BEFORE THE
SCIENTIFIC AND MEDICAL ACCOUNTABILITY
STANDARDS WORKING GROUP
TO THE
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
ORGANIZED PURSUANT TO THE
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

REGULAR MEETING

LOCATION:	LUXE HOTEL 11461 W. SUNSET BOULEVARD LOS ANGELES, CALIFORNIA
DATE:	FEBRUARY 17 AND 18, 2009
REPORTER:	BETH C. DRAIN, CSR CSR. NO. 7152
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I N D E X

LOS ANGELES, CALIFORNIA; TUESDAY, FEBRUARY 17, 2009

1 P.M.

CHAIRMAN LO: GOOD AFTERNOON. WELCOME TO THE MEETING OF THE STANDARDS WORKING GROUP OF THE CIRM. WE'RE DELIGHTED TO BE IN LOS ANGELES, AND THANK SHERRY LANSING AND OTHERS FOR ARRANGING SUCH WONDERFUL WEATHER FOR US, WHICH IS, NO MATTER WHERE WE CAME FROM, IT'S BETTER HERE THAN IT WAS WHERE WE TOOK OFF FROM THIS MORNING.

MS. LANSING: AND IT'S BETTER HERE THAN IT WAS THIS MORNING ALSO AT THE MOMENT.

CHAIRMAN LO: SO WE HAVE A VERY FULL AND INTERESTING AND EXCITING AGENDA FOR THE NEXT TWO DAYS. WHY DON'T WE START -- PAT, DO YOU WANT TO CALL THE -- DO THE ROLL CALL. GEOFF, DO YOU WANT TO DO IT REAL QUICK?

DR. LOMAX: WE WILL DO A ROLL CALL OF THE MEMBERS PRESENT. ANN KIESSLING.

DR. KIESSLING: HERE.

DR. LOMAX: FRANCISCO PRIETO.

DR. PRIETO: HERE.

DR. LOMAX: JEFF SHEEHY.

MR. SHEEHY: HERE.

DR. LOMAX: DOROTHY ROBERTS.

DR. ROBERTS: HERE.
DR. LOMAX: ALTA CHARO.
DR. CHARO: HERE.
DR. LOMAX: BERNARD LO.
CHAIRMAN LO: HERE.
DR. LOMAX: SHERRY LANSING.
MS. LANSING: HERE.
DR. LOMAX: JOHN WAGNER.
DR. WAGNER: HERE.
DR. LOMAX: JOSE CIBELLI.
DR. CIBELLI: HERE.
DR. LOMAX: ROBERT TAYLOR.
DR. TAYLOR: HERE.
DR. LOMAX: TED PETERS.
DR. PETERS: TED PETERS, HERE.
DR. LOMAX: THOSE ARE THE MEMBERS PRESENT.
CHAIRMAN LO: THANK YOU. GEOFF, DO YOU WANT TO START WITH THE STAFF REPORT ALONG AS YOU'RE UP?
DR. LOMAX: YEAH.
CHAIRMAN LO: OKAY. NEXT LET'S TURN TO A STAFF REPORT FROM GEOFF ON SEVERAL ITEMS OF INTEREST AND IMPORTANCE TO THE SWG.
DR. LOMAX: IT ACTUALLY WORKED. THAT'S GOOD. GOOD AFTERNOON. WHAT I WANTED TO COVER IN

THE FIRST STAFF REPORT THIS AFTERNOON IS AN UPDATE ON THE RECENT REGULATORY REVISIONS TO THE MEDICAL AND ETHICAL STANDARDS. THESE WERE REVISIONS WHICH WERE DISCUSSED IN THE DECEMBER MEETING, AND WE WANTED TO PROVIDE AN UPDATE ON THE PROGRESS OF THE REVISIONS.

THE MAJOR ITEMS THAT WERE DEVELOPED AND THE REVISIONS WERE THE CLARIFICATION OF THE OVERSIGHT REQUIREMENTS FOR IPS RESEARCH AND THE CONSENT REQUIREMENTS TO FACILITATE THE USE OF IPS CELLS.

THE ACTUAL LANGUAGE IS INCLUDED IN YOUR PACKET AND IS AVAILABLE FOR THE PUBLIC. WE'VE DONE TWO ITEMS. ONE IS A MARKUP OF THE REGULATIONS, AND THE SECOND ITEM IS A KEY TIES THE MARKUPS TO THE SORT OF POLICY OBJECTIVES. I DO WANT TO MAKE ONE NOTE ON ITEM NO. 6 THERE SHOULD BE STRUCK. I WILL DISCUSS THAT IN A MINUTE, BUT THE KEY IS NOT UP TO DATE, BUT THE REGULATORY LANGUAGE, THE ACTUAL DOCUMENT IS. THERE IS AN ITEM NO. 6 IN THE KEY THAT EFFECTIVELY DOESN'T APPLY BECAUSE THERE'S NOTHING IN THE REGULATIONS THAT CORRESPOND TO THAT ITEM. AND AGAIN, I'LL TOUCH BASE ON THAT IN A MOMENT.

SO IF YOU REMEMBER THE DISCUSSION IN DECEMBER, WE FIRST TALKED ABOUT OVERSIGHT. AND THE

IMPORTANT POINT THERE IS THAT THERE WAS A NEED FOR CLARIFICATION AMONG SCRO COMMITTEES ABOUT WHAT LEVEL OF NOTIFICATION IS REQUIRED FOR GENERAL RESEARCH, GENERAL REPROGRAMMING RESEARCH. AND THE CONCLUSION OF THE DECEMBER MEETING WAS THAT FULL REVIEW WAS NOT REQUIRED FOR DERIVATION OF INDUCED PLURIPOTENCY USING SOMATIC CELLS.

THE CHANGES TO THE REGULATIONS ARE IN SECTION 100070 WHERE IT MAKES CLEAR THAT REPROGRAMMING IS AN ITEM THAT REQUIRES NOTIFICATION OF THE OVERSIGHT COMMITTEE, BUT NOT FULL REVIEW.

IN ADDITION, FOR REPROGRAMMING WORK, THERE WAS A NEED TO ALLOW REPROGRAMMING WORK TO OCCUR ON SOMATIC CELLS WHERE THE DONORS HAD PROVIDED GENERAL CONSENT FOR THE USE OF THE CELLS IN RESEARCH, BUT THE DETAILED CIRM CONSENT THAT IS DESCRIBED IN OUR REGULATION IS NOT -- WOULD NOT BE REQUIRED TO DO BASIC IN-VITRO RESEARCH. SO IF YOU LOOK WHERE THESE MODIFICATIONS ARE INCORPORATED ARE IN SECTION 100090. AND WHAT YOU WILL SEE THERE IS A MORE GENERAL CONSENT REQUIREMENT FOR THE USE OF SOMATIC CELLS WITH THE CAVEAT THAT SPECIFIC CONSENT FOR THE TRANSPLANTATION OF CELL PRODUCTS INTO HUMANS, THERE MUST BE CONSENT FROM THE DONOR FOR TRANSPLANTATION TO HUMANS. AND, AGAIN, THIS WAS CONSISTENT WITH THE

DISCUSSIONS IN THE DECEMBER MEETING.

IN ADDITION, THE REGULATIONS REFLECT PREVIOUSLY APPROVED INTERIM REGULATIONS. THESE WERE REGULATIONS THAT WERE DISCUSSED BY THIS WORKING GROUP ACTUALLY THE LAST TIME WE MET HERE, WHICH I BELIEVE WAS JULY OF LAST YEAR. AND THESE WERE REGULATIONS THAT HAD BEEN APPROVED BY THE ICOC ON AN INTERIM BASIS, WHICH MEANS THEY'RE IN EFFECT FOR 270 DAYS FROM THE DATE OF APPROVAL. THEREFORE, THE ICOC, WE NEED TO -- THE ICOC HAS TO MAKE A FINAL DECISION WHETHER TO INCORPORATE THOSE AS PERMANENT REGULATIONS.

AND THIS WAS -- THESE REGULATIONS WERE THE REGULATIONS THAT AUTHORIZED THE USE OF EMBRYOS CREATED FROM GAMETE DONORS FOR WHICH THE DONOR WAS PAID AND MAKING MODIFICATIONS TO THE REGULATIONS ALLOWING THE USE OF SOME EMBRYOS WHERE THE EXACT CONSENT REQUIREMENTS OF THE CIRM CONSENT REQUIREMENTS ARE NOT REQUIRED. SO LET ME TRY TO -- IT'S A COMPLICATED POINT, SO LET ME HOPEFULLY CLEAR THAT UP WITH A COUPLE OF GRAPHS THAT WILL ILLUSTRATE THIS POINT MORE CLEARLY.

FIRST, WITH REGARD TO EMBRYOS FROM WHICH A GAMETE DONOR WAS PAID, THE POLICY RECOMMENDATION WAS THAT IF THE EMBRYO WAS CREATED PRIOR TO AUGUST 2008

AND THE EMBRYO WAS CREATED FOR REPRODUCTIVE PURPOSES, THEN THOSE EMBRYOS COULD BE UTILIZED IN CIRM-FUNDED RESEARCH. AND AGAIN, SECTION 100090 HAS MODIFICATIONS THAT REFLECT THAT CUTOFF DATE AND THAT RECOMMENDATION.

IN ADDITION, THERE WAS DISCUSSION ABOUT THE CONSENT REQUIREMENTS FOR THE USE OF EMBRYOS. AND HERE, AGAIN, WHAT THE MODIFICATIONS MAKE EXPLICIT IS THAT PRIOR TO NOVEMBER 2006, WHICH WAS THE DATE THE CIRM REGULATIONS TOOK EFFECT, A SORT OF GENERAL RESEARCH CONSENT PROVIDED BY THE GAMETE DONORS IS SUFFICIENT FOR THE PURPOSE OF USING THOSE MATERIALS IN RESEARCH. AND THEN AFTER THAT DATE, AND, IN FACT, THAT GREEN BOX DOESN'T SORT OF CUT OFF IN 2008. IT SHOULD MOVE OUT INTO THE FUTURE -- THE CIRM-SPECIFIC CONSENT REQUIREMENTS THEN TAKE EFFECT AFTER -- FROM ANY EMBRYO CONSENTED FOR RESEARCH AFTER NOVEMBER 2006.

SO PAUSE THERE FOR A MOMENT AND I HOPE THAT WAS CLEAR. ARE THERE ANY QUESTIONS IN TERMS OF WHAT THESE MODIFICATIONS DO?

DR. TAYLOR: GEOFF, THAT WAS FOR RESEARCH ONLY PURPOSES?

DR. LOMAX: NO. THESE WOULD BE FOR -- IN THIS CASE WE'RE DEALING WITH EMBRYOS CREATED FOR IVF

OR REPRODUCTIVE PURPOSES, AND IT'S THE NATURE OF THE CONSENT. SO IF YOU RECALL, OUR REGULATIONS HAVE A VERY DETAILED AND PRESCRIPTIVE SET OF ITEMS THAT NEEDS TO BE CONVEYED IN THE CONSENT. EFFECTIVELY WHAT THIS DOES IS SAY, LOOK, IF YOU PROCURED THE EMBRYO FOR RESEARCH PRIOR TO THE DATE OF THESE REGULATIONS TAKING EFFECT, WE CAN'T HOLD YOU TO A CONSENT STANDARD THAT DIDN'T EXIST AT THAT TIME. SO IT SORT OF SEPARATES SORT OF PREREGULATORY CONSENT TO SORT OF POSTREGULATION, AND THEN AFTER NOVEMBER 2006, THE REGULATIONS PRESCRIBE A MORE SORT OF DETAILED CONSENT. AND AGAIN, THIS IS CONSISTENT WITH THE CONSENT IN THE NATIONAL ACADEMIES AS WELL, SO THERE'S A KIND OF -- SORT OF THE WHOLE FIELD SORT OF SHIFTED AT THE POINT IN TIME, AND WE'RE TRYING TO RECOGNIZE THAT.

SO JUST TO REMIND FOLKS OF THE PROCESS. DR. LO DID A TERRIFIC PRESENTATION IN JANUARY, AND IT WAS VERY WELL RECEIVED BY THE BOARD. IT WILL HAVE TO GO BACK TO THE BOARD IN MARCH FOR FINAL APPROVAL AGAIN BECAUSE THE ISSUE THERE WAS A QUORUM ISSUE, BUT THERE WAS A GOOD DISCUSSION AND A GOOD PRESENTATION AT THE ICOC. AND I THINK EVERYONE LOOKED VERY FAVORABLY ON THIS PACKAGE OF RECOMMENDATIONS. BUT, AGAIN, WE'LL HAVE TO COME

BACK TO THE BOARD ON THE MARCH MEETING TO GET FORMAL APPROVAL, AT WHICH TIME WE'LL BE ABLE TO INITIATE THE PROCESS WITH THE OFFICE OF ADMINISTRATIVE LAW.

AND WHAT THAT PROCESS INVOLVES, THAT'S THE PHASE OF THE PROCESS WHERE WE TAKE WHAT YOU HAVE BEFORE YOU, WE PUT OUT A PUBLIC NOTICE, AND THEN WE'RE OPEN TO A FORMAL PUBLIC COMMENT PERIOD, AT WHICH TIME WE CAN RECEIVE COMMENTS FROM THE PUBLIC AND WE'LL HAVE TO RESPOND TO THOSE COMMENTS. IF THERE ARE ANY SUBSTANTIVE CHANGES WE FEEL ARE REQUIRED AS A RESULT OF THOSE COMMENTS, WE WILL COME BACK EITHER TO THE WORKING GROUP OR THE BOARD DEPENDING ON THE NATURE OF THE COMMENTS.

AND I THINK THAT COVERS IT FOR REGULATIONS. AGAIN, ITEM 6, AS I SAID, I'D MENTION THAT AT THE END. IT SUGGESTS THERE'S LANGUAGE IN THERE THAT WOULD ALLOW THE USE OF EMBRYOS FOR WHICH THERE WAS AN ANONYMOUS DONOR WITH NO CONSENT. IF YOU READ THE LANGUAGE IN THE KEY, AND, AGAIN, THAT'S A PROVISION THAT SIMPLY ISN'T IN THE REGULATIONS WHATSOEVER, IT'S IN THE KEY IN ERROR, AND IT REFLECTS A DISCUSSION THAT WE HAD PREVIOUSLY AND IS UNRELATED TO THESE MODIFICATIONS. SO I APOLOGIZE FOR THAT. IT WAS JUST AN OVERSIGHT IN THE DOCUMENTATION.

CHAIRMAN LO: OKAY. THANKS. THIS WILL BE COMING BACK. GEOFF, DO YOU ALSO WANT TO TELL US ABOUT THE UPDATE ON THE CIRM OUTREACH ACTIVITIES YOU'VE BEEN DOING?

DR. LOMAX: I THINK I WILL TURN THE FLOOR OVER TO DON GIBBONS AND ALLOW HIM TO PROVIDE THAT UPDATE. I'D LIKE TO INTRODUCE DON GIBBONS, THE CHIEF COMMUNICATION OFFICER FOR CIRM.

MR. GIBBONS: CHAIRMAN LO, MEMBERS OF THE WORKING GROUP, THANKS FOR COMING THIS AFTERNOON. FIRST LET ME CLARIFY WHAT A COMMUNICATIONS CHIEF IS DOING UP AT THIS COMMITTEE. FIRST OFF, I DID INTERFACE WITH THIS REALM A LOT WHEN I WAS AT HARVARD, BUT MORE IMPORTANT, WHEN PRESIDENT TROUNSON HIRED ME, HE MADE IT CLEAR THAT HE DIDN'T WANT A TRADITIONAL COMMUNICATIONS OFFICE. MY AREA IS OVERTLY COMMUNICATION AND EDUCATION, AND HE MADE IT QUITE CLEAR THAT HE WANTED ME TO FOCUS EQUALLY ON PUBLIC EDUCATION EFFORTS.

SO GEOFF AND I TEAMED UP A COUPLE WEEKS AGO TO DO A WORKSHOP IN SACRAMENTO THAT WE CALLED "FERTILE GROUND - THE INTERFACE OF REPRODUCTIVE HEALTH AND RESEARCH." AND WE TOOK THE OPPORTUNITY OF THERE NOT BEING ANYTHING TERRIBLY CONTROVERSIAL BEFORE YOU AND BEFORE THE CIRM TO DO AN EDUCATIONAL

OUTREACH IN WHICH THE FIRST HALF OF THE DAY WAS US TRYING TO CREATE A LEVEL PLAYING FIELD OF KNOWLEDGE, AND THE SECOND HALF LISTENING TO, GIVEN THAT, WHAT ARE CONCERNS.

WE HAD AN AUDIENCE OF ABOUT 32 PEOPLE, EQUALLY DIVIDED BETWEEN LEGISLATIVE AIDES IN SACRAMENTO THAT WRITE THE LEGISLATION, PATIENT ADVOCATES, AND MEMBERS OF SOCIAL JUSTICE COMMUNITIES. SUSAN FOGEL AND OTHERS WERE THERE. THE LEAD-OFF SPEAKER WAS ANN KIESSLING, COMMITTEE MEMBER, AND SHE DID A WONDERFUL JOB OF LAYING THE GROUNDWORK OF WHY DO WE HAVE IRB'S AND WHAT ARE THEY SUPPOSED TO DO. SOME OF THE BASICS THAT OFTENTIMES WE GET INTO CONVERSATIONS WITH THE GENERAL PUBLIC, THERE'S A DISCONNECT. ON THE RIDE UP TO SACRAMENTO WITH US, SHE DID SOME INTERNET SEARCHING AND DISCOVERED THAT THE COMMISSION THAT CREATED THE BELMONT RULE, BELMONT REPORT THAT RESULTED IN THE COMMON RULE MAY HAVE BEEN RICHARD NIXON'S LAST SIGNATURE BEFORE HE LEFT OFFICE.

GREAT FRAMEWORK. THE WOMAN THAT YOU HAVE HEARD FROM AT YOUR MEETING LAST SUMMER FROM THE UCSF TISSUE BANKING SERVICE GAVE A GROUNDWORK OF HOW THAT TISSUE BANK WORKS, WHAT CONSENTS THEY REQUIRE, AND DIFFERENT TYPES OF TISSUE, EGGS, EMBRYOS, ETC. AND

THEN WE HAD A LIVELY DISCUSSION IN THE AFTERNOON, AND WE DID HAVE A FACILITATOR WORKING THE MEETING FOR US. WE FELT THAT WE SHOULD NOT RUN THE MEETING. WE WANTED IT RUN BY FACILITATORS SO IT WOULD BE A BETTER GIVE-AND-TAKE. AND AN EXECUTIVE SUMMARY OF THOSE DISCUSSIONS WILL COME TO YOU SOMETIME IN THE NEXT FEW WEEKS, SO LOOK FORWARD TO THAT.

PART OF OUR EDUCATION EFFORT IS TO JUST RAISE THE LEVEL OF KNOWLEDGE OF WHAT CIRM IS ACCOMPLISHING IN TERMS OF SCIENCE THAT IT'S FUNDING. SO OVER THE NEXT EIGHT WEEKS, THERE WILL BE TOWN FORUMS IN SAN FRANCISCO, L.A., AND SAN DIEGO WITH THREE CIRM-FUNDED RESEARCHERS, ONE KIND OF GIVING AN OVERVIEW, ONE GIVING SOME RESEARCH LEADING TOWARD CELL-BASED THERAPY, AND ONE TALKING ABOUT OTHER USES OF STEM CELLS, WHETHER IT BE AN ASSAY OR CANCER STEM CELLS OR THAT SORT OF THING.

AND THEN WE'VE DONE EXTENSIVE WORK ON THE INTERNET THAT IS ACTUALLY BEING ANNOUNCED IN A PRESS RELEASE TODAY. WE HAVE ABOUT 17 VIDEOS UP THAT TAKE PEOPLE ONE STEP AT A TIME, ABOUT FOUR-MINUTE VIDEOS FOR ABOUT 16 DIFFERENT ASPECTS OF STEM CELL RESEARCH. I HATE TO ADMIT THAT THE ONE ON ETHICS IS THE LAST ONE TO GET POSTED BECAUSE OF SCHEDULING ISSUES WITH OUR ETHICIST. BUT THEY ARE UP ON A

UTUBE SITE, SO IF YOU GO INTO UTUBE AND LOOK UNDER CIRM T.V., YOU WILL FIND ALL THESE VIDEOS. AND ALSO TODAY WE'RE ANNOUNCING A FLICKR SITE. IF YOU'RE NOT FAMILIAR WITH FLICKR, IT'S THE NO. 1 SITE FOR SHARING IMAGES.

WE HELD A CONTEST AMONGST CIRM GRANTEES OVER THE SUMMER, AWARDED 12 WINNERS OF THAT. WE HAD ABOUT 80 ENTRIES. YOU'VE SEEN THE CALENDAR THAT RESULTED FROM THAT, BUT I DON'T BELIEVE IN USING ANYTHING JUST ONCE. SO THOSE IMAGES HAVE BEEN USED AS BACKDROPS FOR CNN INTERVIEWS WITH ALAN. THEY'LL BE IN THE ANNUAL REPORT WHEN YOU GET IT IN A FEW WEEKS, AND NOW THEY'RE UP ON THE FLICKR SITE WITH A NUMBER OF IMAGES FROM OUR GRANTEE INSTITUTIONS. THERE ARE ABOUT 30 ALTOGETHER NOW. WE'RE GOING TO SHARE THEM LIBERALLY WITH JOURNALISTS SO THAT WHEN THEY ILLUSTRATE A STORY, IT'S WITH A GOOD, WELL-DEFINED IMAGE RATHER THAN SOMETHING VAGUE OR SOMETHING NEGATIVE.

SO ANY QUESTIONS? THANK YOU VERY MUCH.

CHAIRMAN LO: SO THANKS AGAIN. AND I THINK THE WORK YOU'RE DOING IS REALLY VERY HELPFUL AND SORT OF HELPING THE PUBLIC UNDERSTAND WHAT THE STEM CELL SCIENCE IS ALL ABOUT.

ALAN TROUNSON, WOULD YOU PLEASE JUST GIVE

US A BRIEF UPDATE ON THE SCIENTIFIC PROGRAM AND THE RESEARCH PRIORITIES FOR CIRM.

DR. TROUNSON: THANKS, BERNIE. I HAD A DISCUSSION WITH THE CO-CHAIRS, BERNARD AND SHERRY, ABOUT THE WORKING GROUP REALLY KEEPING UP ON THE CUTTING EDGE OF WHERE CIRM IS CURRENTLY HEADING, AND THAT IS VERY CLEARLY INTO TRANSLATION AND PRECLINICAL PROGRAMS. SO WE HAVE RELEASED RFA'S ON BOTH TRANSLATION AND DISEASE TEAMS. AND THIS IS REALLY TAKING US VERY, VERY CLOSE TO THE CLINIC.

YOU WILL BE AWARE THAT THE COMPANY GERON HAVE BEGUN CLINICAL TRIALS WITH HUMAN EMBRYONIC STEM CELL-DERIVED CELLS. SO WE ARE RIGHT UP AT THAT EDGE. AND I THINK THE ORGANIZATION REALLY NEEDS THE KIND OF INPUTS RIGHT UP AT THAT EDGE FROM THIS GROUP ON WHAT'S REALLY -- WHAT WE'RE REALLY DEALING WITH, WHERE WE'RE ACTUALLY MAKING THE HARD BITE OF WHERE WE'RE GOING. AND TO PUT BACK ON -- TAKE OFF AND PUT IT BACK ON THE BACK BURNER FOR THE TIME SOME ISSUES WHICH NEED TO BE OCCUPIED ABOUT, I THINK, IN THE FUTURE; THAT IS, THE ISSUE OF EGGS, BUT IT'S NOT SUCH A BURNING PRIORITY FOR US AT THE MOMENT AS IS THE CLINICAL TRIALS AREA.

SO WITH THE ENCOURAGEMENT OF THE CHAIRS, AND THANK YOU BOTH, BOTH BERNIE AND SHERRY, FOR

BEING SUPPORTIVE IN THIS AND SAYING, WELL, WE SHOULD BE GOING AS FAST AS YOU CAN GO WITH THE FRONT EDGE OF THE ACTUAL SCIENCE AND THE RFA'S AND THE DELIVERY. AND WHILE WE KEEP ON OUR MIND THAT THERE ARE NUMBERS OF THINGS THAT HAVE TO BE TIDIED UP AND ADDRESSED AND THERE COULD BE HARD MATTERS TO BE ADDRESSED, LET'S MAKE SURE THAT WE'RE DEALING WITH THE THINGS THAT WE'RE COMING ON HARD AT.

SO WE EXPECT TO BE FUNDING SOME OF THE EARLY TRANSLATIONAL WORK IN A RANGE ACROSS THE SPACE; THAT IS, TAKING THE DISCOVERIES INTO THE PHASE WHERE THEY'RE BEING DEVELOPED FOR CLINICAL APPLICATIONS. AND IN THE CASE OF THE DISEASE TEAMS, THESE ARE GOING TO TAKE US RIGHT UP TO IND'S. WE'RE GOING TO BE RIGHT AT THAT INTERFACE WITH PROVIDING FOR CLINICAL TRIALS.

AND THIS IS WHAT CIRM'S MISSION IS ABOUT. IT'S TAKING THE DEVELOPMENTS THAT ARE OCCURRING IN STEM CELLS AND GET THEM INTO THE CLINIC. AND IT'S REALLY, REALLY CRITICAL THAT WE ARE FOCUSED ON WHAT ARE THE KEY ELEMENTS OF CLINICAL TRIALS AND WHERE ARE THE COMPLICATIONS, WHERE ARE THE ETHICAL ISSUES, WHERE SHOULD WE BE ASKING QUESTIONS, AND WHERE SHOULD CIRM BE POSITIONED AT THE FRONT OF THIS WHOLE ENDEAVOR.

SO THIS IS THE REASON WHY WE'RE FOCUSING ON THE CLINICAL TRIALS IN THIS PARTICULAR SESSION. SO I HOPE YOU ENJOY IT BECAUSE THIS IS WHERE WE NEEDED TO GET TO, AND I THINK WE'VE GOT THERE IN A VERY RAPID TIME. I DIDN'T EXPECT JUST AFTER A YEAR OF TAKING HOLD OF THE HELM HERE TO BE TALKING TO YOU ABOUT CLINICAL APPLICATIONS, CLINICAL TRIALS, BUT WE'RE THERE. AND SO I THINK IT'S A FANTASTIC MOMENT. AND IF WE GET YOUR INPUTS INTO SOME OF THESE CLASSICALLY DIFFICULT ISSUES ABOUT CELLS INTO PEOPLE AND HOW IT'S DONE AND WHO OWNS THE CELLS AND WHAT ARE THE ISSUES RELATING TO ALL OF THE THINGS THAT SURROUND THE USE OF CELLS IN THIS PERSPECTIVE, THEN I THINK WE'LL AGAIN, SHOW, THE KIND OF LEADERSHIP THAT WE'VE BEEN DOING IN THE PAST IN THE AREA OF ETHICS WHICH IS WHAT IS REQUIRED ALSO UNDER PROPOSITION 71 THAT WE DEMONSTRATE THE THOUGHTS, THE LEADERSHIP IN THIS PARTICULAR SPACE.

SO I HOPE YOU WILL ENJOY THE SESSION AND WE'RE LOOKING FORWARD TO THE KIND OF INPUTS THAT YOU ARE PREPARED TO GIVE US IN THIS REGARD. THANKS.

CHAIRMAN LO: SHERRY.

MS. LANSING: THANK YOU, ALAN. I TOO WANT TO WELCOME ALL OF THE WORKING GROUP MEMBERS, THE PRESENTERS, AND THE MEMBERS OF THE PUBLIC TO OUR

2009 ANNUAL MEETING OF THE CIRM STANDARDS WORKING GROUP. I THINK OUR ANNUAL MEETING IS A UNIQUE TIME WHEN WE HAVE THE OPPORTUNITY TO REFLECT ON ALL OF OUR PAST ACCOMPLISHMENTS AND REALLY TO CONSIDER THE FUTURE DIRECTION OF THE WORKING GROUP IN A PUBLIC SETTING. AND AS YOU KNOW, WE USE THIS OCCASION REALLY TO CONSIDER THE STATE OF THE STEM CELL SCIENCE WITH REGARD TO CIRM PROGRAMMING AND TO CONSIDER ANY ETHICAL AND POLICY CONSIDERATIONS THAT REQUIRE THE ATTENTION OF THIS WORKING GROUP.

I WOULD LIKE TO REMIND ALL THE PUBLIC PARTICIPANTS AND THE GUESTS THAT THE STANDARD WORKING GROUP IS AN ADVISORY GROUP TO CIRM'S GOVERNING BOARD. WE HAVE A DIVERSE MEMBERS OF SCIENTISTS, ETHICS, LEGAL SCHOLARS, AND PATIENT ADVOCATES. AND REALLY BECAUSE WE HAVEN'T DONE THIS FOR A WHILE, FOR THE BENEFIT OF OUR INVITED GUESTS AND THE PUBLIC, I'D LIKE REALLY TO ASK THE MEMBERS OF THIS GROUP TO INTRODUCE THEMSELVES AND JUST BRIEFLY DESCRIBE YOUR AREA OF EXPERTISE. IT'S BEEN A LONG TIME SINCE WE'VE DONE THAT. SO, ANN, I'M GOING TO START WITH YOU AND JUST GO DOWN THE TABLE.

DR. KIESSLING: I'M ANN KIESSLING. I WEAR TWO HATS ACTUALLY. I'M AT HARVARD MEDICAL SCHOOL AND HAVE BEEN FOR A LONG TIME, AND I'VE ALSO BEEN

HEADING UP A VERY SMALL STEM CELL RESEARCH ORGANIZATION IN SOMERVILLE, MASS. AND I GUESS MY BASIC BACKGROUND IS IN REPRODUCTIVE BIOLOGY.

DR. PRIETO: I'M FRANCISCO PRIETO, AND I'M A PHYSICIAN IN SACRAMENTO, AND MY BACKGROUND HAS BEEN AROUND ISSUES RELATING TO DIABETES AND PATIENT ADVOCACY.

MR. SHEEHY: I'M JEFF SHEEHY, AND ONE OF THE PATIENT ADVOCATE MEMBERS OF THE BOARD OF THE CIRM. I'M SORRY. I'M A LITTLE CONFUSED TODAY. I'M A LITTLE OUT OF IT TODAY, SPACEY. I CAN'T EVEN INTRODUCE MYSELF. CAN YOU HEAR IT IN MY VOICE?

SO I'M COMMUNICATIONS DIRECTOR AT THE AIDS RESEARCH INSTITUTE AT UCSF, AND I ALSO HAVE A BACKGROUND IN AIDS ADVOCACY. THANKS.

DR. ROBERTS: I'M DOROTHY ROBERTS. I'M A PROFESSOR AT NORTHWESTERN UNIVERSITY SCHOOL OF LAW AND ALSO A FACULTY FELLOW AT THE INSTITUTE FOR POLICY RESEARCH THERE. I'VE WRITTEN ON VARIOUS ISSUES OF BIOETHICS, PRINCIPALLY THE ROLE OF RACE, CLASS, AND GENDER IN ISSUES INVOLVING REPRODUCTIVE JUSTICE AND HEALTH. AND I'M CURRENTLY FOCUSING ON RACE-SPECIFIC BIOTECHNOLOGIES.

CHAIRMAN LO: LET ME JUST INTERRUPT TO SAY THIS IS ACTUALLY DOROTHY'S FIRST IN-PERSON MEETING.

SHE'S BEEN ON THE PHONE WITH US.

DR. ROBERTS: YES. RIGHT.

CHAIRMAN LO: AND I JUST WANT TO EXTEND A WARM WELCOME, AND WE'RE DELIGHTED TO HAVE YOU.

MS. LANSING: I DO TOO. WELCOME.

DR. ROBERTS: THANK YOU.

DR. CHARO: I'M ALTA CHARO. I'M A PROFESSOR AT THE UNIVERSITY OF WISCONSIN LAW SCHOOL, A CROSS APPOINTMENT TO THE MEDICAL SCHOOL, AND A FELLOW AT THE MORGRIDGE INSTITUTE FOR RESEARCH IN MADISON, WISCONSIN. I CO-CHAIR THE NATIONAL ACADEMIES HUMAN EMBRYONIC STEM CELL RESEARCH ADVISORY COMMITTEE, AND RECENTLY COMPLETED SERVICE ON THE OBAMA TRANSITION TEAM WORKING FOR THE HHS AGENCY REVIEW FOCUSED MOSTLY ON FDA- AND NIH-SPECIFIC ISSUES.

CHAIRMAN LO: I'M BERNARD LO. I'M PROFESSOR OF MEDICINE AT UCSF WHERE I ALSO DIRECT THE PROGRAM IN MEDICAL ETHICS. AND IT'S BEEN MY HONOR TO BE CO-CHAIR OF THIS GROUP.

MS. LANSING: I'M SHERRY LANSING. I'M THE PATIENT ADVOCATE ON THE CIRM BOARD AND THE CO-CHAIR. VERY HAPPY TO BE SERVING ON THIS BOARD WITH BERNIE AS THE CO-CHAIR. I HAVE A LONG HISTORY OF PATIENT ADVOCACY IN THE SPECIFIC AREA OF CANCER RESEARCH.

DR. WAGNER: MY NAME IS JOHN WAGNER. I'M A PROFESSOR OF PEDIATRICS AT THE UNIVERSITY OF MINNESOTA. I'M THE DIRECTOR OF THE BLOOD AND MARROW TRANSPLANT PROGRAM IN PEDIATRICS. AND MY AREA OF RESEARCH IS THE DEVELOPMENT OF EXPERIMENTAL TREATMENTS FOR LIFE-THREATENING DISEASES, PRIMARILY CANCER AND HEART DISEASE.

DR. CIBELLI: I AM JOSE CIBELLI FROM MICHIGAN STATE UNIVERSITY. WE WORK WITH EMBRYONIC STEM CELLS AND SOMATIC CELL NUCLEAR TRANSFER AND NOW REPROGRAM CELLS. AND I'M ALSO WORKING WITH A GROUP IN SPAIN WHICH IS TRYING ALSO TO TAKE THIS TECHNOLOGY OR NEW TECHNOLOGIES TO THE CLINIC.

DR. TAYLOR: I'M ROD TAYLOR. I'M A PROFESSOR OF GYNECOLOGY AND OBSTETRICS AT EMORY UNIVERSITY AND A REPRODUCTIVE ENDOCRINOLOGIST BY TRAINING. I'M ALSO VICE CHAIR FOR RESEARCH IN THE DEPARTMENT AND HAVE AN ACTIVE REPRODUCTIVE CELL BIOLOGY RESEARCH PROGRAM.

DR. PETERS: I'M TED PETERS. I AM A PROFESSOR OF THEOLOGY AT THE GRADUATE THEOLOGICAL UNION IN BERKELEY. AND I'VE BEEN INVOLVED WITH ETHICAL ISSUES HAVING TO DO WITH GENETIC RESEARCH SINCE THE BEGINNING OF THE HUMAN GENOME PROJECT IN 1990, AND I'VE BEEN WORKING ON STEM CELL ETHICS

SINCE JULY OF 1998.

MS. LANSING: THANK YOU. AS YOU CAN SEE, THIS IS AN INCREDIBLY DISTINGUISHED GROUP THAT I'M HONORED TO BE PART OF. I ALSO WANT TO ADD THAT THIS GROUP HAS BEEN TOGETHER FOR OVER THREE YEARS, AND THOUGH WE HAVE A NEW MEMBER, MOST OF US HAVE BEEN HERE SINCE THE BEGINNING. AND WHAT I WANT TO THANK MY COLLEAGUES FOR IS THE -- I DON'T EVEN KNOW HOW MANY MEETINGS THERE'S BEEN AND PHONE CALLS, BUT FAR MORE THAN THE WORD "NUMEROUS." SO I REALLY WANT TO THANK YOU FOR YOUR COMMITMENT AND FOR YOUR SERVICE.

WE SAID WHEN WE STARTED THIS THAT THIS WOULD BE AN ONGOING PROCESS, AND WE WOULD CONTINUE UNTIL THERE WAS NO MORE NEED, THAT ALL THE DISEASES HAD BEEN CURED. AND I REALLY AM THRILLED TO SAY THAT THIS GROUP HAS STAYED TOGETHER.

SO I PERSONALLY AND ON BEHALF OF BERNIE AND ALL THE CITIZENS OF CALIFORNIA AND ALL THE PATIENT ADVOCATES THANK YOU VERY, VERY MUCH FOR YOUR SERVICE.

2008 WAS A YEAR WHEN CIRM PUT CONSIDERABLE EFFORT INTO UNDERSTANDING THE EFFECTIVENESS OF OUR MEDICAL AND ETHICAL STANDARDS. AND I JUST WANT THE MEMBERS OF THE PUBLIC TO UNDERSTAND THAT THIS EFFORT INCLUDED SITE VISITS TO GRANTEE INSTITUTIONS TO

EVALUATE THEIR OVERSIGHT PROGRAMS AND TO LEARN REALLY ABOUT HOW OUR REGULATIONS COULD BE MORE EFFECTIVE IN ADVANCING STEM CELL SCIENCE. AND WE ALWAYS WANTED TO MAINTAIN THE HIGHEST STANDARDS.

AND BASED ON WHAT WE LEARNED FROM THAT EXPERIENCE, THIS GROUP RECOMMENDED A SERIES OF AMENDMENTS TO THE ICOC. AND THESE AMENDMENTS WERE ATTEMPTS TO ENABLE GREATER ACCESS TO RESEARCH MATERIALS AND TO CLARIFY OUR REQUIREMENTS FOR RESEARCH OVERSIGHTS.

THIS PAST JANUARY BERNIE LO PRESENTED THOSE RECOMMENDATIONS TO THE ICOC, AND THE BOARD VOICED UNANIMOUS CONSENT FOR THIS DIRECTION AND EXPRESSED ITS SINCERE APPRECIATION AND ITS GRATITUDE FOR THE THOUGHTFULNESS AND ONGOING COMMITMENTS OF THIS WORKING GROUP.

IN 2009 WE ARE GOING TO CONTINUE TO LEARN HOW OUR REGULATIONS CAN BE MORE EFFECTIVE. AND I ANTICIPATE THAT, SINCE WE ARE A WORK IN PROGRESS, WE WILL CONTINUE TO CONSIDER POLICY AMENDMENTS. IN FACT, THERE IS TIME SET ASIDE TOMORROW AFTERNOON FOR SUCH DELIBERATIONS. HOWEVER, AS ALAN SAID, 2009 ALSO REPRESENTS A CRUCIAL MILESTONE FOR STEM CELL SCIENCE. I ALONG WITH ALAN AM THRILLED THAT WE ARE WHERE WE ARE TODAY, AND I MUST ADMIT IT IS HAPPENING

EVEN FASTER THAN I ANTICIPATED. WE ARE ALL AWARE THAT THE FDA HAS APPROVED ITS FIRST CLINICAL TRIAL FOR A STEM-CELL BASED THERAPY DERIVED FROM HUMAN EMBRYONIC STEM CELLS. AND CIRM'S SCIENTIFIC PROGRAM IS FOCUSED ON ADVANCING TRANSLATIONAL AND CLINICAL RESEARCH.

GIVEN THIS NEW DEVELOPMENT, IT IS ESSENTIAL THAT WE EDUCATE OURSELVES AND THE PUBLIC ON RESPONSIBLE CONDUCT OF THESE CLINICAL TRIALS. AND WITH THIS GOAL IN MIND, AS YOU CAN SEE, WE'VE PUT TOGETHER A WORKSHOP. THIS WORKSHOP WILL START WITH A BASIC OVERVIEW OF THE CONDUCT OF CLINICAL TRIALS AND WILL CULMINATE WITH CONSIDERATIONS OF ISSUES THAT ARE SPECIFIC TO STEM CELL RESEARCH. WE HAVE GATHERED TOGETHER A TALENTED LIST OF PRESENTERS, ALL OF WHOM HAVE HANDS-ON EXPERIENCE IN CLINICAL MEDICINE.

IN ADDITION, THERE IS CONSIDERABLE EXPERTISE AMONG OUR AUDIENCE. AND WE ALL LOOK FORWARD TO HEARING FROM YOU, THE MEMBERS OF THE PUBLIC AND IN THE AUDIENCE THROUGHOUT THIS WORKSHOP. IT IS REALLY OUR ABILITY TO BRING TOGETHER THIS COLLECTIVE EXPERTISE THAT IS SO IMPORTANT TO ALL OF US IN FULFILLING OUR MISSION FOR CIRM AND IN MAINTAINING THAT CIRM ALWAYS MAINTAINS THE BEST

SCIENCE UNDER THE HIGHEST STANDARDS.

SO I THANK ALL OF YOU FOR YOUR PARTICIPATION, AND I SPEAK ON BEHALF OF ALL OF US THAT WE LOOK FORWARD TO LEARNING FROM ALL OF YOU IN THE NEXT TWO DAYS. AND WITH THAT SAID, I WILL TURN IT OVER TO BERNIE WHO WILL BE FACILITATING THIS WORKSHOP.

CHAIRMAN LO: THANKS VERY MUCH, SHERRY. AS SHERRY AND ALAN HAVE SAID, I THINK THE GOAL OF WHAT WE'RE TRYING TO DO OVER THE NEXT DAY OR SO IS TO REALLY POSITION OURSELVES TO BE ON THE CUTTING EDGE OF SCIENCE AND TO UNDERSTAND AND START TO THINK ABOUT THE ETHICAL ISSUES THAT WILL ARISE AS WE BEGIN TO REALLY MOVE INTO THE CLINICAL TRIALS ARENA.

THIS IS REALLY SORT OF A WONDERFUL OPPORTUNITY FOR THOSE OF US ON THE SWG TO EDUCATE OURSELVES AND INDIRECTLY TO HELP EDUCATE THE PUBLIC ON THE SCIENTIFIC ETHICAL AND REGULATORY ISSUES THAT SURROUND STEM CELL CLINICAL TRIALS. AND I THINK AS WE LISTEN TO THE EXTREMELY TALENTED EXPERT SPEAKERS WE HAVE, I THINK IT WILL BE IMPORTANT FOR US ON THE SWG TO TRY AND SEPARATE OUT WHAT'S ALREADY IN PLACE IN TERMS OF MANAGING ETHICAL ISSUES IN CLINICAL TRIALS AND THE REGULATIONS OF CLINICAL TRIALS AND NOT TRY TO REDUPLICATE WHAT'S ALREADY IN PLACE, BUT

TO THINK ABOUT WHAT'S SPECIAL, WHAT'S DIFFERENT ABOUT STEM CELL CLINICAL TRIALS THAT MAY REQUIRE US TO THINK A LITTLE BIT DIFFERENTLY THAN WE WOULD ABOUT CLINICAL TRIALS OF OTHER INTERVENTION.

SO I'M GOING TO START WITH ASKING MARIE CSETE TO GIVE US SOME OF THE SCIENTIFIC BACKGROUND OF THE NEED FOR CLINICAL TRIALS, WHERE STEM CELL SCIENCE IS, AND WHAT ARE SORT OF THE PIPELINE THAT WE CAN ANTICIPATE FOR ADDITIONAL CLINICAL TRIALS. MARIE, THANKS VERY MUCH.

DR. CSETE: WELL, THANK YOU. AND IT HAS BEEN A GREAT YEAR FOR STEM CELL BIOLOGY, THE TENTH ANNIVERSARY OF THE DISCOVERY OF HUMAN EMBRYONIC STEM CELLS, REALLY A VERY SHORT TIME WHEN YOU CONSIDER THE WORK THAT WENT INTO GETTING THE FIRST IND APPROVED AT THE FDA.

SO I'M GOING TO GO THROUGH A LITTLE BIT OF HISTORY TO TELL YOU WHERE WE ARE AND START WITH TALKING ABOUT STEM CELLS THAT HAVE BEEN IN THE CLINIC FOR A LONG TIME, AND THAT IS BONE MARROW TRANSPLANTATION. BONE MARROW TRANSPLANTATION HAS BEEN USED FIRST TO TREAT A VARIETY OF BLOOD DISEASES. THE MARROW HOLDS BLOOD STEM CELLS. AND WHAT WE'RE SEEING IN THE CLINIC NOW IS APPLICATION OF THESE SOMETIMES AUTOLOGOUS CELLS FROM THE PATIENT

THEMSELVES OR ALLOGENEIC CELLS FROM OTHER PATIENTS. BONE MARROW TRANSPLANTS BEING APPLIED TO A WIDE VARIETY OF DISEASES, SOME WITH GOOD FORETHOUGHT AND SOME WITH ABSOLUTELY NO THEORETICAL BASIS FOR WHY THEY WOULD WORK.

A LOT OF THE WORK THAT WE'RE SEEING NOW IN CASE REPORTS AND OTHER THINGS IS COMING FROM ABROAD, AND A MAJOR CONCERN TO US SHOULD BE THE REGULATION OF WHAT SEEMS TO BE SAFE THERAPIES, AUTOLOGOUS THERAPIES, FOR DISEASES IN WHICH THERE'S NO HOPE OF BENEFIT AND POTENTIAL FOR HARM.

WE'RE ALSO SEEING THE APPLICATION OF ADULT STEM CELL THERAPIES TO DISEASES WHERE THIS WAS NOT REALLY ENVISIONED EVEN JUST A SHORT TIME AGO. SO, FOR EXAMPLE, WE'RE NOW SEEING NEURAL STEM CELLS DERIVED FROM FETAL SOURCES BEING APPLIED TO DEVASTATING DISEASES, INHERITED DISEASES OF CHILDREN. AND STEM CELLS, INC., A CALIFORNIA COMPANY, HAS AN ONGOING PHASE I TRIAL FOR BATTEN'S DISEASE RIGHT NOW, AN ABSOLUTELY DEVASTATING DISEASE OF CHILDREN.

AND THE POTENTIAL FOR ADULT STEM CELLS TO DO GOOD IS ENORMOUS. PEOPLE GENERALLY CONSIDER THEM TO BE SAFER IN TERMS OF THEIR RISK OF TUMOROGENICITY THAN PLURIPOTENT STEM CELLS; BUT, AGAIN, THE

POTENTIAL FOR DOING HARM IS THERE. JUST AS WE WERE COMING INTO THIS MEETING, DR. LO POINTED OUT A CASE REPORT THAT JUST APPEARED THIS MONTH SHOWING TUMORS IN A CHILD THAT WAS TREATED WITH NEURAL STEM CELLS ABROAD FOR ATAXIA TELANGIECTASIA, AND THERE WERE MULTIPLE DONORS INVOLVED IN THESE STEM CELLS, AND THE CHILD DEVELOPED TUMORS FROM TWO DIFFERENT DONOR SOURCES IN THE BRAIN.

SO WE'RE GOING TO HAVE TO AGAIN WITH ADULT STEM CELL THERAPIES THAT ARE ON THE SURFACE THAT LOOK RELATIVELY UNRISKY THINK ABOUT THE RISK AND BALANCE IN TERMS OF APPROPRIATE PATIENT POPULATIONS, THE APPROPRIATE CELL PREPARATIONS, AND BALANCE THE RISKS AND BENEFIT.

THE EXCITING PART FOR US FOR CIRM CERTAINLY IS THE APPLICATION OF PLURIPOTENT STEM CELLS TO THE CLINIC. AND THERE'S ENORMOUS BUZZ IN CALIFORNIA AND WITH OUR COLLABORATIVE PARTNERS ABOUT THE DISEASE TEAM GRANT, ABOUT THE OPPORTUNITY TO RIGOROUSLY APPLY BASIC SCIENCE INTO A VARIETY OF PATIENTS' DISEASES. AND I'M HEARING CERTAINLY THAT WE WILL SEE APPLICATIONS FROM INVESTIGATORS WHO ARE VERY CLOSE AND HAVE BEAUTIFUL ANIMAL DATA TO SUGGEST THAT PLURIPOTENT CELLS CAN GENERATE RPE FOR THE REPAIR OF MACULAR DEGENERATION, CAN GENERATE BETA

CELLS FOR PATIENTS WHO HAVE TYPE 1 DIABETES, WHO CAN GENERATE MOTOR NEURONS POTENTIALLY FOR THE TREATMENT OF PATIENTS WITH ALS, AND WHO CAN GENERATE HEPATOCYTES FOR THE TREATMENT OF ACUTE LIVER FAILURE, AMONG MANY OTHERS THAT WE WILL SEE.

THEIR SAFE APPLICATION WILL BE CIRM'S RESPONSIBILITY TO GUARD AS THESE TRIALS ADVANCE TOWARDS PATIENTS.

THE OTHER MAJOR ADVANCE OF THE PAST COUPLE OF YEARS, AND WE'LL BE FACED WITH THIS CERTAINLY WITH CLINICAL APPLICATIONS COMING IN SOON IS THAT NOT ONLY PRIMARY CELLS, HUMAN EMBRYONIC STEM CELLS, BUT INDUCED PLURIPOTENT STEM CELLS ARE ALSO BEING WORKED TOWARD CLINICAL APPLICATION. THESE CELLS ARE TOUTED AS BEING AN IMMUNOLOGIC CURE IN THAT IF YOU TAKE THE CELLS FROM A PATIENT AND REVERT THEM TO AN EMBRYONIC STEM CELL STATE OR AN ADULT STEM CELL STATE OR ANOTHER CELL TYPE AND THEN PUT THEM BACK IN THE PATIENT AFTER EXPANSION, THERE'S A THOUGHT ON THE PART OF MANY SCIENTISTS THAT THE IMMUNE SYSTEM WILL NOT REACT TO THESE CELLS.

I DON'T THINK THAT'S A SURE BET. THERE'S NO GUARANTEE THAT CELLS WILL GO THROUGH A REGENERATIVE PROCESS IN A DISH IN AN ABNORMAL MICROENVIRONMENT THE SAME WAY THEY WENT THROUGH

DEVELOPMENT. AND YOU CAN ANTICIPATE THAT THERE WOULD BE PROTEINS MADE THAT WEREN'T SEEN BY THE HOST EVEN THOUGH THE CELLS COME FROM THAT HOST. SO WE'RE NOT IN PERFECTLY SAFE TERRITORY IN THAT WAY.

AND I THINK THE DATA IS ALSO SUGGESTING TO US THAT THE KIND OF HETEROGENEITY THAT WE SEE IN DIFFERENTIATION OF HUMAN EMBRYONIC STEM CELLS IN A DISH MAY ACTUALLY BE GREATER IN IPS CELLS BECAUSE OF SOME OF THE BAGGAGE THAT COMES WITH AGING THAT'S NOT COMPLETELY REVERSED WHEN THE CELLS ARE RETURNED TO AN EMBRYONIC STEM CELL LIKE STATE IN A DISH.

SO WE WILL BE FACED WITH ENORMOUS CHALLENGES, AND I HOPE THAT THIS AFTERNOON WHEN E. J. AND I TALK ABOUT CASE STUDIES, WE'LL POINT OUT THE FACT THAT THE PROGRESS TOWARD THE CLINIC HAS RAISED MANY, MANY QUESTIONS, AND PATIENTS HAVE BEEN TREATED WITH A VARIETY OF STEM CELLS ALONG THE WAY WHERE THE QUESTIONS HAVE NOT BEEN ANSWERED FULLY. AND WE WILL HAVE TO BE ASKING OURSELVES AS WE SUPERVISE THESE PLURIPOTENT DERIVED-STEM CELL TRIALS JUST HOW MUCH OF AN ANSWER WE NEED BEFORE WE TAKE THE NEXT STEP BECAUSE THE COMPLETE ANSWER TO THE KINDS OF QUESTIONS THAT WE HAVE RIGHT NOW JUST WON'T BE AVAILABLE IN THE NEXT COUPLE OF YEARS AS THE CELL THERAPIES ARE MADE AVAILABLE TO PATIENTS.

CHAIRMAN LO: THANKS. I WANT TO FIRST ASK IF THERE ARE ANY QUESTIONS JUST OF CLARIFICATION FOR MARIE, AND THEN WE'RE GOING TO HAVE SOME ADDITIONAL COMMENTS FROM ANOTHER SPEAKER. JUST ANY -- TED.

DR. PETERS: DO YOU HAVE ANY INFORMATION YOU CAN SHARE ABOUT THE RECENT ANNOUNCEMENT BY GERON THEY'RE GOING TO DO CLINICAL TRIALS ON THE SPINAL CORD?

DR. CSETE: SO I CAN TELL YOU ABOUT THE PUBLIC STATEMENTS THAT GERON HAS MADE AT THE FDA SAFETY MEETINGS AND IN OTHER CONTEXTS WHERE WE'VE BEEN IN ATTENDANCE.

SO GERON DEVELOPED A CELL PRODUCT THAT IS DERIVED FROM HUMAN EMBRYONIC STEM CELLS. THEY HAVE A MASTER BANK FROM ONE DONOR THAT IS DIFFERENTIATED TO BECOME A KIND OF CELL THAT IS READY TO MAKE AN OLIGODENDROCYTE. SO THE OLIGODENDROCYTES ARE CELLS THAT WRAP AROUND PROTECTOR NEURONS. AND THEIR ANIMAL WORK SUGGESTS THAT TRANSPLANTATION OF THESE OLIGODENDROCYTES INTO ANIMAL MODELS OF SPINAL CORD INJURY RESULTS IN RECOVERY FROM THE SPINAL CORD INJURY.

SO THEY WILL BE -- THEIR CLINICAL TRIAL IS IN PATIENTS WHO HAVE ACUTE INJURY, SO THE PATIENTS SHOULD BE REFERRED IN WITHIN A WEEK OF THEIR INJURY.

THEY ARE THE MOST SEVERELY INJURED IN THAT THE COMPLETENESS OF THE INJURY THROUGH THE SPINAL CORD IS CONSIDERED COMPLETE, AND THEY'RE PATIENTS WHO ARE INJURED AT A LEVEL OF THE THORAX IN A PARTICULAR AREA.

SO THE IND HAS BEEN APPROVED, BUT PATIENTS ARE NOT YET BEING ENROLLED BECAUSE GERON NOW HAS TO GO THROUGH THE PROCESS OF GETTING THE IRB APPROVAL IN ITS TEST SITE CENTERS, AND THEY'RE ACTIVELY OUT THERE DOING THAT.

THE PHASE I TRIAL WILL BE FOR EIGHT TO TEN PATIENTS.

DR. PETERS: COULD I ASK A SECOND QUESTION? COULD YOU UPDATE ME ON THE IPS CELLS? IT WAS OUR UNDERSTANDING THAT THE FOUR IN THE EARLY EXPERIMENTS, THE FOUR INTERPOLATED GENES WERE CARCINOGENIC, SO WHAT'S HAPPENED RECENTLY THAT HAS MOVED IPS CELLS CLOSER TO CLINICAL APPLICATION?

DR. CSETE: SO I THINK THE SCIENCE IS REACHING A POINT WHERE IT'S THE CELL'S PROLIFERATIVE ABILITY RATHER THAN THE WAY THAT THEY WERE MADE INTO IPS CELLS IS THE CONCERN IN TERMS OF TUMORS. SO THE ORIGINAL FOUR GENES HAVE NOW BEEN CONTRACTED TO TWO, MAYBE EVEN ONE. AND THE METHOD OF GETTING THEM EXPRESSED IN THE CELLS NO LONGER REQUIRES A

RETROVIRUS TO INTEGRATE THEM.

SO INVESTIGATORS ARE REPORTING THAT THEY CAN TRANSFER THE GENES AT THE RIGHT TIME AND IN THE RIGHT AMOUNT USING NONINTEGRATING PLASMID VECTORS OR EVEN UNPUBLISHED REPORTS SEEN AT MEETINGS OF JUST INJECTING THE PROTEINS IN.

SO I THINK THE MECHANISM TO GET TO THE IPS CELL WILL NOT BE SO MUCH OF A PROBLEM. NOTHING IS EVER PERFECT.

AND THE OTHER PART OF YOUR QUESTION WAS?

DR. PETERS: THAT HELPS. THANKS A LOT. I APPRECIATE IT.

CHAIRMAN LO: OKAY. NO FURTHER QUESTIONS. MARIE, THANKS VERY MUCH. I'M SURE WE'LL BE COMING BACK TO YOU AS THE DAY GOES ON.

I MISSPOKE. I READ THE AGENDA WRONG. NEXT WE'RE GOING TO TRY AND UNDERSTAND THE REGULATORY FRAMEWORK THAT THE FDA HAS IN PLACE AS WELL AS OTHER REGULATIONS REGARDING CLINICAL TRIALS IN GENERAL AND CELL-BASED THERAPIES IN PARTICULAR. AND ALTA CHARO IS GOING TO START US OUT. AND WHAT SHE DIDN'T SAY WHEN SHE INTRODUCED HERSELF IS SHE TEACHES THE COURSE ON FDA LAW, WHICH IS A FORMIDABLE COURSE AND VERY DETAILED, AND SHE KNOWS THIS STUFF BACKWARD AND FORWARDS. AND THEN AFTER SHE ADOPTS

THE MEDICAL PERSPECTIVE AND ACTUALLY IS GOING TO SHOW SLIDES EVEN THOUGH SHE'S A LAW PROFESSOR, E. J. READ IS GOING TO ADD SOME ADDITIONAL COMMENTS. AND I'LL INTRODUCE E. J. THEN.

DR. CHARO: I HAVE SLIDES TOO. GEOFF, DO YOU WANT TO CHANGE THEM FOR ME, OR DO YOU WANT ME TO GO UP THERE?

DR. LOMAX: WHATEVER YOUR PREFERENCE IS.

DR. CHARO: IF YOU'RE STANDING RIGHT THERE, JUST I'LL SHOUT CHANGE.

DR. LOMAX: ABSOLUTELY.

DR. CHARO: THANKS. OKAY. CHANGE THE FIRST SLIDE. THIS IS GOING TO BE INCREDIBLY SUPERFICIAL AND FOR A NUMBER OF YOU INCREDIBLY DULL BECAUSE YOU KNOW ALL OF THIS, SO FEEL FREE TO CHECK YOUR E-MAIL OR OTHERWISE ENGAGE YOURSELVES. BUT JUST THAT WE ALL HAVE THE SAME COMMON UNDERSTANDING OF THE BASIC STEPS FOR MOVING FROM BASIC RESEARCH TO AN FDA-APPROVED THERAPY, THIS SET OF SLIDES WILL GO VERY QUICKLY AND DO IT CHRONOLOGICALLY.

TO GIVE YOU SOME CONTEXT, IT'S IMPORTANT TO UNDERSTAND THAT THIS IS A SET OF CELL-BASED THERAPIES. CELL-BASED THERAPIES ARE REGULATED AS BIOLOGICS. THE FDA CURRENTLY IS DIVIDED INTO THREE CENTERS, DRUGS, DEVICES, AND BIOLOGICS. MOST

FAMILIAR ARE THINGS LIKE BLOOD TRANSFUSIONS AND VACCINES.

BUT CELL-BASED THERAPIES ALSO FALL WITHIN THE CENTER FOR BIOLOGICS. AND BECAUSE BIOLOGICS CAN BE DEVICES OR DRUGS, FOR EXAMPLE, A CELL-BASED BANDAGE WOULD BE A BIOLOGIC DEVICE IN A SENSE, WOULD BE A KIND OF ORGANIC BAND-AID. THE PRECISE PATH BY WHICH THESE THINGS GET APPROVED CAN BE RATHER COMPLICATED, AND THERE IS, IN FACT, A WHOLE OFFICE DEVOTED JUST TO THE QUESTION OF COMBINATION PRODUCTS. AND E. J. READ IS GOING TO TALK A LITTLE BIT MORE ABOUT THAT IN HER COMMENTS, I THINK.

THE OTHER THING TO NOTE, JUST BY WAY OF CONTEXT, IS THAT WHEN YOU'RE TALKING ABOUT BIOLOGICS, YOU ARE SUBJECT TO TWO DIFFERENT STATUTORY REGIMES. THE FIRST IS THE FOOD, DRUG, AND COSMETIC ACT, THE 1938 ACT AS AMENDED MANY, MANY TIMES, WHICH IS THE ONE WE'RE FAMILIAR WITH WHEN WE THINK ABOUT DRUG APPROVAL PROCESSES. BUT BIOLOGICS ARE ALSO SUBJECT TO THE PUBLIC HEALTH SERVICE ACT, WHICH IS REALLY ABOUT INFECTION CONTROL. AND SO YOU HAVE TWO INDEPENDENT SOURCES OF REGULATIONS, AND IT DOES MEAN BIOLOGICS HAVE SOME ODDITIES THEIR METHOD OF APPROVAL.

THIS IS SIMPLY A KIND OF CHRONOLOGICAL

OUTLINE OF THE STEPS ONE HAS TO GO THROUGH TO MOVE TO THERAPY. THE FIRST IS THE DERIVATION OR IMPORTATION OF A CLINICAL-GRADE CELL LINE, ONE THAT IS GOOD ENOUGH TO BE USED FOR THERAPEUTIC AS OPPOSED TO PURELY LAB PURPOSES. THEN YOU HAVE THE PRECLINICAL OR PREHUMAN RESEARCH WORK, FIRST PURELY IN VITRO IN THE LAB AND THEN WITH ANIMALS. AND IT'S ONLY AT THAT POINT THAT YOU CAN GO TO GET AN IND, WHICH STANDS FOR INVESTIGATIONAL NEW DRUG EXEMPTION, OR AN IDE, WHICH IS INVESTIGATIONAL DEVICE EXEMPTION, IN ORDER TO START TESTING IN HUMANS.

THE REASON THESE THINGS ARE CALLED EXEMPTIONS IS BECAUSE IT IS OTHERWISE A CRIMINAL ACT TO PUT INTO INTERSTATE COMMERCE ANY UNAPPROVED DEVICE OR DRUG. SO YOU NEED AN EXEMPTION IN ORDER TO GO FORWARD WITH HUMAN TRIALS.

SO FIRST IS THE FDA HAS TO OKAY IT, AND THE SECOND IS ALSO YOU HAVE TO GET APPROVAL FROM THE LOCAL IRB. SO YOU'VE GOT TWO DIFFERENT BODIES THAT ARE GOING TO LOOK OVER YOUR WORK. THEN YOU RECRUIT SUBJECTS INTO A SERIES OF TRIALS GOING FROM SMALL TO LARGE. ONE OF THE NEXT SLIDES WILL GO THROUGH WHAT THEY'RE ABOUT. AND THEN AT THE END HERE, I USE DRUGS AS AN EXAMPLE, YOU WOULD LOOK FOR A NEW DRUG APPROVAL FROM THE FDA AFTER YOU FILE YOUR NDA, NEW

DRUG APPLICATION. NOW, MOST RECENTLY, BECAUSE OF THE 2007 AMENDMENTS, THERE'S BEEN A HEIGHTENED EMPHASIS ON SURVEILLANCE AFTER DRUGS AND DEVICES AND BIOLOGICS ARE APPROVED. THIS IS MOST WELL DEVELOPED IN THE DRUG AREA, BUT IT CAN INVOLVE A VARIETY OF FAIRLY FORMAL MECHANISMS INCLUDING FOR CLINICAL TRIALS.

DRIVING A CLINICAL-GRADE CELL LINE IS SOMETHING I WANTED TO POINT OUT BECAUSE FIRST THERE'S A MISTAKE ON THE VERY FIRST BULLET POINT. THE WORK HAS TO BE IN A MANNER CONSISTENT WITH FDA GOOD MANUFACTURING PRACTICE RULES, NOT LABORATORY PRACTICE RULES, WHICH ARE A SEPARATE SET OF VOLUNTARY GUIDELINES. BUT THE BASIC POINT HERE IS THAT YOUR CELL LINES HAVE TO BE MANAGED MORE CAREFULLY WHEN YOU'RE PLANNING TO EVENTUALLY PUT THEM INTO HUMAN BEINGS. AND PARTICULARLY WITH REGARD TO INFECTION CONTROL, YOU NEED TO BE PARTICULARLY CAREFUL.

THE SECOND IMPORTANT POINT ABOUT THIS IS THAT DONOR SUITABILITY IS KEY TO THE INFECTION CONTROL ISSUE. THAT IS, YOU WANT TO KNOW ABOUT THE MEDICAL BACKGROUND OF THE PEOPLE WHO DONATE THE MATERIAL FROM WHICH YOUR LINES ARE DERIVED, AND HERE THAT WOULD BE SPERM AND EGG EMBRYO DONORS IN MOST

CASES. AND IN SOME CASES SOME OF THAT INFORMATION MIGHT BE PRESERVED IN TERMS OF GENETIC INFORMATION SO THAT YOU CAN LINK THAT INFORMATION TO THE SUBSEQUENT CELL LINE. THE TROUBLE THERE IS THAT IF YOU DON'T SUFFICIENTLY ANONYMIZE THE IDENTITY OF THOSE DONORS, YOU MIGHT FIND THAT YOUR CELL LINES NOW HAVE ENOUGH IDENTIFIERS THAT IT TRIGGERS HUMAN SUBJECTS PROTECTIONS WHEN YOU'RE DOING PURELY LABORATORY WORK WITH THAT CELL LINE.

SO THERE'S A KIND OF INTERPLAY BETWEEN HOW IT IS THAT YOU MAKE A LINE SUITABLE, WHICH INVOLVES A LOT OF ATTENTION TO THE DONORS AND THEIR MEDICAL RECORDS, AND HOW YOU AVOID MAKING YOUR CELL LINE INTO THE FUNCTIONAL EQUIVALENT OF A HUMAN FOR THE PURPOSE OF HUMAN SUBJECTS PROTECTIONS WHEN IT COMES TO THE REGULATIONS OF YOUR PURELY LAB WORK.

AND, OF COURSE, HIPAA ADDS YET ANOTHER OVERLAY HERE BECAUSE HIPAA HAS A DIFFERENT PROTOCOL FOR PROTECTING HUMAN PRIVACY THAN THE IRB'S BECAUSE IT'S JUST TOO MUCH FOR US TO THINK ABOUT TRYING TO COORDINATE THIS STUFF.

AND FINALLY, BEFORE YOU MAKE YOUR CELL LINE, YOU WANT TO MAKE SURE THAT, AND THIS IS SOMETHING BERNIE LO IS PARTICULARLY EXPERT IN THESE DAYS, YOU WANT TO MAKE SURE THAT ALL YOUR LOCAL

RULES WERE COMPLIED WITH. OR IF YOU'RE IMPORTING, THAT YOU'VE MET THE BASIC MINIMUM STANDARDS FOR YOUR LOCAL JURISDICTION.

AND THAT IS THE POINT OF THE IMPORTATION OF A CLINICAL-GRADE CELL LINE. OFTEN THE RULES IN ANOTHER JURISDICTION WILL BE DIFFERENT THAN YOUR OWN, SO THERE HAS TO BE SOME SET OF A KIND OF THRESHOLD SET OF PROTECTIONS THAT ONE WILL INSIST UPON BEFORE THE LINE IS IMPORTED.

NOW, FOR HUMAN CELL THERAPIES, THE FDA HAS SOMETHING CALLED THE TISSUE ACCESS PLAN. IT'S NOW A LITTLE OVER A DECADE OLD. IT'S NOT YET ABSOLUTELY COMPLETELY IMPLEMENTED, BUT MOST OF ITS REGULATIONS HAVE FINALLY COME OUT. THE FIRST HAVING TO DO WITH SIMPLY REGISTERING AND LISTING EVERY PLACE THAT IS MANAGING HUMAN TISSUES AND CELL-BASED THERAPIES. I'M NOT GOING TO SPEND ANY MORE TIME ON IT. ALTHOUGH IT WAS VERY HANDY TO FINALLY KNOW HOW MANY PLACES IN THE U.S. ARE DOING THIS. I DO WANT TO GO BACK AND TALK A LITTLE BIT ABOUT DONOR SUITABILITY AND ABOUT THE GOOD TISSUE PRACTICES, WHICH IS REALLY WHAT IS ABOUT THE CONTROL OF COMMUNICABLE DISEASE.

SO, NOW, THE DONOR -- OH, ACTUALLY I KIND OF ANTICIPATED MYSELF. SO THE DONOR SUITABILITY, JUST TO REITERATE AND THEN MOVE ON QUICKLY, WILL AT

TIMES REQUIRE COLLECTION OF INFORMATION THAT YOU MIGHT OTHERWISE NOT WANT TO HAVE AVAILABLE. AND THE KEY IS GOING TO BE IF YOU CAN MEET SOME OF THE EXEMPTIONS THAT WILL PROTECT YOU FROM THIS OUTCOME WHERE YOUR LABORATORY WORK IS SUBJECT TO IRB REVIEW.

ISN'T IT HORRIBLE WHEN YOU ACTUALLY LOOK AT THE REAL TEXT OF A REGULATION AND ITS GUIDANCES? ALL OF THAT DENSENESS BASICALLY COMES DOWN TO IF YOU CAN OBSCURE THE DONOR'S ACTUAL IDENTITY SO THAT THEY'RE NOT READILY ASCERTAINABLE TO THE INVESTIGATOR, THEN YOU CAN PROCEED AS IF THERE ARE NO HUMAN SUBJECTS INVOLVED AND THERE'S NO OVERSIGHT FROM THE IRB NECESSARY. SO YOU CAN HAVE LINKS BACK TO DONOR INFORMATION, BUT YOU HAVE TO MAKE THEM OBSCURE ENOUGH THAT THEY DON'T REALLY IDENTIFY WHO GAVE THE CELLS ORIGINALLY.

NOW, MOVING FORWARD TO THE STUFF THAT I THINK IS MORE APPLICABLE TO THIS MEETING, AFTER YOUR BASIC LABORATORY WORK, THE USUAL NEXT STEP IS GOING TO BE PRECLINICAL ANIMAL WORK WHICH INVOLVES THE CREATION OF TRANSGENIC OR CHIMERIC ANIMALS. GERON, FOR EXAMPLE, WAS TESTING MANY OF ITS CELL-BASED THERAPY EFFORTS IN RATS WHO HAD SEVERED SPINAL CORDS. AND SO WHAT YOU WERE DOING IS YOU WERE CREATING AN ANIMAL THAT HAD HUMAN CELLS IN CONTACT

WITH THE RAT. AND IF YOU TAKE A LOOK AT THE SLIDE, YOU WILL SEE THAT THE ANIMAL WELFARE ACT DOES PROVIDE PROTECTIONS FOR THE USE OF ANIMALS IN RESEARCH, BUT VERY CONVENIENTLY DOES NOT COVER RATS OR MICE THAT ARE SPECIFICALLY BRED FOR USE IN RESEARCH. AND SO THIS ALLOWS YOU, IF YOU'RE WORKING WITH THOSE SPECIES, TO EVADE THE PROTECTIONS OF THE ANIMAL WELFARE ACT AND THE SPECIAL OVERSIGHT OF THE INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE.

NONETHELESS, THERE ARE A SET OF BEST PRACTICES GOVERNING THE USE OF RATS AND MICE. AND I REMEMBER SITTING ONCE IN A MEETING WHERE THERE WAS DISCUSSION AT GREAT LENGTH ABOUT THE NUMBER OF MICE PER PAGE THAT SHOULD BE ALLOWED, AND THE FINANCIAL DIFFERENCES BETWEEN ONE NUMBER AND ANOTHER NUMBER WERE REALLY QUITE SUBSTANTIAL WHEN IT WAS HOWARD HUGHES THINKING ABOUT HOW MUCH IT WOULD COST TO FUND THEIR INVESTIGATORS. SO EVEN WITHOUT THE ANIMAL WELFARE ACT, IT IS A NONTRIVIAL QUESTION HOW YOU ARE GOING TO MANAGE EVEN YOUR MICE AND RATS FOR YOUR EXPERIMENTS.

ASSUMING THAT YOU'VE GOTTEN THESE EXPERIMENTS DONE, AND THAT IS, AGAIN, NOT AT ALL AN EASY THING. I MEAN IMAGINE YOU'VE GOT -- CAN YOU GO BACK JUST FOR A SECOND TO THE PREVIOUS ONE, THE

ANIMAL -- KEEP GOING, KEEP GOING, KEEP GOING, KEEP GOING. YOU WENT ALL THE WAY BACK. I WANTED ONLY ONE BACK.

DR. CSETE: ALTA, I'LL MAKE A CLARIFICATION THOUGH. SO THE ANIMAL WELFARE ACT AND IACUC, I DON'T WANT PEOPLE TO MIX THAT UP. SO WHEN YOU WORK ON RATS AND MICE, YOU STILL REQUIRE IACUC APPROVAL FOR YOUR RESEARCH.

DR. CHARO: WELL, THANK YOU. ACTUALLY I GOT THAT WRONG. I MIXED THEM UP TOO. SO THANK YOU ABOUT THAT. THANK YOU. THAT'S THE ONE I WANTED, GEOFF. I APPRECIATE IT.

WHEN GERON WAS WORKING WITH ITS RATS, FOR EXAMPLE, IT WAS USING IMMUNOSUPRESSED RATS AND SEVERING THEIR SPINAL CORDS SO THAT THEY COULD THEN TEST WHETHER OR NOT THE INJECTION OF HUMAN MATERIAL HAD ANY MEASURABLE EFFECT ON THEIR ABILITY TO MOVE AND ALSO FOR LOOKING FOR RISKS LIKE TUMOROGENICITY. BUT IF YOU IMAGINE TRYING TO HANDLE IMMUNOSUPRESSED RATS FOUR MONTHS ON END, AND REMEMBER NOW THAT THEY CAN'T -- FOR EXAMPLE, THEY CAN'T URINATE ORDINARILY, SO YOU HAVE TO EXPRESS THEIR BLADDERS MANUALLY ONCE OR TWICE A DAY. AND THINK ABOUT THE CHALLENGE OF KEEPING THEM INFECTION FREE IF THEY'RE IMMUNOSUPRESSED. BUT THEY'RE BEING MANIPULATED SO

OFTEN BY HUMAN HANDS, YOU BEGIN TO APPRECIATE WHY THIS PARTICULAR STAGE CAN BE VERY CHALLENGING FOR ANY KIND OF DEVELOPER AND WHY THIS STAGE ALSO GETS A GREAT DEAL OF ATTENTION FROM THE FDA.

SO THIS PARTICULAR STAGE TAKES ONE SLIDE AND MANY, MANY, MANY, MANY, MANY, MANY CONFERENCES WITH THE FDA IN ORDER TO MOVE THROUGH IT AND TO THE POINT OF GOING TO THE FDA FOR YOUR IND OR YOUR IDE. ALL OF YOUR PRECLINICAL DATA IS SUBMITTED, AND, AS I SAID, MOST OF THE TIME YOU'VE BEEN DOING ALL OF YOUR PRECLINICAL WORK IN A KIND OF ITERATIVE PROCESS WITH THE FDA.

NOW, THE FDA WILL HAVE APPROVED YOUR IND AFTER HAVING GONE THROUGH ALL OF YOUR SAFETY DATA AND AFTER HAVING GONE THROUGH IN SOME DETAIL YOUR PROTOCOL BY WHICH YOU PROPOSE TO DESIGN A SUBJECT POPULATION AND DO YOUR STATISTICAL ANALYSES. NONETHELESS, HAVING GONE THROUGH ALL OF THAT, YOU WILL STILL HAVE TO GET LOCAL APPROVAL FROM YOUR IRB, WHICH WILL GO THROUGH SOME OF THE SAME KIND OF CALCULATIONS ABOUT RISKS AND BENEFITS OR POSSIBLE BENEFITS. THEY WILL ALSO THEN TAKE A CLOSE LOOK AT THE PROCESS BY WHICH SUBJECTS WILL BE RECRUITED AND INFORMED OF THE RISKS AND POSSIBLE BENEFITS.

THIS CAN BE MORE RIGOROUS SOMETIMES THAN

THE FDA BECAUSE OF THE KIND OF PATIENT FOCUS THAT ONE FINDS ON SOME IRB'S. THERE'S A REAL VARIATION AROUND THE COUNTRY.

THE FIRST TWO PHASES OF YOUR STUDIES ARE GENERALLY SAFETY PHASES. THEY ARE PRIMARILY ABOUT LOOKING AT SAFETY. IN THE ORDINARY KIND OF PARADIGMATIC DRUG CASE, YOU WOULD USE HEALTHY VOLUNTEERS, TINY AMOUNTS OF THE DRUG YOU'RE PROPOSING TO TEST, AND BE LOOKING SIMPLY AT METABOLIC ACTIVITY. IN THIS CASE I SUSPECT MANY TRIALS WILL ACTUALLY BEGIN WITH PATIENTS WHO ARE SICK OR INJURED, THE WAY IT NOW HAPPENS, FOR EXAMPLE, IN MANY CANCER TRIALS. SO THE PHASE I'S AND II'S WILL LOOK A LITTLE DIFFERENT, BUT THEY WILL STILL BE PRIMARILY SAFETY TRIALS. AND A HUGE PROBLEM, A HUGE PROBLEM THAT IS LURKING FOR ALL OF US NOW IS RIGHT AT THIS LEVEL. YES, JOHN.

DR. WAGNER: I JUST WANT TO JUST EMPHASIZE THE FACT THAT THE PUBLIC UNDERSTANDS THAT A PHASE I TRIAL IS PURELY TO DEMONSTRATE SAFETY. IT HAS NO INTENTION OF EFFICACY. SO THAT WHEN THE TRIALS ARE BEING FIRST DONE, THERE'S TYPICALLY A DOSE ESCALATION TRIAL TO SEE WHERE YOU HIT MAXIMUM TOLERABLE TOXICITY. SO I THINK THAT IT'S CRITICAL THAT PEOPLE UNDERSTAND REALLY WHAT A PHASE I STUDY

IS, AND THAT'S HOW WE DO THIS IN CANCER PATIENTS ALL THE TIME.

DR. CHARO: JOHN, IF I MAY, WHAT DO YOU THINK -- IN WHAT PROPORTION OF TRIALS DO YOU THINK YOU SUCCEED IN PERSUADING PATIENTS, NOT HEALTHY SUBJECTS, BUT PATIENTS THAT THIS IS SAFETY ONLY, AND NOT SAFETY AND MAYBE A LITTLE OF HOPE OF EFFICACY?

DR. WAGNER: I'LL GIVE YOU MY OWN OPINION, THAT I CAN'T SAY WHETHER IT'S TRUE OR NOT BECAUSE OBVIOUSLY I HAVE MY OWN PERSONAL BIASES, BUT I THINK THAT, YOU KNOW, FOR THIS PARTICULAR THERAPY THAT WE'RE TALKING ABOUT, EMBRYONIC STEM CELL-BASED THERAPIES, IT'S SOMETHING WE PROBABLY SHOULD FURTHER DISCUSS HOW WE MIGHT BEST BE ABLE TO CONVINCE THE PATIENT AND THE PUBLIC THAT WE'RE DOING THIS IN THE MOST OBJECTIVE WAY POSSIBLE.

DR. CHARO: YEAH. I THINK FOCUSING HERE FOR A MOMENT IS IMPORTANT BECAUSE THIS IS GOING TO BE A TREMENDOUS CHALLENGE AS WE MOVE INTO THESE TRIALS AND AS GERON MOVES INTO ITS TRIALS. FIRST, PEOPLE, WHEN YOU'RE RECRUITING PEOPLE WHO ARE SICK AS OPPOSED TO HEALTHY VOLUNTEERS, IT'S VERY DIFFICULT TO ELIMINATE ANY SMALL GLIMMER OF HOPE THAT THEY MAY HAVE, THAT EVEN THOUGH YOU'RE USING SUBCLINICAL DOSAGES, THAT NONETHELESS THERE WILL BE

SOME SMALL BENEFIT TO THEM PERSONALLY FROM A MEDICAL POINT OF VIEW.

THE SECOND IS THAT WE HAVE SEEN IN THE AREA OF CANCER ALREADY TREMENDOUS PRESSURE TO OPEN UP ACCESS TO INVESTIGATIONAL DRUGS PRIOR TO THEIR FDA APPROVAL, PARTICULARLY AS SOON AS THEY'VE GONE INTO PHASE II.

THERE'S A GROUP CALLED THE ABIGAIL ALLIANCE, AND IT WENT ALL THE WAY TO THE U.S. SUPREME COURT IN WHAT WAS, I THINK, REALLY ONE OF THE MOST INTERESTING TRULY RIGHT-TO-LIFE CASES I'VE EVER SEEN, WHICH WAS A CLAIM THAT THERE'S NO CONSTITUTIONAL AUTHORITY TO WITHHOLD POSSIBLY BENEFICIAL DRUGS FROM TERMINALLY ILL PATIENTS BECAUSE THEY HAVE A RIGHT TO TRY TO SAVE THEIR LIVES. IT WAS LEGALLY AND CONSTITUTIONALLY QUITE FASCINATING. THE CASES ARE QUITE GUT-WRENCHING, BUT THE ISSUES I THINK ARE GOING TO BE OBVIOUS TO ANYBODY IN THE MEDICAL FIELD ABOUT THE CONCERNS ABOUT ACCESS TO THESE THINGS BEFORE THEY'RE PROVEN.

NOW, WE ALSO KNOW --

MS. LANSING: DID THEY RULE ON THAT?

DR. CHARO: THE SUPREME COURT DID NOT RULE THAT THERE IS A CONSTITUTIONAL RIGHT TO ACCESS TO INVESTIGATIONAL DRUGS. ABIGAIL ALLIANCE IS NOW

MOVING ON A LEGISLATIVE STRATEGY. THEY'VE GOTTEN SAM BROWNBACK, SENATOR FROM KANSAS, TO BE ONE OF THEIR CHAMPIONS IN THE SENATE ON THAT KIND OF ACCESS ACT.

IN THIS AREA OF STEM CELL THERAPY, WE'RE NOT ONLY GOING TO BE DEALING WITH PATIENT THERAPEUTIC MISCONCEPTION, BUT WE'RE GOING TO BE DEALING WITH A HUGE PENT-UP DEMAND TO ACCESS TO THESE PARTICULARLY FROM PEOPLE WHO HAVE DEGENERATIVE DISORDERS WHERE THEY FEEL THE WINDOW OF OPPORTUNITY TO HALT OR REVERSE THE DAMAGE IS VERY, VERY SMALL. AND WE KNOW FROM THE 1980S HERE IN CALIFORNIA THAT THERE IS A WAY TO HANDLE THIS HAVING TO DO WITH COMPASSIONATE USE PROTOCOLS, BUT THEY ARE COMPLICATED, PARTICULARLY IN THE AREA OF BIOLOGICS.

SO FDA HAS A METHOD BY WHICH PEOPLE WHO ARE NOT ENROLLED IN A TRIAL CAN GET HOLD OF AN INVESTIGATIONAL DRUG OR DEVICE. COMPASSIONATE USE IS A NICKNAME. YOU WON'T FIND THAT PHRASE ANYWHERE IN THE REGULATIONS. ONE OF THE OBSTACLES TO DOING THIS, THERE ARE MANY OBSTACLES. FIRST, BUREAUCRATICALLY IT HAS ALWAYS BEEN TRADITIONALLY A PATIENT-BY-PATIENT AD HOC PROCEDURE WITH AN IRB REVIEW FOR EVERY SINGLE PATIENT WHO HAS A COMPASSIONATE USE REQUEST.

SECOND, MANUFACTURERS WILL USUALLY NOT MAKE ENOUGH OF THE INVESTIGATIONAL SUBSTANCE TO SUPPLY MORE THAN A FEW PEOPLE BECAUSE THEY'RE ONLY MAKING SMALL AMOUNTS FOR THEIR TESTS. AND THEY ARE NOT NECESSARILY IN A POSITION TO SCALE UP EVEN IN A DRUG SITUATION TO PROVIDE AMOUNTS THAT WILL MEET THE KIND OF DEMAND THAT WE ARE LIKELY TO SEE. SCALING UP EVEN IN PURELY CHEMICAL MANUFACTURING IS NOT AS SIMPLE AS SIMPLY DOUBLING, TRIPLING, AND QUADRUPLING DOSAGES.

IN THE AREA OF BIOLOGICS, SCALING UP IS EVEN MORE COMPLICATED BECAUSE OF THE WAY IN WHICH BIOLOGICAL SYSTEMS OPERATE. AND AGAIN, CALIFORNIA, AND OAKLAND IN PARTICULAR, A CENTER FOR THE REALIZATION OF THIS WHEN BACK IN THE 1950S THE SCALING UP IN THE AREA OF THE POLIO VACCINE LED TO AN INEFFECTIVE VACCINE THAT LED A NUMBER OF CHILDREN AROUND THE COUNTRY TO WIND UP DEVELOPING POLIO. SO THE SCALING-UP ISSUE, VERY, VERY REAL.

SECOND, THERE IS NOW, AND THIS IS A RELATIVELY RECENT DEVELOPMENT, THERE IS NOW SOME PROVISION IN THE FDA REGULATIONS TO ALLOW MANUFACTURERS TO HAVE COST RECOVERY IF THEY ARE GOING TO PROVIDE DRUG OR DEVICE OR BIOLOGIC BEYOND THE TRIALS ON A COMPASSIONATE USE BASIS, BUT IT IS

COST RECOVERY ONLY, NO PROFIT. AND THE CALCULATION OF COST RECOVERY, JUST LIKE VALUABLE CONSIDERATION, IS ONE OF THOSE TERMS SUBJECT TO A LOT OF DEBATE. AND SO THERE'S CONCERN THAT IT WON'T REALLY COVER THEIR COST. SO HERE THERE'S JUST BOTTOM LINE A LOT OF DISINCENTIVES FOR MANUFACTURERS TO ANSWER THE PATIENT DEMAND. AND YET AT THE SAME TIME PHASE I AND PHASE II TRIALS ARE TRULY DESIGNED TO BE SMALL.

I'M SORRY, JOHN. YOU WANTED TO SAY SOMETHING.

DR. WAGNER: MAYBE AT THE VERY END. I WANT TO GET BACK TO COST BECAUSE COST IS A CRITICAL POINT THAT THE PEOPLE NEED TO UNDERSTAND. YOU MENTION COST RECOVERY. THAT MEANS THAT THE FDA ALLOWS US TO CHARGE FOR THE ACTUAL DRUG OR CELL PREPARATION. IT DOESN'T MEAN THAT THE PEOPLE THAT THIS IS INTENDED FOR COULD ACTUALLY PAY THAT COST OR THEIR INSURANCE WILL DENY THAT COST.

DR. CHARO: ABSOLUTELY. AND THAT'S A REALLY GOOD POINT. IT'S ONE THING TO SAY THAT COST CAN BE RECOVERED. IT'S ANOTHER TO ASK IF THERE'S ANY SOURCE OF FUNDS TO DO SO. AND FOR SURE, INSURANCE COMPANIES, HEALTH INSURANCE COMPANIES, GENERALLY WILL NOT PAY FOR UNAPPROVED DRUGS OR DEVICES.

THE PHASE III TRIALS, AGAIN, PRESENT YET ANOTHER OPPORTUNITY FOR PRESSURE. AT THIS POINT NOW THE PRESSURE REALLY HEIGHTENS BECAUSE THE PHASE II'S PRESUMABLY SHOWED SOME EFFICACY. AND IF YOU TAKE A LOOK AT THE PERCENTAGES ON THE GRAPHS, YOU WILL SEE THAT THINGS THAT SURVIVE PHASE II WILL VERY FREQUENTLY WIND UP SURVIVING PHASE III. SO THERE'S A KIND OF VERY STEEP DROP-OFF CURVE FROM PHASE I TO PHASE II, AND THEN THE SURVIVALS TEND TO PLATEAU A BIT IN TERMS OF TRIAL RESULTS SO THAT BY THE TIME YOU'RE INTO PHASE III, THERE'S A LOT OF PATIENT PRESSURE BECAUSE THEY NOW EXPECT NEW REALLY IS PROBABLY BETTER. AND CERTAINLY THE INVESTIGATORS AREN'T TESTING IT UNLESS THEY SUSPECT THAT NEW IS BETTER.

AND BECAUSE OF THIS, IN THE 1980S THERE WAS A DESIRE TO BALANCE THE NEED TO HAVE CLINICAL TRIALS THAT ARE RANDOMIZED CONTROLLED TRIALS TO GIVE YOU GOLD STANDARD DATA WITH THE NEED TO OPEN UP ACCESS FOR PEOPLE WHO WOULD NOT BE ELIGIBLE. THEIR CONDITIONS MIGHT BE TOO COMPLICATED, THEY HAD TOO MANY COMORBIDITIES OR THEY SIMPLY WERE NOT GEOGRAPHICALLY SITUATED OR THERE WEREN'T ENOUGH SPACES LEFT, AND THAT WAS THE DEVELOPMENT SPECIFICALLY FOR AIDS OF THE PARALLEL TRACK SYSTEM

WHICH ALLOWED FOR A LARGE NUMBER OF PEOPLE EN MASSE TO GET AZT AT THE TIME OF THE CLINICAL TRIALS.

THERE'S A LOT OF PRESSURE SOMETIMES TO ABANDON THIS STAGE COMPLETELY. IT'S FOOLISH. WE SAW WITH BONE MARROW TRANSPLANTS FOR END-STAGE BREAST CANCER HOW IMPORTANT IT IS TO HAVE THESE TRIALS BECAUSE IN THE END THAT INCREDIBLY EXPENSIVE, PAINFUL, HORRIBLE TREATMENT TURNED OUT NOT TO BE EFFECTIVE, AND WE COULD NEVER HAVE KNOWN IT WITHOUT CONTROLLED TRIALS. BUT AT THAT TIME THERE WAS SIMILAR PRESSURE AROUND THE UNITED STATES TO OPEN THOSE THINGS UP TO PATIENTS AND INSURANCE COMPANY PAYMENTS PRIOR TO THE CONCLUSION OF THESE TRIALS BECAUSE PEOPLE WERE DESPERATE. SO WE'VE SEEN THIS STORY BEFORE, AND I THINK WE'RE GOING TO SEE IT AGAIN NOW.

FINALLY, IF YOU COMPLETE ALL OF YOUR TRIALS SUCCESSFULLY, YOU WILL HAVE TO GO TO THE FDA FOR A FINAL APPROVAL OF YOUR DRUG OR DEVICE BEFORE OR YOUR BIOLOGIC BEFORE YOU CAN BEGIN MARKETING IT. AND THAT WILL COME WITH A SET OF CONDITIONS. THE MOST FAMILIAR ONES HAVE TO DO WITH LABELING WHICH WILL DEMONSTRATE THOSE THINGS FOR WHICH IT WAS ACTUALLY TESTED. PHYSICIANS, OF COURSE, ARE FREE TO USE, PRESCRIBE OUTSIDE THE LABEL IN A, QUOTE,

UNQUOTE, OFF-LABEL WAY BASED UPON THEIR OWN GOOD JUDGMENT, BUT THE COMPANIES ARE NOT ALLOWED TO MARKET THE USES OTHER THAN THOSE THAT WERE TESTED AND LABELED FOR AFTER FDA APPROVAL.

MS. LANSING: ALTA, CAN I ASK A QUESTION? JUST GOING BACK TO THIS PARALLEL TRACK. I UNDERSTAND WHAT YOU'RE SAYING, AND MAYBE WE SHOULD HOLD OUR QUESTIONS TILL THE END, BUT I JUST AM CURIOUS. HAVE THERE BEEN OTHER PARALLEL TRACK THINGS THAT HAVE BEEN DONE?

DR. CHARO: WELL, THERE IS A KIND OF STANDARD SYSTEM FOR SO-CALLED COMPASSIONATE USE. THERE'S A STANDARD SYSTEM THAT IS REALLY MORE OF A ONE-ON-ONE AD HOC SYSTEM, AND THEN THIS EN MASSE SYSTEM PARALLEL TRACK WAS CREATED SPECIFICALLY FOR AIDS. AND AS I RECALL, IT'S STILL LIMITED TO AIDS, BUT IT PROVIDES A MODEL IN CASE ONE WANTS TO THINK ABOUT WAYS TO DO THESE THINGS.

IN ADDITION, ALTHOUGH IT HAS NOT YET BEEN ISSUED, IT'S MY UNDERSTANDING THAT THE FDA IS SITTING ON A GUIDANCE THAT IT'S BEEN WORKING ON FOR QUITE A WHILE THAT IS GOING TO CONTINUE TO REFINE ITS COMPASSIONATE USE RULES; BUT WHETHER THAT'S ACTUALLY GOING TO COME OUT AND, IF SO, WHEN, I'M NOT QUITE SURE.

MS. LANSING: SO IS THIS SOMETHING -- I DON'T KNOW IF THIS IS RIGHT, BERNIE, BECAUSE I'M REALLY FASCINATED BY THIS, I GUESS. AS A CANCER ADVOCATE, I HEAR THIS ALL THE TIME, YOU KNOW. AND I DON'T KNOW IF THIS IS RIGHT FOR OUR GROUP OR NOT, SO I'M ASKING YOU. BUT IT SEEMS TO ME WHEN YOU'RE ENTERING INTO PHASE III, I KNOW WHY YOU NEED THE GOLD STANDARD. I REALLY UNDERSTAND THAT. I DON'T THINK THAT SHOULD BE CHANGED. BUT THIS PARALLEL TRACK, AND I'M ONLY GOING TO SPEAK AS A CANCER ADVOCATE, BUT WOULD APPLY TO ALL DISEASES WHERE YOU COULD DO THAT PROVIDING YOU SIGN OFF THE SPECIFIC, YOU KNOW, LIABILITIES AND ALL OF THAT. IS THAT SOMETHING WE SHOULD TALK ABOUT IN OUR GROUP, OR IS THAT NOT FOR US TO EVEN THINK ABOUT AT THIS POINT?

DR. CHARO: WELL, AS A MATTER OF FACT, IF YOU TAKE A LOOK AT THAT THE VERY LAST SLIDE, I'M TRYING TO ANTICIPATE.

MS. LANSING: SORRY.

DR. CHARO: NO. NO. THAT'S OKAY. IT'S OBVIOUS THAT THINGS ARE --

CHAIRMAN LO: COULD I JUST SAY ONE THING. SHERRY, MY UNDERSTANDING IS THAT PARALLEL TRACK IS ACTUALLY INTENDED FOR OTHER LIFE-THREATENING DISEASES AS WELL, BUT IT WAS REALLY SORT OF

PRIMARILY, IF NOT SOLELY, USED FOR AIDS IN SORT OF THE EARLY ANTIRETROVIRAL ERA.

MS. LANSING: I THINK IT'S A WONDERFUL THING PROVIDING YOU DON'T VIOLATE THE GOLD STANDARD AND YOU HAVE THAT CONTROL GROUP.

DR. CHARO: THAT BECOMES VERY DIFFICULT BECAUSE IF YOU HAVE A PARALLEL TRACK WHERE PEOPLE CAN HAVE ACCESS TO THE INVESTIGATIONAL DRUG, DEVICE, OR BIOLOGIC, IT BECOMES MUCH MORE DIFFICULT TO RECRUIT OTHER PEOPLE INTO A RANDOMIZED CONTROLLED TRIAL WHERE THEY MIGHT WIND UP GETTING PLACEBO OR STANDARD THERAPY DEPENDING ON WHAT THE CONTROL IS.

MS. LANSING: I UNDERSTAND WHAT YOU'RE SAYING.

DR. CHARO: SO RECRUITMENT NOW BECOMES FAR MORE CHALLENGING, AND IT DOESN'T REALLY MATTER HOW MANY TIMES YOU TRY TO EXPLAIN TO PEOPLE THAT WE'RE DOING THESE TRIALS BECAUSE WE'RE NOT SURE WHICH IS BETTER, STANDARD OR INVESTIGATIONAL, AND YOU MIGHT TURN OUT TO BE LUCKY TO BE ON STANDARD INSTEAD OF INVESTIGATIONAL BECAUSE I THINK AMERICANS -- AND ACTUALLY DAVID BROOKS MADE THAT POINT TODAY IN THE OP ED PAGE OF THE *NEW YORK TIMES*. AMERICANS HAVE THIS KIND OF OPTIMISTIC VISION ALL THE TIME NO MATTER WHAT'S GOING ON, AND WE ALWAYS TEND TO THINK

THAT NEW IS BETTER. SO THERE'S THIS KIND OF PUSH.

MS. LANSING: SO OFTEN IF YOU'VE BEEN TOLD YOU HAVE FOUR WEEKS LEFT TO LIVE OR WHATEVER IT IS, AND THERE'S SOMETHING OUT THERE AND IT'S BEING HELD BACK FROM YOU --

DR. CHARO: THAT'S RIGHT.

MS. LANSING: -- THAT'S VERY PAINFUL.

DR. CHARO: THAT'S EXACTLY WHAT THE ABIGAIL ALLIANCE PEOPLE SAY.

MR. SHEEHY: I JUST HAD A COUPLE. I DIDN'T THINK THEY DID PLACEBO CONTROLLED TRIALS ON HIV.

DR. CHARO: NO. I SAID PLACEBO OR STANDARD DEPENDING UPON BECAUSE PLACEBO ONLY WHEN YOU -- PLACEBO TRIALS ARE NOT USED WHEN YOU HAVE LIFE-THREATENING OR SERIOUS CONDITIONS WHERE THERE'S GOING TO BE REAL DETERIORATION IN THE ABSENCE OF STANDARD THERAPY.

MR. SHEEHY: BUT IF I COULD FINISH. SO THAT'S ONE THING, AND THAT MAY BE A QUESTION WE WANT TO ADDRESS IS WHETHER WE SHOULD HAVE PLACEBO CONTROLLED TRIALS.

AND THEN THE SECOND ISSUE SPECIFICALLY ABOUT HIV, THOSE PATIENTS WHO ARE OFTEN GETTING COMPASSIONATE USE PROBABLY ARE NOT YOUR BEST TRIAL

PARTICIPANTS. I MEAN YOU DON'T WANT PEOPLE ON DEATH'S DOOR TO TRY A THERAPY. SO I THINK IT'S A LITTLE BIT MORE -- YOU WANT YOUR HEALTHY SICK PEOPLE, NOT YOUR --

DR. CHARO: RIGHT.

MR. SHEEHY: I MEAN BECAUSE THEN YOUR DATA IS GOING TO NOT --

DR. CHARO: THIS IS -- LIKE I SAID, THIS IS VERY SUPERFICIAL. ABSOLUTELY RIGHT, BUT THEN, OF COURSE, THE IRONY IS THAT IF YOU'RE SICK, BUT RELATIVELY -- YOU KNOW, DOING RELATIVELY WELL, YOU'RE PRECLUDED FROM GETTING THE COMPASSIONATE USE INVESTIGATIONAL DEVICE. WE CAN GO INTO IT IN MORE LENGTH LATER.

LET ME JUST MAKE THE LAST POINT HERE, THE LAST TWO POINTS. FIRST IS THE ENHANCED SURVEILLANCE BEYOND LABELING MAY VERY WELL HAVE TO DO WITH THINGS LIKE PATIENT TRACKING OF FORMAL PHASE IV TRIALS, PATIENT SCREENING, THINGS LIKE THAT. AND THEN FOR THE VERY LAST SLIDE, THESE WERE THE THREE THINGS THAT JUST HAD OCCURRED TO ME AFTER THE BAT AS AREAS WHERE THIS PARTICULAR COMMITTEE MIGHT HAVE SOMETHING TO OFFER.

THE FIRST IS ESSENTIALLY STAYING UP TO DATE ON THE SCIENCE FOR THE SAKE OF THE IRB'S, WHICH

IS TO CONTINUALLY MONITOR AND COLLATE AND SYNTHESIZE THE BEST INFORMATION ABOUT RISKS AND BENEFITS OF EACH NEW STEM CELL INTERVENTION, THAT THE IRB'S DON'T HAVE TO KEEP LEARNING IT ALL ON THEIR OWN EACH TIME.

SECOND, TO MAYBE WORK WITH THE IRB'S TO TRY AND DEVELOP COMPREHENSIBLE AND ACCURATE INFORMATION TO BE USED FOR THE PROCESS OF RECRUITING AND INFORMING SUBJECTS BEFORE THEY ENROLL.

AND THIRD, AND THIS GOES DIRECTLY TO WHAT WE WERE JUST BEGINNING TO TALK ABOUT, DEPENDING UPON WHETHER THE MANUFACTURERS AND THE FDA ARE OPEN TO THIS, PERHAPS WORKING WITH IRB'S AND THE FDA AND THE MANUFACTURERS ON TRYING TO THINK TOGETHER ABOUT HOW TO MANAGE PATIENT EXPECTATIONS AND ORGANIZE APPROPRIATE COMPASSIONATE USE PROTOCOLS. SO THAT'S IT.

MS. LANSING: THAT WAS GREAT.

CHAIRMAN LO: ALTA, THANKS VERY MUCH. A LOT OF THE ISSUES THAT ALTA HAS RAISED, SPEAKERS IN SUBSEQUENT PARTS OF OUR SORT OF MINI SYMPOSIUM WILL COME BACK TO. SO, FOR INSTANCE, THE PLACEBO ISSUE WILL COME UP AS WE TALK ABOUT THE SCIENTIFIC DESIGN.

BUT I'M GOING TO ASK E. J. READ TO MAKE SOME ADDITIONAL COMMENTS HERE. ELIZABETH READ IS

THE DIRECTOR OF CELL AND TISSUE THERAPIES FOR THE BLOOD SYSTEMS RESEARCH INSTITUTE. SHE FORMERLY WAS AT NIH WHERE SHE WAS THE CHIEF OF THE CELL PROCESSING SECTION OF THE DIVISION OF TRANSFUSION MEDICINE. AND SHE'S ALSO BEEN THE MEDICAL DIRECTOR OF THE AMERICAN RED CROSS BLOOD AND TISSUE SERVICES IN SOUTHERN CALIFORNIA. AND SHE'S ALSO AN ACTIVE RESEARCHER, AND ACTUALLY SOME OF HER ACTIVE AREAS OF RESEARCH ARE BENCH-TO-BEDSIDE TRANSLATION OF NOVEL CELLULAR THERAPIES.

SO SHE'S BEEN INVOLVED WITH DEVELOPING NEW PRODUCTS FOR CLINICAL TRIALS, NEW CELLULAR-BASED PRODUCTS FOR CLINICAL TRIALS, AND ACTUALLY PARTICIPATING AS AN INVESTIGATOR IN THOSE TRIALS.

SO WHEN WE GET HER SLIDES UP, AND E. J., YOUR WEBSITE AT BLOOD SYSTEMS RESEARCH INSTITUTE HAS YOUR WRONG INITIAL ON THE TOP. SO IT DOESN'T COME UP WHEN YOU GOOGLE YOU AS E. J. READ BECAUSE IT'S E. I. READ ON THE TOP OF THE THING. SO YOU'RE MISSING A LOT OF GOOGLING.

DR. READ: IT'S ACTUALLY CORRECT SINCE I USE MY MAIDEN NAME, WHICH IS IVY IS MY LEGAL MIDDLE NAME.

CHAIRMAN LO: IT'S A GOOGLE PROBLEM FOR THOSE WHO ARE TRYING TO REACH YOU.

DR. READ: SO IN ADDITION TO BEING AT BLOOD SYSTEMS BLOOD RESEARCH INSTITUTE, I'M ON THE ADJUNCT FACULTY AT UCSF IN LAB MEDICINE. AND I'VE ALSO BEEN WORKING QUITE A BIT WITH THE UCSF CTSI IN THE REGULATORY KNOWLEDGE AND SERVICES PROGRAM BECAUSE WE'VE REALLY BEEN GETTING A LOT OF QUESTIONS FROM INVESTIGATORS ON HOW TO DEVELOP THESE PRODUCTS AND HOW THEY SHOULD BE INTERACTING WITH FDA. AND SO I'M JUST GOING TO ADD SOME COMMENTS TO ALTA'S EXCELLENT PRESENTATION SORT OF FROM THE STANDPOINT OF INTERACTING WITH FDA.

SO I'M GOING -- SOME OF THESE SLIDES. I HAVE TOO MANY SLIDES. SO I'M GOING TO SKIP OVER SOME OF THEM AND JUST POINT OUT SOME OF THE THINGS THAT ALTA MAY HAVE TOUCHED ON, BUT I MIGHT GO INTO A LITTLE MORE DETAIL.

SO FDA ACTUALLY REGULATES CLINICAL RESEARCH IF IT INVOLVES DRUGS, DEVICES AND BIOLOGICAL PRODUCTS, AND I THINK THOSE OF YOU WHO ARE INVOLVED WITH IRB'S KNOW THAT. AND THE BASIS OF THAT IS THAT THEY -- WELL, YOU HAVE TO COMPLY WITH THE IND OR IDE REGULATIONS, AND ALSO FDA HAS ITS OWN REGULATIONS THAT ADDRESS IRB'S AND WHAT IRB'S SHOULD LOOK LIKE AND HOW THEY SHOULD OPERATE AND ALSO INFORMED CONSENT. AND THESE REGULATIONS ARE

ACTUALLY VERY MUCH ALIGNED WITH THE OHRP REGULATIONS THAT I THINK YOU ALL ARE FAMILIAR ARE.

ONE THING THAT SOME PEOPLE MAY NOT BE AWARE OF IS THAT FDA HAS SOMETHING CALLED A GOOD CLINICAL PROGRAM OR GCP PROGRAM, AND HAVE I THE LINK TO THE WEBSITE THERE. AND I THINK WHAT'S MOST NOTABLE THERE IS THAT IT SERVES AS THE LIAISON WITH OHRP AND OTHER FEDERAL AGENCIES AND EXTERNAL STAKEHOLDERS, AND THEY'RE VERY CONCERNED WITH PROMOTING GOOD CLINICAL PRACTICES THAT ARE VERY MUCH ALIGNED WITH THE OTHER REGULATORY REQUIREMENTS.

SO THESE ARE THE FDA CENTERS, AND ALTA MENTIONED CDER, CBER, CDRH, THEY ALSO -- FDA IS -- F IS THE FOODS, AND THEN THERE'S ALSO VETERINARY DRUGS, FOOD ADDITIVES, AND DEVICES WHICH REALLY DON'T APPLY TO WHAT WE'RE TALKING ABOUT HERE. BUT WHAT'S NOTABLE ABOUT CBER IS THAT IT'S BIOLOGICS, BUT THERE ARE SOME DEVICES AND IN-VITRO DIAGNOSTICS THAT THEY REGULATE. AND CDER DOES DRUGS, BUT, IN FACT, THERE'S A WHOLE CLASS OF BIOLOGICS THAT GOT TRANSFERRED OVER TO THEM A FEW YEARS AGO THAT ARE CONSIDERED THERAPEUTIC BIOLOGICS. AND WE DON'T NEED TO BE TOO CONCERNED ABOUT THEM HERE, BUT THERE'S BEEN SOME JURISDICTIONAL SHIFTING OVER THE PAST FEW YEARS.

I THINK AN IMPORTANT POINT IS THAT CBER HAS BEEN THINKING ABOUT CELLULAR THERAPIES FOR A FULL 20 YEARS, SO IT'S NOT NEW TO THEM TO BE THINKING ABOUT STEM CELLS. AND REALLY BACK IN 1989 WAS THE FIRST POINT TO CONSIDER GUIDANCE. AND IT WAS REALLY IN RESPONSE TO INVESTIGATORS GETTING MONONUCLEAR CELLS, USUALLY AUTOLOGOUS, FROM PATIENTS AND ACTIVATING THEM EX VIVO AND THEN PUTTING THEM BACK INTO PEOPLE. AND PEOPLE WERE DOING THIS WITHOUT IND'S, AND FDA HEARD ABOUT IT AND SAID WE WILL -- WE NEED TO START THINKING ABOUT THIS. SO THEY PUT OUT THAT GUIDANCE, AND THAT WAS REALLY THE START OF THE WHOLE CELLULAR THERAPY REGULATORY FRAMEWORK.

SO IN 1993 FDA ANNOUNCED THEIR INTENT TO REGULATE HUMAN SOMATIC CELL AND GENE THERAPIES, AND THEN 1997 THERE WAS A GUIDANCE FOR WHAT NEEDED TO BE IN THE CHEMISTRY MANUFACTURING AND CONTROL SECTION OF THE IND AND THE ESTABLISHMENT DESCRIPTION FOR SOMATIC CELL THERAPY PRODUCTS. AND THEN 1997 WAS WHEN THAT WHOLE PROPOSED APPROACH WAS PUBLISHED IN THE *FEDERAL REGISTER*.

SO THEN YOU HAVE THE TEN-YEAR PERIOD FROM 1998 TO 2008 WHERE THERE'S JUST BEEN THIS FLURRY OF ACTIVITY WHERE THEY'VE PROPOSED AND FINALIZED THE

TISSUE RULES THAT ALTA MENTIONED. AND THEY'VE HAD NUMEROUS DRAFT AND FINAL GUIDANCES THAT SORT OF BACK UP THOSE RULES AND FILL IN A LOT OF THE GAPS. AND IN ADDITION, CBER HAS BEEN HAVING LOTS OF INTERACTIONS WITH THE PUBLIC, WITH PROFESSIONAL ORGANIZATIONS, AND SPONSORS, INCLUDING ADVISORY COMMITTEE MEETINGS, PUBLIC WORKSHOPS. THEY ALSO HAVE A CELL THERAPY LIAISON MEETING WITH THE OFFICE OF CELL THERAPY -- CELLS, TISSUES, AND GENE THERAPY. IT'S A TWICE-A-YEAR MEETING.

AND FINALLY, I MENTIONED THE INTERACTIONS WITH THE SPONSORS. THEY ACTUALLY HAVE OVER 1200 ACTIVE FILES IN JUST THE OFFICE OF CELL, TISSUE, AND GENE THERAPY. SO THEY REALLY AREN'T STRANGERS TO LOOKING AT THESE SUBMISSIONS, AND I THINK THEY'RE REALLY WELCOMING HEARING MORE ABOUT WHAT'S GOING ON IN CALIFORNIA AND ELSEWHERE WITH STEM CELLS.

I THINK YOU'VE ALREADY HEARD THIS. CBER REGULATES ALL THESE DIFFERENT PRODUCTS, BLOOD, BLOOD PRODUCTS. AND THEN THERE'S HCTP'S OR HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS AND THEN SOME OTHER PRODUCTS. AND FDA HAS A DEFINITION FOR HCTP, SO ANYTHING CONTAINING HUMAN CELLS OR TISSUES INTENDED FOR IMPLANTATION, TRANSPLANTATION, INFUSION, OR TRANSFER INTO A HUMAN RECIPIENT, THAT'S

VERY STRAIGHTFORWARD. AND THIS IS EVERYTHING THAT HCTP'S INCLUDE. WHAT'S NOTABLE IS THE EXCLUSIONS. IF YOU KNOW THE EXCLUSIONS, THEN EVERYTHING ELSE IS AN HCTP.

INTERESTINGLY, VASCULARIZED WHOLE ORGANS ARE NOT REGULATED BY FDA AT ALL. THEY'RE REGULATED BY HRSA. BONE MARROW THAT'S FROM AUTOLOGOUS OR FAMILY DONORS THAT'S MINIMALLY MANIPULATED IS CONSIDERED PRACTICE OF MEDICINE, SO IT'S NOT REGULATED AT ALL. BONE MARROW, SIMILAR BONE MARROW, IF IT'S FROM AN UNRELATED DONOR, IS ACTUALLY REGULATED BY HRSA. XENOGRAFTS, SEPARATE REGULATIONS. BLOOD AND BLOOD PRODUCTS, SEPARATE REGULATIONS. AND THEN THE OTHERS ARE ALL SEPARATE REGULATIONS. SO THESE ARE EXCLUDED.

AND THEN THERE ARE THE TWO REGULATORY TIERS, AND I THINK ALTA REFERRED TO THIS. SO THE 361 PRODUCTS, AS WE CALL THEM, ARE THE LESS COMPLEX PRODUCTS REGULATED SOLIDLY UNDER SECTION 361 OF THE PHS ACT, AND THOSE ARE TISSUES OF THE BODY, THE THINGS THAT TISSUE BANKS COLLECT AND BANK. REPRODUCTIVE TISSUES ARE ALSO REGULATED UNDER 361, AND THEN PERIPHERAL BLOOD STEM CELLS OR CORD BLOOD IF THEY'RE AUTOLOGOUS OR FAMILY RELATED.

NOW, MOST OF WHAT CIRM IS GOING TO BE

DEALING WITH ARE GOING TO BE THESE MORE COMPLEX PRODUCTS, THE 351S, WE CALL THEM IN POPULAR LINGO. AND THESE HAVE WHAT THEY CALL -- FDA CALLS THESE KICK-UP FACTORS. THEY'RE EITHER MORE THAN MINIMALLY MANIPULATED AND/OR THEY'RE BEING USED IN A NON-HOMOLOGOUS WAY. AND NON-HOMOLOGOUS IS WHERE YOU MIGHT TAKE BONE MARROW, BUT USE IT TO REGENERATE HEART TISSUE. SO THAT WOULD BE NON-HOMOLOGOUS USE.

AND THEN, FINALLY, IF THE CELLS ARE COMING FROM UNRELATED DONORS, PERIPHERAL BLOOD STEM CELLS OR CORD BLOOD FROM UNRELATED DONORS ARE CONSIDERED MORE COMPLEX OR 351 PRODUCTS.

SO THE TISSUE RULES ALTA ALREADY MENTIONED, ESTABLISHMENTS INVOLVED IN THIS HAVE TO REGISTER WITH FDA. THERE ARE DONOR ELIGIBILITY REQUIREMENTS, AND THEN THERE ARE THESE CURRENT GOOD TISSUE PRACTICE, CDTP MANUFACTURING REQUIREMENTS. SO THOSE ARE THE THREE TISSUE RULES. IT TOOK FDA SEVERAL YEARS TO GET THE PROPOSED RULES FINALIZED AND THE GUIDANCES AROUND THESE, BUT THEY'RE OUT NOW AND FINALIZED.

AND THEN THIS IS JUST A SUMMARY OF THE REGULATIONS. SO IF YOU LOOK AT THE 361S, WHICH ARE THE LESS COMPLEX, THEY JUST HAVE TO FOLLOW THE TISSUE RULES. AND THEN THE 351S, THE MORE COMPLEX,

HAVE TO FOLLOW THE TISSUE RULES, BUT ALSO HAVE TO FOLLOW THE CGMP REGULATIONS, THE IND OR IDE REGULATIONS, AND THEN FINALLY A PREMARKET APPROVAL. AND YOU MENTIONED NDA, WHICH IS THE DRUG EQUIVALENT OF BLA, WHICH IS THE BIOLOGICS LICENSE APPLICATION.

SO STEM CELL PRODUCTS FIT IN HERE BECAUSE FDA SAID PUBLICLY THAT IF YOU HAVE PRODUCTS COMING FROM EMBRYONIC, FETAL, OR ADULT STEM CELL SOURCES, WE'RE USING THE HCTP EXISTING FRAMEWORK. SO THEY'RE FITTING IN HERE. AND MY COMMENT IS THAT ALMOST ALL NEW PRODUCTS ARE GOING TO HAVE KICK-UP FACTORS, SO MOST OF THEM ARE GOING TO END UP BEING SUBJECT TO THE REQUIREMENTS FOR THESE 351 HCTP'S.

I DON'T KNOW HOW MUCH TO GO INTO IND'S, BUT AN IND IS NOT AN EASY THING TO PUT TOGETHER FOR A CELL THERAPY PRODUCT. MOST ACADEMIC INVESTIGATORS WHO HAVE DONE COMPANY-SPONSORED OR EVEN INVESTIGATOR-SPONSORED IND'S WITH A DRUG WHERE THE DRUG IS ALREADY MANUFACTURED ARE BASICALLY FOCUSING MOSTLY ON THE CLINICAL TRIAL ITSELF. AND YOU CAN SEE THAT THE CLINICAL TRIAL AND THE CONSENT IS PART OF THAT, BUT THE PRODUCT DESCRIPTION, WHICH IS THE CMC SECTION, OR CHEMISTRY MANUFACTURING AND CONTROL SECTION, IS A HUGE PART OF ANY CELL THERAPY IND. AND THAT'S WHAT TAKES A LOT OF TIME TO PUT TOGETHER.

TYPICALLY IN AN ACADEMIC SETTING, INVESTIGATOR HEARS ABOUT A DRUG AND MAY EVEN BE DOING A PHASE I STUDY, BUT THE CMC IS BASICALLY DONE AND THE PRECLINICAL DATA AND PHARMACOLOGY AND TOXICOLOGY ARE BASICALLY DONE. SO THEN THEY'RE JUST TALKING ABOUT WHETHER OR NOT THERE'S PREVIOUS HUMAN EXPERIENCE AND WHAT THE TRIAL -- WHAT THE PROPOSED TRIAL IS AND WHAT THE INFORMED CONSENT IS GOING TO LOOK LIKE. SO I THINK THAT CIRM IS GOING TO BE DEALING A LOT WITH THESE DISEASE TEAMS STRUGGLING A LOT WITH THE CMC AND HOW TO EVEN PUT THE PRECLINICAL DATA, HOW TO DECIDE ON HOW TO DO THE PRECLINICAL STUDIES, AND THE PHARM TOX BECAUSE THAT'S WHERE THE BIG QUESTIONS ARE WITH STEM CELL THERAPIES.

THIS GUIDANCE IS WHAT I GIVE TO EVERYBODY WHO'S SORT OF STARTING OUT BECAUSE THIS IS A GREAT GUIDANCE FOR WHAT YOU NEED TO THINK ABOUT WHEN YOU'RE TRYING -- WHEN YOU KNOW WHAT YOU ARE GOING TO HAVE TO GIVE TO THE FDA FOR YOUR CMC SECTION, FOR YOUR IND. SO THIS DESCRIBES WHAT FDA IS GOING TO LOOK AT WHEN THEY REVIEW THE PRODUCT PART OF YOUR IND. AND IT'S A VERY GOOD GUIDANCE THAT WAS FINALIZED LAST YEAR.

AND THEN ALTA MENTIONED THE SOURCE, CELLS, TISSUES, AND CELL LINES, THAT ARE USED TO DEVELOP

THE HCTP'S. THEY AREN'T BY THEMSELVES CONSIDERED HCTP'S, BUT THE WAY FDA IS GOING TO REGULATE THOSE IS THAT THEY'RE GOING TO REQUIRE DETAILED QUALIFICATION. AND ALTA MENTIONED THE DIFFERENT TESTING AND SO ON THAT'S GOING TO NEED TO GO INTO THAT. THE CMC GUIDANCE THAT I JUST SHOWED YOU ACTUALLY OUTLINES THE REQUIREMENTS AND THEN REFERENCES A SERIES OF OTHER FDA GUIDANCES ON DONOR SCREENING AND TESTING, THE MANUFACTURING BANKING AND TESTING OF THE CELL LINES, AND ALSO ON THE USE OF XENOGENAIC MATERIALS OR ANIMAL MATERIALS IN CELL BANKING.

CGMP, EVERYBODY ALWAYS SAYS WHAT'S CGMP, CURRENT GOOD MANUFACTURING PRACTICE. WE THROW THAT TERM AROUND A LOT. IT'S REALLY SORT OF A -- IT'S A CONCEPT AND THEN IT'S A REALITY. IT REPRESENTS THE MINIMUM STANDARDS FOR METHODS USED TO MANUFACTURE A DRUG OR A BIOLOGIC TO ASSURE ITS SAFETY, IDENTITY, PURITY, AND POTENCY. AND IT SOUNDS VERY CONCEPTUAL, BUT, IN FACT, THERE ARE CGMP REGULATIONS AND THEN THERE ARE CGMP GUIDANCE, AND THEN THERE'S THE PRACTICE, AND THE COMMUNITY THAT DEVELOPS AND IMPROVES OVER TIME.

ONE THING I TELL PEOPLE OVER AND OVER AGAIN, IT'S NOT JUST ABOUT THE FACILITY. THE

FACILITY IS ONLY ONE ELEMENT OF QUALITY MANUFACTURING AND REGULATORY COMPLIANCE. AND, IN FACT, THE OTHER THING THAT A LOT OF ACADEMIC PEOPLE THINK THAT YOU DON'T HAVE TO FOLLOW CGMP WHEN YOU'RE IN A PHASE I TRIAL. AND THAT'S A COMPLETE MISCONCEPTION, AND FDA CAME OUT WITH THIS GUIDANCE LAST YEAR, FINALIZED IT, IT HAD ACTUALLY COME OUT A FEW YEARS BEFORE, ON CGMP FOR PHASE I INVESTIGATIONAL DRUGS, AND IT ALSO APPLIES TO BIOLOGICS. AND THEY GO THROUGH IN THE GUIDANCE, IT'S ACTUALLY A VERY GOOD GUIDANCE, WHERE THEY GO THROUGH DIFFERENT POINTS ON HOW EVEN IN PHASE I YOU SHOULD THINK ABOUT HOW YOU'RE GOING TO COMPLY WITH CGMP. IN FACT, THE REQUIREMENTS MAY BE A LITTLE BIT LIGHTER IN PHASE I THAN IN PHASE II AND PHASE III, BUT THEY'RE STILL PRETTY DARN STRICT IN PHASE I.

ALTA MENTIONED COMBINATION PRODUCTS. THERE'S ACTUALLY AN OFFICE OF COMBINATION PRODUCTS AT FDA THAT WILL DO A DESIGNATION ABOUT WHICH OF THE CENTERS WILL BE THE LEAD CENTER FOR THE REVIEW. THIS IS AN EXAMPLE OF AN HCTP COMBINATION PRODUCT, AND I THINK YOU'RE GOING TO BE SEEING A LOT OF THINGS LIKE THIS. THIS IS A REAL PRODUCT BY A COMPANY CALLED NEUROTECH-USA THAT'S BASED IN, I THINK IT WAS ORIGINALLY A FRENCH COMPANY, BUT

THEY'RE IN RHODE ISLAND NOW, AND THEY'RE IN PHASE II AND PHASE III CLINICAL TRIALS IN RETINITIS PIGMENTOSA AND MACULAR DEGENERATION OF AGING. AND BASICALLY THEY HAVE A CELL LINE THAT'S A RETINAL EPITHELIAL CELL LINE THAT THEY'VE GENETICALLY ENGINEERED TO OVERPRODUCE A TROPHIC FACTOR OR GROWTH FACTOR, AND THEN THEY'VE ENCAPSULATED IT IN THIS HOLLOW FIBER MEMBRANE DEVICE THAT THEN GETS IMPLANTED INSIDE THE EYEBALL.

AND SO IT'S REALLY SORT OF A DRUG DEVICE AND A BIOLOGIC ALL IN ONE, BUT I THINK CBER IS THE LEAD ON THIS AS IT IS MOST OF THE COMBINATION PRODUCTS THAT HAVE -- WHERE THE CELL IS ACTUALLY PRODUCING THE PRIMARY EFFECT, OR I GUESS THEY HAVE SOMETHING CALLED THE PRIMARY MODE OF ACTION, SOMETHING LIKE THAT. CBER WILL LOOK AT IT, BUT THEY WILL, OF COURSE, BRING IN PEOPLE FROM THE DEVICE SIDE AND THE DRUG SIDE FOR THE REVIEW PROCESS.

THERE'S ALSO A GUIDANCE ON COMBINATION PRODUCTS THAT CAME OUT A FEW YEARS BACK. THAT'S ACTUALLY STILL IN DRAFT. AND THEN I'M NOT SURE HOW MUCH I'M GOING TO GO INTO THIS. I THINK JOHN AND A COUPLE OTHER PEOPLE MAY HAVE MENTIONED THAT BONE MARROW TRANSPLANT WAS SORT OF WHERE THINGS STARTED. AND I WANTED TO TOUCH ON STANDARDS AND ACCREDITATION

IN ADDITION TO FDA REGULATIONS BECAUSE THERE ARE STANDARDS AND ACCREDITATION GROUPS IN THE WORLD OF CELL THERAPIES.

BONE MARROW TRANSPLANT REALLY STARTED OUT AS PRACTICE OF MEDICINE, AND FDA STILL CONSIDERS CLASSIC BASIC BONE MARROW TRANSPLANT AS PRACTICE OF MEDICINE. THEY DON'T REGULATE IT. AND BACK IN THE 1970S AND 1980S THERE REALLY WASN'T MUCH IN TERMS OF QUALITY SYSTEMS AND OVERSIGHT OF THESE ACTIVITIES. BUT IN THE LATE '80S AND EARLY '90S, THERE WAS INCREASING USE OF PERIPHERAL BLOOD AS A SOURCE. THERE WERE MORE TRANSPLANTS GOING ON, AND BY 1991 AND 1992 THERE WERE TWO ORGANIZATIONS THAT PUBLISHED STANDARDS AND STARTED ACCREDITATION PROGRAMS.

ONE OF THEM IS AABB, WHICH IS AMERICAN ASSOCIATION OF BLOOD BANKS AND THE OTHER IS FACT, FOUNDATION FOR ACCREDITATION OF CELL THERAPIES, WHICH IS THE ACCREDITATION ARM OF THE INTERNATIONAL SOCIETY FOR CELL THERAPY AND THE AMERICAN SOCIETY FOR BONE MARROW TRANSPLANT. SO THOSE TWO ORGANIZATIONS HAVE ACCREDITATION PROGRAMS FOR BONE MARROW, PERIPHERAL BLOOD, AND THEN NOW FOR CORD BLOOD SOURCES OF HEMATOPOETIC PROGENITOR CELLS. SO MOST LABS WILL HAVE THOSE.

AND THEN THIS IS JUST SORT OF A SUMMARY OF

THE DIFFERENT KINDS OF PRODUCTS AND WHO'S ACCREDITING WHO AND WHAT FDA IS DOING. AND I THREW CALIFORNIA IN THERE BECAUSE IF YOU WERE A FACILITY IN CALIFORNIA DOING JUST, SAY, YOU KNOW, LOOK AT THE BOTTOM ONE, YOU KNOW, ALLO UNRELATED DONOR CORD BLOOD BANKING, YOU WOULD HAVE AABB OR FACT ACCREDITATION, BUT YOU'D ALSO HAVE NATIONAL MARROW DONOR PROGRAM, AND NMDP, STANDARDS TO FOLLOW. YOU'D BE REGULATED BY FDA AS A 351 HCTP, AND YOU'D ALSO HAVE A LICENSE WITH CALIFORNIA FOR THE BLOOD BANK -- THE BLOOD AND BIOLOGICS LICENSE.

SO THIS IS JUST WHAT CALIFORNIA DOES. AND I'M STILL A LITTLE CONFUSED ABOUT WHAT THEY DO. I'M STILL LEARNING WHAT THEY DO, AND I'LL HAVE TO BRING THAT BACK TO YOU ANOTHER TIME. BUT BASICALLY THEY'VE GOT BLOOD BANK AND BIOLOGICS FACILITIES WHERE THEY LICENSE THOSE, AND THEY ALSO LICENSE TISSUE BANK FACILITIES.

I HIGHLIGHTED THE ASSISTED REPRODUCTIVE TECHNOLOGIES AND THEN THE STEM CELL PROCESSING FROM SOURCES OTHER THAN CORD BLOOD AND CIRCULATING BLOOD. SO I'M ASSUMING, AND GEOFF MAY KNOW THIS BETTER THAN I DO. I'M ASSUMING THAT ANYBODY WHO'S DERIVING CELL LINES, EMBRYONIC STEM CELL LINES, WOULD FIT INTO THAT AND HAVE TO REGISTER AND GET LICENSED AS A

TISSUE BANK, BUT I'M NOT SURE OF THAT. I DON'T KNOW IF GEOFF --

DR. LOMAX: WE HAD THIS DISCUSSION AT LUNCH. I THINK WE'RE GOING TO GO BACK AND TAKE A CLOSER LOOK AT THAT. OFF THE TOP OF MY HEAD -- ACTUALLY I CAN LOOK UP SOME THINGS HERE. SO IF I COME UP WITH AN ANSWER IN THE NEXT TEN MINUTES.

DR. READ: I JUST THOUGHT IT WOULD BE GOOD TO KIND OF GET IT OUT THERE. AND THEN THE OTHER THING I THINK THAT'S VERY GOOD IN CALIFORNIA IS THEY HAVE VERY STRICT STANDARDS FOR LICENSING CLINICAL LABORATORY PERSONNEL AND ALSO CLINICAL LAB FACILITIES THAT DO MODERATE AND HIGH COMPLEXITY TESTING. SO I THINK THAT ACTUALLY SETS THE BAR PRETTY HIGH IN CALIFORNIA.

THERE ARE OTHER STATES THAT HAVE PRETTY HIGH BARS LIKE NEW YORK STATE. I'M NOT FAMILIAR WITH ALL THE STATE REGULATIONS, BUT CALIFORNIA AND NEW YORK KIND OF POP OUT AS THE ONES THAT HAVE FAIRLY WELL-DEVELOPED LAWS AND STANDARDS.

AND THEN THIS IS JUST SOME WEB LINKS TO GETTING THE FINAL RULES OR THE RULES AND THE GUIDANCES. AND YOU CAN GET ON AN E-MAIL LIST AND GET AN E-MAIL FROM CBER EVERY DAY IF YOU WANT IT ON WHAT ALL THEIR ADVISORY MEETINGS AND WORKSHOPS AND

NEW THINGS THAT ARE COMING OUT. AND I THINK I'M GOING TO STOP THERE BECAUSE I'M GOING TO SAVE PART 2 FOR MARIE'S SESSION.

CHAIRMAN LO: OKAY. THANKS VERY MUCH. QUESTIONS FOR EITHER ALTA OR E. J.? DOROTHY.

DR. ROBERTS: I HAVE A QUESTION WHICH PERHAPS EITHER OF YOU OR BOTH COULD ANSWER. WHAT'S THE PRACTICAL EFFECT OF BEING CLASSIFIED AS A DRUG, DEVICE, OR BIOLOGIC OR SOME COMBINATION? WOULD RESEARCHERS PREFER ONE OR THE OTHER BECAUSE THE REGULATORS ARE TOUGHER IN ONE OR THE OTHER? DOES IT MATTER PRACTICALLY?

DR. READ: NO. BUT, YOU KNOW, I MEAN, BUT THE FDA WILL MAKE THAT DETERMINATION. I MEAN YOU CAN'T JUST SAY, OH, I WANT THIS TO BE A DRUG.

DR. ROBERTS: RIGHT. RIGHT.

DR. READ: BUT I MEAN I WOULD SAY CDER, THE DRUG IS MUCH BIGGER THAN ANY OF THE OTHERS BECAUSE MOST OF WHAT GOES INTO THE FDA IS DRUGS, AND SO IN A WAY THE PERCEPTION MAY BE IS THAT THEY'RE TOUGHER. BUT I THINK CBER USED TO BE BUREAU OF BIOLOGICS, AND THEY DIDN'T USED TO BE SO TOUGH. BUT THEY'RE PRETTY TOUGH NOW. SO WHAT DO YOU THINK, ALTA?

DR. CHARO: WELL, I WOULD SUPPLEMENT IT

ONLY BY SAYING THIS. FIRST OF ALL, THE BIGGEST DISTINCTION, IF IT'S A BIOLOGIC, SUDDENLY THE PUBLIC HEALTH SERVICE ACT COMES INTO PLAY. SO THERE ARE ALL THE INFECTIOUS CONTROL MEASURES. BUT THEN AS BETWEEN DRUG AND DEVICE IN PARTICULAR, I'D SAY THAT ON THE GROUND HISTORICALLY THERE HAS BEEN A HUGE PREFERENCE TO GO THROUGH DEVICE BECAUSE IT'S BEEN A MUCH LOOSER REGULATORY CENTER. AND IT'S PARTLY BECAUSE THE RULES ARE DIFFERENT. MANY DEVICES CAN SLIDE IN WITH FAIRLY MINIMAL REGULATORY OVERSIGHT BECAUSE THEY'RE DEEMED TO BE SUBSTANTIALLY EQUIVALENT TO A PREDECESSOR DEVICE THAT EITHER HAS ALREADY BEEN APPROVED OR WAS ON THE MARKET YEARS AGO, IN FACT, GRANDFATHERED.

NOW, MORE RECENTLY THERE HAS BEEN A KIND OF OUTBREAK OF INTERNAL COMPLAINTS FROM THE DEVICE PEOPLE ABOUT CONFLICT OF INTEREST. AND IT'S LEADING TO A VERY OR HEIGHTENED DEGREE OF SCRUTINY, AT LEAST WHEN WE FINALLY GET AN HHS SECRETARY AND AN FDA COMMISSIONER, IT WILL LEAD TO A HEIGHTENED DEGREE OF SCRUTINY FOR THE DEVICE CENTER. BUT I'D SAY FOR THE MOMENT MOST, IF THEY HAVE A CHOICE, WOULD MUCH PREFER TO GO THROUGH DEVICE. BUT YOU'RE CORRECT THAT THE FDA WILL MAKE THE CALL, BUT THIS IS WHY THE INSIDERS WHO USED TO BE AT THE FDA NOW GET PAID A

LOT TO BE THE ATTORNEYS FOR THE OUTSIDERS BECAUSE THEY KNOW HOW TO TALK THE FDA INTO SENDING IT TO ONE CENTER OR THE OTHER.

DR. READ: I'M AWARE OF A SITUATION ABOUT A YEAR AGO WHERE WE HEARD -- WE ACTUALLY WERE ORGANIZING A MEETING, AND WE WERE TRYING TO GET THIS ONE COMPANY TO TALK TO US ABOUT THE REGULATORY STRATEGY, AND WE ACTUALLY HAD AN FDA LIAISON ON OUR CONFERENCE CALLS BECAUSE THEY WERE CO-SPONSORING THE MEETING. AND ON THAT CONFERENCE THEY FOUND OUT THAT THIS COMPANY HAD GONE THROUGH THE DEVICE SIDE AND THEY SHOULD HAVE GONE THROUGH CBER, BUT KIND OF KNEW WHAT THEY WERE DOING. AND IT WAS SHOCKING TO ME THAT THE PERSON IN THE DEVICE SIDE DIDN'T CALL CBER, BUT I DON'T THINK THAT'S GOING TO HAPPEN A LOT IN THE FUTURE. BUT YOU'RE EXACTLY RIGHT. SOME OF THE COMPANIES KNOW HOW TO PLAY THE GAME.

I DON'T THINK ANY OF THE -- ANYTHING WITH STEM CELL -- WELL, I DON'T KNOW. I THINK --

DR. CHARO: WELL, THERE ARE SOME STEM CELL PRODUCTS YOU CAN IMAGINE THAT MIGHT ACTUALLY BE BIOLOGICAL DEVICES. AND THE BANDAGE THAT I WAS TALKING ABOUT --

DR. READ: RIGHT. RIGHT.

DR. CHARO: -- IS AN EXAMPLE OF ONE OF

THOSE. SO THAT'S ONE WHERE YOU WOULD NEED THE CENTER FOR BIOLOGICS AND THE DEVICE CENTER COOPERATING BECAUSE THIS IS NOW A COMBINATION PRODUCT.

DR. READ: RIGHT. RIGHT. I DO THINK THAT FDA WILL CATCH UP WITH PEOPLE, EVERYBODY EVENTUALLY. SO YOU CAN ONLY -- YOU MIGHT BE ABLE TO GET THINGS OUT, AND THEN, YOU KNOW, I MEAN I THINK THAT IT'S GOING TO BE TOUGH FOR PEOPLE TO AVOID CBER.

DR. CHARO: BUT JUST TO BE -- JUST ONE LAST THING BECAUSE IT'S ACTUALLY PERTINENT FOR THE STEM CELL AREA. TO THE EXTENT THINGS ARE GOING THROUGH DEVICES, THE DEVICE CENTER IS WILDLY UNDERFUNDED. I MEAN THE DRUG CENTER IS UNDERFUNDED BADLY. THE DEVICE CENTER IS UNDERFUNDED CATASTROPHICALLY BECAUSE OF THE NUMBER OF COMPONENTS THAT NOW GO INTO MEDICAL DEVICES THAT ARE COMING FROM MANUFACTURERS ALL OVER THE GLOBE, AND THEY HAVE ABSOLUTELY NO WAY YET TO TRACK ALL THE COMPONENTS, LET ALONE ENFORCE STANDARDS FOR THE MANUFACTURING FACILITIES.

SO THIS IS ACTUALLY RATHER PERTINENT. THEY ARE TRULY OVERWHELMED OVER THERE WITH THE REGULAR ORDER OF BUSINESS, LET ALONE TRYING TO LOOK AT THINGS WHICH HAVE THEIR EFFECT BOTH MECHANICALLY

AND BIOLOGICALLY. I MEAN A LOT OF STEM CELL THERAPIES MIGHT INVOLVE THINGS THAT ARE ON SCAFFOLDS, FOR EXAMPLE. AND THE SCAFFOLDING IS A DEVICE, BUT IT HAS CELLS THAT ARE ATTACHED TO THE SCAFFOLD. SO THIS IS TRULY A PROBLEM. AND THE DEVICE CENTER DOES NOT HAVE AN INDEPENDENT SOURCE OF FUNDING LIKE THE PRESCRIPTION DRUG USER FEE ACT WHICH GENERATES REVENUE FOR REVIEWERS FOR THE DRUG CENTER. THERE'S BEEN A LOT OF DISCUSSION. ACTUALLY, NO, THEY DO NOW HAVE PDUFA. THEY DO HAVE SOME MONEY, BUT IT'S NOT NEARLY THE SAME AMOUNT OF MONEY AS PDUFA GETS.

CHAIRMAN LO: AND ANN. THEN WHO ELSE WANTS TO ASK A QUESTION?

DR. KIESSLING: SINCE WE'RE GOING TO NEED TO KNOW -- I DON'T THINK THIS COMMITTEE, THAT WE'RE GOING TO BECOME FDA EXPERTS, BUT BECAUSE WE'RE GOING TO NEED TO KNOW SOME OVERSIGHT FOR THIS, IT'S VERY DIFFICULT TO FIND THESE PUBLICATIONS ON FDA'S WEBSITE. IS THERE -- I MEAN YOU CAN FIND -- I MEAN THE WEB SITE IS COMPLETE, BUT IT'S REALLY CONFUSING TO USE.

DR. READ: RIGHT.

DR. KIESSLING: IS THERE -- CAN SOMEONE COME UP WITH LIKE TWO OR THREE OVERVIEWS OR

REGULATORY BOOKLETS THAT IT WOULD BE REALLY HELPFUL FOR THIS COMMITTEE TO HAVE?

DR. READ: I NEED TO WRITE A REVIEW PAPER, I GUESS. I DON'T KNOW IF THERE'S ONE REALLY GOOD ONE. WE WERE GOING TO PUT --

DR. KIESSLING: WE CAN HANDLE TWO OR THREE, BUT WE'RE NOT GOING TO GET THE INFORMATION OVER THE WEBSITE, I DON'T THINK.

DR. CHARO: YOU KNOW, ANN, THE FDA WEBSITE DOESN'T HAVE WHAT YOU WANT. I KNOW THIS BECAUSE I'VE LOOKED FOR IT FOR MY STUDENTS. BUT IN ADDITION TO SOME OF ITS CONSUMER PUBLICATIONS, THEY'RE NOT GOOD ENOUGH FOR WHAT YOU WANT. THE DEVICE CENTER ACTUALLY HAS A REALLY GOOD FLOW CHART ON ITS WEBSITE, WHICH WE CAN FIND FOR YOU. BUT THE DRUG CENTER DOES NOT HAVE ANYTHING LIKE THAT.

THE FOOD AND DRUG LAW INSTITUTE, FDLI, WHICH IS A PRIVATE INSTITUTE, HAS SOME WONDERFUL PUBLICATIONS THAT PROVIDE OVERVIEW MATERIALS. NOW, THEY HAVE TO BE PURCHASED; BUT IF THERE WERE A COPY THAT WAS PURCHASED BY CIRM FOR USE FOR REFERENCE, IT MIGHT BE WORTH CONSIDERING BECAUSE THEY DO HAVE JUST WHAT YOU'RE LOOKING FOR.

DR. KIESSLING: SO THE PUBLICATIONS THAT YOU MENTIONED WOULD NOT BE HELPFUL TO US?

DR. READ: THEY'RE GOOD IF YOU HAVE INSOMNIA.

CHAIRMAN LO: YOU NEED TO BE A LAWYER TO READ THOSE.

DR. READ: THEY'RE GUIDANCES. I MEAN THEY'RE NOT BAD. IT'S KIND OF TOUGH GOING THROUGH THE GUIDANCE. I THINK IT WOULD BE A GOOD THING TO WRITE A REVIEW PAPER ABOUT.

CHAIRMAN LO: LET'S ASK STAFF AND MAKE GEOFF THE POINT PERSON TO TRY AND FIND US SOME SORT OF APPROPRIATE DOCUMENT.

DR. READ: THE OTHER THING IS WE PUT TOGETHER AT THE CTSI AT UCSF, AND WE'RE GOING ALSO -- WELL, I'LL ADVERTISE THE MEETING LATER THAT'S GOING TO BE IN MAY. BUT WE WERE GOING TO PUT TOGETHER A CD OF ALL THE PERTINENT GUIDANCE DOCUMENTS SO THAT PEOPLE COULD HAVE THEM ALL IN ONE PLACE, THE ONES THAT WE THINK ARE THE MOST RELEVANT DOCUMENTS. AND I DON'T KNOW. THAT'S NOT REALLY WHAT YOU WANT BECAUSE YOU'RE NOT GOING TO READ EVERY GUIDANCE. BUT YOU MIGHT -- THAT MIGHT BE HELPFUL.

DR. KIESSLING: WE'RE GOING TO NEED A REFERENCE OF SOME SORT, I THINK.

DR. READ: YEAH. YEAH. OKAY.

CHAIRMAN LO: OKAY. SO GOING DOWN, I'M

GOING TO PASS JEFF. JOHN WAGNER.

DR. WAGNER: I THINK IN RELATION TO THIS DISCUSSION RIGHT NOW, BECAUSE THE VERY QUESTION THAT YOU ASKED, YOU KNOW, I THINK IT ALSO NEEDS TO BE STATED THEN BECAUSE OF THE DIFFICULTY OF JUST UNDERSTANDING ALL THE REQUIREMENTS THAT ARE REQUIRED, WHAT IS THE LEGAL RESPONSIBILITY WHEN YOU SIGN THE FORM 1571 AND 1572?

DR. CHARO: I DON'T KNOW THE FORMS BY NUMBER, BUT IT LOOKS LIKE YOU DO.

DR. READ: THE 1571 IS SORT OF THE FACE SHEET WHERE YOU SAY I AM A SPONSOR, THE INSTITUTION WHERE I WORK, AND SO ON. AND THEN 1572 --

DR. WAGNER: THE REASON WHY I ASK THE QUESTION IS THAT WHEN YOU SIGN THOSE FORMS, IT'S A LEGAL DOCUMENT TO SAY YOU UNDERSTAND EVERY REGULATION THERE IS RELATED TO.

DR. READ: YEAH.

DR. WAGNER: WHAT PEOPLE DON'T REALIZE IS THAT THEY COULD GO TO JAIL FOR NOT -- YOU CANNOT SAY I DIDN'T KNOW.

DR. READ: RIGHT. MARLENE BARROW, WHO'S OUR COORDINATOR AT THE CTSI, IS CONSTANTLY HAVING PEOPLE SIGN THEIR 1571S AND 1572S, AND SHE COULD PROBABLY TELL YOU HOW MANY OF THOSE PEOPLE ACTUALLY

UNDERSTAND WHAT THEY'RE SIGNING. I MEAN I THINK YOU'VE GOT A POINT. AND ALSO I THINK ONE OF THE FORMS YOU'RE ACTUALLY SAYING WHICH IRB YOU'RE USING AND THAT YOU HAVE AN IRB AND SO ON.

DR. WAGNER: BUT THE REASON FOR POINTING THAT OUT, AND I THINK IT'S ALSO FOR ALAN TO KNOW, IS THAT WHEN YOU'RE THEN DEVELOPING THESE TRIALS AND YOU'RE ASKING PEOPLE THEN TO DEVELOP THESE IND'S, THEY REALLY DO NEED TO BE AWARE OF EVERY DETAIL OF WHAT'S REQUIRED FOR THEM TO KNOW TO DO THESE STUDIES. AND SO IT'S NOT JUST ANY INVESTIGATOR THAT CAN DO THESE STUDIES. IT'S GOING TO BE A VERY SELECT FEW INVESTIGATORS THAT ACTUALLY DO THESE CLINICAL TRIALS.

DR. READ: I MEAN I THINK THERE'S JUST A REAL DEARTH OF REGULATORY EDUCATION IN ACADEMIC SETTINGS, AND THERE'S A TENDENCY FOR PEOPLE TO NOT WANT TO LEARN IT BECAUSE IT CAN BE KIND OF DRY AND BORING, BUT IT'S REALLY, REALLY, REALLY IMPORTANT, ESPECIALLY GOING INTO SOME OF THESE CELLULAR THERAPIES.

DR. WAGNER: ESPECIALLY STEM CELL THERAPIES WHICH IS SO HIGH PROFILE.

DR. READ: ABSOLUTELY. SO ONE OF THE THINGS, AND THE CTSI'S, AND YOU PROBABLY HAVE A

CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE AT YOUR PLACE PROBABLY AT MINNESOTA, AND ALL THE BIG PLACES HAVE THEM. THERE IS THIS COMPONENT, I MEAN ONE SUGGESTION I HAVE IS THAT THE CTSA CONSORTIUM, WHICH IS NIH-FUNDED, HAS REGULATORY KNOWLEDGE AND SERVICE PROGRAMS THAT COULD POTENTIALLY PUT SOME THINGS TOGETHER THAT AT LEAST IN ALL OF THOSE ACADEMIC PLACES COULD START EDUCATING PEOPLE.

CHAIRMAN LO: OKAY. LET'S MOVE ON. ROB.

DR. TAYLOR: MY QUESTION, AND I APPRECIATE ACTUALLY BOTH OF YOUR PRESENTATIONS, IS REALLY ABOUT, PRACTICALLY SPEAKING, ARE THESE FDA REGULATIONS AS STRICT AND AS FORMAL AS YOU'RE MAKING THEM SOUND BECAUSE I'M A LITTLE RELUCTANT TO GO BACK AND REVISIT THIS, BUT LAST SUMMER I THINK IT WAS FAIR TO SAY THAT BOB KLEIN AND I GOT INTO IT A LITTLE BIT OVER HIS -- THE STORY THAT GERON WAS PUTTING FORTH A CELL LINE FOR CLINICAL TRIALS THAT WAS DERIVED FROM AN ANONYMIZED PATIENT FOR WHICH I KNOW THAT THERE WAS NO INFORMATION ABOUT THE MALE PARTNER. AND I THINK THE INFORMATION THAT WAS ACTUALLY AVAILABLE ABOUT THE FEMALE PARTNER WAS ACTUALLY QUITE LIMITED.

NOW, I DON'T KNOW IF THIS IS THE SAME CELL LINE THAT'S ACTUALLY GOING FORWARD; BUT IF IT IS,

THEN REALLY THE STRICTNESS OF THE CMC REGULATIONS ARE NOT, IN MY VIEW, BEING PLAYED OUT THE WAY AT LEAST YOU BOTH SUGGESTED.

DR. READ: YEAH. YOU KNOW, IT ACTUALLY -- I COME FROM THE WORLD OF TRANSFUSION MEDICINE AND BLOOD BANKING WHERE IF YOU ACCIDENTALLY DON'T CHECK THE BOX NEXT TO THE PERSON'S TRAVEL HISTORY, YOU KNOW, YOU CAN GET SHUT DOWN BY THE FDA. AND I WAS A LITTLE SURPRISED AT THE LIGHTNESS OF KNOWING THE FULL DONOR HISTORIES ON SOME OF THESE CELL LINES. AND I THINK THAT'S GOING TO BE A POINT OF DISCUSSION GOING FORWARD.

I DON'T KNOW WHAT THE RESOLUTION IS BECAUSE IF YOU HAVE A GREAT CELL LINE, YOU DON'T REALLY WANT TO GET RID OF IT; BUT ON THE OTHER HAND, IDEALLY EVERY CELL LINE WOULD BE DERIVED WHERE YOU'RE FOLLOWING COMPLETE CURRENT GOOD TISSUE PRACTICE REGULATIONS WITH ALL THE DONOR HISTORY AND THEN GMP FOR THE DERIVATION, BUT YOU'RE RIGHT. IT'S NOT BEING DONE, SO I DON'T -- YOU MAY HAVE SOME INSIGHT ON THAT.

DR. CHARO: JUST TO ADD ON THAT BECAUSE THIS IS A PLACE WHERE CIRM, BECAUSE IT CAN FUND DERIVATIONS, ACTUALLY HAS SOME INTERESTING CHOICES. IF YOU GO BACK INTO THE DETAILS OF THOSE TISSUE

RULES, THEY DISTINGUISH BETWEEN TISSUE DONATION THAT GOES FROM STRANGER TO STRANGER, AND IN THE REPRODUCTIVE CONTEXT TISSUE THAT IS BEING COMBINED AS BETWEEN MARRIED -- WITHIN A MARRIED COUPLE. SO THAT, FOR EXAMPLE, IF YOU WANT TO BE AN ANONYMOUS SPERM DONOR, YOU NOW HAVE TO BE SCREENED FOR A DOZEN DIFFERENT INFECTIOUS DISEASES. IF, ON THE OTHER HAND, IT'S YOU AND YOUR HUSBAND USING YOUR OWN EGGS AND SPERM FOR IVF, THE SCREENING IS VOLUNTARY. THE THEORY BEING YOU COULD HAVE HAD SEX AND INFECTED ONE ANOTHER, SO WHO ARE WE TO INSIST ON THE SCREENING. RIGHT?

DR. TAYLOR: IT WASN'T FOR SEVERAL YEARS THOUGH. I MEAN FOR MANY YEARS IN CALIFORNIA YOU HAD TO SCREEN.

DR. CHARO: RIGHT. I'M TALKING ABOUT THE FDA REGULATIONS UNDER TISSUE PLAN ONLY. AND BECAUSE OF THIS DISTINCTION, ALTHOUGH I SUSPECT MANY CLINICS ARE, IN FACT, ENCOURAGING PEOPLE TO BE SCREENED EVEN IF THEY'RE USING THEIR OWN GAMETES, SOME OF THE EMBRYOS THAT ARE LEFT OVER FROM IVF CLINICS, THE PARADIGMATIC SOURCE FOR DERIVATIONS COME FROM PEOPLE WHO WERE NEVER SCREENED FOR INFECTIOUS DISEASE AND WHOSE GENETIC HISTORIES CERTAINLY WERE NOT NECESSARILY TAKEN.

SO THEY'RE EMBRYOS THAT ARE THE LEAST WELL-KNOWN, LEAST WELL-UNDERSTOOD, AND POTENTIALLY MOST LIKELY TO BE INFECTED. AND SO IF YOU REALLY WANTED TO HAVE THE BEST POSSIBLE SOURCE FOR NEW LINES, YOU WOULD DO DERIVATIONS FROM EMBRYOS THAT WERE SPECIFICALLY MADE FOR RESEARCH FROM PEOPLE WHOSE GAMETES WERE -- FROM GAMETES THAT CAME FROM PEOPLE WHO HAD BEEN VERY CAREFULLY SCREENED FROM THE OUTSET. AND YET WE ALL KNOW THAT MAKING AN EMBRYO SOLELY FOR RESEARCH, WHETHER BY IVF OR BY SCNT OR ANY OTHER METHOD, RAISES ALL SORTS OF HACKLES AMONG ALL SORTS OF PEOPLE.

SO HERE'S AN IRONY HERE, THAT THE SOURCE THAT EVERYBODY WANTS TO USE IS NOT NECESSARILY THE BEST ONE IN TERMS OF SAFETY.

DR. READ: RIGHT.

DR. CHARO: AND BECAUSE CIRM CAN FUND DERIVATIONS, THERE IS THE OPTION OF FUNDING TO CREATE CELL LINES WHERE YOU KNOW EVERYTHING ABOUT THE STATUS OF THE DONORS. AND ALSO, AS YOU WERE SAYING, FROM THE OUTSET CAN MANAGE IT AND IN ACCORDANCE WITH GOOD MANUFACTURING PRACTICES. IN ENGLAND, I THINK IT'S NEWCASTLE, THEY NOW HAVE A SPECIAL SETUP WHERE THE FERTILITY CLINIC IS LOCATED PHYSICALLY PROXIMATE TO THE LABORATORY SO THAT THE

HANDOFF OF MATERIALS CAN BE DONE IN A CLEAN ROOM SO THERE'S ABSOLUTELY NO POSSIBILITY OF CONTAMINATION. AND THEN YOU CAN START RIGHT FROM THE OUTSET WITH LABORATORY PROCEDURES THAT MINIMIZE ANY POSSIBILITY OF SOME KIND OF CONTAMINATION OR INFECTIOUS DISEASE TRANSMISSION.

HAVING A PLACE WHERE YOU'VE GOT GOOD MANUFACTURING FACILITIES THAT MEET GMP REQUIREMENTS IN CONJUNCTION WITH YOUR FERTILITY CLINICS, NOT THAT COMMON. ONE OF THE BIG INNOVATIONS OF WISCONSIN WAS CREATING A GMP FACILITY ON CAMPUS SO WE COULD GO FROM LAB TO ANIMAL TO HUMAN ALL IN ONE CAMPUS. BUT IT IS CLEARLY SOMETHING HERE IN CALIFORNIA AND WITH CIRM FUNDING AND WITH CIRM SUPPORT, RIGHT, THAT IS OPEN TO CONSIDERATION, WHICH IS TO MAKE SURE THAT YOU NOW HAVE THE BEST POSSIBLE MANAGEMENT OF SOURCES AND OF LINES.

DR. READ: RIGHT. AND PROBABLY GERON CONVINCED THE FDA BY RETROSPECTIVE TESTING OF THE CELL LINE THAT IT WAS OKAY, AND MAYBE THAT'S OKAY, BUT IDEALLY YOU'D LIKE TO DO EVERYTHING PROSPECTIVELY --

DR. CHARO: THIS WAS AN OPEN QUESTION.

DR. READ: -- TO HAVE THE BIGGEST SAFETY APPROACH.

DR. CHARO: YEAH. IT WAS AN OPEN QUESTION FOR A LONG TIME. FDA WOULD NOT -- IT WOULD NOT SHOW ITS CARDS. IT WOULD NOT SAY WHETHER OR NOT IT WOULD EVER APPROVE CLINICAL TRIALS USING THE PRESIDENTIAL LINES BECAUSE WE DID NOT HAVE ALL THE INFORMATION ABOUT THOSE DONORS AND COULDN'T GET IT BECAUSE MANY OF THEM WERE LOST IN ANONYMITY. AND THE ALTERNATIVE WAS DIRECT TESTING, BUT DIRECT TESTING DOESN'T LET YOU DO THINGS LIKE SCREEN DONORS FOR THEIR EXPOSURE TO SITUATIONS THAT PUT THEM AT HIGHER THAN TYPICAL RISK FOR THINGS LIKE CJD, YOU KNOW, MAD COW VARIANCE, WHERE YOU CAN'T DO DIRECT TESTING FOR IT, WHICH IS WHY, IF YOU LIVED IN FRANCE AND ATE BEEF IN 1985, YOU KNOW, YOU STILL CAN'T GIVE BLOOD.

SO IT WAS REALLY AN OPEN QUESTION. YEAH, YOU'RE RIGHT. GERON OBVIOUSLY GOT THEM TO AGREE TO DO DIRECT TESTING. BUT IN AN ERA IN WHICH MORE LINES MAY BE AVAILABLE, YOU KNOW, NOW THAT WE'VE HAD HOW MANY YEARS OF PRIVATE FUNDING FOR DERIVATIONS, YOU DO HAVE TO ASK WHETHER THE REASON THAT GERON GOT THEM TO AGREE TO THIS WAS SIMPLY BECAUSE THAT WAS THE BEST CHARACTERIZED LINE. THEY'D BEEN WORKING WITH IT FOR A LONG TIME AS OPPOSED TO IT BEING A DECISION AT A POLICY LEVEL THAT THIS WAS EQUIVALENT IN SAFETY TO HAVING LINES THAT CAME FROM DONORS WITH

KNOWN BACKGROUNDS.

CHAIRMAN LO: IF I CAN JUST ADD SOMETHING TO WHAT ALTA SAID. THE OTHER THING YOU CAN'T GET FROM SCREENING MATERIALS YOU'RE GOING TO TRANSPLANT, OF COURSE, IS A STRONG FAMILY HISTORY OF SOMETHING LIKE CANCER THAT MIGHT BE TRANSMITTED IN THE TRANSPLANT.

DR. CIBELLI: I'D LIKE TO BE MORE PRACTICAL BECAUSE I THINK CIRM IS GOING TO START ENTERTAINING PRECLINICAL STUDIES THAT WILL EVENTUALLY END UP IN AN IND. AS A PI, I WOULD EXPECT THAT CIRM WILL HELP ME OUT AND NAVIGATE THROUGH ALL THESE THINGS.

ONE OF THE THINGS THAT I'VE SEEN AT THE FDA AND TALKING WITH THE FDA IS THAT ALL THE CELL THERAPY TRIALS THAT THEY HAVE GONE THROUGH BEFORE THE GERON ONE DIDN'T INCLUDE THE RISK OF INJECTING CELLS THAT CAN TURN INTO ANYTHING, LIKE PLURIPOTENT CELLS. SO I THINK IT'S FAIR TO SAY THAT THERE IS VERY LITTLE EXPERIENCE FROM THE REGULATORY STANDPOINT. AND HOW ARE YOU GOING TO HANDLE THESE CELLS?

SECOND POINT IS CIRM WILL ENTERTAIN THOSE STUDIES. YOU TELL ME IF I'M WRONG. BUT I'M ASSUMING THAT WE WILL SEE A NUMBER OF PEOPLE TRYING

TO DO THIS. SO THE PHASE THAT CIRM IS GOING TO HAVE HELP THE PI IS IN THE PRECLINICAL -- AT THE SIGN OF PRECLINICAL STUDIES THAT ARE GOING TO BE VALID WHEN YOU GO AND TRY TO DO AN IND. I'VE TALKED TO THE FDA A NUMBER OF TIMES, AND THEY'RE WONDERFUL PEOPLE, BUT FOR REASONS OF CONFIDENTIALITY THEY CANNOT TELL YOU WHAT ARE THE MAJOR HURDLES THAT THEY HAD TO ASK GERON TO GO THROUGH.

SO THEY HAVE THIS MECHANISM WHEREBY ONCE YOU FILE AN IND WITH THEM, THEY HAVE MASTER FILES THAT YOU CAN DIG INTO AND LEARN THINGS THAT GERON LEARNED ALONG THE WAY AND USE THAT TO YOUR ADVANTAGE. SO I WONDER IF CIRM, SINCE YOU'RE GOING TO BE PAYING FOR MOST OF THESE PRECLINICAL STUDIES, IF YOU COULD MAKE AVAILABLE TO OTHER RESEARCHERS THAT ARE PLANNING DIFFERENT STUDIES WHAT ARE THE PROTOCOLS, WHAT KIND OF EXPERIMENTAL DESIGN THEY HAVE TO BE MINDFUL OF WHEN THEY'RE PLANNING ON GOING INTO THESE STUDIES SOON.

DR. CSETE: WE'VE THOUGHT ABOUT THIS, JOSE, AS YOU MIGHT IMAGINE. AND OBVIOUSLY WE CAN'T BE RELEASING CONFIDENTIAL INFORMATION FROM ONE INVESTIGATOR TO ANOTHER. WE CAN'T BE A BROKER IN THAT REGARD. I THINK THE MOST IMPORTANT --

DR. CIBELLI: WHY NOT?

DR. CSETE: WE CAN'T.

DR. READ: I ACTUALLY HAVE A FEW SLIDES ON THAT.

DR. CSETE: IF THE INVESTIGATORS AGREE, I THINK THAT'S ABSOLUTELY FINE. I THINK THE MOST IMPORTANT THING WE CAN DO IS HAVE AN ONGOING DIALOGUE WITH THE FDA AND HAVE A SEAT AT THE TABLE AT THE APPROPRIATE COMMITTEES AND KEEP OURSELVES AS WELL INFORMED TO DISSEMINATE THE INFORMATION TO ALL OF OUR INVESTIGATORS AS POSSIBLE. AND WE HAVE BEEN TRYING TO DO THAT, AS E. J. WELL KNOWS.

DR. READ: RIGHT.

DR. CSETE: WITH A BIT OF DIFFICULTY, BUT I THINK THAT'S GOING TO CHANGE SOON.

DR. CIBELLI: BUT, MARIE, WHAT I'M SAYING IS IF WE HAVE IN MIND THE PATIENT AND WE REALLY WANT TO GET THIS TO THE CLINIC FAST --

DR. CSETE: WE HAVE TO ADVOCATE FOR TRANSPARENCY, THAT EVERY PATIENT WHO GETS A PLURIPOTENT STEM CELL, THAT THE INFORMATION THAT COMES FROM THAT PATIENT IS AVAILABLE TO EVERYONE, NOT JUST TO OUR INVESTIGATORS. AND CERTAINLY WE'RE TRYING TO ENCOURAGE THAT.

DR. CIBELLI: BUT I GUESS I WASN'T MAKING MYSELF CLEAR. LET'S SAY I'M PLANNING TO DO A

CLINICAL STUDY, AND I ASK THE QUESTION -- I ASKED THIS QUESTION TO THE FDA AND THEY COULDN'T ANSWER. I SAID TELL ME HOW MANY ANIMALS I HAVE TO INJECT TO RULE OUT THE POSSIBILITY OF A TERATOMA FORMATION. THE ANSWER WAS WE KNOW HOW MANY. WE CAN'T TELL YOU. YOU HAVE TO READ THIS REFERENCE WHERE THEY TALK ABOUT HOW MANY ANIMALS YOU SHOULD INJECT, HOW MANY CELLS, FOR HOW LONG YOU HAVE TO FOLLOW THE ANIMAL. SO THOSE ARE CORE PROTOCOLS THAT YOU SHOULD TRY TO GET SOME SORT OF CONSENSUS SOON.

DR. READ: I ACTUALLY HAVE A COUPLE SLIDES. MAYBE I'LL -- THIS IS ONLY A FEW MORE SLIDES. I WAS GOING TO DO IT BEFORE MARIE'S SESSION, BUT SINCE YOU'VE ASKED.

SO THIS IS WHAT FDA HAS FOCUSED ON DURING PRODUCT DEVELOPMENT, AND IT'S SAFETY, SAFETY, SAFETY. AND YOU'VE SEEN THIS BEFORE WITH PHASE I, PHASE II, PHASE III, AND THEN PHASE IV IS MARKETING AND WHERE YOU PUT YOUR IND AND BLA IN. BUT LET ME SKIP THAT.

SO THERE ARE A NUMBER OF INTERACTIONS BETWEEN I AS THE POTENTIAL SPONSOR AND CBER OR THE OTHER CENTER -- ANOTHER CENTER IN FDA. SO YOU CAN HAVE THESE DIFFERENT INTERACTIONS THAT RANGE FROM A PRE-PRE-IND MEETING TO A PRE-IND MEETING TO THE

ACTUAL IND SUBMISSION WHERE THEY REVIEW IT AND THEN ONGOING INTERACTIONS. IF YOU JUST ASK THEM GENERAL QUESTIONS, THEY'RE GOING TO GIVE YOU GENERAL ANSWERS AND NOT GIVE YOU A LOT OF SPECIFICS. THEY TEND TO DO BEST IF YOU PROPOSE SOMETHING, AND THEY WILL RESPOND TO IT.

AND THEN THE OTHER THING IS THE COMMUNICATIONS BETWEEN THE SPONSOR AND CBER OR ANYBODY IN FDA ARE CONSIDERED PROPRIETARY TO THE SPONSOR. AND YOU CANNOT ACCESS THEM BY PUBLIC -- THE PUBLIC CAN'T GET TO THEM, OTHER SPONSORS CAN'T GET TO THEM. THEY AREN'T SUBJECT TO FREEDOM OF INFORMATION ACT. YOU JUST CAN'T GET TO THEM.

NOW, IF A GIVEN SPONSOR LIKE GERON OR STEM CELLS, INC., SAYS, "OH, I'LL TELL YOU WHAT I DID AND I'LL SHOW YOU WHAT I DID," THEY'RE ALLOWED TO DO THAT, BUT THE FDA IS NOT ALLOWED TO DO THAT. AND WHETHER OR NOT CIRM IS ALLOWED TO DO THAT, I DOUBT IT BECAUSE THOSE ARE PROPRIETARY. SO THAT'S A BASIC PRINCIPLE.

SO WHAT DO YOU DO TO GET AROUND THAT? AND I THINK AS A GROUP PLEA -- THERE'S GENERAL GUIDANCE THAT THEY PUT OUT. THEY HAVEN'T PUT OUT A LOT OF REALLY SPECIFIC GUIDANCE, YET, BUT I THINK THEY WILL OVER TIME. I THINK IT'S JUST TOO EARLY. THE

SCIENCE HASN'T MATURED ENOUGH, AND I THINK THE BEST WAY TO PROMPT GUIDANCE IS TO JUST KEEP ENGAGING WITH THEM, PROPOSE THINGS, AND PRESENT SCIENTIFIC DATA TO THEM. AND HOW DO YOU DO THAT? YOU DO IT -- I'LL SKIP THAT -- WE'RE ACTUALLY HAVING A MEETING. THIS IS AN ADVERTISEMENT FOR A MEETING WE'RE HAVING IN MAY WHERE WE'RE GOING TO TRY -- WE ACTUALLY -- WE'RE GOING TO HAVE FOUR FDA PEOPLE THERE. WE INVITED THEM AND THEY LOVE COMING TO THESE MEETINGS. THEY MAY NOT GIVE YOU THE EXACT ANSWER YOU WANT, BUT THE MORE YOU PRESENT TO THEM AND THE MORE YOU REPEAT YOURSELF AND SAY THIS IS WHAT I THINK, AND IF YOU CAN GET COMPANIES, WE'RE GOING TO HAVE A FEW COMPANIES GET UP AND TALK ABOUT THEIR PRECLINICAL PROGRAMS, SO I THINK THAT DIALOGUE IS GOING TO HELP YOU, BUT IT MAY NOT GET IT TO YOU AS QUICKLY AS YOU WANT IT.

DR. CIBELLI: I REALLY APPRECIATE THE EXPLANATION. I WAS TRYING TO MAKE IT BETTER. THAT'S MY POINT.

DR. TROUNSON: BERNIE, I'M SENSITIVE TO WHAT JOSE IS SAYING. YOU KNOW, IT'S OUR MISSION TO DEVELOP AS MANY TREATMENTS IN THE CLINIC AS IS POSSIBLE IN THE TIMEFRAME THAT WE HAVE. SO IF THERE WERE STANDARD OPERATING PROCEDURES THAT WE COULD

POINT TO AND WE COULD ACTUALLY THINK ABOUT IN OUR NEGOTIATIONS WITH MAKING OUR GRANTS TO ORGANIZATIONS THAT THE GENERAL STANDARD OPERATING PROCEDURES BE MADE AVAILABLE. I THINK NOT ALL OF THESE THINGS ARE NECESSARILY COMPETITIVELY PLAYED. SO I TAKE IT AS SOMETHING YOU PEOPLE SHOULD GIVE US SOME GUIDANCE ON BECAUSE I THINK THERE ARE SOME CERTAIN CHOICES THAT ARE THERE. AND OUR MISSION IS TO GET TREATMENTS TO THE CLINIC. AND, YOU KNOW, I THINK THAT'S WHAT WE HAVE TO BE MINDFUL OF.

DR. CIBELLI: I THINK CIRM SHOULD TAKE THE INITIATIVE AND HAVE A TASK FORCE, A GROUP OF PEOPLE THAT SHOULD BE THINKING ABOUT THIS, AND HOW CAN WE HELP THE RESEARCHERS, TELL THEM WHAT TO DO, NOT TO MAKE SURE THAT THE HEPATOCYTE IS GOING TO MAKE EVERYTHING THEY NEED TO DO TO MAKE A HEPATOCYTE, BUT FOR SAFETY. WE'RE NOT PREPARED FOR THAT. THIS IS A NEW TERRITORY. AND AS A PI YOU CAN SPEND A LOT OF TIME AND MONEY TALKING TO THE FDA TO GET AN ANSWER THAT CIRM SHOULD PROVIDE OR COULD PROVIDE.

CHAIRMAN LO: OKAY. I'M SORT OF TORN BETWEEN TWO THINGS HERE. WE DO NEED TO GET TO A BREAK. PAT BECKER HAS BEEN TRYING TO SIGNAL ME WE'RE OVERDUE NOW. SO THREE QUICK COMMENTS. WE DON'T HAVE TO SETTLE IT. THIS IS JUST THE WARM-UP

SESSION. I ALSO WANT TO MAKE SURE OUR NEXT TWO SESSIONS ON CLINICAL SCIENTIFIC ISSUES AND DESIGN ISSUES AND A CASE STUDY SESSION ALSO GET THEIR FAIR TIME AND THEN WE GET TO DINNER. SO THREE QUICK COMMENTS, AND THEN I'M GOING TO TAKE A BREAK AND MOVE ON. SO ANN AND JOHN AND SOMEONE ELSE OUT THERE.

DR. KIESSLING: I JUST WANTED TO FOLLOW UP WHAT JOSE WAS SAYING JUST A LITTLE BIT BECAUSE I THINK THE GERON TRIAL IS A REALLY INTERESTING EXAMPLE OF THIS. IN FACT, THAT THEIR ANIMAL MODEL, WHEN THEY LOOKED BACK ON IT AS A THORACIC INJURY, WAS PROBABLY NOT THE MOST IDEAL ANIMAL FOR HUMAN SPINAL CORD INJURY. AND THAT COST EVERYBODY ABOUT THREE YEARS BECAUSE THORACIC INJURIES ARE LESS COMMON IN HUMANS. SO THERE'S SOME REALLY SIMPLE KINDS OF THING THAT I THINK CIRM COULD DO TO REALLY STIMULATE TRANSLATIONAL MEDICINE IN TERMS OF JUST HELPING PI'S KNOW THAT THEIR ANIMAL MODEL MAY BE APPROPRIATE FOR WHATEVER IT IS THEY'RE TRYING TO DO.

DR. CSETE: BUT WE CAN'T MAKE THAT DECISION. THE FDA HAS TO MAKE THAT DECISION, AND WE CAN AS MUCH AS POSSIBLE TRANSMIT THE INFORMATION THAT WE GATHER FROM, YOU KNOW, A MILLION DIFFERENT PLACES TO OUR INVESTIGATORS, WHICH WE ABSOLUTELY TRY

TO DO.

AND THE OTHER THING THAT WE DO ALL THE TIME INFORMALLY, JOSE, BUT IT HAS TO BE INFORMAL, IS WHEN WE KNOW THAT ONE INVESTIGATOR HOLDS SOME INFORMATION THAT MAY BE HELPFUL TO ANOTHER, WE ASK THEM TO TALK TO EACH OTHER. BUT IN TERMS OF BEING A BROKER OF CONFIDENTIAL SCIENTIFIC PRODUCT, WE CAN'T DO THAT.

DR. CIBELLI: YOU'RE PAYING FOR IT.

CHAIRMAN LO: I WANT TO CUT YOU OFF BECAUSE I DO WANT TO GET TWO MORE PEOPLE A CHANCE. WE'RE GOING TO COME BACK TO THIS AND IT'S GREAT, BUT I WANT TO MAKE SURE WE HEAR OTHER MATERIALS. ALTA AND THEN JOHN.

DR. CHARO: I JUST WANTED TO NOTE THAT IN SOME WAYS THIS DISCUSSION SEEMS TO PARALLEL THE ONE AROUND INTELLECTUAL PROPERTY; THAT IS, THERE IS A PROPRIETARY INTEREST IN SOMETHING. CIRM HAS THE CHOICE, IF IT WISHES TO, TO CONDITION THE RECEIPT OF A GRANT ON THE RELINQUISHMENT OF SOME OF OUR PROPRIETARY OR PROPERTY RIGHTS, BUT THAT'S A VERY, VERY DIFFICULT THING TO DO BECAUSE OF THE WAY IT UPSETS ALL SORTS OF INCENTIVE STRUCTURES. SO IT'S NOT STRAIGHTFORWARD AT ALL, BUT IT'S NOT AS IF THESE THINGS ARE BEYOND CIRM'S CONTROL. IT'S JUST THAT

YOU MAY COME TO THE CONCLUSION THAT THE CURRENT SYSTEM, AS BAD AS IT IS, IS BETTER THAN THE ALTERNATIVES.

BUT AT LEAST WE KNOW THAT THE FDA WAS LEARNING ON THE FLY WITH GERON. GERON HAS SAID THAT THEY'RE GOING TO PUBLISH MUCH OF THEIR SAFETY DATA, BUT THEY'RE KEEPING THE ROAD MAP TO THEMSELVES AS PROPRIETARY. BUT NO QUESTION, THAT AS NEW PEOPLE APPROACH THE FDA, THAT PROCESS OF CONVERSATION IS GOING TO GET MORE AND MORE EFFICIENT BECAUSE THERE WILL HAVE BEEN A LOT OF LEARNING ON FDA'S PART ABOUT HOW MANY ANIMALS, HOW MANY CELLS, WHAT TO WATCH FOR. AND SO THE INFORMATION THEY GIVE BACK IS GOING TO BE A WHOLE LOT BETTER. SO IT REALLY IS GOING TO GET A LOT EASIER.

DR. WAGNER: RATHER THAN BEAT THIS TO DEATH, I MEAN, I THINK THAT THE POINT IS -- ALL THE POINTS ARE WELL TAKEN I THINK, BUT JUST KNOW THAT THIS IS NOT UNIQUE TO EMBRYONIC STEM CELLS. IT'S THE EXACT SAME THING THAT WE HAVE DEAL WITH FOR EVERY OTHER STEM CELL SOURCE. AND WHAT WE HAVE TO DO IS WE HAVE TO RECREATE THE WHEEL EVERY TIME, YOU KNOW, AND TRY TO GET IT THROUGH THE FDA. AND SOMETIMES YOU'RE SUCCESSFUL, BUT THEN YOU ALSO FIND OUT THAT YOU COMPARE IT TO SOMEONE ELSE WHO PUT IN

SOMETHING SIMILAR, AND THEN, AGAIN, YOU'RE TRYING TO GUESS.

I THINK THAT WHAT YOU'RE TRYING TO ASK FOR, WHICH MAKES PERFECT SENSE ON THE SIDE OF MOVING STEM CELL THERAPIES FORWARD, IS THAT DO WE HAVE TO REINVENT THE WHEEL EVERY SINGLE TIME? CAN WE DEVELOP BEST PRACTICES? CAN WE DEVELOP THE BEST ANIMAL MODELS? INVEST IN THE ANIMAL MODELS WHICH GETS BEYOND, THEN, THE FDA BECAUSE THEN YOU'RE SAYING THIS IS SCIENTIFIC DATA THAT SAYS THIS IS THE ANIMAL MODEL FOR LOOKING AT TOXICOLOGY. THIS IS THE ANIMAL MODEL FOR LOOKING AT HEART DISEASE. THIS IS THE ANIMAL MODEL LOOKING FOR DIABETES. NO ONE HAS BEEN ABLE TO DO THAT BECAUSE IT'S ALL UNDER THE UMBRELLA OF PROPRIETARY, BUT YOU COULD DEVELOP RFP'S TO SPECIFICALLY ASK THAT QUESTION.

DR. TROUNSON: YOU KNOW, I TAKE THESE POINTS AS BEING VERY IMPORTANT. AND, OF COURSE, JOHN'S ALREADY BEEN IN THIS SPACE QUITE A BIT. IT'S ALL A MATTER OF NEGOTIATION, YOU KNOW, IN MY MIND. YOU KNOW, WHAT WE DO GOING FORWARD, I THINK, IS WHAT WE NEED TO DO IS TAKE ON WHAT IS REALLY BEST FOR DELIVERY OF WHAT WE'RE DOING. AND SO SOME THINGS WILL BE IMPOSSIBLE OR DIFFICULT, OTHERS WILL POSSIBLY BE QUITE EASY TO DO. AND I THINK IT IS

NEGOTIATION, YOU KNOW, PERHAPS EACH TIME, BUT AT LEAST INDICATIVE THAT SETTING UP SOME STANDARDS HERE WOULD BE -- I THINK WOULD BE CLEARLY HELPFUL.

CHAIRMAN LO: OKAY. I WANT TO THANK ALTA AND E. J. FOR GETTING US OFF TO SORT OF A STIMULATING START. LET'S TAKE A 15-MINUTE BREAK. SO WE'LL BE BACK AT 3:30. OKAY. THANKS VERY MUCH.

(A RECESS WAS TAKEN.)

CHAIRMAN LO: OKAY. WHY DON'T WE RECONVENE. WE'VE GOT A LOT OF EXCITING INFORMATION TO PROCESS AND THINK THROUGH. FIRST OF ALL, DOES ANYBODY HAVE A LASER POINTER? GOT ONE. OKAY. WHILE THEY'RE DOING THAT, I'M GOING TO INTRODUCE OUR NEXT SPEAKER. WE'RE NOW GOING TO SHIFT AND TALK ABOUT SCIENTIFIC AND DESIGN ISSUES IN CLINICAL TRIALS IN GENERAL AND STEM CELL CLINICAL TRIALS IN PARTICULAR. AND THEN WE'RE GOING TO FOLLOW THAT WITH SOME CASE STUDIES THAT MARIE CSETE AND E. J. READ HAVE PREPARED FOR US.

OUR NEXT SPEAKER IS DR. BRUCE DOBKIN, WHO'S PROFESSOR OF NEUROLOGY AT UCSF.

DR. DOBKIN: UCLA.

CHAIRMAN LO: OKAY. UCLA, GEFFEN SCHOOL OF MEDICINE. GOOD TRY.

MS. LANSING: I'M GLAD YOU CORRECTED THAT.

CHAIRMAN LO: WHERE HE'S THE DIRECTOR OF THE UCLA NEUROLOGICAL REHABILITATION AND RESEARCH PROGRAM AND CO-DIRECTOR OF THEIR STROKE CENTER. HE'S BEEN INVOLVED IN LOTS OF CLINICAL TRIALS IN NEUROLOGICAL DISEASE AND ACTUALLY HAS BEEN PART OF A GROUP THAT'S ADDRESSED THE ISSUE OF THE DESIGN OF CLINICAL TRIALS IN SPINAL CORD INJURY.

HE IS EDITOR IN CHIEF OF NEURAL REHABILITATION AND NEURAL REPAIR, AND HE'S BEEN ALSO A BASIC SCIENTIST WHO'S BEEN FUNDED CONTINUOUSLY BY NIH.

SO I'VE ASKED BRUCE TO SORT OF REALLY GIVE US A PRIMER ABOUT CLINICAL TRIALS. AND BECAUSE SOME OF US ON THE PANEL ARE EXPERTS AND OTHERS OF US ARE NOT, BRUCE IS REALLY GOING TO SORT OF MAKE SURE WE GET THE FUNDAMENTALS. AND WE'RE GOING TO TRY AND HAVE ENOUGH TIME TO ASK QUESTIONS OF HIM IN THE FORTHCOMING PANEL. SO, BRUCE, THANKS VERY MUCH FOR COMING, AND WE'RE GOING LOOKING FORWARD TO YOUR TALK.

DR. DOBKIN: I'VE BEEN ASKED TO ADDRESS THE QUESTION OF WHY DO HUMAN STEM CELL APPLICATIONS REQUIRE RANDOMIZED CLINICAL TRIALS. I MEAN AFTER ALL THEY'RE CELLS. THEY OUGHT TO WORK. AND SO YOU JUST POP THEM IN AND YOU GET WHATEVER OUTCOME YOU'RE

LOOKING FOR. AND I'M GOING TO GIVE YOU THE UNDERSIDE, THE DARK SIDE OF WHAT HAPPENS WHEN YOU DON'T DO RANDOMIZED CLINICAL TRIALS. AND EVEN IN THE COURSE OF THIS QUESTION, THE ETHICS OF THE WAY PRESENT RESEARCH IN STEM CELL PRECLINICAL AND TRANSLATIONAL STUDIES ARE GOING ON.

I THINK THAT WHEN WE'RE FINISHED, YOU WILL HAVE AN AMAZING AMOUNT OF COCKTAIL PARTY CONVERSATIONAL TALK BECAUSE I'M GOING TO SHOW YOU SOME REALLY AWFUL STUFF. I'VE HAD THE GOOD FORTUNE TO BE ABLE TO DEVELOP SIX OR EIGHT RANDOMIZED CLINICAL TRIALS IN NEUROPROTECTION AND IN PREVENTION, BOTH IN STROKE AND SPINAL CORD INJURY AND IN RECOVERY OF SPINAL CORD INJURY. AND THE PAST TWO YEARS I WAS ON A LEAVE OF ABSENCE TO DEVELOP WHAT WAS CALLED THE ADELSON MEDICAL RESEARCH FOUNDATION, WHICH WAS DESIGNED AROUND THE NOTION THAT RESEARCH -- THAT THERE'S BEEN NO RESEARCH ON HOW TO DO RESEARCH AND THAT WE DON'T REALLY KNOW THE BEST WAY TO GO ABOUT SOLVING PROBLEMS DOING EITHER WITHIN OUR PRECLINICAL STUDIES OR IN OUR TRANSLATIONAL STUDIES.

AND SO ONE OF THE IDEAS WAS TO CREATE A MODEL FOR CARRYING OUT RESEARCH IN A WAY THAT IT COULD BE MEASURED, THE OUTCOMES COULD BE MEASURED,

AND THAT APPROACH WAS A COLLABORATIVE MODEL. AND MUCH OF IT CENTERED ON NEURAL REPAIR. AND SO I'LL BE REFERRING TO THAT A LITTLE BIT.

SO A PATIENT CAME TO ME A COUPLE OF YEARS AGO AND SAT DOWN. AND I SAID, "WHAT CAN I HELP YOU WITH?" HE HAD HAD A STROKE. AND HE SAID, "DOC, I NEED THOSE STEM CELLS." I WAS A LITTLE TAKEN BACK, BUT I'VE HAD MANY CONVERSATIONS WITH PATIENTS WHO ARE DESPERATE, DISABLED, OR DYING. THEIR HOPE IS WANING. AND THIS GUY WANTED ME TO GIVE HIM WHAT THE MEDIA AND WHAT THE PEOPLE WHO SELL STEM CELLS OFFSHORE SAY IS READY FOR PRIME TIME. AND SO THE IDEA THAT HE HAD WAS AND THAT MANY PEOPLE HAVE, ESPECIALLY IN THE SPINAL CORD INJURY COMMUNITY, IS THAT THERE'S SOME SORT OF CONSPIRACY IN THE MEDICAL ESTABLISHMENT TO WITHHOLD STEM CELL TREATMENTS.

SO WHERE DOES THE MEDICAL ESTABLISHMENT STAND ON THIS? WELL, I THINK WE ALL BELIEVE AND HOPE THAT STEM CELLS AND MORE DIFFERENTIATED CELLS WILL HAVE A NICHE IN THE NEAR FUTURE. WE'RE GOING TO NEED THE MULTICENTER RANDOMIZED CLINICAL TRIALS FIRST RATHER THAN PEOPLE JUST SHOWING UP ON OUR DOORSTEP AND ASKING FOR THEM STEM CELLS.

AND THE OTHER THING IS WHEN YOU TALK ABOUT NEUROLOGICAL DISEASES, WE HAVE TO KEEP IN MIND THAT

THE BRAIN IS CONSTANTLY WIRED AND SYNAPSED TO LEARN. IT'S VERY DIFFERENT THAN ANY OTHER ORGAN. I COULD PROBABLY GET MOST OF YOU, EXCEPT MAYBE IF IT WAS A CARDIOLOGIST HERE, TO EVEN THINK THAT THE BRAIN WAS THE MOST IMPORTANT ORGAN IN THE HUMAN BODY. YOU KNOW, IT MAKES US WHAT WE ARE. AND SO WE HAVE TO ASK OURSELVES ARE STEM CELLS REALLY THE ANSWER OR THE ONLY OPTION FOR PATIENTS, AND THERE ARE MANY, MANY OTHER OPTIONS, INCLUDING OTHER BIOLOGICAL OPTIONS, THAT WE WANT TO BEAR IN MIND AS WE THINK ABOUT WHO SHOULD GET STEM CELLS FOR NEUROLOGICAL DISEASES.

AND THEN I'LL ASK THE QUESTION WHETHER OUR RESEARCH IS REALLY MAXIMIZING IN AN ETHICAL AND TRANSPARENT AND MOST PRODUCTIVE WAY THE PATH TO USING STEM CELLS FOR NEUROLOGICAL DISEASES. I'LL TRY TO COVER THAT AND MAYBE ANSWER THIS QUESTION TO MY PATIENT AS TO WHY I CAN'T GIVE HIM THEM STEM CELLS.

SO IF WE THINK ABOUT REPAIRING THE NERVOUS SYSTEM, WHETHER YOU HAVE A STROKE AND YOU'RE HEMIPLEGIC OR YOU HAD A SPINAL CORD INJURY AND YOU'RE PARAPLEGIC, OR YOU HAVE A DEGENERATIVE DISEASE LIKE PARKINSON'S OR ALZHEIMER'S, OR YOU HAVE MULTIPLE SCLEROSIS THAT FLUCTUATES OVER TIME,

DISEASES THAT PROGRESS, DISEASES THAT ARE STATIC, DISEASES THAT VARY, THERE ARE A NUMBER OF WAYS TO THINK ABOUT WHAT WE MIGHT PROVIDE IN TERMS OF BIOLOGICAL ACTIVATION. BUT ONE WOULD BE TO REPLACE CELLS. AND THAT COULD BE CELLS THAT ARE PUT INTO A NETWORK THAT REPLACE CELLS IN THAT NETWORK. THEY COULD BE CELLS THAT SECRETE SOMETHING THAT PRODUCE A TROPHIC FACTOR THAT ENLIVENS THE CELLS AROUND IT. THEY COULD PRODUCE NEUROTRANSMITTERS THAT SEND MESSAGES BETWEEN CELLS. AND SOME OF THEM COULD HAVE BIOLOGICAL EFFECTS AND DIFFERENTIATE INTO CELLS THAT ARE NEEDED LIKE NEURONS OR OLIGODENDROCYTES, THE CELLS THAT PUT MYELIN AROUND CELLS AND ALLOW THEM TO CONDUCT THEIR IMPULSES.

BUT MAYBE MORE IMPORTANT WILL BE TO TRY TO REGROW AXONS, THE OUTCROPPINGS OF THE NERVE CELLS THAT CARRY MESSAGES FROM ONE CELL TO ANOTHER, AND THE DENDRITES THAT ARE LIKE BRANCHES OF A TREE OFF THOSE AXONS AND WHERE ALL OF THE LEARNING AND MEMORY IS DONE IN THE NERVOUS SYSTEM.

AND THEN FINALLY, WHAT IS ESPECIALLY DIFFERENT ABOUT THE NERVOUS SYSTEM WHEN YOU THINK ABOUT BIOLOGICAL INTERVENTIONS BOTH FOR DESIGNING STEM CELL STUDIES AS WELL AS FOR JUST HELPING PATIENTS IS THAT THE BRAIN IS A LEARNING MACHINE.

AND SO UNLIKE MOST OTHER ORGANS, IT'S DESIGNED TO GAIN SKILLS. IT'S DESIGNED TO REMEMBER WHAT WE DID. AND THAT REQUIRES TRAINING. AND TRAINING ALTERS CIRCUITRY. WHILE THERE IS A LOT OF HARD WIRING IN THE NERVOUS SYSTEM, THERE'S A TREMENDOUS AMOUNT OF ADAPTABILITY AND SO-CALLED PLASTICITY WITHIN THE NERVOUS SYSTEM.

SO INDIVIDUAL CIRCUITS, GROUPS OF CIRCUITS THAT FORM NETWORKS, ALL OF WHICH REPRESENT BEHAVIORS, CAN BE CHANGED REMARKABLY AND RATHER QUICKLY BY SIMPLY HEARING SOMETHING. I MAY TELL YOU SOMETHING TODAY THAT CONNECTS WITH OTHER MESSAGES THAT YOU'VE HEARD IN THE PAST, WITH THINGS YOU KNOW ABOUT, WITH THINGS YOU'D LIKE TO KNOW MORE ABOUT, WITH SOMEBODY THAT YOU KNOW WHO HAS SOME PROBLEM LIKE THIS, AND YOU WILL CONSTANTLY BE MASSAGING THAT INFORMATION INTO NEW LEARNING, HOPEFULLY SOMETHING THAT I SAY WILL ACTUALLY BE REMEMBERED.

SO I NEED TO JUST QUICKLY SHOW YOU SOME EXAMPLES OF THIS WITHOUT GETTING TOO COMPLICATED ABOUT WHAT IT'S ALL ABOUT. BUT THIS IS -- LET'S PRETEND THIS IS THE BRAIN OF A RAT SITTING OVER A PARTICULAR AREA CALLED THE PRIMARY MOTOR CORTEX THAT REPRESENTS MOVEMENTS FOR THE RAT'S FORELIMB. AND THE RAT WILL REACH FOR THINGS AND GRAB FOOD AND PUT

IT IN ITS MOUTH WITH THAT FORELIMB, WALKS ON IT. AND THIS IS THE ROSTRAL AND THE CAUDAL FORELIMB AREA. SO THAT IF I TOOK A LITTLE ELECTRODE, TINY, TINY ELECTRODE, PUT IT OVER THE SURFACE OF THE BRAIN, I COULD DO LITTLE STIMULATIONS AND CAUSE MOVEMENTS IN PARTS OF THE ANIMAL'S FOREPAW AND LEG AND TRUNK, DEPENDING ON WHERE I STIMULATED.

SO THIS AREA HAVING BEEN STIMULATED REPRESENTS MOVEMENTS FOR THE ELBOW, SHOULDER, AND FOREPAW, WRIST AND SORT OF CLAW OR PAW OF THE RAT. OVER HERE MAKE A SMALL LITTLE STROKE IN THE TISSUE AND DESTROY THAT TISSUE, AND NOW THE RAT CAN'T USE ITS FOREPAW VERY WELL. BUT OVER TIME AND TRAINING, AREAS THAT HAD NOT REPRESENTED THE MOVEMENT OF THAT FOREPAW THAT MAYBE REPRESENTED MOVEMENTS OF THE SHOULDER TAKE OVER SOME OF THOSE MOVEMENTS OF THE FOREPAW. OTHER AREAS COME IN AND INVADE THAT REGION, AND THE ANIMAL RECOVERS MUCH OF ITS FUNCTION. SO EVEN THOUGH WE PUT A HOLE, LITERALLY DESTROYED THE NEURONS THAT REPRESENTED THOSE MOVEMENTS WHEN WE STIMULATED THEM, OTHER NEURONS MUST HAVE CONTRIBUTED TO THAT MOVEMENT AS WELL, AND THEY'RE ABLE TO PARTICIPATE BY SENDING AXONS DOWN INTO THE SPINAL CORD IN THAT MOVEMENT.

IF WE REMOVE ONE NEUROTRANSMITTER CALLED

ACETYLCHOLINE FROM ITS ABILITY TO BE RELEASED IN THAT AREA, IT TURNS OUT THAT THIS AREA DOESN'T EXPAND. IT SORT OF STAYS ABOUT THE SAME AND THE ANIMAL DOESN'T IMPROVE AS MUCH. AND IF YOU LOOK AT PERCENT RECOVERY, OVER HERE WE CAN SEE THE ANIMAL MAKES A LARGE RECOVERY, ABOUT 60 PERCENT. WHEN IT PRACTICES AFTER ITS INJURY, IF IT HAS ACETYLCHOLINE AVAILABLE, BUT IT DOESN'T RECOVER EVEN WITH PRACTICE IF IT DOESN'T HAVE THE ACETYLCHOLINE AVAILABLE. AND IF IT DOESN'T PRACTICE, IT DOESN'T RECOVER.

SO ALL OF THESE THINGS ARE GOING TO GO INTO ANY NOTION OF TRYING TO DRIVE STEM CELLS TO HAVE A PLACE IN LEADING TO IMPROVEMENT OVER TIME IN PATIENTS. LEARNING AND PRACTICE CAN DRIVE PLASTICITY, AND A NUMBER OF NEUROTRANSMITTERS, CHEMICAL TRANSMITTERS, PLAY AN IMPORTANT ROLE IN UNDERLYING THAT PLASTICITY AND CREATING MOLECULAR CHANGES THAT LEAD TO LEARNING.

HERE'S AN EXAMPLE IN A CHILD. THIS CHILD HAD HALF ITS BRAIN REMOVED AT THE AGE OF SIX FOR WHAT'S CALLED RASMUSSEN'S ENCEPHALITIS, SO IT HAD EPILEPSY. HE HAD EPILEPSY, AND THE ONLY WAY TO STOP IT WAS REMOVE THIS PART OF THE BRAIN. OVER HERE WE SEE A FUNCTIONAL MRI SCAN THAT SHOWS THE ACTIVATION -- WHAT PARTS OF THE BRAIN ARE ACTIVATED

WHEN THE FOOT MOVES A LITTLE BIT. WHEN THE CHILD MOVES THE WEAK ANKLE, WHICH IS IN SORT ORANGE RED HERE, WE SEE THE PART OF THE BRAIN THAT'S ACTIVATED. IT'S KIND OF OUTSIDE THE NORMAL FOOT AREA.

BUT THIS SIDE OF THE BRAIN, THE SAME SIDE AS THE FOOT, IS CONTROLLING THAT FOOT. IN FACT, THIS SIDE SOME OF THE BRAIN IS CONTROLLING BOTH LEGS. SO THIS CHILD WALKS FINE, TALKS FINE, HAS TROUBLE USING HIS HAND AND LITTLE TROUBLE USING THE FOOT. THIS IS NOW FOUR YEARS LATER. SO YOU WOULD THINK THAT THE MAXIMUM AMOUNT OF LEARNING THAT THIS CHILD COULD HAVE TO RECOVER FUNCTION MUST HAVE TAKEN PLACE.

BUT WE THEN TOOK A GROUP OF CHILDREN AND TRAINED THEM TO RUN ON A TREADMILL, KICK A BALL, DO A VARIETY OF THINGS TO SEE IF WE COULD DRIVE THIS ADAPTABILITY EVEN MORE. AND LO AND BEHOLD, NOW WHEN THE CHILD, AFTER JUST A COUPLE WEEKS OF TRAINING, MOVES THE LEFT FOOT, WHICH IS NORMALLY CONTROLLED BY THE RIGHT SIDE OF THE BRAIN, MOVES THE LEFT FOOT, YOU SEE THIS RED AREA HERE. WHEN IT MOVES THE RIGHT FOOT, YOU SEE THE YELLOW AREA, AND THEN IN THE ORANGE HERE YOU SEE THE OVERLAP. THESE NEURONAL ASSEMBLIES CONTROL BOTH SIDES OF THE BODY. AND WE WERE ABLE TO INCREASE THE PLASTICITY, THE

ADAPTABILITY IN THAT SIMPLY BY PRACTICE.

NOW, IF YOU PUT STEM CELLS INTO THIS PART OF THE BRAIN AND HOPE THAT YOU WOULD GET BETTER MOVEMENT, YOU COULDN'T POSSIBLY GET A BETTER RESULT THAN SIMPLY DOING WHAT WE ALL DO WHEN WE WANT TO LEARN A SKILL. WE PRACTICE IT.

SO WE HAVE TO KEEP THAT IN MIND AS WE THINK ABOUT BOTH APPLICATIONS FOR STEM CELLS AND HOW WE'RE GOING TO DRIVE THOSE STEM CELLS TO ACTUALLY PRODUCE SOME FUNCTION.

THIS IS JUST SOMETHING TO GIVE YOU A SENSE OF WHAT UNDERLIES SOME FORMS OF PLASTICITY. SO THIS IS THE CENTRAL CANAL OF THE SPINAL CORD. OH, AND THIS SIDE OF THE SPINAL CORD, THIS IS IN A RAT -- I'M SORRY -- THIS IS IN A MONKEY. THE SPINAL CORD WAS TRANSECTED SO THAT THERE IS NO -- SO THAT THAT SIDE OF THE BODY IS PARALYZED. ANIMAL CAN'T USE ITS LEG. IT RECOVERS OVER TIME. THIS IS THE NORMAL SIDE. THERE IS AXONS THAT ARE COMING DOWN FROM THE BRAIN FROM THIS SIDE OF THE BRAIN, CROSSING OVER, COMING DOWN THE SPINAL CORD, AND ENTERING INTO THE NERVE CELLS OF THE SPINAL CORD. AND THEN AFTER THE INJURY, THEY START CROSSING TO THE OTHER SIDE OF THE SPINAL CORD THAT LOST ITS INPUT FROM THE OTHER SIDE OF THE BRAIN SO THAT SPONTANEOUSLY AXONS ARE

REGENERATING WITHIN THE SPINAL CORD TO ALLOW FUNCTIONAL USE OF THAT LEG.

NOW, IF WE WANTED TO USE STEM CELLS TO GET THIS RESULT BY IMPLANTING THEM IN THE ORIGINAL INJURY, WE'D BE HARD-PRESSED TO GET AS MUCH REGENERATION AS WE'RE GETTING SPONTANEOUSLY, AND THERE ARE WAYS TO MANIPULATE THAT. SO AGAIN, AXONS CAN REGENERATE. WE DIDN'T KNOW UNTIL RECENTLY. SO IF WE WERE TO LOOK AT A SPINAL CORD INJURY MODEL, AND THIS IS A CARTOON, HERE'S THE BRAIN, HERE'S DOWN IN THE SPINAL CORD AT A SPOT WHERE MAYBE WE HAD AN INJURY. HERE'S DOWN BELOW THAT PART OF THE SPINAL CORD THAT NORMALLY WOULD HAVE GOTTEN INFORMATION FROM THE BRAIN TO MOVE, SAY, THE LEGS OR THE HAND. WE MIGHT SEE THAT THERE ARE A VARIETY OF WAYS TO ENHANCE RECOVERY OF FUNCTIONS. SOME HAVE TO DO WITH JUST OPTIMIZING USE OF RESIDUAL PATHWAYS, SPARED PATHWAYS COMING FROM THE BRAIN DOWN THE SPINAL CORD OF WHICH THERE ARE MANY THAT COULD BE PRESERVED.

ANOTHER IS THAT WE CAN INCORPORATE SPROUTS OF AXONS THAT OCCUR WITH TRAINING. WE CAN GET TRAINING-INDUCED CHANGES. WE CAN ALSO USE CELLS TO DO THAT, AND WE CAN ALSO USE VARIOUS MOLECULES TO TRY TO REGENERATE AXONS ACROSS THAT AREA. BUT WHAT I'M GETTING AT IS THERE ARE A DOZEN OR MORE POSSIBLE

WAYS TO LEAD TO IMPROVED FUNCTION AFTER SPINAL CORD INJURY THAT MAY NOT INVOLVE CELLS AT ALL, BUT FOR WHICH SOME CELLS COULD HELP.

I'M GOING TO GET BACK TO THAT GERON STUDY TOO BECAUSE I KNOW A FAIR AMOUNT ABOUT THAT. AND IF WE HAD A STROKE MODEL, WE'D SEE THAT IF WE PUT STEM CELLS IN THE HOLE OF A STROKE, WE MIGHT GET SOME MOTOR RECOVERY, BUT WE CAN ALSO GET SOME MOTOR RECOVERY BY DERIVING REGENERATION OF AXONS AND RETRAINING THE SPARED PATHWAYS ON THE AFFECTED SIDE OF THE BRAIN.

SO WHAT MIGHT WE EXPECT FROM ENDOGENOUS STEM CELLS THAT ARE DERIVED FROM WITHIN THE NERVOUS SYSTEM ITSELF, FOR WHICH THERE ARE MANY EXAMPLES OF THIS NOW WHERE OUR OWN BODIES ARE CONSTANTLY PRODUCING STEM CELLS AND AFTER INJURY PRODUCING STEM CELLS THAT MIGRATE AND SEEM TO INCORPORATE IN SOME PARTS OF THE BRAIN, OR EXOGENOUSLY IMPLANTED STEM CELLS THAT WOULD ALLOW US TO PROVIDE SUBSTANCE.

SO WHAT DO WE WANT THOSE CELLS TO DO? WELL, WE MIGHT WANT TO REPLACE SOME LOST OR POORLY FUNCTIONING NEURONS THAT ARE WITHIN A SMALL REGION OF THE BRAIN. SO WE JUST HAVE TO GET THEM INTO A SMALL SPOT, FOR EXAMPLE, IN PARKINSON'S DISEASE WHERE YOU TRY TO REPLACE DOPAMINERGIC NEURONS OR IN

ALS WHERE YOU MIGHT TRY TO REPLACE MOTOR NEURONS OR IN A SPINAL CORD INJURY WHERE YOU MIGHT TRY TO FILL A GAP AND ALLOW AXONS TO CROSS IT BY LINKING UP WITH CELLS. YOU MAY WANT TO REPLACE A NEUROTRANSMITTER LOCALLY, AND THERE'S ACTUALLY NOW A HUMAN CLINICAL TRIAL GOING ON WHERE FIBROBLASTS HAVE BEEN GENETICALLY MODIFIED TO SECRETE ACETYLCHOLINE AND IMPLANT IN THE BRAINS OF PEOPLE WITH ALZHEIMER'S DISEASE TO REPLACE THE ACETYLCHOLINE THAT'S MISSING BECAUSE CELLS THAT PRODUCE THAT ACETYLCHOLINE ARE DYING RATHER QUICKLY. IT'S A GREAT REPLACEMENT STRATEGY.

A BIT OF A PROBLEM IS THAT ALZHEIMER'S DISEASE INVOLVES FAR MORE THAN JUST THAT PARTICULAR PATHWAY; AND EVENTUALLY, EVEN IF THIS WORKED FOR A SHORT TIME AND MOLLIFIED THE DISEASE, IT CERTAINLY WOULDN'T CURE ANYBODY, BUT IT MIGHT GIVE PEOPLE SOME EXTRA YEARS OF QUALITY OF LIFE.

WE MAY WANT TO STRENGTHEN A NETWORK. WE CAN USE CELLS TO PRODUCE GROWTH SUBSTANCES AND SUBSTANCES THAT ABET LEARNING AND SKILLS LEARNING. WE MIGHT WANT TO PROTECT AREAS OF THE BRAIN AND AUGMENT MOLECULES THAT ALSO ARE INVOLVED IN PLASTICITY, AND THIS HAS BEEN DONE WITH BONE MARROW STROMAL CELLS INJECTED IN THE INFARCT AREA OF PEOPLE

WITH STROKE.

WE MIGHT ALTER SIGNALS TO PROMOTE REGENERATION AND HAVE THE CELLS ACTUALLY MAKE SUBSTANCES THAT WE KNOW TURN ON GROWTH SIGNALS WITHIN AXONS AND HAVE THEM REGENERATE. WE CAN BRING A GAP, AS I TALKED ABOUT, BY PUTTING CELLS INTO A HOLE AN EMBRYONIC TISSUE, AND EMBRYONIC STEM CELLS HAVE BEEN USED FOR THIS ALONG WITH MANMADE FIBERS. AND WE MAY WANT TO REPLACE SOMETHING THAT'S MISSING LIKE A CHILD THAT'S BORN WITHOUT ANY MYELIN. WE MAY WANT TO USE A PARTICULAR KIND OF CELL LIKE OLIGODENDROCYTES THAT MAKE MYELIN IN CERTAIN DISEASES. I'LL TALK ABOUT PELIZAEUS-MERZBACHER DISEASE, ALL OF WHICH WE'LL BECOME EXPERTS IN.

SO THE QUESTION IS ARE THERE ANY DIFFERENCES BETWEEN THESE MOUSE AND RAT BRAINS THAT ALL THIS PRECLINICAL WORK IS DONE ON AND HUMANS? AND HERE'S AN EXAMPLE. THAT IS A MOUSE BRAIN AND SPINAL CORD. THAT'S A RAT BRAIN AND SPINAL CORD. THIS IS ONE SLICE TAKEN FROM FRONT TO BACK OF A HUMAN BRAIN. THAT MOUSE BRAIN IS ONE-THOUSANDTH THE VOLUME OF THE HUMAN BRAIN. AND SO THERE'S NO WAY TO REALLY BE ABLE TO -- WE'VE JUST GOT TO SAY THERE IS DIFFERENCES BETWEEN MICE AND MEN. AND I THINK THIS IS A GOOD VISUALIZATION OF CERTAINLY SPACE AND

DISTANCE. DIFFERENCES IN INJECTING CELLS FOR GROWING AXONS IN A MOUSE OR A RAT IS A VERY DIFFERENT PROPOSAL THAN IN HUMANS.

SO IF YOU WANT AXONS TO GROW FOR SPINAL CORED INJURY, THEY NEED TO REGENERATE JUST TO GO FROM ONE LEVEL TO THE NEXT BY ABOUT 2 TO 3 CENTIMETERS. THAT RAT BRAIN IS LESS THAN 2 CENTIMETERS.

AND SO IT'S VERY EASY -- HERE'S KIND OF A LIST OF PROBLEMS THAT COME ABOUT WITH ANIMAL MODELS. AND IN A SENSE A LOT OF PRECLINICAL STUDIES, CERTAINLY IN NEUROLOGICAL DISEASES, ARE DONE IN ANIMAL MODELS, AND THE RESULTS ARE REALLY UNCERTAIN. AND THIS IS BECAUSE THE ANIMAL MODELS USE A PARTICULAR SINGLE KIND OF RAT OR MOUSE, A PARTICULAR STRAIN OR TRANSGENIC MOUSE. THE RATS AND MICE LIVE A COMPLETELY DIFFERENT LIFE THAN THEY NORMALLY DO. I HAVE A COUPLE MICE IN MY BASEMENT. I CANNOT CATCH THEM. THEY'RE REALLY SMART. A LABORATORY RAT, IT'S FEARLESS. IT'S ECOLOGICALLY DISABLED. IT HAS NO IDEA HOW TO BEHAVE LIKE A REAL MOUSE TO FEND FOR ITSELF, TO FIND FOOD. IT'S NEVER LEARNING ANYTHING UNLESS AN EXPERIMENTER COMES ALONG AND TRYING TO TEACH IT SOMETHING.

AND SO THAT CHANGES THE BRAIN. IT CHANGES

THE GENETICS OF THE BRAIN WHEN YOU'RE ISOLATED LIKE THAT. AND SO THE REAL QUESTION IS WHETHER THOSE MODELS OF INJURY AND REPAIR IN RODENTS ARE REALLY SIMILAR ENOUGH TO WHAT HAPPENS IN HUMAN DISEASE TO HELP US UNDERSTAND THAT.

WHEN YOU LOOK AT ANIMAL MODELS, THE DOSE AND TIMING AND WHERE YOU INJECT CELLS CAN BE VERY DIFFERENT THAN WHAT YOU COULD POSSIBLY DO UNDER THE HUMAN CONDITION. AND SO MANY OF THE STUDIES THAT WILL BE DONE FOR NEURAL REPAIR AND FOR USE OF CELLS IS GOING TO BE DONE -- THEY SORT OF WORKED IN THE ANIMAL MODEL, BUT YOU COULDN'T POSSIBLY SET THE SAME EXPERIMENT UP IN A HUMAN. AND SO YOU'RE LIKELY TO FAIL.

ALSO, MOST ANIMAL STUDIES AREN'T REALLY DONE AS RANDOMIZED CLINICAL TRIALS. YOU KNOW, IF THE MOUSE OR RODENT DIES IN SURGERY, YOU THROW IT AWAY. YOU CAN'T DO THAT WITH PEOPLE. IT'S MESSY. YOU CAN'T -- EVERYBODY COUNTS. IF THE ANIMAL -- IF SOME OF THE ANIMALS DON'T GET INJURED AFTER YOU -- DON'T SEEM TO HAVE MUCH OF AN INJURY AFTER YOU TIE OFF A BLOOD VESSEL OR BOP THEM ON THE HEAD, YOU DON'T USE THEM. WHAT YOU'RE TRYING TO DO IS GET THE PERFECT INJURY. AND YOU CREATE THESE SORT OF STRANGE BOOKENDS. YOU CREATE A MODEL SO THAT

THERE'S SOMETHING WRONG ENOUGH WITH IT THAT YOU KEEP DOING IT OVER AND OVER AGAIN UNTIL YOU GET A MODEL THAT'S JUST RIGHT, NOT TOO BAD, NOT TOO GOOD. AND IT RESPONDS TO SOMETHING YOU'RE DOING AND HAS A BEHAVIOR YOU CAN MEASURE. AND SO WE JUST DON'T DO THAT WITH PEOPLE.

NOW, YOU LOOK AT BIOLOGICAL PROCESSES. THAT'S VERY VALUABLE TO UNDERSTAND HOW DOES THE BRAIN WORK? HOW DO MOLECULES WORK? BUT IN A RANDOMIZED CLINICAL TRIAL IN HUMANS, YOU HAVE ALL COMERS. YOU HAVE PEOPLE WHO ARE VERY DIVERSE IN THEIR DISEASES. EVEN IF THEY'RE THE SAME AGE AND SEX AND THE SAME LENGTH OF DURATION OF THEIR DISEASE, THEIR NERVOUS SYSTEMS WILL ALWAYS BE DIFFERENT AND THEIR GENES WILL BE DIFFERENT. THE DRUGS THAT THEY'RE TAKING WILL BE DIFFERENT.

ANOTHER THING IS THAT IN MOST ANIMAL STUDIES, THE ANIMALS AREN'T TRAINED TO DO ANYTHING. YOU JUST GIVE THEM SOMETHING AND THEN DO AN OUTCOME MEASURE. IN HUMAN STUDIES I'M GOING TO SHOW YOU WE ARE GOING TO HAVE TO TRAIN PEOPLE TO MAKE USE OF THOSE CELLS, OR THEY'RE NOT GOING TO DO ANYTHING. THEY'RE JUST GOING TO SIT THERE. THEY HAVE TO BE BECOME PART OF THE LEARNING MACHINERY, AND WE HAVE TO FIGURE OUT HOW TO DO THAT.

AND ONE OF MY GREATEST PET PEEVES IS THAT TO DATE THE THREE OR FOUR HUMAN STUDIES USING STEM CELLS OR USING PRECURSORS OF OLIGODENDROCYTES OR NEURONS HAVE ALL BEEN TESTED IN A SINGLE ANIMAL MODEL, IN A SINGLE LABORATORY, BY A SINGLE INVESTIGATOR, AND THEN BACKED BY VENTURE CAPITALISTS, BY A PHARMA COMPANY. AND SO NO ONE HAS TRIED TO REPLICATE WHAT'S BEEN DONE. IN FACT, WHEN YOU LOOK ACROSS NEURAL REPAIR STUDIES OR NEURAL PROTECTION STUDIES, THEY'RE NOT REPLICABLE. WHAT WORKS IN ONE LAB TENDS NOT TO WORK IN ANOTHER. IT'S ASTOUNDING. I MEAN THESE ARE THE MOST PERFECT SET-UP EXPERIMENTS. I JUST EXPLAINED HOW WE GET DOWN TO THIS FINE LITTLE PROBLEM THAT THEY HAVE THAT WE CAN TREAT, AND YET IN THE EAST COAST YOU CAN'T REPLICATE WHAT YOU DID ON THE WEST COAST.

BUT DRUG COMPANIES WILL KEEP GOING AHEAD FOR REASONS OF INTELLECTUAL PROPERTY RIGHTS AND PROTECTION AND SECRECY WILL NOT LET OTHER PEOPLE USE THOSE CELLS TO SEE IF THEY CAN REPRODUCE WHAT'S DONE. SO WE ARE IN THE POSITION OF POTENTIALLY GIVING PEOPLE LIKE GERON CELLS, CELLS THAT NO ONE HAS EVERY TESTED OUTSIDE OF GERON AND ITS LABORATORY. AND ONLY THE FDA KNOWS WHAT THE RESULTS OF THOSE STUDIES WERE.

WHAT ARE SOME OF THE POTENTIAL COMPLICATIONS OF CELLULAR INTERVENTIONS, THEN, FOR PEOPLE? THESE ARE THINGS THAT HAVE HAPPENED IN ANIMALS. THEY'RE CERTAINLY LIKELY TO HAPPEN IN PEOPLE. SO ONE IS MALADAPTIVE PLASTICITY. WE MAY INDUCE PAIN. WE MAY INDUCE SEIZURES. WE'VE ALREADY INDUCED MOVEMENT DISORDERS IN PARKINSON'S DISEASE. WE MAY INDUCE HYPERTONICITY AND SPASMS, SPASTICITY AND ODD MOVEMENT DISORDERS, AND WE MAY DEVELOP AUTONOMIC DYSREFLEXIA IN SPINAL CORD INJURY PATIENTS WHERE THEIR BLOOD PRESSURE FLIES ALL OVER THE PLACE BECAUSE WE'RE MESSING AROUND WITH A SYSTEM THAT TRIES TO GET INTO EQUILIBRIUM, AND NOW WE'RE GOING TO DO THINGS THAT EXCITE OR INHIBIT PATHWAYS, AND WE DON'T REALLY KNOW WHAT THEY ARE. WE CAN ONLY LOOK AT SOME OUTCOME MEASURE THAT'S A BEHAVIOR. WE DON'T HAVE ANY BIOLOGICAL MEASURES OF THAT.

WORST THING THAT COULD HAPPEN IS THAT WE'LL MAKE THEIR PHYSICAL OR COGNITIVE IMPAIRMENTS OR THEIR DISABILITIES RELATED TO THAT EVEN WORSE. WE'LL PUT A HOLE IN THE NERVOUS SYSTEM THAT WILL CAUSE INFLAMMATION, OR WE'LL MAKE THE CELLS -- THE CELLS WILL MAKE SOMETHING THAT ACTUALLY DOES HARM TO NEIGHBORING CELLS.

THE IMMEDIATE RISKS HAVE TO DO WITH

REJECTION OF THE CELLS. AND MOST OF THE STUDIES THAT ARE GOING INTO PLAY RIGHT NOW PROVIDE IMMUNOTHERAPY TO TRY TO HAVE THE CELLS SURVIVE. I'M GOING TO TELL YOU ABOUT A CELL STUDY IN CHINA WHERE FIVE OUT OF SEVEN OF THE PATIENTS WHO GOT CELLS INTO THEIR SPINAL CORD DEVELOPED MENINGOENCEPHALITIS AND OTHER COMPLICATIONS. THAT'S AN INFLAMMATION THAT'S LIFE-THREATENING. IMMUNE RESPONSES, LOCAL INFECTIONS, AND GROWTH OF TUMORS. THERE NOW HAVE BEEN SEVERAL TUMORS REPORTED IN DIFFERENT PATIENTS WHO GOT STEM CELLS AND PRECURSOR CELLS. AND THEN PUTTING VIRUSES IN THERE, MAYBE HEPATITIS, MAYBE AIDS, MAYBE SOMETHING ELSE.

AND THEN ANOTHER IMPORTANT THING IS THAT WHEN YOU PUT CELLS INTO A NEURAL ENVIRONMENT, THEY TAKE CUES FROM THEIR SURROUNDS. CELLS TALK TO EACH OTHER CONSTANTLY, BATHING EACH OTHER WITH MESSAGES, NEUROTRANSMITTERS, VARIOUS KINDS OF NEUROTROPHIC FACTORS SIGNALING MOLECULES. THEY ARE NOT ISOLATED. THOSE CELLS CAN POTENTIALLY BE CHANGED BY THEIR ENVIRONMENT.

NOW, YOU MAY WANT THEM TO BE CHANGED INTO SOMETHING THAT'S USEFUL, BUT THEY MAY ALSO BE CHANGED INTO SOMETHING THAT CAN DO HARM. AND THAT HAS TO DO WITH GENETICALLY MODIFYING THE CELLS AND

WHAT'S CALLED EPIGENETICS, WHICH LEADS TO CHANGES IN THE EXPRESSION OF CERTAIN GENES.

AND THEN, FINALLY, WHEN WE LOOK AT THE LIMITATIONS OF ANIMAL MODELS, ONE OF THE THINGS WE CAN SAY IS THAT WE DO NOT GAIN A WHOLE LOT OF INSIGHT ABOUT SAFETY OR EFFICACY FROM RODENT MODELS RELEVANT TO HUMANS. AND SO WE'RE GOING TO GO INTO CLINICAL TRIALS VERY CAREFULLY. OBVIOUSLY IF YOU GET A BIG TUMOR IN AN ANIMAL MODEL, YOU'RE NOT GOING TO USE THAT CELL LINE. BUT MOST OF THE TIME YOU'RE NOT GOING TO SEE HAPPEN IN THE ANIMALS THAT COULD EASILY HAPPEN IN PEOPLE.

SO WHY SHOULD WE DO RANDOMIZED CLINICAL TRIALS? WE'RE ALREADY HAVING ENOUGH TROUBLE DOING THEM IN ANIMAL MODELS. NOW WE'RE GOING TO TRY TO DO THEM IN PEOPLE. WELL, MOST IMPORTANT IS THAT PEOPLE FLUCTUATE. PEOPLE WITH NEUROLOGICAL DISEASES FLUCTUATE. I'VE TAKEN CARE OF THOUSANDS OF PEOPLE WITH STROKE AND SPINAL CORD INJURY AND DEGENERATIVE DISEASES AND MULTIPLE SCLEROSIS, AND EVEN FROM ONE TIME TO THE NEXT THAT I SEE THEM, EVEN WITHIN THE COURSE OF THE DAY, THERE MAY BE DIFFERENCES IN THEIR STRENGTH, THEIR MOBILITY, THEIR ABILITY TO DO SELF-CARE TASKS. YOU KNOW, IT'S NOT, YOU KNOW, A HUGE DIFFERENCE, BUT IT'S WIDE ENOUGH THAT IT'S

WITHIN THE NOISE LEVEL OF SOME OF OUR POTENTIAL INTERVENTIONS. AND SO WE'VE GOT TO KNOW THAT THE CHANGE THE PATIENTS HAVE IS WELL OUTSIDE THAT DAY-TO-DAY NOISE FLUCTUATION. WE CAN'T MEASURE BLOOD SUGARS. WE CAN'T MEASURE THE SIZE OF TUMOR. WE CAN'T MEASURE MANY OF THE THINGS THAT HAVE CHEMICAL OR OTHER BIOLOGICAL MARKERS OR IMAGING MARKERS IN OTHER DISEASES. IN THE NERVOUS SYSTEM WE CAN ONLY LOOK AT BEHAVIOR.

ANOTHER REASON TO DO RANDOMIZED CLINICAL TRIALS IS THAT OUR MINDS ARE WIRED TO HOPE AND TO BELIEVE, AND WE ALL WANT TO THINK THAT WE ARE GOING TO FIGHT OFF THIS DISEASE AND WE'RE GOING TO DO ANYTHING WE CAN TO GET BETTER. THAT'S THE WAY WE'RE MADE UP. IT'S A SURVIVAL INSTINCT. YOU CAN DEMONSTRATE IT ON FUNCTIONAL IMAGING STUDIES, PEOPLE WHO ARE EXPRESSING HOPE OR BEING IN A HOPELESS SITUATION, YOU CAN SEE WHAT AREAS OF THE BRAIN ARE ACTIVATED. THAT'S WHAT WE'RE LIKE. AND SO IF WE DON'T DO RANDOMIZED CLINICAL TRIALS, WE'RE GOING TO HAVE PEOPLE PICKING OUT THAT FLUCTUATION AND SAYING, BOY, THAT GIVES ME HOPE. I THINK I MIGHT GET BETTER. THIS WORKED. I BELIEVE THAT WHATEVER YOU DID TO ME WHEN YOU GAVE ME CELLS REALLY WORKED. WE NEED SOME OTHER THING, SOME OTHER MEASURE OF THAT.

THERE ARE A LOT OF FALSE ALTERNATIVES TO RANDOMIZED CLINICAL TRIALS. I'M GOING TO TALK A LITTLE BIT MORE ABOUT THE SPECIFICS OF THE TRIALS IN A MINUTE, BUT THE FALSE ALTERNATIVES TO DOING RANDOMIZED CLINICAL TRIALS, AND LET ME JUST DEFINE WHAT I MEAN BY THAT. RANDOMIZED CLINICAL TRIAL FOR STEM CELL STUDIES WOULD MEAN THAT YOU HAD MULTIPLE SITES THAT USED A CELLULAR INTERVENTION, YOU COMBINE IT WITH SOME KIND OF PHYSICAL OR COGNITIVE THERAPY DEPENDING ON WHAT YOUR END POINT WAS, YOU GAVE SOME PEOPLE THE EXPERIMENTAL CELLS AND OTHER PEOPLE CELLS OR SIMILAR SUBSTANCE THAT WOULD SERVE AS A PLACEBO, AND YOU WOULD INJECT THESE THINGS IN BOTH SUBJECTS. YOU WOULD TRAIN THEM AND YOU WOULD LOOK FOR OUTCOME MEASURES THAT WERE RELEVANT TO THAT AIM OF YOUR INTERVENTION.

NOW, YOU MIGHT NOT NECESSARILY HAVE TO INJECT CELLS. WE CAN TALK ABOUT THAT IN THE QUESTIONS. BUT YOU HAVE TO DO SOMETHING SO THAT THE PATIENT AND THE PEOPLE AROUND THAT PATIENT, THE CLINICIANS AND THE PEOPLE MEASURING OUTCOMES CANNOT TELL WHO GOT THE CELLS AND WHO DIDN'T. SO ONE OF THE FALSE ALTERNATIVES TO THAT RANDOMIZED KIND OF TRIAL IS THAT GIVE ME ANYTHING. SOMETHING IS ALWAYS BETTER THAN NOTHING. ANY OF YOU WHO ARE PHYSICIANS

KNOW THAT SOMETHING ISN'T ALWAYS BETTER THAN NOTHING AND OFTEN LEADS TO A LOT OF PROBLEMS.

ANOTHER IS THE EXCUSE. THE EXCUSE THAT PLACEBOS ARE NOT ETHICAL OR IN YOUR SITUATION, LIKE LIVING IN CHINA, THEY'RE NOT POSSIBLE OR THAT YOU CAN'T FUND IN A LOT OF COUNTRIES PLACEBO CONTROLLED TRIALS. THIS IS A COMMON EXCUSE USED IN AFRICA, ASIA, AND SOUTH AMERICA, NO LONGER WORKS IN EUROPE.

HUBRIS, THE GUY GIVING THE CELLS KNOWS THEY WORK, SO WHY BOTHER USING A PLACEBO OR DOING A RANDOMIZED TRIAL. YOU KNOW THEY WORK, SO USE THEM. I'LL GIVE YOU SOME REALLY COOL EXAMPLES OF HUBRIS. HISTORICAL CONTROL, SO YOU HAVE A DISEASE IN WHICH YOU KNOW THAT MOST PEOPLE GET WORSE OVER TIME. SO NOW YOU'RE GOING TO GIVE CELLS AND USE THAT HISTORY OF WHAT HAPPENED TO OTHER PEOPLE TO SEE WHETHER OR NOT THEY GOT WORSE. YOU'RE NEW GROUP GOT WORSE WHEN IT GOT THE CELLS. WELL, YOU'RE NOT DOING A RANDOMIZED CONTROLLED TRIAL THERE. YOU'RE NOT MATCHING PATIENTS FOR ALL THE THINGS THAT GO INTO CREATING NOISE.

WE DID A STUDY USING AN INTERVENTION TO ENHANCE WALKING TO TRY TO GET MORE PATIENTS WALKING AFTER SPINAL CORD INJURY WHO HAD INITIALLY PROFOUND SPINAL CORD INJURIES. WE LOOKED AT HISTORICAL

CONTROLS, AND EVERY TRIAL THAT WAS EVER DONE SHOWED THAT ONLY 20 PERCENT OF THE PATIENTS WHO WERE LIKE OUR SUBJECTS RECOVERED THE ABILITY TO WALK. SO WE POWERED THE STUDY TO TRY TO GET TO 35 PERCENT OF PEOPLE WALKING. WHEN WE FINISHED OUR STUDY, IT TURNED OUT THAT THE PATIENTS WHO GOT THE EXPERIMENTAL INTERVENTION AND THE PATIENTS WHO DID NOT GET THE EXPERIMENTAL INTERVENTION WERE THE SAME, AND THAT 85 PERCENT OF THEM RECOVERED THE ABILITY TO WALK. IF WE HAD USED HISTORICAL CONTROLS AND JUST USED OUR INTERVENTION AND DIDN'T HAVE OUR OWN CONTROL GROUP, WE WOULD HAVE SAID, WOW, 85 PERCENT OF OUR PEOPLE WALK, AND THE LITERATURE SAYS ONLY 25 PERCENT WALK. THIS IS THE GREATEST THING SINCE APPLE PIE. LET'S START SPENDING HUNDREDS OF MILLIONS OF DOLLARS SETTING UP THE EQUIPMENT TO DO THIS STUDY.

WELL, IT TURNED OUT THAT THE HISTORICAL CONTROLS WERE WRONG, AND THAT HAD A LOT TO DO WITH THE WAY THEY WERE CAPTURED AND THE WAY THEY WERE STUDIED AND LACK OF CARE IN DOING SOMETHING THAT YOU DO VERY DIFFERENTLY WHEN YOU DO A RANDOMIZED CONTROL TRIAL. YOU REALLY PAY ATTENTION TO DETAILS. AND THAT DOESN'T HAPPEN OUTSIDE OF RANDOMIZED CONTROL TRIALS.

ANOTHER NOTION IS WE'LL USE CHRONICALLY IMPAIRED PATIENTS. SO LET'S SAY YOU HAD A STROKE, YOU CAN'T USE YOUR ARM, THREE MONTHS HAS GONE BY, YOU STILL CAN'T USE YOUR ARM, AND ODDS ARE YOU'RE NOT GOING TO BE ABLE TO USE YOUR ARM. SO WE'LL NOW GIVE OUR INTERVENTION TO THOSE CHRONICALLY IMPAIRED PATIENTS. AND IF THEY GIVE THEM THE CELLS AND THEY CAN USE THEIR ARM SOME, THEN THEY MUST WORK BECAUSE THIS WAS CHRONIC AND THEY WERE STABLE. WELL, THE REALITY IS THAT CHRONIC DOESN'T MEAN STABLE. PEOPLE FLUCTUATE ALL THE TIME. AND I CAN TAKE ANY PATIENT WHO HAS TROUBLE WALKING FIVE YEARS AFTER A STROKE AND INCREASE THEIR WALKING SPEED 20 OR 25 PERCENT IN ABOUT THREE HOURS OF TRAINING. YOU CAN DO THAT WITH ALMOST ANYTHING BECAUSE IF THERE'S ENOUGH SPARE PATHWAY, IT'S TRAINABLE. YOU CAN TEACH A SKILL.

ANOTHER NOTION IS THAT YOU WILL EXCEED THE MINIMAL DETECTABLE DIFFERENCE OR MINIMAL CLINICALLY IMPORTANT DIFFERENCE FOR THE OUTCOME MEASURE. WHAT THAT MEANS IS THAT YOU HAVE AN OUTCOME MEASURE, AND IT HAS A CERTAIN AMOUNT OF NOISE IN IT WHEN YOU LOOK AT A PARTICULAR POPULATION. BUT IF YOU EXCEED THAT NOISE LEVEL OF HOW PEOPLE AGREE ON IS THERE A CHANGE IN THAT MEASURE, IS THE MEASURE IMPROVING OR NOT, THAT'S GOOD ENOUGH. AND IT TURNS OUT THAT'S ANOTHER

FALSE PROPHET AND THAT MINIMALLY DETECTABLE DIFFERENCES ARE JUST STATISTICAL METHODS. AND WHILE THEY'RE USED A LOT IN EARLY TRIALS IN PHASE I, PHASE II TRIALS, IT REALLY IS OF NO VALUE.

SO WHAT'S THE BIGGEST CONSEQUENCES OF THE FAILURE TO DESIGN A RIGOROUS RANDOMIZED CLINICAL TRIAL? WELL, TO ME THE MOST IMPORTANT THING IS THAT YOU DON'T GENERATE ANY KNOWLEDGE FOR THE RISKS THAT ARE TAKEN. YOU JUST DON'T REALLY LEARN ANYTHING. YOU DON'T KNOW WHETHER IT REALLY WORKS OR NOT. IF YOU SAY IT WORKS, WELL, COMPARED TO WHAT? WHAT DOES THIS MEAN THAT IT WORKS? WHAT REALLY HAPPENED? WHO DOES IT WORK FOR? WHAT DOES IT WORK FOR?

I'LL SHOW YOU SOME EXAMPLES IN A MINUTE OF PEOPLE WHO SELL STEM CELLS FOR ANYTHING BECAUSE THEY BELIEVE THAT THEY WORK COMPARED TO NOTHING. WE CAN ONLY WEIGH THE RISKS AND BENEFITS OF INTERVENTIONS IF WE DO RANDOMIZED CONTROLLED TRIALS, AND WE CAN ONLY IMPROVE ON OUR INTERVENTIONS. SO LET'S SAY WE GET SOMETHING AND WE THINK IT WORKS A LITTLE BIT, BUT IT'S NOT THAT MUCH BETTER, BUT IT'S A LITTLE BETTER, IT'S HOPEFUL. HOW ARE WE GOING TO GO TO THE NEXT STEP TO IMPROVE BEYOND THAT UNLESS WE DEFINE WHAT WE'RE DOING VERY CAREFULLY AND CREATE RANDOMIZED CLINICAL TRIALS SO THAT PATIENTS CAN BE

COMPARED AND CAN BE STUDIED WITH EVERYTHING MORE OR LESS THE SAME ABOUT THEM EXCEPT FOR THE INTERVENTION?

MOST IMPORTANT IS THIS SLIPPERY SLOPE OF SLOPPY SCIENCE AND SALES. SO YOU TRY TO SAY THAT QUICKLY. PEOPLE THAT DON'T DO RANDOMIZED CLINICAL TRIALS AND JUST SET UP, FOR EXAMPLE, TO GET A TREATMENT JUST START TO GET SLOPPIER AND SLOPPIER IN WHAT WHAT'S ACCEPTABLE, THEIR OUTCOME MEASURES BECOME WORSE AND WORSE. I MEAN PRETTY SOON YOU JUST HAVE NO IDEA WHAT'S GOING ON, WHAT THEY'RE DOING.

SO HERE'S SOME GUIDING PRINCIPLES FOR CELLULAR RANDOMIZED CLINICAL TRIALS. FIRST OF ALL, THEY'RE VERY ARDUOUS, THEY'RE VERY EXPENSIVE, AND THE PEOPLE INVOLVED IN THEM HAVE TO DELAY GRATIFICATION BECAUSE THEY'RE GOING FOR A LONG TIME. TRIALS WITH CELLULAR INTERVENTIONS ARE GOING TO GO ON FOR AT LEAST A YEAR AFTER PATIENTS GET THEM, AND THEY'RE GOING TO HAVE TO BE MONITORED FOR YEARS TO COME. AND SO WE NEED SOME WAY IN WHICH THE INVESTIGATORS, THE SUBJECTS, PEERS WHO ARE BASIC, AND CLINICAL EXPERTS WHO UNDERSTAND WHAT'S GOING ON WITH THOSE CELLS. IRB'S, FDA, THEY ALL NEED TO BE CONVINCED THAT THAT RANDOMIZED CLINICAL TRIAL IS LIKELY TO PROVIDE KNOWLEDGE AND POSSIBLY IMPROVE

HEALTH OUTCOMES.

THE WAY OUR SYSTEM WORKS RIGHT NOW, NONE OF THAT IS THE CASE. BASICALLY DEVELOP A CELL LINE, ISOLATE IT IN AN ISOLATED LABORATORY, YOU FIND A USE FOR IT, YOU GO TO THE FDA, YOU TRY TO CONVINCE THEM THEY CAN USE IT, THAT THIS WILL BE SAFE, AND YOU TRY TO PROVE SOME EFFICACY WITH IT. AND NO ONE ELSE IS INVOLVED IN THAT DECISION-MAKING EXCEPT THE PEOPLE PUTTING THAT BEFORE THE FDA. NO OTHER PEERS, NO OTHER REAL EXPERTS HAVE BEEN INVOLVED IN THE EXPERIMENTS TO SEE JUST HOW ROBUST THAT CELLULAR INTERVENTION MIGHT BE.

ONE OF THE DIFFERENCES BETWEEN NEUROLOGICAL INTERVENTION WITH CELLS WILL BE THAT WHEN YOU DESIGN THEM, THERE OUGHT TO BE A PHASE-IN BEFORE YOU RANDOMIZE PATIENTS OF SOME KIND OF TASK-RELATED THERAPY, AND THEN YOU GIVE THAT THERAPY UNTIL NO FURTHER GAINS ARE MADE. YOU GOT TO RING OUT THE FLUCTUATIONS THAT PATIENTS HAVE. AND SO ONE WAY TO DO THAT, WHICH IS NEVER DONE IN DRUG STUDIES, AND THAT'S WHY ALL DRUG STUDIES HAVE FAILED, I THINK, IT'S ONE OF THE REASONS IN NEUROLOGICAL DISEASES, YOU'VE GOT TO -- LET'S SAY YOU WANT A PATIENT TO BE ABLE TO USE THE HAND BETTER AND TO BE ABLE TO REACH AND PINCH OR YOU WANT A PATIENT TO BE

ABLE TO WALK OR YOU WANT A PATIENT TO BE ABLE TO RECOVER LANGUAGE FUNCTION. YOU'VE GOT TO PROVIDE SOME THERAPIES THAT MAXIMIZE WHAT IT IS THEY CAN DO AND SORT OF GET THEM TO AN EVEN LEVEL AS BEST YOU CAN BEFORE YOU RANDOMIZE THEM. OTHERWISE WHAT HAPPENS IN EVERY TRIAL, WHETHER IT'S ROBOTICS, DRUGS, NEUROPROTECTION, WHATEVER IT IS THAT YOU START OUT, AND THERE ARE OUTLIERS, AND SOME PEOPLE JUST GET BETTER. AND IT DOESN'T MATTER WHAT YOU DO. AND THE REASON IS THAT THEY HAVE LATENT CAPACITY TO DO BETTER, AND THEY'RE JUST NOT USING IT. IT'S CALLED NONUSE.

YOU KNOW, YOUR GRANDMOTHERS SAY USE IT OR LOSE IT. IT'S REALLY THE CASE. I MEAN KOBE BRYANT, IF HE DOESN'T THROW A THOUSAND SHOTS BEFORE A GAME, HE'S REALLY OFF TO A BAD GAME. HE'LL TELL YOU THAT. HERE'S THE GUY WHO IS THE GREATEST BASKETBALL PLAYER IN THE WORLD. HE'S GOT TO GO OUT AND PRACTICE AND EVERY SEVEN SECONDS SHOOTS THE BALL. IT'S VERY EASY FOR YOUR SKILLS TO DISSOLVE. AND IF YOU CAN'T USE YOUR RIGHT ARM WELL, YOU MAY JUST COMPENSATE WITH YOUR LEFT ARM AND STOP USING IT. NOW YOU'RE GOING TO SUDDENLY PUT SOMEBODY IN A CELL TRIAL TO TRY TO HELP THEM RECOVER THEIR ARM, AND THEY HAVEN'T EVEN TRIED TO USE IT IN YEARS. IT'S NOT FAIR. YOU'RE

GOING TO LOSE. YOU'RE NOT GOING TO SHOW EFFICACY UNLESS YOU TRY TO GET THAT PATIENT USING THAT ARM FOR A WHILE, GET THEM STABLE TO SEE WHAT THEY CAN DO, AND THEN USE YOUR CELLULAR INTERVENTION.

WHEN YOU GIVE THE CELLULAR INTERVENTION, WHOEVER GETS THE CELLS, WHOEVER GET THE PLACEBO IS ALSO GOING TO HAVE TO PRACTICE, AND YOU ARE GOING TO HAVE TO PRACTICE DOING WHATEVER IT IS THAT'S RELEVANT TO THE OUTCOMES THAT YOU'RE SEEKING SO THAT OUR CLINICAL TRIALS CAN BE DESIGNED AROUND VERY SPECIFIC OUTCOMES THAT ARE PERSONAL TO PATIENTS, VALUED BY PATIENTS AND MEASURABLE. THE PRACTICE ITSELF, LIKE I SAID, IS GOING TO INDUCE ADAPTATIONS AND PLASTICITY AND IMPROVE SKILLS.

IN THIS CASE WHAT WE HAVE TO DO IS WE CANNOT COMPARE AN INTERVENTION, A CELLULAR INTERVENTION, TO USUAL CARE. IT DOESN'T COUNT. THE REASON IS THAT USUAL CARE MEANS NOTHING. SO WE HAVE DONE TRIALS, I'VE BEEN ON SAFETY COMMITTEES OF TRIALS THAT WERE SET UP IN WHICH YOU DID A VIGOROUS THERAPY VERSUS USUAL CARE. WHAT HAPPENED IN USUAL CARE? PATIENTS MIGHT TRY TO GET A LITTLE BIT OF THERAPY TO IMPROVE THEIR WALKING; WHEREAS, THE PATIENTS IN THE STUDY GOT, YOU KNOW, 12 WEEKS OF CONSTANT THERAPY AIMED AT WALKING AND WENT FROM NOT

BEING ABLE TO WALK SO WELL TO WALKING. THE PEOPLE WHO DIDN'T GET THE WALKING THERAPY AND GOT USUAL CARE DIDN'T IMPROVE MUCH. SO WHAT HAVE YOU PROVED? SOMETHING IS BETTER THAN NOTHING.

BUT IF YOU HAD DONE -- IF YOU REALLY HAD AN EXPERIMENTAL THERAPY WHICH WERE ONE INVOLVED GIVING CELLS TO TRY TO DRIVE, SAY, WALKING, YOU'D WANT TO HAVE BOTH GROUPS GET A LOT OF THERAPY THAT TRIED TO MAXIMIZE THAT RECOVERY FOR WALKING. AND SO YOU WOULD GIVE THEM BOTH WALKING THERAPIES AS WELL AS THE CELLS. THIS IS EVEN TRUE IF YOU STUDIED ALZHEIMER'S OR PARKINSON'S. THERE OUGHT TO BE A THERAPY ASSOCIATED WITH IT AIMED AT IMPROVING WHATEVER IT IS, BALANCE, COORDINATION, LEARNING, MEMORY. YOU'RE PUTTING IN CELLS, YOU'RE HOPING THEY WILL DRIVE PLASTICITY. WELL, YOU'VE GOT TO GIVE THEM SOMETHING TO DO. YOU GOT TO TRAIN THEM. YOU GOT TO TAKE ADVANTAGE OF THAT NEW NERVOUS SYSTEM THAT YOU'VE CREATED.

THE OUTCOME MEASURES, BERNIE ASKED ME TO MENTION. THE OUTCOME MEASURES HAVE TO BE RELEVANT TO THE INTERVENTION. SO IT DOESN'T MAKE SENSE TO TAKE SOMEONE WITH A SPINAL CORD INJURY, TRY TO PUT IN CELLS, REGENERATE AN AXON PAST THE LESION, TO GO INTO THE SPINAL CORD TO NOW GO BACK AND MAKE THE

MUSCLES OF THE WRIST AND HAND MOVE, AND THEN GO AND SAY MY OUTCOME MEASURE IS WHETHER THE PATIENT DID HIS SELF-CARE BETTER BECAUSE YOU MAY NOT NEED THAT HAND TO DO YOUR SELF-CARE. WHAT YOU NEED IS AN OUTCOME MEASURE THAT'S SPECIFIC TO THE MOVEMENT OF THAT HAND. IT HAS TO BE VALUED BY THE PATIENT, IT HAS TO REDUCE SOME IMPAIRMENT OR DISABILITY.

MOST CLINICAL TRIALS ARE DONE WITH REALLY BIG SAMPLE SIZES. I THINK THAT CELLULAR THERAPIES NEED TO BE VERY ROBUST BECAUSE OF ALL THE POTENTIAL PROBLEMS AROUND THEM. AND TO ME A ROBUST EFFECT SIZE, MEANING HOW MANY PEOPLE DO YOU HAVE TO TREAT TO GET A GOOD OUTCOME, IS THAT AN EFFECT SIZE OF AROUND .4 TO .6. AN EFFECT SIZE OF .4 MEANS THAT IF YOU SET UP THE TRIAL, YOU NEED NO MORE THAN ABOUT 50 SUBJECTS IN EACH ARM OF THE TRIAL, PLACEBO AND THE CONTROL GROUP. AND FOR CERTAIN THINGS LIKE SPINAL CORD INJURY WHERE YOU WOULD TRY TO REGENERATE JUST A SHORT DISTANCE TO GET BELOW THE LESION AND RECOVER ONE OR TWO MUSCLE GROUPS, YOU COULD PROBABLY GET BY WITH A DECENT TRIAL OF AS FEW AS 20 SUBJECTS IN EACH ARM.

SO LET ME GIVE YOU SOME EXAMPLES --

CHAIRMAN LO: BRUCE, I'M GOING TO CUT IN FOR A MINUTE. ASK YOU TO START WINDING DOWN BECAUSE

I WANT TO MAKE SURE THAT WE HAVE TIME TO ASK YOU QUESTIONS. SO I KNOW YOU HAVE A LOT, BUT I'D LIKE YOU TO TRY AND WIND DOWN.

DR. DOBKIN: YOU WANT TO TAKE QUESTIONS?

CHAIRMAN LO: MAYBE YOU COULD SORT OF CONCLUDE AND THEN OPEN IT UP FOR QUESTIONS BECAUSE I THINK THERE MAY BE PEOPLE ASKING A LOT. HOW MANY MORE SLIDES DO YOU HAVE?

DR. DOBKIN: I WAS GOING TO SHOW YOU SOME EXAMPLES OF TRANSPLANTS THAT HAVE BEEN DONE AND THE -- SO THIS ARTICLE, I THINK, IS IN YOUR HANDOUT. AND LET ME GIVE YOU -- THESE ARE SEVEN PATIENTS WHO HAVE SPINAL CORD PROBLEMS, WENT TO CHINA, THE SURGEON ALLOWED US TO EXAMINE THEM. AND LET ME GIVE YOU A REASON WHY YOU NEED RANDOMIZED CLINICAL TRIALS. THIS SURGEON WOULD NOT DO RANDOMIZED CLINICAL TRIALS. HE SAID IT WASN'T ETHICAL. SO PATIENTS CAME BACK TO US, AND SUPPOSEDLY THEY WERE GOING TO HAVE CELLS INJECTED INTO THEIR SPINAL CORD. ONE OF THE PATIENTS CAME BACK WITH TWO HOLES IN THE FRONTAL LOBE AND THEY PUT THE CELLS IN THE FRONTAL LOBES FIGURING THAT THEY COULD THEN SOMEHOW GET DOWN INTO THE SPINAL CORD. THAT'S WHAT HAPPENED WHEN YOU DON'T HAVE A PROTOCOL AND A RANDOMIZED CLINICAL TRIAL. YOU JUST MAKE IT UP AS YOU GO ALONG.

THE SURGEON GOT OUT OF BED, THE CHINESE NEUROSURGEON GOT OUT OF BED ONE DAY AND MUST HAVE SAID TO HIMSELF, WOW, YOU KNOW, MAYBE THE CELLS WILL MIGRATE. SO I'LL STICK THEM IN THE HEAD.

ANOTHER PATIENT HAD ONLY BLADDER PROBLEMS AND A LITTLE TROUBLE WALKING, BUT SHE COULD WALK. SHE COULD EMPTY HER BLADDER, BUT SHE WASN'T HAPPY WITH IT. HE PUT CELLS INTO HER SPINAL CORD. HE COULD HAVE COMPLETELY LEFT HER PARAPLEGIC. BIZARRE.

DR. HUANG IN RESPONDING TO AN E-MAIL, HIS OUTCOME MEASURES WERE E-MAIL NOTES FROM PATIENTS BECAUSE HE NEVER FOLLOWS UP ANY PATIENTS. HE'S DONE A THOUSAND PEOPLE'S SPINAL CORDS, INJECTED CELLS INTO THEIR SPINAL CORDS. THEY'RE CELLS DERIVED FROM EMBRYONIC TISSUE, ABORTED EMBRYONIC TISSUE. HE'S USED THIS FOR ALS. HE'S USED THIS FOR AT LEAST A HALF DOZEN DISEASES.

AND I GOT AN E-MAIL FROM THIS PATIENT THAT I HAD ACTUALLY TAKEN CARE OF FROM THE BEGINNING, AND IT TURNS OUT THAT THE MOTHER WROTE AN E-MAIL TO ME AND TO HUANG AND SAID THAT HER SON'S QUALITY OF LIFE WAS SO MUCH BETTER ABOUT SIX MONTHS AFTER HE HAD GONE TO CHINA TO GET THE CELLS. LATER IN THE NOTE SHE MENTIONS THAT HE ISN'T DOING ANYTHING BETTER. HE ISN'T MOVING ANY BETTER, BUT HE HAS A GIRLFRIEND

AND HE FINALLY WENT BACK TO SCHOOL. AND THE QUALITY OF HIS LIFE HAS IMPROVED TREMENDOUSLY.

HUANG READ IT AS THE CELLS IMPROVED THE QUALITY OF LIFE. I READ IT AS IF I'M A 22-YEAR-OLD WHO'S PARAPLEGIC AND I CAN HAVE A GIRLFRIEND AND GET BACK TO SCHOOL, WHICH I WAS ALWAYS RIDING HIM ON BECAUSE HE DROPPED OUT OF SCHOOL TO GO TO CHINA AND GET BETTER. YOU KNOW, HE'S DOING GREAT. AND THIS IS WHAT DR. HUANG SAID IN FRONT OF AN INTERNATIONAL AUDIENCE OF RESEARCHERS IN CHINA FROM ALL OVER THE WORLD WHO WERE STUDYING STEM CELLS. HE SAID THAT IF I WERE HONEST AND FAIR IN FACE OF THE FACT THAT THE PATIENT OBTAINED IMPROVEMENTS ACCORDING TO AN ASIA STANDARD, WHICH HE DIDN'T, AND HIS QUALITY OF LIFE, YOU SHOULD NOT DENY -- CONTINUE DENYING THE POSITIVE RESULTS. SO TAKE THE OFFENSE.

BUT WHAT MAKES ONE REGRET, A LOT OF TYPING ERRORS, IS THAT NO MATTER WHAT RECOVERED OR HOW THE PATIENT'S NEUROLOGIC FUNCTION RECOVERED AND WHAT HAPPENED IMPROVING HIS QUALITY OF LIFE, YOU KEEP DENYING IT. I'M PART OF THE ESTABLISHMENT. FACING THE FACT AND INSISTING ON ABSOLUTELY DENYING IT, I DENIED THAT HE WAS ANY BETTER IN TERMS OF THE EFFECTS OF THE CELLS. I WONDER IF YOU HATE TO SEE PATIENTS WITH THIS DISEASE IMPROVING THE QUALITY OF

LIFE OR YOUR PERSONALITY AND CREDITS HAVE SOME PROBLEMS EXCEPT UNFAIR AND DISHONEST. AND YOU GET THE GIST OF THIS.

SO I AM THE ONLY PERSON WHO'S BEEN CALLED A LIAR IN BOTH *NATURE* AND IN *SCIENCE* JOURNALS BY HUANG. TO ME IT'S A BADGE OF TRUTH. BUT THE KEY HERE IS THAT THIS IS A TRUE BELIEVER, AND HE'S GIVING OUT CELLS AND PEOPLE ARE LINING UP TO GET THEM.

THIS IS ANOTHER COMPANY THAT GIVES CELLS. LOOK AT ALL THESE THINGS THAT THE SAME STEM CELLS WORK FOR. I MEAN IT'S INCONCEIVABLE. AND IF YOU -- WHAT THEY DO IS THEY SCREEN YOU BY TAKING WHAT YOU SEND THEM IN THE MAIL, YOU KNOW. I WANT TO BE ABLE TO DO THIS AGAIN. I HAD THIS KIND OF PROBLEM. SO THEY SCREEN YOU. AND IT SAYS HERE IF OUR MEDICAL DEPARTMENT DOES NOT BELIEVE YOU WILL BENEFIT FROM THE TREATMENT, WE WILL TELL YOU AND SUGGEST YOU SEEK TREATMENT ELSEWHERE, BUT THEY DON'T TURN ANYBODY AWAY. OF COURSE, WE BY NO MEANS GUARANTEE IMPROVEMENT, BUT OUR TREATMENT CONSISTS OF MULTIPLE INJECTIONS OF STEM CELLS ACCOMPANIED BY DAILY REHABILITATION TO ENSURE THAT THE UMBILICAL CORD STEM CELLS CAN HELP YOUR CONDITION. YOU WILL GET SOME IMPROVEMENT.

THESE FOLKS ALSO CALLED ME A LIAR, TAKING SOMETHING OUT OF CONTEXT SAYING THERE WAS MUCH EVIDENCE TO BACK UP THEIR THEORIES. AND THIS IS AN AMERICAN VENTURE CAPITAL GROUP USING RUSSIAN CELLS, CELLS THAT WERE ORIGINALLY DEVELOPED IN RUSSIA. AND I CAN'T TELL YOU HOW MANY WELL-KNOWN VENTURE CAPITALISTS HAVE INVESTED IN THIS COMPANY. THESE ARE OFFSHORE COMPANIES GIVING CELLS IN MEXICO AND IN THE CARIBBEAN. SO THERE'S A REAL NEED FOR THIS. THERE'S A REAL ETHICAL ISSUE, I THINK, NOT ONLY ABOUT THOSE PEOPLE, THE STEM CELL SELLERS, BUT ALSO THINGS THAT ARE GOING ON RIGHT NOW. FOR EXAMPLE, WE TALKED ABOUT GERON EARLIER AND ITS SPINAL CORD PROJECT.

ONLY ONE LAB HAS PUBLISHED ANY DATA USING THOSE CELLS IN EIGHT RODENTS. THAT'S ALL WE KNOW. GERON HAS GIVEN THESE CELLS TO MANY OTHER RODENTS, BUT NOT WITH PEER REVIEW. AND SO WE HAVE NO IDEA WHAT THOSE CELLS MIGHT BE.

CHAIRMAN LO: BRUCE, I'M GOING TO ASK YOU TO WIND UP SO WE HAVE A CHANCE TO ASK QUESTIONS IF THAT'S OKAY. DO YOU WANT TO JUST GIVE US A QUICK SUMMARY, AND THEN WE'LL BOMBARD YOU WITH QUESTIONS.

DR. DOBKIN: WHAT I WOULD SAY, I GUESS, TO SUMMARIZE IS THAT WE HAVE -- WE OUGHT TO THINK OF

CELLULAR NEURAL REPAIR INTERVENTIONS AS AUGMENTING OUR REHABILITATION OR AUGMENTING OUR TRAINING. SO WE NEED TO THINK ABOUT THE TRAINING AND THE OUTCOMES AHEAD OF TIME AND TRY TO UNDERSTAND WHAT DO WE WANT THOSE CELLS TO BE INVOLVED IN DOING.

ANOTHER IS THAT WE WANT TO HAVE THESE REPAIR STRATEGIES, THEY'VE GOT TO BE CLEARLY DRAWN. WE CAN'T LET PATIENTS DECIDE WHAT THEY WANT TO GET BETTER. WE HAVE TO HAVE CLINICAL TRIALS THAT LOOK AT SPECIFIC EFFECTS OF THAT CELLULAR STRATEGY AND OF THE TASK-RELATED PRACTICE AND TRY TO LESSEN PEOPLE'S IMPAIRMENTS AND DISABILITIES WITH OUR PRIMARY OUTCOME MEASURES.

WE NEED TO TAKE INTO ACCOUNT THAT ANECDOTES AND HISTORICAL CONTROLS AND QUASI EXPERIMENTAL TRIALS AND FAITH ARE RATHER MISLEADING WAYS TO DEVELOP EVIDENCE-BASED PRACTICE. YOU ALL KNOW THAT, BUT IT'S AMAZING HOW MANY PATIENTS AND PHYSICIANS DO NOT AGREE WITH THAT.

PROSPECTIVE BLINDED RANDOMIZED CLINICAL TRIALS IN REALLY WELL-DEFINED SUBJECTS WHERE YOU TALLY THE ADVERSE REACTIONS AND YOU LOOK AT FUNCTIONALLY IMPORTANT OUTCOMES, YOU FOLLOW UP PEOPLE ARE THE BEST WAY TO GO.

AND THEN ONE LAST POINT IS THAT I THINK

THAT TOO MUCH IS DONE IN PRIVATE AND IN SECRECY, AND I THINK THAT BY FUNDING COLLABORATIONS OF SCIENTISTS, CLINICIANS, BASIC RESEARCHERS, AND EXPERTS AND PROVIDING SOME INFRASTRUCTURE FOR THEM TO COMMUNICATE WITH, SHARE THE RESEARCH OBJECTIVES, HELP THEM WORK AROUND PERCEIVED BARRIERS IN INTELLECTUAL PROPERTY AND ACROSS INSTITUTIONAL INTERACTIONS AND ANTAGONISMS, I THINK THAT BY HAVING THE GROUP OF EXPERTS COME UP WITH THE BEST NOTION FOR ARE THESE CELLS OF VALUE? ARE THEY SAFE? DO WE HAVE GOOD PLACES TO USE THEM? IT'S A MUCH MORE ETHICAL AND POTENTIALLY PRODUCTIVE BASIS FOR DOING TRANSLATIONAL RESEARCH, STEM CELL RESEARCH THAN THE WAY WE'RE DOING IT RIGHT NOW. I'LL LEAVE IT THERE.

CHAIRMAN LO: THANKS VERY MUCH, BRUCE. QUESTIONS?

DR. PETERS: DR. DOBKIN, I FOUND YOUR PRESENTATION VERY INFORMATIVE AND INTERESTING, AND THE CAUTIONS AND WARNINGS THAT YOU GIVE US WE REALLY NEED TO HEED. COULD I ASK YOU, AFTER HAVING GRANTED THAT, IF YOU WERE TO SPECULATE OVER THE NEXT FEW YEARS, ARE THERE ANY INSTANCES DO YOU THINK WHERE INTERVENTION WITH HES CELLS ACTUALLY WILL HAVE A POSITIVE EFFECT SUCH AS WITH PARKINSON'S AND ALZHEIMER'S?

DR. DOBKIN: I'M NOT -- I DON'T THINK THAT ALZHEIMER'S DISEASE IS GOING TO BE A TARGET OR AT LEAST MUCH OF A TARGET IN PART BECAUSE IT'S SUCH A DIFFUSE DISEASE AND IT SPREADS THROUGHOUT THE BRAIN OVER TIME. BUT IT IS POSSIBLE. JUST LIKE WITH PARKINSON'S, THESE ARE PROGRESSIVE DISEASES. IT'S POSSIBLE THAT SOME KIND OF CELLULAR STRATEGY MIGHT MOLLIFY THE DISEASE EVEN FOR A FEW YEARS. AND FOR ALZHEIMER'S, OF COURSE, IF YOU JUST COULD REDUCE THE EFFECTS OF THE DISEASE BY A COUPLE OF YEARS, YOU WOULD ADD TREMENDOUS AMOUNT OF QUALITY OF LIFE TO PEOPLE.

BUT WHERE DO YOU PUT -- WHERE IS THE BEST PLACE TO PUT THESE CELLS, AND YOU'RE JUST REPLACING A TRANSMITTER ACETYLCHOLINE, OR DO YOU IN PARKINSON'S JUST REPLACE THE DOPAMINE? I THINK THERE WILL BE LIMITS TO HOW SUCCESSFUL WE ARE WITH THOSE THINGS, BUT THEY ARE LOW HANGING FRUIT, AND IT'S SOMETHING THAT WILL INEVITABLY -- HAS BEEN TRIED AND WILL BE TRIED.

I THINK THAT CELLULAR AND AXONAL GENERATION STRATEGIES WILL BE TERRIFIC FOR DRIVING THOSE PATHWAYS THAT I SHOWED. THERE ARE INTACT AXONS. WE CAN PUT IN CELLS THAT ACT AS A SIREN, PRODUCE TROPHIC FACTORS AND OTHER SIGNALING

MECHANISMS THAT TURN ON REGENERATIVE GENES AND HELP US GUIDE THOSE AXONS TO OTHER MOTOR NEURONS, FOR EXAMPLE, AND HELP LEAD TO RECOVERY. THAT WILL TAKE TRAINING TOO BECAUSE, AGAIN, YOU'RE REWIRING THE NERVOUS SYSTEM A LITTLE BIT, BUT IT'S DOABLE.

I THINK SPINAL CORD INJURY IS A REAL POSSIBILITY, BUT THE GOAL HAS TO BE GETTING INPUT JUST ONE OR TWO LEVELS BELOW THE LEVEL OF INJURY, NOT WALKING AGAIN, BUT TAKING SOMEONE WITH A C-5 SPINAL CORD INJURY AND GIVING THEM FUNCTION AT C-6 AND 7, THAT WOULD BE ABSOLUTELY TERRIFIC. AND THOSE TRIALS ARE RELATIVELY EASY TO DESIGN. THEY CAN BE DESIGNED STARTING AS LITTLE AS TWO TO FOUR WEEKS AFTER ONSET. THEY'RE DOABLE.

IN YOUR REFERENCES THERE'S SOME STUDIES THAT WE DID WITH A WHOLE CONSENSUS GROUP LOOKING AT HOW MANY PATIENTS YOU'D HAVE TO ENTER AND HOW WE WOULD DESIGN THOSE KINDS OF TRIALS. AND A WHOLE GROUP OF EXPERTS FELT THAT THAT WAS REALLY DOABLE. THERE ARE REALLY INTERESTING POSSIBILITIES.

THERE'S THIS DISEASE CALLED PELIZAEUS-MERZBACHER DISEASE, SO CHILDREN ARE BORN WITHOUT MYELIN, MISSING A SINGLE GENE. THIS IS A MOUSE, A TRANSGENIC MOUSE THAT WAS MISSING THE SAME GENE. A FELLOW NAMED STEVE GOLDMAN CREATED

PRECURSORS OF OLIGODENDROCYTES, MYELINATING CELLS. THEY INJECTED THEM AT MULTIPLE SITES WITHIN THE BRAIN. REMEMBER HOW SMALL THAT LITTLE MOUSE BRAIN WAS. WELL, THEY INJECTED HIM IN DIFFERENT PARTS OF THE BRAIN, CERTAIN NUMBER OF CELLS, THE CELLS WOULD MIGRATE ALONG THE AXONS, AND RESCUED THE MICE. HE'S NOW DONE IT IN DOGS.

SO HERE'S A CELLULAR INTERVENTION WHERE YOU TAKE -- THERE ARE ONLY 300 KIDS A YEAR THAT HAVE THIS, BUT THEY DIE, ALL OF THEM DIE WITHIN 18 MONTHS. HERE'S AN OPPORTUNITY TO USE CELLULAR INTERVENTION TO FIX THEM. THESE ARE ALL LITTLE NICHES. IN STROKE, WE HAVE INJURIES WITHIN THE WHITE MATTER OF THE BRAIN. SOME OF THOSE MAY LACK MYELIN, BUT THE AXON MAY BE INTACT. SO IF YOU COULD JUST CONDUCT ELECTRICITY DOWN IT, IT MIGHT WORK. YOU COULD INJECT CELLS LIKE THIS IN THAT LITTLE SPACE AND GO FROM BEING PARALYZED TO BEING ABLE TO USE THE ARM SOMEWHAT. AND THEN YOU CAN TRAIN IT TO TRY TO DO BETTER.

YOU JUST GO ON AND ON, BUT WHAT WE DON'T HAVE IS THE TREATMENT -- WE'RE NOT GOING TO HAVE THE TREATMENT FOR STROKE, A TREATMENT FOR SPINAL CORD INJURY, ALL SPINAL CORD INJURY. WE'RE GOING TO HAVE TO REALLY THINK THROUGH INDIVIDUAL APPLICATIONS.

CHAIRMAN LO: LET ME GET A SENSE OF HOW MANY PEOPLE WANT TO ASK QUESTIONS BECAUSE WE WANT TO SORT OF FINISH BY SIX, AND I WANT IAN SWEEDLER TO SORT OF SAY A LITTLE ABOUT REGULATORY ISSUES, WHICH I THINK ARE VERY IMPORTANT. JUST RAISE YOUR HAND IF YOU WANT TO ASK A QUESTION. QUICK QUESTIONS, QUICK ANSWERS, AND WE'LL TRY AND FINISH UP IN ABOUT TEN MINUTES.

DR. TAYLOR: BRUCE, I REALLY ENJOYED YOUR PRESENTATION, AND I AGREE WITH ALL YOUR POINTS. JUST TO KIND OF BE THE DEVIL'S ADVOCATE A LITTLE AND TO TAKE THE POSITION THAT IN MY YEARS KIND OF SORT OF CLINICAL MEDICINE, SEEING RANDOMIZED CONTROLLED TRIALS HAVE EMERGED AS KIND OF THE MODEL FOR DOING THIS TYPE OF INVESTIGATION, I'M STILL -- I HAVE THE SENSE THERE'S A FAIRLY BIG RISK FOR TYPE TWO ERRORS IN THOSE KINDS OF STUDIES. ALMOST ALL THE BIG STUDIES THAT WE'VE SEEN THAT HAVE KIND OF FAILED ARE BECAUSE I THINK THERE ARE A LOT OF UNACCOUNTED PARAMETERS THAT END OF SORT OF CREATING MORE NOISE.

AND I'M JUST KIND OF WONDERING WHETHER IN A FIELD LIKE STEM CELL THERAPIES WHETHER WE'RE ASKING TOO MUCH TO DEMAND THAT RCT BE THE MODEL. AND I LIKE WHAT YOU TALKED ABOUT BOOKENDING. THAT'S THE WAY WE DO THINGS IN THE LABORATORY. WE CREATE

AN ENVIRONMENT THAT'S FRANKLY TO REDUCE AS MUCH OF THAT VARIABILITY AS POSSIBLE. AND IT SEEMS TO ME TO GIVE STEM CELL THERAPIES A SHOT, AGAIN, I MIGHT ARGUE SORT OF MORE INTELLECTUALLY, THE RIGHT ANSWER ON THE TEST IS GOING TO BE RCT, BUT I'M JUST WONDERING IS IT POSSIBLE THAT THERE'S ANOTHER DESIGN, A DIFFERENT TYPE OF DESIGN THAT MIGHT ALLOW US TO SEE MORE SUBTLE CHANGES AND NOT MISS STUFF, WHICH I EXPECT WE WOULD MISS WITH RCT'S GIVEN ALL OF THE ISSUES THAT YOU'VE KIND OF RAISED.

DR. DOBKIN: SO THE KINDS OF TRIALS WE'RE USED TO ARE THE TRIALS THAT INVOLVE HUNDREDS OF PATIENTS OR THOUSANDS OF PATIENTS TO GET AN ABSOLUTE IMPROVEMENT OR AN ABSOLUTE OF A COUPLE PERCENT, COUPLE PERCENT FEWER PEOPLE DIE FROM HEART DISEASE GIVEN STATINS OR GIVEN ASPIRIN, COUPLE PERCENT OF PEOPLE OVERALL HAVE FEWER STROKES. BUT WE HAVE TO TREAT 99 PEOPLE TO GET ONE DECENT OUTCOME.

WHAT I WAS TRYING TO SUGGEST FOR STEM CELL TREATMENTS AND BIOLOGICAL INTERVENTIONS IS THAT WE OUGHT TO HAVE A HIGHER STANDARD FOR THE NUMBER NEEDED TO TREAT BECAUSE IT'S LIKE A DESPERATE SITUATION TO HAVE A PROOF OF PRINCIPLE THAT YOU CAN ACTUALLY USE THESE CELLS AND REALLY REGENERATE THINGS IN THE NERVOUS SYSTEM.

WE WANT TO USE A LOT OF PHYSIOLOGICAL AND IMAGING MARKERS TO GET A SENSE OF WHAT'S GOING ON THERE, HAVE SECONDARY MEASURES THAT HELP US UNDERSTAND DID THEY REALLY WORK, OR WAS IT SOMETHING FREAKY THAT WE DIDN'T PLAN ON. BUT I THINK YOU PICK SUBJECTS FOR YOUR FIRST TRIALS WHO CAN'T MOVE THEIR HAND, HAVE A STROKE, AND TWO WEEKS LATER AND YOU CAN'T EXTEND YOUR WRIST OR OPEN YOUR FINGERS. I KNOW THAT THAT PATIENT IS NOT GOING TO GET A FUNCTIONAL HAND. IT'S BEEN PROVED AGAIN AND AGAIN. THAT'S THE PATIENT I WOULD GIVE CELLS TO IN THE RIGHT PLACE IF I THOUGHT I COULD DRIVE THAT PLASTICITY.

AND I SHOULD NOT NEED MORE SINCE VIRTUALLY NO ONE IMPROVES. YOU SHOULDN'T NEED A WHOLE LOT OF SUBJECTS TO BE ABLE TO ANSWER YOUR QUESTION. IF THE QUESTION IS ABOUT SPINAL CORD INJURY AND YOU HAVE NO MOVEMENT BELOW THE LESION AND YOU GET MOVEMENT TWO SEGMENTS BELOW, THAT'S SO FAR OUTSIDE THE POSSIBILITY OF RANDOM CHANCE, THAT IT OUGHT TO BE GOOD ENOUGH. BUT YOU WANT TO CONTROL FOR IT, BUT YOU DON'T NEED A THOUSAND PATIENTS IN EACH GROUP.

SO THERE WOULD BE SITUATIONS WHERE YOU COULD GET BY A CLINICAL TRIAL THAT WAS ONE TO ONE. THERE ARE A LOT OF INTERESTING WAYS TO DO STUDIES,

YOU KNOW, BAYESIAN METHODS AS YOU GO ALONG. THERE ARE PLENTY OF OTHER RELATED ACTIVITIES. THIS ISN'T QUITE THE AUDIENCE FOR THAT, BUT I THINK THAT WE'RE AIMING FOR ARE FAIRLY ROBUST INTERVENTIONS WHEN YOU'RE GOING TO DO SOMETHING THAT'S INVASIVE THAT CAN CAUSE HARM, NOT ONLY BY WHAT THE CELLS DO, BY THE FACT THAT YOU MAY DAMAGE TISSUE.

CHAIRMAN LO: JOSE.

DR. CIBELLI: QUICK QUESTION. BASED ON YOUR EXPERIENCE, DO YOU THINK THAT WE HAVE, JUST FOR SPINAL CORD INJURY OR PERHAPS STROKES TOO, DO YOU THINK WE HAVE THE BEST OR WE HAVE ADEQUATE ANIMAL MODEL OR WE SHOULD ALSO SPEND TIME AND MONEY TRYING TO DEVELOP BETTER ANIMAL MODELS? THE FACT THAT YOU SHOWED THE PICTURE OF THE SIZE OF THE SPINAL CORD IN THE RAT VERSUS THE SIZE, SO I WONDERED IF WE SHOULD ALSO BE THINKING ABOUT DEVELOPING BETTER ANIMAL MODELS, OR YOU THINK IT'S FINE? WE'RE OKAY?

DR. DOBKIN: ONE OF THE NOTIONS BEHIND COLLABORATIONS IS THAT EVERY LAB HAS ITS MODEL. AND WHAT YOU'D LIKE TO SHOW IS ROBUST EFFECTS ACROSS MODELS, AND THAT WOULD GIVE YOU MORE CONFIDENCE THAT THESE MODELS THAT REPRESENTED, EVEN IF THEY WERE DIFFERENT STRAINS OF MICE OR RATS OR A RAT AND A PIG MODEL OR A COUPLE OF NONHUMAN PRIMATES TO LOOK AT

SAFETY AND PROOF OF PRINCIPLE ABOUT REGENERATION, ALL THOSE THINGS, I THINK, ARE TERRIBLY IMPORTANT FOR PRECLINICAL STUDIES. AND THEY'RE BEING DONE NOW WITHOUT A LOT OF FANFARE FOR SPINAL CORD INJURY.

A GUY AT UCSD, MARK TUSZYNSKI, HAS AN ABSOLUTELY GREAT SPINAL CORD INJURY MODEL IN NONHUMAN PRIMATES. ANOTHER GUY, LEIF HAVTON, HAS A GREAT CONUS CAUDA EQUINA INJURY MODEL IN MONKEYS. YOU CAN'T DO A LOT OF ANIMALS, BUT YOU DO ALL OF YOUR WORK IN A COUPLE OF RODENT MODELS, AND THEN YOU APPLY THEM TO THE LARGER ANIMAL, AND JUST SEE ARE YOU GETTING A REPRODUCIBLE RESULT.

CHAIRMAN LO: OVER ON THIS SIDE, ALTA.

DR. CHARO: IN ORDER TO MAINTAIN A PROPERLY BLINDED STUDY, WILL IT BE NECESSARY TO PERFORM SHAM SURGERIES FOR MOST OR ALL OF THE NEUROLOGICAL STUDIES YOU'RE TALKING ABOUT? THAT'S CERTAINLY BEEN A TOPIC IN THE PAST THAT'S GENERATED A LOT OF DISCUSSION ABOUT APPROPRIATE RISK LEVELS FOR HUMAN SUBJECTS.

DR. DOBKIN: I THINK THAT THE SHAM SURGERY IS A NO-BRAINER. IT'S EASY TO DO. IT HAS TO BE DONE. WHETHER YOU HAVE TO INJECT SOMETHING DEPENDS ON WHAT YOUR BIOLOGICAL INTERVENTION IS. SO SHAM SURGERIES HAVE BEEN DONE IN -- I MEAN I WAS PART OF

THE ECIC BYPASS TRIAL YEARS AGO. THIS IS A TRIAL WHERE EVERY NEUROSURGEON IN THE UNITED STATES SAID IT IS UNETHICAL TO WITHHOLD THIS SURGERY FROM PATIENTS THAT HAVE HAD A STROKE. AND WE DID IT. IT TURNED OUT THAT THE SURGERY WAS USELESS. IN FACT, IT INDUCED MORE STROKES THAN THE ALTERNATIVE. BUT YOU HAD TO DO A SHAM SURGERY OR EVERYBODY WOULD HAVE KNOWN WHAT WAS GOING ON. THE PARKINSON'S TRIALS SHOWED YOU CAN GET BY WITH SHAM SURGERIES.

SO IT'S EASY TO MAKE A WOUND OPENING, BUT IT CAN BE VERY DIFFERENT WHEN THE ISSUE OF YOU INJECT SOMETHING IN THERE. SO IT DEPENDS ON WHAT YOU'RE TALKING ABOUT, WHAT YOU'RE TRYING TO DO. IF YOU HAVE A CELL-SPECIFIC TYPE, YOU MAY NOT HAVE TO INJECT ANYTHING.

BUT I WOULD PROPOSE TO YOU THAT THE BEST TREATMENT FOR PARKINSON'S DISEASE IS JUST PUTTING A HOLE IN THE BRAIN. THAT'S THE WAY IT WAS DONE FOR 25 YEARS. PEOPLE DID THALAMIC CRYOTHERAPY. I WATCHED DOZENS OF THEM, AND YOU GOT RID OF THE TREMOR, YOU GOT RID OF THE STIFFNESS IN PATIENTS WITH PARKINSON'S DISEASE. SO IF YOU'RE GOING TO PUT CELLS INTO A PARTICULAR REGION OF BRAIN THAT'S PART OF A NETWORK THAT DRIVES TREMORS AND AKINESIAS AND THAT SORT OF THING, YOU HAVE TO INTERRUPT THAT TRACK

THE SAME WAY AND PUT A LESION IN THE SAME SPOT.

IN THE SPINAL CORD IT WOULD BE DIFFERENT. YOU WOULDN'T NECESSARILY HAVE TO STICK SOMETHING IN THERE IF YOU KNOW THAT IT'S SEVERELY DAMAGED. I THINK YOU HAVE TO LOOK AT EVERY -- YOU JUST DON'T WANT TO DRAW GENERAL RULES AND THEN TRY TO STICK WITH THEM.

CHAIRMAN LO: SHERRY.

MS. LANSING: I REALLY HAVE NEVER HEARD THIS, AND THIS IS MY NAIVETE, BUT WHAT IS A SHAM SURGERY? DO YOU ACTUALLY MEAN YOU GO THROUGH AND PRETEND YOU DID THE SURGERY?

DR. DOBKIN: IT COULD TAKE A COUPLE FORMS. IN THE SOME OF THE STUDIES, SO LET'S SAY IT'S A BRAIN SURGERY. SO ONE GROUP YOU OPEN UP THE SKIN, YOU REMOVE SOME OF THE SKULL, AND LET'S SAY YOU IMPLANT A BLOOD VESSEL AND ANOTHER BLOOD VESSEL AND PUT CELLS IN THERE. THAT WOULD BE THE EXPERIMENTAL GROUP. THE OTHER GROUP, YOU WOULD MAKE THE INCISION, HAVE ANESTHESIA, MAKE THE INCISION, YOU MIGHT OPEN THE SKULL, AND THEN YOU CLOSE IT.

MS. LANSING: THAT'S HORRIBLE. THAT'S HORRIBLE.

DR. DOBKIN: AND THE REASON IS --

DR. CHARO: I THINK WE CAN STIPULATE FOR

THE RECORD THAT IT HAS A REAL SHOCK VALUE FOR PEOPLE THAT HAVE NEVER THOUGHT ABOUT THIS BEFORE.

MS. LANSING: I'M JUST STUNNED. I KNOW THIS IS PUBLIC AND I'M A PATIENT ADVOCATE. I NEVER HEARD THAT BEFORE.

DR. DOBKIN: THE REASON IS THAT THE MERE MANIPULATION OF THAT SKULL LEADS TO THE PRODUCTION OF FACTORS IN THE BRAIN THAT CAN ACTUALLY CHANGE WHAT YOU'RE LIKE. THE ANESTHESIA CAN AFFECT THINGS. SO YOU NEED TO DO SOME OF THESE THINGS.

DR. TROUNSON: THERE ARE NOT REALLY A LOT OF THE PATIENTS NECESSARILY WILL AGREE TO UNDERGO THESE TRIALS WHERE YOU HAVE A SHAM PLACEBO. THEY JUST WON'T DO THAT. IT'S NOT IN THEIR INTEREST TO DO THAT. YOU KNOW, THEY EITHER WANT THE TREATMENT OR NOTHING. AND SO IT'S VERY DIFFICULT TO DO WHAT YOU SAY.

DR. DOBKIN: BUT WHAT'S INTERESTING IS THAT TODAY, BECAUSE OF THE NUMBER OF SHAM SURGERY RANDOMIZED CLINICAL TRIALS THAT WE'VE DONE, IT WOULD BE MUCH HARDER IF THIS WAS 1978, BUT BECAUSE OF THE NUMBER THAT HAVE BEEN DONE AND THE TREMENDOUS DIFFERENCE IN OUTCOMES BEYOND WHAT WERE EXPECTED, IT TURNS OUT THAT I THINK MOST SURGEONS WOULD AGREE WITH IT.

HERE'S A GREAT EXAMPLE OF THIS. IN THE '50S AND EARLY '60S, THERE WERE THOUSANDS OF PEOPLE GETTING VEINS GRAFTED ONTO THE SURFACE OF THE HEART. AND THIS PREVENTED HEART ATTACKS. AND AFTER DOING THIS -- IS ANYBODY FAMILIAR WITH THE STORY? THESE VENOUS GRAFTS, THEY WENT ON FOR TEN YEARS, AND SOMEBODY FINALLY SAID, YOU KNOW, I DON'T KNOW WHY THIS WOULD WORK. AND SO THEY DID A CLINICAL TRIAL, AND THEY DID A SHAM SURGERY VERSUS NO SURGERY -- I MEAN DID A SHAM SURGERY VERSUS ACTUALLY PUTTING THE VEINS IN. IT TURNED OUT IT DIDN'T HELP AT ALL. THAT LED TO THE DEVELOPMENT OF CORONARY ARTERY BYPASS SURGERY. IF YOU HADN'T DONE THAT TRIAL, PEOPLE WOULDN'T HAVE TRIED TO IMPROVE ON THE FACT THAT, HEY, THIS DOESN'T REALLY WORK. WE NEED TO GET BLOOD PAST THE BLOCKAGE. THERE'S EXAMPLE AFTER EXAMPLE OF THAT, AND IT'S FRIGHTENING.

MS. LANSING: ARE YOU TELLING ME THAT THEY DID -- I STILL CAN'T EVEN -- I'M SORRY TO TAKE UP EVERYBODY'S TIME AND I DON'T WANT TO. BUT YOU ARE TELLING ME THEY GRAFTED THE VEINS ON AND PEOPLE THOUGHT IT WAS WORKING?

DR. DOBKIN: PEOPLE SAID THEY HAD LESS ANGINA AND LESS SHORTNESS OF BREATH. AND BY HISTORICAL CONTROLS, THESE FOLKS SEEMED TO BE LIVING

A LITTLE LONGER. AND SO THE IDEA WAS IT MUST WORK. BUT THEN YOU ASK YOURSELF COMPARED TO WHAT.

MS. LANSING: THEN PEOPLE THOUGHT THEY HAD THAT DONE TO THEM AND THEY HAD THE SAME LIFE SPAN.

DR. DOBKIN: JUST BECAUSE THEY THOUGHT. THEY THOUGHT -- THE PATIENTS THOUGHT IT MUST BE HELPING THEM, AND SO THEY DID MORE AND THEY ACTUALLY EXERCISED MORE AND PROBABLY IMPROVED BLOOD FLOW TO THE HEART BY EXERCISING MORE, FEELING THAT NOW THEY WERE PROTECTED.

MS. LANSING: BUT IT SEEMS TO ME -- IT'S A WHOLE BIGGER QUESTION. IT SEEMS TO ME IF YOU SAID I'M GOING TO HAVE A CONTROL GROUP AND YOU'RE NOT GOING TO GET IT AND WE'RE GOING TO TELL YOU WE DON'T KNOW IF THIS WORKS AND WE WANT YOU TO EXERCISE MORE AND EAT MORE, YOU MIGHT BE ABLE TO GET THE SAME RESULTS RATHER THAN PUTTING SOMEONE THROUGH, WHICH EVEN THE BEST SURGEON WILL TELL YOU THAT EVEN THE MOST MINOR SURGERY HAS SOME RISK ATTACHED TO IT.

DR. DOBKIN: SO WE HAVE TO LOOK AT EACH INDIVIDUAL ENTITY. LIKE I SAID, FOR PARKINSON'S YOU'VE GOT TO DO IT SIMPLY BECAUSE THE MANIPULATION OF THE SITE, YOU INTERFERE WITH THE CIRCUIT, AND WE ALREADY KNOW BECAUSE IT WAS A TREATMENT THAT WORKED NICELY FOR A WHILE IN EACH PATIENT. WE KNOW WE HAVE

TO INTERRUPT THAT; WHEREAS, OTHER TRIALS YOU MAY NOT HAVE TO GO THAT FAR.

CHAIRMAN LO: SHERRY, THIS IS IMPORTANT. LET'S COME BACK. I THINK MARIE HAS AN EXAMPLE FOR US A LITTLE LAYER OF A STEM CELL --

DR. CSETE: ACTUALLY I THINK IT MAKES SENSE FOR ME TO FOLLOW BRUCE BECAUSE THESE QUESTIONS COME UP IN WHAT I'M GOING TO TALK ABOUT.

CHAIRMAN LO: WHY DON'T WE --

DR. CSETE: AND THEN IAN WILL COME UP.

CHAIRMAN LO: YES. I DEFINITELY WANT TO GET TO IAN. SO LET'S -- IF WE CAN ASK THIS RIGHT SIDE TO HOLD QUESTIONS TILL LATER.

DR. CSETE: BECAUSE IT MAY COME UP HERE.

CHAIRMAN LO: THANK YOU, BRUCE.

DR. CSETE: SO I'M GOING TO TALK TO YOU ABOUT WHAT'S IN THE LITERATURE ABOUT VARIOUS KINDS OF STEM CELL THERAPIES THAT HAVE HAPPENED FOR PARKINSON'S AS WE ANTICIPATE GOING AHEAD TO HUMAN EMBRYONIC STEM CELL-DERIVED THERAPIES FOR PARKINSON'S. THIS WILL TELL YOU AN AWFUL LOT OF WHAT WE KNOW, AND IT WILL TELL YOU AN AWFUL LOT OF WHAT WE DON'T KNOW. AND THE DIFFICULT QUESTIONS I THINK WE'RE GOING TO HAVE TO FACE AS A TRANSLATIONAL COMMUNITY IS WHEN WE ADVANCE A THERAPY, AS I SAID

BEFORE, WITH ACKNOWLEDGED UNKNOWNS. SO YOU ALREADY HAD A LITTLE BIT OF AN INTRODUCTION TO PARKINSON'S DISEASE, BUT EVERYONE WHO WORKS WITH CIRM KNOWS PATIENTS WHO HAVE PARKINSON'S DISEASE. AND THIS IS A TERRIBLE DISEASE THAT'S PROGRESSIVE. IT'S COMMON. PATIENTS HAVE TREMORS, SHAKING THEY CAN'T CONTROL. THEY HAVE RIGID MUSCLES THEY CAN'T CONTROL. THEY HAVE VERY SLOW MOVEMENTS THEY CAN'T CONTROL, AND THEIR POSTURE IS ABNORMAL. BUT IN ADDITION, THEY HAVE ENORMOUS PSYCHOLOGICAL DISTURBANCES, SLEEP DISTURBANCES, AND SYSTEMIC PROBLEMS.

THE CAUSE OF PARKINSON'S IS THE LOSS OF A PARTICULAR NEURONAL POPULATION. AGE IS THE MAJOR RISK FACTOR, AND THE NEURONS THAT ARE LOST MAKE A CHEMICAL CALLED DOPAMINE. AND ITS REPLACEMENT IS CURRENTLY THE MAINSTAY OF TREATMENT.

PEOPLE HAVE BEEN TRYING TO CELLS TO TRANSPLANT -- CELL TRANSPLANTS FOR PATIENTS WITH PARKINSON'S FOR A LONG TIME. AND IN THE '80S ALL OVER THE WORLD THERE WERE MOSTLY FETAL-DERIVED NEURAL CELLS THAT WERE PUT INTO PATIENT'S BRAIN IN AN OPEN LABEL WAY, IN AN UNCONTROLLED WAY. AND THESE INITIAL ATTEMPTS SHOWED THAT THE GRAFTS COULD SURVIVE, AND THERE SEEMED TO BE SOME IMPROVEMENT IN SOME PATIENTS, BUT WE SHOULD ALWAYS SAY THAT THAT'S

A CAUTIONARY TALE. AND, IN FACT, THERE HAVE BEEN SUBSTANTIAL NUMBERS OF PATIENTS WHO HAVE RECEIVED EMBRYONIC TRANSPLANTS, NOT EMBRYONIC STEM CELLS, EMBRYONIC TRANSPLANTS, IN WHICH THERE SEEMED TO BE SAFETY AND IN SOME CASES SOME IMPROVEMENT.

BUT EVERYONE'S ATTENTION WAS ARRESTED WHEN A REPORT CAME OUT IN 2000, THIS WAS A UNITED STATES-BASED STUDY, THAT WAS RANDOMIZED DOUBLE BLIND AND CONTROLLED IN WHICH 40 PATIENTS WERE RANDOMIZED TO EITHER GET CULTURED FETAL CELLS OR A SHAM SURGERY. AND THERE WERE FOUR EMBRYOS USED TO COLLECT CELLS AND PUT INTO ONE PART OF THE BRAIN. NO IMMUNOSUPPRESSION WAS USED. BUT HERE'S AN IMPORTANT THING. FOR EMBRYOS THERE WAS NO MARK OF POTENCY IN THESE CELLS, CELL NUMBER WAS NOT NORMALIZED. OVERALL IF YOU ASK THE PATIENTS ABOUT THEIR OWN PROGRESS, THEY CLAIMED THEY DID NOT GET BETTER AS A RESULT OF THE TRANSPLANTS. DID PATIENTS GET HARMED FROM THIS THERAPY? PERHAPS YES. SEVERAL YEARS OUT FIVE OF THE PATIENTS DEVELOPED VERY SEVERE MOVEMENT DISORDERS.

OTHER TRIALS FOLLOWED, BUT ANOTHER RANDOMIZED TRIAL USED, INSTEAD OF INDIVIDUAL CELLS FROM FETAL BRAINS, USED BASICALLY SLICES OF BRAIN AND COMPARED ONE VERSUS FOUR DONORS. SO THIS WAS

SORT OF A DOSE RESPONSE TEST. AND THERE WAS SOME SUGGESTION THAT THE LARGER DOSE WAS BETTER FOR SOME PATIENTS, AND LONG TERM, AGAIN, NO DIFFERENCE BETWEEN PATIENTS.

SO HOW DO YOU TELL IF PATIENTS ARE GETTING BETTER OR NOT? IT'S ACTUALLY PRETTY DIFFICULT. AND I WANTED TO JUST SAY SOMETHING ABOUT TIMING, AND WE CAN'T GO INTO THE KIND OF NEUROLOGIC TESTS THAT ARE SO CRITICALLY IMPORTANT AND DR. DOBKIN TOUCHED ON. BUT IN THIS PARTICULAR ASSAY OF HOW A PARKINSON'S PATIENT IS DOING, IT'S A SERIES OF TASKS FOR THE PATIENT. THE HIGHER NUMBER IS NOT WHAT YOU WANT. YOU WANT TO HAVE A LOWER NUMBER. YOU'RE PERFORMING BETTER WITH A LOWER NUMBER.

IF YOU JUST COMPARE THIS TIME POINT TO THIS TIME POINT, FOR EXAMPLE, PATIENTS HERE WOULD LOOK SIGNIFICANTLY BETTER AT THIS EIGHT-MONTH TIME POINT AND MAYBE THEN PATIENTS WHO WERE HERE, BUT THE LONG-TERM ANALYSIS REALLY SHOWED THAT THERE WAS NO DIFFERENCE BETWEEN THESE TWO GROUPS OF PATIENTS. FORGET THE DETAILS OF THE STUDY. IT'S REALLY IMPORTANT THAT THE TIMEFRAME GO OUT FOR A VERY, VERY LONG TIME.

DR. TAYLOR: WHAT WAS THE DURATION THOUGH? WHAT WAS THE DURATION? ONE COULD INTERPRET THIS AS

A SHORT-TERM IMPROVEMENT. WHEN DOES IT GO BACK TO BASELINE?

DR. CSETE: THESE ARE MONTHS HERE. SO THIS IS TWO YEARS TOTAL ACROSS THE GRAPH.

SO IT'S REALLY COMPLICATED. DR. DOBKIN TALKED ABOUT THE KIND OF DIFFERENCES THAT ALL THE PATIENTS HAVE, BUT THE CELL SOURCE IS AN ENORMOUS ISSUE. WHAT AGE EMBRYOS ARE USED, WHAT PART OF THE BRAIN, THE CELL NUMBER IS AN IMPORTANT ISSUE. ARE THEY CULTURED? ARE THEY NOT? HOW ARE THEY STORED? AND THERE WERE NO POTENCY ASSAYS IN ANY OF THESE TRIALS.

AND I'LL REMIND PEOPLE THAT SOME INVESTIGATORS ARE NOW TALKING ABOUT STEM CELL THERAPIES WHERE THEY WOULD ARM THE CELLS FOR SURVIVAL USING GROWTH FACTORS LIKE GDNF. AND GDNF TRIALS WERE STOPPED BECAUSE A LITTLE TOO MUCH OF IT GAVE PEOPLE TERRIBLE PSYCHIATRIC PROBLEMS.

WE NEED TO LOOK AT AN EFFECT IN MULTIPLE ANIMAL MODELS, AND IT IS INTERESTING THAT THE GERON IND WAS APPROVED IN CONTRAST TO THE ANIMAL RULE OF THE FDA WITH ONLY ONE SPECIES BEING LOOKED AT. THE DISEASE STATE OF THE PATIENT IS IMPORTANT AND OTHER PATIENT FACTORS. IMMUNOSUPPRESSION IS CLEARLY IMPORTANT. THE OTHER DRUGS THE PATIENT IS ON MAY

AFFECT THE CELLS. THE SURGICAL SITE, THE TECHNIQUE, PLACEMENT, VERY COMPLICATED.

SO TAKING THESE PATIENTS OUT LONG-TERM, SOME OF WHOM WERE FROM THAT ORIGINAL TRIAL THAT I TOLD YOU ABOUT, AND OTHERS FROM EARLY TRIALS, NOW SOME OF THE PATIENTS HAVE PASSED AWAY AND AUTOPSY RESULTS ARE BEING RECORDED IN THE LITERATURE JUST RECENTLY. AND THERE IS SURVIVAL OF THE GRAFTS LONG TERM, BUT SURVIVAL OF THE GRAFT DOES NOT NECESSARILY CORRELATE WITH THE PATIENT OUTCOME.

IN ONE STUDY HALF THE PATIENTS DEVELOPED ACTUAL PARKINSON'S LESIONING IN THE CELLS THAT WERE TRANSPLANTED. SO THE DISEASE THAT WAS IN THE BRAIN OCCURRED IN THE TRANSPLANTED CELLS. AGAIN, NOT WELL CORRELATED NECESSARILY WITH THE PATIENT'S CLINICAL PROGRESS.

IN ANOTHER STUDY FROM CANADA, THE NEURONS THAT THE INVESTIGATORS IMPLANTED IN AN AREA OF THE BRAIN THAT'S DOPAMINERGIC, THINKING THAT THESE PRIMITIVE NEURONS WOULD DEVELOP ONLY INTO DOPAMINERGIC NEURONS, THEY DEVELOPED INTO OTHER KIND OF NEURONS AS WELL. AND GRAFTING IN ONE LOCATION DOESN'T IMPROVE DISEASE IN OTHER IMPORTANT AREAS OF THE BRAIN. SO THIS IS AN IMPORTANT THING TO CONSIDER BECAUSE THE INITIAL DYSKINESIAS, THE

INITIAL MOVEMENT DISORDERS THAT WERE A COMPLICATION OF THE *NEW ENGLAND JOURNAL* TRIAL WERE JUST THE INVESTIGATORS THOUGHT THAT THAT WAS A DOSING PROBLEM. MAYBE THOSE PATIENTS GOT TOO MUCH DOPAMINE. BUT I THINK THAT'S TOO MUCH OF A SIMPLISTIC ANSWER.

SO I TOLD YOU THAT THERE WAS AN AWFUL LOT OF QUESTIONS. THESE VARIABLES THAT HAVE NOT YET BEEN OPTIMIZED IN THE LITERATURE ALTHOUGH QUIETLY IN PLACES LIKE LUND, THERE ARE THESE KINDS OF TRANSPLANTS STILL GOING ON FOR PATIENTS WITH PARKINSON'S DISEASE, AND YOU CAN HEAR SOME RESULTS AT NEUROSOCIETY MEETINGS, ALTHOUGH THEY HAVEN'T REALLY REPORTED LARGE NUMBERS OF PATIENTS IN THE LITERATURE.

WE DON'T KNOW THESE VERY BASIC VARIABLES, AND YET WHY ARE WE GOING AHEAD AND THINKING EMBRYONIC STEM CELL-DERIVED DOPAMINERGIC NEURONS FOR TRANSPLANTATION? WELL, THE OBVIOUS THING IS THAT FETAL SOURCES ARE HARD TO GET, AND EACH ONE WOULD BE DIFFERENT. THEY'D HAVE ENORMOUS VARIABILITY. AND EMBRYONIC STEM CELLS OFFER THE HOPE THAT THIS HOPE ISSUE OF THE CELL PREPARATION, THE CELL STANDARDIZATION, THE POTENCY ISSUES COULD BE WORKED OUT, AND THERE WOULD BE A MASTER BANK WHERE YOU

WOULD HAVE A RELIABLE WAY TO KNOW BASICALLY THE DOSE OF THE CELL THAT YOU'RE GIVING.

BUT WE'RE ALSO GOING TO HAVE TO DO SOME MAJOR WORK IN DEFINING WHAT HAPPENS TO THESE CELLS IN THE ANIMAL MODEL. SO YOU'RE TRYING TO PICK A CELL THAT ISN'T GOING TO PROLIFERATE INAPPROPRIATELY, BUT WILL DIFFERENTIATE APPROPRIATELY. AND FINDING THAT STAGE OF DIFFERENTIATION IN WHICH TO TRANSPLANT THE CELL IS NOT GOING TO BE TRIVIAL, I THINK.

SO IS IT ETHICAL FOR US TO, DESPITE ALL THE GAPS IN KNOWLEDGE, WITH THE FETAL CELL TRANSPLANTS COMPARE EMBRYONIC STEM CELL-DERIVED GRAFTS TO THESE IN A HISTORICAL WAY OR IN AN ACTUAL TRIAL? NOBODY REALLY KNOWS THE ANSWERS TO THESE. BUT I THINK THE IMPORTANT ISSUE IS GOING BACK TO ORIGINAL PATIENTS, AS MANY AS CAN BE FOUND, WITH THE INVESTIGATORS AND GETTING AS MUCH INFORMATION FROM EACH INDIVIDUAL PATIENT AS POSSIBLE. AND IT'S OUR DUTY TO SUPPORT TRIALS THAT ARE ABSOLUTELY TRANSPARENT IN THIS REGARD.

SO THERE ARE FUNDAMENTAL QUESTIONS, SOME OF WHICH WE WON'T HAVE TO ANSWER TO GO AHEAD, BUT WE'LL HAVE TO MAKE DECISIONS AS A COMMUNITY ABOUT HOW MUCH ANSWER WE NEED TO GO AHEAD. WHY DO SOME

GRAFTS GET RECURRENT DISEASE? DOES IT REALLY MATTER? EARLY DISEASE PATIENTS, LATE DISEASE PATIENTS, WHO'S THE RIGHT POPULATION? MAYBE PATIENTS WITH EARLIER DISEASE ARE THE ONES WHO RESPOND BEST TO CELL TRANSPLANT THERAPIES, BUT MAYBE THEY'RE MORE AT RISK FOR THE COMPLICATIONS OF CELL TRANSPLANT THERAPIES.

THE INFLUENCE OF IMMUNOSUPPRESSION ON THE GRAFT IS A WHOLE OTHER ISSUE, AND THAT FUNCTION IS STILL NOT CLEAR.

SO I JUST WANTED TO TANTALIZE YOU A LITTLE BIT WITH THE FACT THAT THERE HAVE BEEN -- THERE'S BEEN A PROCESS THROUGH WHICH VARIOUS KINDS OF STEM CELL THERAPIES HAVE PROCEEDED INTO THE CLINIC AND INCLUDING IN SOME RELATIVELY WELL-DESIGNED SMALL TRIALS WITHOUT THE ANSWERS BEING KNOWN. SOME THINGS HAVE BECOME CLEAR FROM THESE TRIALS, BUT A WHOLE LOT OF QUESTIONS HAVE ARISEN AS WELL, AND YET WE ARE EMBARKING ON A NEW ERA WITH A NEW CELL TYPE, AND NOT HAVING THE FOUNDATION BEING COMPLETELY LAID DOWN FOR US.

CHAIRMAN LO: QUESTIONS. JOHN, THEN WE'LL SWING.

DR. WAGNER: WELL, FIRST OFF, I'M NOT AN EXPERT IN PARKINSON'S DISEASE, SO WHAT I SAY MAY NOT

BE COMPLETELY APPROPRIATE. ON THE OTHER HAND, YOU KNOW, YOU CAN LOOK AT THE CURVE FROM LUND AND SAY THAT'S A FAILURE BECAUSE LONG TERM THERE WAS NO BENEFIT, HOWEVER IT WAS MEASURED. HOWEVER, YOU CAN ALSO LOOK AT THAT AND SAY THAT WAS A TREMENDOUS SUCCESS BECAUSE OF THE FACT THAT YOU HAD SOME TRANSIENT IMPROVEMENT, PERHAPS WHATEVER THE MEASUREMENT WAS. AND LIKE ANY DRUG THERAPY THAT WE GIVE, NO MATTER WHAT THE INDICATION IS, BUT LET'S SAY CANCER, YOU KNOW, OFTENTIMES WE FIND OUT THAT WE LEARN ONE LESSON FROM THE FIRST STUDIES. AND AS YOU SAID, THERE ARE A NUMBER OF VARIABLES.

SO ONE OF THE LESSONS IS CAN YOU DECREASE THE VARIABLES? NO. 2, YOU ALSO HAVE SOME DATA TO SUGGEST THAT MAYBE THESE TRANSPLANTED CELLS ACQUIRED SOME ASPECT OF THE DISEASE ITSELF. AGAIN, THAT GIVES US A PIECE OF INFORMATION FROM WHICH WE CAN MOVE FORWARD ON.

YOU KNOW, COULD HAVE BEEN IMMUNOREJECTION OF SOME SORT TO THOSE CELLS ALTHOUGH THEY HAD A TRANSIENT IMPROVEMENT. AND AGAIN, SO WHAT YOU'VE DONE IS THAT YOU'VE ACTUALLY LEARNED A FAIR AMOUNT OR AT LEAST SOME CLUES, LET'S SAY. I CAN'T SAY LEARNED BECAUSE THE NUMBERS OF PATIENTS ARE TOO TINY. BUT YOU CAN SAY YOU HAVE SOME CLUES THAT

MIGHT HELP YOU DESIGN BETTER TRIALS IN THE FUTURE. YOU'RE RIGHT. IT DOESN'T GIVE US THE BACKGROUND THAT YOU WOULD LOVE TO HAVE HAD OF 300 PATIENTS RECEIVING ONE UNIFORM STANDARD CELL POPULATION ALL DELIVERED THE EXACT SAME WAY IN THE SIMILAR PATIENT POPULATION. IT'S NOT GOING TO EXIST, BUT YOU DO HAVE SOME INFORMATION. ALL YOU CAN SAY IS AT THE END OF THE DAY, I CAN TRY TO IMPROVE UPON THE DESIGN OF THE STUDY, I CAN TRY TO HAVE BETTER READOUT ASSAYS FOR THE NEXT TRIALS, WHETHER IT BE WITH ES-DERIVED THERAPEUTICS OR SOME OTHER STEM CELL OR SOME OTHER CELL POPULATION.

SO THERE'S THINGS THAT YOU CAN DO TO MAKE IT BETTER, BUT I THINK THAT THE ONE THING THAT YOU'RE ALLUDING TO IS IS THAT THE APPROPRIATE DISEASE MODEL FROM WHICH TO EVEN START ES CELL THERAPY IN? AND THAT'S A TOTALLY DIFFERENT QUESTION THAT YOU CAN ANSWER EITHER WAY. I DON'T KNOW WHAT THE RIGHT ANSWER IS.

DR. CSETE: I THINK YOU JUST PARAPHRASED MY TALK.

DR. WAGNER: I DON'T WANT YOU TO LOOK AT THAT AND SAY THAT'S A FAILURE EITHER BECAUSE THERE WERE MANY LESSONS THAT WERE LEARNED ALONG THE WAY THAT WERE NOT BAD ONES.

DR. CSETE: I ABSOLUTELY DIDN'T SAY IT WAS A FAILURE.

DR. WAGNER: I THINK THAT ONE LAST THING YOU SAID WAS TRANSPARENCY, AND THAT GETS BACK TO YOUR COMMENT AND ONE OF YOUR CONCERNS ABOUT THE STUDIES IN CHINA AND CENTRAL AMERICA AND ALL THAT STUFF IS THAT THE TRANSPARENCY DOESN'T EXIST. AND HOPEFULLY IN ACADEMIC CENTERS, AND, OF COURSE, THERE'S EXCEPTIONS BECAUSE IF YOU WANT TO BE NONTRANSPARENT, YOU CAN, BUT THE ONE THING THAT YOU CAN DO HERE IN CALIFORNIA IF YOU WANT CIRM MONEY, YOU CAN SOMEHOW AT LEAST MAKE IT SO THAT YOU CAN HAVE SOME LEVEL OF TRANSPARENCY IN THESE ACADEMIC CENTERS SO THAT YOU AT LEAST HAVE GREATER CHANCE OF LEARNING SOMETHING. BECAUSE IF WE PROMISE NOTHING ELSE TO OUR PATIENTS, WE SHOULD AT LEAST PROMISE THAT WE LEARN SOMETHING FROM WHAT WE DO.

DR. CSETE: RIGHT. SO YOU KNOW IT'S PRETTY CLEAR THAT SOME PATIENTS WERE HELPED. SOME PATIENTS HAD NO CHANGE. SOME PATIENTS WERE HURT. AND I THINK THE INTERESTING THING IS TRYING TO PICK OUT THOSE PATIENTS WHO ARE GOING TO BE HELPED. AND HUGE NUMBERS MAY BE REQUIRED, WHICH IS A TOUGH ONE.

SO, FOR EXAMPLE, IN THE CARDIAC STUDIES THAT WE SEE, MULTIPLE DIFFERENT KINDS OF CELLS BEING

USED, POST-MI, FROM MULTIPLE DIFFERENT KINDS OF SOURCES, IT'S PRETTY CLEAR NOW, WHEN YOU LOOK AT ALL THE LARGE NUMBERS OF THESE, THAT THE PATIENTS WHO HAVE A BENEFIT ARE THOSE WHO ARE MOST SICK. AND SO THE TRIALS THAT ARE NOW COMING OUT WILL BE DESIGNED FOR PATIENTS WHOSE REJECTION FRACTIONS ARE, SAY, LESS THAN 40 PERCENT, SOMETHING LIKE THAT.

AND THAT'S THE KIND OF DATA THAT GOING BACK AGAIN TO TALK TO THE INVESTIGATORS ABOUT THE INDIVIDUAL PATIENT CHARACTERISTICS AND TRYING TO DO SOME SORT OF A META ANALYSIS WITH THESE PUBLISHED DATA AND THINGS THAT ARE ONGOING MAY GET US SOME REAL BENEFIT FOR DESIGNING A NEW CELL THERAPY FOR THESE PATIENTS. EXACTLY RIGHT.

DR. WAGNER: JUST ONE LAST COMMENT THOUGH. AND THAT IS THAT WHEN YOUR COMMENT ABOUT WHETHER OR NOT WE SHOULD BE LOOKING AT EARLIER PHASE PATIENTS VERSUS LATER PHASE PATIENTS, ONE THING THAT WE'VE LEARNED IN CANCER TRIALS, AT LEAST MANY OF THEM, THEY OBVIOUSLY DO BETTER WITH BETTER PATIENTS WHEN YOU START OFF IN A BETTER CIRCUMSTANCE. BUT THAT'S NOT THE WAY YOU DESIGN YOUR FIRST-IN-MAN TRIALS. IT'S ALMOST TYPICALLY ALWAYS DONE IN THE WORST PATIENTS, AGAIN LOOKING AT THE TOXICITY PROFILE. AND, YOU KNOW, OBVIOUSLY YOU CAN CONTEST THAT.

THERE'S ARGUMENTS IN EVERY WAY, BUT AT LEAST THAT'S THE TRADITIONAL WAY TO START OFF. AND THEN WHEN YOU SAY YOU HAVE SOME DOSE FOR HOWEVER YOU CHOOSE THAT, THEN YOU TEND TO GO TO MORE BETTER --

DR. CSETE: RIGHT. SO I THINK THAT THIS -- I'D LIKE TO QUESTION THAT IDEA OF DOING THINGS IN THE SICKEST PATIENTS DEPENDING ON THE DISEASE. I THINK THE MORE IMPORTANT ISSUE IS THAT YOU NARROWLY DEFINE THAT PATIENT POPULATION SO THEY LOOK A LOT LIKE EACH OTHER, AND YOUR END POINTS ARE MORE ANALYZABLE.

DR. WAGNER: I DON'T DISAGREE.

DR. DOBKIN: ONE OF THE THINGS THAT COMES UP IN THE SENSE OF LEARNING OVER TIME IS HOW COMPLICATED PARKINSON'S IS. AND IT JUST WAS A MIRACLE THAT L-DOPA HAD SUCH A BENEFIT IN SOME PATIENTS IN THE MID-'60S. AND THEN THE IDEA WAS, WELL, LET'S MAKE L-DOPA SOMEHOW BE SQUIRTED OUT, SPRITZED OUT IN A MORE PHYSIOLOGICAL FASHION BY HAVING CELLS PRODUCE IT. AND ONE SMALL PART OF A VERY COMPLEX SET OF CIRCUITS WITH INHIBITION AND DISINHIBITION AND EXCITATION. AND WHAT WE'RE LEARNING IS THAT JUST THE SMALLEST MISPLACEMENT OF THOSE CELLS OR THAT DOPAMINE BEING AVAILABLE LEADS TO MOVEMENT DISORDERS. YOU'RE DRIVING A PARTICULAR

PATHWAY MORE THAN ANOTHER. SO, YOU KNOW, THE SCIENCE HAS GOTTEN INCREDIBLE SINCE MENDRAZO WAS DOING ADRENAL IMPLANTS INTO THE STRIATUM IN THE MID-'80S AND EVERYBODY GOT CURED UNTIL SOMEBODY DID A TRIAL AND FOUND OUT NOBODY WAS GETTING CURED.

THIS IS ANOTHER EXAMPLE OF HOW THE NERVOUS SYSTEM IS REALLY DIFFERENT THAN EVERYTHING ELSE. IT'S JUST -- IT JUST DOESN'T GET WIRED THE SAME WAY. IT'S JUST NOT A PANCREATIC --

DR. TROUNSON: BERNIE, THE ARGUMENT FOR HAVING A VARIETY OF ANIMAL SPECIES IS EXTREMELY COMPLICATED BY THE FACT THAT THERE ARE NOT STEM CELLS IN SOME SPECIES. SO YOU ADD ANOTHER FACTOR AS YOU MOVE ACROSS SPECIES THAT YOU'VE GOT TO USE HUMAN CELLS IN A MODEL WHERE YOU'VE GOT TO ADD A HUGE AMOUNT OF IMMUNE THERAPY TO STOP THE ATTACK. SO I DON'T THINK THIS IS A SIMPLE ISSUE EITHER. AND I THINK THAT'S PROBABLY ONE OF THE MATTERS THAT MUST HAVE FACED THE FDA WHEN THEY CONSIDERED THE GERON TRIAL. ALTHOUGH THE GENUINE MERITS OF GETTING ACROSS A WHOLE RANGE OF ANIMAL SPECIES AND REALLY WHAT IS THE ARGUED MERIT OF DOING A LOT OF VERY EXPENSIVE TRIALS WHEN THE MODELING IS REALLY QUITE DIFFERENT. YOU HAVE TO USE WHAT'S AVAILABLE TO YOU, I THINK, WHEREVER YOU MOVE IN THIS AREA, AND THAT

REALLY IS WHAT ARE THE VEHICLES AND OPPORTUNITIES EXISTING TO TEST OUT.

DR. CSETE: SO ALAN IS REFERRING TO THE ANIMAL RULE WHICH WAS JUST REISSUED A COUPLE WEEKS AGO BY THE FDA. AND UNLESS THERE ARE EXCEPTIONS, THE FDA EXPECTS FOR THESE NOVEL CELL THERAPIES THAT YOU WILL HAVE RESULTS IN TWO SEPARATE SPECIES. AND I ASKED GERON IN A PUBLIC MEETING ABOUT THIS, DID THE ANIMAL RULE AFFECT YOU. AND THEY SAID NO.

I MEAN ONE OF THE ISSUES WITH PARKINSON'S AND THE ANIMALS, I THINK THIS IS IMPORTANT TO STATE, IS THAT THERE'S REALLY NOT A GOOD ANIMAL MODEL. SO PHARMACOLOGICALLY INDUCED PARKINSON'S WHEN YOU JUST GO IN AND KIND OF POISON WITH A DRUG DOES NOT REALLY RECAPITULATE THE DISEASE. SO THAT'S ANOTHER LIMITATION THAT WAS THERE WHEN THEY STARTED FETAL TRIALS THAT IS STILL THERE RIGHT NOW AS WE PROCEED TO EMBRYONIC STEM CELL TRIALS.

CHAIRMAN LO: I'M GOING TO TRY AND GET SOME MORE QUESTIONS HERE.

DR. PRIETO: SORT OF A QUESTION AND COMMENT. COMING AT THIS FROM THE CLINICAL SIDE AND PATIENT ADVOCATE SIDE, I REALLY -- YOU KNOW, I FEEL THE KIND OF PRESSURES THAT I THINK YOU WERE ALLUDING TO, DR. DOBKIN, ALL THE TIME. I SAW A PATIENT

YESTERDAY WHO KNOWS OF MY INVOLVEMENT WITH THE CIRM AND HAS A SON WHO'S QUADRAPLEGIC AND SAID, YOU KNOW, WE'RE WAITING FOR YOU TO COME UP WITH SOMETHING FOR US. BUT I THINK THE MOST UNETHICAL THING WE COULD DO WOULD BE TO DO BAD SCIENCE OR INADEQUATE SCIENCE AND GIVE PEOPLE MISLEADING RESULTS.

SO TO SOME EXTENT I THINK YOU'RE PREACHING TO THE CHOIR HERE THAT WE ALL WANT TO SEE VALID RESULTS WITH REAL END POINTS THAT CAN BE MEASURED AND DIFFERENTIATED AND THAT MEANS SOMETHING TO PEOPLE CLINICALLY SO THAT WE CAN TELL THEM, YES, THIS IS A GOOD TREATMENT OR THIS IS NOT A GOOD TREATMENT. AND I UNDERSTAND THE RANDOMIZED CLINICAL TRIAL IS SORT OF THE GOLD STANDARD THAT WE'VE ALL ACCEPTED NOW, BUT I WONDER, ROD, YOU ALLUDED TO THIS EARLIER, ARE THERE OTHER MODELS AND WAYS OF GETTING THAT KIND OF GOOD INFORMATION THAT WE CAN GIVE PEOPLE DOWN THE ROAD.

DR. CSETE: AND IT'S PROBABLY DISEASE DEPENDENT. I'VE BEEN -- I SPENT A FAIR AMOUNT OF TIME THIS YEAR TALKING TO THE ALS PATIENT ADVOCATES, WHO HAVE BEEN VERY CONVINCING AT THE FDA LEVEL THAT THEY SHOULD NOT BE SUBJECT TO RANDOMIZED CLINICAL TRIALS BECAUSE THEIR DISEASE IS SO SHORT-LIVED AND NO PATIENTS WILL SIGN UP FOR IT. AND SO ONE OF THE

THINGS THEY DID AS A RESEARCH COMMUNITY WAS DEVELOP A HISTORICAL DATABASE THAT REALLY SERVES, THAT THE FDA AGREED WILL SERVE AS AN ARM FOR CLINICAL TRIALS IN THAT PARTICULAR POPULATION.

DR. PRIETO: DR. DOBKIN MADE A COMMENT. HISTORICAL CONTROLS SORT OF HAVE A BUILT-IN PROBLEM.

DR. CSETE: THEY ABSOLUTELY DO.

DR. PRIETO: THAT YOU DON'T KNOW HOW GOOD THE HISTORY TAKING WAS.

DR. CSETE: RIGHT.

DR. PRIETO: AND YOU CAN'T GO BACK AND, YOU KNOW, RECOLLECT IT. I THINK THE ARGUMENT THAT YOU HAVE TO MAKE TO PERSUADE PEOPLE FOR RANDOMIZED CLINICAL TRIALS IS THAT WE HAVE THIS NEW TREATMENT AND, YES, IT MAY MAKE YOU BETTER, IT MAY ALSO MAKE YOU WORSE. IT MAY DO NOTHING AT ALL. AND UNLESS WE DO A STUDY THAT CAN ANSWER THAT QUESTION, WE REALLY -- WE DON'T WANT TO SELL YOU FALSE HOPE. YOU CAN'T TELL THEM WE HAVE THIS TREATMENT AND WE THINK IT'S GOING TO BE GREAT. YOU HAVE TO TELL THEM WE THINK IT MIGHT BE GOOD. IT MIGHT BE BAD. IT MIGHT BE INDIFFERENT. AND YOU HAVE TO LAY THAT OUT JUST TO BE HONEST TO PEOPLE.

DR. CSETE: RIGHT. SO I THINK THERE ARE SITUATIONS IN WHICH THE DISEASE IS FATAL IN SUCH A

SHORT TERM, THAT YOU'RE NEVER GOING TO GET A PATIENT POPULATION. AND ALS IS THE EXAMPLE. BUT THERE ARE ALSO OTHER MODELS IN WHICH YOU COULD DESIGN -- WE WERE TALKING ABOUT THIS BEFORE -- IN DESIGNING FOR THE PLACEBO EFFECT THAT'S PART OF THE LITERATURE THAT ALREADY EXISTS TO CHANGE THESE MODELS SO THAT THEY'RE NOT QUITE SO RIGID. BUT IT ALL HAS TO BE DONE EXTREMELY CAREFULLY.

DR. TAYLOR: MARIE, IT DOES SEEM THAT IN A SITUATION LIKE THIS WHERE GETTING PATIENT CONSENT IS GOING TO BE A CHALLENGE, AND I'M NOT A STATISTICIAN, I DON'T KNOW HOW TO SORT OF SET UP THESE TABLES, BUT IF YOU HAD SORT OF MULTIPLES IN THE ACTIVE TREATMENT GROUP WITH SORT OF A SMALL NUMBER OF KIND OF PLACEBO SHAM SURGERY-TYPE INTERVENTIONS, YOU MIGHT GET AROUND SOME OF THE ETHICAL QUEASINESS THAT I THINK SHERRY WAS SORT OF DEMONSTRATING TO US AS WELL AS MAYBE ENCOURAGE MORE PATIENTS TO PARTICIPATE.

DR. CSETE: MOST OF THE BONE MARROW STEM CELL-DERIVED MI TREATMENTS THAT ARE REGISTERED NOW ARE TWO TO ONE OR THREE TO ONE.

DR. TROUNSON: ROB, WOULDN'T IT BE A LOT EASIER TO TALK TO THE PATIENTS THAT ARE NOT SO TERMINALLY ILL? THERE'S A BETTER CHANCE, IS THERE NOT, BECAUSE AT LEAST THEY'RE NOT INTO THAT TERRIBLE

CASCADE OF I'M REALLY HEADING FOR A DISASTER AND THEY'RE MORE LIKELY TO BE RESPONSIVE. IS THAT NOT TRUE?

DR. TAYLOR: I CERTAINLY THINK SO. AND ONE OF THE PROBLEMS WITH THE RCT, AS SOMEBODY WHO MADE IT THROUGH CALCULUS BY PARTIAL CREDIT, YOU KNOW, IT'S REALLY NICE TO DO AN EXPERIMENT WHERE IF THE WHOLE THING DOESN'T WORK PERFECTLY, AT LEAST YOU KIND OF LEARNED SOMETHING GOING ALONG THE WAY. AND UNFORTUNATELY THE RCT IS KIND OF DESIGNED TO HIT A HOME RUN EVERY TIME; WHEREAS, OTHER TYPES OF STUDY DESIGN THAT WE USE IN THE LABORATORY OFTEN, YOU CAN SEE A LITTLE DIP IN THE LINE AND YOU CAN SAY, WELL, YOU KNOW, AT TWO YEARS THIS DIDN'T LOOK ANY BETTER, BUT AT ONE YEAR MAYBE THIS WAS BETTER.

SO I THINK THAT ACTUALLY IDENTIFYING PATIENTS WHO ARE HEALTHIER, YOU HAVE MORE OF AN OPPORTUNITY TO SEE SOME OF THE PARTIAL CREDIT THINGS EVEN IF IT DOESN'T GIVE YOU EXACTLY THE KIND OF HOME RUN THAT YOU WOULD BEING LOOKING FOR. SO, YEAH, I THINK THAT'S A GREAT STRATEGY.

DR. CSETE: BUT I THINK POSTMARKETING SURVEILLANCE IS AN ACKNOWLEDGEMENT THAT THE HOME RUN ISN'T USUALLY THERE.

CHAIRMAN LO: I'M GOING TO TRY AND GET TWO

MORE QUESTIONS AND THEN TURN TO IAN. JEFF AND THEN DOROTHY.

MR. SHEEHY: I HAD A QUESTION MAYBE WITH A LITTLE BIT OF FOLLOW-UP. WHEN TRANSPLANTS WERE DONE, WERE THOSE RANDOMIZED CONTROLLED TRIALS?

DR. CSETE: NO. SO I LIVED THROUGH THE EARLY PARTS OF SOLID ORGAN TRANSPLANTATION, AS JEFF KNOWS. NO. THEY WERE NOT.

MR. SHEEHY: BONE MARROW TRANSPLANTS.

DR. CSETE: BONE MARROW TRANSPLANTATION, JOHN CAN SPEAK TO THE HISTORY THERE. IT WASN'T, I DON'T THINK, AT THE BEGINNING.

MR. SHEEHY: I WONDER BECAUSE I JUST WONDER WHY WE'RE IMPOSING THIS MODEL. IT SEEMS LIKE THE TRANSPLANT MODEL IS TO PRACTICE UNTIL YOU GET IT RIGHT BASICALLY, AND PATIENTS SUFFER A LOT. AND I'M JUST -- SO THAT'S ONE. I JUST -- I'M NOT CONVINCED. AND HAVING TALKED TO JOAN FROM THE PARKINSON'S COMMUNITY, THE VIRULENT ANTIPATHY, THAT I REALLY WISH JOAN WAS HERE, TO SHAM SURGERIES CANNOT BE UNDERSTATED BY SOME MEMBERS OF THE ADVOCACY COMMUNITY AND THE PATIENT COMMUNITY. AND I JUST -- I DON'T KNOW.

DR. CSETE: JEFF, WITH SOLID ORGAN TRANSPLANTATION YOU HAD THE OPPORTUNITY FOR AN

ALL-OR-NONE KIND OF RESULT. AND WE DON'T KNOW WITH REGENERATIVE THERAPIES YET EXCEPT IN A VERY FEW ANIMAL MODELS OF DISEASES THAT THE KIND OF EFFECTS ARE GOING TO BE SO HUGE TO JUSTIFY STEPPING OUT OF THE STATISTICAL HELP THAT WE GET FROM RANDOMIZED CONTROLLED TRIALS.

MR. SHEEHY: AND ALSO BRINGS IT TO THE POINT THAT I THINK DR. DOBKIN WAS TALKING ABOUT WITH THESE NEUROLOGICAL DISEASES. THERE'S SO MUCH THAT WE DON'T UNDERSTAND. YOU ALMOST HAVE TO DO A RANDOMIZED CONTROLLED TRIAL BECAUSE YOU'RE JUST THROWING A DART ON THE BOARD. AND I'M WONDERING IF AT ANY POINT WE WANT TO CONSIDER WHAT KIND OF EVIDENCE IS NECESSARY BEFORE IT'S REALLY ETHICAL TO PROCEED WITH THESE TRIALS. WHAT ANIMAL MODELS? I MEAN WHEN YOU HAVE GOOD ANIMAL MODELS THAT MIMIC THE DISEASE IN HUMAN BEINGS, WHEN YOU HAVE ADULT STEM CELL THERAPIES THAT WE SEE ARE WORKING, AND I GUESS DR. WAGNER IS OUT OF HERE. HIS GREAT EXAMPLE OF A LIMITED ADULT STEM CELL THERAPY IN A VERY SERIOUS DISEASE, THAT YOU MIGHT WANT -- WHERE YOU HAVE GREAT PROOF THAT IT WORKS, BUT I WONDER IF THAT'S MAYBE -- I JUST FEEL LIKE THE NEUROLOGICAL DISEASES WHICH WE'VE SPENT THE LAST COUPLE OF HOURS ON, I REALLY THINK WE'RE JUST TAKING A BIG GUESS WHETHER

THOSE ARE GOING TO WORK AND WHETHER WE'LL EVER REALLY KNOW WHAT HAPPENED IF THEY DO WORK.

DR. CSETE: I THINK THAT'S THE POINT. THE PANELS OF NEUROLOGISTS CAN COME UP WITH CLINICAL ENDPOINTS THAT THE BEST POSSIBLE ENDPOINTS FOR THE DISEASES IN WHICH THEY'RE EXPERT, AND THAT'S WHAT WE REALLY NEED.

DR. DOBKIN: THE ONLY THING I CAN HELP YOU WITH HERE IS TO SAY THAT PHYSICIANS LIVE WITH UNCERTAINTY, AND BIOLOGY IS FILLED WITH UNCERTAINTY. AND WHEN YOU START DOING MANIPULATIONS AND YOU'RE LOOKING AT A PROGRESSIVE DISEASE WHICH HAS AN UNEVEN COURSE AND THAT PROGRESSION IS BASED ON TISSUE DIFFERENCES, DIFFERENCES AMONG CELLS AND CONNECTIONS, AXONS, SYNAPSES, NEUROTRANSMITTERS IN A WIDE AREA, THE COMPLEXITY IS UNIMAGINABLE. AND SO THERE ISN'T EVER GOING TO BE ANY SIMPLE SOLUTION. BUT YOU COULD TAKE SOME ASPECT, SOME PARTICULAR BEHAVIOR IS REALLY DISABLING, IN PARKINSON'S OR ALZHEIMER'S, AND YOU COULD STRUCTURE YOUR CELLULAR INTERVENTIONS SPECIFICALLY FOR THAT, AND YOU COULD TEST THAT, AND YOU WOULD IMPLANT THOSE CELLS WHERE ALL YOUR BASIC SCIENCE TOLD YOU THIS IS THE PLACE TO BE, AND YOU COULD DO A VERY SMALL TRIAL AND GET AN ANSWER.

BUT AS SOON AS YOU SAY I'M GOING TO CURE X DISEASE, YOU'RE JUST -- YOU'RE DEAD IN THE WATER. SO YOUR MODELS CAN BE DESIGNED TO LOOK AT SOMETHING RATHER SPECIFIC WHERE SOME OF THAT PATHOLOGY IS REPLICATED IN THE MODEL. DOESN'T PREDICT WHAT WILL HAPPEN IN HUMANS, BUT IT PUTS YOU A LEG UP IN THINKING THIS THROUGH.

AND ONE OF THE PROBLEMS WITH THE WAY RESEARCH IS CONDUCTED IS THAT PEOPLE HAVE VARIOUS KINDS OF MODELS, AND THEY LOOK AT GLOBAL OUTCOMES BECAUSE THAT'S INTERESTING IN THE ANIMAL MODEL BECAUSE THERE AREN'T A LOT OF BEHAVIORS TO MEASURE, SO YOU LOOK AT SOMETHING GLOBAL. BUT IN PATIENTS, YOU KNOW, I WANT TO FIX THIS PARALYZED ARM. I WANT TO STOP FROM FALLING. I WANT TO REMEMBER SOMETHING THAT JUST HAPPENED. YOU CAN DEFINE THINGS IN CIRCUITS, AND THEN YOU AIM YOUR INTERVENTION AT THE CIRCUIT, NOT NECESSARILY AT THE DISEASE. YOU NEED TO UNDERSTAND THE DISEASE, BUT YOU CAN USE THE SAME CELLS TO FIX A WHITE MATTER INJURY WHETHER IT'S PELIZAEUS-MERZBACHERS OR MULTIPLE SCLEROSIS OR STROKE OR SPINAL CORD INJURY POTENTIALLY IF YOU HIT THE RIGHT CIRCUIT, YOU KNOW, IF YOU AIM WHERE THE FRUIT IS HANGING LOWEST.

MR. SHEEHY: IT JUST SEEMS EERILY

REMINISCENT OF A COMPLETELY DIFFERENT KIND OF THING, BUT IT JUST SEEMS THAT YOU COULD DO THE SAME THING IN TWO DIFFERENT PATIENTS AND ONE IT WOULD WORK AND THE OTHER IT WOULDN'T.

DR. CSETE: ABSOLUTELY.

MR. SHEEHY: AND THAT JUST DOESN'T SEEM APPROPRIATE FOR RANDOMIZED CONTROL TRIAL.

DR. CSETE: THAT'S THE PROBLEM.

MR. SHEEHY: IT JUST SOUNDS LIKE YOU JUST HAPPENED TO HIT THE CIRCUIT IN THIS ONE PATIENT, AND THE OTHER PATIENT IT DIDN'T HIT THE CIRCUIT AND IT DIDN'T QUITE FORM UP RIGHT. AND THEN YOU TAKE THIS DATA AND YOU EXTRAPOLATE AND YOU SAY THE TRIAL DIDN'T WORK BECAUSE MOSTLY WE MISSED. THE ONE YOU HIT SUDDENLY -- I JUST --

DR. DOBKIN: YOU'RE ALWAYS TRYING TO COME UP WITH WAYS TO ENRICH YOUR TRIAL. I MEAN I ACTUALLY COULD HAVE PUT AS A TITLE ENRICHMENT STRATEGIES IN SOME OF THE THINGS THAT I MENTIONED THERE LIKE PRACTICING TO IMPROVE A SKILL BEFORE YOU START THE TRIAL. WHAT YOU'RE TRYING TO DO IS GET DOWN TO THAT ONE THING THAT'S MOST IMPORTANT TO THE PATIENT THAT YOU WANT TO FIX THAT YOU THINK YOU CAN FIX, AND THAT'S WHERE YOU THROW ALL YOUR RESOURCES, AND THAT HELPS ELIMINATE A LOT OF THAT NOISE. IT

MAKES THESE STUDIES FEASIBLE.

THE MOST AMAZING THING ABOUT PARKINSON'S IS THAT ANYTHING WORKED. I MEAN IT'S PHENOMENAL. WE LEARNED MORE ABOUT HOW PARKINSON'S DISEASE DEVELOPS FROM TRIALS OF TRYING TO CURE IT THAN PERHAPS WE'VE DONE FROM TRYING TO MODEL IT BECAUSE YOU SAW WHICH PATHWAYS WERE AFFECTED AND HOW THEY WERE AFFECTED.

CHAIRMAN LO: I'M GOING TO GIVE DOROTHY THE LAST COMMENT. SHE'S BEEN VERY PATIENT.

DR. ROBERTS: I HAD A COMMENT AND A QUESTION. THE COMMENT IS JUST I THINK IF PATIENTS OR PARTICIPANTS IN CLINICAL TRIALS AREN'T LED TO BELIEVE THAT THEY'RE IN THE TRIAL TO RECEIVE A CURE, THEN RATHER THEY'RE PARTICIPATING IN RESEARCH, THEN THE IDEA OF A SHAM SURGERY DOESN'T SEEM SO UNETHICAL BECAUSE NO ONE KNOWS WHEN THEY GO INTO IT IF THEY'RE GOING TO BE HARMED, IF THEY'RE GOING TO BE BENEFITED. THE PURPOSE IS TO LEARN MORE, FOR THE RESEARCHERS TO LEARN MORE. THAT'S THE PURPOSE OF THE RESEARCH. IF PEOPLE BELIEVE THEY'RE PARTICIPATING IN IT TO RECEIVE A CURE, THEY HAVE BEEN MISLED, I THINK.

AND SO IN THAT CASE PEOPLE WHO RECEIVE THE SHAM SURGERY, YOU COULD ALSO LOOK AT IT AS THEY'RE

NOT TAKING THE RISK OF HAVING THIS EXPERIMENT DONE ON THEM, BUT THEY ARE PARTICIPATING IN RESEARCH THAT IS POTENTIALLY GOING TO CREATE A CURE FOR THEM.

DR. CSETE: THAT'S TRUE. AND THAT'S HOW CONSENT FORMS READ.

DR. ROBERTS: YES.

DR. CSETE: AND THE WHOLE IDEA OF SHAM SURGERY OR OTHER CONTROL ARM IS SO THAT PEOPLE DON'T KNOW, YOU KNOW, THE DOUBLE BLIND PART, WHAT IT IS THAT THEY'RE RECEIVING. AND, YOU KNOW, I THINK EVERY CONSENT FORM I'VE EVER READ TO A PATIENT SAYS THIS WILL LIKELY NOT BENEFIT YOU, BUT MAY BENEFIT FUTURE PATIENTS. BUT IT IS A VERY HARD PSYCHOLOGICAL --

DR. ROBERTS: I UNDERSTAND. I UNDERSTAND. BUT I THINK THERE'S A WAY OF THINKING ABOUT IT AS RESEARCH, YOU'RE PARTICIPATING IN RESEARCH THAT KIND OF CHANGES THE PERCEPTION OF THE ETHICS AND THE RISKS OF IT SO THAT IT'S NOT AS IF THE PEOPLE GETTING THE SHAM SURGERY AREN'T UNETHICALLY NOT GETTING A CURE BECAUSE WE DON'T KNOW IF ANYONE IN THE RESEARCH IS GETTING A CURE. THEY MAY BE HARMED BY WHAT WE THINK IS GOING TO BE A CURE.

AND ALSO THEN MY QUESTION WAS ON THIS ISSUE OF PATIENT CONSENT. AGAIN, I RECOGNIZE IT'S

HARDER TO GET PATIENT CONSENT FOR A SHAM SURGERY, BUT NO ONE KNOWS WHEN THEY GO INTO THE TRIAL WHICH THEY'RE GOING TO GET. SO YOU'RE PARTICIPATING PERHAPS WITH THE HOPE THAT YOU'RE THE ONE THAT GETS THE REAL THERAPY, BUT YOU DON'T KNOW AHEAD OF TIME. SO EVERYONE WHO PARTICIPATES IS TAKING THE CHANCE THAT THEY MAY GET ONE OR THE OTHER.

DR. CSETE: THAT'S ABSOLUTELY RIGHT.

DR. ROBERTS: AND IN ORDER TO GET THE SURGERY -- IN ORDER TO PARTICIPATE AT ALL, YOU HAVE TO TAKE THAT RISK THAT YOU MIGHT GET THE SHAM SURGERY. SO IN OTHER WORDS, IF YOU ARE SOMEONE WITH AN ILLNESS, YOU'RE HOPING TO GET THIS CURE, WHAT YOU HOPE IS A CURE. THE ONLY WAY YOU'RE GOING TO GET IT IS TO PARTICIPATE -- TO HAVE A HOPE OF GETTING IT IS TO PARTICIPATE IN THIS RESEARCH. AND IF THAT'S THE WAY IT'S DONE, IT SEEMS TO ME THAT PEOPLE -- YOU WILL HAVE NO CHOICE BUT TO TAKE THAT CHANCE, RIGHT? IN OTHER WORDS --

DR. CSETE: PEOPLE DO HAVE A CHOICE.

DR. ROBERTS: IF YOU WANT TO PARTICIPATE IN THE TRIAL.

DR. CSETE: SO IF YOU WANT TO PARTICIPATE IN A TRIAL, THAT IS TRUE. THAT'S HOW IT'S PRESENTED TO PATIENTS. YOU CAN'T GIVE THEM AN INDICATION OF

WHICH ARM THEY'RE PLACED. BUT THERE ARE PATIENT COMMUNITIES THAT REFUSE TO PARTICIPATE IN TRIALS THAT ARE DESIGNED WITH PLACEBO ARMS, FOR EXAMPLE.

DR. ROBERTS: YEAH. YEAH.

CHAIRMAN LO: I'M GOING -- I REALLY WANT TO CUT THIS OFF. WE OBVIOUSLY ARE GOING TO COME BACK TO THIS TOMORROW AND IN THE FUTURE, SO IT'S A GREAT DISCUSSION. BUT I WANT TO GIVE US SOME TIME TO HEAR IAN SPEAK.

DR. CSETE: HE DIDN'T HAVE HIS FOLLOW-UP THOUGH.

CHAIRMAN LO: WELL, IAN IS NOT GOING TO BE HERE TOMORROW, AND THERE'S AN ISSUE -- LET'S GIVE IAN A CHANCE TO SPEAK FIRST. AND THEN IF WE WANT TO SORT OF GO THROUGH THE ADJOURNMENT TIME, THAT'S FINE. BUT IAN IS THE GENERAL COUNSEL FOR CIRM, AND THERE'S AN ISSUE WITH REGARD TO REPORTING REQUIREMENTS PARTICULARLY WITH REGARD TO OOCYTE DONATION. AND I WANTED HIM TO HELP US THINK THROUGH FROM SORT OF A REGULATORY POLICY PERSPECTIVE.

THERE ARE OTHER REPORTING REQUIREMENTS IN PLACE ALREADY THROUGH THE DEPARTMENT OF PUBLIC HEALTH AND AT INDIVIDUAL INSTITUTIONS. AND THE QUESTION THAT I THINK WE NEED TO THINK ABOUT IS WHAT ADDITIONAL CIRM-SPECIFIC REPORTING REQUIREMENTS

WOULD BE APPROPRIATE AND USEFUL. AND IAN HAS SORT OF A GOOD PERSPECTIVE ON THIS. SINCE HE WON'T BE ABLE TO BE HERE TOMORROW, GIVE HIM A CHANCE TO HELP US THINK THROUGH THIS.

MR. SWEEDLER: THANKS. THIS IS BASICALLY AN OUTGROWTH OF A LUNCHTIME CONVERSATION, SO I DIDN'T HAVE TIME TO PREPARE SLIDES IN THE INTERIM. AND I WASN'T HERE FOR PRIOR MEETINGS WHERE YOU DISCUSSED THIS REPORTING REQUIREMENT, SO I WOULD APPRECIATE GUIDANCE AS TO WHAT'S HELPFUL TO YOU.

BUT WHAT WE WERE DISCUSSING WAS THE DEPARTMENT OF PUBLIC HEALTH HAS REPORTING REQUIREMENTS FOR COLLECTION OF OOCYTES FOR RESEARCH PURPOSES. AND UNDER THE STATUTE THAT THEY'RE WORKING UNDER, THEY'VE SAID THAT THOSE ARE APPLICABLE TO ALL RESEARCH PROJECTS THAT ARE NOT FULLY FUNDED BY CIRM. AND THERE'S BEEN SOME QUESTION ABOUT HOW TO HARMONIZE WHATEVER THOSE REQUIREMENTS ARE WITH WHATEVER THE REQUIREMENTS ARE THAT CIRM HAS UNDER THOSE CIRCUMSTANCES.

AND WE WERE DISCUSSING IT IN PART FROM THE PERSPECTIVE OF WHOSE REGULATIONS WIN. BUT WE WERE ALSO TALKING ABOUT THE FACT THAT THIS IS AN AREA THAT CIRM'S REGULATIONS CURRENTLY DON'T EXACTLY COVER. WE ARE NOT ASKING THOSE WHO ARE USING

OOCYTES THAT WERE COLLECTED FOR PURPOSES OF RESEARCH TO REPORT TO US ABOUT EACH SUBJECT FROM WHOM THEY ARE COLLECTING THOSE OOCYTES. AND IF WE WERE TO ATTEMPT TO COME UP WITH A SIMILAR APPROACH, THEN WE WOULD BE GETTING INTO AN AREA THAT I DON'T THINK WE'VE BEEN IN BEFORE, WHICH IS CIRM TAKING CUSTODY OF INFORMATION ABOUT INDIVIDUAL PATIENTS OR SUBJECTS. AND THERE ARE CERTAINLY IMPLICATIONS TO DOING THAT.

AND THE NATURE OF INFORMATION AND PRIVACY IS THAT ANY TIME YOU COLLECT INFORMATION LIKE THAT IN ONE MORE PLACE THAN IT WAS BEFORE, YOU ARE INCREMENTALLY INCREASING THE RISK OF SOME DISCLOSURE OR PROBLEM. AND OBVIOUSLY THE DEPARTMENT OF PUBLIC HEALTH IS IN THE BUSINESS OF COLLECTING THAT KIND OF INFORMATION AND MAINTAINING IT IN CONFIDENCE.

SO WHAT WE WERE DISCUSSING WAS THE POSSIBILITY THAT IF WE THINK THAT THAT SORT OF INFORMATION SHOULD BE COLLECTED, EVEN REGARDING OOCYTES COLLECTED FOR RESEARCH PURPOSES WITH REGARD TO A FULLY CIRM-FUNDED STUDY, WOULD THE BEST APPROACH BE TO SIMPLY WORK WITH THE DEPARTMENT OF PUBLIC HEALTH AND ADOPT THEIR REGULATIONS AS OURS AND ALLOW OUR RESEARCHERS OR REQUIRE OUR RESEARCHERS TO BE REPORTING THERE RATHER THAN TO HAVE EITHER A

DUPLICATIVE SET OF REPORTING REQUIREMENTS OR CREATE AN ENTIRELY NEW ONE.

BUT THAT'S AGAINST THE BACKGROUND OF DECIDING IS THAT THE KIND OF REPORTING REQUIREMENT WE WANT TO BEGIN WITH. SO I'M NOT SAYING THAT WE SHOULD JUST DO WHAT THEY DO BECAUSE IT'S EASIER TO DO WHAT THEY DID. BUT IF WHAT THEY DID NEEDS AND THE CONCERNS THAT YOU ARE INTENDING TO ADDRESS, THEN IT MIGHT BE THAT THIS IS A CIRCUMSTANCE WHERE EVEN THOUGH THERE'S ROOM FOR TWO DIFFERENT REGULATORY SCHEMES, HAVING THE TWO AGENCIES WORK TOGETHER MIGHT BE THE BEST FORM OF PROTECTION FOR RESEARCH SUBJECTS.

CHAIRMAN LO: GEOFF, DO YOU WANT TO ADD ANYTHING SINCE YOU'VE BEEN SORT OF THINKING ABOUT THIS FOR A WHILE?

DR. LOMAX: WELL, JUST TO ADD A BIT OF CONTEXT. THIS WAS A PROGRAM THAT WAS PRESENTED TO THE WORKING GROUP IN JULY OF 2008, AND WE HAVE SORT OF BECOME EXPERT ON THE CALIFORNIA DEPARTMENT OF PUBLIC HEALTH PROGRAM. SO, FOR EXAMPLE, WE LOOKED AT THE REPORTING FORMS, WE LOOKED AT THE INFORMATION. I THINK EITHER JUST TO REMIND PEOPLE AT THAT MEETING AND I KNOW, DR. KIESSLING, FOR EXAMPLE, I THINK THERE WERE SOME CONCERNS ABOUT THE

SUBSTANCE OF THE REPORTING FORM RAISED AT THAT TIME. I DON'T KNOW IF THOSE CONCERNS STILL PERSIST.

SO JUST TO PUT THAT IN CONTEXT, THE REPORTING PROGRAM WAS PRESENTED TO THE WORKING GROUP, AND AT THE TIME THERE WAS NO DECISION MADE. SO PART OF IT WOULD, IN TERMS OF WHAT IAN IS SAYING, IT'S SORT OF THINKING BACK TO JULY AND WE COULD, FOR EXAMPLE, PULL UP SOME OF THOSE MATERIALS. SO THAT'S THE BACKGROUND OF -- THAT'S THE CONTEXT.

AND SO SINCE WE HAVEN'T HAD A DISCUSSION SINCE THAT JULY MEETING ON THIS ISSUE OF REPORTING, AND SO WE ARE NOW COMING BACK, THAT WE THOUGHT IN ADVANCE OF ANY DISCUSSION, IT IS ON THE AGENDA FOR THIS MEETING THAT WE SHOULD ADDRESS THIS SORT OF POINT IN ADVANCE OF A DISCUSSION ABOUT IS IT SORT OF FEASIBLE AND APPROPRIATE OR WORKABLE TO IF WE WERE TO HAVE -- IF WE DID THINK IT WAS A GOOD IDEA TO HAVE A PROGRAM, USE THE PUBLIC HEALTH, CAN WE DO THAT. AND THAT'S WHAT WE'VE ASKED IAN TO ADDRESS. SO I GUESS THAT'S THE CONTEXT. WE HAVE THE MATERIALS. WE COULD PULL UP FORMS AND THINGS. I DON'T KNOW IF YOU WANT TO DO THAT TODAY, BUT IAN SORT OF ADDRESSED THAT SORT OF THRESHOLD QUESTION, THAT THERE IS A MECHANISM THAT WE COULD MAKE USE OF.

MR. SWEEDLER: AND I JUST WANT TO REPEAT

THIS POINT IF I WASN'T CLEAR ABOUT THIS. PROPOSITION 71 GIVES THE ICOC THE AUTHORITY TO REGULATE IN THIS AREA, AND IT GIVES IT SOMEWHAT EXCLUSIVE AUTHORITY TO REGULATE WITH REGARD TO CIRM GRANTEES. AND IN PART THAT'S TO MAKE SURE THAT THE RIGHT ETHICAL STANDARDS ARE FOLLOWED. AND IN PART IT'S TO MAKE SURE THAT INAPPROPRIATE OR UNNECESSARY ETHICAL STANDARDS ARE NOT INTERPOSED AS AN OBSTACLE TO RESEARCH.

SO ONE THRESHOLD QUESTION YOU WOULD CERTAINLY HAVE TO LOOK AT IS DOES THIS -- DO WE THINK THIS FORM OF REPORTING SERVES A PURPOSE? IS IT ADVANCING THE ISSUES THAT WE'RE CONCERNED ABOUT? SO I'M NOT SUGGESTING THAT YOU SHOULD ADOPT THIS AS A ME TOO. I'M SIMPLY SUGGESTING THAT IF YOU THINK REPORTING IS APPROPRIATE, THAT BEFORE YOU CONSIDER SETTING UP SOME PARALLEL OR CONFLICTING REPORTING REGIME, AT LEAST FACTOR INTO THAT THE COST AND BENEFITS OF THAT AS COMPARED TO WORKING WITH THE ONE THAT'S ALREADY BEEN SET UP.

CHAIRMAN LO: COULD I JUST ASK ALAN OR MARIE SORT OF A VERY NAIVE QUESTION? I MEAN HOW MANY GRANTS DOES CIRM NOW HAVE UNDER WHICH AN INVESTIGATOR IS COLLECTING OOCYTES FOR RESEARCH PURPOSES THAT WOULD FALL UNDER THIS SORT OF

REPORTING?

AND SECONDLY, AS YOU LOOK AT YOUR SORT OF SCIENTIFIC PRIORITIES AND SORT OF CRYSTAL BALL, HOW MANY PROJECTS ARE THERE LIKELY TO BE IN THE FUTURE?

DR. CSETE: THERE'S ONE CURRENTLY FUNDED ONLY. WE'VE SEEN APPLICATIONS THAT HAVEN'T BEEN FUNDED IN THIS AREA. AND WE'RE SEEING NOT A LOT OF GROWTH IN THIS AREA, I THINK, BECAUSE IPS CELLS GET SCIENTISTS TO SOME OF THE ANSWERS THEY WANTED TO GET TO USING SOMATIC CELL NUCLEAR TRANSFER MUCH EASIER. OBVIOUSLY PEOPLE HAVEN'T BEEN SUCCESSFUL WITH SOMATIC CELL NUCLEAR TRANSFER IN HUMANS REALLY. SO I DON'T ANTICIPATE THAT THERE'S GOING TO BE HUNDREDS OF STUDIES, BUT THERE'S CERTAINLY REASONS TO WANT TO TRY TO KEEP THIS AREA OF RESEARCH GOING. I DON'T THINK THAT THAT SHOULD SO MUCH IMPACT OUR REPORTING DECISIONS.

CHAIRMAN LO: ROB.

DR. TAYLOR: YEAH. I GUESS I HAVE A COUPLE OF THOUGHTS. I RECALL FROM LAST -- THAT JULY MEETING. ONE THING THAT I WOULD SAY IS THAT ONE OF THE THINGS THAT OUR SUBCOMMITTEE ADDRESSED WAS THIS IDEA OF A REGISTRY, THE IMPORTANCE OF A REGISTRY FOR EGG DONORS FOR RESEARCH PURPOSES. AND I THINK THIS WOULD CERTAINLY OVERLAP THE VENN DIAGRAM OF THAT

QUITE NICELY. SO I THINK THERE ARE SEVERAL REASONS WHY THIS MIGHT BE AN ATTRACTIVE THING.

WHO COLLECTS THE DATA IS MORE OF A PRAGMATIC ISSUE, AND MY RECOLLECTION OF THE DEPARTMENT OF PUBLIC HEALTH PROFILE REALLY WAS DID IT REALLY HAVE THE RIGHT FIELDS? DID IT HAVE THE FIELDS OF INFORMATION THAT WERE REALLY GOING TO MATTER FOR THIS PURPOSE? SO IT SOUNDS LIKE THE INFRASTRUCTURE MIGHT BE THERE, BUT I'M NOT SURE THAT THEY'VE GOT IT DESIGNED THE RIGHT WAY. AND I DO THINK IT SEEMS LIKE AN ATTRACTIVE IDEA TO KEEP IT OUT OF SORT OF THE CIRM UMBRELLA JUST FOR CONFIDENTIALITY REASONS.

SO IF THAT DATABASE COULD BE TWEAKED, IF THEY WERE KIND OF WILLING TO SORT OF PUT IN THE KIND OF INFORMATION THAT I THINK MIGHT BE USEFUL FOR THE PROGRAM, THAT SEEMS TO ME TO BE AN EFFICACIOUS WAY OF GOING ABOUT IT. IF YOU COULDN'T REALLY TWEAK THEIR DATABASE, THEN I'M NOT SURE THAT IT WOULD BE WORTHWHILE IN MY PERSONAL VIEW.

CHAIRMAN LO: WOULD NOT BE WORTHWHILE USING THEIRS?

DR. TAYLOR: USING DPH, YEAH.

DR. TROUNSON: JUST IN ADDITION TO, BECAUSE MARIE WAS COMPLETELY CORRECT IN WHAT SHE

SAID, THE MOVEMENT IN THE AREA OF SCIENCE, AS I JUDGE IT, IS THE TRANSCRIPTION FACTORS ARE OPENING A MUCH BETTER WINDOW TO UNDERSTANDING WHAT'S WITHIN THE EGG CYTOPLASM THAT REPROGRAMS. AND I HAD THE OPPORTUNITY OF MEETING PHILIPPE CARLAS (PHONETIC) FROM NORWAY, WHO'S DONE A LOT OF WORK ON EGG CYTOPLASM IN LARGE AMOUNTS OF ANIMAL MATERIAL, AND THEY'RE GETTING CLOSER TO IDENTIFYING THE PROTEIN AND MATCHING THEM UP WITH THE TRANSCRIPTION FACTORS.

SO I THINK WITH BOTH PROTEINS AND TRANSCRIPTION FACTORS, YOU'RE PROBABLY GETTING PRETTY CLOSE TO THE WHOLE EGG SITUATION. THEN IF YOU LOOK AT THE ETHICAL ISSUES, AND WE'VE BEEN AT THIS FOR QUITE A WHILE NOW, THE PROBLEM ASSOCIATED WITH GETTING WOMEN TO DONATE LARGE NUMBERS OF EGGS REALLY MAKES THE WORK INTERMINABLY DIFFICULT. AND SO I THINK THAT'S THE REASON WHY WE GET A SMALL NUMBER OF GRANTS. AND, IN FACT, THE ONE WE HAVE CURRENTLY, THE SCIENTIST, IN FACT, WANTS TO MOVE OFF INTO IPS. AND, YOU KNOW, WE THINK THAT THE PROJECT AREA IS IMPORTANT TO KEEP GOING AT THIS POINT IN TIME BECAUSE WE DON'T WANT TO LOSE PERHAPS IMPORTANT INFORMATION.

BUT IN THE DISCUSSIONS I HAD WITH BERNIE AND SHERRY IS THAT WASN'T THE RAGING PRIORITY, THAT

THE CLINICAL ISSUES WERE. AND SO MY FEELING HERE, AND IF IT'S REFLECTIVE OF WHAT WE ALL FEEL, IS THAT, YEAH, WE SHOULD BE THOUGHTFUL ABOUT IT, AND THERE'S GOOD REASON TO SORT OF COMPARE IPS CELLS WITH NUCLEAR TRANSFER CELLS, BUT WE HAVE TO FACE THE REALITY THAT THE ETHICS OF OBTAINING LARGE NUMBERS OF EGGS IS NOT A VERY FAVORABLE ONE NO MATTER WHAT YOU THINK.

DR. TAYLOR: WITH ONLY ONE -- IF THERE'S ONLY ONE PROTOCOL, THAT MAY BE NOT ENOUGH TO CREATE A WHOLE NEW REPORTING STRUCTURE. I DON'T DISAGREE WITH YOU ON THAT.

DR. CSETE: AND THE SAFETY ISSUES PRESUMABLY ARE REPORTED INTERNALLY AT THE UNIVERSITY OR WHEREVER THE STUDY IS BEING DONE WITH THE PUBLIC HEALTH DEPARTMENT AS A BACKUP.

DR. TAYLOR: I'M NOT SO CONCERNED ABOUT THE SAFETY ISSUES AS MUCH AS MAYBE SOME OF THE OTHER REGISTRY KINDS OF ISSUES. BUT I STILL WOULD HOPE THAT, AGAIN, IT'S SORT LIKE THE PARALLEL PATHWAYS WITH SORT OF THERAPEUTIC TRIALS, THAT THIS ISN'T SOMETHING THAT'S GOING TO COMPLETELY GO AWAY BECAUSE I HAVE THE SUSPICION THAT IN ANOTHER COUPLE OF YEARS WE'RE GOING TO WANT TO BE THERE, AND IT WOULD BE NICE TO HAVE SOME PEOPLE THAT ARE SORT OF

FACILITATED TO DO SOME OF THAT WORK.

DR. TROUNSON: MARIE AND I THINK AT THE VERY LEAST THAT WE HAVEN'T EVEN SORT OF STARTED TO ADDRESS THE MITOCHONDRIAL DISEASES FOR WHICH IT MAY WELL BE VERY RELEVANT TO BE ABLE TO ACCESS VERY PRIMITIVE MITOCHONDRIA THAT DON'T EXIST IN OTHER SYSTEMS. SO THERE COULD WELL BE REASONS WHY IT'S ALL PARTICULARLY RELEVANT IN THE LONG TERM.

DR. CHARO: SO I APPRECIATE THE QUESTION ABOUT WHETHER THE DPH HAD THE RIGHT FIELDS FOR QUERYING; BUT ASIDE FROM THAT, A SECOND QUESTION SIMPLY IS HOW URGENT IS IT THAT THIS BE DECIDED NOW? IS IT POSSIBLE TO OVER TIME, IF THERE ARE -- IF THERE'S MORE THAN ONE PROTOCOL THAT CIRM IS FUNDING, IS IT POSSIBLE TO THEN GO BACK AND REVISIT THE DATA OR HAVE SOMEBODY WHO'S GOT ACCESS TO THE DATABASES APPROPRIATELY WITH LEGAL AUTHORITY TO LOOK AT IT, GO BACK AND DO THE SEARCH FOR US? IN OTHER WORDS, DO WE REALLY NEED TO WORRY ABOUT THIS PROSPECTIVELY NOT KNOWING HOW BADLY IT'S NEEDED?

MR. SWEEDLER: WELL, IT SOUNDS LIKE CURRENTLY THERE WOULD BE NOTHING TO REPORT FROM CIRM-FUNDED RESEARCHERS IF WE HAD A REPORTING REQUIREMENT. SO SOUNDS LIKE THERE'S NO URGENCY HERE. THE REPORTING IN PART IS ADDRESSED AT ADVERSE

OUTCOMES FOR THE DONORS, AND THERE'S OBVIOUSLY SOCIAL BENEFIT IN HAVING THAT INFORMATION REPORTED TO THE DEPARTMENT OF PUBLIC HEALTH. BUT IT DOES SOUND LIKE A SOMEWHAT HYPOTHETICAL ISSUE FOR THE WORKING GROUP OR THE ICOC TO BE DEALING WITH AT THIS POINT. THAT DOESN'T MEAN WE DON'T WANT TO BE PREPARED IF THE ISSUE ARISES, BUT IT CERTAINLY DOES NOT SOUND URGENT.

DR. KIESSLING: I MAY HAVE MISSED IT, BUT HAS ANYBODY FILLED OUT ONE OF THESE FORMS?

MR. SWEEDLER: I DON'T KNOW. THEY WOULDN'T BE COMING TO US. I DON'T KNOW IF DR. LOMAX HAS GOTTEN ANY FEEDBACK FROM THEM ABOUT THAT.

CHAIRMAN LO: LET'S ASK STEVE FROM UCLA SCRO.

DR. PECKMAN: STEVE PECKMAN FROM THE GROUND FLOOR AT UCLA. THIS TOPIC WITH CALIFORNIA DEPARTMENT OF PUBLIC HEALTH, I THINK THERE ARE A FEW ISSUES. ALL INSTITUTIONS THAT HAVE BEEN DOING HUMAN EMBRYONIC STEM CELL RESEARCH HAVE BEEN REQUIRED TO COMPLETE THE FORMS AND FILE THEM WITH THE CALIFORNIA DEPARTMENT OF PUBLIC HEALTH.

PRECEDING THE ROLLOUT OF THOSE FORMS, THOUGH, THERE WAS SUBSTANTIAL DEBATE ABOUT THE DATA THAT THE CALIFORNIA DEPARTMENT OF PUBLIC HEALTH HAS

BEEN REQUESTING ON THESE FORMS.

AND AT YOUR JULY MEETING YOU HEARD FROM TWO INSTITUTIONS, UCLA AND UCSD, WHO WERE BOTH VERY CONCERNED ABOUT THE DATA THAT DEPARTMENT OF PUBLIC HEALTH WAS COLLECTING. IF I RECALL CORRECTLY, STANFORD WAS ALSO ON BOARD WITH THOSE CONCERNS.

A THIRD QUESTION IS WHETHER THE CALIFORNIA DEPARTMENT OF PUBLIC HEALTH ACTUALLY THROUGH LEGISLATION HAS THE AUTHORITY TO COLLECT THE AMOUNT OF DATA AT THE LEVEL THAT THEY'RE COLLECTING IT. THAT'S BEEN DEBATED AS WELL.

ANOTHER QUESTION FOR YOU MIGHT BE WHETHER PROP 71 ACTUALLY GIVES YOU THE AUTHORITY TO HAVE ACCESS TO THOSE DATA, LET ALONE COLLECT THEM. SUFFICE TO SAY, NO ONE FROM ANY OF THE INSTITUTIONS I HAVE BEEN WORKING WITH HAVE BEEN IN A POSITION TO REPORT ANYTHING ABOUT OOCYTE COLLECTION FOR RESEARCH PURPOSES. WITH THAT BEING SAID, THERE'S ALWAYS THE OPPORTUNITY THAT THAT COULD START TO OCCUR AND ALL THE QUESTIONS STILL REMAIN.

THE OUTCOME, AS I RECALL THE JULY DISCUSSION THAT HAPPENED IN THIS ROOM, WAS THERE WAS STRONG ENCOURAGEMENT TO A CROSS-AGENCY WORKING GROUP TO COME TOGETHER AND TALK ABOUT THESE ISSUES AND COME TO SOME KIND OF CLOSURE AS TO THE TYPES OF DATA

THAT COULD BE USEFUL, HOW THEY COULD BE COLLECTED, AND THEY COULD BE COLLECTED SAFELY SO THAT PATIENTS ARE ULTIMATELY PROTECTED, IN THIS CASE NOT REALLY PATIENTS, BUT ACTUALLY RESEARCH SUBJECTS WHO ARE GOING TO BE DONATING EGGS FOR THE PURPOSES OF RESEARCH.

I'LL JUST ADD TO THAT THAT AT THE DISCUSSION WE ALSO STRONGLY ENCOURAGED, BESIDES HAVING THE CROSS-AGENCY WORKING GROUP, THAT YOU INCLUDE PEOPLE ON THE GROUND FLOOR IN THIS WORKING GROUP SO THEY COULD BE PART OF THE DISCUSSION TO HELP ILLUMINATE ANY DECISIONS YOU ARE GOING TO MAKE. BUT I APPRECIATE THE FUNDAMENTAL QUESTION THAT SEVERAL OF YOU ARE ASKING, WHICH IS IS THIS AN ISSUE, RIGHT. AND I DON'T KNOW OF ANYONE WHO'S ACTUALLY ABLE TO DO THIS, WHO'S BEEN ABLE TO COLLECT EGGS.

DR. KIESSLING: SO LET ME UNDERSTAND. EVERYONE -- THE DEPARTMENT OF PUBLIC HEALTH FORM IS BEING FILLED OUT FOR EMBRYO DONATION.

DR. PECKMAN: IT'S BEING FILLED OUT, BUT I'M ASSUMING THAT, LIKE UCLA, THEY'RE FILLING IT OUT IN TERMS OF NA, NOT APPLICABLE.

DR. KIESSLING: OH, NOT APPLICABLE.

DR. PECKMAN: RIGHT. BECAUSE THERE

HAVEN'T BEEN ANY EGG DONATIONS FOR RESEARCH PURPOSES.

DR. KIESSLING: OKAY.

DR. PECKMAN: FROM ANY OF THE ACADEMIC CENTERS.

DR. KIESSLING: SO CURRENTLY AT THE CALIFORNIA -- AT THE DEPARTMENT OF PUBLIC HEALTH, THERE'S PROBABLY NO INFORMATION ABOUT ANY RESEARCH SUBJECT ON FILE IN THESE FORMS.

DR. PECKMAN: FROM ACADEMIC MEDICAL CENTERS. I CAN'T SPEAK TO OTHER SITES. AND, OF COURSE, THE CALIFORNIA DEPARTMENT OF PUBLIC HEALTH ARE THE BEST PEOPLE TO GO TO FOR THE ANSWER TO THAT QUESTION. I WOULDN'T HAVE THAT ULTIMATE ANSWER.

DR. KIESSLING: OKAY.

CHAIRMAN LO: I CAN CERTAINLY -- WE HAVE A MEETING SCHEDULED I THINK IT'S NEXT WEEK, MAYBE THIS FRIDAY. I CAN SORT OF TRY AND BRING THIS UP AND ASK AND SORT OF FIND OUT. BUT AS WE ALL KNOW, WITH THE RESTRICTIONS ON PAYMENT FOR RESEARCH, IT'S BEEN VERY HARD TO RECRUIT DONORS. AND THIS WOULD NOT INCLUDE WOMEN WHO DONATE OOCYTES IN AN IVF CONTEXT AND THEN OOCYTES THAT FAIL TO FERTILIZE ARE THEN GIVEN TO RESEARCHERS RATHER THAN BEING DISCARDED.

ANY OTHER COMMENTS FROM THE PUBLIC ON THIS

REPORTING ISSUE?

MS. FOGEL: I'M SUSAN FOGEL WITH THE PRO-CHOICE ALLIANCE FOR RESPONSIBLE RESEARCH. I JUST WANT -- WE'VE BEEN RAISING THIS REPORTING QUESTION, AND I REALIZE IT'S NOT IMMINENT, BUT I THOUGHT I READ THAT ADVANCED CELL TECHNOLOGIES DID COLLECT EGGS FOR SOME RESEARCH THEY DID, BUT I DON'T KNOW. THAT SHOULD HAVE ALSO BEEN REPORTED TO THE STATE. SO IT WOULD BE USEFUL TO KNOW.

DR. CSETE: I THINK IT WAS DONE IN MASSACHUSETTS.

MS. FOGEL: SO IT WOULD BE USEFUL TO GET MORE INFORMATION FROM THE STATE. OBVIOUSLY WE CARE A LOT ABOUT HAVING THIS DATA SHOULD WOMEN PROVIDE EGGS. AND SO WE ENCOURAGE YOU TO KEEP LOOKING AT IT.

CHAIRMAN LO: IAN, DO YOU HAVE ANY OTHER COMMENTS YOU WANTED TO MAKE BECAUSE I KNOW YOU'RE NOT GOING TO BE HERE TOMORROW?

MR. SWEEDLER: NO. OTHER THAN THIS HAS BEEN A FASCINATING DISCUSSION OVERALL TODAY. I WISH I WAS ABLE TO STAY FOR THE SECOND DAY. I'M HAPPY TO CONTINUE WORKING ON THIS ISSUE IN ANY WAY THAT'S HELPFUL.

CHAIRMAN LO: LET ME MAKE A SUGGESTION.

THE DPH MEETING IS FRIDAY THE 20TH, AND I WILL BE ATTENDING. AND LET ME GET SOME BASIC INFORMATION TO SEND BACK TO THE COMMITTEE IN TERMS OF WHAT THE FORMS LOOK LIKE, HOW IS THE REPORTING GOING, AND I GUESS MAYBE GET AN INFORMAL SENSE OF THEIR WILLINGNESS TO SORT OF HAVE A JOINT -- TO WORK WITH US ON OVERSIGHT OF -- POTENTIAL OVERSIGHT OF PROJECTS THAT ARE WHOLLY FUNDED BY CIRM, WHICH IS THE GROUP WE'RE TALKING ABOUT.

IT JUST STRIKES ME THAT TO THE EXTENT THAT WE'RE REALLY TALKING ABOUT SORT OF A PATTERN OR AN INCIDENCE RATHER THAN JUST INDIVIDUAL CASES, IT WOULD BE SCIENTIFICALLY IMPORTANT, AS ROB WAS SUGGESTING, SO SORT OF BE ABLE TO AGGREGATE DATA THAT'S HELD IN DIFFERENT SOURCES INTO ONE KIND OF COMMON NUMERATOR AND DENOMINATOR TO SERIOUS ADVERSE EVENTS.

SO IF THAT'S THE SENSE OF THE COMMITTEE, I WILL SORT OF TAKE IT ON MYSELF ON FRIDAY AND COME BACK THROUGH GEOFF.

OKAY. WE HAVE DINNER SCHEDULED AT WHAT TIME, GEOFF?

MS. LANSING: 6:30.

CHAIRMAN LO: 6:30 IN THE SAME ROOM. ALL THE FOOD, PAT SAYS, IS ALWAYS IN THAT ROOM. THERE

ARE NO MORE OF THOSE SORT OF CHOCOLATE STRAWBERRIES THAT HAD SOME SORT OF ENHANCEMENT WITH EITHER A CHOCOLATE STEM CELL OR A CHOCOLATE GENE INSERTION, BUT THERE WILL BE A DINNER. AND TOMORROW WE CONVENE HERE AT WHAT TIME?

MS. LANSING: 9 O'CLOCK.

CHAIRMAN LO: 9 O'CLOCK. AND THEN WE WILL CONTINUE THESE DISCUSSIONS OF THESE ISSUES, AND WE'LL HEAR ADDITIONAL PERSPECTIVES FROM STEVE PECKMAN AND MICHAEL KALICHMAN AND ALSO FROM INSU FROM ISSCR.

OKAY. ONE MORE QUESTION.

DR. LOMAX: ONE LAST ANNOUNCEMENT.

MR. SHEEHY: I WAS JUST CURIOUS, DR. DOBKIN, AND IT'S STIMULATED BY DOROTHY'S COMMENTS. ASSUMING THAT THERE'S A FEELING THAT RANDOMIZED CONTROLLED PLACEBO TRIALS ARE APPROPRIATE, IN THESE SURGICAL SITUATIONS, ISN'T THE ETHICAL BURDEN THEN ON US TO MAKE SURE THAT WE ACTUALLY DISCOVER SOMETHING AS OPPOSED TO -- YOU KNOW, I'M LOOKING AT THIS PARKINSON'S TRIAL WHERE IT SEEMS LIKE IMMUNOSUPPRESSION MIGHT BE THE ISSUE. BUT ISN'T THE REAL ETHICAL CONSIDERATION TO MAKE SURE, IF WE'RE GOING TO CUT SOMEBODY'S BRAIN OPEN AND NOT DO ANYTHING AND JUST PUT THEM UNDER AND CUT THEM OPEN,

THAT WE ACTUALLY ANSWER A QUESTION? I MEAN IS THAT NOT THE DOMINANT BURDEN IN ANY TRIAL, BUT SHOULD WE NOT HAVE A HIGHER STANDARD?

CHAIRMAN LO: BECAUSE IT'S MORE BASIC, ABSOLUTELY.

MR. SHEEHY: HOW DO WE DO THAT?

MS. LANSING: I'M GOING TO ASSUME THAT WE'RE GOING TO HEAR ABOUT THIS SOME MORE TOMORROW BECAUSE IT IS -- I THINK TO ME ONE OF THE MOST IMPORTANT THINGS WE'RE GOING TO DECIDE, BUT I GUESS RESPONDING AND I WAS GOING TO WAIT TILL TOMORROW TOO, TO WHAT YOU SAID DOROTHY, TO ME EVEN IF YOU TOLD PEOPLE WHAT WAS GOING ON, I MEAN, FIRST OF ALL, IF YOU TOLD PEOPLE THEY WOULD THINK THIS WAS A SCIENCE FICTION MOVIE. I MEAN THEY WOULD NEVER BELIEVE THAT WE ACTUALLY WERE OPENING PEOPLE AND NOT DOING SOMETHING TO THEM.

DR. CHARO: ALL THE TIME.

MS. LANSING: I KNOW. I ACTUALLY, THANKS TO JEFF, HE'S BEEN ON THE COMPUTER, LIKE I'VE BEEN PULLING UP ARTICLES. BUT TO ME THERE IS THE POSSIBILITY AND THIS ISN'T A PURE THING WHERE YOU WOULD ACTUALLY DO SOMETHING THAT COULD BE BENEFICIAL AND COMPARE IT TO SOMETHING ELSE. BUT TO JUST ACTUALLY OPEN SOMEBODY UP AND DO NOTHING IS -- I

JUST DON'T UNDERSTAND IT. I HAVE TO BE HONEST.

MR. SHEEHY: PEOPLE PARTICIPATE -- I THINK THE REAL THING, PEOPLE PARTICIPATE AND PEOPLE ARE MOTIVATED, THEY HAVE A SENSE OF COMMUNITY WITH PEOPLE, YOU KNOW, THAT'S PART OF BEING AN ADVOCATE AND AN ACTIVIST. BUT IN ORDER TO WANT TO MOVE THE SCIENCE FORWARD, YOU ACTUALLY SHOULD BE MOVING THE SCIENCE FORWARD. AND PEOPLE MAKE INCREDIBLE -- IN THE HIV AND AIDS FIELD, PEOPLE MADE INCREDIBLE SACRIFICES IN ORDER TO MOVE THE SCIENCE FORWARD. BUT IF YOU'RE NOT ANSWERING A QUESTION, IF YOUR STUDIES ARE NOT WELL DESIGNED.

MS. LANSING: I THINK WE SHOULD DO THIS TOMORROW.

DR. CHARO: I KNOW WE'RE GOING TO DO THIS. I CANNOT LET YOU GO TO DINNER WITH A BASIC MISCONCEPTION. FIRST, THINGS CAN SOUND DANGEROUS, BUT THE ACTUAL RISK LEVEL NEEDS TO BE CAREFULLY EVALUATED. IT MAY NOT BE AS RISKY AS WHAT YOU'RE IMAGINING.

SECOND, IRB'S ALWAYS AND THE FDA ALWAYS, IF THEY'RE INVOLVED, LOOK AT THE RISK OF THE RESEARCH TO ALL THE SUBJECTS, THOSE IN THE ACTIVE ARM AND THOSE IN THE CONTROL ARM BOTH, AS COMPARED TO POSSIBLE BENEFITS. SO THAT'S TAKEN INTO ACCOUNT.

AND FINALLY, IF I UNDERSTOOD DR. DOBKIN CORRECTLY, AND I HAD HEARD SIMILAR THINGS BEFORE, INTERESTINGLY, ONE OF THE THINGS THAT WAS LEARNED IN THE CASES WHERE THIS WAS CONSIDERED TO BE SAFE ENOUGH, THE RISKS WERE LOW ENOUGH THAT THEY APPROVED IT, WAS THAT RATHER THAN THE SUBSTANCE OF THE SURGERY OR THE INJECTION BEING THE CAUSE FOR CHANGE IN OUTCOMES, IT WAS THE MERE FACT OF DOING THE SURGERY. SO THAT IRONICALLY YOU LEARNED THAT NOT ONLY WAS THE CONTROL ARM NOT UNDULY RISKY, BUT IT WAS ACTUALLY POSITIVELY BENEFICIAL, WHICH NOBODY WAS EXPECTING IN SOME OF THE EARLIER EXPERIMENTS. SO JUST I WOULDN'T WANT TO YOU WALK OUT THINKING THIS IS SOME KIND OF FRANKENSTEIN EXPERIMENT.

MS. LANSING: I ACTUALLY HEARD THAT THEY BENEFITED FROM IT, BUT I THINK IT'S EXTRAORDINARILY COMPLEX. ACTUALLY ON THE COMPUTER GEOFF PULLED UP A COUPLE OF ARTICLES FOR ME TO READ.

CHAIRMAN LO: THIS IS A COMPLICATED, DIFFICULT, CONTROVERSIAL ISSUE, AND I THINK IT IS SOMETHING WE'RE GOING TO NEED TO THINK MORE ABOUT. ARLENE, YOU WANT TO SAY ONE LAST THING.

DR. CHIU: I'M SORRY. I CAN'T CONTAIN MYSELF ANYMORE. ARLENE CHIU, CITY OF HOPE. I KNOW A LITTLE SOMETHING ABOUT THOSE TWO CLINICAL TRIALS

WITH RESPECT TO FETAL TISSUE IMPLANTS FOR PARKINSON'S BECAUSE BOTH OF THEM WERE FUNDED BY NINDS IN 1998 AND THE RESULTS CAME OUT IN 2000.

AND THE FACT OF THE MATTER WAS THAT THE PATIENTS WHO HAD SHAM OPERATIONS WHERE HOLES WERE DRILLED IN THEIR HEADS, BUT THEY DID NOT RECEIVE THE TRANSPLANTS, WERE TOLD THAT WHEN THE KEY WAS BROKEN AND THEY KNEW THAT THEY WERE SHAM, THEY WOULD BE OFFERED THE OPPORTUNITY TO RECEIVE TRANSPLANTS SHOULD THE RESULTS BE EFFICACIOUS. SO THEY WERE WILLING TO SIGN UP FOR A CLINICAL TRIAL KNOWING THAT THEY COULD GET THAT.

THE PROBLEM IS THIS. YOU SAW THE DATA. AT THE END OF THE FIRST YEAR, THERE WERE SIGNS OF EFFICACY FOR ALL PATIENTS FOR THE PATIENTS THAT WERE AROUND 40, 45 YEARS OLD. SO YOU KNOW YOU SAW THAT DIP AND IT LOOKED VERY PROMISING. WHEN THE KEY WAS BROKEN, WHEN THEY THOUGHT AT THE END OF ONE YEAR, YOU SHOULD BE ABLE TO SEE WHAT WAS HAPPENING. SO SEVERAL OF THE SHAM OPERATED PATIENTS ACTUALLY GOT TRANSPLANTS. THE TROUBLE WAS AT THE END OF TWO YEARS YOU SAW WHAT HAPPENED. AND WORSE THAN THAT, SOME OF THE PATIENTS NOW GOT DYSKINESIAS WHICH WAS A SIDE EFFECT THAT WAS NOT A GOOD SIDE EFFECT THAT WAS UNEXPECTED. SO YOU CAN SEE THE DOUBLE-EDGED SWORD

ABOUT EVEN OFFERING SOMETHING THAT SOUNDS SO REASONABLE TO PATIENTS WHO WERE WILLING TO BE SHAM OPERATED SHOULD THEIR NUMBER COME UP THAT WAY IN THE RANDOMIZED CHOICE. SO IT'S NOT THAT SIMPLE EVEN TRYING TO BE AS FAIR AS POSSIBLE IN STUDIES LIKE THIS.

SO THE OTHER LAST POINT I WANTED TO MAKE IS ONE OF THE MOST IMPORTANT THINGS IN THESE TRIALS WERE THAT BECAUSE THEY WERE FUNDED BY THE FEDERAL GOVERNMENT, THE RESULTS WERE PUBLISHED AND YOU SAW EVERYTHING GOOD, BAD, AND UGLY, AND IT WAS ALL PRESENTED AND WE CAN READ ABOUT THEM. IF THEY WERE NOT FUNDED BY THE FEDERAL GOVERNMENT, BY SOME OTHER ENTITY, THEY CAN CHOOSE WHAT DATA TO PRESENT OR WHAT TO TELL YOU. AND SO I WOULD CERTAINLY ENCOURAGE CIRM, NOW THAT YOU'RE EMBARKING ON THIS STAGE, THAT A REQUIREMENT IS THAT WHATEVER THE RESULT THAT CIRM-FUNDED CLINICAL TRIALS HAVE TO BE PUBLISHED SO THAT PEOPLE CAN SEE IN LIGHT OF THE TRANSPARENCY WHAT MAY, MAY NOT WORK BECAUSE OTHERWISE IT WOULD BE MONEY WASTED IF YOU CAN'T REALLY INTERPRET THE RESULTS. THANK YOU.

CHAIRMAN LO: THANKS VERY MUCH, ARLENE. SO I'M GOING TO ADJOURN OURSELVES AND THEN SEE EVERYBODY IN JUST A LITTLE WHILE FOR DINNER.

DR. LOMAX: EVERYONE MAKE SURE THEY CLEAR THEIR STUFF OUT OF THIS ROOM COMPLETELY.

(THE MEETING WAS THEN ADJOURNED AT 6:10 P.M.)

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 PROCEEDINGS BEFORE THE SCIENTIFIC AND MEDICAL ACCOUNTABILITY STANDARDS WORKING GROUP TO THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD AT THE LOCATION INDICATED BELOW

LUXE HOTEL
11461 W. SUNSET BOULEVARD
LOS ANGELES, CALIFORNIA
ON
FEBRUARY 17 AND 18, 2009

WAS HELD AS HEREIN APPEARS AND THAT THIS IS THE ORIGINAL TRANSCRIPT THEREOF AND THAT THE STATEMENTS THAT APPEAR IN THIS TRANSCRIPT WERE DIGITALLY RECORDED AND SUBSEQUENTLY TRANSCRIBED BY ME. I ALSO CERTIFY THAT THIS TRANSCRIPT IS A TRUE AND ACCURATE RECORD OF THE PROCEEDING.

Beth C. Drain

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