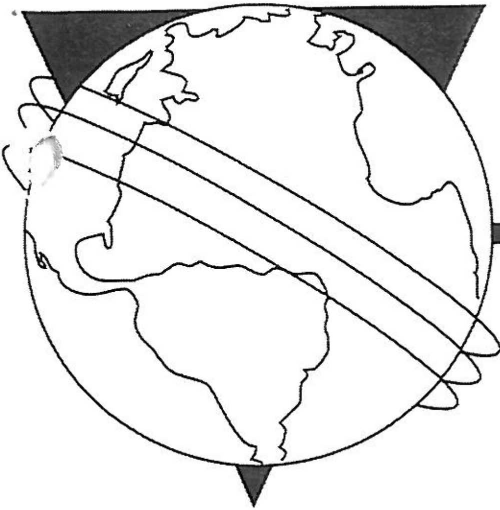

FA family newsletter

SCIENTIFIC SUPPLEMENT TO NEWSLETTER #15

Summaries of Presentations at the Fifth Annual Scientific Symposium

As submitted by each presenter in order of presentation

December 13, 1993, St. Louis, Missouri

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Blanche P. Alter, MD, Children's Hospital, University of Texas Medical Branch, Galveston, Texas

"Fanconi's Anemia: Clinical and Diagnostic Features"

Fanconi's anemia (FA) is a syndrome, ie a set of characteristics which define a condition. The physical findings range from a totally normal appearance to a large variety of characteristics but not diagnostic features. Many patients develop aplastic anemia, myelodysplasia, leukemia, or solid tumors. All patients have increased chromosomal fragility. There are at least 4 complementation groups, defined by correction of chromosome breakage following fusion of cells from different groups. The average life expectancy is approximately 25 years of age. Labelling a patient as "FA" currently depends on observation of the end results of the inability of FA cells to repair damaged DNA. The observation of increased aberrations (breaks, gaps, rearrangements, and radial figures) in chromosomes was first made in the mid-1960's. Subsequently it was shown that the frequency of these aberrations was increased if cells were cultured with chemicals which alkylate or cross-link DNA. The agents used most commonly at this time are diepoxybutane (DEB), mitomycin C (MMC), and nitrogen mustard (NM or HN2). Most laboratories examine the frequency of chromosome breaks per cell in cultures of peripheral blood lymphocytes, or the proportion of cells with radials. FA cells grow more slowly than normal cells, and the addition of alkylators exaggerates this difference.

A recent technique called "flow cytometry", or analysis with a fluorescence activated cell sorter (FACS), allows quantitation of the proportion of cells which have been delayed in cell division (called "arrest at G2/M"). Blood lymphocytes from FA patients have a higher proportion of G2/M arrest than do normals, particularly after culture with alkylators. Since FA is a "syndrome", it may be exclusionary to decide that one specific test is the only one which can diagnose FA. Patients with features consistent with this diagnosis deserve a wide variety of tests, both to determine whether that is the correct diagnosis, and also to identify different subgroups of this "syndrome". The determination of FA will eventually be made by examination of DNA, a technique currently applicable only to the approximately 20% of cases in which there is a mutation in complementation group C (FACC). The other groups, A, B, D, and ? more, are being sought. Identification of all of the mutations will provide specific diagnoses, and permit correlation between mutation type, physical appearance, and hematologic and malignant prognoses.

Manuel Buchwald, PhD, Hospital for Sick Children, Toronto, Canada

"Isolation and Characterization of the Fanconi Anemia Gene"

Dr. Buchwald's laboratory has been working on several areas relating to the Fanconi Anemia group C gene (FACC), which they had previously cloned. These include:

1) Studies aimed at understanding the role of the FACC protein

The protein has the predicted size, about 60,000, and its function requires an intact C terminus (the far end of the protein). Since the Buchwald lab did not have antibodies to the protein, they used a method in which an artificial piece of protein, for which an antibody is available, is added to the native protein (this is called epitope tagging). They then showed that this altered protein is still fully functional. Introduction of the protein into human, monkey and mouse cells and staining with the antibody to the epitope tag showed that the protein was present in both the nucleus and cytoplasm of the cell. The discrepancies with the results of other groups are not understood at this point.

2) Studies aimed at understanding the pattern of expression of the FACC gene

The gene appears to be expressed (active) in every tissue looked at so far. However, in addition, it seems to be active at higher levels in early blood progenitors and in bone progenitors in the mouse. Thus, the gene could be regulated in different ways and failure of this activation in patients might explain some of the problems they have. Many parts of the gene have been isolated. Interestingly, in the region predicted to contain regulatory sequences, the two different starting sequences, previously reported, can be detected. Thus, the original observation of two types of FACC messages is real and not an artifact of the cloning experiments. These regions are now being studied to help define the regulatory regions.

3) Studies aimed at developing a mouse model for FA(C)

The mouse version of FACC (called Facc) has been identified and mapped. It is located near that of a preexisting mouse mutant called flex, which can therefore be considered a candidate mouse model. Flex mice are being studied in the lab. In addition, the lab is in the process of developing a mouse model using the techniques of molecular genetics and mouse embryology. To date portions of the Facc gene have been isolated and put together to start the gene targeting experiments. These will be done using a special type of mouse cell, called embryonic stem cell, that can later be used to help produce mice that are defective in Facc. These mice can help us understand the types of defects found in patients and can also be used to test therapies.

4) Studies aimed at isolating the other FA genes.

Experiments are in progress, using the same method that yielded the FACC gene, to find the other FA genes.

Rachael Gibson, Paediatric Research Unit, Prince Philip Research Labs, Guy's Hospital, London

"Characterization of Inactivating Mutations"

Fanconi Anaemia is a complex genetic disorder which can be caused by a defect in at least four different genes. Only the gene defective in FA group C (FACC) has been identified to date. We have analyzed this gene in FA families in order to determine the proportion of patients that belong to group C, and to find out what kinds of mutations (changes in gene structure) knock out the gene in these patients.

We found a common neutral genetic change (polymorphism) in the FACC gene, and used it to place the FACC gene accurately on the human genetic map. We then analyzed this polymorphism and others from that region in FA families to see whether these markers were inherited together with the disease (linkage analysis). Families in whom FA and the FACC markers were not inherited together could not be from group C, and could be excluded from the panel of patients being screened for FACC mutations.

Like most human genes, FACC contains coding regions (exons), which th[illegible]l copies into RNA, and a large amount of non-coding DNA (introns). We worked out the structure of the FACC gene to help us and the research teams in Oregon and New York to screen for FACC mutations, and found that the coding part is split into 14 exons. So far, we have identified 6 different mutations in our FA families. Three of these are missense mutations, which change one amino acid in the FACC protein to another. These are probably polymorphisms, which don't knock out FACC function. The other three are nonsense mutations, which stop conversion of RNA to protein, and do knock out FACC. It is important to understand that having an FACC mutation does not always mean that a patient is in group C.

In one of the families with FACC mutations we used a DNA test to confirm the result of a prenatal diagnosis done by the chromosome breakage test (DEB). In another family, we diagnosed the fetus as unaffected by DNA analysis within two days of the prenatal biopsy, and this was [illegible] confirmed by chromosome studies.

In summary, both our linkage analysis and mutation screening results suggest that about 9% of our FA families are from group C.

Markus Grompe, MD, Oregon Health Sciences University, Portland, Oregon

"Update on the Mutational Analysis of the FACC Gene at the OHSU Repository"

A detailed report of our activities in mutation detection was published in the July 1993 newsletter and I will therefore be very brief in this update.

A number of different mutations in the FACC gene have been described in the last year by several different laboratories including ours, the lab of Dr. M. Buchwald in Toronto, Dr. C. Mathew in London and Dr. A. Auerbach in New York. However, only two of these mutations appear to be relatively common. The first of these, termed IVS4+4 A->T, is very frequent in Jewish Fanconi anemia patients. Eighty-five percent of Jewish families with Fanconi anemia belong to complementation group C and have this particular mutation. The second mutation, called G322, is found in individuals of Northern European descent. These two mutations together account for >90% of complementation group C patients. We have found the IVS4+4 A->T change in 10/63 (16%) families in the OHSU repository (all Jewish) and the G322 mutation in 3/63 families (5%). Thus, the total frequency of complementation group C in all families is around 20%. However, the frequency is much lower in non-Jewish families: 3/51 (6%).

We are screening all families in the OHSU FA repository for the presence of these 2 mutations. The presence of either of these indicates that this family belongs to complementation group C. Their absence does not entirely rule out the possibility that a family belongs to group C, but makes it very unlikely (<5%).

Information regarding the mutation status will be provided to a family or their physician upon request.

Arleen D. Auerbach, PhD, The Rockefeller University, New York, New York

"Mutation Analysis of the FACC Gene"

We have completed an analysis of mutations in the Fanconi anemia group C gene (FACC) in 174 racially and ethnically diverse families in the International Fanconi Anemia Registry (IFAR), which were not preselected for any specific ancestry. The purpose of this study was to obtain a better estimate of the fraction of Fanconi anemia (FA) patients in group C, as well as to identify mutations for FA carrier testing. We performed our analysis on DNA obtained from a small aliquot of whole blood sent to our laboratory for DEB-testing for FA diagnosis. The unifying feature of the syndrome found in all patients included in this study was hypersensitivity to DEB.

All fourteen separate coding regions of the FACC gene were amplified from each individual using PCR technology; in all, 2,436 separate analyses were performed. We identified two mutations and a polymorphism (variant) that were previously undescribed, in addition to four FACC mutations and a polymorphism that have been described previously. Disease-associated mutations were detected in a total of 25 out of 174 families (14.4%). The most frequent mutations were IVS4+4A->T (12 families) and 322delG (9 families). Thus, these two mutations account for 84% of the families currently assigned to group C. Other less common mutations include Q13X, R185X, D195V, and L554P. All patients in our study with mutations other than IVS4+4A->T are Caucasians of Northern or Eastern European or Southern Italian ancestry, and in all but two families the affected individuals had a relatively mild form of the disease with no major birth defects. All patients with the IVS4+4A->T mutation were of Jewish ancestry; this mutation was not found in anyone not of Jewish heritage. We screened additional Jewish families for FACC mutations, and a total of sixteen of twenty Jewish FA families tested had the IVS4+4A->T mutation. The Jewish FA patients that do not have this mutation may not belong to group C, as no other FACC mutations have been found in these patients. All of the FA group C Jewish patients had a severe form of the disease, with multiple congenital abnormalities. One measure of the severity of the disease is the age of diagnosis of affected individuals. The mean age of diagnosis of FA in patients with IVS4+4A->T was 1.6 years, while the mean age of diagnosis for patients with the other mutations was 9.25 years.

We have now developed an assay system to rapidly screen DNA from a small blood sample for these six known mutations in the FACC gene, in a single PCR reaction. We are offering carrier testing to the extended family of any FA patient with a mutation in the group C gene, and can also use this DNA assay for prenatal diagnosis in these families. We are currently using this rapid assay to screen a variety of different populations to learn more about the carrier frequency of FACC. Our laboratory is also focusing on trying to clone new non-C FA genes.

Alan D. D'Andrea, MD, Dana-Farber Cancer Institute, Boston, Massachusetts

"Characterization of the FACC Polypeptide"

My laboratory at the Dana-Farber Cancer Institute is interested in the molecular cause of Fanconi Anemia. We recently presented our research at the Fifth Annual Fanconi Anemia Scientific Symposium in St. Louis in December, 1993.

Since Dr. Buchwald's laboratory cloned the gene for Fanconi Anemia (type C) in 1992, several significant advances have followed. Most notably, several laboratories are now interested in understanding the actual function of the Fanconi anemia type C protein (FACC protein).

To this end, my laboratory has developed an antibody that identifies the FACC protein. The antibody has provided some clues to the actual function of the FACC protein. For instance, we have been able to determine that the FACC protein is located (normally) in the cytoplasm of the cell, but not in the nucleus. This suggests that the FACC protein is unlikely to play a direct role in DNA repair. (DNA normally resides in the cell nucleus.)

In addition, our antibody has helped us to determine that the FACC protein binds to at least two other (associated) proteins. It is our hope that we will identify these proteins and perhaps clone the genes that encode them. The identification of FACC associated proteins may provide us with further clues to the actual function of the FACC protein. Also, it is possible that the FACC-associated proteins may themselves be products of other Fanconi Anemia genes (there are at least four genes known to exist). In collaboration with Dr. Markus Grompe at the Oregon Health Sciences University, we have begun to analyze Fanconi Anemia cell lines that have been initiated from our patient populations and family members. Our antibody to the FACC protein will provide a useful screening test to determine which patients have type C disease and which have non-C disease.

We continue to be extremely excited by the scientific progress in Fanconi Anemia and hope very much that we can make some further contributions to the molecular understanding of this disease.

Markus Grompe, MD, Oregon Health Sciences University, Portland, Oregon

"Creation of New Immortalized Fibroblast Cell Lines from Fanconi Anemia Patients"

Many laboratories active in FA research utilize cell lines from FA patients for their work. The cell lines are useful for detecting mutations, therapeutic testing, and mapping and cloning of new FA genes. Most of the cell lines available are derived from white blood cells (lymphoblasts). These cells divide rapidly and grow in suspension which makes them excellent sources of DNA and RNA. Lymphoblasts, however, are not very efficient at taking up exogenous DNA. This limits their use in experiments attempting to clone new FA genes. Many of these experiments rely on transferring "normal" DNA into FA cells in order to identify genes that can correct the chromosome breakage of FA cells.

Another source of cell lines from FA patients are fibroblasts or skin cells. These cells grow attached to plastic dishes and more slowly than lymphoblasts. Fibroblasts have a limited life-span and die after around 80 cell divisions. However, fibroblast cells can be made to grow indefinitely by a process called transformation and immortalization. Immortalized fibroblasts are quite good in taking up foreign DNA and are therefore well suited for FA gene cloning experiments. Unfortunately, only two such immortalized fibroblast cell lines from FA patients have been available in the entire world. In contrast, there are hundreds of different lymphoblast lines available. One of the fibroblast lines, GM 6914, is very famous and is being used by many laboratories to search for the Fanconi anemia complementation group A gene. The reason for the small number of immortalized fibroblasts is that it is a much more lengthy and labor intensive process than generating lymphoblasts. It takes approximately one year to create and characterize such a line.

The cloning of the remaining FA genes is a research goal of high importance and we therefore decided to generate and distribute more immortalized FA fibroblast cell lines. Several families have provided us with skin biopsies from their children with Fanconi anemia. At the last family meeting in Minneapolis alone, we obtained 6 such samples. We are currently working on 10 new fibroblast cell lines. Only one of these is from complementation group C. Two of these 10 appear to be immortalized, i.e. growing extremely well past 120 cell divisions. One of these belongs to complementation group C, the other is a new cell line. We have recently shown by cell-cell fusion that this new FA cell line, PD201, does not belong to complementation group A. In cell-cell fusions the cells from 2 different patients with Fanconi anemia are forced to join or fuse and become one cell in the test tube. Both patient cell lines individually are sensitive to Mitomycin C and have chromosome breakage. However, if the defective genes in the 2 patients are different, i.e. from different complementation groups, the fused cell will no longer be Mitomycin C sensitive. Our results indicate that the new cell line is neither complementation group A nor C and therefore can be used for the cloning of a gene from another complementation group.

All other 8 new cell lines will also be tested when they have reached the stage at which we can be certain that they are truly immortalized. We will inform the respective families whether they are part of complementation group A or not.

Grover D. Bagby, Jr., MD, Oregon Health Sciences University

"The FACC Gene Product and Hematopoiesis"

Bone marrow failure is a consistent feature of Fanconi anemia, but it is not known whether the bone marrow failure in this disease is a direct and specific result of the inherited gene mutation or a consequence of stem cell damage in the bone marrow from accumulated non-specific DNA damage. We tested the hypothesis that the protein encoded by the Fanconi anemia C complementing gene (FACC) plays a regulatory role in hematopoiesis. We exposed normal lymphocytes, normal bone marrow cells, and normal fibroblasts to short DNA molecules (known as antisense oligonucleotides) designed to repress expression of the FACC gene. We found that repression of the FACC gene in normal lymphocytes caused the lymphocytes to become genetically unstable in the mitomycin c assay (therefore turning off the gene induced multiple chromosomal abnormalities that were identical to the abnormalities seen in cells of children with Fanconi anemia).

Exposure of normal human bone marrow to the same DNA molecules inhibited the growth committed hematopoietic progenitor cells (primitive bone marrow cells that resemble stem cells). The DNA molecule did not inhibit the expression of hematopoietic growth factor genes and did not inhibit the growth of fibroblasts. We conclude that while the FACC gene product, (the protein encoded by the gene) plays a role in repair of crosslinked DNA, it also functions to regulate growth and differentiation of normal human bone progenitor cells. We suggest that loss of the function of this protein in children with this variant of Fanconi anemia plays a direct contributory role in the development of bone marrow failure.

Albert J. Fornace Jr., MD, National Cancer Institute, National Institutes of Health

"The Role for Tumor Suppressors in Growth Control Responses Induced by DNA-damaging Agents, and Abnormalities in Cancer-prone Individuals"

Cells have developed a variety of approaches to defend themselves against damaging agents in both the environment and from endogenous sources, such as produced during inflammation. An important response seen in virtually all cells from bacteria to man is the activation of growth delays - often called cell cycle checkpoints. This allows the cell time to recover from injuries, particularly DNA damage, prior to progressing into very critical portions of the cell cycle when DNA is replicated or the cells divide. If unrepaired damage is present during these critical portions of the cell cycle then mutations and chromosomal damage can occur that often results in mutations, chromosome abnormalities, and cell death.

My group and others have cloned a variety of human and other mammalian genes that are activated during these potentially protective responses. These genes appear to play a variety of roles in delaying cell cycle progression and cell growth after stress, and in some cases they have roles in apoptosis - programmed cell death. While the damaged cell dies during apoptosis, this may be protective for the organism since damaged cells, which could develop into malignant cells, are removed. Needless to say, abnormalities in these pathways could and almost certainly do have a variety of important adverse effects on the organism. A critical question is how are these responses controlled, so that they are only activated when appropriate.

An exciting recent development has been the finding that the tumor suppressor p53 has a central role in their control and in the activation of some of these responses (Kastan, M.B., Zhan, Q., El-Deiry, W.S., Carrier, F., Jacks, T., Walsh, W.V., Plunkett, B.S., Vogelstein, B., and Fornace, A.J. Jr. A mammalian cell cycle checkpoint utilizing p53 and GADD45 is defective in ataxia telangiectasia. Cell 71: 587-597, 1992).

p53 protein is encoded by a gene, which is frequently mutated in tumor cells leading to inactivation of the tumor suppressor function. In fact, p53 is the most frequently mutated gene found in human cancer to date. In most studies, 75% or more of tumors sampled have been found to have lost normal p53. In addition, certain viruses, which are associated with malignancy, have been found to produce factors that can inactivate p53. Probably the most important function of p53 is to activate these various growth-arrest and cell-cycle-checkpoint genes.

The first human gene shown to be regulated by p53 was isolated in my laboratory and has been called GADD45 (GADD designates growth-arrest and DNA-damage inducible). Current evidence indicates that it along with at least several other more recently isolated genes are "turned on" by p53 protein. Our current view of the response is that during stress, cells have a mechanism for recognizing damage, such as in the chromosomal DNA, that involves p53. After such damage, p53 protein levels rapidly increase; activated p53 then binds to the regulatory regions of genes like GADD45 to "turn them on." The resultant increase in the synthesis of growth-arrest proteins, like Gadd45, affects cell growth and in some cases apoptosis. In the case of the cancer-prone disease ataxia telangiectasia, the signaling mechanism is perturbed and p53 protein does not increase normally after damage. One consequence of this is the lack of a normal checkpoint delay after damage such as caused by radiation or drug exposure. In another cancer-prone disease Li-Fraumeni syndrome, the actual p53 gene is mutated in one of the 2 copies present normally. Since these cells need only incur one mutation to lose the remaining gene, they are at a markedly increased risk of cancer. These injury/damage response pathways are complex and will probably be found to have a variety of roles in human cells. Abnormalities in some aspect of these pathways may very well be found in other hereditary cancer-prone disorders.

Richard E. Harris, MD, Children's Hospital Medical Center, Cincinnati, Ohio

"Transplantation for Fanconi Anemia - An Overview from the Fanconi Anemia Transplant Registry"

Data on 291 patients who have undergone marrow transplant for Fanconi anemia were obtained from the International Bone Marrow Transplant Registry (IBMTR), the National Marrow Donor Program (NMDP), the Fanconi Anemia Research Fund (FARF), the International Fanconi Anemia Registry (IFAR), and the transplant teams in Seattle, Paris, Sloan-Kettering, Univ. Minnesota, Curitiba-Brazil, and Cincinnati, as well as additional transplant centers. Patients were uniquely identified by their date of birth and date of transplant to avoid duplication.

Data are currently available on 210 matched sibling donor (MSD) transplants, 49 related haploidentical (HAP) transplants, and 34 unrelated donor (URD) transplants. The 2-year disease-free survival (DFS) was 62% for MSD, 32% for HAP, and 31% for URD transplants. The DFS for fully matched (HLA-A, B and DR identical) HAP (N=21) and URD (N=27) transplants were 48% and 40% respectively (NS). The DFS for all fully matched alternative donor transplants (N=48) was 43% (p=0.06 vs MSD). The DFS for fully matched URD transplants (N=27, DFS 40%) appears to be higher than that of partially matched HAP transplants (N=28, DFS 20%, p=0.04). Of seven 1-antigen mismatched URD transplants, none survive.

With MSD transplants, the best DFS was seen among patients receiving a preparative regimen of low-dose cyclophosphamide (15-25 mg/kg) combined with low-dose thoracoabdominal or total lymphoid irradiation (400-600 cGy) and GVHD prophylaxis utilizing cyclosporine and ATG or ALS (N=20, 2 yr DFS =94%); with the same conditioning but without ATG/ALS, 2-yr DFS was 74% (N=76; p=0.05 vs group receiving ATG/ALS).

A preliminary risk factor analysis shows the best survival among patients transplanted before the age of 10 yrs, before the development of leukemia, or before receiving more than 10 transfusions.

Current cautious recommendations are as follows: 1) Patients who have a MSD should undergo a transplant as soon as hematologic manifestations dictate a need for therapy; 2) Patients without a MSD but with a fully matched alternative donor could be considered for transplant if they have shown resistance to androgen therapy; 3) patients without either a MSD or a fully matched HAP or URD should be evaluated individually. Future options might include gene therapy, particularly for these high risk patients.

Christopher Walsh, MD, Ph.D., National Institutes of Health

"Gene Transfer Strategies for the Treatment of Fanconi Anemia"

Fanconi's anemia (FA) is an inherited disorder that can produce bone marrow failure. In addition, some patients with FA have physical defects, usually involving the skeleton or kidneys. The major problem for most patients is aplastic anemia. In aplastic anemia, the blood counts for red blood cells, white blood cells, and platelets are low because the bone marrow fails to produce these cells. Some patients with FA also can develop leukemia or cancers in other organs. Many laboratory studies have suggested that Fanconi's anemia is due to an inherited defect in the ability of cells to repair DNA. Recently, the gene for one of the four types of Fanconi's anemia, type C, has been identified. It is known that this gene is defective in patients with FA type C.

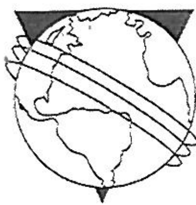
Studies in our laboratory have suggested that FA type C may be a good candidate disease for gene therapy. We have placed the normal FA type C gene into a retroviral vector and introduced the gene into cells, derived from FA type C patients. In the laboratory, when we have compared cell lines and bone marrow cells from FA patients before and after this procedure, we see a return towards normal of cell growth, resistance to the chemical agents that harm FA cells, and a more normal appearance of the cells' chromosomes. Because the cells containing the normal FA type C gene grow better, these cells should have a competitive advantage compared to unaltered FA type C cells.

The purpose of our research is to test whether we can safely introduce the normal FA type C gene into stem cells of patients with this disease. Stem cells are the cells in the bone marrow and blood and give rise to the white cells, platelets, and red cells. We hope that cells that contain the FA gene will grow well in the bone marrow, and that we will be able to detect normal stem cells in special tissue culture studies. The major purpose of our work is to test the safety of this technique and to determine whether we can transfer the Fanconi's anemia gene successfully.

Karin M.L. Gaensler, MD, Department of Medicine, University of California San Francisco

"New Strategies for Gene Therapy"

Genetic diseases, such as Fanconi's anemia, are caused by the absence of a gene which is present in normal individuals. These diseases will become curable if and when the normal gene can be replaced in critical cell types in affected individuals. Our work focuses on using lipid carriers to deliver and express selected genes in the body, after injecting these lipid carrier-DNA complexes into the bloodstream. Using this approach, we have now demonstrated in animal models that these genes can be expressed in virtually every tissue in the body. We find also expression of these genes in cell types crucial to successful gene therapy for Fanconi's, including blood forming cells in the bone marrow. Furthermore, this approach does not appear to produce significant toxicity in treated animals. Currently, we are attempting to develop effective gene therapy for a variety of human genetic diseases, including Fanconi's Anemia.



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