Welcome to the 16th issue of the FA Courier, outlining current requests for materials and clinical trials connected to Fanconi anemia (FA) research. We publish the FA Courier:

- To encourage families to contribute to the urgent need for research materials necessary for FA research;
- To keep families informed about current research projects and clinical trials; and
- To apprise researchers of the availability of research materials.

Thank you for helping to advance Fanconi anemia research.

For FA Patients and Families

Needed: Completion of questionnaires; bone marrow; tumor tissue; blood, serum and plasma samples; mouth washings; skin biopsies

Etiologic Investigation of Cancer Susceptibility in Inherited Bone Marrow Failure Syndromes

This project will identify cancer-prone families with underlying Fanconi anemia prior to the appearance of cancer.

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Funding source: National Cancer Institute, Intramural Research Program

Accepting: International patients

Hypothesis:
This project will identify cancer-prone families with underlying Fanconi anemia (FA) prior to the appearance of cancer. The goal is to learn more about FA, in order to improve the quality of life for persons from affected families. Hypotheses: 1) A prospective cohort will provide new information regarding cancer risk. 2) Mutation in FA genes are relevant to cancer pathways in non-hereditary forms of cancers. 3) Patients with FA who develop cancer differ from patients with FA who do not develop cancer. 4) Carriers of FA mutations are at an increased risk of cancer. 5) A substudy will explore the experiences of healthy siblings of FA patients, in order to determine how we can help families manage FA.

Importance of project to FA patients:
FA patients have a remarkably high risk of leukemia and solid tumors. A large epidemiologic study will determine actual cancer risks, identify individually predictive features and define management. The prognostic significance of specific FA mutations and non-FA genes will be identified. The role of viruses in FA solid tumors will be examined. Features of the bone marrow that are associated with progression to leukemia will be defined. FA patients are at high risk of HPV-associated head and neck and gynecologic cancer.

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Etiologic Investigation of Cancer Susceptibility in Inherited Bone Marrow Failure Syndromes continued

**Background:**
- A prospective cohort of Inherited Bone Marrow Failure Syndrome (IBMFS) will provide new information regarding cancer rates and types in these disorders.
- Mutations in IBMFS genes are relevant to carcinogenesis in sporadic cancers.
- Patients with IBMFS who develop cancer differ in their genetic and/or environmental features from patients with IBMFS who do not develop cancer.
- These cancer-prone families are well suited for cancer screening and prevention trials targeting those at increased genetic risk of cancer.
- Carriers of IBMFS gene mutations are at increased risk of cancer.
- The prototype disorder is Fanconi Anemia (FA); other IBMFS will also be studied.

**Objectives:**
- To determine the types and incidence of specific cancers in patients with an IBMFS.
- To investigate the relevance of IBMFS gene mutations in the carcinogenesis pathway of the sporadic counterparts of IBMFS-associated cancers.
- To identify risk factors for IBMFS-related cancers in addition to the primary germline mutations.
- To determine the risk of cancer in IBMFS carriers.

**Eligibility:**
- North American families with a proband with an IBMFS.
- IBMFS suspected by phenotype, confirmed by mutation in an IBMFS gene, or by clinical diagnostic test.
- Fanconi anemia: birth defects, marrow failure, early onset malignancy; positive chromosome breakage result.
- Diamond-Blackfan anemia: pure red cell aplasia; elevated red cell adenosine deaminase.
- Dyskeratosis congenita: dysplastic nails, lacy pigmentation, leukoplakia; marrow failure.
- Shwachman-Diamond Syndrome: malabsorption; neutropenia.
- Amegakaryocytic thrombocytopenia: early onset thrombocytopenia.
- Thrombocytopenia absent radii: absent radii; early onset thrombocytopenia.
- Severe Congenital Neutropenia: neutropenia, pyogenic infections, bone marrow maturation arrest.
- Pearson Syndrome: malabsorption, neutropenia, marrow failure, metabolic acidosis; ringed sideroblasts.
- Other bone marrow failure syndromes: e.g. Revesz Syndrome, WT, IVIC, radio-ulnar synostosis, ataxia-pancytopenia.
- First degree relatives of IBMFS-affected subjects as defined here, i.e. siblings (half or full), biologic parents, and children.
- Grandparents of IBMFS-affected subjects.
- Patients in the general population with sporadic tumors of the types seen in the IBMFS (head and neck, gastrointestinal, and anogenital cancer), with none of the usual risk factors (e.g. smoking, drinking, HPV).

**Design:**
- Natural history study, with questionnaires, clinical evaluations, clinical and research laboratory test, review of medical records, cancer surveillance.
- Primary endpoints are all cancers, solid tumors, and cancers specific to each type of IBMFS.
- Secondary endpoints are markers of pre-malignant conditions, such as leukoplakia, serum or tissue evidence of carcinogenic viruses, and bone marrow morphologic myelodysplastic syndrome or cytogenetic clones.
Etiologic Investigation of Cancer Susceptibility in Inherited Bone Marrow Failure Syndromes continued

Sponsoring Institute:
National Cancer Institute (NCI)

Recruitment Detail
Type: Participants currently recruited/enrolled
Gender: Male & Female
Referral Letter Required: No
Population Exclusion(s): None

Eligibility Criteria:
INCLUSION CRITERIA - PATIENTS:
• Fanconi anemia.
• Diamond-Blackfan anemia.
• Dyskeratosis congenita.
• Shwachman-Diamond Syndrome.
• Amegakaryocytic thrombocytopenia.
• Thrombocytopenia absent radii.
• Severe congenital neutropenia.
• Pearson Syndrome.
• Other bone marrow failure syndromes.
• First degree relatives of IBMFS-affected subjects as defined here, i.e. siblings (half or full), biologic parents, and children.
• Grandparents of IBMFS-affected subjects, specifically for Hypothesis 4.
• Patients in the general population with sporadic tumors of the types seen in the IBMFS (head and neck, gastrointestinal, and anogenital cancer), with none of the usual risk factors for those tumors (e.g. smoking, drinking, HPV).
• Adult patients and family members who are unable to provide consent.

INCLUSION CRITERIA - UNAFFECTED SIBLING STUDY:
• Eligibility for this amendment will be assessed only after the subject has been deemed eligible for the parent protocol.
• Specific eligibility for the proposed amendment are as follows:
• Ability to read, write, and speak in English.
• Between the ages of 11 & 21.
• Informant has at least one biologically related, living sibling (full or half) who has an IBMFS.

EXCLUSION CRITERIA - PARENT PROTOCOL:
• Evidence that the hematologic disorder is acquired rather than genetic. Such evidence includes temporal relation of the aplastic anemia to known marrow suppressant drugs, chemicals, toxins, or viruses (in the absence of evidence indicative of an inherited marrow failure disorder).
• Known causes of cytopenias such as autoantibodies to red cells, platelets, or neutrophils, viruses (especially hepatitis), micronutrient deficiencies, transient erythroblastopenia of childhood, and cyclic neutropenia.
• Assignment of the patient's physical findings to other syndromes or causes that are not part of the IBMFS disease spectrum.
• Inability or unwillingness to complete the questionnaires or permit access to medical records and pathology specimens.
• There are no other exclusion parameters not related to the primary disease.
### Gene Function in Bone Marrow Cells from Patients with Fanconi Anemia and from Healthy Participants

Patients and healthy volunteers undergo bone marrow aspiration and/or peripheral blood sampling. Blood and bone marrow samples are tested in biological and molecular genetic assays.

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**Alternate Contact:** R. Keaney Rathbun  
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**Funding Source:** NIH: National Heart Lung and Blood Institute  
**Accepting:** US patients only  
**Rationale:**  
Studying samples of bone marrow from patients with Fanconi anemia and from healthy participants in the laboratory may help doctors learn more about biochemical changes that lead to bone marrow failure and leukemia in patients with Fanconi anemia.  
**Purpose:**  
This laboratory study is evaluating gene function in bone marrow cells from patients with Fanconi anemia and from healthy participants.
Importance of project to FA patients:
If the molecular defects that account for bone marrow failure in FA are clarified, pharmacological agents can be tested in novel ways that might lead to the identification of pharmacological approaches to improving bone marrow function.

Objectives:
• Describe the complete hematopoietic transcriptomes of Fanconi cells of every common complementation group (e.g., A, C, G, and F) as well as transcriptomes of neoplastic cells derived from bone marrow of patients with Fanconi anemia.
• Identify the molecular causes of bone marrow failure using gain- and loss-of-function strategies.
• Identify small molecules that correct the molecular defect in hematopoietic cells from FA patients.

Projected Accrual:
A total of 80 patients and 10 healthy volunteers will be accrued for this study.

Eligibility criteria:
Ages Eligible for Study: 1 Year to 55 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: Yes

Disease characteristics:
• Meets one of the following criteria:
  ▫ Diagnosis of Fanconi anemia—requires bone marrow aspiration or biopsy for clinical purposes
  ▫ Healthy volunteer—over 18 years of age, no known blood abnormality

Patient characteristics:
• Platelet count > 150,000/mm^3
• WBC > 4,000/mm^3
• Hemoglobin > 13 g/dL
• No clinical signs or symptoms of acute or subacute infection (e.g., viral, bacterial, or fungal)
• No allergies to lidocaine or xylocaine

Material/Information needed:
Heparinized bone marrow and heparinized peripheral blood.

Cost of participating:
There are no costs for participating. Normal volunteers will be paid $150 for a bone marrow and blood sample.
Laboratory Studies of Gene Transfer for Fanconi Anemia

normal gene to the blood stem cells of patients with Fanconi anemia. At this time, we are focusing on Fanconi anemia complementation group A (FANCA) and Fanconi anemia complementation group C (FANCC). We have developed a genetically modified, non-disease-causing virus that can deliver the FANCA or FANCC gene to blood cells in a laboratory dish. We have tested it in blood cells from people who do and do not have Fanconi anemia, and in blood cells from mice with Fanconi anemia. In order to optimize the delivery of a normal FANCA or FANCC gene to abnormal cells, and to test its ability to correct the Fanconi defect in the laboratory, we need a source of bone marrow and/or blood from patients with FANCA or FANCC.

Importance to FA patients:
Optimizing the gene delivery process is an essential step in developing gene therapy as a safe and effective treatment option for Fanconi anemia patients.

Eligibility criteria:
• Fanconi anemia complementation group A or C as determined by somatic cell hybrids, molecular characterization, Western blot analysis or acquisition of mitomycin C resistance after in vitro transduction with a vector bearing the cDNA for Fanconi complementation group A or C
• Undergoing bone marrow aspiration and/or blood draw for clinical purposes

Material needed:
10 mL (2 teaspoons) of blood and/or 5 mL (1 teaspoon) of bone marrow

Cost of participating:
There is no cost for participating. Dr. Becker’s laboratory will pay for shipment.

Molecular Surveillance for Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Development of a screening test for cancer of the mouth and throat (head and neck cancer): cancers of the mouth and throat may go undetected in their earliest and most treatable stages. A new test that analyzes the DNA from cells released when an individual gargles is being developed at Johns Hopkins.

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Funding Source: National Institute of Health

Accepting: International patients are accepted.

Hypothesis or Rationale:
It is hoped that a detailed understanding of the spectrum of genetic alterations underlying the malignant transformation process for a class of tumors will provide insight into that process to inform strategies aimed at early detection, accurate strategy and prediction of response to therapy.

Purpose:
• Development of an accurate, sensitive and specific test for early detection of head and neck (H&N) cancer using tumor specific promoter hypermethylation markers.
• To evaluate aberrant promoter hypermethylation of candidate tumor suppressor genes as a means to detect epigenetic alterations specific to solid tumors, including head and neck squamous cell carcinoma (HNSCC).

Importance to FA patients:
There is no immediate benefit to subjects. However, as new insight is obtained regarding the
Molecular Surveillance for Squamous Cell Carcinoma of the Upper Aerodigestive Tract

molecular pathogenesis of disease, new treatment modalities may be devised. In addition, the identification of tumor-specific molecular markers may be useful in conjunction with other protocols for the early detection of recurrent disease.

More immediately, there are enormous potential societal benefits to be derived from an improved understanding of HNSCC. Early detection strategies, effective tailoring of existing therapies, and the development of new therapeutic modalities may result directly or indirectly from the study.

**Eligibility:**
Any patient who has already been diagnosed with having Squamous Cell Carcinoma of the mouth or throat is eligible to participate.

**Material/Information needed:**
A sample of the lesion obtained at time of routine surgical resection, blood sample and oral rinse with saline. Additional peripheral blood and saliva samples will be collected (similar to initial collection) at intervals of 3 (+/- 1 month) months for a period of up to 2 years. Collection of follow up samples will be coordinated with patient’s routine clinical visit, and patients will not be required to make extra visits for the study purposes.

**Cost of participating:**
No cost to participants

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### The International Fanconi Anemia Registry

Investigating the correlation between genotype and phenotype will define important regions within the FA genes that may shed light on their function in DNA repair, cell cycle control, and programmed cell death. The cell lines will be studied to understand in detail defects in Fanconi anemia cells.

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Website: http://lab.rockefeller.edu/smogorzewska/ifar/

**Funding source:** The Rockefeller University, NIH, Starr Foundation, Burroughs Wellcome Fund, Rita Allen Foundation

**Accepting:** All patients with Fanconi anemia
Hypothesis:
The Rockefeller University Hospital is home to the International Fanconi Anemia Registry (IFAR) which was established in 1982. The purpose of the Registry is to study a large number of patients exhibiting the full spectrum of diverse features of FA. Questions relating to diagnosis, natural history of the disease, prognosis, treatment and cancer incidence in FA are being addressed by the IFAR studies. In addition, through numerous collaborations, we are using the most current technologies available to try to identify the mutations causing Fanconi anemia in each participating family, as well as identify novel FA genes. Information regarding genotype-phenotype correlation is being obtained, which may help to determine the physiologic roles of the cloned genes. We hypothesize that correlation between genotype and phenotype will define important regions within the FA genes that may shed light on their function in cell cycle control, programmed cell death and DNA repair. This may lead to improvement in prediction of outcome for a given patient, based on genotype, and affect decision-making regarding timing of therapy options.

Importance of project to FA patients:
We aim to more fully define the variable clinical manifestations associated with FA, particularly the congenital malformations and malignancies, and to determine to what extent the clinical findings in FA patients and carrier family members correlates with the specific mutation/region of mutation, i.e. genotype. The recent identification of the genes responsible for ~90% of the cases of FA make it possible to evaluate patients and family members by mutation group, comparing phenotype with genotype. We will conduct a thorough clinical and molecular genetic analysis with the objectives of learning about the extent, the causes and the optimal treatment for FA-associated medical problems. As part of the project, we are developing more rapid methods for mutation screening. Genetic information will be made available to patients’ physicians as appropriate by law.

Eligibility criteria:
Any patient diagnosed as affected with FA, as well as parents and sometimes siblings.

Material/Information needed:
We need to receive a blood specimen from the patient to make a cell line. Mutation testing will be performed in a research laboratory. The paperwork needed to enroll a participant can be downloaded at http://lab.rockefeller.edu/smogorzewska/ifar/ using the tabs on the left hand side under “Forms for New IFAR Enrollments.” If there are questions about enrollment please contact the study coordinator, Erica Sanborn at 212-327-8613 or esanborn@rockefeller.edu.

Cost of participating:
If the blood sample can be drawn on participants in conjunction with a clinical blood draw, the blood drawing fee can usually be waived or covered by insurance. In the event that the referring institution cannot cover costs, we may be able to help. Please contact us for details.

Pioglitazone for Oral Premalignant Lesions
The goal of this clinical research study is to learn how Actos® (pioglitazone) may affect oral pre-malignant lesions (OPLs) and/or the risk of mouth cancer. The safety of this drug will also be studied. Neither you nor the study doctor will know if you are receiving the study drug or the placebo. However, if necessary for your safety, the study doctor will be able to determine which one you are receiving.

Principal Investigator: Jay Boyle, MD, Memorial Sloan-Kettering Cancer Center, New York, N.Y.
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Primary Objective:
To determine the clinical and histologic response of oral premalignant lesions to 24 weeks of therapy with pioglitazone, 45 mg qd, defined as 50% or greater reduction in the sum of all measured products of perpendicular dimensions of target lesions, or improvement in the degree of dysplasia or hyperplasia.
Secondary Objectives:
1. To determine the degree of change of putative biomarkers of pioglitazone efficacy including (but not restricted to) and in order of priority, tissue levels of:
   - PPAR gamma
   - cyclin D1 and p21 as indirect measures of pharmacological effect
   - TUNEL for apoptosis and Ki-67 for proliferation
   - transglutaminase and involucrin as markers of squamous differentiation
   - 15-PGDH, loss of heterozygosity (LOH)
2. To determine the degree of change of C-reactive protein (CRP) in plasma
3. To assess tobacco and alcohol use among trial participants and to examine the relationship of tobacco and alcohol use to treatment response.
4. To assess the safety of this agent in this population.

Study Drug:
Pioglitazone is commonly used to lower the blood sugar in patients with diabetes. It is designed to target a protein that may change how genes affect the body’s metabolism. It also may decrease the growth of cancer cells.

Study Groups:
If you are found to be eligible to take part in this study, you will be randomly assigned (as in the toss of a coin) to a study group. You will have an equal chance of being placed in either group.

Group 1 will take pioglitazone. Group 2 will take a placebo (a substance that looks like the study drug but has no active ingredients).

Neither you nor the study doctor will know if you are receiving the study drug or the placebo. However, if needed for your safety, the study doctor will be able to find out.

Study Drug Administration:
You will take 3 capsules of study drug/placebo by mouth, once a day, at about the same time each day.

If you forget to take a dose and you remember that same day, take the missed dose as soon as you remember it. However, if you do not remember until the next day, do not take 2 doses to make up for the missed dose. Instead, skip the missed dose and continue your regular dosing schedule.

You will be given a pill diary to help you keep track of your doses of the study drug/placebo. Every day, you should write down when you take the study drug/placebo.

You should bring your completed pill diary and your bottle of capsules to every study visit. The study staff will review the diary with you at every study visit and phone call.

Study Visits and Calls:
At Weeks 4, 12 and 24, you will have study visits. The following tests and procedures will be performed:
   - You will have a physical exam, including an exam of your mouth.
   - You will be asked about any drugs you are taking and any side effects you have experienced.
   - Blood (about 3 teaspoons) will be drawn for routine tests.
   - At Weeks 12 and 24 only, the lesions will be measured.
   - At Week 24 only, photos of the lesions will be taken.
   - At Week 24 only, you will have a biopsy of the lesion area and a biopsy of a normal-looking area of your mouth.

At Week 8, the research staff will call you to ask about any drugs you are taking and any side effects you have experienced.
Pioglitazone for Oral Premalignant Lesions

At Week 18, the following tests and procedures will be performed:
- Blood (about 2 teaspoons) will be drawn for routine tests.
- You will be asked about any drugs you are taking and any side effects you have experienced. This may be done by phone if your blood work is done at a location other than M. D. Anderson.

If you stop taking the study drug/placebo before Week 25, the following tests and procedures will be performed:
- You will have a physical exam, including an exam of your mouth.
- You will be asked about any drugs you are taking and any side effects you have experienced.
- Blood (about 3 teaspoons) will be drawn for routine tests.
- The lesions will be measured.
- Photos of the lesions will be taken.
- You will have a biopsy of the lesion area and a biopsy of a normal-looking area of your mouth.

Length of Study Participation:
You may take the study drug/placebo for up to 25 weeks. You will be taken off the study drug/placebo early if intolerable side effects occur or the doctor thinks it is in your best interest.

Follow-Up Phone Call:
After you finish taking the study drug/placebo, the research staff will call you to ask about any drugs you are taking and any side effects you have experienced. You will also be told the results of the Week 24 lesion biopsy.

Eligibility Criteria:

Inclusion Criteria:
1. Males or females with a suspected or histologically confirmed oral premalignant lesion(s) [*up to three target lesions may be followed for the purpose of the study] (OPL) that has a length (longest diameter) of 8 mm or greater and width (diameter perpendicular to greatest length) of 3 mm or greater in size.
2. Continuation of Inclusion 1). If a participant has had a biopsy of the target OPL lesion(s) within 6 weeks prior to the Screening visit and archival tissue is available and the participant agrees to have archival tissue used for histologic confirmation and biomarker analysis, then NO additional biopsies (of the OPL or normal tissue) need to be performed at the Screening Visit.
3. Continuation of Inclusion 2). The pre-Screening biopsy must undergo centralized pathology review before the second stage of registration can be performed. If archival tissue is not available, a waiting period of 6 weeks from the time of the last biopsy must be observed before re-biopsy for study purposes.
4. If a participant has not had a biopsy of the suspected OPL at the time of the Screening Visit, then a biopsy of the lesion and normal tissue must be performed during the Screening Visit. The Screening biopsy must undergo centralized pathology review before the second stage of registration can be performed.
5. Age >/= 18 years
6. The participant’s life expectancy is > 6 months.
7. The participant has discontinued any other oral cancer chemopreventive therapy, including use of more than one multi-vitamin per day and use of any particular vitamin supplement at >3 times the United States Dietary Reference Intake (DRI) (Recommended Dietary Allowance (RDA) or Adequate Intake (AI) as applicable) at least 12 weeks prior to the Baseline visit and all toxicities have been fully resolved. Daily aspirin is permitted.
8. The participant is willing and able to fully participate for the duration of the study.
9. The effects of pioglitazone on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women must not be pregnant or lactating. Women of child-bearing potential (women are considered not of childbearing potential if they are...
at least two years postmenopausal and/or surgically sterile) must have used adequate contraception (abstinence; barrier methods such as IUD, diaphragm with spermicidal gel, condom, or others; and hormonal methods such as birth control pills or others) since her last menses prior to study entry.

10. Continuation of Inclusion 8.) Women of child-bearing potential and men must agree to use adequate contraception for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

11. Ability to understand and the willingness to sign a written informed consent document.

12. Stage Two: The participant has one or more target lesions histologically confirmed by a biopsy obtained no more than 9 weeks prior to randomization, that is either: An EARLY premalignant lesion defined to be at high risk: mild dysplasia of any site, hyperplastic leukoplakia of a high-risk site, dorsal, lateral or ventral tongue and floor of mouth OR An ADVANCED premalignant lesion defined as the presence of at least one of the following: moderate dysplasia, severe dysplasia (excluding carcinoma in situ) or erythroplakia*

13. Continuation of Inclusion 11.) Stage Two: * Due to the high risk for progression associated with erythroplakia, erythroplakia of any histology will be defined as an ADVANCED oral premalignant lesion.

14. The participant meets the following laboratory eligibility criteria during a time not to exceed 6 weeks prior to randomization: Hemoglobin levels equal to or above the lower limit of normal, White blood cells >/= 3,000/microL, Platelets >/= 125,000/microL, Total bilirubin </= 1.5 x ULN, AST (SGOT)/ALT (SGPT) </= 1.5 x ULN, BUN and serum creatinine </= 1.5 x ULN, glucose, serum <200mg/dL

15. The participant's Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1.

16. Refer to Inclusion 8.) & 9.) If the participant is female and of childbearing potential and not lactating she has a documented negative serum pregnancy test within 14 days prior to randomization.

17. The participant has a baseline Electrocardiograph (ECG/EKG) that does not show signs of acute cardiac ischemia or cardiac dysrhythmia (except for 1st degree AV block or chronic atrial fibrillation). EKG can be an earlier report within 12 weeks prior to registration.

18. Both men and women and members of all races and ethnic groups are eligible for this trial. The investigators will strive to recruit subjects of a demographic that reflect those affected with oral premalignant lesions in the general population. Cancer statistics show that the prevalence of oral precancer and oral cancer is higher among males than females, at a ratio of 1.3:1. All consenting investigators and professionals will be informed of the importance of recruiting women to the current trial. This effort will ensure that we have adequate representation of women.

19. Continuation of Inclusion 17.) Similarly, our investigators are extremely aware of the importance of recruiting minorities. In summary, a specific effort will be made to recruit and retain woman and minorities to the current trial. It is anticipated that 40% of the subjects enrolled to the current trial will be female, and that approximately 12% of the study population will be Hispanic or Latino.

Exclusion Criteria:
1. The participant has active cancer or carcinoma in situ of the head and neck.
2. The participant has a contraindication to biopsy.
3. The participant has presence of congestive heart failure (New York Heart Association (NYHA) Class II-IV), uncontrolled hypertension (systolic >150 or diastolic >100), or unstable angina.
4. The participant has any history of congestive heart failure or history of myocardial infarction within the past 6 months.
5. The participant exhibits clinical evidence of active liver disease or history of chronic liver disease.
6. The participant has > CTCAE Grade 1 edema.
7. The participant has known diabetes and is on insulin or oral agents. The participant is
8. The participant currently receives an enzyme inhibitor of CYP2C8 (gemfibrozil, ketoconazole, quercetin, trimethoprim), or enzyme inducer of CYP2C8 (cortisol, dexamethasone, phenobarbital, rifampin), or CYP3A4 substrate.

9. The participant currently receives pregabalin or thioridazine.

10. The participant has experienced jaundice with Rezulin® (troglitazone).

11. The participant has a history of colorectal cancer, familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC).

12. The participant has a history of bladder cancer or in situ bladder cancer.

13. The participant has a history of invasive cancer within the past 18 months (excluding nonmelanoma skin cancer and in situ cervical cancer). Participants (excluding those with a history of colorectal cancer, FAP, HNPCC, bladder cancer or in situ bladder cancer) who received curative treatment and have shown no evidence of recurrence for 18 months will be eligible.

14. The participant has had chemotherapy, cancer-related immunotherapy, hormonal therapy (other than HRT for menopause), or radiation therapy within 18 months of the Baseline visit.

15. The participant will need concurrent chemotherapy, radiotherapy, hormonal (other than HRT for menopause), or cancer-related immunotherapy during the time of study.

16. The participant has received any investigational medication within 30 days of the Baseline visit or is scheduled to receive an investigational drug during the course of the study.

17. The participant has received pioglitazone or rosiglitazone prior to this study.

18. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, HIV-positive, or psychiatric illness/social situations that would limit compliance with study requirements. Medical and scientific reasons for the exclusion of pregnant or nursing participants or participants who are HIV-positive from this study are detailed below. Pregnant women are excluded from this study because pioglitazone is an agent with the potential for teratogenic or abortifacient effects.

21. Continuation of Exclusion 20.) Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pioglitazone, breastfeeding should be discontinued if the mother is treated with pioglitazone.

22. Continuation of Exclusion 21.) HIV-positive: Known HIV-positive participants will be excluded from this study due to the high prevalence of confounding oral lesions in this population. Specifically, HIV infection is a risk factor for developing Epstein-Barr virus related abnormalities including Greenspan's leukoplakia or oral hairy leukoplakia. In addition, HIV-positive patients are susceptible to candidiasis which can cause white patches of the mouth.

Trial Lead Organizations/Sponsors:
M. D. Anderson Cancer Center at University of Texas
National Cancer Institute
Masonic Cancer Center at University of Minnesota
Memorial Sloan-Kettering Cancer Center
University of Wisconsin Paul P. Carbone Comprehensive Cancer Center

Locations:

United States:
UAB Comprehensive Cancer Center, Birmingham, Alabama
Principal Investigator: Eben L. Rosenthal, MD
Telephone: 205-934-9766

Holden Comprehensive Cancer Center at University of Iowa, Iowa City, Iowa
Phase II Study of Single-Agent Cetuximab for Treatment of High-Risk Pre-Malignant Upper Aerodigestive (UAD) Lesions

This is a randomized trial of cetuximab treatment for patients with high-risk, premalignant UAD lesions. Patients will also be followed for development of head and neck cancer. Following the eight-week treatment with cetuximab, assigned groups will undergo lesion resection based on the extent of initial disease.

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Phase II Study of Single-Agent Cetuximab for Treatment of High-Risk Pre-Malignant Upper Aerodigestive (UAD) Lesions

Accepting: International patients

Rationale:
Over 45,000 new cases of Head and Neck Squamous Cell Carcinomas (HNSCC) are diagnosed in the United States yearly, and this disease affects over 600,000 people worldwide. The data identify a set of high-risk patients with oral pre-malignant lesions as a population with extraordinary risk for malignant progression and significant mortality, for whom there is no viable medical or surgical intervention. Cetuximab is an attractive therapeutic agent for these patients, in that it has a low risk toxicity profile and is effective in invasive head and neck cancer.

Purpose:
This is a randomized trial of cetuximab treatment for patients with high-risk, premalignant UAD lesions. Three groups of patients (group 1: diffuse, group 2: recurrent, group 3: dysplastic) will receive cetuximab 400 mg/m2 on week one followed by 250 mg/m2 on weeks 2-8. Patients in the control arm will have the option of moving into a treatment arm after completion of initial treatment. Patients will also be followed for development of HNSCC. Following the eight-week treatment with cetuximab, groups 2 and 3 will undergo lesion resection based on the extent of initial disease. Safety of cetuximab in this patient population will also be evaluated. The projected accrual goal is a total of 60 patients. 20 of the 60 patients are targeted to be enrolled at the Coordinating Center at Johns Hopkins, while enrollment of 40 patients is to be completed at 11 participating sites. IRB approval has been obtained and enrollment has started at Johns Hopkins, Medical University of South Carolina and University of Illinois, Chicago, while other participating site are in the process of obtaining IRB approvals. To date, a total of 17 patients have been enrolled into the study, 6 have been treated, 2 are under treatment and 2 patients are in screening.

The inclusion criteria for enrollment are:
Histologically confirmed, previously untreated, high-risk UAD pre-malignant lesion consisting of one of the following groups:
- Unresectable, diffuse high grade dysplasia, defined as moderate or severe dysplasia whose anatomic extent cannot be assessed by physical examination and/or includes a large enough area or area of anatomic extent that cannot practicably be excised by standard surgical techniques
- Previously treated HNSCC with persistent or recurrent high grade dysplasia with no evidence of head and neck malignancy for three months prior to enrollment
- Dysplastic lesions with 3p or 9p loss of heterozygosity

Patients will undergo the following after enrollment into the study:
1. Informed consent
2. Complete Head and Neck Exam
3. Tolonium staining and Photodocumentation:
   a. Tolonium Staining using vizlite Blue Oral Exam Kit - this is to be provided free of cost
   b. Photodocumentation
4. Biopsy (3mm punch) of lesion OR prior biopsy less than 3 months prior to enrollment
5. Tumor specimen for LOH testing
6. Pre-treatment evaluation which includes:
   a. Blood tests to confirm eligibility to receive study drug and
   b. Imaging studies to assess extent of disease as per the standard of care for the patient.
   Research blood samples to be sent to Coordinating Center.
7. Randomization to one of the two following groups:
   a. Study Drug Group: Patient to receive weekly cetuximab injections for eight weeks on Days 1, 8, 15, 22, 29, 36, 43 and 50.
   b. Control Group: To undergo scheduled follow-up and observation on the same days mentioned above. Patients in this group may choose to receive the study drug after the eight-week period.
Phase II Study of Cetuximab and Lenalidomide in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

8. Post Treatment:
   a. Head and Neck Exam and blood draw
   b. Tolonium Staining and Photodocumentation:
      • Tolonium Staining using Vizlite Blue Oral Exam Kit - this is to be provided free of cost
      • Photodocumentation
   c. Repeat biopsy of tumor for Group 1, and/or excision of lesion for patients in Groups 2 and 3
   d. Repeat biopsy specimen to go for LOH testing

Erlotinib Prevention of Oral Cancer

This study is to determine if an epidermal growth factor receptor (EGFR) inhibitor (erlotinib) can reduce the incidence of oral cancer in high risk-patients with oral leukoplakia. This is tested by randomizing patients to either erlotinib 150mg orally daily or placebo.

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Objectives:
This study will test the ability of an epidermal growth factor receptor (EGFR) inhibitor (erlotinib) to reduce the incidence of oral cancer in the high-risk setting of oral leukoplakia with LOH in two cohorts, oral IEN (Intraepithelial neoplasia) patients with LOH in 3p and/or 9p and one other specific chromosomal locus but without cancer or oral IEN patients with LOH in 3p and/or 9p associated with curatively treated oral cancer. Researchers will test this treatment in a randomized clinical trial with 2 treatment arms: Erlotinib 150mg po QD or placebo.

Primary Aim:
The primary endpoint of the trial will be the oral cancer-free survival in patients receiving erlotinib as compared with the control or placebo group.

Secondary Aims:
1. The size, number, and appearance of oral IEN will be assessed and correlated with cancer risk. A > 50% reduction in the bidimensional measurements of IEN lesions is considered a treatment response. We hypothesize that patients with IEN lesions and LOH of the oral cavity will respond to erlotinib.
2. To examine toxicity associated with erlotinib. Our hypothesis is that patients with oral lesions will tolerate treatment with erlotinib.
3. To assess a panel of molecular markers for correlations with oral cancer development in our oral IEN patients.

Importance of project to FA patients:
No cytoxics.

Eligibility:
Inclusion criteria:
1. Male or female patients with one of the following: (a) loss of heterozygosity (LOH) at 3p14 and/or 9p21 in the oral IEN of patients with a history of curatively treated oral cancer or (b) LOH at 3p14 and/or 9p21 plus at one other chromosomal region in the IEN of patients with no oral cancer history.
Participants must have confirmed diagnosis of oral IEN lesion with LOH. (Note: The initial screening biopsy of oral IEN lesion with LOH must be obtained within 12 months of study enrollment. If initial diagnostic biopsy for LOH is > 3 months prior to study enrollment, investigators may use clinical judgment to order an additional screening biopsy to assess histopathological changes).

3. Age >= 18 years
4. ECOG performance status < 2
5. Participants must have normal organ & marrow function as defined below within 30 days of randomization: CBC w/ differential white cell count-acceptable results must include: WBC >3,000 ul, hemoglobin>10 g/dl, platelet count >125,000 ul, LFTs-total bilirubin & alkaline phosphatase, AST (SGOT) & ALT (SPGT) all w/in <1.5x ULN. Note: At the discretion of the attending physician, participants w/ Gilbert’s disease may still be eligible to participate in the event the total bilirubin value is >1.5xULN. Kidney function-serum creatinine < 1.5xULN Chemistry-Sodium & potassium all w/in normal institutional limits.

6. The effects of the study agent on the developing human fetus are unknown. For this reason, WOCBP & men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry & for the duration of active treatment. Neg. serum pregnancy test in WOCBP. Childbearing potential will be defined as women who have had menses within the past 12 months, who have not had tubal ligation or bilateral oophorectomy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately

7. Ability to understand and the willingness to sign a written informed consent document.

Exclusion criteria:
1. Patients with active cancer or any cancer within the previous two years, excluding oral and non-melanoma skin cancer.
2. Patients with acute intercurrent illness or who have had surgery, radiation therapy, or chemotherapy within the preceding 4 weeks unless they have fully recovered.
3. Patients with a documented history of coagulopathy and/or those taking warfarin or warfarin-derivative anticoagulants
4. Women who are pregnant (confirmed by b-HCG if applicable) or breastfeeding
5. Any medical or psychological condition or any reason that, according to the investigator’s judgment, makes the patient unsuitable for participation in the study
6. Patients who have participated in other experimental therapy studies within 3 months of enrollment to this trial
7. Patients with a history of inflammatory bowel disease
8. Patients with a documented history of interstitial lung disease

Cost of Participating:
The study drug is provided by the study, all other costs will be billed to the insurance company.
Importance of project to FA patients:
There are no cytotoxic chemotherapy agents in the regimen.

Eligibility:

Inclusion criteria:
1. Understand and voluntarily sign an informed consent form.
2. Age ≥18 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Recurrent or metastatic squamous cell or undifferentiated carcinoma of the head and neck that is not amenable to curative therapy. Patients who are candidates for local or locoregional therapy should not be deprived of proven beneficial palliative therapies.
5. All previous cancer therapy, including radiation, hormonal therapy, EGFR inhibitors, and surgery, must have been discontinued at least 4 weeks prior to treatment in this study.
6. ECOG performance status of 0-1 at study entry.
7. Laboratory test results within these ranges:
   a. Absolute neutrophil count to ≥ 1000/mm³
   b. Platelet count ≥ 100,000/mm³
   c. Calculated creatinine clearance ≥ 50ml/min by Cockcroft-Gault estimation
   d. Total bilirubin < 1.5 x ULN
   e. AST (SGOT) and ALT (SGPT) < 3 x ULN or < 5 x ULN if hepatic metastases are present.
8. Disease free of prior malignancies for < 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “in-situ” of the cervix or breast.
9. Patients with malignancies diagnosed less than 3 years prior to study entry are eligible if the first cancer was no greater than stage I and did not recur.
10. Patients with malignancies diagnosed less than 3 years prior to study entry must have the diagnosis of recurrent or metastatic squamous cell carcinoma of the head and neck confirmed pathologically.
11. All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.
12. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 - 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing.
13. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
14. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).
15. Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded), with minimum lesion size ≥ 2 cm on conventional measurement techniques or ≥ 1 cm on spiral computed tomography (CT) scan. Lesions that can be measured clinically must be at least 1 cm in greatest dimension by caliper measurement.

Exclusion criteria:
1. Primary head and neck carcinomas of the salivary gland, skin, or thyroid regardless of pathology.
2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
3. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).
**Phase II Study of Cetuximab and Lenalidomide in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck continued**

4. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

5. Use of any other experimental drug or therapy within 28 days of baseline.


7. Known hypersensitivity to thalidomide.

8. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.

9. Concurrent use of other anti-cancer agents or treatments.

10. Known positive for HIV or infectious hepatitis, type B or C.

**Cost of Participating:**
LENALIDOMIDE is provided by the study, all other costs will be billed to the insurance company.

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**HSV1716 in Patients with Non-Central Nervous System (Non-CNS) Solid Tumors**

This study seeks to evaluate the safety of a single injection of HSV1716 in the treatment of solid tumors, not including brain tumors, in adolescents and young adults. The use of viruses to infect and kill cancer cells is gaining momentum with an increasing number of clinical trials being conducted in adults and several now open for children. Contrary to chemotherapy, because viruses do not damage DNA, there is little or no risk of secondary cancers, making this approach particularly attractive for patients with FA. It should be kept in mind that this is a phase I dose escalation study primarily designed to test safety and therefore is considered early phase research. If the injected tumor shrinks, patients can receive up to a total of four monthly injections.

**Principal Investigator:** Timothy Cripe, MD, PhD, Children's Hospital Medical Center, Cincinnati, Ohio
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**Alternate Contact:** Rebecca Turner
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**Purpose:**
Patients with relapsed solid tumors such as sarcomas and neuroblastoma have a poor survival, generally < 20%. There is an urgent need for new treatments that are safe and effective.

HSV1716, an oncolytic virus, is a mutant herpes simplex virus (HSV) type I, deleted in the RL1 gene which encodes the protein ICP34.5, a specific determinant of virulence. Mutants lacking the RL1 gene are capable of replication in actively dividing cells but not in terminally differentiated cells - a phenotype exploited to selectively kill tumor cells. In previous clinical studies, HSV1716 has been shown to be safe when injected at doses up to 10^5 plaque forming units (pfu) directly into human high-grade glioma and into normal brain adjacent to tumor, following excision of high-grade glioma. In an extension study, HSV1716 has been shown to be safe when injected at a dose of up to 10^6 pfu directly into brain tumours. Replication of HSV1716 in human glioblastoma in situ has been demonstrated. Following a single administration of HSV1716 by direct injection into active recurrent tumor or brain adjacent to tumor, some patients have lived longer than might have been expected.

HSV1716 has also proved safe when given by direct intra-tumoural injection in patients with squamous carcinoma of the head and neck, and in patients with malignant melanoma. Replication of HSV mutants in human sarcomas and neuroblastoma in cultured cells and human xenograft models has been demonstrated.
**HSV1716 in Patients with Non-Central Nervous System (Non-CNS) Solid Tumors continued**

This study is designed in two parts. PART 1 of the study specifies a single virus injection. Participants who experience a partial response, or relapse following a complete response, may qualify for subsequent injections in PART 2, described in Section 16. PART 2 requires signing of a separate consent.

**Primary Outcome Measures:**
- To determine whether intratumoral injection of HSV1716, at dose levels shown to be safe for adult tumors, is safe in adolescents and young adults with non-CNS solid tumors. [Time Frame: Dose limiting toxicities will be assessed at 28 days after injection of HSV1716.]
  [Designated as safety issue: Yes]

**Secondary Outcome Measures:**
- To measure antiviral immune response in patients with refractory cancer treated with HSV1716. [Time Frame: Antiviral immune response will be assessed 28 days after injection. Beginning at 1.5 years post injection assessments will occur every 6 months. Beginning 5 years after the injection, assessments will occur annually until 15 years post injection.]
  [Designated as safety issue: Yes]

**Estimated Enrollment:** 18

**Study Start Date:** March 2010

**Estimated Primary Completion Date:** October 2012 (Final data collection date for primary outcome measure)

**Intervention Details:**
- Biological: HSV1716
- Intra-tumoral injection

**Eligibility:**
- Ages Eligible for Study: 13 Years to 30 Years
- Genders Eligible for Study: Both
- Accepts Healthy Volunteers: No

**Criteria:**

**Inclusion Criteria:**
- Age: Subjects must be greater than or equal to 13 years and less than or equal to 30 years of age at the time of signing consent (study entry);
- Histologic Diagnosis: Subjects must have had histologic verification a non-CNS solid tumor at original diagnosis. The tumor must be amenable to HSV1716 administration without undue risk. Disease must be considered refractory to conventional therapy or for which no conventional therapy exists. There must be no available therapy with demonstrated clinical benefit for the subject as deemed by the subject's primary oncologist;
- Metastatic Disease: Subjects who have metastasis to the brain are eligible for this study; however, no metastatic sites within the brain will be considered for injection.
- Performance Level: Karnofsky greater than or equal to 50. Subjects who are unable to walk because of paralysis, but who are up in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.
- Life Expectancy: Anticipated to be greater than or equal to 8 weeks from time of study entry;
- Subjects must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study;
- Myelosuppressive chemotherapy: Must not have received within 28 days of entry onto this study (42 days if prior nitrosourea) accompanied by hematopoietic recovery, or 14 days of stopping non-myelosuppressive therapy as long as hematopoietic requirements are met;
**For FA Patients and Families continued**

**HSV1716 in Patients with Non-Central Nervous System (Non-CNS) Solid Tumors continued**

- Biologic (anti-neoplastic agent): Must not have received within 28 days of entry onto this study;
- No Radiation Therapy greater than or equal to 14 days for local palliative XRT (small port): greater than or equal to 6 months must have elapsed if prior craniospinal XRT or if greater than or equal to 50% radiation of pelvis; greater than or equal to 42 days must have elapsed if other substantial bone marrow radiation;
- Immunoablative or myeloablative Stem Cell Transplant (SCT): greater than or equal to 6 months must have elapsed from prior autologous transplant. Subjects must not have graft versus host disease post autologous transplant;
- Investigational agent: greater than or equal to 28 days must have elapsed from treatment with a different phase I agent;
- Subjects with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- At the time of enrollment, specified CNS conditions must be less than or equal to Grade II toxicity per CTCAE 3.0 criteria;
- All subjects must have adequate blood counts defined as: peripheral absolute neutrophil count (ANC) greater than or equal to 750/uL, Platelet count greater than or equal to 100,000/uL (may be a post transfusion value), Hemoglobin greater than or equal to 9.0 gm/dL (may be a post transfusion value)
- Adequate renal function defined as: Serum creatinine less than or equal to 1.5 x upper limit of normal (ULN) for age or creatinine clearance or radioisotope GFR greater than or equal 70 ml/min/1.73 m2; Adequate liver function defined as: Total bilirubin less than or equal to 2.0 x ULN for age, and SGPT (ALT) less than or equal to 2.5 x ULN for age and albumin greater than or equal to 2g/dL, GGT < 2.5 x ULN
- Adequate cardiac function as defined by: Shortening fraction >25% by echocardiogram or ejection fraction above the institutional lower limit of normal by MUGA, No focal wall motion abnormalities as determined by either of the above studies, EKG without evidence of ischemia or significant arrhythmia
- Adequate coagulation as defined by: PT/INR and PTT <1.5 x ULN for age;
- Infectious Disease: Documented evidence of negative tests for the presence of Hepatitis B surface antigen, Hepatitis C antibody, HIV1 and HIV2 antibodies within the three months preceding study entry. Subjects who do not have such evidence must undergo appropriate testing prior to virus administration;
- Lesion Size: The targeted lesion must be at least 18 mm in each of 3 dimensions as determined by CT or MRI scans. Lesions not meeting this requirement may be used if volumetric measurements show it to be greater than or equal to 3mL.

**Exclusion Criteria:**
- Stem cell transplant: No subjects who have received an allogeneic hematopoietic stem cell transplant are eligible;
- Pregnancy or Breast-Feeding: There is no available information regarding human fetal or teratogenic toxicities. Pregnant women are excluded and pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method from the time of study entry to a period of no less than four months post the final HSV1716 injection. For the same period of time, women who participate in this study must agree not to breast feed;
- Consent: Unable or unwilling to give voluntary informed consent / assent;
- Leukemia: Subjects with leukemia are not eligible for study participation;
- Infection or any other severe systemic disease or medical or surgical condition deemed significant by the principal investigator;
- Administration of any unlicensed or investigational agent within 4 weeks of entry to the study;
- Growth factor(s): No PEG-GCSF within 14 days of virus injection (day 0);
- Anti-HSV antivirals: Subjects whose physicians determine that anti-HSV antiviral therapy (such as acyclovir, ganciclovir, foscarnet, etc.) cannot be safely discontinued from 2 days prior to the injection to 28 days following the injection should not be in the study.
Subjects who have other conditions which in the opinion of the investigator contra-indicate the receipt of HSV1716 or indicate subject's inability to follow protocol requirements.

Sponsors and Collaborators:
Children's Hospital Medical Center, Cincinnati, Ohio
FDA Office of Orphan Products Development

Safety Study of Recombinant Vaccinia Virus to Treat Refractory Solid Tumors in Pediatric Patients

This trial is designed to determine safe dosage levels of recombinant vaccinia virus to treat unresectable solid tumors in pediatric patients who may not tolerate standard therapies. The use of viruses to infect and kill cancer cells is gaining momentum with an increasing number of clinical trials being conducted in adults and several now open for children. This particular virus also expresses an immune-stimulating gene with the hope of inducing an immune response against the tumor. Contrary to chemotherapy, because viruses do not damage DNA, there is little or no risk of secondary cancers, making this approach particularly attractive for patients with FA. It should be kept in mind that this is a phase I dose escalation study primarily designed to test safety and therefore is considered early phase research. If the injected tumors shrink, patients can receive up to a total of four monthly injections.

Principal Investigator: Timothy Cripe, MD, PhD, Children's Hospital Medical Center, Cincinnati, Ohio
Telephone: 513-636-4553; Email: Timothy.Cripe@cchmc.org
Alternate Contact: Rebecca Turner
Telephone: 513-636-2799; Email: cancer@cchmc.org

Purpose:
This is a Phase I, open-label, dose-escalation trial in pediatric patients with advanced/metastatic, unresectable refractory solid tumors. Tumors are likely to include neuroblastoma, lymphoma, Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcomas, and malignant peripheral nerve sheath tumors. Benign tumors are excluded. These tumor types were selected because evidence of biological activity was observed in cancer cells lines and ex vivo infected primary human tissue samples, specifically pediatric cancer types such as sarcomas and neuroblastomas.

Primary Outcome Measures:
• Determine the maximally-tolerated dose (MTD) and/or maximum-feasible dose (MFD) of JX-594 [ Time Frame: 3 weeks ] [ Designated as safety issue: Yes ]
• Determine the maximally-tolerated dose (MTD) and/or maximum-feasible dose (MFD) of JX-594 administered by intratumoral (IT) injection in pediatric patients with advanced/metastatic, unresectable refractory solid tumors
• Determine the safety/toxicity of JX-594 administered by IT injection in this patient population [ Time Frame: 3 weeks ] [ Designated as safety issue: Yes ]

Secondary Outcome Measures:
• Determine the JX-594 pharmacokinetics and pharmacodynamics over time following IT injection in this patient population [ Time Frame: 3 weeks ] [ Designated as safety issue: No ]
• Determine the immune response to JX-594 following IT injection in this patient population [ Time Frame: 3 weeks ] [ Designated as safety issue: No ]
Safety Study of Recombinant Vaccinia Virus to Treat Refractory Solid Tumors in Pediatric Patients continued

**Intervention Details:**
Drug: Recombinant Vaccinia GM-CSF; RAC VAC GM-CSF (JX-594)
Intratumoral Injection Dosage from 1 x 10^6 pfu/kg to 3 x 10^7 pfu/kg is administered once to 1-3 injectable tumors in pediatric patients.

**Eligibility:**
Ages Eligible for Study: 2 Years to 21 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

**Criteria:**

**Inclusion Criteria:**
- Age between 2 and 21 years
- Histologically-confirmed, advanced/metastatic non-CNS solid tumor that is relapsed and/or refractory to standard therapy (progressive disease despite therapy) and/or the patient does not tolerate standard therapy. Non-CNS solid tumors are eligible and are likely to include such histologies as neuroblastoma, Wilms’ tumor, rhabdomyosarcoma, Ewing’s sarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcomas, and malignant peripheral nerve sheath tumors.
- Cancer is not surgically resectable for cure
- At least one measurable tumor mass by CT/MRI (i.e. lesion that can accurately be measured in at least one dimension with longest diameter ≥ 1 cm) and that can be injected by direct visualization/palpitation or by imaging-guidance (CT or ultrasound)
- Expected survival for approximately 12 weeks or longer
- Lansky Score ≥ 50
- Total bilirubin ≤ 2.5 × ULN
- AST, ALT ≤ 2.5 × ULN
- Serum creatinine ≤ 1.8 x ULN
- INR ≤ 1.5 x ULN
- Hematologic parameters: Patients can be transfused to meet these entry criteria.
  - Hemoglobin ≥ 9 g/dL
    - For bone marrow negative patients: ANC ≥ 750 cells/ mm3 and platelet count ≥ 75,000 pts/mm3
    - For bone marrow positive patients: ANC ≥ 750 cells/ mm3. Platelet count recovery is not a requirement, but platelets should be transfused to ≥ 75,000 pts/ mm3 prior to treatment.
- CD4 count ≥ 200/mm3. Patients who demonstrate intact delayed-type hypersensitivity (DTH) via skin immune response to common antigens (e.g. candida, mumps) are also eligible.
- For patients who are sexually active, able and willing to abstain from sexual activity for 3 weeks following treatment with JX-594. Thereafter, able and willing to use accepted birth control methods through 3 months after last treatment with JX-594. [Acceptable birth control methods include contraceptive pills, condom, IUD, diaphragm or sponge + spermicide, or other methods with >97% effectiveness]
- Able and willing to sign an Institutional Review Board (IRB)/Research Ethics Board (REB)-approved written consent form (patient and/ or parents/guardians).
- Able and willing to comply with study procedures and follow-up examinations, including compliance with the “Infection Control Guidelines for Patients” contained within the written consent form (patient and/ or parents/guardians).

**Exclusion Criteria:**
- Pregnant or nursing infant
- Injected tumor(s) in location that would potentially result in significant clinical adverse effects if post-treatment tumor swelling were to occur or if deemed unsafe by investigator (e.g. tumors impinging on the upper airway or affecting biliary tract drainage, adherent to
• Brain metastases, unless surgically resected and/or irradiated. (Brain metastases cannot be considered as a site for injection).

• Patients with lymphomas

• Use of high dose systemic corticosteroids or other immune suppressive medication within 3 weeks of first treatment (e.g. cortisone, dexamethasone, hydrocortisone, prednisone, prednisolone, interferon, cisplatin, doxorubicin, fluorouracil, etc.). * Note: patients taking low-dose corticosteroids for the treatment of nausea and/or taking maintenance corticosteroids for adrenal insufficiency are permitted to enroll.

• Known infection with HIV or known underlying genetic immunodeficiency disease

• Treatment of the injected tumor(s) with radiotherapy, chemotherapy, surgery, or an investigational drug within 3 weeks prior to first treatment

• Clinically significant active infection or uncontrolled medical condition considered high risk for investigational new drug treatment (e.g. pulmonary, neurological, cardiovascular, gastrointestinal, genitourinary)

• History of exfoliative skin condition (e.g. severe eczema, ectopic dermatitis, or similar skin disorder) requiring systemic therapy

• Clinically significant and/or rapidly accumulating ascites, peri-cardial and/or pleural effusions (e.g. requiring drainage for symptom control)

• Severe or unstable cardiac disease which may include, but is not limited to, any of the following within 6 months prior to screening: myocardial infarct, unstable angina, congestive heart failure, myocarditis, arrhythmias diagnosed and requiring medication, or any clinically-significant change in cardiac status

• Current, active, progressing CNS malignancy, including carcinomatosis meningitis (definitively surgically resected or irradiated metastases allowed)

• Pulse oximetry O2 saturation <90% at rest

• Use of anti-viral, anti-platelet or anti-coagulation medication (for example, heparin, warfarin, aspirin, ticlopidine, clopidogrel, dipyridamole) [Patients who discontinue such medications within 7 days prior to first treatment may be eligible for this study. Any required, chronic medications indicated for other medical issues should not be discontinued in order to meet eligibility criteria for this trial without consultation with both the patient and the treating physician.] Note: Low Dose Heparin to maintain patency of venous catheters is permitted.

• Patients with benign tumors

• Inability or unwillingness to give informed consent (patient or parent/guardian) or comply with the procedures required in this protocol

• Vaccination with a live virus (i.e. measles, mumps, rubella, etc) < 30 days prior to first treatment

• Patients with household contacts who meet any of these criteria will be excluded unless alternate living arrangements can be made during the patient’s active dosing period and for three weeks following the last dose of study medication:
  o Women who are pregnant or nursing an infant
  o Children < 1 years old
  o People with skin disease (eczema, atopic dermatitis and related diseases)
  o Immunocompromised hosts (severe deficiencies in cell-mediated immunity, including AIDS, organ transplant recipients, hematologic malignancies)

Locations:
Cincinnati Children’s Hospital Medical Center
Cincinnati, Ohio
Contact: Timothy Cripe, MD, PhD
Telephone: 513-636-4553
Email: Timothy.Cripe@cchmc.org
Nonmyeloablative Hematopoietic Cell Transplantation for Patients with Fanconi Anemia Using Alternative Marrow Donors

The purpose of this study is to test whether it is possible to use an alternative bone marrow donor who is half-matched, or haploidentical, to the patient's tissue type. Researchers will test whether using lower doses of radiation and a novel immunosuppressive regimen will allow the patient to accept the new donor cells with fewer side effects. This is a dose-finding study. Different doses of radiation will be tested.

Principal Investigator: Hans-Peter Kiem, MD, Fred Hutchinson Cancer Research Center, Seattle, Wash.
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Alternate Contact: Michelle Bouvier, RN, Clinical Trials Nurse, Nonmyeloablative Transplants
Telephone: 206-667-6993; Email: meb@fhcrc.org
Accepting: US patients only

What is the purpose of this study?
Many people with Fanconi anemia develop bone marrow failure or leukemia. Both of these conditions may be cured by stem cell transplantation, but it is sometimes difficult to find an appropriately matched donor to use. The purpose of this study is to test whether it is possible to use an alternative bone marrow donor who is half-matched, or haploidentical, to the patient’s tissue type. The haploidentical donor is related to the patient and is usually the parent or sibling. We can also use matched unrelated donors on this protocol. We will test whether using lower doses of radiation and a novel immunosuppressive regimen will allow the patient to accept the new donor cells with fewer side effects. This is a dose-finding study. Different doses of radiation will be tested.

Who can participate?
This study is open to FA patients who have bone marrow involving two of the following three lineages:
- granulocyte count <0.5 x 10^9/L
- platelet count <20 x 10^9/L
- hemoglobin <8 g/dL

or to FA patients with one of the above and a life-threatening event or to FA patients requiring red blood cell or platelet transfusions because of bone marrow failure.

If being treated for leukemia, the patient must be considered in remission.

What is involved?
Patients will undergo a bone marrow transplant using a novel, dose-finding conditioning and immunosuppressive regimen. Treatment will last 3½ months or more, with follow-up every year thereafter.

What are the benefits?
For FA patients who must undergo stem cell transplant for bone marrow failure or leukemia, but do not have a fully matched donor, this will allow the opportunity for a potentially life-saving...
Nonmyeloablative Hematopoietic Cell Transplantation for Patients with Fanconi Anemia Using Alternative Marrow Donors

This will also allow the opportunity to use lower doses of radiation therapy to lower the risks of long-term side effects.

**What are the risks?**
Risks associated with bone marrow transplant are extensive and include infections, graft-versus-host disease, rejection, secondary cancers and even death. Using a half-matched donor or unrelated donor (instead of a fully matched sibling donor) may increase these risks. The risks of this study will be explained in detail to you.

**Will you be paid to participate in this study?**
No.

Viral Therapy in Treating Young Patients with Relapsed or Refractory Solid Tumors

This phase I trial is studying the side effects and the best dose of viral therapy in treating young patients with relapsed or refractory solid tumors. This is one of the first trials using live human viruses for the treatment of pediatric cancers.

**Principal Investigator:** E. Anders Kolb, MD, Alfred I. duPont Hospital for Children, Wilmington, Del.  
Telephone: 302-651-5567; Email: eakolb@nemours.org

**Rationale:**
Reovirus is an unmodified naturally occurring virus which may be able to kill tumor cells without damaging normal cells. Drugs used in chemotherapy, such as cyclophosphamide, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Giving wild-type reovirus together with cyclophosphamide may kill more tumor cells.

**Primary Outcome Measures:**
- Maximum-tolerated dose (MTD) and/or recommended phase II dose of wild-type reovirus (Reolysin) [Designated as safety issue: Yes]
- Adverse events of Reolysin alone and in combination with oral cyclophosphamide as assessed by NCI CTCAE v. 4.0 [Designated as safety issue: Yes]

**Secondary Outcome Measures:**
- Pharmacokinetics (time course of viral clearance) of Reolysin [Designated as safety issue: No]
- Antitumor activity of Reolysin [Designated as safety issue: No]
- Development of neutralizing antibodies to Reolysin [Designated as safety issue: No]

**Objectives:**

**Primary**
- To estimate the maximum-tolerated dose (MTD) and/or recommended phase II dose of wild-type reovirus (Reolysin) in children with relapsed or refractory solid tumors.
- To define and describe the toxicities of Reolysin in these patients.
- To define the toxicity and tolerability of combining Reolysin with oral cyclophosphamide in these patients.
- To characterize the pharmacokinetics (time course of viral clearance) of Reolysin in children with refractory cancer.

**Second**
- To define the antitumor activity of Reolysin within the confines of a phase I study.
- To evaluate the development of neutralizing antibodies to Reolysin following intravenous
Viral Therapy in Treating Young Patients with Relapsed or Refractory Solid Tumors

administration of reolysin alone and in combination with cyclophosphamide.
• To assess the biologic activity of Reolysin.

Outline:
• This is a multicenter, dose-escalation study of wild-type reovirus (Reolysin).
• Patients receive Reolysin IV over 60 minutes once daily on days 1-5. Some patients also receive oral cyclophosphamide on days 1-21. Treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.
• Patients undergo blood, saliva, and stool specimen collection at baseline and periodically during study for pharmacokinetic and neutralizing antibody studies by RT-PCR. Archived tumor tissue samples (if available) are also analyzed for biomarker studies.
• After completion of study treatment, patients are followed up periodically for up to 1 year.

Eligibility:
Ages Eligible for Study: 3 Years to 21 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria:

Disease Characteristics:
• Diagnosis of relapsed or refractory solid tumors
  o Must have had histologic verification of malignancy at original diagnosis or relapse
  o Disease for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life
  o No primary CNS tumors or lymphomas
• Measurable or evaluable disease
• No known germline mutations affecting Ras activation (e.g., cardio-facial-cutaneous syndrome, Noonan syndrome, Costello syndrome)
• No known metastatic CNS disease

Patient Characteristics:
• Karnofsky performance status (PS) 50-100% for patients > 16 years of age OR Lansky PS 50-100% for patients ≤ 16 years of age
• ANC ≥ 1,000/mm³
• Platelet count ≥ 100,000/mm³ (transfusion independent, defined as ≥ 7 days since platelet transfusion prior to enrollment)
• Creatinine clearance or radioisotope GFR ≥ 70 mL/min OR serum creatinine based on age and/or gender as follows:
  o 0.8 mg/dL (3 to < 6 years of age)
  o 1.0 mg/dL (6 to < 10 years of age)
  o 1.2 mg/dL (10 to < 13 years of age)
  o 1.5 mg/dL (male) or 1.4 mg/dL (female) (13 to < 16 years of age)
  o 1.7 mg/dL (male) or 1.4 mg/dL (female) (≥ 16 years of age)
• Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 times upper limit of normal (ULN)
• ALT ≤ 110 U/L (ULN for ALT is 45 U/L)
• Serum albumin ≥ 2 g/dL
• Shortening fraction ≥ 27% by echocardiogram OR ejection fraction ≥ 50% by gated radionuclide study
• Pulmonary function tests (PFTs), including DLCO, normal for patients with respiratory symptoms (e.g., dyspnea at rest, known requirement for supplemental oxygen)
  o Full PFTs not required for patients without respiratory symptoms
• Seizure disorder allowed provided it is well controlled with anticonvulsants
Nervous system disorders (NCI CTCAE v. 4) resulting from prior therapy must be ≤ grade 2
Not pregnant or nursing
Fertile patients must use effective contraception
No uncontrolled infections
No chronic diarrhea, urinary incontinence during the day or at night, or patients who are not completely toilet trained
No household contacts (living with patient during the 4 weeks of treatment) who are pregnant, immunosuppressed, or infants < 3 months of age
No patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study
No known HIV infection, hepatitis B or C, or any pre-existing infection

Prior Concurrent Therapy:
Recovered from acute toxic effects of all prior anti-cancer chemotherapy and immunizations
More than 3 weeks since prior myelosuppressive chemotherapy (6 weeks for nitrosourea)
At least 14 days since prior long-acting growth factor (e.g., Neulasta) or ≥ 7 days since short-acting growth factor
At least 7 days since prior biologic agent (anti-neoplastic agent)
At least 16 weeks since prior immunotherapy (e.g., tumor vaccines)
At least 3 half-lives since prior monoclonal antibody
At least 2 weeks since prior palliative radiotherapy (small port)
  At least 24 weeks since prior total body irradiation, craniospinal radiotherapy, or ≥ 50% of radiotherapy to the pelvis
  At least 6 weeks since other prior substantial bone marrow radiation
At least 12 weeks since prior stem cell transplant or infusion with no evidence of active graft-vs-host disease
More than 7 days since prior viral immunizations, including influenza vaccine
  Patients may not receive any viral immunizations after enrolling on study and for ≥ 28 days after their last planned Reolysin infusion
More than 7 days since prior corticosteroids, immune modulators, or antiviral therapy
  Intravenous immune globulin (IVIG) may not be given within 2 weeks of Reolysin administration
No prior viral-based anti-neoplastic therapies
No other concurrent investigational drugs
No other concurrent anticancer agents including chemotherapy, radiotherapy, immunotherapy, or biologic therapy
No concurrent cyclosporine, tacrolimus, or other agents to prevent either graft-versus-host disease after bone marrow transplant or organ rejection after transplant
No concurrent corticosteroids (with the exception of hydrocortisone as a treatment for anaphylaxis), immune modulators, antiviral therapy, or IVIG
No concurrent acetaminophen

Locations:
Children's Hospital of Orange County, Orange, Calif.
Contact: Violet Shen
Telephone: 714-532-8636

Alfred I. duPont Hospital for Children, Wilmington, Del.
Contact: Clinical Trials Office
Telephone: 302-651-5755
**Clinical Trial: Danazol**

**Phase I/II Dose Escalation Trial of Danazol in Patients with Fanconi Anemia or Dyskeratosis Congenita**

The purpose of this Phase I/II dose escalation trial is to determine the minimum effective dose of danazol, an attenuated androgen, when used for Fanconi anemia and Dyskeratosis congenita and to evaluate adverse side effects.

**Principal Investigator:** Colin Sieff, MB BCh, Children's Hospital Boston, Boston, Mass.  
Telephone: 617-919-4241; Email: colin.sieff@childrens.harvard.edu

**Accepting:** International patients

**Hypothesis:**
Fanconi anemia (FA) and Dyskeratosis congenita (DC) are inherited bone marrow failure syndromes for which anabolic steroids are often used, but in which specific androgens have never been studied. Masculinizing side effects from the usual androgen (oxymetholone) present major problems, leading to a need for another agent. Danazol is an attenuated androgen, and thus may have fewer side effects; however, its hematologic efficacy in the setting of FA and DC has never been investigated.

The purpose of this Phase I/II dose escalation trial is to determine the minimum effective dose of danazol and to evaluate adverse side effects. An additional goal is to investigate gene expression signatures of patient progenitor cells after exposure to danazol, both in vitro and in vivo, to correlate gene expression with responsiveness to treatment and to identify new treatments.

**Importance of project to FA patients:**
If danazol does not have serious masculinizing or other side effects and is efficacious in stimulating blood cell production, it could prove very useful in the management of bone marrow failure, particularly among patients who do not have a matched sibling donor.

**Eligibility:**

**Inclusion criteria:**
- Patients must be diagnosed with FA that is documented by a positive chromosomal breakage test
- Patients must have at least one of the following peripheral blood cytopenias: Absolute neutrophil count <500 µL; platelet count <30,000/ µL; hemoglobin <8.0 gm/dL
- Patients must have a negative pregnancy test and agree to use medically approved birth control
- Patients must be either three years of age or ≥14 kg (30 lbs)
Phase I/II Dose Escalation Trial of Danazol in Patients with Fanconi Anemia or Dyskeratosis Congenita

Exclusion criteria:
- Concurrent use of anticoagulants
- Use of androgen therapy within past three months
- Patients with liver disease (SGOT, SGPT or bilirubin greater than the upper limit of normal)
- Patients with renal disease (serum creatinine greater than the upper limit of normal for age)
- Patients who have HLA matched sibling donors

Study Procedures:

Screening:
Informed consent, physical exam and blood work, bone marrow aspiration and biopsy, left wrist radiograph, liver ultrasound, post oral glucose test

Treatment weeks 2, 5, 8:
Physical exam and blood work

Treatment week 12:
Physical exam and blood work, post oral glucose

Treatment week 14 (only if dose increase):
Physical exam and blood work

Treatment week 18:
Physical exam and blood work

Treatment week 20 (only if dose increase):
Physical exam and blood work

Treatment week 24:
Physical exam and blood work, liver ultrasound, post oral glucose

Follow-up weeks 38 and 52:
Physical exam and blood work, left wrist radiograph (week 52 only), liver ultrasound (week 52 only), post oral glucose

Phase Ib Study of Erlotinib Prior to Surgery in Patients with Head and Neck Cancer

In this program, patients with head and neck cancer who are candidates for surgical resection receive therapy with erlotinib, a novel molecular-targeted drug, during the period leading up to surgery. The post-treatment surgical specimen is then collected and the tumor is analyzed for changes in cancer cell molecules in response to therapy.

Principal Investigator: William N. William Jr., MD, The University of Texas MD Anderson Cancer Center, Houston, Texas
Telephone: 713-792-6363; Email: wwillia@mdanderson.org
Alternate Contact: Cynthia Trainer, RN
Telephone: 713-792-6363

Purpose of Study:
A major area of interest in head and neck cancer research has been the development of treatment based on molecular targeted agents. These drugs have unique mechanisms of actions and are generally less toxic than traditional chemotherapy. Despite the increased use of molecular targeted agents for treatment of head and neck cancers and other cancers, little is known about which patients are more likely to benefit from these drugs, and how cancer cells become resistant to treatment. In an attempt to better understand the biology of head and neck cancers and how they respond to targeted agents; at MD Anderson we have developed a molecular-based, pre-operative treatment program for patients with head and neck cancers who are candidates for surgical resection.
Phase Ib Study of Erlotinib Prior to Surgery in Patients with Head and Neck Cancer

Eligibility criteria:
Patients with head and neck cancers who are candidates for surgical resection. FA patients are not excluded.

What is involved?
In this program, patients receive therapy with a novel molecular targeted drug during the period leading up to surgery. The post-treatment surgical specimen is then collected and the tumor is analyzed for changes in cancer cell molecules in response to therapy. The first molecular targeted drug to be evaluated in this pre-operative program is erlotinib, an oral inhibitor of the epidermal growth factor receptor. This receptor is present on most head and neck cancer cells and enables them to survive and proliferate, thus contributing to tumor growth and spread. Erlotinib is already FDA-approved for treatment of lung and pancreatic cancers at the doses of 100 - 150 mg/day. However, pre-clinical data suggest that higher doses of erlotinib may be more effective in killing cancer cells. Therefore, patients participating in the study are randomized to receive the standard dose or a higher dose of the drug for two to eight weeks prior to surgery.

What are the benefits?
Since erlotinib is well tolerated, the study allows for enrollment of a broad patient population. So far, more than half of the planned number of participants has been accrued, with promising preliminary results. Additional pre-operative studies, with drugs directed at other molecular targets, will soon be activated at MD Anderson to replace the erlotinib trial. This platform of pre-operative studies allows for patients to receive novel treatments while their surgery is being planned, and provides a rich repository of tumor specimens that will enable us to understand the effects of these treatments on cancer cells, ultimately leading to the design of more effective and less toxic therapies for head and neck cancer.
Testing Services for FA Patients:

Testing for Potentially Beneficial Cancer Therapy

The Knight Diagnostic Laboratories at Oregon Health & Science University have recently made available new molecular tumor tissue tests that are designed to identify potential treatment targets in cancer and to predict the likelihood of benefit for patients treated with the latest therapeutics.

This new testing will be available at NO CHARGE to FA patients.

For more information, contact:
Teresa Kennedy, Director of Family Support Services
Fanconi Anemia Research Fund, Inc.
Telephone: 541-687-4658 or
1-888-FANCONI (888-326-2664)
Email: teresa@fanconi.org

Send samples to:
Christopher Corless, MD, PhD, Medical Director
OHSU Dept. of Pathology (mailcode L113)
3181 SW Sam Jackson Park Road
Portland, OR 97239
Telephone: 503-494-6834
Email: corlessc@ohsu.edu

Help Advance FA Research!

FA researchers are working hard to find effective treatments and a cure for Fanconi anemia, but they can’t do it alone. FA researchers need you.

Researchers need samples to study, such as: blood, bone marrow, skin (fibroblasts), tumor samples and biopsied tissue.

Please consider donating research material. All it takes is a phone call to the Fund and completion of paperwork for the National Disease Research Interchange (NDRI), the Fund’s partner in research material collection.

For more information, contact:
Teresa Kennedy, Director of Family Support Services
Fanconi Anemia Research Fund, Inc.
Telephone: 541-687-4658 or
1-888-FANCONI (888-326-2664)
Email: teresa@fanconi.org

Working together to advance FA research.

To FA Researchers:
The Fund requires that all investigators who publicize their need for research materials in the FA Courier share residual research materials received through the FA Courier and cooperate to the maximum feasible extent with other scientists who are studying Fanconi anemia. Read more about the Fund’s requirements at www.fanconi.org.

To FA Families:
If you need assistance researching a clinical trial or with the costs associated with participating in a clinical trial, please contact Teresa Kennedy, Director of Family Support Services at the Fund. Call toll-free 1-888-FANCONI (888-326-2664) or email teresa@fanconi.org.
FA Antibody Project: Antisera Now Available Against Fanconi Anemia Complementation Group Proteins

FARF has sponsored the development of high-titer, affinity-purified rabbit polyclonal antisera against the Fanconi anemia complementation group proteins in order to facilitate research on Fanconi anemia.

Affinity-purified antisera are currently available against the following 14 FANC proteins: FANCA, B, C, D1/BRCA2 and D2, E, F, G, I, J, L, M and N, and the deubiquitinating enzyme USP1 protein. Antibodies are being developed to the two most recently identified FANC proteins, FANCO/RAD51C and FANCP/SLX4 proteins. In addition to affinity-purified antisera, unpurified sera are available for many FANC proteins for investigators interested in trying alternative purification approaches.

Investigators requesting antisera must complete a request via the website www.ohsu.edu/fa.

Background:
The Fanconi Anemia Research Fund has sponsored the development of affinity-purified rabbit polyclonal antisera against the Fanconi complementation group proteins in order to facilitate research into Fanconi anemia. These rabbit antisera were developed with a commercial partner (Open Biosystems in Huntsville Alabama) using previously identified successful or newly identified peptide epitopes. The antisera have been validated by a combination of peptide ELISA assays and, in many instances, Western blot analyses using patient-derived cell lines or with and without peptide blocking. All successful antisera are available affinity-purified, and in many cases as unpurified sera for investigators wishing to perform a specific, alternative purification (e.g., against full-length protein).

The Fanconi Anemia Research Fund has contracted with Oregon Health & Science University through the laboratory of Markus Grompe, MD, Department of Medical and Molecular Genetics, to manage the FA Antibody Project in conjunction with the FA Cell Repository already housed at OHSU, where Laura Marquez is in charge of distribution.

Availability: Affinity-purified antisera are currently available against the following proteins: FANCA, B, C, D1/BRCA2 and D2, E, F, G, I, J, L, M and N, and the deubiquitinating enzyme USP1 protein. Antisera against the newly identified FANCO/RAD51C and FANCP/SLX4 proteins are in progress (April 2011). For a current listing of available antisera please check the FARF Antibody Project website: http://www.ohsu.edu/fa. These reagents are available without charge to qualified investigators willing to pay shipping (see below).

IMPORTANT: An essential part of this Antibody Project is the collective experience of the Fanconi community in how best to use these antisera for different research applications. All end users need to report their experience on the best protocols and uses of specific antisera for immunofluorescence, immunoprecipitation, Western blot or other analysis to help others to best use these antisera. This feedback can be emailed directly to Laura Marquez at the distribution center and will be compiled and updated every six months. A current compilation of user data can be downloaded from the website as well. We will not honor additional requests for reagents from users who do not provide feedback on their experience using antisera.

How to obtain antisera:
Investigators requesting antisera must complete a request via the website www.ohsu.edu/fa. This includes 1. providing information on intended use in sufficient detail to allow us to assess whether the request fosters FA research; 2. completion of the Use Agreement and Materials Transfer Form; and 3. provision of a valid shipping account number to cover the cost of shipping. Commercial users may arrange to purchase the same antisera via a distribution agreement with Open Biosystems.

Questions?
General inquiries contact: Ray Monnat, MD, University of Washington, Seattle, Wash.
Telephone: 206-616-7392; Email: monnat@u.washington.edu
Antibody distribution contact: Laura Marquez, Oregon Health & Science University, Portland, Ore.
Telephone: 503-494-6889; Email: marquezl@ohsu.edu

Available Research Materials

Biomedical samples collected from Fanconi anemia (FA) patients are available to researchers. Given the rarity of FA, the supply of some biomedical research materials is occasionally limited. Samples are provided only to those researchers who are specifically studying FA. The Fund is partnering with the National Disease Research Interchange to facilitate sample collection and distribution. Visit www.ndriresource.org to learn more.
For FA Researchers continued

Available Research Materials continued

**Background:**
To facilitate collection of biomedical research materials for FA research, the Fanconi Anemia Research Fund has entered into a partnership with the National Disease Research Interchange (NDRI). NDRI is a 501(c)(3) not-for-profit organization with over 25 years experience distributing human cells, tissues and organs to researchers and scientists (www.ndriresource.org). In conjunction with the NIH Office of Rare Diseases, in 2002 NDRI began to develop a program focused on the unmet needs of the rare disease research community for human organs and tissues. NDRI receives funding for its Rare Disease Program from the National Institutes of Health and the Office of Rare Diseases.

**Available Research Materials:**
Biomedical samples of Fanconi anemia are available to researchers. Given the rarity of FA, the supply of some biomedical research materials is occasionally limited. Samples are provided only to those researchers who are specifically studying FA.

In general, NDRI places around 20,000 biospecimens annually with researchers in academic and government laboratories, as well as those in biomedical and pharmaceutical industries. To that end, the organization works with organ procurement organizations, eye banks, tissue banks and major medical centers in the United States. NDRI has also developed unique programs to serve researchers studying rare diseases, such as Fanconi anemia. Importantly, NDRI has developed mechanisms to aseptically obtain tissues with a very short death-to-preservation interval, making them ideal for cell culture, genomic and proteomic research. NDRI also serves the cancer research community with tumor and normal adjacent tissues specimens preserved at 4°C, frozen, snap-frozen or formalin-fixed/paraffin embedded.

NDRI will strive to meet your exact needs for FA research. Please visit www.ndriresource.org to learn how NDRI can be a valuable resource for your research. To receive an application, contact a Rare Disease Coordinator at raredisease@ndriresource.org or by phone at 1-800-222-6374. The application is also available on NDRI’s website under the Quick Links section.

Pilot Study Awards: Funding Available for Research

The Fanconi Anemia Research Fund, Inc. seeks applications for basic or applied research into the mechanisms, pathogenesis and/or treatment of Fanconi anemia. These awards are usually for one year of support and are intended to fund pilot studies designed to test new ideas and to provide initial data to support applications for further funding by other (and larger) agencies that support biomedical research.

Fanconi anemia is an autosomal recessive disease characterized by bone marrow failure, variable congenital anomalies and a predisposition to leukemia. Cells from FA patients exhibit hypersensitivity to alkylating agents such as mitomycin C (MMC) and diepoxynbutane (DEB). Indeed, the hypersensitivity to cytotoxic effects of DNA cross-linking agents is currently used as the basis for the diagnostic tests for FA. It is known that FA is genetically heterogeneous, with at least 15 FA or FA-like genes [A, B, C, D1 (BRCA2), D2, E, F, G, I, J, L, M, N, P and RAD51C] identified thus far.

Better understanding of Fanconi anemia that can lead to effective treatment of the various phases of the disease is so urgently needed. Studies of Fanconi anemia may also have important implications for solid tumor malignancies such as head and neck, gastrointestinal, and gynecological cancers.

**Application Process:**
An abbreviated NIH-style application is used. Under emergency circumstances researchers whom we are currently supporting or who have an established track record in FA research can apply for small supplementary grants on an accelerated basis. Selection for a research award is based upon scientific merit and relevance, as determined by the Fund’s peer review procedure. **Applications are reviewed on an ongoing basis.**

**Apply to:**
Fanconi Anemia Research Fund
1801 Willamette Street, Suite 200 • Eugene, OR 97401
Telephone: 1-541-687-4658 • Fax: 1-541-687-0548
Email: info@fanconi.org
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