO GET THIS VERY PRECIOUS MATERIAL AND DATA. IF THERE'S A WAY TO COORDINATE THAT, IT WOULD BE IMMENSELY VALUABLE.

DR. MILLAN: THANK YOU VERY MUCH. ARE THERE ANY OTHER --

DR. SAMBRANO: MARIA, THERE'S A COUPLE OF QUESTIONS. I THINK KEVIN EGGAN AND CAT JAMIESON HAVE QUESTIONS.

DR. MILLAN: KEVIN, DO YOU WANT TO JUST GO AHEAD?

DR. EGGAN: SURE. I THINK ANOTHER AREA THAT COULD BE WORTH CONSIDERING, PARTICULARLY WITH THIS SIGNAL AND CIRM 2.0 OF SUPPORTING GENE THERAPY OR GENETIC MEDICINES, IS TO CONSIDER DOUBLING DOWN ON STUDYING THE SAFETY OF THESE THERAPEUTIC APPROACHES. WITH RECENT ANNOUNCEMENTS OF AN HCC CASE AND (INAUDIBLE) PATIENTS AND THE RECENT ANNOUNCEMENT OF TWO CANCER PATIENTS AND ONGOING BLUEBIRD TRIALS, I THINK IT'S WORTHWHILE CONSIDERING THAT A GROUP LIKE CIRM COULD MAKE A MAJOR IMPACT IN THE PERCEPTION THAT THE COMMUNITY HAS IN THESE TYPES

OF MEDICINES.

AND ONE OF THE THINGS THAT MAY NOT ALWAYS BE ON THE CRITICAL PATH FOR ACADEMICS OR THOSE IN THE COMMERCIAL SETTING WHO ARE DEVELOPING THESE THERAPEUTICS ARE LONG-TERM STUDIES OF THE SAFETY AND GENOTOXICITY OF THESE TYPES OF THERAPEUTIC APPROACHES. SO THAT'S JUST ONE THING TO THINK ABOUT, MAYBE A SUGGESTION THAT COULD BE CONSIDERED.

DR. MILLAN: THANK YOU SO MUCH.

DR. MARKS SAID HE MAY BE ON AND OFF. PETER, WITHOUT TALKING ABOUT ANY SPECIFIC OBVIOUSLY PROJECTS, JUST YOUR GENERAL SENSE OF THE ABILITY TO KIND OF AGGREGATE EXPERIENCE AND DATASETS REGARDING THE BASIC SCIENCE OR SCIENTIFIC DATABASE FOR SAFETY ISSUES.

DR. MARKS: I THINK I'D SAY IT SEEMS LIKE A VERY, VERY GREAT CONTRIBUTION THAT COULD BE MADE. I THINK ULTIMATELY THIS IS SOMETHING THAT'S GOING TO REAR ITS HEAD NOW IN A WAY THAT IT REALLY DOES REQUIRE ATTENTION BECAUSE IT COULD POTENTIALLY BE A SETBACK FOR THE ENTIRE FIELD IF WE DON'T GET ON TOP OF IT. SO I THINK UNDERSTANDING THAT IS SOMETHING THAT COULD BE A VERY GREAT CONTRIBUTION. THAT'S OBVIOUSLY NOT JUST FOR CALIFORNIA, FOR THE LARGER GLOBAL COMMUNITY EVEN, BUT I THINK YOU HAVE THE



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POTENTIAL TO MAKE A REAL IMPACT HERE?

DR. MILLAN: THANK YOU, DR. MARKS. WE DO HAVE A PORTFOLIO WITH INTERCONNECTIVITY BETWEEN -- CIRM HAS SERVED AS A HUB. WHEN WE HAVE EVENTS OCCUR, WE DO HAVE THE ABILITY TO KIND OF CONVENE OUR INVESTIGATORS WHO ARE IN THAT AREA OF STUDY, AND THEY TEND TO BE THE EXPERTS IN THE FIELD THAT PEOPLE CALL TO. SO I THINK THESE ARE EXCELLENT IDEAS, AND IT'S COMPATIBLE WITH THE NOTION THAT NOT ONLY SHOULD OUR BASIC RESEARCH INFORM OUR LATE STAGE TRANSLATIONAL, CLINICAL, BUT THERE SHOULD BE A FEEDBACK LOOP SO WHEN QUESTIONS ARISE IN THE BIOLOGY OR THE SCIENCE OF WHAT WE ARE SEEING IN LATER STAGE PROGRAMS, THAT THAT SHOULD PROVIDE A WAY THAT THAT CAN COME BACK TO THE BENCH FOR EVALUATION.

AND THEN DR. CAT JAMIESON HAD A COMMENT, AND THEN WE'RE GOING TO MOVE ON TO THE NEXT SPEAKER.

DR. JAMIESON: OKAY. THANKS VERY MUCH, MARIA. I WANTED TO FOLLOW ON FROM WHAT KEVIN WAS BRINGING UP, AND THAT'S ABOUT CIRM'S CAPACITY TO BEHAVE AS A SAFETY VALVE FOR PATIENTS. WE SHOULD BE THE CENTRAL DATA REPOSITORY FOR THESE COMPLEX CLINICAL TRIALS. WE SHOULD ENSURE THAT WE FOLLOW PATIENTS LONGITUDINALLY THROUGH A PATIENT REGISTRY THAT COULD BE PART OF AN ADVANCED CIRM GENOMICS

INITIATIVE THAT DAVID HAUSSLER HAS DONE A GREAT JOB OF INITIATING TOGETHER WITH CIRM. WE SHOULD BE BUILDING ON THAT FOR THE FUTURE JUST LIKE CIBMTR DOES FOR ALL BONE MARROW TRANSPLANTS. WE COULD WORK VERY WELL WITH THE ISSCR.

SO WHAT I WOULD BE INTERESTED IN SEEING IS IS CIRM INTERESTED IN FORMING AN INTERNATIONAL ALLIANCE, JUST LIKE THE CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANTATION RESEARCH. THEY'VE DONE 30 TRIALS SINCE THEY OPENED IN 2001 IN TERMS OF MONITORING TRIAL OUTCOMES. WE'VE DONE 68 SINCE 2015, WHICH IS PRETTY REMARKABLE. THAT'S JUST THE THERAPEUTIC TRIALS. IT DOESN'T INCLUDE THE DIAGNOSTIC.

MY HOPE IS, COMMENT AND QUESTION, IS CAN WE EXPAND TO INCLUDE INTERNATIONAL NETWORKS? I WAS ON STUDY SECTION LAST WEEK WHERE YOU HAD TO EXPLAIN WHY YOU WOULD WORK WITH A FOREIGN GROUP. AND IT'S REALLY HARD TO GET THOSE INTERNATIONAL COLLABORATIONS AND YET OUR CIRM LEUKEMIA GRANT ALLOWED US TO WORK VERY CLOSELY WITH CANADA. SO IF WE EXPAND BEYOND THE PAROCHIAL NATURE OF THE WAY WE DO SCIENCE TO A MORE INTERNATIONAL COMMUNITY, I THINK WE'D BE STRONGER. SO IT'S A COMMENT AND A QUESTION. CAN WE DO THAT THROUGH CIRM?

DR. MILLAN: THANK YOU. WE HAVE DR. DZAU AND DR. WAGERS AS THE FINAL TWO QUESTIONS FOR THIS SESSION.

DR. DZAU: I'LL BE VERY BRIEF. I WANT TO COMMEND AMANDER FOR RAISING TWO ISSUES. ONE IS TO LOOK AT NEURO DISEASES BEYOND NEURODEGENERATION, PARTICULARLY IN NEUROPSYCHIATRIC DISEASES. IT'S VERY CLEAR THAT THE MAJORITY OF MENTAL DISORDER BEGIN VERY EARLY IN LIFE, SOME 70 PERCENT WITHIN 14 TO 24 YEARS. AND TO DATE CIRM HAS NOT EMPHASIZED THIS VERY IMPORTANT GROUP. SO I TOTALLY AGREE WITH HER.

THE SECOND ISSUE IS DIVERSITY. I TOTALLY AGREE WITH HER TOO THAT WE NEED TO LOOK AT DIVERSITY WITH REGARDS TO DIFFERENT RACIAL AND OTHER REPRESENTATION SO THAT WHEN WE STUDY THIS, WE ACTUALLY ARE STUDYING THE HETEROGENEITY, IF YOU WILL, OF GENE CAUSING DISEASES.

AND THEN CAT JAMIESON'S COMMENT, THIS REALLY CREATES AN OPPORTUNITY FOR CREATING COHORTS BOTH IN CALIFORNIA AND GLOBALLY, AND IF THERE'S A CHANCE TO COLLABORATE, IT WILL BE TERRIFIC. THANK YOU.

DR. MILLAN: THANK YOU SO MUCH. DR. WAGERS.



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DR. WAGERS: THANK YOU. MY COMMENT ACTUALLY PICKS UP ON THE COMMENT THAT AMANDER MADE ABOUT DIVERSITY AS WELL. REALLY IMPORTANT IN TERMS OF PREPLANNING YOUR STUDIES TO INCORPORATE THAT, BUT EQUALLY IMPORTANT IS A MECHANISM TO FOLLOW ALONG THROUGH THE RECRUITMENT AND ASSURE THAT THOSE BENCHMARKS ARE BEING MET AND PROVIDE SUPPORT WHERE THEY AREN'T. WE'VE SEEN THIS IN AN ADVISORY PANEL I SERVE ON FOR THE NIH WHERE THE PROPOSALS SET OUT TO RECRUIT A DIVERSE ENROLLMENT OF INDIVIDUALS; BUT THEN WHEN YOU RETROSPECTIVELY LOOK BACK AT WHO ACTUALLY WAS ABLE TO BE ENROLLED, THERE'S NOT THE REFLECTION OF THE DIVERSITY OF THE COMMUNITY THAT ONE REALLY WANTED.

SO IF CIRM COULD PUT IN PLACE SOME MECHANISM. I DON'T MEAN TO POLICE INVESTIGATORS. I MEAN TO SUPPORT THEM IN ACHIEVING THEIR ENROLLMENT GOALS. I THINK THAT WOULD BE VERY HELPFUL.

THE OTHER ASPECT OF THIS THAT I WOULD ADD IS MAYBE AN EFFORT IN SOME OF THE CALLS FOCUSED ON DISPARATE HEALTH CHALLENGES OF THE COMMUNITY, REALLY MAKING AN EFFORT AT ADVERTISING THE IMPORTANCE BY DRAWING IN INVESTIGATORS TO FOCUS THEIR ENERGIES AND EFFORTS ON HEALTH CHALLENGES THAT ARE DISPROPORTIONATE ACROSS THE POPULATION COULD BE A



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LEADERSHIP OPPORTUNITY FOR CIRM IN THIS MOMENT. AND I WOULD INCLUDE IN THAT DISPARATE EFFECTS ACROSS THE LIFE SPAN. AS AMANDER NOTED, CHILDREN AND ALSO OLDER ADULTS WHOSE BIOLOGIES ARE DIFFERENT AND WHO ARE NOT AT EITHER END OF THE SPECTRUM WELL REPRESENTED IN OUR STUDIES.

DR. MILLAN: THANK YOU SO MUCH, DR. WAGERS. THAT IS A MAJOR FOCUS FOR CIRM. IN FACT, ALL OUR PROGRAM ANNOUNCEMENTS NOW, DISCOVERY, TRANSLATIONAL, AND CLINICAL PROGRAMS, ACTUALLY A REVIEW CRITERIA IS DIVERSITY, EQUITY, AND INCLUSION SUBJECT MATTER REGARDING HOW IT'S INCORPORATED INTO THE RESEARCH PLAN. AND IT IS SOMETHING THAT WILL BE IN DEVELOPMENT IN TERMS OF HOW WE TRACK THESE AND BUILD IT INTO KIND OF THE OVERALL DATA PLAN.

AND THEN THERE WAS ONE MORE QUESTION, I THINK, THAT DERRICK ROSSI HAD BROUGHT UP AS A GENERAL QUESTION REGARDING CAN CIRM DEPLOY ITS FUNDING -- THIS SYSTEM IN TERMS OF ADDRESSING SOME GLOBAL ISSUES, MAYBE NOT DIRECTLY RELATED TO STEM CELL BIOLOGY, FOR INSTANCE. I THINK AN EXAMPLE OF THAT WE HAD MENTIONED IS IN RESPONSE TO COVID, WE ACTUALLY LAUNCHED A VERY ACCELERATED PROGRAM THAT WE WERE ABLE TO DEPLOY WITHIN A MONTH FROM CONCEPT TO REVIEW AND HAD WEEKLY REVIEWS FOR PROGRAM



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OPPORTUNITIES RELEVANT TO COVID. SOME OF THEM USED STEM CELL MODELS, SOME OF THEM WERE WITH VITAL RESEARCH OPPORTUNITIES THAT WEREN'T WITHIN SCOPE THAT OUR BOARD HAD DECIDED THAT THAT WAS IMPORTANT TO PURSUE AS UNMET MEDICAL NEEDS.

SO THOSE ARE JUST SOME RESPONSES TO RESIDUAL QUESTIONS. AND SO THANK YOU VERY MUCH FOR ALL. JUST TO LET YOU KNOW, WE HAVE NOTE TAKERS AND THIS IS BEING RECORDED. AND SO ALL OF YOUR INPUT IS DEFINITELY BEING CAPTURED. WE REALLY APPRECIATE THAT.

SO I'M GOING TO NOW MOVE ON. AND, AGAIN, PLEASE IF YOUR QUESTION WASN'T ANSWERED, PLEASE GO AHEAD AND PING US AGAIN, AND WE WILL GET TO IT. BUT I'M GOING TO INTRODUCE DR. CLIVE SVENDSEN FOR THE NEXT TOPIC.

DR. SVENDSEN: GREAT. NICE TO SEE SO MANY PEOPLE, FRIENDS, AND COLLEAGUES ON THIS CALL. I'M PROFESSOR AND DIRECTOR OF REGENERATIVE MEDICINE AT CEDARS-SINAI HERE IN LOS ANGELES. CIRM ASKED ME TO REALLY PROVIDE A FRAMEWORK FOR IPS USE IN MODELING AND TECHNOLOGIES MAINLY FOR NEURODEGENERATIVE DISEASE, LIKE PARKINSON'S AND ALZHEIMER'S, AND HOW CGMP MANUFACTURING MIGHT HELP IN THIS PROCESS. SO I THINK AMANDER DID A GREAT OVERVIEW, THE BIG PICTURE.

I THOUGHT I'D KIND OF TAKE A CASE STUDY ALMOST NOW OF DIVING DOWN INTO THE WEEDS A LITTLE BIT IN THE PRACTICALITIES OF APPLYING CONSORTIUM RESEARCH TO THESE PROBLEMS.

I'VE BEEN INVOLVED WITH NEUROLOGICAL DISEASES AND STEM CELL RESEARCH FOR ALMOST 40 YEARS, WHICH SEEMS TO HAVE GONE LIKE VERY FAST. I'VE WATCHED THE FIELD GROW REALLY FROM SORT OF NEUROCHEMISTRY IN THE '80S AND THEN GENOMIC ANALYSIS IN THE '90S, EMBRYONIC STEM CELL TECHNOLOGY SORT OF IN THE 2000S, AND NOW IPS TECHNOLOGY, WHICH I THINK REALLY IS GOING TO MAKE AN IMPACT.

WHAT'S BEEN REALLY DEPRESSING, TO BE HONEST WITH MY COLLEAGUES, IS HOW FEW DRUGS THERE'S BEEN OVER THIS 40-YEAR TIME POINT, AND WE'VE ALL BEEN TRYING DESPERATELY TO FIND THINGS. AND THE CHALLENGE IS NEURODEGENERATIVE DISEASES OR NEUROPSYCHIATRIC DISEASES ARE NOT ONE DISEASE. THEY HAVE SORT OF THESE DECEPTIVELY SIMPLE TITLES LIKE ALZHEIMER'S OR PARKINSON'S, BUT WE ALL KNOW THEY'RE MADE UP OF SUBTYPES WITHIN THAT CATEGORY OF PARKINSON'S. THERE'S PROBABLY TEN DIFFERENT SUBTYPES. WE JUST DON'T WHAT THEY ARE, HOW TO DEFINE THEM.

EVEN MUTATIONS THAT LEAD TO THESE DISEASES



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CAN BE VERY DIFFERENT. IN ALS YOU CAN HAVE WIDELY DIFFERENT MUTATIONS. THEY ALL LEAD TO THE SAME DISEASE. SO IT KIND OF TELLS US THAT THERE'S A LOT OF VARIATION EVEN IN A DISEASE LIKE HUNTINGTON'S WHERE YOU KNOW THE MUTATION. IT TURNS OUT BACKGROUND MODIFIERS CHANGE THE OUTCOME MASSIVELY OF EACH PATIENT. SO THE SAME EXACT MUTATION HAVING ON YOUR GENETIC BACKGROUND LEADS TO VERY DIFFERENT OUTCOMES.

AND IN SPORADIC CASES OF NEUROLOGICAL DISEASE IT'S EVEN WORSE BECAUSE WE DON'T KNOW THE MUTATION. AND SO WE'RE REALLY STRUGGLING TO FIND TARGETS, AND THIS IS PROBABLY WHY DRUGS FAIL. I WAS JUST TALKING TO MY PARKINSON'S COLLEAGUES YESTERDAY HERE, DR. TAGLIATI, AND HE'S TRYING A NEW THERAPY. AND HE SAID, "IT SEEMS TO WORK PERFECTLY IN THREE OUT OF THE 20 PATIENTS, AND THE REST DIDN'T RESPOND." AND THIS HAPPENS AGAIN AND AGAIN IN NEUROLOGY.

SO THE BIG QUESTION IS, AND I THINK THE POINT FOR DISCUSSION, IS CAN WE PREDICT A PATIENT'S DISEASE TYPE EARLY BEFORE ONSET PERHAPS EVEN AND THEN UNDERSTAND HOW PATIENTS MIGHT RESPOND TO SPECIFIC DRUGS BY PROVIDING A SUBTYPE, THIS KIND OF PRECISION HEALTH THAT'S BEEN USED SO SUCCESSFULLY IN



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CANCER.

IPSC'S ARE A UNIQUE RESOURCE. WE'VE ONLY HAD THEM FOR TEN OR TWELVE YEARS. I SEE THEM MORE LIKE GENOME SEQUENCING. SO ONCE YOU MAKE AN IPS LINE, IT'S YOURS. IT'S YOUR IPS LINE, AND THAT SHOULD LAST A LIFETIME, JUST LIKE A GENOME SEQUENCE WHEN YOU HAVE YOUR GENOME SEQUENCE, PROVIDING THE TECHNOLOGY DOESN'T CHANGE, BUT I THINK AN IPS LINE SHOULD LAST AWHILE. SO ESSENTIALLY EVERYBODY SHOULD PROBABLY HAVE THEIR IPS LINE MADE, AND THEN IT REQUIRES A LOT OF COORDINATION. FOR INSTANCE, YOU PROBABLY NEED AN IDENTIFIER LIKE A GURID TO IDENTIFY YOUR IPS LINE JUST LIKE YOUR GENOME IS IDENTIFIED.

AND IF YOU CAN GENERATE IPS LINES, THEN YOU CAN MAKE ANY TISSUE. AND I THINK THE GOAL IS FOR NEURODEGENERATIVE DISEASES, YOU CAN MORE OR LESS A BRAIN BIOPSY, WHICH IS VERY HARD TO GET, AND THEN UNDERSTAND MORE ABOUT THE DISEASE PROCESS.

SO THE BIG IDEA WHICH WE DISCUSSED LAST YEAR AT A CIRM MEETING IS TO CREATE IPS LINES FROM A LARGE NUMBER OF PATIENTS AND THEN DIFFERENTIATE THEM INTO THE NEURONS THAT ARE AFFECTED BY THE DISEASE. I THINK THIS IS THE BASIS FOR DISCOVERING MOLECULAR SUBTYPES. AND THEN ULTIMATELY THIS IS KIND OF A CIRCLE WHERE YOU'VE GOT THE PATIENT, YOU MAKE THE



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IPS LINE, YOU DIFFERENTIATE THEM INTO THE NEURONS THAT ARE AFFECTED BY THAT DISEASE, AND THEN YOU STILL HAVE THE PATIENT AND YOU CYCLE BACK SO THAT, FROM THE INFORMATION YOU GET FROM THAT IPS LINE AND THE DIFFERENTIATION, YOU CAN THEN DESIGN A CLINICAL TRIAL TO GO BACK INTO THAT PATIENT. THIS IS REALLY EXEMPLIFIED BY DR. OKANO RECENTLY IN JAPAN WHERE THEY CAME UP WITH ROPINIROLE AS A DRUG BASED ON THAT WHOLE CYCLE. WORKED WITH THE FDA IN JAPAN, THE EQUIVALENT, AND HAS JUST GOT THAT NARROWED INTO A CLINICAL TRIAL.

I THINK THE EXCITEMENT IS MASSIVE FOR THIS AREA, AND THE POTENTIAL IS MASSIVE, AND IT ALLOWS YOU TO COLLABORATE WITH INDUSTRY. AND I THINK CIRM WILL BE ABLE TO KEEP THE FOCUS IN THESE KIND OF MODELING SYSTEMS, KEEP IT FOCUSED ON THE PATIENT, AND THEY CAN ALSO REACH OUT FOR DIVERSITY INTO COMMUNITY CLINICS TO OBTAIN THE IPS LINES AND DO THE TRIALS. SO THERE'S A LOT OF POTENTIAL HERE FOR THIS KIND OF TECHNOLOGY. AND IT DEFINITELY WILL REQUIRE A CONSORTIUM APPROACH. I THINK THE BIG QUESTION MARIA HAS IS HOW SHOULD THAT BE STRUCTURED? HOW CAN RFA'S BE DESIGNED TO ENHANCE THAT CAPACITY? AND IF WE CAN DO IT FOR NEUROSCIENCE, WE CAN DO IT FOR OTHER DISEASES AS WELL PROBABLY. THIS IPS MODELING

TECHNOLOGY, I THINK, IS VERY POWERFUL, BUT IT NEEDS A LOT OF COORDINATION.

SO WHAT ARE THE CHALLENGES? IT'S EASY TO SAY THAT, BUT THIS IS VERY HARD. MANY OF YOU HAVE BEEN WORKING IN THIS FIELD FOR A LONG TIME. I THINK THE FIRST THING IS NUMBERS. IN GENOME STUDIES YOU TALK ABOUT THOUSANDS OF PATIENTS. PEOPLE GET SCARED WITH IPS WHEN YOU MENTION A THOUSAND IPS LINES AS WE ALL KNOW HOW HARD THEY ARE TO MAKE. ESSENTIALLY I THINK THERE'S NO DIFFERENCE BETWEEN GENOME GWAS STUDIES AND IPS STUDIES LOOKING FOR PHENOTYPES. IN FACT, THERE'S MORE DIVERSITY IN DIFFERENTIATION PROTOCOLS AND PROBLEMS IN IPS LINES. SO YOU MIGHT ARGUE YOU NEED MORE LINES FOR IPS CELLS TO FIND THESE SUBGROUPS OF PATIENTS.

I THINK, THOUGH, IF YOU COULD DO THAT, WITH ENOUGH PATIENTS AND ENOUGH DIFFERENTIATIONS, YOU MIGHT BE ABLE TO DISCOVER CLUSTERS OF PATIENTS AND DESIGN NEW TARGETS.

THESE ARE THE CHALLENGES THAT WE CAN DISCUSS. THE PROTOCOLS ARE DIFFERENT BETWEEN LABS, A LOT OF VARIETY THERE, AND EVEN THE INDIVIDUAL PATIENT LINES ARE VERY DIFFERENT. A LOT OF ETHNIC DIFFERENCES BETWEEN PATIENT LINES AS WELL. AFRICAN-AMERICANS MAY HAVE A DIFFERENT



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DIFFERENTIATION PATTERN TO CAUCASIANS, FOR EXAMPLE, THAT'S BECOMING VERY EVIDENT NOW. SO I THINK THERE'S A LOT OF NOISE, BUT I THINK WE CAN BY CONSORTIUM APPROACH GET OVER A LOT OF THIS NOISE.

I THINK SALLY MENTIONED THIS. WE NEED KIND OF A ROSETTA STONE, A SET OF IPS LINES THAT CAN BE USED AS A BENCHMARK. WE DON'T KNOW HOW MUCH DIFFERENTIATION WE NEED. NOTHING REALLY HAS BEEN VALIDATED IN THE CLINIC VERY WELL YET. ROPINIROLE WAS ONLY ONE OF A FEW EXAMPLES. WE MIGHT NEED MORE DIFFERENTIATION. THERE'S THIS WONDERFUL ORGANOID TECHNOLOGY. SERGIU PASCA AT STANFORD DOES THESE ASSEMBLOIDS WHERE THEY ACTUALLY CONNECT THE CORTICAL LUMP TO A SPINAL CORD LUMP TO A MUSCLE AND GET THE MUSCLE TO TWITCH BY ACTIVATING THE CORTICAL PART.

I KNOW CHRIS AUSTIN IS ON THE LINE AT NIH. AND THE CHIP SYSTEMS WHERE YOU CAN INTERFACE THE VASCULAR SYSTEM WITH THE BRAIN OR OTHER ORGANS. THAT MIGHT BE CRITICAL FOR GETTING REAL OUTPUTS FROM THESE CHIPS. AND THE KEY IS VALIDATION. IF WE CAN'T VALIDATE ANY OF THESE MODELS, THEY'RE NOT REALLY WORTH ANYTHING. THEY'RE AN INTERESTING MODEL, BUT THEY HAVE TO VALIDATE ACROSS THE PATIENTS. AND THAT'S WHERE CIRM COULD REALLY DO SOME VALIDATION TRIALS USING THIS TECHNOLOGY, I

WOULD SUGGEST IN COLLABORATION WITH NIH AND PERHAPS NCATS. WE'LL HEAR FROM ILYAS LATER ABOUT HOW WE COULD BASICALLY COORDINATE THIS THROUGH CIRM AND NIH TO DO SOME REALLY INTERESTING TRIALS.

SO I'LL FINISH UP WITH THE GMP SIDE. I'VE BEEN INVOLVED WITH GMP. I ACTUALLY ACCIDENTALLY GOT INTO THIS WHEN I MOVED TO THE UNIVERSITY OF WISCONSIN. JAMIE THOMPSON WAS OVER HERE, BUT BELOW ME WAS DEREK HEI. AND HE WAS CREATING A BIOMANUFACTURING FACILITY. THIS IS 20 YEARS AGO. EVERYBODY WAS LIKE WHY ARE YOU DOING THAT. AND THEN THE UNIVERSITY OF WISCONSIN REALLY PUSHED AHEAD IN THIS CGMP FACILITY. I ACTUALLY STARTED PRODUCING A FETAL NEUROPROGENITOR LINE WITHIN THAT FACILITY AND LEARNED ALL ABOUT CGMP METHODOLOGIES. IN FACT, THAT LINE IS THE ONE I TOOK OVER HERE TO CALIFORNIA AND WAS ONE OF THE FIRST TO GO INTO PATIENTS WITH ALS HERE.

SO THEY'RE THE LIFE BLOOD, REALLY, THESE GMP FACILITIES. AND I THINK ULTIMATELY WE KNOW CIRM NEEDS THEM. WE KNOW THERE AREN'T ENOUGH, AND SO I THINK WE NEED MORE IN THE STATE FROM SORT OF MESENCHYMAL CELLS TO CAR-T, BUT THEY'RE REALLY MORE THAN THAT. I THINK BY LEARNING HOW TO GROW CELLS FOR FDA AND UNDER THAT COMPLIANCE, IT ACTUALLY HELPS



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WITH THE DIFFERENTIATION IN DISEASE MODELING BECAUSE YOU CAN GENERATE STANDARD OPERATING PROCEDURES, SOP'S, AND THEN SHARE THAT BETWEEN LABS AND GET MORE CONSISTENCY.

SO I THINK THESE PROTOCOLS ARE REALLY GOING TO HELP. YOU'LL HEAR MORE ABOUT THIS DURING THE DAY. AND ULTIMATELY I THINK ROBOTIC TECHNIQUES ARE ACTUALLY REALLY IMPORTANT. SO I WOULD BE INVESTING IN ROBOTIC TECHNIQUES. IT TURNS OUT THE BIGGEST VARIABLE PROBABLY WITH THE NEUROLINKS CONSORTIUM IN L.A., THE BIGGEST VARIABLE IF YOU TOOK ONE EXPERIMENT AND REPEATED IT ACROSS MULTIPLE LABS IS THE TECHNICIANS. IF YOU AUTOMATE EVERY PART OF THE PROCESS, THE VARIABILITY SEEMS TO DISAPPEAR. SO AUTOMATION, I THINK, IS CRITICAL. AND, AGAIN, ILYAS AT NIH HAS A BEAUTIFUL AUTOMATED SYSTEM FOR GENERATING IPS. I THINK THIS IS THE FUTURE, AUTOMATION. GET THE COST DOWN, MAKE MORE IPS WITH STANDARDIZED PROTOCOLS.

FINALLY, THERE'S A COUPLE OF EXPERIMENTS THAT ARE BEING DONE. YOU WILL HEAR FROM LESLIE THOMPSON LATER ON. THERE'S ONE CALLED ANSWER ALS, WHICH I'M INVOLVED WITH. THE CONCEPT THERE IS TO ACTUALLY DO IT ALL IN HOUSE, SO YOU HAVE JUST ONE UMBRELLA WHERE YOU GET THE PATIENTS, YOU MAKE THE

LINES, DO THE OMICS, GET THE SUBTYPES, AND THEN GO BACK INTO THE PATIENTS WITH A TRIAL, WHICH IS FINE, BUT IT'S A VERY LARGE CONSORTIUM AND IT'S JUST KIND OF ONE GROUP.

AND THE OPPOSITE SIDE OF THAT IS TO UTILIZE ALL THE RESOURCES WE HAVE OUT THERE LIKE AMPD AND ADNI AND THE OUTSUM PROGRAM AND TRY AND CARVE OUT OF THAT, PUT THEM ALL TOGETHER AND GENERATE A SYSTEM FOR ONE OF THESE CONSORTIUM APPROACHES IN NEUROSCIENCE.

SO I THINK OVERALL THIS IS AN EXCITING AREA. I'VE OPENED UP A LOT OF THINGS FOR DISCUSSION. I'M REALLY CONVINCED THAT THIS IPS TECHNOLOGY COMBINED WITH GMP AND PHENOTYPING CAN PROBABLY DISRUPT THE FIELD. THAT'S WHAT NEUROSCIENCE NEEDS IS DISRUPTION. WE GOT TO TAKE A BIG STEP TO DO THIS, AND I THINK CIRM IS IN A GOOD POSITION TO PULL THAT OFF. THE QUESTION IS, THE DISCUSSION IS WHAT'S THE BEST WAY TO DO THESE CONSORTIUM BIG STUDIES WITH IPS, WHETHER IT'S CANCER OR WHETHER IT'S NEURO? IS IT A LARGE CONSORTIUM, OR IS IT JUST LOTS OF SMALL FOCUS GROUPS THAT ARE TIED TOGETHER? SHOULD WE BE LEVERAGING EXISTING RESOURCES, OR IS THAT TOO COMPLICATED GIVEN ALL THE VARIATION IN TECHNOLOGY AND THE WAY THE IPS LINES

ETC. ARE MADE? AND HOW CAN THE FDA HELP SO WE DON'T JUST GO DOWN BLIND ALLEYS? WE GET THE FDA, PETER IS ON THE PHONE, EARLY INVOLVED. THEY CAN ACTUALLY GUIDE US A LITTLE BIT. I KNOW THEY HATE TO DO THAT, BUT GUIDE US A LITTLE BIT INTO HOW WE COULD NOT JUST DO A GREAT MODEL, BUT TAKE THAT IN THIS SETTING IN CALIFORNIA AND ACTUALLY GET INTO PATIENTS IN THIS CYCLE THAT I THINK IS SO, SO IMPORTANT FOR ALL OF US AND FOR THE INDUSTRY.

SO I THINK IT'S A CRITICAL TIME FOR CIRM, AND VERY HAPPY TO OPEN UP THE DISCUSSION. AND I THINK THERE'S A REAL OPPORTUNITY HERE FOR A NEW APPROACH. THANKS.

DR. MILLAN: THANK YOU SO MUCH, CLIVE. SO I'M GOING GO AHEAD AND OPEN IT UP. AND THEN IF PETER MARKS IS ON RIGHT NOW, BECAUSE I KNOW HE'S ON AND OFF, IT WOULD BE GREAT TO GET THE FDA'S INPUT IN TERMS OF THEIR INVOLVEMENT IN KIND OF AN EARLY STAGE RESEARCH AND THOSE DISCUSSIONS.

CHRIS AUSTIN HAS HIS HAND RAISED.

DR. AUSTIN: CLIVE, YOU MADE SO MANY IMPORTANT POINTS. I'M NEVER GOING TO GET TO ALL OF THEM, BUT JUST SOME COMMENTS ON A FEW OF THEM.

I REALLY THINK WE AS A FIELD NEED, AND I KNOW YOU KNOW THIS, BUT MORE EFFICIENT WAYS TO GET

TO REPRODUCIBLE DIFFERENTIATION OF ANY CELL TYPE. BY THAT I MEAN EMPHASIS ON REPRODUCIBLE AND EFFICIENT. AND UNDERSTAND THE NATURE OF THE CHARACTERISTICS OF THE DISEASE THAT MAKE IT THROUGH THE REPROGRAMMING AND DIFFERENTIATION PROCESS BECAUSE WE REALLY DON'T UNDERSTAND THAT, AND THAT'S SORT OF THE CRUX OF THIS WHOLE ARGUMENT.

AND WHAT WE'VE SEEN, AND YOU REFLECTED ON THIS, IS THAT YOU REALLY DO NEED NUMBERS. AND YOU NEED NUMBERS AND YOU NEED A WHOLE NEW LEVEL OF ROBUSTNESS AND REPRODUCIBILITY THAT HUMAN BEINGS ARE JUST NOT VERY GOOD AT, ESPECIALLY GRADUATE STUDENTS WHO ARE TIRED AND THEN THE GRADUATE STUDENT LEAVES AND YOU GET A NEW GRADUATE STUDENT OR A NEW POST-DOC. SO THAT'S WHY AT OUR PLACE WE DO SO MUCH VIA ROBOTICS. WE LIKE GRADUATE STUDENTS AND POST-DOCS TOO, BUT I ALWAYS SAY IF YOU CAN DO WHAT YOU ARE DOING WITH YOUR BRAIN STEM ALONE, I DON'T WANT YOU DOING IT. I WANT YOU USING YOUR CORTEX. AND SO WE HAVE ROBOTS DO EVERYTHING BECAUSE THEY DON'T HAVE A CORTEX. BUT IT REALLY IS AN IMPORTANT CONCEPT. AND, CLIVE, AS YOU KNOW, WE HAVE WRUNG A LOT OF THE IRREPRODUCIBILITY OUT OF THE SYSTEM VIA THAT KIND OF EFFORT. IT IS NOT FOR THE FAINT OF HEART. IT'S NOT CHEAP, BUT IT RETURNS THE



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INVESTMENT MANY, MANY, MANY, MANYFOLD. SO IT'S A CLASSIC HIGH CAPITAL INVESTMENT, LOW OPERATING EXPENSE SORT OF ISSUE.

AND I THINK IT'S THE KIND OF THING THAT CIRM COULD DO REALLY WELL. THERE ARE A FEW ORGANIZATIONS DOING THIS, BUT NOT MANY. WE ARE DOING AT THE NIH, THE OHIO ALIVE PROGRAM THAT I KNOW YOU'RE AWARE OF, AND CLEVELAND IS DOING THIS. OF COURSE, THE NEW YORK STEM CELLS FOUNDATION IS DOING SOME OF THIS AS WELL. BUT I REALLY THINK IT'S SOMETHING THAT CIRM CAN MAKE A BIG IMPACT ON.

JUST OF A COUPLE OF OTHER COMMENTS. OUR EXPERIENCE WITH THE TISSUE CHIP INITIATIVES IS THAT THE LIMITING REAGENTS IN THAT SITUATION ACTUALLY ARE THE IPS CELLS. NOT THE IPS CELLS THEMSELVES. OF COURSE, YOU CAN MAKE IPS CELLS. BUT THE DIFFERENTIATED CELLS AND THE CHARACTERIZATIONS OF THE IPS CELLS TO MAKE REPRODUCIBLE TISSUE CHIPS. AND SO I THINK ONE OF THE THINGS THAT'S HELPED US THERE IS THE INVOLVEMENT OF THE FDA ON THE PROJECT TEAMS FOR THE TISSUE CHIPS FROM THE VERY BEGINNING. THEY WERE BROUGHT IN TO SAY, LOOK, IF WE'RE GOING TO USE THESE FOR REGULATORY APPLICATIONS, I OUGHT TO APPLY THIS TO ANYTHING REALLY, YOU GOT TO HAVE THEM AS A MEMBER OF THE TEAM. AND THEN THEY SEE THE



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WORKS AND THE TECHNOLOGIES AND THE GOOD THINGS IN THE TECHNOLOGY. WE NEVER COULD HAVE GOTTEN THEM. WE WENT FROM ZERO TO A HUNDRED MILES AN HOUR ON TISSUE CHIPS IN TEN YEARS AND THAT WAS BECAUSE OF FDA'S INVOLVEMENT.

THE ONLY OTHER THING I'D ADD IS THAT I WAS HARKENING BACK, CLIVE, WHILE YOU WERE TALKING TO A MEETING ON UTILITY OF STEM CELLS FOR NOT ONLY DRUG DEVELOPMENT, BUT THERAPIES. WHEN I WAS AT MERCK IN THE YEAR 2000, AND THE BIG REASON THAT MERCK DIDN'T GET INTO THEM AT THE TIME WERE ESSENTIALLY CMC ISSUES, CHEMISTRY, MANUFACTURING, CONTROLS ISSUES; THAT IS, WE DIDN'T UNDERSTAND ON A DEEP LEVEL, TO THE LEVEL THAT FDA WOULD REQUIRE, THE CHARACTERISTICS OF THE AGENTS WE WERE GOING TO PUT INTO PEOPLE. AND WE COULDN'T DEMONSTRATE TO THEM AND THE FIELD COULDN'T THAT WE COULD MAKE THE SAME CELLS EVERY TIME AND UNDERSTAND WHAT THEY ARE ON A VERY DEEP LEVEL AND KNOW WHAT THE IMPURITIES ARE ET CETERA, ET CETERA, ET CETERA.

AND I LOOK AT WHERE WE ARE NOW, DESPITE ALL OF OUR EFFORTS, A LOT OF REALLY GREAT PEOPLE WORKING OUR TAILS OFF FOR THE LAST 21 YEARS, WE HAVEN'T REALLY MADE A WHOLE LOT OF HEADWAY THERE. IF WE WANT TO GET INTO PEOPLE IN A REPRODUCIBLE WAY,



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WE'VE GOT TO FOCUS ON THAT. AND IT'S NOT SOMETHING NIH IS REALLY GOOD AT. THEY DON'T KNOW WHAT CMC IS FOR THE MOST PART. AND SO I THINK, AGAIN, IT'S SOMETHING, I THINK, CIRM COULD REALLY MAKE A HUGE FIELD-CHANGING IMPACT ON.

DR. SVENDSEN: I AGREE, CHRIS. I THINK PATRICK MIGHT WANT TO TALK BECAUSE HE'S HAD EXPERIENCE WITH MAKING DOPAMINE NEURONS FOR PARKINSON'S DISEASE. HE'S HAD HIS HAND UP FOR A WHILE. THANKS FOR THE COMMENTS, AND I AGREE WITH EVERYTHING YOU JUST SAID.

DR. MILLAN: THANK YOU, CHRIS. THANK YOU SO MUCH. THIS IS RIGHT SMACK DAB IN THE MIDDLE OF SOME OF THE THINGS THAT WE ARE DEFINITELY CONSIDERING. SO YOUR EXPERT INPUT INTO THAT IS HIGHLY VALUED.

SINCE PEOPLE HAVE KIND OF SAID FDA SEVERAL TIMES, MAYBE WE CAN HEAR FROM PETER MARKS REGARDING HIS THOUGHTS ON THIS IDEA OF A WAY TO CAPTURE THESE TYPES OF DATASETS. AND THE QUESTION IS WHAT TYPE OF OPPORTUNITY IS THERE TO WORK WITH THE FDA EVEN EARLY ON BEFORE PROGRAMS GET INTO KIND OF THE DEVELOPMENT PATH IN TERMS OF THESE KIND OF UMBRELLA EFFORTS TO UNDERSTAND THE TYPES OF DATASETS THAT WERE JUST DISCUSSED?

DR. MARKS: THANKS VERY MUCH. SO I THINK THERE ARE TWO TYPES OF -- OBVIOUSLY IN THE BIOLOGICS END OF THINGS, WE HAVE TWO TYPES OF MEETINGS. ONE WOULD BE PRODUCT SPECIFIC WHICH ARE INTERACT MEETINGS WHICH CAN HAPPEN VERY EARLY ON REALLY ONCE ONE HAS A CONCEPT THAT THERE IS A PRODUCT THAT'S A SPECIFIC PRODUCT.

WE ALSO HAVE ANOTHER TYPE OF MEETING CALLED THE CBER ADVANCED TECHNOLOGY TEAM MEETING, WHICH IS FOR PLATFORMS. SO IF SOMEBODY HAD A GENE THERAPY VECTOR PLATFORM OR A DEVICE PLATFORM OR WE'VE HAD PEOPLE WITH MANUFACTURING PLATFORMS, THEY CAN COME IN FOR THOSE MEETINGS. AND WE FIND THAT THEY'RE VERY INFORMAL AND YET POTENTIALLY VERY HELPFUL BOTH FOR THE SPONSORS, AND I'LL BE A LITTLE BIT HONEST AND SAY THEY'RE ALSO HELPFUL FOR US BECAUSE WE LEARN A LOT ABOUT INTERESTING NEW TECHNOLOGIES. SO EITHER THE CATT MEETING FOR THESE KIND OF PLATFORMS OR THE INTERACT MEETING FOR SPECIFIC PRODUCTS. AND OUR WEBSITE HAS, IF YOU SEARCH UP CBER AND EITHER CATT, WITH TWO T'S, OR INTERACT, SPELLED AS IT SOUNDS, THE SOP'S FOR HOW TO GO ABOUT ASKING FOR ONE OF THESE MEETINGS ARE THERE.

DR. MILLAN: PETER, JUST IN FOLLOW-UP TO THAT, AND THANK YOU FOR THAT INFORMATION, HOW DO YOU



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FEEL IF IT'S KIND OF A SYNDICATE THAT COMES IN FOR A CATT MEETING RATHER THAN INDIVIDUAL INVESTIGATORS OR DEVELOPERS?

DR. MARKS: WE'RE DELIGHTED. THEY'RE INFORMAL MEETINGS, AND WE'VE HAD SYNDICATES IN. IN FACT, WE'VE HAD SIX, SEVEN DIFFERENT ENTITIES COME IN TOGETHER TO DISCUSS THEIR IDEAS ABOUT COLLABORATING ON A CROSS-PRODUCT PLATFORM AND VERY HAPPY TO DO THAT.

DR. MILLAN: SO BASED ON --

DR. MARKS: AS LONG AS EVERYONE IS HAPPY TO PLAY TOGETHER, WE ARE HAPPY TO PLAY WITH THEM.

DR. MILLAN: OKAY. FANTASTIC. SO IT SOUNDS LIKE FROM WHAT, CHRIS, YOU SAID AND WHAT PETER HAS SAID, THERE IS A REAL OPPORTUNITY HERE FOR KIND OF A CONSORTIUM COLLABORATIVE APPROACH EVEN EARLY ON IN EVERYBODY'S DEVELOPMENT LIFE STAGE FOR THEIR PROGRAMS. THAT COULD BE IN THE PRECOMPETITIVE SPACE.

DR. AUSTIN: ABSOLUTELY. FOR THOSE OF YOU WHO DON'T KNOW FDA, EVERYBODY THINKS FDA IS REALLY SCARY AND THEY'RE NOT. THEY'RE REALLY GOOD PEOPLE AS I THINK PETER IS DEMONSTRATING. I CONSTANTLY FIND PEOPLE WHO SAY, "OH, GOSH. WE CAN'T TALK TO FDA. THEY'RE SCARY." BUT I'VE ENJOYED AND

BENEFITED FROM THOSE INTERACTIONS ENORMOUSLY AND I KNOW YOU WOULD.

IF IT'S WORTH IT OR OF INTEREST AFTER THIS MEETING, I'D BE GLAD TO SHARE WHAT WE DID WITH TISSUE CHIPS BECAUSE THAT WAS A MASSIVE COLLABORATION AMONG LITERALLY A HUNDRED ACADEMIC INSTITUTIONS, COMPANIES, THE FDA, AND IT WORKED WONDERFULLY WELL.

I WILL TELL YOU THAT PROJECT MANAGEMENT IS ABSOLUTELY KEY IN THIS AND NOT SOMETHING THAT WE TEND TO DO AS WELL IN THE ACADEMIC WORLD, BUT I'D BE GLAD TO GIVE YOU BECAUSE IT'S A GREAT PARADIGM THAT YOU MIGHT WANT TO FOLLOW BECAUSE IT WORKS.

DR. MILLAN: THAT'S PERFECT. WE WILL FOLLOW UP ON THAT.

BOB NELSEN, I DON'T KNOW IF YOU WANT TO SAY IT YOURSELF, BOB, AS SOMEBODY WHO'S LOOKING INTO SOME OF A DIFFERENT PERSPECTIVE.

DR. NELSEN: I THINK THE POINT THAT YOU MADE IS EXACTLY RIGHT, CHRIS. IT'S ALL ABOUT SYSTEMIZATION OF THE PROCESSES AND DATA. AND HISTORICALLY WHEN YOU APPLY THESE NEW TECHNOLOGIES, UNIVERSITIES, KIND OF THE INNOVATORS ARE NOT VERY GOOD AT THIS. SO YOU NEED TO BRING A DIFFERENT TYPE OF INDIVIDUAL INTO THE SYSTEM VERY, VERY EARLY. ALL



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OF THESE UNIVERSITIES HAVE THESE CELL MANUFACTURING FACILITIES THAT THEY HAVE NO IDEA HOW TO RUN, AND THEY DON'T COORDINATE WITH THE ACADEMICS, AND YET EVERY UNIVERSITY HAS TWO OR $300 MILLION TO DO THIS AND THEY ALL SUCK.

AND SO I THINK CIRM HAS AN OPPORTUNITY TO WORK WITH REGULATORS EARLY AND PEOPLE WHO ARE REALLY GOOD AT MAKING STUFF EARLY TO DEVELOP A MUCH MORE SYSTEMATIC DATA APPROACH TO ALL OF THIS. AND AUTOMATION PLAYS A HUGE PIECE IN THAT AND INVESTING IN AUTOMATION AND MINIATURIZATION. WHEN YOU THINK ABOUT ALL OF THE CELL SYSTEMS THAT WE USE, WE HAVE A LOT OF BIG INSTRUMENTS, BUT THE CELLS ARE ACTUALLY PRETTY SMALL. WHEN YOU MINIATURIZE, WE CAN MAKE AS AN EXAMPLE, ONE OF OUR COMPANIES IS MAKING MRNA ON CHIPS IN A COMPLETELY CLOSED GMP SYSTEM IN 22 DAYS. AND IT'S FULLY FUNCTIONAL ON THE WAY OUT. LIKE AUTOMATING A LOT OF WHAT HAPPENS IN THESE SYSTEMS IS THE KEY TO BEING ABLE TO GO TO PETER AND SAY, WE HAVE A REPEATABLE, SYSTEMITIZABLE THING THAT YOU CAN TRUST.

AND I THINK THAT'S THE DIFFERENCE BETWEEN SUCCESS AND FAILURE. BUT THAT MEANS THAT YOU NEED TO GET A DIFFERENT CLASS OF INDIVIDUALS PLAYING THIS GAME WITH THE INNOVATORS BECAUSE IT'S A DIFFERENT



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WORLD IN SYSTEMATIZING AND SCALING THINGS. ONCE YOU HAVE THE COOL THING, YOU STILL HAVE TO FIGURE OUT HOW TO SCALE IT TO GET INTO HUMANS, AND THAT'S WHERE EVERYBODY FAILS. IT COSTS YEARS. AND I WOULD SAY EVERYBODY, INCLUDING PHARMA AND BIOTECH, ARE NOT VERY GOOD AT THIS. SO I THINK THAT'S WHERE YOU COULD BE HUGELY DIFFERENTIATIVE; AND IF YOU HAVE THAT CAPABILITY, EVERYBODY WILL HAVE TO COME TO YOU.

DR. BRUNDIN: COULD I JUST ADD TO THAT? I WAS GOING TO SAY SOMETHING ALONG THESE LINES.

DR. MILLAN: PATRICK, ONE SECOND. SORRY, PATRICK. SORRY ABOUT THIS. I'M THE TRAFFIC DIRECTOR. SO I WANT TO MAKE SURE THAT OUR PANELISTS HAVE A CHANCE TO WEIGH IN. SO KEVIN EGGAN AND THEN ILYAS SINGEC. PATRICK, YOU CAN ALWAYS BRING IT UP DURING YOUR SESSION.

DR. BRUNDIN: I CAN BRING IT UP IN MY SESSION, BUT I'M VERY INTERESTED IN WHAT WAS JUST SAID, AND I HAVE AN IDEA.

DR. EGGAN: I WOULD SAY APPLAUD CIRM FOR ALREADY BEING A MAJOR PIONEER IN THIS AREA OF PRODUCING RESOURCES FOR SHARED CELL MODELING. AND I THINK IN THE CIRM 1.0, I THINK A LOT OF PEOPLE KIND OF LOOKED ASKEW AT THE EFFORT TO PRODUCE A MAJOR COLLECTION OF IPS CELL LINES FROM A LARGE NUMBER OF

CALIFORNIANS WITH DIFFERENT DISEASE CONDITIONS. AND NOW WE LOOK AT THAT, AND MANY OF US BEGIN TO WONDER WHETHER OR NOT THAT WAS ENOUGH. AND AS METHODOLOGIES FOR ANALYZING CELLS FOR MANY PEOPLE IN PARALLEL WITH DROPLET-BASED SYSTEMS AND THE SAME TECHNOLOGIES THAT ARE USED FOR SINGLE-CELL SEQUENCING REALLY COME TO THE FORE, AND MINIATURIZATION CONTINUES TO ADVANCE. I THINK THE ABILITY TO CARRY OUT THESE SORTS OF GENOMEWIDE ASSOCIATION STUDIES AND INDICIA IS BECOMING MORE AND MORE PRESENT.

AND I THINK AT LEAST OVER THE LAST FIVE YEARS I'VE REALLY SEEN HOW THOSE ARE, I THINK, TRANSCENDING EVEN THESE LARGE CONSORTIUM EFFORTS TO NOW BEING ABLE TO BE CARRIED OUT BY INDIVIDUAL RESEARCHERS IN THE LAB, BUT THEY HAVE TO BE ABLE TO HAVE ACCESS TO A LARGE NUMBER OF CELL LINES, AND THEY HAVE TO BE ABLE TO ACCESS THEM AT A REASONABLE PRICE.

AND I THINK THAT ONE OF THE PROBLEMS THAT WE HAVE IS CURRENTLY THE FINANCIAL MODEL BY WHICH WE DO COST RECOVERY FOR THESE SORTS OF EFFORTS. AND SO IF PEOPLE ARE REALLY SERIOUS ABOUT FINDING A PATH FORWARD TO CARRYING OUT THESE VERY LARGE ENSEMBLE STUDIES THAT WILL BE REQUIRED TO TAKE APART THE



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GENETIC HETEROGENEITY OF DIFFERENT DISEASES OR POWER THEIR WAY TO ASSOCIATION STUDIES TO COMMON PHENOTYPES, THEY'RE GOING TO HAVE TO THINK ABOUT WAYS TO GET LARGE NUMBERS OF CELL LINES INTO INVESTIGATOR'S HANDS TO ACTUALLY MAKE THAT WORK.

THAT WAS THE END OF MY POINT JUST AS I WAS GETTING SOMETHING IN MY THROAT.

DR. MILLAN: THANK YOU. SORRY WE CAN'T PROVIDE YOU WITH WATER FOR THE PANELISTS.

DR. SVENDSEN: -- WHAT KEVIN SAID. ONE OF THE THINGS JUST QUICKLY --

DR. MILLAN: CLIVE, I JUST WANT TO MAKE SURE -- AGAIN, I'M THE MEAN TRAFFIC DIRECTOR HERE. I KNOW THAT THIS IS GOING TO COME UP, BUT I WANT TO, KEVIN, IF YOU'RE DONE WITH YOUR STATEMENT, I WANTED GO TO OUR OTHER PANELISTS, ILYAS SINGEC, TO COMMENT ON THIS, AND THEN DR. CHRISTINE MUMMERY AFTER THAT. THANK YOU. SORRY, CLIVE.

DR. SINGEC: THANKS, MARIA. JUST WANTED TO ADD TO REALLY GREAT INTERESTING DISCUSSION HERE THAT WE SHOULD REALLY THINK ABOUT SOMETHING WE CALL TRANSLATION BY DESIGN. SO ESSENTIALLY NOT JUST QUALITY BY DESIGN, BUT EARLY ON PUTTING TRANSLATION CENTER STAGE AND ALSO TRYING TO DEVELOP PROTOCOLS FROM THE VERY BEGINNING THAT WOULD BE TRANSLATABLE.

SO THIS GOES SOMEWHAT BACK TO THE BASICS OF DEVELOPING THESE PROTOCOLS, AND IN SOME CASES REALLY REVISITING SOME OF THE CONCEPTS OR THE THINGS THAT WE HAVE BEEN NOW TAKING FOR GRANTED. SO THE FIELD HAS MATURED TREMENDOUSLY, BUT STILL THERE ARE A LOT OF GAPS AND OPPORTUNITIES THAT WE SHOULD BE STILL FOCUSING ON.

SO ESSENTIALLY ROBOTICS IS GREAT, BUT FIRST YOU HAVE TO STILL DO THE SYSTEMATIC DISCOVERY BIOLOGY APPROACH AND DEVELOP THESE PROTOCOLS AND TECHNOLOGIES THAT YOU THEN CAN ACTUALLY USE WITH ROBOTICS TECHNOLOGY. SO IT'S REALLY STILL A VERY, I WOULD SAY, COMPLEX, CHALLENGING EFFORT THAT REQUIRES THIS TYPE CONSORTIUM TYPE OF APPROACH AND COLLABORATIVE NETWORKS ACROSS STATE BOUNDARIES. AND SO I THINK THIS IS OVERALL A FANTASTIC OPPORTUNITY TO VOICE THESE KIND OF CHALLENGES AND ALSO TO SHARE SOME OF OUR EXPERIENCE THAT WE HAVE BEEN MAKING AT NCATS OVER THE LAST COUPLE OF YEARS. THANKS.

DR. MILLAN: THANK YOU, ILYAS. CHRISTINE.

DR. MUMMERY: I WAS JUST TO FOLLOW ON WITH THAT. SO PATRICK MADE THE POINT ABOUT IT'S ADDITIONALLY DIFFERENTIATION. SO YOU WANT A LOT OF LINES, BUT NOT SO MANY CELLS SOMETIMES, BUT VERY EFFICIENT DIFFERENTIATION. WE SHOULDN'T FORGET THE

READOUTS. THEY SHOULD BE SENSITIVE, REPRODUCIBLE, ONLINE, REAL-TIME MONITORING. AND WE NEED ANOTHER KIND OF TECHNOLOGY IN THAT AREA TO BE ABLE TO DO ALL OF THIS. AND SOMETIMES WE FORGET ABOUT THE READOUTS AND ALSO THE ROBOTICS AND THE IMAGING AND ALL THOSE FACILITIES THAT ARE NEEDED TO DO THAT.

SO THE PROTEOMICS AND THE TOPOMICS, IT ALL NEEDS TO BE IMPROVED AND MADE MORE SENSITIVE SO THAT WE CAN KNOW WHEN WE SEE CHANGES.

DR. MILLAN: THANK YOU, DR. MUMMERY. AGAIN, COMPATIBLE WITH KNOWLEDGE, AGGREGATION KNOWLEDGE NETWORK, AND KIND OF A CONTINUAL IMPROVEMENT QUALITY BY DESIGN AND TRANSLATION AND CLINICAL.

I THINK WE'VE ADDRESSED -- I ENCOURAGE YOU ALL TO LOOK AT CHATS BECAUSE MEMBERS HAVE BEEN SHARING SOME THEIR THOUGHTS DURING CHAT AS WELL. BUT TO TRY TO KIND OF COVER ALL THE TOPICS, I'D LIKE TO NOW INTRODUCE DR. CLAIRE HENCHCLIFFE.

DR. HENCHCLIFFE: THANKS SO MUCH. AND I WANT TO SAY REALLY THANK YOU TO CIRM, THANK YOU, MARIA, FOR SETTING THIS UP. I'VE BEEN CHARGED WITH SPEAKING ABOUT EMBRYONIC STEM CELLS AND IPS CELLS FOR PARKINSON'S DISEASE. SO I'M GOING TO CHANGE TACK A LITTLE BIT AND MOVE THIS MORE INTO THE

CLINICAL REALM.

AND I THINK PARKINSON'S IS A GREAT PLACE TO LOOK AT SOME CASE STUDIES AS WELL. IT'S REALLY A FIELD THAT IS VERY RICH IN TERMS OF THE HISTORY OF CELL TRANSPLANTATION AS WELL AS GENE THERAPY APPROACHES. AND IT'S GREAT TO SEE SOME REAL EXPERTS IN THE FIELD ON THIS CALL, PATRICK BRUNDIN, JEANNE LORING, CLIVE SVENDSEN, AND ALSO MY COLLEAGUE LESLIE THOMPSON, WHO'S WORKING ON A RELATED NEURODEGENERATIVE DISORDERS.

SO LET ME START OFF BY JUST SAYING A COUPLE OF WORDS ABOUT PARKINSON'S DISEASE. IT'S INCREDIBLY COMMON, AS YOU KNOW. THERE ARE PROBABLY AROUND 10 MILLION PEOPLE WORLDWIDE WHO SUFFER WITH PARKINSON'S AND PROBABLY UP TO A MILLION AND A HALF IN THE UNITED STATES, AND THAT'S NOT EVEN COUNTING THAT IT MAY BE UNDERDIAGNOSED, AND ALMOST 100,000 IN CALIFORNIA. IT'S A HUGE ECONOMIC BURDEN. AS I'M SURE YOU ALL KNOW, THERE WAS A RECENT REPORT ABOUT YEAR AGO OR TWO YEARS AGO ACTUALLY THAT THE ECONOMIC BURDEN IS ABOUT 52 MILLION PER YEAR -- 52 BILLION IN THE U.S. ALONE. SO THIS IS REALLY A COMMON DISORDER; AND AS SOCIETY AGES, IT'S GOING TO GET EVEN MORE COMMON.

SO I THINK A LOT OF YOU KNOW THAT THERE'S



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A FAIRLY LONG TIMELINE AT THIS POINT OF TRYING TO DEVELOP CELL THERAPIES FOR PARKINSON'S DISEASE. I'M GOING TO FOCUS ON THE CELLS, NOT SO MUCH ON THE GENE THERAPIES. ALTHOUGH IF YOU'D LIKE TO SPEAK ABOUT THAT IN THE PANEL DISCUSSION, WE CAN DO THAT.

SO I THINK THE FIRST OPEN LABEL CLINICAL TRIALS REALLY GO BACK TO THE LATE 1980S IN EUROPE, FETAL TISSUE TRANSPLANTATION WITH SMALL PORTIONS OF EMBRYONIC TISSUE THAT CONTAINED DOPAMINE PROGENITOR CELLS AS WELL AS OTHER PROGENITOR CELLS. AFTER A SERIES OF REALLY GROUNDBREAKING CLINICAL TRIALS, THEY CULMINATED IN TWO CLINICAL TRIALS IN THE U.S. THAT WERE PUBLISHED IN 2001 AND 2003, AND THEY WERE BOTH RANDOMIZED CONTROL TRIALS. NEITHER OF THEM REACHED THEIR PRIMARY ENDPOINT, AND IT DID SEND THE FIELD INTO SOMETHING OF A HIATUS UNTIL MORE RECENTLY WHEN ROGER BARKER PICKED UP AGAIN ON THIS APPROACH WITH HIS TRANSEURO TRIAL.

MORE RECENTLY AND BEGINNING WITH THE DERIVATION OF HUMAN EMBRYONIC STEM CELLS, IT WOULD HAVE BEEN THE LATE '90S, AND THEN GENERATION OF HUMAN IPSC'S, SO 2007, THERE'S BEEN INCREASING INTEREST IN REVISITING THESE TRANSPLANTATION APPROACHES IN PARKINSON'S DISEASE USING CELL PRODUCTS THAT JUST HAVE A HUGE NUMBER OF ADVANTAGES



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THAT I THINK I DON'T KNOW NEED TO GO INTO WITH THIS GROUP.

THE TIMELINE IN TERMS OF ACTUALLY TRANSPLANTING THESE CELLS INTO HUMANS, REALLY IT MAKES IT SO TIMELY THAT WE ARE HAVING THIS MEETING NOW. SO IN 2017 THE FIRST PATIENT WAS GRAFTED USING AUTOLOGOUS DOPAMINE PROGENITORS DERIVED FROM IPS CELLS. 2018 IN KYOTO, JUN TAKAHASHI'S GROUP BEGAN A SERIES OF TRANSPLANTS OF SUCH PROGENITORS INTO PEOPLE WITH ADVANCED PARKINSON'S DISEASE. AND NOW WE ARE REALLY AT THE POINT WHERE THERE ARE A NUMBER OF GROUPS WHO ARE PLANNING EITHER FURTHER TRIALS WITH AUTOLOGOUS OR ALLOGENEIC IPS CELLS OR HUMAN EMBRYONIC STEM CELLS. SO MY EXPERIENCES IN THIS FIELD HAVE GONE FROM FOLLOWING CURT FRIEDSEN'S, STAN FAHN'S PATIENTS MANY YEARS AFTER THEIR INITIAL HUMAN FETAL CELL TRANSPLANTS THROUGH BEING INVOLVED IN THE 2017 TRANSPLANTATION THAT WAS PERFORMED AT WILDE CORNELL AND THEN AT MASS GENERAL WITH AUTOLOGOUS CELLS, AND NOW TO BEING PART OF LORENZ STUDOR'S TEAM WITH BLUEROCK WHO ARE PLANNING THE FIRST HUMAN EMBRYONIC STEM CELL-BASED CLINICAL TRIAL. AND THAT WILL LAUNCH IN NEW YORK AND WILL BE A SITE AT IRVINE, AND TORONTO WILL ALSO BE INVOLVED.

SO I THINK THIS INVOLVEMENT HAS BROUGHT UP



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FOR ME SEVERAL NEEDS. AND I JUST WANTED TO GO THROUGH SOME OF THE CHALLENGES THAT WE FACED IN DESIGNING THESE STUDIES AND STARTING TO PERFORM THESE STUDIES.

SO ONE AREA WHERE I THINK SOME COULD REALLY CONTRIBUTE IS SOMEONE HAD MENTIONED DISRUPTION, BUT I THINK THAT THERE SHOULD BE A BALANCE OF DISRUPTING THE FIELD VERSUS HELPING US TO HARMONIZE. SO IN PREVIOUS TRIALS, AND THIS HAS BEEN REALLY WELL WRITTEN ABOUT BY ROGER BARKER, THERE WAS REALLY A LACK OF STANDARDIZED PROTOCOLS. NOW, OBVIOUSLY WE DON'T ALL WANT TO BE BE USING THE SAME STEM CELLS, AND WE DON'T NECESSARILY WANT TO BE USING THE SAME SURGICAL APPROACH, BUT THERE IS VALUE IN HAVING HARMONIZED OUTCOMES.

I THINK ONE OF THE ISSUES THAT WE FACED WHEN WE STARTED UP IN LORENZ STUDOR'S GROUP WAS THE NEED FOR KNOWLEDGE NETWORKS. THERE IS A NEED FOR KNOWLEDGE SHARING IN REAL TIME, NOT NECESSARILY AS PAPERS GET PUBLISHED SEVERAL MONTHS AFTER THE WORK HAS BEEN COMPLETED AND WRITTEN UP. WE DEFINITELY FELT, DURING THE DESIGN PERIOD, THAT THERE WAS NOT ONLY A LACK OF SUFFICIENT BIOMARKER OUTCOME MEASURES, SO THAT'S STILL DEFINITELY AN AREA FOR WORK, BUT A LACK OF HARMONIZATION ACROSS SITES AND



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THE FEELING THAT THERE SHOULD BE A KIND OF CORE PROTOCOL THAT COULD BE INDIVIDUALIZED BY INDIVIDUAL SITES BASED UPON THE CELL TYPES THAT THEY'RE USING, THEIR AIMS, AND THEIR POPULATION.

IN THE OLDER TRIALS THERE WAS REALLY SO MUCH HETEROGENEITY, THAT IT'S ALMOST IMPOSSIBLE TO EVEN PERFORM A META-ANALYSIS. AND SO WE FELT THAT THESE KNOWLEDGE NETWORKS WOULD REALLY KEEP PEOPLE ABREAST OF WHAT THE OTHER TEAMS ARE THINKING. AND IT ACTUALLY PROVES SOMEWHAT, I'M NOT GOING TO SAY STRAIGHTFORWARD, BUT FEASIBLE TO HARMONIZE WITH OTHER GROUPS. I'LL COME BACK TO THAT IN A MINUTE.

WE FELT THAT THERE WAS A NEED TO BETTER DEFINE ANCILLARY TREATMENTS. THIS HARKS BACK TO NOT HAVING SUFFICIENT OUTCOME MEASURES WHEN WE'RE THINKING ABOUT MEASURING INFLAMMATION AND DESIGNING IMMUNOSUPPRESSIVE PROTOCOL. THERE IS A GREAT NEED FOR BETTER DELIVERY TECHNIQUES, AND WE FELT THAT THIS IS AN AREA WHERE THE ENGINEERS COULD REALLY GET INVOLVED. AND I THINK WE'VE SEEN AN ENORMOUS AMOUNT OF PROGRESS IN THE DEEP BRAIN STIMULATION FIELD, INCLUDING WE WERE TALKING ABOUT ROBOTICS A FEW MINUTES AGO, BUT ROBOTICS IN THE OR. THERE'S A NEED TO LOOK AT DIFFERENT DELIVERY TECHNIQUES IN TERMS OF THE ENGINEERING, BUT ALSO IN TERMS OF THE BIOMEDICAL



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ENGINEERING. COULD WE DO BETTER IF WE PUT THESE CELLS IN ON A MATRIX, OR COULD WE STRUCTURE THEM SOMEHOW?

SO I THINK ONE OF THE THINGS THAT, MARIA, YOU HAD BROUGHT UP IN A PREVIOUS CONVERSATION WAS THE IDEA OF PLATFORM TRIALS. AND THE MORE THAT I THINK ABOUT THE VARIOUS APPROACHES THAT CAN BE TAKEN WITH PARKINSON'S DISEASE, THE MORE APPEALING A PLATFORM TRIAL SEEMS TO BE, WHICH IS A KIND OF CORE PROTOCOL THAT ALLOWS FOR SOMEWHAT FASTER TESTING OF VARIOUS APPROACHES. IT COULD BE DIFFERENT PRODUCTS, IT COULD BE DIFFERENT DELIVERIES OF THE SAME PRODUCT, IT COULD BE DIFFERENT OUTCOMES, IT COULD BE A CHANGE IN THE COHORT, FOR EXAMPLE.

SO I THINK THAT ONE AREA THAT I WOULD REALLY LIKE TO SEE CIRM CONTRIBUTE TO IS THE NEXT GENERATION TRIAL DESIGN. AND THIS INCLUDES NOT JUST PLATFORM TRIALS, BUT UMBRELLA TRIALS, BASKET TRIALS, AND SO ON.

I DID HAVE ON MY WISH LIST A BETTER UNDERSTANDING OF EVOLVING REGULATORY PATHWAYS, BUT I WILL CONCUR WITH CHRIS AUSTIN THAT THE FDA ARE VERY HELPFUL. AND BEING INVOLVED WITH THEM FROM THE POINT OF THE PRE-PRE-IND MEETING RIGHT THROUGH THE IND PROVED EXTREMELY ENCOURAGING.

SO JUST A COUPLE MORE THINGS BEFORE I OPEN UP FOR DISCUSSION. I DID WANT TO LOOK AGAIN AT THIS IDEA OF NETWORKS, KNOWLEDGE NETWORKS, AND HOW THAT CAN BE HELPFUL IN TERMS OF PATIENT REGISTRIES, FOR EXAMPLE, DATA REPOSITORIES. THE NETWORKS THAT I'VE BEEN INVOLVED IN I THINK HAVE BEEN INCREDIBLY VALUABLE IN TERMS OF CLINICAL TRIAL IMPLEMENTATION. AND I DO WANT TO MENTION ONE CALLED GLOBAL FORCE PD, WHICH PATRICK AND GENE HAVE BOTH BEEN INVOLVED IN. AND THAT STEMMED FROM A MEETING IN 2014 IN LONDON WITH ROGER BARKER'S GROUP AND A NUMBER OF EUROPEAN GROUPS, AND IT THEN EXPANDED TO INCLUDE THE GROUPS FROM KYOTO, FROM CHICAGO, FROM NEW YORK CITY, ETC.

AND THIS WAS REALLY AN ANNUAL MEETING WHERE WE COULD PRESENT OUR METHODOLOGIES, OUR IDEAS ABOUT TRIAL DESIGN, AND TRY TO HARMONIZE AS MUCH AS POSSIBLE. BUT I THINK THE OTHER ADVANTAGES OF FORMAL NETWORKS THAT I'VE SEEN IN NEURONEXT OR STROKENET OR THE TRIAL INNOVATION NETWORK IS THE ABILITY TO BRING PEOPLE TOGETHER EVEN BEFORE YOU HAVE A TRIAL, WHEN YOU JUST HAVE AN IDEA, AND CREATE THINGS LIKE DESIGN LABS WHERE YOU BRING IN KEY OPINION LEADERS, PEOPLE WITH VARIOUS TYPES OF EXPERTISE, INCLUDING REGULATORY. AND ONE WAY THAT WORKS IS A KIND OF SCRUM APPROACH, WHICH IS TO

PRESENT YOUR PROTOCOL AND HAVE EVERYONE KIND OF JUMP ON. SO I THINK THERE ARE, I THINK, A NUMBER OF DIFFERENT AREAS WHERE NETWORKS COULD BE CONTRIBUTORY.

AND THEN A COUPLE OF LAST THINGS THAT I WANTED TO MENTION. THE TRAINING PROGRAMS AND EDUCATION, I THINK, IS CRITICAL. THAT'S REALLY BEEN ADDRESSED.

DIVERSITY IN THE CLINICAL TRIAL COHORTS AND DIVERSITY OF THE PEOPLE WHO ARE BEING TRAINED, I THINK, IS REALLY IMPORTANT. AND YOU'VE ALREADY MENTIONED THOSE.

ONE THING THAT I DID WANT TO MENTION WAS SUPPORT FOR LONG-TERM FOLLOW-UP BECAUSE, AS WE'RE TAKING OUR PATIENTS INTO THESE CLINICAL TRIALS, IT CAN BE REALLY HARD TO -- YOU RETAIN THEM FOR THE FIRST PART OF THE TRIAL, BUT I THINK LONG-TERM FOLLOW-UP IS JUST ABSOLUTELY INVALUABLE, LET'S SAY, FIVE, TEN, 15 YEARS, OR MORE. SO I WOULD LIKE TO SEE SOME MORE ATTENTION TO THAT AREA.

AND THEN THE LAST THING THAT I WANTED TO MENTION BECAUSE, JUST HAVING MOVED TO UC IRVINE AND FIRST TIME WORKING WITH AN ALPHA STEM CELL CLINIC, WHICH IS JUST AMAZING, I WANTED TO TALK ABOUT THE STRUCTURES FOR THE FUTURE AND INFRASTRUCTURES FOR



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THE CLINIC AND THE HOSPITAL FOR THE FUTURE. I THINK WE SHOULD BE PLANNING FOR SUCCESS.

ONE THING THAT EXCITED ME VERY MUCH ARRIVING AT IRVINE IS WE'RE DESIGNING A NEW HOSPITAL. IT JUST GOT APPROVED, AND IT WILL BE BUILT AT THE IRVINE NEWPORT BORDER. AS PART OF THE STRUCTURE, WE WERE LOOKING AT ARCHITECT'S PLANS THAT SAY STEM CELL CLINIC. SO I THINK ONE THING THAT WOULD BE REALLY GREAT TO START THINKING ABOUT NOW IS WHAT ARE THE HOSPITALS GOING TO LOOK LIKE IN THE FUTURE? AND HOW DO THESE, ASSUMING THAT WE GET MORE OF THESE TYPES OF THERAPIES FDA APPROVED, WHAT IS THAT DELIVERY GOING TO LOOK LIKE IN A HOSPITAL OR A CLINIC SETTING?

SO I WILL STOP RIGHT THERE AND OPEN UP FOR DISCUSSION.

DR. MILLAN: THANK YOU SO MUCH, DR. HENCHCLIFFE.

ANY QUESTIONS? I DON'T SEE ANY HANDS RAISED. SO I'M REALLY -- PLEASE JUST GO AHEAD AND PIPE IN BECAUSE I'M NOT SEEING ALL THE FRAMES AT ONCE HERE. THANK YOU SO MUCH FOR THAT DISCUSSION. WE HAVE A CLINICAL NETWORK, THE ALPHA CLINICS NETWORK, WHICH HAS DEMONSTRATED PROOF OF CONCEPT REGARDING MULTIPLE INSTITUTIONS BEING ABLE TO WORK

TOGETHER AND STANDARDIZING APPROACHES EVEN IN OPERATIONAL APPROACHES, BUT ALSO KIND OF TAKING THESE KNOWLEDGE NETWORKS AND ALSO BRINGING IN THEIR OWN NETWORKS TOWARD IT AS WELL AS EXPERTISE.

AND SO I THINK THAT WE ARE ON THE VERGE OF SOME FIRST-IN-HUMAN TRIALS WITH CELL AND GENE THERAPIES, SOME OF THEM ALREADY IN PLAY. AND THE IDEA OF INVESTMENT INTO THIS INFRASTRUCTURE, IT'S NOT A SMALL INVESTMENT, REGISTRIES, LONG-TERM FOLLOW-UP STUDIES EVEN THOUGH IT SEEMS LIKE OUR PATIENTS ARE SIMPLE. AS A SYSTEM, IT IS AN INVESTMENT.

ANYBODY ON THE PANEL PLEASE FEEL FREE TO PIPE IN IN TERMS OF YOUR EXPERIENCE IN CREATING THESE TYPES OF EFFORTS, AND WHAT HAVE YOU RUN UP AGAINST? WHAT DO YOU SEE AS AN OPPORTUNITY HERE ESPECIALLY RELATED TO WHERE CIRM IS AND WHAT WE ARE LOOKING FOR?

I'M GOING TO PLEASE, DR. DALEY, IF YOU COULD START BECAUSE YOU DO LEAD A PRETTY MAJOR INSTITUTION ALSO WITH A FOCUS WITH THIS INVESTMENT IN REGENERATIVE MEDICINE.

DR. DALEY: IF THERE'S A QUANDARY THAT I HAVE, IT'S ABOUT, AND I'M EAGER TO HEAR WHAT OTHERS THINK, I'M STRONGLY IN SUPPORT OF THE NEED FOR MORE

INFRASTRUCTURE FOR PUSHING THE MANUFACTURING AND CELL PRODUCTION. WE'VE DONE THAT WITH A CONSORTIUM OF INSTITUTIONS IN THE BOSTON COMMUNITY CENTER FOR ADVANCED BIOLOGICS AND MANUFACTURING, HARVARD, MIT, A NUMBER OF THE HOSPITALS, AND THEN A NUMBER OF OUR BIOTECH COLLEAGUES HAVE CO-INVESTED IN THAT. AND RIGHT NOW IT DOES SEEM LIKE THERE'S TOO LITTLE CAPACITY TO SUPPORT THIS.

THE QUESTION IS ALSO -- AND THIS IS WELL DOCUMENTED BY THE BLUEROCK INVESTMENT IN LORENZ STUDOR'S WORK. THERE'S A GROWING NUMBER OF ENTERPRISES VERY, VERY WELL FINANCED ON THE COMMERCIAL SIDE THAT ARE REALLY INVESTING IN THIS SPACE AS WELL. SO WHEN WE THINK ABOUT SANA, WE THINK ABOUT CENTURY, AS WELL AS SOME OF THE OTHERS THAT I'VE MENTIONED, THERE ARE BILLIONS OF DOLLARS THAT ARE BEING PUT INTO IT BY THE VENTURE COMMUNITY.

SO I GUESS WHAT WE HAVE TO THINK ABOUT STRATEGICALLY FOR CIRM IS HOW CAN CIRM CONTINUE TO INVEST IN INFRASTRUCTURE BUT IN A WAY THAT REALLY EXPLOITS THAT LATER STAGE ACADEMIC, EARLY STAGE COMMERCIAL OPPORTUNITY. SO THERE'S A FAIR NUMBER OF VERY, VERY INNOVATIVE CELL AND GENE THERAPY APPROACHES WHICH I THINK STILL REQUIRE THE ACADEMIC INCUBATOR. AND SO I INVITE THOUGHTS FROM BOB AND



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THOSE WHO ARE THINKING ABOUT THIS FROM A VENTURE INVESTMENT SIDE; BUT MY SENSE IS, AS LONG AS CIRM IS REALLY FOCUSED ON THE PARTICULAR TYPE OF TRANSLATIONAL INFRASTRUCTURE, THAT LATER STAGE WHERE YOU WANT TO DERISK THE ACADEMIC WORK SO THAT IT'S INCREASINGLY APPEALING FOR VENTURE INVESTMENTS, THAT'S A NICHE WHERE I THINK WE CAN REALLY EXPLOIT THEM.

DR. MILLAN: THANK YOU SO MUCH. BOB, I DON'T KNOW IF BOB NELSEN IS STILL ON. HE MAY NOT BE ON. I'D LIKE TO HEAR FROM MAYBE CHRIS AND ILYAS IN TERMS OF THE NIH INVESTMENT INTO OBVIOUSLY THE NCATS AND OTHER INITIATIVES FROM THE NIH AND WHAT ARE YOUR THOUGHTS ON THAT, WHAT'S NOT TAKEN CARE OF, WHERE COULD CIRM COME IN?

DR. AUSTIN: I'LL GIVE YOU MY THOUGHTS AND THEN HAVE ILYAS CHIME IN. I REALLY RESONATED WITH GEORGE'S COMMENTS. THE WAY WE'VE TRIED TO THINK ABOUT IT IS TO ASK, WELL, NOT FROM THE PERSPECTIVE OF WHAT COULD WE DO IN ACADEMIA IN SUPPORT OF THE NIH, IS WE COULD DO ALMOST ANYTHING. BUT, RATHER, WHAT DO WE HAVE TO DO IN ORDER TO GET THESE TECHNOLOGIES TO PATIENTS?

AND WHAT, I THINK, ALL OF US REALIZE WHEN WE LOOK AT THIS IS THAT THERE REALLY IS A VERY



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SPECIAL ROLE POTENTIALLY FOR THE ACADEMIC COMMUNITY AND CIRM MORE BROADLY, MORE SPECIFICALLY, IN THIS BECAUSE THERE IS A GREAT NEED FOR TECHNOLOGY DEVELOPMENT FOR UNDERSTANDING OF FUNDAMENTAL PRINCIPLES THAT ARE GOING TO GO INTO A ROBUST MANUFACTURING PROCESS.

AND THERE IS A LOT OF REALLY IMPORTANT, COMPLICATED SCIENCE IN THAT SPACE THAT COMES UNDER THE RUBRIC, I GUESS WE COULD CALL IT, CMC, BUT WE TEND TO THINK ABOUT CMC IN THE SENSE THAT WE DO WITH SMALL MOLECULES WHERE, FOR THE MOST PART, WE REALLY UNDERSTAND WHAT THE ISSUES ARE. IF YOU'VE GOT A SMALL MOLECULE, YOU COULD DO HPLC TO FIGURE OUT WHAT THE IMPURITIES ARE. IT'S PRETTY SIMPLE. OF COURSE, WITH BIOLOGICS IT'S NOT SO SIMPLE. BUT WHAT YOU'D NEED IN ORDER TO WORK THOSE TECHNOLOGIES AND PARADIGMS OUT IS THE SAME TECHNOLOGICAL INFRASTRUCTURE THAT EXISTS IN A PRODUCTION FACILITY. YOU CAN'T DO IT IN A HALF-BAKED, NONSCALED ENVIRONMENT AND DEVELOP THE KIND OF ROBUST TECHNOLOGIES THAT YOU NEED FOR THE PRIVATE SECTOR TO DO ITS THING.

AND SO WE THINK THAT THERE IS A REALLY -- THERE'S A FIRMLY TRANSLATIONAL PIECE OF THIS WHICH IS HIGHLY ATYPICAL OF WHAT NIH HAS DONE

TRADITIONALLY AND, FRANKLY, VERY DIFFICULT TO FUND WITH NIH DOLLARS. NCATS WE DO THIS SORT OF THING ON THE GREATEST LEVEL THAT WE CAN, BUT WE ARE LIMITED ALSO BY THE RESOURCES THAT WE HAVE AND THE MANDATE THAT WE HAVE. AND IT'S REALLY ENABLING KNOWLEDGE AND TECHNOLOGY. AND THE GOOD THING ABOUT THIS FOR CIRM IS THAT THIS WOULD RESULT, TO THE DEGREE THAT I KNOW THIS IS IMPORTANT, THIS REALLY WOULD RESULT IN ECONOMIC RETURN TOO BECAUSE THESE WOULD NOT BE COMPOSITION OR MATTER PATENTS IF YOU WANT TO THINK OF THEM, BUT THEY'RE THE KIND OF PRODUCTION PATENTS THAT ACTUALLY ARE WHAT SUPPORT MOST OF PRIVATE SECTOR INVESTMENT.

AS YOU PROBABLY HAVE FOLLOWED, THERE MIGHT BE ONE PATENT, IT'S A SMALL MOLECULE AGAIN, ONE PATENT ON THE COMPOSITIONAL MATTER, BUT THERE ARE 50 PATENTS ON HOW YOU MAKE IT IN A ROBUST, REPRODUCIBLE WAY THAT COULD ALSO LEAD TO TREMENDOUS ECONOMIC ACTIVITY AND DO IT IN A VERY ENABLING WAY.

SO I THINK YOU NEED THIS INFRASTRUCTURE, BUT NOT SO MUCH TO DUPLICATE THE PRODUCTION OF THE SORT AT ALL, AS GEORGE IS SAYING, BECAUSE THAT IS BEING FILLED BY A DIFFERENT NICHE. BUT WHAT THEY'RE NOT DOING IS TO FIGURE OUT HOW TO DO IT BETTER, FASTER, CHEAPER. AND THAT IS A COMPLETELY



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APPROPRIATELY AND NEEDS TO BE AN ACADEMIC ENDEAVOR.

DR. MILLAN: THANK YOU, CHRIS. ILYAS, IF YOU HAVE JUST A BRIEF AND WE'LL GO TO THE NEXT.

DR. SINGEC: I'LL JUST ADD TO THIS. THINKING CREATIVELY ABOUT PARTNERSHIP MODELS IS, I THINK, KEY IN THIS INSTANCE. AND ESPECIALLY THE PATHWAY TO COMMERCIALIZATION AND HOW CAN YOU ACTUALLY ATTRACT VENTURE CAPITAL BY DEVELOPING ALREADY A PRODUCT THAT IS SO ROBUST AND WILL BE USABLE INCLUDING EXTERNAL VALIDATION. SO I THINK IT'S NOT JUST ENOUGH TO COME UP WITH AN IDEA OR A PRODUCT, BUT ALSO GET ESSENTIALLY THE EXTERNAL VALIDATION OF YOUR QUALITY CONTROLS THAT SHOULD BE ALL ALREADY INTEGRATED INTO THE APPROACH OF GENERATING THE PROCESS. MAKING THINGS MORE COST EFFICIENT, CHEAPER, THIS IS ALL PART OF THE THINKING.

AND ALSO, AS I SAID, ARE THERE NEW WAYS, DISRUPTIVE WAYS OF DEVELOPING THESE PRODUCTS? I THINK THIS IS STILL OUT THERE AS WELL. WE REALLY DON'T HAVE A PERFECT EXAMPLE OF HOW WE ACHIEVED FROM BEGINNING TO END AND STILL GOING INTO THESE UNCHARTED WATERS AS WELL.

DR. MILLAN: THANK YOU SO MUCH. AS MENTIONED IN THE BEGINNING, WE HAVE SPECIFIC



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CONVERSATIONS AROUND THESE VERY TOPICS IN TRANSLATIONAL PROCESS DEVELOPMENT, MANUFACTURING SCIENCES, BUT THEY ALL INTERRELATE IN TERMS OF PRODUCT CHARACTERIZATION AND KNOWING THE SCIENCE FIRST. YOU CAN'T AUTOMATE SOMETHING THAT YOU DON'T KNOW IT'S GOING TO WORK AND DON'T HAVE A BASIS FOR IT.

SO REALLY APPRECIATE THAT. AND SO WE'RE GOING TO GO ON TO THE NEXT SET, AND MANY OF THESE POINTS ALSO, I'M SURE, WILL ARISE IN SOME OF THE OTHER PANEL DISCUSSIONS. BUT I'M NOW GOING TO TURN IT OVER TO DR. LESLIE THOMPSON. LESLIE, PLEASE.

DR. THOMPSON: THANKS VERY MUCH. IT'S ALSO SO NICE TO SEE EVERYONE ON HERE, PEOPLE I HAVEN'T GOTTEN TO SEE ALL YEAR.

YOU WILL HEAR A LOT OF THE SAME THEMES THAT YOU'VE HEARD HERE FROM CLAIRE AND FROM CLIVE AND OTHERS IN THE DISCUSSIONS. BUT WHAT I'M FOCUSING ON IS BASICALLY TRANSLATION OVERALL FOR NEURODEGENERATIVE DISEASES. AND I'LL BREAK IT UP INTO SORT OF THE TRANSPLANTATION END OF THINGS AND THEN THE IPC MODELING END OF OUR WORK AND THINGS THAT I'VE BEEN THINKING ABOUT.

SO STARTING WITH THE TRANSPLANTATION, I'VE BEEN WORKING ON HUNTINGTON'S FOR OVER 30 YEARS,

HUNTINGTON'S DISEASE. AND WE'VE, THROUGH CIRM'S HELP, I THINK IT'S BEEN OVER TEN, FIFTEEN YEARS OF FUNDING OVER THE YEARS, TO BRING THIS APPROACH TO IDENTIFY A CELL PRODUCT, TO BRING IT FORWARD, AND WE'RE ON OUR WAY TO AN IND RIGHT NOW FOR HUNTINGTON'S DISEASE. BUT ONE OF THE THINGS I REALLY LIKE THAT WAS MENTIONED EARLY ON IS THIS IDEA OF ENHANCING TRAINING AT ALL LEVELS, INCLUDING FROM STUDENTS TO PI'S. BECAUSE WHAT WE'VE LEARNED OVER THE YEARS, BOTH FROM OUR PROGRAM OFFICER, FROM THE INTERACTIONS OF OTHER INDIVIDUALS, HAS BEEN TO NAVIGATE THIS WHOLE PROCESS AND SOME OF THE THINGS, THE LESSONS WE'VE LEARNED VERY PAINFULLY OVER THE YEARS, IT'S BEEN CRITICAL TO HAVE THAT INTERACTION, PARTICULARLY WITH -- I CAN'T SAY ENOUGH ABOUT THE PROGRAM OFFICERS WE'VE HAD AT CIRM OVER THE YEARS WHO'VE REALLY WORKED WITH US VERY CLOSELY NAVIGATING THE CRL'S, NAVIGATING THE CELL MANUFACTURING, FDA GUIDANCE. WE'VE HAD REGULATORY PEOPLE BROUGHT INTO OUR PROJECTS THROUGH REALLY CIRM REFERRALS OVER THE YEARS.

AND I THINK ONE THING THAT MAYBE WOULD BE A SUGGESTION WOULD BE TO BRING THOSE CONSULTANTS ON VERY EARLY ON. FOR INSTANCE, WITH THE CELL MANUFACTURING, WE HAVE A PERSON WITH EXPERTISE IN

FLOW WHO'S BEEN WORKING WITH OUR TEAM RECENTLY TO DEVELOP FLOW GUIDELINES FOR THE CELLS. OR TO TALK ABOUT CELL DELIVERY. AND WHAT CLAIRE MENTIONED ALSO, THE HOSPITAL SETTING. ARE YOU GOING TO USE MRI GUIDANCE? ARE YOU NOT GOING TO USE MRI GUIDANCE? DO YOU HAVE THAT SET UP? HOW MUCH WOULD IT COST TO GET THAT SET UP? THERE'S ALL SORTS OF COSTS, AS I'VE BEEN FINDING OUT, INHERENT IN THAT. MATCHING MAYBE WITH FORMER GRANTEES WHO HAVE BEEN THROUGH THIS PROCESS MIGHT HAVE AN ANALOGOUS PROJECT, MIGHT BE ALSO SOMETHING TO SET UP ALSO.

ALSO, AS CAT MENTIONED, THE PATIENT ADVOCATES. WHAT'S IMPORTANT TO THE PATIENTS? WHAT'S THE SAFETY VALVES FOR PATIENTS? CONTINUING THOSE, THOSE HAVE BEEN VERY IMPORTANT FOR US AS WELL.

AND THEN AS YOU HEARD FROM CLAIRE, THIS IDEA OF A NETWORK CONSORTIUM. WE'VE DEVELOPED WHAT WE CALL SC4HD, KIND OF MODELED AFTER G FORCE, STEMS CELLS FOR HD. THIS IS ALSO AN INTERNATIONAL ORGANIZATION, A GROUP WE'VE COME TOGETHER REALLY WITH ANN ROSSER, IN PARTICULAR, IN EUROPE AND OUR GROUP, BUT MULTIPLE SITES ALL OVER THE WORLD TO TRY TO -- IT'S SUCH A HARD PROBLEM TO DO THIS WORK TO INFORM, TO START TO SET GUIDELINES, SHARE THE



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EXPERIENCES. WHAT ARE THE MINIMAL PRECLINICAL STUDIES YOU SHOULD HAVE IN PLACE? WHAT ARE THE OUTCOME MEASURES? WHERE SHOULD YOU DO YOUR INJECTIONS IN AN HD BRAIN THAT'S DEGENERATING? WHAT IS THE STAGE OF HD THAT WOULD BE OPTIMAL? THINGS LIKE THAT AND REALLY BEGINNING TO BRING TOGETHER A WHITE PAPER FOR THIS PROCESS.

AND THIS PROGRAM WAS INITIATED WITH ONE OF THE CIRM CONFERENCE GRANTS ACTUALLY, AND IT'S BEEN MAINTAINED OVER THE LAST THREE YEARS NOW. AND SO THOSE KINDS OF FUNDING EFFORTS ON THE PART OF CIRM HAVE BEEN VERY VALUABLE AND TO KEEP THIS KIND OF THING GOING. AND THE ALPHA STEM CELL CLINIC OBVIOUSLY IS CRITICAL AS WELL.

SO THAT'S KIND OF FOR THE TRANSPLANTATION END OF THINGS. I THINK THOSE EARLY INPUT OF CONSULTANTS, OF FDA GUIDANCE, OF ALL THOSE KINDS OF SHARING EXPERIENCES IS VERY CRITICAL.

AND BUILDING ON THAT FOR THE CLINICAL OUTCOMES THAT ARE IMPORTANT, I WAS ASKED TO TALK ABOUT NATURAL HISTORY, AND THIS RELATES, PARTICULARLY IN MY EXPERIENCE, FOR THE HD WORK, BUT THERE'S AN ORGANIZATION CALLED ENROLL HD THAT'S BEEN DEVELOPED FOR HUNTINGTON'S DISEASE. AND THIS WAS SPEARHEADED BY CHDI FOUNDATION. BUT ITS GOAL IS TO

ACCELERATE DISCOVERY, DEVELOPMENT OF NEW THERAPEUTICS, AND THIS HAS BECOME CRITICAL FOR THE HD FIELD. THERE'S NOT THAT MANY PATIENTS WITH HUNTINGTON'S DISEASE, ALTHOUGH THERE ARE MORE THAN YOU WOULD EXPECT NECESSARILY. BUT WHAT THEY'VE DONE, THEY'VE NOW ENROLLED OVER 20,000 ACTIVE PARTICIPANTS AROUND THE WORLD. THERE'S 180 CLINICAL SITES. THERE'S 21 NATIONS THAT ARE INVOLVED.

AND SO WHAT IT'S CREATED IS REALLY A CLINICAL STANDARDIZATION. SO THEY ALL UNDERGO THE SAME TESTS, THEIR CSF, BLOOD, MRI'S, ALL SORTS OF OUTCOME MEASURES TO TRY TO GET AT THE EARLIEST FEATURES WE CAN TRACK FOR TREATMENT OF THOSE PATIENTS AND ALSO TO HAVE THESE RESOURCES. YOU WANT TO DO A STUDY ON CSF, YOU WANT TO DO A STUDY ON BLOOD, THOSE THINGS ARE ALL THERE. AND IT IS A RAPID POOL OF PARTICIPANTS ALSO FOR CLINICAL TRIALS THAT HAVE BEEN VETTED. WE KNOW THE STAGE OF DISEASE. THEY'RE READY TO GO. AND IT'S A VERY BROAD SHARING OF DATA AND RESOURCES.

SO I THINK THAT TYPE OF ORGANIZATION, AND THAT'S GOING ON NOW MORE BROADLY FOR PD AND ALS AND OTHERS, BUT IT'S BEEN AN ABSOLUTE CRITICAL COMPONENT FOR CLINICAL TRIALS FOR HUNTINGTON'S DISEASE NOW.

AND THEN CHANGING GEARS A BIT IS GOING TO

THE IPS END OF THINGS AND THAT'S MODELING. AS CLIVE MENTIONED, HOW IMPORTANT THIS HAS BEEN FOR PATIENT STRATIFICATION AND DRUG DEVELOPMENT, PREDICTING PATIENT DISEASE TYPES, AND VERY IMPORTANTLY THE EARLIEST MECHANISMS THAT WE MIGHT BE ABLE TO FIND TO DEVELOP NEW THERAPEUTIC TARGETS. I THINK IT'S BEEN REALLY WELL DISCUSSED ABOUT THE CRITICAL NATURE OF THE IPS CELL PLATFORM ITSELF, THE DIFFERENTIATIONS, STANDARDIZATION, ROBOTICS THAT COULD GO INTO THIS.

AND, HERE AGAIN, MY WHOLE CAREER HAS INVOLVED CONSORTIA, BUT THIS HAS BEEN SO CRITICAL TO HAVE A CONSORTIUM FOR THE HD IPS WORK AS WELL AS THE ALS IPS WORK THAT WE'VE BEEN WORKING ON TO GET THE KINDS OF NUMBERS YOU NEED. FOR ANSWER ALS, THERE'S A THOUSAND PATIENTS THAT HAVE BEEN ENROLLED AND CLIVE'S GROUP HAS GENERATED IPS LINES AND DIFFERENTIATED THOSE INTO VERY PARALLEL CULTURES THAT ARE SENT AROUND FOR THE MULTIOMICS. FOR US THAT'S JUST BEEN -- WE WOULD NEVER HAVE THOSE KINDS OF NUMBERS. AND EVEN FOR THE HD IPS CONSORTIUM EARLY ON, HAVING EVERYONE POOL THEIR RESOURCES AND THEIR IPS CELLS AND THEIR EXPERTISE THERE, I THINK SALLY MENTIONED THE PHENOTYPES, THE OUTCOMES THAT YOU ARE GOING TO MEASURE IN THOSE CELLS HAS BENEFITED FROM THE BROAD EXPERTISE OF THE

INDIVIDUALS IN THESE CONSORTIA.

AND BRAINSTORMING, FRANKLY, BEING ON CALLS TOGETHER, THINKING ABOUT THE PROBLEMS THAT YOU'RE FACING, HOW YOU CAN TACKLE THOSE. CRITICAL TO HAVE EARLY DISCUSSIONS OF QUALITY CONTROL, THE METADATA YOU ARE GOING TO TRACK, HOW YOU ARE GOING TO TRACK IT, WHAT NUMBERING YOU'RE GOING TO USE FOR THE DIFFERENT CELL LINES. JUST THE REALLY PRACTICAL THINGS THAT GET WORKED OUT VERY EARLY. EVEN YOUR DIFFERENTIATION PROTOCOLS, THAT MIGHT BE ANOTHER AREA IN ADDITION TO JUST HAVING THESE CONSORTIA IN A VERY STANDARDIZED WAY, BUT EARLY ON EVEN WAYS TO FUND SOME OF THE EARLY DEVELOPMENT OF DIFFERENTIATION PROTOCOLS AND STANDARDIZED DIFFERENTIATIONS WOULD BE VERY BENEFICIAL ACROSS MULTIPLE DISEASES, I THINK.

AND PUBLIC ACCESS IS IMPORTANT, BEING ABLE TO HAVE THOSE INTERACTIONS. AND JUST, AGAIN, THE IMPORTANCE OF CONSORTIA. EVEN FOR COVID, FOR INSTANCE, THERE'S BEEN MULTIPLE AREAS WHERE YOU HAVE HOST GENOMIC CONSORTIA. CZI HAS ONE, CIRM HAS BEEN INVOLVED. THERE'S AN UC-WIDE GENOMICS CONSORTIA. BRINGING THOSE TOGETHER IN SOME WAY OR AT LEAST HAVING INTERACTIVE KNOWLEDGE OF EACH OTHER WOULD BE REALLY BENEFICIAL AS WELL. SO WAYS TO ARCHIVE THAT



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OR TO MAKE THOSE THINGS, I GUESS THE KNOWLEDGE ABOUT THOSE AVAILABLE.

AND I THINK WE'VE TALKED A LITTLE BIT ABOUT THE REFERENCE SAMPLES, ABSOLUTELY CRITICAL. WE'VE FOUND THAT WITH ANSWER ALS. SO I THINK FOR ANSWER ALS IN PARTICULAR, AGAIN, THIS REPRODUCIBILITY, THE EFFICIENCY, QC METRICS, AND ALSO, IN ADDITION TO HAVING OUTCOMES AHEAD OF TIME THAT YOU ARE GOING TO POTENTIALLY USE, I THINK THIS ITERATIVE PROCESS IS CRITICAL AS WELL. AS WE'VE GONE ALONG AND DONE MULTIOMICS, SOMETIMES IT'S A MOLECULAR READOUT THAT YOU FIND FROM HAVING DONE THAT WORK THAT YOU MIGHT NOT HAVE A PRIORI THOUGHT ABOUT, BUT THEN BECOMES AN OUTCOME MEASURE THAT YOU CAN USE, THAT YOU GENERATE A REPORTER FOR, OR SOMETHING ELSE, BUT THEN THERE'S THIS CONSTANT ITERATIVE LOOP THAT YOU GO THROUGH AS YOU LEARN AND INCORPORATE YOUR OUTCOMES INTO NEW OUTCOME MEASURES OR PHENOTYPES THAT YOU WOULD LOOK AT.

AND ALSO UNDERSTANDING SOME OF THE COVARIATES. IT'S REALLY BEEN WITH THESE LARGE NUMBERS WE'VE UNDERSTOOD THAT, FOR INSTANCE, SEX HAS AN INFLUENCE. WE WOULDN'T HAVE KNOWN THAT SEX COULD BE A COVARIATE IN OUR ANALYSIS IF WE HADN'T HAD HUNDREDS OF SAMPLES ALREADY TO DATE FROM THAT. SO



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THAT HELPS.

AND AS HAS BEEN MENTIONING, INCREASING CONTROLS, INCREASING DIVERSITY ACROSS THE POPULATIONS. I THINK THAT'S BEEN A CHALLENGE FOR US TO HAVE ENOUGH DIVERSITY. SOMETIMES FOR A CONSORTIA, THE DISADVANTAGE, I GUESS I WOULD SAY, IS JUST SOMETIMES THE COORDINATION CAN BE UNWIELDY OR IT CAN BE DIFFICULT TO PUBLISH, OR IT JUST TAKES SOME TIME, BUT GETTING THE ORGANIZATION AND, AS HAS BEEN MENTIONED, THE PROJECT MANAGEMENT COORDINATION IN PLACE EARLY ON MAKES A HUGE DIFFERENCE AS WELL.

SO I THINK I CAN END THERE. BUT REALLY HIGHLIGHTING MANY OF THE THINGS THAT HAVE ALREADY BEEN DISCUSSED.

DR. MILLAN: THANK YOU, LESLIE. THERE'S SO MUCH THAT YOU HAVE BROUGHT UP THAT PLAY ON THE DISCUSSION ALREADY, BUT THERE WILL BE OTHERS LATER ON IN THE PROGRAM, BUT WE WILL HAVE AN OPPORTUNITY TO DISCUSS SOME OF THESE IN TERMS OF POTENTIAL HOW-TOS AND MODELS THAT ARE OUT THERE. DAVID HAUSSLER, I KNOW, HAS THOUGHTS BECAUSE HE'S ORGANIZED AND COORDINATED THESE HUGE DATASETS FOR GENOMICS. AND THEN THERE ARE ADDITIONAL CONVERSATIONS THAT WILL HAPPEN LATER.

BUT ASIDE FROM THAT, IF THERE ARE ANY

SPECIFIC COMMENTS OR QUESTIONS REGARDING THIS PARTICULAR AREA, WE'LL TAKE IT NOW. BUT IT WOULD BE GREAT TO MOVE ON TO THE NEXT SPEAKER BECAUSE ACTUALLY IT KIND OF ALL RELATES TO THE NEURO FIELD SO THAT WE CAN HAVE KIND OF A BROADER DISCUSSION IF THAT'S OKAY WITH EVERYBODY. IF I DON'T HEAR FROM ANYBODY WITH AN URGENT STATEMENT, I'M GOING TO GO ON TO INTRODUCE DR. PATRICK BRUNDIN. PATRICK. THANK YOU.

DR. BRUNDIN: THANK YOU. THANK YOU FOR HOSTING ME TODAY AND ALLOWING ME TO BE PART OF THIS. IT'S A VERY INTERESTING AREA THAT'S DEAR TO ME. AND I THINK CLIVE MENTIONED HE'D BEEN WORKING FOR 40 YEARS IN THIS SPACE, AND THAT'S ABOUT THE SAME FOR ME.

SO MY BACKGROUND IS PRIMARILY IN CELL TRANSPLANTATION IN PARKINSON'S. I AM AT THE VAN ANDEL INSTITUTE IN THE U.S. NOW, BUT I USED TO BE IN SWEDEN FOR 30 YEARS.

I'VE BEEN ASKED TO COMMENT ON FOUR AREAS. I'M GOING TO SPEND TWO MINUTES ON EACH. ONE IS ARE THERE AREAS OF BASIC NEUROSCIENCE RESEARCH THAT CIRM COULD FUND, BUT IS NOT TRADITIONALLY FUNDING TODAY? THE SECOND ONE IS ARE THERE NEEDS FOR CRITICAL INFRASTRUCTURE? WE'VE TALKED ABOUT THIS. I'M GOING



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TO HIGHLIGHT A SPECIFIC AREA. THE THIRD THING IS IS THERE A NEED FOR CIRM-SPONSORED DATA SHARING AND PARTNERSHIPS? AND I'M GOING TO GIVE YOU ONE EXAMPLE THAT I THINK IS AN INTERESTING ROLE MODEL. AND FINALLY, FOURTH, IS THERE A POSSIBILITY THAT CIRM SHOULD SPONSOR WORK THAT GOES IN EARLIER IN DISEASES MORE IN THE PREVENTION DOMAIN? SO NOT WHEN THE DISEASE HAS ALREADY WREAKED HAVOC ON THE BRAIN. SO THOSE ARE THE FOUR POINTS.

WELL, WHAT COULD CIRM SPONSOR IN THE FUTURE THAT IS NOT TRADITIONALLY FUNDED BY CIRM? AND REMEMBER JILL SAID THIS MORNING THAT PROPOSITION 14 IS ALLOWED TO BROADEN ITS PURVIEW AS DEEMED NECESSARY BY THE BOARD. SO HOW SHOULD WE INTERPRET REGENERATIVE MEDICINE?

IF YOU HEAR A VOICE BEHIND ME, IT'S MY NINE-YEAR-OLD DAUGHTER OLIVIA WHO'S IN AN ONLINE CLASS.

WELL, SO FAR CIRM HAS FOCUSED ON CELL REPLACEMENT AND GROWTH FACTORS WHEN IT COMES TO THE BRAIN. I WONDER IF WE SHOULD SEE IN SITU REPROGRAMMING OF CELLS AS A WAY FORWARD, NOT JUST IN TERMS OF REPLACING NEURONS THAT HAVE DIED, BUT PERHAPS REPROGRAM INFLAMMATORY IMMUNE CELLS THAT ARE IN THE BRAIN IN SUCH A WAY THAT IT'S A MORE



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FAVORABLE ENVIRONMENT THAT COUNTERACTS NEURODEGENERATION.

I THINK CIRM SHOULD FOCUS MORE ON UNDERSTANDING EPIGENETIC CHANGES THAT FAVOR DISEASE AND PERHAPS IDENTIFY DRUGGABLE TARGETS IN THE EPIGENOME. OF COURSE, A GROWTH FACTOR ACTS BY MODELING OR REMODELING THE EPIGENOME OF THE CELL, BUT THERE MIGHT BE WAYS OF HAVING SMALL MOLECULES THAT TARGET MICROGLIA AND ASTROCYTES. I VIEW THAT AS REGENERATIVE AND PREVENTIVE.

PERHAPS ONE SHOULD DELIVER SOME OF THE THERAPEUTIC AGENTS VIA EXOSOMES.

AND, FINALLY, WHEN WE THINK ABOUT THE FUTURE, WHAT IS THE NEXT PANDEMIC? IT MAY NOT BE A COMMUNICABLE INFECTIOUS DISEASE. THE NEXT PANDEMIC IS ALZHEIMER'S, PARKINSON'S, AND POSSIBLY ALL THOSE NEUROPSYCHIATRIC DISEASES THAT WERE MENTIONED EARLIER TODAY. IF THAT IS THE NEXT PANDEMIC, WE SHOULD ALSO THINK ABOUT VASCULAR DISEASE AND THE CONTRIBUTIONS OF ISCHEMIC DAMAGE. MAYBE CIRM SHOULD BE LOOKING AT HOW TO PREVENT THESE. I'LL COME TO THAT IN MY LAST POINT.

SO HERE'S MY SECOND POINT. WHAT CRITICAL INFRASTRUCTURE SHOULD BE A FOCUS IN THE FUTURE, FIVE, TEN YEARS FROM NOW? I LIKE THE IDEA OF

AUTOMATED HUBS WHERE YOU CAN DO VERY STANDARDIZED CELL CULTURE. HOW CAN THAT BE TAKEN TO THE NEXT LEVEL, AS I HINTED THE CHAT? I THINK THE ACTUAL OUTCOMES ALSO NEED TO BE STANDARDIZED. HOW ABOUT HAVING A CIRM HOTEL, ALMOST LIKE A CRO, WHERE EITHER SCIENTISTS CAN COME THERE AND WORK THERE UNDER EXTREMELY STANDARDIZED CONDITIONS OR THEY SUBMIT PROPOSALS TO TEST THEIR INTERVENTION IN A STEM CELL PLATFORM AND EVERYTHING IS STANDARDIZED. YOU CAN TRUST THE PAPER. WE GET RID OF SOME OF THE ISSUES OF RIGOR AND REPRODUCIBILITY. THAT WILL BE INCREDIBLY VALUABLE TO EVERYBODY IN THIS FIELD BECAUSE WE ALL KNOW IT HAS BEEN A CONCERN THAT PEOPLE ARE NOT EVALUATING THE SAME THING. THAT WAS POINT TWO.

WHAT ABOUT CIRM CREATING SOME KIND OF DATA SHARING PARTNERSHIP THAT DOESN'T EXIST TODAY? I THINK WE HEARD GREAT EXAMPLES OF EFFORTS TO DO DATA SHARING. I'LL GIVE YOU ONE NEW MODEL THAT'S JUST EMERGING RIGHT NOW. SOME OF YOU ARE FAMILIAR WITH THIS. IT'S CALLED THE ALIGNING SCIENCE ACROSS PARKINSON'S RESEARCH, SPONSORED BY THE SERGEY BRIN FAMILY FOUNDATION. AND NOW IT'S A REAL EFFORT THAT'S CHAIRED BY RANDY SCHEKMAN AND THE EXECUTIVE DIRECTOR EKEMINI RILEY.

ALIGNING SCIENCE ACROSS PARKINSON'S GIVES OUT LARGE GRANTS, BUT THEY ALSO REQUIRE AND SUPPORT MEANINGFUL AND MULTIDISCIPLINARY COLLABORATIONS. I'M READING OFF THEIR WEB PAGE NOW. THEY ALSO GENERATE RESEARCH-ENABLING RESOURCES. SO THERE ARE A HUGE DATA BANKS THAT ANYBODY CAN ACCESS. AND THEY DEMOCRATIZE DATA. ANYONE CAN ACCESS THE DATA. YOU CAN'T JUST GET YOUR GRANT AND RUN AWAY AND DO YOUR THING. YOU ARE PART OF ONE TEAM IF YOU ARE AN ASAP GRANT. I'M GOING TO POST THE LINK TO THEIR WEB PAGE AS I FINISH. SO THAT WAS MY THIRD POINT.

NOW I'M GOING TO COME TO MY FOURTH POINT. SO COULD ONE LOOK AT NOVEL PARADIGMS WHERE IT ISN'T A QUESTION OF REPAIRING THE BRAIN IN THE TRADITIONAL SENSE OF REGENERATIVE MEDICINE? PERHAPS DOING EARLIER INTERVENTION AND PREVENTION TRIALS. I'VE SAVED AN EXTRA MINUTE FOR THIS POINT BECAUSE THIS IS SOMETHING THAT I THINK MAY BE INTERESTING IN FIVE OR TEN YEARS FROM NOW.

SO ALL NEURODEGENERATIVE DISEASES, OF COURSE, THEY INVOLVE LOSS OF NEURONS. THAT'S THE DEFINITION. BUT AS A CONSEQUENCE, AS NEURONS ARE LOST, THERE ARE LOTS OF CHANGES IN NEUROPLASTICITY IN THE REMAINING NEURONS. AND WE CAN IMAGINE THAT THESE REALLY OCCUR, NOT BECAUSE THERE'S BEEN AN

EVOLUTIONARY DRIVE FOR THEM TO EXIST AND PROTECT ELDERLY PEOPLE WHO HAVE NEURODEGENERATIVE DISEASE BECAUSE THEY'RE NOT TYPICALLY REPRODUCING, BUT THESE NEUROPLASTIC MECHANISMS ARE REALLY DEVELOPMENTAL MECHANISMS THAT ARE REKINDLED IN THE BRAIN WHEN NEURONS ARE LOST.

AS SUCH, THEY'RE NOT ALWAYS BENEFICIAL. AND MAYBE SOME OF THE ISSUES WE ARE LOOKING AT IN NEURODEGENERATIVE DISEASE IS NOT JUST A CONSEQUENCE OF LOSING NEURONS PER SE, BUT IT COULD BE THE CONSEQUENCE OF MALADAPTIVE PLASTICITY. AND I THINK A GREAT EXAMPLE IS IN THE PARKINSON'S FIELD. WHEN IT COMES TO L-DOPA INDUCED DYSKINESIAS, THIS IS A DRUG THAT'S GIVEN, SO IT'S NOT THE DISEASE PER SE. BUT WE KNOW THAT THE REWIRING OF THE BRAIN IS NOT BENEFICIAL TO THAT INDIVIDUAL'S FUNCTION.

WHY AM I SAYING THIS? WHAT'S THE POINT OF THIS? WHERE DOES CIRM COME IN? WELL, MAYBE CIRM SHOULD GET INVOLVED AT THE VERY, VERY FIRST STAGES OF NEURODEGENERATIVE DISEASE, THE SPACE WHERE ETHICALLY ONE WOULDN'T TYPICALLY INTERVENE. SOMEBODY'S JUST BEEN DIAGNOSED A WEEK BEFORE AND GO IN AND TRY TO PREVENT CELL DEATH, NOT JUST TO PREVENT THE LOSS OF NEURONS, BUT ALSO TO PREVENT MALADAPTIVE PLASTICITY. THIS IS NOT A SPACE THAT

THE INDUSTRY WANTS TO BE IN. IT REQUIRES VERY LONG-TERM TRIALS, FIVE, SEVEN, EIGHT YEARS, VERY EXPENSIVE, AND IN SOME WAYS DISRUPTIVE.

LET ME GET BACK TO VASCULAR DEMENTIA. I MENTIONED THAT IN THE BEGINNING. THAT'S ANOTHER COMING PANDEMIC THAT'S ALREADY HERE. SO MAYBE REGENERATIVE MEDICINE IN THE BRAIN COULD INCLUDE IMPROVING VASCULAR FUNCTION IN THE BRAIN SO WE CAN PREVENT THIS TERRIBLE PANDEMIC WHERE A LARGE PORTION OF OUR POPULATION WILL HAVE TO BE IN NURSING HOMES.

SO WITH THAT, I WANT TO INVITE A DISCUSSION. AND I'M GOING TO POST THE LINK TO THE ASAP PROGRAM, IT'S ACTUALLY CALLED PARKINSONROADMAP.ORG, IN THE CHAT IF ANYBODY WANTS TO SEE THAT.

DR. MILLAN: THANK YOU, PATRICK. THANK YOU VERY MUCH. AND THE ASAP, EKEMINI RILEY WAS INVOLVED IN THAT NEURODEGENERATION WORKSHOP AS WAS RANDY SCHEKMAN. SO THESE DISCUSSIONS ABOUT THE REGISTRIES AND OPEN SOURCE DATA AND ALL THAT IS ALL PART OF THIS ONGOING CONVERSATION SO IMPORTANT.

I'D LIKE TO OPEN UP THE DISCUSSION REGARDING THIS AS WELL AS LESLIE'S AND OTHER RELATED TOPICS THAT NOW MAY BE TRIGGERED OR MAY HAVE BEEN STIMULATED ALONG THE COURSE OF THIS MORNING. SO WHO



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WANTS TO GO FIRST? THANKS AGAIN, PATRICK. I DON'T SEE ANY HANDS RAISED.

DR. BRUNDIN: I LIKE THE HOTEL CIRM CALIFORNIA CONCEPT.

DR. MILLAN: I THINK WE HAVE MUSIC TO GO WITH THAT TOO.

DR. BRUNDIN: I THINK THEY INVOLVE DRUGS, BUT NOT PERHAPS THE SAME DRUGS THAT YOU'RE CONSIDERING DEVELOPING.

DR. MILLAN: WHILE I'M WAITING FOR OTHERS TO RAISE THEIR HANDS OR PIPE IN, AGAIN, WE WANT TO MAKE IT WORTH IT FOR DR. PETER MARKS TO BE HERE FOR HIM BECAUSE I KNOW HE'S EXTREMELY BUSY. PETER, ARE YOU STILL ON? HE MAY NOT BE BECAUSE HE SAID HE HAD TO BE IN AND OUT. BUT I THINK IT REALLY -- MANY OF YOU KNOW THAT PETER MARKS WAS A CO-AUTHOR ON A PAPER IN THE *NEW ENGLAND JOURNAL OF MEDICINE* REGARDING ALL KIND OF THIS RECURRENT THEME THAT WE HAD IN TERMS OF HAVING AN EMPOWERED KNOWLEDGE NETWORK. I'M CALLING IT KNOWLEDGE NETWORK, BUT SHARED DATA AND STANDARDIZED APPROACHES TO COLLECTION OF THAT DATA THAT WOULD ALLOW KIND OF BETTER CHARACTERIZATION EARLY ON. AND THEN, OF COURSE, LATER ON AS TREATMENTS OR INTERVENTIONS ARE BEING DEVELOPED, THAT REALLY WOULD ENABLE THE INTERPRETATION OF

CLINICAL DATA ARISING FROM ALL THESE TRIALS. WE'LL TAP IN LATER WHEN HE'S BACK.

IS THERE ANY INPUT REGARDING SOME OF THE CONVERSATION? I THINK ONE OF THE THINGS I'D LIKE TO MAYBE SOME OF THESE ASSUMPTION TESTING CONCEPTS THAT YOU BROUGHT UP, PATRICK, WHICH IS PREVENTIVE INTERVENTIONS COULD BE IN VASCULAR NEUROBIOLOGY, AS WELL AS -- LET'S START WITH THAT.

DR. BRUNDIN: MAYBE TO THROW SOME MORE FUEL ON THE FIRE ON THAT PREVENTIVE NOTION, IF YOU READ THE COMMENTS ON A PREPRINT THAT WAS POSTED, NOT PEER REVIEWED YET, BUT A LARGE DATABASE FOLLOW-UP IN THE UK ON PEOPLE DIAGNOSED WITH COVID-19. THE NUMBER OF PEOPLE WHO, ON A REGISTRY LEVEL, WHO REPORT PSYCHIATRIC OR NEUROLOGICAL DEFICITS THAT ARE NEW SIX MONTHS AFTER COVID IS QUITE STUNNING. SO WE DON'T REALLY FULLY UNDERSTAND THIS YET. OF COURSE, WE DON'T KNOW HOW MANY YEARS WILL REMAIN ONE OR TWO YEARS OUT FROM THEM SUFFERING FROM COVID. BUT THIS MAY ALSO BE ANOTHER AREA OF REGENERATIVE MEDICINE THAT CIRM IN AN INNOVATIVE-THINKING-OUTSIDE-THE-BOX WAY COULD BE LOOKING AT.

DR. MILLAN: THANK YOU. AND NOW I'LL OPEN IT UP FOR ADDITIONAL INPUT FROM, IF NOT THE PANELISTS, THE SPEAKERS REGARDING YOUR TOPIC AREAS



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RELATED TO SOME OF WHAT YOU'VE HEARD ABOUT FROM THE OTHER SPEAKERS BECAUSE I THINK THERE IS QUITE A BIT OF SYNERGY AND KIND OF SOME OVERLAPS FROM DIFFERENT PERSPECTIVES ON THE VARIOUS ASPECTS OF WHAT YOU'VE PRESENTED. CLIVE, I KNEW YOU'D WANT TO SPEAK.

DR. SVENDSEN: I JUST WANT TO GET BACK TO PATRICK'S IDEA OF HOTEL CALIFORNIA. OBVIOUSLY IT'S AN ATTRACTIVE IDEA, BUT THE CONCEPT -- 70 PERCENT OF WHAT'S OUT THERE IS NOT REPRODUCIBLE IN SCIENCE. I THINK THAT'S THE ISSUE, AND IT'S ALL ABOUT DIFFERENT LABS, DIFFERENT POST-DOCS, DIFFERENT TECHNICIANS. BUT I DO THINK THIS CONCEPT OF A CLEARINGHOUSE THAT PATRICK MENTIONED, SOMEHOW TO VALIDATE A LOT OF THE STUFF THAT YOU READ IN THE *SCIENCE* AND *NATURE* PAPERS. I KNOW THAT CHRIS HAS DONE THIS AT NCATS. THEY HAVE A KIND OF VALIDATION CENTER WHICH A LOT OF THE INDUSTRY HATED BECAUSE THEY'RE GOING TO TAKE THEIR CHIPS AND PUT THEM IN ONE AREA. AND OH, MY GOD. THEY ACTUALLY HAVE TO REPRODUCE SOMETHING AND EVERYBODY GETS SCARED.

SERIOUSLY, WE'RE NOT GOING TO GET MUCH FURTHER UNLESS WE HAVE THESE TESTING REPRODUCTION CENTERS. I THINK IT'S VERY BORING, IT'S VERY BASIC, BUT PATRICK IS RIGHT. THIS MAY BE AN OPPORTUNITY FOR CALIFORNIA TO STEP IN. MAYBE IT DOES INVOLVE

SOME AUTOMATION. THE PROBLEM IS WE DON'T KNOW WHAT THE BEST METHOD OF GROWING IPS OR DIFFERENTIATING IS. WE NEED THESE ISLANDS OF INNOVATION TO TEST THEM OUT; BUT THEN AFTER THEY'VE TESTED THEM AND PUBLISHED THEM IN THE *NATURE* PAPER, THEY SHOULD GO TO A CENTRAL FACILITY AND BE REPRODUCED. AND YOU WILL FIND THAT 90 PERCENT OF THEM WILL DROP OUT. OH, IT'S MY BEST POST-DOC AND I'LL NEVER REPEAT THAT EXPERIMENT KIND OF THING. I THINK THAT WOULD BE VERY VALUABLE. I'D LIKE TO BRING THAT UP FOR DISCUSSION. HOWEVER YOU DO IT, IT'S VERY COMPLICATED TO DO IT, AND IT'S IP AND THERE'S ALL THIS STUFF GOING ON, BUT I THOUGHT IT WAS GOOD TO HAVE A DISCUSSION AROUND THAT.

DR. BRUNDIN: I THINK IT WOULD ALSO HELP BENCHMARKING WHAT ARE THE PROPER OUTCOMES. AS IT IS TODAY, EVERYBODY KNOWS DIFFERENT LABS DO DIFFERENT THINGS IN TERMS OF OUTCOMES TOO. IF THIS SORT OF CENTER WOULD EVOLVE, THEY WOULD SET THE STANDARD AND PEOPLE WOULD PERHAPS IMPROVE THEIR INITIAL PAPERS. AND MAYBE WE WOULD GO FROM 10 PERCENT BEING REPRODUCIBLE TO 50 PERCENT BEING REPRODUCIBLE.

DR. MILLAN: ILYAS HAS A QUESTION OR COMMENT.

DR. SINGEC: YEAH. SO THIS OBVIOUSLY

RESONATES WITH US A LOT. SO WE STARTED THE STEM CELL GROUP AT NCATS IN EXACTLY ALONG THESE LINES. SO WE ENVISION SOMETHING LIKE HAVING A REFERENCE CENTER OF IPS CELL RESEARCH AND APPLICATION AT SOME POINT. SO THIS IS STILL EARLY DAYS. I THINK WE'VE MADE REALLY GOOD HEADWAY IN BRINGING ALL THESE CUTTING-EDGE TECHNOLOGIES TOGETHER, AND NCATS ALREADY PROVIDED THE ENVIRONMENT, PLUS NOW ADDING ADDITIONAL INNOVATIVE TECHNOLOGIES TO THIS, AND REALLY MAKING SURE THAT EVERYTHING WE ARE TRYING TO DO IS DONE IN A COLLABORATIVE FASHION. AND EXTERNAL VALIDATION IS ABSOLUTELY CRITICAL TO US. SO THE ROBUSTNESS.

AS I SAID, WE STARTED THIS FIVE YEARS AGO. WE HAVE JUST FILED OUR FOURTH PATENT. THREE OF THOSE PATENTS ARE NOW BEING PICKED UP BY A MAJOR STEM CELL COMPANY. SO WHAT I'M TRYING TO SAY IS IF YOU BRING ALL THESE REALLY IMPORTANT AND FEARABLE CONDITIONS TOGETHER, YOU CREATE A LOT OF SYNERGY, AND THIS WOULD REALLY HELP TO ADVANCE THE FIELD IN ALMOST UNIMAGINABLE WAYS. AND SO WE ARE REALLY PUSHING HARD TO MAKE THIS KIND OF APPROACH BROADLY AVAILABLE.

SO YOU CAN CALL IT HOTEL CALIFORNIA OR REFERENCE CENTER, BUT OBVIOUSLY THIS SHOULD BE DONE

IN A COLLABORATIVE FASHION NO MATTER WHERE WE ARE LOCATED.

DR. MILLAN: THANK YOU, ILYAS. OH, LOOK AT ALL THESE HANDS. GREAT. CHRIS AUSTIN.

DR. AUSTIN: JUST A SMALL POINT. THE REASON -- AND THANK YOU, CLIVE -- THE REASON THAT THE VALIDATION CENTERS THAT WE'VE FUNDED WORK IS THAT IT WAS A CONDITION OF FUNDING TO THE DEVELOPERS. SO THIS WASN'T A NICE TO HAVE. THIS WASN'T A PLEASE BE NICE AND COOPERATE WITH THE VALIDATION CENTER FOR ALL THE REASONS WE CAN IMAGINE. IF YOU GET YOUR *NATURE* PAPER, THAT'S THE PINNACLE. THE ONLY PLACE TO GO IS DOWN. SO YOU DO NOT HAVE AN INTEREST IN SOMEBODY TRYING TO VALIDATE YOUR DATA. RIGHT? IT'S JUST THE WAY THE INCENTIVES WORK.

AND SO IF YOU SET IT UP IN THE BEGINNING TO SAY, LOOK, NO HARM, NO FOUL. SCIENCE IS SCIENCE. IT FAILS MOST OF THE TIME. AND IF WE SET IT UP AS A COLLABORATION SO THAT PART OF THE PROCESS IS TO GO TO THIS VALIDATION CENTER WITH A REALLY GOOD SCIENTIST, AND THE WHOLE IDEA IS NOT TO SAY YOUR RESULT DOESN'T WORK, ALTHOUGH SOMETIMES YOU RESULT IN THAT. MORE OFTEN WHAT IT IS IS IT ACTUALLY CAN WORK, BUT YOU DON'T KNOW WHAT THE SECRET SAUCE IS.



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WHAT IS THE MAGIC IN THE MAGIC POST-DOC'S HANDS? THERE HAD TO BE SOMETHING, BUT HERE SHE DIDN'T WRITE IT DOWN. AND SO BY HAVING THESE VALIDATION CENTERS, YOU ACTUALLY DISCOVER REALLY INTERESTING SCIENCE IN THE PROCESS OF DOING THE VALIDATION.

NOW, YOU'RE PROBABLY NOT GOING TO GET ANOTHER *NATURE* PAPER, YEAH. BUT IT'S NOT ONLY THAT IT'S CRITICAL FOR THE TRANSLATION AND REPRODUCIBILITY AND ALL THAT STUFF, BUT YOU ALSO DISCOVER REALLY INTERESTING REASONS THAT THINGS DON'T REPRODUCE. THAT'S WHAT SCIENCE IS. RIGHT? ONE THING WORKS, THE OTHER ONE DOESN'T. YOU WORK ON WHY. HMM, MAYBE IT'S, AS FINEMAN USED TO SAY, "THAT'S A DISCOVERY." BUT WHAT CIRM WOULD HAVE TO DO IS PLAY BAD COP HERE, AND WE'VE HAD TO DO THAT AND SAY THIS IS PART OF YOUR FUNDING AGREEMENT, THAT YOU ARE GOING TO WORK WITH THE VALIDATION CENTER. IT'S PART AND PARCEL IN THIS. THIS IS NOT VOLUNTARY EXERCISE.

DR. MILLAN: THANK YOU, CHRIS. SO WHEN WE TALK ABOUT HOTEL CALIFORNIA OR HOTEL NATIONAL OR INTERNATIONAL HOTEL, IT SOUNDS LIKE IT COULD ACTUALLY BE THE CONSORTIUM ITSELF, RIGHT, BECAUSE IT'S EMPOWERED BY ALL OF THE SCIENTISTS AND THE STANDARDS AND THE GENOMICS AND ALL THAT.



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DR. AUSTIN: YEAH. THE OTHER THING I SHOULD EMPHASIZE IS WE CREATED A DATA HUB THAT YOU CAN GO TO. SO YOU DON'T JUST HAVE TO -- YOU DON'T HAVE TO TRUST US TO SAY, YES, IT'S REPRODUCED. ALL THE DATA FROM THE INNOVATOR AND FROM THE VALIDATOR IS ALL THERE. AND SO IF YOU ARE GOING TO USE THIS PLATFORM, CAVEAT EMPTOR. YOU CAN SEE WHAT WORKED AND WHAT DIDN'T, AND YOU GO IN WITH EYES OPEN. I THINK THAT'S WHAT EVERYBODY WANTS.

DR. MILLAN: THAT'S RIGHT. IT'S NOT A PUNITIVE THING. IT'S ACTUALLY AN INCENTIVE TO BE PART OF THIS. MEMBERSHIP HAS ITS REWARDS, AND THAT'S BEING A MEMBER IN KIND OF THIS KNOWLEDGE NETWORK CONSORTIUM. THE REWARD IS YOU CAN HAVE A BETTER INFORMED RESEARCH AND HAVE A DENOMINATOR UPON WHICH TO BASE YOUR DECISIONS AND YOUR SCIENCE.

DR. DZAU HAS HIS HAND RAISED.

DR. DZAU: GREAT DISCUSSION. AND, PATRICK, I REALLY LIKE THE WAY YOU FRAMED THIS BROAD STROKES IN MANY DIFFERENT AREAS. CERTAINLY I TOTALLY SHARE THE ENTHUSIASM OF DEMOCRATIZATION OF DATA. CONDITION TO PLAY IS THAT YOU HAVE TO SHARE. I THINK THAT'S ABSOLUTELY TRUE.

AND I LOVE THE IDEA OF THE HOTEL CIRM CALIFORNIA. LET ME JUST BRING OUT SOME OF THE



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ISSUES YOU TALKED ABOUT WHICH I THOUGHT PARTICULARLY RESONATE WITH ME.

WHEN YOU TALK ABOUT EARLY INTERVENTION, PREVENTION, AND YOU TALK ABOUT PLASTICITY, WHAT YOU REALLY HAVE TO EMPHASIZE IS THAT MUCH OF OUR WORK IS SO FOCUSED ON REGENERATING THE CELL THAT WE WANT, WE FORGOT THE MICROENVIRONMENT THAT THESE CELLS FUNCTION AND HOW THEY GET INJURED EARLY. SO THE VASCULAR SIDE IS PARTICULARLY INTERESTING TO ME BECAUSE I'M A VASCULAR BIOLOGIST. AND THINKING THAT, INDEED, WHEN YOU THINK ABOUT NEURODEGENERATION, DEMENTIA, LARGE PART IS VASCULAR ABNORMALITIES. SO I THINK IT DOES CREATE QUITE A DIFFERENT WAY OF LOOKING AT THINGS.

SO MANY OF THE NEUROBIOLOGISTS ARE LOOKING AT FROM THIS NEUROCELL POINT OF VIEW, AND IT REQUIRED A LOT OF INTERSECTION AND COLLABORATION OF OTHER AREAS TO BE ABLE TO DO THIS KIND OF WORK. SO I JUST WONDER IF CIRM WOULD CONSIDER BROADENING, PARTICULARLY WHEN YOU LOOK AT ANY SPECIFIC AREA, YOU KNOW THAT WHEN YOU REGENERATE A CELL -- I WORK IN THE MITOCHONDRIAL AREA. IT DEPENDS IF YOU HAVE ENOUGH BLOOD SUPPLY FOR THAT CELL TO BE ABLE TO BE VIABLE AND, FOR THAT MATTER, REGENERATE OR EVEN PROLIFERATE. SO I THINK THIS IS A VERY INTERESTING

IDEA OF COLLABORATION ACROSS FIELDS.

NOW, CLEARLY IT'S NOT EASY. AND SECONDLY, AS YOU SAID, IN EARLY DISEASE IT'S SO DIFFICULT, THAT'S WHY PHARMAS DON'T GET INTO IT BECAUSE IT TAKES A LONG TIME TO MEASURE. WE ALL KNOW FOR A LONG TIME HOW DIFFICULT IT IS TO FIND BIOMARKERS AND MEASUREMENTS. SO I THINK THIS IS YET ANOTHER AREA THAT NEEDS TO BE DEVELOPED. SO THANK YOU FOR THOSE THOUGHTS.

DR. MILLAN: THANK YOU, VICTOR. AND THEN I'M GOING TO TAKE IN ORDER OUR PANELISTS, DR. SALLY TEMPLE AND THEN CAT JAMIESON, LESLIE THOMPSON AS OUR SPEAKERS.

DR. TEMPLE: THANK YOU. SO, LESLIE, WHAT YOU WERE TALKING ABOUT IN TERMS OF PUTTING TOGETHER CONSORTIA THAT ARE REALLY SPECIALIZED AROUND THE DISEASE AREA IS SEEN ALSO IN THE PARKINSON'S FIELD. THAT TOTALLY RESONATES WITH ME. I'VE BEEN INVOLVED IN A CONSORTIUM THAT'S AROUND FRONTOTEMPORAL DEMENTIA FOR A WHILE. WITHIN THE CONSORTIUM THERE ARE SUBGROUPS OF SPECIALISTS, EACH OF THEM WORKING ON DIFFERENT ASPECTS, INNOVATING CLINICAL TRIAL DESIGN OR BIOMARKERS, IMAGING, OR STEM CELL MODELING. AND IT REALLY DOES WORK TOGETHER BECAUSE THEN EACH GROUP IS MAKING PROGRESS AND THEN

COMBINING KNOWLEDGE.

AND PART OF THE STEM CELL ASPECT IS NOT JUST TO PROVIDE INFORMATION, BUT ACTUALLY TO PROVIDE RESOURCES. THIS CAN REALLY HELP PEOPLE WHO ARE GETTING INTO THE FIELD WHO DON'T KNOW HOW DIFFICULT IT IS TO GROW IPS CELLS AND STANDARDIZE THEM. THEY WANT TO HAVE AN ORGANOID TO WORK ON. THEY WANT TO HAVE NEUROPROGENITORS TO WORK ON.

SO ONE OF THE THINGS THAT WE'VE DONE IS CENTRALIZE PRODUCTION USING A SORT OF GLP-RELATED PROCESS. SO WE HAVE QC MEASURES, AND WE PRODUCE THESE PRODUCTS THAT ARE THEN SHIPPED OUT TO LABS THAT DON'T HAVE THEN TO INVEST IN ALL THAT FUNDAMENTAL. THEY KNOW THAT THEY'RE GETTING A MATERIAL THAT'S BEEN QC'D TO A STANDARDIZED AND ACCEPTED PROTOCOL.

I REALIZE THIS. IF WE GET CELLS FROM CLIVE, WE KNOW WHAT WE'RE GETTING. WE HAVE CONFIDENCE IN THAT, AND THAT REALLY CAN HELP BUILD RIGOR IN THE PROCESS. SO PERHAPS IT'S NOT JUST A KNOWLEDGE BASE, BUT REALLY RESOURCE DEVELOPMENT AND SHARING THAT COULD BE CENTRALIZED IN THESE CONSORTIA AS WELL.

DR. MILLAN: THANK YOU, SALLY. WE HAVE SOME KIND OF PRECURSORS TO THAT IN THAT WE HAD



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SHARED LABS FOR KIND OF TRAINING AND DIFFERENTIATION AND CULTURE TECHNIQUES THAT WAS CREATED IN THE FIRST ITERATION OF CIRM, AND PROP 14 CALLS FOR INVESTMENT IN SHARED LABS. BUT I THINK THAT WE COULD EVEN EXPAND ON THAT BASED ON THE IDEAS THAT HAVE BEEN CONSIDERED TODAY.

I'D LIKE TO GO TO OUR NEXT PANELIST FIRST -- SORRY, CAT -- GO TO DR. MUMMERY BECAUSE WE DO WANT TO MAKE SURE TO GET OUR PANELISTS, AND THEN WE'LL GET TO YOU, CAT. THANK YOU.

DR. MUMMERY: THIS IS TO ADD TO SALLY. I AGREE WITH HER ENTIRELY. ONE OF THE MISSING ASPECTS SOMETIMES IS GOOD CRYOPRESERVATION PROTOCOLS. SO WHAT ARE THE GOOD SURVIVAL AND CHANGING FUNCTION OF THE THAW, WHAT STAGE DO YOU THAW THEM. AND THIS IS ALL PART OF THE PROCEDURE, AND PARTICULARLY WHEN YOU'RE WORKING IN MULTIDISCIPLINARY CONSORTIA. AN ENGINEER DOESN'T WANT TO GO AND HAVE TO DIFFERENTIATE HIS OWN CELLS OR HER OWN CELLS. YOU'VE GOT TO SEND THEM A VIAL OR EVEN A PLATE OF CELLS WITH THE CELLS FROZEN ON IT TO DO THE MEASUREMENTS YOU WANT. AND THERE'S A LOT OF TECHNOLOGY DEVELOPMENT THERE THAT WOULD MAKE THE WHOLE THING MUCH EASIER IF EVERYBODY WASN'T REDISCOVERING THE WHEEL.

DR. MILLAN: THANK YOU. AND THAT ALSO PROVIDES FOR A GREATER EVIDENCE BASE FOR EVEN THE COMPONENTS AND THE MATERIALS THAT ARE BEING USED. THAT'S A VALUE ALSO. I KNOW THAT PETER MARKS HAS MADE THAT POINT MANY TIMES.

AND THEN I'M GOING TURN TO CAT JAMIESON.

DR. JAMIESON: JUST BRIEFLY. I REALLY LIKE THE IDEA OF THE SPOKE-AND-WHEEL MODEL AND THE IDEA OF INTERCEPTION. THAT'S SOMETHING THAT'S COMING TO THE FORE. I WOULD SAY THE ULTIMATE VALIDATION OF ALL OUR DATA IN THE LAB IS, AT LEAST IF IT'S FOCUSED ON HEALTH, WOULD REALLY BE HOW IT WORKS IN THE CLINIC. AND IF WE CAN HAVE A CALIFORNIA INSTITUTE FOR STEM CELL HEALTH, WE WERE TALKING ABOUT HOW WE'RE STARTING TO GROW OUR HEALTH SYSTEMS, AND WE HAVE THE OPPORTUNITIES TO LOOK AT STEM CELL HEALTH REALLY IN A TRACTABLE WAY NOW THAT WE HAVE THE ALPHA CLINICS AND SCIENTISTS WORKING TOGETHER WITH CLINICIANS, WE CAN HAVE KICHE THAT COLLABORATES WITH THE NICHE, A NATIONAL INSTITUTE OF STEM CELL HEALTH.

SO WE CAN REALLY START TO COLLABORATE ON THE VERY EARLIEST STAGES OF DEGENERATION OF TISSUES BASED ON STEM CELL ASPECTS OF DISEASE. AND THAT INTERCEPTION STRATEGY THAT LIZ BLACKBURN REALLY



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BROUGHT TO THE FORE FOR CANCER I THINK IS MAKING MAJOR INROADS INTO HOW WE REALLY DEVELOP STRATEGIES THAT ARE POTENTIALLY CURATIVE. OF COURSE, THIS STARTED WITH GEORGE DALEY. I HAVE TO PUT YOU ON THE SPOT, GEORGE, WITH YOUR 1990 PAPER WITH DAVID BALTIMORE AND RICK VAN ETTEN ON THE DISCOVERY PCR-ABLE. THAT TAUGHT US THAT WE HAD TO INTERVENE EARLY FOR DISEASES LIKE LEUKEMIA. AMY WAGERS TAUGHT US THAT THERE'S ACTUALLY LITTLE EVIDENCE FOR PLASTISSUE IN TISSUE-SPECIFIC STEM CELLS. GREAT. BECAUSE IF THEY HAD A LOT OF PLASTICITY, THEY'D BE MALIGNANT. AND THEN DERRICK ROSSI TAUGHT US THAT WE CAN USE STEM CELL TECHNOLOGIES FOR ENTIRELY DIFFERENT PURPOSES.

AND A NUMBER OF US HAVE BEEN VACCINATED. I CURSE THE SECOND VACCINE FROM MODERNA, BUT THAT TECHNOLOGY INITIALLY DEVELOPED FOR REPROGRAMMING.

SO I THINK THAT WE CAN LOOK AT THE TECHNOLOGIES WE'VE DEVELOPED VERY BROADLY, BUT I REALLY LIKE THE IDEA OF EARLY INTERVENTION OR THE TERM "INTERCEPTION" WHEN IT COMES TO STEM CELL HEALTH. AND A LOT OF US ARE ON BOARDS AND HAVE OPPORTUNITIES TO HELP CREATE THE NEXT WAY WE LOOK AT HEALTHCARE FROM AN ACCESSIBILITY, AFFORDABILITY, ECONOMY OF SCALE STANDPOINT, BUT FROM A STEM CELL

STANDPOINT. AND THAT'S WHAT I'M GETTING FROM THE CONVERSATIONS TODAY.

DR. MILLAN: THANK YOU SO MUCH, CAT. AMY AND THEN LESLIE.

DR. WAGERS: SORRY, LESLIE. I WANTED TO SAY TWO THINGS. ONE, I THINK EVERYONE ON THE CALL RECOGNIZES THAT MAYBE IT BEARS JUST SAYING AS WE'RE TALKING ABOUT STANDARDIZATION, WHICH I DO STRONGLY BELIEVE IS AN IMPORTANT ASPECT TO FURTHER DEVELOPMENT, BUT I GUESS STANDARDIZATION WITH THE IDEA THAT WE ALWAYS KEEP IN OUR MINDS THAT THIS IS STILL A REALLY YOUNG FIELD, AND THERE ARE STILL A LOT OF NEW DISCOVERIES TO BE HAD. AND SO NOT SORT OF ENCASING THAT IN CONCRETE TOO EARLY AND BEING SURE THAT WHATEVER APPROACH WE WOULD INSTALL HAS THE POSSIBILITY FOR CONTINUOUS EVOLUTION AND QUALITY ENHANCEMENT AND EVEN NEW DIRECTIONALITY IN THE FACE OF NEW EFFORTS.

YOU SET UP A VERY HIGHLY STANDARDIZED PROCESS THAT CAN LEAD TO SOME SQUELCHING OF NEW INNOVATION BECAUSE THERE'S A FEELING FOR NEWCOMERS TO THE FIELD THAT THIS IS ESTABLISHED. I KNOW EVERYONE ON THE CALL RECOGNIZES THAT. I JUST THOUGHT IT MIGHT BE WORTH SAYING THAT WE SHOULD BE THOUGHTFUL ABOUT ENSURING THAT ARM OF INNOVATION

CONTINUES BECAUSE I THINK THERE'S STILL A LOT TO BE LEARNED.

THE SECOND POINT I WANTED TO RAISE ACTUALLY KIND OF CONNECTS BACK TO WHAT VICTOR HAD SAID ABOUT THE MICROENVIRONMENT AND ALSO TO THE IDEA OF CONSORTIA. I WAS STRUCK BY THE PIE CHARTS THAT WERE PRESENTED AT THE BEGINNING, ALSO BY THE STRATIFICATION BY ORGAN TYPE AND BY THE DISCUSSION AROUND DISEASES. AND IT OCCURS TO ME THAT THERE ARE SOME OPPORTUNITIES FOR SYNERGY ACROSS ORGANS AND ACROSS DISEASE TYPES. AND WITH THIS CONCEPT OF EARLY INTERVENTION AND THE SORT OF BATTLE BETWEEN REPAIR AND FIBROSIS, THERE MAY BE SOME OPPORTUNITIES FOR CONSORTIA THAT ARE LOOKING AT COMMONALITIES OF SCARRING, COMMONALITIES OF TISSUE REMODELING THAT ARE ACTUALLY INHIBITORY TO REGENERATION ACROSS SYSTEMS. AND THERE MAY BE SOME OPPORTUNITIES THERE TO GET INVESTIGATORS IN DIFFERENT ORGAN SYSTEMS AND DIFFERENT DISEASE MODELS WORKING TOGETHER ON THAT PROBLEM, WHICH IS STILL A REALLY DIFFICULT ONE AND LARGELY INTRACTABLE ONCE DISEASES ARE QUITE ADVANCED.

DR. MILLAN: THANK YOU, AMY. SO YOU RAISE THE IDEA OF OTHER THEMATIC TYPE OF CONSORTIA VERSUS DISEASE INDICATIONS, AND THAT COULD BE ACCOMPLISHED

IN DIFFERENT WAYS, EITHER ACROSS CONSORTIA TYPE CONNECTIVITY OR SPECIAL PURPOSE TYPE CONSORTIA, PARTICULARLY IN NEURODEGENERATIVE DISEASE WHERE THERE ARE SOME POTENTIAL PATHWAYS THAT ARE VERY MUCH SHARED ACROSS THE DIFFERENT PATHOLOGIES.

AND THEN JUST I KNOW THAT WE HAD ANOTHER PANELIST WHO WANTED TO -- JUST GO AHEAD AND PIPE IN NOW. WE HAVE ONE MORE MINUTE FOR ADDITIONAL COMMENTS. AND THEN CLIVE AND OTHERS, LESLIE DIDN'T GET A CHANCE TO TALK, WE WILL HAVE AN OPPORTUNITY DURING THE NEXT SESSION IF YOU CAN HOLD ON. ANY OTHER PANELIST WANT TO ADD ANYTHING AT THIS POINT? IF NOT, CLIVE AND LESLIE CAN SHARE THE MINUTE.

DR. SVENDSEN: I JUST WANT TO SECOND WHAT AMY WAS SAYING. LESLIE, DO YOU WANT TO GO FIRST?

DR. THOMPSON: IT'S SUPER MINOR. VERY QUICK. JUST WHEN WE WERE TALKING ABOUT VALIDATION, FIRST OF ALL, I REALLY APPRECIATE WHAT YOU SAID, AMY. I THINK THAT'S VERY IMPORTANT. WHEN WE WERE TALKING ABOUT VALIDATION ACROSS LABS OR SUBSEQUENT VALIDATIONS, JUST KEEPING IN MIND ALSO IF THAT INVOLVES MOUSE EFFICACY STUDIES, FOR INSTANCE, TO KEEP THE MICROBIOME IN CONSIDERATION AND DIFFERENCES ACROSS LABS AND ACROSS INSTITUTIONS WITH HOW ANIMALS RESPOND TO SOME OF THESE THERAPIES. JUST A QUICK

NOTE.

DR. SVENDSEN: JUST TO FINISH UP AND JUST TO FOLLOW UP FROM AMY'S COMMENTS, REALLY RIGHT. I'M A ZOOLOGIST BY TRAINING. AND EVOLUTION HAPPENS THROUGH SOMETHING CALLED PUNCTUATED EQUILIBRIUM, WHICH MEANS IT'S SMALL ISLANDS OF EVOLUTION OCCUR RAPIDLY AND THEN THEY SPREAD OUT TO THE COMMUNITY. AND WE HAVE TO HAVE THOSE SMALL ISLANDS OF INNOVATION. WE SHOULD BE FUNDING THOSE FOR SURE. IT'S JUST WHEN YOU FIND THAT BIG THING, RIGHT, IT'S VALIDATING IT, AMY. THAT'S WHERE I THINK THE POWER IS. IF YOU SAY YOU'VE GOT THE BEST PROTOCOLS FOR MAKING EPITHELIAL CELLS, WELL, SEND THE FROZEN TUBES, WHICH I AGREE A HUNDRED PERCENT, CHRISTINE. IF YOU CAN FREEZE YOUR PRODUCT AND THEN JUST THAW IT AND PUT IT ON THE CHIP OR THAW IT AND PUT IT IN THE DISH, SEND A HUNDRED OF THOSE TUBES TO TEN PLACES AND SHOW THEY WORK, AND THEN YOU'VE GOT IT, AND THEN PAY FOR HUGE MANUFACTURING OF THAT PRODUCT WITHOUT STOPPING THE INNOVATION GOING ON FOR THE NEXT.

IT'S LIKE THE IPHONE. WE NEVER STOPPED WITH IPHONE 1. I'M ON IPHONE 11 NOW. WE HAVEN'T EVEN GOTTEN IPHONE 1 YET FOR BRAIN ENDOTHELIAL CELLS, WHICH I WORK ON FOR THE BBB. EVERYBODY HAS A DIFFERENT TYPE. THERE'S LOTS OF ARGUMENTS. IS IT



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RIGHT? IS IT WRONG? WE'VE GOT TO START SOMEWHERE, GET GRANULARITY ON ONE PRODUCT, DISTRIBUTE IT AND TEST IT AND THEN KEEP ITERATING.

DR. MILLAN: THANK YOU.

DR. MUMMERY: -- MATERIAL.

DR. MILLAN: IT'S 10:01, AND WE ARE SCHEDULED FOR A BREAK. THANK YOU, EVERYBODY, FOR HANGING ON. YOU'RE ALL TROOPERS. WE WILL RECONVENE AT 10:15, WHICH ACTUALLY MEANS A 15-MINUTE BREAK. WE'RE ACTUALLY PRETTY GOOD. YOU CAN HAVE A CUP OF COFFEE TOO. WE'LL SEE YOU BACK HERE AT 10:15 PACIFIC TIME. THANK YOU SO MUCH.

(A RECESS WAS TAKEN.)

DR. MILLAN: OKAY. WELL, IT'S 10:16, AND I THINK WE'RE GOING TO BE READY TO START. WE'LL JUST HAVE OTHERS KIND OF JOIN AS THEY ARE AVAILABLE. OKAY. SO THANK YOU SO MUCH, EVERYBODY, FOR RETURNING FROM BREAK.

WE'RE GOING TO GO AHEAD AND START THIS SECTION OFF WITH DOUG KERR. DOUG.

DR. KERR: THANK YOU. GREAT TO BE HERE. GREAT TO SEE SOME FRIENDS, MANY OF WHOM I HAVEN'T SEEN BY ZOOM OR LIVE FOR QUITE A WHILE.

I'VE BEEN INVOLVED WITH CIRM FOR, I DON'T KNOW, PROBABLY 15 YEARS AND HAVE REALLY LOVED THE

OPPORTUNITIES TO REVIEW GRANTS AND TO REALLY THINK ABOUT THE STRATEGIC MISSION OF CIRM. I AM A NEUROLOGIST, NEUROSCIENTIST, ACADEMIC CAREER REALLY IN STEM CELL BIOLOGY AND MOTOR NEURON PLASTICITY FOR A WHILE, AND THEN THE LAST 15 OR 17 YEARS REALLY ON THE BIOTECH SIDE. AND I'M NOW THE CHIEF MEDICAL OFFICER AT A GENE THERAPY COMPANY CALLED GENERATION BIO, WHICH IS BASED IN CAMBRIDGE, MASSACHUSETTS.

AND REALLY JUST A FEW THINGS TO CHAT ABOUT OVER MY FEW MINUTES. WHAT I'VE DONE REALLY IN KIND OF PREPARING FOR THIS IS GO BACK OVER THE LAST 15 YEARS AND REALLY LOOK AT SOME OF THE VERY EARLY GENE AND CELL THERAPY COMPANIES ESSENTIALLY FROM THE BIOTECH SIDE OF IT AND TO FIGURE OUT WHAT'S HAPPENED, HOW HAVE THOSE THINGS PROGRESSED OR NOT; AND IF THEY HAVEN'T PROGRESSED, WHY NOT.

AND CIRM HAS BEEN REALLY IMPORTANT IN PROFESSIONALIZING THIS VERY YOUNG ASPECT OF THERAPY DEVELOPMENT. AND CIRM REALLY FROM THE GET-GO REALLY DEMANDED SOME RIGOR IN TERMS OF THE CMC AND THE MECHANISM OF ACTION AND THE PROPOSED HYPOTHESIS. AND I THINK THAT HAS DONE A REAL SERVICE TO THE COMMUNITY. BUT YOU LOOK BACK TO THOSE HEADY, EARLY DAYS AROUND 2000, FIRST DECADE OF THE 21ST CENTURY, AND WE PROBABLY WERE IRRATIONALLY EXUBERANT IN WHAT

WE THOUGHT STEM CELLS AND CELL-BASED THERAPIES AND EVEN GENE THERAPY COULD DO.

MANY OF THOSE, MOST OF THOSE, SOME WOULD ARGUE ALMOST ALL OF THEM, HAVE FAILED TO ADVANCE. AND SO IT KIND OF BEARS, AS WE EMBARK UPON A NEW CIRM, TO REALLY THINK ABOUT WHAT WE CAN DO TO EVEN FURTHER INCREASE THE LIKELIHOOD OF SUCCESS IN CELL- AND GENE-BASED THERAPY PROGRAMS.

THERE ARE LOTS OF EXAMPLES OF THIS. THERE ARE A COUPLE THAT ARE OF RELEVANCE TO CIRM. FOR EXAMPLE, BRAINSTORM THERAPEUTICS WAS A PROGRAM THAT WAS FUNDED THROUGH CIRM AND RECENTLY HAD A READOUT IN ALS THAT FAILED TO MEET ITS PRIMARY EFFICACY. THE STORY IS NOT YET COMPLETELY WRITTEN ON THAT. THERE ARE SOME SUBGROUP ANALYSES THAT ARE ONGOING, BUT IT DOES BEAR A KIND OF RETROSPECTIVE, ALMOST POSTMORTEM OF WHAT DID WE THINK AT THE TIME? COULD WE HAVE DONE ANYTHING MORE TO BE EVEN MORE RIGOROUS IN THAT PROGRAM, WHICH MANY OF US HAVE REVIEWED AND WERE EXCITED ABOUT, BUT REALLY HASN'T QUITE MEASURED UP TO WHAT WE THOUGHT.

THERE ARE OTHER EXAMPLES. MANY OF US WERE INVOLVED IN THE EARLY DAYS OF GERON TO ASTERIAS AND A SERIES OF ITERATIONS THAT OPC STEM CELL-BASED SPINAL CORD INJURY FIELD HAS GONE THROUGH. AND TO

SOME DEGREE THE LIMITATIONS OF THOSE WERE POTENTIALLY CMC, BUT ALSO MAYBE NOT PERFECTLY CLEARLY IDENTIFIED MECHANISM OF ACTION IN WHICH THESE CELLS WOULD LEAD TO SOMETHING SPECIFICALLY IN THE NERVOUS SYSTEM THAT WOULD LEAD TO ENHANCED FUNCTIONALITY.

CLIVE HAS BEEN IN THIS SPACE FOR A LONG TIME AND HAS DONE A REALLY GOOD JOB OF BEING VERY CLEAR ON THE PROPOSED MECHANISM OF ACTION AND THEN INTERROGATING WHETHER OR NOT THESE CELLS TRANSPLANTED INTO THE NERVOUS SYSTEM ARE TRULY GETTING AT THAT MECHANISM OF ACTION. BUT OTHERS MAYBE NOT AS MUCH, AND THAT LEAVES YOU WITH A LOT OF UNCERTAINTY AS YOU GO INTO THE CLINICAL PROGRAM. AND THEN WHAT'S EVEN WORSE IS YOU'RE NOT SURE AT THE END OF IT WHETHER YOU EVER REALLY INTERROGATED THAT HYPOTHESIS.

AND SO I THINK THAT HAS HAMPERED THE FIELD, AND I THINK THERE'S AN OPPORTUNITY TO BE MORE RIGOROUS AS WE EVALUATE PROGRAMS COMING FORWARD THAT WILL BUILD IN THESE THINGS IN WHICH VERY EARLY ON IN THE PROGRAM YOU CAN KNOW WHETHER OR NOT YOU'RE INTERROGATING A SPECIFIC HYPOTHESIS. AND IF NOT, WALK AWAY.

AND I THINK THAT'S GOING TO BE REALLY



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IMPORTANT. OBVIOUSLY THE NUMBER OF DISEASES, THE MAGNITUDE OF THIS PROBLEM, AND REALLY GETTING A GRIP ON IT WITH RESPECT TO REGENERATIVE THERAPIES IS CRITICAL. AND I WILL SAY THAT OVER THE LAST TWO TO THREE YEARS THE BIOTECH SIDE, THE PHARMA SIDE HAS REALLY TICKED UP IN TERMS OF FUNDING. AND SO FOR A LONG PERIOD OF TIME, THIS HAD EMERGED OUT OF ACADEMIC AND CONSORTIA THAT WERE DOING THIS TO SOME DEGREE WITHOUT SUFFICIENT BIOTECH/PHARMA SUPPORT. THAT IS STARTING TO CHANGE.

JUST AS AN EXAMPLE, FUNDING OF $13 BILLION IN 2020, WHICH IS A HUNDRED-PERCENT INCREASE OVER THE PREVIOUS YEAR IN BIOTECH, VENTURE CAPITAL, PHARMA FUNDING FOR REGENERATIVE CELL-BASED THERAPIES. AND THAT'S 12 IPO'S AND A BUNCH OF OTHER METRICS THAT SAY THAT IT'S REALLY STARTING TO HIT KIND OF PRIME TIME IN TERMS OF SERIOUS MONEY AND SERIOUS CASH.

BUT JUST TO GO BACK FOR THE LAST FEW MINUTES. WE'VE HAD SOME FAILURES AS A LOT OF GROUPS DO, BUT WHY? I MEAN THE BRAIN IS OBVIOUSLY INCREDIBLY COMPLEX, MAYBE THE MOST COMPLEX ORGAN, A HUNDRED TRILLION CONNECTIONS IN THE CENTRAL NERVOUS SYSTEM. WE'VE TALKED ABOUT IT ALREADY TODAY, THAT THERE IS THIS KIND OF ABERRANT AND PROBABLY

INAPPROPRIATE CLUSTERING OF CNS DISORDERS UNDER A SINGLE NAME LIKE PARKINSON'S DISEASE, LIKE ALS. THEY ARE VERY CLEARLY DISTINCT DISORDERS WITH DISTINCT PATHOPHYSIOLOGY. AND SO TO DO A TRIAL IN WHICH YOU ARE LOOKING AT A SPECIFIC MECHANISM UNDER THIS KIND OF VARIABLE PATHOPHYSIOLOGY IN THOSE DISEASES, IT'S A RECIPE FOR DISASTER, AND IT'S JUST NOT GOING TO WORK.

WE TALKED ABOUT HOW VAGUELY DEFINED MECHANISMS OF ACTION ARE VERY CHALLENGING; AND THAT IF WE HAD A BETTER SENSE, A MORE RIGOROUS SENSE OF WHAT THE MECHANISM OF ACTION IS AND BUILT IN BIOMARKERS TO KNOW WHETHER WE HAVE ENGAGED OUR TARGET AND WHETHER WE HAVE HAD SOME DOWNSTREAM PHARMACODYNAMIC CONSEQUENCE THEREOF IS REALLY CRITICAL BECAUSE THE LAST THING YOU WANT IS A LATE-STAGE, UNCERTAIN FAILURE. WHAT YOU WOULD RATHER DO IS KNOW RIGHT UP FRONT THAT YOU DIDN'T HAVE THE EFFECT THAT YOU THOUGHT YOU WERE BASED ON A BIOCHEMICAL MARKER AND WALK AWAY BECAUSE THERE'S LIMITED RESOURCES. AND WE'VE GOT TO BE ABLE TO MOVE THOSE LIMITED RESOURCES INTO THINGS THAT ARE INCREDIBLY EXCITING.

I WILL SAY ONE OF THE OTHER THINGS THAT HAS TIPPED THE SCALE TOWARD BIOTECH AND PHARMA



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INVESTMENT AND VENTURE CAPITAL IN A BIG WAY, THERE ARE SEVERAL THINGS, ONE OF WHICH WE TALKED ABOUT, GENETICS AND GENOMICS TO REALLY IDENTIFY BONA FIDE TARGETS FOR NEURODEGENERATIVE OR NEURODEVELOPMENTAL DISEASES AND SUBSETS OF PATIENTS. THAT FEELS LIKE A CLEANER POPULATION TO STUDY, MUCH MORE LIKELY TO GET A LEGITIMATE READOUT.

ONE OF THE THINGS THAT WE DID VERY EARLY ON WHEN I WAS WORKING ON A PROGRAM THAT BECAME SPINRAZA FOR SPINAL MUSCULAR ATROPHY IS WE SPENT AN AWFUL LOT OF TIME THINKING ABOUT BIODISTRIBUTION, WHERE EXACTLY THE MATERIAL WENT, DID IT GET INTO THE TISSUE IN ENOUGH CONCENTRATION TO HAVE A THERAPEUTIC EFFECT. WE DID THAT IN MICE, WE DID THAT IN NONHUMAN PRIMATES, WE ACTUALLY DID THAT IN HUMANS AS WELL FROM SOME EARLY CLINICAL TRIAL PATIENTS WHO DIED AND WE WERE ABLE TO INVESTIGATE WHETHER OR NOT THE THERAPY THAT BECAME SPINRAZA WAS THERE AND WAS HAVING AN EFFECT. AND IT GAVE US THIS OPPORTUNITY TO THINK REALLY DEEPLY ABOUT WHETHER OR NOT WE SHOULD CONTINUE THIS, THE DOSING, AND THE INTERVAL AT WHICH WE SHOULD DOSE.

ONE FINAL POINT. WE'VE TALKED ABOUT IT ALREADY, BUT PRECOMPETITIVE SPACE IS SOMETHING THAT IS REALLY, I THINK, A FERTILE GROUND FOR



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LONGITUDINAL, DATA RICH, NATURAL HISTORY STUDIES. AND THERE ARE LOTS OF EXAMPLES WHERE THIS ALLOWS YOU TO REALLY UNDERSTAND VARIOUS COMPANIES COMING IN, PLAYING A ROLE, USING BIOMARKERS TO DEFINE SUBSETS WITHIN THAT POPULATION, AND ALLOWING EACH OF THOSE COMPANIES THEN TO DEVELOP BETTER THERAPIES. AND I THINK THAT'S A KEY POINT.

SO THAT'S MY TIME. I THINK I WENT A LITTLE BIT OVER, BUT HOPE THAT STIMULATED SOME CONVERSATION.

DR. MILLAN: THANK YOU, DOUG. ANY QUESTIONS OR ANY COMMENTS FROM THE PANELISTS? PLEASE GO AHEAD AND SPEAK UP. I CAN'T SEE EVERYBODY'S HANDS RAISING AT THIS POINT.

WHILE EVERYBODY IS GATHERING THEIR THOUGHTS, I JUST HAVE A QUESTION, DOUG. YOU HAD MADE A STATEMENT REGARDING MECHANISM OF ACTION AS BEING SOMETHING THAT'S KIND OF IDEAL. AND ACTUALLY REGENERATIVE MEDICINE GENE THERAPY AND, ARGUABLY, STEM CELL THERAPY OR CELL THERAPY DOES HAVE THAT OPPORTUNITY THAT OFTEN THE TRADITIONAL SMALL MOLECULES DID NOT. I THINK THAT THAT IS -- THE BIOLOGY IS -- SOME PART OF THE BIOLOGY IS THE MECHANISM OF ACTION.

BUT OFTEN KIND OF THE IDEA OF HOW THIS

PLAYS OUT IN PEOPLE WHEN YOU HAVE THE OTHER PARTS OF PHYSIOLOGY KICK IN AND EVERYTHING ELSE, EVEN WHEN YOU TALK ABOUT GENETICS AND EPIGENOMIC ENVIRONMENTS AND EVERYTHING KICK IN IS WHEN YOU REALLY START TO GET THE SIGNAL. HOW DO YOU BALANCE THAT WITH SAYING, OKAY, THIS IS WHAT WE THINK IS THE GUIDEPOST, AND THIS IS WHAT WE ARE AIMING FOR; BUT AS OFTEN HAPPENS, YOU MAY BE GOING ALONG AND YOU MAY FIND SOMETHING DIFFERENT THAT ACTUALLY LEADS YOU TO HOME RUN EVENTUALLY OR MAYBE YOU DON'T FIND IT AT ALL, BUT HOW DO YOU TAKE THAT APPROACH OF MAKING SURE YOU HAVE A PRETTY FIRM IDEA OF UNDERSTANDING, BUT NOT NECESSARILY, SPEAKING TO A POINT THAT AMY WAGERS HAD BROUGHT UP IN TERMS OF THE FIELD AND THE APPROACHES ARE SO NEW, SCIENCE IS GOING TO KEEP HAPPENING EVEN AS WE'RE DOING CLINICAL TRIALS BECAUSE IT IS SO NEW WITH THESE TYPES OF INTERVENTIONS. DO YOU HAVE ANY THOUGHTS ON THAT, DOUG?

DR. KERR: IT'S HARD. IT'S A GOOD QUESTION. IT'S A COMPLICATED QUESTION. WHEN DO YOU FEEL LIKE KIND OF YOU HAVEN'T HIT THE TARGET AND IT'S TIME TO MOVE ON VERSUS LEARNING IN THE CLINIC. AND SOMETIMES YOU FIND THINGS THAT YOU DIDN'T EXPECT. I GUESS MY POINT IS YOU CAN DO BOTH.



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RIGHT. YOU REALLY WANT TO MAKE SURE THAT YOU'RE ENGAGING THE TARGET AND THAT YOU'RE HAVING SOME PHARMACODYNAMIC EFFECT DOWNSTREAM OF THAT. YOU DON'T KNOW IF THAT'S GOING TO LEAD TO A CLINICAL CONSEQUENCE. THAT'S WHY YOU HAVE TO DO THE TRIAL.

BUT IF THE CELLS AREN'T ALIVE OR YOU HAVEN'T ACTUALLY ALTERED THAT BIOCHEMISTRY OR YOU HAVEN'T SEEN ANY EARLY SIGNS OF ALTERED CLINICAL FUNCTIONAL CONNECTIVITY, WHATEVER, THEN IT'S PROBABLY TIME TO RETHINK THE HYPOTHESIS OR REDEFINE IT MORE CLEARLY.

DR. MILLAN: THANK YOU SO MUCH. SO MEANING THAT THERE SHOULD BE AT LEAST AN ACTIVE INGREDIENT WHICH YOU ACTUALLY HAVE PLAUSIBLE BIOLOGY FOR, AND THEN YOU DO THE CLINICAL RESEARCH.

DR. MUMMERY, THANK YOU SO MUCH. YOU HAVE A QUESTION OR COMMENT?

DR. MUMMERY: I JUST WONDERED WHETHER WE WERE MISSING THE RIGHT SORT OF IMAGING POSSIBILITIES FOR IN VIVO. CAN WE LOOK AT THE FATE OF CELLS RATHER THAN JUST STICKING IRON PARTICLES IN THAT MACROPHAGES EAT UP? WE NEED BETTER CELL LABELING TECHNIQUES, AND MAYBE WE NEED BETTER TECHNIQUES TO BE ABLE TO MONITOR WHERE OUR GENE THERAPY CONSTRUCTS GO, CERTAINLY IN THE EARLY PHASES. AND THERE MAY BE



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SOME SPACE TO DEVELOP BETTER IMAGING MODALITIES.

AND I WAS THINKING THINGS LIKE SOME OF THIS ULTRAFAST ULTRASOUND. YOU CAN GET BEAUTIFUL NANOMETER MEASURES OF CAPILLARIES. SO IF YOU'VE DONE SOME TRANSPLANTATION OR SOMETHING, YOU WANT VASCULATURE. AND THERE ARE NONINVASIVE WAYS THAT YOU CAN REPETITIVELY MONITOR PATIENTS.

SO MAYBE THERE'S SOME SPACE FOR DOING THAT AND ALSO SPACE FOR LOOKING AT NEW BIOMARKERS OF FUNCTION.

DR. MILLAN: THANK YOU, DR. MUMMERY. TO FOLLOW UP ON THAT, AND I'LL LET DR. KERR RESPOND TO THAT, WE HAVE LOOKED AT IMAGING IN THE CONTEXT OF CLINICAL TRIALS THEMSELVES, BUT NOT ACTUALLY DONE, I DON'T BELIEVE, AND GIL SAMBRANO IS ON SO HE CAN CORRECT ME, WHERE A PROJECT IS SPECIFICALLY ABOUT THE IMAGING ITSELF. SO IT'S AN INTERESTING POINT YOU MAKE, BUT YOU SAY -- I THINK WHAT YOU WERE SAYING, AND YOU CAN CORRECT ME, IS THAT THAT'S SUCH A CRITICAL PIECE THAT THAT IN ITSELF IS RELEVANT TO THE RESEARCH BECAUSE IT'S ENABLING. AND WE DO HAVE TOOLS AND TECHNOLOGY AWARDS IN EARLY STAGE DEVELOPMENT; BUT IN TERMS OF CLINICAL TRIALS, OUR CLINICAL PORTFOLIO, OUR ACTIVE ONE APPARENTLY DOES NOT HAVE THAT.

DR. MUMMERY: IT'S REALLY ESSENTIAL TO BE ABLE TO MONITOR IN REAL TIME WHAT'S HAPPENING IN THE TISSUE. AND WE NEED A NEW GENERATION OF IMAGING MODALITIES, I THINK.

DR. MILLAN: THANK YOU SO MUCH. DOUG, DID YOU WANT TO SAY SOMETHING TO THAT?

DR. KERR: I THINK IT'S A REALLY GOOD POINT. I THINK IT'S SOMETIMES AN ORTHOGONAL SKILL SET, THAT REALLY THINKING ABOUT PET LIGANDS OR NOVEL SPIN LABELING, IMAGING TECHNIQUES IS NOT SOMETHING THAT THE BIOLOGISTS HAVE AT THEIR DISPOSAL. AND SO CIRM CAN REALLY HELP TO BRING IN THAT OTHER TECHNOLOGY THAT WOULD ENABLE TO DERISK A PROGRAM EARLY IN ITS DEVELOPMENT.

DR. MILLAN: THANK YOU. ARE THERE ANY OTHER COMMENTS OR QUESTIONS FROM THE PANELISTS?

DR. DALEY: MAY I JUST ASK DOUG. YOU TALKED ABOUT THE UNIQUE CHALLENGES OF SPINRAZA, LOOKING AT BIODISTRIBUTION AND THE LIKE. JUST WONDERING IS IT WORTH THINKING ABOUT CRITICAL ENABLING TECHNOLOGIES OR COMPETENCIES THAT CIRM COULD PROVIDE AS A CORE FOR ACADEMICS AND EARLY STAGE BIOTECH START-UPS THAT WOULD BE EXCESSIVELY EITHER EXPENSIVE OR CHALLENGING, BUT COULD BE CENTRALIZED AND HAVE SOME ECONOMIES OF SCALE? I'M

THINKING IN THE KIND OF CELLULAR EQUIVALENT OF DMPK OR ADMI. HAVE YOU THOUGHT ABOUT THAT?

DR. KERR: YEAH. I WAS GOING TO THINK OF THE EXACT SAME THING, GEORGE. I THINK THAT'S A REALLY GOOD POINT. THINGS LIKE ADMI, LIKE REALLY WHAT HAPPENS TO YOUR THERAPY IN THE BODY? WHAT TISSUES DOES IT GO TO? HOW QUICKLY IS IT METABOLIZED? HOW LONG DOES IT STAY THERE? THAT'S ONE, RIGHT, THAT A LOT OF YOUNG COMPANIES AND CERTAINLY ACADEMIC GROUPS DO NOT HAVE THE SKILL SET TO REALLY INTERROGATE THAT. IT'S KIND OF A BLACK BOX. ONCE IT GOES IN VIVO, IT'S LIKE, OKAY, YOU HOPE IT WORKS.

ANOTHER ONE IS THAT YOU WOULD THINK ALMOST MIGHT BE A CORE FACILITY WOULD BE KIND OF DOWNSTREAM BIOMARKERS. RIGHT? WE SPENT AN AWFUL LOT OF TIME LOOKING AT EXOSOMES AND EXOSOME-BASED TRANSCRIPTIONAL ALTERATIONS TO SAY, IN THE NERVOUS SYSTEM, HAVE WE ALTERED THIS TRANSCRIPT AS DEFINED BY EXOSOMES CAPTURED FROM THE CSF? THEY GET AN AWFUL LOT. MOST GROUPS, I DON'T THINK, HAVE THE CAPACITY TO DO THAT, BUT YOU CAN IMAGINE THAT BEING A REALLY IMPORTANT EARLY INDICATOR. SO THOSE TYPES OF CORE FUNCTIONS FEEL LIKE THERE WOULD BE SOMETHING FOR CIRM TO DO HERE.

DR. DALEY: LACK OF ACCESS TO THAT OR THE EXPENSE OF THOSE KINDS OF CHARACTERIZATIONS, I THINK, DO ACT AS A HINDRANCE TO ACADEMICS TRANSLATING SOME OF THEIR WORK. SO IT'S WORTH THINKING ABOUT, BUILDING THAT AS SOME KIND OF A CIRM CORE.

DR. MILLAN: THANK YOU SO MUCH. I WANTED TO CALL ON DR. JOSH SANES TO COMMENT ON SOMETHING THAT WE HADN'T TALKED ABOUT SO MUCH HERE BECAUSE WE'RE TALKING ABOUT ESSENTIAL MECHANISMS OF ACTION AND WE'RE TALKING ABOUT CNS. SO, DR. SANES, IF YOU COULD WEIGH IN IN TERMS OF CIRCUITRY, ARE THERE WAYS TO LOOK AT THAT EARLY ON? HOW DOES IT PLAY INTO SOME OF THE PROPOSED AREAS THAT WE'RE DISCUSSING TODAY?

DR. SANES: OKAY. I DO HOPE WE HAVE A CHANCE TO TALK ABOUT THIS AT GREATER LENGTH LATER BECAUSE THERE'S CERTAINLY NO SIMPLE ANSWER.

THOUGHTS I'VE HAD LISTENING TO PEOPLE WHO KNOW MUCH MORE ABOUT THIS THAN I DO IS THAT THERE'S A LOT OF OPPORTUNITY TO USE THE CIRM TECHNOLOGIES AND PLATFORMS TO ADDRESS PSYCHIATRIC DISEASES. I THINK MOST OF THE EMPHASIS SO FAR HAS BEEN ON NEUROLOGICAL DISEASES AND NEURODEGENERATIVE DISEASES. AND FOR PSYCHIATRIC DISEASES, NOT UNIQUE,



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BUT MAYBE MORE THAN SOME NEURODEGENERATIVE DISEASES, THERE ARE HUGE, LET'S SAY, EXPERIENTIAL FACTORS THAT ARE IMPORTANT. AND I THINK SOMEBODY MENTIONED THAT EARLY ON. WHO WAS THAT? AT ANY RATE, SOMEBODY MADE THAT POINT. DR. CLARK. AND I THINK IT'S GOING TO BE A CHALLENGE TO FIGURE OUT WHETHER THERE ARE GOING TO BE WAYS TO PUT TOGETHER GENETIC AND ENVIRONMENTAL, BY WHICH I MEAN EXPERIENTIAL FACTORS, IN A WORLD THAT'S DOMINATED BY STEM CELL APPROACHES.

AND SO ONE OF THE THINGS I THINK WE COULD TALK ABOUT LATER IS WHETHER, FOR THE SORT OF NEUROSCIENCE PART OF THIS NEW ENTERPRISE, WE MIGHT WANT TO COMPLEMENT STEM CELL APPROACHES WITH WHOLE ANIMAL STUDIES, MAYBE ORGANOID STUDIES, BUT IN DIFFERENT WAYS, ANIMAL CHIMERA STUDIES, POSSIBLY WORK ON EPIGENOMICS IN VIVO THAT MIGHT THEN LEAD TO HYPOTHESES THAT CAN BE TESTED IN STEM CELLS.

SO I'M KIND OF NEW TO THIS, BUT THESE WERE SOME OF THE THINGS I WAS THINKING ABOUT IF WE WANT TO ADDRESS CIRCUIT-BASED DISEASES IN A WORLD THAT'S SO FAR BEEN DOMINATED BY STUDIES THAT ARE REALLY LOOKING FOR CELLULAR MECHANISMS.

DR. MILLAN: THANK YOU, DR. SANES. ANY ADDITIONAL COMMENTS ON THAT TOPIC?

DR. SANES, BEFORE WE HAVE ADDITIONAL

COMMENTS, HOW DO YOU FEEL THAT A CONSORTIUM APPROACH SUCH THAT WHICH HAS BEEN DISCUSSED IN THIS MEETING COULD ACTUALLY HELP TO KIND OF CREATE THE CRITICAL MASS OF EFFORT AND THE INTERCONNECTIVENESS, WOULD THAT BE HELPFUL TO A FIELD THAT MAY NOT HAVE SEEN AS MUCH ATTENTION IN OUR SPHERE?

DR. SANES: YEAH. I'M MORE OF A SMALL-SCALE PERSON. I'M NOT THAT FAMILIAR OR COMFORTABLE WITH LARGE CONSORTIA. I THINK THE TREND TOWARDS OPEN ACCESS AND DATA SHARING IS A WONDERFUL THING, ABSOLUTELY ESSENTIAL. IT'S BEEN VERY ESSENTIAL IN ALL THE GWAS STUDIES. THE SORT OF WORK THE ALLEN INSTITUTE IS DOING, WHICH IS A HUGE CONTRIBUTION, IS IMPORTANT. BUT IN TERMS OF SORT OF ORGANIZED CONSORTIA, I HAVE TO CONFESS I DON'T HAVE ANY TERRIFIC IDEAS.

DR. MILLAN: WE HAVE ONE MORE MINUTE FOR THIS SECTION BEFORE WE MOVE ON TO THE NEXT TALK. ARE THERE ANY ADDITIONAL THOUGHTS OR COMMENTS OR QUESTIONS FROM THE PANELISTS? PATRICK, DID YOU WANT TO SAY SOMETHING? NO. OKAY. SO THANK YOU SO MUCH. WE'RE GOING MOVE ON TO THE NEXT TOPIC THAT'S GOING TO BE TEED UP BY FYODOR URNOV. FYODOR, I'M GOING TO HAND IT OVER TO YOU.

DR. URNOV. FOLKS, I HAVE TO ADMIT FOR THE

FIRST TIME, AND I WAS JUST CALCULATING, IN 31 YEARS THAT I'VE BEEN GIVING PRESENTATIONS SINCE MY FIRST TALK AT A LAB MEETING WHEN I WAS A GRADUATE STUDENT ROTATING, MUCH OF MY TALK HAS ALREADY BEEN GIVEN. AND I'M GOING TO DO MY VERY BEST AS I GO THROUGH THE NEXT NINE MINUTES WORTH OF SLIDES, AND I'M SORRY I'M GOING TO HAVE TO USE SLIDES. I LACK THE ELOQUENCE TO EXPRESS THE POINTS I'M GOING TO MAKE WITHOUT VISUALS. I'M GOING TO DO MY VERY BEST TO CREDIT EVERYBODY WHO HAS ALREADY SAID WHAT I'M ABOUT TO SAY, BUT THE PARTICULAR FOCUS WILL BE SOMEWHAT, I'M HOPEFUL, NOVEL FOR THIS AUDIENCE. AND IT WILL BE ON ENABLING EQUITABLE ACCESS SPECIFICALLY TO CRISPR-CAS TREATMENTS FOR SEVERE DISEASE. AND HERE'S HOPEFUL EVERYTHING WORKS. I'M HOPEFUL YOU CAN SEE MY SCREEN.

SO I'M HONORED TO REPRESENT THE INNOVATIVE GENOMICS INSTITUTE LED BY JENNIFER DOUDNA, WHO, OF COURSE, IS SHOWN HERE IN HER GARDEN RECEIVING THE NOBEL PRIZE. THE SWEDES CAME TO HER FOR A METHOD FOR GENOME EDITING USING CRISPR-CAS.

AND THIS, OF COURSE, IS VICTORIA GRAY. SHE'S A SUBJECT AND A PATIENT -- SHE'S A SUBJECT ON THE TRIAL BY CRISPR THERAPEUTICS. SHE'S BEEN FUNCTIONALLY CURED OF HER SICKLE CELL DISEASE, AND A



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NUMBER OF OTHER SUBJECTS, CELL TRANSFUSION DEPENDENT THALASSEMIA BY CRISPR-CAS GENE EDITING --

UNIDENTIFIED SPEAKER: I DON'T THINK YOUR SLIDES ARE ADVANCING.

DR. URNOV: I KNEW THIS WOULD HAPPEN. YEAH. HOW ABOUT NOW? CAN YOU SEE THE -- HOW ABOUT I GO LIKE THIS? CAN YOU SEE MY SLIDES?

UNIDENTIFIED SPEAKER: THEY'RE NOT ADVANCING.

DR. MILLAN: PUT IT ON SLIDE VIEW, FYODOR.

DR. URNOV: HOW ABOUT NOW? HAS IT ADVANCED NOW?

UNIDENTIFIED SPEAKER: NO.

UNIDENTIFIED SPEAKER: YOU CAN ALSO JUST SCROLL DOWN WITH THE DOWN ARROW, AND THEN WE WILL SEE THE SECOND SLIDE.

DR. URNOV: OKAY. LET ME TRY THIS. KOLEDON, COULD YOU BE A SAINT AND SHARE YOUR SCREEN AND THE PDF I SENT? THANK YOU. YOU'RE A SAINT. CLICK.

SO THAT'S JENNIFER RECEIVING THE NOBEL PRIZE IN HER GARDEN. AND, OF COURSE, VICTORIA GRAY, A SUBJECT ON CRISPR THERAPEUTICS' TRIAL.

SO WHEN I JOINED THE IGI, THE INNOVATIVE GENOMICS INSTITUTE, IN 2018, JENNIFER SAID SHE WANTS

TO MAKE CRISPR THE STANDARD OF MEDICAL CARE. AND I'M HERE TO SHARE WITH YOU OVER THE NEXT FEW MINUTES THAT I THINK CIRM HAS A UNIQUE OPPORTUNITY TO MAKE THIS REALITY. CLICK.

SO I HAD THE UNIQUE HONOR OF HAVING BEEN HERE FOR SOME TIME IN THIS SPECIFIC AREA OF THE WORLD, GENE EDITING AS THERAPEUTIC, AND I'M GOING TO CHART TWO PATHS. 2005, WHEN THE FIRST EDIT OF A NATIVE GENE WAS DONE, THROUGH TODAY, AND THEN TWO POSSIBLE PATHS, A NEGATIVE ONE WHICH I'M HOPEFUL IS NOT WHAT'S GOING TO HAPPEN AND A POSITIVE ONE. CLICK.

SO LET ME PRESENT MY CREDENTIALS FIRST. WHO AM I TO TELL SUCH AN EXTRAORDINARILY AUGUST GROUP WHAT SHOULD BE DONE? SO WE STARTED IN 2002 WITH A SCID SEVERE ADVERSE EVENT AT THE L'HOPITAL LA GUERRE. I WAS HONORED TO PARTNER WITH A WHOLE BUNCH OF YOUNG AND HUNGRY PEOPLE, ALL OF WHOM ARE NOW CSO'S OR VP'S AT BIOTECHS WITH ED REBAR, WHO'S AT SANA, PHIL GREGORY AT BLUEBIRD, MIKE HOLMES AT AMBYS, GARY LEE AT SENTI. AND WE SHOWED, WE COINED THE TERM "GENE EDITING," AND IN 2005 *NATURE*, AND AS I'M GOING TO SAY, AND THIS ECHOES A POINT CHRIS AUSTIN MADE, A *NATURE* PAPER IS NOT THE TICKET TO THE REAL WORLD. WE WERE ABLE TO SHOW THAT WE CAN USE



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GENE EDITING TO KNOCK OUT AND REPAIR MUTATIONS AT IL-2RG. WE THEN BUILT, IN PARTNERSHIP WITH A LOT OF ACADEMICS, THE TOOLBOX OF GENOME EDITING, BUT, PERHAPS CRITICALLY, THEN WE TOOK IT TO THE CLINIC. AND WE DID PRETTY MUCH ALL THE FIRST-IN-HUMAN TRIALS WITH CARL JUNE AT PENN. WE DID THE FIRST GENE EDITING TRIAL FOR T-CELL KNOCKOUT OF CCR5, A HUNDRED SUBJECTS HAVE BEEN DOSED, NO TREATMENT RELATED SAE'S.

2010, THE FIRST GENE EDITING TRIAL IN HSPC'S, THE FIRST SUBJECT DOSED IN VIVO, AND YOUR HUMBLE SERVANT HAD THE HONOR OF LEADING THE SANGAMO PROGRAM THAT DISCOVERED BCL11A ENHANCER HOT SPOT THAT WAS RECENTLY USED BY CRISPR THERAPEUTICS TO TREAT THEIR SUBJECTS.

SO WHAT'S THE SYNTHESIS OF ALL OF THAT NOW THAT MY CREDENTIALS TO YOU HAVE BEEN PRESENTED? CLICK.

WELL, THERE'S A CHART OF PRECLINICAL PATH. AGAIN, KUDOS TO PETER MARKS AND THE CBER. EVERYTHING SANGAMO BUILT PRETTY MUCH 2008, 2018 HAS BEEN ROBUSTLY LEVERAGED BY A LARGE NUMBER OF BIOTECHS IN THE TAL EFFECTOR AND CRISPR-CAS AND MEGANUCLEASE SPACE. AND I'M HERE SORT OF DRAWING THIS OUT FOR YOU FROM PATIENT TO TRIAL. AND YOU

KNOW YOU HAVE TO DESIGN A CLINICAL LEAD, SHOW EFFICACY, SHOW IT'S SAFE, DO THE CMC, GO REGULATORY, DO A TRIAL. SOME ARE SLOWER, SOME ARE FASTER, SOME ARE LESS AND MORE EXPENSIVE. IT'S A LOT OF WORK. CLICK.

SO WHERE ARE WE NOW JANUARY 2021? WELL, AS I MENTIONED, THERE'S A LOT OF BIOTECHS. PRETTY MUCH ALL OF THEM ARE WORKING ON SICKLE AND THAL. I'LL EXPLAIN WHY IN A SECOND. TO BE PERFECTLY HONEST WITH YOU, IT'S A BIT SLIM PICKINGS IN THE AREAS OF RARE DISEASE OTHER THAN SICKLE, THAL, AND CANCER. THERE'S JUST A SMATTERING. AND TO BE HONEST WITH YOU, THAT'S AN ISSUE. CLICK.

SO IN CRISPR 2030, IF THE CURRENT TRENDS CONTINUE, THERE WILL BE APPROVED EDITING MEDICINES, CRISPR AND OTHER NUCLEASE PLATFORMS FOR ALLO CAR-T, I THINK. IT'S A HUGE AREA. FOR SICKLE AND THAL, THERE WILL BE A SMALL NUMBER OF GENETIC DISEASES, BUT THEY WILL ALL BE PRICED NORTH OF TWO MILLION PER PATIENT. AND THE VAST MAJORITY OF, QUOTE, RARE GENETIC DISEASE WILL REMAIN UNADDRESSED. AND I SAY RARE BECAUSE THEY'RE RARE ON AN N OF 1 BASIS, BUT IN AGGREGATE THEY'RE QUITE PREVALENT. CLICK.

SO TO EXPLAIN TO YOU WHY THE VISION OF CRISPR CURES FOR ALL IS UNDER THREAT AND WHAT I



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THINK ONE COULD DO. NEXT SLIDE. LET ME GIVE TO YOU A STORY ABOUT KARLY KOCH. I SAW HER IN THE *NEW YORK TIMES* 2015. I BELIEVE SHE HAS DIED. SHE HAD A RARE GENETIC IMMUNE DISEASE. AND IT BREAKS YOUR HEART. HERE SHE'S PLANNING HER FUNERAL WITH HER MOM. SORRY. IT'S KIND OF HARD TO SAY THIS WITHOUT CHOKING UP AND LIKE WHO'S GOING TO GET HER TOYS AFTER HER FUNERAL. AND AS A GENE EDITOR, SHE HAS A POINT MUTATION. WHY DIDN'T SOMEBODY EDIT HER? CLICK

SO HERE'S WHAT HAPPENED. SHE HAD A DEFICIENCY OF DOCK8. CLICK. AND HERE'S A GENE EDITOR'S VIEW. ALLOW ME TO OPEN THE HOOD OF GENE EDITING FOR YOU FOR FIVE SECONDS. THIS IS THE LOCUS. HERE ARE THE MULTIPLE ISOFORMS OF THE CDNA, THE MULTIPLE PROTEIN FORMS. CLICK.

EVERY MARK IN RED IS A SNP THAT CAUSES THE DISEASE. NOW, IF YOU WANT TO DO A THERAPEUTIC, WHICH I'VE DONE MANY TIMES AND HAS OTHERS, CLICK, YOU BUILD. ON THE LEFT YOU SEE IND NO. 1, WHICH IS FOR THE FIRST MUTATION. BUT IF YOU WANT TO SWITCH TO A DIFFERENT MUTATION, IT'S A NEW IND. AND SO YOU'RE BACK TO THE RED SQUARE THAT SAYS EFFECTOR. SO THE LOGISTICS OF DOING THAT OVER AND OVER AGAIN, ESPECIALLY FOR A SITUATION WHERE THE NUMBER OF

PATIENTS IS VANISHINGLY RARE, IT'S ABSOLUTELY PROHIBITIVE. CLICK.

SO NOW YOU HAVE TO MULTIPLY THAT BY 416. AND THANKS TO JENNIFER PUCK, OF COURSE, AT UCSF ACROSS THE BAY, WHO HAS BEEN A HERO IN TERMS OF POSTNATAL DIAGNOSIS OF SCID AND ALSO CATALOGING THEM, THERE IS 416 INHERITED DISORDERS OF THE IMMUNE SYSTEM. CLICK. AND THEY'RE ALL RARE, BUT THE PROBLEM IS NOW WE KNOW THE FACT THAT EDITING REPRESENTS AN APPROACH TO THE MAJORITY OF PRIMARY IMMUNE DEFICIENCIES IN PRINCIPLE. DOESN'T MEAN THAT A GIVEN BIOTECH WILL TAKE ON DISEASE NO. 314 IN PRACTICE. SO WHAT I'M GOING TO ARGUE AND ECHO A LOT OF POINTS EVERYONE'S JUST MADE, WE NEED A FUNDAMENTALLY NEW N-OF-1 FRAMEWORK, AND IT HAS TO BE A PUBLIC SECTOR ONE. WHY PUBLIC SECTOR? CLICK.

NOT A ZERO-SUM GAME WITH INDUSTRY, BUT THE BOTTOM LINE IS THERE'S A GIANT GAP BETWEEN COMMERCIALLY VIABLE PRODUCTS. I THINK ALLO CAR-T WILL BE A HUGE COMMERCIAL PRODUCT. SICKLE, THAL WILL BE AS WELL. HEMOPHILIA WILL BE A HUGE COMMERCIAL PRODUCT. AND ON THE OTHER HAND, N-OF-1 INDICATIONS WHERE THE NET PRESENT VALUE IS SUCH THAT IT MAKES NO COMMERCIAL SENSE FOR A FOR-PROFIT ENTITY TO TAKE A SINGLE HUMAN WITH A SINGLE MUTATION WHERE



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YOU HAVE TO GO BACK TO SQUARE ONE. CLICK.

SO I'M NOT HERE TO HANDWRING. I'M HERE TO SAY TO YOU THAT I BELIEVE WE HAVE A ONCE-IN-GENERATION MOMENT IN BIOTECHNOLOGY. I'M REALLY GLAD PETER MARKS IS HERE BECAUSE I'M GOING TO SHOW YOU A SLIDE FROM HIM. BUT FIRST, A BRIEF VOTE OF DEEP GRATITUDE FOR TIMOTHY YU WHO SHARED THIS SLIDE WITH ME. MANY OF YOU KNOW HE'S A HERO. HE BUILT AN ANTISENSE IN A YEAR FROM DIAGNOSING TO DOSING A SUBJECT IN HIS CLINIC IN CLOSE INTERACTION WITH FDA. MILA UNFORTUNATELY DIED. IT'S A TERRIBLE THING TO SAY. SHE DIED A WEEK AGO; BUT FOR THE LAST TWO YEARS OF HER LIFE, HER SEIZURES WERE LESS PREVALENT.

SO I BORROWED THE NEXT SLIDE FROM PETER MARKS. THANKS, PETER, VERY MUCH FOR LETTING ME SHARE THIS. AND PETER STANDS UP AT THIS WORKSHOP I PUT TOGETHER ON RETT SYNDROME AND SAYS, "LISTEN. IT'S TIME FOR A BESPOKE GENE THERAPY CONSORTIUM," A NONPROFIT UMBRELLA ORGANIZATION WHERE THE FDA WOULD STREAMLINE REGULATORY REQUIREMENTS. THERE WOULD BE STANDARD VECTOR MENUS, PROCESS, DELIVERY, AND THEN EVERYTHING WOULD BE REPORTED BACK TO THE CONSORTIUM FOR ITERATIVE LEARNING. I'M LISTENING TO PETER AND I'M LITERALLY LEVITATING OFF MY CHAIR BECAUSE, OF

COURSE, I WORK WITH JENNIFER DOUDNA ON CRISPR-CAS. CLICK.

SO THE BROAD AREA OF OPPORTUNITY, TO CITE MARIA, IS HOW WE COULD POTENTIALLY ENABLE EQUITABLE ACCESS TO CRISPR-CAS TREATMENTS FOR SEVERE DISEASE IN A WAY THAT WOULD BE NIMBLE TO SCIENTIFIC INNOVATION IN THE NON-FOR-PROFIT SECTOR. CLICK.

SO TO JUST MAKE SURE THAT YOU FOLKS UNDERSTAND THAT I'M NOT JUST TALKING THE TALK, BUT WE WALK THE WALK, VERY QUICKLY JUST A 60-SECOND STORY OF HOW WE ARE DOING THIS AT THE INNOVATIVE GENOMICS INSTITUTE IN PARTNERSHIP WITH THE GLADSTONE UCSF INSTITUTE FOR GENOMIC IMMUNOLOGY FROM AN N OF 1 TO AN N OF MANY, AND THEN JUST WRAP UP. CLICK.

SO THIS BEGINS AND BASED ON SOME IMPORTANT WORK THAT JEFF BLUESTONE DID IN T-REG MANUFACTURING WITH A PATIENT OF KEVAN HEROLD'S. SHE'S NOT REALLY MERELY A LINE ON PAGE 19 OUT OF 41 OF THAT TABLE OF GENETIC DISORDERS. SHE HAS C25 DEFICIENCY, SHE HAS NO T-REGS, SEVERE AUTOIMMUNITY. CLICK.

A LOT OF CREDIT TO ALEX MARSON WHO COLLABORATED WITH JENNIFER DOUDNA ON BUILDING T-CELL EDITING WITH CAS9 RNP AND THEN TRANSITIONING THAT TO ALL NONVIRAL T-CELL MUTATION REPAIR AND THEN LEVERAGING EVERYTHING IN JEFF BLUESTONE'S SHOP AND

PARTNERING WITH JONATHAN ESSENSTEN AND BRIAN SHY TO ACTUALLY DO CLINICAL SCALE REPAIR OF THAT MUTATION. AND, FRANKLY, FOLKS, I'M VERY PROUD TO SAY TOOK A LOT OF PHILANTHROPIC FUND-RAISING AND A LOT OF INTRAMURAL SORT OF COHESION, BUT WE ARE WRAPPING UP FOR 2021 AND AN N-OF-1 IND. GREAT.

WE ARE ABOUT TO TREAT ONE HUMAN BEING, BUT MY CRITICAL KEY POINT TO THE CIRM AND THIS AUDIENCE IS IN THE NEXT SLIDE. SO WE HAVE A VIBRANT CELL AND GENE THERAPY ECOSYSTEM IN RESEARCH UNIVERSITIES. AND IT'S ACTUALLY PRETTY UNIQUE. I RESPECTFULLY -- I ACCEPT BOB NELSEN'S POINT THAT UNIVERSITIES ARE BETTER AT SOME THINGS THAN OTHERS, BUT I GIVE TO YOU THE FACT THAT MARIA GRAZIA RONCAROLO AND MATT PORTEUS, BOTH AT STANFORD, HAVE AN OPEN IND FOR SICKLE THAT HAS JUST APPEARED AND THAT THE INNOVATIVE GENOMICS INSTITUTE, IN PARTNERSHIP WITH DON KOHN AT UCLA AND MARK WALTERS AT UCSF, HAVE AN OPEN IND IN SICKLE. AND THESE ARE NOT JUST -- THIS IS A FULL GRADE IND WITH CMC, QA/QC, CQA'S, GOLD STANDARD IND-ENABLING TALKS. THIS IS THE REAL DEAL.

AND JUST TO HIGHLIGHT THE STRENGTH OF A UNIVERSITY SETTING, SOME UNIVERSITIES, NEXT SLIDE. I JUST WANT TO HIGHLIGHT AN ABSOLUTELY UNIQUE KAPLAN-MEIER CURVE. I'VE NEVER SEEN ANYTHING LIKE



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THAT IN MY LIFE. THIS IS ACADEMIC. THIS IS FROM DON KOHN. IT'S COMING OUT IN THE *NEW ENGLAND JOURNAL*. THIS IS GENE THERAPY LENTI FOR ADA-SCID, A SEVERE DISEASE. FIFTY PEDIATRIC SUBJECTS, 100 PERCENT CURED. FIFTY PEDIATRIC SUBJECTS. ALL IN ACADEMIC SETTINGS LED BY DON KOHN AT UCLA. THAT'S AN EXTRAORDINARY AMOUNT OF FIREPOWER ON EVERY LEVEL. CLICK.

SO IN THINKING ABOUT HYPOTHETICALLY A CIRM CONSORTIUM FOR CRISPR CURES, I'M REALLY WRAPPING UP BECAUSE I'M SUPER EAGER FOR PEOPLE TO COMMENT ON THIS. CLICK. THE VISION WOULD BE TO TEAM UP AVENGER STYLE, TO LEVERAGE EXISTING STRENGTHS TO BUILD CORE HUBS EXACTLY AS LESLIE AND SALLY AND EVERYBODY JUST SAID, TO HAVE A MANIATIS MIND-SET WHERE WE WOULD STANDARDIZE -- AND I WILL EXPLAIN WHERE THE WORD "MANIATIS" COMES FROM -- AND HAVE KEY PARTNERS BETWEEN FDA AND INDUSTRY. AND LET ME EXPLAIN WHAT I MEAN. CLICK.

SO AVENGERS, OF COURSE, IS A TEAM OF SUPERHEROES WITH KNOWN OVERLAPPING SUPERPOWERS. AND I REALLY WANT TO EMPHASIZE THIS IS NOT AN EXCLUSIVE LIST. THIS IS A REPRESENTATIVE LIST. IF YOU HAVE AN IMMUNODEFICIENCY, YOU HAVE JENNIFER PUCK REPRESENTING UCSF WITH HER DEPTH IN GENETICS. YOU



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WANT TO BUILD A CRISPR-CAS, WELL, WE HAVE JENNIFER DOUDNA, THANK YOU VERY MUCH, AND THE INNOVATIVE GENOMICS INSTITUTE. YOU WANT A DEEP INSIGHT INTO BIOLOGY, WELL, WE HAVE THE GIGI AND ALEX MARSON. AND IN TERMS OF THE CLINICAL TRIAL, WELL, I JUST SHOWED YOU WHAT KINDS OF THINGS DON KOHN CAN DO AT UCLA. AND SO THE VISION IS THAT CIRM AND THE FDA WOULD BE THE GLUE THAT COHESES THIS. CLICK

LET ME JUST OPEN THE HOOD. I DON'T WANT TO BORE YOU TO TEARS, BUT JUST WHAT WOULD THE EXPERIENCE LOOK LIKE IN TERMS OF A CAPABILITY HUB? THIS IS ONE FLOOR OF HOTEL CALIFORNIA, HOTEL CIRM CALIFORNIA, WHERE, YOU KNOW, THIS IS MY AREA OF THE WOODS, WHICH IS HOW DO YOU BUILD THE CLINICAL GRADE EFFECTOR.

SO HERE'S A MUTATION FOR A PATIENT. AND MY JOB, OUR JOB AT THE IGI WOULD BE TO DECIDE WHAT EDITING STRATEGY ARE WE USING: KNOCK OFF, REPAIR, TARGETED INTEGRATION, SOMETHING NEW? ARE WE CUTTING, BASE EDITING, PRIME EDITING, EPI-EDITING, NEW EDITING? WHICH CAS9? WELL, WE NEED AN EVERGREEN LIBRARY. CMC. I THINK WE ABSOLUTELY CAN STANDARDIZE IN-HOUSE CMC IF WE DO THIS RIGHT AND IF WE ARE VERY MINDFUL TO BOB'S IMPORTANT POINT THAT UNIVERSITIES DO SOME THINGS WELL, BUT NOT OTHERS.



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BUT ALSO I REALLY WANT TO STRONGLY THANK GEORGE DALEY AND CHRIS AUSTIN AND PATRICK FOR BASICALLY MAKING MY POINT FOR ME, WHICH IS THERE IS A SPECIFIC SWEET SPOT FOR WHERE ACADEMIC INNOVATION COULD REALLY MAKE A DIFFERENCE. AND ALSO REALLY SECOND VERY MUCH KEVIN, PETER, AND CAT FOR SPEAKING ABOUT INNOVATION IN TOX AND LONG-TERM FOLLOW-UP, CHRIS AUSTIN FOR PROJECT MANAGEMENT. COMPLETELY SUPPORT ALL OF THIS, BUT MY POINT TO YOU IS UNDER THE HOOD OF THAT JUST ONE SUBUNIT COULD BE A PRETTY ENABLING TURNKEY CAPABILITY. THAT IS WHAT THAT FLOOR IN HOTEL CIRM CALIFORNIA WOULD LOOK LIKE. CLICK.

I THINK I'M ALMOST DONE.

SO THE VISION. PETER MARKS SAID IN THAT PRESENTATION THAT HE'D LIKE A MANIATIS-LIKE COOKBOOK FOR GENE THERAPY. I COMPLETELY AGREE. THANK YOU, PETER. THE PROPOSAL IS THAT THERE WILL BE MULTIPLE CIRM-POWERED N-OF-1 TRIALS, AND THE INTEGRAL OF THEM WOULD PRODUCE THAT COOKBOOK FOR CRISPR CURES THAT WOULD BE CONTINUOUSLY UPGRADED BY CLINICAL EXPERIENCE. THE ONLY WAY TO FIGURE OUT HOW TO EDIT PEOPLE IS TO ACTUALLY EDIT PEOPLE. NO AMOUNT OF PRECLINICAL EFFORT WILL TEACH YOU WHAT ACTUALLY WORKS AND DOESN'T, BUT PERHAPS CRITICALLY THIS WOULD

BE A FEET FORWARD LOOP WHERE THAT COOKBOOK AND THAT EXPERIENCE, BECAUSE IT WOULD BE EVERGREEN AND CONTINUOUSLY UPDATED, WOULD ENABLE THE NEXT GENERATION OF TRIALS.

I SHOULD ALSO REALLY PUT A VERY LARGE VOTE OF THANKS TO THE CIRM FOR THINKING ABOUT TRAINING BECAUSE IN AN ACADEMIC SETTING, THIS WOULD CREATE A TREMENDOUS OPPORTUNITY, AN ONRAMP, IF YOU WILL, FOR TRAINING THE NEXT GENERATION OF TRANSLATIONAL SCIENTISTS AND CLINICIAN SCIENTISTS. CLICK.

SO I JUST WANT TO SAY ONE LAST THING. THERE IS AN ENORMOUS AMOUNT OF EFFORT IN CELL THERAPY FOR CANCER, AND I THINK IT REPRESENTS A ONCE-IN-A-GENERATION OPPORTUNITY TO GET INTO SOLID TUMORS, TO GET INTO CAR-T ENGINEERING IN VIVO. AND THERE'S A PHENOMENAL AMOUNT OF INDUSTRY EFFORT IN THIS. ALLOGENE, SANGAMO, LYELL, CRISPR, BEAM, CELLECTIS, YOU NAME IT. BUT I DON'T THINK IT'S A ZERO-SUM GAME WITH THE ACADEMIA.

AND SO LET ME JUST CREDIT ALEX MARSON FOR JUST ONE SLIDE, AND IT IS ACTUALLY HIS IDEA. LIKE A CONSORTIUM LIKE THIS COULD BE LEVERAGED INTO CELL ENGINEERING FOR CANCER AS WELL, NOT AS A ZERO-SUM GAME WITH INDUSTRY. TO GIVE TWO EXAMPLES FROM ALEX'S WORK, YOU GO FROM NONVIRAL CELL EDITING TO



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SCREENING, WHICH IS ALSO ALL NONVIRAL IN T-CELLS, AND, CRITICALLY, THIS IS THE KEY IDEA ABOUT NIMBLENESS TO INNOVATION WITH AN ACADEMIC CONSORTIUM WHO COULD THEN RUN A PANEL OF IND'S THAT COULD INFORM THAT COOKBOOK FURTHER. LAST SLIDE.

"A RISING TIDE LIFTS ALL BOATS." I THINK THAT CIRM SUPPORT OF THIS TYPE WOULD LIFT HEALTHCARE IN CALIFORNIA, THAT COOKBOOK AND THE EXAMPLES WOULD LIFT HEALTHCARE IN THIS SPACE, NOT JUST IN THE PUBLIC SECTOR, LIKE ACADEMIC, NON-PROFITS, WHATEVER, BUT I THINK WOULD REALLY RESONATE ACROSS ALL OF INDUSTRY PRECISELY IN THE WAY THAT KENNEDY ALLUDED TO IN 1963.

I GREATLY APPRECIATE THE OPPORTUNITY TO SPEAK WITH YOU ABOUT THIS TODAY.

DR. MILLAN: THANK YOU, FYODOR. I'M GOING TO OPEN IT UP FOR DISCUSSION. PLEASE JUMP IN, FIRST PERSON. OKAY. I'M GOING TO START CALLING ON PEOPLE NOW.

DR. DALEY, DO YOU HAVE ANY THOUGHTS ON THIS AND HOW SUCH AN APPROACH -- HOW DO YOU VIEW THAT FROM YOUR VISION AT THE HARVARD STEM CELL INSTITUTE AT HARVARD AND HOW THAT COULD IMPACT POTENTIAL COLLABORATION WITH CIRM? AND THEN I'D LIKE TO AFTER THAT TALK TO MIKE MCCUNE FROM A

FOUNDATION PERSPECTIVE.

DR. DALEY: I'LL MAKE A QUICK COMMENT, BUT FORTUNATELY WE'VE GOT CHRISTINE AND SALLY ALSO. I WAS SAD TO LEARN FROM FYODOR THAT MILA, TIM YU'S PATIENT, OUR N-OF-1 PATIENT HAD PASSED AWAY RECENTLY. BUT IT DID RAISE A MORE GENERAL ISSUE OF THESE BESPOKE THERAPIES AND THE NEED FOR SOME STRATEGY FOR PLATFORM-BASED APPROVALS. I THINK THAT'S SORT OF A SUBTEXT OF FYODOR'S COMMENTS.

AND I DON'T KNOW IF PETER MARKS IS ON THE CALL, BUT I KNOW THIS HAS BEEN DISCUSSED BEFORE. AND THE FDA SPECIFICALLY APPROVES THE MARKETING OF PRODUCTS. IT DOESN'T APPROVE PLATFORMS. AND ONE COULD IMAGINE A CONSORTIUM COMING TOGETHER IN CIRM WHICH COULD BE A TESTBED FOR A NEW KIND OF STRATEGY FOR ACHIEVING -- INDIVIDUAL INVESTIGATOR-INITIATED TYPE IND'S THAT COULD SUPPORT PLATFORM DEVELOPMENT. AND CRISPR TECHNOLOGY WOULD BE A PERFECT APPLICATION FOR THAT.

SO IT WOULD REQUIRE -- AS CHRIS AUSTIN SAID, THE FDA IS ACTUALLY MADE UP OF EARNEST INDIVIDUALS WHO REALLY WANT TO MAKE A DIFFERENCE. AND GETTING ENGAGED IN INNOVATION OF THIS SORT, I THINK YOU'D FIND THEY'D BE WELCOME PARTNERS. IT WOULD REQUIRE, HOWEVER, A CHANGE IN THE LAW FOR FDA



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TO APPROVE PLATFORMS. BUT WHY NOT BE BOLD? IT'S SOMETHING THAT MAYBE CIRM COULD REALLY SPEARHEAD.

DR. MILLAN: THANK YOU. DR. MARKS, ARE YOU ON THE LINE? HE MAY NOT BE. BUT THERE WAS A PUBLICATION IN THE *NEW ENGLAND JOURNAL OF MEDICINE* DESCRIBING A CONSORTIUM APPROACH WHERE IT PROVIDED THAT THERE -- IT'S A MODEL THAT SPEAKS TO PROVIDED THAT THERE'S A STANDARDIZED WAY OF COLLECTING DATA, MANUFACTURE, DESIGN, EVEN ACROSS DIFFERENT INSTITUTIONS AND SEPARATE IND'S, THAT THE FDA IS LOOKING AT OPPORTUNITIES, WHETHER IT BE SMALL ENDS THAT THE VARIOUS INSTITUTIONS COULD AGGREGATE INTO A LARGER DATASET THAT THEY COULD USE FOR AN APPROVAL DECISION, WHICH WOULD THEN RESULT IN APPROVAL IN THE VARIOUS DIFFERENT PARTICIPANTS. AND IT IS SOMETHING THAT WE HAVE BEEN REALLY INTRIGUED BY. I THINK THAT THERE'S AN OPPORTUNITY FOR THAT.

I'M GOING TO TURN IT OVER TO MIKE MCCUNE WHO MAYBE GIVE US HIS PERSPECTIVE FROM A FOUNDATION THAT ALSO LOOKS GLOBALLY AT THESE TYPES OF OPPORTUNITIES AND ISSUES.

DR. MC CUNE: THANKS, MARIA. AND IT'S BEEN A PLEASURE TO LISTEN IN TODAY. I KNOW MANY OF YOU, BUT NOT ALL OF YOU. THE FOUNDATION THAT MARIA REFERS TO IS THE GATES FOUNDATION. AND FOR THOSE OF

YOU WHO KNOW ME, I MOVED THERE JUST A FEW YEARS AGO AFTER MANY YEARS AS AN HIV DOC IN CALIFORNIA WHERE I STILL LIVE. AND I KNOW SOME OF YOU FROM THE WEISSMAN LAB, F-1S OF MINE, BECAUSE IRV AND I SET UP A COMPANY BACK IN THE LATE '80S TO BRING GENE THERAPY FOR HIV TO FRUITION. AND AT THAT POINT IN TIME, THERE WAS NO ECONOMIC MODEL TO BRING IT FORWARD. ANTIRETROVIRAL THERAPY HAD JUST COME OUT, AND IT WAS THOUGHT BY THE COMPANY THAT ACTUALLY ACQUIRED US THAT THEY MIGHT MAKE MORE MONEY BY SELLING PEOPLE ANTIRETROVIRAL THERAPY FOR THE REST OF THEIR LIFE THAN TO GIVE THEM A CURE WHEN THEY WERE BORN, FOR EXAMPLE.

AND, FYODOR, I THINK THE MOST EXCITING THING THAT I, MANY EXCITING THINGS, THAT YOU SAID IN YOUR EXCITED WAY, THAT THE MOST EXCITING WORD IN THAT PRESENTATION OF YOURS WAS EQUITY. AND I THINK THE KEY -- THIS IS SOMETHING THAT MARIA AND I HAVE TALKED ABOUT IN THE PAST. FOR ME, WHEN IT COMES TO HIV, IS TO BRING EQUITABLE THERAPIES IN CALIFORNIA. I KNOW THAT THERE ARE MANY PATIENTS THAT ARE DISENFRANCHISED THAT WILL NEVER, EVER HAVE THE OPPORTUNITY TO TAKE ADVANTAGE OF AN EX VIVO GENE THERAPY FOR HIV. AND CERTAINLY THAT'S THE CASE, AND IT'S BEEN MENTIONED ALREADY, THAT THERE WILL NOT BE



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AN ECONOMIC MODEL TO BRING THE CURES THAT WE KNOW CAN HAPPEN FOR SICKLE TO PEOPLE IN SOUTH CAROLINA OR OAKLAND THAT HAVE IT.

SO CONSEQUENTLY I MOVED TO THE GATES FOUNDATION AND ASKED THE QUESTION: HOW COULD ONE ACTUALLY DELIVER THESE KINDS OF THERAPIES TO PEOPLE WHO NEED THEM EVERYWHERE IN CALIFORNIA AND ELSEWHERE? AND I THINK, FYODOR, YOU GLOSSED OVER ONE OF THE SLIDES THAT YOU HAD THERE, BUT ONE SHOWED THE POSSIBILITY OF USING A RIBONUCLEOPROTEIN COMPLEX IN AN IN VIVO APPROACH TO MODIFY STEM CELLS.

DR. URNOV: YEP.

DR. MC CUNE: AND THIS, I THINK, ACTUALLY IS STILL VERY ASPIRATIONAL, BUT THE SIGNALS THAT ARE COMING OUT FROM EVEN SPOTLIGHT, A COMPANY THAT WAS SET UP BY ALEX MARSON, AND MANY OTHERS NOW THAT -- WE AT THE FOUNDATION OVER THE PAST COUPLE YEARS HAVE BEEN FUNDING COMPANIES, ALL THE ONES THAT YOU KNOW ABOUT, TO TURN THEIR SIGHTS TO IN VIVO APPROACHES USING VIRAL AND NONVIRAL APPROACHES. WE HAVE FORMED AN ASSOCIATION WITH THE NIH, INCLUDING THE NHLBI, TO BASICALLY A 50-50. IT'S AMOUNTED TO CONSIDERABLE RESOURCES, NOW ABOUT 250 MILLION ACTUALLY RESOURCES, TO FOCUS ON IN VIVO THERAPIES FOR SICKLE AND OTHER HEMOGLOBINOPATHIES IN HIV. OKAY. BUT THAT CAN BE

EXPANDED AS YOU CAN IMAGINE.

WE'VE JUST -- WE'VE RECENTLY BEEN ABLE ALSO TO FORM AN ASSOCIATION WITH NOVARTIS, AND WE'LL STAND UP A 25-MEMBER RESEARCH TEAM IN THEIR WALLS TO WORK ON THESE IN VIVO APPROACHES. ALL OF THIS, AGAIN, IT'S ASPIRATIONAL. IT MAY NOT WORK. THERE'S A LOT OF SAFETY ISSUES THAT HAVE TO BE BROUGHT TO BEAR. IT WILL ONLY HAPPEN WITH PARTNERSHIP. I'M EAGER AND WAS EAGER TO JOIN THIS CALL TODAY BECAUSE I THINK THE PARTNERSHIP IS IMPORTANT, NOT JUST FOR THE COMPLEMENTARY SCIENTIFIC SKILLS THAT ARE BROUGHT IN AND FOR THE ADDITIONAL RESOURCES THAT ARE BROUGHT IN, BUT IT'S A LONG HAUL. AND IT'S NOT SOMETHING THAT A COMPANY CAN DO ALONE. IT'S NOT SOMETHING AN ACADEMIC LAB WILL DO ALONE.

I THINK CIRM'S ROLE HERE IS, AT LEAST IN THE CONTEXT OF TARGETING OF HEMATOPOIETIC CELLS, REALLY WITHIN SIGHT FOR SICKLE TO COMPARE STANDARD OF CARE, IF YOU WILL, EX VIVO THERAPY, MODIFICATION OF STEM CELLS, AND THEN REINFUSION WITH A VARIETY OF IN VIVO APPROACHES INCLUDING, FYODOR, THE ONES THAT YOU MENTIONED AND TALKED ABOUT. SO I THINK CAREFUL THOUGHT SHOULD BE GIVEN TO A WAY IN WHICH -- I LOVE THE WORD "CONSORTIUM AND COLLABORATORY AND TEAM SCIENCE," ALL THESE WORDS ARE, BUT THEY'RE



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DIFFICULT, THEY TAKE TIME, BUT IT'S REALLY IMPORTANT AND PROBABLY ESSENTIAL TO TAKE THE COMPONENT PARTS THAT YOU MENTIONED, FYODOR, AND TO EXPAND IT NOT TO INCLUDE JUST -- NOT JUST CRISPR, AS MUCH AS I LOVE IT, BUT THERE'S A LOT OF OTHER WAYS THAT ONE CAN APPROACH, I THINK, THESE DISEASES IN A WAY IN PARTNERSHIP WHERE CIRM COULD PLAY A PIVOTAL ROLE IN THE COMING YEARS.

DR. MILLAN: THANK YOU, MIKE. I THINK DR. MUMMERY HAD HER HAND UP. SHE MAY HAVE FALLEN OFF. I'LL GO AHEAD WITH DR. TEMPLE FIRST AND THEN TRY TO GET BACK TO DR. MUMMERY, THEN CHRIS AUSTIN. DR. AUSTIN NEXT. THANK YOU.

DR. MUMMERY: I DID HAVE A QUESTION, BUT IT DOESN'T REALLY MATTER. I THOUGHT WE WERE RUNNING OUT OF TIME. IT WAS MORE MY LACK OF KNOWLEDGE ABOUT HOW YOU WOULD ARRANGE SAFETY FOR THESE VERY SMALL PATIENT GROUPS.

DR. URNOV: CHRISTINE, THAT'S A KEY. I'LL JUST DO A ONE-SENTENCE STATEMENT. I'VE SPOKEN WITH PETER MARKS ABOUT THIS.

THERE IS AN ESSENTIAL NEED FOR TOX INNOVATION. THE CURRENT MODELS ARE INADEQUATE, GOING BACK TO KEVIN EGGAN'S POINT ABOUT THE CURE SAE AND THE BLUEBIRD SAE. THIS IS A UNIQUE OPPORTUNITY



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TO, IN PARTNERSHIP WITH THE FDA, INNOVATE ON USING ALL OF THE CONSTELLATION OF NEXT GENERATION TECHNOLOGIES TO DERISK THESE REAGENTS ON AN N-OF-ONE BASIS IN A WAY THAT DOESN'T INVOLVE 18 MONTHS OF NOT ENTIRELY MEANINGFUL IMMUNODEFICIENT MOUSE STUDIES.

SALLY, I'M VERY EAGER FOR YOUR PERSPECTIVE.

DR. TEMPLE: SO ACTUALLY IT FOLLOWS UP VERY NICELY. I WAS PERIPHERALLY INVOLVED IN THE GIANT AXONAL NEUROPATHY TRIAL THAT WAS ORGANIZED HERE IN ALBANY BY A LOVELY MOM WHOSE CHILD WAS THE ONLY PERSON ON THE PLANET WHO WAS A COMPLETE NULL FOR THE PROTEIN. NOT HAVING ANY MEDICAL BACKGROUND AT ALL, SHE MASTERMINDED THIS INCREDIBLE EFFORT TO EVENTUALLY DELIVER THIS AS A GENE THERAPY. I THINK THEY'VE NOW TREATED ABOUT 12 KIDS. HER DAUGHTER IS A TEENAGER NOW. I THINK THIS PROGRESS WOULDN'T HAVE HAPPENED WITHOUT HER.

BUT I LIKEN THE WHOLE PROCESS TO THE STORIES OF MOTHERS WHO LIFT CARS OFF THEIR INJURED CHILD BECAUSE IT WAS SUCH AN INCREDIBLY DIFFICULT PROCESS. AND WHAT YOU'RE DESCRIBING IS A WAY TO REALLY BRING THIS MUCH MORE INTO A MANAGEABLE PROCESS. AND THE SAFETY ISSUE THAT CHRISTINE RAISED WAS SO IMPORTANT FOR THEM BECAUSE THEY WERE

PIONEERING. THEY HAD TO KNOW WAS THERE GOING TO AN IMMUNE RESPONSE TO THIS NEW PROTEIN? WHEN COULD THEY INTERVENE WITH THE FEW KIDS AROUND THE WORLD? AND I THINK THAT THERE'S A LOT OF INFORMATION TO BE GAINED FROM THESE SINGLE INDIVIDUAL TREATMENTS THAT COULD REALLY INFORM FUTURE EFFORTS IN THIS SPACE.

I JUST WANTED TO SAY HOW INSPIRED I WAS BECAUSE I KNOW HOW MUCH IS NEEDED HERE. AND IF WE CAN DEVISE A PATH FORWARD, I THINK THAT WOULD REALLY BE REVOLUTIONARY. THANK YOU.

DR. MILLAN: THANK YOU SO MUCH, SALLY. CHRIS AUSTIN.

DR. AUSTIN: THANKS. I JUST WANT TO SECOND WHAT FYODOR SAID ON TWO LEVELS. ONE, AS A LOT OF YOU KNOW, ONE OF THE THINGS THAT I HAD THE PRIVILEGE OF DOING HERE IS BEING RESPONSIBLE FOR THE OFFICE OF RARE DISEASES RESEARCH. AND THE NUMBERS ARE REALLY QUITE EXTRAORDINARY THERE. YOU PROBABLY KNOW THERE ARE ABOUT 7,000 RARE DISEASES THAT ARE IDENTIFIED NOW. AND WHEN WE THOUGHT ABOUT IT FROM A SMALL MOLECULE POINT OF VIEW OR A GENE REPLACEMENT POINT OF VIEW, IT WAS BAD ENOUGH. BUT NOW THAT WE UNDERSTAND AND HAVE THE POSSIBILITY OF DOING GENE EDITING, YOU HAVE TO MULTIPLY THOSE NUMBERS BY THE, LET'S CALL IT, A HUNDRED DIFFERENT MUTATIONS THAT

THE AVERAGE DISEASE HAS AS FYODOR WAS SHOWING.

SO THAT MEANS THAT WE HAVE 700,000 DISEASES THAT WE NEED TO TREAT FROM A MOLECULAR POINT OF VIEW. SO I THINK IT STANDS TO REASON THAT WE NEED A COMPLETELY DIFFERENT MODEL OF ADDRESSING THESE, BOTH FROM A THROUGHPUT POINT OF VIEW AND FROM A COMMERCIAL POINT OF VIEW.

AND GIVING SUPPORT TO FYODOR'S CONTENTION, WE HAVE BEEN WORKING VERY, VERY CLOSELY WITH THE FDA FOR SOME YEARS NOW ON WHAT IS A PRECURSOR TO THE BESPOKE GENE THERAPY CONSORTIUM, SOMETHING CALLED PAVE-GT THAT ACTUALLY JUST HAD ITS FIRST INTERACT APPLICATION PUT IN YESTERDAY, AS A MATTER OF FACT. AND WE ARE DIRECTLY ADDRESSING THIS QUESTION WITH THE FDA. GOSH, WE WANT THIS. IT NEEDS TO BE A PLATFORM, BUT WE GOT TO FIT INTO A ONE-DISEASE-AT-A-TIME OR ONE-PROJECT-AT-A-TIME MODEL. AND SO WE'RE DOING IT ONE PROJECT AT A TIME, BUT WE'RE ASKING IN THE INTERACT MEETING, OKAY, HOW MANY OF THESE WOULD WE HAVE TO DO BEFORE IT BECOMES A CLASS EFFECT, QUOTE, UNQUOTE?

AND WE'RE DOING THAT AND PAVE-GT IS THAT MODEL FOR FULL-LENGTH GENE THERAPY. AND THE BESPOKE GENE THERAPY CONSORTIUM IS GOING TO DO MANY THINGS, INCLUDING A LOT OF FUNDAMENTAL RESEARCH TRYING TO



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INCREASE MANUFACTURING EFFICIENCY. BUT IT'S ALSO TO PUT THAT MODEL ON STEROIDS AND DO A LOT MORE AND COME UP WITH A, FROM PETER'S POINT OF VIEW, AND I'LL SPEAK FOR PETER BECAUSE HE'S BEEN OUR PARABIOSED PARTNER IN ALL THIS FROM THE BEGINNING, IS THAT THEY REALLY WANT A STREAMLINED REGULATORY PATH. SO ONE OF THE PURPOSES OF BGTC IS TO HAVE A PRODUCT, IF YOU WILL, TO HAVE THE MANIATIS, NOT ONLY FOR THE SCIENCE, BUT FOR THE REGULATORY SIDE.

THERE IS A LOT OF EAGERNESS TO DO THIS. IT HAS TO BE DONE IN A BIG CONSORTIUM. NCATS IS NOT DOING THIS ALONE. WE ARE DOING THIS TOGETHER WITH A LOT OF OTHER REALLY GREAT PEOPLE, PUBLIC AND PRIVATE.

WHEN MILA HAPPENED, I HAPPENED TO SEE JULIA VITARELLO, WHO'S MILA'S MOM, AT A NORD MEETING RIGHT AS THIS WAS GETTING GOING. THIS WAS SOME YEARS AGO NOW. AND IMMEDIATELY TEAMED UP WITH TIM YU AND HIS COLLEAGUES TO ASK THE QUESTION THAT FYODOR IS NOW ASKING. OKAY. IF THIS ACTUALLY WORKS, AND IT HADN'T FOR MILA YET, BUT IF IT DID, THEN HOW MANY OTHER RARE DISEASES COULD BE TREATABLE TO SOME DEGREE OR ANOTHER WITH AN ASO THAT WOULD ADDRESS A SPLICED MUTATION OF THE SORT THAT MILA HAD IN CLN7, WHICH IS A FORM OF BATTEN DISEASE. AND THE

ANSWER TURNS OUT TO BE QUITE ASTOUNDING. IT'S ABOUT 2,000 DIFFERENT DISEASES HAVE AT LEAST ONE MUTATION THAT WOULD BE AMENABLE TO JUST THAT BAND-AID ASO MECHANISM. THINK ABOUT THAT.

AND SO WE STARTED A COLLABORATION WITH TIM AND WITH IONAS AND WITH FDA, AGAIN DEEPLY INVOLVED IN THIS, TO DO EXACTLY WHAT FYODOR IS DESCRIBING. AND, AGAIN, IT'S GROWN INTO A QUITE MASSIVE COLLABORATION. WE ARE ALWAYS -- WE LOVE PARTNERS, BUT JUST TO SAY THAT WHAT FYODOR IS DESCRIBING WITH GENE EDITING, WHICH I THINK WE ALL -- WELL, I THINK IT'S KIND OF THE ULTIMATE SOLUTION AND MAY PUT THE REST OF US OUT OF BUSINESS FOR THESE MORE PRIMITIVE GENE THERAPY TECHNOLOGIES AT LEAST TO SOME DEGREE. I THINK WHAT FYODOR IS DESCRIBING IS DOABLE. IT'S NOT A PIPE DREAM.

I JUST WANTED YOU TO KNOW THAT THERE ARE TWO OTHER ONES THAT ARE LESS ELEGANT, BUT WELL ALONG. AND I THINK THIS WOULD BE A PERFECT THING FOR CIRM TO DO IF YOU'RE WILLING. AND I CAN TELL YOU FROM MY ORGANIZATION AT NCATS, WE'D LOVE TO BE A PARTNER IN THIS, BUT JUST TO SUPPORT THE VISION THAT FYODOR IS SAYING, I THINK IT'S BOTH NECESSARY AND POSSIBLE.

DR. MILLAN: THANK YOU SO MUCH, EVERYBODY.

AND WE'RE GOING TO GO ON TO THE NEXT SETTING, BUT I'M JUST GOING TO REPEAT BACK WHAT I THINK I'VE HEARD, AND IT'S A THEME THAT'S BEEN GOING THROUGH THIS MEETING IS THIS IDEA OF CONSORTIUM. IT COULD BE DISEASE BASED, IT COULD BE TECHNOLOGY PLATFORM BASED, BUT IN THIS CASE, IT'S RARE DISEASE WHERE THE N EQUALS 1 BECOMES 200,000 TYPES OF DIFFERENT INDICATIONS.

SO THANK YOU SO MUCH FOR POINTING OUT ALL THESE VARIOUS FORMS THAT ONE CAN SEE CONSORTIA AND THE IDEAS WE'VE BEEN DISCUSSING TODAY.

BUT SPEAKING OF WHICH, WE HAVE COMING UP NEXT DAVID HAUSSLER, WHO HAS BEEN VERY, VERY MUCH KIND OF ON THE FRONTLINE IN TERMS OF CREATING THESE KNOWLEDGE NETWORKS WITH CUTTING-EDGE RESEARCH STARTING STARTING WITH THE HUMAN GENOME PROJECT AND THEN THEREAFTER ALL OF THE OFFSHOOTS AND THE EXPLOSION IN THAT FIELD WHICH IS KIND OF THE BASIS FOR THE GENE-BASED THERAPEUTICS THAT WE ARE DISCUSSING. DAVID.

DR. HAUSSLER: YES. I'D LIKE TO SHARE MY SCREEN HERE. THIS LOOKS LIKE IT'S WORKING. THANKS, EVERYBODY. I'LL BE TALKING ABOUT DATA AND GENOMICS. WE HAVE IN CIRM A GENOMICS KNOWLEDGE NETWORK. IT WAS CREATED AS A MEANS OF GETTING PEOPLE TO WORK

TOGETHER AND SHARE DATA. THE LEADERS HAVE DONE A GOOD JOB OF GETTING PEOPLE MOTIVATED FOR THIS. MIKE SNYDER AND JOE ECKER AND THEN FOR THE DATA END JOSH STUART AT UCSC.

WE HAVE A NUMBER OF DIFFERENT AREAS IN STEM CELL RESEARCH, AND IT PRODUCED WHAT WE CALL A STEM CELL HUB. SO THIS IS ALL FROM THE FIRST ITERATION OF CIRM. FROM THAT TIME WE'VE ACCUMULATED 84 TERABYTES OF DATA. THAT'S 180,000 DIFFERENT FILES FROM 18 CIRM RESEARCH LABS. THAT IS NOW BECOMING PUBLICLY AVAILABLE AS THE AUTHORS PUBLISH AND RELEASE THE DATA, AND ALL THE DATA ARE MACHINE LEARNING READY, WHICH IS A KEY THING IF YOU WANT TO REALLY TAKE THE LATEST IN MACHINE LEARNING TOOLS AND USE THEM.

MOST OF THE DATA ARE SINGLE CELL RNA SEQ, AND MOST OF THE DATA ARE FROM BRAIN AND PANCREAS, BUT WE DO HAVE A WIDE RANGE OF DATA THAT WAS CREATED AND IS AVAILABLE IN THE STEM CELL HUB.

THERE IS ALSO A STEM CELL BROWSER ASSOCIATED WITH IT. AGAIN, SINCE MOST OF THIS DATA IS SINGLE CELL, YOU WANT TO SEE EXACTLY WHAT CELL TYPES ARE IN YOUR EXPERIMENT AND HOW THEY'RE RELATED TO EACH OTHER. WE HAVE A GOOD DEAL OF FUNCTIONALITY, AND IT'S COORDINATED WITH THE HUMAN



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GENOME -- WITH THE HUMAN CELL ATLAS PROJECT AS WELL SO THAT YOU CAN GO BACK AND FORTH BETWEEN DIFFERENT VIEWERS, EACH OF WHICH HAS SOME UNIQUE FUNCTIONALITY IN TERMS OF UNDERSTANDING YOUR SINGLE CELL DATASETS. AGAIN, IT'S VERY, VERY IMPORTANT THAT THIS IS ALL MACHINE LEARNING READY DATA.

WE ALSO HAVE A GENOME BROWSER THAT IS THE MOST POPULAR BROWSER RIGHT NOW IN HUMAN GENETICS. THERE WILL PROBABLY BE 10,000 USERS OF THIS BROWSER TODAY, FOR EXAMPLE. LINKING THE INFORMATION TO A GLOBAL RESOURCE IN GENOMICS IS ESSENTIAL FOR MAKING SURE THAT IT IS UTILIZED. SO THERE ARE MANY HUNDREDS OF TRACKS OF DATA ON THIS. PEOPLE CAN BUILD TRACK HUBS, PEOPLE CAN SHARE ALL IN THE SAME PLATFORM.

THIS IS PART OF A LARGER PROJECT CALLED THE DATA BIOSPHERE, AND THERE ARE A NUMBER OF PARTICIPANTS IN THAT THAT YOU SEE ON THE RIGHT-HAND SIDE THAT WE ARE WORKING WITH. THIS IS AN EFFORT TO MOVE THESE LARGE DATASETS TO THE CLOUD IN A WAY THAT PEOPLE CAN SHARE AND ACTUALLY COMPUTE ON THEM. COMPUTING HAPPENS WITHIN WHAT ARE CALLED CONTAINERS. THESE ARE SYSTEMS THAT ALLOW THE PROGRAM TO GET THE SAME RESULT NO MATTER WHICH COMPUTING RESOURCE IT'S RUNNING ON. AND IF YOU PUT YOUR COMPUTE IN



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CONTAINERS AND USE THESE CLOUD RESOURCES, THEN WE TRULY HAVE REPRODUCIBILITY OF RESULTS.

THE NEXT PHASE IN GENOMICS, WE THINK, IS REALLY A COMPLETE REFERENCE OF HUMAN GENOME DIVERSITY. LET ME DESCRIBE THIS AND HOW IT MAY BE AN OPPORTUNITY FOR CIRM.

FIRST, HUMAN GENOME FIRST DRAFT WAS ACTUALLY PRODUCED IN THE YEAR 2000. WE HAD THE HONOR AT UCSC OF POSTING IT ON JULY 7TH ONTO THE INTERNET. AND AT THAT TIME WE HAD A NUMBER OF MEETINGS ABOUT WHAT ACCESS TO THE HUMAN GENOME SEQUENCE WILL MEAN. IT WASN'T VERY LONG AFTER THAT THAT CIRM WAS CREATED. SO BOTH CIRM AND THE HUMAN GENOME ARE NOW GETTING OLD. THEY HAVE A LOT OF EXPERIENCE BEHIND THEM. AND YOU CAN SEE, IF YOU WALK THIS PATH, ALL OF THE SUBSEQUENT NIH PROJECTS THAT HAVE BUILT ON THE ORIGINAL HUMAN GENOME, BUT MANY OF YOU MAY NOT BE AWARE THAT IN 2019 A NEW PAN REFERENCE GENOME INITIATIVE WAS LAUNCHED.

WHAT IS THE ISSUE? WE HAVE ONE REFERENCE GENOME THAT'S USED IN CLINICAL PRACTICE. IT CREATES A COORDINATE SYSTEM FOR EACH OF THE CHROMOSOMES. AND IN THERE AT EACH POSITION YOU WILL FIND A STANDARD BASE. SO THIS IS A STANDARD REFERENCING THE GENOME. THE PROBLEM IS THAT THAT COMES FROM



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ESSENTIALLY ALMOST ONE INDIVIDUAL. AND THAT IS A PROBLEM BECAUSE, AS WE HAVE LEARNED ABOUT HUMAN GENETIC DIVERSITY, THERE ARE QUITE DISTINCT AND QUITE MEDICALLY IMPORTANT VARIATIONS THAT OCCUR IN DIFFERENT HUMAN ETHNIC POPULATIONS.

THE HUMAN PANGENOME REFERENCE IS A PROJECT TO ELIMINATE THE DISPARITIES THAT ARE CREATED BY THE CHOICE OF ONE SINGLE ARBITRARILY CHOSEN REFERENCE GENOME. WE WILL CREATE IN THIS PROJECT AN UNBIASED REPRESENTATION OF SEQUENCE DIVERSITY IN THE HUMAN POPULATION, A COMPREHENSIVE MAP OF GENOME VARIATION TIED THE REFERENCE STRUCTURE, AND MAKE TOOLS SO THAT THIS REFERENCE STRUCTURE CAN BE USED IN CLINICAL PRACTICE.

NOT ONLY ARE WE DIVERSIFYING THE REFERENCE GENOME, BUT WE'RE ALSO COMPLETING IT. THIS IS AN ARTICLE IN *NATURE* BY KAREN MIGA, ET AL. WHERE IT WAS ARGUED THAT ACTUALLY 8 PERCENT OF THE REFERENCE GENOME THAT WE CURRENTLY USE IS MISSING. AND THESE REGIONS WERE DISMISSED AS NOT IMPORTANT, BUT, IN FACT, THEY ARE QUITE INVOLVED IN GENOME INSTABILITY IN GENE FAMILIES. MANY DISEASES ARE ASSOCIATED WITH UNRESOLVED INTERCHROMOSOMAL AND INTRACHROMOSOMAL SEGMENTAL DUPLICATIONS AND REARRANGEMENTS. THERE ARE A NUMBER OF AREAS WHERE THIS VARIATION IS

ABSOLUTELY CRITICAL FOR MEDICINE. SO IT'S MORE THAN JUST HAVING A VARIANT THAT ISN'T IN THE REFERENCE GENOME, BUT IS COMMON IN YOUR ETHNIC POPULATION AT THE POINT LEVEL, SO IT'S NOT JUST THE SINGLE SNP VARIANTS, BUT THE LARGER VARIANTS THAT ARE VERY IMPORTANT, AND WE NEED TO CAPTURE ALL OF THE GENOME FROM ALL OF THE DIFFERENT ETHNICITIES ON THE PLANET.

IT'S A VERY AMBITIOUS PROJECT FUNDED BY NIH. HERE'S A LITTLE BIT ABOUT THE SAMPLING THAT'S CURRENTLY GOING ON. WE COLLABORATE WITH THE GLOBAL ALLIANCE FOR GENOMICS AND HEALTH, AND OUR GOALS ARE TO MAKE ALL OF THESE DATA AVAILABLE AND INCLUDING CELL LINES FOR EACH OF THE GENOMES AVAILABLE FROM CORYELL.

WHAT WE'D LIKE TO DO AND WHAT WE THINK IS A GREAT OPPORTUNITY FOR CIRM IS ACTUALLY TO CREATE INDUCED PLURIPOTENT STEM CELL LINES, IPS LINES, FOR EACH OF THESE REFERENCE GENOMES. CURRENTLY THE PROJECT IS FUNDED WITH ABOUT $30 MILLION TO CREATE 350 OF THE FIRST REFERENCE ETHNICALLY DIVERSE GENOMES WITH UNRESTRICTED USE. I THINK IT WOULD BE AN INCREDIBLE OPPORTUNITY TO COLLABORATE TO ACTUALLY CREATE AN IPS LINE FOR EACH OF THOSE THAT WOULD BE ACCOMPANIED BY A COMPLETE HUMAN GENOME. AGAIN, WE ARE SEEING THE FIRST COMPLETE TELOMERE TO TELOMERE



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HUMAN GENOMES THAT HAVE EVER BEEN PRODUCED JUST THIS YEAR. AND NOW WE CAN HAVE IPCS LINES ASSOCIATED WITH THEM.

NOW, WHAT DO YOU DO WITH THESE IPS LINES? YOU CAN MAKE ORGANOIDS, FOR EXAMPLE. WE'VE HAD SOME GREAT DISCUSSION, AND I WOULD ECHO CLIVE AND CHRIS AND CAT AND PATRICK ON THE NEED FOR MORE INDUSTRIALIZATION, MORE AUTOMATION, AND MORE CAREFUL QUALIFICATION AND VALIDATION OF THE MODELS THAT WE GET. THE FIRST THING YOU RUN INTO IS THEY'RE ON A DIFFERENT GENETIC BACKGROUND. WELL, IF WE ALL AGREE THAT WE HAVE THE SAME NORMAL GENETIC BACKGROUNDS, THEN WE CAN ALSO HAVE STANDARDIZED ORGANOIDS THAT ARE BUILT IN DIFFERENT TISSUE TYPES FROM THIS REFERENCE.

AND I LOVE THE HOTEL CALIFORNIA. EVERYONE LOVES HOTEL CALIFORNIA. SO THIS IS ORGANOID HOTEL CALIFORNIA. THINK OF IT AS AN ORGANOID NURSERY. IT ACTUALLY TAKES MONTHS TO GROW TISSUES. AND ONE WOULD LIKE TO ACTUALLY BE ABLE TO ORDER UP A MATURE TISSUE FOR EXPERIMENTATION. THAT IS NOT CURRENTLY POSSIBLE.

IT'S AN OPPORTUNITY TO UNDERSTAND THE EPIGENOME IN THE PROFOUND WAYS THAT WE DON'T WHEN WE JUST HAVE THE REFERENCE GENOME OR WE JUST HAVE



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INFORMATION FROM ONE TYPE OF TISSUE. AND TO VALIDATE WITH PRIMARY TISSUE, IT'S A GREAT OPPORTUNITY FOR DISEASE-SPECIFIC INDUCED PLURIPOTENT STEM CELL LIBRARIES TO COLLABORATE AND ORGANIZE AROUND THE SAME PRINCIPLES THAT ARE USED TO MAKE THE REFERENCE GENOME IPSC'S, AND THOSE COULD SERVE AS MATCH NORMALS IN A VARIETY OF STUDIES.

NOW, EXAMPLE, CEREBRAL ORGANOIDS. SINCE CIRM IS INTERESTED IN BRAINS, WE ARE VERY, VERY EXCITED TO LOOK AT WHAT THE POSSIBILITIES ARE. THESE ARE FROM MY LAB. WE GROW CEREBRAL ORGANOIDS ON A ROUTINE FASHION, IN A ROUTINE WAY. WE, NEVERTHELESS, ARE NOT USING THE EXACT SAME PROCESS THAT OTHER RESEARCHERS ARE. AND SO JUST GROWING A PARTICULAR TYPE OF ORGANOID IS STILL A COTTAGE INDUSTRY AT THIS POINT. EVERYONE DOES IT A LITTLE DIFFERENTLY. THE RESULTS ARE NOT DIRECTLY COMPARABLE. THAT IS A SERIOUS PROBLEM THAT HAS BEEN HIGHLIGHTED ON THIS.

SO I'VE HIT A NUMBER OF TOPICS HERE, BUT I THINK IN THE BIG PICTURE, IF WE CAN MARRY STEM CELL AND GENOMICS RESEARCH, WE CAN CREATE THE RIGHT FOUNDATION FOR A MORE EQUITABLE AND, I WOULD SAY, MORE COMPREHENSIVE REGENERATIVE MEDICINE. SO THERE'S THREE KEY POINTS. WE NEED TO SHARE

REFERENCE RESOURCES, AND IT ALL STARTS WITH THE GENOME. WHEN WE HAVE AN AGREEMENT ON A DIVERSE SET OF GENOMES, THEN WE ARE DEALING WITH THE ISSUE OF FAIRNESS AND DIVERSITY AND EQUITABILITY IN OUR RESEARCH AT THE GENETIC LEVEL, AT THE GENOMIC LEVEL. THEN WE NEED TO CREATE IPSC'S FROM THOSE, AND WE NEED TO HAVE A STANDARDIZED PROCESS IN WHICH WE DIFFERENTIATE THEM INTO THE TISSUES THAT WE USE FOR STUDY AND IN CLINICAL TRIALS.

CHRIS TOLD US A LITTLE BIT ABOUT THE TISSUE CHIP FOR DRUG SCREENING. AND I THINK THIS IS ABSOLUTELY FUNDAMENTAL, ABSOLUTELY FUNDAMENTAL. WE NEED TO PUSH IN THAT DIRECTION. SO I WOULD THANK EVERYBODY.

DR. MILLAN: THANK YOU SO MUCH, DAVID. OPENING IT UP FOR COMMENTS, QUESTIONS.

DR. SVENDSEN: I'M JUST GOING TO ECHO DAVID'S POINT ON DIVERSITY. ONE THING WE'RE FINDING WITH IPS LINES, DAVID, IS YOU'RE ABSOLUTELY RIGHT. RACIAL BACKGROUND MAKES A HUGE DIFFERENCE IN THE DIFFERENTIATION OR EVEN JUST THE IPS MAINTENANCE OF CELLS. WE JUST DON'T UNDERSTAND HOW SIGNIFICANT THIS IS GOING TO BE. SO I THINK YOU'RE ABSOLUTELY RIGHT. MATCHING IT UP AGAINST THE HUMAN GENOME WITH ETHNIC DIVERSITY IS GOING TO BE VERY IMPORTANT AND



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PROVIDE A KIND OF GROUND STATE FOR IPS DIFFERENTIATION RELATED TO THE GENOME.

DR. EGGAN: ARE ALL THE INDIVIDUALS FOR THE PROJECT ALREADY SELECTED? I WOULD POINT OUT THAT, GIVEN THAT CIRM HAS ALREADY MADE CELL LINES FROM A SOLID GROUP OF PEOPLE FROM SOME OF WHICH PHENOTYPIC DATA IS AVAILABLE, I WONDER IF THERE'S AN OPPORTUNITY TO PARTNER IN AN ALTERNATIVE WAY.

DR. HAUSSLER: THERE ABSOLUTELY IS. NOT ALL OF THE GENOMES HAVE BEEN SELECTED EVEN FOR THE FIRST ROUND. WE'VE ACTUALLY ONLY DONE THE FIRST 30 GENOMES AT THIS POINT, AND WE ARE PART WAY THROUGH THE FIRST 60 OR 90 GENOMES, BUT THERE IS PLENTY OF ROOM FOR ADDITIONAL RECRUITMENT. AND THERE IS A STRONG NEED FOR THAT. OF COURSE, YOU HAVE TO CONSOLIDATE CONSENTS AND HARMONIZE CONSENTS.

DR. EGGAN: YEAH. ONE THING THAT COULD HELP WITH THAT IS WE'VE ALREADY HELPED COLLABORATE WITH CIRM TO DO SOME INITIAL GENOTYPING AND SEQUENCING WITHIN THAT POPULATION. AND WE COULD PROVIDE SNP DATA WHICH COULD HELP WITH ACTUAL ANCESTRY AND MAYBE SOME TARGETED SEARCHING. SO MAYBE YOU AND I CAN CONNECT ABOUT THAT OFFLINE.

DR. HAUSSLER: PLEASE CONNECT WITH ME. THE TARGETED SEARCHING IS ESSENTIAL IF WE ARE GOING

TO BE COMPREHENSIVE, YES.

DR. MILLAN: THANK YOU, KEVIN. I THINK KEVIN IS REFERRING TO THE CIRM IPSC BANK WHERE WE HAVE OVER 2500 DIFFERENT IPSC'S GENERATED FROM A VARIETY OF DIFFERENT DISEASE TARGETS AND BACKGROUNDS.

DR. MUMMERY.

DR. MUMMERY: I JUST WANT TO FOLLOW UP ON THE CONCEPT OF SHARING BECAUSE IN SOME CASES THE MTA'S ARE PROVING A LITTLE PROHIBITIVE FOR TRUE SHARING. AND JUST GIVE AN EXAMPLE. IF ONE RESEARCHER IN ONE DEPARTMENT HAS A LINE FROM, FOR EXAMPLE, CORYELL, AND THEN WANTS TO WORK WITH SOMEBODY WITH ANOTHER SET OF SKILLS IN THE SAME DEPARTMENT, WE CAN'T ACTUALLY SHARE THE LINE. SO THE NEW RESEARCHER HAS TO GET THEIR OWN LINE UNDER THEIR OWN MTA AND ACTUALLY HAS TO IMPORT THE LINE AND MAKE THE VIALS AND ALL KIND OF STUFF.

SO I THINK IT'S REALLY IMPORTANT, IF YOU'RE TALKING ABOUT SHARING SOURCES, TO ACTUALLY BE VERY CLEAR ON WHAT YOU MEAN BY SHARING AND MAYBE BE FLEXIBLE IN HOW THAT'S DONE. JUST A SUGGESTION.

DR. HAUSSLER: YES. WE ARE WORKING WITH CORYELL ON A HUB-AND-SPOKE MODEL SO THAT EVERYONE GETS THEIR TISSUE RESOURCES FROM CORYELL. AND THIS



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IS BENEFICIAL IN THE SENSE OF QUALITY CONTROL AND MAKING SURE THAT EVERYTHING IS DONE EXACTLY THE SAME WAY, SHIPPED EXACTLY THE SAME WAY, ETC. THERE ARE LOTS OF SUBTLETIES, AS YOU KNOW, WHEN YOU ARE EXCHANGING THESE LIVING REAGENTS. AND SO WE APPRECIATE THE BENEFITS OF THAT, BUT IT DOES ADD A BUREAUCRATIC LAYER. EVERYONE HAS TO WORK THROUGH CORYELL RATHER THAN JUST SHARING THEM LAB TO LAB. AND WE SHOULD THINK ABOUT THAT. IT'S A GOOD POINT.

DR. MILLAN: I'M GOING TO TURN IT TO DR. SINGEC. BUT BEFORE WE SAY THAT, I THINK FOR CONSIDERATION IS DOES THIS TYPE OF RESOURCE SHARING BELONG WITHIN ACADEMIA VERSUS BELONGING FOR THOSE TOPICS THAT YOU MENTIONED, DR. MUMMERY, ABOUT ALL OF THE DIFFERENT ENCUMBRANCES WITH MTA'S AND OTHER THINGS WITH COMMERCIAL ENTITIES.

MAYBE I CAN TURN TO DR. SINGEC, AND I'D LOVE TO HEAR EVERYBODY'S RESPONSE TO THAT QUESTION.

DR. SINGEC: YEAH. A REALLY FANTASTIC EFFORT. CONGRATULATIONS.

SO I JUST WANTED TO ADD TO THIS THERE ARE QUICKLY ALSO OPPORTUNITIES FOR COLLABORATION. SO WE ARE BUILDING REP-SIDED NCATS THAT WE CALL THE IPSC PORTAL. THIS WILL BE A WEBSITE, A LIVING WEBSITE, WHERE WE WILL BE DEPOSITING LARGE DATASETS PRESENTED



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IN A USER-FRIENDLY FORMAT FOR DATA MINING. THIS WILL ALSO BE A WEBSITE INCLUDING DETAILED PROTOCOLS, HOW WE DIFFERENTIATE CELLS, ALSO LOTS OF DATA ON CHEMICAL BIOLOGY AND SCREENING DATA AS WELL.

I THINK THIS IS A FANTASTIC EFFORT WHERE REALLY MARRYING GENOMICS WITH THE STEM CELL BIOLOGY AND DIFFERENTIATING CELLS AND SPECIFIC PHENOTYPES AND REALLY MONITORING WHAT'S REALLY HAPPENING, INTEGRATING MULTIOMICS TECHNOLOGIES, THIS IS ABSOLUTELY FUNDAMENTAL FOR THE ENTIRE FIELD. AND GOING FORWARD WITH THE NEXT GENERATION TECHNOLOGIES, I THINK THIS IS REALLY PRIME TIME TO TAKE THIS REALLY CENTER STAGE. SO REALLY GREAT EFFORT. CONGRATULATIONS.

DR. HAUSSLER: THANK YOU. WE REALLY LOOK FORWARD TO WORKING MORE CLOSELY WITH NCATS. PLEASE CONTACT ME ON THE SIDE.

DR. MILLAN: KEVIN, YOUR HAND IS STILL UP. IS THAT JUST RESIDUAL?

DR. EGGAN: I'LL PUT IT DOWN.

DR. MILLAN: SO I THINK I HAVE EVERYBODY WHOSE HANDS ARE RAISED.

TO THE QUESTION OF IS THIS A TYPE OF THING THAT -- HOW DOES IT PLAY INTO IT WHEN YOU'RE LOOKING AT KIND, LET'S TALK, THE SUPPLY CHAIN OF MATERIALS

TO FUEL THIS EFFORT, DAVID, IN TERMS OF WE WORK WITH WHAT WE CURRENTLY HAVE; BUT IF YOU WERE TO DESIGN THIS TO BE GEARED TOWARDS SCIENTIFICALLY AND EFFICIENCY AND KNOWLEDGE GENERATING IN THE BEST POSSIBLE FASHION, HOW WOULD IT LOOK? WHO WOULD THE PLAYERS BE?

DR. HAUSSLER: ABSOLUTELY. I SEE CHRIS JUST COMMENTED THAT NEW YORK STEM CELL FOUNDATION CREATED A DIVERSITY PANEL. THERE'S ALSO A LOT OF WORK. WE WORK WITH THE PEOPLE AT MOUNT SINAI WHO ARE COLLECTING FROM NEW YORK. ONE OF THE AMAZING THINGS ABOUT NEW YORK IS SO MUCH ETHNIC DIVERSITY IS REPRESENTED IN ONE PLACE. AND THAT'S A GREAT OPPORTUNITY FOR COLLECTING CONSENTED SAMPLES. AND SO I THINK ALL OF THOSE RESOURCES WORKING TOGETHER WILL BE KEY FOR THIS.

WE'VE ALSO TALKED TO SOME OF THE MORE NEURO-ORIENTED INSTITUTES, AND THEY ARE VERY EXCITED. THERE ARE PROGRAMS TO CREATE STEM CELL LINES FOR DISEASE MODELS, AND I THINK IT WOULD BEHOOVE US ALL TO THINK ABOUT HOW WE CREATE STEM CELLS FOR THE NORMAL REFERENCE GENOME RESOURCES IN THE SAME WAY THAT WE CREATE THEM FOR DISEASE COHORTS. AND THEN WE CAN DO AN APPLES-TO-APPLES COMPARISON AT THAT POINT.

SO I DO THINK, WHILE THE PROJECT I MENTIONED IS ONLY FOR NORMALS, OPENLY CONSENTED, NOT ENCUMBERED CELL LINES FOR GENERAL RESEARCH PURPOSES, THERE WILL BE LOTS OF OTHER CELL LINES THAT ARE DISEASE SPECIFIC AND ARE MORE RESTRICTED, BUT NEVERTHELESS INCREDIBLY VALUABLE.

DR. MILLAN: THANK YOU VERY MUCH. AGAIN, JUST PUTTING IT BACK INTO SOME TERMINOLOGY FOR RECURRENT THEMES THAT HAVE BEEN COMING UP TODAY, IS THIS WHOLE IDEA, IF WE WERE LOOKING AT IT FROM A CONSORTIUM-BASED MODEL, THAT THIS TYPE, ALTHOUGH IT SEEMS RATHER HUGE, IT WOULD BE KIND OF A CORE TECHNOLOGY, RESOURCE SHARING OPPORTUNITY THAT CROSSES ACROSS EITHER THEMATIC-BASED OR DISEASE-BASED CONSORTIA.

DR. HAUSSLER: ABSOLUTELY. AND IF WE DON'T AUTOMATE, INDUSTRIALIZE, AND MAKE IT SMARTER, FASTER, CHEAPER, MORE CONSISTENT THIS TECHNOLOGY, WE WILL NEVER GET ANYWHERE. THE MONEY INVESTED RIGHT NOW IN THE ACCURATE, REPRODUCIBLE REPRODUCTION OF ORGANOIDS MODELING DIFFERENT TISSUES THAT ARE VALIDATED WILL PAY OFF ENORMOUSLY OVER THE NEXT TEN YEARS. I'M NOT TRYING TO STIFLE INNOVATION, BUT I THINK AT THIS POINT WE NEED TO, WHILE WE ENCOURAGE PEOPLE TO INNOVATE NEW ORGANOID METHODS, WE NEED



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THEM ALSO TO COLLABORATE ON A BEST-OF-BREED PROJECT.

DR. MILLAN: THANK YOU, DAVID. CLIVE.

DR. SVENDSEN: JUST TO AGREE. EVERYTHING IS -- THERE'S SO MANY DIFFERENT RESOURCES IN DIFFERENT PLACES. I THINK THE ONE DAVID IS CREATING IS FANTASTIC, BUT IT WOULD BE LOVELY IF, SAY, WE MADE A THOUSAND IPS LINES FROM ALS PATIENTS, WHICH WE HAVE, IT WOULD BE LOVELY JUST TO LINK THOSE DIRECTLY TO THE ONES DAVID IS TALKING ABOUT BECAUSE WE CAN BREAK DOWN THE ETHNICITIES OF THOSE LINES, WE ALREADY HAVE, AND THEN RELATE THEM TO THE GENOME. I THINK IF WE COULD JUST HAVE A MECHANISM TO TIE THE NEW YORK GENOME PROJECTS AND THE NYCF AND SORT OF THE INITIATIVES THAT ARE GOING ON IN CALIFORNIA ALMOST -- SOMEONE LIKE THE ISSCR COULD SUPPORT OF CIRM, KIND OF A BROADBASED, LET'S ALL GET TOGETHER IN THE SAME ROOM AND COLLABORATE. ALL THESE REPOSITORIES AND STEM CELL LINES ARE MADE A LITTLE DIFFERENTLY. SOME ARE USING A DIFFERENT TECHNOLOGY TO MAKE THEM, AND THAT DOES MAKE A DIFFERENCE TO THE IPS CELLS AND HOW THEY GROW AND DIFFERENTIATE.

IN FACT, THE STATE OF THE IPS CELL CAN REALLY DETERMINE WHAT IT CAN DIFFERENTIATE INTO. WE'RE LEARNING THAT NOW. SO IT IS NOT JUST LIKE EVERY IPS CELL IS IDENTICAL, BUT THERE'S ENOUGH



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SIMILARITIES, IF WE ALL GOT TOGETHER TO UTILIZE ALL THESE RESOURCES, NOT TO MENTION, CHRISTINE, THE MASSIVE RESOURCES IN EUROPE NOW THAT ARE GOING ON, ALL THE BIOBANKING AND IPS LINES THERE. SO THERE'S AN OPPORTUNITY HERE, I THINK, FOR A LOT OF VERY LARGE, HIGH LEVEL INTEGRATION OF WHAT WE CAN FIND, AND WHAT CAN WE MATCH TOGETHER AND WHAT CAN'T WE? AND THERE'S GOING TO BE SOME LIMITATIONS, BUT IT'S A BIG VIEW, BUT IT WOULD BE A BIG TASK, BUT IT REQUIRES, I THINK, SOME KIND OF BIG WORKSHOP TO GET US ALL IN THE SAME ROOM AND THRASH OUT WHAT'S AVAILABLE, AND THEN HAVE A JOINT OPEN RESOURCE WAY OF DIVING INTO ALL THESE LINES. WE HAVE TO DO IT ALL SEPARATELY NOW, AND THERE'S ABOUT 40 DIFFERENT PLACES. BE NICE TO GET SOMETHING THAT LINKS THEM ALTOGETHER.

DR. MILLAN: ILYAS HAS HIS HAND UP. ONE OF THE THINGS IS WHEN WE TALK ABOUT REFERENCES, IT DOESN'T NECESSARILY MEAN IT'S THE BEST OR THE MOST APPROPRIATE FOR A GIVEN THING. IT'S JUST A REFERENCE. AND SO AT LEAST TO HAVE AN ANCHORING POINT AGAINST WHICH YOU COMPARE OR RELATE TO SO THAT PEOPLE ARE KIND OF STARTING FROM THE SAME POINT TO MEASURE THE VARIOUS THINGS, I THINK THERE'S GREAT VALUE IN THAT. DAVID, WE DON'T THINK THAT YOU'RE

STIFLING RESEARCH AT ALL. IN FACT, I THINK THIS IS NECESSARY IN ORDER FOR US TO PROMOTE PROGRESS AND ADVANCEMENTS.

SO, ILYAS, I THINK THIS IS A NEW HAND UP.

DR. SINGEC: SO BASED ON THE DISCUSSIONS ABOUT STANDARDIZATION AND SYSTEMATIC APPROACHES, ONE OTHER THING WE ARE DOING CURRENTLY AT NCATS IS WE'RE SYSTEMATICALLY LOOKING AT 150 SMALL MOLECULES THAT WE HAVE SELECTED. SO LOOKING AT WHAT COMPOUNDS, SMALL MOLECULE COMPOUNDS HAVE BEEN USED IN CELL DIFFERENTIATION PROTOCOLS ACROSS DIFFERENT STEM CELL BIOLOGY DISCIPLINES. SO WE SEE THERE'S STILL A LOT TO BE LEARNED. AND SO THERE'S A LOT OF VARIABILITY ALSO HOW FOLKS ARE USING SMALL MOLECULES EVEN THOUGH WE'RE USING THIS TO MAKE THINGS MORE STANDARDIZED AND CHEAPER AND IN SOME CASES TRYING TO DEMOCRATIZE THE CELL DIFFERENTIATION PROTOCOLS, BUT STILL THERE ARE REALLY REFERENCE DATASETS MISSING. SO WE ARE TRYING TO SYSTEMATICALLY APPLY THESE SMALL MOLECULES TO STEM CELLS AT DIFFERENT STAGES AND TRYING TO REALLY COME UP WITH ESSENTIALLY A ROAD MAP THAT WOULD HELP US TO BETTER UNDERSTAND HOW WE CAN INDUCE CERTAIN GENES, TRANSCRIPTION FACTORS SO AT THE SAME TIME AVOIDING TOXICITY. SO THIS IS OFTENTIMES OVERLOOKED. SO THIS CAN BE REALLY A CONFOUNDER IN

INTRODUCING VARIABILITY.

SO DOING IT SYSTEMATICALLY AND THEN REALLY USING RNA SEQ TYPE OF EXPERIMENTS, GETTING THE GENOMIC DATA, AND THEN PUTTING IT OUT SO THAT IT'S PRESENTED IN A USER-FRIENDLY WAY SO WE CAN REALLY LOOK HOW THESE SMALL MOLECULES REALLY REGULATE THE GENOME, AND HOW CAN WE REALLY CHERRY-PICK THE SMALL MOLECULES THAT ACTIVATE OR INHIBIT PATHWAYS SO THAT WE CAN ESSENTIALLY HAVE ALMOST A COOKBOOK FOR FORMULATING BETTER OR MORE EFFICIENT CELL DIFFERENTIATION PROTOCOLS. SO THIS IS ONE OF THE IDEAS BEHIND THIS, AGAIN, AS PART OF THE ENTIRE APPROACH OF HAVING REFERENCE DATASETS AND STANDARDIZATION AND REPRODUCIBILITY.

WE'RE GOING TO CALL THIS THE STEM CAM AT SOME POINT, A RESOURCE.

DR. HAUSSLER: THIS IS AN INCREDIBLY IMPORTANT TOPIC ABOUT VALIDATING COMPARED TO PRIMARY TISSUES. AND WE'VE WORKED WITH KRIEGSTEIN AND NOWAKOWSKI AND POLLEN AT UCSF WHO HAD, UNTIL TRUMP CUT THEM OFF, ACCESS TO FETAL TISSUES AND WERE ABLE TO VALIDATE THE CEREBRAL ORGANOID MODELS. AND WE FIND THAT SINGLE CELL GENE EXPRESSION IN SINGLE CELL RNA IS A VERY POWERFUL TOOL FOR THAT. IF YOU CAN GET THOSE EXPRESSION PATTERNS TO MATCH UP AND SHOW



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THE SAME DIFFERENT TYPES OF CELLS THAT ARE ACTIVE, THAT'S A HUGE BAR AND WE AREN'T THERE YET. THERE'S STILL A LOT OF STRESS AND SO FORTH IN THE ORGANOIDS THAT ARE NOT PRESENT IN THE ACTUAL TISSUE, BUT WE HAVE DEFINITIVE, WHAT WE CALL A REPORT CARD NOW, WHICH IS A MACHINE WAY OF COMPARING WHAT IS THE DISCREPANCY BETWEEN THE ORGANOID MODEL AND THE PRIMARY TISSUE.

DR. MILLAN: THANK YOU SO MUCH, DAVID. AND JUST FOLLOWING ON ILYAS, WE APPROPRIATELY HAVE PETE SCHULTZ AS OUR NEXT PRESENTER.

DR. SCHULTZ: THANKS A LOT, MARIA. THANKS TO EVERYBODY FOR THEIR TIME.

I KIND OF WANTED TO HIT ON THREE TOPICS RELATED TO SMALL MOLECULES AND REGENERATIVE MEDICINE. THE FIRST IS THE OPPORTUNITY, THE SECOND IS THE IMPACT CIRM COULD HAVE IN THIS SPACE, AND THE THIRD IS INFRASTRUCTURE THAT COULD FACILITATE SMALL MOLECULE DISCOVERY AND A LOT OF CIRM-FUNDED PROJECTS.

AS YOU ALL KNOW, SMALL MOLECULES AND NOW BIOLOGICS ARE KIND OF THE CORNERSTONE OF MODERN MEDICINE TO A LARGE DEGREE BECAUSE THEY'RE EASY TO DISTRIBUTE AND ADMINISTER EITHER BY ORAL OR PARENTERAL ROUTES. I WOULD ARGUE THERE'S A HUGE



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OPPORTUNITY, AND, IN FACT, I WOULD ARGUE IT'S A FRONTIER FOR SMALL MOLECULES IN REGENERATIVE MEDICINE THAT IS TO COMPLEMENT CELL-BASED THERAPIES AND TO CONTROL THE ACTIVITY OF ENDOGENOUS STEM CELLS IN VIVO WITH SMALL MOLECULE DRUGS OR WITH ANTIBODIES.

AND THERE ARE A NUMBER OF EXAMPLES ALREADY OF THIS. THERE'S SMALL MOLECULES THAT ARE IN CLINICAL DEVELOPMENT THAT EXPAND CORD BLOOD CELLS FOR BONE MARROW TRANSPLANTS TO MAKE BONE MARROW TRANSPLANTS FAR MORE APPROACHABLE. THEY ACT THROUGH AERO HYDROCARBON RECEPTOR AND OTHERS. THERE'S SMALL MOLECULES THAT ACTIVATE -- AGONIZE TPO RECEPTOR TO EXPAND AND FORM MEGAKARYOCYTES. THERE ARE MOLECULES NOW IN THE CLINIC TO INDUCE A DIFFERENTIATION OF OPC'S TO OLIGODENDROCYTES TO REMYELINATE AND ALSO TO ACTIVATE COCHLEAR PROGENITOR CELLS FOR HEARING LOSS. AND THEN IN JOINT REPAIR, THERE ARE A NUMBER OF PROGRAMS IN THE CLINIC THAT INDUCE CHONDROGENESIS FROM MSC'S, AND THAT COULD HAVE A HUGE IMPACT ON OA. AND ALSO IN INTESTINAL DISEASE, THERE ARE PEPTIDES THAT ARE BEING LOOKED AT FOR BARRIER REPAIR NOW IN SMALL BOWEL SYNDROME, BUT SOON IN IBD.

SO THOSE ARE JUST A FEW EXAMPLES. THERE AREN'T QUITE SO MANY BECAUSE MOST OF THE WORK BEING

DONE IS COMING OUT OF ACADEMIC LABORATORIES AND SMALL BIOTECH START-UPS. PHARMA HASN'T, TO ANY SIGNIFICANT DEGREE, WITH A FEW EXCEPTIONS, REALLY EMBRACED DRUGS AS REGENERATIVE MEDICINE. SO THAT'S INTERESTING BECAUSE IT GIVES CIRM AN OPPORTUNITY TO REALLY KIND OF TAKE THE LEAD IN THIS AREA AND SHOW THE VALUE OF DRUGS AS REGENERATIVE MEDICINES. AND I THINK IF CIRM CONTINUES TO PLOW THE WAY IN THIS REGARD, BIG PHARMA WILL CERTAINLY FOLLOW.

SO THE QUESTION IS CAN YOU DO THIS IN SMALL BIOTECHS? JUST TO MAKE THE POINT THAT YOU CAN, JUST A COUPLE OF EXAMPLES FROM SCRIPPS LABS, WE RECENTLY FOUND MOLECULES IN A SCREEN OF HUMAN LUNG STEM CELLS THAT EXPAND HUMAN LUNG STEM CELLS BY ACTING ON AUTOCRINE SIGNALING LOOPS. AND THESE MOLECULES, WE MADE LONG TARGETED VERSIONS THAT ARE INCREDIBLY POTENT, HAVE GREAT TI'S, AND WORK IN ACUTE AND CHRONIC LUNG INJURY MODELS. IN THE GLIAL MODEL, THEY WORK BETTER THAN ANYTHING WE'VE SEEN, INCLUDING THE STANDARD OF CARE. AND, IN FACT, THEY'RE ADDITIVE WITH THE STANDARD OF CARE IN IPF, WHICH IS NINTEDANIB.

SO WE THINK THESE MOLECULES COULD HAVE HUGE PROMISE IN THE TREATMENT OF PULMONARY FIBROSIS, BUT ALSO ACUTE LUNG INJURY FROM COVID OR CHRONIC



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LUNG INJURY FROM COPD.

WE'VE ALSO FOUND MOLECULES THAT WORK THE NOVEL MECHANISM IN ACTION TOO THAT EXPAND SKIN PROGENITORS. AND THESE ARE ACTIVE IN HUMAN EXPLANTS AND ALSO IN THE MINI PIG MODELS. SO WE THINK THIS COULD BE A REALLY IMPORTANT TOPICAL THERAPY FOR DIABETIC WOUND HEALING, WHICH IS A HUGE UNMET NEED THAT LEADS TO AMPUTATION AND DEATH. AND THEN IF YOU EXPAND, WHICH I THINK THIS PANEL OUGHT TO CONSIDER, EXPAND THE DEFINITION OF HOW SMALL MOLECULES CAN ACT A LITTLE FURTHER. RIGHT NOW THEY HAVE TO ACT ON PROGENITOR CELLS OR STEM CELLS FOR CIRM FUNDING, BUT WE'VE FOUND MOLECULES THAT ACT THROUGH THE HIPPO YAP PATHWAY, AND THOSE COULD ACTUALLY, BASED ON SOME OF THE WORK WITH CARDIOMYOCYTES OUT OF TEXAS, BE A WAY TO EXPAND CARDIOMYOCYTES POST HEART FAILURE AND REPAIR HEART DAMAGE.

AND WE ALSO HAVE MOLECULES THAT INHIBIT MST1 ON THE SAME PATHWAY. AND IN COLLABORATION WITH MAYO CLINIC, WE'VE SHOWN IN PRECLINICAL MODELS THAT THESE REPAIR LIVER WITHIN A COUPLE OF DAYS. SO WE ARE LOOKING AT THESE FOR HEPATECTOMIES ASSOCIATED WITH CANCER METASTASIS. THOSE ARE JUST A COUPLE OF EXAMPLES OUT OF ONE OR TWO LABS AT SCRIPPS THAT SHOW THE NONPROFIT WORLD CAN HAVE A BIG IMPACT IN THIS

SPACE.

THE QUESTION IS WHAT'S THE BEST WAY TO DO THIS? AND WHAT WE HAVE TALKED WITH MARIA BRIEFLY ABOUT IS WE BUILT, AND I KNOW CHRIS KNOWS ABOUT THIS, WE BUILT WITH THE GATES FOUNDATION FOR INFECTIOUS DISEASE A LARGE COLLECTION OF EVERY DRUG THAT'S EVER BEEN PUT INTO THE CLINIC AS WELL AS LATE STAGE PRECLINICAL. THE ADVANTAGE THERE IS YOU KNOW ALL THE PHARMACOLOGY, YOU KNOW THE SAFETY, YOU KNOW THE DOSING, AND SO FORTH. IT'S ALL IN A DATABASE. AND WE BUILT THE COLLECTION WITH GATES FUNDING AND HAVE DISTRIBUTED IT TO NOW TO BETWEEN 1 AND 200 LABS COST FREE. THE ONLY CONSTRAINT, THAT PEOPLE HAVE TO ENTER THEIR DATA INTO A DATABASE AFTER A YEAR THAT'S PUBLICLY AVAILABLE.

AND SO THIS COLLECTION ALLOWS ACADEMIC LABS TO LOOK AT MOLECULES THAT THEY CAN MOVE VERY, VERY QUICKLY INTO THE CLINIC. IN FACT, THE LUNG EXPANSION MOLECULE IS A KNOWN DRUG, AND WE SIMPLY MADE A LONG TARGETED VERSION BY DERIVITIZING IT. AND THE BEAUTY OF THIS COLLECTION IS IT'S VERY HARD TO DO REALLY LARGE SCREENS OF SMALL MOLECULES ON A LOT OF THE COMPLEX STEM CELL SYSTEMS LIKE ORGANOIDS AND WHAT HAVE YOU. BUT 14,000 COMPOUNDS YOU CAN DO IN AN ORGANOID FORMAT. IN FACT, WE'RE DOING THAT



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RIGHT NOW WITH INTESTINAL ORGANOIDS AND ALSO LUNG ORGANOIDS WITH THE GROUP AT CORNELL WILDE.

SO THE BEAUTY IS, BASED ON WHAT WE DID WITH THE GATES FOUNDATION, THE WHOLE NETWORK THERE, IS TO DISTRIBUTE THESE IN PLATES SUITABLE FOR SCREENING AND PUT TOGETHER THE DATABASE, MAKE IT PUBLICLY AVAILABLE. THEN WHEN PEOPLE FIND INTERESTING THINGS, THEY CAN GO RAPIDLY INTO ANIMAL MODELS AND ESSENTIALLY RAPIDLY INTO THE CLINIC EITHER WITH THE MOLECULE ITSELF OR AN ANALOG WITH IMPROVED SPECIFIC PROPERTIES.

SO I'D ARGUE THAT BUILDING -- RIGHT NOW THAT COLLECTION WAS BUILT WITH THE GATES FOUNDATION. IT WAS ROUGHLY $20 MILLION TO BUILD ALL THE INFRASTRUCTURE, AND YOU COULD PROBABLY DO IT AGAIN MORE CHEAPLY. WE HAD TO MAKE HALF THE MOLECULES. YOU COULD PROBABLY DISTRIBUTE IT. AS I SAID, WITH THE GATES, IT'S REALLY FOCUSED ON INFECTIOUS DISEASE, BUT YOU COULD DISTRIBUTE THIS COLLECTION TO ANYBODY INTERESTED IN REGENERATIVE MEDICINE TOO. AND I THINK IT WOULD BE AN INTERESTING RESOURCE.

THAT'S ALL I HAD TO SAY, BUT I THINK THERE IS A LARGE OPPORTUNITY. THERE'S AN OPPORTUNITY FOR CIRM TO TAKE A LEADERSHIP ROLE HERE AND FOR PHARMA TO FOLLOW, AND I THINK THERE'S A WAY THAT YOU CAN



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MAKE THIS APPROACH BROADLY AVAILABLE TO THE COMMUNITY. THANKS A LOT.

DR. MILLAN: THANK YOU SO MUCH, PETE. BEFORE I TAKE THE FIRST QUESTION, JUST A QUESTION. WHAT TYPE OF GENOMICS DATA DO YOU HAVE ASSOCIATED, JUST FOLLOWING ON FROM PREVIOUS CONVERSATION, WITH THESE COMPOUND LIBRARY AND YOUR DATASETS RELATED TO THEM?

DR. SCHULTZ: WE DO MOST OF THE GENOMIC PROFILING. SO WE HAD DISCUSSIONS WITH WELLCOME TRUST WHETHER WE WANT TO JUST ACTUALLY PROFILE ALL THE MOLECULES. AND A GENOMIC DATABASE OF WHAT'S ACTIVATED BY ALL OF THESE SMALL MOLECULES COULD BE A ROAD MAP TO WHERE TO USE THEM IF YOU HAVE A SPECIFIC REGENERATIVE PATHWAY ALSO PROFILE. WE DID NOT DO THAT AT THE TIME BECAUSE THE COST OF DOING THAT ACROSS THE WHOLE DATABASE WAS MORE THAN DOING THE SCREENS AND THEN, AFTER THE FACT, DOING ALL OF THE ANALYSIS, WHICH WE DO WITH EVERY ONE OF THE HITS THAT WE IDENTIFY. SO I THINK IT'S JUST A QUESTION OF COST. IT'S SO SIMPLE TO SCREEN THESE THAT IN GENERAL WE SCREEN AND THEN DO THE POSTSCREEN ANALYSIS ON THE HITS RATHER THAN PROACTIVELY. BUT THAT WOULD BE AN INTERESTING PROJECT TO DO.

WE'VE ALSO PROVIDED THE COLLECTION TO, FOR

EXAMPLE, INSITRO, AND THEY'RE USING IT LOOKING AT MACHINE LEARNING TOOLS TO ACTUALLY FIGURE OUT INTERESTING APPLICATIONS OF THESE MOLECULES, AND SPECIFICALLY THEY ARE LOOKING IN THE STEM CELL ARENA. SO THERE'S A LOT OF OPPORTUNITIES WITH THIS COLLECTION TO TAKE IT IN OTHER DIRECTIONS AS WELL IF ONE WANTED TO BUILD IT.

DR. MILLAN: I DON'T SEE ANY HANDS UP, BUT WHOEVER HAS A COMMENT OR QUESTION, PLEASE GO AHEAD AND PIPE IN AT THIS POINT.

DR. MC CUNE: PETER, I'M FAMILIAR WITH THE LIBRARY THAT PETER MENTIONED. IT IS QUITE POWERFUL AND HAS BEEN USED IN THE CONTEXT OF INFECTIOUS DISEASES LOOKING AT SINGLE COMPOUNDS AGAINST GIVEN AGENTS IN HIGH THROUGHPUT SCREENS. I CAN SEE WHERE YOU ARE HEADED, PETE. THIS WOULD POTENTIALLY, GIVEN THE DISCUSSION THAT WE HAD EARLIER ABOUT ROBOTICS AND COMING UP WITH HIGH THROUGHPUT SCREENS FOR DIFFERENTIATION OF STEM CELLS OR MOBILIZATION OF STEM CELLS OR PUTTING THEM INTO CYCLE TO MAKE THEM MORE RECEPTIVE TO THERAPY OR TO MODIFICATION, I CAN SEE THAT WOULD BE A REAL GOLD MINE ACTUALLY.

SO I WOULD IMAGINE THAT MORE THOUGHT ABOUT THIS WOULD BE WORTHWHILE AT THIS JUNCTURE FOR CIRM.

DR. SCHULTZ: MIKE, WE'VE DONE LARGE



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SCREENS WHEN WE WERE LOOKING AT EXPANDING CORD BLOOD CELLS. EVEN THERE, IF YOU'RE USING PRIMARY CELLS, YOU'RE LIMITED IN THE NUMBER OF CELLS YOU CAN GET. AND THEN AS YOU GO TO ORGANOIDS OR MORE COMPLEX IMAGE-BASED SYSTEM FOR MACHINE LEARNING, IT GETS HARD TO DO LARGE NUMBERS AND ALSO INCREDIBLY EXPENSIVE. THE BEAUTY OF THIS IS IT'S 14,000. ANYBODY CAN DO IT. AND, IN FACT, FOR COVID WE DISTRIBUTED TO PROBABLY 50 LABS AROUND THE WORLD TO LOOK FOR SMALL MOLECULES THAT COULD IMPACT.

DR. MILLAN: DAVID HAUSSLER, CAN YOU COMMENT? I'M WONDERING HOW THIS COULD KIND OF FIT INTO SOME OF WHAT YOU WERE TALKING ABOUT REGARDING KIND OF HAVING REFERENCE SAMPLES -- KIND OF REFERENCES IN ORGANOID MODELS OR WHAT OTHER MODELS LINK TO THE GENOMICS, AGAIN, AGAINST A MORE INFORMED DIVERSE REFERENCE SET. DO YOU SEE THAT THESE TYPES OF COMPOUND LIBRARIES AND DATASETS RELATED TO COMPOUND LIBRARIES WHERE YOU MAY ACTUALLY UNDERSTAND MAYBE SOME OF THE TRIGGERED PATHWAYS OR WHAT HAVE YOU? DO YOU SEE THAT THAT'S SOMETHING THAT EASILY FITS IN, OR IS IT A LITTLE BIT FURTHER OUT IN TERMS OF HOW THESE PIECES CAN COME TOGETHER?

DR. HAUSSLER: I THINK THIS WORKS FROM DAY ONE. AND I WAS EXCITED TO HEAR PETE MENTION THE



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INTESTINAL AND LUNG ORGANOID SCREENS THAT WERE HIGH THROUGHPUT WITH MANY COMPOUNDS SCREENED AGAINST MANY ORGANOIDS. THAT'S THE KEY, PETE, THAT'S SO EXCITING. THIS IS THIS MISSING PIECE REALLY. I THINK THESE ORGANOIDS WILL BE VERY USEFUL FOR RESEARCH IN INDIVIDUAL LABS, BUT ACTUALLY FOR HIGH THROUGHPUT WORK, THE KIND OF SYSTEM THAT THE NCATS PROGRAM IS BUILDING, WHICH CAN BE MINIATURIZED, HIGHLY SCALED, AND WORKED IN PARALLEL IS THE FUTURE REALLY OF DISEASE RESEARCH ALL THE WAY TOWARDS THE LATE STAGES IN PHARMACEUTICAL DEVELOPMENT.

I THINK PHARMA IS STARTING TO RECOGNIZE THE IMPORTANCE OF THESE CHIPS, ORGANOIDS ON CHIPS, AND THE HIGH THROUGHPUT NATURE OF THEM, AND THEY SHOULD BE VERY HAPPY TO, I WOULD SAY, PRECOMPETITIVELY CONTRIBUTE TO SOME STANDARDIZATION IN THAT FIELD.

DR. SCHULTZ: DAVID, WE EVEN STARTED TO DO SOME LYMPH ORGANOIDS WITH MARK DAVIS.

DR. HAUSSLER: FANTASTIC.

DR. SCHULTZ: SO THERE'S A LOT OF -- WHEN YOU GET INTO THOSE COMPLEX SYSTEMS, YOU REALLY DO NEED FOCUSED COLLECTIONS OF MOLECULES. AND WHAT'S AMAZING IS WE'VE FOUND THERE'S SO MANY ACTIVITIES THAT CAN BE REPURPOSED FROM KNOWN OR LATE STAGE

PRECLINICAL DRUGS. AND THE BEAUTY IS BECAUSE PEOPLE HAVEN'T SCREENED THOSE IN REGENERATIVE MEDICINE IN GENERAL, THERE'S A HUGE AMOUNT TO BE FOUND.

DR. MUMMERY: I JUST WANTED TO MAKE THAT'S AN IMPORTANT POINT. IN READING THROUGH THE CIRM SORT OF REMIX, DRUGS AND GENE THERAPIES ALSO FALL IN THE CATEGORY OF REGENERATIVE MEDICINE, WHICH IS REALLY NICE. BUT THESE ASSAYS WILL CRUCIALLY DEPEND ON HAVING THE RIGHT READOUTS. SO YOU HAVE TO KNOW WHAT READOUTS YOU'RE HAVING AND PREFERABLY HAVE A MULTICOLOR WAY OF READING IT OUT IN TIME WITHOUT HAVING TO STOP THE EXPERIMENTS, SO SOME KIND OF FLOW THROUGH OR GENETIC REPORTS OR SOMETHING LIKE THAT.

DR. SCHULTZ: CHRISTINE, THAT'S A GOOD POINT. PART OF THE REASON WE'VE BEEN WORKING WITH MACHINE LEARNING AND HIGH CONTENT IMAGING WITH THE GOOGLE FOLKS AND OTHERS BECAUSE YOU CAN GET A LOT MORE INFORMATION OUT OF THOSE SCREENS AND PROBABLY SOME OF THE CHALLENGES. THE GOOD NEWS IS WE'VE WORKED THROUGH. WE'VE MADE A HUGE NUMBER OF MISTAKES WORKING THROUGH ALL THE BUGS ON THIS. SOME OF THESE DIFFERENTIATION ASSAYS ARE EIGHT DAYS, TEN DAYS, FOURTEEN DAYS. SO IF YOU CAN USE MACHINE LEARNING TO GET EARLY INFORMATION AFTER A FEW DAYS OF WHERE YOU'RE HEADING DOWN A DIFFERENTIATION



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PATHWAY, IT'S INCREDIBLY VALUABLE.

AND NOW WE'RE DOING THAT WITH MDS, ERYTHROCYTE PROGENITORS. QUITE FRANKLY, WE FOUND A REALLY INTERESTING MOLECULE FROM THE REFRAN COLLECTION THAT INDUCES DIFFERENTIATION OF ERYTHROCYTES WHICH WE THINK COULD BE A TREATMENT FOR MDS. AND THE BEAUTY IS IT'S A KNOWN DRUG, SO IT WOULD BE GENERIC AND IT WOULD BE CHEAP TO THE TAXPAYER.

DR. MUMMERY: SO THIS IS EXACTLY THE TYPE OF THING THE ALLEN INSTITUTE IS DOING IN MAKING THEIR RESOURCES AVAILABLE. SO YOU'RE IN A VERY DETAILED, HIGH QUALITY ANALYSIS READY FOR SCREENING.

DR. HAUSSLER: I WANT TO SECOND THAT AS WELL, PETE. AGAIN, WE FOUND THAT IT'S REALLY ESSENTIAL THAT OUR GROWING CEREBRAL ORGANOIDS BE UNDER THE MICROSCOPE ESSENTIALLY CONTINUOUSLY. WE CAN DO THAT WITH SIMPLE CELL PHONE CAMERAS AND SO FORTH SO THAT THAT CAN BE ALL HOOKED UP ON THE INTERNET AND AUTOMATED. THIS IDEA OF HAVING LAB TECHNICIANS COME IN AT ALL HOURS TO FEED AND DEAL WITH THE CELLS AND TAKE THEM OUT OF THE INCUBATOR AND PUT THEM BACK IN, IT JUST CREATES ENORMOUS BURDEN AND INCONSISTENCY IN RESULTS.

DR. SCHULTZ: I JUST WANT TO UNDERSCORE.

I THINK THESE KINDS OF ISSUES CIRM COULD PLOW THE WAY. SOMETIMES WITH PHARMA, BIG PHARMA, THERE ARE FOUR GAS STATIONS ON ONE CORNER. I THINK CIRM COULD BE THE FIRST GAS STATION ON THE CORNER, AND THEN PHARMA WILL BUILD THE OTHER THREE. I DO THINK THIS IS AN INTERESTING CASE. I ALWAYS WORRY WHEN YOU'RE DOING SMALL MOLECULE DRUG DISCOVERY IN THE NONPROFIT WORLD THAT ARE YOU DOING SOMETHING THAT'S GOING TO BE DONE BY BIG PHARMA ANYWAY, IN WHICH CASE MAYBE IT'S NOT THE BEST THING TO DO. BUT I THINK THIS IS A CASE WHERE THE NONPROFIT WORLD AND THE ACADEMIC WORLD CAN TAKE A LEADERSHIP ROLE.

DR. MILLAN: SO THANK YOU SO MUCH. ILYAS.

DR. SINGEC: I JUST WANT TO ALSO EMPHASIZE REALLY THE IMPORTANCE OF USING MORE SMALL MOLECULE SCREENS TO LEVERAGE REGENERATIVE MEDICINE. I THINK THIS IS STILL REALLY AN AREA OF OPPORTUNITY. AND I CAN SHARE SOME OF OUR EXPERIENCE AT NCATS.

SO WHEN I CAME ON BOARD FIVE YEARS AGO, THERE WAS ALREADY PLATFORMS ESTABLISHED AT NCATS. THIS IS REALLY WHAT THEY'RE GOOD AT. SO WE HAVE ON SITE ALMOST HALF A MILLION SMALL MOLECULES DISTRIBUTED IN VARIOUS LIBRARIES, AND YOU ALSO HAVE A DEDICATED GROUP OF COMPOUND MANAGERS, SO ACTUALLY THEY'RE TAKING CARE OF THESE LIBRARIES AND QC-ING



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THEM ON A REGULAR BASIS AND UPDATING THEM. SO INTRODUCING OTHER INTERESTING MOLECULES INTO THESE LIBRARIES AS WELL.

SO WHAT I'M TRYING TO SAY IS THIS REALLY REQUIRES A TEAM SCIENCE APPROACH WHERE YOU HAVE REALLY DEDICATED PERSONNEL REALLY COVERING THESE DIFFERENT AREAS. SO INCLUDING MET CAM AND ANALYTICAL CHEMISTRY ON SITE, TOXICOLOGISTS ON SITE. AND ALSO, AS DR. MUMMERY WAS JUST MENTIONING, YOU STILL NEED TO HAVE GOOD ASSAY DEVELOPMENT AS WELL BECAUSE THE ENDPOINTS ARE ABSOLUTELY CRUCIAL. IN SOME CASES YOU HAVE YOUR READOUT NEXT DAY, AND IN OTHER CASES WE HAVE TO THINK ABOUT READOUTS AFTER A WEEK, FOR INSTANCE. SO REALLY FINDING THE BEST FORMAT, DEVELOPING THE ASSAY, BUT THEN COORDINATING ACROSS TEAMS WHO ARE BASICALLY DEDICATED. MAINTAINING THESE LIBRARIES IS REALLY CRITICAL.

ALSO, USING OTHER ADVANCED TECHNOLOGIES THAT ALLOW US TO ACTUALLY SCREEN SMALL MOLECULES IN A COMBINATORIAL FASHION. SO NOT JUST LIKE ONE SMALL MOLECULE AT A TIME, BUT COMBINING TWO OR THREE SMALL MOLECULES AND ALSO HAVING, AT LEAST, THE AMBITION TO HAVE FULL DOSE RESPONSE CURVES IS ALSO EXTREMELY INFORMATIVE, OTHERWISE YOU ALSO DEAL A LOT WITH FALSE POSITIVE AND FALSE NEGATIVE HITS THAT YOU HAVE

TO ALSO STILL VALIDATE. IT'S AN ENTIRE ECOSYSTEM THAT IS REALLY NEEDED TO LEVERAGE THESE KIND OF APPROACHES. BUT, NEVERTHELESS, I THINK IT'S ABSOLUTELY DOABLE AND SHOULD BE DONE, AND CIRM CAN LEAD DEFINITELY HERE AS WELL.

DR. MILLAN: THANK YOU SO MUCH. WE HAVE TWO MORE MINUTES FOR THIS SECTION. ARE THERE ANY ADDITIONAL COMMENTS OR QUESTIONS FROM THE PANELISTS OR ANY STATEMENTS, PETE, THAT YOU WANTED TO END UP WITH?

DR. MUMMERY: I JUST WANTED TO, IF I MAY, ADD AN ADDITIONAL POINT. AND THAT'S REGARDING WHAT ILYAS SAID ABOUT FALSE NEGATIVES AND FALSE POSITIVES. SO WHAT WE ALSO NEED FOR THE ASSAYS IS FALSE NEGATIVES AND FALSE POSITIVES FOR PARTICULAR ASSAYS. WHAT I MEAN IS WHAT MOLECULE IS ENTIRELY NEGATIVE IN ANY RESPONSE IN A HUMAN AND SHOULD BE NEGATIVE IN OUR ASSAYS? THE OTHER WAY AROUND, WHAT IS THE LIST OF COMPOUNDS THAT'S ALWAYS POSITIVE IN PARTICULAR KIND OF TISSUE? SO THEN WE HAVE A BENCHMARK TO TEST THE ASSAY. AND THEN WHEN WE GO INTO A BUNCH OF UNKNOWNS, THEN WE ALSO KNOW WHETHER THERE ARE FALSE POSITIVES OR NEGATIVES. WE GET A BETTER CLUE.

DR. SCHULTZ: CHRISTINE, THAT'S A GOOD

POINT. THE BEAUTY OF THAT IS WITH THE INFECTIOUS DISEASE GATES EFFORT THAT WE PUT ALL THE SCREEN DATA INTO A COMMONLY ACCESSIBLE DATABASE. SO IT BECOMES VERY CLEAR IF YOU HAVE A NONSPECIFIC ACTIVATOR THAT, FIRST OF ALL, IF IT HAS TOXICITY, IT'S ALREADY ANNOTATED IN THE PHARMACOLOGICAL DATABASE. THE BEAUTY HERE IS WHEN EVERYBODY IS DOING THESE SCREENS AND PUTTING ALL THE DATA INTO A COMMON DATABASE, YOU ACTUALLY GET A HUGE AMOUNT OF CROSS-REFERENCE.

DR. MILLAN: THANK YOU SO MUCH.

DR. SCHULTZ: THANKS A LOT, MARIA.

DR. MILLAN: THANK YOU FOR BEING HERE. REALLY GREAT DISCUSSION.

AND OUR FINAL PRESENTER FOR TODAY IS CAT JAMIESON.

DR. JAMIESON: IT'S REALLY A PLEASURE TO BE ABLE TO FOLLOW PETE SCHULTZ. HE'S A MEMBER OF OUR HEME MALIGNANCIES PROGRAM AT THE MOORES CANCER CENTER WHERE WE REALLY BELIEVE IN COLLABORATION SO WE CAN MAKE OUR TREATMENTS ACCELERATED TO CLINICAL TRIALS.

IN LISTENING TO THIS VERY ERUDITE DISCUSSION TODAY, IT REMINDS ME OF CHARLES DICKENS. I STARTED UNDERGRAD IN ENGLISH LITERATURE, SO PLEASE BEAR WITH ME. "IT WAS BEST OF TIMES, IT WAS THE

WORST OF TIMES, IT WAS THE AGE OF WISDOM, IT WAS THE AGE OF FOOLISHNESS, IT WAS THE EPOCH OF BELIEF, IT WAS THE EPOCH OF INCREDULITY, IT WAS THE SEASON OF LIGHT, IT WAS THE SEASON OF DARKNESS, IT WAS THE SPRING OF HOPE." THAT BASICALLY ENCAPSULATES WHAT I HAVE TO DEAL WITH IN CLINIC ACTUALLY. I ONLY HAVE CLINIC ONCE A WEEK. I SEEM TO BE ON CALL MORE FOR THE INPATIENT SERVICE LATELY BECAUSE NOW WE'VE BLOSSOMED TO HAVE A TELE REGENERATIVE MEDICINE SERVICE IN ADDITION TO OUR CONSULTING HEMATOLOGY SERVICE. BUT WE DON'T WANT PATIENTS TO FACE THE WORST OF TIMES. WE DON'T WANT THEM TO HAVE TO FACE THE CAVEAT EMPTOR PART OF MEDICINE, BUYER BEWARE.

I'LL TALK ABOUT CANCER STEM CELL STUDIES THAT HAVE BEEN DONE AND FUNDED LARGELY BY CIRM, AND I'LL TALK ABOUT THE ALPHA STEM CELL CLINICS AS THE BACKBONE FOR REGENERATIVE MEDICINE EFFORTS IN CALIFORNIA THAT I THINK SHOULD BE A TEMPLATE FOR HOW TO RUN THESE MULTISPECIALTY UNITS IN OTHER PARTS OF THE COUNTRY, BUT ALSO INTERNATIONALLY.

SO JUST TO GO BACK TO CANCER STEMS CELLS, SO WHY DO THEY MATTER? SO CANCER STEM CELLS WERE FIRST DISCOVERED AS AN ENTITY IN 1994 BY JOHN DICK IN CANADA. AND HE SUGGESTED THAT THERE WAS A SMALL POPULATION OF CELLS WITHIN LEUKEMIA THAT COULD



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REGENERATE ALL ASPECTS OF LEUKEMIA IN SERIAL TRANSPLANTATION MODELS, WHICH BECAME THE GOLD STANDARD FOR UNDERSTANDING THESE CELLS AS THE ROOT CAUSE OF RELAPSE IN CANCER.

AS WE LOOK AT THE NUMBER ONE CAUSE OF DEATH IN THE U.S. RIGHT NOW, IT'S ACTUALLY COVID-19 FOLLOWED BY HEART DISEASE AND THEN, THIRDLY, BY CANCER. BUT WHAT THAT DOESN'T TELL YOU IS HOW QUICKLY CANCER CAN TAKE THE LIVES OF PEOPLE ESPECIALLY WHEN YOU LOOK AT LEUKEMIA. THAT ALL CHANGED WITH WORK DONE BY GEORGE DALEY, DAVID BALTIMORE, RICK VAN ETTEN WHEN THEY DISCOVERED THE PRIMARY DRIVER AT THE VERY BEGINNING OF CANCER, ONE PARTICULAR KIND OF CANCER, CHRONIC MYELOID LEUKEMIA, WAS ONE FUSION GENE. AND THAT'S WHY THE WORK DONE BY DAVID HAUSSLER IN TERMS OF INTEGRATING OUR GENOMICS EFFORTS FOR CIRM ARE SO VITALLY IMPORTANT, NOT ONLY SO WE UNDERSTAND THE GENETIC DIVERSITY OF CANCER, BUT THE GENETIC DIVERSITY OF THE HOSTS THAT WE'RE CONSIDERING THESE NOVEL THERAPIES. AND AMY BROUGHT THIS UP, THE HOST, THE ENVIRONMENT, THESE ARE ALL MOVING TARGETS, AND WE HAVE TO CONSIDER THAT WHEN WE ARE APPLYING STEM CELL GENE THERAPIES.

IN TERMS OF CANCER STEM CELL TARGETING, WE'VE USED THE FULL COMPLEMENT OF THERAPIES, SMALL



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MOLECULES, BIOLOGICS, CELLULAR THERAPEUTICS. WHAT INDUSTRY DOES VERY WELL, AND I'VE STARTED A COUPLE OF COMPANIES AND ACTUALLY DID MY PH.D. ON A DRUG THAT BECAME KNOWN AS VISUDYNE WITH QLT, IS THAT THEY DO ONE PARTICULAR APPROACH VERY WELL. ONE SMALL MOLECULE, ONE BIOLOGIC, ONE CELLULAR THERAPEUTIC. WHAT THEY DON'T DO AS WELL, I WOULD ARGUE, AS ACADEMIC INSTITUTES, PARTICULARLY WHEN WE COLLABORATE, IS THE COMBINATION OF THOSE STRATEGIES. THIS IS WHY WE'VE GOTTEN SO FAR WITH HIV BECAUSE OF THE ACT GENE.

THE CAPACITY TO DO CLINICAL TRIALS IN A COLLABORATIVE NETWORK HAS CHANGED THE PARADIGM FOR PATIENTS SO THEY DON'T HAVE TO FACE THE WORST OF TIMES.

I USE THE WORD "PATIENT" ALMOST AS PEJORATIVE. WE'RE ALL GOING TO BE PATIENTS. NOBODY SHOULD FEEL STIGMATIZED BY THAT. WE DO WANT TO HAVE EARLY INTERVENTION MECHANISMS TO PREDICT AND PREVENT DISEASE PROGRESSION, PARTICULARLY IN DEGENERATIVE DISORDERS LIKE CANCER. LARRY GOLDSTEIN AND I HAD A SEED GRANT TOGETHER ON CANCER STEM CELL INITIATION AS ONE OF THE FIRST CIRM GRANTS GIVEN FOR DISCOVERY IN AGENTS THAT MAY TARGET CANCER STEM CELLS. THAT PROVIDED A PARADIGM FOR SCREENING FOR SMALL



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MOLECULES AND HOW TO DEVELOP BIOMARKERS OF POTENTIAL THERAPEUTIC RESISTANCE. IT INFORMED HOW WE WOULD USE THE JAK2 INHIBITOR THAT LATER BECAME KNOWN AS FEDRATINIB. ACTUALLY THIS TECHNOLOGY WAS BASED, AGAIN, ON SOMETHING GEORGE DALEY HAD DEVELOPED IN TERMS OF DIFFERENTIATING HUMAN EMBRYONIC STEM CELLS. THAT BECAME FEDRATINIB. FEDRATINIB IS NOW APPROVED AS INREBIC. INREBIC WAS ACQUIRED FOR 1.1 BILLION. THAT'S ONE-THIRTEENTH OF WHAT MARIA WAS ALLUDING TO IN TERMS OF THE $13 BILLION ROI JUST FROM PARTNERSHIPS WITH INDUSTRY. IT DOESN'T REALLY GIVE YOU THE RIGHT IDEA OF HOW MOMENTOUS THIS COLLABORATION WITH CIRM HAS BEEN FROM A BASIC TRANSLATIONAL CLINICAL STANDPOINT AS AN ITERATIVE PROCESS.

IN TERMS OF THE NEXT SMALL MOLECULE THAT TARGETED A STEM CELL PATHWAY IN CANCER, PFIZER HAD AN IDEA THAT THEY WANTED TO WORK WITH A STEM CELL PROGRAM WITH CIRM FUNDING. WE WERE ABLE TO WORK WITH PFIZER TO DEVELOP PLASTICA, WHICH IS NOW APPROVED AS DAURISMO, AS A TREATMENT TO TARGET LEUKEMIA STEM CELLS.

IF YOU LOOK AT HOW DO STEM CELLS EVADE THE IMMUNE SYSTEM, IRV WEISSMAN, RAVI MAJETI, AND OTHERS SHOWED THAT IT'S BECAUSE THEY UP-REGULATE THE DON'T

EAT ME SIGNAL CD47. MAGROLIMAB, THE CD47 TARGETING ANTIBODY THAT WAS ENTIRELY FUNDED BY CIRM TO DERISK THE EARLY STAGE EFFORTS, WAS RECENTLY SOLD TO GILEAD FOR 4.9 BILLION.

IF YOU LOOK AT ANOTHER BIOLOGIC, CIRMTUZAMAB, WE CALLED IT CIRMTUZAMAB BECAUSE WE WANTED TO KEEP CIRM FUNDING, NO -- BECAUSE WE WERE SO GRATEFUL TO CIRM FOR FUNDING SO MANY ASPECTS OF THIS ROR1 TARGETING MONOCLONAL ANTIBODY, WE WERE ABLE TO DEVELOP CIRMTUZAMAB FOR CLL MANTLE CELL LYMPHOMA WITH A 50-PERCENT COMPLETE REMISSION RATE IN MANTLE CELL LYMPHOMA. THAT IS REALLY ASTOUNDING, IT WAS TO ME ANYWAY. THE ANTIBODY DRUG CONJUGATE WAS JUST SOLD TO MERCK FOR 2.75 BILLION.

IF YOU WANT TO LOOK AT CIRM AS AN ECONOMIC ENGINE, IT ABSOLUTELY IS. IT'S A CATALYST. IT'S A COMBINATOR. WHATEVER YOU WANT TO PUT IT, THIS HAS INCREASED OUR EFFORTS, OUR CAPACITY TO ACCELERATE THERAPIES TO PATIENTS AT LEAST TENFOLD.

BUT IN THE CANCER STEM CELL FIELD, WHAT WE ARE REALLY MISSING IS THE CAPACITY TO USE CELLULAR THERAPEUTICS, IPS-DERIVED NK CELLS, SWITCHABLE CAR-T CELLS, AS PETE SCHULTZ HAS DEVELOPED IN HIS NONPROFIT COMPANY CALLED CALIBER, TOGETHER WITH SMALL MOLECULES. IT'S THAT COMBINATION STRATEGY



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THAT WE CAN DO AS AN ALPHA STEM CELL CLINIC NETWORK AND I THINK WE NEED TO DO TO OBVIATE RELAPSE, WHICH IS THE NO. 1 CAUSE OF DEATH DUE TO CANCER. IT'S NOT THE FIRST DIAGNOSIS. IT'S NOT PEOPLE SAYING, "HEY, DOC, I'VE GOT THIS LUMP. I DON'T KNOW WHAT IT IS." IT'S THE FACT THAT WE CAN'T PREDICT AND PREVENT RECURRENCE. THAT'S WHAT LEADS TO MORTALITY. THAT'S WHY CANCER IS THE NO. 3 CAUSE OF DEATH IN THIS COUNTRY.

I THINK THAT WE CAN START TO MAKE ESSENTIAL INCURSIONS INTO CANCER STEM CELL TARGETING WHEN WE USE THIS COMBINED APPROACH. THE ALPHA STEM CELL CLINICS HAVE ALLOWED US TO DO THAT AND NOT JUST DRINK OUR OWN KOOL-AID. FOR EXAMPLE, WITH THE DENDRITIC CELL TRIAL TARGETING CANCER STEM CELLS FROM AIVITA, DANIELLE ABOTA GAVE US THE OPPORTUNITY TO WORK COLLABORATIVELY THROUGH THE ALPHA CLINIC TO BRING THAT OVER TO UC SAN DIEGO AND ENHANCE SURVIVAL FOR PATIENTS WITH GLIOBLASTOMA MULTIFORMA THAT HAD BEEN REFRACTORY TO ALL OTHER THERAPIES BY AN ADDITIONAL FIVE MONTHS. THAT MAY NOT SEEM LIKE A LOT. BUT IF YOU'RE SOMEBODY WHO WANTS TO JUST HAVE THE LAST FEW MONTHS WITH YOUR FAMILY, IT'S A LOT.

SO BASICALLY WE CAN TALK ABOUT THE IMPACT OF CIRM ON SCIENCE, BUT WE REALLY SHOULD TALK ABOUT



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THE HUMAN ROI FOR CIRM, THE INDIVIDUALS THAT HAVE REALLY BENEFITED. AND IF WE CAN LOOK AT THIS ONE PERSON AT A TIME, WHETHER IT'S THE PATIENT THAT I'VE BEEN INVOLVED IN LOOKING AFTER FOR A NUMBER OF YEARS AND SHE'S LOOKED AFTER US SCIENTIFICALLY HERE AT CIRM AS A MAJOR PROPONENT OF PROP 14, THAT WAS SANDRA, WHO WAS ONE OF THE INITIAL BENEFICIARIES OF FEDRATINIB, OR WHETHER WE LOOK AT PEOPLE WHO CAN'T SPEAK FOR THEMSELVES, THE KEY NOW IS INCLUSION, DIVERSITY, EQUITY, AND ACCESSIBILITY.

AND WITHIN THAT ACCESSIBILITY PIECE WE HAVE TO CONSIDER NOT JUST UNDERREPRESENTED MINORITIES, BUT SOCIOECONOMICALLY DISADVANTAGED GROUPS.

WHEN I WAS WATCHING THE NEWS THIS MORNING, I SAW AN AD FOR THE SAN DIEGO FOOD BANK, "FEEDING SAN DIEGO." THEY HAVE NOW SERVED 600,000 PEOPLE IN THIS COUNTY. WE ONLY HAVE THREE MILLION PEOPLE IN THE COUNTY. SO I THINK IF WE WANT A REALITY CHECK, WE HAVE TO THINK ABOUT ACCESSIBILITY AS BEING SYNONYMOUS WITH AFFORDABILITY. AND THE ONLY WAY TO DO THAT IS WITH ECONOMIES OF SCALE. THE ONLY WAY TO DO THAT IS TO NOT HAVE AN ITERATIVE PROCESS WHERE WE KEEP MAKING MISTAKES BECAUSE WE DON'T REALLY KNOW WHAT WE ARE DOING.



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FORTUNATELY, AND I'LL TRANSITION TO THE CIRM ALPHA STEM CELL CLINICS, WE HAVE A NETWORK THAT HAS ESTABLISHED ITSELF WELL WITH A $40 MILLION SEED FROM CIRM THAT HAD TO BE MATCHED BY THE INSTITUTIONS, AND THOSE ARE UCSF, UC DAVIS, UCLA, UCI, CITY OF HOPE, AND UC SAN DIEGO, WHERE WE'VE BEEN ABLE TO LEVERAGE THAT INFRASTRUCTURE TO WORK AS AN ACCELERATING INFRASTRUCTURE TO ENHANCE BOTH AFFORDABILITY AND ACCESSIBILITY TO CLINICAL TRIALS. THAT INVOLVED BUILDING TEMPLATES FOR CLINICAL TRIAL AGREEMENTS. THAT WAS DONE BY CITY OF HOPE. THEY SHARED IT WITH ALL OF US. IT INVOLVED ACCELERATED CONFIDENTIALITY AGREEMENT IMPLEMENTATION. IT INVOLVED SHARING INFORMATION ACROSS THE NETWORK ABOUT WHEN WE WERE STARTING TO SEE SERIOUS ADVERSE EVENTS. THAT IS EXTREMELY IMPORTANT. WE CAN BE THE HONEST BROKER, THE SAFETY VALVE FOR PATIENTS SO WE CAN START TO GIVE EACH OTHER AN EARLY INDICATION OF WHEN WE'RE SEEING THINGS THAT JUST DON'T LOOK LIKE THEY'RE GOING WELL.

IT HAS NEVER BEEN A MORE IMPORTANT TIME TO DO THIS. CIRM SHOWED THAT THEY COULD FUND COVID SO THAT WE COULD ACCELERATE THERAPIES AND HAVE THEM IMPLEMENTED FOR PATIENTS IN REAL TIME, NOT FIVE YEARS FROM NOW, BUT ALMOST IMMEDIATELY BECAUSE WE



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HAD THE NETWORK READY TO GO.

SO THE MAIN ISSUE SO FAR IS ACTUALLY KNOWLEDGE, EDUCATION, LETTING PEOPLE KNOW THAT WE'RE ACCESSIBLE, LETTING PEOPLE KNOW THAT SCIENCE HAS ITS OWN LANGUAGE, MEDICINE IS A LANGUAGE, BUT WE'RE HERE TO TRANSLATE THAT INTO A SUSTAINABLE WAY OF PREVENTING ENDOGENOUS DEGENERATION BY ENHANCING ENDOGENOUS REPAIR AND REGENERATION. NOT EVERYTHING HAS TO BE CELLULAR THERAPY. I CERTAINLY DID A LOT OF BONE MARROW TRANSPLANT IN MY CAREER, BUT I'VE LEARNED SMALL MOLECULES AND BIOLOGICS PLAY AN ESSENTIAL ROLE IN PREVENTING TISSUE DEGENERATION.

SO I THINK CIRM HAS A MAJOR MANDATE NOW FROM THE VOTERS OF CALIFORNIA TO ENSURE ACCESSIBILITY, AFFORDABILITY, AND ACCOUNTABILITY. AND ACCOUNTABILITY TO ME IS THE CAPITAL A IN ALPHA CLINICS. WE ARE ACCOUNTABLE TO NOT JUST THE VOTERS OF CALIFORNIA, BUT THE NATIONAL AND INTERNATIONAL STEM CELL COMMUNITY TO MAKE SURE THAT WE SOUND THE ALARM WHEN SOMETHING DOESN'T LOOK RIGHT WITH STEM CELL CLINICAL TRIALS. WE NEED TO HAVE SUSTAINABLE FUNDING FOR OUR ALPHA CLINICS AND EXPAND THE ALPHA CLINIC NETWORK TO INCLUDE COMMUNITY CARE CENTERS, BUT NOT AT THE EXCLUSION OR TO THE EXCLUSION OF ALPHA CLINICS.



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THIS HAS BEEN A VITAL NETWORK. WE WORK VERY WELL TOGETHER. MARIA MILLAN HAS REALLY WORKED WELL WITH NATIONAL FUNDING PARTNERS LIKE THE NHLBI TO ENHANCE ACCESSIBILITY FOR THE SICKLE CELL ANEMIA GENE THERAPY TRIALS, ENHANCED ACCESSIBILITY FOR A NUMBER OF OTHER TRIALS LIKE THE ONE WITH DON KOHN AT UCLA. WE HAVE OUR CYSTINOSIS TRIAL HERE WITH DON KOHN MAKING THE PRODUCT AT UCLA. THERE ARE MASSIVE NUMBERS OF COLLABORATIONS. THE POINT IS YOU HAVE TO INTEGRATE AND COLLABORATE. AND IF YOU DON'T INTEGRATE AND COLLABORATE, YOU DON'T HAVE THE ECONOMY OF SCALE TO BE ABLE TO APPLY THESE THERAPIES.

WE NEED TO HAVE DAVID HAUSSLER'S APPROACH INTEGRATED OR IMBUED THROUGHOUT OUR SYSTEM SO THAT WE HAVE A MULTIOMICS INTEGRATED NAVIGATOR FOR DATA -- YOU KNOW I LIKE ACRONYMS -- MIND, M-I-N-D. WE NEED TO BE MINDFUL THAT PATIENTS ARE FACED WITH THIS REALLY DICHOTOMOUS DECISION-MAKING. THEY HAVE TO SAY WAIT A MINUTE. I HAVE ALL THESE DATA. THEY'RE EITHER BEWILDERING OR I'M GOING TO MOVE FORWARD AND MAKE A DECISION.

THE ISSUE WITH CELLULAR THERAPEUTICS IS SOMETIMES THE OUTCOME IS IRREVOCABLE. WITH SMALL MOLECULES AND BIOLOGICS, WE CAN REVERSE SOME OF THE



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EFFECTS BASED ON HALF-LIFE; BUT WITH CELLULAR THERAPEUTICS, SOMETIMES YOU CAN'T REVERSE THAT.

SO THE FINAL PIECE I'D LIKE TO SAY IN TERMS OF COLLABORATIONS IS THAT I THINK THAT THE ONUS IS ON US TO COLLABORATE NATIONALLY AND INTERNATIONALLY AND CONSIDER NOT JUST THE CELL TYPE EFFECTS OF OUR THERAPEUTICS, BUT THE HOST EFFECTS AND THE ENVIRONMENTAL EFFECTS THAT MAY AFFECT THE EFFICACY OF OUR THERAPEUTICS. AND THAT'S SOMETHING THAT CLIVE SVENDSEN AND I ARE GETTING TO WORK ON THROUGH THE INTEGRATED SPACE STEM CELL ORBITAL RESEARCH LAB. THERE ARE DIFFERENT ENVIRONMENTS THAT WE CAN WORK IN TO REALLY UNDERSTAND THE IMPACT OF THE ENVIRONMENT ON STEM CELL BIOLOGY AND THE POTENTIAL EFFICACY OF OUR THERAPEUTICS.

SO THAT'S REALLY WHAT I WANTED TO SAY OTHER THAN THANK YOU VERY MUCH TO CIRM. I WANTED TO REITERATE WHAT LESLIE HAD SAID ABOUT THE IMPORTANCE OF BEING ABLE TO GUIDE US THROUGH PRE-IND, IND, AND IND-ENABLING WORK AS IT TRANSITIONS INTO THE CLINIC AND THEN GET ALL THE WAY THROUGH THE VALLEY OF DEATH WITH PROOF OF CONCEPT AND PROOF OF SAFETY DATA AT THE END OF PHASE 1. THAT'S WHY THIS HAS WORKED. THAT'S WHY WE HAVE ALL THESE WINS BECAUSE CIRM HAS GUIDED US THROUGH THAT WHERE NORMALLY VENTURE

CAPITAL AND LARGE PHARMA WOULD SAY YOU NEED TO DERISK IT FIRST. THAT VALLEY OF DEATH IS NOT BECOMING AS DEEP. IT'S NOW BECOMING A LITTLE SHALLOWER. AND I THINK WE CAN DO AN EVEN BETTER JOB WITH THAT WITH CIRM'S HELP.

DR. MILLAN: THANK YOU SO MUCH, CAT. WE HAVE TEN MINUTES FOR PANEL DISCUSSION. I'M JUST GOING TO GO AHEAD AND OPEN IT UP AND FIRST COME, FIRST SERVED IN COMMENTS.

WE HAVE THE BENEFIT OF DR. MARKS. I THINK HE'S BACK NOW. NO. WE HAVE SALLY. GO AHEAD, SALLY.

DR. TEMPLE: FIRST OF ALL, CAT, THAT WAS, AS USUAL, AN AMAZING SUMMARY, SO INSPIRING. THANK YOU. I THINK IT REALLY DOES UNDERSCORE HOW INCREDIBLE CIRM HAS BEEN AND WILL BE GOING FORWARD.

I JUST WANTED TO THANK YOU FOR TALKING ABOUT THE ALPHA CLINICS AS SETTING THE EXAMPLE AND STANDARD AND THE ROLE TO SOUND THE ALARM. FOR THOSE CLINICS THAT ARE NEFARIOUS, THAT ARE NOT DOING THIS CORRECTLY, I THINK THE BEST WAY TO COMBAT THAT SCOURGE ON OUR FIELD IS TO DO IT RIGHT. AND REALLY THE ALPHA CLINICS ARE SET UP FOR THIS TRANSFORMATION IN MEDICINE THAT WE ANTICIPATE. RIGHT. SO YOU ALREADY HAVE THAT NETWORK. I WOULD LOVE TO SEE THAT

HAPPENING IN NEW YORK AS WELL, COUNTRYWIDE, BUT JUST WANTED TO APPRECIATE WHAT YOU SAID, BUT REALLY UNDERSCORE THAT VERY IMPORTANT ROLE OF MAKING SURE THAT WE ARE PROTECTED AGAINST THOSE CLINICS THAT ARE REALLY HARMING PATIENTS.

DR. MILLAN: THANK YOU, SALLY.

WE HAVE DR. MARKS BACK. AND, PETER, I THINK THAT YOU MAY HAVE HAD TO STEP OFF WHEN WE WERE DISCUSSING IDEAS OF THE CONCEPT OF PLATFORM TRIALS AND THE CONSORTIA MODEL THAT YOU HAD CONCEPTUALIZED IN THE *NEW ENGLAND JOURNAL OF MEDICINE* PAPER. SO DO YOU HAVE ANY ADDITIONAL THOUGHTS ON THAT JUST IN THE CONTEXT OF SOME OF THE CONVERSATIONS TODAY?

DR. SVENDSEN: I DON'T SEE HIM, MARIA. I DON'T THINK HE'S ON.

DR. MILLAN: I SAW HIS NAME AND I SAW THE AUDIO STARTING TO COME ON. SO MAYBE HE WAS TRYING TO COME ON.

SO I'M GOING TO GO AHEAD AND OPEN IT UP NOW FOR ADDITIONAL COMMENTS. WE HAVE EIGHT MORE MINUTES LEFT IN THIS SESSION.

DR. SVENDSEN: THE PLATFORM TRIAL IS SO NICE, MARIA, BECAUSE IF WE'RE DOING, SAY, FOUR DIFFERENT CELL THERAPY APPROACHES, SAY FOR HEART DISEASE OR SOMETHING, YOU CAN ACTUALLY UTILIZE ONE

GROUP AS A PLACEBO. I THINK THAT'S WHY THE PLATFORM TRIAL IS SO POWERFUL. IT'S EASY WHEN YOU'RE GIVING A DRUG; BUT IF YOU'RE DOING INVASIVE TECHNOLOGIES, YOU'RE INFUSING THINGS OR IF YOU'RE DRILLING A HOLE IN THE BRAIN, YOU CAN'T COMPARE ACROSS DIFFERENT SITES VERY EASILY. BUT GIVEN WE'RE ALL DOING VERY SIMILAR TECHNIQUES, I THINK THE VALUE OF THAT PLACEBO GROUP AND BEING ABLE TO HAVE COMPANIES DO MAYBE SIX DIFFERENT DRUGS TESTED AT ONCE WITH ONE PLACEBO IS GOING TO REALLY INCREASE THE ABILITY TO DO THESE KIND OF TRIALS AND ALSO JUST TO HARMONIZE A LITTLE BIT ACROSS CALIFORNIA OF HOW THESE TRIALS GO AHEAD.

CAT HAS REALLY LED THE WAY THERE, BUT, CAT, I THINK WE NEED TO EXPAND THAT FURTHER AND HAVE MORE INFRASTRUCTURE. THE ALPHA STEM CELL CLINICS ARE GREAT, BUT I WOULD LIKE THE ALPHA STEM CELL CLINICS TO INTEGRATE MORE TOGETHER AS WELL AND DO JOINT TRIALS ACROSS HEALTH SYSTEMS, HEALTH CLINICS, AND BETWEEN INSTITUTIONS.

DR. MILLAN: THANK YOU SO MUCH, CLIVE. SALLY, IS THIS HAND A NEW HAND? OKAY. YOU HAVE THE FLOOR.

DR. TEMPLE: THAT WAS FROM BEFORE.

DR. MILLAN: IF THERE'S NO OTHER HANDS FOR

NOW, ONE OF THE THINGS I WANT -- OH, HERE WE GO. ANNE-MARIE DULIEGE.

DR. DULIEGE: GOOD AFTERNOON, EVERYBODY. I'M ANNE-MARIE DULIEGE, AND I'M ON THE BOARD OF CIRM. MARIA, I JUST WANTED TO ADD SOMETHING BRIEFLY. AS YOU PROBABLY KNOW, I JOINED RECENTLY AS THE CHIEF MEDICAL OFFICER OF A NONPROFIT ORGANIZATION CALLED PANCAN, WHICH IS PANCREATIC CANCER ACTION NETWORK. THE REASON WHY I MENTION THAT IS THE REASON WHY THERE'S A CMO POSITION IN A NONPROFIT IS BECAUSE, THANKS TO THE VISION OF THE FOUNDER, WE HAVE STARTED, AND I'M JOINING THAT, A PLATFORM TRIAL WHICH IS AN ADAPTIVE TRIAL DESIGNED VERY MUCH ALONG THE LINE OF WHAT WAS JUST DISCUSSED. AND AT SOME OTHER POINT, IF PEOPLE ARE INTERESTED, I WILL BE VERY HAPPY TO SHARE THE PLUSES AND POTENTIAL CHALLENGES OF PLATFORM TRIALS AND ADAPTIVE DESIGN PLATFORM TRIALS.

DR. MILLAN: THANK YOU, ANNE-MARIE. THAT IS A TRULY, SEVERELY UNMET MEDICAL NEED, PANCREATIC CANCER AND ONCOLOGY, AND I DO HOPE THAT WE MAKE PROGRESS ON THAT.

JUST KIND OF LEVERAGING OFF WHAT CATRIONA HAD SPOKEN ABOUT IN TERMS OF THAT KNOWLEDGE, AGAIN GOING BACK TO SOME OF THESE KEY TERMINOLOGIES, THE



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KNOWLEDGE NETWORKS AND THE SPECIALTY TYPE OF DATASETS AND INFORMATION THAT'S EXCHANGED IN THE ECOSYSTEM THAT WAS CREATED BY CIRM, THERE HAVE BEEN SO MANY DIFFERENT, NOT OBVIOUS, NOT ON THE SURFACE OBVIOUS WAYS THAT THAT'S REALLY ACCELERATED OUR PROGRAMS, THAT WITHOUT GIVING UP PROPRIETARY DATA OR COMPROMISING THE PROGRESS OF ANY SINGLE PROJECT, IT REALLY AS A WHOLE HAS ACCELERATED DIFFERENT PROJECTS. AND WE DO THAT THROUGH OUR CLINICAL ADVISORY PANELS. WE DO THAT THROUGH CONVENING MEETINGS. WE DO THAT FOR INTRODUCING THE DIFFERENT INVESTIGATORS TO CALIFORNIA AS WELL AS INVESTIGATORS OUTSIDE OF CALIFORNIA.

AMY WAGERS HAS HER HAND UP. THANK YOU, AMY.

DR. WAGERS: I HAVE A QUESTION ABOUT POTENTIAL OPPORTUNITIES FOR INNOVATING TRIAL DESIGN AND MAYBE SORT OF TAKING ADVANTAGE OF THE OPPORTUNITY TO PULL TOGETHER DATA FROM TRIALS THAT ARE DONE TOWARDS A SIMILAR ANGLE. SORT OF NOT ALONE BY GETTING THE INVESTIGATORS WHO ARE RUNNING TRIALS TOGETHER, BUT MAYBE EVEN MORE FORMALLY BY A CALL FOR SORT OF EXTERNAL STUDIES OF THOSE TRIALS AND TRYING TO COME UP WITH SORT OF A DATA-DRIVEN, EVIDENCE-BASED SORT OF RECOMMENDATION ABOUT TRIAL

DESIGNS THAT ARE PARTICULARLY EFFICACIOUS FOR REGENERATIVE MEDICINE OR FOR PARTICULAR APPROACHES IN STEM CELL ENGRAFTMENT OR APPROACHES IN GENE THERAPY. AND IT JUST STRIKES ME THAT IF, THROUGH THE ALPHA CLINICS AND BY SORT OF FUNCTIONING TO ACCELERATE THOSE KINDS OF EARLY TRIALS, THERE'S SORT OF MORE DATA TO BE MINED. THAT MAY BE TOO MUCH OF AN ASK TO PUT ON THE INVESTIGATORS WHO ARE ALSO RUNNING THE TRIALS, AND THAT MIGHT BE AN OPPORTUNITY TO BRING IN OTHER EXPERTS TO LOOK AT THAT DATA IN A SORT OF META-TYPE WAY. MAYBE YOU'RE DOING THAT ALREADY.

DR. JAMIESON: MARIA, DO YOU MIND IF I JUST ADDRESS THAT BECAUSE IT'S SUCH A CRITICAL POINT FOR WHERE WE ARE AT THIS JUNCTURE WITH THE ALPHA CLINICS. AMY, YOU'RE EXACTLY RIGHT. I THINK WE'RE AT THE PROCESS NOW WHERE WE NEED TO DO REVERSE TRANSLATION. WE STARTED THREE CLINICAL TRIALS IN 2014 IN THE SAME MONTH, NEURAL STEM CELL, CIRMTUZAMAB, AND THEN THE VIACYTE STUDY. BUT WHAT WE REALLY NEED TO UNDERSTAND IS WHY DOES IT WORK IN SOME AND NOT OTHERS. SOME PEOPLE HAVE SEEN A SPECTACULAR SUCCESS AND OTHER PEOPLE A SPECTACULAR FAILURE, WHICH IS WHY I USED THE *TALE OF TWO CITIES* AS A BASIC METAPHOR FOR WHAT WE'VE BEEN DOING IN

THIS FIELD.

WE NEED TO DO WHAT YOU'RE SAYING AND WHAT CHRISTINE MUMMERY WAS ALLUDING TO AND WHAT DAVID HAUSSLER WAS SAYING. WE NEED TO HAVE A GENOMICS PLATFORM. WE NEED TO HAVE A NONINVASIVE IN VIVO IMAGING PLATFORM, AND WE NEED A DEEP DATA SCIENCE DIG FROM PEOPLE LIKE YOU TO STOP US FROM DRINKING OUR OWN KOOL-AID AND THINK WE'RE DOING JUST A GREAT JOB. I THINK WE NEED AN EXTERNAL VIEW OF THE DATA, BUT ALSO TO APPLY THE BEST TECHNIQUES THAT ARE AVAILABLE TO US IN THE STEM CELL RESEARCH FIELD TO ANALYZE RESPONSES OR LACK THEREOF.

THAT'S WHERE WE ARE WITH CIRMTUZAMAB. APPLYING IT TO DIFFERENT DISEASE INDICATIONS REALLY VARIES IN TERMS OF EFFICACY. WHEN YOU START LOOKING AT COMBINATION STRATEGIES LIKE WE'RE DOING FOR IPS-DERIVED NK CELL STUDIES, SWITCHABLE CAR-T CELLS, SMALL MOLECULES, AND BIOLOGICS COMBINED, WE'RE GOING TO NEED THAT DEEP DATA DIVE FROM EXTERNAL PEOPLE WHO MAY NOT BE AS BIASED AND MAY BE ABLE TO SEE THE FOREST FOR THE TREES. WE GET VERY FOCUSED ON PROCESS.

DR. MILLAN: IT COULD JUST BE ALSO, CAT, JUST HAVING A LARGER DENOMINATOR BECAUSE ANALYSIS IS POWERED BY YOUR DATASET. SO THE WHOLE IDEA OF

KNOWLEDGE NETWORKS AND DATA SHARING. SO THANK YOU BOTH FOR THAT POINT.

WE HAVE VICTOR DZAU. DR. DZAU HAS A COMMENT OR QUESTION.

DR. DZAU: THANK YOU. I THINK TODAY HAS BEEN A TERRIFIC DISCUSSION. WHAT I PARTICULARLY LIKED HEARING ABOUT IS AN INTEREST IN DIVERSITY AND DISPARITIES AND RELATED ISSUES. IN MANY WAYS WE TALKED ABOUT HOW TO LOOK AT FROM THE SCIENTIFIC VIEWPOINT, BUT I HAVEN'T HEARD MUCH ABOUT ENGAGEMENT OF COMMUNITIES AND HOW YOU RECRUIT MORE PEOPLE WHO ARE VULNERABLE, COMMUNITIES OF COLOR, AND ADDRESSING VULNERABLE POPULATIONS WHERE THE DISPARITY IS HUGE.

WHETHER THEY ARE RELATED PER SE TO THE SOCIOECONOMIC CIRCUMSTANCE OR THE BIOLOGIC DIFFERENCES, I THINK, LIKE IN ALL OF US, WHEN THE RECRUITMENT OF PATIENTS THROUGH COMMUNITIES AND PAYING A BIG FOCUS ON ENGAGEMENT, PARTICULARLY VULNERABLE COMMUNITIES, COMMUNITIES OF COLOR. CAN SOMEONE SAY A WORD ABOUT WHERE WE ARE ON THIS ASIDE FROM THE CLINICAL TRIAL DESIGN?

DR. MILLAN: VICTOR, THAT'S A VERY IMPORTANT TOPIC AND SUCH AN IMPORTANT TOPIC THAT WE COULDN'T FULLY GIVE IT ITS ATTENTION IN THIS PARTICULAR FORUM. SO WE'VE BEEN FOCUSING ON

SCIENTIFIC, BUT THAT IS A MAJOR PART OF OUR KIND OF STRATEGIC PLANNING AND TOPICS RELATED TO THOSE VERY TOPICS IN TERMS OF TRULY, NOT JUST ENGAGING OUR OUTREACH TO THE COMMUNITY, BUT A PARTNERSHIP WITH THE COMMUNITY IN ALL RESPECTS, THE COMMUNITY ITSELF, COMMUNITY CENTERS, HOW IS CARE DELIVERED THERE? WHAT DOES MATTER TO THE COMMUNITY?

ONE OF THE THINGS I WANTED TO MENTION ALSO, IN THE TYPES READOUTS WE ARE LOOKING AT, AND THE FDA HAS FUNDED SOME EFFORTS IN THIS, AND LOOKING AT THE PATIENT-CENTRIC OUTCOMES, AND THERE'S SOME KIND OF PILOT STUDIES ON THAT, HOW DOES THAT PLAY INTO IT? WHAT DO OUR READOUTS MEAN? I THINK DR. MUMMERY HAD BEEN STATING WE GOT TO KNOW THE READOUTS. TRUE. WE KIND OF HAVE EFFICACY READOUTS, WE HAVE SAFETY READOUTS, BUT WHAT ARE THE MEANINGFUL READOUTS?

SO THOSE ARE ALL -- THERE ARE OTHER ASPECTS OF THE TYPES OF RESEARCH THAT COULD BE UNDERTAKEN BY CIRM. THAT IS ALSO A TOPIC IN THE BROADER STRATEGIC PLANNING. AS YOU SAW IN MY INTRODUCTORY STATEMENTS, THERE WERE KIND OF FOUR ANCHORING THEMES. WE ARE FOCUSING ON THE ADVANCING WORLD-CLASS SCIENCE THEME, BUT THERE IS SPECIFICALLY A THEME THERE THAT SPEAKS TO EQUITABLE ACCESS OF



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THESE INNOVATIVE TREATMENTS TO PATIENTS IN THE REAL WORLD, MEANING NOT JUST ONE DEMOGRAPHIC CATEGORY, THE PATIENTS IN NEED. SO THAT IS A TOPIC. I WANTED TO ASSURE YOU THAT IT'S AN IMPORTANT TOPIC TO CIRM, AND WE WILL BE DEVOTING SUFFICIENT TIME IN THAT AND HOPE THAT WE CAN ALSO ENGAGE MANY MEMBERS OF THIS GROUP.

DR. DZAU: THANK YOU, MARIA. I'M CERTAIN THAT YOU HAVE ALL THIS COVERED. I WAS JUST MERELY ASKING THE RESEARCH ASPECT AS WELL, WHICH IS RECRUITING THE PATIENTS THROUGH ENGAGEMENT IN COMMUNITY. THAT'S ALL I WAS ASKING.

DR. MILLAN: OH, YEAH. SO EVEN OUR CURRENT PROGRAM ANNOUNCEMENTS THAT STARTED WITH COVID, THERE IS NOW A SPECIFIC PORTION OF OUR APPLICATION WHERE THE RESEARCHERS ARE ASKED TO GIVE A DIVERSITY, EQUITY, INCLUSION, AND COMMUNITY OUTREACH PLAN, FOR CLINICAL STAGE PROGRAMS, HOW THEY DO SO FOR CLINICAL TRIAL RECRUITMENT, NOT JUST RECRUITMENT, BUT THE ENGAGEMENT AND THE EDUCATION RELATED TO THAT; FOR EARLIER STAGE PROGRAMS, HOW IT'S ENVISIONED WITHIN THEIR RESEARCH PROGRAMS SUCH AS THE TYPES OF CELL LINES, WHAT BACKGROUND ARE THEY? IF THERE ARE NOT SUFFICIENT REPRESENTATIVE CELL LINES. WE ACTUALLY HAVE PROGRAMS WHO HAVE

EXPANDED PROGRAMS SPECIFICALLY FOR THAT REASON. THAT'S JUST A START. THIS IS OUR FIRST STEPWISE APPROACH INTO THIS.

DR. MUMMERY.

DR. MUMMERY: JUST TO ADD ON THERE PART OF SOLUTION IS ALSO TO THINK OF MINORITIES AND OTHER GROUPS' REPRESENTATION AMONG THE JUNIOR SCIENTISTS. SO YOU HAVE FANTASTIC EDUCATION PLANNING IN THE SCAFFOLDING, YOU COULD SAY. BUT SALLY AND I ARE NOW ORGANIZING THE ISSCR MEETING 2021, AND IT'S REALLY HARD TO IDENTIFY REALLY GOOD SPEAKERS, LEADERS IN THE FIELD FROM DIFFERENT DIVERSE GROUPS. AND IT IS A WONDERFUL OPPORTUNITY TO EDUCATE AND TRAIN THOSE GROUPS IN STEM CELL RESEARCH. BY THEMSELVES THEY MAY WELL INCORPORATE PATIENT GROUPS FROM THEIR OWN COMMUNITIES, AND THEN WE WILL GET A DOUBLE WHAMMY, YOU COULD SAY, WITH DIVERSITY.

DR. MILLAN: ABSOLUTELY. AS A MATTER OF FACT, THAT IS A MAJOR FOCUS OF OUR EDUCATION PROGRAM, EVEN THAT WE'VE ALREADY HAD SUCCESS WITH KIND OF OUR LEGACY PROGRAMS WHERE THE MAJORITY OR CLOSE TO THE MAJORITY OR MAYBE AT LEAST HALF ARE FIRST-GENERATION COLLEGE STUDENTS, FOR INSTANCE, WHO WILL COME IN THROUGH OUR BRIDGES PROGRAM WHERE THEY HAVE EXPOSURE TO STEM CELL COURSEWORK AND PRACTICAL



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EXPERIENCE IN THE LAB AS WELL AS OUTREACH ACTIVITIES. AND THOSE ARE ACTUALLY REACHING OUT TO THOSE VERY COMMUNITIES BECAUSE WE KNOW THAT IT'S NOT JUST ABOUT RECRUITING PATIENTS. IT'S TRULY BEING THE LEADERS AND THE HEALTHCARE WORKERS AND THE SCIENTISTS WHO COME FROM THOSE COMMUNITIES SO THE COMMUNITIES CAN IDENTIFY.

SO OUR EDUCATION PROGRAM PLATFORMS THAT ARE AT VARIOUS LEVELS OF EDUCATION AND ALSO FACULTY, WE ARE CURRENTLY IN THE PROGRESS OF ROLLING OUT EDUCATIONAL PROGRAMS. THAT IS EMBEDDED IN THERE. IT'S KIND OF AT THE TOP OF THE LIST IN TERMS OF CONSIDERATIONS, IN TERMS OF THE VALUE THAT THOSE WILL BRING IN DEVELOPING A DIVERSE WORKFORCE OF TOMORROW. THAT'S NOT JUST FOR THE PURPOSES OF DOING WHAT'S RIGHT SOCIAL JUSTICEWISE. IT'S FOR THE PURPOSE OF DELIVERING THE BEST THERAPIES. IT'S FOR THE PURPOSE OF TRULY BEING IMPACTFUL TO THE COMMUNITIES THAT WE'RE DEVELOPING THESE PROGRAMS FOR.

SO IT IS IN THERE. AND WE UNFORTUNATELY DIDN'T HAVE A CHANCE TO DESCRIBE THE EDUCATION PROGRAMS IN-DEPTH. I'M HAPPY TO SHARE SOME KIND OF SUMMARY PRESENTATIONS AND MATERIALS TO THE GROUP SO YOU LEARN MORE ABOUT THOSE PROGRAMS.



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I THINK WE'RE A LITTLE OVER. CAT, THANK YOU SO MUCH AND TO ALL THE SPEAKERS FOR YOUR VERY COMPELLING DISCUSSION. YOU CERTAINLY HAVE DONE WHAT WE WANTED TO DO, WHICH IS FRAME THE DISCUSSION. DR. MARKS IS ON NOW. HI, PETER.

DR. MARKS: IF I CAN GET OFF MUTE.

DR. MILLAN: SO THERE'S A LOT OF EXCITEMENT REGARDING CONSORTIUM APPROACHES TO BUILDING EVIDENCE BASE SO THAT WE CAN TAKE MORE OF A RISK-BASED APPROACH TO ENTERING INTO THESE NOVEL, INNOVATIVE TECHNOLOGIES. AND YOU'VE BEEN AN INSPIRATION IN KIND OF YOUR LEADERSHIP AT THE FDA FOR THIS.

DR. MARKS: THAT'S VERY KIND OF YOU. I THINK THIS IS PROBABLY AN IMPORTANT WAY TO TRY TO MOVE FORWARD BECAUSE IF WE DON'T START WORKING TOGETHER LIKE THAT, WE'RE JUST GOING TO END UP WITH A LOT OF -- OTHERWISE YOU END UP WITH A LOT OF SMALL THINGS THAT DON'T ACTUALLY END UP GETTING OVER THE FINISH LANE. SO I THINK THE WHOLE POINT OF THIS CONSORTIUM APPROACH IS TO TRY TO BRING STUFF TOGETHER TO ACTUALLY GET STUFF OVER THAT FINISH LINE.

DR. MILLAN: THANK YOU SO MUCH. SO WE ARE OVER A LITTLE BIT. THIS HAS BEEN SUCH A RICH

DISCUSSION. WE REALLY THANK EVERYBODY WHO'S PARTICIPATED TODAY AND EVERYBODY WHO'S LISTENED IN TODAY. I KNOW THAT EVERYBODY WANTED TO BE ABLE TO SAY SOMETHING AND CONTRIBUTE. WE REALLY APPRECIATE ALL OF YOUR PATIENCE AND WORKING THROUGH THIS KIND OF FORMAT. BUT WE REALLY WANTED TO GET THROUGH THESE TOPIC AREAS, AND I THINK WE DID PRETTY WELL GETTING THROUGH A LOT OF REALLY BROAD BRUSHES, BUT WITH SOME DEPTH IN THE CONVERSATION.

SO I'M GOING TO HAND IT OVER TO JONATHAN THOMAS, OUR CHAIR, ONE OF THE ONES WHO WAS PATIENTLY TAKING THIS ALL IN, TO CLOSE THE MEETING. THANK YOU SO MUCH.

CHAIRMAN THOMAS: SO THANK YOU, MARIA, FOR AN OUTSTANDING JOB IN ORCHESTRATING THIS ENTIRE TOUR DEFORCE SESSION BY ALL OUR PRESENTERS AND ALL OUR MEMBERS OF THE PANEL.

I WANTED TO ADD JUST A 30-SECOND ADDITION ON THE TOPIC WE WERE JUST DISCUSSING ON DEI. ONE OF THE THINGS I ALLUDED TO AT THE OUTSET WAS THE EMPHASIS WE'RE GOING TO HAVE ON ACCESSIBILITY AND AFFORDABILITY. UNDER THE ACCESSIBILITY TOPIC, WE ARE LOOKING, AND CAT ALLUDED TO THIS BRIEFLY, TO AUGMENT THE ALPHA CLINIC NETWORK WITH A NUMBER OF SATELLITE CLINICS CALLED COMMUNITY CARE CENTERS OF

EXCELLENCE, WHICH ARE GOING TO BE LOCATED IN PARTS OF THE STATE THAT SERVE THE UNDERSERVED AND MAKE A POINT OF HAVING GREATER ACCESSIBILITY TO BOTH CLINICAL TRIALS AND TREATMENTS.

AND TOWARDS THAT END, IN FACT, WE HAVE ONE AND A HALF PERCENT OF THE 5.5 BILLION GOING TO BE ALLOCATED SPECIFICALLY TO FACILITIES, EQUIPMENT, AND OPERATIONS FOR THESE COMMUNITY CARE CENTERS OF EXCELLENCE.

SO THIS IS A FURTHER WAY THAT CIRM IS LOOKING TO MAKE SURE THAT WE HAVE ALL COMMUNITIES REPRESENTED AND TREATED IN AN AFFORDABLE WAY. SO I JUST WANTED TO ADD THAT AS A POSTSCRIPT TO CAT'S EXTRAORDINARY SUMMARY OF CIRM AND WHAT WE'VE BEEN UP TO.

SO, AGAIN, WANT TO THANK EVERYBODY VERY MUCH ON BEHALF OF THE BOARD. THIS HAS BEEN AS MUCH OR MORE THAN WE HOPED FOR WHEN MARIA AND I FIRST STARTED DISCUSSING THIS IDEA OF CONVENING THIS PANEL TOGETHER.

I DID WANT TO ASK ARE THERE ANY MEMBERS OF THE PUBLIC WHO ARE ON THE CALL HERE WHO MIGHT WISH TO COMMENT AT THIS POINT?

DR. MILLAN: MARIA BONNEVILLE, COULD YOU HELP COORDINATE THIS FOR US, PLEASE?

CHAIRMAN THOMAS: I THINK WE WOULD BE HEARING. I'M NOT CERTAIN -- KOLEY, ARE YOU HEARING?

DR. MILLAN: I HAVE A HAND RAISED. IRV WEISSMAN.

DR. WEISSMAN: I JUST WANT TO MAKE TWO VERY SMALL COMMENTS. THE FIRST ONE IS THAT FOR DAVID HAUSSLER AND THE OTHERS DOING THE WHOLE GENOME SEQUENCING. I HOPE THAT YOU CAN FIND A WAY IN A HIPPA-CORRECT MANNER TO BE FOLLOWING WHAT HAPPENS TO PEOPLE WHOSE SEQUENCE IS IN IN TERMS OF CLINICAL EVENTS.

AND THE REASON I'M DOING THAT IS THAT WE FOUND AN INTRONIC ENHANCER WHICH CANCERS CAN USE TO TURN ON CD47, AND WE'RE PRETTY SURE THAT THAT WILL LEAD TO A WORSE INCIDENCE. AND SO IN ORDER TO UNDERSTAND THE CHANGE FROM A POISED TO A SUPER ENHANCER, YOU NEED TO BE ABLE TO LOOK AT A LARGE NUMBER OF DATABASES. SO WHETHER IT'S AN IPS LINE OR WHOLE GENOME SEQUENCING, I HOPE THAT PEOPLE, ESPECIALLY WITH THE HELP OF THE FDA AND PEOPLE WHO ARE CONCERNED ABOUT HIPPA, CAN SEE A WAY FORWARD TO GET THE INFORMATION THAT IS GOING TO HELP.

MY SECOND VERY SMALL COMMENT IS I LOVE GENE THERAPY, AS MIKE MCCUNE KNOWS. BUT WE DO HAVE PURIFIED BLOOD-FORMING STEM CELLS TO TREAT BLOOD



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FORMING DISEASES, AND WE HAVE THE ANTIBODIES TO ISOLATE THEM. THEY DO NOT CAUSE GRAFT VERSUS HOST DISEASE IN ALLOGENEIC SITUATIONS. SO THE OTHER ARM OF TREATING GENETIC DISEASE OF THE BLOOD-FORMING SYSTEM AND INDUCING IMMUNOLOGICAL TOLERANCE IS PURIFIED HEMATOPOIETIC STEM CELL TRANSPLANTS.

NOW, THAT'S SOMETHING THAT HAS BEEN AN EXPENSIVE AND LOCALIZED PROCESS, BUT IT IS ONE WHICH WE ARE HAPPY TO DONATE THE ANTIBODIES TO ISOLATE STEM CELLS AT COST OR MAYBE EVEN LESS THAN COST TO TRY TO ENCOURAGE THIS TO GO FORWARD. AND THAT WOULD BE USEFUL, OF COURSE, FOR GENE THERAPY BECAUSE THAT'S THE CELL YOU WANT TO GENETICALLY MODIFY.

I'LL JUST STOP THERE BECAUSE I'VE BEEN TRYING TO GET THAT THROUGH ON THE END OF EVERYBODY'S TALK. THANKS.

DR. HAUSSLER: IRV, YOU JUST HIT THE HARDEST PROBLEM OF ALL IN YOUR FIRST COMMENT. OUTSIDE OF VERY CUMBERSOME AND EXPENSIVE PROJECTS LIKE ALL OF US, WE HAVE VERY, VERY EXTREME DIFFICULTIES IN TRACKING WHAT BECOMES OF INDIVIDUALS WHO ENROLL IN OUR KIND OF STANDARDS PROGRAMS FOR GENOMES OR STEM CELLS.

CHAIRMAN THOMAS: ANY OTHER COMMENTS FROM MEMBERS OF THE PUBLIC AT THIS POINT? SO WITH THAT,



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AGAIN, JOIN MARIA AND THANK EVERYBODY. THIS EXTRAORDINARY PUBLIC SESSION IS NOW OVER. AND THANK YOU VERY MUCH, AND EVERYBODY CAN GO HAVE LUNCH. THANKS VERY MUCH.

(THE MEETING WAS THEN CONCLUDED AT 12:44 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 ZOOM PROCEEDINGS BEFORE THE INDEPENDENT CITIZEN'S OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF THE SCIENTIFIC STRATEGY ADVISORY PANEL MEETING HELD ON FEBRUARY 22, 2021, 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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SANDPOINT, IDAHO
(208) 920-3543