BEFORE THE
SCIENTIFIC AND MEDICAL ACCOUNTABILITY
STANDARDS WORKING GROUP
OF THE
INDEPENDENT CITIZENS' OVERSIGHT COMMITTEE
TO THE
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
ORGANIZED PURSUANT TO THE
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

REGULAR MEETING

LOCATION: VIA ZOOM

DATE: FEBRUARY 9, 2024
8 A.M.

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

FILE NO.: 2024-09

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FEBRUARY 9, 2024; 8 A.M.

DR. LOMAX: WE ARE LIVE. THANKS, EVERYONE. THIS IS THE STANDARDS WORKING GROUP MEETING. THERE'S A GROUP OF US JOINING YOU FROM ASILOMAR BECAUSE WE'VE JUST ATTENDED A TWO-DAY CONFERENCE FUNDED BY CIRM ON THE TOPIC OF MODEL EMBRYO SYSTEMS. SO WE SHOULD HAVE PARTICIPATION FROM SOME OF THE CONFERENCE ATTENDEES TALKING ABOUT THE SCIENCE AND THE WORK HERE.

SO, JEFF, I WANTED TO GIVE YOU AN OPPORTUNITY TO SAY A FEW WORDS, INTRODUCE THE MEETING, AND THEN WE'LL TAKE ROLL AND DO INTRODUCTIONS AFTER THAT JUST TO GIVE PEOPLE A FEW MORE MINUTES TO COME IN.

CO-CHAIRMAN KAHN: GREAT. THANK YOU, GEOFF. AND WELCOME, EVERYBODY. SORRY NOT TO BE WITH YOU IN PERSON FOR LOTS OF REASONS, NOT LEAST OF WHICH IT'S ALWAYS A PLEASURE TO BE IN THAT PART OF CALIFORNIA.

SO REALLY INTERESTING TOPIC THAT WE'RE HERE TO TALK ABOUT TODAY. I LOOK FORWARD TO THE PRESENTATIONS, AND I KNOW WE'LL HAVE A REALLY ENGAGED AND INTERESTING DISCUSSION.

SO, GEOFF, YOU WANT TO TAKE ROLL AND ASK

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PEOPLE TO INTRODUCE THEMSELVES AS YOU DO THAT?

DR. LOMAX: WHY DON'T I GO THROUGH AND JUST GET THROUGH THE ROLL FOR THE RECORD, AND WE THEN WE GO BACK AND, YES, WE'D VERY MUCH LIKE TO HAVE PEOPLE INTRODUCE THEMSELVES. I KNOW AT THE LAST MEETING, WE DIDN'T HAVE THE BENEFIT OF INTRODUCTIONS. SO HAVE THE WORKING GROUP MEMBERS INTRODUCE THEMSELVES. SO I'LL START WITH ROLL.

JEFF KAHN.

CO-CHAIRMAN KAHN: HERE.

DR. LOMAX: FRED FISHER.

CO-CHAIRMAN FISHER: PRESENT.

DR. LOMAX: AKSHAY SHARMA. BENHUR LEE.

DR. LEE: PRESENT.

DR. LOMAX: CHRISTINE MIASKOWSKI.

DR. MIASKOWSKI: HERE.

DR. LOMAX: ELENA FLOWERS.

DR. FLOWERS: HERE.

DR. LOMAX: JANET ROSSANT.

DR. ROSSANT: HERE.

DR. LOMAX: JOHN WAGNER. KAREN ROMMELFANGER. KAROL WATSON. KRIS SAHA. LEONDRA CLARK-HARVEY. MELISSA LOPES.

MS. LOPES: HERE.

DR. LOMAX: RAYNE ROUCE. VITO IMBASCIANI.

CHAIRMAN IMBASCIANI: PRESENT.

DR. LOMAX: SHARON TERRY.

MS. TERRY: HERE.

DR. LOMAX: THANK YOU. AND I KNOW A FEW MEMBERS MAY BE JOINING AS WE GO ON. SO HOPEFULLY WE'LL HAVE THE BENEFIT OF INTRODUCTIONS.

SO, JEFF, DO YOU WANT TO HAVE FOLKS INTRODUCE THEMSELVES? I THINK IT WOULD BE HELPFUL TO HAVE A LITTLE BIT OF BACKGROUND.

CO-CHAIRMAN KAHN: I THINK THAT'S A GREAT IDEA. IF YOU COULD CALL ON PEOPLE, I THINK IT WILL BE EASIEST JUST BECAUSE YOU MAY HAVE AN EASIER LIST TO WORK FROM. I'M JUST LOOKING AT THE ZOOM, AND I'M NOT SURE WHO'S IN THE ROOM WITH YOU.

DR. LOMAX: HAPPY TO DO SO. WHY DON'T WE START WITH YOU AS THE CO-CHAIR.

CO-CHAIRMAN KAHN: HAPPY TO START. JEFF KAHN. I AM THE DIRECTOR OF THE BERMAN INSTITUTE OF BIOETHICS AT JOHNS HOPKINS UNIVERSITY AND A NATIVE ANGELINO. THAT'S MY INTEREST IN CALIFORNIA RELATED THINGS. HAPPY TO BE HERE.

DR. LOMAX: FRED.

CO-CHAIRMAN FISHER: GOOD MORNING. FRED FISHER, CO-CHAIR OF THE STANDARDS WORKING GROUP. AND ALSO I AM THE CIRM REPRESENTATIVE PATIENT

ADVOCATE FOR MS AND ALS. AND VERY HAPPY TO BE HERE.

DR. LOMAX: I'M TRYING TO GO THROUGH. I THINK, ELENA, ARE YOU NEXT. I DON'T THINK ANYONE ELSE HAS JOINED SINCE THEN.

DR. FLOWERS: HI. I'M ELENA FLOWERS. I'M AN ASSOCIATE PROFESSOR AT UC SAN FRANCISCO IN THE SCHOOL OF NURSING AND HERE AS A NURSE AND A PATIENT ADVOCATE.

DR. LOMAX: AND THEN, JANET, I THINK YOU'RE NEXT.

DR. ROSSANT: HI. I'M JANET ROSSANT. I'M FROM THE UNIVERSITY OF TORONTO HOSPITAL FOR SICK CHILDREN AND THE GAIRDNER FOUNDATION. I'M HAPPY TO BE HERE. I'M A CELL BIOLOGIST.

DR. LOMAX: I THINK, MELISSA, ARE YOU NEXT?

MS. LOPES: HI. I'M MELISSA LOPES. I'M THE DIRECTOR OF THE EMBRYONIC STEM CELL OVERSIGHT COMMITTEE AT HARVARD UNIVERSITY AND A SENIOR RESEARCH COMPLIANCE OFFICER THERE.

DR. LOMAX: SORRY, BENHUR, I SKIPPED YOU. I SEE YOU ON THE ZOOM. WOULD YOU INTRODUCE YOURSELF PLEASE.

DR. LEE: HI. MY NAME IS BENHUR LEE. I'M A PROFESSOR OF MICROBIOLOGY AT THE ICAHN SCHOOL OF

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MEDICINE AT MT. SINAI. I WAS PREVIOUSLY AT UCLA, AND THAT'S HOW I WAS INVOLVED IN THE EMBRYONIC STEM CELL OVERSIGHT COMMITTEE SINCE PROPOSITION 71.

DR. LOMAX: THANK YOU. DR. IMBASCIANI.

DR. IMBASCIANI: I'M VITO IMBASCIANI AND CHAIR OF THE INDEPENDENT CITIZENS OVERSIGHT COMMITTEE, THE GOVERNING BODY FOR CIRM. THANK YOU.

DR. LOMAX: I THINK I'M GOING TO GO BACK TO CHRISTINE. DID I MISS YOU?

DR. MIASKOWSKI: YOU DID, GEOFF. NO PROBLEM. GOOD MORNING. I'M CHRIS MIASKOWSKI. I'M A NURSE MEMBER OF THE CIRM BOARD, AND I'M A PROFESSOR OF NURSING AT THE UNIVERSITY OF CALIFORNIA SAN FRANCISCO. I STUDY SYMPTOMS IN PATIENTS WITH CANCER.

DR. LOMAX: THANK YOU. SHARON TERRY.

MS. TERRY: HI. I'M SHARON TERRY, PRESIDENT AND CEO OF GENETIC ALLIANCE, WHICH IS A COALITION OF ABOUT 2,000 PATIENT ADVOCACY GROUPS AND ALSO THE FOUNDER/CEO OF PXE INTERNATIONAL, WHICH IS A DISEASE FOUNDATION FOR A DISEASE MY KIDS HAVE. AND I ALSO AM THE CHAIR OF THE HEALTH SCIENCE POLICY BOARD AT THE NATIONAL ACADEMIES OF MEDICINE AND WAS PART OF THE STUDY THAT LOOKED AT CIRM YEARS AND YEARS AGO. SO HAPPY TO BE HERE.

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DR. LOMAX: FANTASTIC. YOU WILL NOTICE THERE ARE SOME OTHER FOLKS ON ZOOM, BUT THESE ARE SOME OF OUR PANELISTS AND OTHER PRESENTERS. SO I WOULD LIKE INTRODUCE THEM IN FRONT OF THEIR PANEL. SO WE'RE NOT IGNORING YOU, BUT JUST WANT TO LOCATE YOU IN THE CONVERSATION AT THE RIGHT TIME. SO STAND BY.

DID I MISS ANY OF THE WORKING GROUP MEMBERS OR HAS ANYONE JOINED SUBSEQUENTLY?

CO-CHAIRMAN KAHN: MAY I MAKE A REQUEST YOU ALL IN THE ROOM. I KNOW, JANET, YOU DID THIS. IT'S REALLY HELPFUL TO US IF WE CAN SEE YOU WHEN YOU TALK BECAUSE THE CAMERA ANGLE FROM THE ZOOM IN THE ROOM IS REALLY LONG. SO IF IT'S POSSIBLE FOR YOU, LIKE JANET JUST DID, THAT'S SUPER HELPFUL. I KNOW IF YOU HAVE A LAPTOP IN FRONT OF YOU, IT'S POSSIBLE MAYBE YOU DON'T ALL HAVE THAT, BUT IF YOU DO, IT'D BE GREAT IF YOU LOGGED ON.

DR. LOMAX: AND THEN THERE ARE SORT OF TWO OTHER MEMBERS OF THE CIRM LEADERSHIP I'D LIKE TO INTRODUCE THEMSELVES. PRESIDENT THOMAS AND THEN IF MARIA BONNEVILLE, OUR VICE CHAIR, COULD INTRODUCE HERSELF AFTERWARDS, I'D APPRECIATE IT. THANK YOU.

DR. THOMAS: JONATHAN THOMAS, I'M THE PRESIDENT AND CEO OF CIRM AND FORMER CHAIR OF THE

BOARD.

THE REPORTER: GEOFF, THIS BETH, THE REPORTER. WHEN DR. IMBASCIANI TALKED AND WHEN J.T. TALKED, IT'S VERY MUDDLED AND GARBLED. IT'S VERY DIFFICULT TO UNDERSTAND WHAT THEY'RE SAYING.

CO-CHAIRMAN KAHN: I WOULD AGREE WITH THAT. GEOFF, WHEN YOU SPEAK, IT'S NOT. SO I DON'T KNOW WHAT YOU'RE DOING COMPARED TO THE OTHERS, BUT WHATEVER YOU'RE DOING IS WORKING AND WHATEVER THE OTHERS ARE DOING, NOT SO WELL.

DR. LOMAX: WE HAVE A FULL AV TEAM HERE. SO WE'LL HAVE THEM TROUBLESHOOT. IT SEEMS TO BE ISOLATED, SO WE'LL HAVE THEM TAKE CARE OF THAT. JANET, FORTUNATELY, IS SITTING NEXT TO ME. SO WE CAN START AND THEY CAN SORT THIS OUT.

IS THERE ANYTHING ELSE, JEFF, THAT WE WANT TO COVER BEFORE WE MOVE INTO THE --

CO-CHAIRMAN KAHN: JUST A LITTLE HOUSEKEEPING. SO THE AGENDA IS SORT OF BACK TO BACK. DO YOU WANT TO SCHEDULE WHEN WE'RE BREAKING, OR ARE WE GOING TO DO THAT KIND OF ON THE FLY?

DR. LOMAX: WE SCHEDULED A BREAK -- WE HAVE FOUR SESSIONS, AND WE SCHEDULED A BREAK AFTER THE SECOND. I THINK WE CAN STICK TO THAT UNLESS FOR SOME OTHER REASON OR BETH NEEDS A BREAK, WE CAN MAKE

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AN ADJUSTMENT IF NECESSARY.

CO-CHAIRMAN KAHN: PERFECT.

DR. LOMAX: DO YOU WANT TO LAUNCH INTO YOUR PRESENTATION.

DR. ROSSANT: I'M JUST GOING TO SHARE SOME SLIDES WITH PEOPLE. CAN YOU HEAR ME?

CO-CHAIRMAN KAHN: YOU'RE GREAT ACTUALLY. THAT'S THE MAGIC MICROPHONE, WHICHEVER ONE YOU'RE USING.

DR. ROSSANT: EVERYBODY HAS TO USE THIS MICROPHONE. I'M JUST GOING TO SHARE SCREEN. HOLD ON. EVERYBODY SEE THE SLIDES? HOPE YOU CAN SEE THEM ONLINE.

I'M GOING TO GIVE A LITTLE BIT OF BACKGROUND SCIENCE, NOT TOO MUCH BECAUSE WE COULD GET DOWN AND DEEP INTO WHAT'S GOING ON WITH STEM CELL MODELS. BUT I THOUGHT I WOULD START BY TRYING TO COME UP WITH A DEFINITION. AS WAS JUST SAID BY GEOFF, WE'VE BEEN HERE TWO DAYS AT ASILOMAR IN A KEYSTONE MEETING ABSOLUTELY DEDICATED TO STEM CELL EMBRYO MODELS. SO IF I DON'T KNOW WHAT ONE IS BY NOW, I'M JUST NOT DOING MY JOB RIGHT. BUT I HAVE TO SAY THAT BY LISTENING TO THE DIVERSITY OF EXPERIMENTAL SYSTEMS THAT PEOPLE ARE USING RIGHT NOW, ACTUALLY IT'S QUITE HARD TO COME UP WITH A

DEFINITION, BUT HERE IS MINE. I'VE GOT TO GET MYSELF OFF THE SCREEN BECAUSE I'M IN THE WAY.

STEM CELL-BASED EMBRYO MODELS ARE NOT EMBRYOS. THEY ARE IN-VITRO, THREE-DIMENSIONAL CULTURES OF PLURIPOTENT STEM CELLS PLUS OR MINUS OTHER CELL LINES THAT REPRODUCIBLY, THAT IS TO SAY ALWAYS, PEOPLE CAN EVEN TRANSLATE IT FROM LAB TO LAB, ROBUSTLY, THAT MEANS EFFICIENTLY, NOT JUST OCCASIONALLY DO YOU GET SOMETHING, ROBUSTLY GENERATE ORGANIZED STRUCTURES THAT MODEL SPECIFIC STAGES OR STRUCTURES OF THE IN VIVO EMBRYO. I THINK THAT'S QUITE GOOD. WE WILL SEE AT THE END IF WE ALL AGREE WITH THAT.

SO I'M GOING TO TAKE YOU BACK TO THE BEGINNING OF DEVELOPMENT. I SAID I'M A STEM CELL BIOLOGIST, BUT ACTUALLY I'M AN EMBRYOLOGIST. I'VE WORKED MANY, MANY YEARS ON A MOUSE EMBRYO. AND A LOT OF WHAT WE ARE GOING TO BE TALKING ABOUT TODAY COMES FROM OUR UNDERSTANDING OF THE MOUSE BLASTOCYST AND, HENCE, TRANSLATION INTO THE HUMAN BLASTOCYST. IN THE MOUSE BLASTOCYST AND THE HUMAN, JUST BEFORE THE EMBRYO IMPLANTS, IT LOOKS LIKE THIS. THE HUMAN BLASTOCYST ISN'T AS PRETTY. THIS IS A MOUSE ONE. AND IT HAS AN OUTER LAYER OF TROPHECTODERM WHICH GO ON TO FORM THE TROPHOBLAST LAYERS OF THE PLACENTA, A

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LAYER OF PRIMITIVE ENDODERM, WHICH MAKES ENDODERMS OF THE YOLK SACK. AND THE LITTLE PINK CELLS ARE THE CELLS CALLED THE EPIBLAST THAT MAKE THE FETUS ITSELF.

SO IT'S INTERESTING BECAUSE ESSENTIALLY IN EARLY DEVELOPMENT MOST OF THE EMBRYO TISSUES ARE EXTRAEMBRYONIC. TROPHECTODERM AND PRIMITIVE ENDODERM FORM THE MEMBRANES THAT THE MAIN EMBRYO USES TO SURVIVE IN THE UTERUS. IT'S ONLY THE SUBSET OF CELLS THAT ACTUALLY MAKE THE FETUS ITSELF. THEY ARE WHAT WE CALL PLURIPOTENT CELLS BECAUSE THEY CAN MAKE THIS, BUT THEY DON'T MAKE PLACENTA AND THEY DON'T MAKE YOLK SAC.

MANY YEARS AGO NOW FROM MY LAB AND OTHER LABS, IT'S BEEN POSSIBLE TO DERIVE THREE DISTINCT STEM CELL LINES FROM THE MOUSE BLASTOCYST. EMBRYONIC STEM CELL, I DID NOT DERIVE THESE, THEY'RE THE MOST FAMOUS STEM CELLS OF ALL, OF COURSE, AND THEY DERIVE FROM THE EPIBLAST. AND THEY BEHAVE LIKE THE EPIBLAST CELLS IN THE SENSE THAT WHEN YOU PUT THEM BACK IN AN EMBRYO, THEY CAN CONTRIBUTE TO ALL THE CELLS OF THE FETUS, BUT THEY DON'T MAKE THE YOLK SAC AND THEY DON'T MAKE THE PLACENTA. WE MAKE TROPHOBLAST STEM CELLS, PUT THEM BACK IN THE EMBRYO. THEY MAKE PLACENTA, BUT NOT FETUS. AND XEN CELLS

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REPRESENT THE PRIMITIVE ENDODERM LINEAGE THAT CONTRIBUTE TO THE YOLK SAC.

SO THOSE THREE STABLE CELL LINES IN THE MOUSE MIMIC THE CELL COMMITMENT OF THE CELLS OF THE BLASTOCYST. AND SO WITH THOSE CELL LINES, WE AND OTHERS HAVE USED THEM IN MANY, MANY DIFFERENT WAYS TO STUDY DEVELOPMENT, TO MAKE GENETICALLY MODIFIED MICE, ETC., ETC. BUT THIS IS THE MOUSE. CAN YOU IN THE MOUSE TAKE THESE STEM CELLS, SINCE THEY COME FROM THE BLASTOCYST, CAN YOU PUT THEM BACK TOGETHER AND RECONSTITUTE AN EMBRYO?

AND NICOLAS RIVRON DID THIS BY MAKING WHAT HE CALLS BLASTOIDS. HE TOOK ES CELLS AND TS CELLS, AGGREGATED THEM TOGETHER, AND THEY MADE THESE STRUCTURES HERE WHICH MORPHOLOGICALLY RESEMBLE BLASTOCYSTS, CONTAIN TROPHECTODERM CELLS AND INNER CELL MASS CELLS, AND HAVE MANY OF THE PROPERTIES OF THE EMBRYO ITSELF.

MOUSE BLASTOIDS ARE NOT EMBRYOS EITHER. THEY MIMIC SEVERAL ASPECTS. WE PUT THEM BACK IN THE UTERUS. THEY CAN CAUSE WHAT WE CALL A PREGNANCY RESPONSE, BUT THEY DON'T DEVELOP FURTHER. SO THEY'RE NOT PERFECT MODELS, BUT THEY'RE GOOD FOR STUDYING THE EARLY LINEAGE AND HOW TROPHECTODERM.

MAGDA ZERNICKA-GOETZ' LAB DID A DIFFERENT

KIND OF EXPERIMENT WHERE INSTEAD OF TRYING TO MIMIC THE BLASTOCYST ITSELF, THEY SAID, WELL, WE'VE GOT ES, TS, AND XEN. MAYBE IF YOU PUT THEM TOGETHER, THEY'LL ACTUALLY RESEMBLE THE EMBRYO AFTER IT IMPLANTS IN THE UTERUS. THAT'S WHAT YOU SEE HERE. AGAIN, IN THE BEST CASE SCENARIO, YOU GET THE SEGREGATION OF ES CELLS, TS CELLS, AND XEN CELLS TO FORM WHAT WE CALL ETIX EMBRYOS. THIS IS A REAL EMBRYO ON THE RIGHT, AND THIS IS THE STEM CELL MODEL ON THE LEFT.

SO THAT WAS A NICE SYSTEM THEN, AND YOU CAN GROW THOSE TO SOME DEGREE. INITIALLY THEY WERE ABLE TO SHOW THEY COULD GET TO THE POINT WHERE THEY MIGHT MAKE PRIMITIVE STREAK. THEY WENT ON. AND THIS IS ALSO DONE IN JACOB HANNA'S LAB IN ISRAEL. THEY TOOK THOSE ETIX EMBRYOS, SOMEWHAT CHANGED THE CELL LINES A LITTLE BIT, BUT THE DETAILS DON'T MATTER. INSTEAD OF JUST GROWING THEM IN A STATIC CULTURE, THEY GREW THEM IN ROLLER BOTTLES, WHICH HAS BEEN DONE FOR A LONG TIME TO CULTURE MOUSE EMBRYOS. THOSE ETIX EMBRYOS IN THE BEST CASE SCENARIOS COULD GO ON AND LOOK QUITE LIKE A MUCH LATER EMBRYO AT ABOUT EIGHT AND A HALF DAYS. IF YOU LOOK CAREFULLY, WHAT YOU ARE SEEING HERE ON THE TOP, THIS IS AN ETIX EMBRYO FROM THE ROLLER CULTURE.

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THIS IS A REAL EIGHT-AND-A-HALF-DAY EMBRYO. THEY'RE OBVIOUSLY NOT THE SAME, BUT THEY SHOW REMARKABLE SIMILARITIES. THEY SHOW ANTERIOR, POSTERIOR PATTERNING. IF YOU LOOK AT THE TOP, YOU CAN SEE THE NEURAL TUBE IS BEGINNING TO CLOSE. AND IF YOU LET THEM GO A LITTLE BIT LONGER, YOU CAN SEE MARKERS OF THE HEART AND MARKERS OF ANTERIOR NEUROECOTODERM. AGAIN, THIS IS THE ETIX. THIS IS THE REAL EMBRYO.

SO THIS SUGGESTS THEN, AT LEAST IN THE MOUSE, YOU CAN TAKE THESE EMBRYO MODELS AND TAKE THEM FORWARD TO STAGES WHERE THEY DO BEGIN TO ALLOW YOU TO STUDY THE INITIATION OF THE BODY AXIS, FORMATION OF THE HEART, DEVELOPMENT OF THE NERVOUS SYSTEM AND SOMITES IN AN INTACT, AS IT WERE, ALL THE PIECES ARE THERE AND TRYING TO MIMIC THE INTACT EMBRYO.

SO THIS IS A MOUSE. THE QUESTION THEN BECAME, OF COURSE, CAN YOU DO THE SAME THING IN HUMANS? CAN YOU GENERATE HUMAN STEM CELL-DERIVED EMBRYO MODELS? AND HOW FAR CAN THEY DEVELOP? SO WHY WOULD YOU WANT TO DO THAT? WELL, BECAUSE THE STAGES THAT YOU CAN ACCESS WITH THESE EMBRYO MODELS, THE BLASTOCYST IN THE EARLY POST-IMPLANTATION STAGES ARE INACCESSIBLE IN HUMAN. YOU CAN GET TO THE

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BLASTOCYST; BUT ONCE IT IMPLANTS, WE DON'T KNOW WHAT GOES ON. IT'S VERY DIFFICULT TO ACCESS EARLY MATERIAL. THERE IS SOME SECTIONED MATERIAL FROM RARE PREGNANCIES AND THERE'S SOME ABILITY TO COLLECT TERMINATION MATERIAL LATER ON. BUT THIS SORT OF BLACK BOX OF IMPLANTATION AND EARLY PATTERNING CANNOT BE ACCESSED ANY OTHER WAY THAN REALLY EITHER CULTURING A HUMAN EMBRYO, BUT THEY DON'T CULTURE VERY WELL, OR MAKING A STEM CELL MODEL. SO WHY DO YOU WANT TO DO THIS?

I'M JUST GOING TO WHIP THROUGH BECAUSE WHEN SCIENTISTS ARE TRYING TO PRESENT THIS, IT'S VERY IMPORTANT TO SAY WHY ARE WE DOING THIS, NOT JUST TRYING TO MAKE AN EMBRYO. THAT IS NOT WHAT THEY'RE TRYING TO DO. THEY'RE TRYING TO ANSWER SPECIFIC QUESTIONS THAT ARE GOING TO HAVE IMPACT ON HUMAN HEALTH.

SO THERE IS A FUNDAMENTAL QUESTION. THERE'S SOME FUNDAMENTAL BIOLOGY HERE. YOU CAN GET UNDERSTANDING OF HOW A HUMAN EMBRYO, HOW WE DEVELOP OVER THIS PERIOD, BUT YOU CAN'T ACCESS IT ANY OTHER WAY. SO FUNDAMENTAL BIOLOGY. HUMAN AND MOUSE ARE SIMILAR, BUT NOT THE SAME AT THESE STAGES. THE GENES ARE SIMILAR, BUT NOT THE SAME. MORPHOLOGY IS SIMILAR, BUT NOT THE SAME. IF WE WANT TO UNDERSTAND

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HOW WE DEVELOP, WE NEED TO STUDY HUMAN DEVELOPMENT.

YOU CAN START TO DO LIVE IMAGING. YOU CAN REALLY UNDERSTAND THE DYNAMICS PROCESS BECAUSE THESE CAN BE GROWN IN VITRO. YOU CAN USE THESE TO BETTER UNDERSTAND HOW TO MAKE BETTER PLURIPOTENT STEM CELLS BECAUSE THE PLURIPOTENT STEM CELLS HERE ARE THE IMPORTANT PIECES THAT MAKE THE EMBRYO MORTAL GO ON.

IT'S VERY CLEAR FROM THIS MEETING THAT PEOPLE START WITH DIFFERENT KINDS OF PLURIPOTENT STEM CELLS AND THEY GET DIFFERENT RESULTS. SO THERE'S A LOT OF BACKWARDS AND FORWARDS HERE FROM LOOKING AT THESE STRUCTURES TO GO BACK AND MAKE BETTER PLURIPOTENT STEM CELLS.

IMPROVING IVF TECHNOLOGY. IF WE CAN UNDERSTAND THE PROCESS OF IMPLANTATION AND THE GENE PATHWAYS, THEN WE SHOULD BE ABLE TO BETTER CULTURE HUMAN EMBRYOS AND IMPROVE IVF, WHICH IS STILL AFTER ALL THESE YEARS IS NOT A VERY EFFICIENT PROCESS.

MODEL IMPLANTATION PROCESS. THAT'S WHEN THE PLACENTA FORMS. THAT'S THE PERIOD AT WHICH THERE'S A HUGE AMOUNT OF EARLY EMBRYO LOSS. ONLY A THIRD OR SO OF HUMAN PREGNANCIES MAKE IT OVER THIS PERIOD, AND WE DON'T UNDERSTAND WHY. MODELING THIS IN CULTURE IS GOING TO BE AND IS STARTING TO BE VERY IMPORTANT.

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ASSESSING EMBRYOTOXICITY OF DRUGS AND ENVIRONMENTAL TOXINS. IF WE HAD HAD THESE SYSTEMS, MAYBE WE WOULD NOT HAVE HAD THALIDOMIDE PROBLEMS.

ASSESSING THE SAFETY OF NOVEL REPRODUCTIVE TECHNOLOGIES ALSO, MITOCHONDRIAL REPLACEMENT, GAMETES FROM STEM CELLS, TO BE ABLE TO MODEL THIS IN VITRO IS IMPORTANT.

UNDERSTAND WHERE GERM CELLS COME FROM. THEY ARISE DURING THIS EARLY PATTERNING PROCESS. WHAT HAPPENS IN INFERTILE PATIENTS?

DEVELOPMENTAL DEFECTS BEGIN WHEN YOU MODEL THE BODY AXIS.

AND DEVELOPMENTAL ORIGINS IN HEALTH AND DISEASE. WE NOW KNOW MORE AND MORE THAT ADULT DISEASE CAN BE AFFECTED BY EVENTS FROM CONCEPTION ON. SO BEING ABLE TO HAVE A SYSTEM WHERE YOU CAN LOOK AT THE DIFFERENCES AND THE IMPACTS OF ENVIRONMENTAL AGENTS AND GENETICS TOGETHER IS GOING TO BE VERY IMPORTANT.

QUICK. QUICK. QUICK. THERE'S A FEW MORE THINGS AND WE HEARD MORE THINGS AT THE MEETING, BUT THIS IS NOT JUST SOMETHING TO MODEL AN EMBRYO. THIS IS REALLY FUNDAMENTAL BIOLOGY THAT'S GOING TO HAVE IMPACT ON HUMAN REPRODUCTION AND FERTILITY.

SO WHAT DO WE HAVE? I CAN'T GO THROUGH

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ALL THE MODELS WE HEARD ABOUT THIS WEEK, BUT I THINK YOU CAN DIVIDE THEM INTO TWO SETS. JUST AS IN THE MOUSE, THERE'S REALLY A DISTINCTION BETWEEN THE STEM CELL MODELS THAT MIMIC THE BLASTOCYST AND THE STEM CELL MODELS THAT MIMIC THE VARIOUS ASPECTS OF THE POSTIMPLANTATION EMBRYO.

SO IN THE HUMAN, AS IN THE MOUSE, IT'S POSSIBLE TO GENERATE BLASTOIDS. THEY WILL HAVE ALL THREE CELL LINEAGES OF BLASTOCYST: EPIBLAST, HYPOBLAST, AND TROPHECTODERM, IF THEY'RE A GOOD BLASTOID.

WHEN YOU MAKE A POSTIMPLANTATION MODEL, THERE ARE A VARIETY OF DIFFERENT FORMS. THEY ALL START WITH EMBRYONIC STEM CELLS OR IPS CELLS. THEY START WITH PLURIPOTENT STEM CELLS BECAUSE THAT'S THE TISSUE THAT'S GOING TO MAKE THE EPIBLAST AND MAKE THE FETUS. SO EVERYBODY IS FOCUSED ON THAT. BUT THERE ARE SOME MODELS, LIKE GASTRULOIDS, WHERE YOU TAKE THE EPIBLAST ALONE, THE ES CELLS ALONE, AND THEY GENERATE A STRUCTURE THAT MAKES THE MESODERM ALONG THE BODY AXIS. BUT THEN MORE RECENTLY, PEOPLE HAVE BEEN COMBINING PLURIPOTENT CELLS WITH CELLS THAT MAKE HYPOBLASTS OR THE CELLS THAT MAKE TROPHOBLAST TO FORM PERIGASTRULOIDS. I WOULD CALL THE EPIBLASTS AND HYPOBLASTS PERIGASTRULOIDS. THEN

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WHAT WE CALL NOW THE INTEGRATED EMBRYO MODEL THAT ACTUALLY HAS ALL THREE LINEAGES PUT TOGETHER TO GENERATE SOMETHING THAT YOU HOPE LOOKS A LITTLE BIT LIKE THIS. SO A GRADATION OF KINDS OF MODELS FROM QUITE SIMPLE ONES TO MORE COMPLEX ONES THAT MIMIC DIFFERENT ASPECTS OF DEVELOPMENT.

QUICKLY, HUMAN BLASTOIDS, THIS IS ALL VERY RECENT STUFF. SO 2021, 2022, WE'RE LOOKING AT THE FIRST HUMAN BLASTOIDS, A NUMBER OF DIFFERENT GROUPS. NOT GOING TO GO THROUGH IT ALL HERE. THIS IS A NICE LOOKING BLASTOID, AND IT REALLY HAS ALL THE CELL TYPES OF THE EMBRYO ITSELF. AND YOU CAN MAKE THEM IN LARGE AMOUNTS. SO YOU'LL SEE LOTS AND LOTS OF THESE INITIAL WELLS HERE. SO THESE ARE GOING TO BE VERY IMPORTANT PARTICULARLY FOR TOXICITY IN IVF-TYPE STUDIES.

MORE COMPLEX EMBRYO MODELS HAVE COME OUT JUST REALLY IN THE LAST YEAR. AND THERE WAS QUITE A FLURRY OVER THE SUMMER OF PAPERS, AND THEY'RE CONTINUING TO COME OUT. THERE ARE MORE AND MORE PAPERS IN THIS AREA WHERE PEOPLE ARE REALLY NOT MAKING A BLASTOID, BUT STARTING LIKE THE ETIX IN THE MOUSE, STARTING AND LOOKING AT THE POSTIMPLANTATION STAGES. SO THEY CONTAIN -- SOME OF THEM HAVE EPIBLASTS AND HYPOBLASTS, SOME OF THEM HAVE ALL

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THREE CELL TYPES, AND ALL OF THEM ARE GENERATING, HOPEFULLY GENERATING, SOMETHING THAT RESEMBLES THE EARLY POSTIMPLANTATION EMBRYO. THESE THEN MIMIC THIS PERI-IMPLANTATION STAGE.

IT'S VERY IMPORTANT WHEN LOOKING AT THOSE PAPERS AND WHEN REVIEWING THEM, WHICH I'VE DONE QUITE A LOT OF, IT'S NOT ENOUGH TO -- WHAT WE'RE NOT TALKING ABOUT HERE IS JUST TAKING PLURIPOTENT CELLS, MIXING THEM UP WITH OTHER CELLS, AND MAKING A KIND OF MISHMASH OF CELLS. WE'VE BEEN ABLE TO DO THAT FOR A LONG TIME. YOU CAN TAKE ES CELLS AND MAKE WHAT WE CALL EMBRYOID BODIES, AND THEY WILL MAKE A BIT OF HEART TISSUE HERE AND A BIT OF NERVOUS TISSUE HERE, BUT THAT'S NOT A MODEL, ANY PARTICULAR PROCESS.

THESE MODELS ARE INTENDED TO MODEL SPECIFICALLY EVENTS IN THE EMBRYO. SO THEY MUST SHOW ORGANIZED DEVELOPMENT. AND THIS IS JUST TO SHOW YOU THE KIND OF THINGS THAT MOST OF THESE PAPERS HAD IN VARIOUS WAYS. THIS IS ACTUALLY FROM A PAPER FROM JACOB HANNA IN ISRAEL, BUT THE OTHER PAPERS HAVE SIMILAR IMAGES. AND WHAT YOU'RE SEEING HERE IS YOU START WITH THIS SORT OF STRUCTURE WITH THE THREE -- HE HAD THREE CELL TYPES TOGETHER. AND THEY GO ON. THE TROPHOBLAST MAKES A RING ON THE

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OUTSIDE. THEN YOU START TO SEE THE CELLS HERE. THIS IS THE EPIBLAST FORMING THE AMNION. SO YOU GET EPIBLAST AND AMNION. THAT'S THE FIRST ELONGATION OF THE EPIBLAST. THEN IT GOES ON TO FORM THIS DISC-TYPE STRUCTURE WHICH IS WHERE THE PRIMITIVE STREAK AND THE BODY AXIS WILL BEGIN. AND YOU ALSO GET YOLK SAC STRUCTURES FORMING HERE STAINED WITH THE YELLOW MARKER. SO IT'S GETTING THE RIGHT CAVITIES AND THE RIGHT ORIENTATION TO RESEMBLE AN EMBRYO. IT IS NOT VERY EFFICIENT AT THIS POINT. YOU DON'T SEE BEAUTIFUL EMBRYOS LIKE THIS ALL THE TIME. THIS IS STILL VERY EARLY WORK, BUT THE GOAL IS TO MAKE THIS MORE REPRODUCIBLE AND ROBUST.

SO SOME OF THESE MODELS, AS I SAID, CONTAIN DERIVATIVES OF ALL THREE BLASTOCYST CELL LINEAGES. NONE OF THEM IS AN ACCURATE REPLICA OF THE IN VIVO EMBRYO, NONE OF THEM. IT'S NOT SURPRISING THAT'S THE CASE, AND IT'S NOT NECESSARY WHEN YOU'RE MODELING SOMETHING. WE'RE NOT TRYING TO MAKE A COPY. WE'RE TRYING TAKE MAKE A MODEL. THESE ARE MODELS.

MOST WILL FORM AMNION IN THE BEGINNING OF THE PRIMITIVE STREAK. SOME CAN BE USED TO STUDY ONSET OF GERM CELL DEVELOPMENT THAT WE SAW ALREADY. THERE'S A GROUP WORKING QUITE HARD TO LOOK AT THE

YOLK SAC OF BLOOD STEM CELLS FROM THESE EMBRYOS AND PUSHING THEM IN A DIFFERENT DIRECTION. SOME OF THEM MAKE THE INVASIVE TROPHOBLAST NEEDED FOR IMPLANTATION, BUT NOT ALL OF THEM. SO, AGAIN, MANY OF THESE EMBRYOS, EVEN THE ONES THAT STARTED WITH TROPHOBLAST, IT DOESN'T SURVIVE, BUT SOME OF THEM DO. IN FACT, THE BLASTOIDS ARE PROBABLY THE BEST MODELS TO STUDY HOW THE INVASIVE TROPHOBLAST WORKS. THEY ARE MODELS; THEY'RE NOT FACSIMILES OF THE EMBRYO ITSELF.

SO THEN COMES THE SORT OF TAUTOLOGY. SO IF THESE STEM CELL MODELS ARE NOT ACTUALLY REPLICATING NORMAL DEVELOPMENT, ARE THEY VALID MODELS? AND THIS IS -- I THINK YOU CAN ARGUE YOURSELF INTO CIRCLES ON THIS ONE. DEPENDS ON THE SCIENTIFIC QUESTION BEING ASKED. SO IN MOST OF THE QUESTIONS BEING ASKED, IT'S NOT NECESSARY THAT EVERY PART OF THE CONCEPTORS, ALL THE THREE LINEAGES ARE REALLY MOVING TOGETHER IN SYNC AND GOING FORWARD TO MAKE AN EMBRYO. THAT'S NOT THE INTENT. PEOPLE ARE NOT TRYING TO DO ANY FORM OF REPRODUCTIVE PURPOSES.

SO THE MODEL THAT YOU USE DEPENDS ON THE QUESTION BEING ASKED. AND, IN FACT, MANY QUESTIONS IN EARLY DEVELOPMENT CAN BE USED USING STEM CELL SYSTEMS THAT DON'T EVEN ATTEMPT TO REPLICATE THE

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ENTIRE EMBRYO.

SO THE ISSCR GUIDELINES HAS DIVIDED STEM CELL MODELS INTO TWO GROUPS, INTEGRATED VERSUS NONINTEGRATED. AND WE'LL COME BACK TO THIS AT THE END WHETHER THIS IS AN APPROPRIATE DIVISION, BUT THIS IS THE DIVISION THAT WAS MADE.

INTEGRATED MODELS ARE THOSE THAT CONTAIN ALL THREE LINEAGES OF THE BLASTOCYST AND WILL GO ON TO MAKE A BLASTOID NOT SHOWN HERE BECAUSE THIS IS 2021. ALL THOSE OTHER MODELS THAT I JUST SHOWED YOU ON A PREVIOUS SLIDE, THE POSTIMPLANTATION MODELS THAT HAVE ALL THREE LINEAGES, BUT THERE ARE ALSO LOTS OF NONINTEGRATING MODELS THAT INCLUDE GASTRULOIDS, AMNIOTIC SAC STRUCTURES, NEUROLOIDS, AXOLOIDS, SOMITOIDS. MANY OF THESE DIFFERENT THINGS CAN BE USED TO STUDY SPECIFIC PROCESSES BECAUSE THEY MIMIC THE EVENTS OF GASTRULATION, AP PATTERNING. THEY MIMIC THE EVENT OF AMNION FORMATION. WE SAW BEAUTIFUL STUDIES AT THIS MEETING ON MAKING MICE FROM THESE STRUCTURES, BUT THEY DON'T MAKE A WHOLE EMBRYO. YOU CAN STILL STUDY A LOT OF INFORMATION ABOUT THAT PROCESS.

SO WHAT CAN YOU DO WITH NONINTEGRATED MODELS? TROPHOBLASTS. OBVIOUSLY YOU CAN USE BLASTOIDS, BUT YOU CAN ALSO MAKE TROPHOBLASTOIDS.

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IF YOU WANT TO LOOK AT ENDOMETRIAL TROPHOBLAST INTERACTIONS, THIS WOULD BE A GOOD SYSTEM. BREAKING SYMMETRY IN EPIBLAST DEVELOPMENT, ACTUALLY 2D PATTERNING CAN BE USEFUL THERE, 3D PATTERNING. MICROFLUIDIC AMNIOTIC SAC STRUCTURES GIVE YOU THAT. YOU CAN USE EPIBLASTS AND HYPOBLASTS. THAT'S ALL THE COMPLICATED, COMPLEX MODELS THAT WE SAW THAT TAKE YOU THROUGH TO PRIMITIVE STREAK, BUT THEY DON'T MAKE PLACENTA. GERM CELL DEVELOPMENT, MANY DIFFERENT ORGANIZED MODEL SYSTEMS WILL GIVE YOU THAT. NEURAL TUBE DEVELOPMENT. IT'S POSSIBLE TO ACTUALLY GET A NEURAL TUBE ALONE AND STUDY ITS PATTERNING. A VERY NICE PAPER WILL BE COMING OUT SOON IN *NATURE* FROM YAN PING FU LOOKING AT AP PATTERNING OF JUST THE SPINAL CORD FROM THE STEM CELL MODEL. AXIAL MESODERM, BEAUTIFUL WORK ON BASICALLY REPLICATING THE SEGMENTAL CLOCK. NEURAL AND MESODERM AXIAL MODELS PUT TOGETHER, BUT STILL NO OTHER TISSUES. GRASTULOIDS. LOTS OF THINGS. ALL OF THESE NONINTEGRATED MODELS CAN REMIT SPECIFIC PROCESSES.

SO IT'S COMPLICATED. THERE ARE MANY DIFFERENT MODELS SYSTEMS. NOBODY IS PUSHING THESE MODELS TO REPLICATE AN ENTIRE EMBRYO FOR REPRODUCTIVE PURPOSES. THEY ARE IN VITRO, BUT THEY

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HAVE THE POWER TO REALLY HELP YOU ASSESS ASPECTS OF DEVELOPMENT THAT ARE INACCESSIBLE IN OTHER WAYS.

SO HOW DO WE REGULATE IT? SO I'M GOING JUST PUT THE ISSCR GUIDELINES UP HERE, AND WE'RE GOING TO HAVE A LOT MORE DISCUSSION, I'M SURE, ON ALL THIS AS WE GO THROUGH. BUT THE ISSCR STEM CELL GUIDELINES WERE REVISED IN 2021. WE ACTUALLY HAD A WORKING GROUP LOOKING AT STEM CELL MODELS -- HUMAN EMBRYO CULTURE AND STEM CELL MODELS. IN 2021 WHEN THESE CAME OUT, NONE OF THOSE PAPERS THAT I DESCRIBED WERE PUBLISHED AT THAT POINT. WE KNEW WHAT WAS COMING BECAUSE WE KNEW WHAT WAS HAPPENING IN THE MOUSE.

SO WE DID TRY, MAYBE SUCCESSFULLY, MAYBE NOT, TO PUT SOME GUIDELINES IN PLACE TO HELP PEOPLE AND REVIEW COMMITTEES LOOK AT THESE STEM CELL MODELS AND ASKED DO THEY NEED CAREFUL ETHICAL OVERSIGHT.

NO. 1, NO HUMAN STEM CELL-BASED EMBRYO MODEL, INTEGRATED OR NONINTEGRATED, SHOULD BE TRANSPLANTED INTO A HUMAN OR ANIMAL UTERUS, PRECLUDING ANY THOUGHT ABOUT REPRODUCTIVE PURPOSES. PERHAPS RESTRICTING SOME OF THE ASPECTS OF STUDYING IMPLANTATION IF YOU WANTED TO PUT IT IN AN ANIMAL UTERUS, BUT I WOULD ARGUE THAT TROPHOBLAST ENDOMETRIAL INTERACTION IS VERY SPECIES SPECIFIC.

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BETTER TO MIMIC BOTH OF IT IN VITRO THAN TO TRANSPLANT TO THE UTERUS. THIS IS A GUIDELINE THAT I THINK SHOULD BE A HARD LINE IN THE SAND.

INTEGRATED MODELS THAT HAVE POTENTIALLY ALL THREE LINEAGES COULD MAYBE HAVE THE ABILITY TO IMPLANT AND CONTAIN THE CELLS THAT WOULD GO ON TO MAKE THE FETUS SHOULD BE SUBJECT TO A RIGOROUS REVIEW FOR SCIENTIFIC RATIONALE. THERE HAS TO BE A STRONG REASON WHY YOU WANT TO USE THIS PARTICULAR MODEL. I TOLD YOU THERE'S MANY OF THEM. YOU HAVE TO JUSTIFY WHICH MODEL YOU WANT TO USE AND WHY AND WHETHER THERE ARE ANY CONCERNS AND ETHICAL ISSUES ABOUT HOW FAR YOU MIGHT WANT TO TAKE THOSE MODELS.

SO THE LENGTH OF TIME IN CULTURE IS IMPORTANT AND SHOULD BE DEFINED IN THE RATIONALE AND THE REVIEW. IT SHOULD BE APPROPRIATE TO ANSWER A QUESTION AND NOT BE AN OPEN-ENDED, WELL, WE'RE JUST GOING TO CULTURE IT AND SEE HOW IT GOES.

ALL OF THIS, OF COURSE, DEPENDS ON LOCAL GUIDELINES, REGULATION, AND JURISDICTION. AND BECAUSE THESE ARE INTERNATIONAL GUIDELINES, OBVIOUSLY SOME PLACES THERE IS A 14-DAY RULE. THE 14-DAY RULE APPLIES TO EMBRYO CULTURES, AND IN CERTAIN JURISDICTIONS, LIKE AUSTRALIA, STEM CELL MODELS HAVE BEEN DECIDED THAT THE LAW APPLIES TO

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THEM AS WELL. SO THEY CANNOT BE GROWN BEYOND 14 DAYS.

BUT IF YOU'RE LOOKING AT THE SCIENTIFIC RATIONALE, THEN THE ISSCR GUIDELINES SUGGEST THAT THERE ARE STRONG REASONS TO THINK THAT YOU MIGHT WANT TO GO PROGRESSIVELY BEYOND 14 DAYS IN SOME OF THESE CULTURE SYSTEMS TO ANSWER SPECIFIC QUESTIONS ABOUT SOMITE FORMATION, PATTERNING OF THE SPINAL CORD. ALL OF THESE THINGS WOULD REQUIRE YOU TO GROW FURTHER, BUT IT HAS TO BE WELL DEFINED AND IT SHOULD BE SUBJECT TO A SCRO-TYPE REVIEW.

SO WE HAVE A WORKING GROUP THAT'S MEETING BY ZOOM ON TUESDAY BECAUSE THE ISSCR -- PEOPLE HAVE BEEN ASKING ISSCR TO GIVE BETTER DEFINITIONS OF WHAT WE MEAN BY INTEGRATED, WHAT WE MEAN BY REVIEW, WHAT'S THE RATIONALE. WE'RE STRUGGLING. SO WHAT ARE THE KIND OF THINGS WE NEED THINK FOR FURTHER GUIDANCE?

STEM CELL EMBRYO MODELS ARE NOT EMBRYOS. THEY ARE IN VITRO RESEARCH TOOLS. THE 12-DAY, 14-DAY RULE SHOULD NOT BE APPLIED UNLESS IT'S APPLIED BY LAW BECAUSE, IN FACT, IN 12/14 DAYS DOESN'T MAKE ANY SENSE FOR THESE CULTURES. SO IT SHOULD BE AN ENDPOINT DEFINED BY THE QUESTION IN HAND AND THE LOCAL ETHICAL CONCERNS AND CONSTRAINTS.

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THE SCIENTIFIC RATIONALE MUST BE CLEAR. MAKING A BETTER EMBRYO MODEL IS NOT A SUFFICIENT JUSTIFICATION. IT'S WHY DO YOU WANT TO DO THAT.

THEY SHOULD USE THE MOST APPROPRIATE MODEL FOR THE QUESTION BEING ASKED. DOESN'T HAVE TO BE A VERY COMPLEX MODEL IN SOME CASES.

LENGTH OF TIME NEEDS TO BE DEFINED AHEAD OF TIME AND NOT BE OPEN-ENDED.

AND THE USE OF INTEGRATED MODELS THAT CAN INCLUDE EXTRAEMBRYONIC LINEAGES NEEDS TO BE WELL JUSTIFIED.

AND I THINK WE'RE GOING TO END UP DEFINING SUBTYPES OF INTEGRATED MODELS. INITIALLY WE WERE REALLY THINKING OF MODELS THAT HAVE ALL THREE LINEAGES BECAUSE WE WERE FOCUSED ON THE TROPHOBLAST AS BEING REQUIRED FOR EMBRYO TO IMPLANT IN THE UTERUS. IF WE HAVE A REGULATION THAT SAYS YOU CAN'T PUT THEM BACK IN THE UTERUS, THEN THE MODELS THAT HAVE EPIBLASTS AND HYPOBLASTS DO SHOW EXTENSIVE ORGANIZED EMBRYO DEVELOPMENT, INCLUDING YOLK SAC, INCLUDING AMNION. IT WOULDN'T BE ABLE TO SURVIVE IN THE UTERUS, BUT HOW FAR WOULD IT BE ABLE TO GROW IN VITRO? AND WOULD THERE BE CONCERNS ABOUT GROWING THOSE IN VITRO TO THE POINT WHERE THEY MIGHT ACTUALLY SHOW RESEMBLANCE TO A HUMAN FETUS? I WOULD

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SUGGEST, I'M GOING TO SUGGEST NEXT WEEK THAT WE DIVIDE THIS UP. BUT I DO THINK THAT THESE ARE GOING TO NEED SOME FURTHER STUDY.

BETTER DEFINITION OF APPROPRIATE STOPPING POINTS. I DON'T THINK THE PRIMITIVE STREAK PER SE IS AN IMPORTANT STOPPING POINT. IT'S THE BEGINNING OF PATTERNING THE EMBRYO. AND IF YOU DON'T HAVE A PRIMITIVE STREAK, YOU WON'T BE ABLE TO STUDY ANYTHING ELSE.

FORMATION OF THE NERVOUS SYSTEM. SOME OF THESE MODELS DO BEGIN TO MAKE NEUROECTODERM. AND IN A SENSE, AGAIN, IF YOU WANT TO STUDY THAT PROCESS, YOU WANT TO SEE HOW IT BEGINS AND HOW IT FOLDS, YOU PROBABLY NEED TO GET TO THAT. I THINK WE'RE STRUGGLING TO DEFINE WHAT WOULD BE THE KEY STAGES.

SO THAT'S IT. I HOPE THAT'S HELPED SET A LITTLE BIT OF CONTEXT FOR THE DAY.

CO-CHAIRMAN KAHN: THANK YOU. THAT'S SUPER HELPFUL AND I THINK A REALLY GREAT CONTEXT FOR THE DAY.

GEOFF, YOU WANT TO HAVE SOME QUESTIONS AT THIS POINT BEFORE THE NEXT PRESENTATION?

DR. LOMAX: YEAH, THAT WOULD BE TERRIFIC. THANKS.

CO-CHAIRMAN KAHN: OKAY. IT'S GOING TO BE

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MUCH EASIER, FOR ME AT LEAST -- MAYBE, GEOFF, YOU CAN MANAGE IN THE ROOM -- BUT IF PEOPLE CAN USE THE EMOTICON FEATURE IN ZOOM TO RAISE THEIR HANDS IF THEY WOULD LIKE TO ASK A QUESTION OR MAKE A COMMENT, THAT WOULD BE SUPER HELPFUL.

MAYBE I CAN START. SO I THINK WHAT I TOOK AWAY FROM AT LEAST ESPECIALLY THE VERY LAST PART OF WHAT YOU SAID, JANET, WAS FEATURES, NOT TIME IN DISH. SO THAT'S SORT OF A REALLY IMPORTANT KIND OF PRINCIPLE THAT ONE ASSUMES WOULD GET HASHED OUT INTO POLICY AND IMPLEMENTATION, DEVIL BEING IN THE DETAILS, OF COURSE. BUT THAT SEEMS LIKE A REALLY IMPORTANT SORT OF PLACE TO LAND. THAT'S ONE TAKEAWAY. YOU'RE NODDING. SOUNDS LIKE YOU AGREE THAT THAT'S THE CASE.

I GUESS THE SECOND THING I WOULD ASK, AND MAYBE NOT FOR YOU TO ANSWER, BUT RATHER JUST TO KIND OF RAISE FOR THE DISCUSSION IS AT WHAT POINT -- EVERYBODY, I THINK, IS AGREEING THAT THEY'RE MODELS, THEY'RE NOT EMBRYOS. BUT IT SORT OF FEELS LIKE THERE'S A POINT AT WHICH THEY WILL BE FOR ALL EQUIVALENT AND PRACTICAL PURPOSES THE POSSIBILITY OF THERE BEING LIKE EMBRYOS, SUFFICIENTLY LIKE EMBRYOS. I GUESS THE QUESTION IS WHAT WILL THE FEATURES BE THAT WILL TELL US WHEN THAT LINE HAS BEEN CROSSED?

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I'M NOT SURE I SAID THAT PERFECTLY ARTICULATELY, BUT I THINK YOU UNDERSTAND THE POINT.

DR. ROSSANT: YES, I DO. AND, OF COURSE, THERE WAS A RECENT PAPER FROM NICOLAS RIVRON AND COLLEAGUES TRYING TO DO EXACTLY THAT. WHAT'S THE TIPPING POINT? I WASN'T CONVINCED THAT THEY PROVIDED A REAL TIPPING POINT THAT WE WOULD KNOW THAT THIS IS SOMETHING THAT HAS FULL POTENTIAL.

I THINK THAT IT'S SO FAR AWAY ON THAT POINT IN TERMS OF BEING ABLE TO MAKE SOMETHING THAT IS A VIABLE FETUS THAT COULD GO THROUGH PREGNANCY. REMEMBER, THESE MODELS, THE POSTIMPLANTATION ONES, CAN'T, EVEN IF WE ALLOWED THEM TO BE PUT BACK IN THE UTERUS, THEY COULDN'T DEVELOP THERE. THEY DON'T HAVE THE RIGHT STRUCTURES. SO I THINK WE'RE A VERY LONG WAY OFF.

I THINK WHAT'S MORE, THE QUESTION BECOMES WHAT ARE THE CONCERNING FEATURES? OFTEN WHEN WE THINK ABOUT OTHER KINDS OF STUDIES, IT'S GETTING TO THE NERVOUS SYSTEM, BEING SENTIENT. SOME PEOPLE WORRY ABOUT THE HEARTBEAT. THE HEARTBEAT IS A VERY EARLY EVENT IN DEVELOPMENT. I SUSPECT THAT SOME OF THESE MODELS WILL HAVE A BEGINNING OF A BEATING HEART, BUT THAT DOESN'T MEAN THAT THEY HAVE FULL CIRCULATION OR ANY FURTHER. THAT'S JUST ONE OF THE

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STEPS ALONG THE WAY. THAT'S WHY I THINK IT'S GOING TO BE VERY DIFFICULT TO SAY NOW THIS IS AN EMBRYO. I DON'T THINK THEY'RE EVER GOING TO BE EMBRYOS.

CO-CHAIRMAN KAHN: YOU DON'T? WELL, I GUESS -- I SEE FRED'S HAND. BUT ONE MORE QUESTION ABOUT WHAT YOU JUST SAID. SO BEING EMBRYO VERSUS HAVING ALL OF THE FEATURES OF AN EMBRYO MAYBE CAN BE DIFFERENT. AND ONE ASSUMES THAT THAT DISTINCTION AT SOME POINT IS GOING TO NOT BE VERY MEANINGFUL AND THAT PEOPLE WILL TRY. PART OF WHAT I THINK I'M HEARING YOU SAY IS RESPONSIBLE PEOPLE AREN'T GOING TO DO THIS FOR A VERY LONG TIME. OF COURSE, WE HAVE SEEN LACK OF RESPONSIBLE BEHAVIOR IN NOT THE SAME AREAS, BUT CERTAINLY THINGS THAT ARE CLOSE ENOUGH.

SO I DON'T KNOW. IT'S NOT REALLY A QUESTION SO MUCH AS KIND OF DO YOU AGREE WITH THAT AND WE HAVE TO HAVE SOME WAY OF MAKING SURE THAT THERE ARE GUARDRAILS.

DR. ROSSANT: I DO AGREE. THEORETICALLY, AS THESE MODELS GET -- THERE'S NO THEORETICAL REASON TO SAY THAT THEY COULD END UP NEVER BEING ABLE TO MAKE AN EMBRYO, BUT WE'RE A HELL OF A LONG WAY OFF, AND THAT'S NOT THE INTENT OF THE EXPERIMENTS THAT ARE GOING ON IN THE LABS TODAY. HOWEVER, AS YOU SAY, IN FACT, THERE ARE COMPANIES HERE IN CALIFORNIA

TRYING ESSENTIALLY TO PUSH THIS PROCESS FURTHER FOR REASONS THAT ARE NOT THE REASONS I GAVE TODAY.

SO I THINK IT IS -- IT IS A CONCERN, BUT I THINK WHEN YOU'RE LOOKING FOR CIRM, WHERE YOU'RE LOOKING AT THE RESEARCH THAT IS FUNDED BY THIS AGENCY THAT IS UNDER YOUR SORT OF JURISDICTION, I DON'T THINK YOU WANT TO START LOOKING NOW DOWN THE ROAD AND SAYING AT WHAT POINT DO WE REALLY THINK THIS SHOULDN'T HAPPEN. IT SHOULD BE PROGRESSIVE. IF ENSUE WAS HERE, HE WOULD TELL YOU ONE OF THE WAYS TO THINK ABOUT MOVING THIS FORWARD IS TO HAVE A PROGRESSIVE STOPPING POINT. I THINK THAT WOULD BE WHAT I WOULD SAY. IF A PERSON COMES TO THE TABLE WITH HERE'S MY MODEL, HERE'S THE QUESTION, I THINK I NEED TO GROW IT FOR TEN DAYS IN CULTURE TO SEE HOW IT'S GROWING AND WHETHER I CAN ANSWER THE QUESTION, COME BACK AT THAT POINT AND TELL ME WHETHER IT WORKED, UNLESS IT WORKED. AND ACTUALLY NOW IF I GROW IT TWO MORE DAYS, I CAN FINISH THE EXPERIMENT AND GET HEART DEVELOPMENT, WHICH IS WHAT I WANTED TO SEE.

I THINK IT SHOULD BE THAT KIND OF PROGRESSIVE APPROACH SO THAT THE ABILITY TO DO THE EXPERIMENTS IS ALSO GIVEN ON A PROGRESSIVE BASIS. BUT THAT'S WHY WHAT'S DIFFICULT IS DEFINING WHAT

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THOSE PROGRESSIVE STEPPING POINTS ARE.

CO-CHAIRMAN KAHN: IT WOULD BE IMPORTANT LIKE AN HFEA APPROACH WHERE THERE'S THAT KIND OF ITERATIVE REACTION. OKAY.

FRED, I SEE YOUR HAND. SORRY FOR TAKING SO LONG TO GET TO YOU.

CO-CHAIRMAN FISHER: IT'S FINE. THANKS FOR THE TERRIFIC PRESENTATION.

ON THE LAST SLIDE THERE WAS ONE OF YOUR BULLET POINTS THAT I'M NOT SURE I UNDERSTOOD BECAUSE IT SEEMED COUNTERINTUITIVE TO ME. THAT DEVELOPING A BETTER MODEL IS NOT A SUFFICIENT REASON TO MOVE FORWARD. MAYBE YOU COULD SAY MORE ABOUT WHAT THAT MEANS.

DR. ROSSANT: IF I'M A SCIENTIST AND I COME TO THE SCRO AND SAY, YOU KNOW WHAT. IT'S REALLY COOL TO TRY AN MAKE AN EMBRYO IN CULTURE. AND I'VE GOT -- DOWN THE ROAD I'VE GOT TO SIX DAYS, AND I THINK I CAN MAKE IT BETTER. AND THEN THE QUESTION IS WHY. SO IT'S NOT ENOUGH TO JUST BE OUT THERE TO MAKE A BETTER EMBRYO BECAUSE THAT DOES SUGGEST THAT YOU'RE TRYING TO MAKE SOMETHING THAT HAS SORT OF ALL THE CAPACITY OF A HUMAN EMBRYO. WHAT YOU ARE TRYING TO DO IS DEVELOP A MODEL THAT ALLOWS YOU, THE SCIENTIST, TO ADDRESS YOUR QUESTION.

SO THAT MIGHT MEAN THAT YOU NEED TO IMPROVE YOUR INTEGRATED MODEL, BUT YOU HAVE TO JUSTIFY THE REASON FOR DOING THAT.

CO-CHAIRMAN FISHER: THIS SEEMS VERY NUANCED BECAUSE I CAN IMAGINE APPLICANTS DESCRIBING THEIR PROPOSAL AS A WAY TO DEVELOP A BETTER MODEL. AND WE SHOULD UNDERSTAND WHAT OUR REACTION TO THAT OR HOW WE WOULD RESPOND TO THAT.

DR. ROSSANT: THEY WOULD SAY I WANT TO MAKE A BETTER MODEL BECAUSE IT WILL ALLOW ME TO STUDY SOME OF THE THINGS WE HEARD THIS WEEK, STUDY HOW THE YOLK SAC AND THE BLOOD DEVELOPS, BUT I CAN'T DO THAT UNLESS MY MODEL GOES FORWARD AND ACTUALLY MAKES A FUNCTIONAL YOLK SAC. SO THAT'S WHAT I MEAN BY THEY HAVE TO HAVE A REASON THAT THE MODEL HAS TO IMPROVE BECAUSE IT WOULD TAKE THEM TO THE POINT THAT THEY NEED TO STUDY IN THEIR PARTICULAR EXPERIMENTS.

CO-CHAIRMAN FISHER: GOT IT. THANKS SO MUCH.

CO-CHAIRMAN KAHN: MAYBE ON THAT POINT --

DR. ROSSANT: IT IS A BIT NUANCED. I'LL GIVE YOU THAT.

CO-CHAIRMAN KAHN: IT IS. BUT THIS IS REALLY IMPORTANT FOR US OBVIOUSLY, AND WE'LL TALK MORE ABOUT IT, I THINK, OVER THE COURSE OF THE REST

OF THE DAY. SINCE FRED STARTED US, MAYBE JUST TO ASK A QUESTION ABOUT WHERE THE ISSCR IS HEADING ON THIS. BECAUSE IN THE MATERIALS THAT WE SAW BEFORE THE MEETING, IT'S EVEN A LITTLE MORE RIGOROUS, I GUESS, THAN WHAT YOU HAVE JUST SAID. SO NOT ONLY A COMPELLING SCIENTIFIC JUSTIFICATION, BUT THERE IS NOT AN ALTERNATIVE APPROACH THAT WOULD PROVIDE THE --

DR. ROSSANT: YES. YES.

CO-CHAIRMAN KAHN: -- INFORMATION, WHICH I THINK IS AN IMPORTANT ADDITION.

DR. ROSSANT: YES. AND I THINK THAT'S REALLY WHERE THE DISTINCTION BETWEEN DO YOU NEED A FULL INTEGRATED EMBRYO MODEL, OR CAN YOUR QUESTION BE ADDRESSED WITH A SOMITOID OR A GASTRULOID, SO RATHER THAN HAVING TO MAKE AN ENTIRE EMBRYO. YOU CAN'T -- MOST OF THE QUESTIONS THAT PEOPLE WANT TO ADDRESS WITH THESE SYSTEMS CANNOT BE ADDRESSED. THERE IS NO ALTERNATIVE BECAUSE THIS IS SORT OF THE ONLY WAY TO GET AT THESE EARLY EVENTS. ALL THE WORK WITH EMBRYONIC STEM CELLS IN CULTURE IS REALLY OBVIOUSLY VERY IMPORTANT FOR REGENERATIVE MEDICINE. WE'RE USING PLURIPOTENT CELLS TO GENERATE SPECIFIC CELL TYPES; BUT TO BE ABLE TO USE THEM FOR REGENERATIVE MEDICINE, IF YOU WANT TO USE THEM TO

UNDERSTAND THE BEGINNINGS OF THE FORMATION OF THE ORGANS THAT ARE GOING TO GIVE THE CELL TYPES THAT YOU NEED, YOU HAVE TO BE ABLE TO MAKE A MORE COMPLEX STRUCTURE.

SO I THINK THIS IS SPECIFIC TO THE STEM CELL MODELS, BUT YOU DON'T ALWAYS HAVE TO USE THE MOST COMPLICATED.

CO-CHAIRMAN KAHN: OKAY. MAYBE THAT'S ENOUGH FOR NOW. THIS IS OBVIOUSLY A CONVERSATION THAT WILL CONTINUE. GEOFF, I'M COGNIZANT OF TIME. YOU WANT TO MOVE TO THE NEXT PRESENTATION?

DR. LOMAX: THANK YOU. AND THANKS FOR THE DISCUSSION. IT'S VERY HELPFUL.

SO ONE OF THE THINGS WE WANTED TO DO AS PART OF THE SCIENTIFIC BACKGROUND IS NOW RELATE THIS TOPIC TO WORK THAT'S GOING ON THAT CIRM IS FUNDING. I'D LIKE TO ACKNOWLEDGE THE SCIENTIFIC PROGRAM AT CIRM, THE SCIENTIFIC TEAM. DR. UTA GRIESHAMMER IS GOING TO GIVE JUST A HIGH LEVEL OVERVIEW OF WHY THIS IS RELEVANT TO CIRM. AND JUST AS A REMINDER, I THINK THAT IF YOU NOTICE SOME OF THE DATES ON THOSE PAPERS, A LOT OF THEM HAVE BEEN PUBLISHED WITHIN THE LAST TWO YEARS. SO THIS IS CLEARLY A VERY IMPORTANT AREA AND CONTEMPORARY AREA OF SCIENCE. I'D LIKE TO ASK UTA TO GIVE YOU A LITTLE BIT OF A SENSE OF HOW

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THAT RELATES TO CIRM.

DR. GRIESHAMMER: ALL RIGHT. I JUST HAVE BASICALLY TWO SLIDES TO PROVIDE THIS CONTEXT OF HOW THIS RELATES, THIS DISCUSSION RELATES TO CIRM AND CIRM FUNDING. AS A REMINDER, OUR MISSION IS TO ACCELERATE WORLD-CLASS SCIENCE TO DELIVER TRANSFORMATIVE REGENERATIVE MEDICINE TREATMENTS IN AN EQUITABLE MANNER TO A DIVERSE CALIFORNIA AND WORLD.

I'M JUST SHOWING HERE WHERE THE RESEARCH WE JUST TALKED ABOUT FITS INTO THE CIRM FUNDING PIPELINE. I'M SURE IT'S OBVIOUS TO YOU. BUT IT'S PART OF OUR BASIC RESEARCH PIPELINE. AND THOSE FAMILIAR WITH THE CIRM LINGO, THIS WOULD BE THE DISC-0 AWARD TYPE WHERE WE EXPECT TO SEE -- WHERE WE DO FUND GENERAL STEM CELL BIOLOGY WORK, BUT WE ARE VERY MUCH FUNDING STEM CELL-BASED MODELS OF HUMAN BIOLOGY AND DISEASE. AND WE ALSO FUND IN THE BASIC RESEARCH WORK ON ADDRESSING BOTTLENECKS IN THE DEVELOPMENT OF STEM CELL-BASED AND GENE THERAPIES.

THE STEM CELL-DERIVED EMBRYO MODELS THAT JANET JUST DESCRIBED, WE WELCOME APPLICATIONS SINCE THEY ARE INDEED BEAUTIFUL MODELS OF HUMAN BIOLOGY AND DISEASE.

AS MY LAST SLIDE, I JUST WANT TO GIVE YOU

THE CONTEXT OF WHAT HAS CIRM FUNDED SO FAR AND WHERE ARE WE NOW. I'M SHOWING HERE JUST A BRIEF TIMELINE OF THE FIRST DERIVATION OF HUMAN EMBRYONIC STEM CELLS, AND THEN INDUCED PLURIPOTENT STEM CELLS HAPPENED, OF COURSE, AROUND THE TIME WHEN CIRM WAS FIRST FUNDED. IN THIS PROPOSITION 71 PHASE, WE HAD FOUR GRANTS THAT WERE LOOKING AT THE TROPHOBLAST, THE EXTRAEMBRYONIC LINEAGE THAT JANET JUST DESCRIBED.

AS JANET AND JEFF ALSO JUST MENTIONED, THESE EMBRYO MODELS WE'RE TALKING ABOUT DIDN'T EXIST IN THE PROP 71 ERA.

BUT A LOT HAS HAPPENED OVER THE LAST TWO DECADES, AND THE STEM CELL-BASED EMBRYO MODELS ARE NOW REALLY TAKING OFF. AND SO SINCE PROPOSITION 14, WE ARE NOW FUNDING ONE GRANT THAT IS STUDYING EMBRYO MODELS. WE HAVE TWO MORE TROPHOBLAST GRANTS STUDYING THE EXTRAEMBRYONIC LINEAGE.

AND I JUST WANTED TO TELL YOU THAT FROM THE APPLICATIONS WE'VE RECEIVED FROM THE INSTITUTIONS AND PRINCIPAL INVESTIGATORS WE TALK WITH WHO ARE INTERESTED IN CIRM FUNDING, AND ALSO FROM LOOKING AT THE TALKS AND THE POSTERS AT THIS MEETING, THERE ARE AT LEAST SIX CALIFORNIA INSTITUTIONS INTERESTED IN DOING HUMAN EMBRYO --

HUMAN STEM CELL-BASED EMBRYO MODELS. SO WE REALLY ARE EXPECTING THAT WE WILL GET QUITE A FEW APPLICATIONS OVER THE NEXT FEW YEARS. SO THAT'S WHAT I WANTED TO SHARE WITH YOU.

DR. LOMAX: THANK YOU, UTA. JEFF, IF WE MAY, I THINK AND IF FOLKS, IF WE HAVE FOLKS IN THE PUBLIC WHO ARE OUTSIDE OF THE MEETING ROOM, THERE'S INSTRUCTIONS IN THE AGENDA ABOUT HOW IF YOU HAVE A QUESTION. I THOUGHT WE WOULD GO AHEAD, BECAUSE WE'RE ABOUT TO TRANSITION SESSIONS, BUT OFFER AN OPPORTUNITY FOR PUBLIC COMMENT BETWEEN EACH SESSION SO WE DON'T RELEGATE THOSE QUESTIONS OR COMMENTS TILL THE END OF THE MEETING SO THEY'RE IN CONTEXT. AND ADDITIONALLY, IF THE PANELISTS OR ANYONE ELSE ON THE ZOOM HAVE QUESTIONS, JUST WANTED TO PAUSE HERE AND TAKE QUESTIONS OR ADDITIONAL COMMENTS.

CO-CHAIRMAN KAHN: YOU WANT ME TO FIELD THEM, OR DO YOU WANT TO DO THAT, GEOFF?

DR. LOMAX: WHY DON'T I GO AHEAD. I SEE STEVE PECKMAN HAS A QUESTION BECAUSE WE CAN MONITOR BOTH THE PHONE AND ZOOM FROM HERE.

CO-CHAIRMAN KAHN: PERFECT.

DR. PECKMAN: THANK YOU, GEOFF. THIS IS STEVE PECKMAN, UCLA HUMAN PLURIPOTENT STEM CELL RESEARCH OVERSIGHT COMMITTEE. I HAVE A QUESTION FOR

JANET ROSSANT. ONE OF THE THINGS THAT SHE SUGGESTED EARLY ON IN HER PRESENTATION WAS THAT THESE EMBRYO MODELS COULD BE USED FOR EMBRYO TOXICOLOGY. ONE OF THE GREATEST STUMBLING BLOCKS FOR EQUITY AND INCLUSION IN CLINICAL TRIALS IS THE INCLUSION OF WOMEN OF CHILDBEARING POTENTIAL BECAUSE OF FEAR THAT THE DRUG PRODUCT WILL RESULT IN PROBLEMS FOR A DEVELOPING EMBRYO IN UTERO.

AND SO IN ORDER TO ADDRESS THAT EQUITABLE INCLUSION QUESTION AND TO PROMOTE THE INCLUSION OF YOUNG WOMEN IN CLINICAL TRIALS, AS WELL AS WOMEN WHO MAY BECOME PREGNANT IN LIFE-SAVING CLINICAL TRIALS WHO WOULD OTHERWISE THEN BE REMOVED FROM THE TRIAL, MY QUESTION TO JANET ROSSANT IS WITH THE ABILITY TO CREATE THESE EMBRYO MODELS, DO YOU FEEL THAT THIS WOULD BE OF UTILITY IN TERMS OF PRECLINICAL TESTING TO SEE WHAT THE ACTUAL RISK COULD BE TO A DEVELOPING EMBRYO AND HOW THAT MIGHT BE MANAGED IN ORDER TO BROADEN INCLUSION OF WOMEN IN CLINICAL TRIALS?

DR. ROSSANT: THE ANSWER TO THAT WOULD BE YES. I THINK THAT CERTAINLY IS THE INTENT. AND, AGAIN, THE QUESTION IS WHAT WOULD BE THE MOST APPROPRIATE MODEL. AND YOU HAVE TO HAVE SOME SORT OF PROOF OF PRINCIPLE STUDIES WITH KNOWN TOXICANTS AND SO ON IN THOSE SYSTEMS TO SHOW THAT YOU CAN

REPLICATE OR PRODUCE A SPECIFIC REPRODUCIBLE RESPONSE. THAT IS REALLY ONE OF THE GOALS, AND A NUMBER OF GROUPS ARE REALLY TRYING TO MOVE DOWN THAT PATHWAY, YES.

DR. LOMAX: ANY OTHER QUESTIONS? NO. OKAY. I THINK THAT COVERS PUBLIC QUESTIONS AT THIS TIME.

JEFF, SHOULD I GO INTO THE NEXT?

CO-CHAIRMAN KAHN: I THINK SO, YEAH. ANYBODY ON ZOOM WANT TO ASK A QUESTION OR MAKE A COMMENT AT THIS POINT? LOOKS LIKE NOT. LET'S GO AHEAD, GEOFF.

DR. LOMAX: OKAY. SO I'M GOING TO TRANSITION INTO THE OVERSIGHT ASPECTS OF THE RESEARCH. VERY SPECIFICALLY DO A RE-REVIEW OF A PRESENTATION I GAVE TO THIS GROUP ABOUT A YEAR AGO IN TERMS OF HOW THESE PROTOCOLS GET HANDLED IN THE CONTEXT OF CIRM REQUIREMENTS. BUT BEFORE I DO THAT, BECAUSE I'M GOING TO FOCUS ON THE REGULATORY SIDE AND WHAT HAPPENS THROUGH THE INSTITUTIONAL OVERSIGHT, BECAUSE THAT'S THE REMIT OF THE STANDARDS WORKING GROUP REALLY IS TO SUPPORT US IN DEVELOPING THOSE STANDARDS AND THOSE RULES. JANET DID EMPHASIZE THE IMPORTANCE OF SCIENTIFIC RATIONALE, RESEARCH DESIGN, AND HOW THAT WHOLE PROTOCOL PLAYS

OUT. I'D LIKE TO INVITE PRESIDENT JON THOMAS TO COMMENT ON HOW CIRM -- THE PROCESS WHICH CIRM USES TO ACTUALLY REVIEW THOSE PROTOCOLS INITIALLY BECAUSE, IN ADDITION TO THE PROCESS I'M GOING TO DESCRIBE, I THINK IT'S HELPFUL IF FOLKS HAVE A SENSE OF THE PROCESS BECAUSE, AGAIN, WE'RE TALKING ABOUT CIRM-FUNDED PROTOCOLS IN THE CONTEXT OF THIS DISCUSSION, WHAT IT TAKES FOR A PROTOCOL TO BECOME CIRM-FUNDED FROM A SCIENTIFIC SITE.

DR. THOMAS: SO THANK YOU, GEOFF. EVERYBODY HEAR ME NOW? THANK YOU.

SO I THINK IT'S IMPORTANT TO GIVE JUST A LITTLE BIT OF BACKGROUND ON THE PROCESS THAT WE UNDERTAKE IN THE EVALUATION OF GRANTS THAT ARE SUBMITTED FOR CONSIDERATION. ONCE THE GRANTS ARE SUBMITTED, WHICH, BY THE WAY, FOLLOWS A PERIOD WHERE THE INTERNAL TEAM WORKS WITH POTENTIAL APPLICANTS TO HELP THEM FASHION THEIR APPLICATIONS IN A WAY THAT GIVES THEM THE BEST CHANCE OF GETTING A FAVORABLE REVIEW BY OUR PEER REVIEW GROUP, THE GRANTS THEN GO TO THAT GROUP, WHICH WE CALL THE GRANTS WORKING GROUP. AND THE GRANTS WORKING GROUP IS COMPRISED SPECIFICALLY OF EXPERTS IN STEM CELL OR GENE THERAPY SCIENCE, NOTABLY ALL OF WHICH ARE OUTSIDE OF CALIFORNIA TO PRECLUDE ANY CONFLICTS IN THE

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ANALYSIS.

AND THEY WILL SIT DOWN AND EVALUATE EACH GRANT IN AN EXTREMELY RIGOROUS FASHION. THERE ARE ALWAYS PEOPLE PULLED TOGETHER FOR A PARTICULAR REVIEW GROUP THAT HAVE EXPERTISE IN THE SUBJECT MATTERS OF THE GRANTS THAT ARE UNDER CONSIDERATION. AND TO THE EXTENT THEY NEED A LITTLE BIT OF ADDITIONAL HELP, WE HAVE WHAT WE CALL SPECIALISTS WHO MAKE VERY IMPORTANT CAMEO APPEARANCES FOR ONE OR MORE APPLICATIONS IN THE SUBJECT MATTER OF THEIR PARTICULAR EXPERTISE.

BUT IN THE COURSE OF THESE REVIEWS, WHICH ARE EXTREMELY ROBUST, A MOST IMPORTANT QUESTION IS EXACTLY WHAT JANET HIGHLIGHTED. BY THE WAY, JANET, THAT WAS AN EXCELLENT PRESENTATION AND REALLY MADE CLEAR THE FIELD AND THE QUESTIONS AT HAND AND WHERE WE'VE GOTTEN TO. AND REALLY APPRECIATED THAT. SO THANK YOU VERY MUCH.

SO IT ISN'T ENOUGH JUST TO HAVE SOMEBODY PRESENT AN IDEA FOR THE IDEA'S OWN SAKE. THERE'S A VERY DEEP DIVE INTO SCIENTIFIC RATIONALE BEHIND WHATEVER THE PARTICULAR GRANT IS IN QUESTION. AND IF THAT RATIONALE IS NOT READILY IDENTIFIABLE OR EXPLAINED IN THE GRANT, THAT GRANT WILL NOT GET RECOMMENDED FOR APPROVAL AT THE END OF THE DAY. AND

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SO IN ADVANCE OF -- I SHOULD SAY ONCE THEY GET THROUGH THE PROCESS OF EVALUATION, THEN THERE'S PEER REVIEW. THERE'S A WHOLE SCORING SYSTEM WHICH IS TOPPED BY A RECOMMENDED FOR FUNDING CATEGORY WHICH THEN GOES TO THE BOARD FOR CONSIDERATION. AND IF THE BOARD APPROVES A PARTICULAR GRANT, THEN IT GOES IMMEDIATELY INTO THE PROCESS OF IMPLEMENTING THE GRANTS AND DEALING WITH THE GRANTEES TO WORK OUT MILESTONES AND OTHER DETAILS, ET CETERA.

BUT THE POINT IS THAT, IN ADVANCE OF EVER GETTING TO THE SCRO PROCESS, WHICH GEOFF IS GOING TO TALK ABOUT, THERE IS THIS EXTREMELY ROBUST REVIEW SPECIFICALLY INCORPORATING THE MAJOR QUESTION HERE, WHICH IS WHY ARE YOU DOING WHATEVER IT IS YOU'RE PROPOSING? SO I JUST WANT EVERYBODY TO UNDERSTAND IT'S SORT OF A TWO-TIERED REVIEW SYSTEM BEFORE IT EVER ACTUALLY GETS TO LIGHT OF DAY. THANK YOU, GEOFF.

DR. LOMAX: THANKS SO MUCH.

OKAY. SO I'M GOING GIVE SOME CONTEXT OR SOME BACKGROUND ON HOW CIRM EXPECTS INSTITUTIONS RECEIVING OUR FUNDING TO REVIEW THESE PROTOCOLS. AND I THINK YOU WILL SEE THERE'S SUBSTANTIAL ALIGNMENT WITH WHAT WAS DESCRIBED ALSO BY THE INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH.

SO BEFORE I LAUNCH INTO THE STANDARDS, I DID WANT TO COME BACK TO UTA'S SLIDE HERE REALLY TO MAKE THE POINT AGAIN WE'VE BEEN AT A TWO-DAY MEETING LISTENING TO A WHOLE SERIES OF PRESENTATIONS ABOUT THE SCIENCE AND THE POTENTIAL OF THE SCIENCE. AGAIN, THAT WAS REFLECTED IN JANET'S TALK. WHAT I HEARD, AS SOMEONE WHO SITS ON THE POLICY SIDE OF THINGS, WHAT REALLY STRUCK ME IS HOW MANY OF THE PRESENTERS ALLUDED TO CHALLENGES IN DOING SOME OF THIS WORK. CERTAIN PRESENTERS WERE VERY EXPLICIT IN POINTING OUT THAT THEY HAD NO NIH FUNDING TO SUPPORT THIS WORK BECAUSE OF SOME OF THESE MODELS. THERE'S A COMMITTEE PROCESS AT NIH AND THERE'S BEEN PROTOCOLS HELD UP WITHIN THAT PROCESS AND THEY'VE NOT COME THROUGH. AND SO A LOT OF INVESTIGATORS OUTSIDE OF CALIFORNIA THAT DON'T HAVE THE SUPPORT OF AN ORGANIZATION LIKE CIRM ARE ACTUALLY HAVING TO WORK OUTSIDE OF AT LEAST THE NIH SYSTEM BECAUSE THERE ARE SOME RESTRICTIONS IN TERMS OF THIS WORK OR QUESTIONS THAT ARE DOES THIS WORK SORT OF GET RESTRICTED BECAUSE OF OUTSIDE POLICIES.

AS A REMINDER, WE CAME ABOUT AS AN ORGANIZATION IN PART TO OVERCOME SOME OF THOSE BARRIERS.

IN ADDITION, THE OTHER PART OF THE

MEETING, THE OTHER POINT THAT CAME ACROSS CLEARLY IS THERE ARE A LOT OF DIFFERENCES IN HOW THESE REVIEWS ARE BEING CONDUCTED. AND THE IDEA OF HAVING A CLEARER FRAMEWORK, A CONSENSUS FRAMEWORK, WAS CONSIDERED QUITE USEFUL IN PART BECAUSE THERE WERE A NUMBER JOURNAL EDITORS HERE AS WELL. AGAIN, THEY WERE IN THE SPIRIT OF KIND OF ENSURING THE RESPONSIBLE SCIENCE, THAT HAVING A FRAMEWORK WHICH THEY COULD BENCHMARK AGAINST HOW THESE PROTOCOLS CAME THROUGH WOULD BE USEFUL FROM THE STANDPOINT OF SUPPORTING PUBLIC RESPONSIBILITY IN SCIENCE.

I'M GOING TO CLICK THROUGH THESE. AGAIN, JUST AS A REMINDER TO THE WORKING GROUP, I'M NOT GOING TO DO A WHOLE REVIEW OF OUR REGULATIONS AND OUR STANDARDS. THAT WOULD TAKE QUITE A WHILE, BUT WE HAVE PROVIDED THIS PUBLICATION IN THE PAST. I THINK IT PROVIDES A SENSE OF KIND OF THE BROAD FRAMEWORK WE'VE ADOPTED. THIS WAS IN 2005.

IN TERMS OF WHERE OUR SORT OF POLICIES HAVE COME FROM, IF YOU LOOK AT BOTH PROPOSITION 71 AND PROPOSITION 14, THEY DIRECT THE AGENCY TO LOOK TOWARDS THE NATIONAL ACADEMIES. AND WE ORIGINALLY HAD DONE THAT. AND THE NATIONAL ACADEMIES, IN PARTICULAR, DEVELOPED A SET OF EARLY GUIDELINES TO GOVERN EMBRYONIC STEM CELL RESEARCH. AGAIN, BECAUSE

THERE WAS NO FEDERAL GUIDANCE OR POLICY, THE ACADEMIES PROVIDED THIS GUIDANCE WHICH, AGAIN, WE ADOPTED.

NOW, SINCE 2012 THAT COMMITTEE HAS NO LONGER BEEN CONSTITUTED. SO IN TERMS OF ISSUES, MORE CONTEMPORARY ISSUES, THE ACADEMIES HASN'T CONVENED AND OFFERED SPECIFIC GUIDANCE. TO SOME EXTENT, THEY HAVE, BUT NOT IN TERMS OF THESE FORMAL GUIDELINES, BUT THEY HAVE POINTED TO THE ISSCR AS A BODY THROUGH WHICH WE SHOULD LOOK FOR GUIDANCE. SO WE HAVE THIS SORT OF RELATIONSHIP WITH ISSCR VIS-A-VIS THE NATIONAL ACADEMIES VIS-A-VIS PROPOSITION 71 AND PROPOSITION 14; HENCE, WHY WE'RE TRYING TO CONSIDER HOW WE ALIGN AND ARRIVE AT A CONSISTENT PLACE IN TERMS OF THE OVERSIGHT OF THIS RESEARCH.

SO IN TERMS OF OUR RULES, I'D LIKE TO SORT OF THINK OF IT AS THE RED, YELLOW, GREEN TRAFFIC LIGHT WHERE THE RED IS STOP. YOU CAN'T DO THAT. AGAIN, CONSISTENT WITH THE NATIONAL ACADEMIES, WE HAVE -- SORRY -- WITH THE ISSCR, WE HAVE A RESTRICTION ON -- I'M GOING TO GO BACK ONE. GETTING A BUNCH OF ZOOM MESSAGES HERE. PARDON ME. HANG ON. THANK YOU.

REPRODUCTIVE CLONING IS EXPLICITLY

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PROHIBITED IN OUR PROPOSITION AND, IN ADDITION, THE NOTION OF TRANSFERRING A GENETICALLY -- AT THE TIME WE TALKED ABOUT GENETICALLY MODIFIED HUMAN EMBRYOS BECAUSE THIS GOES BACK TO 2005 WHEN WE DIDN'T HAVE THESE MODELS. BUT THERE WAS CLEARLY SCIENCE AT THE TIME IN THE CONTEXT OF DOING EMBRYONIC STEM CELL WORK WHERE THERE COULD BE GENETIC MODIFICATION MADE TO A HUMAN EMBRYO. THE IDEA THAT ANY MODIFIED HUMAN EMBRYO SHOULD NOT BE IMPLANTED EITHER. SO THOSE ARE RESTRICTIONS THAT ALREADY EXIST WITHIN OUR REGULATORY FRAMEWORK.

THE YELLOW IS WHAT I CALL SORT OF THE PAUSE AND GIVE EXTRA CONSIDERATION. SO THIS IS WORK WE'RE TRYING TO ENABLE. AND PART OF ENABLING THIS WORK, IT WAS THE RECOMMENDATIONS OF THIS WORKING GROUP THAT THERE BE ADDITIONAL REVIEW AND OVERSIGHT OF THE PROTOCOLS. AGAIN, THAT IS CONSISTENT WITH THE RECOMMENDATIONS OF THE NATIONAL ACADEMIES. AND, AGAIN, WHERE WE GET THE CLOSEST TOUCHPOINT IN TERMS OF THE WORK DESCRIBED THIS MORNING IN OUR REGULATIONS, BUT JUST TO REITERATE, THAT WE'RE NOT EVEN IN A REGULATORY CONTEXT SAYING THAT THESE ARE HUMAN EMBRYOS BECAUSE, AS JANET ALLUDED TO, IN SOME CASES MAKING THAT CONNECTION THEN BRINGS THEM UNDER EITHER NATIONAL OR SOME OTHER LEGAL REGULATION WHICH

IS RESTRICTIVE. WE'RE NOT SAYING THAT, BUT WHAT I WOULD LIKE TO POINT OUT TO THE COMMITTEE IS WE DO HAVE A PROCESS FOR EMBRYO WORK, AND THAT PROCESS IS POTENTIALLY TRANSFERABLE TO THIS TYPE OF WORK IN SOME WAY.

SO ANY RESEARCH INVOLVING HUMAN EMBRYOS, AND AT THE TIME THE MAJOR NEED WAS HUMAN EMBRYONIC STEM CELL DERIVATION, THAT THAT WORK HAS TO BE OVERSEEN BY AN OVERSIGHT COMMITTEE. THERE'S A NUMBER OF CONSIDERATIONS THAT REALLY NEED TO BE THOUGHT ABOUT IN THE EMBRYO WORK, PARTICULARLY THE NATURE OF THE CONSENT AND THAT IT WAS APPROPRIATELY CONSENTED, THAT THE CONSENT FORM WILL ALLOW THE USE OF THE STEM CELL LINES, AND, IN ADDITION, THERE ARE OTHER SORT OF CONSIDERATIONS, AGAIN, IN TERMS OF THE SCIENTIFIC RATIONALE, BUT AT THE TIME, AGAIN, WE WERE LARGELY TRYING TO ADDRESS THE LIMITATIONS IN TERMS OF STEM CELL LINES BECAUSE BACK THEN THERE VERY FEW LINES AVAILABLE FOR RESEARCH.

AND IN ADDITION TO THE WORK WITH HUMAN EMBRYOS, THERE WAS, AGAIN, CONSENSUS, AND THIS IS REFLECTED BROADLY IN THE GUIDELINES OF THE NATIONAL ACADEMIES AND ISSCR, THAT WHEN YOU TAKE HUMAN STEM CELLS AND IMPLANT THEM IN VIVO, THERE ARE POTENTIAL CONCERNS THAT NEED TO BE CONSIDERED. AND THE

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PROTOCOLS FOR THOSE EXPERIMENTS SHOULD BE SUBJECT TO REVIEW AND OVERSIGHT. AND SOME OF THE ISSUES THAT WERE OF CONCERN WERE MAKING SURE THAT THESE STEM CELLS IN NO WAY WOULD RESULT IN GAMETE CREATION. THERE'S ALWAYS BEEN CONSIDERATION OF TO WHAT EXTENT HUMAN CELLS ARE INTEGRATING INTO THE BRAINS OF OTHER ANIMALS. AND SO, AGAIN, THERE'S A BODY OF, SORT OF HISTORY OF TRYING TO CONDUCT THOSE EXPERIMENTS IN A WAY WHERE THERE HAVEN'T BEEN SORT OF UNFORESEEN OUTCOMES THAT WOULD BE OF CONCERN.

AND FINALLY, THERE'S THIS GREEN ZONE WHICH IS RESEARCH THAT REALLY IF IT COMES TO THE COMMITTEE, IT'S TYPICALLY HANDLED THROUGH AN ADMINISTRATIVE PROCEDURE WHERE THE ADMINISTRATIVE SIDE OF THE COMMITTEE IS REALLY CHECKING TO MAKE SURE THAT, FOR THE MOST PART, THAT THE MATERIALS ARE FIT FOR PURPOSE. THERE'S A LOT OF CONSENT ISSUES, A LOT OF STEM CELL LINES VERY EARLY ON. AGAIN, THIS IS YEARS AGO. WE NOW HAVE LARGE NUMBERS OF BANKS AND A LOT OF MATERIALS THAT ARE GENERALLY AVAILABLE FOR RESEARCH AND FIT FOR PURPOSE, BUT EARLY ON WE HAD A LIMITED NUMBER OF CELL LINES, A LIMITED NUMBER OF INDUCED PLURIPOTENT STEM CELL LINES, AND THERE WAS A REAL NEED TO MAKE SURE THAT WHEN WE WERE PROPOSING TO CREATE NEW STEM CELL LINES AND DO SOME

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OF THESE NEW EXPERIMENTS AND REPROGRAM CELLS, THAT PARTICULARLY THE CONSENTS WERE APPROPRIATE AND THE CELLS COULD BE USED FOR THAT PURPOSE.

IN FACT, WE WORKED WITH THE STANDARDS WORKING GROUP OVER A TWO- OR THREE-YEAR PERIOD TO DEVELOP A NUMBER OF THOUGHT PIECES FOR HOW EXISTING CELL BANKS POTENTIALLY COULD BE REPURPOSED FOR REPROGRAMMING AND THE CREATION OF PLURIPOTENT STEM CELL LINES, AND WE PUBLISHED EXTENSIVELY ON THOSE POINTS TO CONSIDER.

SO THIS IS REALLY TO GIVE YOU A SENSE OF WHAT'S THE DIFFERENCE BETWEEN THE YELLOW LIGHT AND THE GREEN LIGHT. I THINK I'VE KIND OF COVERED THAT IN MY PREVIOUS REMARKS; BUT, AGAIN, THE REVIEW REQUIREMENTS, PARTICULARLY IN THE CONTEXT OF DERIVING A HUMAN EMBRYONIC STEM CELL LINE AND TO THE EXTENT WE MIGHT WANT TO PORT THOSE REQUIREMENTS OVER TO THIS TYPE OF WORK, AGAIN, THE ACCEPTABLE SCIENTIFIC RATIONALE. WE'VE SPENT A LOT OF TIME ON THAT. THE LINES ARE ACCEPTABLY DERIVED. ACCEPTABLY DERIVED IS SORT OF THE LEGALESE WAY OF SAYING WHAT I JUST SAID. THE CONSENTS ARE IN ORDER, THE MATERIAL TRANSFER AGREEMENTS, ALL THE SORT OF ASSURANCE AND PROVENANCE WORK THAT NEEDS TO GO INTO UNDERSTANDING THAT THAT LINE CAN BE USED HAS BEEN LOOKED AT.

ANOTHER PIECE WE HAVE, AND I THINK THIS RELATES TO THE SCIENTIFIC RATIONALE, IT WAS IMPORTANT THAT THE TEAM DOING THE WORK HAD THE EXPERTISE, THE TRAINING, THE ABILITY TO REALLY DO THIS WORK WELL. I THINK THAT RELATES BACK TO WHAT DR. THOMAS JUST MENTIONED, THAT OFTEN, IF THAT EXPERTISE ISN'T THERE, IT'S PROBABLY UNLIKELY TO GET THROUGH OUR PEER REVIEW. BUT NONETHELESS, THE TEAM DOING THE WORK IS WELL TRAINED AND KNOWS WHAT THEY'RE DOING.

AND THEN, FINALLY, THE NOTIFICATION REQUIREMENT IS TELL YOUR COMMITTEE WHAT YOU'RE DOING. THEY'RE RESPONSIBLE FOR CHECKING THAT THE MATERIALS THAT ARE GOING INTO THAT EXPERIMENT ARE APPROPRIATE.

SO WHAT WE'VE PROPOSED AND PRESENTED TO YOU IN TERMS OF A DRAFT IS A GUIDANCE. OUR AIM WITH THAT GUIDE, AND THAT WAS PART OF THE MEETING MATERIALS, WAS TO SUGGEST THAT EMBRYO MODELING, WHICH I HAVEN'T MENTIONED THIS, BUT JUST TO STATE IT QUITE CLEARLY, UP UNTIL NOW IT HAS ALWAYS BEEN IN THAT GREEN ZONE. WE'VE NOT RECOMMENDED ANY HEIGHTENED REVIEW UP UNTIL NOW, BUT WE HAVE NOW HIT A POINT WHERE WE ARE GETTING A LOT OF QUESTIONS. THERE'S, AGAIN, AS EVIDENCED BY THIS CONFERENCE,

THERE'S BEEN A LOT OF SORT OF INTEREST IN UNDERSTANDING WHAT WOULD BE THE APPROPRIATE FRAMEWORK FOR FOLLOWING THROUGH ON THESE EXPERIMENTS. SO, AGAIN, THERE'S INCREASED INTEREST IN THEIR UTILITY. SO THAT'S IMPORTANT.

WE KNOW FROM TALKING TO OUR AWARDEES, AND OFTEN IT'S THE AWARDEE INSTITUTIONS WHO ARE APPROACHING US WITH QUESTIONS, THAT THEY ARE FORMULATING POLICIES ANYWAY IN THE ABSENCE OF CIRM GUIDANCE. FOR THE MOST PART, THEY'VE ALREADY ELEVATED THESE PROTOCOLS TO THE YELLOW ZONE ABSENT ANY CIRM GUIDANCE. SO THEY'RE LOOKING AT THESE PROTOCOLS MORE CAREFULLY.

AND ONE OF THE THINGS THAT WE'VE LEARNED, AND I THINK THIS IS REALLY AN INTERESTING POINT AND REALLY SHOULD BE REFLECTED IN OUR GUIDANCE, THIS GETS BACK TO THE POINT ABOUT WHAT'S THE PURPOSE OF THE EXPERIMENT AND HOW DO YOU MONITOR IT AND WHAT ARE THE RULES, THE BOUNDARIES YOU DRAW AROUND THE EXPERIMENT IS THAT DIFFERENT INSTITUTIONS ARE SETTING UP DIFFERENT, FOR THE WANT OF A BETTER TERM, STOPPING RULES IN TERM OF WHERE WOULD THAT EXPERIMENT END BASED ON THE EXPERIMENTAL AIMS. SO THE POINT THERE IS, FOR EXAMPLE, I THINK JANET MENTIONED THE PRIMITIVE STREAK. IT'S A

MORPHOLOGICAL INDICATOR. IT MIGHT BE USEFUL IN CERTAIN EXPERIMENTAL DESIGNS, BUT THERE MAY BE OTHER INDICATORS DEPENDING ON THE NATURE AND THE PURPOSE OF THE EXPERIMENT.

AND WE ACTUALLY ARE SEEING THAT IN HOW THESE COMMITTEES ARE MANAGING THESE PROTOCOLS. THEY ARE COMING UP WITH RULES OR BOUNDARIES, BUT IT'S NOT A ONE SIZE FITS ALL. IT'S IN RELATION TO THE EXPERIMENTAL AIMS. AND THAT'S GOING ON THROUGH DISCUSSIONS WITH THE INVESTIGATORS.

SO I'LL STOP THERE. I THINK WHAT WE'VE -- HOPING TO GET SOME DISCUSSION. THE AIM WAS TO THEN GIVE YOU A GUIDANCE THAT WE WOULD HOPE COULD THEN BE USED TO SORT OF BASICALLY INDICATE THAT WE RECOMMEND THIS HEIGHTENED REVIEW, BUT WE'RE NOT WRITING IT IN THE SAME SORT OF WAY. WITHOUT INJECTING HARD AND FAST RULES, WE'RE TRYING TO REALLY GIVE OUR AWARDEES A PROCESS RECOMMENDATION FOR HOW THEY WOULD MANAGE THESE PROTOCOLS. SO I HOPE THAT WAS CLEAR. HAPPY TO TAKE QUESTIONS. AND, AGAIN, WANTED TO THEN SORT OF SHIFT THE DISCUSSION TOWARDS THE GUIDANCE AS A STRAW PERSON, IF YOU WILL, IN TERMS OF WHAT WE'RE LOOKING TO GET THE FEEDBACK FROM THE WORKING GROUP ON.

CO-CHAIRMAN KAHN: THANKS, GEOFF. ANYONE

WANT TO RAISE THEIR HANDS? SEEMS LIKE A REASONABLE APPROACH.

I GUESS ONE THING, AND WE'RE GOING TO HEAR, I KNOW, FROM PEOPLE WHO ARE SCRO DIRECTORS AND ARE ENGAGED IN EXACTLY THIS KIND OF OVERSIGHT. SO IT WOULD BE REALLY HELPFUL TO HEAR FROM THEM ABOUT WHETHER THIS IS A SUFFICIENT LEVEL OF GUIDANCE. BUT MAYBE BEFORE WE GET TO THAT, EVEN TO LOOK AT WHAT YOU HAVE PROVIDED TO US, ONE THING, I DON'T KNOW ABOUT THAT JUMPING OUT TO ME, BUT THERE'S A DIFFERENCE, I THINK, IN THE LANGUAGE BETWEEN WHAT ISSCR IS SUGGESTING AND WHAT'S IN THE STRAW PERSON VERSION THAT YOU SHARED WITH US.

SO ACCEPTABLE REASON OR ACCEPTABLE JUSTIFICATION VERSUS COMPELLING JUSTIFICATION. MAYBE THIS IS SPLITTING HAIRS, BUT I THINK IT WOULD BE HELPFUL IF THE LANGUAGE WERE CONSISTENT OR HARMONIZED IN A WAY THAT DOESN'T LEAD TO CONFUSION ABOUT IS THERE A DIFFERENCE BETWEEN COMPELLING AND ACCEPTABLE. PUTTING ON MY PHILOSOPHER'S HAT. SO I DON'T KNOW WHETHER THAT'S A FRIENDLY AMENDMENT OR THAT BLOWS THINGS UP FROM YOUR PERSPECTIVE.

DR. LOMAX: WELL, THE ONE -- SO THE ONE SORT OF POTENTIAL LIMITATION WE HAVE, AND I CAN TALK TO OUR LEGAL TEAM, AND WE CAN TRY TO INVITE THEM

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INTO THE CALL. BUT IN THE GUIDANCE I PROVIDED YOU, THE ACCEPTABLE SCIENTIFIC RATIONALE IS ACTUALLY IN QUOTES, AND IT'S IN QUOTES FOR VERY SPECIFIC REASONS IN THAT THAT FRAMING HAS ALREADY ENTERED INTO OUR ACTUAL REGULATIONS. AND SO WE MAY BE STUCK WITH THAT. WE MIGHT BE ABLE TO MODIFY IT IN THE GUIDANCE TO SORT OF REFLECT COMPELLING, IF THE WORKING GROUP THINKS THAT'S A BETTER CHOICE OF WORDS, BUT IT'S A BIT OF A CHALLENGE FOR US. WHAT WE'D LIKE TO AVOID, IF WE CAN, IS HAVING TO GO THROUGH THE PROCESS OF AMENDING OUR REGULATIONS BECAUSE THAT ENTERS US INTO A VERY LONG AND DEMANDING ADMINISTRATIVE PROCEDURE AT THE STATE LEVEL THAT IS HARD FOR US TO DO. SO JUST TO SORT OF RECOGNIZE THAT. IF WE DON'T NEED TO CHANGE THE REGULATIONS TO GET TO THE RIGHT PLACE, MAYBE WE'RE STUCK WITH A WORD OR TWO. THAT'S BECAUSE IT'S ALREADY EMBODIED IN THE STATE REGULATIONS.

CO-CHAIRMAN KAHN: THAT'S WHAT I THOUGHT YOU WERE GOING TO SAY, WHICH IS WHY I THOUGHT IT MAY BE A SUGGESTION THAT WOULD BLOW THINGS UP.

SO BEFORE WE GET TO FRED, JANET, THIS IS GOING TO PUT YOU ON THE SPOT A LITTLE BIT, AND I KNOW YOU SAID YOU WERE MEETING WITH THE SUBGROUP AT ISSCR ON TUESDAY, MAYBE YOU SAID. I DON'T KNOW

WHETHER THIS LANGUAGE DISTINCTION IS MEANINGFUL FROM YOUR PERSPECTIVE OR WILL BE. AND JUST MAYBE HEAR YOUR THOUGHT ABOUT IT WITHOUT YOU'RE COMMITTING ANYTHING IN THE WAY YOU RESPOND.

DR. ROSSANT: THE DIFFERENCE BETWEEN ACCEPTABLE AND COMPELLING IS A MAJOR CONCERN. IF IT'S EASIER TO RUN YOURS THROUGH WITH ACCEPTABLE, I THINK ACCEPTABLE IS ACCEPTABLE. I THINK THERE'S WAYS, OF COURSE, THAT YOU CAN PUT ADDITIONAL TEXT BEHIND THAT TO DEMONSTRATE HOW CRITICAL YOU THINK THIS IS. THERE MIGHT BE SOME MORE WORDING TO REALLY EMPHASIZE THE IMPORTANCE OF THE SCIENTIFIC JUSTIFICATION AND RATIONALE, BUT I THINK THE ACCEPTABLE STILL WOULD BE FINE.

I SHOULD SAY ISSCR, WE'RE NOT GOING TO BE CHANGING OUR GUIDELINES. WE WILL BE PROVIDING SOME GUIDANCE ON OUR GUIDELINES. THE GUIDELINES COME OUT EVERY FIVE YEARS. LIKE YOUR REGULATIONS, WE CAN'T KEEP GOING BACK AND MODIFYING THEM. SO WHAT WE'RE HOPING TO DO IS TO PRODUCE A WHITE PAPER THAT WILL ADD SOME SORT OF NUANCED GUIDANCE TO THE PROCESS, BUT IT WON'T -- NOTHING IS GOING TO CHANGE DRAMATICALLY FROM WHERE THINGS SIT TODAY.

CO-CHAIRMAN KAHN: THAT'S HELPFUL. I WAS GOING TO ASK ONE OF THE SCRO REPRESENTATIVES TO

OPINE ON THIS. STEVE, YOU RAISED YOUR HAND, SO HOPEFULLY YOU'RE GOING TO SPEAK TO THIS QUESTION.

DR. PECKMAN: THANK YOU, JEFF. THIS IS STEVE PECKMAN AGAIN. I WOULD SAY THAT COMPELLING IS VERY STRONG LANGUAGE. AND AT THE LEVEL OF BASIC SCIENCE RESEARCH, AS JANET DESCRIBED, I WOULD SUGGEST THAT IT MAY BE TOO STRONG AS IT MAY BE OVERLY RESTRICTIVE IN TERMS OF OVERSIGHT REVIEW. AND THAT ACCEPTABLE WILL PROVIDE A LOT MORE FLEXIBILITY.

AND I AGREE WITH WHAT JANET JUST SAID, WHICH IS PROVIDING JUSTIFICATION, SCIENTIFIC JUSTIFICATION, FOR THE PROJECT IS CRITICAL. IF THAT SCIENTIFIC JUSTIFICATION IS THE ACCEPTABLE JUSTIFICATION, THAT SHOULD BE GOOD. COMPELLING RAISES IT TO A DIFFERENT KIND OF LEVEL, WHICH I THINK, CERTAINLY IN VERY BASIC RESEARCH, WE NEED TO BE CAREFUL NOT TO CREATE GUIDELINES OR REGULATIONS THAT ARE OVERLY RESTRICTIVE OF THE SCIENCE.

CO-CHAIRMAN KAHN: THANK YOU. FRED, YOU HAD YOUR HAND UP BEFORE.

CO-CHAIRMAN FISHER: YEAH, I DID. SO JUST IN LISTENING, I THINK OUR CURRENT PROCESS CERTAINLY ADDRESSES THE SCIENTIFIC JUSTIFICATION UNLESS, GEOFF, YOU'RE THINKING THAT MAYBE IT DOESN'T DO THAT

SUFFICIENTLY. AND SO ZOOMING OUT A LITTLE WIDER, GIVEN WHAT YOU HAVE BEEN LISTENING TO FOR THE LAST FEW DAYS, I'M WONDERING IF AT THIS POINT THERE ARE ANY SORT OF GLARING ISSUES OR PROBLEMS THAT YOU'VE IDENTIFIED GIVEN YOUR FAMILIARITY WITH OUR PROCESS AND WHAT YOU'VE BEEN HEARING, WHETHER THERE ARE REALLY SUBSTANTIVE ISSUES THAT WE HAVE TO ADDRESS GOING FORWARD. AND MAYBE THE WHITE PAPER THAT COMES OUT WILL PROVIDE THE CATALYST FOR THAT KIND OF REVIEW. BUT I'M WONDERING SORT OF WHAT YOUR REACTION HAS BEEN IN TERMS OF HOW CIRM IS CURRENTLY POSITIONED AND WHETHER THERE ARE RED FLAGS GOING OFF FOR YOU ABOUT THINGS WE NEED TO ADDRESS.

DR. LOMAX: THANKS FOR THAT QUESTION. SO I THINK THE ONLY -- SO IN TERMS OF THE FRAMEWORK, THE REVIEW AND OVERSIGHT COUPLED, AGAIN, WITH OUR WORKING GROUP PEER REVIEW PROCESS FOR THE SCIENCE, I THINK I WOULD ARGUE OUR SYSTEM IS ROBUST, IT'S EFFECTIVE, AND IT'S WORKING. SO THERE AREN'T ANY -- NOTHING IS BROKEN. THERE'S NO WATER LEAKING FROM THE SHIP THAT NEEDS TO BE PLUGGED UP. AGAIN, THIS BECOMES MORE OF A CLARIFICATION PROCESS. AND THAT'S REALLY VALUABLE BECAUSE THAT'S WHAT WE'RE BEING ASKED BY OUR AWARDEES.

AND AT THE SAME TIME WE KNOW, AGAIN, ISSCR

IS IN THE PROCESS AS WELL. WE REALLY WANTED TO COUPLE THOSE PROCESSES IN A WAY WHERE WE WERE BEING AS CONSISTENT AS WE CAN BE.

I THINK THE ONE THING I WOULD POINT TO IN THE GUIDANCE WHICH BECAME APPARENT FROM THE MEETING, WHAT I DID IN THE GUIDANCE IS, RATHER THAN TRY TO RECOMMEND NEW POLICY, LIKE I ALLUDED TO EARLIER, I KIND OF POURED IT OVER A SET OF RULES THAT WE'RE ALREADY USING AROUND EMBRYOS AS A SORT OF STARTING POINT. I THINK THE FIRST BULLET, THE INTRODUCTION OF ANY STEM CELLS, WHETHER HUMAN OR NONHUMAN, INTO A HUMAN EMBRYO, BY IMPLICATION, YOU COULD READ THAT AND THINK YOU SHOULDN'T PUT STEM CELLS INTO A MODEL. I THINK WE'VE LEARNED, AND I KNOW THE SCIENTISTS CAN SPEAK TO THIS, THAT WE ACTUALLY WOULDN'T WANT TO INCLUDE THAT RESTRICTION IN THE WORK THAT WAS DESCRIBED TODAY. THAT, IN FACT, SOMETHING LIKE THAT IS PART OF WHY YOU WOULD USE THE MODEL.

SO IN A SENSE, AGAIN, I SORT OF JUST MOVED EVERYTHING OVER IN WHOLE CLOTH. I THINK I WOULD ASK THE WORKING GROUP AND THE SCIENTISTS, INVITE THEM TO COMMENT, THAT THAT WOULD ACTUALLY BE COUNTERPRODUCTIVE TO MAINTAIN THAT RESTRICTION OF THESE MODELS SYSTEM. SO TO THE EXTENT, AGAIN, WHAT I LEARNED IN THE LAST COUPLE DAYS IS THAT POINT IS

PROBABLY ERROR IF WE'RE GOING TO CONTINUE WITH OUR CHARGE AROUND PROMOTING THE BEST SCIENCE.

CO-CHAIRMAN KAHN: PEOPLE ARE NODDING. I THINK THERE'S AN AGREEMENT WITH WHAT YOU JUST SAID.

I GUESS ONE MORE CRACK AT THE LANGUAGE, AND MAYBE JUST ASK THE QUESTION. SO, JANET, YOU GAVE US SOME EXAMPLES WHEN YOU MADE YOUR PRESENTATION, THAT IT WOULD BE INTERESTING TO MAKE A MODEL EMBRYO, AN INTEGRATED MODEL EMBRYO FOR THE SCIENCE, BUT THAT WOULDN'T BE A SUFFICIENT REASON FROM YOUR PERSPECTIVE. AND I GUESS I'M ASKING WHETHER THE LANGUAGE IN THE PROPOSED GUIDANCE FROM GEOFF GETS US TO THE RIGHT ANSWER IN AN EXAMPLE LIKE THAT. DOES IT NEED TO BE STRONGER, OR MAYBE YOU JUST SAY -- AND, STEVE, YOU WOULD ANSWER -- THAT THE SCRO IS NOT GOING TO ALLOW THAT TO HAPPEN. AND SO YOU JUST NEED TO ALLOW THE COMMITTEE TO DO THEIR WORK. THEY UNDERSTAND THE REASON FOR THE OVERSIGHT, AND THEY'LL APPLY THE RULES ACCORDINGLY.

DR. LOMAX: I THINK, JEFF, IT'S ALMOST LIKE THE PERFECT SEGUE TO THE NEXT SESSION BECAUSE WE ASKED -- ONE AIM OF THAT SESSION WAS TO INVITE SOME OF THE OVERSIGHT COMMITTEES IN TO TELL US HOW THEY'RE INTERPRETING OUR EXISTING POLICY AND POTENTIALLY REACT TO THIS GUIDANCE. IT MIGHT BE IF

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WE WANT TO GO TO THAT CONVERSATION.

I GUESS THE OTHER QUESTION IS WE NEED A BREAK. I KNOW WE HAVE BETH, AND WE DID SCHEDULE A BREAK HERE. SO WOULD IT BE APPROPRIATE TO TAKE A BREAK FOR TEN MINUTES AND THEN COME BACK TO THAT?

CO-CHAIRMAN KAHN: BEING ON THE SIDE OF STARING AT A SCREEN FOR THE HOUR AND A HALF, SURE. IT WOULD BE NICE TO HAVE A BREAK.

DR. LOMAX: OKAY. SO LET'S RECONVENE AT 9:40 AND JUST TAKE A PAUSE. AND THEN WE WILL INVITE THE SORT OF PANELISTS TO COME IN AND DISCUSS. AND WE CAN DO ANOTHER ROUND OF PUBLIC QUESTION AND COMMENT AS PART OF THAT SESSION. THANK YOU.

(A RECESS WAS TAKEN.)

DR. LOMAX: YOU CAN HEAR US? TERRIFIC. SO WE DID WANT TO -- SO AS NOTED IN THE FINAL SESSION HERE, WE WANTED TO REALLY BASICALLY ENGAGE IN SORT OF REGULATORY POLICY LINGO. WE CALL THIS ENGAGING THE REGULATED PARTIES. IT'S PART OF SORT OF THE PROCESS THAT IS RECOMMENDED BY THE STATE OF CALIFORNIA WHEN YOU'RE CONSIDERING CHANGES IN POLICY. SO THAT'S WHAT WE'RE DOING.

I THINK I'LL JUST ASK THE PARTICIPANTS TO INTRODUCE THEMSELVES, THE FOUR PANELISTS, OR REINTRODUCE THEMSELVES. AND I JUST WANT TO ADD,

AGAIN, I SORT OF NOTED THIS BULLET POINT THAT MAY BE NOT REALLY APPROPRIATE IN TERMS OF THE REGULATION OF THESE SYSTEMS. PARTICULARLY IF YOU HAVE THOUGHTS ON WHETHER THAT -- IF WE DON'T GET RID OF IT, WHETHER THAT WOULD BE DISRUPTIVE, IT WOULD BE GOOD TO KNOW. BUT WE'D LIKE TO HAVE THE PANELISTS JUST GIVE A LITTLE BIT OF THE SENSE OF THE WORK. WE'VE ASKED THEM TO SORT OF TALK A LITTLE BIT HOW THEY GO ABOUT LOOKING AT THESE PROTOCOLS AND REALLY THAT YELLOW PROCESS WE'VE TALKED ABOUT JUST SO EVERYONE HAS A SENSE OF WHAT HAPPENS AT THE INSTITUTIONAL LEVEL AND WHAT THEY'RE EXPERIENCING IN TERMS OF THESE PARTICULAR MODEL SYSTEMS, THE EMBRYO MODEL SYSTEMS.

MAYBE I'LL ASK MELISSA TO START JUST IN TERMS OF INTRODUCTION BECAUSE THAT'S SORT OF OUR OUTSIDE PERSON, AND THEN WE HAVE THREE PANELISTS FROM CALIFORNIA THAT CAN INTRODUCE THEMSELVES.

MS. LOPES: HI. I'M MELISSA LOPES. I'M FROM HARVARD UNIVERSITY. I'M THE DIRECTOR OF THE SCRO COMMITTEE HERE. CAN YOU NOT HEAR ME?

CO-CHAIRMAN KAHN: ACTUALLY WE CAN HEAR HER FINE.

VICE CHAIR BONNEVILLE: WE CAN HEAR HER ONLINE.

DR. LOMAX: DO WE HAVE VOLUME IN THE ROOM?

CO-CHAIRMAN KAHN: CAN YOU HEAR ME?

DR. LOMAX: WE CAN HEAR JEFF.

CO-CHAIRMAN KAHN: OKAY. I'M TALKING. MELISSA, YOU WANT TO TRY AGAIN?

MS. LOPES: CAN YOU HEAR ME NOW? I'LL JUST REPEAT. I'M MELISSA LOPES. I'M FROM HARVARD UNIVERSITY. I'M THE DIRECTOR OF THE SCRO COMMITTEE THERE, AND I ALSO WORK IN THE PRESIDENT PROVOST'S OFFICE ON RESEARCH AND ETHICS AND COMPLIANCE ACROSS THE UNIVERSITY.

DR. LOMAX: STEVE, DO YOU WANT TO RE-INTRODUCE YOURSELF.

DR. PECKMAN: I'M STEVE PECKMAN. I'M THE DEPUTY DIRECTOR EMERITUS, I GUESS, OF THE UCLA BROAD STEM CELL RESEARCH CENTER. AND I CREATED THE HUMAN PLURIPOTENT STEM CELL RESEARCH OVERSIGHT COMMITTEE AT UCLA. AND I JUST WANT TO GIVE A SHOUTOUT TO BENHUR LEE, WHO WAS ONE OF OUR ORIGINAL MEMBERS UNTIL HE GRADUATED.

DR. LOMAX: AND, MARIA, OUR SECOND UCLA PARTICIPANT.

CO-CHAIRMAN KAHN: YOU'RE REALLY HARD TO HEAR FOR SOME REASON, MARIA.

MS. DOMINGUEZ: CAN YOU HEAR ME NOW OR NO?

CO-CHAIRMAN KAHN: NO, NOT GOOD.

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DR. LOMAX: OKAY. YOU MIGHT HAVE AN OPTION. YOU MIGHT WANT TO GO OFF VIDEO, BUT WE WANT TO TRY TO KEEP YOU IN THE CONVERSATION. AND, GRACE, SEARCHING THROUGH THE PANEL HERE.

MS. FISHER-ADAMS: I'M GRACE FISHER-ADAMS. I'M THE CHIEF RESEARCH POLICY OFFICER AT THE CALIFORNIA INSTITUTE OF TECHNOLOGY, CALTECH. AND I AM THE INSTITUTIONAL OFFICIAL WHO OVERSEAS ALL OF OUR COMMITTEES, INCLUDING THE STEM CELL COMMITTEE.

MS. DOMINGUEZ: I CAN GIVE THIS ANOTHER TRY. CAN YOU HEAR ME NOW?

DR. LOMAX: THERE WE GO.

MS. DOMINGUEZ: I'M THE DIRECTOR OF THE OPERATIONS COMPLIANCE AND REGULATORY AFFAIRS AT THE BROAD STEM CELL RESEARCH CENTER AT UCLA. I WORKED WITH STEVE FOR MANY YEARS BEFORE HE GRADUATED. SO ALSO THE LEAD ADMINISTRATOR FOR THE HP SCRO HERE AT UCLA.

DR. LOMAX: GREAT. SO MAYBE JUST TO OFFER A COUPLE OF LEAD-IN QUESTIONS AND THEN INVITE THE WORKING GROUP TO CHIME IN. I KNOW YOU'VE COME TO US WITH QUESTIONS ABOUT SORT OF THE REVIEW AND OVERSIGHT OF THESE PROTOCOLS. ONE OF THE THINGS THAT HAS REALLY BEEN A THEME TODAY HAS BEEN SORT OF LOOKING AT THE SCIENTIFIC -- I'M TRYING TO REMEMBER

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THE WORD -- THE ACCEPTABLE SCIENTIFIC RATIONALE. CAN YOU TALK A LITTLE BIT ABOUT SORT OF HOW YOU MANAGE THAT PROCESS IN YOUR COMMITTEE? GRACE.

MS. FISHER-ADAMS: SO I WILL SAY WHEN THIS ISSUE FIRST CAME TO OUR COMMITTEE, THE QUESTION WAS HOW WERE WE GOING TO REVIEW IT. AND I THINK THE COMMITTEE ACTUALLY REALIZED VERY EARLY ON THAT THESE WERE GOING TO HAVE SOME SERIOUS IMPLICATIONS JUST BECAUSE WE UNDERSTAND THESE ARE EMBRYO MODELS, THEY ARE NOT ACTUAL EMBRYOS, AND THAT THERE'S A LOT OF REALLY VALUABLE SCIENTIFIC POTENTIAL WITH THESE MODELS. AND WE WANTED TO VERY CAREFULLY CONSIDER WHAT WOULD BE APPROPRIATE ENDPOINTS IF WE WERE GOING TO SAY WE HAVE TO HAVE ETHICAL STOPPING POINTS, TO DO SOME STOPPING, REEVALUATING, FIGURING OUT WHAT'S NEXT.

SO WE, FIRST OF ALL, ACTUALLY DID DO A SCIENTIFIC JUSTIFICATION. SO WE HAD THE RESEARCHER COME IN AND HAVE A CONVERSATION WITH THE COMMITTEE AS TO REALLY WHAT THE SCIENTIFIC RATIONALE WAS, WHY THIS MODEL WAS VALUABLE. AND THEN WE WORKED WITH THE RESEARCHER TO IDENTIFY THE APPROPRIATE FIRST STOPPING POINT, WHICH WE THOUGHT WAS A GOOD STOPPING POINT. SO I THINK THOSE THINGS WERE TAKEN INTO CONSIDERATION EVEN THOUGH I DON'T THINK THEY WERE

SPECIFICALLY REQUIRED BY THE REGULATORY FRAMEWORK. WE DECIDED THAT THIS WAS AN IMPORTANT THING FOR US TO LOOK AT.

AND THEN THE SECOND I JUST WANTED TO MENTION, GEOFF, BECAUSE YOU HAD ASKED ABOUT THAT FIRST BULLET POINT. I CERTAINLY THINK THAT THAT FIRST BULLET DOES NEED TO BE REMOVED BECAUSE I THINK THAT IS ACTUALLY THE WHOLE POINT OF THE MODEL.

DR. LOMAX: MAYBE WE'LL GO TO UCLA. HOW DOES WHAT THEY'RE DOING COMPARE TO YOUR PROCESS, AND THEN BE INTERESTED, MELISSA, IN TERMS OF HOW YOU MANAGE THINGS OVER AT HARVARD JUST TO GET A SENSE OF HOW WELL THESE SORT OF GUIDELINES ARE WORKING -- OR REGULATIONS OR GUIDELINES ARE WORKING FROM AN IMPLEMENTATION STANDPOINT.

DR. PECKMAN: SO THIS IS STEVE PECKMAN. I THINK OUR PROCESS WAS VERY SIMILAR TO CALTECH. I THINK, AND MARIA CAN CORRECT ME, I THINK IT WAS ABOUT THREE YEARS AGO, AROUND THE TIME OF THE AUSTRALIAN BLASTOID PAPER, THAT WE FIRST CONVENED TO DISCUSS THIS. AND WE HAVE AREAS THAT WE'VE DESIGNATED AS SENSITIVE RESEARCH SIMILAR TO WHAT GEOFF DESCRIBED THAT REQUIRES CONVENED COMMITTEE REVIEW.

AND ONE OF THE ISSUES THAT WE -- TWO

THINGS THAT I THINK I SHOULD TOUCH UPON THAT GRACE AND CALTECH PROBABLY DID AS WELL IS WHEN WE WERE FIRST CONSIDERING THIS, WHETHER THIS IS AN EMBRYO QUESTION IS THE FIRST QUESTION. AND SO AS A RESULT, THE FIRST THING WE DID IS WE CONTACTED GEOFF TO GET FEEDBACK AS TO WHAT THE REGULATORY AGENCY IN CALIFORNIA WOULD THINK ABOUT THIS KIND OF MODEL BECAUSE WE WANTED TO BE IN COMPLIANCE WITH THE CALIFORNIA RULES THAT WE SUPPORT.

AND WE HAD A NICE CONVERSATION WITH GEOFF ABOUT THIS AND ESSENTIALLY IF THE COMMITTEE AGREED WITH THE IDEA THAT THESE ARE NOT EMBRYOS, THEN WE COULD MOVE FORWARD WITH A VARIETY OF OPTIONS.

ONE OF THE THINGS THAT THE COMMITTEE CONSIDERED, IN ADDITION TO WHAT GRACE DISCUSSED, IS A ROLE OF BUILDING PUBLIC CONFIDENCE IN STEM CELL RESEARCH THROUGH APPROPRIATE REVIEW AND OVERSIGHT. AND THEY TAKE THAT ROLE EXTREMELY SERIOUSLY. SO THE SCIENTIFIC JUSTIFICATION FOR THIS TYPE OF RESEARCH IS REALLY CRITICAL BECAUSE OUR COMMITTEE CONSIDERED THAT, THOUGH THESE BLASTOIDS WERE NOT EMBRYOS, THE RAPID PACE THAT SCIENCE PROGRESSES, IT WOULDN'T BE LONG BEFORE THEY WERE. SO WE NEED TO START CREATING A FRAMEWORK TO ADDRESS SOME OF THESE ISSUES.

AND ONE OF THE WAYS WE DID THAT IS BY

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ENSURING, AS CALTECH DID, THAT THERE'S OPEN COMMUNICATION WITH THE RESEARCH GROUPS THAT ARE INTERESTED IN THIS. AND SO THROUGH A PROCESS OF MULTIPLE MEETINGS AND REVIEWS, ONE OF THE OUTCOMES WAS TO HAVE AN OPEN CONVERSATION WITH THE INVESTIGATORS. AND THEY AGREED TO THIS, WHICH IS THAT THEY WERE TO KEEP, SINCE THEY WERE THE EXPERTS IN THE AREA, THEY WERE OBLIGATED TO KEEP THE COMMITTEE INFORMED AS TO WHAT'S GOING ON SCIENTIFICALLY, NOT ONLY IN THEIR LAB, BUT IN THE AREA IN GENERAL, AND THAT WE WOULD KEEP THE CONVERSATION GOING. AND AS ADJUSTMENTS NEEDED TO BE MADE, THEY WOULD BE MADE BASED ON THE SCIENTIFIC DISCOVERIES IN PROGRESS RATHER THAN ANYTHING ELSE.

AND SO THE CONCEPT HERE WAS TO ENSURE THAT THE COMMITTEE WAS WELL INFORMED ABOUT THE PROGRESS OF SCIENCE AND THAT THE INVESTIGATORS WERE ALWAYS PART OF THE DISCUSSION.

MS. LOPES: THAT REFLECTS BASICALLY SORT OF HOW HARVARD HAS VIEWED THESE AS WELL. FIRST ONE THAT CAME TO US WAS BEFORE COVID, SO A FEW YEARS BACK. AND IT WAS ACTUALLY AN ACCIDENT. IT WASN'T -- THE PI'S HADN'T SET OUT TO CREATE AN EMBRYO MODEL. THEY HAD JUST BEEN DOING SOME WORK IN THE DISH ON A TOTALLY DIFFERENT PROJECT AND STARTED

TO SEE WHAT LOOKED LIKE THE PRIMITIVE STREAK. AND THEY WEREN'T SURE IF THE RULES OF THE SCRO APPLIED TO WHAT THEY WERE DOING OR NOT BECAUSE THEY HADN'T STARTED WITH AN INTACT EMBRYO. AND THAT WAS THE LANGUAGE FROM THE NAS GUIDELINES.

AND SO WE LOOKED AT THAT AND SORT OF HAD CONVERSATIONS WITH THEM, BUT ALSO INVITED OUTSIDE EXPERTS IN THIS AREA TO SORT OF WEIGH IN AND GOT A SENSE OF COMING TO A DEFINITION THAT THESE ARE NOT -- THIS IS NOT AN EMBRYO THAT THEY'RE WORKING ON AND THAT THEY COULD PROCEED AND THAT WE WOULD TAKE THE VIEW THAT, AS WE STARTED TO SEE THINGS, WE WOULD ALLOW PEOPLE TO PROCEED IN A SLOW PACE, BUT HAVE THESE CONVERSATIONS CONTINUE ON.

WE'VE STARTED TO SEE -- WE STILL DON'T HAVE -- IT IS A LOT THAT IS COMPLEX FOR THE COMMITTEE. THESE ARE DIFFICULT CONVERSATIONS BECAUSE WE DON'T EVEN HAVE STATE GUIDELINES LIKE YOU GUYS DO. BUT WE DON'T HAVE ANY TYPES OF GUIDELINES THAT ARE REALLY GIVING US A WAY TO DETERMINE WHAT IS A STOPPING POINT FOR WHEN THE PI NEEDS TO COME BACK TO THE SCRO AND GIVE A REPORT OR WHEN THE PI HAS TO MAYBE TAKE A STEP BACK OR DO SOMETHING DIFFERENTLY. SO WE ARE JUST SORT OF WORKING THROUGH AS WE GO AND SORT OF TAKING THAT PROGRESSIVE APPROACH OF SORT OF

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LEARNING FROM THE RESEARCHERS OF WHAT THEY'RE SEEING AND WHAT WAS ACTUALLY FEASIBLE.

AT THIS POINT WE HAVEN'T -- WE HAVE ALWAYS CHARACTERIZED, WE'VE ALWAYS COME TO THE CONCLUSION THAT WHAT WE'RE LOOKING AT IS NOT AN EMBRYO. IT IS SOMETHING OTHER THAN AN EMBRYO.

MS. FISHER-ADAMS: I'D JUST LIKE TO FOLLOW UP ON THAT. CERTAINLY I THINK THAT WAS OUR STARTING QUESTION. ARE THESE EMBRYO MODELS? IS WHAT WE'RE LOOKING AT, ARE THEY EMBRYOS?

AND THE OTHER THING, JUST TO SORT OF FOLLOW UP ON WHAT STEVE SAID, WE DO HAVE A FOLLOW-UP MECHANISM WITH THE RESEARCHERS. SO WE HAVE A DEFINED ENDPOINT FOR THE EXISTING RESEARCH, AND THEN THE RESEARCHER IS SUPPOSED TO TERMINATE THE EXPERIMENT, THEN COME BACK TO THE SCRO AND HAVE ANOTHER CONVERSATION.

WE ALSO HAVE ASKED THE RESEARCHER, IF SOMETHING SUBSTANTIVELY CHANGES IN THE FIELD, THAT THEY HAVE AN OBLIGATION TO COME BACK TO THE SCRO AND TELL US SO THAT WE CAN REEVALUATE THE RESEARCH AT ANY POINT IN TIME.

MS. DOMINGUEZ: AT UCLA WE HAVE PRETTY MUCH THE SAME THING, THAT IF SOMETHING DEVELOPS IN THE TIME THAT YOU'VE BEEN OUTSIDE OF YOUR LAB,

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ELSEWHERE, THAT YOU COME BACK TO THE COMMITTEE WITH THAT INFORMATION. AND ALSO, IF IT HAPPENS WITHIN YOUR EXPERIMENTS, THAT YOU COME BACK IMMEDIATELY TO THE COMMITTEE AND LET US KNOW.

DR. LOMAX: THANKS FOR THAT. JEFF, I'M GOING TO SORT OF LOOK TO THE CO-CHAIR TO --

CO-CHAIRMAN KAHN: SURE. VERY INTERESTING. I GUESS ONE QUESTION FOR ALL OF YOU IS WHAT WOULD BE HELPFUL TO HAVE IN ADDITION TO WHAT YOU ALREADY DO HAVE, OR MAYBE THE ANSWER IS NOTHING. BUT A LITTLE BIT OF -- I'M JUST TAKING AWAY A FEW THINGS, THAT TALKING TO EACH OTHER MIGHT BE A HELPFUL THING, AND THERE'S A CONVENING FUNCTION THAT OBVIOUSLY CIRM CAN PROVIDE. BUT IS THERE ANYTHING MORE SUBSTANTIVE THAN THAT THAT WOULD BE HELPFUL TO YOUR WORK?

MS. LOPES: FROM MY PERSPECTIVE, AND I'M OUTSIDE OF CALIFORNIA, BUT JUST FROM WHAT I SEE AS MISSING FROM THE ISSCR GUIDELINES IS SORT OF A SCIENTIFIC -- WE HAVE SCIENTISTS ON OUR PANEL THAT ARE DOING THE REVIEWS, AND WE HAVE DEVELOPMENTAL BIOLOGISTS AND EMBRYOLOGISTS. AND SO THEY HELP US SOMETIMES FIGURE OUT WHAT IS ACTUALLY POSSIBLE. BUT IT WOULD BE NICE IN THE GUIDELINES OR IF THERE WERE SOME SORT OF GUIDANCE OF WHAT IS ACTUALLY POSSIBLE

BECAUSE SOMETIMES YOU CAN GET INTO CIRCULAR CONVERSATIONS OF ETHICAL ISSUES THAT WOULD NEVER HAPPEN BECAUSE WHATEVER YOU'RE WORKING IN THIS DISH IS NOT GOING TO GET TO THE POINT OF RAISING THE CONCERNS OF BEING LIKE AN ACTUAL EMBRYO.

DR. PECKMAN: I THINK THERE'S A WAY TO ADDRESS THAT WITHIN THE CURRENT FRAMEWORK AND REGULATIONS THAT MAYBE IS JUST GUIDANCE. IT'S NOT NECESSARILY, I DON'T THINK, SPELLED OUT IN THE STATE CIRM REGULATIONS OR IN THE DEPARTMENT OF PUBLIC HEALTH REGULATIONS, WHICH IS THAT THE COMMITTEES SHOULD, AND THIS GOES DIRECTLY TO WHAT MELISSA IS TALKING ABOUT, THAT THE COMMITTEE SHOULD ENSURE THAT THEY HAVE THE APPROPRIATE AND ADEQUATE EXPERTISE SCIENTIFICALLY TO DISCUSS THE PROJECTS THAT COME BEFORE THEM. I THINK IT'S ALLUDED TO IN THE REGULATIONS, AND SO YOU WOULDN'T NEED TO CHANGE THE REGULATIONS, BUT EXPAND UPON THAT IN TERMS OF GUIDANCE.

THAT'S SOMETHING THAT I THINK WE'VE ALWAYS TRIED TO DO. IF WE DON'T HAVE THE EXPERTISE, WE GO OUT TO CONSULTANTS. I'M SURE THAT THE OTHER INSTITUTIONS DO THAT AS WELL. BUT TO MAKE THAT AS PART OF GUIDANCE SO THAT YOU KNOW THIS IS KIND OF AN ACCEPTABLE PATHWAY TO TAKE AND THAT YOU HAVE AN

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OBLIGATION TO HAVE THE SCIENTIFIC EXPERTISE THERE IN THE REVIEW. ESPECIALLY FOR SENSITIVE RESEARCH, I THINK THAT WOULD BE HELPFUL TO SOME INSTITUTIONS.

CO-CHAIRMAN KAHN: DO ANY OF YOU THINK THAT THERE'S -- THIS IS HARD BECAUSE IT'S SO HYPOTHETICAL ABOUT WHAT I'M ABOUT TO ASK, THAT THERE MIGHT BE DIFFERENCES IN WHAT YOUR SCRO'S WOULD APPROVE SUCH THAT THERE NEEDS TO BE A LITTLE MORE CONCRETE GUIDANCE OR THE STOPPING POINTS MIGHT BE DIFFERENT FOR THINGS THAT LOOK QUITE SIMILAR FROM INSTITUTION TO INSTITUTION. I'M KIND OF GOING TO THE PUBLIC CONFIDENCE IN OVERSIGHT POINT THAT NUMEROUS OF YOU HAVE MADE. OR DO YOU FEEL LIKE THERE'S ENOUGH LIKELY CONSISTENCY THAT THAT WON'T HAPPEN?

MS. FISHER-ADAMS: I THINK THERE IS GOING TO BE INCONSISTENCY JUST BECAUSE THERE'S DIFFERENT SCIENCE GOING ON. AS JANET POINTED OUT, THERE'S DIFFERENT MODELS, THERE'S DIFFERENT WAYS OF LOOKING AT IT, THERE'S DIFFERENT SCIENTIFIC QUESTIONS. SO I THINK IT'S NATURAL THAT WE'RE GOING TO COME TO DIFFERENT CONCLUSIONS IN TERMS OF ENDPOINTS. I'M NOT SURE THAT THAT CAN BE REGULATED BECAUSE, AGAIN, IT GOES BACK TO THE SCIENCE THAT WE'RE LOOKING AT.

DR. PECKMAN: I WOULD AGREE WITH THAT A

HUNDRED PERCENT. WE NEED TO BE CAREFUL NOT TO OVERLY RESTRICT BECAUSE THAT CAN BE VERY DAMAGING. I THINK IT'S OKAY FOR COMMITTEES TO COME TO DIFFERENT CONCLUSIONS OVER WHAT STOPPING POINTS WOULD BE, PARTICULARLY, AS GRACE POINTED OUT, THAT THERE ARE DIFFERENT KINDS OF PROJECTS.

BUT JUST IN OTHER TYPES OF RESEARCH VENUES, WHETHER IT BE NONHUMAN ANIMAL RESEARCH OR HUMAN SUBJECTS RESEARCH, COMMITTEES DO COME TO DIFFERENT CONCLUSIONS. AND OFTENTIMES THAT ACTUALLY MAKES FOR A MORE ROBUST SYSTEM OF OVERSIGHT. AND WE CAN LEARN FROM EACH OTHER. SOME INSTITUTIONS MAY BE A LITTLE BIT MORE CONSERVATIVE IN WHERE THEY WANT TO PUT THAT STOPPING POINT, WHICH IS NOT NECESSARILY BAD, NOR IS IT NECESSARILY BAD THAT AN INSTITUTION THAT'S LESS CONSERVATIVE IN A SIMILAR PROJECT WOULDN'T HAVE THE SAME STOPPING POINT SO LONG AS THEY'RE REASONABLE AND WELL-REASONED AND JUSTIFIED STOPPING POINTS. AGAIN, THAT GOES BACK TO THE DISCUSSION BETWEEN THE COMMITTEE AND THE INVESTIGATOR.

MS. DOMINGUEZ: AND I THINK AN IMPORTANT POINT, JUST TO REITERATE IT, IS THAT THAT CONVERSATION IS ONGOING. AT ONE POINT THE COMMITTEE CAN DECIDE THAT THE STOPPING POINT IS HERE AND THE

INVESTIGATOR GETS TO THAT POINT, AND THEN THE CONVERSATION CONTINUES AT, OKAY. WELL, NOW THAT WE HAVE THE DATA, IS IT APPROPRIATE TO PUSH IT FURTHER OUT?

DR. LOMAX: JEFF, MAYBE I CAN JUST REFERENCE, AGAIN, THIS IS SOMETHING WE'VE DONE HISTORICALLY, YOU NOTED A CONVENING ROLE. AND THIS IS REALLY A QUESTION TO THE COMMITTEE FOLKS IN PARTICULAR. IT'S THE JUICE. WE'RE AT THE SQUEEZE QUESTION BECAUSE IT'S GREAT TO BE IN A CONVENING ROLE, BUT MEETINGS ARE A LOT OF WORK. ARE WE IN A PLACE, AND WE COULD ALSO ENGAGE POTENTIALLY WITH ISSCR IF THEY VIEWED THAT AS HELPFUL. WHAT YOU JUST DESCRIBED, I THINK THAT DYNAMIC FRAMEWORK, HOW YOU MANAGE THOSE INTERACTIONS BETWEEN THE PROTOCOL, THE INSTITUTIONAL CULTURE, ALL THOSE VARIOUS FACTORS, THAT DYNAMIC INTERACTION, JUST HAVING SOME KIND OF A WORKSHOP. WE'VE DONE THIS OVER THE YEARS TO GET THE COMMITTEES TOGETHER JUST SO THEY CAN BENCHMARK THEIR PROCESSES OFF OF EACH OTHER. WOULD SOMETHING LIKE THAT BE HELPFUL AT THIS TIME ON THIS SPECIFIC ISSUE?

MS. FISHER-ADAMS: I FOUND THIS DAY TO BE VERY, VERY INFORMATIVE FOR ME. I DO THINK IT WOULD BE HELPFUL TO HAVE CONTEXT AS TO WHAT OUR PEERS ARE DOING.

DR. PECKMAN: I THINK, IF NOTHING ELSE, THERE USED TO BE AN EMAIL GROUP OF SCRO'S AROUND THE STATE. I DON'T KNOW THAT'S BEEN VERY ACTIVE. AND THERE WAS ONE THAT WAS PUT TOGETHER BY THE NATIONAL ACADEMIES. AND I KNOW THAT WHEN THIS FIRST CAME UP FOR US, I DID SEND OUT AN EMAIL ASKING IF PEOPLE WERE DEALING WITH THIS AND WE GOT CRICKETS. BUT I THINK ONE THAT'S INITIATED BY CIRM THAT HAS THE SCRO'S THAT ARE ALL CIRM-FUNDED AT LEAST WOULD BE VERY HELPFUL IN TERMS OF INTERINSTITUTIONAL COMMUNICATION. SO IT'S ALWAYS GOOD FOR US TO BE ABLE TO TALK TO EACH OTHER.

CO-CHAIRMAN KAHN: AND TOO IT WILL HELP INFORM MELISSA AND OTHERS WHO ARE OUTSIDE OF CALIFORNIA. I THINK THERE'S AN IMPORTANT ROLE AS A RESOURCE AS WELL.

YOU SEE JANET'S HAND, GEOFF?

DR. ROSSANT: GEOFF, JEFF, I WAS ABOUT TO SAY EXACTLY WHAT YOU SAID. I THINK ONE OF THE THINGS, I'M SITTING LISTENING TO THE SCRO'S TALK ABOUT THEIR PROCESS, AND THE SIMILARITIES AND DIFFERENCES IS VERY IMPORTANT.

ONE OF THE THINGS AT ISSCR LEVEL, BECAUSE WE'RE INTERNATIONAL, WE'RE DEALING WITH NOT EVEN BEING ABLE TO PROSCRIBE A PARTICULAR KIND OF REVIEW

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PROCESS. IT'S EASY TO SAY IT'S SCRO IN THE STATES, BUT EVEN SCRO'S VARY ACROSS DIFFERENT JURISDICTIONS. CALIFORNIA, YOU'RE IN GOOD SHAPE; BUT A LOT OF PLACES, THAT'S NOT THE CASE. AND A LOT OF PLACES DON'T KNOW WHAT TO DO AT ALL WITH THIS KIND OF RESEARCH. SO FOR THE OPPORTUNITY TO REALLY BUILD A NETWORK OF THOSE SCRO'S THAT HAVE EXPERIENCE IN THIS, NOT JUST WITHIN CALIFORNIA, BUT NATIONALLY AND MAYBE INTERNATIONALLY WOULD BE VERY GOOD. SO IF CIRM WERE TO PULL TOGETHER SOME KIND OF WORKING GROUP AND NETWORK, I THINK THAT WOULD BE EXCELLENT.

MS. LOPES: IT'S PARTICULARLY IMPORTANT TO KNOW WHO ACTUALLY IS ENGAGED WITH THESE TYPES OF QUESTIONS. WHEN YOU THINK YOU'RE ON THE FOREFRONT OF SOMETHING AND YOUR COMMITTEE IS GRAPPLING WITH SOMETHING, IT IS GOOD FOR US TO BE ABLE TO REACH OUT AND TO KNOW WHO HAS ALREADY DEALT WITH THIS. USUALLY WE LOOK TO PUBLICATIONS TO SEE WHO HAS PUBLISHED ON THIS RESEARCH, AND THEN BACKWARDS GO IN TO SEE WHAT WAS THE OVERSIGHT OF THAT RESEARCH. BUT HAVING A FRONTLINE TO ACTUAL OVERSIGHT COMMITTEES WOULD BE A MORE DIRECT WAY TO KNOW WHO HAS SEEN THIS AND DEALT WITH IT ALREADY BEFORE.

DR. ROSSANT: AT ISSCR AS WELL IT IS SOMETHING THAT CIRM AND ISSCR MIGHT DO TOGETHER. WE

COULD BRING THE INTERNATIONAL PIECE BECAUSE THERE ARE WORKING GROUPS, THERE ARE GUIDELINES WORLDWIDE AS WELL. THE UK HAS GOT A SET OF GUIDELINES IN THIS AREA. THERE'S A LOT OF MOVING PARTS THAT HAVE TO COME TOGETHER IN THE NEXT LITTLE WHILE.

CO-CHAIRMAN KAHN: TO THAT POINT BEFORE I GET TO SAY IT, JANET, I JUST WAS IN LONDON LAST WEEK AND MET WITH PETER THOMPSON, THE DIRECTOR OF THE HFEA. AND THERE'S A CONVERSATION ABOUT OPENING THE HFE ACT BECAUSE OF SOME OF THE CHANGES THAT ARE COMING. SO THE TIMING ACTUALLY IS REALLY GOOD FOR THIS INTERNATIONAL CONVERSATION TO HAPPEN.

MS. FISHER-ADAMS: GEOFF, YOU MENTIONED THAT THERE WERE PUBLISHERS AT THE CONFERENCE THIS WEEK. I'D ALSO BE CURIOUS AS TO WHAT PUBLISHERS' EXPECTATIONS ARE IN TERMS OF THE OVERSIGHT REVIEW. ARE THEY TURNING TO CIRM AND THE ISSCR TO GET THAT FEEDBACK? WHERE ARE WE WITH THAT? AND MAYBE, JANET, YOU CAN ANSWER TOO.

DR. LOMAX: SO I THINK WE HAVE CONTACTS STEMMING FROM THIS MEETING, AND I THINK WE WOULD GO OUT AND DESCRIBE SORT OF WHAT WE HAVE IN PLACE. I THINK SOME OF THEM HAD THE OPPORTUNITY, THEY CAN LISTEN TO THIS CONVERSATION, SOME ARE LISTENING. I THINK WHAT WE CAN DO IS CHARACTERIZE WHAT WE'VE GOT

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IN PLACE AND THEN ASK THEM TO WHAT EXTENT THERE MAY BE A WAY TO HAVE THAT REFLECTED IN PUBLICATIONS. BUT I WOULD HAVE TO DEFER TO THEM.

I'D BE CAREFUL -- ONE HAS TO BE CAREFUL ABOUT HOW YOU SORT OF CHARACTERIZE THINGS AND WHO'S IN AND OUT. WE DON'T WANT TO GET -- AGAIN, AS AN AGENCY, FOR EXAMPLE, WE'VE GOT TO BE SENSITIVE TO HOW OUR DECREES SORT OF DISSEMINATE INTO THE BROADER UNIVERSE. SO I'D ALSO SORT OF PULL IN OUR LEGAL TEAM. BUT THERE WAS INTEREST ON THE PUBLISHER SIDE TO SORT OF LOOK AT WAYS, MAYBE THROUGH A STATEMENT, I THINK, WAS ONE OF THE INTERESTING CONCEPTS THAT CAME UP DURING DISCUSSION AT THIS MEETING. MAYBE IT'S NOT SO MUCH A GOOD HOUSEKEEPING STAMP OF APPROVAL, BUT SOME SORT OF A NARRATIVE STATEMENT ABOUT THE MANAGEMENT OF THESE ISSUES IN THE CONTEXT OF A PUBLICATION.

BUT I THINK I CAN SAY WITH SOME CONFIDENCE THERE WAS INTEREST IN THAT, AND THERE ACTUALLY ARE IN A NUMBER OF THOSE ARE ARTICLES THAT JANET CITED THOSE STATEMENTS ALREADY EXIST. SO YOU SORT OF MIGHT LOOK AT THAT AND THEN SORT OF THINK ABOUT THAT. IS IT SOMETHING WE WOULD RECOMMEND REPLICATING? AND THEN OBVIOUSLY IT WOULD BE UP TO THE PUBLISHERS TO WHAT EXTENT THAT WAS A HARD RULE

OR NOT.

DR. PECKMAN: IF I COULD JUST ADD A POINT HERE. THE BEST REGULATION THAT OUTLINES IMPORTANT PRINCIPLES THAT THEN ARE IMPLEMENTED BY COMMITTEES AND INVESTIGATORS TO ENSURE APPROPRIATE CONDUCT AND OVERSIGHT OF RESEARCH. THAT WHEN YOU START TO BECOME TOO SPECIFIC, THEN AT THAT POINT YOU LOSE FLEXIBILITY FOR SURE, BUT THE SCIENCE MOVES SO FAST, THAT YOU'RE CONSTANTLY THEN STRIVING TO CATCH UP IN TERMS OF HOW YOU MODIFY YOUR RULES TO ADDRESS THE SCIENCE. AND I THINK THAT ONE OF THE BEAUTIES OF WHAT CIRM CREATED IN ITS REGULATIONS, AND THE DEPARTMENT OF PUBLIC HEALTH ACTUALLY FOLLOWED SUIT, WAS CREATING THESE RULES THAT PROVIDE GUIDANCE. THERE ARE SPECIFIC AREAS THAT JUST SAID THERE'S A STOPLIGHT THERE. YOU SHOULDN'T DO THIS, YOU SHOULDN'T DO THAT. IT'S BASED ON WELL-REASONED IDEAS FROM PREVIOUS COMMITTEES LIKE THE NAS.

BUT THE IDEA THAT YOU SET OUT PRINCIPLES AND PROCESSES THAT ARE ACCEPTABLE AND THEN LET THE INSTITUTIONS WITH THE INVESTIGATORS THEN DO THEIR WORK THAT THEY'RE USED TO DOING AND ARE WELL VERSED IN DOING I THINK IS AN APPROPRIATE PROCESS THAT WILL RESULT IN RESPECT FOR THE PROCESS BY THE INVESTIGATORS, THE AGENCY, AND THE PUBLIC AND WILL

ALLOW THE RESEARCH TO MOVE FORWARD IN A WAY THAT'S APPROPRIATE.

DR. LOMAX: STEVE, JUST A QUICK QUESTION. THANK YOU FOR THAT. AND I THINK THAT'S ALWAYS -- THAT, AGAIN, GOES BACK TO THE FUNDAMENTAL FRAMING OF WHAT WAS CREATED MANY YEARS AGO. IS THERE ANYTHING IN THE BULLET POINT CALLED OUT NOTWITHSTANDING, WHICH I THINK GRACE HAS ALREADY ADDRESSED, IS THERE ANYTHING WITHIN THAT SORT GUIDANCE THAT WOULD IMPOSE SORT OF RIGIDITY OR LIMITATIONS THAT YOU SEE? DOES THE GUIDANCE SORT OF CAPTURE THE SPIRIT OF WHAT YOU'RE DESCRIBING?

DR. PECKMAN: IS IT POSSIBLE FOR YOU TO PUT THAT GUIDANCE ON THE SCREEN?

DR. LOMAX: SURE.

CO-CHAIRMAN KAHN: THE DRAFT GUIDANCE, I COULD PROBABLY DO IT.

DR. LOMAX: SURE. I THINK --

CO-CHAIRMAN KAHN: I THINK THIS IS THE ONE YOU MEAN.

DR. PECKMAN: IT'S KIND OF HARD FOR ME TO DEAL WITH THE ABSTRACTION OF IT.

DR. LOMAX: I THINK YOU WANT TO GO DOWN TO THE LAST FULL PARAGRAPH THERE.

DR. ROSSANT: THE PROHIBITION ON THE NEXT

PAGE, MAKE THAT SPECIFIC. THAT'S ALREADY IN THE GUIDELINES FOR GENETICALLY MODIFIED. ADD NO EMBRYO MODEL SHOULD BE TRANSFERRED TO THE UTERUS OF A HUMAN OR ANIMAL AS PER ISSCR GUIDELINES.

CO-CHAIRMAN KAHN: IT SAYS HERE IF CIRM DOES NOT CONSIDER INTEGRATED EMBRYO MODELS TO BE EQUIVALENT, THE RULES SHOULD BE APPLIED. YOU'RE SUGGESTING IT SHOULD BE -- GOT IT.

DR. PECKMAN: SO I THINK THE POINT IN THE MAIN PARAGRAPH THERE, PROTOCOLS INVOLVING INTEGRATED EMBRYO MODELS BE SUBJECT TO FULL HEIGHTENED SCRO REVIEW AND OVERSIGHT. THAT'S WHAT WE IMPLEMENTED. I THINK THAT'S WHAT CALTECH AND HARVARD IMPLEMENTED.

AS JANET SAID, I FORESEE A TIME WHERE THIS KIND PF BASIC RESEARCH I THINK IS NOT GOING TO BE SO SENSITIVE. THE SCIENCE IS GOING TO MOVE FORWARD. WE'RE LIKELY GOING TO GET TO A FULL EMBRYO. SO THERE HAS TO BE A WAY TO BE ABLE TO GO BACK AND LOOSEN THIS A BIT AS THE SCIENCE DEVELOPS AND AS WE BECOME MORE COMFORTABLE WITH DIFFERENT LEVELS OF WORK IN THIS AREA.

SO, FOR EXAMPLE, I THINK WHEN THE RULES WERE FIRST WRITTEN, THERE WAS NO ABILITY TO DO EXPEDITED REVIEW BECAUSE IT'S JUST REVIEWED BY A MEMBER OF THE COMMITTEE AND THEN APPROVED THAT WAY,

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IF APPROPRIATE. BUT WE ALL REALIZED AFTER A SHORT PERIOD OF TIME OUR COMMITTEES BECAME VERY COMFORTABLE WITH STEM CELL RESEARCH WRIT LARGE AND NOT EVERYTHING NEEDED TO BE REVIEWED BY A CONVENED COMMITTEE.

SO I WOULD JUST BE CONCERNED ABOUT THIS POINT NO. 1 HERE, THAT AT LEAST WE HAVE A METHOD OR A PROCESS TO COME BACK AND LOOSEN THAT REQUIREMENT AS THE SCIENCE DEVELOPS AND WARRANTS IT.

DR. ROSSANT: I THINK THAT'S A GOOD SUGGESTION. BECAUSE HE'S NOT HERE, I FEEL OBLIGED TO QUOTE HIM. ENSUE YESTERDAY IN THE ETHICS SESSION ACTUALLY WENT FURTHER. WE SAID WE SHOULD MOVE ALL OF IT INTO WHAT IN ISSCR PARLANCE WOULD BE CATEGORY ONE, WHICH IS YOUR EXPEDITED REVIEW, BECAUSE WHY SHOULD WE RESTRICT WHAT'S GOING ON.

I THINK WE ALL KNOW THE REASONS WHY WE WANT TO LOOK AT IT CAREFULLY NOW BECAUSE IT IS NEW, IT IS SENSITIVE. I THINK IT IS SORT OF THIS SENSITIVITY OF THE RESEARCH, BUT I AGREE OVER TIME THAT WILL CHANGE FOR SURE. SO YOU MIGHT WANT TO ADD IN SOMETHING, THIS MAY BE RECONSIDERED AS SCIENCE PROCEEDS OR SOMETHING LIKE THAT.

DR. LOMAX: WE CERTAINLY HAVE THE PROCESS TO DO THAT. I THINK TO THE EXTENT WE WANT TO

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INCLUDE SOMETHING MORE EXPLICIT, AGAIN, I CAN TAKE THAT BACK TO OUR TEAM AND SEE IF THERE'S A WAY WE WANT TO SORT OF SIGNAL THAT JUST AS AN INTENT, SOMETHING WITH REGARDS TO SUBJECT TO REEVALUATION OR SOMETHING. AT THE MOMENT THERE'S NO REASON WE COULDN'T DO THAT.

SO EVEN ABSENT A STATEMENT LIKE THAT, STEVE, WHAT YOU ARE SUGGESTING IS WITHIN OUR -- WE CAN DO THAT. I THINK POINT TAKEN. I THINK JUST THE FACT -- AGAIN, JUST IN TERMS OF HOW THESE POLICY DEVELOPMENT -- HOW POLICY DEVELOPMENTS WORKS, THE FACT THAT -- TO THE EXTENT I THINK WE SHOULD GET A SENSE OF THE COMMITTEE; BUT IF THAT'S THE SENSE OF THIS COMMITTEE, SIMPLY HAVING THAT POINT ESTABLISHED IN THIS MEETING RECORD GIVES US SOMETHING TO HANG OUR HAT ON, SO TO SPEAK, WITHOUT HAVING TO TWIST INTO KNOTS IN TERMS OF HOW WRITE IT OUT IN SENTENCES. AND, AGAIN, THAT'S JUST HOW POLICYMAKING WORKS. YOU GO BACK TO THE RECORD AND YOU LOOK AT WHAT THE SUPPORTING CONVERSATION WAS ABOUT.

SO, JEFF, I WOULD PERHAPS MAYBE SAY WE SHOULD GET SOME SENSE OF THE COMMITTEE ABOUT THAT POINT AND THE REMOVAL OF THE BULLET, THAT FIRST BULLET, BECAUSE THAT'S A POINT OF PUBLIC RECORD AT THE MOMENT.

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CO-CHAIRMAN KAHN: WHAT DO YOU MEAN? WHICH IS THE FIRST BULLET IN THE WAY YOU'RE JUST REFERRING TO?

DR. LOMAX: SORRY. I'M PUTTING MY TECHNOCRAT HAT ON. I THINK WE SHOULD -- WE DON'T HAVE A QUORUM ON THIS CALL, BUT JUST ASK THE COMMITTEE MEMBERS TO GET A SENSE OF THE COMMITTEE IF THERE'S CONSENSUS OR THEY AGREE WITH THE POINT THAT THIS PARTICULAR -- THE ELEVATING OF THIS TO WHAT WE'RE CALLING FULL REVIEW AND OVERSIGHT SHOULD BE SUBJECT TO REEVALUATION AS THE SCIENCE DEVELOPS, AND THAT WE SHOULDN'T RESTRICT THE INTRODUCTION OF STEM CELLS INTO THESE MODELS. THOSE ARE THE TWO, I THINK, POINTS THAT WE SHOULD HAVE CLARITY ON BEFORE WE CLOSE THE MEETING.

CO-CHAIRMAN KAHN: OKAY.

MR. TOCHER: GEOFF, CAN YOU HEAR ME? THIS IS SCOTT.

DR. LOMAX: THANK YOU, SCOTT. APPRECIATE YOU CHIMING IN. I FELT LIKE I WAS TREADING ON YOUR TERRITORY.

MR. TOCHER: NOT AT ALL. YOU'RE DOING GREAT.

I WOULD JUST SUGGEST, IN THE ABSENCE OF A QUORUM, AND YOU DON'T NEED TO GO THROUGH FORMAL

MOTIONS, JUST ASK THE GROUP IF THERE'S ANY OBJECTIONS TO MAKING THOSE ADJUSTMENTS TO THE LANGUAGE. AND YOU CAN FERRET IT OUT THAT WAY, AND THAT WILL ESTABLISH THE RECORD YOU NEED.

DR. LOMAX: GREAT. THANKS MUCH. SCOTT, CAN YOU JUST GIVE A TWO-SENTENCE INTRODUCTION? I DON'T KNOW IF THE GROUP KNOWS YOU.

CO-CHAIRMAN KAHN: PEOPLE NEED TO KNOW WHO YOU ARE, SCOTT.

MR. TOCHER: SORRY. THIS IS SCOTT TOCHER. I'M THE FORMER GENERAL COUNSEL AND CURRENTLY A MEMBER OF THE LEGAL TEAM AND DIRECTOR OF BOARD GOVERNANCE AT CIRM.

CO-CHAIRMAN KAHN: SO LET'S BE REALLY CLEAR ABOUT WHAT WE'RE ASKING PEOPLE TO EITHER OBJECT TO OR SAY IT'S FINE. I'M NOT SURE I HUNDRED PERCENT KNOW MYSELF. SO CAN YOU REALLY IN AS FEW WORDS AS POSSIBLE TELL US WHAT THE CHANGES TO THIS WOULD BE TO WHAT WE'RE LOOKING AT?

DR. LOMAX: MAYBE I'LL TRY TO TAKE A STAB. AGAIN, THE SPECIFIC POINT WOULD BE TO STRIKE THE FIRST BULLET HERE THAT YOU SEE --

CO-CHAIRMAN KAHN: IT'S NO. 1.

DR. LOMAX: NO, NOT NO. 1 THE ACTUAL BULLET POINT HERE.

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CO-CHAIRMAN KAHN: THIS?

DR. LOMAX: CORRECT. THANK YOU. SO WE WOULD STRIKE THAT BULLET FROM THE GUIDANCE AND NOTE THAT THE REQUIREMENT THAT INTEGRATED EMBRYO MODELS BE SUBJECT TO FULL REVIEW AND OVERSIGHT, THAT THAT REQUIREMENT BE REEVALUATED AS THE SCIENCE PROGRESSES WITH, AGAIN, THE NOTION BEING THAT IT COULD MOVE FROM FULL REVIEW AND OVERSIGHT TO ADMINISTRATIVE REVIEW AT SOME POINT IN THE FUTURE.

CO-CHAIRMAN KAHN: AND THE SECOND BULLET IS ALSO SORT OF INACCURATE FOR THIS PURPOSE. THIS ONE.

DR. LOMAX: I THINK THE SECOND BULLET IS -- AGAIN, THIS TRACKS WITH THE CONSENSUS THAT YOU WOULD NEVER WANT TO TRANSFER ONE OF THESE CONSTRUCTS TO A UTERUS FOR ANY KIND OF REPRODUCTIVE INTENT.

CO-CHAIRMAN KAHN: EXCEPT THAT THE LANGUAGE ISN'T ABOUT ONE OF THESE CONSTRUCTS.

DR. LOMAX: AGAIN, SCOTT, IF YOU WANT OFFER AN OPINION HERE. AGAIN, BECAUSE SORT OF SIMILAR TO THAT POINT I RAISED BEFORE, WE'RE KIND OF BORROWING FROM OUR EXISTING REGULATIONS. WE'RE TRYING TO AVOID OPENING UP THAT PROCESS. SO THE SENTENCE BELOW IS RECOMMENDING OR PROVIDING THE GUIDANCE THAT THAT STANDARD BE APPLIED TO THESE

EMBRYO MODELS.

CO-CHAIRMAN KAHN: MAYBE WE SWITCH THE ORDER. THAT MIGHT ACTUALLY HELP. JUST MOVE THIS PARAGRAPH, THE ONE ABOUT, AS YOU SAID, TREAT THESE -- IN THE SAME WAY THAT WE WOULD TREAT INTRODUCTION OF MODIFIED HUMAN EMBRYOS, PUT IT UP HERE RATHER THAN AFTER. JUST MIGHT BE EASIER TO READ IN THE FLOW.

DR. LOMAX: SURE. SURE. HAPPY TO. WE HAVE SOME --

CO-CHAIRMAN KAHN: SOME HANDS, BUT I ALSO WANT TO MAKE SURE WE GET TO THE MEMBERS OF THE COMMITTEE TO ANSWER THE QUESTION THAT YOU'VE ASKED. GO AHEAD, STEVE.

DR. PECKMAN: I'M JUST GOING TO PUT ON GEOFF'S TECHNOCRAT HAT. AND IN THE SENTENCE THAT TALKS ABOUT FULL HEIGHTENED SCRO REVIEW, I'LL REMIND YOU THAT IT'S ACTUALLY CONVENED SCRO REVIEW BECAUSE EVEN EXPEDITED REVIEW IS A FULL REVIEW.

CO-CHAIRMAN KAHN: THAT'S A FRIENDLY AMENDMENT TO THIS SENTENCE.

DR. LOMAX: YEAH.

CO-CHAIRMAN FISHER: WOULD IT BE USEFUL TO SEE A REDLINE VERSION TRACKING THE CHANGES?

CO-CHAIRMAN KAHN: BUT IT'S A PDF, SO IT'S

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NOT POSSIBLE.

DR. LOMAX: WHAT WE CAN DO, FRED, WE TYPICALLY WOULD DO A REDLINE AND THEN CIRCULATE BACK TO THE CO-CHAIRS. SO AS PART OF THE RESOLUTION, THAT THE COMMITTEE WOULD BE COMFORTABLE DELEGATING THE FINAL DETAILS TO THE CO-CHAIRS.

CO-CHAIRMAN FISHER: I CAN LIVE WITH THAT.

CO-CHAIRMAN KAHN: MAYBE I'LL STOP SHARING FOR A MOMENT SO WE CAN SEE EVERYBODY. IS THERE ANY MEMBERS OF THE WORKING GROUP THAT OBJECT TO THE DIRECTION THIS IS GOING? I THINK THAT'S WHAT GEOFF IS ASKING US FOR. DON'T SEE ANY HANDS.

DR. SAHA: I DON'T HAVE SO MUCH OF AN OBJECTION, BUT WOULD LIKE TO HAVE A BROADER DISCUSSION OF THE COMMITTEE ABOUT THE REDLINE VERSION IN FRONT OF US.

DR. LOMAX: YEAH. SCOTT, I THINK WOULD THE APPROPRIATE PROCESS THEN BE TO DO A REDLINE AND WE JUST SORT OF POST IT AS A PUBLIC DOCUMENT? SO IF THE ENTIRE COMMITTEE WANTED TO REVIEW IT, WOULD THAT BE THE APPROPRIATE PROCEDURE?

MR. TOCHER: YEAH. BAGLEY-KEENE IS SORT OF OUR GUIDING, BUT NOT LEGALLY REQUIRED PARAMETERS THAT WE TRY TO OPERATE THESE MEETINGS UNDER. SO I THINK SINCE THIS WOULD BE SOMETHING THAT PRESUMABLY

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WOULD BE COMING BACK TO THE BOARD AS AN UPDATE OR DISCUSSION ITEM, I THINK CIRCULATING THIS IN ORDER TO GET A REDLINE VERSION THAT'S ACCEPTABLE OUTSIDE OF THE CONTEXT OF THIS MEETING WOULD BE JUST FINE.

DR. LOMAX: THANK YOU. SO WE WILL DO THAT, KRIS. WE WILL MAKE IT GENERALLY AVAILABLE.

DR. SAHA: I MENTION IT BECAUSE I THINK INTENT AND PUBLIC TRUST ARE AT STAKE HERE BY CHANGING ACTUALLY TWO MAJOR BULLET POINTS. SO JUST WANT TO MAKE SURE THAT THE COMMITTEE HAS A CHANCE TO LOOK THROUGH EXACTLY WHAT'S BEING PROPOSED HERE.

CO-CHAIRMAN KAHN: I DON'T THINK THIS IS SUCH MAJOR SURGERY, BUT I AGREE WE NEED TO SEE IT IN WRITING. I THINK THE WAY WE LEFT THE POINT ABOUT HEIGHTENED REVIEW IS TO LEAVE IT AS IS, BUT WITH THE UNDERSTANDING THAT THERE'S FLEXIBILITY TO COME BACK AND ALTER THAT AS THE SCIENCE EVOLVES WITHOUT ADDING ANY WORDS TO THE GUIDANCE. IS THAT RIGHT, GEOFF?

DR. LOMAX: YEAH. I BELIEVE THAT'S CORRECT. AGAIN, THIS CONVERSATION IN ITSELF IS SUBSTANTIVE FROM THE STANDPOINT OF REINFORCING THAT POINT. THERE'S NOTHING THAT PRECLUDES US FROM DOING THAT. AGAIN, KIND OF A BUREAUCRATIC ANSWER, BUT IT'S A LONGWINDED WAY OF SAYING YES.

CO-CHAIRMAN FISHER: IT MIGHT BE HELPFUL

WHEN YOU CIRCULATE THAT REDLINE, THAT YOU PROVIDE A BRIEF DESCRIPTION OF THE CONTEXT FOR THE REASON WE'RE MAKING THESE CHANGES. THAT CREATES A FULL PICTURE FOR EVERYONE TO BE ABLE TO CONSIDER THEM.

DR. LOMAX: NOTED.

CO-CHAIRMAN FISHER: THERE ARE SIMPLE MINDS LIKE MINE THAT CAN'T NECESSARILY FOLLOW THE IN AND OUTS OF THE CONVERSATION.

CO-CHAIRMAN KAHN: I THINK YOU'RE NOT ALONE, FRED.

CO-CHAIRMAN FISHER: GOOD. APPRECIATE THAT.

CO-CHAIRMAN KAHN: ANYONE ELSE HAVE A THOUGHT THEY WANT TO SHARE? ANYONE IN THE ROOM? I CAN'T TELL WHAT'S GOING ON ON YOUR SIDE THERE, GEOFF.

DR. LOMAX: I THINK THE LAST PROCEDURAL THING, AGAIN, TO ASK IF THERE'S ANY PUBLIC COMMENT. I'M LOOKING AT THE BACK. I DON'T BELIEVE THERE'S ANYONE ON THE PHONE LINE. ANYONE IN THE ROOM WITH COMMENTS? NOTHING AT OUR END. I THINK WE'VE BEEN ABLE TO GET THROUGH AND GET SOME VERY PRODUCTIVE RECOMMENDATIONS.

CO-CHAIRMAN KAHN: VERY EFFICIENT GROUP. OKAY.

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DR. LOMAX: TRYING TO THINK ARE THERE ANY FORMAL CLOSING THINGS WE NEED TO DO, SCOTT? I SORT OF FORGET.

MR. TOCHER: NO. YOU ARE DOING A GREAT JOB SO FAR. YOU DON'T NEED TO DO A FORMAL MOTION. JUST ADJOURN WHEN READY.

DR. LOMAX: OKAY. WELL, GEOFF, I'LL LEAVE IT TO YOU TO ADJOURN THE MEETING AS THE CO-CHAIR.

CO-CHAIRMAN KAHN: FRED, YOU AND I, I THINK, HAVE TO DO THIS TOGETHER. SO I THINK WE'RE FORMALLY ADJOURNED. THANK YOU ALL FOR JOINING, PARTICIPATING, AND LOOK FORWARD TO THE NEXT TIME WE MEET.

CO-CHAIRMAN FISHER: ABSOLUTELY. AMAZING GROUP OF PEOPLE. IT'S REALLY GOING TO HELP US MOVE FORWARD. SO APPRECIATE EVERYONE LENDING THEIR TIME TO THIS.

CO-CHAIRMAN KAHN: HOW'S THE WEATHER THERE, BY THE WAY? I DIDN'T ASK YOU THAT.

CO-CHAIRMAN FISHER: I WAS WONDERING THE EXACT SAME THING, LIKE PEOPLE ARE GOING TO GET LIKE AN HOUR AND A HALF EXTRA TIME TO ENJOY THE SURROUNDS UNLESS IT'S POURING RAIN UP THERE.

DR. LOMAX: IT'S BRIGHT AND SUNNY. YOU'RE EXPOSING OUR ULTERIOR MOTIVE HERE.

CO-CHAIRMAN KAHN: ENJOY.

VICE CHAIR BONNEVILLE: THANK YOU, EVERYONE.

(THE MEETING WAS THEN CONCLUDED AT 10:26 A.M.)

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REPORTER'S CERTIFICATE

I, BETH C. DRAIN, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT OF THE VIRTUAL PROCEEDINGS BEFORE THE SCIENTIFIC AND MEDICAL ACCOUNTABILITY STANDARDS WORKING GROUP OF THE INDEPENDENT CITIZEN'S OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD ON FEBRUARY 9, 2024, WAS HELD AS HEREIN APPEARS AND THAT THIS IS THE ORIGINAL TRANSCRIPT THEREOF AND THAT THE STATEMENTS THAT APPEAR IN THIS TRANSCRIPT WERE REPORTED STENOGRAPHICALLY BY ME AND TRANSCRIBED BY ME. I ALSO CERTIFY THAT THIS TRANSCRIPT IS A TRUE AND ACCURATE RECORD OF THE PROCEEDING.

BETH C. DRAIN, CA CSR 7152
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