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: SHERATON GATEWAY LOS ANGELES
6101 WEST CENTURY BOULEVARD
LOS ANGELES, CALIFORNIA

DATE: FEBRUARY 4, 2016
8:30 A.M.

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

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I N D E X

LOS ANGELES, CALIFORNIA; THURSDAY, FEBRUARY 4, 2016

8:30 A.M.

CO-CHAIR LANSING: WELL, IT'S 8:33. WE'RE GOING TO START IN RESPECT FOR EFFICIENCY AND EVERYBODY'S TIME. SO MY NAME IS SHERRY LANSING, AND I'D LIKE TO WELCOME EVERYONE TO THE 2016 ANNUAL MEETING OF THE CIRM STANDARDS WORKING GROUP. ON BEHALF OF THE CIRM BOARD, WE THANK YOU FOR YOUR WILLINGNESS TO TAKE TIME OUT OF YOUR BUSY SCHEDULES TO PROVIDE INSIGHTS AND GUIDANCE ON THE IMPORTANT SCIENCE POLICY QUESTIONS THAT WE CONTINUALLY ADDRESS.

TODAY'S MEETING IS A WORKSHOP WHERE WE WILL CONSIDER THE USE OF POWERFUL NEW TECHNOLOGIES THAT ALLOW SCIENTISTS TO EDIT THE HUMAN GENOME. THE CRISPR GENE EDITING TECHNOLOGY WAS RECENTLY DESCRIBED BY THE JOURNAL *NATURE* AS THE BIGGEST GAME CHANGER TO HIT BIOLOGY IN DECADES.

I HAVE TO SAY ON A PERSONAL LEVEL, WHEN I WAS IN THE MOVIE BUSINESS, WE USED TO DREAM ABOUT THINGS LIKE THIS, AND WE USED TO TALK ABOUT PUTTING THEM IN MOVIES. AND THEN EVERYBODY SAID, "NO. NO. NO. NOBODY WILL BELIEVE THAT. THAT'S TOO FARFETCHED." SO IT'S NO LONGER FARFETCHED. IT'S

THE REALITY.

GENE EDITING TECHNOLOGIES ARE ALREADY HELPING SCIENTISTS ADVANCE CIRM'S MISSION OF ACCELERATING STEM CELL TREATMENTS FOR PATIENTS. FOR EXAMPLE, THE CRISPR TECHNOLOGY OFFERS THE POTENTIAL FOR SCIENTISTS TO CORRECT DAMAGED GENES AND STEM CELLS DERIVED FROM PATIENTS, THUS OPENING THE DOOR FOR PERSONALIZED, PRECISION MEDICINE. AS WE WILL HEAR FROM DR. DAVID BALTIMORE, A RECENT INTERNATIONAL SUMMIT HIGHLIGHTED THE MYRIAD OF BENEFICIAL USAGE OF THIS TECHNOLOGY IN SCIENCE AND MEDICINE. HOWEVER, LEADERS IN SCIENCE AND MEDICINE AS WELL AS SOCIAL SCIENTISTS, POLICYMAKERS, AND THE PUBLIC HAVE EXPRESSED CONCERNS OVER SOME USES OF GENE EDITING TECHNOLOGIES. THE EDITING OF HUMAN GAMETES AND EMBRYOS HAS EMERGED AS A CENTRAL CONCERN.

BECAUSE CIRM WILL BE ASKED TO CONTINUE TO SUPPORT RESEARCH INVOLVING GENOME EDITING, WE TAKE THESE CONCERNS VERY SERIOUSLY, AND WE WANT TO ENSURE IN CIRM THAT ALL THE RESEARCH THAT WE FUND IS CONDUCTED UNDER THE HIGHEST STANDARDS.

SO OUR OBJECTIVE TODAY IS TO CONSIDER THE USE OF GENOME EDITING TECHNOLOGY IN THE CONTEXT OF RESEARCH FUNDED BY CIRM. INTERESTINGLY, ALMOST TEN

YEARS AGO, AND SOME OF YOU WERE HERE AT THAT TIME, THE STANDARDS WORKING GROUP CONSIDERED AND ESTABLISHED POLICIES REGARDING THE GENETIC MODIFICATION OF HUMAN EMBRYOS. AS THE RECORD INDICATES, THESE POLICIES WERE SHAPED BY ROBUST DISCUSSIONS INVOLVING THE WORKING GROUP AND THE PUBLIC. TODAY THE SWG, IN PARTNERSHIP WITH INTERNATIONAL EXPERTS AND THE PUBLIC, HAVE THE OPPORTUNITY TO REVISIT SOME OF OUR PAST THINKING IN LIGHT OF RECENT CHANGES IN SCIENCE AND TECHNOLOGY.

THIS WORKSHOP REFLECTS OUR ONGOING COMMITMENT TO ENSURING HIGH STANDARDS FOR RESEARCH AND THE USE OF CIRM FUNDS. AND I THINK, AS ALL OF YOU REMEMBER, FROM THE VERY BEGINNING WE SAID THAT WE WERE A WORK IN PROGRESS. AND THE SCIENCE HAS PROCEEDED FASTER, I THINK, THAN ANY OF US IMAGINED. AND AS WE ARE A WORK IN PROGRESS, WE ARE CONSIDERING, CONSTANTLY CONSIDERING, AND REEVALUATING OUR PAST POLICIES, RETHINKING AND KEEPING UP WITH THE CURRENT ADVANCES.

I'D ALSO LIKE TO RECOGNIZE THE EXTRAORDINARY CONTRIBUTION OF MY FELLOW BOARD MEMBER JEFF SHEEHY. JEFF WAS INSTRUMENTAL IN BOTH THE INITIATION AND THE PLANNING OF THIS MEETING. BEFORE WE TURN THINGS OVER TO JEFF, IT'S MY PLEASURE TO

INTRODUCE YOU TO MY ESTEEMED COLLEAGUE AND THE CO-CHAIR OF THE STANDARDS WORKING GROUP AND THE PERSON I ADORE, BERNIE LO.

CO-CHAIR LO: THANK YOU VERY MUCH, SHERRY. I WANT TO SECOND SHERRY'S WARM WELCOME AND OUR THANKS TO THE MEMBERS OF THE STANDARDS WORKING GROUP, OUR DISTINGUISHED INVITED SPEAKERS, AND MEMBERS OF THE PUBLIC WHO ARE ALSO ATTENDING.

I WANT TO AMPLIFY SOME OF SHERRY'S REMARKS. AS SHE SAID, OUR CHARGE TODAY IS TO REVIEW CIRM'S POLICIES REGARDING GENE EDITING IN LIGHT OF THE NEW CRISPR-CAS9 TECHNOLOGY. AS WE WILL HEAR IN DETAIL LATER, WE WANT TO CAREFULLY DISTINGUISH BETWEEN, ON THE ONE HAND, GENE EDITING OF HUMAN SOMATIC CELLS AND, ON THE OTHER HAND, GENE EDITING OF HUMAN GAMETES AND EMBRYOS. AND WITHIN GAMETES AND EMBRYOS, WE ALSO WANT TO CAREFULLY DISTINGUISH BETWEEN IN VITRO PRECLINICAL LABORATORY WORK AND CLINICAL RESEARCH. THE LATTER IS OUR FOCUS TODAY, THE CLINICAL RESEARCH WITH GAMETES AND EMBRYOS.

FOR CIRM THERE ARE TWO VERY PRACTICAL ISSUES WE HAVE TO ADDRESS. FIRST, SHOULD CIRM FUND RESEARCH USING GENE EDITING OF HUMAN GAMETES AND EMBRYOS? SECOND, IF SO, ARE THE CURRENT CIRM REGULATIONS AND POLICIES SUFFICIENT TO PROVIDE

ROBUST OVERSIGHT AND PROTECTION FOR THE MANY ETHICAL AND SOCIAL CONCERNS THAT SUCH RESEARCH RAISES?

SHERRY SAID THAT CIRM AND THE SWG HAVE AN ONGOING COMMITMENT TO MAKING SURE THAT CUTTING EDGE CIRM-FUNDED RESEARCH IS CONDUCTED UNDER THE HIGHEST ETHICAL STANDARDS. AND WE TRY AND KEEP ABREAST OF BOTH SCIENTIFIC DEVELOPMENTS AND DEVELOPMENTS IN ETHICS AND POLICY. THESE DEVELOPMENTS OCCUR VERY QUICKLY. JUST THIS WEEK THE UK APPROVED ITS FIRST RESEARCH STUDY INVOLVING THE EDITING OF HUMAN EMBRYOS FOR RESEARCH. AND YESTERDAY THE NATIONAL ACADEMIES OF SCIENCE ISSUED A COMPREHENSIVE REPORT ON "MITOCHONDRIAL REPLACEMENT TECHNIQUES: ETHICAL, SOCIAL, AND POLICY CONSIDERATIONS." WE OBVIOUSLY HAVE NOT HAD THE TIME TO STUDY IN DEPTH THESE RECENT DEVELOPMENTS AND TO LEARN ABOUT THE UNDERLYING SCIENCE. SO TODAY IS OUR NEXT STEP IN OUR ONGOING COMMITMENT TO KEEP CIRM STANDARDS AS RIGOROUS AND AS HIGH AS POSSIBLE.

BEFORE MOVING ON WITH THE EXCITING PROGRAM THAT GEOFF LOMAX AND STAFF HAVE PLANNED, I WANT TO MAKE A PUBLIC DISCLOSURE IN THE SPIRIT OF TRANSPARENCY. ALTA CHARO WILL BE DESCRIBING TO YOU AN ONGOING NATIONAL ACADEMY OF MEDICINE STUDY ON "HUMAN GENE EDITING: SCIENTIFIC, MEDICAL, AND

ETHICAL CONSIDERATIONS." THE GREENWALD FOUNDATION, WHICH I HEAD, IS ONE OF THE SPONSORS OF THIS PRODUCT, SO I WANT TO MAKE THAT DISCLOSURE. OUR FOUNDATION IS COMMITTED TO HELPING TO ADDRESS THE ETHICAL AND POLICY CONCERNS RAISED BY INNOVATIVE BIOMEDICAL RESEARCH. WE PLAYED NO ROLE IN THE SELECTION OF THE COMMITTEE AND WILL PLAY NO ROLE IN THEIR DELIBERATIONS OR OBVIOUSLY IN THEIR CONCLUSIONS.

SO WITH THAT, I THANK YOU AND PASS THE MICROPHONE TO MY ESTEEMED COLLEAGUE AND FRIEND JEFF SHEEHY.

MR. SHEEHY: THANK YOU, BERNIE. AND THANK YOU, SHERRY, FOR THOSE KIND WORDS.

I WANT TO THANK ALL THE EXPERTS THAT HAVE COME HERE TODAY AND THE STANDARDS WORKING GROUP FOR TAKING UP THIS ISSUE AND THE CIRM TEAM FOR PUTTING TOGETHER THIS FABULOUS MEETING AND GEOFF LOMAX WHO'S BEEN LEADING THAT EFFORT.

THIS IS IMPORTANT FOR CIRM BECAUSE WE REALLY HAVE, OUT OF FUNDING AGENCIES, I THINK, IN THE UNITED STATES, THE MOST FLEXIBILITY AND FREEDOM TO FUND SCIENCE ON THE EDGES OF THE FRONTIER IN MEDICINE THAT WE'RE CURRENTLY EXPLORING. AND SOME OF THE EXPERIMENTS THAT HAVE CAUSED A GREAT DEAL OF

CONTROVERSY IN THE MEDIA, THE CHINESE EXPERIMENTS, THE RECENT UK DECISION, THOSE ARE POSSIBLE FOR US TO FUND CURRENTLY. WHEN WE MADE OUR RULES TEN YEARS AGO, AND IT WAS INTERESTING TO SEE THE DELIBERATIONS OF THIS COMMITTEE LOOKING AT THE TRANSCRIPT, WE DIDN'T REALLY REALIZE THE IMPACT OF THE RULES THAT WE WERE MAKING BECAUSE THE SCIENCE HAD NOT PROCEEDED TO THAT POINT. WE HAVE THE ABILITY TO FUND SCIENCE THAT THE NATIONAL INSTITUTES OF HEALTH CAN'T.

AND SO FOR ME THIS IS NOT THE OPPORTUNITY TO REALLY ADDRESS SYSTEMATICALLY THE FUNDAMENTAL ETHICAL QUESTIONS THAT THE NATIONAL ACADEMY OF SCIENCES IS GOING TO TAKE UP. FOR ME THIS IS ABOUT SETTING PRACTICAL RULES THAT ALLOW US TO BE RESPONSIBLE IN OUR FUNDING DECISIONS BECAUSE WE DO HAVE, VIA THE MANDATE OF THE VOTERS OF CALIFORNIA, A GREAT DEAL OF FLEXIBILITY IN WHAT WE FUND. I ALSO THINK IT'S IMPORTANT, AND TO REITERATE SHERRY AND BERNIE'S POINTS, THAT THERE IS A DISTINCTION BETWEEN THE GENETIC MODIFICATION OF ADULT CELLS AND PERMANENT MODIFICATION OF THE HUMAN GERMLINE.

WE'RE FUNDING EXCITING PROJECTS. OTHER PEOPLE ARE PRODUCING PRODUCTS THAT ARE INCREDIBLY EXCITING WHERE IMMUNE CELLS ARE BEING GENE MODIFIED TO FIGHT CANCER AND PEOPLE ARE BEING CURED. WE HAVE

DONALD KOHN AT UCLA WHO HAS CURED KIDS OF SEVERE COMBINED IMMUNODEFICIENCY USING GENE MODIFICATION TECHNIQUES. NONE OF THESE POSE A THREAT TO THE HUMAN GERMLINE.

AND SO THAT DISTINCTION I THINK WE HAVE TO BE VERY CLEAR WHEN WE'RE TALKING TO THE PUBLIC. I'VE TALKED TO PEOPLE WHO ARE VERY KNOWLEDGEABLE, AND THEY BELIEVE THAT THIS CRISPR-CAS9 TECHNOLOGY, WHICH HAS CREATED THESE CONCERNS WITH THE FUNDAMENTAL ALTERING OF REALLY WHAT THE HUMAN GENOME LOOKS LIKE, AND CONFUSED THAT WITH SOME OF THE GENE MODIFICATION THERAPIES THAT ARE BEING DEVELOPED RIGHT NOW THAT ARE REALLY IMPORTANT AND REALLY VALUABLE FOR HELPING PEOPLE ACHIEVE CURES IN TERRIBLE DISEASES.

SO, AGAIN, I THINK THIS IS AN IMPORTANT MEETING. I WANT TO THANK EVERYBODY AGAIN FOR BEING HERE TODAY. AND I LOOK FORWARD TO THE DISCUSSION.

CO-CHAIR LANSING: WITH THAT SAID, THANK YOU, JEFF, BECAUSE YOU ARE SUCH AN IMPORTANT DRIVER OF THIS. AND, AGAIN, I ALSO WANT TO THANK AGAIN EVERYBODY WHO'S HERE.

BUT NOW WE'RE GOING TO GET THE MEETING STARTED, AND IT IS MY PLEASURE AND MY DISTINCT HONOR TO INTRODUCE ALL OF YOU TO SOMEONE I KNOW YOU

ALREADY KNOW AND CERTAINLY KNOW OF DAVID BALTIMORE.

DAVID IS THE 1975 NOBEL LAUREATE FOR HIS DISCOVERIES CONCERNING THE INTERACTION BETWEEN TUMOR VIRUSES AND THE GENETIC MATERIAL OF THE CELL. HE SERVED AS PRESIDENT OF THE CALIFORNIA INSTITUTE OF TECHNOLOGY FROM 1997 TO 2006 AND IS CURRENTLY THE PRESIDENT EMERITUS AND ROBERT ANDREWS MILKEN PROFESSOR OF BIOLOGY AT CALTECH.

IN ADDITION TO THE NOBEL PRIZE, DR. BALTIMORE HAS RECEIVED NUMEROUS AWARDS, INCLUDING THE UNITED STATES NATIONAL MEDAL OF SCIENCE IN 1999. HE HAS PROFOUNDLY INFLUENCED INTERNATIONAL SCIENCE, INCLUDING KEY CONTRIBUTIONS TO IMMUNOLOGY, VIROLOGY, CANCER RESEARCH, BIOTECHNOLOGY, AND RECOMBINANT DNA RESEARCH.

DR. BALTIMORE IS ALSO A LEADER IN SCIENCE POLICY, AND MOST RECENTLY HE CHAIRED THE INTERNATIONAL SUMMIT ON HUMAN GENE EDITING PLANNING COMMITTEE. DR. BALTIMORE HAS KINDLY AGREED TO PROVIDE A SUMMARY OF THIS IMPORTANT INTERNATIONAL MEETING.

AND I JUST WANT TO SAY TO DR. BALTIMORE THAT, ON A PERSONAL LEVEL, I'M EXTRAORDINARILY GRATEFUL TO HIM BECAUSE WHEN I FIRST JOINED THIS COMMITTEE, DR. BALTIMORE WAS PART OF IT. AND NOT

HAVING A SCIENCE BACKGROUND, I HAD THE DISTINCT PLEASURE OF HAVING HIM DRAW PICTURES FOR ME AND EXPLAIN TO ME ALL SORTS OF THINGS. SO, DAVID, YOU HAVE BEEN AN INCREDIBLE INSPIRATION TO ME MY WHOLE LIFE, A TEACHER, AND I AM SO HONORED AND GRATEFUL THAT YOU ARE HERE.

DR. BALTIMORE: GOOD MORNING. IT'S DEJA VU TO BE HERE AGAIN WITH THIS DISTINGUISHED GROUP WHO HAS SUCH IMPORTANT AND DIFFICULT ISSUES IN FRONT OF IT ALL THE TIME.

THE ASILOMAR MEETING WAS HELD IN 1975 TO DISCUSS POSSIBLE DANGERS IN RECOMBINANT DNA TECHNOLOGY. THERE WERE ABOUT A HUNDRED FIFTY SCIENTISTS, MOSTLY SCIENTISTS, A FEW LAWYERS, A FEW ETHICISTS, AND REPORTERS. WE MET FOR THREE DAYS. WE FORMULATED A RESPONSE TO THE WORRY THAT PEOPLE HAD THAT RECOMBINANT DNA METHODS WERE GOING TO CREATE MONSTERS IN THE LABORATORY. AND WE SET UP A PROCESS THAT PLAYED ITSELF OUT OVER THE NEXT DECADES AND ALLOWED RECOMBINANT DNA TECHNOLOGY TO CONTRIBUTE THE ENORMOUS POWER THAT IT HAD TO MODERN BIOLOGY. AND THERE HASN'T BEEN ANOTHER ISSUE OF SUCH DRAMA UNTIL CRISPR-CAS9.

AT ASILOMAR WE PUT ASIDE THE QUESTION OF ALTERING THE DNA OF EMBRYONIC CELLS BECAUSE IT WAS

IMPOSSIBLE. AND SO WE HAD MORE IMMEDIATE CONCERNS. BUT OVER THE YEARS AFTER THAT, WE LEARNED THAT IF YOU CAN MAKE A CUT IN DNA INSIDE A CELL, YOU CAN FOCUS THE ATTENTION OF MANY DIFFERENT SYSTEMS IN THE CELL ON THAT BROKEN PIECE OF DNA. AND IN PARTICULAR THAT YOU CAN ACTIVATE RECOMBINATION MECHANISMS OR REPAIR MECHANISMS THAT CAN ALTER THE GENOME. AND SO WHAT YOU NEED TO DO IS YOU NEED TO PUT A SPECIFIC NUCLEASE INTO A CELL, INTO AN EARLY EMBRYONIC CELL, AND THAT WILL CUT DNA AT A RELEVANT PLACE.

SO IF WE DEFINE A RELEVANT PLACE, WE CAN PUT MOLECULAR SCISSORS AROUND THAT, AND THIS WAS THE FIRST FORMAT IN WHICH THAT WAS SUCCESSFULLY DONE, WHICH IS WITH A ZINC-FINGER NUCLEASE, A NUCLEASE THAT RECOGNIZES TRIPLETS OF BASES, MUCH AS THE GENETIC CODE DOES, WITH LITTLE PIECES OF PROTEIN THAT ARE DESIGNED IN THE LABORATORY. IT'S NOT A PERFECT PROCESS. IT HAS OFF-TARGET WORRIES. IT'S VERY DIFFICULT TO DO. IT WAS ACTUALLY HELD BY A SINGLE COMPANY, THE INTELLECTUAL PROPERTY FOR IT. AND BECAUSE OF THE DIFFICULTIES OF USING IT AND THE ERRORS THAT COULD COME IN, THE IDEA OF USING IT IN HUMANS TO CHANGE GERMLINE SEQUENCE WAS VERY UNLIKELY TO OCCUR.

BUT THEN TALENS WERE DISCOVERED, AND

THEY'RE A NATURAL WAY OF RECOGNIZING SEQUENCE USING LITTLE PROTEIN MODULES THAT RECOGNIZE SINGLE BASES, MUCH EASIER TO MANIPULATE, MUCH FASTER, AND THE INTELLECTUAL PROPERTY WAS MUCH MORE OPEN. SO PEOPLE SAID, WELL, THIS IS GOING TO BE IT. SO IT WAS FASTER, IT WAS BETTER, IT WAS CHEAPER, IT WAS ALL THE WONDERFUL THINGS WE WANT FOR TECHNOLOGY. BUT THERE WAS ACTUALLY A WHOLE OTHER WAY OF GOING AT THIS PROBLEM, THE PROBLEM OF RECOGNIZING SEQUENCE. AND THAT WAS NOT DOING IT WITH PROTEINS, WHICH ARE ACTUALLY FAIRLY CLUMSY AT IT; BUT RATHER, USING THE WATSON-CRICK COMPLEMENTARITY THAT HOLDS THE TWO STRANDS OF DNA TOGETHER. THAT'S A VERY POWERFUL FORCE. IT USES HYDROGEN BONDS WITH INDIVIDUALLY ARE NOT SO STRONG, BUT MULTIPLIED TOGETHER THEY GET ENORMOUS STRENGTH.

AND IF YOU COULD MAKE SOME KIND OF NUCLEIC ACID THAT WAS ABOUT 15 BASES LONG -- REMEMBER THERE ARE 3 BILLION BASE-PAIRS IN THE HUMAN GENOME. SO THAT MEANS YOU'RE RECOGNIZING A VERY, VERY RARE SITE, BUT COMBINATORICS IS SUCH THAT THAT'S ALL YOU NEED TO BE SPECIFIC TO THE WHOLE HUMAN GENOME.

AND IT TURNED OUT THERE IS A PERFECTLY NATURAL SYSTEM THAT DOES THAT. IT'S CALLED CRISPR-CAS9. AND THE HISTORY OF IT IS THAT IT WAS

FOUND IN BACTERIA AS A PROTECTION AGAINST BACTERIOPHAGES. IT'S SORT OF AN IMMUNE SYSTEM THAT BACTERIA HAVE THAT ALLOWS THEM TO SENSE A FOREIGN PIECE OF DNA AND CUT IT IN A SPECIFIC POSITION. AND THE RECOGNITION OF IT IS DONE WITH A LITTLE RNA MOLECULE, WHICH IS JUST LIKE A SECOND STRAND OF DNA FROM THIS POINT OF VIEW. AND SO IT WAS CALLED CLUSTERED REGULARLY INTERSPERSED SHORT INTERSPACED -- IT SAYS THERE. I THINK THAT'S RIGHT -- SHORT PALINDROMIC REPEATS OR CRISPR. AND THAT'S THE LAST TIME I WILL TRY TO SAY THAT.

SO IT WAS SEEN AS THIS STRETCH OF DNA IN A PARTICULAR BACTERIUM, STREPTOCOCCUS PYOGENES, IN WORK IN THE EARLY '90S. AND THE INTERESTING THING ABOUT IT IS WHAT YOU SEE ON THE RIGHT THERE, WHICH ARE THE DIRECT REPEATS IN THE UPPER CARTOON, WHICH HAVE LITTLE SPACERS BETWEEN REGULARLY REPEATED DNA. THE SPACERS ARE WHAT'S IMPORTANT BECAUSE THEY'RE A UNIQUE SEQUENCE. AND IT TURNED OUT WHEN SOMEBODY WORKED HARD ON THE NATURE OF THOSE SEQUENCES, THEY REALIZED THAT THEY ACTUALLY CAME FROM VIRUSES OF BACTERIA, BACTERIOPHAGES.

SO IT WAS PRETTY OBVIOUS THAT WHAT THE BACTERIUM DOES IS PICK UP A LITTLE BIT OF SEQUENCE FROM THE PHAGE AND INCORPORATE IT INTO ITSELF. AND

THEN IN THE SAME REGION OF DNA THERE ARE THESE OTHER PROTEINS, CAS9 AND OTHERS, AS WELL AS A TRACRRNA, AND THAT TOGETHER IT WAS THEN REALIZED AND WORK OVER REALLY A COUPLE OF DECADES THAT THIS IS A WAY OF CUTTING THE INCOMING PHAGE DNA AT A VERY SPECIFIC SITE, WHICH IS A SITE IN THE PHAGE DNA ITSELF BECAUSE IT WAS CAPTURED ORIGINALLY, HISTORICALLY FROM THAT PHAGE.

THEN PEOPLE PUT ALL THIS TOGETHER IN A SIMPLIFIED FORM AND CREATED WHAT IS NOW WHAT WE USE WHICH IS A RELATIVELY SIMPLE RNA MOLECULE THAT HAS TWO SIDES TO IT. ONE IS WHAT'S CALLED THE TRACER IN THE PREVIOUS SLIDE, AND THE OTHER IS THE GUIDE RNA WHICH IS THE ONE THAT RECOGNIZES THE ACTUAL SEQUENCE.

SO HERE'S THE GUIDE RNA, AND THE GUIDE RNA IS HOMOLOGOUS TO A SEQUENCE IN THE PHAGE, BUT NOW IN ANYTHING WE CAN CONSTRUCT, AND THE TRACER FORMS A STRUCTURE THAT BINDS TO THE CAS9 PROTEIN. SO THIS GRAY THING IN THE BACKGROUND IS THE CAS9 PROTEIN. AND SO IT BRINGS INTO THE REGION OF THIS SEQUENCE THE CAS9 PROTEIN. CAS9 PROTEIN HAS TWO NUCLEASES ACTUALLY IN IT, ONE THAT CUTS THE STRAND THAT'S RECOGNIZED BY THE GUIDE, SO IT CUTS THIS STRAND, AND THE OTHER THAT RECOGNIZES THE OPEN SINGLE STRAND

DOWN HERE AND CUTS THAT. AND SO THE END RESULT IS A DOUBLE-STRAND BREAK IN THE DNA AT A VERY SPECIFIC POINT DETERMINED BY ITS SEQUENCE, AND THAT SEQUENCE CAN BE UNIQUE TO THE HUMAN GENOME, TO ANY GENOME THAT WE CARE ABOUT.

NOW, WHY IS IT IMPORTANT TO MAKE THAT CUT? AND THAT'S WHAT THE REST OF THIS SLIDE IS ABOUT BECAUSE THAT DOUBLE-STRAND CUT CAN BE HEALED IN TWO WAYS. ONE IS BY SOMETHING CALLED NON-HOMOLOGOUS END JOINING. AND YOU REALIZE THAT THIS IS AN ABSOLUTELY NEAT CUT, SO THERE'S NO MORE WATSON-CRICK COMPLEMENTARITY THERE. THERE'S NO WAY TO PUT THAT DNA BACK TOGETHER AGAIN.

SO NON-HOMOLOGOUS END JOINING HAS EVOLVED AS A PROCESS IN MAMMALIAN CELLS TO SIMPLY HEAL IT BY THROWING IN A FEW RANDOM NUCLEOTIDES OR SOME NUCLEOTIDES FROM SOMEWHERE ELSE OR ANOTHER GENE OR WHATEVER AND SO IT MAKES A TOTALLY FALSE JOIN. IT WILL INACTIVATE -- IF THERE'S ANY GENE IN HERE, IT'S VERY LIKELY TO INACTIVATE THAT GENE BY THE NATURE OF WHAT IT DOES. AND SO IT IS A WAY OF INACTIVATING GENES IN A VERY SELECTIVE MANNER THAT'S PERFECTLY NATURAL.

NOW, THE OTHER THING THAT CAN HAPPEN TO THIS JOIN IS THAT A PIECE OF DONOR DNA CAN COME BY

THAT HAS HOMOLOGY OUT HERE ON THE FLANKS WHERE THE ORANGE REGIONS ARE. AND THAT THEN CAN BIND, AGAIN USING WATSON-CRICK COMPLEMENTARITY, TO THAT REGION AND HEAL IT BY USING SEQUENCE PRECISION. AND THAT CAN MAKE A PERFECT HEAL HERE IF THE DONOR DNA IS OF HOMOLOGOUS SORT THAT COMES RIGHT FROM THAT REGION. BUT IF THE DONOR DNA IS SOMETHING WE'VE SYNTHESIZED IN THE LABORATORY THAT HAS SOME OTHER SEQUENCE IN THE MIDDLE HERE, IT CAN PUT THAT OTHER SEQUENCE IN THERE.

LET'S SAY THERE WAS SOMETHING WRONG AT THIS POINT IN THE DNA AND WE WANT TO REPAIR IT. WELL, WE CAN PUT IN SEQUENCE THAT WILL REPAIR IT. AND SO WE CAN MAKE A MUTANT INTO A WILD TYPE. WE CAN MAKE A WILD TYPE INTO A MUTANT. WE CAN ADD A GENE, WE CAN SUBTRACT GENES THIS WAY, BUT THAT'S ACTUALLY NOT SO IMPORTANT FOR GERMLINE MODIFICATION BECAUSE WE PROBABLY WOULDN'T WANT TO DO THAT, BUT IT IS IMPORTANT EXPERIMENTALLY AND PEOPLE ARE DOING THAT. SO THAT'S WHY THIS DOUBLE-STRAND BREAK IS SO IMPORTANT AS AN INITIATOR OF A PROCESS.

AND INCIDENTALLY IF THERE'S ANYBODY WHO HAS A QUESTION, I'M HAPPY TO CONSIDER IT AT ANY TIME. I DON'T HAVE TO JUST GO ALONG LIKE A FREIGHT TRAIN. ARE THERE ANY? ALL RIGHT.

SO CRISPR-CAS9 IS A TOOL TO EDIT THE GENOME, AND THE GENOME WE ALL CARE ABOUT IS OUR OWN. SO IT COULD EDIT THE HUMAN GENOME, AND THAT'S WHY IT IS OF CONCERN. AND THE TWO QUESTIONS THAT ARE KEY ARE, FIRST OF ALL, WHY WOULD YOU WANT TO DO THIS TO THE HUMAN GENOME? AND SECONDLY, IS THERE AN ALTERNATIVE METHOD TO ACTUALLY SOLVE THE SAME SET OF PROBLEMS THAT DOESN'T REQUIRE MODIFYING THE GENOME?

SO LET ME JUST REMIND YOU WHY WE ARE CONCERNED ABOUT THIS. AND IT REALLY GOES BACK TO WORK DONE AT CALTECH MANY, MANY YEARS AGO, WHICH ULTIMATELY SHOWED, WITH THE HELP OF VERNON INGRAM AT MIT, THAT SICKLE CELL ANEMIA -- THIS IS A SICKLE CELL -- IS CAUSED BY A SINGLE NUCLEOTIDE CHANGE IN THE DNA OF A PERSON, AND IT'S INHERITED AND IT'S MAINTAINED IN THE GENOME BECAUSE IT HAS A SOMEWHAT BENEFICIAL, ACTUALLY A SIGNIFICANTLY BENEFICIAL ATTRIBUTE IF YOU LIVE IN A HIGH MALARIA AREA. BUT ASIDE FROM THAT, IT'S NOT A POSITIVE THING. AND IF YOU HAVE TWO COPIES OF THAT GENE, THEN YOU HAVE A SERIOUS DISEASE, SICKLE CELL ANEMIA.

SO IT'S THIS LITTLE A TO T TRANSITION THAT CHANGES THE GENETIC CODE FROM GLUTAMIC ACID, A CHARGED AMINO ACID, TO VALIENT AND UNCHARGED AMINO ACID. AND LINUS PAULING AT CALTECH YEARS AGO TOOK

SICKLE CELL HEMOGLOBIN AND NORMAL HEMOGLOBIN AND RAN THEM OUT IN AN ELECTRIC FIELD AND SHOWED THAT THE CHARGE DIFFERENCE BETWEEN GLUTAMIC ACID AND VALINE WAS SUFFICIENT TO ALLOW THEIR SEPARATION AND THAT IT REALLY WAS A PROTEIN MUTATION. AND THAT WAS THE FIRST MOLECULAR DISEASE INDICATION THAT WE HAD. LATER SEQUENCE DATA SHOWED THAT IT WAS THIS. MY AD FOR CALTECH.

SO THAT'S A MONOGENIC DISEASE. IT'S A DISEASE CAUSED BY A SINGLE GENE ALTERATION. WE HAVE FOUND OVER 6,000 SUCH GENES IN RECENT YEARS BECAUSE OF THE ENORMOUS POWER OF SEQUENCING THE HUMAN GENOME. AND TODAY THERE ARE VERY FEW GENES LEFT, IF ANY, SINGLE GENES THAT CAUSE DISEASE THAT WE DON'T KNOW ABOUT. AND WE CAN EASILY FIND OUT ABOUT MORE IF THERE ARE SOME. AND THEY'RE IN ALL SYSTEMS IN THE BODY, AND THEY HAVE MANY DIFFERENT CHARACTERISTICS.

SO WE NEED A WAY OF CORRECTING TYPOGRAPHICAL ERRORS IN THE SEQUENCE. NOW, THAT CORRECTION COULD BE DONE IN SOMATIC CELLS. FOR INSTANCE, IN THE CASE OF SINGLE CELL HEMOGLOBIN, IT DERIVES FROM THE HEMATOPOIETIC STEM CELL WHICH IS IN ALL OF OUR BONE MARROWS, AND WE CAN GO IN AND GET OUT THAT STEM CELL, CORRECT THE GENE IN THE STEM

CELL USING CRISPR TECHNOLOGY OR OTHER TECHNOLOGY, BUT CRISPR NOW, PUT THOSE CELLS BACK IN A PERSON, AND ACTUALLY CURE THAT PERSON OF SICKLE CELL DISEASE. AND THAT IS UNDER WAY IN MANY LABORATORIES.

IT'S NOT CONTROVERSIAL FROM AN ETHICAL POINT OF VIEW BECAUSE IT DOESN'T CONTRIBUTE TO THE GERMLINE. IT'S SIMPLY SOMATIC, AS BERNIE CORRECTLY POINTED OUT. IT'S CORRECTION TO THE GERMLINE THAT IS CONTROVERSIAL. AND THE CORRECTION OF AN INHERITED GERMLINE GENE IS SOMETHING THAT HAS TO BE DONE VERY NEAR CONCEPTION. AND THAT'S TRUE BECAUSE YOU WANT TO HAVE ONE CELL THAT YOU TARGET, AND THEN ALL THE OTHER CELLS OF THE BODY ARE DERIVED FROM THAT CELL BY CELL DIVISION. AND SO IF YOU CORRECT IT ONCE IN THAT CELL, EVERY CELL IN THE BODY OF AN INDIVIDUAL BORN FROM THAT CELL WOULD BE CORRECTED.

AND SO THIS REALLY IS OF VALUE TO PARENTS MORE THAN TO SUFFERERS FROM GENETIC DISEASE BECAUSE PARENTS HAVE A DRIVE, AND GENETICISTS WILL TELL YOU THAT IT IS A VERY IMPORTANT INHERENT DRIVE, TO HAVE OFFSPRING THAT MAINTAIN THEIR GENETIC CHARACTER. WE WANT TO HAVE OUR OWN CHILDREN, NOT CHILDREN FROM SOME OTHER GENETIC LINEAGE. AND THAT'S, AS I SAY, A VERY IMPORTANT DRIVING FORCE IN EVOLUTION.

AND IN ORDER TO DO THAT, IF YOU HAVE ONE OF THESE 6,000 INHERITED GENES, WHAT YOU WANT TO DO IS TO MAKE SURE THAT YOUR CHILDREN DON'T HAVE THAT. ONE OF THE WAYS TO DO THAT WOULD BE TO EDIT THE FERTILIZED EGG OR AT LEAST VERY EARLY EMBRYONIC CELLS.

NOW, THAT REQUIRES GETTING AT THE RECENTLY CREATED FERTILIZED EGG. AND FOR THAT REASON, IT PRETTY WELL REQUIRES IN VITRO FERTILIZATION. AND IN VITRO FERTILIZATION IS SOMETHING THAT'S USED VERY WIDELY TODAY. SOMEBODY TOLD ME FIVE MILLION CHILDREN HAVE BEEN BORN FROM IN VITRO FERTILIZATION. SO IT'S NOTHING TO BE SCARED OF ALTHOUGH THERE ARE SOME PEOPLE WHO CONSIDER IT ETHICALLY IMPROPER EVEN IF IT IS DONE VERY ROUTINELY.

AND IT REQUIRES ACTUALLY, IF YOU THINK ABOUT IT, GENETIC DIAGNOSIS OF THE CELLS THAT DERIVE FROM THAT MODIFIED FERTILIZED EGG BECAUSE YOU HAVE TO BE SURE THAT YOU'VE DONE WHAT YOU THINK YOU'VE DONE AND THAT IT'S IN THE RIGHT PLACE AND EVERYTHING IS KOSHER. AND SO PRENATAL GENETIC DIAGNOSIS, PGD, IS ALSO A PART OF THIS PROCESS THAT CERTAINLY IN THE EARLY STAGES IS LIKELY TO BE IMPORTANT.

NOW, SO THAT'S WHAT YOU WANT TO DO IF YOU WANT TO GET RID OF A DELETERIOUS GENE. BUT IF THE

MUTATION IS A DOMINANT MUTATION, AND MOST GENETIC DISEASES IN HUMANS ARE DOMINANT MUTATIONS, THEN YOU DON'T NEED TO DO THIS AT ALL BECAUSE IF YOU ARE GOING TO GO THROUGH IN VITRO FERTILIZATION, YOU'RE GOING TO GO THROUGH PGD, THEN YOU CAN SIMPLY DO THAT ON THE EMBRYOS FROM AN INDIVIDUAL FROM IN VITRO FERTILIZATION OR EVEN NOT NECESSARILY, BUT I THINK THAT WOULD BE REQUIRED, BECAUSE THERE WILL BE A FRACTION OF THOSE EMBRYOS THAT ARE NORMAL. AND SO YOU CAN AVOID THE GENE, YOU CAN SELECT AGAINST THE GENE THAT'S MUTATED. YOU DON'T REALLY NEED TO MODIFY IT.

AND THAT WAS A VERY IMPORTANT CONCLUSION OF THE MEETING IN WASHINGTON. THAT'S BECAUSE A LOT OF PEOPLE HAVE NOT THOUGHT THAT THROUGH. THEY SEE A PICTURE LIKE SICKLE CELL. SICKLE CELL IS ACTUALLY A DIFFERENT SITUATION, BUT WE CAN TALK ABOUT THAT. SO THE ACTUAL UTILITY OF GENE EDITING FROM THE POINT OF VIEW OF CORRECTING MUTATIONS IN THE HUMAN GENOME IS RELATIVELY SMALL. I CAN'T PUT A NUMBER ON IT, BUT I CAN TELL YOU THAT WHEN A PHYSICIAN IS FACED WITH A NEED FOR IT, THE PHYSICIAN WANTS THAT CAPABILITY IN HIS OR HER HANDS.

AND THIS JUST SHOWS YOU THAT IF YOU HAVE A PARENT THAT HAS A SINGLE DOMINANT MUTATION AND THAT

PARENT MARRIES SOMEBODY OR HAS A CHILD WITH SOMEBODY, DOESN'T HAVE TO MARRY, THAT'S NORMAL, THEN HALF OF THE EMBRYOS WILL BE NORMAL. AND IT'S JUST A MATTER OF FINDING THOSE NORMAL ONES AND REIMPLANTING THOSE AND NOT THE MUTANT ONES.

IF, ON THE OTHER HAND, THAT INDIVIDUAL IS HOMOZYGOUS, THAT'S RARE FOR A DOMINANT HOMOZYGOTE, BUT NOT UNHEARD OF -- THE BEST CASE IS HUNTINGTON'S DISEASE WHERE THERE, AS IT SAYS HERE, A FEW DOZENS OF SUCH -- THEN EVEN IF THEY HAVE A CHILD WITH SOMEBODY WHO'S NORMAL, EVERYONE WILL INHERIT THE GENE AND THE GENE IS DOMINANT AND SO WILL HAVE THE DISEASE. SO THAT WOULD BE A SITUATION THAT ABSOLUTELY WOULD REQUIRE SOME KIND OF GENE EDITING.

SO I'M NOT TALKING ABOUT DISEASES THAT ARE GENERALLY RARE, SERIOUS MENDELIAN GENE INHERITED DISEASES LIKE CYSTIC FIBROSIS, LIKE HUNTINGTON'S, LIKE SICKLE CELL. BUT, IN FACT, THERE'S A WHOLE SET OF DISEASES THAT DON'T FALL INTO THAT CATEGORY. THEY ARE POLYGENE. THEY CAN BE CAUSED BY MANY GENES, THE INTERACTION OF MANY GENES, AND DIFFERENT GENES IN DIFFERENT PEOPLE. HEART DISEASE IS A CLASSIC CASE. ALZHEIMER'S IS THOUGHT TO BE THAT. SCHIZOPHRENIA IS CERTAINLY THAT. AND FOR THOSE MY WHOLE ANALYSIS IS IRRELEVANT BECAUSE NO ONE GENE IS

CRITICAL.

NOW, YOU CAN IMAGINE DOING THIS TO TEN GENES OR A HUNDRED GENES, AND MAYBE SOMEDAY WE WILL, BUT I THINK AT THE MOMENT WE NEEDN'T THINK TOO HARD ABOUT THAT.

AND THERE ARE ALSO COMMON TRAITS, THEY'RE NOT GENERALLY CONSIDERED TO BE DISEASES, THAT ARE POLYGENIC IN THIS WAY, LIKE HEIGHT. IF YOU EVER HEAR IT, ERIC LANDER USES THAT AT EVERY TALK HE GIVES, SO I STOLE IT FROM HIM, THE HEIGHT DIFFERENCE BETWEEN THESE TWO GENTLEMEN, AND INTELLIGENCE AND OTHER TRAITS OF HUMAN BEINGS. AND THOSE ARE THE THINGS WE REALLY WORRY ABOUT ACTUALLY BECAUSE YOU CAN IMAGINE A PARENT WANTING TO ENHANCE THE GENETIC INHERITANCE OF HIS OR HER CHILDREN. AND THAT ENHANCEMENT, WHICH COULD BE INCREASED HEIGHT, IT COULD BE INCREASED INTELLIGENCE IF YOU COULD REALLY DEFINE IT, IT COULD BE OTHER THINGS, COULD JUST BE SIMPLE THINGS LIKE EYE COLOR, ARE THINGS THAT MAYBE PEOPLE WOULD WANT TO TRY TO DO. AND I THINK THAT ACTUALLY IS THE IMPETUS FOR THIS DEEP CONCERN THAT PEOPLE HAVE ABOUT THIS TECHNOLOGY BECAUSE ARE WE SMART ENOUGH TO DEFINE WHAT'S BETTER? DO WE REALLY WANT TO DETERMINE WHAT OUR OFFSPRING AND THEIR OFFSPRING AND THEIR OFFSPRING HAVE TO DEAL WITH?

SO BECAUSE OF THAT, IN 2014, AS PEOPLE BEGAN THINKING ABOUT HUMAN GENE EDITING, THERE WAS A MEETING CALLED IN NAPA VALLEY, WHICH TOOK PLACE IN JANUARY '15, JUST A YEAR AGO, TO THINK ABOUT WHETHER THIS WAS SOMETHING THAT POSED A THREAT IN SOME WAY TO OUR FUTURE. THE TECHNOLOGY WAS CLEARLY NOT PERFECTED AT THAT TIME. IT IS NOT PERFECTED TODAY. AND SO YOU CAN MAKE THE SIMPLE ARGUMENT WE SHOULDN'T DO THIS BECAUSE IT'S DANGEROUS BECAUSE WE JUST DON'T KNOW HOW TO HANDLE THESE POWERFUL TECHNIQUES, AND THAT'S TRUE, BUT THAT REALLY DOESN'T GET YOU VERY FAR BECAUSE WE'LL SOLVE THOSE PROBLEMS. THEY'RE TOO EASILY DEFINED NOT TO BE SOLVED.

AND SO THE GROUP THAT MET, THERE WERE, I CAN'T REMEMBER, 12 OF US OR 20 OF US, PUBLISHED IN *SCIENCE* A PLEA THAT THERE BE DISCUSSION OF THIS ISSUE BEFORE ANY ACTION TOOK PLACE, AND HERE IS WHAT WAS PUBLISHED. AND WE WERE REALLY CALLING HERE FOR A FRAMEWORK FOR OPEN DISCOURSE ON THE USE OF CRISPR-CAS9 TECHNOLOGY TO MANIPULATE THE HUMAN GENOME AND SAYING THAT THAT WAS URGENTLY NEEDED.

SO WE MADE FOUR RECOMMENDATIONS. I'LL REALLY ONLY TALK ABOUT THREE OF THEM. TO STRONGLY DISCOURAGE ANY ATTEMPTS AT GERMLINE GENOME MODIFICATION FOR CLINICAL APPLICATION IN HUMANS

WHILE WE THOUGHT THROUGH THE SOCIETAL, ENVIRONMENTAL, AND ETHICAL ISSUES.

TWO WAS TO ENCOURAGE AND EVEN SUPPORT RESEARCH, TRANSPARENT RESEARCH, OPEN RESEARCH, TO EVALUATE THE EFFICACY AND SPECIFICITY OF THE SYSTEM JUST TO MAKE IT BETTER.

AND, THREE, TO CONVENE A GLOBALLY REPRESENTATIVE GROUP OF DEVELOPERS AND USERS OF THE TECHNOLOGY OF EXPERTS IN GENETICS, LAW, AND BIOETHICS, OTHER MEMBERS OF THE SCIENTIFIC COMMUNITY, THE PUBLIC, AND RELEVANT GOVERNMENT AGENCIES AND INTEREST GROUPS TO FURTHER CONSIDER THESE IMPORTANT ISSUES AND, WHERE APPROPRIATE, RECOMMEND POLICIES.

AND THAT LED TO THE NATIONAL ACADEMY OF SCIENCES TAKING THIS OVER AND APPOINTING A COMMITTEE. AND ULTIMATELY THE MEETING THAT WAS HELD WAS SPONSORED BY THESE ACADEMIES NOW CALLED THE NATIONAL ACADEMIES OF SCIENCE AND ENGINEERING AND, BY INVITATION, THE ROYAL SOCIETY OF ENGLAND AND THE CHINESE ACADEMY OF SCIENCES BECAUSE SO MUCH ACTIVITY WAS GOING ON IN CHINA. AND I WAS ASKED TO CHAIR THAT 12-PERSON ORGANIZING COMMITTEE WHICH HAD TWO SCIENTISTS FROM CHINA, TWO FROM ENGLAND, ONE FROM GERMANY, A BIOETHICIST, A PROFESSOR OF LAW AND

BIOETHICS, A PHYSICIAN/SCIENTIST, AND FOUR SENIOR U.S. SCIENTISTS.

AND WE MET ON MANY PHONE MEETINGS AND ONE FACE-TO-FACE MEETING IN OCTOBER AND CALLED A MEETING IN DECEMBER. THIS IS THE GROUP IN CASE YOU'RE CURIOUS ABOUT THE EXACT PEOPLE WHO WERE INVOLVED. AND I WON'T GO THROUGH AND READ THAT EXCEPT TO ACKNOWLEDGE ANNE-MARIE MAZZA, WHO WAS THE PROJECT DIRECTOR FOR THE ACADEMY AND WHO, WITHOUT HER, THIS WOULDN'T HAVE HAPPENED.

THE MEETING TOOK PLACE IN THREE EARLY DAYS IN DECEMBER. FIVE HUNDRED PEOPLE CAME FROM 20 COUNTRIES, MOSTLY FROM THE U.S. AND IT WAS EXACTLY THAT GROUP OF PEOPLE THAT WE WANTED TO HAVE COME TOGETHER. IN RETROSPECT, WE MIGHT HAVE HAD SOMEWHAT BETTER REPRESENTATION FROM THE PATIENT ADVOCATE COMMUNITY. WE TRIED AND FAILED, BUT MAYBE WE SHOULD HAVE TRIED HARDER. BUT OTHERWISE, I THINK IT WAS PRETTY BALANCED AND REPRESENTED OPINIONS FROM MANY DIFFERENT WALKS OF LIFE.

WE MET IN PLENARY SESSIONS, WE MET IN BREAK-OUT SESSIONS. BREAK-OUT SESSIONS TURNED OUT TO BE VERY IMPORTANT BECAUSE THEY REPRESENTED A TIME WHEN EVERYBODY WHO WAS AT THE MEETING COULD TALK TO EACH OTHER IN RELATIVELY SMALL GROUPS. AND NEW

IDEAS CAME UP IN THOSE, AND A SENSE OF INVOLVEMENT, I THINK, WAS HAD BY ALL.

WE ISSUED A FINAL STATEMENT. THAT STATEMENT WAS ISSUED BY THE ORGANIZING COMMITTEE IN ITS OWN NAME AND IS NOT AN OFFICIAL DOCUMENT OF THE ACADEMIES. AND THAT'S IMPORTANT ALTHOUGH PEOPLE TEND TO FORGET IT AND SAY THERE'S AN ACADEMY POLICY, WHICH THERE ISN'T. WE ACTUALLY WROTE A LOT OF IT AHEAD OF TIME, FULL DISCLOSURE, BECAUSE OTHERWISE WE WOULDN'T HAVE BEEN ABLE TO DO IT. AND THERE ARE FOUR MAJOR CONCLUSIONS.

FIRST OF ALL, THAT BOTH BASIC AND PRECLINICAL RESEARCH SHOULD CONTINUE ON THE EDITING TECHNOLOGIES AND ON THE BENEFITS THAT CAN RESULT FROM EDITING AND ON THE BIOLOGY OF HUMAN EMBRYOS AND GERMLINE CELLS. LET ME UNDERLINE THE BIOLOGY OF HUMAN EMBRYOS AND GERMLINE CELLS BECAUSE THAT'S EXACTLY WHAT THIS WOMAN IN BRITAIN WANTS TO DO AND THAT THE BRITISH AUTHORITIES HAVE AGREED SHE SHOULD DO. SO IT IS NOT ONLY WITHIN THE GUIDELINES; IT'S SOMETHING WE EXPLICITLY CALLED FOR. AND ACTUALLY THE CHINESE EXPERIMENT, WHICH HAD TAKEN PLACE BEFORE THIS, WOULD HAVE FIT UNDER THAT GUIDELINE. AND IT FITS UNDER THE GUIDELINES THAT YOU ALL HAVE AS YOU WERE SAYING EARLIER. AND LET ME JUST ADD MY

OPINION, THAT YOU SHOULD ALLOW EXPERIMENTS, YOU SHOULD FUND EXPERIMENTS OF THIS SORT AND ENCOURAGE THEM BECAUSE WE REALLY KNOW VERY LITTLE ABOUT THE EARLY STAGES OF HUMAN DEVELOPMENT. IT'S REMARKABLE HOW LITTLE WE KNOW. WE KNOW A LOT ABOUT THE EARLY STAGES OF MOUSE DEVELOPMENT, BUT THAT MAKES MORE MICE. DOESN'T MAKE HUMANS.

TURNS OUT WE HAVE VERY DIFFERENT STRATEGIES EVOLVED OVER TIME, AND WE NEED TO UNDERSTAND THOSE STRATEGIES. WE NEED TO UNDERSTAND WHAT ROLE DIFFERENT GENES PLAY. AND THAT'S WHAT CAN BE DONE. AND THAT EXPERIMENT THAT THIS WOMAN IN BRITAIN -- I FORGOT HER NAME -- IS GOING TO DO IS RIGHT ALONG THOSE LINES.

THAT THE CLINICAL USE FOR EDITING OF SOMATIC TISSUES SHOULD GO AHEAD BECAUSE IT DOESN'T PRODUCE HERITABLE ALTERATIONS AND, THEREFORE, IS NOT OF THE SAME KIND OF DEEP CONCERN ALTHOUGH WE WANT IT TO BE ACCURATE, WE WANT IT TO BE PRECISE, WE WANT IT TO BE EFFECTIVE BEFORE IT'S DONE IN HUMANS. BUT THAT'S THE KIND OF THING WE ASK OF ANY MEDICINE IN HUMANS.

THE THIRD IS THAT THE CLINICAL USE OF EDITING FOR GAMETES AND EMBRYOS DOES POSE RISKS. THERE'S A RISK OF INACCURACY, OF OFF-TARGET EFFECTS.

MANY OF THE EXPERTS AT THE MEETING SAID THAT'S GOING TO GO AWAY, BUT IT HAS TO GO AWAY AND IT HAS TO BE DEMONSTRABLY GONE. IT'S NOT SO EASY. PERHAPS A MORE SERIOUS PROBLEM IS INCOMPLETE EDITING BECAUSE WHEN YOU PUT CRISPR-CAS9 SYSTEM INTO A FERTILIZED EGG, NOW THE EGG STARTS DIVIDING. IT'S TWO CELLS, IT'S FOUR CELLS, IT'S EIGHT CELLS. DURING THAT TIME CRISPR-CAS9 CAN STILL BE ACTIVE. AND SO ONE OF THOSE CELLS MIGHT BE EDITED, BUT NOT ANOTHER. AND THAT WOULD LEAD TO A MOSAIC IN THE OFFSPRING, WHICH IS SOMETHING YOU DON'T WANT JUST IN PRINCIPLE, BUT IT COULD BE A MOSAIC GERMLINE AND, THEREFORE, NOT ACTUALLY BE PASSED ON TO LATER GENERATIONS OR DONE SO SPORADICALLY.

THAT THERE MAY BE HARMFUL EFFECTS OF THE GENES THAT ARE CHOSEN FOR EDITING IN SOME POPULATION LATER DOWN THE ROAD OF HUMAN BREEDING. AND THAT'S VERY HARD TO KNOW AND HARD TO DEAL WITH; BUT I MUST SAY IF WHAT YOU WERE DOING WAS CORRECTING A CLEARLY DELETERIOUS GENE, YOU'RE CORRECTING IT TO A WILD TYPE, AND WILD TYPE IS A GENE WHOSE INTERACTION WITH THE OTHER GENES IN THE GENOME IS EXTREMELY WELL KNOWN. ALL OF US ARE CONTROLS FOR THAT EXPERIMENT. AND SO I DON'T THINK IT'S ACTUALLY AS SERIOUS A PROBLEM AS WE IMAGINE AT LEAST FOR THOSE KINDS OF

GENES. FOR GENES THAT WOULD BE IN THAT CATEGORY OF ENHANCEMENT, IT WOULD BE A VERY DIFFERENT SITUATION.

AND I QUOTE, THE OBLIGATION TO CONSIDER IMPLICATIONS FOR FUTURE GENERATIONS, WHICH IS WHAT I'VE BEEN SAYING, THE DIFFICULTY OF EVER REVERSING AN EDITING EVENT, LET'S SAYS WE SOMEHOW DISCOVER THAT WE REALLY WANT TO GO BACK TO NORMAL OR GO BACK TO THE PREVIOUS SITUATION, THAT'S NOT SO EASY. AND, OF COURSE, AS PEOPLE BREED -- I MAKE US SOUND LIKE ANIMALS, BUT WE ARE -- THAT WILL CONTINUE DOWN THE ROAD.

THAT THERE ARE THEN VERY DIFFICULT SOCIETAL ISSUES THAT PEOPLE ARE CONCERNED ABOUT, IN PARTICULAR SOCIAL INEQUITIES BECAUSE GENETIC ENHANCEMENTS ARE LIKELY TO GO TO THE WEALTHY BECAUSE THEY CAN AFFORD TO DO IT, TO THE HIGHLY EDUCATED BECAUSE THEY'RE IN BETTER CONTROL OF THEIR OWN REPRODUCTION, AND THAT'S EXACTLY WHO DOESN'T NEED ENHANCEMENT TODAY GIVEN THE INEQUITIES THAT ALREADY EXIST IN OUR SOCIETY. AND SO THAT IS A CONCERN THAT ETHICISTS HAVE, BUT NOT A SCIENTIFIC CONCERN.

AND THE USE COERCIVELY IS REALLY A REFLECTION OF ALDUS HUXLEY'S *BRAVE NEW WORLD* IN WHICH NOT GENETIC ALTERATION BECAUSE HE COULDN'T TELL THAT THERE WOULD BE GENETIC ALTERATION, BUT

SELECTIVE BREEDING WAS BEING USED TO CREATE LEVELS OF HUMAN BEINGS IN THE SOCIETY.

AND FINALLY, A CATCH-ALL OF THE MORAL AND ETHICAL CONSIDERATIONS AND PURPOSELY ALTERING HUMAN EVOLUTION USING THIS TECHNOLOGY. IT IS A CATCH-ALL, BUT IT IS A CONCERN.

SO WE SUMMED THAT UP BY SAYING IT WOULD BE IRRESPONSIBLE TO PROCEED WITH ANY CLINICAL USE OF GERMLINE EDITING UNLESS AND UNTIL WE KNEW IT WAS SAFE AND THERE WAS A BROAD SOCIETAL CONSENSUS THAT IT WAS TIME WE DID THIS, THAT THERE WAS A NEED FOR IT IN ANY PARTICULAR SITUATION. AND I UNDERLINE THAT THAT HAS TO BE THOUGHT OF IN THE CONTEXT OF A PARTICULAR SITUATION.

AND FOUR, WE CALLED FOR AN ONGOING FORUM. NO COMMITTEE HAS DONE ITS JOB UNTIL IT CALLS FOR ANOTHER COMMITTEE. AND WHEN YOU THINK WHERE THE AUTHORITY IS TO REGULATE THIS TECHNOLOGY, IT IS IN EACH JURISDICTION, EACH COUNTRY OR EACH STATE IN THE UNITED STATES MAYBE. AND SINCE THE HUMAN GENOME IS SORT OF SHARED EQUALLY THROUGHOUT THE WORLD, THAT DOESN'T SEEM LIKE AN APPROPRIATE WAY OF REGULATION. SO WE NEED SOME KIND OF INTERNATIONAL AGREEMENT, A SET OF NORMS, THAT COUNTRIES ARE NOT GOING TO SIGN ONTO AND TURN INTO LAW. LAW IS VERY INFLEXIBLE, AND

WE HAVE A LOT TO LEARN BEFORE WE START PASSING LAWS, BUT AT LEAST AS OVERSIGHT.

AND SO WE ASKED THE NATIONAL ACADEMIES TO TAKE THE LEAD HERE, AND THEY HAVE AGREED TO. THEY ISSUED A STATEMENT IN WHICH THEY SAID WE'LL TAKE RESPONSIBILITY FOR THIS. WE STAND READY TO ESTABLISH A CONTINUING FORUM. AND SO THEY'RE IN THE PROCESS OF DOING THAT.

AS I SAID, THERE WERE FIVE ACADEMIES -- FOUR ACADEMIES INVOLVED WITH THE MEETING, BUT A NUMBER OF OTHERS HAVE ALREADY SAID THEY WANT TO BE INVOLVED.

SO WITH THAT, LET ME THANK YOU FOR YOU ATTENTION. AND I'D BE HAPPY TO ANSWER ANY QUESTIONS THAT MIGHT HAVE BUILT UP.

DR. LUBIN: THAT WAS SUPERB. THANK YOU VERY MUCH.

SO I JUST WANTED TO MAKE ONE COMMENT ABOUT THE SICKLE CELL STORY THAT YOU DESCRIBED. AS YOU KNOW, BONE MARROW TRANSPLANTATION CAN CURE PATIENTS WITH SICKLE CELL ANEMIA, BUT THE DIFFICULTY IN FINDING AN HOA-MATCHED DONOR IS REALLY A CHALLENGE. AND SO THIS TECHNOLOGY WITH CRISPR-CAS9 ADDRESSES THAT REALLY IN THE BEST WAY POSSIBLE. AND I THINK THAT'S IMPORTANT TO KEEP IN MIND AS YOU PRESENT THE

STORY RELATED TO SICKLE CELL. AND I THANK YOU FOR THAT INTRODUCTION.

DR. BALTIMORE: THANK YOU. THAT'S ABSOLUTELY TRUE.

DR. BOTKIN: JEFF BOTKIN FROM UNIVERSITY OF UTAH. THANKS FOR THAT. I HAVE A QUESTION ABOUT TWO TYPES OF POTENTIAL OFF-TARGET EFFECTS. AND YOU MENTIONED THAT THE SPECIFICITY IS PRETTY GOOD FOR THE 15 BASE PAIR SEQUENCE. AND ARE THE OFF-TARGET INSERTIONS AT THE CELLULAR LEVEL DUE TO MINOR VARIATIONS? I WOULD GUESS THERE'S PROBABLY HUNDREDS OR THOUSANDS OR MILLIONS OF SEQUENCES THAT ARE OFF BY ONE OR TWO BASES. IS THAT WHAT'S OCCURRING AT THE CELLULAR LEVEL IN TERMS OF THOSE OFF-TARGET INSERTIONS?

DR. BALTIMORE: YES. THAT'S THE FIRST CONCERN IS SEQUENCES VERY SIMILAR TO THE TARGET. NOW, YOU CAN ACTUALLY MINIMIZE THAT BY BIOINFORMATIC ANALYSIS AND CHOOSING A SEQUENCE WHICH IS MORE HIGHLY UNIQUE THAN OTHER SEQUENCES. I'VE BEEN TOLD FOR YEARS THAT THERE ARE NO LEVELS OF UNIQUENESS. YOU'RE EITHER UNIQUE OR NOT. SO YOU HAVE TO LOOK FOR THINGS THAT ARE HIGHLY SPECIFIC, AND YOU CAN DO THAT, BUT ULTIMATELY, YES, THAT IS A MAJOR CONCERN.

DR. BOTKIN: OKAY. AND THEN THE SECOND

TYPE OF OFF-TARGET --

DR. BALTIMORE: WHEN I SAID THAT PEOPLE ARE SAYING THAT ISN'T GOING TO BE A PROBLEM, THEY'VE BEEN LOOKING FOR THAT, THEY'VE BEEN ACTUALLY OPTIMIZING THE SYSTEM TO MINIMIZE THAT. AND THERE ARE A LOT OF PEOPLE WHO FEEL THAT THAT'S VIRTUALLY SOLVED.

DR. BOTKIN: OKAY. THE SECOND TYPE OF OFF-TARGET IS SORT OF OFF-TARGET TISSUE. SO IF YOU ARE TREATING A BONE MARROW, SAY, IN VITRO, YOU TRANSPLANT THAT BONE MARROW BACK INTO THE PATIENT. DOES THAT CRISPR-CAS9 COMPLEX STAY WITHIN THE PATIENT? AND IS THERE ANY RISK THAT THAT WOULD THEN IMPACT THE OVARIES OR TESTES OF THAT INDIVIDUAL TO CREATE ALTERATIONS IN OFF-TARGET TISSUES?

DR. BALTIMORE: I THINK THERE IS NO SUCH DANGER. IT DEPENDS ON HOW YOU PUT CRISPR-CAS9 INTO THE CELLS. MOST OF WHAT PEOPLE ARE DOING NOW IS USING VIRAL VECTORS THAT DON'T REPLICATE AND ACTUALLY INFECTING IN VITRO. AND SO YOU CAN THEN WASH OFF ANY EXCESS VIRUS. YOU CAN GIVE ENOUGH TIME SO THAT THE VIRUS WILL INACTIVATE ITSELF IF THERE IS ANY RESIDUUM AND THEN PUT THE CELLS BACK. FOR INSTANCE, YOU CAN MODIFY T-CELLS THAT WAY. YOU CAN COULD MODIFY HEMATOPOIETIC STEM CELLS THAT WAY. AND

I THINK THERE REALLY IS NO DANGER OF IT GETTING TO THE GERMLINE. GERMLINE IS VERY HIGHLY PROTECTED.

MR. SHEEHY: WHILE THEY'RE DOING THIS, AGAIN, FOCUSED ON THE PRACTICAL APPLICATION OF THESE RULES FOR CIRM, DOES THE PURPOSE OF THE BASIC AND PRECLINICAL STUDIES THAT GENERALLY YOUR MEETING SAID WAS ALLOWABLE, SHOULD THAT AFFECT WHETHER OR NOT WE FUND THOSE? SO THE TWO EXAMPLES WE HAVE, THE CHINESE EXPERIMENT WAS BETA THALASSEMIA, WHICH IS A MONOGENIC DOMINANT GENE DISEASE, AND THE OTHER WAS ON EARLY EMBRYOLOGY, BASIC HUMAN UNDERSTANDING OF HUMAN DEVELOPMENT. BUT WHAT IF THE BASIC AND PRECLINICAL STUDIES ARE THOSE THAT SEEK TO ENHANCE HUMAN DEVELOPMENT, FOR INSTANCE? WHERE DOES OUR SCREEN START, FOR INSTANCE? WHERE DO WE START SAYING THAT THIS IS SCIENCE THAT WE DON'T WANT TO FUND? DOES IT START EARLIER AT THAT BASIC AND PRECLINICAL SITE WHERE YOU CAN ANTICIPATE THE OUTCOME OF SUCCESSFUL SCIENTIFIC RESEARCH WOULD BE THAT PURPOSE? OR JUST IT'S ALL BASICALLY PRECLINICAL AND SAY WE HAVE A LINE WHERE YOU CANNOT USE THAT --

DR. BALTIMORE: YOU CAN'T IMPLANT. I THINK MAKING DISTINCTIONS BETWEEN, QUOTE, ENHANCEMENTS AND OTHER GENES AND DISEASE GENES TURNS

OUT TO BE A NOT TERRIBLY BRIGHT LINE. AND THE IMPROVEMENT IN TECHNOLOGY THAT WILL COME ABOUT REALLY DOESN'T MATTER WHAT GENE YOU'RE TALKING ABOUT, THAT IMPROVEMENT WILL BE AN IMPROVEMENT FOR ALL GENES. AND SO THE TARGET GENES THAT ARE USED IN PRECLINICAL WORK DON'T REALLY MATTER. THE CHINESE DID FOCUS ON THE HEMOGLOBIN GENE BECAUSE OF THALASSEMIA, BUT THEY COULD HAVE FOCUSED ON SOME OTHER GENE AND IT WOULDN'T HAVE MATTERED. THEY WOULD HAVE GOTTEN THE SAME ANSWERS, AND WE WOULD HAVE LEARNED THE SAME THINGS. IT'S JUST THEY CHOSE -- THEY WEREN'T ACTUALLY TRYING TO DEAL WITH THALASSEMIA. THEY WERE JUST TRYING TO DEAL WITH TECHNOLOGY.

SO I DON'T THINK YOU SHOULD GET CONCERNED ABOUT THAT ISSUE AND TRY TO MAKE THAT VALUE JUDGMENT. I DON'T THINK IT'S WORTH IT. AND I THINK YOU WILL FIND IT'S NOT AN EASY THING TO DO IF YOU TRY.

BACK THERE THERE WAS A QUESTION.

DR. WAGNER: MY NAME IS JOHN WAGNER. I'M AT THE UNIVERSITY OF MINNESOTA, AND I TAKE CARE OF A NUMBER OF THOSE GENETIC DISEASES YOU WERE TALKING ABOUT. AND IN CONTRAST TO SICKLE CELL DISEASE, WHICH IS PURELY A BONE MARROW ISSUE, I TAKE CARE OF

EPIDERMOLYSIS BULLOSA, WHICH IS A DISEASE THAT AFFECTS THE ENTIRE BODY MUCOSAL LINING AND OTHER DISEASES. FOR EXAMPLE, I TAKE CARE OF CANCER PATIENTS AS WELL WHO HAVE BRCA II. SO THE PATIENT ALREADY EXISTS.

I THINK AN EXTENSION, JEFF, OF YOUR COMMENT IS WHAT HAPPENS IF I WANT TO GO AHEAD AND USE AAV VECTOR AS A WAY OF CORRECTING A NEUROLOGIC DISEASE OR THIS OVERWHELMING DISEASE THAT AFFECTS ALL PARTS OF THE BODY? WHAT IS THE RISK THAT I WOULD GET INTO THE GERMLINE IF I PROVIDE AAV AS A DELIVERY MECHANISM WHERE I HAVE TO CORRECT THE ENTIRE BODY OR AT LEAST TO CREATE A MOSAIC? WHAT'S THE RISK TO THE GENOME OF PASSING IT DOWN?

DR. BALTIMORE: MY HONEST ANSWER IS I DON'T KNOW.

DR. WAGNER: BECAUSE I THINK THIS IS MORE THE BIGGER RISK. I THINK THAT THE ISSUE IS THAT -- YOUR FOCUS ON CORRECTING THE EMBRYO IS CERTAINLY AN IMPORTANT FOCUS, BUT THAT'S NOT GOING TO BE THE ONLY REASON WHY WE MIGHT WANT TO USE THIS TECHNOLOGY IF THIS IS A BETTER APPROACH TO THE CLASSIC GENE THERAPY.

DR. BALTIMORE: AS I SAID, I DON'T REALLY KNOW HOW TOTALLY PROTECTED THE GERMLINE IS -- OTHER

PEOPLE MIGHT KNOW HERE OR ELSEWHERE -- TO AAV OR LENTIVIRAL VECTORS. IF REPLICATING VECTORS WERE USED AND USED IN VIVO RATHER THAN IN VITRO, AND THE POINT YOU MAKE IS A GOOD ONE, WE HAVE TO FIND OUT. MY GUESS IS NO ONE KNOWS BECAUSE NO ONE HAS EVER DONE IT. AND YOU COULD DO IT IN A MOUSE, AND THEN YOU'D HAVE THE VERY DIFFICULT QUESTION OF WHETHER THAT TOLD YOU ANYTHING ABOUT HUMANS, BUT I THINK YOU SHOULD DO IT IN A MOUSE FIRST.

MS. BELLCOUERS: I'M ADRIENNE BELLCOUERS (PHONETIC). I'M A SICKLE CELL MOM AND --

DR. BALTIMORE: I THINK THE OTHER MICROPHONE IS PICKING IT UP IS WHAT IT SOUNDS LIKE.

MS. BELLCOUERS: I'M ADRIENNE, AND I'VE GOT A BIT OF A REPUTATION AS A STEM CELL ADVOCATE AND A SICKLE CELL ACTIVIST AS I AM, AS SOME OF YOU KNOW, FOURTH GENERATION IN MY FAMILY OF MOTHERS TO HAVE A CHILD WITH SICKLE CELL. AND I'VE SPENT THE LAST FOUR YEARS LEARNING ABOUT THIS TECHNOLOGY AND TRULY, TRULY BELIEVING THAT IT'S GOING TO MAKE ME THE LAST MOTHER IN MY GENERATION. SO I'M HERE AS AN ACTIVIST.

AND WHAT I WANT TO SAY IS I WOULD LIKE TO KNOW YOUR PLAN, WHILE YOU'RE CREATING ALL OF THESE COMMITTEES, WHAT IS YOUR PLAN TO MAKE SURE THAT YOU

HAVE THOSE OF US FROM THE DISEASE COMMUNITIES PRESENT ON THOSE AND PRESENT AND GIVING INPUT ON THESE COMMITTEES BECAUSE I FEEL LIKE THE SCIENCE IS AT A POINT WHERE IT'S REALLY READY TO INCLUDE US. AND IT'S AT A POINT WHERE WE REALLY NEED TO REACH OUT TO PEOPLE WHO ARE LOOKING FOR YOU AS AN ANSWER AND LOOKING FOR AN ANSWER AND WANT TO BE PART OF THAT PROCESS. SO I WOULD LOVE IT IF, WHEN YOU HAVE THOSE KIND OF RECOMMENDATIONS, THAT YOU HAD SOME PLAN THERE THAT YOU'RE REACHING OUT AND HAVING PEOPLE FROM OUR COMMUNITIES, NOT ONLY MY COMMUNITY, BUT ALL DISEASE COMMUNITIES. THANK YOU.

DR. BALTIMORE: SO WHEN I SPEAK, AS I DID HERE, I EMPHASIZE THAT MAYBE THAT WAS A FAILING OF THE WASHINGTON MEETING. AND I REALLY BELIEVE THAT, AND I THINK PEOPLE LIKE YOU CAN MAKE AN IMPORTANT INPUT TO THE COMMUNITY DISCUSSION.

MS. BELLCOUERS: HOW DO WE DO THAT? YOU DON'T HAVE TO ANSWER NOW. BUT IF ALL OF YOU PEOPLE IN THIS ROOM, LIKE MY GRANDMOTHER SAID, YOU CAN'T DO BADLY WHEN YOU GET A BUNCH OF SMART PEOPLE IN THE ROOM. IF YOU GUYS CAN COME UP WITH SOMETHING OR YOU HAVE SOMETHING THAT WORKS, THEN YOU NEED TO LET ME KNOW AND I WILL CERTAINLY TRY TO DUPLICATE THAT, GET THAT GOING, SUPPORT IT, DO WHATEVER I CAN.

DR. BALTIMORE: ONE OF THE WONDERFUL THINGS ABOUT THE INVOLVEMENT OF THE PRESS IS THAT THERE'S NOT GOING TO BE AN ADVANCE IN THIS FIELD THAT ISN'T WIDELY KNOWN. FIRST OF ALL, WE ALL PUBLISH, AND PUBLICATION IS CONSIDERED TO BE -- SCIENCE DOESN'T EXIST UNTIL IT'S PUBLISHED. SO WE WANT TO SEE THAT THAT HAPPENS AND HAPPENS RAPIDLY, AND THEN IT WILL BE PICKED UP, AND YOU WILL KNOW ABOUT IT IF YOU HAVEN'T HEARD ABOUT IT THROUGH VARIOUS GRAPEVINES. BUT I DO THINK THAT WHAT YOU SAID BEFORE IS SOMETHING THAT NEEDS TO BE TAKEN TO HEART BY EVERYBODY ORGANIZING A MEETING OF THIS SORT, WHICH IS THAT THE PATIENT ADVOCATE COMMUNITY IS AN IMPORTANT CONTRIBUTOR.

CO-CHAIR LANSING: WELL, I JUST WANT TO SECOND AND EMPHASIZE AND THANK YOU FOR BRINGING THIS UP. I THINK THAT THE PATIENT ADVOCATE COMMUNITY IS, A, IMPORTANT, AND WE FOUND THIS IN CIRM, IN THE EARLY MEETINGS IN PROVIDING INPUT. JEFF AND I ARE BOTH PATIENT ADVOCATES. AND SO I THINK THAT WE'RE VERY, VERY, AND MANY OTHERS HERE WHO ARE ALSO PATIENT ADVOCATES, VERY IMPORTANT EARLY ON IN GETTING THE PATIENT ADVOCATE'S PERSPECTIVE, BUT EXTRAORDINARILY IMPORTANT, AND THIS IS WHAT YOU'RE BRINGING OUT, IN GETTING THE SCIENCE TO THE POINT

WHERE THE PUBLIC ACCEPTS IT. AND THERE ARE SO MANY WRONG IMPRESSIONS, DO YOU KNOW, FROM VERY WELL-EDUCATED PEOPLE. AND CIRM, I ACTUALLY HAVE ALWAYS BELIEVED THIS, WAS PASSED. I'M NOT TAKING AWAY ANYTHING THAT ANYBODY ELSE DID, BUT I THINK THE PATIENT ADVOCATES AND ALL OF THE COMMUNITIES COMING TOGETHER, BECAUSE WE REPRESENT ALL THE DISEASES, I ACTUALLY THINK, AND MAYBE THIS IS SELF-SERVING, BUT I ACTUALLY THINK WAS THE DOMINANT REASON THAT THIS BILL WAS PASSED.

DR. BALTIMORE: LET US NOT FORGET THAT BOB KLEIN IS A PATIENT ADVOCATE.

CO-CHAIR LANSING: THAT'S WHAT I WAS JUST GOING TO SAY. BOB KLEIN. IT STARTED WITH A PATIENT ADVOCATE. ALL THE DISEASE GROUPS UNIFIED TOGETHER AND REALLY WERE THE FACE OF WHAT THE SCIENCE COULD DO, DO YOU KNOW. AND SO I BELIEVE THAT WHEN WE COME TO RECOMMENDATIONS AND AS THE SCIENCE ADVANCES, THERE WILL BE A LOT OF MISCOMMUNICATIONS, YOU'LL NEED THE SUPPORT OF THE PRESS, YOU'LL NEED THE SUPPORT OF SOCIAL MEDIA, AND THE ONLY PEOPLE THAT REALLY CAN GET THAT DONE -- AGAIN, THE SCIENTISTS ARE THE GENIUS, BUT THE ONLY PEOPLE ARE THE FACE OF THE DISEASE, AND IT IS THE PATIENT ADVOCATES WHO MOVE THE PRESS AND WHO MOVE THE PUBLIC. AND I THINK

WE'LL GET THIS ACCEPTED IN WHATEVER TERM WE DECIDE TO DO IT. SO THANK YOU FOR BRINGING THIS UP.

DR. BALTIMORE: I THINK MAYBE WE SHOULD GO ON.

CHAIRMAN THOMAS: I ECHO SHERRY'S COMMENTS AND YOURS AS WELL, ADRIENNE. DAVID, THANK YOU VERY MUCH FOR THAT PRESENTATION. I JUST WANTED TO QUICKLY REPORT I RECENTLY SPOKE WITH SEAN MORRISON, KNOWN TO MANY OF YOU HERE, FROM UT SOUTHWESTERN AND CURRENT PRESIDENT OF ISSCR WHO POINTED OUT THAT THE GUIDELINES ON THIS SUBJECT FROM ISSCR ARE DUE OUT FAIRLY IMMINENTLY AND, AS CONSISTENT WITH WHAT YOU SAID, WOULD ALLOW FOR THINGS LIKE THE UK AND CHINA EXPERIMENTATION.

ALSO LIKE TO ADD FOR ANYBODY WHO WONDERED ABOUT THE PICTURE OF THE VERY TALL MAN AND THE VERY SHORT MAN, THAT IS A FAMOUS SPORTS PICTURE OF WILT CHAMBERLAIN AND JOCKEY WILLIE SHOEMAKER. DAVID, YOU CAN WORK THAT INTO YOUR FUTURE SPEECHES.

CO-CHAIR LO: SO I'M SORT OF TORN BETWEEN WANTING TO HAVE THIS WONDERFUL CONVERSATION WITH DR. BALTIMORE CONTINUE, BUT ALSO TO TRY AND MOVE US THROUGH WHAT'S A VERY RICH PROGRAM. SO ARE THERE ANY QUESTIONS FROM THE MEMBERS OF THE STANDARDS WORKING GROUP TO DR. BALTIMORE ABOUT HIS TALK?

LET'S MAKE SURE WE GET THOSE. THERE WILL BE TIME LATER TO COME BACK FOR MORE QUESTIONS, BUT I THINK WE SHOULD TAKE ADVANTAGE OF DR. BALTIMORE'S BEING HERE AND FOCUSED. SO TED AND ROB TAYLOR AND THEN JEFF BOTKIN.

DR. PETERS: DR. BALTIMORE, ON THE COMMITMENT TO POSTPONE GERMLINE MODIFICATION, THE REASONS THAT I THOUGHT YOU GAVE WERE SAFETY, UNANTICIPATED NEGATIVE CONSEQUENCES. THERE ARE TWO OTHER BIOETHICAL ARGUMENTS, ONE FROM THE VATICAN, ONE FROM LEON KASS, WHO WAS AN ADVISOR TO PRESIDENT BUSH, AND THOSE ARE NATURALIST ARGUMENTS. WE SHOULDN'T CHANGE MOTHER NATURE. WAS THAT DISCUSSED? DID IT HAVE ANY INFLUENCE, OR IS IT STRICTLY A SAFETY ISSUE?

DR. BALTIMORE: I THINK THAT WAS DISCUSSED IN BREAK-OUT SESSIONS. IT WASN'T REALLY DISCUSSED IN THE PLENARIES BECAUSE IT'S A VERY HARD DISCUSSION TO HAVE SINCE IT'S ABOUT FEELINGS, NOT ABOUT ANYTHING CONCRETE. FEELINGS ARE IMPORTANT. I'M NOT FOR A MOMENT DENIGRATING THEM, BUT THEY'RE HARD TO DISCUSS AND THEY'RE HARD TO COMPARE AND THEY'RE HARD TO EVALUATE. AND SO IN THE END, THAT'S WHY WE HAVE DEMOCRACY SO WE CAN VOTE. AND 49.9 PERCENT IS NOT ENOUGH. IT'S GOT 50.1 PERCENT, ALTHOUGH HILLARY DID

DO IT WITH ARE 49.WHATEVER. SO THAT SORT OF DROWNS OUT MINORITY VIEWS OF WHICH I THINK THAT IS A MINORITY VIEW, BUT IT'S A VERY DEEPLY FELT VIEW, AND I UNDERSTAND THAT.

CO-CHAIR LO: LET ME JUST SAY THAT THERE'S AN ONGOING NATIONAL ACADEMY OF MEDICINE COMMITTEE THAT DR. BALTIMORE ALLUDED TO THAT ALTA CHARO IS THE CO-CHAIR OF THAT WILL TRY TO ADDRESS THOSE ISSUES. SO WHEN ALTA GETS ON THE PHONE A LITTLE BIT LATER, WE CAN SORT OF TALK ABOUT THAT.

AGAIN, TRYING TO COMPROMISE, ROB TAYLOR HAS BEEN VERY PATIENT, THEN FRANCISCO WANTS A CHANCE TO ASK A QUESTION, THEN JEFF BOTKIN. WE CAN COME BACK TO ISSUES TODAY. IS THIS SOMETHING SPECIFICALLY FOR DR. BALTIMORE?

MS. DARNOVSKY: RESPONDS TO THE PREVIOUS STATEMENT.

CO-CHAIR LO: WHY DON'T YOU GO AHEAD. WELL, YOU KNOW WHAT. LET'S COME BACK TO THAT BECAUSE ALTA CHARO IS IN A BETTER POSITION TO ADDRESS THAT. I'LL MAKE SURE THAT WE GET YOUR INPUT THEN.

DR. ROD TAYLOR: ROD TAYLOR, WAKE FOREST UNIVERSITY. NICE TO SEE YOU HERE. THANKS FOR YOUR TALK.

MY QUESTION ACTUALLY, AND I REALLY LIKE THE WAY YOU SORT OF FRAMED A STRATEGY FOR THIS, THAT DOMINANT DISEASES WE CAN ACTUALLY DIAGNOSE AND EXCLUDE ESSENTIALLY BY PREIMPLANTATION GENETIC DIAGNOSIS. AND THAT WOULD MEAN THAT THE RECESSIVE DISEASES ARE THE ONES THAT WE SHOULD POTENTIALLY BE TARGETING. AND FROM THAT PERSPECTIVE, I DON'T REALLY SEE THE MOSAICISM ISSUE AS BEING PARTICULARLY PROBLEMATIC. GENE DOSAGE, BUT WHY WAS THERE SO MUCH EMPHASIS ON -- IF YOU TAKE THAT STRATEGY, WHY WOULD MOSAICISM BE AS MUCH OF A CONCERN AS YOU SEEM TO LAY OUT?

DR. BALTIMORE: BECAUSE TO CARRY OUT PREIMPLANTATION GENETIC DIAGNOSIS, YOU TAKE A SINGLE CELL FROM THE EMBRYO AND ANALYZE IT OR TWO CELLS FROM THE EMBRYO, WHATEVER, AND YOU HAVE THE REST THERE, AND THEY GIVE RISE TO THE OFFSPRING. BUT YOU HAVEN'T TESTED WHAT THEIR GENETIC NATURE IS. AND IF THERE HAS BEEN MOSAICISM, YOU'RE GOING TO GET A FALSE VIEW OF WHAT THE OTHER CELLS LOOK LIKE.

DR. ROD TAYLOR: WE CAN TALK ABOUT THAT MORE.

DR. BALTIMORE: I THINK YOU KNOW ABOUT THAT, RIGHT?

DR. CLARK: I CAN ANSWER THAT. HI, I'M

AMANDER CLARK. I'M THE GERMLINE EXPERT IN THE ROOM, ONE OF THEM. SO WE KNOW FROM THE MOUSE, AND I THINK THIS IS IMPORTANT BECAUSE MICE ARE NOT HUMANS. I THINK DAVID DID AN EXCELLENT JOB OF REMINDING US THAT WE NEED TO DO THESE STUDIES IN MODEL ORGANISMS FIRST, BUT WE NOW APPRECIATE, FOR THOSE OF US WHO DO STUDY THE HUMAN EMBRYO, THAT THE HUMAN EMBRYO IS MOLECULARLY VERY DIFFERENT TO THE MOUSE EMBRYO. BUT WHAT WE'VE LEARNED IN THE MOUSE EMBRYO IS THAT CRISPR IS REALLY GOOD. IT'S REALLY EFFICIENT. SO IT WILL MAKE A CUT, BUT IT CAN KEEP ON CUTTING. SO THAT MEANS ALL OF THE CELLS IN THE EMBRYO MIGHT HAVE SLIGHTLY DIFFERENT CUTS AND REPAIRS.

SO AS DAVID POINTS OUT, YOU MIGHT EVALUATE ONE THROUGH PREIMPLANTATION GENETIC DIAGNOSIS, BUT THAT DOESN'T GUARANTEE THAT THE CUT THAT YOU SAW IN THAT CELL WILL BE THE SAME CUT THAT MIGHT BE FOUND IN ANOTHER CELL, OR THE OTHER CELL MIGHT NOT HAVE CUT AT ALL. SO THAT'S WHERE THE TECHNOLOGY IS TODAY. AS DAVID SAID, THESE ARE DETAILS, THESE ARE QUESTIONS THAT CAN BE ADDRESSED SCIENTIFICALLY OVER TIME; BUT THIS, ROB, IS THE MOSAICISM THAT WE'RE WORRIED ABOUT, AND WE CERTAINLY SEE IT RIGHT NOW IN EMBRYOS WHEN YOU'RE PUTTING CRISPR-CAS9 INTO THE FERTILIZED EGG. THERE'S MOSAICISM IN THE RESULTING

EMBRYO.

DR. BALTIMORE: THERE ARE PEOPLE WHO HAVE SAID TO ME THAT THEY BELIEVE THIS TECHNOLOGY WILL NEVER BE USABLE WITH EMBRYOS, AND THAT WHAT YOU HAVE TO DO IS TO WED IT TO ES CELL TECHNOLOGY, IPS CELLS ACTUALLY, GET CELL LINES, MODIFY A SINGLE CELL IN A CELL LINE, ALLOW THAT CELL TO DIVIDE. NOW YOU HAVE AN EXACT UNDERSTANDING OF WHAT THE OTHER CELLS IN THE DISH HAVE AS A GENETIC INHERITANCE, AND YOU CAN BE GUARANTEED. BUT WE'RE NOWHERE NEAR THAT TECHNOLOGY. YOU DO THE SAME THING WITH SPERM AND EGG INDIVIDUALLY. THERE ARE LOTS OF TRICKS THAT YOU CAN IMAGINE. WHAT WE DON'T KNOW TODAY IS WHETHER YOU NEED THOSE TRICKS OR WHETHER WE CAN GET A SOLID ENOUGH VIEW WITHOUT THEM, AND IT'S NOT CLEAR, AT LEAST TO ME. APPARENTLY TO AMANDER WATCHING HER HEAD SHAKE.

CO-CHAIR LO: TWO MORE COMMENTS, AND THEN WE SHOULD TAKE A BREAK BECAUSE THE AV PEOPLE ARE GOING TO TRY AND FIX THE AV PROBLEMS WE'VE BEEN HAVING AND IMPROVE THE QUALITY OF LIFE IN THE ROOM. FRANCISCO AND THEN JEFF BOTKIN.

DR. PRIETO: FRANCISCO PRIETO. I'M A PATIENT ADVOCATE MEMBER OF THE CIRM BOARD. THANK YOU FOR THE TALK BECAUSE I THINK I HAVE A MUCH

BETTER UNDERSTANDING OF HOW THIS TECHNOLOGY WORKS. AND I UNDERSTAND HOW FOR SOMETHING LIKE SICKLE CELL DISEASE YOU WOULD APPLY THIS TO BONE MARROW TRANSPLANT AND POTENTIALLY CURE THE DISEASE. BUT HOW WOULD YOU MAKE A CORRECTION IN SOMATIC CELLS, IF YOU COULD GIVE ME AN EXAMPLE, AND AT WHAT POINT WOULD YOU DO THAT AND HOW WOULD THAT CORRECTION BE MAINTAINED?

DR. BALTIMORE: WELL, WHEN YOU DO THIS IN BONE MARROW, YOU'RE ACTUALLY TARGETING BONE MARROW STEM CELLS. THOSE STEM CELLS WHEN MODIFIED WILL THEN GIVE RISE TO NORMAL RED BLOOD CELLS THAT WON'T SICKLE OR WHATEVER. YOU CAN ALSO CURE OTHER DISEASES THAT WAY. BUBBLE BABY DISEASE COULD BE, WHICH SORT OF WAS ON MY SLIDE, BUT I DIDN'T EMPHASIZE IT. SO THE ANSWER IS STEM CELLS. YOU'VE GOT TO FIND STEM CELLS, WHETHER THEY BE LIVER STEM CELLS FOR A LIVER-BASED DISEASE OR SKIN STEM CELLS FOR A SKIN-BASED DISEASE OR WHATEVER, BECAUSE THEN IT WILL REPRODUCE ITSELF CONTINUALLY AND BE A REAL CURE FOR AN ORGAN-BASED DISEASE.

IN SOME CASES WE DON'T KNOW ENOUGH ABOUT STEM CELLS YET, BUT WE'RE LEARNING.

DR. BOTKIN: SO I JUST HAD A QUICK POINT FOR CLARITY. SO THE PROHIBITION AGAINST THE

GERMLINE ALTERATION AT THIS TIME WITH THIS TECHNOLOGY MAKES A GREAT DEAL OF SENSE. IS THE CONTROL POINT FOR THAT IMPLANTATION?

DR. BALTIMORE: YES. IT REALLY ISN'T AGAINST GERMLINE. IT'S AGAINST IMPLANTATION.

DR. BOTKIN: OKAY. SO REALLY NO LIMITS, THEN, ON WHAT MIGHT BE DONE WITH HUMAN EMBRYOS IN THE LAB AS LONG AS THEY'RE NOT GOING TO BE IMPLANTED.

DR. BALTIMORE: YES. SO THE LAW IN CHINA AND THE LAW IN BRITAIN IS EXACTLY WHAT YOU JUST SAID. YOU CAN BASICALLY DO ANYTHING AS LONG AS YOU DON'T IMPLANT. WE DON'T HAVE A LAW IN THE UNITED STATES. WE HAVE A PROHIBITION AGAINST USING NIH FUNDS FOR ANY RESEARCH OF THAT SORT. BUT IF YOU CAN DO IT WITHOUT NIH FUNDS, WE DON'T HAVE ANY LEGAL STATUS THERE BECAUSE THE CONGRESS IS UNABLE TO PASS A LAW OF THAT SORT BECAUSE IT WOULD GET ALL TIED UP WITH THE ISSUES IN CONGRESS.

CO-CHAIR LO: JUST WANTED TO MAKE A CLARIFICATION.

DR. BALTIMORE: IT'S 14 DAYS, WHICH IS BASICALLY IMPLANTATION. IT'S UNTIL THE EMBRYO HAS TO BE IMPLANTED ACTUALLY.

CO-CHAIR LO: SO I WANT TO THANK DR.

BALTIMORE FOR A MASTERFUL TEACHING OF THIS GROUP. AND THE CLARITY, THE THOUGHTFULNESS, AND THE WAY HE ANSWERED QUESTIONS REALLY HELPED US A LOT. DAVID, WE'RE IN YOUR DEBT. THANK YOU.

(APPLAUSE.)

CO-CHAIR LO: LET'S TAKE A BREAK AND COME BACK IN 15 MINUTES. MEANWHILE WE'LL TRY AND FIX THESE AV PROBLEMS.

(A RECESS WAS TAKEN.)

CO-CHAIR LO: ALTA, WE CAN HEAR YOU AND THAT'S WHAT'S IMPORTANT. I'M JUST GOING TO QUICKLY INTRODUCE YOU AND THEN TURN IT OVER TO YOU. WE ARE PUTTING YOU AHEAD OF JONATHAN KIMMELMAN BECAUSE WE KNOW YOUR VERY TIGHT TEACHING SCHEDULE.

SO ALTA CHARO IS THE WARREN P. KNOWLES PROFESSOR OF LAW AND BIOETHICS AT THE LAW SCHOOL AND MEDICAL SCHOOL AT THE UNIVERSITY OF WISCONSIN, MADISON. SHE HAS BEEN A PROLIFIC SCHOLAR ON BIOTECHNOLOGY POLICY, HUMAN SUBJECTS RESEARCH, REPRODUCTIVE RIGHTS, PHARMACEUTICAL DEVELOPMENT, AND SAFETY.

SHE'S A FORMER MEMBER OF THIS COMMITTEE. AND, ALTA, WE ALL HAVE FOND MEMORIES OF YOUR STIMULATING CONVERSATIONS AND CONTRIBUTIONS.

ALTA IS A MEMBER OF THE NATIONAL ACADEMY

OF MEDICINE AND SHE SERVES ON THEIR COUNCIL, THEIR GOVERNING BODY. SHE CHAIRED THE NATIONAL -- CO-CHAIRED THE NATIONAL ACADEMY OF SCIENCE'S SERIES OF REPORTS SOME YEARS AGO ON GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH WHICH WERE VERY IMPORTANT TO THIS COMMITTEE AS WE RECOMMENDED GUIDELINES FOR CIRM FUNDING.

SHE CURRENTLY IS THE CO-CHAIR OF THE NATIONAL ACADEMY OF MEDICINE'S PANEL, ONGOING PANEL, ABOUT TO HAVE ITS SECOND MEETING, ON HUMAN GENE EDITING: ETHICAL, SOCIAL, AND LEGAL ISSUES, WHICH WAS ALLUDED TO EARLIER THIS MORNING.

SO, ALTA, WE NOTE --

MS. CHARO: BERNIE, CAN YOU STILL HEAR ME?

CO-CHAIR LO: WE CAN HEAR YOU GREAT.

MS. CHARO: THERE WAS SOME KIND OF INTERFERENCE.

CO-CHAIR LO: WE'VE BEEN HEARING A LOT OF THAT HERE IN LOS ANGELES. OTHERWISE IT'S A GREAT CITY. ALTA, OBVIOUSLY YOU CAN'T SPEAK FOR THE REST OF THE COMMITTEE. THEY HAVE NOT MET TO START -- THEY HAVE NOT STARTED TO WORK ON THEIR RECOMMENDATIONS AND CONCLUSIONS. AND SHE CLEARLY CAN'T SPEAK ABOUT THAT, BUT WE HAVE ASKED HER TO SORT OF GIVE US THE BACKGROUND AND THE CHARGE OF THE

COMMITTEE AND WHAT THEY'RE CURRENTLY DOING. ALTA, WITH THAT, LET US TURN IT OVER TO YOU. THANK YOU AGAIN SO MUCH.

MS. CHARO: THANK YOU, BERNIE, VERY MUCH FOR WHATEVER IT IS THAT YOU SAID THAT I COULDN'T HEAR. LET ME JUST ASK. DO YOU GUYS HAVE THE SLIDES THAT I SENT LAST WEEK?

CO-CHAIR LO: YES, AND GEOFF WILL ADVANCE THEM FOR YOU.

MS. CHARO: OKAY. GREAT. SO THE FIRST SLIDE JUST HAS THE NAME NATIONAL ACADEMY OF SCIENCES, ENGINEERING, AND MEDICINE. SO MY FAULT FOR NOT HAVING THE SLIDES NUMBERED. GEOFF, IF YOU CAN JUST MOVE TO SLIDE NO. 2.

WHAT WE HAVE AT THE NATIONAL ACADEMIES IS AN OVERALL INITIATIVE IN THE AREA OF HUMAN GENE EDITING. IT WAS STARTED PARTLY IN RESPONSE TO THE PIECES THAT WERE PUBLISHED LAST JANUARY IN BOTH *SCIENCE* AND *NATURE*. THE *NATURE* PIECE, WHICH HAD A NUMBER OF INDUSTRY SPONSORS THAT WERE AUTHORING IT, TALKED ABOUT THE IMPORTANCE OF MAKING SURE THAT THIS NEW TECHNOLOGY OF CRISPR-CAS9 AND ITS VARIATIONS NOT BE DISCUSSED WITH REGARD TO GERMLINE EDITING, WHICH GETS EVERYBODY VERY NERVOUS, WHEN YOU'RE ACTUALLY TRYING TO FOCUS MORE ON SOMATIC CELL EDITING WHERE

THEY THOUGHT THERE WERE FAR MORE APPLICATIONS.

THE *SCIENCE* PIECE, WHICH WAS LED BY DAVID BALTIMORE AND JENNIFER DABNA, AND REFLECTED A CONVERSATION THAT TOOK PLACE IN NAPA A COUPLE OF MONTHS EARLIER WITH A NUMBER OF PEOPLE FROM THE SCIENTIFIC COMMUNITY AND WITH HANK GREELY FROM STANFORD AND MYSELF THERE AS THE KIND OF LAW ETHICS PEOPLE, WAS A PIECE THAT CALLED FOR A MORATORIUM ON ANY GERMLINE ATTEMPTS UNTIL THERE HAD BEEN A CHANCE TO HAVE A MORE THOROUGH DISCUSSION ABOUT BOTH THE SAFETY AND THE ETHICS OF IT.

THOSE TWO PIECES REALLY STARTED WHAT TURNED OUT TO BE A VERY SUBSTANTIAL AMOUNT OF PRESS COVERAGE CONCERNING THE POTENTIAL APPLICATION OF CRISPR-CAS9, WHICH, AS YOU KNOW, IS A GENE EDITING TECHNIQUE THAT IS SIMPLY MORE EFFICIENT AND EASIER AND MORE WIDELY UNDERSTOOD AND USABLE THAN THE PREVIOUS GENE EDITING TECHNIQUES OF ZINC-FINGER NUCLEASES AND TALENS. AND SO THIS EXPANDED RANGE OF APPLICATIONS AND EXPANDED RANGE OF POTENTIAL USERS REALLY CHANGED THE COMPLEXION OF THIS FIELD QUALITATIVELY AS WELL AS QUANTITATIVELY.

SO THE ACADEMIES, AT THE URGING OF KEITH YAMAMATO AND OTHERS, DECIDED THAT IT WOULD HAVE SEVERAL DIFFERENT KINDS OF ACTIVITIES. THE FIRST

WAS AN INTERNATIONAL SUMMIT. THIS SUMMIT WAS COSPONSORED BY THE U.S. ACADEMIES AND BY THE UK AND CHINESE ACADEMIES OF MEDICINE RESPECTIVELY. AND IT WAS VERY IMPORTANT TO INCLUDE THE CHINESE BECAUSE THERE'S A LOT WORK GOING ON IN THEIR LABORATORIES, AND THEY HAD REALLY SET OFF ANOTHER KIND OF FIRESTORM OF PRESS COVERAGE WITH THE ANNOUNCEMENT THAT AT LEAST ONE OF THEIR LABS HAD BEGUN WORKING WITH HUMAN EMBRYOS. THESE WERE NONVIABLE HUMAN EMBRYOS, BUT NONETHELESS, ESPECIALLY IN THE UNITED STATES, IT SET OFF ALARM BELLS.

THE RESULT WAS A COLLECTION OF ACTIVITIES THAT INCLUDED AN INTERNATIONAL SUMMIT IN DECEMBER, A STUDY THAT BERNIE HAS ALREADY REFERENCED, AND IN THE FUTURE SOME KIND OF ONGOING FORUM THAT WILL BE COHOSTED AT LEAST BY THOSE THREE ACADEMIES, CHINESE, UK, U.S., AND POTENTIALLY OTHER INTERNATIONAL PLAYERS AS WELL. THE INTERNATIONAL SUMMIT WAS A THREE-DAY MEETING. IT WAS HEAVY ON SCIENCE. IT HAD A FAIR AMOUNT OF COVERAGE OF REGULATORY AND POLICY ISSUES AS WELL AS SOME DISCUSSION OF ETHICAL ISSUES. AND YOU CAN FIND IT ONLINE WITH THE PRESENTATIONS AS WELL AS A NUMBER OF PHOTOGRAPHS.

GEOFF, IF YOU GO TO THE NEXT SLIDE, THE ONE THAT SAYS INTERNATIONAL SUMMIT ON HUMAN GENE

EDITING, YOU WILL SEE THAT YOU CAN GET THE BIOS OF EVERYBODY AND ALSO YOU CAN GET RECORDED VIDEO WEBCASTS. GEOFF, BY THE WAY, THERE'S A FABULOUS PICTURE OF YOU IN THERE, BUT I COULDN'T MANAGE TO GRAB IT UNDER THE SUMMIT PHOTOS, THAT SHOWS YOU STANDING AT A MICROPHONE ASKING A QUESTION.

AND NEXT SLIDE, THE NEWS ON THE INTERNATIONAL SUMMIT ON HUMAN GENE EDITING. SO THIS WAS A THREE-DAY MEETING THAT WAS ORGANIZED BY A GROUP OF ACADEMICS, AND THOSE PEOPLE WHO ORGANIZED IT CAME OUT WITH A STATEMENT AT THE END OF THE SUMMIT. THIS IS A STATEMENT THAT REPRESENTS THE VIEWS OF THOSE INDIVIDUALS WHO WERE ON THE ORGANIZING COMMITTEE. IT DOES NOT NECESSARILY REPRESENT THE VIEWS OF ANY OF THE SPONSORING ACADEMIES OF MEDICINE IN CHINA, UK, U.S., BUT IT WAS A SUMMIT STATEMENT.

AND IF ONE GOES TO THE NEXT SLIDE, YOU CAN SEE THAT THE CRUCIAL PART OF THE STATEMENT WITH REGARD TO GERMLINE EDITING, WHICH WAS WHAT HAD REALLY SPARKED A LOT OF THE CONTROVERSY, READS AS FOLLOWS: IT'D BE IRRESPONSIBLE TO PROCEED WITH ANY CLINICAL USE OF GERMLINE EDITING -- NOTICE CLINICAL USE, NOT RESEARCH USE -- AND IRRESPONSIBLE, NOT ILLEGAL, BUT UNLESS AND UNTIL, AND THEN THERE ARE

SOME CONDITIONS. THE FIRST FOCUSES ON RELEVANT SAFETY AND EFFICACY ISSUES, AND WE HEARD A LOT AT THIS SUMMIT ABOUT SOME OF THE CHALLENGES THAT STILL LIE AHEAD FOR BOTH THE ACCURACY AND PRECISION OF GENE EDITING TECHNIQUES, A LOT OF CONCERN ABOUT OFF-TARGET EFFECTS AND UNANTICIPATED ADVERSE EVENTS.

SO RELEVANT SAFETY AND EFFICACY WITH BALANCING OF RISKS AND BENEFITS AND ALTERNATIVES, FOCUSING THERE ON THE FACT THAT FOR GERMLINE IN PARTICULAR THERE ARE A NUMBER OF EXISTING MECHANISMS FOR PEOPLE TO AVOID THE BIRTH OF CHILDREN WHO HAVE PARTICULAR PROBLEMS, MOST PROMINENTLY THROUGH THE USE OF PREIMPLANTATION GENETIC DIAGNOSIS OR THE USE OF DONOR GAMETES. SO THAT GERMLINE EDITING DOES HAVE A NUMBER OF ALTERNATIVES THAT THIS GROUP OF ORGANIZERS FELT SHOULD BE FACTORED INTO THE NET BENEFIT THAT GERMLINE EDITING WOULD OFFER WHEN YOU'RE BALANCING THAT AGAINST THE RISKS TO THE IMMEDIATE OFFSPRING AND TO ANY OFFSPRING IN THE FUTURE SINCE THIS WOULD BE A HERITABLE, MULTIGENERATIONAL CHANGE.

THE SECOND IS A CONDITION THAT THERE BE BROAD SOCIETAL CONSENSUS ABOUT THE APPROPRIATENESS OF THE APPLICATION AND REGULATORY OVERSIGHT. NOW, BROAD SOCIETAL CONSENSUS IS NOT DEFINED. WE ALREADY

KNOW THAT THERE IS LIKELY TO BE SOME DEGREE OF DIFFERENCE OF OPINION, NOT ONLY AMONG INDIVIDUALS, BUT AMONG COUNTRIES. THERE ARE A NUMBER OF COUNTRIES IN EUROPE THAT ARE PARTY TO AN AGREEMENT TO NOT APPROVE ANY TECHNOLOGIES THAT WOULD ALTER THE HUMAN GENOME. THE U.S. IS NOT A PARTY TO THAT PARTICULAR AGREEMENT. SOME COUNTRIES THAT ARE PARTY TO IT HAVE NEVER ACTUALLY ENFORCED IT, I GUESS WOULD BE THE RIGHT WORD, IN THE SENSE THAT THEY'VE NEVER ADOPTED DOMESTIC LEGISLATION THAT WOULD ACTUALLY TAKE THAT LANGUAGE AND PUT IT INTO ENFORCEABLE LAW.

BUT THERE ARE MANY OTHER COUNTRIES THAT HAVE NOT TAKEN A POSITION AT ALL ON THIS. AND SO THERE IS AN OPEN QUESTION REALLY ABOUT WHAT WE MEAN BY BROAD SOCIETAL CONSENSUS AND HOW BROAD THAT MUST BE AND HOW PERFECT THE CONSENSUS MUST BE.

THE ORGANIZERS, OF COURSE, CONCLUDED THAT THE CRITERIA HAVE NOT YET BEEN MET FOR ANY PROPOSED CLINICAL USE IN THE CONTEXT OF GERMLINE. THE SAFETY ISSUES ARE ONLY AT THEIR VERY EARLIEST STAGES OF BEING EXPLORED. BECAUSE OF THE MANY ALTERNATIVES, THE COMPELLING BENEFITS ARE LIMITED IN NUMBER. AND AS I WAS MENTIONING, WE'VE GOT A VERY DIVERSE SET OF REGULATORY POSITIONS.

I'LL NOTE FOR THOSE OF YOU THAT ACTUALLY

WANT MORE DETAIL ON THIS, YOU'LL FIND IT IN THOSE PRESENTATIONS. FOR EXAMPLE, ON THE LEGISLATIVE AND REGULATORY, I DID A PRESENTATION AT THE VERY BEGINNING OF THE FIRST DAY OF THE CONFERENCE, AND THE SLIDES ARE ALL UP ON THAT. BUT NOTABLY, THE ORGANIZERS DID NOT CONCLUDE THAT WE SHOULD NEVER REVISIT THE QUESTION OF GERMLINE EDITING. SO THEY TOO IN A SENSE HAVE CALLED FOR WHAT IS EFFECTIVELY A MORATORIUM UNTIL THESE QUESTIONS HAVE BEEN ANSWERED AND SOME UNDERSTANDING OF A CONSENSUS HAS BEEN FORMED.

THIS IS NOTABLE BECAUSE THE ASILOMAR CONFERENCE, AS YOU KNOW, HAD COME OUT WITH A STATEMENT ABOUT HOW THE GERMLINE SHOULD NEVER BE CROSSED, AND THAT PARTICULAR STATEMENT HAS REALLY BEEN A KIND OF LINE IN THE SAND UP UNTIL NOW, BUT PEOPLE DIDN'T HAVE TO INVESTIGATE VERY MUCH BECAUSE THERE REALLY WERE NO TECHNIQUES BY WHICH YOU MIGHT ACTUALLY BE ABLE TO CROSS THAT GERMLINE. SO IT'S ONLY NOW THAT WE'RE REALLY BEING FORCED TO EVALUATE THE ASILOMAR STATEMENT AND ASK WHETHER OR NOT THAT IS STILL A POSITION WE WANT TO TAKE.

THE NEXT SLIDE, GEOFF, IS THE ONE THAT SAYS CONSENSUS STUDY. SO THE CONSENSUS STUDY FOLLOWS ON THE INTERNATIONAL SUMMIT. SOME PEOPLE

WERE CONFUSED AND THOUGHT THAT THE SUMMIT STATEMENT ABOUT THE GERMLINE EDITING WAS THE END OF EVERYTHING, BUT IT IS NOT. IT WAS SIMPLY A BEGINNING. THE CONSENSUS STUDY IS NOW GOING TO BE LOOKING AT A BROADER SET OF QUESTIONS AND LOOKING AT THEM IN SOME DEPTH.

SO THIS IS A STUDY I'M CO-CHAIRING WITH RICHARD HYNES FROM MIT. AND IF YOU GO TO THE NEXT SLIDE, STATEMENT OF TASK, YOU WILL SEE THE RANGE OF THINGS THAT WE'VE BEEN ASKED TO DO BY OUR SPONSORS. THERE ARE A NUMBER OF SPONSORS BOTH U.S. AND UK BASED FOR THIS, INCLUDING THE FDA AND THE WELLCOME TRUST.

SO, FIRST, WE'RE GOING TO BE LOOKING AT SCIENTIFIC UNDERPINNINGS OF THE FULL RANGE OF APPLICATIONS, SOMATIC AND GERMLINE, AND ASKING WHAT THE CURRENT STATE OF THE SCIENCE IS AND WHERE IT MIGHT BE GOING. THAT'S A VERY DIFFICULT THING TO DO BECAUSE, AS YOU KNOW, THE SCIENCE HAS BEEN MOVING VERY FAST. IT SEEMS LIKE THERE'S AN ARTICLE ALMOST EVERY SINGLE DAY ABOUT SOME NEW DEVELOPMENT EITHER IN A VARIATION ON CRISPR-CAS9 THAT MIGHT BE MORE EFFICIENT, THAT MIGHT BE MORE ACCURATE, THAT MIGHT BE MORE PRECISE, AS WELL AS NEWS ABOUT THE POTENTIAL AREAS OF APPLICATION. WE'RE SEEING ALSO ADDITIONAL

NEWS ABOUT THE OLDER FORMS OF GENE EDITING LIKE THE ZINC-FINGER NUCLEASES. NONETHELESS, AN EFFORT TO KIND OF CAPTURE, AT LEAST IN A SNAPSHOT, CURRENT STATE OF THE SCIENCE AND POTENTIAL CLINICAL APPLICATIONS AND WHAT WE KNOW ABOUT THE EFFICACY AND THE RISKS.

THEN LOOKING SPECIFICALLY AT WHAT AREAS OF RESEARCH NEED TO BE FUNDED OR PROMOTED IN ORDER TO BASICALLY IMPROVE THE QUALITY OF THIS TECHNIQUE SO THAT WE CAN MAKE IT MORE EFFICACIOUS AND WE CAN ALSO REDUCE ITS RISKS, AND A SPECIFIC LOOK AT WHETHER OR NOT THERE OUGHT TO BE SOME STANDARDS FOR QUANTIFYING THE OFF-TARGET EFFECTS.

I WANT TO SAY TWO THINGS AS AN ASIDE ON THIS. ONE IS THAT IN OUR NEXT UPCOMING MEETING NEXT WEEK, AND I'LL SAY A FEW WORDS ABOUT THAT IN A MOMENT, WE ARE HAVING AN ENTIRE PANEL MADE UP OF PEOPLE WHO REPRESENT VARIOUS COMPANIES THAT ARE IN THIS SPHERE NOW LOOKING TO USE CRISPR FOR THERAPEUTIC PRODUCTS. THEY'RE ALL WORKING ON SOMATIC CELL PRODUCTS, BUT WE WANTED TO REALLY HEAR FROM THEM ABOUT WHAT THEY THINK THE MOST LIKELY APPLICATION AREAS MIGHT BE AND ALSO HEAR FROM THEM WHAT THEY THINK IN TERMS OF THE LIKELY MARKETS, THE NUMBER OF PEOPLE, THE KINDS OF PEOPLE WHO MIGHT BE

INTERESTED OR IN NEED OF THESE THERAPIES, AND TO TALK WITH THEM ABOUT WHAT THEY SEE AS THE REGULATORY PATHWAY AND ANY OBSTACLES TO IT.

IN ADDITION, ON THE STANDARDS, ONE OF THINGS THAT THEY'LL BE TALKING ABOUT, WE HOPE, IS THE KIND OF STANDARD SETTING THAT MIGHT BE HELPFUL IN FACILITATING A COLLABORATION BETWEEN INDUSTRY AND THE REGULATORS SO THAT ONE CAN MOVE THROUGH THIS FIELD WITH SOME DEGREE OF CONFIDENCE AND EFFICIENCY. I DON'T KNOW THAT ANYTHING WILL COME OF THIS, BUT THERE WAS A BILL THAT WAS INTRODUCED, IN FACT, BY MY OWN SENATOR HERE, TAMMY BALDWIN FROM WISCONSIN, INTRODUCED IN CONGRESS THAT WOULD ACTUALLY CREATE A SPECIAL BODY FOR STANDARD SETTING IN THE AREA OF STEM CELL RESEARCH. BECAUSE, AGAIN, THERE'S BEEN SOME INTEREST IN TRYING TO MOVE SOME OF THE REGENERATIVE MEDICINE THERAPIES THROUGH THE FDA MORE EFFICIENTLY, AND FOR THAT WE NEED WHAT WE WOULD CALL REGULATORY SCIENCE, RESEARCH THAT HELPS THE FDA FIGURE OUT HOW TO MEASURE WHATEVER IT IS THAT THEY NEED TO MEASURE TO DETERMINE SAFETY AND EFFICACY.

NEXT, FOR OUR STATEMENT OF TASK, THERE WAS A SPECIFIC QUESTION ASKED ABOUT WHETHER THE CURRENT ETHICAL AND LEGAL STANDARDS FOR HUMAN SUBJECTS RESEARCH ARE ADEQUATE FOR HUMAN GENE EDITING. AND

THAT WOULD APPLY TO BOTH SOMATIC AND GERMLINE EDITING TECHNOLOGIES. GERMLINE EDITING TECHNOLOGIES OBVIOUSLY HAVE SOME UNIQUE ISSUES. FOR EXAMPLE, BECAUSE YOU MAKE CHANGES THAT MIGHT REVERBERATE DOWN THE GENERATIONS, THE NORMAL NOTIONS ABOUT CONSENT TO RESEARCH SIMPLY DON'T APPLY. YOU ARE GOING TO BE ESSENTIALLY MAKING CHANGES IN FUTURE PEOPLE WHO ARE IN SOME RESPECTS NOW THE SUBJECT OF AN EXPERIMENT, BUT WHO OBVIOUSLY HAD NO SAY IN WHETHER OR NOT THEY WOULD BE SUCH SUBJECTS AND EXPERIMENT, NOR IF THEY WOULD EVER HAVE SUCH CHANGES MADE IN THEM. SO THIS IS A PROBLEM, AND IT IS A PROBLEM NOT JUST HERE, BUT FOR OTHER THINGS THAT AFFECT CHILDREN.

SO WE'VE SEEN A LITTLE BIT OF THIS IN OTHER REPRODUCTIVE TECHNOLOGIES THAT ARE USED TO HELP CONCEIVE CHILDREN, SUCH AS IVF; BUT IN THOSE AREAS THE TECHNOLOGIES WERE BEING DEVELOPED BEFORE THE FDA'S CURRENT TISSUE ACTION PLAN HAD BEEN ADOPTED AND ITS CURRENT JURISDICTION OVER THESE SELF-BASED THERAPIES HAD BEEN FINALIZED. SO THEY WERE NOT DEVELOPED WITH SOME OF THE SAME REGULATORY ATTENTION AS THIS MIGHT.

YESTERDAY, AS I THINK YOU MAY KNOW ALREADY, A DIFFERENT COMMITTEE FROM THE NATIONAL ACADEMY OF MEDICINE, ON WHICH I SERVE AS A MEMBER,

NOT AS CHAIR, CHAIRED BY JEFF KAHN FROM HOPKINS, CAME OUT WITH A REPORT CONCERNING MITOCHONDRIAL REPLACEMENT TECHNIQUES WHICH HAVE THE POTENTIAL TO HAVE THIS MULTIGENERATIONAL EFFECT AS WELL BY TRANSPLANTING THE NUCLEUS FROM AN EGG THAT HAS MUTATED MITOCHONDRIA INTO AN ENUCLEATED EGG WITH HEALTHY MITOCHONDRIA AND ALLOWING WOMEN TO HAVE OFFSPRING THAT THEY ARE NUCLEAR GENETICALLY RELATED TO, BUT WITHOUT THE RISK OF THE SERIOUS MITOCHONDRIAL DNA DISEASES THEY SUFFER FROM.

NOW, OUR COMMITTEE RECOMMENDED THAT FOR THE MOMENT, IF THE FDA GOES FORWARD, AMONG OTHER CONDITIONS, THAT THEY ONLY USE MALE EMBRYOS SO THAT THE ONLY AFFECTED CHILDREN WOULD BE THOSE IN THIS FIRST GENERATION. SINCE THE MITOCHONDRIA PASS DOWN THROUGH EGG AND NOT THROUGH SPERM, YOU WOULD NOT HAVE THIS MULTIGENERATIONAL HERITABLE EFFECT. BUT IN THEORY THIS MITOCHONDRIAL REPLACEMENT TECHNIQUE COULD BE USED IN A WAY WITH FEMALE EMBRYOS THAT WOULD RESULT IN THIS MODIFIED MITOCHONDRIAL ENVIRONMENT FOR MULTIPLE GENERATIONS.

AND, INDEED, THE UNITED KINGDOM HAS APPROVED THIS TECHNIQUE FOR LICENSING, ALTHOUGH IT HAS YET TO ACTUALLY LICENSE SOMEBODY, AND THEY HAVE APPROVED IT FOR BOTH MALE AND FEMALE EMBRYOS. SO WE

HAVE THERE THE FIRST EXAMPLE OF WHAT WOULD BE MULTIGENERATIONAL CHANGE. THEY DO NOT VIEW THE CHANGE OF MITOCHONDRIA AS GERMLINE EDITING. OUR COMMITTEE DID. SO THERE'S A NOMENCLATURE DIFFERENCE THAT REFLECTS A DIFFERENT EVALUATION OF WHAT KIND OF COUNTS AS ENOUGH GENETIC INFORMATION TO BE ENCOMPASSED IN THE NOTION OF GERMLINE.

I'M EMPHASIZING THIS ONLY BECAUSE THIS QUESTION ABOUT HOW WE DEVELOP AN INTERNATIONAL FRAMEWORK FOR RESEARCH THAT INCORPORATES THE POSSIBILITY OF HUMAN GENE EDITING REQUIRES THAT WE AGREE ON WHAT GERMLINE EDITING IS BEFORE WE EVEN DECIDE ON WHAT THE FRAMEWORK MIGHT BE. AND THEN WE CAN ASK WHETHER OR NOT THE EXPERIENCE WITH MITOCHONDRIAL REPLACEMENT TECHNIQUE OFFERS ANY INSIGHTS INTO WHETHER AND HOW WE SHOULD ALSO LOOK AT THIS IN THE CONTEXT OF GENE EDITING WHICH CAN AFFECT A FAR WIDER RANGE OF TRAITS BECAUSE IT CAN BE USED ON NOT ONLY MITOCHONDRIAL DNA, BUT ON NUCLEAR DNA.

IT'S ALSO WORTH NOTING THAT, IN ADDITION TO EDITING THE SEQUENCE, THERE'S ALSO THE POTENTIAL FOR SIMPLY EDITING THE EPIGENOME. THAT'S PROBABLY A SOMEWHAT LESS DEVELOPED AREA ALTHOUGH ALL OF THEM ARE MOVING AT HYPER SPEED. SO THAT ALSO IS GOING TO BE SOMETHING THAT WE'LL LOOK AT, AND THERE THERE ARE

ADDITIONAL QUESTIONS ABOUT THE HERITABILITY OF EPIGENOMIC CHANGES WHICH IS DIFFERENT FROM THE HERITABILITY OF CHANGES IN SEQUENCE.

OUR COMMITTEE IS ALSO GOING TO BE LOOKING AT THE PROSPECTS FOR HARMONIZING POLICIES OVER THE COURSE OF MANY COUNTRIES AND MANY YEARS. WE KNOW THAT THERE ARE DIFFERENT SYSTEMS FOR EVALUATING GENE THERAPIES GENERALLY, AND SO WE WANT TO LOOK AND SEE IF THERE ARE LESSONS FROM THEM, WHETHER OR NOT THERE'S AN OPPORTUNITY TO HARMONIZE EITHER THE PROCEDURES OR AT LEAST THE KIND OF UNDERLYING POLICIES AND GOALS OF THESE BECAUSE WE UNDERSTAND THAT RESEARCH IS TRANSNATIONAL AND THAT COLLABORATIONS ARE TRANSNATIONAL.

INDEED, THE LAST THING THAT WE'VE BEEN ASKED TO DO, AS IF WE DIDN'T HAVE ENOUGH TO DO, TO DEVELOP SOME KIND OF LIST OF FUNDAMENTAL UNDERLYING PRINCIPLES THAT COULD BE ADAPTED OR ADOPTED BY ANY NATION TOWARD THE GOAL OF SOME DEGREE OF HARMONIZATION. SO THOSE COULD RANGE FROM ANYTHING LIKE TYPICAL HUMAN SUBJECTS CONCERNS OVER MINIMIZATION OF RISK OR WHETHER RISK SHOULD BE PARTICULARLY MINIMIZED FOR THOSE PEOPLE WHO HAVE THE LEAST CAPACITY TO VOLUNTEER TO BE PART OF THIS WHOLE ENDEAVOR. THAT WAS ONE OF THE THINGS THAT, FOR

EXAMPLE, OUR MITOCHONDRIAL REPLACEMENT COMMITTEE HAD SAID, BUT IT COULD ALSO ENCOMPASS THINGS HAVING TO DO WITH THE PRACTICE OF SCIENCE.

WE SAW IN THE AREA OF STEM CELL RESEARCH THAT THE VARYING DIFFERENT RULES WERE AT TIMES PROBLEMATIC FOR COLLABORATION. IT EVEN MEANT IN SOME CASES, SUCH AS GERMANY, THAT GERMAN NATIONALS WERE NOT ONLY PROHIBITED FROM PERFORMING CERTAIN EXPERIMENTS IN THEIR OWN COUNTRY, BUT THEY WERE PROHIBITED FROM GOING TO OTHER COUNTRIES AND DOING THE EXPERIMENTS THERE EVEN IF THOSE EXPERIMENTS WOULD HAVE BEEN LEGAL IN THE SECOND COUNTRY. SO THERE ARE QUESTIONS THAT WE COULD CHOOSE TO ADDRESS HAVING TO DO WITH PRINCIPLES OF SCIENTIFIC RESEARCH IN THE LABORATORY AS WELL AS IN HUMAN SUBJECT PROTECTION OR ON HOW ONE EVALUATES THE KIND OF SOCIAL IMPLICATIONS OR THE EFFECT ON THE SO-CALLED MORAL FABRIC OF SOCIETY OF ADOPTING ANY OR ALL OF THESE TECHNIQUES.

GEOFF, IF YOU'LL GO TO THE NEXT SLIDE, WHICH IS LABELED PUBLIC MEETINGS. SO WE HAD OUR FIRST PUBLIC MEETING RIGHT AFTER THE INTERNATIONAL SUMMIT. WE STARTED RIGHT ON THE HEART AND HEELS OF THE SUMMIT, AND WE SPENT MOST OF OUR TIME DISCUSSING THE CHARGE, WHICH WAS, AS YOU JUST SAW, FAIRLY LONG

AND COMPLEX, AND ALSO BEGAN WORKING ON DIVIDING OURSELVES UP INTO LITTLE WORKING GROUPS TO TRY TO GET A HANDLE ON ALL OF THIS WORK.

NOW, OUR NEXT MEETING IS NEXT WEEK. AND ON FEBRUARY 11TH, STARTING 8 A.M. EASTERN TIME, WE'LL BE HAVING A DAY THAT IS OPEN TO THE PUBLIC. AND SO PEOPLE WHO WANT TO CALL IN, I THINK THERE'S GOING TO BE A CALL-IN LINE. I'LL DOUBLE-CHECK FOR YOU, GEOFF, IF YOU LIKE. IT'S GOING TO BE AT THE KECK CENTER IN WASHINGTON, D.C. AND I HAD THE AGENDA UP JUST A SECOND AGO. I HOPE I STILL HAVE IT UP HERE ON MY COMPUTER.

SO HERE'S SOMETHING I ONLY GOT YESTERDAY, SO I COULDN'T GET IT IN TIME FOR YOU ALL FOR THESE SLIDES. LET ME TELL YOU THAT THERE'S GOING TO BE A PANEL ON MODELS FOR PUBLIC ENGAGEMENT IN SCIENCE POLICY THAT WILL BEGIN AT 8:15 A.M. EASTERN TIME. IT WILL BE MODERATED BY TWO OF OUR COMMITTEE MEMBERS, JOHN EVANS, WHO IS AT UC SAN DIEGO AND IS A SOCIOLOGIST WHO HAS SPECIALIZED IN LOOKING AT THE EFFECT OF RELIGIOUS VIEWS ON ATTITUDES ABOUT GENETIC TECHNOLOGIES IN AMERICA, AND DIETRAM SCHEUFELE, WHO IS HERE AT THE UNIVERSITY OF WISCONSIN AND SPECIALIZES IN SCIENCE COMMUNICATION. PANELISTS WILL INCLUDE DOMINIQUE BRESSARD, WHO CHAIRS THE

COMMUNICATIONS DEPARTMENT HERE AT UW. SORRY. IT'S NOT INTENDED TO BE AN INSIDE GAME. AND WE'VE INVITED BRUCE LEWENSTEIN FROM CORNELL UNIVERSITY AS WELL.

WE WANTED TO MAKE SURE WE GAVE A LOT OF ATTENTION TO THE QUESTION OF PUBLIC ENGAGEMENT. HOW CAN IT BE ACHIEVED? AND IN THE U.S. CONTEXT, TO WHAT EXTENT IS IT POSSIBLE TO INCORPORATE THAT INTO A REGULATORY SYSTEM THAT BY AND LARGE LEAVES POLITICAL QUESTIONS TO THE CONGRESS, BUT TECHNICAL QUESTIONS TO THE AGENCIES? THAT IS, IF FDA IS ASKED TO APPROVE SOMETHING, IT'S REALLY NOT UP TO FDA TO DECIDE IF IT AFFECTS THE MORAL FABRIC OF SOCIETY WHEN IT DECIDES WHETHER OR NOT TO APPROVE A TECHNIQUE. SO WHAT IS THE MODE FOR PUBLIC ENGAGEMENT AND WHAT ROLE SHOULD IT HAVE IN POLICYMAKING ARE ALL UP FOR GRABS.

THERE'S ALSO A PUBLIC COMMENT PERIOD FROM 9:15 TO 9:30 THAT DAY. THEN AT 9:45 WE HAVE PERSPECTIVES FROM THE AFFECTED COMMUNITIES. IT WILL BE MODERATED BY OUR COMMITTEE MEMBER SHARON TERRY AS WELL AS BY NANCY WECHSLER FROM THE HEREDITARY DISEASE FOUNDATION. WE HAVE PANELISTS REPRESENTING THE SICKLE CELL FOUNDATION, UNITED MITOCHONDRIAL DISEASE FOUNDATION, THE DISTRICT OF COLUMBIA

ASSOCIATION OF THE DEAF, AND THE PARENT PROJECT MUSCULAR DYSTROPHY. THESE ARE ALL REPRESENTATIVES OF DISEASE AREAS THAT HAVE SOME POTENTIAL APPLICATION FOR GENE EDITING.

ANOTHER PUBLIC COMMENT PERIOD FOLLOWING THAT BEGINNING AT 11:45 EASTERN, AND THEN AT 1 P.M. WE HAVE A PUBLIC SESSION ON THE PROCESS OF GETTING TO A THERAPEUTIC. THIS IS THE ONE I MENTIONED EARLIER ABOUT INDUSTRY. IT'S GOING TO BE MODERATED BY MICHAEL WERNER, THE ALLIANCE FOR REGENERATIVE MEDICINE. THE PANELISTS WILL INCLUDE REPRESENTATIVES FROM INTELLIA THERAPEUTICS, EDITAS MEDICINE, CARIBOU BIOSCIENCES, AS WELL AS THE NATIONAL INSTITUTES OF HEALTH, AND PARTNERS HEALTHCARE TALKING ABOUT HUMAN SUBJECTS PROTECTIONS. AND YET ANOTHER PUBLIC COMMENT PERIOD AFTER THAT BEFORE THE PUBLIC SESSION ADJOURNS AT 3:30.

AND I WILL, OF COURSE, SEND THIS AGENDA OFF TO GEOFF IMMEDIATELY AFTER I GET OFF THE CALL SO HE CAN DISTRIBUTE IT IF YOU ARE INTERESTED. YOU'LL ALSO FIND IT ON OUR WEBSITE.

GOING BACK TO THE SLIDE ABOUT THE MEETINGS, WE WILL ALSO, OF COURSE, BE MEETING THE NEXT DAY AS A COMMITTEE AS WE CONTINUE TO KIND OF WORK AWAY ON OUR TOPICS. AND THEN OUR THIRD MEETING

HAS NOW BEEN SET FOR APRIL 29TH AND 30TH. WE WANTED VERY MUCH TO GET MORE INPUT FROM THE INTERNATIONAL COMMUNITY. AND TO MAKE THAT EASIER, THIS IS GOING TO BE A PUBLIC MEETING THAT IS HELD IN EUROPE, AND WE'VE NOW DETERMINED IT'S GOING TO BE HELD IN PARIS ON APRIL 29 AND 30. FOR ANYBODY WHO'S INTERESTED IN ATTENDING, YOU SHOULD KNOW ALSO THAT APRIL 28TH IS GOING TO BE A MEETING OF THE EUROPEAN FEDERATION OF ACADEMIES OF MEDICINE. SO IT WILL BE THREE DAYS ON CRISPR AND GENE EDITING. THEY WILL ALL OR MOST OF THEM BE TAKING PLACE AT THE FRENCH ACADEMY OF MEDICINE'S BUILDING, WHICH IS ON THE LEFT BANK, NOT FAR FROM SAINT GERMAIN DES PRES.

NEXT SLIDE, GEOFF. JUST SO THAT YOU HAVE AN IDEA OF THE PEOPLE WHO ARE ON THIS COMMITTEE THAT THE NAS HAS CREATED, THAT IS A SLIDE OF THE COMMITTEE MEMBERS. YOU CAN SEE MYSELF AND RICHARD HYNES LISTED AS CO-CHAIRS. DAVID BEIER IS FROM BAY CITY CAPITAL OUT THERE IN CALIFORNIA IN THE BAY AREA. AND WE'VE GOT A NUMBER OF PEOPLE WHO COME FROM THE BASIC SCIENCES AND THE CLINICAL SCIENCE AREAS, EPIGENETICS, AS WELL AS GENETICS. AND IN ADDITION, WE HAVE PEOPLE FROM SOCIOLOGY LIKE JOHN EVANS, FROM ETHICS LIKE JEFF KAHN, FROM REGULATION, EPHRAT LEVY-LAHAD FROM HEBREW UNIVERSITY DOES

REGULATION AS WELL AS MEDICINE. AND WE HAVE DIETRAM SCHEUFELE AS WELL AS INTERNATIONAL HEALTH POLICY PEOPLE LIKE ISMAIL SERAGELDIN AND PATIENT ADVOCACY PEOPLE LIKE SHARON TERRY. SO IT'S A NICE ARRAY OF PEOPLE. IT'S A FAIRLY HUGE ARRAY OF PEOPLE. IT IS A CHALLENGING COMMITTEE, BUT WE WANTED TO MAKE SURE THAT WE COVERED OUR GROUND. WE'VE ALSO MADE SURE THERE'S SOME INTERNATIONAL REPRESENTATION FROM FRANCE, FROM ISRAEL, FROM ITALY, FROM CHINA. EVEN SOME OF THE AMERICANS ACTUALLY HAVE STRONG CONNECTIONS TO THEIR HOME COUNTRIES, SUCH AS RUDY JAENISCH WITH CONNECTIONS INTO GERMANY AND SUCH, AND ROBIN LOVELL-BADGE, OF COURSE, FROM THE FRANCIS CRICK INSTITUTE.

NEXT SLIDE IS SIMPLY TO GIVE YOU THE WEBSITE FOR OUR CONSENSUS STUDY COMMITTEE INFORMATION WHERE YOU CAN FIND ALL OF THIS AS WELL AS AGENDAS, BACKGROUND MATERIAL, SLIDES, ETC. AND I'M HAPPY, IF THERE ARE QUESTIONS, TO ANSWER ANY OF YOUR QUESTIONS. WE HOPE TO FINISH THIS PROJECT AND COME OUT WITH A REPORT BY DECEMBER OF 2016. SO WE'RE ON A 12-MONTH TRACK HERE TO DO SOMETHING AND TO COME OUT WITH RECOMMENDATIONS THAT WILL ADDRESS THAT ENTIRE SET OF QUESTIONS AND THE STATEMENT OF TASK RECOMMENDATIONS OF THE DOMESTIC LEVEL HERE IN

THE U.S. ON SOME OF THE ETHICAL ISSUES FOR THE FDA CONCERNING THE EFFICACY AND SAFETY ISSUES AS WELL AS THE HUMAN SUBJECTS PROTECTION ISSUES, AND THEN, INTERNATIONALLY SPEAKING, SUGGESTIONS FOR GRAND PRINCIPLES THAT MIGHT POSSIBLY HARMONIZE.

WE WILL BE MAKING A VERY STRONG EFFORT TO DISTINGUISH BETWEEN SOMATIC CELL THERAPIES AND GERMLINE THERAPIES BECAUSE OF THE GREATER RANGE OF SOMATIC CELL APPLICATION AREAS, BUT AT THE SAME TIME A HIGHER DEGREE OF CONTROVERSY AND NOVELTY ASSOCIATED WITH THE GERMLINE APPLICATIONS.

WITH THAT, I'LL STOP AND TURN BACK OVER TO BERNIE.

DR. LOMAX: THIS IS GEOFF LOMAX.

MS. CHARO: I CAN JUST BARELY HEAR, BUT I'LL KEEP TRYING.

DR. LOMAX: WE'RE GOING TO SEE IF WE CAN GET A QUESTION IN FROM JEFF BOTKIN HERE. NO. JOHN WAGNER.

DR. WAGNER: ALTA, CAN YOU HEAR ME?

MS. CHARO: NO, JOHN, I CAN'T HEAR YOU AT ALL. I'M SORRY. MAYBE SOMEBODY NEAR THE MICROPHONE CAN REPEAT THE QUESTION.

DR. WAGNER: ALTA, I'M TRYING AGAIN. CAN YOU HEAR ME NOW?

MS. CHARO: IT'S LIKE WE'RE IN A VERIZON COMMERCIAL. BARELY, YES. KEEP SHOUTING.

DR. WAGNER: I ASKED THE SAME QUESTION TO DAVID BALTIMORE A FEW MINUTES AGO. I JUST WANT TO MAKE SURE WHETHER OR NOT YOU ARE ASKING THE QUESTION AT THE NATIONAL ACADEMY WHICH IS REALLY FOCUSED ON WHAT YOUR WORK SO FAR HAS BEEN FOCUSED ON IS PURPOSEFUL GERMLINE EDITING. I UNDERSTAND THAT. WHAT HAPPENS IF ONE OF THE OFF-TARGET EFFECTS OF IN VIVO GENE EDITING IS A MODIFICATION OF THE GERMLINE?

MS. CHARO: INTERESTING QUESTION, JOHN. I CAN'T SAY THAT WE HEARD MUCH DISCUSSION ABOUT THAT YET. BUT IN THE CONVERSATIONS ABOUT SOMATIC CELL WORK, WE ARE GOING TO BE DISCUSSING VERY SPECIFICALLY THE RANGE OF POTENTIAL OFF-TARGET EFFECTS. WITH THAT PROMPT, I WILL MAKE SURE THAT THE PEOPLE WHO ARE PRESENTING ON THAT, WE'VE ORGANIZED OURSELVES INTO LITTLE WORKING GROUPS, I'LL MAKE SURE THAT THEY INCLUDE THAT IN THEIR DESCRIPTION OF WHAT WE KNOW AND WHAT WE DON'T KNOW AND HOW WOULD WE LEARN WHAT WE NEED TO KNOW ABOUT WHAT WE DON'T KNOW.

DR. WAGNER: RIGHT. BECAUSE IN VIVO GENE EDITING, I THINK, IS GOING TO BE MORE IMPORTANT IN TERMS OF TREATMENT OF SYSTEMATIC DISEASES OR

SPECIFIC DISEASES FOR WHICH YOU CANNOT DO A SOMATIC CELL THERAPY. SO, FOR EXAMPLE, EPIDERMOLYSIS BULLOSA, WHICH YOU KNOW I WORK ON, THAT'S NOT GOING TO BE INVOLVING JUST CORRECTING THE SKIN STEM CELL, FOR EXAMPLE, AND YOU JUST CAN'T DO ADOPTIVE GENE MODIFIED CELL TRANSFER. SO YOU ARE GOING TO HAVE TO THINK ABOUT THIS BIGGER ISSUE. OR THE TREATMENT OF LEUKODYSTROPHIES WHERE WE HAVE TO PERHAPS INSERT AAV VECTOR INTO THE BRAINS OF THESE KIDS AND WITH A POTENTIAL OFF-TARGET EFFECT OF SOMEHOW GENETICALLY MODIFYING THE SPERM OR THE EGG.

MS. CHARO: IT'S A REALLY INTERESTING POINT, JOHN. I HAVE TO CONFESS, SINCE I AM NOT THE MEDICAL SCIENTIFIC EXPERT ON THESE COMMITTEES OR THE SCIENTIFIC EXPERT, IT'S NOT ONE THAT I HAD CONSIDERED BECAUSE I WASN'T THINKING IN TERMS OF THE WAY THE IN VIVO THERAPIES OF SOMATIC CELLS MIGHT AFFECT YOUR GERM CELLS AS WELL. LIKE I SAID, I WILL MAKE SURE THAT WE TALK ABOUT THAT WITH THE PEOPLE ON OUR COMMITTEE WHO ARE OUR TECHNICAL PEOPLE BECAUSE IT'S AN INTERESTING OBSERVATION. WE WILL BE LOOKING AT BOTH EX VIVO AND IN VIVO SOMATIC CELL THERAPIES FOR BOTH GENETIC AND EPIGENETIC KINDS OF APPROACHES. AND I WILL NOW MAKE SURE TO LAYER THIS ONTO THAT CONVERSATION AS WELL.

I SHOULD SAY ALSO WE'RE GOING TO BE LOOKING AT THINGS THAT INCLUDE DELETIONS AS WELL AS ADDITIONS TO SEQUENCES AND ALSO QUESTIONS ABOUT ENHANCEMENT VERSUS THERAPY, QUESTIONS ABOUT THE DIFFERENCE BETWEEN CREATING SEQUENCES THAT HAVE NEVER BEFORE BEEN SEEN VERSUS THINGS THAT OCCUR IN NATURE EVEN IF THEY MAY EXIST AT ONE END OF THE SPECTRUM OR ANOTHER OF HUMAN CAPACITY.

DR. ROBERTS: ALTA, THIS IS DOROTHY ROBERTS. CAN YOU HEAR ME? ALTA, HI. IT'S DOROTHY ROBERTS. HOW ARE YOU?

MS. CHARO: I'M FINE. I'M GLAD MY HEARING IS HOLDING UP.

DR. ROBERTS: AND OUR VOICES HAVE TO HOLD UP.

I HAVE A COUPLE QUESTIONS. BOTH IN YOUR TALK AND ALSO DR. BALTIMORE'S, THERE ARE QUESTIONS OF WHERE IS THE DIVIDING LINE. YOU MENTIONED BETWEEN SOMATIC CELL AND GERMLINE EDITING. ONE OTHER ISSUE THAT CAME UP WAS THE DIVIDING LINE BETWEEN RESEARCH ON GERMLINE EDITING AND ACTUAL GERMLINE EDITING. SO WHERE IS THE DISTINCTION BETWEEN WHEN IT BECOMES PART OF WHAT THE MORATORIUM PREVENTS AND THE RESEARCH THAT IS STILL ALLOWED OR ACCEPTABLE TO GO FORWARD? THAT'S ONE.

AND THE OTHER QUESTION I HAD WAS AN ISSUE ABOUT THE VARIOUS COMMUNITIES THAT SHOULD BE HEARD IN THESE DISCUSSIONS. IN THE PRIOR SESSION WE HAD A DISCUSSION ABOUT INCLUDING PATIENTS RIGHTS AND DISEASE COMMUNITIES, AND YOU MENTIONED ON THE NAS COMMITTEE THAT THERE WERE REPRESENTATIVES OF PATIENT RIGHTS. AND I THINK THAT IN A WAY THERE'S BEEN THIS DIVIDING LINE OR EVEN INCLUSIVE LINE BETWEEN PATIENT RIGHTS AND SCIENTISTS. AND I WONDERED ABOUT OTHER COMMUNITIES LIKE SOCIAL JUSTICE COMMUNITIES, DISABILITY RIGHTS COMMUNITIES, HOW ARE THEY REPRESENTED IN YOUR COMMITTEE OR JUST IN GENERAL IN THESE DISCUSSIONS ABOUT WHAT'S ETHICAL AND APPROPRIATE FOR CONTINUING DOWN THIS PATH?

MS. CHARO: BOTH FINE QUESTIONS FOR ME TO TRY TO ANSWER, AND I'LL DO MY BEST, DOROTHY. LET ME START WITH THE RESEARCH VERSUS ACTUAL GERMLINE.

AS I HAD ALLUDED TO, THERE ARE DIFFERENT WAYS IN WHICH PEOPLE DEFINE GERMLINE, BUT THE ONE THAT DOES SEEM TO BE IN COMMON IS THIS NOTION OF HERITABILITY. SO THAT IF ONE WERE TO WORK OFF THE DEFINITIONS THAT WERE ADOPTED BY OUR MITOCHONDRIAL REPLACEMENT COMMITTEE OR THE ONES ADOPTED BY THE HUMAN FERTILISATION EMBRYOLOGY AUTHORITY IN THE UK, ONE WOULD COME TO THE CONCLUSION THAT RESEARCH ON AN

EMBRYO OR A GAMETE IN A LABORATORY THAT IS NEVER ACTUALLY TRANSFERRED FOR GESTATION WOULD NOT CONSTITUTE GERMLINE EDITING. IT WOULD CONSTITUTE RESEARCH ON GERMLINE EDITING. IN OTHER WORDS, IT DOESN'T ALLOW FOR THE POSSIBILITY OF HERITABILITY BECAUSE IT'S NEVER TRANSFERRED FOR GESTATION AT ALL. SO THERE'S NEVER A GENERATION THAT CAN ACTUALLY FEEL THE EFFECTS.

OBVIOUSLY FOR PEOPLE WHO VIEW THE EMBRYO AS THE MORAL EQUIVALENT OF A LIVE-BORN CHILD, THIS MAY NOT SATISFY, BUT IT IS CONSISTENT WITH BOTH OUR MITO COMMITTEE AND THE UK AND IS CONSISTENT WITH HOW HUMAN SUBJECTS ARE UNDERSTOOD, AT LEAST UNDER U.S. LAW, WHERE A LIVING INDIVIDUAL AS A HUMAN SUBJECT DOES NOT ENCOMPASS EMBRYOS THAT ARE EX VIVO.

THAT WOULD, IN A SENSE, THEN ANSWER YOUR QUESTION ABOUT WHETHER RESEARCH AT A PURELY IN VITRO LABORATORY LEVEL IS WITHIN THE MORATORIUM OR NOT WOULD SUGGEST IT IS NOT. AND IF YOU HAVE BEEN FOLLOWING THE NEWS, OF COURSE, YOU'VE SEEN THAT THE UK HAS NOW ALREADY AGREED TO ONE EXPERIMENT THAT WOULD USE CRISPR GENE EDITING ON A VIABLE HUMAN EMBRYO BUT WITH NO INTENT TO TRANSFER FOR GESTATION. THAT JUST HAPPENED THREE DAYS AGO OR FOUR DAYS AGO.

ON COMMUNITIES, BOY, THIS IS A REALLY HARD

ONE, DOROTHY, BECAUSE EVERY ONE OF THESE COMMUNITIES NEEDS TO BE PART OF THE CONVERSATION. AND WE ARE LIMITED AS A COMMITTEE ON THE AMOUNT OF TIME WE HAVE TO ACTUALLY HAVE FORMAL PANELS. SO ABSOLUTELY PEOPLE IN THE DISABILITY RIGHTS COMMUNITY, PEOPLE WHO ARE IN THE DISABILITY, PEOPLE WHO ARE DISABLED, PERIOD, NEED TO BE HEARD FROM. AND WHAT YOU'RE LOOSELY CALLING SOCIAL JUSTICE, WHICH IS A MUCH BROADER RANGE OF GROUPS THAT WORRY ABOUT INEQUITIES IN SOCIETY, WHETHER THEY'RE RACIAL OR ECONOMIC OR GEOGRAPHIC OR EDUCATIONAL, ALSO NEED TO BE HEARD FROM.

I'M PLEASED THAT THE INTERNATIONAL SUMMIT THAT DAVID BALTIMORE CHAIRED MADE A SPECIAL POINT OF INCLUDING EXACTLY THESE KINDS OF PEOPLE IN THEIR SESSIONS. WE ARE HOPING THAT REPRESENTATIVES OF THESE COMMUNITIES WILL BE TAKING ADVANTAGE OF THE PUBLIC COMMENT PERIOD AS WELL AS ADVANTAGE OF THE OPPORTUNITY TO SEND IN MATERIALS. WE ALSO HAVE THE CAPACITY TO HAVE WHITE PAPERS PREPARED FOR OUR COMMITTEE ON A CONTRACT BASIS THAT CAN ADDRESS THINGS THAT ARE NOT PART OF THE PANELS THAT WE'RE PUTTING TOGETHER.

AND FINALLY, I'VE GOT TO SAY THAT THE WHOLE POINT OF THE EMPHASIS ON MODELS FOR PUBLIC

ENGAGEMENT IS TO TRY AND ANTICIPATE THE NEED TO HAVE THESE BROADER CONVERSATIONS AND FIGURE OUT THE BEST WAYS TO RECOMMEND THAT THIS BE DONE IN THESE VERY DIFFERENT REGULATORY ENVIRONMENTS. THE UK HAS AN ENTIRELY DIFFERENT SET OF NORMS FOR HOW PUBLIC ATTITUDES AND PUBLIC PREFERENCES ARE INCORPORATED INTO REGULATORY DECISIONS THAN THE U.S., FOR EXAMPLE. SO WE REALLY WANT TO HEAR ABOUT THE RANGE OF MODELS AND HOW THEY CAN FIT INTO EACH NATIONAL CULTURE SO THAT ALL OF THESE KINDS OF GROUPS ARE PART OF THESE GLOBAL CONVERSATIONS BEFORE ANYTHING IS DONE THAT IS DEFINITIVE WITH REGARD TO EITHER PROHIBITING, CONTINUING A MORATORIUM, OR GOING FORWARD WITH SOMETHING LIKE GERMLINE EDITING EVEN WHILE WE CONTINUE TO WORK SEPARATELY ON THE SOMATIC CELL EDITING THAT WE WERE TALKING ABOUT BEFORE.

DR. LOMAX: I THINK WE HAVE NO FURTHER QUESTIONS AT THIS TIME. SO, ALTA, I'D LIKE TO THANK YOU VERY MUCH FOR BEING ABLE TO JOIN US TODAY. AND WE WILL -- I WILL FORWARD ON THE AGENDA AND THE ADDITIONAL MATERIALS, AND WE LOOK FORWARD TO TRACKING THE PROCESS OF THE COMMITTEE. IT WILL OBVIOUSLY INFORM OUR WORK. IT WILL DEFINITELY BE A VERY INFORMATIVE PROCESS.

CO-CHAIR LANSING: THANKS, ALTA.

MS. CHARO: I'M PLEASED TO HAVE BEEN ABLE TO DO THIS. I APOLOGIZE I COULDN'T BE IN THERE IN PERSON. MY TEACHING SCHEDULE JUST DID NOT MAKE IT POSSIBLE, BUT I'LL LOOK FORWARD TO HEARING WHAT YOU GUYS COME OUT WITH. THANKS VERY MUCH.

CO-CHAIR LANSING: ALTA, THIS IS SHERRY. THANK YOU AGAIN ON BEHALF OF THE WHOLE COMMITTEE AND BERNIE AND MYSELF.

MS. CHARO: YOU'RE VERY WELCOME. BYE-BYE.

CO-CHAIR LO: SO THANKS VERY MUCH. BIG DEEP BREATH, STRETCH IN YOUR CHAIRS.

JONATHAN KIMMELMAN VERY GRACIOUSLY ALLOWED US TO GO OUT OF ORDER. HE'S AN ASSOCIATE PROFESSOR IN THE BIOETHICS UNIT OF SOCIAL STUDIES OF MEDICINE PROGRAM AT MCGILL. AND HE HOLDS CROSS APPOINTMENTS IN EXPERIMENTAL MEDICINE, EPIDEMIOLOGY, BIOSTATISTICS, OCCUPATIONAL HEALTH, AND HUMAN GENETICS. HE'S THE CHAIR OF THE ETHICS COMMITTEE OF ISSCR, THE INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH, WHICH HAS ISSUED A SERIES OF REPORTS THAT ARE OF GREAT RELEVANCE TO US AND, AGAIN, SET INTERNATIONAL STANDARDS. HE HAS A WIDE RANGE OF RESEARCH INTERESTS. HE'S PUBLISHED WIDELY, AND ACTUALLY HE ALSO WAS A MEMBER OF THIS NATIONAL ACADEMY OF MEDICINE'S COMMITTEE ON MITOCHONDRIAL

REPLACEMENT THERAPY.

JONATHAN, THANKS VERY MUCH FOR COMING. WE'RE GLAD WE COULD GIVE YOU SOME WARM WEATHER, AND WE LOOK FORWARD TO YOUR PRESENTATION.

DR. KIMMELMAN: I CAN SAY THAT THESE VISITS TO CALIFORNIA, FOR SOMEONE COMING FROM MONTREAL, ARE MOST WELCOME IN JANUARY. I LEFT FREEZING RAIN. THE AIRPLANE WAS GLAZED OVER WITH ABOUT AN INCH OF ICE ON THE RUNWAY AS THEY DEICED, AND I LANDED AND PALM TREES. IT'S GREAT.

OKAY. SO I'M OBVIOUSLY PRESENTING THE PERSPECTIVE OF THE INTERNATIONAL SOCIETY OF STEM CELL RESEARCH. AND BEFORE I GET INTO THE LANGUAGE OF OUR DOCUMENT, I WANT TO PROVIDE A LITTLE BIT OF CONTEXT BECAUSE I THINK THE CONTEXT MATTERS FOR UNDERSTANDING THE POSITION AND THE LANGUAGE THAT ISSCR HAS ARTICULATED ON THE EDITING OF NUCLEAR DNA IN HUMAN EMBRYOS.

SO AS PROBABLY MANY PEOPLE KNOW, PREVIOUSLY IN 2006 AND 2008, THE ISSCR ISSUED TWO SETS OF GUIDELINES, ONE INVOLVING THE CONDUCT OF HUMAN EMBRYONIC STEM CELL RESEARCH, THE ETHICS THEREOF, AND THE OTHER ONE ON CLINICAL TRANSLATION. AND OVER THE LAST YEAR AND A HALF, WE HAVE BEEN REVISING AND UPGRADING AND UPDATING THOSE TWO SETS

OF GUIDELINES AND MERGING THEM INTO A SINGLE SET OF GUIDELINES THAT WILL CONTINUE TO PROVIDE SOME GUIDANCE FOR THE ETHICAL CONDUCT OF LABORATORY STUDIES AS WELL AS GUIDANCE FOR THE CONDUCT OF CLINICAL RESEARCH INVOLVING STEM CELLS.

NOW, ONE THING THE PREVIOUS GUIDELINES HAD NOT ADEQUATELY ADDRESSED WAS THIS OTHER STREAM OF RESEARCH. IT COUNTS AS CLINICAL RESEARCH, BUT OFTENTIMES PEOPLE DON'T QUITE GLOSS IT AS CLINICAL RESEARCH; NAMELY, THE ASSISTED REPRODUCTION ELEMENTS. AND SO THE WAY THAT THE PREVIOUS GUIDELINES THOUGHT OF CLINICAL TRANSLATION MAINLY WAS THROUGH THE LENS OF STANDARD CELL THERAPY TRIALS IN, SAY, CARDIOLOGY, BUT WE'RE ALSO TRYING TO COVER OTHER PATHWAYS OF INNOVATION IN CELL THERAPY RESEARCH.

NOW, THESE GUIDELINES ASPIRE TO BE INTERNATIONAL GUIDELINES, AND THAT'S RELEVANT FOR UNDERSTANDING SOME OF THE AIMS AND ASPIRATIONS OF THE GUIDELINES. SO FOR ONE, THE GOAL HERE IS TO ESTABLISH SOME KIND OF A UNIVERSAL BASELINE FOR ETHICAL CONDUCT. THE GUIDELINES NEED TO RECOGNIZE THAT THERE IS GOING TO BE WIDE VARIATION ACROSS DIFFERENT JURISDICTIONS ON MANY IMPORTANT MORAL ISSUES; FOR EXAMPLE, THE MORAL STATUS OF THE HUMAN

EMBRYO. AND SO THE GOAL IS TO SORT OF ESTABLISH A FLOOR OR A BASELINE OF CONDUCT, RECOGNIZING THAT OTHER JURISDICTIONS MAY WANT TO GO BEYOND THE STANDARDS.

SECONDLY, THE GUIDELINES TAKE A VERY LIGHT TOUCH TO THE INSTITUTIONAL MECHANISMS THROUGH WHICH WE IMPLEMENT THE PRINCIPLES CONTAINED IN THE GUIDELINES, RECOGNIZING THAT DIFFERENT GOVERNMENTS, DIFFERENT INSTITUTIONAL CONTEXTS ARE GOING TO HAVE DIFFERENT APPROPRIATE AND EFFICIENT MEANS OF IMPLEMENTING THE CONCEPTS AND RECOMMENDATIONS WITHIN THE GUIDELINES.

SO THE GUIDELINES BEGIN BY ARTICULATING A CORE SET OF PRINCIPLES. AND I AGAIN THINK IT'S REALLY IMPORTANT TO UNDERSTAND THESE PRINCIPLES NOT ONLY FOR UNDERSTANDING THE RATIONALE FOR WHAT WE SAY ON GENE EDITING, BUT ALSO FOR UNPACKING EXACTLY WHAT THE PRESCRIPTIONS ENTAIL, THE ENTAILMENTS OF THE RECOMMENDATIONS.

I THINK THE THREE MOST RELEVANT PRINCIPLES THAT WE ARTICULATE IS THE NOTION OF INTEGRITY OF THE RESEARCH ENTERPRISE, TRANSPARENCY, AND PRIMACY OF PATIENT WELFARE. SO FOR THE FIRST ONE, I THINK THE CORE TAKE-HOME MESSAGE HERE IS THAT ONE WANTS TO CONFIGURE RESEARCH IN A WAY THAT'S GOING TO BE

SUSTAINABLE, THAT'S GOING TO CONTINUE TO SUSTAIN SUPPORT FROM THE MANY DIFFERENT KINDS OF STAKEHOLDERS WHOSE ENGAGEMENT IS CRITICAL IN ORDER TO ENABLE A PRODUCTIVE RESEARCH ENTERPRISE.

AND SO THE VEHICLE FOR DOING THAT, AT LEAST ONE OF THE CORE VEHICLES, IS ESTABLISHING INDEPENDENT PEER REVIEW MECHANISMS, TRANSPARENCY, CONTINUED MONITORING, ETC.

WITH RESPECT TO TRANSPARENCY, ONE WANTS TO ESTABLISH MECHANISMS TO ENSURE TIMELY ENGAGEMENT OF RELEVANT STAKEHOLDER COMMUNITIES, INCLUDING THE PUBLICS, BUT ALSO ENSURING TIMELY COMMUNICATION OF FINDINGS WITHIN THE SCIENTIFIC COMMUNITY. WE'VE HEARD A LOT OVER THE LAST FEW YEARS ABOUT THE LACK OF TRANSPARENCY, CERTAINLY IN THE CLINICAL RESEARCH REALM, AND THIS IS SOMETHING THAT THE GUIDELINES REALLY TRY TO ADDRESS.

AND THIRDLY, OF COURSE, IS THE ISSUE OF PRIMACY OF THE PATIENT WELFARE, THE NOTION THAT THE INTERESTS OF FUTURE PATIENTS SHOULD NEVER OVERRIDE THE WELFARE INTERESTS OF CURRENT PATIENTS OR HUMAN SUBJECTS IN CLINICAL RESEARCH.

SO WITH THOSE PRINCIPLES ESTABLISHED, WHAT DO THE GUIDELINES SAY WITH RESPECT TO THE ETHICS OF GENE EDITING, NUCLEAR GENE EDITING, IN THE CONTEXT

OF THE HUMAN EMBRYO? WELL, THE GUIDELINES ARTICULATE TWO SETS OF PRESCRIPTIONS. THE FIRST SET OF PRESCRIPTIONS HAVE TO DO WITH THE PROCESS. AND THE GUIDELINES HOLD THAT OR RECOMMEND THAT ANY RESEARCH INVOLVING HUMAN EMBRYOS, INCLUDING GENE EDITING WITHIN HUMAN EMBRYOS, OUGHT TO BE OVERSEEN BY AN EMRO PROCESS, AN EMBRYO RESEARCH OVERSIGHT PROCESS. AGAIN, BECAUSE WE TAKE A LIGHT TOUCH, WE ARE NOT NECESSARILY PRESCRIBING EXACTLY WHAT THAT EMRO PROCESS IS. IT COULD IN SOME CONTEXT SUFFICE TO GO THROUGH AN IRB. IN OTHER CONTEXTS ONE MIGHT WANT TO HAVE THESE SEPARATE COMMITTEES, SCRO'S OR ESCRO'S AS THEY'RE CALLED IN THE UNITED STATES, BUT THE PRINCIPAL REQUIREMENT OF THE EMRO IS THAT THERE BE SOME KIND OF PROSPECTIVE REVIEW OF RESEARCH PROPOSALS, THAT THERE'S AN APPROVAL MECHANISM, AND THAT THERE'S SOME KIND OF ONGOING MONITORING MECHANISM WITHIN THE EMRO. SO THAT'S THE BASIC PROCESS THAT WE PRESCRIBED.

NOW, WHAT KIND OF CRITERIA ARE EMRO'S SUPPOSED TO EMPLOY IN REVIEWING RESEARCH? THAT GETS INTO SUBSTANCE. WE BREAK INTO THREE CATEGORIES ALL RESEARCH THAT WOULD GO TO AN EMRO, GREENLIGHTED RESEARCH WHICH REALLY DOESN'T REQUIRE FULL EMRO REVIEW, YELLOWLIGHTED WHICH WOULD MEAN THAT THERE IS

SORT OF A RIGOROUS EMRO VETTING PROCESS, AND THEN, OF COURSE, REDLIGHTED RESEARCH, WHICH WOULD BE RESEARCH THAT IS VERBOTEN.

SO FROM THE STANDPOINT AT LEAST FOR THE YELLOW CATEGORY, ANY KIND OF GENETIC MANIPULATION OF HUMAN EMBRYOS OR GAMETES SHOULD UNDERGO AN EMRO PROCESS. WHAT KIND OF CRITERIA OUGHT EMRO'S APPLY WHEN THEY ARE DOING SUCH PROPOSALS? WELL, THE PRINCIPAL CRITERIA THAT ARE ARTICULATED IN THE ISSCR GUIDELINES IS THAT THE PROPOSALS NEED TO BE VETTED FOR SCIENTIFIC MERIT. FOR EXAMPLE, THEY NEED TO HAVE APPROPRIATE DESIGN, THAT THEY'RE GOING TO REALLY RESOLVE A LIVE SCIENTIFIC QUESTION. THERE NEEDS TO BE ADEQUATE EXPERTISE ON THE PART OF PERSONNEL WHO ARE PROPOSING TO PURSUE THE INVESTIGATIONS, AND THERE NEEDS TO BE AN ETHICAL JUSTIFICATION. FOR EXAMPLE, ONE WANTS TO MINIMIZE THE USE OF HUMAN EMBRYOS, ONE WANTS TO ENSURE THAT THERE IS NO WAY OF ATTAINING THE SAME KIND OF INFORMATION OR KNOWLEDGE USING NONHUMAN EMBRYOS, FOR EXAMPLE. AND, OF COURSE, THAT THE SCIENTIFIC FINDINGS OUTWEIGH THE MORAL CONCERNS ABOUT THE POTENTIAL DESTRUCTION OF HUMAN EMBRYOS. SO THAT'S THE YELLOWLIGHTED COMPONENT.

NOW, WHAT ABOUT THE FORBIDDEN OR THE

REDLIGHTED KINDS OF ACTIVITIES? THERE REALLY ARE TWO THAT PERTAIN TO THE DISCUSSION TODAY. THE FIRST IS ONE THAT'S BEEN WIDELY ARTICULATED IN MANY OTHER DOCUMENTS, THERE'S NOTHING REALLY TOO NEW HERE, WHICH IS THE NOTION WHAT WHEN YOU ARE CONDUCTING RESEARCH ON HUMAN EMBRYOS, WHETHER YOU ARE GENETICALLY MODIFYING THEM OR NOT, THAT THAT RESEARCH MUST STOP AT 14 DAYS OR THE BEGINNING OF THE FORMATION OF THE PRIMITIVE STREAK. SO THAT WOULD OBVIOUSLY APPLY IN THE CONTEXT OF GENE EDITING OF HUMAN EMBRYOS.

AND THE SECOND PROSCRIPTION, THE SECOND TYPE OF RESEARCH THAT IS DISCOURAGED UNDER THE ISSCR GUIDELINES IS THE CLINICAL DIMENSIONS, THAT THE ISSCR GUIDELINES HOLD THAT THERE MUST NOT BE ANY KIND OF IMPLANTATION OF GENETICALLY MODIFIED HUMAN EMBRYOS INTO THE UTERUS OF A HUMAN OR NONHUMAN SPECIES.

NOW, OBVIOUSLY THAT REFERS TO GENETIC MODIFICATION OF HUMAN EMBRYONIC, BUT ALSO THE FINE PRINT OF THE GUIDELINES SPECIFY THAT WOULD ALSO PERTAIN TO THE NUCLEAR DNA MODIFICATION OF ANY HUMAN GAMETES THAT ARE USED TO CREATE HUMAN EMBRYOS. SO THOSE ARE THE THREE PRINCIPAL COMPONENTS.

THERE'S, IN ADDITION TO THE LANGUAGE ON

THE YELLOW, GREEN, AND REDLIGHTED ACTIVITIES, THERE IS A SPECIAL SECTION THAT COVERS EMERGING CATEGORIES OF EMBRYO RESEARCH THAT MERIT CLOSE REVIEW. HERE WE SPEAK DIRECTLY TO THE NUCLEAR EDITING OF HUMAN GENOMES. AND WHAT THAT LANGUAGE DOES IN THE RECOMMENDATION IS SANCTION THE IDEA OF CONTINUING RESEARCH ON THE RECOGNITION THAT GENETIC EDITING OF HUMAN EMBRYOS CAN LEAD TO IMPORTANT INSIGHTS AND BASIC SCIENCE, PERHAPS EVEN IMPORTANT INSIGHTS FOR CLINICAL APPLICATION. AND SO THE GUIDELINES ARE VERY CLEAR THAT THEY WANT TO SANCTION AT LEAST A SPACE FOR CONDUCTING RESEARCH ON HUMAN EMBRYOS THAT MIGHT INVOLVE NUCLEAR DNA EDITING. HOWEVER, THEY ALSO SPECIFY THAT ANY KIND OF CLINICAL APPLICATION SHOULD BE PROHIBITED AT THIS TIME.

WHAT'S THE RATIONALE OR BASIS FOR THAT PROHIBITION? WE SPECIFIED TWO AND THEY'RE NOT TOO SURPRISING BECAUSE THEY'RE SIMILAR TO THE PRINCIPLES THAT WERE ARTICULATED IN THE NATIONAL ACADEMIES OF SCIENCE REPORT. NO. 1, UNCERTAINTY CONCERNING THE SAFETY AND LONG-TERM RISKS. SO THOSE ISSUES NEED TO BE RESOLVED BEFORE WE START GOING INTO CLINICAL APPLICATIONS. AND SECONDLY, THERE NEEDS TO BE SOME KIND OF ADEQUATE PUBLIC AND INTERNATIONAL DIALOGUE ABOUT THE PERMISSIBILITY OF EDITING HUMAN EMBRYOS IN

A CLINICAL CONTEXT. AGAIN, IF WE READ THE EXPLICATORY LANGUAGE WITHIN THE RECOMMENDATIONS, YOU WILL SEE THAT THE ISSCR GUIDELINES WOULD SAY THAT, TO DATE AT LEAST, THERE HAVE NOT BEEN ADEQUATE PUBLIC OR INTERNATIONAL DIALOGUE ON THESE ISSUES.

AS WELL, THE ISSCR GUIDELINES PIVOT WITHIN THIS PARAGRAPH AND RECOGNIZE AND DISTINGUISH THE EDITING OF NUCLEAR DNA OF HUMAN EMBRYOS FROM MITOCHONDRIAL REPLACEMENT TECHNIQUES. AND SO THE GUIDELINES IN PRINCIPLE SANCTION THOSE KINDS OF ACTIVITIES PROVIDED THAT THEY UNDERGO THE PROPER FORMS OF HUMAN PROTECTIONS AND EMRO OVERSIGHT.

NOW, COMING BACK TO THE PRINCIPLES, THERE ARE A COUPLE LITTLE DETAILS THAT I THINK ARE KIND OF IMPORTANT TO RECOGNIZE WHEN ONE LOOKS AT THE TOTALITY OF THE ISSCR REPORT. SO FIRST OF ALL, REMINDER, WE CALL OUT THIS NOTION OF INTEGRITY OF THE RESEARCH ENTERPRISE AND TRANSPARENCY. AND WHAT THAT ENTAILS IN THIS CONTEXT IS THAT FINDINGS OF ANY KIND OF RESEARCH, PARTICULARLY BECAUSE THIS IS HIGHLY SENSITIVE RESEARCH, BECAUSE IT'S USING HIGHLY SENSITIVE TISSUES, THIS RESEARCH OUGHT TO BE PUBLISHED IN FULL SO THAT THE SCIENTIFIC COMMUNITY CAN MAXIMIZE THE EFFICIENCY WITH WHICH IT'S LEARNING ABOUT THESE TECHNIQUES. AND, OF COURSE, THERE NEEDS

TO BE OPEN LINES OF COMMUNICATION WITH THEIR PUBLICS OWING TO THE SENSITIVITIES OF THIS RESEARCH.

NOW, I WANT TO CLOSE BY POINTING OUT THREE ISSUES THAT I THINK ARE NOT ADEQUATELY RESOLVED AS YET, AT LEAST IN THE ISSCR GUIDELINES. AND AS I HAVE SPENT HOURS AND HOURS PICKING OVER THE LANGUAGE OF THE ISSCR GUIDELINES AND LOOKING AT THE LANGUAGE OF VARIOUS OTHER REPORTS, ETC., I SEE SOME ISSUES THAT OCCASIONALLY ARE KIND OF SHUNTED TO THE SIDE THAT REALLY NEED TO BE CONFRONTED IF WE WANT TO CREATE EFFECTIVE AND COMPREHENSIVE POLICY IN THIS ARENA. SO I'LL MENTION THREE THAT COME OUT TO ME RIGHT AWAY.

SO THE FIRST ISSUE IS BIOSAFETY. BIOSAFETY IS NOT NECESSARILY AS LOOMING AN ISSUE IF WE ARE RESTRICTING THIS IS TO HUMAN NUCLEAR DNA EDITING, BUT IT DOES BECOME RELEVANT WHEN WE ARE TALKING ABOUT THE PROSPECT OF COMBINING THIS RESEARCH WITH ANIMAL HUMAN CHIMERA RESEARCH. AND WHEN THE ISSCR BEGAN REVISING ITS GUIDELINES, BIOSAFETY WAS JUST A TINY LITTLE BLIP ON THE HORIZON. AND OVER THE LAST FEW MONTHS, THAT HAS BECOME A VERY KIND OF LOOMING AND IMPORTANT SET OF ISSUES. AND SO I WOULD ENCOURAGE ANY KIND OF RULEMAKING IN THIS ARENA TO REALLY CONTEMPLATE THE

MORAL DIMENSIONS OF BIOSAFETY, NOT TO MERELY VIEW THAT THROUGH THE LENS THAT WE TYPICALLY VIEW THIS THROUGH, THE INSTITUTIONAL BIOSAFETY COMMITTEE, ETC.

THE SECOND ISSUE AND ONE THAT ACTUALLY ENCOURAGINGLY HAS BEEN CALLED OUT TWICE AT THIS MEETING IS THAT WE ARE VERY FIXATED OVER THE LAST FEW MONTHS, FOR REASONS EXPLAINED BY DAVID BALTIMORE, ON THE EDITING OF NUCLEAR DNA OF HUMAN EMBRYOS. BUT THERE ARE MANY DIFFERENT TECHNIQUES WE CAN USE THAT INVOLVE NONEDITING TECHNIQUES. WE CAN USE LENTIVIRAL VECTORS, FOR EXAMPLE, TO INTRODUCE DNA IN A NONTARGETED FASHION. AND SO IT'S IMPORTANT THAT WE MAKE SURE THAT WHATEVER LANGUAGE WE CREATE IS GOING TO BE COMPREHENSIVE ENOUGH TO COVER TECHNIQUES BEYOND MERELY THOSE HIGHLY TARGETED, HIGHLY SPECIFIC KINDS OF TECHNIQUES THAT WE'VE BEEN FOCUSED ON.

AND I THINK THE THIRD ISSUE AND ONE THAT REALLY BOTHERS ME THE MOST AS SOMETHING THAT I THINK HAS BEEN DODGED IN ALL OF THESE DISCUSSIONS IS THE ISSUE ABOUT NONINHERITABLE MODIFICATION OF HUMAN EMBRYOS OR FETAL TISSUES, PARTICULARLY IN THE CONTEXT OF ASSISTED REPRODUCTION. SO I'M THINKING OF TWO PARTICULAR CATEGORIES HERE. FIRST OF ALL, THE INTRODUCTION OF EPISOMAL VECTORS WITHIN THE

HUMAN EMBRYO THAT MIGHT NOT NECESSARILY BE PASSED DOWN THROUGH FUTURE GENERATIONS BECAUSE THEY ARE NOT STABLY INTEGRATED NECESSARILY, BUT THEY WILL AFFECT THE FIRST GENERATION. I THINK THAT NEEDS TO BE CONTEMPLATED AT LEAST IN TERMS OF HOW WE BOUND WHAT'S PERMISSIBLE AND WHAT'S NOT.

AND THEN, OF COURSE, THERE'S THE ISSUE OF APPLYING THESE TECHNIQUES IN SETTINGS, FOR EXAMPLE, IN UTERO GENE TRANSFER WHERE, AGAIN, YOU MIGHT HAVE NONINHERITABLE TO THE EXTENT OF NOT BEING PASSED INTO THE GERMLINE, BUT YOU DO HAVE AN ORGANISM THE TOTALITY OF WHICH OR AT LEAST A LARGE COMPONENT OF WHICH IS AFFECTED BY THESE GENETIC MODIFICATIONS. I THINK THAT THE PRESCRIPTIONS AND PROSCRIPTIONS THAT ISSCR HAS ARTICULATED AND MANY OTHERS HAVE ARTICULATED HAVE WALLED OFF CERTAIN DIMENSIONS, BUT I THINK THERE ARE LOTS OF OTHER AREAS THAT ARE NOT REALLY ADEQUATELY RESOLVED AND NEED TO HAVE SOME ATTENTION. SO I'LL STOP THERE.

CO-CHAIR LO: THANKS VERY MUCH. QUESTIONS?

MR. SHEEHY: SO IN THINKING ABOUT THE ABILITY TO CONDUCT ALL THIS RESEARCH ON EMBRYOS, I WONDER ABOUT THE RIGHTS OF THE DONOR, THE FAMILY THAT DONATED THE EMBRYOS. SO DOES OUR INFORMED

CONSENT PROCESS REALLY ANTICIPATE THE CEDING OR THE DISPENSING OF THEIR RIGHTS? SO LET'S SAY THAT YOU GET AN EMBRYO FROM A FAMILY WITH HUNTINGTON'S, AND THIS TECHNOLOGY HAS BEEN SIGNIFICANTLY PERFECTED. WE JUST ASSUME THAT IN SIGNING AN INFORMED CONSENT, THEY ANTICIPATED THAT THEY WOULD NOT HAVE ACCESS TO THEIR OWN GENETIC MATERIAL, THEIR OWN EMBRYO IN WHICH THIS TERRIBLE GENETIC DISEASE HAS BEEN ELIMINATED. TO ME THAT DOESN'T SEEM ENTIRELY CONSISTENT WITH WHAT THEY MAY HAVE ANTICIPATED WHEN THEY SIGNED AN INFORMED CONSENT, THAT A VIABLE EMBRYO WITH THE GENE THAT HAS TORMENTED THEIR FAMILY FOR GENERATIONS HAS BEEN ELIMINATED, AND HAS THAT JUSTICE ASPECT BEEN CONTEMPLATED? IS IT ON THE TABLE IN THESE DISCUSSIONS?

DR. KIMMELMAN: NICE QUESTION. SO THERE IS OBVIOUSLY A LARGE COMPONENT OF THE GUIDELINES THAT I WASN'T ABLE TO GET TO, AND THERE ARE CERTAINLY MANY PARAGRAPHS DEVOTED TO THE INFORMED CONSENT DISCUSSION. I THINK YOU'RE ASKING TWO DISTINCT QUESTIONS. ONE OF THEM IS THE JUSTICE IMPLICATIONS OF DENYING PEOPLE WHO ARE TISSUE DONORS OF WHAT THEY MIGHT WANT TO DO WITH THESE TISSUES, PARTICULARLY IN THE REPRODUCTIVE CONTEXT, AND TECHNICALLY WHAT YOU TELL PEOPLE IN THE INFORMED

CONSENT PROCESS. LET ME START WITH THE INFORMED CONSENT.

THE ISSCR GUIDELINES DO STIPULATE THAT, WHEN YOU ARE CONDUCTING RESEARCH ON HUMAN EMBRYOS AND OTHER KINDS OF SENSITIVE TISSUES AND PURSUING RESEARCH THAT COULD BE ETHICALLY SENSITIVE, THAT THERE OUGHT TO BE SPECIFIC CONSENT SO THAT THERE OUGHT TO BE SOME DESCRIPTION OF THE RESEARCH APPLICATIONS IF THEY ARE GOING TO BE SENSITIVE SO THAT TISSUE DONORS CAN DECIDE WHETHER OR NOT THEY'RE COMFORTABLE WITH THEIR EMBRYONIC TISSUE BEING USED IN THAT CAPACITY.

SO IN THAT RESPECT, I THINK THAT AN INFORMED CONSENT DISCUSSION COULD ADDRESS THE POINT THAT YOU'RE CONCERNED ABOUT THERE, WHICH IS THAT THERE ARE -- YOU WOULD TELL THE PATIENT THAT THERE ARE LIMITS OR PROHIBITIONS ON THE USE OF THESE GENETICALLY MODIFIED EMBRYOS IN A REPRODUCTIVE CONTEXT. SO BY YOUR ALLOWING US TO PURSUE RESEARCH ON YOUR HUMAN EMBRYOS, YOU SHOULD UNDERSTAND THAT YOU WILL NOT BE AUTHORIZED OR AT LEAST WE WILL NOT BE AUTHORIZED TO USE THESE EMBRYOS IN A REPRODUCTIVE CONTEXT, BUT THAT DOESN'T NECESSARILY ADDRESS THE QUESTION OF WHETHER OR NOT THAT'S FAIR OR APPROPRIATE OR NOT. THAT'S A SEPARATE QUESTION, BUT

I THINK YOU ASKED ABOUT THE INFORMED CONSENT.

MR. SHEEHY: WELL, I HAD NOT THOUGHT ABOUT THIS ISSUE BEFORE, AND ESPECIALLY WE'VE BEEN TALKING ABOUT PGD BEING ABLE TO RESOLVE A LOT OF ISSUES RELATED TO HERITABLE DISEASES. WELL, THAT ANTICIPATES PRODUCTION OF A NUMBER OF EMBRYOS, SO THOSE EMBRYOS ARE THERE. PRESUMABLY THOSE EMBRYOS WOULD BE SOME OF THE EMBRYOS THAT ARE USED FOR THIS RESEARCH. AND I AM CONCERNED -- IF I WERE A HUNTINGTON'S PARENT, TO USE AS AN EXAMPLE, I WOULD WANT THAT EMBRYO BACK, AND I WOULD WANT TO USE THAT. AND I DON'T THINK -- AND THIS IS REALLY, AGAIN, GETTING TO WHAT THE PURPOSE OF THIS MEETING IS IS REAL PRACTICAL QUESTIONS SURROUNDING RULES THAT WE ALREADY IN HAVE IN PLACE. I DO NOT THINK OUR INFORMED CONSENT THAT WE ASK OUR INSTITUTIONS TO USE ANTICIPATE THE CREATION OF A VIABLE EMBRYO WITH THE GENE THAT CAUSES A DISEASE EDITED OUT AND TELLS PARENTS THAT THEY WILL NOT HAVE ACCESS TO THOSE EMBRYOS IF THEY DO -- IF THEY DESIRE -- OBVIOUSLY THEY'RE DONATING TO RESEARCH BECAUSE THEY WANT TO ELIMINATE THIS FROM THEIR GERMLINE. SO TO HAVE THAT ACCOMPLISHED AND THEN NOT HAVE ACCESS, ESPECIALLY IF YOU LOOK AT THE TIMELINE, THAT PEOPLE MAY BE DONATING WHEN THEY'RE YOUNG AND THAT THEY COULD

STILL -- YOU DONATE IN YOUR TWENTIES AND YOU COULD STILL POSSIBLY USE THAT EMBRYO IN YOUR FORTIES.

DR. KIMMELMAN: I THINK JUST TO ADD ANOTHER DIMENSION, THIS IS CERTAINLY SOMETHING, PUTTING ON A DIFFERENT HAT, WHEN I WAS ON THE IOM REPORT FOR MITOCHONDRIAL REPLACEMENT, SOMETHING WE SPENT A LOT OF TIME TALKING ABOUT. SO YOU GET A BUNCH OF HUMAN EMBRYOS, YOU REPLACE THEIR MITOCHONDRIA. SOME OF THEM ARE MALE, SOME OF THEM ARE FEMALE. UNDER THE RECOMMENDATIONS IN THE REPORT, PROVIDED CONDITIONS ARE MET, YOU ONLY IMPLANT THE MALE, BUT YOU HAVE THESE OTHER FEMALE THAT ARE CORRECTED MITOCHONDRIALLY. AND THE QUESTION IS DO THE DONORS, DO THE PARENTS OF THOSE EMBRYOS HAVE ANY KIND OF LEGAL OWNERSHIP OF THOSE EMBRYOS SUCH THAT THEY COULD PUT THEM IN A DEWAR FLASK AND FLY TO WHEREVER THEY'RE GOING TO FLY TO AND HAVE THEM IMPLANTED? I'M NOT IN ANY WAY AN EXPERT ON GLOBAL, MUCH LESS CANADIAN OR U.S. LAW ON OWNERSHIP OF TISSUES, BUT I DO THINK THAT THAT BECOMES A REALLY IMPORTANT ISSUE TO RESOLVE AS WHO OWNS THESES EMBRYOS WHEN YOU INTRODUCE GENETIC MODIFICATIONS IN A RESEARCH SETTING.

CO-CHAIR LO: THIS SEEMS TO HAVE SPARKED A LOT OF DISCUSSION. I WANT TO FIRST TAKE PEOPLE WHO

ARE ADDRESSING THIS POINT THAT JEFF RAISED ABOUT THE CONSENT PROCESS AND SORT OF A MORAL OR LEGAL RIGHT OF THE DONORS OF EMBRYOS WITH SERIOUS DISEASE TO RECOVER THEM FROM THE RESEARCHERS IF THE EMBRYOS HAVE BEEN GENE EDITED FOR THE DEFECT. STICK YOUR HANDS UP IF THIS IS THE POINT YOU WANT TO SPEAK ON. SO DR. CLARK, DR. WAGNER, DR. PRIETO, DR. LEE. THERE WERE HANDS IN THE BACK AS WELL ON THIS POINT.

MS. DARNOVSKY: RELATED BUT DIFFERENT.

CO-CHAIR LO: LET'S GET THESE FIRST AND THEN GET THE RELATED ONES.

DR. CLARK: SO I THINK, JEFF, YOU RAISE AN INCREDIBLY GOOD POINT, BUT I WONDER IF WE MIGHT HAVE SKIPPED OVER BASIC RESEARCH. AND SO COMING FROM AN INSTITUTION WHERE WE DO WORK WITH HUMAN EMBRYOS, WHEN THE EMBRYOS ARE DONATED TO OUR RESEARCH PROGRAM, IT'S VERY CLEAR IN THE INFORMED CONSENT THAT THE DONORS DO NOT GET THEIR EMBRYOS BACK. AND SO THIS COMES BACK TO THE CLARITY OF AN INFORMED CONSENT PROCESS.

AND SO IF A COUPLE WANTS THEIR EMBRYO BACK, THEN THEY WOULD NOT SIGN THAT CONSENT AND THE RESEARCHER WOULD NOT GET THE EMBRYO. BUT WE WOULDN'T KNOW IF WE'VE CORRECTED HUNTINGTON'S DISEASE, WHICH IS A GREAT EXAMPLE BECAUSE IT'S NOT

IN THE GENE ITSELF. IT'S IN A REGULATORY REGION. WE WON'T KNOW IF WE CORRECTED THAT UNLESS WE DO THE RESEARCH TO DEMONSTRATE THAT THESE GENE EDITING TECHNOLOGIES WOULD ACTUALLY WORK IN HUMAN EMBRYOS. IT IS LIKELY, POSSIBLY, THAT GENE EDITING WON'T WORK IN HUMAN EMBRYOS AT ALL BECAUSE OF UNIQUE REPAIR PATHWAYS THAT THEY MIGHT FOLLOW THAT DON'T WORK IN SOMATIC CELLS AND WORK DIFFERENTLY IN EMBRYOS. WE JUST DON'T KNOW ANY OF THAT INFORMATION YET.

SO I THINK WITH REGARD TO AN INFORMED CONSENT FOR RESEARCH, IF THEY WANT THE EMBRYO BACK, THEY'RE NOT GOING TO SIGN THAT INFORMED CONSENT WOULD BE MY THOUGHT ON THE PROCESS, BUT I'M VERY OPEN TO WHAT OTHER PEOPLE ARE THINKING AS WELL.

MR. SHEEHY: IT REALLY GOES TO THE GRANULARITY OF THE INFORMED CONSENT. AGAIN, I THINK THE 30,000 FEET ISSUES, THIS MIGHT BE AN ISSUE THAT MAYBE THE NAS OR OTHER FOLKS WHO ARE LOOKING AT IT, BUT FROM A PRACTICAL STANDPOINT FOR INFORMED CONSENT THAT WE ASK FOR RESEARCH THAT WE FUND, IS THIS A NEW FEATURE THAT WE NEED TO -- DO WE NEED TO CHANGE OUR INFORMED CONSENT IN ORDER THAT THE DONORS RECOGNIZE THIS AS A POTENTIAL POSSIBILITY? THAT'S NOT TRYING TO COMPLETELY DEFINE OUT THE MORAL AND ETHICAL ISSUES, BUT I THINK IT'S AN INTERESTING THING TO

THINK ABOUT. BUT TO REALLY LOOK, OUR INFORMED CONSENTS, I DO NOT BELIEVE, ANTICIPATE THIS USE. I DO NOT THINK NOW DONORS THINK THAT THEIR EMBRYOS WILL BE CORRECTED AND VIABLE, WHICH IF YOUR RESEARCH IS SUCCESSFUL, IS A POTENTIAL REALITY.

CO-CHAIR LANSING: I DON'T NEED TO JUMP THE QUEUE. I THINK THIS IS WHAT WE SHOULD DISCUSS, BUT I THINK IT'S A SLIPPERY SLOPE BECAUSE ONCE YOU START DOING THIS, THE BRCA GENE, WE'LL EDIT THAT OUT. WE HAVE TO TELL THEM THIS, WE HAVE TO TELL THEM THAT. AND I BELIEVE, AND WE HAVE TO GO BACK AND LOOK AT THIS, THAT OUR INFORMED CONSENT WAS REALLY BROAD AND THAT PEOPLE -- THERE'S MANY, MANY DISEASES THAT CAN BE CURED BY THIS. AND SO WHAT WOULD BE THE EXHAUSTIVE LIST THAT WE PUT DOWN? SO I BELIEVE WE WENT OVER THIS ISSUE REALLY CAREFULLY EARLY ON AND WE SHOULD CHECK IT, THAT OUR INFORMED CONSENT WAS AS BROAD AS YOU'RE TALKING ABOUT AND REALLY WAS A LOT OF PEOPLE TALKING TO LOT OF PEOPLE.

I REMEMBER ALL THE ISSUES THAT WE WENT THROUGH, THAT THERE WERE ENDLESS POSSIBILITIES THAT COULD HAPPEN. THAT'S WHAT WE HOPED FOR, ENDLESS CURES. SO HUNTINGTON'S IS JUST ONE EXAMPLE, BUT THERE'S MANY, MANY OTHERS.

DR. BALTIMORE: AS A MATTER OF FACT, I

THINK THERE IS AN IMPOSSIBILITY IN THIS QUESTION. AND THAT IS THAT RESEARCH THAT'S DONE IN THE LABORATORY IS NOT DONE UNDER CONDITIONS THAT GUARANTEE THAT THE EMBRYO CAN BE REIMPLANTED. AND THOSE WILL BE GOOD LABORATORY PRACTICES OR GOOD MANUFACTURING PRACTICES, GMP FACILITY. AND YOU WON'T DO RESEARCH IN THAT.

SO I THINK IT WOULD BE UNETHICAL, I THINK IT WOULD BE PROBABLY ILLEGAL TO REIMPLANT AN EMBRYO THAT HAD GONE INTO THE RESEARCH LAB. NOW, MAYBE THAT SHOULD BE INCORPORATED INTO THE INFORMED CONSENT, THE CONDITIONS UNDER WHICH THE EMBRYO WILL BE MANIPULATED DON'T ALLOW REIMPLANTATION.

CO-CHAIR LO: LET ME JUST -- JEFF OPENED UP A REALLY IMPORTANT SET OF ISSUES. I WANT TO TRY AND GET BACK TO THE QUEUE FOR PEOPLE WHO HAVE BEEN PATIENT. BUT I WANT TO DISTINGUISH SEVERAL DIFFERENT SITUATIONS. ONE IS EMBRYOS THAT HAVE BEEN DONATED IN THE PAST, WHEN WE WERE THINKING OF THIS, WE BEING THE RESEARCHERS, SWG, OR THE PEOPLE WHO ARE ASKED TO DONATE. SO THEY SIGN SOMETHING THINKING CERTAIN THINGS ARE GOING TO HAPPEN AND NOW THERE'S A NEW POSSIBILITY. HOW DO WE DEAL WITH THAT?

SECOND, THERE'S A DIFFERENT SITUATION ABOUT WHAT ARE PEOPLE DONATING NOW WHERE THEY GET TO

HAVE A DISCUSSION AND SIGN A CONSENT FORM? HOW SHOULD WE MODIFY CURRENT AND FUTURE CONSENT TO TAKE INTO ACCOUNT THE NEW SCIENCE, THE NEW IMPLICATIONS? IT'S A HUGELY IMPORTANT ISSUE, AND I THINK WE NEED -- THIS IS SOMETHING THIS COMMITTEE REALLY NEEDS TO ADDRESS, DIG INTO, AND WE HAVE TO GET DOWN -- CIRM ACTUALLY NEEDS VERY GRANULAR ADVICE HERE. SO THIS IS SOMETHING THAT'S IMPORTANT.

JOHN AND THEN FRANCISCO.

DR. WAGNER: IN RESPONSE TO YOUR QUESTION, I THINK REALLY AN EXTENSION OF WHAT YOU JUST SAID IS THAT THIS WOULD NOT BE A VIABLE EMBRYO BECAUSE ONE OF THE THINGS I WAS SURPRISED YOU DIDN'T ADD WAS THE QUESTION ABOUT MOSAICISM. YOU WOULD ACTUALLY BE LOOKING AT EVERY ONE OF THE BLASTOMERES. YOU WOULD NOT BE LOOKING AT ONE LIKE YOU WOULD DO IN TYPICAL PGD AND THEN JUST KEEPING THE REST ALIVE. AS PART OF THE RESEARCH, IT HAS TO BE CLEARLY STATED IN THE CONSENT FORM, NOT JUST BECAUSE IT MAY BE IN A RESEARCH LABORATORY BECAUSE I CAN IMAGINE HOW YOU COULD CONTRIVE THAT SO I COULD DO THIS ACTUALLY IN THE IVF PGD CENTER AND KEEP THIS UNDER "GMP" CONDITIONS AND DO ONE BLASTOMERE EVALUATION AND SAY, OH, YES. WE DID WHAT WE WANTED TO DO, BUT THAT'S NOT WHAT WE WOULD DO. WE WOULD ACTUALLY LOOK AT

EVERY SINGLE ONE OF THEM TO SEE REALLY WHAT WAS THE EXTENT OF THE CORRECTION AND WHETHER OR NOT THERE WAS ANY MOSAICISM OR ANY DIFFERENT CUTS AND DIFFERENT CELLS. SO THAT WOULD NEVER BE THE CASE. YOU DON'T HAVE A VIABLE EMBRYO.

DR. PRIETO: I THINK AT THIS POINT THAT'S TRUE, BUT WE ALL ARE FORESEEING THAT AT SOME POINT THAT TRUTH TO THAT REALITY IS GOING TO CHANGE. I THINK THE DISTINCTION HERE IS BETWEEN OWNERSHIP OF THE MATERIAL THAT YOU ARE DONATING FOR RESEARCH AS A MATTER OF PROPERTY AND ACCESS DOWNSTREAM TO A THERAPY THAT COMES OUT OF THAT. AND THAT I THINK BRINGS UP THE SOCIAL JUSTICE ISSUES, THE OTHER TOPICS THAT WERE JUST TOUCHED ON. I THINK CERTAINLY EVERY DONOR SHOULD HAVE THE SAME ACCESS THAT ANYONE ELSE HAS TO THOSE DOWNSTREAM BENEFITS, BUT THAT'S DIFFERENT FROM OWNERSHIP OF YOUR OWN MATERIAL. YOU HAVE TO GIVE THAT UP IN ORDER TO ALLOW THIS RESEARCH TO HAPPEN AND YIELD A RESULT.

MS. DARNOVSKY: MARCY DARNOVSKY FROM THE CENTER FOR GENETICS AND SOCIETY. SO THIS IS THE RELATED, AND I THINK IT FOLLOWS THE PREVIOUS COMMENT ABOUT HOW WE TALK ABOUT SOCIAL JUSTICE. AND, JONATHAN, IT WAS ONE OF YOUR FIVE PRINCIPLES THAT THE ISSCR HAD IDENTIFIED, BUT IT WAS GRAYED OUT, THE

WORDS "SOCIAL JUSTICE," AND DIDN'T ADDRESS THAT. AND ALTA, WHEN SHE WAS ON THE PHONE, ACKNOWLEDGED HOW DIFFICULT IT IS TO ADDRESS SOCIAL JUSTICE AND TO REALLY BRING IN THE RANGE OF COMMUNITIES THAT NEED TO BE PART OF THIS KIND OF DISCUSSION.

SO I WANTED TO JUST COMMENT ON THE CONVERSATION SO FAR. ONE PREVIOUS COMMENT TODAY SEEMED TO BE SUGGESTING, MAYBE IT WASN'T WHAT YOU MEANT, THAT THE ONLY ETHICAL OBJECTIONS TO HUMAN GERMLINE MODIFICATION OTHER THAN SAFETY WERE BASED ON NATURALNESS. I THINK THERE'S A WHOLE SET OF VERY IMPORTANT SOCIAL JUSTICE CONCERNS THAT DAVID ALLUDED TO EARLIER THAT WE SAY SOCIAL JUSTICE, BUT WE GRAY IT OUT. AND I THINK THAT'S A TENDENCY IN THESE CONVERSATIONS. AND I WOULD LIKE TO SUGGEST THAT ONE OF THE THINGS THAT WE HAVE TO DO IS LOOK AT THE BROADER SYSTEMIC STRUCTURES. AND IT'S HARD FOR A COMMITTEE LIKE THIS. SO IT'S COMPLETELY THE OPPOSITE DIRECTION THAT JUST IMPORTANT QUESTION ABOUT GRANULARITY OF CONSENT FORMS GOES TO GOING IN A MUCH BROADER DIRECTION; BUT IF YOU LEAVE IT OUT, WE'RE LEAVING OUT REALLY, REALLY CRUCIAL THINGS.

SO IT INCLUDES CIRM IS A PUBLICLY FUNDED PROGRAM, THE RESEARCH IS PUBLICLY FUNDED. THERE SEEMS TO ME TO BE A NEED TO CONSIDER PRIORITIES FOR

THE GREATEST NUMBER OF PEOPLE WITH THE USE OF PUBLIC FUNDS. I THINK ALSO WE HAVE TO LOOK AT THE KIND OF SOCIAL DYNAMICS AND COMMERCIAL DYNAMICS THAT WOULD BE SET IN MOTION IF GERMLINE MODIFICATION WERE TO BE APPROVED AND PUT INTO A MARKETING CONTEXT OF A COMMERCIAL FERTILITY INDUSTRY. THOSE ARE SUCH HARD THINGS TO DO, BUT TO IGNORE THEM DOESN'T SEEM TO ME TO BE A GOOD COURSE.

AND I THINK SPECIFICALLY, IT WOULD BE INTERESTING TO HEAR FROM YOU, JONATHAN, IF ISSCR HAS HAD ANY OF THOSE KINDS OF CONVERSATIONS. AND I THINK IT WOULD BE REALLY IMPORTANT FOR THIS COMMITTEE, STANDARDS WORKING GROUP, TO TALK ABOUT ITS ROLE IN HAVING AND THEN DISSEMINATING THOSE KINDS OF CONSIDERATIONS.

DR. KIMMELMAN: THOSE ARE EXCELLENT POINTS. SO LET ME RESPOND IN A COUPLE OF DIFFERENT WAYS. IN TERMS OF THE GRAYING OUT OF JUSTICE, I HAD TEN OR FIFTEEN MINUTES HERE TO PRESENT, AND SO I THINK THERE ARE THREE PRINCIPLES THERE THAT PROBABLY HAVE THE MOST PROXIMATE APPLICATION IN TERMS OF EXPLAINING THE RATIONALE OF ISSCR'S RECOMMENDATIONS. IF YOU SCRATCH BENEATH THE SURFACE, THE SECOND COMPONENT, NOT SO MUCH THE SAFETY ISSUE, ALTHOUGH THERE IS A JUSTICE COMPONENT TO THE SAFETY ISSUE ON

MANY DIFFERENT DIMENSIONS, BUT THE NOTION OF THERE NEEDING TO BE AN APPROPRIATE SET OF PUBLIC DELIBERATIONS ABOUT THE IMPLICATION, IF YOU SCRATCH UNDERNEATH THE SURFACE, THAT IS LARGELY ANIMATED BY THE SAME KINDS OF JUSTICE CONCERNS THAT I THINK YOU HAVE IN MIND. SO EXACTLY THOSE ISSUES OF SLIPPERY SLOPE AND EQUITABLE ACCESS, ETC. SO I THINK THAT'S THE FIRST POINT.

YOUR OTHER QUESTION, THE EXTENT TO WHICH THESE CONCERNS ABOUT JUSTICE WERE INFLUENTIAL IN THE ISSCR'S DISCUSSION, THEY WERE. REMEMBER THE GUIDELINES ARE NOT MERELY ON THIS ONE PARTICULAR APPLICATION OF EDITING OF HUMAN EMBRYOS. THEY COVER EVERYTHING FROM FUNDAMENTAL EMBRYONIC STEM CELL RESEARCH ALL THE WAY THROUGH TO THE CLINICAL APPLICATION. SO WHEN YOU LOOK AT THE GUIDELINES, YOU WILL SEE JUSTICE MOTIVATING MANY OF THE DIFFERENT KINDS OF PRESCRIPTIONS INCLUDING LANGUAGE IN THERE ABOUT EQUITABLE ACCESS TO THE APPLICATIONS OF STEM CELL RESEARCH.

SO, AGAIN, I'VE BEEN ASKED TODAY TO PRESENT A FAIRLY NARROW, FRANKLY JUST A FEW PARAGRAPHS IN THE ENTIRE DOCUMENT, BUT CERTAINLY JUSTICE IS ONE OF THOSE PRINCIPLES THAT WOULD FALL OUT, AND IT ARTICULATES MANY OF THE PRESCRIPTIONS

INCLUDING WHAT FOR NOW WE ARE RECOMMENDING, WHICH IS THE PROHIBITION ON CLINICAL APPLICATION OF NUCLEAR DNA EDITING.

CO-CHAIR LO: SO I WANT TO TRY AND CUE THIS UP. JEFF BOTKIN, DOROTHY ROBERTS. OTHER PRESSING ISSUES? WE DO HAVE LUNCH.

DR. BOTKIN: THANKS, JONATHAN. GREAT TALK. VERY THOUGHTFUL AS ALWAYS. IT SEEMS TO ME THAT THE PROHIBITION AGAINST IMPLANTATION AND PROHIBITIONS, THEY HAVE 14 DAYS, BOTH OF THOSE DO A LOT OF WORK, AND IT MAY ALLOW US TO BE SORT OF AGNOSTIC ABOUT WHAT HAPPENS BEFORE THAT TIME PERIOD. SO I'M GOING TO ASK THE QUESTION ABOUT WHETHER THERE'S A ROLE FOR ENTITIES LIKE ISSCR THINKING ABOUT PRIORITIES WITHIN THAT KIND OF PRECLINICAL PHASE.

IT SEEMS TO ME THAT THERE'S AT LEAST THREE EDITING APPROACHES TO EMBRYOS THAT WE MIGHT WANT TO THINK ABOUT. ONE IS ONE DR. BALTIMORE TALKED ABOUT, KNOCK-IN, KNOCKOUT SORT OF THINGS, WHAT HAPPENS WITH HUMAN DEVELOPMENT, HOW DO WE BETTER UNDERSTAND HUMAN DEVELOPMENT. THAT SEEMS TO ME TO BE HUGELY IMPORTANT. WHETHER IT'S IMPORTANT FOR CIRM, I DON'T KNOW BECAUSE IT DOESN'T SEEM LIKE THERE'S A DIRECT CLINICAL REACH FOR THAT.

THEN THERE'S THE MITOCHONDRIAL GENE EDITING USING CRISPR-CAS9. THAT SEEMS TO ME TO BE VERY VALUABLE. IT'S A DIRECT CLINICAL LINE TO THAT, AND WE CAN DEBATE ABOUT THE HERITABLE ASPECT OF THAT, BUT THAT SEEMS TO ME TO BE AN EXTREMELY VALUABLE LINE.

THE ONE ALSO THAT DR. BALTIMORE AND ALTA TALKED ABOUT IS THE GENE EDITING FOR THERAPEUTIC PURPOSES FOR THE EMBRYO. AND THAT'S ONE THAT SEEMS TO ME TO BE JUST A COMPLETE, NOT COMPLETE, BUT VIRTUAL WASTE OF TIME GIVEN THE ALTERNATIVE TECHNOLOGIES THAT ARE THERE TO MEET COUPLE'S NEEDS WHO ARE IN THAT SORT OF CIRCUMSTANCES. AND THAT'S WHAT REALLY THE PUBLIC IS CONCERNED ABOUT. IT'S THAT THIRD PHASE THAT WE THINK DOESN'T HAVE MUCH CLINICAL UTILITY THAT EVERYBODY IS REALLY CONCERNED ABOUT, AND WE MIGHT BE CONCERNED FROM A JUSTICE STANDPOINT TO SAY WHY SHOULD WE BE SPENDING MONEY ON THAT APPLICATION WHEN THERE'S MANY OTHER VALUABLE COURSES OF RESEARCH TO BE PURSUED.

SO IS THERE A ROLE WITH THESE SORT OF PROFESSIONAL ORGANIZATIONS IN TRYING TO SET THOSE SORTS OF EXPERIMENTAL PRIORITIES, OR IS IT BETTER TO BE AGNOSTIC AND ALLOW ACADEMIC FREEDOM TO MOVE FORWARD AND ALLOW THE COMMUNITY TO DO THAT?

IMPLICITLY I'M SORT OF MAKING A PITCH HERE FOR SOMEBODY TO SAY HERE ARE THE VALUABLE APPROACHES THAT OUGHT TO BE TAKEN HERE, AND HERE ARE THINGS THAT ARE MUCH LESS VALUABLE FOR US AS A SOCIETY TO PURSUE.

DR. KIMMELMAN: THAT'S A REALLY INTERESTING AND DEEPLY PHILOSOPHICAL QUESTION, WHICH IS THE EXTENT TO WHICH ONE OUGHT TO BE PRESCRIPTIVE ABOUT PRIORITIES IN FUNDAMENTAL AND BASIC SCIENCE RESEARCH. ON THE ONE HAND, ONE MIGHT WANT TO ARGUE THAT CUTTING-EDGE RESEARCHERS ARE IN A POSITION TO RECOGNIZE WHERE THE SCIENCE IS MOST LIKELY TO ADVANCE AND WHICH PARTICULAR AREAS OF SCIENTIFIC RESEARCH ARE THE MOST HOSPITABLE IN TERMS OF IMPORTANT KINDS OF CLINICAL APPLICATIONS. WHILE ON THE OTHER HAND, ONE WOULD WANT TO ALSO PRESERVE A SPACE FOR RECOGNIZING THAT, IN FACT, OFTENTIMES MAJOR DISCOVERIES COME OUT OF LEFT FIELD OR THEY COME OUT OF BASIC AND FUNDAMENTAL RESEARCH. THE CLINICAL APPLICATIONS ARE DECADES AWAY AND THEY'RE ONLY DISCOVERED BECAUSE OF SOME PARTICULAR CONSTELLATION OF EVENTS.

I MEAN DAVID BALTIMORE CAN PROBABLY SPEAK TO THE REVERSE TRANSCRIPTASE AS A REALLY GOOD EXAMPLE WHERE YOU DON'T WANT TO SET PRIORITIES THAT

WOULD TAKE PEOPLE AWAY FROM THAT KIND OF BASIC SCIENCE RESEARCH. SO I CAN'T ANSWER YOUR QUESTION, BUT I GUESS I'M INCLINED TOWARDS HAVING MUCH MORE OF AN INVISIBLE HAND CONCEPT OF SCIENCE, THAT THERE'S A SENSE IN WHICH YOU WANT, AT LEAST IN BASIC SCIENCE RESEARCH AND FUNDAMENTAL RESEARCH, YOU WANT TO ALLOW A THOUSAND FLOWERS TO BLOOM AND THOSE PRIORITIES KIND OF EMERGE ORGANICALLY OUT OF THAT RESEARCH. I THINK THAT CHANGES AS YOU BEGIN TO ADVANCE ALONG THE TRANSLATION TRAJECTORY TO WHERE IT'S CLINICAL APPLICATIONS WHERE IT IS REALLY CRITICAL TO SET PRIORITIES.

AND SO THERE'S A LITTLE BIT OF LANGUAGE IN THE GUIDELINES ABOUT SETTING PRIORITIES IN THE CLINICAL RESEARCH REALM, BUT THERE REALLY ISN'T TOO MUCH LANGUAGE ABOUT PRIORITY IN THE BASIC SCIENCE.

DR. ROBERTS: THANK YOU FOR YOUR TALK. I WANT TO ASK A QUESTION ABOUT THE CONCEPT OF SAFETY IN THE PRINCIPLES THAT YOU TALKED ABOUT. IT SEEMS AS IF SAFETY, THE CONCERN ABOUT SAFETY, IS FOCUSED ON CURRENT PATIENTS. SO, IN FACT, THERE WAS A LINE, I BELIEVE I WROTE IT DOWN RIGHT, THE INTEREST OF FUTURE PATIENTS SHOULD NOT OVERRIDE THE INTERESTS OF CURRENT PATIENTS, WHICH SEEMS TO ASSUME THAT THESE TECHNOLOGIES WOULD IMPROVE THE SAFETY OR THE HEALTH

OF FUTURE PATIENTS, BUT MIGHT HARM CURRENT PATIENTS. AND I JUST WONDER ABOUT THE CONCERN THAT THESE TECHNOLOGIES WILL IMPROVE THE HEALTH OF CURRENT PATIENTS, BUT HARM PEOPLE IN THE FUTURE.

AND THEN FOR UNRESOLVED POINTS, YOU USE THE TERM "BIOSAFETY," AND I WASN'T SURE EXACTLY WHAT THAT MEANT, BUT IT SEEMED TO INCLUDE A CONCERN ABOUT FUTURE HARMS. BUT YOUR EXAMPLES ONLY INVOLVED THE INVOLVEMENT OF ANIMALS. AND SO IT SEEMED TO BE A NARROW CONCEPT. AND I WONDERED IF THERE'S A BROADER CONCEPT OF BIOSAFETY THAT CONSIDERS THE SAFETY OF THE FUTURE, FUTURE GENERATIONS, FUTURE ORGANISMS INCLUDING HUMAN BEINGS. AND I JUST WONDERED IF YOU WOULD SAY SOMETHING MORE ABOUT THIS CONCEPT OF BIOSAFETY AND WHAT IT INCLUDES, WHAT IT ENCOMPASSES, AND WHETHER IT MIGHT INCLUDE MORE THAN JUST CONCERN ABOUT ANIMALS WHO AREN'T HUMAN, NONHUMAN ANIMALS.

DR. KIMMELMAN: SURE. THANKS FOR THE QUESTION. WHEN I GLOSSED THE BIOSAFETY, I MEANT IT STRICTLY IN THE NONHUMAN ANIMAL CONTEXT. I DID HAVE A BOUNDED CONCEPT OF THAT. SO GENETICALLY MODIFYING ANIMALS, THE ANIMALS ESCAPE, THEY HAVE HUMAN TISSUES OR THEY DON'T HAVE HUMAN TISSUES OR WHATEVER. SO THAT'S THE KIND OF THING THAT I HAD IN MIND.

CLEARLY THE ISSUES ABOUT THE TRANSMISSION

OF DELETERIOUS EFFECTS THROUGH FUTURE GENERATIONS IS EMBEDDED IN THE LANGUAGE ABOUT THE SAFETY NOT BEING ESTABLISHED IN THE CONTEXT OF CRISPR-CAS9. SO I THINK THE CONCERNS OR THE ISSUES THAT YOU'RE RAISING HERE ARE MOTIVATING MANY OF THE PROHIBITIONS THAT THE ISSCR IS ARTICULATING. I GUESS THAT'S PROBABLY ABOUT AS MUCH AS I CAN SAY.

DR. ROBERTS: OKAY. I WAS MOSTLY WONDERING WHAT BIOSAFETY ENCOMPASSES.

DR. KIMMELMAN: I MEANT THAT IN A FAIRLY BOUNDED WAY.

CO-CHAIR LO: LAST COMMENT.

MS. DAAR: THANK YOU SO MUCH. GOOD MORNING. MY NAME IS JUDY DAAR. I'M CURRENTLY THE CHAIR OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE ETHICS COMMITTEE. I'M ALSO A PROFESSOR OF LAW. AND THANKS FOR THE OPPORTUNITY TO MAKE JUST TWO QUICK COMMENTS.

I WANTED TO COMMENT ON WHAT DR. BALTIMORE SAID BOTH HERE AND IN DECEMBER. I HAD THE PRIVILEGE OF ATTENDING THAT SUMMIT. WITH RESPECT TO THE PREFERENCING FOR PGD OVER EMBRYO EDITING, AGAIN, WE'RE TALKING MORE THEORETICALLY, ABOUT THE OPPORTUNITY TO ACHIEVE EQUIVALENT RESULTS. AND JUST TWO POINTS ABOUT THAT THAT STRUCK ME.

FIRST OF ALL, THERE'S AN ASSUMPTION THAT ANY PARTICULAR CYCLE WILL YIELD EMBRYOS THAT ARE BOTH AFFECTED AND UNAFFECTED SO THAT PGD MIGHT BE APPROPRIATE IN THOSE CIRCUMSTANCES, BUT THAT'S NOT ALWAYS THE CASE. THE EMBRYOS COULD ALL BE AFFECTED, OR THERE ARE MANY COUPLES WHO JUST HAVE A SINGLE EMBRYO THAT'S PRODUCED AND IT COULD BE AFFECTED. SO STATISTICALLY WE COULD SPEAK ABOUT IT, BUT IN THE CLINICAL ISN'T ALWAYS GOING TO BE A PRIORITY TECHNIQUE.

AND THEN SECOND, WITH RESPECT TO THAT, FOR SOME COUPLES THE OPPORTUNITY FOR AN EMBRYO SPARING OPPORTUNITY, WHICH GENE EDITING PRODUCES, IS PREFERENCED OVER AN EMBRYO DISCARD TECHNIQUE, WHICH PGD ESSENTIALLY ASSUMES. SO FOR COUPLES WHO DO NOT WANT TO DISCARD THEIR EMBRYOS UNDER ANY CIRCUMSTANCES, PGD DOESN'T REALLY OFFER THE KIND OF RESULT THAT THEY'RE SEEKING. I THINK THAT'S A BIT UNDER APPRECIATED.

IF I CAN ALSO SPEAK TO THE QUESTION ABOUT THE RETRACTION, THE IDEA THAT SOMEBODY WOULD CONSENT TO AN EMBRYO BEING DONATED INTO RESEARCH AND THEN HAVE A CHANGE OF HEART. LET ME SUGGEST TO CIRM THAT THERE MIGHT BE CLINICAL OPPORTUNITIES TO EXPLORE THAT TODAY THAT WOULD BE ANALOGOUS. THAT'S IN THE

EMBRYO AND GAMETE REPRODUCTIVE DONATION REALM. THERE ARE CASES ACROSS THE COUNTRY TODAY RIGHT HERE IN SOUTHERN CALIFORNIA WHERE COUPLES ARE DISPUTING THE DISPOSITION OF THEIR EMBRYOS DESPITE HAVING SIGNED AGREEMENTS THAT THEY WOULD BE DISPOSED OF IN A PARTICULAR WAY. SO THEY ESSENTIALLY REPRESENT THIS CHANGE OF HEART WITH RESPECT TO THE DISPOSITION OF REPRODUCTIVE MATERIAL.

LIKEWISE, THE DEVELOPMENT OF SPERM BANKS, EGG BANKS, AND EMBRYO BANKS ARE CONFRONTING THIS QUESTION OF CHANGE OF HEART AND THE DESIRE TO RECALL MATERIAL THAT WAS DONATED FOR USUALLY ANOTHER'S REPRODUCTIVE USE.

SO THOSE MIGHT PRESENT ANALOGOUS CIRCUMSTANCES FOR CIRM TO CONSIDER IN DEVELOPING YOUR MORE ROBUST CONSENT FORMS AND THINKING AHEAD TO HOW THE LAW MIGHT REGARD THOSE RECALL DECISIONS.

CO-CHAIR LO: THANK YOU. DR. BALTIMORE GETS THE LAST WORD.

DR. BALTIMORE: THANK YOU VERY MUCH FOR THAT COMMENT. AND IT REMINDS ME OF SOMETHING I WANTED TO SAY EARLIER. I SORT OF DID, BUT I WANT TO EMPHASIZE. IT GOES TO YOUR QUESTION ABOUT THE DIRECTIONS OF RESEARCH. IT IS TRUE THAT THE GENE EDITING CAN BENEFIT A RELATIVELY SMALL NUMBER OF

PEOPLE BECAUSE THERE ARE OTHER WAYS TO GO ABOUT IT. BUT AS THE QUESTION JUST NOW POINTED OUT, THERE ARE CIRCUMSTANCES IN WHICH GENE EDITING IS THE ONLY OPPORTUNITY FOR DOING THINGS THAT A PATIENT WANTS, MAINLY IN RELATION TO HIS OR HER OFFSPRING, BECAUSE OF RESTRICTIONS ON THE NUMBERS OF EMBRYOS OR BECAUSE OF OTHER LOGISTIC QUESTIONS, INCLUDING A VERY INTERESTING ONE THAT GEORGE DALEY RAISED AT THE WASHINGTON SUMMIT THAT I'M NOT GOING TO GO INTO, BUT IS A VERY POINTED QUESTION ABOUT THE NEEDS OF A PATIENT REQUIRING THIS ACTIVITY.

SO EVEN THOUGH THOSE MAY BE RELATIVELY SMALL IN TERMS OF NUMBERS, THEY ARE VERY IMPORTANT TO CERTAIN PATIENTS. AND AS ANY PHYSICIAN WILL TELL YOU, IN FACING A PATIENT, THE MOST IMPORTANT THING IS TO PROVIDE WHAT THAT PATIENT NEEDS, NOT WHAT YOU WOULD LIKE TO SEE. AND SO WE HAVE DEVELOPED HERE A TECHNOLOGY THAT WILL BE BENEFICIAL TO SOME PATIENTS. AND TO ME, ANYWAY, TUTORED BY MY PHYSICIAN FRIENDS, THAT'S SUFFICIENT REASON TO BRING IT TO CLINICAL USE.

CO-CHAIR LO: OKAY. SO I WANT TO THANK JONATHAN KIMMELMAN FOR AN EXCELLENT TALK AND STIMULATING A LOT OF GOOD DISCUSSION. WE NOW HAVE REACHED A WELL DESERVED LUNCH BREAK. SO I'D LIKE TO

ADJOURN AND RECONVENE PROMPTLY AT 12:15 BECAUSE WE'RE QUITE A BIT BEHIND SCHEDULE. IT'S QUARTER OF TWELVE RIGHT NOW. THE LUNCH IS IN BACK, I HOPE, OR IT'S OUTSIDE. WE COME BACK HERE, ATTEND TO OUR OTHER NEEDS AS WELL, AND THEN WE'LL START WITH GEOFF LOMAX SORT OF SUMMARIZING FOR US THE CURRENT CIRM REGULATORY FRAMEWORK AND THE QUESTIONS THAT HE WOULD LIKE US TO REALLY THINK ABOUT. THANKS VERY MUCH.

(A RECESS WAS TAKEN.)

DR. LOMAX: FOLKS, TAKE YOUR SEATS AND GET COMFORTABLE. WE'LL GET GOING HERE TO TRY TO GET EVERYTHING DONE IN THE TIME WE HAVE.

CO-CHAIR LO: THANKS FOR RECONVENING. WE'VE HAD A VERY RICH, INSIGHTFUL DISCUSSION WHICH IS GREAT. UNFORTUNATELY THE OLD AGENDA IS OUT THE WINDOW. SO I'M GOING TO SUGGEST THAT WE THINK PROSPECTIVELY AND SAY THAT SINCE PEOPLE DO HAVE COMMITMENTS TO FINISH THIS MEETING AT FOUR, WE WANT TO RESPECT THOSE. LET ME SORT OF RESTATE THE GOAL OF THIS MEETING. WE'RE NOT GOING TO SETTLE THESE ISSUES TODAY. IN FACT, WHAT WE'VE DONE IS UNCOVERED A LOT OF NEW ISSUES THAT HAVE NOT REALLY BEEN ADDRESSED AND MAY NEED TO BE FOR CIRM AT THE LEVEL OF FUNDING DECISIONS AND REGULATORY OVERSIGHT.

WHAT I THINK IS REALISTIC IS TO SAY WHAT

ARE THE TOPICS THAT THE SWG NEEDS TO CONSIDER. AND OUR GOAL AT THE END OF THE MEETING IS TO GET A SET OF TOPICS AND TASK STAFF, GEOFF LOMAX AND THE CO-CHAIRS, JEFF SHEEHY AND ME AND OTHER MEMBERS OF THE WORKING GROUP IN CONSULTATION, TO DRAFT RECOMMENDATIONS THAT WE'RE GOING TO HAVE TO COME BACK ON REALISTICALLY ON A PHONE MEETING. I JUST THINK WE SHOULDN'T RUSH INTO THINGS WITHOUT HAVING TIME TO THINK ABOUT IT. SO I THINK WHAT WE'RE TRYING TO FOCUS ON NOW IS WHAT ARE THE BIG TOPICS.

GEOFF LOMAX IS GOING TO TALK ABOUT WHAT THE CURRENT REGULATORY FRAMEWORK THAT CIRM HAS SO THAT WE ALL CAN SEE THAT. WE HAVE A NUMBER OF DISTINGUISHED SCIENTISTS HERE TO TALK ABOUT THE KINDS OF RESEARCH THEY THINK CIRM SHOULD BE FUNDING THAT WOULD REALLY ADVANCE CIRM'S MISSION. I'M GOING TO THEN TRY AND BRIEFLY SUM UP WHAT I'VE BEEN HEARING TODAY IN TERMS OF A CANDIDATE LIST OF TOPICS. THEN WE HAVE CHARIS THOMPSON AND HANK GREELY BY PHONE TO MAKE SURE WE'VE THOUGHT ABOUT THE SOCIAL, LEGAL REGULATORY, AND ETHICAL ISSUES AND COMMUNITY ISSUES TO TRY, AGAIN, ARE THERE ISSUES CIRM NEEDS TO ADD TO THE LIST OF TOPICS. AND THEN I THINK WE CAN TRY AND DISCUSS THAT.

I'M GOING TO HAVE TO STEP OUT AT 2:15.

AND SO WHEREVER THIS COMES IN THE PROGRAM, I'M SORRY TO MISS WHAT'S GOING TO HAPPEN. THAT'S NO REFLECTION ON THE TOPICS. WITH THAT, I'M GOING TO TURN IT OVER TO GEOFF LOMAX.

DR. LOMAX: YOU WILL BE BACK AT THREE. OKAY. SO I'M GOING TO SORT OF FINISH. IF YOU NOTICED, THESE SORT OF PRESENTATIONS HAVE REALLY BEEN LOOKING AT SORT OF POLICY RECOMMENDATIONS, THE POLICY SPACE. I'M GOING TO NOW RELATE IT TO THE MOST GRANULAR LEVEL, THE CIRM POLICY AS IT RELATES TO THIS TYPE OF RESEARCH. AND THEN WE'LL MOVE INTO A DISCUSSION ABOUT THE ASPIRATIONS OF THE SCIENTISTS.

AND SO I THINK AT THIS STAGE I'LL BE ABLE TO RELATE TO A LOT OF THE PREVIOUS TALKS, SO I'M GOING TO TRY TO MOVE FAIRLY QUICKLY IN THE INTEREST OF TIME.

SO, AGAIN, I'M TALKING ABOUT CIRM'S MISSION AND PROGRAM AREAS, THE EXISTING RESTRICTIONS IN TERMS OF CIRM'S REGULATIONS, SOME OF THE PROCEDURAL REQUIREMENTS THAT WE HAVE THAT WERE INTRODUCED BY JONATHAN, AND A LITTLE BIT OF INSIGHT INTO WHAT WE VIEW THE IMPACT OF OUR REGULATIONS, WHAT THEY HAVE BEEN.

JUST TO REITERATE, OUR MISSION IS TO

ACCELERATE STEM CELL TREATMENTS TO PATIENTS WITH UNMET MEDICAL NEEDS. SO WE'RE VERY FOCUSED AT THIS STAGE OF OUR LIFE CYCLE ON REALLY THE DEVELOPMENT OF PATIENT TREATMENTS. IF YOU HAVE THE OPPORTUNITY, I ENCOURAGE YOU TO LOOK AT OUR NEW STRATEGIC PLAN. IT REALLY LAYS OUT A SERIES OF FIVE PROGRAM AREAS THAT ALLOW US TO ACCELERATE THERAPY DEVELOPMENT. AND TO CALL OUT A COUPLE OF KEY POINTS, THAT WE SUPPORT THE EXPLORATION OF GROUNDBREAKING STEM CELL TREATMENTS REALLY FROM INCEPTION TO TRANSLATION INTO CLINICAL TRIALS, AND WE STILL HAVE THE ABILITY TO SUPPORT RESEARCH THAT MIGHT OTHERWISE NOT SEE THE LIGHT OF DAY FROM OTHER FUNDING SOURCES.

SO QUICKLY TO FOCUS VERY QUICKLY ON OUR RULES THAT RELATE TO THE USE OF GENETICALLY MODIFIED EMBRYOS. AS A REMINDER, WE DEVELOPED A COMPREHENSIVE SET OF REGULATIONS IN 2006. THESE REGULATIONS NEEDED TO BE IN PLACE AS A CONDITION OF CIRM BEING ABLE TO RELEASE FUNDS FOR RESEARCH. IT WAS THROUGH THE WORK OF THIS WORKING GROUP THAT THOSE REGULATIONS CAME ABOUT. AGAIN, THEY APPLY TO ALL RESEARCH THAT WE FUND.

AND RULES ON THE CLINICAL USE OF GAMETES AND EMBRYOS ARE REALLY CONSISTENT WITH THE NUMBER OF POLICY STATEMENTS WE'VE HEARD TODAY; NAMELY, THE

SUMMIT ON HUMAN GENOME EDITING AND THE DRAFT ISSCR GUIDELINES.

TO PUT THAT IN AN INTERNATIONAL CONTEXT, I WON'T READ THIS WHOLE QUOTE, BUT THIS IS A NICE PIECE DONE BY ISASI, ET AL. THEY LOOKED INTERNATIONALLY AT THE POLICY LANDSCAPE WITH REGARD TO GAMETE AND EMBRYO RESEARCH, AND THEY'VE ALSO POINTED TO THE FACT THAT IN AREAS -- IN JURISDICTIONS WHERE THE INTEREST IS IN TRYING TO ACCELERATE THIS SCIENTIFIC SPACE, THEY'VE TRIED TO NOT SORT OF COMPLETELY BAN CERTAIN ACTIVITIES, BUT THEY MIGHT RESTRICT CERTAIN APPLICATIONS OR HAVE CERTAIN STANDARDS FOR REVIEW. AND, AGAIN, THIS ARTICLE WAS INCLUDED, THE LINK IS INCLUDED IN YOUR BACKGROUND MATERIALS. AND THE REASON I PUT IT UP HERE IS IT REALLY REFLECTS, I THINK, THE APPROACH AND THE PHILOSOPHY THAT'S EMBEDDED IN OUR GUIDELINES OR OUR REGULATIONS.

FOCUSING ON THE REGULATIONS SPECIFICALLY, AND, AGAIN, THESE POINTS HAVE COME UP EARLIER, BUT JUST REITERATE AND POINT YOU TO THE EXACT LANGUAGE, SO THERE IS A SECTION IN OUR REGULATIONS THAT SPECIFICALLY INDICATE ACTIVITIES THAT WOULD NOT BE ELIGIBLE FOR FUNDING BY CIRM. AND IT'S THE CULTURE OF AN EMBRYO BEYOND, IN THIS CASE IT'S 12 DAYS -- SO

THERE'S A SLIGHT DEVIATION FROM THE 14 DAYS THAT WAS CITED EARLIER, BUT IT'S ACTUALLY 12 IN OUR REGULATIONS -- AND THE TRANSFER TO THE UTERUS OF A GENETICALLY MODIFIED EMBRYO. AND THAT PROVISION F, I WENT BACK TO THE TRANSCRIPT AND EXCISED THAT DISCUSSION. AND IF YOU HAVE A CHANCE TO LOOK AT IT, I KNOW IT'S A BIT LONG, BUT I THINK IT REALLY IS A REALLY INTERESTING READ CONSIDERING IT WAS SOMETHING THAT HAPPENED A DECADE AGO.

IT CAME ABOUT, IF YOU'RE NOT CLEAR, AS A RESULT OF PUBLIC COMMENT. SO IT WAS THE PUBLIC COMMENT PROCESS. AT THAT STAGE OF THE DEVELOPMENT OF THE REGULATIONS, WE WERE IN A MEETING THAT WAS SOLELY DEDICATED TO RESPONDING TO THE OVER 100 PUBLIC COMMENTS AS A MATTER OF FACT. I THINK THAT'S INDICATIVE OF THE PROCESS AND THE LEVEL OF DISCUSSION THAT'S BEHIND THAT DOCUMENT. I, AS SOMEONE WHO'S BEEN ABLE TO CONTRIBUTE TO THAT, FEEL QUITE PROUD OF WHAT WE WERE ABLE TO PRODUCE.

AND I THINK, AGAIN, THE RECORD SUPPORTS THE INTENT OF THE WORKING GROUP WAS TO ALLOW FOR IN VITRO USE OF HUMAN EMBRYOS WHILE HAVING A PROHIBITION ON THE REPRODUCTIVE USE.

AND, AGAIN, THIS WAS -- I THINK THIS WAS ALTA CHARO AND HER WONDERFUL ABILITY TO PARAPHRASE

THE SENSE OF THE COMMITTEE OR WHAT THE WORKING GROUP WAS DRIVING AT, BUT IT WAS CLEARLY THIS BOUNDARY BETWEEN ANY FORM OF HUMAN REPRODUCTION AND RESEARCH. I GIVE YOU THE CITE THERE.

SO MOVING ON, JUST I WANT TO MOVE TO ALSO AS A REMINDER BEYOND THE RULES ON PAPER, THE OVERALL PROCESS OF HOW CIRM GOES ABOUT FUNDING AWARDS. FIRST AND FOREMOST, THEY'RE SUBJECT TO PEER REVIEW BY OUR GRANTS WORKING GROUP. AND, AGAIN, THIS SORT OF ECHOES, I THINK, WHAT JONATHAN WAS ARTICULATING IN THE ISSCR GUIDELINES IS SHOULD YOU DO THE RESEARCH IN THE FIRST PLACE. AND THAT'S SORT OF TYPICAL REVIEW QUESTIONS, TYPICAL QUESTIONS POSED TO THE REVIEWERS, THE PEER REVIEW BODY WOULD BE SCIENTIFIC IMPACT. IS THIS IMPACTFUL SCIENCE? IS THE PROJECT SOUND AND WELL THOUGHT OUT? IS IT DESIGNED PROPERLY? AND IS IT FEASIBLE? SO THOSE ARE -- FIRST ORDER, THERE'S A REVIEW DONE ON THE SCIENTIFIC LEVEL. AND THEN IF THAT PROPOSAL WERE TO GO THROUGH SCIENTIFIC REVIEW AND BE VIEWED AS MERITORIOUS, IT WOULD ALSO HAVE TO THEN RECEIVE LOCAL REVIEW BY THE INSTITUTION. AND, AGAIN, THEIR COMMITTEE WOULD BE TASKED WITH CONSIDERING A SET OF ISSUES. IN THE CASE OF GAMETE AND EMBRYO RESEARCH, THERE'S VERY CLEAR EXPECTATION THAT THERE'S

COMPREHENSIVE CONSENT FROM ALL GAMETE DONORS. AND WE HAVE POINTS IN THE REGULATIONS THAT TALK ABOUT WHAT ISSUES SHOULD CERTAINLY BE WITHIN A CONSENT. ALMOST ALL INSTITUTIONS GO WELL BEYOND THE LETTER OF THE RECOMMENDATIONS BECAUSE OVER TIME THEY DISCOVERED THAT THERE ARE OTHER THINGS THAT NEED TO BE IN THE CONSENT DOCUMENT.

ALSO, THAT THE USE OF GAMETES AND EMBRYOS IS WELL JUSTIFIED, INCLUDING THE NUMBERS USED. SO THIS SORT OF REINFORCES THE SCIENTIFIC RATIONALE THAT ALLOWS THAT TO BE MADE VERY EXPLICIT THROUGH A REVIEW COMMITTEE. AND, AGAIN, ENSURING THE TEAM HAS SCIENTIFIC EXPERTISE TO PERFORM THE WORK. SO KIND OF A DUAL REVIEW. IN SOME WAYS THE SCIENTIFIC REVIEW ECHOES THE ETHICS REVIEW, BUT I THINK HAVING THAT DUAL REVIEW IS STILL QUITE VALUABLE.

AND SO IN TERMS OF THE IMPACT, SO WE HAVE OVER THE YEARS GONE OUT AND ACTUALLY VISITED THE INSTITUTIONS AND REALLY LOOKED AT THIS PROCESS. WE'VE LOOKED BEHIND THE PIECE OF PAPER WE GET THAT SAYS SO-AND-SO IS APPROVED FOR THIS PROTOCOL. ALL OUR MAJOR GRANTEES MAINTAIN STEM CELL RESEARCH OVERSIGHT COMMITTEES. THEY HAVE WELL-ESTABLISHED PROCEDURES, POLICIES, GUIDELINES THAT THEY'RE BOTH CONSISTENT WITH OUR REQUIREMENTS AND THEY ALSO TEND

TO GO BEYOND OUR EXPECTATIONS. AND ALL THE COMMITTEES INCLUDE NONSCIENTIST MEMBERS AND PATIENT ADVOCATES. SO THE REVIEW PROCESS IS INFORMED QUITE BROADLY AND, IN MY VIEW, QUITE EFFECTIVELY.

SO I THINK I'LL STOP THERE AND SEE IF THERE ARE ANY QUESTIONS, ANYTHING ELSE I CAN ADDRESS ABOUT THE CIRM RULES SPECIFICALLY.

MR. SHEEHY: SO, GEOFF, AS HAVING SEEN WHAT THE GUIDELINES ARE AT THE ISSCR AND WHAT'S COMING OUT IN THE INTERNATIONAL PROCESS AND THE NAS, I WONDER -- I DON'T WONDER. I ACTUALLY HAVE A QUESTION WHETHER CIRM NEEDS TO RELOOK AT ITS RESEARCH PRIORITIES AND ALSO RELOOK AT ITS STRATEGIC PLAN. AND IF THIS COMMITTEE GOES FORWARD AND, FOR INSTANCE, OUR CURRENT RULES ARE SUFFICIENT FOR GOVERNING OUR RESEARCH, THEN I THINK THAT PROP 71 OBLIGATES US TO GIVE A RESEARCH PRIORITY FOR THIS RESEARCH. THIS IS NOT RESEARCH THAT COULD BE FUNDED BY THE NIH. AND PROP 71 SPECIFICALLY REQUIRES US, AS A MATTER OF LAW, TO FUND RESEARCH THAT IS NOT FUNDABLE BY THE NIH.

SO I THINK THAT THAT'S SOMETHING THAT SHOULD RUN PARALLEL TO OUR DISCUSSIONS BECAUSE IF WE DO -- I DO THINK WE MAY HAVE TO DO SOME TWEAKING. I CERTAINLY HAVE CONCERNS ABOUT INFORMED CONSENT; BUT

IF WE PROCEED DOWN THIS PATH, THEN CIRM NEEDS TO LOOK AT ITS STRATEGIC PLAN, ITS RFA'S AT THE BASIC AND PRECLINICAL LEVEL, AND CLEARLY ARTICULATE A HIGH PRIORITY FOR PROJECTS SUCH AS THESE, SUCH AS THE TYPE THAT ARE -- BECAUSE WE CAN AND THE NIH CAN'T.

DR. LOMAX: I TOOK THAT AS A STATEMENT. AM I CORRECT IN THAT?

MR. SHEEHY: MAYBE IT'S SOMETHING THAT NEEDS -- THESE TWO -- THESE SHOULD BE INTEGRATED, I GUESS, IS MY POINT.

DR. LOMAX: IS THERE ANYTHING ELSE? I WAS KIND OF HOPING -- AT THIS STAGE WE'VE KIND OF REPEATED THIS REGULATORY, WHICH IS GOOD. REDUNDANCY CAN BE GOOD IN SOME CASES. THIS IS ONE CASE WHERE I THINK THERE'S VALUE TO IT; BUT IF THERE'S NO ADDITIONAL QUESTIONS, I'D BE MORE THAN HAPPY TO MOVE TO THE SCIENTIFIC PART NOW BECAUSE IT'S A SORT OF DRAMATIC CHANGE IN THE CONTENT.

DR. BOTKIN: GEOFF, CAN YOU JUST GO BACK TO THE RESTRICTION LANGUAGE THERE FOR A SECOND? I WANTED TO TAKE A LOOK AT THIS AGAIN JUST TO SEE WHETHER THERE ARE OBVIOUS GAPS HERE THAT WOULD BE THE TOPIC OF ADDITIONAL FOCUS.

DR. LOMAX: LET ME GIVE YOU ONE OTHER VIEW THAT'S COME UP TODAY BECAUSE THIS MAY HELP US ALL.

IF THIS SLIDE'S HELPFUL, WE CAN PUT IT UP LATER. WE TRIED TO ARRAY IT IN TERMS OF -- AND JONATHAN AND I ACTUALLY DIDN'T COORDINATE IN TERMS OF OUR COLOR CODING. BUT IF YOU LOOK AT THAT TWO-BY-TWO TABLE WHERE, AGAIN, THE YELLOW -- I'VE USED YELLOW TO INDICATE NEEDS TO PAUSE, TAKE A LOOK. THERE'S SORT OF PROCEDURAL WORK. AND SO IF YOU'RE WORKING WITH GAMETE AND EMBRYOS AND THE RESEARCH USE IS IN VITRO, YOU'VE GOT THE 12-DAY LIMIT, BUT ALL THAT WORK HAS TO GO THROUGH THE OVERSIGHT COMMITTEE REVIEW.

IF YOU WERE TO DO THE -- SWOOPING TO THE OTHER YELLOW BOX REALLY BECOMES THE PURVIEW OF THE IRB. THAT WOULD BE SOME SORT OF -- AT SOME OF THE CLINICAL TRIALS WHICH WE'RE ACTUALLY ALREADY SUPPORTING THAT INVOLVE MODIFIED SOMATIC CELLS. AND THEN REALLY THE IMPORTANT PART IS THE RED ZONE THERE, WHAT I'M CALLING IN VIVO CLINICAL USE. THAT WOULD BE THE IMPLANTING THE EMBRYO. THAT'S THE RED ZONE. SO WE KIND OF COPIED EACH OTHER WITH OUR RED LIGHT/GREEN LIGHT ANALOGY.

DR. BALTIMORE: TWO THINGS OCCUR TO ME. ONE IS WHY 12 DAYS AND NOT 14 DAYS?

DR. LOMAX: THAT'S THE WAY IT WAS WRITTEN IN PROPOSITION 71 ACTUALLY I BELIEVE IS WHERE IT'S WRITTEN.

DR. BALTIMORE: IN PROPOSITION 71?

DR. LOMAX: YEAH. IT WAS JUST THE WAY IT WAS DRAFTED. WE DO HAVE A PROCEDURE, I BELIEVE, WHERE THERE CAN BE APPEAL TO THE ICOC, BUT BETWEEN 12 AND 14.

DR. ROD TAYLOR: PRIMITIVE STREAK WAS KIND OF DEFINING.

DR. BALTIMORE: EVERYBODY ELSE TALKS ABOUT 14. JUST WANT TO GIVE PEOPLE THE MOST FREEDOM.

THE SECOND THING IS YOU SAY REPRODUCTIVE USE PROHIBITED. YOU'VE PRESUMABLY PUBLISHED THAT. AND I THINK IT'S WORTH THINKING ABOUT WHEN THAT WON'T BE TRUE.

DR. LOMAX: IT'S THE PERILS OF POWERPOINT. IT IS ACTUALLY THE LANGUAGE THAT WAS UP ON THE EARLIER SLIDE. THE IMPLANTATION OF A GENETICALLY MODIFIED EMBRYO TO THE UTERUS.

DR. BALTIMORE: IS PROHIBITED.

DR. LOMAX: THAT'S CODE.

DR. BALTIMORE: SO I WANT TO THINK ABOUT WHEN YOU WON'T WANT TO PROHIBIT THAT. AND THAT IS AT A TIME WHEN THE QUESTIONS THAT HAVE BEEN RAISED ABOUT SAFETY, ABOUT ACCEPTABILITY, WHATEVER HAVE BEEN IN SOME WAY SATISFIED. BUT IT REALLY WILL COME ABOUT WHEN A PHYSICIAN IS FACED WITH A PATIENT WHO

DESPERATELY NEEDS THIS TECHNOLOGY AND THE TECHNOLOGY HAS REACHED THE POINT WHERE THE PHYSICIAN CAN SAY HONESTLY TO THE PATIENT, "I CAN HELP YOU WITH YOUR PROBLEM AND THERE IS A TECHNOLOGY NOW WHERE WE CAN DO THAT." AND SO THE LESS WE USE ABSOLUTE PROHIBITION TERMS AND THE MORE WE SAY THE DAY HASN'T COME YET TO USE THIS, THE MORE I THINK WE WILL BENEFIT PATIENTS. AND THAT'S BASICALLY HOW THE NATIONAL ACADEMY LANGUAGE READS BECAUSE I WORRIED ABOUT THAT.

MR. SHEEHY: SO MY ONE QUESTION IS DO WE NEED TO ADDRESS DR. WAGNER'S QUESTION UNDER SOMATIC CELLS, HIS EARLIER QUESTION ABOUT GERMLINE MODIFICATION THROUGH GENETIC MODIFICATION OF SOMATIC CELLS, NOT BY INTENTION.

DR. ROD TAYLOR: I THINK THE LIKELIHOOD IS PROBABLY A LOT GREATER WITH SPERMATOGONIAL STEM CELLS THAN IT WOULD BE WITH OOGONIAL STEM CELLS FROM WHAT WE KNOW. WHEN YOU GO BACK TO THAT EXCERPT THAT YOU PUT IN FROM TEN YEARS AGO, THIS WAS ACTUALLY THE DISCUSSION WE WERE HAVING AT THAT TIME. I WON'T REITERATE IT HERE, BUT I THINK THE SCIENCE HAS KIND OF MOVED BEYOND THE THOUGHT THAT YOU CAN GIVE A BONE MARROW TRANSPLANT AND GET BONE MARROW CELLS REPOPULATING AN OOCYTE POOL. I THINK WE DON'T

BELIEVE THAT THAT HAPPENS, BUT WHETHER SOMETHING LIKE THIS COULD HAPPEN IN THE SPERMATOGONIAL STEM CELL LINE, AMANDER, MAYBE YOU CAN SPEAK TO THAT, BUT I'M NOT AWARE THAT IT HAS HAPPENED, BUT IT SEEMS LIKE IT'S A MORE LIKELY THING.

GEOFF, I WANTED TO MAKE A COMMENT THAT IN YOUR PREVIOUS TERMINOLOGY, ESSENTIALLY KIND OF INTRODUCTION OF THE GENETICALLY MODIFIED, I THINK THAT WAS THE TERM, EMBRYO, I JUST THINK -- I WANT US TO BE CLEAR ABOUT THE TERMINOLOGY OF GENETICALLY BECAUSE MITOCHONDRIAL TRANSFER IS WITH US NOW AND IS GOING TO HAPPEN. AND WHETHER YOU WANT TO SORT OF BELIEVE THAT THAT'S A FORM OF GENETICALLY MODIFIED EMBRYO OR NOT, I THINK WE SHOULD HAVE SOME CLARITY ABOUT THAT.

DR. LOMAX: YES. THAT CURRENTLY IS NOT DEFINED. I THINK THAT WOULD BE SOMETHING, IN TALKING TO DR. LO, I THINK WE SHOULD ADD TO OUR LIST OF FOLLOW-UP ITEMS.

DR. WAGNER: JUST TO GO ONE STEP FURTHER FROM WHAT YOU MENTIONED, GEOFF. SO ALTA IN HER PRESENTATION SAYS, YES, WE'VE NOT ADDRESSED THIS INADVERTENT CONSEQUENCE OF IN VIVO GENE MODIFICATION. AND MAYBE THAT'S AN OPPORTUNITY FOR CIRM TO ACTUALLY THEN SET THE STAGE OF AT LEAST

ADDRESSING AND ADDING TO YOUR BOXES. I THINK IT'S PROBABLY REALLY AN ISSUE OF IN VIVO GENE CORRECTION AND IF THERE IS A RISK TO MODIFICATION OF THE GERMLINE. CAN WE ADD SOMETHING ABOUT THAT?

DR. LOMAX: MY THOUGHT WAS ACTUALLY WE COULD SEND A NOTE BACK TO ALTA, EXPLAINING THAT WE HAD THIS MEETING AND THIS WAS ONE OF OUR TOP QUESTIONS, AND PUSH IT BACK TO THEM BECAUSE THEY'VE GOT A PROCESS AND A COMMITTEE BEING FORMED THAT SEEMS LIKE THEY COULD BENEFIT FROM OUR VIEW.

DR. WAGNER: I'LL FORWARD YOU THE NOTE I JUST SENT TO HER AFTER OUR MEETING.

DR. LOMAX: I THINK IT'S ENTIRELY APPROPRIATE FOR US TO MAKE SOME FORMAL ASK GIVEN WHAT WE'VE LEARNED TODAY. SO I WOULD APPRECIATE SEEING YOUR NOTE.

DR. KIMMELMAN: I JUST HAVE A COUPLE QUESTIONS ABOUT THIS LANGUAGE. SO THE FIRST QUESTION I HAVE IS THE LANGUAGE STATES "AFTER THE APPEARANCE OF THE PRIMITIVE STREAK." AND I'M JUST ALERTING YOU THAT THAT WORD "AFTER" VARIES FROM ONE POLICY TO ANOTHER. SO THE 12 DAYS WAS REALLY STRIKING TO ME TOO AS ODD. BUT I THINK THAT YOU WOULD BE WISE TO ANTICIPATE THAT WORD "AFTER" IS WHERE THERE'S GOING TO BE A LOT OF DISCUSSION IN THE

NEAR TERM. AND YOU MAY WANT TO THINK ABOUT WHETHER THAT'S EXACTLY WHERE YOU WANT TO DRAW THE LINE.

AND THE OTHER QUESTION I HAD IS I ASSUME THAT THE TRANSFER TO A UTERUS REFERS TO EITHER AN ANIMAL OR -- A NONHUMAN ANIMAL OR A HUMAN BEING, CORRECT? OR IS THAT MEANT ONLY TO REFER TO A HUMAN UTERUS?

DR. LOMAX: WELL, THE PLAIN LANGUAGE IS THE PLAIN LANGUAGE. THE RECORD REFLECTS -- AGAIN, THAT'S WHY I WANTED TO PROVIDE PEOPLE WITH A COMPLETE TRANSCRIPT. THE TRANSCRIPT REFLECTS A SORT OF HUMAN CONTEXT. I GUESS I COULD ASK HOW ONE WOULD ADJUDICATE THAT. I COULD ASK MY COLLEAGUE, SCOTT, BUT I WON'T ASK HIM AT THE MOMENT UNLESS WE WANT TO GET INTO THAT. YOU'D HAVE TO SORT OF LOOK AT THE RECORD AND THE CONTEXT IN WHICH THAT PROVISION CAME ABOUT. AND WE HAVE NOT BEEN ASKED TO MAKE A DETERMINATION ON THAT. YOU GENERALLY TRY TO WRITE YOUR LANGUAGE AS LEAN AND AS UNAMBIGUOUS AS POSSIBLE, AND EVENTUALLY SOMEBODY COMES BACK TO YOU SAYS, "WHAT DO YOU MEAN BY THAT?" BUT WE HAVEN'T HAD THAT OCCASION ARISE.

CO-CHAIR LO: THIS IS VERY HELPFUL. WHAT WE'RE HOPING FOR AND WHAT YOU'RE DOING IS SAYING THESE ARE TOPICS CIRM NEEDS TO REALLY THINK ABOUT

AND CONSIDER WHETHER THE CURRENT OVERSIGHT FRAMEWORK IS ADEQUATE OR NEEDS TO BE MODIFIED. I THINK IT WOULD BE IMPRUDENT FOR US TO TRY AND RESOLVE THESE ISSUES TODAY. I THINK FLAGGING THESE THINGS AS THINGS WE SHOULD ADDRESS AND THEN COME BACK AT A SUBSEQUENT MEETING FOR RECOMMENDATIONS WILL BE VERY HELPFUL. WE'RE RAISING ISSUES THAT ARE NEW AND IMPORTANT.

DR. ROD TAYLOR: BERNIE, AT THE TIME WE TALKED ABOUT CHIMERICS. AND MAYBE THIS LANGUAGE ISN'T SO BAD BECAUSE HISTORICALLY WE TALKED ABOUT HUMAN EMBRYOS AND ANIMAL MODELS.

CO-CHAIR LO: AGAIN, THIS WHOLE DISCUSSION IN THE CONTEXT OF, GIVEN HOW THE SCIENCE HAS CHANGED AND GIVEN HOW OUR THINKING ABOUT THE ETHICS, THE REGULATORY ISSUES, THE SOCIAL ISSUES MAY HAVE CHANGED, IT'S TIMELY TO GO BACK AND REVISIT. AND WE MAY SAY THAT DISCUSSION WAS FINE, THE CONCLUSIONS. WELL, IT'S CHANGED IT A BIT, OR WE COULD SAY WE MISSED THE BOAT. IT WAS GREAT THEN, BUT WE NEED TO CHANGE. SHERRY ALWAYS SAYS WE'RE A WORK IN PROGRESS, AND WE WANT TO DO THE BEST WORK WE CAN DO.

DR. PATRICK TAYLOR: WE'LL DO A LOT OF THIS LATER, BUT WHAT THIS LITERALLY SAYS IS YOU CAN'T FUND THE TRANSFER. CERTAINLY AN INVITATION TO

DO WHAT THE NIH DID. DEFINITELY TRANSFER, THAT YOU CAN CREATE BEFORE AND AFTER YOU FUND. CLEARLY THEY DEAL WITH THAT ISSUE OF GENERALITY.

DR. LOMAX: WELL, I'M GETTING THAT THIS IS GOOD. WE WERE HOPING TO GET DONE BY 12:40 AND WE HAVE. DO WE WANT TO --

CO-CHAIR LO: DO YOU WANT TO INTRODUCE THE PANEL SINCE YOU'RE UP THERE?

DR. LOMAX: I DON'T HAVE EVERYONE'S BIO, BUT COULD WE GET THE THREE PANELISTS TO COME UP FOR THE NEXT SESSION? CAN YOU BRING YOUR NAME CARDS WITH YOU AS WELL?

CO-CHAIR LO: WHILE YOU'RE COMING UP, I WANT TO IN ADVANCE THANK OUR THREE DISTINGUISHED SCIENTISTS FOR SPENDING THE DAY WITH US AND IN ADVANCE FOR ENLIGHTENING US.

IN ALPHABETICAL ORDER, I'M GOING TO GIVE A VERY SHORT BIOSKETCH. THEIR IMPRESSIVE ACHIEVEMENTS ARE ON THE WEB AND THEY'RE ACTUALLY ON A HANDOUT IN THE BACK.

JUAN CARLOS BELMONTE IS AT THE SALK INSTITUTE FOR BIOLOGICAL STUDIES DOWN IN LA JOLLA. HE'S A PROFESSOR IN THE GENE EXPRESSION LABORATORIES, AND HE'S DIRECTOR OF THE CENTER FOR REGENERATIVE MEDICINE IN BARCELONA; IS THAT CORRECT?

DR. BELMONTE: NOT ANYMORE.

CO-CHAIR LO: NOT ANYMORE.

TO HIS LEFT IS AMANDER CLARK, WHO'S PROFESSOR AND VICE CHAIR FOR THE DEPARTMENT OF MOLECULAR CELL AND DEVELOPMENTAL BIOLOGY AT UCLA, ACROSS TOWN. HER GROUP HAS DONE SOME REALLY IMPORTANT STEM CELL RESEARCH; FOR EXAMPLE, DERIVING HUMAN IPS CELLS FROM HUMAN FIBROBLASTS AND UNCOVERING THE TRANSCRIPTOME OF MALE AND FEMALE GERMLINE CELLS DURING EMBRYO DEVELOPMENT.

AND TO HER LEFT IS JACOB CORN, WHO IS THE MANAGING DIRECTOR AND SCIENTIFIC DIRECTOR OF THE INNOVATIVE GENOMICS INITIATIVE AT UC BERKELEY. AND PRIOR TO THAT, HE WORKED FOR GENENTECH IN EARLY DISCOVERY BIOCHEMISTRY. SO HE HAS AN INDUSTRY DEVELOPMENT BACKGROUND AND EXPERIENCE TRYING TO BRING NEW SCIENTIFIC DISCOVERIES THROUGH PRODUCT DEVELOPMENT TO HELP PATIENTS. AND HE'S ACTIVELY ENGAGED IN PROMOTING ENTREPRENEURSHIP IN THE BIOLOGICAL SCIENCES.

WITH THAT, I'M GOING TO -- I'M NOT SURE HOW THIS SUPPOSED TO GO. DO WE HAVE AN ORDER, OR WE JUST GOING TO GO ALPHABETICALLY?

DR. LOMAX: IT'S IN THE AGENDA.

DR. CLARK.

DR. CLARK: SO THANK YOU VERY MUCH FOR INVITING ME HERE TODAY TO TALK ABOUT THE TYPES OF RESEARCH THAT WE'VE BEEN DOING WITH HUMAN GERMLINE CELLS AND HUMAN EMBRYOS. AND I'VE BEEN IN PARTICULAR CHARGED TO TALK A LITTLE BIT ABOUT THE RESEARCH THAT WE DO IN ORDER TO IMPROVE STEM CELL BIOLOGY. I'M GOING TO TALK ABOUT THAT TODAY.

THERE'S A DEFINITION QUESTION THAT I'D LIKE TO BRING UP ON WHAT THE WORD "GERMLINE" ACTUALLY MEANS BECAUSE I'VE HEARD IT TALKED ABOUT TODAY IN GENERAL CONVERSATION. BUT TO A CELL BIOLOGIST, A SCIENTIST, A GERMLINE MEANS SOMETHING VERY SPECIFIC. AND SO WHAT I WANT TO ENSURE, AS THE WORKING GROUP MAKES THEIR DECISIONS, IS THAT THEY DON'T INADVERTENTLY DISALLOW RESEARCH THAT IS ETHICALLY RESPONSIBLE AND THAT IS ALLOWABLE UNDER EXISTING REGULATIONS, BUT WE USED THE WRONG WORD AND ALL OF A SUDDEN YOU ERASE RESEARCH THAT IS CURRENTLY ALLOWABLE. AND I'LL TALK ABOUT WHAT THAT IS.

AND SO I WOULD CONSIDER MYSELF A STEM CELL AND GERMLINE BIOLOGIST. WHY DO I DO THIS? I'M INTERESTED IN MAKING A TOOL THAT SCIENTISTS CAN USE TO UNDERSTAND HUMAN INFERTILITY. INFERTILITY IS A DISEASE THAT AFFECTS 6.7 WOMEN AND THEIR PARTNERS OF REPRODUCTIVE AGE IN THE UNITED STATES. I'M

INTERESTED IN UNDERSTANDING WHY 30 PERCENT OF PREGNANCIES END IN MISCARRIAGE. WE HAVE NO IDEA WHY THAT IS. I'M ALSO VERY INTERESTED IN UNDERSTANDING WHY THE SUCCESS RATE OF IVF IS ONLY LESS THAN 50 PERCENT. IF YOU'RE A WOMAN IN HER 40S WHO'S USING HER OWN EGGS, THEN YOUR SUCCESS RATE OF IVF IS LESS THAN 10 PERCENT, PERHAPS LESS THAN 5 PERCENT.

WE KNOW VERY LITTLE ABOUT HOW TO ADVANCE TECHNOLOGIES TO HELP OVERCOME INFERTILITY BECAUSE OF TWO MAIN REASONS. NO. 1, WE DON'T UNDERSTAND A LOT ABOUT THE GERMLINE, THE BASIC BIOLOGY OF THE GERMLINE. AND WE UNDERSTAND EVEN LESS ABOUT THE BASIC BIOLOGY OF THE HUMAN EMBRYO. AND AS A DISCOVERY SCIENTIST, UNTIL WE CAN UNDERSTAND MORE ABOUT THE FUNDAMENTAL DEVELOPMENT OF THE GERMLINE AND THE EMBRYO, IT'S VERY HARD TO MAKE PROGRESS IN THESE PARTICULAR DISEASES.

AND I BELIEVE THAT CRISPR-CAS9 AND OTHER GENE EDITING TECHNOLOGIES AS THEY COME ALONG IN THE FUTURE COULD HAVE TREMENDOUS IMPACT IN US UNDERSTANDING INFERTILITY, UNDERSTANDING HOW TO ADVANCE IVF. AND THESE ARE SOME OF THE EXACT SAME RATIONALE THAT DR. NIAKAN USED IN ORDER FOR HER TO RECEIVE APPROVAL FOR HER LICENSE, WHICH WAS, IN FACT, A RENEWAL OF AN EXISTING LICENSE WITH THE

HUMAN FERTILISATION AND EMBRYO AUTHORITY IN THE UNITED KINGDOM.

AND SO WITH THAT SAID, WHEN A CELL BIOLOGIST TALKS ABOUT A GERMLINE, WHAT WE'RE TALKING ABOUT IS ACTUALLY CELLS THAT ARE FOUND NATURALLY IN YOUR BODY. WE'RE NOT TALKING ABOUT THE HERITABILITY OF INFORMATION. SO A GERMLINE CELL IS A CELL THAT STARTS TO FORM RIGHT AT THE TIME OF IMPLANTATION DURING PRENATAL LIFE, AND IT CONTINUES TO DIFFERENTIATE AND SPECIALIZE TO FORM THESE BEAUTIFUL CELLS THAT YOU CAN SEE HERE. AND I THINK I HAVE A POINTER ON HERE SOMEWHERE.

THESE ARE THE GAMETES THAT WERE TALKED A LOT ABOUT TODAY. THE GAMETES ARE GERMLINE CELLS. SPERMATOGONIAL STEM CELLS ARE ALSO GERMLINE CELLS. THE PRENATAL PRIMORDIAL GERM CELLS THAT WE FIND IN THE EMBRYO THAT WILL BECOME THE GAMETES DECADES LATER ARE REFERRED TO AS GERMLINE CELLS. SO WHEN WE TALK ABOUT BANNING RESEARCH ON THE GERMLINE, WE WANT TO MAKE SURE THAT WE'RE TALKING ABOUT CELLS THAT ARE FOUND NATURALLY IN OUR BODY THAT ARE NOT FERTILIZED. SO THESE CELLS ON THEIR OWN, THE EGG AND THE SPERM, HAVE NO CHANCE OF PASSING GENETIC INFORMATION ON TO FUTURE GENERATIONS UNLESS, OF COURSE, THEY'RE FERTILIZED.

SO I THINK THAT'S JUST A LITTLE TERMINOLOGY POINT THAT I WANT TO MAKE, THAT WE NEED TO DISTINGUISH GAMETES THAT ARE NOT FERTILIZED AND RESEARCH ON HUMAN GERMLINE CELLS WHICH IS FUNDABLE BY THE NIH. I HAVE NIH GRANTS TO STUDY HUMAN GERMLINE CELLS WITHOUT FERTILIZATION AND RESEARCH THAT IS NOT FUNDABLE BY THE NIH, WHICH CIRM HAS SUCH A TREMENDOUS OPPORTUNITY TO BE ABLE TO ENABLE SCIENTISTS TO PURSUE, AND THAT IS THE RESEARCH THAT OCCURS AFTER THE POINT OF FERTILIZATION AND UNDERSTANDING THIS LITTLE WINDOW OF HUMAN DEVELOPMENT TO FORM THE HUMAN BLASTOCYST. AND THAT'S WHAT WE TRULY DON'T UNDERSTAND MUCH ABOUT.

SO THIS IS A PICTURE OF A HUMAN BLASTOCYST THAT WE TOOK IN OUR LABORATORY WHERE WE DO HUMAN EMBRYO RESEARCH. THIS IS A BLASTOCYST AT AROUND SEVEN DAYS POST FERTILIZATION. THE BLASTOCYST IS HATCHING OUT OF ITS COAT AS YOU CAN SEE HERE. THERE IS NO UTERUS. THIS BLASTOCYST IS CONSENTED FOR RESEARCH PURPOSES. AND WE USE HUMAN EMBRYOS IN OUR RESEARCH PROGRAM BECAUSE WE ARE INTERESTED IN CREATING THE HIGHEST QUALITY AND THE BEST STEM CELL FOR REGENERATIVE MEDICINE.

AND WHY IS THE HUMAN EMBRYO IMPORTANT TO THIS? BECAUSE NATURAL PLURIPOTENCY ONLY EXISTS IN

ONE PLACE, AND THAT IS WITHIN THE INNER CELL MASS OF THIS BLASTOCYST, WHICH IS IN HERE AND YOU CAN'T SEE IT. IT'S DEEP INSIDE THE EMBRYO. IF WE WANT TO CREATE NATURAL HIGH QUALITY STEM CELLS FOR USE IN REGENERATIVE MEDICINE, WE HAVE TO UNDERSTAND WHAT NATURAL PLURIPOTENCY LOOKS LIKE. AND SOMETHING WE'RE STARTING TO APPRECIATE AS STEM CELL SCIENTISTS IS THE SORT OF PLURIPOTENCY THAT WE HAVE HARVESTED IN THE LABORATORY, WHETHER IT BE BY MAKING STEM CELLS THROUGH EMBRYONIC STEM CELL DERIVATION OR MAKING PLURIPOTENT STEM CELLS THROUGH INDUCED REPROGRAMMING. WE'RE MAKING A PLURIPOTENT CELL. THAT'S GREAT, BUT IS IT AS GOOD AS WE CAN GET IT? IS IT THE BEST CELL THAT WE CAN USE FOR PATIENTS IN THE FUTURE? AND THAT'S UNDERSTANDING NATURAL PLURIPOTENCY. SO THAT'S UNDERSTANDING THE GENES THAT ARE REQUIRED TO GIVE PLURIPOTENCY TO AN EMBRYO.

SO IN OUR RESEARCH PROGRAM, IN ORDER FOR US TO OBTAIN HUMAN EMBRYOS, WE HAVE AN INFORMED CONSENT PROCESS. AND THE HUMAN EMBRYOS THAT WE RECEIVE INTO OUR RESEARCH PROGRAM ARE EMBRYOS THAT ARE SURPLUS EMBRYOS FOLLOWING IN VITRO FERTILIZATION. SO THESE ARE COUPLES THAT HAVE FINISHED THEIR FAMILY OR ARE AT LEAST MORE THAN ONE YEAR OUT FROM STARTING THEIR THERAPY FOR

INFERTILITY.

THE INFORMED CONSENT PROCESS IS VERY, VERY CLEAR. IT'S WRITTEN IN BIG LANGUAGE ON THE FRONT PAGE OF THE CONSENT THAT WE SEND TO THE DONORS AS WELL AS ON THE FLIER THAT THEY RECEIVE IN THE MAIL AT THE TIME THAT USUALLY THEY'RE GETTING THEIR BILL FROM THE IVF LAB. AND WHAT'S WRITTEN ON IT IS THAT THESE DONATED EMBRYOS THAT YOU'RE MAKING THAT VERY DIFFICULT DECISION FOR, NO ONE THINKS THIS IS AN EASY DECISION FOR COUPLES THAT MADE EMBRYOS IN ORDER TO OVERCOME INFERTILITY, THEY HAVE SURPLUS EMBRYOS LEFT, THAT THESE EMBRYOS WILL NOT BE USED TO CREATE A BABY.

WHAT WE'VE DISCOVERED IN COUPLES THAT HAVE DONATED TO OUR RESEARCH PROGRAM IS THAT THEY WANT CONFIRMATION THAT THEY'VE ALREADY MADE THE DECISION THAT THEY'RE NOT GOING TO DONATE THEIR EMBRYO TO ANOTHER COUPLE TO HAVE A BABY. THEY'VE MADE THIS DIFFICULT DECISION THAT THEY'RE GOING TO DONATE THE EMBRYO TO US RATHER THAN HAVE THE DISPOSITION BE TO DESTROY THEM THROUGH THE APPROPRIATE PROCESS USED IN THE IVF CLINIC. SO THEY WANT TO KNOW WHEN THEY'RE DONATING THEIR EMBRYOS TO US THAT THEIR EMBRYOS WILL NOT BE USED TO CREATE A BABY. AND WE ASSURE IN THE CONSENT PROCESS THAT THE EMBRYOS ARE USED FOR

RESEARCH PURPOSES TO UNDERSTAND HUMAN EMBRYO DEVELOPMENT AND TO BE USED TO UNDERSTAND STEM CELL BIOLOGY, THE BASIC BIOLOGY OF STEM CELLS, TO CREATE HIGH QUALITY STEM CELLS FOR REGENERATIVE MEDICINE.

SO WHEN WE STARTED THIS PROGRAM, OUR PROGRAM HAS BEEN RUNNING FOR EIGHT YEARS, IT'S BEEN FUNDED BY CIRM DURING THIS TIME, AS WELL AS FUNDS FROM THE BROAD STEM CELL CENTER BECAUSE, OF COURSE, NONE OF THE WORK WITH HUMAN EMBRYOS THAT WE DO CAN BE FUNDED BY THE NIH, INCLUDING THE ROOMS THAT WE ARE WORKING WITH THESE EMBRYOS IN. SO I HAVE A SEPARATE SPACE. ONE SPACE IS FOR NIH-FUNDED RESEARCH AND ALL THE REAGENTS AND EQUIPMENT AND TOOLS, AND THEN I HAVE TO HAVE A COMPLETELY DIFFERENT SPACE WHICH IS FUNDED BY A COMPLETELY DIFFERENT MECHANISM IN ORDER TO DO ANY RESEARCH WITH HUMAN EMBRYOS BECAUSE OF THE WAY THE FUNDING WORKS FOR HUMAN EMBRYO RESEARCH.

SO THIS IS JUST TO GIVE YOU A LITTLE SENSE OF WHETHER PEOPLE ACTUALLY DONATE EMBRYOS TO RESEARCH. SO THE PRESIDENT OF CIRM, ALAN TROUNSON, WROTE A REVIEW ABOUT THREE YEARS AGO TRYING TO ESTIMATE THE TOTAL NUMBER OF SURPLUS EMBRYOS THAT ARE IN IVF CLINICS WITHIN THE UNITED STATES. AND HE CAME UP WITH A NUMBER THAT IS MORE THAN A MILLION

EMBRYOS. SO THERE'S A MILLION EMBRYOS IN STORAGE WITHIN THE U.S.

NOW, THE DECISION OF WHAT HAPPENS TO THOSE EMBRYOS IS QUITE DIFFICULT. THE PARENTS, THE DONORS, THE GAMETE DONORS OF THESE EMBRYOS HAVE THE DECISION TO DISCARD THEM, TO DONATE THEM TO RESEARCH, OR DONATE THEM TO OTHER COUPLES. THERE IS A PROBLEM THAT ASRM IS SEEING, AND I'M GLAD THAT WE HAVE REPRESENTATION FROM ASRM TODAY. THERE ARE A LOT OF EMBRYOS THAT SEEM TO BE ABANDONED IN IVF CLINICS BECAUSE THEY CAN'T TRACK DOWN THE PARENTS WHO DONATED THE GAMETES. SO WHAT DO YOU DO WITH THESE SURPLUS EMBRYOS THAT ARE IN IVF CLINICS? AND THAT'S SOMETHING THAT ASRM IS TRYING TO SET GUIDELINES FOR.

FOR US, WE GET OUR EMBRYOS BECAUSE THE COUPLE CONTACTS US. WE SEND A FLIER OUT IN THE MAIL. WE DON'T CHASE ANYONE DOWN. WE DON'T GO TO IVF CLINICS TO MEET WITH PARENTS THEMSELVES. THEY RECEIVE OUR FLIER, THEY MAKE THE DECISION TO DONATE, AND THEN THEY CALL US TO FIND OUT MORE ABOUT OUR PROGRAM, AND THAT WE'LL BE USING THE HUMAN EMBRYOS FOR RESEARCH. NOT ALL OF THE COUPLES WHO CALL WILL SIGN A CONSENT, AND WE DON'T FOLLOW UP ON THEM EITHER. THE PROCESS OF DONATING EMBRYOS TO OUR

RESEARCH PROGRAM AT UCLA IS DRIVEN BY THE DESIRE OF THE PARENTS TO DONATE TO RESEARCH.

ONCE WE RECEIVE THE EMBRYOS INTO OUR RESEARCH PROGRAM, IT IS POSSIBLE FOR THE DONORS WHO DONATED TO REQUEST THAT THE EMBRYO BE REMOVED FROM THE RESEARCH PROGRAM. BUT WE SAY IN OUR CONSENT FORM THAT THE EMBRYO WILL BE REMOVED, BUT NOT GIVEN BACK TO THEM. THE EMBRYO WILL BE DESTROYED. SO WHEN THEY SIGN THE CONSENT PROCESS, WE VERY CLEARLY TALK ABOUT THAT AS WELL. IF THE EMBRYO HAS ALREADY BEEN USED FOR RESEARCH, IT WILL BE DESTROYED. SO IF ONE OF THE DONORS CALLS UP A YEAR LATER AND SAYS I'VE CHANGED MY MIND, BUT THE EMBRYO HAS ALREADY BEEN USED FOR RESEARCH, THEN THEY HAVE ALREADY RELINQUISHED THEIR RIGHTS TO ANY DATA THAT WE'VE OBTAINED ON THAT EMBRYO ACCORDING TO THE WAY OUR CONSENT IS WRITTEN.

SO THIS IS JUST SHOWING YOU THAT OVER THESE EIGHT YEARS THAT WE ARE HAVING A GROWING AND CONSISTENT INTEREST IN EMBRYO DONATION TO OUR RESEARCH PROGRAM AT UCLA. SO YOU CAN SEE THAT IN THE LAST TWO YEARS, 2014, 2015, WE'VE HAD AROUND A HUNDRED OR MORE DONORS THAT HAVE DONATED THEIR EMBRYOS TO OUR RESEARCH PROGRAM. AND THIS IS RESEARCH FOR STEM CELL BIOLOGY AND ALSO

UNDERSTANDING THE BASIC BIOLOGY OF THE EMBRYO.

NOW, AT STANFORD FOR THEIR HUMAN EMBRYO RESEARCH PROGRAM, THEY'VE PUBLISHED A VERY INTERESTING PAPER IN *CELL STEM CELL* IN 2013 WHERE THEY ASKED THE DONORS OF THE EMBRYOS WHAT CHOICE DO YOU WANT WHEN YOU DONATE YOUR EMBRYOS? WE'RE GIVING YOU TWO CHOICES. IF YOU DONATE YOUR EMBRYOS TO OUR RESEARCH PROGRAM, YOU CAN EITHER GO SPECIFICALLY TO STEM CELL RESEARCH DERIVING NEW EMBRYONIC STEM CELL LINES OR THE EMBRYO COULD BE USED TO UNDERSTAND THE BASIC BIOLOGY OF THE HUMAN EMBRYO IN ORDER TO IMPROVE IVF APPROACHES, OR IT COULD BE USED FOR EITHER. WHAT THE STUDY DEMONSTRATED WAS THAT 70 PERCENT OF THE DONORS WERE WILLING FOR THEIR EMBRYOS TO BE USED FOR EITHER STEM CELL RESEARCH AND UNDERSTANDING HUMAN EMBRYO DEVELOPMENT OR JUST SIMPLY UNDERSTANDING HUMAN EMBRYO DEVELOPMENT.

SO THESE DONORS ARE VERY INTERESTED IN TRYING TO HELP OTHER COUPLES WHO COME BEHIND THEM TO HAVE IMPROVEMENTS IN IVF TECHNIQUES SO THAT THEY DON'T HAVE TO GO THROUGH THE SAME PROCESS THAT THEY HAVE. THEY REALLY ARE VERY INTERESTED IN HELPING OTHER COUPLES BY HAVING IMPROVEMENTS IN THE IVF STRATEGY. AND THAT'S ONE OF THE REASONS WHY THEY WILL DONATE THEIR HUMAN EMBRYOS TO RESEARCH

PURPOSES. I THINK THAT'S VERY IMPORTANT TO NOTE.

SO I WANT TO CONCLUDE BY TALKING ABOUT HOW DOES CRISPR-CAS9 FIT INTO ALL OF THIS. THERE ARE A NUMBER OF BASIC RESEARCH QUESTIONS THAT CRISPR-CAS9 CAN BE USED FOR AS A DISCOVERY TOOL. SO WE'RE NOT TALKING ABOUT EDITING THE GENOMES OF EGGS AND SPERM OR GERMLINE AND EMBRYOS IN ORDER FOR TRANSFER AND ESTABLISHING A PREGNANCY. WE'RE TALKING ABOUT THE WAY A BASIC SCIENTIST THINKS. I WANT TO KNOW THE PATHWAYS THAT MAKE A GERMLINE CELL GROW. SO I'M GOING TO START TO LOOK AT THESE DIFFERENT GENES BY DELETING THEM OR BY CHANGING THE WAY THEY WORK AND SEEING WHAT HAPPENS WITHOUT ANY INTENT OF ESTABLISHING A PREGNANCY. THIS IS BASIC RESEARCH QUESTIONS.

SO YOU CAN DO THIS IN IMPROVING IVF OUTCOMES BY SIMPLY UNDERSTANDING GERMLINE DEVELOPMENT BY USING CRISPR-CAS9 OF EGGS AND SPERM OR SPERMATOGONIAL CELLS OR GERM CELLS WE CREATE FROM STEM CELLS AND FIND OUT THE PROPERTIES THAT MAKE THEM WORK BETTER.

WITH REGARD TO THE LICENSE THAT WAS RECENTLY APPROVED IN THE UNITED KINGDOM, ONE OF THOSE AIMS OF USING CRISPR-CAS9 IS TO UNDERSTAND HOW THE CELLS THAT WILL ULTIMATELY FORM THE PLACENTA,

HOW DO THEY FORM IN THE EMBRYO? WHEN YOU FORM A BLASTOCYST, YOU NEED TO MAKE THE CELLS THAT MAKE THE EMBRYO AND THEN THE CELLS THAT WILL ULTIMATELY MAKE THE PLACENTA. AND THIS IS A REALLY IMPORTANT QUESTION.

CRISPR-CAS9 CAN BE USED TO HELP US UNDERSTAND WHAT ARE THE PATHWAYS THAT ARE NECESSARY TO MAKE A REALLY GOOD QUALITY EMBRYO. AND THESE ARE THE PATHWAYS PERHAPS WE SHOULD THINK ABOUT AS WE'RE CREATING NEW MEDIA FORMULATIONS FOR IVF IN ORDER TO GET BLASTOCYST FORMATION.

WE CAN USE CRISPR-CAS9 IN ORDER TO UNDERSTAND THAT NATURAL PLURIPOTENCY IN THE HUMAN EMBRYO IN ORDER TO HELP US UNDERSTAND THE ESTABLISHMENT OF SELF-RENEWAL. THAT'S CRITICAL FOR MAKING IPS CELLS AS WELL AS MAKING ES CELLS. WHAT ARE THE KEY COMPONENTS TO HUMAN PLURIPOTENCY? WE APPRECIATE THAT MASS PLURIPOTENCY IS ACTUALLY A LITTLE BIT DIFFERENT THAN HUMAN PLURIPOTENCY. SO IF WE WANT TO KNOW WHAT NATURAL PLURIPOTENCY IS, THEN THE HUMAN BLASTOCYST IS WHERE WE HAVE TO STUDY IT. AND REPROGRAMMING IS BUILT ON THE FOUNDATION OF THE WORK TO HUMAN EMBRYONIC STEM CELLS AND ALSO HUMAN EMBRYOS. IF YOU WANT TO UNDERSTAND REPROGRAMMING, YOU NEED TO START THINKING ABOUT PATHWAYS THAT CAN

BE MODIFIED AS A DISCOVERY TOOL IN THE HUMAN EMBRYO.

AND THEN FINALLY, WE TOUCHED ON THIS A LITTLE BIT TODAY, IF WE ARE THINKING ABOUT CRISPR-CAS9 IN THE FUTURE, WE ALL RECOGNIZE, I THINK ALL SCIENTISTS, RATIONAL, REASONABLE SCIENTISTS RECOGNIZE THAT THE CRISPR-CAS9 TECHNOLOGY IS NOWHERE NEAR READY FOR USE FOR REPRODUCTIVE PURPOSES TO ESTABLISH A PREGNANCY. IF WE ARE INCLINED TO THINK IN THAT DIRECTION, I PERSONALLY THINK THAT THERE ARE DISEASES THAT WILL BENEFIT FROM A GENE CORRECTION IN AN EMBRYO. ONE OF THEM WE HAVEN'T TALKED ABOUT TODAY IS FRAGILE X. AND FRAGILE X IS A SET OF MUTATIONS THAT HAPPEN OUTSIDE OF THE CODING REGION OF THE GENE. AND THAT CHANGE THROUGH THE GAMETE, THROUGH THE FEMALE GAMETE, THE EGG AND THE EMBRYO, CAN LEAD TO AUTISM IN CHILDREN. SO PERHAPS THERE'S WAYS THAT WE CAN CORRECT THAT MUTATION IN THE GENOME WITHOUT AFFECTING THE GENE ITSELF. AND SO FOR THINKING ABOUT THOSE SORTS OF TOOLS AND WHETHER THIS IS EVEN POSSIBLE FOR THAT POPULATION IS INCREDIBLY IMPORTANT.

SO THE ONE STUDY ON HUMAN EMBRYOS THAT WAS PERFORMED IN CHINA WAS PERFORMED ON A 3PN EMBRYO, AN EMBRYO THAT HAD MORE GENOME THAN A NORMAL EMBRYO SHOULD. IT SHOWED US THAT CRISPR-CAS9 DOESN'T WORK.

BUT GIVEN THAT THE EMBRYO WAS ALREADY ABNORMAL, WE REALLY STILL DON'T HAVE A GOOD UNDERSTANDING OF WHAT IF WE TESTED CRISPR-CAS9 IN A EUPLOID EMBRYO? WOULD WE RESULT IN A BETTER OUTCOME THAN OF THE 3PN EMBRYO USED? SO THERE'S AN IMPORTANCE IN STUDYING THE CRISPR-CAS9 TECHNOLOGY IN A EUPLOID EMBRYO TO SEE IF IT'S EVEN GOING TO WORK.

WE ALSO DON'T KNOW THE NATURAL MUTATION RATE. WE TALK A LOT ABOUT OFF-TARGET EFFECTS, AND THE CRISPR CAN CAUSE OFF-TARGET EFFECTS. BUT IT IS A TRUE STATEMENT THAT OUR GENOME IS CHANGING AND EVOLVING ALL THE TIME TO NATURAL MUTATIONS THAT OCCUR JUST BECAUSE OUR CELL PHYSIOLOGY IS DRIVEN TOWARDS NATURAL MUTATIONS. WE HAVE VERY HIGH FIDELITY DNA DAMAGE RESPONSE REPAIR PATHWAYS TO DEAL WITH IT, BUT THEY'RE NOT A HUNDRED PERCENT PRECISE ALL THE TIME EITHER. NON-HOMOLOGOUS END JOINING IS PART OF OUR NATURAL DNA DAMAGE RESPONSE PATHWAY.

SO WE DON'T KNOW THAT WHEN EMBRYOS ARE GROWING OVER THOSE 14 DAYS IN THE IVF LAB WHAT NATURAL MUTATIONS THEY ARE ACQUIRING DURING THIS TIME. AND HOW CAN WE UNDERSTAND THAT VERSUS OFF-TARGET EFFECTS FROM CRISPR? THERE'S JUST LITTLE INFORMATION ON DNA DAMAGE RESPONSE PATHWAYS WE NEED TO KNOW.

IT'S VERY IMPORTANT TO HAVE COST EFFICIENCY OF ON-TARGET, AND WE TALKED ABOUT MOSAICISM TODAY. SO THE HUMAN EMBRYO IS A VERY SPECIAL TYPE OF CELL. I FEEL VERY PRIVILEGED AS A SCIENTIST TO BE ABLE TO WORK ON IT. I RECOGNIZE THE DIFFICULTY AND THE DECISION OF COUPLES THAT ARE WILLING TO DONATE THE EMBRYOS TO US TO DO THIS RESEARCH AND THE TRUST THEY HAVE IN US THAT WE WILL DO ETHICALLY RESPONSIBLE RESEARCH. BUT TESTING OUT CRISPR IN SOMATIC CELLS AND ASSUMING THEY'RE GOING TO WORK EXACTLY THE SAME WAY IN HUMAN EMBRYOS I THINK IS NOT THE RIGHT APPROACH TO TAKE. IF WE'RE REALLY THINKING THIS IS GOING TO BE SOMETHING IN THE FUTURE THAT COULD HELP A SMALL GROUP OF PEOPLE, THEN WE NEED TO START TESTING THIS OUT ON THE HUMAN EMBRYO. THAT'S ALL I HAVE TO SAY. THANK YOU.

(APPLAUSE.)

CO-CHAIR LO: UNLESS THERE'S A BURNING QUESTION FOR PROFESSOR CLARK, LET'S GO THROUGH ALL OUR PANELS AND HAVE DISCUSSION AFTERWARDS.

DR. CORN.

DR. CORN: RATHER THAN HAVE SLIDES, I THOUGHT THAT I WOULD TALK A LITTLE BIT MORE INFORMALLY BECAUSE I REALLY WANTED THIS TO BE A DISCUSSION. I SORT OF HAVE THE PRIVILEGE TO BE ABLE

TO SAY WHAT SHE SAID, BASICALLY TO STRESS WHAT SHE SAID. I THINK THAT A LOT OF REALLY GREAT POINTS ABOUT THIS TECHNOLOGY HAVE COME UP. SOMETHING I WANT TO POINT OUT IS IN OUR LAB, WE'RE REALLY PROFESSIONAL GENE EDITORS. WE WORK ON A LOT OF DIFFERENT CELL TYPES. WE'RE ESPECIALLY FOCUSED ON HEMATOPOIETIC STEM CELLS. WORKING WITH A LOT OF DIFFERENT CELL TYPES, IT'S BECOME REALLY APPARENT THAT, LIKE DAVID POINTED OUT THIS MORNING, CAS9 IS A GREAT SCISSORS. IT'S GOING TO GO INTO THE GENOME AND IT'S GOING TO CUT. EVERYTHING THAT HAPPENS AFTERWARDS IS DEPENDENT ON THE CELL THAT IT'S IN.

SO DAVID POINTED OUT, FOR EXAMPLE, THAT YOU MAKE A CUT, YOU HAVE HHA, YOU HAVE HDR. ONE CAN KNOCK OUT A GENE, ONE CAN REPLACE GENES IN HUMAN CELLS. HHA IS DOMINANT, SO IT'S VERY EASY AT THIS POINT TO GO IN AND KNOCK GENES OUT IN CAS9. IT'S MUCH HARDER TO KNOCK THINGS IN. THAT'S ONE OF THE THINGS THAT WE'RE TRYING TO FIX IN MY LAB.

IF YOU GO INTO YEAST, THE EXACT OPPOSITE. IT'S VERY HARD TO MAKE A KNOCKOUT. IT'S VERY EASY TO PUT THINGS IN. AND WHAT WE START TO FIND OUT IS THAT IF YOU EVEN CHANGE DIFFERENT CELL TYPES IN THE HUMAN BODY, YOU GET DIFFERENT ANSWERS. DIFFERENT CELL TYPES ARE EASIER TO EDIT, HARDER TO EDIT. THEY

HAVE DIFFERENT EDITING OUTCOMES. AND FOLLOWING UP ON WHAT AMANDER SAYS, WE HAVE NO IDEA HOW THIS IS GOING TO WORK IN EMBRYOS. WE HAVE ALMOST NO DATA.

THERE ARE A COUPLE OF LABS WORKING IN ES CELL LINES. AND WHAT WE'VE ALREADY STARTED TO SORT OF UNDERSTAND THROUGH THE GRAPEVINE IS THAT DIFFERENT ES CELL LINES ARE EASIER OR HARDER TO EDIT, AND WE DON'T KNOW WHY.

SO THIS REALLY GETS US TO THE NEED, WHICH, AS AMANDER POINTED OUT AND WE'VE HEARD BEFORE, IS NOT FUNDABLE BY NIH TO ESTABLISH NEW ES CELL LINES, TO TRY TO DO EDITING IN EARLY STAGE EMBRYOS, MAYBE TO ESTABLISH LINES FROM THOSE, TO UNDERSTAND THE WAY THESE SYSTEMS WORK BECAUSE WITHOUT THAT KIND OF INFORMATION, WE WON'T HAVE ANY OF THE GROUNDWORK TO DO ANY OF THE IMPORTANT FUNDAMENTAL RESEARCH.

TO GIVE YOU SORT OF A FLAVOR OF THE TYPES OF THINGS YOU MIGHT WANT TO DO WITH THIS, HARKENING BACK TO MY MORE TRANSLATIONAL DAYS BEFORE I WENT TO BERKELEY, EMBRYONIC STEM CELL LINES CAN BE VERY USEFUL FOR FIGURING OUT THE WAYS THAT DIFFERENT PATIENT-OBSERVED SNP'S CAN HAVE EFFECTS. SO IF YOU OBSERVE SOME SNP IN A PATIENT, IS IT A CARRIER? IS IT A DRIVER? HOW DOES IT AFFECT DEVELOPMENT? THERE ARE ALL KINDS OF DEVELOPMENTAL DISEASES THAT HAVE

BEEN LINKED TO DO VARIOUS THINGS. AND, AGAIN, AS AMANDER POINTED OUT, IPS CELLS ARE NOT ES CELLS NECESSARILY. SO I THINK THAT THERE IS A NEED TO BE ABLE TO INTRODUCE THESE KINDS OF SNP'S TO MAKE CHANGES INTO THESE LINES AND TO FIGURE OUT HOW THESE DIFFERENT MUTATIONS CAN LEAD TO DIFFERENT DISEASES WITH THE HOPE THERE COULD BE SOME SORT OF GENE THERAPY OR GENE EDITING CURE FOR THOSE DISEASES.

ALSO, FROM A FUNDAMENTAL THERAPEUTIC POINT OF VIEW, ONCE YOU HAVE A CELL MODEL, YOU CAN USE THAT TO TEST VARIOUS THERAPIES, EVEN TRADITIONAL THERAPIES, SMALL MOLECULES, LARGE MOLECULES. THE POINT IS YOU NEED A MODEL. YOU NEED THAT MODEL TO BE A VERY FAITHFUL MODEL OF HUMAN DISEASE.

ONE LAST THING TO SAY TO REALLY BRING HOME THE NECESSITY FOR THESE KINDS OF ROBUST MODELS IS JUST THE SCALE OF THE PROBLEM. AS DAVID POINTED OUT, 6,000 MONOGENIC DISEASES. ON ONE OF THE SLIDES, HE SHOWED ONE OF -- THE SCID, BUBBLE BOY ALLELES WITH ALL THE DIFFERENT MUTATIONS. SO IT'S NOT JUST ABOUT 6,000 GENES. IT'S ABOUT ALL OF THE DIFFERENT ALLELES FOR THOSE GENES.

SO THERE'S ONE PATIENT POPULATION THAT WE WORK WITH WHERE THERE ARE 49 PATIENTS KNOWN, AND EVERY PATIENT HAS A DIFFERENT MUTATION IN THAT GENE,

AND THEY ALL HAVE DIFFERENT PRESENTATION. AND IT'S TOTALLY UNCLEAR WHY THAT IS. AND IT'S POSSIBLE THIS IS A DEVELOPMENTAL DEFECT. IT'S POSSIBLE THAT THROUGH GENE EDITING WE'LL BE ABLE TO UNDERSTAND SOMETHING ABOUT THE BASIC MECHANISMS OF THIS. I THINK THERE'S REALLY A NEED FOR THIS KIND OF RESEARCH, WHICH IS, AGAIN, UNFUNDABLE BY THE NIH, BUT REALLY, REALLY KEY FOR BASIC UNDERSTANDING OF MECHANISMS OF DISEASE AS WELL AS FOR POTENTIALLY THERAPIES FOR THESE DISEASES. THANKS.

(APPLAUSE.)

CO-CHAIR LO: ANY PRESSING QUESTIONS FOR DR. CORN? IF NOT, DR. BELMONTE.

DR. BELMONTE: WHEN THIS GETS SET UP, I HAD PREPARED A DIFFERENT TALK, AND I WAS GOING TO GIVE YOU AN OVERVIEW OF TECHNOLOGIES AND THE GERMLINE. BUT AFTER THIS MORNING'S DISCUSSION, I THOUGHT IT WOULD BE MORE PRACTICAL TO DIG INTO SOME OF THE QUESTIONS WE ARE DISCUSSING. SO I HAVE BEEN CHANGING MY SLIDES AS WE WERE DISCUSSING.

AND ONE OF THE THINGS THAT I SENSE FROM THE DISCUSSION IS UNMET CLINICAL NEEDS. AND ONE OF THE ISSUES WAS THE MITOCHONDRIAL DISEASES. ONE OF THE DISCUSSIONS WE ARE HAVING IS WE HAVE PGD. WHY THEN TO GO GENETICALLY NUCLEAR DNA? OBVIOUSLY THIS

IS SOMETHING WE CANNOT DO WITH MITOCHONDRIAL DNA. THE MENDELIAN DOESN'T WORK IN THE MITOCHONDRIAL DNA. THEREFORE, ANY PREIMPLANTATION DIAGNOSIS THAT IS DONE THERE WILL BE OF NO USE. DEFINITELY THERE IS A NEED TO DEVELOP TECHNOLOGIES TO CORRECT MITOCHONDRIAL DNA DISEASES.

ONE OF THEM IS THE ONE THAT WAS A FEW MONTHS APPROVED IN THE UK, WHICH IS THE USE OF HEALTHY DONOR OOCYTE TO COMPENSATE AND TO PUT FOR THE BAD MITOCHONDRIA THAT A WOMAN HAS THE PROBLEM. SO THIS IS SOMETHING THAT HAS BEEN CAUSED GENETICALLY, AND I DISAGREE. IT'S NOT CUTTING. IT'S NOT PASTING. IT'S JUST REPLACEMENT. JUST MY PERSONAL OPINION. NOW, THAT'S GREAT. IT'S A WONDERFUL TECHNOLOGY. AS I SAID, HAS BEEN APPROVED IN THE UK.

THE MAJOR PROBLEM THAT THIS TECHNOLOGY HAS, YOU KNOW THAT MITOCHONDRIA AND THE NUCLEAR COMPONENTS OF THE CELL, THEY NEED TO TALK TO ONE ANOTHER. AND THEY NEED TO TALK TO ONE ANOTHER FROM THE VERY FIRST MOMENT THEY MEET. AND HERE WE'RE INTRODUCING TWO DIFFERENT INDIVIDUALS, SO TO SPEAK, IF YOU WANT TO CALL IT THAT, THAT COME FROM DIFFERENT ORIGINS. FROM THE VERY BEGINNING OF THESE EMBRYO BEING DEVELOPED, THE COMMUNICATION THERE WILL

NOT BE PERFECT. AND WE KNOW THIS FROM DIFFERENT MOUSE EXPERIMENTS.

SO THIS IS NOT TO SAY THAT THIS IS NOT A NEED AS WE GO FORWARD. WE NEED TO STUDY IT AND WHETHER THAT COMMUNICATION FOR THE FORMATION OF HEALTHY EMBRYO.

ANOTHER POSSIBILITY IS RATHER THAN DOING MITOCHONDRIAL REPLACEMENT WILL BE THIS ONE. SO IF WE HAVE IN RED THE MUTANT MITOCHONDRIAL DNA, TRYING TO ELIMINATE AS MANY OF THAT MUTANT DNA SO THAT THE EMBRYO HAS THE MINIMUM AMOUNT OF MITOCHONDRIAL DNA PRESENT. AND YOU KNOW THAT FOR THE DISEASE TO BE MANIFESTED, YOU NEED TO GO OVER A CERTAIN THRESHOLD. ABOUT 60 TO 70 PERCENT OF THE MITOCHONDRIAL DNA NEEDS TO BE MUTATED. SO WE CAN ACHIEVE THAT PROPORTION. THAT CERTAINLY WILL BE OF HELP.

WE MADE THIS ABOUT A YEAR AGO, AND THIS IS SHOWN HERE IN THESE GEL. SO YOU CAN SEE THAT ON THE LEFT THE AFFECTED MICE HAVE -- SO YOU CAN SEE THAT THE AFFECTED MICE HAVE THE MUTANT DNA. THERE ARE TWO BANDS THERE. AND JUST BY GENE EDITING YOU CAN REMOVE, SPECIFICALLY IN THE MITOCHONDRIA, THAT MUTANT DNA. THERE IS STILL SOMETHING THAT THAT MINIMAL AMOUNT WILL NOT BE ABLE TO GENERATE ANY PHENOTYPE IN THE MOUSE.

THE ADVANTAGES OF THIS TECHNOLOGY IS THAT YOU ARE NOT CONFRONTING DIFFERENT MITOCHONDRIA OR NUCLEI NOT COMING FROM THE SAME ORIGIN. ANOTHER ADVANTAGE IS THAT MANY DOCTORS IN AN IVF CLINIC CAN GO WITH A NEEDLE AND DO THE EXPERIMENT. THE PREVIOUS EXPERIMENT YOU NEED TO BE REALLY GOOD WITH YOUR HANDS. DOING CLONING IS SOMETHING THAT TWO OR THREE LABS CAN DO IT IN THE WORLD EFFICIENTLY. AND AT THIS MOMENT I FEEL IT WOULD BE NOT THAT PRACTICAL. THESE METHODOLOGIES, JUST INJECTING AN ENZYME INSIDE THE MITOCHONDRIA. AND AS YOU CAN SEE IN THE MICE, PROBLEM GETS FIXED.

ANOTHER PROBLEM WE DISCUSSED TODAY AND DR. BALTIMORE PRESENTED IS THAT CELLS KNOW HOW TO FIX THE PROBLEM EITHER THROUGH A HOMOLOGOUS RECOMBINATION OR THROUGH NON-HOMOLOGOUS END JOINING. THE PROBLEM THAT WE HAVE THERE IS THAT THIS DOESN'T WORK IN NONDIVIDING CELLS, THE HOMOLOGOUS COMBINATION. AND THE IDEA IS WHETHER WE CAN HAVE SOMETHING THAT WORKS IN SOMATIC CELLS. WE DISCUSSED THIS MORNING ABOUT PRIORITIES. AND WE KNOW THAT THERE IS NOT ANY SPECIFIC PROBLEM MODIFYING SOMATIC CELLS; BUT SO FAR WE COULDN'T DO THAT IN VIVO BECAUSE CELLS, MOST OF THE CELLS, DO NOT DIVIDE. WE NOW HAVE SOME METHODOLOGY WHERE WE CAN DO THIS IN

PRIMARY NEURONS; BUT, MORE IMPORTANTLY, IN VIVO. AND HERE'S AN EXAMPLE OF NEURONS THAT ARE WELL-KNOWN FOR NOT BEING ABLE TO DIVIDE.

SO WE CAN PUT THINGS INSIDE THE GENOME OF CELLS THAT DO NOT DIVIDE IN VIVO. THEREFORE, WE COULD THINK OF TARGETING MANY, MANY DISEASES THAT HAPPEN IN THE SOMATIC CELLS. BUT FOR THE PURPOSE OF TODAY AS WELL, AND THIS GOES BACK TO THE WORK OF AMANDER AND OTHERS, THERE IS THE POSSIBILITY THAT WE COULD GENERATE GERM CELLS IN VITRO FOR IPS THROUGH DIFFERENTIATION. AND THIS TECHNOLOGY OF BEING ABLE TO ALTER THE GENOME OF NOT JUST EMBRYOS, BUT CELLS THAT WE CREATE IN THE LAB, CERTAINLY WITH THIS TECHNOLOGY WILL BE ADDRESSABLE.

I'M GOING TO GIVE YOU AN EXAMPLE OF JUST ONE OF THE LATEST RESULTS WE ARE GETTING. SOMATIC CELLS, GENE EDITING CELLS THAT DO NOT DIVIDE, SAY THIS EYE PROBLEM. SO IN THE ANIMALS WE CAN GO IN AND THROUGH THIS NON-HOMOLOGOUS END JOINING, WE CAN MAKE THE ANIMALS TO SEE AGAIN. SO THE QUESTION THAT WAS PUT BEFORE BY JEFF ON WE NEED TO SET UP PRIORITIES, AND PRIORITIES IS PRACTICAL NEEDS. MITOCHONDRIA IS CERTAINLY ONE OF THEM. THERE'S NO WAY TO SOLVE THE PROBLEM, AND PGD WILL NOT WORK. THERE IS MANY SOMATIC CELLS THAT WE -- PROBLEMS THAT

WE HAVE NOT ADDRESSED TODAY, BUT WITH TECHNOLOGIES LIKE THIS COULD BE ADDRESSABLE BECAUSE THEY NORMALLY DO NOT DIVIDE. AND EVEN THOSE THAT DIVIDE, LIKE CELLS IN THE LIVER, CELLS IN THE BONE MARROW, METABOLIC DISEASES, SICKLE CELL ANEMIA, THEY ARE DIFFICULT TO TARGET BECAUSE THE EFFICIENCY OF MANY HOMOLOGOUS RECOMBINATIONS, NO, WHILE THIS OTHER ONE IS MUCH, MUCH HIGHER. AND, THEREFORE, WE COULD EVEN THINK OF GERMLINE STEM CELLS BEING TARGETED BY THIS TECHNOLOGY.

SO WITH THAT, I'M FINISHED. AND JUST TO RECAPITULATE AND SUMMARIZE WHAT I HAVE TOLD YOU, IT IS IMPORTANT THAT WE MAKE DECISIONS FOR THE PROBLEMS THAT WE HAVE IN FRONT OF US. AND CERTAINLY PROBLEMS IN THE GERMLINE ARE VERY IMPORTANT, BUT THE PREVALENCE OF MANY OF THE PROBLEMS THAT WE HAVE TODAY WILL BE SOLVED WITH TECHNOLOGIES THAT IS TAKING PLACE. I MENTIONED THE SOMATIC THERAPY AND THE MITOCHONDRIAL IS ALSO A GERMLINE PROBLEM, AND I'M FINISHED THERE. THANK YOU.

(APPLAUSE.)

DR. LOMAX: DO WE HAVE QUESTIONS?

DR. ROD TAYLOR: JUAN CARLOS, VERY, VERY NICE PRESENTATION. THANKS. AND I LIKE THE -- YOU KNOW, THE TERMINOLOGY, WE'RE KIND OF FINDING TODAY

THAT THE TERMS THAT WE USE ARE REALLY IMPORTANT. AND THIS IDEA OF MAYBE MITOCHONDRIAL REPLACEMENT VERSUS MITOCHONDRIAL CORRECTION, OR YOU MIGHT COME UP WITH A BETTER TERMINOLOGY THAN THAT, ARE KIND OF DIFFERENT THINGS.

ONE OF THE QUESTIONS THAT I HAD REGARDING, I GUESS, FIXING MITOCHONDRIA IS THAT IN YOUR MOUSE MODEL, IT APPEARS THAT THERE'S KIND OF A CONSERVATION OF MITOCHONDRIA MASS WITHIN THE CELL. WHEN YOU ACTUALLY KNOCKED OUT THE ABNORMAL MITOCHONDRIA, THERE WAS AN INCREASE IN THE BAND MASS OF THE WILD TYPE MITOCHONDRIA. SO DO CELLS SORT OF MANAGE? I KNOW THAT THE NUMBER OF MITOCHONDRIA PER CELL CAN BE QUITE VASTLY DIFFERENT DEPENDING ON THE CELL TYPE. SO IF YOU WERE TO GO IN AND KIND OF KNOCK OUT THE BAD MITOCHONDRIA, THOSE WILL BE REPLACED, DO YOU THINK, PRETTY MUCH BY HEALTHY MITOCHONDRIA? IS THAT A PREMISE WE CAN TRUST?

DR. BELMONTE: YOU ARE RIGHT BECAUSE DURING DEVELOPMENT THERE IS -- YOU STUDY THE NUMBER OF MITOCHONDRIA THAT APPEAR AT ONE SPECIFIC STAGE. IT'S VERY DIFFERENT THAN ANOTHER STAGE, AND THERE IS A BOTTLENECK NEAR THAT PARTICULAR STAGE FOR THAT. WE REALLY DON'T KNOW WHAT'S THE MINIMAL AMOUNT OF MITOCHONDRIA THAT HAVE TO BE PRESENT FOR THE EMBRYO

TO DEVELOP.

CERTAINLY THIS SHOWS THAT THESE ANIMALS ARE OKAY AND THEY'RE FINE. BUT WHAT WE MAY LEARN IS THAT JUST BY REDUCING A LITTLE BIT THE AMOUNT OF MUTATED MITOCHONDRIA, THAT'S ENOUGH BECAUSE THE PHENOTYPE, AS YOU VERY WELL KNOW, ONLY MANIFESTS ABOVE A CERTAIN THRESHOLD. SO EVEN IF THAT WERE TO BE A PROBLEM, JUST BY LOWERING THE, SO TO SPEAK, THE ELIMINATION OF BAD MITOCHONDRIA, THIS WOULD BE SOLVABLE.

DR. BALTIMORE: JUAN, TELL US. YOU VERY NICELY SHOWED US THAT YOU CAN GET GENETIC MATERIAL IN THROUGH NON-HOMOLOGOUS END JOINING IN CELLS THAT DON'T CARRY OUT HOMOLOGOUS RECOMBINATION, BUT YOU NEVER SAID HOW YOU DID IT. IT WAS SORT OF MAGIC.

DR. BELMONTE: SORRY. I WAS TOLD TO GIVE SIX MINUTES OR SEVEN MINUTES.

DR. BALTIMORE: THIS IS YOUR CHANCE FOR ANOTHER SIX.

DR. BELMONTE: COMBINATION OF CAS9 TECHNOLOGY AND USING AAV FOR DELIVERY. OBVIOUSLY THE EFFICIENCY OF THAT METHOD TO BE PRACTICAL DEPENDS ON BOTH PARAMETERS. THE DELIVERY, WHAT IS THE VIRUS THAT WE NEED TO USE TO TARGET A SPECIFIC CELL TYPE, AND AS WELL THE TRANSDUCTION EFFICIENCY

OF THE CAS9. BUT I FEEL THAT THESE, AND WE SEE IT EVERY DAY, IS THINGS THAT COULD IMPROVE DRAMATICALLY IN JUST A YEAR, SO TO SPEAK. AND, THEREFORE, AND FOLLOWING JEFF'S COMMENT BEFORE ON WHERE SHOULD WE PRIORITIZE AND PUT OUR RESOURCES, CERTAINLY THE GERMLINE IS A CASE THERE. AND PERHAPS THE MITOCHONDRIA IS THE CLEAREST ONE. CERTAINLY BASIC RESEARCH IS NEEDED TO UNDERSTAND HOW WE DEVELOP PARTICULARLY THE MOST IMPORTANT CELL OF OUR BODIES, THE GERM CELL.

BUT AT THE SAME TIME, WE DISCUSS ABOUT SICKLE CELL ANEMIA, WHICH IS AFFECTING MANY, MANY, MANY PEOPLE. AND THAT SO FAR IT WAS DIFFICULT TO TARGET. SO THESE GENE EDITING TECHNOLOGIES IS ALLOWING US TO THINK OF TARGETS THAT PERHAPS ARE MORE IMMEDIATE. SO WE NEED TO EVALUATE ALL THIS AND MAKE DECISIONS FROM THERE.

DR. BOTKIN: QUESTION PROBABLY PRIMARILY FOR DR. CLARK, BUT ANYBODY ELSE TOO. YOU'VE TALKED ABOUT USING RESIDUAL EMBRYOS FROM CLINICAL SERVICES FOR YOUR RESEARCH. IS THERE A SCIENTIFIC INTEREST OR NEED IN CREATING EMBRYOS FOR RESEARCH PURPOSES?

DR. CLARK: SO, OF COURSE, WE KNOW THAT THIS IS A VERY CONTROVERSIAL TOPIC, AND I BELIEVE THE STANDARDS WORKING GROUP HAS ADDRESSED IT BEFORE,

MAKING EMBRYOS SOLELY FOR THE PURPOSE OF RESEARCH. SO, YES, I THINK THAT THERE IS SCIENTIFIC JUSTIFICATION FOR MAKING EMBRYOS SOLELY FOR THE PURPOSE OF RESEARCH.

ONE OF THE TECHNOLOGIES THAT WE'RE BUILDING IN OUR LAB, THAT OTHER LABS AROUND THE WORLD ARE WORKING ON, IS CAN WE CREATE A GAMETE FROM STEM CELLS THAT COULD BE USED TO RECOVER INFERTILITY FOLLOWING CANCER THERAPY. SO YOU KNOW THAT MANY CHILDHOOD CANCERS ARE TREATABLE NOW, BUT ONE OF THE SIDE EFFECTS IS INFERTILITY. SO IF YOU STAND IN A ROOM WITH A YOUNG GIRL THAT WAS TREATED 30 YEARS AGO AND SHE'S NOW MARRIED AND WANTS TO HAVE A FAMILY, ONE OF HER BIGGEST REGRETS IS THAT NOBODY TOLD HER THAT HER FERTILITY WAS GOING TO BE AFFECTED BY THE CHEMOTHERAPY THAT SHE WAS GIVEN.

NOW WE'RE TRYING AS A FIELD TO DEVELOP WAYS THAT WE CAN RESTORE AND PRESERVE FERTILITY. ONE OF THE RESTORING MECHANISMS IS TO USE STEM CELLS TO REMAKE THE GERMLINE AGAIN. WE HAVE ABSOLUTELY NO WAY OF TESTING WHETHER THAT'S GOING TO WORK. AND THE ONLY WAY THAT WE CAN TEST IF THAT'S GOING TO WORK IS AS WE MAKE THE GERM CELL WOULD BE TO FERTILIZE IT TO SEE IF WE CAN MAKE AN EMBRYO AND NOT EVEN IMPLANT. AGAIN, THIS IS STOPPING BEFORE WE GET

TO TRANSPLANTATION. AND SO THERE'S A LOT OF ENERGY TO BUILD THIS TECHNOLOGY, BUT WE RECOGNIZE RIGHT NOW THAT CREATING EMBRYOS FOR RESEARCH PURPOSES IS SOMETHING THAT NOT EVERYBODY AGREES WITH, YET IT IS ESSENTIAL FOR THIS TYPE OF RESEARCH TO GO FORWARD AS WELL. I THINK ALSO TESTING MITOCHONDRIAL THERAPIES AS WELL, GENERATING EMBRYOS FOR RESEARCH, IS ALSO ANOTHER AREA THAT WOULD BENEFIT FROM THAT BEING SOMETHING THAT SCIENTISTS ARE ABLE TO DO.

DR. BELMONTE: MAY I ADD ANOTHER COMMENT? ALTA CHARO MENTIONED ABOUT TRANSGENERATIONAL EPIGENETICS. I THINK THAT WE KNOW VERY LITTLE TODAY ABOUT THAT, BUT CERTAINLY WE START TO KNOW MORE AND MORE CASES OF THE IMPORTANCE OF THAT PHENOMENON. THE DEVELOPING OF TECHNOLOGIES TO MODIFY THE EPIGENOME IS SOMETHING THAT I WOULD LIKE CIRM, AMONG MANY OTHERS, TO CONSIDER. IT MAY HAVE A VERY IMPORTANT ROLE IN NOT JUST GENE, BUT EPIGENETIC TECHNOLOGIES THAT COULD BE DONE ON A VERY BASIC LEVEL STILL, BUT CERTAINLY THAT WILL MAKE A MAJOR DIFFERENCE IN MANY, MANY DISEASES IN MY VIEW.

DR. KIMMELMAN: SUPER QUICK EASY QUESTION.

CO-CHAIR LO: YOU HAVE TO TALK INTO A MIC. NOTHING IS EASY HERE.

DR. KIMMELMAN: YOU DISTINGUISH BETWEEN --

YOU WERE VERY CLEAR TO GIVE A DEFINITION OF GERMLINE CELLS. AND I JUST WONDERED IF YOU COULD CLARIFY FOR ME THE DIFFERENCE BETWEEN GERM CELLS AND GERMLINE CELLS.

DR. CLARK: TO THE CELL BIOLOGIST, A GERM CELL AND A GERMLINE CELL IS THE SAME THING, THE EXACT SAME THING. THE ONLY CELL TYPE IN THE BODY THAT'S CAPABLE OF MAKING AN EGG AND A SPERM IS A GERM CELL. AND WE REFER TO THAT AS A LINEAGE BECAUSE THE VERY EARLIEST GERM CELL IS CALLED A PRIMORDIAL GERM CELL, AND THAT'S A GERMLINE CELL.

A LITTLE LATER IN DEVELOPMENT IT'S CALLED AN OOGONIA. THAT'S A GERMLINE CELL, ALSO CALLED A GERM CELL. AND THEN IT GOES THROUGH MIOSIS. SO THE WORLD "GERMLINE" AND "GERM CELL," AS A CELL BIOLOGIST, WE USE INTERCHANGEABLY.

THE GERM LINEAGE IS THE LINEAGE TO GET TO THE GAMETE, BUT EACH STEP ALONG THE WAY IT'S A CELL. IT'S IN A SLIGHTLY DIFFERENT DEVELOPMENTAL STATE.

DR. KIMMELMAN: OKAY. THANKS. I THINK I NOW UNDERSTAND WHY WE ETHICISTS GET CONFUSED BETWEEN THOSE TWO TERMS.

DR. CLARK: WHEN I WAS AT THE HINXTON GROUP, WE ALSO HAD THIS DISCUSSION AS WELL BECAUSE WHEN YOU MODIFY THE GERMLINE, AND CLINICIANS USE THE

GERMLINE MUTATION, THAT'S WHERE YOU ARE FAMILIAR WITH USING IT, GERMLINE MUTATION THAT'S DETECTED IN CHILDREN. AND WHEN YOU GO TO THE PEDIGREE, IT'S DETECTED IN THE PARENT. SO THAT'S ABSOLUTELY A GERMLINE MUTATION. BUT WE'RE ACTUALLY TALKING ABOUT MODIFYING SPECIFIC CELLS. AND SO IF WE SAY CAN'T MODIFY THE GERMLINE, MY WORRY IS THAT WE WON'T BE ABLE TO MODIFY GERM CELLS, SO THE INTENT OF DISCOVERY SCIENCE, NOT EVEN FERTILIZATION, NOT EVEN EMBRYO FORMATION.

I'VE RUN INTO THIS PROBLEM BEFORE WITH FUNDING AGENCIES TALKING ABOUT GERM CELLS, FOR EXAMPLE, MAKING GERM CELLS IN VITRO FROM STEM CELLS. SO SOME OF THE COMMENTS THAT I RECEIVED ON GRANTS IS HOW CAN YOU CONFIRM THE GERM CELL YOU'VE MADE DOESN'T UNDERGO PARTHENOGENESIS BECAUSE THE NIH DOESN'T FUND PARTHENOGENESIS EITHER. AND SO WHAT WE NEED TO BE CLEAR ABOUT IS IF WE ARE GOING TO THIS RESEARCH RIGHT NOW, WE'RE GOING TO PUT IN THIS BOX, AND THIS BE PUT IN THAT BOX, THAT WE USE THE RIGHT WORDS TO PUT THEM IN THOSE BOXES.

DR. ROD TAYLOR: IS THERE A PLOIDY KIND OF A CONCEPT WITH GERM CELLS VERSUS GERMLINE CELLS? TO BE A GERM CELL, YOU'RE SAYING IT CAN BE 2N OR 4N.

DR. CLARK: THAT'S RIGHT. THAT'S RIGHT

BECAUSE THESE EARLY PROGENITORS ARE ALL 2N. AND IT'S NOT UNTIL THE VERY END, AT LEAST IN MALES, THAT IT BECOMES HAPLOID AND, THEREFORE, FERTILIZATION REALLY, AND IN FEMALES THIS HAPPENS AT SOME POINT DURING PRENATAL LIFE. SO YOU CAN ABSOLUTELY BE 2N AND BE A GERM CELL, A GERMLINE CELL. THOSE WORDS ARE INTERCHANGEABLE.

CO-CHAIR LO: I WANTED TO THANK OUR THREE SCIENTISTS. VERY, VERY INTERESTING AND IMPORTANT DIRECTIONS FOR RESEARCHING THIS TOPIC.

(APPLAUSE.)

CO-CHAIR LO: SO WE HAVE HEARD A LOT OF INTERESTING PRESENTATIONS, AND WE'VE HAD A LOT OF GOOD DISCUSSION IN THE ROOM. AND WHAT I WOULD LIKE TO DO IS TRY AND PRESENT YOU ONE PERSON'S SORT OF SYNTHESIS OF WHAT WE'VE HEARD WITH THE POINT OF VIEW OF SAYING WHAT IS IT WE WANT TO END WITH AT END OF THE DAY AND WHAT DO WE WANT TO END UP WITH TO BRING BACK TO CIRM LEADERSHIP AND THE ICOC.

AND AS I SAID, EVENTUALLY WE WANT TO MAKE THE SWG RECOMMENDATIONS TO THE CIRM LEADERSHIP, THE ICOC, WHETHER THERE SHOULD BE MODIFICATIONS, AMENDMENTS TO THE CURRENT CIRM REGULATIONS IN LIGHT OF THE SCIENCE WE'VE BEEN HEARING ABOUT OR THE POSSIBILITIES, OR WHETHER WE WANT TO SAY WE THOUGHT

ABOUT IT, AND WE THINK EVERYTHING IS FINE. WE'RE NOT GOING TO SETTLE ALL THAT TODAY, BUT WHAT I WOULD LIKE TO HAVE US DO AT THE END OF THIS MEETING IS FOR THE SWG TO CHARGE GEOFF, SHERRY, AND ME WITH A SET OF TOPICS THAT THEY WOULD LIKE TO SEE US DEVELOP TO THE POINT OF BRINGING RECOMMENDATIONS FOR POLICY GUIDANCE BACK TO ANOTHER MEETING OF THE SWG THAT WILL BE OPEN TO THE PUBLIC AND PUBLIC COMMENT SO THAT WE CAN MAKE RECOMMENDATIONS TO THE ICOC AND TO CIRM LEADERSHIP.

SO WE'RE JUST TALKING ABOUT WHAT TOPICS DO YOU WANT SHERRY, GEOFF, AND ME TO WORK ON, AND WE WOULD CONSULT WITH YOU AS WE DEVELOP DRAFT RECOMMENDATIONS. SO WHAT I'M LOOKING FOR IS PEOPLE TO SAY, WELL, WAIT A MINUTE. YOU MISSED A REALLY IMPORTANT ONE. NOT THAT WE HAVE TO TRY AND SETTLE WHAT WE'RE GOING TO SAY. SO THAT'S OUR FIRST SLIDE.

SO I HAVE A LIST OF TOPICS. I THINK WE GO TO SEVEN OR EIGHT. INFORMED CONSENT, AND THERE IS A LOT OF GRANULARITY HERE. WHAT ABOUT PREVIOUSLY DONATED BIOMATERIALS THAT YOU COULD USE CRISPR ON? BIOMATERIALS TO BE COLLECTED GOING FORWARD WHERE YOU HAVE MORE CHANCE TO DISCUSS, IF YOU WISH OR IF WE THINK IT'S DESIRABLE, THESE NEW TECHNOLOGIES. EMPHASIS, I THINK, ON NOT JUST THE CONSENT FORM, BUT

THE PROCESS OF EDUCATION AND ANSWERING QUESTIONS.

SECOND, I'VE SORT OF TRIED TO BRING TOGETHER OVERSIGHT AND DONOR PROTECTIONS. THERE ARE A LOT OF NEW COMPLEX SCIENTIFIC DEVELOPMENTS THAT RAISE A HOST OF ETHICAL, SOCIAL, REGULATORY ISSUES.

GEOFF'S TWO-BY-TWO MATRIX SLIDE SORT OF LAID OUT WHEN ESCRO REVIEW IS NECESSARY. AND THERE WAS A SEPARATE SET OF GUIDELINES FOR IRB REVIEW. DO WE THINK THAT OVERSIGHT STRUCTURE IS ROBUST TO COVER THE NEW TYPE OF RESEARCH, NEW TYPES OF RESEARCH? OR DO YOU THINK WE WANT TO DO SOMETHING ADDITIONAL OR NOT?

SO ONE QUESTION IS DO LOCAL ESCRO'S HAVE THE KIND OF EXPERTISE THAT WE DO TOGETHER IN THIS ROOM, BUT MAY NOT BE AVAILABLE EVEN TO A BIG RESEARCH? THERE ARE DIFFERENT REGULATORY OPTIONS THAT WE MIGHT CONSIDER IF WE DECIDE THIS NEEDS TO BE ADDRESSED. THEY RANGE FROM REVISING THE REGULATIONS TO AMENDING OR RECOMMENDING CHANGES TO THE CIRM OF REVIEW PROCESS, THE GRANTS REVIEW COMMITTEE, OF THE TERMS AND CONDITIONS OF AN AWARD.

MORE SORT OF SPECIFIC TOPICS, NO. 3, CLARIFY WHETHER GENETIC MODIFICATION, THE REGULATORY TERM THAT WE USE, INCLUDES MODIFICATION OF MITOCHONDRIAL DNA. WE HEARD A LOT OF DISCUSSION

ABOUT THAT. I THINK THAT'S THE KIND OF AMBIGUITY THAT WOULD BE IMPORTANT TO A RESEARCHER SAYING, HEY, I WANT TO STUDY MITOCHONDRIAL DNA.

THE POSSIBILITY THAT SOMATIC CELL GENE EDITING MAY LEAD TO INADVERTENT GENE LINE EDITING. JOHN WAGNER GAVE US SOME EXAMPLES OF THAT.

WHEN, IF AT ALL, SHOULD WE RECONSIDER THE WORDING OF OUR PROHIBITION ON IMPLANTATION OF 12 DAYS OR AFTER THE APPEARANCE OF THE PRIMITIVE STREAK? WE HAD SOME CONCERNS THAT LANGUAGE WAS NOT VERY GOOD.

THEN OTHER TOPICS, ENGAGEMENT WITH PATIENT ADVOCATES AND OTHER PUBLICS. IS THE PROCESS THAT CIRM HAS WITH PATIENT ADVOCATES ON THE ICOC, ON THE GRANTS REVIEW COMMITTEE, DO WE NEED TO DO MORE PUBLIC OUTREACH AND OBTAIN INPUT ON THE KINDS OF NEW RESEARCH WE'VE TALKED ABOUT TODAY?

WE'VE HEARD CONCERNS ABOUT CIRM FUNDING PRIORITIES WITH ISSUES OF JUSTICE AND EQUITY, AND I THINK WE NEED TO THINK ABOUT THAT. WHETHER THAT'S SOMETHING FOR THE SWG TO DEAL WITH OR SOMETHING FOR THE ICOC AND CIRM LEADERSHIP, I THINK THAT'S AN OPEN QUESTION.

GEOFF, AS IS HIS WONT, IS AS AN AVID READER OF THE CIRM TRANSCRIPTS. AND AFTER CAREFULLY

PERUSING THE TRANSCRIPT OF TODAY, THERE MAY BE OTHER TOPICS THAT EMERGE THAT SORT OF SNUCK UNDER THE RADAR. WHAT I WOULD LIKE THE CIRM SWG TO START TO THINK ABOUT AND THE PUBLIC THAT ARE HERE OR ON THE PHONE TO HELP US WITH ARE THERE BIG TOPICS WE MISSED, THAT THIS SHOULD BE NO. 2, 3, 4, OR WHATEVER.

NOW, TO GET THAT, SO WE HAVE A LITTLE TIME TO TALK ABOUT THIS; BUT THEN WE ALSO HAVE TWO EXPERTS IN THIS AREA, CHARIS THOMPSON, I HOPE HANK GREELY IS ON THE PHONE, WHO WE'VE INVITED TO SORT OF TALK ABOUT ETHICAL, LEGAL, CULTURAL, SOCIAL, STRUCTURAL ISSUES. AND PLEASE FEEL FREE TO SAY THERE'S THREE, FOUR, FIVE, SIX THAT YOU OMITTED OR SEVEN THERE IS JUST WORDED WRONG OR WHATEVER.

I FIRST WANT TO GIVE THE -- AND THE PUBLIC WILL HAVE A CHANCE TO COMMENT. FIRST, I JUST WANT TO GIVE THE SWG A CHANCE TO SAY, JUST AS A FIRST CUT, THERE'S A MAJOR -- THERE'S A PROBLEM HERE. AND I THINK AT THIS POINT WE'RE GOING TO BE IN LISTENING MODE. GEOFF AND OTHER STAFF ARE GOING TO KIND OF HAVE EARS OPEN, FINGERS AT THE KEYBOARD. JUST A LIST OF TOPICS FOR US, SHERRY, ME, AND GEOFF, TO COME BACK WITH.

CO-CHAIR LANSING: I WAS JUST TO GOING TO

REEMPHASIZE EXACTLY WHAT YOU SAID. THE POINT OF THIS MEETING WAS TO LISTEN, TO HEAR, AND THEN TO FORMULATE QUESTIONS THAT WE NEED TO LOOK INTO. AND I THINK THE ONES THAT YOU LISTED ARE PRETTY MUCH THE ONES THAT I WOULD HAVE HAD, BUT WE WANT TO HEAR FROM ALL OF YOU WHAT ELSE WE'RE MISSING. THEN WE NEED TO LOOK AT WHAT EXISTS ALREADY, SEE WHETHER OR NOT IT CAN BE IMPROVED, OR WHETHER IT'S OKAY, OR WHETHER WE NEED TO COMPLETELY CHANGE IT. AND THAT'S THE POINT OF THIS MEETING IS TO GET INPUT. OBVIOUSLY GIVE US INPUT TODAY, BUT LET'S SAY OVER THE NEXT WEEK, YOU'RE GOING TO THINK OF STUFF, AND THEN WE'LL BEGIN THE WORK.

CO-CHAIR LO: COMMENTS RIGHT OFF? JEFF, IT LOOKS YOU'RE ABOUT TO PUT YOUR HAND UP.

MR. SHEEHY: I'M HESITANT WHETHER TO RAISE THIS ISSUE, AND MAYBE CHARIS AND HANK CAN ADDRESS IT. WHAT IS THE -- ONE THING THAT I'VE MISSED ALL DAY, AND IT JUST OCCURRED TO ME, IS THE SCOPE OF FDA REGULATORY OVERSIGHT IN THE SPACE. IVF GENERALLY DOES NOT FALL UNDER THE FDA REGULATORY SCHEME. THERE'S NO LAWS THAT PREVENT THE IMPLANTATION OF A GENETICALLY MODIFIED EMBRYO. IN FACT, LOOKING AT THE DISCUSSION AGAIN, NEWS ARTICLES, OF THE MITOCHONDRIAL TRANSFER PROCESS, THE FDA CAN'T USE

FEDERAL FUNDS TO EXAMINE THAT PROCESS.

SO ONE QUESTION IS IS THERE ANY REGULATORY FRAMEWORK THAT WILL BE APPLIED TO THE EMBRYOS THAT WE CREATE PRESUMABLY IN RESEARCH THAT HAVE BEEN GENETICALLY MODIFIED? WHY WOULD THE FDA --

DR. WAGNER: THE RACK. THE RACK EXISTS. AND EVEN DESPITE THE FACT THAT WE HAVE CHANGED THE MANDATE OF THE RACK --

MR. SHEEHY: THE RACK, AGAIN, IS AROUND FUNDING. IT DOESN'T POSSESS THE LEGAL FORCE TO STOP AN IVF CLINIC FROM --

DR. WAGNER: NO.

MR. SHEEHY: -- FROM IMPLANTING AN EMBRYO?

DR. WAGNER: I DON'T THINK IT HAS -- IT DOESN'T HAVE THE LEGAL COURSE. THE FDA, THEY DEPEND ON THE FDA FOR THE LEGAL COURSE. HOWEVER, THE RACK IS TO OVERSEE GENETIC MODIFICATION OF CELLS. AND INTERESTINGLY, WHAT I HAVE IN HERE WAS DO WE HAVE SOMETHING LIKE THE GEM CRESS (PHONETIC) DATABASE, WHICH IS WHAT TRACKS ALL GENE MODIFIED CELL THERAPIES, BECAUSE IT IS POSSIBLE THAT YOU WILL FIND SOME NEGATIVE OR ILL CONSEQUENCES BETWEEN PROTOCOLS RATHER THAN JUST THROUGH ONE PROTOCOL.

SO IN ANY EVENT, THIS IS A UNIQUE ISSUE IN THAT I DON'T KNOW WHAT THE ROLE IS OF THE FDA

BECAUSE THAT'S AN IMPORTANT PART OF ALL THIS. BUT THE RACK WOULD BE A GROUP THAT WOULD BE EVALUATING THE USE OF GENE MODIFIED CELLS, BUT THAT'S PROBABLY -- ACTUALLY AS I THINK ABOUT THAT, IT PROBABLY RELATES SPECIFICALLY TO NIH. THIS IS AN INTERESTING TWIST BECAUSE IT MIGHT FALL THROUGH THE CRACKS.

MR. SHEEHY: I THINK SOME PROJECTS THAT MIGHT GO TO FDA ALSO MIGHT GO TO THE RACK, BUT I DON'T THINK THAT THERE'S ANY REQUIREMENT FOR THE IMPLANTATION OF A GENE MODIFIED EMBRYO.

DR. WAGNER: AS I RECALL, THE RACK -- DOES IT REQUIRE? THE ANSWER IS NO UNLESS IT'S NIH FUNDED. HOWEVER, EVEN FOR PROJECTS THAT ARE NOT NIH FUNDED HAVE GONE OR PRIMARILY GO THROUGH THE RACK, BUT I CAN'T TELL YOU THE DENOMINATOR.

CO-CHAIR LO: SO THE QUESTION THAT JEFF SHEEHY POSED IS SOMETHING THAT WE'LL CHARGE GEOFF AND PARTICULARLY SCOTT, UNLESS HANK GREELY OR ALTA CAN ANSWER OFF THE TOP OF THEIR HEADS. IT'S ANOTHER QUESTION TO ADD TO THE LIST. WE CLEARLY DON'T HAVE THE EXPERTISE IN THE ROOM TO SETTLE THIS TODAY.

DR. LEE: I'M BENHUR LEE, ONE OF THE SWG MEMBERS. THERE WAS SO MUCH TALK ABOUT THIS NEW CRISPR-CAS TECHNOLOGY JUST IN THE LAST TWO YEARS.

SO OBVIOUSLY THAT'S FILTERING DOWN TO THE PUBLIC AS WELL. AND A LOT OF WORK HAS GONE INTO THE INFORMED CONSENT AND THE RULES, AND LOTS OF DEBATE HAS SET THESE RULES OUT, BUT THESE ALL DONE BEFORE THE CRISPR-CAS. SO AS THIS FLOWS DOWN TO THE PUBLIC, WHEN YOU ARE TALKING ABOUT DONOR PROTECTION AND OVERSIGHT, HOW ABOUT DONOR EDUCATION?

CHARIS HAD MENTIONED EARLIER THAT THERE ARE CASES OF REVERSAL, PEOPLE HAVE REVERSED THEIR DECISION AFTER THEY'VE GIVEN CONSENT. IF THEY HEAR ABOUT THESE NEWFANGLED TECHNIQUES THAT WE'VE TALKED ABOUT, CAN WE HEAD OFF PROBLEMS BY SOME SORT OF DONOR EDUCATION CAMPAIGN THAT WE BUILT WITH INFORMED CONSENT TO LET THEM KNOW. BECAUSE THEY'LL HEAR THESE MAGIC THINGS NOW, WE CAN CORRECT GENETIC DISEASES IN YOUR GERMLINE, THERE MIGHT BE A LOT MORE REVERSALS THAN WHAT WE HAD ANTICIPATED BEFORE.

CO-CHAIR LO: UNDER CONSENT BOTH PUBLIC EDUCATION OR DONOR EDUCATION, BUT ALSO REVERSAL OF CONSENT AFTER CONSENT HAS PREVIOUSLY BEEN GIVEN, HOW DO WE HANDLE THAT? KNOTTY TOPIC AND IMPORTANT ONE.

DR. CORN: I THINK THE IDEA OF PUBLIC EDUCATION IS REALLY FANTASTIC. SO JUST TO GIVE YOU AN IDEA, I'M NOT EVEN AT A MEDICAL SCHOOL, AND I HAVE PATIENTS CALLING ME IN MY OFFICE LINE FROM

ITALY, ALL ACROSS THE WORLD BECAUSE THEY'VE READ ABOUT GENE EDITING. THEY'VE READ IT IN THE *NEW YORK TIMES*. THEY ASK ME WHEN CAN WE GET THIS? WHERE ARE WE GOING TO SEE IT? AND SO I THINK THERE'S A LOT OF HYPE AROUND GENE EDITING IN THE PUBLIC PRESS, AND THERE'S NOT A LOT OF KNOWLEDGE ABOUT WHERE IS IT, WHERE IS THE TECHNOLOGY, AND WHEN CAN WE EXPECT IT IN THE CLINIC. SO I THINK THAT HAVING SOME SORT OF REALLY GOOD EDUCATION PROGRAM AROUND THAT COULD REALLY TELL PEOPLE WHERE THE TECHNOLOGY IS AND WHAT THEY MIGHT EXPECT IN THE FUTURE.

DR. PAT TAYLOR: IT'S A GREAT LIST. ONE THING THAT MAY BE MISSING IS WHAT THE PURPOSE IS. IT WAS INTERESTING TO READ IN THE DOCUMENTS THE QUESTION OF WHETHER OR NOT SOMETHING WAS MOTIVATED BY ENHANCEMENT FOR RECTIFYING A LETHAL GENE THAT WAS EXPOSED IN THE NEONATE PERIOD. IT SEEMS TO ME, DEALING WITH THE PURPOSE IS GOING TO BE INEVITABLE SOMEHOW, WHETHER IT'S ENHANCEMENT OR NOT. ONE THING.

CO-CHAIR LO: CIRM DOES HAVE A MANDATED MISSION TO FOCUS ON CURES. I DON'T REMEMBER THE EXACT WORDING, BUT NEEDS FOR TREATMENT AND CURE FOR SERIOUS DISEASES.

DR. PAT TAYLOR: I THINK IT REALLY TIES IN

VERY MUCH WITH WHAT YOU SAID BEFORE ABOUT THE NECESSITY OF FOCUSING ON NUCLEAR (INAUDIBLE). THE OTHER KIND OF PURPOSE IS WHETHER OR NOT THE PURPOSE IS ACTUALLY TO SHOW WHAT'S NECESSARY TO DO THIS RIGHT. ONE COULD READ THE CHINESE ARTICLE. I THINK THE BEST POSSIBLE ARGUMENT FOR WHY ONE SHOULDN'T GO TO COMMERCIALLY AVAILABLE CLINICS RIGHT NOW TO GO GET THIS DONE. SO TO THE EXTENT THAT RESEARCH IS ACTUALLY DIRECTED TOWARDS SETTING STANDARDS FOR WHAT THIS COULD BE IS AN ARGUMENT THAT IS DIFFERENT THAN RESEARCH DIRECTED TOWARDS USING IT.

DR. BOTKIN: TWO THINGS. I DON'T KNOW WHAT THE STANDARDS ARE FOR CIRM AT THIS POINT, BUT QUESTIONS AROUND IDENTIFIABILITY OF CELLS AND EMBRYOS. I THINK THE REGULATORY STANDARD IS USUALLY DEIDENTIFIED FOR THE INVESTIGATOR, BUT OFTENTIMES THERE'S A LINKAGE, A CODE, ETC. WHAT ARE THE EXPECTATIONS IN TERMS OF WHETHER THINGS ARE COMPLETELY DEIDENTIFIED SO THAT RECONSENT FOR GOING BACK TO REPURPOSE EMBRYOS WOULD OR WOULD NOT BE POSSIBLE, SO SOME DISCUSSION ABOUT IDENTIFIABILITY I'M INTERESTED IN.

SOMEBODY DID MENTION ALONG THE WAY THE QUESTION OF THE LANGUAGE THAT SAYS A UTERUS, WHICH SEEMS RATHER DISEMBODIED TO BEGIN WITH, BUT THE

SPECIFIC QUESTION WAS ARE WE TALKING ABOUT HUMAN UTERUSES ONLY OR WHAT. SO MAYBE SOME --

CO-CHAIR LO: A HUMAN EMBRYO INTO A NONHUMAN.

MS. DARNOVSKY: CAN WE GO BACK TO YOUR PREVIOUS SLIDE, BERNIE?

CO-CHAIR LO: I'LL TRY.

MS. DARNOVSKY: NO. 5, WHEN WE CONSIDER WORDING OF PROHIBITION ON IMPLANTATION. SO DOES THAT MEAN THAT THIS COMMITTEE WOULD RECONSIDER WHETHER A GENETICALLY MODIFIED EMBRYO CAN BE PUT INTO A WOMAN'S UTERUS, OR WERE YOU JUST TALKING ABOUT THE 12-DAY, 14-DAY DEVELOPMENT OF THE EMBRYO THERE?

CO-CHAIR LO: WELL, I WAS TRYING TO -- GOOD QUESTION. SO I WAS TRYING TO PICK UP ON DAVID BALTIMORE'S POINT, THAT A LOT OF THE CURRENT GUIDANCE IS FRAMED AS AT THIS TIME IT WOULD BE UNWARRANTED TO TRY AND USE GENE EDITING TECHNIQUES FOR CLINICAL USE BECAUSE OF QUESTIONS ABOUT SAFETY.

THESE ARE DRAFT TOPICS. DO WE WANT TO SAY THAT WE SHOULD THINK ABOUT WHETHER WE WANT TO START TO THINK ABOUT CHANGING THE WORDING, OR SHOULD WE SAY NO. IT SAYS NO CLEAR LANGUAGE, CAN'T DO IT. JUST SOMETHING, DO WE WANT THIS TO BE DISCUSSED SO

WE CAN MAKE OUR RECOMMENDATIONS BACK TO CIRM LEADERSHIP?

DR. ROBERTS: JUST QUICKLY FOLLOW UP. I ALSO NOTED THAT WHEN DR. BALTIMORE WAS SPEAKING THAT THERE'S THIS ASSUMPTION THAT WE ARE GOING TO CHANGE IT AT SOME POINT, THE WAY IT'S WORDED. SO I THINK IT'S IMPORTANT TO CLARIFY THAT THERE'S NO ASSUMPTION THAT AT SOME POINT, AS LONG AS THE SAFETY CONCERNS ARE MET AND THE TECHNOLOGY IS PERFECTED, THIS IS GOING TO BE CHANGED. THAT'S A BIG QUESTION THAT WE'RE CONSIDERING. JUST WANT TO MAKE THAT CLEAR.

CO-CHAIR LO: ABSOLUTELY.

DR. PETERS: ALSO ON NO. 5, REGARDLESS OF WHAT WE DO IMMEDIATELY, I WOULD LIKE TO THINK THAT WE WOULD RECONSIDER THIS PERHAPS ANNUALLY BECAUSE OF THE CHANGES. I'D LIKE TO MAKE TWO POINTS FROM WHAT DR. BALTIMORE WAS SAYING.

THE FIRST ONE IS THAT EVEN THOUGH WE'RE CONCERNED ABOUT HUMAN GENETICS, THERE'S A MUCH LARGER CONTEXT FOR CRISPR-CAS9 THAT INCLUDES ANIMAL GENETICS. AND RIGHT NOW ONE OF THE DEBATES HAS TO DO WITH MOSQUITOES, GERMLINES FROM MOSQUITOES, BECAUSE IT'S A GENETIC CONDITION THAT MAKES IT POSSIBLE FOR THEM TO CARRY VIRUSES SUCH AS MALARIA AND ZIKA. AND SO THERE IS A PROPOSAL THAT THERE'S

GENE EDITING IN THE GERMLINE OF MOSQUITOES THAT WOULD KNOCK OUT THAT GENE.

AND ON THE ONE HAND, WE'RE GOING TO HAVE SAFETY QUESTIONS, UNPREDICTABLE REPERCUSSIONS, BUT THE ISSUE OF URGENCY, URGENCY TO PROTECT THE HUMAN BEINGS FROM THESE VIRUSES IS GOING TO BECOME AN ETHICAL FACTOR. WILL THAT BECOME A FACTOR AT SOME POINT IN HUMAN GENETICS AS WELL? AND SO IT WOULD SEEM TO ME THAT WE HAVE TO MEASURE PROGRESS ON THE SAFETY QUESTION EACH YEAR AS IT IMPROVES, BUT THEN ALSO ASK TO WHAT EXTENT THERE MIGHT BE GROWING PUBLIC APPROVAL OF GERMLINE MODIFICATION IF SOME OF THESE EXPERIMENTS IN ANIMAL AND PLANT GENETICS PROVE SUCCESSFUL.

CO-CHAIR LO: GEOFF LOMAX, IN JUGGLING THE SCHEDULE, WE MAY HAVE LEFT HANK -- CHARIS IS HERE, BUT HANK MAY OR MAY NOT BE ON THE LINE. SO COULD YOU JUST ASK IF HANK GREELY IS ON THE LINE BECAUSE HE'S -- NO, HE'S NOT ON THE LINE. HAS HE EVER BEEN ON THE LINES?

MS. SCHAFFER: HE'S LISTENING OVER THE PHONE LINE, BUT HE'S NOT ABLE TO SPEAK LIVE RIGHT NOW. I TOLD HIM 2:15.

CO-CHAIR LO: OTHER COMMENTS?

MR. SHEEHY: SO I THINK THIS WORD

"PROHIBITION" IS A LITTLE BIT MISLEADING. AND SO ONE OF THE THINGS I WOULD LIKE TO EXAMINE, AND HOPEFULLY THE CIRM TEAM CAN HELP US, PROHIBITION JUST MEANS WE CAN'T FUND IT. THERE ARE WAYS THAT WE SHOULD EXPLORE OF HAVING A FIRMER HAND ON THIS. FOR INSTANCE, THIS IS A PRODUCT OF CIRM RESEARCH. IF A THERAPY GETS DEVELOPED, WE HAVE -- I CAN'T REMEMBER THE TERM NOW -- WE CAN PULL RESEARCH BACK. WE HAVE REACH-THROUGH RIGHTS FOR RESEARCH THAT'S BEEN FUNDED IF IT'S VIABLE, BUT THE PERSON WHO'S DEVELOPED THAT THERAPY --

CHAIRMAN THOMAS: MARCH-IN RIGHTS.

MR. SHEEHY: MARCH-IN RIGHTS. THAT'S WHAT IT IS. WE HAVE MARCH-IN RIGHTS. SO IF SOMEONE HAS A THERAPY AND DECIDES NOT TO DEVELOP IT, THOUGH IT'S A GOOD AND VIABLE THERAPY, WE CAN GO AND RECLAIM THAT THERAPY, AND THEN EITHER HAVE SOMEONE ELSE DEVELOP IT OR DEVELOP IT OURSELVES. GIVEN THE LACK OF FDA OVERSIGHT, I THINK THAT -- AND ALL OF OUR GRANTS ARE CONTRACTS THAT WE CAN PUT SOMETHING INTO THE CONTRACT THAT PREVENTS SOMEONE FROM IMPLANTING AN EMBRYO, NOT JUST YOU CAN'T USE OUR MONEY. THE METAPHOR I'VE BEEN USING FOR THIS ALL ALONG IS YOU CAN USE OUR MONEY TO BUY A GUN, TO BUY THE BULLETS, YOU CAN USE OUR MONEY TO LOAD THE GUN, TO COCK THE

RECEIVER. THE ONLY THING YOU CAN'T USE OUR MONEY FOR IS TO FIRE THE GUN.

SO FROM MY PERSPECTIVE, I THINK OUR REGULATIONS GOING FORWARD SHOULD GIVE CIRM THE ABILITY TO GIVE CONSENT AS THE TECHNOLOGY IS DEVELOPED AND NOT JUST MERELY BE LIMITED TO A PROHIBITION ON FUNDING FOR IMPLANTATION. I WOULD HOPE THAT WE COULD DRAFT LANGUAGE, OUR LAWYERS COULD LOOK AT SOMETHING AND SEE IF THAT'S POSSIBLE.

CHAIRMAN THOMAS: SO THIS IS A QUESTION FOR THE SCIENTISTS IN THE ROOM. WE HAD ZINC-FINGER WHICH BEGAT TALENS, WHICH BEGAT CRISPR. IS THERE ANYTHING YOU'RE HEARING OUT THERE ABOUT THE NEXT GENERATION OF GENE EDITING TOOLS? AND IF SO, WHAT MIGHT THAT BE, AND HOW MIGHT THAT AFFECT OUR CONSIDERATION OF WHAT WE'RE TALKING ABOUT HERE?

DR. CORN: I GUESS WHAT I WOULD SAY IS DOES IT REALLY MATTER. YOU CAN'T PUT THE GENIE BACK IN THE BOX. IF YOU JUST ASSUME TECHNOLOGY IS GOING TO GET BETTER AND BETTER AND BETTER. SO WHETHER IT'S TWO YEARS, FIVE YEARS, OR TEN YEARS, I THINK YOU HAVE TO MAKE THE ASSUMPTION THAT AT SOME POINT IT'S JUST GOING TO WORK PERFECTLY. THERE'S SO MANY PEOPLE TRYING TO DO THIS. THERE ARE VARIETIES OF DIFFERENT ENZYMES, PEOPLE ARE WORKING ON WAYS OF

IMPROVING HDR. I GUESS FROM MY POINT OF VIEW, WHETHER CAS9 OR CAS10 OR CAS11 OR CAS12, WHATEVER ITERATION, VERSION 1.0, 2.0 YOU WANT TO PUT ON IT, IT'S A TECHNOLOGY. AND OUR EXPERIENCE WITH TECHNOLOGY IS THAT IT DOESN'T GO BACKWARDS. IT ONLY GOES FORWARDS. IT'S BETTER TO PLAN AHEAD.

CO-CHAIR LO: OTHER COMMENTS?

DR. CLARK: I THINK MAYBE FROM A SLIGHTLY DIFFERENT PERSPECTIVE IS IF WE RESTRICT THE LANGUAGE TO JUST GENE EDITING OR JUST CRISPR OR JUST CAS9, THEN WHEN SOMETHING NEW DOES COME ALONG AND IT'S CALLED SOMETHING ELSE THAT'S OUTSIDE OF WHAT WE'VE JUST BEEN THINKING ABOUT FOR HOURS AND HOURS, SO I AGREE WITH YOU. I THINK THE FUNDAMENTAL THING IS CHANGING THE GENOME, GETTING IT PASSED ONTO GENERATIONS, WHATEVER THE VEHICLE IS FOR CHANGING THE GENOME, AND IF WE FOCUS ON THAT IN THE LANGUAGE, THEN I THINK THAT WE'VE GOT SOMETHING GOOD TO WORK WITH.

DR. BELMONTE: THAT'S PRECISELY WHAT I SAID. WE COULDN'T CUT THE GENOME OF CELLS THAT DO NOT DIVIDE. I SHOWED A SLIDE TODAY THAT WE CAN DO THAT IN VIVO. MY FEELING THAT THIS TECHNOLOGY IS GOING TO EVOLVE AND BE ABLE TO ATTACK MANY MAJOR DECISIONS THAT WE HAVE TODAY IN THE SOMATIC CELL.

SO WE NEED TO CONSIDER THAT SERIOUSLY. IT'S NOTHING TO DO TODAY WITH THE GERMLINE, I KNOW, BUT YOU ASKED WHAT IS OUT THERE.

CHAIRMAN THOMAS: THANK YOU.

CO-CHAIR LO: OTHER QUESTIONS, COMMENTS?

DR. ROD TAYLOR: JUST A RELATED THING. AND I WOULD SAY THIS IS KIND OF THE EASY PART. YOU'VE GOT A LIST OF SOME FAIRLY CHALLENGING THINGS HERE; BUT IN THE PREVIOUS SLIDE, I ACTUALLY BELIEVE THAT YOUR CURRENT ESCRO'S HAVE THE EXPERTISE TO DEAL WITH THIS NEW INFORMATION. THEY HAVE BEEN DOING A WONDERFUL JOB, I THINK, FOLLOWING THE RAPID EVOLUTION OF THIS FIELD FOR THE LAST DECADE. AND I THINK TO REESTABLISH SOME NEW MECHANISM FOR OVERSIGHT IS GOING TO BE A LITTLE BULKY, AND I WOULD RECOMMEND THAT YOU ACTUALLY KIND OF THIS IS A GROUP THAT'S ACTUALLY BEEN EDUCATED NOW IN THESE NEW ENZYMATIC APPROACHES FOR GENE EDITING. AND I THINK THEY'RE PERFECTLY WELL QUALIFIED TO DEAL WITH THIS. JUST AN OPINION.

CO-CHAIR LO: SO LET'S TRY AND MOVE ON. HANK GREELY IS ON THE LINE, SO I'M GOING TO ASK PROFESSOR CHARIS THOMPSON AND PROFESSOR GREELY TO TAKE CENTER STAGE.

DR. GREELY: WHO DO YOU WANT FIRST,

BERNIE?

CO-CHAIR LO: WE'RE HAVING AV TROUBLES, BUT GLAD TO HEAR YOUR VOICE. DO YOU HAVE A TIME LIMIT ON WHEN YOU CAN BE LIVE US, OR ARE YOU WITH US TILL FOUR?

DR. GREELY: I'M OKAY UNTIL 3:15.

CO-CHAIR LO: OUR NEXT SESSION IS WITH CHARIS THOMPSON AND HANK GREELY. CHARIS IS THE CHANCELLOR'S PROFESSOR AND CHAIR OF THE DEPARTMENT OF GENDER AND WOMEN'S STUDIES AND THE CENTER FOR SCIENCE, TECHNOLOGY, AND MEDICINE AND SOCIETY AT UC BERKELEY. SHE'S ALSO THE DIRECTOR OF THE LI KA-SHING PROGRAM IN GENDER AND SCIENCE AND ALSO HAS A NAMED PROFESSORSHIP AT THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE. SHE'S PUBLISHED A LOT OF BOOKS ON THE TOPICS WE'VE BEEN TALKING ABOUT AND WILL NEED TO THINK ABOUT, AND SHE'S CURRENTLY A MEMBER OF THE UK NUFFIELD COUNCIL ON BIOETHICS WORKING GROUP ON GENOME EDITING.

HANK GREELY, WHO IS ON THE PHONE, IS THE DEANE F. AND KATE EDELMAN JOHNSON PROFESSOR OF LAW WITH A JOINT APPOINTMENT OR COURTESY APPOINTMENT IN GENETICS AT STANFORD. HE CHAIRS THE CALIFORNIA ADVISORY COMMITTEE ON HUMAN STEM CELL RESEARCH. THAT'S THE STATE ADVISORY COMMITTEE THAT MAKES

RECOMMENDATIONS ON NON-CIRM-FUNDED STEM CELL RESEARCH. SO IT'S THE COUSIN OR SIBLING OF THIS COMMITTEE.

SO, CHARIS, YOU ARE GOING TO START. WE WELCOME YOU. AS I SAID BEFORE, I NEED TO RUN OUT AT 2:15, BUT YOU ARE GOING TO BE RECORDED SO I CAN READ THE TRANSCRIPT AND ALSO LISTEN TO IT. THANKS VERY MUCH.

DR. THOMPSON: SO SOME OF THIS MAY BE A LITTLE BIT REPETITIVE BY THIS POINT IN THE AFTERNOON, BUT I'M COMING FROM A SLIGHTLY DIFFERENT PERSPECTIVE. HOPEFULLY THERE WILL BE A BIT OF TRIANGULATION THAT WILL MAKE IT MAKE SENSE.

SO WE WERE PROMPTED TO THINK ABOUT WHAT WE THOUGHT WERE PROMISING APPLICATIONS OF HUMAN GENOME EDITING TO PROMOTE CIRM'S MISSION. AND THE THINGS THAT CAME TO MY MIND, TRAINED INITIALLY AS A SCIENTIST, BUT A NONSCIENTIST, WERE THE FOLLOWING. I'M WORRIED THAT WHEN I TURN TOWARD MY SLIDES, YOU LOSE THE MICROPHONE.

SO THE FIRST THING THAT CAME TO MY MIND WAS THE VALUE OF DISEASE MODELING IN DRUG TESTING ARENAS. AND ALSO, AS SOMEBODY WHO'S VERY CONCERNED WITH DONOR RIGHTS, ESPECIALLY EGG DONOR RIGHTS, I'M INTERESTED IN ANYTHING THAT DECREASES THE NEED FOR

GAMETES AND EMBRYOS. SO WAYS TO GET THOSE CELLS TO INDUCE PLURIPOTENCY OR TO IMMORTALIZE FROM THE FEW EMBRYOS OR GAMETES YOU HAD ORIGINALLY.

I'M REALLY INTERESTED, IT SEEMS TO ME IT WOULD BE VERY, VERY GOOD TO HAVE LOTS AND LOTS OF MODELS ABOUT HOW DIFFERENTIATION HAPPENS AFTER GENE EDITING, OR REASONS TO DO IT, INSOFAR AS I UNDERSTAND THEM, WITH RESPECT TO MOSAICISM AND SO ON. I THINK THAT THAT WOULD BE REALLY HELPFUL FOR MONITORING RISK FOR SOMATIC AS WELL AS GERMLINE GENOME EDITING.

I THOUGHT ABOUT CONDITIONS THAT COULD BE TREATED WITH SOMATIC GENE EDITING WHERE AN AUTOLOGOUS DONATION FROM YOUR OWN CELLS COULD CURE YOU AND HELP, WHICH IS SOMETHING THAT BERT LUBIN MENTIONED THIS MORNING, WHICH CAN HELP YOU WITH HLA MATCH AND MORE, AGAIN, DONATION POLITICS. AND ALSO THAT WOULD PRESUMABLY BE INVALUABLE IN THE GRANTING HOST IN THE DISEASE ARENA.

AND THEN I THOUGHT THAT IF CONSENSUS DOES MOVE TOWARD USING CRISPR FOR GERMLINE GENE EDITING FOR REPRODUCTIVE PURPOSES, IN THE CASE OF THOSE VERY MONOGENIC AND OLIGOGENIC SERIOUS MEDICAL CONDITIONS, WITHOUT OTHER BETTER OPTIONS SUCH AS PGD, BUT IT SUMMARIZES A LOT OF WHAT PEOPLE SAID THIS MORNING,

THAT THIS WORK COULD BE VERY HELPFUL FOR ESTABLISHING SAFETY AND EFFICACY AND PERHAPS EVEN PRODUCING EDITED GAMETES FOR IMPLANTATION IF IT MADE THE TECHNIQUE MORE RELIABLE. SO IF IT'S EASIER TO EDIT GAMETES THAT WERE MADE RATHER THAN EMBRYOS PER SE THAT WERE MADE FROM STEM CELLS, THEN THAT, IT SEEMED TO ME, WOULD BE A REALLY WORTH FOLLOWING UP LINE OF RESEARCH.

I ALSO THOUGHT ABOUT WHAT'S GOING TO HAPPEN TO THE CATEGORY THAT WE THOUGHT OF IN MANY COUNTRIES THAT WE'VE LEGISLATED AND THOUGHT ABOUT AROUND DESELECTED EMBRYOS. SO A LOT OF PLACES WHERE PEOPLE HAVE PROBLEMS WITH THE DISPOSITION OF EMBRYOS, THEY'LL MAKE AN EXCEPTION FOR MEDICAL DESELECTION; BUT IF THOSE EMBRYOS ARE NO LONGER MEDICALLY NECESSARILY UNUSABLE BECAUSE THEY COULD BE EDITED, DO THOSE COUNTRIES NEED TO CHANGE? IT SEEMS LIKE IT'S A VERY INTERESTING AND URGENT AREA OF RESEARCH IF YOU CAN. SO IF YOU HAVE A REASON NOT TO WANT TO DESTROY EMBRYOS, IF YOU COULD EDIT THEM AND KEEP THEM VIABLE FOR REPRODUCTIVE PROJECTS, WE NEED TO LOOK INTO WHAT THAT WOULD MEAN. WE TALK ABOUT SOMETHING THAT JEFF BROUGHT UP THAT WAS ALIGNED TO THIS, WHICH WAS THE RIGHTS OF THE PEOPLE WHOSE EMBRYOS THEY WERE. SO THOSE WERE THE THINGS THAT AS

A LAYPERSON CAME TO MY HEAD.

I THINK THERE ARE A FEW THINGS FROM MY PERSPECTIVE AS A SCHOLAR THAT CIRM REALLY NEEDS TO ATTEND TO. ONE OF THEM IS CLARITY ABOUT THE GERMLINE AND SOMATIC CELLS AND WHETHER OR NOT THEY'RE HERITABLE. SO FROM THE POINT OF VIEW OF EVERYDAY LANGUAGE, CIRM NEEDS TO BE ABSOLUTELY CLEAR ABOUT THE DIFFERENCE BETWEEN GERMLINE AND SOMATIC GENE EDITING, WHICH CAN EASILY GET BLURRED WITH STEM CELLS, FIRST OF ALL, AND GET BLURRED ACROSS THE LIFE COURSE OF CELL LINES. SO I'M VERY CONCERNED THAT WE NOT REPEAT SOME OF THE PROBLEMS THAT AROSE FROM THE ADULT VERSUS EMBRYONIC STEM CELL DISTINCTION, THINGS ABOUT PLANNED PARENTHOOD THIS SUMMER. YOU DON'T WANT PEOPLE TO BE SHOCKED WHEN THEY DISCOVER THAT ADULT CELLS ARE TAKEN FROM THINGS LIKE FORESKINS AND ABORTUSES. THAT'S WHAT ADULT STEM CELL MEANS, BUT IT DOESN'T MEAN THAT TO NORMAL PEOPLE. AND IT'S VERY, VERY COUNTERPRODUCTIVE TO TRUST AND ADJUST FOR X FACTOR TO USE THOSE EUPHEMISMS. I THINK IT'S SHORTSIGHTED TO THINK THAT IF YOU USE A CERTAIN KIND OF A WORD YOU CAN GET AROUND THINGS THAT EVERYDAY PEOPLE MIGHT ASSOCIATE WITH THOSE WORDS.

I THINK THAT BEING CLEAR THAT GERM CELLS AND EMBRYOS CAN BE EDITED WITHOUT IMPLANTATION AND

THUS HERITABILITY AND THAT SOMATIC CELLS, SUCH AS GAMETE PRECURSOR CELLS, ALTHOUGH WE'VE JUST BEEN TOLD BY AMANDER CLARK THAT ACTUALLY YOU WOULD CONSIDER THOSE TO BE STILL ALL GERMLINE CELLS, BUT CELLS THAT AREN'T YET HAPLOID NONETHELESS CAN BE PRECURSORS TO WHAT EVERYDAY PEOPLE THINK OF AS GERM CELLS. AND IF YOU EDIT THOSE, THEY WILL GO INTO GERMLINE EVENTUALLY ALTHOUGH YOU MIGHT STILL SAY THAT IT'S OKAY TO EDIT THEM. SO, AGAIN, JUST BEING VERY, VERY CLEAR ABOUT THIS.

AND I HAD ALSO THOUGHT ABOUT EDITING SOMATIC GENES IN PATIENTS OF REPRODUCTIVE AGE OR YOUNGER. IS THERE ANY WAY TO MAKE SURE THAT THEIR GAMETES ARE NOT AFFECTED? AND I WONDERED -- AGAIN, THAT CAME UP THIS MORNING, BUT I WONDERED ABOUT WHETHER THAT MIGHT BE EXACTLY THE KIND OF ARENA WHERE YOU'D WANT TO SAY THAT'S ALL ABOUT PATIENT PRIVACY. AND SOME PEOPLE MIGHT ACTIVELY WANT THAT ACTUALLY. THEY MIGHT ACTIVELY WANT TO SECURE THEIR CERTAIN KIND OF REPRODUCTIVE OUTCOME AT THE SAME TIME AS BEING TREATED. SO THAT WAS MORE THAN I WAS THINKING ALONG WITH WOULD BE SOMETHING THAT PEOPLE WOULD ALSO BE SEEKING TO HAVE AND HAVING SOMATIC TREATMENT. SO, AGAIN, IT WOULD BE BLURRING THAT LINE BETWEEN SOMATIC AND GERMLINE TREATMENT.

AND I THINK IT'S ONE CASE THAT WE THOUGHT THAT PRIVACY USE MIGHT BE ONE THAT WOULD BE, EVEN THOUGH THE CIRM RESEARCH MIGHT SUPPORT THE SOMATIC WORK, IT HAS AN EFFECT ON GERMLINE OF WHAT HAPPENS TO ALL THE THINGS THAT COULD HAPPEN OUTSIDE OF THE DIRECT INTENTION OF THE CIRM-FUNDED RESEARCH. WHETHER IT'S PHARMA, WHETHER IT'S THE PRIVATE SECTOR, WHETHER IT'S MILITARY, WHETHER IT'S PRIVATE OR PERSONAL KIND OF USE, HOW DO YOU KEEP TABS IF YOU WANT TO ON WHAT HAPPENS NEXT AND HOW THAT CROSSES THAT SOMATIC GERMLINE BOUNDARY. I THINK IT'S REALLY, REALLY HARD TO KEEP THOSE TABS. SO I THINK IT'S REALLY IMPORTANT TO BE EXTREMELY CLEAR ABOUT THAT.

SO CIRM'S ETHICAL POTENTIAL, I WANT TO REMIND EVERYONE, I'M ALWAYS WANTING TO REMIND EVERYONE THAT PROP 71 WAS ETHICALLY AS WELL AS SCIENTIFICALLY INNOVATIVE, AND THAT THAT LEGACY SHOULDN'T BE LOST.

I ALSO WANT TO REMIND EVERYBODY, AS I ALWAYS DO, THAT CIRM HAS TWO KINDS OF CORE PUBLICS, PATIENTS AND ALL THEIR VARIOUS SIGNIFICANT OTHERS, MEDICAL AND FAMILIAL AND OTHERS, AND ALSO THE TAXPAYING AND VOTING ELECTORATE. AND THINKING ABOUT THOSE TWO PUBLICS NEEDS TO ALWAYS GO HAND IN HAND, I

THINK.

SO ARE THE SCIENTIFIC AND TECHNICAL RESULTS OF CIRM-FUNDED WORK BEING USED FOR PURPOSES THAT ARE NOT LIKELY TO BE APPROVED OF BY THE ELECTORATE AS IT PASSES INTO THE PRIVATE SECTOR AND THE CLINIC AND NATIONAL SECURITY CONTEXT? IS THIS AN AREA WHERE WE NEED SOME KIND OF RULES AND WHAT MIGHT THAT LOOK LIKE?

I ALSO THINK THAT FOR MY CORE AREAS OF RESEARCH, WE NEED IMMEDIATELY RATHER THAN AFTER THE FACT TWO KINDS OF MONITORING CAPACITY SET UP SO THAT WE DON'T GET INTO THE SITUATION WE DID WITH, FOR EXAMPLE, IN VITRO FERTILIZATION WHERE WE HAD 20 PLUS YEARS OF CHILDREN TRYING TO COLLECT DATA POST HOC ON WHETHER OR NOT THERE WERE ANY BIRTH DEFECTS TENDENCIES OR ANY ASSOCIATIONS WITH CANCER FOR WOMEN WHO'D TAKEN GONADOTROPINS AND THINGS LIKE THAT. WE DON'T WANT TO GET INTO THAT SITUATION AGAIN. WE HAVE THE TIME NOT TO DO THAT.

TWO REALLY, REALLY CORE THINGS ARE ARE WE BECOMING AN UNACCEPTABLY SELECTING SOCIETY. AND ANOTHER ONE IS IS THIS GOING TO PLAY INTO HEALTH DISPARITIES? THERE ARE PLENTY OF PEOPLE WORKING IN THESE FIELDS WHO ARE EXPLICITLY AGAINST THOSE TWO THINGS ALREADY, SCIENTISTS AND SOCIAL SCIENTISTS AND

ACTIVISTS, BUT THEY ARE REAL TENDENCIES. SO WE KNOW FROM MANY, MANY ARENAS RANGING FROM CLEAR BIOETHICS TO DISABILITY JUSTICE, SCHOLARSHIP THAT WHAT'S CONSIDERED A SERIOUS CONDITION AT ONE TIME CAN CHANGE OVER TIME, AND A SERIOUS CONDITION FROM ONE POINT OF VIEW IS NOT NECESSARILY A SERIOUS CONDITION FROM SOMEONE ELSE'S POINT OF VIEW.

IT'S REALLY, REALLY IMPORTANT TO HEAR FROM PATIENT ADVOCATES, NOT ONLY THEIR CAREGIVERS AND SIGNIFICANT OTHERS, BUT PATIENTS THEMSELVES.

I HEAR, I THINK, ABOUT A YOUNG WOMAN I WAS RECENTLY TALKING TO WHO HAS A CONDITION THAT MAY BE TREATABLE DOWN THE LINE WITH THESE TECHNOLOGIES, AND SHE SAID TO ME, "I REALLY WANT TO BE TREATED. AND I REALLY DON'T WANT ANYONE TO DESELECT ME." THOSE TWO THINGS TOGETHER, PEOPLE DON'T WANT TO NOT EXIST. THEY WANT THE RIGHT TO EXIST IN THE FORM THAT THEY'RE IN AS WELL AS -- AND FOR PEOPLE TO BE OKAY WITH HOW THEY ARE AND FOR PEOPLE TO MAKE THE WORLD MASSES BETTER FOR HOW THEY ARE AND NOT TO MEDICALIZE EVERYTHING ABOUT HOW BAD THE WORLD IS FOR THEM AS THEY CURRENTLY ARE. AT THE SAME TIME, CURES AND THE SOCIAL MODEL OF THIS NEED TO GO TOGETHER.

AND SO HAVING PATIENT ADVOCATES AND DISABILITY JUSTICE SCHOLARS AT THE TABLE TOGETHER IN

ANYTHING THAT WE DO ABOUT MAKING SURE THAT WE'RE NOT AN UNACCEPTABLY SELECTING SOCIETY. AND THIS IS A MOMENT IN OUR SOCIETY WHERE WE'RE WAITING TO SELECT ALREADY AROUND COMPETITION FOR SCHOOLING, WHAT WE THINK OF AS THE PROJECT OF CHILDHOOD AT THE MOMENT. SO THIS IS A REALLY -- THE CULTURE IS REALLY PRIME FOR THIS. SO WE DO HAVE TO BE VERY, VERY ATTENTIVE.

AND THEN THE OTHER ONE THAT IS ALSO JUST UNBELIEVABLY IMPORTANT BACKGROUND IS THAT THE FIELD OF HEALTHCARE IS RIVEN HISTORICALLY WITH CONDITIONED HEALTH DISPARITIES, AND I'M LOOKING AT SOME PEOPLE WHO DO EVERYTHING THEY CAN TO GO AGAINST THAT, BUT THOSE HEALTH DISPARITIES ARE WITH US IN EVERY ASPECT OF SOCIETY. AND HAVING COMMITTEES IN PLACE TO MAKE SURE THAT THE PEOPLE DOING THE SCIENCE, DOING THE REGULATORY CAPACITY, AND THAT THE WAY THAT THESE TECHNIQUES ARE BROUGHT TO THE MARKET, TO CLINICS, AND THE WAY THAT THEY'RE ROLLED OUT ARE EQUALLY AVAILABLE TO EVERYBODY. AGAIN, THESE ARE PAID FOR BY THE TAXPAYER, BY THE CITIZENS OF THE STATE, AND IT NEEDS TO BE EQUALLY AVAILABLE TO EVERYBODY.

SO HEALTH DISPARITIES EXPERTS ON ACCESS AND INCLUSION, LOOKING FOR RACIALIZED AND SOCIOECONOMIC STATUS-BASED GRADIENTS OF ACCESS SHOULD BE AT THE TABLE ALL THE TIME RIGHT FROM THE

START WELL BEFORE THESE THINGS ARE ROLLED OUT CLINICALLY, IN MY OPINION.

WE ALSO NEED TO HAVE REAL CONSEQUENCES IF THERE IS EVIDENCE OF HEALTH DISPARITIES AND EUGENIC TRENDS ARE EMERGING. SO IF WE NOTICE THAT, OH, GOSH, YES, NOW AS WE DO, FOR EXAMPLE, IF WE FIND MORE AND MORE PEOPLE ARE USING PRENATAL SCREENING TODAY FOR QUITE TRIVIAL THINGS, AN EXTRA FINGER, GET RID OF THAT ONE, IF WE START SEEING THAT THERE IS EVIDENCE THAT WE'RE MOVING TOWARDS TRAITS OR THAT WE'RE CONSIDERING SERIOUS -- AND AGAIN I DON'T MEAN TO MAKE TOO LIGHT OF IT ACTUALLY BECAUSE IT'S QUITE POSSIBLE THAT ECONOMICALLY, FOR EXAMPLE, IT IS A SERIOUS PROBLEM IF YOU ARE TOO SHORT OR WHATEVER IT MIGHT BE. THAT IF WE START NOTICING THAT THERE ARE TRENDS THAT PEOPLE OF CALIFORNIA THINK ARE NOT OKAY, THAT WE HAVE REAL TEETH, REAL WAYS OF STOPPING WHAT'S HAPPENING AND REELING IT BACK IN SOME WAY.

SO JUST THEN TO FINISH UP, THEN WHAT I WANTED TO SAY IN SHORT IS THAT I DO THINK THAT THERE'S GREAT POTENTIAL, ESPECIALLY IN THE DISEASE IN A DISH ARENA AND IN THE INTERFACE BETWEEN SOMATIC AND PLURIPOTENT STEM CELLS, TO COMBINE STEM CELL RESEARCH AND GENE EDITING. I THINK CALIFORNIA DESERVES AND CAN HAVE THE VERY BEST SCIENCE AND

ETHICS. GREAT ETHICS DOESN'T NEED TO SLOW DOWN SCIENCE. THERE ARE THINGS THAT PEOPLE SAY LIKE THAT THAT'S NOT EVIDENCE BASED. IF YOU HAVE GOOD ETHICS, IT'S A REGULATORY BURDEN. AND IT'S ALSO, PLEASE, IT'S NOT ANTISCIENCE TO NOTICE HISTORICALLY THAT SLOPES ARE INDEED SLIPPERY.

I'M A REAL TECHNOFILE AND I'M REALLY, REALLY CONCERNED ABOUT SELECTING AND DISCRIMINATORY SOCIETY. THOSE THINGS ARE NOT INCOMPATIBLE ONE WITH ANOTHER. THANK YOU FOR YOUR ATTENTION.

(APPLAUSE.)

DR. LOMAX: PROFESSOR GREELY, CAN YOU HEAR ME?

DR. GREELY: I CAN.

DR. LOMAX: WE CAN HEAR YOU LOUD AND CLEAR.

DR. GREELY: I CAN HEAR YOU FAINTLY AND NOT VERY CLEARLY, BUT I'M GLAD I'M COMING THROUGH WELL. THANKS FOR ASKING ME TO TALK. I WANT TO APOLOGIZE FOR NOT BEING THERE IN PERSON. GEOFF AND I WENT ROUND AND ROUND ON SOME OF THE POSSIBILITIES; BUT UNTIL THE HYPER LOOP OR THE TRANSPORTER BEAM BECOMES A REALITY, THIS ONE WASN'T GOING TO WORK FOR ME. I'VE GOT A THREE-HOUR SEMINAR THAT I'M TEACHING IN A FEW MINUTES THAT COULD NOT BE RESCHEDULED AT

THIS STAGE OF THE TERM, AND MY STUDENTS GOT PRIORITY OVER CIRM, I'M AFRAID. BUT I HOPE I CAN SAY A FEW USEFUL THINGS OVER THE PHONE.

I DO WANT TO NOTE THAT I HAVEN'T BEEN ABLE TO HEAR THE ENTIRE CONFERENCE IN PART BECAUSE OF SOME OF THE AV DIFFICULTIES AND IN PART BECAUSE AROUND LUNCHTIME I WENT OFF TO A PRESS CONFERENCE AT WHICH STANFORD ANNOUNCED ITS NEXT PRESIDENT. I DON'T KNOW WHETHER THIS HAS BEEN MENTIONED IN TODAY'S MEETING, BUT IT'S GOOD NEWS, I THINK, FOR CIRM AND PEOPLE INTERESTED IN BIOMEDICINE. STANFORD'S ELEVENTH PRESIDENT WILL BE MARC TESSIER-LAVIGNE, CURRENT PRESIDENT OF ROCKEFELLER, AND FOR SEVERAL YEARS CHIEF SCIENTIFIC OFFICER AT GENENTECH. SO STANFORD'S NEW PRESIDENT WILL HAVE, I THINK, A STRONG PERSONAL INTEREST IN THE KINDS OF ADVANCES CIRM IS TRYING TO CREATE.

A COUPLE OF THOUGHTS THAT I HOPE WILL BE CONCRETE AND USEFUL ABOUT CIRM AND THE IMPACT ON CIRM AND PARTICULARLY THE SOCIAL AND ETHICAL WORKING GROUP OF CRISPR-CAS9 AND RELATED TECHNOLOGIES. FIRST, AND I THINK REALLY IMPORTANT TO REMEMBER, THERE ARE AN AWFUL LOT OF ISSUES AROUND CRISPR-CAS9 THAT AREN'T CIRM'S BUSINESS. AND CIRM IS ABOUT HUMAN STEM CELLS AND FUNDING OF HUMAN STEM CELLS.

AND SO, ALTHOUGH FRANKLY I THINK SOME OF LIKE THE MOSQUITO MODIFICATION ISSUE THAT SOMEONE BROUGHT UP IS TO ME ONE OF THE SINGLE MOST IMPORTANT THINGS ABOUT CRISPR-CAS9, NONHUMAN USES DWARF, AT LEAST IN THE NEXT 10 TO 20 YEARS, TO INSIGNIFICANT ANY OF THE HUMAN USES. IT'S NOT CIRM'S ISSUE. SO CIRM DOESN'T HAVE TO AND SHOULDN'T TRY TO SOLVE EVERY ETHICAL ISSUE RAISED BY CRISPR-CAS9.

WHEN I LOOK AT THE THINGS THAT CIRM IS INVOLVED WITH, THE STEM CELL RESEARCH -- FUNDING STEM CELL RESEARCH, I ACTUALLY AM PRETTY IMPRESSED AT HOW WELL THE NOW ALMOST TEN-YEAR-OLD REGULATIONS THAT YOUR WORKING GROUP RECOMMENDED AND THAT THE ICOC ADOPTED HOLD UP IN THIS CONTEXT. I THINK YOU'RE GENERALLY IN PRETTY GOOD SHAPE FOR DEALING WITH THESE NEW ISSUES.

HAVING SAID THAT, THERE ARE A COUPLE OF THINGS I THINK NEED THOUGHT, AND SOME OF THIS WILL BE REPEATING WHAT SOME OTHER FOLKS HAVE SAID. I WISH I COULD GIVE WHOEVER SAID THEM CREDIT, BUT IT WAS NEVER QUITE CLEAR TO ME WHO WAS TALKING AT ANY GIVEN TIME. I THINK THERE ARE THREE TECHNICAL ISSUES RAISED BY THE USE OF CRISPR-CAS9 WITH RESPECT TO HUMAN STEM CELLS THAT REQUIRE AT LEAST SOME THOUGHT ABOUT WHETHER THE WORDING OF THE REGULATIONS

NEEDS TO BE CHANGED.

ONE, AS SOMEONE ALREADY POINTED OUT, WAS DEFINITION OF GENETICALLY MODIFIED. CIRM IS NOT ALLOWED TO FUND ANY RESEARCH WHERE THERE'S THE TRANSFER OF A GENETICALLY MODIFIED HUMAN EMBRYO INTO A WOMAN'S UTERUS. WHAT GENETICALLY MODIFIED MEANS MAY USE A LITTLE MORE DEFINITION. SOMEBODY POINTED OUT MITOCHONDRIAL TRANSFER AS A QUESTION. I ACTUALLY THINK THE BIGGER QUESTION, AND THIS IS A SEMI-INDEPENDENT SECOND POINT, I THINK, FRANKLY, IF WE EVER DO DO HUMAN GERMLINE GENOME EDITING, AND I'M NOT CONVINCED THAT IT WILL MAKE MUCH SENSE, IF WE EVER DO DO IT, I DON'T THINK WE'RE GOING TO DO IT THROUGH GENETICALLY MODIFIED OR EDITING EMBRYOS. WE'LL DO IT THROUGH MODIFYING AND EDITING THE GAMETES THAT LEAD TO THE EMBRYOS. AND IT NEEDS TO BE CLEAR IN THE CIRM DEFINITIONS THAT AN EMBRYO THAT IS NOT WHERE THE EMBRYO ISN'T GENETICALLY MODIFIED, BUT THE EGG OR THE SPERM THAT YIELDED THE EMBRYO IS GENETICALLY MODIFIED PROBABLY SHOULD FALL UNDER THAT PROHIBITION ON CIRM FUNDING. IT'S A KIND OF SECOND ORDER GENETIC MODIFICATION, BUT I THINK, GIVEN THE INTENT OF THAT INITIAL PROHIBITION, IT SHOULD PROBABLY BE CLEAR.

I ALSO THINK THE COMMITTEE, THE WORKING

GROUP, SHOULD GIVE SOME MORE THOUGHT TO WHETHER IT NEEDS TO SAY ANYTHING SPECIFIC ABOUT RESEARCH THAT MODIFIES HUMAN GAMETES AND WHAT MIGHT OR MIGHT NOT BE DONE WITH IT. AS A WHOLE SET OF SPECIFIC KINDS OF RESEARCH AND THE EXTENT TO WHICH THEY REQUIRE SCRO REVIEW, I DON'T THINK THERE'S ANYTHING IN THERE THAT SPECIFICALLY TALKS ABOUT MODIFICATION OF HUMAN GAMETES, BUT MAYBE THERE SHOULD BE. I'M NOT ENTIRELY SURE THERE SHOULD BE, BUT MAYBE THERE SHOULD BE.

CHARIS POINTED OUT ANOTHER ISSUE KIND OF ALONG THE SAME LINE, ACCIDENTAL GERMLINE MODIFICATION WHERE THE GOAL WAS SOMATIC CELL GERMLINE MODIFICATION, BUT IT SPILLED OVER. THE CIRM REGS ACTUALLY DO KIND OF DEAL WITH THAT BECAUSE THEY REQUIRE THE SCRO, WHEN IT'S CONSIDERING ANY PUTTING OF HUMAN STEM CELLS INTO HUMANS, TO CONSIDER THEIR PATTERNS OF DIFFERENTIATION AND, I'M FORGETTING THE EXACT WORD, BASICALLY DIFFERENTIATION AND SPREAD AND INTEGRATION WHICH WAS TAKEN FROM THE NATIONAL ACADEMIES GUIDELINES. I THINK MAKING THE POINT THAT A PARTICULAR AREA WHERE THE INTEGRATION IS IMPORTANT AND WHERE IT SHOULD BE AVOIDED IS THE INTEGRATION OF ANY STEM CELLS WITH GENETIC MODIFICATIONS INTO THE GONADS IN A WAY WHERE THEY

MIGHT BECOME EGGS OR SPERM.

SO THOSE ARE THREE SUBSTANTIVE CONCERNS. I DON'T THINK ANY OF THEM IS A HUGE CONCERN. AS SEVERAL PEOPLE HAVE MENTIONED, I THINK THE INFORMED CONSENT ISSUES COULD USE FURTHER THOUGHT. I THINK CIRM WAS A LEADER IN TRYING TO SPECIFY INFORMED CONSENT FOR PARTICULAR KINDS OF USES, LIKE TO MAKE HUMAN EMBRYONIC STEM CELL LINES. THIS IS ONE THAT CERTAINLY DESERVES SOME THOUGHT AND CHANGE TO THE REGULATIONS.

I DO THINK, HAVING SAID THAT THE MOSQUITOES FOR THE MOST PART ARE NOT A CIRM ISSUE, RESEARCH WITH NONHUMANS IS A CIRM ISSUE. THE INTRODUCTION OF HUMAN STEM CELLS INTO NONHUMANS IS FUNDED BY CIRM, AND CIRM REQUIRES IT TO GO THROUGH SCRO APPROVAL PROCESSES. I THINK THAT WITH CRISPR-CAS9 AND THE KINDS OF RESEARCH AND POSSIBLE APPLICATIONS THAT IT'S LEADING TO, THINGS LIKE REALLY EXCITING RESEARCH ABOUT PERHAPS MAKING HUMAN ORGANS AND NONHUMAN ORGANISMS, YOU MAY WANT TO GIVE SOME MORE EMPHASIS TO THINKING ABOUT THE IMPORTANCE OF THE DISSEMINATION AND INTEGRATION OF THOSE HUMAN STEM CELLS IN NONHUMANS. NOT SO MUCH BECAUSE I THINK CRISPR-CAS9 CHANGES THE -- OBVIOUSLY IT WOULD BE CHANGING THE STEM CELLS, BUT IT'S JUST THAT I

THINK THE POTENTIAL -- CRISPR-CAS9 MAKES THE POTENTIAL INTEREST IN THAT FIELD AND APPLICATIONS OF THAT KIND OF WORK TO MODIFY HUMAN STEM CELLS AND THEN PUT THEM INTO NONHUMANS MAKES THAT MORE LIKELY IN A WAY THAT PERHAPS WOULD LEAD YOU TO WANT TO REINFORCE THIS ISSUE ABOUT DISSEMINATION AND INTEGRATION.

THOSE ARE THE CHANGES THAT COME TO MY MIND THAT YOU MIGHT WANT TO THINK ABOUT WITH RESPECT TO THE REGULATIONS. I DO THINK THERE'S ANOTHER THING I WOULD RECOMMEND, AND IT'S REALLY A CONTINUATION OF WHAT CIRM, THROUGH GEOFF LOMAX AND OTHERS, HAVE ALREADY BEEN DOING. BERNIE RAISED AS ONE OF THE POSSIBILITIES, SHOULD THERE BE SOME LEVEL OF REVIEW HIGHER THAN THE SCRO. AND I'M NOT SURE WHO RESPONDED BY SAYING NO. THE SCRO'S ARE DOING A GOOD JOB. WE'VE CREATED THESE GOOD ENTITIES. WE SHOULD LET THEM GO ON. MY GUT SENSE IS WITH THE LATTER SPEAKER, THAT YOU DON'T NEED A HIGHER REVIEW ENTITY; BUT ON ISSUES AROUND CRISPR-CAS9, I THINK PROVIDING EDUCATIONAL MATERIALS AND EDUCATIONAL OPPORTUNITIES FOR THE SCRO'S ON HOW CRISPR-CAS9 MIGHT AFFECT THEIR WORK COULD BE A VERY USEFUL THING, NOT TO REPLACE THEM OR DISPLACE THEM, BUT TO HELP THEM DO THEIR JOB BETTER.

I'VE GOT ONE LAST POINT. A LOT OF THE -- MAYBE IT'S TWO POINTS. MOST OF THE CONCERN ABOUT CRISPR-CAS9, MOST OF THE THEATER HAS BEEN AROUND HUMAN GERMLINE GENETIC MODIFICATION. CIRM CAN'T FUND THAT OR AT LEAST IT CAN'T FUND AND PROBABLY SHOULDN'T FUND, BUT AT ANY RATE CAN'T FUND TRANSFER OF A GENETICALLY MODIFIED EMBRYO INTO A WOMAN FOR POSSIBLE PREGNANCY AND BIRTH. THAT'S THE BIG TICKET VISCERAL ISSUE, AND YOU JUST NEED TO MAKE SURE THAT THAT LINE CONTINUES TO BE POLICED, BUT THE LINE IS THERE. AND I DON'T THINK IT IS PARTICULARLY CONTROVERSIAL.

THERE WILL BE PEOPLE, AND I THINK THERE MAY BE SOME IN THE ROOM, WHO WOULD LIKE CIRM MONEY NOT TO BE USED TO MAKE GENOME-EDITED EMBRYOS THAT ARE NOT INTENDED FOR TRANSFER. EXPERIMENTS LIKE THE CHINESE EXPERIMENT, WHICH NOT ONLY USED EMBRYOS NOT INTENDED FOR TRANSFER, BUT EMBRYOS THAT WERE ON PURPOSE NONVIABLE OR THE RECENTLY APPROVED BRITISH EXPERIMENT WHICH WOULD USE ORDINARY HUMAN EMBRYOS, BUT PROMISES UNDER VARIOUS PENALTIES NOT TO TRANSFER THEM, I THINK THAT'S THE SORT OF RESEARCH THAT CIRM SHOULD FUND WHEN IT'S SCIENTIFICALLY APPROPRIATE. I THINK THERE ARE LOTS OF TIMES WHEN IT WILL BE SCIENTIFICALLY APPROPRIATE.

CIRM IS IN THE HUMAN EMBRYO EXPERIMENTATION WORLD. IT FUNDS RESEARCH AS LONG AS THE EMBRYOS ARE NOT IMPLANTED. IT FUNDS IT WITH SPECIAL PROTECTIONS AND SPECIAL REVIEW CONSIDERATIONS AND SPECIAL INFORMED CONSENT CONSIDERATIONS. I DON'T THINK CRISPR-CAS9 CHANGES THAT. SO IF YOU WANTED TO BAN THE CREATION OF GENETICALLY MODIFIED EMBRYOS FOR RESEARCH PURPOSES ONLY, NEVER TO BE IMPLANTED, THAT WOULD TAKE NEW ACTION. IT IS THE CASE THAT, AS I UNDERSTAND IT, FDA AND RACK CANNOT BAN THAT. RACK DEALS WITH THE FEDERALLY FUNDED SIDE, WHICH NIH ISN'T GOING TO FUND ANYWAY. FDA DOESN'T REALLY HAVE A HANDLE WITH RESPECT TO NONCLINICAL USE. YOU WANT TO PUT A MODIFIED EMBRYO INTO A HUMAN, FDA COMES INTO PLAY. BUT I DON'T THINK THERE IS ANY FEDERAL REGULATORY AUTHORITY WITH RESPECT TO EMBRYOS THAT ARE NOT GOING TO BE IMPLANTED OTHER THAN THE VARIOUS FUNDING BANS AND FUNDING LIMITATIONS. SO IT ISN'T REGULATED RIGHT NOW, BUT I DON'T SEE ANY GOOD REASON FOR CIRM TO RESTRICT ITS FUNDING IN A WAY THAT STARTS REGULATING IT BECAUSE I THINK WE'VE, AT LEAST IN CALIFORNIA, CROSSED THAT LINE. EMBRYO RESEARCH FOR A GOOD PURPOSE THAT DOES NOT INVOLVE PUTTING THE EMBRYOS INTO A UTERUS FOR POSSIBLE PREGNANCY AND

BIRTH IS SOMETHING THAT WE ARE WILLING TO SUPPORT. I DON'T SEE CRISPR-CAS9 CHANGING THAT.

SO I HOPE THAT'S A USEFUL THOUGHT. I'D BE HAPPY, ALONG WITH CHARIS, TO TAKE ANY QUESTIONS.

DR. BOTKIN: JEFF BOTKIN. I'M FILLING IN FOR BERNIE UNTIL HE COMES BACK. SO THANKS FOR A VERY RICH SET OF COMMENTS. THANKS TO CHARIS ALSO. I THINK WHAT WE'RE GOING TO DO IS GO AHEAD AND GO TO QUESTIONS.

JEFF A LITTLE EARLIER ASKED ABOUT FDA REGULATIONS. DID YOU GET AN ADEQUATE ANSWER? I THINK HANK MIGHT BE A WONDERFUL PERSON TO PROVIDE AN ANSWER AS TO HOW FDA -- WHAT FDA'S REACH IS ON MODIFIED HUMAN CELLS. ANOTHER MICROPHONE HERE. SO, JEFF'S, HANK, GOING TO RE-EXPRESS HIS QUESTION HERE FOR YOU.

MR. SHEEHY: SO, DR. GREELY, SO WHAT EXACTLY IS THE REACH OF THE FDA BECAUSE THEY DON'T REGULATE IVF CLINICS? AND SINCE, AS CURRENT LAW STATED, THEY ACTUALLY AREN'T FUNDED TO DO ANY WORK AROUND GENETICALLY MODIFIED EMBRYOS, AT LEAST IN THE CONTEXT OF THE MITOCHONDRIA CASE, WHAT THEY'RE DOING IN GREAT BRITAIN, THERE'S NO PATHWAY. WHAT EXACTLY -- WHAT IS THE EXACT ROLE THAT THEY WOULD PLAY? IS THERE A STATUTE THAT GIVES THEM OVERSIGHT

HERE? ARE WE JUST ASSUMING THAT BECAUSE FDA IS ALWAYS THERE, IN THIS CASE THEY ARE THERE?

DR. BOTKIN: HANK, WERE YOU ABLE TO HEAR THAT QUESTION?

MS. SCHAFFER: I JUST WORD THAT AT&T DROPPED. SO WE NEED TWO MINUTES TO GET BACK UP ON AT&T.

DR. BOTKIN: SO WE'LL HAVE TO GET BACK TO THAT QUESTION THEN HOPEFULLY ONCE HANK IS ABLE TO JOIN US.

DR. ROD TAYLOR: THERE'S A MORATORIUM CURRENTLY ON MITOCHONDRIAL TRANSFER IN THE U.S. IN CANADA, I THINK, IT'S HAPPENING COMMERCIALLY. SO SOMEONE -- I THINK YOU RAISED A QUESTION, BUT PEOPLE ARE DOING IT IN CANADA AS PART OF THEIR. BUT WHETHER THE FDA WOULD ACTUALLY STEP IN WERE WE TO CHANGE THAT, I'M NOT GOING TO SAY THAT IT WOULD.

MS. DARNOVSKY: CORRECT ME IF I'M WRONG, BUT I THINK WHAT YOU WERE REFERRING TO, WHICH IS HAPPENING IN CANADA, IS THE PROCEDURE BY THE COMPANY OVASCIENCE. AND THAT IS A LITTLE BIT DIFFERENT THAN WHAT WAS APPROVED. IT'S QUITE DIFFERENT ACTUALLY THAN WHAT WAS APPROVED FOR POSSIBLE USE IN THE UK. IT DOESN'T INVOLVE A THIRD PERSON'S CELLS -- EMBRYOS AND IT'S ALL AUTOLOGOUS. THAT'S VERY DIFFERENT.

AND THE MORATORIUM ON THE FDA, I THINK WHAT YOU'RE REFERRING TO, JEFF, IS THIS PROVISION THAT WAS PUT IN THE OMNIBUS FUNDING BILL. AND AS I UNDERSTAND IT, FIRST OF ALL, THAT'S SOMETHING THAT WILL EXPIRE AFTER A YEAR UNLESS IT'S APPROVED AGAIN, AND IT IS THE WAY THAT THESE THINGS HAPPEN, I GUESS, IN CONGRESS, BUT IT'S NOT -- I DON'T THINK IT'S COMPLETELY CLEAR WHAT THAT WOULD AND WOULD NOT APPLY TO THE FDA BEING ABLE TO DO. FOR EXAMPLE, IF THE MITOCHONDRIAL TRANSFER TECHNIQUES ARE APPROVED FOR MALES, WOULD THAT CONSTITUTE GERMLINE MODIFICATION? AND I THINK WHAT THE -- I THINK THAT WHAT THE COMMITTEE, THE IOM COMMITTEE, SAID IS FDA COUNSEL IS GOING TO HAVE TO RULE ON THAT. I THINK THAT'S STILL UP IN THE AIR. I HOPE THAT HELPS.

DR. BOTKIN: IT WAS MY UNDERSTANDING, I WAS ON THE MITOCHONDRIAL PANEL, THAT AS SOON AS YOU GET INTO THE MANIPULATION OF CELLS THAT WILL BE IMPLANTED BACK IN THE BODY, THE FDA THEN HAS AUTHORITY AS OPPOSED TO, SAY, IVF AND THOSE SORTS OF WHERE THERE'S NOT ANY INTRINSIC CHANGE TO THE CELLS BEING TRANSFERRED. THAT'S MY NONREGULATORY UNDERSTANDING OF THE SITUATION.

DR. GREELY: I'M BACK ON.

DR. BOTKIN: HANK, DID YOU HEAR JEFF'S

QUESTION?

DR. GREELY: I THINK I HEARD MOST OF IT WHILE DEALING WITH AT&T. I SHOULD SAY I THINK I SCREWED UP AND CUT THE LINE MYSELF. IT'S PROBABLY NOT AT&T'S FAULT.

SO FIRST, I WISH ALTA WERE ON BECAUSE ALTA HAS FORGOTTEN MORE ABOUT FDA THAN I KNOW, BUT I DO TEACH FDA LAW. FDA'S AUTHORITY -- FDA TAKES THE POSITION, WHICH I THINK A COURT WOULD UPHOLD, THAT A GENETICALLY MODIFIED HUMAN CELL FOR THE MOST PART THAT HAS BEEN MORE THAN MINIMALLY MANIPULATED IS A DRUG OR BIOLOGICAL PRODUCT SUBJECT TO FDA REGULATION. SO THAT A HUMAN CLONE OR THE MITOCHONDRIAL TRANSFER PROCEDURE, EITHER OF THE TWO WAYS OF GOING MITOCHONDRIAL TRANSFER, FDA'S POSITION IS IT REGULATES THOSE, AND YOU CANNOT DO THEM WITHOUT FDA APPROVAL. BUT WHAT YOU CAN'T DO IS EITHER INTRODUCE IT INTO INTERSTATE COMMERCE AS A TREATMENT, WHICH REQUIRES FDA APPROVAL, OR EVEN DO IT IN HUMANS FOR RESEARCH, WHICH DOES NOT REQUIRE FULL FDA APPROVAL, BUT DOES REQUIRE AN IND, AN INVESTIGATIVE NEW DRUG EXEMPTION, WHICH REQUIRES YOU TO CONVINCE THE FDA THAT AT LEAST IT'S SAFE AND PROMISES TO BE EFFECTIVE ENOUGH AND IT'S NOT CRAZY TO TRY TO DO THIS.

SO IF ONE WERE TO TRY TO TAKE A GENETICALLY MODIFIED EMBRYO EVEN AS RESEARCH AND PUT IT INTO A WOMAN'S WOMB, THAT THE FDA, I'M CONFIDENT, WOULD TAKE THE POSITION IS RESEARCH THAT'S COVERED BY THEM AND YOU WOULD NEED AN IND TO DO IT. WHAT CONGRESS HAS SAID IS, FDA, YOU'RE NOT ALLOWED TO CONSIDER ANY OF THOSE IND'S. SO THEY CAN'T BE APPROVED BECAUSE THEY CAN'T BE CONSIDERED. OR IT'S TRICKIER THAN THAT. WHAT CONGRESS ORIGINALLY WANTED TO DO IS SAY, FDA, YOU CAN'T SPEND ANY MONEY CONSIDERING THEM. WITH AN IND, IF FDA DOESN'T ACT WITH AN IND APPLICATION, IF FDA DOESN'T ACT WITHIN 30 DAYS, THE COMPANY CAN GO FORWARD, THAT RESEARCH CAN GO FORWARD. SO IN THE FINAL BILL, THEY SAID YOU CAN'T SPEND ANY MONEY AND SUCH APPLICATIONS WILL NOT DEEMED TO HAVE BEEN RECEIVED. SINCE THEY ARE NOT RECEIVED, THE 30 DAYS CAN'T RUN. THAT'S IN THIS YEAR'S BILL. WILL IT BE IN NEXT YEAR'S APPROPRIATIONS BILL, NO GUARANTEE, BUT DICKIE WICKER INVOLVING DESTRUCTION OR RISKY RESEARCH WITH EMBRYOS HAS BEEN IN ANNUAL APPROPRIATIONS BILLS EVERY YEAR SINCE 1995. SO I WOULDN'T BET AGAINST A CONTINUATION OF THAT.

SO I THINK FDA MAY BE FACING FOR A LONG TIME A BAN ON ITS ABILITY TO APPROVE EITHER IND'S,

LET ALONE NEW DRUG APPLICATIONS OR BIOLOGICAL LICENSE APPLICATIONS, FOR THIS KIND OF RESEARCH; BUT THAT, AS FAR AS I CAN TELL, DOESN'T AFFECT NONCLINICAL RESEARCH, RESEARCH THAT DOES NOT INVOLVE PUTTING THIS INTO A BORN, LIVING HUMAN BEING. IS THAT HELPFUL? DOES THAT ANSWER THE QUESTION, OR DOES IT, AS I OFTEN DO, MORE THAN ANSWER A QUESTION THAT WASN'T ASKED?

MR. SHEEHY: NO, DR. GREELY. THAT'S HELPFUL. THERE'S NO OTHER PROHIBITION OTHER THAN THE FDA THAT WOULD STOP THE IMPLANTATION OF AN EMBRYO. NO LAWS AGAINST IT.

DR. GREELY: NOT IN THE FEDERAL GOVERNMENT. THERE ARE STATES THAT HAVE BANNED EMBRYO RESEARCH IN WAYS THAT PROBABLY WOULD BAN THIS. CALIFORNIA, AS FAR AS I KNOW, ISN'T ONE OF THEM; BUT I THINK NORTH DAKOTA, LOUISIANA, A VARIETY OF STATES, I WOULD SUSPECT, HAVE BANNED THIS. AND THERE ARE CLEAR PROHIBITIONS IN A VARIETY OF FOREIGN COUNTRIES. SO AS FAR AS I KNOW, THERE IS NO FEDERAL LAW OTHER THAN THE FUNDING LIMITATIONS AND THE FDA LIMITATIONS AND THE RACK AS A REGULATORY MATTER WORKING THROUGH THE FUNDING REGULATIONS THAT WOULD STOP THIS KIND OF RESEARCH, BUT THE FDA WOULD BE ABLE TO STOP AT LEAST, UNLESS IT GOT A VERY

UNSYMPATHETIC COURT, WOULD BE ABLE TO STOP THE IMPLANTATION -- THE TRANSFER FOR POSSIBLE IMPLANTATION AND PREGNANCY.

MR. SHEEHY: AND, DR. GREELY, WHAT THIS RELATES TO IS, ASSUMING THAT WE BELIEVE THIS RESEARCH SHOULD GO FORWARD, AND I'VE EVEN ARGUED ALREADY THAT THIS RESEARCH ACTUALLY FALLS UNDER THE PRIORITY FOR NON-NIH FUNDING THAT'S IN PROP 71, I WANT JUST PEOPLE -- OUR PROHIBITION, WE DON'T REALLY HAVE A PROHIBITION. WE JUST SAY WE WON'T PAY FOR IT. AND SO TRYING TO FIGURE OUT WHAT BARRIERS EXIST TO THE IMPLANTATION OF AN EMBRYO IN CALIFORNIA THAT'S BEEN GENETICALLY MODIFIED, HAVING SOME UNDERSTANDING OF WHERE THOSE LIMITS ARE FOR ME RELATES TO WHAT KIND OF REGULATIONS WE PUT IN PLACE AND WHETHER WE NEED TO STRENGTHEN OUR PROHIBITION BEYOND JUST NOT FUNDING THIS PARTICULAR ACTIVITY, BUT TRYING TO HAVE SOME REACH-THROUGH SUCH AS OUR MARCH-IN RIGHTS THAT ALLOW US TO HAVE A LITTLE BIT -- AT LEAST IT'S STILL UP IN THE PUBLIC THAT WE'RE TAKING VERY STRONG ACTION, THE STRONGEST POSSIBLE ACTION WE CAN TO MAKE SURE THAT IF AN EMBRYO IS DEVELOPED, WE'VE DONE EVERYTHING THAT WE CAN DO TO NOT ALLOW IT TO BE IMPLANTED UNLESS SOMETHING CHANGES. THIS MAY TURN OUT TO BE VERY

SAFE AND ADDRESSES A LOT OF ISSUES FOR A LOT OF PATIENTS AND MAKES A DIFFERENCE IN A LOT OF PEOPLE'S LIVES; BUT UNTIL EVERYBODY MOVES FORWARD COLLECTIVELY, I JUST WANT TO HAVE SOME SENSE OF SECURITY, IF WE DO GO FORWARD WITH THIS RESEARCH, THAT WE CAN ASSURE THE PUBLIC IN CALIFORNIA THAT WE'VE TAKEN ALL THE STEPS WE CAN. DOES THAT MAKE SENSE?

DR. GREELY: IT MAKES SENSE. I'M NOT -- I DO THINK THE FDA'S POSITION ON THIS IS A PRETTY STRONG LEGAL PROHIBITION AND APPLIES IN CALIFORNIA. AS FAR AS I CAN THINK OF, I DON'T THINK CALIFORNIA HAS ANY OTHER PROHIBITION, AND YET CIRM EXISTS AS A FUNDING AGENCY. CIRM IS NOT A REGULATORY AGENCY. IT'S A FUNDING AGENCY THAT PUTS LIMITS ON WHAT CAN BE DONE WITH ITS FUNDING. IT MAY BE POSSIBLE TO USE MARCH-IN AND OTHER LIMITATIONS WITH RESPECT TO THE RESULTS OF EARLIER FUNDED, EARLIER CIRM-FUNDED RESEARCH TO TRY TO STOP THIS. I DON'T THINK IT WOULD BE -- I THINK THERE'S A VERY, VERY GOOD CHANCE THAT IF ANYBODY WANTED TO DO TRY TO DO THIS IN CALIFORNIA, THEY WOULDN'T BE USING ANYTHING THAT CIRM HAD A HANDLE ON.

SO MY OWN PERSPECTIVE ON THIS IS IF CALIFORNIA WANTS TO BAN IT, FINE; BUT CALIFORNIA

SHOULD BAN IT THROUGH THE LEGISLATURE. CIRM IS A FUNDING AGENCY OR FUNDING ENTITY. IT SHOULD NOT FUND IT, BUT I DON'T THINK CIRM NEEDS TO -- IS LIKELY TO BE ABLE VERY EFFECTIVELY TO OR SHOULD TRY TO GO BEYOND TO TRY MAKE ITSELF WHAT WOULD BE A NOT VERY EFFECTIVE VEHICLE FOR A BROADER BAN ON THE PROCESS, ESPECIALLY SINCE THE FDA IS STILL THERE.

DR. BOTKIN: THANK YOU, HANK. OTHER QUESTIONS FOR CHARIS OR HANK? I THINK OUR BROAD AGENDA HERE IS TRYING TO ESTABLISH AN AGENDA FOR THE FURTHER DISCUSSIONS BY THE WORKING GROUP, WHICH I THINK BOTH OF THEM DID NICELY.

DR. THOMPSON: ONE QUESTION I WANTED TO RAISE THAT CAME UP THIS MORNING THAT I HADN'T ADDRESSED IN MY PRESENTATION. GEOFF LOMAX ACTUALLY KNOWS THIS VERY, VERY WELL, REMINDING US WHAT CAME FROM PUBLIC COMMENT AND WHAT THE RATIONALE FOR WHERE WE ARE WITH CIRM REGULATIONS IS FROM, AS IT WERE, THE PEOPLE. BUT CORRECT ME IF I'M WRONG, GEOFF, BUT I'M REMEMBERING A BACK A DECADE OR SO THAT THE REAL RATIONALE BEHIND THE PROHIBITION ON REPRODUCTION WAS ABOUT PROHIBITING CLONING. SO THERE IS A QUESTION ABOUT WHETHER OR NOT THOSE TWO THINGS ARE SIMILAR AND WHETHER -- OR JUST BECAUSE THE EXPRESSION REPRODUCTION OR REPRODUCTIVE WILL TRANSFER TO A

UTERUS DOESN'T SEEM TO COVER BOTH THE EDITING CONTEXT AND THE PRODUCT OF SCNT IN THE CLONING CONTEXT THAT JEFF WAS RAISING ORIGINALLY, WHETHER IN FACT THE INTENT OF THE WAY PEOPLE WERE TALKING AND THINKING ABOUT IT COMES OUT THE SAME WAY IN FOLLOWING DOWN BOTH LINES OF THOUGHT.

DR. LOMAX: WELL, THE CLONING ASPECT IS BAKED INTO PROPOSITION 71. SO THAT DISCUSSION WAS A DELIBERATE EFFORT TO KIND OF EXPAND THE SCOPE OF THE -- IT WAS EXPANSION IN SCOPE THAT WAS ABOVE AND BEYOND SCNT. SCNT KIND OF OCCASIONALLY DROPS INTO THAT DISCUSSION IN THE TRANSCRIPT TO POINT OUT THE ANALOGY AS A COMPARATOR, BUT IT WAS CLEARLY A DELIBERATE EFFORT TO EXPAND THE SCOPE OF THE REPRODUCTIVE PROHIBITION ABOVE AND BEYOND JUST SCNT. THAT'S CERTAINLY MY RECOLLECTION. I THINK IF YOU GO FURTHER BACK IN THAT RECORD, IT'S REFLECTED IN THE RECORD AS WELL.

DR. ROD TAYLOR: I WAS JUST GOING TO SAY BECAUSE AT THE TIME A DECADE AGO THAT WAS REALLY THE ONLY WAY WE COULD CONCEIVE OF, AND I AGREE WITH YOU ACTUALLY, CHARIS, THAT THE CLONING, THE ETHICS OF CLONING IS KIND OF DIFFERENT THAN THE ETHICS OF THE GENETICALLY MODIFIED HUMAN EMBRYO, AND THAT THOSE WERE KIND OF CONFLUENT AT THE TIME BECAUSE WE DIDN'T

REALLY HAVE ANOTHER WAY TO THINK ABOUT IT. I THINK YOUR POINT IS REALLY A VERY INTERESTING ONE.

WHETHER IT'S GOING TO SORT OF CHANGE THE WAY WE OPERATE IS SORT OF ANOTHER QUESTION, BUT I WOULD SAY THAT TEN YEARS AGO I WOULD HAVE THOUGHT DIFFERENTLY ABOUT THAT THAN I WOULD THINK ABOUT IT TODAY.

DR. BOTKIN: A QUESTION FOR CHARIS THEN. SO I WAS VERY INTERESTED IN YOUR COMMENTS ABOUT THE MONITORING AND LOOKING FOR ADVERSE CONSEQUENCES SORT OF LONG TERM AND HAVING SOME REAL CONSEQUENCES FOR THAT. IT SEEMS TO ME WE'VE TALKED ABOUT SOME ISSUES THAT ARE PROCESS ISSUES, AND THAT'S WHERE I'M GOING TO GO WITH THIS QUESTION. SOME OF THE ISSUES WERE DEFINITIONAL ISSUES, WHAT DO WE MEAN BY WHAT WE SAID, AND THEN SOME ARE SORT OF NORMATIVE ISSUES, WHAT'S THE RIGHT THING TO DO.

SO DOES CIRM HAVE GOOD MONITORING PROCESSES NOW? YOU HEAR QUITE A BIT ABOUT HOW PUBLIC COMMENT HAD A BIG IMPACT ON HOW THINGS WERE STRUCTURED EARLY ON, BUT IS THERE ONGOING MONITORING OF THE PUBLIC SPHERE IN A WAY THAT MIGHT HELP FULFILL YOUR REQUEST TO MAKE SURE THAT IF THINGS ARE GOING AWRY, AT LEAST IN THE PUBLIC'S VIEW, THAT THINGS MIGHT BE CHANGED?

DR. THOMPSON: AND I WOULD GUESS GEOFF AND THE CIRM PEOPLE WOULD BE THE BEST TO ANSWER THIS, BUT I THINK THERE NEEDS TO BE SOME KIND OF CIRM AND EXTERNAL PARTNERSHIPS SO THAT THE RIGHT KIND OF OVERSIGHT IS IN PLACE TO MAKE SURE THAT THOSE ARE TAKEN UP SOONER RATHER THAN LATER. YOU CAN PROBABLY TELL FROM THE WAY I'M TALKING THAT I'M ASSUMING THAT WHETHER OR NOT DIRECTLY WITHIN CIRM'S AMBIT OF NEXT HOWEVER MANY YEARS OR WHETHER IT HAPPENS OUTSIDE BECAUSE OF THE PARTICULAR WAY THAT THE U.S. REGULATORY SYSTEM WORKS ON PROHIBITIONS ON FUNDING RATHER THAN REGULATIONS, THAT I'M ASSUMING THAT THESE THINGS WILL HAPPEN. AND SO IT'S THE RELATION BETWEEN THE TWO AND THE KIND OF OVERSIGHT ESPECIALLY OF BASIC SCIENCE AND CLINICAL RESEARCH INTERFACES THAT WERE SET UP USING CIRM FUNDING, OTHER THINGS ABOUT THE LAUNCHPADS FOR THAT DIFFUSION INTO COMMERCIAL CLINICS AND THINGS LIKE THAT.

MR. SHEEHY: SO I JUST WANT TO MAKE A GENERAL COMMENT. WE'VE BEEN LIVING THROUGH THIS SINCE I'VE BEEN ON THIS BOARD. VIRTUALLY SINCE STEM CELL RESEARCH HAS COME UP, WE'VE HAD STEM CELL RESEARCH, STEM CELL CLINICAL WORK TAKING PLACE OUTSIDE THE SANCTION OF THE FDA. ONE OF THE BIGGEST PROBLEMS THEN, WORK THAT'S BEING DONE OUTSIDE ANY

LEGAL SANCTION OUT OF ANY RESEARCH CONTEXT, AND SO THAT'S TAKEN PLACE. SO THAT'S WHAT I HAVE TO LOOK AT. I ALSO HAVE TO LOOK AT WHAT DOES IT TAKE FOR THAT LAST STEP? IT'S ONE THING TO SAY YOU'RE NOT GOING TO FUND RESEARCH WHEN YOU KNOW SOMETHING IS NOT GOING TO HAPPEN, BUT WHAT IS THE REAL COST OF IMPLANTING AN EMBRYO? WHAT IS THE BIG -- THERE'S NO BARRIER THERE, I THINK, THAT'S SO SIGNIFICANT THAT SOMEONE COULD NOT OR WOULD NOT JUST IMPLANT AN EMBRYO. ONCE THAT EMBRYO IS IMPLANTED IT'S IMPLANTED. WE'RE NOT GOING TO FORCE AN ABORTION BECAUSE THEY'VE IMPLANTED A GENETICALLY MODIFIED EMBRYO.

AND SO, AGAIN, I COME BACK, SIMPLY SAYING WE'RE NOT GOING TO FUND IT, I'M NOT SAYING I'M AGAINST THIS RESEARCH GOING FORWARD, I JUST THINK THAT WE NEED TO -- BECAUSE I LOOK AT IT AS BEING A BOARD MEMBER FUNDAMENTALLY. IF WE'RE GOING TO BE COMFORTABLE GOING FORWARD FUNDING THIS, FROM MY PERSPECTIVE, WE HAVE TO TAKE ALL THE STEPS WE CAN LEGALLY TAKE TO PREVENT AN EMBRYO FROM BEING IMPLANTED WITHOUT OUR CONSENT. AND I USE THE WORDS "WITHOUT OUR CONSENT" BECAUSE I DON'T WANT TO SAY IF THIS -- BECAUSE I'M LOOKING BACK AND I'M THINKING THAT AS THE SCIENCE PROGRESSES AND THERE IS A WAY

FOR YOU TO NOT HAVE TO EXPERIENCE SICKLE CELL, I WANT THAT TO BE POSSIBLE. BUT FOR THE RESEARCH TO GO FORWARD, I THINK WE HAVE TO PUT IN THE STRICTEST SAFETY GUIDELINES THAT WE CAN AS AN AGENCY IN ORDER TO ASSURE THE PUBLIC THAT WE'VE DONE EVERYTHING WE CAN UP TO THAT POINT. DOES THAT MAKE SENSE?

SO THAT'S WHERE I'M COMING FROM. WE DON'T HAVE LAWS AGAINST IT. WE HAVE A REGULATORY APPARATUS THAT ONLY GETS ENGAGED ONCE IT'S ASKED TO GET ENGAGED, AND WE'RE BASICALLY SAYING WE'RE JUST NOT GOING TO FUND THE LAST STEP, WHICH IS RELATIVELY INEXPENSIVE AND NOT THAT CUMBERSOME. THAT'S MY FRAMEWORK. AGAIN, IT'S JUST LIKE BEING RESPONSIVE. IT'S NOT TO STOP THE RESEARCH NECESSARILY, BUT ACTUALLY TO FACILITATE THE RESEARCH BY ASSURING THE PUBLIC THAT WE'VE TAKEN EVERY STEP WE CAN TO MAKE SURE THAT EMBRYOS ARE NOT IMPLANTED UNTIL IT'S APPROPRIATE. SO THAT'S MY POINT JUST TO BE CLEAR.

CO-CHAIR LO: ARE THERE OTHER COMMENTS?

MS. BELLCOUERS: I REALLY HEAR WHAT YOU'RE SAYING. AND COMING FROM MY DISCUSSIONS WITH MY COMMUNITY WHERE THERE WERE MANY SCIENTIFIC EXPERIMENTS THAT WERE DONE IN OUR COMMUNITY, SUCH AS THE TUSKEGEE EXPERIMENTS, THERE WAS ALL THE STUFF THAT HAPPENED IN VIETNAM, THERE WAS THE

STERILIZATION OF WOMEN IN CALIFORNIA MINORITIES, BUT WHAT I HAVE TO SAY IS THAT PEOPLE ARE MESSY. AND IF YOU DEVELOP THIS TECHNOLOGY, SOMEBODY IS GOING TO FIND A WAY TO USE IT. I THINK THAT WITHIN THIS ORGANIZATION YOU HAVE PEOPLE WHO ARE REALLY WORKING TO A HIGHER CAUSE, AND I JUST NEED FOR YOU TO KEEP THAT IN MIND BECAUSE I BELIEVE THAT YOUR PEOPLE ARE VETTED. I HAVE SEEN THE KINDS OF THINGS THAT THEY HAVE TO DO. I'VE SEEN REPORTS OF THEIR LABS AND KIND OF PAPERWORK THAT THEY HAVE TO DO. I THINK THE LIKELIHOOD THAT ONE OF THE PEOPLE OR PROJECTS FUNDED BY CIRM IS GOING TO GO AND DO THIS; BUT, AGAIN, PEOPLE ARE MESSY, AND I DON'T KNOW THAT YOU CAN REGULATE PEOPLE'S BEHAVIOR BECAUSE THEY'RE GOING TO KIND OF DO WHAT IT IS THEY DO. BUT I REALLY UNDERSTAND WHAT YOU'RE SAYING BECAUSE I KIND OF GET THAT KIND OF PUSHBACK FROM PART OF MY COMMUNITY TOO IS THAT YOU SHOULDN'T BE MESSING WITH NATURE.

I DON'T KNOW WHERE YOU ARE GOING TO GO WITH THIS, BUT I KIND OF AM ON THE SIDE OF EXPECTING PEOPLE TO BEHAVE IN THE HIGHER -- TAKE THE HIGHER ROAD AND THAT YOU'RE GOING TO HAVE ROGUES. I DO NOT BELIEVE THAT THEY'RE GOING TO BE UNDER THE UMBRELLA OF THIS GROUP, AT LEAST THE QUALITY AND THE PEOPLE I'VE DEALT WITH IN THE LAST FOUR YEARS.

CO-CHAIR LO: SO SOME PEOPLE ARE GOING TO HAVE TO LEAVE SOON. I THINK SHERRY HAS A HARD CUTOFF AT THREE. SO, AGAIN, GOING BACK TO THE IDEA OF WHAT WE WANT TO DO IS MAKE SURE GEOFF LOMAX, SHERRY, AND I HAVE OUR MARCHING ORDERS ON THE ISSUES YOU WANT US TO DIVE DEEP ON, CONSULT WITH YOU ON, AND COME BACK -- SCHEDULE A FOLLOW-UP PUBLIC MEETING OR PHONE CALL MOST LIKELY WHERE WE PRESENT DRAFT RECOMMENDATIONS FOR YOUR APPROVAL OR REFUSAL.

ARE THERE BIG TOPICS? YOU'VE GIVEN US A PRETTY LONG LIST. ARE THERE BIG THINGS THAT YOU THINK WE HAVEN'T DISCUSSED YET THAT ARE JUST BURNING ISSUES? YOU CAN ALSO RAISE THEM IN THE NEXT WEEK OR SO. SAY, OH, MY GOSH. ON MY FLIGHT HOME, I REALIZED WE DIDN'T TALK ABOUT THIS. MAKE SURE WE GET GEOFF STARTED, GEOFF, SHERRY, AND I STARTED ON THE RIGHT TRACK.

SHERRY, DO YOU HAVE ANY COMMENTS?

CO-CHAIR LANSING: NO. I'M SORRY I HAVE TO LEAVE AT THREE, BUT THAT DOESN'T MEAN THE MEETING SHOULDN'T GO ON TILL FOUR OR AS LONG AS YOU WANT. I JUST THINK IT'S BEEN REALLY VERY, VERY STIMULATING FOR ME AS A PATIENT ADVOCATE TO LISTEN. IT'S BEEN VERY, VERY STIMULATING TO LISTEN TO ALL OF THIS. I'M REALLY THRILLED WITH THE DIRECTION THIS IS GOING

INTO. AS I SAID AT THE BEGINNING OF THE MEETING, WE ARE A CONTINUAL WORK IN PROGRESS. WE'LL DIG DEEP. WE'RE LOOKING FOR INPUT FROM ALL OF YOU ALREADY. I THINK WE'VE GOTTEN GREAT INPUT, AND I KNOW WITH YOUR HELP WE'LL COME TO THE RIGHT CONCLUSIONS. NEEDLESS TO SAY, WITH BERNIE'S INCREDIBLE LEADERSHIP.

(APPLAUSE.)

CO-CHAIR LO: FINAL CHARGE FROM YOU AS THE LEADER.

I WANT TO THANK EVERYONE, STARTING WITH OUR SPEAKERS, WHO REALLY, REALLY GAVE US VERY THOUGHTFUL PRESENTATIONS, ANSWERED QUESTIONS. I WANT TO THANK THE PUBLIC FOR COMING AND RAISING ISSUES AND HIGHLIGHTING THINGS. AND I WANT TO THANK THE SWG. YOU'VE RAISED SOME GOOD QUESTIONS. FRANKLY, YOU'VE COME UP WITH ISSUES THAT HAVEN'T BEEN MENTIONED IN REPORTS SO FAR.

CHAIRMAN THOMAS: I WANT TO JUST THANK EVERYBODY. BY THE WAY, FOR THOSE WHO DON'T KNOW, I'M JON THOMAS, CHAIR OF THE CIRM BOARD. FOR THOSE OF YOU WHO HAVE BEEN LONGTIME VETERANS, WHICH THERE ARE MANY, THANK YOU SO MUCH FOR BEING WITH US ALL THESE YEARS. THE CONTINUITY AND THE INSTITUTIONAL MEMORY OF HOW THINGS CAME ABOUT AND HOW THINGS APPLY AS THEY'VE EVOLVED IS ENORMOUSLY BENEFICIAL. AND

FOR THOSE WHO ARE A LITTLE BIT NEWER TO THE GAME, THANK YOU AS WELL. IT'S IMMEASURABLY HELPFUL TO HAVE NEW INPUT AND FRESH INSIGHTS INTO THIS FIELD AS IT EVOLVES REMARKABLY AS QUICKLY AS ANY TIME IN MEDICAL RESEARCH HISTORY. SO I THINK WE'RE ALL PART OF A GRAND RIDE HERE. AND THANK YOU, BERNIE; THANK YOU, SHERRY; THANK YOU, JEFF, THANK YOU SO MUCH. AND SPECIAL SHOUT-OUT TO GEOFF LOMAX FOR PUTTING THIS ALTOGETHER. ON BEHALF OF THE CIRM BOARD, THANKS TO EVERYBODY AND WE WILL CONTINUE OUR DIALOGUE GOING FORWARD.

CO-CHAIR LANSING: I JUST FEEL BAD BECAUSE I THOUGHT YOU WERE GOING TO KEEP TALKING MORE. I WANT TO THANK THE MEMBERS OF THE COMMITTEE ALSO, SOME OF WHOM HAVE BEEN THERE SINCE THE VERY BEGINNING. I LOVE SEEING YOU ALL AGAIN. AND I WANT TO WELCOME THE NEW MEMBERS, SOME OF WHOM I'VE ONLY HEARD THEIR VOICES ON THE PHONE. OBVIOUSLY THE SPEAKERS AND OBVIOUSLY BOTH JEFFS ACTUALLY, SO I DON'T NEED TO SAY ANY MORE EXCEPT THANK YOU, AND WE LOOK FORWARD TO CONTINUING THE DIALOGUE.

(THE MEETING WAS THEN CONCLUDED AT 2:55 P.M.)

REPORTER'S CERTIFICATE

I, BETH C. DRAIN, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT OF THE PROCEEDINGS BEFORE THE SCIENTIFIC AND MEDICAL ACCOUNTABILITY STANDARDS WORKING GROUP OF THE INDEPENDENT CITIZEN'S OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD AT THE LOCATION INDICATED BELOW

SHERATON GATEWAY LOS ANGELES
6101 WEST CENTURY BOULEVARD
LOS ANGELES, CALIFORNIA
ON
THURSDAY, FEBRUARY 4, 2016

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.

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