BEFORE 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:	UNIVERSITY OF CALIFORNIA LOS ANGELES GRAND HORIZON ROOM, COVEL COMMONS LOS ANGELES, CALIFORNIA
DATE:	THURSDAY, OCTOBER 21, 2010 9:30 A.M.
REPORTER:	BETH C. DRAIN, CSR CSR. NO. 7152
BRS FILE NO.:	85136

I N D E X

LOS ANGELES, CALIFORNIA; THURSDAY, OCTOBER 21, 2010

10:23 A.M.

CHAIRMAN KLEIN: THANK YOU. WE'VE HAD THE TREMENDOUS PRIVILEGE OF LISTENING TO A STIMULATING, MOTIVATIONAL, AND INSPIRING PRESENTATION ON NMO OR DEVIC'S DISEASE. WE'VE TAKEN MORE TIME THAN BUDGETED BECAUSE OF THE QUALITY AND IMPORTANCE OF THIS PRESENTATION. AND I'M GOING TO EFFECTIVELY SAVE SOME TIME IN OUR AGENDA BY COMBINING THE EXECUTIVE SESSIONS FOR THE LEADERSHIP AWARD AND FOR TRANSLATIONAL MEDICINE SO WE DON'T HAVE TWO EXECUTIVE SESSIONS.

I WILL ALSO TAKE THE CHAIRMAN'S PREROGATIVE OF MAKING CERTAIN THAT OUR DISCUSSION OF THE LEADERSHIP AWARD IN THE PUBLIC SESSION AND THE DISCUSSION OF THE TRANSLATIONAL MEDICINE IN THE PUBLIC SESSION WILL BE DONE JOINTLY BEFORE THE EXECUTIVE SESSION RATHER THAN HAVING ONE FOLLOW.

FOLLOWING THE EXECUTIVE SESSIONS, WE WILL HAVE ADDITIONAL DISCUSSION ON THESE DISEASES AS WE CONSIDER MOVING ANY OF THESE FROM THEIR RECOMMENDED POSITIONS INTO NEW DESIGNATED POSITIONS.

I'M GOING TO ASK SENATOR ART TORRES WHO HAS A COMMENT TO SPEAK AT THIS POINT.

MR. TORRES: YES. TWO THINGS. THANK YOU SO MUCH, SHERRY, FOR BRINGING THAT PRESENTATION TO US. IT JUST UNDERLIES THE IMPORTANCE OF PATIENT ADVOCATES AND TO GET THEM OUT THERE AND EXPOSE THEIR STORIES AND HOPEFULLY THEIR MESSAGE AS MUCH AS WE CAN.

I LOST A VERY DEAR FRIEND LAST NIGHT, STATE SENATOR JENNY OROPEZA, AGE 53, FROM LIVER, RECTAL CANCER, AND A BLOOD CLOT TOOK HER LIFE LAST NIGHT AT 10 P.M. SHE WAS THE CHAIR OF THE PUBLIC HEALTH COMMITTEE, SHE WAS THE CHAIR OF THE SENATE REVENUE AND TAXATION COMMITTEE, AND I WILL MISS HER DEEPLY, BUT WE WILL MISS HER DEEPLY BECAUSE SHE WAS A TREMENDOUS FORCE IN THE SENATE FOR OUR MISSION. SO GOD BLESS YOU, JENNY.

CHAIRMAN KLEIN: THANK YOU FOR THOSE REMARKS.

TODAY WE ALSO HAVE THE PRIVILEGE OF A NEW BOARD MEMBER. DR. SHLOMO MELMED HAS BEEN APPOINTED BY THE GOVERNOR. DR. MELMED RECEIVED HIS MEDICAL DEGREE WITH DISTINCTION FROM THE UNIVERSITY OF CAPETOWN IN 1970. HE'S BEEN AT CEDARS-SINAI SINCE 1980. HE'S NOW A SENIOR VICE PRESIDENT FOR ACADEMIC AFFAIRS AND DEAN OF THE MEDICAL FACULTY. HE IS ALSO A PROFESSOR AND ASSOCIATE DEAN OF THE UNIVERSITY OF

CALIFORNIA LOS ANGELES, UCLA. AND IN THAT SENSE WE SHARE HIS HOSPITALITY TODAY. AND HE IS DIRECTOR OF THE RESEARCH INSTITUTE AT CEDARS-SINAI MEDICAL CENTER. HE HAS A VERY EXTENSIVE BIOGRAPHY WHICH WE BE WILL POSTING IN ADDITION TO DISTRIBUTING IT TO THE BOARD MEMBERS. BUT, DR. MELMED, THANK YOU FOR SERVING WITH US. IT IS A GREAT HONOR TO HAVE YOU ON THE BOARD. LET US WELCOME HIM.

(APPLAUSE.)

CHAIRMAN KLEIN: IN ORDER NOT TO HAVE THE LEADERSHIP AWARD FOLLOW A GREAT DEAL OF INFORMATION ON THE TRANSLATIONAL RESEARCH AWARDS, AFTER WE DO THE PLEDGE OF ALLEGIANCE AND THE ROLL CALL, AS A MATTER OF INFORMATION, I WILL LEAD WITH THE LEADERSHIP AWARD. WE WILL TRY AND PACE OURSELVES. AND, DR. TROUNSON, BECAUSE WE HAVE SOME BOARD MEMBERS THAT NEED TO LEAVE AT A CERTAIN POINT, I WANT TO SEE WHERE WE CAN GO TIMEWISE IN TERMS OF SCHEDULING THE PRESIDENT'S REPORT. YOU ALWAYS HAVE THESE FABULOUS PRESENTATIONS THAT EVERYONE LOOKS FORWARD TO, BUT WE'RE GOING TO MAKE SURE THIS HAPPENS, BUT I WANT TO MAKE SURE WE GET SOME KEY ITEMS DONE WITHIN OUR QUORUM. AND SO WE NEED TO PACE OURSELVES IF THAT'S ACCEPTABLE. ALL RIGHT. THANK YOU.

MELISSA KING, WILL YOU LEAD US IN THE PLEDGE OF ALLEGIANCE.

(THE PLEDGE OF ALLEGIANCE.)

CHAIRMAN KLEIN: ROLL CALL.

MS. KING: ROBERT BIRGENEAU. FLOYD BLOOM. GORDON GILL FOR DAVID BRENNER.

DR. GILL: HERE.

MS. KING: WILLIAM BRODY. JACOB LEVIN FOR SUSAN BRYANT.

DR. LEVIN: HERE.

MS. KING: MARCY FEIT. MARCY IS JOINING US BY PHONE. MARCY, ARE YOU THERE? COME BACK TO YOU.

MICHAEL FRIEDMAN. LEEZA GIBBONS.

MS. GIBBONS: HERE.

MS. KING: MICHAEL GOLDBERG.

MR. GOLDBERG: HERE.

MS. KING: SAM HAWGOOD. BOB KLEIN.

CHAIRMAN KLEIN: HERE.

MS. KING: SHERRY LANSING.

MS. LANSING: HERE.

MS. KING: TED LOVE. SHLOMO MELMED.

DR. MELMED: HERE.

MS. KING: ED PENHOET. PHIL PIZZO.

DR. PIZZO: HERE.

MS. KING: KEN BURTIS FOR CLAIRE POMEROY.
DR. BURTIS: HERE.
MS. KING: FRANCISCO PRIETO.
DR. PRIETO: HERE.
MS. KING: CARMEN PULIAFITO.
DR. PULIAFITO: HERE.
MS. KING: ROBERT QUINT.
DR. QUINT: HERE.
MS. KING: JEANNIE FONTANA FOR JOHN REED. DUANE ROTH.
MR. ROTH: HERE.
MS. KING: JOAN SAMUELSON. DAVID SERRANO-SEWELL. JEFF SHEEHY.
MR. SHEEHY: HERE.
MS. KING: JON SHESTACK. OSWALD STEWARD. ART TORRES.
MR. TORRES: HERE.
MS. KING: JAMES ECONOMOU FOR EUGENE WASHINGTON.
DR. ECONOMOU: HERE.
CHAIRMAN KLEIN: THANK YOU VERY MUCH. IS IT MY UNDERSTANDING WE HAVE A QUORUM?
MS. KING: WE DO NOT, BUT WITH THE MEMBERS THAT ARE PRESENT BUT NOT YET IN THE ROOM, WE SHOULD.
CHAIRMAN KLEIN: WE HAVE TWO MEMBERS THAT

JUST CAME IN FROM THE BACK.

MS. KING: TED LOVE AND JEANNIE FONTANA.

CHAIRMAN KLEIN: THIS IS A HIGHLY ORCHESTRATED DELIVERY SYSTEM OF A QUORUM. ALL RIGHT.

WE ARE GOING TO BEGIN OUR DISCUSSIONS IF WE COULD. DR. TROUNSON, IF YOU COULD DO THE GENERAL DESCRIPTION OF THE LEADERSHIP AWARD, AND THEN WE'LL GO INTO THE GENERAL DESCRIPTION OF THE TRANSLATIONAL II RESEARCH AWARDS.

DR. TROUNSON: SO DR. MICHAEL YAFFE WILL PROVIDE THAT.

DR. YAFFE: MR. CHAIRMAN, AND MEMBERS OF THE COMMITTEE, I PRESENT FOR YOUR CONSIDERATION RECOMMENDATIONS OF THE GRANTS WORKING GROUP ON THE RESEARCH LEADERSHIP AWARDS. THIS IS ROUND 2, AGENDA ITEM NO. 10 IN YOUR BOOKS.

I WILL GO RATHER QUICKLY IN THE INTEREST OF TIME AND JUST REMIND YOU THAT THE GOALS OF THIS AWARD ARE TO FACILITATE THE RECRUITMENT TO CALIFORNIA OF THE MOST PRODUCTIVE AND PROMISING EARLY TO MIDCAREER SCIENTISTS IN STEM CELL BIOLOGY AND REGENERATIVE MEDICINE. AND ONCE WE RECRUIT THESE INDIVIDUALS SUCCESSFULLY, TO SUPPORT ROBUST AND INNOVATIVE RESEARCH PROGRAMS FOCUSED ON

FUNDAMENTAL STUDIES OF PLURIPOTENT AND PROGENITOR STEM CELL BIOLOGY AND ALSO TRANSLATIONAL STUDIES LEADING TO INNOVATIVE STEM CELL-BASED THERAPIES FOR DISEASES AND INJURY.

THE PROGRAM DETAILS ARE THAT IT'S OPEN TO NONPROFIT CALIFORNIA INSTITUTIONS. CANDIDATES MUST HAVE BEEN INDEPENDENT FOR AT LEAST THREE YEARS. CANDIDATES MUST BE UNDER CONSIDERATION FOR RECRUITMENT TO AN ELIGIBLE FULL-TIME POSITION HERE IN CALIFORNIA. INDIVIDUAL INSTITUTIONS MAY RECEIVE ONLY ONE AWARD DURING THE COURSE OF THIS PROGRAM, AND UP TO EIGHT AWARDS WILL BE MADE OVER A TWO-YEAR PERIOD. ONE AWARD YOU HAVE ALREADY MADE. THIS IS BRINGING TO YOU YOUR CONSIDERATION OF THE SECOND AWARD.

THE AWARD FEATURES ARE RESEARCH SUPPORT FOR UP TO SIX YEARS. AWARDEES MUST COMMIT AT LEAST 75 PERCENT OF THEIR TIME TO STEM CELL AND REGENERATIVE MEDICINE-RELATED RESEARCH. ELIGIBLE COSTS WOULD INCLUDE THE PI'S SALARY, LABORATORY OPERATIONS, LAB RELOCATION, AND EQUIPMENT WHICH CAN BE MATCHED BY THE INSTITUTION, MUST BE MATCHED, FACILITIES AND INDIRECT COSTS AS USUAL.

REVIEW CRITERIA I THINK WE'VE GONE OVER BEFORE. LET ME JUST HIGHLIGHT RESEARCH VISION AND

PLANS WHERE WE CONSIDER SIGNIFICANCE AND INNOVATION. PI ACCOMPLISHMENTS AND POTENTIAL AND THE INSTITUTIONAL COMMITMENT AND THE ENVIRONMENT, RESEARCH ENVIRONMENT.

SO THIS IS CYCLE 2. THE APPLICATION DEADLINE WAS IN MID-JUNE. THE GRANT WAS REVIEWED IN JULY. THIS IS LA1-2068. TITLE IS "DEVELOPMENT OF CELLULAR THERAPIES FOR RETINAL DISEASES." YOU SEE THE REQUESTED FUNDS. THE SCORE OF THIS WAS 85. IT'S RECOMMENDED FOR FUNDING. MR. SHEEHY MAY HAVE COMMENTS OR MR. KLEIN.

CHAIRMAN KLEIN: JEFF, WOULD YOU LIKE TO MAKE ANY COMMENTS?

MR. SHEEHY: I DON'T THINK SO. I THINK THIS IS PRETTY STRAIGHTFORWARD. THANK YOU.

CHAIRMAN KLEIN: DR. YAFFE, DO WE HAVE A KNOWLEDGE OF THE STATUS OF THE COMMITMENT OF THE PROPOSED RECIPIENT?

DR. YAFFE: WE KNOW THAT THE COMMITMENT IS VERY STRONG. WE DELAYED BRINGING THIS TO YOU SO THAT THE CANDIDATE COULD LINE UP AND FINALIZE A NUMBER OF FEATURES. CERTAINLY THE CANDIDATE IS WAITING FOR THIS BOARD'S DECISION ON THEIR AWARD BEFORE, I THINK, MAKING FINAL COMMITMENTS. ALSO HAD AN INDICATION FROM THE INSTITUTION THAT THEY ARE

EXTREMELY OPTIMISTIC THAT THIS IS GOING TO GO FORWARD.

CHAIRMAN KLEIN: THANK YOU. AND THIS HAS CERTAINLY BEEN VERY SUCCESSFUL IN RECRUITING WORLD-CLASS CANDIDATES. DR. TROUNSON, WOULD YOU LIKE TO MAKE A STATEMENT?

DR. TROUNSON: THANK YOU VERY MUCH, CHAIR. I MET WITH THE INSTITUTION, AND THEY PROVIDED ALL OF THE REQUIREMENTS THAT THE CANDIDATE NEEDED. THE CANDIDATE WAS MADE AWARE THAT WE WOULD BE ANNOUNCING, IF THE AWARD WAS WON, HIS NAME IN RELATIONSHIP TO THIS.

I THINK THIS PARTICULAR CANDIDATE IS CLEARLY ONE OF THE BEST SCIENTISTS IN THE WORLD. AND I DON'T THINK THERE'S ANY DOUBT AMONGST PEOPLE THAT I KNOW, COLLEAGUES IN THE SPACE. I THINK IT'S A TERRIFIC MATCH FOR THE INSTITUTION AND THE INSTITUTIONS THAT ARE AFFILIATED WITH THIS APPOINTMENT. AND I THINK IT WILL ATTRACT A LOT OF ENERGY IN THE AREAS OF TRANSLATION AROUND THE WORK OF THIS INDIVIDUAL, AND IT WILL BE SOMETHING THAT WE'LL BE INCREDIBLY PROUD OF.

SO I JOIN THE GRANTS WORKING GROUP IN A VERY STRONG ENDORSEMENT FOR THIS PARTICULAR INDIVIDUAL. AND WE'RE QUITE HAPPY TO RELEASE THAT

NAME IF THAT'S WHAT YOU WANT TO DO. AND THE INDIVIDUAL IS AWARE AND SO IS THE INSTITUTION AWARE THAT THAT WILL BE DONE ANYWAY TODAY IF IT WAS AWARDED.

CHAIRMAN KLEIN: CERTAINLY. JUST KEEPING WITH OUR PROCESS AND MAKING CERTAIN IN OUR PROCESS THAT THERE WILL BE INDIVIDUALS THAT COME BEFORE US THAT ARE NOT AWARDED, AND WE DON'T ANNOUNCE THE NAME UNTIL AFTER THE EXECUTIVE SESSION. WE GET A SENSE PENDING THE VOTE; AND IF THE VOTE IS POSITIVE, WE WILL BE ANNOUNCING THIS NAME OF WHAT IS CLEARLY, AS YOU SAY, ONE OF THE WORLD'S LEADING SCIENTISTS IN THE FIELD. SO I THINK WE'LL ANNOUNCE IT AT THAT TIME, MR. PRESIDENT.

I WOULD ALSO LIKE TO SEE IF THERE'S ANY PUBLIC COMMENT OR OTHER BOARD COMMENTS ON THIS APPLICATION. SEEING NO PUBLIC COMMENT, I WILL ASK THAT -- WE ARE GOING TO ANNOUNCE THE EXECUTIVE SESSIONS STATUTORY PROVISIONS FOR THIS AT THE SAME TIME AS WE ANNOUNCE THE STATUTORY PROVISIONS FOR THE FOLLOWING ITEM.

WE WILL MOVE IMMEDIATELY INTO ITEM 9, EARLY TRANSLATION II RESEARCH AWARDS. AND WE'RE GOING TO DO A PUBLIC PRESENTATION OF THIS ITEM, THE CRITERIA, THE RELATIVE RANKINGS. TRY AND

IDENTIFY -- REMEMBER FOR ALL THE BOARD MEMBERS, LET US TRY AND IDENTIFY IN THE PUBLIC SESSION IF WE CAN ALL OF THE APPLICATIONS BY NUMBER THAT WE'D LIKE TO HAVE DISCUSSED, SEE IF THERE'S ANY GENERAL COMMENTS THE SCIENTIFIC STAFF WANTS TO MAKE ABOUT THOSE THAT ARE NONPROPRIETARY, GET ANY PUBLIC COMMENT ON ANY APPLICATION, THEN WE WILL GO INTO EXECUTIVE SESSION AND COME BACK AND HAVE DRILLED-DOWN DISCUSSIONS ON ANY APPLICATIONS AND THE APPROVALS OF APPLICATIONS THAT WILL MOVE FORWARD.

WITH THAT, DR. TROUNSON, HOW WOULD YOU LIKE THIS TO BE PRESENTED?

DR. TROUNSON: I'D LIKE TO HAVE IT PRESENTED BY DR. LILA COLLINS IF THAT'S OKAY WITH YOU.

CHAIRMAN KLEIN: THANK YOU. DR. COLLINS.

DR. COLLINS: THANK YOU. GOOD MORNING, MR. CHAIRMAN AND LADIES AND GENTLEMEN OF THE BOARD, CIRM MEMBERS, AND GUESTS.

TODAY I'D LIKE TO REFRESH YOU FIRST REGARDING OUR SECOND CALL OF THE EARLY TRANSLATIONAL RFA. AND THEN I'D LIKE TO PRESENT TO YOU THE RECOMMENDATIONS FROM OUR RECENT GRANTS WORKING GROUP MEETING LAST MONTH.

SINCE WE HAVEN'T DISCUSSED THIS RFA IN

DETAIL SINCE CONCEPT CLEARANCE LAST DECEMBER, FIRST I'D LIKE TO ORIENT YOU WHERE THE RFA FALLS ON CIRM'S DEVELOPMENTAL PIPELINE. AND REALLY THE GOAL OF THIS RFA IS TO BEGIN TO TRANSLATE BASIC STEM CELL DISCOVERIES TO THE POINT WHERE THEY CAN ULTIMATELY BE DEVELOPED INTO TREATMENTS FOR HUMAN DISEASE.

NOW, EARLY TRANSLATIONAL II WILL SUPPORT PROGRESSION OF PROJECTS UP TO THE DEVELOPMENT CANDIDATE STAGE. AND A DEVELOPMENT CANDIDATE IS A POTENTIAL THERAPY THAT'S READY FOR IND-ENABLING PRECLINICAL DEVELOPMENT. SO HOPEFULLY BY THE END OF THE EARLY TRANSLATIONAL II FUNDING PERIOD, CIRM WILL HAVE DEVELOPMENT CANDIDATES READY TO APPLY FOR FUNDING UNDER RFA'S SUCH AS DISEASE TEAMS II. AND EXAMPLES OF THE TYPES OF ACTIVITIES TO BE PURSUED UNDER THESE AWARDS WOULD INCLUDE PRECLINICAL PROOF OF CONCEPT STUDIES TO DEMONSTRATE DISEASE MODIFYING ACTIVITY IN RELEVANT MODELS AS WELL AS PROCESS DEVELOPMENT AND ASSAY DEVELOPMENT ACTIVITIES.

SO IN DECEMBER YOU APPROVED TWO AWARD TYPES. AND BY FAR THE MOST COMPREHENSIVE AND FIRST AWARD TYPE I'D LIKE TO DISCUSS IS THE DEVELOPMENT CANDIDATE AWARD CLASS, AND YOU MAY HEAR ME SLIP INTO CALLING THESE DC'S. A DEVELOPMENT CANDIDATE IN MY MIND IS ACTUALLY FAIRLY ADVANCED. AS I MENTIONED,

BY THE END OF THE AWARD, WE HOPE TO HAVE DEVELOPMENT CANDIDATES READY FOR IND-ENABLING STUDIES. AND BASICALLY THAT MEANS THAT YOU HAVE A CANDIDATE THERAPY WHERE IT'S KNOWN TO BE EFFECTIVE IN MODELS OF DISEASE OR INJURY. IT CAN BE MADE CONSISTENTLY AND AT ADEQUATE SCALE AND PURITY TO SUPPORT PRECLINICAL STUDIES, IS FAIRLY WELL CHARACTERIZED, AND THERE ARE IN PLACE ASSAYS TO CHARACTERIZE IDENTITY, PURITY, AND SOME PRELIMINARY POTENCY ACTIVITIES. IN ADDITION, WOULD LIKE TO HAVE SOME IDEA OF MECHANISM OF ACTION OR HOW THE CANDIDATE THERAPY WORKS.

SO IN ALL HONESTY, FOR A STEM CELL-BASED THERAPY TO ACHIEVE THIS MILESTONE IN THREE YEARS, IT'S QUITE LIKELY THAT SIGNIFICANT, COMPELLING PRELIMINARY DATA WILL NEED TO BE IN PLACE AT THE TIME OF APPLICATION. AND I'LL GO OVER SOME OF THE KEY REQUIREMENTS OF DEVELOPMENT CANDIDATES IN THE NEXT SLIDE.

BEFORE I DO THAT, I'D LIKE TO DISCUSS THE SECOND CLASS OF AWARDS TO BE FUNDED UNDER THIS RFA, AND THOSE ARE THE DEVELOPMENT CANDIDATE FEASIBILITY AWARDS. AND YOU CAN THINK OF THESE AS KIND OF A BRIDGE TO SEE IF YOUR STEM CELL DISCOVERY MIGHT BE SUITABLE FOR FURTHER DEVELOPMENT INTO A DEVELOPMENT

CANDIDATE.

SO THE GOAL IS REALLY TO DETERMINE THE FEASIBILITY OF A CANDIDATE APPROACH. FOR EXAMPLE, A COMPANY MIGHT LIKE TO SEE SOME ACTIVITY OF RESEARCH GRADE MATERIAL IN A DISEASE MODEL BEFORE FURTHER COMMITTING ADDITIONAL RESOURCES TOWARDS ACTIVITIES LIKE PROCESS DEVELOPMENT.

ANOTHER EXAMPLE MIGHT BE A CANDIDATE STEM CELL THERAPY THAT YOU KNOW WORKS IN DISEASE MODELS, BUT YOU AREN'T SURE IF IT CAN BE PREPARED AT ADEQUATE SCALE OR IN A METHOD THAT'S COMPLIANT WITH REGULATORY REQUIREMENTS. SO THOSE WOULD BE IDEAL SORT OF DEVELOPMENT CANDIDATE FEASIBILITY STUDIES.

SO I THINK OF THESE AS SORT OF PRODUCT ORIENTED-RESEARCH AWARDS WHERE THE FULL SPECTRUM OF ACTIVITIES TO ACHIEVE A DEVELOPMENT CANDIDATE DON'T NEED TO BE COMPLETED, BUT YOU STILL WANT TO EVALUATE A POTENTIAL THERAPY. SO THESE ARE A BIT MORE FLEXIBLE THAN THE DEVELOPMENT CANDIDATE AWARDS IN THAT ONLY A SUBSET OF THE ACTIVITIES TO ACHIEVE A DEVELOPMENT CANDIDATE ARE REQUIRED.

THESE ARE THE KEY REQUIREMENTS OF DEVELOPMENT CANDIDATES THAT WE'D LIKE TO SEE AT THE END OF THE AWARD PERIOD, AND WE'RE LOOKING REALLY AT FIVE KEY AREAS. WE WANT CANDIDATES THAT ARE, OF

COURSE, SUITABLE FOR HUMAN USE AND COMPATIBLE WITH REGULATORY PROGRESSION. THAT MEANS THAT ULTIMATELY THESE WILL NEED TO BE PREPARED UNDER GMP, BUT NOT DURING THE COURSE OF THIS AWARD. WE'RE JUST LOOKING THAT THOSE PROCESSES BE COMPATIBLE.

AS FAR AS PRECLINICAL ACTIVITY, WE'RE LOOKING TO SEE THAT THE CANDIDATES ARE EFFECTIVE IN DISEASE MODELS, AND WE'D LIKE TO HAVE AN IDEA OF HOW THEY'LL BE DELIVERED AS WELL AS SOME MECHANISM OF ACTION. WE'RE SUPPORTING EARLY PROCESS DEVELOPMENT EFFORTS. WHAT WE'RE LOOKING FOR THERE IS CONSISTENT PRODUCTION AT HIGH PURITY. AND, AGAIN, WE'D LIKE TO SEE A PROCESS THAT CAN BE SCALED UP AND ULTIMATELY BE MADE COMPATIBLE WITH GMP.

AS FAR AS ASSAY DEVELOPMENT, WE'RE LOOKING NOT FOR FINALIZED, VALIDATED ASSAYS AT THIS STAGE, BUT RESEARCH GRADE ASSAYS TO ASSESS SOME IDENTITY AND COMPOSITION OF THE CANDIDATE.

AND FINALLY, SOME ADDITIONAL PRECLINICAL CHARACTERIZATION IN TERMS OF BIODISTRIBUTION OR FORMULATION SHOULD ALSO BE DETERMINED UNDER THIS RFA.

WITH THIS IN MIND, I'D LIKE TO BRIEFLY HIGHLIGHT THE REVIEW CRITERIA SO WE CAN DISCUSS HOW THESE PROPOSALS WERE EVALUATED. AND THESE ARE

FAMILIAR REVIEW CRITERIA. SO I'D LIKE TO JUST HIGHLIGHT TWO KEY AREAS THAT I THINK ARE PARTICULARLY RELEVANT TO THIS RFA. AND THE FIRST I'D LIKE TO DISCUSS IS FEASIBILITY. AND THAT WOULD BE BECAUSE WE HAVE TWO DIFFERENT AWARD CLASSES AND THEY WERE EVALUATED DIFFERENTLY. AND REALLY THE FEASIBILITY IS THE AREA WHERE THEY DIFFERED, SO I'D LIKE TO DRAW YOUR ATTENTION.

AND ONE THING THAT WE DID FOR THE DEVELOPMENT CANDIDATE AWARDS, BECAUSE THERE'S A DEFINED SET OF END POINTS THAT WE WANT FOR THESE, EVALUATION OF THESE AWARDS WERE FOCUSED, IN ADDITION TO ON THE PRELIMINARY DATA AND THE QUALITY OF THE PLAN, THEY WERE FOCUSED ON COMPLETENESS. IN ORDER TO ACHIEVE THAT, IN ADDITION TO BEING EVALUATED BY THE GRANTS WORKING GROUP MEMBERS WITH EXPERTISE IN THE AREA OF DISEASES OR INJURIES BEING STUDIED AND THE APPROACHES BEING TAKEN, THESE WERE ALSO EVALUATED BY SPECIALISTS WHO WERE FAMILIAR WITH THE FDA REGULATORY PRACTICES AND CELL THERAPY DEVELOPMENT, AS WE SAW FOR DISEASE TEAMS I.

SO FOR THE DEVELOPMENT CANDIDATE FEASIBILITY AWARDS, THESE WERE EVALUATED ON THE PRELIMINARY DATA, OF COURSE, AND THE QUALITY OF THE PLAN, BUT THE COMPLETENESS WASN'T A REQUIREMENT FOR

THESE. AND THE TWO AWARDS WERE REVIEWED SEPARATELY AND ON DIFFERENT DAYS.

AND I'D ALSO LIKE TO HIGHLIGHT UNDER OBJECTIVES, THE TARGET PRODUCT PROFILE THAT WOULD BE ULTIMATELY THE PATIENT POPULATION THAT WOULD BE TARGETED BY THESE DRUGS IN ADDITION TO WE WANT TO SEE A MEANINGFUL IMPACT ON DISEASE, SO THESE WERE -- ALSO PARTICULAR ATTENTION WAS GIVEN TO THE APPROPRIATENESS OF DISEASE MODEL SELECTED, AND THE REMAINING CRITERIA, I THINK, ARE FAMILIAR TO US. SO I'D LIKE TO MOVE TO THE NEXT SLIDE.

AT CONCEPT CLEARANCE YOU APPROVED A MAXIMUM BUDGET OF $60 MILLION FOR DEVELOPMENT CANDIDATE AWARDS AND $20 MILLION FOR THE DEVELOPMENT CANDIDATE FEASIBILITY AWARDS FOR A PROGRAM MAXIMUM COST OF $80 MILLION.

AND NOW I'D LIKE TO MOVE TO THE RESULTS OF THE WORKING GROUP EVALUATION. SO I'VE INCLUDED THESE HISTOGRAMS TO AGAIN REITERATE THAT THE TWO AWARDS CLASSES WERE REVIEWED AND RECOMMENDED SEPARATELY, AND THE TOP HISTOGRAM IS THE SCORES OF THE DEVELOPMENT CANDIDATE APPLICATIONS. AND YOU CAN SEE THOSE LITTLE NUMBERS, THAT THE DEVELOPMENT CANDIDATE RECOMMENDATION LINE WAS SET AT ABOUT 74 AND UP; WHEREAS, THE DEVELOPMENT CANDIDATE

FEASIBILITY AWARDS WERE RECOMMENDED AT A SLIGHTLY LOWER SCORE OF 71 AND UP.

AND SO OUR FINAL TOTAL RECOMMENDATIONS ARE ON THE NEXT SLIDE FOR 12 DEVELOPMENT CANDIDATE AWARDS AND SIX DEVELOPMENT CANDIDATE FEASIBILITY AWARDS FOR A TOTAL OF $66 MILLION. AS YOU MAY RECALL FROM CONCEPT CLEARANCE, THE ACHIEVEMENT OF PLURIPOTENT STEM CELL-DERIVED DEVELOPMENT CANDIDATES WERE A PRIORITY FOR THIS RFA. AND OF THE TOTAL RECOMMENDED AWARDS, EIGHT ARE UTILIZING PLURIPOTENT STEM CELLS.

AND WE'LL DISCUSS INDIVIDUAL APPLICATIONS NEXT. BUT IF YOU LOOK IN YOUR BINDERS, YOU SHOULD HAVE A SUMMARY TABLE WITH BRIEF DESCRIPTORS OF THE DISEASES ADDRESSED AS WELL AS THE SELECTED APPROACHES FOR ALL OF THE APPLICATIONS IN THIS ROUND. AND THAT CONCLUDES MY SUMMARY.

CHAIRMAN KLEIN: ALL RIGHT. AND COULD WE IDENTIFY THOSE APPLICATIONS THAT HAVE EXTRAORDINARY PETITIONS FILED SO THAT WE CAN JUST ASK THE BOARD MEMBERS IF THEY WOULD LIKE TO HAVE ANY OF THOSE DISCUSSED? AND JUST TELL US WHAT THE SUBJECT MATTER IS OF THE APPLICATION, PLEASE.

DR. SAMBRANO: SO THE PETITIONS CAME IN FOR APPLICATION 1763, 1797, 1768, AND 1785. 1763

AND 1797 RELATE TO CANCER, LEUKEMIAS. 1768 HAS TO DO WITH EYE DISEASE, AND 1785 WITH SPINAL CORD INJURY AND RECOVERY OF BLADDER CONTROL.

MS. KING: BOARD MEMBERS HAVE BOTH THE EXTRAORDINARY PETITIONS THEMSELVES AND THE STAFF RESPONSES TO THEM IN YOUR BINDERS. IN THE POCKET IN THE FRONT OF YOUR BINDERS, YOU HAVE THOSE FOUR DOCUMENTS.

CHAIRMAN KLEIN: SO, DR. SAMBRANO, 1763, 1768, AND WHAT WAS 1797 AND 1785? WHAT WERE THOSE SUBJECT MATTERS?

DR. SAMBRANO: 1797 IS LEUKEMIAS, AS WELL AS 1768.

CHAIRMAN KLEIN: OKAY. MR. SHEEHY, IF YOU'D PLEASE FOR GENERAL COMMENTS AS WELL AS ANY SPECIFIC COMMENTS YOU'D LIKE TO MAKE.

MR. SHEEHY: WELL, FIRST, I DO THINK WE SHOULD TAKE UP 1768. AND IT WOULD BE HELPFUL IF YOU COULD DISTINGUISH BETWEEN WHICH ONES ARE DEVELOPMENT CANDIDATES AND WHICH ONES ARE DEVELOPMENT CANDIDATE FEASIBILITY.

DR. SAMBRANO: SURE. SO IT'S UP ON THE CHART, AND I THINK IT SHOULD BE ALSO IN YOUR NOTEBOOKS IN TERMS OF THE TYPE. JUST I'D READ THEM OUT. OF THE ONES THAT DID RECEIVE PETITIONS, 1763

IS A DEVELOPMENT CANDIDATE, 1797 IS A DEVELOPMENT CANDIDATE, 1768 IS A FEASIBILITY, AND 1785 IS ALSO A FEASIBILITY.

MR. SHEEHY: SO WOULD THE CHAIR ALLOW ME SOME GENERIC COMMENTS ABOUT THE REVIEW?

CHAIRMAN KLEIN: ABSOLUTELY. AS THE VICE CHAIR OF THE WORKING GROUP, PLEASE GIVE US SOME FRAMEWORK FOR THIS ENTIRE REVIEW.

MR. SHEEHY: WELL, FIRST OF ALL, I THOUGHT WE HAD AN OUTSTANDING PROGRAMMATIC REVIEW. AND I ALWAYS THINK IT'S GOOD WHEN THEY DON'T RUN DOWN STRAIGHT IN NUMERICAL ORDER, KIND OF INDICATES THAT THEY WERE VERY THOUGHTFUL AND WERE MOVING THINGS AROUND WITH SOME REAL ATTENTIVENESS.

I WOULD LIKE TO NOTE THAT, AT LEAST FROM MY PERSPECTIVE, THAT THE DEVELOPMENTAL CANDIDATE REVIEW, I THOUGHT, WENT REALLY WELL. IT WAS INCREDIBLY RIGOROUS. THE GRANTS THAT MOVED FORWARD, IN FACT, WERE AHEAD OF WHAT WE INITIALLY TRIED TO SET OUT. WE GOT 12 WHEN WE WERE LOOKING FOR TEN. AND FRANKLY, AS A PERCENTAGE OF APPLICATIONS, IT'S EVEN A BIT HIGHER THAN WHAT WE USUALLY DO.

HOWEVER, ON THE DISEASE CANDIDATE FEASIBILITY AWARDS, I THINK I DID FEEL LIKE THAT THERE WAS SORT OF AN OVERHANG. WE DID THE

DEVELOPMENT CANDIDATE AWARDS FIRST WITH THE COMPLETENESS, A REAL RIGOR, LIKE, YOU ARE AT THE END OF THIS PROCESS GOING TO HAVE A CANDIDATE, A PRODUCT THAT YOU ARE GOING TO BE ABLE TO MOVE FORWARD WITH. AND I FELT LIKE THERE WAS ALMOST A HANGOVER FROM THAT ON THE DISEASE CANDIDATE FEASIBILITY AWARDS, WHICH IS REFLECTED IN THE FACT THAT WE ONLY HAVE FIVE GOING FORWARD.

AND SO ONE OF THE REASONS WHY I THINK 1768 IS INTERESTING IS THAT IT IS, FRANKLY, THE HIGHEST DCF THAT DIDN'T MAKE IT. AND SO I THINK, AT LEAST FOR ME, THOSE ARE THE ONES, IF I'M GOING TO GIVE SOMETHING A SECOND LOOK, THAT'S WHERE I WOULD BE LOOKING BECAUSE I DON'T THINK -- I THOUGHT THE DEVELOPMENT CANDIDATES, THAT WAS SO CLEAR AND PEOPLE WERE -- WE HAD REGULATORY SPECIALISTS. I APPLAUD STAFF FOR BRINGING THE REGULATORY SPECIALISTS IN SO THAT PEOPLE WERE REALLY CLEAR ABOUT HEADING DOWN A PRODUCT PATHWAY.

BUT THE DEVELOPMENT CANDIDATE FEASIBILITY, THAT KIND OF RIGOR KIND OF BLED OVER INTO THAT ANALYSIS. AND I'M NOT SURE THAT THERE WERE NOT SOME INTERESTING PROJECTS IN THAT WITH SOME INTERESTING CANDIDATES THAT WERE A LITTLE BIT EARLIER IN THE DEVELOPMENTAL PATHWAY THAT WE MIGHT WANT TO TAKE A

LOOK AT.

CHAIRMAN KLEIN: ALL RIGHT. DR. TROUNSON.

DR. TROUNSON: TOTALLY DIFFERENT MATTER, BUT, CHAIR, I THINK THE BOARD SHOULD DISCUSS 1789 AND 1857 BECAUSE THE GRANTS WORKING GROUP HAD SOME VIEWS ABOUT THEIR SUPPORT OF THOSE TWO PROJECTS, AND I THINK SOME REVISIONS OF THE TOTAL PROJECTS, THEY MADE SOME RECOMMENDATIONS ABOUT WHAT MIGHT BE REVISED IN THOSE PROJECTS. SO I THINK THEY'LL NEED TO BE DISCUSSED BECAUSE OF THOSE RECOMMENDATIONS FROM THE GRANTS WORKING GROUP REVIEW.

SO IF YOU DON'T MIND MAKING A NOTE OF THESE, WE'LL EXPLAIN THE ISSUES TO YOU IN THE EXECUTIVE SESSION AND REMIND THOSE THAT WERE THERE AT THE MEETING ABOUT THAT.

CHAIRMAN KLEIN: CERTAINLY, DR. TROUNSON. AND AFTER WE'VE COVERED ANY EXTRAORDINARY PETITIONS WE WANT TO BRING THE ATTENTION OF THE BOARD AND THE PUBLIC, IF THERE COULD BE A GENERAL PRESENTATION BY THE STAFF ON THE TWO APPLICATIONS YOU'VE JUST MENTIONED SO THAT THERE IS A FRAMEWORK FOR THE PROPRIETARY DISCUSSION. FIRST, WE WILL DEAL WITH ANY OTHER IDENTIFICATION OF APPLICATIONS, WHETHER EXTRAORDINARY PETITIONS ACTUALLY OR NOT, AND THEN PERHAPS WE COULD HAVE SOME PRESENTATIONS ON THOSE

TWO APPLICATIONS.

DR. SAMBRANO: I JUST WANTED TO POINT OUT THAT IN YOUR BOOKS YOU ALSO HAVE A COMPILATION OF THE PROGRAMMATIC DISCUSSION IN A SINGLE SHEET. SO WE'VE INCLUDED THE PROGRAMMATIC DISCUSSION AS PART OF THE SUMMARY FOR EACH APPLICATION. BUT JUST FOR YOUR CONVENIENCE, YOU CAN LOOK AT THE SPECIFIC PROGRAMMATIC DISCUSSION OF ABOUT EIGHT OR NINE THAT HAD SUBSTANCE, SO WE COMPILED THOSE IN A DOCUMENT FOR YOU.

CHAIRMAN KLEIN: THANK YOU.

MR. SHEEHY: WHERE IS THAT AT?

DR. SAMBRANO: IT SHOULD BE IN THE SAME TAB.

CHAIRMAN KLEIN: MELISSA KING, IF YOU COULD TAKE A MIC, PLEASE.

MS. KING: IT IS BEHIND TAB 9.

CHAIRMAN KLEIN: MELISSA KING IS STATING IT'S BEHIND TAB 9. DR. TROUNSON, YOU SAID 1789, AND WHAT WAS THE SECOND ONE?

DR. TROUNSON: 1857. I DON'T KNOW IF YOU WANT ME TO COMMENT ON IT, WHETHER YOU NEED TO INDICATE THERE MIGHT BE CONFLICTS OF INTEREST OVER THOSE.

CHAIRMAN KLEIN: RIGHT.

DR. TROUNSON: I WAS ONLY GOING TO MAKE GENERALIZED COMMENT, BUT THAT WOULD REFLECT THE GRANTS WORKING GROUP VIEW.

CHAIRMAN KLEIN: THE CONFLICTS ISSUE WOULD COME BEFORE ANY BOARD DISCUSSION. SO ONE ITEM HERE, DUANE ROTH, DID YOU HAVE A QUESTION?

MR. ROTH: I'M STILL TRYING TO FIND THIS ONE.

MS. KING: IT'S NOT IN THERE. WE DIDN'T GET THAT DOCUMENT. THERE WAS A MISCOMMUNICATION.

CHAIRMAN KLEIN: SO IN THE SPIRIT OF TRYING TO MOVE FORWARD TO A NEW LEVEL OF SOPHISTICATION, THE DOCUMENT HAS BEEN PRODUCED, BUT IT LOOKS LIKE WE DIDN'T GET IT IN TIME FOR THE BINDER. IF ONE OF THE STAFF MEMBERS CAN SEE IF --

MS. KING: AMY CAN MAKE COPIES OF IT.

CHAIRMAN KLEIN: THAT'S VERY HELPFUL. SO WE WILL LOOK FORWARD TO THAT INFORMATION. THANK YOU VERY MUCH. AND THANK YOU FOR THE SPECIAL EFFORT, DR. SAMBRANO AND THE SCIENTIFIC STAFF, FOR MOVING THAT REFINEMENT OF THE PROCESS FORWARD. WE REALLY APPRECIATE IT.

ALL RIGHT. ADDITIONAL ITEMS THAT INDIVIDUALS WOULD LIKE TO IDENTIFY.

DR. TROUNSON: DID YOU WANT ME TO MAKE

SOME COMMENT ON THOSE?

CHAIRMAN KLEIN: YES. SO, IN FACT, DR. TROUNSON, BECAUSE THOSE ARE FAIRLY COMPLICATED, WE WILL DEFINITELY WANT YOU TO MAKE THOSE COMMENTS. BUT FIRST LET ME GET A SENSE OF HOW MANY MEMBERS OF THE AUDIENCE WOULD LIKE TO SPEAK AND WHICH APPLICATIONS THEY WOULD LIKE TO SPEAK ON. COULD YOU JUST GO TO THE MIC TO IDENTIFY THE APPLICATION? WE'RE GOING TO ORGANIZE THE COMMENTS SEPARATELY.

MR. SAVINE: THE APPLICATION, MR. CHAIRMAN, THAT I'D LIKE TO SPEAK ON IS 1841, THE DEVELOPMENT CANDIDATE FOR HUNTINGTON'S DISEASE. MY NAME IS CHARLES SAVINE.

CHAIRMAN KLEIN: OKAY. FINE. WE'RE GOING TO MAKE SURE YOU HAVE THE OPPORTUNITY TO DO THAT. ADDITIONAL SPEAKERS?

DR. BHATIA: I'D LIKE TO SPEAK ABOUT 1763, TARGETING SIRT1 IN LEUKEMIA STEM CELLS. MY NAME IS RAVI BHATIA. I'M FROM CITY OF HOPE.

CHAIRMAN KLEIN: 1763. ALL RIGHT.

DR. LAM: I'M KIT LAM FROM UC DAVIS. I WANT TO SPEAK FOR THE 1797, TARGETING NANOTHERAPEUTICS TO ERADICATE AND CURE LEUKEMIA STEM CELLS.

CHAIRMAN KLEIN: ALL RIGHT.

DR. HAVTON: MY NAME IS LEIF HAVTON. I'D LIKE SPEAK ON BEHALF OF 1785, A PROPOSAL WITH TITLE "REPAIR OF CONUS MEDULLARIS/CAUDA EQUINA INJURY USING HUMAN ES CELL-DERIVED MOTOR NEURONS," A PROPOSAL THAT WAS SUBMITTED THROUGH UCLA.

CHAIRMAN KLEIN: ALL RIGHT.

DR. DENG: MY NAME IS SOPHIE DENG FOR PROPOSAL 1768 ENTITLED "REGENERATION OF FUNCTIONAL LIMBAL STEM CELLS FOR TRANSPLANTATION."

CHAIRMAN KLEIN: THANK YOU VERY MUCH. WE WILL BE INFORMED TODAY.

SO GIVEN THE COMPLEXITY OF THE REVIEWS ON THE TWO APPLICATIONS THAT YOU RAISED, DR. TROUNSON, I THINK IT WOULD BE GOOD TO BEGIN ACTUALLY WITH THOSE. THEY MAY OFFER US SOME SIGNIFICANT CHALLENGE. AND WHY DON'T WE HAVE WHOMEVER YOU'D LIKE TO DESIGNATE TO BEGIN WITH THOSE REVIEWS.

DR. TROUNSON: I THINK WE'LL ASK THE STAFF OFFICER TO COME FORWARD, BUT IT'S FAIRLY SIMPLE IN TERMS OF THE PROPOSALS, THE RECOMMENDATIONS TO THE GRANTS WORKING GROUP.

IN THE FIRST ONE, 1789, THE GRANTS WORKING GROUP RECOMMENDED THAT THE PROSTATE CANCER PORTION AND ASSOCIATED SUBCONTRACT BE EXCISED AND THE BUDGET ADJUSTED TO REFLECT THE CHANGES. THEY FELT VERY

STRONGLY ABOUT THE BLOOD DISEASE COMPONENT OF THAT PROJECT, BUT THEY FELT VERY NEGATIVE ABOUT THE PROSTATE CANCER SECTION OF THAT PROJECT.

IF YOU WOULD LIKE, THE SCIENCE OFFICERS OR MYSELF TO DISCUSS THAT FURTHER --

CHAIRMAN KLEIN: I THINK IT IS IMPORTANT TO JUST GIVE US THE FRAMEWORK FOR IT, PLEASE.

DR. TROUNSON: ESSENTIALLY THE FRAMEWORK IS THAT THIS IS A LEADING SCIENTIST IN THE AREA OF BLOOD DISEASES WHO BELIEVES THAT THE MOVEMENT INTO THE PROSTATE CANCER SECTION WOULD BE A VIABLE PART OF THE PROJECT. THE REVIEWERS FELT THAT THERE WAS LITTLE EVIDENCE PROVIDED FOR THAT, THAT THAT WORK WOULD BE OF ANY REAL SIGNIFICANCE.

SO I DON'T KNOW IF ONE OF THE SCIENCE OFFICERS, GIL WANTS TO SPEAK SPECIFICALLY ON IT. MICHAEL YAFFE CAN PROVIDE YOU SOME FURTHER DETAILS OF THAT IF YOU WISH.

CHAIRMAN KLEIN: DR. YAFFE, IF YOU COULD GIVE US THE KEY POINTS IN OUTLINE. MY UNDERSTANDING HERE IS RECOMMENDATION TO FUND THE LEUKEMIA WORK, BUT NOT THE PROSTATE WORK. THE PROSTATE WORK, ONE OF THE FUNDAMENTAL CRITICISMS WAS IT WASN'T REALLY RELATED TO THE CORE STUDY THAT THEY WERE DOING UNDER THE PRIMARY PI'S EXPERIENCE. SO WOULD YOU GIVE US

SOME ORIENTATION?

DR. YAFFE: THAT'S CORRECT. AND THE PROPOSAL HAD THREE SPECIFIC AIMS. THE FIRST TWO RELATED TO LEUKEMIC AND BLOOD CANCER WERE WELL DEVELOPED, WELL RECEIVED BY THE REVIEW COMMITTEE, AND FELT TO BE EXTREMELY STRONG AND IMPORTANT.

THE THIRD SPECIFIC AIM WAS TO EXTEND THESE STUDIES INTO PROSTATE CANCER. REVIEWERS WERE CONCERNED ABOUT A NUMBER OF FEASIBILITY ASPECTS OF THAT WORK, INCLUDING THE PROPOSED XENOGRAFT MODEL, WHICH HAS NOT BEEN DEVELOPED AND HAS NOT BEEN VALIDATED. QUESTIONS ABOUT WHETHER THE MODEL, IN FACT, REVEALS FEATURES OF METASTASES TO BONE AND OTHER FEATURES COMMON TO PROSTATE CANCER. SO THERE WAS A STRONG CONCERN ABOUT THAT.

THERE WAS ALSO DOUBT OR SOME QUESTION ABOUT THE NATURE OF THE RELATIONSHIP OF THE CANCER STEM CELL MODEL UPON WHICH THE EARLIER RESEARCH IS BASED AND THE BEHAVIOR OF CANCER CELLS IN THE PROSTATE. SO IT WAS FELT THAT THAT PART OF THE WORK WAS MUCH MORE BASIC, DID NOT BELONG IN A TRANSLATIONAL GRANT, AND WAS NOT CONTRIBUTING TO MEANINGFUL MEDICAL ADVANCES AT THIS STAGE OF RESEARCH. FOR THAT REASON, THEY RECOMMENDED ALTERING THE GRANT IN THE GRANTS WORKING GROUP IN

PROGRAMMATIC, RECOMMENDED SUPPORTING AND FUNDING THIS WITH DELETION OF THE THIRD SPECIFIC AIM AND AN APPROPRIATE CHANGE IN THE BUDGET TO REFLECT THAT.

CHAIRMAN KLEIN: AND MY UNDERSTANDING WAS THE PI FOR THE PRIMARY GRANT TARGETS LEUKEMIA WAS VERY STRONG.

DR. YAFFE: ABSOLUTELY. FIRST-RATE.

CHAIRMAN KLEIN: OKAY. THANK YOU. CAN WE LOOK AT THE SECOND OF THOSE, DR. TROUNSON?

DR. TROUNSON: THE SECOND PROJECT IS 1857. AND THE GRANTS WORKING GROUP RECOMMENDED THAT THE PRECLINICAL MODEL STUDIES, GMP, CELL BANKING, AND OTHER ACTIVITIES NOT REQUIRED FOR FEASIBILITY, SHOULD BE REMOVED FROM THE PROJECT AND THE AWARD BE CHANGED TO A DC FEASIBILITY. BASICALLY THEY FELT THAT THE STUDY WAS A VERY IMPORTANT STUDY, BUT IT WAS MUCH MORE ALIGNED TO A FEASIBILITY PROJECT THAN A DISEASE CANDIDATE PROJECT.

THEY FELT THAT WE SHOULD -- THAT THEY WOULD BE SUPPORTIVE OF THE PROJECT IN THE DCF CATEGORY, BUT THEY WERE FEELING RATHER UNSUPPORTIVE AS A DEVELOPMENTAL CANDIDATE WITH THE AMOUNT OF WORK THAT HAD TO BE DONE IN THERE. WE RECOGNIZE THAT THIS IS QUITE DIFFICULT BECAUSE YOU SEE THERE'S A BIG DIFFERENCE IN THE BUDGETS FROM DC TO A DCF. AND

THAT IF THE ICOC DOES AWARD THAT PROJECT, THEN I THINK WHAT WE WOULD TRY TO DO IS WORK WITH THE PI AND SEE IF WE CAN REDUCE SOME OF THE STUDIES WHICH ARE NOT REALLY REQUIRED AS A DC FEASIBILITY AND BRING THE BUDGET DOWN, NOT WAY DOWN TO THE DCF LEVEL, BUT TRY AND BRING IT BACK INTO SOME SORT OF ORDER.

WE'RE TRYING TO MAKE THIS -- BE SUPPORTIVE OF THIS PROJECT. THE GRANTS WORKING GROUP WAS SUPPORTIVE OF IT AS A FEASIBILITY. WE DON'T WANT TO UNHINGE THE PROJECT COMPLETELY. WE WANT TO SORT OF LOOK IN A WAY WHERE WE CAN RECONSTRUCT THIS PROJECT IN ORDER FOR IT TO BE A FEASIBILITY STUDY AND NOT BE EXPECTED TO MAKE THAT CANDIDATE IN THE TIME BECAUSE THE GRANTS WORKING GROUP DIDN'T BELIEVE THAT THEY WERE GOING TO BE ABLE TO DO THAT IN THIS PARTICULAR PROJECT, BUT WERE STRONGLY SUPPORTIVE AS A DCF STUDY.

SO THERE'S A LITTLE COMPLEX -- LITTLE BIT COMPLICATED PERHAPS, BUT I THINK WITH THE BOARD'S SUPPORT, WE CAN REFASHION THIS IN SOME WAY IF THAT'S WHAT YOU THINK IS APPROPRIATE.

CHAIRMAN KLEIN: AND, DR. TROUNSON, WOULD YOU OR ONE OF THE OTHER SCIENTISTS GIVE US SOME SENSE OF THE STRENGTH OF THE GROUP, THE SCIENTIFIC

GROUP, THE STRENGTH OF THE SCIENTIFIC THEORIES THEY HAD HERE?

DR. TROUNSON: SO IF I CAN INVITE DR. COLLINS, I THINK, TO ADDRESS THAT ISSUE FOR YOU.

DR. COLLINS: THE GRANTS WORKING GROUP WAS VERY SUPPORTIVE OF THE TEAM, THE PI AND THE CO-PI, AND, IN FACT, CALLED THEM AN OUTSTANDING TEAM. AND IF YOU'D LIKE, I'D BE HAPPY TO GIVE SORT OF A BIRD'S-EYE VIEW OF THE PROPOSAL ITSELF.

CHAIRMAN KLEIN: WHY DON'T YOU DO THAT.

DR. COLLINS: THIS IS A DEVELOPMENTAL CANDIDATE PROPOSAL, RECEIVED AS A DEVELOPMENT CANDIDATE PROPOSAL, TO GENERATE HUMAN EMBRYONIC STEM CELL-DERIVED HEPATOCYTES TO SERVE AS A BRIDGE TO REGENERATION FOR ACUTE LIVER FAILURE AND ALSO TO SUPPORT PATIENTS WHO REQUIRE LARGE LIVER RESECTIONS TO THE POINT WHERE THERE WOULD BE INADEQUATE LIVER LEFT TO PROMOTE SURVIVAL UNTIL THE PATIENT'S OWN LIVER WOULD REGENERATE. SO THAT'S THE TARGET INDICATION FOR THE THERAPY.

AND THE APPLICANTS PLAN TO ESTABLISH CONSISTENT PRODUCTION OF HIGH PURITY CANDIDATE AS WELL AS DEVELOP METHODS TO REMOVE RESIDUAL UNDIFFERENTIATED STEM CELLS AND TEST THE CELLS FOR ENGRAPHMENT AND THEIR ABILITY TO RESCUE LIVER

FAILURE IN AN ANIMAL MODEL OF ACUTE LIVER DISEASE.

AND REVIEWERS WERE VERY ENTHUSIASTIC ABOUT THE CONCEPT OF THIS PROPOSAL AND IN PARTICULAR ABOUT THE CONCEPT OF AN UNLIMITED SUPPLY OF SAFE AND RELATIVELY METABOLICALLY MATURE HUMAN HEPATOCYTES FOR LIVER FAILURE AS THIS IS A HUGE UNMET MEDICAL NEED. BUT THEY DID HAVE SOME SERIOUS CONCERNS REGARDING THE RATIONALE BEHIND THE PROPOSED LARGE ANIMAL PRECLINICAL MODELS, AND THEY FELT VERY STRONGLY THAT THESE MODELS WOULD NOT CONTRIBUTE TO ACHIEVING THE GOALS OF THE PROPOSAL. AND I THINK THAT WAS BEHIND THE RECOMMENDATION TO REMOVE THOSE FROM THE PLAN.

REGARDING FEASIBILITY OF THE PLAN, REVIEWERS REALLY APPRECIATED THE PRELIMINARY DATA SUPPORTING BOTH THE METABOLIC ACTIVITY OF THE CELLS AS WELL AS THE APPLICANT'S ABILITY TO GENERATE THEM AT HIGH PURITY. HOWEVER, THEY HAD SOME FEASIBILITY CONCERNS REGARDING THE REGULATORY PATH FOR THIS PROPOSED DC AS IT WOULD BE CLASSIFIED AS BOTH A XENOTRANSPLANT AND A POTENTIALLY IMMUNOGENIC GENE THERAPY BY THE FDA. AND THE APPLICANTS, THEY FELT, DID NOT ADEQUATELY ADDRESS THE NECESSARY TESTING TO ENSURE FURTHER REGULATORY PROGRESSION OF THE DEVELOPMENT CANDIDATE AT THIS POINT.

THEREFORE, THEY FELT THAT THIS WAS AN OUTSTANDING APPLICANT TEAM THAT WAS LIKELY TO SUCCEED AT MAKING THE CANDIDATE AND GENERATING IN VIVO PROOF OF CONCEPT, BUT THEY FELT THAT THEY WOULD NOT HAVE A DEVELOPMENT CANDIDATE READY FOR IND-ENABLING STUDIES AT THE END OF THE AWARD PERIOD. SO THEY, THEREFORE, RECOMMENDED IN PROGRAMMATIC REVIEW THAT THE APPLICATION BE FUNDED AS A DEVELOPMENT CANDIDATE FEASIBILITY AWARD ON THE CONDITION THAT THE LARGE ANIMAL MODELS AS WELL AS THE PROPOSED GMP WORK AND ANY OTHER ELEMENTS THAT WERE NOT NECESSARY FOR ESTABLISHING REALLY THE PROOF OF CONCEPT OF THIS DEVELOPMENT CANDIDATE BE EXCISED FROM THE PROJECT AND THE BUDGET ADJUSTED ACCORDINGLY. THAT WAS THE FINAL RECOMMENDATION.

MR. ROTH: OKAY. ANY FOLLOW-ON QUESTIONS FOR ALAN OR JEFF OR ANY OF THE OTHER APPLICANTS? SO HEARING NONE, JAMES, I THINK WE HAVE TO IDENTIFY THOSE THAT THE BOARD WISHES TO HAVE A CLOSED SESSION ON.

CHAIRMAN KLEIN: WE'LL HAVE A CLOSED SESSION ON ALL OF THEM AND CHOOSE THOSE, BUT TO THE EXTENT THAT I THINK, DUANE, YOU'RE FOCUSING ON, TO THE EXTENT THAT WE EXPECT TO REALLY GO INTO THEM IN DEPTH IN THE CLOSED SESSION, WE WANT TO MAKE SURE WE

IDENTIFY THEM HERE. I THINK, JEFF SHEEHY, YOU HAD ANOTHER APPLICATION?

MR. SHEEHY: YEAH. I WAS JUST LOOKING AT 1797, AND I THINK IT MIGHT BE USEFUL TO LOOK AT THAT ONE TOO.

CHAIRMAN KLEIN: AS WELL, IF WE COULD HAVE A LOOK AT 1778, WHICH I BELIEVE HAD A STRONG TEAM, BUT SOME VERY CHALLENGING ISSUES. SO, DR. TROUNSON, 1797, WHO WOULD PRESENT ON THAT?

ON 1797 WE'RE NOW PRESENTING A STAFF REPORT ON AN EXTRAORDINARY PETITION FOR WHICH THERE'S AN AUDIENCE COMMENT. SO I'M GOING TO CALL THE AUDIENCE COMMENT IMMEDIATELY AFTER THE STAFF PRESENTATION.

DR. ABO: MY NAME IS ARI ABO. I AM A NEW MEMBER OF THE SCIENCE OFFICER AT CIRM. SO I'M HERE TO PRESENT TO YOU 1797. OVERALL, THE REVIEWERS FELT VERY POSITIVELY ABOUT THIS APPLICATION. IT'S AN APPLICATION THAT IS USING A NANOMICELLE TECHNOLOGY TO TARGET LEUKEMIC CANCER STEM CELLS.

SO THE HYPOTHESIS IS THAT TAKING A HIGH CONCENTRATION OF CHEMOTHERAPEUTIC AGENTS AND DELIVER IT USING A NANOMICELLE TECHNOLOGY TO TARGET CANCER STEM CELLS MAY PROVIDE IMPORTANT THERAPEUTICS FOR AML, ACUTE MYELOID LEUKEMIA, WHICH IS AN UNMET NEED.

AND MOST OF THE PATIENTS TREATED WITH CHEMOTHERAPIES, THERE'S A VERY HIGH PERCENTAGE OF RECURRENCE OF THIS DISEASE. HOWEVER, THE REVIEWERS FOUND THAT WHILE THIS HYPOTHESIS IS VERY STRONG AND VERY IMPORTANT, THEY FOUND VERY LITTLE EVIDENCE WAS PROVIDED ON CHARACTERIZATION OF THE CANCER STEM CELLS IN MYELOID LEUKEMIA.

ALTHOUGH THE MARKERS ARE KNOWN VERY WELL WHAT ARE THE SPECIFIC MARKERS, IN THE PRELIMINARY DATA PROVIDED BY THE PI, THERE WAS VERY LITTLE INFORMATION ABOUT HOW THE CHEMOTHERAPEUTIC AGENT IS GOING TO TARGET SPECIFICALLY THE CANCER STEM CELLS. AND INCREASED CONCENTRATIONS OF THE CHEMOTHERAPEUTIC AGENTS COULD ACTUALLY KILL CANCER STEM CELLS. AND THAT WAS THE MAJOR CONCERN RAISED BY THE REVIEWER, AND THEY FELT THAT THAT WAS A WEAKNESS OF THIS PROPOSAL.

CHAIRMAN KLEIN: THANK YOU. COULD WE --

MR. SHEEHY: COULD I ASK A COUPLE OF QUESTIONS? THANK YOU. BUT THE CANCER STEM CELL IS CHARACTERIZED FOR THIS TARGET, RIGHT? SO WE DO KNOW THAT THERE IS -- I'M KIND OF CONFUSED. IT SOUNDS LIKE THE REVIEWERS SAID, WELL, THEY DIDN'T KNOW IF THERE WAS A CANCER STEM CELL, BUT THEN IT'S KIND OF ESTABLISHED THAT THERE IS A CANCER STEM CELL?

DR. ABO: ABSOLUTELY. SO THERE IS A SPECIFIC MARKER FOR LEUKEMIC CANCER STEM CELL CD34-/38+ WHERE IT'S TRUE, DURING THE REVIEWING PROCESS, I FELT THAT THE REVIEWERS FAILED TO RECOGNIZE THAT THOSE MARKERS ARE CANCER STEM CELL MARKERS. HOWEVER, ALTHOUGH IT'S KNOWN THAT THIS IS A MARKER FOR THE CANCER STEM CELL LEUKEMIA, IN THE PROPOSAL ITSELF, THERE WAS VERY LITTLE INFORMATION OR DATA SHOWING THAT SPECIFIC CANCER STEM CELLS WITH THESE SPECIFIC MARKERS ARE TARGETED WITH THIS TECHNOLOGY IS EFFECTIVE AS A PRELIMINARY INFORMATION TO SHOW THAT THIS TECHNOLOGY IS GOING TO BE EFFECTIVE.

CHAIRMAN KLEIN: HOW MUCH DATA DO WE REQUIRE ON A CONSISTENT BASIS IN THIS ROUND?

DR. ABO: YOU WOULD EXPECT AT LEAST TO SHOW THAT THE SCHEMA THERAPEUTIC AGENT WORKS EFFECTIVELY ON THE CANCER CELLS, THAT YOU WOULD SHOW SOME PRELIMINARY DATA AND SOME SORT OF A DOSE ESCALATION TO SHOW THAT THERE ARE SOME CORRELATIONS THAT IF YOU INCREASE THE DOSE BY 10 OR 50 FOLDS AND YOU HAVE EFFECTIVE KILLING OF CANCER STEM CELLS WITH THE MARKERS. THAT WAS NOT PROVIDED IN THE APPLICATION.

MR. SHEEHY: BUT THEN HOW WILL WE EVER

ANSWER THIS QUESTION IF WE DON'T LET THEM SEE HOW MUCH IT TAKES TO KILL THE CANCER STEM CELLS? I JUST WANT -- EVERYBODY SEEMED TO BE VERY ENTHUSIASTIC ABOUT THE PLATFORM. AND THAT SEEMS LIKE THAT THAT WOULD HAVE THIS NANOTECHNOLOGY TO DELIVER VERY PRECISELY CHEMOTHERAPEUTIC AGENTS. THEY SAID IF THIS WORKED OUT, IT WOULD HAVE SOME BENEFIT ON ELDERLY PATIENTS WHO CAN'T TOLERATE THE DOSES OF CHEMOTHERAPY THAT THEY GET NOW. IT'S A MORE SPECIFIC TARGETING.

HOW DO WE ANSWER THAT QUESTION? THEY CAN'T ANSWER IT IF WE DON'T GIVE THEM THE MONEY TO ANSWER IT.

DR. ABO: THAT'S TRUE. IN ADDITION, I SHOULD ADD THAT THAT'S SOMETHING THAT THE REVIEWER FAILED TO SEE, WHICH IS IDENTIFICATION OF A SPECIFIC MOLECULE FOUND IN CANCER STEM CELL, THE CLL1, BY THE PI SHOWING THAT THEY FIND A SPECIFIC LIGAND THAT CAN BIND THIS RECEPTOR WHICH COULD -- ACTUALLY WILL BE AN EFFECTIVE AND A NOVEL WAY TO TARGET THIS NANOMICELLE TO THE CANCER STEM CELLS. I THINK THAT'S A NOVEL DISCOVERY THAT WAS MADE BY THE APPLICANT, SO IT COULD BE VERY IMPORTANT FOR LEUKEMIC THERAPIES.

MS. SAMUELSON: MIGHT THAT SERVE AS THE

PRELIMINARY DATA THAT COULD BE THE BASIS FOR DECIDING IT'S WORTHWHILE TO PROCEED IN FUNDING THIS GRANT?

DR. ABO: IT WOULD BE -- IT WOULD ADD MORE VALUE FOR THIS HYPOTHESIS SINCE THE HYPOTHESIS SAYS THAT INCREASING EXISTING CHEMOTHERAPEUTIC AGENTS BY TARGETING THE CANCER STEM CELLS IS THE HYPOTHESIS AND IS BASED ON STUDIES THAT WERE PUBLISHED IN *NEW ENGLAND JOURNAL OF MEDICINE*, THAT IF YOU INCREASE EXISTING CHEMOTHERAPEUTIC AGENTS IN LEUKEMIC PATIENTS, YOU GET MUCH MORE EFFECTIVE THERAPY. AND IT WOULD ADD A LOT OF VALUE IF THERE WAS PRELIMINARY DATA SHOWN IN THIS APPLICATION TO SUPPORT THIS IN VITRO AT LEAST, AND THERE WAS VERY LITTLE DATA PROVIDED ON THAT, ALTHOUGH IT'S A VERY ATTRACTIVE APPROACH.

CHAIRMAN KLEIN: SO COULD YOU CLARIFY THAT. WHAT WAS PUBLISHED IN THE *NEW ENGLAND JOURNAL*?

DR. ABO: IT WAS PUBLISHED THAT IF YOU TREAT LEUKEMIC PATIENTS WITH INCREASED EXISTING CHEMOTHERAPEUTIC AGENT THAT IS USED IN THIS THERAPY, YOU GET EFFECTIVE -- A BETTER THERAPY. AND THIS APPROACH IS TRYING TO INCREASE THE CONCENTRATION OF EXISTING CHEMOTHERAPY AGENTS BY TENFOLD, THAT WE

CANNOT DO IT WITH THE CURRENT APPROACH. ALTHOUGH PEOPLE SHOWING THAT IF YOU CAN INCREASE THE CONCENTRATION, YOU MAY GET BETTER EFFICACY. SO IT'S BASED ON THAT OBSERVATION.

CHAIRMAN KLEIN: AND THIS WAS IN THE CONTEXT THAT THIS NANOTECHNOLOGY MAY BE AN EFFECTIVE WAY OF DELIVERING MORE CONCENTRATED DOSES AS VERSUS CURRENT THERAPEUTIC APPROACHES?

DR. ABO: EXACTLY.

DR. TROUNSON: I GUESS, CHAIR, THAT YOU'VE GOT TO BE CERTAIN THAT THEY'RE GOING TO DELIVER IT TO THE RIGHT CELLS. I THINK THAT'S THE QUESTION THAT'S BEING RAISED. ARE YOU DELIVERING IT TO THE RIGHT CELL? IF YOU'RE DELIVERING IT TO THE WRONG CELLS, IT'S NOT A GOOD IDEA. SO THAT'S REALLY THE HUB OF THE QUESTION AS I SEE IT.

CHAIRMAN KLEIN: RIGHT. AND THE CLL1 DISCOVERY HELPS US IDENTIFY CORRECT CELLS?

DR. ABO: DEFINITELY. CLL1 WAS A MOLECULE THAT WAS CLONED BY A DUTCH GROUP SHOWING THAT IT WAS SPECIFICALLY, IN TWO PUBLICATIONS, SPECIFICALLY EXPRESSED IN CANCER STEM CELLS, LEUKEMIC CANCER STEM CELLS. AND THE PI OF THIS APPLICATION, HE DISCOVERED THE LIGAND THAT CAN BIND TO THIS RECEPTOR, AND HE WANTS TO USE THIS LIGAND TO TARGET

THE CHEMOTHERAPEUTIC AGENTS TO THESE LEUKEMIC CELLS. THAT MAKES IT VERY ATTRACTIVE TO REALLY TARGET YOUR CHEMOTHERAPEUTIC AGENT WITH THE SPECIFIC RECEPTORS THAT WAS SHOWN TO BE EXPRESSED IN THE SPECIFIC MARKERS THAT PEOPLE BELIEVE ARE THE MARKERS FOR THE LEUKEMIC CANCER STEM CELLS.

CHAIRMAN KLEIN: I THINK WE'VE GOTTEN TO THE EDGE OF WHAT WE CAN BECAUSE WE'RE GETTING INTO PROPRIETARY INFORMATION, BUT I THINK IT'S BEEN VERY ELUCIDATING.

MR. ROTH: I CANNOT FIND 1857. WHAT DID YOU DO WITH THAT? I CAN'T SEEM TO FIND IT ON THE LIST. IT'S ON THE PROGRAMMATIC REVIEW? I SEE IT. YOU RECOMMEND IT FOR FUNDING, RIGHT? THIS IS THE ONE THAT WILL BE CHANGED. THANK YOU.

CHAIRMAN KLEIN: WE WERE JUST GOING THROUGH 1797. ALL RIGHT. SO IF WE COULD HAVE THE PUBLIC COMMENT ON 1797.

DR. LAM: GOOD MORNING. THANK YOU SO MUCH. I'M KIT LAM. I'M THE CHIEF OF HEMATOLOGY ONCOLOGY IN UC DAVIS. AND I AM THE PI OF THIS PROPOSAL. AND I'D LIKE TO REPORT TO YOU THAT CHONG PAN WHO WAS THE CO-PI ACTUALLY GOT A JUNIOR INVESTIGATIVE AWARD FROM CIRM, AND IT IS THROUGH THIS RESEARCH HE DISCOVERED THESE LEUKEMIA TARGETING

LIGANDS. SEVERAL OF THEM ARE IDENTIFIED.

AND I MYSELF I DEVELOP A LOT OF NANOPARTICLE DRUGS. SOME OF THEM ACTUALLY WE JUST FILE AN IND. WE HOPEFULLY WILL START WITH THE CLINICAL TRIAL IN SOLID TUMOR NEXT YEAR.

SO I THINK THIS IS A VERY PROMISING PROJECT BECAUSE WE HAVE A LOT OF TRANSLATION OF DATA. ACTUALLY THE NANOPARTICLE HAS BEEN ALREADY TESTED IN DOGS AND IT WORKS VERY WELL, AND SOME REALLY GOOD RESULTS ALREADY IN SOLID TUMOR IN DOGS.

RIGHT NOW IT'S THE COMBINED LIGANDS THAT DR. PAN DISCOVERED THROUGH THIS JUNIOR INVESTIGATOR AWARD WITH THESE NANOPARTICLES SO THAT WE CAN TARGET THE CANCER.

THE THREE CONCERNS THE REVIEWER SAW IS, NO. 1, SPECIFICITY. I THINK CERTAINLY WE ARE VERY SURE THOSE LIGANDS DO BIND IN LEUKEMIA STEM CELLS THROUGH PHOTOCYTOMETRY STUDIES. AND WE ALSO DEMONSTRATED THOSE LIGANDS DO NOT BIND TO THE NORMAL HEMATOPOETIC STEM CELL, INCLUDING THE STEM CELL DONATED AS A DONOR FOR STEM CELL TRANSPLANT IN LEUKEMIC PATIENT. SO THAT'S THE KEY THING IS IT DOES NOT BIND IN NORMAL HEMATOPOETIC STEM CELL.

WE CANNOT SAY FOR SURE YET IT DOESN'T BIND TO ANY OTHER CELLS, BUT THEN THE IMPORTANT THING IS

REALLY THE SPECIFICITY. IT DOES BIND TO LEUKEMIA STEM CELL.

THE CLL1 LIGAND, HOWEVER, DO ALSO BIND TO SOME MATURE MYELOCYTIC CELL AS WELL AS THE MATURE LEUKEMIA CELLS, BUT THAT DOESN'T MATTER BECAUSE WE CAN ALSO TARGET THOSE CELL AND REMOVE THOSE MATURE LEUKEMIA CELL AS WELL.

FOR EXAMPLE, IN RITUXAN, WHICH IS A VERY USEFUL DRUG FOR TREATING LYMPHOMA, B-CELL LYMPHOMA, YOU CURE ALL THE B CELLS, NORMAL B CELL, BUT THE PATIENT DO WELL WITHOUT ANY PROBLEM, AND IT'S REALLY -- AND THAT THE B CELL WILL COME BACK A MONTH OR TWO LATER AFTER THE DRUG IS GONE. SO ABSOLUTE SPECIFICITY IS NOT REQUIRED, BUT WE CERTAINLY KNOW THAT OUR LIGAND DO BIND TO THE LEUKEMIA STEM CELL.

THE SECOND CONCERN IS ASSESSMENT OF EFFICACY THE REVIEWER HAS. I THINK THAT REALLY THE FINAL ASSESSMENT IS REALLY THE NSG MOUSE THAT HAS BEEN IMPLANTED WITH HUMAN LEUKEMIA CELL, AND WE CAN CURE THOSE MICE. THIS IS REALLY THE FINAL ASSESSMENT. I THINK WE CAN DO IT VERY EASILY BY LOOKING AT SURVIVAL DATA.

IN TERMS OF DRUG RESISTANT IN LEUKEMIA CELL, CAN WE GIVE MORE DRUG TO LEUKEMIA STEM CELL ACTUALLY TO CURE THEM? WE HAVE AMPLE EVIDENCE

SHOWING THAT MULTIDRUG RESISTANT CAN BE OVERCOME BY USING NANOPARTICLE. THOSE PARTICLE GO THROUGH THE CELL, THROUGH A LOCYTIC PATHWAY, VERY HIGH LEVEL DRUG CAN GO INSIDE THE CELL. AND ALSO THROUGH OTHER MECHANISMS I THINK YOU CAN EVEN OVERCOME SOME OF THE (UNINTELLIGIBLE) PROTEIN EFFECTS MECHANISMS AS WELL.

SO I THINK REALLY WE HAVE A LOT OF REALLY GOOD PRELIMINARY DATA AND ALSO PUBLISHED LITERATURE SHOWING THAT THIS IS REALLY A PROMISING APPROACH, AND ALSO THE NANOPARTICLE WE ALREADY GOING TO IND, I THINK, BY THE END OF THREE YEARS. THE SECOND YEAR, THE THREE-YEAR WE SHOULD BE ABLE TO COMBINE BOTH USING THE LIGAND THAT TARGET LEUKEMIA STEM CELL AS WELL AS NANOMICELLE TO REALLY GO INTO THE CLINIC.

CHAIRMAN KLEIN: THANK YOU. ARE THERE ADDITIONAL QUESTIONS OF THIS PRESENTER? MR. SHEEHY.

MR. SHEEHY: SO I JUST WANT TO BE CLEAR. SO THE LIGAND THAT'S THE TARGETING ISSUE WE PAID TO DISCOVER THAT BASICALLY WITH A NEW FACULTY AWARD. SO DOESN'T -- AND YOU HAVE THIS NANOTARGETING TECHNOLOGY THAT'S REALLY NOVEL AND EVERYBODY THINKS IS REALLY COOL?

DR. LAM: CORRECT.

MR. SHEEHY: SO WE'RE GETTING AN OPPORTUNITY TO PUT THIS TOGETHER AND KIND OF ADVANCE

OUR SCIENTIFIC PROGRAM WITH THIS GRANT, RIGHT?

DR. LAM: I THINK SO. I THINK IT'S REALLY GETTING THERE.

MR. SHEEHY: THANK YOU.

DR. LAM: THANK YOU SO MUCH.

CHAIRMAN KLEIN: THANK YOU VERY MUCH. VERY MUCH APPRECIATE THAT.

SO AT THIS POINT DOES ANY MEMBER OF THE BOARD WANT TO TALK ABOUT 1763, WHICH IS ONE OF THE EXTRAORDINARY PETITIONS? DOES ANYONE WANT ANY PRESENTATION FROM THE STAFF ON THAT ITEM? I'M GOING TO CALL, THEN, ON THE PUBLIC COMMENT ON THAT ITEM 1763.

DR. BHATIA: I'D LIKE THANK YOU FOR THIS OPPORTUNITY TO DESCRIBE OUR PROPOSAL AND ITS IMPACT. OUR APPLICATION IS 1763, "TARGETING SIRT1 IN LEUKEMIA STEM CELLS." AND IT AIMS TOWARD DEVELOPING A CURATIVE TREATMENT FOR CANCER.

MY NAME IS RAVI BHATIA, AND I'M A CO-PRINCIPAL INVESTIGATOR ON THIS PROPOSAL WITH DR. WEN YONG CHEN, WHO COULD NOT BE HERE TODAY. I'M A PHYSICIAN AND A SCIENTIST, AND I WORK AT THE CITY OF HOPE COMPREHENSIVE CANCER CENTER.

AS A HEMATOLOGY ONCOLOGY PHYSICIAN TAKING CARE OF PATIENTS WITH LEUKEMIA AND OTHER

HEMATOLOGICAL MALIGNANCIES, I KNOW FROM FIRSTHAND EXPERIENCE THAT CANCER STEM CELLS ARE EXTREMELY RESISTANT TO ELIMINATION WITH EXISTING THERAPIES. AND THE PERSISTENCE OF CANCER STEM CELLS IN PATIENTS WHO ARE IN REMISSION AFTER TREATMENT IS A MAJOR CAUSE OF RELAPSE IN THESE PATIENTS.

AND OUR REASONING WAS THAT IF WE CAN DEVELOP AGENTS THAT CAN SELECTIVELY AND EFFECTIVELY TARGET AND ELIMINATE LEUKEMIA STEM CELLS, THAT WE COULD POTENTIALLY PROVIDE A CURE FOR LEUKEMIA AND NOT MERELY A TREATMENT FOR THESE PATIENTS.

SO OUR PROPOSAL WAS TO DEVELOP A SMALL MOLECULE TO ENERVATE THE SIRT1 DEACETYLASE GENE. DR. CHEN AND I HAVE DISCOVERED THAT SIRT1 PLAYS A KEY ROLE IN SURVIVAL AND GROWTH OF LEUKEMIA STEM CELLS. THERE IS TOO MUCH SIRT ACTIVITY IN LEUKEMIA STEM CELLS FROM PATIENTS WITH AML AND CML. AND THE INCREASED SIRT1 ACTIVITY PLAYS A ROLE IN PROMOTION OF NEW MUTATIONS IN THESE STEM CELLS, AND THESE MUTATIONS CONTRIBUTE TO PROGRESSION OF DISEASE AND RESISTANCE TO TREATMENT.

OUR STUDIES HAVE SHOWN THAT SIRT1 IS NOT ONLY CRITICAL FOR THE PERSISTENCE OF LEUKEMIA STEM CELLS IN THESE CANCERS, BUT THAT IT ALSO PLAYS A ROLE IN THEIR RESISTANCE TO EXISTING TREATMENT. WE

HAVE SHOWN THAT IF SIRT1 IS INHIBITED, LEUKEMIA STEM CELLS STOP DIVIDING, THE DEATH RATE INCREASES, AND NEW MUTATIONS ARE PREVENTED FROM TAKING PLACE. THIS, I THINK, IS VERY IMPORTANT AND DISTINGUISHES THIS APPROACH FROM SEVERAL OTHER APPROACHES WHICH ARE AVAILABLE.

CHAIRMAN KLEIN: AND YOUR DEMONSTRATION OF THIS WAS WITH DATA THAT WAS IN THE APPLICATION?

DR. BHATIA: THE DATA IS IN THE APPLICATION.

CHAIRMAN KLEIN: DID THE REVIEWERS TAKE ISSUE WITH THAT DATA?

DR. BHATIA: NO, THEY DID NOT. I THINK THEY APPRECIATED THAT DATA.

IMPORTANTLY, SIRT1 INHIBITION ALSO MAKES LEUKEMIA STEM CELLS MORE SENSITIVE TO EXISTING TREATMENT. IT'S IMPORTANT TO NOTE THAT SIRT1 IS SELECTIVE FOR CANCER STEM CELLS. IT'S NOT TOXIC TO NORMAL HEMATOPOETIC STEM CELLS AND IS, THEREFORE, EXPECTED TO HAVE A HIGH THERAPEUTIC INDEX.

WE FEEL ON THE BASIS OF THESE FINDINGS THAT SIRT1 IS CLEARLY A NOVEL AND ATTRACTIVE TARGET FOR DRUG DEVELOPMENT TO TARGET LEUKEMIA STEM CELLS.

ONE OF THE ISSUES THAT WAS BROUGHT UP BY THE REVIEWERS WAS THAT THERE WERE EXISTING SIRT1

INHIBITORY DRUGS, BUT WE'D LIKE TO POINT OUT RESPECTFULLY THAT WE'RE NOT AWARE OF ANY SIRT1 INHIBITORY DRUGS AT PRESENT WHICH ARE IN CLINICAL PRACTICE OR DEVELOPMENT. WE ARE PROPOSING TO DEVELOP A POTENT DRUG TO INHIBIT SIRT1. AND DR. CHEN HAS ALREADY IDENTIFIED A COUPLE OF VERY PROMISING NOVEL LEAD COMPOUNDS THAT TARGET THE ENZYME IN A 1-TO-5 MICROMOLAR CONCENTRATION. AND HE PROPOSES TO FURTHER MODIFY THESE COMPOUNDS TO DEVELOP A POTENT DRUG. AND FOR THIS PURPOSE, WE PLAN TO USE THE OUTSTANDING RESOURCES TOWARDS DRUG DEVELOPMENT THAT ARE AVAILABLE AT OUR INSTITUTION.

WE SEE THIS STRATEGY AS A POTENTIAL CURE FOR LEUKEMIA. AND I'D JUST LIKE TO EMPHASIZE AGAIN WHILE MANY APPROACHES ARE BEING CONSIDERED TO TARGET LEUKEMIA STEM CELLS, WE FEEL THAT THIS APPROACH IS UNIQUE IN THAT IT NOT ONLY KILLS LEUKEMIA STEM CELLS, BUT ALSO PREVENTS THEM FROM ACQUIRING NEW MUTATIONS THAT CONTRIBUTE TO PROGRESSION AND DRUG RESISTANCE.

WE PLAN TO INITIALLY APPLY THIS ANTI-SIRT1 DRUG TO CML AND AML, CHRONIC MYELOID LEUKEMIA AND ACUTE MYELOID LEUKEMIA. THERE ARE ABOUT 5,000 NEW CASES OF CML AND 13,000 NEW CASES OF AML EVERY YEAR. NOW, FOR CML WE HAVE A GREAT TREATMENT, WHICH IS

GLEEVEC, BUT WHAT GLEEVEC HAS DONE IS TO MAKE CML A CHRONIC DISEASE BECAUSE IT IS NOT CAPABLE OF ELIMINATING THE LEUKEMIA STEM CELLS THAT GENERATE THE DISEASE.

AND AS A RESULT, IT'S PROJECTED THAT THERE ARE GOING TO BE A QUARTER MILLION PATIENTS WITH CML IN THE U.S. BY 2040, AND MOST OF THESE PATIENTS ARE GOING TO NEED CONTINUED TREATMENT WITH GLEEVEC FOR LIFE BECAUSE OF PERSISTENT LEUKEMIA STEM CELLS. WE KNOW THAT DISCONTINUATION GLEEVEC LEADS TO RELAPSE OF DISEASE IN OVER 90 PERCENT OF CML PATIENTS. UNFORTUNATELY CONTINUED GLEEVEC TREATMENT IS ASSOCIATED WITH RISK OF SIDE EFFECTS, THE POSSIBILITY OF NONCOMPLIANCE, AND DRUG RESISTANCE. AND IT'S ALSO ASSOCIATED WITH CONSIDERABLE EXPENSE, 50,000 PER YEAR OR UPWARDS PER PATIENT.

IN CASE OF AML, WE KNOW THAT THE SURVIVAL OF AML PATIENTS WITH CURRENT TREATMENTS IS ONLY IN THE RANGE OF ABOUT 25 PERCENT. SO WE, THEREFORE, BELIEVE THAT DEVELOPMENT OF CURATIVE APPROACHES FOR AML AND CML BASED ON ERADICATION OF LEUKEMIA STEM CELLS HAVE OBVIOUS BENEFITS TO PATIENTS, BUT ALSO TOWARDS HEALTH COSTS AND SIGNIFICANT BENEFITS TO SOCIETY.

WE ALSO KNOW THAT SIRT1 IS OVEREXPRESSED

IN OTHER CANCERS, INCLUDING BREAST CANCER AND PROSTATE CANCER. SO THAT THIS APPROACH IS LIKELY TO BE NOT ONLY APPLICABLE TO LEUKEMIA, BUT MAY BE APPLICABLE TO SOLID TUMORS IN THE FUTURE. AND DR. CHEN HAS PRELIMINARY DATA SHOWING THE IMPORTANCE OF SIRT1 IN PROSTATE CANCER.

SO, IN SUMMARY, WE FEEL THAT THERE IS A STRONG SCIENTIFIC RATIONALE FOR DEVELOPING A SIRT1 INHIBITOR TO SELECTIVELY TARGET CANCER STEM CELLS, AND WE FEEL THAT SUCH AN AGENT COULD BE A MAJOR ADVANCE IN CANCER STEM CELL THERAPY AND COULD HAVE A MAJOR IMPACT ON PATIENTS WITH LEUKEMIAS AND OTHER CANCERS. THANK YOU FOR YOUR ATTENTION.

CHAIRMAN KLEIN: DR. PIZZO. LET US MAKE SURE WE HAVE A LIST IDENTIFYING CONFLICTS SO WE'RE NOT GOING TO ASK QUESTIONS IF WE HAVE CROSS-CHECKED WITH OUR LIST OF CONFLICTS AND HAVE IDENTIFIED A CONFLICT. THANK YOU.

DR. PIZZO: THIS IS A BROADER SCIENTIFIC QUESTION. SO I UNDERSTAND, OF COURSE, THE SPECIFICITY OF GLEEVEC AS A TK INHIBITOR AND HOW IT RELATES TO THE C-ABL GENE. I DON'T UNDERSTAND THE SPECIFICITY OF SIRT1 TO LEUKEMIA. CAN YOU BE MORE SPECIFIC AS TO WHY THAT WOULD BE A TARGET WITH A SIMILAR DEGREE OF SPECIFICITY THAT MIGHT, IN FACT,

ACHIEVE THE AIM THAT YOU PUT FORTH?

DR. BHATIA: THAT'S A VERY GOOD QUESTION. THAT'S ONE OF THE THINGS THAT WE'RE STRUGGLING WITH AS WE ARE TRYING TO TARGET LEUKEMIA STEM CELLS. AND WHAT WE KNOW IS THAT GLEEVEC IS ACTUALLY ACTIVE IN THE LEUKEMIA STEM CELLS. IT INHIBITS THE BCR-ABL KINASE IN THOSE STEM CELLS, AND IT TAKES AWAY THE LEUKEMOGENIC CAPACITY, BUT IT DOES NOT ELIMINATE THOSE CELLS. IT'S NOT REQUIRED FOR THE SURVIVAL OF THOSE CELLS. AND SO WE WERE, THEREFORE, LOOKING FOR OTHER TARGETS THAT DIFFERENTIATED LEUKEMIC FROM NORMAL CELLS.

SIRT1 IS OVEREXPRESSED IN LEUKEMIA STEM CELLS, AND SIRT1 IS A STRESS RESPONSE GENE. IT'S ACTUALLY A GENE ASSOCIATED WITH AGING AND CANCER, AND WE KNOW THAT IT'S OVEREXPRESSED IN THOSE CELLS. ACTUALLY GLEEVEC -- AND WE KNOW SOME OF THE MECHANISM BY WHICH SIRT1 ACTS. IT ACTS THROUGH P53, AND IT ACTS THROUGH NONHOMOLOGOUS ENJOINING DOUBLE STRAND BREAK REPAIR. THESE PATHWAYS CONTINUE TO BE ABNORMAL IN CML CELLS EVEN AFTER GLEEVEC TREATMENT.

ONE OF THE THINGS THAT WE'RE FINDING IS THAT SIRT1 ACTUALLY ACTIVATES P53 IN CML STEM CELLS. AND NOW WITH THE ACTIVATION OF P53 AND DEVELOPMENT OF A P53 RESPONSE, THESE CELLS ARE NOW MORE

SENSITIVE TO GLEEVEC. SO IT'S ACTUALLY THE COMBINATION OF GLEEVEC WITH THE SIRT1 INHIBITION THAT GIVES US THE THERAPEUTIC INDEX IN CML.

CHAIRMAN KLEIN: ADDITIONAL QUESTIONS FROM THE BOARD?

MS. SAMUELSON: I HAVE A COUPLE, BOB. COULD YOU DESCRIBE THE SUPPORT YOU HAVE FROM THE INSTITUTION?

DR. BHATIA: SO AT CITY OF HOPE IN THE CANCER CENTER WE HAVE A DEVELOPMENTAL CANCER THERAPEUTICS PROGRAM, AND THIS IS HEADED BY DR. RICHARD JOVE WHO'S THE DIRECTOR OF THE BECKMAN RESEARCH INSTITUTE. HE HAS DONE AN EXCELLENT JOB IN RECRUITING A TEAM OF INDIVIDUALS WHO CAN WORK WITH MEMBERS OF THE CANCER CENTER TOWARDS DRUG DEVELOPMENT. SO WE'VE RECRUITED DR. DAVID HORNE, WHO IS A MEDICINAL CHEMIST, WHO HAS RECRUITED A TEAM OF INDIVIDUALS WHO WORK WITH STRUCTURAL BIOLOGY, MAKING MODIFICATIONS TO DRUGS, DOING SCREENINGS TO PROVIDE ALL THE SORT OF FACILITIES THAT WE NEED IN ORDER TO WORK TOWARDS DRUG DEVELOPMENT.

AND WE ALSO HAVE A VERY ACTIVE GROUP AT CITY OF HOPE THAT ALSO HELPS US WITH REGULATORY ISSUES WITH THE PROCESSES THAT ARE REQUIRED IN TERMS OF BRINGING A DRUG TO THE CLINIC. AND SO THIS TEAM

HAS ALREADY SORT OF BEEN SUCCESSFUL IN WORKING WITH A RIBONUCLEOTIDE REDUCTASE WHICH IS DEVELOPED IN-HOUSE, BASED ON SCREENING DONE IN-HOUSE, AND THEN THE DRUG WAS DEVELOPED IN-HOUSE AND IS NOW GOING INTO CLINICAL TRIALS.

MS. SAMUELSON: ONE MORE QUESTION. THERE'S SOME CONCERN THAT THERE WAS OVERRELIANCE ON A MOUSE MODEL. CAN YOU SPEAK TO THAT?

DR. BHATIA: AND WE SAW THAT CONCERN. AND, YOU KNOW, I THINK THIS IS ALMOST A PHILOSOPHICAL ISSUE IN TERMS OF DRUG DEVELOPMENT BECAUSE WE KNOW THAT WE DEVELOP A NUMBER OF DRUG CANDIDATES WHICH ARE TAKEN INTO CLINIC AND ARE NOT SUCCESSFUL. AND I THINK ONE OF THE PROBLEMS WITH OUR DRUG DEVELOPMENT PROCESS AS IT IS IS NOT USING RELEVANT MODELS TO TEST EFFICACY GOING FORWARD.

SO OBVIOUSLY THE INITIAL SCREENING WOULD BE DONE USING IN VITRO ASSAYS AND BIOCHEMICAL ASSAYS, BUT WE WOULD EVENTUALLY LIKE TO SHOW EFFICACY IN A RELEVANT IN VIVO MODEL. AND WE'RE PLANNING TWO IN VIVO MODELS. ONE IS A MOUSE MODEL OF CML AND THE OTHER IS HUMAN CML CELLS ENGRAFTED IN IMMUNODEFICIENT MICE.

WE REALIZE THAT THESE MODELS ARE IMPERFECT AS ALL MODELS ARE RIGHT NOW. THERE'S NO LARGE

ANIMAL MODEL AVAILABLE FOR LEUKEMIA FOR US TO LOOK AT, BUT THESE ARE THE BEST AVAILABLE MODELS THAT WE HAVE RIGHT NOW. SO WE DO WANT TO TEST THESE DRUGS ON THOSE MODELS BEFORE TAKING THEM OUT.

MS. SAMUELSON: YOU SAID THERE'S NO LARGE --

DR. BHATIA: THERE'S NO LARGE ANIMAL MODEL.

DR. TROUNSON: JUST WHILE THE APPLICANT'S THERE, CHAIR, WE AGREE THAT THERE'S NO REAL SPECIFIC INHIBITORS FOR SIRT1 BECAUSE THERE'S NO CRYSTAL STRUCTURE AVAILABLE, AND THE REVIEWERS NOTED THIS. AND THE APPLICANT PROPOSED TO CRYSTALLIZE SIRT1, WHICH HAS NEVER REALLY EVER BEEN DONE, AND SOLVE THE STRUCTURE. THIS IS A LARGE BASIC EFFORT. IT'S NOT REALLY THE TYPE OF WORK ENVISAGED UNDER THIS RFA.

CHAIRMAN KLEIN: COULD YOU SAY THAT AGAIN, DR. TROUNSON?

DR. TROUNSON: WELL, IN ORDER TO FIND A SPECIFIC INHIBITOR FOR SIRT1, THEY NEED TO WORK OUT THE CRYSTAL STRUCTURE. THEY'VE NEVER BEEN ABLE TO DO THIS UP UNTIL NOW. SO THAT'S A PRETTY MAJOR EXERCISE TO DO THAT, AND THAT'S NOT WHAT WE'D NORMALLY EXPECT TO SEE ACCOMPANYING THIS KIND OF DC APPLICATION. THAT WAS ONE POINT. AND SO I'D BE

INTERESTED TO HEAR WHAT THE APPLICANT MIGHT RESPOND TO THAT.

THE OTHER THING IS THAT THE GLEEVEC ALREADY DECREASES SIRT1. IT WASN'T REALLY CLEAR TO THE REVIEWERS WHY A SECOND COMPOUND WOULD ADD VALUE. WHY WOULD IT ADD VALUE TO ADD ON A SECOND COMPOUND? ALSO FELT THAT IF GLEEVEC DOWNREGULATES SIRT1, IT'S UNLIKELY THAT SIRT1 IS CRITICAL FOR THE LEUKEMIC STEM CELL PERSISTENCE. THIS WAS THE REVIEWERS' THOUGHT, THAT THAT HADN'T ADEQUATELY DEMONSTRATED. IF YOU'VE GOT A DRUG THAT ACTUALLY DOES IT, MAYBE IT DOESN'T MATTER IF YOU DECREASE IT. YOU ARE GOING TO GET THIS REBOUND. SO WHY ADD THE SECOND COMPOUND THAT MIGHT CAUSE THE SAME REDUCTION IN REBOUND? OR WHAT'S THE REASONING FOR USING A SECOND DRUG? IS IT A PRIMARY OR A SECONDARY TARGETING TYPE OF APPROACH?

SO THESE WERE TWO QUITE CORE TO HOW THE REVIEWERS FELT ABOUT THE PROJECT, THAT THERE WAS STILL A LOT OF QUESTIONS OVER THIS APPROACH. AND THAT'S WHY THEY DIDN'T -- IT WASN'T SORT OF ELEVATED BASICALLY BECAUSE OF THOSE SORT OF REASONINGS.

CHAIRMAN KLEIN: SO COULD YOU ADDRESS THE TWO QUESTIONS DR. TROUNSON HAS RAISED FOR YOU?

DR. BHATIA: I CAN. SO THE FIRST QUESTION WAS RELATED TO THE CRYSTAL STRUCTURE. AND I THINK

THIS WAS AN ISSUE OF, I THINK, AN ERROR IN GRANTSMANSHIP. THIS IS SOMETHING THAT WE WOULD WANT TO DO, AND WE REALIZE THAT IT WOULD BE -- IT COULD POTENTIALLY BE A CHALLENGE TO GET THIS RESOLVED WITHIN THE PERIOD OF TIME OF THIS GRANT. I WANT TO EMPHASIZE THAT WE ALREADY HAVE TWO COMPOUNDS WHICH ARE WORKING IN THE LOW MICROMOLAR RANGE. AND THE INITIAL PLAN IS TO MODIFY THESE COMPOUNDS, USE A PHARMACO MODEL, AND BASICALLY IDENTIFY ADDITIONAL COMPOUNDS WITH INCREASED ACTIVITY. AND THAT IS ACTUALLY THE FIRST ITERATION OF WHAT WE'RE PLANNING TO DO.

WE DID PLAN TO -- WE HAVE JOHN WILLIAMS AT CITY OF HOPE WHO IS AN OUTSTANDING STRUCTURAL BIOLOGIST WHO IS WORKING WITH US IN TERMS OF SOLVING THE CRYSTAL STRUCTURE. THAT WAS TO BE FOR A SECOND ROUND OF ITERATION TO TRY AND DEVELOP DRUGS WHICH WERE EVEN BETTER THAN THOSE THAT WE COULD DEVELOP IN THE FIRST ROUND OF ITERATION. THAT MAY HAVE BEEN TOO COMPLICATED, I GUESS, IN TERMS OF HOW WE SHOULD HAVE PRESENTED THIS FOR THIS PROPOSAL.

THE OTHER QUESTION WAS RELATED TO IMATINIB IN SIRT1. SO THE REGULATION OF SIRT1 IS COMPLEX, AND WE DO SEE A DECREASE IN LEVEL OF EXPRESSION OF SIRT1 WITH IMATINIB, BUT WE DO NOT SEE A REDUCTION

IN SIRT1 ACTIVITY. SO IF YOU LOOK AT SIRT1 TARGETS SUCH AS P53 AND ITS ACETYLATION, THOSE ARE NOT AFFECTED BY IMATINIB TREATMENT. SO THAT'S WHY IT'S FELT THAT SIRT1 IS A KINASE INDEPENDENT TARGET IN CML. IT'S NOT DEPENDENT ON THE BCR-ABL KINASE.

AND, AGAIN, I APOLOGIZE THAT THIS WAS NOT MADE ABSOLUTELY CLEAR IN THE GRANT PROPOSAL.

CHAIRMAN KLEIN: ALL RIGHT.

DR. LOVE: I THINK THERE'S AT LEAST ONE COMPANY THAT I KNOW OF THAT SUPPOSEDLY HAS A POTENT SIRT1 INHIBITOR, A COMPANY CALLED ELIXIR. I CAN'T REMEMBER THE INDICATION, BUT IT MIGHT RELATE -- YOU MAY KNOW. SO MY QUESTION REALLY IS IF THERE ARE ALREADY POTENT INHIBITORS THAT HAVE BEEN IDENTIFIED, HAVE YOU THOUGHT ABOUT USING SOME OF THOSE INHIBITORS IN SOME OF THE MODELS TO VALIDATE THE CONCEPT BEFORE GOING BACK TO MEDICINAL CHEMISTRY?

DR. BHATIA: WE HAVE USED OTHER DRUGS THAT HAVE SIRT1 ACTIVITY IN OUR MODEL TO SHOW THAT THIS IS A DRUGABLE TARGET. SO AS FAR AS THAT'S CONCERNED, I THINK SOME OF THE DATA WAS IN THE GRANT AS WELL.

WE HAVE USED ONE OF THE EX COMPOUNDS, BUT THAT COMPOUND WAS NOT VERY POTENT IN OUR HANDS. SO I DON'T KNOW IF IT'S THE SAME COMPOUND THAT YOU'RE

TALKING ABOUT.

DR. LOVE: ELIXIR.

DR. BHATIA: IT'S AN E-X SOMETHING.

CHAIRMAN KLEIN: OKAY. OTHER POINTS? THANK YOU VERY MUCH.

DR. LOVE: I HAVE ONE OTHER QUESTION. HAVE PEOPLE USED THINGS LIKE RNAI TO INHIBIT SIRT1? THAT SHOULD WORK PRETTY EFFECTIVELY.

DR. BHATIA: THAT'S THE METHOD THAT WE HAVE USED TO TEST IT AS A TARGET. SO OUR RESULTS ARE BASED ON RNAI BASE KNOCK-DOWN AS WELL AS THE USE OF A KNOCKOUT MOUSE.

CHAIRMAN KLEIN: OKAY. THANK YOU VERY MUCH.

1768, THERE'S A PRESENTATION FROM THE AUDIENCE. DOES ANYONE WANT STAFF PRESENTATION BEFORE THAT? 1768 FROM THE AUDIENCE, PLEASE. PLEASE IDENTIFY YOURSELF.

DR. DENG: I'M SOPHIE DENG. I'M THE PI OF THIS PROPOSAL. I'M AN OPHTHALMOLOGIST SPECIALIZED IN CORNEAL TRANSPLANT, LIMBAL STEM CELL DEFICIENCY, AND OCULAR SURFACE RECONSTRUCTION. I DEVOTE HALF MY TIME TO PATIENT CARE, THE OTHER HALF OF MY TIME TO TRANSLATIONAL RESEARCH.

THE LONG-TERM GOAL OF MY RESEARCH IS TO

DEVELOP NEW CLINICAL TESTS TO ACCURATELY DIAGNOSE AND STAGE LIMBAL STEM CELL DEFICIENCY OR CORNEAL EPITHELIAL STEM CELL DEFICIENCY AND TO DEVELOP EFFECTIVE AND SAFE TREATMENT FOR THIS EYE DISEASE.

DURING MY LAST THREE YEARS AT THE JULES STEIN EYE INSTITUTE AT UCLA, I HAVE SEEN MANY, MANY OF THESE PATIENTS WITH LIMBAL STEM CELL DEFICIENCY WHO ARE IN NEED OF TREATMENT TO REGAIN THEIR SIGHT.

THIS IS A VERY DEVASTATING DISEASE AND CAN BE CURED WITH LIMBAL STEM CELL TRANSPLANT. THE IDEAL TREATMENT, AS YOU KNOW, IS TO REGENERATE THESE LIMBAL STEM CELL AND THEN TRANSPLANT IT BACK TO THE PATIENT'S EYE, OR THIS IS A PATIENT-SPECIFIC LIMBAL STEM CELL-BASED THERAPY.

THIS THERAPY IS AVAILABLE IN EUROPE AND ASIA, AND IT HAS A THREE-YEAR SUCCESS RATE AS HIGH AS 68 PERCENT, WHICH WAS PUBLISHED TWO MONTHS AGO IN THE *NEW ENGLAND JOURNAL OF MEDICINE*.

THE MOST EFFICIENT METHOD TO GROW THIS STEM CELL REQUIRES THE MOUSE FEEDER CELLS, WHICH ALSO REQUIRE CALF SERUM. BECAUSE USE OF THESE ANIMAL PRODUCTS MAKES IT NEARLY IMPOSSIBLE TO PASS THE FDA BECAUSE OF THE POTENTIAL CROSS CONTAMINATION, THEREFORE, THE FIRST PART OF OUR PROPOSAL IS TO ESTABLISH A NEW CULTURING SYSTEM THAT

DOES NOT REQUIRE ANY ANIMAL PRODUCT SO THAT WE CAN BRING THIS THERAPY TO THE UNITED STATES AND BE AVAILABLE TO THE PATIENT. AND THAT WOULD BE THE FIRST PART OF -- A STARTING POINT IN THE FOUNDATION FOR DEVELOPING THE NEW TREATMENT IN THE FUTURE.

IN SUBSEQUENT PART OF THE PROPOSAL, WE PLAN TO FURTHER IMPROVE THE EXPANSION EFFICIENCY OF THE STEM CELL POPULATION SPECIFICALLY BY USING A NOVEL APPROACH, USING A SMALL MOLECULE TO MODULATE THE PROLIFERATION AND MEANWHILE INHIBITING THE DIFFERENTIATION OF LIMBAL STEM CELLS. THIS WILL IMPROVE THE LONG-TERM CLINICAL OUTCOME BECAUSE YOU GENERATE LARGER PORTIONS OF THE STEM CELL POPULATION FOR TRANSPLANTATION.

FOR PATIENTS WHO HAVE TOTAL LIMBAL STEM CELL DEFICIENCY MEANS THAT THERE'S NO STEM CELL THEY CAN EXPAND ANYMORE, THEN AN ALTERNATIVE CELL POPULATION IS NECESSARY. WE PROPOSE TO TRANSDIFFERENTIATE SKIN STEM CELLS INTO THE CORNEAL STEM CELLS. AND WE SPECIFICALLY DESIGNED THE EXPERIMENT IN A WAY THAT ANY POSITIVE FINDING CAN BE APPLIED DIRECTLY TO THE CLINICAL APPLICATION.

SO IN SUMMARY, OUR APPLICATION WE WILL FIRST ENABLE THE INITIATION OF THE PHASE I AND II CLINICAL TRIAL TO START PATIENT-SPECIFIC STEM CELL

THERAPY FOR PARTIAL OR UNILATERAL LIMBAL STEM CELL DEFICIENCY. IN ADDITION, THE SUBSEQUENT RESEARCH IN THIS PROPOSAL HAS THE GREAT POTENTIAL TO DEVELOP NOVEL AND MORE EFFICIENT BIOENGINEERING METHODS TO REGENERATE LIMBAL STEM CELL FOR TRANSPLANTATION.

AND WE BELIEVE THAT WE HAVE A TEAM WITH EXPERTISE IN THE LIMBAL STEM CELL BIOLOGY, CLINICAL AND TRANSLATION RESEARCH, THE REAGENTS, AND AN ENVIRONMENT NECESSARY FOR OUR PROJECT. THANK YOU VERY MUCH FOR YOUR CONSIDERATION. AND HOPEFULLY IN THE NEAR FUTURE I WILL NOT TURN AWAY MY PATIENTS AND TELLING THEM THAT, NO, WE DON'T HAVE THIS THERAPY IN THE UNITED STATES. YOU CAN GO TO ITALY OR JAPAN FOR YOUR THERAPY. HOPEFULLY IN THE FUTURE, WE CAN SAY, YES, I CAN OFFER YOU THIS PATIENT-SPECIFIC THERAPY IN CALIFORNIA. THANK YOU.

CHAIRMAN KLEIN: THANK YOU VERY MUCH. ANY MEMBER? JEFF SHEEHY. ANY OTHER MEMBERS?

MR. SHEEHY: SO I JUST WANT TO SET THIS UP. NO. 1, THIS IS A DEVELOPMENT CANDIDATE FEASIBILITY, SO THIS IS THE LOW END. IT'S 1.5 MILLION, RIGHT. SO WHAT YOU WANT TO DO, YOU HAVE A PROCEDURE THAT PEOPLE ARE DOING RIGHT NOW IN ITALY, THEY'RE DOING RIGHT NOW IN JAPAN THAT YOU CANNOT DO IN THE UNITED STATES. WE KNOW IT WORKS BECAUSE THE

FEEDER CELLS THAT THEY CULTURE THESE CELLS, THEY TAKE FROM A PATIENT'S OWN CELLS. SO THIS IS AN AUTOLOGOUS TRANSPLANT.

SO YOUR FIRST AIM IS JUST TO DO THIS ON ANIMAL-FREE FEEDER. WHY WOULDN'T WE TRY TO SEE IF THAT WAS FEASIBLE SO THAT PEOPLE -- DEVELOP THIS TECHNOLOGY HERE IN A WAY THAT THE FDA WOULD APPROVE IT. THAT JUST SEEMS LIKE A NO-BRAINER. AND THE AMOUNT OF MONEY WE'RE TALKING ABOUT INVESTING HERE IS RELATIVELY INSIGNIFICANT IF WE CAN HELP PEOPLE SEE.

THE OTHER AIMS, JUST ON THAT ALONE, I CAN IMAGINE YOU WOULD BE IN A CLINICAL TRIAL FAIRLY QUICKLY AS SOON AS YOU DEVELOPED A SAFE FEEDER PROCESS, AND THERE MUST BE ALL SORTS OF FEEDER --

DR. DENG: YES. WE HAVE THREE CANDIDATES IN OUR PROPOSAL.

MR. SHEEHY: THIS SEEMS TO ME --

DR. TROUNSON: WELL, YOU GOT TO HAVE HEALTHY LIMBAL CELLS. SO I UNDERSTOOD IN THESE DISEASES THERE ARE NO HEALTHY LIMBAL CELLS IN THESE PATIENTS.

MR. SHEEHY: WHAT ARE THEY USING IN EUROPE? THEY'RE TAKING CELLS IN EUROPE FROM -- THERE ARE AUTOLOGOUS TRANSPLANTS THAT ARE GOING ON

RIGHT NOW IN EUROPE.

CHAIRMAN KLEIN: WHY DON'T WE GET THE SCIENTIST WHO IS THE PI TO COMMENT ON THAT, AND LET'S GO TO THE LITTLE FURTHER.

DR. DENG: YES. THIS IS A SPECIAL DISEASE. I THINK THERE'S A MISUNDERSTANDING OF THE PROPOSAL AND ALSO THE APPLICATION TOO. THERE ARE TWO. ONE IS PARTIAL LIMBAL STEM CELL DEFICIENCY, MEANING THAT IN THIS EYE, THERE'S DEFICIENCY, BUT NOT TO A TOTAL LIMBAL STEM CELL DEFICIENCY. THAT MEANS THERE IS A SMALL POPULATION OF STEM CELLS STILL ASSIST IN THIS EYE SO THEY CAN BIOPSY IT AND EXPAND THEM IN CULTURE. SO THE APPLICATION IN THE *NEW ENGLAND JOURNAL OF MEDICINE* IS FOR THOSE POPULATIONS THAT STILL HAVE STEM CELLS EITHER IN ONE EYE OR BOTH EYES.

SO FOR TOTAL LIMBAL STEM CELL DEFICIENCY, EXACTLY WHAT YOU REFER TO, THERE'S NO MORE STEM CELL ON THIS OCULAR SURFACE, THEN THERE'S NO CELLS TO BE EXPAND. FOR THOSE WE PROPOSED TO TRANSDIFFERENTIATE THE SKIN STEM CELL, WHICH IS ABUNDANT ON THE PATIENT, AND THEN TRANSDIFFERENTIATE THEM INTO THE CORNEAL PHENOTYPE. SO WE HAVE TARGETED BOTH POPULATION OF PATIENTS.

DR. TROUNSON: SO YOU'VE GOT TO HAVE AT

LEAST SOME LIMBAL CELLS THERE IN ONE EYE OR THE OTHER IN ORDER TO DO IT. THAT'S REALLY CRITICAL. IF PATIENTS HAVE LOST THOSE LIMBAL CELLS, THEN YOU HAVE TO GO TO ANOTHER CELL TYPE. I THINK THAT WAS THE ISSUES OF AIMS 2 AND 3. WHAT SORT OF CELLS WOULD YOU USE, AND HOW WOULD YOU GET THERE?

MS. SAMUELSON: JUST SO I UNDERSTAND, WHAT WAS THE ANSWER TO THAT? THERE ARE SOME HEALTHY CELLS?

DR. DENG: AS I MENTIONED, THERE'S TWO -- THIS IS A SPECIAL DISEASE. FOR THOSE PATIENTS STILL HAS STEM CELLS, REMAINING STEM CELLS, WE CAN EXPAND THEM. THIS IS THE PROPOSAL AIM 1 AND 2 BEFORE END-STAGE DISEASE BECAUSE YOU HAVE FROM EARLY STAGE, PARTIAL TO SEVERE TO END STAGE. WHEN IT'S THE END STAGE, THERE'S NO MORE STEM CELL ASSIST. THEN WE NEED TO LOOK FOR ALTERNATIVE CELL SOURCE. THAT WOULD BE AIM 3 OF OUR PROPOSAL.

CHAIRMAN KLEIN: SO DID YOU SAY THAT THE PARTIAL -- THE CONDITION WHERE IT'S PARTIAL APPLIES TO AIMS 1 AND 2?

DR. DENG: YES.

CHAIRMAN KLEIN: IT'S AIM 3 THAT IS THE TOTAL?

DR. DENG: YES.

CHAIRMAN KLEIN: DR. PIZZO.

DR. PIZZO: FIRST JUST A GENERAL A STATEMENT. THIS WILL SOUND CRITICAL, JEFF, SO PLEASE BEAR WITH ME. THERE ARE LOTS OF THINGS THAT ARE GIVEN AROUND THE WORLD, INCLUDING STEM CELLS, AND THEY DON'T NECESSARILY WORK AND WE DON'T EMBRACE THEM. I DON'T KNOW THE DATA WITH REGARD TO HOW WELL THIS, QUOTE, WORKS IN OTHER COUNTRIES. HAVE WE LOOKED INTO THAT? IS THERE ANY SUBSTANTIVE DATA TO SUPPORT THIS BECAUSE THERE ARE MANY CLAIMS ABOUT OTHER THERAPIES, INCLUDING STEM CELLS?

CHAIRMAN KLEIN: COULD WE HAVE FOR JUST A MOMENT, COULD THE STAFF TALK ABOUT THE *NEW ENGLAND JOURNAL OF MEDICINE* AND THE VERIFICATION OF THAT IN OTHER COUNTRIES?

DR. YAFFE: THERE WAS A RECENT PUBLICATION IN *NEW ENGLAND JOURNAL OF MEDICINE* THAT CHARACTERIZED THE TRANSPLANT THAT DR. DENG HAS DESCRIBED WHERE SURVIVING LIMBAL CELLS GENERALLY FROM THE OTHER EYE ARE USED FOR THE TRANSPLANT. AND, IN FACT, THAT STUDY SHOWED THAT -- THAT STUDY SEEMED TO VERIFY -- I'M NOT A MEDICAL DOCTOR -- BUT THAT STUDY VERIFIED THE EFFICACY OF THIS APPROACH BEING DONE IN EUROPE USING ANIMAL FEEDER CELLS, AS MR. SHEEHY HAS MENTIONED.

AND THE OTHER THING THAT STUDY SHOWED IS A FEW PERCENT OF REMAINING LIMBAL CELLS WAS ADEQUATE. THIS IS THE SOURCE OF THE CELLS FOR SPECIFIC AIMS 1 -- SPECIFIC AIM 1 AND 2 IN THE APPLICATION.

DR. PIZZO: THAT STUDY WAS PUBLISHED, YOU SAID, IN THE *NEW ENGLAND JOURNAL OF MEDICINE*.

DR. YAFFE: *NEW ENGLAND JOURNAL OF MEDICINE*.

DR. PIZZO: DO YOU KNOW WHAT YEAR OR WHEN?

CHAIRMAN KLEIN: IT'S ABOUT 60 DAYS AGO, I BELIEVE.

DR. YAFFE: IT'S THIS YEAR.

MR. SHEEHY: THE PROBLEM IS ANIMAL FEEDER CELLS.

CHAIRMAN KLEIN: WE'RE GOING TO GO TO --

DR. PIZZO: JEFF IS COMMENTING ON ANIMAL FEEDERS.

MR. SHEEHY: I JUST SAID THE PROBLEM IS ANIMAL FEEDER CELLS. THAT'S WHY WE CAN'T DO IT HERE. IT'S NOT BECAUSE IT'S SOME WACKY THING. IT'S PUBLISHED IN THE *NEW ENGLAND JOURNAL*. IT'S BECAUSE THEY DID IT ON THE FEEDER CELLS THE FDA DOESN'T APPROVE OF. SO THEY WANT TO TRY TO USE A DIFFERENT METHOD THAT THE FDA WILL APPROVE OF.

CHAIRMAN KLEIN: WE'RE GOING TO GO TO DR.

JEANNIE FONTANA, THEN WE'RE GOING TO GO TO DR. PULIAFITO AND THEN TO DR. OS STEWARD.

DR. FONTANA: I HAD A QUESTION, JEFF, THAT MAYBE YOU CAN ENLIGHTEN US ON WHAT WAS HAPPENING IN THE ROOM BECAUSE THIS DATA THAT YOU ARE PRESENTING AND THAT WAS PRESENTED TO US BY THE PI, IT SEEMS TO BE PRETTY CLEAR. AND I'M CURIOUS WHY THE REVIEWERS WERE SO HARSH.

MR. SHEEHY: I THINK THAT'S A MORE EXISTENTIAL QUESTION. IT WOULD BE BETTER IF WE JUST FOCUSED ON -- I DON'T KNOW. I CAN'T REMEMBER ALL OF THIS, EVERY DISCUSSION. I JUST THINK, IN GENERAL -- IF I HAD TO SAY ANYTHING, IT'S THE HALO EFFECT FROM DEVELOPMENTAL CANDIDATE REVIEWS WHICH WERE SO "UMM." EVERY NOW AND THEN PEOPLE MISS STUFF TOO.

CHAIRMAN KLEIN: SO IF WE CAN PROGRESS TO DR. FONTANA, AND WE HAVE SEVERAL SPEAKERS. LET'S MAKE SURE AS WE GO THAT WE CHECK OUR CONFLICTS LIST.

THIS INVOLVES UCLA.

DR. FONTANA: I CEDE MY QUESTION.

CHAIRMAN KLEIN: YOU ASKED YOUR QUESTION. DR. PULIAFITO.

DR. PULIAFITO: I'LL CHIME UP AS THE OPHTHALMOLOGIST. STEM CELL THERAPY OF CORNEAL DISEASES IS CONCEPTUALLY A VERY WELL-ESTABLISHED

THING. SO THIS IS NOT SOME OFFBEAT IDEA. AND I THINK THAT THIS PROPOSAL IS MERITORIOUS FROM THAT POINT OF VIEW. SO IT'S NOT LIKE THIS IS INJECTING STEM CELLS IN SOMEBODY'S KNEE IN SOME FOREIGN COUNTRY OR SOMETHING.

CHAIRMAN KLEIN: OKAY. AND --

DR. PIZZO: I AGREE THAT'S NOT SO MERITORIOUS.

DR. STEWARD: I GUESS A QUESTION TO JEFF. I THINK YOU WERE -- I DON'T WANT TO PUT WORDS IN YOUR MOUTH, BUT I THINK YOU WERE MORE OR LESS SAYING THAT AIM 1 WAS STRONG AND IMPORTANT, AIM 2 MAYBE, AIM 3 NOT. I'M ASKING REALLY IF YOU'RE SUGGESTING AN APPROVAL WITH PERHAPS A REDUCTION IN SCOPE AND FUNDS?

CHAIRMAN KLEIN: SO COULD WE WAIT TILL WE HAVE A PROPRIETARY REVIEW TO COME BACK IN AND BE ABLE TO SEE AND GET A PROPRIETARY DISCUSSION THAT WILL MAYBE INFORM THAT QUESTION, AND WE CAN SAVE THAT QUESTION? IS THAT POSSIBLE, DR. STEWARD?

MR. SHEEHY: TO BE HONEST, JUST TO BE CLEAR, THIS IS A DEVELOPMENTAL CANDIDATE FEASIBILITY ONE. SO IT'S ALREADY GREATLY REDUCED. IF YOU LOOK AT THESE, MOST OF THEM ARE FOUR TO SIX. THE DEVELOPMENTAL FEASIBILITY ONES ARE ONLY ABOUT ONE

AND A HALF MILLION, SO IT'S ALREADY NOT ONE OF THE GIANT GRANTS.

DR. PRIETO: I JUST WANTED TO RESPOND TO PHIL'S QUESTION. I THINK IN THE REVIEW WE DON'T HAVE THE BENEFIT OF SOME OF THIS BACK AND FORTH AND HAVING THE PI PRESENT TO ANSWER QUESTIONS ABOUT THE APPLICATION. I THINK THAT ENLIGHTENS OUR DISCUSSION.

MR. SHEEHY: SINCE -- CAN I CUT TO THE CHASE, BOB, NOT TO INTERRUPT? BUT WHY COULDN'T I JUST GO AHEAD AND MAKE A MOTION? WE'VE HAD THIS DISCUSSION. I DON'T THINK WE NEED TO TAKE TIME IN CLOSED SESSION. I WOULD LIKE TO MOVE TO MOVE THIS INTO THE FUNDABLE CATEGORY. WE'VE HAD THE OPHTHALMOLOGIST SAY THIS IS MERITORIOUS.

CHAIRMAN KLEIN: IF WE CAN DO IT ON AN OVERALL BASIS, JEFF, SO WE ARE SYSTEMATIC IN OUR APPROACH AND CONSISTENT WITH ALL THE APPLICATIONS, I'D APPRECIATE THAT.

DR. PIZZO: I AGREE. I DON'T THINK WE SHOULD FOOL WITH THIS.

CHAIRMAN KLEIN: DR. LOVE.

DR. LOVE: DR. YAFFE HAD A COMMENT.

DR. YAFFE: I JUST WANTED TO REPRESENT WHAT THE GRANTS WORKING GROUP DISCUSSED AND POINT

OUT THERE WERE THREE SPECIFIC AIMS. AS JEFF HAS CHARACTERIZED, THE GRANTS WORKING GROUP FELT THE FIRST SPECIFIC AIM HAD QUITE A BIT OF MERIT. THE OTHER TWO SPECIFIC AIMS, THEY FELT, WERE NOT SUPPORTED ADEQUATELY BY PRELIMINARY DATA. THEY INVOLVE VERY BASIC STUDIES WHICH MIGHT NOT BE WITHIN THE SCOPE OF THIS AWARD.

SO I THINK THAT THEY'RE -- IN ADDRESSING DR. FONTANA'S INQUIRY, I THINK THAT THEIR JUDGMENT AND WHERE THEY PLACED THIS REFLECTED THOSE CONCERNS ABOUT SPECIFIC AIMS 2 AND 3, WHICH WERE TWO-THIRDS OF THE GRANT.

CHAIRMAN KLEIN: DR. YAFFE, FOR A DCF GRANT, WAS IT REQUIRED THAT WE HAVE DATA SUPPORTING THIS, OR WAS THIS A CATEGORY WHERE THE STRENGTH OF THE TEAM, THE STRENGTH OF THE CONCEPT, THE SCIENTIFIC METHODOLOGY WAS SUFFICIENT? IT'S A QUESTION.

DR. YAFFE: THEY STILL NEEDED ADEQUATE AND APPROPRIATE PRELIMINARY DATA TO SUPPORT THE SPECIFIC AIMS.

DR. TROUNSON: IT DID REQUIRE TRANSDIFFERENTIATION FROM SKIN CELLS TO CORNEAL EPITHELIAL CELLS. I SUGGEST THAT'S A PRETTY BIG STEP.

CHAIRMAN KLEIN: AND THAT'S AIM 3; IS THAT RIGHT, DR. TROUNSON?

DR. TROUNSON: YEAH.

MR. SHEEHY: I JUST WOULD CAUTION US NOT TO BE CAUGHT UP IN THE TYRANNY OF THE RFA AND ASK IS THIS INTERESTING SCIENCE THAT'S WORTH DOING. FRANKLY, I THINK A LOT OF THE DCF'S HAD SOME VERY OUTSTANDING BASIC SCIENCE IN THEM, AND I THINK THAT THAT PENALIZED THEM. AND PEOPLE HEARD QUESTIONS THAT THEY WANTED TO HEAR ANSWERS TO. WE'VE GOT A GRANT THAT'S GOT ONE GOOD AIM THAT WE SHOULD DO BECAUSE THEY'LL BE IN THE CLINIC POTENTIALLY WITHIN A VERY SHORT TIME, WHICH IS ACTUALLY THE GOAL OF THIS INSTITUTE. AND IF THEY WANT TRY TO DO SOME OTHER COOL STUFF WHILE THEY'RE AT IT AND THEY DON'T SUCCEED, WE FUND BASIC SCIENCE ALL THE TIME THAT DOESN'T SUCCEED. I THINK THEY'LL ANSWER SOME QUESTIONS THAT WE NEED TO HAVE ANSWERED.

I WOULDN'T GET CAUGHT UP SAYING, WELL, IT DOESN'T QUITE FIT THIS RFA. THEY HAVE ONE AIM THAT CLEARLY FITS THE RFA. I WOULDN'T WHACK THE OTHER TWO AIMS BECAUSE THEY DON'T HAVE PRELIMINARY DATA. THEY SEEM A PRETTY GOOD TEAM TO ME.

CHAIRMAN KLEIN: I'M GOING TO -- WE'RE GOING TO GO INTO EXECUTIVE SESSION VERY QUICKLY.

WANT TO COVER 1785. THERE'S A PUBLIC PRESENTATION.

DR. HAVTON: MY NAME IS LEIF HAVTON. I'M A NEUROLOGIST AND NEUROSCIENTIST. I'M HERE TO REPRESENT THE EXTRAORDINARY PETITION FOR 1785. THE PROPOSAL IS "REPAIR OF CONUS MEDULLARIS/CAUDA EQUINA INJURY USING HUMAN ES CELL-DERIVED MOTOR NEURONS." THIS IS A PROPOSAL SUBMITTED THROUGH UCLA. THIS IS A PROPOSAL THAT I'M THE PI FOR, AND I HAVE TWO CO-INVESTIGATORS, DR. KORNBLUM AND DR. NOVITCH, BOTH AT UCLA.

FIRST, I WOULD LIKE TO THANK THE MEMBERS OF THE ICOC FOR THIS OPPORTUNITY TO SUBMIT AND PRESENT THIS PETITION. WE VERY MUCH APPRECIATE THIS OPPORTUNITY. I ALSO WISH TO THANK THE REVIEWERS FOR THE FEEDBACK AND HELPFUL COMMENTS.

OUR PROPOSAL AIMS AT RESTORING BLADDER FUNCTION AFTER A FORMAL SPINAL CORD INJURY THAT AFFECTS THE MOST CAUDAL PORTION, THE SACRAL PORTION OF THE SPINAL CORD. IT'S ABOUT 20 PERCENT OF ALL SPINAL CORD INJURIES. WE TARGET RECOVERY OF THE BLADDER FUNCTION THERE USING A STEM CELL THERAPY.

THE REVIEWERS WERE SUPPORTIVE ALTHOUGH THEY DID HAVE SOME CONCERNS, WHICH I WILL ADDRESS NEXT.

FIRST, ONE OF THE CONCERNS PRESENTED BY

THE REVIEWERS WAS THAT OUR PRELIMINARY DATA SUGGESTED THAT OUR APPROACH WAS A NEUROPROTECTIVE APPROACH. AND I THINK THAT THIS IS A MISUNDERSTANDING OF OUR PROPOSAL. OUR PRELIMINARY DATA THAT WE HAVE OBTAINED TO DATE AND THE PROPOSAL SHOW THAT OUR PROPOSAL IS A CELL REPLACEMENT THERAPY AND NOT A NEUROPROTECTIVE APPROACH. HOWEVER, WE HAVE PROVIDED DATA ON A NEUROPROTECTIVE EFFECT PROVIDED BY THE NERVE ROOT REPLANTATION THAT IS PART OF THE COMBINATORIAL STRATEGY HERE. THIS UNEXPECTED NEUROPROTECTIVE EFFECT PROVIDED BY THE NERVE ROOTS IS THAT THEY INCREASE THE SURVIVAL OF THE TRANSPLANTED CELLS. WE DON'T SEE THIS AS A PROBLEM. WE SEE THIS AS A FEATURE OF OUR DESIGN AND OUR MODEL.

A SECOND CONCERN BY THE REVIEWERS WAS THAT THEY HAD SOME CONCERNS ABOUT OUR ABILITY TO PRODUCE THE THERAPEUTIC CELL POPULATIONS, INCLUDING AUTONOMIC NEURONS, AND ALSO SOME CONCERNS ABOUT THE PURITY OF MOTOR NEURONS. AND WE RESPECTFULLY DISAGREE WITH THIS ASSESSMENT. OUR TEAM IS VERY EXPERIENCED IN THE PRODUCTION OF MOTOR NEURONS. WE HAVE PUBLISHED ON OUR ABILITY TO DERIVE MOTOR NEURONS FROM HUMAN ES CELLS AND TO SORT CELLS EXPRESSING HB9, WHICH IS A MOTOR NEURON MARKER,

USING CURRENT METHODS WHICH ARE ALL AVAILABLE TO US AND PART OF WHAT WE DO. WE CAN EASILY SCALE UP OUR PROTOCOLS TO PRODUCE THE NEEDED NUMBERS OF CELLS FOR OUR PROPOSED TRANSPLANTATION EXPERIMENTS.

WITH REGARDS TO PURITY, WE EXPECT THAT THE SORTED HB9 CELLS WILL INCLUDE SUBTYPES OF NEURONS, INCLUDING AUTONOMIC NEURONS AND MOTOR NEURONS. AGAIN, THIS IS A FEATURE, NOT A PROBLEM. WHEN RESTORING BLADDER FUNCTION, YOU NEED BOTH AUTONOMIC NEURONS AND MOTOR NEURONS. AND HB9 AS A TRANSCRIPTION FACTOR IS A COMMON DENOMINATOR THAT WE FEEL LUCKY TO HAVE AS A MARKER TO SORT CELLS TO COVER BOTH CELL TARGETS IN ONE EXPERIMENT.

A THIRD COMMENT FROM THE REVIEWERS WAS THAT THEY WERE NOT CONVINCED THAT WE WILL BE ABLE TO ACHIEVE ANATOMICALLY ACCURATE AND TOPOGRAPHICALLY PRECISE RE-ENERVATION OF OUR TARGETS USING THE TRANSPLANTED CELLS. I THINK HERE THAT OUR MODEL OF RESTORING BLADDER FUNCTION WORKS TO OUR ADVANTAGE IN THAT THE TARGET IS A PROXIMAL TARGET. IT'S VERY CLOSE TO THE SPINAL CORD AND THE INJECTION SITES. IT'S NOT A DISTAL TARGET SUCH AS GETTING, FOR INSTANCE, HAND FUNCTION BACK.

ALSO WITH BLADDER FUNCTION, IT'S A YES-OR-NO OR AN ON-AND-OFF TYPE OF RESPONSE. EITHER

THE SUBJECT IS VOIDING OR NOT. AND WITH THAT LEVEL OF ACTIVATION PATTERN, WE FEEL THAT WE HAVE A BETTER SUCCESS THAN IF WE WERE TARGETING A VERY FINE MOTOR SKILL SUCH AS HAND FUNCTION. SO I THINK, AGAIN, HERE THAT THE FEATURE IS IN THE MODEL AND OUR DISEASE TARGET HERE, AND THAT WE DO NOT THINK THAT THE DEGREE OF ANATOMICAL PRECISION WILL BE AS HIGH HERE COMPARED TO OTHER NEUROLOGICAL CONDITIONS.

THE FOURTH CONCERN AND FINAL CONCERN I WOULD LIKE TO ADDRESS HERE IS THE CONCERNS REVIEWERS HAD WITH REGARDS TO OUR TEAM AND WHETHER WE HAD ADEQUATE EXPERIENCE TO PERFORM A CELL THERAPY FOR THE DAMAGED SPINAL CORD. HERE WE, AGAIN, RESPECTFULLY DISAGREE WITH THE ASSESSMENT. WE HAVE DEMONSTRATED IN OUR PRELIMINARY STUDIES THAT WE ARE ABLE TO PREPARE AND TRANSPLANT STEM CELLS FROM BOTH HUMAN AND RODENT SOURCES. WE CAN IDENTIFY THEM. WE CAN PERFORM A VARIETY OF FUNCTIONAL TESTS TO ASSESS SUCCESS OF EXPERIMENTS.

MY OWN LAB HAS EXTENSIVE EXPERIENCE WITH TRANSLATIONAL STUDIES AFTER SPINAL CORD INJURY. IT'S WHAT WE DO. IT'S OUR MAIN FOCUS.

PROFESSOR KORNBLUM HAS PUBLISHED EXPERIENCE IN NEURAL STEM CELL GRAFTING OF THE BRAIN AND IDENTIFYING AND CHARACTERIZING SPINAL CORD STEM

CELLS. DR. NOVITCH IS A RECOGNIZED AUTHORITY ON SPINAL CORD AND MOTOR NEURON DEVELOPMENT. SO WE BELIEVE THAT WE ARE VERY WELL SUITED FOR THE PROPOSED STUDIES. IN FACT, WE BELIEVE THAT WE ARE UNIQUELY POISED TO SUCCEED IN THE PROPOSED EXPERIMENTS. AND WE ALSO BELIEVE THAT THESE TYPES OF EXPERIMENTS ARE VERY MUCH NEEDED.

STUDIES ON THIS FORM OF SPINAL CORD INJURY AND RECOVERY OF BLADDER FUNCTION IS CLEARLY AN UNDERSTUDIED AREA IN MEDICAL SCIENCE AND TRANSLATIONAL STUDIES. THANK YOU VERY MUCH.

CHAIRMAN KLEIN: THANK YOU. ANY OTHER QUESTIONS?

DR. STEWARD: I'M IN CONFLICT, RIGHT, JAMES.

MR. HARRISON: YOU ARE.

DR. STEWARD: I JUST WANTED TO MAKE THAT CLEAR.

CHAIRMAN KLEIN: SO YOU CANNOT SPEAK. ANY OTHER COMMENTS FROM ANYONE? THANK YOU VERY MUCH. APPRECIATE YOUR PRESENTATION. QUESTION, DR. FONTANA.

DR. FONTANA: THIS HAS NOT BEEN DONE IN RATS?

DR. HAVTON: NO. THESE ARE NEW AND NOVEL

EXPERIMENTS.

DR. FONTANA: I'M KIND OF CURIOUS WHY IT HASN'T, JUST BACKGROUND INFORMATION WHY IT HASN'T. WE'VE SEEN SO MANY WONDERFUL VIDEOS OF SPINAL CORD INJURIES IN RATS AND THEM HAVING POSITIVE EFFECTS WITH STEM CELLS.

DR. HAVTON: LET ME CLARIFY THAT THIS PARTICULAR FORM OF SPINAL CORD INJURY IS DIFFERENT FROM WHAT I BELIEVE ARE THE TYPES OF SPINAL CORD INJURY THAT YOU ARE REFERRING TO. THE SPINAL CORD INJURY MODELS THAT HAVE BEEN PUBLISHED AND PRESENTED IS MORE OF A DISCONNECTION BETWEEN THE UPPER AND THE LOWER PART OF THE SPINAL CORD. IN MEDICINE WE REFER TO THOSE INJURIES AS AN UP THE MOTOR NEURON INJURY. WE ARE STUDYING A LOWER MOTOR NEURON INJURY WHICH IS THE DAMAGE AND INJURY TO THE CELLS THAT GO FROM THE SPINAL CORD TO THE PERIPHERAL TARGET, LIKE MOTOR NEURONS.

THIS TYPE OF INJURY IS VERY WELL KNOWN CLINICALLY TO CREATE DIFFERENT TYPES OF CLINICAL PRESENTATION. AND ALSO IT HAS A UNIQUE NEED FOR A DIFFERENT STRATEGY FOR REPAIR. AND THIS IS IN MANY WAYS THE FORGOTTEN PART OF SPINAL CORD INJURY WHERE THERE HISTORICALLY HAVE BEEN VERY, VERY FEW STUDIES ADDRESSING THE NEEDS OF THIS PATIENT POPULATION.

CHAIRMAN KLEIN: OKAY. THANK YOU VERY MUCH. I'D LIKE TO CALL OUR REMAINING PUBLIC COMMENT. I BELIEVE IT'S ON 1841; IS THAT CORRECT? WE HAVE A COMMENT FROM DR. CHARLES SAVINE, AND THANK YOU FOR COMING FROM LONDON FOR YOUR COMMENT.

MR. SAVINE: THANK YOU. THANK YOU VERY MUCH, MR. CHAIRMAN, LADIES AND GENTLEMEN OF THE BOARD. THANK YOU SO MUCH FOR ALLOWING ME THE HONOR AND THE OPPORTUNITY TO SPEAK TO YOU. I KNOW YOU'RE EXTREMELY BUSY HERE TODAY, SO I WILL BE VERY BRIEF.

MY NAME IS CHARLES SAVINE. I'VE SPENT MORE HALF MY LIFE WORKING AS A JOURNALIST FOR NBC NEWS. SO I SPEAK TO YOU NOT AS A RESEARCHER OR SCIENTIST, BUT AS A FAMILY MEMBER BECAUSE MY FATHER DIED FROM HUNTINGTON'S DISEASE, MY BROTHER IS NOW VERY SICK WITH THE DISEASE, AND I HAVE BEEN TESTED POSITIVE FOR THE MUTATION FOR THE DISEASE.

I'M NOT HERE TO TELL YOU ABOUT THE CRUELTY OF THE DISEASE BECAUSE OF ITS SYMPTOMS AND ITS COLLATERAL DAMAGE AND ITS HEREDITARY NATURE. I WOULD, HOWEVER, LIKE TO TELL YOU ABOUT THE SIGNIFICANCE, I BELIEVE, FOR THE SUPPORT FOR PROFESSOR THOMSON'S WORK AT IRVINE FROM THE HD COMMUNITY, NOT JUST IN CALIFORNIA AND IN THE UNITED STATES, BUT AROUND THE WORLD AND HOW THIS COULD

POTENTIALLY HAVE SIGNIFICANCE BEYOND THE HUNTINGTON'S DISEASE COMMUNITY.

I'M ONE HUNDREDS OF PEOPLE AROUND THE WORLD WHO ARE IN THE PRESYMPTOMATIC OR THE EARLY STAGES OF THE DISEASE WHO ARE PART OF AN ONGOING LONGITUDINAL STUDY COHORT ALREADY ESTABLISHING EXTENSIVE AND RELIABLE BIOMARKERS FOR ALL STAGES OF HUNTINGTON'S DISEASE, INCLUDING THOSE THAT WOULD HAVE BEEN UNTIL NOW, TILL RECENTLY, DESCRIBED AS PRESYMPTOMATIC. BECAUSE OF THE UNIQUE NATURE, THE UNIQUE IDENTIFIABLE NATURE OF HUNTINGTON'S DISEASE, WE PROVIDE A PERFECT RESEARCH GROUP THAT CAN SERVE TO ENABLE PROFESSOR THOMSON'S GROUNDBREAKING WORK TO HAVE ACCESS TO CLINICAL TRIALS AS WELL AS ALL FORMS OF CELL SAMPLES.

AND THAT'S BECAUSE OVER TWO DECADES PROFESSOR THOMSON HAS DEVELOPED A RELATIONSHIP OF TRUST WITH THE HUNTINGTON'S COMMUNITY AROUND THE WORLD WHICH GIVES UNBOUNDED SUPPORT. AND THE COMBINATION, I BELIEVE, OF THAT UNIQUE COLLABORATION OF THE TRACTABLE NATURE OF THE DISEASE GIVES US AS A TEAM A REAL OPPORTUNITY TO BENEFIT RESEARCH INTO ALL NEUROLOGICAL AND GENETIC DISEASES BY GIVING THE OPPORTUNITY FOR FUTURE RESEARCH TO BE APPLIED TO PRESYMPTOMATIC SUBJECTS.

NOW, THOSE OF US WHO ARE IN THOSE RESEARCH GROUPS IN THE UK WHERE I AM AND ELSEWHERE IN EUROPE AND IN CANADA UNDERSTAND, WE UNDERSTAND, THAT OUR PARTICIPATION IN THIS RESEARCH IS NOT LIKELY TO BE OF DIRECT BENEFIT TO US, BUT WE ARE HONORED TO BE A PART OF A NOBLE CAUSE, WHICH IS TO GIVE HOPE TO THE HIDDEN OR THE GROWING COMMUNITY OF THOSE SUFFERING DEMENTIA AND THE EVEN GREATER NUMBER WHO CARE FOR THEM. AND WE TRUST PROFESSOR THOMSON. AND ON BEHALF OF THAT COMMUNITY AND THE NEXT GENERATION, I WOULD LIKE TO URGE YOU TO SUPPORT HER TOO.

VERY BRIEFLY, I MENTIONED THE CRUELTY OF THIS DISEASE, AND I JUST WANTED TO ASK FRANCES SOLDANA TO GIVE YOU A LITTLE BIT MORE OF AN IDEA OF THE CRUELTY INVOLVED IN THIS DISEASE.

CHAIRMAN KLEIN: SINCE SHE IS SUCH AN ELOQUENT SPOKESPERSON, SHE'S SPOKEN WITH US BEFORE, SO IF YOU WILL TRY IN THREE MINUTES TO CAPTURE THAT SENTIMENT.

MS. SOLDANA: I THINK I CAN DO IN ONE MINUTE. YOU ALL MET MY DAUGHTER MARGIE HAYES THREE YEARS AGO, AND SHE WAS ABLE TO COME HERE AND SPEAK TO YOU. SHE'S NOW FACING THE END STAGES OF HUNTINGTON'S DISEASE. AND I LOST MY YOUNGEST DAUGHTER ELEVEN MONTHS AGO, AND MY SON IS NOW FACING

END OF LIFE. SO THROUGH YOUR GENEROUS SUPPORT, I THINK WE'LL HAVE A CURE FOR THE NEXT GENERATION. THAT'S MY HOPE BECAUSE MY TWO GRANDCHILDREN ARE NOW AT RISK. AND WHERE THEY ARE JUST BEAUTIFUL AND HEALTHY AS MY CHILDREN ONCE WERE, THEY COULD BE THE NEXT GENERATION THAT IS SUFFERING, THAT WILL SUFFER THE WAY MY CHILDREN HAVE SUFFERED. ALSO THE KRAWL'S LOST THEIR DAUGHTER 12 MONTHS AGO.

SO I JUST WANT TO THANK YOU, JUST MAKE YOU AWARE THAT WE REALLY ARE IN A RACE AGAINST TIME, AND THAT THE RESEARCHERS ARE SO CLOSE, THEY REALLY NEED ALL OUR SUPPORT, BOTH OUR FAMILIES, RESEARCHERS, PHILANTHROPISTS, CIRM, JUST EVERYBODY. I JUST WANT TO THANK YOU FOR GIVING ME THIS TIME TO GIVE YOU AN UPDATE ON HUNTINGTON'S DISEASE. THANK YOU.

CHAIRMAN KLEIN: THANK YOU VERY MUCH. AND THANK YOU, CHARLES, FOR COMING FROM LONDON. IT'S TREMENDOUS THAT ACROSS THE GLOBE THERE'S PARTICIPATION OF PATIENTS IN THESE GROUPS BECAUSE IT WILL GIVE SOME PRECLINICAL HISTORY THAT, AS WE HEARD EARLIER THIS MORNING WITH DEVIC'S DISEASE, COULD HELP ACCELERATE TRIALS BY HAVING LONG-TERM BENCHMARKS FOR THE CONDITION OF THE PATIENTS. SO THANK YOU VERY MUCH FOR BEING HERE. THIS IS PART OF THE RECOMMENDED APPLICATIONS COMING FROM THE PEER

REVIEW GROUP.

MS. SAMUELSON: THANK YOU VERY MUCH.

MR. SHEEHY: CAN I JUST SAY SOMETHING, ESPECIALLY THIS COUPLE WHO LOST THEIR DAUGHTER AND JUDY ROBERSON. WHEN I'M SITTING THERE AND WE'RE LOOKING AT THESE GRANTS AND WE GET ONE THAT COMES IN THAT'S GOOD LIKE THIS, I SEE YOUR FACES. I SEE THE FACES. IT MEANS A LOT FOR YOU TO COME HERE. I NEVER FORGET THAT. I'M SO HAPPY THAT WE HAVE SOMETHING FOR YOU THIS TIME THAT THE SCIENTISTS FEEL ENTHUSIASTIC ABOUT, THAT WE'RE GOING TO BE ABLE TO DO SOMETHING. SO THANK YOU.

CHAIRMAN KLEIN: AND THE LAST ITEM, JUST BEFORE WE GO INTO EXECUTIVE SESSION, I'M GOING TO CALL ON JAMES HARRISON TO RECITE THE STATUTORY BASIS. CAN WE HAVE THREE OR FOUR MINUTES FROM STAFF ON THE BASIC -- ON 1778. REALIZE THAT THIS IS ONE WHERE IT WAS THOUGHT THAT THEY DID NOT HAVE ADEQUATE DATA AND ADEQUATE DEFINITION OF A TARGET TO QUALIFY FOR THE DC CATEGORY. BASIC QUESTION IS THE QUALITY OF THE TEAM, THE QUALITY OF THE SCIENTIFIC THEORY. AND I'M ASKING FOR THIS PRESENTATION IN THE CONTEXT OF WHETHER THERE'S VERY GOOD SCIENCE HERE THAT COULD BE THE BASIS OF A DCF APPLICATION, NOT A DC APPLICATION. THIS IS A QUESTION.

DR. SAMBRANO: SO THIS PARTICULAR APPLICATION IS ONE THAT I THINK CERTAINLY REVIEWERS RECOGNIZED THAT THE PI AND THE TEAM INVOLVED ARE EMINENT SCIENTISTS WORKING IN THE FIELD OF NEURAL BIOLOGY.

NOW, THE MAJOR CONCERN WAS THAT THIS APPLICATION CAME IN LARGELY AS A BASIC BIOLOGY STUDY AND ONE THAT IS VERY BROAD AND COMPREHENSIVE. IT INCLUDES NINE SPECIFIC AIMS. AND THEY ACTUALLY THOUGHT THAT ANY ONE OF THOSE AIMS ALONE COULD BE THE SUBJECT OF A GRANT PROPOSAL. SO THEY THOUGHT IT WAS VERY VAST.

AND ONE OF THE THINGS THAT THEY DID CONSIDER DURING THE PROGRAMMATIC REVIEW WAS THE POSSIBILITY THAT THIS MIGHT POTENTIALLY BE A FEASIBILITY AWARD. HOWEVER, IN THE DISCUSSION THEY REALLY COULDN'T IDENTIFY AMONG THOSE AIMS SOMETHING THAT WAS SUBSTANTIVE ENOUGH THAT WOULD ACTUALLY ADDRESS THE OBJECTIVES OF THE RFA.

SO THEY TOOK A VOTE AND FELT THAT EVEN AS A DCF AWARD, THAT THIS WAS NOT AMENABLE UNDER THIS RFA. THEY, AGAIN, DID PRAISE THE PI AS A STRONG INVESTIGATOR, BUT FELT THAT THIS REASON ALONE WAS NOT SUFFICIENT REALLY TO MOVE A PROJECT THAT THEY THOUGHT WAS POORLY RESPONSIVE FORWARD UNDER THIS

RFA.

CHAIRMAN KLEIN: THANK YOU VERY MUCH. WITH THAT, I'D LIKE TO --

MR. SHESTACK: CAN I JUST ASK A QUESTION OF THE SCIENTIFIC STAFF ON ONE THING IN PARTICULAR, WHICH WAS GRANT 1830, WHICH IS IMMUNE-MATCHED NEURAL STEM CELL TRANSPLANTATION FOR PEDIATRIC NEUROGENERATIVE DISORDERS LIKE LYSOSOMAL STORAGE DISORDERS IN PARTICULAR.

I HAD NOTICED THAT THE PRELIMINARY SCORES HAD BEEN SOMETHING LIKE 68 OR -- NOT SOMETHING LIKE -- 68. AND THEN THEY WERE BROUGHT DOWN TO 60. AND I WONDERED WHY THAT WAS. AND IF THAT WAS POSSIBLE BECAUSE REALLY THIS GRANT MIGHT BE BETTER AS A DCF, NOT A DC, AND WHETHER WE CAN MAKE THAT RECOMMENDATION AT THIS POINT BECAUSE IT SEEMS LIKE AN AREA THAT HAS POTENTIAL THAT CIRM HAS NOT REALLY DONE MUCH IN YET.

DR. OLSON: SO WHAT I'D LIKE TO DO IS MAYBE JUST GIVE THE BOARD AND MEMBERS OF THE PUBLIC AND STAFF AN IDEA OF WHAT THIS AWARD WAS ABOUT TO USE AS A BASIS FOR FURTHER DISCUSSION. JUST A SECOND. WHAT I'D LIKE TO DO IS GIVE THE BOARD AND THE MEMBERS OF THE PUBLIC AND STAFF A LITTLE BIT OF AN IDEA OF WHAT THIS AWARD IS ABOUT. IT WAS A

DEVELOPMENT CANDIDATE APPLICATION, AS MR. SHESTACK HAS NOTED. AND IT FOCUSED ON THE USE OF A COMBINED HEMATOPOETIC STEM CELL TRANSPLANTATION IN CONJUNCTION WITH A NEURAL STEM CELL TRANSPLANTATION DERIVED FROM IPS CELLS FROM THE SAME DONOR.

SO THE IDEA HERE IS THAT THIS IS A LYSOSOMAL STORAGE DISEASE THAT HAS BOTH CNS MANIFESTATIONS AND PERIPHERAL MANIFESTATIONS, AND THAT IT HAS BEEN SHOWN IN SOME INSTANCES THAT HEMATOPOETIC STEM CELL TRANSPLANTATION CAN HELP WITH THE PERIPHERAL MANIFESTATIONS. BUT THE ISSUE IS THAT DOESN'T DEAL WITH THE CNS MANIFESTATIONS AND THE NEURAL DEGENERATION THAT COMES FROM THIS. EVEN IN SPITE OF THE PERIPHERAL TREATMENT, YOU DON'T DEAL WITH THE CNS.

BUT WHEN YOU'RE TALKING ABOUT A DUAL TRANSPLANTATION, THE OTHER THING THAT THIS APPLICANT HOPED TO ADDRESS WAS THE NOTION OF NOT ONLY WILL WE TREAT THE PERIPHERAL, BUT ALSO THE CNS, BUT THEN YOU'RE DEALING WITH THE NOTION OF IMMUNE MATCHING. I THINK WE'VE ALL HEARD IN CERTAIN CANCERS THAT IF YOU CAN SET UP A MICROCHIMERIC SITUATION IN YOUR HEMATOPOETIC SYSTEM, THAT THEN ALLOWS OR THE HYPOTHESIS -- ACTUALLY IT'S BEEN SHOWN TO WORK IN SOME CASES, MOST RECENTLY WITH SOLID ORGAN

TRANSPLANT, LUNG, HEART TRANSPLANTS AND SUCH, THAT YOU CAN, IF YOU SET UP A MICROCHIMERISM SYSTEM THROUGH HEMATOPOETIC STEM CELL TRANSPLANT, YOU CAN GET ACCEPTANCE OF A GRAFT FROM THE SAME DONOR.

SO THAT'S THE HYPOTHESIS THAT THEY'RE PROPOSING TO TEST. AND BASICALLY THE QUESTIONS -- I DID SAY THIS WAS A DEVELOPMENT CANDIDATE AWARD. AND WHAT THE APPLICANT PROPOSES TO DO IS, FIRST, USE -- FIRST, THEY WILL DERIVE IMMUNE-MATCHED NSC'S FROM THE SAME SOURCE AS THE HSC AND TEST THE HEMATOPOETIC BY THEMSELVES, THEY WILL TEST THE NSC BY THEMSELVES, AND THEY WILL TEST THE TWO TOGETHER IN AN ANIMAL MODEL OF THE DISEASE. SO THAT'S WHAT THEY'RE TRYING TO DO.

SO I CAN GO THROUGH THE STRENGTHS AND THE WEAKNESSES OF IT, BUT IT'S VERY MUCH SORT OF A COMBINATION STRATEGY. AND TO TELL THE TRUTH, IT ALMOST IS -- I THINK THAT WAS ONE OF THE REVIEWERS' BIGGEST OBJECTIONS IS THAT THEY'RE LOOKING AT PROOF OF PRECLINICAL CONCEPT, AND THEY WERE NOT DEALING WITH ANY OF THE OTHER ISSUES THAT WOULD BE ASSOCIATED WITH A DEVELOPMENT CANDIDATE. THE REVIEWERS NOTED THAT THEY ARE NOT KEY EXPERIMENTS ADDRESSING CRITICAL ISSUES, SUCH AS APPROPRIATE DOSE, PRELIMINARY TUMOROGENICITY, IMMUNE RESPONSE TO

THE SECRETED ENZYME, PERSISTENCE, LOCATION, AND FUNCTION OF THE NSC'S. NONE OF THOSE WAS ADDRESSED.

THEY WERE CONCERNED THAT THEY WERE ONLY TALKING ABOUT A SINGLE DOSE, PARTICULARLY WHEN YOU ARE TALKING ABOUT NSC'S DERIVED FROM A PLURIPOTENT CELL SOURCE, YOU NEED SOME DOSE RANGE TO GIVE YOU A RANGE FOR TUMOROGENICITY. SO YOUR POINT IS WELL TAKEN IN THE SENSE THAT IT REALLY WAS THE KINDS OF QUESTIONS THEY WERE ASKING WAS MORE SUITABLE FOR A DCF BECAUSE THEY WERE REALLY FOCUSED SOLELY ON PRECLINICAL PROOF OF PRINCIPLE AS OPPOSED TO THE OTHER.

NOW, WHETHER IT WOULD BE POSSIBLE TO ADDRESS THAT AWARD IN THAT WAY I BELIEVE IS HARD TO SAY. BECAUSE ESSENTIALLY THE EXPERIMENTS OUTLINED WERE ALL PRECLINICAL PROOF OF PRINCIPLE EXPERIMENTS.

CHAIRMAN KLEIN: OKAY. THANK YOU.

DR. TROUNSON: JUST ONE ADDITIONAL THING, I THINK, JONATHAN. ONE OF THE BIG BARRIERS IS WE CAN'T GET BLOOD CELLS TO GO TO HEMATOPOETIC STEM CELLS. WE CAN'T GET THE EMBRYONIC OR THE PLURIPOTENTIAL STEM CELLS TO GO TO THE PROPER BONE MARROW HEMATOPOETIC STEM CELLS YET. SO THAT'S STILL A BIG BARRIER, AND IT'S REALLY ONE WHICH WE'RE EXPECTING TO GET BROKEN AT SOME STAGE, BUT IT HASN'T

YET. WE DIDN'T REALLY SEE THIS PROJECT WAS GOING TO BREAK THAT BARRIER, WHICH IS REALLY WHAT'S REQUIRED IF YOU HAVE A DUAL SET OF CELLS.

MR. ROTH: SO THANK YOU, EVERYBODY, FOR YOUR WORK ON ALL OF THESE GRANTS AND THE INPUT YOU'VE GIVEN US. I MUST SAY I FIND MYSELF HERE THINKING ABOUT HOW HARD THIS IS. WE HAVE AN OUTSIDE REVIEW, WHICH WE'VE GOT IN FRONT OF US THAT WAS SCORED, WE HAVE A PROGRAMMATIC REVIEW. AND THANK YOU VERY MUCH FOR THE SUMMARY. THAT REALLY HELPS TO SORT OF GO THROUGH TO SEE WHICH GRANTS YOU LOOKED AT. I THINK THAT WRITTEN SUMMARY IS GREAT. THEN WE HAVE THE EXTRAORDINARY PETITIONS. AND WE HAD A NUMBER OF THEM THIS TIME, ALL OF WHICH APPEAR TO HAVE COME IN LATE; SO, THEREFORE, THERE WAS NO RESPONSE TO. AND THEN TODAY WE HAVE INPUT FROM THE STAFF ON GRANTS, WE HAVE INPUT FROM THE CO-CHAIRS OF THE GRANTS WORKING GROUP, WHICH OBVIOUSLY IS DATED BECAUSE THINGS HAVE CHANGED. AND JEFF FOUND HIMSELF A COUPLE OF TIMES JUST STRUGGLING TO RECALL WHY THINGS ARE THERE. AND THEN, IN ADDITION, WE HAVE AUDIENCE PRESENTATIONS TODAY.

SO IT'S A VERY COMPLICATED WAY FOR ME TO TRY TO FIGURE OUT, WITHOUT HAVING GONE THROUGH THE COMPLETE REVIEW PROCESS, HOW WE SHOULD DETERMINE

WHAT TO FUND AND NOT FUND. AND PARTICULARLY I WONDER ABOUT THE THINGS WHERE THERE WASN'T ANYBODY HERE ADVOCATING. SHOULD I ASSUME THAT THEY, THEREFORE, AGREED WITH THE REVIEW, OR SHOULD I ASSUME THAT HAD THEY KNOWN, THEY MIGHT HAVE BEEN HERE TO IMPART THAT ON US.

BOTTOM LINE, JEFF AND THE WORKING GROUP, YOU DO A LOT OF THINGS, BUT I THINK -- AND THE STAFF -- IT WOULD BE VERY HELPFUL IF YOU SUMMARIZED THOSE THAT YOU THINK WE SHOULD TAKE A LOOK AT AND REALLY HAVE THAT PUT IN FRONT OF US AND SAY, YOU SAID IT TODAY, BUT IT WOULD BE NICE TO HAVE THOSE SORT OF IN ADVANCE SO WE CAN FOCUS ON THOSE AND TRY TO FIGURE OUT WHY YOU WANT US TO LOOK. AND SAME THING WITH YOU, ALAN AND OTHERS. IF YOU THINK THERE'S SOMETHING -- THERE'S THIS DESIRE TO DO THE BEST WE CAN TO FUND THE THINGS THAT ARE REAL AND SHOULD BE FUNDED. BUT IF WE CAN FIND A PROCESS SO THAT THERE REALLY IS A LEVEL PLAYING FIELD, I THINK -- AND I'M NOT SAYING THERE ISN'T, BUT I THINK IT BECOMES VERY HARD FOR US TO MAKE THESE DECISIONS.

DR. TROUNSON: MAYBE IN THE FUTURE I SHOULD MEET WITH JEFF AND WE JUST SORT OF HELP IN THIS PROCESS IF THAT'S AGREEABLE TO THE BOARD AND TO JEFF. ANYTHING WE CAN DO TO HELP THE PROCESS I

THINK WE'D WANT TO DO.

CHAIRMAN KLEIN: I'D ALSO POINT OUT THAT THE STAFF IN GETTING SOME OF THESE LATE, WE NEED THE INFORMATION. THE APPLICANT HAS A BETTER CHANCE IF THEY DO IT EARLY BECAUSE IT GIVES THE STAFF A CHANCE TO REALLY SEE IF THERE'S MERIT THERE AND GIVES THEM A CHANCE TO THEN WRITE ABOUT IT. SO ENCOURAGE STRONGLY FOR PEOPLE TO PUT THEM IN AS EARLY AS POSSIBLE TO GIVE THE STAFF THE BEST CHANCE TO RESPOND.

MS. SAMUELSON: MAY I ASK STAFF A QUESTION ON THAT POINT?

CHAIRMAN KLEIN: I WOULD ALSO SAY THAT THE INTERCHANGE HERE ON CERTAIN GRANTS WHERE THERE'S AN EXTRAORDINARY PETITION IS INTENDED TO PICK UP MISUNDERSTANDINGS BETWEEN THE WORKING GROUP AND THE APPLICANT ON CERTAIN POINTS, AND IN SOME CASES THERE'S BEEN NEW INFORMATION PUBLISHED. SO WE DO HAVE A VERY CHALLENGING JOB, BUT WE HAVE A LOT OF INFORMATION BEFORE US. DR. TROUNSON, DID YOU WANT TO SAY ANYTHING ELSE? JOAN.

MS. SAMUELSON: QUICK QUESTION ON THE EXTRAORDINARY PETITION TIMING ISSUE. WHEN WOULD THE APPLICANT HAVE RECEIVED THE REVIEW SUMMARIES SO THAT THEY HAVE SOMETHING TO RESPOND TO?

DR. TROUNSON: GIL, CAN YOU ANSWER THAT QUESTION?

CHAIRMAN KLEIN: THE QUESTION, GIL, WHEN WOULD THE APPLICANT HAVE RECEIVED THE REVIEW SUMMARIES? AND THE FRAMEWORK HERE IS WE'RE TRYING TO MOVE GRANTS THROUGH AS RESPONSIBLY, ACCURATELY, AND QUICKLY AS POSSIBLE, WHICH, JOAN, I KNOW IS ONE OF YOUR PRIORITIES, SO WE HAVE A CONFLICT FOR THE STAFF BETWEEN MOVING VERY TIMELY. AND WHEN YOU HAVE A LOT OF GRANTS, HAVING ENOUGH TIME FOR THE STAFF TO GET THOSE REVIEWS OUT, HOW MUCH TIME DID THEY HAVE BEFORE THE MEETING?

DR. SAMBRANO: SO WE GIVE TYPICALLY TWO WEEKS BEFORE THE MEETING. THAT'S WHEN WE SEND OUT THE SUMMARIES TO APPLICANTS. BUT, OF COURSE, THIS IS BY E-MAIL, AND SO THEY MAY SEE THEIR E-MAIL AT DIFFERENT TIMES. I THINK MANY APPLICANTS WILL HAVE VARIABLE TIME TO RESPOND. I THINK THAT'S THE ISSUE AND PROBLEM WITH HAVING A PROCESS WHICH WE DO TRY TO SPEED UP, BUT THAT'S KIND OF THE TIME FRAME THAT WE'RE LOOKING AT GENERALLY.

MS. SAMUELSON: JUST SO IT'S CLEAR IN MY HEAD, TWO WEEKS BEFORE, SO THAT'S ROUGHLY 14 DAYS BEFORE NOW?

DR. SAMBRANO: YES.

MS. SAMUELSON: WHAT WAS THE DEADLINE?

DR. SAMBRANO: IT'S FIVE BUSINESS DAYS BEFORE THE BOARD MEETING.

MS. SAMUELSON: IN THIS CASE THAT WOULD HAVE BEEN LAST THURSDAY.

DR. SAMBRANO: IT WOULD HAVE BEEN LAST WEDNESDAY. SO SOMETIMES THEY'LL HAVE MAYBE A WEEK TO PUT SOMETHING TOGETHER.

CHAIRMAN KLEIN: ONE OF THE CHALLENGES IS, AS GIL POINTS OUT, THEY MAY BE OFF GIVING A SPEECH IN LONDON OR A SCIENTIFIC PRESENTATION IN NEW YORK. SO WE'RE TRYING AND STAFF HAS DONE HEROIC EFFORTS IN TRYING TO MAKE SURE, AS YOU'VE SEEN TODAY, THAT THEY CAN COME INFORMED WHEN YOU HAVE QUESTIONS EVEN THOUGH THEY DIDN'T HAVE TIME TO DO A WRITE-UP. SO WE'RE ALL WORKING TOGETHER TO DO THE BEST JOB POSSIBLE.

DR. TROUNSON: YOU WOULDN'T GIVE ME A WEEK TO RESPOND TO YOUR E-MAIL, WOULD YOU, CHAIR?

CHAIRMAN KLEIN: YOU KNOW, SOME OF THEM, I THINK I GIVE YOU TWO OR THREE MONTHS.

MR. HARRISON, COULD WE HAVE THE STATUTORY BASIS FOR BOTH EXECUTIVE SESSIONS, AND DO WE NEED TO SEPARATELY STATE THOSE?

MR. HARRISON: NO. I THINK WE CAN JUST

CITE THE HEALTH AND SAFETY CODE PROVISION WHICH PERMITS THE BOARD TO CONVENE IN CLOSED SESSION TO CONSIDER PROPRIETARY INFORMATION, IN THIS CASE RELATING BOTH TO THE EARLY TRANSLATION II APPLICATIONS AND THE RESEARCH LEADERSHIP APPLICATION. AND THAT IS HEALTH AND SAFETY CODE SECTION 125290.30(D)(3)(B) AND (C).

CHAIRMAN KLEIN: OKAY. WHERE LOGISTICALLY ARE WE GOING?

MS. KING: OUT THE BACK DOOR OF THE ROOM AND ACROSS TO THE OTHER SIDE OF THIS FLOOR OF THE BUILDING TO THE WEST COAST ROOM. LUNCH IS AVAILABLE IN THERE FOR THE BOARD AND THE STAFF. I'D LIKE TO INVITE THE STAFF TO GO IN REALLY QUICKLY AND GRAB YOURS UNLESS YOU'RE STAYING IN THE CLOSED SESSION, THAT IS.

CHAIRMAN KLEIN: SO I'D LIKE US TO TRY AND GET BACK IN 45 MINUTES BECAUSE WE HAVE SOME MEMBERS WHO ARE GOING TO TRY -- WHO HAVE DEADLINES TODAY IN TERMS OF THEIR ABILITY TO STAY IN THE SESSION. SO GETTING THE LARGEST GROUP IN THESE VOTES IS VERY IMPORTANT. SO LET'S TRY AND MOVE QUICKLY. WE ARE IN EXECUTIVE SESSION AT THIS POINT.

(A RECESS WAS TAKEN.)

CHAIRMAN KLEIN: WE'RE GOING TO RECONVENE

HERE. JEFF, CAN I ASK YOU, DID YOU HAVE AN APPLICATION THAT YOU WANTED TO ADDRESS, JEFF?

MR. SHEEHY: I DID. I DID. AND I THINK THE NUMBER IS 1767. JUST LET ME CONFIRM THAT THAT'S THE ONE. NO. 1768. AND I WOULD LIKE TO MOVE TO -- MOTION TO MOVE THAT INTO THE FUNDABLE CATEGORY, THOUGH I DID THINK DR. FRIEDMAN MAY HAVE A FRIENDLY AMENDMENT THAT I WOULD TAKE TO MY MOTION. THIS IS THE EYE ONE. SO I'M GOING TO MOTION TO MOVE THAT UP. MAYBE IF YOU'D LIKE TO MAKE YOUR FRIENDLY AMENDMENT AND THEN DO THE SECOND, BUT I WANT TO MOVE IT INTO THE FUNDABLE CATEGORY.

CHAIRMAN KLEIN: QUESTION FOR DR. FRIEDMAN. DO YOU HAVE A MOTION THAT WOULD ALLOW YOU TO MAKE A SECOND?

DR. FRIEDMAN: YES. I THINK SO. AND ALL MY AMENDMENTS ARE FRIENDLY, SO THIS WILL BE NO DIFFERENT THAN ANY OF THE OTHERS. I SUGGEST THAT BEFORE MAKING THE AWARD AN AGREEMENT BE FORMALIZED WITH THE PRINCIPAL INVESTIGATOR TO SAY THAT THEY WILL BE IN CONTACT WITH THE FOOD AND DRUG ADMINISTRATION PRIOR TO INITIATING STUDIES TO MAKE SURE THAT THE LABORATORY PROCEDURES THAT THEY'RE TALKING ABOUT, THE GMP-LIKE PROCEDURES THEY'RE TALKING ABOUT, WILL FIT WELL WITHIN THE REGULATORY

FRAMEWORK THAT ALREADY EXISTS. IT WOULD BE A SHAME TO HAVE THE RESEARCH PROCEED AND THEN FIND LATER THAT IT WAS OUT OF COMPLIANCE IN SOME WAY THAT WOULDN'T ALLOW FOR THE PROMPT CLINICAL APPLICATION, WHICH, AS I UNDERSTAND FROM JEFF AND JOAN AND MANY OTHER PEOPLE, IS GETTING THIS SPEEDILY, AND CARMEN, GETTING THIS SPEEDILY TO THE CLINIC IS ONE OF THE GOALS HERE. I WOULD ASK FOR THAT TO BE A FORMAL EXPECTATION.

WITH RESPECT TO THE SIZE OF THE GRANT, I'M NOT GOING TO MAKE ANY OBSERVATION. I WOULD RATHER KEEP IT MORE NARROWLY FOCUSED ON THE FIRST PART OF THE ACTIVITY, BUT I'LL LEAVE THAT TO YOU, JEFF. AND I SECOND IT.

MR. SHEEHY: YEAH. AND WE'RE TALKING ABUT FOR AIM 1 THAT THEY DO SOME COMPLIANCE, WHICH I'M VERY COMFORTABLE WITH.

CHAIRMAN KLEIN: SOME REGULATORY VETTING.

MR. SHEEHY: YEAH. BECAUSE IT'S REALLY ABOUT THE MEDIUM, THE FEEDER MEDIUM, TO GET THE RIGHT ONE.

CHAIRMAN KLEIN: SO WE HAVE A MOTION AND A SECOND. ARE THERE COMMENTS FROM THE BOARD?

MR. ROTH: JUST IN FOLLOWING THAT LOGIC, AND I REALIZE IT'S A SMALL AMOUNT OF MONEY, BUT I'D

LIKE TO SEE THE MONEY GO INTO AIM 1 AND FUND THAT EVEN IF IT'S A LITTLE MORE THAN THEY ASKED FOR. I DON'T UNDERSTAND WHY WE WOULD FUND AIMS THAT THERE'S CLEARLY CONSENSUS DON'T MAKE SENSE.

MR. SHEEHY: I DON'T THINK THAT THE CONSENSUS IS THAT THEY DON'T MAKE SENSE. THEY ACTUALLY FOLLOWED QUITE LOGICALLY. THE FIRST AIM IS TO TAKE A PROCEDURE THAT IS WELL ESTABLISHED IN EUROPE, BUT DONE ON THE WRONG TYPES OF FEEDER MATERIAL. THE SECOND AIM IS TO TRY TO EXPAND THE CELLS THAT THEY GET. AND THE THIRD AIM IS TO TRY TO DERIVE THE CELLS THAT THEY'RE USING FROM A DIFFERENT SOURCE. SO THE AIMS DO FOLLOW LOGICALLY. THEY JUST GET PROGRESSIVELY MORE AMBITIOUS.

AND I WOULD NOT WANT -- GIVEN THAT THE AMOUNT OF MONEY IS RELATIVELY SMALL, I WOULD LIKE TO SEE THE SCIENTISTS MOVE DOWN THIS PATH. I MEAN THE FIRST AIM SEEMS RELATIVELY -- SEEMS LIKE SOMETHING THAT THEY'RE GOING TO BE ABLE TO ACHIEVE. THE SECOND IS PROGRESSIVELY MORE DIFFICULT; BUT IN THE CONTEXT OF SUCCEEDING WITH AIM 1 WOULD MEAN THAT THIS PROCEDURE COULD BE AVAILABLE TO MORE PATIENTS. AND IF BY SOME CHANCE THEY DID SUCCEED IN AIM 3, THEY WOULD HAVE SOMETHING THAT WAS AVAILABLE TO AN ENORMOUS NUMBER OF PATIENTS.

SO I WOULDN'T SAY JUST BECAUSE YOU HAVE A RELATIVELY -- YOU HAVE A VERY AMBITIOUS AIM 3, THAT WE DON'T WANT TO FUND IT. I MEAN GIVEN THE AMOUNT OF MONEY THAT WE'RE SPENDING HERE AND THERE, I'D LIKE TO SEE IF SOMEBODY HAS SOMETHING THAT WORKS TO MAKE SURE THAT WE EXPAND IT TO GET TO AS MANY PATIENTS AS POSSIBLE. SO I WOULD LIKE TO ACTUALLY SEE IT FULLY FUNDED WITH ALL AIMS.

DR. STEWARD: SO I THINK I REMEMBER THAT THE CRITICISMS WEREN'T THAT THE AIMS WERE AMBITIOUS, BUT RATHER THAT THEY WERE FLAWED. AND I WONDER IF WE COULD GO BACK. I THINK THERE WAS A MAYBE TWO-SENTENCE SUMMARY OF THAT. CAN WE JUST HEAR THAT AGAIN? I'LL TELL YOU WHY.

I MEAN LOOKING AT THE BUDGET, YOU SAY, OH, THIS IS NOT A LARGE AMOUNT MONEY. ACTUALLY IT'S CLOSE TO $2 MILLION. THAT SOUNDS LIKE A LOT OF THE MONEY FOR ME. IT MAY NOT BE IN THE CONTEXT OF WHAT WE'RE GIVING OUT FOR OTHER THINGS, BUT SORT OF NIH TERMS, THAT'S A TON OF MONEY. IF WE HAVE -- I THINK WE'RE HEARING THAT THERE'S A VERY STRONG AIM 1. GREAT. IF THE OTHER TWO AIMS ARE FLAWED, THEN I THINK WE OUGHT TO CUT THE BUDGET SO THAT THEY CAN DO THE WORK ON AIM 1 AND MAKE IT VERY CLEAR THAT THAT'S WHAT THEY SHOULD DO AND NOT WASTE MONEY ON THINGS

THAT ARE FLAWED. HEAR THE SUMMARY AGAIN IF WE COULD.

CHAIRMAN KLEIN: DR. YAFFE. AND I THINK THERE'S A DISTINCTION HERE. AIM 2 DOES NOT RELY ON GENERATING THE NEW CELLS WITH IPS CELLS. AIM 2 IS EXPANDING THE CELLS. SO I'M NOT -- I THINK THERE'S A MISUNDERSTANDING THAT WAS CLARIFIED IN THIS DISCUSSION THAT AIM 2, I THINK, FOLLOWS MUCH MORE CLOSELY INTO THE SAME CATEGORY AS AIM 1. DR. YAFFE, COULD YOU EDUCATE US HERE?

DR. YAFFE: THE CRITICISM ABOUT AIM 2 WAS THE REVIEWERS FELT THE PROPOSAL LACKED COMPELLING PRELIMINARY DATA IN SUPPORT OF THE USE OF WNT-TO-NOTCH MODULATION TO REGULATE LIMBAL STEM CELL DIFFERENTIATION. IT WAS THE CRUX OF AIM 2 WAS TO EXPAND LIMBAL STEM CELLS BY TWEAKING THE NOTCH AND WNT PATHWAYS.

IN ADDITION, THE CRITICISM -- THAT WAS THE SUBSTANTIVE CRITICISM ABOUT AIM 2. AIM 3 WAS SIMILAR. THE ABSENCE OF PUBLISHED OR PRELIMINARY DATA SUPPORTING THE TRANSDIFFERENTIATION OF EPIDERMAL STEM CELLS INTO CORNEAL EPITHELIAL CELLS. SO CRITICISMS WERE LACK OF PRELIMINARY DATA WHICH RAISED SERIOUS QUESTIONS ABOUT THE FEASIBILITY OF THOSE TWO SPECIFIC AIMS.

DR. STEWARD: I WAS GOING TO SAY I CAN'T VOTE FOR THIS AT FULL LEVEL OF FUNDING. I'LL JUST ANNOUNCE THAT NOW.

CHAIRMAN KLEIN: CAN I ASK, LACK OF PRELIMINARY DATA OR LACK OF SUFFICIENT DATA?

DR. YAFFE: FOR THE SECOND AIM WAS LACK OF SUFFICIENT AND CONVINCING AND COMPELLING DATA. FOR THE THIRD IT WAS LACK OF ANY DATA. NO ONE HAS PUBLISHED ON THAT TRANSDIFFERENTIATION YET.

CHAIRMAN KLEIN: THE SECOND AIM DID HAVE DATA.

MR. SHEEHY: HOW ABOUT WE SPLIT THE DIFFERENCE? AIM 3 IS CLEARLY INCREDIBLY AMBITIOUS. AIM 1 AND 2 SEEM REASONABLE. AIM 1 IS VERY -- SO I WOULD AGREE TO A FRIENDLY AMENDMENT THAT WE PROCEED FUNDING AIM 1 AND AIM 2 AND NOT AIM 3.

DR. STEWARD: WITH AN APPROPRIATE REDUCTION IN BUDGET.

MR. SHEEHY: ABSOLUTELY. AND DR. FRIEDMAN IS COMFORTABLE WITH THAT?

CHAIRMAN KLEIN: IS THE SECOND COMFORTABLE?

MR. SHEEHY: IS THE CHAIR COMFORTABLE WITH THAT?

DR. FRIEDMAN: VERY MUCH.

CHAIRMAN KLEIN: THANK YOU. SO THE AMENDMENT HAS BEEN ACCEPTED. ARE THERE ADDITIONAL COMMENTS? PARTICIPATING IN THE PEER REVIEW SESSION THAT'S BEING REFERENCED, I THINK THAT THERE ARE SOME REVIEWERS THAT HELD EVERYONE TO A HIGH LEVEL OF DATA, THERE WERE SOME THAT DIDN'T. AND THIS HAD DATA AND THERE WAS AN ARGUMENT ABOUT SUFFICIENCY. AND IF WE'RE GOING TO MOVE THIS FIELD FORWARD, THE SECOND AIM IS REACHING, BUT WITHIN A REASONABLE RANGE.

MS. GIBBONS: WHAT ABOUT THE REDUCTION OF THE BUDGET?

CHAIRMAN KLEIN: THEY'RE GOING TO LEAVE IT TO THE SCIENTIFIC STAFF TO MAKE THOSE DECISIONS. THAT'S THE PROPOSAL.

ALL RIGHT. IS THERE ADDITIONAL COMMENTS FROM THE BOARD?

MS. SAMUELSON: YES. JUST TO SAY I THINK IT'S IMPORTANT THAT THE BOARD KNOW THAT THERE WAS A REAL SPLIT IN THE VIEW ABOUT SUFFICIENCY OF DATA. SOME SEEING THIS AS IMPORTANTLY AMBITIOUS AND SUPPORTED BY SUFFICIENT DATA.

CHAIRMAN KLEIN: THANK YOU. PUBLIC COMMENT?

MR. JENSEN: MY COMMENTS ARE NOT TO THE

SUBSTANCE OF THE GRANT APPLICATION, BUT TO THE PROCESS HERE. THIS APPLICATION, THIS PETITION CAME IN LATE AS DID OTHER PETITIONS, AND THERE'S A FUNDAMENTAL QUESTION OF FAIRNESS INVOLVING THE OTHER GRANT APPLICATIONS WHOSE AUTHORS DO NOT UNDERSTAND THAT THERE'S A FICTITIOUS DEADLINE FOR SUBMITTING THESE KINDS OF PETITIONS. SO YOU'VE GOT A FAIRNESS ISSUE. I DON'T THINK IT NECESSARILY DISQUALIFIES THIS FROM FUNDING, BUT THERE'S MORE THAN ONE PETITION AND THIS HAS BEEN A REPEATED PROBLEM.

CHAIRMAN KLEIN: MR. JENSEN, THAT PREJUDICES THE PETITIONER BECAUSE THE STAFF DOESN'T HAVE THE TIME TO RESEARCH ALL THEIR CLAIMS. PETITIONERS ARE IN MUCH BETTER SHAPE IF THEY COME IN EARLY. OUR FUNDAMENTAL OBLIGATION IS TO PATIENTS AND SCIENCE. AND SO AS YOU SAY, IT DOESN'T DISQUALIFY IT. IT PUTS THE APPLICANT IN A DISADVANTAGED POSITION IF THEY'RE GOING TO MAKE AN EXTRAORDINARY PETITION AT ALL.

MR. JENSEN: WHAT I WOULD SUGGEST THEN IS THAT THE BOARD, THE AGENCY, REMOVE THE DEADLINE REQUIREMENT ENTIRELY BECAUSE YOU'RE PUTTING ON INFORMATION THAT DISADVANTAGES OTHERS WHO DON'T UNDERSTAND THIS IS A FICTITIOUS DEADLINE.

MR. SHEEHY: CAN I SPEAK TO THIS, BOB,

REALLY QUICKLY? AS OUR ESTEEMED JOURNALIST FRIEND KNOWS, BAGLEY-KEENE DOESN'T ALLOW US TO PRESENT ANY KIND OF DEADLINE FOR RECEIVING INPUT FROM THE PUBLIC. WE'RE MEETING IN PUBLIC. SO THE DEADLINE NEVER APPLIED TO ANYTHING BUT THE ABILITY OF STAFF TO REVIEW IT. SOMEONE CAN WALK IN RIGHT NOW WITH AN EXTRAORDINARY PETITION WITH 29 COPIES AND GET THREE MINUTES OF TIME AND PASS OUT THOSE COPIES TO THE BOARD PER OUR OPEN GOVERNMENT LAWS THAT EXIST.

SO I THINK THE MISUNDERSTANDING MAY BE ON THE PART OF THE APPLICANTS, BUT WE HAVE BEEN VERY CLEAR FROM THE BEGINNING THAT IF YOU SUBMIT IT EARLY, IF YOU SUBMIT IT BY THE DEADLINE, STAFF CAN REVIEW IT. IF YOU HAVE MATERIAL INFORMATION THAT STAFF CAN MAKE A COMMENT ON THAT WOULD HELP YOUR APPLICATION, THAT GIVES YOU THAT OPPORTUNITY. AND THOSE THAT STAFF HAVE COMMENTED ON FAVORABLY HAVE DONE BETTER THAN THE OTHER ONES.

MR. JENSEN: I UNDERSTAND THAT. ISN'T THERE A QUASI DEADLINE ON THE SITE IN THIS PETITION PROCESS?

CHAIRMAN KLEIN: I THINK YOUR POINTS HAVE BEEN TAKEN, MR. JENSEN. AND WE'LL TRY AND TAKE THIS UNDER CONSIDERATION HOW WE CAN PROVIDE BETTER INFORMATION.

SO WE HAVE NO OTHER PUBLIC COMMENTS. I'D LIKE TO CALL THE QUESTION. DO WE HAVE MEMBERS ON THE PHONE?

MS. KING: I WAS JUST ABOUT TO CHECK THAT. MARCY FEIT, ARE YOU ON THE PHONE WITH US RIGHT NOW? IF SHE'S NOT, WE HAVE A QUORUM IN THE ROOM ANYWAY, BUT IT WAS GOOD TO CHECK IT. APPARENTLY SHE IS NOT ON THE LINE CURRENTLY.

CHAIRMAN KLEIN: THANK YOU. SO I'M GOING TO CALL THE QUESTION.

MS. KING: I ALSO WANTED TO LET YOU KNOW THAT DR. DENG, THE PI, ASKED ME TO LET YOU KNOW THAT SHE WAS CALLED INTO THE OPERATING ROOM, I BELIEVE, FOR A PATIENT, BUT SHE WOULD COME BACK, AND SHE'S SORRY TO HAVE MISSED ANY QUESTIONS THAT THE BOARD HAS.

CHAIRMAN KLEIN: THANK YOU. SO I AM GOING TO CALL THE QUESTION. IF IT APPEARS CLOSE, I WILL DO A ROLL CALL. OTHERWISE, WE'LL GO WITH A GENERAL CALL OF THE QUESTION.

MR. SHEEHY: BECAUSE OF CONFLICTS, WE HAVE TO DO ROLL CALL.

CHAIRMAN KLEIN: THAT'S RIGHT. ABSOLUTELY. WE DO HAVE A CONFLICT ON THIS? WE DO. THANK YOU VERY MUCH. SO MELISSA.

MS. KING: THE WAY WE WILL HANDLE IT IS I WILL ONLY CALL YOU IF YOU ARE PRESENT AND NOT IN CONFLICT.

GORDON GILL.

DR. GILL: YES.

MS. KING: JACOB LEVIN.

DR. LEVIN: YES.

MS. KING: MICHAEL FRIEDMAN.

DR. FRIEDMAN: YES.

MS. KING: LEEZA GIBBONS.

MS. GIBBONS: YES.

MS. KING: MICHAEL GOLDBERG.

MR. GOLDBERG: YES.

MS. KING: BOB KLEIN.

CHAIRMAN KLEIN: YES.

MS. KING: TED LOVE.

DR. LOVE: YES.

MS. KING: PHIL PIZZO.

DR. PIZZO: I'VE BEEN GOING BACK AND FORTH.

MS. KING: WOULD YOU LIKE ME TO COME BACK TO YOU?

DR. PIZZO: COULD YOU?

MS. KING: OKAY.

KEN BURTIS.

DR. BURTIS: YES.
MS. KING: FRANCISCO PRIETO.
DR. PRIETO: AYE.
MS. KING: ROBERT QUINT.
DR. QUINT: YES.
MS. KING: JEANNIE FONTANA.
DR. FONTANA: YES.
MS. KING: DUANE ROTH.
MR. ROTH: YES.
MS. KING: JOAN SAMUELSON.
MS. SAMUELSON: YES.
MS. KING: JEFF SHEEHY.
MR. SHEEHY: YES.
MS. KING: OSWALD STEWARD.
DR. STEWARD: ACTUALLY I'D LIKE TO JUST SAY I'M GOING TO MAKE MY VOTE NOT BASED ON THE EXTRAORDINARY PETITION, BUT RATHER BASED ON THE INFORMATION THAT WAS PROVIDED TO US IN THE REVIEW AND THE INFORMATION THAT WAS DISCUSSED IN THE PROPRIETARY SESSION. JUST TO MAKE IT CLEAR THAT THIS IS A VOTE THAT IS IRRESPECTIVE OF THE EXTRAORDINARY PETITION. AND THAT VOTE IS YES.
MS. KING: ART TORRES.
MR. TORRES: AYE.
MS. KING: AND I WILL COME BACK TO PHIL

PIZZO.

DR. PIZZO: JUST FOR THE RECORD, I'M GOING TO SAY NO.

MS. SHEEHY: YOU MISSED JON SHESTACK.

MS. KING: JON SHESTACK.

MR. SHESTACK: YES.

MS. KING: THANK YOU.

CHAIRMAN KLEIN: ALL RIGHT. WHILE THEY'RE TABULATING THAT, IS THERE A BOARD MEMBER WHO WOULD LIKE TO MAKE A MOTION ON ANY OTHER CANDIDATE NOT CURRENTLY RECOMMENDED?

MS. SAMUELSON: YES.

MR. HARRISON: FOR THE RECORD THAT MOTION CARRIED.

CHAIRMAN KLEIN: THANK YOU.

MS. SAMUELSON: I WOULD LIKE TO MOVE THAT APPLICATION NO. 1778 BE MOVED INTO THE FUNDABLE CATEGORY. THIS IS A GRANT REGARDING INFLAMMATION IN PARKINSON'S DISEASE IN A HUMANIZED IN VITRO MODEL.

THERE WAS -- IN THE DISCUSSION IN THE WORKING GROUP, THERE WAS A GREAT SPLIT AMONG THE REVIEWERS WITH SOME FINDING THIS TO BE A HIGH RISK, HIGH IMPACT PROPOSAL AND WITH VERY, VERY LAUDATORY COMMENTS ABOUT THE SCIENTIST TEAM, SAYING THAT IT'S A REASONABLE AND ACHIEVABLE PLAN, THAT THIS WOULD

USE SKIN CELLS FROM PARKINSON'S PATIENTS AND REPROGRAM THEM INTO NEURONS AND OTHER SURROUNDING CELLS IN THE BRAIN. AND IT TALKED ABOUT THE FACT THAT THE TEAM HAS EXPERIENCE WITH THE NEURONAL DIFFERENTIATION OF HESC'S AND IPSC'S INTO NEURONS WITH SPECIFIC NEUROTRANSMITTER PHENOTYPES. AND THAT THE PI IS A LEADING INTERNATIONAL AUTHORITY IN NEUROSCIENCE, AN IDEAL PARTNER -- THAT HIS PARTNER HAS ACCESS TO AND EXPERTISE IN THE ANALYSIS OF PARKINSON'S PATIENTS AND IS AN IDEAL PARTNER FOR THESE STUDIES AND FINDING THAT THE TEAM IS HIGHLY APPROPRIATE IN MEETING THE NEEDS OF THE PROJECT.

AND THEN, OF COURSE, THERE WAS DISCUSSION ABOUT THE FACT THAT THIS IS ENORMOUSLY IMPORTANT INFORMATION TO MAKE PROGRESS WITH TO FIND SOMETHING THAT WILL STOP THE PROGRESSION OF PARKINSON'S AND ELIMINATE THE EFFECTS OF IT IN PEOPLE AROUND THE WORLD.

SO I'D LIKE TO MOVE ITS MOVEMENT INTO THE FUNDABLE CATEGORY.

MR. SHEEHY: SECOND.

CHAIRMAN KLEIN: THERE'S A SECOND FROM JEFF SHEEHY. BEFORE ADDITIONAL DISCUSSION, I'D LIKE TO HAVE STAFF PRESENTATION SO WE'RE ALL ON A LEVEL PLAYING FIELD HERE.

DR. SAMBRANO, MY RECOLLECTION IS THAT ONE OF THE CRITICISMS HERE IS THAT THERE WAS A LACK OF AN APPROPRIATE TARGET TO QUALIFY FOR A DC. AND COULD YOU COMMENT WHAT -- IN TERMS OF YOUR VIEW OF VALUE THAT COULD BE DERIVED BY TRYING TO DEAL WITH THIS AS A DCF? IS THE TEAM AND THE SCIENCE THAT HAS BEEN PROPOSED AND THE DEVELOPMENT AT THIS POINT SUFFICIENT TO GIVE US REAL VALUE AS A DCF IN ADDITION TO GIVING US AN OVERVIEW?

DR. SAMBRANO: SURE. I THINK PERHAPS ANSWERS TO THOSE QUESTIONS LIE IN THE SUMMARY AND THE OVERVIEW. LET ME JUST KIND OF TAKE IT FROM THE TOP.

AND SO THIS PROPOSAL IS A DEVELOPMENT CANDIDATE AWARD APPLICATION, AND ITS GOAL IS TO UNDERSTAND AND MODIFY NEURAL INFLAMMATION AS A MEANS FOR TREATING PARKINSON'S DISEASE. AND SO THE PI HAS IDENTIFIED A SPECIFIC NUCLEAR RECEPTOR, WHICH IS THE TARGET THAT THEY ARE AFTER, AS WELL AS POTENTIAL OTHER RELATED NUCLEAR RECEPTORS. SO THIS PARTICULAR NUCLEAR RECEPTOR HAS BEEN SHOWN TO IMPACT OR AFFECT NEURAL INFLAMMATION. AND SO THEY WANT TO TEST THAT IN THE CONTEXT OF PARKINSON'S DISEASE.

AND SO THE APPLICANT PROPOSES A GENERAL STRATEGY TO IDENTIFY SMALL MOLECULE AGONISTS OF THE

RECEPTOR USING PARKINSON'S DISEASE PATIENT-DERIVED IPSC CELLS AND THEIR DERIVATIVES.

NOW, THE REVIEWERS THOUGHT THAT THE PROPOSAL OVERALL WAS INTERESTING AND THAT THE USE OF THIS PARTICULAR NUCLEAR RECEPTOR WAS AN INTERESTING FOCUS. HOWEVER, THE STUDIES, AS I REITERATED BEFORE, THERE WERE A TOTAL OF NINE AIMS PROPOSED UNDER THIS GRANT PROPOSAL, WERE FOCUSED ON TARGET DISCOVERY AND BASIC MECHANISTIC INVESTIGATION. SO THEY STRONGLY FELT THAT THIS WAS NOT RESPONSIVE TO THE OBJECTIVES OF THE RFA.

AND IN ADDITION, I THINK THEY ALSO WERE NOT CONVINCED THAT THE UNDERLYING ASSUMPTION THAT A REDUCTION IN INFLAMMATION IN PATIENTS WITH PARKINSON'S DISEASE WOULD NECESSARILY BE OF CLINICAL BENEFIT SINCE IT'S BEEN SHOWN THAT INFLAMMATION IN MANY CASES ACTUALLY HAS REGENERATIVE EFFECTS.

AND SO THE OVERALL IMPACT, THEY FELT, OUT OF PURSUING THESE STUDIES WOULD ACTUALLY RELATE TO THE DEVELOPMENT OF DIFFERENTIATION PROTOCOLS FOR MICROGLIA, FOR EXAMPLE, AND THE USE OF INDUCED PLURIPOTENT STEM CELL-BASED TOOLS FOR POTENTIAL SCREENING AND DRUG DISCOVERY EFFORTS. AND I THINK THAT IS THE CRUX OF WHAT THE OUTCOMES OF THIS MIGHT BE.

AND, AGAIN, OVERALL THEY THOUGHT IT WAS BROAD AND COMPREHENSIVE IN TERMS OF ADDRESSING THESE BASIC MECHANISMS AND WERE CONTINGENT IN MANY CASES ON TECHNIQUES OR PROTOCOLS THAT HAD NOT YET BEEN DEVELOPED AND WOULD BE THE SUBJECT OF THE FUNDING UNDER THIS AWARD. AND SO THAT WAS ANOTHER REASON THEY FELT IT WAS A BIT EARLY.

AND THEN PRIMARILY IN TERMS OF LOOKING AT IT FROM THE DEVELOPMENT CANDIDATE PERSPECTIVE, THEY DIDN'T THINK THAT THE STUDIES PROPOSED WOULD NECESSARILY GET THEM TO A SINGLE WELL-DEFINED DEVELOPMENT CANDIDATE, AND THEY THOUGHT THAT THE STUDY WAS MORE SUITED FOR A BASIC BIOLOGY DISCOVERY PROJECT. AND, AGAIN, THE REVIEWERS PRAISED THE PI. THEY THOUGHT BOTH THE PI AND THE TEAM WERE EXCELLENT. THEY HAVE EXCELLENT RESOURCES TO CARRY OUT THE PROPOSED WORK. SO I DON'T THINK THEY HAD ANY DOUBT THAT WHAT WAS PROPOSED COULD BE CARRIED OUT. I THINK THEY FELT MOSTLY THAT IT DIDN'T FIT WITHIN THE CONTEXT OF THIS PARTICULAR RFA, THAT THEY WOULD NOT GET TO A DEVELOPMENT CANDIDATE, AND THAT THE INDIVIDUAL AIMS BEING SO BROAD COULD ACTUALLY BE THE SUBJECT OF INDIVIDUAL GRANT PROPOSALS.

AND, AGAIN, THIS WAS BROUGHT UP DURING THE PROGRAMMATIC DISCUSSION, AND THE WORKING GROUP DID

CONSIDER WHETHER THIS COULD BE A DCF AWARD GIVEN THE BASIC NATURE OF THE WORK. BUT I THINK IN CONSIDERING THAT, THEY FELT THAT THERE WASN'T ANYTHING AMONG THOSE AIMS THAT WOULD NECESSARILY DIRECTLY ADDRESS THE OBJECTIVES OF THE RFA. AND SO A MOTION TO MOVE THE AWARD INTO TIER I -- THE APPLICATION INTO TIER I WAS ULTIMATELY WITHDRAWN.

CHAIRMAN KLEIN: MY RECOLLECTION ACTUALLY IS THAT THERE WAS A DISCUSSION, AND THE SCIENTIFIC STAFF THOUGHT THE TIMING MIGHT WORK OUT SO THAT THE APPLICANT COULD THEN SUBMIT THIS IN THE BASIC SCIENCE RFA BECAUSE THERE WAS QUITE A BIT OF VERY HIGH LEVEL OF INTEREST IN THE SCIENTIFIC THEORY AND THE PI TEAM. AND AT THAT TIME IN THE PEER REVIEW, IT WAS THOUGHT THAT THEY COULD MEET THE TIMING TO DO SO. THAT, IN FACT, DIDN'T TURN OUT TO BE THE CASE BECAUSE THE DEADLINES DID NOT WORK OUT. AND SO THIS ISSUE OF A DCF WAS DROPPED WITH THE PEER REVIEWERS THINKING THAT, IN FACT, THIS COULD MAKE -- COULD BE CAPTURED AND SAVED IN THE BASIC SCIENCE ROUND.

SO THOSE FACTS ACTUALLY DIDN'T WORK OUT TO BE CORRECT, SO WE HAVE A LITTLE BIT OF A DIFFICULT INTERPRETATION HERE IN WEIGHING WHAT THE DECISION-MAKING WAS OF THE PEER REVIEWERS; IS THAT RIGHT?

DR. SAMBRANO: THAT'S CORRECT. THE QUESTION OF WHETHER THIS TYPE OF PROJECT WOULD QUALIFY FOR A BASIC BIOLOGY RFA WAS BROUGHT UP, AND IT WAS SAID THAT THERE WAS IN OCTOBER A DEADLINE COMING UP. AND THE TIMING WAS NOT SPECIFICALLY DISCUSSED, BUT NEVERTHELESS, I THINK ONE OF THE IMPORTANT ISSUES IS THAT THE REVIEWERS THOUGHT HERE IS A PROJECT THAT HAS NINE AIMS THAT COULD EACH BE ESSENTIALLY A BASIC BIOLOGY PROPOSAL. SO IT'S NOT NECESSARILY THE CASE THAT YOU COULD TAKE THIS SPECIFIC APPLICATION AND TURN IT INTO A BASIC BIOLOGY APPLICATION.

IT WOULD REQUIRE THE APPLICANT TO ESSENTIALLY SELECT AND CHOOSE SOMETHING AMONG WHAT WAS PROPOSED AND BRING IT FORWARD TO SOMETHING LIKE THE BASIC BIOLOGY RFA.

CHAIRMAN KLEIN: OKAY. JEFF SHEEHY AND THEN OS STEWARD.

MS. SAMUELSON: I WANT TO RESPOND TO SOME OF THOSE COMMENTS.

MR. SHEEHY: I WANT TO BE REALLY CLEAR ABOUT WHAT HAPPENED IN PROGRAMMATIC REVIEW BECAUSE WE NEVER GOT TO A VOTE ON THIS. AND THE REASON WHY WAS THAT PEOPLE FAIRLY STRONGLY ASSUMED, MYSELF INCLUDED, THAT THIS GRANT WOULD HAVE AN OPPORTUNITY

TO BE RESUBMITTED IN BASIC BIOLOGY. THE DEADLINES DIDN'T MESH, AND THE NEXT OPPORTUNITY FOR THIS TO GO INTO A BASIC BIOLOGY GRANT WILL BE TWO YEARS FROM NOW. I JUST PULLED UP THE SCHEDULE THAT WE WERE GIVEN LAST NIGHT.

SO ONE OF THE KEY FACTORS THAT WAS VERY MOTIVATING WAS THE STATURE OF THE SCIENTIST AND PAUCITY OF PEOPLE WORKING IN PARKINSON'S IN CALIFORNIA. EMINENT NEUROLOGISTS WITHIN THE ROOM SAID WE CAMPAIGNED, WE HAD MICHAEL J. FOX ON T.V., WE TALKED ABOUT PARKINSON'S AS A TARGET. BUT ONE OF THE PROBLEMS IN OUR ABILITY TO FUND THIS IN CALIFORNIA IS THAT THERE'S A LACK OF A SUFFICIENT NUMBER OF OUTSTANDING PARKINSON'S -- OTHER DISEASES ARE MORE OR BETTER REPRESENTED, AT LEAST THIS IS WHAT IS STATED. AND THE OPPORTUNITY TO GET THIS PARTICULAR EMINENT SCIENTIST INTO THIS ARENA WAS A VALUE IN AND OF ITSELF.

I DON'T KNOW WHAT THE WORKING GROUP WOULD HAVE RECOMMENDED IF WE HAD KNOWN THAT THERE WAS NOT AN OPPORTUNITY FOR TWO YEARS FOR THIS TO BE RESUBMITTED, BUT THERE WAS A STRONG SENSE THAT THERE WAS VALUE IN THIS APPLICATION. I'M SITTING NEXT TO SOMEONE WHO HAS A CLOCK TICKING, AND I WOULD SUPPORT STRONGLY FUNDING THIS APPLICATION MAYBE AT A REDUCED

LEVEL OF FUNDING. BUT I'M NOT COMFORTABLE LOOKING AT THE DECISION THAT THE WORKING GROUP AS BEING DEFINITIVE BECAUSE THE WORKING GROUP WAS OPERATING ON INCOMPLETE INFORMATION. AND I THINK WE WOULD HAVE AT LEAST HAD A MINORITY REPORT COMING FROM THE WORKING GROUP IF IT HAD BEEN KNOWN THERE WAS NO REAL OPPORTUNITY TO RESUBMIT WITHIN TWO YEARS.

CHAIRMAN KLEIN: DR. STEWARD AND THEN DR. PIZZO.

DR. STEWARD: I THINK AT THIS POINT WE NORMALLY SEE THE SCORES. TRUE? AND THEN MY QUESTION BECOMES IT SEEMS TO ME, GIL, THAT THERE ARE TWO ISSUES HERE. ONE, NINE AIMS MAYBE INCOMPLETELY DEVELOPED KIND OF SEEMS LIKE A DIFFUSE AND UNFOCUSED APPLICATION IF I WAS GOING TO SUMMARIZE IT IN A SENTENCE, AND AT THE SAME TIME A MISMATCH TO THE RFA.

WHICH OF THOSE DO YOU THINK MOST CRITICALLY INFLUENCED WHATEVER THE SCORES ARE THAT WE'RE GOING TO SEE?

DR. SAMBRANO: I THINK IT'S HARD TO SAY. I THINK IT'S CERTAINLY BOTH OF THEM BECAUSE THE REVIEWERS ARE LOOKING AT SEVERAL THINGS. AMONG THEM IS CAN THEY REACH THE OBJECTIVE IN THREE YEARS. AND SO IN THIS CASE CAN THEY ACHIEVE A DEVELOPMENT

CANDIDATE? THE ANSWER TO THAT QUESTION WAS NO.

AND IN TERMS OF ARE THE STUDIES NECESSARY, IMPORTANT, I THINK THEY WOULD AGREE, YES, THEY ARE; BUT THEY DON'T NECESSARILY FIT WITHIN THE SCOPE OF THE RFA. AND SO I THINK THAT'S A QUESTION FOR YOU IN TERMS OF THE FLEXIBILITY THAT YOU WANT TO AFFORD FOR PROJECTS THAT COME BEFORE US THAT ARE NOT NECESSARILY RESPONSIVE.

I THINK PART OF THE GOAL HAS BEEN TRYING TO INSTRUCT REVIEWERS AS WELL AS APPLICANTS TO WHAT IT IS THAT WE WOULD LIKE THEM TO SUBMIT AND PROVIDE SPECIFIC CRITERIA AGAINST WHICH THESE ARE REVIEWED. SO THAT'S WHAT THESE RANKINGS REPRESENT. IF WE WERE TO LOOK AT ALL OF THESE IN THE CONTEXT OF BASIC BIOLOGY, THEY MAY BE COMPLETELY DIFFERENTLY ORDERED, AND I CAN'T SAY WHAT THAT WOULD LOOK LIKE.

DR. STEWARD: COULD I JUST THEN FOLLOW UP BY SAYING I PERSONALLY FEEL THAT EVEN THOUGH I'M HUGELY SUPPORTIVE OF RESEARCH IN AN AREA THAT'S UNDERREPRESENTED, IT SEEMS LIKE WE'RE CHANGING THE RULES IN A WAY THAT REALLY ISN'T CONSISTENT WITH OUR LEVEL PLAYING FIELD HERE IF WE SUDDENLY SAY, WELL, THIS IS NOT PART OF THIS RFA, BUT WE'RE GOING TO FUND IT ANYWAY. EITHER WE HAVE TO MAKE IT CLEAR THAT THAT'S AN OPTION FOR EVERY GRANT THAT'S

CONSIDERED, OR WE JUST REALLY CAN'T GO DOWN THAT ROAD, I THINK, TO MAINTAIN CONSISTENCY.

MS. SAMUELSON: I HAVE A COMMENT I'D LIKE TO RESPOND TO THAT, BOB. IF IT WERE ONLY BECAUSE THERE'S AN IMPORTANT GAP OF LEARNING AND UNDERSTANDING IN PARKINSON'S DISEASE, THAT FOR ME WOULD HIT IT OUT OF THE PARK. BUT I THINK THE OTHER THING IT'S IMPORTANT TO SEE IS THAT THESE WERE SCIENTISTS WHO ARE PREEMINENT IN THEIR FIELD, AND YOU SEE THIS HUGE NUMBER OF DIFFERENT TARGETS THEY'D LIKE TO ACHIEVE SOME PROGRESS IN, AND I SEE THAT AS EAGERNESS AND IMPATIENCE WITH THE STATE OF THE SCIENCE IN THE FIELD BECAUSE THERE HASN'T BEEN ENOUGH INVESTMENT. NOW THERE'S SOME MONEY FINALLY AND SOME EXPERTISE IN THE STATE THAT CAN BEGIN TO TACKLE THESE QUESTIONS, AND THEY HAVE THE CAPACITY TO DO IT. THANK GOODNESS.

IT SEEMS TO ME THAT THAT'S A SITUATION WHERE WE CAN EXERCISE OUR DISCRETION AS A BOARD BECAUSE WE HAVE THE FINAL DECISION OURSELVES AND SAY THESE GUYS AREN'T GOING TO WASTE THIS MONEY. MAYBE THEY DON'T ACHIEVE ALL THE AIMS IN THREE YEARS. MAYBE IT WILL TAKE THREE AND A HALF OR FOUR. THAT'S NOT A DEFEAT. THAT'S GETTING ALL THAT INFORMATION AND MOVING THE FIELD AHEAD IN A FIELD WITH A TICKING

TIME BOMB.

CHAIRMAN KLEIN: DR. TROUNSON, I'M GOING TO CALL ON DR. PIZZO IN A SECOND. BUT IN LOOKING AT THESE AIMS AND REALIZING THAT THE PEER REVIEW GROUP THOUGHT IT WAS EXTRAORDINARY THAT THESE PARTICULAR SCIENTISTS HAD BEEN RECRUITED INTO THIS FIELD FOR THIS SPECIFIC AREA AND THAT THEIR SCIENCE, THEIR THEORY AND APPROACH AND CONCEPTS WERE NOVEL AND VERY IMPORTANT. ARE THERE ANY OF THOSE AIMS THAT YOU COULD SEE FROM THE SCIENTIFIC STAFF'S POSITION OF ISOLATING APPROPRIATELY IN A DCF CATEGORY, NOT A DC CATEGORY, BUT A DCF CATEGORY AT A REDUCED BUDGET THAT'S APPROPRIATE TO A DCF LEVEL?

DR. TROUNSON: CHAIR, I HAVEN'T TIME -- I HAVEN'T HAD THE OCCASION TO LOOK AT THAT QUESTION. I THINK THAT WOULD TAKE MORE TIME THAN WE'VE GOT AT THE MOMENT TO GIVE YOU A REASONABLE ANSWER. I DARE SAY IT'S SUCH A HUGE ASK. THE WORK IS VERY BROAD. I THINK THAT WAS ONE OF THE CONCERNS WAS A VERY BROAD STRETCH. AND SO TO FOCUS ON SOMETHING THAT WOULD BE IMPORTANT TO GO FORWARD, I'D NEED TO DO SOME MORE ANALYSIS THAN WHAT I CAN PROVIDE YOU AT THE MOMENT.

I WOULD SAY THAT PROFESSOR GAGE IS REALLY ONE OF THE KEY PEOPLE IN STEM CELLS IN THE WORLD.

HE'S ALSO VERY BUSY IN AUTISM AND LOTS OF OTHER THINGS, OF COURSE. SO HE CAN'T BE OVER ABSOLUTELY EVERY DISEASE. THAT'S FOR CERTAIN. BUT HIS ENTRY INTO PARKINSON'S, I THINK, WOULD BE WELCOMED. I ACTUALLY THINK THIS SORT OF UNDERLIES A REAL PROBLEM THAT I THINK WE'VE GOT FROM WHICH I THINK THE EXTERNAL REVIEW STARTED TO POINT OUT TO US, THAT, YOU KNOW, THERE ARE GREAT OPPORTUNITIES HERE, THAT YOU SHOULD DO IT IN A DIFFERENT WAY. AND IF I HAD A THOUGHT ABOUT THIS, I WOULD BE WANTING TO ENCOURAGE PROFESSOR GAGE AND HIS COLLEAGUES BROADLY TO COME INTO THE AREA IN A WAY WHICH MADE A LOT OF SENSE.

I'M NOT SURE THIS MAKES ABSOLUTE SENSE, BUT I'M SURE THAT THERE WOULD BE PARTS OF IT THAT WE COULD LOOK INTO THAT WE COULD REFORMAT FOR GETTING HIS INTEREST MORE INVOLVED IN PARKINSON'S DISEASE. BUT I THINK IT'S GOING TO TAKE A LITTLE BIT MORE THAN ME GIVING YOU JUST AN ANSWER OFF THE CUFF TO BE REASONABLE. I WOULD LIKE TO TALK TO HIM IN MORE DETAIL ABOUT IT. THAT'S THE SORT OF THING I'D LIKE TO BE ABLE TO DO, FIND OUT WHERE THE REALLY KEY POINTS ARE, AND WHERE WE CAN ACTUALLY START TO LEAD HIS INFLUENCE AND HIS GROUP'S INFLUENCE AND SOME OTHER PEOPLE'S INFLUENCES IN THESE AREAS.

SO I HOPE AS AN EVOLUTION OF ALL OF THIS

THAT WE'LL HAVE A DIFFERENT PROCESS. I'D LIKE TO TALK TO PROFESSOR GAGE ABOUT IT IF THERE'S AN OPPORTUNITY TO SEE REALLY WHERE HE CAN BE MOST EFFECTIVE WITHIN THE SET OF PARAMETERS THAT ARE PUT HERE.

CHAIRMAN KLEIN: THANK YOU. DR. PIZZO.

DR. PIZZO: FIRST, I'M ENORMOUSLY SYMPATHETIC TO THE POINTS THAT HAVE BEEN MADE BY JOAN AND JEFF. AND I THINK BOTH THE NEED OF INVESTIGATORS AND HIGHLY CREDIBLE ONES, WE GENERALLY DON'T GET TO KNOW THE NAME OF THE INVESTIGATOR, BUT NOW WE DO, AND I AGREE THAT THIS PERSON IS AN EXTRAORDINARY ONE, AND THAT, I THINK, IS AN IMPORTANT VALIDATING FACTOR.

I WOULD SAY A COUPLE OF THINGS. ONE OF THEM IS, AS I'VE SEEN REALLY AT JUST THE COMMENTS, PART OF THE ISSUE IS NOT THE QUALITY OF THE INVESTIGATOR OR EVEN THE QUESTIONS BEING ASKED, BUT WHETHER IT WAS TOO PRELIMINARY AND WHETHER IF MORE TIME WAS AVAILABLE, THERE WOULD BE SOMETHING MORE MATURE. YOU OFFERED A VERY COMPELLING CAVEAT TO THAT, JEFF, IN SAYING THE NEXT ROUND ISN'T GOING TO BE FOR A COUPLE OF YEARS. A RESPONSE WHICH MAY NOT BE SATISFYING TO THAT IS THAT MAY BE ABOUT HOW MUCH TIME IT TAKES TO GET THAT KIND OF DATA TO MAKE A

CREDIBLE APPLICATION.

BUT GIVEN ALL OF THESE THINGS AND TRYING TO BE RESPONSIVE AND ALSO RECOGNIZING THAT WE DO HAVE TO BE CAREFUL THAT WE'RE STAYING TRUE TO A PROCESS BECAUSE IT IS -- OTHERWISE WE'RE GOING TO SEND A VERY MIXED MESSAGE TO OUR COMMUNITY, WHAT I WOULD LIKE TO SEE OR PROPOSE IS THAT THE PRESIDENT HAVE AN OPPORTUNITY TO DO A REVIEW AND COME BACK AT THE NEXT MEETING WITH A RECOMMENDATION THAT WOULD SPECIFICALLY DEFINE THE SCOPE OF THE SUPPORT FOR THIS BECAUSE I THINK IT IS A KEY AREA. IT IS AS NOW YOU'VE MENTIONED, NOW WE KNOW, A HIGHLY MERITORIOUS INVESTIGATOR, AND I THINK THAT WOULD GIVE US SOME BOUNDARY CONDITIONS.

MR. SHESTACK: WHAT DOES MEAN, COME BACK WITH A REPORT?

DR. PIZZO: SO WHAT I'D LIKE TO HEAR IS RIGHT NOW THIS IS A PRETTY EXPENSIVE.

CHAIRMAN KLEIN: WAIT. IN ORDER TO GET BOTH OF YOU ON THE TRANSCRIPT, IF, JEFF, YOU'D PASS JONATHAN --

MR. SHESTACK: WHAT DOES THAT MEAN, DR. PIZZO? DO YOU MEAN ACTUALLY CREATING A NEW CATEGORY OF AWARD THAT DOESN'T EXIST, SOME WAY TO ACTUALLY --

DR. PIZZO: I'M CERTAINLY NOT RECOMMENDING

THAT. I THINK THE EASY THING TO DO AT THIS POINT WOULD BE TO SIMPLY VOTE, AND WE'LL ALL MAKE OUR RECOMMENDATIONS ACCORDINGLY. WHAT I'M TRYING TO DO IS BE RESPONSIVE OR TRY TO THINK ABOUT HOW TO BE RESPONSIVE TO A CLEAR NEED WITH A LABORATORY AND INVESTIGATOR OF HIGH CREDIBILITY, BUT WITH A BIG ASK AND DATA THAT APPEARS TO BE PRELIMINARY. JUST SO IT IS A WAY OF TRYING TO SEE WHETHER WE CAN MANAGE OUR EXPECTATIONS TO GET TO SOMETHING THAT WE COULD VOTE CREDIBLY ON.

I THINK IN THE ABSENCE OF THAT, WE'LL TAKE OUR VOTES AND IT MAY OR MAY NOT FLY ACCORDINGLY.

CHAIRMAN KLEIN: SO WE HAVE A VERY CREATIVE SUGGESTION. COULD I ASK, JEFF. WE HAVE A MOTION AND A SECOND. IF THE MAKER OF THE MOTION, ARE YOU RECEPTIVE TO AN AMENDMENT WHERE THE BOARD WOULD POSTPONE ACTION ON THIS INDIVIDUAL GRANT, ASK THE PRESIDENT TO COME BACK WITH A SUGGESTION OF WHETHER THIS CAN BE REFORMULATED IN AN EFFECTIVE WAY THAT FITS EITHER DCF OR FITS INTO THIS APPROPRIATELY SO THAT WE CAN SEE IF THERE'S AN OPPORTUNITY TO SALVAGE THIS OR IF THERE'S NOT?

MS. SAMUELSON: I AM, BUT FIRST, SOUNDS LIKE IN CONCEPT IT LOOKS LIKE MY COLLEAGUE HAS AN IDEA.

MR. SHEEHY: AS THE SECOND, I WOULD BE SUPPORTIVE OF THIS WITH A FRIENDLY AMENDMENT. I WANT TO KEEP THE LINKAGE TO THE WORKING GROUP, AND THE ADMINISTRATIVE CHAIR OF THE WORKING GROUP WAS AN INDIVIDUAL THAT WAS SUPPORTIVE OF A PROGRAMMATIC CONSIDERATION. SO I WOULD LIKE THIS BE A THREE-WAY CONVERSATION THAT INCLUDES INPUT FROM THE ADMINISTRATIVE CHAIR OF THE WORKING GROUP, THE PRESIDENT, AND THE POTENTIAL GRANTEE AND WE POSTPONE IT.

DR. PIZZO: I EVEN LIKE THAT BETTER.

MR. SHEEHY: I THOUGHT YOU WOULD. THAT TIES IT BACK. BECAUSE I REALLY THINK THE ADMINISTRATIVE CHAIR, WHO MADE THE MOTION ORIGINALLY TO MOVE THIS TO DCF AND THEN WITHDREW IT BASED ON THE ASSUMPTION THAT IT WOULD GO INTO BASIC BIOLOGY, COULD ACTUALLY --

CHAIRMAN KLEIN: MY UNDERSTANDING IS THE MOTION HAS BEEN ACCEPTED, THE AMENDMENT HAS BEEN ACCEPTED BY THE MAKER AND THE SECOND AND HAS BEEN MODIFIED ADDITIONALLY, AND THAT'S ACCEPTABLE TO DR. PIZZO. ADDITIONAL COMMENTS?

MR. TORRES: CALL FOR THE QUESTION.

MR. SHESTACK: I'M JUST TRYING TO REALLY UNDERSTAND IT. SO WHAT YOU ARE SAYING IS THIS GRANT

WILL BE POTENTIALLY VOTED ON AGAIN OUTSIDE OF THIS CYCLE AS A DCF INSTEAD OF A DC? IS THAT WHAT THE MOTION IS FOR?

CHAIRMAN KLEIN: I THINK THAT THAT'S THE NATURE --

MR. SHESTACK: AFTER EXPLORATION BETWEEN DR. GAGE, ETC.

CHAIRMAN KLEIN: YES. AND WE HAVE MOVED OTHERS FROM DC TO DCF'S WITHIN THIS CYCLE.

MR. SHESTACK: IN THIS PROCESS SORT OF IN BETWEEN -- WITH WORK BEING DONE IN BETWEEN ICOC MEETINGS?

CHAIRMAN KLEIN: YES.

MR. SHESTACK: SO THERE IS A PRECEDENT FOR THAT?

CHAIRMAN KLEIN: YES. OKAY. IS THERE PUBLIC COMMENT? SEEING NONE, I'D LIKE TO HAVE A ROLL CALL VOTE, PLEASE.

MS. KING: JACOB LEVIN.

DR. LEVIN: YES.

MS. KING: MARCY FEIT, ARE YOU ON THE LINE? MICHAEL FRIEDMAN.

DR. FRIEDMAN: YES.

MS. KING: LEEZA GIBBONS.

MS. GIBBONS: YES.

MS. KING: MICHAEL GOLDBERG.
MR. GOLDBERG: YES.
MS. KING: BOB KLEIN.
CHAIRMAN KLEIN: YES.
MS. KING: TED LOVE.
DR. LOVE: YES.
MS. KING: SHLOMO MELMED.
DR. MELMED: YES.
MS. KING: PHIL PIZZO.
DR. PIZZO: YES.
MS. KING: KEN BURTIS.
DR. BURTIS: YES.
MS. KING: FRANCISCO PRIETO.
DR. PRIETO: YES.
MS. KING: ROBERT QUINT.
DR. QUINT: YES.
MS. KING: DUANE ROTH.
MR. ROTH: ABSTAIN.
MS. KING: JOAN SAMUELSON.
MS. SAMUELSON: YES.
MS. KING: JEFF SHEEHY.
MR. SHEEHY: YES.
MS. KING: JON SHESTACK.
MR. SHESTACK: YES.
MS. KING: OSWALD STEWARD.

DR. STEWARD: ABSTAIN.
MS. KING: ART TORRES.
MR. TORRES: AYE.
MS. KING: JAMES ECONOMOU.
DR. ECONOMOU: YES.
CHAIRMAN KLEIN: SO ARE THERE ANY OTHER --
DR. LEVIN: I WANT TO MAKE ONE COMMENT, THAT SOMETHING THAT I FOUND A LITTLE DISTURBING THAT CAME OUT OF THIS DISCUSSION WAS THAT BASIC BIOLOGY IS NOT GOING TO BE -- THERE'S CLEARLY A NEED FOR MORE RESEARCH IN BASIC BIOLOGY. I THINK WE ALL UNDERSTAND THAT, AND THIS JUST BRINGS TO BEAR AGAIN THAT THERE'S A LOT OF DISEASES THAT HAVE SOME REAL BASIC STEM CELL BIOLOGY THAT NEED TO BE EXPLORED. AND IT'S GOING TO BE TWO YEARS NOW UNTIL THE NEXT GRANT GETS FUNDED.
CHAIRMAN KLEIN: THERE IS A CURRENT ROUND IN PROCESS THAT --
DR. LEVIN: BUT THE NEXT ONE IS 18 MONTHS AFTER THAT, AND THE NEXT ONE AFTER THAT IS 18 MONTHS AFTER THAT.
CHAIRMAN KLEIN: THE ISSUE IS THAT THIS GRANTEE DID NOT GET THEIR INFORMATION IN TIME TO BE ABLE TO APPLY FOR THE ROUND THAT JUST STARTED.
DR. LEVIN: RIGHT. I ACTUALLY UNDERSTAND

THE PROBLEM WITH THE TIMING, BUT I'M STILL -- ORIGINALLY BASIC BIOLOGY WAS SUPPOSED TO COME EVERY 12 MONTHS AS I RECALL.

DR. TROUNSON: IT'S COMING EVERY 12 MONTHS.

CHAIRMAN KLEIN: IT IS STILL COMING EVERY 12 MONTHS.

DR. LEVIN: BUT THERE'S ONLY TWO MORE ROUNDS BETWEEN NOW AND -- THE CURRENT ONE THAT JUST WENT IN AND THEN TWO MORE BY 2014.

DR. SAMBRANO: SO THERE'S A CURRENT ROUND FOR WHICH PREAPPLICATIONS WERE DUE THIS OCTOBER, AND THEN THE NEXT POSTING OF THE RFA WILL BE IN NOVEMBER OF NEXT YEAR.

CHAIRMAN KLEIN: SO THERE WILL BE --

DR. LEVIN: IT WILL BE POSTED IN NOVEMBER AND THEN DUE IN JANUARY.

CHAIRMAN KLEIN: THE ROUNDS ARE POSTED -- BASIC BIOLOGY IS BEING POSTED AT A 13-MONTH CYCLE.

DR. LEVIN: NO. IT'S LONGER THAN THAT. IT'S POSTED 13 MONTHS AFTER THEY WERE DUE AND THEN IT'S ANOTHER THREE MONTHS.

DR. SAMBRANO: SO BETWEEN NOW AND THE NEXT ONE, WHICH IS NOVEMBER, IS GOING TO BE MORE THAN 12 MONTHS. SO THE NEXT ONE THAT'S COMING IS POSTING

NOVEMBER, BUT THE GOAL IS TO DO THIS EVERY 12 MONTHS.

DR. LEVIN: I GUESS MY QUESTION IS SHOULD WE AT SOME POINT AS A BOARD CONSIDER ACCELERATING THAT, TRYING TO SQUEEZE ONE MORE BASIC BIOLOGY INTO THE WHOLE CYCLE. THEY'RE SMALL FOR US, SMALL, 30 TO $45 MILLION ROUNDS.

CHAIRMAN KLEIN: WE'VE GOT SOME VERY TIGHT TIME FRAMES HERE. TRYING TO MAINTAIN A QUORUM FOR A VOTE HERE. CAN I ASK ARE THERE ANY OTHER APPLICATIONS ANYONE WANTS TO MOVE? OKAY. GIVEN THAT THERE'S NONE -- THERE'S NO OTHER APPLICATIONS ANYONE WANTS TO MOVE, I'D LIKE TO KNOW IF WE HAVE A MOTION.

DR. PRIETO: I MAKE A MOTION TO MOVE APPLICATION 1785, THE SPINAL CORD INJURY APPLICATION, MOVE THAT INTO THE FUNDABLE CATEGORY.

MR. TORRES: IS THERE A SECOND?

CHAIRMAN KLEIN: HOW CLOSE ARE WE TO A QUORUM?

MS. KING: WE HAVE A QUORUM CURRENTLY.

CHAIRMAN KLEIN: I'M ASKING HOW CLOSE WE ARE.

MS. KING: WE HAVE A QUORUM. I DON'T UNDERSTAND. YOU WANT TO KNOW WHEN WE'RE LOSING IT?

MR. TORRES: NO. IF HE LEAVES, DO WE LOSE THE QUORUM?

MS. KING: SO EVEN IF YOU LEAVE, WE WOULD STILL HAVE A QUORUM, BUT NOT IF TED LEAVES.

MR. SHEEHY: I DON'T THINK WE HAVE A SECOND FOR THE MOTION, BOB.

CHAIRMAN KLEIN: DO WE HAVE A SECOND FOR THE MOTION?

MR. SHEEHY: IN THE ABSENCE OF A SECOND --

DR. FONTANA: I'LL SECOND.

DR. GILL: CAN YOU TAKE UP THE FULL SLATE AND THEN COME BACK TO THE MOTION?

CHAIRMAN KLEIN: YES. MR. HARRISON, WE COULD TAKE UP THE BALANCE OF THE SLATE AND COME BACK TO THIS MOTION.

MR. HARRISON: WE COULD.

MR. ROTH: I'LL MAKE A MOTION THAT WE FUND ALL THE ONES THAT ARE IN TIER I.

MR. TORRES: SECOND.

CHAIRMAN KLEIN: THERE WAS -- IF YOU WOULD TAKE A FRIENDLY AMENDMENT THAT FOR 1844, THAT APPROVAL WOULD BE CONDITIONAL UPON THE STAFF REVIEW OF FINANCIAL AND LEGAL INFORMATION AND DUE DILIGENCE THAT IS NECESSARY FOR THE FINANCE SUBCOMMITTEE APPROVAL ON THAT MOTION.

MR. ROTH: THERE'S TWO THAT HAVE THAT. WE'VE MOVED TWO UP?

DR. TROUNSON: THERE'S TWO.

CHAIRMAN KLEIN: THIS IS DEALING WITH A LOAN APPLICATION. WE'RE ASKING FOR AN APPROVAL OF 1844 SUBJECT TO THE LOAN REVIEW AND THE FINANCE COMMITTEE APPROVAL.

MR. HARRISON: COULD I JUST BE CLEAR, CHAIR? WE GOT THE FINANCIAL AND DUE DILIGENCE LATE, SO WE NEED TO COMPLETE OUR STAFF REVIEW. DEPENDING UPON THE OUTCOME OF THAT REVIEW, FINANCE SUBCOMMITTEE APPROVAL MAY ALSO BE NECESSARY. SO IT'S JUST AWARDED CONTINGENT UPON COMPLETION OF FINANCIAL AND LEGAL DUE DILIGENCE AND ANY NECESSARY FINANCE SUBCOMMITTEE APPROVAL.

MR. ROTH: MR. HARRISON SAID THAT VERY NICELY AND I'LL JUST ACCEPT THAT LANGUAGE.

CHAIRMAN KLEIN: AND DOES THE SECOND ACCEPT THAT?

MR. TORRES: ABSOLUTELY. LET'S GO.

CHAIRMAN KLEIN: SO IF WE HAVE ANY PUBLIC COMMENT? IF YOU COULD PROCEED WITH THE ROLL CALL.

MS. KING: AS A REMINDER, YOUR RESPONSE, IF YOU HAVE CONFLICTS WITH ANY --

DR. STEWARD: I'M SORRY. JUST

PROCEDURALLY, WHO MADE THE MOTION?

MR. ROTH: I DID.

MS. KING: AND THE SECOND WAS ART TORRES.

CHAIRMAN KLEIN: AND THIS IS FOR ALL THE APPLICATIONS PREVIOUSLY MOVED AND PREVIOUSLY IN TIER I.

MS. KING: YOUR RESPONSE, IF YOU HAVE A CONFLICT WITH ONE OR MORE OF THE APPLICATIONS THAT WE ARE VOTING ON RIGHT NOW, SHOULD BE YES OR NO WITH THE EXCEPTION OF THOSE WITH WHICH I HAVE A CONFLICT OR SOMETHING SIMILAR TO THAT.

GORDON GILL.

DR. GILL: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: JACOB LEVIN.

DR. LEVIN: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: MICHAEL FRIEDMAN.

DR. FRIEDMAN: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: LEEZA GIBBONS.

MS. GIBBONS: YES.

MS. KING: MICHAEL GOLDBERG.

MR. GOLDBERG: YES.

MS. KING: BOB KLEIN.

CHAIRMAN KLEIN: YES.
MS. KING: TED LOVE.
DR. LOVE: YES.
MS. KING: SHLOMO MELMED.
DR. MELMED: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: PHIL PIZZO.
DR. PIZZO: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: KEN BURTIS.
DR. BURTIS: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: FRANCISCO PRIETO.
DR. PRIETO: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: ROBERT QUINT.
DR. QUINT: YES, I HAVE NO CONFLICTS.
MS. KING: JEANNIE FONTANA.
DR. FONTANA: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: DUANE ROTH.
MR. ROTH: YES.
MS. KING: JOAN SAMUELSON.
MS. SAMUELSON: YES.
MS. KING: JEFF SHEEHY.

MR. SHEEHY: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: JON SHESTACK.

MR. SHESTACK: YES.

MS. KING: OSWALD STEWARD.

DR. STEWARD: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: ART TORRES.

MR. TORRES: AYE.

MS. KING: JAMES ECONOMOU. NOT CURRENTLY PRESENT, BUT WE HAVE A QUORUM WITHOUT HIM. SO IT APPEARS THAT THAT MOTION CARRIES. WE'RE GOING TO LEAVE THE ROLL OPEN UNTIL DR. ECONOMOU RETURNS.

CHAIRMAN KLEIN: AND DO WE NEED THEN ANOTHER MOTION TO ADDRESS ALL THOSE TO NOT FUND EXCEPT FOR THE ONE THAT'S STILL UNDER CONSIDERATION?

MR. SHEEHY: AND 1778.

CHAIRMAN KLEIN: 1778.

MS. KING: IS THE ONE THAT IS GOING BACK TO DR. TROUNSON.

MR. HARRISON: WE'VE ALREADY TAKEN ACTION ON 1778 TO POSTPONE ACTION, SO IT WILL NOT BE ENCOMPASSED IN THE MOTION NOT TO FUND.

CHAIRMAN KLEIN: IS A MOTION NOT TO FUND APPROPRIATE HERE?

MS. KING: DR. ECONOMOU, IF I COULD GET YOUR VOTE ON THE PREVIOUS MOTION, WHICH WAS TO FUND ALL OF THE APPLICATIONS CURRENTLY IN TIER I. AND YOUR VOTE WOULD NEED TO BE EITHER YES OR NO WITH THE EXCEPTION OF THOSE APPLICATIONS WITH WHICH YOU HAVE A CONFLICT.

DR. ECONOMOU: AND THOSE HAVE ALL UNDERGONE PEER REVIEW?

MS. KING: YES.

DR. ECONOMOU: WITH RECOMMENDATIONS FOR FUNDING?

CHAIRMAN KLEIN: THEY'RE ALL ITEMS THIS BOARD HAS PASSED, EITHER ELEVATED, BUT THEY'VE ALL GONE THROUGH PEER REVIEW.

DR. ECONOMOU: YES.

CHAIRMAN KLEIN: EXCEPT FOR THOSE WITH WHICH YOU HAVE A CONFLICT.

DR. ECONOMOU: CORRECT.

CHAIRMAN KLEIN: DUANE, DO YOU HAVE A MOTION?

MR. ROTH: YES. I'LL MAKE A MOTION THAT WE NOT FUND ALL EXCEPT, WHICH NUMBER IS IT?

MS. KING: REALLY ONLY 1778. AND THEN IF DR. PRIETO WANTS 1785.

MR. ROTH: THERE'S ONLY ONE THAT WE'RE

GOING TO VOTE. 1775 -- 85, SORRY. SO WE WILL NOT FUND ALL THE OTHERS WITH THE EXCEPTION OF 1785, AND THAT HAS TO BE CONSIDERED.

MR. HARRISON: AND WE MIGHT AS WELL BE CLEAR THAT 1778 IS EXCLUDED FROM THAT MOTION AS WELL BECAUSE WE'VE ALREADY ACTED UPON IT.

CHAIRMAN KLEIN: IS THERE A SECOND?

MR. TORRES: SECOND.

CHAIRMAN KLEIN: IS THERE PUBLIC COMMENT? ROLL CALL.

MS. KING: GORDON GILL.

DR. GILL: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: JACOB LEVIN.

DR. LEVIN: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: MICHAEL FRIEDMAN.

DR. FRIEDMAN: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: LEEZA GIBBONS.

MS. GIBBONS: YES.

MS. KING: MICHAEL GOLDBERG.

MR. GOLDBERG: YES.

MS. KING: BOB KLEIN.

CHAIRMAN KLEIN: YES.

MS. KING: TED LOVE.
DR. LOVE: YES.
MS. KING: SHLOMO MELMED.
DR. MELMED: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: PHIL PIZZO.
DR. PIZZO: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: KEN BURTIS.
DR. BURTIS: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: FRANCISCO PRIETO.
DR. PRIETO: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: ROBERT QUINT.
DR. QUINT: YES.
MS. KING: JEANNIE FONTANA.
DR. FONTANA: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.
MS. KING: DUANE ROTH.
MR. ROTH: YES.
MS. KING: JOAN SAMUELSON.
MS. SAMUELSON: YES.
MS. KING: JEFF SHEEHY.
MR. SHEEHY: YES, EXCEPT FOR THOSE WITH

WHICH I HAVE A CONFLICT.

MS. KING: JON SHESTACK.

MR. SHESTACK: YES.

MS. KING: OSWALD STEWARD.

DR. STEWARD: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: ART TORRES.

MR. TORRES: AYE.

MS. KING: JAMES ECONOMOU.

DR. ECONOMOU: YES, EXCEPT FOR THOSE WITH WHICH I HAVE A CONFLICT.

MS. KING: FOR THE RECORD THAT MOTION CARRIES.

CHAIRMAN KLEIN: DO WE HAVE -- FOR THE LEADERSHIP AWARD DO WE HAVE A MOTION FOR APPROVAL?

MR. TORRES: SO MOVED.

DR. STEWARD: I DON'T THINK I'M IN CONFLICT. SECOND.

CHAIRMAN KLEIN: SECOND BY DR. STEWARD.

MR. TORRES: CALL FOR THE QUESTION.

CHAIRMAN KLEIN: DOES THE PUBLIC HAVE COMMENT? LEADERSHIP AWARD.

MS. KING: GORDON GILL.

DR. GILL: YES.

MS. KING: JACOB LEVIN.

DR. LEVIN: YES.
MS. KING: MICHAEL FRIEDMAN.
DR. FRIEDMAN: ARE THERE NO CONFLICTS ON THIS?
MR. HARRISON: YOU CAN ABSTAIN IF YOU CHOOSE. YOU DON'T HAVE A LEGAL CONFLICT.
MS. KING: ACCORDING TO OUR RECORDS, YOU DON'T HAVE A CONFLICT.
CHAIRMAN KLEIN: I'D ABSTAIN IF YOU HAVE ANY QUESTION.
DR. FRIEDMAN: ABSTAIN.
MS. KING: LEEZA GIBBONS.
MS. GIBBONS: YES.
MS. KING: MICHAEL GOLDBERG.
MR. GOLDBERG: YES.
MS. KING: BOB KLEIN.
CHAIRMAN KLEIN: YES.
MS. KING: TED LOVE.
DR. LOVE: YES.
MS. KING: SHLOMO MELMED.
DR. MELMED: YES.
MS. KING: PHIL PIZZO.
DR. PIZZO: YES.
MS. KING: KEN BURTIS.
DR. BURTIS: YES.

MS. KING: FRANCISCO PRIETO.
DR. PRIETO: YES.
MS. KING: ROBERT QUINT.
DR. QUINT: YES.
MS. KING: JEANNIE FONTANA.
DR. FONTANA: YES.
MS. KING: DUANE ROTH.
MR. ROTH: YES.
MS. KING: JOAN SAMUELSON.
MS. SAMUELSON: ABSTAIN.
MS. KING: JEFF SHEEHY.
MR. SHEEHY: YES.
MS. KING: JON SHESTACK.
MR. SHESTACK: YES.
MS. KING: OSWALD STEWARD.
DR. STEWARD: YES.
MS. KING: ART TORRES.
MR. TORRES: AYE.
MS. KING: JAMES ECONOMOU.
DR. ECONOMOU: YES.
MS. KING: FOR THE RECORD THAT MOTION CARRIES.
MR. TORRES: ALL RIGHT. THAT MOTION CARRIES. THERE'S -- WE STILL HAVE A QUORUM WITH MR. KLEIN'S IMMEDIATE ABSENCE. IF WE CAN GO TO THE

NEXT ITEM, MR. HARRISON, WHAT IS THE NEXT ITEM THAT WE NEED TO DISCUSS? IS IT THE ONLINE JOURNAL?

MS. KING: ITEM 14 AND THEN 15.

MR. TORRES: ITEM 14, CONSIDERATION OF PROPOSAL --

MR. SHEEHY: COULD I RECOMMEND --

MR. TORRES: YES, MR. SHEEHY.

MR. SHEEHY: I THINK WE SHOULD ADJOURN. I MEAN EVERYBODY IS LEAVING, AND WE CAN PICK THIS UP AT ANOTHER POINT.

MR. TORRES: WE'VE JUST LOST A QUORUM, SO I SUGGEST THAT WE CAN HAVE DISCUSSION ON THESE ISSUES, BUT ALL OF THEM WILL BE POSTPONED FOR A VOTE UNTIL OUR NOVEMBER 11TH MEETING.

MR. SHEEHY: I THINK MAYBE THE ONLY THING THAT SEEMS REALLY LIVE TO ME IS 1785 AND THE REST --

MR. TORRES: WE CAN'T TAKE ACTION ON IT.

MR. ROTH: IF WE GET MARCY ON THE PHONE, WE MIGHT.

MR. TORRES: WERE WE ABLE TO GET MARCY ON THE PHONE? WILL MARCY ADD TO THE QUORUM?

MS. SAMUELSON: I'M NOT SURE IT'S APPROPRIATE.

MR. SHEEHY: I KIND OF FEEL LIKE WE'VE LOST A WHOLE BUNCH OF PEOPLE, AND I THINK WE'RE

GOING TO START LOSING PEOPLE AS THE CLOCK TICKS.

MS. SAMUELSON: I DON'T THINK WE CAN DO JUSTICE.

MR. SHEEHY: WE DON'T HAVE A QUORUM.

MR. TORRES: DO WE HAVE A QUORUM OR NOT? WE DO NOT. WELL, THEN, I SUGGEST THAT WE -- WHAT I WOULD SUGGEST IS THAT WE DON'T WANT TO DISCUSS THESE ISSUES TODAY. LET'S RESOLVE THAT WE PUT THEM OVER UNTIL THE NOVEMBER 11TH MEETING, WHICH IS ALREADY SCHEDULED AND NOTICED. AND I WOULD ARGUE THAT WE SHOULD DO THAT. ARE WE ALL IN ACCORD? THANK YOU. MEETING ADJOURNED.

(THE MEETING WAS THEN CONCLUDED AT 02:37 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 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

GRAND HORIZON ROOM, COVEL COMMONS
SUNSET VILLAGE, UCLA
LOS ANGELES, CALIFORNIA
ON
THURSDAY, OCTOBER 21, 2010

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

BETH C. DRAIN, CSR 7152
BARRISTER'S REPORTING SERVICE
1072 BRISTOL STREET
SUITE 100
COSTA MESA, CALIFORNIA
(714) 444-4100